Towards the Total Synthesis of (+)-Lophotoxin

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Doctor of Philosophy

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Declaration

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

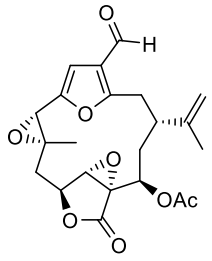
Oskar Hoff

University of Oxford, Trinity Term 2021

Abstract

Chapter 1: Introduction

This chapter gives an overview of the furanocembranoid family of natural products, and its most prominent member (+)-lophotoxin. Biosynthetic, biological, and structural properties, as well as interconversion and synthetic studies are discussed. The chapter ends with a research proposal and lays out the synthetic strategy which was developed to approach this project.



lophotoxin

Chapter 2: Synthesis of the right-hand furan fragment and model furans

This chapter describes the retrosynthesis and forward synthesis of several furan fragments used in our approach to lophotoxin. The organocatalytic Baylis–Hillman reaction to introduce the secondary alcohol alcohol at position *C*-13 stereoselectively, as well as the RCM-based furan methodology to introduce the core furan heterocycle, are described as key steps.

Chapter 3: Cross-coupling approaches for fragment linkage

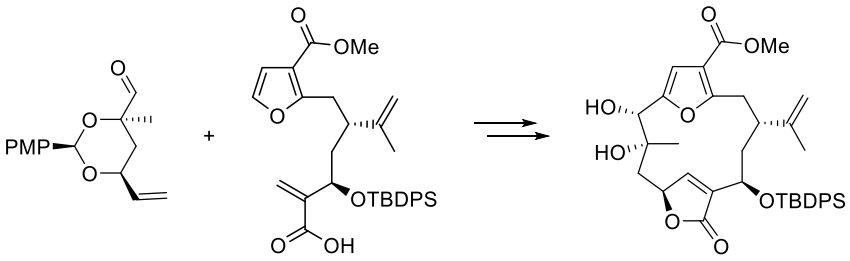
This chapter discusses the synthesis of literature-known vinyl iodide, intended as the left-hand fragment, and attempts to couple it with various furan fragments *via* cross-coupling methods. The biggest challenge was a competing intramolecular Heck reaction.

Chapter 4: Synthesis of aldehyde left-hand fragments

This chapter details the restrosynthesis and forward synthesis of several aldehyde fragments, intended for an alternative fragment coupling strategy. The crucial Sharpless dihydroxylation of a 1,1-disubstituted olefin to introduce the tertiaty alcohol at position *C*-8 stereoselectively is discussed. The stereochemical assignment of *C*-8 and different protecting group strategies are summarised.

Chapter 5: Fragment coupling and synthesis of the carbon skeleton

This chapter depicts coupling reactions of furan and aldehyde fragments. Shiina macrolactonisation and RCM-mediated butenolide synthesis are reported as key steps to provide the carbon skeleton of (+)-lophotoxin. Different protecting group strategies are evaluated for their efficiency.



aldehyde fragment | furan fragment | synthesised carbon skeleton

Chapter 6: Experimental procedures and supporting Information

This chapter lists all procedures for experiments described in this thesis. Additionally, all spectral data for the characterisation of synthesised compounds are given.

Acknowledgements

Firstly, I must thank Prof. Tim Donohoe for his supervision. Entrusting such a project to me, I felt very comfortable with the compromise between independent work and expedient guidance. Most memorable to me, however, is “Big Tim’s” contagious enthusiasm for the subject of chemistry and his never-ending patience to talk about it. Thank you!

I also want to thank my industrial supervisor, Dr. Mark Healy, whose support from a practical perspective was invaluable to me. Prof. Darren Dixon, thank you for supervising me during my SBM rotation project. Additionally, I want to thank the entire SBM team – Prof. Martin Smith, Dr. Lara Lourenço Venda, Laura Thomas, and Dr. Maitane Fernandez Chento – for organising this program. I really enjoyed the cohesion within the program and especially within my cohort. I also have a lot of gratitude for all the technical support within the CRL: I want to thank Prof. Tim Claridge and Dr. Nader Amin for helping with NMR problems; Maria Marshall and Tina Jackson for running NMRs in the first place; Prof. James McCullagh and Dr. Victor Mikhailov for their mass-spec service; as well as Ron, Colin, and Jude for fixing pretty much anything instantly.

There are so many memories with members of the Donohoe group that I am grateful for. It is hardly possible for words to do them justice. Within Team Lophotoxin, Johannes, thanks for handing over your project in such an organised manner and all the mentoring you provided even after leaving. Dana, it was exceptional to work with you. Still, it will be hard for me to accept that you will not be a Part II student at some point anymore. Nik, thanks for all your help at the end and for taking over this beast. Best of luck!

I was very fortunate to have a lot of post-doctoral support in the lab during my DPhil: James, Maria, Hamish, Marvin, Nik, and especially Roly and Simon, thanks for always being approachable and for making sure the lab was running smoothly.

The day-to-day working environment in the lab was always important to me. Mel, Johannes, Sandra, Chris D., and Waz, it was great to join such a pleasant and productive environment in F7. Timmy and Chris, we must have spent most hours together in the lab. I am very glad I shared this journey with such gifted and outstanding individuals as the two of you are. Ciaran, apologies for sometimes being rough with you. I hope you know that it came from a good place. Dani, it was a pleasure to work with and next to you. I am glad you joined F7. Bruno and Lydia, it always made me happy to see one of you when I came over to F8 (a solid *5.5* on a scale from *2* to *7*.) Dana, maybe you are a DPhil student now. I might consider that possibility (when Big Tim is comfortable with you using *t*BuLi). Best of luck to all of you!

I am thankful to all the proofreaders of this thesis: Roly, Nik, Dani and especially Timmy, who read the whole thing.

Outside the lab I was fortunate enough to meet very fascinating people during my time in Oxford. I am grateful for the people I met within the Wadham MCR, especially from my first year. Also, the members of the university’s basketball club, especially Felix, Alex, and Danny. I will miss our work-out sessions. Dana, Timmy, and Simon, I hope our card nights will become a long-lasting tradition.

Finally, I want to thank my parents, Karen and Kurt, who always supported me throughout this long stretch of education. I would not have made it this far without your help and encouragement. Danke!

Abbreviations and Acronyms

°	Degrees
Å	Ångström
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aryl
App.	Apparent
aq.	aqueous
α-ICPN	Alpha-iscopreine
β-ICD	Beta-isocupreidine
Bu	Butyl
C	Celsius
CBS	Corey–Bakshi–Shibata
CD	circular dichroism
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
Cys	Cysteine
δ	Chemical shift
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DIC	*N*,*N*'-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	*N,N'*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
ent	Enantiomer
epi	Epimer
eq	Equivalent(s)
ESI	Electrospray Ionisation
Et	Ethyl
FT-IR	Fourier-transform infrared
dr	Diastereomeric ratio
HG II	Hoveyda-Grubbs 2nd generation

HFIP	Hexafluoroisopropyl
HMPA	Hexamethylphosphoramide
Hz	Hertz
i	*Iso*
IBX	2-Iodoxybenzoic acid
J	Coupling constant
ν_{max}	FT-IR absorption maximum
LD_{50}	Median lethal dose
LDA	Lithium diisopropylamide
M	Molar (mol/L)
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
Mes	Mesityl
MNBA	2-Methyl-6-nitrobenzoic anhydride
mol%	Mole percent
MS	Molecular sieves
n	normal
NBS	*N*-Bromosuccinimide
NHK	Nozaki–Hiyama–Kishi
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhouser Effect
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
Pr	Propyl
quant.	Quantitative
R	Generic group
rac	Racemate
RCM	Ring-closing metathesis
rpm	Rounds per minute
rsm	Recovered starting material
rt	Room temperature
SAD	Sharpless asymmetric dihydroxylation
sat.	Saturated
SET	single electron transfer
SPS	Solvent purification system
t	*Tertiary*
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*t*-Butyldiphenylsilyl
TBS	*t*-Butyldimethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THT	Tetrahydrothiophene
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TMSE	(Trimethylsilyl)ethyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl
TST	Temporary silicon tether
Tyr	Tyrosine
UV	Ultraviolet
wrt.	With respect to
wt%	Weight percent

Chapter 1

Introduction

1 Introduction

The identification, isolation and total syntheses of natural products have fascinated biologists, biochemists, and organic chemists for decades. The often complex structures of secondary metabolites have intellectual appeal and put analytical and synthetic methods available to the test. Most important, however, is their impact on the healthcare industry. The majority of all small molecule drugs on the market today are natural products, natural product derivatives, or compounds containing pharmacophores discovered in natural products.[1] Blockbuster drugs like the analgesic agent morphine, the antibiotic penicillin, and the chemotherapeutic agent paclitaxel (trade name: Taxol®) were originally discovered in nature, then synthesised in laboratories and are now used on a daily basis to treat patients.

1.1 Furanocembranoids

Lophotoxin (**1**) and lophodiol B (**2**) are two prominent members of the furanocembranoids, a family of diterpenoid natural products isolated from marine corals (**Figure 1**).[2] Furanocembranoids bear the eponymous furan heterocycle between positions *C*-3 and *C*-6 embedded in the 14-membered carbocycle of the cembrane framework (**3**). Related diterpenoid secondary metabolites such as providencianes (**4**), pseudopteranes (**5**), gersolanes (**6**), bielschowskyanes (**7**) and intricaranes (**8**) bear contracted macrocycles or have additional transannular carbon-carbon bonds and have often been isolated together with furanocembranoid natural products.[3] All of these related groups of natural products have received wide attention in the synthetic, biosynthetic, and pharmacological communities.[4-5]

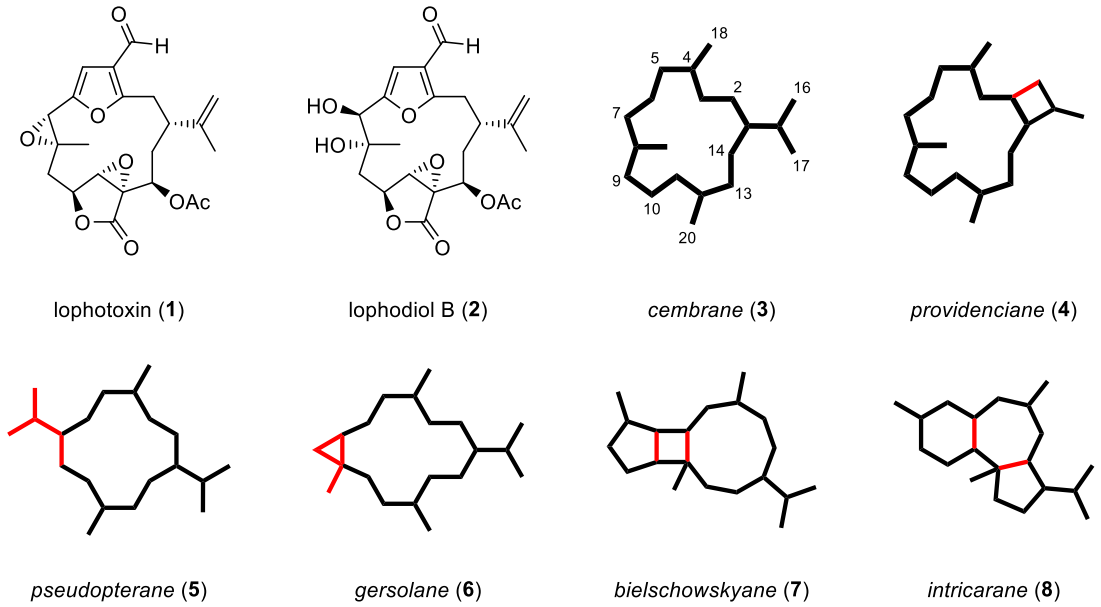
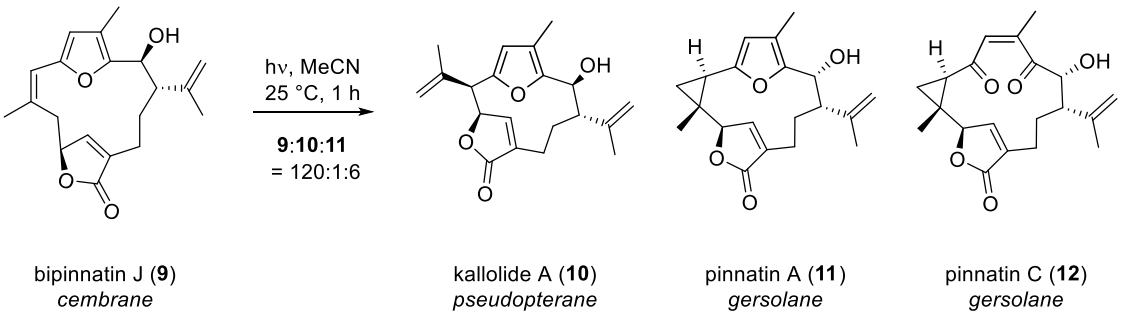


Figure 1 Furanocembranoid natural products (+)-lophotoxin (**1**) and lophodiol B (**2**) as well as the cembrane (**3**), providenciane (**4**), pseudopterane (**5**), gersolane (**6**), bielschowskyne (**7**) and intricarane (**8**) carbon skeletons.

Experimental evidence for a biosynthetic link between furanocembranoids, pseudopteranes and gersolanes was first provided by Rodríguez and co-workers (**Scheme 1**).[6] Upon treatment with light, the cembrane bipinnatin J (**9**) underwent a photochemical [1,3]-sigmatropic rearrangement with retention of configuration at the migrating butenolide group (*C*-10) and the pseudopterane kallolide A (**10**) as well as the gersolanes pinnatin A (**11**) and C (**12**) were observed. This process was later analysed in depth and expanded to other furanocembranoids by Pattenden and co-workers.[7-8] Building on this work, the transformation was synthetically exploited by Mulzer and co-workers in the total synthesis of 11-gorgiacerol (chapter 1.2.9).



Scheme 1 Photochemical suprafacial [1,3]-sigmatropic rearrangement of cembrane **9** by Rodríguez and co-workers.[6]

Although there are multiple biological as well as synthetic connections to related classes of natural products, this chapter will focus mainly on cembranes, in particular

furanocembranoids. Informative and interesting reviews on these were published by the groups of Trauner,[2] Kerr,[5] Rodríguez,[6] Pattenden,[9-10] and Stoltz.[4]

1.1.1 (+)-Lophotoxin

(+)-Lophotoxin (**1**), a highly oxidised furanocembranoid, was first isolated and characterised in 1981 by Fenical and co-workers from soft corals of the genus *Lophogorgia* harvested in the Pacific Ocean.[11] The structure and relative configuration of **1** was later confirmed *via* X-ray crystallography by Riguera and co-workers (**Figure 2**).[12] Due to its complexity and unique biological activity (*vide supra*) **1** was the target for multiple synthetic campaigns as demonstrated in Chapter 1.2. Nevertheless, a successful total synthesis of (+)-lophotoxin (**1**) remains elusive to date.

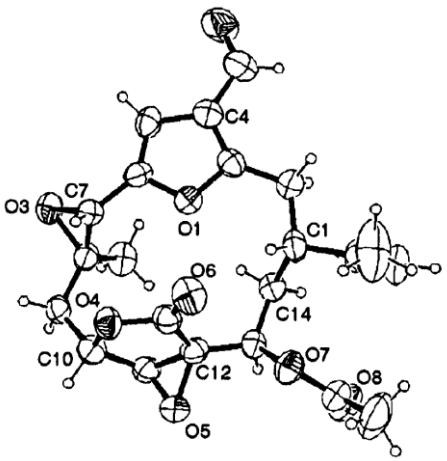


Figure 2 X-ray crystal structure of (+)-lophotoxin (**1**) with 30% thermal probability ellipsoids by Riguera and co-workers proofing the relative configuration. The figure was modified from the original publication.[12]

(+)-Lophotoxin (**1**) is synthesised by the stationary coral as a defence and paralysing agent. The neurotoxin acts as an irreversible inhibitor for the nicotinic acetylcholine receptor (nAChR), which is a membrane receptor for the neurotransmitter acetylcholine and an ion channel functioning as a communicational link between nerve and muscle cells.[13] In their original publication, Fenical and co-workers reported an LD_{50} of 8.0 µg/g for subcutaneous injection in a mouse study.[11] In subsequent tritium-labelling studies Palmer and co-workers identified that lophotoxin (**1**) covalently binds Tyr^{190} of the

nAChR's α-subunit.[14-15] Extensive structure–activity relationship (SAR) studies showed that analogues of **1** with modifications at positions *C*-1, *C*-2, *C*-4 and *C*-13 (marked as R in **Figure 3**) still induced irreversible nAChR-inhibition.[16] Moreover, an analogue containing a plain butenolide instead of the epoxide at *C*-11/*C*-12 was active as well. The *C*-7/*C*-8 epoxide and the *C*-20 lactone, however, proved crucial as altering these functionalities averted covalent inhibition. Thus, the authors proposed a binding mode shown in **Figure 3**. The lactone (*C*-20) mimics the acetyl group of acetylcholine and interacts with Cys^{192}. The hydroxyl group of Tyr^{190}, which is located within the quaternary ammonium binding subsite, attacks the *C*-7/*C*-8 epoxide nucleophilically resulting in irreversible alkylation.

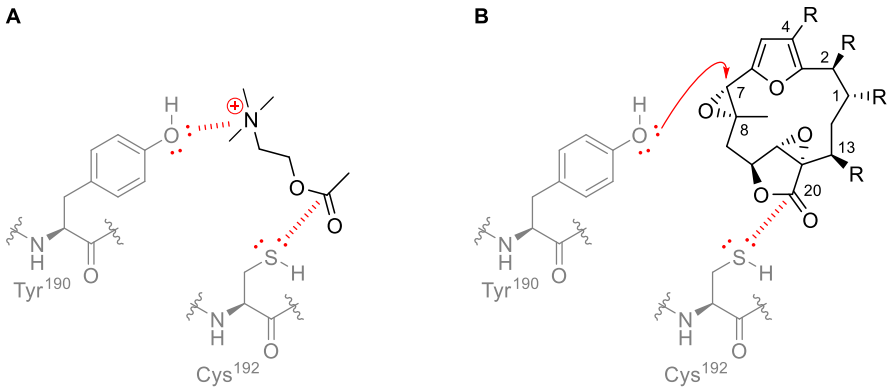
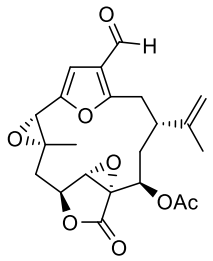


Figure 3 Proposed binding modes of acetylcholine (**A**) and furanocembranoids (**B**) to the α-subunit of nAChR

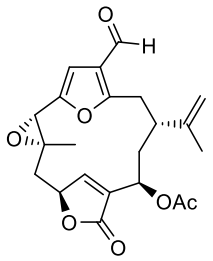
Lophotoxin, like all other furanocembranoids, does not contain a nitrogen atom or any other charged functional groups. This makes **1** unique among nAChR inhibitors and ligands such as nicotine.[17]

1.1.2 Selected furanocembranoids

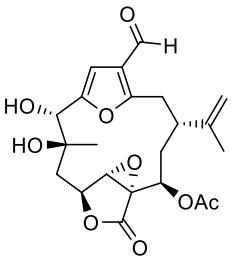
To date, well over 80 furanocembranoids have been isolated, characterised, and screened for their biological activities. **Figure 4** shows a representative selection of furanocembranoids and closely related secondary metabolites. Lophotoxin (**1**, *vide supra*), its deoxy-analogue keikipukalide E[18-19] (**14**) as well as lophodiols A (**15**) and B[20] (**2**) all bear an aldehyde moiety attached to the furan heterocycle and were all first isolated from gorgonian corals of the genus *Lophogorgia*. Lophodiol B (**2**) exhibited cytotoxic activity in human tumour cell lines.[20] Lopholide[21] (**16**) and leptodiol[22] (**17**) are the respective methyl ester analogues to **1** and **15**. Pukalide (**18**) also possesses a methyl ester and was the first furanocembranoid isolated by Scheuer and co-workers in 1975.[23] Molestin E[24] (**19**) possesses a different relative configuration of the *C*-7/*C*-8 diol compared to **2** and **15**. Rubifolide[25] (**20**) and bipinnatin J[26] (**9**) are two scarcely oxidised furanocembranoids. Acerosolide[27] (**21**) and keikipukalide D[19] (**22**) show unique oxidation patterns at positions *C*-13/*C*-14 with a ketone and an olefin instead of the acetoxy group, respectively. Leptolide[12] (**23**) lacks any substitution at the same position. Unnamed cembranoid **24**[20] and lophodione[28] (**25**) demonstrate that the furan ring is prone to reaction with methanol and oxidation. Lophodione (**25**) was assigned a relative configuration of 1*R*,10*R* by X-ray crystallography, a rare exception among furanocembranoids which predominantly exhibit a 1*R*,10*S* relationship. An allylic rearrangement of the acetoxy butenolide motif resulted in the formation of keikipukalide C (**26**).[19] The isopropenyl group at position *C*-1 was modified in 15,16-epoxilophotoxin[20] (**27**) and providencin[29] (**28**). Mayotolide A[30] (**29**) is one of the few dimeric furanocembranoids and exhibits a carboxylic acid moiety at the non-linking *C*-18 position.



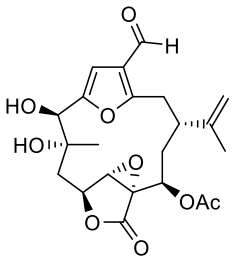
lophotoxin (**1**)



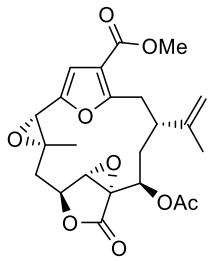
keikipukalide E (**14**)



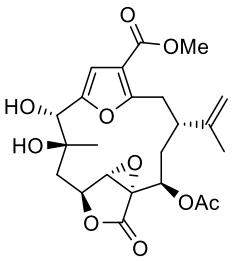
lophodiol A (**15**)



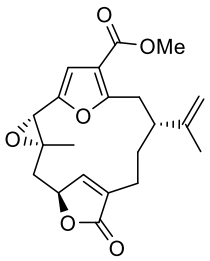
lophodiol B (**2**)



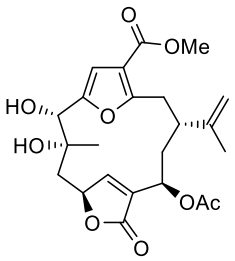
lopholide (**16**)



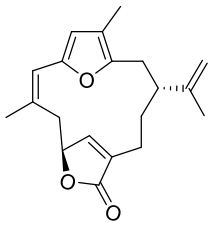
leptodiol (**17**)



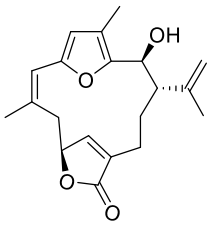
pukalide (**18**)



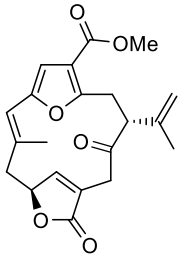
molestin E (**19**)



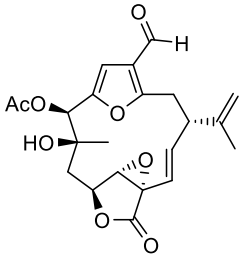
rubifolide (**20**)



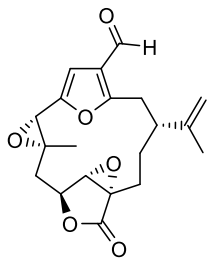
bipinnatin J (**9**)



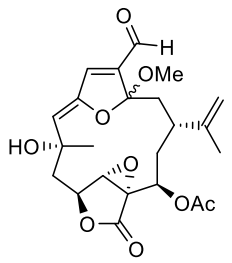
acerosolide (**21**)



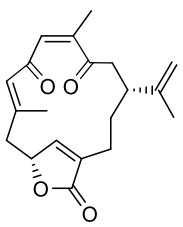
keikipukalide D (**22**)



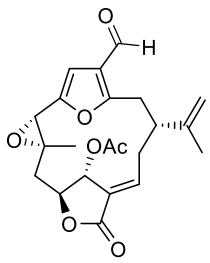
leptolide (**23**)



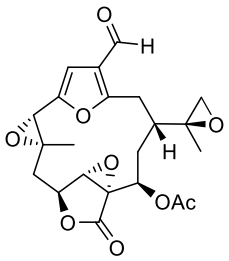
unnamed (**24**)



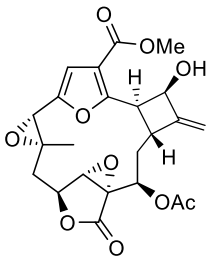
lophodione (**25**)



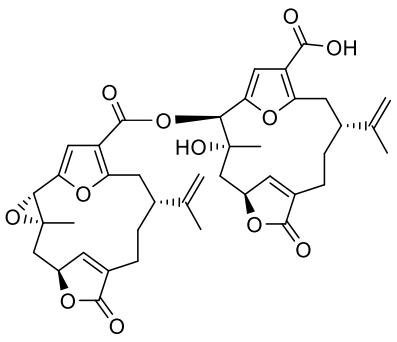
keikipukalide C (**26**)



15,16-epoxilophotoxin (**27**)



providencin (**28**)

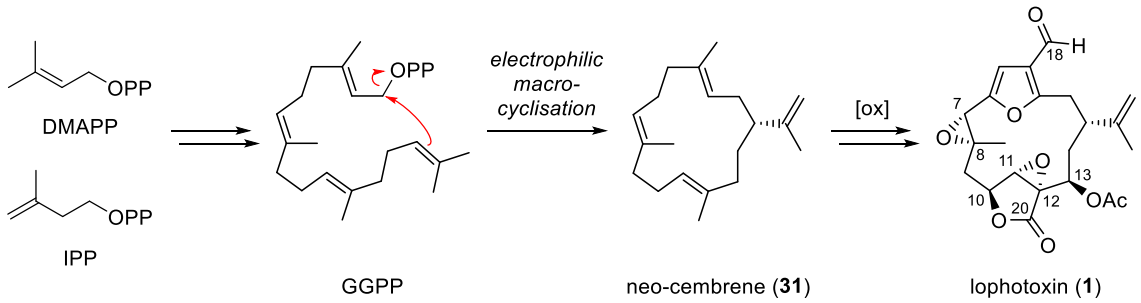


mayotolide A (**29**)

Figure 4 Selected members of the furanocembranoid family and related natural products

1.1.3 Biosynthesis

Biosynthetically furanocembranoids originate from neo-cembrene (**31**, **Scheme 2**).[2] The electrophilic isoprenoid precursor dimethylallyl pyrophosphate (DMAPP) reacts three consecutive times with its nucleophilic isomer isopentenyl pyrophosphate (IPP) to assemble geranylgeranyl pyrophosphate (GGPP), containing all carbon atoms for the final diterpenoid scaffold. GGPP then undergoes electrophilic macrocyclization to give hydrocarbon neo-cembrene (**31**), assembling the furanocembranoid carbon skeleton. Subsequently, multiple regio- and stereoselective oxidation manipulations are performed. In the case of lophotoxin, a highly oxidised furanocembranoid, the furan (*C*-3/*C*-6), butenolide (*C*-10/*C*-20), and epoxide (*C*-7/*C*-8 & *C*-11/*C*-12) heterocycles as well as the acetoxy (*C*-13) and aldehyde (*C*-18) moieties are then installed selectively. The order of steps and responsible enzymes for these manipulations can only be speculated on, but most likely cytochrome P450 monooxygenases are involved.[9]



Scheme 2 DMAPP: dimethylallyl pyrophosphare, IPP: isopentenyl pyrophosphate, GGPP: geranylgeranyl pyrophosphate, PP: $P_2O_6^{3-}$.

As demonstrated in **Figure 4** furanocembranoids with various degrees of oxidation have been isolated, from lipophilic rubifolide (**20**) to highly oxidised lopholide (**16**). Interestingly, the oxidation state of the single carbon atom attached to the furan ring (position *C*-18) correlates highly with the genus of the organism the natural products were isolated from (**Figure 5**).[9,31] Most furanocembranoids isolated to date bear a methyl group or a methyl ester at *C*-18. Members with a methyl group at this centre have been

isolated from genera *Alcynium*, *Gersemia and Pseudopterogorgia*. C-18 methyl esters have been isolated from *Sarcophyton*, *Sinularia* and *Leptogorgia*. Only a few candidates with a carboxylic acid moiety at this position were found in *Sinularia* as well as *Pseudopterogorgia.* C-18 aldehydes, such as lophotoxin (**1**), are also common and have been isolated from *Lophogorgia* and *Leptogorgia*. Based on this pattern Darias and co-workers suggested to use the C-18 position as chemotaxanomic marker for several genera of octocorals.[31] Furthermore, the authors also drew biosynthetical conclusions based on the observed oxidation pattern.

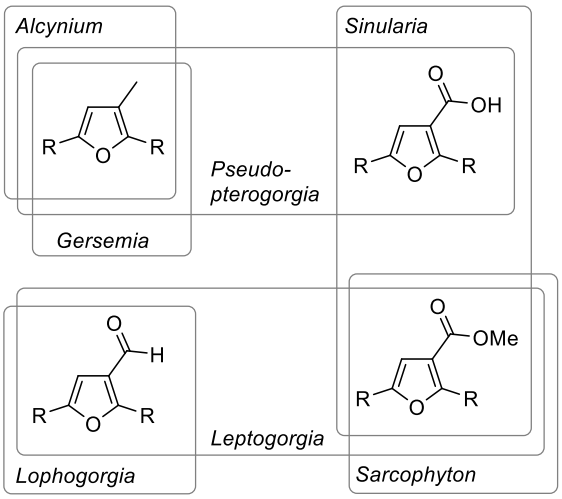
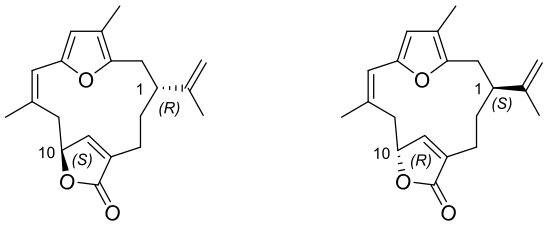


Figure 5 *C*-18 oxidation states of furanocembranoids are genus specific.

1.1.4 Absolute configuration

The first proof of absolute stereochemistry for a furanocembranoid was provided by Marshall and co-workers with the total synthesis of (–)-rubifolide (*ent*-**20**) in 1997 (Chapter 1.2.4). At this point, furanocembranoids were already known for over 20 years and relative configurations for multiple members had been confirmed by X-ray crystallography. Thus, the originally arbitrarily proposed 1*R*,10*S* absolute configuration for (+)-rubifolide (**20**) was confirmed (**Figure 6**).



(+)-rubifolide (**20**)
isolated and assigned by Clardy and co-workers

(–)-rubifolide (*ent*-**20**)
synthesised by Marshall and Sehon

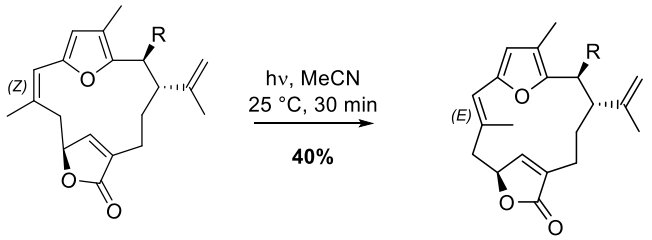
Figure 6 The absolute stereochemistry of (+)-rubifolide (**20**) was confirmed by the synthesis of *ent*-**20**.

In 2005, Riguera and co-workers published X-ray crystal structures of lophotoxin (**1**, **Figure 2**) and leptolide (**23**), confirming the relative stereochemistry only.[12] In the same study the authors analysed pukalide (**18**) and related butenolide-containing furanocembranoids applying circular dichroism (CD), a method developed to determine the absolute configuration of γ-substituted butenolides.[32-33] Together with interconversion studies by Fenical and co-workers,[11] this allowed for the assignment of the absolute configuration for naturally occurring (+)-lophotoxin (**1**), (+)-pukalide (**18**) and further furanocembranoids as 1*R*. Although this assignment is not generally accepted to date,[34-35] furanocembranoids without confirmed absolute configuration are drawn in analogy to this assignment throughout this thesis.

1.1.5 Relative configuration at *C*-7/*C*-8

Furanocembranoids containing olefins, epoxides, and diols at positions *C*-7/*C*-8 have been isolated. Intriguingly, *C*-7/*C*-8 olefins are predominantly isolated as their *Z*-isomers (**9** and **20**), whereas almost exclusively *trans*-epoxides (equivalent to *E*-olefins) have been isolated (**1** and **16**). Exceptions to these patterns are the *E*-olefins acerosolide (**21**) and lophodione (**25**, **Figure 4**) as well as *trans*-epoxide 8-*epi*-lopholide, the epimer of lopholide (**16**) isolated by Darias and co-workers.[22] In 2011, Pattenden and co-workers published a light-induced isomerisation study of rubifolide (**20**) and bipinnatin J (**9**) using a sunlamp.[8] When the compounds were subjected to prolonged irradiation, the authors

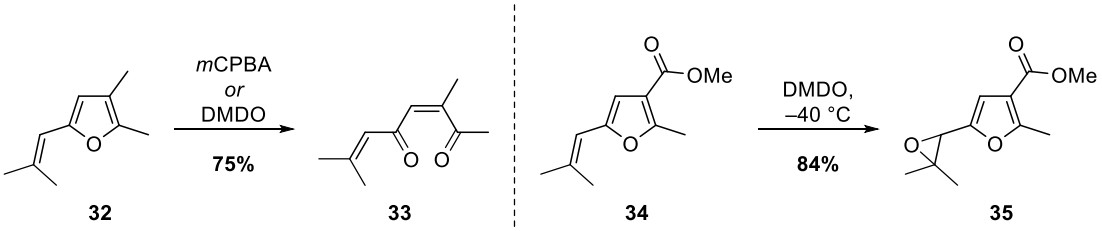
observed the same ring-contractions discussed in chapter 1 (**Scheme 1**). Under reduced reaction times, however, *Z*/*E*-isomerisation occurred instead to afford unstable *E*-rubifolide (*E*-**20**), which was isolated in 40% yield (**Scheme 3**). Although furanocembranoids containing *E*-olefins at positions *C*-7/*C*-8 are rarely isolated, it is justified to assume that they are precursors for their *trans*-epoxides derivatives.



rubifolide (**20**) *E*-rubifolide (*E*-**20**)

Scheme 3 Light-mediated isomerisation of rubifolide (**20**)

In a simple but seminal model study, Pattenden and co-workers investigated the reaction of olefinic furans **32** and **34** with epoxidising agents *meta*-chloroperoxybenzoic acid (*m*CPBA) and dimethyldioxirane (DMDO).[36] Electron-rich furan **32** reacted with both reagents directly and dienedione **33** was observed in approximately 75% yield (**Scheme 4**). However, when furanoate **34** was treated with DMDO at –40 °C epoxide **35** was isolated in 84% yield. The deactivating effect of the electron-withdrawing ester on the furan heterocycle allowed for this crucial change in regioselectivity.

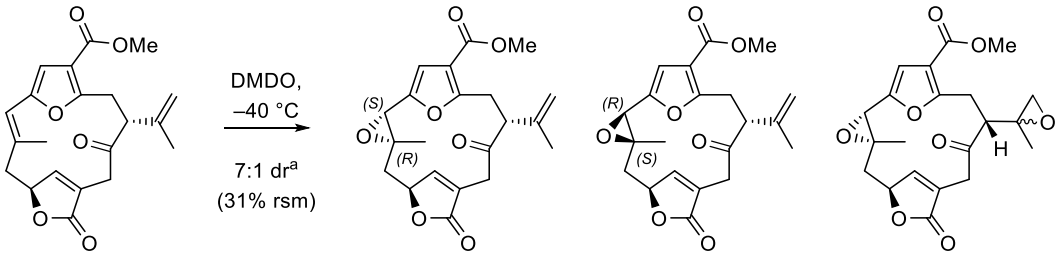


32 **33** **34** **35**

Scheme 4 Model studies by Pattenden and co-workers.[36]

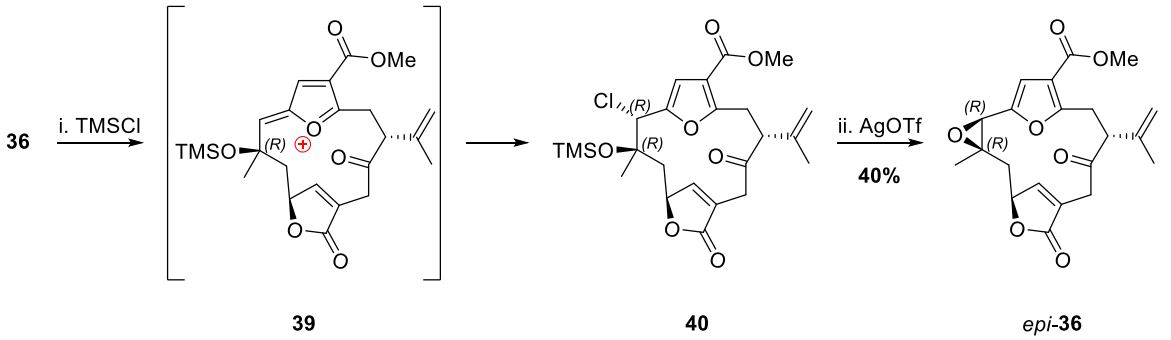
In 2014, Mulzer and co-workers utilised this DMDO-mediated epoxidation in the total synthesis of 17-deoxyprovidencin (Chapter 1.2.8).[37] Later in 2018, Roche and co-workers used the same method to epoxidise naturally isolated acerosolide (**21**).[38] The authors treated **21** with 1.0 equivalent DMDO at –40 °C and stopped the reaction after 10 h (69%

conversion) to prevent overoxidation and the formation of **38** (**Scheme 5**). The facial selectivity of the transformation was controlled by the restricted conformational flexibility of the macrocycle and epoxidation occurred on the convex face. Thus, a diastereoselectivity (dr = **36**:**37**) of 7:1 was observed and the major diastereomer **36** was isolated in 52% yield.



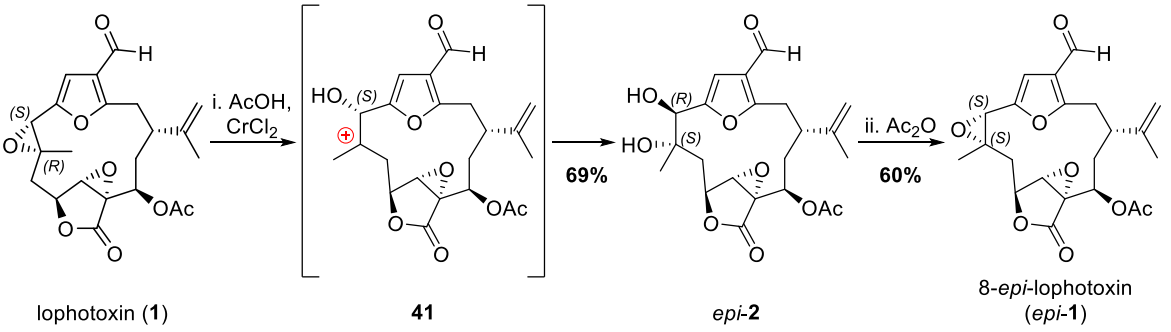
Scheme 5 Epoxidation of acerosolide by Roche and co-workers. Reagents and conditions: DMDO (1.0 eq), acetone, –40 °C, 10 h; a) ratio **36**:**37** = 7:1 observed in crude NMR; b) isolated yield of the major diastereomer.

The authors, who developed a dearomatisation protocol, found a method to epimerise epoxide **36** at position *C*-7 (**Scheme 6**). Treatment with TMSCl opened epoxide **36** in a stepwise fashion *via* proposed oxonium ion **39**, which was subsequently trapped by chloride to give unstable chlorohydrin **40**. The retentive manner of this TMSCl-mediated epoxide opening could be explained by a tight ion pair or by the same facial selectivity the epoxidation originally occurred (*vide supra*). When the authors exposed **40** to palladium(0) and AgOTf to mediate chloride abstraction together with methanol and lutidine, epoxidation *via* inversion at position *C*-7 occurred and epoxide *epi*-**36**, the *C*-7 epimer of epoxide **36**, was isolated in 40% yield.



Scheme 6 Formal epimerisation of **36**. Reagents and conditions: i) TMSCl (1.1 eq), CH_2Cl_2 (26 mM), 0 °C, 1 h; ii) $Pd(PPh_3)_4$ (0.1 eq), AgOTf (1.1 eq), lutidine (1.1 eq), MeOH (5 eq), CH_2Cl_2, –78 °C, 3 h.

A similar epoxide epimerisation was observed by Zubía and co-workers when they performed interconversion studies with naturally isolated lophotoxin (**1**).[20] Exposing **1** to $CrCl_2$ in a mixture of AcOH and acetone gave diol *epi*-**2** in 69% yield, the *C*-8 epimer of lophodiol B (**2**). Intriguingly, this transformation proceeded *via* inversion of both stereogenic centres *C*-7 and *C*-8. The authors proposed that **1** first epimerised at position *C*-8 *via* tertiary carbocation **41** to give less strained 8-*epi*-lophotoxin (*epi*-**1**); subsequent SN2 attack at position *C*-7 with inversion afforded diol *epi*-**2**. Acetylation of diol *epi*-**2** with Ac_2O in pyridine, in turn, yielded 8-*epi*-lophotoxin (*epi*-**1**) in 60% *via* selective activation of the secondary alcohol *OH*-7, followed by stereospecific cyclisation.



Scheme 7 Synthesis of 8-*epi*-lophotoxin (*epi*-**1**) from **1**. Reagents and conditions: i) $CrCl_2$ (3 eq), acetone:AcOH (8:2), 2 h; ii) Ac_2O, pyridine, 80 °C, 2 h.

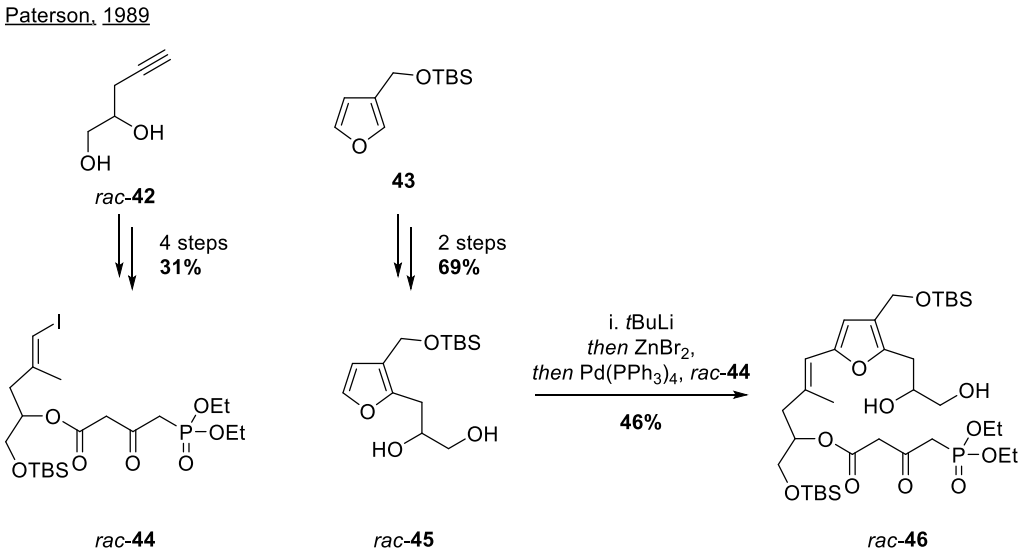
Compared to olefins and epoxides, furanocembranoids with diols in positions *C*-7/*C*-8 are less common. Nevertheless, with lophodiols A (**15**) and B (**2**) as well as molestin E (**19**) and keikipukalide D (**22**), all four possible relative configurations of the *C*-7/*C*-8 unit have been isolated (**Figure 4**).

1.2 Synthetic efforts towards furanocembranoids

An overview of various synthetic campaigns towards furanocembranoids and related structures of relevance to this thesis is provided. A comprehensive review on this topic was published by Roethe and Trauner.[2]

1.2.1 Synthesis of furan 46

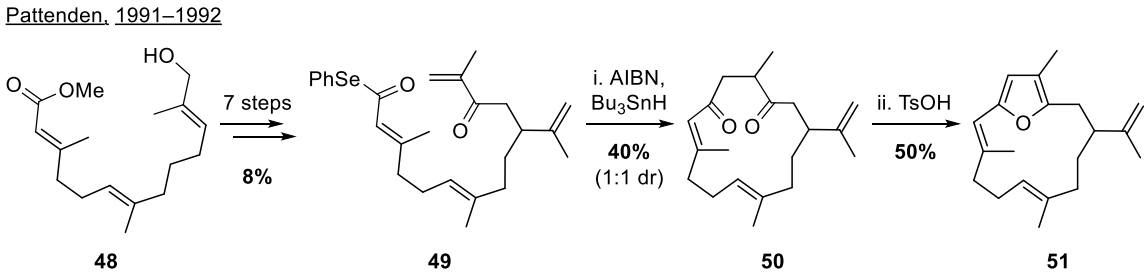
Following the isolation of the first furanocembranoids, the first synthetic attempts to synthesise them were published during the 1980's. Paterson and Gardner reported cross-coupling methods to link various vinyl iodides, such as *rac*-**44**, to di-substituted furans like *rac*-**45**.[39] The two coupling partners shown in **Scheme 8** were synthesised from diol *rac*-**42** and furan **43** in 31% and 69% yield, respectively. Investigating Stille as well as Negishi protocols, the authors succeeded in both approaches. Furan *rac*-**46** was lithiated regioselectively with excess *t*BuLi and the resulting trianion was treated with $ZnBr_2$. After transmetalation, vinyl iodide *rac*-**44** was added *via* syringe pump and the subsequent Negishi coupling afforded fragment *rac*-**46** in 46% yield.



Scheme 8 Synthesis of furan fragment *rac*-**46** by Paterson and Gardner. Reagents and conditions: i) *t*BuLi (3.6 eq), THF, –78 °C, 1 h *then* $ZnBr_2$, rt *then* $Pd(PPh_3)_4$, *rac*-**44** *via* syringe pump (2 h) *then* 4 h.

1.2.2 First synthesis of the furanocembranoid scaffold

In the past decades, much of the synthetic and biosynthetic progress on furanocembranoids was contributed by the group of Pattenden. In the early 1990's, Astley and Pattenden reported the first synthesis of the furanocembranoid skeleton (**Scheme 9**).[40-41] The authors elaborated enone **48** to selenyl ester **49** over 7 steps in 8% overall yield. The key step in their route was the radical macrolactonisation *via* intramolecular conjugate addition of an acyl radical derived from selenyl ester **49**. Using this method, **50** was obtained in 40% yield as an inconsequential mixture of diastereomers. Submission of 1,4-diketone **50** to Brønsted-acidic conditions afforded furan **51** in 50% yield.

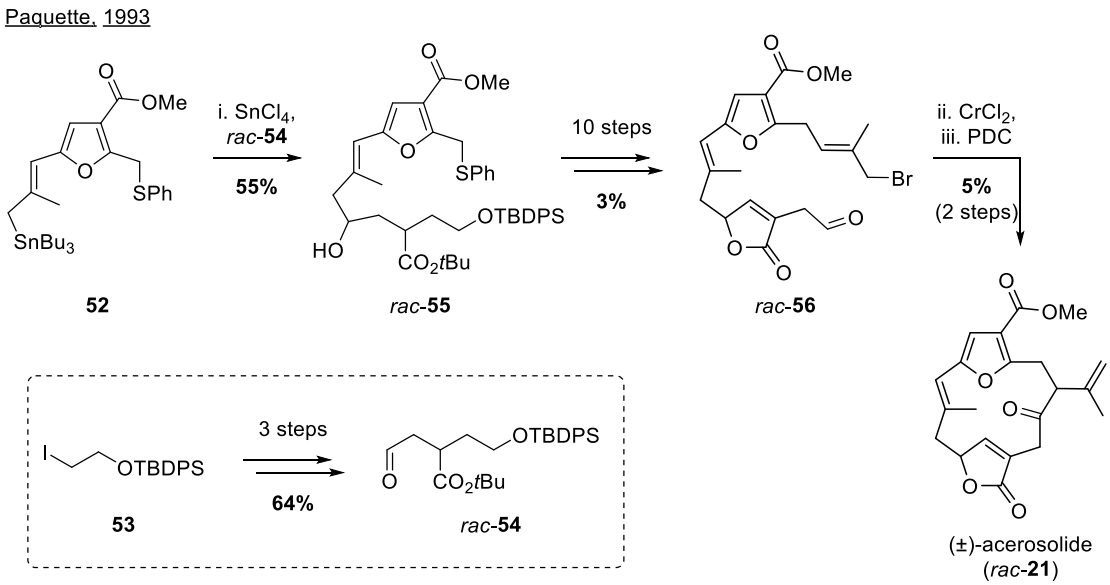


Scheme 9 Synthesis of furanocembranoid **51** by Pattenden and Astley. Reagents and conditions: i) AIBN (0.1 eq), PhH, reflux *then* Bu_3SnH (1.3 eq) *via* syringe pump (1.5 h) *then* 1.3 h; ii) TsOH, $CHCl_3$, reflux, 3.5 h.

1.2.3 Synthesis of (±)-acerosolide

In 1992, Paquette and co-workers reported the synthesis of the pseudopterane gorgiacerone.[42-43] Following a similar strategy, the same group disclosed the first completed chemical synthesis of a furanocembranoid, namely acerosolide **21**, shortly after (**Scheme 10**).[44] A fundamental step at an early stage of the synthesis was the regioselective coupling of allylstannane **52** and aldehyde *rac*-**54**; the latter was synthesised from TBDPS-protected 2-iodoethanol (**53**) over 3 steps in 64% overall yield. The authors hypothesised that primary allylstannane **52** underwent rearrangement to the corresponding secondary allylstannane upon treatment with $SnCl_4$ prior to addition

reaction with aldehyde *rac*-**54**. The *E*-geometry of the olefin was preserved throughout this process and *rac*-**55** was isolated in 55% yield. In 10 further steps, the authors synthesised allylic bromide *rac*-**56** in 3% yield. Macrolactonisation was achieved *via* Nozaki–Hiyama–Kishi (NHK) reaction of *rac*-**56**. Notably, the NHK product was isolated as a single diastereomer, but unfortunately the authors were unable to assign the relative configuration. PDC oxidation gave (±)-acerosolide (*rac*-**21**). Spectral data of natural and synthetic acerosolide matched, but confirmation of the stereochemical configuration remained elusive at the time.

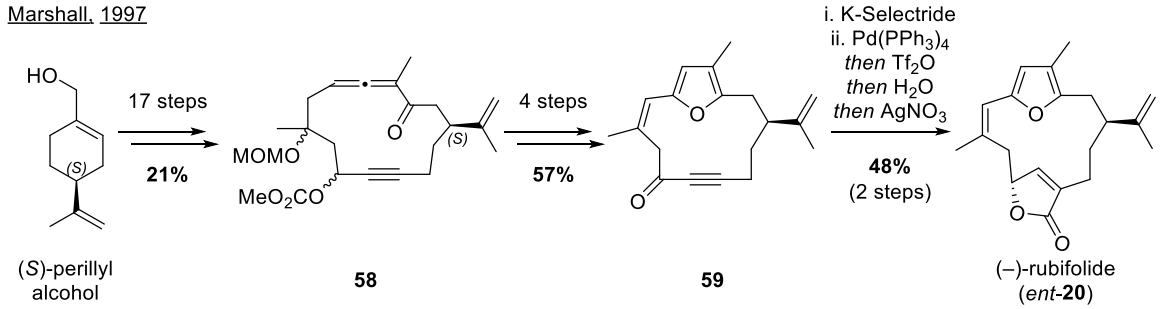


Scheme 10 Synthesis of (±)-acerosolide (*rac*-**21**) by Paquette and Astles. Reagents and conditions: i) SnCl4 (1.5 eq), **52** (1.0 eq), THF, –78 °C then *rt*, 90 min; ii) $CrCl_3$ (15 eq), $LiAlH_4$ (7 eq), 0 °C, 20 min *then* rt, 30 min *then* *rac*-**54**, 36 h; iii) PDC, DMF, 4 Å-MS, 2 h.

1.2.4 Total synthesis of (–)-rubifolide

The first enantioselective synthesis, and thus synthetic proof of absolute configuration for a furanocembranoid, was disclosed by Marshall and Sehon in 1997 in their total synthesis of (–)-rubifolide (*ent*-**20**).[45] Key to their successful strategy was to install the sensitive furan and butenolide heterocycles at a late stage of the route (**Scheme 11**), an approach the authors adopted in later projects. (*S*)-Perillyl alcohol was advanced to macrocycle **58** over 17 steps in 21% overall yield. The authors installed the furan ring first and

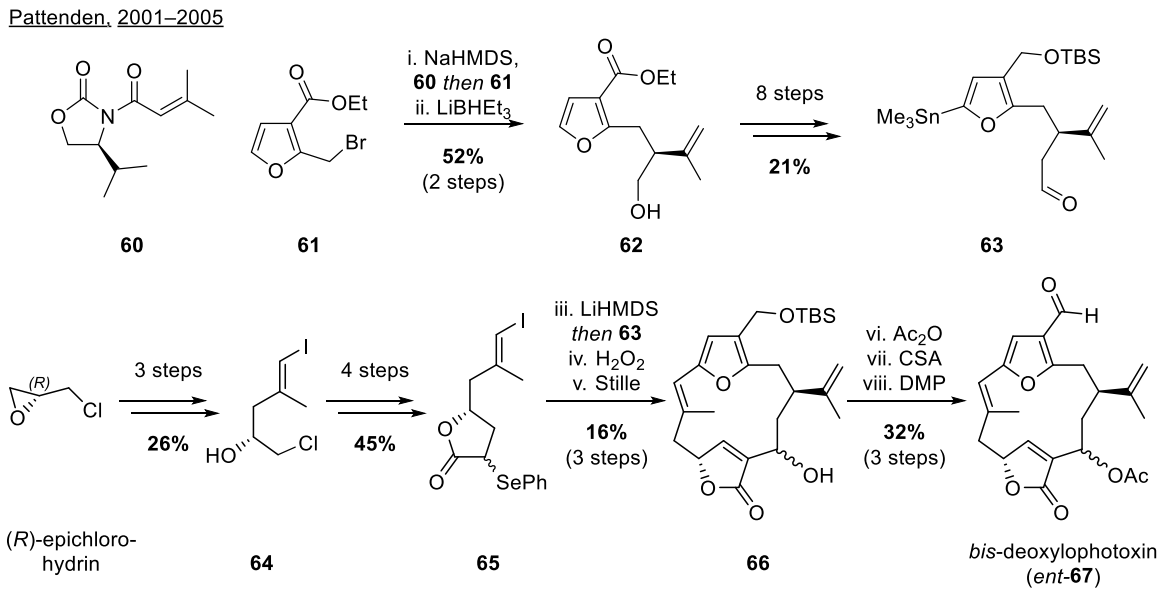
synthesised **59** in four further steps (57% yield). Stereoselective reduction of ketone **59** was achieved using K-Selectride at cryogenic temperatures. The resulting propargylic alcohol was converted into (–)-rubifolide (*ent*-**20**) employing a palladium-catalysed butenolide methodology.



Scheme 11 Synthesis of (–)-rubifolide (*ent*-**20**) by Marshall and Sehon. Reagents and conditions: i) K-Selectride, THF, –78 °C, 15 min; ii) $Pd(PPh_3)_4$ (10 mol%), CO, THF *then* Tf_2O *then* H_2O, rt, 15 min *then* AgNO3 on silica, hexane, rt, 3 h.

1.2.5 Synthesis of *bis*-deoxylophotoxin

A route to an advanced furanocembranoid was reported by the group of Pattenden with their synthesis of *bis*-deoxylophotoxin (*ent*-**67**, **Scheme 12**).[46-47] The absolute configuration at position *C*-1 was controlled using Evans' auxiliary: stereoselective alkylation of oxazolidinone **60** with furyl bromide **61** and subsequent cleavage of the auxiliary afforded alcohol **62** in 52% yield. In 8 further steps, alcohol **62** was homologated and the furan ring functionalised to give right-hand furan fragment **63**. The left-hand fragment was constructed from (*R*)-epichlorohydrin. Vinyl iodide was synthesised in 3 steps (26% yield) and elaborated to organo-selenium **65** in 4 more steps. Fragment coupling was achieved *via* a non-stereoselective aldol reaction. Subsequent butenolide formation *via* selenide oxidation/elimination and key Stille macrocyclization afforded **66** in 16% yield over 3 steps. Acetylation, TBS deprotection in acidic methanol and Dess–Martin oxidation gave *bis*-deoxylophotoxin (*ent*-**67**), the closest reported synthesis to lophotoxin to date.

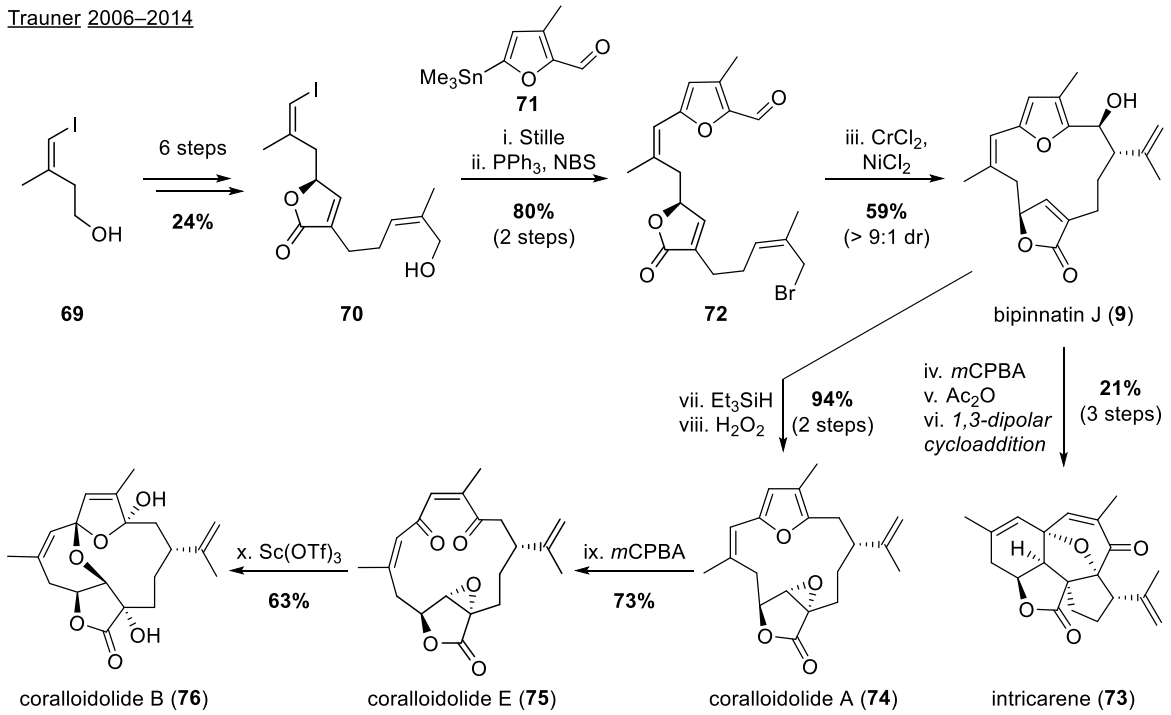


Scheme 12 Synthesis of *bis*-deoxylophotoxin (*ent*-**67**) by Pattenden and co-workers. Reagents and conditions: i) NaHMDS, THF, –78 °C, 1 h *then* **61** (1.2 eq); ii) $LiBHEt_3$, PhMe, –78 °C, 20 min; iii) LiHMDS, –78 °C, 20 min *then* **63**, 50 min; iv) H_2O_2, CH_2Cl_2/pyridine; v) $AsPh_3$, Pd_2dba_3, 40 °C, 14 h; vi) Ac_2O, Et_3N, DMAP, rt, 4 h; vii) CSA, MeOH:CH_2Cl_2, 0 °C, 3 h; (viii) DMP, pyridine, CH_2Cl_2, 0 °C, 3 h.

1.2.6 Total synthesis of bipinnatin J and interconversion to related natural products

In 2006, the groups of Rawal,[48] Trauner,[49-50] and Pattenden[51] all published successful syntheses of bipinnatin J (**9**) following similar strategies. In subsequent work, Trauner and co-workers synthesised a series of related natural products from **9** (**Scheme 13**).[52-53] In their approach, Trauner and co-workders elaborated vinyl iodide **69** to butenolide **70** over 6 steps in 24% overall yield. Stille coupling with furyl stannane **71** followed by an Appel-type reaction afforded aldehyde **72**. NHK macrocyclization was achieved in a similar manner as Paquette's synthesis of (±)-acerosolide (Chapter 1.2.3). The transformation was highly diastereoselective (dr > 9:1) and bipinnatin J (**9**) was isolated in 59% yield. During further studies, **9** was prepared on gram scale, underpinning the robustness of the synthetic route. Intercarene (**73**) was synthesised from **9** in 3 steps: *m*CPBA-mediated Achmatowicz rearrangement of the furan ring, followed by acetylation and elimination enabled the transannular 1,3-dipolar cycloaddition to give **73** in 21% yield.[50,53] In addition, Trauner and co-workers converted **9** into coralloidolide A (**74**), E (**75**) and B (**76**):[52]

deoxygenation of **9** was achieved by exposure to Et_3SiH and TFA. Subsequent treatment with hydrogen peroxide under basic conditions resulted in chemo- and stereoselective butenolide epoxidation, producing **74** in excellent yield. Oxidation of furan **74** with *m*CPBA gave dienone **75** in 73% yield. Lewis acidic activation resulted in a cascade of cyclisations to give **76** in 63% yield. The authors propose that the water formally required for this transformation was introduced as a contaminant in the Lewis acid.

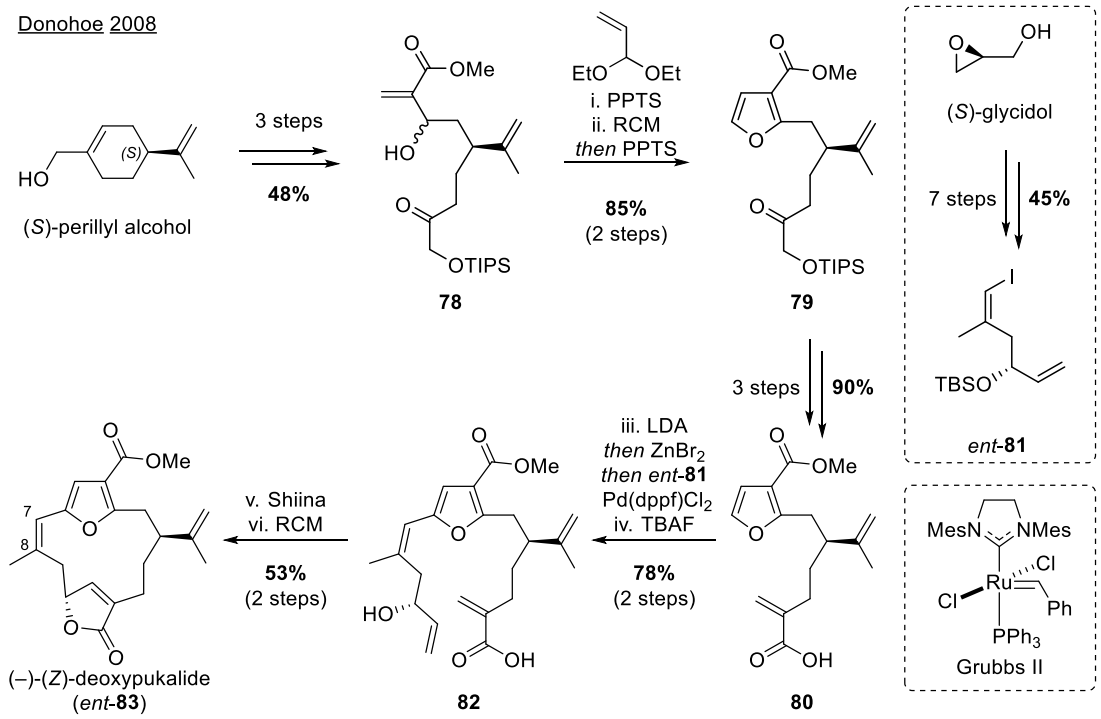


Scheme 13 Synthesis of multiple furanocembranoids by Trauner and co-workers. Reagents and conditions: i) **71** (1.3 eq), $Pd(PPh_3)_4$ (4 mol%), CuI (8 mol%), CsF (2.0 eq), DMF, rt, 20 min; ii) PPh_3 (1.1 eq), NBS (1.1 eq), CH_2Cl_2, –5 °C, 20 min; iii) $CrCl_2$ (12 eq), $NiCl_2 \cdot$ DME (3.0 eq), 4 Å-MS, THF, **72** *via* syringe pump (1.5 h) *then* 12 h; iv) *m*CPBA (1.0 eq), CH_2Cl_2, 0 °C; v) Ac_2O (25 eq), DMAP (0.1 eq), pyridine (5.0 eq), rt, 2 h; vi) TMP (3.0 eq), DMSO, 140 °C, 16 h, sealed vial; vii) Et_3SiH (2.2 eq), TFA (1.1 eq), CH_2Cl_2, 0 °C, 20 min; viii) H_2O_2 (aq.), NaOH (3 M, aq.), MeOH:CH_2Cl_2 (1:1), 0 °C, 13 h; ix)) *m*CPBA (2.2 eq), CH_2Cl_2, 0 °C, 1 h; x) $Sc(OTf)_3$ (0.2 eq), dioxane, rt, 3 h.

1.2.7 Synthesis of (–)-(*Z*)-deoxypukalide

In 2001, Marshall and co-workers disclosed their synthesis of (*Z*)-deoxipukalide (*ent*-**83**) succeeding with their proven "heterocycle-last" strategy.[54] Later, the Donohoe group published their approach to *ent*-**83**, demonstrating their furan methodology relying on ring-closing metathesis (RCM, **Scheme 14**):[55] (*S*)-Perillyl alcohol was advanced to enone **78** over 3 steps in 48% overall yield. Transacetalisation with acrolein diethylacetal under

acidic conditions and subsequent RCM followed by aromatisation gave furan **79** in 85% yield over 2 steps. To allow *ortho*-lithiation of the furan ring, ketone **79** was elaborated to α,β-unsaturated carboxylic acid **80** over 3 steps in 90% yield. Furan lithiation using excess LDA at cryogenic temperatures was now possible as the deprotonated carboxylate moiety was inert under these conditions. The lithiated furan species underwent transmetalation upon treatment with $ZnBr_2$, allowing the resulting organozinc species to participate in a Negishi cross-coupling reaction with vinyl iodide *ent*-**81**, which was synthesised from (*S*)-glycidol in 7 steps. TBS deprotection gave allylic alcohol **82** in 78% yield over two steps from limiting vinyl iodide *ent*-**81**. Shiina macrolactonisation of hydroxy acid **82** followed by RCM-butenolide synthesis afforded (–)-(*Z*)-deoxypukalide (*ent*-**83**) in 53% yield (2 steps).



Scheme 14 Synthesis of (–)-(*Z*)-deoxypukalide (*ent*-**83**) by Donohoe and co-workers. Reagents and conditions: i) acrolein diethylacetal (8.0 eq), PPTS (0.1 eq), PhMe, 40 °C, 80 mbar, 3 h; ii) Grubbs II (7 mol%), CH_2Cl_2, 40 °C, 16 h *then* PPTS (1 eq), 1 h; iii) LDA (2.0 eq), THF, –78 °C, 1 h *then* $ZnBr_2$ (3.0 eq) *then ent*-**81** (0.9 eq), $Pd(dppf)Cl_2$ (9 mol%), 50 °C, 4 h; iv) TBAF (1.1 eq), THF, 50 °C, 2 h; v) 2-methyl-6-nitrobenzoic anhydride (MNBA, 1.2 eq), Et_3N (2.2 eq), DMAP (0.1 eq), CH_2Cl_2 (1 mM), **82** *via* syringe pump (16 h) then 3 h, vi) Grubbs II (20 mol%), PhMe, 110 °C, 16 h.

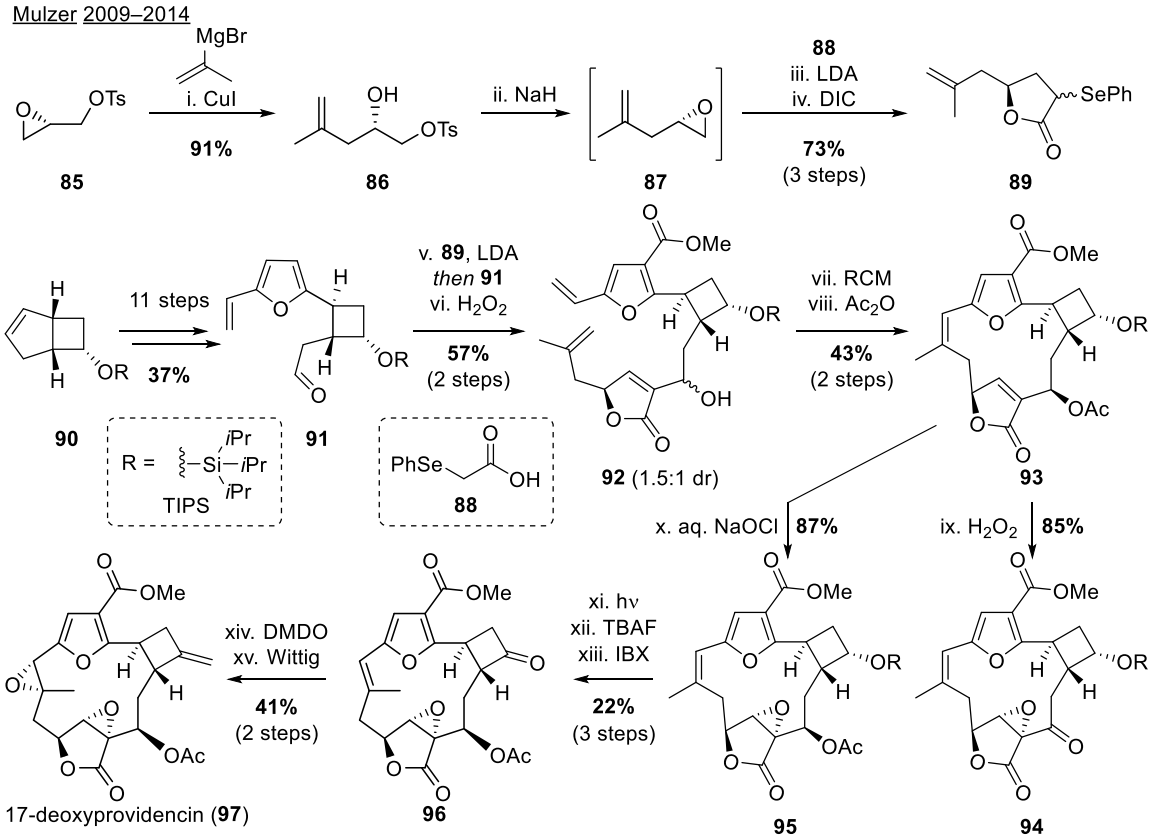
Although (+)-(*E*)-deoxypukalide is a reported natural product,[31] only a single epoxidation step at positions *C*-7/*C*-8 is required to synthesise pukalide (**18**) from deoxypukalide (**83**).

The reports from Marshall and Donohoe do not discuss this epoxidation, but chemoselectivity for the epoxidation of triene *ent*-**83** *via* non-enzymatic methods would presumably be the largest issue.

1.2.8 Synthesis of 17-deoxyprovidencin

The first total synthesis of a furanocembranoid-like natural product bearing an epoxide in positions *C*-7/*C*-8 was achieved by Mulzer and co-workers in 2014, with the synthesis of 17-deoxyprovidencin (**Scheme 15**).[37,56] Providencianes are related to furanocembranoids; they bear an additional carbon–carbon bond, connecting *C*-2 with *C*-17 and thus feature a cyclobutene ring instead of the isopropenyl moiety. The synthesis commenced with construction of butenolide fragment **89** from tosylated glycidol (**85**, **Scheme 15**). Epoxide opening with isopropenylmagnesium bromide was copper-catalysed and required careful temperature control to give tosylate **86** in 91% yield. Treatment of **86** with NaH formed volatile epoxide **87**, which was reacted with *bis*-deprotonated acid **88** *in situ*. Lactonisation with DIC afforded butenolide **89** in 73% yield over 3 steps. Furan fragment **91** was prepared from cyclobutane **90** over 11 steps in 37% overall yield. Fragment coupling was achieved by reacting deprotonated selenyl ester **89** with aldehyde **91**. The diastereoselectivity of this transformation was poor and the undesired diastereomer had to be separated chromatographically at a later stage of the synthesis. Butenolide synthesis was achieved *via* selenide oxidation/elimination and **92** was isolated in 57% yield (2 steps) as a mixture of diastereomers (1.5:1 dr). RCM was *Z*-selective and **93** was isolated as a single diastereomer after acetylation in 43% yield. H_2O_2-mediated butenolide epoxidation, as used by Trauner and co-workers (Chapter 1.2.6), also oxidised the acetoxy group at position *C*-13 to the corresponding ketone and **94** was isolated in 85% yield. However, treatment of **93** with sodium hypochlorite achieved selective butenolide

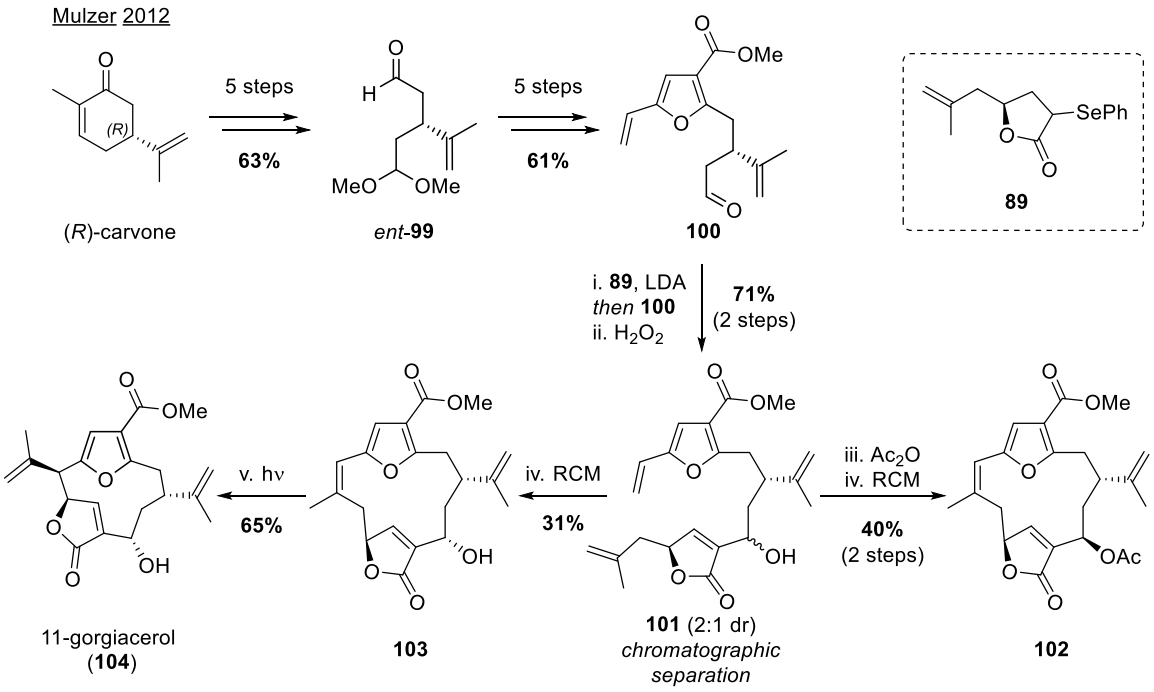
epoxidation without the undesired ketone formation, affording **95** in 87% yield. Exposure of **95** to UV light isomerised the *C*-7/*C*-8 olefin to the *E*-geometry without any further rearrangements. TIPS deprotection using TBAF followed by IBX oxidation of the formed alcohol afforded ketone **96**. Besides the furan's π-system, which is deactivated by the methyl ester, the *E*-olefin at positions *C*-7/*C*-8 of **96** is the only double bond present in the compound. Thus, selectivity during epoxidation was a non-issue and treatment with DMDO gave the desired epoxide. Subsequent Wittig olefination gave 17-deoxyprovidencin (**97**) in 41% yield over 2 steps.



Scheme 15 Synthesis of 17-deoxyprovidencin (**97)** by Mulzer co-workers. Reagents and conditions: i) isopropenylmagnesium bromide (2.1 eq), CuI (0.2 eq), THF, –78 °C, 1 h *then* **85**, –40 °C, 2 h; ii) NaH (1.0 eq), THF, 0 °C, 30 min; iii) LDA (3.2 eq), **88** (2.5 eq) rt, 90 min *then* **87**, –78 °C to rt, 16 h; iv) DIC (1.1 eq), DMAP (0.1 eq), CH_2Cl_2, 0 °C, 90 min; v) LDA (1.2 eq), **89** (1.1 eq), THF, –78 °C, 30 min *then* **91**, 1 h; vi) H_2O_2 (aq., 3.0 eq), NH_4Cl (aq.), CH_2Cl_2, 0 °C, 1 h; vii) PhH (2 mM), 80 °C, Grubbs II (20 mol%) *via* syringe pump (15 h); viii)) Ac_2O (1.1 eq), DIPEA (1.1 eq), DMAP (0.1 eq), CH_2Cl_2, 0 °C, 45 min; ix) H_2O_2, iPr_4NOH, THF:H_2O; x) pyridine, NaOCl, –15 °C, 5 min; xi) hν (UV-B), MeCN, 2 x 40 min; xii) TBAF (1.5 eq), THF, 1 h; xiii) IBX (2.2 eq), THF:DMSO (10:1), 15 h; xiv) DMDO (1.5 eq), acetone, 0 °C, 18 h; xv) *t*BuOK (10 eq), $MePPh_3Br$ (12 eq), THF, Et_2O, 15 min.

1.2.9 Total synthesis of 11-gorgiacerol

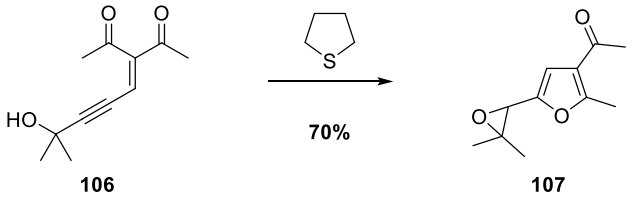
Following a similar strategy Mulzer and co-workers also synthesised the pseudopterane 11-gorgiacerol (**104**, **Scheme 16**).[57] The authors elaborated (*R*)-carvone to pseudo-symmetrical aldehyde *ent*-**99** over 5 steps in 63% overall yield. Furan **100** was then synthesised over 5 further steps in 61% yield. As with in the synthesis of 17-deoxyprovidencin (*vide supra*), selenyl ester **89** was used as butenolide fragment, and coupling with **100** was achieved *via* the established aldol, oxidation/elimination sequence to give butenolide **101** in 71% yield (2:1 dr). The diastereomers of **101** were separated chromatographically and unnatural furanocembranoid **102** was synthesised from the minor diastereomer by acetylation and *Z*-selective RCM in 40% yield. The major diastereomer of **101** was subjected to RCM directly, affording macrocycle **103** in 31% yield. Exposure of **103** to UV light induced [1,3]-sigmatropic rearrangement – a method pioneered by Rodriguez and Pattenden (Chapter 1.1) – which afforded **104** in 65% yield.



Scheme 16 Synthesis of furanocembranoid **102** and 11-gorgiacerol by Mulzer and co-workers. Reagents and conditions: i) LDA (1.2 eq), **89** (1.1 eq), THF, –78 °C, 30 min *then* **100**, –78 °C, 1 h; ii) H_2O_2 (aq., 3.0 eq), NH_4Cl (aq.), CH_2Cl_2, 0 °C, 1 h; iii) Ac_2O (2.0 eq), pyridine (3.0 eq), DMAP (0.1 eq), CH_2Cl_2, 0 °C, 45 min; iv) PhH (1 mM), 80 °C, Grubbs II (20 mol%) *via* syringe pump (15 h); v) hv (UVB), MeCN, 1 h.

1.2.10 Synthesis of 7-*epi*-pukalide and 7-acetylsinumaximol B

The challenge of selectively forming the *C*-7/*C*-8 epoxide adjacent to the furan was addressed by Clark and co-workers *via* a fundamentally different approach. This approach involved using an organocatalytic methodology they had developed for accessing tri-substituted furans from enynediones. [58] When hydroxy enynedione **106** was treated with substoichiometric tetrahydrothiophene (THT), epoxy furan **107** was isolated in 70% yield.

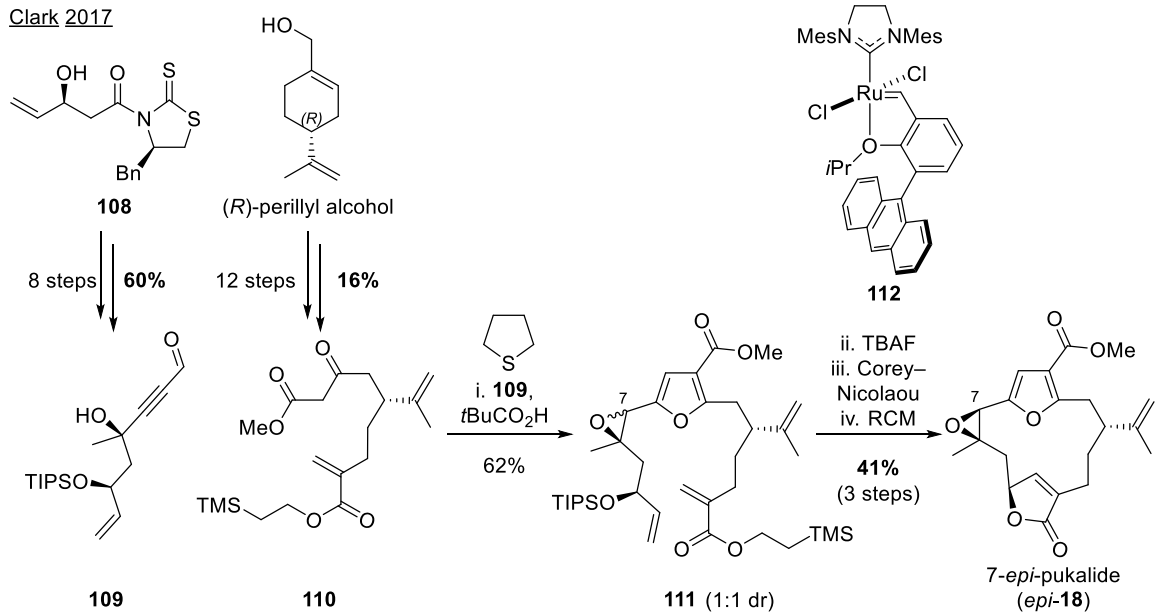


106 **107**

Scheme 17 Model study by Clark co-workers. Reagents and conditions: THT (20 mol%), CH_2Cl_2, 40 °C, 48 h.

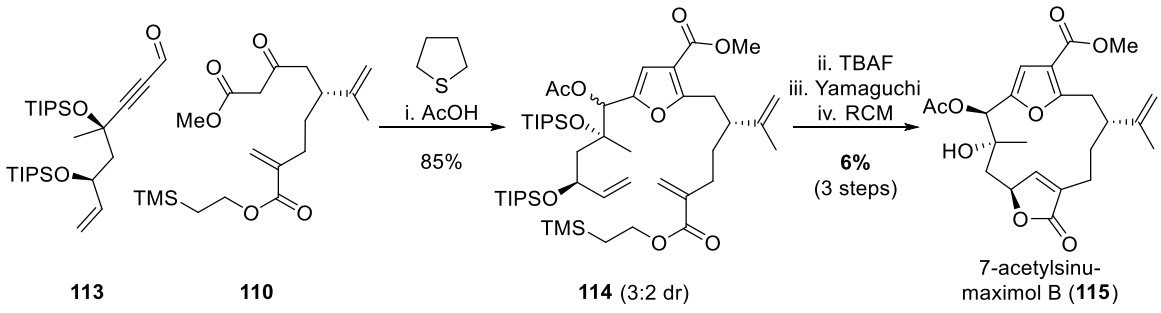
In 2017, the Clark group reported the application of their epoxy furan methodology with the synthesis of 7-*epi*-pukalide (*epi*-**18**, **Scheme 17**).[59] The authors synthesised fragments **109** and **110** from allylic alcohol **108** and (*R*)-perillyl alcohol in 8 and 12 steps, respectively. The corresponding Knoevenagel product from fragments **109** and **110** required for the furan methodology was unstable. Therefore, the authors adopted a one-pot procedure: Treatment of fragments **109** and **110** with a buffer of pivalic acid and piperidine in THT induced Knoevenagel condensation as well as epoxy furan formation in a single operation, allowing furan **111** to be isolated in 62% yield as a 1:1-mixture of diastereomers at position *C*-7. Treatment of **111** (diastereomeric mixture) with TBAF deprotected the TIPS ether and the TMSE ester of both diastereomers. However, only one diastereomer was reactive under the subsequent Corey–Nicolaou macrolactonisation conditions. Subsequent RCM with modified Hoveyda–Grubbs catalyst **112** gave 7-*epi*-pukalide (*epi*-**18**) over 3 steps in 41% yield as a single diastereomer from **111** (1:1 dr). The fact that only the *cis*-epoxide underwent macrolactonisation to give 7-*epi*-pukalide (*epi*-**18**) is consistent with findings from Zubía and co-workers discussed in Chapter 1.1.5

(**Scheme 7**): Furanocembranoids with *cis*-epoxides at *C*-7/*C*-8 exhibit less macrocyclic strain than the corresponding – and naturally more abundant – *trans*-epoxides.



Scheme 18 Synthesis of 7-*epi*-pukalide (*epi*-**18**) by Clark co-workers. Reagents and conditions: i) **110** (1.0 eq), **109** (2.5 eq), *t*$BuCO_2H$ (0.6 eq), piperidine (1.0 eq), 4Å-MS, THT, 35 °C, 16 h; ii) TBAF (2.1 eq), THF, 3 h; iii) 2,2′-dipyridyl disulfide (1.4 eq), PPh_3 (1.4 eq), PhMe, 7 h *then* PhMe (1 mM), 110 °C, 14 h; iv) **112** (10 mol%), CH_2Cl_2, 40 °C, 17 h.

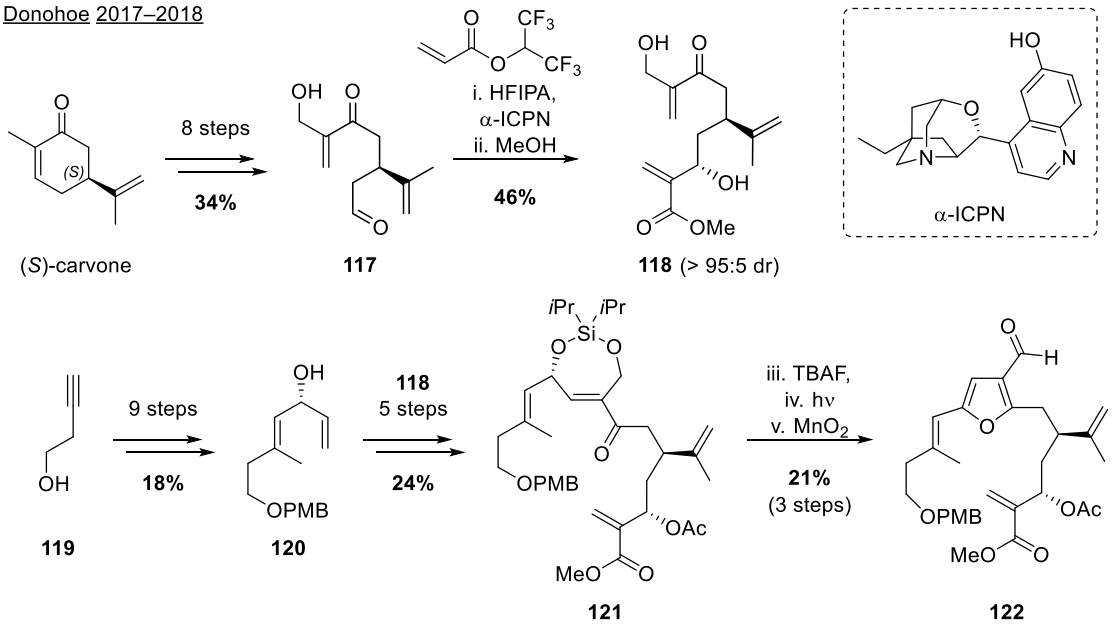
When the authors reacted *bis*-silyl ether **113** with fragment **110** using acetic acid instead of pivalic acid, acetoxy furan **114** was synthesised in 85% yield (3:2 dr). Following the same deprotection/macrolactonisation/RCM sequence allowed the synthesis of 7-acetyl-sinumaximol B (**115**) in 6% yield. In contrast to the macrolactonisation of the analogous epoxide **111**, both diastereomers of **114** reacted using Yamaguchi conditions. However, only one diastereomer was reactive in the RCM step, giving **115** as a single diastereomer.



Scheme 19 Synthesis of 7-acetylsinumaximol B (**115**) by Clark co-workers. Reagents and conditions: i) **110** (1.0 eq), **113** (2.5 eq), AcOH (1.2 eq), piperidine (0.2 eq), 4Å-MS, THT, 35 °C, 18 h; ii) TBAF (4.4 eq), THF, 10 °C, 7 h; iii) DIPEA (13 eq), 2,4,6-tichlorobenzoyl chloride (13 eq), PhH, rt, 5 h *then* DMAP (40 eq), 16 h; **112** (10 mol%), CH_2Cl_2, 40 °C, 16 h.

1.2.11 Synthesis of lophotoxin fragment 122

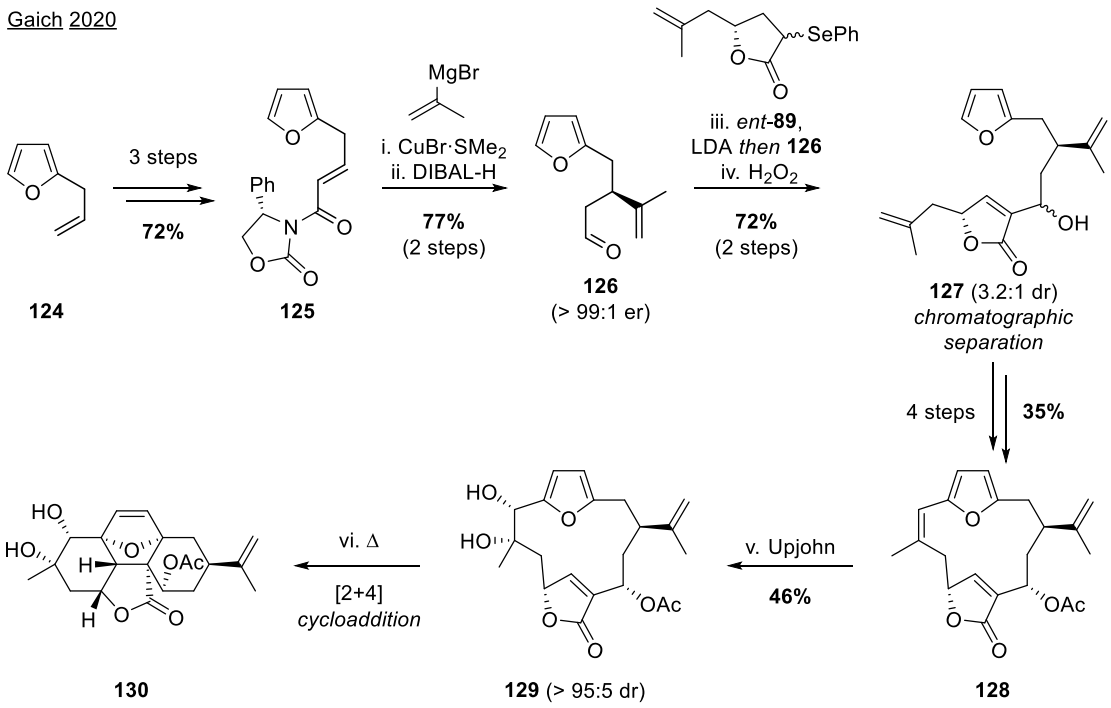
In a different approach, the Donohoe group developed a methodology to access trisubstituted furans capitalising on a silicon-tethered RCM followed by a photochemical olefin isomerisation.[60] Using this method, the authors synthesised lophotoxin fragment **122** (**Scheme 20**):[61-62] (*S*)-Carvone was advanced to aldehyde **117** over 8 steps in 34% overall yield. Asymmetric Baylis–Hillman reaction of **117** with hexafluoroisopropyl acrylate (HFIPA) was catalysed by *cinchona* alkaloid-based organocatalyst α-isocupreine (α-ICPN) and methyl ester **118** was isolated in 46% yield as a single diastereomer after methanolysis of the fragile HFIP ester. The second fragment was synthesised from 3-butyn-1-ol (**119**) in 9 steps. Silicon-containing heterocycle **121** was synthesised from fragments **118** and **120** in 5 further steps. Tether cleavage was achieved by treatment with TBAF. Subsequent light-mediated furan synthesis and MnO_2 oxidation gave furan **122** in 21% yield.



Scheme 20 Synthesis of furan **122** by Donohoe and co-workers. Reagents and conditions:
i) HFIPA (5.0 eq), α-ICPN (25 mo%), DMF, –55 °C, 48 h; ii) Et_3N (3.0 eq), MeOH, 25 °C, 12 h; iii) TBAF (3.0 eq), THF:buffer (aq., pH = 7), 0 °C to rt, 2 h; iv) UV-P (Pen-Ray), EtOAc, 0 °C, 21 h; v) MnO_2 (4 × 20 eq), CH_2Cl_2, 60 h.

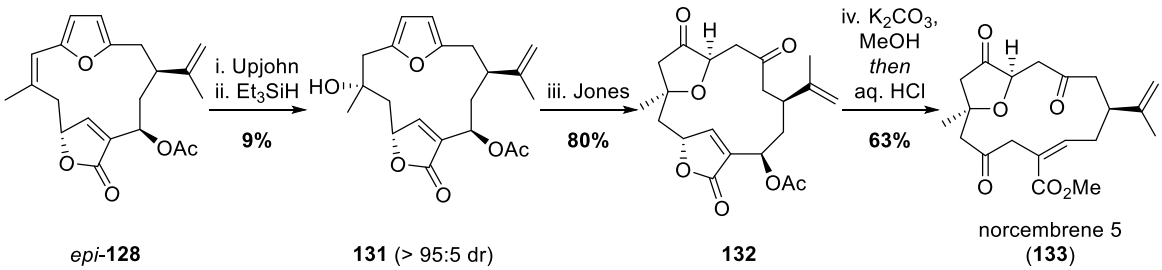
1.2.12 Total synthesis of norcembrene 5

Recently Gaich and co-workers reported the synthesis of norcembrene 5 (**133**), a natural product closely related to the furanocembranoid family.[63] First, the authors synthesised the Evans-type oxazolidinone **125** in 3 steps from 2-allylfuran (**124**, **Scheme 21**). The isopropenyl group was installed diastereoselectively *via* a conjugate organocuprate addition. Subsequent reduction with diisobutylaluminium hydride (DIBAL-H) afforded aldehyde **126** in 77% yield over 2 steps. Selenyl lactone *ent*-**89**, the enantiomer of **89** used in the syntheses of **97** and **104** (Chapters 1.2.8 and 1.2.9), was used in a similar manner to install butenolide **127** as a mixture of diastereomers (3.2:1 dr). After chromatographic separation of the diastereomers, macrocycle **128** was synthesised in 4 steps from the major diastereomer. There was precedent for the regio-, chemo- and stereoselective Upjohn dihydroxylation of **128**: Theodorakis and co-workershad demonstrated that the *C*-7/*C*-8 olefin can be oxidised selectively even without deactivating the furan heterocycle with an electron-withdrawing group.[64] Diol **129** spontaneously underwent unexpected transannular [2+4] cycloaddition to give densely functionalised *exo*-Diels–Alder product **130**. The authors accelerated the process by heating in benzene but did not report a yield for this transformation.



Scheme 21 Synthesis of cycloaddition product **130** by Gaich and co-workers. Reagents and conditions: i) isopropenylmagnesium bromide (1.3 eq), $CuBr{\cdot}SMe_2$ (1.3 eq), THF, –78 °C, 70 min *then* **125**, 1 h; ii) DIBAL-H (2.0 eq), CH_2Cl_2, –78 °C, 20 min; iii) LDA (1.2 eq), *ent*-**89** (1.1 eq), THF, –78 °C, 30 min *then* **126**, 10 min; vi) H_2O_2 (aq., 18 eq), NH_4Cl (aq.), CH_2Cl_2, 0 °C, 7 h; v) OsO_4 (10 mol%), NMO (0.95 eq), acetone:THF:H_2O (1:1:1), 0 °C, 2 h; vi) PhH, 80 °C (no yield given).

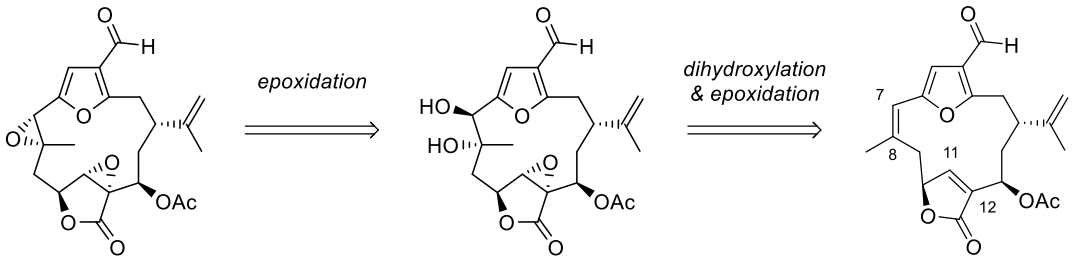
Macrocycle *epi*-**128**, obtained analogous to **128** from the minor diastereomer of **127** (*vide supra*), underwent formal hydration (Markovnikov) by Upjohn dihydroxylation and deoxygenation to give tertiary alcohol **131**. Treatment with the Jones reagent oxidised the furan moiety and subsequent 5-*exo*-trig cyclisation gave norcembrenolide **132** in 80% yield. Exposure of **132** to K_2CO_3 in MeOH for 15 min followed by aqueous HCl triggered elimination of the acetoxy group, affording **133** in 63% yield.



Scheme 22 Synthesis of norcembrene 5 (**133**) by Gaich and co-workers. Reagents and conditions: i) OsO_4 (10 mol%), NMO (0.95 eq), acetone:THF:H_2O (1:1:1), 0 °C, 3 h; ii) Et_3SiH (6.0 eq), $BF_3{\cdot}OEt_2$ (3.0 eq), CH_2Cl_2, –40 °C, 40 min; iii) CrO3/H2SO4 (1.1 eq), acetone, rt, 35 min; K_2CO_3 (1.5 eq), MeOH, rt, 15 min *then* HCl (1 M, aq.).

1.3 Research proposal

Despite the efforts of multiple research groups using different strategies, a chemical synthesis of lophotoxin in the laboratory remains elusive to date. Introducing the epoxide ring at position *C*-7/*C*-8 was identified as a major challenge. Previously, direct epoxidation of the corresponding olefin has only been achieved by the groups of Mulzer[37] and Roche.[38] However, in both cases the transformed macrocycles showed different functionalities to lophotoxin. Unspecific cyclisation of the tertiary alcohol (*C*-8) with an adjacent leaving group (*C*-7) by Zubía,[20] Clark,[59] and Roche[38] resulted in epoxide formation, providing the undesired epimer for lophotoxin. This epimerisation can be rationalised by minimisation of macrocyclic strain. Thus, we proposed to synthesise lophotoxin by activating the secondary alcohol of **2** selectively to trigger stereospecific cyclisation (**Scheme 23**). Diol **2** can in turn be prepared by dihydroxylation of the *C*-7/*C*-8 olefin and butenolide epoxidation of **67**, strategies demonstrated by Gaich[63] and Mulzer.[37]

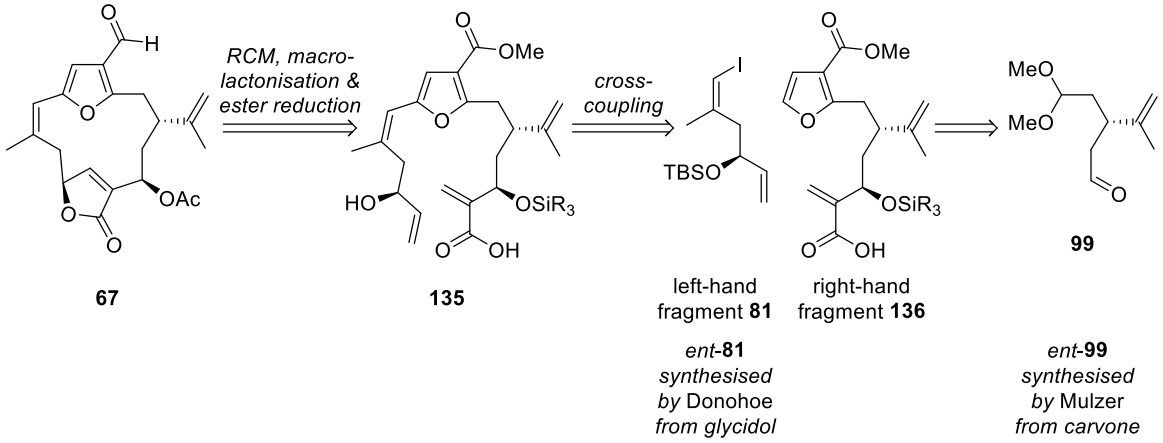


lophotoxin (**1**) lophodiol B (**2**) **67**

Scheme 23 Synthetic strategy to access lophotoxin *via* lophodiol B from **67**.

For the synthesis of macrocycle **67**, we initially planned to rely on proven strategies and methodologies. Consequently, we envisioned to construct the butenolide heterocycle by RCM, macrolactonisation and reduction of methyl ester **135**. Butenolide synthesis has been demonstrated on similar substrates by the groups of Donohoe[55] and Clark.[59] Compound **135** can be prepared from vinyl iodide **81** and furan **136** *via* Negishi cross-

coupling. The enantiomer of **81** was used by the Donohoe group in the synthesis of (*Z*)-deoxypukalide (Chapter 1.2.7). Furthermore, right-hand furan fragment **136** was thought to be synthesised from pseudo-symmetrical aldehyde **99**. The enantiomer of **99** was previously used by the Mulzer and co-workers in their synthesis of 11-gorgiacerol (Chapter 1.2.9).



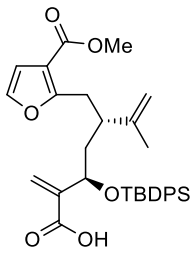
Scheme 24 Retrosynthetic analysis of macrocycle **67** to fragments **81** and **136**

Chapter 2

Synthesis of the right-hand furan fragment and model furans

2 Synthesis of the right-hand furan fragment and model furans

This chapter opens by introducing the two key methods used in the synthesis of right-hand fragment **137** (**Figure 7**): an RCM-based furan synthesis developed by the Donohoe group[65] (Chapter 2.1) and an asymmetric Baylis–Hillman reaction developed by Hatakeyama and co-workers (Chapter 2.2).[66] After the retrosynthetic analysis, various tested approaches to furan **137** are elucidated. The depicted routes vary in protecting group strategies and order of bond forming steps. The end of the chapter covers the route we chose to successfully synthesise furan **137** on gram scale.



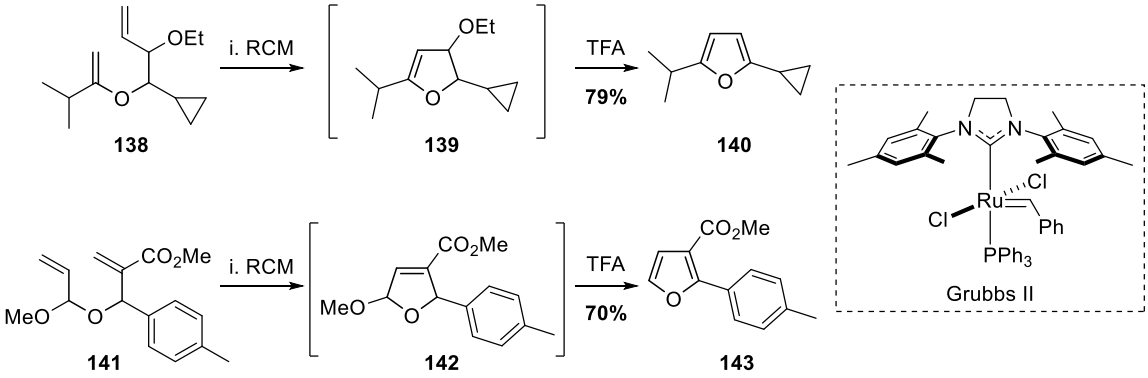
137

Figure 7 Right-hand fragment **137**.

2.1 RCM-based approach to furan synthesis

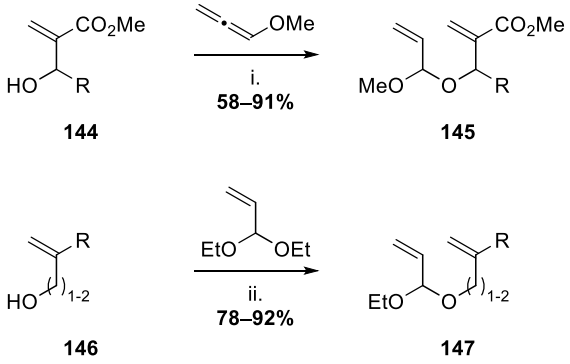
The development of transition-metal-catalysed methods for the synthesis of heterocycles is an ongoing effort in the Donohoe group. To this end, several olefin metathesis-based methodologies for the synthesis of di- and trisubstituted furans have been reported.[67-68] These methodologies often rely on UV-mediated isomerisation[60] or Brønsted acid-catalysed aromatisation.[69-70] Two selected examples for the latter are shown in **Scheme 25**. The first involved an RCM reaction of **138** between a secondary allylic ether and a 1,1-disubstituted enol. Both moieties can be considered suitable reaction partners for RCM reactions of small rings.[71-72] Subsequent treatment with acid induced the elimination of ethanol and aromatisation, providing furan **140** in 79% yield in a one-pot process. In the second process, 2,3-disubstituted furans, such as right-hand fragment **136** (**Scheme**

31), were accessed in a similar manner starting from mixed acetal **141**. However, compared to the first example, the 1,1-disubstituted enone is a slow reaction partner for olefin metathesis.[73] Nevertheless, formation of 5-membered rings was favoured and the reaction provided furan **143** in 70% yield.



Scheme 25 Selected examples for RCM-based furan syntheses.
Reagents and condition: i) Grubbs II (10 mol%), CH_2Cl_2, 40 °C *then* TFA (0.6 eq).

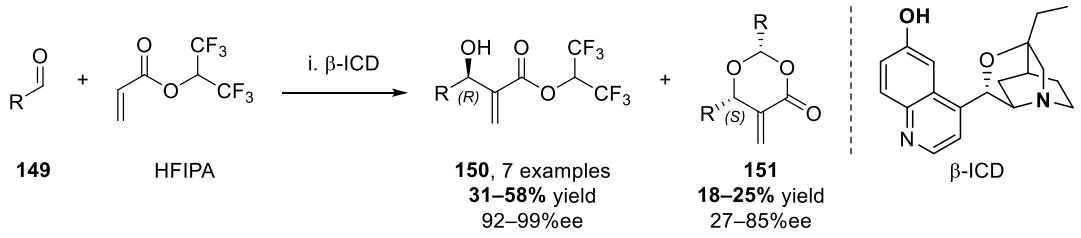
Two complementary approaches to access mixed acetals **145** and **147**, required for RCM-based furan synthesis, are shown in **Scheme 26**. Substrate **144** can undergo a palladium-catalysed addition reaction with methoxy allene under basic conditions to form mixed acetal **145**.[69] Under mildly Brønsted acidic conditions, **146** can undergo a transacetalisation reaction with acrolein diethyl acetal.[74-75] Both methods have been used successfully in the Donohoe group and allow flexibility in the protecting group strategy.[55,70]



Scheme 26 General approach to scaffolds **145** and **147**. Reagents and conditions: i) methoxyallene, $Pd(OAc)_2$ (5 mol%), dppp (5 mol%), Et_3N, MeCN, reflux; ii) acrolein diethyl acetal, PPTS (25 mol%), 40 °C, 80 mbar.

2.2 Asymmetric Baylis–Hillman reaction

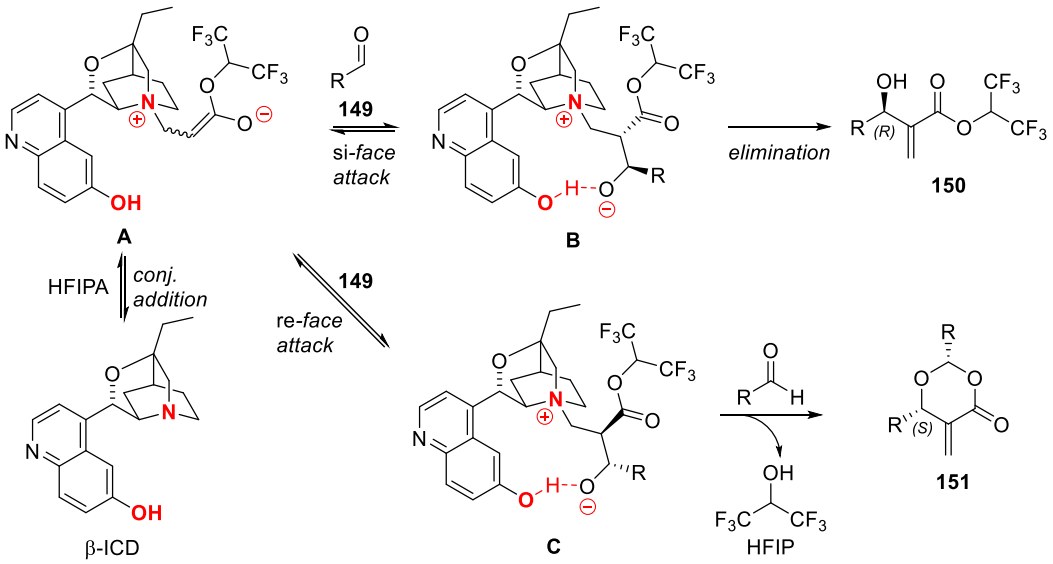
In 1999, Hatakeyama and co-workers reported a highly enantioselective modification of the Baylis–Hillman reaction (**Scheme 27**).[66] Key to good enantioselective induction was the use of activated 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as coupling partner, *cinchona* alkaloid-based organocatalyst β-Isocupreidine (β-ICD) and DMF at low temperatures. Tested derivatives of β-ICD not bearing a free phenoxyl group and/or lacking the caged-like ether moiety gave poor enantioselectivity. The same was true when methyl acrylate was used instead of HFIPA.[66] The original substrate scope was diverse and included electron-poor and electron-rich aromatics as well as linear and branched aliphatic aldehydes **149**. Only pivaldehyde was reported to be unreactive, demonstrating the steric limitation of this method to afford coupling products **150**. In most cases, diastereomerically pure dioxanone side-product **151** was isolated in low yields and with moderate enantioselectivities.



Scheme 27 Asymmetric Baylis–Hillman reaction of prochiral aldehydes.
Reagents and conditions: HFIPA (1.3 eq), β-ICD (10–20 mol%), DMF (0.1 M), –55 °C, 1–72 h.

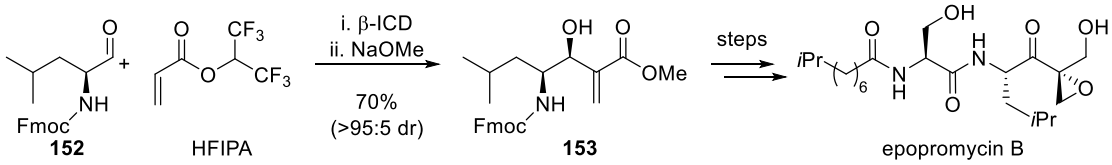
The fact that dioxanone **151** exhibits the opposite absolute configuration to product **150** gave interesting insight into the reaction mechanism proposed by Hatakeyama and co-workers (**Scheme 28**). Reversible conjugate addition reaction between HFIPA and the amine moiety of β-ICD can result in two possible olefin isomers of **A**. Enolate addition reaction with aldehyde **149** can then cause the formation of four possible diastereomers, with two possible ones (**B** and **C**) shown. It was proposed that both are stabilised with an intramolecular hydrogen bond. The authors suggest that these two intermediates then

undergo different reactions. Thus, elimination of **B** is most rapid after *Si*-face attack of the aldehyde yielding ester **150**. However, acetalisation of **C** with a second molecule of aldehyde outcompetes elimination after *Re*-face attack, causing the formation of dioxanone **151**. This selectivity might be explained by the varying probability of different diastereomers to populate conformational states favourable for E_2 or E_{1cb} elimination reaction. The formation of dioxanone **151** *via* a dynamic kinetic resolution (DKR) of ester **150** was ruled out based on resubmission experiments.[66]



Scheme 28 Proposed mechanism for the formation of Baylis–Hillman adduct **150** and dioxanone **151**.

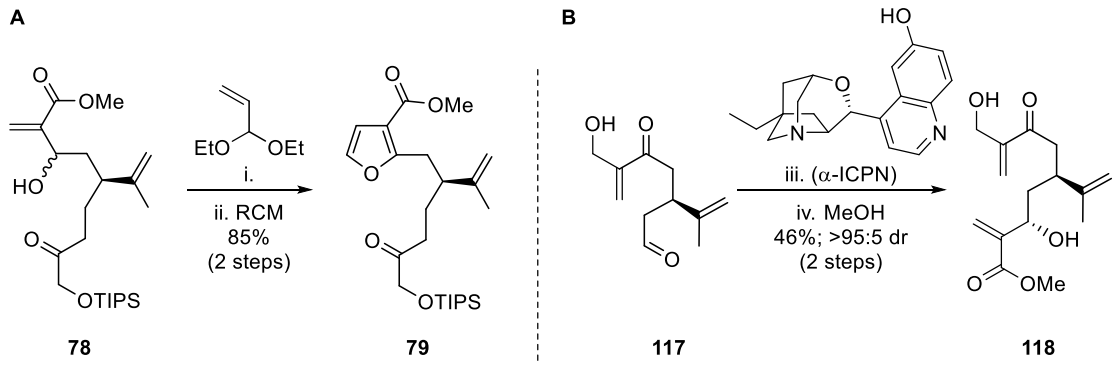
Hatakeyama and co-workers applied their methodology successfully in the formal synthesis of epopromycin B (**Scheme 29**).[76] Stoichiometric β-ICD facilitated the diastereoselective coupling of (*S*)-*N*-Fmoc-leucinal (**152**) and HFIPA. Methanolysis of the resulting mixture gave the major *syn*-product **153** in 70% yield. The minor *anti*-diastereomer of **153** was isolated in 2% yield (not shown). Ester **153** was further elaborated in several steps into epopromycin B.



Scheme 29 Application of the developed methodology in the total synthesis of Epopromycin B.
Reagents and conditions: i) HFIPA (1.3 eq), β-ICD (1.0 eq), DMF (0.1 M), –55 °C, 48 h; ii) NaOMe, MeOH.

2.3 Retrosynthetic analysis and strategic approach

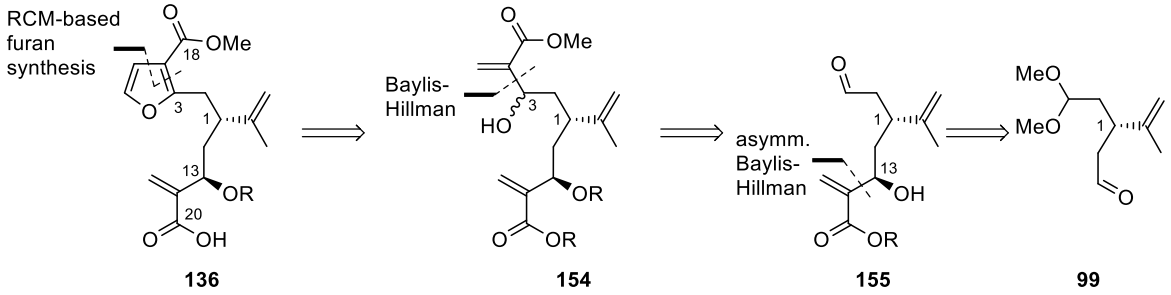
The initial focus of the project was aimed towards the synthesis of right-hand fragment **136**. The construction of the furan moiety was inspired by the RCM-based furan methodology (Chapter 2.1) and its successful application in the total synthesis of (*Z*)-deoxypukalide (Chapter 1.2.7), both reported by the Donohoe group.[55]



Scheme 30 Application of RCM-based furan synthesis (**A**) and asymmetric Baylis–Hillman reaction (**B**) on similar substrates. Reagents and conditions: i) acrolein diethyl acetal, PPTS; ii) Grubbs II, CH_2Cl_2 then PPTS; iii) α-ICPN (25 mol%), HFIPA (5 eq), DMF (0.1 M), –55 °C, 2 days; iv) Et_3N, MeOH (0.1 m), 25 °C, 12 h.

An orthogonal protecting group strategy is required in order to access right-hand fragment **137** (**Scheme 31**), which contains a carboxylic acid (*C*-20), a methyl ester (*C*-18) and a protected secondary alcohol (*C*-13). There is no need to control the stereochemistry at *C*-3 in **154**, as *C*-3 will eventually become sp^2-hybridised in the furan ring. Disconnection *via* a conventional Baylis-Hillman, or equivalent transformation, leads back to aldehyde **155**. Stereoselectivity at *C*-13, however, needs to be high, as this centre remains as a secondary acetoxy group in (+)-Lophotoxin.[11] In addition to the β-ICD-based method described above (Chapter 2.2), Hatakeyama and co-workers also developed an asymmetric Baylis–Hillman reaction with inverted selectivity. The pseudo-enantiomer α-isocupreidine (α-ICPN) was shown to give similarly high selectivity and yield providing the opposite enantiomer of the product.[11] Two previous members of the Donohoe group, Dr. Johannes Walker and Dr. Simon Werrel, showed that aldehyde **117**, a very similar fragment to aldehyde **99**, can be converted to ester **118** with excellent

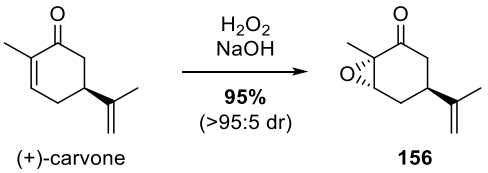
diastereoselectivity in moderate yield (**Scheme 30B**).[77-78] Aldehyde **99** and its enantiomer (*ent*-**99**), in turn, are literature-known compounds derived from the respective enantiomer of carvone. Aldehyde **99** has been synthesised by Pattenden et *al* from (+)-carvone;[79] Mulzer and co-workers have used *ent*-**99**, derived from (–)-carvone, in the total synthesis of 11-gorgiacerol (Chapter 1.2.9).[57]



Scheme 31 Retrosynthetic analysis of right-hand fragment **136**.

2.4 Synthesis of aldehyde 99

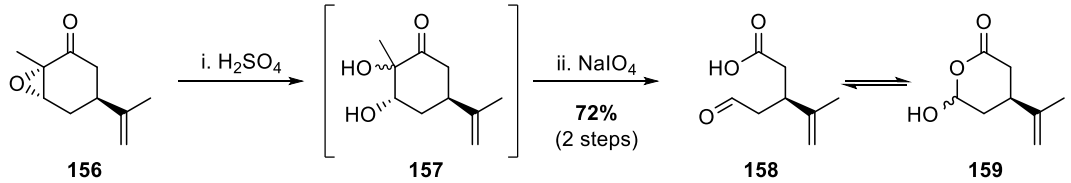
The longest linear route of the entire total synthesis project began by the synthesis of aldehyde **99** using the route previously reported by Mulzer and co-workers.[57] Dropwise addition of both hydrogen peroxide and sodium hydroxide at cryogenic temperatures was required to epoxidise (+)-carvone (**Scheme 32**). [57,78] Epoxide **156** was formed in 95% on a 25 gram scale as a single detectable diastereomer and purification by column chromatography was not required. The relative diastereoselectivity of this transformation is dictated by the steric bulk of the isopropenyl group and is inconsequential for this synthesis. The relative stereochemistry was assigned based on previous reports.[57]



Scheme 32 Epoxidation of (+)-carvone.
Reagents and conditions: H_2O_2 (2.1 eq), NaOH (0.3 eq), MeOH (0.4 m), –20 to 0 °C, 3 h.

Epoxide **156** was converted into diol **157** in THF and H_2O at 80 °C and strongly acidic conditions (**Scheme 33**). Due to inconsequential unselective epoxide opening, diol **157**

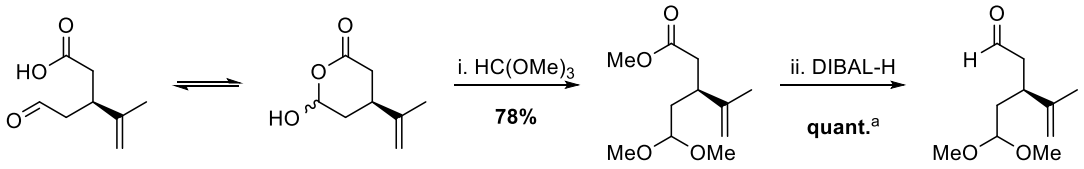
was isolated as a mixture of diastereomers. No purification by column chromatography was necessary and periodate cleavage was performed on the crude material using a silica gel supported protocol.[78] This step was somewhat capricious and correct formation of the H_2O:CH_2Cl_2:silica gel slurry proved crucial prior to addition of the starting material. Furthermore, it was observed that the $NaIO_4$:H_2O ratio was important and was kept as reported when reduction of solvent was necessary during scale-up of the process. Product **158** could in principle exist as an equilibrium mixture of linear carboxylic acid **158a** and cyclic acetal **159b**. However, **158a** was the dominant form observed by NMR spectroscopy in $CDCl_3$ with characteristic aldehyde peaks at 9.69 ppm (^{1}H NMR) and 201.1 ppm (^{13}C NMR). The spectral data were consistent with those previously reported.[57]



Scheme 33 Synthesis of aldehyde **158**. Reagents and conditions: i) H_2SO_4 (0.3 eq), THF:H_2O (20:1, 0.2 M), 80 °C, 36 h; ii) $NaIO_4$ (3 eq), silica gel, CH_2Cl_2:H_2O (88:12), 0 °C, 16 h.

Compound **158** was converted into methyl ester **160** under acidic conditions in MeOH utilising trimethyl orthoformate as a desiccant (**Scheme 34**). Characteristic for all chiral compounds bearing a di-methyl acetal was the presence of two distinct singlets at 3.25–3.35 ppm in the ^{1}H NMR, accounting for the diastereotopic methyl groups as well as the acetal signal at approximately 103 ppm in the ^{13}C NMR. Acetal **160** was synthesised in decagram batches and a total of 46 g was synthesised using the described route. The material was stable to bench storage for several months and, for strategic reasons, material was often stored at this stage. As some of the subsequent steps proved to be capricious, the quality of ester **160** was closely monitored. Purification by vacuum distillation was attempted, but unsuccessful due to decomposition. Treatment of ester **160** with DIBAL-H at –78 °C gave a clean reduction reaction to aldehyde **99**, even on a

decagram scale. On large scales, slow addition of DIBAL-H as a solution in toluene *via* syringe pump or canula was crucial to avoid the formation of the corresponding primary alcohol. Moreover, prolonged vigorous stirring with Rochelle salt after quenching increased the isolated yield of **99**. Attempts to purify aldehyde **99** by column chromatography provided clean material, but with significantly reduced yields. Therefore, column chromatography was not performed, and crude aldehyde **99** was used in the next step on the same day.



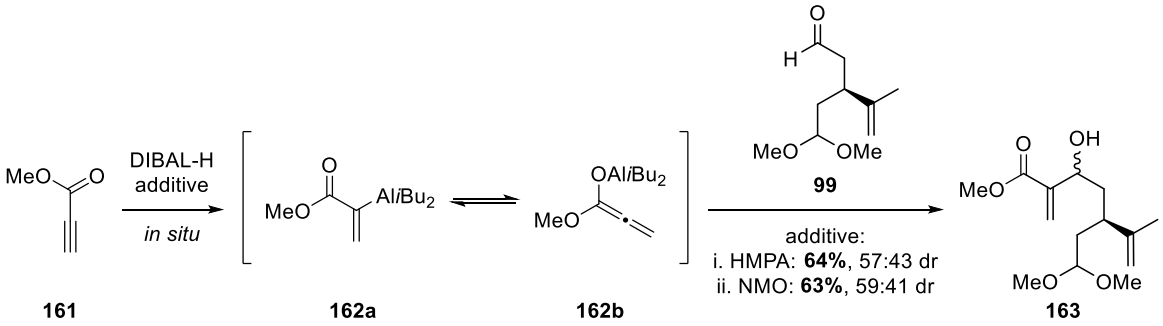
Scheme 34 Synthesis of aldehyde **99**. Reagents and conditions: i) $HCO(OMe)_3$ (5 eq), TsOH · H_2O (5 mol%), MeOH (0.4 M), rt, 24 h; ii) DIBAL-H (1 eq), CH_2Cl_2, –78 °C, 2 h; a) crude aldehyde **99** was used in the following step without purification, yields over two steps from ester **160** are reported.

All characterisation data of and synthesised intermediates matched the spectra published by Mulzer and co-workers.[57] Notably, aldehyde **99** is pseudo-symmetric, bearing an aldehyde and an acetal equidistant to the central isopropenyl group. This provides the strategic possibility to either install the furan ring (Chapters 2.5 and 2.6) or perform the asymmetric Baylis–Hillman reaction (Chapters 2.7 to 2.9) first.

2.5 Synthesis of acetal containing furan 167

With aldehyde **99** in hand, efforts were focused on installation of the furan heterocycle. To this end, a method published by Saegusa and co-workers to react α,β-acetylenic carbonyl compounds, such as methyl propiolate (**161**), with aldehydes and ketones was investigated.[80] The obtained product from this transformation is equivalent to that of a Baylis–Hillman reaction. However, due to the involvement of a more reactive nucleophilic intermediate, this method is superior when less reactive electrophiles, such as ketones and aliphatic aldehydes, are used. We decided to adopt Saegusa‘s methodology to

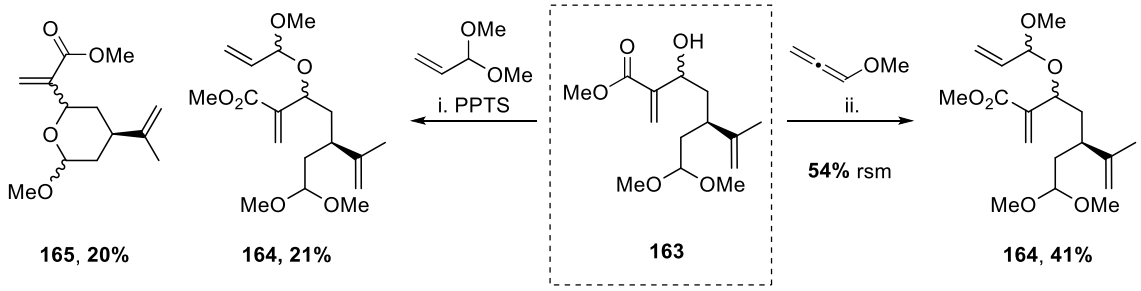
prepare secondary alcohol **163** (**Scheme 35**). Methyl propiolate was added to a mixture of DIBAL-H and HMPA, resulting in the formation of vinyl aluminium **162a** and/or aluminium allenolate **162b**. Addition of aldehyde **99** to *in situ* formed **162** caused the formation alcohol **163** in 64% yield (57:43 dr). Ramachandran and co-workers reported that less toxic NMO can be used as an additive instead of cancerogenic HMPA.[81] This alternative method was tested and provided the desired product in 63% yield (59:41 dr). Later results of similar transformations showed that the aldehyde addition step was completed after 2.5 h and vigorous stirring with Rochelle salt overnight increased the isolated yield (Chapter 2.6).



Scheme 35 Synthesis of alcohol **163**. i) DIBAL-H (4.5 eq), HMPA (12 eq), THF, 0 °C *then* methyl propiolate (5 eq) *then* **99**, 45 °C, 16 h; ii) DIBAL-H (3.5 eq), NMO (3.5 eq), THF, 0 °C *then* methyl propiolate (4 eq) *then* **99**, 45 °C, 18 h.

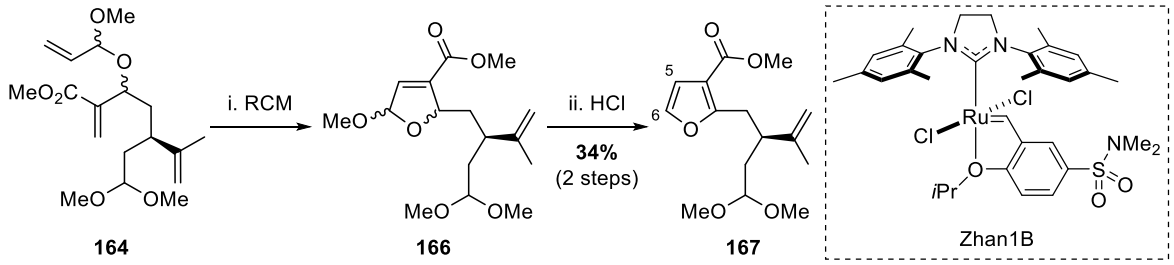
Formation of mixed acetal **164** in high yields was not straightforward (**Scheme 36**). Initial attempts included transacetalisation with acrolein dimethoxy acetal under mildly acidic conditions. Mixed acetal **164** was isolated in 21% yield as an inconsequential mixture of four diastereomers, together with undesired with cyclic acetal **165** in 20% yield. Heavily contaminated recovered started material was isolated (18%) as well. The alternative method using methoxy allene and palladium catalysis gave a much cleaner reaction. Nevertheless, low conversion (41% product and 54% recovered starting material) hampered this transformation. The reaction was performed in a sealed tube at 60 °C. As methoxyallene has a boiling point of 53 °C, it may cause over-pressurisation of the reaction vessel, which would be a potential hazard during scale-up. Moreover, Anderson

and co-workers demonstrated that the safe formation and storage of methoxy allene from methyl propargyl ether on large scales is non-trivial.[82]



Scheme 36 Synthesis of mixed acetal **164**. Reagents and conditions:
i) Acrolein dimethoxy acetal (16 eq), PPTS (0.1 eq), PhMe, 40 °C, 100 mbar, 5 h;
ii) methoxy allene (2.5 eq), $Pd(OAc)_2$ (3 mol%), dppp (5 mol%), Et_3N (1.5 eq), THF, 60 °C, sealed, 24 h.

Due to the complexity of the sample (mixture of four diastereomers), mixed acetal **164** was not characterised and was instead directly carried through to the next step. Exposure of **164** to olefin metathesis catalyst Zhan1B afforded dihydrofuran **166** (**Scheme 37**). The desired furan **167** was isolated after treatment in acidic methanol in a separate operation, albeit in only 34% yield over two steps from mixed acetal **164**. Synthesised 2,3-disubstituted furans bearing an ester showed a small coupling constant of J = 2.0 Hz between *H*-5 (d, 6.60 ppm) and *H*-6 (d, 7.18 ppm) in the ^{1}H NMR.



Scheme 37 Synthesis of furan **167**. Reagents and conditions:
i) Zhan1B (5 mol%), PhMe (50 mM), 40 °C, 24 h; ii) AcCl (0.6 eq), MeOH, 40 °C, 24 h.

As metathesis catalysts are Lewis acidic and the final aromatisation step required Brønsted acid, having an acid-sensitive dimethoxy acetal moiety present in the substrate was considered a high-risk strategy. Because of the safety concerns using methoxy allene and the low yields of the furan formation this route was abandoned.

2.6 Synthesis of PMB containing furan 169

A potential synthetic route to right-hand fragment **137** could involve PMB ether **169** (**Figure 8**) as a precursor. Although carboxylic acid **137** was the desired coupling partner, furan **169** could additionally be used as a model substrate for various furan coupling strategies. Ether **169** is less complex and therefore more readily prepared. Furthermore, purification and analysis of **169** was expected to be easier than that of carboxylic acid **137**. If a coupling strategy were to be successful with PMB furan **169** but not with carboxylic acid **137**, there would also be the option to deprotect the PMB ether and derivatise it after fragment coupling.

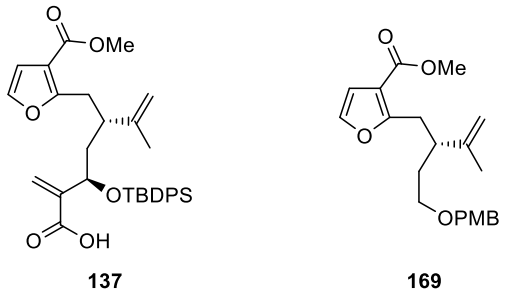
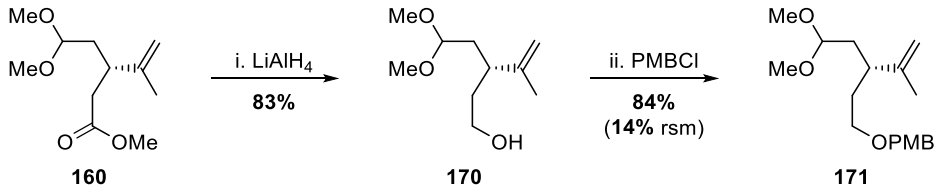


Figure 8 Carboxylic acid **137** and PMB ether **169** are two possible furan coupling partners.

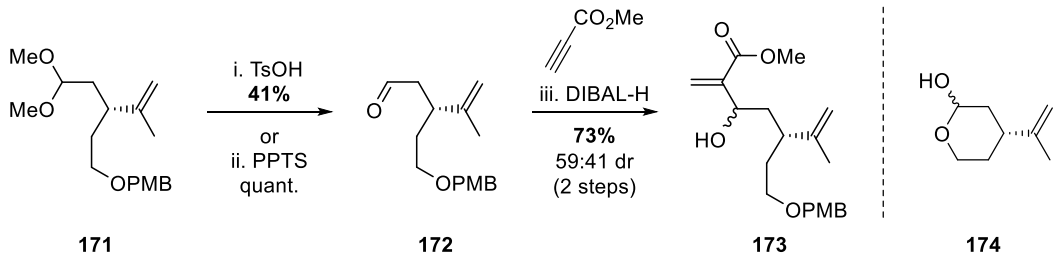
The synthesis of furan **169** commenced with ester **160**, which was prepared from (+)-carvone in 53% yield over four steps on a decagram scale (Chapter 2.4). Reduction with $LiAlH_4$ on a 5-gram scale afforded alcohol **170** in good yield (**Scheme 38**). Subsequent PMB protection of primary alcohol **170** with *p*-methoxybenzyl chloride utilised TBAI as nucleophilic catalyst.



Scheme 38 Synthesis of PMB ether **171**. Reagents and conditions: i) $LiAlH_4$ (1 eq), THF (0.1 M), 0 °C to rt, 16 h; ii) NaH (2 eq), THF *then* PMBCl (1.1 eq), TBAI (5 mol%), 75 °C, 16 h.

Acetal deprotection required fine-tuning of conditions. Conventional conditions using TsOH at 50 °C or at rt in acetone and H_2O resulted in the formation of cyclic hemi-acetal

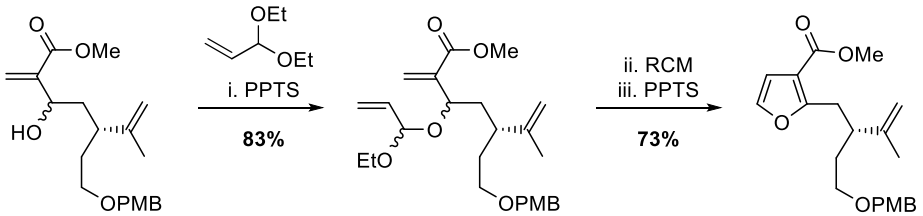
174 and desired aldehyde **172** (**Scheme 39**).[54] Isolation of side-product **174** was hampered by co-elution with *p*-methoxy benzyl alcohol (51:49 mixture). Hemi-acetal **174** is a literature-known compound; observed NMR signals (^{1}H and ^{13}C) of the prepared sample match the data reported by Pattenden and co-workers.[47] Although *p*-methoxy benzyl alcohol and **174** were isolated in equimolar amounts, the cleavage of PMB ether to *p*-methoxy benzyl alcohol became evident when the ^{1}H-signals at the benzylic position (4.3–4.5 ppm) were analysed. The strong, characteristic $^{2}J_{H\text{-}H}$-coupling (J = 11–12 Hz) between the geminal diastereotopic protons in chiral PMB ethers vanished and a singlet (4.58 ppm) was observed. It was hoped that formation of side-product **174** could be suppressed by using a weaker acid, pyridinium *p*-toluenesulfonate (PPTS). Initial attempts using PPTS were closely monitored by TLC, but reaction times varied unpredictably (2–6 h). Therefore, it was decided to perform the reaction overnight as the formation of hemi-acetal **174** under those conditions was minimal. Aldehyde **172** was not purified by column chromatography and subjected to the next step on the same day. The hydroalumination coupling sequence using NMO as an additive (Chapter 2.5) worked well and provided alcohol **173** in 73% yield (59:41 dr) in two steps from acetal **171** on gram scale. Crucial for high isolated yields was prolonged vigorous stirring of the quenched reaction mixture with Rochelle salt overnight.



Scheme 39 Synthesis of alcohol **173**. Reagents and conditions: i) TsOH · H_2O (0.25 eq), acetone/H_2O (4:1), 50 °C, 24 h; ii) PPTS (0.25 eq), acetone/H_2O (4:1), 50 °C, 16 h; iii) DIBAL-H (3.5 eq), NMO (3.5 eq), THF, 0 °C *then* methyl propiolate (4 eq) *then* **172**, 45 °C, 2.5 h.

Reduced pressure was required for the transacetalisation of alcohol **173** with acrolein diethyl acetal (**Scheme 40**). The conversion was increased by concomitant removal of

ethanol (bp = 78 °C)**.** Thus, the combination of toluene (bp = 110–111 °C) and acrolein diethyl acetal (bp = 125 °C) was chosen.[83] This reaction was performed on a rotary evaporator (60–100 mbar) and the choice of reagents ensured that the formed ethanol and the solvent evaporated before the reagent would. The transformation afforded mixed acetal **175** in 83% yield as a mixture of four diastereomers.



173 **175** **169**

Scheme 40 Synthesis of furan **169**. Reagents and conditions: i) acrolein diethyl acetals (8 eq), PPTS (0.1 eq), PhMe, 40 °C, 100 mbar, 3 h; ii) for RCM see **Table 1**; iii) PPTS (1 eq), CH_2Cl_2, 40 °C, 2 h.

To increase conversion, a gentle flow of nitrogen was used to removed evolved ethene by-product from the head space of the reaction mixture (**Figure 9**). Reactions performed under this set-up, compared to sealed vessels, exhibited higher conversions and fewer side-products.

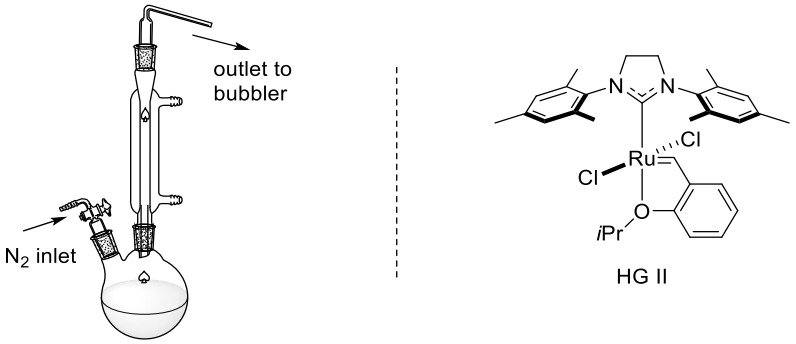


Figure 9 Set-up for RCM reactions and chemical structures for Hoveyda-Grubbs 2nd.

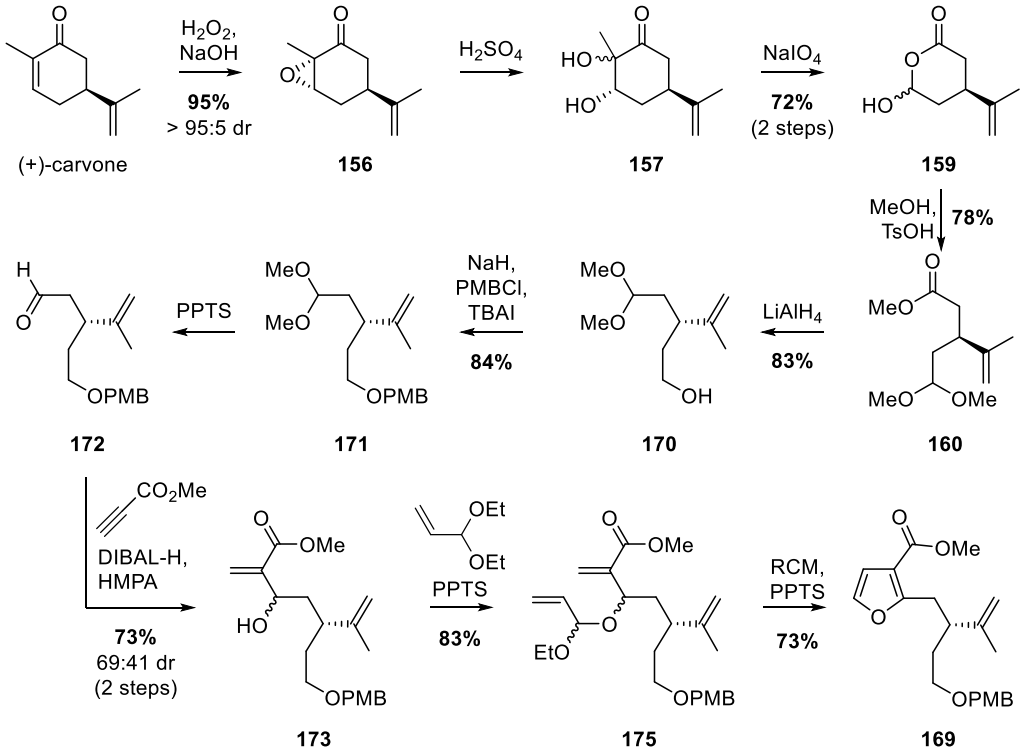
Different conditions for the RCM step in the synthesis of furan **169** were screened to maximise the yield while minimising catalyst loading (**Table 1**). The cost for olefin metathesis catalysts HG II (£ 498 for 2.0 g/3.2 mmol) and Zhan1B (£ 480 for 2.0 g/2.7 mmol) could turn into a limiting factor otherwise.[83] Temperature (40–80 °C), reaction time (20–69 h), substrate concentration (50–100 mM) and catalyst loading (5–

15 mol%) were varied. The best results were achieved when the catalyst was added in portions over the course of the reaction (entries 4 and 5), which suggests that catalyst decomposition was a yield-limiting factor. Moreover, it was observed that the solvent level of RCM reactions with nitrogen flow dropped over the course of the experiment. If this happened too rapidly, the reaction stalled. However, reduction of solvent in a controlled manner increased the conversion. Nevertheless, Schmidt and co-workers have reported that RCM reactions can stall, if performed at high concentration,[84] a trend similar to what we have observed.

Table 1 Conditions for RCM reactions to synthesise furan **169** (**Scheme 40**): PhMe, N_2-flow; a) solvent had evaporated after 24 h and was filled up.

entry	scale [mmol]	concen-tration	reaction time	reaction temp.	RCM catalyst	catalyst loading	isolated yield of **169**
1	0.32	50 mM[a]	42 h	40 °C	Z1B	7.5 mol%	**63%**
2	0.68	50 mM[a]	60 h	60 °C	Z1B	10 mol%	**59%**
3	1.33	75 mM	69 h	80 °C	Z1B	7.5 mol%	**58%**
4	1.35	75 mM	63 h	60 °C	Z1B	3 x 5.0 mol%	**67%**
5	2.47	75 mM	63 h	60 °C	HG II	2 x 5.0 mol%	**73%**
6	7.70	0.10 M	20 h	40 °C	HG II	5.0 mol%	**55%**

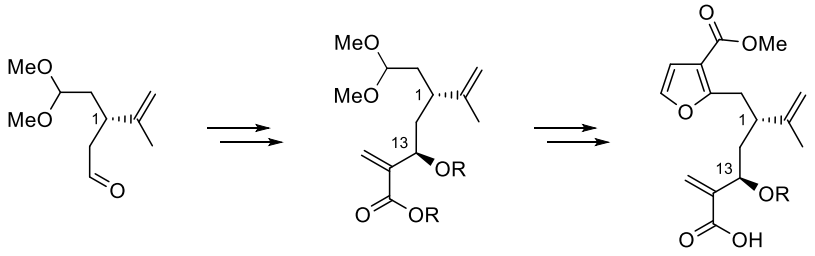
In summary furan **169** was synthesised from (+)-carvone in 10 steps with 23% overall yield.



Scheme 41 Overview of the synthetic route to furan **169**.

2.7 Asymmetric Baylis–Hillman reaction

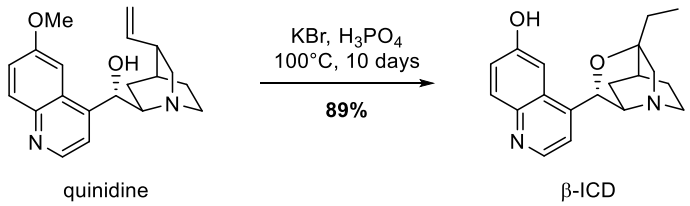
With a scalable route to pseudo-symmetrical aldehyde **99** at hand (Chapter 2.4), a synthetic route was now required to elaborate **99** into right-hand fragments **136** (**Scheme 42**). To that end, an approach that involved establishing the stereocentre at *C*-13 *via* an asymmetric Baylis–Hillman reaction prior to the synthesis of the furan ring was proposed. Such a route would require an orthogonal protecting group strategy of enone **177** to access **136**. Nevertheless, it also re-located the RCM step requiring expensive catalyst to a later stage of the synthesis, making the synthesis more cost-efficient.



99 **177** **136**

Scheme 42 Strategic approach to right-hand fragment **136** through enone **177**.

Although the organocatalyst β-ICD required for the asymmetric Baylis–Hillman reaction was commercially available, when larger quantities were used it was synthesised using a procedure reported by Hatakeyama and co-workers; under this procedure, quinidine was heated with potassium bromide in orthophosphoric acid at 100 °C for 10 days (**Scheme 19**).[85] Although spectroscopically pure β-ICD was isolated in 89% yield on a 25 g scale as bright yellow foam, the material was recrystallised to give a pale white powder. It was found that recrystallisation from methanol by dropwise addition of H_2O at room temperature gave the best mass recovery. Surprisingly, partial decomposition was observed when recrystallisation was attempted in a refluxing mixture of MeOH and H_2O.

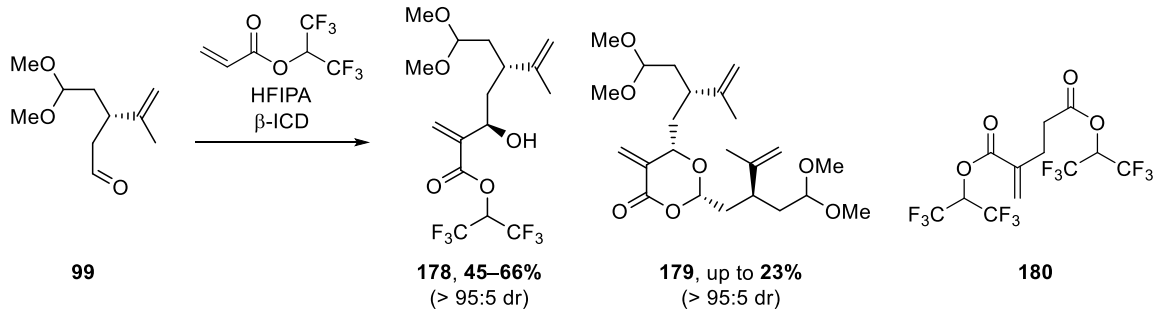


quinidine β-ICD

Scheme 43 Synthesis of β-ICD. Reagents and condition: KBr (10 eq), H_3PO_4 (0.2 M), 100 °C, 10 days.

With aldehyde **99** and catalyst β-ICD in hand the asymmetric Baylis–Hillman reaction was attempted (**Scheme 44**). HFIPA was added *via* syringe-pump (1 h addition time) and the reaction mixture was cooled to –55 °C using a cryostat for 3 days. Desired HFIP ester **178** was isolated as a single diastereomer (> 95:5 dr) in moderate yield and was stable to storage at –20 °C for at least 4 weeks. The proton adjacent to the two CF_3-groups displayed a coupling constant of $^3J_{H\text{-}F}$ = 6.1 Hz and appeared as a septet (5.83 ppm) in the ^{1}H NMR. Side-product dioxanone **179** was also isolated as a single diastereomer in up to

23% yield. However, the isolation of dioxanone **179** was occasionally hampered by co-elution of unidentified side-products. When a large excess of HFIPA was used, increased quantities of non-volatile dimer **180** were observed. It was also possible to recover up to 71% of the amount of β-ICD used from the acidic wash of the aqueous work-up. Proof for the observed stereoselectivity for **178** and **179** is presented in Chapter 2.7.2; the stereochemical outcome was consistent with similar compounds synthesised using β-ICD.[66,76]



Scheme 44 Synthesis of HFIP ester **178**. Conditions and reagents: see **Table 2**

The conditions for addition experiments are listed in **Table 2**. Yields are calculated over two steps and include the formation of aldehyde **99** from corresponding methyl ester **160** (Chapter 2.4). To ease purification by column chromatography, the formation of dimer **180** was successfully suppressed by reducing the amount of HFIPA used. Furthermore, the effect the source of β-ICD had on reaction outcome was investigated: Organocatalysts that were obtained commercially, synthesised, or recovered from previous reactions were tested (entries 1–3). The differences in yield using these catalysts from different sources were within experimental error and this aspect was disregarded. When aldehyde **99** was partially contaminated with the corresponding primary alcohol (up to 20 wt%) from an unselective DIBAL-H reduction, HFIP ester **178** was still observed in 35–40% yield over two steps (not shown in **Table 2**). Unfortunately, the yields diminished slightly when the scale of the reaction was increased (entries 7–9). It was surmised that in such cases a portion of aldehyde **99** was lost during aqueous work-up of the DIBAL-H reduction step

(entry 7). This issue was not completely resolved by prolonged vigorous stirring with Rochelle salt (entries 8–9).

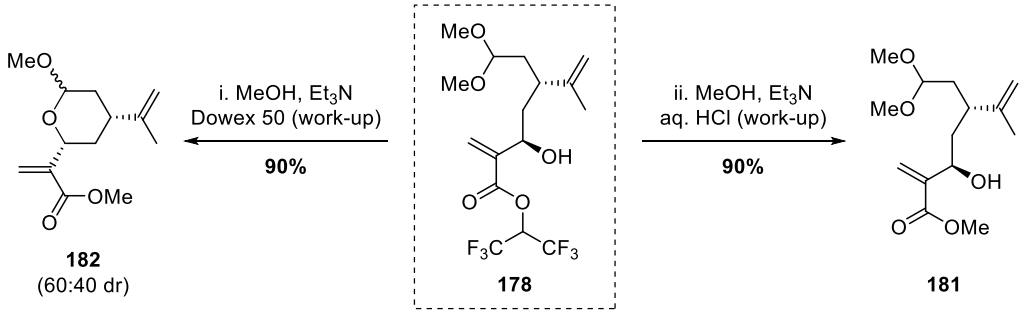
Table 2 Conditions for asymmetric Baylis–Hillman reaction (**Scheme 44**): β-ICD (25 mol%), DMF (0.1 M), –55 °C, 3 days; a) the yield was calculated over two steps from methyl ester **160**. Crude aldehyde contained less than 10% of the corresponding primary alcohol **170**; b) commercial β-ICD was used.

entry	scale [mmol]	HFIPA	isolated yield of **178**[a]	dr of **178**	comment
1	1.3	5.0 eq	**61%**[b]	> 95:5	**179** (**18%**)
2	1.9	2.5 eq	**58%**	> 95:5	synthetic β-ICD used
3	1.9	2.5 eq	**57%**	> 95:5	recovered β-ICD used
4	3.0	5.0 eq	**66%**[b]	> 95:5	-
5	8.3	1.0 eq	**61%**	> 95:5	**179** (**23%**)
6	17	2.5 eq	**60%**	> 95:5	rec. β-ICD (**59%**)
7	23	2.5 eq	**45%**	> 95:5	-
8	25	2.5 eq	**53%**	> 95:5	rec. β-ICD (**71%**)
9	58	2.5 eq	**52%**	> 95:5	**179** (**23%**)

2.7.1 Methanolysis of HFIP ester 178

Due to their high tendency to decompose, HFIP esters have previously been converted to more stable methyl esters prior to further derivatisation.[78,85] To use such a strategy, HFIP ester **178** was treated with Et_3N in MeOH and clean conversion to methyl ester **181** was observed by TLC (**Scheme 45**). However, work-up with acidic ion exchange resin Dowex 50, as reported in the literature, yielded undesired cyclic acetal **182** as a mixture of two inseparable diastereomers (60:40 dr) in 90% yield. Only trace amounts of methyl ester **181** were isolated. To suppress this undesired cyclisation, different options for reaction work-up were considered. It was speculated that the acid-catalysed cyclisation

would be suppressed due to separation of the reactive partners into different layers, if an aqueous acidic work-up was used. This plan of action was successful and methyl ester **181** was isolated in 90% yield when the reaction mixture was diluted with EtOAc prior to quenching the reaction with an aqueous solution of HCl (1 M). As Dowex 50 consists of immobilised sulfonic acid units, this vast difference in selectivity was most likely not caused by the difference in acidic strength of the two acids used. Moreover, it was observed that precise control of reaction temperature at 25 °C was crucial for a clean methanolysis reaction of HFIP ester **178**. To this end, the reaction temperature was regulated with an oil bath.

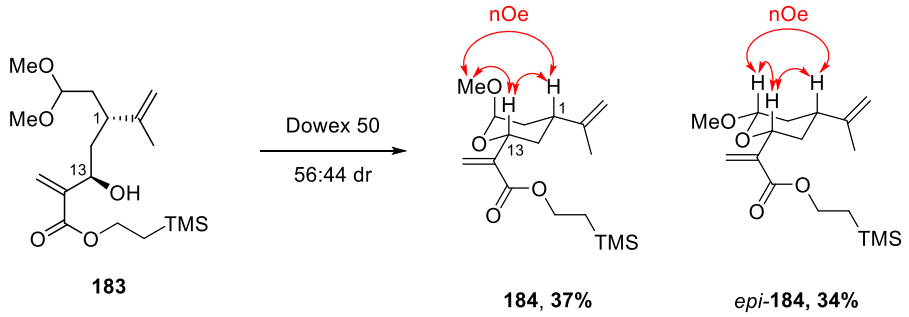


Scheme 45 Formation of cyclic acetal **182** and ester **181**. Reagents and conditions: i) Et_3N (3 eq), MeOH (0.2 M), 0 to 25 °C, 16 h *then* work-up with Dowex 50WX8; ii) Et_3N (3 eq), MeOH (0.2 M), 0 to 25 °C, 16 h *then* work-up with aq. HCl.

2.7.2 Assignment of stereocentre *C*-13

Although cyclised methyl ester **182** was an undesired side-product, careful nOe analysis of the cyclic compound could be conducted to assign the configuration of the *C*-13 stereocentre formed in the stereoselective Baylis–Hillman reaction, hence deriving structural information of side-product **182** itself and of HFIP ester **178**. However, **182** was isolated as an inseparable mixture of two diastereomers (60:40 dr). Drawing unambiguous conclusions was therefore not possible. However, TMSE ester **183**, a later synthesised derivative of methyl ester **163** (Chapter 2.9.1), was subjected to similar cyclisation conditions (**Scheme 46**). Surprisingly, the cyclisation of **183** was a much slower reaction and was only completed after 16 h. Nevertheless, cyclic acetal **184** was formed

as a 56:44 mixture of diastereomers and attempted separation of both diastereomers by column chromatography was successful. Acetals **184** and *epi*-**184** where isolated in 37% and 34% yields, respectively. Both compounds were analysed by nOe to assign their relative configuration. Key 1,3-diaxial interactions provided proof for the desired relative stereochemical relationship between *C*-1 and *C*-13 (**Scheme 46**). The fact that the all-equatorial diastereomer *epi*-**184** was not dominant can be explained by the anomeric effect. This analysis is in alignment with the later obtained X-ray crystal structure of butenolide **322** (Chapter 5.4).

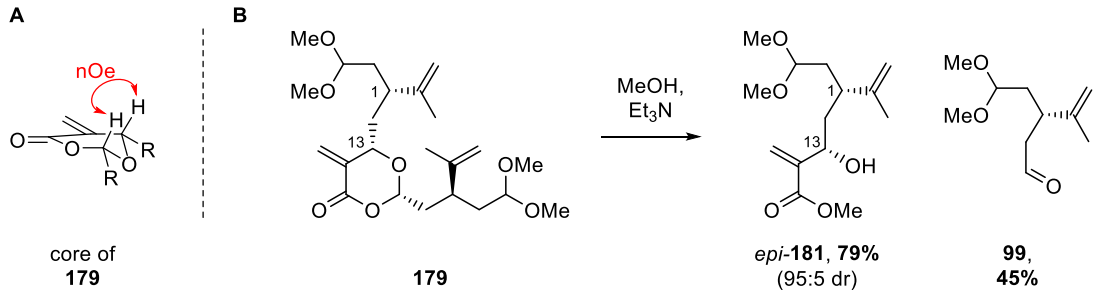


183 **184**, **37%** *epi*-**184**, **34%**

Scheme 46 Cyclisation of TMSE ester **183**. Reagents and conditions: Dowex 50WX8, MeOH (0.1 M), rt, 16 h.

The second product isolated from the β-ICD-catalysed Baylis–Hillman reaction with a defined stereocentre at *C*-13 was dioxanone **179** (**Scheme 44**). The relative stereochemistry across the six-membered ring was confirmed by nOe analysis to be the thermodynamically favoured *cis* configuration (**Scheme 47A**). When Hatakeyama and co-workers first applied this method in their formal synthesis of epopromycin B, they reported that the methanolysis step was performed on a mixture of their obtained HFIP ester and the respective dioxanone.[76] Thus, isolated dioxanone **179** was subjected to the same methanolysis conditions developed for HFIP ester **178** (**Scheme 47B**). Interestingly, **179** was not stable to these conditions and methyl ester *epi*-**181** (95:5 dr) and aldehyde **99** were isolated in 79% and 45% yield, respectively. As *epi*-**181** exhibited undesired stereochemistry at *C*-13, increased attention was paid to the fact that every synthesised batch of HFIP ester **178** was free of any dioxanone contaminations prior to methanolysis.

This was especially true as full separation of diastereomers was not achieved when methyl ester **181** was synthesised as a 59:41-mixture (Chapter 2.5, **Scheme 35**). A possibility to make use of isolated dioxanone **179** would involve the stereospecific inversion of alcohol *epi*-**181** by means of a Mitsunobu protocol for example. Furthermore, in principle aldehyde **99** could be regenerated form separated side-product **179**. However, both options were judged to be impractical.

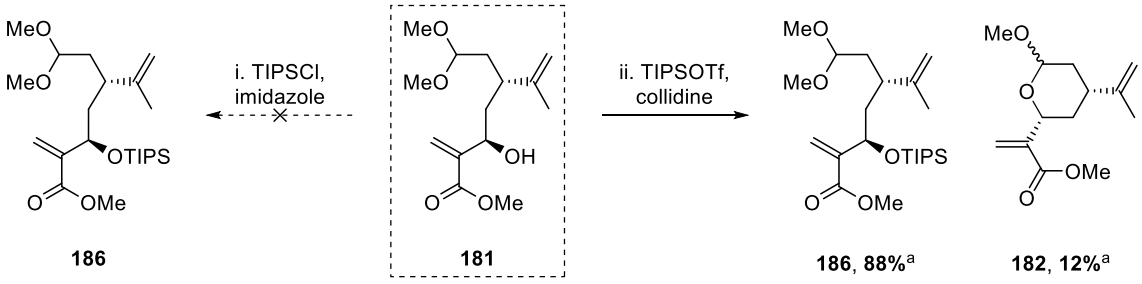


Scheme 47 Confirmation of relative stereochemistry of dioxanone **179** by nOe and methanolysis of **179**. Reagents and conditions: Et_3N (3 eq), MeOH (0.2 M), 0 to 25 °C, 16 h *then* work-up with aq. HCl.

2.8 Synthesis of bis-methyl furan 191

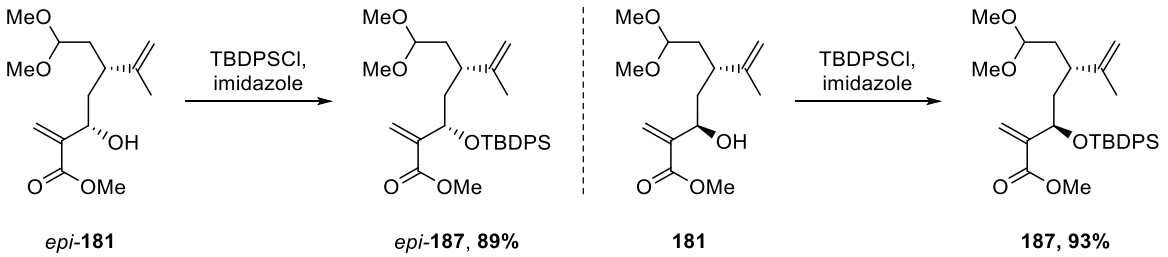
With a scalable route to stereodefined methyl ester **181** in hand, synthetic efforts were focused on installation of the furan heterocycle. First, a suitable protecting group for the secondary alcohol *C*-13 had to be chosen. (+)-Lophotoxin bears an acetoxy group at this position. However, as a furan lithiation step and an ester hydrolysis step were planned in the synthesis, an acetyl ester was judged to be too labile to be carried through multiple steps. Bulky silyl ethers, such as triisopropylsilyl (TIPS) or *tert*-butyldiphenylsilyl (TBDPS), were considered. Both groups should be inert through the planned synthetic steps and selective deprotection at a late stage was judged to be feasible. Thus, TIPS protection of alcohol **181** was attempted (**Scheme 48**). Exposure to TIPS chloride and imidazole gave no conversion by TLC after 16 h and this method was therefore abandoned. Treatment with more reactive TIPS triflate and collidine gave full conversion of alcohol **181** and desired silyl ether **186** was obtained, albeit as an impure sample due to its co-elution with formed

cyclic acetal **182** and TIPS silanol side-product. Yields for silyl ether **186** and acetal **182** were calculated from NMR-ratios of the mixture to be 88% and 12%, respectively. The activation of acetals using silyl triflates has been reported in the literature and this approach was therefore abandoned.[86]



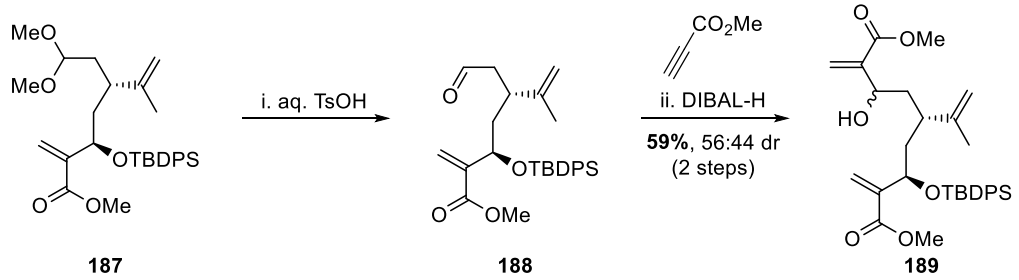
Scheme 48 Synthesis of TIPS ether **186**. Reagents and conditions:
i) TIPSCl (1.5 eq), imidazole (2 eq), CH_2Cl_2 (0.3 M), rt, 16 h;
ii) TIPSOTf (4 eq), collidine (4 eq), CH_2Cl_2 (0.2 M), –40 °C to rt, 16 h;
a) calculated from NMR-ratios of the isolated mixture.

To conserve precious alcohol **181** starting material, alcohol *epi*-**181** was first used as a substrate for subsequent protecting group test reactions (**Scheme 49**). Treatment with TBDPS chloride and imidazole gave clean conversion, and silyl ether *epi*-**187** was isolated in 89% yield. The same conditions were applied to desired diastereomer **181**, and **187** was isolated in 93% yield. Separation from TBDPS derived silanol required a specific solvent system (CH_2Cl_2:acetone instead of pentane:Et_2O) for purification. TBDPS silyl ethers exhibited a characteristic pattern of up to 8 signals at 137–127 ppm in the ^{13}C NMR, accounting for the 12 carbon-atoms incorporated in the two phenyl rings of the protecting group.



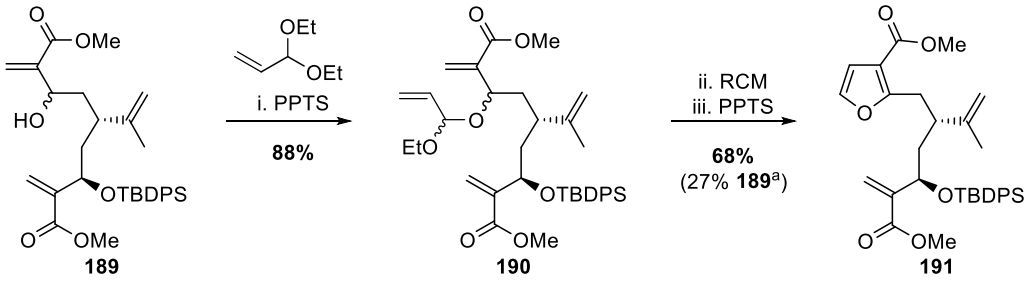
Scheme 49 Synthesis of TBDPS silyl ethers *epi*-**187** and **187**.
Reagents and conditions: TBDPSCl (1.5 eq), imidazole (2 eq), CH_2Cl_2 (0.3 M), rt, 16 h.

Acetal deprotection of **187** following standard conditions gave clean conversion to aldehyde **188** (**Scheme 50**).[54] The hydroalumination coupling sequence using HMPA as an additive (Chapter 2.5) worked well and provided alcohol **189** as an inconsequential mixture of two diastereomers in 59% yield over two steps.



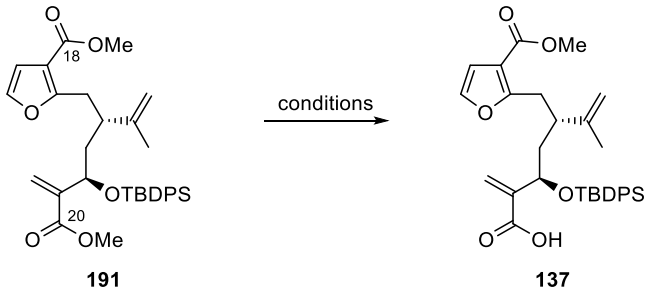
Scheme 50 Synthesis of alcohol **189**. Reagents and conditions: i) TsOH · H_2O (0.25 eq), acetone/H_2O (4:1), 50 °C, 4 h; ii) DIBAL-H (3.5 eq), HMPA (10 eq), THF, 0 °C *then* methyl propiolate (4 eq) *then* **188**, 45 °C, 2 h.

Transacetalisation with acrolein diethyl acetal at reduced pressure was performed on a rotary evaporator (**Scheme 51**) and provided **190** as a mixture of four diastereomers in 88% yield. RCM reaction using olefin metathesis catalyst Zhan1B, followed by aromatisation provided furan **191** in 68% yield. Because volatile CH_2Cl_2 was used as the reaction solvent, the experiment was performed in a closed system without a flow of nitrogen to prevent the solvent from drying out. Interestingly, although a 56:44 diastereomeric mixture of alcohol **189** was used as the starting material in this sequence, after aromatisation 27% of alcohol **189** was recovered as an 80:20 mixture of diastereomers. The enrichment of the **189** diastereomeric mixture implies that the four diastereomers of mixed acetal **190** underwent RCM reaction at different rates.



Scheme 51 Synthesis of bis-methyl furan **191**. Reagents and conditions: i) acrolein diethyl acetals (8 eq), PPTS (0.1 eq), 40 °C, 60 mbar, 2 h; ii) Zhan1B (2 × 5 mol%), CH_2Cl_2 (50 mM), 40 °C, 40 h; iii: PPTS (1 eq), 40 °C, 2 h; a) 80:20 dr.

With *bis*-methyl furan **191** in hand, selective methyl ester cleavage was attempted (**Scheme 52**). It was speculated that the electron-rich furan ring would deactivate ester *C*-18 and selective hydrolysis of α,β-unsaturated *C*-20 could be accomplished.



191 **137**

Scheme 52 Ester hydrolysis to access right-hand fragment **137**. For reagents and conditions see **Table 3**.

Limited by the amount of *bis*-methyl ester **191** synthesised, only three hydrolysis experiments were attempted (**Table 3**). All three reactions were performed at 0 °C and did not show any conversion when warmed to rt overnight. Barium hydroxide in MeOH led to the formation of multiple compounds (entry 1).[87] Ester **191** was stable when treated with lithium hydroxide in THF:H_2O (entry 2).[88] Potassium hydroxide in MeOH:H_2O gave no conversion initially, but a complex mixture was isolated after more reagent was added.[89]

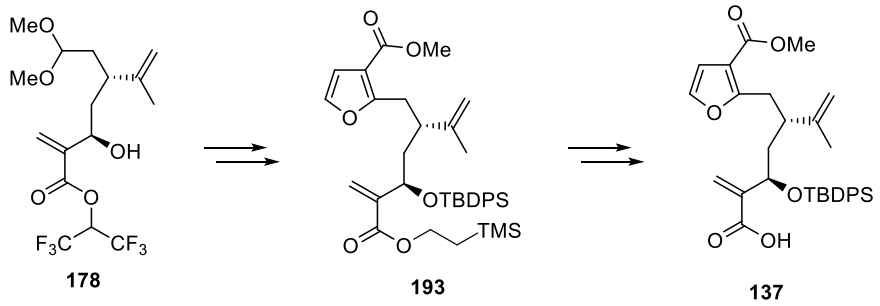
Table 3 Conditions for attempted ester hydrolysis of *bis*-methyl ester **191**; a) 0 °C to rt, 3 days.

entry	conditions[a]	comment
1[87]	$BaOH_2 \cdot 8\ H_2O$, MeOH	complex mixture
2[88]	LiOH, THF:H_2O	no conversion
3[89]	KOH, MeOH:H_2O	complex mixture

2.9 Synthesis of TMSE containing furan 193

Although all options for selective methyl ester hydrolysis had not been exhausted, it was decided to switch to an orthogonal protecting group strategy once all the synthesised material of *bis*-methyl ester **191** had been consumed. The potential protecting group

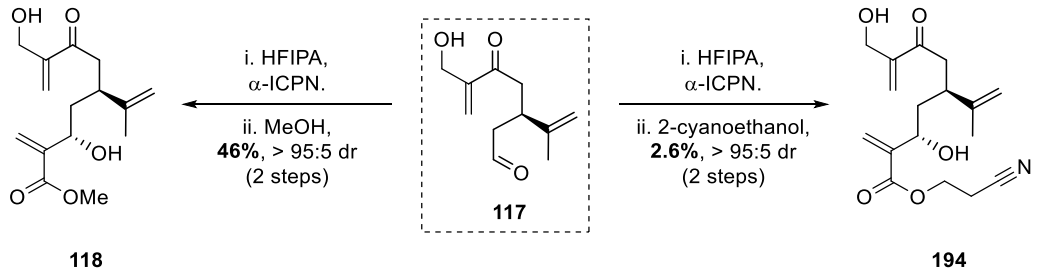
would be derived from the analogous HFIP ester **178**, most likely *via* transesterification (**Scheme 53**). The ester would need to be stable to acidic conditions during furan synthesis yet reactive enough to be selectively cleaved at a later point to unveil the corresponding α,β-unsaturated carboxylic acid. We thus sought inspiration from Clark and McAulay, who used a (trimethylsilyl)ethyl (TMSE) α,β-unsaturated ester in their right-hand fragment in the total synthesis of 7-*epi*-pukalide (*epi*-**18**, Chapter 1.2.10).[59] That selective deprotection of TMSE esters bearing secondary TBDPS silyl ethers are known in the literature gave us additional confidence in the protecting group strategy.[90] The subsequent section discusses experiments incorporating TMSE ester **193** in an orthogonal protecting group strategy to access right-hand fragment **137**.



Scheme 53 Strategic approach to right-hand fragment **137** *via* TMSE ester **193**.

2.9.1 Transesterification

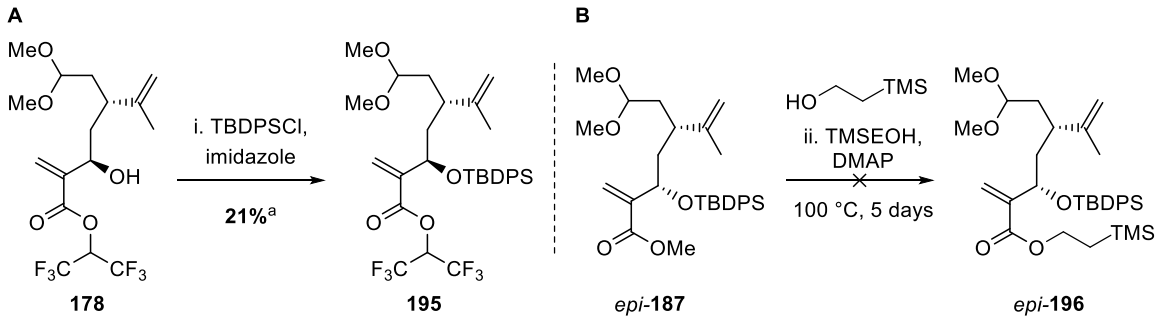
In previous efforts Johannes Walker investigated the transesterification of the HFIP ester derived from the α-ICPN-catalysed Baylis–Hillman reaction of HFIPA and aldehyde **117** (**Scheme 54**).[78] Whereas methanolysis led to the formation of methyl ester **118** in 46% yield, transesterification with 2-cyanoethanol afforded ester **194** in only 2.6% yield.



118 **194**

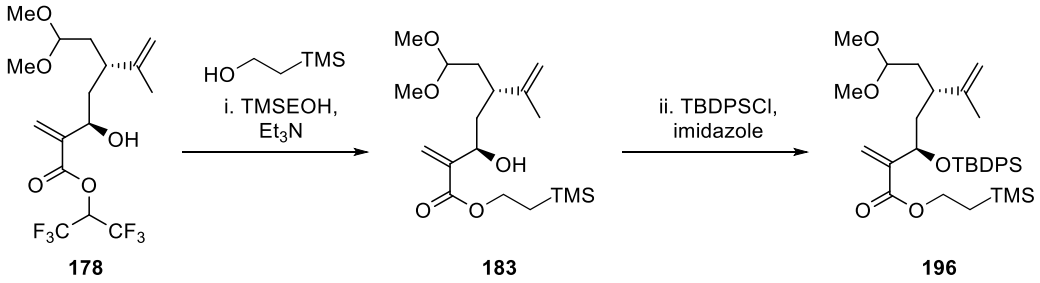
Scheme 54 Synthesis of methyl ester **118** and cyanoethyl ester **194** by Johannes Walker. Reagents and conditions: i) α-ICPN (25 mol%), HFIPA (5 eq), DMF (0.1 M), –55 °C, 2 days; ii) Et_3N, MeOH (0.1 M), 25 °C, 12 h; ii) Et_3N, 2-cyanoethanol (0.4 M), 18 h.

Thus, it was concluded that methanolysis of HFIP ester **178** established conditions (Chapter 2.7.1) could not simply be adopted for transesterification with 2-(trimethylsilyl)ethanol (TMSEOH). Consequently, alternative strategies were investigated. An initial approach included masking the free hydroxy group of HFIP ester **178** prior to transesterification. TBDPS protection of **178** resulted in the formation of silyl ether **195** (**Scheme 55A**). However, isolation was hampered by co-elution of TBDPS silanol and the yield of **195** was calculated to be 21% from NMR ratios after purification by column chromatography. No starting material was observed and drastic reduction in mass balance was unexplained. Thus, this strategy was no longer investigated. A different plan of action was based on the fact that methanolysis of HFIP esters **178** and *epi*-**178** and subsequent TBDPS protection had already been shown to be high yielding. Transesterification of methyl ester *epi*-**187** was attempted (**Scheme 55B**). The substrate was heated with TMSEOH and catalytic DMAP in PhMe to 100 °C in a sealed vessel for 5 days. Nonetheless, no conversion was observed by TLC or NMR and so this method was abandoned as well.



Scheme 55 Attempted TBDPS protection of HFIP ester **178** (**A**) and transesterification of *epi*-**187**; a) Calculated from NMR ratios. Reagents and conditions: i) TBDPSCl (1.5 eq), imidazole (1.4 eq), CH_2Cl_2 (0.3 M), rt, 16 h; ii) TMSEOH (2 eq), DMAP (0.1 eq), PhMe (0.5 M), sealed tube, 100 °C, 5 days.

In parallel with the above described experiments, a way to translate the reliable methanolysis conditions of HFIP ester **178** to transesterification with TMSEOH was sought (**Scheme 56**). Due to the vast difference in cost of MeOH (0.75 £/mol) and TMSEOH (1.22 £/mmol) using a similarly large excess of TMSEOH was not practical.[83] Conditions and yields for transesterification experiments are listed in **Table 4**. Subsequent TBDPS protection of the transesterification product worked reliably if enough excess reagent (1.5 eq TBDPSCl) was used. A reduction of TBDPSCl to 1.15 eq resulted only in partial conversion and alcohol **183** was recovered. Initially, isolation of silyl ether **196** was hampered by co-elution of TBDPS silanol. On decagram-scales, MeOH was used in the reaction quench to react with excess TBDPSCl and minimise generation of TBDPS silanol contaminant. These precautions to minimise silanol contamination notwithstanding, batches of silyl ether **196** contaminated with up to 30 wt% of TBDPS silanol were used in the subsequent reaction steps without significant reductions in yield.



Scheme 56 Synthesis of TMSE ester **196**. Reagents and conditions: i) see **Table 4**; ii) TBDPSCl (1.5 eq), imidazole (2 eq), CH_2Cl_2 (0.3 M), rt, 16 h.

Product isolation and purification at the stage of the initial transesterification to make **183** was also non-trivial. It was found that HFIP ester **178**, TMSE ester **183** and TMSEOH had almost identical R_f-values using TLC as well as flash column chromatography. In-process-control was therefore achieved by quantitative ^{19}F and ^{1}H NMR rather than TLC. Furthermore, removal of excess TMSEOH under high vacuum (0.1 mbar for 16 h) was only possible when small quantities (< 0.1 g) of TMSE ester **183** were synthesised. When the transesterification reaction was performed on larger scales, TMSE ester **183** was not purified by column chromatography. TMSEOH contamination was quantified by NMR and the increased amount of reactive alcohol was accounted for in the following TBDPS protection step. Yields over two steps are reported in **Table 4**. Additionally, yields calculated from the mass of the crude reaction mixture and their NMR-ratios for the transesterification step have been included in **Table 4** as an additional indicator of reaction outcome. Similar to the analogous methanolysis reaction, the reaction temperature had a drastic effect on clean formation of TMSE ester **183**: No conversion was observed after 16 h when the reaction was performed in CH_2Cl_2 at 25 °C. Raising the reaction temperature to 40 °C resulted in partial conversion (entry 1). Although heating the reaction mixture to 60 °C, using PhMe as co-solvent led to full conversion, **183** was not formed cleanly and only 46% of silyl ether **196** were isolated after TBDPS protection (entry 2). It was concluded that increased temperatures promoted decomposition pathways. The decomposition side-products were most likely water-soluble or even volatile, as they were not detected in the crude reaction mixture. When the reaction was run neat at 40 °C, slow conversion was observed. After 16 h, the temperature was increased to 50 °C and TBDPS protection gave **196** in 67% yield over two steps (entry 3). Performing the reaction at 50 °C gave a similar result (entry 4). A significant jump in isolated yield was observed when the reaction was performed at 40 °C with an increased

reaction time of three days (entry 5). These conditions were robust even at larger reaction scales (entries 6–7). When synthesised on decagram scale (entry 7), silyl ether **196** was not completely separated from TBDPS silanol, as sample purity had previously been demonstrated to be unnecessary for success in the subsequent reaction step.

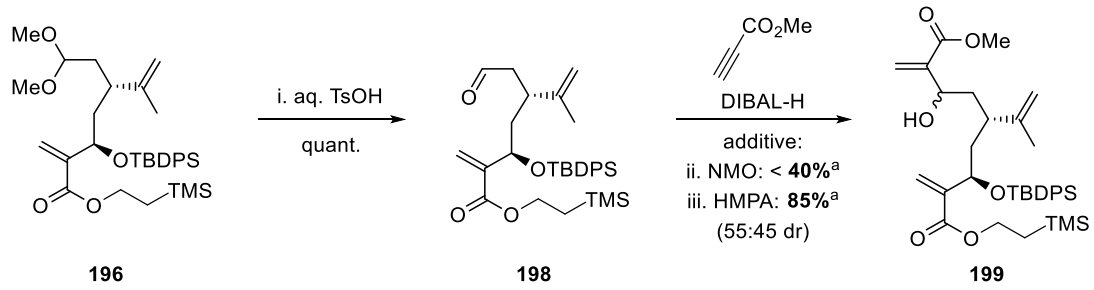
Table 4 Transesterification of HFIP ester **178** (**Scheme 56**): TMSEOH (5 eq), Et_3N (3 eq); a) calculated from NMR-ratios of the isolated mixture; b) 10 eq TMESOH used; c) 16% recovered **178**; d) partially contaminated with TBDPS silanol; e) temperature increased after 16 h.

entry	scale [mmol]	solvent	reaction temp.	reaction time	calculated yield for **183**[a]	yield for **196** (2 steps)
1	0.54	CH_2Cl_2[b]	25 to 40 °C	48 h[e]	65%[c]	**47%**[a,d]
2	3.5	PhMe[b]	60 °C	18 h	69%	**46%**
3	0.62	-	40 to 50 °C	40 h[e]	74%	**67%**
4	1.8	-	50 °C	45 h	77%	**65%**
5	6.6	-	40 °C	3 days	95%	**82%**
6	13	-	40 °C	3 days	91%	**77%**
7	40	-	40 °C	3 days	96%	**87%** (71% + 16%[a,d])

2.9.2 Furan synthesis

With a robust and scalable route for silyl ether **196** in hand, installation of the furan ring was attempted. Due to time constraints of the subsequent step, acid-catalysed acetal hydrolysis was performed as an overnight reaction (**Scheme 57**). Although conversion was usually completed after 3–5 h, aldehyde **198** could still be isolated in sufficient purity and in quantitative yield under longer reaction times. Crude reaction mixtures of **198** were subjected to the next step without purification by chromatography on the same day. Using NMO as an additive in the hydroalumination coupling sequence (Chapter 2.5) resulted in the formation of many side-products which hampered purification;

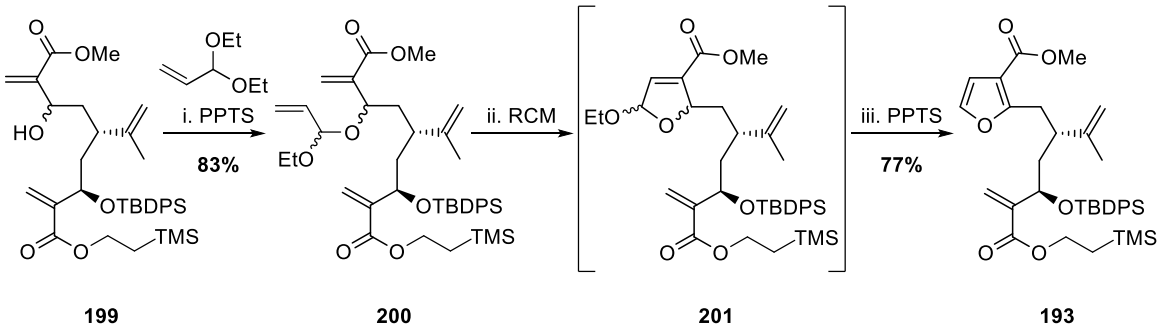
contaminated alcohol **199** was isolated in only 40% yield after multiple purification steps. Using HMPA instead as an additive gave superior results and provided alcohol **199** in 85% yield (55:45 dr) in two steps from acetal **196** on decagram scale. As previously mentioned, vigorous stirring of the crude reaction mixture with Rochelle salt overnight was crucial for high isolated yields. To avoid such a time-consuming procedure, a work-up with aqueous NaOH and $MgSO_4$, also known as the Fieser work-up, was attempted. However, only trace quantities of desired alcohol **199** were isolated using this method.



196 **198** **199**

Scheme 57 Synthesis of alcohol **199**. Reagents and conditions: i) TsOH · H_2O (0.25 eq), acetone/H_2O (4:1), 50 °C, 20 h; ii) DIBAL-H (3.5 eq), NMO (3.5 eq), THF, 0 °C *then* methyl propiolate (4 eq) *then* **198**, 45 °C, 18 h; iii) DIBAL-H (3.5 eq), HMPA (10 eq), THF, 0 °C *then* methyl propiolate (4 eq) *then* **198**, 45 °C, 2 h; a) the yield was calculated over two steps from acetal **196**.

Transacetalisation with acrolein diethyl acetal under reduced pressure provided mixed acetal **200** in 83% yield as a mixture of four diastereomers (**Scheme 58**). Metathesis catalysts Zhan1B and Hoveyda-Gruss II (HG II) have both been used successfully for the RCM step (**Table 5**). Aromatisation with PPTS in the same pot resulted in a clean transformation from dihydrofuran **201** to desired furan **193**. Unreacted diene **200** hydrolysed in this step to give alcohol **199**. The diastereomeric ratio of subjected and recovered alcohol differed in the same manner as discussed in Chapter 2.8, suggesting different reaction rates of the four diastereomers of mixed acetal **200** in the RCM step.



Scheme 58 Synthesis of TMSE furan **193**. Reagents and conditions: i) acrolein diethyl acetals (8 eq), PPTS (0.1 eq), 40 °C, 60 mbar, 2 h; ii) HG II (10 + 2 × 5 mol%), PhMe (50 mM), 40 to 60 °C, 5 days; iii: PPTS (1 eq), 40 °C, 3 h.

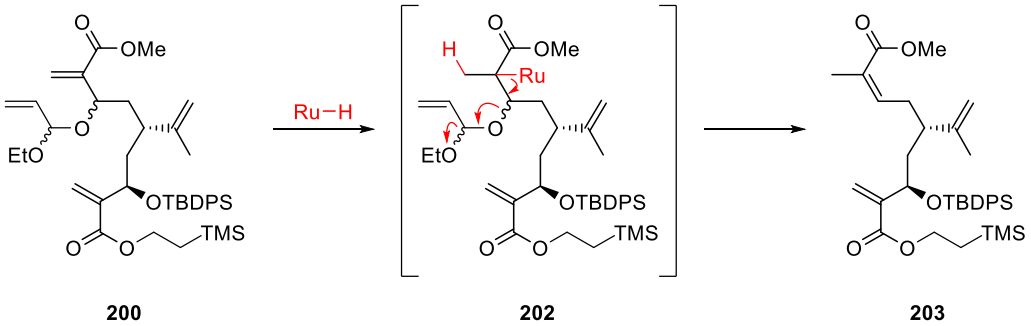
Based on previous results of RCM reaction with similar substrates (chapters 2.6 and 2.8), reaction temperature (40–60 °C), substrate concentration (25–100 mM) and reaction time were varied in order to maximise the isolated yield of furan **193** with acceptable catalyst loading (**Table 5**). Conversion of diene **200** was estimated by TLC and the aromatisation step was initiated by addition of PPTS in CH_2Cl_2 accordingly. A yield of 70% could be achieved with as little as 7.5 mol% of catalyst Zhan1B (entry 1). To increase conversion, metathesis catalyst was added in multiple portions (entries 2 and 3). A flow of nitrogen gas was used to remove volatile ethene when PhMe was used as a solvent (**Figure 9** in Chapter 2.6). It was observed that the concomitant loss of solvent was more severe at small scales (entries 1 and 3). However, this gradual reduction of solvent correlated with increased formation of furan **193**. When the reaction was scaled up to 2.6 mmol, this effect was successfully replicated (entry 4). The catalyst was added in portions over the first 48 h. After which, the nitrogen inlet was submerged into the reaction mixture and the temperature was increased to 60 °C. This led to partial evaporation of the solvent and clean formation of furan in 77% yield after aromatisation. Unfortunately, the formation of furan **193** suffered from reproducibility issues. Occasionally, runs suffered from low isolated yields (27–54%) and formation of unidentified side-products (entries 5 and 6). Only trace amounts of these side-products were observed in the crude reaction mixture of entries 1–4. One major side-product consisted of a mixture of multiple isomers and

accounted for up to 34% of the isolated mass. A second – initially unidentified – side product co-eluted with furan **193** in up to 55 mol% (entry 6). Attempts to separate the two species using multiple solvent eluent systems, fine silica gel (15–40 μm) and preparative TLC were all unsuccessful. It was initially proposed that use of catalyst that had decomposed during storage led to the formation of both side-product. However, the effect of using fresh catalyst from newly opened bottles on side-reaction formation was inconsistent at best – no side-product formed in some instances, but in others the species was present at high levels using HG II and Zhan1B. Finally, the described inseparable impurity was identified to be enone **203** (**Scheme 60**) by Dr. Kratena, a postdoctoral researcher who joined the project. To sequester any formed ruthenium hydride, causing side reactions (*vide infra*), the transformation was performed in DCE and 2,6-dichloro-1,4-benzoquinone was used as an additive (entry 7).[91] Under these conditions none of the side products were observed and furan **193** was isolated in 77% yield.

Table 5 Selected conditions for the synthesise furan **193** (**Scheme 58**): PhMe (25 mM), N_2-flow; a) CH_2Cl_2 (0.1 M) and no N_2-flow used; b) the solvent level was gradually reduced by submerging the N_2-inlet into the reaction mixture and heating the reaction mixture to 60 °C after 2 days; c) contains enone **203** (27 mol%); d) contains enone **203** (55 mol%); e) DCE (25 mM), N_2-flow and 2,6-dichloro-1,4-benzoquinone (10 mol%) used.

entry	scale [mmol]	reaction time	reaction temp.	RCM catalyst	catalyst loading	isolated yield
1	0.24	36 h	60 °C	Z1B	7.5 mol%	**70%**
2	1.1[a]	72 h	40 °C	Z1B	3 × 5.0 mol%	**72%**
3	0.25	36 h	40 °C	HG II	10 + 5.0 mol%	**69%**
4	2.6[b]	5 days	40 to 60 °C	HG II	10 + 2 × 5.0 mol%	**77%**
5	0.69	66 h	60 °C	Z1B	7.5 mol%	**47%**[c]
6	4.4	96 h	40 to 60 °C	HG II	8.0 + 7.0 mol%	**36%**[d]
7	0.25[e]	16 h	60 °C	HG II	10 mol%	**77%**

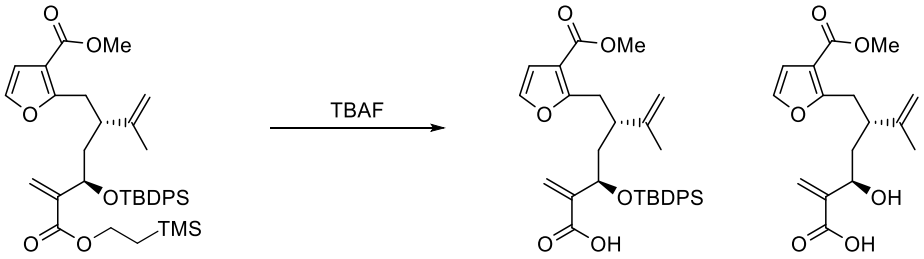
The decomposition of ruthenium carbenes, such as HG II, was established by Louie and Grubbs.[92] The formation of undesired enone **203** was rationalised by a conjugate addition reaction of emerged ruthenium hydride with mixed acetal **200** (**Scheme 59**). Subsequent fragmentation of formed ruthenium enolate **202** affords enone **203** as well as acrolein and ethanol. Side reactions of ruthenium hydrides can be supressed successfully, because of the high reaction rate of ruthenium hydride with benzoquinones.[91]



Scheme 59 Mechanistic rationalisation for the formation of enone **203**.

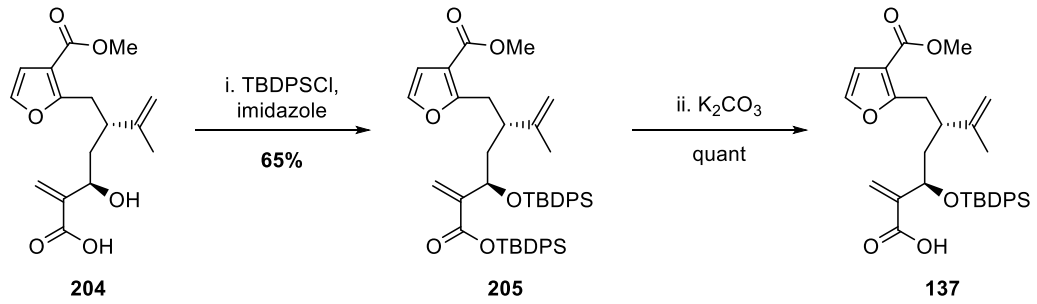
2.9.3 TMSE deprotection

With TMSE ester in hand, selective deprotection was accomplished using TBAF in THF at 0 °C. Excess TBAF (3 eq) was necessary to achieve full conversion. The reaction was closely monitored by TLC and quenched when TMSE ester **193** was consumed or when the formation of hydroxy acid **204** was observed. Surprisingly, the selectivity of this reaction depended on the batch quality of TBAF, which was purchased as a 1 M solution in THF. On one occasion, carboxylic acid was only isolated in 66% yield. Recovered substrate **193** was isolated in 16% and hydroxy acid **204** in 22% yield. Thus, new TBAF batches were always tested on a small scale prior to committing large quantities of ester **193** to the reaction.



Scheme 60 Deprotection of TMSE ester **193**.
Reagents and conditions: TBAF (3 eq), THF (0.1 M), 0 °C, 1 h 50 min.

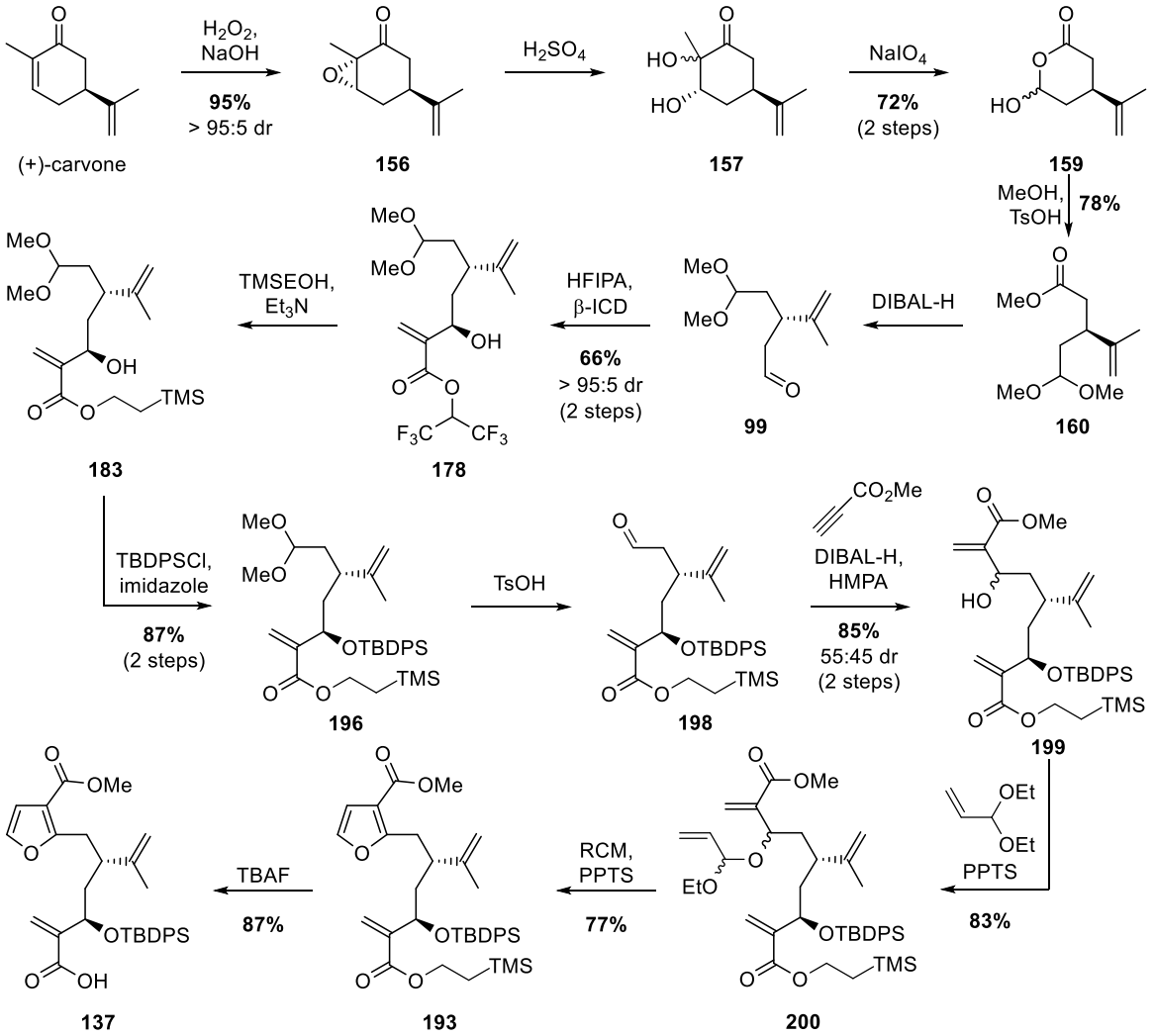
It was hoped that isolated hydroxy acid **204** could be recycled and transformed into right-hand fragment **137** (**Scheme 61**). To this end, **20** was subjected to TBDPS protection conditions with excess reagent. Surprisingly, formed *bis*-silyl ether **205** was stable during aqueous work-up. Neither hydroxy acid **204** nor silyl ether **137** was observed in the crude reaction mixture or isolated after purification by column chromatography. Selective mono-deprotection of *bis*-silyl ether **205** was performed by treatment with K_2CO_3 in a MeOH:THF:H_2O mixture. The mixture was a suitable compromise to solvate relatively unpolar substrate **205** and ionic K_2CO_3. Right-hand fragment **137** was isolated in 65% over two steps from hydroxy acid **204**.



Scheme 61 Selective TBDPS protection of hydroxy acid **204**. Reagents and conditions: i) TBDPSCl (4 eq), imidazole (5 eq), CH_2Cl_2 (0.3 M), rt, 16 h; ii) K_2CO_3 (1 eq), MeOH:THF:H_2O (60:20:20).

2.9.4 Overview

In summary, right-hand fragment **137** was synthesised from (+)-carvone in 13 steps (**Scheme 62**) with 14% overall yield; the overall yield was calculated using the highest yields achieved on a synthetically useful scale. Gram quantities of pure TMSE ester **137** have been synthesised following this route.



Scheme 62 Overview of the synthetic route to right-hand fragment **137**.

Chapter 3

Cross-coupling approaches for fragment linkage

3 Cross-coupling approaches for fragment linkage

This chapter details the synthesis of literature-known vinyl iodide **81**[55] and investigations to couple it with right-hand fragments **137** and **169** (**Figure 10**).

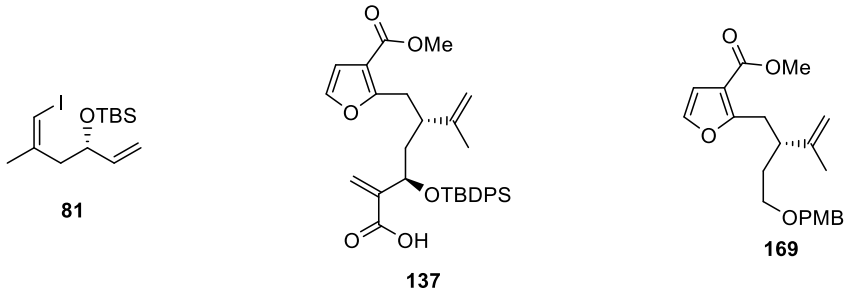
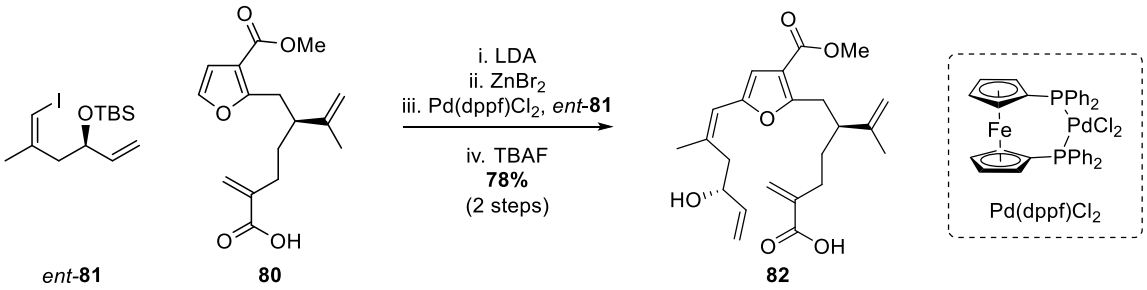


Figure 10 Left-hand fragment **81** and right-hand fragments **137** and **169**.

3.1 Synthesis of vinyl iodide left-hand fragment 81

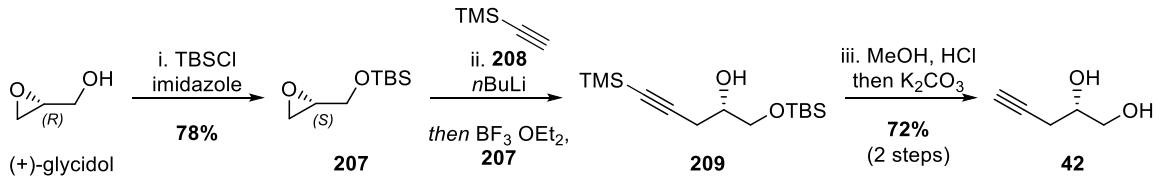
In their total synthesis of (–)-(*Z*)-deoxypukalide, Donohoe and co-workers demonstrated the Negishi coupling of vinyl iodide *ent*-**81** and furan **80** (Chapter 1.2.7).[55] Lithiation of furan **80** with LDA was followed by transmetalation with $ZnBr_2$. Treatment of the resulting organozinc intermediate with vinyl iodide *ent*-**81** and substoichiometric $Pd(dppf)Cl_2$ gave the corresponding cross-coupling product. Subsequent TBS deprotection with TBAF afforded hydroxy acid **82** in 78% yield over two synthetic steps.



Scheme 63 Coupling of fragments *ent*-**81** and **80** in the total synthesis of (–)-(*Z*)-deoxypukalide by Donohoe and co-workers. Reagents and conditions: i) LDA (2.0 eq), THF, –78 °C; ii) $ZnBr_2$ (3.0 eq); iii) *ent*-**81** (0.9 eq), $Pd(dppf)Cl_2$ (9 mol%), 50 °C, 4 h; iv) TBAF (1.1 eq), THF, 50 °C, 2 h.

Inspired by this result, we envisioned a similar coupling strategy for our project and set out to synthesise the enantiomeric vinyl iodide **81** following the same synthetic route: Although enantiopure TBS-protected glycidol (**207**) was commercially available, it was

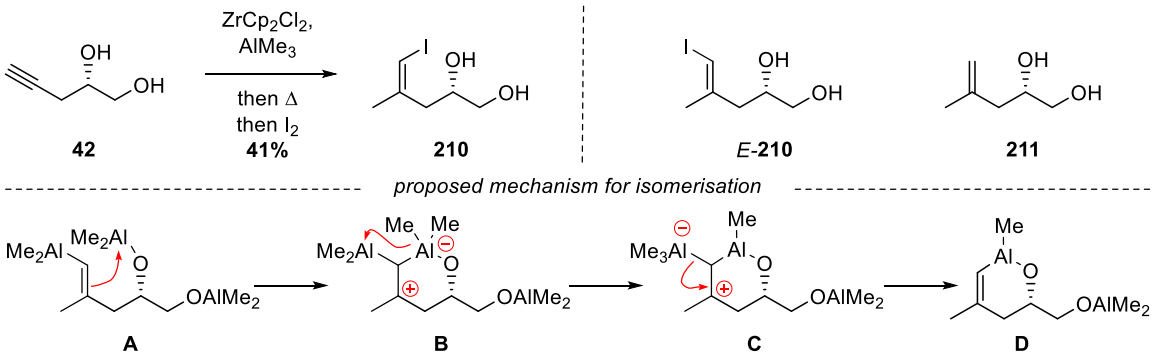
instead prepared from cheaper (+)-glycidol by treatment with TBS chloride and imidazole in 78% yield (**Scheme 64**). Epoxide opening with lithiated trimethylsilylacetylene, employing $BF_3 \cdot OEt_2$ as a Lewis acid, resulted in the formation of alcohol **209**. Without purification by column chromatography, the crude mixture was directly subjected to acidic methanol generated *in situ* from acetyl chloride and methanol to cleave the TBS ether. After full conversion of **209**, K_2CO_3 was added to deprotect the terminal alkyne. Diol **42** was isolated in 72% yield over two synthetic steps from epoxide **207**. The spectral data of diol **42** were consistent with those previously reported.[55]



Scheme 64 Synthesis of diol **42**. Reagents and conditions: i) TBSCl (1.3 eq), imidazole (1.6 eq), DMF (1.6 M), rt, 2.5 h; ii) **208** (1.1 eq), *n*BuLi (1.2 eq), THF (0.4 M), –78 °C, 30 min *then* **207** (1 eq), $BF_3 \cdot OEt_2$ (1.1 eq); iii) AcCl (0.1 eq), MeOH (0.3 M), rt, 14 h *then* K_2CO_3 (2 eq), rt, 7 h.

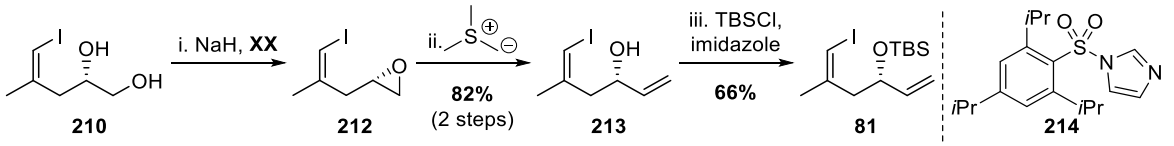
Synthesis of vinyl iodide **210** form alkyne **42** *via* zirconium-catalysed carbometallation and thermal isomerisation was low yielding (**Scheme 65**). Thus, certain reaction parameters were carefully examined to maximise the yield. Catalyst $ZrCp_2Cl_2$ and $AlMe_3$ were pre-mixed prior to dropwise addition of substrate **42** *via* syringe pump. The deprotonation of both hydroxy groups on diol **42** and the concomitant formation of gaseous methane were violent and strongly exothermic processes. The *syn*-selective carboalumination step was completed after 30 min at 0 °C, as judged by full conversion of alkyne **42** by TLC. Isomerisation from intermediate **A** to **D**, however, required elevated temperatures and prolonged reaction times. The reaction temperature had to be tightly controlled for this step; excessively high temperatures decreased the yield – most likely due to increased side-reactions – while lower temperatures resulted in incomplete isomerisation and formation of diol *E*-**210** after treatment with iodide.[93] A reaction temperature of 75 °C over 3 days was chosen as the best compromise and vinyl iodide **210** was isolated in 41%

yield under these conditions. Side-product **211** was sometimes observed; its formation can be explained by reaction of intermediates **A** or **D** with adventitious water. Both side-products could not be isolated as pure samples due to their high polarity and co-elution with product **210**. Negishi and co-workers proposed a mechanism for the isomerisation process of homo-allylic alcohols under such conditions, which proceeds through chelated betaines **B** and **C**.[94]



Scheme 65 Synthesis of vinyl iodide **210**, side products of the process and proposed mechanism for isomerisation. Reagents and conditions: $ZrCp_2Cl_2$ (25 mol%), $AlMe_3$ (4.5 eq), DCE, rt, 10 min *then* **42**, 0 °C, 20 min *then* 75 °C, 3 days then I_2 (2 eq) –30 °C to rt, 2h.

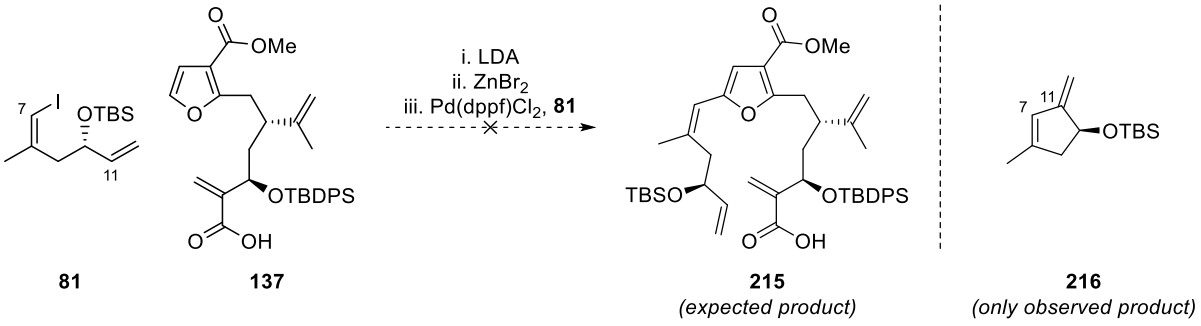
With literature-known diol **210** in hand, the synthesis was resumed (**Scheme 66**). Treatment of **210** with NaH and 1-(2,4,6-triisopropylbenzenesulfonyl)imidazole (**214**) resulted in the formation of epoxide **212**. To avoid product loss of volatile epoxide **212**, solvent residues were not completely removed after aqueous work-up and purification by column chromatography. In a Corey–Chaykovsky-type reaction, epoxide **212** was then transformed into allylic alcohol **213**. An internal thermometer was used for the ylide formation: *n*BuLi was added dropwise to trimethylsulfonium iodide without allowing the reaction mixture to warm above –5 °C. Alcohol **213** was isolated in 82% yield over two steps. Subsequent TBS protection afforded literature-known left-hand fragment **81** in 66% yield. The spectral data of **81** and every intermediate synthesised were consistent with those previously reported.[55]



Scheme 66 Synthesis of left-hand fragment **81**. Reagents and conditions: i) NaH (3 eq), rt, 1 h *then* **214** (1.1 eq), 0 °C to rt, 1 h; ii) Me_3SI (7 eq), *n*BuLi (3 eq), –10 °C then **212**, 16 h; iii) TBSCl (3 eq), imidazole (6 eq), DMF (0.9 M), rt, 2 h.

3.2 Negishi coupling

With fragments **81** (Chapter 3.1) and **137** (Chapter 2.9.3) in hand, the key Negishi coupling could now be investigated (**Scheme 67**): Initial Negishi coupling attempts using the procedure reported by Donohoe and co-workers on vinyl iodide *ent*-**81** and furan **137** (**Scheme 63**) gave no coupling product **215**. Modified conditions incorporating excess LDA, different batches of $Pd(dppf)Cl_2$ and prolonged reaction times were similarly ineffective. Although right-hand fragment **137** was recovered, left-hand fragment **81** was consumed when the cross-coupling step was performed overnight. Cyclic diene **216**, formed *via* an intramolecular Heck reaction, was isolated. The newly formed bond between positions *C*-7 and *C*-11 was confirmed by HMBC analysis.

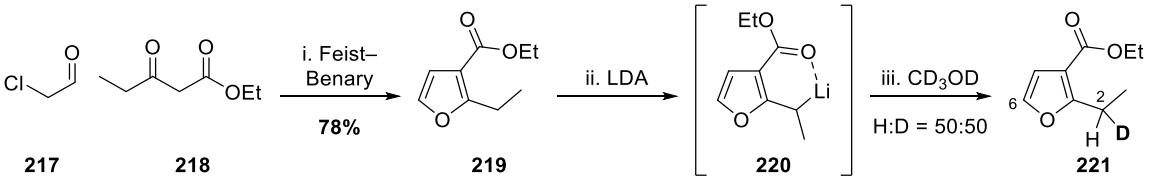


Scheme 67 Attempted Negishi coupling of fragments **81** and **137**. Reagents and conditions:
i) LDA (2–3.5 eq), THF, –78 °C; ii) $ZnBr_2$ (3 eq); iii) **81** (0.9 eq), $Pd(dppf)Cl_2$ (9 mol%), 50 °C, 4–16 h.

3.2.1 Furan lithiation

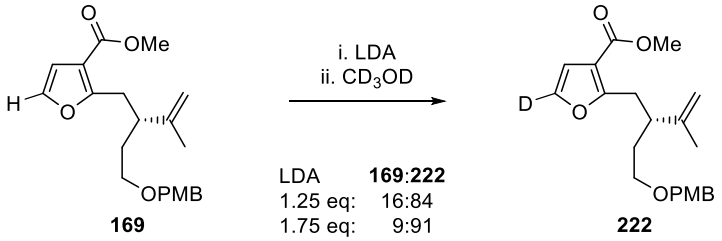
Frustrated by the failure of our initial attempts to couple fragments **81** and **137**, it was decided to investigate the initial furan lithiation step. To this end, literature-known model furan **219** was synthesised from chloroacetaldehyde (**217**) and propionyl acetate (**218**) under basic conditions (Feist–Benary synthesis) in 78% yield (**Scheme 68**).[95] However,

exposure of **219** to excess LDA under Schlenk conditions followed by quench with deuterated methanol resulted in quantitative *mono*-deuteration at benzylic *H*-2 rather than desired position *H*-6. This was rationalised by the formation of 6-membered organolithium intermediate **220**, in which the ester acted as a directing group that chelated the metal. The deuterium incorporation was determined by integration of the corresponding ^{1}H NMR signal in the crude reaction mixture using a quantitative pulsing sequence.



Scheme 68 Synthesis and lithiation of model furan **219**. Reagents and conditions: i) **218** (1 eq), pyridine (3 eq), 0 °C *then* aq. **217** (2 eq), 45 °C, 3 days; ii) LDA (2.5 eq), THF (0.1 M), –78 °C, 1 h *then* CD_3OD, –78 °C, 1 h.

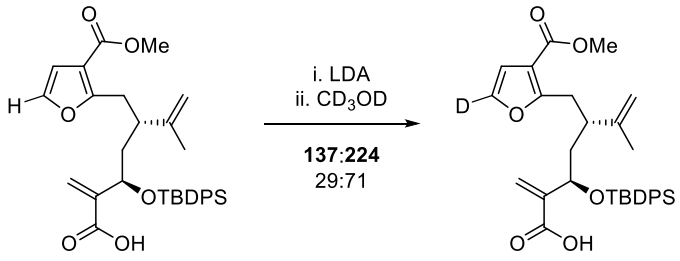
Due to the unexpected regioselectivity in the lithiation reaction of furan **219**, advanced intermediate PMB furan **169** was tested under similar conditions (**Scheme 69**). To our satisfaction, high levels of deuterium incorporation were observed at *H*-6 when a slight excess of LDA was used. No deuterium incorporation in the benzylic *H*-2 position was observed. This reversal in selectivity can be explained by the increased steric hindrance of the branched side-chain in **169** bearing an isopropenyl group adjacent to the benzylic methylene group.



Scheme 69 Lithiation reaction of PMB furan **169**. Reagents and conditions: i) LDA, THF (0.1 M), –78 °C, 1 h *then* CD_3OD, –78 °C, 5 min.

Inspired by these results, we subjected right-hand fragments **137** to the same lithiation/deuteration conditions (**Scheme 70**). As **137** contains an acidic carboxylic acid a

minimum of 2 eq of base are required for furan lithiation. Due to the limited amount of precious starting material available at the time, the experiment was performed using 5 mg of **137**. Excess LDA was used and deuterium incorporation of 71% was obtained. Only trace amounts of decomposition products and deuteration exclusively at *H*-6 were observed.



137 **224**

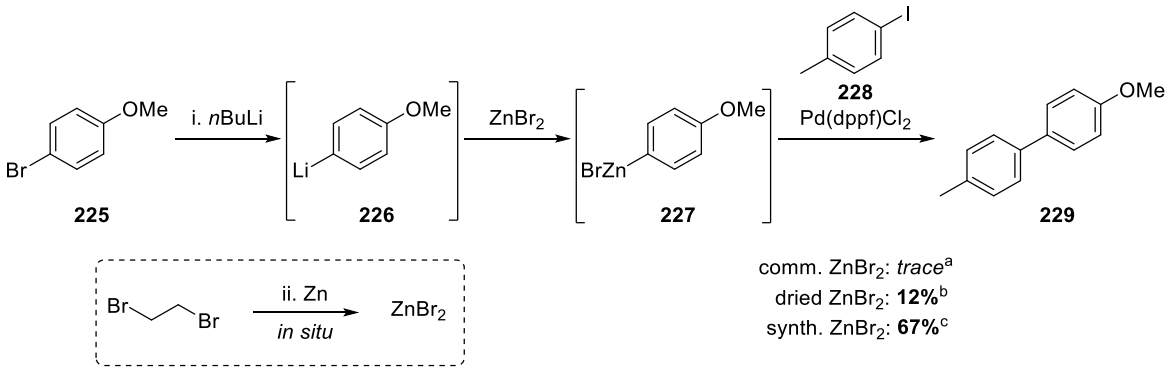
Scheme 70: Lithiation reaction of right-hand fragment **137**. Reagents and conditions: i) LDA (5 eq), THF (0.05 M), –78 °C, 1 h *then* CD_3OD, –78 °C, 5 min.

With the results discussed in this section, we were confident that regioselective lithiation at *H*-6 was possible for right-hand fragments **137** and **169** when performed on scales of sufficient size (> 30 mg) with excess base.

3.2.2 Transmetalation

To investigate the transmetalation step of the Negishi reaction, cross-coupling of *p*-bromoanisole (**225**) and *p*-iodotoluene (**228**) to give literature-known biaryl **229** was used as a model system (**Scheme 71**).[96] Lithium–halogen exchange with *n*BuLi followed by transmetalation with different grades of $ZnBr_2$ provided organozinc intermediate **227** *via* **226**. Treatment with *p*-iodotoluene (**228**) and catalytic $Pd(dppf)Cl_2$ afforded coupling product **229**. When commercial $ZnBr_2$ without treatment was used, only trace amounts of **229** were observed due to undesired quenching of organometallic intermediates with adventitious water. When $ZnBr_2$ was melted under high vacuum in a Schlenk tube and added to the reaction as a stock solution in THF, **229** was isolated in 12% yield. The best results were obtained, however, when the $ZnBr_2$ used was prepared from

1,2-dibromoethane and excess zinc metal; the cross-coupling reaction using this source of $ZnBr_2$ gave **229** in 67% yield.

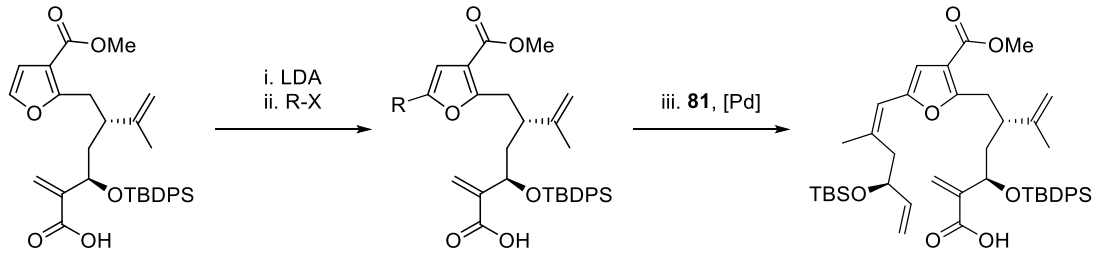


Scheme 71 Synthesis of biaryl **229**. i) Reagents and conditions: **225** (1.1 eq), *n*BuLi (1.1 eq), THF (0.5 M), –78 °C, 45 min *then* $ZnBr_2$ (1.3 eq), –50 °C, 30 min *then* **228** (1.0 eq), $Pd(dppf)Cl_2$ (5 mol%), 50 °C, 16 h; ii) 1,2-dibromoethane (1 eq), Zn (2 eq), THF (1 M), reflux, 1 h; a) commercial $ZnBr_2$ used; b) commercial $ZnBr_2$ was melted under high vacuum and dissolved in THF; c) $ZnBr_2$ was synthesised from 1,2-dibromoethane and Zn.

With these results, we were confident that all the reagents used had the required grade and purity to achieve the coupling of fragments **81** and **137** (**Scheme 67**). However, when the coupling reaction was repeated using 100 mg of starting material under these optimised conditions (with respect to $ZnBr_2$ preparation and excess LDA), the desired coupling product **215** was not observed. Recovered furan **137** and cyclic diene **216** was isolated instead.

3.3 Alternative cross-coupling strategies

Given the disappointing results of the Negishi coupling, we proposed a complementary approach that involved the formation of an isolatable furan coupling partner **230** rather than preparing an unstable organozinc species *in situ* (**Scheme 72**). Coupling partners considered included boronic esters (R = $B(OMe)_2$) or boronic acids (R = $B(OH)_2$) for Suzuki couplings; organosilanes (R = TMS) or hydroxysilanes (R = $SiMe_2OH$) for Hiyama and Hiyama–Denmark couplings, respectively; stannanes (R = $SnBu_3$) for Stille couplings; and organohalides (R = Br) for a polarity reversal cross-coupling strategy.

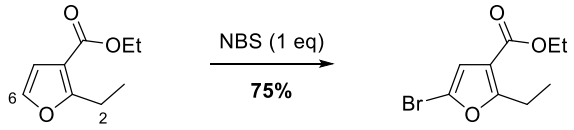


137 **230** **215**

Scheme 72 Proposed stepwise approach for fragment coupling.

3.3.1 Bromination

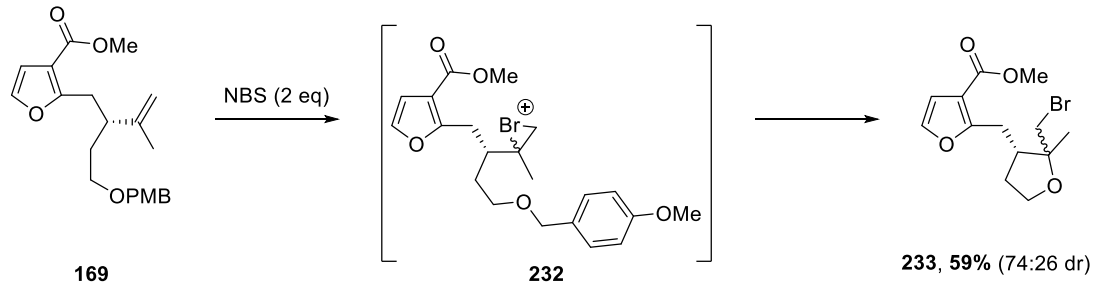
Although lithiation with LDA of model furan **219** occurred exclusively at the benzylic *H*-2 position (**Scheme 68**), when **219** was exposed to NBS (1 eq) in the absence of a strong base, bromination occurred at *H*-6 instead of at *H*-2 to give **231** in 75% yield (**Scheme 73**). This reversal of regioselectivity was taken advantage of in the formation of the corresponding organolithium species by metal–halogen exchange with *n*BuLi (Chapter 5.1, **Scheme 105**).



219 **231**

Scheme 73 Synthesis of bromide **231**. Reagents and conditions: NBS (1 eq), DMF (1 M), rt, 16 h.

Encouraged by this result, we subjected PMB furan **169** to the same conditions (**Scheme 74**). However, 2 eq of NBS were required to achieve full conversion of **169** and the formation of *p*-anisaldehyde was observed. THF **233**, formed *via* bromonium ion **232**, was isolated in 59% yield as a mixture of diastereomers (74:26 dr). Examples for cleaving PMB ethers with specific chemical environments by exposure to NBS have been reported in the literature.[97-98]

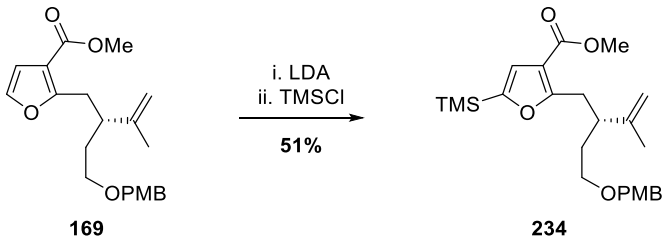


Scheme 74 Bromination of PMB furan **169**. Reagents and conditions:
NBS (1 eq), DMF, rt, 22 h *then* NBS (1 eq), DMF, rt, 24 h.

Attempts to brominate lithiated PMB furan **169** or right-hand fragment **137** were unsuccessful and complex mixtures were observed. This could be explained by the formation of bromonium ions analogous to intermediate **232** and subsequent decomposition.

3.3.2 Cross-coupling

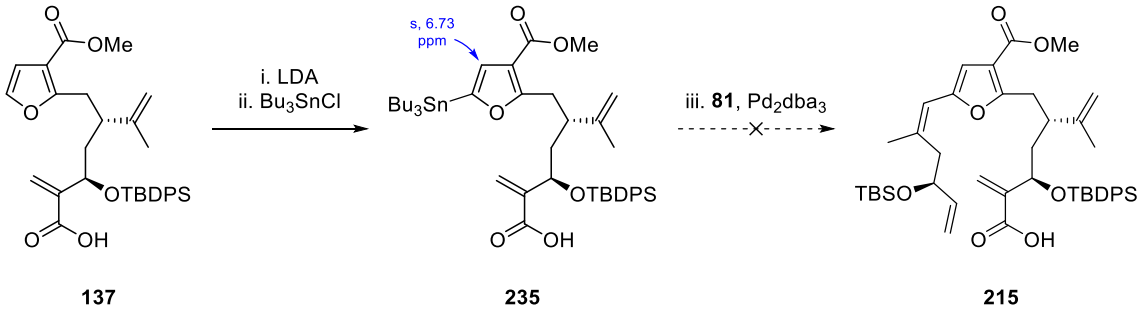
The first successful isolation of an organometallic compound was achieved when PMB furan **169** was deprotonated with LDA to give an organolithium intermediate that was then treated with TMSCl (**Scheme 75**), producing TMS furan **234** in 51% yield.



Scheme 75 Synthesis of TMS furan **234**. Reagents and conditions:
i) LDA (2 eq), THF (0.05 M), –78 °C, 1 h *then* TMSCl (5 eq), –78 °C, 1.5 h.

In the same manner, right-hand fragment **137** was converted into stannane **235** by using Bu_3SnCl as metalation agent (**Scheme 76**). Tri-substituted furan **235** was identified in the crude reaction mixture as the major product by LRMS and NMR exhibiting a characteristic singlet at 6.73 ppm for the remaining aromatic proton (*H*-5). However, when purification of the excess tin reagent by column chromatography was attempted, protodestannylation occurred to give di-substituted furan **137**, which was re-isolated. Subjecting the crude

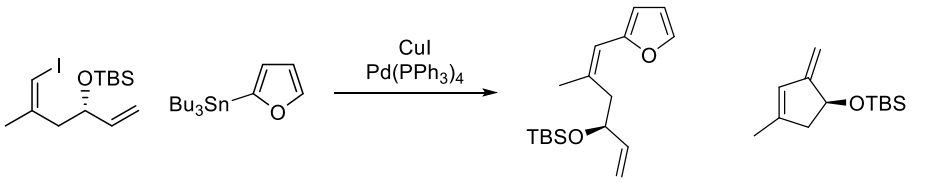
reaction mixture together with vinyl iodide **81** to Stille coupling conditions did not give desired product **215**.



137 **235** **215**

Scheme 76 i) LDA (2.5 eq), THF (0.05 M), –78 °C, 1 h *then* ii) Bu_3SnCl (5 eq), –78 °C to rt, 16 h; iii) Pd_2dba_3 (10 mol%), PPh_3 (25%), NMP (0.5 M), rt, 16 h.

Finally, a Stille coupling between left-hand fragment **81** and commercially obtained 2-(tributylstannyl)furan (**236**) was attempted. However, after exposure to catalytic $Pd(PPh_3)_4$ and CuI, recovered stannane **236** and cyclic diene **216** were the only two species detected in the crude reaction mixture. Because the intramolecular Heck cyclisation could not be outcompeted using furyl stannane **236**, we decided to abandon the cross-coupling strategy to link the two fragments. Chapter 5 details an alternative coupling method involving the nucleophilic addition of lithiated furans to aldehydes.



81 **236** **237** (*not observed*) **216** (*only observed product*)

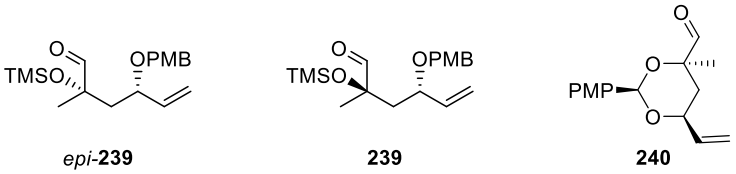
Scheme 77 Attempted Stille coupling. Reagents and conditions: $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), DMF (0.2 M), rt, 16 h.

Chapter 4

Synthesis of aldehyde left-hand fragments

4 Synthesis of aldehyde left-hand fragments

This chapter starts with a discussion about the Sharpless asymmetric dihydroxylation (SAD) reaction of 1,1-disubstituted olefins, a key step in our synthesis of lophotoxin. The main section of the chapter covers the syntheses of aldehydes *epi*-**239**, **239** and **240** (**Figure 10**).



epi-**239** **239** **240**

Figure 11 Left-hand fragments *epi*-**239**, **239** and **240**.

4.1 Sharpless dihydroxylation of 1,1-disubstituted olefins

A key finding in the Sharpless group's seminal report on *syn*-selective dihydroxylation reactions of olefins in 1980 was the discovery that enantioselectivity can be introduced when OsO_4 together with chiral, tertiary amine ligands were used.[99] Eventually, this led to the development of the now commercially available and widely used reagent cocktails AD-mix α and AD-mix β, comprising *cinchona* alkaloid-based chiral ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ in a catalytic manner (**Figure 12**).[100] The transformation has exceptional functional group tolerance and induces excellent enantioselectivies for most substrates.[101]

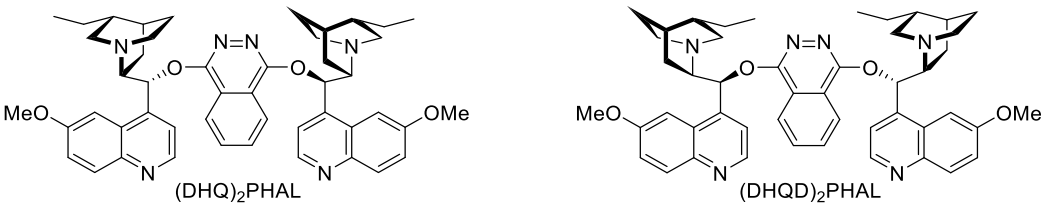
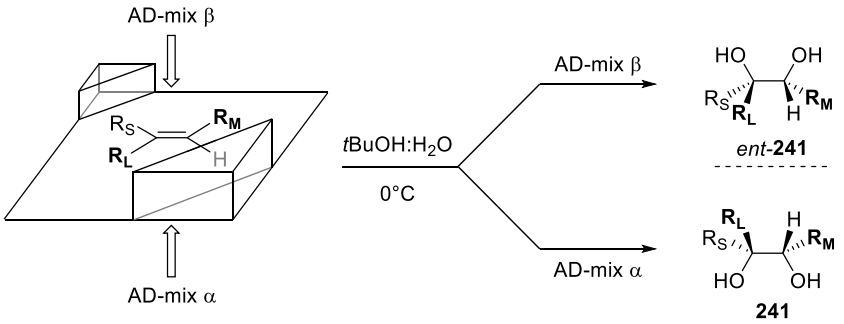


Figure 12 Chiral ligands $(DHQ)_2PHAL$ (AD-mix α) and $(DHQD)_2PHAL$ (AD-mix β).

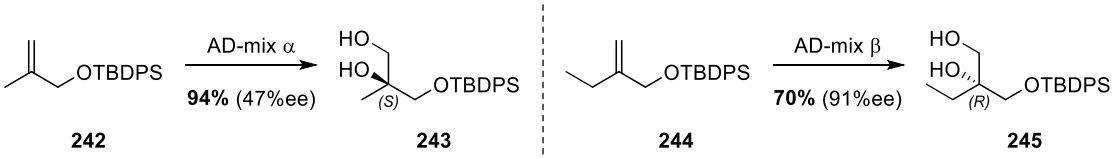
Sharpless and co-workers also reported a highly useful mnemonic to predict the stereochemical outcome of an SAD reaction (**Scheme 78**).[100] The four olefin substituents are ranked by their steric size and the substrate is arranged accordingly. AD-mix α is

predicted to favour bottom face attack, resulting in the formation of diol **241**. AD-mix β, on the other hand, is predicted to favour top face attack and *ent*-**241** is formed.



Scheme 78 Mnemonic to predict the stereochemical outcome of the SAD reaction by Sharpless

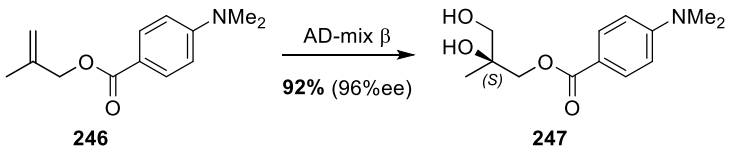
Although the SAD mnemonic works reliably for most terminal, *trans*-disubstituted and trisubstituted olefins, Hale and co-workers were the first to demonstrated that multiple 1,1-disubstituted allyl alcohol derivatives do not abide by the mnemonic and give the opposite enantiomer in varying enantioselectivities of 11–91%ee (see **Scheme 79** for selected examples).[102-103] The steric bulk of a TBDPS ether moiety greatly exceeds that of a methyl and an ethyl group. Nevertheless, subjecting olefins **242** and **244** to an SAD reaction with AD-mix α and AD-mix β, respectively, gave diols **243** and **245**, whose stereochemistry was opposite to what was predicted by the mnemonic. The absolute configuration of both diols was assigned by measuring the specific rotation after converting them into known derivatives.



Scheme 79 SAD reaction of 1,1-disubstituted olefins **242** and **244** did not give the diol enantiomers predicted by the Sharpless mnemonic. Reagents and conditions: *t*BuOH, H_2O, 0 °C.

However, this is not a general trend; Wang and co-workers reported the highly selective SAD reaction of 1,1-disubstituted olefin **246** bearing electron-rich, aromatic *N*,*N*-dimethylaminobenzoic esters following the mnemonic (**Scheme 80**).[104] The authors

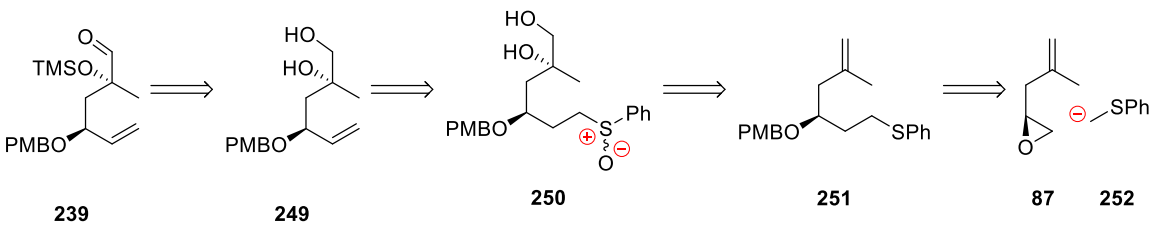
propose beneficial catalyst–substrate interactions *via* π–π stacking of the aromatic ring of the substrate with the linker of the catalyst to be responsible for the high selectivity.



Scheme 80 SAD reaction of olefin **246** following the mnemonic by Sharpless.

4.2 Retrosynthetic analysis

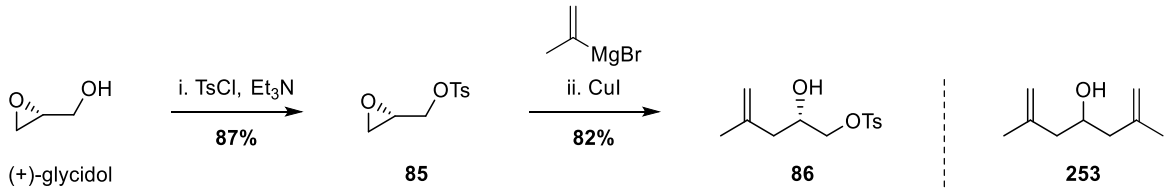
Together with Daniya Aynetdinova, who investigated addition reactions of lithiated furans with aldehydes for her Part II project, the synthesis of left-hand fragment **239** was planned (**Scheme 81**). Based on model studies we envisioned introducing the α-siloxy aldehyde moiety by Parikh–Doering oxidation followed by TMS protection of diol **249**. The terminal olefin moiety could then be introduced *via* Cope-type elimination of sulfoxide **250** after SAD reaction to avoid expected regioselectivity issues. We hoped to control the stereoconfiguration of the tertiary alcohol in diol **250** using *cinchona* alkaloid-based chiral ligands. A PMB protecting group was also chosen, because we speculated that the electron-rich aromatic ring could enhance the selectivity of the SAD reaction by π–π stacking with the linker moiety of the ligand, as described by Wang.[104] Compound **251** could be accessed *via* PMB protection and epoxide opening of **87** with lithiated thioanisole (**252**). Enantiopure epoxide **87**, synthesised from (+)-glycidol, is a literature-known compound that was an intermediate in the total synthesis of 11-gorgiacerol by Mulzer and co-workers (Chapter 1.2.9).[57]



Scheme 81 Retrosynthetic analysis of left-hand fragment **239**.

4.3 Synthesis of alcohol 254

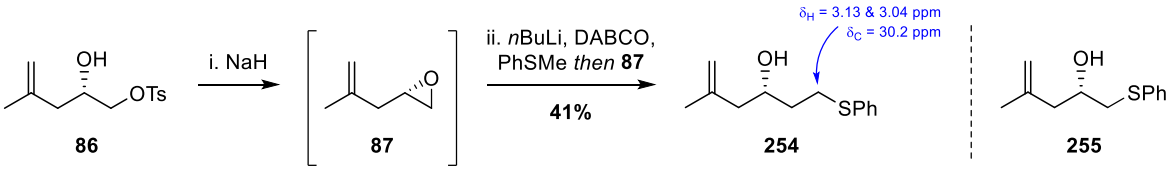
The synthesis commenced with repeating the published synthetic route to epoxide **87**.[57] Tosylation of (+)-glycidol afforded epoxide **85** as a white crystalline solid in 87% yield (**Scheme 82**). Strict temperature control was required for high isolated yields of alcohol **86** in the copper-catalysed epoxide opening of **85** with isopropenyl Grignard reagent to avoid the formation of undesired symmetrical diene **253**. At elevated temperatures epoxide **87** (**Scheme 83**) was formed *in situ* under such basic conditions. A second alkylation reaction resulted in the formation of diene **253**.



Scheme 82 Synthesis of 1,1-disubstituted olefin **86**. Reagents and conditions: i) TsCl (1.3 eq), Et_3N (1.5 eq), CH_2Cl_2 (0.7 M), 0 °C, 1.5 h; ii) isopropenylmagnesium bromide (2.1 eq), CuI (0.2 eq), THF (0.2 M), –78 to –40 °C, 2 h.

Due to its low boiling point, epoxide **87** was formed *in situ* by treatment of tosylate **86** with NaH (**Scheme 83**). In parallel with the synthesis of epoxide **87**, in a separate pot thioanisole was lithiated by treatment with DABCO and *n*BuLi. Both processes were timed to finish at the same time and the reaction mixture containing epoxide **87** was added to the one containing lithiated thioanisole *via* canula or syringe. Following this procedure, alcohol **254** was isolated in 41% yield on gram scales. The enantiopurity was confirmed to be > 99%ee by chiral HPLC analysis for all batches synthesised. Preliminary attempts to vary parameters such as reaction times and temperatures of the individual steps, ratios of reagents and identities of the base did not improve the low yield of the transformation. Moreover, when the scale of the reaction was increased to multi-gram quantities, the yield dropped to 34%. Careful analysis of the crude reaction mixture by NMR revealed the increased formation of side product **255**. Separation of homologues **254** and **255** by column chromatography was tedious and time-consuming. The characteristic effect of the

sulphur atom on the NMR signals of its adjacent methylene group in compound **254** was interesting. The diastereotopic protons (3.13 & 3.04 ppm) were shifted much further downfield than the carbon signal (30.2 ppm). This effect was very noticeable when analysing HSQC data of similar compounds.

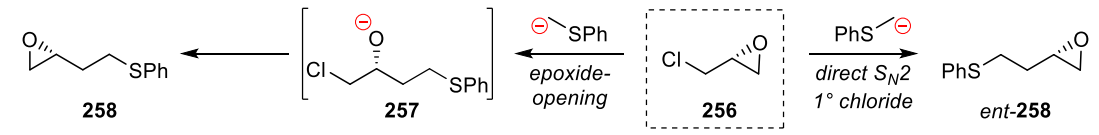


Scheme 83 Synthesis of alcohol **254**. Reagents and conditions: i) NaH (1.1 eq), THF, 0 °C, 1.5 h; ii) MeSPh (2.5 eq), nBuLi (2.5 eq), DABCO (0.25 eq), THF (0.1 M), 0 °C, 1.5 h *then* **87**, 0 °C, 16 h.

Due to the aforementioned issues, an alternative synthetic route for alcohol **254** was sought. Such a route would place the low yielding epoxide opening step with lithiated thioanisole earlier in the synthesis before the introduction of the 1,1-disubstituted olefin moiety. This different order of events was advantageous because the isopropenyl Grignard reagent required to introduce the olefin moiety was more expensive (1.39 £/mmol) than any other reagent used at this stage of the synthesis, including enantiopure (+)-glycidol (1.29 £/mmol).[105] The following section details this modified route.

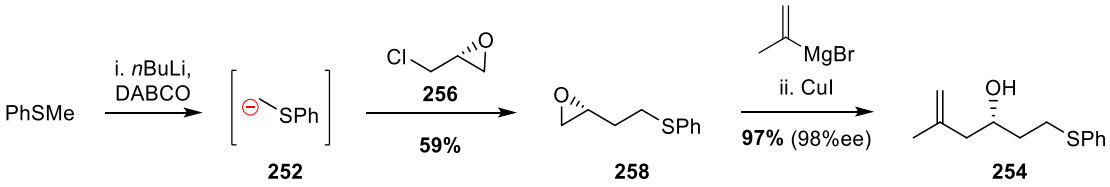
4.3.1 Synthesis of alcohol 254 from (–)-epichlorohydrin

The reaction of racemic epichlorohydrin (*rac*-**256**) with lithiated thioanisole to form epoxide *rac*-**258** has been reported by Taber and Guo[106] as well as by Nakashima and co-workers[107] to proceed with 59% and 34% yield, respectively. In the reaction, chlorohydrin **257** was first formed by epoxide opening, which then recyclised to form epoxide **258** (**Scheme 84**). Following this pathway, readily available (–)-epichlorohydrin (**256**, 0.10£/mmol[108]) should give desired epoxide **258** in an enantiopure manner. Nevertheless, possible direct displacement of the primary chloride moiety would result in the formation *ent*-**258** and thereby compromise the enantiopurity of the product.



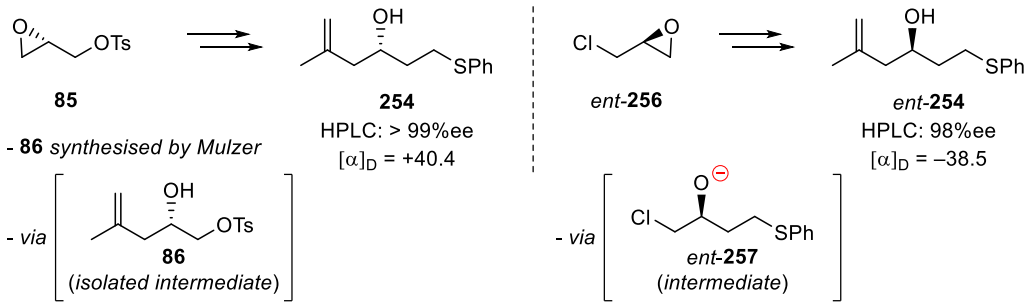
Scheme 84 Possible stereochemical outcomes for the reaction of (–)-epichlorohydrin (**256**) with lithiated thioanisole.

To enable better comparison with the previous route *via* tosylate **86**, different batches of epoxide **258**, derived from epichlorohydrin and thioanisole, were converted separately into alcohol **254** (**Scheme 85**). The copper-catalysed Grignard addition reliably gave excellent yields and it was possible to reduce the amount of expensive isopropenyl Grignard reagent from 2.1 eq to 1.5 eq.



Scheme 85 Synthesis of alcohol **254**. Reagents and conditions:
i) *n*BuLi (1.2 eq), DABCO (0.1 eq), THF (1 M), 0 °C, 1 h *then* **256** (2 eq), –78 °C *then* –50 to 0 °C, 2 h *then* rt 30min;
ii) isopropenylmagnesium bromide (1.5 eq), CuI (0.2 eq), THF (0.2 M), –40 °C, *then* 0 °C, 2 h.

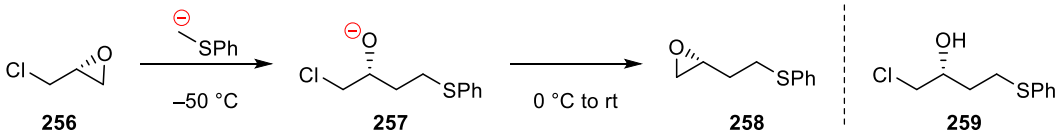
In the same manner, enantiomeric alcohol *ent*-**254** was synthesised from (+)-epichlorohydrin (*ent*-**256**) in 43% over two steps. The enantiopurity of each batch of alcohol **254** synthesised was analysed by chiral HPLC. Material synthesised from tosylate **85** (Chapter 4.3) exhibited extremely high enantiopurity (> 99%ee) and a specific rotation of $[\alpha]_D = +40.4$ was measured (**Scheme 86**). Alcohol *ent*-**254** synthesised from (+)-epichlorohydrin (*ent*-**256**) was also highly enantiopure (98%ee) but showed a specific rotation of $[\alpha]_D = -38.5$, confirming the high stereospecificity of the transformation following the proposed mechanism *via* intermediate *ent*-**257**.



Scheme 86 Absolute configuration and enantiopurity of alcohol **254** synthesised from tosylate **85** and alcohol *ent*-**254** from (+)-epichlorohydrin (*ent*-**256**).

However, it was found that a specific temperature protocol was necessary to isolate epoxide **258** in high yields and in excellent enantiopurity (**Table 6**). When the reaction was performed at –78 °C and warmed to rt for 30 min, enantiopure epoxide **258** was isolated in 30% yield as well as chlorohydrin **259** in 27% yield (entry 1). Although **258** was isolated in 53% yield, a slight drop of enantiopurity was observed when the reaction was performed at rt (entry 2). When (–)-epichlorohydrin was added dropwise at –78 °C, it was observed that the temperature of the reaction mixture increased much more quickly than expected when the cooling bath was removed. This was most likely due to the amount of energy freed from the exothermic transformation. However, when the reaction mixture was warmed gradually over-night, the yield dropped to 39% and numerous unidentified side-products were observed in the crude reaction mixture by NMR (entry 3). The best result was observed when the reaction mixture was gradually warmed from –50 °C to 0 °C over the course of 3 h (entry 4). Subsequently the temperature was raised to rt to ensure full conversion of chlorohydrin **257**. Epoxide **258** was isolated in 59% yield and in high enantiopurity (98%ee).

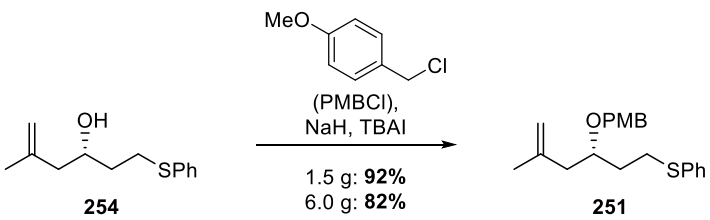
Table 6 Conditions for the reaction of (–)-epichlorohydrin (**256**) to epoxide **258**: Reagents and conditions: PhSMe (16.2 mmol, 1 eq), DABCO (0.1 eq), *n*BuLi (1.2 eq), 0 °C, 1 h *then* cooled to –78 ° *then* **256** (2 eq). a) The reaction mixture was cooled to –78 °C for further 30 min after addition of **256** before being warmed to the stated temperature; b) ee was measured by chiral HPLC after conversion to alcohol **254**.



entry	temperature	isolated yield of **258**	ee[b] (**254**)	comment
1	–78 °C (4 h) *then* rt (30 min)	**30%**	98%	27% **259** isolated
2	rt[a] (2.5 h)	**53%**	95%	exotherm reaction
3	–78 °C to –15 °C (15 h) *then* rt (1 h)	**39%**	98%	multiple impurities
4	–50 °C[a] to 0 °C (3 h) *then* rt (1 h)	**59%**	98%	

4.4 Synthesis of left-hand fragment 239

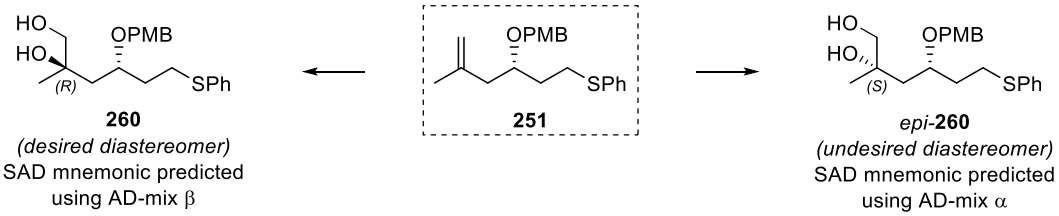
With a scalable and efficient synthetic route for alcohol **254** in hand, PMB protection was then attempted (**Scheme 87**). Initial efforts using 5 mol% of nucleophilic catalyst TBAI suffered from low conversions even with prolonged reaction times (3 days) and elevated temperatures (65 °C). An increase of TBAI to 50 mol%, however, resolved the poor conversions, allowing PMB ether **251** to be isolated in 92% yield on gram scale. Unfortunately, the yield dropped slightly to 82% when the scale was further increased to 6.0 g starting material.



Scheme 87 Synthesis of PMB ether **251**. Reagents and conditions: NaH (2 eq), DMF (1.5 M), 0 °C to rt, 1 h *then* PMBCl (2.1 eq), TBAI (0.5 eq), rt, 16 h.

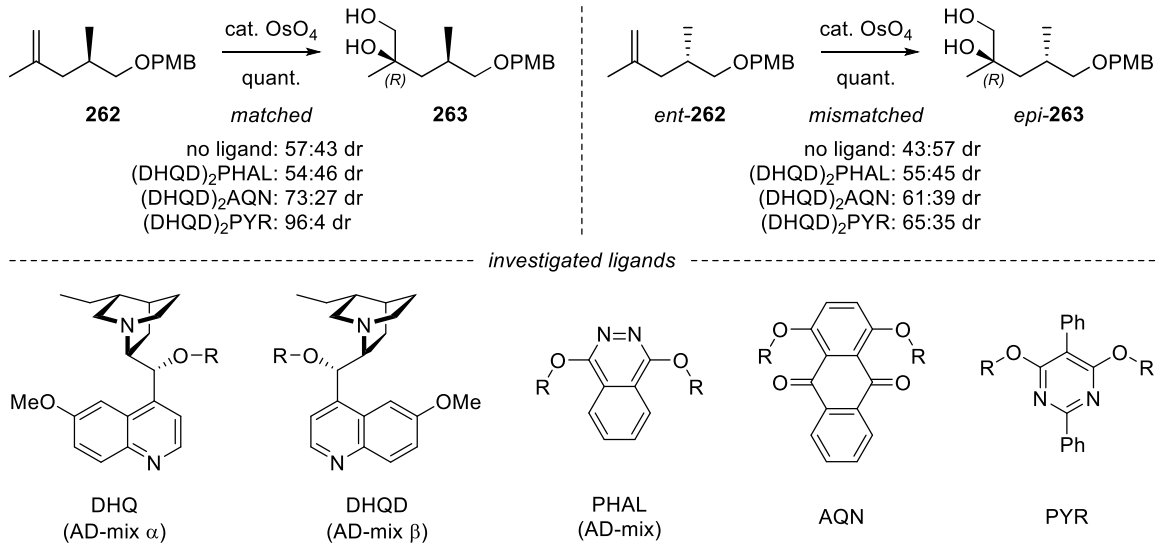
4.4.1 Synthesis of diol *epi*-249

The next step was the diastereoselective dihydroxylation of 1,1-disubstituted olefin **251** to desired diol **260**. Applying the mnemonic developed by Sharpless (Chapter 4.1, **Scheme 78**), the alkyl chain was assigned as the largest olefin substituent (R_L). Thus, AD-mix β, containing enantiopure ligand $(DHQD)_2PHAL$ (Chapter 4.1, **Figure 12**), was predicted to give desired diastereomer **260** (**Scheme 88**). Using AD-mix α, in turn, would produce undesired diastereomer *epi*-**260**.



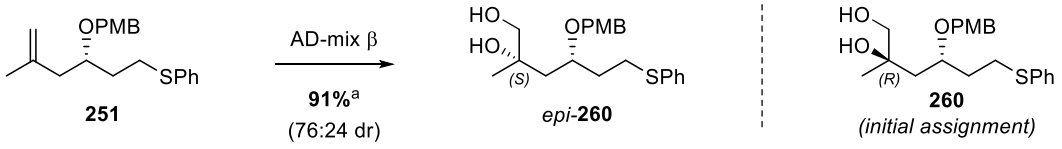
Scheme 88 SAD reaction of 1,1-disubstituted olefin **251**.

Moreover, the SAD reaction of structurally comparable 1,1-disubstituted olefins **262** and *epi*-**262** had been investigated in detail by Lannou and co-workers (**Scheme 89**).[109] The authors analysed the diastereomeric ratios observed for SAD reactions of **262** and *epi*-**262** using both pseudo-enantiomers DHQ and DHQD linked together in a homo-dimeric fashion with linkers PHAL, AQN and PYR. The study showed that although all catalysts gave quantitative yields, the origin of the linker had a significant impact on the diastereoselectivity observed. As expected, the asymmetric induction was much greater in the matched case to form diol **263**, rather than the mismatched case to form *epi*-**263**. In both cases, $(DHQD)_2PYR$ gave the highest selectivity. Most importantly, in all cases the stereoisomer predicted using the Sharpless mnemonic was the dominant one.



Scheme 89 Investigation of the SAD reaction by Lannou and co-workers. Reagents and conditions: $K_2OsO_4 \cdot H_2O$ (1 mol%), ligand (2.5 mol%), K_2CO_3 (3 eq), $K_3Fe(CN)_6$ (3 eq), $MeSO_2NH_2$ (1 eq), *t*BuOH:H_2O (1:1), 0 °C, 2 to 12 h.

Because of the reasons discussed above, the major diastereomer obtained from SAD reaction of 1,1-disubstituted olefin **251** using AD-mix β ($(DHQD)_2PHAL$) was initially wrongly assumed to be diol **260** (**Scheme 90**). However, due to unambiguous structure determination of advanced derivatives **273** and *epi*-**273** (Chapter 4.4.3), the relative configuration was re-assigned retrospectively and is shown as such for all compounds henceforth: Using AD-mix β and $MeSO_2NH_2$, diol *epi*-**260** was isolated in 91% yield as an inseparable mixture of diastereomers (76:24 dr). As purification of *epi*-**260** was hampered by co-elution with $MeSO_2NH_2$, the yield was calculated from the mass and the NMR ratios of the isolated mixture. It was observed that the isolated yield for the SAD reaction decreased when older AD-mix batches were used. This effect was successfully compensated by using increased amounts of reagent.



Scheme 90 Synthesis of diol *epi*-**260**. Reagents and conditions: AD-mix β (2.5 eq), $MeSO_2NH_2$ (1 eq), *t*BuOH:H_2O (1:1, 0.3 M), 0 °C, 16 h; a) calculated from NMR ratios of the isolated mixture with $MeSO_2NH_2$.

Inspired by the results from Lannou and co-workers,[109] different conditions were tested for the dihydroxylation of olefin **251** (**Table 7**). Quinuclidine, previously used to mimic

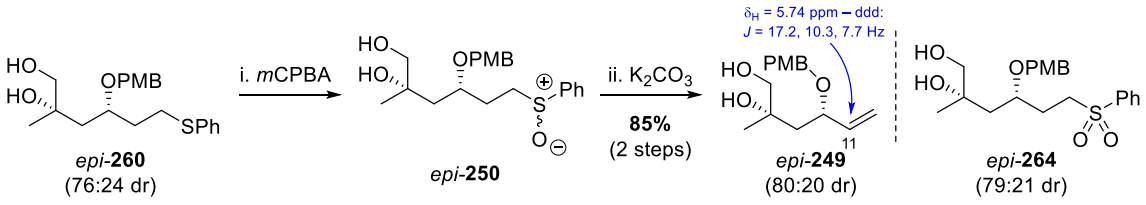
racemic SAD conditions by Warren and co-workers,[110] gave a 50:50 mixture of inseparable diastereomers (entry 1). Thus, it was concluded that any diastereomeric induction of the substrate was negligible. AD-mix α gave the opposite diastereomer in slightly diminished selectivity (entry 2). Using AD-mix β gave diol *epi*-**260** in 79% yield and 78:22 dr (entry 3). Removing $MeSO_2NH_2$ resulted in a marginal increase in stereoselectivity, but the reaction suffered from low conversion and gave unreacted starting material (entry 4). Using $(DHQD)_2AQN$ gave *epi*-**260** lower yield and worse selectivity than AD-mix β (entry 5) and $(DHQD)_2PYR$ gave the opposite diastereomer in similar selectivity (entry 6). Therefore AD-mix β with $MeSO_2NH_2$ as additive was chosen, which afforded *epi*-**260** in 91% yield (76:24 dr) upon scale-up.

Table 7 Ligand screening for SAD reaction of olefin **251** (**Scheme 90**). Reagents and conditions: $K_2OsO_4 \cdot H_2O$ (1 mol%), ligand (3 mol%), K_2CO_3 (3 eq), $K_3Fe(CN)_6$ (3 eq), $MeSO_2NH_2$ (1 eq), *t*BuOH:H_2O (1:1), 0 °C, 16 h; a) calculated from NMR ratios of the isolated mixture with $MeSO_2NH_2$; b) racemic substrate *rac*-**251** used; c) prepared reagent cocktail AD-mix used; d) no $MeSO_2NH_2$; e) not determined.

entry	ligand	comment	Yield of *epi*-**260**	dr (*epi*-**260**:**260**)
1	quinuclidine[b]	no chiral induction	**51%**	50:50
2	AD-mix α[c]		**55%**	29:71
3	AD-mix β[c]	-	**79%**	78:22
4	AD-mix β[c,d]	no $MeSO_2NH_2$	**48%**	81:19
5	$(DHQD)_2AQN$	-	**57%**	68:32
6	$(DHQD)_2PYR$	-	**NA**[e]	33:67
7	AD-mix β[c]	scale-up	**91%**	76:24

With diol *epi*-**260** in hand, the focus was set on installation of the terminal olefin from thioether moiety *via* oxidation and Cope elimination. Although Matsuo and co-workers had reported a one-pot procedure for this transformation, the author's method relied on explosive *O*-mesitylenesulfonylhydroxylamine as a reagent.[111] Thus, as a safer alternative,

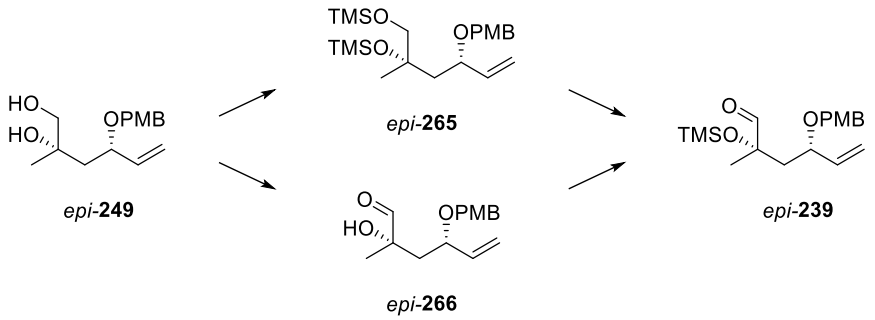
a procedure involving oxidation of *epi*-**260** to sulfoxide *epi*-**250**, followed by *syn* elimination to *epi*-**249** was tested first (**Scheme 91**). Oxidation of thioether *epi*-**260** required an exact amount of *meta*-chloroperoxybenzoic acid (*m*CPBA) to avoid the formation of over-oxidised sulfone *epi*-**264**. Precise determination by weight was hampered by varying purity of *m*CPBA batches, most likely due to the presence of H_2O and *meta*-chlorobenzoic acid contaminants. However, the oxidation reaction was very rapid. Portions of *m*CPBA were added and the conversion was controlled by TLC five minutes after addition. Due to the high polarity of *epi*-**250**, an aqueous work-up was avoided and the reaction mixture was subjected directly to column chromatography. Sulfoxide *epi*-**250** was isolated in 93% yield as an inseparable mixture of four diastereomers. Cope-type elimination was achieved by treating *epi*-**250** (76:24 dr) with K_2CO_3 in refluxing PhMe for three days at high dilution and terminal olefin *epi*-**249** was isolated in 85% yield over two steps. Both diols *epi*-**260** and *epi*-**249** were obtained as inseparable mixtures of diastereomers. However, it was possible to increase the diastereomeric ratio of *epi*-**249** marginally (80:20 dr). Terminal allylic ether *epi*-**249** exhibited a proton signal for *H*-11 at 5.74 ppm characteristic for similar compounds: The signal had a distinct coupling pattern (ddd: J = 17.2, 10.3, 7.7 Hz) that was easily recognisable.



Scheme 91 Synthesis of terminal olefin *epi*-**249**. Reagents and conditions:
i) *m*CPBA (1 eq), DCE, 0 °C, 5 min; ii) K_2CO_3 (5 eq), PhMe (15 mM), reflux, 3 days.

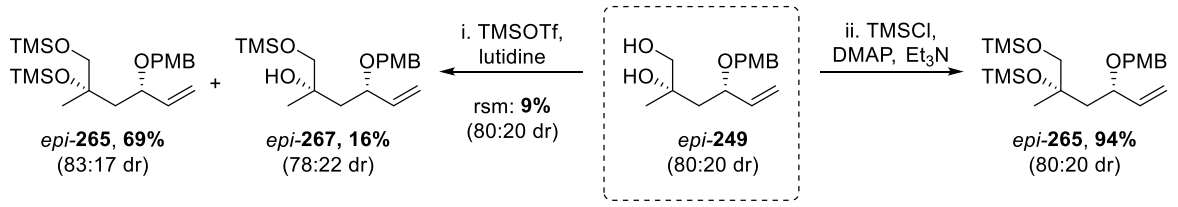
4.4.2 Synthesis of aldehyde *epi*-239

Having established a robust synthetic route for diol *epi*-**249**, a way to derivatise it to α-siloxy aldehyde *epi*-**239** while avoiding additional protecting group operations was sought. A possible strategy involved the formation of *bis*-silyl ether *epi*-**265** followed by either direct oxidation or selective deprotection of the primary TMS ether and subsequent oxidation (**Scheme 92**). Another strategy involved oxidation to hydroxy aldehyde *epi*-**266** first, followed by TMS protection. Both strategies were investigated in parallel and are described in this chapter. It was also important to separate the minor diastereomers by chromatography because diol *epi*-**249** was isolated as an inseparable mixture (80:20 dr).



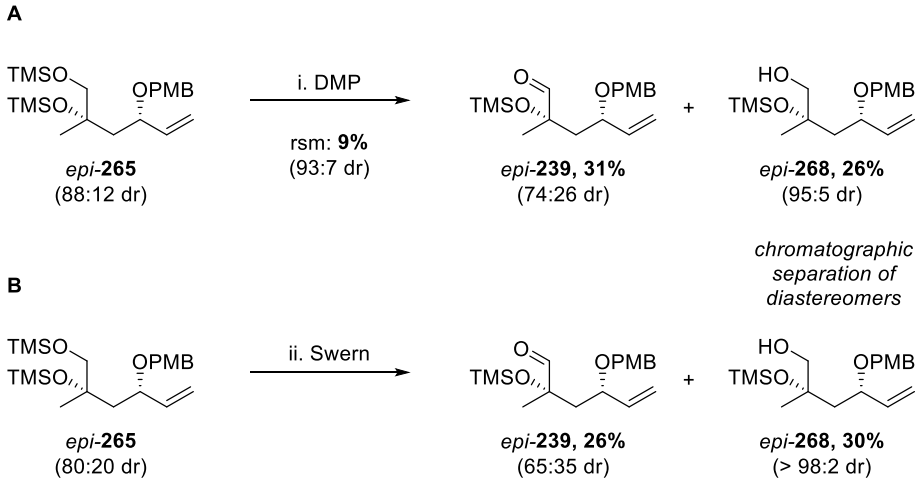
Scheme 92 Two possible strategies to synthesise α-siloxy aldehyde *epi*-**239** from diol *epi*-**249**.

Formation of *bis*-TMS ether *epi*-**265** was achieved using two methods (**Scheme 93**): Treatment with TMSOTf and 2,6-lutidine afforded *epi*-**265** in 69% yield as a mixture of inseparable diastereomers (83:17 dr). Although the diastereoselectivity was slightly improved, undesired TMS ether *epi*-**267** and recovered starting material were isolated in 16% (78:22 dr) and 9% yield (80:20 dr), respectively as well. Using excess TMSCl and nucleophilic catalyst 4-dimethylaminopyridine (DMAP), desired *epi*-**265** was isolated in 94% yield. Moreover, the material obtained by this method was clean by NMR after aqueous work-up and purification by chromatography was not necessary. Thus, TMSCl/DMAP was chosen over TMSOTf/lutidine.



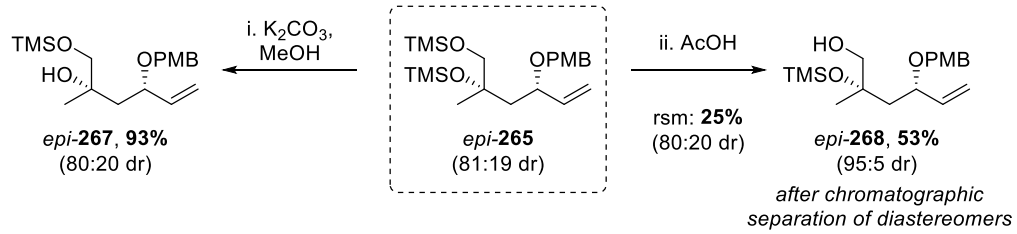
Scheme 93 Synthesis of bis-silyl ether *epi*-**265**. Reagents and conditions: i) TMSOTf (2.1 eq), 2,6-lutidine (4.1 eq), CH_2Cl_2 (0.1 M), –78 °C, 30 min; ii) TMSCl (6 eq), DMAP (1 eq), Et_3N (8 eq), CH_2Cl_2 (0.1 M), rt, 16 h.

Direct oxidation of primary TMS silyl ethers to the corresponding aldehyde was attempted next. Dess-Martin periodinane (DMP) and Swern oxidation have been reported to achieve this transformation.[112] To this end, *bis*-TMS ether *epi*-**265** to was treated with DMP and desired left-hand fragment *epi*-**239** as was obtained as an inseparable mixture of diastereomers (74:26 dr) in 31% yield (**Scheme 94A**). Moreover, diastereomerically enriched starting material (*epi*-**265**) was recovered in 9% yield (93:7 dr) and mono-deprotected alcohol *epi*-**268** was isolated in 26% yield after chromatographic separation of its minor diastereomer. Swern oxidation of *bis*-silyl ether *epi*-**265** gave left-hand fragment *epi*-**239** in 26% yield (65:35 dr, **Scheme 94B**) and again *epi*-**268** was isolated in 30% as a single diastereomer (>98:2 dr) after chromatographic separation from its minor diastereomer. Regioisomers *epi*-**267** (**Scheme 93**) and *epi*-**268** (**Scheme 94**) were assigned based on the coupling of *H*-7 and the free hydroxy group: In primary alcohol *epi*-**268** both groups exhibited a coupling constant of $J = 6.9$ Hz and a corresponding cross-peak was observed in the COSY spectrum. Furthermore, primary alcohol *epi*-**268** exhibited significantly higher polarity than tertiary alcohol *epi*-**267** on TLC and chromatographic purification.



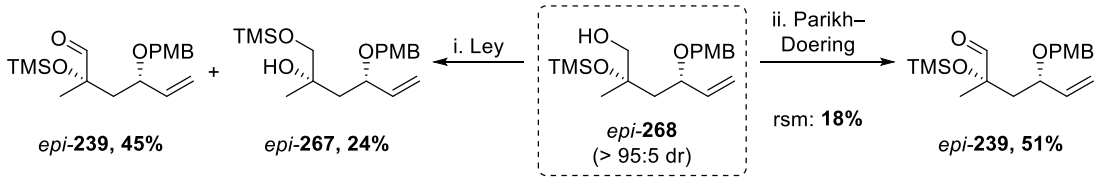
Scheme 94 Synthesis of left-hand fragment *epi*-**239**. Reagents and conditions:
i) DMP (1.2 eq), pyridine (10 eq), CH_2Cl_2 (0.1 M), 0 °C, 18 h;
ii) oxalyl chloride (2.3 eq), DMSO (1.4 eq), CH_2Cl_2, –78 °C *then epi*-**265**, 1 h *then* Et_3N (10 eq), 2 h.

Although these preliminary results for direct oxidation were promising, straightforward separation from the undesired diastereomer seemed unlikely at any stage of the synthesis. As full separation of both diastereomers *epi*-**268** by a single column chromatography operation had already been achieved, the strategy was changed to a selective deprotection tactic involving the isolation of alcohol *epi*-**268**: Various methods for mono-deprotection of *bis*-TMS ether *epi*-**265** were tested. Treatment with PPTS in CH_2Cl_2:MeOH (9:1) gave undesired diol *epi*-**249** in 97%. Silica gel in CH_2Cl_2 with EtOH as co-solvent gave no conversion and starting material was recovered. Under basic condition (K_2CO_3 in MeOH) only undesired regioisomer *epi*-**267** was observed (**Scheme 96**); this was most likely due to silyl migration to the less bulky primary alcohol after deprotection. The best results were achieved when *epi*-**265** was treated with a mixture of AcOH:THF:H_2O (4:20:1,). The reaction mixture was gradually warmed from 0 °C to 10 °C and the conversion closely followed by TLC. The reaction was quenched when the formation of diol *epi*-**249** was observed. Following this method, *epi*-**268** was isolated as a single diastereomer in 53% yield and 25% starting material was recovered after purification by chromatography.



Scheme 95 Deprotection of bis-silyl ether *epi*-**268**. Reagents and conditions: i) K_2CO_3 (0.5 eq), MeOH (0.1 M), –10 °C to rt, 4.5 h; ii) AcOH:THF:H_2O (4:20:1), 0 to 10 °C, 24 h.

Ley oxidation of *epi*-**268** provided desired α-siloxy aldehyde *epi*-**239** in 45% yield and 24% of undesired regioisomer *epi*-**267** were isolated (**Scheme 96**). Tetrapropylammonium perruthenate (TPAP) for this reaction was stored and weighed out in a glove box as a free-flowing powder. In contrast, TPAP stored outside the glove box appeared darker and sticky. Reactions attempted with such material failed and only starting material was recovered. Parikh–Doering oxidation of alcohol *epi*-**268** afforded aldehyde *epi*-**239** in 51% yield with 18% recovered starting material. In summary, a synthesis for left-hand fragment *epi*-**239** was developed in 8 to 10 steps.

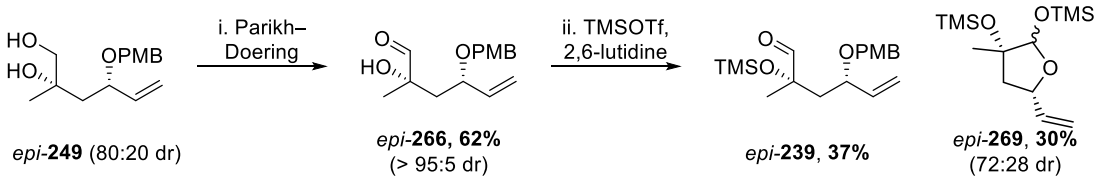


Scheme 96 Synthesis of left-hand fragment *epi*-**239** from *epi*-**268**. Reagents and conditions: i) TPAP (0.1 eq), NMO (2.1 eq), 3Å-MS, CH_2Cl_2 (0.1 M), rt, 1 h; ii) $SO_3 \cdot$ pyridine (4.0 eq), Et_3N (6 eq), DMSO (25 eq), CH_2Cl_2 (0.1 M), rt, 5 h.

4.4.2.1 Synthesis of aldehyde *epi*-239 *via* hydroxy aldehyde *epi*-266

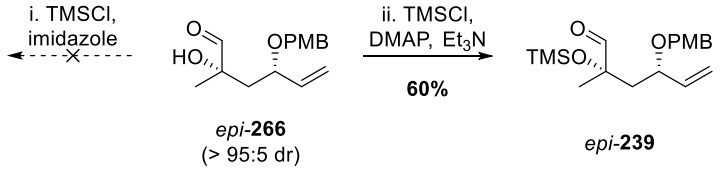
In parallel with the above described studies, the synthesis of α-siloxy aldehyde *epi*-**239** through hydroxy aldehyde *epi*-**266** was investigated by Daniya Aynetdinova. Parikh–Doering oxidation of diol *epi*-**249** and subsequent purification by column chromatography using finer silica gel (15–40 µm) afforded aldehyde *epi*-**266** in 62% as a single diastereomer (95:5 dr, **Scheme 97**). Although TMS protection using TMSOTf and 2,6-lutidine resulted in the formation of left-hand fragment *epi*-**239**, the reaction was hampered by formation of undesired cyclised side-product *epi*-**269**. It was speculated that TMSOTf activated the aldehyde as a Lewis acid and induced the cyclisation and

subsequent PMB deprotection. The amount of cyclised acetal *epi*-**269** formed varied greatly even when reaction temperature and ratios of reagents were tightly controlled. The best result was obtained at –78 °C with 1 equivalent of TMSOTf: siloxy aldehyde *epi*-**239** was isolated in 37% yield and acetal *epi*-**269** was isolated in 30% yield as an inseparable mixture of anomers (72:28 dr).



Scheme 97 Synthesis of left-hand fragment *epi*-**239** by Daniya Aynetdinova. Reagents and conditions: i) $SO_3 \cdot$ pyridine (3.0 eq), Et_3N (5 eq), DMSO (28 eq), CH_2Cl_2 (0.1 M), 0 °C to rt, 5 h; ii) TMSOTf (1 eq), 2,6-lutidine (2 eq), –78 °C, 1 h.

A different method to avoid the formation of cyclic acetal aldehyde *epi*-**269** was sought and less reactive TMSCl was investigated. Treatment of sterically bulky tertiary alcohol *epi*-**266** with TMSCl and imidazole only gave starting material (**Scheme 98**). However, using the more reactive nucleophilic catalyst DMAP with Et_3N as a general base resulted in full conversion of *epi*-**266** and gave left-hand fragment *epi*-**239** in 60% yield.

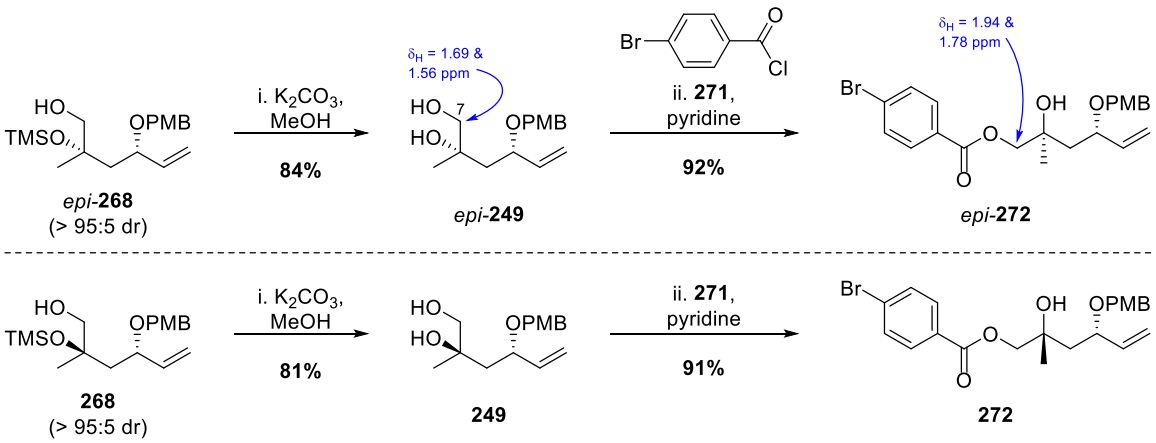


Scheme 98 TMS protection of hydroxy aldehyde *epi*-**239**. Reagents and conditions: i) TMSCl (6 eq), imidazole (9 eq), CH_2Cl_2 (0.3 M), rt, 16 h; ii) TMSCl (6 eq), DMAP (1.5 eq), Et_3N (9 eq), DMF (0.1 M), rt, 16 h.

4.4.3 Assignment of stereocentre *C*-8

Although a robust and scalable route for left-hand fragment *epi*-**239** had been developed successfully at this stage of the project, the stereogenic centre *C*-8 was still assigned relying on the mnemonic developed by Sharpless and co-workers and comparison to similar compounds reported in the literature (Chapter 4.4.1). Therefore, we sought a way to determine the stereochemical configuration at position *C*-8 either by X-ray crystallography of a crystalline compound, Mosher's ester analysis or nOe analysis of a

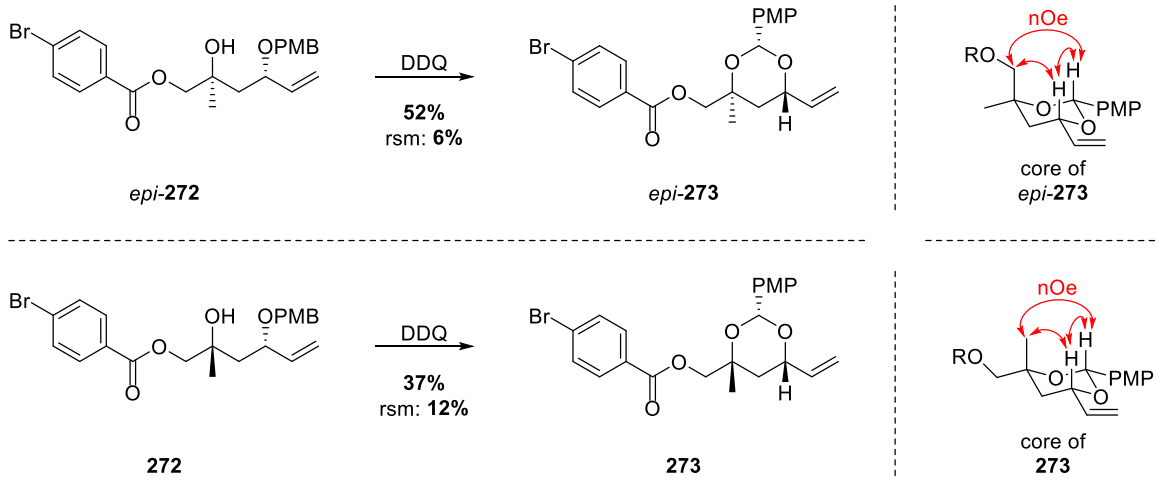
cyclic structure. Careful nOe analysis of cyclic acetal *epi*-**269** (**Scheme 97**) suggested that the initial assignment was incorrect but were not conclusive. The fact that *epi*-**269** was isolated as an inseparable mixture of diastereomers hampered the analysis. Primary alcohols *epi*-**268** and **268** on the other hand have both been obtained as single diastereomers *via* separation by column chromatography after selective deprotection of *bis*-TMS ether *epi*-**265** (**Scheme 96**). Both TMS ethers were deprotected separately in alkaline MeOH to afford diols *epi*-**249** and **249** as single diastereomers in 84% and 81% yield, respectively (**Scheme 99**). Exposure of both diols to 4-bromobenzoyl chloride (**271**) in pyridine:CH_2Cl_2 (1:1) resulted in the selective mono-esterification and diastereomers *epi*-**272** and **272** were isolated in 92% and 91% yield, respectively. The use of PhMe during purification by column chromatography facilitated separation from excess reagents for both esters. The expected selective benzoylation of primary alcohol *OH*-7 over sterically hindered tertiary alcohol *OH*-8 was confirmed by a significant change of the ^{1}H NMR signal at position *H*-7 from δ_H = 1.69 & 1.56 ppm in diol *epi*-**249** to δ_H = 1.94 & 1.78 ppm in ester *epi*-**272**. Unfortunately, neither *epi*-**272** nor **272** solidified upon storage at –20 °C.



Scheme 99 Synthesis of diastereomerically pure esters *epi*-**272** and **272**. Reagents and conditions: i) K_2CO_3 (0.5 eq), MeOH (0.1 M), 1.5 h; ii) **271** (5 eq), pyridine:CH_2Cl_2 (1:1, 0.1 M).

Subsequently, PMB ethers *epi*-**272** and **272** were converted into cyclic acetals *epi*-**273** and **273** by treatment with DDQ under anhydrous conditions in 52% and 37% yield, respectively (**Scheme 100**). In both transformations, only a single diastereomer of the

respective products was observed by NMR in the crude reaction mixture. The relative configuration of all three stereocentres of both compounds was assigned by nOe analysis, which revealed that the SAD reaction of 1,1-disubstituted olefin **251** (**Scheme 88**, Chapter 4.4.1) was the exception to the rule and did not follow the prediction of the mnemonic. Thus, the major diastereomer obtained from dihydroxylation using AD-mix β did not possess the desired configuration and the other diastereoisomer had to be synthesised.



Scheme 100 Synthesis and crucial nOe interactions of acetals *epi*-**273** and **273**.
Reagents and conditions: DDQ (1 eq), CH_2Cl_2 (50 mM), 0 °C to rt, 4–5 h.

These results were corroborated by nOe analysis of aldehydes **240** and *epi*-**240**, which were prepared at a later point (Chapter 4.5). The same interactions across and along the 6-membered ring were observed (**Figure 13**), confirming the assigned configuration. Moreover, X-ray crystal structure **321** (Chapter 5.4, **Figure 16**) confirms this assignment.

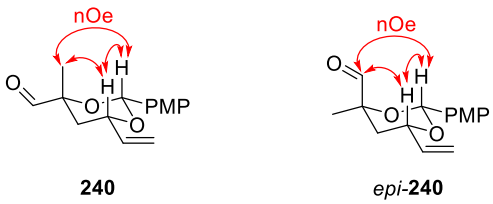
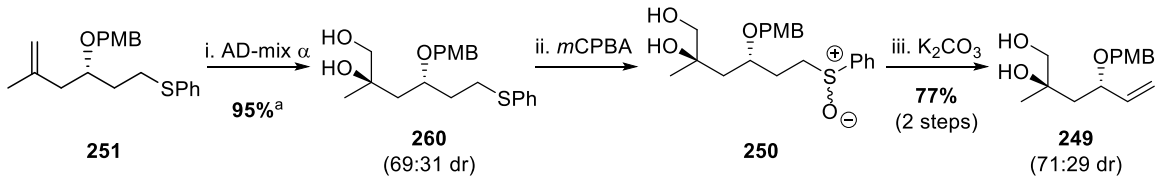


Figure 13 Crucial nOe interactions of aldehydes *epi*-**240** and **240**.

4.4.4 Synthesis of aldehyde 239

Because of the structural re-assignment described above, the synthetic sequence was repeated starting with SAD reaction of 1,1-disubstituted olefin **251** using AD-mix α

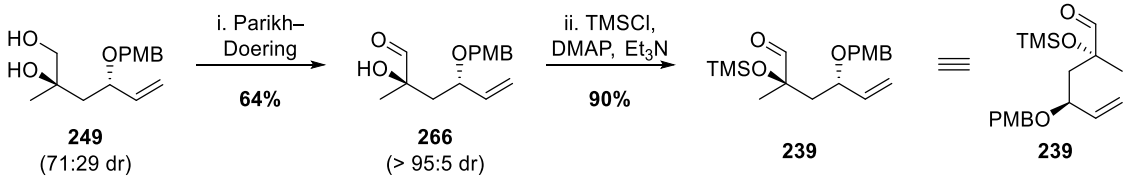
instead (**Scheme 101**). Diol **260** was isolated in 95% NMR yield as a 69:31 mixture of inseparable diastereomers contaminated with methanesulfonamide. Exposure to *m*CPBA at 0 °C caused an instant conversion to sulfoxide **250**. The oxidation agent was added in portions and the conversion was closely followed by TLC to avoid overoxidation to the corresponding sulfone. Sulfoxide **250** was isolated as a mixture of four diastereomers. Sulfoxide elimination was achieved by prolonged treatment with K_2CO_3 in refluxing PhMe and olefin **249** was isolated as a mixture of diastereomer (71:29 dr) in 77% yield over two steps.



251 **260** (69:31 dr) **250** **249** (71:29 dr)

Scheme 101 Synthesis of diol **249**. Reagents and conditions: i) AD-mix α (2.5 eq), $MeSO_2NH_2$ (1 eq), *t*BuOH:H_2O (1:1, 0.1 M), 40 °C, 2 h; ii) *m*CPBA (1.3 eq), DCE (50 mM), 0 °C, 1 h; iii) K_2CO_3 (5 eq), PhMe (50 mM), reflux, 3 days. a) calculated from NMR ratios of the isolated mixture with $MeSO_2NH_2$.

Parikh–Doering oxidation afforded hydroxy aldehyde **266** (**Scheme 102**) and isolation of the desired diastereomer was achieved by repeated column chromatography operations using finer silica gel (15–40 µm) and CH_2Cl_2:acetone. Because decomposition of similar hydroxy aldehydes was known, **266** was stored at –20 °C for a maximum of 48 h. TMS protection, using DMAP as nucleophilic catalyst, yielded left-hand fragment **239** in 90%. In contrast to hydroxy aldehyde **266**, it was stable to storage at –20 °C and has been stored for 4 months without signs of decomposition.

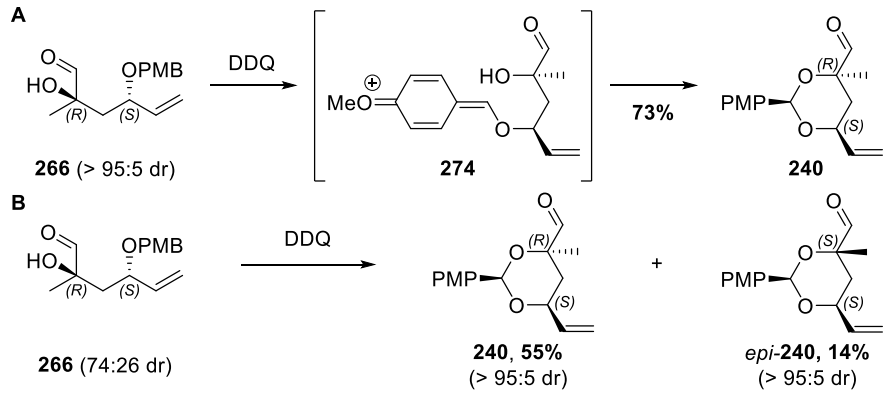


249 (71:29 dr) **266** (> 95:5 dr) **239** **239**

Scheme 102 Synthesis of left-hand fragment **239**. Reagents and conditions: i) SO_3 · pyridine (3.0 eq), Et_3N (5 eq), DMSO (28 eq), CH_2Cl_2 (0.1 M), 0 °C to rt, 2 h; ii) TMSCl (6 eq), DMAP (1 eq), Et_3N (8 eq), DMF (0.1 M), rt, 16 h.

4.5 Synthesis of left-hand fragment 240

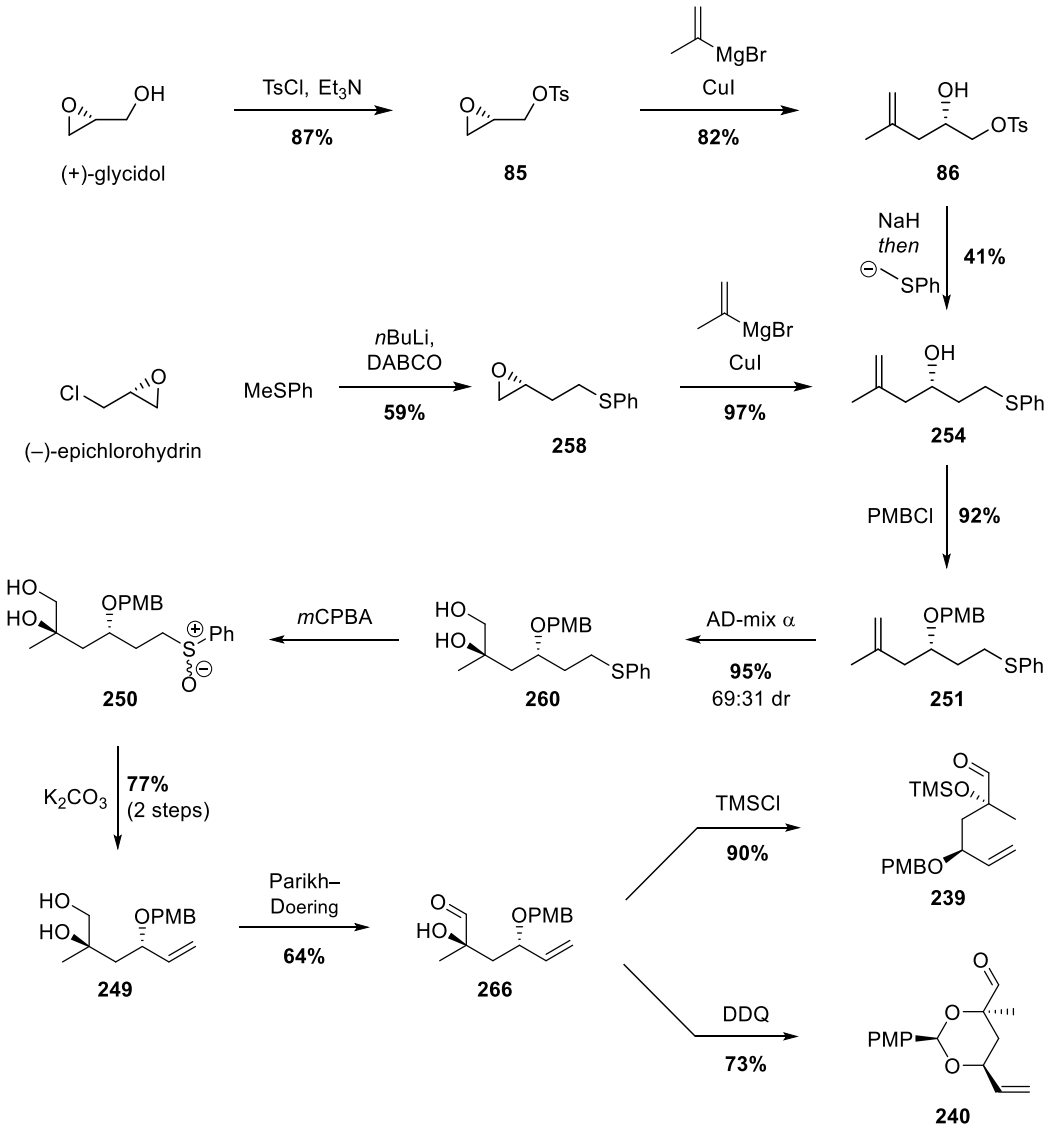
Enabling an alternative protecting group strategy after fragment coupling, cyclic aldehyde **240** was proposed as a substitute for TMS containing left-hand fragment **239**. Treatment of hydroxy aldehyde **266** (95:5 dr) with molecular sieves (4 Å) and DDQ afforded acetal **240** (>95:5 dr) in 73% yield (**Scheme 103A**). The transformation is believed to proceed through cationic intermediate **274**, followed by 6-exo-trig cyclisation. Although tertiary alcohols are sterically hindered nucleophiles, the intramolecularity of the reaction and the charged intermediate promoted the otherwise difficult transformation. When hydroxy aldehyde **266** was subjected to the same conditions as a 74:26 mixture of diastereomers, acetals **240** and *epi*-**240** were isolated in 55% and 14% yield, respectively (**Scheme 103B**). Separation of the two diastereomers by chromatography was straightforward and less labour intensive than separation of hydroxy aldehydes **266** and *epi*-**266**. The relative configuration of all three stereocentres in both isolated products was confirmed by nOe analysis of the isolated compounds (Chapter 4.4.3, **Figure 13**).



Scheme 103 Synthesis of fragment **240**. Reagents and conditions: 4Å-MS, CH_2Cl_2, 30 min *then* DDQ (1 eq), 0 °C, 5 h.

4.6 Overview

In summary, left-hand fragments **239** and **240** have been synthesised from (+)-glycidol or (–)-epichlorohydrin in 9 and 8 steps, respectively (**Scheme 104**). Following the more efficient route from (–)-epichlorohydrin, siloxy aldehyde **239** and acetal **240** were synthesised in 22% and 18% overall yield respectively; these overall yields were calculated using the highest yields achieved on preparative scales. Gram quantities of **239** as well as **240** have been synthesised following this route.



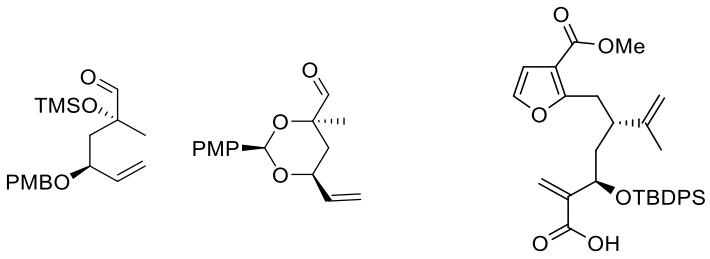
Scheme 104 Overview of the synthetic route to left-hand fragments **239** and **240**.

Chapter 5

Fragment coupling and synthesis of the carbon skeleton

5 Fragment coupling and synthesis of the carbon skeleton

For completeness, this chapter first describes the work of Daniya Aynetdinova, a former Part II student in the Donohoe group, which concerns the addition reaction of lithiated furans with α-siloxy aldehydes. This method was then applied to couple left-hand aldehyde fragments **239** and **240** with right-hand furan fragment **137** (**Figure 7**), the syntheses of which were previously described in Chapters 2 and 4, respectively.

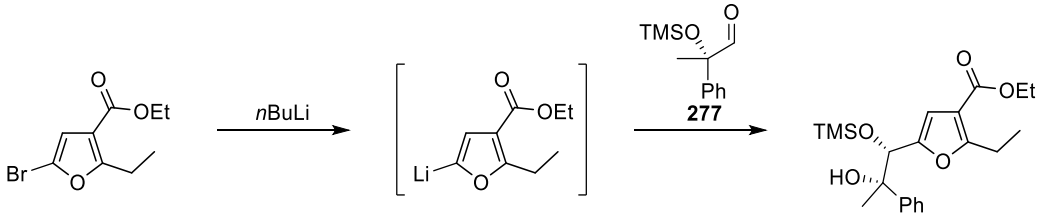


239 **240** **137**

Figure 14 Left-hand fragments **239** and **240** and right-hand fragment **137**

5.1 Model studies for aldehyde coupling

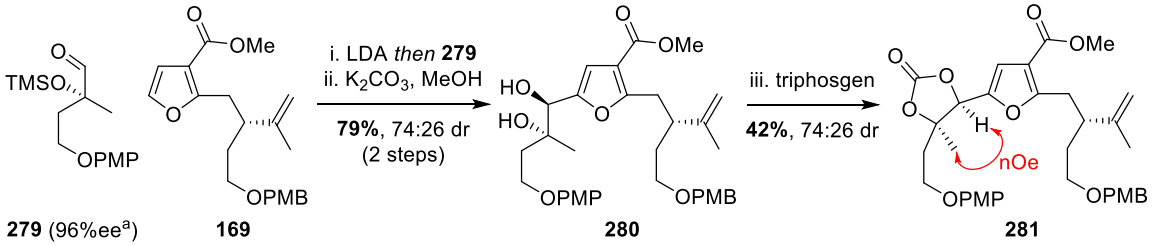
For her project, Daniya Aynetdinova investigated addition reactions of lithiated furans with aldehydes as an alternative method for fragment coupling in the synthesis of (+)-lophotoxin. Early in the project, she discovered that α-siloxy aldehydes were suitable coupling partners.[113] Treatment of bromofuran **231** with *n*BuLi produced lithiated furan **276** *via* rapid metal–halogen exchange (**Scheme 105**). Subsequent addition of α-siloxy aldehyde **277** resulted in an addition reaction followed by a silyl migration to afford product **278** in 65% yield and high diastereoselectivity (93:7 dr).



231 **276** **278**, **65%** (93:7 dr)

Scheme 105 Synthesis of tri-substituted furan **278** by Daniya Aynetdinova.
Reagents and conditions: *n*BuLi (1 eq), THF, –78 °C, 40 min *then* **277** (1.5 eq), 1 h.

Daniya Aynetdinova also synthesised model aldehyde **279**[113] and coupled it with lithiated PMB furan **169** (**Scheme 106**). Subsequent cleavage of the TMS ether in alkaline MeOH afforded diol **280** in 79% yield over two steps as a mixture of two inseparable diastereomers (74:26 dr). The relative configuration of the adjacent stereocentres was confirmed by nOe analysis of carbonate **281**, which was derivatised from diol **280**. Surprisingly, diastereomeric mixtures of compounds like diol **280** could often not be observed by either ^{1}H or ^{13}C NMR because all signals of both diastereomers were overlapping.



279 (96%ee[a]) **169** **280** **281**

Scheme 106 Synthesis of carbonate **281** by Daniya Aynetdinova. Reagents and conditions: i) LDA (1.5 eq), THF, –78 °C, 1 h *then* **279** (1.8 eq), 45 min *then* 0 °C, 15 min; ii) K_2CO_3 (1 eq), MeOH, rt, 2 h; iii) triphosgene (1 eq), pyridine (5 eq), CH_2Cl_2, 0 °C, 15 min. a) measured by chiral HPLC; absolute configuration confirmed by optical rotation of a known compound.

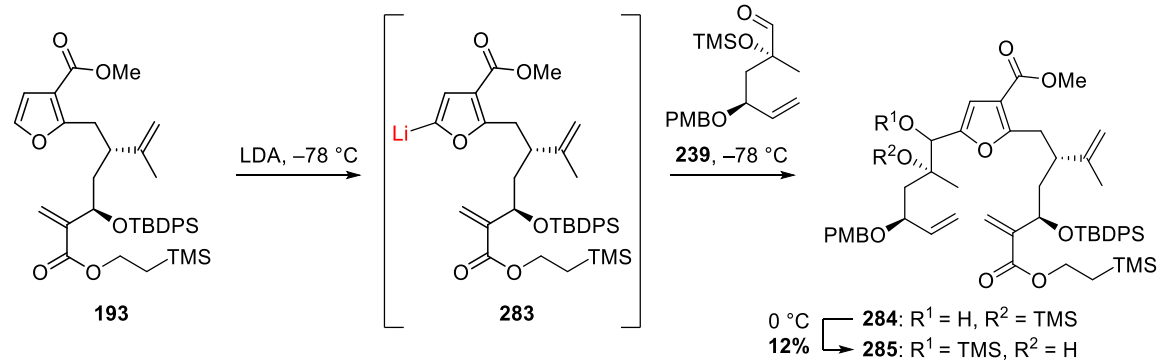
The difference in diastereoselectivity of the two coupling reactions shown above can be rationalised by the different substitution pattern of aldehydes **277** and **279**. Both bear a TMS ether and a methyl group in α-position to the reactive aldehyde. The third substituent, however, is a bulky phenyl group for **278** and an alkyl chain for **279**.

5.2 Coupling of α-siloxy aldehyde 239

Inspired by these results, I initially attempted the coupling reaction of α-siloxy aldehyde **239** with TMSE ester **193** (**Scheme 107**) – rather than with carboxylic acid **137** – to allow for easier product isolation and purification for subsequent steps (**Scheme 107**).

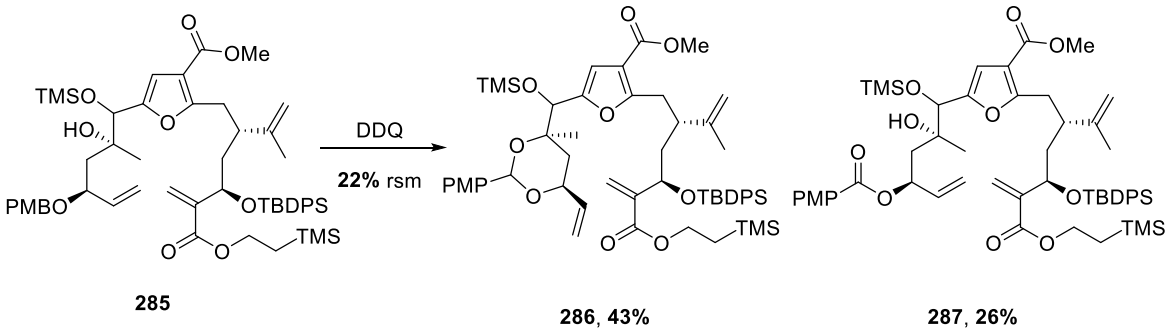
5.2.1 Synthesis of TMSE ester 291

TMSE ester **193** was subjected to LDA at –78 °C for 1 h. The formed organolithium species 2**83** was quenched by addition of aldehyde **239** at the same temperature. Thereafter, the mixture was warmed to 0 °C for 30 min to ensure complete TMS migration from tertiary silyl ether **284** to secondary silyl ether **285**. This migration only partially occurred when the reaction was quenched at –78 °C. Following this procedure, a myriad of unidentified compounds was observed by NMR analysis of the crude mixture and coupling product **285** was isolated in 12% yield. It was postulated that lithiated furan **283** was inherently unstable even at –78 °C, but neither a reduction of reaction time for the lithiation step to 15 min nor a temperature protocol to warm the reaction mixture more quickly to 0 °C after addition of aldehyde **239** improved the isolated yield. In an alternative approach, a mixture of furan **193** and aldehyde **239** was treated with LDA to reduce the window of opportunity for decomposition pathways of lithiated furan **283** to a minimum. However, the desired product **285** was not observed in this experiment. Moreover, the ^{1}H and ^{13}C NMR spectra of isolated coupled product **285** did not indicate the presence of a second diastereomer. Although it is possible for the reaction to be highly diastereoselective or for the minor diastereomer to be lost during isolation, due to previous results we suspected that the spectral properties of the two formed diastereomers are too similar to determine their ratio by NMR.[113]



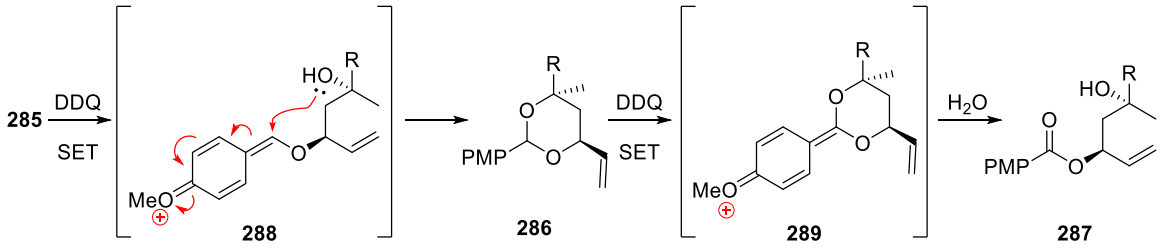
Scheme 107 Synthesis of TMSE coupling product **285**. Reagents and conditions:
LDA (1.5 eq), THF (0.05 M), –78 °C, 1 h *then* **239** (1.5 eq), –78 °C, 1.5 h *then* 0 °C, 30 min.

With coupled product **285** in hand, PMB deprotection was attempted. To this end, **285** was subjected to oxidative conditions (DDQ) in a biphasic mixture of CH_2Cl_2 and an aqueous buffer solution of NaH_2PO_4/Na_2HPO_4 (1 M, pH = 7). However, the expected allylic alcohol was not observed; instead, PMP acetal **286** and PMP ester **287** were isolated in 43% and 26% yield respectively, and 22% of ether **285** was recovered.



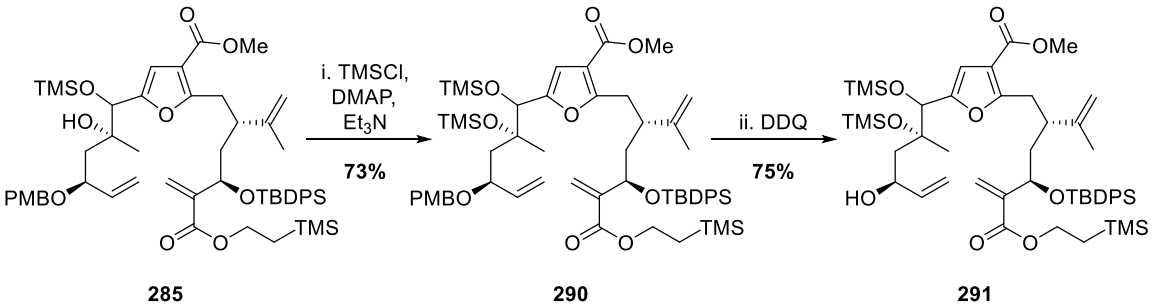
Scheme 108 PMB deprotection attempt of TMSE ester **285**. Reagents and conditions:
DDQ (10 eq), CH_2Cl_2:buffer (6:1, aq., pH = 7), 0 °C, 3 h.

The emergence of undesired side-products **286** and **287** can be rationalised by unanticipated reactivity of oxonium ion **288**, formed *via* single-electron transfer (SET) with DDQ from ether **285** (**Scheme 109**).[114] Intermolecular trapping of the tertiary alcohol outcompeted hydrolysis to *p*-anisaldehyde and the desired allylic alcohol. Formed acetal **286** was then partially oxidised to oxonium ion **289** which finally underwent hydrolysis to give ester **287**.



Scheme 109 Mechanistic considerations to the formation of acetal **286** and ester **287**.

It seemed unlikely that the intramolecular reaction of tertiary alcohol **285** could be outcompeted by adjusting reagents and reaction conditions. Therefore, reprotection of tertiary alcohol was attempted (**Scheme 110**). Treatment of alcohol **285** with TMSCl and DMAP under basic conditions in DMF afforded bis-silyl ether **290** in 73% yield. As high concentrations were crucial for this reaction and limited starting material was available, a very thin Schlenk tube (Ø = 4 mm) was utilised for this transformation to minimise reaction solvent volume. Subsequent treatment of bis-silyl ether **290** with DDQ afforded desired allylic alcohol **291** in 75% without cyclisation.

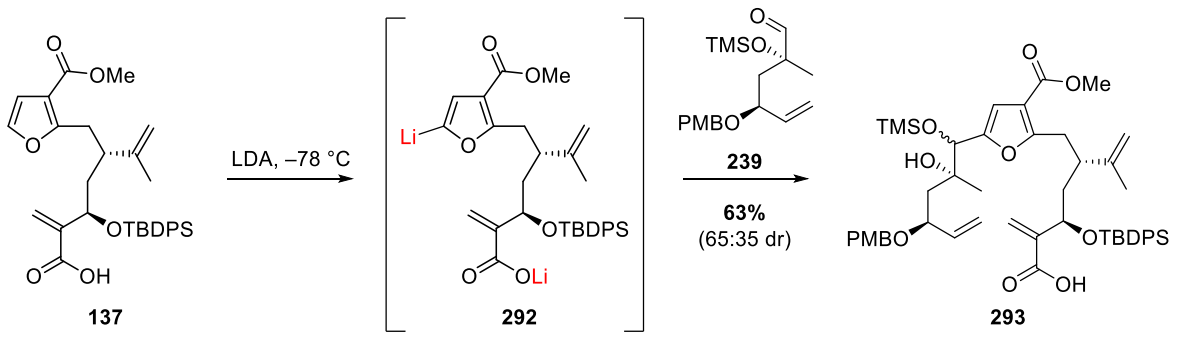


Scheme 110 Synthesis of allylic alcohol **291**. Reagents and conditions:
i) TMSCl (5 eq), DMAP (1 eq), Et_3N (7 eq), DMF (0.1 M), 16 h; ii) DDQ (10 eq), CH_2Cl_2:buffer (6:1, aq., pH = 7), 0 °C, 1 h.

Although selective deprotection of TMSE ester **291** to the corresponding hydroxy acid required for macrolactonisation was possible, this route was not pursued due to the low isolated yield of the initial coupling reaction (*vide supra*). In summary, TMSE ester **291** was synthesised in three steps from fragments **239** and **193** in 7% yield and it was established that the tertiary alcohol (*C*-8) needs to be protected to achieve deprotection of the allylic PMB ether (*C*-10).

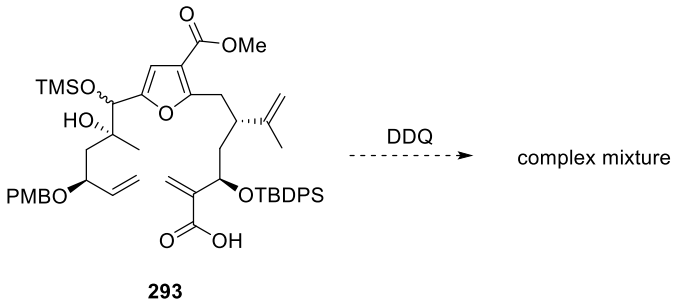
5.2.2 Synthesis of macrocycle 296

Inspired by the findings gained from coupling TMSE ester **193** with α-siloxy aldehyde **239**, we focused our efforts on coupling carboxylic acid **137** with α-siloxy aldehyde **239**. Regioselective furan lithiation of carboxylic acid **137** using LDA had already been established to be a reliable transformation (Chapter 3). The negative charge of the formed lithium carboxylate **292** diminishes the electrophilic enone reactivity and prevents decomposition (**Scheme 111**). Treatment of dianion **292** with α-siloxy aldehyde **239** results in an addition reaction followed by silyl migration to give carboxylic acid **293** in 63% yield as an inseparable mixture of diastereomers. After multiple NMR solvents were screened, the ratio of diastereomers was determined to be 65:35 by ^{1}H NMR in acetone-d6. Furthermore, the ^{1}H and ^{13}C NMR chemical shifts of carboxylic acids such as **293** were inconsistent across different batches of the same compound. These discrepancies were rationalised by agglomeration of the carboxylic acids, variable pH levels, and different compound concentrations. Consequently, each synthesised batch was additionally analysed by LRMS and TLC co-elution. Additionally, purification and isolation of **293** were hampered by the compound's tendency to decompose under Brønsted acidic conditions, such as when AcOH was present as a chromatography eluent. This decomposition was encountered with all compounds in this project featuring an TMS ether or a free alcohol in the benzylic position with respect to the furan moiety (*C*-7).



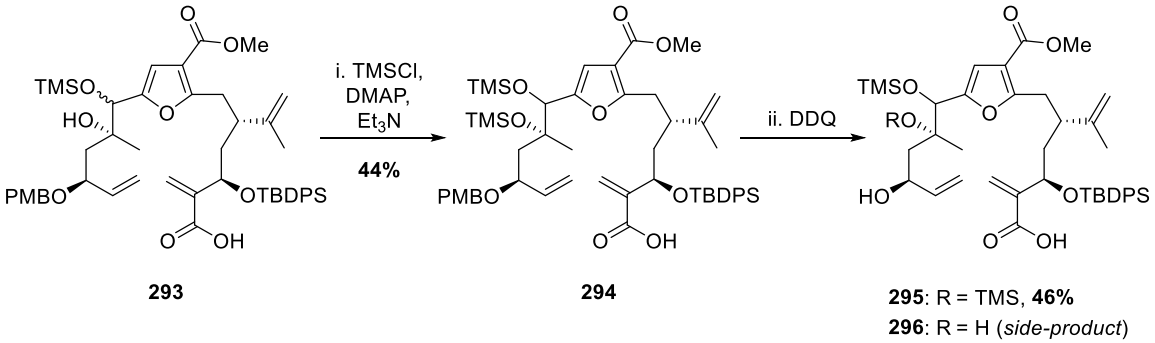
Scheme 111 Synthesis of coupling product **293**. Reagents and conditions:
LDA (2.5 eq), THF (0.05 M), –78 °C, 1 h *then* **239** (1.2 eq), –78 °C, 1.5 h *then* 0 °C, 30 min.

Multiple attempts to deprotect PMB ether **293** with DDQ gave complex mixtures (**Scheme 112**), which is consistent with the formation of acetal **286** and ester **287** when TMSE ester **285** was treated with DDQ, as described previously (**Scheme 108**).



Scheme 112 Attempts to deprotect PMB ether **293** were unsuccessful.

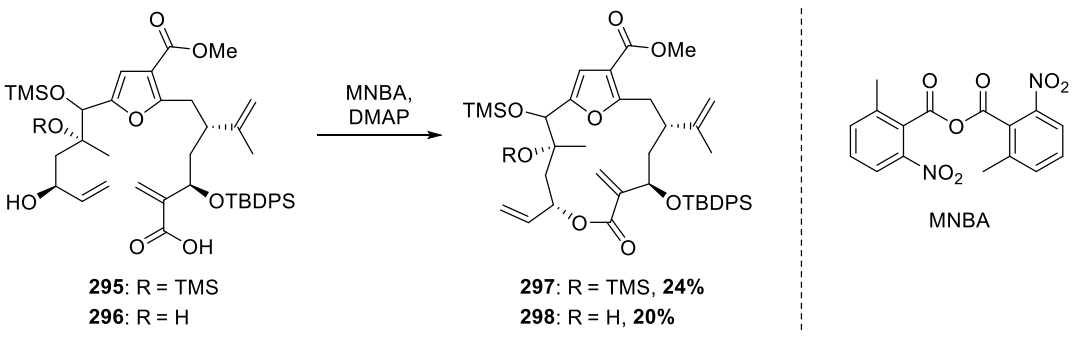
Thus, hydroxy acid **293** was converted into *bis*-silyl ether **294** in 44% yield (**Scheme 113**). Subsequent PMB deprotection with DDQ at 0 °C afforded hydroxy acid **295** in 46% yield. When the reaction mixture was warmed to room temperature immediately after the quench with aqueous $Na_2S_2O_3$ (instead of being stirred at 0 °C for 15 min), diol **296** was produced. The moderate yields for these two protecting group manipulations were reproduced when the sequence was repeated and are detrimental at this stage of a synthesis. As the same two transformations proceeded in sufficiently high yields (73% and 75%) in the TMSE ester sequence (**Scheme 110**), this discrepancy must be caused by an inherent difference in reactivity and chemical properties of the carboxylic acid moiety.



Scheme 113 Synthesis of allylic alcohol **295**. Reagents and conditions: i) TMSCl (12 eq), DMAP (1 eq), Et_3N (16 eq), DMF (0.10 M), 16 h; ii) DDQ (11 eq), CH_2Cl_2:buffer (6:1, aq., pH = 7), 0 °C, 1 h.

With hydroxy acids **295** and **296** in hand, macrolactonisation was attempted. Most macrolactonisation protocols rely on high dilution and slow addition of the starting

material *via* syringe pump. Such precautions keep the effective concentration of hydroxy acid in the reaction vessel low and suppress dimerisation. The protocol developed by Shiina and co-workers[115] utilising 2-methyl-6-nitrobenzoic anhydride (MNBA) had previously been adapted by Donohoe and co-workers[55] for a very similar transformation and was therefore investigated first (**Scheme 114**). To ensure even addition of the starting material solution in CH_2Cl_2 over a long duration (16 h), a glass syringe and slight over pressurisation of the reaction apparatus were required. Polypropylene syringes are not inert to chlorinated solvents over long timescales and leakage occurred when they were used. When slow addition (flow rate < 1.0 mL/h) was attempted with a glass syringe and the usual gauge pressure of a manifold, no addition occurred. This lack of addition was caused by solvent evaporation, due to the low boiling point of CH_2Cl_2 and the imperfect seal of the glass plunger. However, smooth addition was at last achieved when excess pressure was reduced to a minimum, allowing hydroxy acids **295** and **296** to be converted to macrolactones **297** and **298** in 24% and 20% yields, respectively. Oligomerisation was demonstrated to not have occurred by LRMS and HRMS analysis. Macrolactone **297** was carefully analysed at 700 MHz (^{1}H NMR) and 175 MHz (^{13}C NMR). Nevertheless, only one set of signals was detected. The same is true for all intermediates except coupling product **293** in this synthetic sequence. Therefore, no conclusion can be drawn for the diastereomeric ratios at *C*-7 for these intermediates.

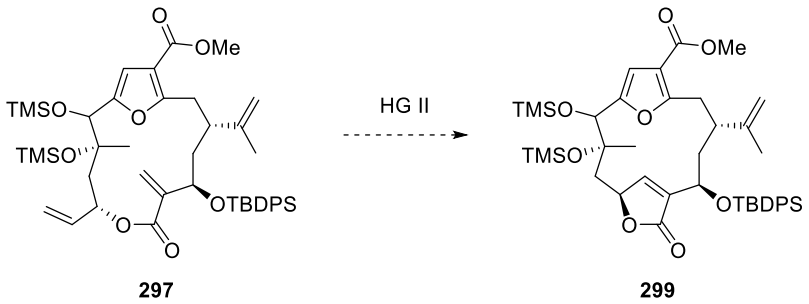


295: R = TMS
296: R = H

297: R = TMS, **24%**
298: R = H, **20%**

Scheme 114 Synthesis of macrolactones **297** and **298**. Reagents and conditions:
i) MNBA (1.2 eq), DMAP (2.4 eq), CH_2Cl_2 (1 mM) starting material added *via* syringe pump over 16 h.

Because a limited amount of macrolactone **297** had been synthesised, butenolide synthesis was attempted at a scale of 5.0 mg (**Scheme 115**). Enone **297** was treated with olefin metathesis catalyst HG II in PhMe at 80 °C for 16 h. A trace amount of butenolide **299** was observed by HRMS and ^{1}H NMR; however, it was not possible to isolate pure **299**.



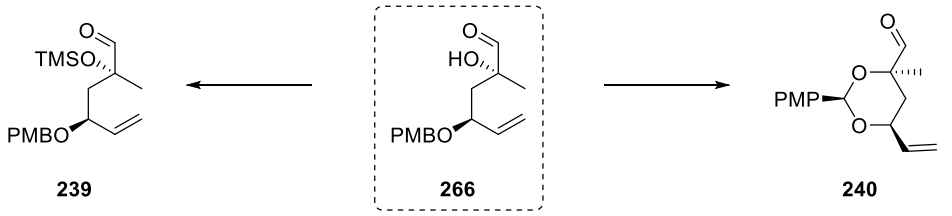
297 **299**

Scheme 115 RCM reaction of *bis*-silyl ether **299**. Reagents and conditions: HG II (20 mol%), PhMe (10 mM), 80 °C, 16 h.

In summary, macrolactone **297** was synthesised from fragments **137** and **293** in four steps with a low overall yield of 3.1%. In addition, the results of the attempted butenolide synthesis by RCM were inconclusive. Furthermore, the relative configuration at *C*-7 remained unknown.

5.3 Coupling of PMP aldehyde 240

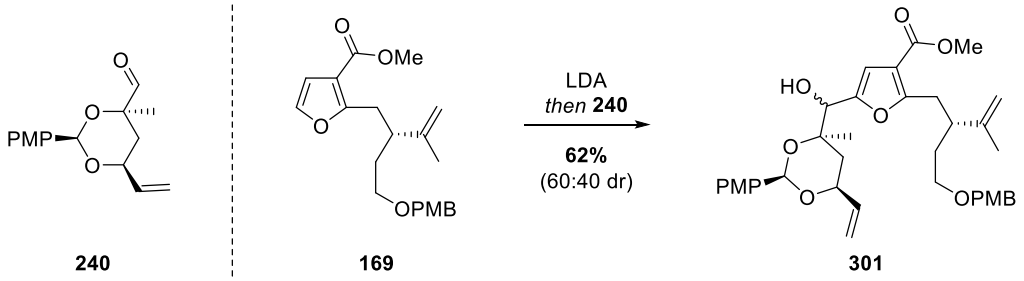
Given the low overall yield of the four-step route to prepare **297**, we re-evaluated our protecting group strategy. A way to replace the migrating and acid-sensitive TMS ether (*C*-7) as well as the recalcitrant PMB group (*C*-10) without fundamentally redesigning the synthesis of the left-hand fragment was sought. To this end, PMP acetal **240** was synthesised from hydroxy aldehyde **266** (**Scheme 116**), the direct precursor of α-siloxy aldehyde **239** (Chapter 4).



Scheme 116 α-Siloxy aldehyde **239** and acetal **240** were both synthesised from hydroxy aldehyde **266** in one step.

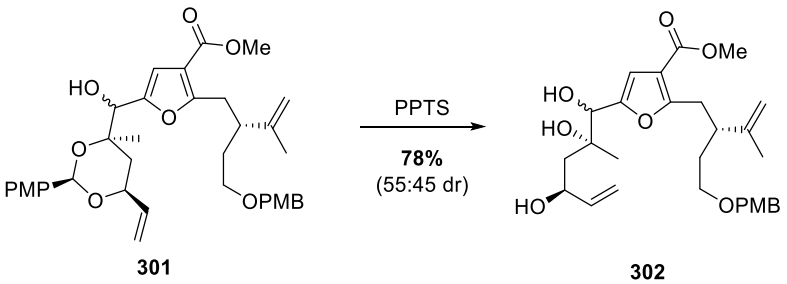
5.3.1 Synthesis of PMB containing triol 302 and hydroxy ketone 305

To aid with purification and analysis, the coupling of PMP acetal **240** and PMB furan **169** (instead of carboxylic acid **137**) was investigated initially (**Scheme 117**). Lithiation of **169** with LDA and subsequent addition reaction with aldehyde **240** afforded alcohol **301** in 62% yield as an inseparable mixture of diastereomers (60:40 dr).



Scheme 117 Synthesis of coupling product **301**. Reagents and conditions: LDA (1.5 eq), THF (0.05 M), –78 °C, 1 h *then* **240** (1.3 eq), –78 °C, 1.5 h.

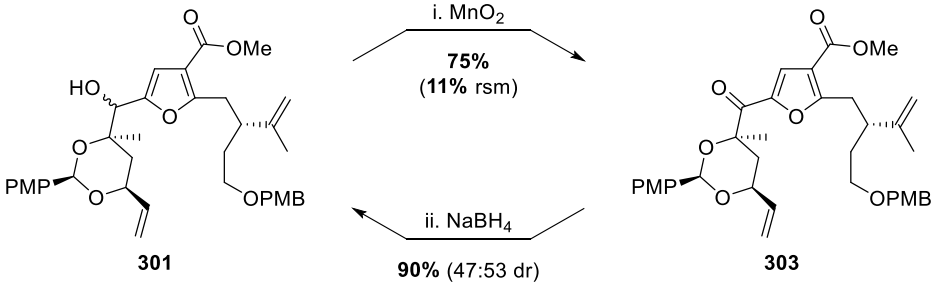
With alcohol **301** in hand, acetal deprotection was explored (**Scheme 118**). Treatment with substoichiometric quantities of PPTS in MeOH afforded triol **302** as an inseparable mixture of diastereomers (55:45 dr) in 78% yield, which suggested that the α-hydroxy furan motif was reasonably tolerant of acidic conditions.



Scheme 118 Synthesis of triol **302**. Reagents and conditions: PPTS (0.3 eq), MeOH (10 mM), 44 h.

In an alternative approach, the oxidation of the undefined stereocentre *C*-7 in alcohol **301** was attempted (**Scheme 119**). The reaction time for the MnO_2-mediated oxidation was

inadvertently extended by a nationwide lockdown due to the Covid19 pandemic to three months. Despite the long reaction time, ketone **303** was isolated in 75% yield as well as 11% recovered starting material **301**. The reverse transformation was examined as well. Treatment of ketone **303** with $NaBH_4$ afforded alcohol **301** in 90% yield. Although the diastereoselectivity of the reduction was poor (47:53 dr), it was inverted compared to the aldehyde addition reaction (**Scheme 117**).



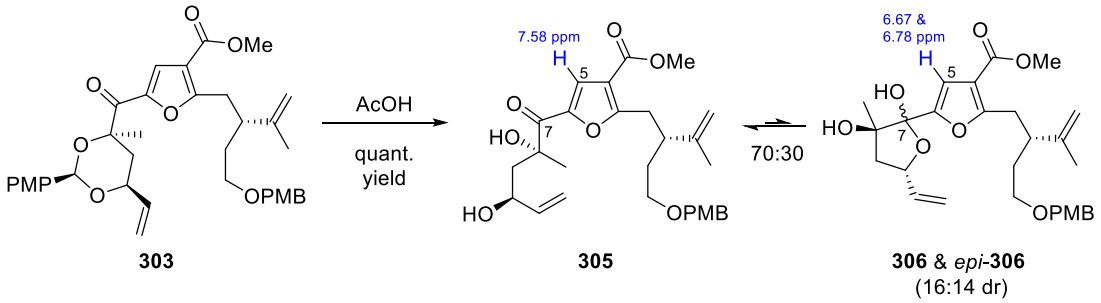
Scheme 119 Oxidation and reduction at *C*-7. Reagents and conditions:
i) MnO_2 (10 eq), CH_2Cl_2 (0.16 M), 3 months; ii) $NaBH_4$ (3.0 eq), MeOH (10 mM), 20 h.

When acetal deprotection was attempted on ketone **303** in acidic MeOH, only undesired cyclic acetal **304** was formed (**Scheme 120**). Careful analysis of the crude reaction mixture suggested the formation of two diastereomers (77:23 dr) and the major diastereomer was isolated in 70% yield. However, **304** isomerised and partially hydrolysed to the corresponding hydroxy ketone **305** and hemiacetals **306** and *epi*-**306** in $CDCl_3$ within hours (**Scheme 121**).

Scheme 120 Synthesis of acetal **304**. Reagents and conditions: PPTS (0.25 eq), MeOH (10 mM), 20 h.

To prevent the formation of cyclic acetals such as **304**, nucleophilic alcohols were henceforth avoided as solvents. Treatment of **303** with AcOH in aqueous THF gave smooth deprotection and a mixture of linear hydroxy ketone **305** and the two

corresponding anomeric hemiacetals **306** and *epi*-**306** was isolated in quantitative yield (**Scheme 121**). Ketone **305** and hemiacetals **306** and *epi*-**306** were assigned by their *C*-7 ^{13}C chemical shifts (191.9 ppm for **305**; 104.3 and 103.1 ppm for **306** and *epi*-**306**) and their *H*-5 ^{1}H chemical shifts (7.58 ppm for **305**; 6.67 and 6.78 ppm for **306** and *epi*-**306**). HMBC enhancements between *C*-7 and *H*-5 were found for all three compounds. Moreover, NOESY analysis suggested interconversion of all three species on an NMR timescale. Because these three species were rapidly interconverting and because hydroxy ketone **305** was the dominant species (**305**:**306**:*epi*-**306** = 70:16:14), this motif became attractive for macrolactonisation, as a free allylic alcohol (*C*-10) is required for this transformation.

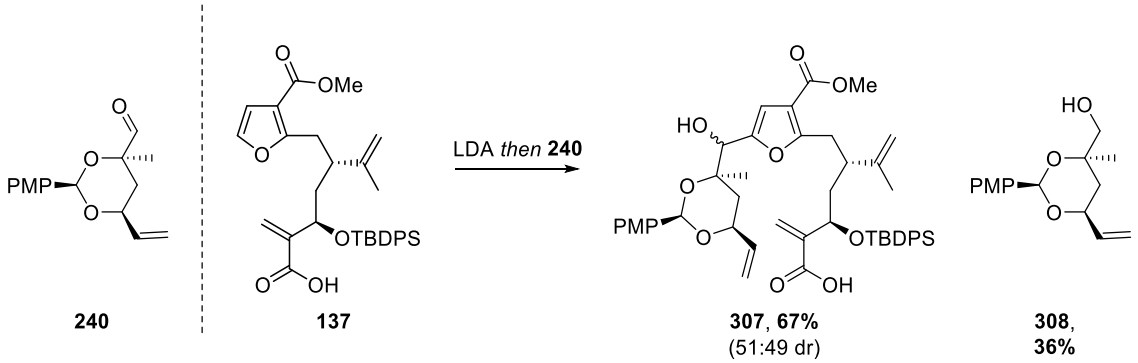


Scheme 121 Synthesis of hydroxy ketone **305**. Reagents and conditions: H_2O:THF:AcOH (45:45:10, 10 mM), 4 days. In $CDCl_3$ a mixture **305**:**306**:*epi*-**306** = 70:16:14 was observed.

5.3.2 Synthesis of triol 313

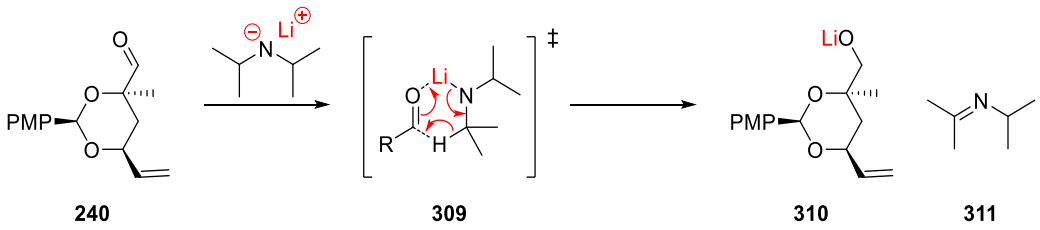
Encouraged by the results of the described model studies, we applied the lithiation-coupling sequence to furan **137**, and alcohol **307** was isolated in 67% yield as a mixture of inseparable, but clearly detectable diastereomers (**Scheme 122**). Facial selectivity for the organolithium attacking the carbonyl was negligible (51:49 dr); side-product **308** was also isolated in 36% yield (based on 1.3 eq **240**). The formation of this side product can be explained by the excess LDA acting as a reductant (**Scheme 123**). However, chromatographic separation of coupling product **307** from alcohol **308** was significantly

easier than from unreacted carboxylic acid **137**, which was observed when LDA was not used in excess.



Scheme 122 Synthesis of coupling product **307**. Reagents and conditions:
LDA (2.5 eq), THF (0.05 M), –78 °C, 1 h *then* **240** (1.3 eq), –78 °C, 1.5 h *then* 0 °C, 30 min.

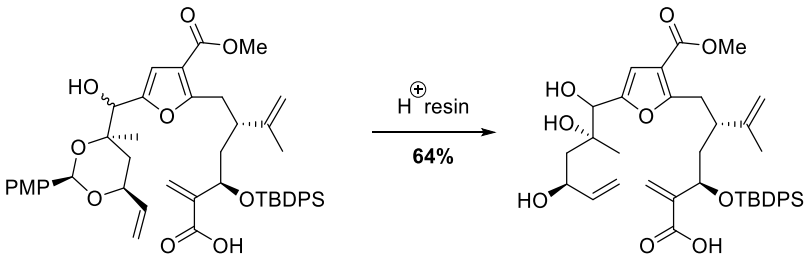
The described reduction of aldehydes and other carbonyls to the corresponding alcohols was investigated by Majewski among others and was even found to be a competing process to enolisation, when enolisable aldehydes were used.[116] The intermolecular hydride transfer proceeds through a chelated six-membered transition state **309**, in which LDA acts as a hydride donor and is oxidised to imine **311** (**Scheme 123**).



Scheme 123 Mechanism for carbonyl reduction with LDA.

In initial attempts to deprotect coupling product **307**, substoichiometric PPTS in MeOH was used, mimicking the optimal conditions for the equivalent deprotection of PMB-containing model substrate **301** (**Scheme 118**). In this case however, the reaction was unsuccessful giving only a complex mixture. Despite this poor outcome, TLC and LRMS analysis indicated the starting material had in fact formed the product; the product was lost due to its decomposition when the acidic reaction mixture was concentrated. Thus, a pre-treated acidic ion exchange resin was used and filtered away from the mixture before sample concentration. Using this method, triol **313** was synthesised in 64% yield (**Scheme**

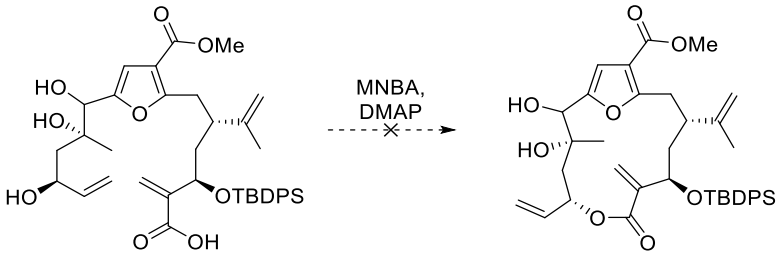
124). As was frequently observed with TMS-containing coupling products (Chapter 5.2), only one set of signals was observed by ^{1}H- and ^{13}C NMR for triol **313.**



307 (51:49 dr) **313**

Scheme 124 Synthesis of triol **313**. Reagents and conditions: Dowex®50WX8 H-form, MeOH (21 mM), 2 h.

Triol **313** was subjected to Shiina macrolactonisation conditions. A signal consistent with the M^{+} peak of **314** was observed by LRMS. However, a myriad of compounds was detected by NMR analysis of the crude reaction mixture and desired macrolactone **314** could not be isolated (**Scheme 125**). Poor regioselectivity and the presence of multiple hydroxyl groups in **313** and its derivatives frustrated purification efforts.

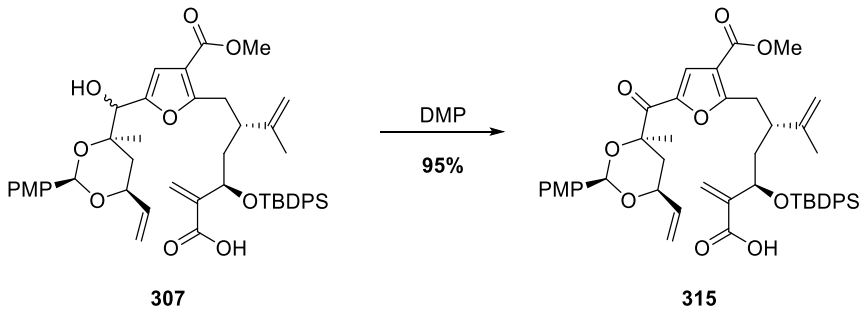


313 **314**

Scheme 125 Attempted synthesis of macrolactone **314**

5.3.3 Synthesis of butenolide 321

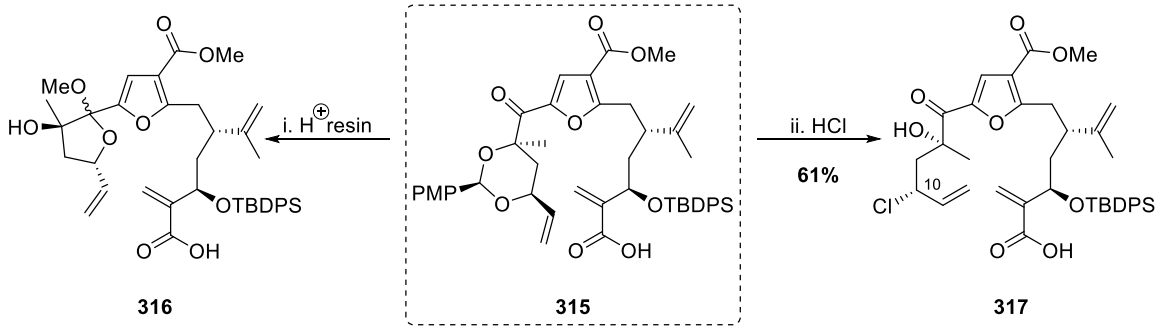
To circumvent the aforementioned isolation issues and to address the uncontrolled stereocentre *C*-7, alcohol **307** was converted to ketone **315** in 95% yield *via* a DMP oxidation reaction (**Scheme 126**).



307 315

Scheme 126 Synthesis of ketone **315**. Reagents and conditions: DMP (3.0 eq), $NaHCO_3$ (10 eq), CH_2Cl_2 (0.1 M), 0 °C, 2.5 h.

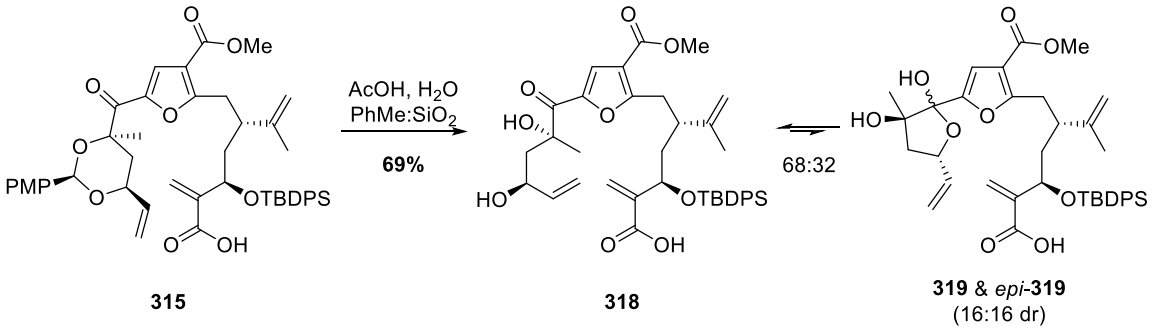
With ketone **315** in hand, conditions established for the deprotection of model substrate **303** (**Scheme 121**) were applied to remove the PMP acetal. However, when **307** was subjected to a mixture of H_2O:THF:AcOH (45:45:10), a complex mixture was formed. When the transformation was attempted using acidic ion exchange resin in MeOH:H_2O (90:10), undesired methoxy acetal **316** was predominantly formed and desired hydroxy ketone **318** was not observed (**Scheme 127**). Attempts to hydrolyse methoxy acetal **316** only gave contaminated hydroxy ketone **318**. When ketone **315** was subjected to HCl (0.4 M in 1,4-dioxane) with a limited amount of H_2O (10 eq), undesired allylic chloride **317** was isolated in 61% yield, presumably due to the high chloride concentration. The regioselectivity of this transformation was confirmed by NMR analysis and indicates an S_N2, rather than S_N1 or S_N2', transition state. Only one diastereomer was observed by NMR. However, that is not conclusive evidence for the absence of a second diastereomer (*vide supra*).



316 315 317

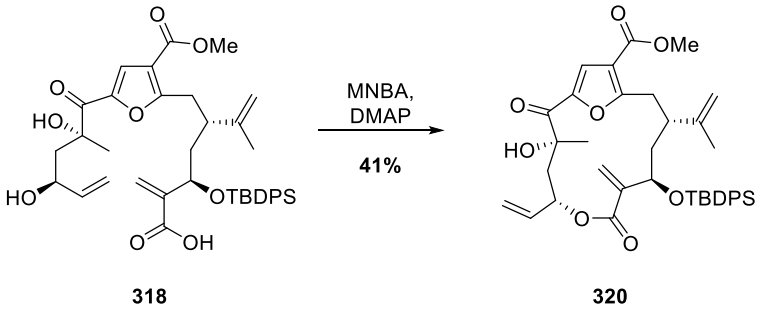
Scheme 127 Deprotection of acetal **315**. Reagents and conditions: i) Dowex50WX8 H-form, MeOH:H_2O (90:10, 10 mM), 24 h; ii) HCl (0.4 M in 1,4-dioxane, 2 mM), H_2O (10 eq).

The first analytically pure batch of hydroxy ketone **318** was isolated unintentionally when PMP acetal **315** was chromatographically purified using formic acid as an acidic additive. Mimicking those conditions, **318** was successfully synthesised from **315** in 69% yield using a mixture of PhMe, silica gel, AcOH and H_2O (**Scheme 128**). In $CDCl_3$, a mixture of hydroxy ketone **318** and both diastereomers of hemiacetal **319** (**318**:**319**:*epi*-**319** = 68:16:16) were detected. The mixture was assigned by analogy to model substrate **305** (**Scheme 121**). In contrast to most other carboxylic acids synthesised in this project, hydroxy ketone **305** was stable to concentration from acidic solutions and thus amenable to chromatographic purification with acidic additives such as formic acid.



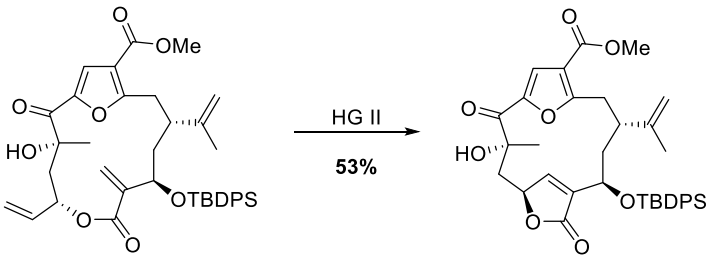
Scheme 128 Synthesis of hydroxy ketone **318**. Reagents and conditions: silica gel, PhMe:AcOH:H_2O (85:10:5), 4 days. In $CDCl_3$ a mixture **318**:**319**:*epi*-**319** = 68:16:16 was observed.

Shiina macrolactonisation of hydroxy acid **318** required an elaborate setup to ensure smooth and continuous addition of starting material over the course of 16 h (see Chapter 5.2.2). Using the described setup, macrolactone **320** was isolated in 41% yield (**Scheme 129**).



Scheme 129 Synthesis of macrolactone **320**. Reagents and conditions: MNBA (1.2 eq), DMAP (2.4 eq), CH_2Cl_2 (1 mM) starting material added *via* syringe pump over 16 h.

With enone **320** in hand, butenolide synthesis was then attempted. Initially, olefin metathesis catalyst HG II in PhMe at 100 °C was used. Although butenolide **321** was isolated from these attempts, it was contaminated with inseparable Ru impurities derived from catalyst decomposition. Switching the solvent to DCE instead of PhMe reduced this decomposition. No conversion was observed by TLC analysis in DCE at 60 °C (**Scheme 130**). Thus, the mixture was heated to 90 °C in a sealed vessel for an additional 2 days, and butenolide **321** was isolated in 53% yield.

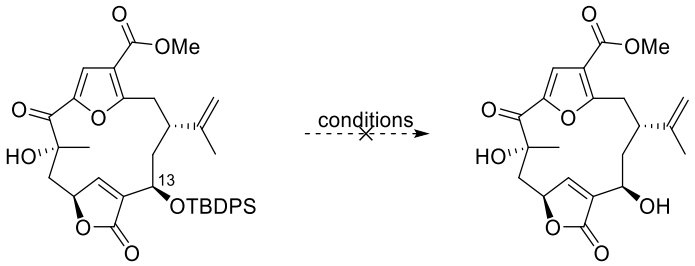


320 **321**

Scheme 130 Synthesis of butenolide **321**. Reagents and conditions:
HG II (18 mol%), DCE (10 mM), 60 °C, 16 h *then* 90 °C, 24 h *then* HG II (17 mol%), 90 °C, 19 h.

5.3.4 TBDPS ether cleavage

With the carbon skeleton of (+)-lophotoxin assembled and a robust synthesis established, we focused our efforts on the cleavage of the *C*-13 TBDPS ether (**Scheme 131**).



321 **322**

Scheme 131 TBDPS cleavage of butenolide **321**. Reagents and conditions: see **Table 4**

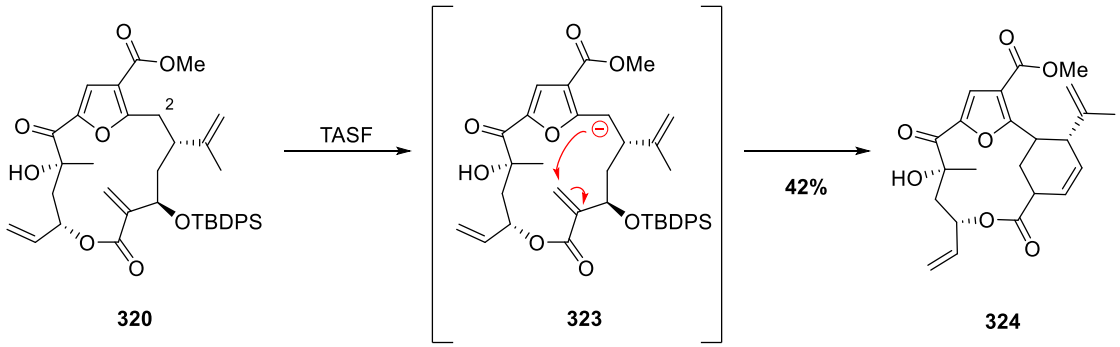
As excess TBAF at ambient temperatures removed both the TBDPS group and the targeted TMSE ester of right-hand fragment **137** (Chapter 2), these conditions were tested first (**Table 4**). TBDPS ether **321** was consumed after 1.5 h, but the reaction ultimately gave a complex mixture and poor mass recovery (entry 1). To buffer potential

hydroxide contaminant in the commercial THF solution of TBAF used, AcOH was used as an additive in a subsequent deprotection attempt (entry 2). This decreased the rate of conversion drastically, but ultimately gave a complex mixture as well. When milder TASF was used as a fluoride source, **321** was consumed within 1.5 h in DMF at 0 °C. LRMS signals at 409.2 (M + 23) and 385.1 (M – 1) suggested that TBDPS cleavage followed by elimination of water might have occurred, but a complex mixture was yet again obtained.

Table 8 TBDPS cleavage conditions of butenolide **321**;
a) the reaction was stopped after full conversion of TBDPS ether **321** by TLC.

entry	conditions	reaction time[a]	conclusion
1	TBAF (5.0 eq), THF, 0 °C to rt	1.5 h	complex mixture
2	TBAF (3.0 eq), AcOH (5.0 eq), THF, rt	18 h	complex mixture
3	TASF (1.2 eq), DMF, 0 °C	1.5 h	complex mixture

For these described deprotection attempts butenolide **321** contaminated with HG II-derived impurities (*vide supra*) were used. To rule out any interference, macrolactone **320** was treated with TASF in DMF instead (**Scheme 132**). To our surprise, cyclohexene **324** was isolated in 42% yield. We postulate that this unexpected transformation proceeds through benzylic anion **323**, which undergoes an intramolecular conjugate addition, followed by E1cB elimination of TBDPS silanol and olefin migration *via* deprotonation and re-protonation to give skipped enone **324**. Deprotonation at this benzylic position (*C*-2) had been observed previously when model substrate **219** was treated with LDA at –78 °C in THF (Chapter 3.2.1, **Scheme 68**). Although TASF is a far weaker base than LDA, deprotonation at *C*-2 in **321** is expected to be easier (relative to *C*-2 in **219**) because the negative charge of the deprotonated species (**323**) would be stabilised by ketone *C*-8 as well as ester *C*-18 through conjugation of the furan's π-system.



Scheme 132 Unexpected formation of cyclohexene **324**. Reagents and conditions: TASF (1.2 eq), DMF (10 mM), 16 h *then* TASF (0.6 eq), 3 h.

The formation of cyclohexene **324** and the detection of a signal corresponding to the M^+ peak of **325** (**Figure 15**) in the mass spectrometer suggest that the analogous transformation proceeded as well. However, the expected product **325** or any isomer from this transformation could not be isolated, presumably because it was highly strained and therefore likely to decompose.

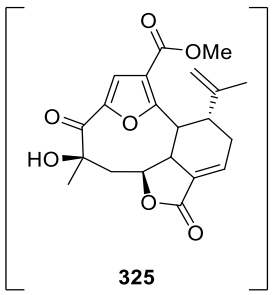
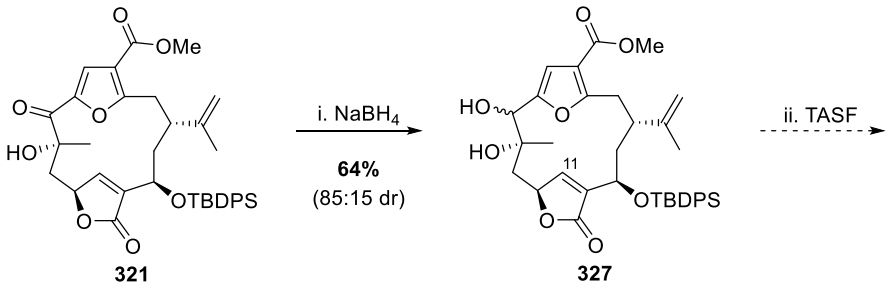


Figure 15 Proposed polycyclic intermediate **325** derived from butenolide **321** is highly strained.

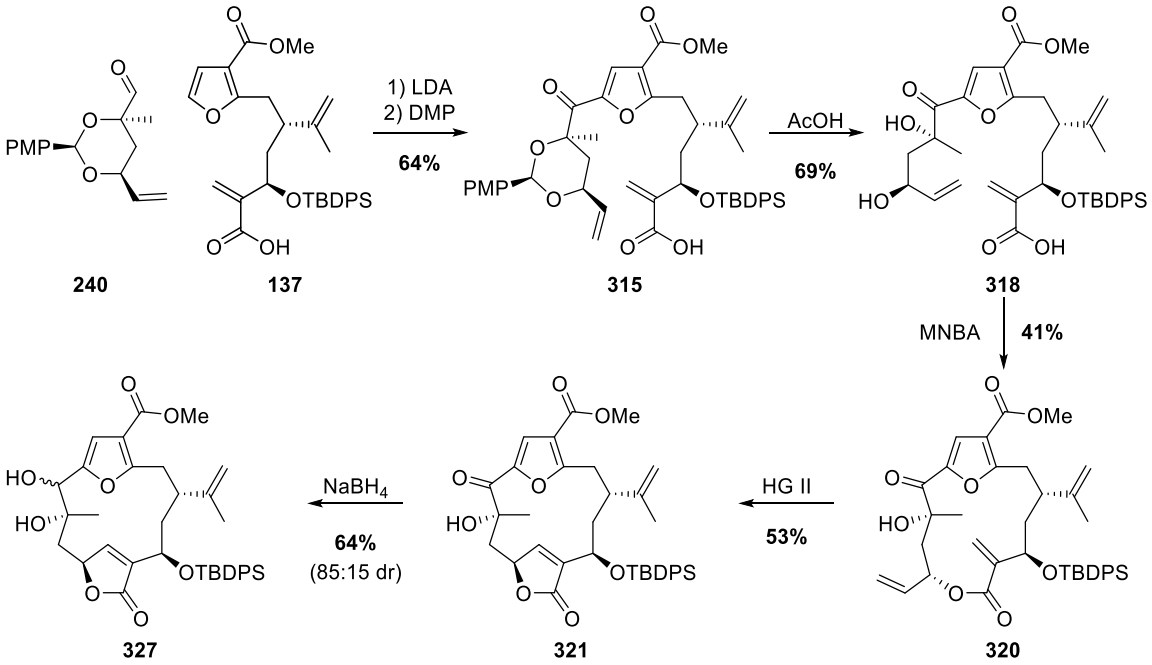
To suppress the undesired benzylic deprotonation, ketone **321** was successfully reduced using $NaBH_4$, and alcohol **327** was isolated in 64% yield as an inseparable mixture of diastereomers (85:15 dr, **Scheme 133**), with the configuration at *C*-7 of the major diastereomer unassigned. Subsequent treatment of alcohol **327** with TASF again suffered from low mass recovery and a complex mixture was formed.



Scheme 133 Synthesis of alcohol **327**. Reagents and conditions:
i) NaBH4 (3.0 eq), MeOH (10 mM), 0 °C, 1.5 h; ii) TASF (1.2 eq), DMF (10 mM), 16 h.

5.3.5 Overview & conclusion

In summary, the carbon skeleton of (+)-lophotoxin was successfully assembled and alcohol **327** was synthesised from fragments **240** and **137** in 6 steps and in 6.1% overall yield (**Scheme 134**). The synthetic route from (+)-carvone (to prepare the right-hand fragment **137**) is the longest linear sequence with 19 steps and an overall yield of 0.86%.



Scheme 134 Overview of the synthetic route to furanocembranoid **327**.

A new coupling strategy was found after the well-precedented Negishi-coupling approach failed. Thus, two very robust and high-yielding routes for fragments **137** and **240** were developed and successfully executed, providing both fragments in decagram scales. Further, the synthesis of (+)-lophotoxin's carbon skeleton was achieved *via* a novel strategic approach.

5.4 Future work

At the time of writing, this project was being continued by Dr. Nicolas Kratena, a postdoctoral research associate in the Donohoe group. The project was handed over to Dr. Kratena with 4 g of both fragments **137** and **240** as well as 140 mg of macrolactone **320** available. With this material Kratena made substantial progress, which is described for completion in this chapter. Butenolide **321** was crystalised and an X-ray crystal structure was obtained (**Figure 16**). Thus, confirming the assignment of all stereocentres described in Chapters 2.7.2 and 4.4.3.

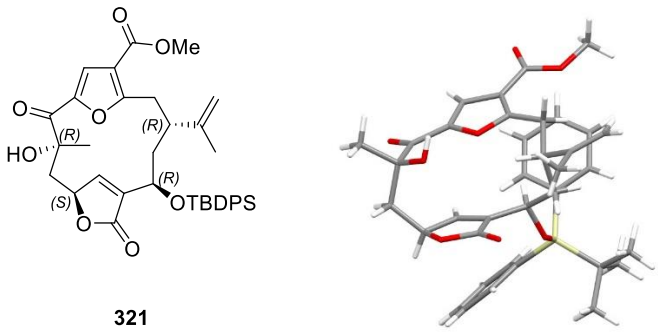
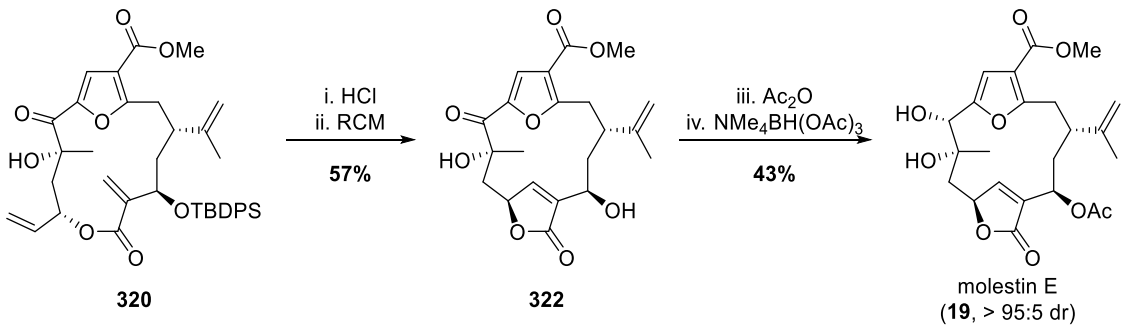


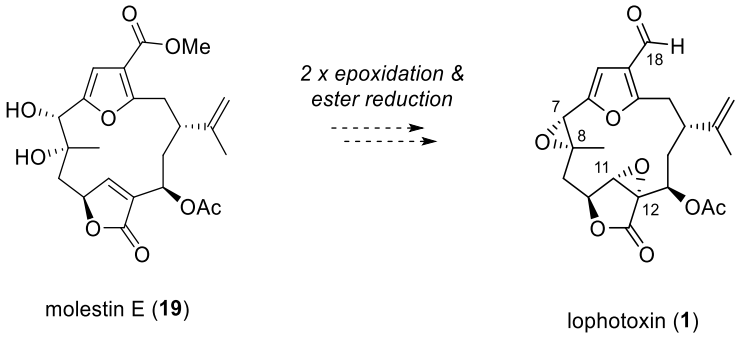
Figure 16 X-ray crystal structure of synthesised butenolide **321** obtained by Kratena.

Furthermore, TBDPS deprotection was achieved under acidic conditions (HCl in MeOH) and prolonged reaction times of 5 days (**Scheme 135**). RCM reaction proceeded smoothly in 2 h and butenolide **322** was isolated in 57% over 2 steps. This is remarkable, as RCM reaction of TBDPS ether **320** required reaction times of multiple days at the same temperature. Acetylation followed by diastereoselective ketone reduction then afforded molestin E (**19**) as a single diastereomer. Spectral data of synthesised **19** matched the data of **19** isolated from nature by Li and co-workers.[24]



Scheme 135 Synthesis of Molestin E (**19**) by Kratena. Reagents and conditions: i) AcCl (60 eq), MeOH *then* **320** in Et_2O, rt, 5 days; ii) HG II (11 mol%), DCE, 85 °C, 2 h; iii) Ac_2O (1.3 eq), pyrididne (5.0 eq), DMAP (0.4 eq), CH_2Cl_2, 0 °C, 30 min *then* rt, 30 min; iv) NMe_4BH_4 (7.0 eq), MeCN:AcOH (1:1) *then* sm, –20 °C, 2 h *then* 0 °C, 1 h.

Formally, only 3 steps are required to synthesise lophotoxin (**1**) from molestin E (**19**): butenolide to epoxide (*C*-11/*C*-12), diol to epoxide (*C*-7/*C*-8), and ester to aldehyde (*C*-18). However, the order of steps to install these fragile functionalities must be carefully investigated and considered. It might be necessary to introduce aldehyde (*C*-18) at an earlier stage of the synthesis to avoid chemoselectivity issues for the reduction step.



Scheme 136 Formal steps from molestin E (**19**) to lophotoxin (**1**)

Chapter 6

Experimental Procedures and Supporting Information

6 Experimental Procedures and Supporting Information

General: Descriptions given in this section only account if not otherwise stated in the individual procedures. Glassware for all non-aqueous reactions were flame dried under vacuum or in a high temperature oven (200 °C) and placed under high vacuum immediately. Anhydrous solvents and reagents were used for such reactions and solvent residues of starting materials were removed by azeotropic distillation with PhMe (× 3) and storage under high vacuum (> 15 min). Reactions were performed in round-bottom flasks, under Ar atmosphere and were followed by analytical thin layer chromatography (TLC). Procedure times represent reaction completion as judged accordingly. Reaction mixtures were heated with oil baths using silicone oil and values given represent bath temperatures. Reaction vessels were cooled in a Dewar using acetone/dry ice (–78 °C), MeCN/dry ice (–40 °C), or water/ice (0 °C). Deionized water was used for extractions and aqueous solutions. Calculated yields, concentrations and equivalents are given in maximum two digits. Concentrations given with the main solvent refer to the concentration of the limiting starting material in the overall amount of solvent used at the start of the experiment.

Anhydrous solvents: CH_2Cl_2, PhMe and Et_2O were purified by filtration through two activated alumina purification columns. Anhydrous DCE, DMF, DMSO, Et_3N, HMPA, Hünig's base, MeOH and pyridine were used as commercially supplied. Solutions of *n*BuLi, DIBAL-H, LDA, $AlMe_3$ and isopropenly magnesiumbromide were used as supplied. THF was filtered through two activated alumina purification columns and dried over activated (150 °C, 16 h) molecular sieves (4 Å) for 48 h prior to use. Solvents were degassed by purging with Ar gas using a needle for a minimum of 10 min.

Reagents: All reagents were used as supplied commercially.

Chromatography: Solvents for chromatography were used as commercially supplied. In cases where mixtures of solvents were used, the ratios refer to the component volumes. In cases where gradients where used, the start and the end ratio are stated. Flash column chromatography was carried out using silica gel 40-63 µm from Aldrich, Merck, or Alfa. Analytical thin layer chromatography (TLC) was performed using aluminium backed pre-coated silica gel 60 F254 plates from Merck and visualised under UV radiation at 254 nm and staining with $KMnO_4$ (3 g), K_2CO_3 (20.0 g), NaOH (5 wt%, aq., 5.0 mL) in H_2O (300 mL); vanillin (15.0 g), H_2SO_4 (conc., 2.5 mL) in EtOH (250 mL) or phosphomolybdic acid (7.00 g) in EtOH (100 mL).

Optical Rotation: Specific rotations (α') were recorded on a Perkin Elmer 341 Polarimeter, with a cell pathlength (l) of 1.0 dm, at the stated temperature (°C) and concentration (c) (measured in units of g/100 mL); specific rotations were converted to optical rotations, $[\alpha]_D^{25}$, *via* the equation: $[\alpha]_D^T = \frac{100\,\alpha'}{l\,c}$. D refers to the Na-D-line (λ = 589 nm). For diastereomeric mixtures (dr < 95:5) a specific rotation was not recorded.

Mass Spectrometry: Low resolution mass spectra were recorded on an Agilent 6120 Quadrupole spectrometer equipped with an Agilent 1260 Infinity LC pump, with a flow rate of 0.2 mL/min using H_2O:MeOH:HCO_2H (10:89.9:0.1) as eluent. The mass reported is that containing the most abundant isotopes under electrospray ionisation (ESI). High resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory mass-spec facilities. For the ESI accurate mass service, analyses were performed using a Thermo Exactive mass spectrometer equipped with Waters Acquity liquid chromatography system using the same flow rate and eluent as above. Instrument control and data processing were performed using Thermo Xcalibur Software. The mass spec was operated using the heated electrospray (HESI-II) probe and resolution was set to

50,000 FWHM. Electrospray source conditions were adjusted to maximise sensitivity. For the electron ionisation (EI) and Chemical ionisation (CI) accurate mass service, analyses were performed on an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. Source conditions for both EI and CI were adjusted to maximise sensitivity, the reagent gas used in CI was ammonia. Both systems were calibrated on the day of the analysis and its mass accuracy with external calibration (as used for these experiments) is better than 5 ppm for 24 h following calibration. The mass reported is that containing the most abundant isotopes, with each value to 5 decimal places and within 5 ppm of the calculated mass. Mass to charge ratios (m/z) are reported in Daltons.

NMR Spectroscopy: Proton (^{1}H), fluorine (^{19}F) and carbon (^{13}C) spectra were recorded on Bruker AV700 (AVIII 700 with inverse cryoprobe), Bruker AVC500 (AVII 500 with cryoprobe), Bruker AVB500 (AVIII HD 500), Bruker AVX500 (AVIII HD 500), Bruker AVF400 (AVIII HD 400 nanobay), AVG400 (AVIII HD 400) or Bruker AVH400 (AVIII HD 400) spectrometers in deuterated solvents. ^{13}C spectra were recorded with broadband decoupling. Chemical shifts (δH, δF and δC) are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR or 0.1 ppm for ^{19}F and ^{13}C NMR. ^{1}H and ^{13}C NMR spectra were referenced to the solvent residual peak ($CDCl_3$, δ 7.26 and 77.00 ppm respectively).[117] Peak assignments were made based on chemical shifts, integrations and coupling constants, using COSY, HSQC, HMBC and NOESY experiments where appropriate. Multiplets are described as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), double triplet (dt), doublet of doublet of doublets (ddd), etc., multiplet (m), broad (br.) and apparent (app.). Coupling constants (*J*) are rounded to the nearest 0.1 Hz. For diastereomeric mixtures (dr > 85:15) only the major isomer is reported. For

diastereomeric mixtures (dr < 85:15) both isomers are reported separately. When ^{1}H and ^{13}C NMR data for the major diastereoisomer is reported, any signals that overlap with the minor isomer have been integrated without the contribution from the minor isomer being included. In such a case, signals of the minor isomer are not reported. For equimolar mixtures of diastereomers (dr < 55:45) and mixtures of more than two isomers the signals were not explicitly assigned to the corresponding isomer.

IR Spectroscopy: Infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).

6.1 Experimental procedures

The numbering system as represented for compounds **163**–**216**, **222**–**224**, and **233**–**327**, *en route* to the synthesis of (+)-lophotoxin (**1**), is in accordance with the natural product numbering system for lophotoxin introduced by Fenical and co-workers.[11] The numbering system for compounds **156**–**160** and **99** is based on the numbering system of (+)-(*S*)-carvone.[118] Therefore, the numbering system may not reflect that in the systematic name, derived according to IUPAC nomenclature. Stereoisomers and mixtures of such are described using *rac* for racemates, *ent* for enantiomers and *epi* for epimers.

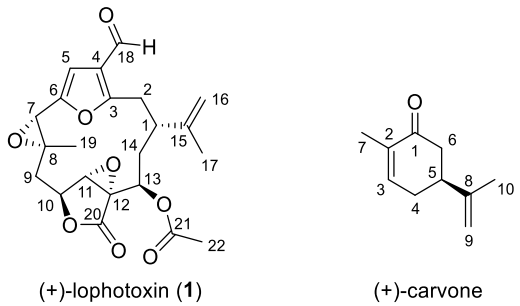


Figure 17 Lophotoxin (**1**) and (+)-(*S*)-carvone numbering scheme.

General set-up A for Ring-Closing Metathesis (RCM)

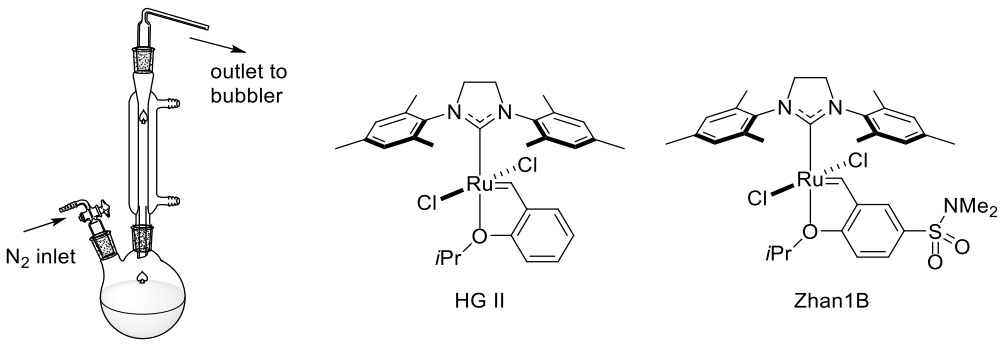
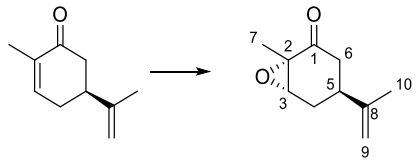


Figure 18 General set-up A and olefin metathesis catalysts Hoveyda-Grubbs 2nd generation (HG II) and Zhan1B.

For RCM reactions in high boiling solvents such as PhMe and DCE, a constant stream of N_2 was used to remove volatile compounds from the reaction mixture without lowering the solvent level. This method is generally applicable, drives conversion, and often results in the formation of less side products. Olefin metathesis catalyst Zhan1B is a derivative of Hoveyda-Grubbs 2nd generation (HG II). In our hands both catalysts behave very similarly.

6.1.1 Synthesis of aldehyde 99

(1*S*,4*S*,6*S*)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (156)



(+)-(S)-carvone **156**

To a solution of (+)-(*S*)-carvone (23.4 g, 156 mmol, 1.0 eq) in MeOH (375 mL, 0.40 M final concentration) at –20 °C (cryostat/acetone) was added NaOH (4.0 M, aq., 12 mL, 29 mmol, 0.31 eq) *via* addition funnel causing the reaction mixture to turn dark green. Dropwise addition of H_2O_2 (30 wt%, aq., 33 mL, 0.32 mol, 2.1 eq) *via* addition funnel caused a yellow colour change. After 30 min, the cooling bath temperature was adjusted to 0 °C and left for 3 h. The reaction was quenched with HCl (3.0 M, aq., 16 mL) and $Na_2S_2O_3$ (sat., aq., 250 mL), diluted with H_2O (150 mL), warmed to rt and extracted with Et_2O (3 × 500 mL). The combined organic extracts were washed with brine (3 × 300 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford epoxide **156** (24.5 g, 95%) as a yellow oil. The material was pure by ^{1}H NMR and was used in the next step without any further purification.

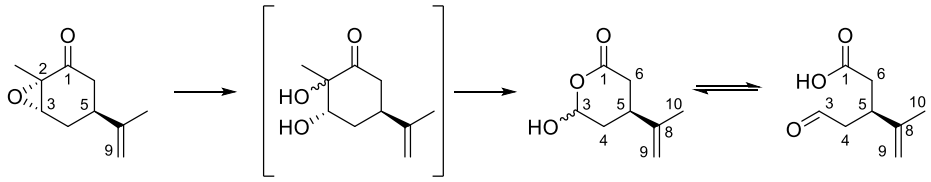
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85–4.76 (m, 1H, *H*-9a), 4.71 (q, *J* = 1.1 Hz, 1H, *H*-9b), 3.44 (dd, *J* = 3.1, 1.2 Hz, 1H, *H*-3), 2.77–2.66 (m, 1H, *H*-5), 2.58 (ddd, *J* = 17.6, 4.7, 1.4 Hz, 1H, *H*-6a), 2.36 (app. dddd, *J* = 14.7, 4.4, 3.0, 1.3 Hz, 1H, *H*-4a), 2.02 (dd, *J* = 17.6, 11.6 Hz, 1H, *H*-6b), 1.90 (ddd, *J* = 14.8, 11.1, 1.2 Hz, 1H, *H*-4b), 1.75–1.66 (m, 3H, 3 × *H*-10) and 1.41 ppm (s, 3H, 3 × *H*-7);

^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.6 (*C*-1), 146.5 (*C*-8), 110.6 (*C*-9), 61.5 (*C*-3), 59.0 (*C*-2), 41.9 (*C*-6), 35.2 (*C*-5), 28.9 (*C*-4), 20.7 (*C*-10) and 15.4 ppm (*C*-7);

FT-IR ν_{max} (thin film): 3649, 3459, 2980, 2360, 2342, 1717, 1457, 1380, 1100 and 669 cm^{-1}.

The spectral data were consistent with those previously reported.[57]

(*S*)-4-Methyl-3-(2-oxoethyl)pent-4-enoic acid (158)



156 **157** **159** **158**

To a solution of epoxide **156** (23.9 g, 143 mmol, 1.0 eq) in THF (alumina filtrated, 680 mL, 0.20 M final concentration) was added a solution of H_2SO_4 (4.23 g, 43.1 mmol, 0.30 eq) in H_2O (34 mL, THF:H_2O = 20:1). The reaction was heated to 80 °C for 36 h, cooled to rt and then diluted with pentane (300 mL) and H_2O (300 mL). The resulting mixture was extracted with Et_2O (3 × 250 mL). The combined organic extracts were washed with brine (3 × 250 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford a diastereomeric mixture of crude diol **157** (25.8 g, 96%). To a slurry of $NaIO_4$ (92.3 g, 431 mmol, 3.0 eq) and SiO_2 (180 mL) in CH_2Cl_2 (820 mL, 0.10 M final concentration) at 0 °C was added H_2O (119 mL) *via* cannula over 1.5 h. A solution of diol **157** (25.8 g) in CH_2Cl_2 (100 mL + 3 × 15 mL rinse) was added *via* cannula and the mixture was gradually warmed to rt overnight. After 16 h, the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 (3 × 100 mL) and concentrated *in vacuo.* The resulting residue was purified by column flash chromatography (SiO_2, CH_2Cl_2:MeOH = 90:10) to afford aldehyde **158** (16.3 g, 72% over two steps) as a colourless oil.

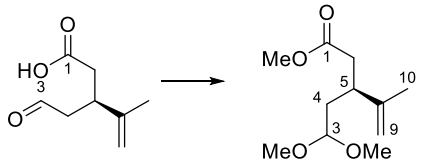
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1H, *H*-3), 4.93–4.78 (m, 2H, 2 × *H*-9), 3.15 (br. s, 1H, *H*-5), 2.62–2.42 (m, 4H, 2 × *H*-4, 2 × *H*-6) and 1.74 ppm (s, 3H, 3 × *H*-10); CO_2H not observed;

^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.1 (*C*-3), 177.2 (*C*-1), 144.9 (*C*-8), 112.7 (*C*-9), 46.6 (*C*-4), 38.0 (*C*-6), 37.2 (*C*-5) and 19.9 ppm (*C*-10);

FT-IR ν_{max} (thin film): 2972, 1716, 1648, 1379, 1236, 1162, 1048 and 899 cm^{-1}.

The spectral data were consistent with those previously reported.[57]

Methyl (*S*)-3-(2,2-dimethoxyethyl)-4-methylpent-4-enoate (160)



158 **160**

Note: Aldehyde **158** (16.2 g, 104 mmol) was converted in two separate batches in parallel. The procedure for the larger batch is provided here. The same relative amounts of reagents and solvent and equal reaction time were used in the conversion of the smaller batch.

To a solution of aldehyde **158** (11.7 g, 74.9 mmol, 1.0 eq) in MeOH (150 mL, 0.39 mM final concentrations) was added TsOH · H_2O (714 mg, 3.76 mmol, 5.0 mol%) and trimethoxy orthoformate (41 mL, 0.37 mmol, 5.0 eq). After 24 h, both batches were combined, quenched with $NaHCO_3$ (sat., aq., 200 mL), diluted with H_2O (250 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (2 × 200 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 95:5 to 85:15) to afford acetal **160** (17.5 g, 78%) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.79 (app. q, *J* = 1.3 Hz, 2H, 2 × *H*-9), 4.32 (dd, *J* = 7.4, 4.2 Hz, 1H, *H*-3), 3.64 (s, 3H, $CO_2C\underline{H}_3$), 3.30 (s, 3H, $OC\underline{H}_3$), 3.29 (s, 3H, $OC\underline{H}_3$), 2.83–2.67 (m, 1H, *H*-5), 2.42–2.37 (m, 2H, 2 × *H*-6) and 1.77–1.60 ppm (m, 5H, 2 × *H*-4, 3 × *H*-10);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.8 (*C*-1), 146.0 (*C*-8), 112.5 (*C*-9), 102.9 (*C*-3), 52.9 ($O\underline{C}H_3$), 52.7 ($O\underline{C}H_3$), 51.6 ($CO_2\underline{C}H_3$), 39.8 (*C*-5), 39.1 (*C*-6), 35.8 (*C*-4) and 19.0 ppm (*C*-10);

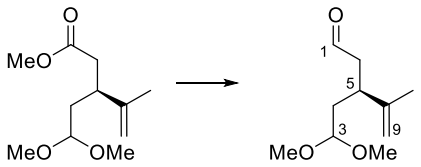
FT-IR ν_{max} (thin film): 2952, 2831, 2361, 1738, 1647, 1437, 1377, 1158, 961 and 895 cm^{-1};

HRMS (ESI^+): Calc. for $C_{11}H_{20}O_4{}^{23}Na^+$ $[M+Na]^+$ 239.1254; found 239.1254 (Δ 0.00 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +3.8 (c = 1.27, CH_2Cl_2).

The spectral data were consistent with those previously reported.[57]

(*R*)-3-(2,2-dimethoxyethyl)-4-Methylpent-4-enal (99)



160 **99**

Note: Aldehyde **99** was used in the next step immediately after isolation. On large scale (>10 g) solvent impurities were not fully removed and a yield was calculated over two steps.

Procedure A (< 10 g):

To a solution of ester **160** (1.80 g, 8.32 mmol, 1.0 eq) in CH_2Cl_2 (80 mL, 0.10 M) at –78 °C was added DIBAL-H (1.0 M in PhMe, 9.2 mL, 9.2 mmol, 1.1 eq) dropwise *via* syringe pump (25 mL/h). After 2 h, the reaction was quenched with Rochelle's salt (sat., aq., 80 mL). The mixture was slowly warmed to rt with vigorous stirring (900 rpm) for 1 h. The resulting mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed with brine (80 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford spectroscopically clean aldehyde **99** (1.59 g, quant. yield) as a colourless liquid.

Procedure B (> 10 g):

A solution of ester **160** (12.6 g, 58.0 mmol, 1.0 eq) in CH_2Cl_2 (0.59 L, 0.10 M) was cooled to –78 °C. DIBAL-H (1.0 M in PhMe, 49.9 g, 58.2 mmol, 1.0 eq) was cooled to –78 °C in a flask and transferred into the reaction vessel *via* cannula over a period of 70 min. After 1.5 h, Rochelle's salt (sat., aq., 100 mL) was added and the heterogenous mixture was carefully allowed to warm to rt. The biphasic mixture was vigorously stirred (700 rpm) for 2 h. The separated aqueous layer was extracted with Et_2O (1 × 200 mL) and the combined organic extracts were washed with brine (1 × 250 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford crude aldehyde **99** as a colourless liquid (12.1 g) which was used in the

next step without further purification. Analysis of the crude product by ^{1}H NMR shows a ratio of **99**:**170** > 95:5.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.65 (t, *J* = 2.3 Hz, 1H, *H*-1), 4.83–4.81 (m, 2H, 2 × *H*-9), 4.32 (dd, *J* = 6.2, 5.3 Hz, 1H, *H*-3), 3.31 (s, 3H, OC$\underline{H}_3$), 3.28 (s, 3H, OC$\underline{H}_3$), 2.94–2.75 (m, 1H, *H*-5), 2.48–2.45 (m, 1H, *H*-6a), 2.44 (dd, *J* = 2.3, 1.5 Hz, 1H, *H*-6b) and 1.73–1.66 ppm (m, 5H, 2 × *H*-4, 3 × *H*-10);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.9 (*C*-1), 145.7 (*C*-8), 112.8 (*C*-9), 102.8 (*C*-3), 53.2 (O$\underline{C}$H$_3$), 52.7 (O$\underline{C}$H$_3$), 47.5 (*C*-6), 37.6 (*C*-5), 36.1 (*C*-4) and 19.1 ppm (*C*-10);

FT-IR ν_{max} (thin film): 2950, 2831, 2360, 1724, 1646, 1441, 1379, 1261, 1190, 1128, 1053, 963 and 897 cm^{-1};

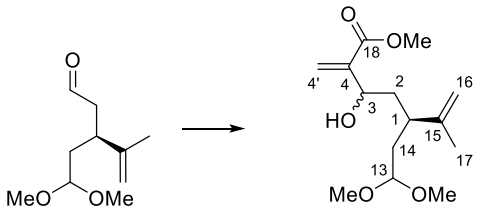
HRMS (ESI^{+}): Calc. for $C_{10}H_{18}O_3{}^{23}Na^{+}$ [M+Na]$^{+}$ 209.1148; found 209.1150 (Δ 0.74 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –4.3 (c = 1.00, CH_2Cl_2).

The spectral data were consistent with those previously reported.[57]

6.1.2 Synthesis of acetal containing furan 167

Methyl (3*R*/*S*,5*R*)-5-(2,2-dimethoxyethyl)-3-hydroxy-6-methyl-2-methylenehept-6-enoate (163)



Note: Diastereomeric ratios for alcohol **163** were determined at *H*-4'b.

Procedure A (HMPA):

To a solution of HMPA (2.6 mL, 15 mmol, 12 eq) in THF (3.0 mL, 0.10 M final concentration) at 0 °C was added DIBAL-H (1.0 M in PhMe, 5.3 mL, 5.3 mmol, 4.4 eq) dropwise *via* syringe pump (50 mL/h). The resulting mixture was stirred for 1.5 h and a solution of methyl propiolate (0.55 mL, 6.2 mmol, 5.1 eq) in THF (0.50 mL) was added dropwise. After an additional 1.5 h, a solution of aldehyde **99** (226 mg, 1.21 mmol, 1.0 eq) in THF (0.75 mL + 2 × 0.5 mL wash) was added dropwise and the resulting red solution was stirred for 30 min. After which the mixture was heated to 45 °C (oil bath) for 16 h before being cooled to 0 °C. The reaction was quenched with Rochelle's salt (sat., aq., 15 mL), warmed to rt, vigorously stirred (600 rpm) for 20 min and extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. After which, the residue was re-dissolved in Et_2O (30 mL), washed with brine (3 × 15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was analysed by ^1H NMR (55:45 dr) and purified by flash column chromatography (SiO_2, pentane:Et_2O = 50:50) to afford a diastereomeric mixture of alcohol **163** (110 mg, 33%, 54:46 dr) as a colourless oil. Mixed fractions were re-purified

by flash column chromatography (SiO_2, pentane:Et_2O = 70:30 to 50:50) to afford alcohol **163** (101 mg, 57:43 dr; total 211 mg, 64%).

Procedure B (NMO):

To a slurry of NMO (354 mg, 3.04 mmol, 3.5 eq) in THF (5.0 mL, 83 mM final concentration) at 0 °C was added DIBAL-H (1.0 M in PhMe, 3.0 mL, 3.0 mmol, 3.5 eq) dropwise *via* syringe pump (30 mL/h). The resulting homogeneous, clear reaction mixture was stirred for 1 h. After which, methyl propiolate (0.32 mL, 3.5 mmol, 4.0 eq) was added dropwise, causing a yellow colour change. After an additional 2 h, a solution of aldehyde **99** (145 mg, 859 µmol assumed quant. from previous step, 1.0 eq) in THF (1.0 mL + 2 × 0.5 mL rinse) was added. After addition, the cooling bath was removed, and the mixture heated to 45 °C for 18 h. The reaction was quenched at 0 °C with HCl (1M, aq., 5 mL), diluted with brine (5 mL), EtOAc (5 mL) and warmed to rt. The mixture was transferred into an Erlenmeyer flask, diluted with Rochelle's salt (sat., aq., 20 mL) and vigorously stirred (900 rpm) for 1 h. The separated aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with $NaHCO_3$ (sat., aq., 50 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 70:30 to 50:50) to afford a diastereomeric mixture of alcohol **163** (151 mg, 63% over two steps, 59:41 dr) as a colourless oil.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 6.22 (d, *J* = 1.0 Hz, 1H, *H*-4'a), 5.85 (d, *J* = 1.2 Hz, 1H, *H*-4'b), 4.92–4.85 (m, 2H, 2 × *H*-16), 4.43–4.27 (m, 2H, *H*-3, *H*-13), 3.77 (s, 3H, $CO_2C\underline{H}_3$), 3.32 (s, 3H, $OC\underline{H}_3$), 3.29 (s, 3H, $OC\underline{H}_3$), 2.69–2.56 (m, 1H, *H*-1), 2.33 (d, *J* = 6.2 Hz, 1H, O*H*-3) and 1.81–1.48 ppm (m, 7H, 2 × *H*-2, 2 × *H*-14, 3 × *H*-17);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 167.0 (*C*-18), 146.2 (*C*-4/*C*-15), 143.3 (*C*-4/*C*-15), 124.7 (*C*-4'), 113.5 (*C*-16), 103.2 (*C*-13), 69.0 (*C*-3), 53.2 (OCH_3), 52.7 (OCH_3), 52.0 (CO_2CH_3), 40.2 (*C*-2), 40.0 (*C*-1), 36.6 (*C*-14) and 17.8 ppm (*C*-17);

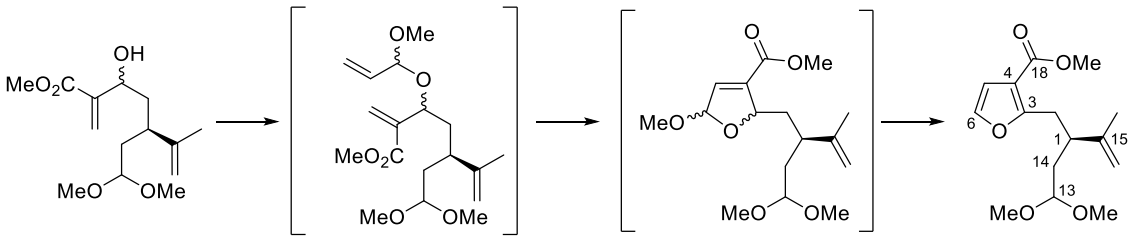
^{1}H NMR (minor diastereomer, 400 MHz, $CDCl_3$) δ = 6.23 (d, *J* = 1.2 Hz, 1H, *H*-4'a), 5.80 (d, *J* = 1.1 Hz, 1H, *H*-4'b), 4.82 (t, *J* = 1.8 Hz, 1H, *H*-16a), 4.80–4.76 (m, 1H, *H*-16b), 4.43–4.27 (m, 2H, *H*-3, *H*-13), 3.78 (s, 3H, CO_2CH_3), 3.31 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 2.87 (d, *J* = 7.1 Hz, 1H, O*H*-3), 2.39–2.29 (m, 1H, *H*-1) and 1.81–1.48 ppm (m, 7H, 2 × *H*-2, 2 × *H*-14, 3 × *H*-17);

^{13}C NMR (minor diastereomer, 101 MHz, $CDCl_3$) δ = 167.0 (*C*-18), 147.3 (*C*-4/*C*-15), 141.7 (*C*-4/*C*-15), 125.8 (*C*-4'), 112.8 (*C*-16), 103.1 (*C*-13), 70.7 (*C*-3), 53.3 (OCH_3), 52.7 (OCH_3), 52.0 (*C*-CO_2CH_3), 40.5 (*C*-1), 40.0 (*C*-2), 35.9 (*C*-14) and 18.4 ppm (*C*-17);

FT-IR ν_{max} (thin film): 3445, 2951, 1717, 1645, 1439, 1378, 1265, 1194, 1149 and 820 cm^{-1};

HRMS (ESI^+): Calc. for $C_{14}H_{24}O_5{}^{23}Na^+$ $[M+Na]^+$ 295.1516; found 295.1512 (Δ –1.29 ppm).

Methyl (*R*)-2-(2-(2,2-dimethoxyethyl)-3-methylbut-3-en-1-yl)furan-3-carboxylate (167)



163 **164** **166** **167**

Procedure A:

Note: For the second step, general set-up A was used.

To a solution of alcohol **163** (345 mg, 1.27 mmol, 54:46 dr, 1.0 eq) in THF (4.0 mL, 0.32 M) was added to $Pd(OAc)_2$ (15.1 mg, 36.6 µmol, 2.9 mol%) and dppp (27.1 mg, 65.7 µmol, 5.2 mol%) in a pressure tube. Methoxy allene (225 mg, 3.21 mmol, 2.5 eq) and Et_3N (0.26 mL, 1.9 mmol, 1.5 eq) were added and the sealed vessel heated to 60 °C for 24 h. After which, the reaction mixture was cooled to rt, diluted with H_2O (5 mL) and brine

(5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 50:50) to afford alcohol **163** (rsm, 188 mg, 54%, 51:49 dr) and desired intermediate **164** (176 mg, 41%, mixture of 4 diastereoisomers). Mixed acetal **164** (166 mg, 484 µmol, 1.0 eq) was dissolved in PhMe (degassed, 10 mL, 48 mM), charged with Zhan1B (18.4 mg, 25.1 µmol, 5.2 mol%) and heated to 40 °C for 24 h. After which, the reaction mixture was filtered through a plug of silica and washed with MeOH (50 mL). The product containing fraction was transferred into a round-bottom flask and AcCl (20 µL, 0.28 mmol, 0.58 eq) was added. The resulting mixture was heated to 40 °C for 24 h. After which, the reaction was quenched with $NaHCO_3$ (sat., aq., 25 mL), diluted with H_2O (10 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 70:30) to afford furan **167** (48.3 mg, 14% over three steps) as a colourless oil.

Procedure B:

To a solution of alcohol **163** (43.0 mg, 158 µmol, 57:43 dr, 1.0 eq) in acrolein dimethyl acetal (0.30 mL, 2.5 mmol, 16 eq) was added PPTS (4.1 mg, 16 µmol, 0.10 eq). The resulting mixture was stirred at rt for 24 h after which no conversion of starting material was observed by TLC. The mixture was diluted with PhMe (1.0 mL), placed on a rotary evaporator, and rotated at 40 °C and 100 mbar pressure. After 5 h the reaction was quenched with $NaHCO_3$ (sat., aq., 1.0 mL) and extracted with Et_2O (3 × 2.0 mL). The combined organic extracts were washed with brine (2 × 1.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 95:5 to 40:60) to afford desired intermediate **164**

(11.5 mg, 21%, mixture of 4 diastereoisomers) and cyclic acetal **166** (7.7 mg, 20%, mixture of 4 diastereomers), both as a colourless film. Due to their complexity neither of the products were characterised, but key ^{1}H and ^{13}C NMR signals matched with mixed acetal **164**, isolated following procedure A, and cyclized acetal **166** (*vide supra*), respectively. Due to low quantity, the material was not advanced further.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 2.0 Hz, 1H, *H*-6), 6.61 (d, *J* = 2.0 Hz, 1H, *H*-5), 4.75–4.69 (m, 1H, *H*-16a), 4.71–4.68 (m, 1H, *H*-16b), 4.30 (dd, *J* = 6.3, 5.4 Hz, 1H, *H*-13), 3.81 (s, 3H, $CO_2C\underline{H}_3$), 3.29 (s, 3H, $OC\underline{H}_3$), 3.25 (s, 3H, $OC\underline{H}_3$), 3.11 (dd, *J* = 14.4, 8.2 Hz, 1H, *H*-2a), 3.05 (dd, *J* = 14.4, 7.2 Hz, 1H, *H*-2b), 2.74 (p, *J* = 7.6 Hz, 1H, *H*-1) and 1.72–1.67 ppm (m, 5H, 2 × *H*-14, 3 × *H*-17);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.3 (*C*-3/*C*-18), 161.2 (*C*-3/*C*-18), 146.0 (*C*-15), 140.7 (*C*-6), 113.9 (*C*-4), 112.4 (*C*-16), 110.5 (*C*-5), 102.9 (*C*-13), 53.0 ($O\underline{C}H_3$), 52.5 ($O\underline{C}H_3$), 51.3 (CO_2CH_3), 42.3 (*C*-1), 35.3 (*C*-14), 32.1 (*C*-2) and 18.5 ppm (*C*-17);

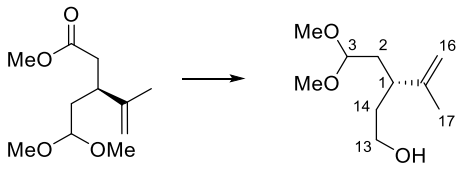
FT-IR ν_{max} (thin film): 2951, 2830, 2360, 1720, 1601, 1520, 1440, 1378, 1305, 1198, 1153, 1127, 1081, 959, 894 and 748 cm^{-1};

HRMS (ESI^+): Calc. for $C_{15}H_{22}O_5{}^{23}Na^+$ $[M+Na]^+$ 305.1359; found 305.1360 (Δ 0.32 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +11.2 (c = 0.80, CH_2Cl_2).

6.1.3 Synthesis of PMB containing furan 169

(*R*)-3-(2,2-dimethoxyethyl)-4-Methylpent-4-en-1-ol (170)



160 **170**

To a solution of ester **160** (5.00 g, 23.1 mmol, 1.0 eq) in THF (230 mL, 0.10 M) was added $LiAlH_4$ (878 mg, 23.1 mmol, 1.0 eq) in portions at 0 °C. The reaction mixture was gradually warmed to rt over 16 h. After which, the mixture was cooled to 0 °C, diluted with Et_2O (250 mL) and quenched with H_2O (0.88 mL). The resulting mixture was diluted with NaOH (15%, aq., 0.88 mL) and H_2O (2.6 mL). After 30 min, $MgSO_4$ was added and the resulting slurry was stirred for 45 min before it was filtered through Celite®. The filtrate was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 70:30 to 0:100) to afford alcohol **170** (3.60 g, 83%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.82–4.79 (m, 2H, 2 × *H*-16), 4.32 (dd, *J* = 7.2, 4.4 Hz, 1H, *H*-3), 3.68–3.54 (m, 2H, 2 × *H*-13), 3.32 (s, 3H, OC*H*$_3$), 3.29 (s, 3H, OC*H*$_3$), 2.47–2.34 (m, 1H, *H*-1), 1.73–1.57 (m, 7H, 2 × *H*-2, 2 × *H*-14, 3 × *H*-17) and 1.52 ppm (s, 1H, *OH*-13);

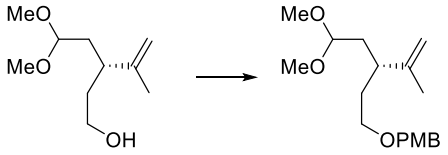
^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.9 (*C*-15), 112.7 (*C*-16), 103.1 (*C*-3), 61.4 (*C*-13), 53.3 (O*C*H$_3$), 52.7 (O*C*H$_3$), 40.2 (*C*-1), 36.3 (*C*-2), 36.2 (*C*-14) and ppm 18.0 (*C*-17);

FT-IR ν_{max} (thin film): 3416, 2939, 2834, 1444, 1377, 1188, 1126, 1057, 962 and 892 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{10}H_{20}O_3{}^{23}Na^+$ $[M+Na]^+$ 211.1305; found 211.1307 (Δ 0.85 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +6.2 (c = 1.00, CH_2Cl_2).

(*R*)-1-(((3-(2,2-dimethoxyethyl)-4-Methylpent-4-en-1-yl)oxy)methyl)-4-methoxybenzene (171)



170 **171**

To a solution of alcohol **170** (3.60 g, 19.1 mmol, 1.0 eq) in THF (35 mL, 0.55 M) at 0 °C was added NaH (1.56 g, 39.0 mmol, 2.0 eq) in portions over a period of 15 min. After the slurry was stirred for 1 h, it was warmed to rt. 4-Methoxybenzyl chloride (2.9 mL, 21 mmol, 1.1 eq) and tetrabutylammonium iodide (354 mg, 956 µmol, 5.0 mol%) were added. The reaction mixture was heated to 75 °C for 17 h. After which, it was cooled to 0 °C and quenched with NH_4Cl (sat., aq., 50 mL), diluted with brine (100 mL) and extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 0:100) to afford desired ether **171** as a colourless syrup (4.96 g, 84%) and recovered alcohol **170** (508 mg, 14%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.20 (m, 2H, 2 × Ar*H*^{PMB}), 6.91– 6.84 (m, 2H, 2 × Ar*H*^{PMB}), 4.78–4.76 (m, 1H, *H*-16a), 4.75–4.73 (m, 1H, *H*-16b), 4.40 (d, *J* = 11.5 Hz, 1H, OC*H*aHb^{PMB}), 4.39 (d, *J* = 11.5 Hz, 1H, OCHa*H*b^{PMB}), 4.31 (dd, *J* = 7.5, 4.1 Hz, 1H, *H*-3), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.41–3.34 (m, 2H, 2 × *H*-13), 3.30 (s, 3H, OC*H*$_3$), 3.29 (s, 3H, OC*H*$_3$), 2.43–2.32 (m, 1H, *H*-1) and 1.75–1.54 ppm (m, 7H, 2 × *H*-2, 2 × *H*-14, 3 × *H*-17);

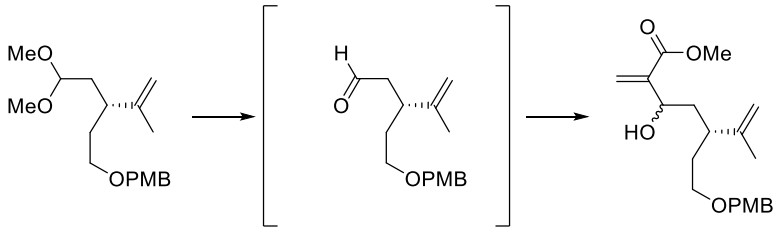
^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.2 (Ar*C*^{PMB}), 146.4 (Ar*C*^{PMB}), 130.8 (*C*-12), 129.4 (2 × Ar*C*^{PMB}), 113.8 (2 × Ar*C*^{PMB}), 112.6 (*C*-16), 103.1 (*C*-3), 72.8 (O*C*H$_2^{PMB}$), 68.4 (*C*-13), 55.4 (O*C*H$_3^{PMB}$), 53.0 (O*C*H$_3$), 52.8 (O*C*H$_3$), 40.1 (*C*-1), 36.3 (*C*-2), 33.4 (*C*-14) and 18.1 ppm (*C*-17);

FT-IR ν_{max} (thin film): 2937, 1613, 1513, 1442, 1364, 1302, 1247, 1174, 1126, 1087, 1054, 1037, 961, 892 and 821 cm^{-1};

HRMS (ESI^+): Calc. for $C_{18}H_{28}O_4{}^{23}Na^+$ $[M+Na]^+$ 331.1880; found 331.1881 (Δ 0.21 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +13.2 (c = 1.00, CH_2Cl_2).

Methyl (5*R*)-3-hydroxy-5-(2-((4-methoxybenzyl)oxy)ethyl)-6-methyl-2-methylenehept-6-enoate (173)



171 **172** **173**

To a solution of acetal **171** (1.40 g, 4.50 mmol, 1.0 eq) in acetone (36 mL) and H_2O (9.0 mL) was added pyridinium *p*-toluenesulfonate (284 mg, 1.13 mmol, 25 mol%). The resulting mixture was heated to 50 °C for 18 h. After which, the reaction was quenched with $NaHCO_3$ (sat., aq., 50 mL), diluted with H_2O (10 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford crude aldehyde **172** as pale oil (1.21 g). In a separate flask, a solution of NMO (1.80 g, 15.8 mmol, 3.5 eq) in THF (15 mL, 0.12 M final concentration) was cooled to 0 °C and DIBAL-H (1.0 M in PhMe, 15.5 mL, 15.5 mmol, 3.45 eq) was added dropwise *via* syringe pump (60 mL/h). The resulting solution was stirred for 1 h and then methyl propiolate (1.7 mL, 18 mmol, 4.0 eq) was added dropwise. After an additional 1 h, a solution of crude aldehyde **172** (1.21 g) in THF (5.0 mL + 2 × 1 mL rinse) was added dropwise and the resulting bright yellow mixture was heated to 45 °C for 2.5 h. After which, the now dark red solution was cooled to 0 °C, diluted with Et_2O (20 mL), quenched with Rochelle's salt (sat., aq., 20 mL), warmed to rt, diluted with Et_2O (100 mL) and vigorously stirred (900 rpm) for 16 h. The mixture was filtered through

Celite®, rinsed with CH_2Cl_2 (100 mL) and the filtrate was concentrated *in vacuo*. The residue was analysed by ^{1}H NMR (59:41 dr determined at *H*-4b) and purified by flash column chromatography (SiO_2, pentane:Et_2O = 70:30 to 50:50) to afford alcohol **173** (1.14 g, 73% over two steps, 59:41 dr) as a pale-yellow syrup. For spectroscopic reasons, an analytic sample was subjected to flash column chromatography (SiO_2, pentane:Et_2O = 70:30) in order to partially separate the two diastereomers.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.19–7.15 (m, 2H, 2 × Ar*H*^{PMB}), 6.84–6.77 (m, 2H, 2 × Ar*H*^{PMB}), 6.15 (t, *J* = 1.4 Hz, 1H, *H*-4'a), 5.72 (t, *J* = 1.2 Hz, 1H, *H*-4'b), 4.74–4.70 (m, 1H, *H*-16a), 4.69–4.65 (m, 1H, *H*-16b), 4.38–4.26 (m, 3H, OC*H*$_2^{PMB}$, *H*-3), 3.73 (s, 3H, OC*H*$_3^{PMB}$), 3.70 (s, 3H, CO_2CH_3), 3.39–3.23 (m, 2H, 2 × *H*-13), 2.87 (d, *J* = 7.1 Hz, 1H, *OH*-3), 2.35–2.23 (m, 1H, *H*-1) and 1.75–1.41 ppm (m, 7H, 2 × *H*-2, 2 × *H*-14, 3 × *H*-17);

^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ = 167.0 (*C*-18), 159.2 (Ar*C*^{PMB}), 146.3 (*C*-15), 143.3 (*C*-4), 130.8 (Ar*C*^{PMB}), 129.4 (2 × Ar*C*^{PMB}), 124.6 (*C*-4'), 113.9 (2 × Ar*C*^{PMB}), 113.3 (*C*-16), 72.8 (*C*-3), 69.1 (O*C*H$_2^{PMB}$), 68.5 (*C*-13), 55.4 (CO_2CH_3), 52.0 (O*C*H$_3^{PMB}$), 40.9 (*C*-1), 40.1 (*C*-2), 33.6 (*C*-14) and 17.7 ppm (*C*-17);

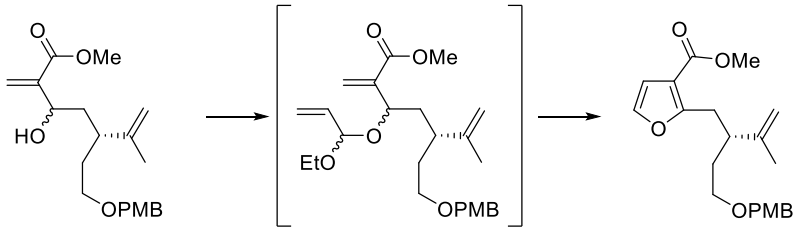
^{1}H NMR (minor diastereomer, 400 MHz, $CDCl_3$) δ = 7.25–7.22 (m, 2H, 2 × Ar*H*^{PMB}), 6.90–6.84 (m, 2H, 2 × Ar*H*^{PMB}), 6.22 (t, *J* = 1.4 Hz, 1H, *H*-4'a), 5.79 (t, *J* = 1.2 Hz, 1H, *H*-4'b), 4.80–4.77 (m, 1H, *H*-16a), 4.75–4.71 (m, 1H, *H*-16b), 4.45–4.33 (m, 3H, OC*H*$_2^{PMB}$, *H*-3), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.76 (s, 3H, CO_2CH_3), 3.45–3.30 (m, 2H, 2 × *H*-13), 2.93 (d, *J* = 7.1 Hz, 1H, *OH*-3), 2.41–2.29 (m, 1H, *H*-1) and 1.82–1.48 ppm (m, 7H, 2 × *H*-2, 2 × *H*-14, 3 × *H*-17);

^{13}C NMR (minor diastereomer, 126 MHz, $CDCl_3$) δ = 167.0 (*C*-18), 159.3 (Ar*C*^{PMB}), 147.4 (*C*-15), 141.8 (*C*-4), 130.7 (Ar*C*^{PMB}), 129.4 (2 × Ar*C*^{PMB}), 125.8 (*C*-4'), 113.9 (2 × Ar*C*^{PMB}), 112.6 (*C*-16), 72.8 (*C*-3), 70.8 (O*C*H$_2^{PMB}$), 68.3 (*C*-13), 55.4 (O*C*H$_3^{PMB}$), 52.0 (CO_2CH_3), 41.4 (*C*-1), 40.2 (*C*-2), 32.9 (*C*-14) and 18.3 ppm (*C*-17);

FT-IR ν_{max} (thin film) 2981, 1717, 1613, 1514, 1439, 1379, 1151, 1083, 1035, 955 and 820 cm^{-1};

HRMS (ESI^+): Calc. for $C_{20}H_{29}O_5^+$ $[M+H]^+$ 349.2010; found 349.2010 (Δ 0.02 ppm);

Methyl (*R*)-2-(2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylbut-3-en-1-yl)furan-3-carboxylate (169)



173 **175** **169**

Note: For the second step general set-up A was used.

To a solution of alcohol **173** (1.13 g, 3.24 mmol, 59:41 dr, 1.0 eq) in acrolein diethyl acetal (4.0 mL, 26 mmol, 8.0 eq) and PhMe (4.0 mL, PhMe:acrolein diethyl acetal = 50:50) was added PPTS (85.9 mg, 341 µmol, 10 mol%). The reaction vessel was placed on a rotary evaporator and the pressure was slowly lowered to 100 mbar at 40 °C. After 3 h, the vessel was removed from the rotary evaporator. The reaction mixture was diluted with EtOAc (60 mL) and washed with $NaHCO_3$ (sat., aq., 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 85:15 to 75:25) to afford mixed acetal **175** (1.08 g, 77%, mixture of 4 diastereomers) as a colorless oil. To a solution of mixed acetal **175** (1.07 g, 2.47 mmol, 1.0 eq) in PhMe (degassed, 31 mL, 75 mM) was added HGII (75.5 mg, 120 µmol, 4.9 mol%) and the reaction was heated to 60 °C for 18 h under a stream of N_2. After which, the reaction mixture was cooled to rt, charged with a second portion of HGII (75.7 mg, 121 µmol, 4.9 mol%), degassed, and re-heated to 60 °C for 45 h. The mixture was cooled to rt, diluted with CH_2Cl_2 (30 mL) and PPTS (621 mg, 2.47 mmol, 1.0 eq) was added. After further heating at 40 °C for 2 h the reaction was

quenched at rt with $NaHCO_3$ (sat., aq., 20 mL), diluted with brine (20 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 85:15 to 50:50) to afford furan **169** as a colourless oil (651 mg, 56% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.31–7.25 (m, 3H, *H*-6, 2 × Ar*H*^{PMB}), 6.94–6.87 (m, 2H, 2 × Ar*H*^{PMB}), 6.64 (d, *J* = 2.0 Hz, 1H, *H*-5), 4.73–4.70 (m, 1H, *H*-16a), 4.70–4.66 (m, 1H, *H*-16b), 4.42 (d, *J* = 11.5 Hz, 1H, OC*H*aHb^{PMB}), 4.41 (d, *J* = 11.5 Hz, 1H, OCHa*H*b^{PMB}), 3.84 (s, 3H, CO_2CH_3), 3.83 (s, 3H, OC*H*$_3^{PMB}$), 3.47–3.35 (m, 2H, 2 × *H*-13), 3.15 (dd, *J* = 14.3, 8.4 Hz, 1H, *H*-2a), 3.08 (dd, *J* = 14.4, 7.0 Hz, 1H, *H*-2b), 2.79 (p, *J* = 7.6 Hz, 1H, *H*-1), 1.75 (app. q, *J* = 7.1 Hz, 2H, 2 × *H*-14) and 1.70 ppm (s, 3H, 3 × *H*-17);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.4 (*C*-18), 161.5 (*C*-3), 159.1 (Ar*C*^{PMB}), 146.1 (*C*-15), 140.6 (*C*-6), 130.6 (Ar*C*^{PMB}), 129.3 (2 × Ar*C*^{PMB}), 113.7 (*C*-4, 2 × Ar*C*^{PMB}), 112.2 (*C*-16), 110.5 (*C*-5), 72.6 (O*C*H$_2^{PMB}$), 68.2 (*C*-13), 55.3 (O*C*H$_3^{PMB}$), 51.3 (CO_2CH_3), 43.3 (*C*-1), 32.5 (*C*-14), 32.1 (*C*-2) and 18.2 ppm (*C*-17);

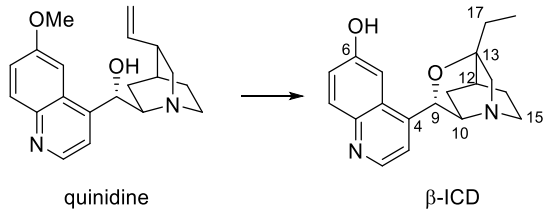
FT-IR ν_{max} (thin film): 2981, 1718, 1603, 1514, 1440, 1302, 1247, 1199, 1154, 1133, 1100, 1035, 894, 820, 745, 642 and 613 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{21}H_{27}O_5^+$ $[M+H]^+$ 359.1853; found 359.1854 (Δ 0.26 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +7.8 (c = 1.00, CH_2Cl_2).

6.1.4 Synthesis of bis-methyl furan 191

4-((3*R*,5*S*,6*R*,8*S*)-3-Ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]decan-5-yl)quinolin-6-ol (β-ICD)



Quinindine (25.0 g, 77.1 mmol, 1.0 eq) was mixed with ortho-phosphoric acid (85%, 375 mL, 0.21 M) and KBr (91.7 g, 770 mmol, 10 eq). The mixture was heated to 100 °C for 10 days. After which, it was poured into a to 0 °C pre-cooled solution of KOH (6 M, 320 mL). The solution was neutralised to pH = 7 by addition of KOH (326 g) and a beige gum precipitate formed. The precipitate was filtered off and dissolved in $CHCl_3$:*i*PrOH (9:1, 500 mL). The filtrate was extracted with $CHCl_3$:*i*PrOH (4:1, 1 × 600 mL). The combined organic layers were washed with brine (400 mL), dried with K_2CO_3 and concentrated *in vacuo*. The resulting red foam was purified by flash column chromatography (SiO_2, CH_2Cl_2:MeOH = 98:2 to 92:8) to afford spectroscopically clean β-ICD (21.2 g, 89%) as a bright yellow solid. Prior to use the material was re-crystallised in small batches: Crude β-ICD (5.05 g) was dissolved in MeOH (10 mL). H_2O (6 mL) was added in one portion and further H_2O (24 mL; final MeOH:H_2O = 25:75) was added *via* syringe pump (2 mL/h). After completed addition the mixture was stirred for 6 h and filtered (sinter). The filter cake was washed with H_2O (2 × 2 mL) and dried under high vacuum to give β-ICD (2.17 g, 43% mass recovery) as a beige powder. The filtrate was concentrated *in vacuo* and re-subjected for recrystallisation.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 (d, *J* = 4.4 Hz, 1H, *H*-2), 8.16 (d, *J* = 2.5 Hz, 1H, *H*-5), 7.97 (d, *J* = 9.0 Hz, 1H, *H*-8), 7.65 (dd, *J* = 4.4, 1.0 Hz, 1H, *H*-3), 7.22 (dd, *J* = 9.0, 2.5 Hz, 1H, *H*-7), 6.05 (s, 1H, *H*-9), 3.72 (dd, *J* = 13.6, 1.7 Hz, 1H, *H*-14a), 3.45 (d, *J* = 6.1 Hz, 1H, *H*-10), 3.24 (dd, *J* = 12.8, 8.4 Hz, 1H, *H*-16a), 3.09 (dd, *J* = 13.2, 11.3, 5.0 Hz, 1H, *H*-16b), 2.80 (d,

J = 13.6 Hz, 1H, *H*-14b), 2.22 (t, *J* = 5.4 Hz, 1H, *H*-12), 1.89 (ddd, *J* = 12.8, 6.7, 2.2 Hz, 1H, *H*-11a), 1.84–1.58 (m, 4H, 2 × *H*-15, 2 × *H*-17), 1.24 (dd, *J* = 13.0, 6.1 Hz, 1H, *H*-11b) and 1.05 ppm (t, *J* = 7.4 Hz, 3H, 3 × *H*-18); OH not observed;

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.6 (*C*-6), 147.0 (*C*-2), 143.4 (C_q), 142.3 (C_q), 131.3 (*C*-8), 127.6 (C_q), 122.3 (*C*-7), 119.2 (*C*-3), 107.0 (*C*-5), 77.3 (*C*-13), 72.8 (*C*-9), 56.5 (*C*-10), 54.2 (*C*-14), 46.8 (*C*-16), 33.0 (*C*-12), 27.6 (*C*-11), 23.5 (*C*-15), 17) and 7.5 ppm (*C*-18);

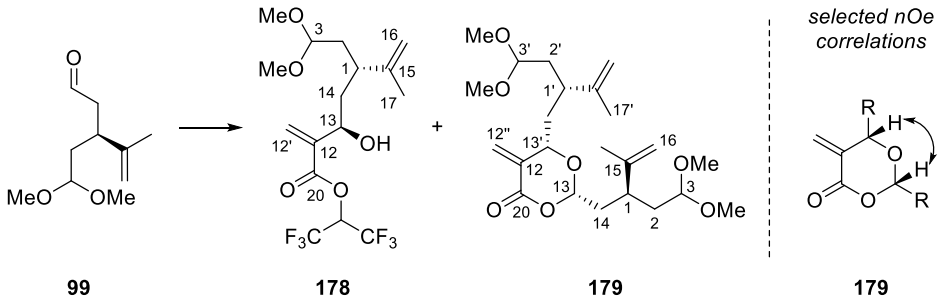
FT-IR ν_{max} (thin film): 2969, 2360, 1619, 1594, 1509, 1472, 1407, 1352, 1236, 1179, 1134, 1099, 1081, 1055, 1017, 977, 911, 856, 829, 801, 737, 708 and 646 cm^{-1};

HRMS (ESI^+): Calc. for $C_{19}H_{23}O_2N_2^+$ $[M+H]^+$ 311.1754; found 311.1752 (Δ –0.75 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –63.2 (c = 0.90, CH_2Cl_2).

The spectral data were consistent with those previously reported.[85]

1,1,1,3,3,3-Hexafluoropropan-2-yl (3*R*,5*R*)-5-(2,2-dimethoxyethyl)-3-hydroxy-6-methyl-2-methylenehept-6-enoate (178)



To a solution of aldehyde **99** (12.1 g, 58.0 mmol assumed quant. from previous step, 1.0 eq) in DMF (filtered through activated alumina, 0.59 L, 0.10 M) and β-ICD (4.49 g, 14.5 mmol, 25.0 mol%) at –55 °C (cryostat/acetone) was added HFIP acrylate (24 mL, 144 mmol, 2.5 eq) dropwise *via* syringe pump (8 mL/h). After 62 h, the reaction was quenched at –55 °C by dropwise addition of HCl (1.0 M, aq., 115 mL) and diluted with brine (500 mL) and EtOAc (500 mL). The resulting mixture was warmed to rt and the separated aqueous layer was extracted with EtOAc (2 × 500 mL). The combined organic extracts were washed with $NaHCO_3$ (sat., aq., 150 mL), LiCl (5 wt%, 3 × 300 mL) and brine

(1 × 500 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR (95:5 dr) and purified by flash column chromatography (SiO_2, pentane:Et_2O = 80:20 to 20:80) to afford desired HFIP ester **178** (13.6 g, 57% over two steps, > 98:2 dr determined at *H*-12'b) as a colourless oil and dioxanone **179** (2.79 g, 23% over two steps) as a colourless syrup. The relative stereochemistry of the dioxanone **179** was confirmed by nOe analysis.

HFIP ester **178**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.49 (t, *J* = 0.7 Hz, 1H, *H*-12'a), 6.21 (dd, *J* = 1.3, 0.7 Hz, 1H, *H*-12'b), 5.83 (sept, $^3J_{H\text{-}F}$ = 6.1 Hz, 1H, C*H*$(CF_3)_2$), 4.88 (d, *J* = 1.4 Hz, 2H, 2 × *H*-16), 4.49–4.40 (m, 1H, *H*-13), 4.36–4.26 (m, 1H, *H*-3), 3.32 (s, 3H, OC*H*$_3$), 3.29 (s, 3H, OC*H*$_3$), 2.62 (dddd, *J* = 10.9, 8.2, 6.6, 4.1 Hz, 1H, *H*-1), 2.13 (d, *J* = 5.6 Hz, 1H, O*H*-13), 1.78–1.72 (m, 1H, *H*-14a), 1.69 (s, 3H, 3 × *H*-17), 1.68–1.63 (m, 2H, 2 × *H*-2) and 1.50 ppm (ddd, *J* = 14.2, 10.2, 4.1 Hz, 1H, *H*-14b);

^{19}F NMR (377 MHz, $CDCl_3$) δ = –73.2 (m, 6F, CH(C*F*$_3)_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.7 (*C*-20), 146.0 (*C*-15), 141.2 (*C*-12), 129.0 (*C*-12'), 113.7 (*C*-16), 103.1 (*C*-3), 68.3 (*C*-13), 66.7 (*C*H$(CF_3)_2$), 53.3 (O*C*H$_3$), 52.7 (O*C*H$_3$), 40.1 (*C*-1), 40.0 (*C*-14), 36.4 (*C*-2) and 17.6 ppm (*C*-17); CH(*C*F$_3)_2$ not observed;

FT-IR ν_{max} (thin film): 3751, 3674, 3649, 2981, 2888, 2360, 2342, 1717, 1699, 1653, 1558, 1541, 1521, 1507, 1473, 1458, 1386, 1252, 1152, 1074, 955 and 669 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{16}H_{22}O_5F_6{}^{23}Na^+$ $[M+Na]^+$ 431.1264; found 431.1260 (Δ –0.79 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +23.9 (c = 1.08, CH_2Cl_2).

Dioxanone **179**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.44 (d, *J* = 2.4 Hz, 1H, *H*-12''a), 5.58 (d, *J* = 2.2 Hz, 1H, *H*-12''b), 5.16 (dd, *J* = 8.1, 3.1 Hz, 1H, *H*-13'), 4.92–4.75 (m, 4H, 2 × *H*-16, 2 × *H*-16'), 4.49 (dq, *J* = 5.7, 2.1 Hz, 1H, *H*-13), 4.35–4.28 (m, 2H, *H*-3, *H*-3'), 3.32 (s, 3H, OC*H*$_3$), 3.32 (s, 3H,

OC$\underline{H}_3$), 3.30 (s, 6H, 2 × OC$\underline{H}_3$), 2.62–2.46 (m, 2H, *H*-1, *H*-1') and 1.94–1.56 ppm (m, 14H, 2 × *H*-2, 2 × *H*-14, 3 × *H*-17, 2 × *H*-2', 2 × *H*-14', 3 × *H*-17');

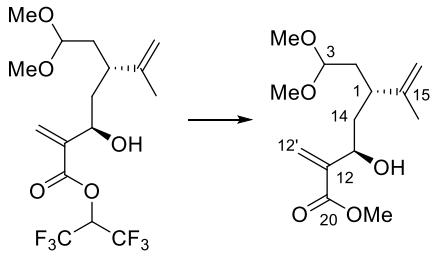
^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.0 (*C*-20), 146.3 (*C*-15), 145.2 (*C*-15'), 137.4 (*C*-12), 125.5 (*C*-12''), 113.6 (*C*-16/16'), 112.7 (*C*-16/16'), 102.9 (*C*-3/3'), 102.7 (*C*-3/3'), 100.4 (*C*-13'), 76.1 (*C*-13), 53.4 (O$\underline{C}H_3$), 53.0 (O$\underline{C}H_3$), 52.7 (O$\underline{C}H_3$), 52.7 (O$\underline{C}H_3$), 39.6 (*C*-1/1', *C*-14/14'), 38.2 (*C*-1/1'), 37.5 (*C*-14/14'), 36.2 (*C*-2/2'), 35.4 (*C*-2/2'), 18.6 (*C*-17/*C*-17') and 17.8 ppm (*C*-17/*C*-17');

FT-IR ν_{max} (thin film): 2950, 2831, 2359, 1737, 1645, 1440, 1378, 1281, 1193, 1127, 1054, 988, 896, 807 and 731 cm^{-1};

HRMS (ESI^+): Calc. for $C_{23}H_{38}O_7{}^{23}Na^+$ $[M+Na]^+$ 449.2510; found 449.2511 (Δ 0.21 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –28.8 (c = 0.87, CH_2Cl_2).

Methyl (3*R*,5*R*)-5-(2,2-dimethoxyethyl)-3-hydroxy-6-methyl-2-methylenehept-6-enoate (181)



178 **181**

To a solution of HFIP ester **178** (796 mg, 1.95 mmol, 1.0 eq) in MeOH (10 mL, 0.20 M) at 0 °C was added Et_3N (0.82 mL, 5.9 mmol, 3.0 eq). The resulting mixture was warmed to 25 °C (oil bath) and stirred for 14 h. After which, the reaction was diluted with EtOAc (10 mL), quenched with HCl (1.0 M, aq., 2.0 mL) and diluted with brine (2.0 mL). The separated aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with $NaHCO_3$ (sat., aq., 10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column

chromatography (SiO_2, pentane:Et_2O = 70:30 to 50:50) to afford ester **181** (478 mg, 90%, 97:3 dr determined at *H*-12'b) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.22 (dd, *J* = 1.2, 0.7 Hz, 1H, *H*-12'a), 5.85 (t, *J* = 1.2 Hz, 1H, *H*-12'b), 4.87 (d, *J* = 1.2 Hz, 2H, 2 × *H*-16), 4.43–4.29 (m, 2H, *H*-13, *H*-3), 3.77 (s, 3H, $CO_2C\underline{H}_3$), 3.32 (s, 3H, $OC\underline{H}_3$), 3.29 (s, 3H, $OC\underline{H}_3$), 2.62 (dtd, *J* = 11.3, 7.6, 4.1 Hz, 1H, *H*-1), 2.33 (d, *J* = 6.1 Hz, 1H, O*H*-13), 1.76–1.62 (m, 6H, 2 × *H*-2, *H*-14a, 3 × *H*-17) and 1.54 ppm (ddd, *J* = 14.1, 10.0, 4.2 Hz, 1H, *H*-14b);

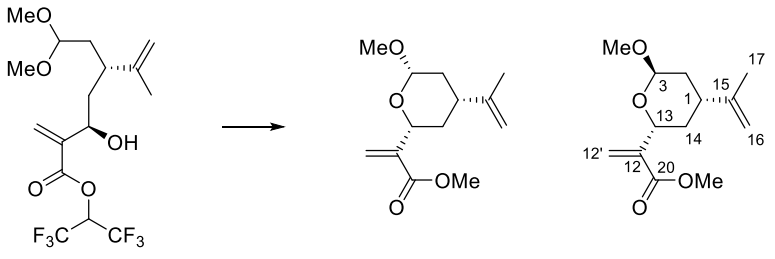
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.8 (*C*-20), 146.0 (*C*-12), 143.1 (*C*-15), 124.6 (*C*-12'), 113.4 (*C*-16), 103.0 (*C*-3), 68.9 (*C*-13), 53.0 ($O\underline{C}H_3$), 52.6 ($O\underline{C}H_3$), 51.8 ($CO_2\underline{C}H_3$), 40.7 (*C*-1), 40.0 (*C*-14), 36.4 (*C*-2) and 17.6 ppm (*C*-17);

FT-IR ν_{max} (thin film): 3435, 2952, 2360, 1717, 1645, 1439, 1379, 1267, 1195, 1127, 1068, 957, 895 and 820 cm^{-1};

HRMS (ESI^+): Calc. for $C_{14}H_{24}O_5{}^{23}Na^+$ $[M+Na]^+$ 295.1516; found 295.1513 (Δ –1.19 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +33.0 (c = 0.64, CH_2Cl_2).

Methyl 2-((2*R*,4*R*,6*S*)-6-methoxy-4-(prop-1-en-2-yl)tetrahydro-2*H*-pyran-2-yl)acrylate (182)



178 **182** *epi*-**182**

To a solution of HFIP ester **178** (319 mg, 781 µmol, 1.0 eq) in MeOH (4.0 mL, 0.20 M) at 0 °C was added Et_3N (0.32 mL, 2.3 mmol, 3.0 eq). The resulting mixture was warmed to 25 °C (oil bath) and stirred for 14 h. After which, the reaction was quenched with Dowex 50WX8 (washed with MeOH, 1 M HCl and MeOH, 0.5 g). The mixture was stirred,

filtered, and washed with EtOAc (50 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, pentane:Et_2O = 70:30) to afford an inseparable anomeric mixture of **182** and *epi*-**182** (168 mg, 90%, **182**:*epi*-**182** = 60:40 dr determined at *H*-3) as a pale oil. The diastereomers were assigned by their coupling constant at *H*-3.

^{1}H NMR (**182**, 400 MHz, $CDCl_3$) δ = 6.35–6.26 (m, 1H, *H*-12'a), 6.02 (t, *J* = 1.5 Hz, 1H, *H*-12'b), 4.77–4.66 (m, 2H, 2 × *H*-16), 4.47 (dd, *J* = 9.6, 2.1 Hz, 1H, *H*-3), 4.40–4.28 (m, 1H, *H*-13), 3.77 (s, 3H, $CO_2C\underline{H}_3$), 3.51 (s, 3H, $OC\underline{H}_3$), 2.32 (ddd, *J* = 12.4, 8.7, 3.6 Hz, 1H, *H*-1), 2.04–1.87 (m, 2H, *H*-2a, *H*-14a), 1.71 (q, *J* = 1.1 Hz, 3H, 3 × *H*-17), 1.45–1.29 (m, 1H, *H*-2b) and 1.09 ppm (td, *J* = 12.5, 11.0 Hz, 1H, *H*-14b);

^{13}C NMR (**182**, 101 MHz, $CDCl_3$) δ = 166.5 (*C*-20), 147.6 (*C*-15), 140.9 (*C*-12), 125.1 (*C*-12'), 109.8 (*C*-16), 103.5 (*C*-3), 66.6 (*C*-13), 56.4 ($O\underline{C}H_3$), 52.0 ($CO_2\underline{C}H_3$), 41.5 (*C*-1), 36.5 (*C*-14), 36.1 (*C*-2) and 20.7 ppm (*C*-17);

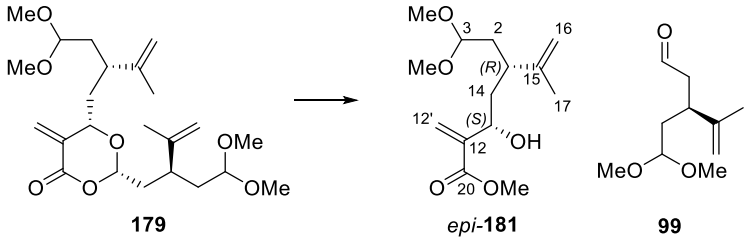
^{1}H NMR (*epi*-**182**, selected signals, 400 MHz, $CDCl_3$) δ = 5.94 (t, *J* = 1.5 Hz, 1H, *H*-12'b), 4.90 (d, *J* = 3.4 Hz, 1H, *H*-3), 4.77–4.66 (m, 3H, *H*-13, 2 × *H*-16), 3.77 (s, 3H, $CO_2C\underline{H}_3$), 3.38 (s, 3H, $OC\underline{H}_3$), 2.70–2.56 (m, 1H, *H*-1), 1.87–1.78 (m, 1H, *H*-2a), 1.71 (q, *J* = 1.1 Hz, 3H, 3 × *H*-17), 1.55 (td, *J* = 13.0, 3.5 Hz, 1H, *H*-2b) and 1.22 ppm (td, *J* = 12.5, 11.3 Hz, 1H, *H*-14b);

^{13}C NMR (*epi*-**182**, 101 MHz, $CDCl_3$) δ = 166.7 (*C*-20), 148.6 (*C*-15), 141.7 (*C*-12), 125.0 (*C*-12'), 109.3 (*C*-16), 99.1 (*C*-3), 72.7 (*C*-13), 54.9 ($O\underline{C}H_3$), 52.0 ($CO_2\underline{C}H_3$), 36.6 (*C*-1), 36.4 (*C*-14), 34.9 (*C*-2) and 20.8 ppm (*C*-17);

FT-IR ν_{max} (thin film): 2953, 2161, 1719, 1645, 1440, 1377, 1356, 1296, 1275, 1202, 1176, 1145, 1126, 1095, 1069, 1052, 964, 889, 819 and 679 cm^{-1};

HRMS (ESI^+): Calc. for $C_{13}H_{20}O_4{}^{23}Na^+$ $[M+Na]^+$ 263.1254; found 263.1254 (Δ 0.06 ppm);

Methyl (3*S*,5*R*)-5-(2,2-dimethoxyethyl)-3-hydroxy-6-methyl-2-methylenehept-6-enoate (*epi*-181)



To a solution of dioxanone **179** (53.4 mg, 135 µmol, 1.0 eq) in MeOH (1.0 mL, 0.14 M) was added Et_3N (0.05 mL, 1 mmol, 9 eq). The resulting mixture was warmed to 25 °C and stirred for 16 h. After which, the reaction was quenched with HCl (1.0 M, aq., 1.0 mL), diluted with brine (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with $NaHCO_3$ (sat., aq., 1 mL) and brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 70:30 to 50:50) to afford aldehyde **99** as a colourless film (10.4 mg, 45%) and ester *epi*-**181** as a colourless oil (26.7 mg, 79%, 95:5 dr determined at *H*-12'b).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.23 (d, *J* = 1.2 Hz, 1H, *H*-12'a), 5.80 (t, *J* = 1.1 Hz, 1H, *H*-12'b), 4.81 (dd, *J* = 2.2, 1.4 Hz, 1H, *H*-16a), 4.78 (dt, *J* = 2.2, 0.8 Hz, 1H, *H*-16b), 4.36 (q, *J* = 6.5, 6.3 Hz, 1H, *H*-13), 4.31 (dd, *J* = 7.6, 4.0 Hz, 1H, *H*-3), 3.77 (s, 3H, $CO_2C\underline{H}_3$), 3.31 (s, 3H, $OC\underline{H}_3$), 3.28 (s, 3H, $OC\underline{H}_3$), 2.89 (d, *J* = 6.8 Hz, 1H, O*H*-13), 2.34 (tt, *J* = 9.2, 5.6 Hz, 1H, *H*-1), 1.81–1.65 (m, 6H, *H*-2a, 2 × *H*-14, 3 × *H*-17) and 1.61 ppm (ddd, *J* = 13.8, 9.7, 4.0 Hz, 1H, *H*-2b);

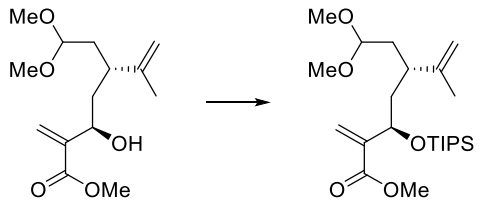
^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.0 (*C*-20), 147.2 (*C*-15), 141.7 (*C*-12), 125.9 (*C*-12'), 112.8 (*C*-16), 103.1 (*C*-3), 70.7 (*C*-13), 53.3 ($O\underline{C}H_3$), 52.7 ($O\underline{C}H_3$), 52.0 ($CO_2\underline{C}H_3$), 40.5 (*C*-1), 40.0 (*C*-14), 35.9 (*C*-2) and 18.4 ppm (*C*-17);

FT-IR ν_{max} (thin film): 3434, 2950, 2832, 2360, 1718, 1645, 1439, 1378, 1289, 1194, 1149, 1126, 1074, 957, 894 and 820 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{14}H_{24}O_5{}^{23}Na^+$ [M+Na]$^+$ 295.1516; found 295.1516 (Δ 0.16 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –38.0 (c = 0.93, CH_2Cl_2).

Methyl (3*R*,5*R*)-5-(2,2-dimethoxyethyl)-6-methyl-2-methylene-3-((triisopropylsilyl)oxy) hept-6-enoate (186)



181 **186**

To a solution of alcohol **181** (60.8 mg, 223 µmol, 1.0 eq) in CH_2Cl_2 (1.1 mL, 0.20 M) at –40 °C (MeCN/dry ice) was added collidine (0.06 mL, 0.4 mmol, 2 eq) and TIPSOTf (0.09 mL, 0.3 mmol, 2 eq). After 1.5 h, a further portion of collidine (0.06 mL, 0.4 mmol, 2 eq) and TIPSOTf (0.09 mL, 0.3 mmol, 2 eq) was added and the mixture was gradually warmed to rt over the course of 16 h. The reaction was quenched with H_2O (1.0 mL) and extracted with CH_2Cl_2 (3 × 1.0 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 100:0 to 90:10) to afford an inseparable mixture (94.8 mg) of silyl ether **186** (88 wt% by ^{1}H NMR, 86% calc. yield), cyclic acetal **182** (7 wt% by ^{1}H NMR, 12% calc. yield) and TIPSOH (5 wt%) as a colourless syrup.

Silyl ether **186**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.26 (d, *J* = 1.7 Hz, 1H, *H*-12'a), 5.96 (s, 1H, *H*-12'b), 4.80 (dd, *J* = 2.4, 1.4 Hz, 1H, *H*-16a), 4.77 (d, *J* = 2.3 Hz, 1H, *H*-16b), 4.70 (ddd, *J* = 7.1, 4.0, 1.1 Hz, 1H, *H*-13), 4.29 (dd, *J* = 7.3, 4.3 Hz, 1H, *H*-3), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.27 (s, 6H, 2 × $OC\underline{H}_3$), 2.48 (tt, *J* = 9.6, 5.0 Hz, 1H, *H*-1), 1.75 (td, *J* = 9.5, 4.7 Hz, 1H, *H*-14a), 1.65 (t, *J* = 1.0 Hz, 3H, 3 × *H*-17), 1.63–1.48 (m, 3H, *H*-2, 14b) and 1.04 ppm (br. s, 21H, $Si(CH(C\underline{H}_3)_2)_3{}^{TIPS}$, $Si(C\underline{H}(CH_3)_2)_3{}^{TIPS}$);

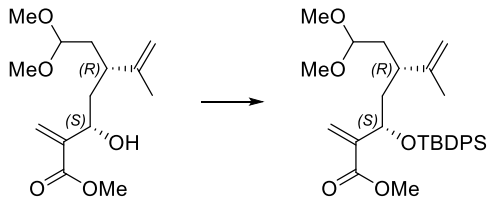
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.9 (*C*-20), 146.7 (*C*-12/*C*-15), 144.9 (*C*-15/*C*-12), 125.2 (*C*-12'), 112.9 (*C*-16), 103.2 (*C*-3), 69.3 (*C*-13), 53.0 (O*C*H$_3$), 52.6 (O*C*H$_3$), 51.9 (CO_2*C*H$_3$), 43.0 (*C*-14), 39.3 (*C*-1), 36.7 (*C*-2), 18.3 (Si(CH(*C*H$_3$)(CH$_3$))$_3^{TIPS}$), 18.3 (Si(CH(CH$_3$)(*C*H$_3$))$_3^{TIPS}$), 18.1 (*C*-17) and 12.9 ppm (Si(*C*H(CH$_3$)$_2$)$_3^{TIPS}$);

FT-IR ν_{max} (thin film): 2946, 2867, 2160, 2042, 1720, 1644, 1463, 1439, 1381, 1277, 1192, 1127, 1100, 1066, 1014, 954, 919, 884, 820, 681 and 614 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{23}H_{44}O_5Si^{23}Na^+$ $[M+Na]^+$ 451.2850; found 451.2846 (Δ –0.85 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +26.1 (c = 0.95, CH_2Cl_2).

Methyl (3*S*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-(2,2-dimethoxyethyl)-6-methyl-2-methylenehept-6-enoate (*epi*-187)



epi-**181** *epi*-**187**

To a solution of alcohol *epi*-**181** (402 mg, 1.48 mmol, 1.0 eq) in CH_2Cl_2 (5.0 mL, 0.30 M) was added imidazole (204 mg, 2.95 mmol, 2.0 eq) and TBDPSCl (0.58 mL, 2.2 mmol, 1.5 eq). The resulting mixture was stirred for 16 h. After which, the reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 95:5) to afford silyl ether *epi*-**187** (674 mg, 89%, 92:8 dr determined at *H*-12'b) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72–7.66 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.64–7.56 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.48–7.29 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.14 (d, *J* = 1.5 Hz, 1H, *H*-12'a), 5.71 (t, *J* = 1.2 Hz, 1H, *H*-12'b), 4.58 (dt, *J* = 2.9, 1.5 Hz, 1H, *H*-16a), 4.52 (ddd, *J* = 7.9, 4.9, 0.8 Hz,

1H, *H*-13), 4.49–4.46 (m, 1H, *H*-16b), 4.19 (dd, *J* = 7.4, 4.2 Hz, 1H, *H*-3), 3.64 (s, 3H, $CO_2C\underline{H}_3$), 3.23 (s, 3H, $OC\underline{H}_3$), 3.22 (s, 3H, $OC\underline{H}_3$), 2.23–2.11 (m, 1H, *H*-1), 1.79 (ddd, *J* = 13.8, 7.8, 5.1 Hz, 1H, *H*-14a), 1.74–1.63 (m, 1H, *H*-14b), 1.59 (ddd, *J* = 14.0, 7.4, 5.3 Hz, 1H, *H*-2a), 1.44 (ddd, *J* = 14.0, 9.8, 4.2 Hz, 1H, *H*-2b), 1.36–1.30 (m, 3H, 3 × *H*-17) and 1.05 ppm (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$);

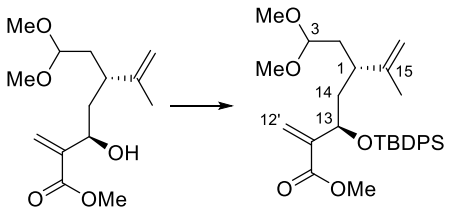
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.6 (*C*-20), 146.4 (*C*-15), 142.2 (*C*-12), 136.0 (2 × $Ar\underline{C}^{TBDPS}$), 135.9 (2 × $Ar\underline{C}^{TBDPS}$), 133.9 ($Ar\underline{C}^{TBDPS}$), 133.7 ($Ar\underline{C}^{TBDPS}$), 129.7 ($Ar\underline{C}^{TBDPS}$), 129.6 ($Ar\underline{C}^{TBDPS}$), 127.5 (2 × $Ar\underline{C}^{TBDPS}$), 127.4 (2 × $Ar\underline{C}^{TBDPS}$), 126.3 (*C*-12'), 112.1 (*C*-16), 102.8 (*C*-3), 70.9 (*C*-13), 52.8 ($O\underline{C}H_3$), 52.4 ($O\underline{C}H_3$), 51.5 ($CO_2\underline{C}H_3$), 40.3 (*C*-14), 38.9 (*C*-1), 36.5 (*C*-2), 27.0 ($C(\underline{C}H_3)_3^{TBDPS}$), 19.3 ($\underline{C}(CH_3)_3^{TBDPS}$) and 18.1 ppm (*C*-17);

FT-IR ν_{max} (thin film): 3071, 2950, 2858, 2160, 2030, 1722, 1645, 1428, 1389, 1288, 1194, 1127, 1105, 1083, 999, 956, 893, 852, 821, 741 and 703 cm^{-1};

HRMS (ESI^+): Calc. for $C_{30}H_{42}O_5Si^{23}Na^+$ $[M+Na]^+$ 533.2694; found 533.2693 (Δ –0.04 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –16.7 (c = 1.00, CH_2Cl_2).

Methyl (3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-(2,2-dimethoxyethyl)-6-methyl-2-methylenehept-6-enoate (187)



181 **187**

To a solution of alcohol **181** (320 mg, 1.17 mmol, 1.0 eq) in CH_2Cl_2 (4.0 mL, 0.29 M) was added imidazole (163 mg, 2.39 mmol, 2.0 eq) and TBDPSCl (0.46 mL, 1.8 mmol, 1.5 eq). The resulting mixture was stirred for 15 h. After which, the reaction mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The

resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 95:5) to afford silyl ether **187** (564mg, 93%, 97:3 dr determined at *H*-12'b) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70–7.66 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.62–7.57 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.45–7.30 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.13 (d, *J* = 1.5 Hz, 1H, *H*-12'a), 5.82 (t, *J* = 1.3, 1.3 Hz, 1H, *H*-12'b), 4.65–4.58 (m, 2H, *H*-13, *H*-16a), 4.38 (d, *J* = 2.2 Hz, 1H, *H*-16b), 4.20 (dd, *J* = 7.5, 4.1 Hz, 1H, *H*-3), 3.60 (s, 3H, CO_2CH_3), 3.24 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 2.42–2.33 (m, 1H, *H*-1), 1.72–1.59 (m, 2H, 2 × *H*-2), 1.55–1.46 (m, 4H, *H*-14a, 3 × *H*-17), 1.42 (ddd, *J* = 13.9, 9.8, 4.1 Hz, 1H, *H*-14b) and 1.05 ppm (s, 9H, $C(CH_3)_3$^{TBDPS});

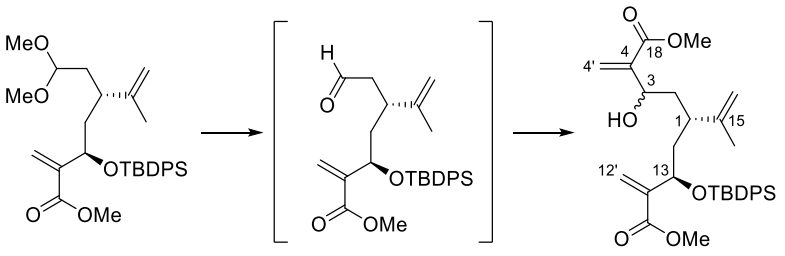
^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.4 (*C*-20), 146.2 (*C*-15), 143.5 (*C*-12), 136.1 (4 × Ar*C*^{TBDPS}), 134.0 (Ar*C*^{TBDPS}), 133.7 (Ar*C*^{TBDPS}), 129.5 (Ar*C*^{TBDPS}), 129.5 (Ar*C*^{TBDPS}), 127.4 (2 × Ar*C*^{TBDPS}), 127.4 (2 × Ar*C*^{TBDPS}), 125.9 (*C*-12'), 112.6 (*C*-16), 103.0 (*C*-3), 70.3 (*C*-13), 52.7 (OCH_3), 52.6 (OCH_3), 51.5 (CO_2CH_3), 42.1 (*C*-2), 39.1 (*C*-1), 36.3 (*C*-14), 27.1 ($C(CH_3)_3$^{TBDPS}), 19.4 ($C(CH_3)_3$^{TBDPS}) and 17.9 ppm (*C*-17);

FT-IR ν_{max} (thin film): 2953, 2858, 2360, 1721, 1646, 1429, 1389, 1271, 1191, 1126, 1105, 999, 955, 821, 741, 703 and 611 cm^{-1};

HRMS (ESI^+): Calc. for $C_{30}H_{42}O_5{}^{23}NaSi^+$ $[M+Na]^+$ 533.2694; found 533.2686 (Δ –1.42 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +1.6 (c = 0.58, CH_2Cl_2).

Dimethyl (3*R*,5*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-7-hydroxfy-2,8-dimethylene-5-(prop-1-en-2-yl)nonanedioate (189)



187 **188** **189**

To a solution of acetal **187** (545 mg, 1.07 mmol, 1.0 eq) in acetone (8.0 mL, 0.11 M final concentration) was added a solution of TsOH · H_2O (55.4 mg, 292 µmol, 27 mol%) in H_2O (2.0 mL). The resulting mixture was heated to 50 °C for 4 h. After which, the reaction was quenched with $NaHCO_3$ (sat., aq., 10 mL), diluted with brine (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford crude aldehyde **188** (463 mg, 93%) as pale oil. A solution of HMPA (1.75 mL, 10.1 mmol, 11 eq) in THF (3.0 mL, 0.10 M final concentration) was cooled to 0 °C and DIBAL-H (1.0 M in PhMe, 3.5 mL, 3.5 mmol, 3.8 eq) was added dropwise *via* syringe pump (25 mL/h). The resulting solution was stirred for 1.5 h and a separately prepared solution of methyl propiolate (0.37 mL, 4.0 mmol, 4.0 eq) in THF (0.50 mL + 2 × 0.25 mL rinse) was added dropwise. After an additional 1.5 h, a solution of crude aldehyde **25a** (429 mg, 923 µmol, 1.0 eq) in THF (0.50 mL + 2 × 0.25 mL rinse) was added dropwise and the mixture was heated to 45 °C for 2 h. After which, the reaction was cooled to 0 °C, quenched with Rochelle's salt (sat., aq., 2 mL), warmed to rt, vigorously stirred (600 rpm) for 15 min, diluted with brine (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (2 × 30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was re-dissolved in Et_2O (30 mL), washed with brine (3 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 75:25 to 65:35) to afford a diastereomeric mixture of alcohol **189** (322 mg, 59% over two steps, 56:44 dr determined at *H*-12'b) as a yellow oil. For spectroscopic reasons, an analytical sample was purified by flash column chromatography in order to partially separate the two diastereomers.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.72–7.64 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.63–7.55 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.45–7.28 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.21 (d, *J* = 1.5 Hz, 1H, *H*-12'a),

6.19 (t, *J* = 1.0 Hz, 1H, *H*-4'a), 5.95 (d, *J* = 1.3 Hz, 1H, *H*-12'b), 5.78 (t, *J* = 1.4 Hz, 1H, *H*-4'b), 4.67 (dd, *J* = 2.3, 1.4 Hz, 1H, *H*-16a), 4.63 (t, *J* = 5.9 Hz, 1H, *H*-13), 4.42 (d, *J* = 2.3 Hz, 1H, *H*-16b), 4.21 (ddd, *J* = 8.0, 6.6, 2.4 Hz, 1H, *H*-3), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 3.63 (s, 3H, $CO_2C\underline{H}_3$), 2.40 (dtd, *J* = 10.9, 7.0, 3.9 Hz, 1H, *H*-1), 2.14 (d, *J* = 6.8 Hz, 1H, O*H*-3), 1.74–1.55 (m, 2H, 2 × *H*-14), 1.52 (dd, *J* = 1.4, 0.7 Hz, 3H, 3 × *H*-17), 1.50–1.39 (m, 2H, 2 × *H*-2) and 1.04 ppm (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 166.9 (*C*-18/*C*-20), 166.9 (*C*-18/*C*-20), 146.3 (*C*-15), 143.9 (*C*-4/*C*-12), 143.4 (*C*-4/*C*-12), 136.1 (4 × $Ar\underline{C}^{TBDPS}$), 134.1 ($Ar\underline{C}^{TBDPS}$), 133.6 ($Ar\underline{C}^{TBDPS}$), 129.7 (2 × $Ar\underline{C}^{TBDPS}$), 127.6 (2 × $Ar\underline{C}^{TBDPS}$), 127.6 (2 × $Ar\underline{C}^{TBDPS}$), 126.1 (*C*-12'), 124.4 (*C*-4'), 113.1 (*C*-16), 70.0 (*C*-13), 68.7 (*C*-3), 51.8 ($CO_2\underline{C}H_3$), 51.8 ($CO_2\underline{C}H_3$), 43.1 (*C*-14), 39.8 (*C*-2), 39.8 (*C*-1), 27.2 ($\underline{C}(CH_3)_3^{TBDPS}$), 19.4 ($C(\underline{C}H_3)_3^{TBDPS}$) and 17.7 ppm (*C*-17);

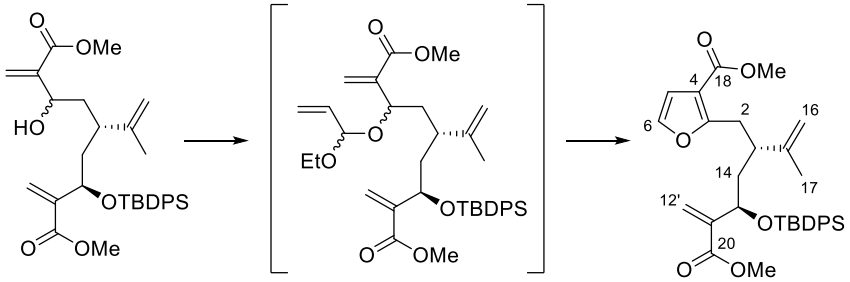
^{1}H NMR (minor diastereomer, 400 MHz, $CDCl_3$) δ = 7.72–7.63 (m, 2H, 2 × $Ar\underline{H}^{TBDPS}$), 7.63–7.54 (m, 2H, 2 × $Ar\underline{H}^{TBDPS}$), 7.47–7.29 (m, 6H, 6 × $Ar\underline{H}^{TBDPS}$), 6.18 (d, *J* = 1.3 Hz, 1H, *H*-12'a), 6.14 (d, *J* = 1.4 Hz, 1H, *H*-4'a), 5.85 (d, *J* = 1.2 Hz, 1H, *H*-4'b), 5.71 (d, *J* = 1.2 Hz, 1H, *H*-12'b), 4.69–4.55 (m, 2H, *H*-13, *H*-16'), 4.33 (d, *J* = 2.1 Hz, 1H, *H*-16''), 4.22 (q, *J* = 6.7 Hz, 1H, *H*-3), 3.76 (s, 3H, $CO_2C\underline{H}_3$), 3.62 (s, 3H, $CO_2C\underline{H}_3$), 2.75 (d, *J* = 7.1 Hz, 1H, O*H*-3), 2.26 (qd, *J* = 8.2, 6.0 Hz, 1H, *H*-1), 1.70–1.62 (m, 2H, 2 × *H*-14), 1.57–1.47 (m, 5H, 2 × *H*-2, 3 × *H*-17) and 1.04 ppm (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$);

^{13}C NMR (minor diastereomer 101 MHz, $CDCl_3$) δ = 166.9 (*C*-18), 166.5 (*C*-20), 147.3 (*C*-15), 143.6 (*C*-4), 141.5 (*C*-12), 136.1 (4 × $Ar\underline{C}^{TBDPS}$), 134.1 ($Ar\underline{C}^{TBDPS}$), 133.7 ($Ar\underline{C}^{TBDPS}$), 129.7 ($Ar\underline{C}^{TBDPS}$), 129.7 ($Ar\underline{C}^{TBDPS}$), 127.6 (2 × $Ar\underline{C}^{TBDPS}$), 127.5 (2 × $Ar\underline{C}^{TBDPS}$), 125.9 (*C*-4'), 125.8 (*C*-12'), 112.8 (*C*-16), 70.9 (*C*-3), 70.3 (*C*-13), 51.9 ($CO_2\underline{C}H_3$), 51.7 ($CO_2\underline{C}H_3$), 42.0 (*C*-14), 40.4 (*C*-1), 40.3 (*C*-2), 27.2 ($\underline{C}(CH_3)_3^{TBDPS}$), 19.5 ($C(\underline{C}H_3)_3^{TBDPS}$) and 18.2 ppm (*C*-17);

FT-IR ν_{max} (thin film): 2952, 2858, 1718, 1630, 1438, 1390, 1270, 1195, 1147, 1093, 999, 958, 820, 741, 703 and 611 cm^{-1};

HRMS (ESI^+): Calc. for $C_{32}H_{42}O_6{}^{23}NaSi^+$ $[M+Na]^+$ 573.2643; found 573.2639 (Δ –0.75 ppm).

Methyl 2-((2*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-5-(methoxycarbonyl)-2-(prop-1-en-2-yl)hex-5-en-1-yl)furan-3-carboxylate (191)



To a solution of alcohol **189** (274 mg, 497 µmol, 56:44 dr, 1.0 eq) in acrolein diethyl acetal (0.60 mL, 4.0 mmol, 8.0 eq) was added PPTS (13.3 mg, 52.9 µmol, 11 mol%). The reaction vessel was placed on a rotary evaporator and the pressure was gradually lowered to 60 mbar at 40 °C. After 2 h, the vessel was removed from the rotary evaporator. The reaction was quenched by addition of $NaHCO_3$ (sat., aq., 10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 80:20) to afford mixed acetal **190** (279 mg, 88%, mixture of 4 diastereoisomers) as a yellow oil. To a solution of mixed acetal **190** (203 mg, 320 µmol, 1.0 eq) in CH_2Cl_2 (degassed, 6.5 mL, 50 mM) was was added metathesis catalyst Zhan1B (12.2 mg, 16.6 µmol, 5.2 mol%) and the resulting reaction mixture heated to 38 °C for 18 h. After which, Zhan1B (10.4 mg, 14.2 µmol, 4.5 mol%) was added and the reaction was stirred for an additional 22 h, before being cooled to rt. PPTS (78.9 mg, 315 µmol, 1.0 eq) was then added and the resulting mixture was heated to 40 °C for 3 h. After which, the reaction was quenched with $NaHCO_3$ (sat., aq., 10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4

and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 70:30) to afford alcohol **189** as a colourless oil (rsm, 47.8 mg, 27%, 80:20 dr determined at *H*-12'b) and desired furan **191** (122 mg, 60% over two steps) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.69–7.61 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.60–7.55 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.44–7.28 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 7.20 (d, *J* = 2.0 Hz, 1H, *H*-6), 6.60 (d, *J* = 2.0 Hz, 1H, *H*-5), 6.11 (d, *J* = 1.5 Hz, 1H, *H*-12'a), 5.81 (t, *J* = 1.3 Hz, 1H, *H*-12'b), 4.69–4.63 (m, 1H, *H*-13), 4.53 (t, *J* = 1.7 Hz, 1H, *H*-16a), 4.32 (d, *J* = 2.0 Hz, 1H, *H*-16b), 3.78 (s, 3H, *C*-20 $CO_2C\underline{H}_3$), 3.59 (s, 3H, *C*-18 $CO_2C\underline{H}_3$), 3.00 (dd, *J* = 14.3, 8.1 Hz, 1H, *H*-2a), 2.86 (dd, *J* = 14.3, 7.0 Hz, 1H, *H*-2b), 2.77 (ddq, *J* = 12.0, 7.7, 4.4, Hz, 1H, *H*-1), 1.79 (ddd, *J* = 13.7, 9.2, 4.2 Hz, 1H, *H*-14a), 1.66 (ddd, *J* = 14.3, 7.0, 4.3 Hz, 1H, *H*-14b), 1.54 (t, *J* = 1.0 Hz, 3H, 3 × *H*-17) and 1.03 ppm (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.4 (*C*-20), 164.4 (*C*-18), 161.6 (*C*-3), 146.1 (*C*-15), 143.5 (*C*-12), 140.6 (*C*-6), 136.2 (4 × Ar$\underline{C}^{TBDPS}$), 134.1 (Ar$\underline{C}^{TBDPS}$), 133.9 (Ar$\underline{C}^{TBDPS}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 127.5 (2 × Ar$\underline{C}^{TBDPS}$), 127.5 (2 × Ar$\underline{C}^{TBDPS}$), 126.1 (*C*-12'), 113.9 (*C*-4), 112.5 (*C*-16), 110.6 (*C*-5), 70.4 (*C*-13), 51.6 (*C*-20'), 51.3 (*C*-18'), 42.4 (*C*-1), 41.2 (*C*-14), 32.6 (*C*-2), 27.2 ($\underline{C}(CH_3)_3^{TBDPS}$), 19.5 ($C(\underline{C}H_3)_3^{TBDPS}$) and 18.5 ppm (*C*-17);

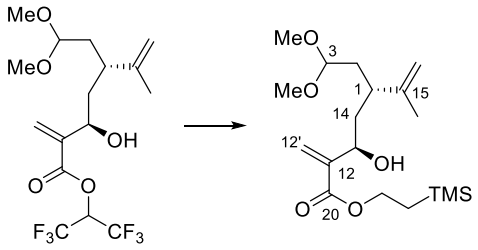
FT-IR ν_{max} (thin film): 2970, 2360, 1720, 1601, 1438, 1390, 1198, 968, 740 and 703 cm^{-1};

HRMS (ESI^+): Calc. for $C_{33}H_{40}O_6{}^{23}NaSi^+$ $[M+Na]^+$ 583.2486; found 583.2475 (Δ –1.95 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –3.8 (c = 0.69, CH_2Cl_2).

6.1.5 Synthesis of furan fragment 193

2-(trimethylsilyl)Ethyl (3*R*,5*R*)-5-(2,2-dimethoxyethyl)-3-hydroxy-6-methyl-2-methylenehept-6-enoate (183)



178 **183**

A solution of HFIP ester **178** (16.4 g, 40.2 mmol, 1.0 eq) in 2-(trimethylsilyl)ethanol (23.8 g, 201 mmol, 5.0 eq) was treated with Et_3N (17 mL, 0.12 mol, 3.0 eq) and heated to 40 °C for 6 days. The reaction mixture was diluted with PhMe (500 mL), washed with a mixture of HCl (3 M, aq., 50 mL) and brine (50 mL), $NaHCO_3$ (sat., aq., 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* (2 h) to give crude ester **183** (16.8 g, 82 wt% purity by ^{1}H NMR, 96% calculated yield) as a colourless oil. The material was used in the next step without any further purification. For spectroscopic reasons an analytical sample was purified by flash column chromatography (SiO_2, pentane: CH_2Cl_2 = 50:50 to CH_2Cl_2:acetone = 100:0 to 98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.19 (dd, *J* = 1.3, 0.7 Hz, 1H, *H*-12'a), 5.81 (t, *J* = 1.3 Hz, 1H, *H*-12'b), 4.88–4.85 (m, 2H, 2 × *H*-16), 4.40–4.30 (m, 2H, *H*-3, *H*-13), 4.30–4.22 (m, 2H, $Si(CH_2)(C\underline{H}_2)O^{TMSE}$), 3.32 (s, 3H, $OC\underline{H}_3$), 3.29 (s, 3H, $OC\underline{H}_3$), 2.70–2.55 (m, 1H, *H*-1), 2.39 (d, *J* = 6.3 Hz, 1H, O*H*-13), 1.76–1.62 (m, 6H, 2 × *H*-2, *H*-14a, 3 × *H*-17), 1.55 (ddd, *J* = 14.1, 10.0, 4.2 Hz, 1H, *H*-14b), 1.11–0.98 (m, 2H, $Si(C\underline{H}_2)(CH_2)O^{TMSE}$) and 0.05 ppm (s, 9H, $Si(C\underline{H}_3)_3^{TMSE}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.8 (*C*-20), 146.3 (*C*-15), 143.7 (*C*-12), 124.2 (*C*-12'), 113.4 (*C*-16), 103.3 (*C*-3), 69.2 (*C*-13), 63.2 ($Si(CH_2)(\underline{C}H_2)O^{TMSE}$), 53.2 ($O\underline{C}H_3$), 52.8 ($O\underline{C}H_3$),

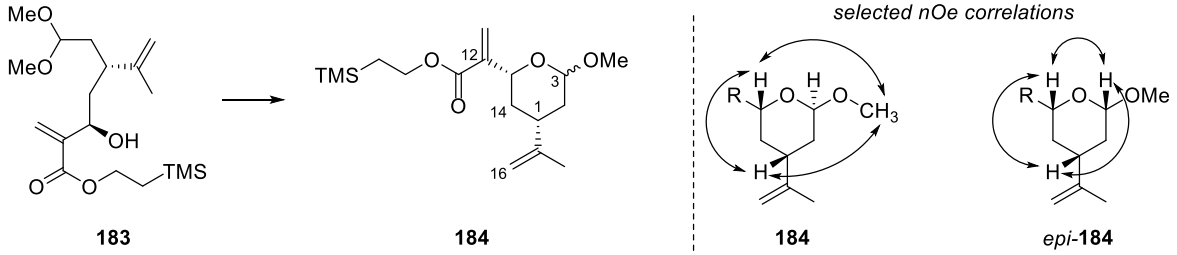
40.3 (*C*-14), 40.1 (*C*-1), 36.7 (*C*-2), 18.0 (*C*-17), 17.5 (Si(<u>*C*</u>H_2)(CH_2)O^{TMSE}) and –1.3 ppm (Si(<u>*C*</u>H_3)$_3{}^{TMSE}$);

FT-IR ν_{max} (thin film): 3459, 2953, 2361, 1712, 1645, 1381, 1251, 951, 894 and 694 cm^{-1};

HRMS (ESI^+): Calc. for $C_{18}H_{34}O_5{}^{23}NaSi^+$ $[M+Na]^+$ 381.2068; found 381.2061 (Δ –1.80 ppm);

Specific Rotation: $[\alpha]_D^{25}$ 23.9 (c = 0.63, CH_2Cl_2).

2-(trimethylsilyl)Ethyl 2-((2*R*,4*R*)-6-methoxy-4-(prop-1-en-2-yl)tetrahydro-2*H*-pyran-2-yl)acrylate (184)



183 **184** **184** *epi*-**184**

To a solution of acetal **183** (45.2 mg, 126 µmol, 1.0 eq) in MeOH (1.25 mL, 0.10 M final concentration) was added Dowex 50WX8 acidic ion exchange resin (90 mg, washed with MeOH, 3 M HCl, H_2O and MeOH). The resulting mixture was agitated at 25 °C for 16 h and filtered. The filter cake was washed with MeOH (15 mL) and the filtrate concentrated *in vacuo*. The resulting residue was analysed by ^1H NMR in $CDCl_3$ (**184**:*epi*-**184** = 56:44 dr determined at *H*-12'b) and purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 98:2) to afford acetal **184** as a colourless oil (15.3 mg, 37%) and acetal *epi*-**184** (14.1 mg, 34%) as a pale oil. The relative stereochemistry was confirmed by nOe analysis.

Acetal **184**:

^1H NMR (500 MHz, $CDCl_3$) δ = 6.26 (dd, *J* = 1.6, 0.8 Hz, 1H, *H*-12'a), 5.91 (t, *J* = 1.5 Hz, 1H, *H*-12'b), 4.90 (dd, *J* = 3.2, 1.2 Hz, 1H, *H*-3), 4.75–4.65 (m, 3H, *H*-13, 2 × *H*-16), 4.32–4.23 (m, 2H, Si(CH_2)(C<u>*H*</u>$_2$)O^{TMSE}), 3.38 (s, 3H, OC<u>*H*</u>$_3$), 2.62 (tt, *J* = 12.5, 3.6 Hz, 1H, *H*-1), 2.02–1.94 (m, 1H, *H*-14a), 1.83 (ddt, *J* = 13.2, 3.6, 1.7 Hz, 1H, *H*-2a), 1.71 (dd, *J* = 1.4, 0.8 Hz, 3H,

3 × *H*-17), 1.55 (td, *J* = 13.0, 3.5 Hz, 1H, *H*-2b), 1.21 (td, *J* = 12.5, 11.4 Hz, 1H, *H*-14b), 1.09–1.01 (m, 2H, Si(C*H*$_2$)(CH$_2$)O^{TMSE}) and 0.05 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMSE}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.4 (*C*-20), 148.6 (*C*-15), 142.2 (*C*-12), 124.5 (*C*-12'), 109.2 (*C*-16), 99.1 (*C*-3), 66.6 (*C*-13), 63.2 (Si(CH$_2$)(*C*H$_2$)O^{TMSE}), 54.9 (O*C*H$_3$), 36.6 (*C*-1), 36.5 (*C*-14), 34.9 (*C*-2), 20.8 (*C*-17), 17.4 (Si(*C*H$_2$)(CH$_2$)O^{TMSE}) and –1.3 ppm (Si(*C*H$_3$)$_3^{TMSE}$);

^{1}H NMR (500 MHz, CD_3CN = 1.94 ppm) δ = 6.17 (dd, *J* = 1.5, 0.8 Hz, 1H, *H*-12'a), 5.86 (t, *J* = 1.5 Hz, 1H, *H*-12'b), 4.85 (d, *J* = 3.3 Hz, 1H, *H*-3), 4.76–4.72 (m, 1H, *H*-16a), 4.70 (dt, *J* = 2.0, 1.0 Hz, 1H, *H*-16b), 4.62 (dt, *J* = 11.3, 1.7 Hz, 1H, *H*-13), 4.29–4.22 (m, 2H, Si(CH$_2$)(C*H*$_2$)O^{TMSE}), 3.31 (s, 3H, OC*H*$_3$), 2.60–2.50 (m, 1H, *H*-1), 1.94 (p, *J* = 2.5 Hz, 10H, *H*-14a), 1.77 (ddt, *J* = 13.3, 3.5, 1.7 Hz, 1H, *H*-2a), 1.71 (t, *J* = 1.1 Hz, 3H, 3 × *H*-17), 1.51 (td, *J* = 13.0, 3.5 Hz, 1H, *H*-2b), 1.21 (td, *J* = 12.5, 11.4 Hz, 1H, *H*-14b), 1.07–1.00 (m, 2H, Si(C*H*$_2$)(CH$_2$)O^{TMSE}) and 0.05 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMSE}$);

^{13}C NMR (126 MHz, CD_3CN = 1.32 ppm) δ = 167.0 (*C*-20), 149.9 (*C*-15), 143.5 (*C*-12), 124.5 (*C*-12'), 109.5 (*C*-16), 99.7 (*C*-3), 67.3 (*C*-13), 63.7 (Si(CH$_2$)(*C*H$_2$)O^{TMSE}), 55.0 (O*C*H$_3$), 37.6 (*C*-1), 37.0 (*C*-14), 35.6 (*C*-2), 20.8 (*C*-17), 17.7 (Si(*C*H$_2$)(CH$_2$)O^{TMSE}) and –1.5 ppm (Si(*C*H$_3$)$_3^{TMSE}$);

FT-IR ν_{max} (thin film): 2955, 1715, 1636, 1518, 1365, 1262, 1199, 960, 765 and 700 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{17}H_{30}O_4{}^{23}Na^{28}Si^+$ $[M+Na]^+$ 349.1806; found 349.1803 (Δ –0.92 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –54.7 (c = 1.00, CH_2Cl_2).

Acetal *epi*-184:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.22 (app. t, *J* = 1.2 Hz, 1H, *H*-12'a), 5.94 (app. t, *J* = 1.5 Hz, 1H, *H*-12'b), 4.68 (app. t, *J* = 1.6 Hz, 1H, *H*-16a), 4.65 (app. dt, *J* = 1.9, 0.9 Hz, 1H, *H*-16b), 4.42 (dd, *J* = 9.5, 2.1 Hz, 1H, *H*-3), 4.28 (app. dq, *J* = 12.0, 1.3 Hz, 1H, *H*-13), 4.24–4.17 (m, 2H, Si(CH$_2$)(C*H*$_2$)O^{TMSE}), 3.46 (s, 3H, OC*H*$_3$), 2.27 (tt, *J* = 12.4, 3.7 Hz, 1H, *H*-1), 1.94 (ddt,

J = 12.9, 3.8, 1.9 Hz, 1H, *H*-14a), 1.86 (ddt, *J* = 12.6, 3.7, 1.9 Hz, 1H, *H*-2a), 1.66 (t, *J* = 1.1 Hz, 3H, 3 × *H*-17), 1.30 (td, *J* = 12.6, 9.5 Hz, 1H, *H*-2b), 1.08–0.96 (m, 3H, *H*-14b, Si(C$\underline{H}_2$)(CH$_2$)O^{TMSE}) and 0.00 ppm (s, 9H, Si(C$\underline{H}_3$)$_3^{TMSE}$);

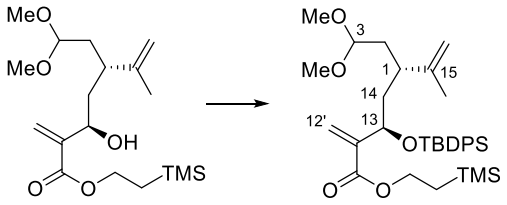
^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.5 (*C*-20), 149.0 (*C*-15), 142.7 (*C*-12), 125.9 (*C*-12'), 111.1 (*C*-16), 104.8 (*C*-3), 74.1 (*C*-13), 64.5 (Si(CH$_2$)($\underline{C}$H$_2$)O), 57.7 (O$\underline{C}$H$_3$), 42.9 (*C*-1), 37.9 (*C*-14), 37.5 (*C*-2), 22.1 (*C*-17), 18.8 (Si($\underline{C}$H$_2$)(CH$_2$)O) and 0.0 ppm (Si($\underline{C}$H$_3$)$_3$;

FT-IR ν_{max} (thin film): 2965, 1714, 1637, 1448, 1387, 1257, 1147, 1067, 953, 846, 762 and 694 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{17}H_{30}O_4{}^{23}NaSi^+$ [M+Na]$^+$ 349.1806; found 349.1806 (Δ –0.04 ppm);

Specific Rotation: $[\alpha]_D^{25}$ 58.4 (c = 1.00, CH_2Cl_2).

2-(trimethylsilyl)Ethyl (3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-(2,2-dimethoxyethyl)-6-methyl-2-methylenehept-6-enoate (196)



183 **196**

Note: Starting material (16.8 g) was contaminated with 2-(trimethylsilyl)ethanol (12 wt%, 16.7 mmol, 0.30 eq). This was considered w.r.t the amount of reagents used.

To a solution of crude alcohol **183** (16.8 g, 81 wt%, 38.4 mmol, 0.70 eq) in CH_2Cl_2 (170 mL, 0.30 M) was added imidazole (8.81 mg, 129 mmol, 2.3 eq) and TBDPSCl (27 mL, 103 mmol, 1.9 eq). After 15 h, MeOH (17 mL, 420 mmol, 7.5 eq) was added and the mixture was stirred for an additional 4 h. After which, the reaction was quenched with H_2O (150 mL) and the separated aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane: CH_2Cl_2 = 50:50 to CH_2Cl_2:acetone = 100:0 to 98:2) to afford silyl ether **196** (16.9 g, 71%

over two steps) as a colourless oil. Mixed fractions of silyl ether **196** (3.87 g, 81 wt% purity by ^{1}H NMR, 6.49 mmol, 16 % calc. yield) contained TBDPSOH (19 wt% by ^{1}H NMR) and were used in the next step in a separate batch without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72–7.65 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.63–7.57 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.46–7.28 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.12 (d, *J* = 1.6 Hz, 1H, *H*-12'a), 5.81 (t, *J* = 1.2 Hz, 1H, *H*-12'b), 4.67–4.58 (m, 2H, *H*-13, *H*-16a), 4.42–4.35 (m, 1H, *H*-16b), 4.20 (dd, *J* = 7.4, 4.1 Hz, 1H, *H*-3), 4.09 (dd, *J* = 9.6, 7.7 Hz, 2H, Si(CH_2)(C*H*$_2$)O ^{TMSE}), 3.26–3.22 (m, 6H, 2 × OC*H*$_3$), 2.39 (tt, *J* = 9.7, 5.2 Hz, 1H, *H*-1), 1.65 (app. qdd, *J* = 14.2, 7.7, 4.8 Hz, 2H, 2 × *H*-14), 1.55–1.46 (m, 4H, *H*-2a, 3 × *H*-17), 1.42 (ddd, *J* = 14.0, 9.7, 4.2 Hz, 1H, *H*-2b), 1.05 (s, 9H, C(C*H*$_3$)$_3^{TBDPS}$), 0.92 (td, *J* = 7.8, 2.0 Hz, 2H, Si(C*H*$_2$)(CH_2)O ^{TMSE}) and 0.03 ppm (s, 9H, Si(C*H*$_3$)$_3$ ^{TMSE});

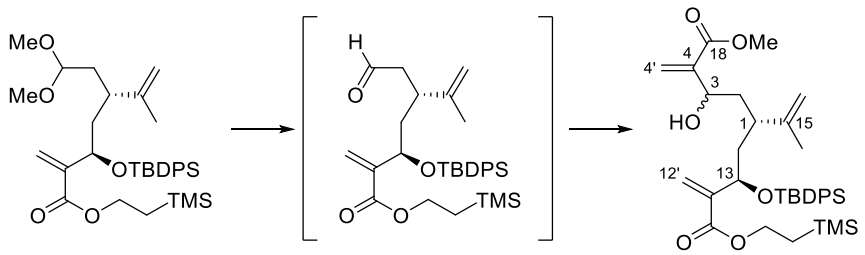
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2 (*C*-20), 146.4 (*C*-15), 144.2 (*C*-12), 136.2 (4 × Ar*C*^{TBDPS}), 134.2 (Ar*C*^{TBDPS}), 134.0 (Ar*C*^{TBDPS}), 129.7 (2 × Ar*C*^{TBDPS}), 127.5 (2 × Ar*C*^{TBDPS}), 127.5 (2 × Ar*C*^{TBDPS}), 125.5 (*C*-12'), 112.7 (*C*-16), 103.2 (*C*-3), 70.5 (*C*-13), 62.8 (Si(CH_2)(*C*H$_2$)O^{TMSE}), 52.8 (O*C*H$_3$), 52.7 (O*C*H$_3$), 42.2 (*C*-14), 39.2 (*C*-1), 36.6 (*C*-2), 27.3 (*C*(CH_3)$_3^{TBDPS}$), 19.6 (C(*C*H$_3$)$_3^{TBDPS}$), 18.2 (*C*-17), 17.4 (Si(*C*H$_2$)(CH_2)O ^{TMSE}) and -1.4 ppm (Si(*C*H$_3$)$_3$ ^{TMSE});

FT-IR ν_{max} (thin film): 2955, 2896, 2859, 2360, 2342, 1716, 1473, 1428, 1388, 1251, 1127, 1075, 953, 859, 838, 822, 741 and 702 cm^{-1};

HRMS (ESI^{+}): Calc. for $C_{34}H_{52}O_5{}^{23}NaSi_2^+$ $[M+Na]^+$ 619.3245; found 619.3247 (Δ 0.16 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +8.7 (c = 0.34, CH_2Cl_2).

9-Methyl 1-(2-(trimethylsilyl)ethyl) (3*R*,5*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-7-hydroxy-2,8-dimethylene-5-(prop-1-en-2-yl)nonanedioate (199)



196 **198** **199**

To a solution of acetal **196** (17.9 g, 30.0 mmol, 1.0 eq) in acetone (250 mL, 0.10 M final concentration) and H_2O (60 mL) was added TsOH · H_2O (1.43 g, 7.50 mmol, 25 mol%). The resulting mixture was heated to 50 °C for 20 h before the reaction was cooled to rt, quenched with $NaHCO_3$ (sat., aq., 150 mL) and diluted with brine (150 mL), Et_2O (250 mL), H_2O (50 mL) and pentane (50 mL). The separated aqueous layer was extracted with Et_2O (250 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford crude aldehyde **198** as a pale syrup (17.5 g). In a separate flask, a solution of HMPA (49 mL, 0.28 mol, 9.4 eq) in THF (100 mL, 0.10 M final concentration) was cooled to 0 °C (ice bath) and DIBAL-H (1.0 M in PhMe, 87.3 mL, 102 mmol, 3.4 eq) was added dropwise *via* cannula (25 min). The resulting solution was stirred for 1.5 h and methyl propiolate (11 mL, 120 mmol, 4.0 eq) was added dropwise. After an additional 1.5 h, a solution of crude aldehyde **198** (17.5 g, 1.0 eq) in THF (20 mL + 2 × 6.0 mL rinse) was added dropwise. The reaction mixture was heated to 45 °C for 2 h. After which, the mixture was cooled to 0 °C, quenched with Rochelle's salt (sat., aq., 60 mL), warmed to rt, diluted with Rochelle's salt (sat., aq., 240 mL) and Et_2O (200 mL). The heterogeneous mixture was vigorously stirred (800 rpm) for 16 h. The separated aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with H_2O (3 × 150 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was analysed by ^1H NMR (55:45 dr

determined at *H*-12'a) and purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 70:30) to afford a diastereomeric mixture of alcohol **199** (15.0 g, 78% two step yield, 54:46 dr) as a yellow oil. Mixed fractions were re-purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 70:30) to afford alcohol **199** (1.37 g, 7%, 70:30 dr; total 16.4 g, 85% yield) as a yellow oil. For spectroscopic reasons an analytic sample was subjected to flash column chromatography in order to partially separate the two diastereomers.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.72–7.65 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.64–7.57 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.45–7.28 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.20 (d, *J* = 1.6 Hz, 1H, *H*-12'a), 6.18 (dd, *J* = 1.4, 0.7 Hz, 1H, *H*-4'a), 5.97–5.92 (m, 1H, *H*-12'b), 5.78 (t, *J* = 1.4, 1.4 Hz, 1H, *H*-4'b), 4.69–4.60 (m, 2H, *H*-13, *H*-16a), 4.44 (d, *J* = 2.2 Hz, 1H, *H*-16b), 4.22 (dd, *J* = 9.4, 6.9 Hz, 1H, *H*-3), 4.17–4.08 (m, 2H, Si(CH_2)(C$\underline{H}_2$)O^{TMSE}), 3.74 (s, 3H, $CO_2C\underline{H}_3$), 2.40 (dtd, *J* = 10.8, 6.8, 6.8, 3.8 Hz, 1H, *H*-1), 2.13 (d, *J* = 6.8 Hz, 1H, O*H*-3), 1.74–1.55 (m, 2H, 2 × *H*-14), 1.53 (s, 3H, 3 × *H*-17), 1.44 (ddd, *J* = 13.9, 11.3, 2.6 Hz, 1H, *H*-2a), 1.29 (ddd, *J* = 14.1, 10.1, 3.8 Hz, 1H, *H*-2b), 1.05 (s, 9H, C(C$\underline{H}_3$)$_3^{TBDPS}$), 0.99–0.92 (m, 2H, Si(C$\underline{H}_2$)(CH_2)O^{TMSE}) and 0.04 ppm (d, *J* = 1.0 Hz, 9H, Si(C$\underline{H}_3$)$_3^{TMSE}$);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 166.9 (*C*-18/*C*-20), 166.6 (*C*-18/*C*-20), 146.4 (*C*-15), 144.4 (*C*-4/*C*-12), 143.5 (*C*-4/*C*-12), 136.2 (4 × Ar$\underline{C}^{TBDPS}$), 134.3 (Ar$\underline{C}^{TBDPS}$), 133.8 (Ar$\underline{C}^{TBDPS}$), 129.7 (2 × Ar$\underline{C}^{TBDPS}$), 127.6 (2 × Ar$\underline{C}^{TBDPS}$), 127.6 (2 × Ar$\underline{C}^{TBDPS}$), 125.7 (*C*-12'), 124.3 (*C*-4'), 113.0 (*C*-16), 70.0 (*C*-13), 68.8 (*C*-3), 63.0 (Si(CH_2)($\underline{C}H_2$)O^{TMSE}), 51.8 ($CO_2\underline{C}H_3$), 43.2 (*C*-14), 39.9 (*C*-2), 39.7 (*C*-1), 27.2 (C($\underline{C}H_3$)$_3^{TBDPS}$), 19.5 ($\underline{C}(CH_3)_3^{TBDPS}$), 17.8 (*C*-17), 17.4 (Si($\underline{C}H_2$)(CH_2)O^{TMSE}) and –1.3 ppm (Si($\underline{C}H_3$)$_3^{TMSE}$);

^{1}H NMR (minor diastereomer, 400 MHz, $CDCl_3$) δ = 7.72–7.64 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.63–7.56 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.45–7.29 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.18 (d, *J* = 1.4 Hz, 1H, *H*-4'a), 6.12 (d, *J* = 1.6 Hz, 1H, *H*-12'a), 5.83 (t, *J* = 1.3 Hz, 1H, *H*-12'b), 5.71 (t, *J* = 1.2 Hz, 1H,

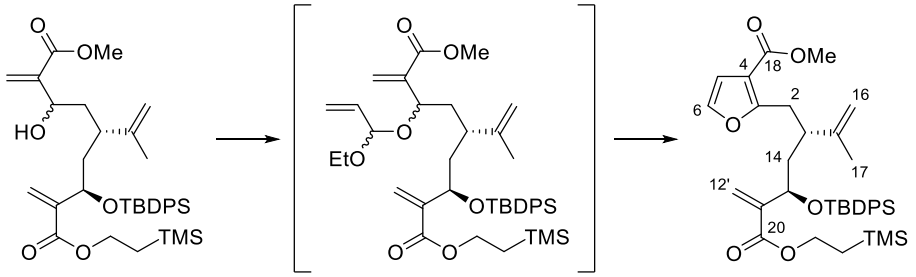
H-4'b), 4.67–4.58 (m, 2H, *H*-13, *H*-16a), 4.35 (dt, *J* = 2.2, 0.7 Hz, 1H, *H*-16b), 4.23 (q, *J* = 6.6 Hz, 1H, *H*-3), 4.16–4.07 (m, 2H, Si(CH_2)($C\underline{H}_2$)O^{TMSE}), 3.76 (s, 3H, $CO_2C\underline{H}_3$), 2.71 (d, *J* = 7.0 Hz, 1H, O*H*-13), 2.33–2.22 (m, 1H, *H*-1), 1.74–1.62 (m, 2H, 2 × *H*-14), 1.62–1.48 (m, 5H, 2 × *H*-2, 3 × *H*-17), 1.04 (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$), 0.99–0.89 (m, 2H, Si($C\underline{H}_2$)($CH_2$)$O^{TMSE}$) and 0.04 ppm (s, 9H, $Si(C\underline{H}_3)_3^{TMSE}$);

^{13}C NMR (minor diastereomer, 101 MHz, $CDCl_3$) δ = 167.0 (*C*-18/*C*-20), 166.2 (C18/*C*-20), 147.4 (*C*-15), 144.1 (*C*-4/*C*-12), 141.7 (*C*-4/*C*-12), 136.2 (4 × Ar$\underline{C}^{TBDPS}$), 134.2 (Ar$\underline{C}^{TBDPS}$), 133.8 (Ar$\underline{C}^{TBDPS}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 127.6 (2 × Ar$\underline{C}^{TBDPS}$), 127.6 (2 × Ar$\underline{C}^{TBDPS}$), 125.7 (*C*-4'), 125.5 (*C*-12'), 112.7 (*C*-16), 70.8 (*C*-3), 70.4 (*C*-13), 62.9 (Si(CH_2)($\underline{C}H_2$)O^{TMSE}), 51.9 ($CO_2\underline{C}H_3$), 42.1 (*C*-14), 40.4 (*C*-1), 40.4 (*C*-2), 27.2 ($C(\underline{C}H_3)_3^{TBDPS}$), 19.5 ($\underline{C}(CH_3)_3^{TBDPS}$), 18.3 (*C*-17), 17.4 (Si($\underline{C}H_2$)(CH_2)O^{TMSE}) and –1.4 ppm ($Si(\underline{C}H_3)_3^{TMSE}$);

FT-IR ν_{max} (thin film): 2954, 1719, 1429, 1378, 1251, 1149, 1110, 1063, 838 and 704 cm^{-1};

HRMS (ESI^+): Calc. for $C_{36}H_{52}O_6{}^{23}NaSi_2^+$ $[M+Na]^+$ 659.3195; found 659.3203 (Δ 1.29 ppm).

Methyl 2-((2*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(prop-1-en-2-yl)-5-((2-(trimethylsilyl)ethoxy)carbonyl)hex-5-en-1-yl)furan-3-carboxylate (193)



199 **200** **193**

Procedure A:

Note: For the second step general set-up A was used. Only a fraction of crude intermediate **200** was reacted in the second step.

To a solution of alcohol **199** (3.20 g, 5.02 mmol, 54:46 dr, 1.0 eq) in PhMe (6.0 mL, PhMe:acrolein diethyl acetal = 50:50) and acrolein diethyl acetal (6.0 mL, 40 mmol, 8.0 eq) was added PPTS (126 mg, 502 µmol, 10 mol%). The reaction vessel was placed on

a rotary evaporator and the pressure was slowly lowered to 80 mbar at 40 °C. After 5 h, the vessel was removed from the rotary evaporator. The reaction was diluted with EtOAc (150 mL), washed with $NaHCO_3$ (sat., aq., 50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 95:5 to 90:10) to afford mixed acetal **200** (3.00 g, 83%, mixture of 4 diastereomers) as a colourless oil. To a solution of mixed acetal **200** (1.87 g, 2.59 mmol, 1.0 eq) in PhMe (degassed, 100 mL, 26 mM) was added HGII (189 mg, 257 µmol, 10 mol%) and the reaction was heated to 40 °C under a constant flow of N_2 (general set-up A) for 27 h. After which, the reaction mixture was cooled to rt, charged with HGII (104 mg, 142 µmol, 5.4 mol%), degassed, and re-heated to 40 °C for an additional 16 h. At this point the N_2-inlet was changed to a needle and submerged into the reaction mixture in order to partial evaporate the solvent. The reaction was charged with HGII (96.2 mg, 131 µmol, 5.1 mol%) and re-heated to 60 °C for an additional 3 days. At this point the solvent level was reduced to approximately 15 mL. The reaction mixture was cooled to rt diluted with CH_2Cl_2 (50 mL), PPTS (651 mg, 2.59 mmol, 1.0 eq) was added and the resulting mixture heated to 40 °C for 3 h before being quenched with $NaHCO_3$ (sat., aq., 10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 97.5:2.5 to 90:10) to afford furan **193** (1.29 g, 63% over two steps from alcohol **199**) as a colourless oil.

Procedure B:

Alcohol **199** (9.61 g, 15.1 mmol, 54:46 dr, 1.0 eq) was converted into mixed acetal **200** (8.96 g, 82%) as described in procedure A. To a solution of mixed acetal **200** (184 mg, 250 µmol, 1.0 eq) in DCE (degassed, 10 mL, 25 mM) was added 4,6-dichloro-

1,4-benzoquinone (5.6 mg, 31.7 µmol, 13 mol%) and HGII (16.3 mg, 26.0 µmol, 10 mol%). The reaction mixture was heated to 60 °C for 16 h under a constant flow of N_2 (general set-up A). After which, the solvent was completely evaporated. The residue was cooled to rt, dissolved in CH_2Cl_2 (10 mL), PPTS (65.6 mg, 261 µmol, 1.0 eq) was added and the resulting mixture heated to 40 °C for 1.5 h. After which, the reaction was quenched with $NaHCO_3$ (sat., aq., 10 mL) and the separated aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 97.5:2.5 to 90:10) to afford furan **193** (114 mg, 63% over two steps from alcohol **199**) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.66–7.62 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.60–7.55 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.43–7.28 (m, 6H, 6 × Ar*H*^{TBDPS}), 7.20 (d, *J* = 2.0 Hz, 1H, *H*-6), 6.60 (d, *J* = 2.0 Hz, 1H, *H*-5), 6.10 (d, *J* = 1.6 Hz, 1H, *H*-12'a), 5.80 (t, *J* = 1.4 Hz, 1H, *H*-12'b), 4.68 (dd, *J* = 6.4, 4.3 Hz, 1H, *H*-13), 4.53 (p, *J* = 1.4 Hz, 1H, *H*-16a), 4.32 (d, *J* = 2.0 Hz, 1H, *H*-16b), 4.12–4.05 (m, 2H, Si(CH_2)(CH_2)O^{TMSE}), 3.78 (s, 3H, CO_2CH_3), 3.00 (dd, *J* = 14.3, 8.1 Hz, 1H, *H*-2a), 2.86 (dd, *J* = 14.3, 7.0 Hz, 1H, *H*-2b), 2.78 (qd, *J* = 8.2, 4.3 Hz, 1H, *H*-1), 1.79 (ddd, *J* = 14.3, 9.1, 4.1 Hz, 1H, *H*-14a), 1.65 (ddd, *J* = 14.2, 7.0, 4.3 Hz, 1H, *H*-14b), 1.56–1.52 (m, 3H, 3 × *H*-17), 1.03 (s, 9H, C(CH_3)$_3^{TBDPS}$), 0.95–0.87 (m, 2H, Si(CH_2)(CH_2)O^{TMSE}) and 0.03 ppm (s, 9H, Si(CH_3)$_3^{TMSE}$);

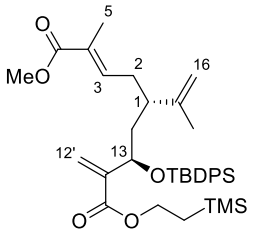
^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.1 (*C*-20), 164.4 (*C*-18), 161.7 (*C*-3), 146.1 (*C*-15), 144.0 (*C*-12), 140.6 (*C*-6), 136.2 (4 × Ar*C*^{TBDPS}), 134.1 (Ar*C*^{TBDPS}), 133.9 (Ar*C*^{TBDPS}), 129.6 (Ar*C*^{TBDPS}), 129.6 (Ar*C*^{TBDPS}), 127.5 (2 × Ar*C*^{TBDPS}), 127.5 (2 × Ar*C*^{TBDPS}), 125.7 (*C*-12'), 113.9 (*C*-4), 112.5 (*C*-16), 110.6 (*C*-5), 70.4 (*C*-13), 62.8 (Si(CH_2)(*C*H_2)O^{TMSE}), 51.3 (CO_2*C*H_3), 42.3 (*C*-1), 41.3 (*C*-14), 32.6 (*C*-2), 27.2 (C(*C*H_3)$_3^{TBDPS}$), 19.5 (*C*(CH_3)$_3^{TBDPS}$), 18.6 (*C*-17), 17.3 (Si(*C*H_2)(CH_2)O^{TMSE}) and –1.4 ppm (Si(*C*H_3)$_3^{TMSE}$);

FT-IR ν_{max} (thin film): 2953, 2360, 2341, 1719, 1303, 1251, 1198, 1152, 1090, 858, 838, 823, 739 and 702 cm^{-1};

HRMS (ESI^+): Calc. for $C_{37}H_{50}O_6{}^{23}NaSi_2^+$ $[M+Na]^+$ 669.3038; found 669.3027 (Δ –1.70 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –0.8 (c = 1.15, CH_2Cl_2).

1-Methyl 9-(2-(trimethylsilyl)ethyl) (5*S*,7*R*)-7-((*tert*-butyldiphenylsilyl)oxy)-2-methyl-8-methylene-5-(prop-1-en-2-yl)non-2-enedioate (203)



203

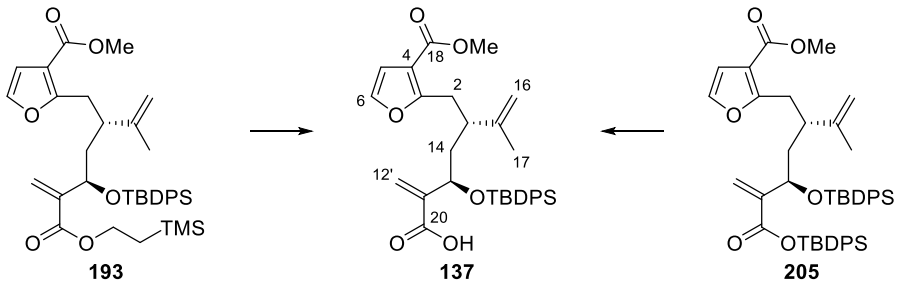
When furan **193** was synthesised from alcohol **199**, enone **203** was occasionally observed as an inseparable impurity. Attempts to separate furan **193** from **203** were unsuccessful, but **203** was identified from an obtained mixture (**193**:**203** = 45:55). The configuration of the *C*-3/*C*-4 double bond was not assigned.

^{1}H NMR (selected signals, 400 MHz, $CDCl_3$) δ = 7.71–7.66 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.62–7.58 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 6.57 (td, *J* = 7.2, 1.5 Hz, 1H, *H*-3), 6.16 (app. d, *J* = 1.6 Hz, 1H, *H*-12'a), 5.87 (app. t, *J* = 1.3 Hz, 1H, *H*-12'b), 4.64–4.60 (m, 1H, *H*-16a), 4.42 (app. dt, *J* = 2.0, 0.8 Hz, 1H, *H*-16b), 4.17–4.10 (m, 2H, Si(CH_2)(C$\underline{H}_2$)O^{TMSE}), 3.71 (s, 3H, $CO_2C\underline{H}_3$), 2.24 (ddd, *J* = 13.8, 8.1, 5.5 Hz, 1H, *H*-1), 2.15–1.93 (m, 2H, 2 × *H*-2), 1.74 (s, 3H, 3 × *H*-5), 1.48 (s, 3H, 3 × *H*-17) and 0.00 ppm (s, 9H, Si($C\underline{H}_3$)$_3{}^{TMSE}$);

^{13}C NMR (selected signals, 101 MHz, $CDCl_3$) δ = 168.7 (*C*-18), 166.2 (*C*-20), 146.2 (*C*-15), 144.2 (*C*-12), 141.1 (*C*-3), 125.6 (*C*-12'), 112.4 (*C*-16), 70.3 (*C*-13), 62.9 (Si(CH_2)($\underline{C}H_2$)O^{TMSE}), 51.8 ($CO_2\underline{C}H_3$), 42.1 (*C*-1), 33.0 (*C*-2), 18.9 (*C*-17) and 12.7 ppm (*C*-5);

HRMS (ESI^+): Calc. for $C_{36}H_{52}O_5{}^{23}NaSi_2^+$ $[M+Na]^+$ 643.3245; found 643.3240.

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((3-(methoxycarbonyl)Furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (137)



Procedure A:

To a solution of TMSE ester **193** (96.0 mg, 148 µmol, 1.0 eq) at 0 °C (ice bath) in THF (1.5 mL, 0.10 M) was added TBAF (1.0 M in THF, 0.45 mL, 0.45 mmol, 3.0 eq). After 1 h 50 min, the reaction was judged to be complete by TLC (CH_2Cl_2:acetone:AcOH = 94.5:5:0.5, vanillin stain), quenched with NH_4Cl (sat., aq., 0.5 mL), warmed to rt and extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:HCO_2H = 100:0 to 99.5:0.5) to afford carboxylic acid **137** (70.7 mg, 87%) as a colourless syrup.

Procedure B:

To a solution of bis-silyl ether **205** (50.0 mg, 63.6 µmol, 1.0 eq) in MeOH (0.64 mL, 60 mM final concentration; MeOH:THF:H_2O = 6:2:2) and THF (212 µL) was added to a solution of K_2CO_3 (8.8 mg, 64 µmol, 1.0 eq) in H_2O (212 µL; stock solution: 109 mg in 2.6 mL) at rt. After 1.5 h, the reaction mixture was diluted with brine (1 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone:HCO_2H = 100:0:0 to 98.5:1:0.5) to afford carboxylic acid **137** (37.2 mg, quant. yield) as a colourless wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.66–7.63 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.60–7.56 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.45–7.29 (m, 6H, 6 × Ar*H*^{TBDPS}), 7.16 (d, *J* = 2.0 Hz, 1H, *H*-6), 6.58 (d, *J* = 2.0 Hz, 1H, *H*-5), 6.24 (s, 1H, *H*-12'a), 5.81 (s, 1H, *H*-12'b), 4.62 (t, *J* = 5.7 Hz, 1H, *H*-13), 4.53 (t, *J* = 1.7 Hz, 1H, *H*-16a), 4.36–4.31 (m, 1H, *H*-16b), 3.77 (s, 3H, CO_2CH_3), 2.94 (dd, *J* = 14.4, 8.2 Hz, 1H, *H*-2a), 2.82 (dd, *J* = 14.4, 6.9 Hz, 1H, *H*-2b), 2.67 (qd, *J* = 8.0, 4.9 Hz, 1H, *H*-1), 1.80 (ddd, *J* = 14.0, 8.7, 5.2 Hz, 1H, *H*-14a), 1.67 (ddd, *J* = 14.2, 6.4, 4.8 Hz, 1H, *H*-14b), 1.52 (s, 3H, *H*-17) and 1.05 ppm (s, 9H, C(C*H*$_3$)$_3^{TBDPS}$); CO_2H not observed;

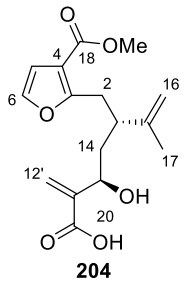
^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.0 (*C*-20), 164.4 (*C*-18), 161.4 (*C*-3), 146.0 (*C*-15), 142.1 (*C*-12), 140.7 (*C*-6), 136.1 (4 × Ar*C*^{TBDPS}), 133.5 (Ar*C*^{TBDPS}), 133.3 (Ar*C*^{TBDPS}), 129.9 (2 × Ar*C*^{TBDPS}), 128.4 (*C*-12'), 127.7 (2 × Ar*C*^{TBDPS}), 127.7 (2 × Ar*C*^{TBDPS}), 113.9 (*C*-4), 112.5 (*C*-16), 110.6 (*C*-5), 71.1 (*C*-13), 51.4 (CO_2CH_3), 42.3 (*C*-1), 40.8 (*C*-14), 32.3 (*C*-2), 27.2 (C(*C*H$_3$)$_3^{TBDPS}$), 19.5 (*C*(CH$_3$)$_3^{TBDPS}$) and 18.6 ppm (*C*-17);

FT-IR ν_{max} (thin film): 2932, 2858, 1719, 1696, 1601, 1428, 1303, 1199, 1152, 1134, 1091, 1008, 969, 895, 822, 739, 702 and 611 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{32}H_{38}O_6{}^{23}NaSi^+$ $[M+Na]^+$ 569.2330; found 569.2325 (Δ –0.88 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –5.4 (c = 2.32, CH_2Cl_2, obtained from TMSE ester **193**); $[\alpha]_D^{25}$ –5.7 (c = 1.00, CH_2Cl_2, obtained from silyl ester **205**).

(3*R*,5*R*)-3-Hydroxy-5-((3-(methoxycarbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (204)



204

For the selective deprotection of ester **193** using different batches of TBAF hydroxy acid **204** was occasionally isolated in varying quantities.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 2.0 Hz, 1H, *H*-6), 6.54 (d, *J* = 2.0 Hz, 1H, *H*-5), 6.31 (t, *J* = 0.9 Hz, 1H, *H*-12'a), 5.89 (t, *J* = 1.2 Hz, 1H, *H*-12'b), 4.73–4.67 (m, 2H, 2 × *H*-16), 4.35 (dd, *J* = 10.2, 2.7 Hz, 1H, *H*-13), 3.75 (s, 3H, $CO_2C\underline{H}_3$), 3.08 (dd, *J* = 14.2, 8.4 Hz, 1H, *H*-2a), 2.98 (dd, *J* = 14.2, 6.7 Hz, 1H, *H*-2b), 2.95–2.86 (m, 1H, *H*-1), 1.83–1.73 (m, 1H, *H*-14a), 1.65 (dd, *J* = 1.5, 0.8 Hz, 3H, 3 × *H*-17) and 1.52 ppm (ddd, *J* = 14.1, 10.1, 4.0 Hz, 1H, *H*-14b); OH and CO_2H not observed;

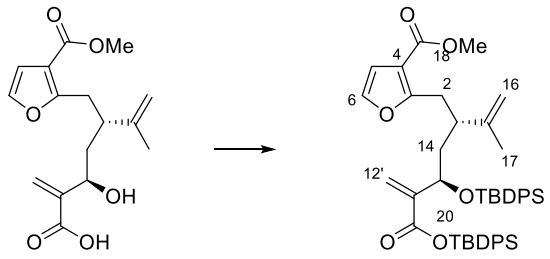
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.8 (*C*-20), 164.6 (*C*-18), 161.5 (*C*-3), 146.0 (*C*-15), 142.5 (*C*-12), 140.9 (*C*-6), 127.2 (*C*-12'), 113.9 (*C*-4), 113.4 (*C*-16), 110.7 (*C*-5), 68.9 (*C*-13), 51.5 ($CO_2\underline{C}H_3$), 43.4 (*C*-1), 39.2 (*C*-14), 32.4 (*C*-2) and 18.1 ppm (*C*-17);

FT-IR ν_{max} (thin film): 2952, 1698, 1630, 1600, 1520, 1440, 1307, 1201, 1155, 1134, 1090, 1035, 959, 895, 745 and 657 cm^{-1};

HRMS (ESI^+): Calc. for $C_{16}H_{20}O_6{}^{23}Na^+$ $[M+Na]^+$ 331.1152; found 331.1153 (Δ 0.17 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +21.5 (c = 1.00, CH_2Cl_2).

Methyl 2-((2*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-5-(((*tert*-butyldiphenylsilyl)oxy) carbonyl)-2-(prop-1-en-2-yl)hex-5-en-1-yl)furan-3-carboxylate (205)



204 **205**

To a solution of hydroxy acid **204** (47.3 mg, 153 µmol, 1.0 eq) in CH_2Cl_2 (0.50 mL, 0.31 M) was added imidazole (51.0 mg, 749 µmol, 4.9 eq) and TBDPSCl (0.16 mL, 619 µmol, 4.0 eq). After 16 h, the solvent level had lowered drastically and additional CH_2Cl_2 (0.50 mL) was added. The reaction was quenched with H_2O (1 mL) and extracted with Et_2O (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column

chromatography (SiO_2, pentane: Et_2O = 95:5 to 90:10) to afford bis-silyl ether **205** (78.0 mg, 65%) as a colourless wax. The isolation of bis-silyl ether **205** was hampered by co-elution of TBDPSOH.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68–7.56 (m, 8H, 8 × Ar$\underline{H}^{TBDPS}$), 7.46–7.24 (m, 12H, 12 × Ar$\underline{H}^{TBDPS}$), 7.11 (d, *J* = 2.0 Hz, 1H, *H*-6), 6.56 (d, *J* = 2.0 Hz, 1H, *H*-5), 6.33 (d, *J* = 1.7 Hz, 1H, *H*-12'a), 5.96 (s, 1H, *H*-12'b), 4.76 (dd, *J* = 6.4, 4.2 Hz, 1H, *H*-13), 4.48 (t, *J* = 1.8 Hz, 1H, *H*-16a), 4.30 (d, *J* = 2.0 Hz, 1H, *H*-16b), 3.75 (s, 3H, $CO_2C\underline{H}_3$), 3.06–2.94 (m, 1H, *H*-2a), 2.87–2.71 (m, 2H, *H*-1, *H*-2b), 1.89–1.77 (m, 1H, *H*-14a), 1.72–1.59 (m, 1H, *H*-14b), 1.48 (s, 3H, 3 × *H*-17) and 1.14–1.02 ppm (m, 18H, 2 × C(C$\underline{H}_3)_3^{TBDPS}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.7 (*C*-20/*C*-18), 164.4 (*C*-18/*C*-20), 161.6 (*C*-3), 146.2 (*C*-15), 144.4 (*C*-12), 140.6 (*C*-6), 136.1 (4 × Ar$\underline{C}^{TBDPS}$), 135.4 (4 × Ar$\underline{C}^{TBDPS}$), 134.0 (Ar$\underline{C}^{TBDPS}$), 134.0 (Ar$\underline{C}^{TBDPS}$), 132.0 (Ar$\underline{C}^{TBDPS}$), 132.0 (Ar$\underline{C}^{TBDPS}$), 130.1 (Ar$\underline{C}^{TBDPS}$), 130.1 (Ar$\underline{C}^{TBDPS}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 127.8 (2 × Ar$\underline{C}^{TBDPS}$), 127.8 (2 × Ar$\underline{C}^{TBDPS}$), 127.6 (4 × Ar$\underline{C}^{TBDPS}$), 127.4 (*C*-12'), 113.9 (*C*-4), 112.4 (*C*-16), 110.6 (*C*-5), 70.7 (*C*-13), 51.3 ($CO_2\underline{C}H_3$), 42.2 (*C*-1), 41.0 (*C*-14), 32.6 (*C*-2), 27.2 (C($\underline{C}H_3)_3^{TBDPS}$), 27.1 (C($\underline{C}H_3)_3^{TBDPS}$), 19.6 ($\underline{C}(CH_3)_3^{TBDPS}$), 19.4 ($\underline{C}(CH_3)_3^{TBDPS}$) and 18.6 ppm (*C*-17);

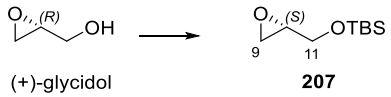
FT-IR ν_{max} (thin film): 3072, 2932, 2858, 2160, 1703, 1601, 1472, 1428, 1392, 1303, 1198, 1151, 1112, 1090, 1008, 969, 893, 822, 739, 700 and 609 cm^{-1};

HRMS (ESI^+): Calc. for $C_{48}H_{56}O_6{}^{23}NaSi_2^+$ $[M+Na]^+$ 807.3508; found 807.3499 (Δ –1.13 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –0.5 (c = 0.99, CH_2Cl_2).

6.1.6 Synthesis of vinyl iodide 81

(*S*)-*tert*-Butyldimethyl(oxiran-2-ylmethoxy)silane (207)



(+)-glycidol **207**

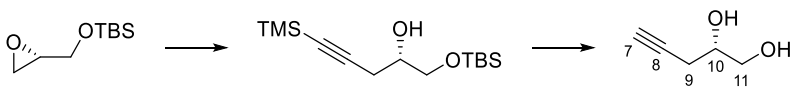
To a solution of TBSCl (13.2 g, 87.7 mmol, 1.3 eq) and imidazole (7.40 g, 108 mmol, 1.6 eq) in DMF (40 mL, 1.6 M) was added (*R*)-glycidol (4.97 g, 66.9 mmol, 1.0 eq) at 0 °C. After 30 min the mixture was allowed to warm to rt. After a further 2 h, brine (100 mL) was added, and the resulting mixture was stirred for 1 h. The mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (2 × 200 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by distillation (20 mbar, 90 °C head temperature) to afford silyl ether **207** (6.87 g, 54%) as a transparent liquid. Mixed fractions were purified by flash column chromatography (SiO_2, pentane:EtOAC = 97:3) to afford silyl ether **207** (3.05 g, 24%; total 9.92 g, 78%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.84 (dd, *J* = 11.9, 3.2 Hz, 1H, *H*-11a), 3.66 (dd, *J* = 11.9, 4.8 Hz, 1H, *H*-11b), 3.08 (dddd, *J* = 4.8, 4.1, 3.2, 2.7 Hz, 1H, *H*-10), 2.76 (dd, *J* = 5.2, 4.1 Hz, 1H, *H*-9a), 2.63 (dd, *J* = 5.2, 2.7 Hz, 1H, *H*-9b), 0.90 (s, 9H, $C(C\underline{H}_3)_3^{TBS}$), 0.08 (s, 3H, $SiC\underline{H}_3^{TBS}$) and 0.07 (s, 3H, $SiC\underline{H}_3^{TBS}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 63.9 (*C*-11), 52.6 (*C*-10), 44.6 (*C*-9), 26.0 ($C(\underline{C}H_3)_3^{TBS}$), 18.5 ($\underline{C}(CH_3)_3^{TBS}$), –5.2 ($Si\underline{C}H_3^{TBS}$) and –5.2 ppm ($Si\underline{C}H_3^{TBS}$);

The spectral data were consistent with those previously reported.[55]

(*S*)-Pent-4-yne-1,2-diol (42)



207 **209** **42**

To a solution of TMS acetylene (2.55 mL, 18.3 mmol, 1.14 eq) in THF (30 mL, 0.35 M final concentration) at –78 °C was added *n*BuLi (2.3 M in hexanes, 8.0 mL, 18 mmol, 1.2 eq) dropwise *via* syringe pump (25 mL/h). After 30 min, a solution of (*S*)-TBS-glycidol (**30**, 3.01 g, 16.0 mmol, 1.0 eq) in THF (5.0 mL + 2 × 1.0 mL rinse) was added, followed by $BF_3 \cdot OEt_2$ (2.3 mL, 18 mmol, 1.1 eq). After 2 h, the mixture was warmed to rt and stirred for an additional 4 h. The reaction was quenched with NH_4Cl (sat., aq., 30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* to give crude alcohol **209** as colourless oil (6.60 g). To a solution of crude alcohol **209** in MeOH (65 mL, 0.25 M) was added AcCl (0.11 mL, 1.6 mmol, 10 mol%) and the mixture was stirred for 14 h. After which, K_2CO_3 (4.40 g, 31.9 mmol, 2.0 eq) was added. After additional 7 h, the reaction mixture was filtered through Celite®, washed with MeOH (2 × 30 mL). The filtrate was concentrated *in vacuo*, re-dissolved in brine (10 mL) and extracted with EtOAc (6 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (SiO_2, pentane:EtOAc = 70:30 to 0:100) to afford diol **42** (1.15 g, 72%) as a colourless oil which crystallized into a white solid upon standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.88 (qd, *J* = 6.5, 3.2 Hz, 1H, *H*-10), 3.74 (dd, *J* = 11.4, 3.2 Hz, 1H, *H*-11a), 3.58 (dd, *J* = 11.4, 6.9 Hz, 1H, *H*-11b), 3.56–3.39 (m, 1H, O*H*), 2.41 (ddd, *J* = 6.3, 2.7, 1.5 Hz, 2H, 2 × *H*-9), 2.07 (t, *J* = 2.7 Hz, 1H, *H*-7) and 1.73–1.56 ppm (m, 1H, O*H*).

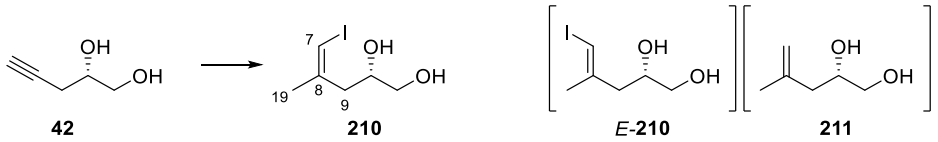
^{13}C NMR (101 MHz, $CDCl_3$) δ = 80.5 (*C*-8), 70.9 (*C*-7), 70.3 (*C*-10), 65.5 (*C*-11) and 23.5 ppm (*C*-9);

FT-IR ν_{max} (thin film): 2936, 1638, 1424, 1093, 1035, 898 and 647 cm^{-1};

Specific Rotation: $[\alpha]_D^{25}$ +7.6 (c = 1.36, CH_2Cl_2).

The spectral data were consistent with those previously reported.[55]

(*S*,*Z*)-5-Iodo-4-methylpent-4-ene-1,2-diol (210)



To a solution of $ZrCp_2Cl_2$ (271 mg, 912 µmol, 25 mo%) in DCE (3.8 mL, 0.23 M) at 0 °C was added $AlMe_3$ (2 M in hexanes, 8.3 mL, 17 mmol, 4.5 eq) *via* syringe pump (50 mL/h). The mixture was warmed to rt and stirred for 10 min before being cooled to 0 °C again. A solution of diol **42** (369 mg, 3.69 mmol, 1.0 eq) in DCE (11 mL + 2 × 0.5 mL rinse) was added *via* syringe pump (66 mL/h). 20 min after addition the reaction mixture was gradually heated to 75 °C and stirred for 3 days. After which, the reaction mixture was cooled to –30 °C (acetone/dry ice) and a freshly prepared solution of iodine (1.87 g, 7.37 mmol, 2.0 eq) in THF (7.6 mL; stock solution: 2.72 g in 11 mL) was added *via* syringe pump (45 mL/h) causing a dark colour change. After addition, the cooling bath was removed and the mixture was stirred for 2 h, causing the dark colour to fade. The reaction was quenched at 0 °C with dropwise addition of Rochelle's salt (2.5 mL). The heterogenous mixture was diluted with EtOAc (35 mL) and Rochelle's salt (35 mL) and vigorously stirred (600 rpm) for 16 h and the separated aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 80:20) to afford vinyl iodide **210** (231 mg, 26%) as a colourless liquid. The isolation was hampered by the separation from side products *E*-**210** and **211**. Mixed fractions of desired product **210** (190 mg, 72 wt% purity by ^{1}H NMR, 15% calc. yield; total 41% calc. yield) were isolated.

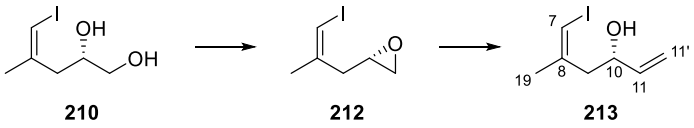
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.06–6.01 (m, 1H, *H*-7), 4.02–3.91 (m, 1H, *H*-10), 3.71 (dd, *J* = 11.1, 3.2 Hz, 1H, *H*-11a), 3.54 (dd, *J* = 11.1, 6.8 Hz, 1H, *H*-11b), 2.50 (dd, *J* = 13.5, 8.2 Hz,

1H, *H*-9a), 2.37 (dd, *J* = 13.6, 5.4 Hz, 1H, *H*-9b), 2.22–2.09 (m, 1H, *OH*-10) and 2.00–1.95 ppm (m, 4H, *OH*-11, 3 × *H*-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.4 (*C*-8), 77.2 (*C*-7), 70.6 (*C*-10), 66.5 (*C*-11), 42.3 (*C*-9) and 24.6 ppm (*C*-19);

The spectral data were consistent with those previously reported.[55]

(*S*,*Z*)-6-Iodo-5-methylhexa-1,5-dien-3-ol (213)



210 **212** **213**

Note: The starting material diol **210** (955 mg, 87 wt% purity by ^{1}H NMR) was contaminated with diol *E*-**210** (7.9 wt%, 0.30 mmol, 7.2 mol%) and diol **211** (0.54 wt%, 0.44 mmol, 0.11 eq). This was considered w.r.t the amount of reagents used. The first step was stirred using a mechanical stirrer.

To a solution of diol **210** (955 mg, 87 wt%, 3.43 mmol, 0.82 eq) in THF (45 mL, 0.1 M) was added NaH (60 wt%, 506 mg, 12.7 mmol, 3.0 eq) at 0 °C. The mixture was warmed to rt and stirred for 1 h before being cooled to 0 °C again. Trisylimidazole (1.52 g, 4.54 mmol, 1.1 eq) was added in one portion. The reaction mixture was warmed to rt after 30 min and quenched after a further 30 min with H_2O (3 mL). The separated aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organic extracts were dried over Na_2SO_4 and carefully concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 95:5) to afford epoxide **212** (1.1 g; contaminated with solvent residues) as a transparent liquid. In a separate flask trimethylsulfonium iodide (powdered, 5.65 g, 27.2 mmol, 6.6 eq) in THF (0.17 L, 25 mM) was cooled to –10 °C internal temperature (cryostat/acetone) and *n*BuLi (2.26 M in hexanes, 6.0 mL, 14 mmol, 3.3 eq) was added dropwise without allowing the internal temperature to rise above –5 °C. A solution of epoxide **212** (1.1 g) in THF (10 mL + 2 × 2.5 mL rinse) was added

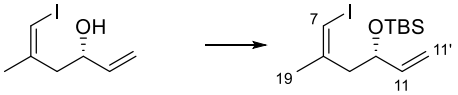
dropwise. After 16 h the reaction was quenched with NH_4Cl (sat., aq., 100 mL) dropwise without letting the internal temperature rise above 0 °C. The mixture was warmed to rt, diluted with H_2O (20 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 100:0 to 80:20) to afford allylic alcohol **213** (672mg, 82% over two steps) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) = δ 6.03 (q, *J* = 1.5 Hz, 1H, *H*-7), 5.94 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H, *H*-11), 5.29 (dt, *J* = 17.2, 1.4 Hz, 1H, *H*-11'a), 5.15 (dt, *J* = 10.4, 1.3 Hz, 1H, *H*-11'b), 4.42–4.33 (m, 1H, *H*-10), 2.54 (dd, *J* = 13.5, 8.4 Hz, 1H, *H*-9a), 2.43 (dd, *J* = 13.5, 5.4 Hz, 1H, *H*-9b), 1.96 (d, *J* = 1.5 Hz, 3H, 3 × *H*-19) and 1.59 ppm (d, *J* = 4.7 Hz, 1H, *OH*-10);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.5 (*C*-8), 140.4 (*C*-11), 115.2 (*C*-11'), 77.1 (*C*-7), 71.6 (*C*-10), 46.0 (*C*-9) and 24.7 ppm (*C*-19).

The spectral data were consistent with those previously reported.[55]

(*S*,*Z*)-*tert*-Butyl((6-iodo-5-methylhexa-1,5-dien-3-yl)oxy)dimethylsilane (81)



213 **81**

To a solution of allylic alcohol **213** (663 mg, 2.78 mmol, 1.0 eq) in DMF (0.30 mL, 0.93 M) was added imidazole (1.18 g, 17.3 mmol, 6.2 eq) and TBSCl (1.28 g, 8.48 mmol, 3.1 eq). After 2 h the reaction was quenched with brine (15 mL) and stirred for 20 min. After which, the mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 40 mL), brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane) to afford **81** (799 mg, 66%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.95 (q, *J* = 1.5 Hz, 1H, *H*-7), 5.91–5.78 (m, 1H, *H*-11), 5.19 (dt, *J* = 17.1, 1.5 Hz, 1H, *H*-11'a), 5.05 (dt, *J* = 10.3, 1.4 Hz, 1H, *H*-11'b), 4.39 (dtt, *J* = 7.3,

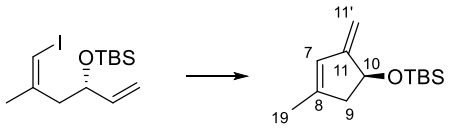
5.9, 1.2 Hz, 1H, *H*-10), 2.45 (dd, *J* = 13.1, 7.6 Hz, 1H, *H*-9a), 2.35 (dd, *J* = 13.1, 5.8 Hz, 1H, *H*-9b), 1.93 (d, *J* = 1.4 Hz, 3H, 3 × *H*-19), 0.90 (s, 9H, C(C$\underline{H}_3$)$_3^{TBS}$), 0.06 (s, 3H, SiC$\underline{H}_3^{TBS}$) and 0.04 ppm (s, 3H, SiC$\underline{H}_3^{TBS}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.2 (*C*-8), 141.1 (*C*-11), 114.2 (*C*-11'), 76.3 (*C*-7), 72.5 (*C*-10), 46.9 (*C*-9), 26.1 (C($\underline{C}H_3$)$_3^{TBS}$), 25.7 (*C*-19), 18.3 ($\underline{C}(CH_3)_3^{TBS}$), –4.3 (Si$\underline{C}H_3^{TBS}$) and –4.6 ppm (Si$\underline{C}H_3^{TBS}$);

The spectral data were consistent with those previously reported.[55]

6.1.7 Model studies and cross-coupling attempts

(*S*)-*tert*-Butyldimethyl((4-methyl-2-methylenecyclopent-3-en-1-yl)oxy)silane (216)



81 **216**

Diene **216** was observed in crude reaction mixtures when palladium-catalysed cross-coupling attempts with vinyl iodide **81** were made. Bond formation between *C*-7 and *C*-11 was confirmed by HMBC analysis. An analytical sample of diene **216** was purified by preperative TLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85 (q, *J* = 1.8 Hz, 1H, *H*-7), 4.87–4.83 (m, 1H, *H*-11'a), 4.82–4.76 (m, 2H, *H*-10, 11'b), 2.68–2.57 (m, 1H, *H*-9a), 2.32 (ddt, *J* = 17.5, 3.4, 1.8 Hz, 1H, *H*-9b), 1.81 (d, *J* = 1.4 Hz, 3H, 3 × *H*-19), 0.93 (s, 9H, $C(C\underline{H}_3)_3^{TBS}$) and 0.15–0.09 ppm (m, *J* = 4.3 Hz, 6H, 2 × $SiC\underline{H}_3^{TBS}$);

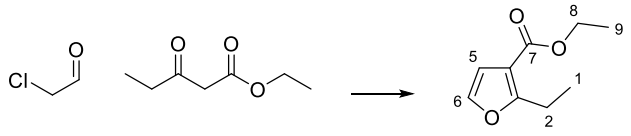
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.2 (*C*-8), 146.5 (*C*-11), 127.6 (*C*-7), 102.3 (*C*-11'), 73.8 (*C*-10), 46.5 (*C*-9), 26.1 ($C(\underline{C}H_3)_3^{TBS}$), 18.5 ($\underline{C}(CH_3)_3^{TBS}$), 17.6 (*C*-19), –4.4 ($Si\underline{C}H_3^{TBS}$) and –4.5 ppm ($Si\underline{C}H_3^{TBS}$);

FT-IR ν_{max} (thin film): 3422, 2955, 2931, 2857, 2160, 2029, 1715, 1463, 1363, 1255, 1111, 1006, 879, 838, 779, 669, 626 and 614 cm^{-1};

HRMS (ESI^+): Calc. for $C_{13}H_{25}OSi^+$ $[M+H]^+$ 225.1669; not found by ESI or APCI;

Specific Rotation: $[\alpha]_D^{25}$ +9.4 (c = 0.30, CH_2Cl_2).

Ethyl 2-ethylfuran-3-carboxylate (219)



217 **218** **219**

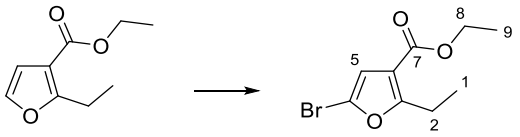
A mixture of ethyl propionyl acetate (**218**, 1.00 mL, 7.02 mmol, 1.0 eq) and pyridine (1.7 mL, 21.1 mmol, 3.0 eq) was cooled to 0 °C and chloroacetaldehyde (**217**, 2.0 mL, 14 mmol, 2.0 eq) was added dropwise. The reaction mixture was then heated to 45 °C for 3 days. After which, the mixture was cooled to rt, diluted with Et_2O (50 mL), washed with $NaHSO_4$ (sat., aq., 3 × 20 mL), HCl (2 M, aq., 2 × 15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 97.5:2.5) to afford furan **219** (922 mg, 78%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 2.0 Hz, 1H, *H*-6), 6.64 (d, *J* = 2.0 Hz, 1H, *H*-5), 4.28 (q, *J* = 7.1 Hz, 2H, 2 × *H*-8), 3.01 (q, *J* = 7.6 Hz, 2H, 2 × *H*-2), 1.35 (t, *J* = 7.1 Hz, 3H, 3 × *H*-9) and 1.25 ppm (t, *J* = 7.6 Hz, 3H, 3 × *H*-1);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.1 (*C*-3), 164.0 (*C*-7), 140.2 (*C*-6), 112.6 (*C*-5), 110.7 (*C*-4), 60.1 (*C*-8), 21.2 (*C*-2), 14.4 (*C*-9) and 12.2 ppm (*C*-1);

The spectral data were consistent with those previously reported.[95]

Ethyl 5-bromo-2-ethylfuran-3-carboxylate (231)



219 **231**

A solution of furan **219** (711 mg, 4.23 mmol, 1.0 eq) in DMF (4.2 mL, 1 M) was cooled to 0 °C and NBS (789 mg, 4.44 mmol, 1.0 eq) was added in one portion. After addition, the reaction mixture was warmed to rt and stirred for 16 h. After which, the reaction was quenched with H_2O (10 mL) and extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column

chromatography (SiO_2, pentane:Et_2O = 99:1 to 96:4) to afford bromide **231** (777 mg, 75%) as a colourless liquid.

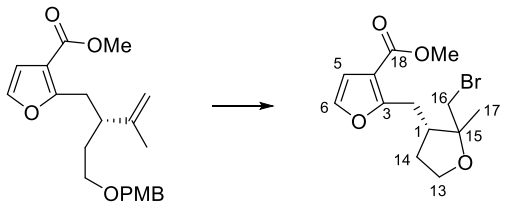
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.56 (s, 1H, *H*-5), 4.27 (q, *J* = 7.1 Hz, 2H, 2 × *H*-8), 2.99 (q, *J* = 7.6 Hz, 2H, 2 × *H*-2), 1.33 (t, *J* = 7.1 Hz, 3H, 3 × *H*-9) and 1.24 ppm (t, *J* = 7.5 Hz, 3H, 3 × *H*-1);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.6 (*C*-7), 162.8 (*C*-3), 119.9 (*C*-4), 115.2 (*C*-6), 112.0 (*C*-5), 60.4 (*C*-8), 21.3 (*C*-2), 14.3 (*C*-9) and 12.2 ppm (*C*-1);

FT-IR ν_{max} (thin film): 2984, 1808, 1782, 1720, 1604, 1524, 1463, 1374, 1298, 1231, 1158, 1115, 1056, 1025, 933, 902, 863, 778 and 734 cm^{-1};

HRMS (ESI^+): Calc. for $C_9H_{12}O_3{}^{79}Br^+$ $[M+H]^+$ 246.9964; not found by ESI or APCI.

Methyl 2-(((3*R*)-2-(bromomethyl)-2-methyltetrahydrofuran-3-yl)methyl)furan-3-carboxylate (233)



169 **233**

PMB ether **169** (28.4 mg, 79.2 µmol, 1.0 eq) was dissolved in a solution of NBS (14.7 mg, 82.5 µmol, 1.0 eq) in DMF (797 µL; stock solution: 44.2 mg in 2.4 mL). The mixture was stirred at rt for 24 h before NBS (15.5 mg, 87.1 µmol, 1.1 eq) was added. After an additional 22 h, the reaction mixture was diluted with H_2O (1.0 mL) and extracted with Et_2O (2 × 3 mL). The combined organic extracts were washed with H_2O (2.0 mL), brine (2.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR (74:26 dr determined at *H*-1; also contains stoichiometric amounts of *p*-anisaldehyde) and purified by flash column chromatography (SiO_2, pentane:Et_2O = 80:20 to 60:40) to afford an inseparable mixture of diastereomers of tetrahydrofuran **233** (14.8 mg, 59%, 74:26 dr) as a colourless syrup.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.28 (dd, *J* = 2.0, 0.7 Hz, 1H, *H*-6), 6.66 (d, *J* = 2.0 Hz, 1H, *H*-5), 3.94 (dtd, *J* = 11.5, 8.5, 3.6 Hz, 1H, *H*-13a), 3.83 (s, 3H, CO_2CH_3), 3.81–3.73 (m, 1H, *H*-13b), 3.46–3.39 (m, 1H, *H*-16a), 3.32 (d, *J* = 10.5 Hz, 1H, *H*-16b), 3.16–3.07 (m, 1H, *H*-2a), 3.03 (dd, *J* = 14.3, 9.7 Hz, 1H, *H*-2b), 2.64 (tdd, *J* = 9.9, 7.3, 5.6 Hz, 1H, *H*-1), 2.10–1.96 (m, 1H, *H*-14a), 1.96–1.78 (m, 1H, *H*-14b) and 1.29 ppm (s, 3H, 3 × *H*-17);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 164.3 (*C*-18), 161.0 (*C*-3), 141.0 (*C*-6), 113.9 (*C*-4), 110.9 (*C*-5), 82.2 (*C*-15), 66.3 (*C*-13), 51.6 (CO_2CH_3), 44.4 (*C*-1), 41.5 (*C*-16), 32.4 (*C*-14), 28.4 (*C*-2) and 20.6 ppm (*C*-17);

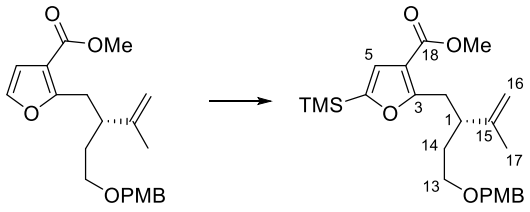
^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 3.50 (d, *J* = 10.7 Hz, 1H, *H*-16a), 3.19 (dd, *J* = 14.2, 5.8 Hz, 1H, *H*-2a), 2.51 (tdd, *J* = 9.9, 7.6, 5.8 Hz, 1H, *H*-1) and 1.32 ppm (s, 3H, 3 × *H*-17);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 141.1 (*C*-6), 110.9 (*C*-5), 81.9 (*C*-15), 65.9 (*C*-13), 47.4 (*C*-1), 38.2 (*C*-16), 31.7 (*C*-14), 27.4 (*C*-2) and 24.8 ppm (*C*-17);

FT-IR ν_{max} (thin film): 3322, 2950, 2160, 2021, 1745, 1718, 1602, 1499, 1451, 1402, 1260, 1235, 1200, 1135, 1099, 1029, 966, 914, 824, 738, 701 cm^{-1};

HRMS (ESI^+): Calc. for $C_{13}H_{18}O_4{}^{79}Br^+$ $[M+H]^+$ 317.0383; found 317.0384 (Δ 0.29 ppm).

Methyl (*R*)-2-(2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylbut-3-en-1-yl)-5-(trimethylsilyl)furan-3-carboxylate (234)



169 **234**

To a solution of furan **169** (27.1 mg, 75.6 µmol, 1.0 eq) in THF (1.5 mL, 50 mM) at –78 °C in a Schlenk tube was added LDA (1.0 M in THF, 0.15 mL, 0.15 mmol, 2.0 eq). After 1 h,

trimethyl silylchloride (0.05 mL, 0.4 mmol, 5 eq) was added. After an additional 1.5 h, the reaction was quenched with NH_4Cl (sat., aq., 1.5 mL), diluted with H_2O (1.0 mL) and extracted with Et_2O (3 × 3.0 mL). The combined organic extracts were washed with brine (3.0 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 95:5 to 85:15) to afford silane **234** (16.6 mg, 51%) as a colourless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28–7.21 (m, 2H, 2 × Ar*H*^{PMB}), 6.90–6.83 (m, 2H, 2 × Ar*H*^{PMB}), 6.81 (s, 1H, *H*-5), 4.66–4.63 (m, 1H, *H*-16a), 4.63–4.58 (m, 1H, *H*-16b), 4.39 (d, *J* = 11.6 Hz, 1H, OC*H*aHb^{PMB}), 4.39 (d, *J* = 11.6 Hz, 1H, OCHa*H*b^{PMB}), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.79 (s, 3H, CO_2CH_3), 3.45–3.32 (m, 2H, 2 × *H*-13), 3.16 (dd, *J* = 14.3, 9.0 Hz, 1H, *H*-2a), 3.04 (dd, *J* = 14.4, 6.5 Hz, 1H, *H*-2b), 2.78 (tt, *J* = 8.7, 6.5 Hz, 1H, *H*-1), 1.77–1.69 (m, 2H, 2 × *H*-14), 1.65 (br s, 3H, 3 × *H*-17) and 0.24 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMS}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.7 (*C*-3), 164.8 (*C*-18), 159.2 (Ar*C*^{PMB}), 158.7 (*C*-6), 146.2 (*C*-15), 130.8 (Ar*C*^{PMB}), 129.3 (2 × Ar*C*^{PMB}), 120.3 (*C*-5), 113.9 (2 × Ar*C*^{PMB}), 113.8 (*C*-4), 112.3 (*C*-16), 72.7 (O*C*H$_2^{PMB}$), 68.4 (*C*-13), 55.4 (O*C*H$_3^{PMB}$), 51.3 (CO_2CH_3), 43.3 (*C*-1), 32.8 (*C*-14), 32.4 (*C*-2), 18.3 (*C*-17) and –1.7 ppm (Si(*C*H$_3$)$_3^{TMS}$);

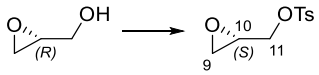
FT-IR ν_{max} (thin film): 2981, 1716, 1597, 1513, 1440, 1376, 1221, 1172, 1038 and 758 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{24}H_{35}O_5Si^+$ $[M+H]^+$ 431.2248; found 431.2250 (Δ 0.27 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +6.4 (c = 1.00, CH_2Cl_2).

6.1.8 Synthesis of alcohol 254

(*S*)-Oxiran-2-ylmethyl 4-methylbenzenesulfonate (85)



(+)-glycidol **85**

A solution of (*R*)-(+)-glycidol (5.44 g, 73.4 mmol, 1.0 eq) and Et_3N (15.5 mL, 111 mmol, 1.5 eq), in CH_2Cl_2 (100 mL, 0.73 M) was cooled to 0 °C and TsCl (17.5 g, 91.8 mmol, 1.3 eq) was added in portions. After completed addition, the mixture was warmed to rt and stirred for 90 min. After which, the mixture was diluted with Et_2O (300 mL) and washed with HCl (2 M, aq., 100 mL), Na_2CO_3 (sat., aq., 100 mL) and H_2O (100 mL). The organic extract was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 80:20 to 20:80) to afford epoxide **85** (14.6g, 87%) as a white crystalline solid upon storage at –20 °C.

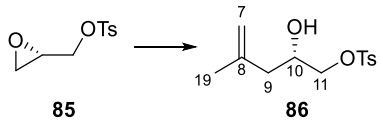
Following the same procedure racemic glycidol (1.00 mL, 15.0 mmol) was converted into *rac*-**85** (2.68 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85–7.77 (m, 2H, 2 × Ar$\underline{H}^{Ts}$), 7.40–7.32 (m, 2H, 2 × Ar$\underline{H}^{Ts}$), 4.25 (dd, *J* = 11.4, 3.4 Hz, 1H, *H*-11a), 3.95 (dd, *J* = 11.4, 6.0 Hz, 1H, *H*-11b), 3.19 (dtd, *J* = 6.1, 3.8, 2.5 Hz, 1H, *H*-10), 2.82 (dd, *J* = 4.8, 4.1 Hz, 1H, *H*-9a), 2.59 (dd, *J* = 4.8, 2.5 Hz, 1H, *H*-9b) and 2.45 ppm (s, 3H, C$\underline{H}_3^{Ts}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (Ar$\underline{C}^{Ts}$), 132.8 (Ar$\underline{C}^{Ts}$), 130.1 (2 × Ar$\underline{C}^{Ts}$), 128.1 (2 × Ar$\underline{C}^{Ts}$), 70.6 (*C*-11), 49.0 (*C*-10), 44.8 (*C*-9) and 21.8 ppm ($\underline{C}H_3^{Ts}$);

The spectral data were consistent with those previously reported.[57]

(*S*)-2-Hydroxy-4-methylpent-4-en-1-yl 4-methylbenzenesulfonate (86)



85 **86**

To a slurry of copper(I) iodide (1.02 g, 5.40 mmol, 20 mol%) in THF (17 mL, 0.17 M final concentration) was added isopropenyl magnesiumbromide (0.50 M in THF, 113 mL, 57 mmol, 2.1 eq) dropwise *via* cannula at –78 °C. After 1.5 h a solution of epoxide **85** (6.16 g, 27.0 mmol, 1.0 eq) in THF (31 mL) was added *via* syringe pump (30 mL/h). The reaction mixture was warmed to –40 °C and stirred at this temperature for 2 h. Then the reaction was quenched with NH_4Cl (sat., aq., 150 mL) and diluted with ammonia (sat., aq., 50 mL). The bright blue mixture was extracted with Et_2O (300 mL). The organic extract was washed with a 3:1 mixture (2 × 150 mL) of NH_4Cl (sat., aq.) and ammonia (sat., aq.), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 70:30 to 50:50) to afford tosylate **86** (5.96 g, 82%) as a colourless liquid.

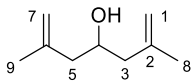
Following the same procedure *rac*-**85** (1.46 mL, 15.0 mmol) was converted into *rac*-**86** (1.30 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.77 (m, 2H, Ar$\underline{H}^{Ts}$), 7.41–7.32 (m, 2H, Ar$\underline{H}^{Ts}$), 4.88–4.84 (m, 1H, *H*-7a), 4.77–4.73 (m, 1H, *H*-7b), 4.05 (dd, *J* = 9.5, 3.2 Hz, 1H, *H*-11a), 4.03–3.96 (m, 1H, *H*-10), 3.93 (dd, *J* = 9.5, 6.2 Hz, 1H, *H*-11b), 2.45 (s, 3H, C$\underline{H}_3^{Ts}$), 2.18 (d, *J* = 1.0 Hz, 1H, *H*-9a), 2.17 (t, *J* = 1.4 Hz, 1H, *H*-9b), 2.11 (d, *J* = 3.8 Hz, 1H, *OH*-10) and 1.72 ppm (t, *J* = 1.2, 1.2 Hz, 3H, 3 × *H*-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (*C*-8), 141.0 (Ar$\underline{C}^{Ts}$), 132.8 (Ar$\underline{C}^{Ts}$), 130.1 (2 × Ar$\underline{C}^{Ts}$), 128.1 (2 × Ar$\underline{C}^{Ts}$), 114.4 (*C*-7), 73.4 (11), 67.2 (*C*-10), 41.5 (*C*-9), 22.4 (*C*-19) and 21.8 ppm ($\underline{C}H_3^{Ts}$);

The spectral data were consistent with those previously reported.[57]

2,6-Dimethylhepta-1,6-dien-4-ol (253)



253

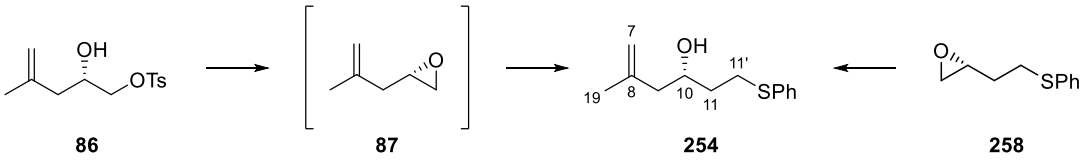
In the synthesis of olefin **86** from epoxide **85** (*vide supra*), the formation of diene **253** was observed by TLC and ^{1}H NMR analysis of the crude reaction mixture. For spectroscopic reasons, an analytic sample of **253** was purified by column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.87 (q, *J* = 1.7 Hz, 2H, *H*-1a, *H*-7a), 4.80 (dq, *J* = 2.0, 1.0 Hz, 2H, *H*-1b, *H*-7b), 3.89 (dddd, *J* = 13.0, 8.1, 4.9, 2.3 Hz, 1H, *H*-4), 2.23–2.12 (m, 4H, 2 × *H*-3, 2 × *H*-5), 1.84 (d, *J* = 2.3 Hz, 1H, O*H*-4) and 1.77 ppm (t, *J* = 1.2 Hz, 6H, 3 × *H*-8, 3 × *H*-9);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.9 (*C*-2, *C*-6), 113.4 (*C*-1, *C*-7), 66.6 (*C*-4), 45.8 (*C*-3, *C*-5) and 22.6 ppm (*C*-8, *C*-9).

The spectral data were consistent with those previously reported.[119]

(*S*)-5-Methyl-1-(phenylthio)hex-5-en-3-ol (254)



86 **87** **254** **258**

Note: The enantiomeric excess of alcohol **254,** synthesised with methods described below, was analysed *via* chiral HPLC: Chiralpak ID with guard, hexane:*i*PrOH = 90:10, 1 mL/min, 25 °C, λ = 210 nm, 10 µL injection, 15 min.

Procedure A:

Note: The preparation of volatile epoxide **87** and the lithiation of thioanisole were run in parallel and timed to complete both processes at the same time.

A solution of tosylate **86** (1.95 g, 7.32 mmol, 1.0 eq) in THF (20 mL, 0.26 M) was added to a slurry of NaH (60 wt.%, 308 mg, 1.1 eq) in THF (8.0 mL) at 0°C. The resulting mixture was stirred for 1.5 h and full conversion to epoxide **87** was observed by TLC. In a separate flask *n*BuLi (2.4 M in hexanes, 2.7 mL, 2.5 eq) was added to a solution of DABCO (208 mg, 1.81 mmol, 26 mol%) and thioanisole (2.1 mL, 18 mmol, 2.5 eq) in THF (27 mL, 0.13 M final concentration) at 0 °C. After 1.5 h the solution was cooled to –78 °C and the mixture

containing epoxide **87** was added dropwise *via* cannula. The resulting mixture was stirred at 0 °C for 16 h. After which, the dark red reaction was quenched with NH_4Cl (sat., aq., 15 mL) and diluted with brine (15 mL). The colourless mixture was warmed to rt and extracted with Et_2O (3 × 60 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 70:30) to afford sulfide **254** (663 mg, 41%, > 99% ee) as a colourless liquid.

Following the same procedure *rac*-**86** (303 mg, 1.12 mmol) was converted into *rac*-**254** (150 mg, 60%).

Procedure B:

To a solution of TMEDA (0.33 mL, 2.2 mmol, 3.5 eq) and thioanisole (0.26 mL, 2.2 mmol, 3.5 eq) in THF (11 mL, 43 mM final concentration) at –78 °C was added *n*BuLi (2.5 M in hexanes, 0.88 mL, 2.2 mmol, 3.5 eq). The mixture was warmed to 0 °C before being cooled to –78 °C again. A solution of tosylate **86** (170 mg, 628 µmol, 1.0 eq) in THF (1.0 mL + 2 × 0.5 mL rinse) was added dropwise. After 30 min the temperature was raised to 0 °C and the mixture stirred for 2.5 h. The reaction was quenched with NH_4Cl (5 mL), diluted with brine (10 mL) and extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 70:30) to afford sulfide **254** (46.0 mg, 33%) as a colourless liquid.

Procedure C:

To a slurry of copper(I) iodide (360 mg, 1.90 mmol, 20 mol%) in THF (6.0 mL, 0.17 M final concentration) at –40 °C was added isopropenyl magnesiumbromide (0.50 M in THF, 29 mL, 15 mmol, 1.5 eq) and a solution of epoxide **258** (1.71 g, 9.49 mmol, 1.0 eq) in THF (4.0 mL + 2 × 2 mL rinse). After addition, the reaction mixture was warmed to 0 °C and

stirred at this temperature for 2 h. Then the black reaction mixture was quenched with NH_4Cl (sat., aq., 30 mL) and diluted with ammonia (sat., aq., 10 mL). The bright blue mixture was extracted with Et_2O (3 × 40 mL). The organic extract was washed with a 3:1 mixture (2 × 40 mL) of NH_4Cl (sat., aq.) and ammonia (sat., aq.), brine (40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 60:40) to afford alcohol **254** (2.05 g, 97%, 98% ee) as a colourless liquid.

Following the same procedure *ent*-**258** (124 mg, 688 µmol) was converted into *ent*-**254** (146 mg, 95%, –98% ee).

Specific Rotation: $[\alpha]_D^{25}$ –38.5 (c = 1.00, CH_2Cl_2).

Alcohol **254**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.33 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.32–7.25 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.21–7.14 (m, 1H, Ar$\underline{H}^{Ph}$), 4.89 (app. p, *J* = 1.6 Hz, 1H, *H*-7a), 4.81–4.77 (m, 1H, *H*-7b), 3.97–3.85 (m, 1H, *H*-10), 3.13 (ddd, *J* = 13.0, 7.3, 6.5 Hz, 1H, *H*-11'a), 3.04 (dt, *J* = 12.9, 7.7 Hz, 1H, *H*-11'b), 2.22–2.16 (m, 1H, *H*-9a), 2.13 (ddd, *J* = 13.7, 8.9, 0.9 Hz, 1H, *H*-9b), 1.85 (d, *J* = 3.0 Hz, 1H, *OH*-10), 1.84–1.76 (m, 2H, 2 × *H*-11) and 1.75 ppm (s, 3H, 3 × *H*-19);

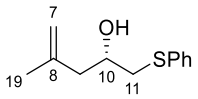
^{13}C NMR (101 MHz, CDCl3) δ = 142.4 (*C*-8), 136.5 (Ar$\underline{C}^{Ph}$), 129.1 (2 × Ar$\underline{C}^{Ph}$), 129.0 (2 × Ar$\underline{C}^{Ph}$), 126.0 (Ar$\underline{C}^{Ph}$), 114.0 (*C*-7), 67.5 (*C*-10), 46.3 (*C*-9), 36.4 (*C*-11), 30.2 (*C*-11') and 22.5 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3053, 2936, 1647, 1584, 1481, 1439, 1265, 1072, 896 and 692cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{13}H_{19}OS^+$ $[M+H]^+$ 223.1151; found 223.1154 (Δ 1.3 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +40.4 (c = 1.00, CH_2Cl_2).

(*S*)-4-Methyl-1-(phenylthio)pent-4-en-2-ol (255)



255

When tosylate **86** (5.35 g, 19.8 mmol) was converted to alcohol **254** (1.51 g, 34%) following *procedure A* on larger scale, impurity **255** was generated. ^{1}H NMR analysis of the crude reaction mixture showed 86:14 ratio of **254**:**255**. Purification by flash column chromategraphy was labour intensive. An analytic sample of clean side-product **255** was isolated.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.37 (m, 2H, 2 × Ar*H*^{Ph}), 7.32–7.27 (m, 2H, 2 × Ar*H*^{Ph}), 7.24–7.18 (m, 1H, Ar*H*^{Ph}), 4.87 (app. p, *J* = 1.7 Hz, 1H, *H*-7a), 4.79 (dq, *J* = 2.1, 1.0 Hz, 1H, *H*-7b), 3.86 (csm, 1H, *H*-10), 3.13 (dd, *J* = 13.7, 4.3 Hz, 1H, *H*-11a), 2.94 (dd, *J* = 13.6, 7.9 Hz, 1H, *H*-11b), 2.38 (d, *J* = 2.9 Hz, 1H, *OH*-10), 2.31 (ddd, *J* = 13.9, 5.1, 1.2 Hz, 1H, *H*-9a), 2.26 (ddd, *J* = 13.8, 8.0, 1.0 Hz, 1H, *H*-9b) and 1.73 ppm (t, *J* = 1.2 Hz, 3H, *H*-19);

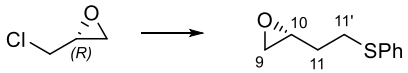
^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.2 (*C*-8), 135.6 (Ar*H*^{Ph}), 130.1 (2 × Ar*H*^{Ph}), 129.2 (2 × Ar*H*^{Ph}), 126.7 (Ar*H*^{Ph}), 113.8 (*C*-7), 67.6 (*C*-10), 44.8 (*C*-9), 41.6 (*C*-11) and 22.6 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3421, 3075, 2968, 2932, 1647, 1584, 1481, 1439, 1376, 1303, 1072, 1025, 979, 894, 739, 691 and 618 cm^{-1};

HRMS (ESI^+): Calc. for $C_{12}H_{17}OS^+$ $[M+H]^+$ 209.0995; found 209.0998 (Δ 1.43 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +35.7 (c = 0.97, CH_2Cl_2).

(*R*)-2-(2-(phenylthio)Ethyl)oxirane (258)



256 **258**

Note: For safety reasons high vacuum and a liquid nitrogen trap, rather than a rotary evaporator, were used to removed volatiles after work-up.

To a solution of DABCO (185 mg, 1.65 mmol, 10 mol%) and thioanisole (1.9 mL, 16 mmol, 1.0 eq) in THF (15 mL, 1.2 M final concentration) at 0 °C was added *n*BuLi (2.5 M in hexanes, 7.5 mL, 19 mmol, 1.2 eq). After 1 h the mixture was cooled to –78 °C and

(*R*)-epichlorohydrin (**256**, 2.5 mL, 32 mmol, 2.0 eq) was added dropwise. After 30 min the mixture was warmed to –50 °C (cryostat/acetone) and gradually warmed to 0 °C over a period of 2 h. The reaction mixture was stirred for 30 min at 0 °C, warmed to rt and stirred for further 1 h. After which the reaction was quenched at 0 °C with NH_4Cl (sat., aq., 15 mL), warmed to rt, diluted with brine (15 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 95:5 to 80:20) to afford epoxide **258** (1.72 g, 59%) as a colourless liquid.

Following the same procedure (*S*)-epichlorohydrin (*ent*-**256**, 0.24 mL, 3.06 mmol) was converted into *ent*-**258** (125 mg, 45%) and racemic epichlorohydrin (*rac*-**256**, 0.40 mL, 5.12 mmol) was converted into *rac*-**258** (222 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.33 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.32–7.25 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.22–7.16 (m, 1H, Ar$\underline{H}^{Ph}$), 3.14–2.98 (m, 3H, *H*-10, 2 × *H*-11'), 2.77 (dd, *J* = 5.0, 3.9 Hz, 1H, *H*-9a), 2.51 (dd, *J* = 5.0, 2.7 Hz, 1H, *H*-9b), 1.98–1.87 (m, 1H, *H*-11a) and 1.87–1.77 ppm (m, 1H, *H*-11b);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.1 (Ar$\underline{C}^{Ph}$), 129.5 (2 × Ar$\underline{C}^{Ph}$), 129.1 (2 × Ar$\underline{C}^{Ph}$), 126.3 (Ar$\underline{C}^{Ph}$), 51.2 (*C*-10), 47.3 (*C*-9), 32.4 (*C*-11) and 30.3 ppm (*C*-11');

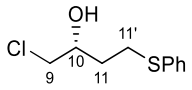
FT-IR ν_{max} (thin film): 2922, 2362, 1734, 1583, 1481, 1439, 1260, 1090, 1025, 912, 855, 740 and 691 cm^{-1};

HRMS (ESI^+): Calc. for $C_{10}H_{13}OS^+$ $[M+H]^+$ 181.0682; found 181.0682 (Δ 0.21 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +25.7 (c = 1.00, CH_2Cl_2).

The spectral data were consistent with those previously reported.[106]

(*R*)-1-Chloro-4-(phenylthio)butan-2-ol (259)



259

When the synthesis of epoxide **258** from thioanisole (1.9 mL, 16 mmol) and (*R*)-epichlorohydrin (**256**, 2.5 mL, 32 mmol) was performed at –20 °C (*vide supra*), epoxide **258** (872 mg, 30%) as well as chlorohydrin **259** (939 mg, 27%) were isolated.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.33 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.33–7.27 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.23–7.17 (m, 1H, Ar$\underline{H}^{Ph}$), 4.09–3.96 (m, 1H, *H*-10), 3.61 (dd, *J* = 11.2, 3.5 Hz, 1H, *H*-9a), 3.48 (dd, *J* = 11.1, 7.0 Hz, 1H, *H*-9b), 3.13 (ddd, *J* = 13.3, 7.7, 5.7 Hz, 1H, *H*-11'a), 3.04 (dt, *J* = 13.2, 7.6 Hz, 1H, *H*-11'b), 2.32 (dt, *J* = 5.0, 0.9 Hz, 1H, *OH*-10) and 1.94–1.76 ppm (m, 2H, 2 × *H*-11');

^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.9 (Ar$\underline{C}^{Ph}$), 129.5 (2 × Ar$\underline{C}^{Ph}$), 129.1 (2 × Ar$\underline{C}^{Ph}$), 126.3 (Ar$\underline{C}^{Ph}$), 70.2 (*C*-10), 50.3 (*C*-9), 33.6 (*C*-11) and 30.0 ppm (*C*-11');

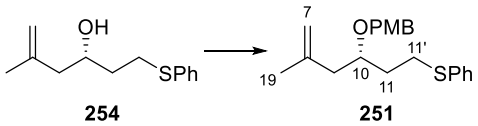
FT-IR ν_{max} (thin film): 3402, 2951, 1583, 1480, 1439, 1304, 1273, 1088, 1057, 1025, 914, 854, 739 and 691 cm^{-1};

LRMS (ESI^+): Calc. for $C_{10}H_{14}OS^{35}Cl$ $[M+H]^+$ 217.0; not found; 181.0 found matches $[M+H]^+$ for epoxide **258**;

Specific Rotation: $[\alpha]_D^{25}$ +39.6 (c = 1.00, CH_2Cl_2).

6.1.9 Synthesis of aldehyde *epi*-239

(*S*)-(3-((4-methoxybenzyl)oxy)-5-Methylhex-5-en-1-yl)(phenyl)sulfane (251)



254 **251**

To a solution of alcohol **254** (6.00 g, 27.0 mmol, 1.0 eq) in DMF (20 mL, 1.4 M) at 0 °C was added NaH (60%, 2.17 g, 54.0, 2.0 eq) in one portion. The resulting slurry was warmed to rt, stirred for 30 min before being cooled to 0 °C again. 4-Methoxybenzyl chloride (7.5 mL, 56 mmol, 2.1 eq) and tetrabutylammonium iodide (4.99 g, 13.5 mmol, 50 mol%) were added at 0 °C. The reaction mixture was stirred at rt for 16 h. After which, it was cooled to 0 °C, quenched with NH_4Cl (sat., aq., 20 mL), diluted with H_2O (20 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane: Et_2O = 95:5 to 80:20) to afford ether **251** (7.61 g, 82%) as a colourless oil.

Following the same procedure, alcohol **254** (1.50 g, 6.75 mmol) was converted into ether **251** (2.12 g, 92%).

Following a similar procedure, alcohol *rac*-**254** (307 mg, 1.38 mmol) was converted into ether *rac*-**251** (315 mg, 67%) using less tetrabutylammonium iodide (26.5 mg, 71.7 µmol, 5.2 mol%) at 65 °C with 3 days reaction time.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.23 (m, 6H, 2 × Ar$\underline{H}^{PMB}$, 4 × Ar$\underline{H}^{Ph}$), 7.21–7.14 (m, 1H, Ar$\underline{H}^{Ph}$), 6.92–6.84 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 4.82–4.78 (m, 1H, *H*-7a), 4.77–4.73 (m, 1H, *H*-7b), 4.53 (d, *J* = 11.0 Hz, 1H, OC$\underline{Ha}$Hb^{PMB}), 4.40 (d, *J* = 11.1 Hz, 1H, OCHa$\underline{Hb}^{PMB}$), 3.81 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.78–3.68 (m, 1H, *H*-10), 3.06 (ddd, *J* = 12.8, 8.1, 5.8 Hz, 1H, *H*-11'a), 2.96 (ddd, *J* = 12.9, 8.3, 7.3 Hz, 1H, *H*-11'b), 2.41 (ddd, *J* = 14.0, 5.9, 1.2 Hz, 1H, *H*-9a), 2.16 (ddd, *J* = 13.8, 7.1, 1.0 Hz, 1H, *H*-9b), 1.88–1.80 (m, 2H, 2 × *H*-11) and 1.74 ppm (s, 3H, 19);

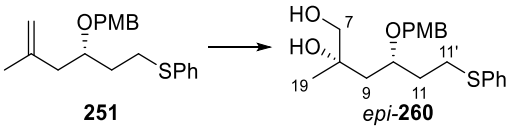
^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.2 (Ar*C*^{PMB}), 142.4 (*C*-8), 136.7 (Ar*C*^{Ph}), 130.7 (Ar*C*^{PMB}), 129.4 (2 × Ar*C*^{PMB}), 128.9 (2 × Ar*C*^{Ph}), 128.8 (2 × Ar*C*^{Ph}), 125.7 (Ar*C*^{Ph}), 113.8 (2 × Ar*C*^{PMB}), 113.1 (*C*-7), 75.6 (*C*-10), 70.9 (O*C*H$_2^{PMB}$), 55.3 (O*C*H$_3^{PMB}$), 42.5 (*C*-9), 33.6 (*C*-11), 29.6 (*C*-11') and 22.9 ppm (*C*-19);

FT-IR ν_{max} (thin film): 2934, 2861, 2835, 1613, 1585, 1513, 1481, 1464, 1439, 1349, 1302, 1247, 1173, 1089, 1074, 1036, 892, 821, 739 and 691 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{21}H_{26}O_2{}^{23}NaS^+$ [M+Na]$^+$ 365.1546; found 365.1545 (Δ –0.25 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +43.2 (c = 1.00, CH_2Cl_2).

(2*S*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methyl-6-(phenylthio)hexane-1,2-diol (*epi*-260)



251 *epi*-**260**

To a solution of olefin **251** (2.01 g, 5.87 mmol, 1.0 eq) in *t*BuOH:H_2O (1:1, 22 mL, 0.27 M) and methanesulfonamide (574 mg, 6.04 mmol, 1.0 eq) at 0 °C was added AD-mix β (6.61 g, 2.4 eq). After 16 h, $Na_2S_2O_3$ (0.5 g) was added, and the reaction was stirred at rt for 1.5 h. The mixture was extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, Et_2O:MeOH = 100:0 to 95:5) to afford an inseparable mixture of diastereomers of diol *epi*-**260** contaminated with methanesulfonamide (2.63 g, 76:24 dr determined at *H*-19, 78 wt% purity by ^{1}H NMR, 91% calc. yield) as a crystalline solid. The relative stereochemistry of major diastereomer *epi*-**260** was assigned retrospectively by nOe analysis of cyclic acetals **273** and *epi*-**273**.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.38–7.33 (m, 2H, 2 × Ar*H*^{Ph}), 7.30 (ddd, *J* = 7.8, 7.0, 1.4 Hz, 2H, 2 × Ar*H*^{Ph}), 7.23–7.17 (m, 3H, 2 × Ar*H*^{Ph}, 2 × Ar*H*^{PMB}), 6.91–6.83 (m, 2H, 2 × Ar*H*^{PMB}), 4.48 (d, *J* = 10.8 Hz, 1H, OC*H*aHb^{PMB}), 4.29 (d, *J* = 10.7 Hz, 1H, OCHa*H*b^{PMB}), 3.87 (ddt, *J* = 10.0, 5.8, 2.6 Hz, 1H, *H*-10), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.54–3.23

(m, 3H, *OH*-8, 2 × *H*-7), 3.02 (ddd, *J* = 12.9, 8.4, 6.4 Hz, 1H, *H*-11'a), 2.95–2.85 (m, 1H, *H*-11'b), 2.28 (app. d, *J* = 11.4 Hz, 1H, *OH*-7), 2.05–1.90 (m, 2H, 2 × *H*-11), 1.83 (dd, *J* = 14.8, 9.9 Hz, 1H, *H*-9a), 1.67 (dd, *J* = 14.9, 2.5 Hz, 1H, *H*-9b) and 1.14 ppm (s, 3H, 3 × *H*-19);

^{1}H NMR (major diastereomer, 400 MHz, CD_3OD = 4.87 ppm) δ = 7.42–7.36 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.36–7.30 (m, 1H, Ar$\underline{H}^{Ph}$), 7.29–7.25 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 7.25–7.18 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 6.95–6.89 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 4.49–4.38 (m, 2H, OC$\underline{H}_2^{PMB}$), 4.02–3.86 (m, 1H, *H*-10), 3.81 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.41–3.34 (m, 2H, 2 × *H*-7), 3.02 (ddd, *J* = 8.6, 6.5, 2.0 Hz, 2H, 2 × *H*-11'), 2.09–1.78 (m, 3H, *H*-9a, 2 × *H*-11), 1.69 (dd, *J* = 14.6, 4.0 Hz, 1H, *H*-9b) and 1.19 ppm (s, 3H, 3 × *H*-19); 2 × OH not observed;

^{13}C NMR (major diastereomer, 101 MHz, CD_3OD = 49.0 ppm) δ = 160.8 (Ar$\underline{C}^{PMB}$), 137.9 (Ar$\underline{C}^{Ph}$), 131.5 (Ar$\underline{C}^{PMB}$), 130.8 (2 × Ar$\underline{C}^{PMB}$), 130.2 (2 × Ar$\underline{C}^{Ph}$), 130.0 (2 × Ar$\underline{C}^{Ph}$), 126.9 (Ar$\underline{C}^{Ph}$), 114.8 (2 × Ar$\underline{C}^{PMB}$), 76.0 (*C*-10), 73.4 (*C*-8), 71.3 (*C*-7), 70.8 (O$\underline{C}H_2^{PMB}$), 55.7 (O$\underline{C}H_3^{PMB}$), 43.1 (*C*-9), 35.2 (*C*-11), 29.8 (*C*-11') and 24.4 ppm (*C*-19);

^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 4.52 (d, *J* = 10.7 Hz, 1H, OC$\underline{Ha}$Hb^{PMB}), 4.06–3.98 (m, 1H, *H*-10), 2.39 (s, 1H, *OH*-7), 1.44 (dd, *J* = 14.8, 2.3 Hz, 1H, *H*-9b) and 1.13 ppm (s, 3H, 3 × *H*-19);

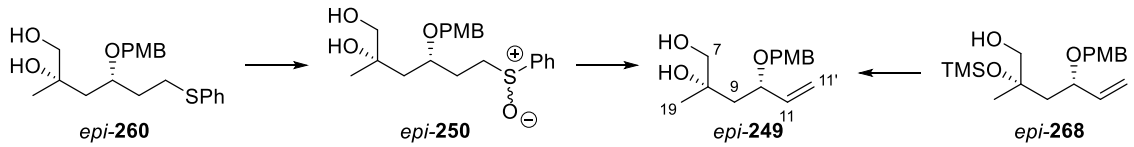
^{1}H NMR (methane sulfonamide, 400 MHz, $CDCl_3$) δ = 4.83 (s, 2H, $H_3CSO_2N\underline{H}_2$) and 3.09 ppm (s, 3H, $\underline{H}_3CSO_2NH_2$);

^{13}C NMR (methane sulfonamide, 101 MHz, $CDCl_3$) δ = 43.6 ppm ($H_3\underline{C}SO_2NH_2$).

FT-IR ν_{max} (thin film): 3398, 2934, 1612, 1585, 1514, 1481, 1464, 1439, 1322, 1303, 1248, 1175, 1154, 1112, 1055, 1033, 821, 740 and 692 cm^{-1};

HRMS (ESI^+): Calc. for $C_{21}H_{28}O_4{}^{23}NaS^+$ $[M+Na]^+$ 399.1601; found 399.1597 (Δ –0.81 ppm);

(2*S*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methylhex-5-ene-1,2-diol (*epi*-249)



Procedure A:

Note: Diol *epi*-**260** (583 mg) was contaminated with methanesulfonamide (22 wt% by ^{1}H NMR) from the previous step. Due to variations in purity of *m*CPBA batches the first step was executed in two separate batches in order to avoid overoxidation to sulfone *epi*-**264**. The two batches were combined for the second step.

To a solution of diol *epi*-**260** (583 mg, 76:23 dr, 78 wt% by ^{1}H NMR, 1.21 mmol, 1.0 eq) in DCE (24 mL, 50 mM) at 0 °C was added *m*CPBA (233 mg, 1.35 mmol, 1.1 eq). After 10 min the reaction mixture was directly purified by flash column chromatography (SiO_2, CH_2Cl_2 to acetone) to afford sulfoxide *epi*-**250** (439 mg, 93%, mixture of 4 diastereomers) as a colourless wax. A heterogeneous mixture of sulfoxide *epi*-**250** (831 mg, 2.12 mmol, 1.0 eq), PhMe (140 mL, 15 mM) and K_2CO_3 (1.46 g, 10.6 mmol, 5.0 eq) was heated to reflux (aluminium block, 130 °C). After 3 days the reaction was cooled to rt, diluted with H_2O (50 mL) and extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 95:5 to 0:100) to afford olefin *epi*-**249** (477 mg, 85%, 80:20 dr determined at *H*-9a) as colourless oil.

Procedure B:

To a solution of silyl ether *epi*-**268** (93.5 mg, 95:5 dr, 276 µg, 1.0 eq) in MeOH (2.9 mL, 0.10 M) was added K_2CO_3 (19.1 mg, 0.50 eq) at rt. After 1 h silica gel was added and the mixture concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 90:10 to 80:20) to afford diol *epi*-**249** (61.7 mg, 84%, > 98:2 dr) as a colourless syrup.

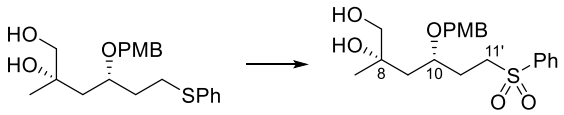
^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.25–7.20 (m, 2H, 2 × Ar*H*^{PMB}), 6.91–6.85 (m, 2H, 2 × Ar*H*^{PMB}), 5.74 (ddd, *J* = 17.2, 10.3, 7.7 Hz, 1H, *H*-11), 5.31–5.23 (m, 2H, 2 × *H*-11'), 4.53 (d, *J* = 11.0 Hz, 1H, OC*H*aHb^{PMB}), 4.25 (d, *J* = 11.0 Hz, 1H, OC*H*aHb^{PMB}), 4.09 (ddd, *J* = 10.4, 7.6, 2.4 Hz, 1H, *H*-10), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.61 (s, 1H, *OH*-8), 3.48 (dd, *J* = 11.1, 4.1 Hz, 1H, *H*-7a), 3.35 (dd, *J* = 11.1, 7.5 Hz, 1H, *H*-7b), 2.35–2.23 (m, 1H, *OH*-7), 1.90 (dd, *J* = 15.0, 10.5 Hz, 1H, *H*-9a), 1.69 (dd, *J* = 15.0, 2.5 Hz, 1H, *H*-9b) and 1.14 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 159.6 (Ar*C*^{PMB}), 138.3 (*C*-11), 130.0 (2 × Ar*C*^{PMB}), 129.6 (Ar*C*^{PMB}), 117.6 (*C*-11'), 114.1 (2 × Ar*C*^{PMB}), 78.3 (*C*-10), 72.6 (*C*-8), 70.1 (O*C*H$_2^{PMB}$), 69.6 (*C*-7), 55.4 (O*C*H$_3^{PMB}$), 44.4 (*C*-9) and 25.3 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3468, 3412, 3393, 2926, 2360, 2342, 2229, 2176, 2159, 2144, 1996, 1976, 1614, 1515, 1250, 1176, 1034, 822, 681 and 656 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{15}H_{22}O_4{}^{23}Na^+$ [M+Na]$^+$ 289.1410; found 289.1411 (Δ 0.29 ppm).

(2*S*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methyl-6-(phenylsulfonyl)hexane-1,2-diol (*epi*-264)



epi-**260** → *epi*-**264**

Sulfone *epi*-**264** (79:21 dr determined at *H*-10) was isolated when diol *epi*-**260** was treated with excess *m*CPBA. Co-elution with methanesulfonamide hampered the isolation of sulfone *epi*-**264**.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.94–7.88 (m, 2H, 2 × Ar*H*^{Ph}), 7.71–7.64 (m, 1H, Ar*H*^{Ph}), 7.62–7.55 (m, 2H, 2 × Ar*H*^{Ph}), 7.22–7.14 (m, 2H, 2 × Ar*H*^{PMB}), 6.92–6.80 (m, 2H, 2 × Ar*H*^{PMB}), 4.99 (s, 1H, *OH*-8), 4.43 (d, *J* = 10.8 Hz, 1H, OC*H*aHb^{PMB}), 4.28 (d, *J* = 10.8 Hz, 1H, OCHa*H*b^{PMB}), 3.92 (tt, *J* = 6.3, 3.2 Hz, 1H, *H*-10), 3.79 (s, 3H, OC*H*$_3^{PMB}$), 3.41 (d, *J* = 11.2 Hz, 1H, *H*-7a), 3.36–3.30 (m, 1H, *H*-7b), 3.22–3.11 (m, 2H, *H*-11'), 2.33–2.17 (m,

1H, *H*-11a), 2.02–1.87 (m, 1H, *H*-11b), 1.69 (dd, *J* = 14.8, 9.5 Hz, 1H, *H*-9a), 1.56 (dd, *J* = 14.7, 2.9 Hz, 1H, *H*-9b) and 1.11 ppm (s, 3H, 3 × *H*-19); *OH*-7 not observed;

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 159.7 (Ar$\underline{C}^{PMB}$), 139.2 (Ar$\underline{C}^{Ph}$), 134.0 (Ar$\underline{C}^{Ph}$), 130.1 (Ar$\underline{C}^{PMB}$), 129.9 (2 × Ar$\underline{C}^{PMB}$), 129.5 (2 × Ar$\underline{C}^{Ph}$), 128.1 (2 × Ar$\underline{C}^{Ph}$), 114.2 (2 × Ar$\underline{C}^{PMB}$), 73.8 (*C*-10), 72.4 (*C*-8), 70.5 (O$\underline{C}H_2^{PMB}$), 69.5 (*C*-7), 55.4 (O$\underline{C}H_3^{PMB}$), 51.4 (*C*-11'), 42.1 (*C*-9), 26.1 (*C*-11) and 24.9 ppm (*C*-19);

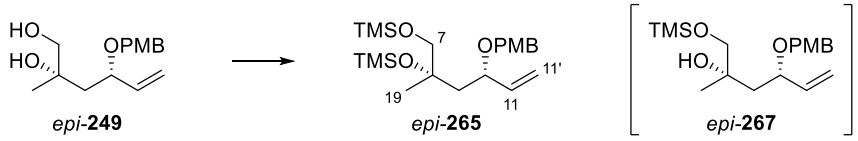
^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 4.49 (d, *J* = 10.8 Hz, 1H, OC$\underline{Ha}$Hb^{PMB}), 4.30 (d, *J* = 10.8 Hz, 1H, OCHa$\underline{Hb}^{PMB}$), 4.04 (ddt, *J* = 11.1, 5.7, 2.7 Hz, 1H, *H*-10), 3.27 (d, *J* = 11.2 Hz, 1H, *H*-7b) and 1.32 ppm (dd, *J* = 14.7, 2.5 Hz, 1H, *H*-9b);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 133.5 (Ar$\underline{C}^{Ph}$), 130.2), 129.9 (2 × Ar$\underline{C}^{PMB}$), 129.5 (2 × Ar$\underline{C}^{Ph}$), 128.8 (Ar$\underline{C}^{Ph}$), 128.3 (2 × Ar$\underline{C}^{Ph}$), 114.2 (2 × Ar$\underline{C}^{PMB}$), 73.5 (*C*-10), 72.5 (*C*-8), 70.7 (O$\underline{C}H_2^{PMB}$), 70.4 (*C*-7), 51.2 (*C*-11'), 40.8 (*C*-9), 25.6 (*C*-11) and 24.2 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3448, 2933, 1613, 1586, 1514, 1447, 1405, 1303, 1248, 1175, 1144, 1086, 1057, 1032, 905, 821, 754, 689 and 628 cm^{-1};

HRMS (ESI^+): Calc. for $C_{21}H_{28}O_6{}^{23}NaS^+$ $[M+Na]^+$ 431.1499; found 431.1498 (Δ –0.09 ppm);

(*S*)-4-((*S*)-2-((4-methoxybenzyl)oxy)but-3-en-1-yl)-2,2,4,7,7-Pentamethyl-3,6-dioxa-2,7-disilaoctane (*epi*-265)



epi-**249** *epi*-**265** *epi*-**267**

Procedure A:

To a solution of diol *epi*-**249** (97.4 mg, 80:20 dr, 365 µmol, 1.0 eq) and 2,6-lutidine (0.17 mL, 1.5 mmol, 4.1 eq) in CH_2Cl_2 (3.8 mL, 96 mM) at –78 °C in a Schlenk tube was added trimethylsilyl triflate (0.14 mL, 0.77 mmol, 2.1 eq). After 30 min the reaction was quenched with NH_4Cl (sat., aq., 1.0 mL), warmed to rt, diluted with brine (1.0 mL) and

extracted with CH_2Cl_2 (3 × 2.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 0:100 to Et_2O:MeOH = 90:10) to afford desired bis-silyl ether *epi*-**265** (103 mg, 69%, 83:17 dr determined at *H*-9) as a colourless oil, silyl ether *epi*-**267** (19.3 mg, 16%, 78:22 dr determined at $Si(C\underline{H}_3)_3^{TMS}$) and recovered diol **249** (9.1 mg, 9%, 80:20 dr determined at *H*-9).

Procedure B:

To a solution of diol *epi*-**249** (244 mg, 80:20 dr, 916 µmol, 1.0 eq) and DMAP (114 mg, 933 µmol 1.0 eq) in CH_2Cl_2 (9.0 mL, 0.10 M) was added Et_3N (1.00 mL, 7.19 mmol, 7.8 eq). The mixture was cooled to 0 °C and treated with trimethylsilyl chloride (distilled, 0.70 mL, 5.5 mmol, 6.0 eq). Cooling was removed after addition. The reaction was quenched after 16 h with NH_4Cl (sat., aq., 10 mL), diluted with H_2O (10 mL) and extracted with Et_2O (40 mL). The organic extract was washed with NH_4Cl (sat., aq., 10 mL), H_2O (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford crude bis-silyl ether *epi*-**265** (364 mg, 94%, 80:20 dr determined at *H*-9a). The material was clean and used in the next step without further purification. For spectroscopic reasons, an analytical sample was purified by flash column chromatography (SiO_2, pentane:Et_2O = 98:2 to 94:6).

Bis-silyl ether *epi*-**265**:

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.29–7.23 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.89–6.83 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 5.89–5.69 (m, 1H, *H*-11), 5.24–5.15 (m, 2H, 2 × *H*-11'), 4.47 (d, *J* = 11.1 Hz, 1H, OC$\underline{H}$aHb^{PMB}), 4.27 (d, *J* = 11.1 Hz, 1H, OCHa$\underline{H}$b^{PMB}), 4.06–3.98 (m, 1H, *H*-10), 3.80 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.37 (d, *J* = 9.9 Hz, 1H, *H*-7a), 3.32 (d, *J* = 9.8 Hz, 1H, *H*-7b), 1.78 (dd, *J* = 14.5, 7.4 Hz, 1H, *H*-9a), 1.72–1.61 (m, 1H, *H*-9b), 1.23 (s, 3H, 3 × *H*-19) and 0.11–0.07 ppm (m, 18H, 2 × $Si(C\underline{H}_3)_3^{TMS}$);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 159.2 (Ar*C*^{PMB}), 140.0 (*C*-11), 131.0 (Ar*C*^{PMB}), 129.6 (2 × Ar*C*^{PMB}), 115.9 (*C*-11'), 113.9 (2 × Ar*C*^{PMB}), 77.4 (*C*-10), 76.1 (*C*-8), 71.0 (O*C*H$_2^{PMB}$), 69.8 (*C*-7), 55.4 (O*C*H$_3^{PMB}$), 45.3 (*C*-9), 24.9 (*C*-19), 2.8 (Si(*C*H$_3$)$_3^{TMS}$) and –0.4 ppm (Si(*C*H$_3$)$_3^{TMS}$);

^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 4.46 (d, *J* = 11.1 Hz, 1H, OC*H*aHb^{PMB}), 4.25 (d, *J* = 11.0 Hz, 1H, OCHa*H*b^{PMB}), 3.51–3.45 (m, 1H, *H*-7a), 3.42–3.37 (m, 1H, *H*-7b), 1.84 (dd, *J* = 14.5, 7.4 Hz, 1H, *H*-9a) and 1.20 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 140.1 (*C*-11), 129.6 (2 × Ar*C*^{PMB}), 76.1 (*C*-8), 69.9 (*C*-7), 46.2 (*C*-9), 26.2 (*C*-19), 2.7 (Si(*C*H$_3$)$_3^{TMS}$) and –0.3 ppm (Si(*C*H$_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 2953, 2364, 2339, 1614, 1514, 1249, 1172, 1087, 1038, 992, 926, 881, 841, 754, 685, 657, 643 and 626 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{21}H_{38}O_4{}^{23}NaSi_2{}^+$ [M+Na]$^+$ 433.2201; found 433.2198 (Δ –0.61 ppm).

Silyl ether *epi*-**267**:

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.26–7.21 (m, 2H, 2 × Ar*H*^{PMB}), 6.90–6.84 (m, 2H, 2 × Ar*H*^{PMB}), 5.84–5.67 (m, 1H, *H*-11), 5.31–5.19 (m, 2H, 2 × *H*-11'), 4.52 (d, *J* = 11.1 Hz, 1H, OC*H*aHb^{PMB}), 4.26 (d, *J* = 11.1 Hz, 1H, OCHa*H*b^{PMB}), 4.17–4.07 (m, 1H, *H*-10), 3.79 (s, 3H, OC*H*$_3^{PMB}$), 3.41–3.28 (m, 2H, 2 × *H*-7), 1.89–1.61 (m, 3H, *OH*-8, 2 × *H*-9), 1.13 (s, 3H, 3 × *H*-19) and 0.07 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMS}$);

^{13}C NMR (major diastereomer), 101 MHz), $CDCl_3$) δ = 159.9 (Ar*C*^{PMB}), 139.2 (*C*-11), 130.5 (Ar*C*^{PMB}), 130.4 (2 × Ar*C*^{PMB}), 117.5 (*C*-11'), 114.5 (*C*-j2 × Ar*C*^{PMB}), 78.6 (*C*-10), 72.8 (*C*-8), 70.3 (O*C*H$_2^{PMB}$), 69.5 (*C*-7), 55.8 (O*C*H$_3^{PMB}$), 43.6 (*C*-9), 26.1 (*C*-19) and 0.0 ppm (*C*-TMS);

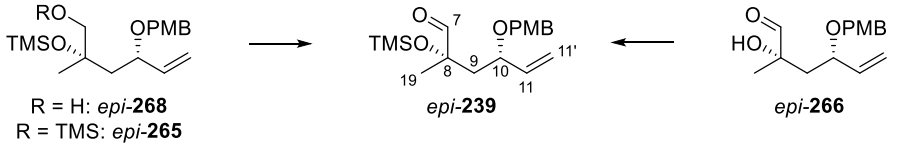
^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 4.54 (d, *J* = 11.1 Hz, 1H, OC*H*aHb^{PMB}), 4.28 (d, *J* = 11.1 Hz, 1H, OCHa*H*b^{PMB}) and 0.09 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMS}$);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 139.2 (*C*-11), 117.7 (*C*-11'), 114.4 (2 × Ar*C*^{PMB}), 78.8 (*C*-10), 73.0 (*C*-8), 71.3 (*C*-7), 70.4 (O*C*H$_2^{PMB}$), 43.6 (*C*-9), 24.4 (*C*-19) and 0.1 ppm (Si(*C*H$_3$)$_3^{TMS}$).

FT-IR ν_{max} (thin film): 3408, 2923, 2853, 2345, 2166, 2122, 1988, 1730, 1613, 1587, 1515, 1463, 1302, 1250, 1175, 1036, 930, 822, 694, 650, 619 and 611 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{18}H_{31}O_4Si^+$ $[M+H]^+$ 339.1986; not found by ESI or APCI.

(2*S*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methyl-2-((trimethylsilyl)oxy)hex-5-enal (*epi*-239)



Note: When mixtures of diatereomers were subjected bis-silyl ether *epi*-**265**, siloxy aldehyde *epi*-**239** and tertary alcohol *epi*-**267** were isolated as inseparable mixtures of diastereomers.

*Procedure A (Swern from epi-**265**):*

A solution of oxalyl chloride (13 µL, 0.16 mmol, 2.3 eq) in CH_2Cl_2 (0.30 mL; stock solution: 0.13 mL in 3.0 mL) was diluted with CH_2Cl_2 (0.55 mL, 50 mM final concentration) and cooled to –78 °C in a Schlenk tube. DMSO (7.1 µL, 99 µmol, 1.4 eq) in CH_2Cl_2 (0.15 mL; stock solution: 0.15 mL in 3.0 mL) was added dropwise. After 15 min, a solution of bis-silyl ether *epi*-**265** (28.7 mg, 88:12 dr, 69.9 µmol, 1.0 eq) in CH_2Cl_2 (300 µL; stock solution: 95.7 mg in 1.00 mL) was added dropwise. After a further 1 h, Et_3N (0.10 mL, 0.72 mmol, 10 eq) was added and the mixture was stirred for 2 h. The reaction was quenched with NH_4Cl (sat., aq., 1.0 mL), warmed to rt, diluted with brine (1.0 mL) and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, pentane: Et_2O = 96:4 to 0:100) to afford desired aldehyde *epi*-**239**

(6.2 mg, 26%, 65:35 dr determined at Si(C$\underline{H}_3)_3^{TMS}$) as colourless film as well as primary alcohol *epi*-**268** (7.1 mg, 30%, > 98:2 dr).

*Procedure B (Dess-Martin from epi-**265**):*

Bis-silyl ether *epi*-**265** (17.1 mg, 80:20 dr, 41.6 µmol, 1.0 eq) was dissolved in a solution of pyridine (34 µL, 0.42 mmol, 10 eq) in CH_2Cl_2 (0.50 mL, 83 mM; stock solution: 0.15 mL in 2.2 mL) and Dess-Martin periodane (21.1 mg, 49.7 µmol, 1.2 eq) was added. After 18 h, the reaction was cooled to 0 °C, quenched with NH_4Cl (sat., aq., 1.0 mL), warmed to rt, diluted with brine (1.0 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, pentane: Et_2O = 96:4 to 80:20) to afford recovered bis-silyl ether *epi*-**265** (1.5 mg, 9%, 93:7 dr), desired aldehyde *epi*-**239** (4.3 mg, 31%, 74:26 dr determined at *H*-7) and primary alcohol *epi*-**268** (6.5 mg, 46%). Primary alcohol **268** was partially separated to afford minor diastereomer **268** (1.6 mg, 95:5 dr) and major diastereomer *epi*-**268** (3.7 mg, 26%, 95:5 dr).

*Procedure C (Ley from epi-**268**):*

To a mixture of alcohol *epi*-**268** (18.9 mg, 97:3 dr, 54.7 µmol, 1.0 eq), NMO (17.3 mg, 150 µmol, 2.7 eq) and molecular sieves (3 Å, 44 mg, activated) in a Schlenk tube was added a solution of TPAP (1.8 mg, 5.1 µmol, 9.4 mol%, stored and weighed out in glove box) in CH_2Cl_2 (0.3 mL + 2 × 0.2 mL rinse, 78 mM). After 45 min the mixture was filtered through a silica plug and rinsed with CH_2Cl_2 (2 mL) and Et_2O (6 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography (SiO_2, pentane:Et_2O = 100:0 to 80:20) to afford desired aldehyde *epi*-**239** (8.3 mg, 45%) as a colourless film as well as regioisomer *epi*-**267** (4.5 mg, 24%) as a colourless film.

*Procedure D (Parikh-Doehring from epi-**268**):*

To a solution of alcohol *epi*-**268** (13.0 mg, 94:6 dr, 38.4 µmol, 1.0 eq) in CH_2Cl_2 (0.38 mL, 85 mM final concentration) was added Et_3N (0.03 mL, 0.2 mmol, 6 eq). The solution was cooled to 0 °C and a solution of $SO_3 \cdot$ pyridine (25 mg, 0.15 mmol, 4.0 eq) in DMSO (0.07 mL, 25 eq; stock solution: 107 mg in 0.30 mL) was added. After 5 h the reaction was diluted with CH_2Cl_2 (4.0 mL) and washed with H_2O (2 × 2.0 mL) as well as brine (2.0 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2 pentane:Et_2O = 100:0 to 50:50) to afford desired aldehyde *epi*-**239** (6.6 mg, 51%, 96:4 dr determined at *H*-7) as a colourless syrup as well as recovered alcohol *epi*-**268** (2.5 mg, 18%, > 98:2 dr).

*Procedure E (from epi-**266**):*

Note: Hydroxy aldehyde *epi*-**266** (20.1 mg, 85:15 dr, 76.0 µmol) was converted into siloxy aldehyde *epi*-**239** in two equal batches using different solvents (CH_2Cl_2 and DMF). Both reactions had comparable NMR-yields and the purification was performed on the combined crude reaction mixtures.

To a solution of aldehyde *epi*-**266** (10.2 mg, 85:15 dr, 38.6 µmol, 1.0 eq) and DMAP (6.9 mg, 57 µmol, 1.5 eq) in DMF (0.38 mL, 0.10 M) was added Et_3N (0.05 mL, 0.4 mmol, 9 eq). At 0 °C trimethylsilyl chloride (0.03 mL, 0.2 mmol, 6 eq) and the mixture was allowed to warm to rt. After 16 h, the reaction was diluted with CH_2Cl_2 (6.0 mL), washed with NH_4Cl (sat., aq., 1.0 mL), H_2O (3 × 1.0 mL) and brine (1.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue of the combined batches was purified by flash column chromatography (SiO_2, pentane: Et_2O = 95:5 to 80:20) to afford aldehyde *epi*-**239** (15.4 mg, 60%, 79:21 dr determined at *H*-7) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.44 (s, 1H, *H*-7), 7.24–7.18 (m, 2H, 2 × Ar*H*^{PMB}), 6.89–6.84 (m, 2H, 2 × Ar*H*^{PMB}), 5.69 (ddd, *J* = 16.9, 10.5, 7.9 Hz, 1H, *H*-11), 5.26–5.18 (m, 2H, 2 × *H*-11'), 4.40 (d, *J* = 11.0 Hz, 1H, OC*H*aHb^{PMB}), 4.17 (d, *J* = 11.0 Hz, 1H, OCHa*H*b^{PMB}), 3.84 (td, *J* = 7.9, 4.7 Hz, 1H, *H*-10), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 2.07 (dd, *J* = 14.2, 8.0 Hz, 1H, *H*-9a), 1.84 (dd, *J* = 14.2, 4.7 Hz, 1H, *H*-9b), 1.31 (s, 3H, 3 × *H*-19) and 0.12 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMS}$);

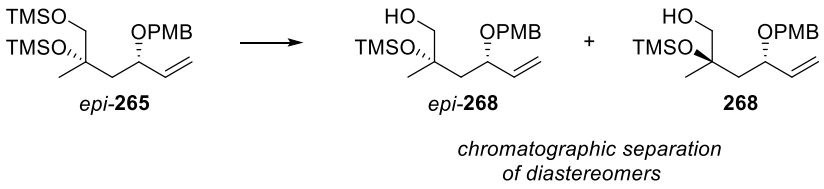
^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.6 (*C*-7), 159.3 (Ar*C*^{PMB}), 138.7 (*C*-11), 130.3 (Ar*C*^{PMB}), 129.8 (2 × Ar*C*^{PMB}), 117.9 (*C*-11'), 113.9 (2 × Ar*C*^{PMB}), 79.3 (*C*-8), 76.7 (*C*-10), 69.9 (O*C*H$_2^{PMB}$), 55.4 (O*C*H$_3^{PMB}$), 46.1 (*C*-9), 22.9 (*C*-19) and 2.5 ppm (Si(*C*H$_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 2956, 1736, 1613, 1514, 1250, 1174, 1146, 1108, 1036, 842 and 686 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{18}H_{28}O_4{}^{23}NaSi^+$ $[M+Na]^+$ 359.1649; found 359.1665 (Δ 4.34 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –9.9 (c = 0.65, CH_2Cl_2).

(2*S*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methyl-2-((trimethylsilyl)oxy)hex-5-en-1-ol (*epi*-268)



epi-**265** *epi*-**268** **268**

chromatographic separation of diastereomers

Note: The reaction was closely followed by TLC and was stopped when formation of diol *epi*-**249** was observed.

To a solution of bis-silyl ether *epi*-**265** (48.3 mg, 81:19 dr, 118 µmol, 1.0 eq) in THF (725 µL, 0.15 M final concentration) at 0 °C (cryostat) was added a mixture of AcOH:H_2O (4:1, 85 µL). After 16 h, the mixture was gradually warmed to 10 °C and AcOH:H_2O (4:1, 85 µL) was added. After an additional 24 h, the reaction was diluted with EtOAc (2.0 mL) and washed with Na_2CO_3 (sat., aq., 10 mL). The separated aqueous layer was extracted

with EtOAc (2 × 2.0 mL) and the combined organic layers washed with brine (1.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 95:5 to 50:50) to afford recovered bis-silyl ether *epi*-**265** (12.0 mg, 25%) and desired alcohol *epi*-**268** (21.0 mg, 53%, 95:5 dr determined at *H*-9a) as a colourless oil. Isolation of the minor diastereomer **268** was hampered by contamination of alcohol *epi*-**268**. A clean sample of alcohol **268** (42.1 mg, 95:5 dr) was isolated from combined batches.

Following a similar procedure bis-silyl ether *epi*-**265** (331 mg, 80:20 dr, 806 µmol) was converted into desired product *epi*-**268** (70.6 mg, 26%, 95:5 dr) with 22 h reaction time. Additionally, recovered *epi*-**265** (149 mg, 45%) and diol *epi*-**249** (37.4 mg, 17%) were isolated.

Silyl ether *epi*-**268** (major diastereomer):

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25–7.20 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.91–6.84 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 5.83–5.72 (m, 1H, *H*-11), 5.26–5.24 (m, 1H, *H*-11'a), 5.23–5.20 (m, 1H, *H*-11'b), 4.49 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}$aHb^{PMB}), 4.22 (d, *J* = 11.1 Hz, 1H, OCHa$\underline{H}$b^{PMB}), 3.85 (dddt, *J* = 8.8, 7.8, 2.8, 0.8 Hz, 1H, *H*-10), 3.80 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.38 (app. dd, *J* = 6.9, 0.8 Hz, 2H, 2 × *H*-7), 2.76 (t, *J* = 6.9 Hz, 1H, *OH*-7), 1.97 (dd, *J* = 14.6, 9.0 Hz, 1H, *H*-9a), 1.71 (dd, *J* = 14.7, 2.7 Hz, 1H, *H*-9b), 1.21 (s, 3H, 3 × *H*-19) and 0.11 ppm (s, 9H, Si(C$\underline{H}_3$)$_3^{TMS}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.4 (Ar$\underline{C}^{PMB}$), 139.1 (*C*-11), 130.0 (Ar$\underline{C}^{PMB}$), 129.9 (2 × Ar$\underline{C}^{PMB}$), 116.9 (*C*-11'), 114.0 (2 × Ar$\underline{C}^{PMB}$), 77.8 (*C*-10), 76.6 (*C*-8), 70.8 (*C*-7), 70.1 (O$\underline{C}H_2^{PMB}$), 55.4 (O$\underline{C}H_3^{PMB}$), 46.2 (*C*-9), 24.7 (*C*-19) and 2.7 ppm (Si($\underline{C}$H$_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 3455, 2954, 2871, 2837, 1613, 1587, 1514, 1464, 1421, 1302, 1248, 1174, 1142, 1109, 1036, 926, 839, 755 and 683 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{18}H_{30}O_4{}^{23}NaSi^+$ [M+Na]$^+$ 361.1806; found 361.1806 (Δ 0.13 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –34.4 (c = 1.00, CH_2Cl_2).

Silyl ether **268** (minor diastereomer):

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26–7.22 (m, 2H, 2 × Ar*H*^{PMB}), 6.93–6.83 (m, 2H, 2 × Ar*H*^{PMB}), 5.75 (ddd, *J* = 17.2, 10.2, 7.8 Hz, 1H, *H*-11), 5.29–5.20 (m, 2H, 2 × *H*-11'), 4.48 (d, *J* = 10.7 Hz, 1H, OC*H*aHb^{PMB}), 4.25 (d, *J* = 10.7 Hz, 1H, OCHa*H*b^{PMB}), 4.13–4.03 (m, 1H, *H*-10), 3.80 (s, 3H, O*C*H$_3^{PMB}$), 3.44 (dd, *J* = 11.2, 5.3 Hz, 1H, *H*-7a), 3.31–3.22 (m, 1H, *OH*-7), 2.98 (dd, *J* = 9.5, 5.4 Hz, 1H, *H*-7b), 1.88 (dd, *J* = 15.2, 9.3 Hz, 1H, *H*-9a), 1.64–1.56 (m, 1H, *H*-9b), 1.26 (s, 3H, 3 × *H*-19) and 0.10 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMS}$);

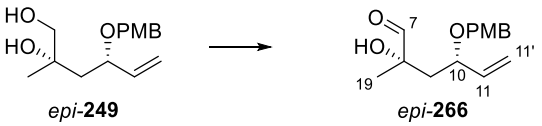
^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.5 (Ar*C*^{PMB}), 139.0 (*C*-11), 130.0 (2 × Ar*C*^{PMB}), 129.9 (Ar*C*^{PMB}), 116.6 (*C*-11'), 114.1 (2 × Ar*C*^{PMB}), 77.1 (*C*-8), 75.8 (*C*-10), 70.4 (*C*-7), 69.5 (O*C*H$_2^{PMB}$), 55.4 (O*C*H$_3^{PMB}$), 45.7 (*C*-9), 27.6 (*C*-19) and 2.7 ppm (Si(*C*H$_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 3495, 2955, 2837, 1613, 1587, 1515, 1464, 1422, 1402, 1371, 1302, 1249, 1174, 1155, 1109, 1081, 1058, 1036, 927, 839, 755 and 683 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{18}H_{30}O_4{}^{23}NaSi^+$ $[M+Na]^+$ 361.1806; found 361.1803 (Δ 0.83 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –48.7 (c = 1.00, CH_2Cl_2).

(2*S*,4*S*)-2-Hydroxy-4-((4-methoxybenzyl)oxy)-2-methylhex-5-enal (*epi*-266)



epi-**249** → *epi*-**266**

chromatographic separation of diastereomers possible

To a solution of diol *epi*-**249** (33.3 mg, 87:13 dr, 125 µmol, 1.0 eq) in CH_2Cl_2 (1.0 mL, 93 mM) at 0 °C was added Et_3N (0.09 mL, 0.6 mmol, 5 eq). A solution of SO_3 · pyridine (60 mg, 0.38 mmol, 3.0 eq) in DMSO (0.25 mL, 3.5 mmol, 28 eq; stock solution: 148 mg in 0.62 mL) was added dropwise and the mixture was warmed to rt. After 5 h the reaction was quenched with H_2O (1.0 mL) and extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 95:5) to

afford aldehyde *epi*-**266** (20.8 mg, 63%, 85:15 dr determined at *H*-9b) as colourless oil. For spectroscopic reasons both diastereomers of aldehyde **266** were separated (> 95:5 dr) from an analytic sample using finer silica gel (SiO_2 15–40 µm, CH_2Cl_2:acetone = 100:0 to 98:2).

Result by Daniya Aynetdinova: Following the same procedure *epi*-**249** (140 mg, 80:20 dr, 530 µmol) was converted to aldehyde *epi*-**266** (86 mg, 62%, 95:5 dr).

Aldehyde *epi*-**266** (major diastereomer):

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.63 (d, *J* = 0.9 Hz, 1H, *H*-7), 7.24–7.17 (m, 2H, 2 × Ar*H*^{PMB}), 6.90–6.82 (m, 2H, 2 × Ar*H*^{PMB}), 5.70 (ddd, *J* = 16.7, 10.7, 7.7 Hz, 1H, *H*-11), 5.32–5.22 (m, 2H, 2 × *H*-11'), 4.58 (br s, 1H, *OH*-8), 4.50 (d, *J* = 11.0 Hz, 1H, OC*H*aHb^{PMB}), 4.19 (d, *J* = 11.0 Hz, 1H, OCHa*H*b^{PMB}), 4.02–3.94 (m, 1H, *H*-10), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 2.04–1.87 (m, 2H, 2 × *H*-9) and 1.21 ppm (s, 3H, 3 × *H*-19);

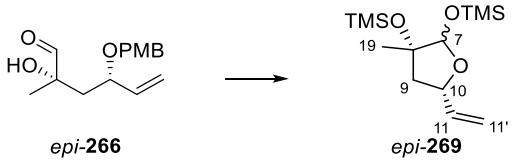
^{13}C NMR (101 MHz, $CDCl_3$) δ = 205.9 (*C*-7), 159.6 (Ar*C*^{PMB}), 137.6 (*C*-11), 129.9 (Ar*C*^{PMB}), 129.5 (2 × ArC^{PMB}), 118.6 (*C*-11'), 114.1 (2 × ArC^{PMB}), 78.1 (*C*-10), 77.8 (*C*-8), 70.2 (OC*H*$_2^{PMB}$), 55.4 (OC*H*$_3^{PMB}$), 43.3 (*C*-9) and 23.9 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3655, 3442, 2980, 1731, 1613, 1514, 1463, 1392, 1303, 1249, 1175, 1099, 1074, 1033, 935 and 823 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{15}H_{20}O_4{}^{23}Na$ [M+Na$^+$] 287.1254; found 287.1256 (Δ +0.91 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –48.9 (c = 0.43, $CHCl_3$).

(((3*S*,5*S*)-3-Methyl-5-vinyltetrahydrofuran-2,3-diyl)bis(oxy))bis(trimethylsilane) (*epi*-269)



epi-**266** → *epi*-**269**

Note: Experiment performed by Daniya Aynetdinova.

To a solution of aldehyde *epi*-**266** (80.0 mg, 303 µmol, 1.0 eq) in CH_2Cl_2 (1.4 mL, 0.22 mM) 2,6-lutidine (0.08 ml, 0.7 mmol, 2 eq) was added and the mixture was cooled to –78 °C. TMSOTf (0.06 ml, 0.3 mmol, 1 eq) was added dropwise and the mixture was stirred for 40 min. The reaction was quenched with $NaHCO_3$ (sat., aq., 0.6 mL), warmed to rt, diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 98:2) to afford aldehyde *epi*-**239** as a single diastereomer (37 mg, 37%) and cyclic TMS protected acetal *epi*-**269** (24 mg, 30%, 72:28 dr) as an inseparable mixture of diastereoisomers.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 5.99 (m, 1H, *H*-11), 5.15 (m, 1H, *H*-11'a), 5.07–5.01 (m, 2H, *H*-7, H11'b), 4.54 (m, 1H, *H*-10), 2.18 (dd, *J* = 12.8, 8.8 Hz, 1H, *H*-9a), 1.75 (dd, *J* = 12.7, 3.9 Hz, 1H, *H*-9b), 1.34 (s, 3H, 3 × *H*-19) and 0.23–0.07 ppm (m, 18H, 2 × $Si(C\underline{H}_3)_3^{TMS}$);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 140.6 (*C*-11), 115.2 (*C*-11'), 104.5 (*C*-7), 83.8 (*C*-8), 79.7 (*C*-10), 44.4 (*C*-9), 22.3 (*C*-19), 2.5 ($Si(\underline{C}H_3)_3^{TMS}$) and 0.3 ppm ($Si(\underline{C}H_3)_3^{TMS}$);

^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 5.88 (m, 1H, *H*-11), 4.77 (s, 1H, *H*-7), 4.28 (m, 1H, *H*-10), 2.10–2.00 (m, 1H, *H*-9a), 1.91 (dd, *J* = 11.5, 6.6 Hz, 1H, *H*-9b), 1.31 (d, *J* = 0.9 Hz, 3H, 3 × *H*-19);

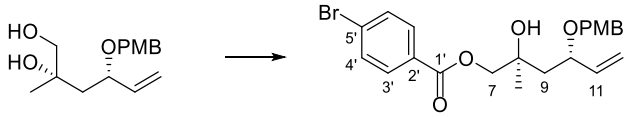
^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 115.8 (*C*-11'), 101.2 (*C*-7), 79.2 (*C*-10), 42.5 (*C*-9), 26.0 (*C*-19), 2.4 ($Si(\underline{C}H_3)_3^{TMS}$) and 0.7 ppm ($Si(\underline{C}H_3)_3^{TMS}$);

FT-IR ν_{max} (thin film): 2956, 2361, 2342, 1251, 1171, 1091, 1035, 840, 751, 668, 654 cm^{-1};

HRMS (ESI^+): Calc. for $C_{13}H_{28}O_3{}^{23}NaSi_2$ [M+Na^+] 311.1469; found 311.1469 (Δ 0.07 ppm).

6.1.10 Assignment of stereocentre *C*-8:

(2*S*,4*S*)-2-Hydroxy-4-((4-methoxybenzyl)oxy)-2-methylhex-5-en-1-yl 4-bromobenzoate (*epi*-272)



epi-**249** *epi*-**272**

A mixture of diol *epi*-**249** (15.6 mg, 58.6 µmol, 1.0 eq) and 4-bromobenzoyl chloride (67.2 mg, 306 µmol, 5.2 eq) was dissolved in CH_2Cl_2 (0.38 mL, CH_2Cl_2:pyridine = 1:1) and pyridine (0.38 mL, 4.7 mmol, 81 eq) was added. After 1.5 h, the reaction was quenched with HCl (1 M, aq., 2.0 mL) and extracted with Et_2O (3 × 4 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, PhMe:acetone = 98:2 to 92:8) to afford ester *epi*-**272** (24.3 mg, 92%) as a colourless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93–7.83 (m, 2H, 2 × *H*-3'), 7.62–7.56 (m, 2H, 2 × *H*-4'), 7.25–7.20 (m, 2H, 2 × Ar*H*^{PMB}), 6.90–6.84 (m, 2H, 2 × Ar*H*^{PMB}), 5.75 (ddd, *J* = 16.5, 10.9, 7.7 Hz, 1H, *H*-11), 5.27 (s, 1H, *H*-11'a), 5.25–5.21 (m, 1H, *H*-11'b), 4.55 (d, *J* = 11.0 Hz, 1H, OC*H*aHb^{PMB}), 4.28 (d, *J* = 11.0 Hz, 1H, OCHa*H*b^{PMB}), 4.27–4.12 (m, 4H, *OH*-8, 2 × *H*-7, *H*-10), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 1.94 (dd, *J* = 15.0, 10.9 Hz, 1H, *H*-9a), 1.78 (dd, *J* = 15.0, 2.8 Hz, 1H, *H*-9b) and 1.28 ppm (s, 3H, 3 × *H*-19);

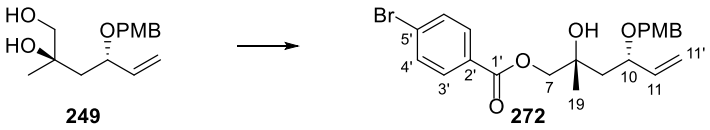
^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.5 (*C*-1'), 159.5 (Ar*C*^{PMB}), 137.9 (*C*-11), 131.8 (2 × *C*-4'), 131.1 (2 × *C*-3'), 129.7 (2 × Ar*C*^{PMB}), 129.4 (Ar*C*^{PMB}), 129.0 (*C*-2'), 128.2 (*C*-5'), 117.9 (*C*-11'), 114.0 (2 × Ar*C*^{PMB}), 78.3 (*C*-10), 71.3 (*C*-8), 70.1 (O*C*H$_2^{PMB}$), 70.0 (*C*-7), 55.3 (O*C*H$_3^{PMB}$), 43.4 (*C*-9) and 26.6 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3482, 2920, 2851, 1720, 1613, 1590, 1514, 1485, 1464, 1397, 1269, 1251, 1174, 1115, 1103, 1070, 1035, 1012, 928, 848, 822, 756 and 683 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{22}H_{25}O_5{}^{23}Na^{79}Br^+$ $[M+Na]^+$ 471.0778; found 471.0776 (Δ –0.26 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –49.0 (c = 0.17 CH_2Cl_2).

(2*R*,4*S*)-2-Hydroxy-4-((4-methoxybenzyl)oxy)-2-methylhex-5-en-1-yl 4-bromobenzoate (272)



A mixture of diol **249** (14.3 mg, 90:10 dr, 53.7 µmol, 1.0 eq) and 4-bromobenzoyl chloride (57.3 mg, 261 µmol, 4.9 eq) were dissolved in CH_2Cl_2:pyridine (1:1, 0.70 mL, 77 µM). After 1.5 h, the reaction was quenched with HCl (1 M, aq., 2.0 mL) and extracted with Et_2O (3 × 4.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, PhMe:acetone = 99:1 to 94:6) to afford ester **272** (22.0 mg, 91%) as a colourless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97–7.85 (m, 2H, *H*-3'), 7.62–7.54 (m, 2H, *H*-4'), 7.30–7.21 (m, 2H, 2 × Ar*H*^{PMB}), 6.92–6.84 (m, 2H, 2 × Ar*H*^{PMB}), 5.77 (ddd, *J* = 17.2, 10.2, 7.8 Hz, 1H, *H*-11), 5.33–5.26 (m, 2H, 2 × *H*-11'), 4.57 (d, *J* = 11.0 Hz, 1H, OC*H*aHb^{PMB}), 4.31 (d, *J* = 11.1 Hz, 1H, OCHa*H*b^{PMB}), 4.26–4.18 (m, 2H, *OH*-8, *H*-10), 4.18–4.11 (m, 2H, 2 × *H*-7), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 2.02 (dd, *J* = 14.7, 10.9 Hz, 1H, *H*-9a), 1.63 (dd, *J* = 14.7, 2.7 Hz, 1H, *H*-9b) and 1.26 ppm (s, 3H, 3 × *H*-19);

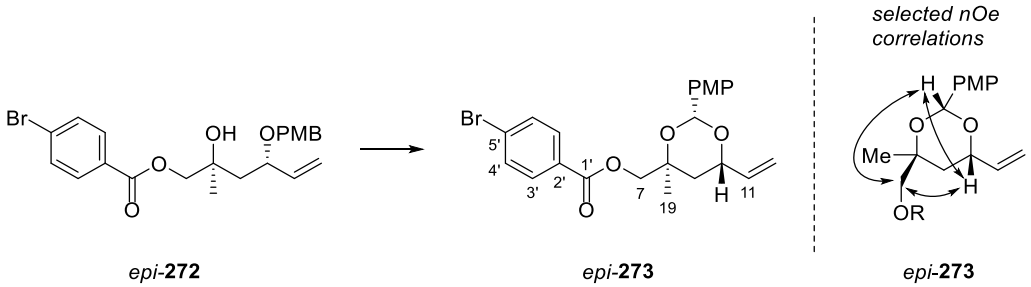
^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.8 (*C*-1'), 159.6 (Ar*C*^{PMB}), 138.0 (*C*-11), 131.8 (2 × *C*-4'), 131.3 (2 × *C*-3'), 130.1 (2 × Ar*C*^{PMB}), 129.5 (*C*-2'), 129.2 (*C*-5'), 128.2 (Ar*C*^{PMB}), 118.1 (*C*-11'), 114.1 (2 × Ar*C*^{PMB}), 78.0 (*C*-10), 72.4 (*C*-7), 71.6 (*C*-8), 70.1 (O*C*H$_2^{PMB}$), 55.4 (O*C*H$_3^{PMB}$), 42.9 (*C*-9) and 24.1 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3476, 2979, 1720, 1613, 1590, 1514, 1484, 1464, 1398, 1270, 1250, 1174, 1103, 1070, 1034, 1012, 929, 848, 822, 756 and 683 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{22}H_{25}O_5{}^{23}Na^{81}Br^+$ [M+Na]$^+$ 473.0758; found 473.0756;

Specific Rotation: $[\alpha]_D^{25}$ –38.3 (c = 1.00, CH_2Cl_2).

((2*R*,4*S*,6*S*)-2-(4-methoxyphenyl)-4-Methyl-6-vinyl-1,3-dioxan-4-yl)methyl 4-bromobenzoate (*epi*-273)



epi-**272** *epi*-**273** *epi*-**273**

To a solution of ether *epi*-**272** (24.3 mg, 54.1 µmol, 1.0 eq) in CH_2Cl_2 (1.0 mL, 54 mM) at 0 °C was added DDQ (12.8 mg, 56.4 µmol, 1.0 eq). The mixture was warmed to rt after 2 h. After an additional 2 h, the reaction was quenched with $NaHCO_3$ (sat., aq., 1.0 mL), extracted with Et_2O (3 × 2.0 mL). The combined organic extracts were washed with brine (2.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane to Et_2O) to afford desired acetal *epi*-**273** (12.5 mg, 52%, > 98:2 dr) as a colourless syrup as well as recovered ether *epi*-**272** (1.5 mg, 6%). The relative stereochemistry was confirmed by nOe analysis.

^{1}H NMR (500 MHz, acetone-d6 = 2.05 ppm) δ = 8.02–7.97 (m, 2H, 2 × *H*-3'), 7.77–7.72 (m, 2H, 2 × *H*-4'), 7.43–7.37 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.91–6.83 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.00 (s, 1H, C$\underline{H}O_2^{PMP}$), 5.93 (ddd, *J* = 17.4, 10.7, 5.1 Hz, 1H, *H*-11), 5.34 (dt, *J* = 17.3, 1.7 Hz, 1H, *H*-11'a), 5.14 (dt, *J* = 10.7, 1.6 Hz, 1H, *H*-11'b), 5.10 (d, *J* = 11.8 Hz, 1H, *H*-7a), 4.70–4.62 (m, 1H, *H*-10), 4.40 (d, *J* = 11.8 Hz, 1H, *H*-7b), 3.77 (s, 3H, OC$\underline{H}_3^{PMP}$), 1.94 (dd, *J* = 13.9, 2.6 Hz, 1H, *H*-9a), 1.63 (dd, *J* = 13.9, 12.1 Hz, 1H, *H*-9b) and 1.40 ppm (s, 3H, 3 × *H*-19);

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97–7.89 (m, 2H, 2 × *H*-3'), 7.64–7.56 (m, 2H, 2 × *H*-4'), 7.47–7.39 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.91–6.82 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 5.96–5.85 (m, 2H, C$\underline{H}O_2^{PMP}$, *H*-11), 5.35 (dt, *J* = 17.3, 1.4 Hz, 1H, *H*-11'a), 5.19 (dt, *J* = 10.6, 1.3 Hz, 1H,

H-11'b), 4.90 (d, *J* = 11.6 Hz, 1H, *H*-7a), 4.53 (dtt, *J* = 10.7, 5.4, 1.4 Hz, 1H, *H*-10), 4.42 (d, *J* = 11.6 Hz, 1H, *H*-7b), 3.79 (s, 3H, OC$\underline{H}_3^{PMP}$), 1.80–1.74 (m, 2H, 2 × *H*-9) and 1.45 ppm (s, 3H, × *H*-19);

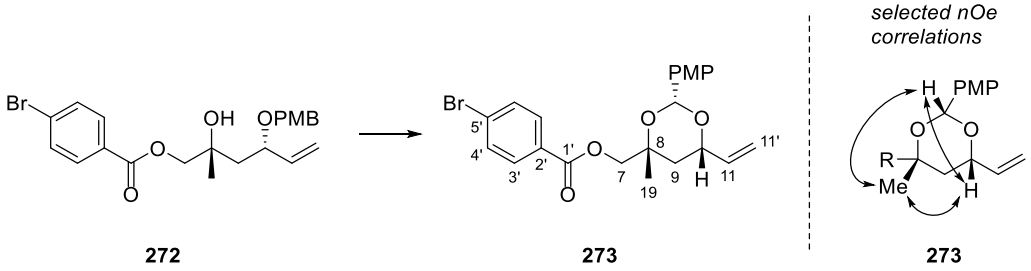
^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.8 (*C*-1'), 160.1 (Ar$\underline{C}^{PMP}$), 137.8 (*C*-11), 132.0 (2 × *C*-4'), 131.3 (2 × *C*-3'), 131.3 (*C*-2'), 128.9 (*C*-5'), 128.5 (Ar$\underline{C}^{PMP}$), 127.7 (2 × Ar$\underline{C}^{PMP}$), 116.2 (*C*-11'), 113.8 (2 × Ar$\underline{C}^{PMP}$), 95.6 ($\underline{C}HO_2^{PMP}$), 73.8 (*C*-10), 73.3 (*C*-8), 65.0 (*C*-7), 55.5 (O$\underline{C}H_3^{PMP}$), 37.7 (*C*-9) and 27.6 ppm (*C*-19);

FT-IR ν_{max} (thin film): 2924, 2851, 1721, 1615, 1591, 1518, 1484, 1463, 1397, 1286, 1250, 1172, 1115, 1103, 1071, 1034, 1012, 926, 830, 772, 756 and 683 cm^{-1};

HRMS (ESI^+): Calc. for $C_{22}H_{23}O_5{}^{23}Na^{81}Br^+$ $[M+Na]^+$ 471.0602; found 471.0600;

Specific Rotation: $[\alpha]_D^{25}$ +30.8 (c = 0.77, CH_2Cl_2).

((2*R*,4*R*,6*S*)-2-(4-methoxyphenyl)-4-Methyl-6-vinyl-1,3-dioxan-4-yl)methyl 4-bromobenzoate (273)



272 **273** **273**

To a solution of ether **272** (19.4 mg, 43.2 µmol, 1.0 eq) in CH_2Cl_2 (0.87 mL, 50 mM) at 0 °C was added DDQ (10.7 mg, 47.4 µmol, 1.0 eq). The mixture was warmed to rt after 1.5 h. After additional 3.5 h, the reaction was quenched $NaHCO_3$ (sat., aq., 1.0 mL), extracted with Et_2O (3 × 2.0 mL). The combined organic extracts were washed with brine (2.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane to Et_2O) to afford desired acetal **273** (7.1 mg, 37%, > 98:2 dr) as a colourless syrup as well as recovered ether **272** (2.3 mg, 12%). The relative stereochemistry was confirmed by nOe analysis.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98–7.88 (m, 2H, *H*-3'), 7.64–7.56 (m, 2H, *H*-4'), 7.49–7.39 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.92–6.85 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 5.91 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1H, *H*-11), 5.82 (s, 1H, C$\underline{H}O_2^{PMP}$), 5.35 (dt, *J* = 17.3, 1.4 Hz, 1H, *H*-11'a), 5.19 (dt, *J* = 10.6, 1.3 Hz, 1H, *H*-11'b), 4.54 (dddt, *J* = 11.8, 5.3, 2.5, 1.3 Hz, 1H, *H*-10), 4.31 (d, *J* = 11.1 Hz, 1H, *H*-7a), 4.26 (d, *J* = 11.2 Hz, 1H, *H*-7b), 3.79 (s, 3H, OC$\underline{H}_3^{PMP}$), 1.92–1.82 (m, 1H, *H*-9a), 1.60 (dd, *J* = 13.1, 2.5 Hz, 1H, *H*-9b) and 1.56 ppm (s, 3H, 3 × *H*-19);

^{1}H NMR (400 MHz, acetone-d6 = 2.05 ppm) δ = 8.04–7.96 (m, 2H, *H*-3'), 7.79–7.68 (m, 2H, *H*-4'), 7.46–7.36 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.95–6.82 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.01–5.86 (m, 2H, C$\underline{H}O_2^{PMP}$, *H*-11), 5.33 (dt, *J* = 17.3, 1.7 Hz, 1H, *H*-11'a), 5.12 (dt, *J* = 10.7, 1.6 Hz, 1H, *H*-11'b), 4.66 (dtd, *J* = 9.6, 3.5, 1.8 Hz, 1H, *H*-10), 4.31 (d, *J* = 11.1 Hz, 1H, *H*-7a), 4.25 (d, *J* = 11.0 Hz, 1H, *H*-7b), 3.78 (s, 3H, OC$\underline{H}_3^{PMP}$), 1.84–1.69 (m, 2H, 2 × *H*-9) and 1.61 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.7 (*C*-1'), 160.2 (Ar$\underline{C}^{PMP}$), 137.9 (*C*-11), 131.9 (2 × *C*-4'), 131.3 (2 × *C*-3'), 131.3 (*C*-2'), 129.1 (*C*-5'), 128.4 (Ar$\underline{C}^{PMP}$), 127.8 (2 × Ar$\underline{C}^{PMP}$), 116.2 (*C*-11'), 113.8 (2 × Ar$\underline{C}^{PMP}$), 95.0 ($\underline{C}HO_2^{PMP}$), 73.5 (*C*-8), 73.4 (*C*-10), 72.3 (*C*-7), 55.5 (O$\underline{C}H_3^{PMP}$), 36.8 (*C*-9) and 18.7 ppm (*C*-19);

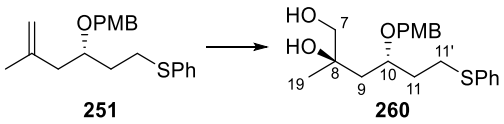
FT-IR ν_{max} (thin film): 2958, 2837, 1722, 1615, 1590, 1518, 1484, 1462, 1397, 1270, 1249, 1172, 1116, 1103, 1071, 1033, 1012, 928, 832, 773, 756, 683 and 628 cm^{-1};

HRMS (ESI^+): Calc. for $C_{22}H_{23}O_5{}^{23}Na^{79}Br^+$ $[M+Na]^+$ 469.0621; found 469.0623;

Specific Rotation: $[\alpha]_D^{25}$ +21.1 (c = 0.55, CH_2Cl_2).

6.1.11 Synthesis of aldehyde *epi*-239

(2*R*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methyl-6-(phenylthio)hexane-1,2-diol (260)



251 **260**

To a solution of olefin **251** (7.60 g, 22.2 mmol, 1.0 eq) and methanesulfonamide (2.11 g, 22.2 mmol, 1.0 eq) in *t*BuOH:H_2O (1:1, 222 mL, 0.1 M) at 0 °C was added AD-mix α(26.1 g, 2.5 eq). The reaction was stirred (400 rpm) for 15 h. After which, the stirring rate was increased to 700 rpm. After additional 25 h, $Na_2S_2O_3$ (10.1 g) was added and the mixture stirred at rt for 30 min before being diluted with H_2O (30 mL) and extracted with EtOAc (3 × 120 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. An analytic sample was concentrated *in vacuo* separately and analysed by ^{1}H NMR (69:31 dr determined at *H*-19). The resulting residue was purified by flash column chromatography (SiO_2, Et_2O:MeOH = 100:0 to 95:5) to afford an inseparable mixture of diastereomers of diol **260** contaminated with methanesulfonamide (8.91 g, 69:31 dr, 89 wt% purity by ^{1}H NMR, 95% calculated yield) as a crystalline solid. The relative stereochemistry of major diastereomer **260** was assigned retrospectively by nOe analysis of cyclic acetals **273** and *epi*-**273**.

Following the same procedure **251** (2.96 g, 8.64 mmol) was converted into diol **260** (3.51 g, 73:27 dr, 81 wt% purity by ^{1}H NMR, 87% calc. yield) over 16 h reaction time with more efficient stirring.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.39–7.33 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.33–7.27 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.25–7.17 (m, 3H, Ar$\underline{H}^{Ph}$, 2 × Ar$\underline{H}^{PMB}$), 6.92–6.84 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 4.52 (d, *J* = 10.7 Hz, 1H, OC$\underline{H}$aHb^{PMB}), 4.36–4.25 (m, 1H, OCHa$\underline{H}$b^{PMB}), 4.02 (dddd, *J* = 10.6, 6.2, 3.9, 2.3 Hz, 1H, *H*-10), 3.92–3.83 (m, 1H, *OH*-8), 3.80 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.42–3.34 (m, 1H, *H*-7a), 3.34–3.25 (m, 1H, *H*-7b), 3.07–2.98 (m, 1H, *H*-11'a), 2.95–2.84

(m, 1H, *H*-11'b), 2.37 (dd, *J* = 8.0, 5.2 Hz, 1H, *OH*-7), 2.08–1.90 (m, 3H, 2 × *H*-11, *H*-9), 1.44 (dd, *J* = 14.8, 2.3 Hz, 1H, *H*-9b) and 1.13 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 159.7 (Ar$\underline{C}^{PMB}$), 136.2 (Ar$\underline{C}^{Ph}$), 130.9 (Ar$\underline{C}^{PMB}$), 130.0 (2 × Ar$\underline{C}^{PMB}$), 129.7 (2 × Ar$\underline{C}^{Ph}$), 129.2 (2 × Ar$\underline{C}^{Ph}$), 126.4 (Ar$\underline{C}^{Ph}$), 114.2 (2 × Ar$\underline{C}^{PMB}$), 75.0 (*C*-10), 72.5 (*C*-8), 71.0 (*C*-7), 70.4 (O$\underline{C}H_2^{PMB}$), 55.4 (O$\underline{C}H_3^{PMB}$), 40.9 (*C*-9), 32.9 (*C*-11), 28.9 (*C*-11') and 24.1 ppm (*C*-19);

^{1}H NMR (minor diastereomer, 400 MHz, $CDCl_3$) δ = 7.39–7.33 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.33–7.27 (m, 2H, 2 × Ar$\underline{H}^{Ph}$), 7.25–7.17 (m, 3H, Ar$\underline{H}^{Ph}$, 2 × Ar$\underline{H}^{PMB}$), 6.92–6.84 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 4.48 (d, *J* = 10.7 Hz, 1H, OC$\underline{Ha}$Hb^{PMB}), 4.36–4.25 (m, 1H, OCHa$\underline{Hb}^{PMB}$), 3.92–3.83 (m, 1H, *H*-10), 3.80 (s, 3H, OC$\underline{H_3}^{PMB}$), 3.53–3.42 (m, 1H, *H*-7a), 3.42–3.34 (m, 1H, *OH*-8), 3.34–3.25 (m, 1H, *H*-7b), 3.07–2.98 (m, 1H, *H*-11'a), 2.95–2.84 (m, 1H, *H*-11'b), 2.27 (dd, *J* = 8.0, 5.1 Hz, 1H, *OH*-7), 2.08–1.90 (m, 2H, 2 × *H*-11), 1.83 (dd, *J* = 14.9, 9.9 Hz, 1H, *H*-9a), 1.67 (dd, *J* = 14.9, 2.5 Hz, 1H, *H*-9b) and 1.14 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 129.9 (2 × Ar$\underline{C}^{PMB}$), 129.6 (2 × Ar$\underline{C}^{Ph}$), 129.3 (2 × Ar$\underline{C}^{Ph}$), 126.4 (Ar$\underline{C}^{Ph}$), 114.2 (2 × Ar$\underline{C}^{PMB}$), 75.3 (*C*-10), 72.5 (*C*-8), 70.5 (O$\underline{C}H_2^{PMB}$), 69.5 (*C*-7), 42.5 (*C*-9), 33.1 (*C*-11), 29.0 (*C*-11') and 25.2 ppm (*C*-19);

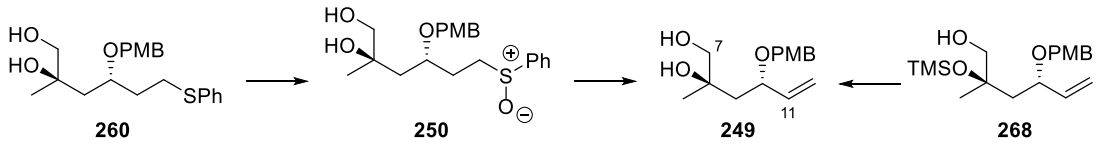
^{1}H NMR (methane sulfonamide, 400 MHz, $CDCl_3$) δ = 4.78 (s, 2H, $H_3CSO_2N\underline{H_2}$) and 3.10 ppm (s, 3H, $\underline{H_3}CSO_2NH_2$);

^{13}C NMR (methane sulfonamide, 101 MHz, $CDCl_3$) δ = 43.6 ppm ($H_3\underline{C}SO_2NH_2$).

FT-IR ν_{max} (thin film): 3372, 2490, 2242, 2073, 1745, 1613, 1514, 1440, 1317, 1249, 1154, 1118, 1061, 973, 822, 742, 692, 647 and 620 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{21}H_{28}O_4{}^{23}NaS^+$ $[M+Na]^+$ 399.1601; found 399.1599 (Δ –0.50 ppm);

(2*R*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methylhex-5-ene-1,2-diol (249)



Procedure A:

Note: Diol **260** (9.97 g) was contaminated with methanesulfonamide (11 wt% by NMR) from the previous step. The reaction was carefully monitored by TLC to avoid overoxidation. The reaction is instantaneous and excess *m*CPBA used is due to batch purity.

To a solution of thio ether **260** (9.97 g, 69:31 dr, 89 wt% by ^{1}H NMR, 23.6 mmol, 1.0 eq) in DCE (470 mL, 50 mM) at 0 °C was added *m*CPBA (5.10 g, 29.6 mmol, 1.3 eq) in portions over 1 h. After which, the reaction mixture was directly purified by flash column chromatography (SiO_2, CH_2Cl_2 to acetone) to afford sulfoxide **250** (9.06 g, 98%, mixture of 4 diastereomers) as a colourless syrup. A heterogeneous mixture of sulfoxide **250** (9.02 g, 23.0 mmol, 1.0 eq), PhMe (460 mL, 50 mm) and K_2CO_3 (15.9 g, 115 mmol, 5.0 eq) was heated to reflux (130 °C). After 3 days, the reaction was cooled to rt, diluted with H_2O (30 mL) and extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 97:3 to 80:20) to afford olefin **249** (4.81 g, 77% over two steps, 72:28 dr determined at *H*-9a) as colourless oil.

Procedure B:

To a solution of silyl ether **268** (39.6 mg, 95:5 dr, 117 µmol, 1.0 eq) in MeOH (1.2 mL, 98 mM) was added K_2CO_3 (9.3 mg, 67 µmol 0.58 eq) at rt. After 1.5 h silica gel was added and the mixture concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, Et_2O:MeOH = 100:0 to 90:10) to afford diol **249** (25.3 mg, 81%, 91:9 dr determined at *H*-9a) as a colourless syrup.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.27–7.20 (m, 2H, 2 × Ar*H*^{PMB}), 6.91–6.84 (m, 2H, 2 × Ar*H*^{PMB}), 5.76 (ddd, *J* = 17.1, 10.3, 7.8 Hz, 1H, *H*-11), 5.33–5.24 (m, 2H, 2 × *H*-11'), 4.56 (d, *J* = 11.1 Hz, 1H, OC*H*aHb^{PMB}), 4.29 (d, *J* = 11.0 Hz, 1H, OCHa*H*b^{PMB}),

4.25–4.17 (m, 1H, *H*-10), 4.01 (s, 1H, *OH*-8), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.37 (dd, *J* = 11.0, 5.6 Hz, 1H, *H*-7a), 3.31 (dd, *J* = 10.9, 7.5 Hz, 1H, *H*-7b), 2.53 (dd, *J* = 7.5, 5.7 Hz, 1H, *OH*-7), 2.04 (dd, *J* = 14.9, 11.1 Hz, 1H, *H*-9a), 1.47 (dd, *J* = 14.9, 2.4 Hz, 1H, *H*-9b) and 1.14 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ = 159.6 (Ar*C*^{PMB}), 138.2 (*C*-11), 130.1 (2 × Ar*C*^{PMB}), 129.5 (Ar*C*^{PMB}), 117.9 (*C*-11'), 114.1 (2 × Ar*C*^{PMB}), 78.0 (*C*-10), 72.5 (*C*-8), 71.0 (*C*-7), 70.1 (O*C*H$_2^{PMB}$), 55.4 (O*C*H$_3^{PMB}$), 43.0 (*C*-9) and 24.2 ppm (*C*-19);

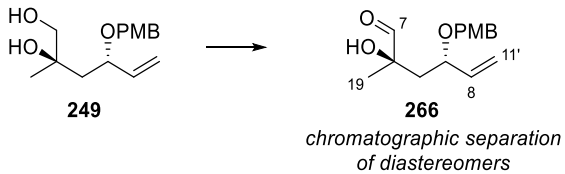
^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 4.25 (d, *J* = 11.1 Hz, 1H, OCHa*H*b^{PMB}), 4.09 (ddd, *J* = 10.4, 7.7, 2.5 Hz, 1H, *H*-10), 3.48 (dd, J = 11.1, 5.1 Hz, 1H, *H*-7a), 3.63 (s, 1H, *OH*-8), 2.35 (dd, *J* = 8.0, 5.1 Hz, 1H, *OH*-7), 1.90 (dd, *J* = 15.0, 10.5 Hz, 1H, *H*-9a) and 1.68 ppm (dd, *J* = 15.0, 2.5 Hz, 1H, *H*-9b);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 138.3 (*C*-11), 130.0 (2 × Ar*C*^{PMB}), 129.6 (Ar*C*^{PMB}), 117.6 (*C*-11'), 78.3 (*C*-10), 72.6 (*C*-8), 70.1 (O*C*H$_2^{PMB}$), 69.5 (*C*-7), 44.3 (*C*-9) and 25.3 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3419, 2936, 2160, 1613, 1586, 1514, 1464, 1400, 1302, 1249, 1175, 1110, 1034, 930, 822, 759 and 687cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{15}H_{22}O_4{}^{23}Na^+$ [M+Na]$^+$ 289.1410; found 289.1410 (Δ –0.14 ppm);

(2*R*,4*S*)-2-Hydroxy-4-((4-methoxybenzyl)oxy)-2-methylhex-5-enal (266)



249 **266**

chromatographic separation of diastereomers

To a solution of diol **249** (1.31 g, 71:29 dr, 4.92 mmol, 1.0 eq) in CH_2Cl_2 (40 mL, 93 mM final concentration) was added Et_3N (3.4 mL, 24 mmol, 5.0 eq) and DMSO (10 mL, 0.14 mol, 28 eq). The mixture was cooled to 0 °C, $SO_3 \cdot$ pyridine (2.36 g, 14.8 mmol, 3.0 eq) was added in one portion and cooling was removed. After 2 h, the reaction was

quenched at 0 °C with H_2O (20 mL) and the separated aqueous layer extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed with brine (2 × 40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2 15–40 µm, CH_2Cl_2:acetone = 100:0 to 98:8) to afford aldehyde **266** (838 mg, 64%, 95:5 dr determined at *H*-7) as a colourless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.46 (d, *J* = 1.1 Hz, 1H, *H*-7), 7.23–7.16 (m, 2H, 2 × Ar*H*^{PMB}), 6.92– 6.82 (m, 2H, 2 × Ar*H*^{PMB}), 5.72 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H, *H*-11), 5.31–5.19 (m, 2H, 2 × *H*-11'), 4.31 (d, *J* = 10.5 Hz, 1H, OC*H*aHb^{PMB}), 4.08 (d, *J* = 10.5 Hz, 1H, OCHa*H*b^{PMB}), 3.94 (dddt, *J* = 11.1, 7.3, 2.1, 0.9 Hz, 1H, *H*-10), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.72 (d, *J* = 1.2 Hz, 1H, *OH*-8), 2.11 (ddd, *J* = 14.7, 10.9, 1.1 Hz, 1H, *H*-9a), 1.86 (dd, *J* = 14.7, 2.1 Hz, 1H, *H*-9b) and 1.24 ppm (s, 3H, 3 × *H*-19);

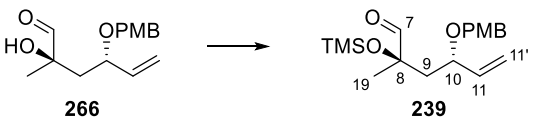
^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.9 (*C*-7), 159.4 (Ar*C*^{PMB}), 137.7 (*C*-11), 130.3 (2 × Ar*C*^{PMB}), 129.8 (Ar*C*^{PMB}), 117.5 (*C*-11'), 113.9 (2 × Ar*C*^{PMB}), 76.2 (*C*-8), 75.8 (*C*-10), 70.2 (O*C*H$_2^{PMB}$), 55.4 (O*C*H$_3^{PMB}$), 44.9 (*C*-9) and 23.9 ppm (*C*-19);

FT-IR ν_{max} (thin film): 2981, 1727, 1613, 1515, 1463, 1392, 1339, 1303, 1249, 1176, 1075, 1035, 936 and 824 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{15}H_{20}O_4{}^{23}Na$ [M+Na$^+$] 287.1254; found 287.1257 (Δ + 1.12 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –23.3 (c = 1.00, CH_2Cl_2).

(2*R*,4*S*)-4-((4-methoxybenzyl)oxy)-2-Methyl-2-((trimethylsilyl)oxy)hex-5-enal (239)



266 **239**

To a solution of hydroxy aldehyde **266** (838 mg, 95:5 dr, 3.17 mmol, 1.0 eq) and DMAP (388 mg, 3.17 mmol, 1.0 eq) in DMF (32 mL, 0.10 M) at 0 °C was added Et_3N (3.5 mL, 25 mmol, 7.9 eq). Trimethylsilyl chloride (2.4 mL, 19 mmol, 6.0 eq) was added and the mixture was allowed to warm to rt. After 16 h, the reaction was quenched at 0 °C with

NH_4Cl (sat., aq., 15 mL), diluted with brine (15 mL), EtOAc (150 mL) and H_2O (5 mL). The separated organic layer was washed with LiCl (5%, 3 × 30 mL) and brine (30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo.* The resulting residue of the combined batches was purified by flash column chromatography (SiO_2, pentane: Et_2O = 95:5 to 80:20) to afford siloxy aldehyde **239** (958 mg, 90%, 95:5 dr determined at *H*-7) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.47 (s, 1H, *H*-7), 7.24–7.17 (m, 2H, 2 × Ar*H*^{PMB}), 6.90–6.82 (m, 2H, 2 × Ar*H*^{PMB}), 5.72 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H, *H*-11), 5.30–5.15 (m, 2H, 2 × *H*-11'), 4.37 (d, *J* = 10.8 Hz, 1H, OC*H*aHb^{PMB}), 4.18 (d, *J* = 10.8 Hz, 1H, OCHa*H*b^{PMB}), 4.02 (dddd, *J* = 9.7, 7.5, 2.3, 1.2 Hz, 1H, *H*-10), 3.79 (s, 3H, OC*H*$_3^{PMB}$), 2.06 (dd, *J* = 14.4, 10.7 Hz, 1H, *H*-9a), 1.72 (dd, *J* = 14.4, 2.2 Hz, 1H, *H*-9b), 1.29 (s, 3H, 3 × *H*-19) and 0.17 ppm (s, 9H, TMS);

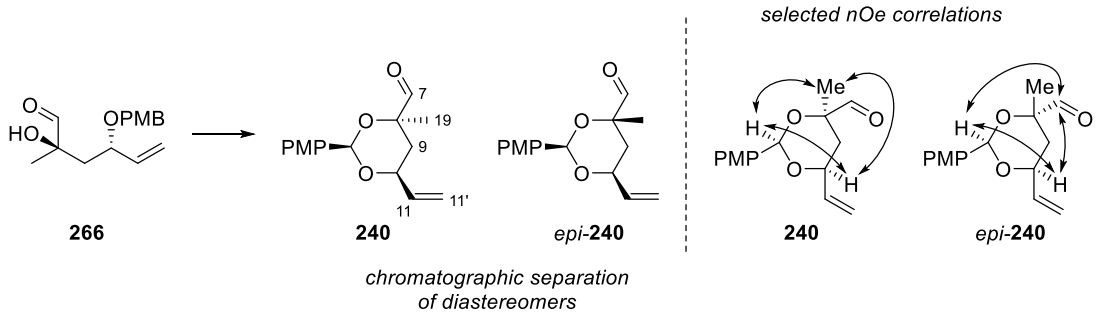
^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.7 (*C*-7), 159.2 (Ar*C*^{PMB}), 138.2 (*C*-11), 130.4 (Ar*C*^{PMB}), 129.8 (2 × Ar*C*^{PMB}), 117.1 (*C*-11'), 113.9 (2 × Ar*C*^{PMB}), 79.6 (*C*-8), 76.2 (*C*-10), 70.3 (O*C*H$_2^{PMB}$), 55.4 (O*C*H$_3^{PMB}$), 48.0 (*C*-9), 24.8 (*C*-19) and 2.6 ppm (Si(*C*H$_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 3659, 2980, 2889, 1736, 1515, 1383, 1249, 1153, 1087, 954 and 841 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{18}H_{28}O_4{}^{23}NaSi^+$ $[M+Na]^+$ 359.1649; found 359.1649 (Δ –0.06 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –16.9 (c = 0.98, CH_2Cl_2).

(2*R*,4*R*,6*S*)-2-(4-methoxyphenyl)-4-Methyl-6-vinyl-1,3-dioxane-4-carbaldehyde (240)



To a solution of ether **266** (25.8 mg, 95:5 dr, 97.6 µmol, 1.0 eq) in CH_2Cl_2 (1.0 mL, 98 mM) was added molecular sieves (activated, 4 Å, 44.9 mg) in Schlenk tube. After 30 min, the mixture was cooled to 0 °C and DDQ (22.3 mg, 1.0 eq) was added in one portion. After 5 h, the reaction was quenched with Na_2SO_4 (30 mg), filtered through a plug of Celite®, rinsed with $NaHCO_3$ (2.0 mL) and H_2O (1.0 mL). The filtrated was extracted with Et_2O (3 × 6.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2 15–40 µm, CH_2Cl_2:acetone = 100:0 to 98:2) to afford acetal **240** (18.6 mg, 73%, > 98:2 dr) as well as recovered ether **266** (4.0 mg, 16%), both as a colourless films.

Following the same procedure hydroxyaldehyde **266** (50.3 mg, 74:26 dr) was converted into minor diastereoisomer *epi*-**240** (7.0 mg, 14%, > 98:2 dr) and desired major diastereoisomer **240** (27.6 mg, 55%, > 98:2 dr). Both compounds were isolated as colourless oil. The relative stereochemistry of both diastereomers was confirmed by nOe analysis by 1,3-diaxial interactions.

Major diastereoisomer **240**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.61 (s, 1H, *H*-7), 7.52–7.42 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.96–6.86 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 5.97–5.84 (m, 2H, C$\underline{H}O_2^{PMP}$, *H*-11), 5.36 (dt, *J* = 17.3, 1.4 Hz, 1H, *H*-11'a), 5.21 (dt, *J* = 10.6, 1.3 Hz, 1H, *H*-11'b), 4.53 (dddd, *J* = 10.2, 5.4, 2.5, 1.2 Hz, 1H, *H*-10), 3.81 (s, 3H, OC$\underline{H}_3^{PMP}$), 1.80 (dd, *J* = 13.4, 11.6 Hz, 1H, *H*-9a) and 1.60–1.52 ppm (m, 4H, *H*-9b,3 × *H*-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.2 (*C*-7), 160.3 (Ar$\underline{C}^{PMP}$), 137.2 (*C*-11), 130.6 (Ar$\underline{C}^{PMP}$), 127.8 (2 × Ar$\underline{C}^{PMP}$), 116.5 (*C*-11'), 113.8 (2 × Ar$\underline{C}^{PMP}$), 95.1 ($\underline{C}HO_2^{PMP}$), 78.9 (*C*-8), 73.2 (*C*-10), 55.5 (O$\underline{C}H_3^{PMP}$), 34.0 (*C*-9) and 17.1 ppm (*C*-19);

FT-IR ν_{max} (thin film): 2931, 2839, 1737, 1615, 1589, 1518, 1458, 1390, 1304, 1249, 1171, 1144, 1071, 1033, 997, 930, 832, 775 and 669 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{15}H_{18}O_4{}^{23}Na^+$ $[M+Na]^+$ 285.1097; found 285.1098 (Δ 0.21 ppm);

Specific Rotation: $[\alpha]_D^{25}$ 86.3 (c = 1.00, CH_2Cl_2).

Minor diastereoisomer *epi*-**240**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.79 (d, *J* = 1.8 Hz, 1H, *H*-7), 7.52–7.44 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.95–6.87 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 5.88 (ddd, *J* = 17.4, 10.6, 5.4 Hz, 1H, *H*-11), 5.59 (s, 1H, C$\underline{H}O_2{}^{PMP}$), 5.34 (dt, *J* = 17.3, 1.4 Hz, 1H, *H*-11'a), 5.19 (dt, *J* = 10.6, 1.3 Hz, 1H, *H*-11'b), 4.21 (dddt, *J* = 12.0, 5.4, 2.7, 1.4 Hz, 1H, *H*-10), 3.81 (s, 3H, OC$\underline{H}_3{}^{PMP}$), 2.28 (dd, *J* = 13.5, 2.7 Hz, 1H, *H*-9a), 1.67 (ddd, *J* = 13.6, 11.9, 1.8 Hz, 1H, *H*-9b) and 1.33 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 204.5 (*C*-7), 160.4 (Ar$\underline{C}^{PMP}$), 137.3 (*C*-11), 130.6 (Ar$\underline{C}^{PMP}$), 127.7 (2 × Ar$\underline{C}^{PMP}$), 116.3 (*C*-11'), 113.9 (2 × Ar$\underline{C}^{PMP}$), 98.8 ($\underline{C}HO_2{}^{PMP}$), 80.3 (*C*-8), 74.9 (*C*-10), 55.5 (O$\underline{C}H_3{}^{PMP}$), 36.0 (*C*-9) and 23.4 ppm (*C*-19);

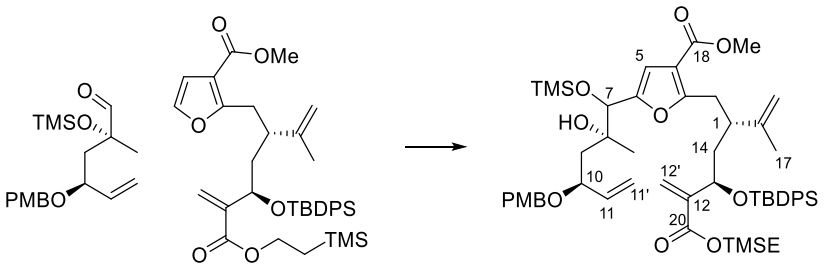
FT-IR ν_{max} (thin film): 2926, 2839, 2362, 2246, 2138, 1733, 1615, 1519, 1463, 1391, 1304, 1250, 1163, 1141, 1068, 1032, 931, 831, 776, 692, 639 and 609 cm^{-1};

HRMS (ESI$^+$): Calc. for for $C_{15}H_{18}O_4{}^{23}Na^+$ $[M+Na]^+$ 285.1097; found 285.1099 (Δ 0.55 ppm);

Specific Rotation: $[\alpha]_D^{25}$ 100.5 (c = 1.00, CH_2Cl_2).

6.1.12 Synthesis of TMSE ester 291

Methyl 2-((2*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(prop-1-en-2-yl)-5-((2-(trimethylsilyl) ethoxy)carbonyl)hex-5-en-1-yl)-5-((2*R*,4*S*)-2-hydroxy-4-((4-methoxybenzyl)oxy)-2-methyl-1-((trimethylsilyl)oxy)hex-5-en-1-yl)furan-3-carboxylate (285)



Note: At no stage were separate signals for diastereomers detected by ^{1}H- or ^{13}C NMR.

To a solution of furan **193** (140 mg, 216 µmol, 1.0 eq) in THF (4.4 mL, 49 mM) at –78 °C in a Schlenk tube was added LDA (1.0 M in THF, 0.25 mL, 0.25 mmol, 1.2 eq). After 1 h, α-siloxy aldehyde **239** (109 mg, 324 µmol, 1.5 eq) in THF (0.5 mL + 2 × 0.5 mL rinse) was added dropwise. After further 1.5 h, the reaction mixture was warmed to 0 °C and stirred for 45 min. The reaction was quenched with NH_4Cl (sat., aq., 5.0 mL), diluted with brine (5.0 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR and purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 50:50 and CyH:EtOAc = 92:8 to 85:15) to afford coupling product **285** (25.0 mg, 12%) as a colourless syrup.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67–7.62 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.62–7.56 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.42–7.27 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 7.25–7.19 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.88–6.82 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.44 (s, 1H, *H*-5), 6.07 (d, *J* = 1.6 Hz, 1H, *H*-12'a), 5.79 (t, *J* = 1.3 Hz, 1H, *H*-12'b), 5.74 (ddd, *J* = 17.6, 9.9, 7.9 Hz, 1H, *H*-11), 5.27–5.19 (m, 2H, 2 × *H*-11'), 4.67 (dd, *J* = 7.1, 3.7 Hz, 1H, *H*-13), 4.52 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}$aHb^{PMB}), 4.50–4.45 (m, 1H, *H*-16a), 4.33 (br. s, 1H, *H*-7), 4.30–4.23 (m, 2H, *H*-16b, OCHa$\underline{H}$b^{PMB}), 4.15–4.04 (m, 3H, *H*-10,

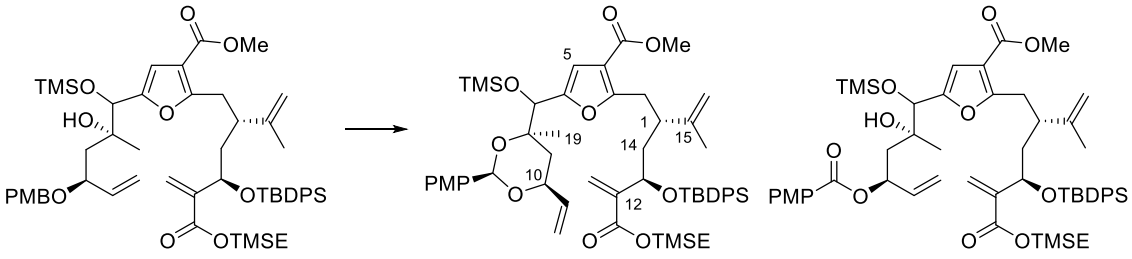
$Si(CH_2)(C\underline{H_2})O^{TMSE}$), 4.00 (s, 1H, *OH*-8), 3.79 (s, 3H, $OC\underline{H_3}^{PMB}$), 3.75 (s, 3H, $CO_2C\underline{H_3}$), 2.94 (dd, *J* = 15.7, 11.0 Hz, 1H, *H*-2a), 2.86–2.77 (m, 2H, *H*-1, *H*-2b), 1.97 (dd, *J* = 14.8, 10.4 Hz, 1H, *H*-9a), 1.76 (ddd, *J* = 14.3, 8.7, 4.0 Hz, 1H, *H*-14a), 1.70–1.61 (m, 2H, *H*-14b, *H*-9b), 1.54–1.50 (m, 3H, 3 × *H*-17), 1.07 (s, 3H, 3 × *H*-19), 1.03 (s, 9H, $C(C\underline{H_3})_3^{TBDPS}$), 0.96–0.87 (m, 2H, $Si(C\underline{H_2})(CH_2)O^{TMSE}$), 0.03 (s, 9H, $Si(C\underline{H_3})_3^{TMS}$) and 0.01 ppm (s, 9H, $Si(C\underline{H_3})_3^{TMS}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4 (*C*-20), 165.8 (*C*-18), 162.1 ($Ar\underline{C}^{PMB}$), 160.8 (*C*-3), 154.6 (*C*-6), 147.0 (*C*-15), 145.3 (*C*-12), 140.0 (*C*-11), 137.5 (4 × $Ar\underline{C}^{TBDPS}$), 135.4 ($Ar\underline{C}^{TBDPS}$), 135.3 ($Ar\underline{C}^{TBDPS}$), 131.3 ($Ar\underline{C}^{PMB}$), 131.0 ($Ar\underline{C}^{TBDPS}$), 131.0 ($Ar\underline{C}^{TBDPS}$), 128.9 (2 × $Ar\underline{C}^{TBDPS}$), 128.8 (2 × $Ar\underline{C}^{TBDPS}$), 127.0 (*C*-12'), 118.8 (*C*-11'), 115.5 (*C*-4), 115.4 (2 × $Ar\underline{C}^{PMB}$), 114.3 (*C*-16), 110.1 (*C*-5), 79.7 (*C*-10), 77.3 (*C*-7), 76.0 (*C*-8), 71.7 (*C*-13), 71.3 ($O\underline{C}H_2^{PMB}$), 64.1 ($Si(CH_2)(\underline{C}H_2)O^{TMSE}$), 56.8 ($O\underline{C}H_3^{PMB}$), 52.6 ($CO_2\underline{C}H_3$), 44.1 (*C*-1), 42.9 (*C*-14), 42.5 (*C*-9), 34.1 (*C*-2), 28.6 ($C(\underline{C}H_3)_3^{TBDPS}$), 24.1 (*C*-19), 20.9 ($\underline{C}(CH_3)_3^{TBDPS}$), 19.7 (*C*-17), 18.7 ($Si(\underline{C}H_2)(CH_2)O^{TMSE}$), 1.5 ($Si(\underline{C}H_3)_3^{TMS}$) and 0.0 ppm ($Si(\underline{C}H_3)_3^{TMS}$);

FT-IR ν_{max} (thin film): 2955, 2857, 1716, 1612, 1515, 1441, 1428, 1392, 1303, 1250, 1224, 1174, 1083, 933, 882, 840, 783, 741 and 703 cm^{-1};

HRMS (ESI^+): Calc. for $C_{55}H_{78}O_{10}{}^{23}NaSi_3^+$ $[M+Na]^+$ 1005.4795; found 1005.4787 (Δ –0.82 ppm);

Methyl 2-((2*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(prop-1-en-2-yl)-5-((2-(trimethylsilyl)ethoxy) carbonyl)hex-5-en-1-yl)-5-(((2*R*,4*R*,6*S*)-2-(4-methoxyphenyl)-4-methyl-6-vinyl-1,3-dioxan-4-yl)((trimethylsilyl)oxy)methyl)furan-3-carboxylate (286)



285 **286** **287**

Note: At no stage were separate signals for diastereomers detected by ^{1}H- or ^{13}C NMR. A batch of coupling product **285** (19.9 mg) was split into four equal portions. One of which was used for this experiment.

To a solution of PMB ether **285** (5.0 mg, 5.1 µmol, 1.0 eq) in CH_2Cl_2 (500 µL, 10 mM) at 0 °C was added NaH_2PO_4/Na_2HPO_4-buffer (1 M, aq., pH = 7, 83 µL; CH_2Cl_2:buffer = 6:1) and DDQ (11.9 mg, 52.4 µmol, 10 eq) was added. After 3 h, the reaction was quenched with $Na_2S_2O_3$ (sat., aq., 1.0 mL), diluted with H_2O (1.0 mL) and extracted with EtOAc (3 × 4.0 mL). The combined organic extracts were washed with brine (4.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 on aluminium, CyH:EtOAc = 90:10, 3 elusions) to afford acetal **286** (2.1 mg, 43%), recovered ether **285** (1.1 mg, 22%) and ester **287** (1.3 mg, 26%). All three compounds were isolated as colourless films.

Acetal **286**:

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.66 (dt, *J* = 6.6, 1.5 Hz, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.60 (dt, *J* = 6.9, 1.4 Hz, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.46–7.30 (m, 8H, 2 × Ar$\underline{H}^{PMP}$, 6 × Ar$\underline{H}^{TBDPS}$), 6.90–6.85 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.51 (s, 1H, *H*-5), 6.08 (d, *J* = 1.5 Hz, 1H, *H*-12'a), 5.94 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H, *H*-11), 5.80 (d, *J* = 1.3 Hz, 1H, *H*-12'b), 5.75 (s, 1H, C$\underline{H}O_2^{PMP}$), 5.35 (dt, *J* = 17.2, 1.5 Hz, 1H, *H*-11'a), 5.19 (dt, *J* = 10.6, 1.3 Hz, 1H, *H*-11'b), 4.69 (dd, *J* = 7.4, 3.6 Hz, 1H, *H*-13), 4.52 (t, *J* = 1.8 Hz, 1H, *H*-16a), 4.51 (s, 1H, *H*-7), 4.50–4.44 (m, 1H, *H*-10), 4.34–4.32 (m, 1H, *H*-16b), 4.13–4.05 (m, 2H, Si(CH_2)(C$\underline{H}_2$)O^{TMSE}), 3.82 (s, 3H, OC$\underline{H}_3^{PMP}$), 3.79 (s, 3H, $CO_2C\underline{H}_3$), 2.99–2.81 (m, 3H, *H*-1, 2 × *H*-2), 1.89 (t, *J* = 12.6 Hz, 1H, *H*-9a), 1.79 (ddd, *J* = 13.0, 9.1, 3.6 Hz, 1H, *H*-14a), 1.70–1.60 (m, 2H, *H*-14b, *H*-9b), 1.57 (s, 3H, 3 × *H*-19), 1.31 (s, 3H, 3 × *H*-17), 1.05 (s, 9H, C(C$\underline{H}_3$)$_3^{TBDPS}$), 0.97–0.87 (m, 2H, Si(C$\underline{H}_2$)(CH_2)O^{TMSE}) and 0.06–0.04 ppm (m, 18H, 2 × Si(C$\underline{H}_3$)$_3^{TMS}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.0 (*C*-20), 164.5 (*C*-18), 160.9 (*C*-3), 159.8 (Ar$\underline{C}^{PMP}$), 152.7 (*C*-6), 145.6 (*C*-15), 144.0 (*C*-12), 138.4 (*C*-11), 136.2 (4 × Ar$\underline{C}^{TBDPS}$), 134.0 (Ar$\underline{C}^{TBDPS}$), 133.9 (Ar$\underline{C}^{TBDPS}$), 131.7 (Ar$\underline{C}^{PMP}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 129.6 (Ar$\underline{C}^{TBDPS}$), 127.7 (2 × Ar$\underline{C}^{PMP}$), 127.5 (2 × Ar$\underline{C}^{TBDPS}$), 127.5 (2 × Ar$\underline{C}^{TBDPS}$), 125.6 (*C*-12'), 115.7 (*C*-11'), 114.1 (*C*-4), 113.5 (2 × Ar$\underline{C}^{PMP}$), 113.0 (*C*-16), 109.0 (*C*-5), 94.3 (PMP$\underline{C}HO_2$), 76.7 (*C*-8), 75.7 (*C*-7), 73.9 (*C*-10), 70.3 (*C*-13), 62.8 (Si(CH_2)($\underline{C}H_2$)O^{TMSE}), 55.4 (O$\underline{C}H_3^{PMP}$), 51.3 ($CO_2\underline{C}H_3$), 42.8 (*C*-1), 41.6 (*C*-14), 36.4 (*C*-9), 32.8 (*C*-2), 27.3 (C($\underline{C}H_3$)$_3^{TBS}$), 19.6 ($\underline{C}(CH_3)_3^{TBS}$), 18.5 (*C*-19), 17.3 (*C*-17), 16.8 (Si($\underline{C}H_2$)(CH_2)O^{TMSE}), 0.2 (Si($\underline{C}H_3$)$_3^{TMS}$) and –1.4 ppm (Si($\underline{C}H_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 2980, 2888, 1473, 1462, 1383, 1252, 1152, 1073, 954 and 816 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{55}H_{76}O_{10}{}^{23}NaSi_3^+$ $[M+Na]^+$ 1003.4638; found 1003.4631 (Δ –0.71 ppm);

Ester **287**:

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.03 (d, *J* = 8.9 Hz, 2H, 2 × Ar$\underline{H}^{PMP}$), 7.69–7.64 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.63–7.58 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.45–7.30 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.97–6.90 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.52 (s, 1H, *H*-5), 6.12 (d, *J* = 1.5 Hz, 1H, *H*-12'a), 5.90 (ddd, *J* = 17.0, 10.4, 6.3 Hz, 1H, *H*-11), 5.84 (s, 1H, *H*-12'b), 5.77 (q, *J* = 6.2 Hz, 1H, *H*-10), 5.33 (dt, *J* = 17.2, 1.3 Hz, 1H, *H*-11'a), 5.17 (dt, *J* = 10.5, 1.2 Hz, 1H, *H*-11'b), 4.70 (dd, *J* = 7.1, 3.7 Hz, 1H, *H*-13), 4.51 (s, 1H, *H*-16a), 4.41 (s, 1H, *H*-7), 4.29 (s, 1H, *H*-16b), 4.15–4.06 (m, 2H, Si(CH_2)($C\underline{H}_2$)O^{TMSE}), 3.88 (s, 3H, OC$\underline{H}_3^{PMP}$), 3.79 (s, 3H, $CO_2C\underline{H}_3$), 3.05–2.94 (m, 1H, *H*-2a), 2.90–2.78 (m, 2H, *H*-1, *H*-2b), 2.18 (dd, *J* = 15.0, 7.7 Hz, 2H, *H*-9a), 1.86–1.77 (m, 1H, *H*-14a), 1.77–1.66 (m, 2H, *H*-9b, 14b), 1.56 (s, 3H, 3 × *H*-17), 1.19 (s, 3H, 3 × *H*-19), 1.05 (s, 9H, C($C\underline{H}_3$)$_3^{TBDPS}$), 0.99–0.88 (m, 2H, Si($C\underline{H}_2$)(CH_2)O^{TMSE}), 0.06 (s, 9H, Si($C\underline{H}_3$)$_3^{TMS}$) and 0.05 ppm (s, 9H, Si($C\underline{H}_3$)$_3^{TMSE}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.1 (*C*-20), 165.5 (PMP-$\underline{C}$O), 164.3 (*C*-18), 163.5 (Ar$\underline{C}^{PMP}$), 161.1 (*C*-3), 152.3 (*C*-6), 145.6 (*C*-15), 143.9 (*C*-12), 137.8 (*C*-11), 136.2 (4 × Ar$\underline{C}^{TBDPS}$),

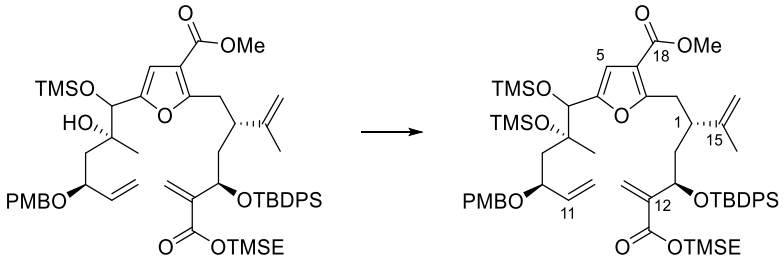
134.0 (Ar$\underline{C}^{TBDPS}$), 133.8 (Ar$\underline{C}^{TBDPS}$), 131.8 (2 × Ar$\underline{C}^{PMP}$), 129.7 (2 × Ar$\underline{C}^{TBDPS}$), 127.5 (2 × Ar$\underline{C}^{TBDPS}$), 127.5 (2 × Ar$\underline{C}^{TBDPS}$), 125.7 (*C*-12'), 123.1 (Ar$\underline{C}^{PMP}$), 116.4 (*C*-11'), 114.2 (*C*-4), 113.7 (2 × Ar$\underline{C}^{PMP}$), 113.1 (*C*-16), 109.2 (*C*-5), 75.9 (*C*-7), 74.1 (*C*-8), 72.1 (*C*-10), 70.4 (*C*-13), 62.8 (Si(CH_2)($\underline{C}H_2$)O^{TMSE}), 55.6 (O$\underline{C}H_3^{PMP}$), 51.4 ($CO_2\underline{C}H_3$), 42.8 (*C*-1), 41.5 (*C*-14), 40.6 (*C*-9), 33.8 (*C*-2), 27.2 (C($\underline{C}H_3$)$_3^{TBDPS}$), 23.3 (*C*-19), 19.6 ($\underline{C}(CH_3)_3^{TBDPS}$), 18.3 (*C*-17), 17.3 (Si($\underline{C}H_2$)(CH_2)O^{TMSE}), 0.0 (Si($\underline{C}H_3$)$_3^{TMS}$) and –1.4 ppm (Si($\underline{C}H_3$)$_3^{TMSE}$);

FT-IR ν_{max} (thin film): 3650, 2981, 2889, 2363, 2340, 1717, 1473, 1461, 1382, 1252, 1152, 1074, 955, 840, 751, 703 and 616 cm^{-1};

HRMS (ESI$^+$ in MeCN): Calc. for $C_{55}H_{76}O_{11}{}^{23}NaSi_3^+$ $[M+Na]^+$ 1019.4588; found 1019.4584 (Δ –0.38 ppm);

HRMS (ESI$^+$ in MeOH) *in-situ* TMS deprotection and formation of the corresponding ortho ester was observed: Calc. for $C_{52}H_{67}O_{10}Si_2^+$ $[M+H]^+$ 907.4267; found 907.4260 (Δ 0.77 ppm);

Methyl 2-((2*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(prop-1-en-2-yl)-5-((2-(trimethylsilyl)ethoxy) carbonyl)hex-5-en-1-yl)-5-((4*S*,5*R*)-5-((*S*)-2-((4-methoxybenzyl)oxy)but-3-en-1-yl)-2,2,5,7,7-pentamethyl-3,6-dioxa-2,7-disilaoctan-4-yl)furan-3-carboxylate (290)



285 **290**

Note: At no stage were separate signals for diastereomers detected by ^1H- or ^{13}C NMR.

Procedure A:

Note: A batch of coupling product **285** (19.9 mg) was split into four equal portions. One of which was used for this experiment.

Alcohol **285** (5.0 mg, 5.1 µmol, 1.0 eq) was dissolved in a solution of 2,6-lutidine (6 µL, 0.05 mmol, 10 eq) in CH_2Cl_2 (0.05 mL; stock solution: 0.30 mL in 2.5 mL) and cooled to –78 °C in a Schlenk tube. Trimethylsilyl triflate (5 µL, 0.03 mmol, 5 eq) in CH_2Cl_2 (0.05 mL; stock solution: 0.23 mL in 2.5 mL) was added. After 2 h, the reaction was quenched with $NaHCO_3$ (sat., aq., 0.50 mL), warmed to rt and extracted with Et_2O (3 × 1 mL). The combined organic extracts were washed with brine (1.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 on aluminium, CyH:EtOAc = 96:4, 4 elusions) to afford bis-silyl ether **290** (2.8 mg, 56%) as a colourless film.

Procedure B:

A stock solution of DMAP (33.0 mg, 270 µmol) and Et_3N (0.31 mL, 2.2 mmol) in DMF (1.6 mL) was prepared. Alcohol **285** (8.7 mg, 8.9 µmol, 1.0 eq) was dissolved in the described stock solution (0.05 mL; DMAP: 7 µmol, 1 eq; Et_3N: 0.06 mmol, 7 eq). A solution of trimethylsilyl chloride (6 µL, 0.05 mmol, 5 eq) in DMF (0.05 mL; stock solution: 0.34 mL in 2.5 mL) was added and the mixture stirred for 16 h. The reaction was diluted with CH_2Cl_2 (5.0 mL), quenched with NH_4Cl (sat., aq., 0.5 mL) and washed with brine (0.5 mL), H_2O (2 × 1.0 mL) and brine (2 × 2.0 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 on aluminium, CyH:EtOAc = 95:5, 3 elusions) to afford bis-silyl ether **290** (6.8 mg, 73%) as a colourless film.

Following the same procedure alcohol **285** (19.8 mg, 20.1 µmol) was converted into *bis*-silyl ether **290** (11.0 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71–7.63 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.63–7.57 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.42–7.27 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 7.28–7.23 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.90–6.83 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.36 (s, 1H, *H*-5), 6.09 (d, *J* = 1.6 Hz, 1H, *H*-12'a), 5.85–5.67 (m, 2H,

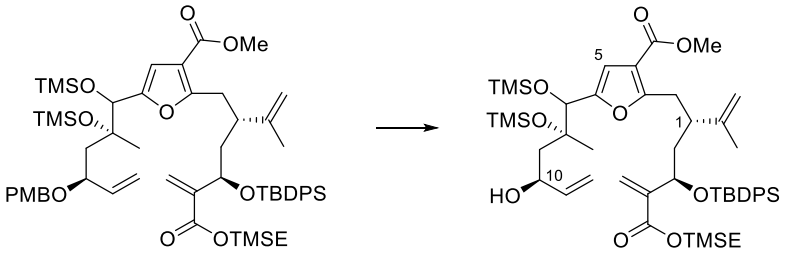
H-12'b, *H*-11), 5.23–5.14 (m, 2H, 2 × *H*-11'), 4.72–4.63 (m, 2H, *H*-13, *H*-7), 4.52–4.45 (m, 2H, *H*-16a, OC*H*aHb^{PMB}), 4.33–4.29 (m, 1H, *H*-16b), 4.25 (d, *J* = 11.2 Hz, 1H, OCHa*H*b^{PMB}), 4.14–4.01 (m, 3H, *H*-10, Si(CH_2)(C*H*$_2$)O^{TMSE}), 3.80 (s, 3H, OC*H*$_3^{PMB}$), 3.77 (s, 3H, CO_2CH_3), 2.92–2.80 (m, 3H, *H*-1, 2 × *H*-2), 2.10 (dd, *J* = 14.6, 7.2 Hz, 1H, *H*-9a), 1.86–1.73 (m, 1H, *H*-14a), 1.71–1.61 (m, 1H, *H*-14b), 1.55 (d, *J* = 1.4 Hz, 4H, 3 × *H*-17, *H*-9b, overlaps with HOD peak), 1.20 (s, 3H, 3 × *H*-19), 1.04 (s, 9H, C(C*H*$_3$)$_3^{TBDPS}$), 0.95–0.87 (m, 2H, Si(C*H*$_2$)(CH_2)O^{TMSE}), 0.02 (s, 9H, Si(*C*H$_3$)$_3^{TMS}$) and –0.07 ppm (s, 18H, 2 × Si(*C*H$_3$)$_3^{TMS}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.1 (*C*-20), 164.7 (*C*-18), 160.2 (*C*-3), 159.1 (2 × Ar*C*^{PMB}), 153.9 (*C*-6), 145.5 (*C*-15), 143.9 (*C*-12), 140.2 (*C*-11), 136.2 (4 × Ar*C*^{TBDPS}), 134.1 (Ar*C*^{TBDPS}), 133.9 (Ar*C*^{TBDPS}), 131.0 (Ar*C*^{TBDPS}), 129.8 (2 × Ar*C*^{PMB}), 129.6 (Ar*C*^{TBDPS}), 129.6 (Ar*C*^{TBDPS}), 127.5 (Ar*C*^{TBDPS}), 127.5 (2 × Ar*C*^{TBDPS}), 125.7 (*C*-12'), 116.2 (*C*-11'), 114.0 (*C*-4), 113.8 (2 × Ar*C*^{PMB}), 113.1 (*C*-16), 109.0 (*C*-5), 77.4 (*C*-10), 73.7 (*C*-7), 70.3 (*C*-13), 69.7 (O*C*H$_2^{PMB}$), 62.8 (Si(CH_2)(*C*H$_2$)O^{TMSE}), 55.4 (O*C*H$_3^{PMB}$), 51.3 (CO_2*C*H$_3$), 45.4 (*C*-9), 42.6 (*C*-1), 41.6 (*C*-14), 32.8 (*C*-2), 27.3 (C(*C*H$_3$)$_3^{TBDPS}$), 23.8 (*C*-19), 19.5 (*C*(CH_3)$_3^{TBDPS}$), 18.4 (*C*-17), 17.4 (Si(*C*H$_2$)(CH_2)O^{TMSE}), 2.5 (Si(*C*H$_3$)$_3^{TMS}$), 0.2 (Si(*C*H$_3$)$_3^{TMS}$) and –1.4 ppm (Si(*C*H$_3$)$_3^{TMS}$); *C*-8 not observed, but HMBC data suggest overlap with solvent signal;

FT-IR ν_{max} (thin film): 3296, 2930, 2161, 1978, 1747, 1695, 1547, 1433, 1374, 1223, 1047, 934, 813 and 766 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{58}H_{86}O_{10}{}^{23}NaSi_4^+$ $[M+Na]^+$ 1077.5190; found 1077.5189 (Δ –0.10 ppm);

Methyl 2-((2*R*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(prop-1-en-2-yl)-5-((2-(trimethylsilyl)ethoxy) carbonyl)hex-5-en-1-yl)-5-((4*S*,5*R*)-5-((*S*)-2-hydroxybut-3-en-1-yl)-2,2,5,7,7-pentamethyl-3,6-dioxa-2,7-disilaoctan-4-yl)furan-3-carboxylate (291)



290 **291**

Note: At no stage were separate signals for diastereomers detected by ^{1}H- or ^{13}C NMR.

To a solution of PMB ether **290** (10.9 mg, 10.3 µmol, 1.0 eq) in CH_2Cl_2 (882 µL, 12 mM) at 0 °C was added NaH_2PO_4/Na_2HPO_4-buffer (1 M, aq., pH = 7, 148 µL; CH_2Cl_2:buffer = 6:1) and DDQ (26.2 mg, 115 µmol, 11 eq) was added in one portion. After 1 h, the reaction was quenched with $Na_2S_2O_3$ (sat., aq., 1.0 mL), diluted with H_2O (1.0 mL) and extracted with Et_2O (3 × 4.0 mL). The combined organic extracts were washed with brine (4.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 500 µm on glass, CH_2Cl_2:acetone = 99:1) to afford allylic alcohol **291** (7.2 mg, 75%) as colourless film.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (dt, *J* = 6.7, 1.5 Hz, 2H, 2 × Ar*H*^{TBDPS}), 7.62–7.54 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.42–7.25 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.49 (s, 1H, *H*-5), 6.09 (d, *J* = 1.5 Hz, 1H, *H*-12'a), 5.87–5.73 (m, 2H, *H*-12'b, *H*-11), 5.26 (dt, *J* = 17.2, 1.7 Hz, 1H, *H*-11'a), 5.04 (dt, *J* = 10.5, 1.5 Hz, 1H, *H*-11'b), 4.67 (dd, *J* = 7.2, 3.6 Hz, 1H, *H*-13), 4.50–4.47 (m, 1H, *H*-16a), 4.48–4.39 (m, 1H, *H*-10), 4.37 (s, 1H, 3 × *H*-7), 4.26–4.23 (m, 1H, *H*-16b), 4.20 (s, 1H, *OH*-10), 4.14–4.02 (m, 2H, Si(CH_2)(CH_2)O^{TMSE}), 3.77 (s, 3H, CO_2CH_3), 2.95 (dd, *J* = 15.5, 11.2 Hz, 1H, *H*-2a), 2.88–2.75 (m, 2H, *H*-1, *H*-2b), 1.84–1.71 (m, 2H, *H*-14a, *H*-9a), 1.67 (ddd, *J* = 14.3, 7.2, 4.2 Hz, 1H, *H*-14b), 1.54–1.51 (m, 3H, 3 × *H*-17), 1.48–1.35 (m, 1H, *H*-9b), 1.25 (s, 3H, 3 × *H*-19), 1.03 (s, 9H, C(CH_3)$_3^{TBDPS}$), 0.96–0.86 (m, 2H,

Si(C<u>*H*</u>$_2$)(CH$_2$)O^{TMSE}), 0.16 (s, 9H, Si(C<u>*H*</u>$_3$)$_3^{TMSE}$), 0.04 (s, 9H, Si(C<u>*H*</u>$_3$)$_3^{TMS}$) and 0.03 ppm (s, 9H, Si(C<u>*H*</u>$_3$)$_3^{TMS}$);

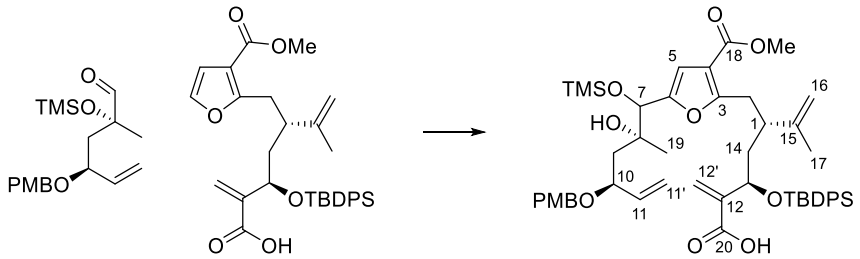
^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.1 (*C*-20), 164.4 (*C*-18), 160.8 (*C*-3), 152.5 (*C*-6), 145.4 (*C*-15), 143.9 (*C*-12), 141.4 (*C*-11), 136.2 (4 × Ar<u>*C*</u>^{TBDPS}), 134.1 (Ar<u>*C*</u>^{TBDPS}), 133.8 (Ar<u>*C*</u>^{TBDPS}), 129.7 (2 × Ar<u>*C*</u>^{TBDPS}), 127.5 (4 × Ar<u>*C*</u>^{TBDPS}), 125.7 (*C*-12'), 114.3 (*C*-4), 113.7 (*C*-11'), 113.3 (*C*-16), 109.6 (*C*-5), 79.0 (*C*-8), 76.0 (*C*-7), 70.4 (*C*-13), 69.0 (*C*-10), 62.8 (Si(CH$_2$)(<u>*C*</u>H$_2$)O^{TMSE}), 51.4 (CO_2<u>*C*</u>H$_3$), 44.9 (*C*-9), 42.8 (*C*-1), 41.6 (*C*-14), 32.6 (*C*-2), 27.2 (C(<u>*C*</u>H$_3$)$_3^{TBDPS}$), 25.4 (*C*-19), 19.6 (<u>*C*</u>(CH$_3$)$_3^{TBDPS}$), 18.2 (*C*-17), 17.4 (Si(<u>*C*</u>H$_2$)(CH$_2$)O^{TMSE}), 2.8 (Si(<u>*C*</u>H$_3$)$_3^{TMS}$), 0.0 (Si(<u>*C*</u>H$_3$)$_3^{TMS}$) and –1.4 ppm (Si(<u>*C*</u>H$_3$)$_3^{TMS}$).

FT-IR ν_{max} (thin film): 2954, 2898, 2858, 1718, 1440, 1428, 1391, 1376, 1251, 1223, 1198, 1146, 1104, 1085, 999, 920, 840, 783, 756, 742 and 702 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{50}H_{78}O_9{}^{23}NaSi_4^+$ [M+Na]$^+$ 957.4615; found 957.4609 (Δ –0.65 ppm);

6.1.13 Synthesis of macrocycle 296

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((5-((2*R*,4*S*)-2-Hydroxy-4-((4-methoxybenzyl)oxy)-2-methyl-1-((trimethylsilyl)oxy)hex-5-en-1-yl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (293)



To a solution of furan **137** (109 mg, 199 µmol, 1.0 eq) in THF (4.0 mL, 50 mM) at –78 °C in a Schlenk tube was added LDA (1.0 M in THF, 0.50 mL, 0.50 mmol, 2.5 eq). After 1 h, α-siloxy aldehyde **239** (82.5 mg, 245 µmol, 1.2 eq) in THF (1.0 mL) was added dropwise (5 min). After 1.5 h, the mixture was warmed to 0 °C and stirred for further 30 min. The

reaction was quenched with NH_4Cl (sat., aq., 2.5 mL), diluted with brine (2.5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (6 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 80:20) to afford coupling product **293** (110 mg, 63%, 65:35 dr determined at $Si(C\underline{H}_3)_3^{TMS}$ in acetone-d6) as a colourless syrup.

^{1}H NMR (major diastereomer, 400 MHz, acetone-d6 = 2.05 ppm) δ = 7.72–7.66 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.64 (app. dq, *J* = 6.6, 1.4 Hz, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.49–7.33 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 7.32–7.26 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.96–6.86 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.45 (d, *J* = 0.7 Hz, 1H, *H*-5), 6.16 (t, *J* = 1.8 Hz, 1H, *H*-12'a), 5.92–5.87 (m, 1H, *H*-12'b), 5.84–5.71 (m, 1H, *H*-11), 5.29 (ddd, *J* = 17.3, 1.8, 0.8 Hz, 1H, *H*-11'a), 5.25 (s, 1H, *H*-11'b), 4.82–4.76 (m, 1H, *H*-13), 4.54 (d, *J* = 10.9 Hz, 1H, OC$\underline{H}$aHb^{PMB}), 4.50–4.45 (m, 1H, *H*-16a), 4.37 (d, *J* = 0.7 Hz, 1H, *H*-7), 4.36–4.29 (m, 2H, OCHa$\underline{H}$b^{PMB}, *H*-16b), 4.25 (ddd, *J* = 10.5, 7.7, 3.0 Hz, 1H, *H*-10), 3.79 (s, 3H, OC$\underline{H}_3^{PMB}$) 3.73 (d, *J* = 1.6 Hz, 3H, OC$\underline{H}_3$), 3.02 (td, *J* = 11.5, 5.1 Hz, 1H, *H*-2a), 2.92–2.72 (m, 2H, *H*-1, *H*-2b), 2.03–1.94 (m, 1H, *H*-9a), 1.91–1.77 (m, 1H, *H*-14a), 1.77–1.67 (m, 1H, *H*-14b), 1.59–1.48 (m, 4H, *H*-9b, 3 × *H*-17), 1.14 (s, 3H, 3 × *H*-19), 1.05 (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$) and 0.06 ppm (s, 9H, $Si(C\underline{H}_3)_3^{TMS}$); OH not observed;

^{13}C NMR (major diastereomer, 101 MHz, acetone-d = 29.8 ppm) δ = 167.1 (*C*-20), 164.6 (*C*-18), 160.9 (Ar$\underline{C}^{PMB}$), 160.4 (*C*-3), 154.4 (*C*-6), 146.9 (*C*-15), 144.7 (*C*-12), 139.6 (*C*-11), 136.8 (4 × Ar$\underline{C}^{TBDPS}$), 134.7 (Ar$\underline{C}^{TBDPS}$), 134.5 (Ar$\underline{C}^{TBDPS}$), 130.8 (Ar$\underline{C}^{PMB}$), 130.7 (2 × Ar$\underline{C}^{TBDPS}$), 130.6 (2 × Ar$\underline{C}^{PMB}$), 130.6 (2 × Ar$\underline{C}^{TBDPS}$), 128.4 (2 × Ar$\underline{C}^{TBDPS}$), 126.0 (*C*-12'), 117.6 (*C*-11'), 114.9 (*C*-4), 114.6 (2 × Ar$\underline{C}^{PMB}$), 113.0 (*C*-16), 108.7 (*C*-5), 78.8 (*C*-10), 75.3 (*C*-7), 75.0 (*C*-8), 71.3 (*C*-13), 70.5 ($O\underline{C}H_2^{PMB}$), 55.5 ($O\underline{C}H_3^{PMB}$), 51.4 ($CO_2\underline{C}H_3$), 43.5 (*C*-1), 42.1 (*C*-14), 41.9 (*C*-9), 32.9 (*C*-2), 27.5 ($C(\underline{C}H_3)_3^{TBDPS}$), 24.2 (*C*-19), 20.0 ($\underline{C}(CH_3)_3^{TBDPS}$), 18.6 (*C*-17) and 1.6 ppm ($Si(\underline{C}H_3)_3^{TMS}$);

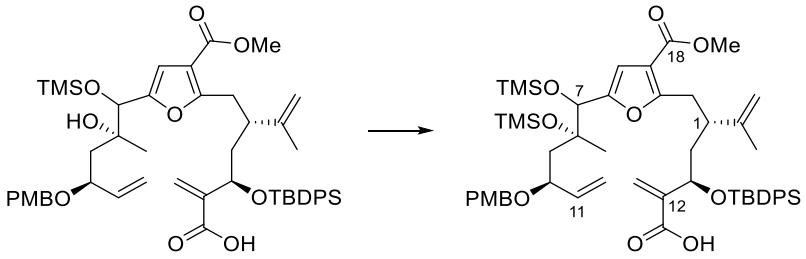
^{1}H NMR (minor diastereomer, selected signals, 400 MHz, acetone-d6 = 2.05 ppm) δ = 4.53 (d, *J* = 10.9 Hz, 2H, OCHa*Hb*^{PMB}) and 0.03 (s, 9H, Si(C*H*$_3$)$_3^{TMS}$);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, acetone-d = 29.8 ppm) δ = 161.1 (Ar*C*^{PMB}), 139.9 (*C*-11), 130.6 (2 × Ar*H*^{PMB}), 117.4 (*C*-11'), 114.6 (2 × Ar*C*^{PMB}), 113.1 (*C*-16), 109.3 (*C*-5), 79.0 (*C*-10), 76.5 (*C*-7), 33.0 (*C*-2), 27.6 (C(*C*H$_3$)$_3^{TBDPS}$), 23.5 (*C*-19), 18.7 (*C*-17) and 0.2 ppm (Si(*C*H$_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 3072, 2952, 2932, 2858, 1716, 1612, 1573, 1514, 1440, 1428, 1391, 1303, 1250, 1224, 1105, 1083, 1036, 999, 967, 931, 881, 782, 740, 703 and 611 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{50}H_{67}O_{10}Si_2$ [M+H]$^+$ 883.4267; found 883.4269 (Δ –1.01 ppm).

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((5-((5*R*)-5-((*S*)-2-((4-methoxybenzyl)oxy)but-3-en-1-yl)-2,2,5,7,7-Pentamethyl-3,6-dioxa-2,7-disilaoctan-4-yl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (294)



Note: At no stage were separate signals for diastereomers detected by ^{1}*H*- or ^{13}C NMR for bis-silyl ether **294**.

To a solution of alcohol **293** (110 mg, 125 µmol, 1.0 eq) in DMF (1.2 mL, 0.10 M) was added DMAP (16.0 mg, 131 µmol, 1.1 eq) and Et_3N (0.28 mL, 2.0 mmol, 16 eq). At 0 °C trimethylsilyl chloride (0.19 mL, 1.5 mmol, 12 eq) was added and the mixture was stirred at rt for 16 h. After which, the reaction was diluted with CH_2Cl_2 (5.0 mL) and quenched at 0 °C with NH_4Cl (sat., aq., 0.5 mL). The mixture was washed with brine (0.5 mL), LiCl (5%, 3 × 1.0 mL) and brine (1.0 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2,

CH_2Cl_2:MeOH = 100:0 to 99:1) to afford bis-silyl ether **294** (52.0 mg, 44%) as a colourless syrup.

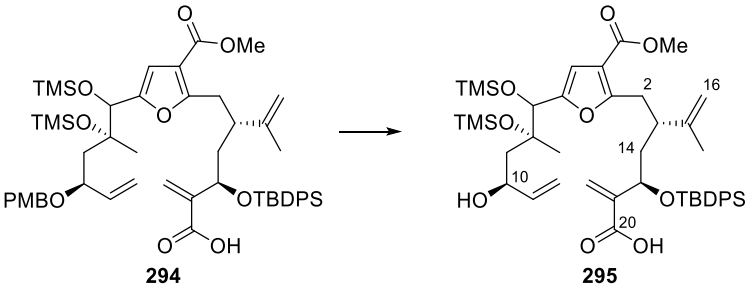
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71–7.64 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.63–7.55 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.48–7.30 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 7.25 (dq, *J* = 5.1, 2.8 Hz, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.92–6.82 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.34 (s, 1H, *H*-5), 6.23 (d, *J* = 1.6 Hz, 1H, *H*-12'a), 5.84 (s, 1H, *H*-12'b), 5.78 (ddd, *J* = 17.0, 10.4, 8.0 Hz, 1H, *H*-11), 5.25–5.13 (m, 2H, 2 × *H*-11'), 4.69 (t, *J* = 5.9 Hz, 1H, *H*-13), 4.58 (s, 1H, *H*-7), 4.53–4.47 (m, 2H, OC$\underline{H}$aHb^{PMB}, *H*-16a), 4.36–4.33 (m, 1H, *H*-16b), 4.27 (d, *J* = 11.4 Hz, 1H, OCHa$\underline{H}$b^{PMB}), 4.04 (dt, *J* = 8.1, 6.2 Hz, 1H, *H*-10), 3.80 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.76 (s, 3H, $CO_2C\underline{H}_3$), 2.84–2.68 (m, 2H, 2 × *H*-2), 2.66–2.54 (m, 1H, *H*-1), 2.12 (dd, *J* = 14.5, 6.5 Hz, 1H, *H*-9a), 1.80–1.64 (m, 2H, 2 × *H*-14), 1.61 (dd, *J* = 14.5, 5.7 Hz, 1H, *H*-9b), 1.52 (s, 3H, 3 × *H*-17), 1.15 (s, 3H, 3 × *H*-19), 1.07 (s, 9H, C($C\underline{H}_3$)$_3^{TBDPS}$), –0.05 (s, 9H, Si($C\underline{H}_3$)$_3^{TMS}$) and –0.08 ppm (s, 9H, Si($C\underline{H}_3$)$_3^{TMS}$); CO_2H not observed;

^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7 (*C*-20), 164.6 (*C*-18), 160.2 (*C*-3), 159.2 (Ar$\underline{C}^{PMB}$), 153.7 (*C*-6), 145.7 (*C*-15), 142.0 (*C*-12), 140.1 (*C*-11), 136.1 (4 × Ar$\underline{C}^{TBDPS}$), 133.5 (Ar$\underline{C}^{TBDPS}$), 133.2 (Ar$\underline{C}^{TBDPS}$), 130.7 (Ar$\underline{C}^{PMB}$), 130.0 (Ar$\underline{C}^{TBDPS}$), 129.9 (2 × Ar$\underline{C}^{PMB}$, Ar$\underline{C}^{TBDPS}$), 127.9 (*C*-12'), 127.7 (2 × Ar$\underline{C}^{TBDPS}$), 127.7 (2 × Ar$\underline{C}^{TBDPS}$), 116.8 (*C*-11'), 114.0 (*C*-4), 113.8 (2 × Ar$\underline{C}^{PMB}$), 112.7 (*C*-16), 109.0 (*C*-5), 77.3 (*C*-10), 74.2 (*C*-7), 71.1 (*C*-13), 69.4 (O$\underline{C}H_2^{PMB}$), 55.4 (O$\underline{C}H_3^{PMB}$), 51.3 ($CO_2\underline{C}H_3$), 44.6 (*C*-9), 42.4 (*C*-1), 41.4 (*C*-14), 31.9 (*C*-2), 27.2 (C($\underline{C}H_3$)$_3^{TBDPS}$), 24.0 (*C*-19), 19.4 ($\underline{C}(CH_3)_3^{TBDPS}$), 18.6 (*C*-17), 2.6 (Si($\underline{C}H_3$)$_3^{TMS}$) and 0.1 ppm (Si($\underline{C}H_3$)$_3^{TMS}$); C-8 not observed, but HMBC data suggest overlap with solvent signal;

FT-IR ν_{max} (thin film): 3073, 2954, 2931, 2857, 1719, 1698, 1653, 1646, 1635, 1613, 1569, 1559, 1514, 1472, 1457, 1439, 1428, 1393, 1374, 1362, 1302, 1250, 1225, 1194, 1174, 1105, 1088, 1039, 962, 922, 870, 842, 824, 783, 753, 741, 703 cm^{-1};

HRMS (ESI^+): Calc. for $C_{53}H_{74}O_{10}{}^{23}NaSi_3^+$ $[M+Na]^+$ 977.4482; found 977.4479 (Δ –0.29 ppm).

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((5-((5*R*)-5-((*S*)-2-hydroxybut-3-en-1-yl)-2,2,5,7,7-Pentamethyl-3,6-dioxa-2,7-disilaoctan-4-yl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (295)



Note: At no stage were separate signals for diastereomers detected by ^{1}H- or ^{13}C NMR.

To a solution of PMB ether **294** (52.0 mg, 54.4 µmol, 1.0 eq) in CH_2Cl_2 (4.6 mL, 12 mM) at 0 °C was added NaH_2PO_4/Na_2HPO_4-buffer (1 M, aq., pH = 7, 0.78 mL; CH_2Cl_2:buffer = 6:1) and DDQ (125 mg, 115 µmol, 11 eq) was added in one portion. After 1 h, the reaction was quenched with $Na_2S_2O_3$ (sat., aq., 2.0 mL), diluted with H_2O (2.0 mL) and stirred for 15 min at 0 °C. The mixture was warmed to rt, extracted with EtOAc (3 × 4.0 mL). The combined organic extracts were washed with brine (4.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 90:10) to afford allylic alcohol **295** (21.1 mg, 46%) as colourless syrup.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.73–7.68 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.66–7.60 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.48–7.31 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.35 (s, 1H, *H*-5), 6.26 (s, 1H, *H*-12'a), 6.00–5.90 (m, 2H, *H*-11, *H*-12'b), 5.26 (dt, *J* = 17.3, 1.5 Hz, 1H, *H*-11'a), 5.10 (dt, *J* = 10.4, 1.4 Hz, 1H, *H*-11'b), 4.88 (dd, *J* = 9.1, 4.4 Hz, 1H, *H*-13), 4.54–4.47 (m, 1H, *H*-10), 4.43 (br s, 1H, *H*-16a), 4.35 (s, 1H, *H*-7), 4.25 (br s, 1H, *H*-16b), 3.75 (s, 3H, $CO_2C\underline{H}_3$), 2.78 (dd, *J* = 14.1, 10.7 Hz, 1H, *H*-2a), 2.70 (dd, *J* = 14.1, 4.5 Hz, 1H, *H*-2b), 2.31 (td, *J* = 10.4, 9.9, 4.8 Hz, 1H, *H*-1), 2.04 (dd, *J* = 15.3, 9.9 Hz, 1H, *H*-9a), 1.75–1.66 (m, 1H, *H*-14a), 1.62–1.53 (m, 1H, *H*-14b), 1.49 (d, *J* = 15.1 Hz, 1H, *H*-9b), 1.44 (s, 3H, 3 × *H*-17), 1.13 (s, 3H, 3 × *H*-19), 1.09 (s,

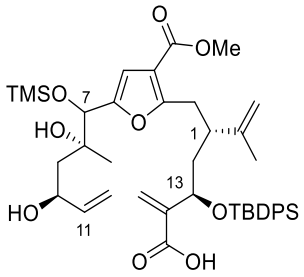
9H, C(C<u>*H*</u>$_3$)$_3^{TBDPS}$), 0.16 (s, 9H, Si(C<u>*H*</u>$_3$)$_3^{TMS}$) and 0.05 ppm (s, 9H, Si(C<u>*H*</u>$_3$)$_3^{TMS}$); CO_2H not observed;

^{13}C NMR (126 MHz, $CDCl_3$) δ = 168.0 (*C*-20), 164.3 (*C*-18), 161.4 (*C*-3), 150.9 (*C*-6), 146.3 (*C*-15), 144.3 (*C*-12), 140.3 (*C*-11), 136.1 (2 × Ar<u>*C*</u>^{TBDPS}), 136.0 (2 × Ar<u>*C*</u>^{TBDPS}), 134.0 (Ar<u>*C*</u>^{TBDPS}), 133.5 (Ar<u>*C*</u>^{TBDPS}), 129.9 (Ar<u>*C*</u>^{TBDPS}), 129.9 (Ar<u>*C*</u>^{TBDPS}), 127.8 (2 × Ar<u>*C*</u>^{TBDPS}), 127.7 (2 × Ar<u>*C*</u>^{TBDPS}), 125.1 (*C*-12'), 114.8 (*C*-11'), 114.4 (*C*-4), 111.7 (*C*-16), 109.7 (*C*-5), 77.7 (*C*-7), 69.8 (*C*-13), 69.5 (*C*-10), 51.3 (CO_2<u>*C*</u>H_3), 45.8 (*C*-9), 44.0 (*C*-14), 42.9 (*C*-1), 30.2 (*C*-2), 27.9 (*C*-19), 27.2 (C(<u>*C*</u>H_3)$_3^{TBDPS}$), 19.4 (<u>*C*</u>$(CH_3)_3^{TBDPS}$), 18.3 (*C*-17), 2.7 (Si(<u>*C*</u>H_3)$_3^{TMS}$) and –0.2 ppm (Si(<u>*C*</u>H_3)$_3^{TMS}$); C-8 not observed, but HMBC data suggest overlap with solvent signal;

FT-IR ν_{max} (thin film): 2359, 2162, 2027, 2019, 2006, 1976, 1717, 1685, 1653, 1647, 1636, 1607, 1576, 1559, 1541, 1508, 1473, 1457, 1437, 1428, 1419, 1395, 1363, 1256, 1224, 1168, 1089, 1033, 938, 880, 845, 785, 770, 743, 703, 668 cm^{-1};

HRMS (ESI^+): Calc. for $C_{45}H_{66}O_9{}^{23}NaSi_3^+$ $[M+Na]^+$ 857.3907; found 857.3906 (Δ –0.14 ppm);

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((5-((2*R*,4*S*)-2,4-Dihydroxy-2-methyl-1-((trimethylsilyl) oxy)hex-5-en-1-yl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (296)



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Following a similar procedure PMB ether **295** (43.1 mg, 45.1 µmol) was converted into bis-silyl ether **295** (20.5 mg) and silyl ether **296** (12.6 mg) when the reaction mixture was warmed to rt immediately after the reaction was quenched. Both batches were

contaminated with inseparable impurities and used in the next steps without further purification.

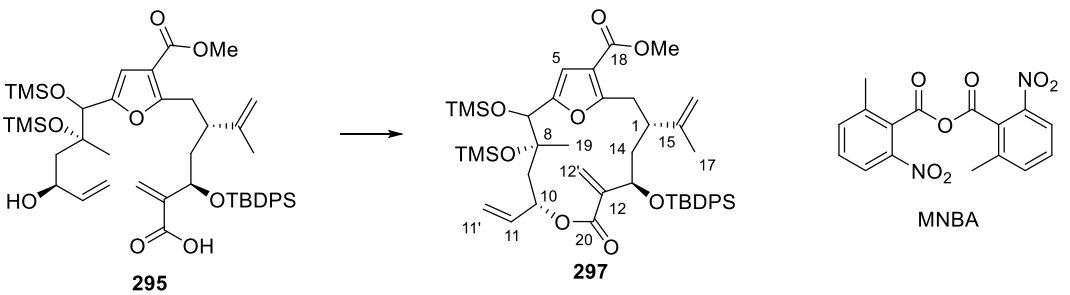
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (ddd, *J* = 6.6, 2.6, 1.5 Hz, 2H, 2 × Ar*H*^{TBDPS}), 7.59 (dt, *J* = 6.7, 1.5 Hz, 2H, 2 × Ar*H*^{TBDPS}), 7.46–7.31 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.50 (s, 1H, *H*-5), 6.26 (d, *J* = 1.5 Hz, 1H, *H*-12'a), 5.92–5.80 (m, 2H, *H*-11, *H*-12'b), 5.26 (dt, *J* = 17.2, 1.5 Hz, 1H, *H*-11'a), 5.09 (dt, *J* = 10.4, 1.4 Hz, 1H, *H*-11'b), 4.72 (t, *J* = 5.8 Hz, 1H, *H*-13), 4.55–4.46 (m, 3H, *H*-7, *H*-10, *H*-16a), 4.37–4.32 (m, 1H, *H*-16b), 3.76 (s, 3H, CO_2CH_3), 2.84–2.76 (m, 2H, 2 × *H*-2), 2.53 (p, *J* = 6.9 Hz, 1H, *H*-1), 1.97 (dd, *J* = 15.1, 9.6 Hz, 1H, *H*-9a), 1.76–1.65 (m, 2H, 2 × *H*-14), 1.54–1.47 (m, 4H, *H*-9b, 3 × *H*-17), 1.23 (s, 3H, 3 × *H*-19), 1.07 (s, 9H, $C(CH_3)_3^{TBDPS}$) and 0.16 ppm (s, 9H, $Si(CH_3)_3^{TMS}$); 2 × OH and CO_2H not observed;

^{13}C NMR (selected signals, 101 MHz, $CDCl_3$) δ = 161.0 (*C*-3), 146.3 (*C*-15), 140.8 (*C*-12), 136.1 (2 × Ar*C*^{TBDPS}), 136.1 (2 × Ar*C*^{TBDPS}), 130.0 (Ar*C*^{TBDPS}), 130.0 (Ar*C*^{TBDPS}), 127.8 (2 × Ar*C*^{TBDPS}), 127.7 (2 × Ar*C*^{TBDPS}), 114.6 (*C*-4), 109.6 (*C*-11'), 78.4 (*C*-8), 75.1 (*C*-7), 69.3 (*C*-10), 51.4 (CO_2CH_3), 44.7 (*C*-9), 42.4 (*C*-1), 41.2 (*C*-14), 31.6 (*C*-2), 30.5 ($C(CH_3)_3^{TBDPS}$), 25.8 (*C*-19), 19.4 ($C(CH_3)_3^{TBDPS}$), 18.6 (*C*-17) and 2.5 ppm ($Si(CH_3)_3^{TMS}$);

FT-IR ν_{max} (thin film): 3649, 2955, 2924, 2854, 2361, 2085, 1984, 1717, 1459, 1378, 1263, 1082, 823, 742, 703 and 616 cm^{-1};

HRMS (ESI^+): Calc. for $C_{42}H_{58}O_9{}^{23}NaSi_2^+$ $[M+Na]^+$ 785.3512; found 785.3507 (Δ –0.65 ppm);

Methyl (3*R*,5*S*,9*R*,11*R*)-9-((*tert*-butyldiphenylsilyl)oxy)-3-methyl-8-methylene-7-oxo-11-(prop-1-en-2-yl)-2,3-bis((trimethylsilyl)oxy)-5-vinyl-6-oxa-1(2,5)-furanacyclododecaphane-14-carboxylate (297)



Note: At no stage were separate signals for diastereomers detected by ^{1}H- or ^{13}C NMR.

To a solution of MNBA (10.3 mg, 29.9 µmol, 1.2 eq) and DMAP (8.3 mg, 68 µmol, 2.7 eq) in CH_2Cl_2 (20 mL, 1.0 mM final concentration) was added hydroxy acid **295** (21.1 mg, 25.3 µmol. 1.0 eq) in CH_2Cl_2 (7.0 mL + 3.0 mL rinse) *via* syringe pump (0.4 mL/h). After completed addition, the reaction mixture was stirred for further 3 h before being cooled to 0 °C. The reaction was quenched with NH_4Cl (sat., aq., 6.0 mL), diluted with brine (6.0 mL) and the aqueous layer extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:Et_2O = 90:10 to 80:20) and preparative TLC (SiO_2 on aluminium, CyH:CH_2Cl_2 = 40:60) to afford macrocycle **297** (5.0 mg, 24%) as a colourless syrup.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70–7.66 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.60–7.55 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.46–7.41 (m, 1H, Ar$\underline{H}^{TBDPS}$), 7.41–7.35 (m, 3H, 3 × Ar$\underline{H}^{TBDPS}$) 7.29 (s, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 6.42 (s, 1H, *H*-5), 6.37–6.33 (m, 1H, *H*-12'a), 6.00 (t, *J* = 1.8 Hz, 1H, *H*-12'b), 5.69–5.60 (m, 2H, *H*-10, *H*-11), 4.93–4.89 (m, 1H, *H*-11'a), 4.81–4.72 (m, 3H, *H*-11'b, *H*-13, *H*-16a), 4.66 (t, *J* = 1.4 Hz, 1H, *H*-16b), 4.23 (s, 1H, *H*-7), 3.80 (s, 3H, $CO_2C\underline{H}_3$), 2.95 (dd, *J* = 14.8, 10.1 Hz, 1H, *H*-2a), 2.82 (dd, *J* = 14.7, 4.3 Hz, 1H, *H*-2b), 2.63 (tt, *J* = 9.6, 4.2 Hz, 1H, *H*-1), 1.91–1.81 (m, 1H, *H*-14a), 1.78–1.67 (m, 5H, *H*-9a, *H*-14b, 3 × *H*-17), 1.57–1.49 (m, 1H, *H*-9b), 1.27 (s, 3H, 3 × *H*-19), 1.07 (s, 9H, C(C$\underline{H}_3$)$_3^{TBDPS}$), 0.17 (s, 9H, Si(C$\underline{H}_3$)$_3^{TMS}$) and 0.02 ppm (s, 9H, Si(C$\underline{H}_3$)$_3^{TMS}$);

^{1}H NMR (700 MHz, C_6D_6 = 7.16 ppm) δ = 7.81–7.73 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.73–7.68 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.24–7.14 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.63 (d, *J* = 2.2 Hz, 1H, *H*-12'a), 6.59 (s, 1H, *H*-5), 6.14 (t, *J* = 1.8 Hz, 1H, *H*-12'b), 5.94 (s, 1H, *H*-10), 5.74 (ddd, *J* = 17.3, 10.5, 5.4 Hz, 1H, *H*-11), 5.13–5.09 (m, 1H, *H*-13), 5.02 (dt, *J* = 17.2, 1.4 Hz, 1H, *H*-11'a), 4.93 (dt, *J* = 10.5, 1.4 Hz, 1H, *H*-11'b), 4.91 (s, 1H, *H*-16a), 4.85 (s, 1H, *H*-16b), 4.06 (s, 1H, *H*-7), 3.44

(s, 3H, $CO_2C\underline{H}_3$), 3.16 (dd, *J* = 14.5, 10.0 Hz, 1H, *H*-2a), 3.01 (dd, *J* = 14.5, 4.3 Hz, 1H, *H*-2b), 2.93 (csm, 1H, *H*-1), 2.11 (ddd, *J* = 14.1, 9.6, 4.2 Hz, 1H, *H*-14a), 1.99 (dt, *J* = 14.7, 4.5 Hz, 1H, *H*-14b), 1.80 (dd, *J* = 15.3, 4.9 Hz, 4H, *H*-9a, 3 × *H*-17), 1.43–1.36 (m, 1H, *H*-9b), 1.17 (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$), 1.09 (s, 3H, 3 × *H*-19), 0.31 (s, 9H, $Si(C\underline{H}_3)_3^{TMS}$) and 0.01 ppm (s, 9H, $Si(C\underline{H}_3)_3^{TMS}$);

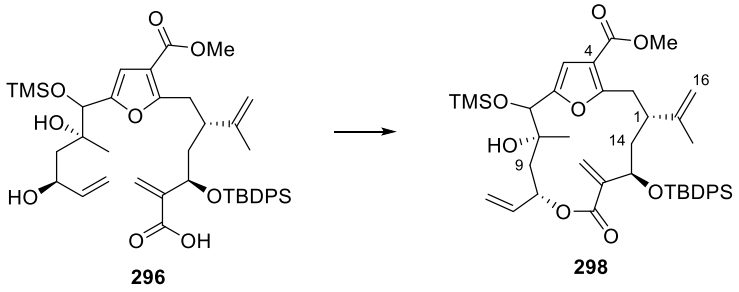
^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.4 (*C*-18, *C*-20), 160.7 (*C*-3), 152.4 (*C*-6), 147.7 (*C*-15), 141.8 (*C*-12), 138.5 (*C*-11), 136.1 (2 × $Ar\underline{C}^{TBDPS}$), 136.0 (2 × $Ar\underline{C}^{TBDPS}$), 134.1 ($Ar\underline{C}^{TBDPS}$), 133.7 ($Ar\underline{C}^{TBDPS}$), 129.8 ($Ar\underline{C}^{TBDPS}$), 129.7 ($Ar\underline{C}^{TBDPS}$), 128.2 (*C*-12'), 127.6 (4 × $Ar\underline{C}^{TBDPS}$), 114.5 (*C*-4), 113.7 (*C*-11'), 111.4 (*C*-16), 110.2 (*C*-5), 76.5 (*C*-8), 75.3 (*C*-7), 71.8 (*C*-10), 70.9 (*C*-13), 51.4 ($CO_2\underline{C}H_3$), 44.2 (*C*-9), 41.6 (*C*-1), 36.4 (*C*-14), 33.1 (*C*-2), 27.8 (*C*-19), 27.2 ($C(\underline{C}H_3)_3^{TBDPS}$), 19.6 (*C*-17), 19.4 ($\underline{C}(CH_3)_3^{TBDPS}$), 3.1 ($Si(\underline{C}H_3)_3^{TMS}$) and 0.0 ppm ($Si(\underline{C}H_3)_3^{TMS}$);

^{13}C NMR (176 MHz, C_6D_6 = 128.1 ppm) δ = 164.2 (*C*-20), 163.9 (*C*-18), 161.0 (*C*-3), 152.7 (*C*-6), 148.0 (*C*-15), 142.8 (*C*-12), 139.1 (*C*-11), 136.4 (2 × $Ar\underline{C}^{TBDPS}$), 136.3 (2 × $Ar\underline{C}^{TBDPS}$), 134.4 ($Ar\underline{C}^{TBDPS}$), 134.0 ($Ar\underline{C}^{TBDPS}$), 130.0 (6 × $Ar\underline{C}^{TBDPS}$), 128.4 (*C*-12'), 115.3 (*C*-4), 114.0 (*C*-11'), 111.7 (*C*-16), 110.8 (*C*-5), 76.8 (*C*-8), 75.4 (*C*-7), 71.8 (*C*-10), 71.6 (*C*-13), 50.9 ($CO_2\underline{C}H_3$), 44.4 (*C*-9), 42.1 (*C*-1), 36.9 (*C*-14), 33.3 (*C*-2), 27.6 (*C*-19), 27.4 ($C(\underline{C}H_3)_3^{TBDPS}$), 19.9 (*C*-17), 19.6 ($\underline{C}(CH_3)_3^{TBDPS}$), 3.3 ($Si(\underline{C}H_3)_3^{TMS}$) and –0.1 ppm ($Si(\underline{C}H_3)_3^{TMS}$);

FT-IR ν_{max} (thin film): 2953, 2927, 2856, 1721, 1440, 1428, 1303, 1251, 1199, 1154, 1133, 1112, 1072, 1016, 842, 823, 741 and 703 cm^{-1};

HRMS (ESI^+): Calc. for $C_{45}H_{64}O_8{}^{23}NaSi_3^+$ $[M+Na]^+$ 839.3801; found 839.3792 (Δ –1.08 ppm).

Methyl (3*R*,5*S*,9*R*,11*R*)-9-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-3-methyl-8-methylene-7-oxo-11-(prop-1-en-2-yl)-2-((trimethylsilyl)oxy)-5-vinyl-6-oxa-1(2,5)-furanacyclododecaphane-14-carboxylate (298)



Note: At no stage were separate signals for diastereomers detected by ^{1}H- or ^{13}C NMR.

To a solution of MNBA (7.5 mg, 21.8 µmol, 1.2 eq) and DMAP (5.2 mg, 42 µmol, 2.4 eq) in CH_2Cl_2 (14 mL, 1.2 mM final concentration) was added hydroxy acid **296** (13.5 mg, 17.7 µmol. 1.0 eq) in CH_2Cl_2 (4.0 mL) *via* syringe pump (0.25 mL/h). After completed addition, the mixture was stirred for further 2 h. The reaction was washed with HCl (1 M, aq., 7.0 mL) and the separated aqueous layer extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 500 µm on glass, CyH:EtOAc = 80:20) to afford macrocycle **298** (2.3 mg, 20%) as a colourless film.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.62 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.59–7.54 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.45–7.27 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.46 (s, 1H, *H*-5), 6.38–6.33 (m, 1H, *H*-12'a), 5.98 (t, *J* = 1.7 Hz, 1H, *H*-12'b), 5.92–5.85 (m, 1H, *H*-10), 5.67 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1H, *H*-11), 4.97 (dt, *J* = 10.6, 1.3, 1.3 Hz, 1H, *H*-11'a), 4.90 (dt, *J* = 17.1, 1.3 Hz, 1H, *H*-11'b), 4.81–4.75 (m, 1H, *H*-13), 4.73–4.66 (m, 1H, *H*-16a), 4.58 (br s, *J* = 1.8 Hz, 1H, *H*-16b), 4.37–4.33 (m, 1H, *H*-7), 3.76 (s, 3H, CO_2CH_3), 2.97–2.87 (m, 1H, *H*-2a), 2.83 (dd, *J* = 15.6, 4.5 Hz, 1H, *H*-2b), 2.66 (tt, *J* = 9.3, 5.2 Hz, 1H, *H*-1), 1.87–1.69 (m, 7H, 2 × *H*-9, 2 × *H*-14, 3 × *H*-17), 1.29 (s, 3H, 3 × 19), 1.06 (s, 9H, C(C*H*$_3$)$_3^{TBDPS}$) and 0.20 ppm (s, 9H, Si(C*H*$_3$)$_3^{TMS}$); OH not observed;

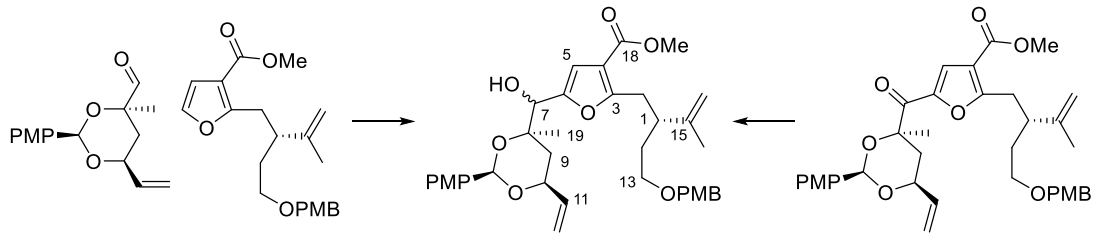
^{13}C NMR (126 MHz, $CDCl_3$) δ = 165.0 (*C*-20), 164.1 (*C*-18), 160.7 (*C*-3), 150.4 (*C*-6), 147.7 (*C*-15), 141.9 (*C*-12), 138.2 (*C*-11), 135.9 (2 × Ar$\underline{C}^{TBDPS}$), 135.8 (2 × Ar$\underline{C}^{TBDPS}$), 133.9 (Ar$\underline{C}^{TBDPS}$), 133.6 (Ar$\underline{C}^{TBDPS}$), 129.7 (Ar$\underline{C}^{TBDPS}$), 129.6 (Ar$\underline{C}^{TBDPS}$), 127.7 (*C*-12'), 127.5 (4 × Ar$\underline{C}^{TBDPS}$), 114.6 (*C*-4), 114.5 (*C*-11'), 111.2 (*C*-16), 110.2 (*C*-5), 77.2 (*C*-8), 76.1 (*C*-7), 71.6 (*C*-10), 70.4 (*C*-13), 51.3 ($CO_2\underline{C}H_3$), 44.3 (*C*-9), 39.9 (*C*-1), 36.8 (*C*-14), 32.7 (*C*-2), 27.6 (*C*-19), 27.1 (C($\underline{C}H_3$)$_3^{TBDPS}$), 19.9 (*C*-17), 19.3 ($\underline{C}(CH_3)_3^{TBDPS}$) and 2.6 ppm (Si($\underline{C}H_3$)$_3^{TMS}$);

FT-IR ν_{max} (thin film): 2953, 2926, 2855, 2248, 2161, 2035, 2025, 2018, 1979, 1820, 1719, 1535, 1458, 1439, 1429, 1379, 1346, 1300, 1261, 1207, 1087, 993, 807, 742 and 705 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{42}H_{56}O_8{}^{23}NaSi_2^+$ [M+Na]$^+$ 767.3406; found 767.3400 (Δ –0.84 ppm).

6.1.14 Synthesis of PMB containing hydroxy ketone 305

Methyl 5-(hydroxy((2*R*,4*R*,6*S*)-2-(4-methoxyphenyl)-4-methyl-6-vinyl-1,3-dioxan-4-yl)methyl)-2-((*R*)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylbut-3-en-1-yl)furan-3-carboxylate (301)



240 **169** **301** **303**

Procedure A:

To a solution of furan **169** (48.7 mg, 136 μmol, 1.0 eq) in THF (2.7 mL, 50 mM) at –78 °C in a Schlenk tube was added LDA (1.0 M in THF, 0.20 mL, 0.20 mmol, 1.5 eq). After 1 h, aldehyde **240** (45.0 mg, 172 μmol, 1.3 eq) in THF (0.25 mL + 0.25 mL rinse) was added dropwise. After an additional 1.5 h, the reaction was quenched with NH_4Cl (sat., aq., 2.0 mL), diluted with brine (2.0 mL) and extracted with Et_2O (3 × 5.0 mL). The combined organic extracts were washed with brine (5.0 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was analysed by ^{1}H NMR (55:45 dr, determined at *H*-7) and

purified by flash column chromatography (SiO_2, pentane:Et_2O = 80:20 to 40:60) to afford an inseparable mixture of diastereomers of coupling product **301** (52.2 mg, 62%, 60:40 dr) as a colourless syrup.

An analytic sample was subjected to preparative TLC (SiO_2 aluminium plate, cyclohexane:EtOAc = 80:20, 6 elusions) in order to partially separate the two diastereomers.

Procedure B:

To a solution of ketone **303** (3.0 mg, 4.9 µmol, 1.0 eq) in MeOH (0.50 mL, 9.8 mM) was added $NaBH_4$ (0.5 mg, 0.01 mmol, 3 eq) in one portion. After 20 h, the volatiles were removed, the residue redissolved in EtOAc and filtered through a pad of celite. The filtrate was concentrated *in vacuo* and analysed by ^{1}H NMR (47:53 dr determided at *H*-7). The crude product was purified by flash column chromatography (SiO_2, pentane:Et_2O = 80:20 to 40:60) to afford alcohol **301** as an inseparable mixture of diastereomers (2.7 mg, 90%, 47:53 dr) as a colourless film.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.48–7.40 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 7.26–7.21 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.94–6.84 (m, 4H, 2 × Ar$\underline{H}^{PMP}$, 2 × Ar$\underline{H}^{PMB}$), 6.60 (s, 1H, *H*-5), 5.97–5.84 (m, 1H, *H*-11), 5.80 (s, 1H, C$\underline{H}O_2^{PMP}$), 5.37–5.30 (m, 1H, *H*-11'a), 5.22–5.15 (m, 1H, *H*-11'b), 4.63 (csm, 1H, *H*-16a), 4.58 (d, *J* = 2.1 Hz, 1H, *H*-16b), 4.55 (d, *J* = 1.8 Hz, 1H, *H*-7), 4.48–4.41 (m, 1H, *H*-10), 4.39 (app. t, *J* = 2.4 Hz, 2H, OC$\underline{H}_2^{PMB}$), 3.85–3.75 (m, 9H, $CO_2C\underline{H}_3$, OC$\underline{H}_3^{PMP}$, OC$\underline{H}_3^{PMB}$), 3.47–3.32 (m, 2H, 2 × *H*-13), 3.19–2.98 (m, 3H, *OH*-7, 2 × *H*-2), 2.72 (ddd, *J* = 15.2, 8.5, 6.8 Hz, 1H, *H*-1), 2.18 (t, *J* = 12.8 Hz, 1H, *H*-9a), 1.77–1.68 (m, 2H, 2 × *H*-14), 1.66 (s, 3H, 3 × *H*-17), 1.38 (s, 3H, 3 × *H*-19) and 1.33 ppm (dd, *J* = 6.5, 2.4 Hz, 1H, *H*-9b);

^{13}C NMR (major, diastereomer 101 MHz, $CDCl_3$) δ = 164.3 (*C*-18), 161.4 (*C*-3), 160.2 (Ar$\underline{C}^{PMP}$), 159.2 (Ar$\underline{C}^{PMB}$), 150.1 (*C*-6), 146.1 (*C*-15), 137.8 (*C*-11), 131.0 (Ar$\underline{C}^{PMP}$), 130.8

(Ar<u>*C*</u>^{PMB}), 129.3 (2 × Ar<u>*C*</u>^{PMB}), 127.7 (2 × Ar<u>*C*</u>^{PMP}), 116.1 (*C*-11'), 113.9 (*C*-4), 113.8 (2 × Ar<u>*C*</u>^{PMP}), 113.7 (*C*-2 × Ar<u>*C*</u>^{PMB}), 112.6 (*C*-16), 109.9 (*C*-5), 95.0 (<u>*C*</u>HO$_2$^{PMP}), 77.2 (*C*-8), 74.5 (*C*-7), 73.8 (*C*-10), 72.7 (O<u>*C*</u>H$_2$^{PMB}), 68.3 (*C*-13), 55.5 (O<u>*C*</u>H$_3$^{PMB}), 55.4 (O<u>*C*</u>H$_3$^{PMP}), 51.4 (CO_2<u>*C*</u>H$_3$), 43.8 (*C*-1), 32.9 (*C*-9), 32.9 (*C*-14), 32.0 (*C*-2), 18.8 (*C*-19) and 18.2 ppm (*C*-17);

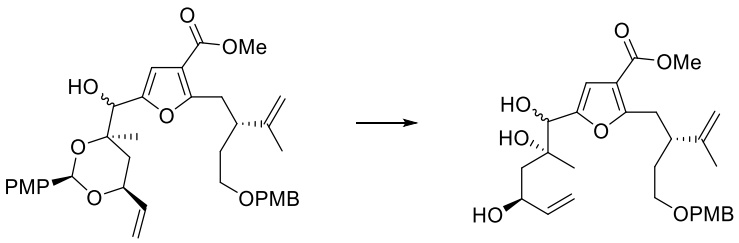
^{1}H NMR (minor diastereomer, 400 MHz, $CDCl_3$) δ = 7.48–7.40 (m, 2H, 2 × Ar<u>*H*</u>^{PMP}), 7.25–7.17 (m, 2H, 2 × Ar<u>*H*</u>^{PMB}), 6.95–6.81 (m, 4H, 2 × Ar<u>*H*</u>^{PMB}, 2 × Ar<u>*H*</u>^{PMP}), 6.57 (d, *J* = 0.6 Hz, 1H, *H*-5), 5.88 (ddd, *J* = 17.3, 10.6, 5.6 Hz, 1H, *H*-11), 5.78 (s, 1H, C<u>*H*</u>O$_2$^{PMP}), 5.32 (dt, *J* = 17.3, 1.4 Hz, 1H, *H*-11'a), 5.18 (dt, *J* = 10.6, 1.3 Hz, 1H, *H*-11'b), 4.64–4.60 (m, 1H, *H*-16a), 4.58 (s, 1H, *H*-16b), 4.50 (d, *J* = 4.6 Hz, 1H, *H*-7), 4.47–4.40 (m, 1H, *H*-10), 4.38 (d, *J* = 2.1 Hz, 2H, OC<u>*H*</u>$_2$^{PMB}), 3.84–3.77 (m, 9H, CO_2C<u>*H*</u>$_3$, OC<u>*H*</u>$_3$^{PMB}, OC<u>*H*</u>$_3$^{PMP}), 3.37 (dtd, *J* = 16.5, 9.3, 6.8 Hz, 2H, *H*-13), 3.16–2.99 (m, 2H, *H*-2), 2.89 (d, *J* = 4.7 Hz, 1H, *OH*-7), 2.71 (ddd, *J* = 15.1, 8.7, 6.3 Hz, 1H, *H*-1), 1.88 (t, *J* = 12.6 Hz, 1H, *H*-9a), 1.76–1.67 (m, 2H, 2 × *H*-14), 1.66–1.62 (m, 3H, 3 × *H*-17), 1.39 (s, 3H, 3 × *H*-19) and 1.35 ppm (dd, *J* = 13.3, 2.6 Hz, 1H, *H*-9b);

^{13}C NMR (minor diastereomer, selected signals, 101 MHz, $CDCl_3$) δ = 164.4 (*C*-18), 161.2 (*C*-3), 160.2 (Ar<u>*C*</u>^{PMP}), 159.2 (Ar<u>*C*</u>^{PMB}), 150.9 (*C*-6), 146.0 (*C*-15), 138.0 (*C*-11), 131.1 (Ar<u>*C*</u>^{PMP}), 130.8 (Ar<u>*C*</u>^{PMB}), 129.3 (2 × Ar<u>*C*</u>^{PMB}), 127.8 (2 × Ar<u>*C*</u>^{PMP}), 116.1 (*C*-11'), 114.4 (*C*-4), 112.6 (*C*-16), 109.2 (*C*-5), 95.1 (<u>*C*</u>HO$_2$^{PMP}), 76.9 (*C*-8), 75.7 (*C*-7), 73.5 (*C*-10), 72.7 (O<u>*C*</u>H$_2$^{PMB}), 68.3 (*C*-13), 55.5 (O<u>*C*</u>H$_3$^{PMB}), 55.4 (O<u>*C*</u>H$_3$^{PMP}), 51.4 (CO_2<u>*C*</u>H$_3$), 43.8 (*C*-1), 36.8 (*C*-9), 32.9 (*C*-14), 32.0 (*C*-2), 18.1 (*C*-17) and 15.9 ppm (*C*-19);

FT-IR ν_{max} (thin film): 2923, 2161, 2032, 1716, 1614, 1514, 1454, 1392, 1303, 1248, 1172, 1079, 1031, 909, 828, 776, 732, 701 and 648 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{36}H_{44}O_9{}^{23}Na^+$ $[M+Na]^+$ 643.2878; found 643.2874 (Δ –0.62 ppm);

Methyl 2-((*R*)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylbut-3-en-1-yl)-5-((2*R*,4*S*)-1,2,4-trihydroxy-2-methylhex-5-en-1-yl)furan-3-carboxylate (302)



301 **302**

To a solution of acetal **301** (2.7 mg, 4.4 µmol, 1.0 eq) in MeOH (0.35 mL, 8.7 mM) was added a solution of PPTS (0.37 mg, 1.5 µmol, 0.34 eq) in MeOH (0.15 mL; stock solution: 5.0 mg in 2.0 mL). After 44 h, excess K_2CO_3 was added, and the mixture concentrated under a flow of N_2. The residue was redissolved in EtOAc, filtered through a pad of celite and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 on aluminium, cyclohexane:EtOAc = 50:50, 2 elusions) to afford an inseparable mixture of diastereomers of triol **302** (1.7 mg, 78%, 55:45 dr, determinded at *H*-5) as a transparent film.

^{1}H NMR (major diastereomer, 400 MHz, $CDCl_3$) δ = 7.23 (dd, *J* = 8.5, 1.6 Hz, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.91–6.82 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.55 (s, 1H, *H*-5), 5.91–5.78 (m, 1H, *H*-11), 5.31–5.25 (m, 1H, *H*-11'a), 5.11 (app. dd, *J* = 10.3, 3.5 Hz, 1H, *H*-11'b), 4.65 (s, 1H, *H*-16a), 4.58 (s, 1H, *H*-16b), 4.51 (s, 1H, *H*-10), 4.45 (s, 1H, *H*-7), 4.38 (d, *J* = 4.1 Hz, 2H, OC$\underline{H}_2^{PMB}$), 3.80 (d, *J* = 1.8 Hz, 6H, $CO_2C\underline{H}_3$,OC$\underline{H}_3^{PMB}$), 3.46–3.27 (m, 2H, 2 × *H*-13), 3.18–2.94 (m, 2H, 2 × *H*-2), 2.72 (csm, 1H, *H*-1), 1.94–1.78 (m, 1H, *H*-9a), 1.71 (app. q, *J* = 6.3 Hz, 2H, 2 × *H*-14), 1.65 (s, 3H, 3 × *H*-17), 1.55 (s, 1H, *H*-9b) and 1.30 ppm (s, 3H, 3 × *H*-19); 3 × OH not observed;

^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ = 164.3 (*C*-18), 161.2 (*C*-3), 159.3 (Ar$\underline{C}^{PMB}$), 151.8 (*C*-6), 146.1 (*C*-15), 140.7 (*C*-11), 130.7 (Ar$\underline{C}^{PMB}$), 129.5 (2 × Ar$\underline{C}^{PMB}$), 115.0 (*C*-11'), 114.4 (*C*-4), 113.9 (2 × Ar$\underline{C}^{PMB}$), 112.6 (*C*-16), 109.1 (*C*-5), 75.2 (*C*-8), 75.0 (*C*-7),

72.8 (O<u>C</u>H$_2^{PMB}$), 70.4 (*C*-10), 68.2 (*C*-13), 55.4 (O<u>C</u>H$_3$), 51.5 (O<u>C</u>H$_3$), 43.6 (*C*-9), 43.6 (*C*-1), 32.7 (*C*-14), 32.0 (*C*-2), 21.9 (*C*-19) and 18.2 ppm (*C*-17);

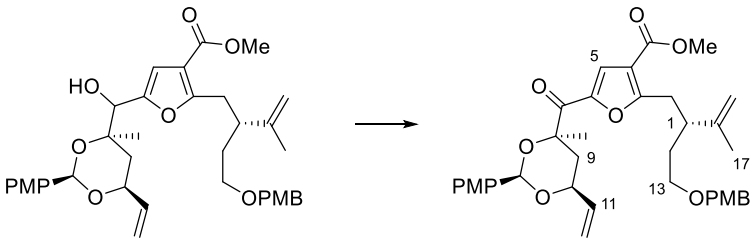
^{1}H NMR (minor diastereomer, selected signals, 400 MHz, $CDCl_3$) δ = 6.54 (s, 1H, *H*-5), 5.23 (d, *J* = 9.4 Hz, 1H, *H*-11'a), 4.60 (s, 1H, *H*-16b) and 1.20 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (minor diastereomer, selected signals, 126 MHz, $CDCl_3$) δ = 164.4 (*C*-18), 161.2 (*C*-3), 151.6 (*C*-6), 146.1 (*C*-15), 140.7 (*C*-11), 130.7 (Ar<u>C</u>^{PMB}), 129.5 (2 × Ar<u>C</u>^{PMB}), 129.4), 114.8 (*C*-11'), 114.4 (*C*-4), 109.0 (*C*-5), 75.4 (*C*-8), 74.5 (*C*-7), 70.3 (*C*-10), 68.2 (*C*-13), 43.5 (*C*-1), 41.2 (*C*-9), 32.8 (*C*-14), 31.9 (*C*-2) and 24.0 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3412, 2923, 2853, 2362, 1717, 1646, 1613, 1575, 1514, 1441, 1377, 1302, 1248, 1226, 1174, 1082, 1038, 906 and 822 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{28}H_{38}O_8{}^{23}Na^+$ [M+Na]$^+$ 525.2459; found 525.2458 (Δ –0.19 ppm);

Methyl 2-((*R*)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylbut-3-en-1-yl)-5-((2*R*,4*R*,6*S*)-2-(4-methoxyphenyl)-4-methyl-6-vinyl-1,3-dioxane-4-carbonyl)furan-3-carboxylate (303)



A solution of alcohol **301** (38.7 mg, 62.4 µmol, 60:40 dr, 1.0 eq) in CH_2Cl_2 (0.40 mL, 0.16 mM) was treated with MnO_2 (55.2 mg, 635 µmol, 10 eq) in a sealed vial for 3 months. After which, the mixture was filtered though celite, rinsed with CH_2Cl_2 and the obtained filtrate concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, PhMe:acetone = 100:0 to 95:5) to afford ketone **303** (29.0 mg, 75%) as a pale syrup as well as recovered alcohol **301** (4.2 mg, 60:40 dr, 11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (s, 1H, *H*-5), 7.50 (d, *J* = 8.8 Hz, 2H, 2 × Ar<u>H</u>^{PMB}), 7.22 (d, *J* = 8.5 Hz, 2H, 2 × Ar<u>H</u>^{PMP}), 6.93 (d, *J* = 8.8 Hz, 2H, 2 × Ar<u>H</u>^{PMB}), 6.86 (d, *J* = 8.7 Hz, 2H,

2 × Ar$\underline{H}^{PMP}$), 6.00–5.85 (m, 2H, C$\underline{H}O_2^{PMP}$, *H*-11), 5.43–5.32 (m, 1H, *H*-11'a), 5.21 (dt, *J* = 10.5, 1.3 Hz, 1H, *H*-11'b), 4.72–4.64 (m, 2H, 2 × *H*-16), 4.64–4.55 (m, 1H, *H*-10), 4.37 (s, 2H, OC$\underline{H}_2^{PMB}$), 3.82 (s, 3H, OC$\underline{H}_3^{PMP}$), 3.79 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.78 (s, 3H, $CO_2C\underline{H}_3$), 3.44–3.29 (m, 2H, *H*-13), 3.19 (dd, *J* = 14.2, 8.3 Hz, 1H, *H*-2a), 3.11 (dd, *J* = 14.3, 7.1 Hz, 1H, *H*-2b), 2.89–2.76 (m, 1H, *H*-1), 1.99 (dd, *J* = 13.6, 11.6 Hz, 1H, *H*-9a), 1.86 (dd, *J* = 13.6, 2.6 Hz, 1H, *H*-9b), 1.75 (s, 3H, 3 × *H*-19), 1.73–1.69 (m, 2H, 2 × *H*-14) and 1.67 ppm (s, 3H, 3 × *H*-17);

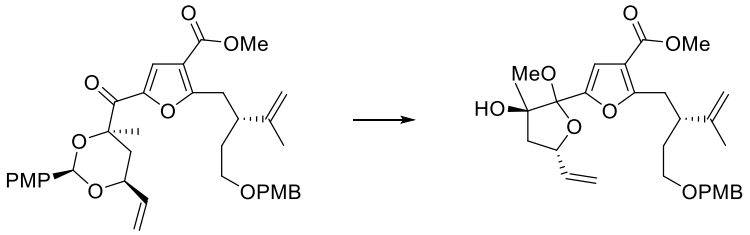
^{13}C NMR (101 MHz, $CDCl_3$) δ = 189.1 (*C*-7), 165.9 (*C*-18), 163.3 (*C*-3), 160.1 (Ar$\underline{C}^{PMP}$), 159.1 (Ar$\underline{C}^{PMB}$), 146.9 (*C*-6), 145.6 (*C*-15), 137.2 (*C*-11), 130.7 (Ar$\underline{C}^{PMP}$), 130.6 (Ar$\underline{C}^{PMB}$), 129.2 (2 × Ar$\underline{C}^{PMB}$), 127.7 (2 × Ar$\underline{C}^{PMP}$), 123.3 (*C*-5), 116.3 (*C*-11'), 116.0 (*C*-4), 113.8 (2 × Ar$\underline{C}^{PMP}$), 113.7 (2 × Ar$\underline{C}^{PMB}$), 112.7 (*C*-16), 95.3 ($\underline{C}HO_2^{PMP}$), 80.8 (*C*-8), 73.6 (*C*-10), 72.6 (O$\underline{C}H_2^{PMB}$), 68.1 (*C*-13), 55.3 (O$\underline{C}H_3^{PMP}$), 55.3 (O$\underline{C}H_3^{PMB}$), 51.5 ($CO_2\underline{C}H_3$), 43.2 (*C*-1), 36.8 (*C*-9), 32.5 (*C*-14), 32.4 (*C*-2), 19.6 (*C*-19) and 18.3 (*C*-17);

FT-IR ν_{max} (thin film): 2923, 2852, 2361, 2115, 1722, 1670, 1614, 1588, 1516, 1443, 1394, 1303, 1247, 1172, 1115, 1073, 1034, 998, 928, 906, 826, 782 and 764 cm^{-1};

HRMS (ESI^+): Calc. for $C_{36}H_{42}O_9{}^{23}Na^+$ $[M+Na]^+$ 641.2721; found 641.2717;

Specific Rotation: $[\alpha]_D^{25}$ +6.1 (c = 1.00, CH_2Cl_2).

Methyl 5-((3*R*,5*S*)-3-hydroxy-2-methoxy-3-methyl-5-vinyltetrahydrofuran-2-yl)-2-((*R*)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylbut-3-en-1-yl)furan-3-carboxylate (304)



303 **304**

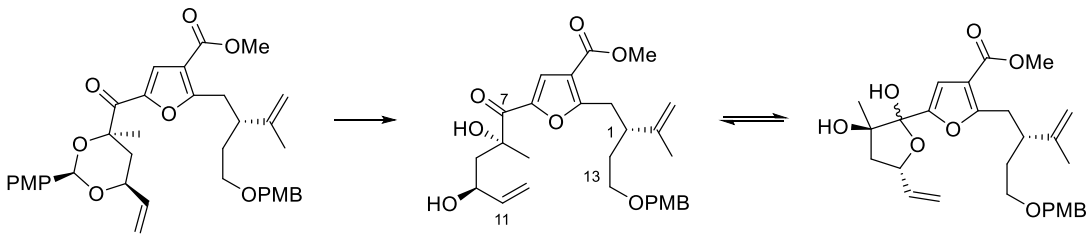
To a solution of acetal **303** (3.0 mg, 4.9 µmol, 1.0 eq) in MeOH (0.35 mL, 0.01 M final concentration) was added solution of PPTS (1.2 µmol, 0.25 eq) in MeOH (0.15 mL; stock solution: 5.0 mg in 2.0 mL) at rt. After 20 h, the reaction was neutrlised by addition of

K_2CO_3 and the mixture was concentrated under a stream of N_2. The resulting residue was dissolved in EtOAc, filtered, and concentrated *in vacuo*. Crude product **304** was observed as a mixture of diastereomers (77:23 dr, determined at *H*-5) and purified by preparative TLC (SiO_2 on aluminium, cyclohexane:EtOAc = 70:30, 2 elusions) to afford recovered **303** (0.6 mg, 20%) and major diastereomer **304** (1.7 mg, 70%) as a single diastereomer. Although clean ^{1}H NMR data was recorded, decomposition and the formation of *epi*-**304**, ketone **305** as well as hemiacetals **306** and *epi*-**306** were observed in the time frame of recording the ^{13}C NMR spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H, 2 × Ar*H*^{PMB}), 6.86 (d, *J* = 8.6 Hz, 2H, 2 × Ar*H*^{PMB}), 6.82 (s, 1H, *H*-5), 5.85 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1H, *H*-11), 5.32–5.23 (m, 1H, *H*-11'a), 5.15 (app. dt, *J* = 10.1, 1.2 Hz, 1H, *H*-11'b), 4.81 (ddd, *J* = 9.9, 7.4, 6.2 Hz, 1H, *H*-10), 4.67 (dd, *J* = 2.3, 1.4 Hz, 1H, *H*-16a), 4.61 (d, *J* = 2.3 Hz, 1H, *H*-16b), 4.41 (d, *J* = 11.6 Hz, 1H, OC*H*aHb^{PMB}), 4.37 (d, *J* = 11.6 Hz, 1H, OCHa*H*b^{PMB}), 3.80 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.36 (app. td, *J* = 6.6, 2.6 Hz, 2H, 2 × *H*-13), 3.17 (dd, *J* = 14.4, 7.0 Hz, 1H, *H*-2a), 3.13 (s, 3H, OC*H*$_3$), 3.04 (dd, *J* = 14.4, 8.7 Hz, 1H, *H*-2b), 2.85–2.74 (m, 1H, *H*-1), 2.17 (dd, *J* = 12.6, 6.3 Hz, 1H, *H*-9a), 2.02 (t, *J* = 11.4 Hz, 2H, *H*-9b), 1.71–1.63 (m, 5H, 2 × *H*-14, 3 × H17) and 1.45 ppm (s, 3H, 3 × *H*-19);

HRMS (ESI$^+$): Calc. for $C_{29}H_{38}O_8{}^{23}Na^+$ [M+Na]$^+$ 537.2459; found 537.2458 (Δ –0.19 ppm).

Methyl 5-((2*R*,4*S*)-2,4-dihydroxy-2-methylhex-5-enoyl)-2-((*R*)-2-(2-((4-methoxybenzyl)oxy)ethyl)-3-methylbut-3-en-1-yl)furan-3-carboxylate (305)



303 **305** **306**

Acetal **303** (2.7 mg, 4.4 μmol, 1.0 eq) was treated with a mixture of H_2O:THF:AcOH (45:45:10, 0.44 mL, 10 mM) for 4 days. After which, the reaction mixture was diluted with Et_2O (1.0 mL) and basified with excess K_2CO_3 until the evolution of gaseous CO_2 ceased. The separated aqueous layer was estracted with Et_2O (2 × 1.0 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 on aluminium, cyclohexane:EtOAc = 50:50, single elusion) to afford **305** (2.2 mg, quant. yield) as a pale oil. In deuterated chloroform a mixture of linear hydroxy ketone **305** and two hemiacetal (**305**:**306**:*epi*-**306** = 70:16:14, determined at *H*-5) was observed.

^{1}H NMR (ketone **305**, 500 MHz, $CDCl_3$) δ = 7.58 (s, 1H, *H*-5), 7.25–7.21 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 6.90–6.83 (m, 2H, 2 × Ar$\underline{H}^{PMB}$), 5.82 (ddd, *J* = 17.2, 10.4, 5.6 Hz, 1H, *H*-11), 5.22 (dt, *J* = 17.2, 1.5 Hz, 1H, *H*-11'a), 5.06 (dt, *J* = 10.4, 1.4 Hz, 1H, *H*-11'b), 4.68 (t, *J* = 1.7 Hz, 1H, *H*-16a), 4.65 (s, 1H, *H*-16b), 4.57–4.48 (m, 2H, *OH*-10, *H*-10), 4.43–4.34 (m, 2H, OC$\underline{H}_2^{PMB}$), 3.84 (s, 3H, $CO_2C\underline{H}_3$), 3.80 (s, 3H, OC$\underline{H}_3^{PMB}$), 3.43 (dt, *J* = 9.5, 6.2 Hz, 1H, *H*-13a), 3.37 (dt, *J* = 9.5, 7.0 Hz, 1H, *H*-13b), 3.23 (dd, *J* = 14.5, 9.2 Hz, 1H, *H*-2a), 3.13 (dd, *J* = 14.5, 6.3 Hz, 1H, *H*-2b), 2.80 (app. dq, *J* = 13.4, 6.7, 6.1 Hz, 1H, *H*-1), 2.43 (s, 1H, *OH*-8), 2.24 (dd, *J* = 14.4, 10.2 Hz, 1H, *H*-9a), 2.09 (dd, *J* = 14.6, 2.3 Hz, 1H, *H*-9b), 1.75 (q, *J* = 6.9 Hz, 2H, *H*-14), 1.67 (d, *J* = 1.4 Hz, 3H, 3 × *H*-17) and 1.55 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (ketone **305**, 126 MHz, $CDCl_3$) δ = 191.9 (*C*-7), 165.3 (*C*-3), 163.2 (*C*-18), 159.3 (Ar$\underline{C}^{PMB}$), 148.3 (*C*-6), 145.4 (*C*-15), 140.6 (*C*-11), 130.6 (Ar$\underline{C}^{PMB}$), 129.4 (2 × Ar$\underline{C}^{PMB}$), 120.7 (*C*-5), 116.4 (*C*-4), 114.7 (*C*-11'), 113.9 (2 × Ar$\underline{C}^{PMB}$), 113.2 (*C*-16), 77.1 (*C*-8), 72.9 (O$\underline{C}H_2^{PMB}$), 69.1 (*C*-10), 68.0 (*C*-13), 55.4 (O$\underline{C}H_3^{PMB}$), 51.9 ($CO_2\underline{C}H_3$), 45.9 (*C*-9), 43.6 (*C*-1), 33.0 (*C*-14), 32.4 (*C*-2), 26.2 (*C*-19) and 18.3 ppm (*C*-17);

^{1}H NMR (hemiacetal **306**, selected signals, 500 MHz, $CDCl_3$) δ = 6.67 (s, 1H, *H*-5), 5.98–5.87 (m, 1H, *H*-11), 5.35 (dt, *J* = 17.0, 1.4 Hz, 1H, *H*-11'a), 5.20–5.14 (m, 1H, *H*-11'b), 4.84

(app. q, *J* = 7.5, 7.0 Hz, 1H, *H*-10), 4.63 (br. s, 1H, *H*-16a), 4.61 (br. s, 1H, *H*-16b), 3.10–3.03 (m, 1H, *H*-2a), 2.34 (app. t, *J* = 7.6 Hz, 1H, *H*-9a), 1.95 (dd, *J* = 12.8, 8.8 Hz, 1H, *H*-9b) and 1.06 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (hemiacetal **306**, selected signals, 126 MHz, $CDCl_3$) δ = 137.9 (*C*-11), 116.7 (*C*-4), 114.5 (*C*-11'), 112.9 (*C*-16), 109.3 (*C*-5), 104.3 (*C*-7), 72.8 ($O\underline{C}H_2^{PMB}$), 51.5 ($CO_2\underline{C}H_3$) and 23.9 ppm (*C*-19);

^{1}H NMR (hemiacetal *epi*-**306**, selected signals, 500 MHz, $CDCl_3$) δ = 6.78 (s, 1H, *H*-5), 5.28 (app. dd, *J* = 17.2, 1.5 Hz, 1H, *H*-11'a) and 1.43 ppm (s, 3H, 3 × *H*-19);

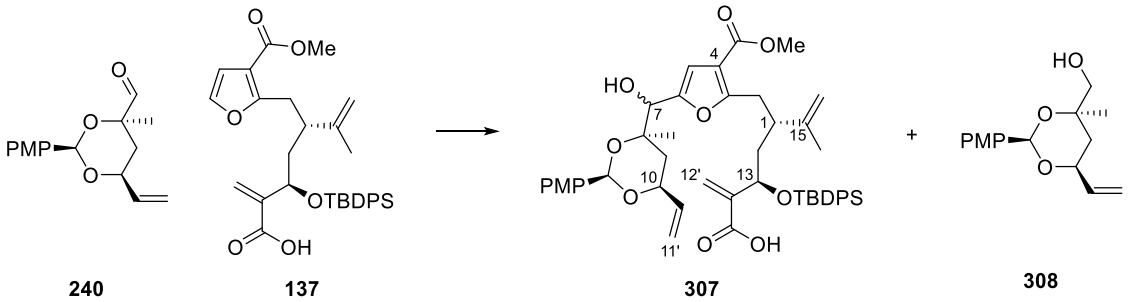
^{13}C NMR (hemiacetal *epi*-**306**, selected signals, 126 MHz, $CDCl_3$) δ = 139.5 (*C*-11), 116.8 (*C*-4), 114.6 (*C*-11'), 112.5 (*C*-16), 110.3 (*C*-5), 103.1 (*C*-7), 72.7 ($O\underline{C}H_2^{PMB}$), 51.5 ($CO_2\underline{C}H_3$) and 21.3 ppm (*C*-19);

FT-IR ν_{max} (thin film): 2926, 2853, 2361, 2341, 2226, 2174, 2158, 2034, 1721, 1613, 1514, 1441, 1248, 1172, 1084, 1034, 912, 805 and 677 cm^{-1};

HRMS (ESI^+): Calc. for $C_{28}H_{35}O_8$ $[M-H]^-$ 499.2337; found 499.2349 (Δ +2.29 ppm);

6.1.15 Synthesis of butenolide 321

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((5-(hydroxy((2*R*,4*R*,6*S*)-2-(4-methoxyphenyl)-4-Methyl-6-vinyl-1,3-dioxan-4-yl)methyl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (307)



To a solution of furan **137** (835 mg, 1.53 mmol, 1.0 eq) in THF (30 mL, 50 mM) at –78 °C in a Schlenk tube was added LDA (1.0 M in THF, 3.8 mL, 3.8 mmol, 2.5 eq) dropwise over 3 min. After 1 h, aldehyde **240** (501 mg, 1.91 µmol, 1.3 eq) in THF (4.0 + 2 × 0.50 mL rinse)

was added dropwise over 15 min. After 1.5 h, the mixture was warmed to 0 °C and stirred for further 30 min. The reaction was quenched with NH_4Cl (sat., aq., 13 mL), diluted with brine (13 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, cyclohexane:EtOAc = 90:10 to 0:100 to EtOAc:MeOH = 90:10) to afford alcohol **308** (184 mg, 36%) and desired coupling product **307** (828 mg, 67%, 51:49 dr determined at *H*-5) as a yellow foam.

Coupling product **307**:

^{1}H NMR (**307**, 400 MHz, $CDCl_3$) δ = 7.70–7.63 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.62–7.57 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.47–7.30 (m, 8H, 6 × Ar$\underline{H}^{TBDPS}$, 2 × Ar$\underline{H}^{PMP}$), 6.93–6.90 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.59 (s, 1H, *H*-5), 6.23 (d, *J* = 1.3 Hz, 1H, *H*-12'a), 5.97–5.84 (m, 1H, *H*-11), 5.83–5.81 (m, 1H, *H*-12'b), 5.80 (s, 1H, C$\underline{H}O_2^{PMP}$), 5.37–5.26 (m, 1H, *H*-11'a), 5.21–5.13 (m, 1H, *H*-11'b), 4.70–4.61 (m, 1H, *H*-13), 4.51–4.47 (m, 1H, *H*-16, *H*-7), 4.47–4.37 (m, 1H, *H*-10), 4.34–4.31 (m, 1H, *H*-16a), 4.29 (app. d, *J* = 2.2 Hz, 1H, *H*-16b), 3.81 (s, 3H, OC$\underline{H}_3^{PMP}$), 3.76 (s, 3H, $CO_2C\underline{H}_3$), 2.88 (dd, *J* = 14.4, 9.1 Hz, 1H, *H*-2a), 2.83–2.73 (m, 1H, *H*-2b), 2.70–2.54 (m, 1H, *H*-1), 2.14 (app. t, *J* = 12.8 Hz, 1H, *H*-9a), 1.85–1.74 (m, 1H, *H*-14a), 1.69 (dt, *J* = 13.2, 5.5 Hz, 1H, *H*-14b), 1.52 (s, 3H, 3 × *H*-17), 1.39 (s, 3H, 3 × *H*-19), 1.33–1.29 (m, 1H, *H*-9b) and 1.06 ppm (s, 9H, C(C$\underline{H}_3)_3^{TBDPS}$); OH and CO_2H not observed;

^{13}C NMR (**307**, 101 MHz, $CDCl_3$) δ = 164.2 (*C*-20), 161.2 (*C*-3), 160.2 (Ar$\underline{C}^{PMP}$), 150.6 (*C*-6), 146.0 (*C*-15), 141.9 (*C*-12), 137.9 (*C*-11), 136.1 (4 × Ar$\underline{C}^{TBDPS}$), 133.4 (Ar$\underline{C}^{TBDPS}$), 131.1 (Ar$\underline{C}^{PMP}$), 130.0 (2 × Ar$\underline{C}^{PMP}$), 130.0 (Ar$\underline{C}^{TBDPS}$), 127.8 (*C*-12'), 127.8 (2 × Ar$\underline{C}^{TBDPS}$), 127.7 (4 × Ar$\underline{C}^{TBDPS}$), 127.7 (*C*-12'), 116.2 (*C*-11'), 114.4 (*C*-4), 113.8 (2 × Ar$\underline{C}^{PMP}$), 112.7 (*C*-16), 109.8 (*C*-5), 95.1 ($\underline{C}HO_2^{PMP}$), 77.4 (*C*-8), 75.7 (*C*-7), 73.8 (*C*-10), 71.2 (*C*-13), 55.5 (O$\underline{C}H_3^{PMP}$), 51.4 ($CO_2\underline{C}H_3$), 42.8 (*C*-1), 40.8 (*C*-14), 36.9 (*C*-9), 32.1 (*C*-2), 27.2 (C($\underline{C}H_3)_3^{TBDPS}$), 19.5 ($\underline{C}(CH_3)_3^{TBDPS}$), 18.7 (*C*-19) and 18.5 ppm (*C*-17);

^{1}H NMR (*epi*-**307**, selected signals, 400 MHz, $CDCl_3$) δ = 6.90–6.87 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.56 (s, 1H, *H*-5), 6.22 (d, *J* = 1.4 Hz, 1H, *H*-12'a), 5.77 (s, 1H, C$\underline{H}O_2{}^{PMP}$), 4.52 (s, 1H, *H*-7), 3.80 (s, 3H, OC$\underline{H}_3{}^{PMP}$), 3.76 (s, 3H, $CO_2C\underline{H}_3$) and 1.35 ppm (s, 3H, 3 × *H*-19);

^{13}C NMR (*epi*-**307**, selected signals, MHz, $CDCl_3$) δ = 161.1 (*C*-3), 160.2 (Ar$\underline{C}^{PMP}$), 150.1 (*C*-6), 145.9 (*C*-15), 137.8 (*C*-11), 133.2 (Ar$\underline{C}^{TBDPS}$), 112.7 (*C*-16), 109.4 (*C*-5), 131.0 (Ar$\underline{C}^{PMP}$), 113.8 (2 × Ar$\underline{C}^{PMP}$), 94.9 ($\underline{C}HO_2{}^{PMP}$), 74.5 (*C*-7), 73.4 (*C*-10), 42.7 (*C*-1), 32.8 (*C*-9), 18.4 (*C*-17) and 15.8 ppm (*C*-19);

FT-IR ν_{max} (thin film): 2595, 2564, 2555, 2493, 2456, 2357, 2320, 2271, 2253, 2230, 2219, 2204, 2180, 2103, 2018, 2009, 1988, 1978, 1920, 1895, 1884, 1717, 1638, 1441, 1428, 1250, 1222, 1109, 1089, 1048, 1033, 824 and 703 cm^{-1};

HRMS (ESI^-): Calc. for $C_{47}H_{55}O_{10}{}^{23}Si^-$ $[M-H]^-$ 807.3570; found 807.3570 (Δ –0.02 ppm);

Alcohol **308**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46–7.39 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.94–6.85 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 5.92 (ddd, *J* = 17.3, 10.6, 5.5 Hz, 1H, *H*-11), 5.79 (s, 1H, C$\underline{H}O_2{}^{PMP}$), 5.34 (dt, *J* = 17.3, 1.4 Hz, 1H, *H*-11'a), 5.18 (dt, *J* = 10.5, 1.4 Hz, 1H, *H*-11'b), 4.51 (dddd, *J* = 10.6, 5.5, 2.6, 1.3 Hz, 1H, *H*-10), 3.80 (s, 3H, OC$\underline{H}_3{}^{PMP}$), 3.55 (d, *J* = 11.3 Hz, 1H, *H*-7a), 3.41 (dd, *J* = 11.0, 4.3 Hz, 1H, *H*-7b), 2.15 (br. s, 1H, *OH*-7), 2.00 (ddd, *J* = 13.0, 12.1, 0.8 Hz, 1H, *H*-9a), 1.42 (s, 3H, 3 × *H*-19) and 1.38 ppm (dd, *J* = 13.3, 2.6 Hz, 1H, *H*-9b);

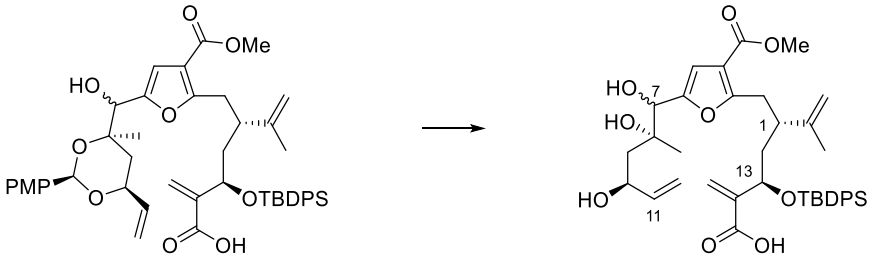
^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.2 (Ar$\underline{C}^{PMP}$), 138.0 (C11), 131.4 (Ar$\underline{C}^{PMP}$), 127.7 (2 × Ar$\underline{C}^{PMP}$), 115.9 (*C*-11'), 113.8 (2 × Ar$\underline{C}^{PMP}$), 95.0 ($\underline{C}HO_2{}^{PMP}$), 74.9 (*C*-8), 73.5 (*C*-10), 71.0 (*C*-7), 55.5 ($O\underline{C}H_3{}^{PMP}$), 35.3 (*C*-9) and 18.6 ppm (*C*-19);

FT-IR ν_{max} (thin film): 3450, 2934, 2839, 1615, 1589, 1518, 1461, 1433, 1413, 1389, 1359, 1304, 1248, 1213, 1197, 1171, 1148, 1113, 1075, 1032, 996, 928, 832 and 771 cm^{-1};

HRMS (ESI^+): Calc. for $C_{15}H_{20}O_4{}^{23}Na^+$ $[M+Na]^+$ 287.1254; found 287.1255 (Δ +0.26 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +29.5 (c = 1.00, CH_2Cl_2).

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((3-(methoxycarbonyl)-5-((2*R*,4*S*)-1,2,4-Trihydroxy-2-methylhex-5-en-1-yl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (313)



Note: Ion exchange resin Dowex 50WX8 H-form (2 g) was washed with MeOH (2 × 5 mL), HCl (1 M, aq., 5 mL), H_2O (3 × 5 mL), MeOH (3 × 5 mL), Et_2O (3 × 5 mL) and dried under reduced pressure for 1 h prior to use.

A solution of acetal **307** (33.6 mg, 41.5 µmol, 51:49 dr, 1.0 eq) in MeOH (2.0 mL, 21 mM) was treated with excess prepared Dowex 50WX8. The reaction mixture was agitated at 100 rpm rather than stirring with magnetic stirring. After 2 h, the mixture was diluted with PhMe (1.0 mL) and then concentrated under a stream of N_2. The concentrated mixture was directly subjected to flash column chromatography (SiO_2, cyclohexane:EtOAc = 50:50 0:100 to EtOAc:MeOH = 90:10) to afford triol **313** (18.4 mg, 64%) as a colourless oil. Only a single set of ^{1}H and ^{13}C NMR signals were observed in $CDCl_3$ at 500 MHz and 126 MHz, respectively.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.71–7.65 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.63–7.57 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.49–7.31 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.44 (s, 1H, *H*-5), 6.24 (app. d, *J* = 1.3 Hz, 1H, *H*-12'a), 5.93 (ddd, *J* = 17.2, 10.3, 6.9 Hz, 1H, *H*-11), 5.75 (s, 1H, *H*-12'b), 5.39–5.29 (m, 1H, *H*-11'a), 5.23–5.15 (m, 1H, *H*-11'b), 4.74–4.67 (m, 2H, *H*-7, *H*-10), 4.63 (t, *J* = 6.0 Hz, 1H, *H*-13), 4.49 (app. t, *J* = 1.7 Hz, 1H, *H*-16a), 4.30 (s, 1H, *H*-16b), 3.75 (s, 3H, $CO_2C\underline{H}_3$), 2.77–2.70 (m, 2H, 2 × *H*-2), 2.53–2.43 (m, 1H, *H*-1), 2.10 (dd, *J* = 12.8, 5.6 Hz, 1H, *H*-9a), 1.87 (dd, *J* = 12.9, 10.3 Hz, 1H, *H*-9b), 1.76 (dt, *J* = 13.8, 6.8 Hz, 1H, *H*-14a), 1.70 (dt, *J* = 14.2,

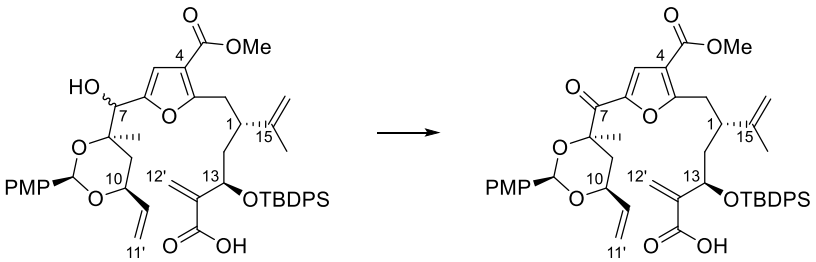
6.0 Hz, 1H, *H*-14b), 1.51 (s, 3H, 3 × *H*-17), 1.06 (s, 9H, C(C<u>*H*</u>$_3$)$_3^{TBDPS}$) and 1.04 ppm (s, 3H, 3 × *H*-19); 3 × OH and CO_2H not observed;

^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.5 (*C*-20), 164.2 (*C*-18), 161.1 (*C*-3), 151.7 (*C*-6), 145.6 (*C*-15), 141.1 (*C*-12), 138.1 (*C*-11), 136.1 (2 × Ar<u>*C*</u>^{TBDPS}), 136.1 (2 × Ar<u>*C*</u>^{TBDPS}), 133.2 (Ar<u>*C*</u>^{TBDPS}), 132.7 (Ar<u>*C*</u>^{TBDPS}), 130.2 (Ar<u>*C*</u>^{TBDPS}), 130.2 (Ar<u>*C*</u>^{TBDPS}), 128.2 (*C*-12'), 127.9 (2 × Ar<u>*C*</u>^{TBDPS}), 127.8 (2 × Ar<u>*C*</u>^{TBDPS}), 117.0 (*C*-11'), 114.3 (*C*-4), 112.8 (*C*-16), 108.5 (*C*-5), 84.7 (*C*-7), 81.6 (*C*-8), 79.9 (*C*-10), 72.0 (*C*-13), 51.4 (CO_2<u>*C*</u>H_3), 46.0 (*C*-9), 42.7 (*C*-1), 40.8 (*C*-14), 31.5 (*C*-2), 27.1 (C(<u>*C*</u>H_3)$_3^{TBDPS}$), 23.6 (*C*-19), 19.4 (<u>*C*</u>$(CH_3)_3^{TBDPS}$) and 18.6 ppm (*C*-17);

FT-IR ν_{max} (thin film): 3432, 3072, 2928, 2856, 1718, 1646, 1615, 1440, 1428, 1390, 1225, 1170, 1111, 1088, 999, 966, 926, 823, 783, 741, 703 and 608 cm^{-1};

HRMS (ESI^+): Calc. for $C_{39}H_{50}O_9{}^{23}NaSi^+$ $[M+Na]^+$ 713.3116; found 713.3115 (Δ –0.24 ppm);

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((3-(methoxycarbonyl)-5-((2*R*,4*R*,6*S*)-2-(4-methoxyphenyl)-4-Methyl-6-vinyl-1,3-dioxane-4-carbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (315)



To a solution of alcohol **307** (797 mg, 985 µmol, 51:49 dr, 1.0 eq) in CH_2Cl_2 (10 mL, 99 mM) was added $NaHCO_3$ (830 mg, 9.88 mmol, 10 eq) and DMP (1.25 g, 2.96 mmol, 3.0 eq) at 0 °C. The cooling bath was removed after completed addition and the reaction stirred for 2.5 h. After which, it was quenched with $Na_2S_2O_3$ (sat., aq., 10 mL), stirred for 5 min, diluted with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with NaOH (3 M, 2 × 20 mL), $KHSO_4$ (1 M, saturated with NaCl, 20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford crude ketone **315** (752 mg,

95%) as a pale foam. The material was used in the next step without further purification. For spectroscopic reasons, an analytical sample was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 97:3 to 80:20).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.72 (s, 1H, *H*-5), 7.68–7.65 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.60–7.57 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.49–7.45 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 7.44–7.29 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.94–6.90 (m, 2H, 2 × Ar$\underline{H}^{PMP}$), 6.28 (d, *J* = 1.7 Hz, 1H, *H*-12'a), 5.92–5.80 (m, 3H, C$\underline{H}O_2^{PMP}$, *H*-11, *H*-12'b), 5.34 (app. dt, *J* = 17.3, 1.4 Hz, 1H, *H*-11'a), 5.19 (app. dt, *J* = 10.6, 1.3 Hz, 1H, *H*-11'b), 4.74 (app. t, *J* = 6.3 Hz, 1H, *H*-13), 4.59–4.49 (m, 1H, *H*-10), 4.42 (s, 1H, *H*-16a), 4.27 (s, 1H, *H*-16b), 3.81 (s, 3H, OC$\underline{H}_3^{PMP}$), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 2.85 (dd, *J* = 14.2, 9.8 Hz, 1H, *H*-2a), 2.78 (dd, J = 14.2, 5.4 Hz, 1H, *H*-2b), 2.53–2.44 (m, 1H, *H*-1), 1.90–1.82 (m, 1H, *H*-9a), 1.73–1.65 (m, 3H, *H*-9b, 2 × *H*-14), 1.61 (s, 3H, 3 × *H*-19), 1.43 (s, 3H, 3 × *H*-17) and 1.06 ppm (s, 9H, C(C$\underline{H}_3)_3^{TBDPS}$); CO_2H not observed;

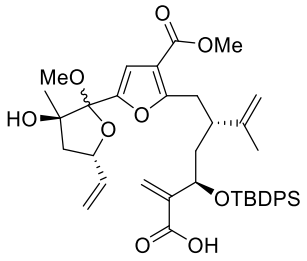
^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.0 (*C*-7), 166.6 (*C*-3), 163.0 (*C*-18), 160.2 (Ar$\underline{C}^{PMP}$), 146.4 (*C*-6), 145.8 (*C*-15), 137.0 (*C*-11), 135.9 (2 × Ar$\underline{C}^{TBDPS}$), 135.9 (2 × Ar$\underline{C}^{TBDPS}$), 133.6 (Ar$\underline{C}^{TBDPS}$), 133.1 (Ar$\underline{C}^{TBDPS}$), 130.5 (Ar$\underline{C}^{PMP}$), 129.9 (Ar$\underline{C}^{TBDPS}$), 129.8 (Ar$\underline{C}^{TBDPS}$), 127.7 (2 × Ar$\underline{C}^{TBDPS}$), 127.7 (2 × Ar$\underline{C}^{PMP}$), 127.6 (2 × Ar$\underline{C}^{TBDPS}$), 125.6 (*C*-12'), 124.3 (*C*-5), 116.4 (*C*-11'), 116.3 (*C*-4), 113.7 (2 × Ar$\underline{C}^{PMP}$), 112.1 (*C*-16), 95.4 ($\underline{C}HO_2^{PMP}$), 80.8 (*C*-8), 73.6 (*C*-10), 70.2 (*C*-13), 55.3 (O$\underline{C}H_3^{PMP}$), 51.5 ($CO_2\underline{C}H_3$), 42.9 (*C*-14), 42.3 (*C*-1), 36.6 (*C*-9), 30.9 (*C*-2), 27.0 (C($\underline{C}H_3)_3^{TBDPS}$), 19.7 (*C*-19), 19.3 ($\underline{C}(CH_3)_3^{TBDPS}$) and 18.5 (*C*-17); *C*-20 and *C*-12 not observed;

FT-IR ν_{max} (thin film): 2958, 2929, 2856, 1723, 1697, 1673, 1616, 1590, 1519, 1442, 1428, 1392, 1303, 1249, 1171, 1111, 1087, 1033, 999, 928, 904, 823, 805, 742 and 704 cm^{-1};

HRMS (ESI^+): Calc. for $C_{47}H_{54}O_{10}{}^{23}NaSi^+$ $[M+Na]^+$ 829.3378; found 829.3372 (Δ –0.83 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –10.2 (c = 1.00, CH_2Cl_2).

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((5-((3*R*,5*S*)-3-Hydroxy-2-methoxy-3-methyl-5-vinyltetrahydrofuran-2-yl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-methyl-2-methylenehept-6-enoic acid (316)

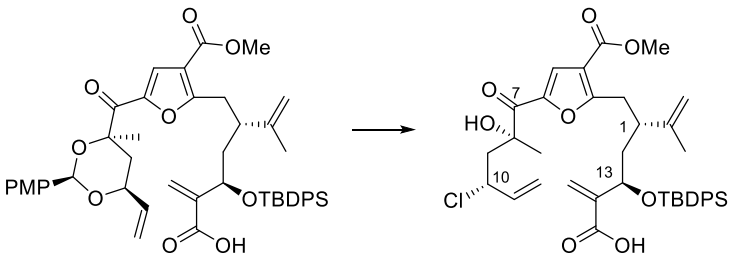


316

When MeOH was used as co-solvent in the deprotection of acetal **315** the formation of mixed acetal **316** was observed predominanty by TLC and HRMS.

HRMS (ESI$^+$): Calc. for $C_{40}H_{50}O_9{}^{23}NaSi^+$ [M+Na]$^+$ 725.3116; found 725.3111 (Δ –0.74 ppm);

(3*R*,5*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((5-((2*R*)-4-chloro-2-hydroxy-2-methylhex-5-enoyl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-Methyl-2-methylenehept-6-enoic acid (317)



315 317

To a solution of acetal **315** (12.3 mg, 15.2 µmol, 1.0 eq) in 1,4-dioxane (0.70 mL, 20 mM) and H_2O (2.8 µL, 0.15 mmol, 10 eq) was added HCl (4 M in 1,4-dioxane, 76 µL, 3.0 mmol, 200 eq). After 4 days, the mixture was diluted with brine (0.50 mL) and H_2O (0.20 mL) and extracted with Et_2O (3 × 1.5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 100:0 to 80:20) to afford chloride **317** (6.6 mg, 61%) as a colourless film. Only a single set of ^1H and ^{13}C NMR signals were observed in $CDCl_3$ at 500 MHz and 126 MHz, respectively.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70–7.65 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.63–7.58 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.54 (s, 1H, *H*-5), 7.46–7.32 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.29 (s, 1H, *H*-12'a), 5.89 (s, 1H, *H*-12'b), 5.46 (dt, *J* = 16.9, 9.6 Hz, 1H, *H*-11), 5.14 (d, *J* = 16.9 Hz, 1H, *H*-11'a), 4.93 (d, *J* = 10.0 Hz, 1H, *H*-11'b), 4.67 (t, *J* = 5.7 Hz, 1H, *H*-13), 4.62 (td, *J* = 8.8, 5.1 Hz, 1H, *H*-10), 4.54 (s, 1H, *H*-16a), 4.36 (s, 1H, *H*-16b), 3.82 (s, 3H, CO_2CH_3), 2.98 (dd, *J* = 14.5, 10.0 Hz, 1H, *H*-2a), 2.88 (dd, *J* = 14.4, 5.4 Hz, 1H, *H*-2b), 2.75–2.59 (m, 2H, *H*-1, *H*-9a), 2.47 (dd, *J* = 14.5, 5.2 Hz, 1H, *H*-9b), 1.83 (ddd, *J* = 13.6, 7.5, 5.8 Hz, 1H, *H*-14a), 1.72 (dt, *J* = 14.3, 6.0 Hz, 1H, *H*-14b), 1.54 (s, 3H, 3 × *H*-17), 1.48 (s, 3H, 3 × *H*-19) and 1.07 ppm (s, 9H, $C(CH_3)_3^{TBDPS}$); OH and CO_2H not observed;

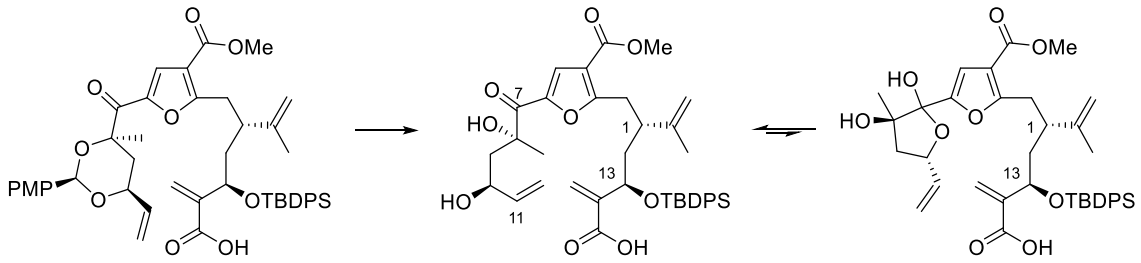
^{13}C NMR (126 MHz, $CDCl_3$) δ = 191.1 (*C*-7), 168.5 (*C*-20), 165.4 (*C*-3), 162.9 (*C*-18), 148.2 (*C*-6), 145.1 (*C*-15), 141.6 (*C*-12), 137.3 (*C*-11), 136.1 (2 × Ar*C*^{TBDPS}), 136.1 (2 × Ar*C*^{TBDPS}), 133.3 (Ar*C*^{TBDPS}), 133.0 (Ar*C*^{TBDPS}), 130.1 (Ar*C*^{TBDPS}), 130.1 (Ar*C*^{TBDPS}), 128.5 (*C*-12'), 127.9 (2 × Ar*C*^{TBDPS}), 127.8 (2 × Ar*C*^{TBDPS}), 121.3 (*C*-5), 118.7 (*C*-11'), 116.5 (*C*-4), 113.4 (*C*-16), 71.0 (*C*-13), 58.6 (*C*-10), 52.0 (CO_2CH_3), 47.3 (*C*-9), 42.4 (*C*-1), 41.2 (*C*-14), 32.1 (*C*-2), 27.8 (*C*-19), 27.2 ($C(CH_3)_3^{TBDPS}$), 19.4 ($C(CH_3)_3^{TBDPS}$) and 18.5 ppm (*C*-17); *C*-8 not observed, but HMBC data suggest overlap with solvent signal;

FT-IR ν_{max} (thin film): 3073, 2955, 2931, 2857, 1726, 1696, 1665, 1590, 1527, 1443, 1428, 1259, 1235, 1159, 1111, 1088, 1051, 1003, 969, 930, 907, 822, 782, 741 and 704 cm^{-1};

HRMS (ESI^+): Calc. for $C_{39}H_{46}O_8Si^{35}Cl^-$ $[M-H]^-$ 705.2656; found 705.2646 (Δ –1.35 ppm);

Specific Rotation: $[\alpha]_D^{25}$ –10.8 (c = 0.66, CH_2Cl_2).

(3*R*,5*R*)-3-((*tert*-b utyldiphenylsilyl)oxy)-5-((5-((2*R*,4*S*)-2,4-dihydroxy-2-methylhex-5-enoyl)-3-(methoxycarbonyl)furan-2-yl)methyl)-6-Methyl-2-methylenehept-6-enoic acid (318)



To a solution of acetal **315** (752 mg, 931 µmol, 1.0 eq) in PhMe (42 mL, 20 mM) was added silica gel (42 mL; PhMe:SiO_2 = 50:50) and AcOH (4.8 mL). Finally, H_2O (2.4 mL: PhMe:AcOH:H_2O = 85:10:5) was added dropwise. After maintained stirring for 4 days the mixture was filtered, rinsed with EtOAc (5 × 50 mL) and the combined filtrates concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, PhMe:EtOAc:HCO_2H = 98.5:1:0.5 to 79.5:20:0.5) to afford hydroxy ketone **318** (446 mg, 69%) as a white foam. In $CDCl_3$ a mixture of hydroxy ketone **318** and both epimeric forms of hemiacetal **319** were observed (**318**:**319**:*epi*-**319** = 68:16:16).

^{1}H NMR (ketone **318**, 500 MHz, $CDCl_3$) δ = 7.70–7.63 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.59–7.54 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.53 (s, 1H, *H*-5), 7.47–7.31 (m, 6H, 6 × Ar$\underline{H}^{TBDPS}$), 6.27–6.26 (m, 1H, *H*-12'a), 5.88 (s, 1H, *H*-12'b), 5.81 (ddd, *J* = 17.3, 10.5, 5.5 Hz, 1H, *H*-11), 5.20 (dt, *J* = 17.2, 1.4 Hz, 1H, *H*-11'a), 5.07 (dt, *J* = 10.5, 1.3 Hz, 1H, *H*-11'b), 4.69 (app. t, *J* = 5.0 Hz, 1H, *H*-13), 4.61 (d, *J* = 1.6 Hz, 1H, *H*-16a), 4.52 (br. s, 1H, *H*-10), 4.50 (br. s, 1H, *H*-16b), 3.81 (s, 3H, $CO_2C\underline{H}_3$), 2.94–2.83 (m, 2H, 2 × *H*-2), 2.64–2.55 (m, 1H, *H*-1), 2.26 (dd, *J* = 14.5, 10.2 Hz, 1H, *H*-14a), 2.08–2.00 (m, 1H, *H*-14b), 1.88–1.75 (m, 1H, *H*-9a), 1.72–1.64 (m, 1H, *H*-9b), 1.58 (s, 3H, 3 × *H*-17), 1.52 (s, 3H, 3 × *H*-19) and 1.06 ppm (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$); 2 × OH and CO_2H not observed;

^{13}C NMR (ketone **318**, 126 MHz, $CDCl_3$) δ = 192.2 (*C*-7), 167.4 (*C*-20), 165.3 (*C*-3), 163.0 (*C*-18), 147.8 (*C*-6), 146.4 (*C*-15), 140.1 (*C*-11), 136.1 (2 × Ar$\underline{C}^{TBDPS}$), 136.0 (2 × Ar$\underline{C}^{TBDPS}$), 133.5 (Ar$\underline{C}^{TBDPS}$), 133.1 (Ar$\underline{C}^{TBDPS}$), 130.1 (Ar$\underline{C}^{TBDPS}$), 130.0 (Ar$\underline{C}^{TBDPS}$), 127.9 (*C*-12'), 127.8 (2 × Ar$\underline{C}^{TBDPS}$), 127.8 (2 × Ar$\underline{C}^{TBDPS}$), 121.1 (*C*-5), 116.5 (*C*-4), 114.9 (*C*-11'), 112.6 (*C*-16), 80.4 (*C*-10), 71.6 (*C*-8), 71.4 (*C*-13), 69.2 (*C*-10), 51.9 ($CO_2\underline{C}H_3$), 46.5 (*C*-9), 41.8 (*C*-1), 38.9 (*C*-14), 32.8 (*C*-2), 27.2 ($C(\underline{C}H_3)_3^{TBDPS}$), 27.0 (*C*-19), 19.4 ($\underline{C}(CH_3)_3^{TBDPS}$) and 19.0 ppm (*C*-17);

^{1}H NMR (hemiacetal **319**, selected signals, 500 MHz, $CDCl_3$) δ = 6.73 (s, 1H, *H*-5), 6.28 (s, 1H, *H*-12'a), 5.30 (d, *J* = 7.7 Hz, 1H, *H*-11'a), 5.15 (d, *J* = 10.2 Hz, 1H, *H*-11'b), 4.87–4.82 (m, 1H, *H*-10), 4.63 (s, 1H, *H*-16a), 4.36 (s, 1H, *H*-16b), 3.77 (s, 1H, $CO_2C\underline{H}_3$), 2.76 (d, *J* = 7.2 Hz, 1H, 2 × *H*-2), 2.52–2.45 (m, 1H, *H*-1), 2.20–2.11 (m, 1H, *H*-14a), 1.61 (s, 1H, 3 × *H*-17), 1.41 (s, 1H, 3 × *H*-19) and 1.07 ppm (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$);

^{13}C NMR (hemiacetal **319**, selected signals, 126 MHz, $CDCl_3$) δ = 164.1 (*C*-18), 162.2 (*C*-3), 139.4 (*C*-11), 117.4 (*C*-11'), 114.6 (*C*-7), 110.9 (*C*-5), 51.5 ($CO_2\underline{C}H_3$), 44.8 (*C*-9), 42.3 (*C*-1), 37.8 (*C*-14), 33.0 (*C*-2) and 19.3 ppm (*C*-17);

^{1}H NMR (hemiacetal *epi*-**319**, selected signals, 500 MHz, $CDCl_3$) δ = 6.60 (s, 1H, *H*-5), 6.21 (s, 1H, *H*-12'a), 5.27 (d, *J* = 7.6 Hz, 1H, *H*-11'a), 4.82–4.77 (m, 1H, *H*-10), 3.76 (s, 1H, $CO_2C\underline{H}_3$), 2.69 (dd, *J* = 14.1, 8.6 Hz, 1H, *H*-2b), 2.44–2.38 (m, 1H, *H*-1) and 1.05 ppm (s, 1H, $C(C\underline{H}_3)_3^{TBDPS}$);

^{13}C NMR (hemiacetal *epi*-**319**, selected signals, 126 MHz, $CDCl_3$) δ = 161.5 (*C*-3), 137.7 (*C*-11), 116.8 (*C*-11'), 115.5 (*C*-7), 109.4 (*C*-5), 51.5 ($CO_2\underline{C}H_3$), 44.1 (*C*-9), 41.9 (*C*-1), 31.2 (*C*-2) and 18.7 ppm (*C*-17);

FT-IR ν_{max} (thin film): 2981, 2955, 2929, 2855, 1722, 1701, 1626, 1472, 1443, 1428, 1392, 1378, 1261, 1221, 1163, 1112, 1089, 898, 821, 766, 740, 704 and 620 cm^{-1};

HRMS (ESI^+): Calc. for $C_{39}H_{48}O_9{}^{23}NaSi^+$ $[M+Na]^+$ 711.2960; found 711.2957 (Δ –0.35 ppm);

Methyl (3*R*,5*S*,9*R*,11*R*)-9-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-3-methyl-8-methylene-2,7-dioxo-11-(prop-1-en-2-yl)-5-vinyl-6-oxa-1(2,5)-furanacyclododecaphane-1^4-carboxylate (320)

318 **320**

Note: A glass syringe and pressure just above atmospheric pressure in the apparatus were required to ensure even and consistent addition of starting material to the reaction mixture *via* syringe pump.

A solution of MNBA (259 mg, 752 µmol, 1.2 eq) and DMAP (183 mg, 1.50 mmol, 2.4 eq) in CH_2Cl_2 (0.62 L, 1.0 mM) was stirred (600 rpm) at rt. To this a solution of hydroxy acid **318** (425mg, 617 µmol, 1.0 eq) in CH_2Cl_2 (10 mL) was added over the course of 16 h *via* syringe pump (0.7 mL/h). After completed addition, the syringe was rinsed with CH_2Cl_2 (3.0 mL) and the resulting solution added to the reaction mixture over the course of 1 h and the mixture was stirred for an additional 4 h. After which, the reaction mixture was concentrated *in vacuo* to approximately 50 mL, diluted with Et_2O (100 mL), washed with $NaHCO_3$ (sat., aq., 30 mL), KHSO4 (1 M, aq., 30 mL), brine (30 mL) dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, pentane:CH_2Cl_2:MeCN = 45:45:10) to afford macrolactone **320** (171 mg, 41%) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61–7.58 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.51–7.47 (m, 2H, 2 × Ar$\underline{H}^{TBDPS}$), 7.45–7.27 (m, 7H, 6 × Ar$\underline{H}^{TBDPS}$, *H*-5), 6.26 (s, 1H, *H*-12'a), 5.79 (s, 1H, *H*-12'b), 5.58 (ddd, *J* = 16.9, 10.5, 5.8 Hz, 1H, *H*-11), 5.24–5.19 (m, 1H, *H*-10), 4.98–4.89 (m, 2H, 2 × *H*-11'), 4.80 (s, 1H, *H*-16a), 4.77 (s, 1H, *H*-16b), 4.53 (s, 1H, *OH*-8), 4.29 (d,

J = 7.3 Hz, 1H, *H*-13), 3.82 (s, 3H, $CO_2C\underline{H}_3$), 3.00–2.93 (m, 2H, 2 × *H*-2), 2.71–2.59 (m, 2H, *H*-1, *H*-9a), 2.17 (dd, *J* = 15.3, 2.9 Hz, 1H, *H*-9b), 1.99 (ddd, *J* = 13.7, 7.6, 5.1 Hz, 1H, *H*-14a), 1.70 (s, 4H, *H*-14b, 3 × *H*-17), 1.56 (s, 3H, 3 × *H*-19) and 0.97 ppm (s, 9H, $C(C\underline{H}_3)_3^{TBDPS}$);

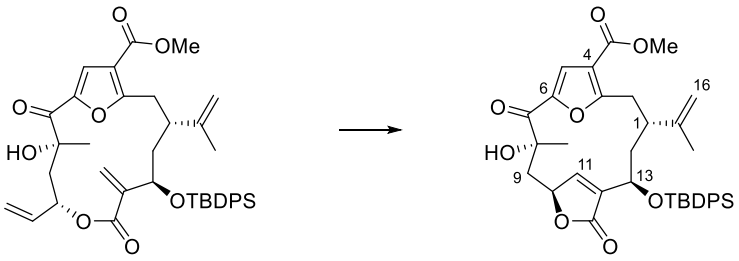
^{13}C NMR (126 MHz, $CDCl_3$) δ = 191.3 (*C*-7), 165.5 (*C*-3), 164.4 (*C*-20), 162.8 (*C*-18), 148.8 (*C*-15), 147.2 (*C*-6), 140.6 (*C*-12), 136.3 (*C*-11), 136.1 ($2 \times Ar\underline{C}^{TBDPS}$), 135.8 ($2 \times Ar\underline{C}^{TBDPS}$), 134.1 ($Ar\underline{C}^{TBDPS}$), 133.8 ($Ar\underline{C}^{TBDPS}$), 129.8 ($Ar\underline{C}^{TBDPS}$), 129.7 ($Ar\underline{C}^{TBDPS}$), 127.9 (*C*-12'), 127.6 ($4 \times Ar\underline{C}^{TBDPS}$), 120.9 (*C*-5), 116.5 (*C*-4), 116.2 (*C*-11'), 111.3 (*C*-16), 76.3 (*C*-8), 72.0 (*C*-10), 69.8 (*C*-13), 52.0 ($CO_2C\underline{H}_3$), 46.0 (*C*-9), 40.4 (*C*-1), 37.6 (*C*-14), 34.1 (*C*-2), 27.5 (*C*-19), 27.1 ($C(\underline{C}H_3)_3^{TBDPS}$), 19.8 (*C*-17) and 19.3 ppm ($\underline{C}(CH_3)_3^{TBDPS}$);

FT-IR ν_{max} (thin film): 2953, 2857, 1724, 1664, 1591, 1527, 1472, 1444, 1428, 1377, 1269, 1237, 1158, 1111, 1088, 1005, 986, 958, 923, 822, 788, 741, 703 and 611 cm^{-1};

HRMS (ESI^+): Calc. for $C_{39}H_{46}O_8{}^{23}NaSi^+$ $[M+Na]^+$ 693.2854; found 693.2851 (Δ –0.46 ppm);

Specific Rotation: $[\alpha]_D^{25}$ 19.2 (c = 2.09, CH_2Cl_2).

Methyl (1^2*S*,3*R*,7*R*,9*R*,*Z*)-9-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-3-methyl-1^5,4-dioxo-7-(prop-1-en-2-yl)-1^2,1^5-dihydro-1(2,4),5(2,5)-difuranacyclononaphane-5^4-carboxylate (321)



320 **321**

A solution of enone **320** (21.0 mg, 31.3 µmol, 1.0 eq) in DCE (4.0 mL, 10 mM) in a Schlenk tube was degassed with a stream of Ar until the solvent level was reduced 3.0 mL (20 min). Olefin metathesis catalyst HG II (3.6 mg, 5.8 µmol, 18 mol%) was added and the mixture heated to 60 °C. After 16 h, the mixture was heated to 90 °C and sealed. After an additional 24 h, the reaction mixture was cooled to rt, diluted with DCE (1.0 mL) and

olefin metathesis catalyst HG II (3.4 mg, 5.4 µmol, 17 mol%) was added. The mixture was degassed, heated to 90 °C and sealed. After 19 h, the reaction was cooled to rt and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 99:1 to 95:5) to afford butenolide **321** (10.6 mg, 53%) as a pale syrup.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.62–7.56 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.55–7.50 (m, 2H, 2 × Ar*H*^{TBDPS}), 7.47–7.43 (m, 2H, Ar*H*^{TBDPS}, *H*-5), 7.42–7.35 (m, 3H, 3 × Ar*H*^{TBDPS}), 7.34–7.28 (m, 2H, 2 × Ar*H*^{TBDPS}), 6.09–5.98 (m, 1H, *H*-11), 4.78 (br. s, 1H, *H*-16a), 4.69–4.57 (m, 2H, *H*-10, *H*-16b), 4.34 (dd, *J* = 10.5, 4.0 Hz, 1H, *H*-13), 3.83 (s, 3H, CO_2CH_3), 3.33 (s, 1H, *OH*-8), 3.10 (dd, *J* = 15.4, 4.9 Hz, 1H, *H*-2a), 2.88 (dd, *J* = 15.4, 9.0 Hz, 1H, *H*-2b), 2.75–2.60 (m, 2H, *H*-1, *H*-14a), 2.48 (dd, *J* = 15.3, 6.1 Hz, 1H, *H*-9a), 2.26 (dd, *J* = 15.3, 6.8 Hz, 1H, *H*-9b), 1.94 (ddd, *J* = 14.2, 9.7, 4.1 Hz, 1H, *H*-14b), 1.82 (s, 3H, 3 × *H*-17), 1.37 (s, 3H, 3 × *H*-19) and 0.98 ppm (s, 9H, C(CH_3)$_3^{TBDPS}$);

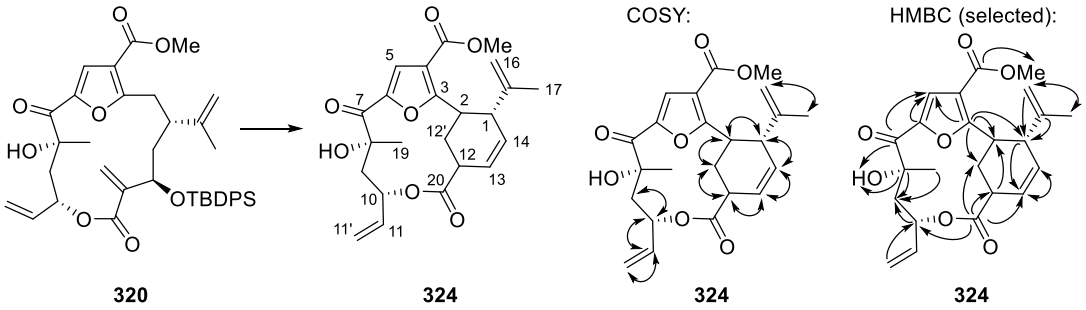
^{13}C NMR (126 MHz, $CDCl_3$) δ = 191.6 (*C*-7), 169.9 (*C*-20), 164.4 (*C*-3), 162.6 (*C*-18), 151.1 (*C*-11), 148.0 (*C*-6), 147.3 (*C*-15), 135.8 (2 × Ar*H*^{TBDPS}), 135.7 (2 × Ar*H*^{TBDPS}), 133.8 (*C*-12), 133.6 (Ar*H*^{TBDPS}), 133.1 (Ar*H*^{TBDPS}), 129.9 (Ar*H*^{TBDPS}), 129.8 (Ar*H*^{TBDPS}), 127.8 (2 × Ar*H*^{TBDPS}), 127.6 (2 × Ar*H*^{TBDPS}), 121.3 (*C*-5), 116.3 (*C*-4), 110.9 (*C*-16), 78.0 (*C*-8), 77.2 (*C*-10), 66.6 (*C*-13), 51.8 (CO_2CH_3), 42.4 (*C*-9), 41.4 (*C*-1), 38.0 (*C*-14), 31.1 (*C*-2), 28.2 (*C*-19), 26.7 (C(CH_3)$_3^{TBDPS}$), 21.0 (*C*-17) and 19.2 ppm ($C(CH_3)_3^{TBDPS}$); HMBC and NOESY interaction between *H*-11/*C*-11 and *H*-13/*C*-13;

FT-IR ν_{max} (thin film): 3072, 2980, 2931, 2891, 2858, 1761, 1725, 1661, 1587, 1510, 1472, 1442, 1428, 1378, 1332, 1238, 1165, 1111, 1074, 1058, 1009, 953, 918, 822 and 779 cm^{-1};

HRMS (ESI$^+$): Calc. for $C_{37}H_{42}O_8Si^{23}Na^+$ $[M+Na]^+$ 655.2541; found 665.2539 (Δ –0.32 ppm);

Specific Rotation: $[\alpha]_D^{25}$ +78.2 (c = 1.00, CH_2Cl_2).

Methyl (2^6*R*,5*S*,7*R*)-7-hydroxy-7-methyl-3,8-dioxo-2^6-(prop-1-en-2-yl)-5-vinyl-4-oxa-1(2,5)-furana-2(1,3)-cyclohexanacyclooctaphan-2^4-ene-1^3-carboxylate (324)



320 **324** **324** **324**

To a solution of enone **320** (8.0 mg, 12 µmol, 1.0 eq) in DMF (1.0 mL, 10 mM) was added TASF (3.9 mg, 1.2 eq) in DMF (0.20 mL; stock solution: 7.5 mg in 0.38 mL) at 0 °C. The cooling bath was removed after addition. After 16 h, TASF (2.0 mg, 0.6 eq) in DMF (0.10 mL; stock solution: vide supra) was added at 0 °C and the reaction was allowed to warm to rt. After an additional 3 h, the mixture was diluted with EtOAc (2.0 mL), washed with $KHSO_4$ (1 M, 1 mL) and brine (0.5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by preparative TLC (SiO_2 on aluminium, pentane:CH_2Cl_2:MeCN = 45:45:10) to afford cyclohexene **324** (2.1 mg, 42%) as a transparent film and a mixture of diastereomers (73:27 dr determined by ^{13}C NMR peak height *C*-14).

^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ = 7.62 (s, 1H, *H*-5), 6.29–6.21 (m, 1H, *H*-14), 6.11–6.04 (m, 1H, *H*-13), 5.70 (ddd, *J* = 17.3, 10.5, 5.8 Hz, 1H, *H*-11), 5.18 (app. dt, *J* = 17.2, 1.2 Hz, 1H, *H*-11'a), 5.14 (app. dt, *J* = 10.5, 1.1 Hz, 1H, *H*-11'b), 4.99–4.89 (m, 1H, *H*-10), 4.69 (app. dd, *J* = 6.2, 3.3 Hz, 1H, *H*-2), 4.67 (br. s, 1H, *H*-16a), 4.64 (app. t, *J* = 1.6 Hz, 1H, *H*-16b), 4.07 (app. d, *J* = 0.9 Hz, 1H, *OH*-8), 3.85 (s, 3H, $CO_2C\underline{H}_3$), 3.24–3.16 (m, 2H, *H*-1, *H*-12), 2.79–2.70 (m, 1H, *H*-12'a), 2.36 (dd, *J* = 14.7, 12.3 Hz, 1H, *H*-9a), 2.30 (ddd, *J* = 13.9, 7.5, 4.5 Hz, 1H, *H*-12'b), 1.94 (dd, *J* = 14.8, 2.8 Hz, 1H, *H*-9b), 1.90 (s, 3H, 3 × *H*-19) and 1.68 ppm (s, 3H, 3 × *H*-17);

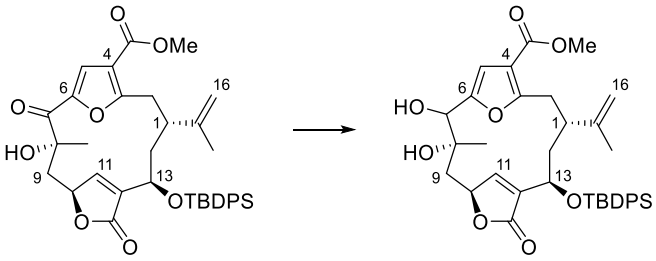
^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ = 192.8 (*C*-7), 173.0 (*C*-20), 166.9 (*C*-3), 163.1 (*C*-18), 149.3 (*C*-6), 144.7 (*C*-15), 136.1 (*C*-11), 130.7 (*C*-13), 125.1 (*C*-14), 122.1 (*C*-5), 117.2 (*C*-4, *C*-11'), 111.8 (*C*-16), 72.5 (*C*-10), 52.0 ($CO_2\underline{C}H_3$), 48.4 (*C*-9), 44.8 (*C*-1), 38.0 (*C*-12), 32.4 (*C*-2), 30.2 (*C*-12'), 25.0 (*C*-19) and 22.4 ppm (*C*-17); *C*-8 not observed, but HMBC data suggests overlap with solvent signal;

^{13}C NMR (minor diastereomer, selected signals, 126 MHz, $CDCl_3$) δ = 130.7 (*C*-13), 125.0 (*C*-14), 32.4 (*C*-2) and 30.1 ppm (*C*-12');

FT-IR ν_{max} (thin film): 2980, 2889, 1382, 1242, 1151, 1075, 954, 904, 724 and 650 cm^{-1};

HRMS (ESI^+): Calc. for $C_{23}H_{26}O_7{}^{23}Na^+$ $[M+Na]^+$ 437.1571; found 437.1659.

Methyl (1^2*S*,3*R*,7*R*,9*R*,*Z*)-9-((*tert*-butyldiphenylsilyl)oxy)-3,4-dihydroxy-3-methyl-1^5-oxo-7-(prop-1-en-2-yl)-1^2,1^5-dihydro-1(2,4),5(2,5)-difuranacyclononaphane-5^4-carboxylate (327)



321 **327**

Note: The stock solution of $NaBH_4$ in MeOH was prepared just before it was used.

To a solution of ketone **321** (11.4 mg, 17.7 µmol, 1.0 eq) in MeOH (1.5 mL, 10 mM) was cooled to 0 °C and $NaBH_4$ (1.3 mg, 2.0 eq) in MeOH (0.26 mL; stock solution: 18.3 mg in 3.55 mL) was added. After 1.5 h, the reaction was diluted with NH_4Cl (sat., aq., 1.0 mL) and H_2O (1.0 mL). The mixture was extracted with EtOAc (3 × 4.0 mL), the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (SiO_2, CH_2Cl_2:acetone = 95:5 to 70:30) to afford alcohol **327** (7.3 mg, 64%, 85:15 dr determined at *H*-5) as a pale film syrup.

^{1}H NMR (major diastereomer, 500 MHz, C_6D_6) δ = 7.75–7.62 (m, 4H, 4 × Ar*H*^{TBDPS}), 7.13–7.05 (m, 6H, 6 × Ar*H*^{TBDPS}), 6.46 (s, 1H, *H*-5), 4.84 (br. s, 1H, *H*-16a), 4.74 (app. t, *J* = 1.4 Hz, 1H, *H*-16b), 4.70 (dd, *J* = 11.4, 5.5 Hz, 1H, *H*-13), 4.40 (d, *J* = 1.5 Hz, 1H, *H*-11), 4.00 (ddd, *J* = 11.5, 6.1, 1.5 Hz, 1H, *H*-10), 3.88 (d, *J* = 2.4 Hz, 1H, *H*-7), 3.67 (dd, *J* = 15.0, 10.6 Hz, 1H, *H*-2a), 3.34 (s, 3H, CO_2CH_3), 3.32–3.25 (m, 1H, *H*-14a), 2.66 (bd, *J* = 15.0 Hz, 1H, *H*-2b), 2.44–2.34 (m, 1H, *H*-1), 2.32–2.21 (m, 2H, *H*-9a, *H*-14b), 1.75 (app. t, *J* = 1.1 Hz, 3H, 3 × *H*-17), 1.58 (d, *J* = 2.7 Hz, 1H, *OH*-7), 1.47 (dd, *J* = 14.6, 11.5 Hz, 1H, *H*-9b), 1.19 (s, 9H, $C(CH_3)_3^{TBDPS}$) and 0.80 ppm (s, 3H, 3 × *H*-19); OH not observed;

^{13}C NMR (major diastereomer, 126 MHz, C_6D_6) δ = 169.6 (*C*-20), 163.5 (*C*-18), 160.6 (*C*-3), 152.5 (*C*-6), 151.6 (*C*-11), 149.8 (*C*-15), 136.3 (2 × Ar*C*^{TBDPS}), 136.2 (2 × Ar*C*^{TBDPS}), 134.5 (Ar*C*^{TBDPS}), 134.5 (Ar*C*^{TBDPS}), 132.1 (*C*-12), 130.1 (Ar*C*^{TBDPS}), 129.9 (Ar*C*^{TBDPS}), 128.6 (4 × Ar*C*^{TBDPS}), 115.4 (*C*-4), 110.0 (*C*-16), 108.6 (*C*-5), 76.9 (*C*-10), 76.2 (*C*-7), 73.1 (*C*-8), 67.7 (*C*-13), 51.1 (CO_2CH_3), 43.0 (*C*-9), 42.4 (*C*-1), 41.7 (*C*-14), 32.6 (*C*-2), 27.2 ($C(CH_3)_3^{TBDPS}$), 21.3 (*C*-17), 19.5 ($C(CH_3)_3^{TBDPS}$) and 17.7 ppm (*C*-19);

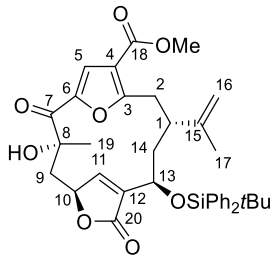
^{1}H NMR (minor diastereomer, selected signals, 500 MHz, C_6D_6) δ = 6.49 (s, 1H, 5-H), 3.36 (s, 3H, CO_2CH_3), 3.11 (m, 1H, *H*-14a) and 1.22 ppm (s, 9H, $C(CH_3)_3^{TBDPS}$)

^{13}C NMR (minor diastereomer, selected signals, 126 MHz, C_6D_6) δ = 136.6 (*C*-18), 161.6 (*C*-3), 152.5 (*C*-6), 151.6 (*C*-11), 134.7 (Ar*C*^{TBDPS}), 132.4 (*C*-12), 68.1 (*C*-13), 51.0 (CO_2CH_3), 43.1 (*C*-9) and 27.2 ppm ($C(CH_3)_3^{TBDPS}$);

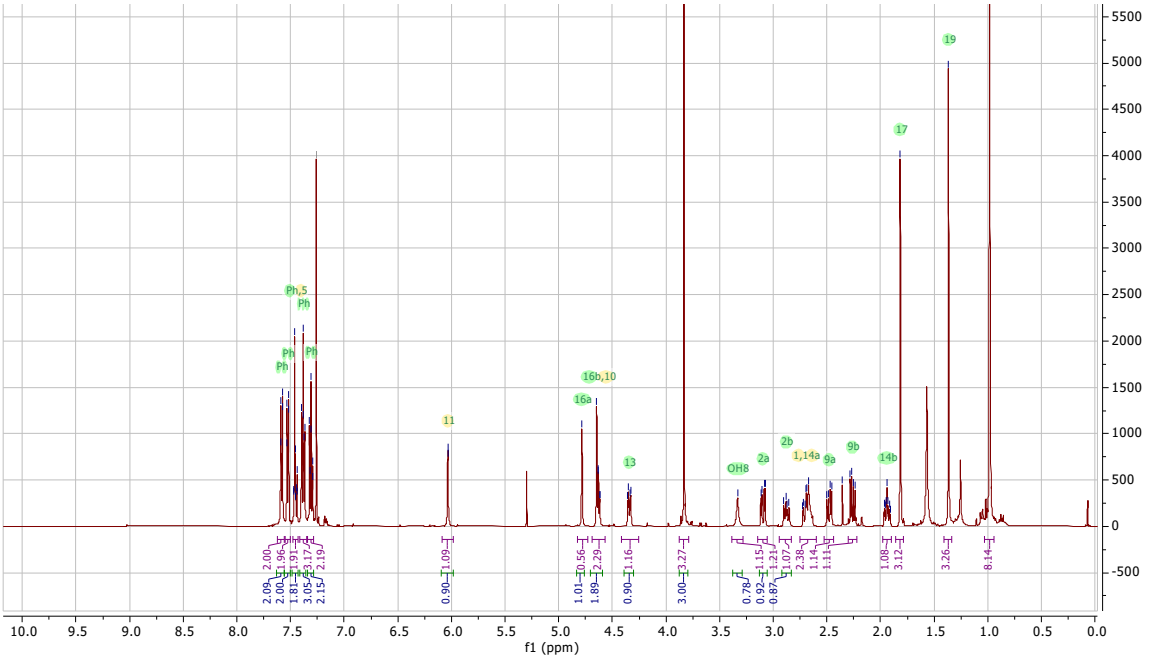
FT-IR ν_{max} (thin film): 2980, 2280, 1768, 1743, 1719, 1618, 1452, 1428, 1391, 1330, 1261, 1223, 1193, 1163, 1111, 1059, 978, 966, 951, 919, 892, 812, 779, 742, 691 and 613 cm^{-1};

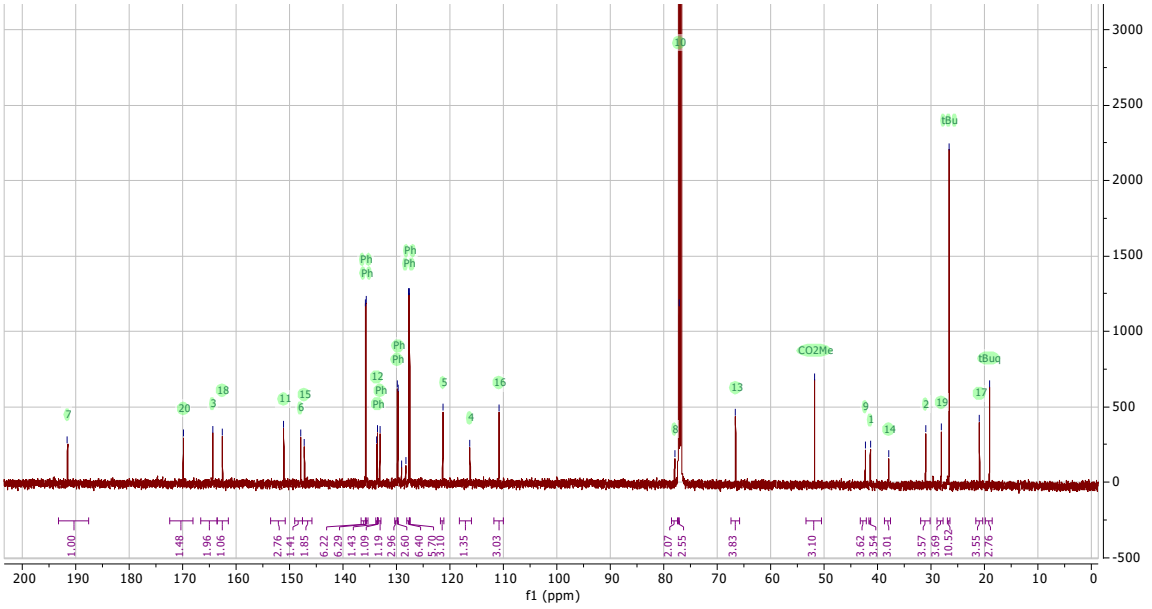
HRMS (ESI$^+$): Calc. for $C_{37}H_{44}O_8Si^{23}Na^+$ $[M+Na]^+$ 667.2698; found 667.2693 (Δ –0.63 ppm).

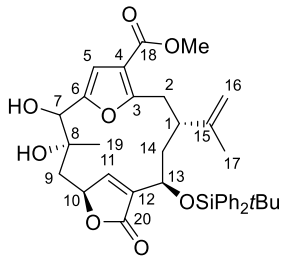
6.2 Selected NMR spectra



321

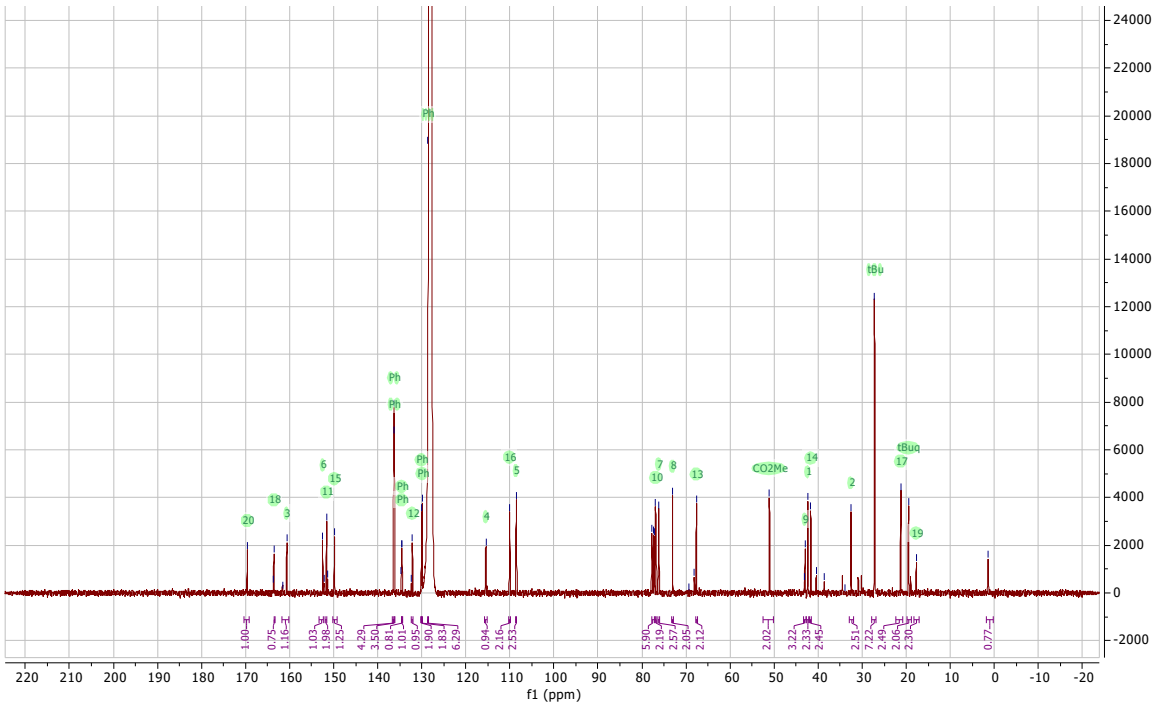





O
OMe
5
4
18
6
2
16
HO
7
O
3
1
15
8
19
14
HO
11
17
9
13
10
12
OSiPh2tBu
O
20
O

327


Ph
5
Ph
16b
16a
11
13
7
10
2a
14a
2b
14b,9a
1
OH-7
9b
17
f1 (ppm)


Ph
Ph
Ph
Ph
Ph
Ph
tBu
tBuq
CO2Me
6
15
11
18
3
20
12
4
16
5
7
10
8
13
14
1
2
9
17
19
f1 (ppm)

Chapter 7

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7 References

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