

Towards the Synthesis of the ABC Fragment of Pectenotoxin-4

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

Doctor of Philosophy

in the

University of Oxford

by

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and

The Chemistry Research Laboratory

Hilary Term 2016

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Declaration

This thesis and the work described in it is 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.

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Hilary Term 2016

Abstract

A thesis submitted for the degree of Doctor of Philosophy

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This thesis details the optimisation and development to the synthesis of the ABC fragment of pectenotoxin-4, a 26-membered macrolide marine natural product bearing 19 stereogenic centres, three tetrahydrofuran rings, one spiroketal and one bicyclic ketal.

Introduction

This section briefly discusses the isolation, structure elucidation, and biological activity of pectenotoxins, along with a review of previous synthetic efforts on the pectenotoxin family, especially the ABC fragment. It also summarises our group's work in pursuing the total synthesis of this compound.

Results and Discussion

This section details synthetic efforts to improve the overall yield of the ABC fragment. In particular, it contains the optimisation of a low yield Carreira alkynylation reaction and a revised protecting group strategy to allow orthogonal deprotection on the ABC fragment for further elaborations. The revised route for the ABC fragment of pectenotoxin-4 contains 21 longest linear steps (27 steps in total) from D-mannitol with an overall yield of 2.1% (on average 83% per step).

Acknowledgement

First and foremost, I would like to thank Prof Tim Donohoe for providing me the fantastic opportunity to work in his group at University of Oxford. The knowledge of science and attitude of research that he taught over the pass four year has been invaluable.

I would also show my thanks to all the past and present members of the Donohoe group, especially to the pectenotoxin team - Raddy (“Bigfoot”), Alice, Paul, Kirsty, Mike, Yifan and Ahria. In particular, I would show my great appreciation to Raddy, who took care of me in the lab in the first year. We have done remarkable work in the synthesis together. Many thanks to all my colleagues in F8, including Raddy, Kirsty, Alice (Queen of F8), Rob (the Goblin Alchemist), Darren (the Chipmunk), Jackie, Louis, “little” Kate, Anatol, Simon (the Squirrel), Ignacio and Henrique (the “dirty” guy). They have to tolerate the smell of litres of Et₃N, propargyl bromide and Me₂S from my fumehood over the past a few years. Hopefully it will not cause any chronic side effect on their health. Special thanks to my proofreaders, CB, Ignacio, James (the Panda Master) and Johannes (Johnny Bear). They did excellent work to help me finish writing in a relatively short time.

Finally I am eternally grateful to my family, for their excellent family education for the past years, and also for their continuing support to my growth. I am not the best, but I will always be better.

Abbreviations and Acronyms

[α]	Specific rotation
Ac	acetyl
acac	acetylacetonate
AIBN	2,2-azobis- <i>iso</i> -butyronitrile
aq.	aqueous
Asn	asparagine
atm	atmosphere
<i>b. p.</i>	boiling point
BBN	borabicyclo[3.3.1]nonane
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
BOX.	bisoxazoline
br. s	broad singlet
brsm	based on recovered starting material
Bt	benzothiazole
Bu	butyl
Bz	benzoyl
<i>c</i>	cyclo
CBS	Corey–Bakshi–Shibata
CNS	central nervous system
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
<i>d</i>	doublet
Da	Dalton
DCC	1,3-dicyclohexylcarbodiimide

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEIPS	diethylisopropylsilyl
DEPT	distortionless enhancement by polarization transfer
DET	diethyl tartarate
(DHQ) ₂ PHAL	hydroquinine-1,4-phthalzinediyl diether
(DHQD) ₂ PYR	hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess–Martin periodinane
DMPU	<i>N,N'</i> -dimethylpropylene urea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dpm	dipivaloylmethanato
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphanyl)ferrocene
dppp	[1,3-bis(diphenylphosphino)]propyl
DSP	diarrhetic shellfish poisoning
d. r.	diastereomeric ratio
<i>ee</i>	enantiomeric excess
eq	equivalent
ESI	electrospray ionisation
Et	ethyl
h(s)	hour(s)
His	histidine
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
HWE	Horner–Wadsworth–Emmons
Hz	Hertz
<i>i</i>	iso
Ile	isoleucine
IR	infrared
<i>J</i>	coupling constant
KAPA	potassium 3-aminopropylamide
KHMDS	potassium bis(trimethylsilyl)amide
L	ligand
LDA	lithium diisopropylamide
Leu	leucine
LiDBB	lithium 4,4'-di- <i>tert</i> -butylbiphenyl
LiHMDS	lithium bis(trimethylsilyl)amide
M	general metal
<i>m</i>	multiplet
<i>m</i> CPBA	3-chloroperbenzoic acid
Me	methyl
<i>m</i> F-Bn	3-fluorobenzyl
min(s)	minute(s)
MOM	methoxymethyl
m. p.	melting point
MS	molecular sieves
Ms	methanesulfonyl
<i>n</i>	normal
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	<i>N</i> -bromosuccinimide
NHK	Nozaki–Hiyama–Kishi

NIS	<i>N</i> -iodosuccinimide
NME	<i>N</i> -methylephedrine
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
<i>nOe</i>	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
P	general protecting group
pH	decimal logarithm of the reciprocal of the hydrogen ion activity in a solution
PHAL	phthalazinediyl
Phe	phenylalanine
Piv	pivaloyl
PMB	4-methoxybenzyl
PNB	4-nitrobenzyl
PNO	pyridine- <i>N</i> -oxide
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
Pr	propyl
Pro	proline
<i>p</i> TSA	<i>para</i> -toluenesulfonic acid
PTX(s)	pectenotoxin(s)
Py	pyridine
<i>q</i>	quartet
<i>quin.</i>	quintet
R	general organic group
Red-Al [®]	Sodium bis(2-methoxyethoxy)aluminum dihydride
R _f	retention factor
rt	room temperature
<i>s</i>	singlet
<i>t</i> (NMR)	triplet

<i>t/tert</i>	tertiary
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAB	tetra- <i>n</i> -butylammonium bromide
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAI	tetra- <i>n</i> -butylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBODPS	<i>tert</i> -butoxydiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA/TfOH	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl
TPS	triphenylsilyl
TsOH	toluenesulfonic acid
UV	ultraviolet
wt%	weight percentage
X	general halogen
δ	chemical shift
$\nu_{\max}$	infrared absorption

Chapter 1

Introduction

1.1 General introduction

This chapter provides a brief overview of a class of marine natural product named pectenotoxins (PTXs, see **Figure 1** for the structure of PTX-4). The first section introduces the discovery, isolation, structural elucidation, and biological activity of PTXs. The following section discusses previous synthetic efforts to making the PTX family, in particular to the spiroketal ABC ring fragment. The final section details the approach by the Donohoe group towards the total synthesis of PTX-4, from retrosynthetic analysis to current progress on the molecule.

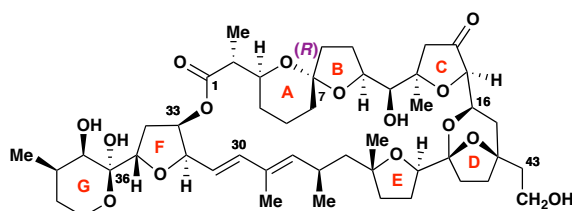


Figure 1. Structure of PTX-4

1.2 Introduction to the PTX family

As the ocean occupies more than 70% of the surface of earth and 95% of the biosphere, it is an enormous treasury for the discovery of new natural products.¹ A wide range of marine natural products are biologically active, and some of them possess unique mechanisms targeting ion channels, enzymes, DNAs or other sites.² Developments in technology for the collection, isolation, purification and characterisation have allowed an increase in marine natural products to be identified as therapeutic leads. However, due to the difficulties in harvesting enough material from microorganisms that produce them, as well as growing environmental concerns, it is the synthetic organic chemists' opportunity to provide sufficient

materials for further biological evaluation and potential clinical application. Amongst all the marine natural products, the PTX family is one that receives increasing interest from the synthetic chemistry community in recent years.³ It is a family of more than 20 cytotoxic secondary metabolites that widely exists in the bivalve class *Pectininae* in oceans all over the world.⁴⁻⁸

1.3 Isolation and characterisation

The first literature record of the PTXs dates back to 1985, when Yasumoto and co-workers reported the isolation and structural determination of several PTXs from the digestive glands of the scallop *Patinopecten yessoensis* collected near Japan.⁹ Further research on the PTXs indicated that PTX-2 was the parent compound of this family, since PTX-2 was detected in both the extract of scallop gut and the algal extract of *D. fortii*, while other PTXs were only detected in the extract of scallop gut.^{4, 7}

The relative stereochemistry of PTX-1 was proposed by the Yasumoto group using X-ray crystallography,¹⁰ but it was not until 1997 that the absolute configuration of the PTX was determined by NMR studies using a chiral amide derivative of PTX-6 by the same group.¹¹ In total 16 members of the PTX family, differing at the oxidation state of C43, the structure of the AB spiroketal rings and the FG ring configurations,³ have been isolated and characterised up to this day (**Figure 2**). All members of the PTX family contain a 34-carbon skeleton macrolide consisting of one spiroketal, one bicyclic ketal, one pyran ring, and three substituted THF rings. PTXs have 43 carbons, in which 19 are stereocenters. It is believed

that other PTXs are generated from PTX-2 *via* acid-catalysed spiroketal equilibration and enzymatic oxidation of the C43 methyl group in the hepatopancreas of the scallop.^{4, 7} The parent compound PTX-2 has a non-anomeric 6,5-spiroketal with an (*R*)-configuration at C7. PTX-1, PTX-3 and PTX-6 are oxidation products of PTX-2 at the C43-*Me* group. PTX-11 and PTX-13 belong to another group of oxidation products in which a selective oxidation takes place at C33 or C34 of the F ring. PTX-2b, PTX-4, PTX-7 and PTX-11b are anomeric 6,5-spiroketal obtained from kinetic acidic equilibration of the corresponding non-anomeric isomers. The thermodynamically more stable 6,6-spiroketal in PTX-2c, PTX-8 and PTX-9 result from further acidic equilibration, and these PTXs are not isolated from natural sources.³ It was also discovered that other variations on the FG rings are possible in the cases of PTX-11, 12, 13, and 14.^{6, 12-14}

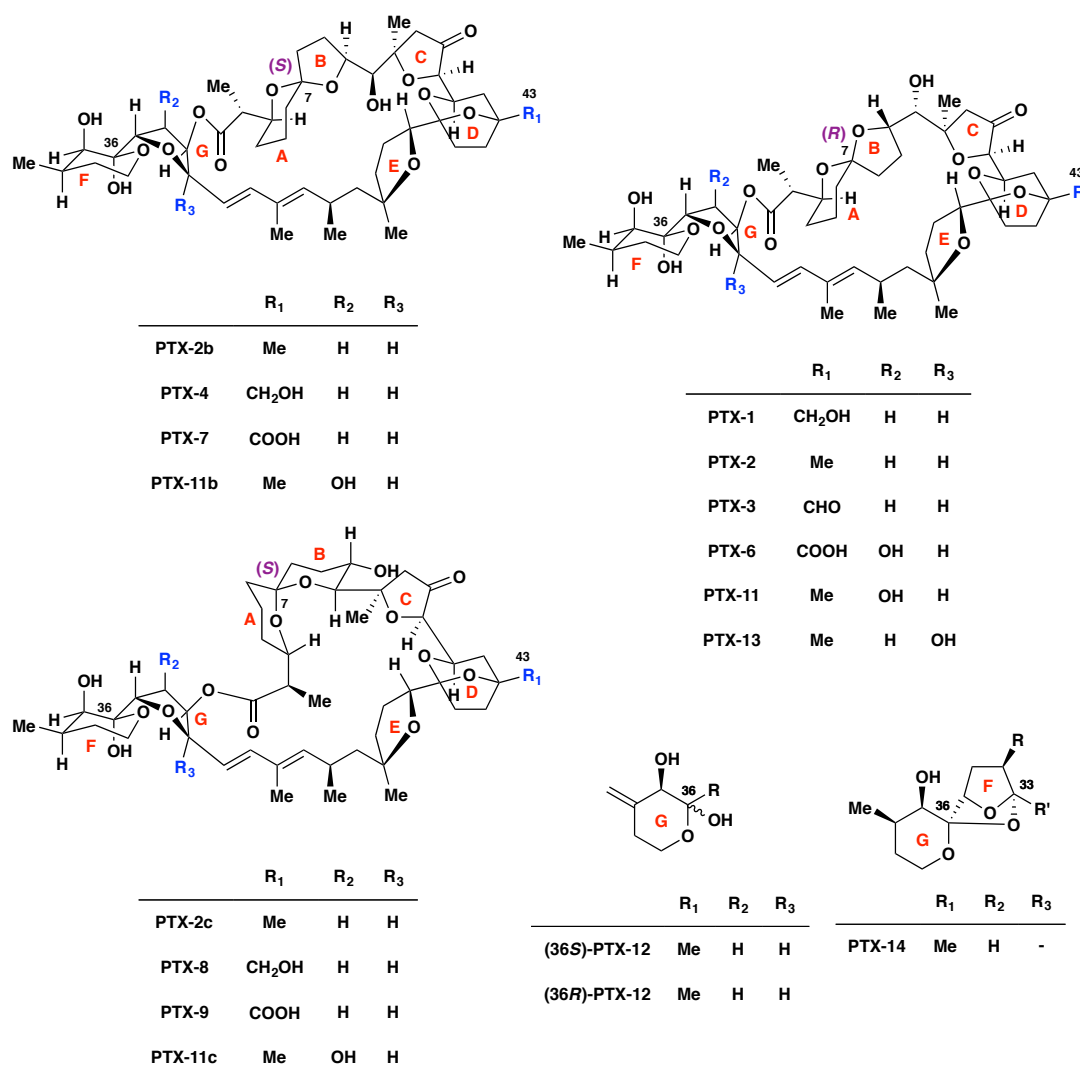


Figure 2. Structure of the PTXs

Another series of the PTX derivatives isolated are the PTX *seco* acids (**Figure 3**). PTXs are metabolised at the C1–C33 ester bond *via* an enzymatic hydrolysis by the shellfish to give a mixture of PTX *seco* acids and 7-*epi*-PTX *seco* acids.¹⁵ Predictably, the acidic equilibration also affects the labile AB spiroketal simultaneously, resulting in a mixture of both epimers at C7 in all the PTX *seco* acids discovered up to date.

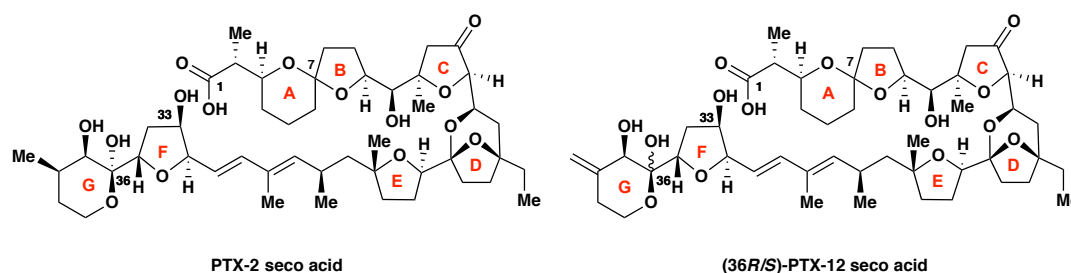


Figure 3. Selected structures of the PTX *seco* acids

1.4 Biological activity of PTXs

The PTXs are reported to be causative agents of the acute diarrhetic shellfish poisoning (DSP) and liver damage from eating toxic shellfish, in association with other toxins such as okadaic acid and dinophysistoxins produced by dinoflagellates, which cause problems to both public health and the shellfish industry in Japan.^{9, 16}

However, the toxicity of PTXs is in doubt now. The Yasumoto group reported in 1986 that the PTXs only had a mild diarrhetic effect while in 2004 the Miles group having isolated PTXs from a different source reported that the acute DSP was not observed.^{16, 17} A comparison of the recent literature data on the acute intraperitoneal injection toxicity of the PTXs is summarised in **Table 1**. PTX-2 as the parent compound is the most potent in the family. Oxidation of the C43-*Me* group or epimerisation to the non-anomeric 6,5-spirokel AB rings significantly reduces its toxicity. The 6,6-spiroketal analogues and PTX *seco* acid does not show any toxicity at all. The oral toxicity of the PTXs are even weaker than that of intraperitoneal injection, reflecting a low level of uptake from the gastrointestinal tract.¹⁸

Considering their low abundance in nature,* PTX is unlikely to cause DSP. The toxicity shown by eating shellfish was thought to be a result of the coexistence of other DSP toxins, including okadaic acid, yessotoxins and dinophysistoxins.³ Consequently, the PTXs are classified as a separate group of marine natural products other than DSP toxins.

Table 1. Acute lethality of PTXs in mice following intraperitoneal administration¹⁸

PTX	Dose (µg/kg body weight)	Parameter*
PTX-1	250	MLD
PTX-2	192-400	MLD
PTX-3	350	MLD
PTX-4	770	MLD
PTX-6	500	MLD
PTX-7	>5000	MLD
PTX-8	>5000	MLD
PTX-9	>5000	MLD
PTX-11	250	MLD
PTX-2 SA	>5000	MLD
7- <i>epi</i> -PTX-2 SA	>5000	MLD

*MLD: minimum lethal dose

* The Yasumoto group obtained less than 100 mg of a combination of PTX-1–5 from 200 kg of the digestive glands of the scallop *Patinopecten yessoensis*.⁹

Although PTXs are not toxic, recent biological studies have shown that these polyether macrolide compounds are potent against a series of cancer cell lines.^{4, 19-21} *In vivo* studies indicate that PTX-2 exhibits unique cytotoxicity. It was initially observed that the PTXs are hepatotoxic, inducing apoptosis in rat and salmon hepatocytes.^{9, 10, 22} Further experiments indicated that the PTX-2 had potent cytotoxic effects against several cancer cell lines, including lung, colon, CNS, melanoma, ovarian, renal and breast cancer cell lines (**Table 2**).²³ Assays for DNA cleavage as well as the rats' plasma membrane assay proved that PTX-2 did not affect DNA synthesis or oxidation–reduction process on the cell membrane.²³ Subsequent research elucidated a mechanism of cytotoxicity involving a polymerisation process of actin.^{24, 25} PTX-2 binds to actin at a unique site between subdomain **1** and subdomain **3** primarily through hydrophobic interactions, which is supported by the X-ray crystallography of the PTX-2–actin complex (**Figure 4**).²⁶

Table 2. Cytotoxicity of PTX-2 against human cancer cell lines²³

Cancer type	Cell line	LD ₅₀ (nM)
Non-Small Cell Lung Cancer	EK VX	62.0
Colon Cancer	COLO 205	7.82
CNS Cancer	SF-295	77.7
Melanoma	SK-MEL-28	42.3
Ovarian Cancer	OVCAR-3	61.6
Renal Cancer	CAKI-1	19.1
Breast Cancer	BT-549	62.7

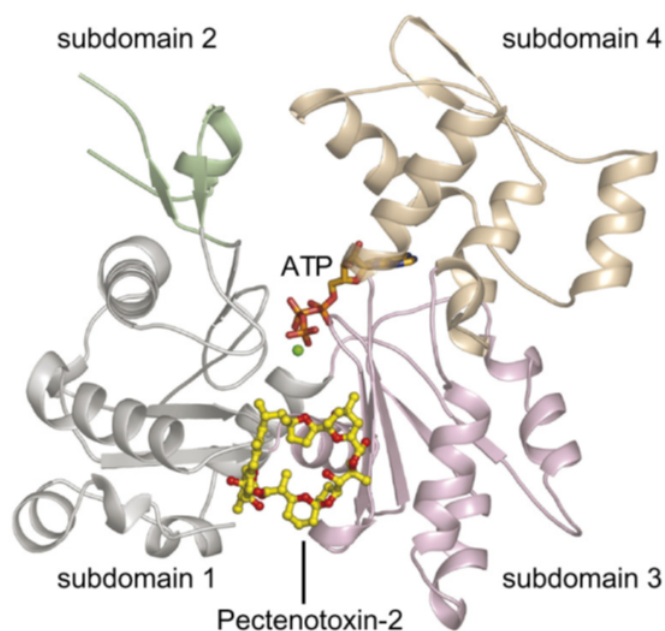


Figure 4. X-ray crystallography structure of the PTX-2–actin complex (reprinted from Allingham, J. S., Miles, C. O. and Rayment, I., 2007)²⁶

The binding interactions between PTX-2 and actin is depicted in **Figure 5**.²⁶ PTX-2 is situated between Pro-112 and His-173, and is further directed by the hydrophobic interactions of the FG rings (the “tail”) with Phe-375 and Ile-136. Apart from these interactions, the molecule also interacts with actin *via* hydrogen bonding on the C, F and G rings to Pro-109 and Asn-111, and a key hydrophobic interaction between the C45-*Me* group and Ile-75. These interactions are presented in the complex due to the conformational constraints of the diene unit (C28–C31). The conformation of the non-anomeric 6,5-spiroketal is critical for positioning the AB ring between Leu-110 and His-173.

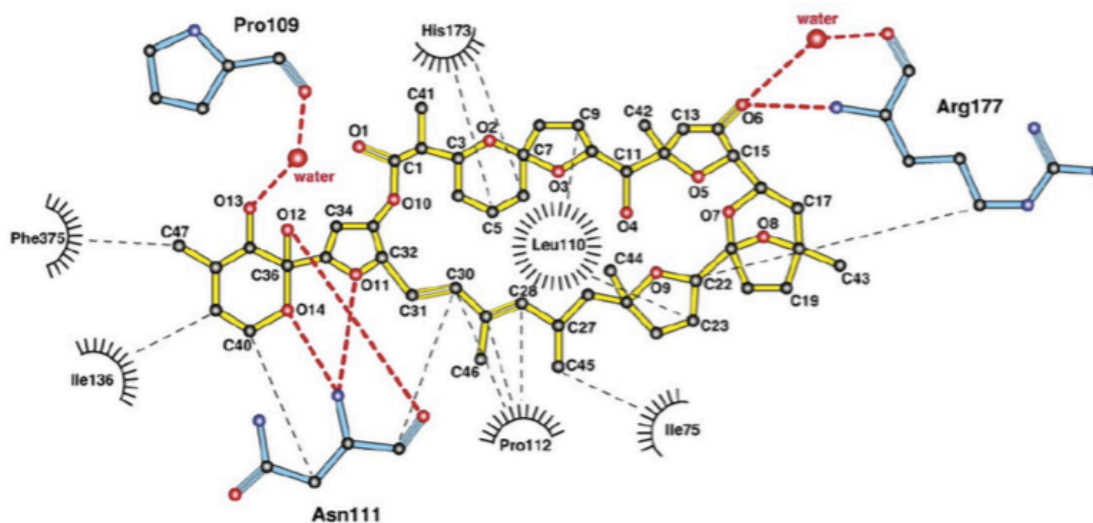


Figure 5. Interactions between PTX-2 and actin (The red dashed lines represent hydrogen bonding, the black dashed line represents van der Waals interactions, and the actin residues involved in the polar interactions are represented in blue, reprinted from Allingham, J. S., Miles, C. O. and Rayment, I., 2007)²⁶

The binding sites of the PTX-2 have not been observed in other natural products before, which explains its unique mechanism against the cancer cell lines. Recent research demonstrated that the PTX-2 inhibited the polymerisation of actin, affecting the growth of cancer cells and resulting in an increased apoptosis.^{27, 28} It was also shown that the PTX-2 was more active towards the cancer cells than normal cells.²¹ Consequentially, the PTX family became an interesting drug lead in cancer research.

1.5 Previous synthetic efforts to the PTXs

The synthetic efforts towards PTXs started with PTX-2, which is the most potent member and the parent compound for the PTX family.³ However, PTX-2 has the least stable

non-anomeric 6,5-spiroketal AB ring system **1**, which has a strong tendency to isomerise to the 6,5-anomeric spiroketal **2** (**Figure 6**).²⁹ Consequentially, PTX-4 or the artificial product PTX-2b, which bears the more stable anomeric 6,5-spiroketal **2** are more attractive targets, as they are expected be converted to the more potent PTX-1 and PTX-2 *via* a late stage acidic equilibration.^{30, 31} This strategy is widely employed in most of the syntheses discussed in the following paragraph.

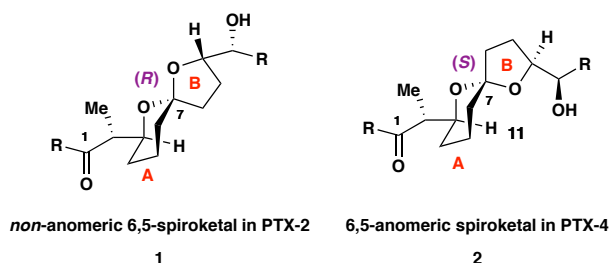


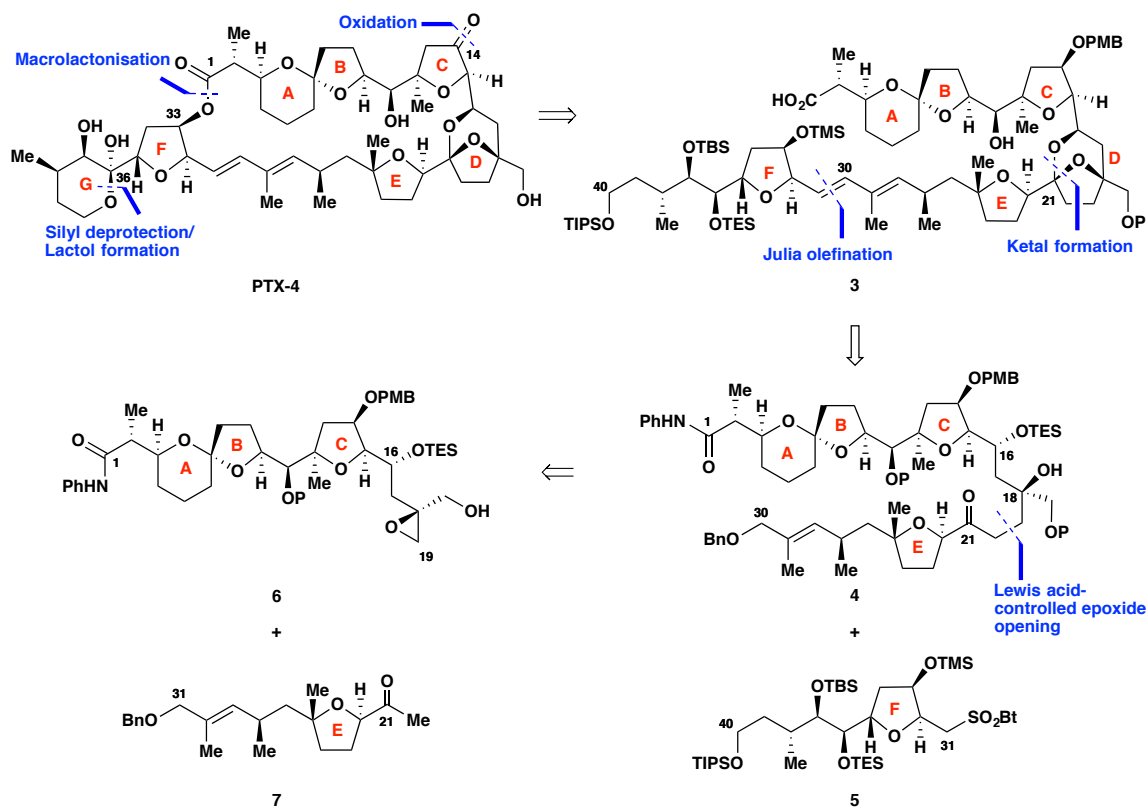
Figure 6. Spiroketal structures in PTXs

There are two total syntheses of the PTXs accomplished to date. The Evans group finished the first total synthesis of PTX-4, and they obtained PTX-1 and PTX-8 *via* an acid-mediated equilibration in 2002.^{30, 32} The Fujiwara group completed the total synthesis of PTX-2 *via* a similar acid-mediated equilibration from PTX-2b in 2013.^{29, 31, 33-36} Several other research groups are also working on the PTX family and have completed some of the fragments towards these molecules. These include Micalizio's synthesis of the C1–C26 analogue of PTX-2,³⁷⁻³⁹ Paquette's synthesis of the C1–C26 analogue of PTX-2,⁴⁰⁻⁴³ Pihko's synthesis of the 10-*epi*-C1–C22 fragment of PTX-2,^{5, 44-47} Brimble's syntheses of the C1–C16, C12–C28 and C31–C40 fragments of PTX-4,⁴⁸⁻⁵³ Rychnovsky's synthesis of the C1–C11 fragment of PTX-2,⁵⁴ Williams's syntheses of the C1–C19 precursor and C21–C28 fragment of

PTX-4,⁵⁵⁻⁵⁷ Vassilikogiannakis' synthesis of the C3–C24 analogue of PTX,^{58, 59} and Donohoe's synthesis of the C1–C16 fragment of PTX-4.⁶⁰ These syntheses will be discussed in the following section, with particular attention to the two completed total syntheses and the formation of the AB spiroketal rings.

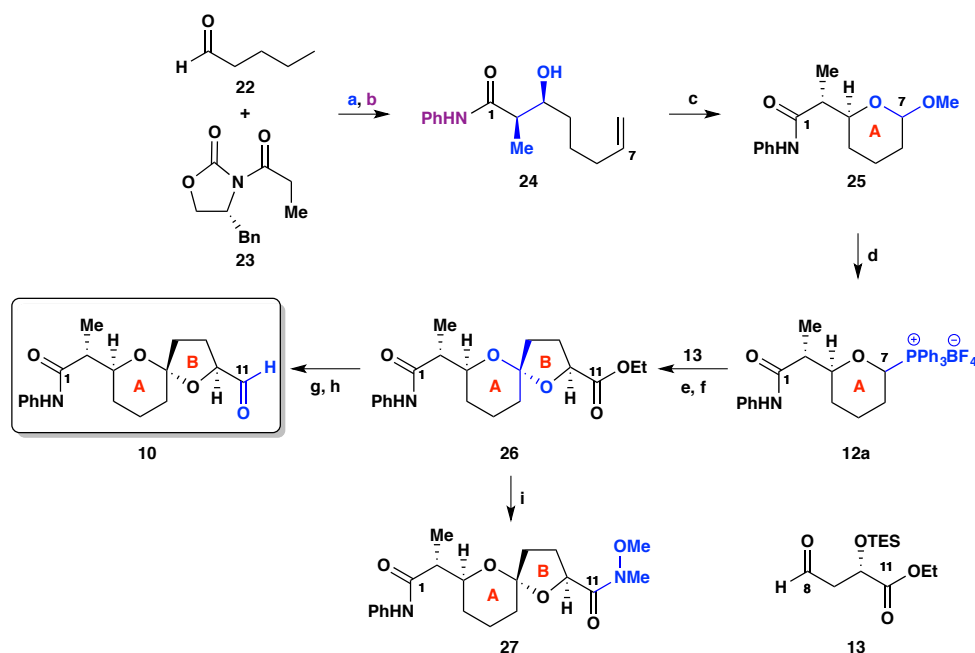
1.5.1 Evans' total synthesis of PTX-4

In 2002, Evans and co-workers finished the first total synthesis of PTX-4.^{30, 32} In their retrosynthetic analysis, the Evans group sought to disconnect PTX-4 to several fragments with similar complexities with the aim of using a convergent strategy (**Scheme 1**). They proposed that PTX-4 would be formed *via* a macrolactonisation from its *seco* acid **3**. The G ring lactol was envisaged to form spontaneously under acidic conditions following global deprotection, and the bicyclic D ring acetal would be generated from the C21 ketone. Further disconnections at C19–C20 and C30–C31 resulted in 3 fragments, sulfone **5**, epoxide **6** and ketone **7**. It was planned to connect the C21–C30 E ring fragment with the ABC fragment *via* a Lewis acid-assisted epoxide opening by a metallo-enamine. The connection between E ring fragment **7** and F ring fragment **5** would be achieved through a Julia–Kocienski olefination.



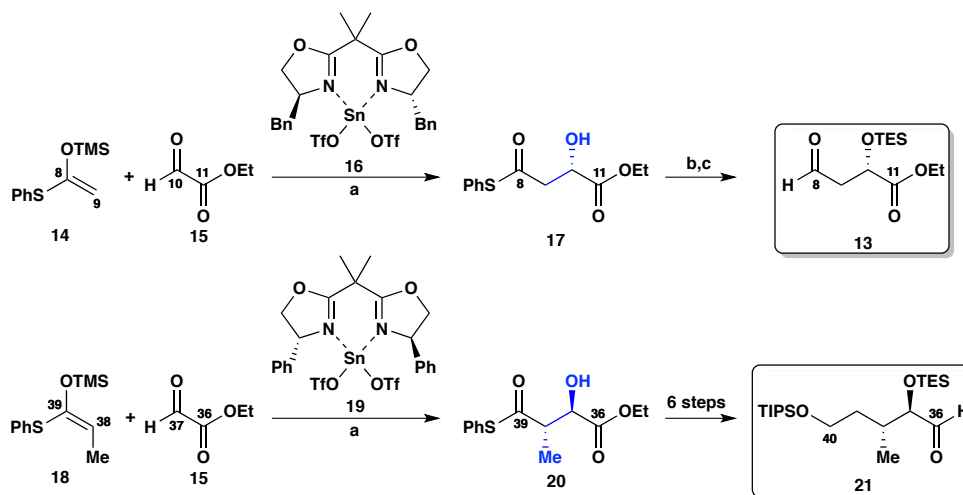
Scheme 1. Evans' retrosynthetic analysis of PTX-4

The disconnection approach for the C1–C19 ABC spiroketal fragment is shown in **Scheme 2**. Felkin–Anh controlled addition of vinyl bromide **11** and stannane **9** to corresponding aldehydes would generate the C11 and C16 stereocentres respectively. The spiroketal would be formed through an olefination–spiroketalisation process from phosphonium salt **12** and aldehyde **13**.



Scheme 2. Evans' retrosynthesis of the C1–C19 spiroketal fragment **6**

The Evans group planned to use a chiral Lewis acid-catalysed aldol reaction between silyl enol ether **14** and ethyl glyoxylate **15** to form the C10 stereocentre (alcohol **17**, **Scheme 3**).⁶¹ Bidentate chelation between Lewis acid $[\text{Sn}((S,S)\text{-Bn-BOX})](\text{OTf})_2$ **16** and the ethyl glyoxylate **15** blocked the *Re*-face of aldehyde **15** to nucleophilic addition, resulting in high yield and enantioselectivity (86%, 98% *ee*). Subsequent TES protection followed by reduction of the thioester with Pd/C in the presence of Et_3SiH afforded the C8–C11 aldehyde **13** in near quantitative yield. The catalytic aldol reaction was also applied to the synthesis of the C36–C40 aldehyde **20** from silyl enol **18** and ethyl glyoxylate **15** to give aldol product **21** in 97% yield (95% *ee*, 96:4 d.r.).

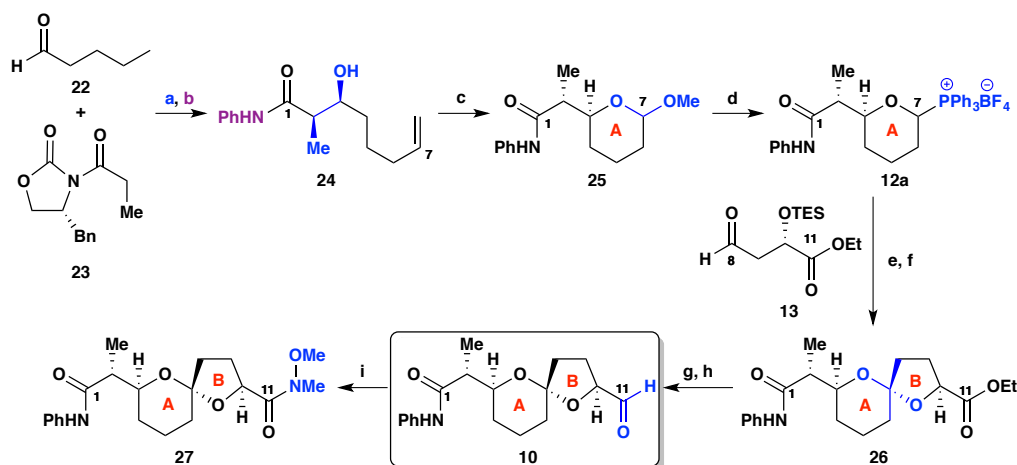


Scheme 3. Sn(II) catalysed aldol reactions in the synthesis of PTX-4

Reagents and conditions: (a) [Sn((*S,S*)-Bn-BOX)](OTf)₂ or [Sn((*R,R*)-Ph-BOX)](OTf)₂ (10 mol%), CH₂Cl₂, -78 °C, 5 min 86% **17**, 98% *ee* or 97% **20**, 95% *ee*, 94:6 d.r.; (b) TESOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 99%; (c) Et₃SiH, Pd/C, acetone, 97%.

The forward synthesis of ABC spiroketal fragment **27** commenced with a *syn*-aldol reaction between 5-hexenal **22** and (*R*)-4-benzyl-oxazolidinone **23** (**Scheme 4**). Transamidation of aldol product with phenylaniline in the presence of AlMe₃ afforded the amide **24** in an excellent yield of 98%. Ozonolysis of **24** with reductive workup (Me₂S), followed by treatment with CSA allowed formation of the A ring acetal **25** in near quantitative yield. After formation of phosphonium salt at C7, precursor **12a** was subsequently coupled with aldehyde **8** to form an unstable enol ether, in which the TES group was immediately cleaved under acidic conditions to give the spiroketal **26** in 80% overall yield over 3 steps. The product was obtained with a d.r. of 95:5 in favour of the desired anomeric 6,5-spiroketal in PTX-4. Reduction of ester **26** with LiBH₄ followed by Parikh–Doering oxidation afforded

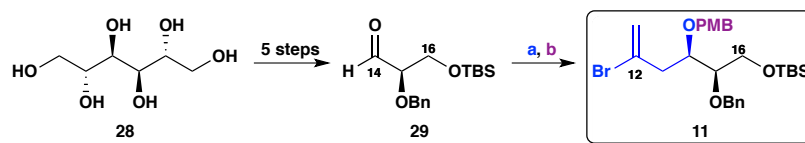
the AB ring aldehyde **10**. Ester **26** could be further converted to the more stable Weinreb amide **27** for storage.



Scheme 4. Evans' synthesis of the AB spiroketal fragment **10**

Reagents and conditions: (a) $n\text{Bu}_2\text{BOTf}$, Et_3N , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, then 5-hexenal **22**, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 87%; (b) Me_3Al , PhNH_2 , CH_2Cl_2 , 98 %; (c) O_3 , MeOH , DMS , $-78\text{ }^\circ\text{C}$, then CSA , 96%; (d) $\text{PPh}_3\cdot\text{HBF}_4$, MeCN , $60\text{ }^\circ\text{C}$; (e) $n\text{BuLi}$, THF , $-78\text{ }^\circ\text{C}$, then **13**; (f) CSA , $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1:1), 80% (3 steps); (g) LiBH_4 , THF , $-10\text{ }^\circ\text{C}$, 93%; (h) $\text{SO}_3\cdot\text{Py}$, Et_3N , $\text{DMSO}/\text{CH}_2\text{Cl}_2$ (1:1), 91%; (i) $\text{MeONHMe}\cdot\text{HCl}$, $i\text{PrMgCl}$, THF , $-78\text{ }^\circ\text{C}$, then **10**, $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, 91%.

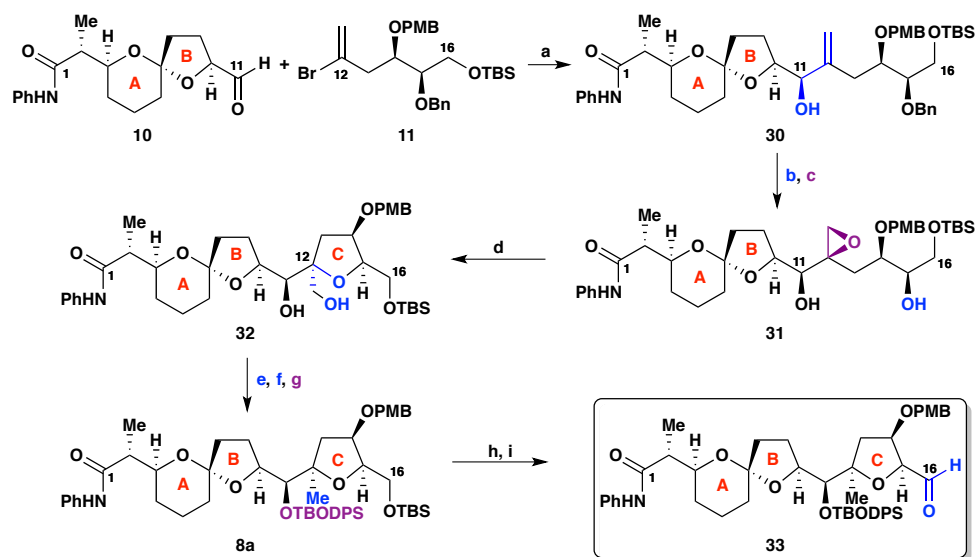
The C12–C16 vinyl bromide **11** was prepared from aldehyde **29**, which in turn was synthesised from D-mannitol **28** in five steps (**Scheme 5**). Treatment of aldehyde **29** with 2-bromoallyltrimethylsilane under the chelation control of $\text{Ti}(\text{OiPr})\text{Cl}_3$ afforded the *syn*-product in 87% yield, which then underwent an acidic PMB protection to give vinyl bromide **11** in 79% yield.⁶²



Scheme 5. Evans' synthesis of the C12–C16 vinyl bromide **11**

Reagents and conditions: (a) 2-bromoallyltrimethylsilane, $\text{Ti}(\text{O}i\text{Pr})\text{Cl}_3$, $-78\text{ }^\circ\text{C}$, 87%; (b) PMB-trichloroacetimidate, TfOH , Et_2O , -20 to $0\text{ }^\circ\text{C}$, 79 %.

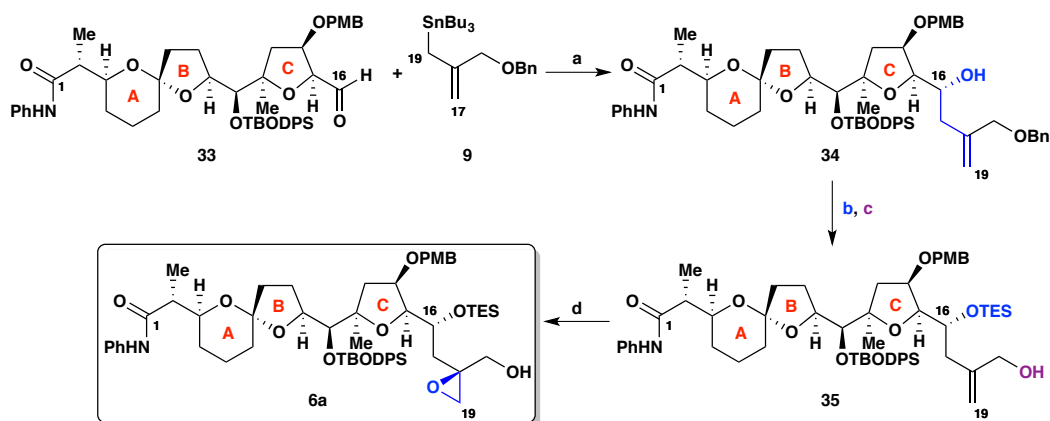
Treatment of vinyl bromide **11** with $t\text{BuLi}$ followed by an *in situ* transmetallation with MgBr_2 afforded the corresponding Grignard reagent, which underwent a Felkin–Anh controlled addition to aldehyde **10** to give alcohol **30** with a yield of 68% and a d.r. of 86:14 (**Scheme 6**). Selective deprotection of the Bn group with LiDBB in the presence of a PMB group was achieved in 81% yield. $\text{VO}(\text{acac})_2$ catalysed allylic epoxidation *via* Sharpless' protocol gave epoxide **31** in an excellent yield of 99% and >95:5 d.r..⁶³ Epoxide **31** was treated with PPTS to initiate a cyclisation to form the C ring in 87% yield (spiroketal **32**). The $\text{C12-CH}_2\text{OH}$ group was converted to a phenyl xanthate and cleaved *via* a Barton–McCombie radical deoxygenation in 72% yield. Note that an unusual *tert*-butoxydiphenylsilyl (TBODPS) group was installed at C11 in compound **8a**. This silyl protecting group was more stable than the C16-OTBS group under acid-mediated desilylation conditions, but would be easily removed with TASF under the proposed global deprotection conditions. Treatment with CSA at $-20\text{ }^\circ\text{C}$ selectively cleaved the primary TBS group at C16 in a good yield of 85%, and a quantitative Parikh–Doering oxidation afforded the C16 aldehyde **33** for the next Felkin–Anh controlled addition.



Scheme 6. Evans' synthesis of the C1-C16 spiroketal **33**

Reagents and conditions: (a) *t*BuLi, Et₂O, -78 °C, then MgBr₂, then **10**, 68%, 86:14 d.r.; (b) LiDBB, THF, -78 °C, 81%; (c) VO(acac)₂, TBHP, PhH, 99%; (d) PPTS, CH₂Cl₂, 87%; (e) PhOC(S)Cl, DMAP, CH₂Cl₂, -10 °C, 75%; (f) *n*Bu₃SnH, AIBN, xylenes, 160 °C, 72%; (g) TBODPSCl, Et₃N, DMAP, DMF, 90%; (h) CSA, MeOH/CH₂Cl₂ (1:1), -20 °C, 85%; (i) SO₃•Py, Et₃N, DMSO/CH₂Cl₂ (1:1), -10 °C, 98%.

The synthesis of the C1-C19 fragment began with a Felkin-Anh controlled allylation to aldehyde **33** with 2-(benzyloxymethyl)allyltributyl stannane **9** to afford homoallyl alcohol **34** in >95:5 d.r. with a good yield of 80% (**Scheme 7**). TES protection of the C16-OH group followed by selective debenzoylation with LiDBB gave homoallyl alcohol **35** in 80% yield over two steps. Sharpless asymmetric epoxidation afforded the C18-C19 epoxide **6a** in near quantitative yield.

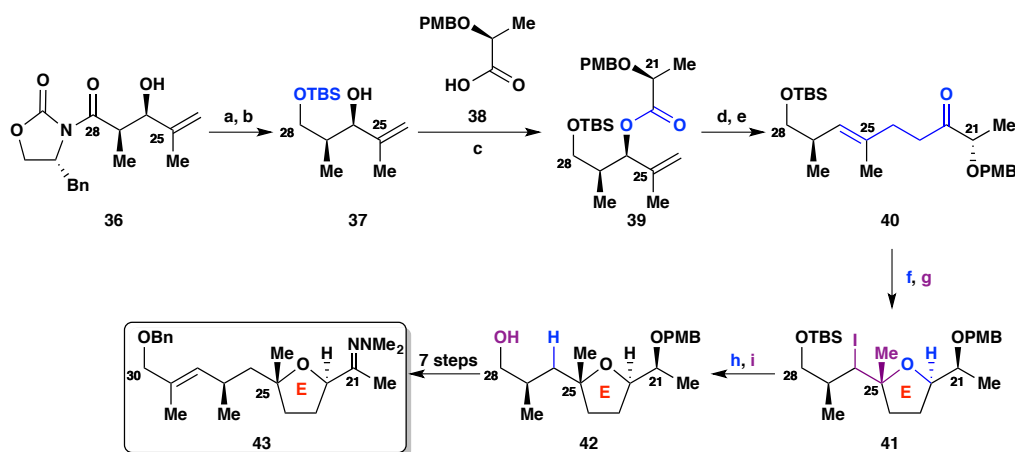


Scheme 7. Evans' synthesis of the C1–C19 fragment **35**

Reagents and conditions: (a) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C , 80%, >95:5 d.r.; (b) TESCl , imidazole, CH_2Cl_2 , 92%; (c) LiDBB , THF, -78°C , 87%; (d) $\text{Ti}(\text{OtBu})_4$, (L)-(+)-DET, TBHP, 3 Å MS, CH_2Cl_2 , -30°C , 99%.

The synthesis of the C21–C30 fragment **43** commenced from *syn*-aldol adduct **36** (**Scheme 8**). Reductive cleavage of the oxazolidinone with LiBH_4 followed by selective primary TBS protection afforded secondary alcohol **37** in quantitative yield. Acylation of **37** with PMB-protected lactic acid **38** gave ester **39** in 53% yield. Compound **39** was then treated with Tebbe's reagent (generated *in situ* from Cp_2TiCl_2 and AlMe_3), and a subsequent Claisen rearrangement constructed the C21–C28 carbon skeleton in a good yield of 82%. Chelation-controlled reduction of ketone **40** with $\text{Zn}(\text{BH}_4)_2$ generated the C ring cyclisation precursor **41** with reasonable selectivity of 86:14 d.r. in 86% yield. An iodoetherification with NIS provided the *trans*-THF E ring in good yield (89 %) with moderate stereoselectivity (72:28 d.r. at C25). Radical dehalogenation with $n\text{Bu}_3\text{SnH}$ and AIBN followed by TBS deprotection with TBAF gave primary alcohol **42** in quantitative yield. Further elaboration afforded the C21–C30 fragment **43** in 7 steps. The C21 ketone was converted to a hydrazine,

as it gave a better yield and selectivity for the C19–C20 epoxide opening comparing to use the C21 ketone (see *vide supra*).

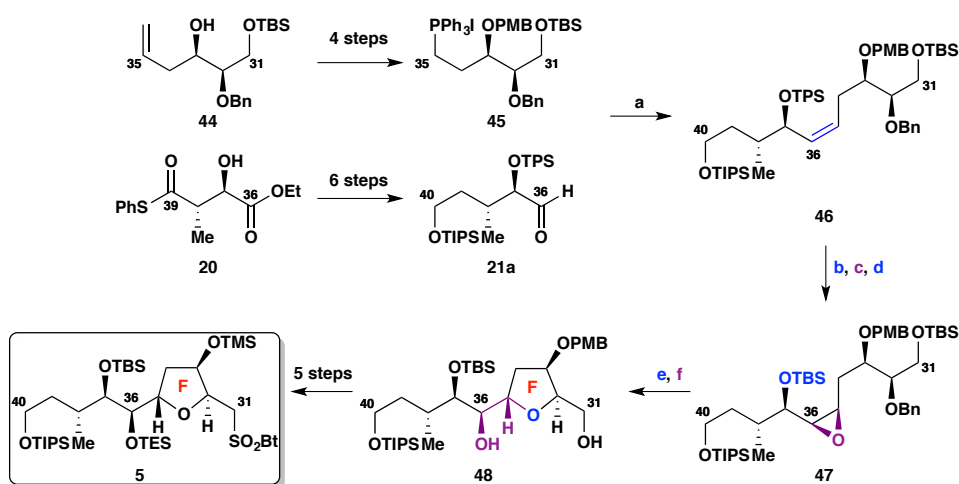


Scheme 8. Evans' synthesis of the C21–C30 fragment **43**

Reagents and conditions: (a) LiBH_4 , THF, 0 °C; (b) TBSCl, imidazole, CH_2Cl_2 , 100% for 2 steps; (c) DCC, DMAP, CH_2Cl_2 , 52%; (d) Cp_2TiCl_2 , AlMe_3 ; (e) PhMe, 110 °C, 82% over 2 steps; (f) $\text{Zn}(\text{BH}_4)_2$, Et_2O , –78 °C, 86%, 86:14 d.r.; (g) NIS, MeCN, –40 °C, 89%, 72:28 d.r.; (h) $n\text{Bu}_3\text{SnH}$, AIBN, PhMe, 100%; (i) TBAF, THF, 95%.

The synthesis of the C31–C40 fragment **5** commenced with phosphonium salt **45** and aldehyde **21a** (Scheme 9). Compound **45** was obtained from an orthogonally protected D-mannitol derivative **44**, and compound **20** was prepared *via* the Sn^{2+} catalysed diastereoselective aldol reaction discussed earlier. After further elaboration, the C31–C35 fragment **45** and the C36–C40 portion **21a** were subjected to a Wittig reaction to afford the C35–C36 *trans*-alkene **46** in 79% yield with 95:5 *Z:E* selectivity. The triphenylsilyl (TPS) group on the C37 was then selectively deprotected under basic conditions (K_2CO_3 in MeOH) in the presence of a TIPS group and a TBS group. Epoxidation directed by allylic hydroxyl group, followed by a TBS protection gave epoxide **47** as a single diastereoisomer in 95%

yield.⁶³ After selective debenzoylation with LiDBB, epoxide **47** underwent an acid-promoted epoxide opening–cyclisation process to generate the F ring fragment **48** in 73% yield. Compound **48** was further elaborated to sulfone **5** for the desired Julia–Kocienski olefination in 5 additional steps.

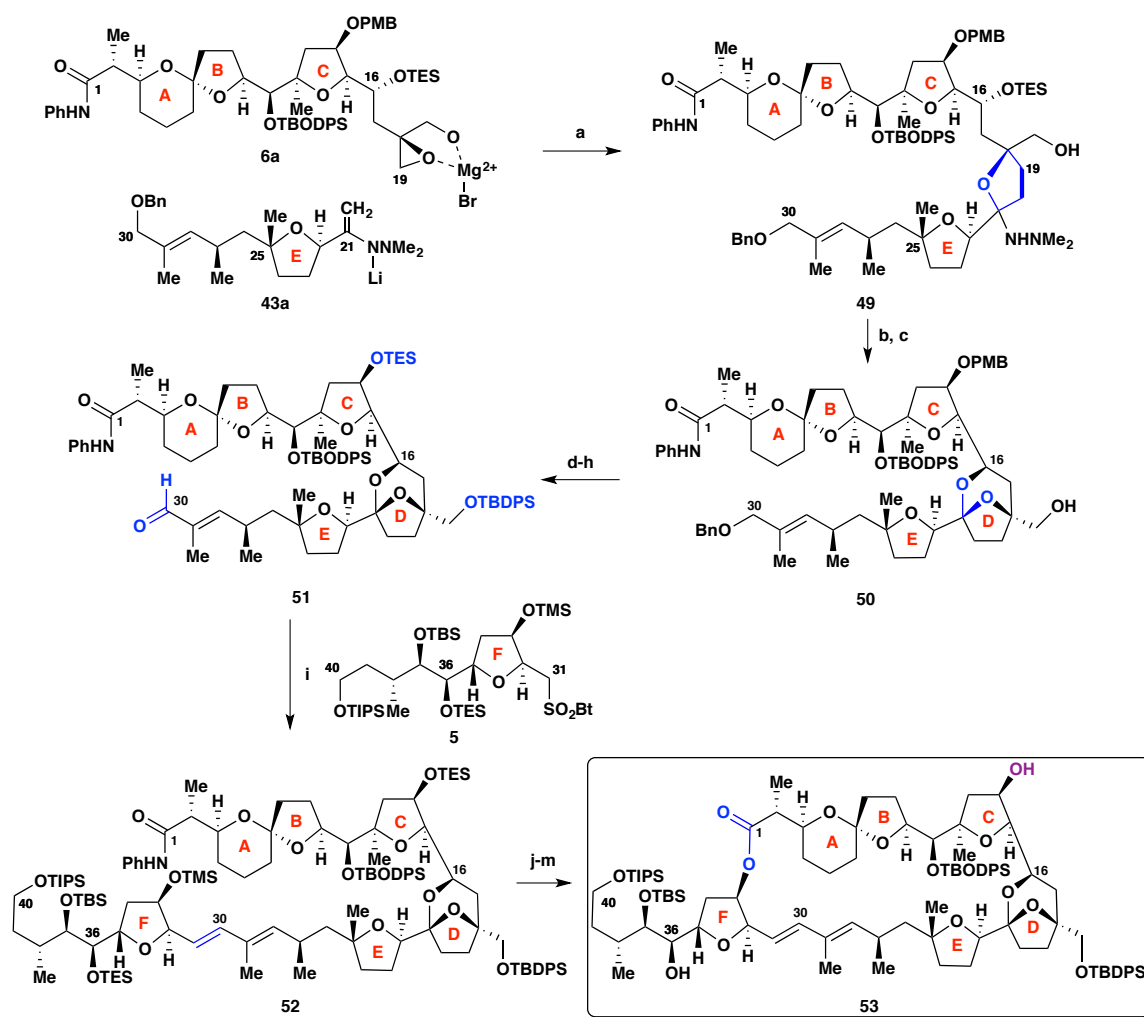


Scheme 9. Evans' synthesis of the C31–C40 fragment **5**

Reagents and conditions: (a) LiHMDS, THF, $-78\text{ }^{\circ}\text{C}$, then **21a** $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$, 79%; (b) K_2CO_3 , $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (2:1), 87%; (c) *m*CPBA, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 95%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$, 95%; (e) LiDBB, THF, $-78\text{ }^{\circ}\text{C}$, 79%; (f) PPTS, $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1:1), 73%.

The completion of PTX-4 started with the coupling of the ABC-ring fragment **6a** and the E ring fragment **43a** (**Scheme 10**). Epoxide **6a** was activated with MgBr_2 , and then opened by the metalloenamine derived *in situ* from **43a** and LDA. The resulting hydrazinyl lactol was exposed to a mixture of pentane/ CH_2Cl_2 /10% aq. NaHSO_4 to form the corresponding lactol. The C16-OTES group was also cleaved under the reaction conditions to afford the bicyclic D ring with a 52% yield over 3 steps. It was noteworthy that 5 equivalent of hydrazone **43a** was required to drive the reaction to completion, of which 48% of the unreacted **43a** was

recovered after the reaction.⁶⁴ The ABCDE ring fragment **49** was further manipulated in 5 steps to give aldehyde **50**. The PMB group was changed to a TES group at this stage because the deprotection of PMB with DDQ was reported to be incompatible with the conjugated diene moiety.⁶⁵ Julia–Kocienski olefination between aldehyde **51** and sulfone **5** afforded the ABCDEF ring fragment **52** in 72% yield with a selectivity of >95:5 *E:Z* at the C30–C31 double bond. However, some epimerisation of the stereocentre at C32 was observed, resulting in an 88:12 mixture of epimers. The C1 secondary amide was activated as a good leaving group with Boc₂O after olefination in 91% yield. Oxazolidinone cleavage with LiOOH (generated *in situ* from LiOH and H₂O₂) followed by Yamaguchi macrolactonisation afforded the macrocyclide ring. Treatment with PPTS selectively removed the C14-OTES and C36-OTES groups and afforded macrolide **53** in 35% yield over 3 steps.

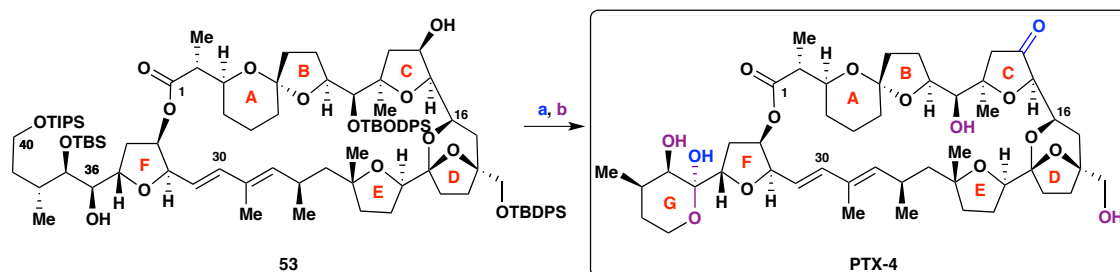


Scheme 10. Evans' fragments couplings of PTX-4

Reagents and conditions: (a) add **6a**•MgBr₂ to Li-**43a**, THF, 10 °C; (b) Pentane/CH₂Cl₂/10% NaHSO₄ (4.5:1.5:4); (c) PPTS, CH₂Cl₂/MeOH (1:1), 52% over 3 steps; (d) TBDPSCl, imidazole, DMAP, CH₂Cl₂, 90%; (e) DDQ, CH₂Cl₂/pH 7 buffer (6:1), 90%; (f) TESCl, imidazole, CH₂Cl₂, 100%; (g) LiDBB, THF, −78 °C, 85%; (h) SO₃•Py, Et₃N, CH₂Cl₂/DMSO (1:1); (i) **40**, LiHMDS, THF, −78 °C to 0 °C, 72% over 2 steps; (j) Boc₂O, DMAP, MeCN, 91%; (k) LiOH, H₂O₂, THF/H₂O (3:1); (l) trichlorobenzoyl chloride, *i*Pr₂NEt, then DMAP, PhMe, rt; (l) PPTS, CH₂Cl₂/MeOH (1:1), 35% over 3 steps.

Dess–Martin oxidation of the C14-*OH* and C36-*OH* groups afforded a diketone in 72% yield (**Scheme 11**). Global deprotection by treatment with TASF removed all the remaining silyl protecting groups, spontaneously forming the G ring lactol to give PTX-4 in a good yield of

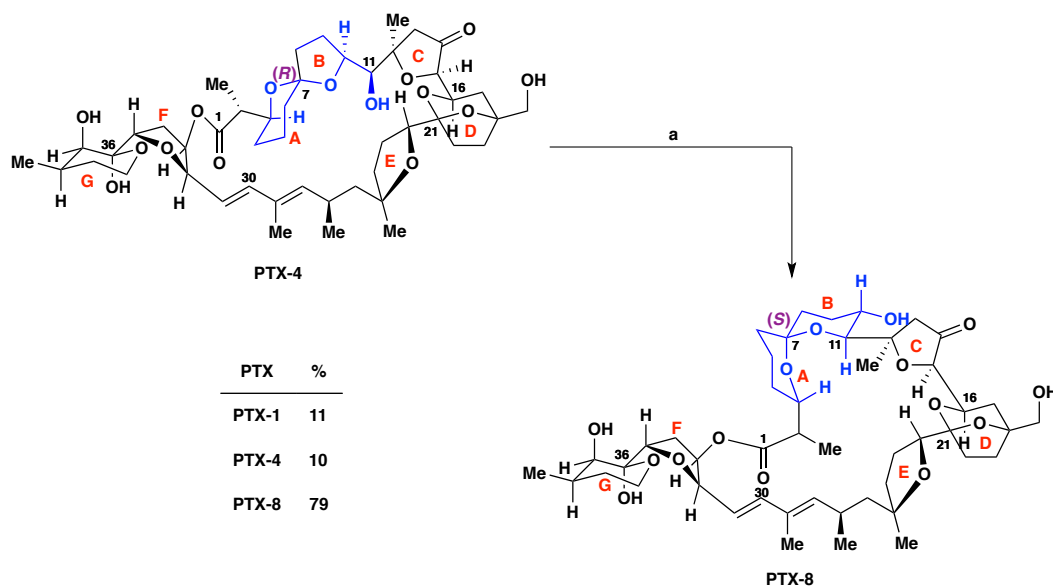
85%. In total Evans' synthesis of PTX-4 took 36 longest linear steps with an overall yield of 0.3%.



Scheme 11. Evans' completion of PTX-4

Reagents and conditions: (a) Dess–Martin periodinane, Py, CH₂Cl₂, 72%; (b) TASf, H₂O, DMF, 85%.

Finally, the Evans group also obtained PTX-1 and PTX-8 from PTX-4 *via* an acid-mediated equilibration (**Scheme 12**). Synthetic PTX-4 was treated with 1% TFA in MeCN/H₂O for 12 hours to afford a mixture of PTX-1, 4 and 8 in an observed ratio of 11:10:79. PTX-8 was purified *via* preparative HPLC with an isolated yield of 40%. The structure of synthetic PTX-4 and -8 were confirmed by comparison of the ¹H NMR and UV data to authentic natural samples isolated by the Yasumoto group.⁶⁴ The ratio of PTXs after equilibration was inconsistent with Yasumoto's observation with a ratio of 29:14:57 for PTX-1, -4 and -8, after subjecting PTX-4 under similar conditions for 48 hours.⁷ It was proposed that at least one set of the samples did not reach equilibrium.⁶⁶



Scheme 12. Evans' acidic equilibration of PTX-1, 4 and 8

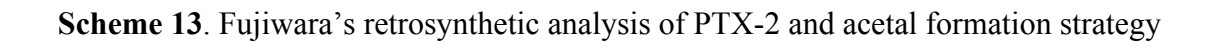
Reagents and conditions: (a) 1% TFA (v/v), MeCN/H₂O (9:1), 12 h, 11% PTX-1, 10% PTX-4, 79% PTX-8.

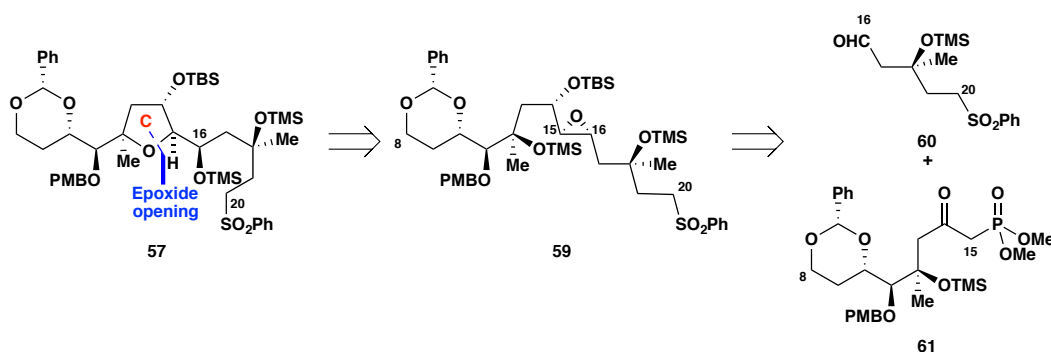
1.5.2 Fujiwara's total synthesis of PTX-2

Being the most potent member of the PTX family, PTX-2 is an attractive target for the synthetic community. However, bearing an unstable non-anomeric 6,5-spiroketal, its synthesis is also more challenging than PTX-4. It was not until 2014 that Fujiwara and co-workers finished the first total synthesis of PTX-2 after 20 years of work.^{29, 31, 33-36, 67}

Fujiwara's retrosynthetic analysis is depicted in **Scheme 13**. To circumvent the instability of the non-anomeric spiroketal system, Fujiwara's strategy was planned to apply an acid-mediated equilibration towards the end of the synthesis to construct the non-anomeric 6,5-spiroketal in PTX-2 from the 6,5-anomeric spiroketal present in PTX-2b. It was noteworthy that the anomeric 6,6-spiroketal in PTX-2c is more stable than both of the 6,5-spiroketal, but its rate of formation was much slower in the equilibration than the other

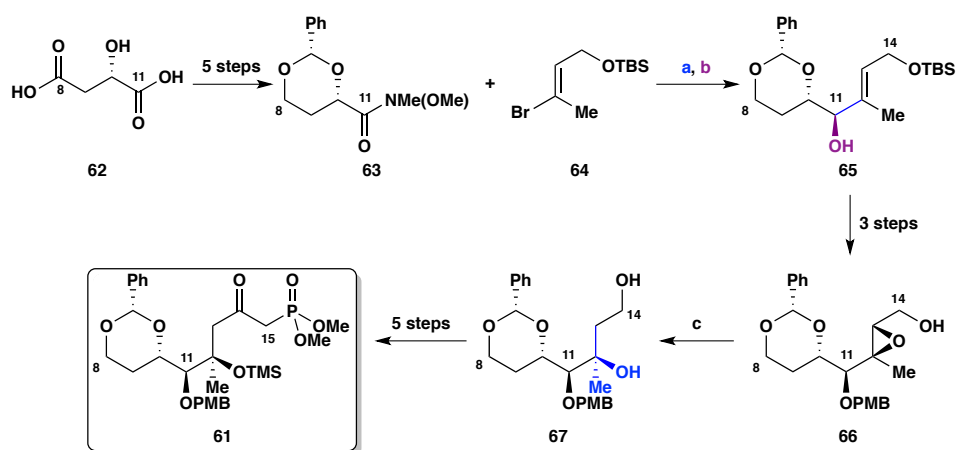
two under acidic conditions.¹² Thus, it should be possible to obtain the kinetic product PTX-2 and minimise the formation of PTX-2c using suitable acidic conditions.³¹ Unlike Evans' macrolactonisation strategy to close the C1–C33 ester (See **Section 1.3.1**), Fujiwara proposed another strategy *via* a ring-closing metathesis at the C30–C31 double bond, avoiding the exposure of the spiroketal moiety to acidic conditions. The key steps to form the AB spiroketal and bicyclic acetal D ring were a sulfone coupling–desulfonylation process, which was efficiently employed in Brimble's synthesis of the AB spiroketal of PTX-2b (**Scheme 13**).⁴⁸ Consequently, PTX-2b was disconnected at C8–C9 and C20–C21 to the C8–C20 sulfone **57**, C21–C30 aldehyde **58** and ester **56**, which contains the FG rings and the C1–C7 fragment.





Scheme 14. Fujiwara's retrosynthetic analysis of the C8–C20 fragment **57**

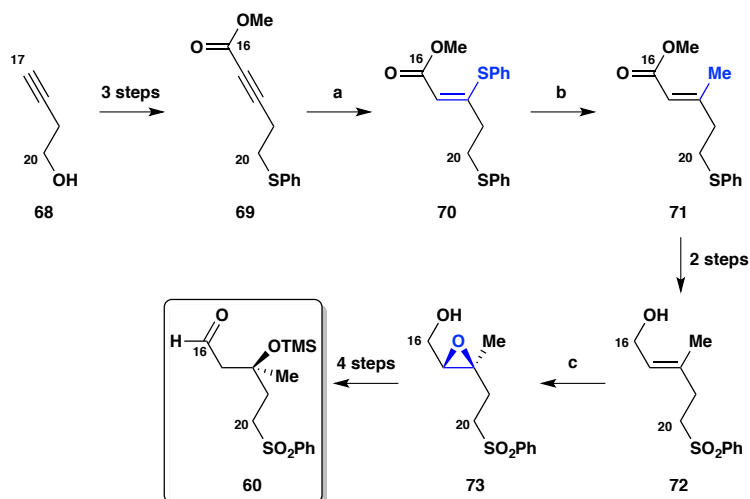
The forward synthesis of the C8–C15 phosphate **61** began with L-malic acid **62**, which was converted to Weinreb amide **63** in 5 steps (**Scheme 15**). Lithium halogen exchange was performed on bromoalkene **74** with *t*BuLi, and the resulting alkenyllithium was reacted with Weinreb amide **63** to form a ketone, and subsequently reduced by $\text{Zn}(\text{BH}_4)_2$ under chelation control to afford the C11 allylic alcohol **65** in 82% yield (single diastereoisomer isolated). Following the formation of epoxide **66** over 3 steps, a regioselective epoxide ring opening was achieved with LiAlH_4 at $-15\text{ }^\circ\text{C}$ to produce the diol **67** quantitatively. Diol **67** was then converted to the phosphate **61** in 5 steps.



Scheme 15. Fujiwara's synthesis of the C8–C15 phosphate **67**

Reagents and conditions: (a) **64**, *t*BuLi, THF, $-78\text{ }^{\circ}\text{C}$, then, **63**, 87%; (b) $\text{Zn}(\text{BH}_4)_2$, Et_2O , $-78\text{ }^{\circ}\text{C}$ to $-30\text{ }^{\circ}\text{C}$, 94% **65**, 16:1 d.r.; (c) LiAlH_4 , THF, $-15\text{ }^{\circ}\text{C}$, 100%.

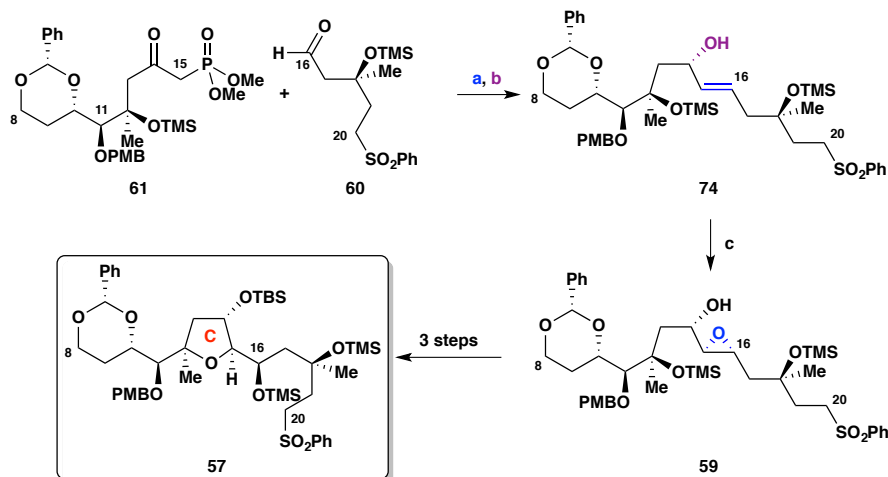
The synthesis of the C16–C20 fragment started with 3-butyn-1-ol **68**, which was converted to ynoate **69** in 3 steps (**Scheme 16**). The C18 methyl group was installed *via* the Kobayashi–Mukaiyama procedure.⁶⁸ Thiophenol first added to **70** with the *Z*-isomer as the major product (89% isolated yield), which was subsequently reacted with MeMgBr in the presence of CuI to afford enoate **71** in 98% yield. Enoate **71** was turned to the C16 allylic alcohol **72** in 2 steps, and the C14–C15 epoxide **73** was formed diastereoselectively *via* a Sharpless asymmetric epoxidation using (+)-DET in 72% isolated yield of the desired isomer. Epoxide **73** was further elaborated to the C16 aldehyde **60** in 4 steps.



Scheme 16. Fujiwara's synthesis of the C16–C20 aldehyde **60**

Reagents and conditions: (a) PhSH, PhSNa, MeOH, 23 °C, Z:E (8:1), 89% Z-isomer isolated; (b) MeMgBr, CuI, THF, –78 °C, 98%; (c) (+)-DET, Ti(OiPr)₄, TBHP, –15 °C, 72%.

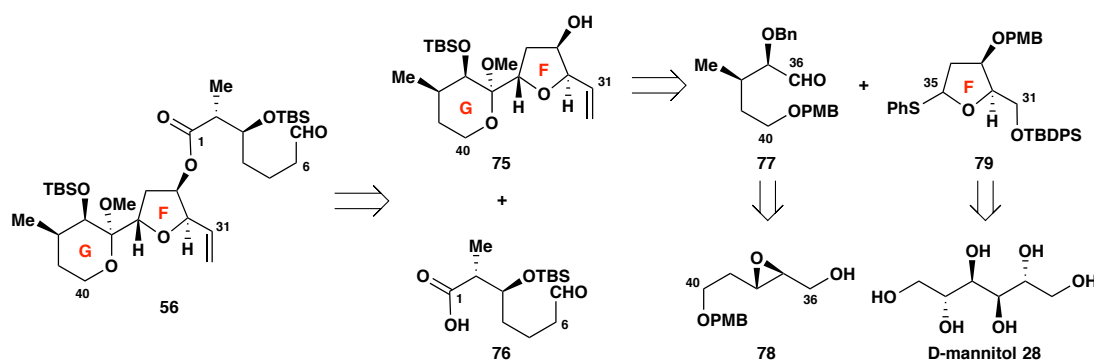
The completion of the C8–C20 fragment commenced with a HWE reaction between phosphate **61** and aldehyde **60** to afford 91% *E*-isomer, which was subsequently reacted with DIBAL-H at –104 °C to afford allylic alcohol **74** as an inseparable mixture of 9.4:1 epimers at C14 (**Scheme 17**). *m*CPBA epoxidation of allylic alcohol **74** in the presence of NaHCO₃ afforded the C15–C16 epoxide **59** in 3.7:1 d.r. and an isolated yield of 68% (single diastereoisomer). Epoxide **59** was converted to the C8–C20 fragment **57** in 3 steps.



Scheme 17. Fujiwara's completion of the C8–C20 sulfone **57**

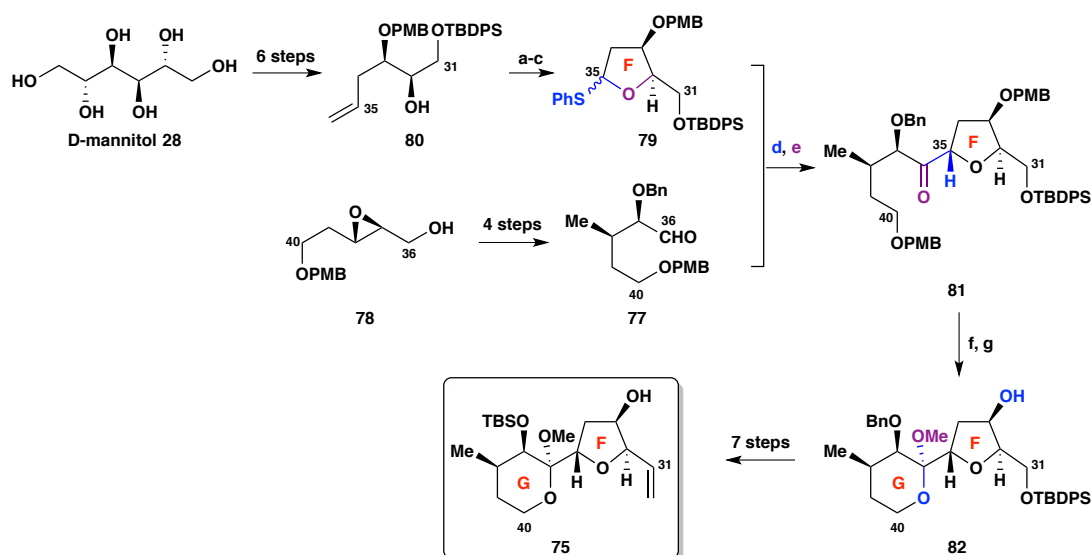
Reagents and conditions: (a) NaH, PhH/THF (1:3), 0 °C, 91%; (b) DIBAL-H, CH₂Cl₂, –104 °C, 99%, 9.4:1 d.r.; (c) *m*CPBA, NaHCO₃, CH₂Cl₂, 0 °C, 68%.

The left fragment **56** of PTX-2 was disconnected to the FG ring fragment **75** and the C1–C7 acid **76** *via* an esterification approach (**Scheme 18**). The FG fragment **75** was further dissembled to aldehyde **77** and F ring fragment **79**.⁶⁷ Aldehyde **77** was derived from known epoxide **78**, and F ring fragment **79** would be prepared from D-mannitol **28**.⁶⁹



Scheme 18. Fujiwara's retrosynthetic analysis of ester **56**

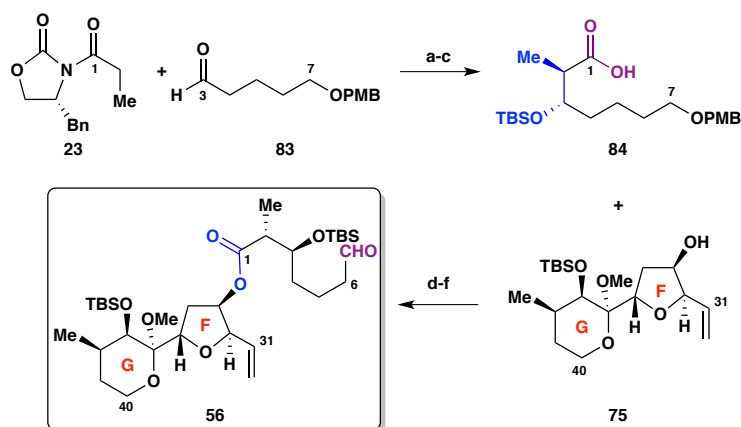
The synthesis of the C31–C40 fragment **75** commenced with D-mannitol **28**, which was converted to the cyclisation precursor **80** in 6 steps (**Scheme 19**).⁷⁰ Dihydroxylation and oxidative cleavage of the double bond afforded a hemiacetal, which was trapped with Ac₂O. The acetate was further treated with thiophenol to give α -thiophenyltetrahydrofuran **79** as a mixture of anomers at C35 in 80% yield over 3 steps. Treatment of **79** with LiDBB generated an organolithium intermediate at C35, which reacted with aldehyde **77**, derived from known epoxide **78** in 4 steps, to afford a mixture of diastereoisomers at C35 and C36 in 71% yield.⁶⁹ The reaction was selective for the *trans*-THF ring because the C32 substituent preferentially formed a 2,5-*trans*-relationship with the C36 substituent, driving by steric hindrance.⁶⁷ Swern oxidation of the C36-*OH* group gave ketone **81** in 98% yield with a 4.2:1 d.r. at C35. After cleavage of both PMB groups with DDQ, the C40-*OH* group attacked the C36 ketone to afford a hemiacetal, which was trapped with trimethyl orthoformate to afford cyclic methyl acetal **82** in a good yield of 83%. Acetal **82** was elaborated to alkene **75** in 7 steps to adjust the protecting groups and install the C31–C32 alkene in preparation of a later metathesis reaction.



Scheme 19. Fujiwara's synthesis of the C31–C40 FG ring fragment **82**

Reagents and conditions: (a) OsO_4 , NMO, 1,4-dioxane/ H_2O (3:1), rt, 19 h, then NaIO_4 , rt, 12 h, 94%; (b) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , rt, 1.5 h, 98%; (c) PhSH , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -40°C , 15 min, 87%; (d) LiDBB (2 eq), THF, -95°C , 1 min, then **77** (1.8 eq), -78°C , 40 min, 71%; (e) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , 10 min, then Et_3N , -78°C to 0°C , 20 min, 98%, 4.2:1 d.r. at C35; (f) DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10:1), 0°C , 1 h, 70%; (g) CSA, $\text{MeOH}/(\text{MeO})_3\text{CH}$ (1:1), 21°C , 2 h, 83%.

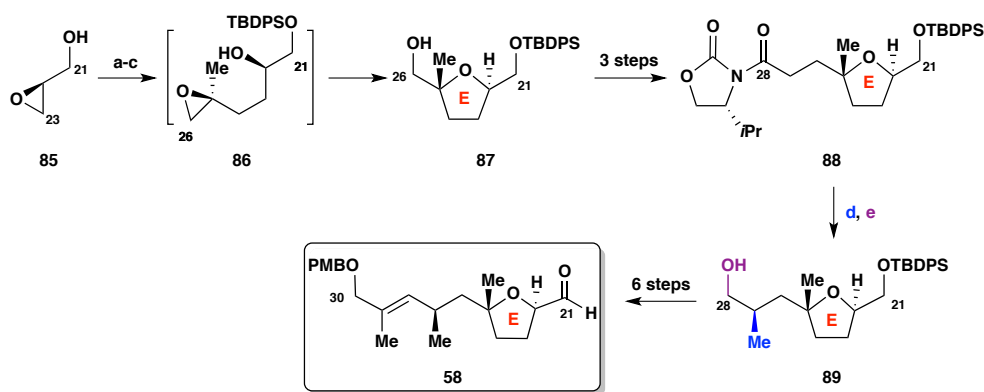
The C1–C7 fragment **84** was prepared from an Evans *syn*-aldol product from aldehyde **83**, which was derived from pentane-1,5-diol, and oxazolidione **23** (**Scheme 20**). Treatment of the aldol product with TBSOTf followed by oxazolidine cleavage with LiOOH (generated *in situ* from LiOH and H_2O_2) gave the C1 acid **84** in 92% yield over 2 steps. The acid was coupled with the FG fragment **75** in the presence of DCC and DMAP to form the C1–C33 ester in 82% yield. Deprotection of the PMB group with DDQ (82%) and subsequently Swern oxidation (52%) furnished the C7 aldehyde **56** for further elaboration.



Scheme 20. Fujiwara's completion of the left-hand half fragment **56** of PTX-2

Reagents and conditions: (a) **23** (2 eq), $n\text{Bu}_2\text{BOTf}$, Et_3N , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 1 h, then **83** (1 equiv), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 4 h, 100%; (b) TBSOTf, 2,6-lutidine, $0\text{ }^\circ\text{C}$, 1 h, 98%; (c) LiOH, H_2O_2 , THF/ H_2O , $24\text{ }^\circ\text{C}$, 4 h, 94%; (d) **75** (0.25 equiv), DCC, DMAP, CH_2Cl_2 , $23\text{ }^\circ\text{C}$, 2 h, 82%; (e) DDQ, $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10:1), $0\text{ }^\circ\text{C}$, 50 min, 82%; (f) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 10 min, then Et_3N , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 20 min, 52%.

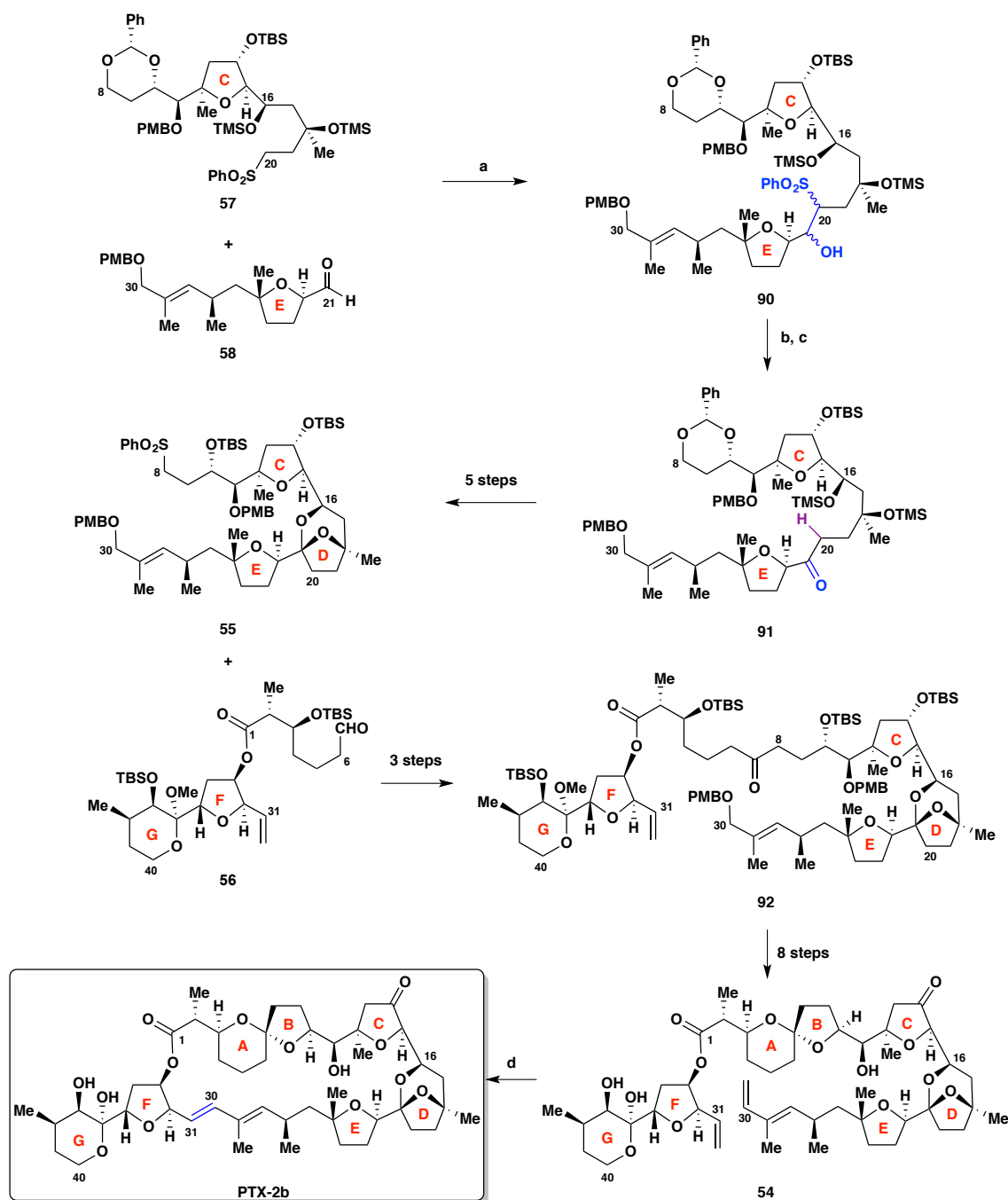
The synthesis of the C21–C30 E ring fragment **58** started with (*S*)-glycidol **85** (Scheme 21). Following a TBDPS protection of the C21-*OH* group, the epoxide was opened with Grignard reagent formed from 3-chloro-2-methylpropene, giving an alcohol in quantitative yield. $\text{VO}(\text{acac})_2$ catalysed epoxidation of the C25–C26 alkene followed by treatment with CSA afforded *trans*-THF E ring fragment **87** in 57% yield. Compound **87** was elaborated to oxazolidinone **88** in 3 steps. Stereoselective methylation that directed by Evans' oxazolidinone afforded the C27-*Me* group in 93% yield. Subsequent cleavage of the C28 oxazolidinone with NaBH_4 gave alcohol **89** in quantitative yield. Alcohol **89** was further converted to the C21–C30 aldehyde **58** in 6 steps.



Scheme 21. Fujiwara's synthesis of the C21–C30 fragment of PTX-2 **58**

Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 25 °C, 1 h, 100%; (b) 3-chloro-2-methylpropene, Mg, THF, 24 °C, 1 h, *then* epoxide, –40 °C, 5 h, 100%; (c) VO(acac)₂, TBHP, benzene, 55 °C, 21 h, *then* CSA, 21 °C, 2 h, 57% **87**, 18% 25-*epi*-**87**, 11% rsm; (d) NaHMDS, THF, –78 °C, 1 h, *then* MeI, –78 °C, 4 h, 93%; (e) NaBH₄, THF/H₂O (3:1), 23 °C, 22 h, 100%.

The fragment assembly of PTX-2 commenced with the connection between sulfone **57** and aldehyde **58** to form the D ring (**Scheme 22**). Sulfone **57** was treated with *n*BuLi, and the subsequent reaction with aldehyde **58** afforded α -hydroxylsulfone **90** in 69% yield. Compound **90** was obtained as a mixture of 4 diastereoisomers at C20 and C21. The C20-OH group was oxidised with Dess–Martin periodinane, and the C21 sulfone group was removed with SmI₂ to generate the C21 ketone **91** in 49% over 2 steps. After selective cleavage of the C16 and C18-OTMS groups, the bicyclic D ring was formed spontaneously under acidic conditions as a single isomer. The anomeric 6,5-spiroketal system was subsequently formed using the same strategy outlined above to give macrolide precursor **92** over 8 steps. Macrolide precursor **92** was converted to alkene **54** in another 8 steps, which was then treated with 10 mol% Grubbs 2nd generation catalyst at 40 °C to afford PTX-2b in 64% yield without isomerisation of the sensitive spiroketal moiety.

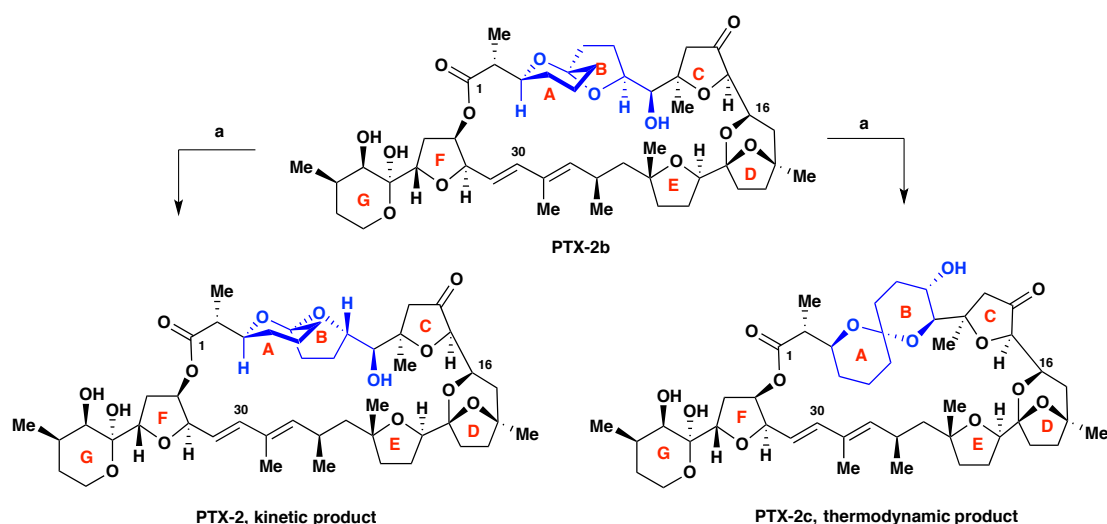


Scheme 22. Fujiwara's fragments assembly and completion of PTX-2b

Reagents and conditions: (a) **57**, *n*BuLi, $-78\text{ }^{\circ}\text{C}$, then **58**, $-78\text{ }^{\circ}\text{C}$, 67%; (b) DMP, NaHCO_3 , CH_2Cl_2 , rt, 79%; (c) SmI_2 , MeOH/THF (1:1), $0\text{ }^{\circ}\text{C}$, 62%; (d) Grubb's 2nd generation catalyst, CH_2Cl_2 (0.5 mM), $40\text{ }^{\circ}\text{C}$, 64%.

PTX-2b was treated with 0.1% (v/v) TFA in 7:3 MeCN/ H_2O (**Scheme 23**). The formation of kinetic product PTX-2 reached a maximum after 1.5 h, with an isolated yield of 50%. A

thermodynamic equilibrium was finally established after 96 h, with a 28:7:65 ratio of PTX-2/PTX-2b/PTX-2c. The isolated yield for PTX-2c was 46%. Fujiwara and co-workers also tested the cytotoxicity of synthetic PTXs on hepatocellular carcinoma cells (HepG2) and human colonic carcinoma cells (Caco2) and the results are summarised in **Table 3**. PTX-2 was significantly more potent than PTX-2b and PTX-2c against the two cancer cell lines. It supported that the non-anomeric 6,5-spiroketal structure was critical for the potent biological activities of PTXs, which is consistent with that observed in binding studies (see **Section 1.4**, **Figure 5**).²⁶



Scheme 23. Fujiwara's acidic equilibration to PTX-2 and PTX-2c

Reagents and conditions: (a) TFA (0.1% v/v), MeCN/H₂O (7:3), 1.5 h, 50% PTX-2, 96 h, 46% PTX-2c.

Table 3. Biological activity of the synthetic PTXs³¹

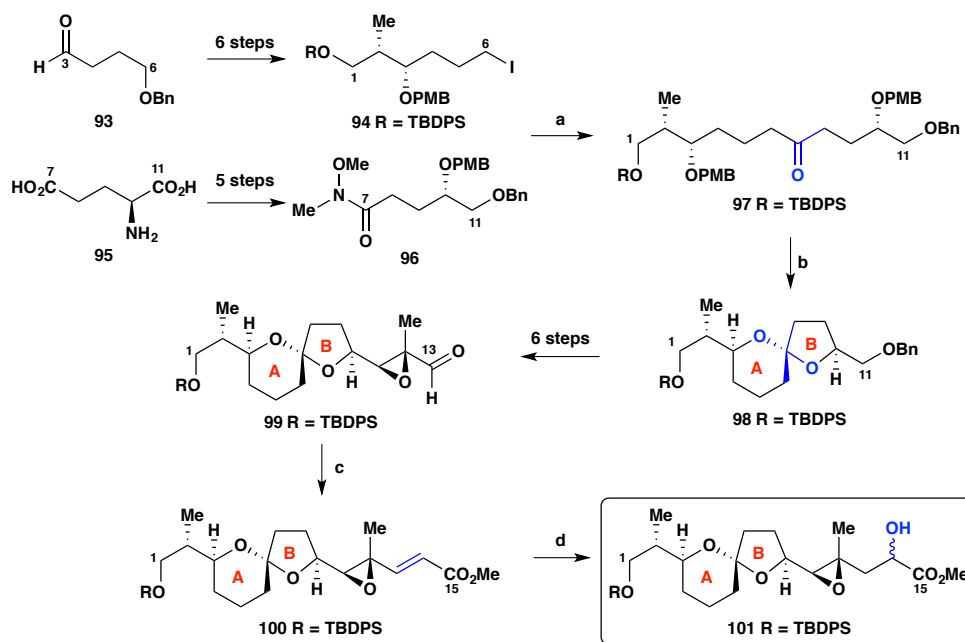
PTX	IC ₅₀ (HepG2, nmol/L)	IC ₅₀ (Caco2, nmol/L)
2	3.6	2.6
2b	1.5×10^3	3.8×10^3
2c	0.56×10^3	3.6×10^3

1.5.3 Paquette's synthesis of the C1–C26 fragment of PTX-2

In 2005, Paquette and co-workers reported a synthesis of the C1–C15 fragment of PTX-2, and later in 2007, they expanded the synthesis to the C1–C26 fragment with a revised protecting group strategy.⁴⁰⁻⁴³

The forward synthesis began with aldehyde **93** (prepared from butan-1,4-diol in 2 steps) and *L*-glutamic acid **95** (Scheme 24). Aldehyde **93** was converted to iodide **94** in 6 steps, and acid **95** was turned to Weinreb amide **96** in 5 steps. Lithiation of iodide **94** with *t*BuLi followed by addition of Weinreb amide **96** afforded ketone **97** in 72% yield. Cleavage of the C3- and C10-*PMB* groups of ketone **97** with DDQ in moist CH₂Cl₂ initiated a spontaneous spiroketalisation to afford the anomeric 6,5-spiroketal **98** in an excellent yield of 92%. The C1–C11 spiroketal unit was converted to aldehyde **99** in 6 steps. It was expected the C ring would be formed in an epoxide opening process. Wittig reaction of aldehyde **99** with methyl-(triphenylphosphoranylidene)acetate afforded the C13–C14 *trans* double alkene **100** in 86%

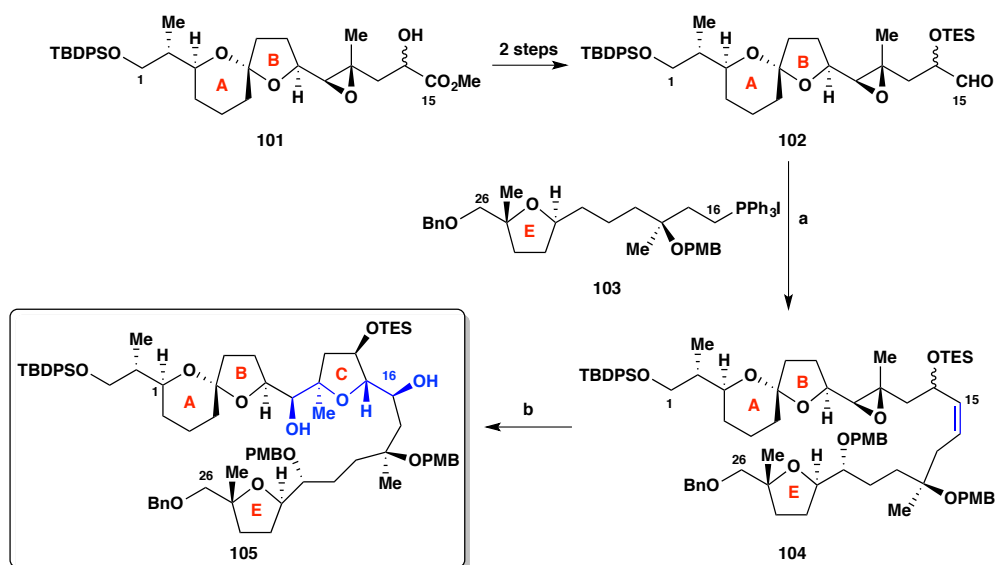
yield. Oxidation of double bond in the presence of *tris*(dipivaloylmethanato)manganese(III) ($\text{Mn}(\text{dpm})_3$) complex gave the C14-OH group in 76% yield (Compound **101**).⁷¹



Scheme 24. Paquette's synthesis of the C1–C15 spiroketal fragment **101** of PTX-2

Reagents and conditions: (a) **94**, $t\text{BuLi}$, Et_2O , then **96**, 72%; (b) DDQ, CH_2Cl_2 , pH 7 Buffer, 92%; (c) $\text{Ph}_3\text{P}=\text{CMeCOOMe}$, CH_2Cl_2 , 86%; (d) PhSiH_3 , O_2 , $\text{Mn}(\text{dpm})_3$, $\text{ClCH}_2\text{CH}_2\text{Cl}$, $i\text{PrOH}$, 76%.

The C1-C15 spiroketal fragment **101** was converted to aldehyde **102** in two steps (**Scheme 25**). Wittig reaction between aldehyde **102** and *in situ* formed ylide from phosphonium salt **103** afforded Z-alkene **104** in 40% yield. The low yield was ascribed to the instability of the spiroketal epoxide under the reaction conditions. Dihydroxylation of alkene **104** in the presence of a stoichiometric amount of OsO_4 followed by a spontaneous cyclisation generated the C ring in 37%. Unfortunately, the absolute stereochemistry at C15 was opposite to that in the natural products. It was expected that the stereocenter could be epimerised after formation the C14 ketone.

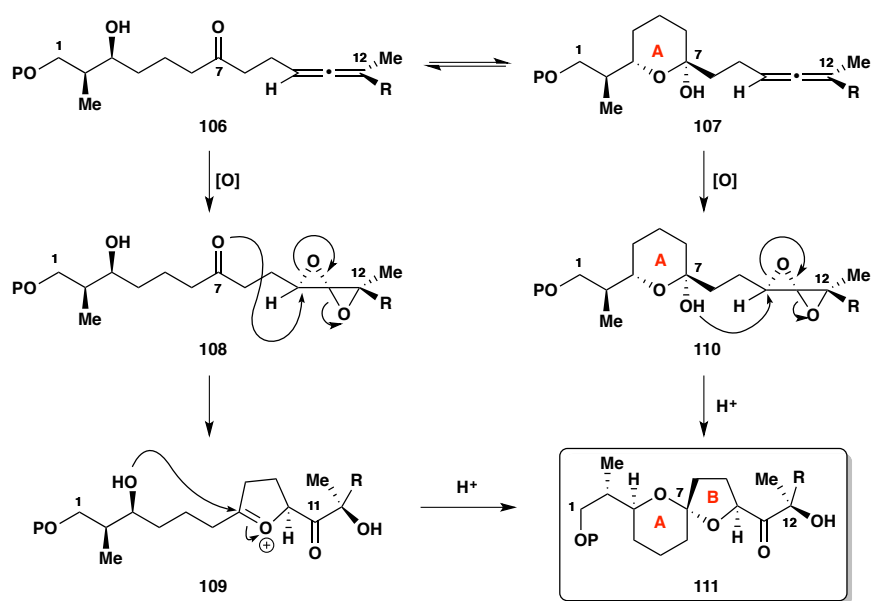


Scheme 25. Paquette's assembly of the C1–C26 fragment **105** of PTX-2

Reagents and conditions: (a) **103** (1.05 eq), KHMDS, then **102** (1 eq), $-78\text{ }^{\circ}\text{C}$, 40%; (b) OsO_4 (2 eq), NMO, acetone/water, rt, 37%.

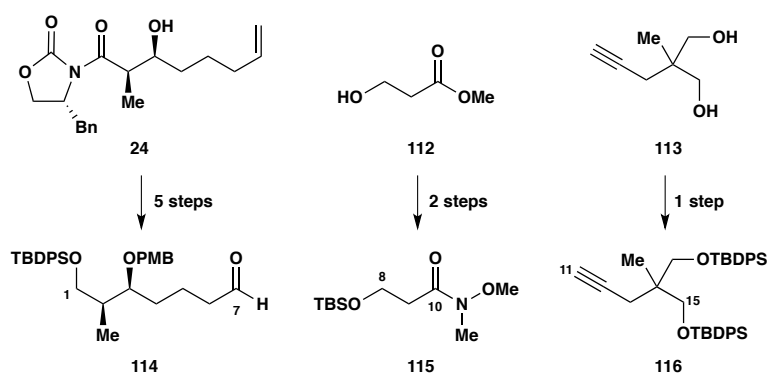
1.5.4 Williams's spirodiepoxide strategy to the C1–C19 fragment of PTX-4

In 2007, Williams and co-workers reported a synthesis of the AB spiroketal of PTX-4.^{55, 72} The synthesis was expanded to the C1–C19 precursor of PTX-4 in 2010.⁵⁷ The key strategy involved in Williams' synthesis was the diastereoselective formation of a spirodiepoxide moiety **108** from allene **106**, which was expected to cyclise to the anomeric 6,5-spiroketal in PTX-4 under acidic conditions (**Scheme 26**).



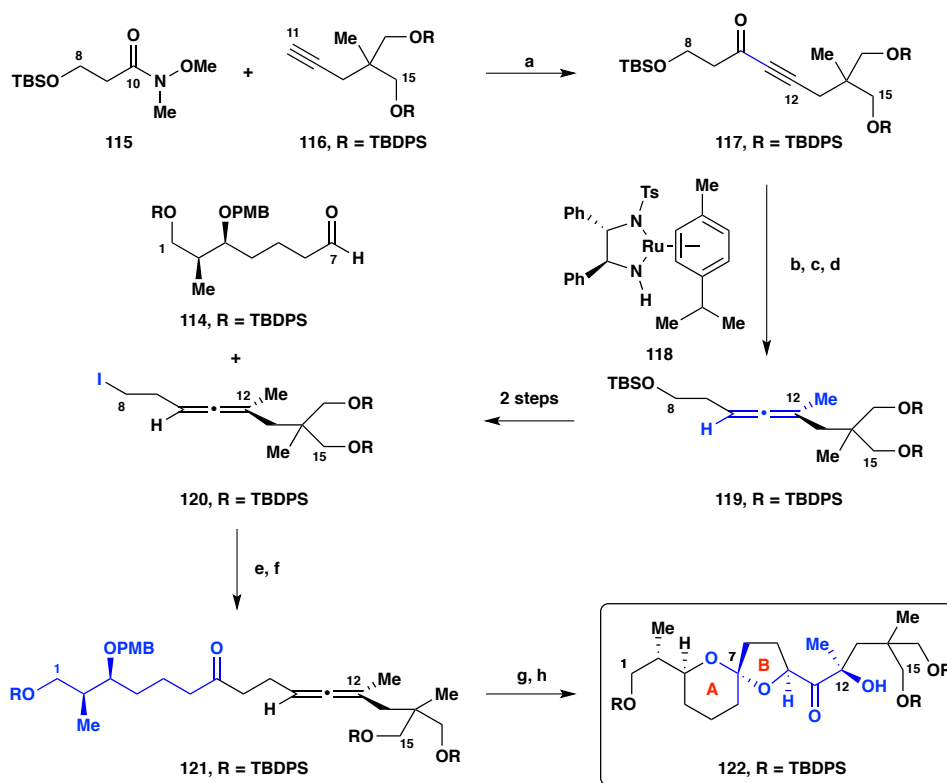
Scheme 26. Williams' proposed spirodiepoxide strategy for AB spiroketal rings

To synthesis the key allene precursor **106**, Williams group prepared the C1–C7 aldehyde **114**, the C8–C10 Weinreb amide **115** and the C11–C15 alkyne **116** from known aldol product **24**, commercially available β -hydroxylester **112** and known alkyne **113** respectively (**Scheme 27**).⁷³



Scheme 27. Williams' fragments for the C1–C15 spiroketal unit of PTX-4

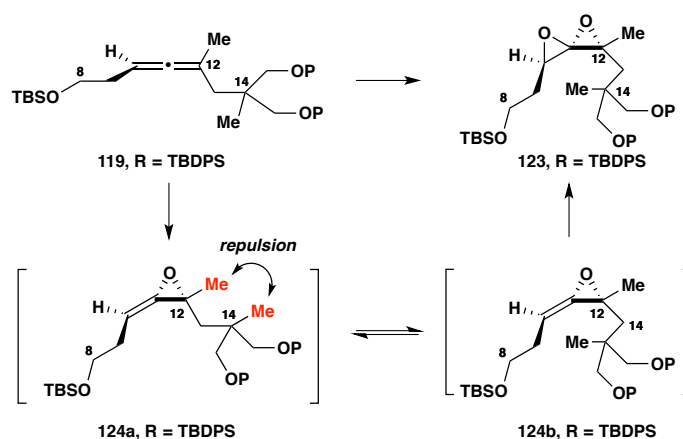
Williams' assembly of the C1–C15 spiroketal fragment **122** started with the coupling of Weinreb amide **115** and alkyne **116** (Scheme 28). Treatment of alkyne **116** with *n*BuLi generated a lithium acetylide, reacting with Weinreb amide **115** to give propargylic ketone **117** in 90% yield. The C10 ketone was reduced diastereoselectively in the presence of Noyori's catalyst **118** in 99% yield and 98:2 d.r.. The propargylic alcohol was converted to a mesylate, and subsequent reaction with MeLi in the presence of CuCN afforded allene **119** in an excellent yield of 96% over two steps. The C8-OTBS group in allene **119** was converted to iodide in 2 steps. Iodide **120** underwent lithium–halogen exchange in the presence of *t*BuLi and coupled with the C1–C7 aldehyde **114** in 55% yield. A subsequent Dess–Martin oxidation gave the spirodiepoxide precursor **121** in 85% yield. Treatment of **121** with DMDO furnished the desired spirodiepoxide, which cyclised to the AB spiroketal **122** under acidic conditions in 72% yield over 2 steps.



Scheme 28. Williams' synthesis of the C1-C15 spiroketal fragment **122** of PTX-4

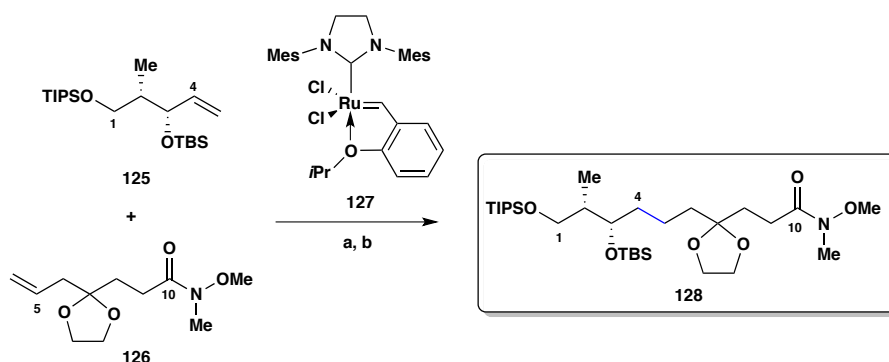
Reagents and conditions: (a) **116**, *n*BuLi, THF, then **115**, $-20\text{ }^{\circ}\text{C}$, 90%; (b) **118**, *i*PrOH, rt, 99%, 98:2 d.r.; (c) MsCl, Et_3N , CH_2Cl_2 , rt; (d) MeLi, CuCN, Et_2O , $-78\text{ }^{\circ}\text{C}$ to rt, 96% over two steps; (e) **120**, *t*BuLi, Et_2O , $-78\text{ }^{\circ}\text{C}$, then **114**, $-78\text{ }^{\circ}\text{C}$ to rt, 55%; (f) DMP, Py, CH_2Cl_2 , 85%; (g) DMDO, CHCl_3 , MeOH, $-40\text{ }^{\circ}\text{C}$ to rt; (h) TsOH (25 mol %), 72% over two steps.

Williams illustrated the diastereoselectivity in spirodiepoxide formation in **Scheme 29**.⁵⁵ The first epoxidation event took place at the electron-rich more substituted double bond of allene **119**. The alkyl chain with bulky TBS group blocked the front face, rendering high selectivity of epoxide formation from the back (20:1 d.r.). In the second epoxidation event, the more electron-rich of allene oxide with increased reactivity compared to allene **119** led to a less selective reaction (5:1 d.r.). The C12-Me group and the C14-Me group preferred to minimise the 1,3-interaction, so the bottom face of double bond was blocked by the *neo*-pentyl substituents.



Scheme 29. Diastereoselectivities in epoxidations of allene **119**

Williams and co-workers expanded the spirodiepoxide strategy to the C1–C19 precursor of PTX-4. A revised metathesis approach was used to prepare the Weinreb amide **128** (**Scheme 30**). Treatment of alkenes **125** and **126** (2:1) with Hoveyda-Grubbs 2nd generation catalyst **127** in refluxing CH_2Cl_2 afforded an alkene in 85% yield after 7 days.[†] The alkene was hydrogenated in the presence of Pd/C to give the C1–C10 Weinreb amide **128** in 97% yield.

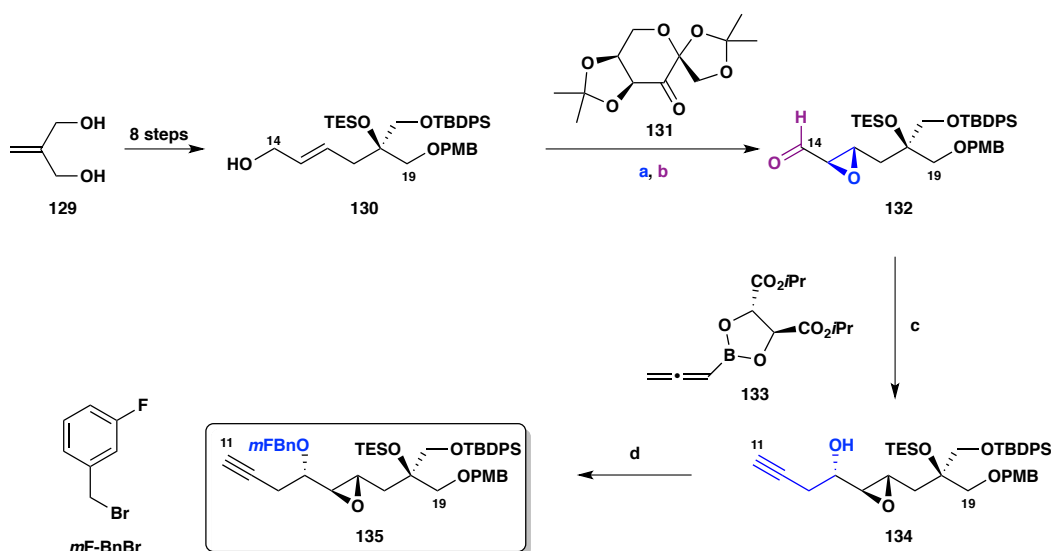


Scheme 30. Williams' synthesis of the C1–C10 Weinreb amide **128**

Reagents and conditions: (a) CH_2Cl_2 , reflux, 7 days, 85%; (b) H_2 , Pd/C, MeOH, rt, 12 h, 97%.

[†] An extra amount of Grubbs catalyst (~0.6 mol%) was added every 24 hours.

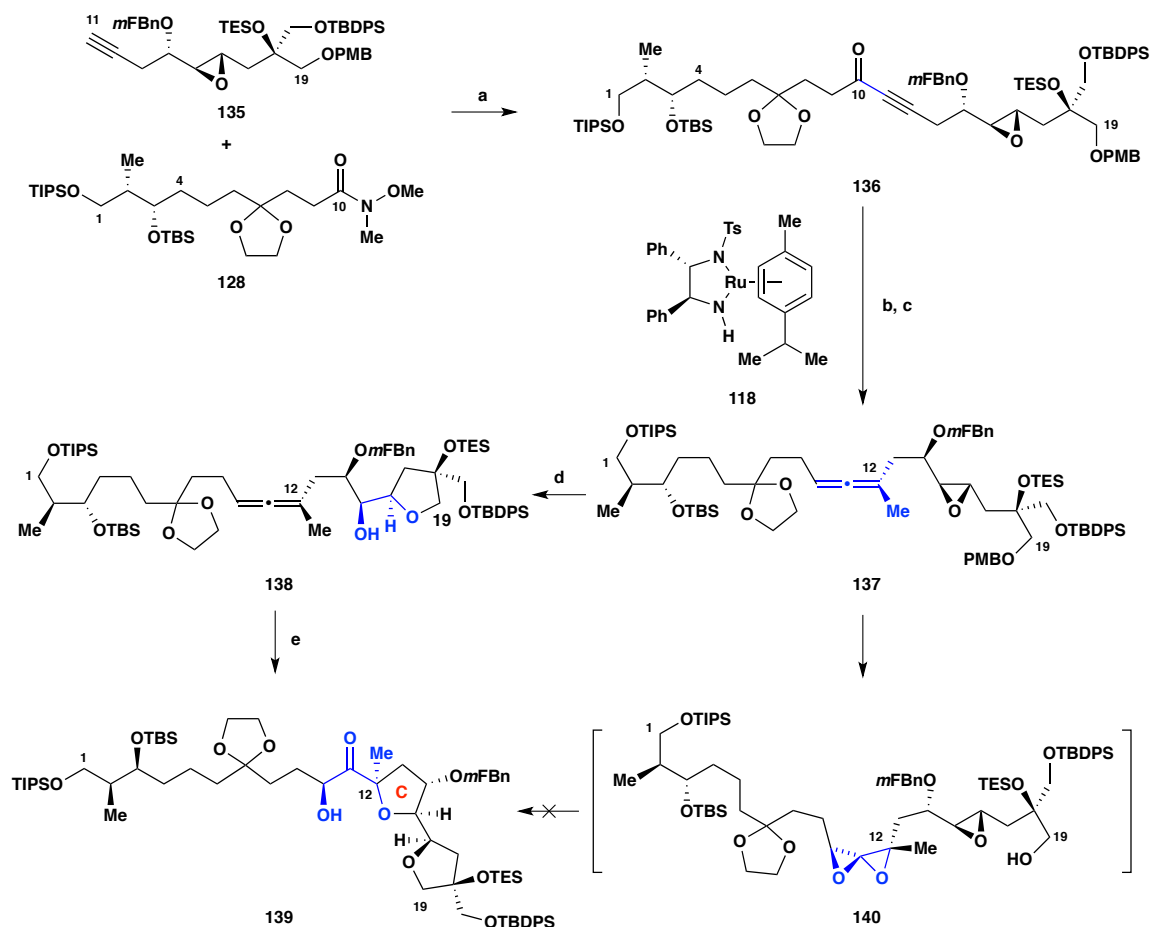
The synthesis of the C11–C19 fragment **135** began with commercially available 2-methylene-1,3-propanediol **129** (Scheme 31). Diol **129** was orthogonally protected as allylic alcohol **130** in 8 steps. Allylic alcohol **130** was epoxidised *via* Shi's protocol in a moderate yield of 60%. Sharpless asymmetric epoxidation was not suitable for this process, as it accompanied by undesired PMB cleavage and subsequent epoxide opening, as well as formation of the diastereometric epoxide.⁵⁷ After Dess–Martin oxidation of the C14-*OH* group to afford aldehyde **132**, Yamamoto propargylation of aldehyde **132** with boronic ester **133** afforded propargylic alcohol **134** in 80% yield with >20:1 d.r..⁷⁴ The C14-*OH* group was protected with a 3-fluorobenzyl bromide (*m*F-Bn) instead of a PMB group because the later was observed to be labile in a subsequent epoxidation of the C10–C12 allene unit with DMDO (*vide infra*).



Scheme 31. Williams' synthesis of the C11–C19 fragment of PTX-4

Reagents and conditions: (a) **131**, Oxone, K₂CO₃, −5 °C, 2 h, 60%; (b) DMP, CH₂Cl₂, rt, 12 h, 80 %; (c) **133**, PhMe, 4 Å MS, −78 °C, 12 h, then −20 °C, 12 h; (d) *m*F-BnBr, KOH, *n*BuNH₄SO₄, PhH, rt, 12 h, 82 %.

The completion of the C1–C19 precursor **139** started from the coupling of lithium acetylide of alkyne **135** and Weinreb amide **128** in a moderate yield of 55% (**Scheme 32**). The low yield shown was due to the partial cleavage of the *m*F-Bn group under these conditions, as control experiments using a TBS group instead of the *m*F-Bn group gave an excellent yield of 95%. Propargylic ketone **136** was converted to allene **137** via a Noyori asymmetric hydrogenation–allene formation process catalysed by Ru-complex **118** discussed earlier (**Scheme 28**) in 73% yield. Direct treatment of allene **137** with DMDO did not afford the desired product **139**, as the C14–C15 epoxide would open the spirodiepoxide to give undesired side products. Fortunately, a two-step process circumvented this problem. Cleavage of PMB in allene **137** with DDQ triggered a spontaneous epoxide opening to furnish alkene **138** in 65% yield. DMDO epoxidation of **138** smoothly generated the C1–C19 spiroketal precursor **139** in 54% yield as a single diastereoisomer without epimerisation at C10.



Scheme 32. Williams' completion of the C1–C19 precursor of PTX-4

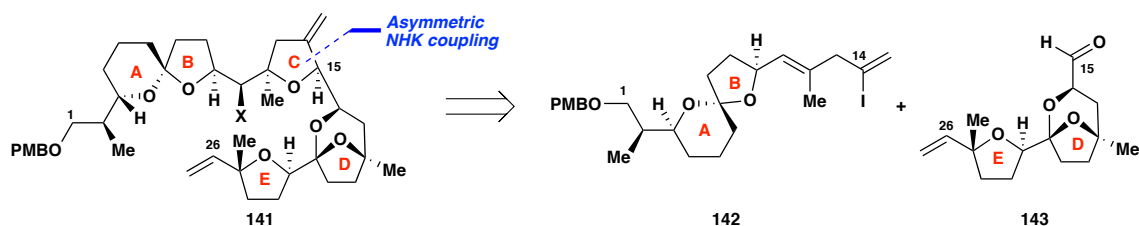
Reagents and conditions: (a) LiHMDS, THF, 0 °C, 0.5 h, then **136**, 1 h, 55%; (b) **118**, *i*PrOH, rt, 1 h, 86%, >20:1 d.r.; (c) MsCl, Et₃N, CH₂Cl₂, 0 °C, 1 h, then MeLi, CuCN, Et₂O, –78 °C, 0.7 h, 85%; (d) DDQ, CH₂Cl₂/H₂O (5:1), rt, 12 h, 65%; (e) DMDO, CHCl₃, –40 °C to rt, 2 h, 54%, >10:1 d.r..

Williams' spirodiepoxide strategy provided a unique way to construct the AB spiroketal ring structure. However, it was noted that the C11 *neo*-pentyl position was a ketone rather than the desired chiral hydroxyl group. Considering the highly hindered sterical environment of this position, it would likely be challenging to carry out an asymmetric reduction of this ketone.

1.5.5 Micalizio's NHK coupling approach to the C1–C26 fragment of PTX-2

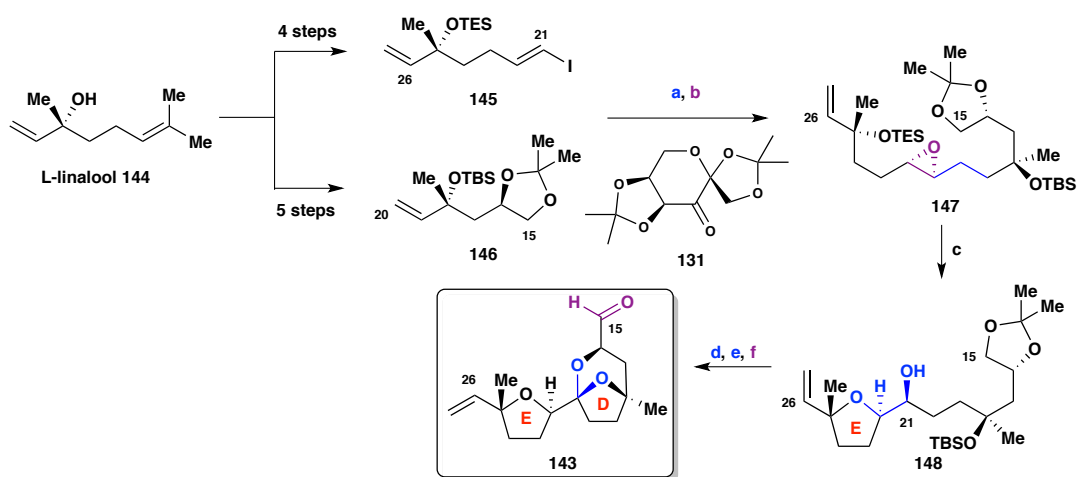
The disconnection approaches of PTXs discussed before often took a key disconnection on the bicyclic D ring, which brought about two problems. Firstly, the synthesis of the ABC tricyclic fragment was tedious compared to other fragments of the molecule. Secondly, the construction of the bicyclic D ring was completed at a late stage of the synthesis. It was challenging to mimic the steric and chemical environment around the D ring in model studies. Both Evans and Fujiwara's total syntheses involved several moderate yielding steps in D ring formation, which significantly increased the efforts required at the back end (See section 1.5.1 and 1.5.2).

Conversely, a strategy that disconnects the C ring to divide the ABCDE ring fragment to two fragments of similar complexity would be highly attractive. In 2012, Micalizio reported a synthesis of the C1–C26 fragment **141** of PTX-2 utilising the strategy discussed above. The disconnection was made at the C14–C15 bond on the C ring to separate fragment **141** into two segments, vinyl iodide **142** and aldehyde **143** (Scheme 33).³⁷⁻³⁹ It was proposed the two segments could be coupled using an asymmetric Nizaki–Hiyama–Kishi (NHK) reaction without affecting the sensitive AB spiroketal ring and the bicyclic D ring.



Scheme 33. Micalizio's retrosynthetic analysis of the C1–C26 fragment **141** of PTX-2

The synthesis of the C15–C26 fragment **143** was depicted in **Scheme 34**. The two fragments, vinyl iodide **145** and alkene **146**, were both prepared from the abundant natural product L-linalool. Treatment of alkene **146** with 9-BBN afforded a hydroboration product, which coupled with vinyl iodide **145** in a Suzuki reaction to generate the C15–C26 carbon skeleton. A subsequent Shi epoxidation with fructose derivative **138** provided epoxide **147** in 59% yield (80% brsm) with >20:1 d.r.. Selective desilylation of epoxide **147** with TBAF cleaved the less stable TES group in the presence of a TBS group, and a subsequent acid promoted epoxide opening afforded the E ring in a good yield of 86%. The C21-*OH* group in aldol **148** was oxidised to a ketone through a Parikh–Doering reaction in 77% yield, which was subsequently treated with CSA to remove the C18-*OTBS* group and the C15–C16 acetonide group. The product spontaneously cyclised to form the D ring in 59% yield. A Swern oxidation converted the C15-*OH* group to an aldehyde in preparation for the NHK coupling.



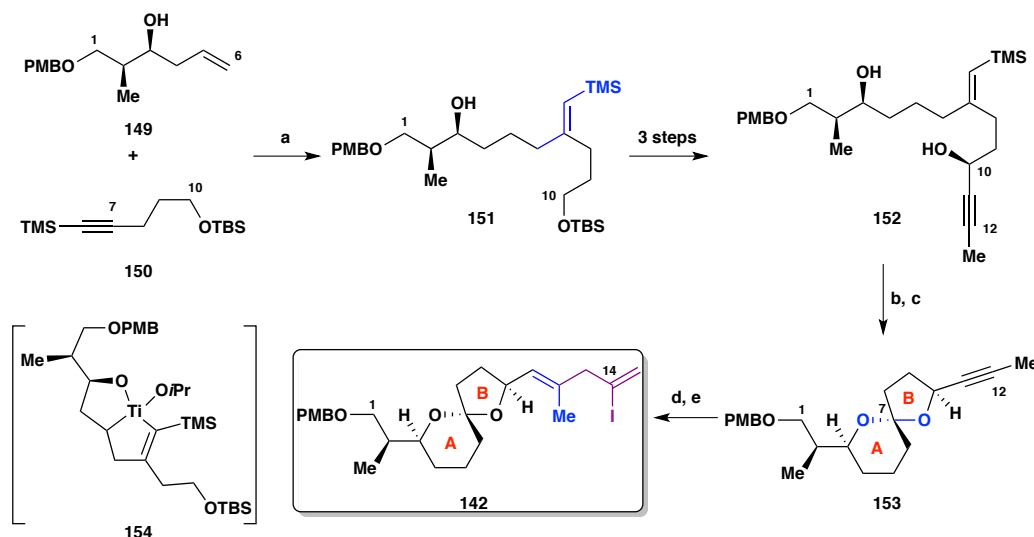
Scheme 34. Micalizio's synthesis of the C15–C26 aldehyde **143** of PTX-2

Reagents and Conditions: (a) **146**, 9-BBN, THF, then **145**, Pd(dppf)Cl₂, Ti₂CO₃, THF/H₂O, 81%; (b) **138**, Oxone, MeCN, EtOH, CH₂Cl₂, 59% (80% brsm), >20:1 d.r.; (c) TBAF (1.1 eq), THF, 3 Å MS, then HCl, CHCl₃, 86%; (d) SO₃•Py, DMSO, *i*Pr₂NEt, CH₂Cl₂, 77%; (e) CSA, MeOH, 59%; (f) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 66%.

The synthesis of the C1–C14 vinyl iodide **142** started with a reductive cross coupling of alkene **149** and alkyne **150** (Scheme 35).^{75–77} The diastereoselectivity of this titanium-catalysed coupling was directed by the hydroxyl group, affording alkene **151** in 77% yield *via* a bicyclic intermediate **154**. The regioselectivity of this reaction was controlled by the relative size of the substituents on the alkyne. Compound **151** was converted to propargylic alcohol **152** in 3 steps. Treatment of **152** with HCl cleaved the TMS group, and the resultant alkene was subjected to ozonolysis to afford the C7 ketone, which readily cyclised to the AB spiroketal **153** in the presence of TsOH (84% yield over 2 steps).[‡] A regioselective hydrozirconation–iodonation (Cp₂ZrCl₂, DIBAL-H, then I₂) and subsequent

[‡] Not surprisingly, the anomeric 6,5-spiroketal was formed. It was expected to isomerise to the non-anomeric 6,5-spiroketal under acidic conditions after macrocyclisation.

coupling with 2-iodoallylbromide ($n\text{BuLi}$, $i\text{PrMgBr}$, $\text{CuCN}\cdot\text{LiCl}$) afforded vinyl iodide **142** in 43% yield over 2 steps.

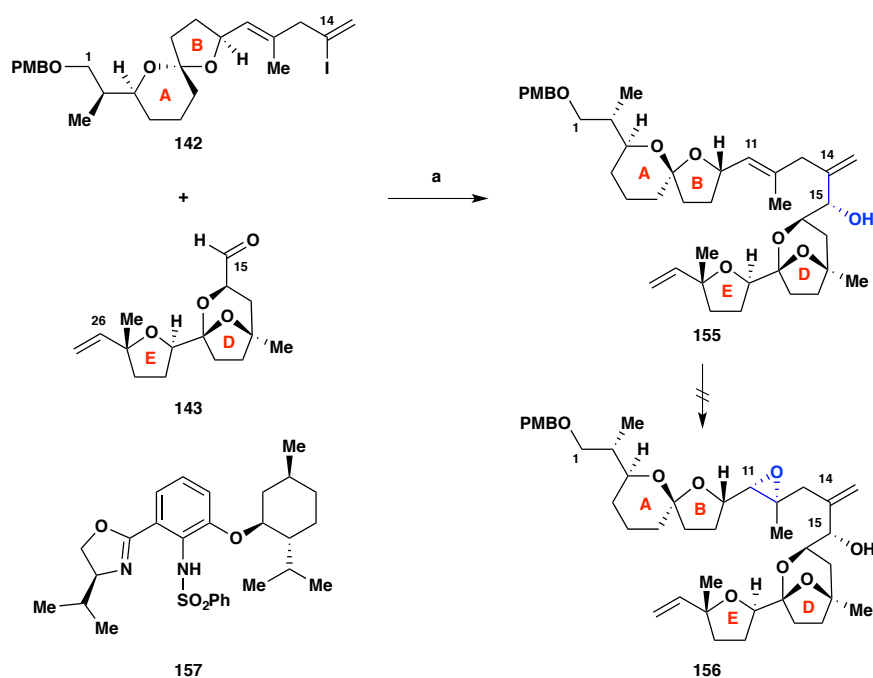


Scheme 35. Micalizio's synthesis of the C1–C14 vinyl iodide **142** of PTX-2

Reagents and Conditions: (a) **150** $\text{Ti}(\text{OiPr})_4$, $c\text{-C}_3\text{H}_9\text{MgCl}$, Et_2O , $-78\text{ }^\circ\text{C}$ to $-30\text{ }^\circ\text{C}$, then add Li-alkoxide of **149**, then HCl , 77%; (b) HCl , THF , EtOH ; (c) O_3 , MeOH , then TsOH , 84% over two steps; (d) Cp_2ZrCl_2 , DIBAL-H , THF , then I_2 ; (e) $n\text{BuLi}$, $i\text{PrMgBr}$, $\text{CuCN}\cdot\text{LiCl}$, 2-iodoallylbromide, 43% over two steps.

The attempted completion of the C1–C26 fragment commenced with an asymmetric NHK coupling between vinyl iodide **142** and aldehyde **143** with ligand **157** (Scheme 36). The reaction smoothly afforded the C1–C26 skeleton in 79% yield with >20:1 d.r. at C15. The mild conditions (CrCl_2 , Mn , LiCl , NiCl_2 , Cp_2ZrCl_2 , proton sponge, rt) left the sensitive AB spiroketal ring and the bicyclic acetal D ring untouched. However, selective epoxidation at the C11–C12 double bond to prepare epoxide **156** proved to be extremely difficult. Both Shi epoxidation and $m\text{CPBA}$ were not effective for this process, as a competing epoxidation at the C14 double bond took place as well. In the model study, there was a free hydroxyl group

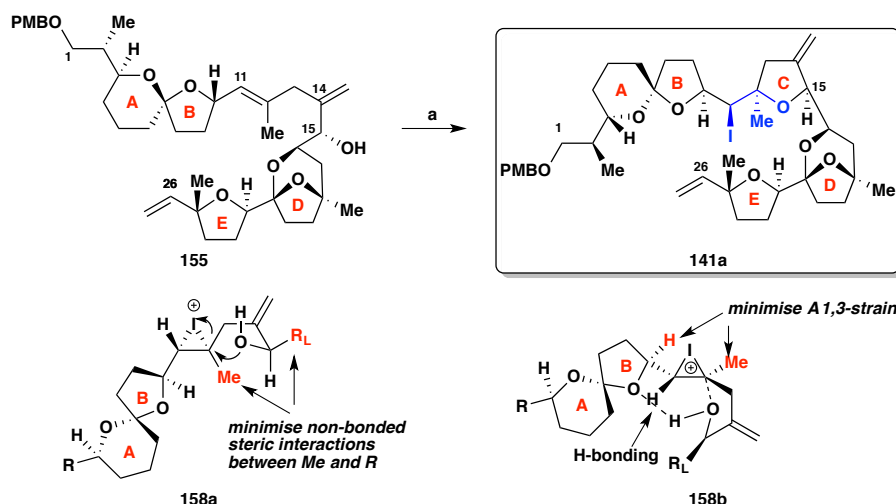
and the C11–C12 epoxide was installed *via* a Sharpless asymmetric epoxidation in good yield and selectivity. If the same strategy is used here, the AB spiroketal has to be constructed after the C ring formation. It also requires the protection of the C15-*OH* group to avoid competitive epoxidation at the C14 alkene moiety.



Scheme 36. Micalizio's attempted completion of the C1-C26 fragment of PTX-2

Reagents and Conditions: (a) CrCl_2 , Mn, LiCl, NiCl_2 , Cp_2ZrCl_2 , 1,8-bis(dimethylamino)naphthalene (proton sponge), **157**, MeCN, rt, 2 h, 79%.

To complete the C ring, Micalizio chose an iodoetherification reaction triggered by NIS to prepare the C11-*I* analogue **141a** with 87% yield and 12:1 d.r. (**Scheme 37**). The transition state model **158a** was not adequate to explain the observed stereochemistry, so Micalizio proposed there might be hydrogen bonding between the C10 ether and the C15-*OH* group in organising the transition state (**158b**).



Scheme 37. Micalizio's completion of the C ring

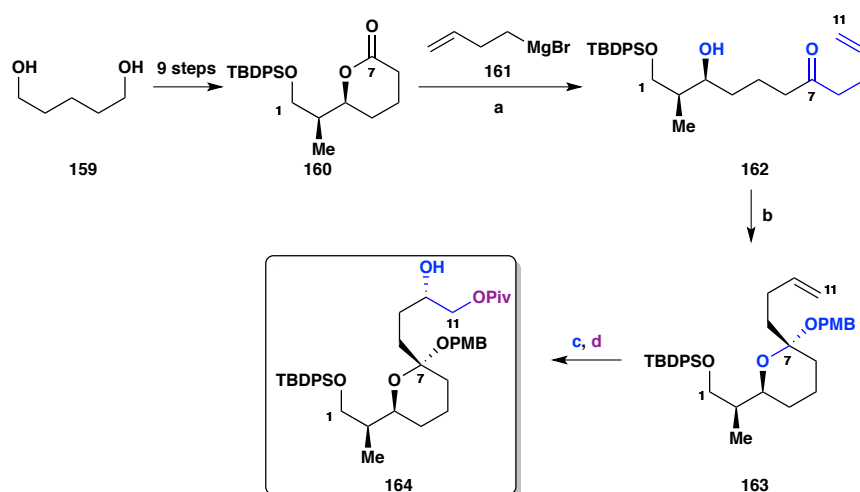
Reagents and Conditions: (a) NIS, CH_2Cl_2 , -78°C , 87%, 12:1 d.r..

In both approaches by Williams and Micalizio's, the C11 *neo*-pentyl position need further modifications in the later stages, while in Evans' total synthesis of PTX-4 and Donohoe's synthesis of the ABC fragment, this position was inaccessible to many reagents due to its highly hindered environment.^{64, 66} These problems cause doubts over the plausibility of any late-stage adjustments to prepare the C11-(*S*) hydroxyl group in PTXs.

1.5.6 Pihko's approach to the 10-*epi*-C1–C20 fragment of PTX-2

While many other research groups relied on a late stage acidic equilibration to obtain the non-anomeric 6,5-spiroketal from its anomeric analogue, Pihko and co-workers reported a direct spiroketalisation strategy to form both 6,5-spiroketals under different acidic conditions in 2004.⁴⁴ The group employed this strategy to the synthesis to the 10-*epi*-C1–C20 fragment of PTX-2 in 2011.⁴⁵⁻⁴⁷

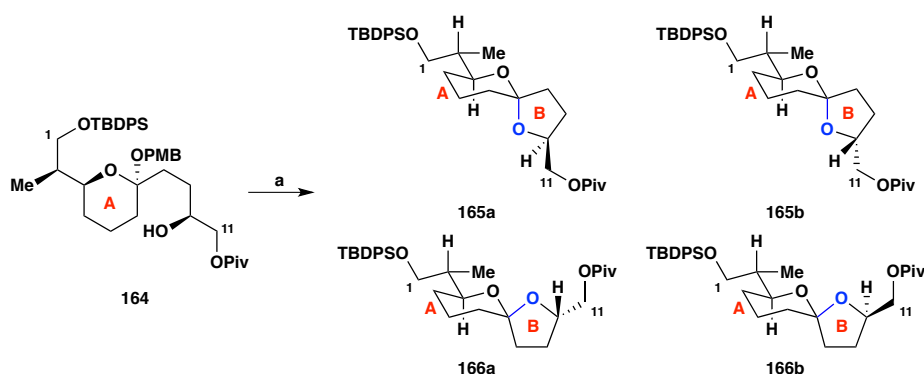
The Pihko group first prepared the C1–C11 spiroketal model of PTXs. Starting with 1,5-pentanediol **159**, lactone **160** was prepared in 9 steps (Scheme 38). Grignard addition of 4-butenylmagnesium bromide to lactone **160** gave secondary alcohol **162** in 60% after two recycles of the starting material. Treatment of **162** with 4-methoxybenzyl alcohol under acidic condition afforded acetal **163** in 83% yield. It was noteworthy that simpler alcohols such as MeOH or *i*BuOH gave a mixture of elimination products rather than the desired acetal in this reaction.⁴⁴ Sharpless asymmetric dihydroxylation of acetal **163** using (DHQ)₂PYR ligand afforded the diol with the required stereochemistry at the C10-*OH* group in 70:30 d.r., and the C11-*OH* group was subsequently selectively protected with pivaloyl chloride to afford acetal **164** to prevent the competitive formation of a more stable 6,6-spiroketal in spiroketalisation.



Scheme 38. Pihko's synthesis of the C1–C11 spiroketal precursor **164** of PTX-2

Reagents and conditions: (a) **161**, THF, $-78\text{ }^{\circ}\text{C}$, 60% after 2 recycles; (b) PMBOH, PPTS, CH_2Cl_2 , rt, 83%; (c) $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$, $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , $\text{CH}_3\text{SO}_2\text{NH}_2$, (DHQ)₂PYR, *t*BuOH:H₂O (1:1), $0\text{ }^{\circ}\text{C}$, 70:30 d.r.; (d) PivCl, Py, rt, 62% for 2 steps.

With acetal **164** in hand, Pihko and co-workers developed two sets of acidic conditions to maximise the yield of either anomeric *or* non-anomeric 6,5-spiroketal (**Scheme 38**). It was observed that stronger acids and longer reaction time favoured the thermodynamically more stable anomeric spiroketal **165**, while weaker acids and shorter reaction time gave more of the kinetic product **166**. Treatment of acetal **164** with 80 mol% ClCH_2COOH ($\text{pK}_a = 2.86$ in DMSO) for 4 h afforded a 51:49 ratio of **165**:**166**, while exposure to 20 mol% TsOH ($\text{pK}_a = -1.3$ in DMSO) for 90 mins gave almost quantitative anomeric 6,5-spiroketal (70:30 **165a**:**165b**). Pihko further pointed out that the pK_a values for acids in DMSO were more reliable for the spiroketalisation, because the reaction was performed in aprotic CH_2Cl_2 .

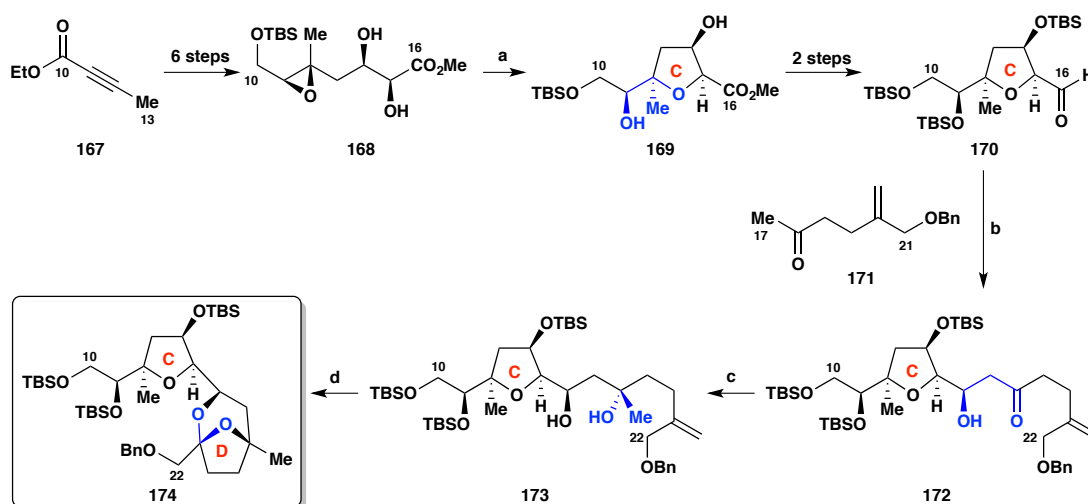


Scheme 39. Pihko's spiroketalisation of the AB ring of PTX-2 and -4

Reagents and conditions: (a) ClCH_2COOH (80 mol%), rt, 4 h, 29:22:44:5 **165a**:**165b**:**166a**:**166b**, or TsOH (20 mol%), 90 min, 70:30 **165a**:**165b**.

The forward synthesis commenced with dihydroxyl epoxide **168**, which was prepared from commercially available ethyl 2-butynoate **167** in 6 steps (**Scheme 40**). Treatment of **168** with PPTS in CH_2Cl_2 initiated an intramolecular epoxide opening process to form the *cis*-THF C ring fragment **169** in 90% yield. The C ring fragment **169** was converted to aldehyde **170** in

2 steps, and subsequently coupled with the lithium enolate of ketone **171** (derived from commercially available methallyl dichloride in 5 steps) in 82% yield as a single diastereoisomer. The stereoselectivity was rationalised using Cornforth's model.⁴⁵ Treatment of compound **172** with $\text{MeTi}(\text{OiPr})_3$ furnished the desired C18-OH group with 9:1 d.r. in 91% isolated yield. Ozonolysis of alkene **173** with reductive workup followed by a spontaneous one-pot ketalisation gave the bicyclic D ring fragment **174** in 63% yield.

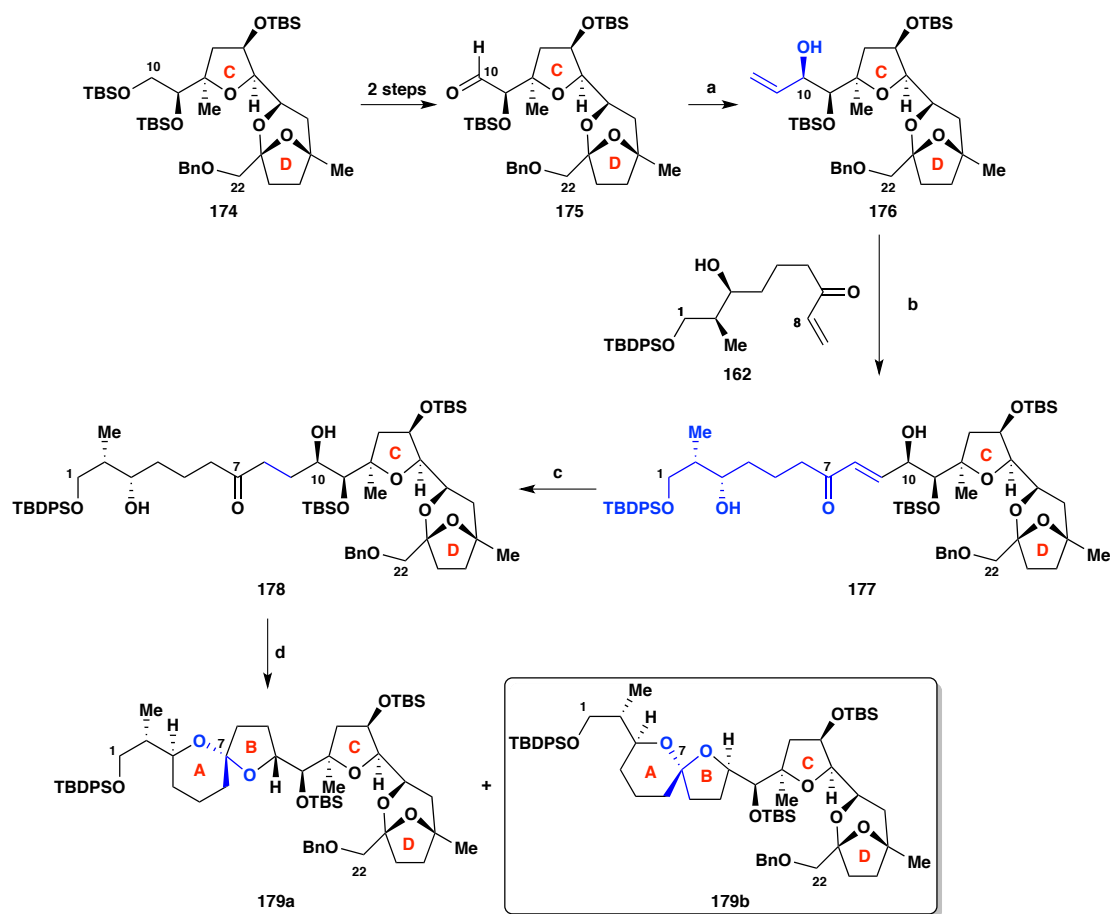


Scheme 40. Pihko's synthesis of the C10–C22 fragment **174** of PTX-2

Reagents and conditions: (a) PPTS, CH_2Cl_2 , 90%; (b) **171**, LDA, THF, then **170**, 82%; (c) $\text{MeTi}(\text{OiPr})_3$, Et_2O , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 91% **172**; (d) O_3 , CH_2Cl_2 , then Me_2S , 63%.

The completion of the C1–C22 fragment started with aldehyde **175**, which was obtained from compound **174** in 2 steps (**Scheme 41**). Treatment of aldehyde **175** with vinylmagnesium bromide afforded an 83:17 mixture of C10 epimers in 95% yield. The allylic alcohol **176** was coupled to the C1–C8 alkene **162** in the presence of Grubbs 2nd generation catalyst in 55% yield. Hydrogenation of the C8–C9 double bond catalysed by Pd/C afforded diol **178** in 94%

yield, which was subsequently subjected to the previous optimised kinetic spiroketalisation conditions to afford 1:3 anomeric spiroketal **179a**:non-anomeric spiroketal **179b** in near quantitative yield (98%). Unfortunately, further analysis of the spiroketal indicated that the absolute stereochemistry at C10 was opposite to that in the PTXs, and the selectivity could not be reversed under various conditions in model study.[§]



Scheme 41. Pihko's synthesis of the 10-*epi*-C1–C22 fragment **179** of PTX-2

Reagents and conditions: (a) $\text{CH}_2=\text{CHMgBr}$, THF, 95%, 83:17 d.r.; (b) Grubbs 2nd generation catalyst, CH_2Cl_2 , 55%; (c) Pd/C, Py, EtOAc, 94%; (d) ClCH_2COOH , CH_2Cl_2 , 0.5 h, 98%, 1:3 **179a**:**179b**.

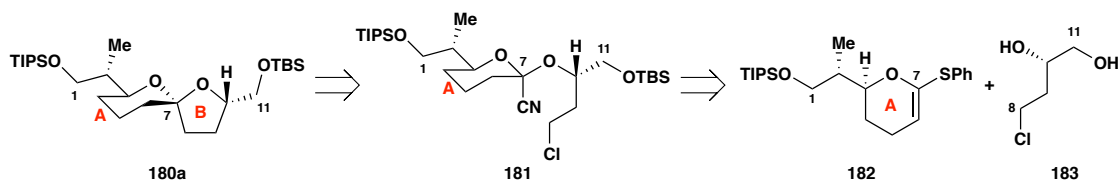
[§]The group attempted to change solvent (THF, PhMe, CH_2Cl_2 , MeCN), nucleophile (MeMgBr, MeLi), reaction temperature and time, but under all the conditions the undesired 10-*R* isomer was favoured.

Pihko successfully prepared the non-anomeric 6,5-spiroketal of PTXs using a kinetic acidic spiroketalisation. Although the allylation of the C10 aldehyde gave the unexpected 10-*R* epimer, it might be possible to revise the route and obtain the desired stereochemistry in the early stage of synthesis.

1.5.7 Rychnovsky's synthesis of the C1–C11 fragment of PTX-2

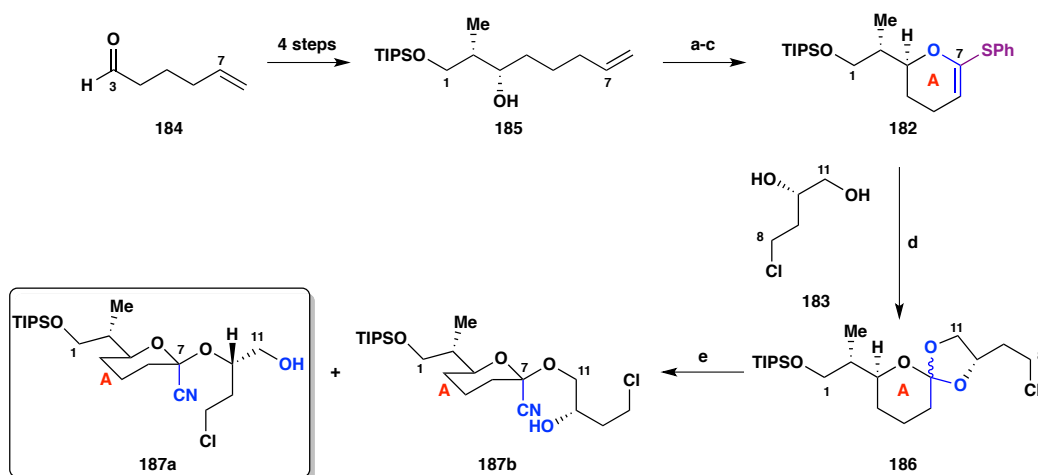
Whilst most groups focused on preparing the more stable anomeric 7-(*S*) AB spiroketal moiety and performing a late stage isomerisation to the non-anomeric 7-(*R*) spiroketal, Rychnovsky published a brilliant method in 2007 to directly synthesise the non-anomeric spiroketal employing a reductive cyclisation strategy.⁵⁴

Before applying to the PTXs, Rychnovsky had previously prepared non-anomeric 5,4- and 5,5-spiroketal with excellent selectivity and proven the feasibility of the concept in the synthesis of the spirofungin B core.^{78, 79} Rychnovsky chose to disconnect the C7–C8 bond of the AB spiroketal when other approaches normally disconnected at the C7–O bond (**Scheme 42**). It was proposed that a reductive lithiation would generate an axial alkyl lithium intermediate at C7 selectively, which would cyclise to the B ring with retention of stereochemistry. Further disconnection at the C7–C8 bond resulted in dihydropyran **182** and diol **183** as the key precursors.



Scheme 42. Rychnovsky's retrosynthetic analysis of the AB spiroketal **180**

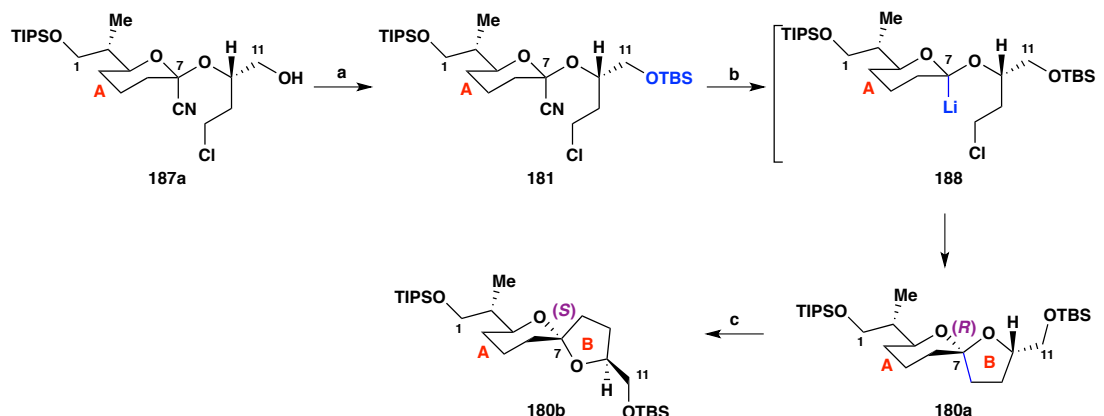
The forward synthesis started with the C1–C7 secondary alcohol **185**, which was prepared from 5-hexenal **184** in 4 steps (**Scheme 43**). Ozonolysis of **185** in the presence of PPh_3 afforded a lactol as a 1.5:1 mixture of diastereoisomers at C7 in 97% yield, which was dehydrated with POCl_3 to generate a dihydropyran in 66% yield. Deprotonation with Schlosser's base followed by addition of diphenyl disulfide produced the desired 2-thiophenyl dihydropyran **182** in 76%. It was noted that this sulfurisation must be performed under strictly anhydrous conditions, using rigorously dried starting material.⁵⁴ Treatment of **182** with diol **183** in the presence of benzenesulfonic acid gave a 1:1 diastereoisomer mixture of the orthoester **186** in 74% yield. When subjected to trimethylsilyl cyanide (TMSCN) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, orthoester **186** afforded two regioisomers, with the preferred isomer **187a** in 50% yield, and the undersired **187b** in 28% yield.



Scheme 43. Rychnovsky's synthesis of the reductive cyclisation precursor **187a**

Reagents and conditions: (a) O_3 , CH_2Cl_2 , PPh_3 , 97%, 1.5:1 d.r.; (b) POCl_3 , Py, 66%; (c) $n\text{BuOK}$, $n\text{BuLi}$, $-78\text{ }^\circ\text{C}$, THF, then $(\text{PhS})_2$, 76% **182**, 16% rsm; (d) **183**, PhSO_2H , CH_2Cl_2 , 74%; (e) TMSCN , $\text{BF}_3\cdot\text{OEt}_2$, $-78\text{ }^\circ\text{C}$ to $-40\text{ }^\circ\text{C}$, 50% **187a** and 28% **187b**.

TBS protection of **187a** gave compound **181** in 85% yield (**Scheme 44**). Slow addition of freshly prepared LiDBB (from Li wire and 4,4'-di-*tert*-butylbiphenyl) to compound **181** afforded the non-anomeric spiroketal **180a** in a good yield of 76% yield with retention of stereochemistry. Treatment of non-anomeric spiroketal **180a** with CSA initiated the spiroketal equilibration and resulted in the anomeric 6,5-spiroketal **180b** in a good yield of 83%. The structures of both spiroketals were confirmed based on the chemical shifts of C7 in ^{13}C NMR spectra. For the anomeric spiroketal **180b**, the chemical shift is 106.9 ppm, and for the non-anomeric spiroketal **180a**, it is 108.0 ppm. These chemical shifts are consistent with those observed in natural PTXs.⁵⁴ Rychnovsky's reductive lithiation strategy provides a powerful tool to access both 6,5-spiroketal in PTXs.



Scheme 44. Rychnovsky's completion of the AB spiroketal **180**

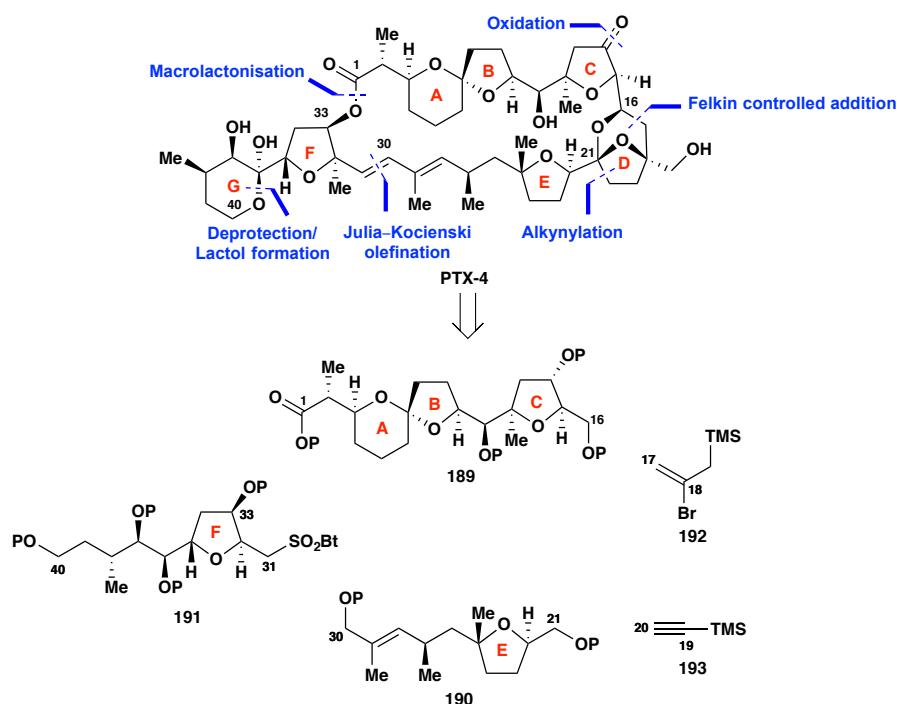
Reagents and conditions: (a) TBSCl, imidazole, CH₂Cl₂, 85%; (b) LiDBB, THF, -78 °C, 76%; (c) CSA (20 mol%), CH₂Cl₂, 83%.

1.6 Donohoe group's progress on the total synthesis of PTX-4

1.6.1 Retrosynthetic analysis of PTX-4

Our retrosynthetic analysis of PTX-4 aimed to disconnect the macrolide into three fragments: C1–C16 spiroketal fragment **189**, C21–C30 alkene fragment **190** and C31–C40 lactol fragment **191** (**Scheme 45**). It was envisioned that the C1–C33 bond would be formed *via* a Yamaguchi lactonisation from PTX-4 *seco* acid analogue in the final stage, and the G ring would be assembled *via* a deprotection–lactol formation process subsequently. The C30–C31 double bond would be formed *via* a Julia–Kocienski olefination in the latter stage to avoid deprotection of the C14-*OPMB* group in the presence of a conjugated diene moiety. We planned to connect the C ring and E ring using a Felkin–Anh controlled addition of vinyl bromide **192** to the C16 aldehyde, and an alkynylation of trimethylsilylacetylene to the C21 aldehyde. It was expected that the sterically well-defined dihydroxyketone would cyclise to the D ring after deprotection.⁸⁰ The retrosynthetic analysis also features an osmium-catalysed

oxidative cyclisation strategy to diastereoselectively assemble the B, C and E THF rings developed by our group,⁸¹ and a complementary cobalt catalyzed-oxidative cyclisation reaction to form the *trans*-THF F ring, which will be discussed later.⁸²

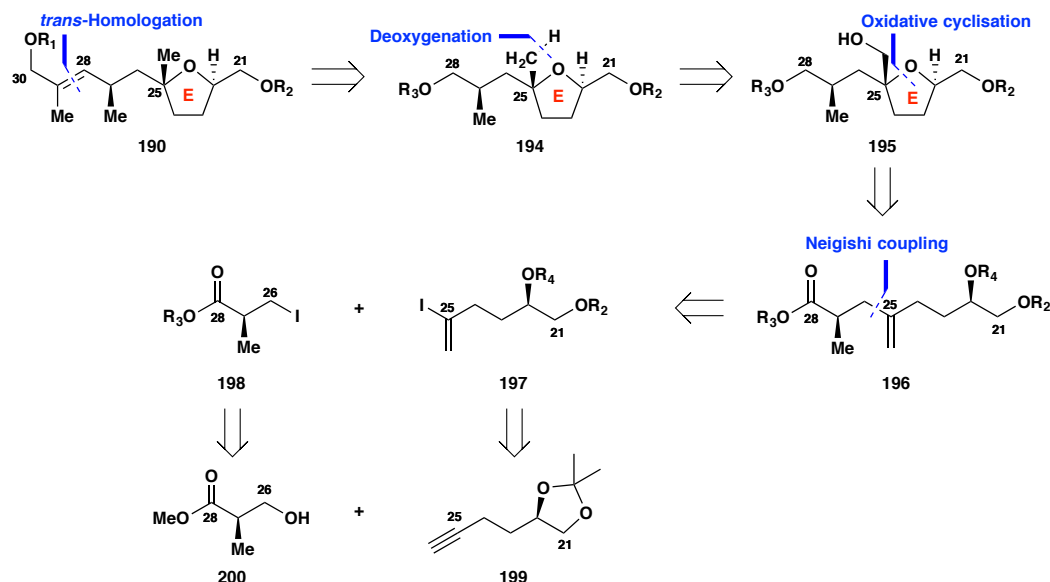


Scheme 45. Donohoe's key disconnections of PTX-4

1.6.2 Synthesis of the C21–C30 fragment **190**

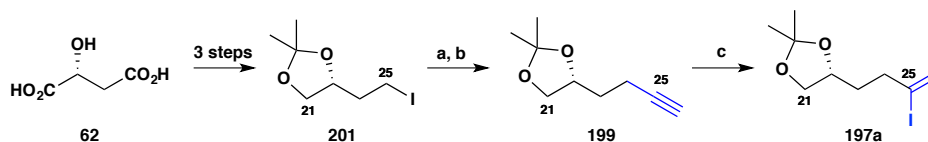
In 2011, the Donohoe group first completed the synthesis of the C21–C30 fragment **190** of PTX-4 using an osmium catalysed oxidative cyclisation as key step to form the E ring.⁸³ The retrosynthetic analysis of the C21–C30 E ring fragment is depicted in **Scheme 46**. Alkene **190** could be formed *via* a *trans*-selective homologation of the C28 aldehyde, which was derived from protected alcohol **194** *via* a selective deprotection and subsequent oxidation. Compound **194** was achieved from deoxygenation of THF fragment **195**, which was assembled by osmium-catalysed oxidative cyclisation of intermediate **196**. Alkene **196** was

further disconnected by a Negishi coupling at C25–C26 to iodides **197** and **198**. These two compounds were readily available from alkyne **199** and chiral hydroxyl ester **200**.



Scheme 46. Donohoe's retrosynthetic analysis of C21–C30 fragment **190**

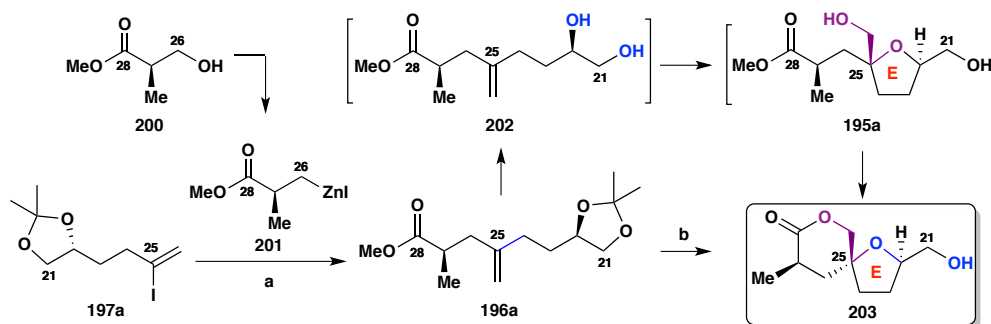
For the forward synthesis, iodide **201** was prepared from (D)-malic acid **62** in 3 steps with a yield of 68% (**Scheme 47**). Alkynylation with trimethylsilylacetylene followed by TMS cleavage afforded terminal alkyne **199** in 77% yield. Nickel-catalysed hydroalumination afforded highly selective α -vinylaluminium intermediate, which was quenched with electrophilic iodide to generate alkenyl iodide **197a** in 74% yield.⁸⁴



Scheme 47. Donohoe's synthesis of terminal alkyne **197a**

Reagents and conditions: (a) Trimethylsilylacetylene, *n*BuLi, DMPU, THF, $-78\text{ }^{\circ}\text{C}$, 85%; (b) K_2CO_3 , MeOH, rt, 90%; (c) DIBAL-H, $\text{Ni}(\text{dppp})\text{Cl}_2$, THF, $0\text{ }^{\circ}\text{C}$, then NIS, 74%.

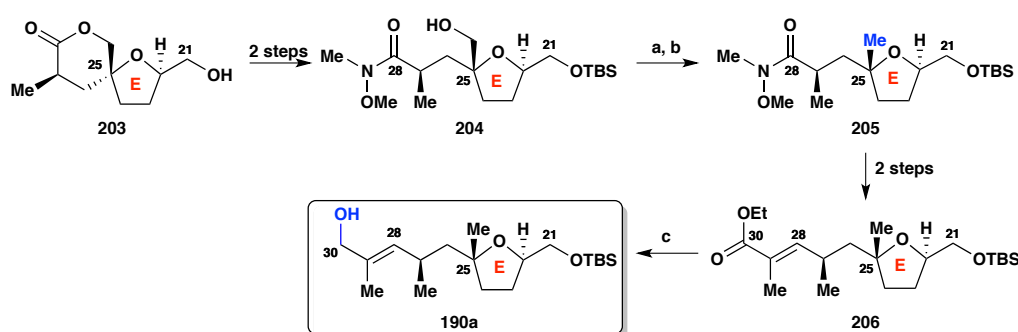
Negishi coupling between organozinc reagent **201** (generated from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate **200**) and vinyl iodide **197a** afforded 1,1-disubstituted alkene **196a** in 90% yield (**Scheme 48**). It was subjected to Lewis acid promoted osmium-catalysed oxidative cyclisation to assemble the E ring.⁸¹ Scandium triflate was chosen because its acidity was enough to deprotect the acetonide *in situ*. Upon construction of the E ring, lactone **203** was also formed in the same pot. The formation of lactone avoided differentiating the C21-OH and C25-CH₂OH groups in the next step. The three-step, one-pot reaction gave a good yield 76% of single diastereoisomer.



Scheme 48. Donohoe's synthesis of the E ring fragment **203**

Reagents and conditions: (a) $\text{Pd}(\text{PPh}_3)_4$, PhH, HMPA, $80\text{ }^{\circ}\text{C}$, 90%; (b) $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$, PNO, citric acid, $\text{Sc}(\text{OTf})_3$, MeCN/H₂O, $60\text{ }^{\circ}\text{C}$, 76%.

The completion of C21–C30 fragment commenced with converting lactone **203** to Weinreb amide **204** in 2 steps (**Scheme 49**). The deoxygenation of the C25-CH₂OH group was achieved by hydrogenation of its iodide derivative. The *trans*-alkene at C28–C29 was formed *via* Wittig homologation, and reduction of ester **206** afforded primary alcohol **190a** in 81% yield for further elaboration.



Scheme 49. Donohoe's completion of the C21–C30 fragment **190a**

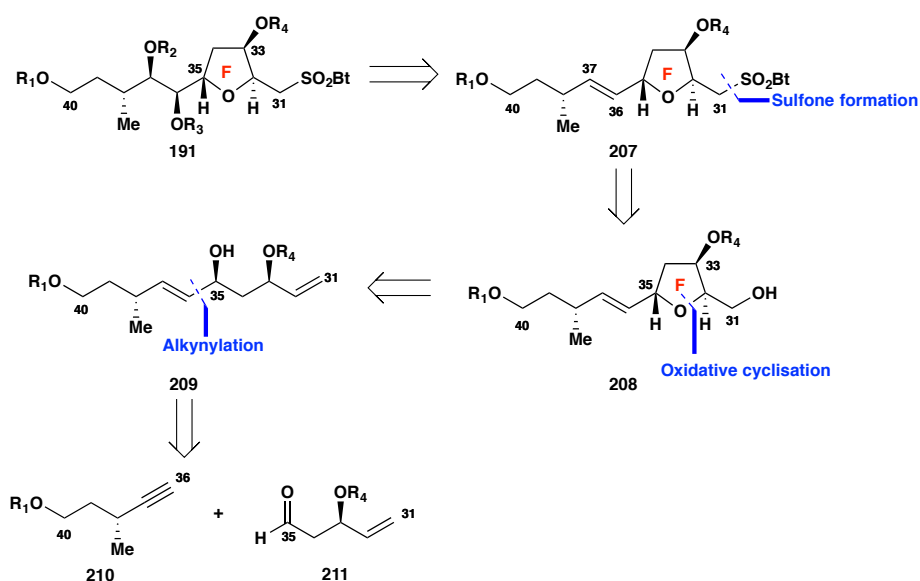
Reagents and conditions: (a) I₂, PPh₃, Imidazole, PhMe, 80 °C, 79%; (b) H₂, Pd/C, EtOH, 97%; (c) LiBHEt₃, ClCH₂CH₂Cl, –78 °C, 81%.

In summary, Donohoe group's synthesis of the C21–C30 fragment **190a** was finished in 15 linear steps from commercially available starting material with an overall yield of 7.5%, on average 84% per step.⁸³ The key feature of the route was a stereoselective osmium-catalysed oxidative cyclisation to form the E ring in good yield as a single diastereoisomer.

1.6.3 Synthesis of the C31–C40 fragment **191**

Later in 2012, the Donohoe group prepared the C31–C40 FG ring fragment **191** of PTX-4, featuring a cobalt-catalysed oxidative cyclisation to form a *trans*-THF ring.^{82, 85} The

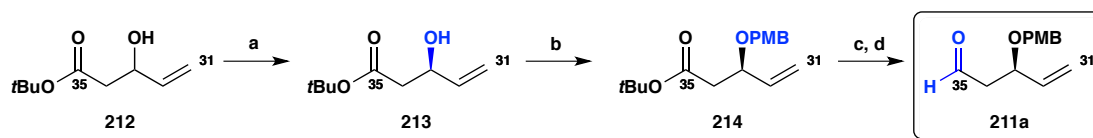
retrosynthetic analysis of the FG ring fragment is depicted in **Scheme 50**. The unstable hemiacetal G ring was planned to be formed in the latter stage *via* a deprotection–lactol formation process. It required that C36 and C37 hydroxyl groups could be differentiated during deprotection. A Sharpless asymmetric dihydroxylation would introduce the stereochemistry of these two centres in **191**. The C31 sulfone group needed for Julia–Kocienski olefination could be prepared from the corresponding primary alcohol using a Mitsunobu reaction. The step forming the *trans*-THF F ring fragment **208** could be accomplished by Mukaiyama’s cobalt-catalysed oxidative cyclisation from 5-hydroxy alkene **209**.⁸² The linear precursor **209** for cyclisation was further disconnected to alkyne **210** and aldehyde **211**.



Scheme 50. Donohoe’s retrosynthetic analysis of the C31–C40 fragment **191**

The forward synthesis started with an enzymatic resolution of allylic alcohol **212** (**Scheme 51**).⁸⁶ The desired (*R*)-isomer was obtained in a good yield of 45%. The base

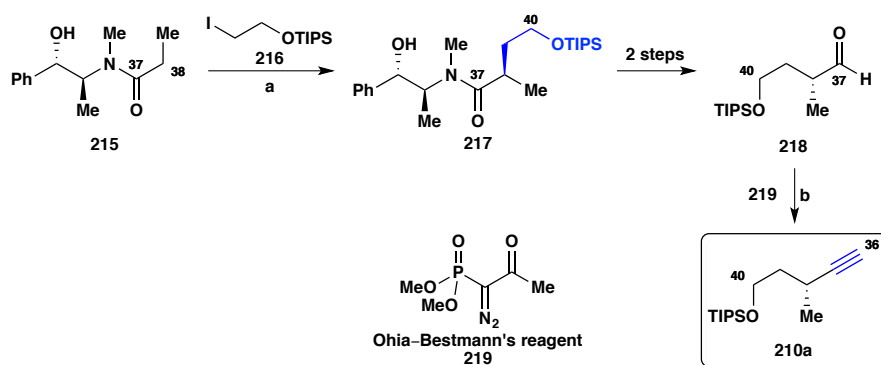
sensitive allylic alcohol **213** was protected under acidic PMB protection conditions in excellent yield (91%). PMB protected alcohol **214** was converted to aldehyde **211a** in 2 steps, involving reduction of the ester and oxidation to aldehyde.



Scheme 51. Donohoe's synthesis of aldehyde **211a**

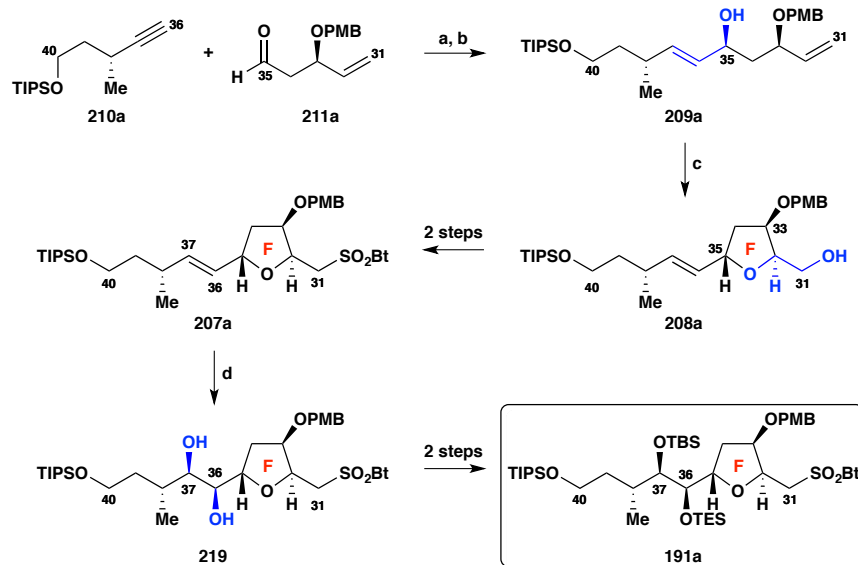
Reagents and conditions: (a) Amano lipase, 4Å MS, pentane, 35 °C, 45%; (b) 4-methoxybenzyl 2,2,2-trichloroacetimidate, CSA, CH₂Cl₂/*c*-hexane (4:1), 91%; (c) LiAlH₄, Et₂O, 0 °C, 80%; (d) Dess–Martin periodinane, CH₂Cl₂, 0 °C to rt, 82%.

Synthesis of alkyne **210a** began with a Myers asymmetric alkylation between pseudoephedrine propionamide **215** and iodide **218** to establish the stereochemistry at C38 (**Scheme 52**).⁸⁷ After removal of the chiral auxiliary and oxidation state adjustment, the C36–C37 alkyne was installed *via* a Seyferth–Gilbert homologation reaction using Ohia–Bestmann's reagent **219**.^{88, 89}

Scheme 52. Synthesis of alkyne **210a**

Reagents and conditions: (a) **215**, *n*BuLi, *i*Pr₂NH, LiCl, THF, then **216**, 0 °C to –78 °C, 97%; (b) **219**, NaOMe, –78 °C to rt, 76%.

The completion of the C31–C40 fragment **191a** started with coupling of alkyne **210a** and aldehyde **211a** (Scheme 53). Deprotonation of alkyne **210a** with *n*BuLi in THF followed by addition of aldehyde **211a** gave the desired C35-(*R*) alcohol in 42% yield. The C35-(*S*) side product was also isolated in 30% yield and could be converted to the desired product *via* a Mitsunobu reaction. Reduction of propargylic alcohol with Red-Al[®] in Et₂O provided *E*-alkene **209a** exclusively in a good yield of 81%. Treatment of **209a** with O₂, bis(1-morpholino-carbamoyl-4,4'-dimethyl-1,3-pentanedionato) Cobalt(II) (Co(modp)₂) and TBHP in *i*PrOH at elevated temperature (70 °C) afforded the *trans*-THF ring product **208a** in 57% yield. The C31 sulfone moiety for Julia–Kocienski olefination was then installed in two steps. Sulfone **207a** was then subjected to Sharpless asymmetric dihydroxylation with (DHQD)₂PHAL ligand to afford diol **219** in 84% yield with 12.5:1 d.r.. The diol was orthogonally protected in 2 further steps to provide the C31–C40 fragment **191a**. The protecting group strategy to differentiate the C36-*OH* and C37-*OH* groups suffered from lack of selectivity and it is currently under further investigation.

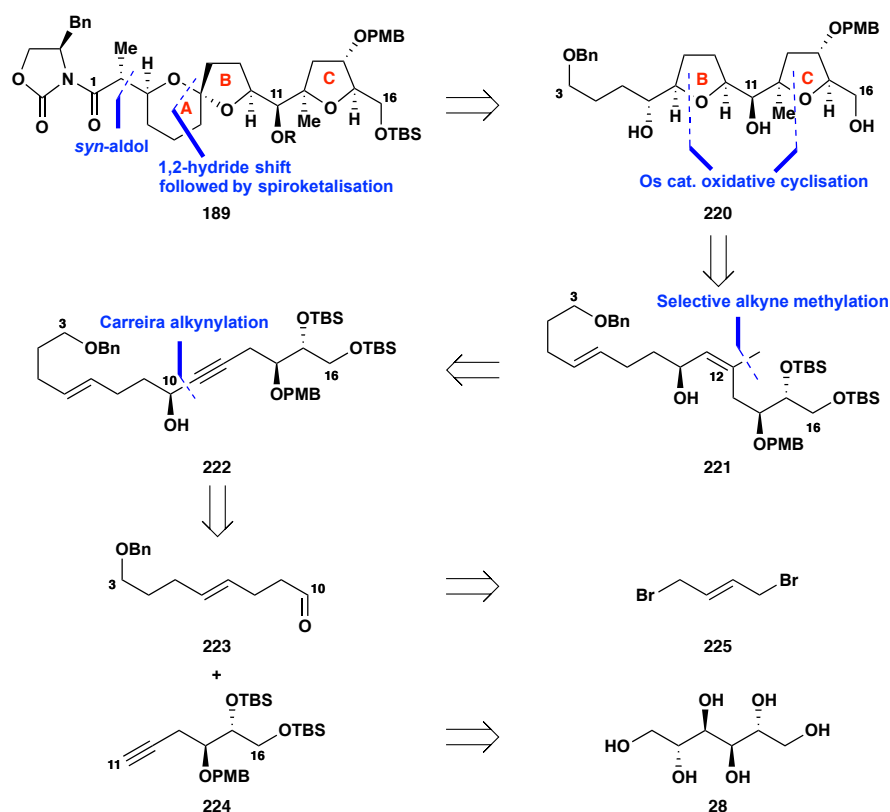


Scheme 53. Donohoe's completion of the C31–C40 fragment **191a** of PTX-4

Reagents and conditions: (a) **210a**, *n*BuLi, then **211a**, THF, -78°C , 42%, 30% C35 epimer; (b) Red-Al[®], 0°C , Et₂O, 81%; (c) O₂, Co(*n*mp)₂, TBHP, *i*PrOH, 70°C , 57%; (d) K₂OsO₄•2H₂O, (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, *t*BuOH:H₂O (1:1), 0°C to rt, 84%, 12.5:1 d.r..

1.6.4 Previous synthetic study on the C1–C16 fragment **189**

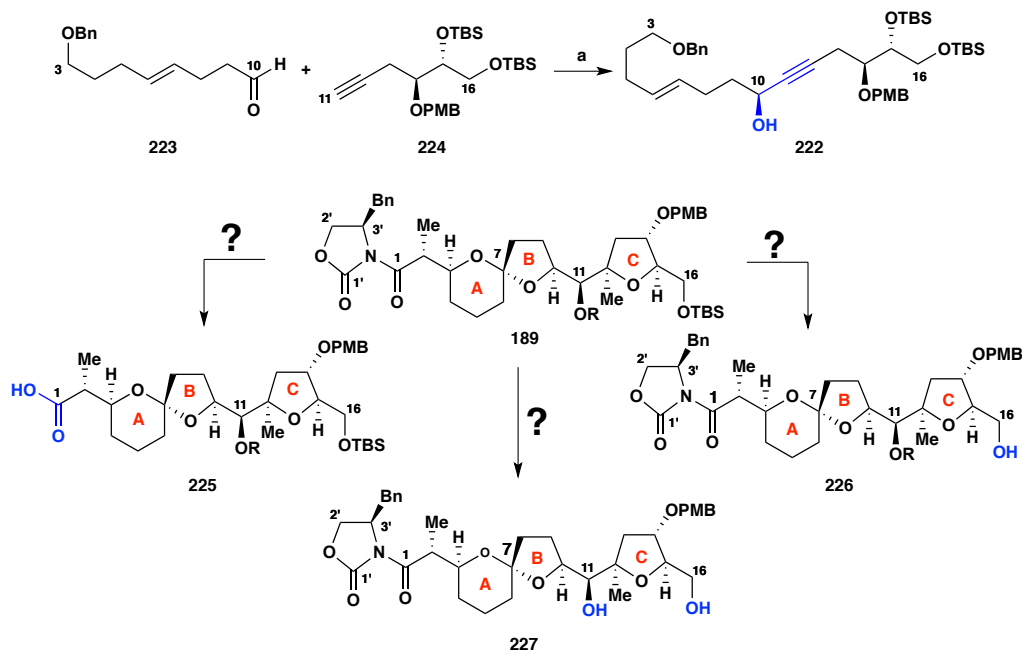
Previous study in the Donohoe group also worked out the first generation of synthesis of the C1–C16 fragment **189**.^{60, 66} The retrosynthetic analysis was depicted in **Scheme 54**. The AB spiroketal ring was planned to be assembled *via* a 1,2-hydride shift–spiroketalisation process in the late stage. The C2–C3 *syn* relationship was installed by an Evans aldol reaction. Both B and C *cis*-THF rings would be formed in an osmium-catalysed oxidative cyclisation in one pot, which required diene **221** with defined double bond geometry.⁸¹ The C11–C12 *cis*-alkene was obtained from a *trans*-selective methylation of propargyl alcohol **222**,⁹⁰ and the C10 stereocenter was determined *via* an asymmetric alkynylation between aldehyde **223** and alkyne **224**, developed by the Carreira group.^{91–93} The aldehyde **223** and alkyne **224** were derived from 1,4-dibromobut-2-ene **225** and D-mannitol **28** and respectively.



Scheme 54. Donohoe's retrosynthetic analysis of the C1–C16 fragment **189** of PTX-4

However, there were three problems encountered in the forward synthesis (**Scheme 55**, see Chapter 2 for detailed forward synthesis). Firstly, the Carreira reaction between aldehyde **223** and alkyne **224** only provided a low yield of 44% even after optimisation. Secondly, it was largely unknown if the protecting group strategy required further adjustments. In principle, it should allow a selective deprotection of the C16-OTBS group in the presence of C11-OTBS group and a mild cleavage of the highly sterically hindered C11-OTBS group in the final stage. Thirdly, we chose an oxazolidinone to mask the C1 acid moiety after the Evans aldol reaction to set up the absolute stereochemistry at C2 and C3, but it was not proven if the oxazolidinone group was removable in the final stages. My research on this fragment aims to

answer these three questions mentioned above and scale up the preparation of spiroketal **189** from 10 mg to 100 mg scale to enable the completion of the synthesis of PTX-4.



Scheme 55. Problems related to the C1–C16 fragment **189** of PTX-4

Reagents and conditions: (a) $\text{Zn}(\text{OTf})_2$, Et_3N , (–)-*N*-methylephedrine, PhMe, 44%.

Chapter 2

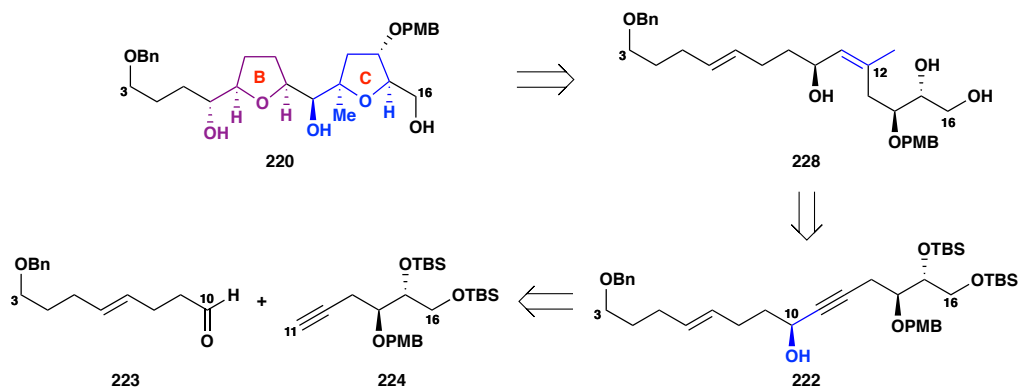
Results and Discussion

2.1 General introduction

This chapter details synthetic efforts towards the C1–C16 spiroketal fragment of PTX-4, focusing on the three major problems mentioned before (**Section 1.6.4**). The chapter is divided into three major parts: the optimisation of the Carreira alkylation between aldehyde **223** and alkyne **224**, the development of a new protecting group strategy for the BC *bis*-THF fragment, and removal of the C1 oxazolidinone on the spiroketal.

2.2 Synthesis of the C3–C16 oxidative cyclisation precursor 228

Previous research in Donohoe group had worked out a synthetic route to triol **220** by employing an osmium-catalysed oxidative cyclisation to form both *cis*-THF rings simultaneously (**Scheme 56**). However, the overall yield of the route was largely affected by a low yield in the Carreira alkylation reaction between aldehyde **223** and alkyne **224**. The yield did not exceed 44% even after optimisation, while in a typical reaction it was between 30% to 40%.⁶⁶ This part details synthetic efforts to increase the yield of this reaction and other optimisations along the route to produce triol **220** on a multigram scale.

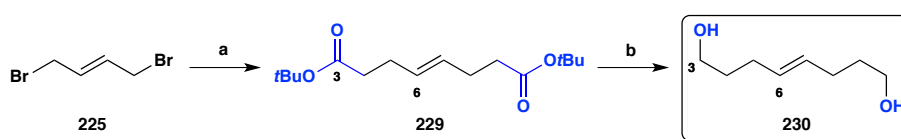


Scheme 56. Retrosynthetic Analysis of the BC *bis*-THF fragment **220**

2.2.1 Synthesis of the C3–C10 aldehyde **223**

Before optimising the Carreira reaction between aldehyde **223** and alkyne **224**, it was important to prepare both substrates on a multigram scale. Here the previous protocol was followed with a few modifications, especially regarding to the *mono*-benzylation of diol **230**.

The synthesis of aldehyde **223** started with 1,4-dibromo-but-2-ene **225** (Scheme 57). Following the reported two step procedure, diol **230** was prepared at 10 g scale in good yield.⁶⁶ An *in situ* formed enolate attacked 1,4-dibromo-but-2-ene **225** twice to generate diester **229** containing the C3–C10 carbon skeleton in 68% yield. LiAlH₄ reduction of diester **229** afforded symmetric diol **230** in an excellent yield of 98%. The structure of diol **230** was confirmed by the absence of *t*Bu proton singlet at 1.44 ppm in ¹H NMR spectrum, as well as loss of the *t*Bu methyl signal at 28.1 ppm in the ¹³C NMR spectrum. The NMR data of diol **230** was consistent with those previously reported by the Donohoe group.⁶⁶

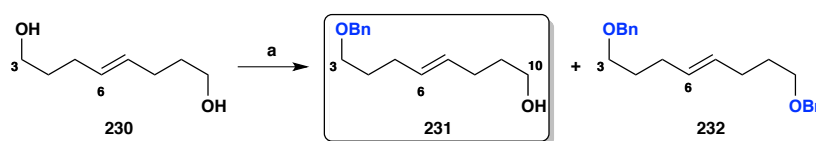


Scheme 57. Synthesis of diol **230**

Reagents and conditions: (a) LDA, *t*BuOAc, **225**, THF, −78 °C to rt, 16 h, 68%; (b) LiAlH₄, THF, 0 °C to rt, 4 h, 98%.

The next step was a *mono*-benzylation of diol **230**. Previously, diol **230** reacted with Ag₂O (1.5 eq) and BnBr (1.1 eq) in Et₂O to give a modest 55% yield of desired product **231** and 26% side product (Scheme 58).⁶⁰ The side product obtained was the *di*-benzyl ether **232**,

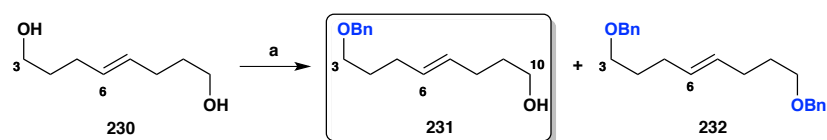
which was difficult to recycle under hydrogenation conditions because the double bond was reduced as well. The structure of *mono*-benzylated alcohol **231** formed was confirmed by NMR spectroscopy. A Bn-CH₂ singlet (2 H) was observed at 4.42 ppm, and the previously equivalent C3-H₂ and C10-H₂ in diol **230** were distinguished because in diol **230**, they were both at 3.60 ppm, while in **231** the C3-H₂ moved to 3.51 ppm.



Scheme 58. *mono*-Benzylation of diol **230** (Lipinski, R., DPhil thesis)⁶⁰

Reagents and conditions: (a) Ag₂O (1.5 eq), BnBr (1.1 eq), Et₂O, 55% **231**, 26% **232**.

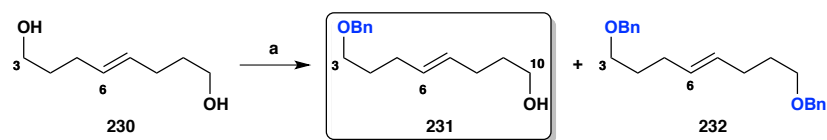
To reduce the formation of side product **232**, another protocol was tested (**Scheme 59**). Diol **230** was deprotonated with insufficient base (0.5 eq) and reacted with insufficient BnBr (0.33 eq) to afford desired *mono*-benzylated product **231** in 27%, with 45% unreacted starting material **230** and 3% side product **232** isolated. The formation of **232** was reduced, but the yield of desired product **231** also decreased. Practically, this reaction was repeated 4 to 5 times to maximise the conversion of diol **230** to *mono*-benzyl ether **231**, which was time and labour intensive.



Scheme 59. *mono*-Benzylation with insufficient base and BnBr-I

Reagents and conditions: (a) NaH (0.5 eq), BnBr (0.33 eq), DMF, 27% **231**, 45% **230**, 3% **232**

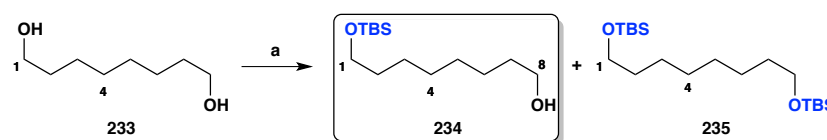
It was postulated that the high polarity of DMF assisted the solvation of a *di*-anionic intermediate, which resulted in the formation of the dialkylated side product. In a less polar solvent system, e.g. THF, the *mono*-deprotonated anion might form more selectively under the same conditions, allowing increasing equivalents of base and BnBr to be used, resulting in a higher conversion of the starting material. After several screenings of the stoichiometry, using 0.8 eq NaH, 0.8 eq BnBr and catalytic amount of TBAI in THF, the reaction gave a maximum in yield up to 45% **231** with only 5% side product **232** and 40% unreacted diol **230** recovered (**Scheme 60**). The new procedure afforded similar yield to the Ag₂O method but minimised the formation of side product **232**, and was therefore significantly more practical than the original procedure.



Scheme 60. *mono*-Benzylation with insufficient base and BnBr-II

Reagents and conditions: (a) NaH (0.8 eq), BnBr (0.8 eq), TBAI (0.05 eq), THF, 45% **231**, 40% **230**, 5% **232**.

In summary, all of the three methods tested could not afford a high yield of **231** and a good selectivity between *mono*- and *di*-alkylated products simultaneously. The formation of side product **232** was inevitable even with insufficient base and BnBr. This restricted the potential to use excess reagents to increase the conversion of diol **230** to the *mono*-benzylated product **231**. As another way to solve the problem, it was wondered if the *mono*-protected product could be removed from the reaction without further over protection. A literature search revealed that a similar *mono*-silyl protection of symmetrical diols in a biphasic system had been reported, in which the desired *mono*-protected product left the reaction phase immediately after formation.⁹⁴ For example, treatment of 1,8-octanediol **233** with Et₃N and TBSCl in 1:8 MeCN:Pentane afforded *mono*-silylation product **234** in high yield and selectivity and a small amount of side product **235** was detected (Scheme 61).⁹⁴

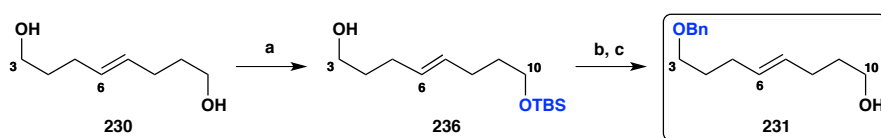


Scheme 61. Selective *mono*-silylation of 1,8-octanediol⁹⁴

Reagents and conditions: (a) TBSCl, Et₃N, MeCN/Pentane (1:8), 0 °C to rt, 24 h, 80% **234**, 10% **235**.

It was expected that diol **230** would have similar reactivity in the same reaction; the silylated product could be transformed to the desired *mono*-benzylated ether **231** in two steps (Scheme 62). Therefore, treatment of **230** with Et₃N (1.2 eq) and TBSCl (1 eq) in a biphasic solvent system (1:7 MeCN:Pentane) afforded *mono*-silylation product **236** in 77% yield, while only 12% unreacted starting material **230** and 10% *bis*-silyl ether were isolated after

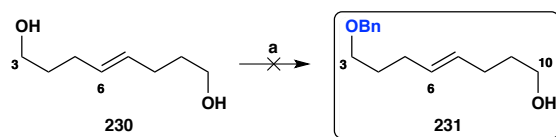
the reaction. The *mono*-TBS ether **236** had the *t*Bu proton singlet at 0.87 ppm and TBS-SiCH₃ signal at 0.02 ppm in ¹H NMR spectrum. These NMR data were consistent with those reported in literature.⁹⁵ Benzylation of alcohol **236** and removal of the TBS group under standard conditions then afforded the desired *mono*-benzylated product **231** in quantitative yield. The indirect procedure took two extra steps, but the overall yield was significantly higher (76% versus 32% to 55%). All of the three steps in this indirect route were reproducible at a 20 g scale.



Scheme 62. Indirect synthesis of *mono*-benzylated ether **231**

Reagents and conditions: (a) TBSCl, Et₃N, MeCN/Pentane (1:7), 0 °C to rt, 24 h, 77% **231**, 12% **230**, 10% *bis*-TBS side product; (b) NaH, BnBr, TBAI, THF, 0 °C to 60 °C, 16 h, 99%; (c) TBAF•3H₂O, THF, 0 °C to rt, 3 h, 100%.

Finally, it was considered that the selective *mono*-protection conditions of symmetric diol could possibly be applied to benzylation directly. Unfortunately, using BnBr instead TBSCl only afforded unreacted starting material **230** (**Scheme 63**).



Scheme 63. Attempted *mono*-benzylation using biphasic system

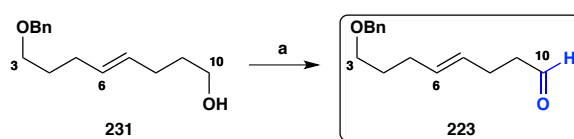
Reagents and conditions: (a) BnBr, Et₃N, MeCN/Pentane (1:7), 0 °C to rt, 24 h, >90% **230** recovered.

In conclusion, the indirect 3-step method is the most efficient way to prepare *mono*-benzylated product **231**. It benefits from both high conversion of diol **230** and high selectivity of *mono*-protected product over *di*-protected product. The following table summarises the results of different *mono*-benzylation procedures.

Table 4. *mono*-Benzylation of diol 230

Conditions	Results
Ag ₂ O (1.5 eq), BnBr (1.1 eq), Et ₂ O	55% 231 , 26% 232 ⁶⁶
NaH (0.5 eq), BnBr (0.33 eq), DMF	27% 231 , 45% 230 , 3% 232
NaH (0.8 eq), BnBr (0.8 eq), TBAI, THF	45% 231 , 40% 230 , 5% 232
(a) Et ₃ N (1.2 eq), TBSCl (1 eq), 1:7 MeCN:Pentane	76% 231 over 3 steps Reproducible on 20 g scale
(b) NaH (1.1 eq), BnBr (1.05 eq), TBAI (0.05 eq), THF	
(c) TBAF•3H ₂ O (2 eq), THF	
Et ₃ N (1.2 eq), BnBr (1 eq), 1:7 MeCN:Pentane	No reaction

With the *mono*-benzyl ether **231** in hand, aldehyde **223** was readily prepared *via* a standard oxidation of the primary alcohol. Both Parikh–Doering and Dess–Martin oxidations were tested for this process (**Scheme 64**). Comparatively, the Parikh–Doering oxidation gave better yield (97% versus 86%) and it was chosen for large-scale synthesis. Aldehyde **223** obtained had a typical aldehyde proton signal at 9.75 ppm in the ^1H NMR spectrum, and a carbonyl carbon signal at 202.4 ppm in the ^{13}C NMR spectrum, which were consistent with previous reports within the group.⁶⁰ It was important to mention that aldehyde **223** was not stable at room temperature, but when stored in freezer ($-18\text{ }^\circ\text{C}$), the compound was stable for over 6 months.



Scheme 64. Oxidation of alcohol **223**

Reagents and conditions: (a) $\text{SO}_3\cdot\text{Py}$, $i\text{Pr}_2\text{NEt}$, DMSO, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 1 h, 97%, *or* DMP, H_2O (catalytic), CH_2Cl_2 , rt, 2 h, 86%.

It was noteworthy that sometimes the Parikh–Doering reaction turned into dark red from the usual pale yellow colour. On these occasions, the yield of aldehyde **223** dreadfully decreased without recovery of the starting material. A literature search suggested the problem was caused by partial hydrolysis of $\text{SO}_3\cdot\text{Py}$ in production.⁹⁶ The ^1H NMR spectrum of a bottle of poor quality $\text{SO}_3\cdot\text{Py}$ in $\text{DMSO}-d^6$ clearly indicated two, rather than one, sets of pyridium signals present in the oxidant, which corresponded to the $\text{SO}_3\cdot\text{Py}$ complex and pyridinium

cation in pyridinium sulfuric acid respectively (**Figure 7**). The proton signals at 9.28 ppm, 8.66 ppm and 8.15 ppm belonged to $\text{SO}_3\cdot\text{Py}$, while the signals at 8.90 ppm, 8.52 ppm and 8.01 ppm corresponding to pyridinium cation were from the decomposed reagent. In the ^1H NMR spectrum, the two sets had a ratio of 4:3, which meant approximately 43% of the reagent had decomposed. This bottle of oxidant did not afford any desired aldehyde in a test reaction. It was suggested the decomposed reagents could be reactivated by stirring with extra equivalents of pyridine before use.⁹⁶ The previous unreacted $\text{SO}_3\cdot\text{Py}$ was stirred with equimolar pyridine before being used in the Parikh–Doering oxidation and it afforded a good yield over 80% of aldehyde **223**.

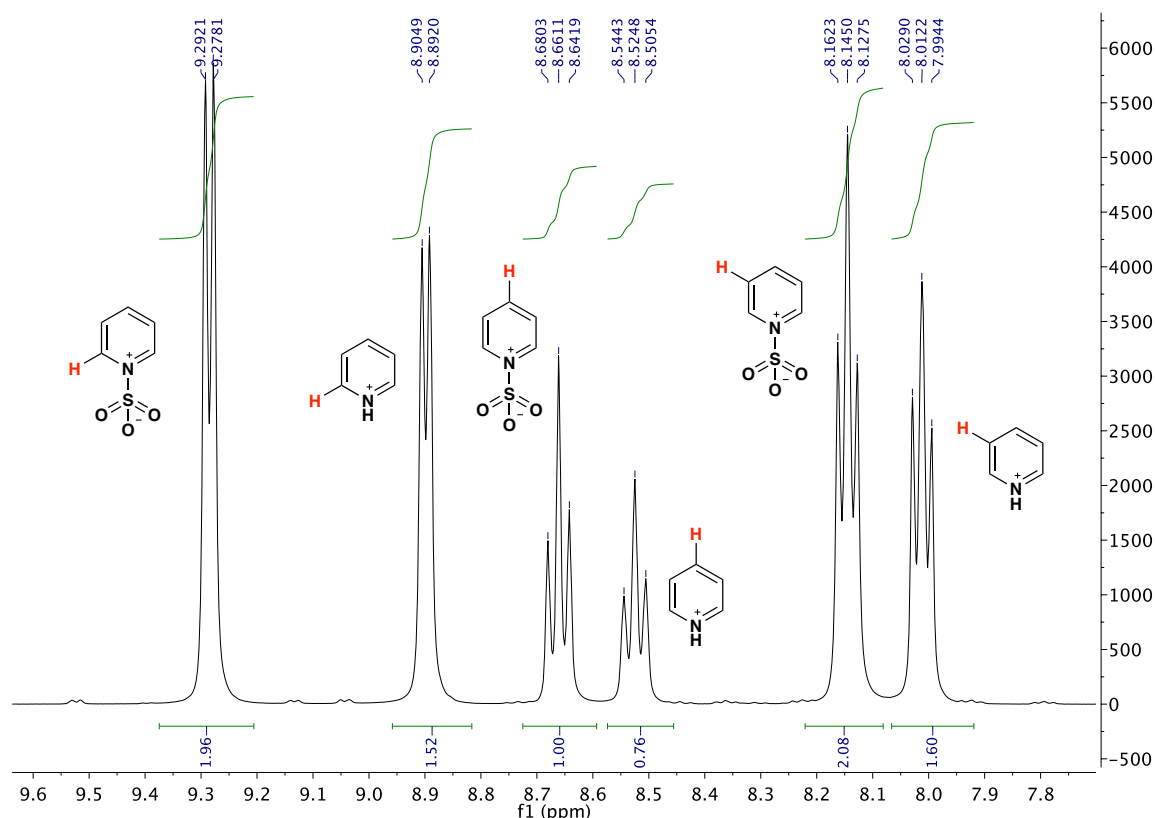
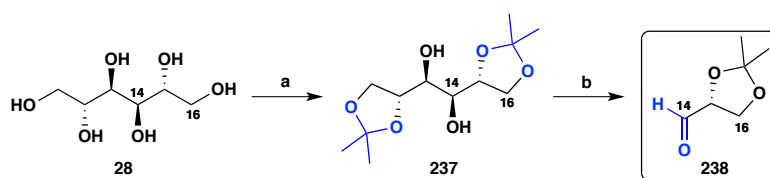


Figure 7. ^1H NMR spectrum of partially hydrolysed $\text{SO}_3\cdot\text{Py}$

The revised route to synthesis of the aldehyde **223** takes 6 steps with an overall yield of 49% ignoring recycling unreacted starting material and side products in the *mono*-benzylation of diol **230**, and on average the yield was 89% for each step. Comparatively, the old route with 4 steps has an overall yield of 18%, on average 65% for each step.⁶⁶ The revised route contains two extra steps, but much more efficient overall. It also avoids recycling large percentage of unreacted starting material and re-subjecting it to the same reaction. With the new route, aldehyde **223** was effectively prepared on a 20 g scale in 4 days.

2.2.2 Synthesis of the C11–C16 alkyne **224**

With aldehyde **223** in hand, the next object of this project was to prepare alkyne **224** on a multigram scale, following a previous route reported by the Donohoe group with some minor optimisation.⁶⁰ The synthesis of alkyne **224** started with the commercially available aldehyde **238**. This aldehyde was expensive and unstable to store. Consequently, it was prepared from D-mannitol **28** in two steps according to known literature procedures.⁶⁶ Treatment of D-mannitol **28** with 2,2-dimethoxypropane and a catalytic amount of *p*TSA afforded *bis*-acetonide **237** in 60% yield at 50 g scale (**Scheme 65**). Periodate cleavage of **237** gave glyceraldehyde **238** in an excellent yield of 92% at 20 g scale. Aldehyde **238** was purified by vacuum distillation (b.p. 52 °C at 15 mbar), but the crude aldehyde was pure enough to use in the next step.⁶⁶ The isolated aldehyde **238** has a typical aldehyde proton shift at 9.72 ppm in the ¹H NMR spectrum and a corresponding carbonyl carbon shift at 201.8 ppm in the ¹³C NMR spectrum, which are consistent with those previously reported.⁶⁶

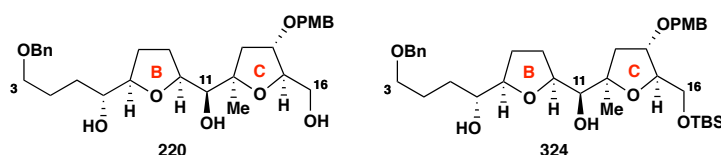


Scheme 65. Synthesis of (*R*)-isopropylideneglyceraldehyde **238**

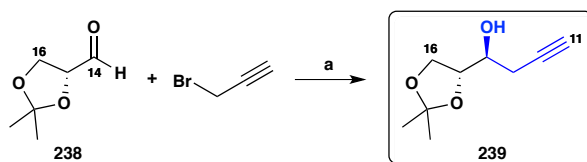
Reagents and conditions: (a) 2,2-dimethoxypropane, *p*TSA, DMSO, rt, 18 h, 60%; (b) NaIO₄, CH₂Cl₂, 0 °C to rt, 2 h, 92%.

Following the reported route, the next step is a diastereoselective Barbier-type propargylation of glyceraldehyde **238** in favour of the Felkin–Anh model predicted product **239**.^{66**} Treatment of aldehyde **238** with *in situ* formed propargylic zinc bromide afforded a disappointing yield of 30–40% of the desired alcohol **239**, while TLC of the reaction crude clearly indicated the product was the only component in the reaction mixture (**Scheme 66**). The inconsistency in TLC observation and isolated yield suggested that some of the product decomposed during purification. Carefully flushing the silica with a large excess of EtOAc provided a small portion of another unknown oil, which had a peak at 153.1 Da in mass spectrometry, corresponding to $[M + Na^+]$ of the desired product with the loss of the acetonide-protecting group. In the ¹H NMR spectrum, the acetonide CH₃ peaks at 1.36 ppm and 1.30 ppm had disappeared as well. This evidence suggested that the desired product had

** The absolute stereochemistry at C14 is not important because this hydroxyl group will be oxidized to a ketone in PTX-4. However, NOESY of *bis*-THF compounds **220** and **324** suggested that the C13-*H* and the C14-*H* (from D-mannitol) are *anti* to each other (See Experimental for assignments of the ¹H NMR spectra of these compounds and Appendix for their NOESY spectra).



lost acid labile acetonide protecting group during purification. It was suspected that the batch of silica used was too acidic. In the next purification, 1% Et₃N was used to neutralise the silica and the eluent for flash column chromatography, and the yield was increased to 72%. The isolated product has an alkyne proton shift at 2.04 ppm in the ¹H NMR spectrum, and a terminal alkyne carbon shift at 71.2 ppm in the ¹³C NMR spectrum. The data are consistent with those previously reported.⁶⁰



Scheme 66. Propargylation of aldehyde **238**

Reagents and conditions: (a) Zn, propargyl bromide, THF, 0 °C, then **238** in THF, 0 °C to rt, 8 h, 72%, 6:1 d.r..

It was noticed that alcohol **239** obtained from propargylation was contaminated with two impurities, which were difficult to purify by flash column chromatography. The major impurity with chemical shifts at 70.8 ppm (C11'), 70.2 ppm (C14') and 65.9 ppm (C16') in the ¹³C NMR spectrum was assigned to the C14 epimer of alcohol **239** (**Figure 8**, compound **14-R-239**). The minor impurity with an allenic carbon chemical shift at 207.7 ppm was assigned to the allene **240** (**Figure 8**). Propargyl bromide would partially isomerise to an allene in the presence of zinc, so there could be a competition between propargylation and allenylation under the reaction conditions.⁹⁷ The diastereoselectivity of this literature known reaction, which was under Felkin–Anh model control preferred to form the 14-*S*-alkyne **239**, but the C14 epimer **14-R-239** was also formed.^{98, 99} While the formation of allene **240** was

less than 5% by analysis of both ^1H and ^{13}C NMR spectra, the diastereoisomer **14-*R*-239** was typically formed in 10–20%. Although the C14-*OH* group was to be oxidised to a ketone in PTX-4, the presence of a diastereoisomer in the synthetic sequence complicated the NMR spectra, and a reliable method to minimise the *anti*-Felkin–Anh product was required.

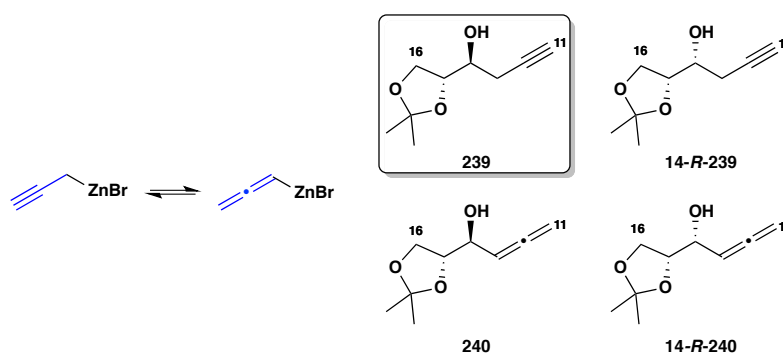


Figure 8. Possible isomers from the Barbier-type propargylation

The optimisation of the propargylation of aldehyde **238** to increase diastereoselectivity is summarised in **Table 5**. Following the reported procedure, the addition of aldehyde **238** was carried out at 0 °C with a 6:1 d.r. and a good yield of 72% (Entry 1). The yield and selectivity got worse if the addition was performed at room temperature (53%, 4:1 d.r., Entry 2). A further detrimental yield and selectivity was observed if Mg was used instead of Zn (48%, 3:1 d.r., Entry 3). The highest diastereoselectivity (10:1) was obtained when an *in situ* formed organolithium reagent in combination with TMEDA was used as the nucleophile (Entry 4).⁹⁷ However, this reaction only afforded a low yield of 43% even after optimisation. It was ascribed to the instability of alcohol **239** under strongly basic conditions.^{††} The best balance

^{††} Treatment of alcohol **239** with *n*BuLi (2 eq) in THF at room temperature resulted in the decomposition of starting material.

of yield and selectivity was obtained when aldehyde **238** was added dropwise to the reaction solution at $-78\text{ }^{\circ}\text{C}$ (76%, 8:1 d.r., Entry 5). In all the entries *ex supra*, the 14-*S*-epimer **239** was the major product. The presence of both diastereoisomers was visualised by the ^{13}C NMR spectra. C11 and C16 were at 71.2 ppm and 70.1 ppm respectively in the major diastereoisomer **239**, while they were at 70.8 ppm and 70.2 ppm in the minor isomer **14-*R*-239**. The exact ratio of C14 epimer and allene were determined by analysing the ^{19}F NMR of the (*R*)-Mosher's ester of **239** after purifications. The high yield and selectivity was maintained at a 20 g scale.

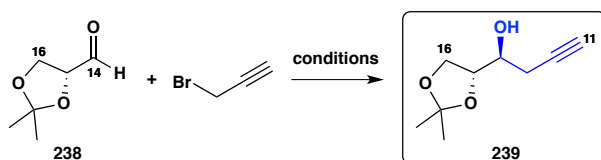
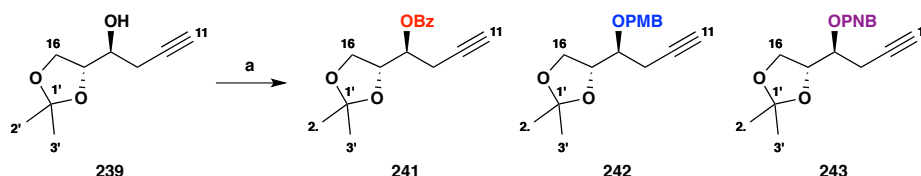


Table 5. Propargylation of aldehyde 238

Entry	Conditions	Results
1	Zn, THF, 0 $^{\circ}\text{C}$ to rt	72%, 6:1 d.r.
2	Zn, THF, rt	53%, 4:1 d.r.
3	Mg, I ₂ , HgCl ₂ , Et ₂ O, 0 $^{\circ}\text{C}$ to rt	48%, 3:1 d.r.
4	<i>n</i> BuLi, TMEDA, Et ₂ O, $-78\text{ }^{\circ}\text{C}$ to rt	43%, 10:1 d.r.
5	Zn, THF, $-78\text{ }^{\circ}\text{C}$ to rt, dropwise addition of aldehyde	76%, 8:1 d.r.

Giving the difficulties in purification of alcohol **239** by flash column chromatography, we checked to see if the derivatives of **239**, e.g., benzoate ester **241**, PMB ether **242**, and PNB ether **243**, could be purified from the C14 epimer.¹⁰⁰ Alcohol **239** was converted to its

derivatives with BzCl, PMBCl and PNBCl in excellent yields respectively (**Scheme 67**). However, none of them had a good separation ($R_f > 0.05$) with their corresponding C14 epimers in common solvent systems.

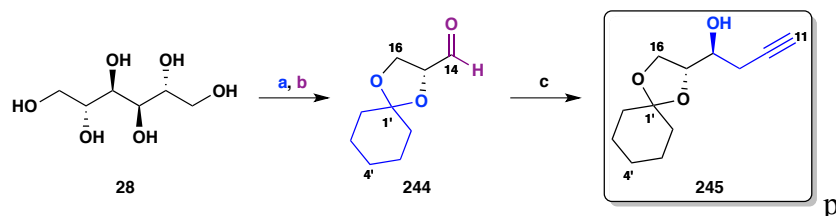


Scheme 67. Synthesis of the derivatives of **241**, **242** and **243**

Reagents and conditions: (a) BzCl, Et₃N, DMAP, CH₂Cl₂, 0 °C to rt, 10 h, 90% **241**; or NaH, PMBCl, TBAI, THF, 0 °C to 60 °C, 16 h, 100% **242**; or PNBCl, Et₃N, CH₂Cl₂, rt, 16 h, 87% **243**.

Changing the acetonide protecting group of the C15–C16 diol moiety might have allowed the separation of C14 epimers. It was reported that in the propargylation of (*R*)-cyclohexylidene-glyceraldehyde **244**, the C14 epimers in the product could be separated by flash column chromatography.^{98, 99} Alcohol **245** was prepared according to a literature known procedure from D-mannitol **28** (**Scheme 68**).^{98, 99, 101, 102} Treatment of D-mannitol **28** with cyclohexanone in the presence of trimethylorthoformate and boron trifluoride diethyl etherate afforded protected D-mannitol in 69% yield. Periodate cleavage of protected D-mannitol gave (*R*)-cyclohexylidene-glyceraldehyde **244** in near quantitative yield. The crude aldehyde **244** was used in the propargylation without further purification to afford alcohol **245** in 80% yield with 8:1 d.r.. The structure of alcohol **245** was confirmed by comparison NMR spectra with literature data.⁹⁸ Unfortunately, following the literature

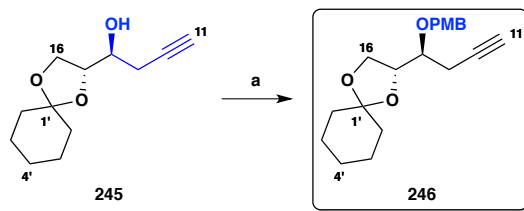
method, alcohol **245** could not be fully separated from its C14 epimer by flash column chromatography.^{98, 99}



Scheme 68. Synthesis of (*S*)-1-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-yn-1-ol **245**

Reagents and conditions: (a) trimethylorthoformate, cyclohexanone, $\text{BF}_3 \cdot \text{OEt}_2$, DMSO, rt, 12 h, 69%; (b) NaIO_4 , NaOH, H_2O , EtOAc, rt, 2.5 h, 98%; or NaIO_4 , TBAB, H_2O , Et_2O , rt, 3 h, 97%; (c) Zn, propargyl bromide, THF, 0 °C to rt, 8 h, 80%, 8:1 d.r..

Although propargylation of (*R*)-cyclohexylideneglyceraldehyde **244** afforded slightly better yield and selectivity under the same conditions (80%, 8:1 d.r. versus 72%, 6:1 d.r.), it was noticed that alcohol **245** was not as reactive as **239** in the next PMB protection step (**Scheme 69**). Treatment of alcohol **245** with PMBCl in the presence of NaH and TBAI at reflux did not provide a high conversion of the starting material after 24 hours. After adding extra equivalents of NaH and PMBCl, the reaction was stirred for another 10 hours, but it did not improve. A disappointing yield of 36% was obtained for the isolated product **246**. Therefore, the whole route based on the cyclohexylidene protecting group was terminated.



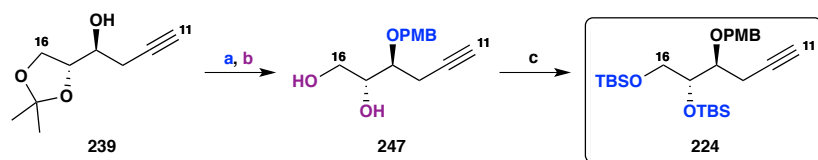
Scheme 69. Synthesis of PMB protected alcohol **246**

Reagents and conditions: (a) PMBCl, NaH, TBAI, THF, 0 °C to 75 °C, 34 h, 36%.

In summary, the homopropargylation of aldehyde **238** afforded the best balance of yield and selectivity when aldehyde **238** was added dropwise to the reaction solution at -78 °C. The minor isomers, C14 epimer **14-R-239** was not readily separable from alcohol **239**. Considering the C14-*OH* group would be oxidised to a ketone moiety in PTX-4, it was decided to carry on the synthesis with the minor impurities present in the compound.

Alcohol **239** was converted to *bis*-TBS alkyne **224**, for a Carreira alkynylation, in three steps based on the previous route reported by the Donohoe group (**Scheme 70**).⁶⁰ Treatment of alcohol **239** with NaH and PMBCl in the presence of catalytic amount of TBAI afforded PMB ether **242** in quantitative yield. Ether **242** was subjected to HCl at slightly elevated temperature (40 °C) to remove the acetonide in a good yield of 82%. TBS protection of diol **247** afforded *bis*-TBS alkyne **224** in quantitative yield. All three steps were scaled up to 20 g without affecting the yield. The structure of alkyne **224** was confirmed by NMR spectra. Alkyne **224** had a pair of characteristic diastereotropic PMB-*CH*₂ signals at 4.64 ppm and 4.56 ppm respectively in ¹H NMR spectrum, and two singlets both at 0.90 ppm corresponding to the two TBS *t*Bu protons. The terminal alkyne triplet ($J=2.6$ Hz) at

1.98 ppm was also observed. The NMR data of *bis*-TBS ether **224** was consistent with those previously reported.⁶⁶



Scheme 70. Synthesis of *bis*-TBS compound **224**

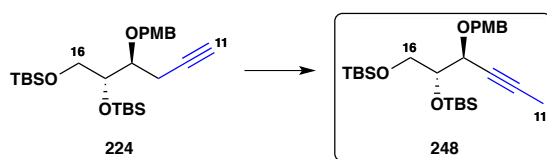
Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 0 °C to 60 °C, 16 h, 100%; (b) HCl, MeOH, H₂O, 40 °C, 20 h, 82%; or AcOH, H₂O, 40 °C, 16 h, 72%; (c) TBSCl, imidazole, CH₂Cl₂, 0 °C to rt, 18 h, 99%; or TBSCl, imidazole, DMF, 0 °C to rt, 12 h, 90%.

In summary, alkyne **224** was prepared in 6 steps with an overall yield of 34%, an average 84% for each step. All of the steps were carried out at a 20 to 50 g scale to allow an efficient synthesis of 50 to 60 g alkyne **224** from commercially available starting materials in one week.

2.2.3 An unexpected isomerisation of alkyne **224**

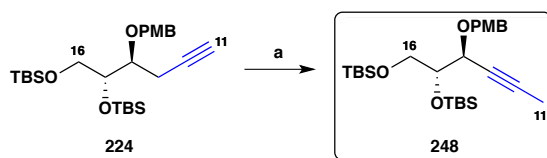
It is known that internal alkynes are thermodynamically more stable than their terminal regioisomers. The energy barrier for the isomerisation is high, so basic condition and elevated temperatures are normally required for isomerisation of a terminal alkyne to an internal alkyne.¹⁰³ Therefore, we assumed that the fully protected alkyne **224** was a stable compound to store until one batch of freshly prepared alkyne **224** lost its reactivity in the next alkynylation reaction. TLC indicated that a new compound was formed in the sample with a

close R_f value to alkyne **224**, but they had different colours when stained with vanillin. Mass spectrometry of this sample showed that the new compound had the same molecular weight as alkyne **224**, with the $[M + Na^+]$ peak at 501.3 Da. It was likely to be an isomer of alkyne **224**. In the ^1H NMR spectrum, the most obvious changes included the disappearance of the alkyne proton triplet at 1.98 ppm and C(13) H_2 multiplets between 2.59 ppm to 2.43 ppm. It was also observed that a new doublet at 1.88 ppm corresponding to 3 H appeared in the spectrum. These changes suggested the terminal alkyne **224** had isomerised to its internal alkyne isomer **248** (Scheme 71); this isomerisation explained the loss of reactivity in the alkynylation reaction.



Scheme 71. Unexpected isomerization of alkyne **224**

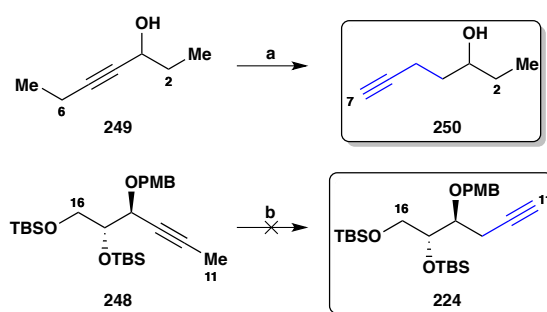
To avoid the isomerisation of terminal alkyne **224** to internal alkyne **248**, it was important to investigate the conditions for this process. Terminal alkyne **224** was dissolved in Et_2O and treated with NaOH (Scheme 72). TLC indicated that most of the starting material was consumed in 10 minutes. The ^1H NMR spectrum proved that the major product was the internal alkyne **248**. A possible explanation for what happened to the isomerised sample was that some of the glassware used might contain $tBuOK$ residues from the base bath, though there was no solid evidence. An acid rinse of the glassware with 1 M HCl as a precaution prevented this isomerisation happening again.



Scheme 72. Isomerisation of alkyne **224**

Reagents and conditions: (a) NaOH, Et₂O, rt, 10 min, 95%.

To convert the isomerised alkyne **248** back to **224**, an alkyne zipper reaction was tested (**Scheme 73**).^{104, 105} Model internal alkyne **249** was subjected to *in situ* formed potassium 3-aminopropyl amide (KAPA) in 1,3-diaminopropane to afford terminal alkyne **250** in an average yield of 59%. In the ¹H NMR spectrum, C(7)H₃ at 1.13 ppm disappeared and a new terminal alkyne signal was observed at 1.98 ppm. When the same conditions were applied to internal alkyne **248**, the reaction disappointingly resulted in the decomposition of starting material without isolating of any product or side products (**Scheme 73**). It was not possible to convert internal alkyne **248** to its regioisomer **224** *via* the alkyne zipper reaction.



Scheme 73. Alkyne zipper reaction

Reagents and conditions: (a) Li, H₂N(CH₂)₃NH₂, *t*BuOK, rt, 12 h, 59%; (b) Li, H₂N(CH₂)₃NH₂, *t*BuOK, rt, 12 h,

decomposition of starting material.

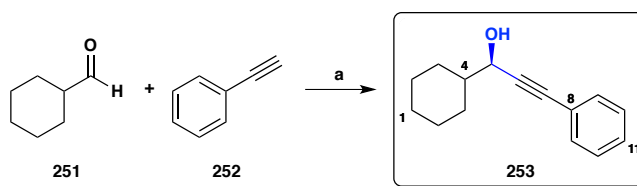
In summary, terminal alkyne **224** isomerised to internal alkyne **248** under basic conditions, and it was difficult to convert the isomerised compound **248** back to alkyne **224**.

2.2.4 Model study on the Carreira alkynylation reaction

With high yielding multigram scale (>10 g) syntheses to both aldehyde **223** and alkyne **224**, it was possible to study the Carreira asymmetric alkynylation reaction between them. Considering the difficulties in this reaction reported in literature, in particular from previous unsuccessful optimisations in our group, the reaction was tested on two model substrates first.^{66, 85, 106-108} Cyclohexaldehyde **251** and phenylacetylene **252** were chosen as model substrates because they were widely used in the original research reported in Carreira's publications with an excellent yield over 90%.^{91, 93} It was important to reproduce the yield and selectivity before moving on to the real system.

A series of reactions were carried out under slightly different conditions and the results are summarised in **Table 6**. Alkyne **252** was treated with Et₃N and Zn(OTf)₂ to generate a chiral zinc acetylide, which underwent nucleophilic attack to aldehyde **251** to give propargylic alcohol **253** enantioselectively (**Table 6**). Commercially available reagents without any further purification failed to form a heterogeneous solution after addition of all the reactants and only afforded trace amount of desired product **253** (Entry 1). The reagents coagulated to blocks in the reaction mixture, which proved it was highly moisture sensitive. This was against Carreira's early controversial report in which the reaction with these two particular substrates was not moisture sensitive.^{93, 106} To avoid any influence from moisture, Zn(OTf)₂

was strictly dried at 120 °C under high vacuum for 2 hours until a free flowing fine powder was formed, and the yield of the reaction was increased slightly to 28% (Entry 2). A further experiment using freshly distilled Et₃N instead of commercially available anhydrous Et₃N did not give any improvement (Entry 3). This indicated that the dryness of the Et₃N used was not the determining factor for the low yield. A literature search showed that agreement had been reached that rigorous drying of Zn(OTf)₂ was compulsory for the Carreira alkynylation reaction.^{60, 85, 109-112} Based on this argument, Zn(OTf)₂ was further strictly dried by either azeotropic distillation with PhMe three times or heated under high vacuum for 12 hours, and the more strictly dried Zn(OTf)₂ provided a better yield of up to 52% (Entry 4, 5). It was observed that the unreacted alkyne was isolated, but the unreacted aldehyde was not observed in the crude product. The missing aldehyde was proposed to participate in a self-aldol reaction in the presence of base. To solve the problem, aldehyde **251** was added over 2 hours *via* a syringe pump so as to be maintained at a low concentration, and afforded a good yield of 72% (Entry 6). It was documented that using a sterically hindered Hünig base instead of Et₃N reduced undesired epimerisation in the late stage of natural product synthesis.^{112, 113} In case that the epimerisation might happen on alkyne **224** for the real system, using Hünig base instead of Et₃N was tested on the model substrates with a good yield of 81% (Entry 7). It was also observed that a longer reaction time (20 hours) was required for a better yield of 89% at high dilution of aldehyde **251** (Entry 8). After optimisations, the yield for the model reaction was consistent with those reported in literature ranging from 90% to 94%.^{91, 93} The product had a characteristic chemical shift at 4.38 ppm in the ¹H NMR spectrum corresponding to the propargylic proton.⁹¹



Reagents and conditions: (a) Cyclohexaldehyde (1.0 eq), phenylacetylene (1.2 eq), Zn(OTf)₂ (1.1 eq), Et₃N or *i*Pr₂NEt (1.2 eq), (+)-*N*-methylephedrine (1.2 eq), PhMe (0.3 M), rt.

Table 6. Model Studies on Carreira Reaction^{†‡, 91}

Entry	Conditions	Results
1	Commercial reagents without purifications	<10%
2	Entry 1, drying Zn(OTf) ₂ for 2 h at 120 °C	28%
3	Entry 2, distilled Et ₃ N on CaH ₂	25%
4	Azeotropic distillation of Zn(OTf) ₂ and anhydrous Et ₃ N	46%
5	Drying Zn(OTf) ₂ 12 h at 120 °C and anhydrous Et ₃ N	52%
6	Entry 5, add aldehyde 251 over 2 h	74%
7	Entry 6, Hünig base	81%
8	Entry 6, 20 h reaction	89%

In summary, model studies found three crucial factors for a successful Carreira alkynylation reaction. Firstly, the Zn(OTf)₂ must be rigorously dried; the aldehyde should be kept at high dilution in the reaction mixture, and finally the reaction required longer time to complete than

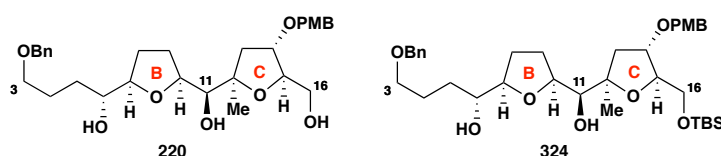
^{†‡} The different conditions tested did not affect the enantioselectivity of the Carreira reaction. In all the entries, an over 90% *ee* was maintained. To increase the efficiency of model study, all the *ee* were roughly determined by Mosher's ester analysis and comparing the specific rotations with literature value that the Carreira group previously reported.⁹¹

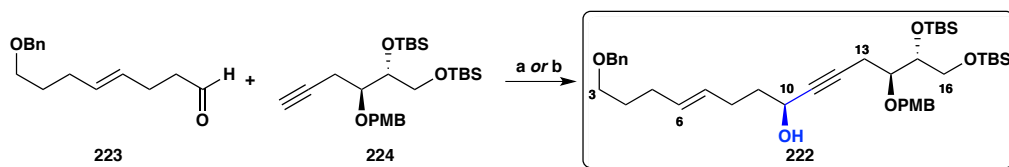
originally reported.^{91, 93} Sterically hindered Hünig base provided a better result compared to Et₃N by reducing α -deprotonation of the cyclohexaldehyde.

2.2.5 Carreira reaction between aldehyde **223** and alkyne **224**

Disappointingly, when the optimised conditions *vide supra* was applied to aldehyde **223** and alkyne **224**, it only afforded 16% of propargylic alcohol **222** with Et₃N and 9% with Hünig base (**Scheme 74**).^{§§} The slightly better yield for Et₃N might be rationalised by the crowded steric environment on alkyne **224** disfavours deprotonation with bulky base. These yields were significantly lower than that observed for the model substrates (over 80%), which meant the conclusions drawn from model studies were not the exclusive factors to perform a successful Carreira reaction. Further investigations on the Carreira reaction between aldehyde **223** and alkyne **244** were required to improve the yield.

§§ The absolute stereochemistry at C10 determined by comparing the ¹³C NMR spectra to the literature data, which was supported by the *nOe* enhancements of *bis*-THF compounds **220** and **324** after steps (See Experimental for assignments of the ¹H NMR spectra of these compounds and Appendix for their NOESY spectra).⁶⁶ C10-*H*, C12-*Me* and C15-*H* (from D-mannitol) are *syn* to each other based on the *nOe* effect.



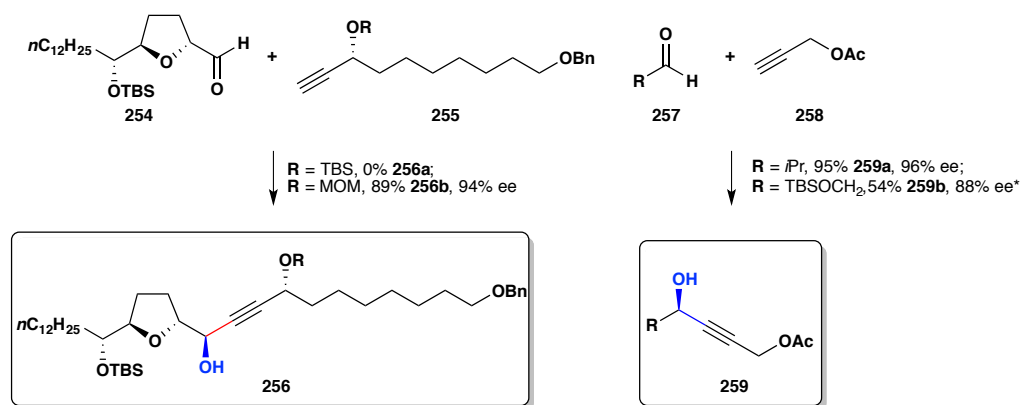


Scheme 74. Carreira alkynylation between aldehyde **223** and alkyne **224**

Reagents and conditions: (a) aldehyde **223** (1.0 eq, slow addition as a PhMe solution over 2 hours), alkyne **224** (1.2 eq), Zn(OTf)₂ (1.65 eq), Et₃N (1.2 eq), (–)-NME (1.2 eq), PhMe (0.3 M), rt, 16 h, 15%; *or* (b) aldehyde **223** (1.0 eq, slow addition as a PhMe solution over 2 hours), alkyne **224** (1.2 eq), Zn(OTf)₂ (1.65 eq), *i*Pr₂NEt (1.2 eq), (–)-NME (1.2 eq), PhMe (0.3 M), rt, 16 h, 9%.

It was observed that only unreacted alkyne **224** was detected and isolated from the crude reaction mixture. This observation was the same as in the model reactions with low yield (**Table 6**, Entry 1-5). It was postulated that the aldehyde **223** was more rapidly consumed in side reactions because the desired pathway was sluggish. In the literature, Carreira and Tanaka had reported a similar phenomenon separately (**Scheme 75**).^{92, 114-116} It was found that bulky substituents close to the reaction sites on both alkyne and aldehyde had a negative effect on the rate, yield and selectivity. Sterically bulky groups such as TBS fully sequestered the reaction while less hindered groups such as MOM allowed the reaction to proceed smoothly. The reactivity and diastereoselectivity were also affected by the spatial relationship between chiral substituents close to the reaction site.^{111, 115} There was no detailed mechanistic study on the Carreira reaction to the best of our knowledge, but it was widely believed that the reaction involved the formation of a ligand-coordinated chiral zinc alkynylidene.^{117, 118} There were “matched” and “mismatched” chiral substituents near the

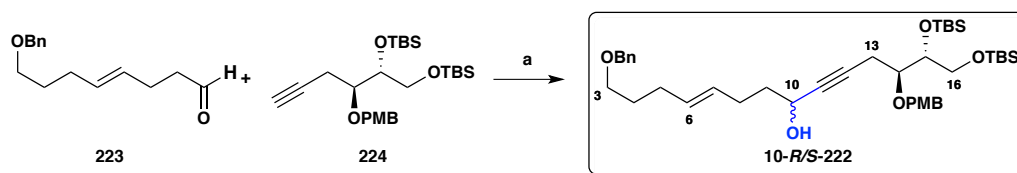
reaction site.^{114, 115} Although the inherent selectivity of the chiral ligand dominated the outcome, the “mismatched” substrates retarded the rate and selectivity of the reaction.



Scheme 75. Steric influence on Carreira reaction^{92, 116}

*This reaction required 2 equivalents of alkyne and longer time.

The substrate preference in our case was proved in a non-selective *n*BuLi alkynylation reaction, in which our desired product was relatively disfavoured compared to its C10 epimer (40:60 d.r., **Scheme 76**).



Scheme 76. non-Selective alkynylation between aldehyde **223** and alkyne **224**

Reagents and conditions: (a) aldehyde **223** (1 eq), alkyne **224** (1.5 eq), *n*BuLi (1.2 eq), THF, -78°C to rt, 12 h,

93%, 40:60 d.r. favoured (*S*)-epimer at C10.

Therefore, it was decided to use large excess of alkyne, higher concentrations of reactants and longer reaction times to increase the conversion of aldehyde **223** and the yield of this reaction. Further optimisations on the Carreira alkynylation reaction between aldehyde **223** and alkyne **224** are summarised in **Table 7**. Aldehyde **223** was diluted with PhMe, and the addition was carried out over 12 hours *via* a syringe pump; this afforded an extra 20–30% yield compared to dropwise addition over 15 minutes (Entry 1-4). A large excess of alkyne **224** and a high concentration of reactants were needed in order to increase the reaction rate of the desired pathway. The concentration was recalculated according to Tanaka's suggestion to maintain $\text{Zn}(\text{OTf})_2$ at 0.45 mmol/mL.¹¹⁵ The yield of the reaction was increased from 40% to 96% when more equivalents of alkyne **224** was used (Entry 2, 4, 5). The reaction afforded an excellent yield of 96% with 3 eq alkyne **224** (Entry 5). The high yield was reproducible when the reaction was scaled up from 100 mg scale to 20 g scale, and over 85% of unreacted alkyne **224** was recovered after purification (Entry 5, 6). Propargyl alcohol **222** had a chemical shift at 4.35 ppm in the ^1H NMR spectrum, corresponding to C10-*H*. The aldehyde proton at 9.75 ppm and the terminal alkyne proton at 1.98 ppm both disappeared after the reaction. ^{19}F NMR of the (*R*)-Mosher's ester of propargyl alcohol **222** indicated a 93:7 d.r. in favour of the desired product was obtained on 20 g scale reaction, which was consistent with those previously reported (94:6 d.r.) by the Donohoe group.⁶⁰



Table 7. Optimisation of the Carreira reaction in real system ***

Entry	Aldehyde	Alkyne	Yield
1	1 eq	1.2 eq	15%
2	1 eq, Slow addition over 12 h	1.2 eq	40%
3	1 eq	2 eq	43%
4	1 eq, Slow addition over 12 h	2 eq	71%
5	1 eq, Slow addition over 12 h	3 eq	96%
6	1 eq (20 g scale), Slow addition over 12 h	3 eq	87%

Reagents and conditions: aldehyde **223** (1.0 eq), alkyne **224** (x eq), Zn(OTf)₂ (1.2x eq), Et₃N (1.2x eq),

(-)-NME (1.1x eq), PhMe (0.45 M regarding to Zn(OTf)₂), rt.

In summary, the yield of the Carreira alkyne-aldol reaction between aldehyde **223** and alkyne **224** was successfully improved from 40% to 96% (87% on 20 g scale) without sacrifice of the high diastereoselectivity. It was found that using higher equivalents of alkyne **224**, maintaining a high concentration of reagents, and keeping aldehyde **223** at low concentration were important to obtain a good yield.

*** ¹⁹F NMR of the (*R*)-Mosher's ester of propargyl alcohol **222** indicated a d.r. between 92:8 to 96:4 were obtained in all the entries.

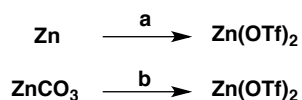
2.2.6 Further explorations on the Carreira reaction

During our research, it was observed the quality of $\text{Zn}(\text{OTf})_2$ and (-)-NME were crucial to reproduce the high yield and selectivity. Failure to purify the reagents resulted in lower yield and longer reaction times.

It was reported that different sources of $\text{Zn}(\text{OTf})_2$ gave different results.^{106, 110, 114-116} Baldwin further pointed out that it was ascribed to the different particle size and surface structure of $\text{Zn}(\text{OTf})_2$.¹⁰⁶ In our repeat experiments, $\text{Zn}(\text{OTf})_2$ obtained from different sources were slightly different in formulation. Some were fine powders, while the others are small blocks. If $\text{Zn}(\text{OTf})_2$ was not rigorously dried at elevated temperature under high vacuum (12 hours at 0.05 mbar), the solids in the reaction mixture coagulated and only trace amounts of product were formed (**Table 6**, Entry 1). However, activated $\text{Zn}(\text{OTf})_2$ from different sources did not show any difference in the reaction. In our experiments, $\text{Zn}(\text{OTf})_2$ from Sigma-Aldrich, Alfa Aesar and TCI were used and they all provided similar results.

Various experimental procedures reported $\text{Zn}(\text{OTf})_2$ must be heated at high temperature (120 °C to 145 °C) for long time (7 hours to 16 hours) under high vacuum (<0.1 mbar) to be fully activated, and it was claimed that this process would remove the “moisture” present in the solid. The argument is not convincing because water’s boiling point is below 0 °C at 0.1 mbar. It must be another high boiling point impurity that is present in commercially available $\text{Zn}(\text{OTf})_2$ that needs to be removed. Literature procedures suggested that $\text{Zn}(\text{OTf})_2$ was prepared from treating Zn or ZnCO_3 with trifluoromethanesulfonic acid in MeCN or

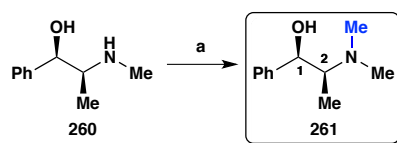
MeOH (**Scheme 77**).^{119, 120} Considering the production process, the impurity in Zn(OTf)₂ was more likely to be the excess acid residues (TfOH, b.p. 162 °C at 1 atm).



Scheme 77. Preparation of Zn(OTf)₂

Reagents and conditions: (a) TfOH, MeCN, 24 h, 50%;¹²⁰ (b) TfOH, MeOH, rt, 0.33 h, *then* reflux, 2 h, 98%.¹¹⁹

Once three equivalents of reagents were used, the reagents cost of (–)-NME was significantly increased. It would be helpful if (–)-NME could be prepared from a cheaper precursor. Treatment of (1*R*, 2*S*)-(–)-ephedrine **250** with formaldehyde and formic acid afforded (–)-NME in quantitative yield, and the cost of (1*R*, 2*S*)-(–)-ephedrine was 90% cheaper than (–)-NME.¹²¹ (**Scheme 78**, ~£0.5/g *versus*. ~£6/g from Sigma-Aldrich) It was worthwhile to prepare this reagent for stoichiometric reactions. As (–)-NME is a highly hygroscopic solid, the reaction failed to form a good heterogeneous solution when wet (–)-NME was used after addition of reagents, in which case the reaction took more time to complete. Recent reports from the Smith group suggested that NME should be azeotropically distilled with PhMe in advance.¹⁰⁹ However, the small-crystallised solid became an amorphous sticky powder after azeotropic distillation, and it was difficult to weigh or transfer. We were pleased to find that leaving (–)-NME under high vacuum for 12 hours at room temperature before the reaction would provide enough dryness.



Scheme 78. Preparation of (-)-*N*-methylephedrine

Reagents and conditions: (a) HCHO (37 wt% solution in H₂O, 6 eq), HCOOH (10 eq), 0 °C to 90 °C, 12 h, 99%.

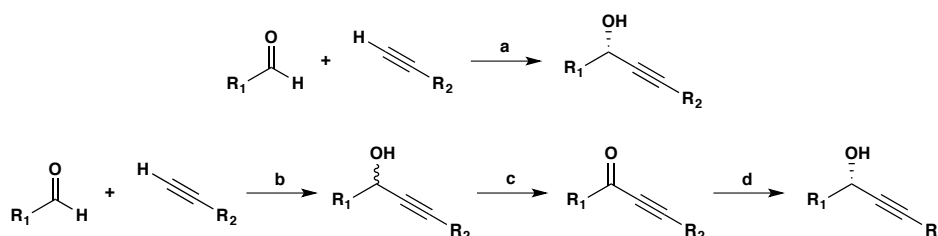
Commercially available anhydrous Et₃N was used in the Carreira reaction because in model study Et₃N freshly distilled from CaH₂ did not give any better result (**Table 6**, Entry 3). The potential C10 epimerisation was not observed for propargyl alcohol **222** in NMR spectra, so there was no need to use sterically hindered Hünig base (more expensive) instead of Et₃N. PhMe was dried over activated 4 Å molecular sieves and filtered through an activated aluminium purification column. The quality was enough to afford good results in the reaction.

In summary, the other reagents that might affect the results of Carreira alkynylation reaction were investigated, in particular to Zn(OTf)₂ and (-)-NME. It was important to activate the Zn(OTf)₂ and dry (-)-NME properly to permit relative reaction time and yield.

2.2.7 Alternative routes to synthesis the chiral propargylic alcohol **222**

While optimisation of the Carreira reaction was in progress, parallel research on alternative methods to prepare the chiral propargylic alcohol **222** were also under investigation. Two possible alternative approaches were Shibasaki's catalytic indium alkynylation and an

indirect method using asymmetric reduction (**Scheme 79**). To the best of our knowledge, there was no report on natural product synthesis using Shibasaki's method up to date. In contrast, the indirect method involving asymmetric reductions of propargylic ketones, especially Corey–Bakshi–Shibata (CBS) reduction and Noyori's catalytic hydrogenation, were widely reported in the literature.¹²²⁻¹²⁴ We would like to study this indirect synthesis as a backup plan for the Carreira alkynylation reaction.



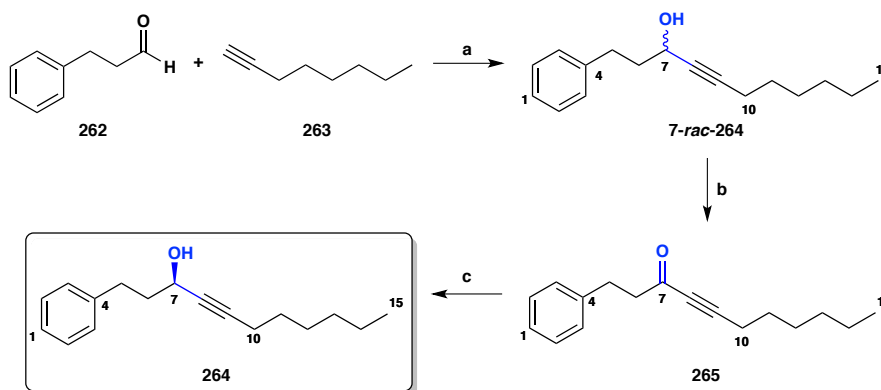
Scheme 79. Alternative routes to prepare chiral propargyl alcohol

Reagents and conditions: (a) InBr_3 , (*R*)-BINOL, Cy_2NMe , CH_2Cl_2 ,^{125, 126} (b) $n\text{BuLi}$, alkyne, THF, *then* aldehyde; (c) oxidation; (d) Diastereoselective reduction (Noyori, CBS, alpine-borane, etc).^{106, 127, 128}

A model study employing CBS reduction was performed on propargylic ketone **265**. Treatment of oct-1-yne **263** with $n\text{BuLi}$ followed by addition of hydrocinnamaldehyde **262** afforded propargylic alcohol **7-rac-264** in 78% yield, which was converted to ketone **265** using Parikh–Doering oxidation with a yield of 80% (**Scheme 80**). Treatment of ketone **265** with catecholborane in the presence of (*R*)-CBS catalyst provided chiral alcohol **264** in excellent yield and selectivity (99%, >20:1 e.r.)^{†††} The structure of the product was

^{†††} The absolute stereochemistry and *ee* of propargyl alcohol **264** was determined by comparing the ^{19}F NMR spectrum of the corresponding (*R*)-Mosher's ester with literature data.^{129, 130}

confirmed by the appearance of a triplet at 4.37 ppm corresponding to C(7)-*H* propargylic proton in the ^1H NMR spectrum.

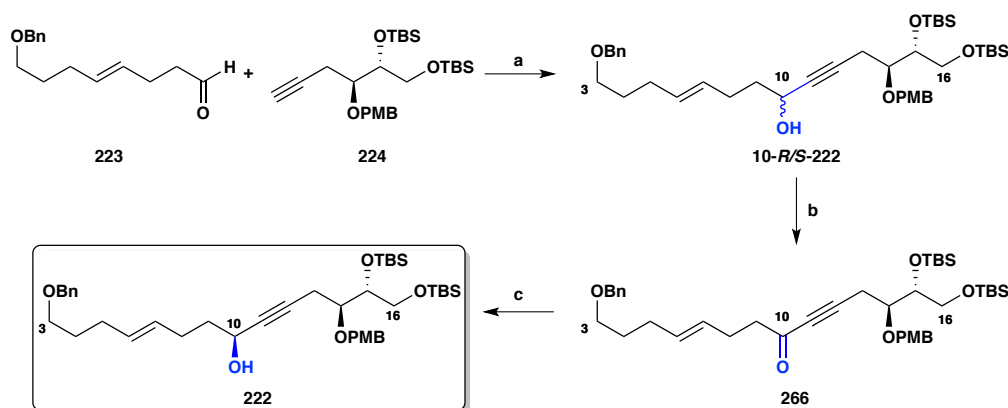


Scheme 80. Model study on indirect preparation of chiral propargyl alcohol

Reagents and conditions: (a) $n\text{BuLi}$, **263**, THF, $-78\text{ }^\circ\text{C}$, 0.33 h, then **262**, $0\text{ }^\circ\text{C}$, 0.33 h, 78%; (b) $\text{SO}_3\cdot\text{Py}$, $i\text{Pr}_2\text{NEt}$, DMSO, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 12 h, 80%; (c) *R*-CBS catalyst, catecholborane, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 5 h, 99%, 20:1 d.r..

With the promising results from model substrates, the procedure was then applied to aldehyde **223** and alkyne **224** (**Scheme 81**). Carefully controlled lithium acetylide formation at $-78\text{ }^\circ\text{C}$ allowed the addition to aldehyde **223** to give an excellent yield of 93%. Parikh–Doering oxidation of propargyl alcohol **10-(R/S)-222** afforded propargylic ketone **266** in 90% yield. However, CBS reduction of **266** failed to near to completion even with stoichiometric amount of (*R*)-CBS catalyst and elongated reaction time (12 h). The high selectivity (20:1 d.r. judged by ^{13}C NMR) was maintained but the yield was disappointingly low (27%). Propargylic ketone **266** was relatively inert under standard CBS conditions. As

the optimisation on the Carreira reaction had begun to give good yields over 80%, further investigation on the asymmetric reduction route was terminated.



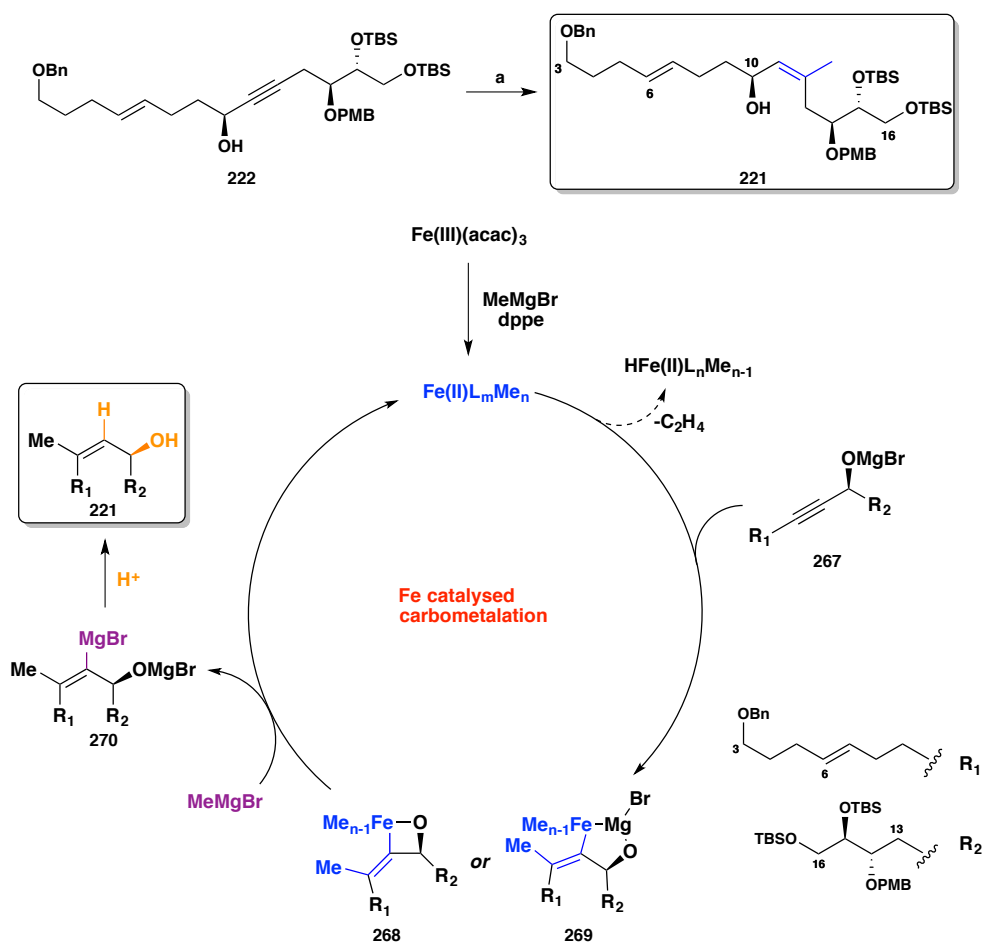
Scheme 81. Indirect method to prepare chiral propargyl alcohol **222**

Reagents and conditions: (a) **224**, *n*BuLi, THF, $-78\text{ }^{\circ}\text{C}$, 1 h, then **223**, rt, 12 h, 93%; (b) $\text{SO}_3\cdot\text{Py}$, *i*Pr₂NEt, DMSO, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$ to rt, 12 h, 90%; (c) *R*-CBS catalyst, catechoborane, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$ to rt, 12 h, 27%, 20:1 d.r..

2.2.8 Elaboration to the oxidative cyclisation precursor **228**

Propargylic alcohol **222** obtained from the Carreira alkynylation reaction was then converted to triol **228** in two steps. The C12-*Me* group was formed in a *trans*-carbometallation reaction reported by Ready.⁹⁰ Treatment of propargylic alcohol **222** with MeMgBr in the presence of a catalytic amount of $\text{Fe}(\text{acac})_3$ and 1,2-*bis*(diphenylphosphino)ethane (dppe) afforded *cis*-allylic alcohol **221** exclusively (**Scheme 82**).^{66, 90} The proposed mechanism for this reaction is depicted in **Scheme 82**. $\text{Fe}(\text{acac})_3$ undergoes ligand exchange and is reduced to Fe(II) upon addition of MeMgBr. Subsequent alkoxide-directed carbometallation affords vinyl iron species **268** or **269**, which reacts with further Grignard reagent to generate

carbometalated intermediate **270**, with regeneration of the iron catalyst. Aqueous workup of intermediate **270** with NH_4Cl (sat.) gives allylic alcohol **221**. The Donohoe group was the first to apply this methodology in total synthesis.⁶⁰ The structure of the product was confirmed by the ^1H NMR spectra. A new doublet appeared at 5.32 ppm corresponding to C(11)-H. The C(12)- CH_3 singlet was also observed at 1.74 ppm. These data were consistent with those previously reported.⁶⁰ The geometry of the newly formed double bond was also determined by NMR methods, which will be discussed later.



Scheme 82. *trans*-Carbometalation of propargylic alcohol **222**

Reagents and conditions: (a) MeMgBr (8 eq), Fe(acac)_3 (0.2 eq), dppe (0.2 eq), $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 18 h.

It was noticed that the yield of this carbometalation reaction varied from 50% to 80% without the isolation of other side products. A few experiments were performed to provide a reproducible yield and the results are summarised in **Table 8**. Adding more equivalents of Grignard reagent (10 eq *versus*. 8 eq) and increasing the catalyst loading did not give much improvement (Entry 2 and 3). Drying the catalyst and ligand in advance did not increase the yield as well (Entry 4). It was noticed by accident that the good yield was only obtained when freshly opened Fe(acac)₃ was used (Entry 5 and 6). A control experiment using the old catalyst gave 25% less yield. Consequently, it was hypothesised that Fe(acac)₃ decomposed when exposed to air. The catalyst stored under an inert atmosphere in desiccators was proved to have longer shelf life. The yield was reproducible on up to 15 g scale.

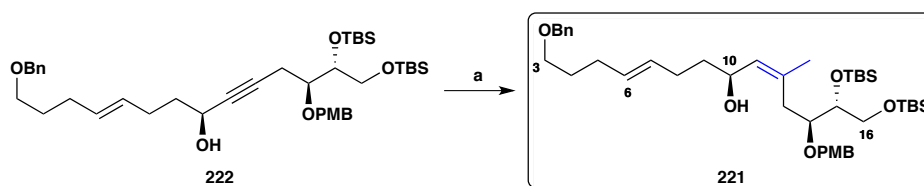
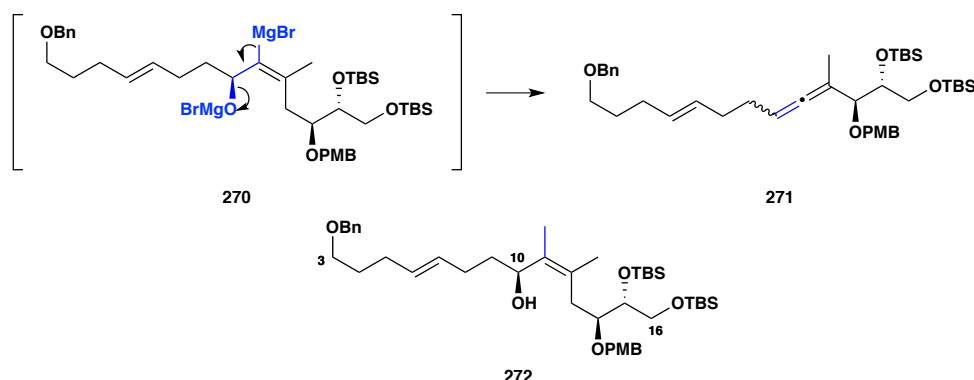


Table 8. Optimisation of *trans*-selective carbometalation reaction

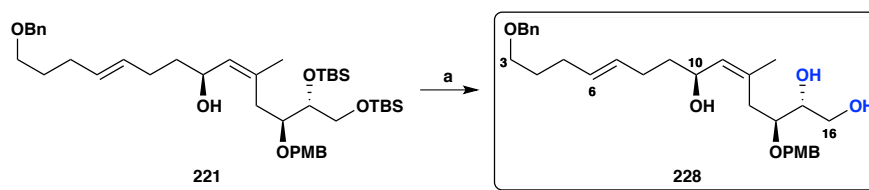
Entry	Condition	Yield
1	Fe(acac) ₃ (0.2 eq), dppe (0.2 eq), MeMgBr (8 eq)	55%
2	Fe(acac) ₃ (0.2 eq), dppe (0.2 eq), MeMgBr (10 eq)	61%
3	Fe(acac) ₃ (0.3 eq), dppe (0.3 eq), MeMgBr (10 eq)	64%
4	Entry 1, dry catalyst under high vacuum	63%
5	Entry 1, fresh Fe(acac) ₃	79%
6	Entry 1, fresh Fe(acac) ₃ (15 g scale)	72%

There were two side products isolated from the carbometalation reaction. One of them has an allenic carbon signal at 201 ppm in the ^{13}C NMR spectrum and the absence of allylic proton multiplet between 4.39–4.31 ppm was allene **271**, which was generated from an elimination reaction of the carbometalated intermediate **270** (Scheme 83).⁶⁶ This side reaction was minimised when the carbometalation reaction was strictly quenched at $-78\text{ }^{\circ}\text{C}$. The other side product with $[\text{M} + \text{Na}^+]$ peak at 763.5 Da in mass spectrometry was the over methylated product **272** (Scheme 83). The amount of **272** was less than 5% under the optimised reaction conditions, but it might significantly increase if the reaction time was left for more than 24 hours.



Scheme 83. Side products from carbometalation

TBAF deprotection of allylic alcohol **221** afforded triol **228** in an excellent yield of 96% (Scheme 84). The structure of the product was confirmed by the loss of a *t*Bu signal at 0.09 ppm and Si-CH₃ signal at 0.06 ppm in the ^1H NMR spectrum.



Scheme 84. Deprotection of allylic alcohol **221**

Reagents and conditions: (a) TBAF (3 eq), THF, 0 °C to rt, 3 h, 96%.

It was important to confirm the double bond geometry in triol **228** because it dictated the absolute stereochemistry to be generated in the next oxidative cyclisation step. The geometry was determined by *nOe* interactions of allylic alcohol **221** and triol **228** (**Figure 9**).^{†††} For allylic alcohol **221**, there was a strong spatial correlation between C(11)-*H* at 5.32 ppm and C(12)-*CH*₃ at 1.74 ppm. For triol **228**, the spatial correlation was weak but also observable. If the double bond was (*E*)-, only *nOe* between C(10)-*H* (4.35 ppm and 4.26 ppm separately) and C(12)-*CH*₃ might be observed and there would be no spatial correlation between C(11)-*H* and C(12)-*CH*₃ (**Figure 9**).

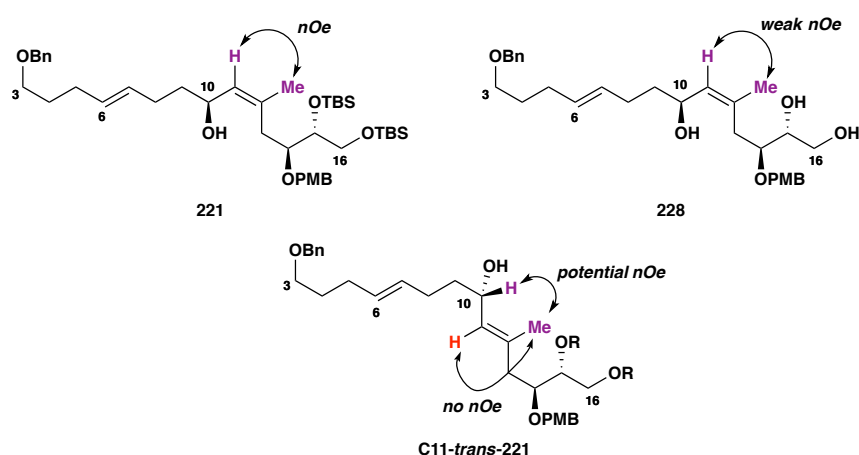
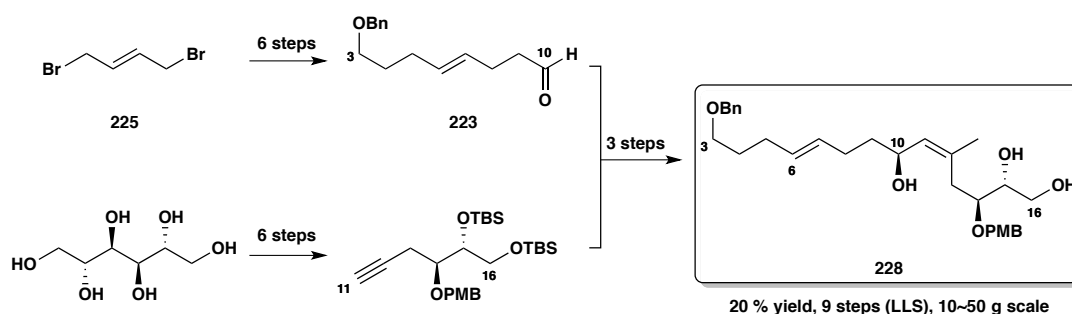


Figure 9. Determination of C11-C12 double bond geometry

^{†††} See Appendix for the 1D *nOe* spectra for compounds **221** and **228**.

In summary, the oxidative cyclisation precursor **228** was prepared in 9 steps (longest linear steps, 15 steps in total) with an overall yield of 20% (**Scheme 85**). All of the steps were successfully performed at 10 g to 50 g scale. Compared to the previous route from D-mannitol **28** and 1,4-dibromobut-2-ene **225** (9 longest linear steps, 13 steps in total, 7% overall yield), the productivity of the optimised route was significantly improved.



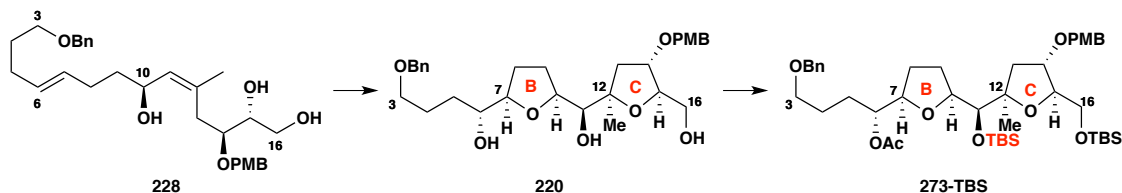
Scheme 85. Optimised synthetic route for oxidative cyclisation precursor **228**^{§§§}

2.3 Synthesis of the C3–C16 *bis*-THF fragment **273**

The Donohoe group has successfully prepared the C3–C16 *bis*-THF fragment **220** from triol **228** *via* an osmium-catalysed oxidative cyclisation. It was then protected in 3 steps to afford compound **273-TBS** (**Scheme 86**).^{60, 66} However, conditions for the selective deprotection of the C16-OTBS group in the presence of the C11-OTBS group were not developed. This reaction was required for further synthetic elaborations to connect C17 at a later stage in the synthesis. It was also questionable as to whether the C11-OTBS group could be removed under global deprotection conditions at the end. Previous research in the Evans group had suggested that cleavage of a C11-OTBS group in their system was irreproducible, and so a TBODPS group was used instead.⁶⁴ Unfortunately, the TBODPS group was found

^{§§§} The overall yield based on best yield on large-scale reactions.

not to compatible with our route (see **Scheme 90**). This discussion details our synthetic efforts to solve these two problems.

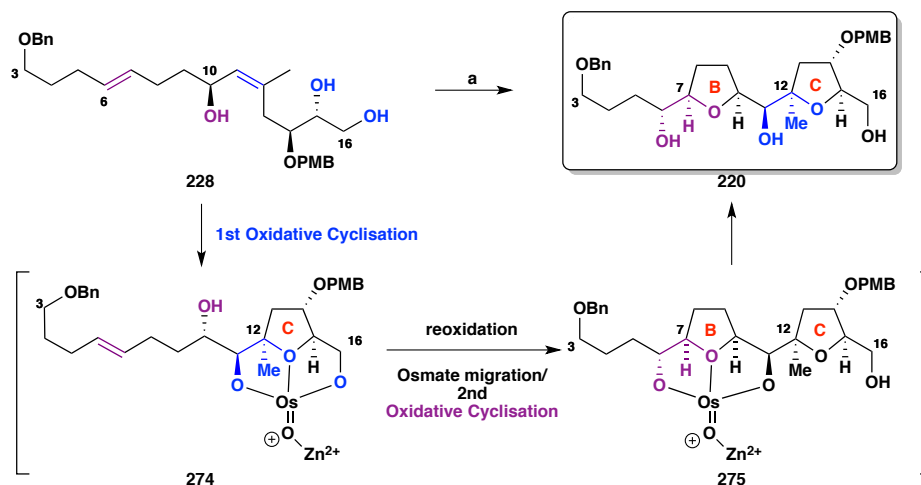


Scheme 86. Previous plan for the C3–C16 *bis*-THF fragment **273-TBS**

2.3.1 Oxidative cyclisation of triol **228**

The core framework of the BC fragments was assembled using the Donohoe group's cascade osmium catalysed oxidative cyclisation as discussed in **Chapter 1**.^{60, 66} Treatment of triol **228** in the presence of $K_2OsO_2(OH)_4$, $Zn(OTf)_2$, reoxidant (PNO) and ligand (citric acid) in a mixture of MeCN and pH 6.5 phosphate buffer afforded triol **220** diastereoselectively in an average yield of 40%. This key reaction assembled both THF rings and 4 stereocenters in one step. The proposed intermediate is depicted in **Scheme 87**. Os(VI) coordinates to the C15–C16 diol and the C11–C12 double bond in **228** and forms the C ring. Os(IV) is reduced to Os(IV) in the process. The catalyst was then reoxidised in the presence of PNO and relocates to the C10–C11 diol and adds to the C6–C7 double bond to facilitate the second cyclisation. It was noticed that the second oxidative cyclisation required higher temperature (80 °C *versus*. 60 °C) to proceed.⁶⁶ The structure of *bis*-THF triol **220** was confirmed with NMR spectra. The alkene-*H* signal at 5.36–5.28 ppm (C6-*H* and C7-*H*) and 5.18 ppm (C11-*H*) disappeared, and 4 new carbon signals (C6, C7, C11 and C12) were detected between 86–73 ppm in the ^{13}C NMR spectrum. These observations were identical with those

previously reported.⁶⁰ The structures of both *cis*-THF rings were confirmed by NOESY spectra.^{****} C7-*H*, C10-*H*, C11-*H*, and C12*Me* are *syn* to C15-*H*, which is from D-mannitol.



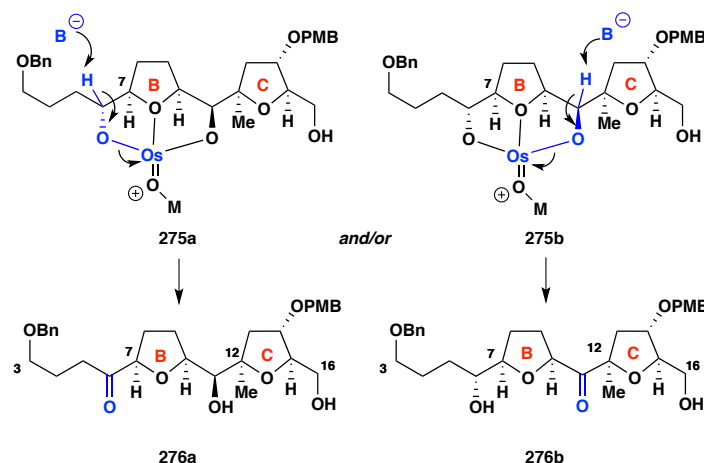
Scheme 87. Oxidative cyclisation of triol **228**

Reagents and conditions: (a) K₂OsO₄•2H₂O (5 mol%), citric acid (0.75 eq), Zn(OTf)₂ (0.5 eq), PNO (4 eq), 3:2 pH 6.5 phosphate buffer/MeCN, 60 °C, 12 h, then 80 °C, 24 h, 40%.

¹³C NMR spectrum indicated that the triol **220** obtained from the oxidative cyclisation process was contaminated with some impurities that could not be separated by flash column chromatography. The impurities had two characteristic carbonyl carbon signals at 211 and 213 ppm in ¹³C NMR spectrum, whilst the mass spectrometry showed that a molecular peak at 528 Da (2 Da less than **220**). It was proposed that these impurities were most likely the result of over-oxidation, giving the corresponding ketone at C6 or C11. Previous research in the Donohoe group showed similar over-oxidation process as in the total synthesis of

**** See Experimental and Appendix for ¹H NMR assignments and NOESY spectra for compounds **220** and **324**.

sylvaticin.^{131, 132} In the case of the PTX-4 BC rings system **220**, use of elevated temperatures resulted in the hydroxyl groups at C6 or C11 being over-oxidised (Scheme 88).



Scheme 88. Proposed mechanism for over-oxidation of triol **220**

In order to increase the yield and reduce the amount of over-oxidised products, we chose to optimise the reaction by changing the catalyst and reoxidant loading. Our optimisation study is summarised in **Table 9**. A slight increase in the catalyst loading had a positive effect on the yield, but it also increased the ratio of side products (Entry 2 and 3). It was beneficial to add the catalyst in several batches to minimise the over-oxidation product and increase the yield, but 5 mol% catalyst did not give a good yield (Entry 4). At higher catalyst loading (7 mol%), a significant amount of over-oxidised product was formed even if the catalyst was added in batches (Entry 5). It was important to reduce the number of equivalents of the reoxidant to provide adequate catalyst regeneration, but not over-oxidation to Os(VIII), which was believed to favour ketone side products (Entry 6 and 7).¹³² The yield of this reaction was

eventually increased to 84% following the adjustment of the re-oxidant stoichiometry (Entry 7, 2 to 3 g scale).

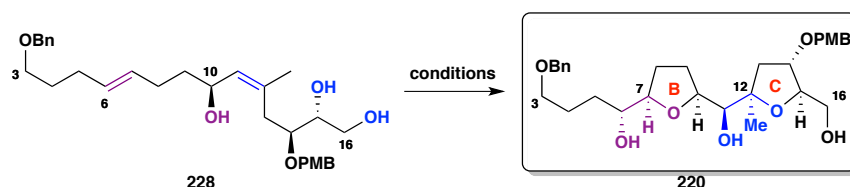


Table 9. Optimisation of Os catalysed cascade oxidative cyclisation

Entry	Conditions	Yield
1	K ₂ OsO ₂ (OH) ₄ (5 mol%), PNO (4 eq)	40%
2	K ₂ OsO ₂ (OH) ₄ (7 mol%), PNO (4 eq)	65%*
3	K ₂ OsO ₂ (OH) ₄ (8 mol%), PNO (4 eq)	71%*
4	K ₂ OsO ₂ (OH) ₄ (5 mol%, added in 3 batches), PNO (4 eq)	48%*
5	K ₂ OsO ₂ (OH) ₄ (5 mol% + 2 mol%), PNO (4 eq)	67%*
6	K ₂ OsO ₂ (OH) ₄ (5 mol% + 2 mol%), PNO (3.75 eq)	81%
7	K₂OsO₂(OH)₄ (5 mol% + 2 mol%), PNO (3.5 eq)	84%
8	K ₂ OsO ₂ (OH) ₄ (5 mol% + 2 mol%), PNO (3.25 eq)	69%

Reagents and conditions: (a) K₂OsO₄•2H₂O, citric acid (0.75 eq), Zn(OTf)₂ (0.5 eq), PNO, 3:2 pH 6.5 phosphate buffer/MeCN, 60 °C, 12 h, *then* 80 °C, 24 h (2 to 3 g scale).

*In these entries the amount of inseparable ketone side products were significantly higher (5% to 10 %).

In summary, the osmium catalysed oxidative cyclisation condition of **228** was optimised by use of slightly more catalyst (7 mol% *versus*. 5 mol%) and a lower loading of reoxidant

(PNO, 3.5 eq *versus*. 4 eq). In order to reduce the amount of over-oxidation side products, catalyst addition was performed portionwise.

2.3.2 Orthogonal protecting group strategy for triol **220**

With triol **220** in hand, an orthogonal protecting group strategy was needed to distinguish between the hydroxyl groups. The key requirements are depicted in **Figure 10**. Previously, an acetate protecting group was installed at C6 and both the C11 and C16 hydroxyl groups were masked as the TBS ethers. Selective deprotection of the primary TBS in the presence of a secondary TBS has been previously reported.¹³³ At the start of our study we chose to use the existing protecting group strategy developed in the Donohoe group to test whether the C11-OTBS group could be removed using mild desilylation conditions (e.g., TASF).⁶⁶ We were also curious to know if selective deprotection of the C16-OTBS in the presence of the C11-OTBS could be achieved.

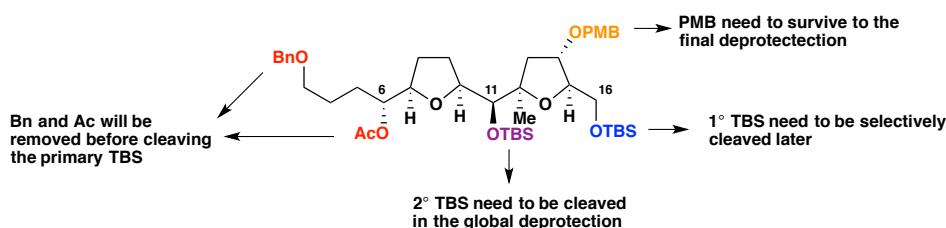
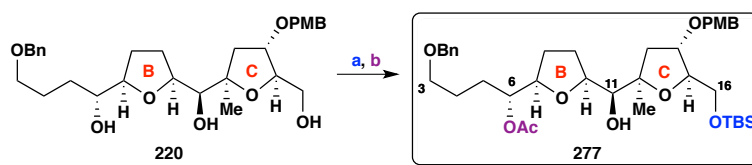


Figure 10. Orthogonal protecting group strategy requirements

Following the literature known method, triol **220** was reacted with 1 equivalent of TBSCl to afford primary TBS ether in 93% yield (**Scheme 89**).⁶⁰ Treatment of primary TBS ether with Ac₂O, pyridine and DMAP in CH₂Cl₂ at high dilution (60 mL/mmol) gave acetate **277** in a

good yield of 87% with trace amounts of *bis*-protected product (at C11-*OH*). The structure of acetate **277** was confirmed by NMR spectra. The TBS-*t*Bu proton singlet at 0.88 ppm, the TBS-SiCH₃ singlet at 0.04 ppm and the Ac-CH₃ singlet at 2.05 ppm appeared in the ¹H NMR spectrum. The C6-*H* also shifted from 3.40 ppm to 4.87 ppm following these two steps.^{†††}

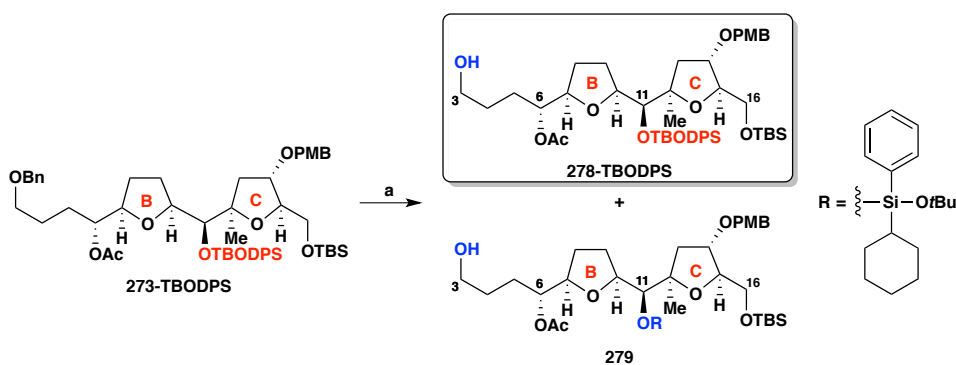


Scheme 89. Protection of C16 and C6 hydroxyl groups

Reagents and conditions: (a) TBSCl (1.05 eq), Imidazole (2.5 eq), CH₂Cl₂, 0 °C to rt, 12 h, 93%; (b) Ac₂O (1.5 eq), Py (10.0 eq), DMAP (0.1 eq), CH₂Cl₂, 0 °C to rt, 18 h, 87%.

Previous work by the Evans group had shown that the *tert*-butoxyldiphenylsilyl (TBODPS) protecting group could be used at the C11 *neo*-pentyl hydroxyl group, with successful removal at a latter stage of the synthesis of PTX-4 using TASF.³⁰ However, the TBODPS group was later found not to be compatible with our route.⁶⁶ Hydrogenation of the TBODPS ether **273-TBODPS** in the presence of Raney-Ni afforded an inseparable mixture of the desired product **278-TBODPS** and side product **279** after flash column chromatography (**Scheme 90**).⁶⁶ The partial reduction of the TBODPS group was unavoidable even after optimisation, so a different silyl protecting group was required.

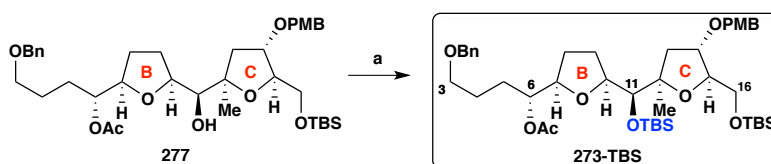
^{†††}C6-*H* (4.90–4.84 ppm, m) and C11-*H* (3.50 ppm, d, *J* = 6.1 Hz) were identified *via* COSY of acetate **277**.



Scheme 90. Hydrogenative debenzylization of **273-TBODPS**⁶⁶

Reagents and conditions: (a) H₂ (balloon pressure), Raney[®]-Ni 2800 slurry, EtOH, 47% mixture of **278-TBODPS** and **279**.

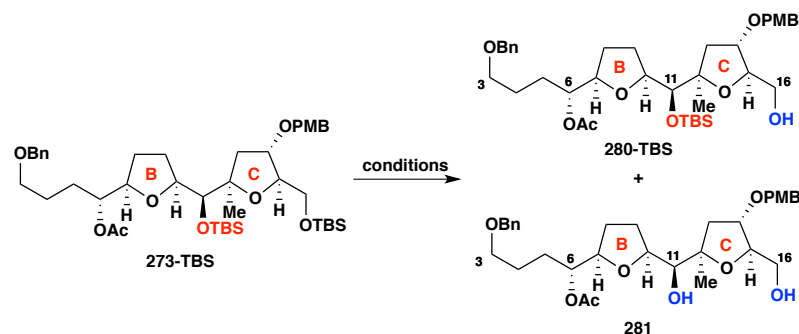
It was planned that the C11 silyl protecting group would need to be more stable than the C16-OTBS group and allow deprotection of the C16-OTBS group. TIPS group was chosen initially, but unfortunately this could not be installed at this sterically hindered position under various conditions (TIPSOTf, 2,6-lutidine).⁶⁶ We therefore chose to put a less bulky TBS group and study the deprotection process, which was expected to be more stable than the C16-OTBS group under certain silyl deprotection conditions due to steric hindrance. Treatment of acetate **277** with a large excess of TBSOTf (5 eq) and 2,6-lutidine successfully afforded the desired *bis*-TBS ether **273-TBS** in an excellent yield of 92% (**Scheme 91**).



Scheme 91. Synthesis of the *bis*-TBS ether **273-TBS**

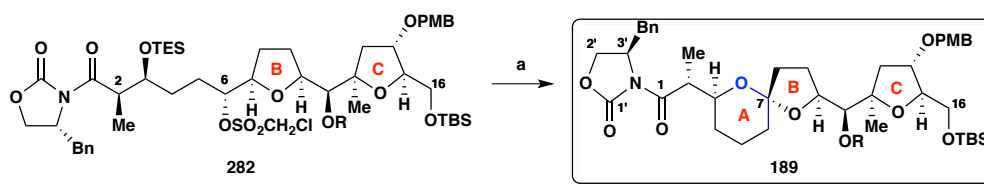
Reagents and conditions: (a) TBSOTf (5 eq), 2,6-lutidine (10 eq), CH₂Cl₂, -78 °C to rt, 12 h, 92%.

With *bis*-TBS ether **273-TBS** in hand, a range of deprotection conditions based on TBAF and TASF were tested. The results are summarised in **Table 10**. The mild deprotection conditions reported by the Evans group for the global deprotection of PTX-4 (TASF in DMF) did not cleave either TBS group (Entry 1).³⁰ Treatment of the *bis*-TBS ether **273-TBS** with a large excess of TASF in THF afforded only 21% of the desired diol **281** and 40% of deprotection product **280-TBS** (Entry 2).^{134, 135} Reducing the amount of TASF to 1.5 equivalents did not give primary alcohol **280-TBS** predominately, but instead a complex mixture of the starting material and both products (Entry 3). Cleavage of the C11-OTBS group could be achieved using TBAF (3 eq) in a moderate yield of 56% after 12 hours (Entry 4). This long reaction time was potentially undesirable as exposure of the AB spiroketal rings and the bicyclic acetal D ring to these basic conditions may result in side reactions. Instead, treatment of the *bis*-TBS ether **273-TBS** with excess TBAF (3 eq) in THF for 2 hours resulted in exclusively 76% of the primary deprotection product **280-TBS** (Entry 5). However, considering the difficulties in the removal of the C11-OTBS group, a less stable silyl protecting group was required at this position.

Table 10. Deprotection study on the *bis*-TBS ether 273-TBS

Entry	Conditions	Results
1	TASF (6 eq), DMF, H ₂ O, 0 °C to rt, 12 h	Only 273-TBS recovered
2	TASF (6 eq), THF, Ar, 0 °C to rt, 12 h	40% 280-TBS and 21% 281
3	TASF (1.5 eq), THF, Ar, 0 °C to rt, 12 h	Complex mixture
4	TBAF (3 eq), THF, Ar, 0 °C to rt, 12 h	56% 281
5	TBAF (3 eq), THF, Ar, 0 °C to rt, 2 h	76% 280-TBS

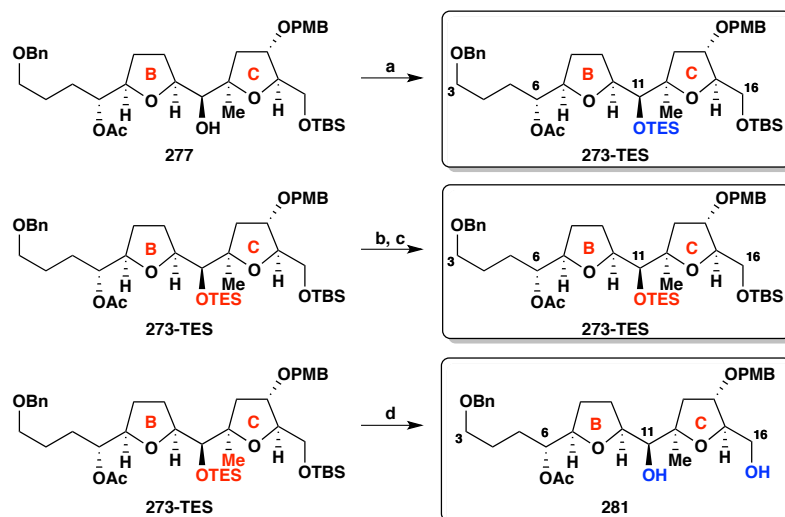
There were two fundamental requirements in choosing any new protecting groups. Firstly, in order to prevent latter complications in the synthetic sequence, we chose to use silyl protecting groups. Furthermore, the group of choice should tolerate the acidic conditions depicted in **Scheme 92** for 1,2-hydride shift and spiroketalisation. In particular, it should be more stable than the C3-OTES group cleaved in this process. The minimum stability requirement was a TES group at C11, which was expected to be more stable than the C3-OTES due to steric hindrance of this position.



Scheme 92. 1,2-Hydride shift and spiroketalisation

Reagents and conditions: (a) $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (10.0 eq), $\text{DMF}/\text{H}_2\text{O}$, (4:3), 75°C , 8 h; (b) PPTS (0.5 eq), $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (1:1), 0.5 h.

To facilitate smooth removal of the C11 silyl protecting group, a TES group was installed at this position. Treatment of acetate **277** with a large excess of TESOTf (5 eq) and 2,6-lutidine afforded *bis*-silyl ether **273-TES** in an excellent yield of 90% (**Scheme 93**). Compound **273-TES** was then subjected to the 1,2-hydride shift and spiroketalisation conditions with 48% of the starting material **273-TES** recovered after the reaction (**Scheme 93**). Treatment of *bis*-silyl ether **273-TES** with excess TASF (3 eq) in THF afforded a good yield of 71% of the desired diol **281** in 1 hour (**Scheme 93**). The C11-OTES group showed moderate stability under the 1,2-hydride shift and spiroketalisation conditions, with feasible removal under mild deprotection conditions (TASF in THF), and therefore it has the potential to be used in our synthetic route.



Scheme 93. Preparation of the *bis*-silyl ether **273-TES** and its reactivities

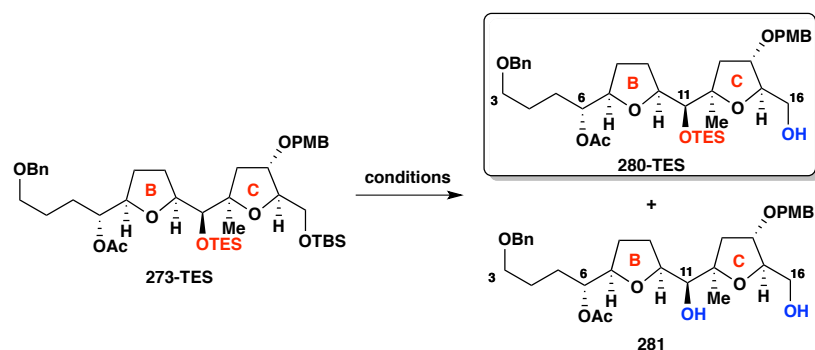
Reagents and conditions: (a) TESOTf (5 eq), 2,6-lutidine (10 eq), CH₂Cl₂, -78 °C to rt, 12 h, 90%; (b) Zn(OAc)₂•2H₂O (10.0 eq), DMF/H₂O, (4:3), 75 °C, 8 h; (c) PPTS (0.5 eq), MeOH/CH₂Cl₂ (1:1), 0 °C, 0.5 h, 48% recovery of **273-TES** over two steps; (d) TASF (3 eq), THF, 0 °C to rt, 1 h, 71%.

We next began to study the selective removal of the primary TBS group. Generally, a TES group is less stable than a TBS group, which increases the difficulty of this deprotection.⁸⁰ Literature reported examples to cleave a primary TBS in the presence of a secondary TES group are rare.^{65, 133, 136} However, we supposed that the primary TBS group would be more accessible compared to the sterically hindered *neo*-pentyl TES group under certain deprotection conditions in our molecule.

Several conditions to deprotect a primary TBS group in the presence of a secondary silyl protecting group were examined (**Table 11**).^{133, 136} Unfortunately, most of them showed no selectivity between the TES and TBS (Entry 1–4). The presence of the acid labile AB spiroketal in the real system would not tolerate most of the acidic deprotection conditions,

which increased the difficulty to find compatible conditions. Treatment of the *bis*-silyl ether **273-TES** with TBAF at 0 °C, which was used to selectively remove the primary TBS in the *bis*-TBS ether **273-TBS** (see Table 10, Entry 5) did show any selectivity for *bis*-silyl ether **280-TES** (Entry 5). The only promising result came from using pyridine-buffered HF•Py. The Paterson group had previously reported similar conditions during their total synthesis of (–)-rhizopodin (Entry 6).¹³⁷ However, Paterson's approach proved to be substrate dependent. When applied to the *bis*-silyl ether **273-TES**, only 25% of the desired product **280-TES** was isolated after the reaction, together with over 50% of unreacted starting material. Interestingly, it was the only conditions did not produce the C11-OTES over-deprotected product. We postulated that the yield and selectivity of the selective deprotection was determined by a combination of temperature, time, concentration and reagent stoichiometry. To test to what extent the deprotection reaction would proceed, the reaction was left under the same conditions for 1 week (Entry 7).^{###} Not surprisingly, both of the C11-OTES group and the C16-OTBS group were cleaved. Only diol **281** was isolated, while other functional groups present in the molecule were not affected. Based on these results (Entry 6 and 7), we planned to further optimise these conditions.

Due to the large excess of pyridine existed and low concentration of the starting material, it is difficult to monitor this reaction on TLC.

Table 11. Selective deprotection study on the *bis*-silyl ether **280-TES**

Entry	Conditions	Results
1	TMSOTf, Al ₂ O ₃ , CH ₂ Cl ₂ , 0 °C to rt, 2 h	Lose TBS, TES, PMB
2	NBS, DMSO, H ₂ O, Ar, 30 °C, 8 h	Only 281
3	AcOH, H ₂ O, THF, rt, 8 h	Only 281
4	AcOH, H ₂ O, THF, 0 °C, 3 h	280-TES and 281
5	TBAF, THF, 0 °C, 0.5 h	280-TES and 281
6	HF•Py, Pyridine, THF, 0 °C to rt, 20 h	Only 280-TES
7	HF•Py, Pyridine, THF, 0 °C to rt, 1 week	Only 281

With the principles mentioned above, good conditions to selectively deprotect the C16-OTBS group were soon determined (**Table 12**). The best result was obtained when the previous reaction concentration was doubled and the temperature was kept at 0 °C (Entry 5). Treatment of the *bis*-silyl ether **273-TES** with HF•pyridine/pyridine (2:3) in THF (160mL/mmol) at 0 °C afforded a good yield of 72% of the desired product **280-TES**. NMR analysis confirmed the structure of **280-TES** by the absence of the *t*Bu-*H* singlet at 0.90 ppm and Si-CH₃ at 0.06 ppm and the presence of the TES-CH₃ and TES-CH₂ at 1.00–0.89 ppm

and 0.70–0.59 ppm respectively. It was also noticed that the C16- H_2 signals at 3.69 ppm and 3.47 ppm moved to 3.74 ppm and 3.52 ppm after the reaction.

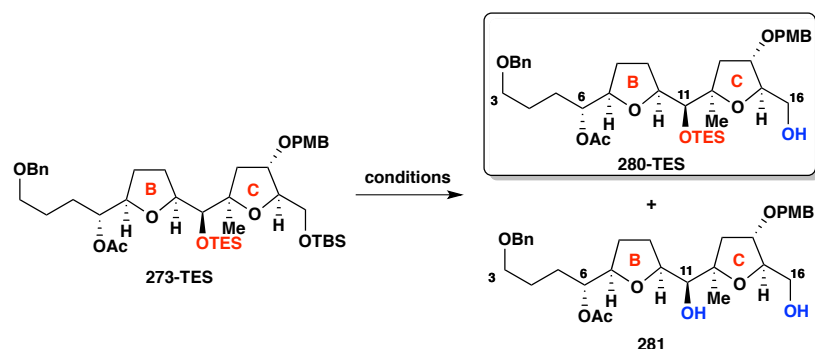


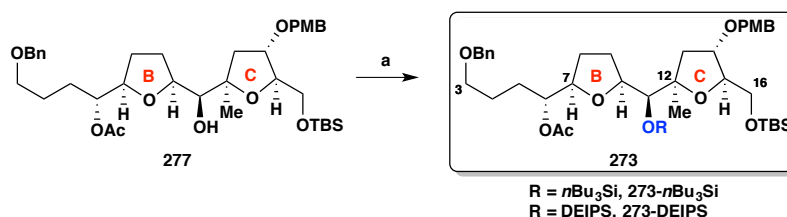
Table 12. Optimisations on HF•Py deprotection conditions

Entry	Conditions	Results
1	HF•Py:Py (2:3), THF (320 mL/mmol), 0 °C to rt, 20 h	25% 280-TES
2	HF•Py:Py (2:3), THF (320 mL/mmol), 0 °C to rt, 1 week	Only 281
3	HF•Py:Py (1:1), THF (6 mL/mmol), 0 °C to rt, 3 h	Only 281
4	HF•Py:Py (2:3), THF (80 mL/mmol), 0 °C, 3 h	Only 281
5	HF•Py:Py (2:3), THF (160 mL/mmol), 0 °C, 5.5 h	72% 280-TES

In summary, the TES group was a better substitute for the *neo*-pentyl TBS group for several reasons. Firstly, it was easily removed under mild conditions using TASF. Selective deprotection of the primary TBS group in the presence of this *neo*-pentyl TES could also be achieved in good yield and selectivity. However, the instability of the C11-OTES group under the 1,2-hydride shift and spiroketalisation conditions caused some concerns. To avoid further complication in the planned synthetic sequence, a more stable protecting group was required at this position.

2.3.3 Further development of the protecting group strategy

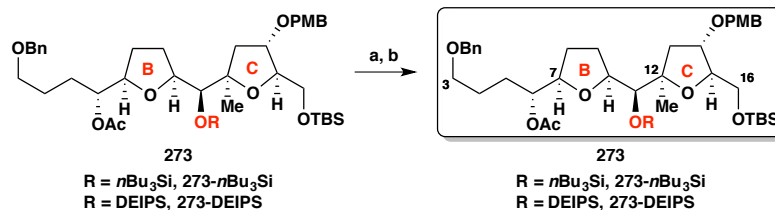
Previous studies had shown that a trialkylsilyl protecting group more stable than the TES group would be a better choice for the *neo*-pentyl position. Two new protecting groups; tri-*n*-butylsilyl and diethylisopropylsilyl (DEIPS), were tested. The silyl protections were carried out using a similar procedure to the TBODPS method discussed previously (Section 2.4). Treatment of the acetate **277** with a large excess of silyl chloride (8 eq) in DMF afforded both *bis*-silyl ethers **273-*n*Bu₃Si** and **273-DEIPS** in good yields separately (Scheme 94). It is noteworthy that protections with the corresponding silyl chlorides were much slower than those with the corresponding silyl triflates.



Scheme 94. Synthesis of the *bis*-silyl ethers **273** with new protecting groups

Reagents and conditions: (a) Silyl chloride (8 eq), Et₃N (15 eq), DMAP (2 eq), DMF, 0 °C to rt, 18 h, R = *n*Bu₃SiCl, 81% **273-*n*Bu₃Si**; R = DEIPS, 85% **273-DEIPS**.

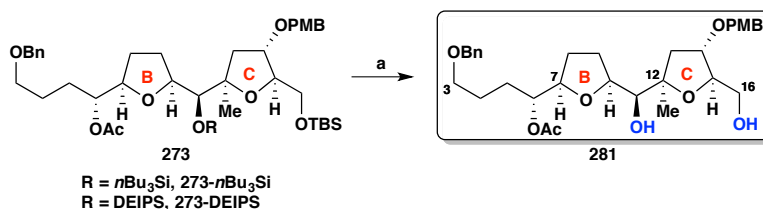
The new compounds **273-*n*Bu₃Si** and **273-DEIPS** were subjected to the 1,2-hydride shift and spiroketalisation conditions to test their stability (Scheme 95). As expected, both compounds were more stable than the TES analogue **273-TES** under these conditions with increased recovery of the starting material. Compared to the TES compound **273-TES**, the deprotection of the C11-OSiR₃ was not detected by either TLC or mass spectrometry.



Scheme 95. Stability test of *bis*-silyl ethers **273**

Reagents and conditions: (a) Zn(OAc)₂•2H₂O (10 eq), DMF/H₂O, (4:3), 75 °C, 12 h; (b) PPTS (0.5 eq), MeOH/CH₂Cl₂ (1:1), 0.5 h. R = *n*Bu₃Si, 56% **273-*n*Bu₃Si**; R = DEIPS, 54% **273-DEIPS**.

It was also important to know whether the increased stability of the C11-OSiR₃ would cause any problems upon the global deprotection with TASF. Treatment of both compounds **273-*n*Bu₃Si** and **273-DEIPS** with TASF in THF afforded diol **281** in 80% and 81% yields respectively (**Scheme 96**). The new protecting groups were therefore compatible with the designed global deprotection conditions.

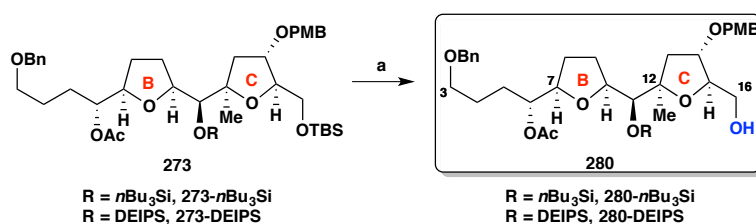


Scheme 96. Deprotection test on the *bis*-silyl compounds **273-*n*Bu₃Si** and **273-DEIPS**

Reagents and conditions: (a) TASF (3 eq), THF, 0 °C to rt, 1 h, R = *n*Bu₃Si, 80%, R = DEIPS, 81%.

After proving that both new silyl ethers **273-*n*Bu₃Si** and **273-DEIPS** were compatible with the planned future manipulations, they were subjected to the selective C16-OTBS deprotection conditions optimised for their TES analogue **273-TES** (**Scheme 97**). After

3 hours, both compounds **273-*n*Bu₃Si** and **273-DEIPS** gave excellent selectivity and moderate yields of the desired primary alcohol **280-*n*Bu₃Si** and **280-DEIPS** separately. The DEIPS compound **273-DEIPS** was superior to the tri-*n*-butyl compound **273-*n*Bu₃Si** in this reaction because it converted faster in the selective cleavage, which reduced the time required to expose the sensitive AB spiroketal. In theory, less reaction time was also beneficial to avoid the deprotection at the C11-OSiR₃ group. Consequently, we chose to use the DEIPS group in the synthetic sequence. The yield for this reaction was not optimised for the model system because further adjustments might be required with other functional groups installed in the real system. The structure of **280-DEIPS** was confirmed with the absence of *t*Bu-*H* at 0.90 ppm and Si-CH₃ at 0.06 ppm and the presence of the DEIPS-CH₃ at 1.00–0.89 ppm and the DEIPS-CH₂ at 0.70–0.59 ppm in the ¹H NMR spectra. It was also noticed that the C16-*H*₂ signals at 3.69 ppm and 3.48 ppm shifted to 3.74 ppm and 3.52 ppm following reaction.

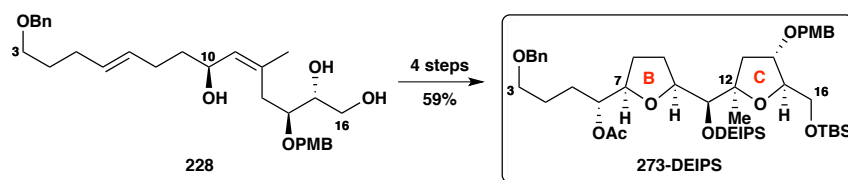


Scheme 97. Selective deprotection test on the *bis*-silyl ether **273**

Reagents and conditions: (a) HF•Py, Py, 0 °C, 3 h, R = *n*Bu₃Si, 42% **280-*n*Bu₃Si**, R = DEIPS, 53% **280-DEIPS**.

In summary, the *bis*-THF core **273-DEIPS** was prepared from triol **220** in 4 steps with an overall yield of 59% (**Scheme 98**, 13 longest linear steps from commercially available

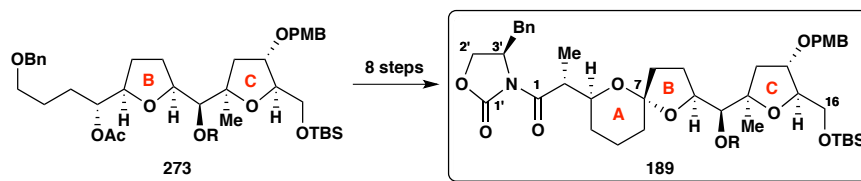
starting materials, 11.8 % overall yield). All the reactions were conducted on a multigram scale. The orthogonal protecting group strategy was fully revised, with the *neo*-pentyl protecting group (DEIPS) able to survive under the 1,2-hydride shift and spiroketalisation conditions. Deprotection could then be realised under mild conditions, with a new strategy to selectively deprotect the C16-OTBS group in the presence of the *neo*-pentyl protecting group (DEIPS) developed.



Scheme 98. Revised synthesis for the orthogonal protected *bis*-THF core **273**

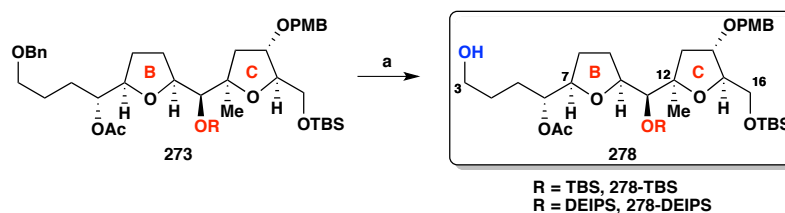
2.4 Elaboration to the C1–C16 spiroketal fragment **189**

Following the successful synthesis of **273**, further elaboration to the ABC spiroketal fragment **189** was necessary (**Scheme 99**). In doing so, it was clearly important to test whether the new protecting group strategy was compatible in the real system. The remaining TBS ether **273-TBS** was also carried along the sequence for test reactions and data comparison with the previous published results by the Donohoe group and the new DEIPS analogues.⁶⁰ The following section details the synthetic efforts to convert **273** to the C1–C16 ABC spiroketal fragment **189**.



Scheme 99. Planned synthesis of the C1–C16 spiroketal fragment **189**

The sequence began with debenzylation of **273** to give the C3 primary alcohol **278**. Treatment of **273-DEIPS** with H₂ in the presence of Raney[®]-Ni 2800 slurry afforded alcohol **278-DEIPS** in a good yield of 79% (**Scheme 100**, 81% for *bis*-TBS compound **278-TBS**). Both the TBS and DEIPS compounds gave similar yields for this reaction, with the PMB group left untouched. The structure of the product was verified by the disappearance of the Bn-CH₂ singlet at 4.49 ppm and the aromatic signals from 7.28 to 7.35 ppm in the ¹H NMR spectra and the data obtained was consistent with those previously reported by the Donohoe group (primary alcohol **278-TBS**).⁶⁰

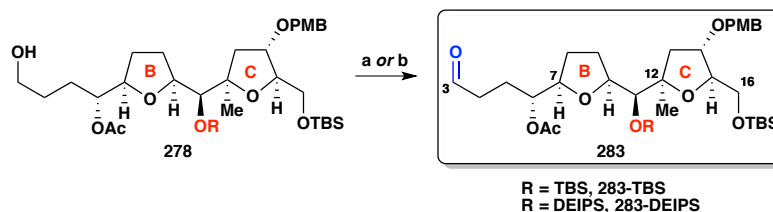


Scheme 100. Debenzylation of the *bis*-silyl ether **273**

Reagents and conditions: (a) Raney[®]-Ni 2800 slurry, H₂, EtOAc, 45 °C, 12 h, R = TBS, 81% **278-TBS**, R = DEIPS, 79% **278-DEIPS**.

Parikh–Doering oxidation of alcohol **278** afforded aldehyde **283** in quantitative yield at gram scale (**Scheme 101**). Dess–Martin conditions were also tested for this transformation but

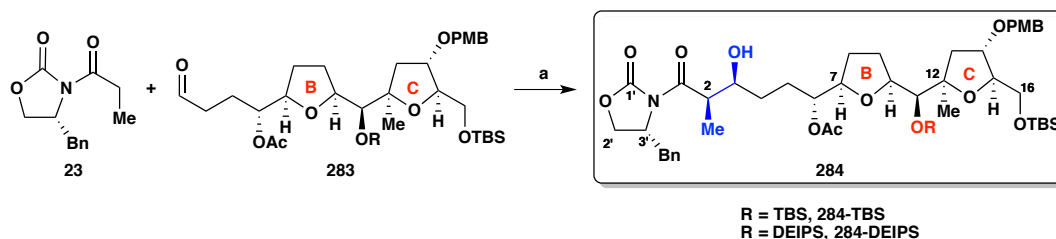
gave a slightly lower yield of 88%. The structure of aldehyde **283-DEIPS** was confirmed with the appearance of the C3-*H* aldehyde triplet at 9.74 ppm in the ^1H NMR spectra.



Scheme 101. Oxidation of primary alcohol **278**

Reagents and conditions: (a) $\text{SO}_3 \cdot \text{Py}$ (3 eq), $i\text{Pr}_2\text{NEt}$ (8 eq), DMSO (10 eq), CH_2Cl_2 , $-50\text{ }^\circ\text{C}$ to $-10\text{ }^\circ\text{C}$, 1 h, R = TBS, 99% **283-TBS**, R = DEIPS, 99% **283-DEIPS**; (b) Dess–Martin periodinane (3 eq), pyridine (15 eq), H_2O (cat.), CH_2Cl_2 , 88% **283-DEIPS**.

With aldehyde **283** in hand, we chose to set the C2-C3 stereochemistry by means of an Evans *syn*-aldol reaction (**Scheme 102**).^{138, 139} Treatment of aldehyde **283-DEIPS** with the *Z*-boron enolate of **23** afforded secondary alcohol **284-DEIPS** in moderate yield (40% to 50%, >95:5 d.r. by ^1H NMR spectra).⁶⁰ The yield could be increased to 68% when slightly more equivalents of the oxazolidinone and dibutylboron trifluoromethanesulfonate were used (1.5 eq oxazolidinone **23** and 1.7 eq of $n\text{Bu}_2\text{BOTf}$ *versus* 1.1 eq oxazolidinone **23** and 1.3 eq of $n\text{Bu}_2\text{BOTf}$).¹³⁹ The *syn*-selectivity was suggested by the $J_{2,3}$ coupling constant ($J_{2,3} = 2.5\text{ Hz}$ for **284-TBS**, 2.6 Hz for **284-DEIPS**). If C2-*H* and C3-*H* are *syn*-, the coupling constant is expected be 2 to 6 Hz, and if they are *anti*-, the typical $J_{2,3}$ coupling is between 7 to 10 Hz.^{140, 141} The absolute stereochemistry at C2 and C3 was predicted by the Zimmerman-Traxler model.



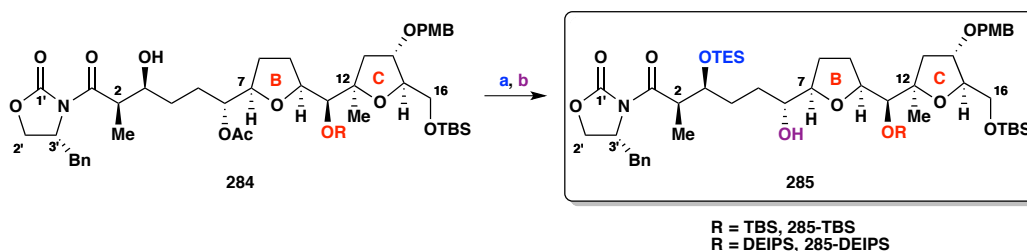
Scheme 102. Evans *syn*-aldol reaction of aldehyde **283**

Reagents and conditions: (a) $n\text{Bu}_2\text{BOTf}$ (1.7 eq), Et_3N (2 eq), CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 3 h, R = TBS, 62%

284-TBS, R = DEIPS, 68% **284-DEIPS**.

Standard TES protection of secondary alcohol **284-DEIPS** with TESCl gave the product **285-DEIPS** in quantitative yield (**Scheme 103**, 87% for TBS). A relatively labile TES group was installed at C3-*OH* to allow early stage spiroketalisation. Previous model studies conducted in the Donohoe and Fujiwara groups demonstrated a more stable group such as TBS or PMB could be used at this position if the spiroketalisation was conducted at a late stage after macrolactonisation.^{31, 131} Although Evans proved it was possible to carry the AB spiroketal through the synthetic sequence from a relatively early stage, it was debatable whether a late stage spiroketalisation was beneficial.^{30, 142} The main problem relating to the spiroketal was its acid sensitivity. This limitation would restrict many versatile reactions and reagents that could be used in the synthesis. For example, an acidic cleavage of the C16-*OTBS* group or the C1 oxazolidinone might be problematic. Furthermore, the effect of the AB spiroketal system on the macrolide formation also needed to be considered. In order to complete the 1,2-hydride shift precursor, the C6-*OAc* group needed to be substituted by a good leaving group. Cleavage of the acetate functionality could not be achieved by the commonly used method involving K_2CO_3 in MeOH due to the presence of the C3-*OTES*

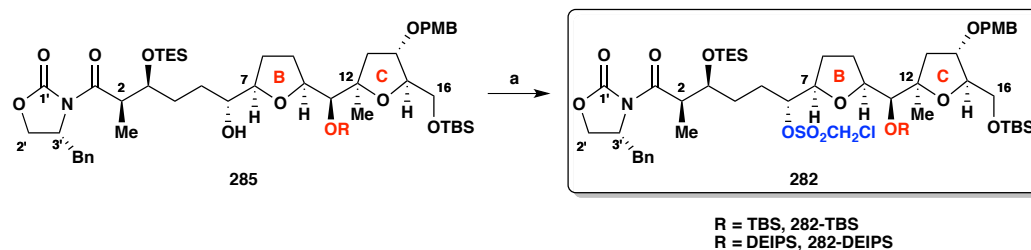
group. Instead, the acetate was cleaved by reduction with DIBAL-H (5 eq) at $-78\text{ }^{\circ}\text{C}$ to afford secondary alcohol **285-DEIPS** in good yield (75%, 81% for **285-TBS**), leaving the oxazolidinone untouched (**Scheme 103**). Solvent played an important role in this reaction. A control experiment using CH_2Cl_2 instead of THF resulted in less than 10% conversion during the same period.



Scheme 103. TES protection and acetate deprotection of aldohol **284**

Reagents and conditions: (a) TESCO (2 eq), imidazole (4 eq), DMAP (0.1 eq), $0\text{ }^{\circ}\text{C}$ to rt, 2 h, R = TBS, 87%, R = DEIPS 99%. (b) DIBAL-H (5 eq), THF, $-78\text{ }^{\circ}\text{C}$, 3.5 h, R = TBS, 81% **285-TBS**, R = DEIPS, 75% **285-DEIPS**.

Chloromethanesulfonylation of **285-DEIPS** using chloromethanesulfonyl chloride in pyridine gave 1,2-hydride shift precursor **282-DEIPS** in an excellent yield of 90% (99% for the TBS compound **282-TBS** reported by the Donohoe group before).⁶⁰ The formation of the desired product was proved by the presence of the ClCH_2SO_2 AB doublets at 4.87 ppm and 4.74 ppm in the ^1H NMR spectrum. The C6-*H* also moved from 3.45–3.38 ppm to 4.69–4.63 ppm after the reaction. The observation was consistent with those previously reported by the Donohoe group for *bis*-TBS chloromethanesulfonyl ether **282-TBS**.⁶⁰

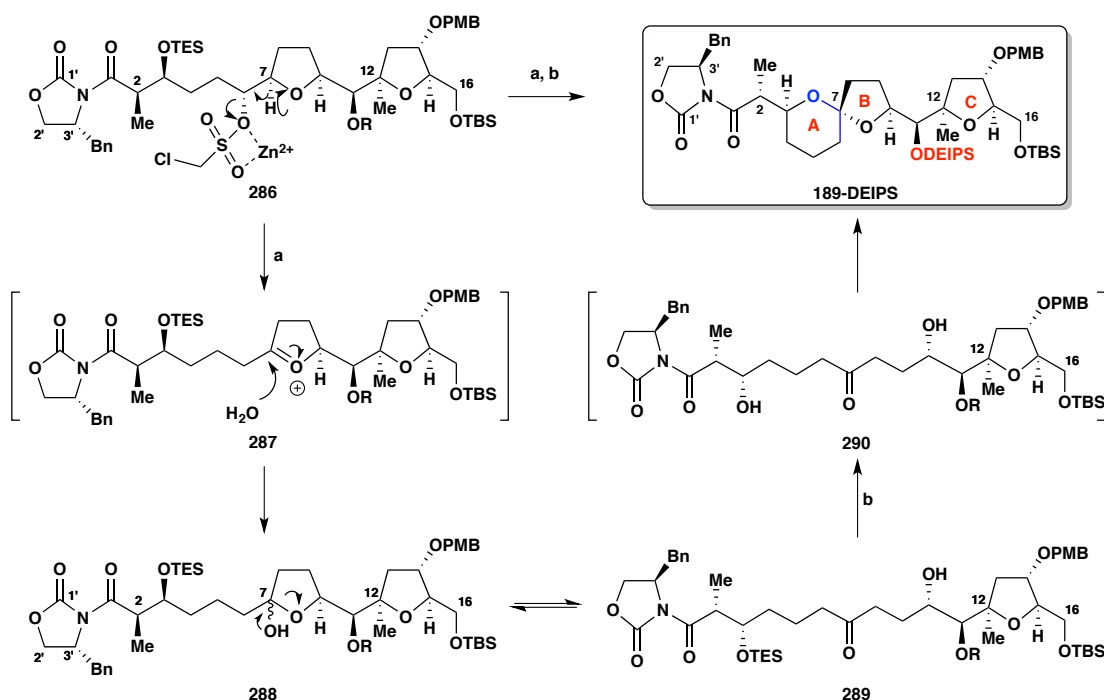


Scheme 104. Chloromethanesulfonylation of **282**

Reagents and conditions: (a) $\text{ClSO}_2\text{CH}_2\text{Cl}$ (5 eq), py, 0 °C to rt, 2.5 h, R = TBS, 99% **282-TBS** (reported by Lipinski, R.),⁶⁰ R = DEIPS, 90% **282-DEIPS**.

Chloromethanesulfonyl ester **282-DEIPS** was subjected to the previously optimised 1,2-hydride shift and spiroketalisation conditions to afford the C1–C16 spiroketal fragment **189-DEIPS** (Scheme 105).⁶⁶ The chloromethanesulfonyl group was activated by $\text{Zn}(\text{OAc})_2$ (10 eq) in a mixture of DMF and H_2O (4:3) to become a good leaving group (intermediate **286**), and it was sequentially cleaved in a 1,2-hydride shift. The oxonium ion generated from the hydride shift was readily trapped by water to afford a mixture of hemiacetal **288** and hydroxyl ketone **289**. The two compounds were in a rapid equilibrium and could not be separated by flash column chromatography. The mixture was then treated with PPTS (0.5 eq) in a mixture of MeOH and CH_2Cl_2 (1:1) at 0 °C to enable the cleavage of the C3-OTES group. The ketone diol **290** formed after the TES cleavage underwent *in situ* spiroketalisation to afford the C1–C16 spiroketal fragment **189-DEIPS** of PTX-4. The overall yield for 1,2-hydride shift, TES cleavage and spiroketalisation was 57%. It was slightly lower than the reported yield with the *bis*-TBS analogue **189-TBS** (64%), but the yield was still satisfying considering the complicated process involved.⁶⁰ The spiroketalisation afforded the anomeric 6,5-anomeric spiroketal. The C7 spiroketal carbon

has a chemical shift of 105.0 ppm in the ^{13}C NMR spectrum, which is consistent with the data previously reported in the Donohoe group for the *bis*-TBS analogue **189-TBS**.^{§§§§} It was also consistent with naturally occurred and synthetic PTX with anomeric 6,5-spiroketal reported by the Fujiwara group, while in the *non*-anomeric 6,5-spiroketal and 6,6-spiroketal C7 had a chemical shift between 107.0–111.0 ppm.³¹



Scheme 105. 1,2-Hydride shift and spiroketalisation

Reagents and conditions: (a). $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (10 eq), DMF/ H_2O , (4:3), 75 °C, 8 h, 60%; (b). PPTS (0.5 eq), MeOH/ CH_2Cl_2 (1:1), 0 °C, 0.5 h. 95%.

In summary, the new DEIPS protected compound **273-DEIPS** was successfully carried through the required synthetic sequence to form spiroketal **189-DEIPS** without significant

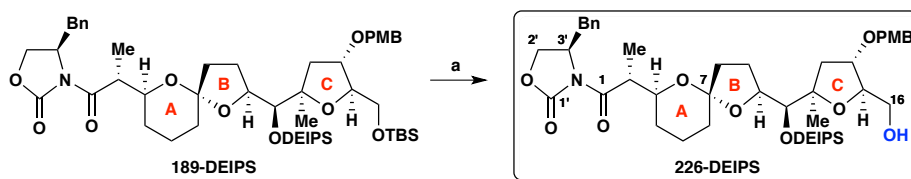
§§§§ See Appendix for a full comparison of NMR spectra between DEIPS spiroketal **189-DEIPS** and previously published data of *bis*-TBS spiroketal **189-TBS** (structure fully assigned with *nOe* correlations).

compatibility issues. The overall yield for the last 8 steps was 17.8%, giving an average of 81% for each step. The C1–C16 spiroketal fragment was prepared on a 100 mg scale reproducibly.

2.5 Protecting group manipulations on the ABC spiroketal fragment 189

Three important protecting group manipulations needed to be considered for further elaborations of the C1–C16 ABC spiroketal fragment; notably selective C16-OTBS group, C11-ODEIPS group, and C1 oxazolidinone group cleavage. The following section details an application of the optimised conditions on the real system, with particular focus on cleavage of the C1 oxazolidinone group.

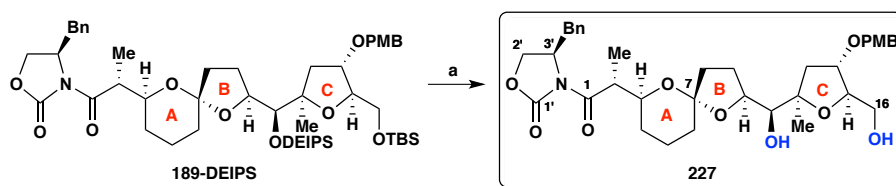
With the previous optimisations on the model substrate **273-DEIPS** containing the BC rings (**Scheme 97**), selective deprotection of the primary C16-OTBS group using HF•Py/Py (2:3) in THF at 0 °C for 5.5 hours afforded the desired product **226-DEIPS** in a good yield of 80% (**Scheme 106**). The structure of **226-DEIPS** was confirmed by the disappearance of the *t*Bu-*H* singlet at 0.09 ppm and the TBS-SiCH₃ signal at 0.06 ppm in the ¹H NMR spectrum. Another obvious change in the ¹H NMR was that the C16-*H_AH_B* protons at 3.67 ppm and 3.42 ppm moved to 3.75 ppm and 3.53 ppm after the reaction. The chemical shift change was similar to those previously observed in the model study (**Scheme 97**). The product also has a peak of at 804.40915 Da corresponding to [M + Na⁺] of **226-DEIPS** in the high resolution mass spectrometry. Therefore, selective deprotection of the C16-OTBS group proved to be successful.



Scheme 106. Selective primary TBS deprotection on the spiroketal **189**

Reagents and conditions: (a) HF•Py, Py, THF, 0 °C, 5.5 h, 80%.

Moreover, treatment of the spiroketal **189-DEIPS** with TASF in THF afforded compound **227-DEIPS** in a good yield of 75%. The structure of **227-DEIPS** was confirmed by the disappearance of the *t*Bu-*H* singlet at 0.09 ppm, the TBS-SiCH₃ signal at 0.06 ppm, the DEIPS-CH₃ signal at 1.04–0.93 ppm and the DEIPS-CH₂ signal at 0.76–0.52 ppm in the ¹H NMR spectrum. Another obvious change in the ¹H NMR spectrum was the C16-*H_AH_B* at 3.67 ppm and 3.42 ppm moved to 3.73 ppm and 3.52 ppm after the reaction. The chemical shift change was similar to those previously observed in the model study (**Scheme 96**). The product had a peak at 676.30853 Da corresponding to [M + Na⁺] of diol **227** in high resolution mass spectrometry. The global deprotection condition tested was successful.

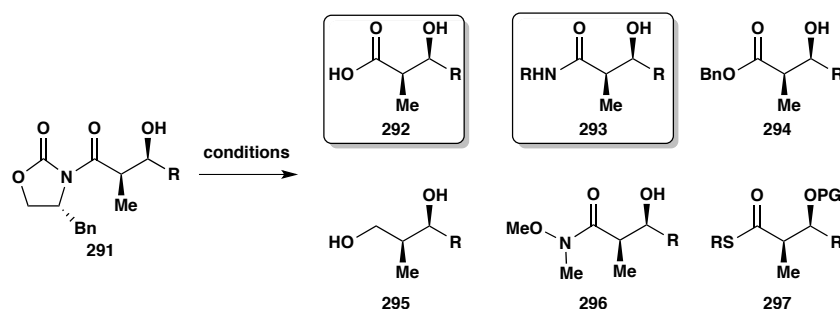


Scheme 107. Global deprotection test of **189-DEIPS** with TASF

Reagents and conditions: (a) TASF, THF, 0 °C to rt, 1 h, 75%.

With ample quantities of spiroketal **189-DEIPS** in hand, attention shifted to cleavage of the C1 oxazolidinone moiety. Following the previous plan in the retrosynthetic analysis (**Section 1.4**), the oxazolidinone moiety would be carried through the synthetic sequence as a *pseudo*-carboxylic acid protecting group. Literature research suggests that the Evans oxazolidinone is commonly removed immediately after an aldol reaction,^{142, 143} and rarely is an oxazolidinone was carried through a synthetic sequence.

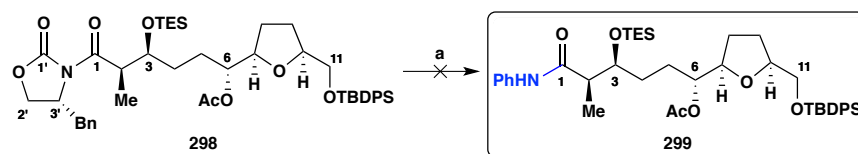
The cleavage of oxazolidinones is known to be versatile, since it could be cleaved to form the carboxylic acid, alcohol, ester, amide, or thioester depending on the requirements of the synthesis (**Scheme 108**).¹⁴⁴ In our case, the most convenient functional group to prepare was the carboxylic acid, which would readily participate in the macrolactonisation step without further modification at late stage. Another attractive conversion was a transamidation with phenylaniline, which was known to work well for the later stage manipulations in Evans's synthesis of PTX-4.³⁰



Scheme 108. Cleavage of the oxazolidinone moiety

Reagents and conditions: (a) LiOH, H₂O₂, **292**; (b) RNH₂, AlMe₃, **293**; (c) LiOBn, **294**; (d) LiBH₄, **295**; (e) MeONHMe•HCl, **296**; (f) LiSBn, AlMe₃, **297**.

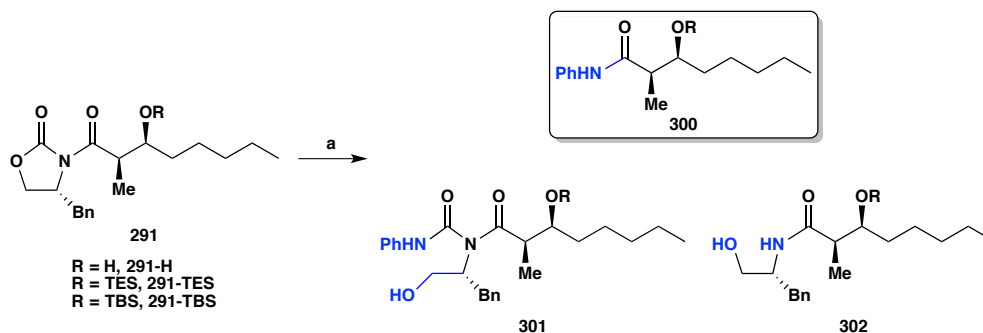
Previous research in the Donohoe group tested the transamidation method on the C1–C10 model compound of PTX-4 **298** (Scheme 109).⁶⁶ Treatment of **298** with PhNH₂ and AlMe₃ in CH₂Cl₂ only afforded a complex mixture of products. Further optimisation by varying the temperature and stoichiometry of reagents did not improve this reaction.



Scheme 109. Failed transamidation with PhNH₂⁶⁶

Reagents and conditions: (a) PhNH₂, AlMe₃, CH₂Cl₂, 0 °C.

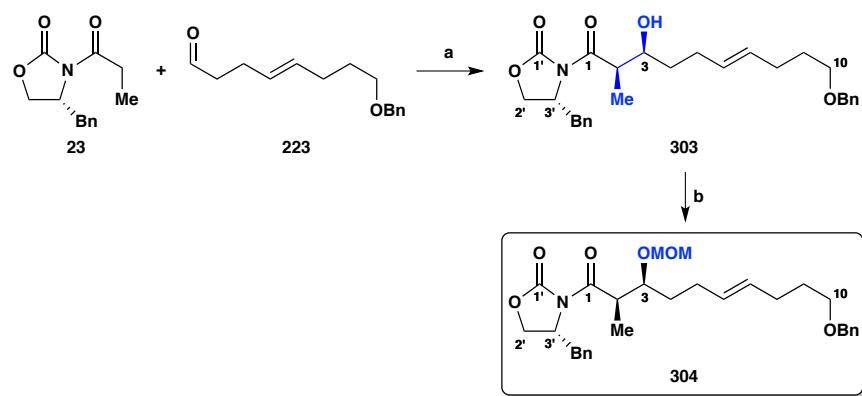
The failure of the transamidation of **298** was ascribed to the presence of a protecting group at C3-*OH* group, since treatment of compound **291-H** with PhNH₂ and AlMe₃ in CH₂Cl₂ afforded amide **300-H** in a good yield of 82% (Scheme 110). If the C3-*OH* group was protected with a TES group or a TBS group, the yield of the desired amide (**300-TES** and **300-TBS**) decreased to 37% and 52% respectively under the same reaction conditions, with significant amounts of side products **301** and **302** formed. These side products are the result of nucleophilic attack of PhNH₂ at the C1' carbonyl carbon in the oxazolidinone. As a result, the transamidation method was not applicable to the C1–C16 spiroketal fragment **189-DEIPS** without a free hydroxyl group at C3.



Scheme 110. Transamidation investigations on model substrates⁶⁶

Reagents and conditions: (a) PhNH_2 , AlMe_3 , CH_2Cl_2 , 0°C to rt, 12 h, $\text{R} = \text{H}$, 82% **300-H**, $\text{R} = \text{TES}$, 37% **300-TES**, $\text{R} = \text{TBS}$, 52% **300-TBS**.

Considering the difficulties encountered in the Lewis acid promoted transamidation, we instead chose to cleave the oxazolidinone moiety to the corresponding carboxylic acid. A model aldol product **303** and its C3-*OH* protected derivatives **304** was prepared to investigate the reactivity under the acidic cleavage conditions (**Scheme 111**). A MOM group was chosen since it was also expected that this acid labile protecting group would mimic the stability of the spiroketal moiety in the real system. Treatment of aldehyde **223** with the *Z*-boron enolate of **23** afforded compound **303** in 82% yield. The C3-*OH* group was protected with MOMI in the presence of *i* Pr_2NEt and DMAP to generate **304** in 86%.

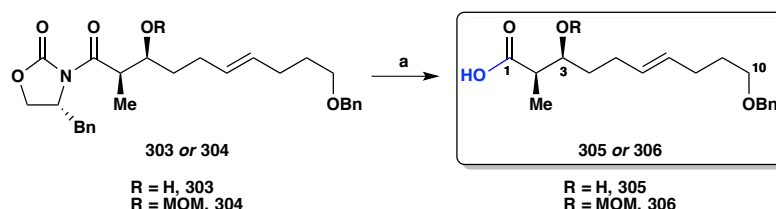


Scheme 111. Preparation of model oxazolidinone cleavage substrates

Reagents and conditions: (a) *n*Bu₂BOTf, Et₃N, CH₂Cl₂, -78 °C to 0 °C, 3 h, 82%; (b) MOMI, *i*Pr₂NEt, DMAP, THF, 0 °C to 65 °C, 16 h, 86%.

Studies commenced with aldol product **303**. Treatment with *in situ* formed LiOOH (generated from LiOH and H₂O₂) provided the crude acid **305** in quantitative yield (**Scheme 112**). The formation of acid **305** was confirmed by ¹H NMR spectrum, which showed the absence of the oxazolidinone proton signals at 4.69 ppm (C3'-H), 2.43 ppm and 2.39 ppm (C2'-H₂). In the standard acidic cleavage of the oxazolidinones, an acidification to adjust the pH to 1~2 during workup was required to allow the product enter the organic phase. This could potentially cause problems to the spiroketal system since it was reported that the AB spiroketal of PTXs would isomerise under acidic conditions.^{30, 31} In practice, we found that the acidification process was not compulsory for acid **305** if CH₂Cl₂ or CHCl₃ was used for extraction. The optimised conditions were successfully applied to compound **304** to give the corresponding acid **306** in 83% yield. The presence of two doublets at 4.68 ppm (*J* = 6.9 Hz, MOM-CH_AH_B), and 4.65 ppm (*J* = 6.9 Hz, MOM-CH_AH_B), in addition to a singlet at 3.37 ppm (MOM-CH₃) in the ¹H NMR spectrum indicated the acid labile MOM

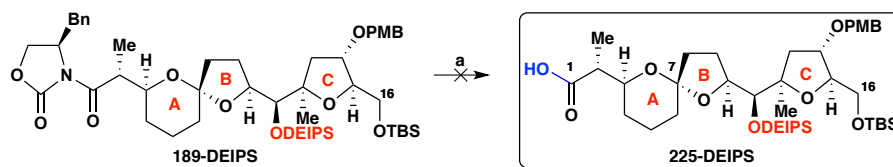
group had survived under these conditions. It was therefore expected that the acid labile spiroketal would also not be affected during the cleavage of oxazolidinone to the carboxylic acid.



Scheme 112. Acidic oxazolidinone cleavage on model substrates.

Reagents and conditions: (a) LiOH, H₂O₂, H₂O, THF, 0 °C, 3 h, R = H, 99% **305**, R = MOM, 83% **306**.

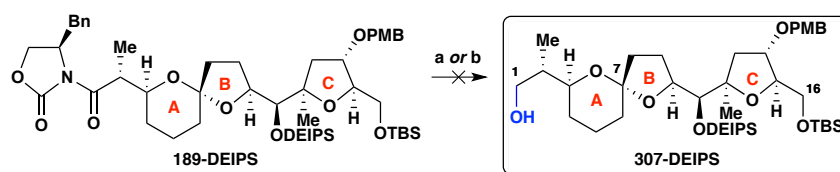
Following this promising result, the spiroketal fragment **189-DEIPS** was treated under the same conditions (**Scheme 113**). Unfortunately, this resulted in a disappointingly low conversion of the starting material (0 °C, 3 h). Although the $[M - H^+]$ peak at 735.4 ppm was detected in the mass spectrometry, the isolated yield of the carboxylic acid **225-DEIPS** was less than 10% after a further 3 hours at room temperature. In another test reaction (5 mg scale, 5.6 μ mol), TLC of the reaction mixture indicated that the conversion of the starting material to the desired product was still minimal after 3 days at room temperature. The acidic oxazolidinone cleavage conditions were unfortunately not applicable to the spiroketal fragment **189-DEIPS**. It was ascribed that the C3-*O* might be crucial to assist the activation at C1 by a cation (e.g., Li) chelated to both C1-*O* and C3-*O*. When restricted in the spiroketal rings, C3-*O* was possibly not able to participate this process, leading to a failure in the reaction.



Scheme 113. Acidic oxazolidinone cleavage of the spiroketal **189-DEIPS**

Reagents and conditions: (a) LiOH, H₂O₂, H₂O, THF, 0 °C to rt, 6 h.

Given the difficulties encountered when attempting to remove the oxazolidinone in **190-DEIPS** to an acid directly, reductive cleavage to the alcohol was considered. The alcohol could then be converted to the corresponding carboxylic acid in additional steps. However, treatment of **189-DEIPS** with LiBH₄ and H₂O in THF only afforded unreacted starting material rather than the desired product **307-DEIPS** (Scheme 114). Furthermore, the starting material (**189-DEIPS**) decomposed if harsher conditions involving LiAlH₄ was used. Thus it did not prove possible to use the oxazolidinone group as a *pseudo*-protecting group for the C1 acid moiety in our synthesis.

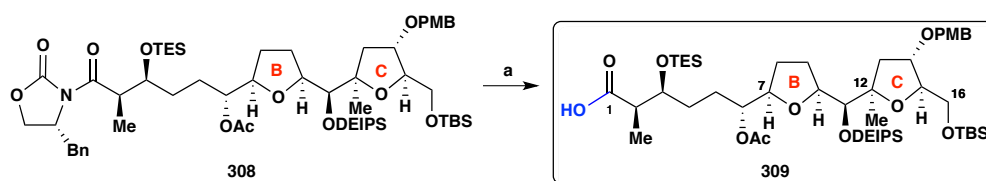


Scheme 114. Reductive cleavage of oxazolidinone auxiliary

Reagents and conditions: (a) LiBH₄, H₂O, THF, 0 °C to rt; (b) LiAlH₄, THF, 0 °C.

Considering the failure to remove the C1 oxazolidinone of **189-DEIPS**, the synthetic route was revised to finish so that the oxazolidinone was cleaved prior to the 1,2-hydride shift and

spiroketalisation steps. Treatment of compound **308** with LiOOH (formed *in situ* from LiOH and H₂O₂) in THF pleasingly afforded 81% of desired acid **309** (Scheme 115). It was noticed that all the signals corresponding to the oxazolidinone disappeared after the reaction in NMR spectra. The Ac-CH₃ at 2.05 ppm in ¹H NMR spectra, the TES-CH₃ at 6.9 ppm and the TES-CH₂ at 5.1 ppm in the ¹³C NMR spectra were all observed for the isolated product **309**, which proved that both Ac and TES protecting groups survived the reaction conditions. The product had a peak at 933.53638 Da corresponding to [M + Na⁺] of acid **309** in high resolution mass spectrometry. The oxazolidinone cleavage proved to be successful. Future work should therefore involve cleavage of the C1 oxazolidinone before the formation of the AB spiroketal of PTX-4.



Scheme 115. Alternative oxazolidinone auxiliary cleavage before spiroketalisation

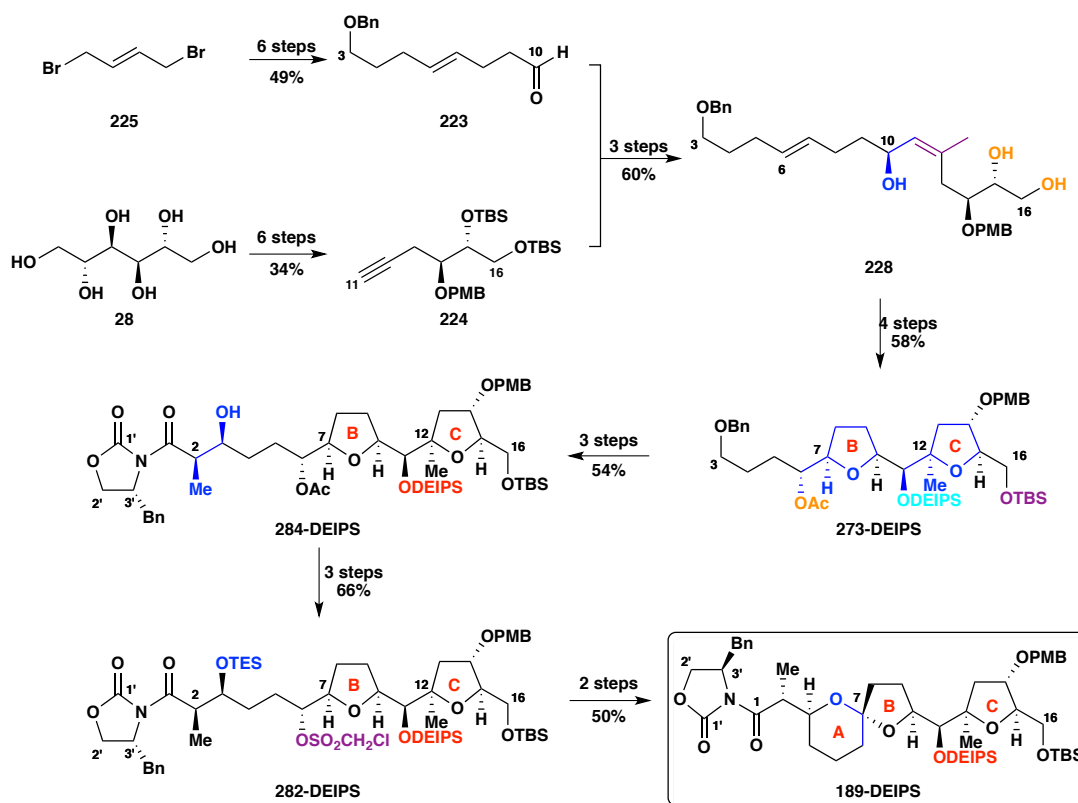
Reagents and conditions: (a) LiOH, H₂O₂, H₂O, THF, 0 °C, 3 h, 81%.

In summary, the selective deprotection of the C16-OTBS group was successful in presence of HF•py/py. It was also demonstrated that the C11-ODEIPS group could be cleaved under the mild desilylation conditions (TASF). The cleavage of the C1 oxazolidinone to the carboxylic acid was unsuccessful when LiOOH were applied to the spiroketal fragment **189-DEIPS**. However, the desired removal of oxazolidinone could be achieved when the same conditions were performed prior to the 1,2-hydride shift and spiroketalisation.

2.6 Conclusions and Future work

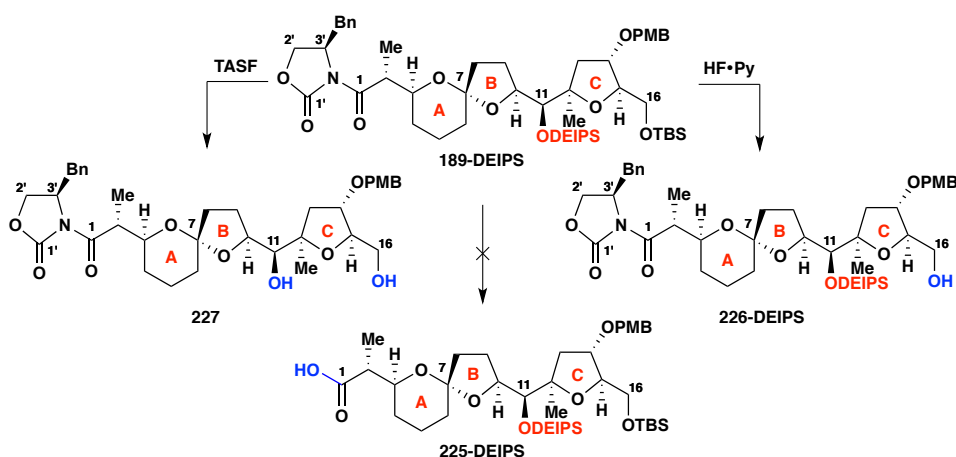
The previous synthetic route towards the C1–C16 spiroketal fragment of PTX-4 was further optimised. The problematic Carreira alkynylation between aldehyde **223** and alkyne **224** was systematically studied, and now affords reproducible yields on a large scale (up to 20 g). The protecting group strategy has been revised so that cleavage of the C1 oxazolidinone, selective silyl deprotection (of the C16-OTBS group) removal of the C11-ODEIPS group can now be accomplished.

The optimised route is summarised in **Scheme 116**. The route commences from commercially available D-mannitol **28** and *trans*-1,4-dibromo-but-2-ene **225**. It contains 21 longest linear steps with a total number of steps of 27. The overall yield for the longest linear sequence is 2.1% (83% per step). All the steps before the osmium catalysed oxidative cyclisation to form the BC rings were successfully performed on a 10 to 50 g scale. The oxidative cyclisation, protecting group manipulations and Evans *syn*-aldol reaction were carried out on a 1 to 5 g scale. Further protecting group manipulations and formation of the AB spiroketal were at over 100 mg scale.



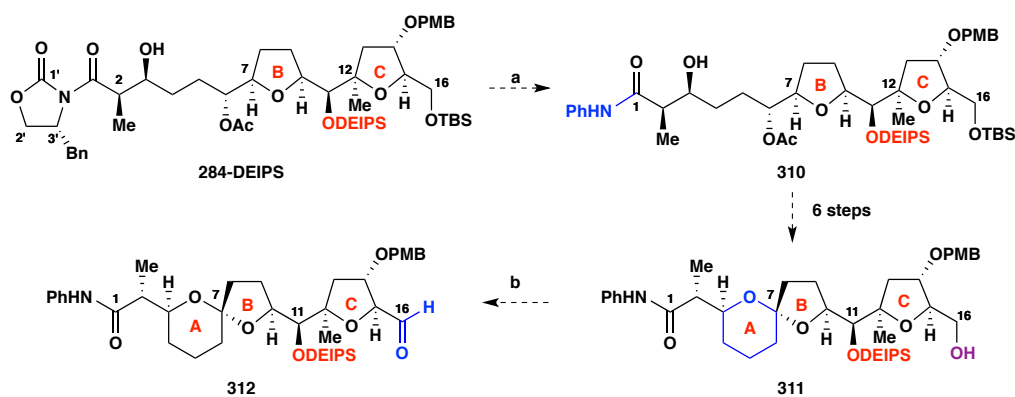
Scheme 116. Summary of optimised route for the C1-C16 fragment **189-DEIPS**

The final optimised protecting group strategy is compatible with our proposed global deprotection conditions using TASF, and it is possible to selectively deprotect the C16-OTBS group (**Scheme 117**). Unfortunately, removal of the C1 oxazolidinone was not successful on spiroketal fragment **189-DEIPS**, but it was proven that this transformation could be achieved before 1,2-hydride shift and spiroketalisation (Section 2.6).



Scheme 117. Protecting group operation on spiroketal

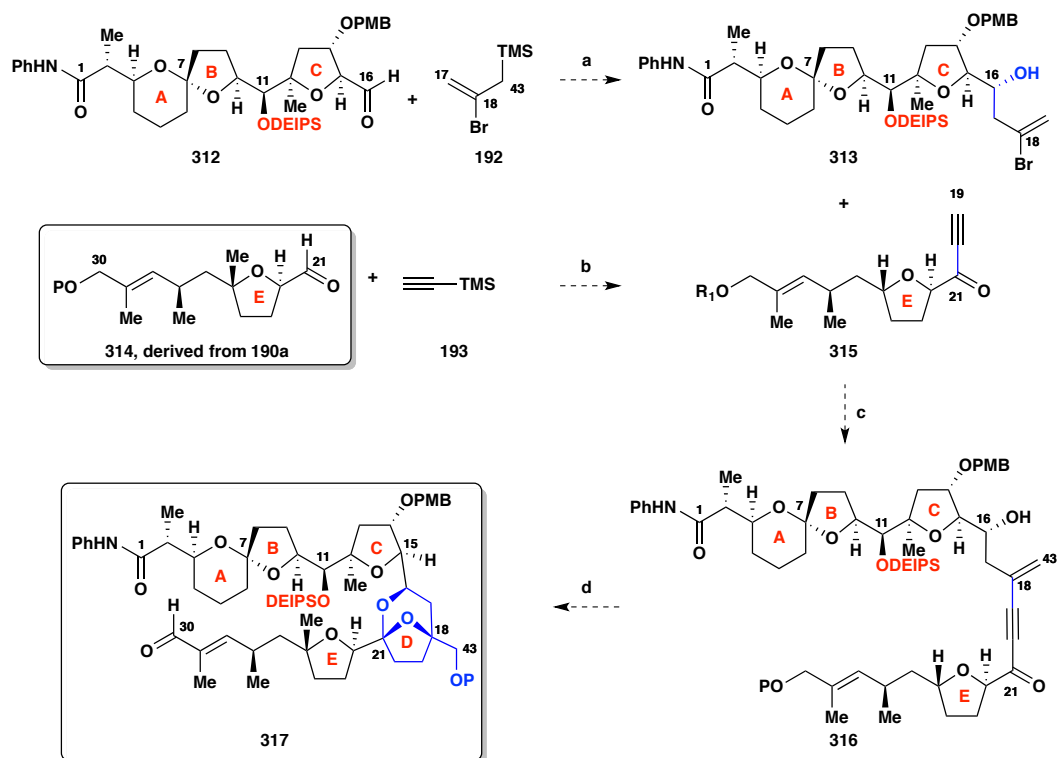
Future work involving the C1–C16 spiroketal fragment **189-DEIPS** is shown in **Scheme 118**. We plan to mask the C1 acid moiety with the phenylaniline group. Aldol product **284-DEIPS** will be subjected to the transamidation conditions directly, rather than cleaved to the C1 acid moiety first. Compound **310** would then be converted to the C16 primary alcohol spiroketal **311** using the existing route. The C16-*OH* group will be oxidised to the aldehyde for further synthetic manipulations.



Scheme 118. Planned future work on the ABC spiroketal

Reagents and conditions: (a) i. LiOH, H₂O₂, THF, H₂O; ii. PhNH₂, AlMe₃, CH₂Cl₂; (b) i. TESCl, DMAP, Imidazole, CH₂Cl₂; ii. DIBAL-H, THF; iii. Chloromethanesulfonyl chloride, Py; iv. Zn(OAc)₂•2H₂O, DMF, H₂O; v. PPTS, MeOH, CH₂Cl₂; vi. HF•Py, Py, THF; (c) Dess–Martin periodinane, Py, CH₂Cl₂.

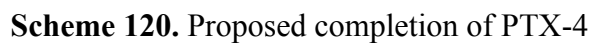
The formation of the bicyclic D-ring is currently under investigation in the Donohoe group (**Scheme 119**).¹⁴⁵ A Felkin–Ahn controlled addition of vinylbromide **192** to **312** will afford bromide **313**. Sonogashira coupling with alkyne **315** (prepared from **190a** derivative **314** and trimethylacetylene **193**) should then provide D ring precursor **316**. The stereochemistry of the C18-*OH* group and C43-*OH* group is to be set by a Sharpless asymmetric dihydroxylation. After hydrogenation of the C19–C20 triple bond, the D-ring will then be formed under acidic ketalisation conditions. Further protecting group and oxidation state manipulations will give rise to the C30 aldehyde **317**.



Scheme 119. Planned fragment assembly for PTX-4

Reagents and conditions: (a) Felkin-Ahn controlled addition; (b) alkynylation and propargylic alcohol oxidation; (c) Sonogashira coupling; (d) C18-C43 Sharpless asymmetric dihydroxylation, C19-C20 hydrogenation, C43 protection, ketal formation, C30 deprotection and oxidation.

The proposed completion of PTX-4 is depicted in **Scheme 120**. The C31-C40 FG ring fragment is to be connected to the rest of molecule *via* a Julia-Kocienski olefination to form the C30-C31 double bond. Macrolactonisation between the C1 acid and the C33-OH will complete the ring framework of PTX-4. Subsequent deprotection and oxidation at the C36-OPMB group and global silyl deprotection with TASF will complete the total synthesis of PTX-4.



Chapter 3

Experimental

3.1 General Methods

^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded either on a Bruker Avance DPX 200, AVIIIHD 400, AVII 500 spectrometers in CDCl_3 , CD_3OD , $\text{DMSO}-d_6$ or C_6D_6 and referenced to residual solvent peaks. Chemical shifts are quoted in ppm (parts per million) to the nearest 0.01 ppm for ^1H NMR and 0.1 ppm for ^{13}C NMR and ^{19}F NMR. Signal splittings are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), multiplet (m) and broad singlet (br. s). Coupling constants, J , are measured in Hz to the nearest 0.1 Hz. Assignments are based on DEPT, COSY, HSQC, HMBC and NOESY experiments and by comparison with those of known compounds.

Infrared spectra were recorded as thin films of neat samples or powders on a Bruker Tensor 27 FT-IR spectrometer equipped with attenuated total sample reflectance sampling accessories. Absorption maxima are quoted in wavenumbers (cm^{-1}) in the range 3500–1000 cm^{-1} .

High resolution mass spectra (HRMS) were recorder on a Bruker MicroTOF spectrometer (resolution = 10000 FWHM) under conditions of electrospray (ESI) or field ionization (FI), calibrated *via* the lock-mass of tetraoctyl ammonium bromide for positive ions and sodium dodecyl sulfate for negative ions. Masses are reported as the ratio of mass to charge in Daltons to four decimal places.

Melting points (m.p.) were measured from recrystallised samples using a Leica VMTG heated-stage microscope and are uncorrected.

Specific optical rotations were measured on a Perkin Elmer 241 Polarimeter at the sodium D line (589.3 nm) in CHCl_3 or ACS photo spectroscopic grade CH_2Cl_2 and are reported in the units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Solution concentrations are given in units of $10^{-2} \text{ g mL}^{-1}$.

Reagents obtained from Sigma-Aldrich, Alfa Aesar, Acros, Fluorochem and TCI were used directly as supplied unless otherwise stated. Sensitive reagents were stored in dessiccators. Anhydrous triethylamine, *N,N*-disopropylethylamine and pyridine were used directly from Sure Seal[®] bottles (Sigma-Aldrich).

MeCN , CH_2Cl_2 , Et_2O , MeOH , THF and PhMe were dried by filtration through an activated alumina purification column.

Anhydrous reactions were carried out under an inert atmosphere of argon. Glassware in these reactions was flame-dried under vacuum prior to use. All reactions were carried out at room temperature unless otherwise specified.

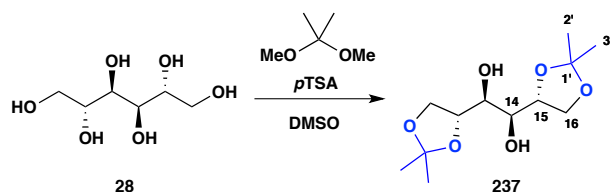
Flash column chromatography was performed using silica gel (60 Å, 0.033–0.070 mm, Merck). Thin layer chromatography (TLC) analyses were performed on Merck Kieselgel 60 F_{254} 0.25 mm precoated silica plates. Products spots were visualized under UV light ($\lambda_{\text{max}} =$

254 nm or 365 nm) and/or by staining with vanillin, potassium permanganate or phosphomolybdic acid solution.

All the compounds related to PTX-4 were numbered according to their positions in the natural product.

3.2 Experimental

(1*S*,2*S*)-1,2-bis((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol **237**



2,2-Dimethoxypropane (80.0 mL, 67.7 g, 656 mmol) was added to a solution of D-mannitol **28** (50.0 g, 275 mmol) and *p*-toluensulfonic acid (276 mg, 1.45 mmol) in DMSO (82 mL) under an atmosphere of air. The solution was stirred for 2 hours until all of the solids were dissolved and then a further 16 hours under an atmosphere of air, before being quenched by addition of aqueous NaHCO₃ solution (3% w/v, 300 mL). The mixture was extracted with EtOAc (4 × 400 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. A flask containing the crude product was fitted with an air condenser. EtOAc (150 mL) was added to the white solid and gently heated until all the solids had dissolved. The solution was diluted with hot pentane (450 mL) and allowed to cool down slowly to room temperature, before further cooling down to in a freezer overnight (−18 °C). The resulting solid was filtered, and washed with cold ether. The product was dried under vacuum to give a white crystalline solid **237** (42.7 g, 164 mmol, 60%).

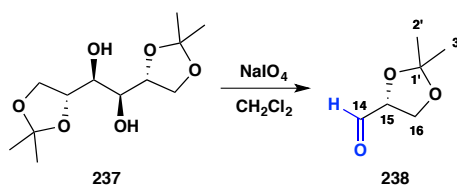
$[\alpha]_D^{25} +9.4$ ($c = 1.05$, CHCl₃; lit. +6.0, $c = 5$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 4.19 (2 H, q, $J = 6.2$ Hz, C(15)H × 2), 4.14–4.10 (2 H, dd, $J = 8.4, 6.5$ Hz, C(16)H_AH_B × 2), 4.00–3.96 (2 H, dd, $J = 8.5, 5.5$ Hz, C(16)H_AH_B × 2), 3.75 (2 H, t, $J = 6.3$ Hz, C(14)H × 2), 2.68 (2 H, s, OH × 2), 1.42 (6 H, s, CH₃ × 2), 1.36 (6 H, s, CH₃ × 2); ¹³C NMR (100 MHz,

CDCl_3) δ_{C} 109.4 ($\text{C1}' \times 2$), 76.2 ($\text{C15} \times 2$), 71.2 ($\text{C14} \times 2$), 66.7 ($\text{C16} \times 2$), 26.7 ($\text{CH}_3 \times 2$), 25.2 ($\text{CH}_3 \times 2$); **m.p.** 118–119 °C (lit. 120–122 °C).

Spectroscopic data were consistent with those previously reported.⁶⁶

(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde **238**

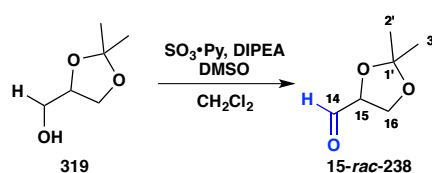
Procedure A:



Diol **237** (10.0 g, 38.4 mmol) was dissolved in CH_2Cl_2 (100 mL) under an atmosphere of air.

An aqueous solution of NaHCO_3 (sat., 8 mL) was added and the mixture was cooled to 0 °C in an ice-water bath. NaIO_4 (16.4 g, 76.8 mmol) was added to the vigorously stirring mixture in small portions at 0 °C over 10 minutes. Once the addition was complete, the reaction was allowed to gradually warm to room temperature. After 2 hours, MgSO_4 (6.0 g) was added and the solution was stirred for a further 20 minutes. The slurry was filtered through celite and the solvent was concentrated *in vacuo* (**Caution:** product is volatile). Crude aldehyde **238** (9.2 g, 92%) was obtained as colourless oil and used in the next step without further purification.

Procedure B:



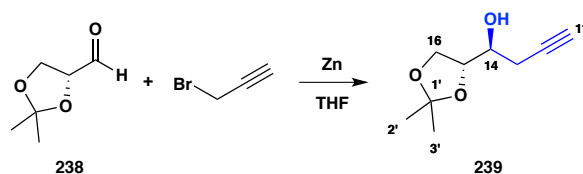
DL-1,2-Isopropylidenglycerol **319** (0.47 mL, 3.80 mmol) and DMSO (0.80 mL, 11 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. $i\text{Pr}_2\text{NEt}$ (1.98 mL, 11 mmol) and sulfur trioxide pyridine complex (1.80 g, 11.4 mmol) were added and the mixture was stirred at 0 °C for 45 minutes. The reaction was quenched by addition of H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 5:95 EtOAc:Pentane) to afford **15-*rac*-238** as a colourless oil (320 mg, 64 %).

$R_f = 0.8$ (20:80 EtOAc:Pentane); $[\alpha]_D^{25} +63.2$ ($c = 1.27$, CHCl_3 ; lit. $+53.8$, $c = 2$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ_H 9.72 (1 H, d, $J = 1.8$ Hz, C(14)*H*), 4.42–4.35 (1 H, m, C(15)*H*), 4.21–4.03 (2 H, m, C(16)*H*₂), 1.48, (3 H, s, CH_3), 1.41 (3 H, s, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_C 201.8 (C14), 111.2 (C1'), 76.7 (C15), 65.6 (C16), 26.2 (CH_3), 25.1 (CH_3)

Spectroscopic data were consistent with those previously reported.⁶⁶

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-yn-1-ol **239**

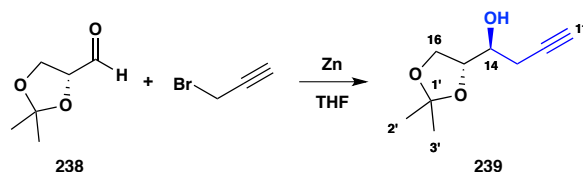
Procedure A:



Zinc powder (13.6 g, 208 mmol) was suspended in THF (80 mL) and cooled in an ice-water bath to 0 °C under an atmosphere of air. Propargyl bromide (80% in PhMe, 14.9 mL, 138 mmol) was added dropwise at 0 °C. After stirring for 30 minutes, crude aldehyde **238** (9.00 g,

69.2 mmol) was added dropwise as a THF solution (20 mL). The suspension was warmed to room temperature and stirred for 12 hours. The reaction was then cooled to 0 °C and quenched by addition of an aqueous solution of NH₄Cl (sat., 80 mL). (**Caution:** strongly exothermic) The insoluble solid was removed *via* filtration, and the aqueous layer extracted with EtOAc (4 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 to 20:80 EtOAc:pentane, 1% Et₃N added as co-eluent) to give alcohol **239** as a pale yellow oil (8.4 g, 72%, 66% over two steps, 6:1 d.r.).

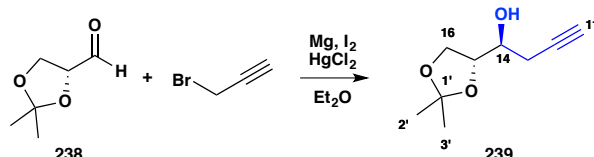
Procedure B:



Zinc powder (1.51 g, 23.1 mmol) was suspended in THF (8 mL) and cooled in an ice-water bath to 0 °C under an atmosphere of air. Propargyl bromide (80% in PhMe, 1.65 mL, 15.4 mmol) was added dropwise at 0 °C. The mixture was warmed to room temperature and crude aldehyde **238** (1.0 g, 7.7 mmol) was added in one portion as a THF solution (2 mL). The suspension was stirred for 12 hours. The reaction was quenched by addition of an aqueous solution of NH₄Cl (sat., 10 mL) and the insoluble solid was removed *via* filtration. The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 to 20:80 EtOAc:Pentane,

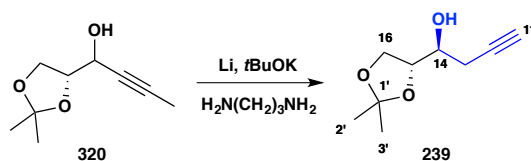
1% Et₃N added as co-eluent) to give alcohol **239** as a pale yellow oil (698 mg, 53% over two steps, 4:1 d.r.).

Procedure C:



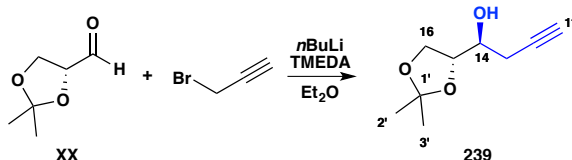
Magnesium turnings (0.37 g, 15 mmol), HgCl₂ (5.0 mg, 20 μmol), and I₂ (5.0 mg, 20 μmol) were added to Et₂O (8 mL) and the mixture spontaneously refluxed. After 5 minutes, the mixture was cooled to 0 °C and propargyl bromide (80% in PhMe, 1.7 mL, 15 mmol) was added dropwise. The reaction was heated at reflux for 1 hour before being cooled to 0 °C. Crude aldehyde **238** (1.0 g, 7.7 mmol) was added in one portion as an Et₂O solution (2 mL). The reaction was allowed to warm to room temperature and stir 12 hours, before being quenched by addition of an aqueous solution of NH₄Cl (sat., 10 mL). The insoluble solid was removed *via* filtration and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 to 20:80 EtOAc:Pentane, 1% Et₃N added as co-eluent) to give alcohol **239** as a pale yellow oil (491 mg, 48%, 38% over two steps, 3:1 d.r.).

Procedure D:



Lithium wire (32 mg, 4.6 mmol) was cleaned with towel paper, cut into small pieces, added to 1,3-diaminopropane (2 mL), and stirred for 30 minutes before heating to reflux until all the blue colour had disappeared. The mixture was cooled to room temperature and $t\text{BuOK}$ (345 mg, 3.10 mmol) was added portionwise into the reaction mixture. At room temperature, propargyl alcohol **320** (80 mg, 0.61 mmol, 1:1 d.r.) was added dropwise and the reaction was stirred overnight. The mixture was then poured into an ice-water bath. The aqueous layer was extracted with EtOAc (4×10 mL) and the combined organic layers were washed with water (10 mL), 10% aqueous HCl solution (10 mL), brine (10 mL), and dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 1:99 EtOAc:Pentane to 20:80 EtOAc:Pentane, 1% Et_3N added as co-eluent) to afford **239** as pale yellow oil (35 mg, 44%, 4:1 d.r.).

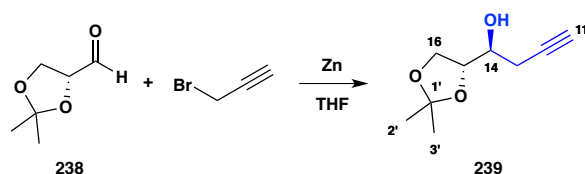
Procedure E:



A solution of $n\text{BuLi}$ (1.6 M in hexane, 19.2 mL, 30.7 mmol) in Et_2O (20 mL) was cooled to -78°C in a dry ice-acetone bath. TMEDA (1.15 mL, freshly distilled from CaH_2) was added dropwise to the solution, followed by propargyl bromide (80% w/v in PhMe, 1.69 mL, 15.2 mmol). The solution was stirred at -78°C for 20 minutes. Aldehyde **238** (1.00 g, 7.68

mmol) was dissolved in Et₂O (5 mL) and added dropwise over 5 minutes at. The reaction was allowed to warm to room temperature over 2 hours and stirred for a further 24 hours before quenching with an aqueous solution of NH₄Cl (sat., 20 mL). The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 to 20:80 EtOAc:Pentane, 1% Et₃N added as co-eluent) to give alcohol **239** as a pale yellow oil (559 mg, 43%, 10:1 d.r.).

Procedure F:



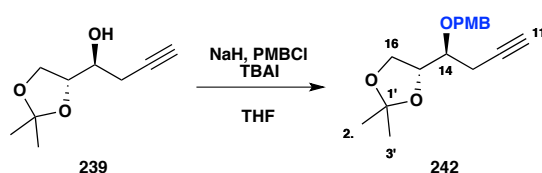
Zinc powder (8.20 g, 125 mmol) was suspended in THF (30 mL) and cooled to 0 °C under an atmosphere of air. Propargyl bromide (80% w/v in PhMe, 13.9 mL, 125 mmol) was added dropwise *via* a syringe pump (0.5 mL/min) at 0 °C. After stirring 1 hour, the reaction mixture was cooled to −78 °C in a dry ice-acetone bath. Crude aldehyde **238** (8.10 g, 62.2 mmol) was added dropwise as a THF solution (10 mL) *via* a syringe pump (0.3 mL/min). The suspension was stirred at −78 °C for 2 hours before being warmed to 0 °C in an ice-water bath. The mixture was allowed to warm to room temperature in the bath and stirred for 12 hours. (**Caution:** extremely exothermic) The reaction was then cooled to 0 °C in an ice-water bath and quenched by addition of an aqueous solution of NH₄Cl (sat., 40 mL). The precipitate was removed *via* filtration. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with brine (40 mL),

dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 10:90 to 20:80 EtOAc:Pentane, 1% Et_3N added as co-eluent) to give alcohol **239** as a pale yellow oil (8.06 g, 76%, 62% over two steps, 8:1 d.r.).

$R_f = 0.4$ (40:60 EtOAc:Pentane); $[\alpha]_D^{20} +3.6$ ($c = 1.17$, CHCl_3 ; lit. $+3.6$, $c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3), major diastereoisomer δ_{H} 4.11–4.05 (2 H, m, C(16) H_AH_B , C(15) H), 4.08–3.95 (1 H, m, C(16) H_AH_B), 3.77 (1 H, m, C(14) H), 2.55 (1 H, br, OH), 2.50 (2 H, m, C(13) H_2), 2.07 (1 H, t, $J = 2.6$ Hz, C(11) H), 1.41 (3 H, s, CH_3), 1.35 (3 H, s, CH_3); ^{13}C NMR (100 MHz, CDCl_3), major diastereoisomer δ_{C} 109.4 (C1'), 80.0 (C12), 77.4 (C15), 71.2 (C11), 70.1 (C14), 65.9 (C16), 26.7 (CH_3), 25.1 (CH_3), 23.6 (C13).

Spectroscopic data were consistent with those previously reported.^{60, 146}

(*R*)-4-((*S*)-1-((4-Methoxybenzyl)oxy)but-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane 242

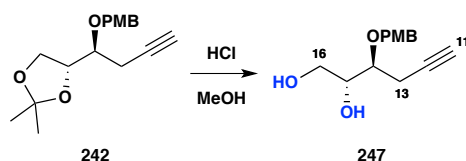


Alcohol **239** (20.0 g, 118 mmol) was dissolved in THF (200 mL) and cooled to 0 °C in an ice-water bath. NaH (57–63% suspension in mineral oil, 5.40 g, 135 mmol) was added portionwise over 5 minutes, and the solution was stirred at 0 °C for 1 hour. *tetra*-Butylammonium iodide (TBAI, 2.20 g, 5.90 mmol) was added in one portion, followed by dropwise addition of 4-methoxybenzyl chloride (PMBCl, 16.8 mL, 123 mmol). The flask was then equipped with an air condenser and the mixture was heated at 60 °C for 16 hours

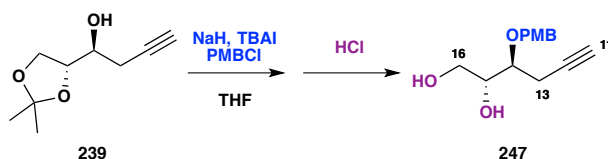
before being cooled to room temperature. The reaction was quenched by addition of an aqueous solution of NH_4Cl (sat., 100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4×150 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 5:95 Et_2O :Pentane to 20:80 Et_2O :Pentane, 1% Et_3N added as co-eluent) to give **242** as pale yellow oil (34.1 g, 100%).

$R_f = 0.5$ (40:60 Et_2O :Pentane); $[\alpha]_D^{25} +37.5$ ($c = 1.16$, CH_2Cl_2 ; lit. $+37.3$, $c = 1.64$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_H 7.29 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 6.88 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 4.73 (1 H, d, $J = 11.2$ Hz, PMB- CH_AH_B), 4.53 (1 H, d, $J = 11.2$ Hz, PMB- CH_AH_B), 4.18 (1 H, q, $J = 6.3$ Hz, C(15)H), 4.06 (1 H, dd, $J = 8.4, 6.4$ Hz, C(16) H_AH_B), 3.88 (1 H, dd, $J = 8.5, 5.4$ Hz, C(16) H_AH_B), 3.81 (3 H, s, PMB- OCH_3), 3.55 (1 H, dt, $J = 7.1, 4.9$ Hz, C(14)H), 2.66–2.60 (1 H, m, C(13) H_AH_B), 2.54–2.48 (1 H, m, C(13) H_AH_B), 2.05–2.04 (1 H, m, C(11)H), 1.41 (3 H, s, CH_3), 1.35 (3 H, s, CH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_C 159.3 (PMB- C_{Ar}), 130.4 (PMB- C_{Ar}), 129.7 (PMB- $\text{C}_{Ar} \times 2$), 113.8 (PMB- $\text{C}_{Ar} \times 2$), 109.3 (C1'), 80.6 (C12), 77.2 (C14), 76.5 (C15), 72.0 (PMB- CH_2), 70.4 (C11), 66.7 (C16), 55.2 (PMB- OCH_3), 26.7 (CH_3), 25.3 (CH_3), 21.0 (C13).

Spectroscopic data were consistent with those previously reported.⁶⁰

(2*R*,3*S*)-3-((4-Methoxybenzyl)oxy)hex-5-yn-1,2-diol **247***Procedure A:*

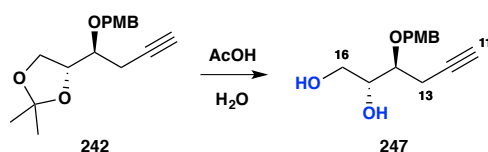
bis-Acetonide **242** (10.0 g, 6.88 mmol) was dissolved in a mixture of aqueous HCl (1 M) and MeOH (1:10, 340 mL) and stirred for 20 hours at 40 °C under an atmosphere of air. The reaction was quenched by slow adding of an aqueous solution of NaHCO₃ (sat., 50 mL), followed by small portions of solid NaHCO₃ until the pH reached 7. MeOH was then removed from the mixture under reduced pressure. After diluting with H₂O (100 mL), the aqueous phase was extracted by EtOAc (4 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 1:99 Acetone:Petane to 20:80 Acetone:Petane) to afford diol **247** as a pale yellow oil (7.1 g, 82%).

Procedure B:

Alcohol **239** (2.00 g, 11.8 mmol) was dissolved in THF (60 mL) and cooled to 0 °C in an ice-water bath. NaH (60% suspension in mineral oil, 541 mg, 13.5 mmol) was added, and the solution was stirred for 1 hour. *tetra*-Butylammonium iodide (TBAI, 217 mg, 0.587 mmol) was added, followed by dropwise addition of 4-methoxybenzyl chloride (PMBCl, 1.90 mL, 14.1 mmol). The flask was then equipped with an air condenser and the mixture was heated

to reflux for 16 hours before being allowed to cool to room temperature. An aqueous solution of HCl (3 M, 2 mL) was then added to the solution and the mixture was stirred for a further 24 hours at 40 °C. The reaction was quenched by addition of an aqueous solution of NaHCO₃ (sat., 50 mL), followed by small portions of solid NaHCO₃ until the pH reached 7. The aqueous phase was extracted with EtOAc (4 × 75 mL). The combined organic layers were washed with brine (75 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 1:99 Acetone:petane to 20:80 Acetone:Petane) to afford diol **247** (2.03 g, 69%) as a pale yellow oil.

Procedure C:



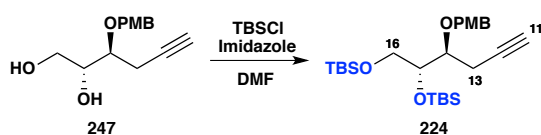
bis-Acetonide **242** (10.3 g, 35.9 mmol) was dissolved in AcOH and H₂O (4:1, 110 mL) and the mixture was stirred for 16 hours at 40 °C. The reaction was diluted with EtOAc (200 mL) and quenched by addition of small portions of solid NaHCO₃ until the pH reached 7. The aqueous phase was extracted with EtOAc (4 × 150 mL). The combined organic layers were washed with an aqueous solution of NaHCO₃ (sat., 100 mL), brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 1:99 Acetone:Pentane to 20:80 Acetone:Petane) to afford diol **247** as a pale yellow oil (6.4 g, 72%).

$R_f = 0.5$ (40:60 Acetone:Pentane); $[\alpha]_D^{25} +37.7$ ($c = 1.07$, CH_2Cl_2 ; lit. $+39.5$, $c = 1.10$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_H 7.27 (2 H, d, $J = 8.5$ Hz, PMB-ArH $\times 2$), 6.87 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 4.67 (1 H, d, $J = 11.2$ Hz, PMB-CH_AH_B), 4.46 (1 H, d, $J = 11.2$ Hz, PMB-CH_AH_B), 3.78 (3 H, s, PMB-OCH₃), 3.70 (2 H, m, C(16)H₂), 3.72–3.66 (1 H, m, C(15)H), 3.62–3.58 (1 H, m, C(14)H), 3.10 (1 H, br. s, OH), 2.65 (1 H, br. s, OH), 2.56 (2 H, dd, $J = 5.3, 2.6$ Hz, C(13)H₂), 2.04 (1 H, t, $J = 2.6$ Hz, C(11)H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_C 159.4 (PMB-C_{Ar}), 129.8 (PMB-C_{Ar}), 129.7 (PMB-C_{Ar} $\times 2$), 113.9 (PMB-C_{Ar} $\times 2$), 80.7 (C12), 77.7 (C14), 72.3 (C15), 72.1 (PMB-CH₂), 70.5 (C11), 63.2 (C16), 55.3 (PMB-OCH₃), 20.4 (C13).

Spectroscopic data were consistent with those previously reported.⁶⁰

(R)-5-((S)-1-((4-Methoxybenzyl)oxy)but-3-yn-1-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxaspiro[3.5]undecane 224

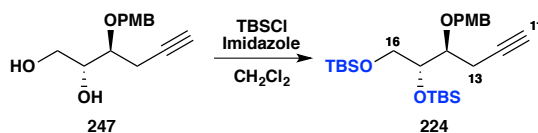
Procedure A:



Diol **247** (6.0 g, 24 mmol) was dissolved in DMF (70 mL) at 0 °C. TBSCl (10.8 g, 72.0 mmol) and imidazole (8.20 g, 120 mmol) were added to the solution and the mixture was stirred for 12 hours. The reaction was quenched by addition of H₂O (70 mL). The mixture was extracted with EtOAc (4 $\times$ 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product

was purified by flash column chromatography (SiO₂, 1:99 Et₂O:Pentane to 10:90 Et₂O:Pentane) to afford **224** as a colourless oil (10.3 g, 90%).

Procedure B:



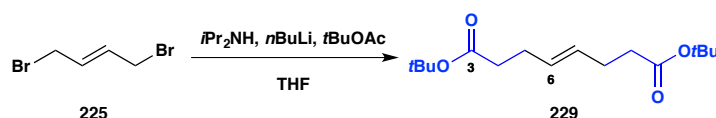
Diol **247** (10.0 g, 40.0 mmol) was dissolved in CH₂Cl₂ (80 mL) and cooled to 0 °C in an ice-water bath. TBSCl (18.1 g, 120 mmol) and imidazole (13.6 g, 200 mmol) were added to the solution slowly with vigorous stirring. After warming to room temperature, the mixture was stirred for 18 hours before being quenched by addition of H₂O (80 mL). The mixture was extracted with EtOAc (4 × 80 mL). The combined organic layers were washed with brine (80 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 1:99 Et₂O:Pentane to 5:95 Et₂O:Pentane) to afford **224** as a colourless oil (18.2 g, 95 %).

R_f = 0.7 (20:80 Et₂O:Pentane); $[\alpha]_D^{25}$ -5.6 (c = 0.94, CH₂Cl₂; lit. -5.3, c = 1.25, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.30 (2 H, d, J = 8.4 Hz, PMB-ArH × 2), 6.88 (2 H, d, J = 8.4 Hz, PMB-ArH × 2), 4.65 (1 H, d, J = 11.2 Hz, PMB-H_AH_B), 4.57 (1 H, d, J = 11.2 Hz, PMB-CH_AH_B), 3.85 (1 H, dd, J = 9.6, 4.8 Hz, C(15)H), 3.81 (3 H, s, PMB-CH₃), 3.71–3.65 (3 H, m, C(16)H₂, C(14)H), 2.59–2.44 (2 H, m, C(13)H₂), 1.98 (1 H, t, J = 2.7 Hz, C(11)H), 0.91 (9 H, s, TBS-C(CH₃)₃), 0.90 (9 H, s, TBS-C(CH₃)₃), 0.11–0.06 (12 H, m, TBS-Si(CH₃)₂ × 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 159.1 (PMB-C_{Ar}), 130.6 (PMB-C_{Ar}), 129.5 (PMB-C_{Ar} × 2), 113.7 (PMB-C_{Ar} × 2), 82.1 (C12), 78.0 (C14), 74.2 (C15), 72.4 (PMB-CH₂), 69.6 (C11),

64.5 (C16), 52.2 (PMB-CH₃), 26.0 (TBS-C(CH₃)₃), 25.9 (TBS-C(CH₃)₃), 20.4 (C13), 18.3 (TBS-C(CH₃)₃), 18.1 (TBS-C(CH₃)₃), -4.3 (TBS-Si(CH₃)₂), -4.5 (TBS-Si(CH₃)₂), -4.7 (TBS-Si(CH₃)₂ × 2).

Spectroscopic data were consistent with those previously reported.⁶⁰

(*E*)-Di-*tert*-butyl-oct-4-enedioate **229**



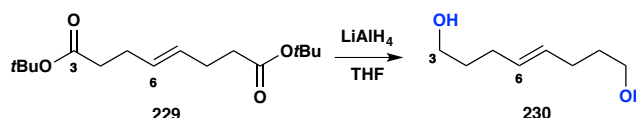
*i*Pr₂NH (45.3 mL, 322 mmol) was dissolved in THF (400 mL) and cooled to -78 °C in a dry ice-acetone bath. *n*BuLi (2.5 M in hexane, 126.4 mL, 316 mmol) was added dropwise and the solution was stirred for 15 minutes. *t*BuOAc (39.3 mL, 293 mmol) was added dropwise and the solution was stirred for further 30 minutes. *trans*-1,4-Dibromobutene **225** (25 g, 117 mmol) was dissolved in THF (100 mL) and added dropwise at -78 °C. The reaction was stirred at -78 °C for 5 hours before being allowed to warm to room temperature. After a further 16 hours, the reaction was quenched by addition of an aqueous solution of NH₄Cl (sat., 200 mL) and the resulting mixture was extracted with EtOAc (4 × 200 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 1:99 EtOAc:Pentane to 10:90 EtOAc:Pentane) to afford **229** as a white solid (22.5 g, 68%).

R_f = 0.7 (10:90 EtOAc:pentane); ¹H NMR (400 MHz, CDCl₃) δ_H 5.45 (2 H, br. s., C(6)*H* × 2), 2.26 (8 H, br. s., C(5)*H*₂ × 2, C(4)*H*₂ × 2), 1.44 (18 H, s, C(CH₃)₃ × 2); ¹³C NMR (100 MHz,

CDCl₃) δ_C 172.5 (C3 $\times$ 2), 129.4 (C6 $\times$ 2), 80.1 ((CH₃)₃C $\times$ 2), 35.4 (C4 $\times$ 2), 28.1 (*t*Bu-(CH₃)₃ $\times$ 2), 28.0 (C5 $\times$ 2), **m.p.** 57–58 °C (lit. 59–60 °C).

Spectroscopic data were consistent with those previously reported.⁶⁰

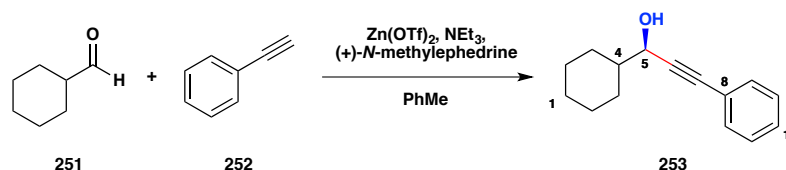
(E)-Oct-4-ene-1,8-diol 230



Diester **229** (10.0 g, 35.2 mmol) was dissolved in THF (210 mL) and cooled to 0 °C in an ice-water bath. LiAlH₄ (5.40 g, 141 mmol) was added to the solution in small portions over 15 minutes. The mixture was allowed to warm to room temperature and stirred for 4 hours before cooled to 0 °C. The reaction was quenched by sequential dropwise addition of H₂O (5.4 mL), an aqueous solution of NaOH (15 % w/v, 5.4 mL) and H₂O (16.2 mL) (**Caution:** Strongly exothermic). Et₂O (100 mL) was added and the mixture was stirred for further 30 minutes. The insoluble solid was filtered through celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 50:50 EtOAc:Pentane) to afford diol **230** as a colourless oil (4.98 g, 98%).

R_f = 0.5 (EtOAc); ¹H NMR (400 MHz, CDCl₃) δ_H 5.44 (2 H, t, *J* = 3.7 Hz, C(6)*H* $\times$ 2), 3.60 (4 H, t, *J* = 6.5 Hz, C(3)*H*₂ $\times$ 2), 2.49–2.38 (2 H, br. s, OH $\times$ 2), 2.09–2.01 (4 H, m, C(5)*H*₂ $\times$ 2), 1.60 (4 H, *quin*, *J* = 6.8 Hz, C(4)*H*₂ $\times$ 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 130.2 (C6 $\times$ 2), 62.2 (C3 $\times$ 2), 32.3 (C4 $\times$ 2), 28.8 (C5 $\times$ 2).

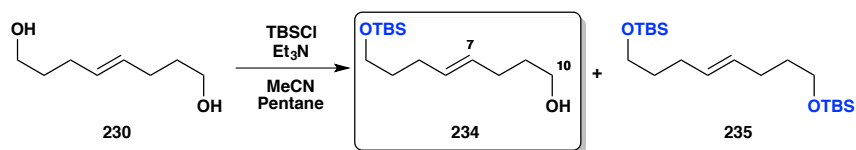
Spectroscopic data were consistent with those previously reported.⁶⁰

(R)-1-Cyclohexyl-3-phenylprop-2-yn-1-ol 253

Zn(OTf)₂ (3.20 g, 8.80 mmol) and (+)-*N*-methylephedrine (1.72 g, 9.60 mmol) were added to a flame-dried flask. After purging with argon for 15 minutes, PhMe (24 mL) and NEt₃ (0.43 mL, 3.1 mmol) were added and the mixture was stirred for 2 hours. Phenylacetylene **252** (1.05 g, 9.60 mmol) was added to the resulting slurry and stirred for a further 15 minutes. Cyclohexanecarboxaldehyde **251** (0.97 mL, 8.0 mmol) was dissolved in PhMe (3 mL) and added dropwise. The mixture was stirred for a further 2 hours at room temperature. The reaction was diluted with Et₂O (20 mL), quenched by addition of an aqueous solution of NH₄Cl (sat., 40 mL) and extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 EtOAc:Petroleum ether) to afford **253** as a colourless oil (1.52 g, 89%, 97:3 d.r.).

R_f = 0.4 (20:80 EtOAc:Petroleum ether); $[\alpha]_D^{25}$ -9.9 (c = 1.16, CH₂Cl₂; lit. -9.2, c = 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.46–7.43 (2 H, m, C(9)*H* × 2), 7.32–7.27 (3 H, m, C(11)*H*, C(10)*H* × 2), 4.38 (1 H, t, J = 5.7 Hz, C(5)*H*), 2.03 (1 H, br, OH), 1.88–1.63 (6 H, m, C₆H₁₁), 1.28–1.04 (5 H, m, C₆H₁₁); ¹³C NMR (100 MHz, CDCl₃) δ_C 131.7 (C11), 128.3 (C9 × 2 or C10 × 2), 128.3 (C9 × 2 or C10 × 2), 122.8 (C8), 89.3 (C6), 85.6 (C7), 67.7 (C5), 44.3 (C4), 28.7 (C3), 28.2 (C3), 26.4 (C1), 25.9 (C2), 25.9 (C2).

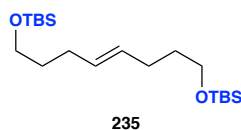
Spectroscopic data were consistent with those previously reported.⁹¹

(*E*)-8-((*tert*-Butyldimethylsilyl)oxy)oct-4-en-1-ol **234**

Diol **230** (5.00 g, 34.7 mmol) and Et₃N (5.80 mL, 41.6 mmol) were dissolved in a mixture of acetonitrile (45 mL) and pentane (315 mL). After cooling to 0 °C, *tert*-butyldimethylsilyl chloride (5.23 g, 34.7 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stirred for 24 hours, before being quenched by addition of an aqueous solution of NH₄Cl (sat., 100 mL). The organic layers were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc:Pentane to EtOAc) to give *mono*-TBS ether **234** as a colourless oil (6.9 g, 77%). Unreacted diol **230** was recycled (0.62 g, 12 %). *bis*-TBS ether **235** was also obtained as a side product (1.23 g, 10%)

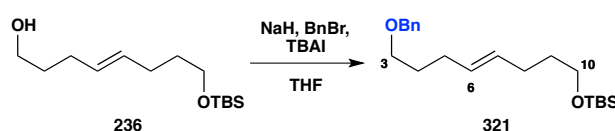
R_f = 0.5 (1:1 EtOAc:Pentane); ¹H NMR (400 MHz, CDCl₃) δ_H 5.75–5.03 (2 H, m, (C(6)H, C(7)H), 3.60 (2 H, t, *J* = 6.5 Hz, C(3)H₂), 3.57 (2 H, t, *J* = 6.5 Hz, C(10)H₂), 2.29–1.77 (5 H, m, C(5)H₂, C(8)H₂, OH), 1.64–1.51 (4 H, m, C(4)H₂, C(9)H₂), 0.87 (9 H, s, TBS-C(CH₃)₃), 0.02 (6 H, s, TBS-Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_C 130.4 (C7), 129.8 (C6), 62.6 (C10), 62.3 (C3), 32.6 (C9), 32.4 (C4), 28.9 (C8), 28.8 (C5), 26.0 (TBS-C(CH₃)₃), 18.3 (TBS-C(CH₃)₃), –5.3 (TBS-Si(CH₃)₂).

Spectroscopic data were consistent with those previously reported.⁹⁵

(E)-2,2,3,3,14,14,15,15-Octamethyl-4,13-dioxa-3,14-disilahexadec-8-ene 235

bis-TBS ether **235** was obtained as a colourless oil from *mono*-TBS production of diol **230**.

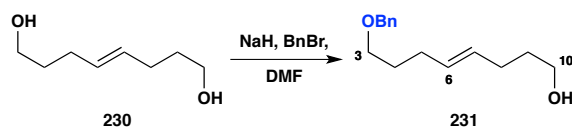
$R_f = 0.9$ (1:1 EtOAc:Pentane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 5.41 (2 H, td, $J = 3.7, 1.9$ Hz, $\text{C}(7)\text{H} \times 2$), 3.60 (4 H, t, $J = 6.5$ Hz, $\text{C}(10)\text{H}_2 \times 2$), 2.03 (4 H, ddt, $J = 7.6, 3.4, 1.4$ Hz, $\text{C}(9)\text{H}_2 \times 2$), 1.57 (4 H, dt, $J = 14.8, 6.6$ Hz, $\text{C}(8)\text{H}_2 \times 2$), 0.89 (18 H, s, $\text{TBS-C}(\text{CH}_3)_3 \times 2$), 0.04 (12 H, $\text{TBS-Si}(\text{CH}_3)_2 \times 2$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 130.2 ($\text{C}7 \times 2$), 62.8 ($\text{C}10 \times 2$), 32.8 ($\text{C}8 \times 2$), 29.0 ($\text{C}9 \times 2$), 26.1 ($\text{TBS-C}(\text{CH}_3)_3 \times 2$), 18.5 ($\text{TBS-C}(\text{CH}_3)_3 \times 2$), -5.1 ($\text{TBS-Si}(\text{CH}_3)_2 \times 2$). **IR** ν_{max} (film)/ cm^{-1} 2928, 2858, 1644, 1260, 1101, 839, 774; **HRMS** (ESI^+ , m/z) $\text{C}_{20}\text{H}_{44}\text{NaO}_2\text{Si}_2$ calculated 395.2772, found $[\text{M} + \text{Na}^+]$ 395.2776 ($\Delta = 1.01$ ppm).

(E)-((8-(Benzyloxy)oct-4-en-1-yl)oxy)(tert-butyl)dimethylsilane 321

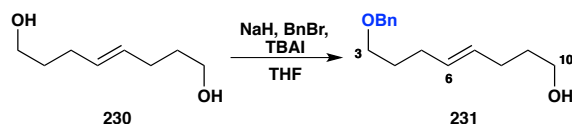
Alcohol **236** (10.0 g, 38.7 mmol) was dissolved in THF (80 mL) and cooled to 0 °C. NaH (60% in mineral oil, 1.78 g, 44.5 mmol) was added in one portion and the mixture was stirred for 1 hour at 0 °C. *tetra*-butylammonium iodide (TBAI, 715 mg, 1.90 mmol) was added followed by dropwise addition of benzyl bromide (4.80 mL, 40.6 mmol). The mixture was allowed to warm to room temperature before heating to reflux for 16 hours. After cooling to room temperature, the reaction was quenched by addition of an aqueous solution of NH_4Cl (sat., 50

mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 Et₂O:Pentane to 20:80 Et₂O:Pentane) to afford **321** as a colourless oil (13.3 g, 99%).

R_f = 0.4 (30:70 Et₂O:Pentane); **¹H NMR** (500 MHz, CDCl₃) **δ_H** 7.36–7.33 (4 H, m, Bn-ArH × 4), 7.31–7.26 (1 H, m, Bn-ArH), 5.52–5.31 (2 H, m, C(6)H, C(7)H), 4.51 (2 H, s, Bn-CH₂), 3.60 (2 H, t, *J* = 6.5 Hz, C(10)H₂), 3.48 (2 H, t, *J* = 6.5 Hz, C(3)H₂), 2.13–1.98 (2 H, m, C(5)H₂), 2.03 (2 H, dt, *J* = 7.3, 3.3 Hz, C(8)H₂), 1.73–1.64 (2 H, m, C(4)H₂), 1.61–1.52 (2 H, m, C(9)H₂), 0.91 (9 H, s, TBS-C(CH₃)₃), 0.05 (6 H, s, TBS-Si(CH₃)₂); **¹³C NMR** (125 MHz, CDCl₃) **δ_C** 138.7 (Bn-C_{Ar}CH₂), 130.4 (C7), 129.8 (C6), 128.4 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar} × 2), 127.5 (Bn-C_{Ar}), 72.9 (Bn-CH₂), 69.8 (C3), 62.6 (C10), 32.7 (C9), 29.6 (C4), 29.2 (C5), 28.8 (C8), 26.0 (TBS-C(CH₃)₃), 18.4 (TBS-C(CH₃)₃), –5.2 (TBS-Si(CH₃)₂); **IR** **v_{max}** (film)/cm^{–1} 3345, 2929, 2857, 1645, 1472, 1388, 1361, 1254, 1100, 967, 834, 774; **HRMS** (ESI⁺, *m/z*) C₂₁H₃₆NaO₂Si calculated 371.2377, found [M + Na⁺] 371.2693 (Δ = –2.15 ppm).

(E)-8-(Benzyloxy)oct-4-en-1-ol 231*Procedure A:*

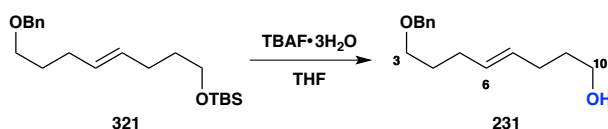
Diol **230** (5.00 g, 34.7 mmol) was dissolved in DMF (70 mL) and cooled to 0 °C in an ice-water bath. NaH (60 % in mineral oil, 693 mg, 17.3 mmol) was added and the mixture was stirred for 1 hour at 0 °C. Benzyl bromide (1.43 mL, 11.6 mmol) was slowly added dropwise and the solution then allowed warming to room temperature over 1 hour. After being stirred for a further 4 hours, the reaction was quenched by addition of H₂O (50 mL) and extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, Pentane to 50:50 EtOAc:Pentane to 80:20 EtOAc:Pentane) to afford **231** as a colourless oil (2.19 g, 27%). The unreacted diol **231** was recovered (2.25 g, 45%).

Procedure B:

Diol **230** (4.00 g, 27.7 mmol) was dissolved in THF (55 mL) and cooled to 0 °C. NaH (60% in mineral oil, 888 mg, 22.2 mmol) was added and the mixture was stirred for 1 hour at 0 °C. *tetra*-Butylammonium iodide (TBAI, 500 mg, 1.40 mmol) was added followed by dropwise addition of benzyl bromide (2.64 mL, 22.2 mmol). The mixture was allowed to warm to

room temperature and heated to reflux for 16 hours. After cooling to room temperature, the reaction was quenched by addition of an aqueous solution of NH_4Cl (sat., 25 mL). The organic layers were separated and the aqueous phase was extracted with EtOAc (4×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , Pentane to 50:50 EtOAc:Pentane to 20:80 EtOAc:Pentane) to afford **231** as a colourless oil (2.88 g, 44%). The unreacted diol **230** was recovered (1.80 g, 45%).

Procedure C:



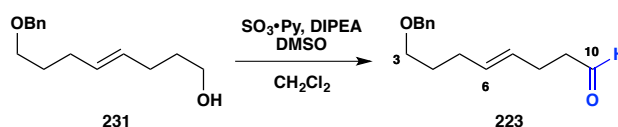
TBS ether **321** (10.0 g, 28.7 mmol) was dissolved in THF (300 mL) and cooled to 0 °C under an atmosphere of air. TBAF· $3\text{H}_2\text{O}$ (18.1 mL, 57.7 mmol) was added at 0 °C and the mixture stirred at 0 °C for approximately half an hour until all the solids had dissolved. The reaction was stirred at room temperature for a further 3 hours before an aqueous solution of NH_4Cl (sat., 150 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc (4×150 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 50:50 EtOAc:Pentane) to afford **231** as a colourless oil (6.7 g, 100%).

$R_f = 0.5$ (50:50 EtOAc:Pentane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.34–7.29 (5 H, m, $\text{Bn-ArH} \times 5$), 5.44 (2 H, t, $J = 5.2$ Hz, C(6) H , C(7) H), 4.50 (2 H, s, Bn-CH_2), 3.59 (2 H, t, $J = 6.5$ Hz, C(10) H_2), 3.47 (2 H, t, $J = 6.5$ Hz, C(3) H_2), 2.13–2.00 (5 H, m, C(5) H_2 , C(8) H_2 , OH), 1.69 (2 H, quin, $J = 6.6$ Hz, C(4) H_2), 1.61 (2 H, quin, $J = 6.7$ Hz, C(9) H_2); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 138.5 ($\text{Bn-C}_{\text{Ar}}\text{CH}_2$), 130.2 (1 C, C6 or C7), 130.1 (1 C, C6 or C7), 128.4 ($\text{Bn-C}_{\text{Ar}} \times 2$), 127.7 ($\text{Bn-C}_{\text{Ar}} \times 2$), 127.5 (Bn-C_{Ar}), 72.9 (Bn-CH_2), 69.7 (C3), 62.3 (C10), 32.4 (C9), 29.5 (C4), 29.1 (C5), 28.9 (C8).

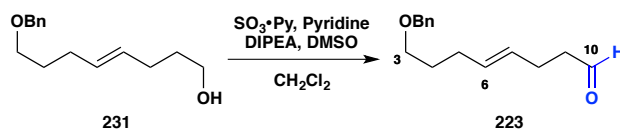
Spectroscopic data were consistent with those previously reported.⁶⁰

(*E*)-8-(Benzyloxy)oct-4-enal **223**

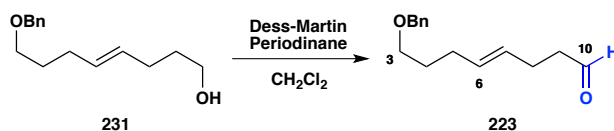
Procedure A:



Alcohol **231** (8.00 g, 34.1 mmol) and DMSO (7.20 mL, 102 mmol) were dissolved in CH_2Cl_2 (140 mL) and cooled to 0 °C. After adding *i*Pr₂NEt (17.8 mL, 102 mmol) and sulfur trioxide pyridine complex (16.3 g, 102 mmol), the mixture was stirred at 0 °C for 1 hour. The reaction was quenched by addition of H_2O (100 mL) and extracted with EtOAc (4×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 5:95 EtOAc:Pentane) to afford **223** as a colourless oil (7.69 g, 97%).

Procedure B:

Alcohol **231** (6.95 g, 29.7 mmol) and DMSO (10.4 mL, 148 mmol) were dissolved in CH_2Cl_2 (45 mL) and cooled to 0 °C. After adding *i*Pr₂NEt (25.8 mL, 148 mmol) and sulfur trioxide pyridine complex (23.6 g, 148 mmol, pre-basified by stirring with 12.0 mL pyridine for one hour), the mixture was stirred at 0 °C for 1 hour. The reaction was quenched by addition of H_2O (40 mL) and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude produce was purified by flash column chromatography (SiO_2 , 5:95 EtOAc:Pentane) to afford **223** as a colourless oil (5.5 g, 80%).

Procedure C:

CH_2Cl_2 (150 mL) and water (150 mL) were added to a separating funnel and the mixture vigorously shaken. Once separated, the water-saturated CH_2Cl_2 was collected and used to dissolve alcohol **231** (4.00 g, 17.1 mmol) under an atmosphere of air. Dess-Martin periodinane (21.6 g, 51.2 mmol) was added to the reaction flask and the white suspension was stirred for two hours at room temperature. The reaction mixture was cooled to 0 °C and quenched by addition of a pre-mixed aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (sat., 50 mL) and NaHCO_3 (sat., 50 mL). The resulting solution was warmed to room temperature and stirred

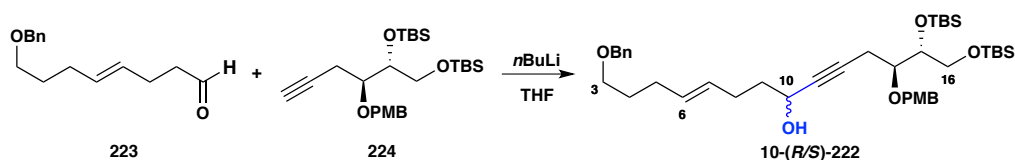
for a further 30 minutes. The organic layers were separated and the aqueous layer was extracted with EtOAc (4×100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 5:95 EtOAc:Pentane) to afford **223** as a colourless oil (3.4 g, 86%).

$R_f = 0.7$ (20:80 EtOAc:Pentane); ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.75 (1 H, s, C(10)H), 7.37–7.27 (5 H, m, Bn-ArH $\times$ 5), 5.44 (2 H, m, C(6)H, C(7)H), 4.50 (2 H, s, Bn-CH₂), 3.48 (2 H, t, $J = 6.5$ Hz, C(3)H₂), 2.47–2.41 (2 H, m, C(9)H₂), 2.33 (2 H, dd, $J = 7.0, 6.5$ Hz, C(8)H₂), 2.09 (2 H, dt, $J = 7.9, 5.9$ Hz, C(5)H₂), 1.68 (2 H, dt, $J = 8.1, 6.5$ Hz, C(4)H₂); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 202.4 (C10), 138.6 (Bn-C_{Ar}), 131.2 (C6), 128.3 (C7), 128.3 (Bn-C_{Ar} $\times$ 2), 127.6 (Bn-C_{Ar} $\times$ 2), 127.5 (Bn-C_{Ar}), 72.9 (Bn-CH₂), 69.6 (C3), 43.5 (C9), 29.4 (C4), 29.0 (C5), 25.1 (C8).

Spectroscopic data were consistent with those previously reported.⁶⁰

(2*R*,3*S*,7*S*,*E*)-14-(Benzyloxy)-1,2-bis((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)tetradec-10-en-5-yn-7-ol **222**

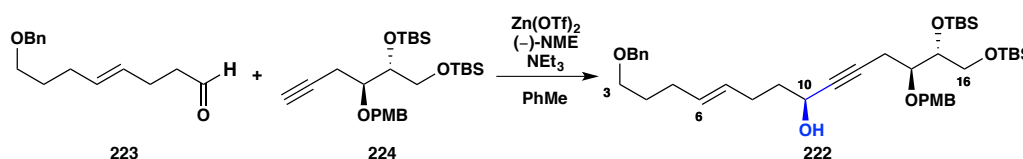
Procedure A:



Alkyne **224** (1.55 g, 3.23 mmol) was dissolved in THF (40 mL) and cooled to -78°C in a dry ice-acetone bath. $n\text{BuLi}$ (1.61 mL, 1.6 M in hexane, 2.58 mmol) was slowly added to the

solution dropwise. The resulting mixture was transferred to an ice-water bath and stirred for one hour. Aldehyde **223** (500 mg, 2.15 mmol) was added dropwise as a THF (10 mL) solution. The reaction was allowed to warm to room temperature slowly and stirred for 12 hours, before quenched by addition of H₂O (20 mL). The mixture was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 EtOAc:Petroleum ether) to afford **10-(R/S)-222** as a pale yellow oil (1.43 g, 93%, 1:1.5 d.r.).

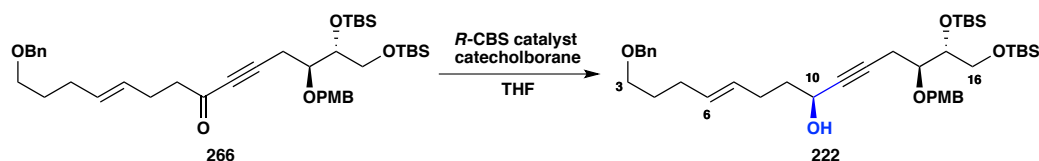
Procedure B:



Zn(OTf)₂ (32.0 g, 88.1 mmol) was heated to 125 °C under high-vacuum (0.05 mbar) over night with stirring until the solid became a fine powder. The flask was then cooled to room temperature and (-)-*N*-methylephedrine (17.2 g, 96.1 mmol, pre-dried over high-vacuum over night) was added. After purging with argon for 15 minutes, PhMe (100 mL) and NEt₃ (13.4 mL, 96.1 mmol) were added to the mixture and stirred for 2 hours. Alkyne **224** (38.3 g, 80.1 mmol) was dissolved in PhMe (50 mL) and added dropwise to the reaction and the resulting slurry was vigorously stirred for a further 2 hours. Aldehyde **223** (6.20 g, 26.7 mmol) was dissolved in PhMe (15 mL) and added dropwise over 12 hours *via* syringe pump. The mixture was then stirred vigorously for a further 48 hours at room temperature. The reaction was quenched by addition of an aqueous solution of NH₄Cl (sat., 100 mL) and

extracted with EtOAc (4×150 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 5:95 to 20:80 EtOAc:Pentane) to afford **222** as a colourless oil (16.5 g, 87%, 93:7 d.r.). Excess alkyne was recycled. (20.1 g, 79%).

Procedure C:



Propargylic ketone **266** (100 mg, 0.140 mmol) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine (38.8 mg, 0.140 mmol) were dissolved in THF (5 mL), and cooled to -40 °C. Catecholborane (70.0 μL , 700 μmol) was added and the reaction was allowed to warm to room temperature before being stirred overnight. The reaction was then cooled to -78 °C and MeOH (2 mL) was added. The resulting mixture was allowed to gently warm to room temperature before being diluted with Et_2O (20 mL) and washed with 2:1 NaOH (1 M, aq.): NaHCO_3 (sat., aq.) until the aqueous washings were colourless. The organic layer was washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 5:95 to 20:80 EtOAc: Petroleum ether) to afford **222** as pale yellow oil (27.1 mg, 27%, 20:1 d.r.).

R_f = 0.4 (20:80 EtOAc:Pentane); $[\alpha]_D^{25}$ -1.3 (c = 1.14, CH_2Cl_2 , lit. -2.4 , c = 1.08, CH_2Cl_2);

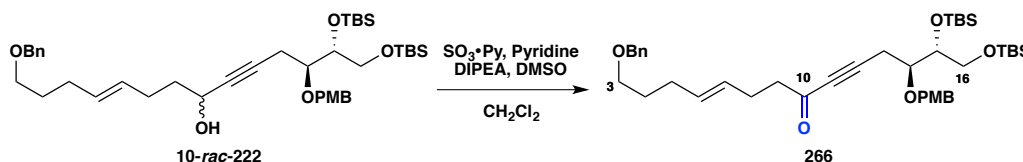
^1H NMR (400 MHz, CDCl_3) δ_H 7.39–7.34 (4 H, m, Bn-ArH $\times$ 4), 7.33 (2 H, d, J = 8.4 Hz,

PMB-ArH $\times$ 2), 7.29 (1 H, m, Bn-ArH), 6.89 (2 H, d, J = 8.5 Hz, PMB-ArH $\times$ 2), 5.45 (2 H,

m, C(6)*H*, C(7)*H*), 4.66 (1 H, d, $J = 10.9$ Hz, PMB-CH_AH_B), 4.60 (1 H, d, $J = 11.2$ Hz, PMB-CH_AH_B), 4.51 (2 H, s, Bn-CH₂), 4.34 (1 H, m, C(10)*H*), 3.87 (1 H, m, C(15)*H*), 3.79 (3 H, s, PMB-CH₃), 3.74–3.64 (3 H, m, C(14)*H*, C(16)*H*), 3.49 (2 H, t, $J = 6.5$ Hz, C(3)*H*), 2.67–2.50 (2 H, m, C(13)*H*), 2.50–2.37 (1 H, m, OH), 2.25–2.14 (2 H, m, C(8)*H*), 2.15–2.07 (2 H, m, C(5)*H*), 1.73 (4 H, m, C(9)*H*, C(4)*H*), 1.10–0.76 (18 H, m, TBS-C(CH₃)₃ × 2), 0.19–0.03 (12 H, m, TBS-Si(CH₃)₂ × 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 159.1 (PMB-C_{Ar}OMe), 138.6 (Bn-C_{Ar}CH₂), 130.7 (PMB-C_{Ar}CH₂), 130.4 (C6), 129.7 (C7), 129.5 (PMB-C_{Ar} × 2), 128.4 (Bn-C_{Ar} × 2), 127.7 (Bn-C_{Ar} × 2), 127.5 (Bn-C_{Ar}), 113.7 (PMB-C_{Ar} × 2), 83.2 (C12), 82.3 (C11), 78.1 (C14), 74.4 (C15), 72.9 (Bn-CH₂), 72.1 (PMB-CH₂), 69.7 (C3), 64.5 (C16), 62.2 (C10), 55.2 (PMB-CH₃), 37.7 (C9), 29.5 (C4), 29.1 (C5), 28.4 (C8), 26.1 (TBS-C(CH₃) × 3), 26.0 (TBS-C(CH₃) × 3), 20.8 (C13), 18.4 (TBS-C(CH₃)₃), 18.2 (TBS-C(CH₃)₃), -4.2 (TBS-SiCH₃), -4.7 (TBS-SiCH₃), -5.3 (TBS-SiCH₃), -5.3 (TBS-SiCH₃).

Spectroscopic data were consistent with those previously reported.⁶⁰

(2*R*,3*S*,*E*)-14-(Benzyloxy)-1,2-bis((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy) tetradec-10-en-5-yn-7-one 266



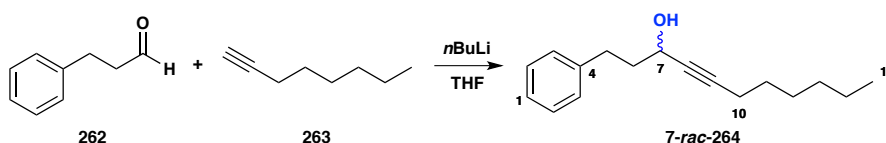
Propargyl alcohol **10-(*R/S*)-222** (1.00 g, 1.41 mmol) and DMSO (0.300 mL, 4.22 mmol) were dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C in an ice-water bath. After adding *i*Pr₂NEt (0.730 mL, 4.22 mmol) and sulfur trioxide pyridine complex (671 mg, 4.22 mmol)

the mixture was stirred initially at 0 °C and then allowed to warm slowly to room temperature over night. The reaction was quenched by addition of H₂O (10 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 EtOAc:Petroleum ether) to afford **266** as a colourless oil (899 mg, 90%).

R_f = 0.7 (2:8 EtOAc:Petroleum ether); $[\alpha]_D^{25}$ -4.1 (c = 0.90, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.37–7.29, (4 H, Bn-ArH × 4), 7.30–7.24 (1 H, m, Bn-ArH), 7.28 (2 H, d, J = 8.4 Hz, PMB-ArH × 2), 6.86 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 5.41 (2 H, m, C(6)H, C(7)H), 4.58 (1 H, d, J = 11.6 Hz, PMB-CH_AH_B), 4.56 (1 H, d, J = 11.2 Hz, PMB-CH_AH_B), 4.49 (2 H, s, Bn-CH₂), 3.81–3.72 (2 H, m, C(14)H, C(15)H), 3.79 (3 H, s, PMB-CH₃), 3.61 (2 H, dd, J = 4.9, 2.0 Hz, C(16)H₂), 3.45 (2 H, t, J = 6.5 Hz, C(3)H₂), 2.74–2.62 (2 H, m, C(13)H₂), 2.56 (2 H, t, J = 7.2 Hz, C(9)H₂), 2.33 (2 H, dd, J = 14.1, 6.7 Hz, C(8)H₂), 2.06 (2 H, dd, J = 13.7, 6.8 Hz, C(5)H₂), 1.65 (2 H, dt, J = 14.3, 6.8 Hz, C(4)H₂), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.09–0.02 (12 H, m, TBS-Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_C 187.3 (C10), 159.2 (PMB-C_{Ar}OMe), 138.6 (Bn-C_{Ar}CH₂), 131.0 (PMB-C_{Ar}CH₂), 130.2 (C6), 129.5 (C7), 128.3 (PMB-C_{Ar} × 2), 128.3 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar} × 2), 127.5 (Bn-C_{Ar}), 113.7 (PMB-C_{Ar} × 2), 92.3 (C11), 81.7 (C12), 77.4 (C14), 74.0 (C15), 72.9 (Bn-CH₂), 72.3 (PMB-CH₂), 69.7 (C3), 64.3 (C16), 55.2 (PMB-CH₃), 45.3 (C9), 29.4 (C4), 29.1 (C5), 26.9 (C8), 25.9 (TBS-C(CH₃)₃), 25.9 (TBS-C(CH₃)₃), 21.0 (C13), 18.3 (TBS-C(CH₃)₃), 18.1 (TBS-C(CH₃)₃), -4.4 (TBS-Si(CH₃)), -4.8 (TBS-Si(CH₃)), -5.4

(TBS-Si(CH₃) × 2); **IR** ν_{max} (film)/cm⁻¹ 2953, 2929, 2856, 1613, 1587, 1514, 1463, 1248, 1036, 831, 776, 697; **LRMS** (ESI⁺, m/z) 709.4 [M + H⁺, 100%]; **HRMS** (ESI⁺) C₄₁H₆₄NaO₆Si₂ [M + Na⁺] calculated 731.4134, found 731.4129 (Δ = -0.68 ppm).

Phenylundec-4-yn-3-ol 7-*rac*-264



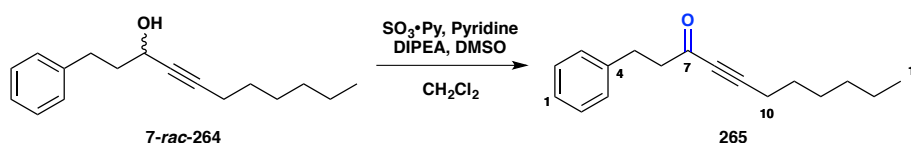
Alkyne **263** (0.920 mL, 6.25 mmol) was dissolved in THF (30 mL) and cooled to -78 °C. *n*BuLi (1.6 M in hexane, 3.75 mL, 6.00 mmol) was added dropwise and the solution was stirred for 20 minutes before adding aldehyde **262** (0.66 mL, 3.00 mmol) dropwise. The mixture was stirred for a further 20 minutes at 0 °C before being quenched by addition of H₂O (10 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 to 10:90 EtOAc: Petroleum ether) to afford **7-*rac*-264** as pale yellow oil (975 mg, 80%).

R_f = 0.5 (20:80 EtOAc:Pentane). **¹H NMR** (400 MHz, CDCl₃) δ_H 7.32–7.27 (2 H, m, C(3)*H* × 2), 7.24–7.18 (3 H, m, C(1)*H*, C(2)*H* × 2), 4.37 (1 H, t, J = 6.5 Hz, C(7)*H*), 2.80 (2 H, t, J = 7.8 Hz, C(5)*H*₂), 2.23 (2 H, dt, J = 7.0, 1.7 Hz, C(6)*H*₂), 1.97–1.91 (2 H, m, C(10)*H*₂), 1.76 (1 H, br. s, OH), 1.56–1.22 (8 H, m, C(11)*H*₂, C(12)*H*₂, C(13)*H*₂, C(14)*H*₂), 0.91 (3 H, t, J = 6.6 Hz, C(15)*H*₃); **¹³C NMR** (100 MHz, CDCl₃) δ_C 141.5 (C4), 128.5 (C3 × 2), 128.4

(C2 $\times$ 2), 125.9 (C1), 86.1 (C8), 80.9 (C9), 62.1 (C7), 39.7 (C6), 31.5 (C11), 31.3 (C13), 28.6 (C12), 28.5 (C5), 22.5 (C14), 18.7 (C10), 14.1 (C15).

Spectroscopic data were consistent with those previously reported.¹²⁹

Phenylundec-4-yn-3-one **265**

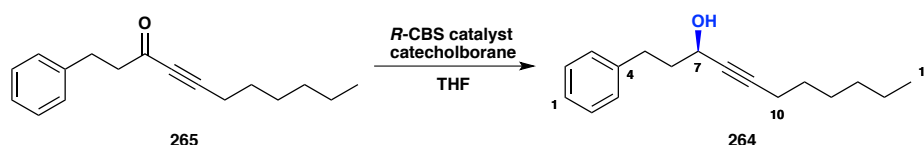


Alcohol **7-rac-264** (800 mg, 3.27 mmol) and DMSO (1.68 mL, 9.82 mmol) were dissolved in CH₂Cl₂ (20 mL) and cooled to 0 °C in an ice-water bath. After adding *i*Pr₂NEt (1.68 mL, 9.82 mmol) and sulfur trioxide pyridine complex (1.60 g, 9.82 mmol), the mixture was stirred initially at 0 °C and then allowed to warm to room temperature over night. The reaction was quenched by addition of H₂O (20 mL) and extracted with EtOAc (4 $\times$ 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 EtOAc:Petroleum ether) to afford **265** as a colourless oil (638 mg, 80%).

R_f = 0.7 (20:80 EtOAc:Petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ_H 7.32–7.27 (2 H, m, C(3)H $\times$ 2), 7.24–7.19 (3 H, m, C(1)H, C(2)H $\times$ 2), 3.00 (2 H, t, J = 7.3 Hz, C(5)H₂), 2.88 (2 H, t, J = 7.4 Hz, C(6)H₂), 2.37 (2 H, t, J = 7.1 Hz, C(10)H₂), 1.62–1.28 (8 H, m, C(11)H₂, C(12)H₂, C(13)H₂ and C(14)H₂), 0.91 (3 H, t, J = 6.6 Hz, C(15)H₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 187.1 (C7), 140.4 (C1), 128.5 (C3 $\times$ 2), 128.3 (C2 $\times$ 2), 126.2 (C4), 95.0 (C8), 80.8 (C9), 47.0 (C6), 31.2 (C13), 30.0 (C5), 28.5 (C11), 27.7 (C12), 22.5 (C14), 19.0 (C10),

14.0 (C15); **IR** ν_{max} (film)/ cm^{-1} 2954, 2930, 2860, 2213, 1672, 1454, 1159, 769, 698; **LRMS** (ESI^+ , m/z) 243.2 [$\text{M} + \text{H}^+$, 100%]; **HRMS** (ESI^+) $\text{C}_{17}\text{H}_{22}\text{NaO}$ [$\text{M} + \text{Na}^+$] requires 265.1563, found 265.1558 ($\Delta = -1.89$ ppm).

(R)-1-Phenylundec-4-yn-3-ol 264



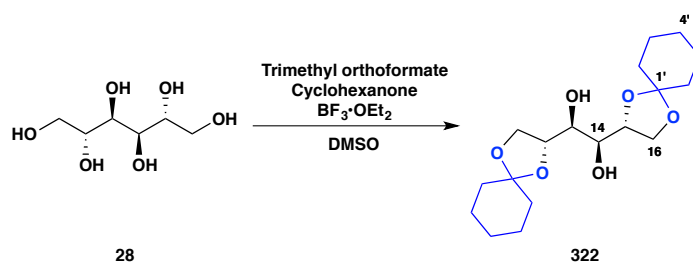
Propargyl ketone **265** (100 mg, 0.410 mmol) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine (2.6 mg, 20 μmol) were dissolved in CH_2Cl_2 (2 mL) and cooled to -78°C in a dry ice-acetone bath. Catecholborane (0.053 mL, 0.50 mmol) was added and the reaction was stirred for 5 hours. MeOH (2 mL) was added and the reaction was allowed to warm to room temperature. The reaction mixture was diluted with Et_2O (20 mL), washed with 2:1 NaOH (1 M, aq.): NaHCO_3 (sat., aq.) until the aqueous washings were colourless. The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 5:95 to 10:90 EtOAc: Petroleum ether) to afford **264** as pale yellow oil (99.8 mg, 100%, 95% *ee*).

$R_f = 0.5$ (20:80 EtOAc:Petroleum ether); $[\alpha]_D^{25} -27.1$ ($c = 1.15$, CH_2Cl_2 ; lit. -26.6 , $c = 1.00$, CH_2Cl_2); **^1H NMR** (400 MHz, CDCl_3) δ_{H} 7.31–7.27 (2 H, m, $\text{C}(3)\text{H} \times 2$), 7.23–7.17 (3 H, m, $\text{C}(1)\text{H}$, $\text{C}(2)\text{H} \times 2$), 4.37 (1 H, t, $J = 4.6$ Hz, $\text{C}(7)\text{H}$), 2.81 (2 H, t, $J = 7.9$ Hz, $\text{C}(5)\text{H}_2$), 2.59 (1 H, br. s, OH), 2.23 (2 H, dt, $J = 7.0, 1.9$ Hz, $\text{C}(6)\text{H}_2$), 1.95 (2 H, m, $\text{C}(10)\text{H}_2$), 1.56–1.21 (8 H, m, $\text{C}(11)\text{H}_2$, $\text{C}(12)\text{H}_2$, $\text{C}(13)\text{H}_2$ and $\text{C}(14)\text{H}_2$), 0.91 (3 H, t, $J = 6.8$ Hz, $\text{C}(15)\text{H}_3$);

^{13}C NMR (100 MHz, CDCl_3) δ_{C} 141.6 (C4), 128.5 ($\text{C3} \times 2$), 128.4 ($\text{C2} \times 2$), 125.9 (C1), 85.8 (C8), 81.2 (C9), 61.9 (C7), 39.7 (C6), 31.5 (C11), 31.3 (C13), 28.6 (C12), 25.0 (C5), 22.5 (C14), 18.7 (C10), 14.1 (C15).

Spectroscopic data were consistent with those previously reported.¹²⁹

(1*S*,2*S*)-1,2-Di((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)ethane-1,2-diol **322**

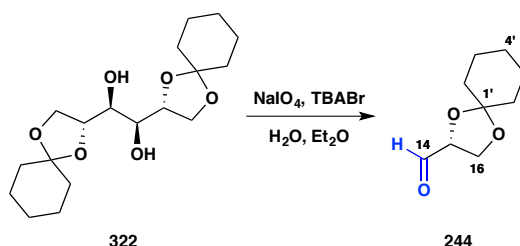


D-mannitol **28** (5.00 g, 27.5 mmol), cyclohexanone (8.54 mL, 82.4 mmol), trimethyl orthoformate (3.00 mL, 27.5 mmol) and boron trifluoride etherate (0.27 mL, 2.20 mmol) were dissolved in DMSO (11 mL) and stirred overnight. The mixture was poured into an ice-cooled aqueous solution of NaHCO_3 (sat., 100 mL) and the aqueous phase was extracted with Et_2O (4×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was recrystallized from hot pentane to afford **322** as fine needles (6.48 g, 69%).

$[\alpha]_{\text{D}}^{25} +7.5$ ($c = 1.35$, CH_2Cl_2 ; lit. $+5.8$, $c = 3.00$, CH_2Cl_2) ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.20–3.89 (6 H, m, $\text{C(16)H}_2 \times 2$, $\text{C(15)H} \times 2$), 3.74 (2 H, d, $J = 6.6$ Hz, $\text{C(14)H} \times 2$), 2.64 (2 H, br. s, $\text{OH} \times 2$), 1.68–1.48, (20 H, br. s, $\text{C(2')H}_2 \times 4$, $\text{C(3')H}_2 \times 4$, $\text{C(4')H}_2 \times 2$); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 110.0 ($\text{C1}' \times 2$), 75.9 ($\text{C15} \times 2$), 71.3 ($\text{C14} \times 2$), 66.4 ($\text{C16} \times 2$),

(R)-1,4-Dioxaspiro[4.5]decane-2-carbaldehyde 244

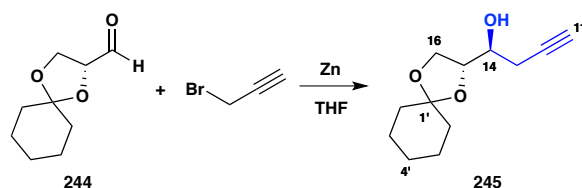
187

Procedure B:

Diol **322** (1.0 g, 2.9 mmol) was dissolved in Et₂O (10 mL) under an atmosphere of air. NaIO₄ (0.73 g, 3.4 mmol) and tetrabutylammonium bromide (20 mg, 60 μmol) were dissolved in H₂O (6 mL). After adding the aqueous solution to the organic phase, the mixture was vigorously stirred for 3 hours. The organic layer was separated and the aqueous layer was extracted with Et₂O (4 × 25 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated at 50 mmbar to afford crude aldehyde **244** as colourless oil (965 mg, 97%), which was used in the next step without further purifications.

$[\alpha]_D^{25} +57.5$ ($c = 1.30$, CH₂Cl₂; lit. $+61.2$, $c = 1.00$, C₆H₆) **¹H NMR** (400 MHz, CDCl₃) δ_H 9.72 (1 H, d, $J = 3.6$ Hz, C(14)H), 4.42–3.95 (3 H, m, C(16)H₂, C(15)H), 1.75–1.55 (10 H, br. s, C(2')H₂ × 2, C(3')H₂ × 2, C(4')H₂);

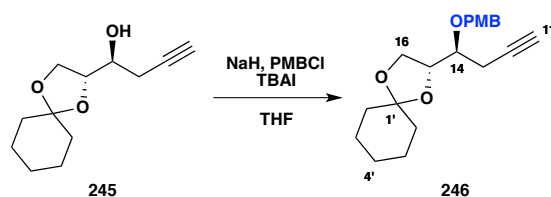
Spectroscopic data were consistent with those previously reported.¹⁴⁸

(S)-1-((R)-1,4-Dioxaspiro[4.5]decan-2-yl)but-3-yn-1-ol 245

Zinc powder (5.80 g, 84.2 mmol) was suspended in THF (80 mL) and cooled to 0 °C in an ice-water bath under an atmosphere of air. Propargyl bromide (80% in PhMe, 6.50 mL, 58.8 mmol) was added dropwise at 0 °C. After stirring for 30 minutes, aldehyde **244** (5.00 g, 29.4 mmol) was added dropwise as a THF solution (20 mL). The suspension was gradually warmed to room temperature and stirred for 8 hours. The reaction was quenched by addition of an aqueous solution of NH₄Cl (sat., 50 mL). The precipitated was removed *via* filtration. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 150 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, petroleum ether to 25:75 EtOAc:Petroleum ether) to give alcohol **245** as a pale yellow oil (4.8 g, 8:1 d.r., 78% over two steps).

R_f = 0.4 (40:60 EtOAc:Petroleum ether); $[\alpha]_D^{25}$ +7.9 (c = 1.01, CH₂Cl₂; lit. +9.5, c = 1.22, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ_H 4.11–4.05 (2 H, m, C(16)*H_AH_B*, C(15)*H*), 3.95–3.86 (1 H, dd, J = 7.1, 4.6 Hz, C(16)*H_AH_B*), 3.70–3.72 (1 H, m, C(14)*H*), 2.50–2.46 (2 H, dd, J = 5.9, 2.6 Hz, C(13)*H₂*), 2.05 (1 H, t, J = 2.7 Hz, C(11)*H*), 1.58–1.37 (10 H, br. m, C(2')*H₂* × 2, C(3')*H₂* × 2, C(4')*H₂*); ¹³C NMR (100 MHz, CDCl₃) δ_C 109.9 (C1'), 79.8 (C12), 77.3 (C15), 71.2 (C11), 70.2 (C14), 65.5 (C16), 36.4 (C2'), 34.6 (C2'), 25.1 (C4'), 24.0 (C3'), 24.8 (C3'), 23.6 (C13).

Spectroscopic data were consistent with those previously reported.⁹⁹

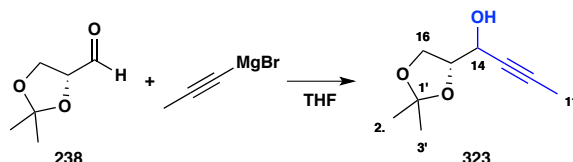
(*R*)-2-((*S*)-1-(4-Methoxyphenoxy)but-3-yn-1-yl)-1,4-dioxaspiro[4.5]decane **246**

Alcohol **245** (2.0 g, 9.5 mmol) was dissolved in THF (50 mL) was cooled to 0 °C in an ice-water bath. NaH (60% in mineral oil, 438 mg, 10.9 mmol) was added to the stirring solution and the solution was stirred for 1 hour at 0 °C. 4-Methoxybenzyl chloride (PMBCl, 1.60 mL, 11.4 mmol) was added dropwise and followed by *tetra*-butylammonium iodide (TBAI, 176 mg, 0.480 mmol). The mixture was allowed to warm to room temperature before being heated at reflux for 24 hours. The reaction was then cooled to room temperature and quenched by addition of an aqueous solution of NH₄Cl (sat., 25 mL). The resulting mixture was diluted with water (25 mL), the organic layers were separated and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, Petroleum ether to 20:80 Et₂O:Petroleum ether, 1% Et₃N added as co-eluent) to give **246** as pale yellow oil (1.1 g, 36%).

R_f = 0.5 (30:70 Et₂O:Petroleum ether); $[\alpha]_D^{25}$ +33.4 (c = 1.04, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.30–7.26 (2 H, m, PMB-ArH × 2), 6.89–6.85 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 4.72 (1 H, d, J = 11.1 Hz, PMB-CH_AH_B), 4.52 (1 H, d, J = 11.1 Hz, PMB-CH_AH_B), 4.14–4.00 (2 H, m, C(16)H_AH_B, C(15)H), 3.86 (1 H, dd, J = 8.4, 5.4 Hz, C(16)H_AH_B), 3.80 (3 H, s, PMB-CH₃), 3.54 (1 H, dt, J = 7.0, 4.8 Hz, C(14)H), 2.70–2.41 (2 H, m, C(13)H₂), 2.04 (1 H, s, C(11)H), 1.60–1.30 (10 H, br. m, C(2')H₂ × 2, C(3')H₂ × 2, C(4')H₂); ¹³C NMR (100

MHz, CDCl₃) δ_C 159.8 (PMB-C_{Ar}OMe), 130.5 (PMB-C_{Ar}CH₂), 129.6 (PMB-C_{Ar} × 2), 114.3 (PMB-C_{Ar} × 2), 110.3 (C1'), 81.2 (C12), 77.8 (C14), 76.6 (C15), 72.5 (PMB-CH₂), 66.4 (C16), 55.7 (PMB-CH₃), 36.9, 35.2 (C2' × 2), 25.6 (C4'), 24.5, 24.2 (C3' × 2), 21.6 (C13); **IR** $\nu_{\max}$ (film)/cm⁻¹ 3290, 2935, 2861, 1737, 1513, 1246, 1095, 1035, 958, 823, 636; **LRMS** (ESI⁺, *m/z*) 353.2 [M + H⁺, 100 %]; **HRMS** (ESI⁺, *m/z*) C₂₀H₂₆NaO₄ [M + Na⁺] calculated 353.1723, found 353.1713 (Δ = -2.83 ppm).

1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-ol **323**

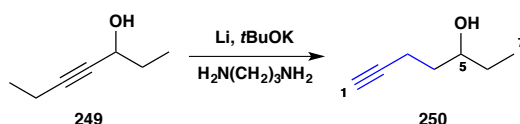


Aldehyde **238** (1.0 g, 7.7 mmol) was dissolved in THF and cooled to 0 °C. 1-Propargylmagnesium bromide (0.5 M in THF, 23.2 mL, 11.6 mmol) was added dropwise to the solution at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of an aqueous solution of NH₄Cl (sat., 25 mL) and diluted with distilled water (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, Petroleum ether to 20:80 EtOAc:Petroleum ether) to give propargyl alcohol **323** as pale yellow oil (496 mg, 38%, 1:1 d.r.).

$R_f = 0.4$ (40:60 EtOAc:Petroleum ether); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 4.40 (1 H, br. s, C(14) H , diastereoisomer A), 4.16 (1 H, br. s, C(14) H , diastereoisomer B), 4.20–4.00 (5 H, m, C(16) $H_A H_B \times 2$, diastereoisomer A and B, C(15) $H \times 2$, diastereoisomer A and B, C(16) $H_A H_B$, diastereoisomer A), 3.89–3.85 (1 H, dd, $J = 6.8, 5.6$ Hz, C(16) $H_A H_B$, diastereoisomer B), 3.31 (1 H, d, $J = 4.0$ Hz, OH), 3.20 (1 H, d, $J = 4.6$ Hz, OH), 1.85 (6 H, m, C(11) $H_3 \times 2$, diastereoisomer A and B), 1.46 (6 H, s, C(2') H_3 or C(3') H_3 , diastereoisomer A and B), 1.38 (6 H, s, C(2') H_3 or C(3') H_3 , diastereoisomer A and B); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 110.2 (C1'), 109.9 (C1'), 82.3 (C12), 82.1 (C12), 79.0 (C14), 78.2 (C14), 76.9 (C13), 76.6 (C13), 66.1 (C15), 65.4 (C15), 64.2 (C16), 62.4 (C16), 26.6 (CH_3), 26.2 (CH_3), 25.2 (CH_3), 25.1 (CH_3), 3.5 (C11), 3.4 (C11).

Spectroscopic data were consistent with those previously reported.¹⁴⁹

Hept-6-yn-3-ol **250**



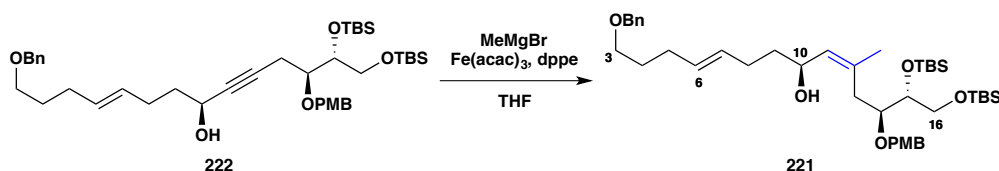
Lithium wire (42 mg, 6.0 mmol, stored under mineral oil) was cleaned with paper tissue, cut into small pieces, and mixed with 1,3-diaminopropane (3 mL, freshly distilled from CaH_2). The reaction was stirred for 30 minutes before being heated to reflux until the blue colour disappeared. The mixture was allowed to cool to room temperature and $t\text{BuOK}$ (0.45 g, 4.0 mmol) was slowly added to the reaction mixture. After dropwise addition of 4-heptyne-3-ol **249** (0.13 mL, 1.0 mmol), the reaction was stirred for 8 hours before the mixture was poured into an ice-water bath. The aqueous layer was extracted with EtOAc (4×10 mL) and the combined organic layers were washed with water (10 mL), 10% aqueous

HCl (10 mL), brine (10 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, Petroleum ether to 20:80 Et₂O:Petroleum ether,) to give terminal alkyne **250** as pale yellow oil (59 mg, 53%).

R_f = 0.5 (30:70 EtOAc:Petroleum ether); ¹H NMR (400 MHz, CDCl₃) δ_H 3.72–3.64 (1 H, m, C(5)H), 2.35 (2 H, dt, J = 6.9, 2.6 Hz, C(3)H₂), 1.98 (1 H, t, J = 2.6 Hz, C(1)H), 1.66 (1 H, br. s, OH), 1.76–1.42 (4 H, m, C(4)H₂, C(6)H₂), 0.96 (3 H, t, J = 7.5 Hz, C(7)H₃) ; ¹³C NMR (100 MHz, CDCl₃) δ_C 84.3 (C2), 72.1 (C5), 68.7 (C1), 35.2 (C4), 30.1 (C6), 15.0 (C3), 9.8 (C7).

Spectroscopic data were consistent with those previously reported.¹⁵⁰

(2*R*,3*S*,5*Z*,7*S*,10*E*)-14-(Benzyloxy)-1,2-bis((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-5-methyltetradeca-5,10-dien-7-ol 221



Propargylic alcohol **222** (14.8 g, 20.8 mmol) was dried under high-vacuum with stirring for 12 hours before being dissolved in THF (150 mL) at 0 °C in an ice-water bath. Iron(III) acetylacetonate (1.48 g, 4.20 mmol) and 1,2-bis(diphenylphosphino)ethane (1.66 g, 4.20 mmol) were added to the solution. The flask was evacuated and filled with argon three times before cooling to −78 °C and the reaction mixture was then stirred for 10 minutes. Methylmagnesium bromide (3.0 M in Et₂O, 55.5 mL, 167 mmol) was added dropwise *via* a syringe pump (2 mL/min). The reaction was then stirred for 2 hours at −78 °C and a further 18

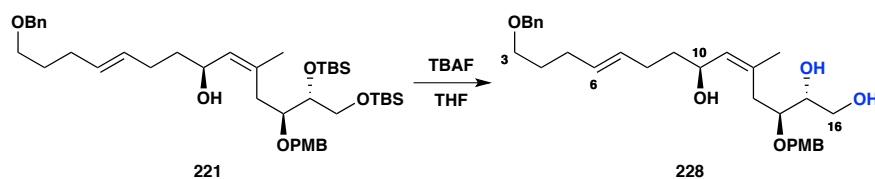
hours at 0 °C. The mixture was cooled to -78 °C and quenched by dropwise addition of an aqueous solution of NH₄Cl (sat., 50 mL). The mixture was allowed to warm to room temperature and diluted with ether (150 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (4 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 Et₂O:Pentane to 30:70 Et₂O:Pentane) to afford **221** as a colourless oil (10.9 g, 72%).

R_f = 0.4 (30:70 Et₂O:Pentane); $[\alpha]_D^{20}$ -7.1 (c = 1.13, CH₂Cl₂; lit. -6.5, c = 0.90, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ_H 7.39–7.35 (4 H, m, Bn-ArH × 4), 7.32–7.29 (1 H, m, Bn-ArH), 7.26, (2 H, d, J = 8.3 Hz, PMB-ArH × 2), 6.88 (2 H, d, J = 8.4 Hz, PMB-ArH × 2), 5.42 (2 H, m, C(6)H, C(7)H), 5.32 (1 H, d, J = 9.1 Hz, C(11)H), 4.61 (1 H, d, J = 11.7 Hz, PMB-CH_AH_B), 4.54 (2 H, s, Bn-CH₂), 4.44 (1 H, d, J = 11.4 Hz, PMB-CH_AH_B), 4.39–4.31 (1 H, m, C(10)H), 3.94 (1 H, ddd, J = 7.0, 5.8, 2.6 Hz, C(15)H), 3.81 (3 H, s, PMB-CH₃), 3.75 (1 H, ddd, J = 7.9, 4.8, 2.1 Hz, C(14)H), 3.66–3.62 (2 H, m, C(16)H₂), 3.50 (2 H, t, J = 6.5 Hz, C(3)H₂), 2.50 (1 H, dd, J = 13.7, 8.7 Hz, C(13)H_AH_B), 2.29 (1 H, dd, J = 13.9, 4.9 Hz, C(13)H_AH_B), 2.27–2.23, (1 H, m, OH), 2.14–2.06 (3 H, m, C(5)H₂, C(8) H_AH_B), 2.06–1.98 (1 H, m, C(8) H_AH_B), 1.74 (3 H, s, C(12)CH₃), 1.70 (2 H, dd, J = 7.9, 6.4 Hz, C(4)H₂), 1.64–1.46 (2 H, m, C(9)H₂), 0.96 (9 H, s, TBS-C(CH₃)₃), 0.94 (9 H, s, TBS-C(CH₃)₃), 0.15–0.10 (12 H, m, TBS-Si(CH₃)₂ × 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 159.1 (PMB-C_{Ar}OMe), 138.7 (Bn-C_{Ar}CH₂), 135.6 (C12), 131.0 (C11), 130.8 (PMB-C_{Ar}CH₂), 130.7 (C6), 129.6 (C7), 129.4 (PMB-C_{Ar} × 2), 128.4 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar} × 2),

127.5 (Bn- C_{Ar}), 113.6 (PMB- $C_{Ar} \times 2$), 77.8 (C_{14}), 74.9 (C_{15}), 72.9 (Bn- CH_2), 71.8 (PMB- CH_2), 69.8 (C_3), 67.9 (C_{10}), 64.6 (C_{16}), 55.2 (PMB- CH_3), 37.3 (C_9), 32.9 (C_{13}), 29.7 (C_4), 29.2 (C_5), 28.8 (C_8), 26.0 (TBS- $C(CH_3)_3$), 26.0 (TBS- $C(CH_3)_3$), 24.1 ($C_{12}-CH_3$), 18.3 (TBS- $C(CH_3)_3$), 18.2 (TBS- $C(CH_3)_3$), -4.5 (TBS-Si(CH_3) $_2$), -4.5 (TBS-Si(CH_3) $_2$), -5.3 (TBS-Si(CH_3) $_2$), -5.4 (TBS-Si(CH_3) $_2$).

Spectroscopic data were consistent with those previously reported.⁶⁰

(2*R*,3*S*,5*Z*,7*S*,10*E*)-14-(Benzyloxy)-3-((4-methoxybenzyl)oxy)-5-methyltetradeca-5,10-diene-1,2,7-triol **228**



bis-TBS ether **221** (5.0 g, 6.9 mmol) was dissolved in THF (70 mL) and cooled to 0 °C under an atmosphere of air. TBAF (1 M in THF, 20.6 mL, 20.6 mmol) was added dropwise, and the resulting solution was warmed to room temperature and stirred for 3 hours. The reaction was quenched by addition of an aqueous solution of NH_4Cl (sat., 50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 50:50 Acetone:Pentane) to afford triol **228** as a viscous colourless oil (3.3 g, 96%).

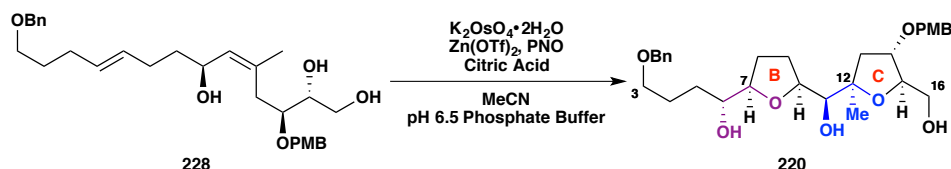
R_f = 0.4 (40:60 Acetone:Pentane); $[\alpha]_D^{25}$ +14.1 (c = 1.17, CH_2Cl_2 ; lit. +13.5, c = 1.00, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.29–7.24, (4 H, m, Bn-ArH × 4), 7.23–7.18 (1 H,

m, Bn-ArH), 7.15 (2 H, d, $J = 8.7$ Hz, PMB-ArH $\times$ 2), 6.87 (2 H, d, $J = 8.7$ Hz, PMB-ArH $\times$ 2), 5.36–5.28 (2 H, m, C(6)H, C(7)H), 5.18 (1 H, dd, $J = 8.5, 1.5$ Hz, C(11)H), 4.44 (1 H, d, $J = 11.2$ Hz, PMB-CH_AH_B), 4.41 (1 H, d, $J = 11.2$ Hz, PMB-CH_AH_B), 4.42 (2 H, s, Bn-CH₂), 4.26 (1 H, dt, $J = 8.7, 6.6$ Hz, C(10)H), 3.95–3.85 (1 H, m, OH), 3.70 (3 H, s, PMB-CH₃), 3.67–3.49 (4 H, m, C(15)H, C(16)H₂, C(14)H), 3.39 (2 H, t, $J = 6.5$ Hz, C(3)H₂), 3.36 (1 H, br. s, OH), 2.71 (1 H, br. s, OH), 2.44 (1 H, dd, $J = 13.9, 6.8$ Hz, C(13)H_AH_B), 2.24 (1 H, dd, $J = 13.9, 6.7$ Hz, C(13)H_AH_B), 2.02–1.96 (2 H, m, C(5)H₂), 1.96–1.86 (2 H, m, C(8)H₂), 1.69 (3 H, d, $J = 1.5$ Hz, C(12)CH₃), 1.59 (2 H, dq, $J = 8.6, 6.6$ Hz, C(4)H₂), 1.53 (1 H, ddt, $J = 13.2, 9.0, 6.6$ Hz, C(9)H_AH_B), 1.40 (1 H, ddt, $J = 13.0, 9.0, 6.3$ Hz, C(9)H_AH_B).; **¹³C NMR** (100 MHz, CDCl₃) δ_{C} 159.3 (PMB-C_{Ar}OMe), 138.6 (Bn-C_{Ar}CH₂), 135.9 (C12), 130.5 (C11), 130.2 (C7), 130.1 (PMB-C_{Ar}CH₂), 130.0 (C6), 129.6 (PMB-C_{Ar} $\times$ 2), 128.4 (Bn-C_{Ar} $\times$ 2), 127.7 (Bn-C_{Ar} $\times$ 2), 127.5 (Bn-C_{Ar}), 113.8 (PMB-C_{Ar} $\times$ 2), 78.1 (C14), 74.3 (C15), 72.9 (Bn-CH₂), 72.03 (PMB-CH₂), 69.8 (C3), 67.5 (C10), 63.4 (C16), 55.3 (PMB-CH₃), 37.4 (C9), 34.5 (C13), 29.6 (C4), 29.1 (C5), 28.6 (C8), 24.1 (C12-CH₃).

Spectroscopic data were consistent with those previously reported.⁶⁰

(R)-4-(Benzyloxy)-1-((2R,5S)-5-((S)-hydroxy((2R,4S,5R)-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butan-1-ol

220



Triol **228** (2.73 g, 5.47 mmol), pyridine-*N*-oxide (1.82 g, 19.1 mmol) and citric acid (788 mg, 4.10 mmol) were dissolved in a mixture of MeCN (66 mL) and aqueous pH 6.5 phosphate buffer (44 mL). Potassium osmate dihydrate (99 mg, 0.27 mmol) and Zn(OTf)₂ (996 mg, 2.74 mmol) were added and the flask was fitted with a water condenser before heating to 60 °C with vigorous stirring. After 12 hours another portion of potassium osmate dihydrate (41 mg, 0.11 mmol) was added and the reaction was warmed to 80 °C for a further 24 hours. The mixture was allowed to cool to room temperature and an aqueous solution of Na₂SO₃ (sat., 40 mL) was added to quench the reaction. After 30 minutes of vigorous stirring, the mixture was diluted with water (50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 Acetone:Pentane to 50:50 Acetone:Pentane) to afford triol **220** as a white amorphous solid (2.48 g, 85%).

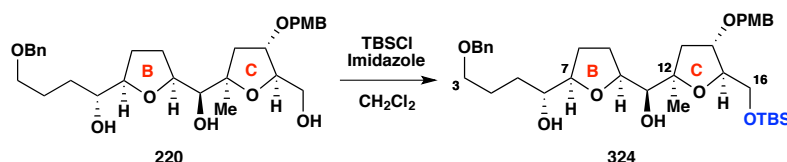
R_f = 0.4 (40:60 Acetone:Pentane); $[\alpha]_D^{25}$ +14.7 (c = 1.27, CH₂Cl₂; lit. +13.5, c = 1.00, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ_H 7.35–7.29 (4 H, m, Bn-ArH × 4), 7.29–7.25 (1 H,

m, Bn-ArH), 7.24 (2 H, d, $J = 8.7$ Hz, PMB-ArH $\times 2$), 6.86 (2 H, d, $J = 8.7$ Hz, PMB-ArH $\times 2$), 4.48 (2 H, s, Bn-CH₂), 4.44 (1 H, d, $J = 11.3$ Hz, PMB-CH_AH_B), 4.39 (1 H, d, $J = 11.2$ Hz, PMB-CH_AH_B), 4.15–4.12 (1 H, m, C(14)H), 4.12–4.09 (1 H, m, C(15)H), 4.00 (1 H, ddd, $J = 8.4, 6.6, 3.3$ Hz, C(10)H), 3.94 (1 H, d, $J = 3.4$ Hz, C(11)H), 3.84–3.79 (1 H, m, C(7)H), 3.78 (3 H, s, PMB-CH₃), 3.75 (1 H, dd, $J = 11.6, 2.6$ Hz, C(16)H_AH_B), 3.52 (1 H, dd, $J = 11.7, 2.9$ Hz, C(16)H_AH_B), 3.49 (2 H, t, $J = 6.2$ Hz, C(3)H₂), 3.40 (1 H, dt, $J = 8.5, 4.4$ Hz, C(6)H), 2.36 (1 H, dd, $J = 13.5, 6.8$ Hz, C(13)H_AH_B), 2.11–1.89 (2 H, m, C(9)H_AH_B, C(8)H_AH_B), 1.89–1.74 (2 H, m, C(8)H_AH_B, C(4)H_AH_B), 1.73–1.62 (3 H, m, C(4)H_AH_B, C(9)H_AH_B, C(13)H_AH_B), 1.59 (2 H, ddt, $J = 14.0, 8.6, 3.9$ Hz, C(5)H₂), 1.34 (3 H, s, C(12)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 159.2 (PMB-C_{Ar}COMe), 138.3 (Bn-C_{Ar}CH₂), 130.3 (PMB-C_{Ar}H₂), 129.2 (PMB-C_{Ar} $\times 2$), 128.4 (Bn-C_{Ar} $\times 2$), 127.8 (Bn-C_{Ar} $\times 2$), 127.6 (Bn-C_{Ar}), 114.00 (PMB-C_{Ar} $\times 2$), 86.0 (C12), 84.0 (C14), 81.9 (C15), 81.3 (C7), 80.0 (C10), 77.1 (C11), 73.8 (C6), 73.0 (Bn-CH₂), 71.0 (PMB-CH₂), 70.4 (C3), 63.7 (C16), 55.3 (PMB-CH₃), 37.8 (C13), 31.5 (C5), 28.8 (C8), 26.2 (C4), 25.0 (C9), 24.5 (C12-CH₃); **m.p.** 75–78 °C.

Spectroscopic data were consistent with those previously reported.⁶⁰

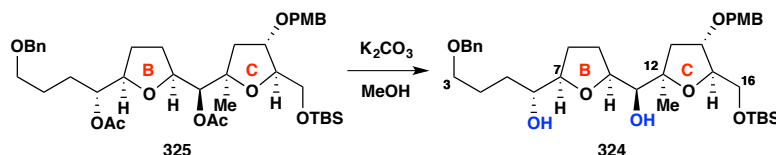
(R)-4-(Benzyloxy)-1-((2R,5S)-5-((S)-((2R,4S,5R)-5-(((tert-butyl)dimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)(hydroxy)methyl)tetrahydrofuran-2-yl)butan-1-ol 324

Procedure A:



Triol **220** (2.0 g, 3.8 mmol) and imidazole (641 mg, 9.40 mmol) were dissolved in CH_2Cl_2 (35 mL) and cooled to 0°C in an ice-water bath. *tert*-Butyldimethylsilyl chloride (600 mg, 4.00 mmol) was dissolved in CH_2Cl_2 (5 mL) and added dropwise to the solution at 0°C . The reaction mixture was allowed to warm to room temperature and stirred for 12 hours before quenched by addition of an aqueous solution of NH_4Cl (sat., 20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (4×20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude produce was purified by flash column chromatography (SiO_2 , 50:50 EtOAc:Pentane) to afford *mono*-TBS ether **324** as a viscous colourless oil (2.26 g, 93 %).

Procedure B:



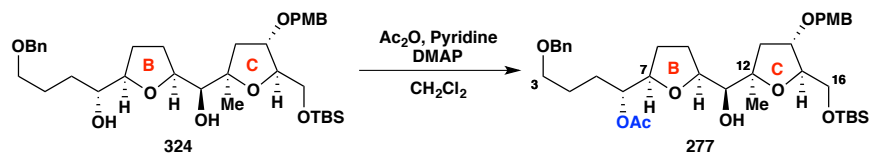
To a stirring solution of *bis*-acetate **325** (750 mg, 1.03 mmol) in MeOH (10 mL) potassium carbonate (711 mg, 5.14 mmol) was added. The reaction mixture was vigorously stirred for 3 hours before MeOH was removed *in vacuo*. The crude product was purified by flash

column chromatography (SiO₂, 50:50 EtOAc:Pentane) to afford *mono*-TBS ether **324** as a viscous colourless oil (584 mg, 88%).

$R_f = 0.4$ (40:60 EtOAc:Pentane); $[\alpha]_D^{25} +16.3$ ($c = 1.22$, CH₂Cl₂; lit. $+14.0$, $c = 1.30$, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.33–7.30 (4 H, m, Bn-ArH $\times$ 4), 7.28–7.25 (1 H, m, BnArH), 7.23 (2 H, d, $J = 8.5$ Hz, PMB-ArH $\times$ 2), 6.87 (2 H, d, $J = 8.5$ Hz, PMB-ArH $\times$ 2), 4.49 (2 H, s, Bn-CH₂), 4.45 (1 H, d, $J = 11.3$ Hz, PMB-CH_AH_B), 4.39 (1 H, d, $J = 11.3$ Hz, PMB-CH_AH_B), 4.14 (1 H, dt, $J = 7.2, 3.6$ Hz, C(14)H), 4.05 (1 H, td, $J = 3.5, 2.0$ Hz, C(15)H), 3.98 (1 H, ddd, $J = 8.4, 6.5, 3.7$ Hz, C(10)H), 3.86–3.80 (2 H, m, C(7)H, OH), 3.83 (1 H, d, $J = 3.9$ Hz, C(11)H), 3.78 (3 H, s, PMB-CH₃), 3.77 (1 H, dd, $J = 10.8, 3.3$ Hz, C(16)H_AH_B), 3.64 (1 H, dd, $J = 10.8, 2.0$ Hz, C(16)H_AH_B), 3.49 (2 H, m, C(3)H₂), 3.35 (1 H, m, C(6)H₂), 2.32 (1 H, dd, $J = 13.1, 7.2$ Hz, C(13)H_AH_B), 2.13 (1 H, m, C(9)H_AH_B), 2.03–1.78 (3 H, m, C(8)H₂, C(4)H_AH_B), 1.77–1.68 (2 H, m, C(4)H_AH_B, C(9)H_AH_B), 1.65 (1 H, m, C(13)H_AH_B), 1.61–1.49 (2 H, m, C(5)H₂), 1.35 (3 H, s, C(12)CH₃), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.04 (6 H, m, TBS-Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_C 159.3 (PMB-C_{Ar}COMe), 138.6 (Bn-C_{Ar}CH₂), 130.2 (PMB-C_{Ar}H₂), 129.3 (PMB-C_{Ar} $\times$ 2), 128.3 (Bn-C_{Ar} $\times$ 2), 127.7 (Bn-C_{Ar} $\times$ 2), 127.5 (Bn-C_{Ar}), 113.9 (PMB-C_{Ar} $\times$ 2), 86.2 (C12), 83.3 (C15), 81.6 (C7), 81.0 (C14), 79.8 (C10), 78.1 (C11), 76.8 (C6), 74.5 (Bn-CH₂), 71.3 (PMB-CH₂), 70.5 (C3), 63.9 (C16), 55.3 (PMB-CH₃), 37.4 (C13), 31.3 (C5), 29.2 (C8), 26.2 (C4), 25.9 (TBS-CCH₃ $\times$ 3), 25.8 (C9), 25.0 (C12-CH₃), 18.4 (TBS-C(CH₃)₃), –5.5 (TBS-SiCH₃), –5.6 (TBS-SiCH); **m.p.** 70–73 °C.

Spectroscopic data were consistent with those previously reported.⁶⁰

(R)-4-(Benzyloxy)-1-((2R,5S)-5-((S)-((2R,4S,5R)-5-(((tert-butyl)dimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)(hydroxy)methyl)tetrahydrofuran-2-yl)butyl acetate **277**



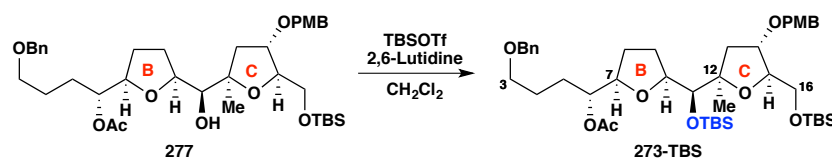
mono-TBS ether **324** (850 mg, 1.32 mmol), pyridine (1.10 mL, 13.2 mmol) and DMAP (161 mg, 0.130 mmol) were dissolved in CH₂Cl₂ (80 mL) and cooled to 0 °C. Acetic anhydride (0.187 mL, 1.98 mmol) was added dropwise and the resulting solution was allowed to gradually warm to room temperature before being stirred for 18 hours. The reaction was quenched by addition of an aqueous solution of NaHCO₃ (sat., 40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with brine (40 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 25:75 EtOAc:Pentane) to afford acetate **277** as a colourless oil (784 mg, 87%).

R_f = 0.7 (40:60 EtOAc:Pentane); $[\alpha]_D^{25}$ +15.9 (c = 1.15, CH₂Cl₂; lit. +18.9, c = 1.20, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.36–7.28 (4 H, m, Bn-ArH × 4), 7.28–7.25 (1 H, m, Bn-ArH), 7.23 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 6.86 (2 H, d, J = 8.4 Hz, PMB-ArH × 2), 4.90–4.84 (1 H, m, C(6)H), 4.48 (2 H, s, Bn-CH₂), 4.46 (1 H, d, J = 11.1 Hz, PMB-CH_AH_B), 4.40 (1 H, d, J = 11.2 Hz, PMB-CH_AH_B), 4.16–4.08 (1 H, m, C(14)H), 4.05 (1 H, td, J = 4.2, 2.9 Hz, C(15)H), 3.96–3.88 (1 H, m, C(7)H), 3.84 (1 H, dt, J = 7.4, 6.0 Hz, C(10)H), 3.78 (3 H, s, PMB-CH₃), 3.67 (2 H, m, C(16)H₂), 3.50 (1 H, d, J = 6.1 Hz, C(11)H), 3.45 (2 H, t,

$J = 5.8$ Hz, C(3) H_2), 3.40 (1 H, br. s, OH), 2.41–2.27 (1 H, m, C(13) H_AH_B), 2.05 (3 H, s, Ac- CH_3), 2.01–1.81 (3 H, m, C(9) H_2 , C(8) H_AH_B), 1.76 (1 H, dd, $J = 13.1, 3.7$ Hz, C(13) H_AH_B), 1.72–1.55 (5 H, m, C(8) H_AH_B , C(4) H_2 , C(5) H_2), 1.39 (3 H, s, C(12) CH_3), 0.88 (9 H, s, TBS-C(CH_3) $_3$), 0.04 (6 H, s, TBS-Si(CH_3) $_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.1 (Ac-CO), 159.2 (PMB- $C_{Ar}OMe$), 138.5 (Bn- $C_{Ar}CH_2$), 130.4 (PMB- $C_{Ar}CH_2$), 129.2 (PMB- $C_{Ar} \times 2$), 128.4 (Bn- $C_{Ar} \times 2$), 127.6 (Bn- $C_{Ar} \times 2$), 127.5 (Bn- C_{Ar}), 113.8 (PMB- $C_{Ar} \times 2$), 86.1 (C12), 83.4 (C15), 80.5 (C14), 80.2 (C10), 79.9 (C7), 77.7 (C11), 75.4 (C6), 72.9 (Bn- CH_2), 71.2 (PMB- CH_2), 69.8 (C3), 63.4 (C16), 55.3 (PMB- CH_3), 38.1 (C13), 27.9 (C5), 27.8 (C8), 27.7 (C9), 26.0 (TBS-C $CH_3 \times 3$), 25.7 (C4), 24.8 (C12- CH_3), 21.2 (Ac- CH_3), 14.2 (TBS-C(CH_3) $_3$), -5.5 (TBS-Si CH_3), -5.5 (TBS-Si CH_3).

Spectroscopic data were consistent with those previously reported.⁶⁰

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butyl acetate 273-TBS



Acetate **277** (540 mg, 0.790 mmol) and 2,6-lutidine (0.92 mL, 7.9 mmol) were dissolved in CH_2Cl_2 (8 mL) and cooled to -78 °C in a dry ice-acetone bath. *tert*-Butyldimethylsilyl trifluoromethane- sulfonate (0.91 mL, 3.9 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 12 hours before being quenched by addition of an aqueous solution of $NaHCO_3$ (sat., 10 mL). The organic layer was separated

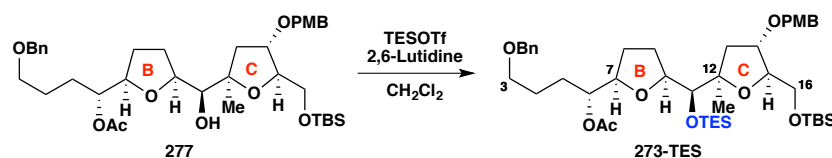
and the aqueous layer was extracted with Et₂O (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 25:75 Et₂O:Petroleum ether) to afford *bis*-TBS ether **273-TBS** as a colourless oil (566 mg, 92%).

R_f = 0.7 (40:60 EtOAc:Petroleum ether); $[\alpha]_D^{25}$ +4.4 (c = 1.30, CH₂Cl₂; lit. +4.8, c = 0.80, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.37–7.29 (4 H, m, Bn-ArH × 4), 7.29–7.26 (1 H, m, Bn-ArH), 7.25 (2 H, d, J = 8.7 Hz, PMB-ArH × 2), 6.86 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 5.02–4.95 (1 H, m, C(6)H), 4.48 (2 H, s, Bn-CH₂), 4.46 (1 H, d, J = 11.4 Hz, PMB-CH_AH_B), 4.39 (1 H, d, J = 11.5 Hz, PMB-CH_AH_B), 4.12–4.06 (1 H, m, C(15)H), 4.03 (1 H, dt, J = 7.1, 2.8 Hz, C(14)H), 4.00–3.93 (1 H, m, C(10)H), 3.80 (1 H, d, J = 1.1 Hz, C(11)H), 3.78 (3 H, s, PMB-CH₃), 3.70–3.58 (2 H, m, C(16)H₂), 3.51–3.47 (1 H, m, C(7)H), 3.45 (2 H, d, J = 5.9 Hz, C(3)H₂), 2.11–2.05 (1 H, m, C(13)H_AH_B), 2.05 (3 H, s, Ac-CH₃), 1.98–1.87 (1 H, m, C(9)H_AH_B), 1.86–1.77 (2 H, m, C(8)H_AH_B, C(13)H_AH_B), 1.63 (5 H, m, C(5)H₂, C(9)H_AH_B, C(4)H₂), 1.48–1.37 (1 H, m, C(8)H_AH_B), 1.25 (3 H, s, C(12)CH₃), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.09 (3 H, s, TBS-Si(CH₃)₃), 0.06 (6 H, s, TBS-Si(CH₃)₃), 0.03 (3 H, s, TBS-Si(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.5 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 138.5 (Bn-C_{Ar}H₂), 130.6 (PMB-C_{Ar}H₂), 129.1 (PMB-C_{Ar} × 2), 128.4 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar} × 2), 127.5 (Bn-C_{Ar}), 113.8 (PMB-C_{Ar} × 2), 85.0 (C12), 84.4 (C15), 81.1 (C14), 79.8 (C10), 78.8 (C7), 78.0 (C11), 74.6 (C6), 72.9 (Bn-CH₂), 71.0 (PMB-CH₂), 69.9 (C3), 64.0 (C16), 55.2 (PMB-CH₃), 42.5 (C13), 28.3 (C5), 28.1 (C8), 26.2 (TBS-C(CH₃)₃), 26.0 (TBS-C(CH₃)₃), 25.4 (C4),

23.9 (C9), 22.0 (C12-CH₃), 21.2 (Ac-CH₃), 18.4 (TBS-C(CH₃)₃), 18.3 (TBS-C(CH₃)₃), -3.3 (TBS-SiCH₃), -4.8 (TBS-SiCH₃), -5.3 (TBS-SiCH₃), -5.4 (TBS-SiCH₃).

Spectroscopic data were consistent with those previously reported.⁶⁰

(R)-4-(Benzyloxy)-1-((2R,5S)-5-((S)-((2R,4S,5R)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((triethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butyl acetate 273-TES

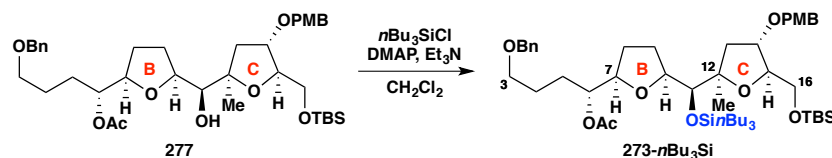


Acetate **277** (200 mg, 0.290 mmol) and 2,6-lutidine (0.34 mL, 2.9 mmol) were dissolved in CH₂Cl₂ (3 mL) and cooled to -78 °C in a dry ice-acetone bath. Triethylsilyl trifluoromethanesulfonate (0.33 mL, 1.5 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 12 hours before being quenched by addition of an aqueous solution of NaHCO₃ (sat., 3 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (4 × 5 mL). The combined organic layers were washed with brine (3 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 25:75 Et₂O:Petroleum ether) to afford *bis*-silyl ether **273-TES** as a colourless oil (210 mg, 90%).

R_f = 0.7 (40:60 EtOAc:Petroleum ether). [**α**]_D²⁵ +2.8 (c = 1.20, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) **δ_H** 7.37–7.29 (4 H, m, Bn-ArH × 4), 7.28–7.26 (1 H, m, Bn-ArH), 7.25 (2 H, d, *J* = 8.6 Hz, PMB-ArH × 2), 6.87 (2 H, d, *J* = 8.6 Hz, PMB-ArH × 2), 5.00–4.94 (1 H, m,

$C(6)H$), 4.49 (2 H, s, Bn- CH_2), 4.47 (1 H, d, $J = 11.4$ Hz, PMB- CH_AH_B), 4.40 (1 H, d, $J = 11.5$ Hz, PMB- CH_AH_B), 4.07 (1 H, dt, $J = 6.0, 3.8$ Hz, $C(14)H$), 4.03 (1 H, dt, $J = 6.7, 3.0$ Hz, $C(15)H$), 3.94 (1 H, t, $J = 7.8$ Hz, $C(10)H$), 3.82 (1 H, d, $J = 1.3$ Hz, $C(11)H$), 3.80 (3 H, s, PMB- CH_3), 3.72–3.59 (2 H, m, $C(16)H_AH_B$, $C(7)H$), 3.47 (3 H, m, $C(16)H_AH_B$, $C(3)H_2$), 2.11 (1 H, dd, $J = 13.0, 2.6$ Hz, $C(13)H_AH_B$), 2.06 (3 H, s, Ac- CH_3), 1.97–1.86 (1 H, m, $C(9)H_AH_B$), 1.80 (2 H, m, $C(8)H_AH_B$, $C(13)H_AH_B$), 1.75–1.59 (5 H, $C(4)H_2$, $C(5)H_2$, $C(9)H_AH_B$), 1.39 (1 H, m, $C(8)H_AH_B$), 1.25 (3 H, s, $C(12)CH_3$), 0.95 (9 H, t, $J = 8.0$ Hz, TES- $CH_3 \times 3$), 0.91–0.88 (9 H, br. s, TBS- $C(CH_3)_3$), 0.62 (6 H, q, $J = 7.8$ Hz, TES- $CH_2 \times 3$), 0.07–0.04 (6 H, br. s, TBS-Si(CH_3) $_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.6 (Ac-CO), 159.1 (PMB- $C_{Ar}OMe$), 138.5 (Bn- $C_{Ar}CH_2$), 130.6 (PMB- $C_{Ar}CH_2$), 129.1 (PMB- $C_{Ar} \times 2$), 128.4 (Bn- $C_{Ar} \times 2$), 128.2 (Bn- $C_{Ar} \times 2$), 127.6 (Bn- C_{Ar}), 113.8 (PMB- $C_{Ar} \times 2$), 85.0 (C12), 84.4 (C15), 80.7 (C14), 79.8 (C10), 78.6 (C7), 78.1 (C11), 74.8 (C6), 72.9 (Bn- CH_2), 71.0 (PMB- CH_2), 70.0 (C3), 63.8 (C16), 55.3 (PMB- CH_3), 41.7 (C13), 28.3 (C5), 28.1 (C8), 26.0 (TBS- $C(CH_3)_3$), 25.4 (C4), 24.1 (C9), 22.3 (C12- CH_3), 21.1 (Ac- CH_3), 18.4 (TBS- $C(CH_3)_3$), 7.1 (TES- $CH_3 \times 3$), 5.3 (TES- $CH_2 \times 3$), –5.4 (TBS-Si CH_3), –5.4 (TBS-Si CH_3). IR ν_{max} (film)/ cm^{-1} 2947, 2858, 1739, 1612, 1514, 1463, 1370, 1246, 1101, 1040, 832, 727; HRMS (ESI $^+$, m/z) $C_{44}H_{73}O_9Si_2$ [M + H $^+$] calculated 801.4788, found 801.4778 ($\Delta = -1.24$ ppm).

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((tributylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butyl acetate **273-*n*Bu₃Si**

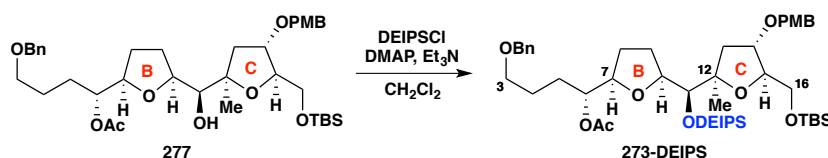


Acetate **277** (50 mg, 0.073 mmol), Et₃N (0.152 mL, 1.09 mmol) and 4-(dimethylamino)-pyridine (18 mg, 0.15 mmol) were dissolved in *N,N*-dimethylformamide (0.7 mL) and cooled to 0 °C in an ice-water bath. Chlorotributylsilane (78 µL, 0.29 mmol) was added dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred for 18 hours before being quenched by addition of an aqueous solution of NaHCO₃ (sat., 2 mL). The mixture was diluted with water (2 mL) and Et₂O (2 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 Et₂O:Pentane to 30:70 Et₂O:Pentane) to give *bis*-silyl ether **273-*n*Bu₃Si** as a pale yellow oil (52 mg, 81%).

$R_f = 0.7$ (40:60 Et₂O:Pentane); $[\alpha]_D^{25} +4.3$ ($c = 0.87$, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.37–7.30 (4 H, m, Bn-ArH × 4), 7.30–7.26 (1 H, m, Bn-ArH), 7.25 (2 H, d, $J = 8.6$ Hz, PMB-ArH × 2), 6.87 (2 H, d, $J = 8.6$ Hz, PMB-ArH × 2), 5.08–4.89 (1 H, m, C(6)H), 4.48 (2 H, s, Bn-CH₂), 4.47 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.40 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.07 (1 H, dt, $J = 6.5, 3.8$ Hz, C(15)H), 4.02 (1 H, dt, $J = 6.3, 2.8$ Hz, C(14)H), 3.94 (1 H, dt, $J = 7.1, 1.4$ Hz, C(10)H), 3.80 (3 H, s, PMB-CH₃), 3.78 (1 H, d, $J = 1.4$ Hz,

C(11)*H*), 3.69–3.61 (2 H, m, C(16)*H_AH_B*, C(7)*H*), 3.46 (3 H, m, C(16)*H_AH_B*, C(3)*H₂*), 2.15–2.07 (1 H, m, C(13)*H_AH_B*), 2.05 (3 H, s, Ac-CH₃), 1.96–1.75 (3 H, m, C(9)*H_AH_B*, C(8)*H_AH_B*, C(13)*H_AH_B*), 1.73–1.58 (5 H, m, C(5)*H₂*, C(9)*H_AH_B*, C(4)*H₂*), 1.49–1.37 (1 H, m, C(8)*H_AH_B*), 1.36–1.27 (12 H, m, *n*Bu-CH₃(CH₂)₂ × 3), 1.24 (3 H, s, C(12)CH₃), 0.96–0.80 (18 H, m, TBS-C(CH₃)₃, *n*Bu-CH₃ × 3), 0.68–0.53 (6 H, m, *n*Bu-SiCH₂ × 3), 0.06 (6 H, s, TBS-Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.4 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 138.5 (Bn-C_{Ar}CH₂), 130.6 (PMB-C_{Ar}CH₂), 129.1 (PMB-C_{Ar} × 2), 128.4 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar} × 2), 127.5 (Bn-C_{Ar}), 113.8 (PMB-C_{Ar} × 2), 84.9 (C12), 84.4 (C15), 80.8 (C14), 79.8 (C10), 78.8 (C7), 78.3 (C11), 74.9 (C6), 72.9 (Bn-CH₂), 71.0 (PMB-CH₂), 70.0 (C3), 63.8 (C16), 55.3 (PMB-CH₃), 41.9 (C13), 28.2 (C5, C8), 26.8 (*n*Bu-CH₃CH₂ × 3), 26.0 (TBS-C(CH₃)₃), 25.6 (*n*Bu-CH₃CH₂CH₂ × 3), 25.4 (C4), 24.2 (C9), 22.3 (C12-CH₃), 21.2 (Ac-CH₃), 18.4 (TBS-C(CH₃)₃), 14.3 (*n*Bu-CH₃ × 3), 13.9 (*n*Bu-SiCH₂ × 3), –5.3 (TBS-Si(CH₃)₂), –5.4 (TBS-Si(CH₃)₂); IR ν_{max} (film)/cm^{–1} 2963, 2862, 1740, 1611, 1513, 1462, 1368, 1245, 1100, 1041, 839, 726; HRMS (ESI⁺, *m/z*) C₅₀H₈₅O₉Si₂ [M + H⁺] calculated 884.5648, found 884.5643 (Δ = –0.57 ppm).

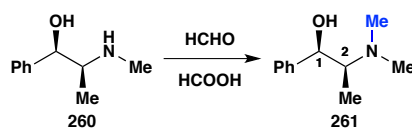
(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)butyl acetate **273-DEIPS**



Acetate **277** (870 mg, 1.27 mmol), triethylamine (2.6 mL, 19 mmol) and 4-(dimethylamino)-pyridine (310 mg, 2.53 mmol) were dissolved in *N,N*-dimethylformamide (13 mL) and cooled to 0 °C in an ice-water bath. Chlorodiethylisopropylsilane (DEIPSCl, 1.87 mL, 10.1 mmol) was added dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred for 72 hours before being quenched by addition of an aqueous solution of NaHCO₃ (sat., 15 mL). The mixture was diluted with water (15 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 Et₂O:Pentane to 30:70 Et₂O:Pentane) to give *bis*-silyl ether **273-DEIPS** as a pale yellow oil (875 mg, 85%).

$R_f = 0.7$ (40:60 Et₂O:Pentane); $[\alpha]_D^{25} +5.1$ ($c = 1.11$, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ_H 7.37–7.31 (4 H, m, Bn-ArH × 4), 7.31–7.27 (1 H, m, Bn-ArH), 7.25 (2 H, d, $J = 8.6$ Hz, PMB-ArH × 2), 6.87 (2 H, d, $J = 8.7$ Hz, PMB-ArH × 2), 4.98 (1 H, dq, $J = 7.5, 3.8$ Hz, C(6)H), 4.49 (2 H, s, Bn-CH₂), 4.48 (1 H, d, $J = 11.7$ Hz, PMB-CH_AH_B), 4.41 (1 H, d, $J = 11.6$ Hz, PMB-CH_AH_B), 4.08 (1 H, dt, $J = 6.2, 3.9$ Hz, C(15)H), 4.04 (1 H, dt, $J = 6.7, 3.1$ Hz, C(14)H), 3.97 (1 H, ddd, $J = 8.7, 7.1, 1.3$ Hz, C(10)H), 3.87 (1 H, d, $J = 1.3$ Hz, C(11)H),

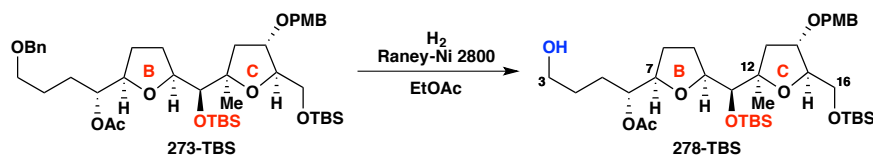
3.80 (3 H, s, PMB-CH₃), 3.72–3.63 (2 H, m, C(16)H_AH_B, C(7)H), 3.53–3.48 (1 H, m, C(16)H_AH_B), 3.47 (2 H, t, $J = 5.8$ Hz, C(3)H₂), 2.14 (1 H, dd, $J = 13.0, 7.2$ Hz, C(13)H_AH_B), 2.05 (3 H, s, Ac-CH₃), 1.98–1.90 (1 H, m, C(9)H_AH_B), 1.86–1.78 (2 H, m, C(8)H_AH_B, C(13)H_AH_B), 1.76–1.62 (5 H, m, C(5)H₂, C(9)H_AH_B, C(4)H₂), 1.48–1.37 (1 H, m, C(8)H_AH_B), 1.26 (3 H, s, C(12)CH₃), 1.06–0.93 (13 H, m, DEIPS-CH₃ × 4, DEIPS-CH), 0.90 (9 H, br. s., TBS-C(CH₃)₃), 0.73–0.54 (4 H, m, DEIPS-CH₂ × 2), 0.06 (6 H, s, TBS-Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.5 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 138.5 (Bn-C_{Ar}CH₂), 130.6 (PMB-C_{Ar}CH₂), 129.1 (PMB-C_{Ar} × 2), 128.4 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar} × 2), 127.5 (Bn-C_{Ar}), 113.8 (PMB-C_{Ar} × 2), 84.9 (C12), 84.3 (C15), 80.7 (C14), 79.9 (C10), 78.6 (C7), 78.1 (C11), 74.7 (C6), 72.9 (Bn-CH₂), 71.1 (PMB-CH₂), 70.0 (C3), 63.8 (C16), 55.3 (PMB-CH₃), 42.2 (C13), 28.3 (C5), 28.1 (C8), 26.0 (TBS-C(CH₃)₃), 25.4 (C4), 24.0 (C9), 22.1 (C12-CH₃), 21.1 (Ac-CH₃), 18.4 (TBS-C(CH₃)₃), 17.7 (DEIPS-*i*PrCH₃), 17.6 (DEIPS-*i*PrCH₃), 13.2 (DEIPS-*i*PrCH), 7.4 (DEIPS-EtCH₃), 7.3 (DEIPS-EtCH₃), 4.5 (DEIPS-EtCH₂), 4.5 (DEIPS-EtCH₂), -5.4 (TBS-Si(CH₃)₂), -5.4 (TBS-Si(CH₃)₂); IR ν_{max} (film)/cm⁻¹ 2953, 2860, 1738, 1613, 1513, 1463, 1368, 1246, 1099, 1039, 837, 726; HRMS (ESI⁺, *m/z*) C₄₅H₇₅O₉Si₂ calculated 815.49441, found [M + H⁺] 815.49418 (Δ = -0.28 ppm).

(1*R*,2*S*)-2-(Dimethylamino)-1-phenylpropan-1-ol 261

(1*R*, 2*S*)-(-)-ephedrine **260** (20.0 g, 121 mmol) was dissolved in formaldehyde (20.0 mL, 37% w/v in H₂O, 726 mmol) and cooled to 0 °C under an atmosphere of air. Formic acid (45.7 mL, 1.21 mol) was added and the mixture was allowed to warm to room temperature, before being heated to 90 °C overnight. The mixture was allowed to cool to room temperature, transferred to a conical flask, and further cooled to 0 °C in an ice-water bath. The reaction was quenched by addition of an aqueous solution of NaOH (1 M, 100 mL), and further basified by carefully adding NaOH pellets with stirring at 0 °C until the product crashed out from solution. (**Caution:** strongly exothermic) The aqueous phase and solid products were extracted with Et₂O (4 × 200 mL). The combined organic layers were dried over K₂CO₃, filtered and concentrated *in vacuo* to afford (1*R*, 2*S*)-(-)-*N*-methylephedrine **261** as small white crystals (21.5 g, 99%).

$[\alpha]_D^{25}$ -32.5 (*c* = 4.6, MeOH; lit. -29.2, *c* = 5.0, MeOH); ¹H NMR (400 MHz, CDCl₃) δ_H 7.36–7.30 (4 H, m, Ph-Ar*H* × 4), 7.28–7.19 (1 H, m, Ph-Ar*H*), 4.94 (1 H, d, *J* = 3.7 Hz, C(1)*H*), 2.52 (1 H, qd, *J* = 6.8, 3.7 Hz, C(2)*H*), 2.33 (6 H, br.s, N(CH₃)₂), 0.81 (3 H, d, *J* = 6.8 Hz, C(2)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 142.2 (*C*_{Ar}), 128.0 (*C*_{Ar} × 2), 126.8 (*C*_{Ar} × 2), 125.9 (*C*_{Ar}), 67.0 (C1), 65.4 (C2), 43.2 (NCH₃), 43.1 (NCH₃), 10.2 (C2-CH₃); **m.p.** 83–86 °C (lit. 86–88 °C).

Spectroscopic data were consistent with those previously reported.¹²¹



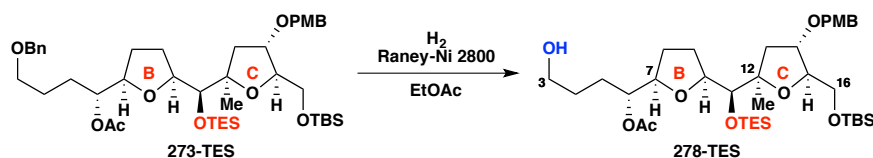
Raney[®]-nickel 2800 (slurry in H₂O, 5 mL) was added to the flask and washed with water (3 × 5 mL), EtOH (3 × 5 mL), and EtOAc (3 × 5 mL). Benzyl ether **273-TBS** (380 mg, 0.450 mmol) was dissolved in EtOAc (9 mL) and added to the reaction flask. The flask was evacuated and backfilled with hydrogen five times. The resulting slurry was warmed to 45 °C and stirred vigorously under hydrogen atmosphere (balloon pressure) for 12 hours. The reaction mixture was cooled to room temperature and filtered through celite, eluting with a 1:1 mixture of EtOH and EtOAc (3 × 5 mL). (**Caution:** Dry Raney[®]-nickel is spontaneously flammable.) The combined organic layers were concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 40:60 EtOAc:Pentane) to afford primary alcohol **278-TBS** as a colourless oil (273.6 mg, 81%).

R_f = 0.4 (40:60 EtOAc:Pentane); **[α]_D²⁵** -15.8 (c = 0.63, CH₂Cl₂; lit. -17.4, c = 0.80, CH₂Cl₂); **¹H NMR** (400 MHz, CDCl₃) **δ_H** 7.24 (2 H, d, *J* = 8.7 Hz, PMB-Ar*H* × 2), 6.86 (2 H, d, *J* = 8.6 Hz, PMB-Ar*H* × 2), 5.05–4.90 (1 H, C(6)*H*), 4.46 (1 H, d, *J* = 11.4 Hz, PMB-CH_AH_B), 4.38 (1 H, d, *J* = 11.5 Hz, PMB-CH_AH_B), 4.08 (1 H, dt, *J* = 6.4, 3.8 Hz, C(15)*H*), 4.02 (1 H, dt, *J* = 7.2, 2.8 Hz, C(14)*H*), 3.97 (1 H, ddd, *J* = 8.7, 5.0, 1.2 Hz, C(10)*H*), 3.80 (1 H, d, *J* = 1.4 Hz, C(11)*H*), 3.79 (3 H, s, PMB-CH₃), 3.70–3.59 (4 H, m,

C(3) H_2 , C(7) H , C(16) H_AH_B , 3.51–3.43 (1 H, m, (C16) H_AH_B), 2.06 (3 H, s, Ac- CH_3), 2.06–2.04 (1 H, m, C(13) H_AH_B), 1.92 (1 H, ddd, $J = 11.6, 8.9, 4.9$ Hz, C(9) H_AH_B), 1.88–1.77 (2 H, m, C(8) H_AH_B , C(13) H_AH_B), 1.76–1.63 (3 H, m, C(9) H_AH_B , C(5) H_2), 1.63–1.56 (2 H, m, C(4) H_2), 1.43 (1 H, ddt, $J = 11.9, 9.7, 6.0$ Hz, C(8) H_AH_B), 1.24 (3 H, s, C(12) CH_3), 0.89 (9 H, s, TBS-C(CH_3) $_3$), 0.89 (8 H, s, TBS-C(CH_3) $_3$), 0.08 (3 H, s, TBS-Si CH_3), 0.05 (6 H, s, TBS-Si $CH_3 \times 2$), 0.03 (3 H, s, TBS-Si CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.8 (Ac-CO), 159.1 (PMB- $C_{Ar}OMe$), 130.6 (PMB- $C_{Ar}CH_2$), 129.1 (PMB- $C_{Ar} \times 2$), 113.8 (PMB- $C_{Ar} \times 2$), 85.0 (C12), 84.4 (C15), 81.1 (C14), 79.9 (C10), 78.7 (C7), 78.0 (C11), 74.6 (C6), 71.0, (PMB- CH_2) 64.0 (C16), 62.6 (C3), 55.3 (PMB- CH_3), 42.5 (C13), 28.2 (C4), 28.0 (C5), 28.0 (C8), 26.1 (TBS-C(CH_3) $_3$), 26.0 (TBS-C(CH_3) $_3$), 23.9 (C9), 22.0 (C12- CH_3), 21.2 (Ac- CH_3), 18.4 (TBS-C(CH_3) $_3$), 18.3 (TBS-C(CH_3) $_3$), -3.3 (TBS-Si(CH_3) $_2$), -4.7 (TBS-Si(CH_3) $_2$), -5.4 (TBS-Si(CH_3) $_2$), -5.4 (TBS-Si(CH_3) $_2$).

Spectroscopic data were consistent with those previously reported.⁶⁰

(*R*)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((triethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-hydroxybutyl acetate 278-TES



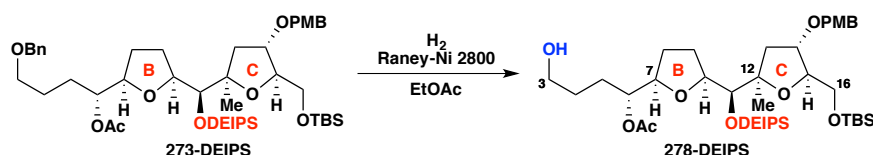
Raney[®]-nickel 2800 (slurry in H_2O , 1 mL) was added to the flask and washed with water (3×1 mL), EtOH (3×1 mL), and EtOAc (3×1 mL). Benzyl ether **273-TES** (51 mg, 64 μ mol) was dissolved in EtOAc (1.5 mL) and added to the reaction flask. The flask was evacuated

and backfilled with hydrogen five times. The resulting slurry was warmed to 45 °C and stirred vigorously under hydrogen atmosphere (balloon pressure) for 12 hours. The reaction mixture was cooled to room temperature and filtered through celite, eluting with a 1:1 mixture of EtOH and EtOAc (3×1 mL). (**Caution:** Dry Raney nickel is spontaneously flammable.) The combined organic layers were concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 40:60 EtOAc:Pentane) to afford primary alcohol **278-TES** as a colourless oil (30 mg, 66%).

$R_f = 0.4$ (40:60 EtOAc:Pentane); $[\alpha]_D^{25} -24.8$ ($c = 1.05$, CH₂Cl₂); $^1\text{H NMR}$ (400 MHz, CDCl₃) δ_H 7.25 (2 H, d, $J = 8.5$ Hz, PMB-ArH $\times 2$), 6.6 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 4.97 (1 H, td, $J = 7.0, 4.5$ Hz, C(6)H), 4.47 (1 H, d, $J = 11.6$ Hz, PMB-CH_AH_B), 4.39 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.07 (1 H, dt, $J = 6.4, 3.8$ Hz, C(15)H), 4.02 (1 H, dt, $J = 6.5, 3.0$ Hz, C(14)H), 3.94 (1 H, ddd, $J = 8.8, 7.0, 1.5$ Hz, C(10)H), 3.81 (1 H, d, $J = 1.3$ Hz, C(11)H), 3.80 (3 H, s, PMB-CH₃), 3.71–3.60 (4 H, m, C(3)H₂, C(7)H, C(16)H_AH_B), 3.47 (1 H, dd, $J = 10.5, 6.4$ Hz, C(16)H_AH_B), 2.10 (1 H, dd, $J = 13.3, 7.1$ Hz, C(13)H_AH_B), 2.07 (3 H, s, Ac-CH₃), 1.99–1.87 (1 H, m, C(9)H_AH_B), 1.87–1.81 (1 H, m, C(8)H_AH_B), 1.78 (1 H, dd, $J = 13.3, 2.7$ Hz, C(13)H_AH_B), 1.69 (2 H, ddd, $J = 13.4, 5.8, 3.1$ Hz, C(5)H₂), 1.64–1.54 (3 H, m, C(4)H₂, C(9)H_AH_B), 1.46–1.40 (1 H, m, C(8)H_AH_B), 1.24 (3 H, s, C(12)CH₃), 0.94 (9 H, t, $J = 7.9$ Hz, TES-CH₃ $\times 3$), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.61 (6 H, q, $J = 7.9$ Hz, TES-CH₂ $\times 3$), 0.05 (6 H, s, TBS-Si(CH₃)₂); $^{13}\text{C NMR}$ (100 MHz, CDCl₃) δ_C 170.8 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 130.6 (PMB-C_{Ar}H₂), 129.1 (PMB-C_{Ar} $\times 2$), 113.8 (PMB-C_{Ar} $\times 2$), 84.9 (C12), 84.4 (C15), 80.7 (C14), 79.8 (C10), 78.6 (C7), 78.1 (C11), 74.8 (C6),

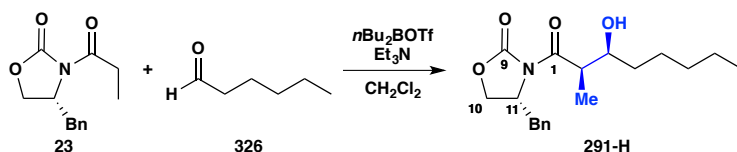
71.0 (PMB-CH₂), 63.8 (C16), 62.6 (C3), 55.3 (PMB-CH₃), 41.8 (C13), 28.2 (C4), 28.0 (C8), 28.0 (C5), 26.0 (TBS-C(CH₃)₃), 24.2 (C9), 22.2 (C12-CH₃), 21.1 (Ac-CH₃), 18.4 (TBS-C(CH₃)₃), 7.1 (TES-CH₃ × 3), 5.3 (TES-CH₂ × 3), -5.4 (TBS-Si(CH₃)₂), -5.4 (TBS-Si(CH₃)₂); **IR** ν_{max} (film)/cm⁻¹ 3447, 2947, 1737, 1534, 1368, 1243, 1091; **HRMS** (ESI⁺, m/z) C₃₇H₆₇O₉Si₂ [M + H⁺] calculated 711.4318, found 711.4315 (Δ = -0.42 ppm).

(R)-1-((2R,5S)-5-((S)-((2R,4S,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)-4-hydroxybutyl acetate 278-DEIPS



Raney[®]-nickel 2800 (slurry in H₂O, 11 mL) was added to the flask and washed with water (3 × 15 mL), EtOH (3 × 15 mL), and EtOAc (3 × 15 mL). Benzyl ether **273-DEIPS** (0.79 g, 0.97 mmol) was dissolved in EtOAc (1.5 mL) and added to the reaction flask. The flask was evacuated and backfilled with hydrogen five times. The resulting slurry was warmed to 45 °C and stirred vigorously under hydrogen atmosphere (balloon pressure) for 12 hours. The reaction mixture was cooled to room temperature and filtered through celite, eluting with a 1:1 mixture of EtOH and EtOAc (3 × 15 mL). (**Caution:** Dry Raney nickel is spontaneously flammable.) The combined organic layers were concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 40:60 EtOAc:Pentane) to afford primary alcohol **278-DEIPS** as a colourless oil (0.55 g, 79%).

$R_f = 0.4$ (40:60 EtOAc:Pentane); $[\alpha]_D^{25} +3.9$ ($c = 1.17$, CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} 7.24 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 6.86 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 4.95 (1 H, td, $J = 7.1, 4.3$ Hz, C(10)H), 4.46 (1 H, d, $J = 11.6$ Hz, PMB-CH_AH_B), 4.38 (1 H, d, $J = 11.6$ Hz, PMB-CH_AH_B), 4.08–4.04 (1 H, m, C(15)H), 4.01 (1 H, dt, $J = 6.6, 3.0$ Hz, C(14)H), 3.95 (1 H, ddd, $J = 8.7, 7.1, 1.3$ Hz, C(10)H), 3.84 (1 H, d, $J = 1.3$ Hz, C(11)H), 3.78 (3 H, s, PMB-CH₃), 3.69–3.57 (4 H, m, C(16)H_AH_B, C(3)H₂, C(7)H), 3.47 (1 H, dd, $J = 10.5, 6.2$ Hz, C(16)H_AH_B), 2.10 (1 H, dd, $J = 13.3, 7.1$ Hz, C(13)H_AH_B), 2.05 (3 H, s, Ac-CH₃), 1.98–1.85 (2 H, m, C(9)H_AH_B, C(8)H_AH_B), 1.85–1.74 (2 H, m, C(5)H_AH_B, C(13)H_AH_B), 1.74–1.61 (2 H, m, C(9)H_AH_B, C(5)H_AH_B), 1.59–1.52 (2 H, m, C(4)H₂), 1.47–1.34 (1 H, m, C(8)H_AH_B), 1.24 (3 H, s, C(12)-CH₃), 1.03–0.91 (13 H, m, DEIPS-CH₃ $\times 4$, DEIPS-*i*PrCH), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.70–0.52 (4 H, DEIPS-CH₂ $\times 2$), 0.03 (6 H, s, TBS-Si(CH₃)₂); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 170.7 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 130.5 (PMB-C_{Ar}CH₂), 129.1 (PMB-C_{Ar} $\times 2$), 113.8 (PMB-C_{Ar} $\times 2$), 84.9 (C12), 84.3 (C15), 80.7 (C14), 79.8 (C10), 78.6 (C7), 78.1 (C11), 74.8 (C6), 71.1 (PMB-CH₂), 63.8 (C16), 62.5 (C3), 55.2 (PMB-CH₃), 42.1 (C13), 28.2 (C4), 28.0 (C8), 28.0 (C5), 25.9 (TBS-C(CH₃)₃), 24.0 (C9), 22.1 (C12-CH₃), 21.1 (Ac-CH₃), 18.3 (TBS-C(CH₃)₃), 17.7 (DEIPS-*i*PrCH₃), 17.5 (DEIPS-*i*PrCH₃), 13.2 (DEIPS-*i*PrCH), 7.3 (DEIPS-EtCH₃), 7.3 (DEIPS-EtCH₃), 4.5 (DEIPS-EtCH₂), 4.5 (DEIPS-EtCH₂), –5.4 (TBS-SiCH₃), –5.4 (TBS-SiCH₃); **IR** ν_{max} (film)/cm^{–1} 3452, 2952, 2863, 1739, 1514, 1465, 1371, 1247, 1171, 1132, 1093, 883, 724; **HRMS** (ESI⁺, m/z) C₃₈H₆₉O₉Si₂⁺ [M + H⁺] calculated 725.44746, found 725.44744 ($\Delta = -0.03$ ppm).

(R)-4-Benzyl-3-((2R,3S)-3-hydroxy-2-methyloctanoyl)oxazolidin-2-one 291-H

(R)-4-Benzyl-3-propionyloxazolidin-2-one **23** (0.2 g, 0.9 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and cooled to 0 °C in an ice-water bath. Dibutylboron trifluoromethanesulfonate (1.0 M in CH_2Cl_2 , 1.11 mL, 1.11 mmol) was added dropwise, followed by Et_3N (0.42 mL, 3.0 mmol). The reaction was stirred at 0 °C for 10 minutes before being cooled to –78 °C in a dry ice-acetone bath. After another 10 minutes, hexanal **326** (0.12 mL, 1.0 mmol) was added dropwise, and the mixture was stirred at –78 °C for 30 minutes, before being warmed to 0 °C and stirred for 1 hour. The reaction was quenched by addition of aqueous pH 7 phosphate buffer (2 mL) and MeOH (2.5 mL) followed by a 2:1 mixture of MeOH and 30% hydrogen peroxide solution (2.5 mL). The resulting mixture was stirred vigorously for 1 hour. The aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were washed with water (5 mL), sodium bicarbonate solution (sat., aq., 5 mL), brine (5 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 10:90 EtOAc: Pentane to 30:70 EtOAc:Pentane) to afford aldol product **291-H** as a colourless oil (225 mg, 79%).

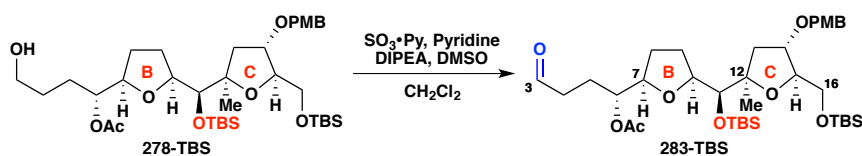
$R_f = 0.7$ (40:60 EtOAc:Pentane); $[\alpha]_D^{25} -50.4$ ($c = 1.36$, CH_2Cl_2 ; lit. -53.2 , $c = 1.85$, CHCl_3);

^1H NMR (400 MHz, CDCl_3) δ_{H} 7.32–7.26 (2 H, m, Bn-ArH $\times 2$), 7.26–7.20 (1 H, m, Bn-ArH), 7.19–7.13 (2 H, m, Bn-ArH $\times 2$), 4.66 (1 H, ddt, $J = 9.3, 7.5, 3.2$ Hz, C(11)H), 4.26–4.09 (2 H, m, C(10)H₂), 3.97–3.84 (1 H, m, C(3)H), 3.73 (1 H, qd, $J = 7.0, 3.0$ Hz,

C(2)*H*), 3.20 (1 H, dd, $J = 13.4, 3.4$ Hz, Bn-CH_AH_B), 3.07–2.93 (1 H, br. s., OH), 2.76 (1 H, dd, $J = 13.4, 9.3$ Hz, Bn-CH_AH_B), 1.57–1.18 (11 H, m, C(4)*H*₂, C(5)*H*₂, C(6)*H*₂, C(7)*H*₂, C(2)CH₃), 0.92–0.77 (3 H, m, C(8)*H*₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 177.4 (C1), 153.0 (C9), 135.1 (Bn-C_{Ar}H₂), 129.4 (Bn-C_{Ar} × 2), 128.9 (Bn-C_{Ar} × 2), 127.3 (Bn-C_{Ar}), 71.5 (C3), 66.1 (C10), 55.1 (C11), 42.2 (C2), 37.7 (Bn-CH₂), 33.9 (C4), 31.8 (C6), 25.7 (C7), 22.6 (C5), 14.0 (C8), 10.5 (C2-CH₃).

Spectroscopic data were consistent with those previously reported.⁶⁶

(*R*)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-Butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-4-oxobutyl acetate 283-TBS



Alcohol **278-TBS** (142 mg, 0.200 mmol) and DMSO (0.15 mL, 2.0 mmol) were dissolved in CH₂Cl₂ (2 mL) and cooled to 0 °C. *i*Pr₂NEt (0.15 mL, 2.0 mmol) was added and the mixture was cooled to –50 °C. Sulfur trioxide pyridine complex (0.32 g, 2.0 mmol) was added in one portion and the reaction was then warmed to –10 °C and stirred for 1 hour. The reaction was quenched by addition of a 1:1 mixture of Na₂S₂O₃ and NaHCO₃ (sat., 4 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (4 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography

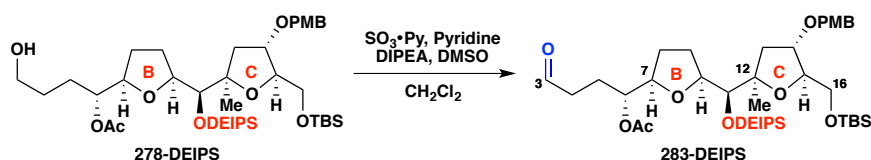
(SiO₂, 30:70 EtOAc:Petroleum ether) to afford aldehyde **283-TBS** as a colourless oil (140 mg, 99%).

$R_f = 0.7$ (40:60 EtOAc:Pentane); $[\alpha]_D^{25} +5.3$ ($c = 1.23$, CH₂Cl₂; lit. $+2.6$, $c = 0.50$, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 9.76–9.73 (1 H, br. s., C(3)*H*), 7.25 (2 H, d, $J = 8.6$ Hz, PMB-Ar*H* × 2), 6.87 (2 H, d, $J = 8.6$ Hz, PMB-Ar*H* × 2), 4.97 (1 H, ddd, $J = 8.6, 6.4, 4.0$ Hz, C(6)*H*), 4.46 (1 H, d, $J = 11.4$ Hz, PMB-CH_AH_B), 4.38 (1 H, d, $J = 11.4$ Hz, PMB-CH_AH_B), 4.08 (1 H, dt, $J = 6.3, 3.7$ Hz, C(15)*H*), 4.02 (1 H, dt, $J = 7.2, 2.7$ Hz, C(14)*H*), 3.97 (1 H, dt, $J = 7.0, 1.1$ Hz, C(10)*H*), 3.79 (3 H, s, PMB-CH₃), 3.79 (1 H, d, $J = 1.1$ Hz, C(11)*H*), 3.69–3.59 (2 H, m, C(16)*H*_AH_B, C(7)*H*), 3.48 (1 H, dd, $J = 10.5, 6.3$ Hz, C(16)*H*_AH_B), 2.61–2.40 (2 H, m, C(4)*H*₂), 2.09–2.02 (1 H, m, C(13)*H*_AH_B), 2.06 (3 H, s, Ac-CH₃), 2.02–1.93 (2 H, m, C(9)*H*_AH_B, C(5)*H*_AH_B), 1.93–1.78 (4 H, m, C(8)*H*_AH_B, C(13)*H*_AH_B, C(5)*H*_AH_B, C(9)*H*_AH_B), 1.53–1.38 (1 H, m, C(8)*H*_AH_B), 1.24 (3 H, s, C(12)-CH₃), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.09–0.01 (12 H, m, TBS-Si(CH₃)₂ × 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 201.2 (C3), 170.6 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 130.6 (PMB-C_{Ar}CH₂), 129.1 (PMB-C_{Ar} × 2), 113.8 (PMB-C_{Ar} × 2), 84.9 (C12), 84.5 (C15), 81.1 (C14), 80.0 (C10), 78.6 (C7), 78.0 (C11), 73.7 (C6), 71.1 (PMB-CH₂), 64.0 (C16), 55.3 (PMB-CH₃), 42.5 (C13), 39.8 (C4), 27.9 (C8), 26.1 (TBS-C(CH₃)₃), 26.0 (TBS-C(CH₃)₃), 24.1 (C5), 23.8 (C9), 21.9 (C12-CH₃), 21.1 (Ac-CH₃), 18.3 (TBS-C(CH₃)₃ × 2), –3.3 (TBS-SiCH₃), –4.7 (TBS-SiCH₃), –5.3 (TBS-SiCH₃), –5.4 (TBS-SiCH₃).

Spectroscopic data were consistent with those previously reported.⁶⁰

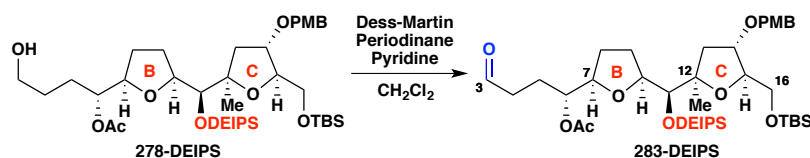
(R)-1-((2R,5S)-5-((S)-((2R,4S,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)-4-oxobutyl acetate 283-DEIPS

Procedure A:



Alcohol **278-DEIPS** (1.50 g, 2.07 mmol) and DMSO (1.5 mL, 20 mmol) were dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. $i\text{Pr}_2\text{NEt}$ (3.0 mL, 17 mmol) was added and the mixture was cooled to −50 °C. Sulfur trioxide pyridine complex (1.2 g, 7.5 mmol) was added in one portion and the reaction was then warmed to −10 °C and stirred for 1 hour. The reaction was quenched by addition of a 1:1 mixture of $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 (sat., 30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (4×30 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 30:70 EtOAc :Petroleum ether) to afford aldehyde **283-DEIPS** as a colourless oil (1.48 g, 99%).

Procedure B:



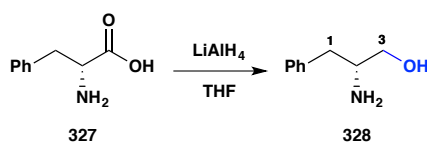
CH_2Cl_2 (6 mL) and water (6 mL) were added to a separating funnel and the mixture was shaken vigorously. Once separated, the water-saturated CH_2Cl_2 was collected and used to

dissolve alcohol **278-DEIPS** (400 mg, 0.550 mmol). After adding pyridine (0.70 mL, 8.6 mmol), Dess–Martin periodinane (700 mg, 1.65 mmol) was added and the white suspension was stirred for 3 hours. The reaction mixture was cooled to 0 °C and quenched by addition of a 1:1 mixture of Na₂S₂O₃ and NaHCO₃ (sat., 10 mL). The resulting solution was stirred for a further 30 minutes. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 EtOAc:Pentane) to afford aldehyde **283-DEIPS** as a colourless oil (353 mg, 88%).

R_f = 0.7 (40:60 EtOAc:Pentane); $[\alpha]_D^{25}$ +13.2 (c = 0.48, CH₂Cl₂); $^1\text{H NMR}$ (400 MHz, CDCl₃) δ_H 9.73 (1 H, br. s., C(3)*H*), 7.24 (2 H, d, J = 8.6 Hz, PMB-Ar*H* × 2), 6.86 (2 H, d, J = 8.6 Hz, PMB-Ar*H* × 2), 4.95 (1 H, ddd, J = 8.5, 6.5, 3.9 Hz, C(6)*H*), 4.46 (1 H, d, J = 11.5 Hz, PMB-CH_AH_B), 4.38 (1 H, d, J = 11.5 Hz, PMB-CH_AH_B), 4.05 (1 H, dt, J = 6.0, 3.8 Hz, C(15)*H*), 4.01 (1 H, dt, J = 6.6, 3.0 Hz, C(14)*H*), 3.95 (1 H, dt, J = 7.0, 1.3 Hz, C(10)*H*), 3.83 (1 H, d, J = 1.3 Hz, C(11)*H*), 3.78 (3 H, s, PMB-CH₃), 3.69–3.60 (2 H, m, C(16)*H*_AH_B, C(7)*H*), 3.48 (1 H, dd, J = 10.5, 6.1 Hz, C(16)*H*_AH_B), 2.58–2.38 (2 H, m, C(4)*H*₂), 2.15–2.06 (1 H, m, C(13)*H*_AH_B), 2.04 (3 H, s, Ac-CH₃), 2.00–1.90 (2 H, m, C(9)*H*_AH_B, C(5)*H*_AH_B), 1.89–1.76 (3 H, m, C(5)*H*_AH_B, C(8)*H*_AH_B, C(13)*H*_AH_B), 1.74–1.62 (1 H, m, C(9)*H*_AH_B), 1.39 (1 H, m, C(8)*H*_AH_B), 1.22 (3 H, s, C(12)-CH₃), 1.01–0.92 (13 H, m, DEIPS-CH₃ × 4, DEIPS-*i*PrCH), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.75–0.49 (4 H, m, DEIPS-CH₂ × 2), 0.08–0.01 (6 H, m, TBS-Si(CH₃)₂); $^{13}\text{C NMR}$ (100 MHz, CDCl₃) δ_C

201.2 (C3), 170.6 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 130.5 (PMB-C_{Ar}CH₂), 129.1 (PMB-C_{Ar} × 2), 113.8 (PMB-C_{Ar} × 2), 84.9 (C12), 84.3 (C15), 80.6 (C14), 80.0 (C10), 78.5 (C7), 78.1 (C11), 73.9 (C6), 71.1 (PMB-CH₂), 63.8 (C16), 55.2 (PMB-CH₃), 42.2 (C13), 39.8 (C4), 28.0 (C8), 26.0 (TBS-C(CH₃)₃), 24.1 (C5), 23.9 (C9), 22.0 (C12-CH₃), 21.0 (Ac-CH₃), 18.4 (TBS-C(CH₃)₃), 17.7 (DEIPS-*i*PrCH₃), 17.5 (DEIPS-*i*PrCH₃), 13.2 (DEIPS-*i*PrCH), 7.3 (DEIPS-EtCH₃), 7.3 (DEIPS-EtCH₃), 4.5 (DEIPS-EtCH₂), 4.2 (DEIPS-EtCH₂), -5.4 (TBS-Si(CH₃)₂), -5.4 (TBS-Si(CH₃)₂); **IR** $\nu_{\max}$ (film)/cm⁻¹ 2944, 2868, 2358, 1737, 1514, 1462, 1371, 1244, 1130, 1043, 838, 724; **HRMS** (ESI⁺, *m/z*) C₃₈H₆₇O₉Si₂⁺ [M + H⁺] calculated 723.43181, found 723.43223 (Δ = +0.58 ppm).

(*R*)-2-Amino-3-phenylpropan-1-ol **328**



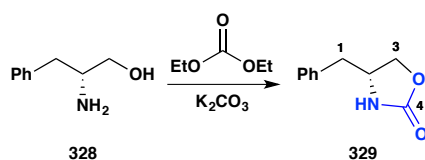
D-Phenylalanine **327** (10.0 g, 60.5 mmol) was dissolved in THF (90 mL) and cooled to 0 °C in an ice-water bath. Lithium aluminum hydride (4.60 g, 121 mmol) was added portionwise over 15 minutes. The reaction was gradually allowed to warm to room temperature before being heated to reflux for 16 hours. (**Caution:** strongly exothermic and gas release) The reaction was cooled to 0 °C and diluted with Et₂O (90 mL) before being quenched by addition of water (4.6 mL), NaOH solution (15% w/v, 4.6 mL) and water (13.8 mL). After stirring for one hour, the mixture was filtered through celite and washed with Et₂O (3 × 50 mL), and the combined organic layers were concentrated *in vacuo*. The crude product

was purified by recrystallization from EtOAc to yield amino alcohol **328** as white crystals (8.6 g, 94%).

$[\alpha]_D^{25} +26.1$ ($c = 1.15$, CH_2Cl_2 ; lit. $+25.9$, $c = 1.10$, CHCl_3) $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.33–7.27 (2 H, m, $\text{Ph-ArH} \times 2$), 7.27–7.21 (1 H, m, Ph-ArH), 7.21–7.15 (2 H, m, $\text{Ph-ArH} \times 2$), 3.63 (1 H, dd, $J = 10.7, 3.9$ Hz, $\text{C}(3)\text{H}_\text{A}\text{H}_\text{B}$), 3.39 (1 H, dd, $J = 10.7, 7.2$ Hz, $\text{C}(3)\text{H}_\text{A}\text{H}_\text{B}$), 3.11 (1 H, dddd, $J = 8.9, 7.2, 5.2, 3.9$ Hz, $\text{C}(2)\text{H}$), 2.79 (1 H, dd, $J = 13.5, 5.1$ Hz, $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$), 2.51 (1 H, dd, $J = 13.5, 8.7$ Hz, $\text{C}(1)\text{H}_\text{A}\text{H}_\text{B}$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 138.7 ($\text{Ph-C}_{\text{Ar}}\text{CH}_2$), 129.2 ($\text{Ph-C}_{\text{Ar}} \times 2$), 128.6 ($\text{Ph-C}_{\text{Ar}} \times 2$), 126.4 (Ph-C_{Ar}), 66.3 (C3), 54.2 (C2), 40.9 (C1); **m.p.** 90–92 °C (EtOAc).

Spectroscopic data were consistent with those previously reported.¹⁵¹

(*R*)-4-Benzyloxazolidin-2-one **329**



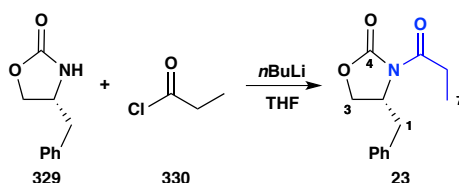
Amino alcohol **328** (8.6 g, 57 mmol), K_2CO_3 (0.80 g, 5.7 mmol) and diethylcarbonate (15.0 mL, 114 mmol) were added to a reaction flask. The flask was fitted with a distillation kit and the receiver flask was cooled in an ice-water bath. The reaction flask was heated to 135 °C for approximately 5 minutes until all the starting material had dissolved and then a further 2.5 hours until all the EtOH formed in the reaction had been collected in the receiver flask. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (45 mL). The combined organic layers were washed with water (3×15 mL), dried over MgSO_4 ,

filtered and concentrated *in vacuo*. The crude product was purified by dissolving in hot 2:1 EtOAc:hexane (35 mL) and filtered to afford **329** as white crystals (9.0 g, 89%).

$[\alpha]_D^{25} +66.5$ ($c = 1.46$, CHCl_3 ; lit. $+64.1$, $c = 1.00$, CHCl_3) **^1H NMR** (400 MHz, CDCl_3) δ_{H} 7.33 (2 H, dd, $J = 8.1, 6.5$ Hz, Ph-ArH $\times 2$), 7.30–7.24 (1 H, m, Ph-ArH), 7.21–7.14 (2 H, m, Ph-ArH $\times 2$), 6.07–5.70 (1 H, br. s., NH), 4.43 (1 H, tt, $J = 8.1, 2.3$ Hz, C(3) $H_{\text{A}}H_{\text{B}}$), 4.22–3.98 (2 H, m, C(3) $H_{\text{A}}H_{\text{B}}$, C(2)H), 3.02–2.73 (2 H, m, C(1) H_2); **^{13}C NMR** (100 MHz, CDCl_3) δ_{C} 159.5 (C4), 135.9 (Ph- $\text{C}_{\text{Ar}}\text{CH}_2$), 129.0 (Ph- $\text{C}_{\text{Ar}} \times 2$), 129.0 (Ph- $\text{C}_{\text{Ar}} \times 2$), 127.3 (Ph- C_{Ar}), 69.6 (C3), 53.8 (C2), 41.4 (C1); **m.p.** 90–92 °C (CH_2Cl_2).

Spectroscopic data were consistent with those previously reported.¹⁵²

(*R*)-4-Benzyl-3-propionyloxazolidin-2-one **23**



Oxazolidinone **329** (9.0 g, 51 mmol) was dissolved in THF (150 mL) and cooled to -78 °C in a dry ice-acetone bath. *n*-Butyllithium solution (2.5 M, 22.4 mL, 55.9 mmol) was added dropwise and the reaction was stirred for 30 minutes at -78 °C. Propionyl chloride **330** (5.4 mL, 61 mmol) was added dropwise and the reaction was stirred for a further 30 minutes at -78 °C before being quenched by addition of aqueous NH_4Cl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4×50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography

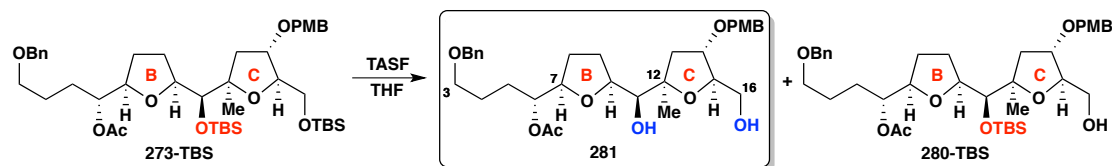
(SiO₂, 15:85 EtOAc:Pentane to 25:75 EtOAc:Pentane) to afford **23** as white crystals. (10.5 g, 89%).

R_f = 0.3 (20:80 EtOAc:Pentane); $[\alpha]_D^{25}$ -53.2 (c = 1.18, CHCl₃; lit. -57.4, c = 1.00, CHCl₃)
¹H NMR (400 MHz, CDCl₃) δ_H 7.40–7.24 (3 H, m, Ph-ArH $\times$ 3), 7.20 (2 H, dd, J = 7.6, 1.9 Hz, Ph-ArH $\times$ 2), 4.88–4.50 (1 H, m, C(2)H), 4.34–3.90 (2 H, m, C(3)H₂), 3.29 (1 H, dd, J = 13.3, 3.3 Hz, C(1)H_AH_B), 2.95 (2 H, qd, J = 7.3, 3.1 Hz, C(6)H₂), 2.76 (1 H, dd, J = 13.3, 9.6 Hz, C(1)H_AH_B), 1.20 (3 H, t, J = 7.3 Hz, C(7)H₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.1 (C5), 149.6 (C4), 131.4 (Ph-C_{Ar}CH₂), 125.5 (Ph-C_{Ar} $\times$ 2), 125.0 (Ph-C_{Ar} $\times$ 2), 123.4 (Ph-C_{Ar}), 62.3 (C3), 51.2 (C2), 33.9 (C1), 25.2 (C6), 4.4 (C7); **m.p.** 44–46 °C (EtOAc).

Spectroscopic data were consistent with those previously reported.¹⁵²

(R)-4-(Benzyloxy)-1-((2R,5S)-5-((S)-hydroxy((2R,4S,5R)-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butyl acetate
281

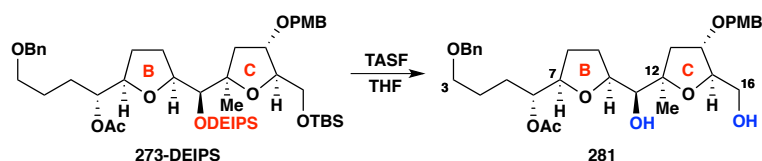
Procedure A:



bis-TBS ether **273-TBS** (72 mg, 90 μ mol) was dissolved in THF (2.25 mL) and tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TASF, 149 mg, 0.540 mmol) was added in one portion at room temperature. The reaction was stirred for one hour before being

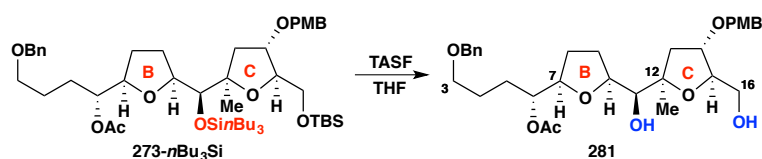
225

Procedure C:



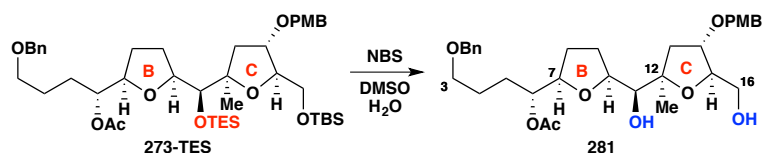
bis-Silyl ether **273-DEIPS** (50 mg, 56 μ mol) was dissolved in THF (1.4 mL) and tris(dimethylamino)- sulfonium difluorotrimethylsilicate (TASF, 47 mg, 0.168 mmol) was added in one portion at room temperature. The reaction was stirred for one hour before being diluted with EtOAc (10 mL). The mixture was poured into an aqueous solution of NaHCO_3 (sat., 5 mL). The organic layer was separated and the aqueous layer was extracted with CHCl_3 (4×10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 10:90 Acetone:Pentane to 30:70 Acetone:Pentane) to afford diol **281** as a colourless oil (26 mg, 80%).

Procedure D:



bis-Silyl ether **273-*n*Bu₃Si** (30 mg, 37 μ mol) was dissolved in THF (1 mL) and tris(dimethylamino)sulfonium difluorotrimethylsilicate (30 mg, 0.109 mmol) was added in one portion at room temperature. The reaction was stirred for one hour before being diluted with EtOAc (10 mL). The mixture was poured into an aqueous solution of NaHCO_3 (sat., 5 mL). The organic layer was separated and the aqueous layer was extracted with CHCl_3 (4×10 mL). The combined organic layers were washed with brine (5 mL), dried over

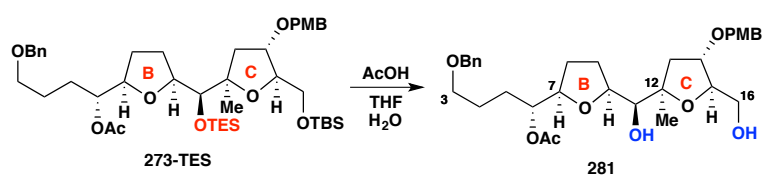
Procedure F:



227

temperature. The reaction mixture was diluted with Et₂O (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 Acetone:Pentane to 30:70 Acetone:Pentane) to afford diol **281** as a colourless oil (13 mg, 67%).

Procedure G:

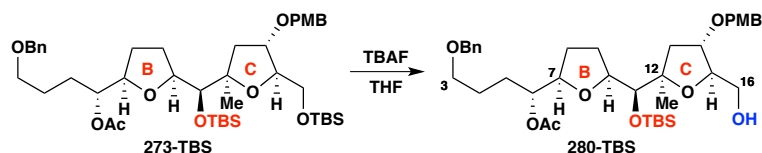


bis-Silyl ether **273-TES** (20 mg, 25 μ mol) was dissolved in a solution of 3:1:1 AcOH:H₂O:THF (1 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 12 hours. The reaction was diluted with EtOAc (10 mL) and quenched by addition of an aqueous solution of NH₄Cl (sat., 2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 $\times$ 2 mL). The combined organic layers were washed with brine (2 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 Acetone:Pentane to 30:70 Acetone:Pentane) to afford diol **281** as a viscous colourless oil (12 mg, 83%).

R_f = 0.4 (30:70 Acetone:Pentane); $[\alpha]_D^{25}$ +17.8 (c = 0.56, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.38–7.26 (5 H, m, Bn-ArH $\times$ 5), 7.24 (2 H, d, J = 8.6 Hz, PMB-ArH $\times$ 2), 6.87 (2 H, d, J = 8.6 Hz, PMB-ArH $\times$ 2), 4.84–4.77 (1 H, m, C(6)H), 4.49 (2 H, s, Bn-CH₂), 4.45 (1 H, d, J = 11.3 Hz, PMB-CH_AH_B), 4.41 (1 H, d, J = 11.3 Hz, PMB-CH_AH_B), 4.21 (1 H, d, J = 1.9 Hz, C(15)H), 4.19 (1 H, d, J = 1.7 Hz, C(14)H), 4.00–3.96 (2 H, m, C(10)H, C(11)H),

3.93 (1 H, ddd, $J = 8.6, 7.0, 3.4$ Hz, C(7) H), 3.83 (1 H, dd, $J = 11.9, 2.2$ Hz, C(16) H_AH_B), 3.80 (3 H, s, PMB- CH_3), 3.52 (1 H, dd, $J = 11.9, 2.2$ Hz, C(16) H_AH_B), 3.49–3.41 (2 H, m, C(3) H_2), 2.46 (1 H, dd, $J = 13.4, 6.4$ Hz, C(13) H_AH_B), 2.08 (3 H, s, Ac- CH_3), 2.06–1.87 (3 H, m, C(8) H_AH_B , C(9) H_AH_B , C(13) H_AH_B), 1.80 (1 H, m, C(8) H_AH_B), 1.70–1.55 (6 H, m, C(9) H_AH_B , C(13) H_AH_B , C(4) H_2 , C(5) H_2), 1.33 (3 H, s, C(12) CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 172.0 (AcCO), 159.2 (PMB- $C_{\text{Ar}}\text{OMe}$), 138.4 (Bn- $C_{\text{Ar}}\text{CH}_2$), 130.3 (PMB- $C_{\text{Ar}}\text{CH}_2$), 129.1 (PMB- $C_{\text{Ar}} \times 2$), 128.4 (Bn- $C_{\text{Ar}} \times 2$), 127.7 (Bn- $C_{\text{Ar}} \times 2$), 127.6 (Bn- C_{Ar}), 113.9 (PMB- $C_{\text{Ar}} \times 2$), 85.4 (C12), 84.6 (C15), 82.9 (C14), 80.8 C(10), 79.6 (C7), 76.3 (C11), 76.1 (C6), 73.0 (Bn- CH_2), 70.9 (PMB- CH_2), 69.6 (C3), 64.8 (C16), 55.3 (PMB- CH_3), 37.4 (C13), 28.7 (C8), 27.9 (C5), 25.6 (C12- CH_3), 25.5 (C4), 23.9 (C9), 21.2 (Ac- CH_3); IR ν_{max} (film)/ cm^{-1} 3433, 2934, 2859, 2360, 2341, 1718, 1612, 1514, 1454, 1369, 1302, 1247, 1098, 1032, 911, 822, 740, 699; HRMS (ESI $^+$, m/z) $\text{C}_{32}\text{H}_{44}\text{NaO}_9^+$ $[\text{M} + \text{Na}^+]$ calculated 595.2878, found 595.2860 ($\Delta = -3.02$ ppm).

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butyl acetate 280-TBS



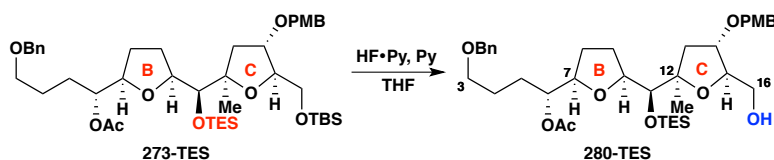
bis-Silyl ether **273-TBS** (20 mg, 25 μmol) was dissolved in THF (0.6 mL) and cooled to 0 $^{\circ}\text{C}$. Tetra-*n*-butylammonium fluoride (TBAF, 1.0 M, 0.075 mL, 0.075 mmol) was added dropwise at 0 $^{\circ}\text{C}$. The reaction was allowed to warm to room temperature and stirred for 2

hours. The reaction was diluted with EtOAc (10 mL) and quenched by addition of an aqueous solution of NaHCO_3 (2 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (4×2 mL). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 10:90 Acetone:Pentane to 30:70 Acetone:Pentane) to afford primary alcohol **280-TBS** as a colourless oil (13 mg, 76%).

$R_f = 0.4$ (30:70 Acetone:Pentane); $[\alpha]_D^{25} +4.0$ ($c = 0.24$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_H 7.37–7.29 (4 H, m, $\text{Bn-ArH} \times 4$), 7.29–7.26 (1 H, m, Bn-ArH), 7.24 (2 H, d, $J = 8.6$ Hz, $\text{PMB-ArH} \times 2$), 6.87 (2 H, d, $J = 8.6$ Hz, $\text{PMB-ArH} \times 2$), 5.11–4.86 (1 H, m, C(6)H), 4.49 (2 H, s, Bn-CH_2), 4.46–4.38 (2 H, m, PMB-CH_2), 4.10–4.04 (1 H, m, C(15)H), 4.04–4.00 (1 H, m, C(14)H), 4.00–3.96 (1 H, m, C(10)H), 3.80 (3 H, s, PMB-CH_3), 3.79–3.70 (3 H, m, C(7)H , C(11)H , $\text{C(16)H}_A\text{H}_B$), 3.52 (1 H, dd, $J = 11.9$, 3.8 Hz, $\text{C(16)H}_A\text{H}_B$), 3.48–3.43 (2 H, m, C(3)H_2), 2.15 (1 H, dd, $J = 13.2$, 7.1 Hz, $\text{C(13)H}_A\text{H}_B$), 2.07 (3 H, s, Ac-CH_3), 1.99–1.81 (2 H, m, $\text{C(9)H}_A\text{H}_B$, $\text{C(8)H}_A\text{H}_B$), 1.77 (1 H, dd, $J = 13.2$, 3.8 Hz, $\text{C(13)H}_A\text{H}_B$), 1.73–1.57 (5 H, m, $\text{C(9)H}_A\text{H}_B$, C(4)H_2 , C(5)H_2), 1.54–1.43 (1 H, m, $\text{C(8)H}_A\text{H}_B$), 1.27 (3 H, s, C(12)CH_3), 0.89 (9 H, s, $\text{TBS-C(CH}_3)_3$), 0.10 (3 H, s, $\text{TBS-Si(CH}_3)_2$), 0.06 (3 H, s, $\text{TBS-Si(CH}_3)_2$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_C 170.8 (Ac-CO), 159.2 ($\text{PMB-C}_{Ar}\text{OMe}$), 138.5 ($\text{Bn-C}_{Ar}\text{CH}_2$), 130.2 ($\text{PMB-C}_{Ar}\text{CH}_2$), 129.2 ($\text{PMB-C}_{Ar} \times 2$), 128.4 ($\text{Bn-C}_{Ar} \times 2$), 127.6 ($\text{Bn-C}_{Ar} \times 2$), 127.6 (Bn-C_{Ar}), 113.9 ($\text{PMB-C}_{Ar} \times 2$), 84.9 (C12), 83.8 (C15), 80.2 (C10), 79.8 (C14), 79.2 (C7), 78.1 (C11), 74.7 (C6), 72.9 (PMB-CH_2), 71.5 (Bn-CH_2), 69.9 (C3), 63.1 (C16), 55.3 (PMB-CH_3), 42.4 (C13), 28.2 (C5), 27.8 (C8), 26.1 ($\text{TBS-C(CH}_3)_3$),

25.4 (C4), 25.3 (C9), 22.2 (C12-CH₃), 21.2 (Ac-CH₃), 18.3 (TBS-C(CH₃)₃), -3.4 (TBS-Si(CH₃)₂), -4.4 (TBS-Si(CH₃)₂); **IR** $\nu_{\max}$ (film)/cm⁻¹ 3449, 2956, 2933, 1738, 1613, 1514, 1459, 1372, 1247, 1096, 1036, 836; **HRMS** (ESI⁺, *m/z*) C₃₈H₅₉O₉Si⁺ calculated 687.39229, found [M + H⁺] 687.39100 (Δ = -1.88 ppm).

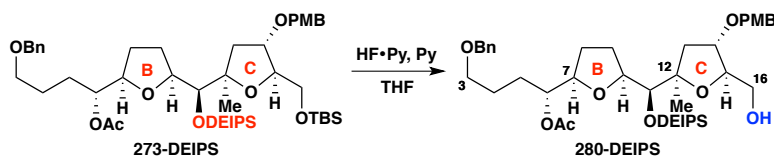
(R)-4-(Benzyloxy)-1-((2R,5S)-5-((S)-((2R,4S,5R)-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((triethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butyl acetate 280-TES



Hydrogen fluoride-pyridine (200 μ L) was dissolved in THF (3 mL) and cooled to 0 °C in an ice-water bath. Pyridine (300 μ L) was added dropwise and the reagent solution was stirred for 10 minutes at 0 °C. *bis*-Silyl ether **273-TES** (17 mg, 0.021 mmol) was dissolved in THF (1 mL) and cooled to 0 °C in an ice-water bath. The hydrogen fluoride-pyridine solution was added to the reaction dropwise and the reaction was stirred for 6 hours at 0 °C before being quenched by addition of an aqueous solution of NaHCO₃ (sat., 4 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (4 $\times$ 4 mL). The combined organic layers were washed with brine (2 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc:Pentane to 30:70 EtOAc:Pentane) to afford primary alcohol **280-TES** as a colourless oil (10.5 mg, 72%).

$R_f = 0.4$ (40:60 EtOAc:Pentane); $[\alpha]_D^{25} +1.3$ ($c = 0.41$, CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_H 7.39–7.29 (4 H, m, Bn-ArH $\times$ 4), 7.29–7.27 (1 H, m, Bn-ArH), 7.24 (2 H, d, $J = 8.7$ Hz, PMB-ArH $\times$ 2), 6.87 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times$ 2), 4.94 (1 H, td, $J = 7.6, 4.0$ Hz, C(6)H), 4.49 (2 H, s, Bn-CH₂), 4.47–4.38 (2 H, m, PMB-CH₂), 4.12–4.07 (1 H, m, C(15)H), 4.05 (1 H, dt, $J = 7.8, 3.9$ Hz, C(14)H), 3.96–3.92 (1 H, m, C(10)H), 3.87 (1 H, d, $J = 4.2$ Hz, C(11)H), 3.80 (3 H, s, PMB-CH₃), 3.78 (1 H, dd, $J = 1.9$ Hz, C(7)H), 3.74 (1 H, dd, $J = 11.8, 3.9$ Hz, C(16)H_AH_B), 3.52 (1 H, dd, $J = 11.8, 3.6$ Hz, C(16)H_AH_B), 3.49–3.44 (2 H, m, C(3)H₂), 2.20 (1 H, dd, $J = 13.1, 6.1$ Hz, C(13)H_AH_B), 2.07 (3 H, s, Ac-CH₃), 1.92–1.81 (2 H, m, C(9)H_AH_B, C(8)H_AH_B), 1.71–1.68 (3 H, m, C(5)H_AH_B, C(9)H_AH_B, C(13)H_AH_B), 1.67–1.59 (3 H, m, C(4)H₂, C(5)H_AH_B), 1.53–1.47 (1 H, m, C(8)H_AH_B), 1.29 (3 H, s, C(12)CH₃), 1.00–0.89 (9 H, m, TES-CH₃ $\times$ 3), 0.70–0.59 (6 H, m, TES-CH₂ $\times$ 3); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ_C 169.7 (Ac-CO), 159.2 (PMB-C_{Ar}OMe), 138.4 (Bn-C_{Ar}CH₂), 130.2 (PMB-C_{Ar}CH₂), 129.2 (PMB-C_{Ar} $\times$ 2), 128.3 (Bn-C_{Ar} $\times$ 2), 127.6 (Bn-C_{Ar} $\times$ 2), 127.5 (Bn-C_{Ar}), 112.8 (PMB-C_{Ar} $\times$ 2), 84.1 (C12), 83.0 (C15), 79.2 (C10), 79.0 (C14), 78.2 (C7), 77.3 (C11), 73.7 (C6), 71.9 (Bn-CH₂), 70.4 (PMB-CH₂), 68.9 (C3), 62.2 (C16), 54.3 (PMB-CH₃), 40.5 (C13), 27.2 (C5), 26.7 (C8), 24.8 (C9), 24.4 (C4), 21.9 (C12-CH₃), 20.1 (Ac-CH₃), 6.0 (TES-CH₃ $\times$ 3), 4.2 (TES-CH₂ $\times$ 3); **IR** ν_{max} (film)/cm⁻¹ 3449, 2980, 2931, 2884, 2857, 1737, 1514, 1461, 1372, 1247, 1172, 1038, 836; **HRMS** (ESI⁺, m/z) C₃₈H₅₈NaO₉Si⁺ [M + Na⁺] calculated 709.3742, found 709.3714 ($\Delta = -3.95$ ppm).

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((diethyl(isopropyl)silyl)oxy)((2*R*,4*S*,5*R*)-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butyl acetate **280-DEIPS**

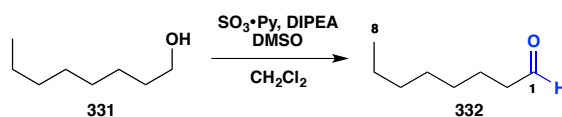


Hydrogen fluoride-pyridine (500 μ L) was dissolved in THF (8 mL) and cooled to 0 $^{\circ}$ C in an ice-water bath. Pyridine (750 μ L) was added dropwise and the reagent solution was stirred for 10 minutes at 0 $^{\circ}$ C. *bis*-Silyl ether **273-DEIPS** (50 mg, 0.06 mmol) was dissolved in THF (2 mL) and cooled to 0 $^{\circ}$ C in an ice-water bath. The hydrogen fluoride-pyridine solution was added to the reaction dropwise and the reaction was stirred for 3 hours at 0 $^{\circ}$ C before being quenched by addition of an aqueous solution of NaHCO₃ (5 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (4 $\times$ 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography SiO₂, 10:90 EtOAc:Pentane to 30:70 EtOAc:Pentane) to afford primary alcohol **280-DEIPS** as a colourless oil (22.9 mg, 53%).

R_f = 0.4 (40:60 EtOAc:Pentane) $[\alpha]_D^{25} +4.5$ (c = 1.23, CH₂Cl₂); $^1\text{H NMR}$ (400 MHz, CDCl₃) δ_H 7.37–7.28 (4 H, m, Bn-ArH $\times$ 4), 7.28–7.26 (1 H, m, Bn-ArH), 7.24 (2 H, d, J = 8.6 Hz, PMB-ArH $\times$ 2), 6.87 (2 H, d, J = 8.6 Hz, PMB-ArH $\times$ 2), 5.02–4.86 (1 H, m, C(6)H), 4.49 (2 H, s, Bn-CH₂), 4.46–4.38 (2 H, m, PMB-CH₂), 4.12–4.06 (1 H, m, C(15)H), 4.04 (1 H, dt, J = 7.2, 4.1 Hz, C(14)H), 3.96 (1 H, ddd, J = 9.0, 6.7, 2.9 Hz, C(10)H), 3.82 (1 H, d, J = 2.9

Hz, C(11)*H*), 3.80 (3 H, s, PMB-CH₃), 3.80–3.76 (1 H, m, C(7)*H*), 3.74 (1 H, dd, *J* = 11.9, 3.0 Hz, C(16)*H_AH_B*), 3.52 (1 H, dd, *J* = 11.8, 3.5 Hz, C(16)*H_AH_B*), 3.50–3.42 (2 H, m, C(3)*H₂*), 2.19 (1 H, dd, *J* = 13.2, 7.2 Hz, C(13)*H_AH_B*), 2.06 (3 H, s, Ac-CH₃), 1.96–1.81 (2 H, m, C(9)*H_AH_B*, C(8)*H_AH_B*), 1.81–1.69 (3 H, m, C(13)*H_AH_B*, C(9)*H_AH_B*, C(5)*H_AH_B*), 1.69–1.58 (3 H, m, C(5)*H_AH_B*, C(4)*H₂*), 1.50 (1 H, ddt, *J* = 11.7, 5.5, 2.2 Hz, C(8)*H_AH_B*), 1.28 (3 H, s, C(12)CH₃), 1.06–0.91 (13 H, m, DEIPS-CH₃ × 4, DEIPS-*i*PrCH), 0.74–0.56 (4 H, m, DEIPS-CH₂ × 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 170.7 (Ac-CO), 159.2 (PMB-C_{Ar}OMe), 138.5 (Bn-C_{Ar}CH₂), 130.2 (PMB-C_{Ar}CH₂), 129.2 (PMB-C_{Ar} × 2), 128.4 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar} × 2), 127.6 (Bn-C_{Ar}), 113.9 (PMB-C_{Ar} × 2), 85.1 (C12), 83.9 (C15), 80.3 (C10), 79.8 (C14), 79.2 (C7), 78.3 (C11), 74.8 (C6), 72.9 (Bn-CH₂), 71.5 (PMB-CH₂), 69.9 (C3), 63.2 (C16), 55.3 (PMB-CH₃), 42.0 (C13), 28.2 (C5), 27.7 (C8), 25.5 (C9), 25.4 (C4), 22.6 (C12-CH₃), 21.1 (Ac-CH₃), 17.6 (DEIPS-*i*PrCH₃), 17.6 (DEIPS-*i*PrCH₃), 13.3 (DEIPS-*i*PrCH), 7.3 (DEIPS-EtCH₃ × 2), 4.5 (DEIPS-EtCH₂), 4.3 (DEIPS-EtCH₂); IR ν_{max} (film)/cm⁻¹ 3439, 2939, 2874, 1737, 1612, 1514, 1456, 1370, 1245, 1099, 1037, 810, 725; HRMS (ESI⁺, *m/z*) C₃₉H₆₁O₉Si⁺ [M + H⁺] calculated 701.40794, found 701.40692 (Δ = −1.45 ppm).

Octanal 332



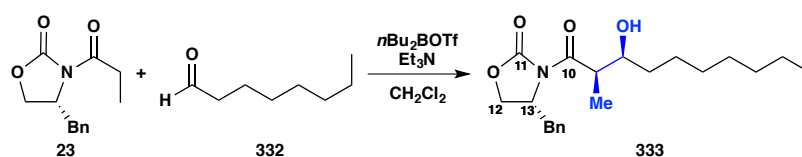
1-Octanol **331** (0.157 mL, 1.00 mmol) and DMSO (0.70 mL, 10 mmol) were dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C. *i*Pr₂NEt (0.7 mL, 4 mmol) and sulfur trioxide pyridine complex (640 mg, 4 mmol) were added and the mixture was stirred at 0 °C for 45 minutes.

The reaction was quenched by addition of H₂O (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 5:95 EtOAc:Petroleum ether) to afford octanal **332** as a colourless oil (118 mg, 92%).

R_f = 0.7 (20:80 EtOAc:Petroleum ether); ¹H NMR (200 MHz, CDCl₃) δ_H 9.71 (1 H, t, J = 1.9 Hz, C(1)H), 2.37 (2 H, td, J = 7.3, 1.9 Hz, C(2)H₂), 1.67–1.49 (2 H, m, C(3)H₂), 1.38–1.10 (8 H, m, C(4)H₂, C(5)H₂, C(6)H₂, C(7)H₂), 0.83 (3 H, t, J = 6.7 Hz, C(8)H₃); ¹³C NMR (50 MHz, CDCl₃) δ_C 203.2 (C1), 44.3 (C2), 32.0 (C3), 29.5 (C4), 29.4 (C5), 23.0 (C6), 22.5 (C7), 14.4 (C8).

Spectroscopic data were consistent with those previously reported.¹⁵³

(R)-4-Benzyl-3-((2R,3S)-3-hydroxy-2-methyldecanoyl)oxazolidin-2-one 333

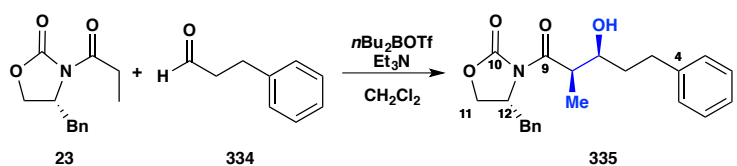


(R)-4-Benzyl-3-propionyloxazolidin-2-one **23** (136 mg, 0.580 mmol) was dissolved in CH₂Cl₂ (0.8 mL) and cooled to 0 °C. Dibutylboron trifluoromethanesulfonate (1.0 M in CH₂Cl₂, 0.66 mL, 0.66 mmol) and Et₃N (0.11 mL, 0.78 mmol) were added dropwise and the reaction was stirred at 0 °C for 10 minutes before being cooled to –78 °C. After a further 10 minutes, Octanal **332** (50 mg, 0.39 mmol, dissolved in 0.4 mL CH₂Cl₂) was added dropwise. The mixture was stirred at –78 °C for 30 minutes, before being warmed to 0 °C and stirred

for 1 hour. The reaction was quenched by addition of pH 7 phosphate buffer (1 mL) and MeOH (1.5 mL), followed by a 2:1 mixture of MeOH and 30 % hydrogen peroxide solution (1.5 mL). The resulting mixture was stirred vigorously for 1 hour. The aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with water (2 mL), an aqueous solution of NaHCO₃ (sat., 2 mL), brine (2 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc: Pentane to 30:70 EtOAc:Pentane) to afford aldol product **333** as a colourless oil (88 mg, 62%, 95:5 d.r.).

R_f = 0.5 (40:60 EtOAc:Pentane); [**α**]_D²⁵ −58.2 (c = 0.65, CHCl₃; lit. −59.3, c = 0.54, CHCl₃); **¹H NMR** (200 MHz, CDCl₃) **δ_H** 7.46–7.05 (5 H, m, Bn-ArH × 5), 4.69 (1 H, ddt, *J* = 9.8, 6.0, 3.7 Hz, C(13)H), 4.21–4.11 (2 H, m, C(12)H₂), 3.98–3.86 (1 H, m, C(8)H), 3.82–3.66 (1 H, m, C(9)H), 3.26–3.22 (1 H, m, Bn-CH_AH_B), 2.75 (1 H, dd, *J* = 13.4, 9.6 Hz, Bn-CH_AH_B), 2.63–2.46 (1 H, br. s., OH), 1.65–1.04 (15 H, m, C(2)H₂, C(3)H₂, C(4)H₂, C(5)H₂, C(6)H₂, C(7)H₂, C(1)CH₃), 0.97–0.76 (3 H, m, C(9)CH₃); **¹³C NMR** (50 MHz, CDCl₃) **δ_C** 177.4 (C10), 153.2 (C11), 135.1 (Bn-C_{Ar}CH₂), 129.4 (Bn-C_{Ar} × 2), 128.9 (Bn-C_{Ar} × 2), 127.3 (Bn-C_{Ar}), 71.5 (C8), 67.9 (C13), 66.1 (C7), 55.1 (C12), 42.0 (C9), 37.7 (Bn-CH₂), 33.9 (C6), 31.8 (C5), 29.5 (C4), 25.7 (C3), 22.6 (C2), 14.0 (C1), 10.5 (C9-CH₃).

Spectroscopic data were consistent with those previously reported.¹⁵⁴

(R)-4-Benzyl-3-((2R,3S)-3-hydroxy-2-methyl-5-phenylpentanoyl)oxazolidin-2-one 335

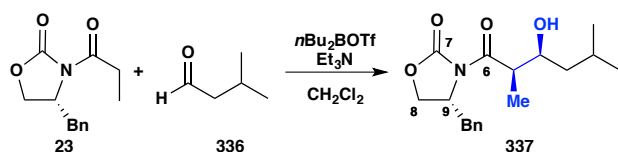
(R)-4-Benzyl-3-propionyloxazolidin-2-one **23** (0.35 g, 1.5 mmol) was dissolved in CH₂Cl₂ (3 mL) and cooled to 0 °C. Dibutylboron trifluoromethanesulfonate (1.0 M in CH₂Cl₂, 1.7 mL, 1.7 mmol) and Et₃N (0.28 mL, 2.0 mmol) were added dropwise and the reaction was stirred at 0 °C for 10 minutes before being cooled to –78 °C. After a further 10 minutes, 3-phenylpropanal **334** (0.12 mL, 1.0 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 minutes, before being warmed to 0 °C and stirred for 1 hour. The reaction was quenched by addition of pH 7 phosphate buffer (3.4 mL) and MeOH (5.1 mL), followed by a 2:1 mixture of MeOH and 30 % hydrogen peroxide solution (3.4 mL). The resulting mixture was stirred vigorously for 1 hour. The aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with water (10 mL), an aqueous solution of NaHCO₃ (sat., 10 mL), brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc: Pentane to 30:70 EtOAc:Pentane) to afford aldol product **335** as a colourless oil (294 mg, 88%, 97:3 d.r.).

R_f = 0.5 (40:60 EtOAc:Petroleum ether); [α]_D²⁵ –47.6 (c = 1.25, CH₂Cl₂; lit. *ent*-**336**, +55.9, c = 1.73, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.53–6.86 (10 H, m, Bn-ArH × 5, C(1)H, C(2)H × 2, C(3)H × 2), 4.71 (1 H, ddt, *J* = 10.4, 7.1, 3.5 Hz, C(12)H), 4.34–4.13 (2 H, m, C(11)H₂), 4.01 (1 H, dt, *J* = 9.1, 2.7 Hz, C(7)H), 3.79 (1 H, dq, *J* = 9.1, 6.7 Hz, C(8)H), 3.25

(1 H, dd, $J = 13.5, 3.6$ Hz, Bn-CH_AH_B), 2.99 (1 H, br. s., OH), 2.98–2.87 (1 H, m, C(5)H_AH_B), 2.87–2.77 (1 H, m, Bn-CH_AH_B), 2.73 (1 H, ddd, $J = 14.1, 9.6, 7.1$ Hz, (C5)H_AH_B), 1.94 (1 H, dtd, $J = 14.4, 9.4, 5.2$ Hz, C(6)H_AH_B), 1.74 (1 H, dtt, $J = 17.3, 6.4, 3.1$ Hz, C(6)H_AH_B), 1.32 (3 H, d, $J = 8.8$ Hz, C(8)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 177.4 (C9), 153.1 (C10), 141.9 (C4), 135.1 (Bn-C_{Ar}CH₂), 129.5 (Bn-C_{Ar} × 2), 129.0 (Bn-C_{Ar} × 2), 128.6 (C3 × 2), 128.4 (C2 × 2), 127.5 (Bn-C_{Ar}), 125.9 (C1), 70.7 (C7), 66.2 (C11), 55.1 (C12), 42.4 (C8), 37.8 (Bn-CH₂), 35.6 (C6), 32.2 (C5), 10.8 (C8-CH₃).

Spectroscopic data were consistent with those previously reported.¹⁵⁵

(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-2,5-dimethylhexanoyl)oxazolidin-2-one 337



(*R*)-4-Benzyl-3-propionyloxazolidin-2-one **23** (0.35 g, 1.5 mmol) was dissolved in CH₂Cl₂ (3 mL) and cooled to 0 °C. Dibutylboron trifluoromethanesulfonate (1.0 M in CH₂Cl₂, 1.7 mL, 1.7 mmol) and Et₃N (0.28 mL, 2.0 mmol) were added dropwise and the reaction was stirred at 0 °C for 10 minutes before being cooled to –78 °C. After a further 10 minutes, aldehyde **336** (0.12 mL, 1.0 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 minutes, before being warmed to 0 °C and stirred for 1 hour. The reaction was quenched by addition of pH 7 phosphate buffer (3.4 mL) and MeOH (5.1 mL), followed by a 2:1 mixture of MeOH and 30 % hydrogen peroxide solution (3.4 mL). The resulting mixture was stirred vigorously for 1 hour. The aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with water (10 mL), an aqueous solution of

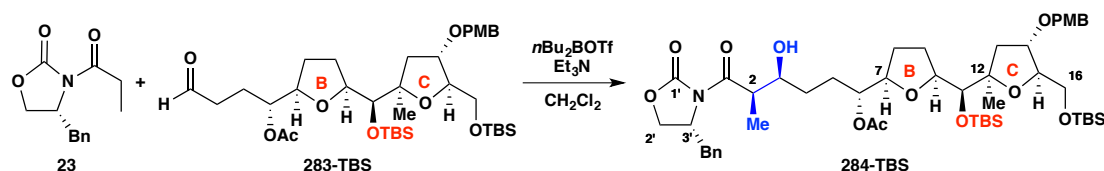
NaHCO₃ (sat., 10 mL), brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*.

The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc: Pentane to 30:70 EtOAc:Pentane) to afford aldol product **337** as a white solid (230 mg, 70%, 92:8 d.r.).

R_f = 0.5 (40:60 EtOAc:Petroleum ether); $[\alpha]_D^{25}$ -58.2 (c = 1.17, CH₂Cl₂; **ent-338**, lit. +59.1, c = 1.63, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.38–6.97 (5 H, m, Bn-ArH $\times$ 5), 4.67–4.57 (1 H, m, C(9)H), 4.19–4.07 (2 H, m, C(8)H₂), 3.97 (1 H, dt, J = 10.1, 3.5 Hz, C(4)H), 3.64 (1 H, qd, J = 7.0, 3.2 Hz, C(5)H), 3.16 (1 H, dd, J = 13.7, 4.3 Hz, Bn-CH_AH_B), 2.97–2.76 (1 H, br. s., OH), 2.71 (1 H, dd, J = 13.1, 9.4 Hz, Bn-CH_AH_B), 1.73 (1 H, ddt, J = 12.2, 9.0, 4.8 Hz, C(2)H), 1.44 (1 H, ddd, J = 13.9, 9.3, 4.5 Hz, C(3)H_AH_B), 1.18 (3 H, d, J = 6.8 Hz, C(5)CH₃), 1.09 (1 H, ddd, J = 13.8, 8.3, 3.2 Hz, C(3)H_AH_B), 0.88–0.81 (6 H, m, C(1)H₃ $\times$ 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 177.5 (C6), 153.1 (C7), 135.1 (Bn-C_{Ar}CH₂), 129.4 (Bn-C_{Ar} $\times$ 2), 129.0 (Bn-C_{Ar} $\times$ 2), 127.4 (Bn-C_{Ar}), 69.4 (C4), 66.2 (C8), 55.1 (C9), 42.9 (C3), 42.6 (C5), 37.8 (Bn-CH₂), 24.5 (C2), 23.5, 21.9 (C1 $\times$ 2), 10.6 (C5-CH₃).

Spectroscopic data were consistent with those previously reported.¹⁵⁶

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-4-hydroxy-5-methyl-6-oxohexyl acetate **284-TBS**



(*R*)-4-Benzyl-3-propionyloxazolidin-2-one **23** (70 mg, 0.30 mmol) was dissolved in CH₂Cl₂ (0.4 mL) and cooled to 0 °C. Dibutylboron trifluoromethanesulfonate (1.0 M in CH₂Cl₂, 0.34 mL, 0.34 mmol) and Et₃N (55 µL, 0.40 mmol) were added dropwise and the reaction was stirred at 0 °C for 10 minutes before being cooled to −78 °C. After a further 10 minutes, aldehyde **283-TBS** (0.14 g, 0.20 mmol, dissolved in 0.2 mL CH₂Cl₂) was added dropwise. The mixture was stirred at −78 °C for 1 hour, before being warmed to 0 °C and stirred for 2 hour. The reaction was quenched by addition of pH 7 phosphate buffer (0.3 mL) and MeOH (0.45 mL), followed by a 2:1 mixture of MeOH and 30 % hydrogen peroxide solution (0.45 mL). The resulting mixture was stirred vigorously for 1 hour. The aqueous phase was extracted with Et₂O (3 × 1 mL). The combined organic layers were washed with water (1 mL), an aqueous solution of NaHCO₃ (sat., 1 mL), brine (1 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc:Pentane to 40:60 EtOAc:Pentane) to afford aldol product **284-TBS** as a colourless oil (115 mg, 62 %, 95:5 d.r.).

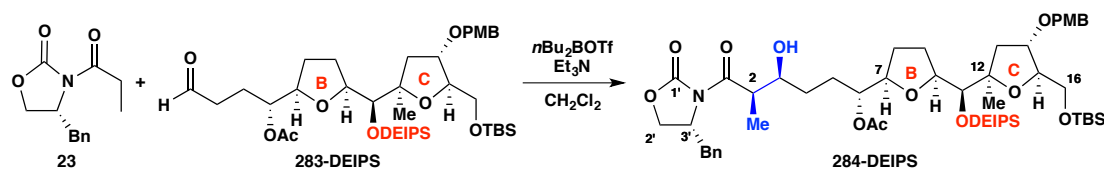
$R_f = 0.4$ (40:60 EtOAc:Petane). $[\alpha]_D^{25} -14.9$ ($c = 0.57$, CH_2Cl_2 ; lit. -16.1 , $c = 0.60$, CH_2Cl_2);

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.33 (2 H, dd, $J = 8.1, 6.4$ Hz, Bn-ArH $\times 2$), 7.30–7.26 (1 H, m, Bn-ArH), 7.26–7.22 (2 H, m, Bn-ArH $\times 2$), 7.19 (2 H, d, $J = 6.8$ Hz, PMB-ArH $\times 2$), 6.86 (2 H, d, $J = 6.8$ Hz, PMB-ArH $\times 2$), 5.07–4.91 (1 H, m, C(6)H), 4.73–4.64 (1 H, m, C(3')H), 4.46 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.38 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.27–4.15 (2 H, m, C(2')H₂), 4.08 (1 H, dt, $J = 6.9, 3.6$ Hz, C(15)H), 4.02 (1 H, dt, $J = 7.0, 2.7$ Hz, C(14)H), 3.96 (1 H, ddd, $J = 8.6, 6.7, 2.5$ Hz, C(10)H), 3.93–3.88 (1 H, m, C(3)H), 3.79 (3 H, s, PMB-CH₃), 3.79–3.77 (1 H, m, C(11)H), 3.72 (1 H, dd, $J = 7.1, 2.6$ Hz, C(2)H), 3.69–3.59 (2 H, m, C(7)H, C(16)H_AH_B), 3.48 (1 H, dd, $J = 10.4, 6.4$ Hz, C(16)H_AH_B), 3.24 (1 H, dd, $J = 13.4, 3.4$ Hz, Bn-CH_AH_B), 2.78 (1 H, dd, $J = 13.4, 9.4$ Hz, Bn-CH_AH_B), 2.07 (3 H, s, Ac-CH₃), 2.06 (1 H, dd, $J = 10.8, 8.2$ Hz, C(13)H_AH_B), 2.00–1.75 (4 H, m, C(9)H_AH_B, C(8)H_AH_B, C(5)H_AH_B, C(13)H_AH_B), 1.72–1.50 (3 H, m, C(9)H_AH_B, C(8)H_AH_B, C(4)H_AH_B), 1.50–1.36 (2 H, m, C(5)H_AH_B, C(4)H_AH_B), 1.31–1.17 (6 H, m, C(2)CH₃, C(12)CH₃), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.09–0.01 (12 H, m, TBS-Si(CH₃)₂ $\times 2$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ_{C} 177.4 (C1), 170.8 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 153.0 (C1'), 135.0 (Bn-C_{Ar}CH₂), 130.6 (PMB-C_{Ar}CH₂), 129.4 (Bn-C_{Ar} $\times 2$), 129.1 (PMB-C_{Ar} $\times 2$), 129.0 (Bn-C_{Ar} $\times 2$), 127.5 (Bn-C_{Ar}), 113.8 (PMB-C_{Ar} $\times 2$), 85.0 (C12), 84.4 (C15), 81.2 (C14), 79.9 (C10), 79.0 (C7), 78.0 (C11), 75.0 (C6), 71.5 (C3), 71.0 (PMB-CH₂), 66.2 (C2'), 64.0 (C16), 55.3 (PMB-CH₃), 55.1 (C3'), 42.4 (C13), 42.3 (C2), 37.8 (Bn-CH₂), 29.5 (C4), 28.5 (C5), 28.1 (C8), 26.1 (TBS-C(CH₃)₃), 26.0 (TBS-C(CH₃)₃), 23.9 (C9), 22.0 (C12-CH₃), 21.3 (Ac-CH₃), 18.4 (TBS-C(CH₃)₃),

18.3 (TBS- $C(CH_3)_3$), 10.4 (C_2-CH_3), -3.3 (TBS-Si CH_3), -4.8 (TBS-Si CH_3), -5.3 (TBS-Si CH_3), -5.4 (TBS-Si CH_3).

Spectroscopic data were consistent with those previously reported.⁶⁰

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl))((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)-4-hydroxy-5-methyl-6-oxohexyl acetate 284-DEIPS



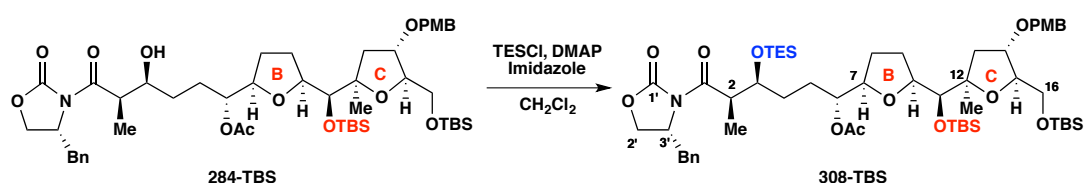
(*R*)-4-Benzyl-3-propionyloxazolidin-2-one **23** (145 mg, 0.620 mmol) was dissolved in CH_2Cl_2 (0.4 mL) and cooled to 0 °C. Dibutylboron trifluoromethanesulfonate (1.0 M in CH_2Cl_2 , 0.71 mL, 0.71 mmol) and Et_3N (116 μ L, 0.820 mmol) were added dropwise and the reaction was stirred at 0 °C for 10 minutes before being cooled to -78 °C. After a further 10 minutes, aldehyde **283-DEIPS** (0.30 g, 0.41 mmol, dissolved in 0.4 mL CH_2Cl_2) was added dropwise. The mixture was stirred at -78 °C for 1 hour, before being warmed to 0 °C and stirred for 2 hour. The reaction was quenched by addition of pH 7 phosphate buffer (0.6 mL) and MeOH (0.9 mL), followed by a 2:1 mixture of MeOH and 30 % hydrogen peroxide solution (0.9 mL). The resulting mixture was stirred vigorously for 1 hour. The aqueous phase was extracted with Et_2O (3 $\times$ 3 mL). The combined organic layers were washed with water (2 mL), an aqueous solution of $NaHCO_3$ (sat., 2 mL), brine (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column

chromatography (SiO₂, 10:90 EtOAc:Pentane to 40:60 EtOAc:Pentane) to afford aldol product **284-DEIPS** as a colourless oil (270 mg, 68 %, 95:5 d.r.).

$R_f = 0.4$ (40:60 EtOAc:Petane); $[\alpha]_D^{25} -22.8$ ($c = 0.48$, CH₂Cl₂); $^1\text{H NMR}$ (500 MHz, CDCl₃) δ_H 7.33 (2 H, dd, $J = 8.1, 6.5$ Hz, Bn-ArH $\times 2$), 7.30–7.27 (1 H, m, Bn-ArH), 7.25 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 7.22–7.17 (2 H, m, Bn-ArH $\times 2$), 6.87 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 4.97 (1 H, td, $J = 7.7, 3.7$ Hz, C(6)H), 4.73–4.66 (1 H, m, C(3')H), 4.47 (1 H, d, $J = 11.6$ Hz, PMB-CH_AH_B), 4.39 (1 H, d, $J = 11.6$ Hz, PMB-CH_AH_B), 4.25–4.16 (2 H, m, C(2')H₂), 4.06 (1 H, dt, $J = 6.4, 3.8$ Hz, C(15)H), 4.02 (1 H, dt, $J = 6.6, 3.0$ Hz, C(14)H), 3.95 (1 H, ddd, $J = 8.8, 7.1, 1.2$ Hz, C(10)H), 3.90 (1 H, dt, $J = 8.5, 2.9$ Hz, C(3)H), 3.85 (1 H, d, $J = 1.3$ Hz, C(11)H), 3.79 (3 H, s, PMB-CH₃), 3.72 (1 H, qd, $J = 7.0, 2.7$ Hz, C(2)H), 3.69–3.61 (2 H, m, C(16)H_AH_B, C(7)H), 3.48 (1 H, dd, $J = 10.5, 6.4$ Hz, C(16)H_AH_B), 3.24 (1 H, dd, $J = 13.5, 3.4$ Hz, Bn-CH_AH_B), 3.03 (1 H, br. s., OH), 2.78 (1 H, dd, $J = 13.4, 9.4$ Hz, Bn-CH_AH_B), 2.11 (1 H, dd, $J = 13.3, 7.2$ Hz, C(13)H_AH_B), 2.06 (3 H, s, Ac-CH₃), 1.98–1.90 (1 H, m, C(9)H_AH_B), 1.90–1.83 (2 H, m, C(8)H_AH_B, C(5)H_AH_B), 1.79 (1 H, dd, $J = 13.3, 2.8$ Hz, C(13)H_AH_B), 1.67 (1 H, ddt, $J = 12.1, 9.5, 6.7$ Hz, C(9)H_AH_B), 1.63–1.52 (2 H, m, C(8)H_AH_B, C(4)H_AH_B), 1.50–1.37 (2 H, m, C(4)H_AH_B, C(5)H_AH_B), 1.25 (3 H, d, $J = 7.2$ Hz, C(2)CH₃), 1.24 (3 H, s, C(12)CH₃), 1.03–0.93 (13 H, m, DEIPS-EtCH₃ $\times 2$, DEIPS-*i*PrCH₃ $\times 2$, DEIPS-*i*PrCH), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.72–0.58 (4 H, m, DEIPS-EtCH₂ $\times 2$), 0.05 (6 H, s, TBS-Si(CH₃)₂); $^{13}\text{C NMR}$ (125 MHz, CDCl₃) δ_C 177.3 (C1), 170.7 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 153.0 (C1'), 135.0 (Bn-C_{Ar}CH₂), 130.6 (PMB-C_{Ar}CH₂), 129.4 (Bn-C_{Ar} $\times 2$), 129.1 (PMB-C_{Ar} $\times 2$), 129.0 (Bn-C_{Ar} $\times 2$), 127.5

(Bn- C_{Ar}), 113.8 (PMB- $C_{Ar} \times 2$), 84.9 (C12), 84.3 (C15), 80.8 (C14), 79.9 (C10), 78.8 (C7), 78.1 (C11), 75.1 (C6), 71.5 (C3), 71.1 (PMB- CH_2), 66.2 (C2'), 63.8 (C16), 55.3 (PMB- CH_3), 55.1 (C3'), 42.3 (C2), 42.1 (C13), 37.8 (Bn- CH_2), 29.5 (C4), 28.6 (C5), 28.2 (C8), 26.0 (TBS- $C(CH_3)_3$), 24.0 (C9), 22.1 (C12- CH_3), 21.2 (Ac- CH_3), 18.4 (TBS- $C(CH_3)_3$), 17.7 (DEIPS- $iPrCH_3$), 17.6 (DEIPS- $iPrCH_3$), 13.2 (DEIPS- $iPrCH$), 10.4 (C2- CH_3), 7.4 (DEIPS-Et CH_3), 7.3 (DEIPS-Et CH_3), 4.5 (DEIPS-Et CH_2), 4.2 (DEIPS-Et CH_2), -5.4 (TBS-Si CH_3), -5.4 (TBS-Si CH_3); **IR** ν_{max} (film)/ cm^{-1} 3532, 2977, 2891, 2358, 1780, 1735, 1698, 1463, 1385, 1248, 1148, 1079, 956, 884; **HRMS** (ESI $^+$, m/z) $C_{51}H_{81}NNaO_{12}Si_2^+$ [M + Na $^+$] calculated 978.5190, found 978.5179 ($\Delta = -1.12$ ppm).

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-(((triethylsilyl)oxy)hexyl acetate 308-TBS



Alcohol **284-TBS** (80 mg, 85 μ mol) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 $^{\circ}C$ in an ice-water bath. Imidazole (23 mg, 0.34 mmol) and 4-(dimethylamino)pyridine (1.0 mg, 8.5 μ mol) were added, followed by chlorotriethylsilane (28 μ L, 0.17 mmol). The reaction was allowed to warm to room temperature and stirred for 2 hours before being quenched by addition of an aqueous solution of $NaHCO_3$ (sat., 1 mL). The mixture was diluted with water (1 mL) and Et_2O (3 mL). The aqueous layer was separated and extracted

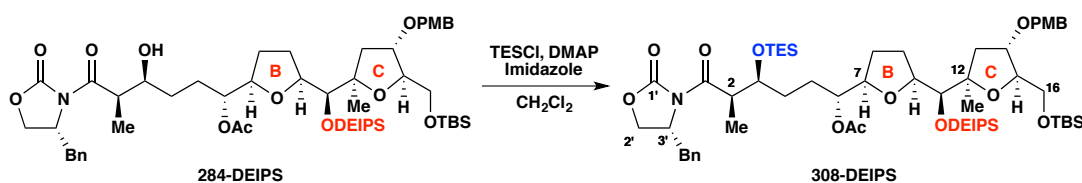
with Et₂O (3 × 3 mL). The combined organic layers were washed with brine (1 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 30:70 EtOAc:Petroleum ether) to afford **308-TBS** (78 mg, 87%) as a colourless oil.

R_f = 0.75 (30:70 EtOAc:Petane); $[\alpha]_D^{25}$ -19.2 (c = 0.53, CH₂Cl₂; lit. -18.4, c = 0.50, CH₂Cl₂);
¹H NMR (400 MHz, CDCl₃) δ_H 7.33 (2 H, dd, J = 7.9, 6.5 Hz, Bn-ArH × 2), 7.30–7.26 (1 H, m, Bn-ArH), 7.25 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 7.23–7.18 (2H, m, Bn-ArH × 2), 6.87 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 4.91 (1 H, td, J = 7.4, 3.5 Hz, C(6)H), 4.63–4.56 (1 H, m, C(3')H), 4.47 (1 H, d, J = 11.5 Hz, PMB-CH_AH_B), 4.38 (1 H, d, J = 11.5 Hz, PMB-CH_AH_B), 4.24–4.14 (2 H, m, C(2')H₂), 4.08 (1 H, dt, J = 7.0, 3.8 Hz, C(15)H), 4.05–3.99 (2 H, m, C(14)H, C(3)H), 3.99–3.91 (1 H, m, C(10)H), 3.90–3.82 (1 H, m, C(2)H), 3.80 (3 H, s, PMB-CH₃), 3.79 (1 H, d, J = 1.2 Hz, C(11)H), 3.69–3.57 (2 H, m, C(16)H_AH_B, C(7)H), 3.45 (1 H, dd, J = 10.4, 6.7 Hz, C(16)H_AH_B), 3.27 (1 H, dd, J = 13.3, 3.2 Hz, Bn-CH_AH_B), 2.76 (1 H, dd, J = 13.3, 9.6 Hz, Bn-CH_AH_B), 2.08 (1 H, d, J = 7.0 Hz, C(13)H_AH_B), 2.05 (3 H, s, Ac-CH₃), 1.98–1.88 (2 H, m, C(9)H_AH_B, C(8)H_AH_B), 1.86–1.77 (1 H, m, C(13)H_AH_B), 1.75–1.63 (2 H, m, C(5)H_AH_B, C(9)H_AH_B), 1.63–1.49 (3 H, m, , C(5)H_AH_B, C(4)H₂), 1.45–1.36 (1 H, m, C(8)H_AH_B), 1.24 (3 H, s, C(12)CH₃), 1.21 (3 H, d, J = 6.8 Hz, C(2)CH₃), 0.94 (9 H, t, J = 7.9 Hz, TES-CH₃ × 3), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.87 (9 H, s, TBS-C(CH₃)₃), 0.62–0.52 (6 H, m, TES-CH₂ × 3), 0.09–0.01 (12 H, m, TBS-Si(CH₃)₂ × 2);
¹³C NMR (100 MHz, CDCl₃) δ_C 175.1 (C1), 170.5 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 153.1 (C1'), 135.3 (Bn-C_{Ar}CH₂), 130.6 (PMB-C_{Ar}CH₂), 129.5 (Bn-C_{Ar} × 2),

129.3 (PMB- $C_{Ar} \times 2$), 129.0 (Bn- $C_{Ar} \times 2$), 127.4 (Bn- C_{Ar}), 113.8 (PMB- $C_{Ar} \times 2$), 85.0 (C12), 84.4 (C15), 81.3 (C14), 79.9 (C10), 78.9 (C7), 78.0 (C11), 75.0 (C6), 72.7 (C3), 71.0 (PMB- CH_2), 66.1 (C2'), 64.1 (C16), 55.7 (C3'), 55.3 (PMB- CH_3), 42.6 (C2), 42.3 (C13), 37.7 (Bn- CH_2), 30.8 (C4), 28.2 (C8), 26.9 (C5), 26.2 (3 C, TBS- $C(CH_3)_3$), 26.0 (3 C, TBS- $C(CH_3)_3$), 23.9 (C9), 22.0 (C12- CH_3), 21.2 (Ac- CH_3), 18.4 (TBS- $C(CH_3)_3$), 18.3 (TBS- $C(CH_3)_3$), 12.0 (C2- CH_3), 7.0 (3 C, TES- $CH_3 \times 3$), 5.1 (3 C, TES- $CH_2 \times 3$), -3.3 (TBS-Si CH_3), -4.8 (TBS-Si CH_3), -5.3 (TBS-Si CH_3), -5.4 (TBS-Si CH_3).

Spectroscopic data were consistent with those previously reported.⁶⁰

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl acetate 308-DEIPS



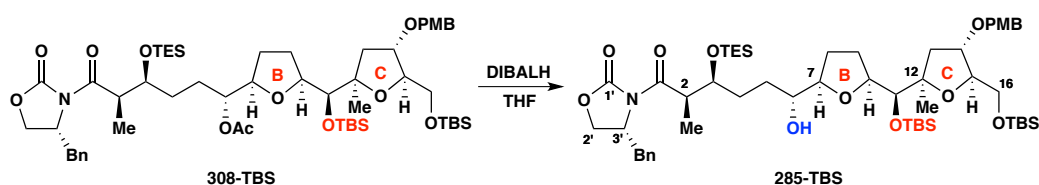
Alcohol **284-DEIPS** (0.70 g, 0.73 mmol) was dissolved in CH₂Cl₂ (7 mL) and cooled to 0 °C. Imidazole (0.21g, 3.1 mmol) and 4-(dimethylamino)pyridine (8.0 mg, 65 μmol) were added, followed by chlorotriethylsilane (0.240 mL, 1.42 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for 2 hours before being quenched by addition of an aqueous solution of NaHCO₃ (sat., 5 mL). The aqueous layer was separated and extracted with Et₂O (3 × 5 mL). The combined organic extracts was washed with brine (1 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash

column chromatography (SiO₂, 30:70 EtOAc:Petroleum ether) to afford **308-DEIPS** (772 mg, 99%) as a colourless oil.

$R_f = 0.75$ (30:70 EtOAc:Petane); $[\alpha]_D^{25} -28.2$ ($c = 0.46$, CH₂Cl₂); $^1\text{H NMR}$ (400 MHz, CDCl₃) δ_H 7.36–7.30 (2 H, m, Bn-ArH $\times$ 2), 7.28 (1 H, dt, $J = 7.3, 1.4$ Hz, Bn-ArH), 7.24 (2 H, d, $J = 8.2$ Hz, PMB-ArH $\times$ 2), 7.22–7.18 (2 H, m, Bn-ArH $\times$ 2), 6.86 (2 H, d, $J = 8.5$ Hz, PMB-ArH $\times$ 2), 4.89 (1 H, dt, $J = 7.2, 3.4$ Hz, C(6)H), 4.59 (1 H, ddt, $J = 9.7, 6.4, 3.2$ Hz, C(3')H), 4.46 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.38 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.21–4.14 (2 H, m, C(2')H₂), 4.06 (1 H, td, $J = 6.7, 3.4$ Hz, C(15)H), 4.02–3.96 (2 H, m, C(14)H, C(3)H), 3.94 (1 H, ddd, $J = 8.7, 7.0, 1.3$ Hz, C(10)H), 3.87–3.82 (2 H, m, C(11)H, C(2)H), 3.79 (3 H, s, PMB-CH₃), 3.69–3.59 (2 H, m, C(16)H_AH_B, C(7)H), 3.45 (1 H, dd, $J = 10.4, 6.6$ Hz, C(16)H_AH_B), 3.30–3.22 (1 H, m, Bn-CH_AH_B), 2.76 (1 H, dd, $J = 13.3, 9.5$ Hz, Bn-CH_AH_B), 2.10 (1 H, dd, $J = 13.4, 7.2$ Hz, C(13)H_AH_B), 2.04 (3 H, s, Ac-CH₃), 1.97–1.89 (1 H, m, C(9)H_AH_B), 1.89–1.81 (1 H, m, C(8)H_AH_B), 1.79 (1 H, dd, $J = 13.3, 2.5$ Hz, C(13)H_AH_B), 1.73–1.62 (2 H, m, C(5)H_AH_B, C(9)H_AH_B), 1.60–1.48 (3 H, m, C(5)H_AH_B, C(4)H₂), 1.45–1.33 (1 H, m, C(8)H_AH_B), 1.23 (3 H, s, C(12)CH₃), 1.20 (3 H, d, $J = 6.8$ Hz, C(2)CH₃), 1.01–0.90 (22 H, m, DEIPS-*i*PrCH₃ $\times$ 2, DEIPS-EtCH₃ $\times$ 2, DEIPS-*i*PrCH, TES-CH₃ $\times$ 3), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.69–0.49 (10 H, m, DEIPS-EtCH₂ $\times$ 2, TES-CH₂ $\times$ 3), 0.05 (6 H, s, TBS-Si(CH₃)₂); $^{13}\text{C NMR}$ (100 MHz, CDCl₃) δ_C 175.1 (C1), 170.4 (Ac-CO), 159.1 (PMB-C_{Ar}OMe), 153.1 (C1'), 135.4 (Bn-C_{Ar}CH₂), 130.6 (PMB-C_{Ar}CH₂), 129.5 (Bn-C_{Ar} $\times$ 2), 129.1 (PMB-C_{Ar} $\times$ 2), 128.9 (Bn-C_{Ar} $\times$ 2), 127.3 (Bn-C_{Ar}), 113.8 (PMB-C_{Ar} $\times$ 2), 85.0 (C12), 84.3 (C15), 80.9 (C14), 79.9 (C10), 78.8 (C7),

78.1 (C11), 75.2 (C6), 72.8 (C3), 71.0 (PMB-CH₂), 66.1 (C2'), 63.9 (C16), 55.7 (C3'), 55.3 (PMB-CH₃), 42.7 (C2), 42.0 (C13), 37.7 (Bn-CH₂), 30.8 (C4), 28.2 (C8), 27.0 (C5), 26.0 (TBS-C(CH₃)₃), 23.9 (C9), 22.1 (C12-CH₃), 21.0 (Ac-CH₃), 18.3 (TBS-C(CH₃)₃), 17.7 (DEIPS-*i*PrCH₃), 17.6 (DEIPS-*i*PrCH₃), 13.2 (DEIPS-*i*PrCH), 11.9 (C2-CH₃), 7.3 (DEIPS-EtCH₃), 7.3 (DEIPS-EtCH₃), 6.9 (3 C, TES-CH₃ × 3), 5.1 (3 C, TES-CH₂ × 3), 4.5 (DEIPS-EtCH₂), 4.2 (DEIPS-EtCH₂), -5.3 (TBS-SiCH₃), -5.4 (TBS-SiCH₃); **IR** $\nu_{\max}$ (film)/cm⁻¹ 3535, 2980, 2888, 1782, 1735, 1462, 1382, 1251, 1151, 1073, 955; **HRMS** (ESI⁺, *m/z*) C₅₇H₉₅NNaO₁₂Si₃⁺ [M + Na⁺] calculated 1092.60543, found 1092.60182 (Δ = -3.30 ppm).

(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*)-6-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-6-hydroxy-2-methyl-3-((triethylsilyl)oxy)hexanoyl)oxazolidin-2-one 285-TBS



Acetate **308-TBS** (45 mg, 43 μ mol) was dissolved in THF (1.3 mL) and cooled to -78 °C in a dry ice-acetone bath. Diisobutylaluminum hydride (1.0 M in PhMe, 0.12 mL, 0.12 mmol) was added dropwise and the resulting solution was stirred at -78 °C for 90 minutes before another portion of diisobutylaluminum hydride (1.0 M in PhMe, 0.08 mL, 0.08 mmol) was added. The reaction was stirred for a further 2 hours at -78 °C before being quenched by dropwise addition of EtOAc (3 mL). The reaction mixture was stirred for 10 minutes before

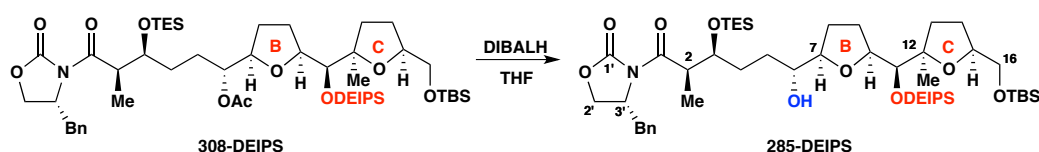
adding an aqueous solution of Rochelle's salt (sat., 5 mL). The resulting mixture was allowed to warm to room temperature and stirred for 45 minutes. The organic layer was separated and the aqueous layer was extracted with Et₂O (4 × 5 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 50:50 Et₂O:Pentane) to *bis*-THF compound **285-TBS** as a colourless oil (35 mg, 81%).

$R_f = 0.3$ (40:60 Et₂O: Pentane); $[\alpha]_D^{25} -18.3$ ($c = 0.38$, CH₂Cl₂; lit. -21.6 , $c = 0.50$, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.38–7.30 (2 H, m, Bn-ArH × 2), 7.30–7.27 (1 H, m, Bn-ArH), 7.25 (2 H, d, $J = 8.8$ Hz, PMB-ArH × 2), 7.23–7.18 (2 H, m, Bn-ArH × 2), 6.86 (2 H, d, $J = 8.7$ Hz, PMB-ArH × 2), 4.61 (1 H, ddt, $J = 9.6, 6.5, 3.3$ Hz, C(3')H), 4.47 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.39 (1 H, d, $J = 11.6$ Hz, PMB-CH_AH_B), 4.16 (2 H, td, $J = 6.7, 3.8$ Hz, C(2')H₂), 4.10 (1 H, dt, $J = 6.3, 2.9$ Hz, C(15)H), 4.05–3.96 (3 H, m, C(14)H, C(3)H, C(10)H), 3.92–3.85 (1 H, m, C(2)H), 3.80 (3 H, s, PMB-CH₃), 3.71 (1 H, d, $J = 2.1$ Hz, C(11)H), 3.66 (1 H, dd, $J = 10.5, 3.8$ Hz, C(16)H_AH_B), 3.56–3.40 (3 H, m, C(16)H_AH_B, C(6)H, C(7)H), 3.28 (1 H, dd, $J = 13.5, 7.2$ Hz, Bn-CH_AH_B), 2.78 (1 H, dd, $J = 13.2, 9.7$ Hz, Bn-CH_AH_B), 2.05–2.00 (1 H, m, C(13)H_AH_B), 1.97–1.89 (1 H, m, C(9)H_AH_B), 1.89–1.80 (1 H, m, C(8)H_AH_B), 1.87–1.74 (1 H, m, C(13)H_AH_B), 1.70–1.58 (2 H, m, C(5)H_AH_B, C(9)H_AH_B), 1.58–1.48 (3 H, m, C(5)H_AH_B, C(4)H₂), 1.44–1.36 (1 H, m, C(8)H_AH_B), 1.27 (3 H, s, C(12)CH₃), 1.22 (3 H, d, $J = 7.0$ Hz, C(2)CH₃), 0.98–0.91 (9 H, m, TES-CH₃ × 3), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.88 (9 H, s, TBS-C(CH₃)₃), 0.66–0.49 (6 H, m, TES-CH₂ × 3), 0.07–0.04 (12 H, m, TBS-Si(CH₃)₂ × 2); ¹³C NMR (100 MHz, CDCl₃) δ_C 175.3 (C1),

159.1 (PMB- $C_{Ar}OMe$), 153.1 (C1'), 135.4 (Bn- $C_{Ar}CH_2$), 130.6 (PMB- $C_{Ar}CH_2$), 129.5 (Bn- $C_{Ar} \times 2$), 129.1 (PMB- $C_{Ar} \times 2$), 128.9 (Bn- $C_{Ar} \times 2$), 127.3 (Bn- C_{Ar}), 113.8 (PMB- $C_{Ar} \times 2$), 85.2 (C12), 84.6 (C15), 82.0 (C7), 80.9 (C14), 80.0 (C10), 78.7 (C11), 74.4 (C6), 73.4 (C3), 71.1 (PMB- CH_2), 66.0 (C2'), 63.9 (C16), 55.8 (C3'), 55.3 (PMB- CH_3), 43.0 (C2), 42.7 (C13), 37.7 (Bn- CH_2), 31.3 (C4), 29.2 (C5), 27.9 (C8), 26.1 (TBS- $C(CH_3)_3$), 26.0 (TBS- $C(CH_3)_3$), 25.4 (C9), 21.6 (C12- CH_3), 18.3 (TBS- $C(CH_3)_3$), 18.3 (TBS- $C(CH_3)_3$), 12.1 (C2- CH_3), 7.0 (3 C, TES- $CH_3 \times 3$), 5.1 (3 C, TES- $CH_2 \times 3$), -3.1 (TBS- $SiCH_3$), -4.2 (TBS- $SiCH_3$), -5.3 (TBS- $SiCH_3$), -5.4 (TBS- $SiCH_3$).

Spectroscopic data were consistent with those previously reported.⁶⁰

(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*)-6-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)-6-hydroxy-2-methyl-3-((triethylsilyl)oxy)hexanoyl)oxazolidin-2-one 285-DEIPS



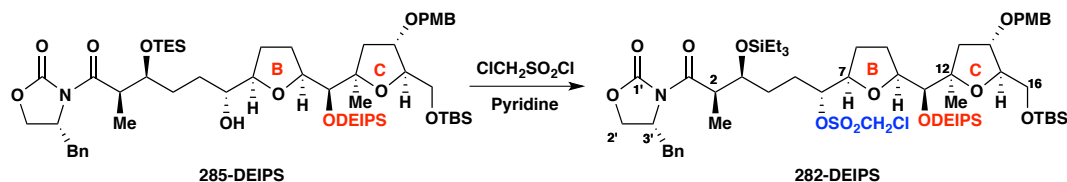
Acetate **308-DEIPS** (0.77 g, 0.43 mmol) was dissolved in THF (22 mL) and cooled to $-78\text{ }^{\circ}\text{C}$ in a dry ice-acetone bath. Diisobutylaluminum hydride (1.0 M in PhMe, 2.16 mL, 2.16 mmol) was added dropwise and the resulting solution was stirred for 90 minutes before another portion of diisobutylaluminum hydride (1.0 M in PhMe, 1.44 mL, 1.44 mmol) was added. The reaction solution was stirred for a further 2 hours at $-78\text{ }^{\circ}\text{C}$ before quenched by dropwise addition of EtOAc (20 mL). The reaction mixture was stirred for 10 minutes before

adding an aqueous solution of Rochelle's salt (sat., 30 mL). The resulting mixture was allowed to warm to room temperature and stirred for 45 minutes. The organic layer was separated and the aqueous layer was extracted with Et₂O (4 × 30 mL). The combined organic extracts was washed with brine (20 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 50:50 Et₂O:Pentane) to *bis*-THF compound **285-DEIPS** as a colourless oil (543 mg, 75%).

$R_f = 0.3$ (40:60 Et₂O: Pentane); $[\alpha]_D^{25} -30.5$ ($c = 0.43$, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ_H 7.35–7.30 (2 H, m, Bn-ArH × 2), 7.29–7.26 (1 H, m, Bn-ArH), 7.25 (2 H, d, $J = 6.7$ Hz, PMB-ArH × 2), 7.23–7.19 (2 H, m, Bn-ArH × 2), 6.87 (2 H, d, $J = 6.7$ Hz, PMB-ArH × 2), 4.61 (1 H, ddt, $J = 9.6, 6.6, 3.3$ Hz, C(3')H), 4.48 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.40 (1 H, d, $J = 11.5$ Hz, PMB-CH_AH_B), 4.18–4.12 (2 H, m, C(2')H₂), 4.10 (1 H, dt, $J = 6.3, 3.7$ Hz, C(15)H), 4.06–3.99 (3 H, m, C(14)H, C(10)H, C(3)H), 3.90 (1 H, qd, $J = 6.8, 5.2$ Hz, C(2)H), 3.79 (3 H, s, PMB-CH₃), 3.74 (1 H, d, $J = 2.6$ Hz, C(11)H), 3.68 (1 H, dd, $J = 10.4, 3.9$ Hz, C(16)H_AH_B), 3.53 (1 H, dt, $J = 8.6, 6.8$ Hz, C(7)H), 3.51–3.45 (1 H, m, C(16)H_AH_B), 3.45–3.38 (1 H, m, C(6)H), 3.28 (1 H, dd, $J = 13.5, 3.4$ Hz, Bn-CH_AH_B), 2.76 ((1 H, dd, $J = 13.4, 9.8$ Hz, Bn-CH_AH_B), 2.75 (1 H, br. s., OH), 2.06 (1 H, dd, $J = 13.5, 7.2$ Hz, C(13)H_AH_B), 2.01–1.90 (1 H, m, C(9)H_AH_B), 1.90–1.75 (4 H, m, C(4)H_AH_B, C(13)H_AH_B, C(8)H_AH_B, C(9)H_AH_B), 1.63–1.45 (3 H, m, C(4)H_AH_B, C(5)H_AH_B, C(8)H_AH_B), 1.42–1.32 (1 H, m, C(5)H_AH_B), 1.29 (3 H, s, C(12)CH₃), 1.23 (3 H, d, $J = 6.9$ Hz, C(2)CH₃), 1.03–0.92 (22 H, m, TES-CH₃ × 3, DEIPS-EtCH₃ × 2, DEIPS-*i*PrCH₃ × 2, DEIPS-*i*PrCH), 0.89 (9 H, s, TBS-C(CH₃)₃), 0.70–0.53 (10 H, m, TES-CH₂ × 3, DEIPS-EtCH₂ × 2), 0.06 (6 H, s,

TBS-Si(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ_C 175.3 (C1), 159.1 (PMB-C_{Ar}OMe), 135.4 (Bn-C_{Ar}CH₂), 130.6 (PMB-C_{Ar}CH₂), 129.5 (Bn-C_{Ar} × 2), 129.1 (PMB-C_{Ar} × 2), 128.9 (Bn-C_{Ar} × 2), 127.3 (Bn-C_{Ar}), 113.8 (PMB-C_{Ar} × 2), 85.3 (C12), 84.6 (C15), 82.0 (C7), 80.5 (C14), 80.0 (C10), 79.0 (C11), 74.4 (C6), 73.4 (C3), 71.1 (PMB-CH₂), 66.0 (C2'), 63.7 (C16), 55.8 (C3'), 55.3 (PMB-CH₃), 43.0 (C2), 42.6 (C13), 37.7 (Bn-CH₂), 31.4 (C4), 29.3 (C5), 27.8 (C8), 25.9 (3 C, TBS-C(CH₃)₃), 25.7 (C9), 21.5 (C12-CH₃), 18.3 (TBS-C(CH₃)₃), 17.6 (DEIPS-*i*PrCH₃), 17.6 (DEIPS-*i*PrCH₃), 13.4 (DEIPS-*i*PrCH), 12.0 (C2-CH₃), 7.4 (DEIPS-EtCH₃), 7.3 (DEIPS-EtCH₃), 7.0 (3 C, TES-EtCH₃ × 3), 5.2 (3 C, TES-EtCH₂ × 3), 4.8 (DEIPS-EtCH₂), 4.4 (DEIPS-EtCH₂), -5.4 (TBS-SiCH₃), -5.4 (TBS-SiCH₃); IR ν_{max} (film)/cm⁻¹ 3657, 2981, 2888, 2361, 2341, 1462, 1383, 1252, 1152, 1073, 955, 816; HRMS (ESI⁺, *m/z*) C₅₅H₉₃NNaO₁₁Si₃⁺ [M + Na⁺] calculated 1050.59486, found 1050.59218 (Δ = -2.55 ppm).

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl))((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl chloromethanesulfonate **282-DEIPS**



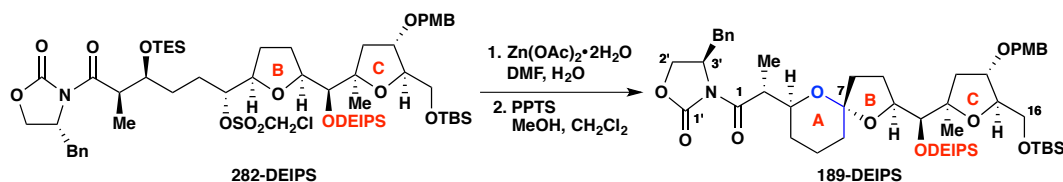
Alcohol **285-DEIPS** (130 mg, 0.126 mmol) was dissolved in pyridine (1 mL) and cooled to 0 °C. Chloromethanesulfonyl chloride (90 % purity, 29 μL, 0.316 mmol) was added dropwise and the resulting mixture was stirred for 30 minutes before being warmed to room

temperature and stirred for a further 2 hours. The reaction was quenched by addition of water (2 mL) and diluted with diethyl ether (5 mL). The aqueous layer was separated and extracted with diethyl ether (4×2 mL). The combined organic layers were washed with brine (2 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 10:90 to 20:80 EtOAc:petane) to afford chloromesylate **282-DEIPS** as a viscous yellow oil (130 mg, 90%).

$R_f = 0.6$ (20:80 EtOAc:petane); $[\alpha]_D^{25} -41.9$ ($c = 0.42$, CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} 7.36–7.30 (2 H, m, Bn-ArH $\times 2$), 7.29–7.23 (1 H, m, Bn-ArH), 7.25 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 7.23–7.18 (2 H, m, Bn-ArH $\times 2$), 6.87 (2 H, d, $J = 8.6$ Hz, PMB-ArH $\times 2$), 4.87 (1 H, d, $J = 12.4$ Hz, $\text{SO}_2\text{CH}_A\text{H}_B\text{Cl}$), 4.74 (1 H, d, $J = 12.0$ Hz, $\text{SO}_2\text{CH}_A\text{H}_B\text{Cl}$), 4.69–4.63 (2 H, m, C(3')H, C(6)H), 4.47 (1 H, d, $J = 11.5$ Hz, PMB- CH_AH_B), 4.40 (1 H, d, $J = 11.5$ Hz, PMB- CH_AH_B), 4.25 (1 H, dd, $J = 9.0, 7.6$ Hz, C(2') H_AH_B), 4.14 (1 H, dd, $J = 9.1, 2.1$ Hz, C(2') H_AH_B), 4.11–4.07 (2 H, m, C(10)H, C(15)H), 4.05–3.98 (2 H, m, C(3)H, C(14)H), 3.94–3.87 (1 H, m, C(2)H), 3.80 (3 H, s, PMB- CH_3), 3.76–3.71 (1 H, m, C(7)H), 3.70 (1 H, d, $J = 1.8$ Hz, C(11)H), 3.64 (1 H, dd, $J = 10.5, 4.1$ Hz, C(16) H_AH_B), 3.47 (1 H, dd, $J = 10.5, 6.2$ Hz, C(16) H_AH_B), 3.25 (1 H, dd, $J = 13.4, 3.3$ Hz, Bn- CH_AH_B), 2.79 (1 H, dd, $J = 13.4, 9.5$ Hz, Bn- CH_AH_B), 2.13–2.02 (1 H, m, C(9) H_AH_B), 2.01–1.94, (1 H, m, C(13) H_AH_B) 1.92–1.60 (6 H, m, C(13) H_AH_B , C(5) H_AH_B , C(8) H_2 , C(4) H_2), 1.47–1.32 (1 H, m, C(5) H_AH_B), 1.26 (3 H, s, C(12) CH_3), 1.25 (3 H, d, $J = 6.9$, C(2) CH_3), 1.06–0.92 (22 H, m, DEIPS- $\text{CH}_3 \times 4$, DEIPS-CH, TES- $\text{CH}_3 \times 3$), 0.89 (9 H, s, TBS- $\text{C}(\text{CH}_3)_3$), 0.72–0.53 (10 H, m, TES- $\text{CH}_2 \times 3$, DEIPS- $\text{CH}_2 \times 2$), 0.05 (3 H, s, TBS-Si CH_3), 0.04 (3 H, s, TBS-Si CH_3);

^{13}C NMR (125 MHz, CDCl_3) δ_{C} 175.3 (C1), 159.1 (PMB- $\text{C}_{\text{Ar}}\text{OMe}$), 153.2 (C1'), 135.4 (Bn- $\text{C}_{\text{Ar}}\text{CH}_2$), 130.5 (PMB- $\text{C}_{\text{Ar}}\text{CH}_2$), 129.5 (Bn- $\text{C}_{\text{Ar}} \times 2$), 129.1 (PMB- $\text{C}_{\text{Ar}} \times 2$), 128.9 (Bn- $\text{C}_{\text{Ar}} \times 2$), 127.3 (Bn- C_{Ar}), 113.8 (PMB- $\text{C}_{\text{Ar}} \times 2$), 88.8 (C6), 85.1 (C12), 84.7 (C15), 80.9 (C14), 80.8 (C10), 79.8 (C7), 79.4 (C11), 73.2 (C3), 71.0 (PMB- CH_2), 66.2 (C2'), 64.0 (C16), 55.6 (C3'), 55.3 (PMB- OCH_3), 54.3 ($\text{SO}_2\text{CH}_2\text{Cl}$), 42.8 (2 C, C13, C2), 37.7 (Bn- CH_2), 30.4 (C4), 28.4 (C5), 27.7 (C8), 25.9 (TBS- $\text{C}(\text{CH}_3)_3$), 24.4 (C9), 21.3 (C12- CH_3), 18.3 (TBS- $\text{C}(\text{CH}_3)_3$), 17.6 (DEIPS- $i\text{PrCH}_3$), 17.5 (DEIPS- $i\text{PrCH}_3$), 13.3 (C2- CH_3), 13.3 (DEIPS- $i\text{PrCH}$), 7.4 (DEIPS-Et CH_3), 7.3 (DEIPS-Et CH_3), 7.0 (3 C, TES- $\text{CH}_3 \times 3$), 5.2 (3 C, TES- $\text{CH}_2 \times 3$), 4.8 (DEIPS-Et CH_2), 4.4 (DEIPS-Et CH_2), -5.3 (TBS- SiCH_3), -5.4 (TBS- SiCH_3); IR ν_{max} (film)/ cm^{-1} 2954, 2877, 2358, 1781, 1736, 1695, 1612, 1514, 1461, 1378, 1248, 1111; HRMS (ESI $^+$, m/z) $\text{C}_{56}\text{H}_{94}\text{ClINaO}_{13}\text{SSi}_3^+$ $[\text{M} + \text{Na}^+]$ calculated 1162.5334, found 1162.5312 ($\Delta = -1.88$ ppm).

(*R*)-4-Benzyl-3-((*R*)-2-((2*S*,5*S*,7*S*)-2-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((diethyl(isopropyl)silyl)oxy)methyl)-1,6-dioxaspiro[4.5]decan-7-yl)propanoyl)oxazolidin-2-one 189-DEIPS



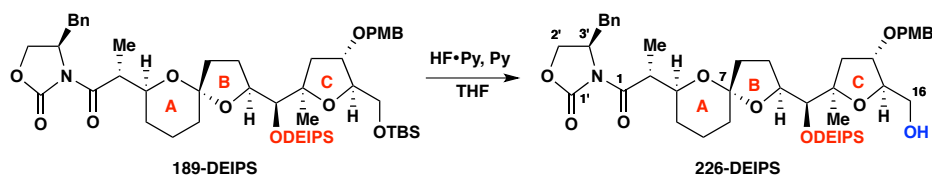
Chloromesylate **282-DEIPS** (120 mg, 0.105 mmol) was dissolved in *N,N*-dimethylformamide (1.6 mL) and water (1.2 mL). Zinc acetate dihydrate (240 mg, 1.05 mmol) was added and the reaction was heated to 75 °C and stirred for 12 hours. After cooling to room temperature, the reaction was diluted with brine (15 mL). The mixture was extracted with

Et₂O (3 × 15 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Silica, 25:75 EtOAc:Pentane) to afford a mixture of ketone **288** and lactol **289** (65 mg, 60%) as a viscous oil. The mixture of **288** and **289** was dissolved in CH₂Cl₂ (2.5 mL) and MeOH (2.5 mL) and cooled to 0 °C. Pyridinium *p*-toluenesulfonate (PPTS, 9.0 mg, 36 μmol) was added and the mixture was stirred for 2 hours at 0 °C. The reaction was quenched by addition of an aqueous solution of NaHCO₃ (sat., 4.5 mL). The resulting mixture was diluted with Et₂O (30 mL), washed with water (5 mL), brine (5 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc:Pentane) to afford spiroketal **189-DEIPS** (54 mg, 95%, 57% over two steps) as a viscous colourless oil.

R_f = 0.7 (20:80 EtOAc:Pentane); **[α]_D²⁵** −6.8 (*c* = 0.49, CH₂Cl₂); **¹H NMR** (400 MHz, CDCl₃) **δ_H** 7.36–7.23 (5 H, m, Bn-ArH × 5), 7.21 (2 H, d, *J* = 8.6 Hz, PMB-ArH × 2), 6.86 (2 H, d, *J* = 8.6 Hz, PMB-ArH × 2), 4.62 (1 H, ddt, *J* = 10.0, 7.1, 4.4 Hz, C(3')H), 4.47 (1 H, d, *J* = 11.5 Hz, PMB-CH_AH_B), 4.38 (1 H, d, *J* = 11.5 Hz, PMB-CH_AH_B), 4.22 (1 H, dt, *J* = 8.3, 1.3 Hz, C(10)H), 4.18–4.10 (2 H, m, C(2')H₂), 4.08–3.93 (3 H, m, C(15)H, C(14)H, C(3)H), 3.89–3.82 (2 H, m, C(2)H, C(11)H), 3.80 (3 H, s, PMB-CH₃), 3.67 (1 H, dd, *J* = 10.3, 4.1 Hz, C(16)H_AH_B), 3.42 (1 H, dd, *J* = 10.3, 7.1 Hz, C(16)H_AH_B), 3.29–3.22 (1 H, m, Bn-CH_AH_B), 2.75 (1 H, dd, *J* = 13.3, 9.7 Hz, Bn-CH_AH_B), 2.08 (1 H, dd, *J* = 12.5, 6.3 Hz, C(13)H_AH_B), 1.98–1.91 (1 H, m, C(9)H_AH_B), 1.90–1.70 (4 H, m, C(5)H_AH_B, C(8)H_AH_B, C(13)H_AH_B, C(9)H_AH_B), 1.69–1.54 (5 H, m, C(5)H_AH_B, C(6)H₂, C(4)H_AH_B, C(8)H_AH_B), 1.32–1.20 (7 H,

m, C(4) H_AH_B , C(12) CH_3 , C(2) CH_3), 1.04–0.93 (13 H, m, DEIPS- $CH_3 \times 4$, DEIPS- $iPrCH$), 0.89 (9 H, s, TBS- $C(CH_3)_3$), 0.70–0.53 (4 H, m, DEIPS- $CH_2 \times 2$), 0.09–0.03 (6 H, m, TBS- $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.2 (C1), 159.1 (PMB- $C_{Ar}OMe$), 153.0 (C1'), 135.4 (Bn- $C_{Ar}CH_2$), 130.7 (PMB- $C_{Ar}CH_2$), 129.4 (PMB- $C_{Ar} \times 2$), 129.1 (Bn- $C_{Ar} \times 2$), 128.9 (Bn- $C_{Ar} \times 2$), 127.3 (Bn- C_{Ar}), 113.8 (PMB- $C_{Ar} \times 2$), 105.1 (C7), 85.1 (C12), 84.3 (C15), 81.7 (C14), 78.5 (C11), 77.9 (C10), 70.9 (PMB- CH_2), 70.9 (C3), 65.9 (C2'), 64.0 (C16), 55.5 (C3'), 55.3 (PMB- CH_3), 42.5 (C2), 41.3 (C13), 38.0 (C8), 37.9 (Bn- CH_2), 32.3 (C6), 28.0 (C4), 26.0 (TBS- $C(CH_3)_3$), 22.7 (C9), 22.3 (C12- CH_3), 20.2 (C5), 18.4 (TBS- $C(CH_3)_3$), 17.7 (DEIPS- $iPrCH_3$), 17.6 (DEIPS- $iPrCH_3$), 13.3 (DEIPS- $iPrCH$), 13.3 (C2- CH_3), 7.4 (DEIPS-Et CH_3), 7.3 (DEIPS-Et CH_3), 4.6 (DEIPS-Et CH_2), 4.3 (DEIPS-Et CH_2), -5.3 (TBS- $SiCH_3$), -5.3 (TBS- $SiCH_3$); IR ν_{max} (film)/ cm^{-1} 3658, 2980, 2888, 1783, 1740, 1462, 1382, 1249, 1151, 1073, 955, 834, 724; HRMS (ESI $^+$, m/z) $C_{49}H_{77}NNaO_{10}Si_2^+$ [$M + Na^+$] calculated 918.49782, found 918.49647 ($\Delta = -1.47$ ppm).

(*R*)-4-Benzyl-3-((*R*)-2-((2*S*,5*S*,7*S*)-2-((*S*)-((diethyl(isopropyl)silyl)oxy))((2*R*,4*S*,5*R*)-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)-1,6-dioxaspiro[4.5]decan-7-yl)propanoyl)oxazolidin-2-one 226-DEIPS



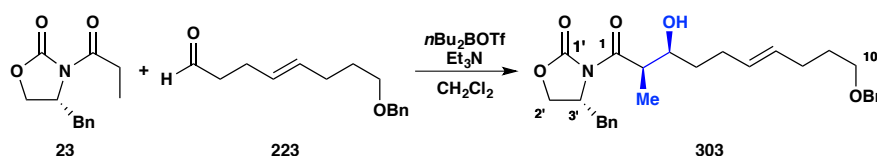
Hydrogen fluoride-pyridine (200 μ L) was dissolved in THF (3 mL) and cooled to 0 $^{\circ}C$ in an ice-water bath. Pyridine (300 μ L) was added dropwise and the reagent was stirred for 10

minutes at 0 °C. Spiroketal **189-DEIPS** (30 mg, 0.033 mmol) was dissolved in THF (1 mL) and cooled to 0 °C in an ice-water bath. The hydrogen fluoride-pyridine solution was added to the reaction solution dropwise and the reaction was stirred for 3 hours at 0 °C before being quenched by addition of an aqueous solution of NaHCO₃ (sat., 5 mL). The organic layer was separated and the aqueous layer was extracted with CHCl₃ (4 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography SiO₂, 10:90 EtOAc:Pentane to 30:70 EtOAc:Pentane) to afford primary alcohol **226-DEIPS** as a colourless oil (21 mg, 80%).

R_f = 0.4 (40:60 EtOAc:Pentane); $[\alpha]_D^{25}$ -3.6 (c = 0.23, CH₂Cl₂); $^1\text{H NMR}$ (400 MHz, CDCl₃) δ_H 7.36–7.23 (5 H, m, Bn-ArH × 5), 7.21 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 6.86 (2 H, d, J = 8.6 Hz, PMB-ArH × 2), 4.72–4.55 (1 H, m, C(3')H), 4.45 (1 H, d, J = 11.5 Hz, PMB-CH_AH_B), 4.41 (1 H, d, J = 11.5 Hz, PMB-CH_AH_B), 4.22 (1 H, dt, J = 8.3, 1.2 Hz, C(10)H), 4.13 (2 H, dd, J = 9.0, 2.6 Hz, C(2')H₂), 4.08–4.01 (3 H, m, C(15)H, C(14)H, C(3)H), 3.90–3.83 (2 H, m, C(2)H, C(11)H), 3.80 (3 H, s, PMB-CH₃), 3.75 (1 H, dd, J = 11.7, 2.6 Hz, C(16)H_AH_B), 3.53 (1 H, dd, J = 11.8, 3.7 Hz, C(16)H_AH_B), 3.27 (1 H, dd, J = 13.4, 3.3 Hz, Bn-CH_AH_B), 2.75 (1 H, dd, J = 13.3, 9.7 Hz, Bn-CH_AH_B), 2.22 (1 H, dd, J = 13.0, 6.5 Hz, C(13)H_AH_B), 1.98–1.91 (1 H, m, C(9)H_AH_B), 1.90–1.70 (4 H, m, C(5)H_AH_B, C(8)H_AH_B, C(13)H_AH_B, C(9)H_AH_B), 1.69–1.54 (5 H, m, C(5)H_AH_B, C(6)H₂, C(4)H_AH_B, C(8)H_AH_B), 1.32–1.20 (7 H, m, C(4)H_AH_B, C(12)CH₃, C(2)CH₃), 1.04–0.93 (13 H, m, DEIPS-CH₃ × 4, DEIPS-*i*PrCH), 0.76–0.52 (4 H, m, DEIPS-CH₂ × 2); $^{13}\text{C NMR}$ (100 MHz, CDCl₃) δ_C

175.1 (C1), 159.0 (PMB- $C_{Ar}OMe$), 153.0 (C1'), 135.5 (Bn- $C_{Ar}CH_2$), 130.7 (PMB- $C_{Ar}CH_2$), 129.4 (PMB- $C_{Ar} \times 2$), 129.2 (Bn- $C_{Ar} \times 2$), 129.0 (Bn- C_{Ar}), 127.2 (Bn- $C_{Ar} \times 2$), 113.8 (PMB- $C_{Ar} \times 2$), 105.1 (C7), 85.1 (C12), 84.3 (C15), 81.9 (C14), 78.6 (C11), 77.9 (C10), 70.9 (PMB- CH_2), 70.9 (C3), 65.5 (C2'), 66.8 (C16), 55.6 (C3'), 55.3 (PMB- CH_3), 42.3 (C2), 41.3 (C13), 38.0 (C8), 37.8 (Bn- CH_2), 32.3 (C6), 28.0 (C4), 22.7 (C9), 22.3 (C12- CH_3), 20.1 (C5), 17.6 (DEIPS- $iPrCH_3$), 17.5 (DEIPS- $iPrCH_3$), 13.4 (DEIPS- $iPrCH$), 13.4 (C2- CH_3), 7.4 (DEIPS-Et CH_3), 7.3 (DEIPS-Et CH_3), 4.6 (DEIPS-Et CH_2), 4.3 (DEIPS-Et CH_2); **IR** ν_{max} (film)/ cm^{-1} 3378, 2980, 2961, 1633, 1403, 1222, 1210, 1156, 1013, 815; **HRMS** (ESI⁺, m/z) $C_{43}H_{63}NNaO_{10}Si^+$ [M + Na⁺] calculated 804.41134, found 804.40915 ($\Delta = -2.72$ ppm).

(R)-4-Benzyl-3-((2R,3S,E)-10-(benzyloxy)-3-hydroxy-2-methyldec-6-enoyl)oxazolidin-2-one 303

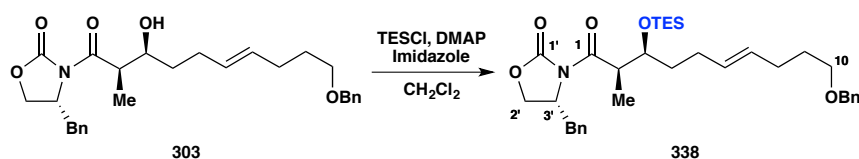


(*R*)-4-Benzyl-3-propionyloxazolidin-2-one **23** (3.76 g, 16.1 mmol) was dissolved in CH_2Cl_2 (90 mL) and cooled to 0 °C. Dibutylboron trifluoromethanesulfonate (1.0 M in CH_2Cl_2 , 19 mL, 19 mmol) and Et_3N (2.96 mL, 21.2 mmol) were added dropwise. The reaction was stirred for 10 minutes and cooled to -78 °C in a dry ice-acetone bath. After a further 10 minutes, aldehyde **223** (3.4 g, 14.6 mmol), dissolved in CH_2Cl_2 (20 mL) was added dropwise and the mixture was stirred for 30 minutes before being warmed to 0 °C and stirred for a further hour. The reaction was quenched by addition of an aqueous pH 7 phosphate buffer (20 mL) and MeOH (30 mL), followed by a 2:1 mixture of MeOH and hydrogen peroxide

(30 %, aq., 60 mL). The resulting mixture was stirred vigorously for 1 hour and the aqueous phase was extracted with Et₂O (4 × 100 mL). The combined organic layers were washed with water (100 mL), an aqueous solution of NaHCO₃ (sat., 100 mL), brine (100 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 10:90 EtOAc: Pentane to 30:70 EtOAc:Pentane) to afford aldol product **303** as a colourless oil (5.7 g, 80%).

R_f = 0.3 (40:60 EtOAc:Pentane); **[α]_D²⁵** -42.7 (*c* = 1.13, CH₂Cl₂); **¹H NMR** (400 MHz, CDCl₃) **δ_H** 7.38–7.31 (6 H, m, ArH × 6), 7.31–7.25 (2 H, m, ArH × 2), 7.23–7.13 (2 H, m, ArH × 2), 5.55–5.33 (2 H, m, C(6)H, C(7)H), 4.69 (1 H, ddt, *J* = 9.4, 7.5, 3.2 Hz, C(3')H), 4.50 (2 H, s, OCH₂Ph), 4.29–4.13 (2 H, m, C(2')H₂), 3.96 (1 H, ddd, *J* = 9.1, 4.2, 2.7 Hz, C(3)H), 3.76 (1 H, qd, *J* = 7.0, 2.7 Hz, C(2)H), 3.47 (2 H, t, *J* = 6.5 Hz, C(10)H₂), 3.24 (1 H, dd, *J* = 13.4, 3.4 Hz, CHCH_AH_BPh), 3.06–2.91 (1 H, br. s., OH), 2.78 (1 H, dd, *J* = 13.4, 9.4 Hz, CHCH_AH_BPh), 2.26–2.12 (1 H, m, C(5)H_AH_B), 2.12–1.99 (3 H, m, C(5)H_AH_B, C(8)H₂), 1.75–1.55 (3 H, m, C(9)H₂, C(4)H_AH_B), 1.50–1.40 (1 H, m, *J* = 7.9 Hz, C(4)H_AH_B), 1.32–1.19 (3 H, m, C2CH₃); **¹³C NMR** (100 MHz, CDCl₃) **δ_C** 177.5 (C1'), 153.1 (C1), 138.6 (C_{Ar}CH₂CH), 135.0 (C_{Ar}CH₂O), 130.4 (C6), 129.9 (C7), 129.4 (2 C, C_{Ar} × 2), 129.0 (2 C, C_{Ar} × 2), 128.4 (2 C, C_{Ar} × 2), 127.7 (2 C, C_{Ar} × 2), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 72.9 (OCH₂Ph), 71.0 (C10), 69.8 (C3), 66.2 (C2'), 55.1 (C3'), 42.1 (C2), 37.8 (CHCH₂Ph), 33.5 (C4), 29.5 (C9), 29.1 (C8), 29.0 (C5), 10.5 (C2-CH₃); **IR** **v_{max}** (film)/cm⁻¹ 3504, 2935, 2855, 1779, 1696, 1480, 1385, 1210, 1105, 1014, 739, 700; **HRMS** (ESI⁺, *m/z*) C₂₈H₃₆NO₅⁺ [M + H⁺] calculated 466.25880, found 466.25860 (Δ = -0.43 ppm).

(R)-4-Benzyl-3-((2R,3S,E)-10-(benzyloxy)-2-methyl-3-((triethylsilyl)oxy)dec-6-enoyl)oxazolidin-2-one 338

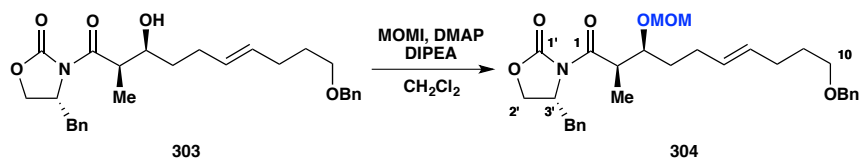


Secondary alcohol **303** (0.90 g, 2.1 mmol), 4-(dimethylamino)pyridine (26 mg, 0.21 mmol) and imidazole (282 mg, 4.14 mmol) were dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C in an ice-water bath. Chlorotriethylsilane (0.52 mL, 3.1 mmol) was added dropwise and the reaction was allowed to warm to room temperature and stirred for 12 hours. The reaction was quenched by addition of an aqueous solution of NH_4Cl (sat., 10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2 , 10:90 Et_2O :Pentane) to afford Silyl ether **338** as a viscous colourless oil (1.20 g, 90%).

$R_f = 0.5$ (20:80 Et_2O :Pentane); $[\alpha]_D^{25} -51.3$ ($c = 0.80$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} 7.38–7.31 (6 H, m, $\text{ArH} \times 6$), 7.31–7.25 (2 H, m, $\text{ArH} \times 2$), 7.23–7.13 (2 H, m, $\text{ArH} \times 2$), 5.55–5.33 (2 H, m, C(6)*H*, C(7)*H*), 4.69 (1 H, ddt, $J = 9.4, 7.5, 3.2$ Hz, C(3')*H*), 4.50 (2 H, s, OCH_2Ph), 4.29–4.13 (2 H, m, C(2')*H*₂), 3.96 (1 H, ddd, $J = 9.1, 4.2, 2.7$ Hz, C(3)*H*), 3.76 (1 H, qd, $J = 7.0, 2.7$ Hz, C(2)*H*), 3.47 (2 H, t, $J = 6.5$ Hz, C(10)*H*₂), 3.24 (1 H, dd, $J = 13.4, 3.4$ Hz, $\text{CHCH}_A\text{H}_B\text{Ph}$), 3.06–2.91 (1 H, br. s., OH), 2.78 (1 H, dd, $J = 13.4, 9.4$ Hz, $\text{CHCH}_A\text{H}_B\text{Ph}$), 2.26–2.12 (1 H, m, C(5)*H*_A*H*_B), 2.12–1.99 (3 H, m, C(5)*H*_A*H*_B, C(8)*H*₂), 1.75–1.55 (3 H, m, C(9)*H*₂, C(4)*H*_A*H*_B), 1.50–1.40 (1 H, m, $J = 7.9$ Hz, C(4)*H*_A*H*_B), 1.32–1.19 (3 H,

m, C2CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 177.5 (C1'), 153.1 (C1), 138.6 (C_{Ar}CH₂CH), 135.0 (C_{Ar}CH₂O), 130.4 (C6), 129.9 (C7), 129.4 (2 C, C_{Ar} × 2), 129.0 (2 C, C_{Ar} × 2), 128.4 (2 C, C_{Ar} × 2), 127.7 (2 C, C_{Ar} × 2), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 72.9 (OCH₂Ph), 71.0 (C10), 69.8 (C3), 66.2 (C2'), 55.1 (C3'), 42.1 (C2), 37.8 (CHCH₂Ph), 33.5 (C4), 29.5 (C9), 29.1 (C8), 29.0 (C5), 10.5 (C2-CH₃); IR ν_{max} (film)/cm⁻¹ 2956, 2879, 1782, 1701, 1455, 1382, 1354, 1235, 1209, 1108, 1012, 968, 738, 701; HRMS (ESI⁺, *m/z*) [M + Na⁺] C₃₄H₄₉NO₅NaSi calculated 602.32722, found 602.32660 (Δ = -1.03 ppm).

(*R*)-4-Benzyl-3-((2*R*,3*S*,*E*)-10-(benzyloxy)-3-(methoxymethoxy)-2-methyldec-6-enoyl)oxazolidin-2-one **304**

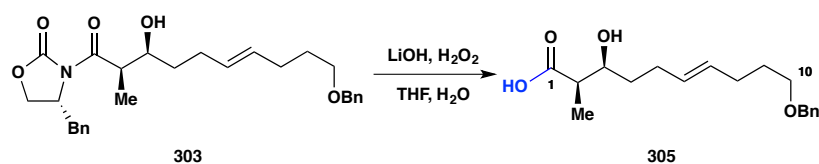


Secondary alcohol **303** (500 mg, 1.08 mmol) was dissolved in THF (1.1 mL) and cooled to 0 °C in an ice-water bath. *N,N*-diisopropylethylamine (0.30 mL, 1.7 mmol) was added, followed by iodomethyl methyl ether (0.14 mL, 1.6 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.11 mmol). The mixture was stirred for 3 hours at room temperature and then heated to reflux for a further 24 hours. The mixture was cooled to room temperature and quenched by addition of an ice-cooled aqueous solution of K₂CO₃ (sat., 10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (4 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, and filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography

(SiO₂, Pentane to 20:80 Et₂O:Pentane, 1% Et₃N added as co-eluent) to give **304** as a colourless oil (471 mg, 86%).

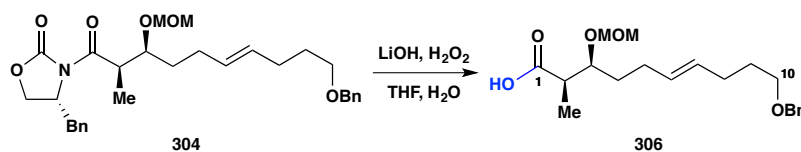
R_f = 0.4 (20:80 Et₂O:Pentane); $[\alpha]_D^{25}$ -45.9 (c = 0.94, CH₂Cl₂); $^1\text{H NMR}$ (400 MHz, CDCl₃) δ_H 7.38–7.31 (6 H, m, ArH $\times$ 6), 7.30–7.24 (2 H, m, ArH $\times$ 2), 7.24–7.19 (2 H, m, ArH $\times$ 2), 5.52–5.34 (2 H, m, C(6)H, C(7)H), 4.69–4.55 (3 H, m, C(3')H, OCH₂OMe), 4.50 (2 H, s, OCH₂Ph), 4.23–4.09 (2 H, m, C(2')H₂), 4.00 (1 H, qd, J = 6.9, 4.2 Hz, C(2)H), 3.82 (1 H, td, J = 6.2, 4.2 Hz, C(3)H), 3.47 (2 H, t, J = 6.5 Hz, C(10)H₂), 3.34 (3 H, s, CH₃OCH₂), 3.31 (1 H, dd, J = 13.5, 3.3 Hz, CHCH_AH_BPh), 2.77 (1 H, dd, J = 13.3, 9.7 Hz, CHCH_AH_BPh), 2.23–1.97 (4 H, m, C(5)H₂, C(8)H₂), 1.77–1.52 (4 H, m, C(4)H₂, C(9)H₂), 1.24 (3 H, d, J = 7.0 Hz, C(2)CH₃); $^{13}\text{C NMR}$ (100 MHz, CDCl₃) δ_C 174.9 (C1'), 153.3 (C1), 138.7 (C_{Ar}CH₂CH), 135.5 (C_{Ar}CH₂O), 130.2 (C6), 130.0 (C7), 129.5 (2 C, C_{Ar} $\times$ 2), 129.1 (2 C, C_{Ar} $\times$ 2), 128.4 (2 C, C_{Ar} $\times$ 2), 127.6 (2 C, C_{Ar} $\times$ 2), 127.5 (C_{Ar}), 127.3 (C_{Ar}), 96.6 (OCH₂OCH₃), 78.8 (C3), 72.9 (OCH₂Ph), 69.8 (C10), 66.1 (C2'), 56.1 (CH₃OCH₂), 56.0 (C3'), 41.5 (C2), 37.8 (CHCH₂Ph), 32.8 (C4), 29.6 (C9), 29.2 (C8), 28.7 (C5), 11.6 (C2-CH₃); $\text{IR } \nu_{\text{max}}$ (film)/cm⁻¹ 2948, 2869, 1780, 1698, 1455, 1381, 1352, 1210, 1108, 1013, 969, 738, 700; HRMS (ESI⁺, m/z) C₃₄H₄₉NO₅NaSi⁺ [M + Na⁺] calculated 532.2670, found 532.2663 (Δ = -1.32 ppm).

(2*R*,3*S*,*E*)-10-(Benzyloxy)-3-hydroxy-2-methyldec-6-enoic acid 305



Lithium hydroxide monohydrate (20 mg, 0.84 mmol) was dissolved in 30 % hydrogen peroxide aqueous solution (0.2 mL) at 0 °C and stirred for 5 minutes. Aldol product **303** (200 mg, 0.42 mmol) was dissolved in tetrahydrofuran (3.2 mL) and added to the mixture dropwise at 0 °C. The reaction was stirred for 1.5 hours at 0 °C before quenched by addition of an aqueous solution of Na₂SO₃ (sat., 0.5 mL), followed by an aqueous solution of NaHCO₃ (sat., 0.5 mL). The organic layers were separated and the aqueous phase was extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 50:50 EtOAc:Pentane, 1% acetic acid as co-eluent) to afford acid **305** as a viscous, colourless oil (203 mg, 97%).

R_f = 0.4 (50:50 EtOAc:Pentane); $[\alpha]_D^{25}$ -5.8 (c = 0.66, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ_H 7.38–7.30 (4 H, m, Ph-ArH × 4), 7.30–7.25 (1 H, m, Ph-ArH), 5.53–5.32 (2 H, m, C(6)H, C(7)H), 4.50 (2 H, s, Bn-CH₂), 3.87 (1 H, dt, J = 7.8, 4.9 Hz, C(3)H), 3.47 (2 H, t, J = 6.5 Hz, C(10)H₂), 2.70 (1 H, qd, J = 7.1, 5.0 Hz, C(2)H), 2.21–2.04 (3 H, m, C(8)H₂, C(5)H_AH_B), 2.04–1.95 (1 H, m, C(5)H_AH_B), 1.76–1.62 (3 H, m, C(9)H₂, C(4)H_AH_B), 1.55 (1 H, dddd, J = 14.3, 9.5, 6.3, 5.2 Hz, C(4)H_AH_B), 1.17 (3 H, d, J = 7.1 Hz, C(2)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 179.7 (C1), 138.6 (C_{Ar}CH₂), 130.5 (C6), 129.6 (C7), 128.4 (C_{Ar} × 2), 127.7 (C_{Ar} × 2), 127.5 (C_{Ar}), 78.8 (C3), 72.9 (Bn-CH₂), 69.7 (C10), 43.0 (C2), 31.9 (C4), 29.5 (C9), 29.1 (C8), 28.7 (C5), 11.1 (C2-CH₃); IR ν_{max} (film)/cm⁻¹ 3558, 2978, 2886, 1709, 1453, 1381, 1241, 1129, 1099, 1032, 835, 737; HRMS (ESI⁺, m/z) C₁₈H₂₄NaO₄⁺ [M + Na⁺] calculated 329.1723, found 329.1718 (Δ = -1.52 ppm).

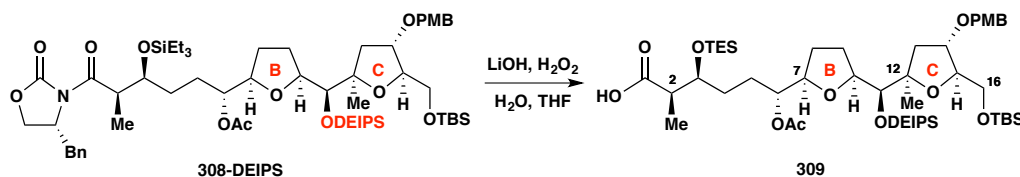
(2*R*,3*S*,*E*)-10-(Benzyloxy)-3-(methoxymethoxy)-2-methyldec-6-enoic acid 306

Lithium hydroxide monohydrate (10 mg, 0.42 mmol) was dissolved in 30 % hydrogen peroxide aqueous solution (0.1 mL) at 0 °C and stirred for 5 minutes. Oxazolidinone **304** (100 mg, 0.21 mmol) was dissolved in THF (0.7 mL) and added dropwise to the mixture. The reaction was stirred for 90 minutes at 0 °C before being quenched by addition of an aqueous solution of Na₂SO₃ (sat., 0.5 mL), followed by an aqueous solution of NaHCO₃ (sat., 0.5 mL). The organic layers were separated and the aqueous phase was extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 50:50 EtOAc:Pentane, 1% acetic acid as co-eluent) to afford acid **306** as a viscous, colourless oil (62 mg, 90%).

R_f = 0.6 (50:50 EtOAc:Pentane); [**α**]_D²⁵ −9.5 (*c* = 0.63, CH₂Cl₂); **¹H NMR** (400 MHz, CDCl₃) **δ_H** 7.38–7.30 (4 H, m, Ph-ArH × 4), 7.30–7.25 (1 H, m, Ph-ArH), 5.53–5.32 (2 H, m, C(6)H, C(7)H), 4.68 (1 H, d, *J* = 6.9 Hz, OCH_AH_BOMe), 4.65 (1 H, d, *J* = 6.9 Hz, OCH_AH_BOMe), 4.50 (2 H, s, Bn-CH₂), 3.87 (1 H, dt, *J* = 7.8, 4.9 Hz, C(3)H), 3.47 (2 H, t, *J* = 6.5 Hz, C(10)H₂), 3.37 (3 H, s, OCH₂OCH₃), 2.70 (1 H, qd, *J* = 7.1, 5.0 Hz, C(2)H), 2.21–2.04 (3 H, m, C(8)H₂, C(5)H_AH_B), 2.04–1.95 (1 H, m, C(5)H_AH_B), 1.76–1.62 (3 H, m, C(9)H₂, C(4)H_AH_B), 1.55 (1 H, dddd, *J* = 14.3, 9.5, 6.3, 5.2 Hz, C(4)H_AH_B), 1.17 (3 H, d, *J* = 7.1 Hz,

C(2)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ_C 179.7 (C1), 138.6 (C_{Ar}CH₂), 130.5 (C6), 129.6 (C7), 128.4 (C_{Ar} × 2), 127.7 (C_{Ar} × 2), 127.5 (C_{Ar}), 96.6 (OCH₂OCH₃), 78.8 (C3), 72.9 (Bn-CH₂), 69.7 (C10), 55.9 (OCH₂OCH₃), 43.0 (C2), 31.9 (C4), 29.5 (C9), 29.1 (C8), 28.7 (C5), 11.1 (C2-CH₃); IR ν_{max} (film)/cm⁻¹ 3567, 2981, 2889, 1708, 1455, 1382, 1240, 1131, 1098, 1032, 967, 737; HRMS (ESI⁺, *m/z*) C₂₀H₃₀NaO₅ calculated 373.19855, found [M + Na⁺] 373.19813 (Δ = -1.13 ppm).

(2*R*,3*S*,6*R*)-6-acetoxy-6-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((diethyl(isopropyl)silyl)oxy)methyl)tetrahydrofuran-2-yl)-2-methyl-3-((triethylsilyl)oxy)hexanoic acid **309**



Lithium hydroxide monohydrate (3.1 mg, 74 μmol) was dissolved in 30 % hydrogen peroxide aqueous solution (0.1 mL) at 0 °C and stirred for 5 minutes. Oxazolidinone **308-DEIPS** (40 mg, 37 μmol) was dissolved in THF (0.2 mL) and added dropwise to the mixture. The reaction was stirred for 90 minutes at 0 °C before being diluted with dichloromethane (3 mL) and quenched by addition of an aqueous solution of Na₂SO₃ (sat., 0.3 mL), followed by an aqueous solution of NaHCO₃ (sat., 0.3 mL). The organic layers were separated and the aqueous phase was extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂, 50:50 EtOAc:Pentane, 1% acetic acid as co-eluent) to afford acid **309** as a viscous, colourless oil (28 mg, 81%).

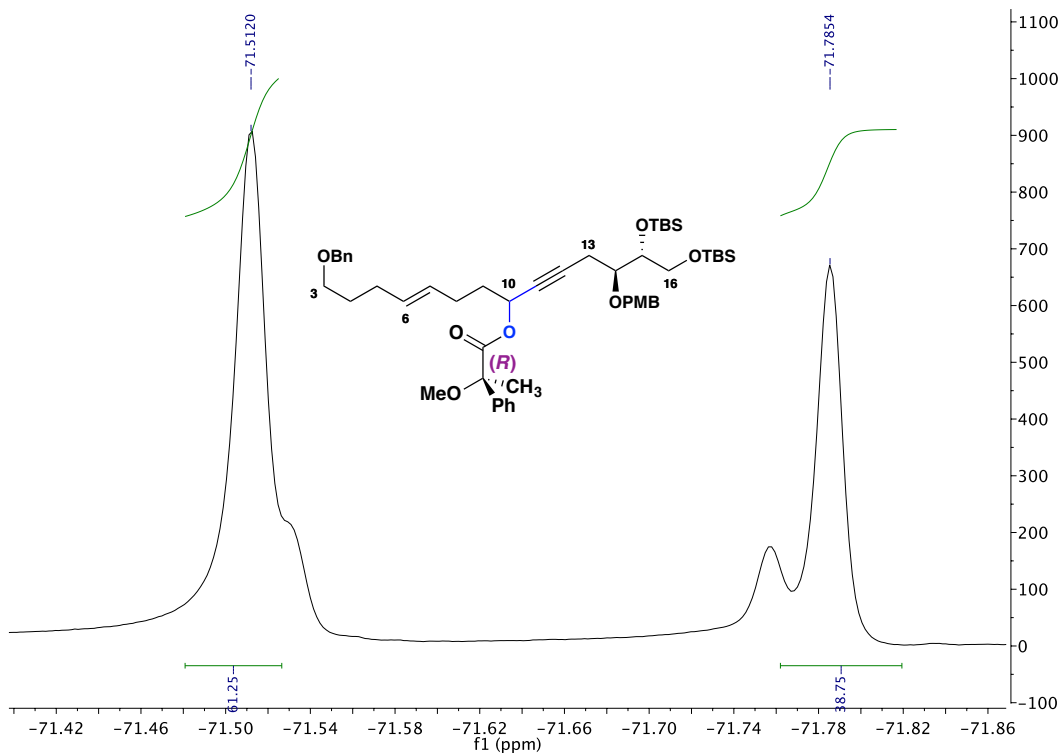
$R_f = 0.5$ (50:50 EtOAc:Petane); $[\alpha]_D^{25} +16.4$ ($c = 0.42$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3)
 δ_{H} 7.25 (2 H, d, $J = 8.4$ Hz, $\text{PMB-ArH} \times 2$), 6.86 (2 H, d, $J = 8.5$ Hz, $\text{PMB-ArH} \times 2$), 4.90
 (1 H, dt, $J = 6.7, 3.5$ Hz, C(6)H), 4.47 (1 H, d, $J = 11.5$ Hz, $\text{PMB-CH}_A\text{H}_B$), 4.40 (1 H, d,
 $J = 11.5$ Hz, $\text{PMB-CH}_A\text{H}_B$), 4.07 (1 H, dt, $J = 6.3, 3.9$ Hz, C(15)H), 4.01 (1 H, dt, $J = 6.6,$
 3.0 Hz, C(14)H), 3.98–3.90 (2 H, m, C(3)H , C(10)H), 3.85 (1 H, d, $J = 1.6$ Hz, C(11)H), 3.79
 (3 H, s, PMB-CH_3), 3.73–3.59 (2 H, m, $\text{C(16)H}_A\text{H}_B$, C(7)H), 3.45 (1 H, dd, $J = 10.4, 6.6$ Hz,
 $\text{C(16)H}_A\text{H}_B$), 3.30–3.22 (1 H, m, $\text{Bn-CH}_A\text{H}_B$), 2.76 (1 H, dd, $J = 13.3, 9.5$ Hz, $\text{Bn-CH}_A\text{H}_B$),
 2.60–2.50 (1 H, m, C(2)H), 2.10 (1 H, dd, $J = 13.3, 7.2$ Hz, $\text{C(13)H}_A\text{H}_B$), 2.05 (3 H, s,
 Ac-CH_3), 1.97–1.89 (1 H, m, $\text{C(9)H}_A\text{H}_B$), 1.89–1.81 (1 H, m, $\text{C(8)H}_A\text{H}_B$), 1.79 (1 H, dd,
 $J = 13.3, 2.5$ Hz, $\text{C(13)H}_A\text{H}_B$), 1.73–1.62 (2 H, m, $\text{C(5)H}_A\text{H}_B$, $\text{C(9)H}_A\text{H}_B$), 1.60–1.48 (3 H, m,
 $\text{C(5)H}_A\text{H}_B$, C(4)H_2), 1.45–1.33 (1 H, m, $\text{C(8)H}_A\text{H}_B$), 1.24 (3 H, s, C(12)CH_3), 1.13 (3 H, d,
 $J = 7.1$ Hz, C(2)CH_3), 1.05–0.92 (22 H, m, $\text{DEIPS-}i\text{PrCH}_3 \times 2$, $\text{DEIPS-EtCH}_3 \times 2$,
 $\text{DEIPS-}i\text{PrCH}$, $\text{TES-CH}_3 \times 3$), 0.89 (9 H, s, $\text{TBS-C(CH}_3)_3$), 0.69–0.49 (10 H, m,
 $\text{DEIPS-EtCH}_2 \times 2$, $\text{TES-CH}_2 \times 3$), 0.06 (6 H, s, $\text{TBS-Si(CH}_3)_2$); $^{13}\text{C NMR}$ (100 MHz, CDCl_3)
 δ_{C} 180.2 (C1), 170.6 (Ac-CO), 159.3 (PMB- $\text{C}_{\text{Ar}}\text{OMe}$), 130.7 (PMB- $\text{C}_{\text{Ar}}\text{CH}_2$), 129.3
 (PMB- $\text{C}_{\text{Ar}} \times 2$), 113.9 (PMB- $\text{C}_{\text{Ar}} \times 2$), 85.2 (C12), 84.5 (C15), 81.0 (C14), 80.1 (C10),
 78.7 (C7), 78.3 (C11), 74.9 (C6), 73.8 (C3), 71.2 (PMB- CH_2), 64.0 (C16), 55.4 (PMB- CH_3),
 44.4 (C2), 42.2 (C13), 29.9 (C4), 28.1 (C8), 27.5 (C5), 26.1 ($\text{TBS-C(CH}_3)_3$), 24.3 (C9),
 22.2 (C12- CH_3), 21.1 (Ac- CH_3), 18.5 ($\text{TBS-C(CH}_3)_3$), 17.8 ($\text{DEIPS-}i\text{PrCH}_3$), 17.7
 ($\text{DEIPS-}i\text{PrCH}_3$), 13.4 ($\text{DEIPS-}i\text{PrCH}$), 12.0 (C2- CH_3), 7.5 (DEIPS-EtCH_3), 7.5
 (DEIPS-EtCH_3), 6.9 (3 C, $\text{TES-CH}_3 \times 3$), 5.1 (3 C, $\text{TES-CH}_2 \times 3$), 4.7 (DEIPS-EtCH_2),

4.4 (DEIPS-EtCH₂), -5.2 (TBS-SiCH₃), -5.3 (TBS-SiCH₃); **IR** ν_{max} (film)/cm⁻¹ 3559, 2983, 2887, 1711, 1463, 1380, 1255, 1149, 1032, 968; **HRMS** (ESI⁺, m/z) C₄₇H₈₆NaO₁₁Si₃⁺ [M + Na⁺] calculated 933.53701, found 933.53638 (Δ = -0.67 ppm).

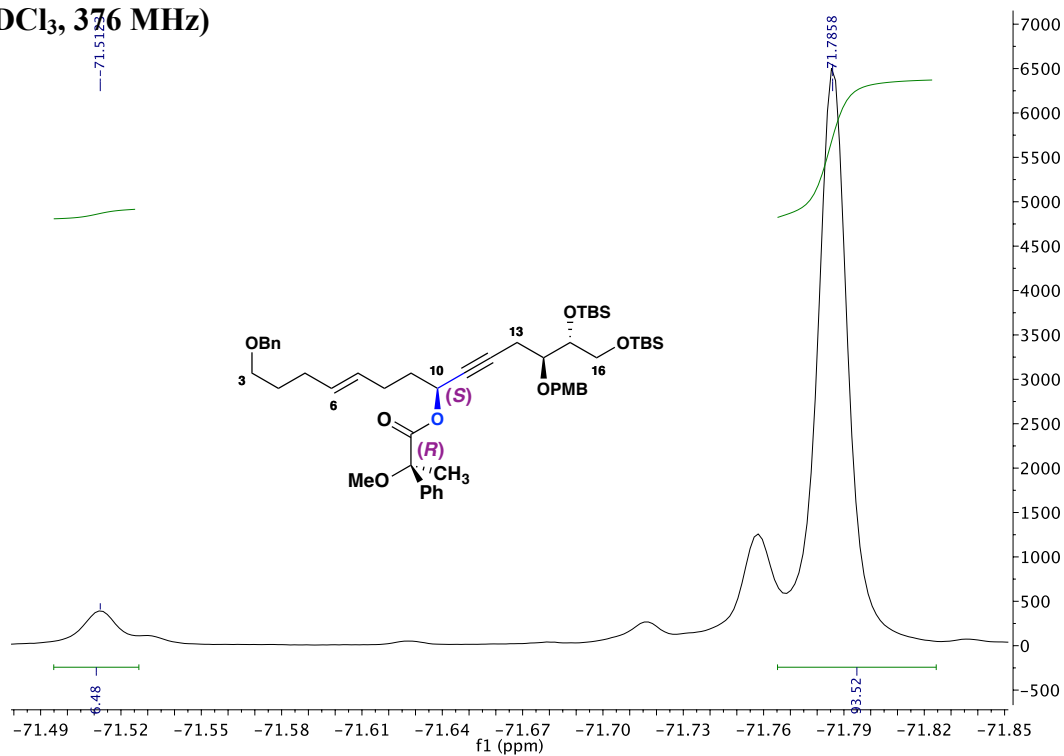
Appendix

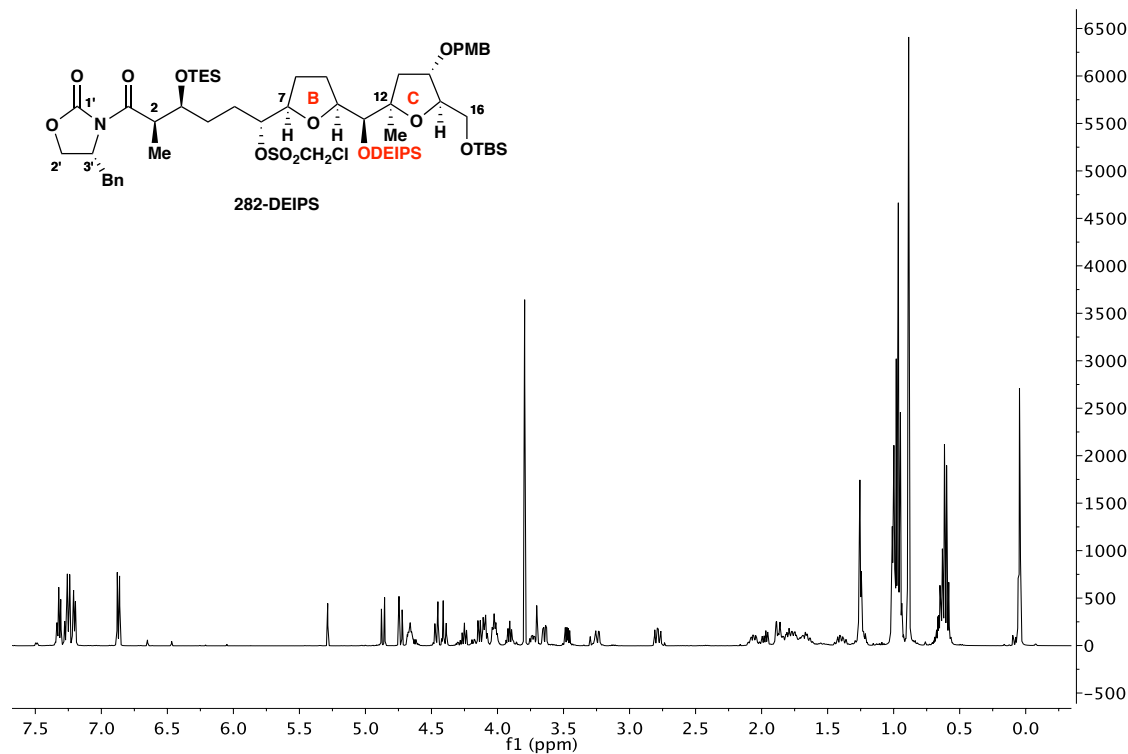
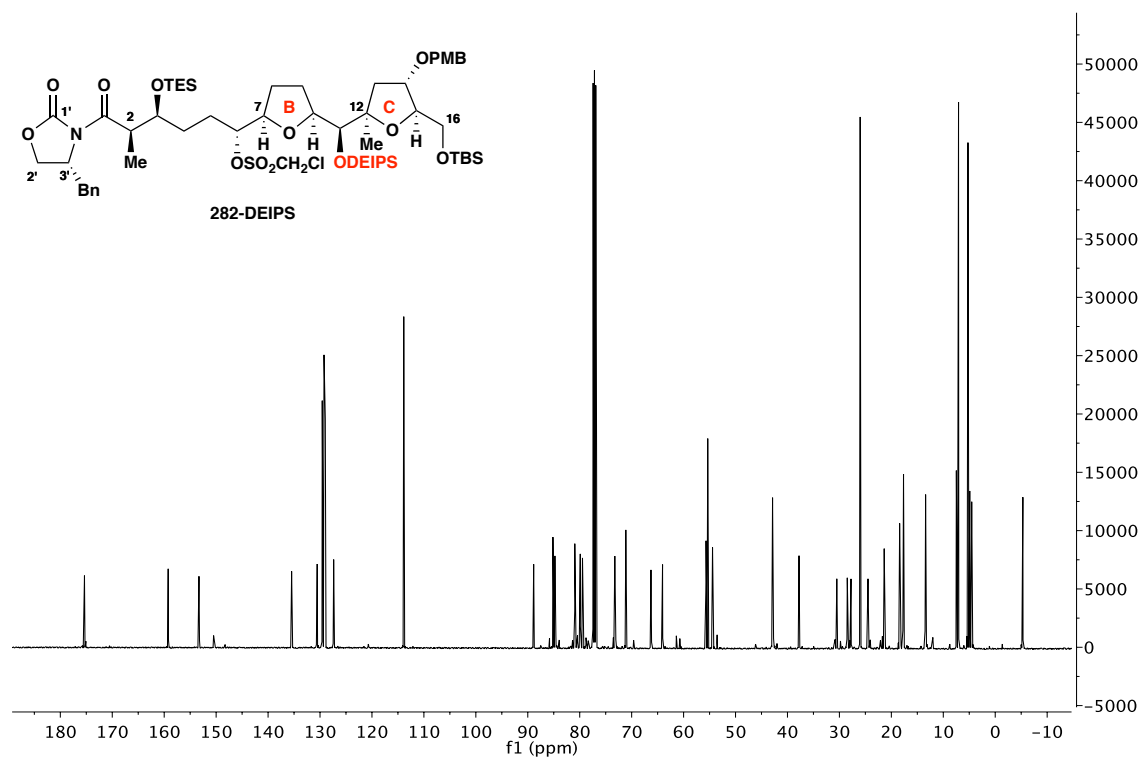
Selected NMR spectra

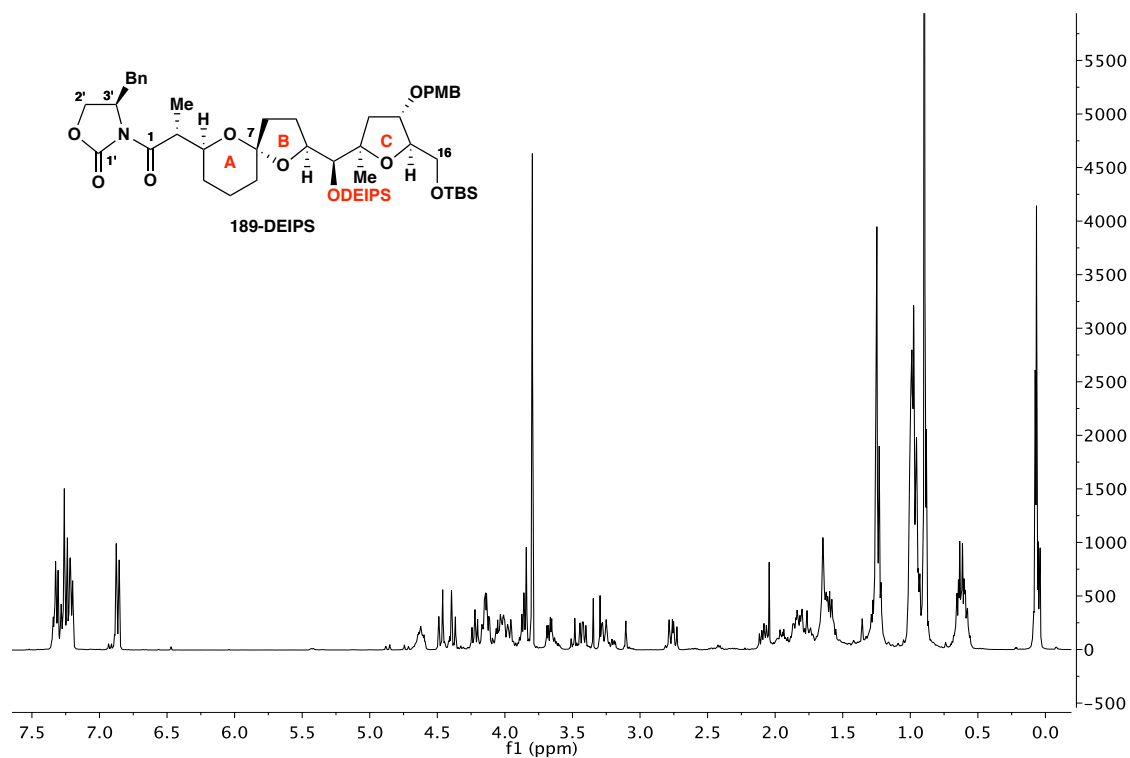
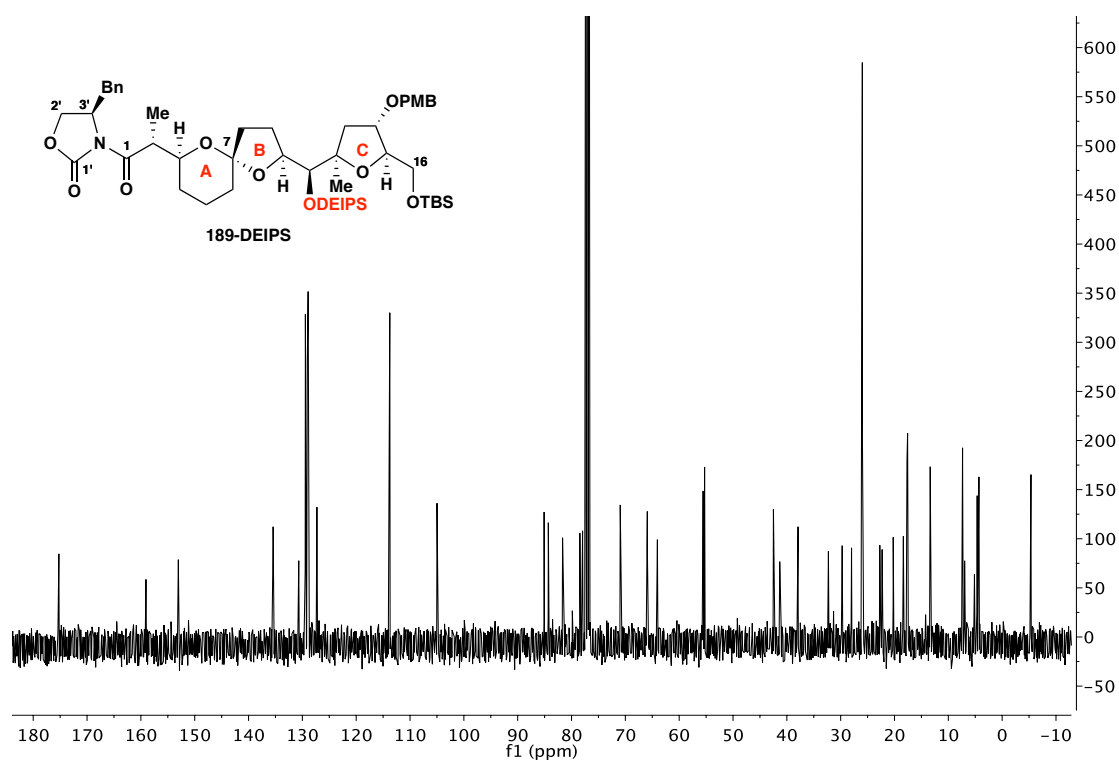
Mosher's ester analysis of Carreira alkynylation product 10-(*R/S*)-222 (CDCl_3 , 376 MHz)

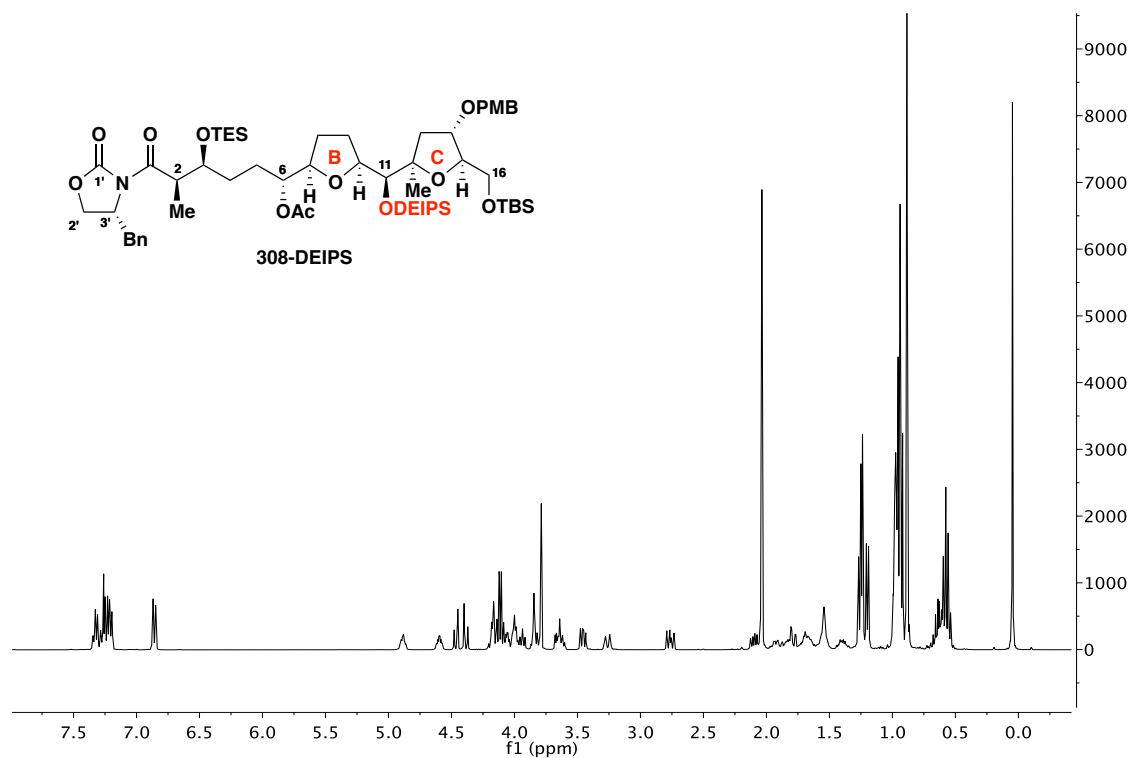
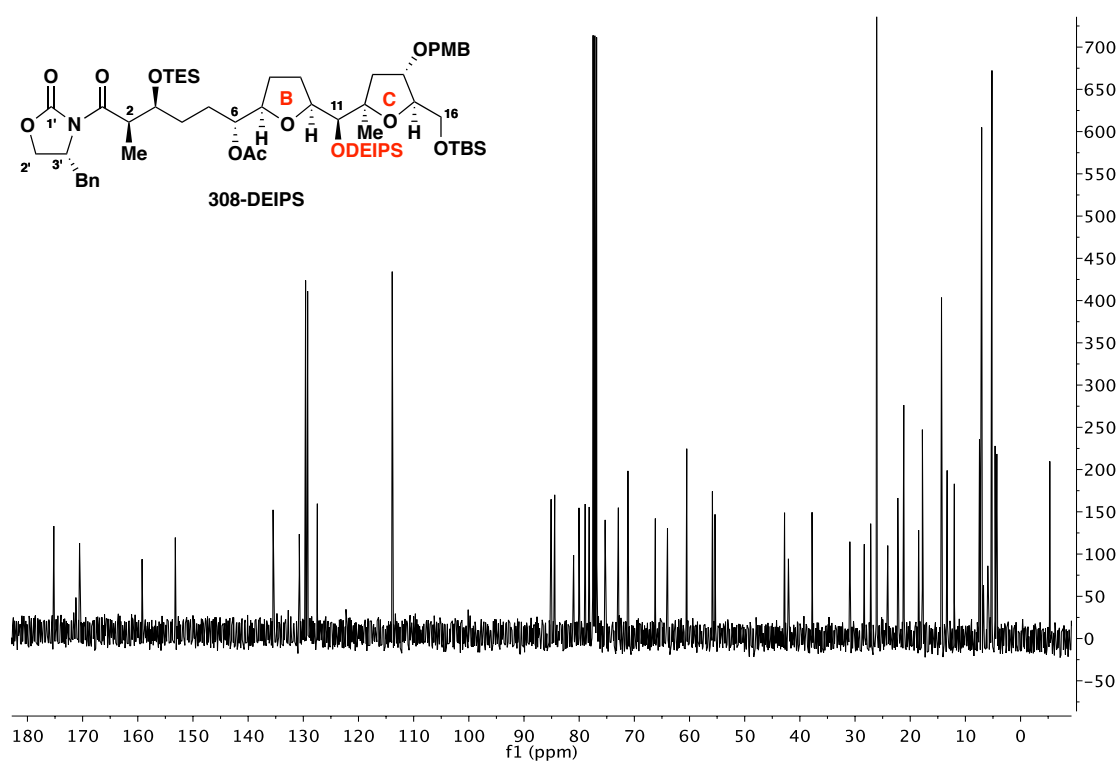


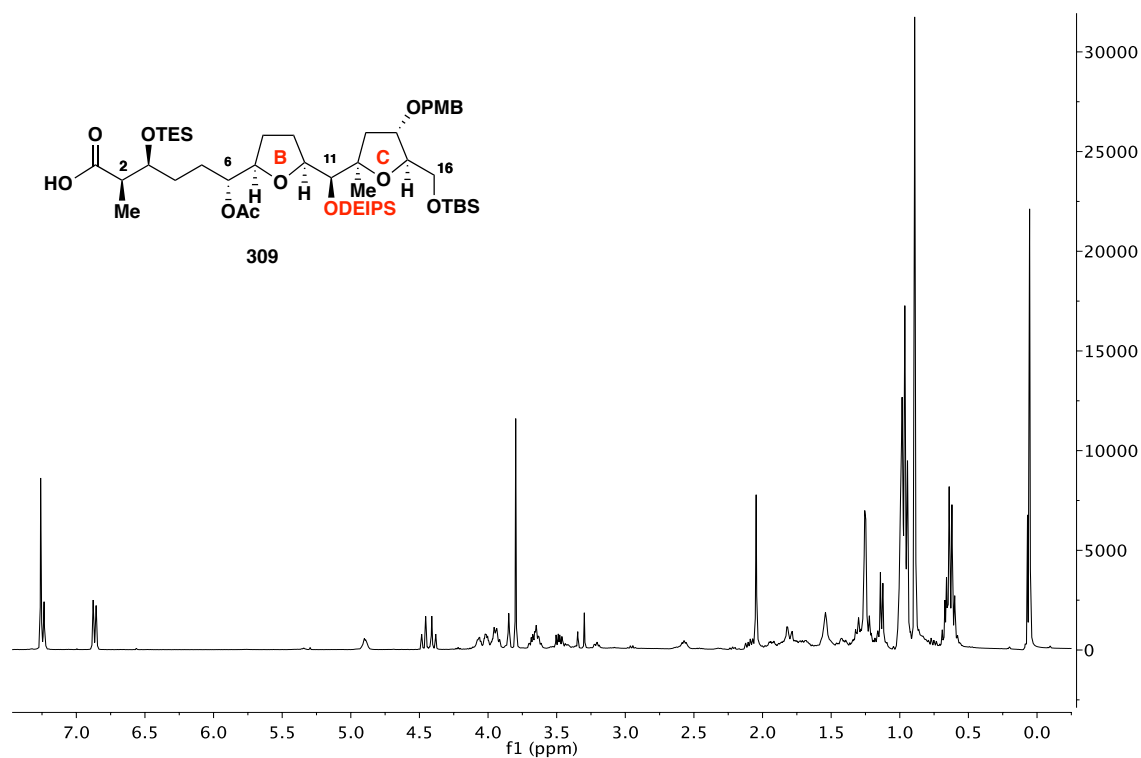
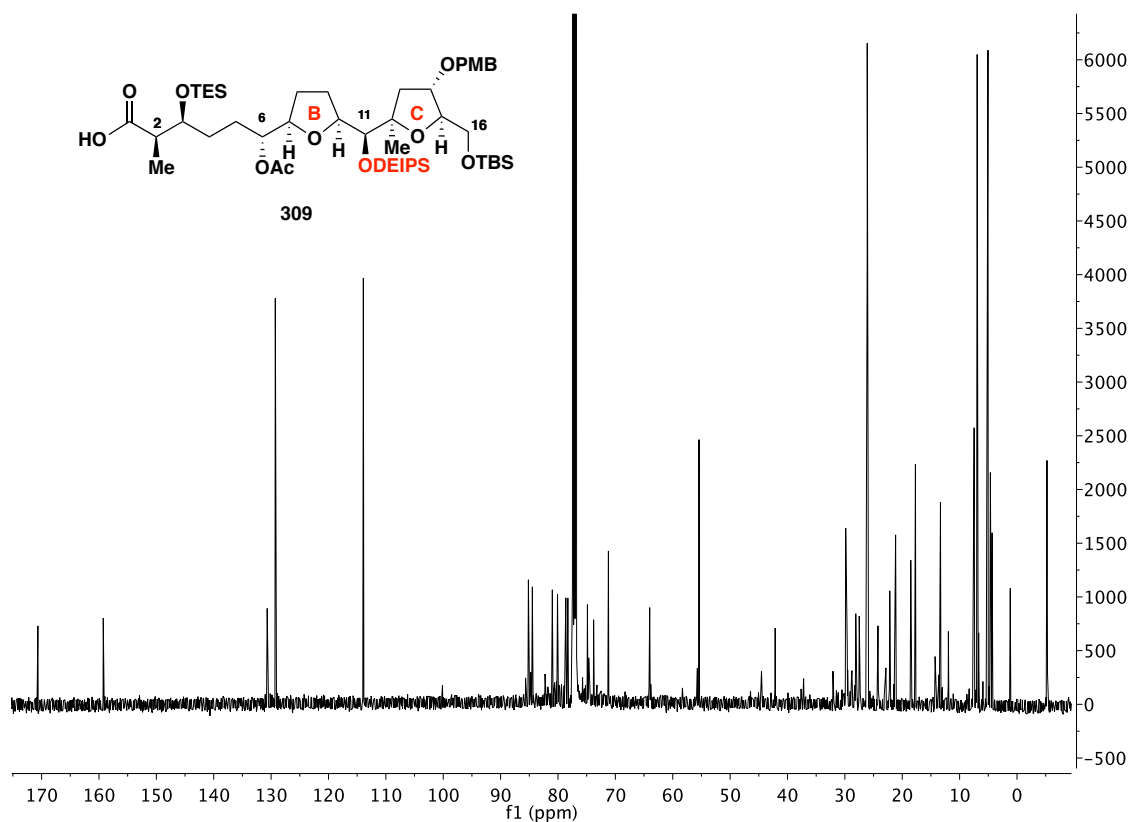
Mosher's ester analysis of Carreira alkynylation product 222 (20 g scale reaction, CDCl_3 , 376 MHz)



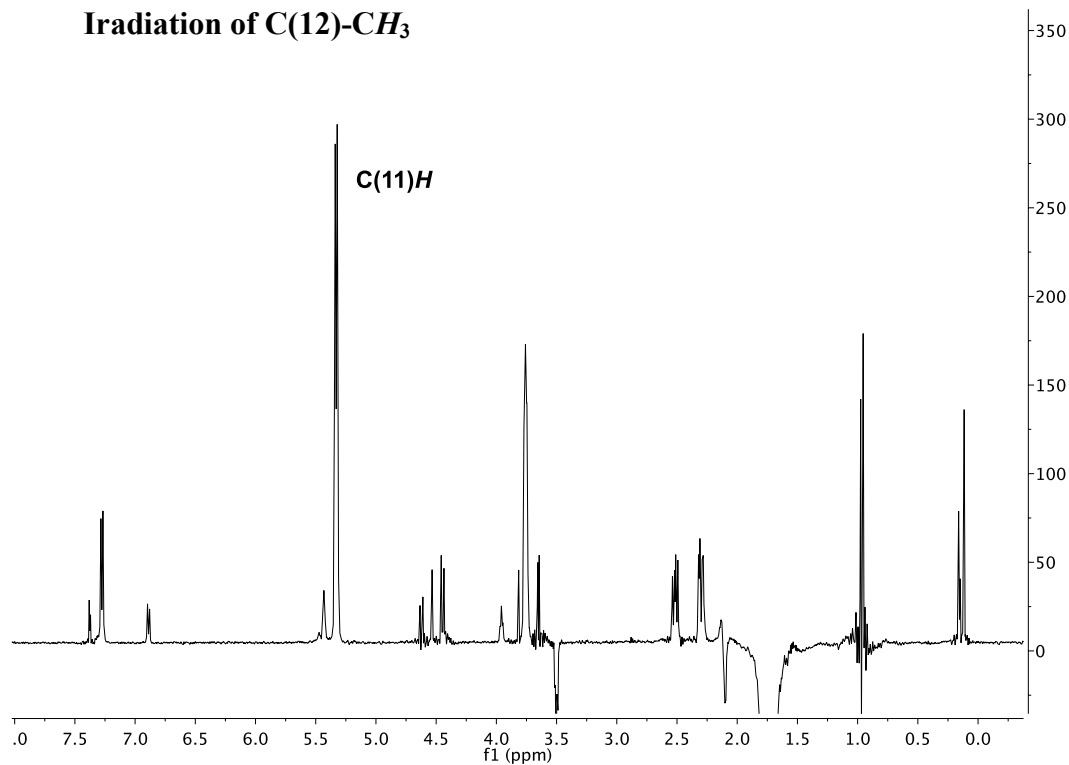
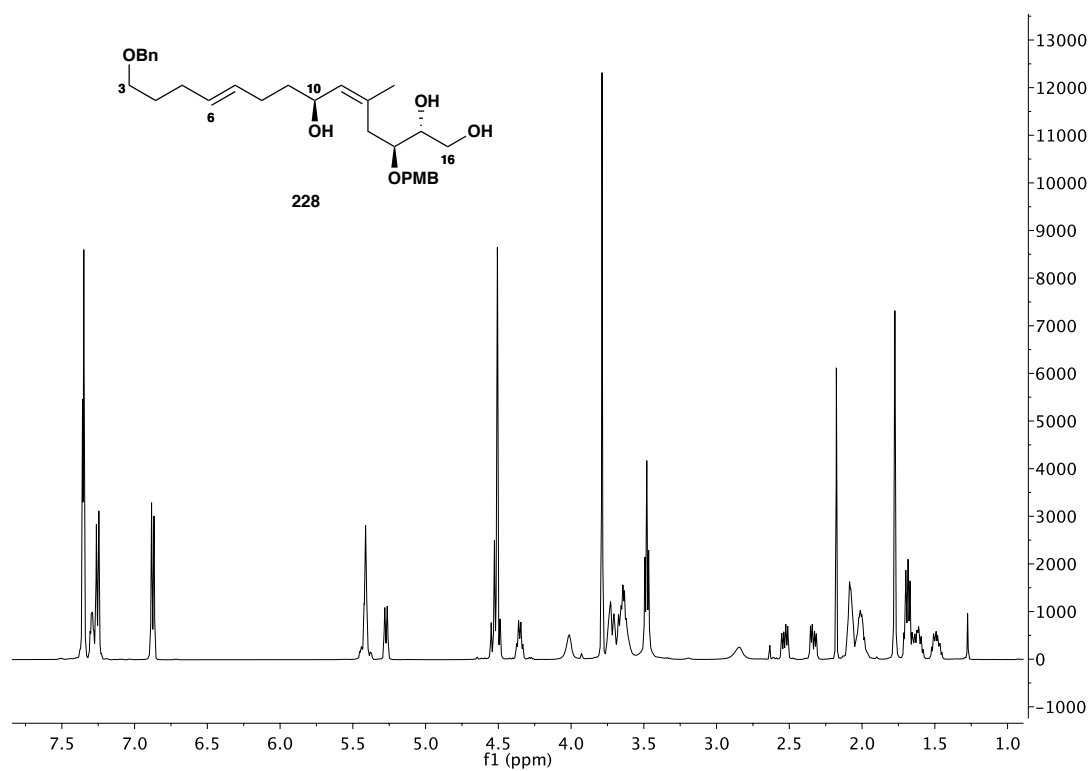
^1H NMR of chloromethanesulfonate 282-DEIPS (CDCl_3 , 500 MHz) **^{13}C NMR of chloromethanesulfonate 282-DEIPS (CDCl_3 , 125 MHz)**

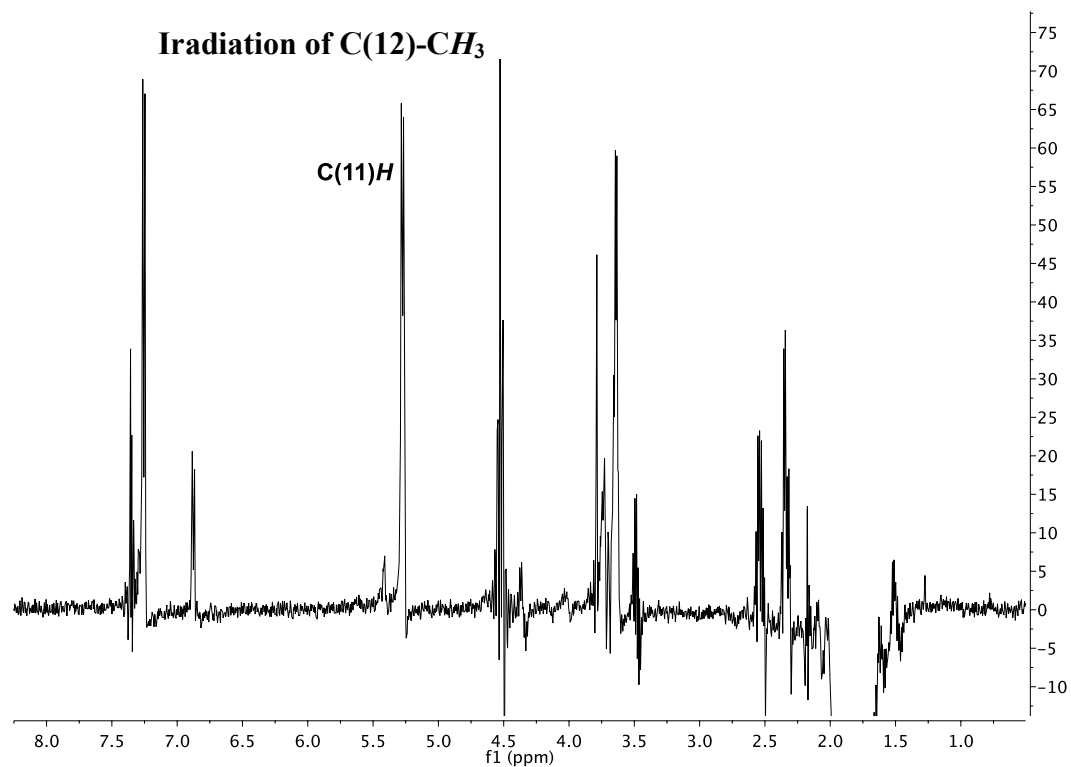
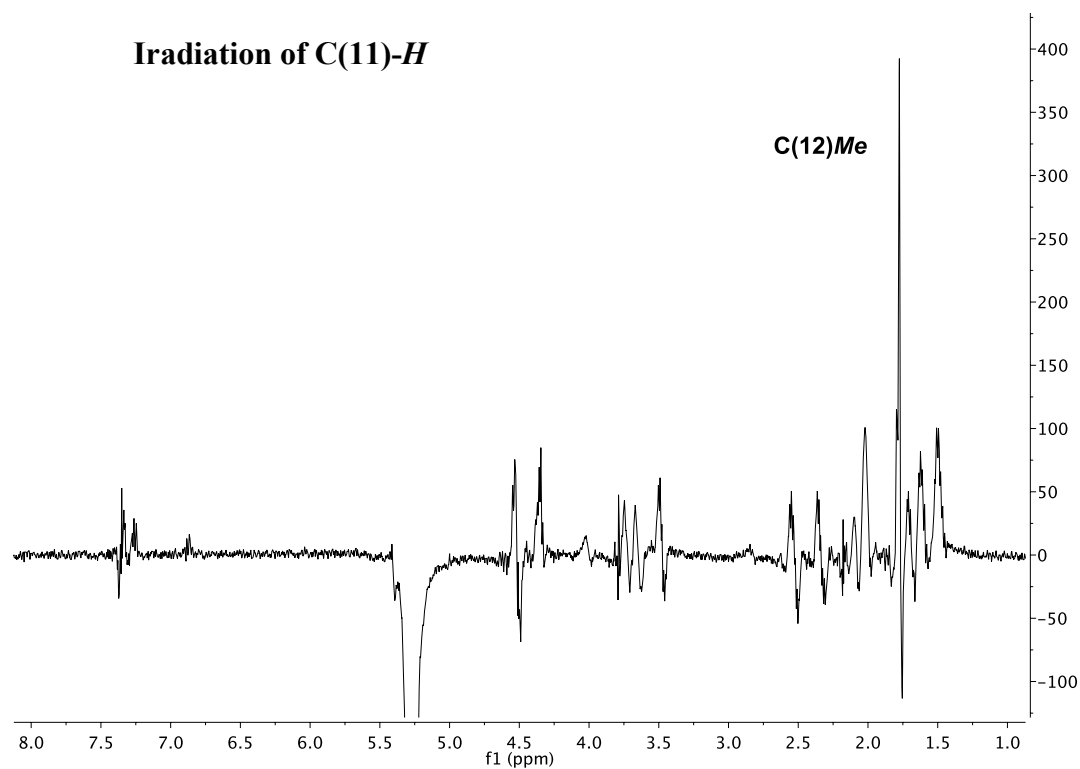
^1H NMR of spiroketal 189-DEIPS (CDCl_3 , 400 MHz) **^{13}C NMR of spiroketal 189-DEIPS (CDCl_3 , 100 MHz)**

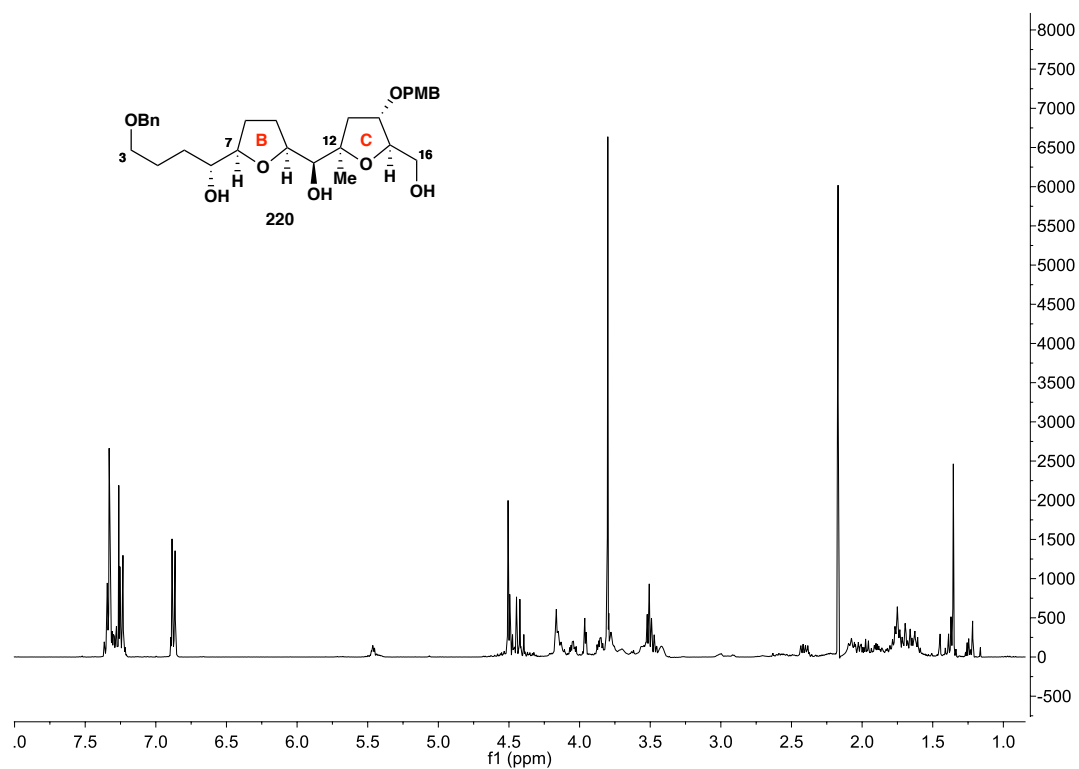
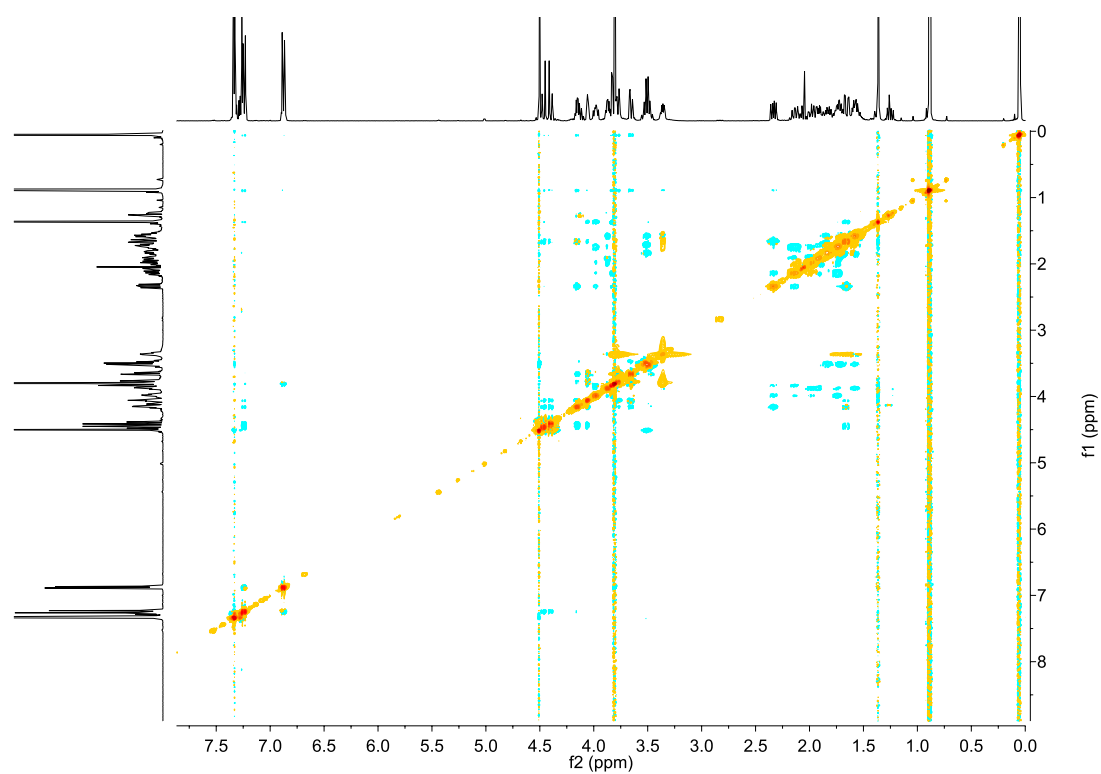
^1H NMR of acetate 308-DEIPS (CDCl_3 , 400 MHz) **^{13}C NMR of acetate 308-DEIPS (CDCl_3 , 100 MHz)**

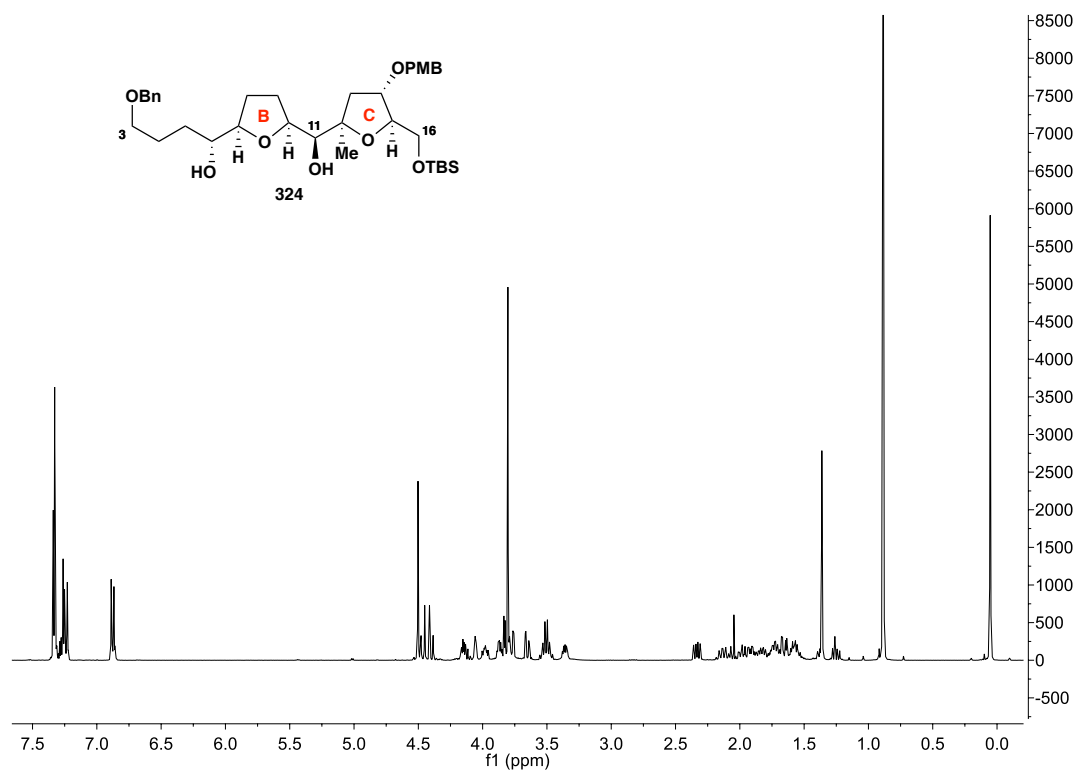
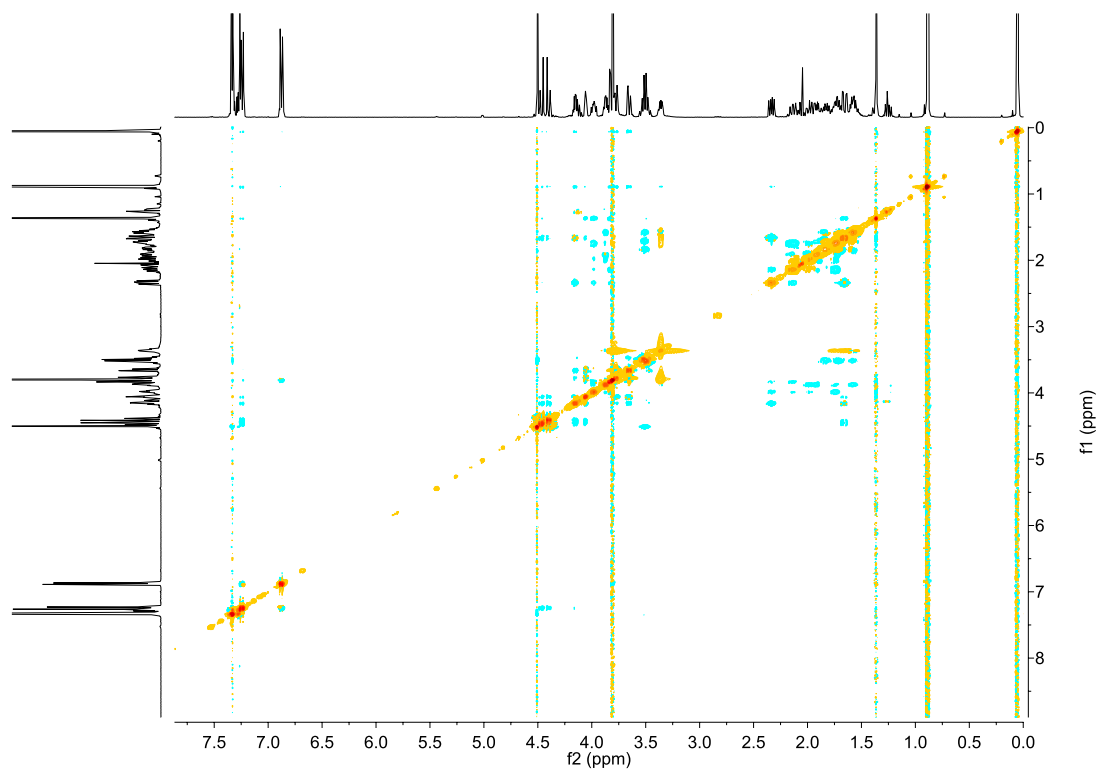
^1H NMR of oxazolidinone cleavage product 309 (CDCl_3 , 400 MHz) **^{13}C NMR of oxazolidinone cleavage product 309 (CDCl_3 , 100 MHz)**

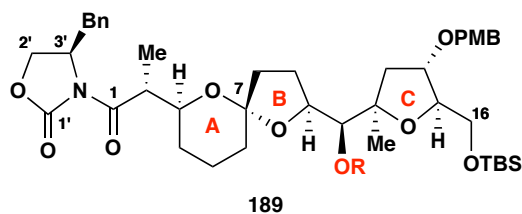


Irradiation of C(12)-CH₃¹H NMR spectra of oxidative cyclisation precursor 228

1D *n*Oe spectra of oxidative cyclisation precursor 228

^1H NMR of oxidative cyclisation product 220 (CDCl_3 , 400 MHz)**NOESY spectrum of oxidative cyclisation product 220 (CDCl_3 , 400 MHz)**

^1H NMR of primary TBS protection product 324 (CDCl_3 , 400 MHz)**NOESY spectrum of primary TBS protection product 324 (CDCl_3 , 400 MHz)**

Comparison of ^{13}C NMR data between spiroketal 189-DEIPS and 189-TBS

Carbon	189-DEIPS (ppm)	189-TBS (ppm) ⁶⁶	Difference (Δ ppm)
1	175.2	175.3	-0.1
2	42.5	42.6	-0.1
3	70.9	71.0	-0.1
4	28.0	28.1	-0.1
5	20.2	20.3	-0.1
6	32.3	32.2	+0.1
7	105.1	105.1	0
8	38.0	38.1	-0.1
9	22.7	22.8	-0.1
10	77.9	78.0	-0.1
11	78.5	78.2	+0.3
12	85.1	85.2	-0.1
13	41.3	41.6	-0.3
14	81.7	not reported	
15	84.3	84.5	-0.2
16	64.0	64.3	-0.3

C(2)CH₃	13.3	13.5	-0.2
C(12)CH₃	22.3	22.4	-0.1
1'	153.0	153.2	-0.2
2'	65.9	66.0	-0.1
3'	55.5	55.7	-0.2
BnCH₂	37.9	38.0	-0.1
BnC_{Ar}	135.4, 129.1,	135.6, 129.2,	-0.2, -0.1
	128.9, 127.3	129.1, 127.4	-0.2, -0.1
PMBCH₂	70.9	71.1	-0.2
PMBOCH₃	55.3	55.4	-0.1
PMBC_{Ar}	159.1, 130.7,	159.2, 130.8,	-0.1, -0.1,
	129.4, 113.8	129.6, 113.9	-0.2, -0.1
TBS-C(CH₃)₃			
(C16)	18.4	18.4	0
TBS-C(CH₃)₃			
(C16)	26.0	26.1	-0.1
TBS-SiCH₃			
(C16)	-5.3, -5.3	-5.1, -5.2	-0.2, -0.1
DEIPS-<i>i</i>PrCH₃	17.7, 17.6	-	-
DEIPS-<i>i</i>PrCH	13.3	-	-
DEIPS-EtCH₃	7.4, 7.3	-	-
DEIPS-EtCH₂	4.6, 4.3	-	-

TBS-C(CH₃)₃	-	18.5	-
(C16)			
TBS-C(CH₃)₃	-	26.2	-
(C16)			
TBS-SiCH₃	-	-3.3, -4.1	-
(C16)			

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