Towards the total synthesis of dolabelide C using metathesis reactions

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Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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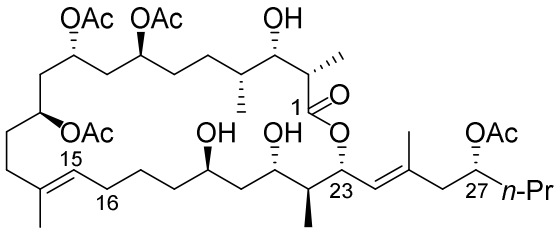
September 2019

«Μέτρον ἄριστον» - Κλεοβουλος (6ος αιωνας π.Χ.)

Contents

Abstract

Dolabelide C is a 24-membered macrolide isolated from the Japanese sea hare *Dolabella auricularia* that exhibits cytotoxicity against cervical cancer HeLa-S3 cells with an IC_{50} values of 1.9 µg/mL. Its complex molecular structure, which encompasses eight hydroxylated and three methylated stereogenic centers as well as two *E*-trisubstituted alkenes, makes it a synthetically challenging target. The synthesis of dolabelide C as well as the rest of the molecules of the dolabelide family have therefore been studied by several groups.



Dolabelide C

Herein, published synthetic efforts towards the construction of dolabelides found in the literature, as well as the use of silicon-tether ring closing metathesis in natural product synthesis, are described in the first chapter. A summary of the previous work carried out in the Prunet group is also discussed.

Our envisioned retrosynthesis involves disconnecting dolabelide C at the C1 lactone and at the C15-C16 bond. The second chapter of this thesis gives a detailed account of the investigation that took place while finding a reliable and high yielding route to prepare the protected C16-C30 fragment enantioselectivity using a silicon-tether ring closing metathesis strategy.

Synthetic endeavours to construct the C1-C15 fragment using cross metathesis as the key step between an enone and a few different homoallylic alcohol partners took place. Although we found a successful route to prepare a key advanced alkyne intermediate, the final step of the synthesis that involved transforming the alkyne into a vinyl iodide employing a Negishi carboalumination was unsuccessful. Installation of the required vinyl iodide moiety earlier during the synthesis was also attempted with no luck.

Finally, the silicon-tether ring closing metathesis sequence originally developed in the group to prepare *E*-trisubstituted alkenes selectively was successfully extended to the construction of *Z*-trisubstituted olefins starting from vinyldimetheylchlorosilane and an allylic alcohol.

Authors declaration

I declare that, except where explicit reference is made to the contribution of others, the substance of this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

A portion of the work described herein has been published elsewhere as listed below. “Novel Synthesis of Trisubstituted Olefins for the Preparation of the C16-C30 Fragment of Dolabelide C” Tiniakos, A. F.; Wittmann, S.; Audic, A.; Prunet, J. *Org. Lett.* **2019**, *21*, 589.

Acknowledgements

I would like to express my sincere gratitude to my supervisor Dr Joëlle Prunet for her continuous help, support and guidance for the past 4 years. I would also like to thank my second supervisor Dr Andrew Sutherland as well as Dr David France and Professor Richard Hartley for their advice and inspiration.

I would also like to thank some support staff members of the Chemistry department who have been most helpful and without them this work would have not been possible: Andrew Monaghan, James Tweedy, Ted Easdon, Finlay Smith, K. McLachlan, James Mciver for special ops lab, Frank McGeoch, Deborah Cleary and Ross Slavin for accommodating us in the Cullen teaching lab and for their support and help during undergraduate teaching labs.

I will be forever grateful to Alexandre Audic for always been patient and always in a pleasant mood while teaching and explaining everything I needed to know when I first arrived. I am also most grateful be to my dearest and fondest friend and unique person, lab partner, flat mate Andrea Carolina Ojeda Porras for her unlimited help, positive and cheerful attitude, I learned many things from you but not enough Spanish.

I couldn't have imagined meeting and spending the past four years with such a good bunch of people in the Chemistry department. I would like to specially thank the 'smoking group' that we started off together and have shared some of the best and worst moments these past years: Albane Neckebroeck, Laura Pala, Stephan Warrington, Sean O' Byrne, Smiley Jim (Skardon-Duncan), Isabel Abánades, Michele Cariello and Ezequiel Silva. I would also like to thank Stephene Morrison, Liam Adair, Johnny Bell, Jake McGuire, John Marquez, Davide Cappelluti, Ana Mari, Sarah Memarzadeh, Claire McMaster, Mike P, Stuart Caldwell, Angus Campbell Martyn Henry, Mike Shipman, Mo, Skye Brettell for being the best and most helpful student I ever supervised, Claire Armstrong and Liliana Marcela.

I would like to take the opportunity to also acknowledge a few friends from Glasgow: Dimitris Sympouras, Panagiotis Nomikos, Aggelos Alexopopilsos, Ira Bitsola, Giannis Psyhas, Argiris Kermenlis (Korinthios), Aimilia Nteka, Anastasia, (E)Stefania, Sal Bennette as well as the rest of the Bennette-Morrison family.; Λέλα Τσάκαλη και Δρ. Αργυρώ Βίγγου

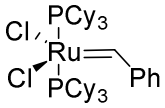
Big thanks to my family: John & Jay Rendall, Αργυρώ Ζαγοραίου, Αναστασία Σταματης Τηνιακος, Kate Rendall. Επισης ευχαριστώ στους Sergiu Podgoret, Θανάσης Φλόκα (Μαρούλιακας), Brian Βελέτζα, Ντινο Μπακουνάκη, Γιώργο Νεόφυτο (Χρεοοο), Θοδωρή Μουτουλα, Ορέστη Καρδαρα που είναι αδέλφια, πάντα δίπλα μου οπου και αν βρησκόμαστε. Ευχαριστώ επίσης σε ολους τους υπόλοιπους ομοϊδεάτες και αλόσκινους φιλους μου που παραθερίζουνε αλλα παντα το κρατάνε αληθηνό.

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
ADmix	Asymmetric dihydroxylation mixture
b.r.s.m.	Based recovery starting material
BINAP	2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl
BOM	Benzyloxymethyl
Bu	Butyl
Bz	Benzoyl
c-hex	Cyclohexyl
CM	Cross metathesis
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
d.r.	Diastereomeric ratio
DBB	4 4'-di-*tert*-butylbiphenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMPU	*N,N′*-Dimethylpropyleneurea
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
e.e	Enantiomeric excess
Et	Ethyl
HKR	Hydrolytic kinetic resolution
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
Im	Imidazole
Ipc	Isopinocampheyl
LDA	Lithium diisopropylamide
Me	Methyl

MEK	Methyl ethyl ketone
Mes	Mesityl
MOM	Methoxymethyl
MOP	Methoxypropyl
MS	Molecular sieves
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
PMB	*p*-Methoxybenzyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
py	Pyridine
quant	Quantitative
R	Generalised group
RCM	Ring-closing metathesis
t	*tert*
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

Table of metathesis catalysts



G-I
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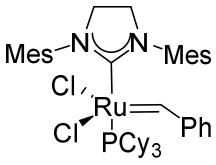
Grubbs' catalyst



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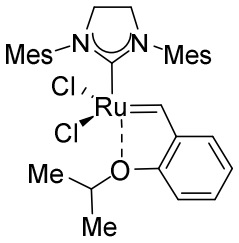

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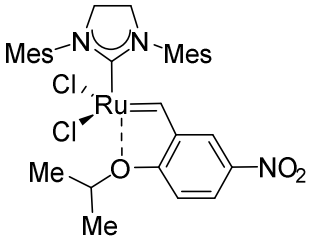

nitro-Grela
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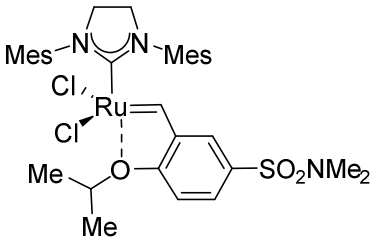

Zhan-1B
modified 2nd generation
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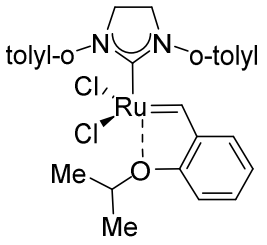

G-II-*o*-tol
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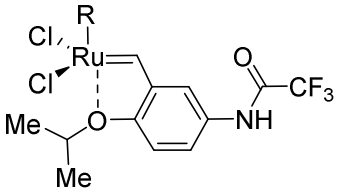
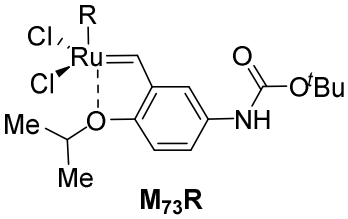


$M_{71}R$
modified 2nd generation
Hoveyda-Grubbs' catalyst



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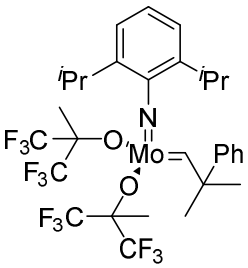
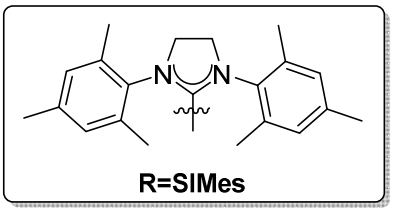
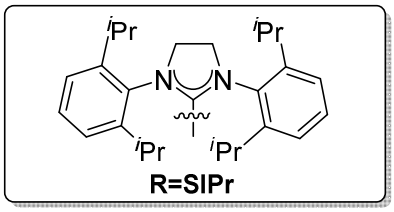


Mo-I
Shrock's catalyst



R=SIMes



R=SIPr

Chapter 1: Introduction

1.1 Presentation of dolabelides

It is well known that natural products are the basis for a large number of the modern medicines used and treatments for diseases.[1] During the mid-1990s, a family of unique peptides and macrolides known as dolastatins and dolabelides were isolated from the sea hare *Dolabella auricularia* (Figure 1.1) in the Western Indian Ocean. Dolabelides A and B (Figure 1.2) are 22-membered macrolides and were the first of the dolabelide family to be isolated and characterised in 1995 by Yamada *et al*.[2] Two years later, from the same sea hare, Yamada *et al.* isolated and characterised two novel 24-membered macrolides, dolabelides C and D.[3]

Figure 1.1: *Dolabella auricularia*[4]

Dolabelides exhibited cytotoxicity against cervical cancer HeLa-S_3 cells with IC_{50} values of 6.3, 1.3, 1.9 and 1.5 μg/mL for dolabelides A, B, C and D respectively. However, 138 kg (wet weight) of *Dolabella auricularia* was required to isolate just 99 mg of dolabelide C.[3] Thus the total synthesis of these complex macrolides has been of great interest and pursued by several groups in the last 20 years.

[1] Lahlou, M. *Pharmacology & Pharmacy*, **2013**, *4*, 17.
[2] Ojika, M.; Nagoya, T.; Yamada K. *Tetrahedron Lett.* **1995**, *36*, 7491.
[3] Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155.
[4] http://www.medslugs.de/E/Ind-SW/Dolabella_auricularia/Dolabella_auricularia_15.htm, accessed 03/01/19.

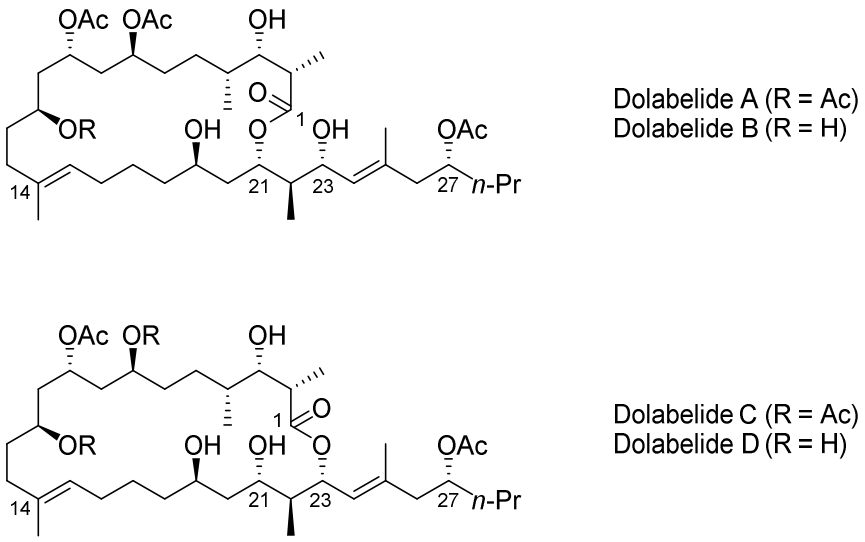


Figure 1.2: Structures of dolabelides A, B, C and D

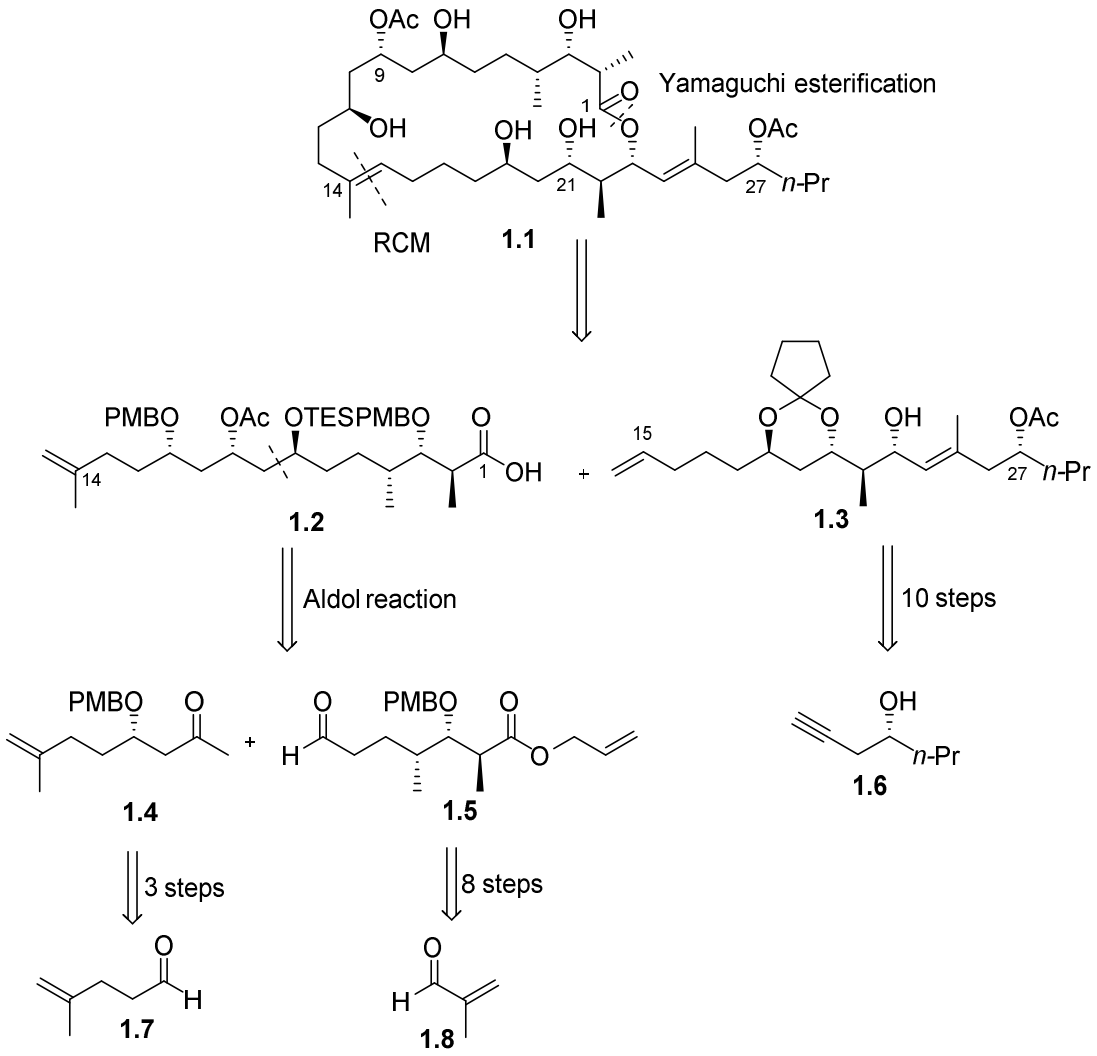
The molecular structure of dolebelides encompasses 11 stereogenic centers, 2 *E*-configured trisubstituted olefins and a 22- (Dolabelides A and B) or 24- (Dolabelides C and D) membered lactone.

1.2 Syntheses of dolabelides

1.2.1 Total synthesis of dolabelide D by *Leighton et al*

In 2006 Leighton *et al.* reported the total synthesis of dolabelide D **1.1**, the first of the dolabelide family to be synthesised.[5] The key steps were the coupling of two fragments **1.2** and **1.3** using a Yamaguchi esterification and the subsequent macrocyclization utilising ring-closing metathesis as shown in Scheme 1.1. The C1-C14 segment **1.2** could be prepared by an aldol reaction between aldehyde **1.4** and ketone **1.5** which in turn would be synthesised from aldehydes **1.7** and **1.8** respectively. Allylic alcohol **1.3** could be prepared from alkyne **1.6**.

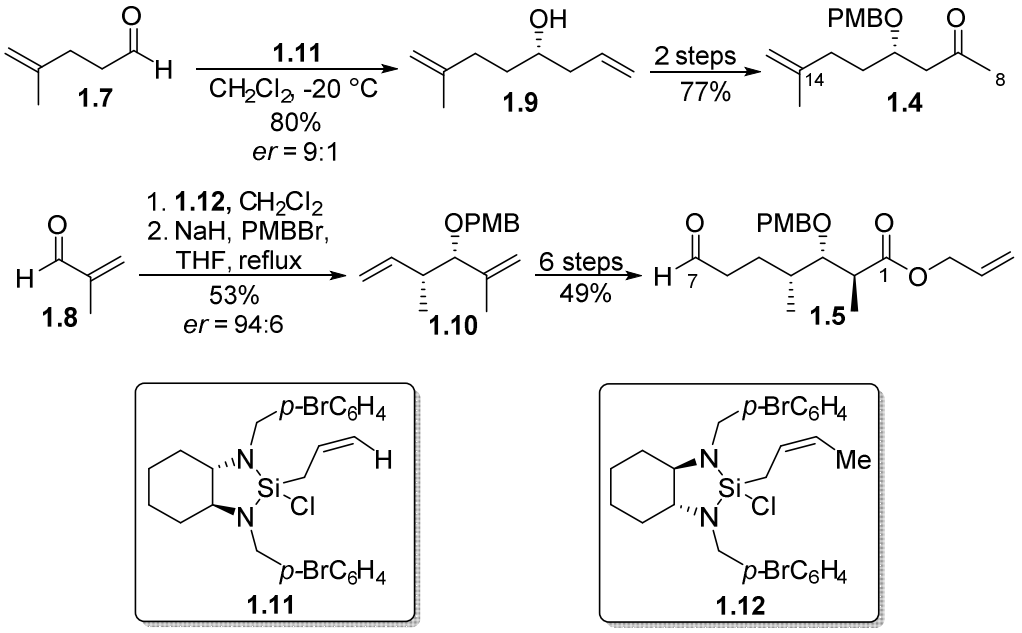
[5] Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796.



Scheme 1.1: Leighton's retrosynthesis of dolabelide D

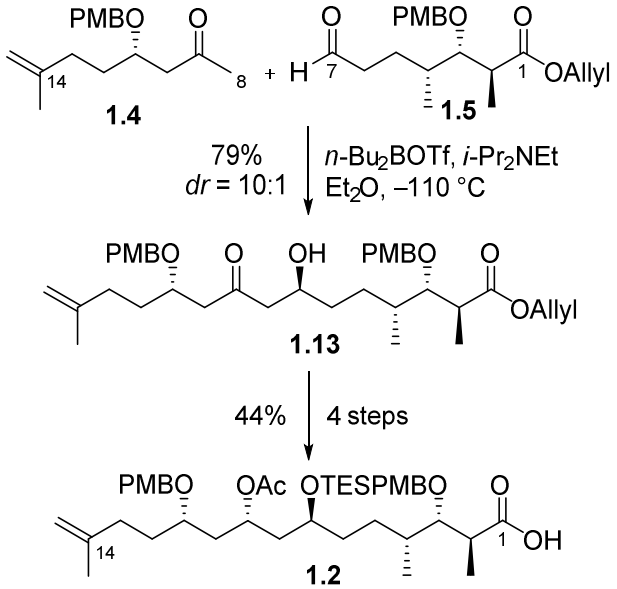
The synthesis of the C1-C14 fragment commenced from aldehydes **1.7** and **1.8** that were subjected to allylation and crotylation reactions using reagents **1.10**[6] and **1.12**[7] respectively, which had been developed in the Leighton group (Scheme 1.2). After two extra steps, ketone **1.4** was obtained in 77% yield from alcohol **1.9**. Transformation of diene **1.10** in to aldehyde **1.5** was achieved over 6 steps in 49% yield.

[6] Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946.
[7] Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375.



Scheme 1.2: Synthesis of coupling intermediates **1.4** and **1.5**

Coupling of the two fragments was achieved with a 1,5-*anti* selective aldol reaction giving **1.13** as a 10:1 mixture of diastereomers favouring the correct configuration. The synthesis of the C1-C14 fragment **1.2** was completed by a further 4 steps in 44% yield (Scheme 1.3).



Scheme 1.3: Completion of the synthesis of the C1-C14 fragment **1.2**.

The synthesis of the C15-C30 fragment (Scheme 1.4) commenced from enantiopure alcohol **1.6** and *tert*-butyl-*cis*-crotylsilane **1.14** that were coupled in 95% yield and in 4:1 diastereomeric ratio using a catalytic asymmetric silane alcoholysis,[8] that has been developed in the Leighton group. Stereospecific rhodium-catalysed tandem silylformylation-

[8] Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190.

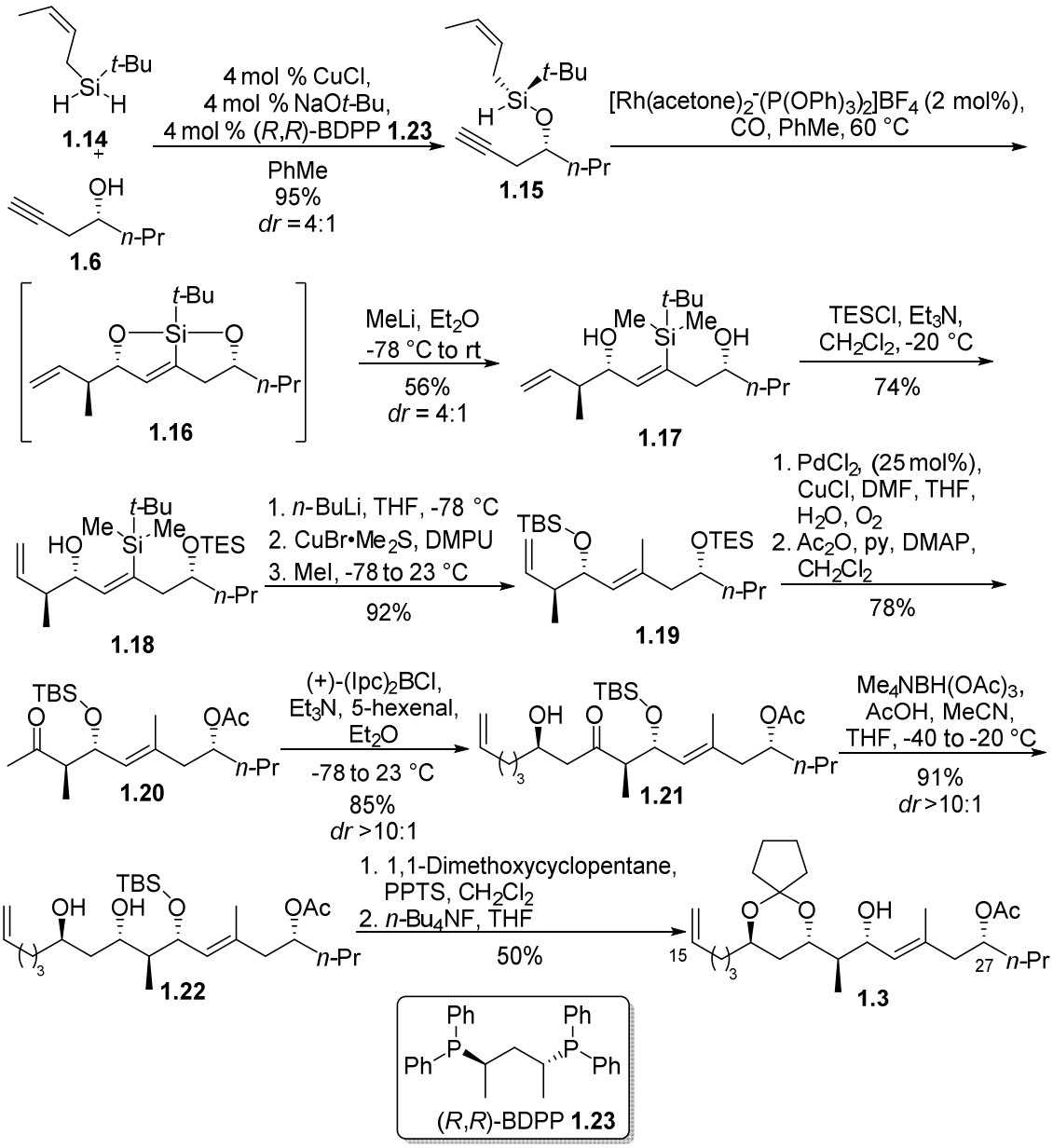
crotylsilylation[9] of hydrosilane **1.15** gave intermediate **1.16** that was immediately quenched with methyllithium, furnishing 1,5-*syn*-diol **1.17** in 56% yield and in a 4:1 diastereomeric ratio. After selective protection of the less hindered alcohol as the corresponding triethylsilyl ether, the separation of diastereomers at this stage was possible, thus giving **1.18** as a single diastereomer in 74% yield. Treatment of **1.18** with BuLi followed by $CuBr{\cdot}Me_2S$ and DMPU initiated a Brook-like 1,4-carbon (sp^2) to oxygen silane migration,[10] the resulting vinylcopper species was then alkylated using MeI, thus furnishing **1.19** in 92% yield. Wacker oxidation of alkene **1.19** was achieved with concomitant removal of the triethylsilyl ether group and the resulting alcohol was then acetylated to give **1.20** in 78% yield over two steps. Ketone **1.20** was then coupled with 5-hexenal using an asymmetric Paterson aldol coupling,[11] providing **1.21** in 85% yield and with >10:1 diastereoselectivity. Treatment of alkene **1.21** with tetramethylammonium triacetoxyborohydride[12] provided 1,3-*anti*-diol **1.22** in 91% yield and excellent diastereomeric ratio (>10:1). Protection of diol **1.22** as a cyclopentylidene ketal and deprotection of the *tert*-butylydimethylsilyl ether with tetrabutylammonium fluoride gave the C15-C30 fragment **1.3** in 50% yield for the two steps. Overall the C15-C30 fragment was synthesised in ten steps from alcohol **1.6** and in 11% yield.

[9] (a) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890. (b) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889.

[10] Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811.

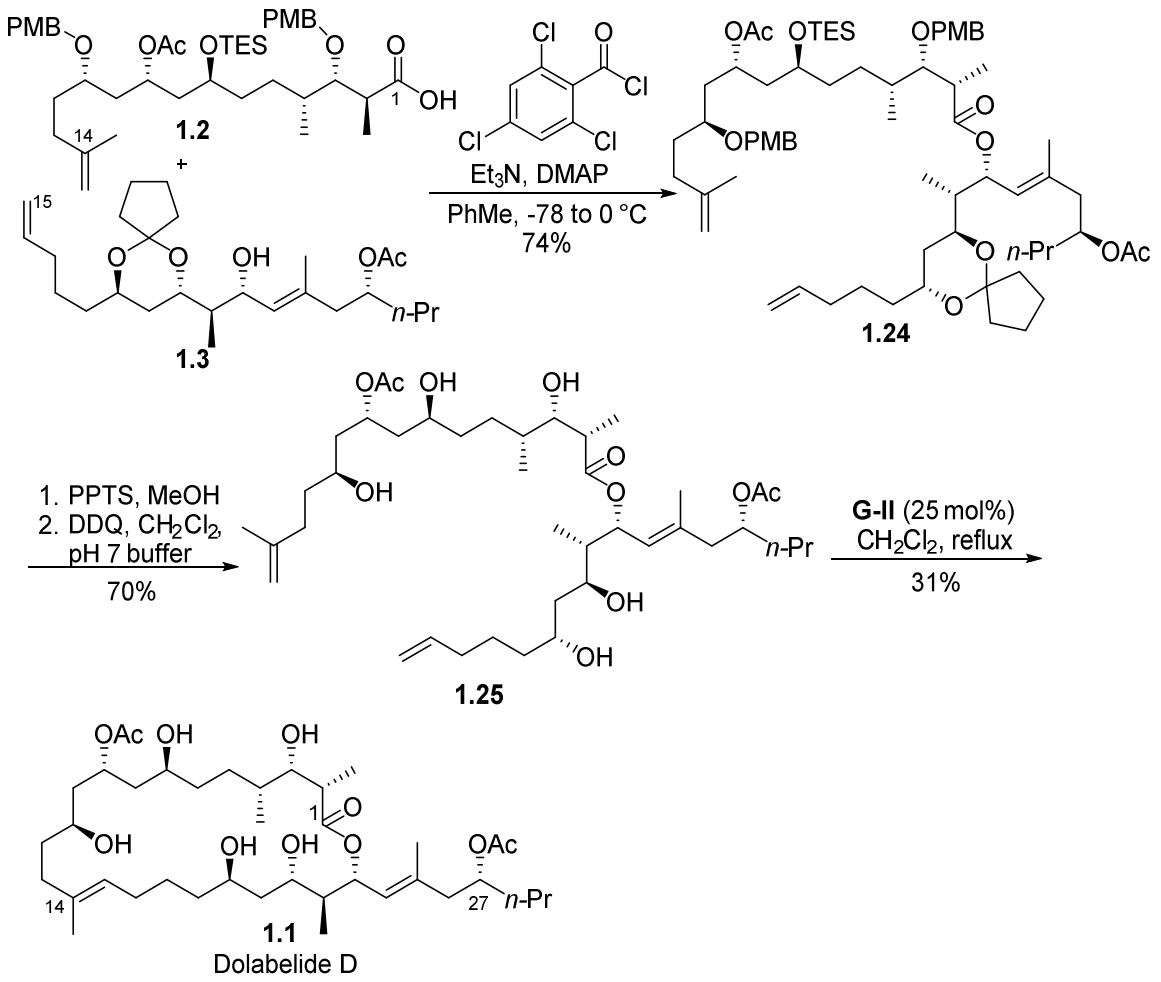
[11] (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R.D. *Tetrahedron* **1990**, 46, 4663. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

[12] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am*. Chem. Soc. **1988**, *110*, 3560.



Scheme 1.4: Synthesis of the C15-C30 fragment **1.3**

The two fragments were coupled using a Yamaguchi esterification to form ester **1.24** in 74% yield. Cleavage of the cyclopentylidene ketal and the triethylsilyl ether groups using pyridinium *p*-toluenesulfonate was followed by the oxidative cleavage of the *p*-methoxybenzyl ether using DDQ to furnish **1.25** in 70% yield. Finally, macrocyclisation using ring-closing metathesis proceeded with low selectivity (*E*/*Z* = 1.3:1) but after repeated tedious chromatography dolabelide D was isolated in 31% yield (Scheme 1.5).



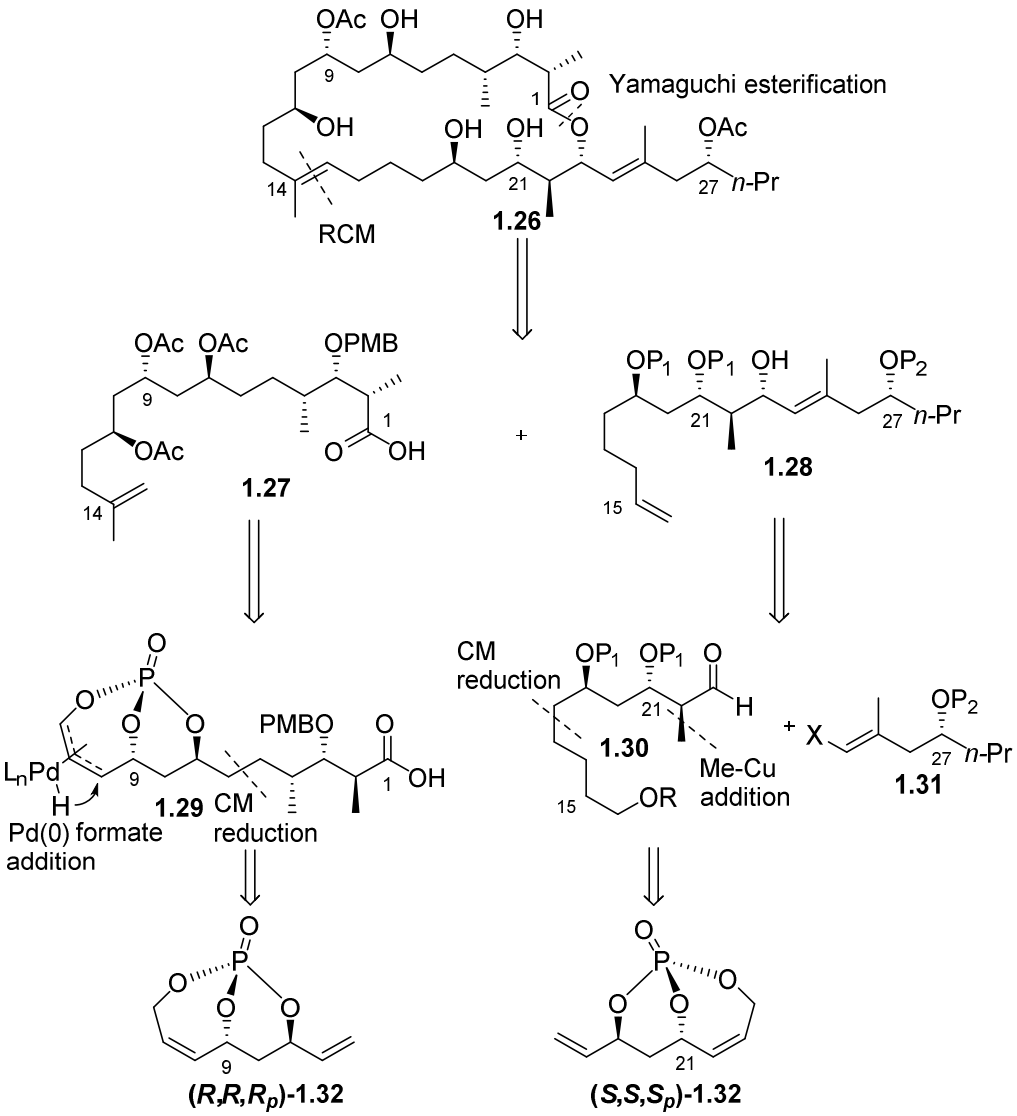
Scheme 1.5: Completion of the synthesis of dolabelide D

To summarise the synthesis of dolabelide D was achieved in seventeen steps starting from methacrolein and in 1.4% yield for the longest linear sequence.

1.2.2 Total synthesis of dolabelide C by *Hanson et al*

The Hanson group were the first and only up to this date to report the total synthesis of dolabelide C **1.26** in 2011.[13] The synthetic strategy involves the same disconnections as Leighton and co-worker's synthesis of dolabelide D (chapter 1.21), thus having two target fragments the C1-C14 **1.27** and C15-C30 **1.28** (Scheme 1.6). Carboxylic acid **1.27** could be prepared from intermediate **1.29** while allylic alcohol **1.28** could be synthesised by coupling aldehyde **1.30** with vinyl halide **1.31**. Both, carboxylic acid **1.27** and aldehyde **1.30** were assembled from phosphate triesters **(*R,R,R*$_p$)-1.32** and **(*S,S,S*$_p$)-1.32** respectively and using a phosphate-tether mediated approach.

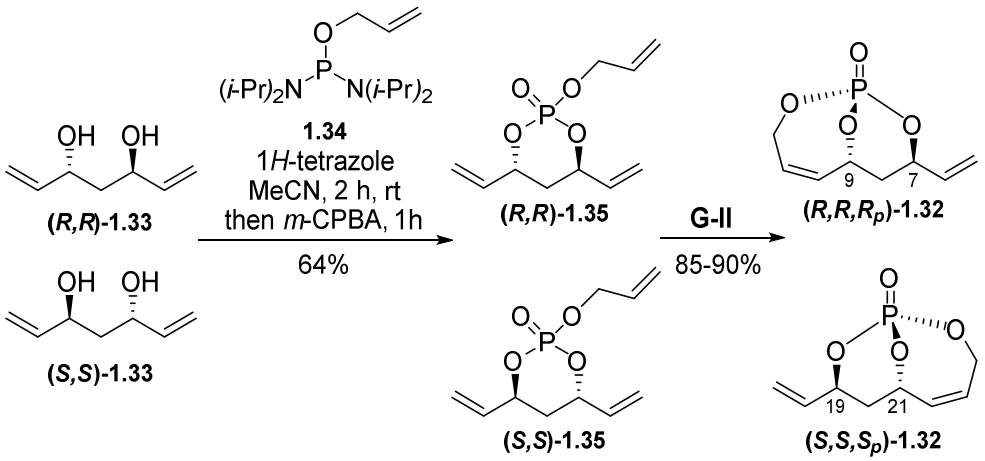
[13] Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J. D.; Whitehead, A. *J. Org. Chem.* **2011**, *76*, 4358.



Scheme 1.6: Hanson's retrosynthesis of dolabelide C

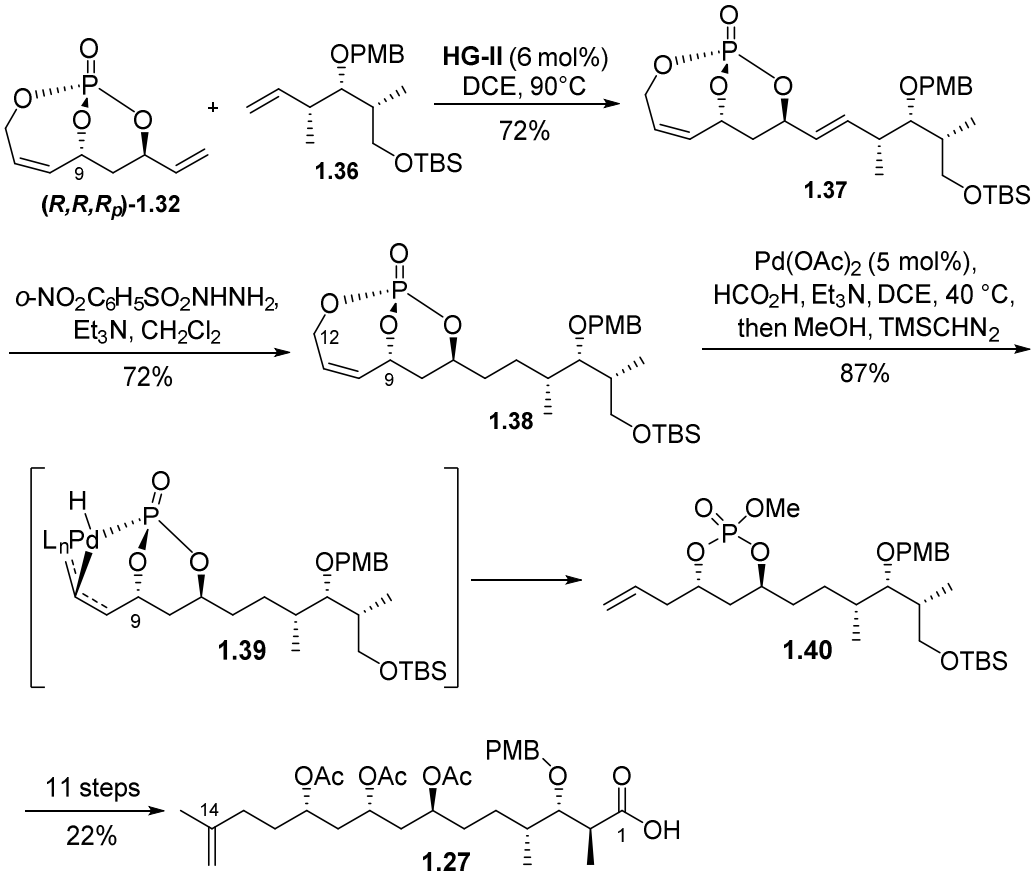
The enantiopure phosphate triesters **(*R,R,R*$_p$)-1.32** and **(*S,S,S*$_p$)-1.32** were prepared by a phosphate tether/RCM desymmetrisation approach.[14] (Scheme 1.7) Coupling of *anti*-diols **(*R,R*)-1.33** and **(*S,S*)-1.33** with commercially available allyl tetraisopropylphosphorodiamidite **1.34** gave pseudo-C_2-symmetric trienes (**R,R**)-1.35 and **(*S,S*)-1.35** respectively through a one-step coupling/oxidation sequence. Desymmetrisation of trienes **(*R,R*)-1.35** and **(*S,S*)-1.35** using ring-closing metathesis (RCM) afforded *P*-chiral bicyclo[4.3.1]phosphates **(*R,R,R*$_p$)-1.32** and **(*S,S,S*$_p$)-1.32** respectively. This desymmetrisation is based on the hypothesis that only the terminal olefin *cis* to the phosphate-tethered olefin reacts to generate **(*R,R,R*$_p$)-1.32** and **(*S,S,S*$_p$)-1.32** possessing two sterically differentiated olefins.

[14] (a) Burke, S. D.; Muller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827. (b) Burke, S. D.; Voight, E. A. *Org. Lett.* **2001**, *3*, 237. (c) Lambert, W. T.; Burke, S. D. *Org. Lett.* **2003**, *5*, 515. For desymmetrisation of a C_2-symmetric diol using the Prins cyclisation, see: (d) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022.



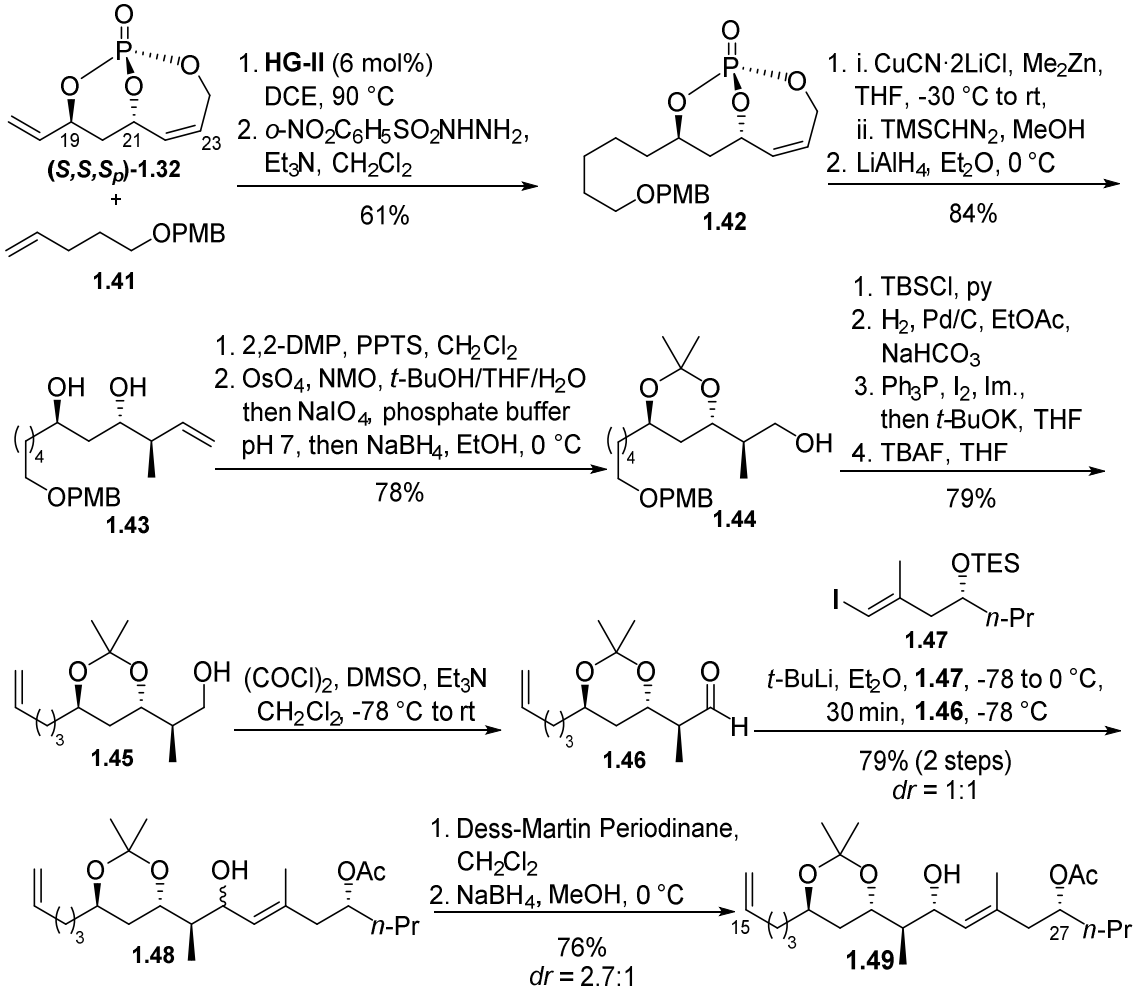
Scheme 1.7: Synthesis of the phosphate triesters **(*R,R,R*$_p$)-1.32** and **(*S,S,S*$_p$)-1.32**

The forward synthesis of the C1-C14 fragment **1.27** (Scheme 1.8) started with a cross-metathesis reaction between phosphate triester **(*R,R,R*$_p$)-32** and homoallyl alcohol **1.36** to form the *E*-alkene **1.37**. Alkene **1.37** was then regioselectivly reduced using a diamide reduction to form compound **1.38** in 72% yield. Pd-catalysed formate reduction, followed by methylation of the phosphate intermediate **1.39** provided compound **1.40** in 87% yield. This reduction was found to be regioselective due to the orthogonal alignment of orbitals within **1.38**, thus allowing the selective Pd(0)-catalysed ionisation of C12 over C9. Further steps allowed the synthesis of the C1-C14 fragment **1.27**. Overall the C1-C14 fragment **1.27** was synthesised in sixteen steps from diol **(*R,R*)-1.33** and in 5.7% yield.



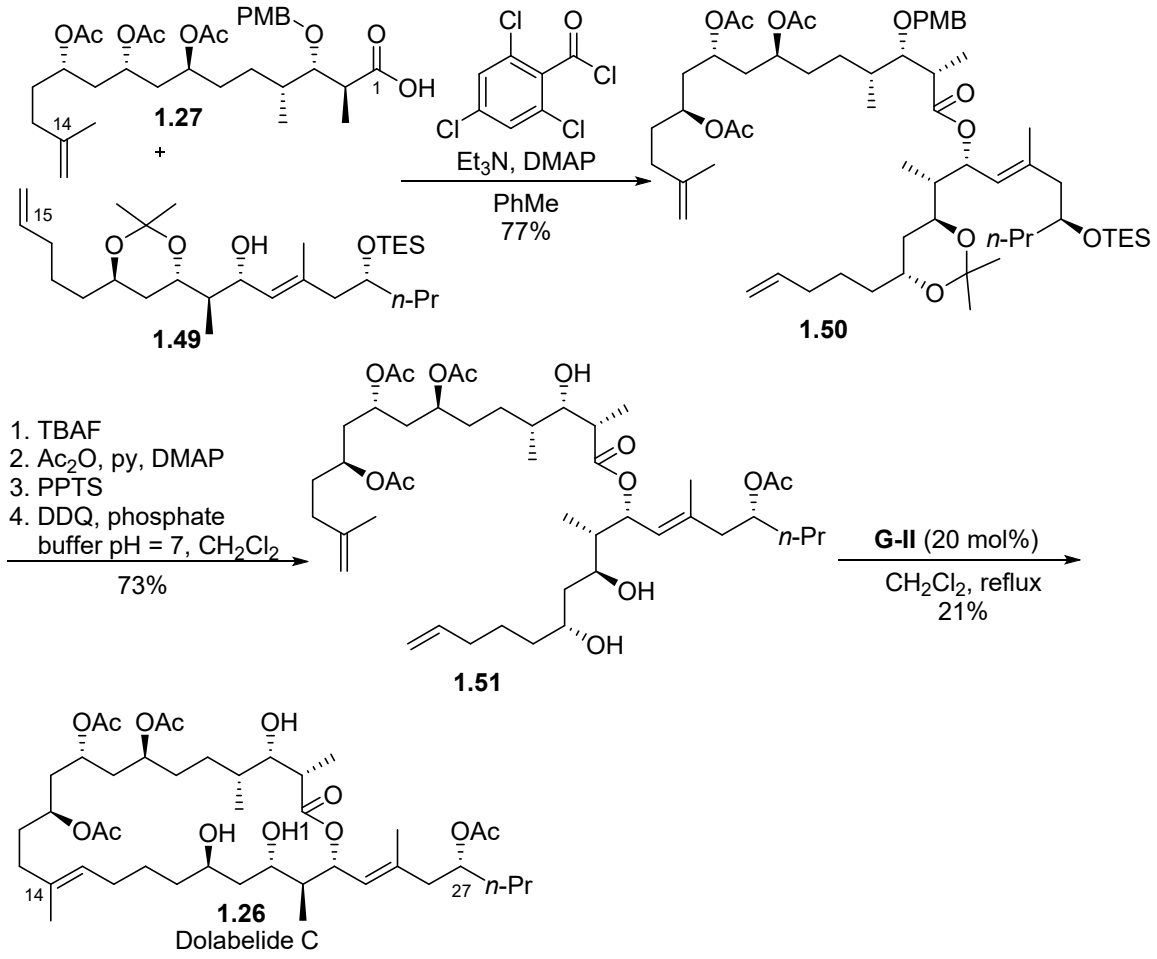
Scheme 1.8: Synthesis of the C1-C14 fragment **1.27**

The synthesis of the C15-C30 fragment **1.49** (Scheme 1.9) started with a cross-metathesis reaction between **(*S,S,S*$_p$)-1.32** and **1.41** to form the *E*-configured (>20:1) alkene that was selectively reduced using *o*-nitrobenzenesulfonyl hydrazine to form **1.42** in 61% yield over two steps. Diastereo- and regioselective methyl cuprate addition to **1.42** followed by phosphate cleavage led to diol **1.43** in 84% yield. The 1,3-*anti*-diol **1.43** was protected as an acetonide, and the terminal olefin was transformed into the corresponding primary alcohol using an oxidative cleavage/reduction sequence to give **1.44** in 78% yield. The primary alcohol was then protected as its *t*-butyldimethylsilyl ether, the *p*-methoxybenzyl ether was cleaved to give the free alcohol, which was converted into the terminal olefin through an iodination/elimination sequence. Finally, removal of the *t*-butyldimethylsilyl ether group furnished **1.45** in 79% yield over 4 steps. Alcohol **1.45** was subjected to a Swern oxidation to form aldehyde **1.46**, that was added to the lithiated derivative of the C24-C30 fragment **1.47**, thus yielding alcohol **1.48** in 79% yield and as a 1:1 mixture of diastereomers. The diastereoisomers were separated by column chromatography and the undesired isomer was recycled by oxidising and then selectively reducing to form the C15-C30 fragment **1.49** in 76% yield with a 2.7:1 diastereomeric ratio. Overall the C15-C30 fragment **1.49** was synthesised in 13 steps from triester **(*S,S,S*$_p$)-1.32** and in 14% yield.



Scheme 1.9: Synthesis of the C15-C30 fragment **1.49**

Completion of the synthesis of dolabelide C (Scheme 1.10) was achieved by the following series of steps. First, the two fragments **1.27** and **1.49** were coupled by a Yamaguchi esterification to form the ester **1.50** in 77% yield. Then the triethylsilyl ether was cleaved to form the free alcohol that was immediately acetylated. The acetylated intermediate was then subjected to PPTS to remove the acetonide before using DDQ to oxidatively cleave the *p*-methoxybenzyl ether, thus furnishing the RCM precursor **1.51** in 73% yield over 4 steps. Finally, cyclisation of compound **1.51** using RCM with **G-II** catalyst produced dolabelide C initially in 57% yield and in a *E/Z* ratio of 1:1. After two sequential flash column chromatography purifications the diastereomers were separated giving dolabelide C **1.26** in 21% yield. Overall, the synthesis of dolabelide C **1.26** was achieved in 24 steps for the longest linear sequence from diol **(*S,S*)-1.33** and in 1.2% yield.



Scheme 1.10: Completion of the synthesis of dolabelide C

1.2.3 Synthesis of the C1-C13 fragment of dolabelides and the C15-C30 fragment of dolabelide A by Genêt and Phansavath

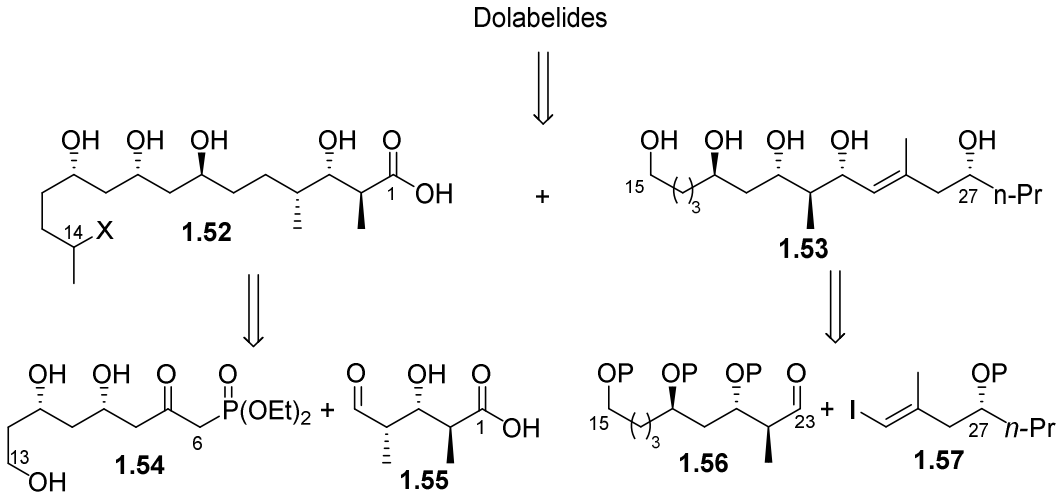
Genêt and Phansavath and coworkers envisaged retrosynthetic analysis involved disconnecting dolabelides at the C1 lactone and at the C14-C15 bond resulting in two fragments **1.52**[15] and **1.53**[16] (Scheme 1.11). The C14-C15 bond could be formed via a modified Julia olefination by having an aldehyde at C15 and a sulfonyl benzothiazole at C14 or via a Horner-Wadsworth-Emmons reaction were the C14 group would be a phosphonate.

The C1-C14 fragment **1.52** could be made by the coupling of β-keto phosphonate **1.54** with aldehyde **1.55** by a Horner-Wadsworth-Emmons reaction followed by a homologation reaction at C13. Coupling of aldehyde **1.56** with vinyl iodide **1.57** using a lithium-halogen

[15] Le Roux, R.; Desroy, N.; Phansavath, P.; Genêt, J.P. *Synlett* **2005**, 429.

[16] (a) Desroy N.; Le Roux R.; Phansavath P.; Chiummiento L.; Bonini C.; Genêt J. P. *Tetrahedron Lett.* **2003**, *44*, 1763. (b) Roche C.; Desroy N.; Haddad M.; Phansavath P.; Genêt J. P. *Org. Lett.* **2008**, *10*, 3911.

exchange reaction would lead to the C15-C30 fragment **1.53**. The synthesis of all these advanced intermediates (**1.54, 1.55, 1.56, 1.57**) depicted in Scheme 1.11 involved the use of their developed methodology for the asymmetric reduction of β-ketoesters and β-hydroxyketones.[17]



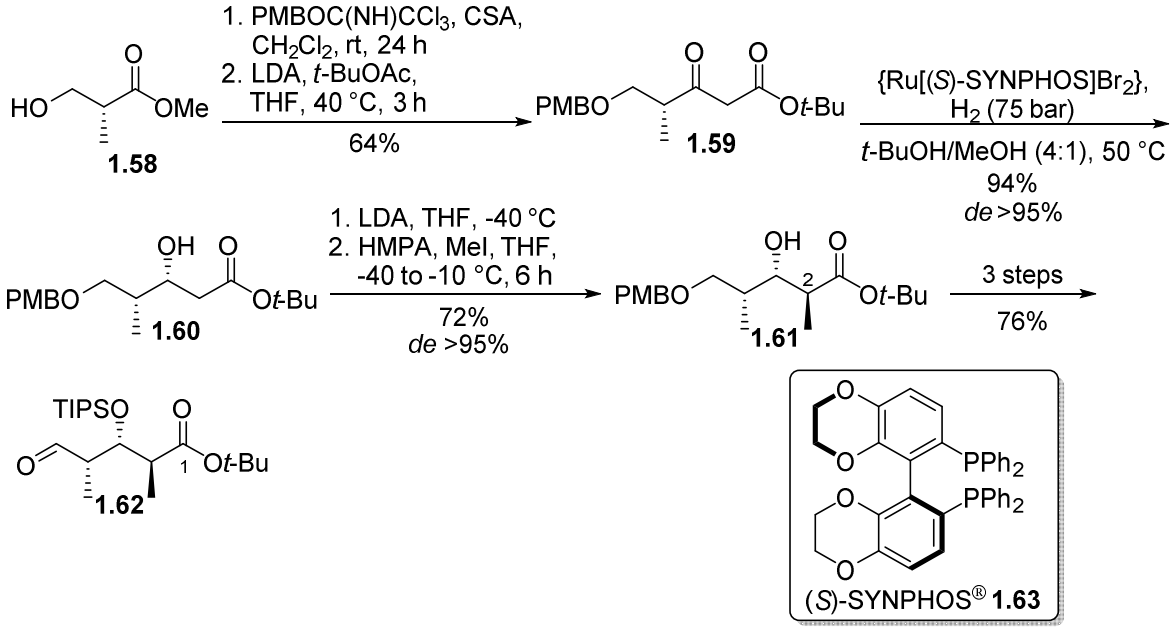
Scheme 1.11: Genêt and Phansavath's retrosynthesis of dolabelides

Preparation of the C1-C5 segment **1.62** started from the commercially available Roche ester **1.58**. Protection of the alcohol as its corresponding PMB ether under acidic conditions followed by side-chain extension with lithio *t*-butyl acetate[18] formed the required chiral ester **1.59** (Scheme 1.12). Asymmetric hydrogenation of β-ketoester **1.59** was achieved using chiral ruthenium complex {Ru[(*S*)-SYNPHOS]Br_2} generated in situ from ligand **1.63** under 75 bar of H_2, furnishing β-hydroxyketoester **1.60** in excellent yield and diastereoselectivity. The C2 stereocenter was installed using a Frater diastereoselective methylation[19] in good diastereomeric excess. A further 3 steps gave aldehyde **1.62** in 76% yield. Overall the C1-C5 **1.62** fragment was synthesised in 33% and in 7 steps starting from Roche ester **1.58**.

[17] (a) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Champion, N.; Dellis, P. *Tetrahedron Lett.* **2003**, *44*, 823. (b) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J. P. Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931. (c) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Caño de Andrade, M. C.; Laffite, J.A. *Tetrahedron Asymmetry* **1994**, *5*, 665. (d) Genêt, J. P.; Ratovelomanana-Vidal, V. *J. Organomet. Chem*. **1998**, *567*, 163.

[18] Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc*. **1971**, *93*, 2318.

[19] (a) Fráter, G. *Helv. Chim. Acta* **1979**, 62, 2825; (b) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197.

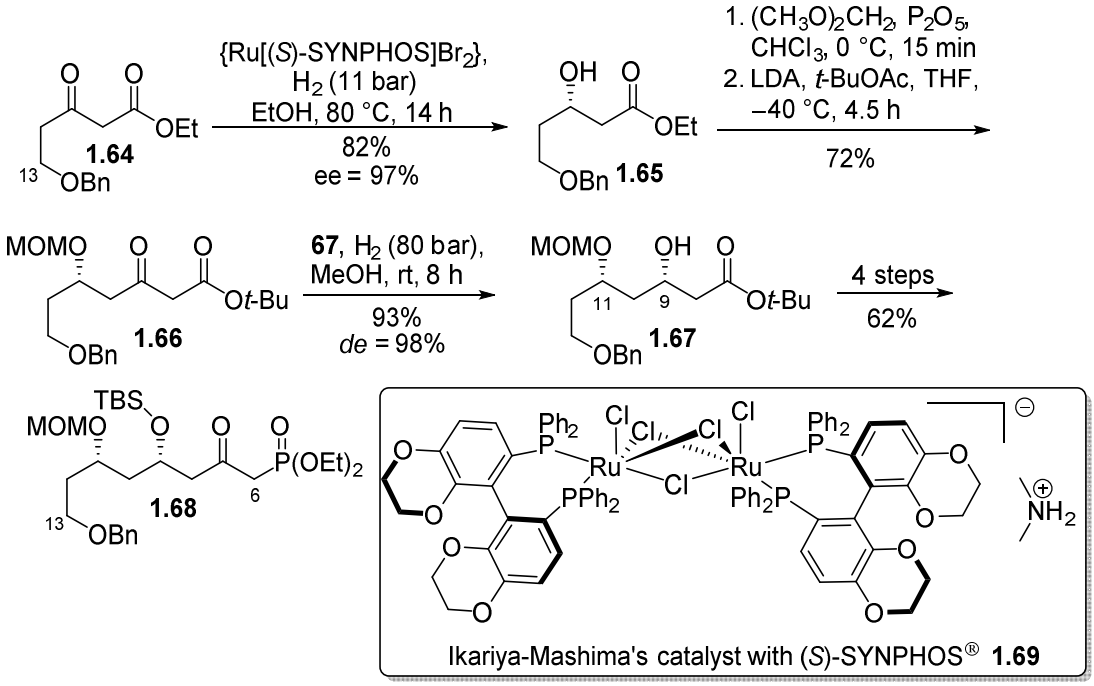


Scheme 1.12: Synthesis of the C1-C5 fragment **1.62**

The synthesis of the C6-C13 fragment **1.68** (Scheme 1.13), commenced from β-ketoester **1.64** that was prepared in 3 steps from propan-1,3-diol.[20] Subjection of prochiral β-ketoester **1.64** to an asymmetric hydrogenation using chiral ruthenium complex {Ru[(*S*)-SYNPHOS]Br_2} gave alcohol **1.65** in 82% yield and with an enantiomeric excess of 97%. Protection of the secondary alcohol as a MOM ether was then followed by side-chain extension with lithio *t*-butyl acetate furnishing β-ketoester **1.66**. Another asymmetric hydrogenation was used to set the stereocentre at the C9 position, thus forming **1.67**, this time using Ikariya-Mashima's catalyst **1.69**[21] with their (*S*)-SYNPHOS ligand, since the {Ru[(*S*)-SYNPHOS]Br_2} complex cleaved the MOM ether on the alcohol at the C11 position. Completion of the synthesis of the C6-C13 fragment **1.68** was achieved in 62% yield over 4 steps from β-hydroxyketoester **1.67** and in 34% overall yield over 8 steps from β-ketoester **1.64**.

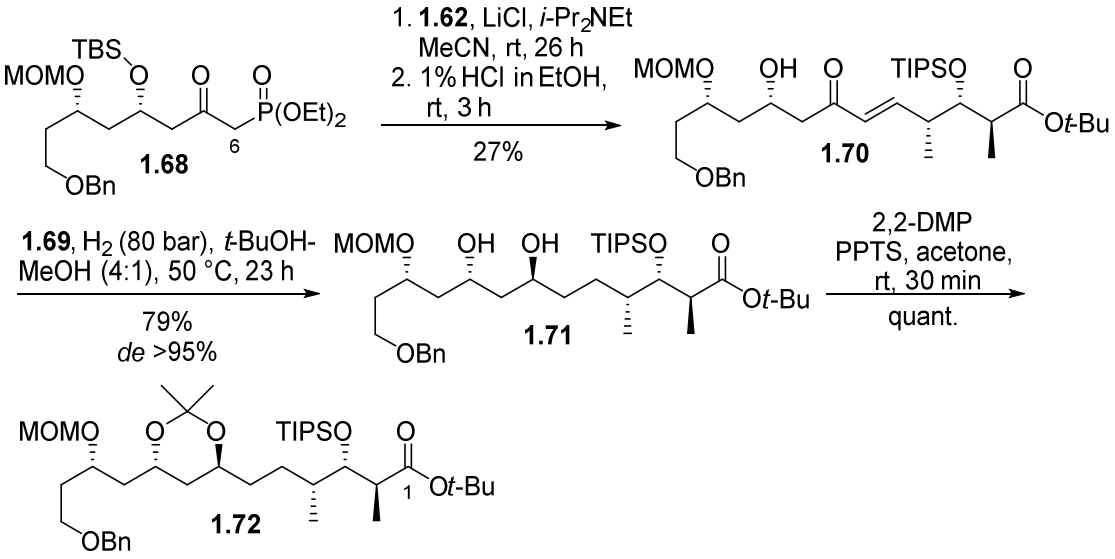
[20] (a) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (b) Claffey, M. M.; Hayes, C. J.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8267.

[21] (a) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922. (b) Ohta, T.; Tonomura, Y.; Nozaki, K.; Takaya, H.; Mashima, K. *Organometallics* **1996**, *15*, 1521. (c) Mashima, K.; Nakamura, T.; Matsuo, Y.; Tani, K. *J. Organomet. Chem.* **2000**, *607*, 51.



Scheme 1.13: Synthesis of the C6-C13 fragment **1.68**

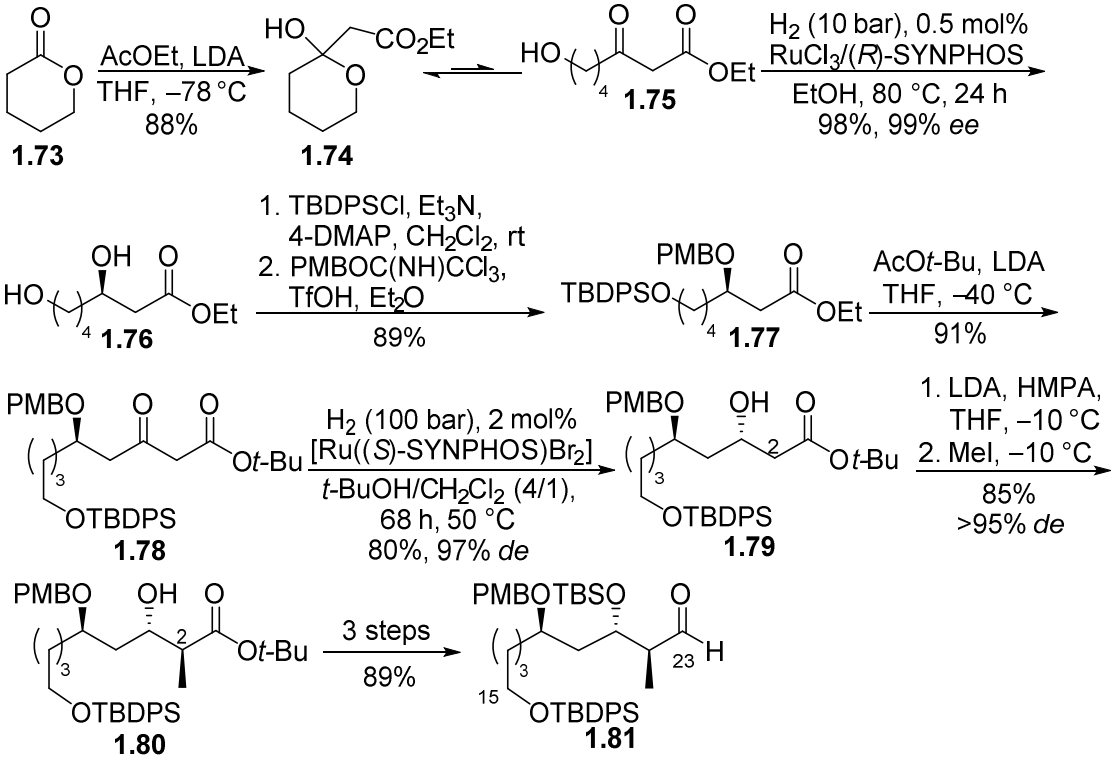
Coupling of the two fragments was then carried out using a Horner-Wadsworth-Emmons reaction to give the asymmetric hydrogenation precursor **1.70** in 27% yield (Scheme 1.14). Asymmetric hydrogenation of enone **1.70** was performed using Ikariya-Mashima's catalyst **1.69** once again, in good diastereomeric ratio. Finally, protection of diol **1.71** as the corresponding acetonide furnished the C1-C13 fragment **1.68** in quantitative yield. Summarising the C1-C13 was prepared over 12 steps from β-ketoester **1.64** in 7.3% yield and over 15 steps from propan-1,3-diol.



Scheme 1.14: Completion of the synthesis of the C1-C13 fragment **1.72**

The synthesis of the C15-C23 fragment **1.81** (Scheme 1.15) started from lactone **1.73**, to which the enolate of EtOAc was added, leading to the formation of hemiketal **1.74** in 88%

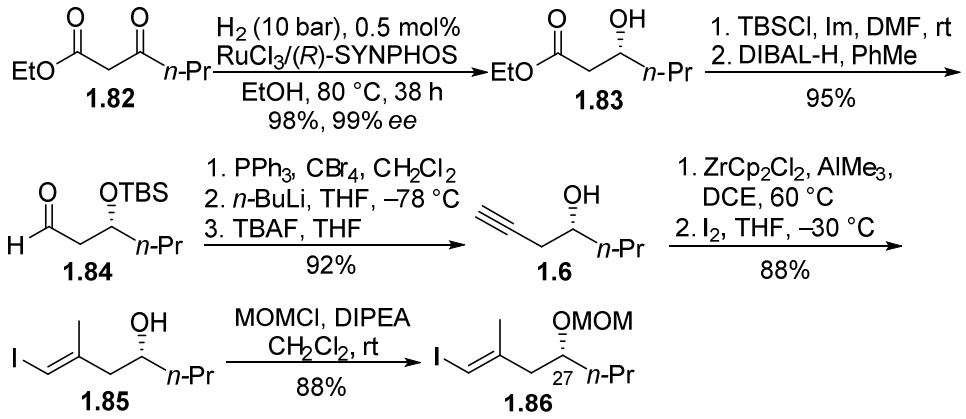
yield. Since this compound is in equilibrium with the β-keto ester **1.75**, it is a suitable substrate for the ruthenium-mediated asymmetric hydrogenation of the ketone function. The reduction gave β-hydroxy ester **1.76** in excellent yield and enantioselectivity and was followed by the protection of the primary alcohol as a *t*-butyldiphenylsilyl ether. Then the remaining alcohol was protected as a *p*-methoxybenzyl ether, giving compound **1.77** in 89% yield over 2 steps. The β-keto ester **1.78** was prepared by a chain extension with the enolate of *t*-butyl acetate in 91% yield. This was followed by an asymmetric hydrogenation using ruthenium-SYNPHOS catalyst, thus delivering alcohol **1.79** in 80% yield with a diastereomeric excess of 97%. The C2 stereocentre was then installed by a diastereoselective Frater methylation to provide compound **1.80** in 85% yield with a diastereomeric ratio greater than 95:5. The C15-C23 segment **1.81** was completed in 3 steps in 89% yield from ester **1.80**. Overall, the C15-C23 fragment **1.81** was obtained in ten steps with a yield of 42% starting from lactone **1.73**.



Scheme 1.15: Synthesis of the C15-C23 fragment **1.81**

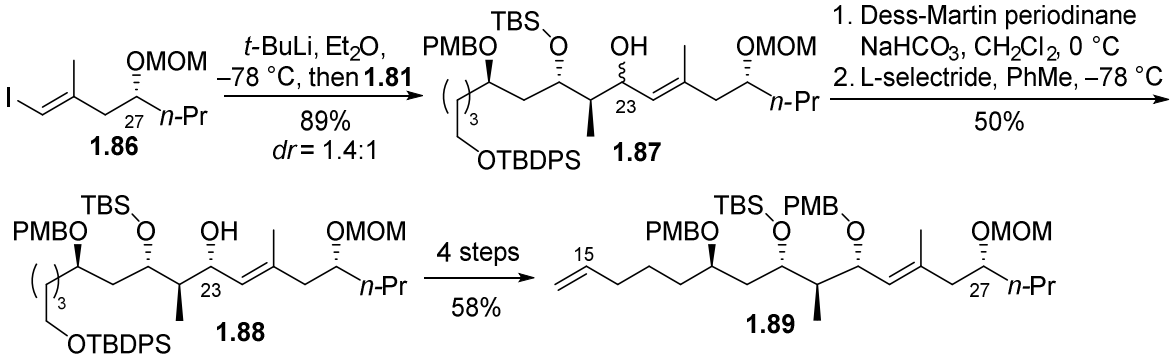
The synthesis of the C24-30 fragment **1.86** (Scheme 1.16) commenced once again with the asymmetric hydrogenation of ethyl 3-oxohexanoate **1.82** giving β-hydroxy ester **1.83** in 98% yield with an enantiomeric excess of 99%. Protection of the alcohol as a *t*-butyldimethylsilyl ether followed by reduction of the corresponding protected ester intermediate to the aldehyde furnished **1.84** in 95% yield over 2 steps. The alkyne **1.6** was then prepared by a Corey-Fuchs reaction, prior to the deprotection of the alcohol. Zirconium-promoted carboalumination reaction, followed by quenching with iodine gave the desired vinyl iodide **1.85** in good yield. Finally, the alcohol was protected as a MOM ether providing the C24-

C30 fragment **1.86**. To summarise, the synthesis of the C24-C30 fragment **1.86** was achieved in eight steps and in 66% yield from the commercially available ethyl 3-oxohexanoate **1.82**.



Scheme 1.16: Synthesis of the C24-C30 segment **1.86**

Conversion of vinyl iodide **1.86** to the corresponding organolithium reagent was followed by the addition of aldehyde **1.81**, which led to alcohol **1.87** in 89% yield and a 1.4:1 diastereomeric ratio (Scheme 1.17). The alcohol at C23 in **1.87** was then oxidised and the resulting ketone subsequently reduced with L-selectride to give alcohol **1.88** as a single diastereomer in 50% yield for the two steps. A further 4 steps from alcohol **1.88** furnished the C15-C30 fragment **1.89** in 58% yield. Overall the C15-C30 **1.89** fragment of dolabelide A was synthesized in 17 steps and 11% yield for the longest linear sequence.



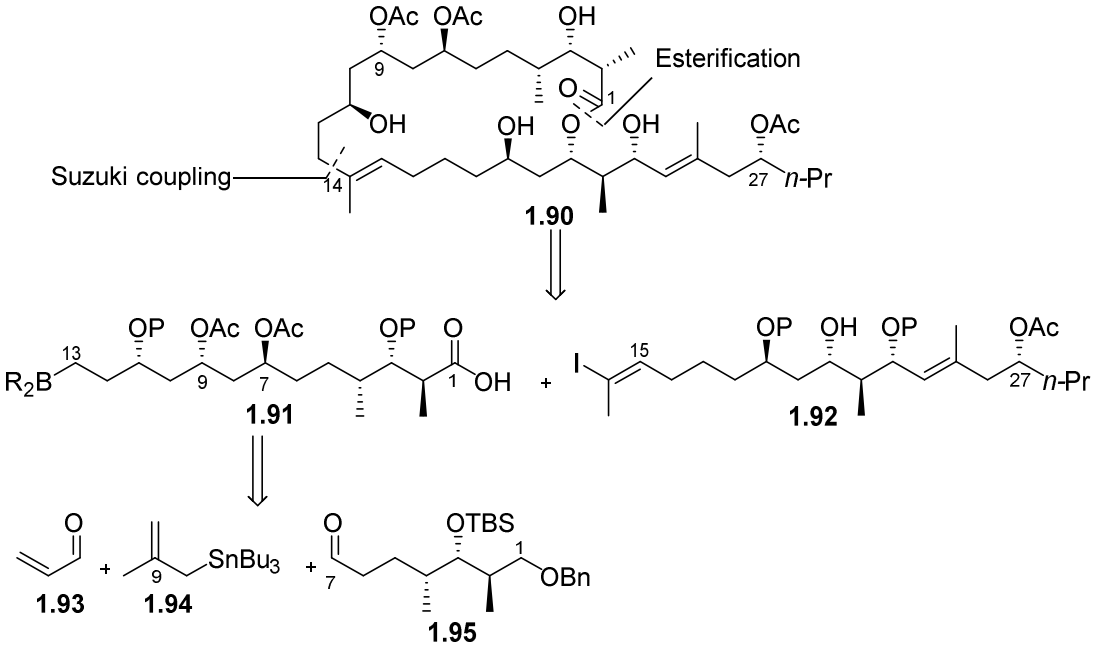
Scheme 1.17: Synthesis of the C15-C30 fragment **1.89**

1.2.4 Keck's synthesis of the C1-C13 subunit of dolabelide B9

Keck and co-workers envisaged the retrosynthesis of dolabelide B **1.90** (Scheme 1.18)[22] by disconnecting at the C1 lactone, which could be formed by an esterification and at the C13-C14 bond, which could be formed by a Suzuki coupling. The C1-C13 fragment **1.91**

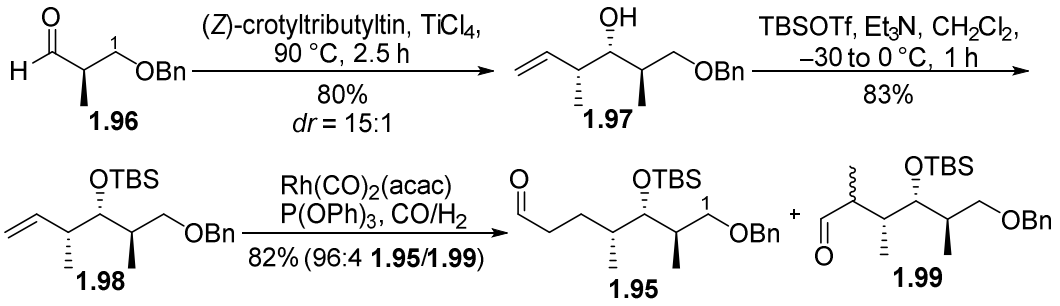
[22] Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911.

could then be synthesised from aldehyde **1.95** and allylstannane **1.94** by an asymmetric allylation. The resulting compound would then be transformed into a ketone and engaged into a 1,5-directed aldol with **1.93** followed by a 1,3-directed reduction to install the C9 alcohol stereocenter.



Scheme 1.18: Keck's retrosynthesis of dolabelide B **1.90**

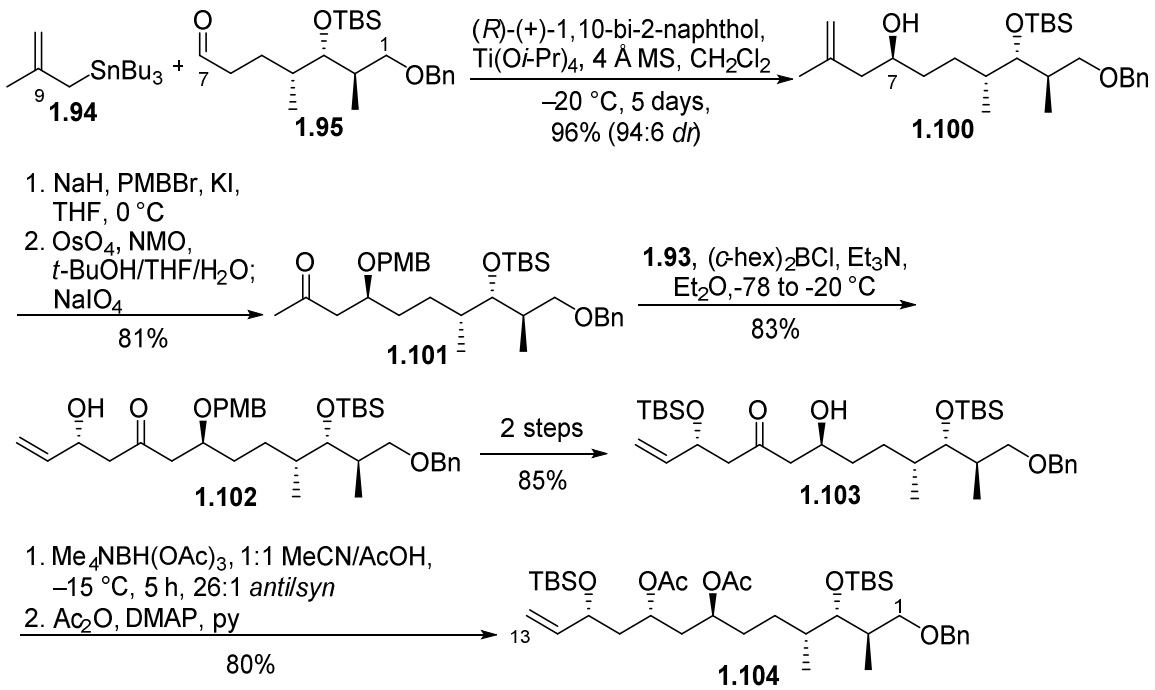
Construction of the C1-C7 fragment started from aldehyde **1.96**, which underwent diastereoselective addition of a crotylstannane in the presence of titanium tetrachloride (Scheme 1.19). This methodology developed by Keck and co-workers allowed the formation of homoallylic alcohol **1.97** in 80% yield and excellent diastereoselectivity. Protection of the alcohol as a *t*-butyldimethylsilyl ether, followed by a hydroformylation catalysed by dicarbonyl(acetylacetonato)rhodium(I) gave aldehyde **1.95** in 82% yield with a 96:4 ratio of regio-isomers. Overall, the C1-C7 **1.95** was synthesised in 3 steps and 54% yield.



Scheme 1.19: Synthesis of the C1-C7 fragment

Aldehyde **1.95** was then coupled with allylstannane **1.94** through a methallylation using titanium isopropoxide and a chiral binaphthyl ligand to furnish alcohol **1.100** in 96% yield and a 94:6 diastereomeric ratio (Scheme 1.20). Protection of the alcohol as the

corresponding *p*-methoxybenzyl ether was followed by oxidative cleavage of the alkene, giving ketone **1.101** in 81% yield over two steps. Aldol condensation of ketone **1.101** with acrolein **1.93** provided the 1,5-*anti*-diol **1.102** as a single isomer and in 83% yield. Further steps led to the formation of ketone **1.103** in 85% yield for the 2 steps. Using tetramethylammonium triacetoxyborohydride, the ketone was then diastereoselectivly reduced and the resulting 1,3-*anti* diol was acetylated in 80% yield for the two steps. Overall the C1-C13 fragment **1.104** was synthesised in 11 steps and 24% yield.



Scheme 1.20: Completion of the synthesis of the C1-C13 fragment **1.104**

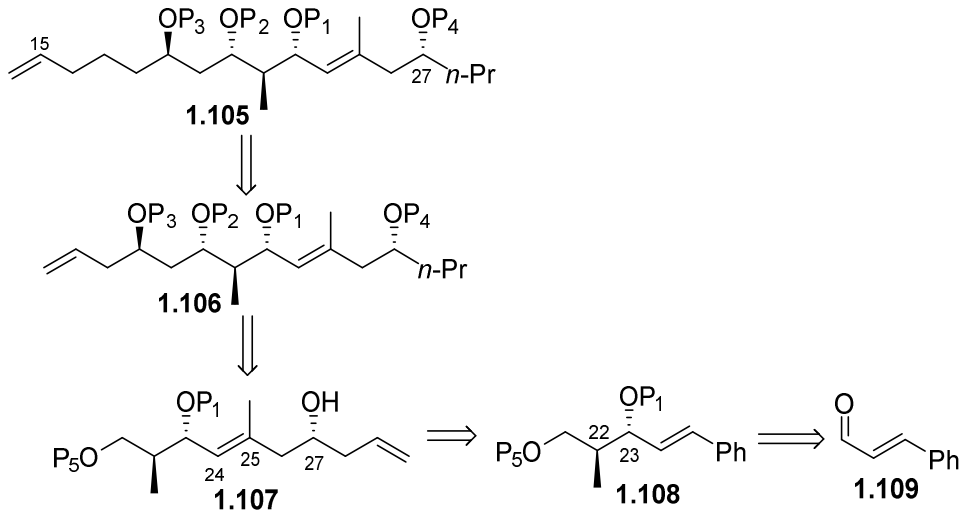
1.2.5 Synthesis of the C15-C30 fragment of dolabelides by *Yadav et al*

Yadav and coworkers' approach for the synthesis of the C15-C30 fragment of dolabelides is depicted in Scheme 1.21.[23] The C15-C30 subunit **1.105** could be constructed from **1.106** by oxidative cleavage of the double bond, Grignard addition and diastereoselective reduction of the ketone. A Wilkinson hydrogenation and Brown asymmetric allylation[24] could be employed as the key steps to prepare diene **1.106** from compound **1.107**. In turn, **1.107** could be synthesised from **1.108** using a Wittig olefination to install the C24-C25 trisubstituted olefin and an asymmetric allylation to install the C27 stereocenter. An aldol

[23] Yadav J. S.; Nayak S.; Sabitha G. *RSC Adv.*, **2013**, *3*, 21007.

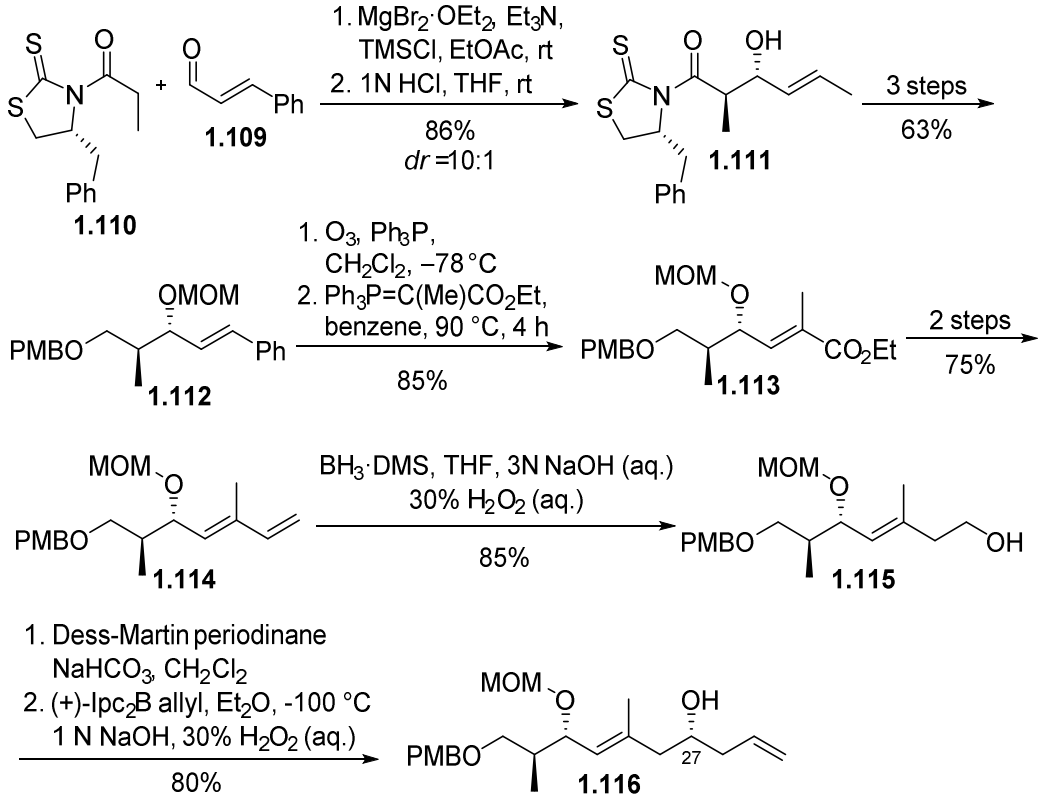
[24] (a) Brown H. C.; Ramachandran P.V. *J. Organomet. Chem.* **1995**, *500*, 1. (b) Fortanet J. G.; Murga, J.; Carda, M.; Marco, J.A.; Matesanz, R.; Diaz J.F.; Barasoain, I. *Chem. Eur. J.* **2007**, *13*, 5060. (c) Ramachandran P.V. *Aldrichimica Acta*, **2002**, *35*, 23.

reaction of **1.109** with a chiral auxiliary could be used to set the C22 and C23 stereocenters as the basic step in the preparation of **1.108**.



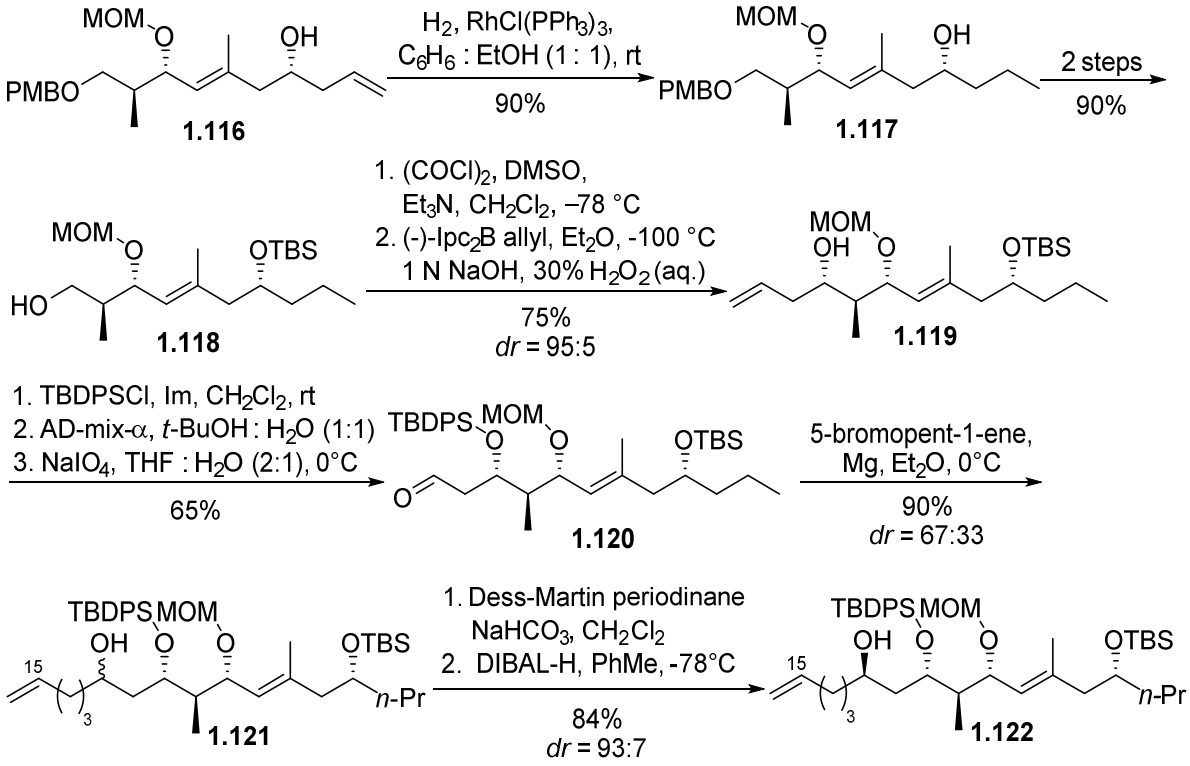
Scheme 1.21: Yadav's retrosynthesis of the C15-C30 fragment of dolabelides

The synthesis commenced with a diastereoselective aldol reaction of *trans*-cinnamaldehyde **1.109** using Crimmins auxiliary **1.110** in the presence of stoichiometric amount of $MgBr_2 \cdot OEt_2$, Et_3N and TMSCl, to furnish adduct **1.111** in 10:1 diastereomeric ratio (Scheme 1.22). Auxilary removal and protection of the alcohols then gave **1.112** over 3 steps in 63% yield. Ozonolysis of the alkene in **1.112** gave the corresponding aldehyde that was immediately subjected to a Wittig reaction resulting in ester **1.113**. A further two chemical transformations furnished diene **1.114** that underwent a selective hydroboration giving alcohol **1.115** in 85% yield; only 5% of the undesired 1,4-diol was observed. Oxidation of **1.115** to the aldehyde followed by an asymmetric Brown allylation using the (+)-Ipc_2B allyl reagent formed homoallylic alcohol **1.116** as a single diastereomer in 80% yield over two steps.



Scheme 1.22: Synthesis of intermediate **1.116**

Selective hydrogenation of the terminal double bond in **1.116** took place using Wilkinson's catalyst and a 1:1 mixture of ethanol/benzene that was found to accelerate the reaction and increase the yield compared to using a non-polar solvent alone (Scheme 1.23). Sequence of protection/deprotection provided intermediate **1.118** in 90% yield over 2 steps. After oxidation of the primary alcohol in **1.118** to the corresponding aldehyde, the C21 stereocentre was then installed by another asymmetric allylation using (-)-Ipc_2B allyl to afford the homoallylic alcohol **1.119** in a 95:5 diastereomeric ratio and in 75% yield over 2 steps. Protection of the secondary alcohol as the *t*-butyldiphenylsilyl ether followed by a Sharpless asymmetric dihydroxylation using AD-mix-α gave the corresponding diol as a 6:4 ratio of inseparable diastereomers. The diol intermediate was then subjected to oxidative cleavage conditions using $NaIO_4$, furnishing aldehyde **1.120** in 65% yield over 3 steps. Grignard addition to aldehyde **1.120** gave alcohol **1.121** as a 67:33 mixture of diastereomers that were separated by preparative HPLC. To further improve the diastereopurity of **1.121** an oxidation/reduction sequence was investigated; DIBAL-H was found to be the reducing agent of choice, giving **1.122** in 84% yield over 2 steps and a 93:7 diastereomeric ratio.



Scheme 1.23: Synthesis of the C15-C30 fragment **1.122** of dolabelides

To summarise, Yadav *et al.* successfully synthesised the C15-C30 fragment **1.122** of dolabelides in 22 steps and 5.1% overall yield.

1.3 Background on olefin metathesis

Metathesis, in all its variations, is one of the most frequently employed reactions in carbon-carbon bond formation,[25] while also keeping the integrity of the alkene functional group. Especially during the past 20 years, where there has been significant development in catalysts that are stable, easy to use and can tolerate a wide range of functional groups, it has been used extensively in natural product synthesis.[25c] Variations of the metathesis reaction have been extended to different π-systems including cross metathesis (CM), ring-closing metathesis (RCM), ring-opening metathesis (ROM), enyne metathesis, ring-closing enyne metathesis (RCEYM), ring-opening metathesis polymerisation (ROMP) among others. Nowadays the most practically utilised catalysts fall into two types, the molybdenum complex **Mo-I** and its derivatives developed by Schrock and co-workers,[26] and ruthenium

[25] Reviews on metathesis: (a) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490. (c) *Metathesis in Natural Product Synthesis*; Cossy, J.; Arseniyadis, S.; Meyer, C.; Eds.; Wiley: New York, **2010**. (d) Prunet, J. *Eur. J. Org. Chem.* **2011**, 3634. (e) Cheng-Sánchez, I.; Sarabia, F. *Synthesis* 2018, *50*, 3749.

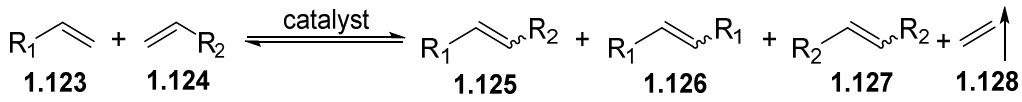
[26] a) Schrock, R. R. *Acc. Chem. Res.* **1986**, *19*, 342. (b) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260.

catalysts such as **G-I**, **G-II** initially developed by Grubbs *et al*[27] and further improved by Hoveyda *et al*[28] as well as other groups. (see page 11 for structure of catalysts)

Although molybdenum-based catalysts are highly reactive towards a variety of substrates, even for sterically hindered cases, their high instability to air, moisture and impurities as well as their limited functional group tolerance make them impractical in synthesis, so they are less commonly used.[29] Ruthenium-based catalysts featuring increased stability, shelf life and substrate tolerance are more appealing and therefore are the most frequently employed in synthesis.

1.3.1 Cross metathesis

Cross metathesis is the interaction between two alkenes that undergo bond reorganisation in the presence of a metal catalyst with the driving force of the reaction being the release of ethylene **1.128** (Scheme 1.24). [27,29] Compounds **1.126** and **1.127** are the homodimerization products of cross metathesis, whereas **1.125** in most cases is the desired product.



Scheme 1.24: Cross metathesis

In 2002 Grubbs and co-workers introduced a general model for the categorisation of olefins based on their reactivity and ability to homodimerize, which can be used to predict the selectivity of a cross-metathesis reaction.[30] This model categorises olefins into four types (Table 1.1), with type I alkenes being the most reactive and type IV alkenes being spectators to metathesis reactions. The classification also depends on the catalyst used. In Table 1.1 the profile shown is for the most commonly used **G-II** catalyst.

[27] (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

[28] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

[29] Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

[30] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360

Olefin type	Reactivity	Examples
Type I	Rapid homodimerization, homodimers consumable	Terminal olefins, 1^0 allylic alcohols, allyl halides, allyl silanes
Type II	Slow homodimerization, homodimers sparingly consumable	Acrylates, acrylamides, acrolein, vinyl ketones, 2^0 allylic alcohols
Type III	No homodimerization	1,1 disubstituted olefins, non-bulky trisubstituted olefins, vinyl siloxanes
Type IV	Inert to CM	Protected trisubstituted allyl alcohols

Table 1.1: Classification of olefins

Generally, sterically unhindered electron-rich olefins are categorized as type I; increasing steric hindrance and/or electron deficiency makes olefins less reactive, falling into types II to IV.

To maximize selectivity in CM reactions, it is important to minimize homodimer formation. This can be done by preventing initial homodimer formation or by using olefins leading to homodimers that can participate in secondary metathesis pathways. For example, when reacting two type I olefins, the rates of homodimerization are comparable with the reactivity of their corresponding homodimers, therefore secondary metathesis is likely to take place. In such reactions a statistical product mixture is observed, where the desired CM product is in equilibrium with its various homodimers through secondary metathesis pathways. Using one of the olefins in excess for example **1.123** (Scheme 1.24) shifts the equilibrium to the non-homodimerised, desired CM product **1.125** (Table 1.2).

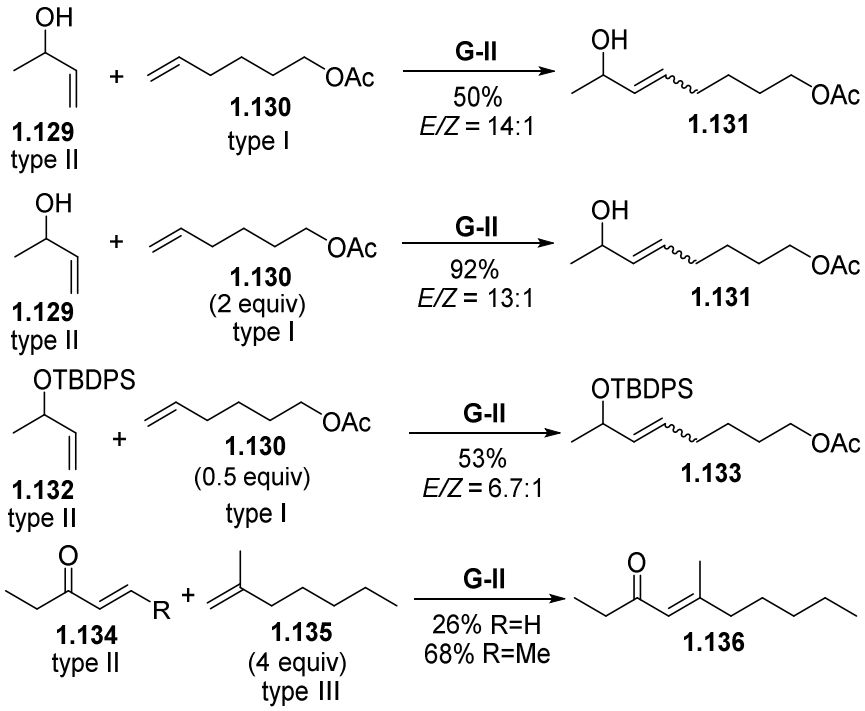
Entry	1.123:1.124 (Scheme 24)	CM product selectivity (1.125)
1	1:1	50%
2	2.1	66%
3	4:1	80%
4	10:1	91%
5	20:1	95%

Table 1.2: Statistical distribution of CM products

Reaction between two type I or type two olefins results in statistical CM mixtures. Selectivity is thus achieved when reacting two different types of olefins.

Examples of cross metathesis reactions between different types of olefins are shown in Scheme 1.25. Cross-metathesis reactions between type I and type II olefins such as **1.130** and **1.129** respectively are in most cases diastereoselective and high yielding. Worth mentioning is that when a bulky silyl protecting group is present such as the one in **1.132**, the selectivity and yield are reduced. To drive the reaction to completion, usually the type II olefin is used in excess; this is because the type I homodimers formed are reactive leading

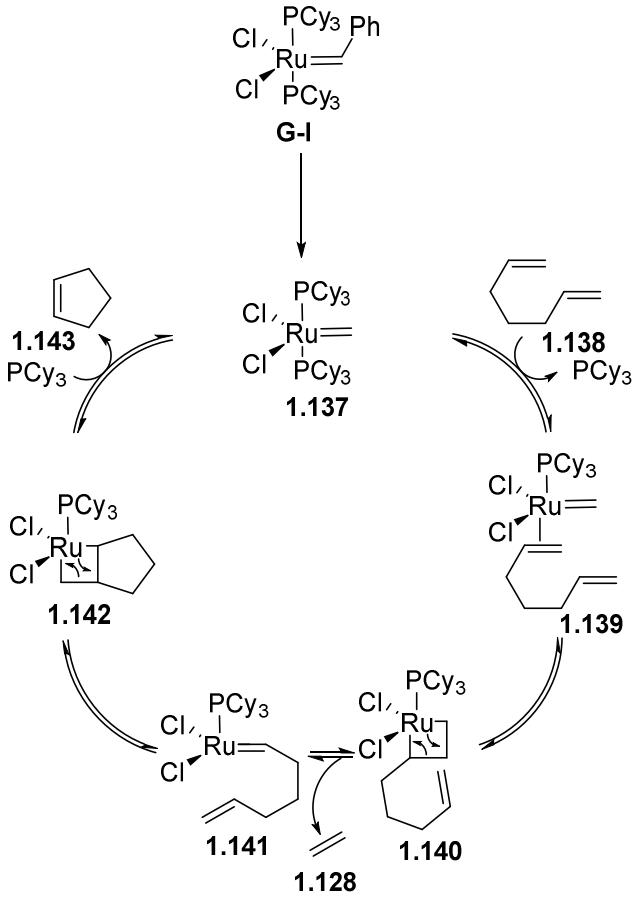
to secondary metathesis reactions to take place. Running the reaction under reduced pressure in this case also shifts the reaction forward because in most cases the driving force of olefin metathesis is the release of ethylene. Reaction between enone **1.134** and trisubstituted alkene **1.135** is a good example of the importance of the relative rates of homodimerization of type II olefins. Even when using an excess of **1.135** (type III), the rate of homodimerization of **1.134** competes with the formation of the desired product, especially as type II homodimers do not participate in secondary metathesis. When R=Me however, homodimerization is slower, resulting in higher selectivity in favour of the desired CM product. Another way to combat this issue is by slow addition of the type II olefin, thus maintaining a low concentration of type II olefin therefore minimising the amount of dimerisation.



Scheme 1.25: Examples of cross metathesis reactions

1.3.2 Ring-closing metathesis

The formation of cyclopentene **1.143** from 1,6-heptadiene **1.138** using a **G-I** catalyst is illustrated in Scheme 1.26 as an example to explain the mechanism of RCM.



Scheme 1.26: Mechanism of the RCM reaction

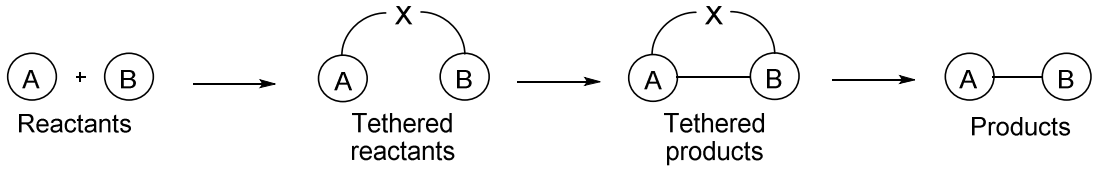
Transformation of **G-I** in to the catalytic species **1.137** is the first step of the reaction. Dissociation of the phosphine ligand leads to the formation of a 14 electron carbene species, which then coordinates to the olefin generating the 16 electron species **1.139**. [2+2] cycloaddition then gives metallocyclobutane intermediate **1.140**, which after the release of ethylene gives alkylidene **1.141**. Finally, another [2+2] cycloaddition produces intermediate **1.142** that undergoes cycloreversion forming cyclopentene **1.143** and regenerating the methylidene active species **1.137**

1.3.3 Use of silicon tether in RCM for the synthesis of trisubstituted olefins

Intermolecular cross-metathesis reactions are generally found to give low reactivity and/or selectivity compared to intramolecular RCM reactions. Thus, one way to reduce this problem is to change the transformation from being intermolecular to intramolecular by installing temporary tethers (Scheme 1.27). This would place functional groups that need to react in closer proximity, thus decreasing entropic demand and more often allowing for milder reaction conditions and more facile reactions.[31] Ideally the tethers should be easily

[31] Cusak, A. *Chem. Eur. J.* **2012**, *18*, 5800.

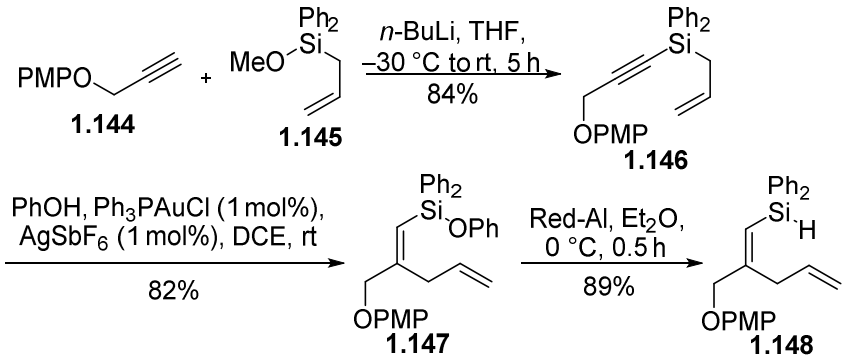
introduced and removed and stable under the reaction conditions. Usually elements such as silicon, phosphorous, sulfur, boron, zinc, aluminium and magnesium are part of the tethers.



Scheme 1.27: Temporary tether representation. Where X = Si, P, S, B, Al, Mg, Zn

Using temporary silicon tethers in combination with cross metathesis favours the formation of *Z*-olefins by adding a ring strain in the product. Moreover, increasing the size of geminal alkyl substitution on silicon leads to bond angle distortion in which the angle between the substituents containing reactive alkenes decreases. This facilitates the cyclisation of tethered alkenes and is also known as the Thorpe-Ingold effect. There are two types of silicon tethers that are most commonly used: the O-Si-O tether and the O-Si-C; this project will focus on the latter.

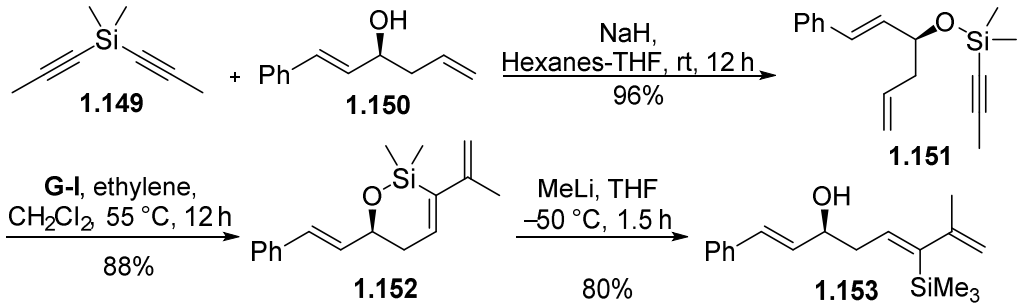
An example of the use of silicon-tether RCM in natural product synthesis can be found in Lee and Volchkov total synthesis of (-)-amphidinolide V (Schemes 1.28, 1.29 and 1.30).[32]



Scheme 1.28: Synthesis of hydrosilane **1.148**

Initially the hydrosilane fragment **1.148** was prepared from alkyne **1.144**, (Scheme 1.28) which was coupled with silane **1.145** to form alkynylsilane **1.146** in 84% yield. Intramolecular allylation using a gold catalyst in the presence of phenol provided phenoxysilane **1.147** that was then reduced to the desired hydrosilane **1.148**.

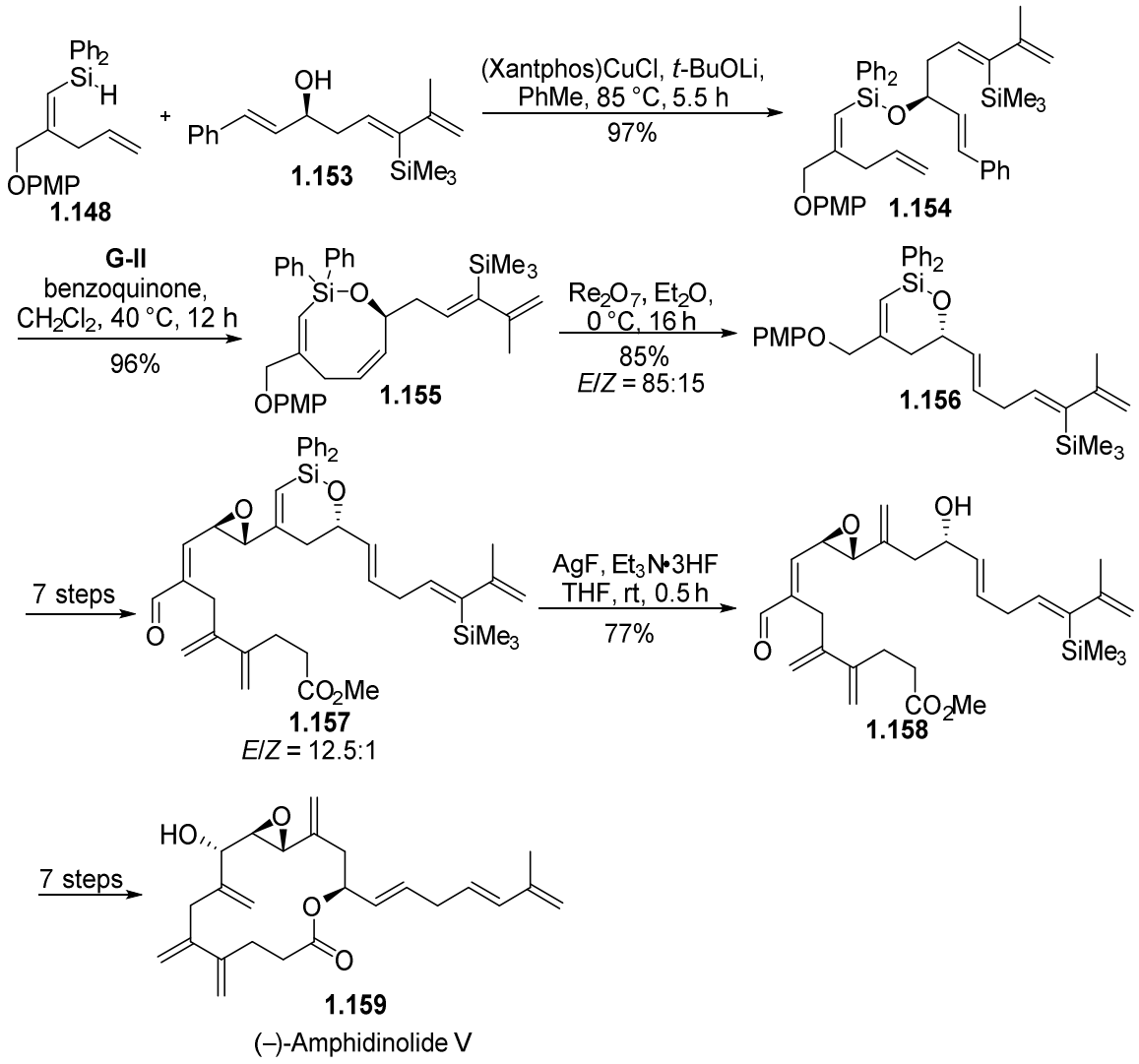
[32] Volchkov, I.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 5324.



Scheme 1.29: Synthesis of alcohol **210**

Synthesis of the alcohol partner **1.153** was achieved in 68% yield over 3 steps from **1.149** and **1.150** (Scheme 1.29) in the following order of steps: Coupling of silane **1.149** and alcohol **1.150** by silane alcoholysis, silicon-tether enyne RCM to form silacycle **1.152** and ring opening using MeLi, thus furnishing allylic alcohol **1.153**.

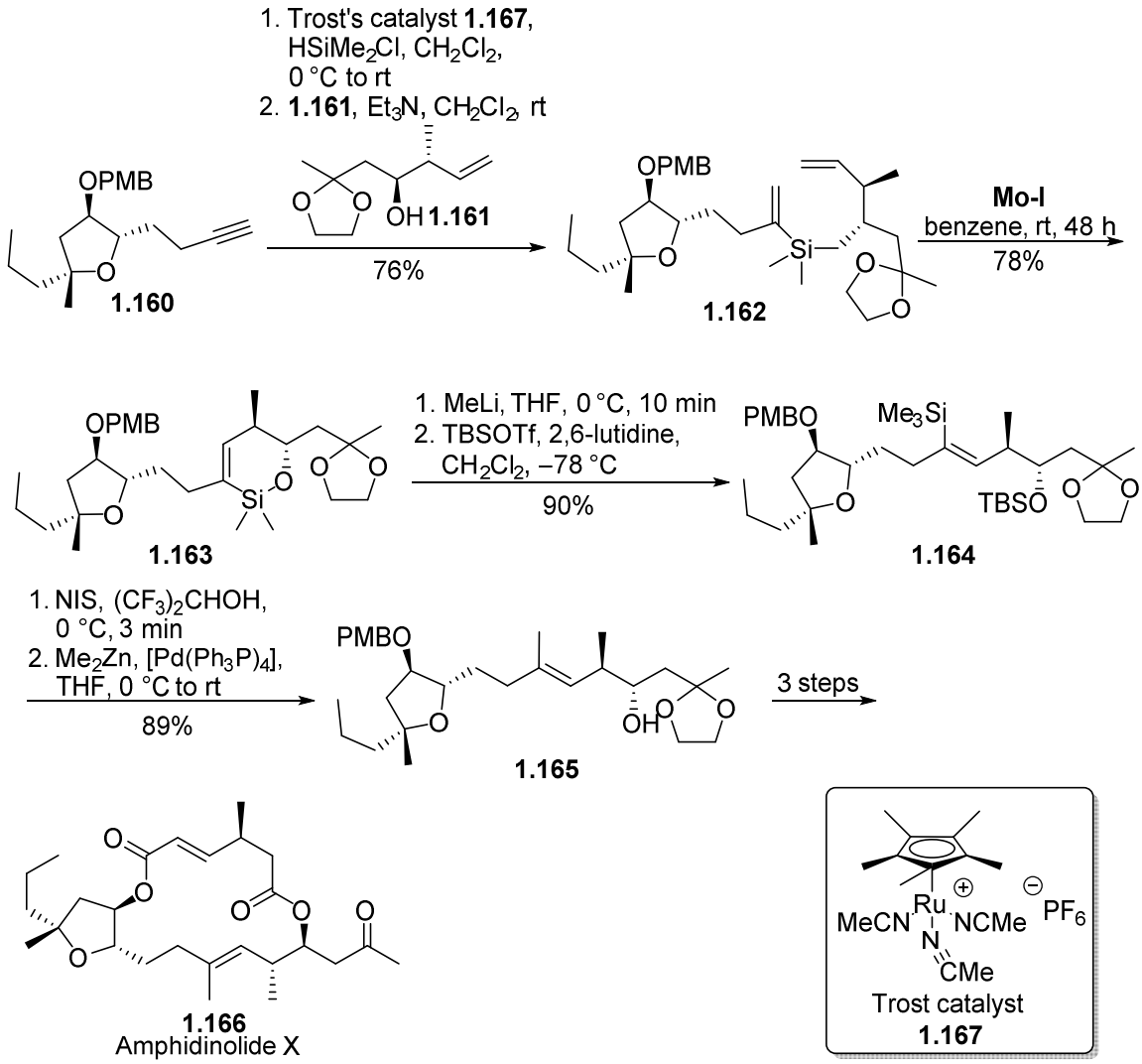
The coupling of the two fragments **1.148** and **1.153** to obtain **1.154** was achieved employing a silane dehydrogenative coupling in excellent yield (Scheme 1.30). Cyclisation to form **1.155** then took place by silicon-tether RCM using **G-II** catalyst in the presence of benzoquinone. Eight-membered ring **1.155** was then converted to six-membered ring **1.156** using rhenium oxide via a 1,3 allylic transposition reaction, thus giving **1.156** in 85% yield as a 85:15 *E/Z* mixture of diastereomers. Further chemical transformations gave silacycle **1.157** that underwent selective desilylation using Et_3N•3HF and AgF. Completion of the synthesis of (-)-amphidinolide V **1.159** was then accomplished through 7 further steps.



Scheme 1.30: Synthesis of (-)-amphidinolide V **1.159**

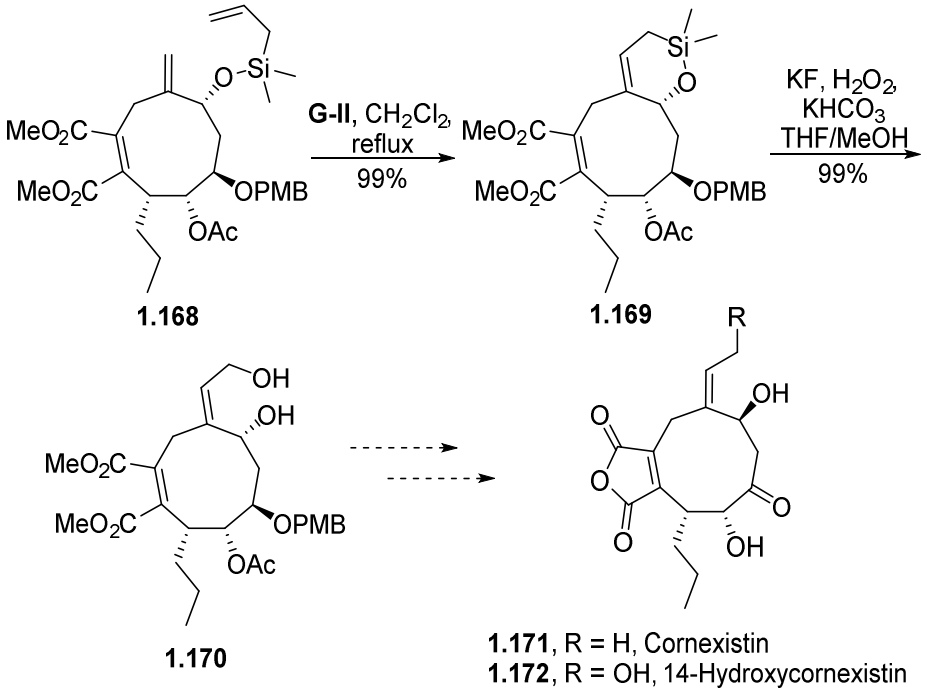
Vilarrasa *et al.* used a O-Si-C tether RCM strategy to install a trisubstituted olefin and complete their total synthesis of amphidinolide X **1.166** (Scheme 1.31).[33] The terminal alkyne in **1.160** was hydrosilylated with dimethychlorosilane using Trost's catalyst **1.167** and the resulting chlorosilane was coupled to alcohol **1.161** *in situ* to form **1.162**. RCM of the diene **1.162** using Schrock's catalyst **Mo-I** furnished **1.163** in 78% yield. For cleavage of the tether, the silacycle was treated with MeLi, which opened the ring, followed by TBS protection of secondary alcohol. The trimethylsilyl group was then subjected to iododesilylation using *N*-iodosuccinimide and methylation with dimethyl zinc to form **1.165** in 89% yield over 4 steps. Additional steps allowed the completion of the synthesis of amphidinolide X **1.166**.

[33] Rodriguez-Escrich, C.; Urpi, F.; Vilarrasa, J. *J. Org. Lett.* **2008**, *10*, 5191



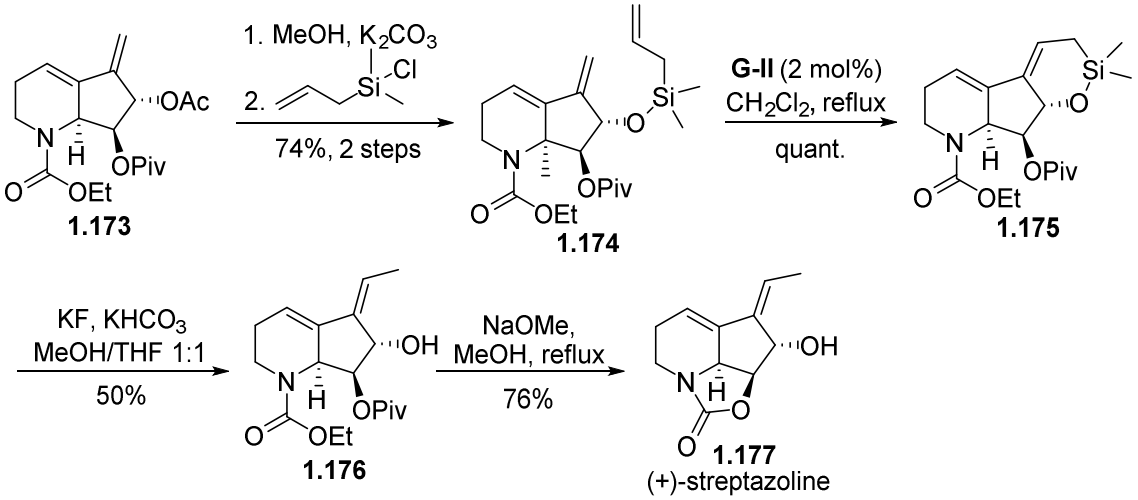
Scheme 1.31: Synthesis of Amphidinolide X **1.166** using silicon tethered RCM.

Cornexistin **1.171** bears an allylic alcohol in its structure, a motif also found in dolabelides (Scheme 1.32). In 2007 Taylor *et al.* employed a silicon-tether RCM strategy in their synthesis towards cornexistin **1.171** and its analogue **1.172**. Oxasilane **1.168** was subjected to RCM using **G-II** catalyst giving **1.169** in almost quantitative yield and the tether was removed using a Flemming-Tamao oxidation in excellent yield.



Scheme 1.32: Synthesis of 14-Hydroxycornexistin intermediate **1.170**

Another example of the use of silicon-tether RCM to synthesise trisubstituted alkenes would be by Miller and Li, who employed it for the total synthesis of (+)-straptazolin **1.177** (Scheme 1.33).[34] Removal of acetyl group in **1.173** followed by coupling with allyldimethylchlorosilane gave the silicon tethered RCM precursor **1.174** in 74% over two steps. The RCM reaction of diene **1.174** using **G-II** catalyst provided **1.175** in quantitative yield. After different attempts to remove the tether, they found that by using KF with $KHCO_3$ they could obtain compound **1.176** in 50% yield. Completion of the synthesis was achieved by removing the pivaloate group using NaOMe in MeOH with concomitant cyclisation, thus yielding **1.177**.

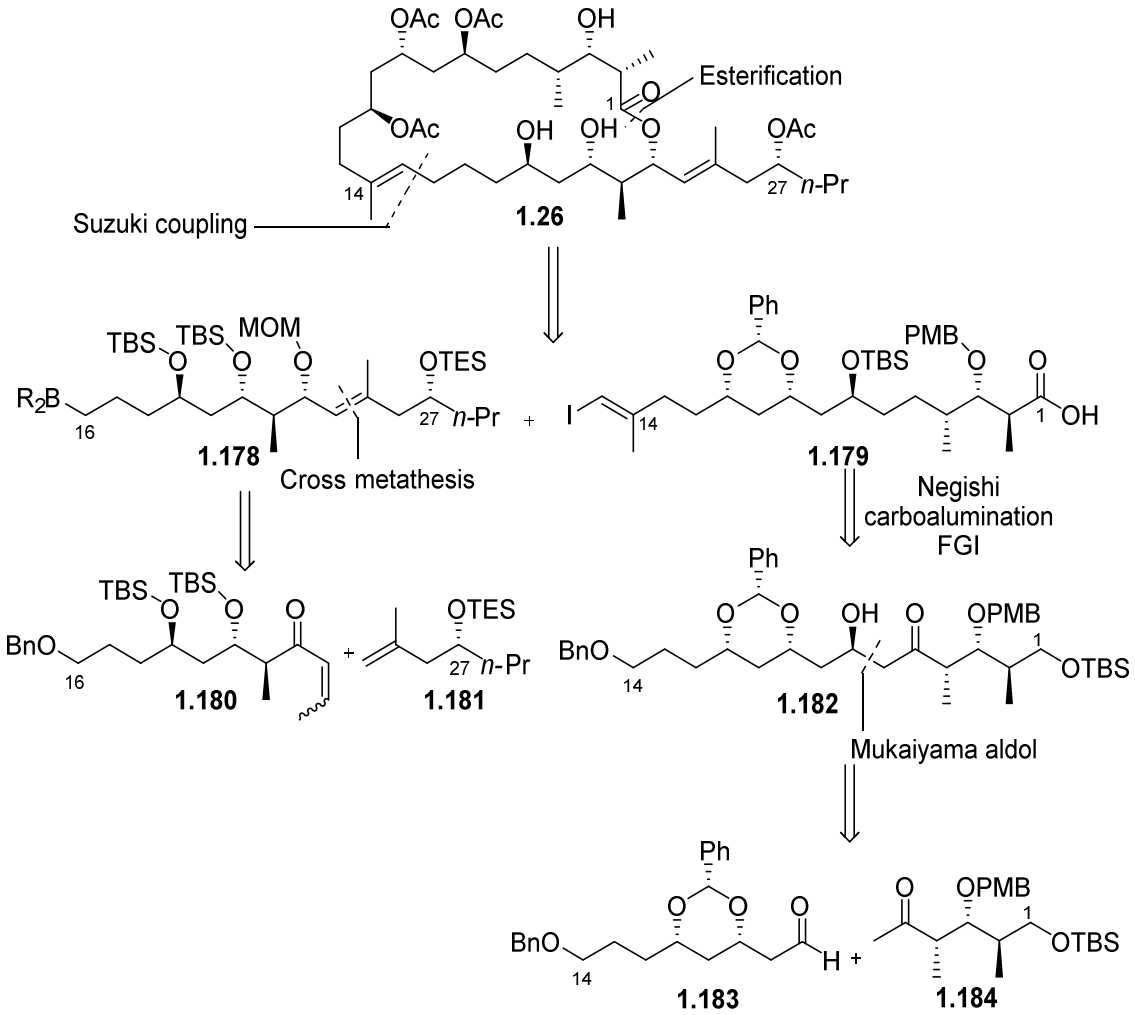


Scheme 1.33: Synthesis of (+)-straptazoline **1.177** using silicon tethered RCM.

[34] Li, F.; Miller, M. J. *J. Org. Chem.* **2006**, *71*, 5221

1.4 Previous work in the Prunet group

The retrosynthesis of dolabelide C envisaged in the Prunet group is shown in Scheme 1.34. Disconnections at the C15-C16 and macrolactone bonds lead to two fragments: C1-C15 **1.179** and C16-C30 **1.178**. Vinyl iodide **1.179** could be synthesised by a Negishi carboalumination from the corresponding alkyne obtained from the homologation of **1.182**. Intermediate **1.182** could be formed by a Mukaiyama aldol reaction between aldehyde **1.183** and ketone **1.184**. The C16-C30 fragment **1.178** could be synthesised by cross metathesis between enone **1.180** and trisubstituted olefin **1.181**.



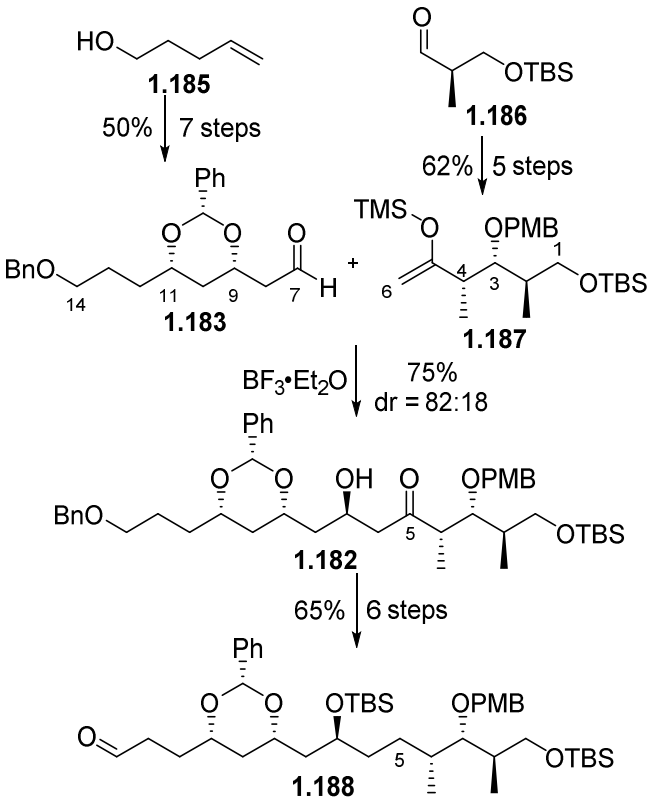
Scheme 1.34: Retrosynthesis of dolabelide C **1.26**

1.4.1 Synthesis of the C1-C15 fragment using a Mukaiyama aldol reaction

Aurélie Vincent previously synthesised an advanced intermediate **1.190** (Scheme 1.36) of the C1-C15 fragment.[35] The C7-C14 aldehyde **1.183** was synthesised in 7 steps and in 50%

[35] Vincent, A.; Prunet, J. *Synlett* **2006**, 2269.

yield from commercially available 4-penten-1-ol **1.185** (Scheme 1.35). The key steps were a Jacobsen kinetic resolution[36] to install the C11 stereocenter and a diastereoselective oxa-Michael addition[37] using benzaldehyde to install the *syn*-diol. The TMS-enol ether **1.187** was prepared in 5 steps from known aldehyde **1.186** with the C3 and C4 stereocentres being introduced using an Evans auxiliary. The coupling of the two fragments was achieved by a Mukaiyama aldol in 75% yield and with a diastereomeric ratio of 82:18. Aldehyde **1.188** was then prepared in 6 steps and in 65% yield; this involved a Barton-McCombie deoxygenation to remove the ketone at C5 that is present in intermediate **1.182** but not in dolabelides.



Scheme 1.35: Synthesis of aldehyde **117**

The alkyne precursor **1.190** was prepared by a Seyferth-Gilbert homologation[38] in good yield using the Bestmann-Ohira reagent **1.189**[39] and aldehyde **1.188**. However, attempting to install the required vinyl iodide by a Negishi carboalumination led to decomposition (Scheme 1.36).

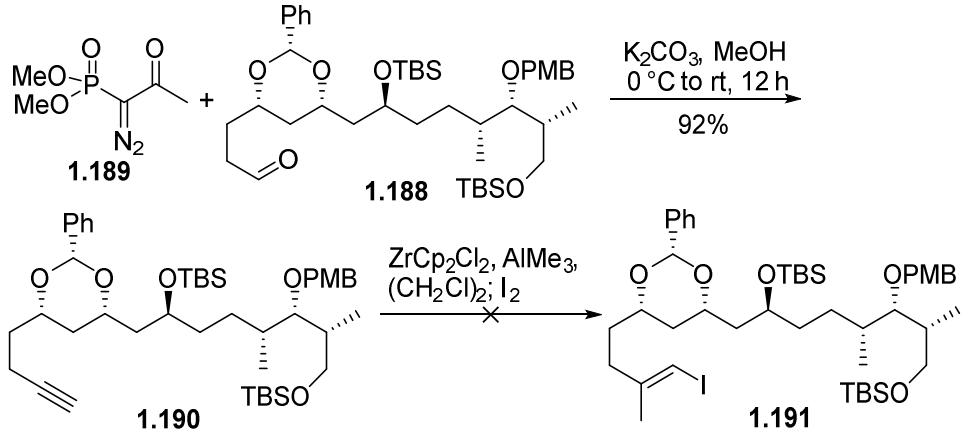
---

[36] (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (d) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

[37] Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

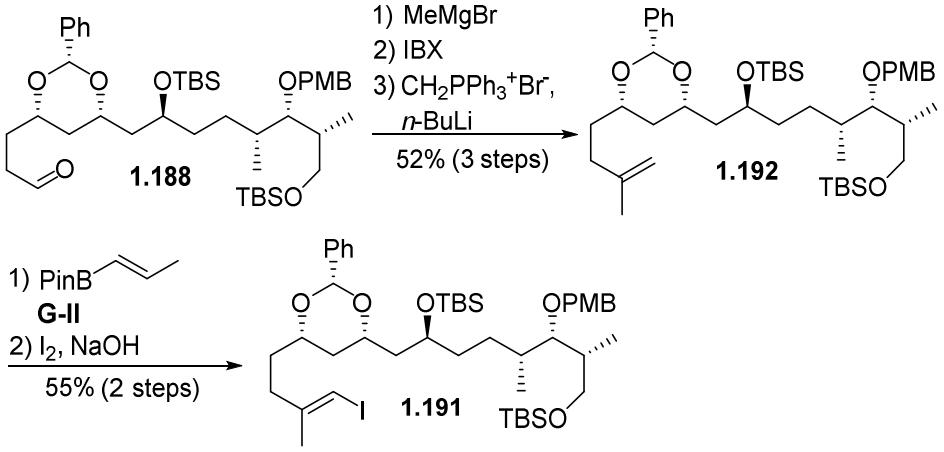
[38] Gilbert, J. C.; Weerasooriya U. *J. Org. Chem.*, **1982**, *47*, 1837.

[39] (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett*, **1996**, 521. (b) Ohira, S. *Synth. Commun.*, **1989**, *19*, 561.



Scheme 1.36: Failed attempt to synthesise vinyl iodide **1.191**

The end game of Aurélie Vincent's synthesis (Scheme 1.37) involved the formation of alkene **1.192** using the following sequence of steps: Methyl Grignard addition to aldehyde **1.188**, oxidation of the resulting secondary alcohol using IBX and Wittig olefination of the obtained ketone with methyltriphenylphosphonium bromide. Cross metathesis of **1.192** with *trans*-crotylboronic acid pinacol ester followed by boron-iodine exchange furnished the C1-C15 protected fragment of dolabelide C **1.191** in 55% yield for the two steps.



Scheme 1.37: Successful attempt to synthesise vinyl iodide **1.191**

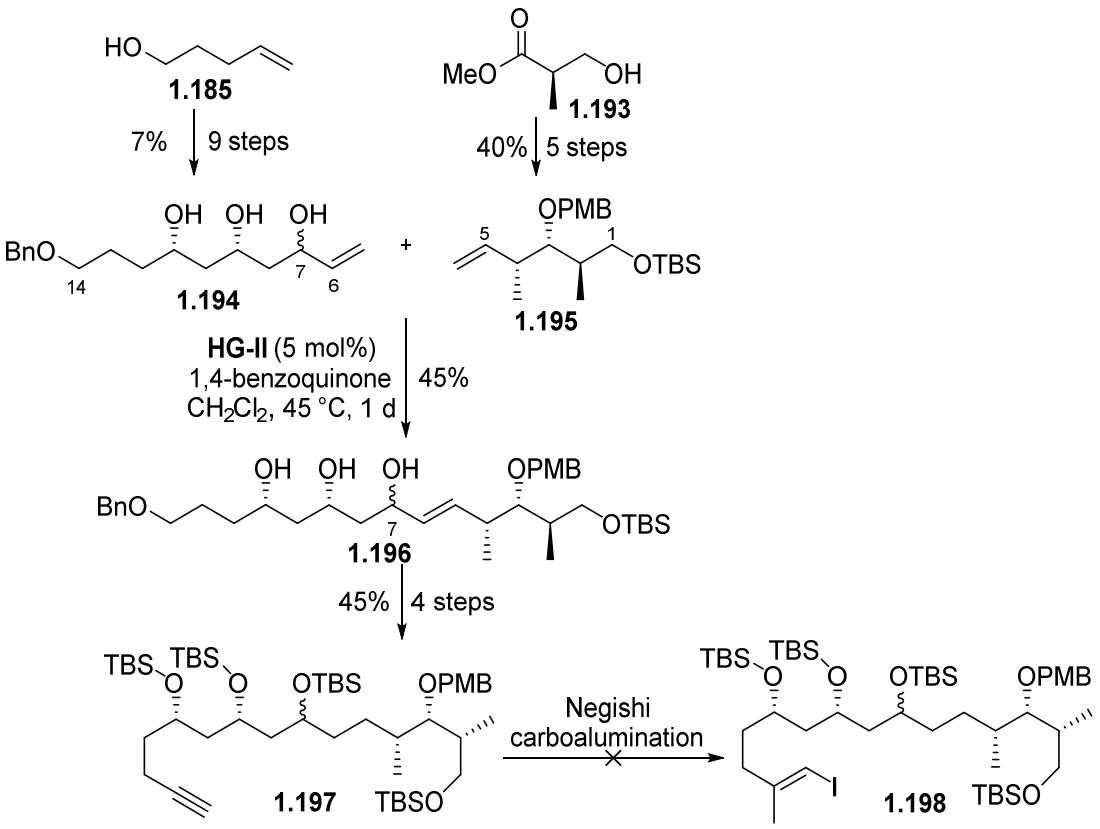
Overall, Aurélie Vincent synthesised the C1-C15 protected fragment of dolabelide C **1.191** in 19 steps and 7% yield from 4-penten-1-ol.

1.4.2 Synthetic efforts towards the C1-C15 fragment using cross metathesis

A more recent route for the synthesis of an advanced intermediate of the C1-C15 fragment **1.197** by Stéphane Wittmann[40] that involves the coupling of the C6-C14 **1.194** with the C1-C5 **1.195** segment by cross metathesis is described in scheme 1.38. This route avoided the

[40] Wittmann, S. PhD Thesis, University of Glasgow, **2015**.

extra steps of removing the ketone present in **1.182**; however, a drawback is that the stereocentre at C7 was not set, thus a mixture of diastereomers was carried through a large part of the synthesis.



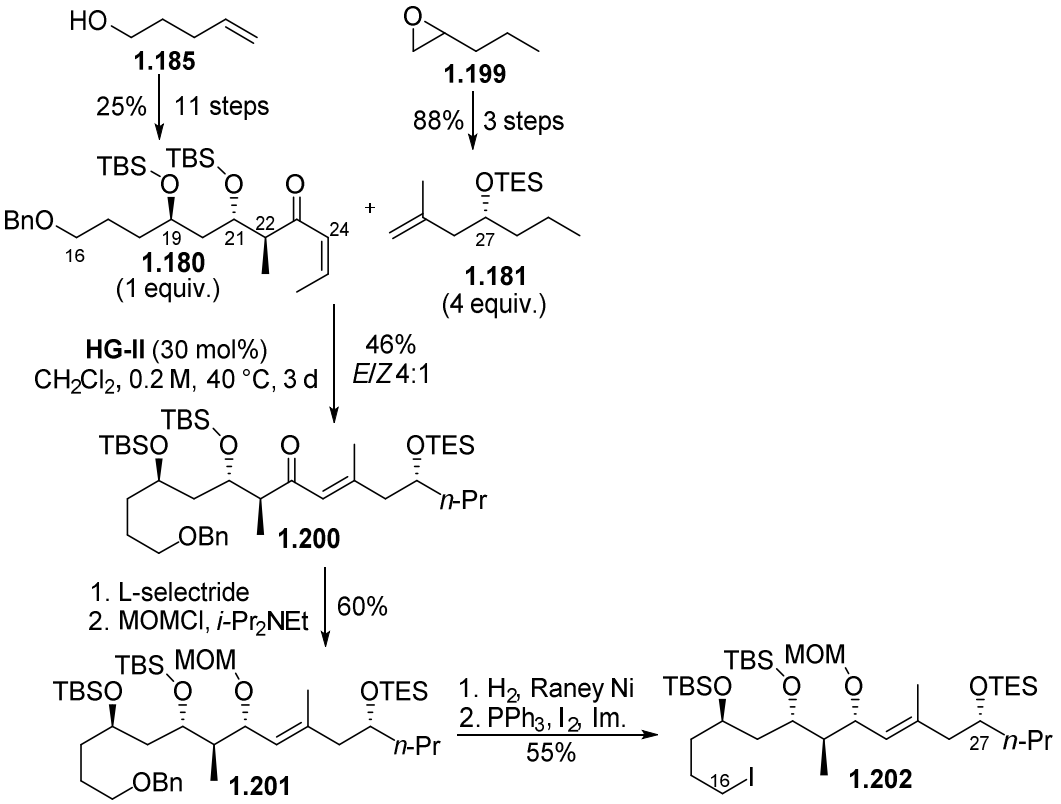
Scheme 1.38: Unsuccessful attempt to synthesise vinyl iodide **1.198**

Starting from the same starting materials as in the previous synthesis, alcohol **1.185** was converted to triol **1.194** over 9 steps in 7% yield whereas Roche ester **1.193** was converted to alkene **1.195** over 5 steps in 40% yield. Coupling of the two fragments using 5 mol% of **HG-II** catalyst as well as 1,4-benzoquinone to prevent double bond isomerisation gave the desired allylic alcohol **1.196** in 45% yield. Alkyne **1.197** was then obtained in 45% yield over 4 steps. Unfortunately, a couple of attempts to perform the Negishi carbolumination on small scale (14.0-18.0 mg, 16-20 µmol) were unsuccessful. In summary Stéphane Wittmann prepared advance intermediate **1.197** in 14 steps and 0.14% overall yield from alcohol **1.185**.

1.4.3 Synthesis of the C16-C30 fragment using cross metathesis

The first synthetic route leading to the C16-C30 fragment **1.202** in the group is summarised in scheme 1.39.[41]

[41] Braun, M.-G.; Vincent, A.; Boumediene, M.; Prunet, J. *J. Org. Chem.* **2011**, *76*, 4921



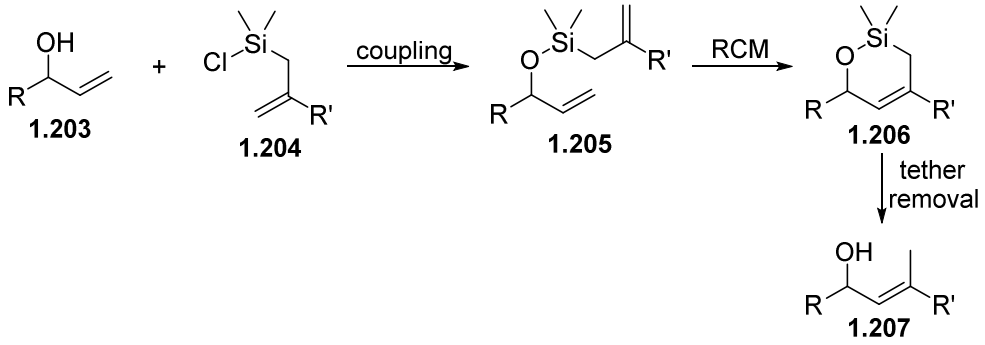
Scheme 1.39: First approach for the synthesis of the C16-C30 fragment

Similarly, to the C1-C15 fragment **1.191**, the synthesis of the C16-C30 fragment **1.202** started from 4-penten-1-ol **1.185**, which was transformed into enone **1.180** over 11 steps in 25% yield (Scheme 1.39). The key steps include a Jacobsen kinetic resolution to install the C19 stereocentre as well as a Duthalder crotylation[42] to set the C21 and C22 stereocentres in one step. Trisubstituted olefin **1.181** was prepared from commercially available epoxide **1.199** in 88% yield over 3 steps, the C27 stereocenter being installed once again using a Jacobsen kinetic resolution. Coupling of the two fragments was achieved by cross metathesis giving **1.200** in 46% yield after separation of the undesired minor *Z*-isomer. Diastereoselective reduction of enone **1.200** using L-selectride was followed by protection of the formed alcohol as a methoxymethyl ether giving **1.201** as a single diastereomer in 60% yield over two steps. Finally, deprotection of the benzyl ether prior to iodination of the resulting alcohol furnished **1.202**, in 3.8% overall yield over 16 steps from **1.185**.

[42] Hafner, A.; Duthaler, R. O.; Marti, R.; Rhis, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321

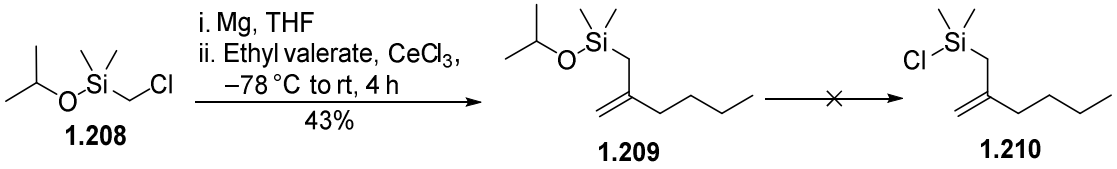
1.4.4 Work in the group on the O-Si-C tether RCM methodology for the synthesis of *E*-configured trisubstituted olefins

Initial investigation to prepare *E*-configured trisubstituted olefins selectively, such as the one present at the C24-C25 position in dolabelide C, via O-Si-C ring-closing metathesis in the group was done by Mehdi Boumediene.[43] The construction of the silicon tether was sought by coupling an allylic alcohol **1.203** with an allyl chlorosilane **1.204** to form a diene RCM precursor **1.205** that would then undergo RCM followed by silicon tether removal to give *E*-alkene **1.207**. (Scheme 1.40)



Scheme 1.40: Silicon-tether RCM strategy to prepare *E*-alkene **1.207**

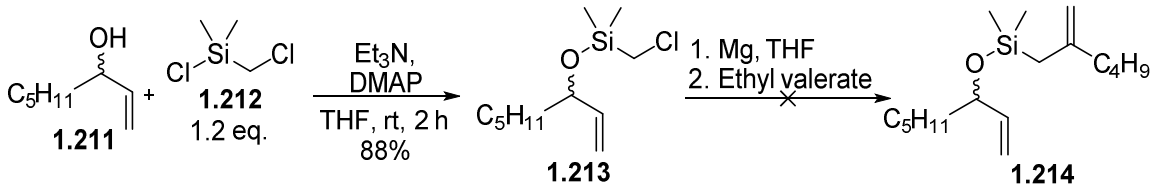
The first approach commenced from chlorosilane **1.208** and ethyl valerate that were transformed into alkoxysilane **1.209** *via* a Peterson olefination reaction in 43% yield (Scheme 1.41). Various conditions were tested for the chlorination of alkoxysilane **1.209**, unfortunately with no success.



Scheme 1.41: Unsuccessful attempt to prepare chlorosilane **1.210**

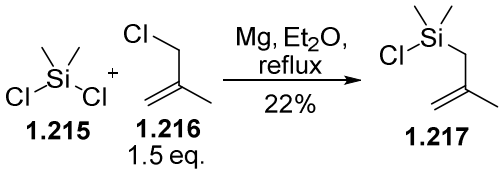
Another route (Scheme 1.42) in which alkoxysilane **1.213** was prepared by coupling allylic alcohol **1.211** and chlorosilane **1.212** prior to the Peterson olefination reaction was investigated. Disappointingly the Peterson olefination reaction to form diene **1.214** using chlorosilane **1.213** and ethyl valerate failed.

[43] Boumediene, M., Master thesis, Ecole Polytechnique **2007**



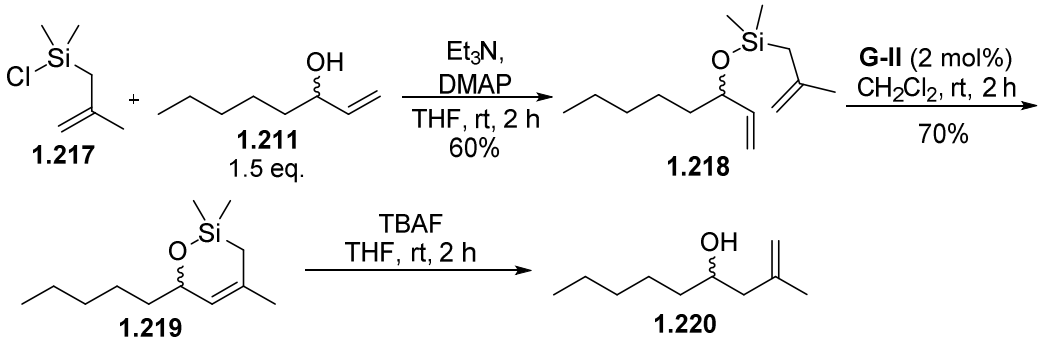
Scheme 1.42: Attempt to synthesise diene **1.214**

Mehdi Boumediene's last and most promising approach started with a Grignard reaction between silane **1.215** and allyl chloride **1.216** to form the desired chlorosilane **1.217** in 22% yield (Scheme 1.43).[44]



Scheme 1.43: synthesis of allyl chlorosilane **1.217**.

Chlorosilane **1.217** was then coupled with allylic alcohol **1.211** to form alkoxysilane **1.218** in 60% yield (Scheme 1.44). Diene **1.218** was then subjected to RCM using **G-II** catalyst forming six-membered heterocycle **1.219** in moderate yield. The last step to remove the silicon tether using TBAF in THF, however, led to the isomerized alkene **1.220**.

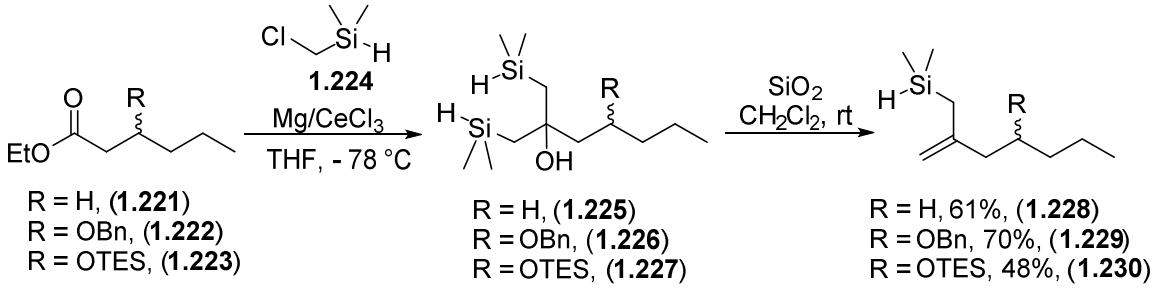


Scheme 1.44: Silicon tether formation, RCM and tether cleavage

Stéphane Wittmann[40] also attempted to prepare the required allyl chlorosilanes but after many failed attempts to come up with a reliable route he started investigating a different approach by preparing allyl hydrosilanes instead. Using a modified Peterson olefination, allyl silanes **1.228**, **1.229** and **1.230** were prepared in reasonable yields starting from chloromethylsilane **1.224** (Scheme 1.45). *In situ* preparation of the organocerium reagent derived from **1.224** was followed by treatment with various esters (**1.221**, **1.222** and **1.223**) producing tertiary alcohol intermediates **1.225**, **1.226** and **1.227**. Stirring these

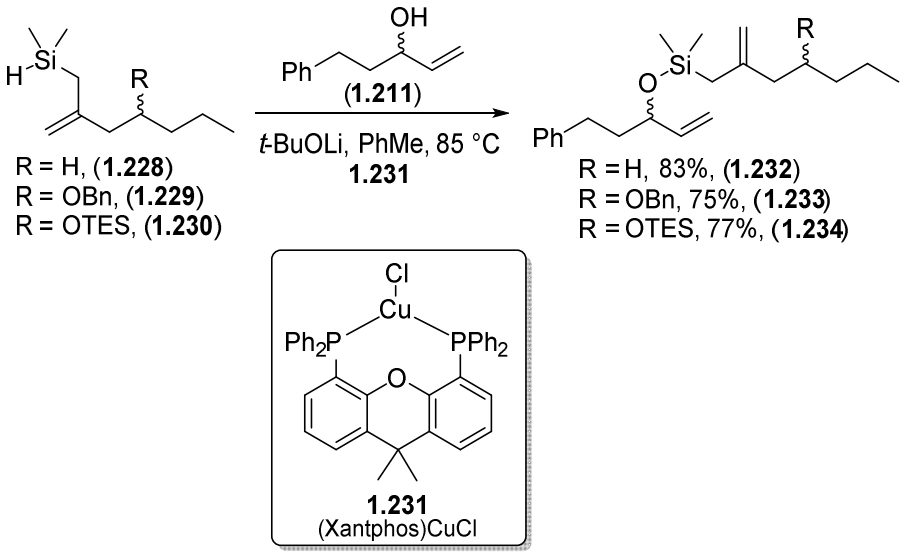
[44] Fürstner, A.; Voigtländer, D. *Synthesis* **2000**, 7, 959.

intermediates in a slurry of silica in CH_2Cl_2 caused elimination of the β-hydroxysilanes, thus furnishing the desired allyl silanes **1.228**, **1.229** and **1.230**.



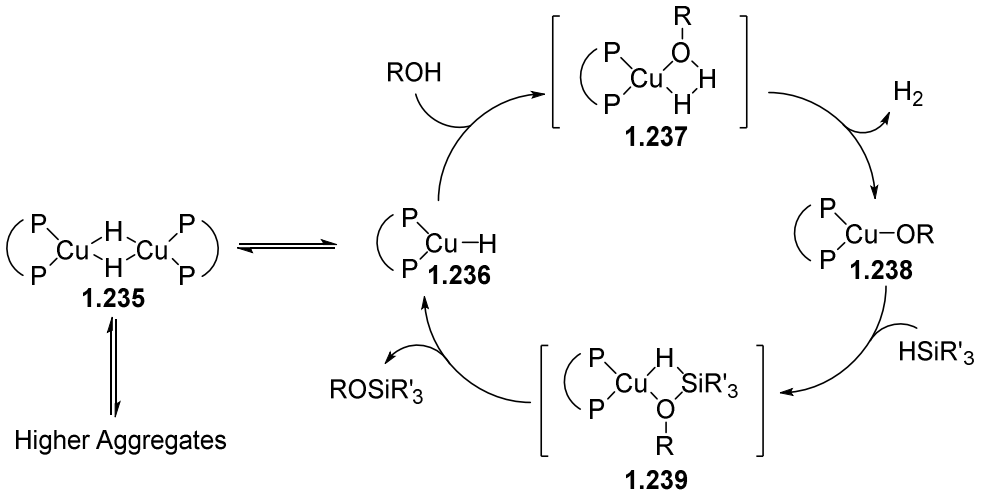
Scheme 1.45: Novel Peterson olefinations for the preparation of allyl hydrosilanes

Inspired from the strategy used by Lee and Volchkov in their total synthesis of (-)-amphidinolide V,[32] alkoxysilanes were then constructed (Scheme 1.46) *via* a copper catalyzed silane dehydrogenative coupling (Scheme 1.47) between allylic alcohol **1.211** and the hydrosilanes prepared earlier. (Scheme 1.45)



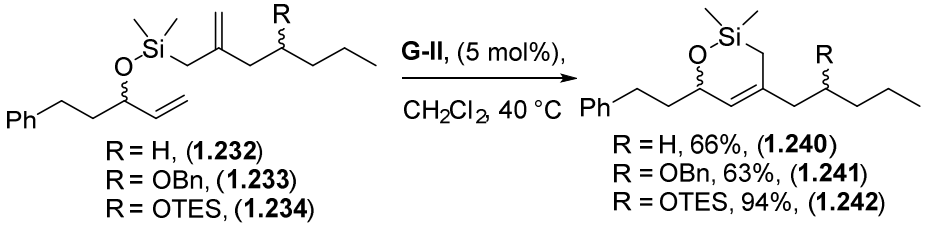
Scheme 1.46: Preparation of alkoxysilanes using a dehydrogenative coupling reaction

In Scheme 1.47 the mechanism of the silane dehydrogenative coupling reaction is presented. The active species is the copper (I) hydride **1.236**, which is generated when mixing *t*-BuOLi with (Xanthphos)CuCl and the hydrosilane. This copper (I) hydride species **1.236** is in equilibrium with it's dimer **1.235** and higher aggregates. The alcohol then reacts with **1.236** *via* σ-bond metathesis releasing hydrogen and resulting in the formation of alkoxycopper species **1.238**. Hydrosilane then reacts with **1.238** through another σ-bond metathesis reaction, thus furnishing the coupled alkoxysilane as well as regenerating the active species **1.236**.



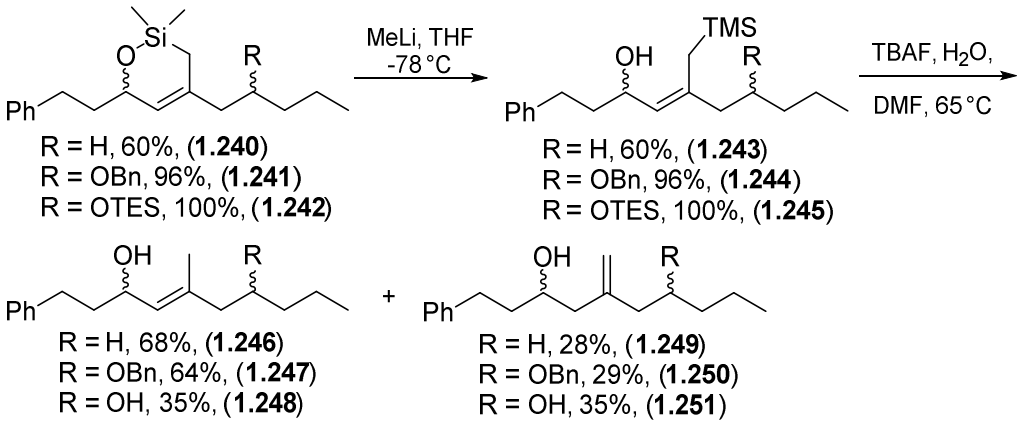
Scheme 1.47: Mechanism of the copper catalysed silane dehydrogenative coupling reaction

The alkoxysilanes prepared earlier (Scheme 1.46) were then subjected to RCM conditions using **G-II** catalyst that lead to the formation of the six-membered silacycles **1.240**, **1.241** and **1.242** in moderate or good yields (Scheme 1.48).



Scheme 1.48: Silicon-tether RCM

Coming up with a successful one-step silicon-tether removal procedure was not possible, therefore, the six-membered silacycles were opened using MeLi furnishing allyl trimethylsilanes **1.243**-**1.245** (Scheme 1.49). After screening various acid and/or fluoride reagents, it was found that using 6 equiv TBAF (1M in THF), 6 equiv of H_2O in DMF at 65 °C gave the most encouraging results. The desired *E*-olefins **1.246**-**1.248** were thus obtained in acceptable yields along with the isomerised olefins **1.249**-**1.251** that were separable by column chromatography in most cases.



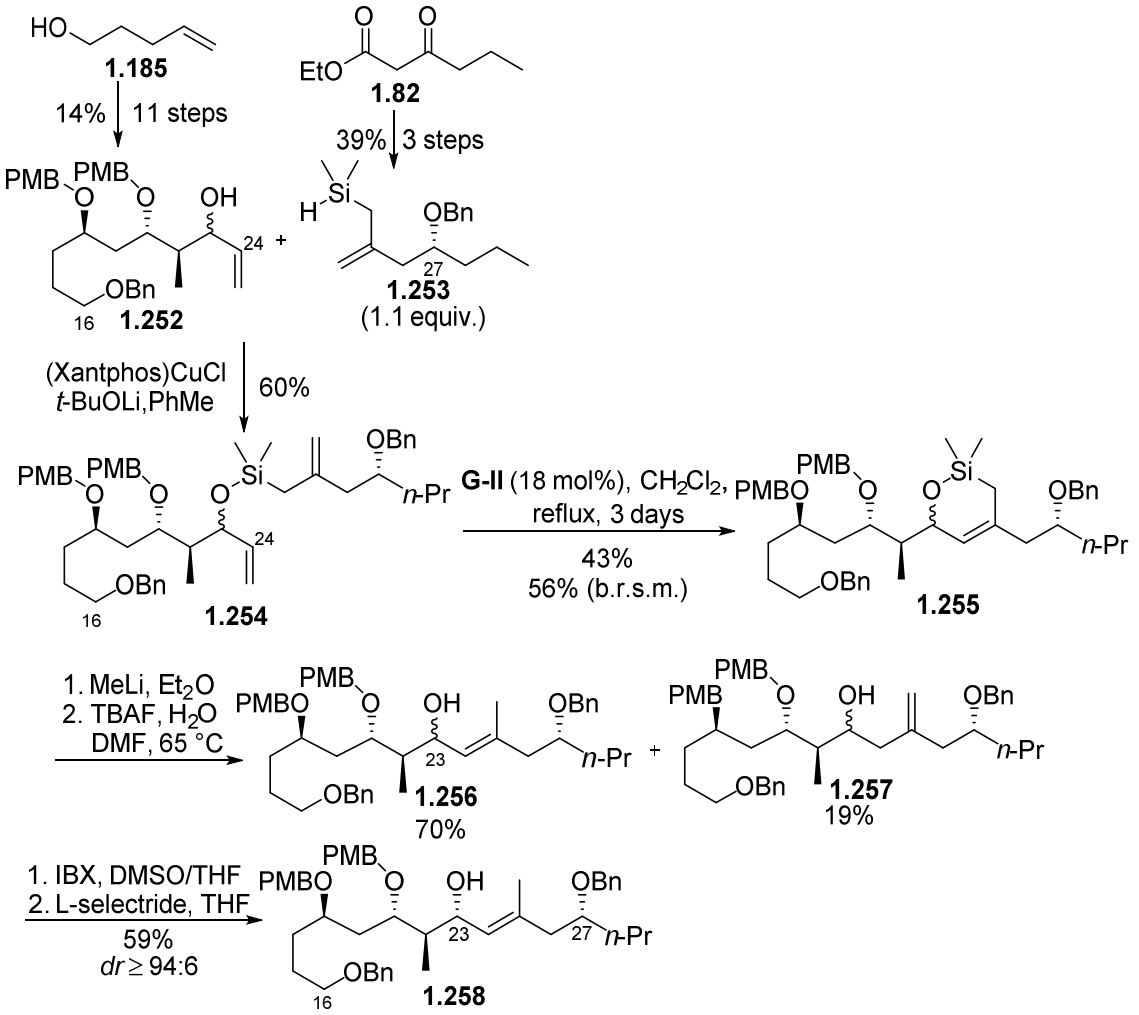
Scheme 1.49: Silicon tether cleavage

With the silicon-tether RCM methodology already developed and successfully applied in the synthesis of allylic trisubstituted olefin models, Alexandre Audic[45] later extended this sequence to homoallylic alcohols.

1.4.5 Synthesis of the C16-C30 fragment using the silicon tether RCM methodology

Stéphane Wittmann then applied the newly developed methodology for the preparation of the protected C16-C30 fragment (Scheme 1.50). Allylic alcohol **1.252** was synthesised from **1.185** in 14% yield over 11 steps whereas hydrosilane **1.253** was prepared from β-ketoester **1.82** over 3 steps in 39% yield. The two fragments were then coupled using a silane dehydrogenative coupling followed by RCM to provide silacycle **1.254** in 26% yield over 2 steps. Tether removal was achieved in two steps, first ring opening using MeLi and then desilylation using TBAF to give 70% yield of the desired product **1.256** as well as 19% of undesired isomer **1.257**. Oxidation of the alcohol at C23 followed by followed by diastereoselective reduction of the resulting ketone gave **1.258** in 59% yield and with a diastereomeric ratio greater than 94:6. To summarise, this route allowed the synthesis of the C16-C30 protected fragment **1.258** in 17 steps and in 1.5% overall yield.

[45] Audic, A. PhD Thesis, University of Glasgow, **2016**



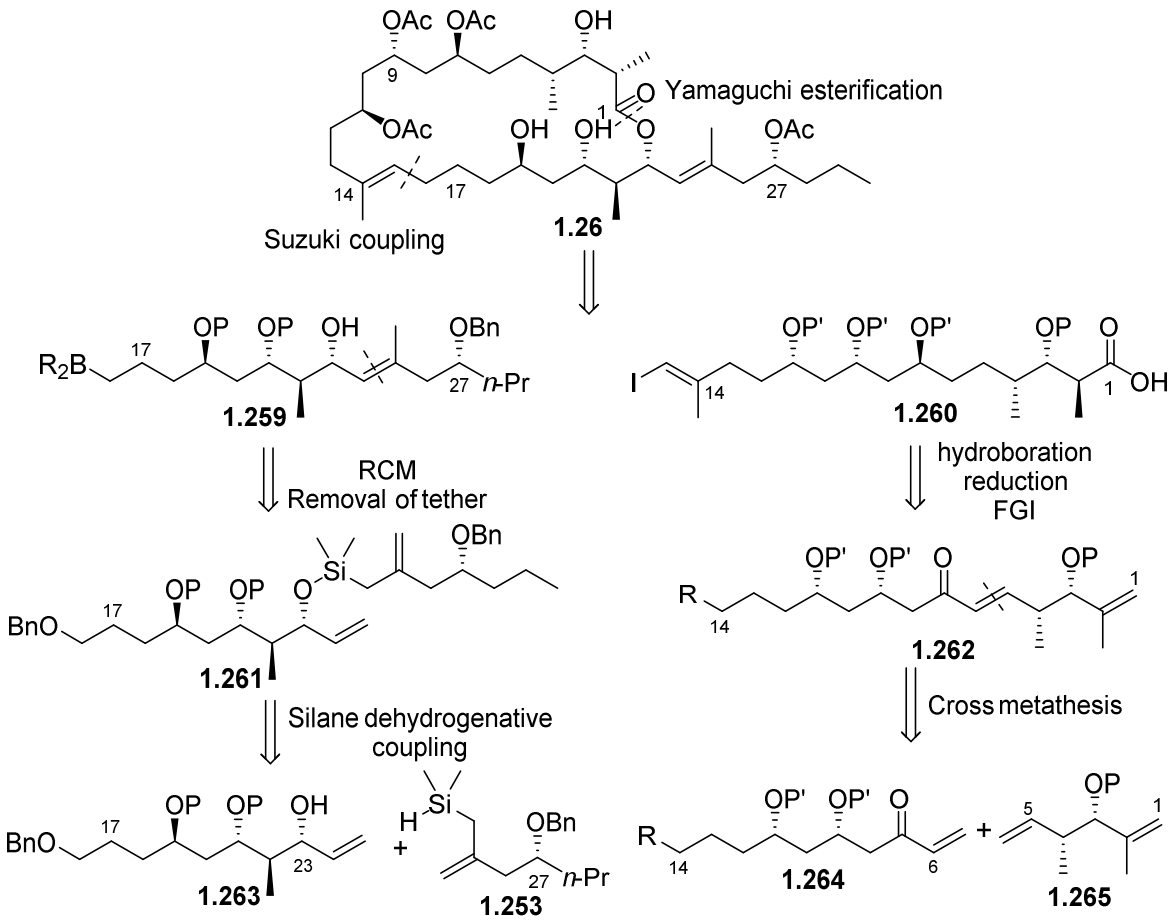
Scheme 1.50: Stéphane Wittmann's approach for the synthesis of the C16-C30 fragment

1.5 Project aims

A reliable synthetic route for the C16-C30 fragment that would allow the correct stereochemistry to be installed at the C23 position at an earlier stage of the synthesis as well as possibly shortening the synthesis was our primary objective. Furthermore, the low yielding silicon-tethered RCM and tether removal steps needed to be optimised.

The second objective would be the asymmetric synthesis of the C1-C15 fragment while also investigating a possible route to install the required vinyl iodide moiety at an earlier stage of the synthesis.

Our revised retrosynthetic analysis of dolabelide C **1.26** is depicted in the scheme below. (Scheme 1.51)



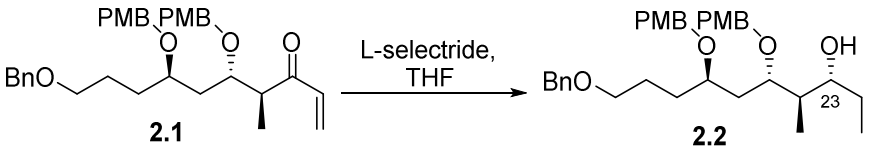
Scheme 1.51: Revised retrosynthesis of Dolabelide C

Following the footsteps of our predecessors, the synthesis envisaged involved the same disconnections to give two fragments the C1-C15 **1.260** and C16-C30 **1.259** which could be coupled by a Suzuki-Miyaura coupling followed by a Yamaguchi lactonisation. The key steps to arrive to the C16-C30 segment **1.259** of the natural product would involve the use of the newly developed methodology to install trisubstituted olefins *E*-selectivly by silicon-tethered ring-closing metathesis, thus coupling allylic alcohol **1.263** with silane **1.253**. The C1-C15 segment **1.260**, could be synthesised from diene **1.262**, which in turn would be prepared by the cross metathesis of enone **1.264** with homoallylic alcohol **1.265**.

Chapter 2: Synthesis of the C16-C30 fragment of dolabelide C

2.1 Background, objectives and retrosynthesis

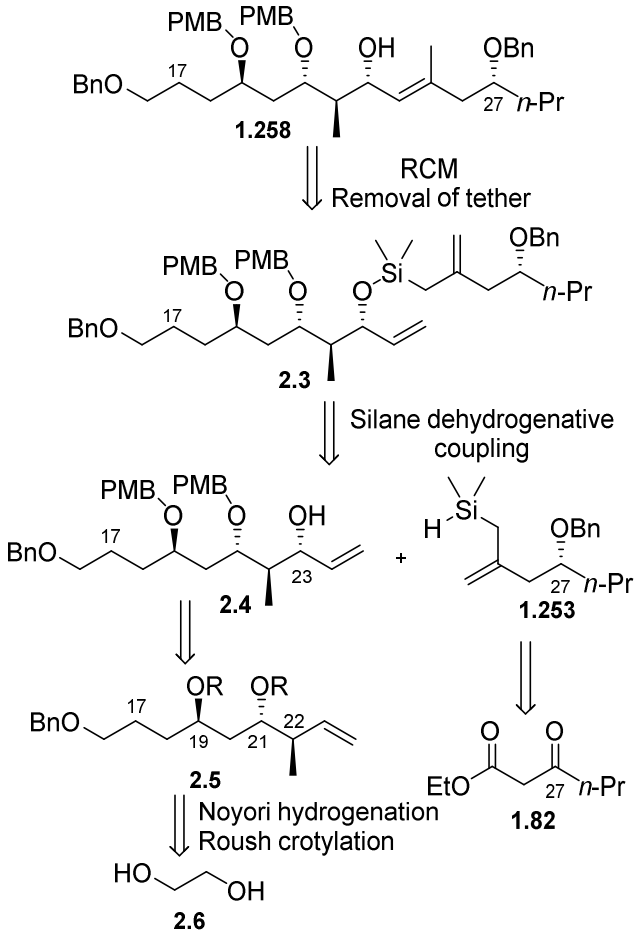
As discussed earlier (chapter 1.4.5) silicon-tether RCM methodology was applied for the synthesis of the C16-C30 fragment of dolabelide C previously in the group[40] however, this four-step sequence from allylic alcohol **1.252** to trisubstituted *E*-alkene **1.256** (Scheme 1.50) was not very high yielding. After the coupling of the fragment C16-C24 **1.252** and C25-C30 **1.253** segments, *E*-alkene **1.256** was isolated in just 18% yield. One of the biggest drawbacks was the low yield obtained in the RCM (43%, 56% b.r.s.m). This yield was slightly lower than the CM reaction of enone **1.180** with **1.181** previously employed to couple the two fragments (Scheme 1.39). Furthermore, the previous attempts within the group to set the correct stereochemistry at the C23 position at an earlier stage of the synthesis were unsuccessful due to the conjugate reduction of the enone (Scheme 2.1). As a result, a mixture of diastereomers was carried through several steps before oxidising/reducing the alcohol at C23 to obtain the correct stereochemistry.



Scheme 2.1: Undesired conjugate reduction of enone

Additionally, the starting material 4-pent-1-ol was pricey (≈ £ 70 for 10 g) and there was an inevitable loss of 50% of material from the HKR reaction on the third step of a multistep synthesis. Therefore, the synthesis of considerable amounts of allylic alcohol **2.4** (Scheme 2.2) as a single diastereomer, needed to optimize the route to the final target, was unfeasible. Development of a route to prepare this alcohol that would be affordable, reliable and could be conveniently carried out on large scale was therefore needed.

We thus envisaged a retrosynthesis for the C16-C30 fragment **1.258** (Scheme 2.2), which could be prepared from allylic alcohol **2.4** and silane **1.253** *via* oxasilane **2.3** using the silicon-tether RCM strategy. Diverse methods will be investigated for the diastereoselective synthesis of **2.4** from homoallylic alcohol **2.5**. The key steps for the new route to prepare **2.5** from ethylene glycol **2.6** were a Noyori asymmetric hydrogenation to install the C19 stereocentre and a Roush crotylation to set the correct stereochemistry at C21 and C22. Silane fragment **1.253** had been synthesised before in the group from β-ketoester **1.82** using a novel Peterson olefination.[40]

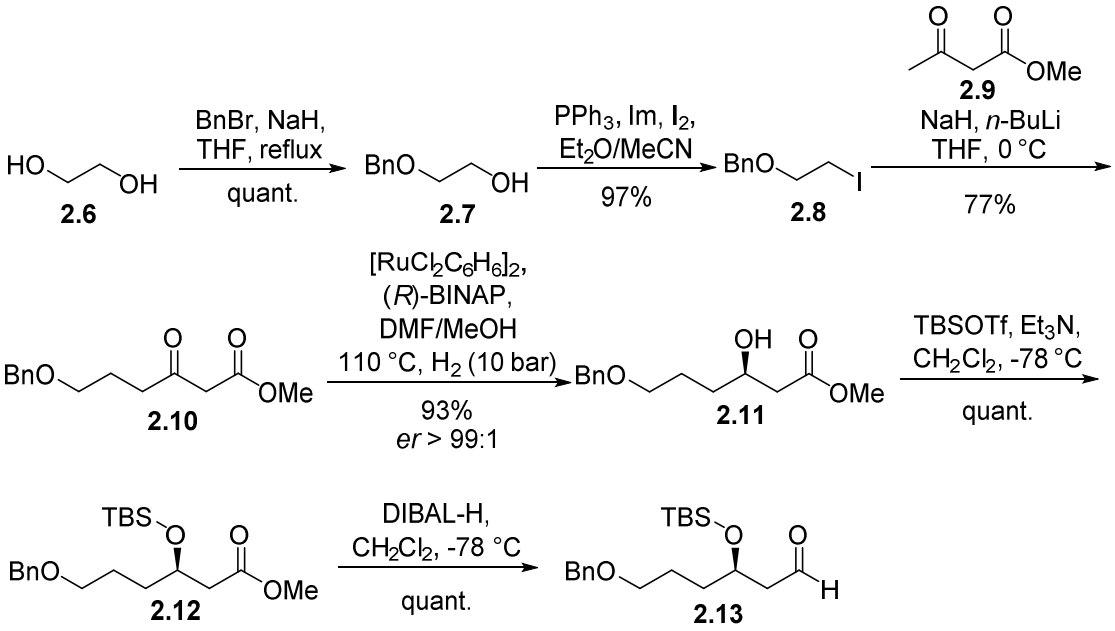


Scheme 2.2: Retrosynthesis of the C16-C30 fragment **1.258**

2.2 Synthesis of homoallylic alcohol intermediate

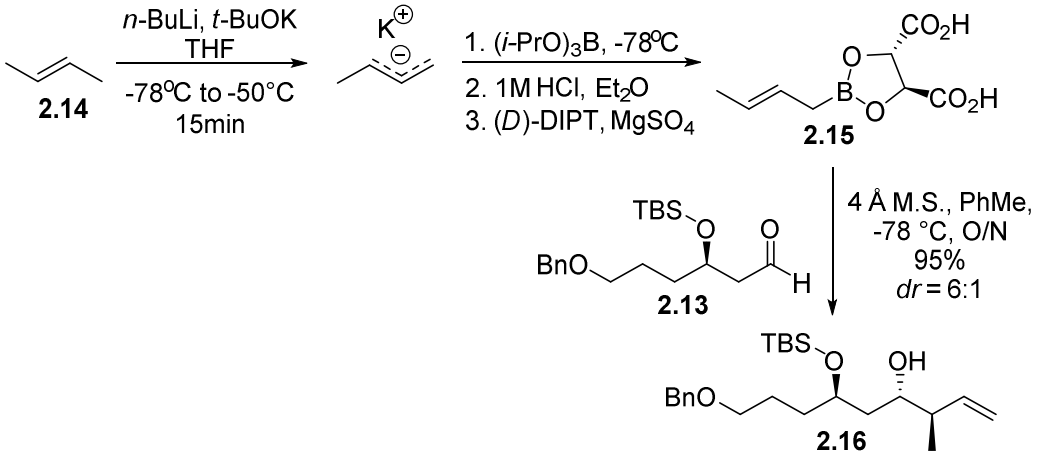
Aldehyde **2.13** was synthesised in 6 steps and 69% overall yield following a slightly modified route from the one previously used in the group and starting from inexpensive ethylene glycol **2.6** (Scheme 2.3).[46] Excess **2.6** treated by benzyl bromide resulted in the selective mono- benzyl ether protection in quantitative yield, alcohol **2.7** was then iodinated using Appel conditions to give **2.8** in 97% yield. Addition of two equivalents of base to methyl acetoacetate **2.9** resulted in the di-enolate, which was treated with iodide **2.8** to form β-ketoester **2.10**. Noyori asymmetric hydrogenation of **2.10** then furnished β-hydroxyketoester **2.11** in excellent yield and was easily performed on large scale (44.0 g, 180 mmol). The enantioselectivity of this reaction was determined by chiral HPLC comparing with racemic **2.11** (obtained by sodium borohydride reduction of **2.10**). Subsequent protection of alcohol **2.11** as its *t*-butyldimethylsilyl ether followed by reduction of the resulting ester **2.12** gave aldehyde **2.13** in quantitative yield over two steps. This aldehyde was used with no further purification.

[46] Vincent, A. PhD Thesis, École Polytechnique, **2006**.



Scheme 2.3: Synthesis of aldehyde **2.13**

Next, various discouraging attempts to set the stereocentres at the C21 and C22 positions were performed. Roush crotyl boronate **2.15**[47] was prepared from *trans*-2-butene **2.14** (Scheme 2.4). Crotylation of aldehyde **2.13** using **2.15** gave homoallylic alcohol **2.16** in 95% yield and as a 6:1 mixture of *anti*-diastereomers following reaction optimisation. Both, the enantio and the disatereoselectivity observed on the product were dictated by the Roush crotyl boronate **2.15**.

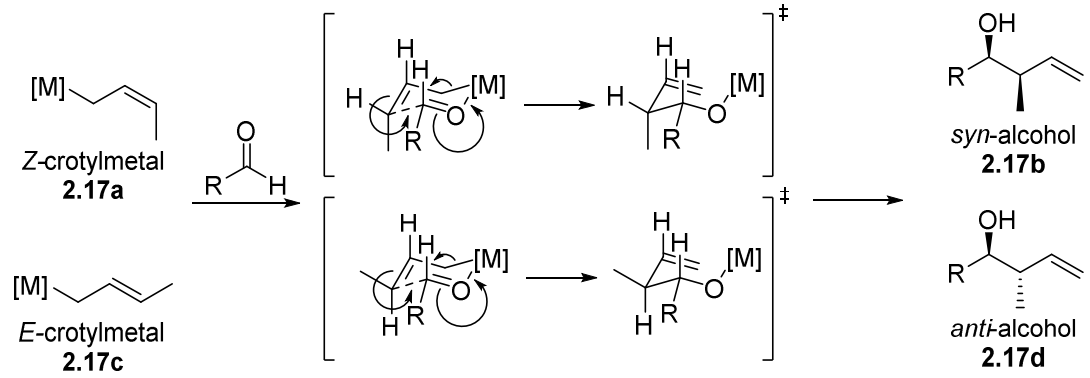


Scheme 2.4: Synthesis of homoallylic alcohol **2.16** using Roush crotyl boronate **2.15**

Roush crotyl boronate **2.15** is a type I crotyl reagent and thus the reaction proceeds *via* a closed chair-like transition state (Schemes 2.5 and 2.6). Selectivity of the product therefore would depend on the *E/Z* geometry of the crotylboronate as well as on the absolute configuration of the chiral auxiliary on the crotylboronate, in our case diisopropyl tartrate.

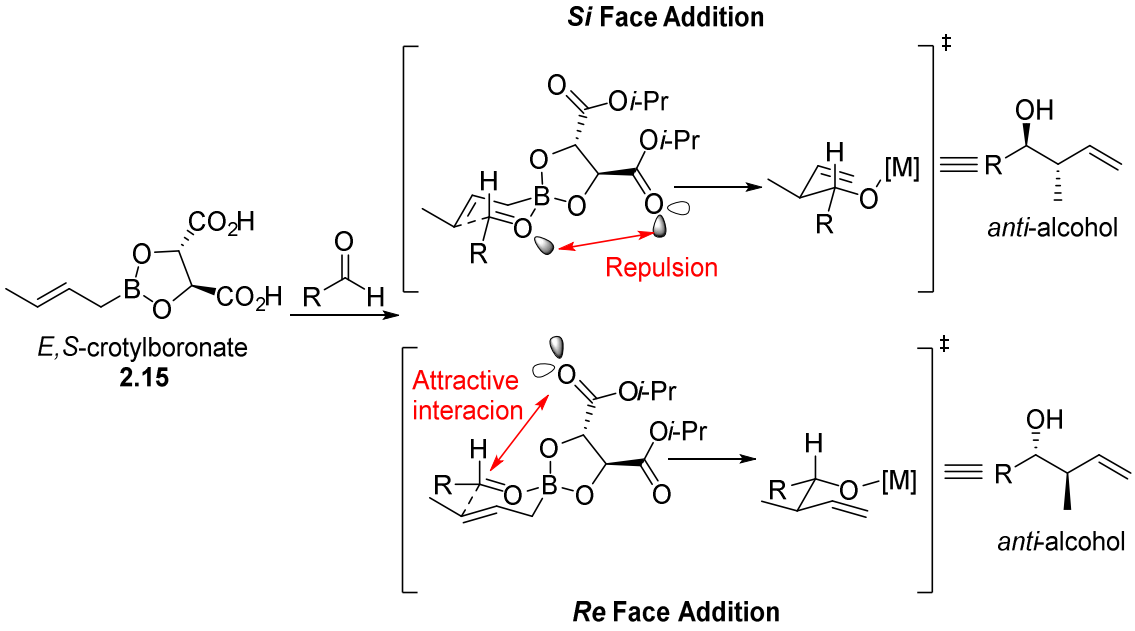
[47] Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

The *syn/anti* ratio of the homoallylic alcohol formed is dictated by the geometry (*Z* or *E*) of the crotyl metal reagent (Scheme 57). In both isomers, a cyclic chair-like transition state will be formed with the R group of the aldehyde in the equatorial position. When using the *Z*-alkene **2.17a**, the methyl group will be positioned in the axial position and thus a *syn* alcohol **2.17b** will be formed. In the case of the *E*-alkene **2.17c**, the equatorial position of the methyl group results in the formation of the *anti* alcohol **2.17d**.



Scheme 2.5: Transition state of type I crotylreagents; effect on diastereoselectivity

The enantioselectivity of the product is determined by the addition of the (*E,S*)-crotylborane reagent to the aldehyde. In this case, the *Si* face addition is disfavoured due to a repulsive interaction between the lone pair of the ester carbonyl with lone pair of the oxygen in the aldehyde. In the *Re* face addition, there is an attractive interaction between the carbon atom of the aldehyde and the lone pair of the oxygen atom of the ester carbonyl, resulting in the formation of the major compound. As mentioned before, in both cases the *anti*-alcohol is obtained.

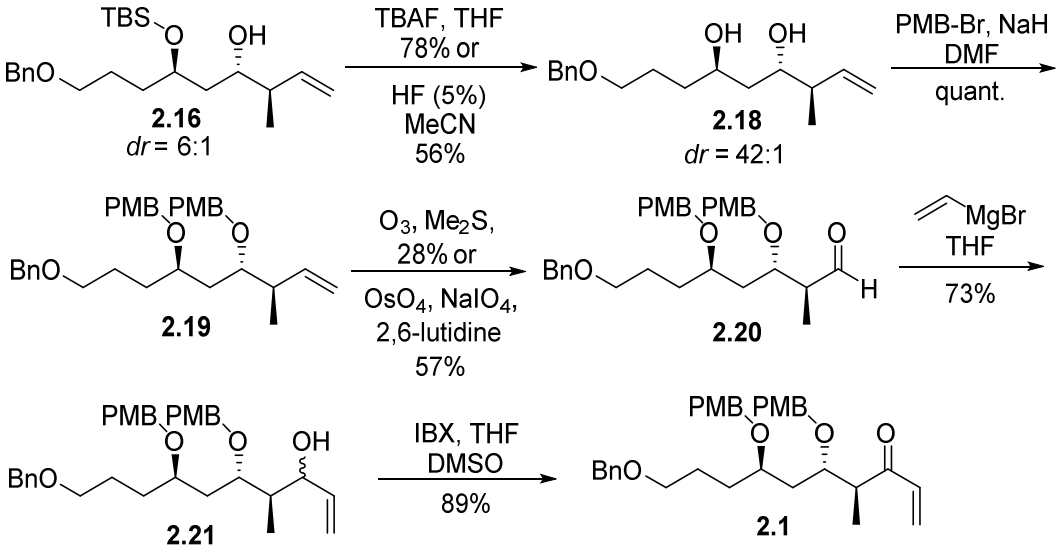


Scheme 2.6: Transition state of type I crotylreagents; effect on enantioselectivity

2.3 Synthetic attempts leading to the formation of allylic alcohol 2.4 as a single diastereomer

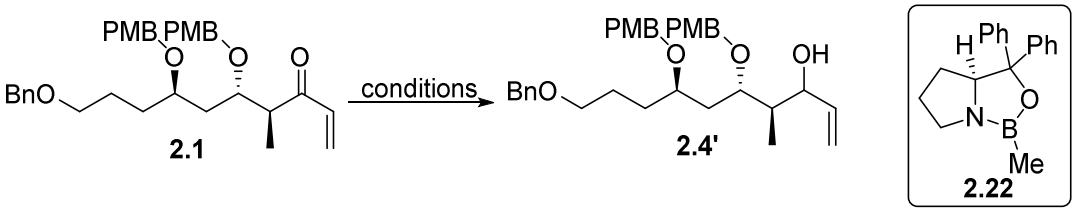
2.3.1 Oxidation/selective reduction attempt

Reduction of enone **2.1** using L-selectride leads to the conjugate reduction of the terminal double bond as previously mentioned (Scheme 2.1). However, we envisioned investigating other conditions such as a Luche reduction or even the use of a chiral reagent if necessary. The forward synthesis of enone **2.1** commenced from homoallylic alcohol **2.16** (Scheme 2.7). Cleavage of the *t*-butyldimethylsilyl ether was carried out initially with HF in acetonitrile as previously done in the group. However, we found using TBAF gave superior yields and this reagent is also safer and easier to handle than HF. At this stage, separation of the diastereomers by column chromatography was possible, which accounts for the moderate yields. Diol **2.18** was then protected as its corresponding *bis p*-methoxybenzyl ether **2.19**. This deprotection/reprotection sequence is necessary since any silyl moiety would interfere with the silicon-tether cleavage step used at a later stage of the synthesis. Terminal alkene **2.19** was then oxidatively cleaved using either ozonolyis or osmium tetroxide/sodium periodide in the presence of 2,6-lutidine, with the latter conditions giving a better yield. The resulting aldehyde **2.20** was found to epimerise during purification by column chromatography on silica gel. Therefore, freshly prepared crude **2.20** was treated with vinyl magnesium bromide to give allylic alcohol **2.21** as a 1:1 mixture of diastereomers, which were subsequently oxidised to give the desired enone **2.1** in 89% yield.



Scheme 2.7: Synthesis of enone **2.1**

Screening of reaction conditions for the diastereoselective reduction of enone **2.1** is summarised in Table 2.1. This was first attempted using only substrate control. Luche reduction of enone **2.1** gave an inseparable 2:1 mixture of diastereomers favouring the desired one in good yield (entry 1). The diastereoselectivity of this reaction is explained by the Felkin-Anh model (Figure 2.1). Reduction using (*S*)-(-)-2-Me-CBS-oxazaborolidine **2.22**[48] in either catalytic (entry 2) or stoichiometric amounts (entry 3) in combination with BH_3•THF complex gave unexpectedly even lower selectivity. Attempts to use alternative hydride sources such as boron dimethyl sulfide (BMS) (entry 4) or the more bulky catechol borane (entry 5) resulted in inseparable product mixtures along with starting material **2.1**.



Entry	Reagent	Solvent	Outcome
1	$NaBH_4$, $CeCl_3 \cdot 7H_2O$	MeOH	dr: 2: 1, 91%
2	**2.22** (0.4 eq.), BH_3-THF (1 eq.)	THF	dr: 1.7: 1, 85%
3	**2.22** (1.0 eq.), BH_3-THF (1 eq.)	THF	dr: 1.7: 1, 80%
4	**2.22** (1.0 eq.), BMS (1 eq.)	THF	Complex mixture
5	**2.22** (1.0 eq.), catechol borane	Toluene/THF	Complex mixture

Table 2.1: Reaction conditions for the diastereoselective reduction of **2.1**

[48] (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J. *et al. J. Am. Chem. Soc.* **1987**, *109*, 7925.

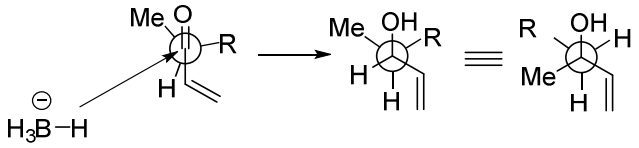
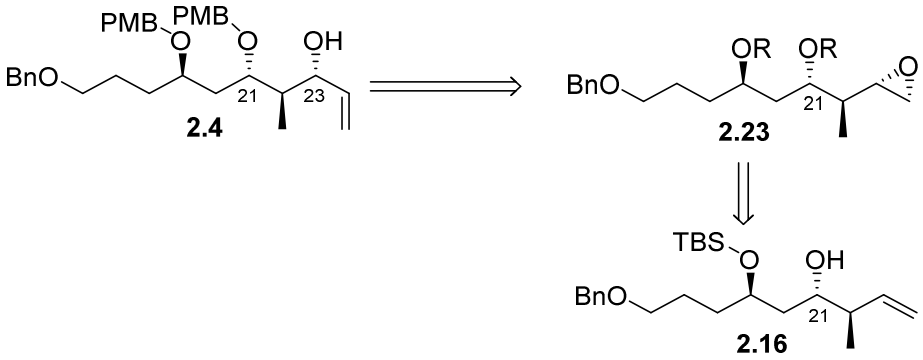


Figure 2.1: Felkin-Anh model

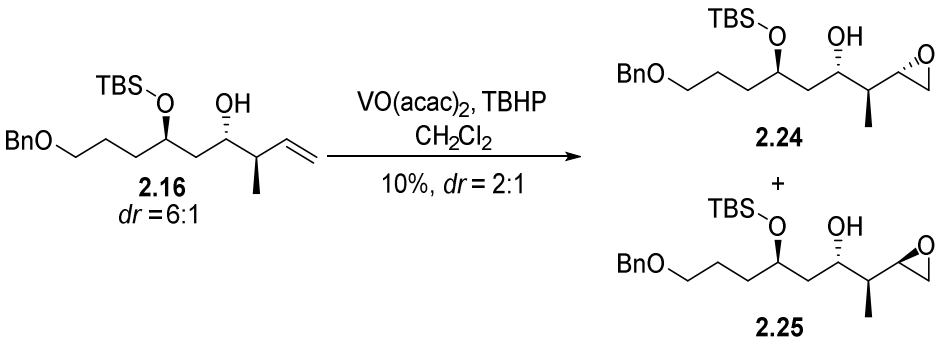
2.3.2 The C21 directed epoxidation/iodocarbonatation approach

Failure to produce **2.4** as a single diastereomer from the reduction of enone **2.1** (Table 2.1), prompted the planning of a new synthetic strategy to set the C23 stereocenter. Thus, we proposed a new route (Scheme 2.8) going *via* epoxide intermediate **2.23** that could undergo ring opening with trimethylsulfonium iodide to give **3.4**. The configuration of epoxide **2.23** could be directed by the alcohol at C21 in **2.17**.



Scheme 2.8: Revised retrosynthesis of allylic alcohol **2.4**

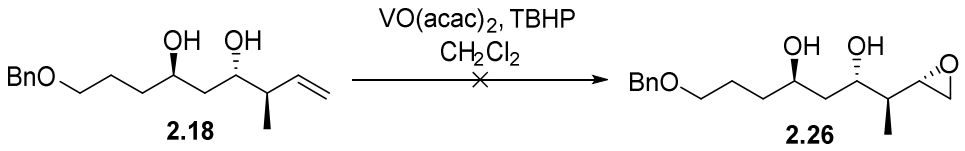
Our first attempt to epoxidise **2.16** by using $VO(acac)_2$ with TBHP as described in the literature,[49] gave a 2:1 mixture of both epoxides **2.24** and **2.25** in 10% yield (Scheme 2.9).



Scheme 2.9: Epoxidation of **2.16** using $VO(acac)_2$ with TBHP

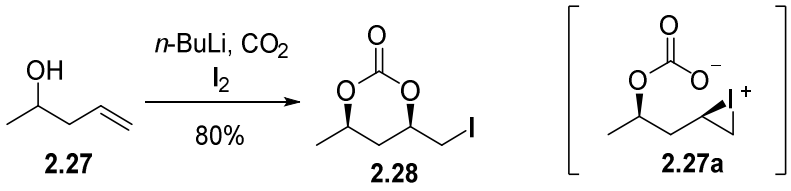
[49] Mihelich, E. D.; Daniels, K.; Eickhoff J. D. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

Trying the same reaction conditions on the free diol **2.18** led to either partial recovery of **2.18** or a mixture of unidentified by-products when the amount of oxidant and time were increased (Scheme 2.10). Not even traces or **2.26** were observed.



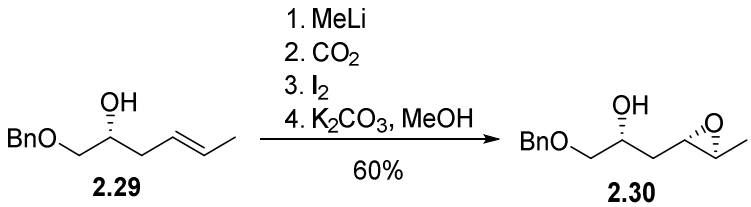
Scheme 2.10: Attempt to epoxidize diol **2.18**.

Cardillo *et al*.[50] reported the preparation of iodocarbonate **2.28** from homoallylic alcohol **2.27**, giving exclusively the *syn*-1,3-diol in good yield (Scheme 2.11). The reaction involves the formation of the iodonium ion **2.27a** and its opening by the oxygen of the formed carbonate.



Scheme 2.11: Iodocarbonatation of 4-penten-2-ol **3.27**.

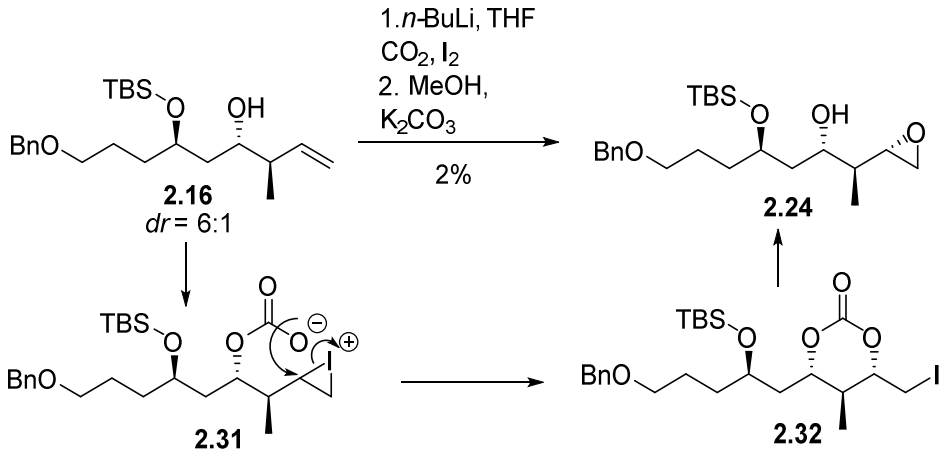
Soon after other groups[51,52] furthered the application of this reaction (Scheme 2.12). Alkene **2.29** was transformed into epoxide **2.30** in a one-pot reaction by treating the corresponding iodocarbonate intermediate with potassium carbonate in methanol.



Scheme 2.12: One-pot formation of **2.30** from allyl alcohol **2.29**

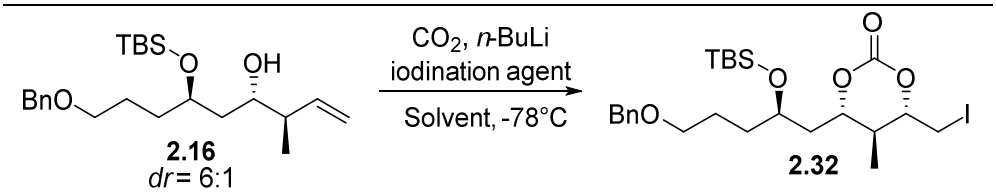
When carrying out a one-pot reaction using homoallylic alcohol **2.16** as starting material**,** a complicated mixture of products was obtained. After tedious purifications, a small amount of the desired epoxide **2.24** was isolated. Deprotonation of the free alcohol in **2.16** using *n*-BuLi was followed by bubbling CO_2 into the reaction mixture forming the carbonate intermediate, which upon addition of iodine gave the short lived iodonium species **2.31** that rapidly converted into iodocarbonate **2.32** (Scheme 2.13)**.**

[50] Cardillo, G.; Orena, M.; Porzi, G.; Sandri S. *J. Chem. Soc. Chem. Commun*. **1981**, 465.
[51] Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.
[52] Tiradot, R.; Prieto, J. A. *J. Org. Chem*. **1993**, *58*, 5666.



Scheme 2.13: Iodocarbonatation of **2.16**.

In an attempt to understand where the reaction was failing in order to optimise it, isolation of the iodocarbonate intermediate **2.32** was then investigated. Table 2.2 summarizes the different reaction conditions tested. Initially, iodine was used as the iodination agent (entries 1, 2 and 3). However, irrespectively of the solvent employed (ether, THF or acetonitrile) decomposition of the staring material was observed. No reaction proceeded when using NIS, a milder source of I^+, in THF and recovery of the starting material was possible (entry 4). Finally, the use of iodine monochloride led to decomposition (entry 5).



Entry	Iodination agent	Solvent	Outcome
1	I_2 (2.0-4.0 eq.)	Ether	Decomposition
2	I_2 (2.0-4.0 eq.)	THF	Decomposition
3	I_2 (2.0-4.0 eq.)	MeCN	Decomposition
4	NIS (2 eq.)	THF	0% (SM)
5	ICl (2 eq.)	THF	Decomposition

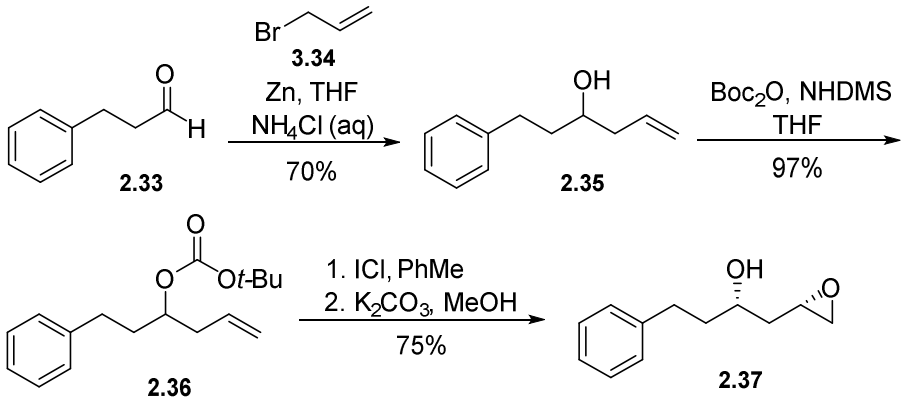
Table 2.2: Attempts to synthesise iodocarbonate **2.32**

After thorough analysis of the proton and carbon NMR spectra of the decomposition products obtained, it was apparent they were missing the TBS ether signals. We thus speculated that the iodide present in the reaction media could potentially generate HI *in situ* resulting in the acid accelerated cleavage of the TBS ether, thus, leading to complex product mixtures. The selective cleavage of alkyl silyl ethers over aryl silyl ethers using 1% w/w iodine in methanol at room temperature has been previously reported by Lipshutz and Keith.[53] Also, when using a milder source of I^+ such as N-Iodosuccinimide, no

[53] Lipshutz, B. H.; Keith, J. *Tettrahedron Lett.* **1998**, *39*, 2495.

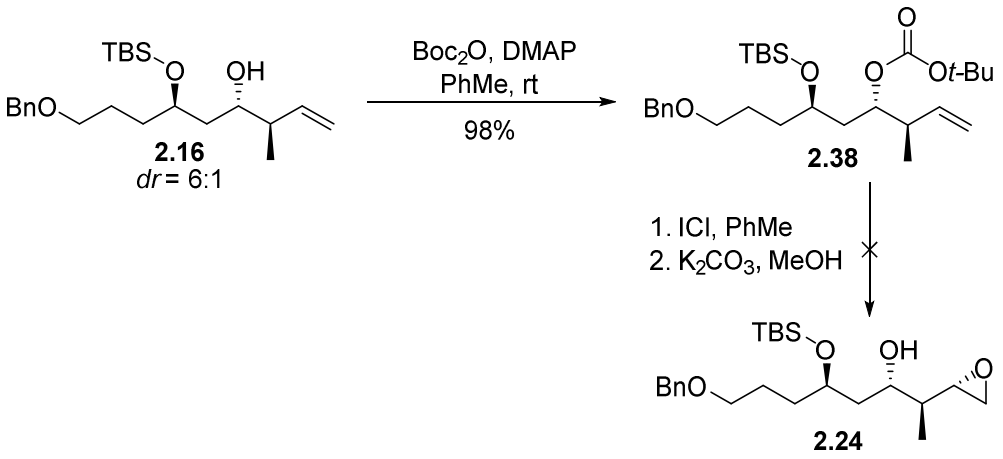
decomposition was observed, but recovery of the starting material instead supported this theory.

Formation of carbonate intermediary **2.31** requires extreme anhydrous conditions to deprotonate the alcohol motif by *n*-BuLi. Having this in mind, we decided to install the carbonate function prior the formation of the iodonium species. This was initially tested on a model system. Allylation of hydrocinnamaldehyde **2.33** was achieved under Barbier conditions in 70% yield. The resulting alcohol **2.35** was converted to *tert*-butoxy carbonate **2.36** using di-*tert*-butyl dicarbonate. Then, treatment of **2.36** with iodine monochloride was done and the reaction was periodically monitored by TLC. Once all starting material was consumed, the solvent was evaporated, the mixture was re-dissolved in methanol and K_2CO_3 was added furnishing the desired epoxide **2.37** in 75% yield (Scheme 2.14).



Scheme 2.14: Synthesis of epoxy alcohol **2.37**.

Motivated by these results, carbonate **2.38** was prepared in 98% yield from alcohol **2.16** and subjected to the same reactions conditions used on the model substrate **2.36**. Disappointingly, only decomposition of **2.38** was observed (Scheme 2.15).

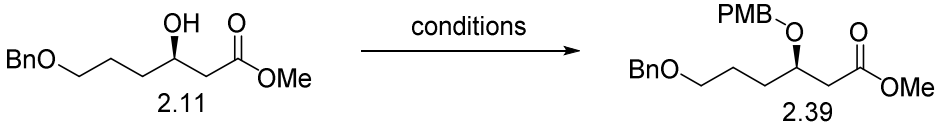


Scheme 2.15: Attempt to synthesise **2.24** from **2.16**

The fact that these reactions conditions worked on the model substrate **2.36** led us to conclude that the *t*-butyldimethylsilyl ether protecting group was in fact interfering with the

reaction and thereby changing the protecting group would give better results. Since the planned route required alcohols at C19 and C21 protected as their corresponding *p*-methoxybenzyl ethers at a later stage, we consider installing the *p*-methoxybenzyl ether at C19 earlier in the synthesis. As shown in Table 2.3, protection of **2.11** as its corresponding *p*-methoxybenzyl ether proved to be more challenging that initially anticipated.

Most common conditions[54] for alcohol protection as the corresponding *p*-methoxybenzyl ether are carried out under acidic conditions and involves the use of 4-methoxybenzyl-2,2,2-trichloroacetimidate as well as a source of acid. Attempting this on substrate **2.11**, however, led to recovery of starting material (entries 1 and 3) or decomposition (entry 2) when harsher reaction conditions where used. The use of PMB-Br and Sc(OTf) in catalytic amounts resulted in decomposition of the starting material when performing the reaction under reflux in benzene (entry 4). Mixing **2.11** with PMB-Br followed by slowly addition of sodium hydride in portions resulted in a mixture of side products that made purification difficult and gave disappointing yields (entry 5). To our delight, using *p*-methoxybenzyl alcohol with Amberlyst H-15 resin[55] and refluxing for 1 week in DCE resulted in the desired product **2.39** in 77% yield (entry 6). Unfortunately, this reaction was not always reproducible, giving inconsistent yields that were often much lower.



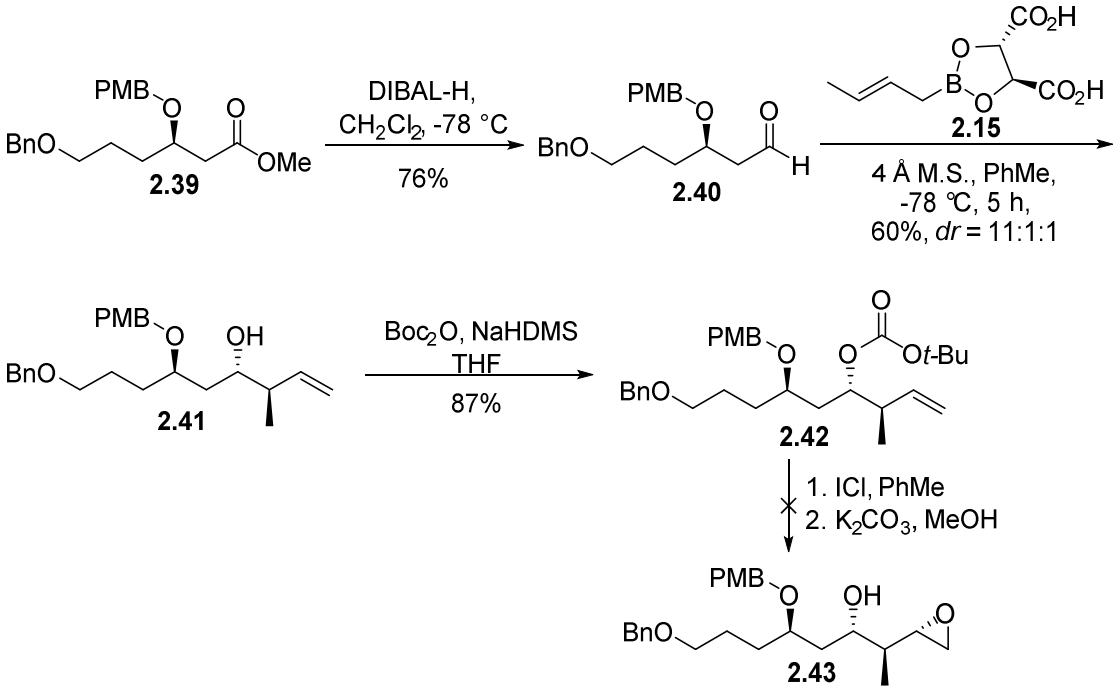
Entry	Reagent (equiv)	Catalyst (equiv)	Solvent	T (°C)	C (M)	Outcome
1	PMB-OC(NH)CCl_3 (2-3)	CSA (0.1-0.3)	CH_2Cl_2 or THF	0°C to rt	0.5-1.0	SM
2	PMB-OC(NH)CCl_3 (3)	TfOH (0.08-0.17)	CH_2Cl_2	0°C to rt	0.5-0.8	SM or decomposition
3	PMB-OC(NH)CCl_3 (3)	Sc(OTf) (0.1)	CH_2Cl_2	0°C to rt	0.6	SM
4	PMB-Br (2)	$SnOBu_2$ (1.3)	Benzene	reflux	0.8	Decomposition
5	PMB-Br (2.5)	NaH (1.5)	DMF	0°C to rt	1.0	54%
6	PMB-OH (1.4)	Amberlyst H15 resin	DCE	reflux	0.6	77%

Table 2.3: Conditions for the PMB protection of alcohol **2.11**.

Despite these mixed results, we carried on with the synthesis. Protected ester **2.39** was reduced to aldehyde **2.40** and subsequently crotylated using **2.15** providing homoallylic

[54] Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
[55] Chavan, S. P.; Harall, K. R. *Tetrahedron Lett*. **2002**, *53*, 4683.

alcohol **2.41** in a 11:1:1 (*anti*:*anti*:*syn*) diastereomeric ratio after purification (Scheme 2.16). After preparing carbonate **2.42** in 87% yield using Boc anhydride, we tested the conditions found to work on the model substrate **2.36.** However, once again, they disappointingly led to decomposition of the starting material.

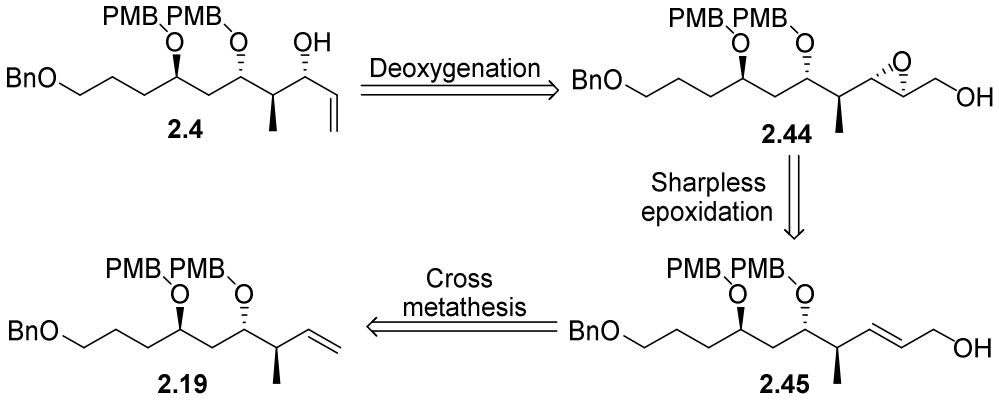


Scheme 2.16: Attempt to synthesise **2.43**

2.3.3 Cross metathesis/Sharpless epoxidation route

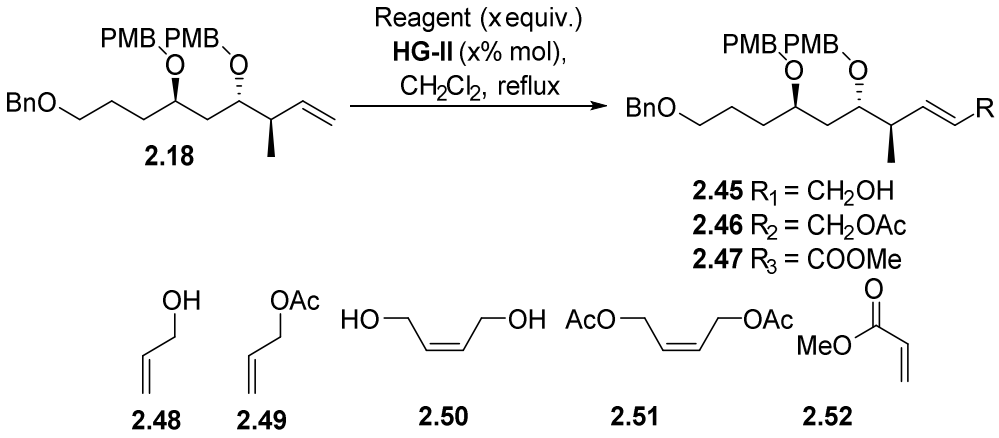
After a lot of time spent endeavouring into the dead-end routes discussed earlier (Chapters 2.3.1 and 2.3.2), a new route was envisaged (Scheme 2.17). Allylic alcohol **2.4** could be obtained from the deoxygenation of epoxide **2.44** that in turn could be prepared from allylic alcohol **2.45** using a well-established Sharpless epoxidation.[56] Compound **2.45** would be synthesised by cross-metathesis reaction between protected homoallylic alcohol **2.19** and a suitable cross-metathesis partner.

[56] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.



Scheme 2.17: Envisaged retrosynthesis of allylic alcohol **3.4**

According to the general model for the categorisation of olefins discussed earlier (chapter 1.3), **2.18** is a type I olefin and thus a selective CM reaction should by attainable by using a type II olefin partner. Table 2.4 summarises the cross-metathesis reactions using **2.18** with different olefins.



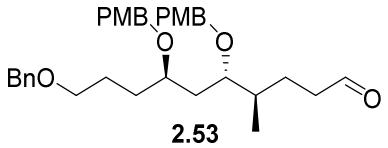
Entry	Reagent	x% mol	Time	Product	Yield
1	**2.48** (9 equiv)	20%	1 day	**2.45**	7% (9% b.r.s.m.)
2	**2.49** (10 equiv)	20%	8 days	**2.46**	17% (38% b.r.s.m.)
3	**2.50** (5 equiv)	15%	2 days	**2.45**	67%*
4	**2.51** (6 equiv)	10%	4 days	**2.46**	76% (83% b.r.s.m.)
5	**2.52** (6 equiv)	11 %	O/N	**2.47**	99%
6	**2.52** (6 equiv)	2.5 %	O/N	**2.47**	91%**
7	**2.52** (6 equiv)	5%***	5 days	**2.47**	88%

*Conversion; a mixture of products was observed, along with 29% recovered starting material **2.18**. **Full conversion. ***__G-II__ catalyst used instead.

Table 2.4: Finding a suitable cross metathesis partner

Even though we had in mind that the reaction between two type I olefins would lead to nonselective product mixtures, initially allyl alcohol **2.48** was used as the metathesis partner to avoid further steps in the synthesis. As anticipated, alcohol **2.45** was only isolated in 7%

yield (entry 1). When 1,4-*cis*-butene diol **2.50** was used instead, the desired allyl alcohol **2.45** and aldehyde **2.53** (Figure 2.2) were obtained as major products along with a mixture of other unidentified by-products (entry 3). Decomposition of ruthenium catalysts leading to undesired by-products has been well studied,[57] as well as the isomerisation of allylic alcohols.[58]



2.53

Figure 2.2: Structure of isomerised aldehyde **2.53**

Cross-metathesis reaction of **2.18** with allyl acetate **2.49** was sluggish and adding more catalyst or prolonging reaction times only resulted in further decomposition (entry 2). When the corresponding dimer *cis*-1,4-diacetoxy-2-butene **2.51** was used however, the desired allyl acetate **2.46** was formed in 76% yield using 10% mmol **HG-II** (entry 4). The highest yields for the desired product were achieved from the cross-metathesis reaction of **2.18** with type II olefin **2.52**, giving the conjugate ester **2.47** in almost quantitative yield (entry 5).

The improvement of the yield can be explained by the stability of the homodimerization products formed. Type II olefins undergo homodimerization to a small extent and the homodimers formed cannot undergo further metathesis reactions. Opposite to **2.48**-**2.51**, the homodimer of **2.52** (methyl fumarate) is inert towards additional CM reactions and thus formation of secondary products is avoided. On the other hand, the dimer of **2.18** reacts with **2.52** to give desired product **2.47**.

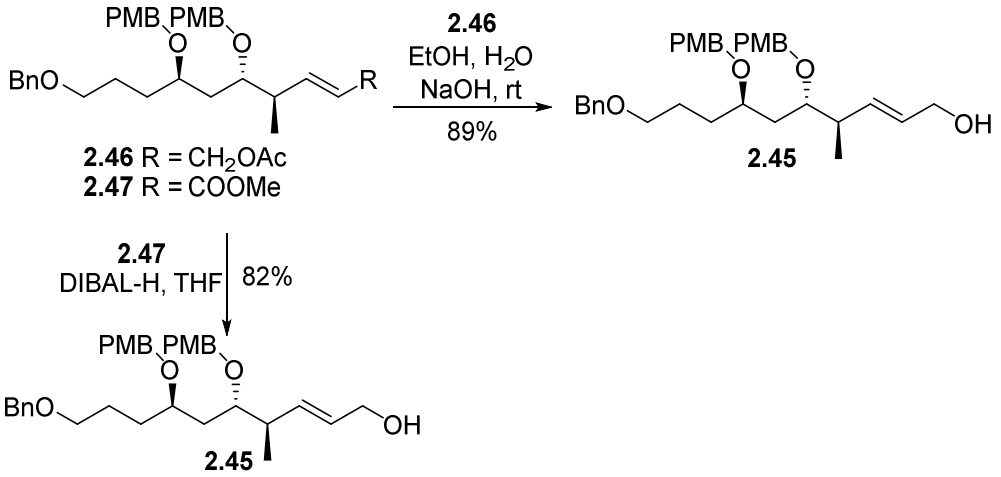
Once **2.47** was successfully synthesised, the next challenge was to scale up this reaction, which implied reducing the cost by diminishing the amount of catalyst employed. Indeed **2.47** was successfully obtained in 91% yield by using just 2.5 mmol% **HG-II** (Table 2.4 entry 6). The more affordable **GII** catalyst could also be used to carry out this process with a small drop in yield (entry 7). Even though it was initially intended to avoid going *via* conjugate ester, it was found to be the most reliable and efficient way to bring forward the large amounts of material necessary for the rest of the synthesis.

---

[57] Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961. (b) Courchay, F. C.; Sworen, J. C.; Ghiviriga, I.; Abboud, K. A.; Wagener, K. B. *Organometallics* **2006**, *25*, 6074.

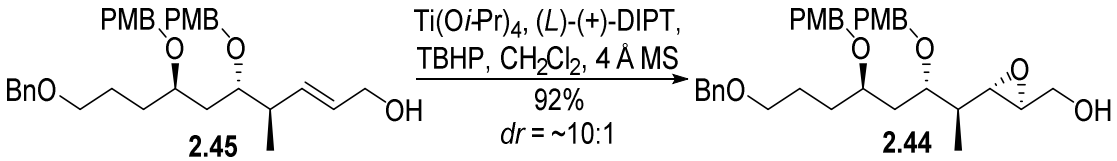
[58] (a) Werner, H.; Grunwald, C.; Stuer, W.; Wolf, J. *Organometallics* **2003**, *22*, 1558. (b) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817. (c) Edlin, C. D.; Faulkner, J.; Fengas, D.; Knight, C. K.; Parker, J.; Preece, I.; Quayle, P.; Richards, S. N. *Synlett* **2005**, 572. (d) Schmidt, B.; Hauke, S. *Org. Biomol. Chem*. **2013**, *11*, 4194.

The required allylic alcohol **2.45** was then prepared in one step, either by the hydrolysis of acetate **2.46** under basic conditions or by the reduction of ester **2.47** to the alcohol using DIBAL-H (Scheme 2.18).



Scheme 2.18: Synthesis of epoxidation precursor **2.45**

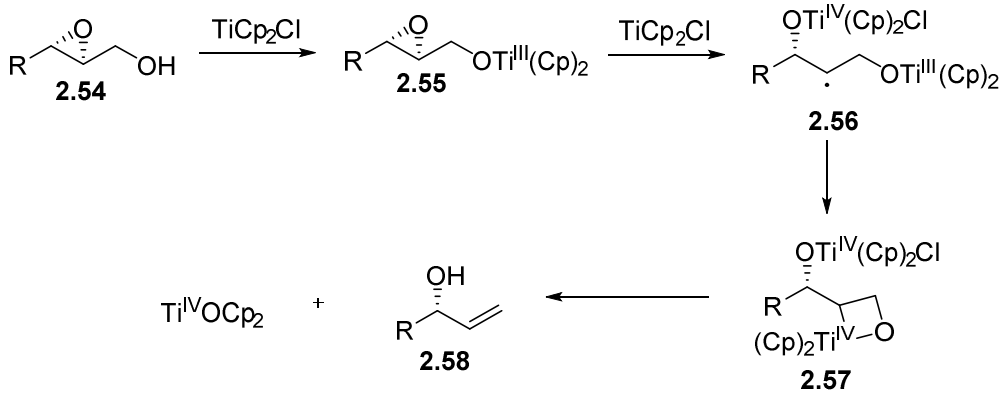
Sharpless epoxidation[56] of allylic alcohol **2.45** successfully furnished the epoxy alcohol **2.44** (Scheme 2.19). After optimisation, **2.44** could be prepared in 92% yield and with 10:1 *dr* when performed on 5 mmol scale. Generally, the results obtained showed that this reaction worked better on larger scale.



Scheme 2.19: Sharpless epoxidation of allylic alcohol **2.46**

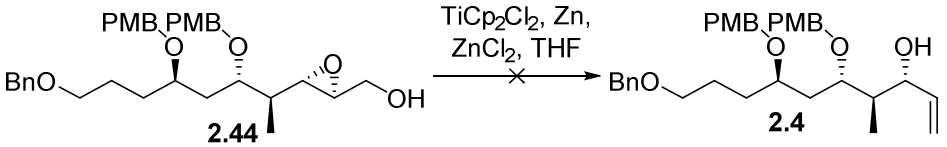
Synthesis of allylic alcohol **2.4** in one step was initially attempted employing a titanocene induced regioselective deoxidation.[59] The general mechanism for this reaction is shown in Scheme 2.20. Initially, formation of Ti^{iii}-alkoxide **2.55** and HCl that consumes a stoichiometric amount of $TiCp_2Cl$ occurs. By reaction with an extra equivalent of $TiCp_2Cl$, radical **2.56** is then formed. This radical engages intramolecularly with the unfilled d-orbital of Ti^{III} to form the **2.57** intermediate. Finally, this intermediate deoxygenates to form the desired allylic alcohol **2.58**.

[59] Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, *11*, 843.



Scheme 2.20: Mechanism of the titanocene mediated deoxidation

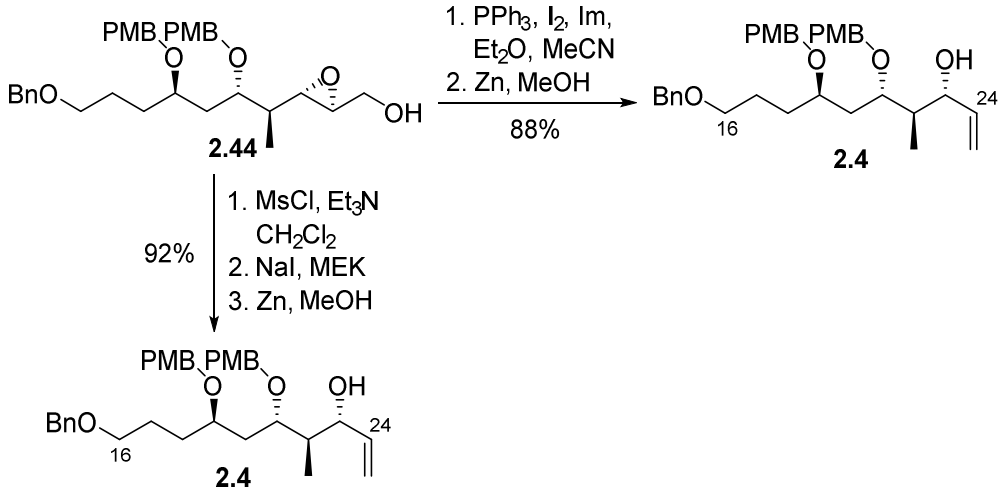
In our case, formation of $TiCp_2Cl$ was achieved *in situ* by stirring $TiCp_2Cl_2$, granulated zinc and $ZnCl_2$, which caused colour change of the reaction mixture from red to green due to the change in oxidation state of titanium. Even though the colour change was always observed, the subsequent addition of the epoxy alcohol only led to recovery of starting material. Attempts to mix $TiCp_2Cl_2$, granulated zinc and $ZnCl_2$ and stir for longer time prior to addition of **2.44** as well as the use of different batches of the reagent had no effect and only starting material was isolated (Scheme 2.21).



Scheme 2.21: Unsuccessful titanocene mediated deoxygenation

Appel-type reaction of 2,3-epoxy alcohol **2.44** followed by reductive elimination of the iodoepoxide intermediate in the presence of zinc in excess and refluxing methanol furnished the desired allylic alcohol **2.4** in 88% over 2 steps (Scheme 2.22). Unfortunately, this route was not reproducible and any attempts to scale up resulted in complex mixtures with only trace amounts of alcohol **2.4** being isolated. Therefore, an alternative route[60] that involved the formation of the corresponding mesylate followed by purification using column chromatography prior to iodination with NaI and subsequent elimination was employed. The desired alcohol **2.4** was obtained in 92% yield for the three steps.

[60] Ishibashi, Y.; Nishiyama, S.; Shizun, Y.; Yamamura, S *Tetrahedron Lett.* **1992**, *33*, 521.



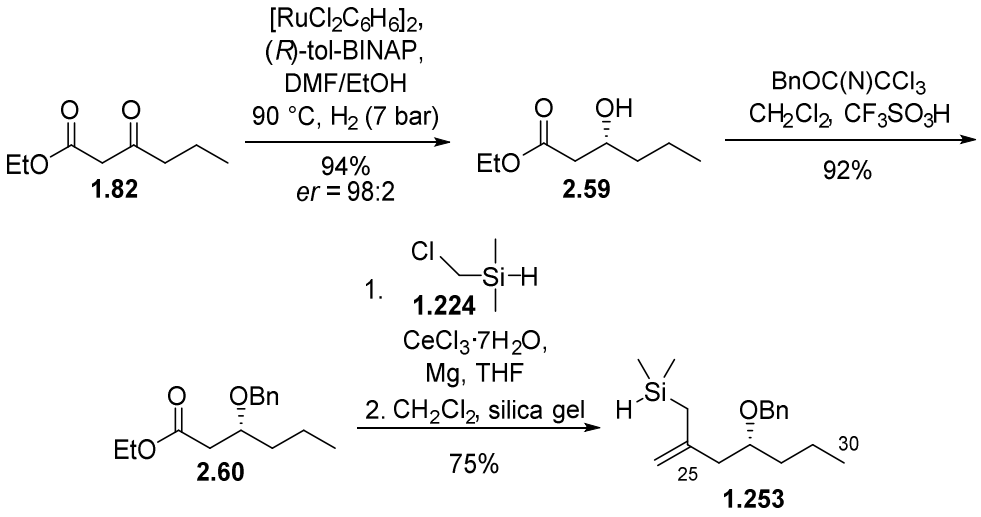
Scheme 2.22: Synthesis of allylic alcohol **2.4**

Overall the C16-C30 fragment **2.4** was obtained in 14 steps and in 35% yield from ethylene glycol **2.6**.

2.4 Synthesis of the C25-C30 silane fragment

As previously reported in the group,[40] synthesis of the C25-C30 fragment commenced from 3-ethyloxohexanoate **1.82**, which was subjected to an asymmetric hydrogenation under Noyori's conditions[61] to yield hydroxyester **2.59**. Subsequent protection of the alcohol as the corresponding benzyl ether was achieved using benzyl 2,2,2-trichloroacetimidate under acidic conditions, giving **2.60** in 92% yield. The enantiomeric ratio of **2.60** was determined by chiral HPLC and was found to be 98:2. Protected hydroxyester **2.60** was then subjected to Peterson olefination conditions using freshly distilled silane **1.224**, which led to the hydroxysilane intermediate that subsequently eliminated when stirring in dichloromethane with silica gel for 5 days giving hydrosilane **1.253** in 75% yield (Scheme 2.23).

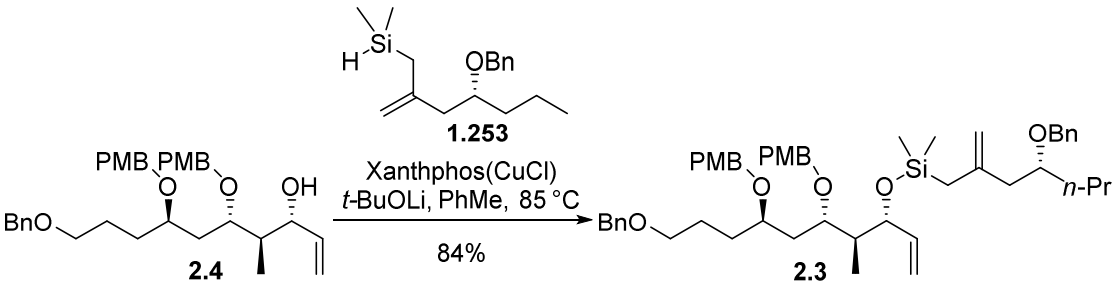
[61] Noyori, R.; Okhuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akuragawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.



Scheme 2.23: Synthesis of hydrosilane **1.253**

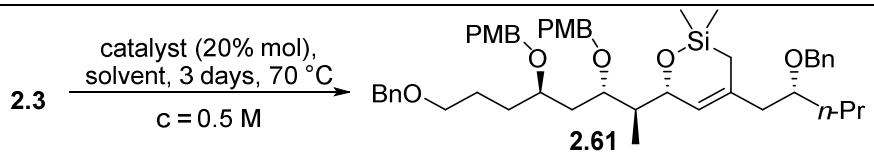
2.5 Fragment coupling using a silicon-tether ring-closing metathesis strategy

Following the silicon-tether ring-closing metathesis methodology developed in the group, the two fragments were first coupled together by a copper-catalysed silane dehydrogenative coupling (Scheme 2.24).



Scheme 2.24: Coupling of the C16-C24 **2.4** and C25-C30 **1.253** fragments

Using 2 equiv of silane **1.253** gave the desired diene **2.3** in 84% yield as well as 95% recovery of the excess silane used. With diene **2.3** in hand, a series of conditions and catalysts were tested for the RCM step to yield silacycle **2.61** (Table 2.5).



Entry	Catalyst	Solvent	Yield
1	**G-II**	CH_2Cl_2 (40 °C)	43% (56% b.r.s.m.)*
2	**G-II**	1,2-Dichloroethane (reflux)	57% (66% b.r.s.m.)
3	**G-II**	Toluene	63% (78% b.r.s.m.)
4	**GII-*o*-tol**	Toluene	59%
5	**HG-II**	Toluene	76% (87% b.r.s.m)
6	**Zhan 1B**	Toluene	46% (58% b.r.s.m.)
7	**nitro-Grela**	Toluene	79% (84% b.r.s.m.)
8	**Umicore M_{73}SIPr**	EtOAc	4% (29 % b.r.s.m.)
9	**Umicore M_{73}SIPr**	DCE	12% (29% b.r.s.m.)
10	**Umicore M_{73}SIPr**	Toluene	20% (48% b.r.s.m.)
11	**Umicore M_{71}SIPr**	Toluene	SM recovered
12	**Umicore M_{73}SIMes**	Toluene	74% (88% b.r.s.m.)
13	**Umicore M_{71}SIMes**	Toluene	81% (100% b.r.s.m.)

*Performed on the mixture of diastereomers by Stéphane Wittmann.[40]

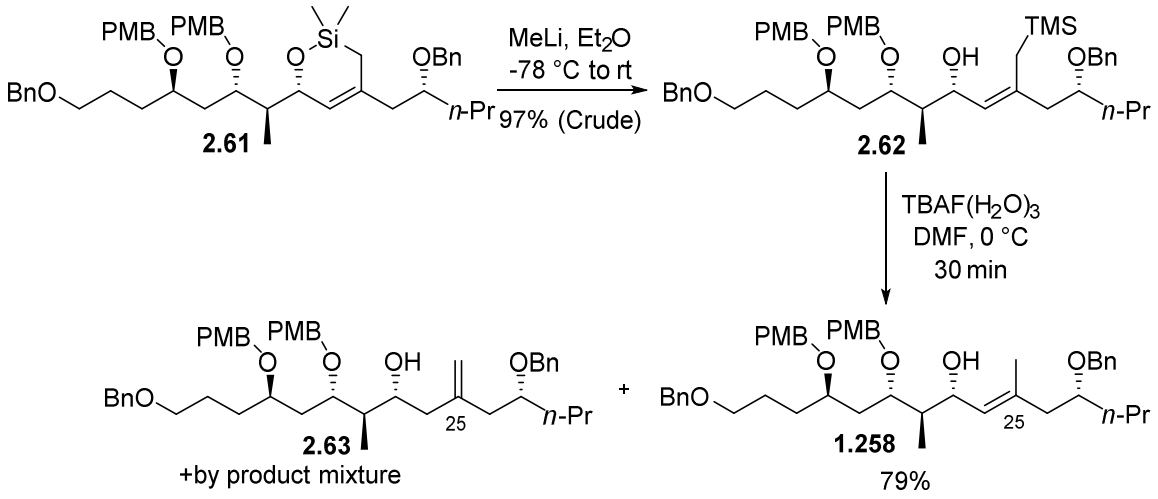
Table 2.5: RCM catalyst screening

Initially the reaction mixture was performed using **GII** in CH_2Cl_2 under reflux (Table 2.5, entry 1). Refluxing **2.3** with **GII** in a higher boiling point solvent such as 1,2-dichloroethane (entry 2) gave slightly better yields (57%, 66% b.r.s.m). Switching to toluene and performing the reaction at 70°C resulted in a further improvement of the reaction yield (entry 3); however when trying the reaction at temperatures higher than 70°C in toluene, faster decomposition and a decrease in the yield was observed. The use of **HGII** (entry 5) and nitro-Grela (entry 7) in toluene formed desired **2.61** in good yield (76% and 79% respectively), contrary to Zhan 1B (entry 6) or GII-*o*-tol (entry 4). Furthermore, when employing GII-*o*-tol, recovery of unreacted starting material was not possible.

Umicore catalysts were also tested. Initially the use of solvents recommended by the supplier in the Umicore brochure was chosen. After conducting the reaction with Umicore **M_{73}SIPr** in EtOAc (entry 8), DCE (entry 9) and toluene (entry 10), we were able to conclude that once again toluene was the best solvent, even though **2.61** was isolated in poor yield (20%, 48% b.r.s.m). We then proceed to change the Umicore catalyst employed. Catalysts with more steric bulk around the N-heterocyclic carbene ligand i.e. **M_{73}SIPr** (entry 10) and **M_{71}SIPr** (entry 11) were less reactive, giving mostly starting material or/and decomposition. Additionally, results obtained with the Umicore catalysts **M_{73}SIMes** (entry 12) and **M_{71}SIMes**

(entry 13) were not reproducible, presumably due to their instability since use of **HG-II** (entry 5) gave consistent results. It is also noteworthy that when attempting to purify by dry loading on silica gel followed by column chromatography, even though the crude NMR was essentially clean with only starting material present, after the column the product had decomposed. The most efficient way to purify this compound minimising decomposition was to cool the reaction mixture to room temperature and subsequently poor it directly onto the column. A pure NMR sample of **2.3** in $CDCl_3$ showed apparent decomposition after just 2 days, suggesting the silacycle was not stable.

Removing the silicon tether was then achieved in two steps; the six-membered ring **2.61** was opened using MeLi affording the TMS allylic alcohol **2.62** (Scheme 2.25), which was immediately subjected to desilylation using tetrabutylammonium fluoride trihydrate. Purification using column chromatography on silica gel gave the desired *E*-trisubstituted olefin **1.258** along with isomerised olefin **2.63** that co-eluted with a mixture of by-products.

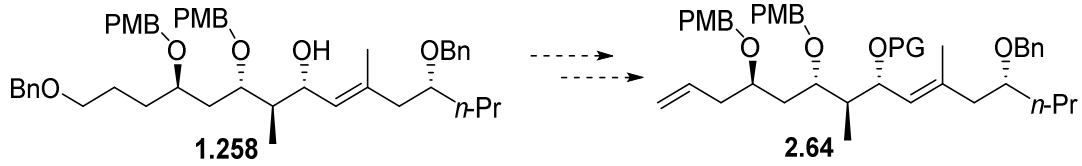


Scheme 2.25: Two-step desilylation procedure for the synthesis of **1.258**

2.6 End game of synthesis

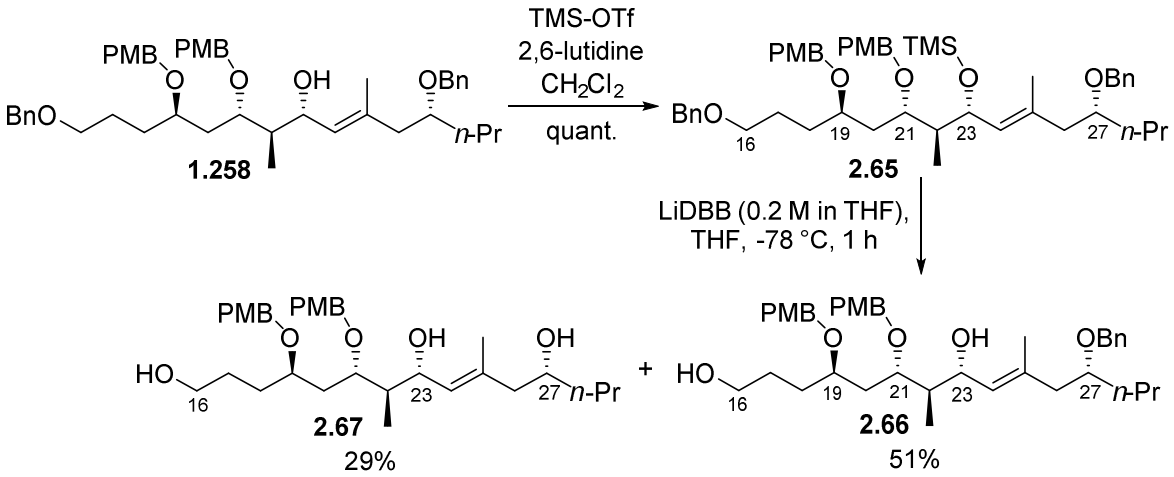
We anticipated coupling the C1-C15 and C16-30 fragments using a Suzuki-Miyaura cross-coupling reaction[62] prior to the macrocyclization, therefore alkene substrate **2.64** needed to be prepared (Scheme 2.26).

[62] Winne, J. M.; Guang, B.; D´herde, J.; De Clercq, P.J. *Org. Lett.* **2006**, *8 (21)*, 4815.

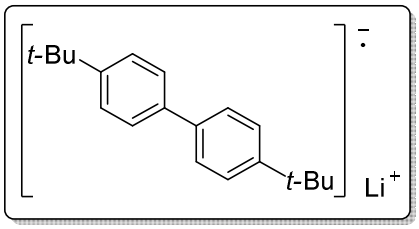


Scheme 2.26: Envisaged substrate for Suzuki-Miyaura cross-coupling

Allylic alcohol **1.258** was thus protected as its corresponding trimethylsilyl ether in quantitative yield (Scheme 2.27). The selective cleavage of the primary benzyl ether at C16 over the secondary benzyl ether at C27 and the PMB ethers at C21 and C23 was next attempted using LiDBB[63] free radical (figure 2.3). Although managing to obtain the primary free alcohol **2.66** in 51% yield along with triol **2.67**, concomitant removal of the TMS ether was also observed.



Scheme 2.27: Preparation of allylic alcohol **2.66**

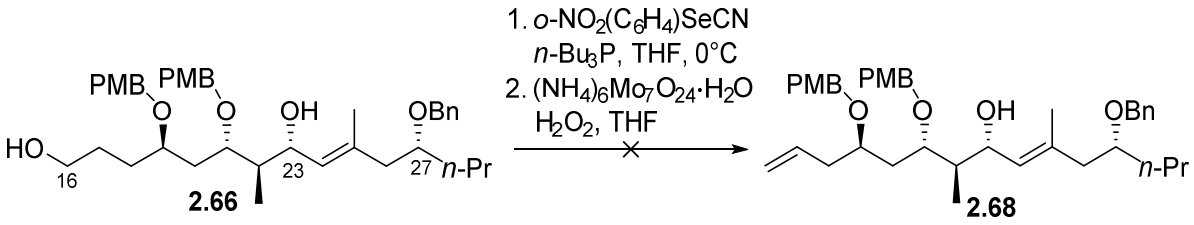


LiDBB

Figure 2.3: Structure of LiDBB

Despite this discouraging result, an attempt to form alkene **2.68** via a Grieco dehydration of **2.66** on very small scale (9.0 mg, 13.9 µmol) was made (Scheme 2.28); however, we only achieved to recover a fraction of the starting material.

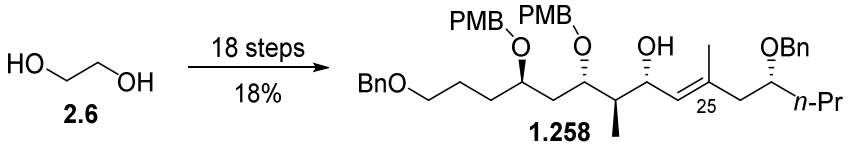
[63] (a) Hutchinson, L.L.; Freeman, P.K. *J. Org. Chem.,* **1980**, *45*, 1924. (b) Ireland, R. E.; Smith, M.G. *J. Am. Chem. Soc.*, **1988**, *110*, 854



Scheme 2.28: Attempt to prepare diene **2.68** via Grieco dehydration

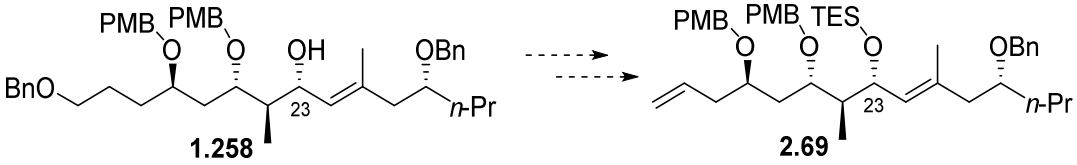
2.7 Conclusion and future work

A reliable and high yielding route to prepare the protected C16-C30 fragment **1.258** as a single enantiomer starting from inexpensive ethylene glycol **2.6** was achieved in 18% yield over 18 steps (Scheme 2.29).



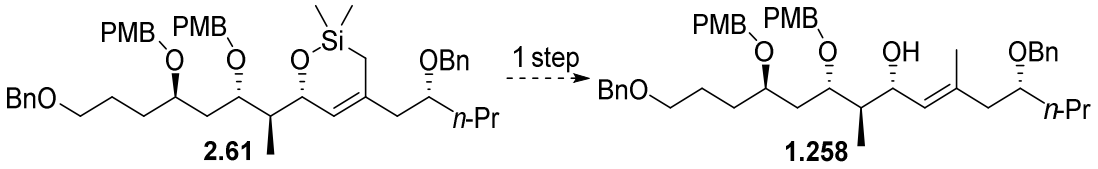
Scheme 2.29: Summary of the synthesis of the C16-C30 fragment

It would be interesting to try and use a slightly more stable protecting group such as a TES ether for the protection of the C23 alcohol and attempt to prepare diene **2.69** (Scheme 2.30).



Scheme 2.30: Alternative substrate for Suzuki-Miyaura cross-coupling

Finally, it would be convenient to find a single step procedure to remove the silicon tether, ideally avoiding or minimising the formation of undesired isomerised alkene **2.63** as well (Scheme 2.31).

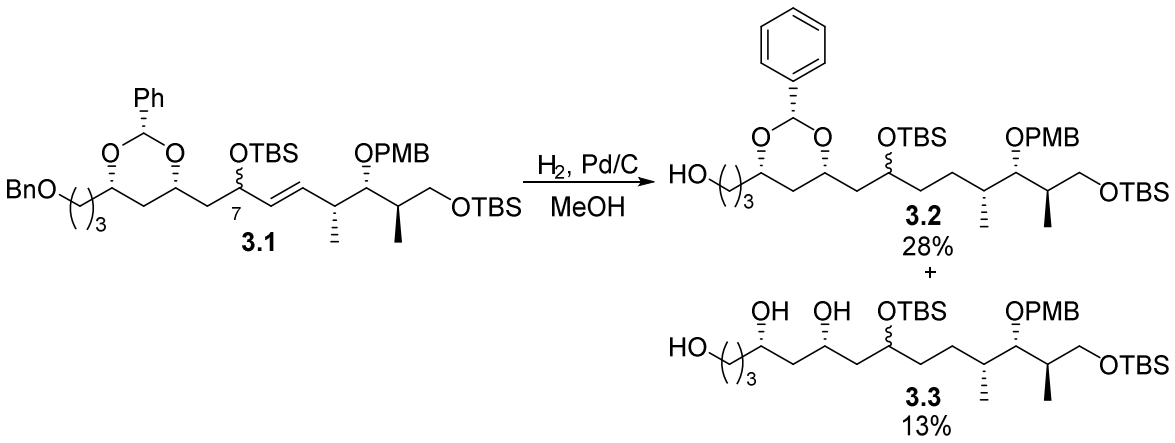


Scheme 2.31: One step desilylation procedure to prepare **1.258**

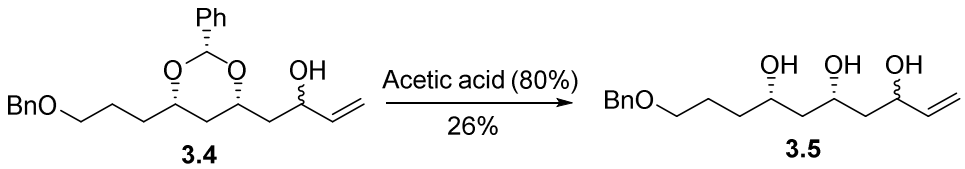
Chapter 3: Synthesis of the C1-C15 fragment of dolabelide C

As mentioned in chapter 1.4.1, previously in the group A. Vincent[46] used a Mukaiyama aldol reaction to couple the two fragments and set the correct stereochemistry of alcohol at C7 (Scheme 1.35). The disadvantage of this approach was the formation of a ketone at C5 that was not present in dolabelides and thus required additional steps for its removal. Also, the failure to obtain the desired vinyl iodide **1.191** (Scheme 1.36) by Negishi carboalumination of alkyne **1.190,** led to the use of an alternative route (Scheme 1.37) that was longer and had other complications.

S. Wittman[40] also tested a Negishi carboalumination on alkyne **1.197** (Scheme 1.38) on very small scale, suggesting repeating this experiment on a more reasonable amount of substrate would be appropriate. The key step to couple the two fragments *via* cross metathesis with allylic alcohol **1.194** and **1.195** (Scheme 1.38) was low yielding giving large amounts of undesired isomerisation products. Furthermore, the C7 stereocenter was not installed and that was not possible at a later stage thus a mixture of diastereomers was carried through all the synthesis. Finally, the selective deprotection of the benzylidene acetal was troublesome (Scheme 3.1) while removal at an earlier stage proved to be very low yielding (Scheme 3.2).



Scheme 3.1: Selective deprotection of benzylidene acetal **3.1**



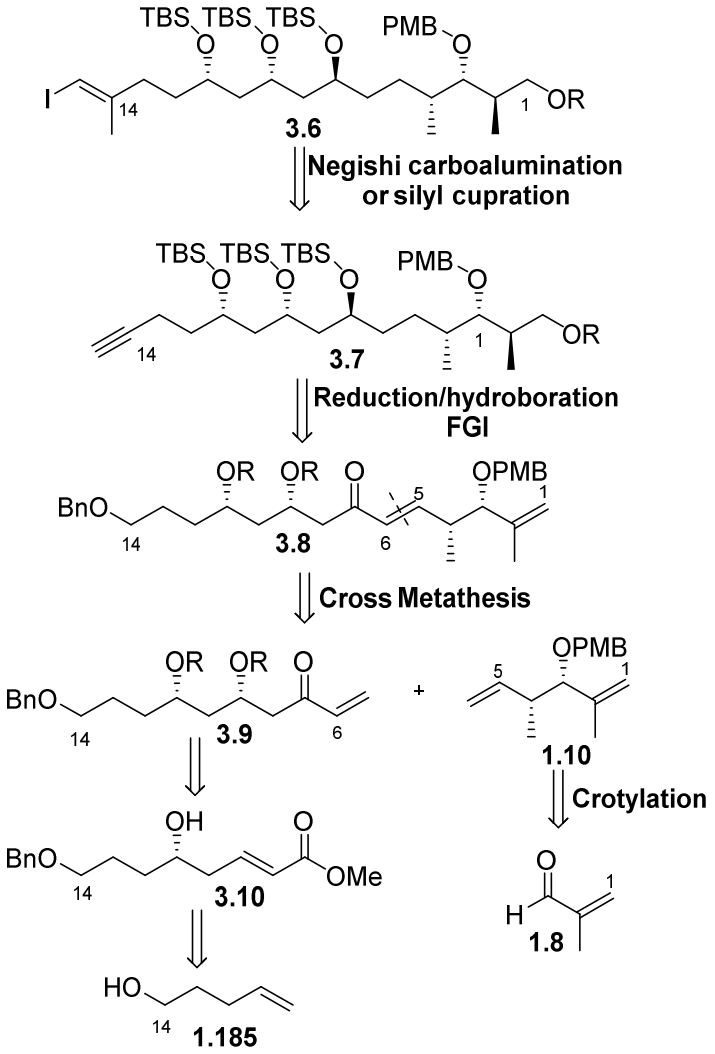
Scheme 3.2: Deprotection of benzylidene acetal **3.4** at an earlier stage of the synthesis

Bearing in mind all the above disadvantages of the previous route, we needed a new synthetic route where the efficient removal of benzylidene acetal, as well as setting the

correct stereochemistry at C7 at an earlier stage, would be possible. Also, coupling of the two fragments using cross metathesis needed optimisation.

3.1 Approach 1: Coupling of the C6-C14 and unfunctionalized C1-C5 fragments by cross metathesis

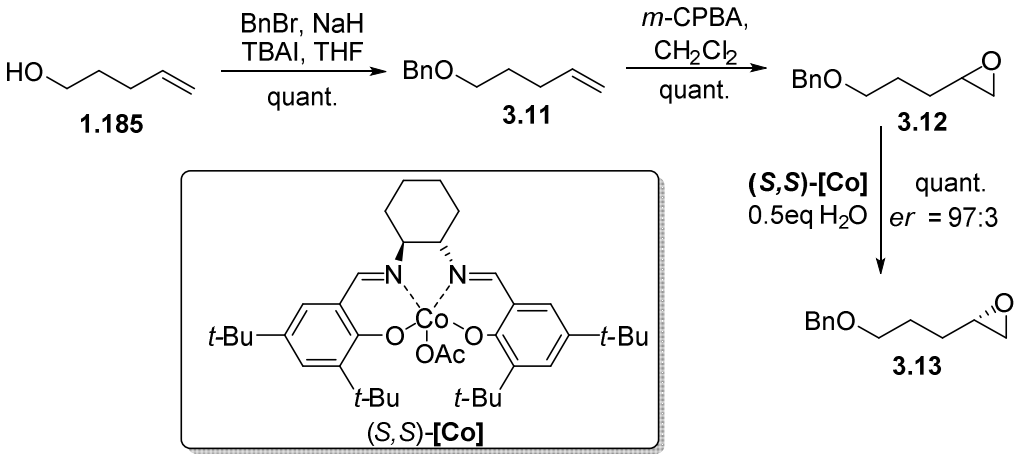
The required vinyl iodide **3.6** could be prepared from alkyne **3.7** using a Negishi carboalumination or alternatively a silylcupration (Scheme 3.3). Preparation of **3.7** from **3.8** could be achieved through a series of transformations, key steps including hydroboration or terminal alkene, enone reduction, and the a Seyferth-Gilbert homologation to install alkyne moiety present in **3.7.** Cross metathesis of enone **3.9** with diene **1.10** should allow the formation of **3.8.** Enone **3.9** would be synthesised from known ester intermediate **3.10** that is prepared from alcohol **1.185**. Crotylation of methacrolein **1.8** followed by protection of the formed alcohol would afford the unfunctionalized C1-C5 fragment of dolabelide C **1.10**.



Scheme 3.3: Retrosynthesis of the C1-C15 fragment **3.6** of dolabelide C

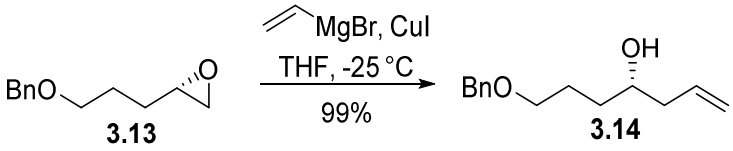
3.1.1 Synthesis of the C6-C14 fragment 3.9

As shown in Scheme 3.4, the forward synthesis to enone **3.9** started with the protection of the primary alcohol **1.185** as its benzyl ether and was followed by the alkene epoxidation using *m*-CPBA, thus affording racemic epoxide **3.12**. Hydrolytic kinetic resolution[64] of **3.12** using **(*S,S*)-[Co]** catalyst gave the epoxide **3.13** in excellent enantioselectivity and yield.



Scheme 3.4: Synthesis of enantiopure epoxide **3.13**

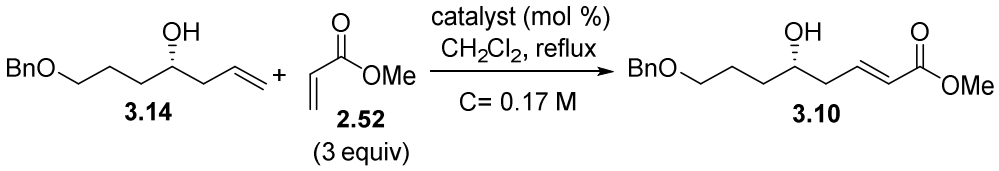
It was also possible to perform the sequence of steps (Scheme 3.4) on large scale (370 mmol) using 1.2 equiv of benzyl bromide and 1.1 equiv of *m*-CPBA and purifying only the final enantiopure epoxide **3.13** in 78% overall yield. Selective ring opening on the least hindered side of epoxide **3.13** was achieved using an organocuprate reagent furnishing homoallyl alcohol **3.14** in excellent yield (Scheme 3.5).



Scheme 3.5: Synthesis of homoallylic alcohol **4.9**

Cross metathesis of methyl acrylate **2.52** with homoallyl alcohol **3.14** proceed smoothly to give conjugated ester **3.10** using either **GII** or **M_{71}SIPr** catalyst with the later giving 89% yield using just 1 mol% loading of catalyst.

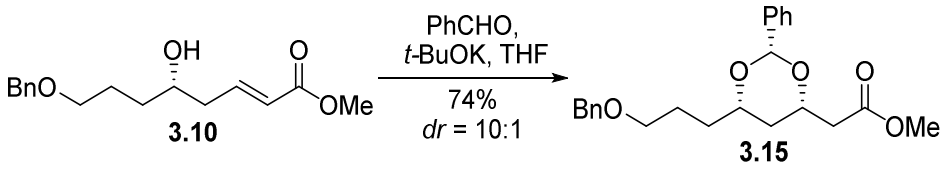
[64] (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (d) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.



Entry	Catalyst	Time	Loading	Yield
1	**G-II**	2 days	3.2%	92%
2	Umicore **M_{71}SIPr**	3 days	1%	89%

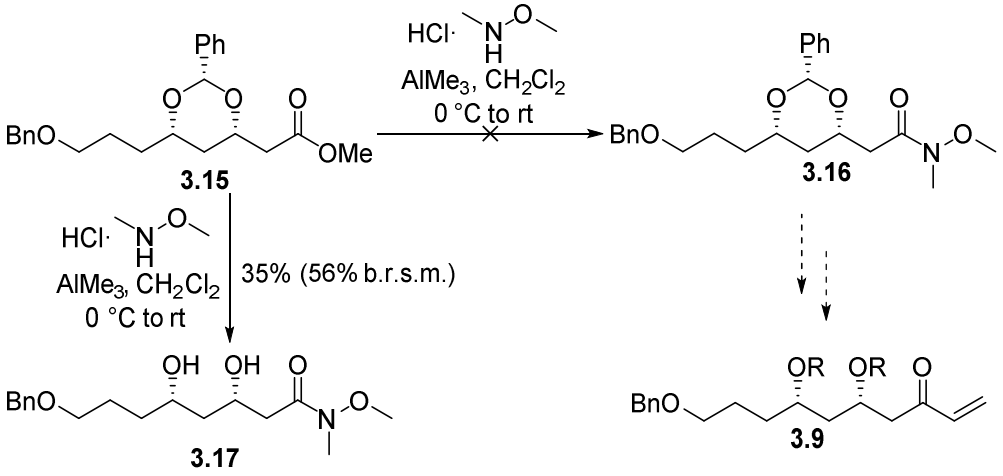
Table 3.1: Cross metathesis of **3.14** with methyl acrylate **2.52** with different catalysts

Ester **3.10** was then subjected to a diastereoselective oxa-Michael conjugate addition[65] using a catalytic amount of *t*-BuOK, leading to benzylidene acetal **3.15** in 74% yield (Scheme 3.6).



Scheme 3.6: Synthesis of enantiopure epoxide **3.15**

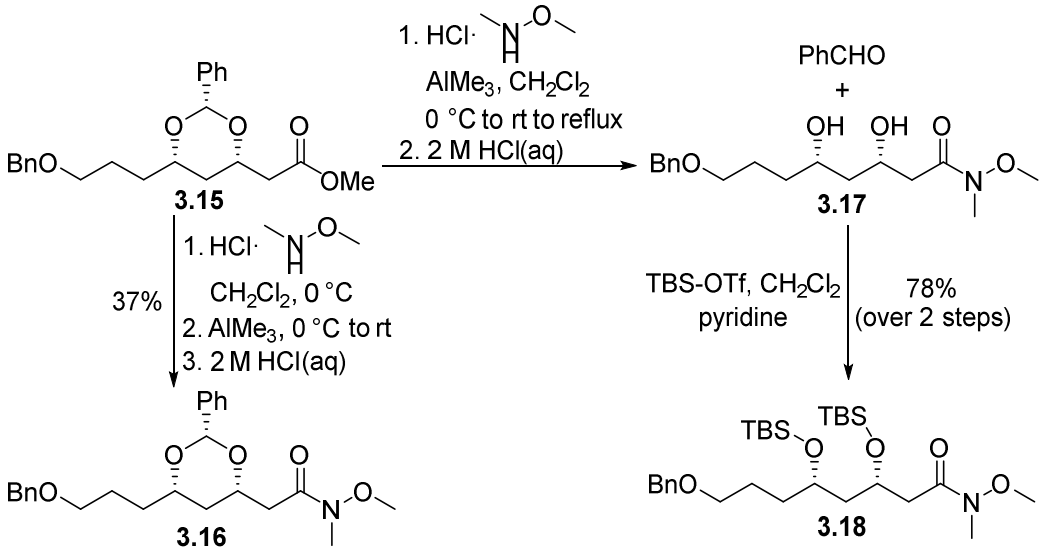
The next challenge was to transform the ester moiety in **3.15** into the corresponding enone **3.9** *via* Weinreb amide intermediate **3.16.** (Scheme 3.7). However, we were delightfully surprised to achieve the concomitant removal of the benzylidene acetal when treating **3.15** with a pre-mixed solution of $AlMe_3$/*N,O*-dimethoxyhydroxylamine, thus obtaining free diol **3.17** as the major product of the reaction.



Scheme 3.7: Weinreb amide formation with concomitant benzylidene acetal removal using **3.15** as starting material.

[65] Evans, D.A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

Further investigation in the reaction led us to employ the following optimised experimental conditions: Dropwise addition of a 2M toluene solution of $AlMe_3$ to a solution of *N,O*-dimethoxyhydroxylamine in dichloromethane at 0°C; warming the reaction mixture to room temperature and stirring for 2 h before slowly adding a solution of benzylidene acetal **3.15** in dichloromethane followed by refluxing overnight; quenching the reaction with a 2 M aqueous HCl solution at room temperature before saturating the reaction mixture with NaCl to ensure minimal loss of product by its solvation in the aqueous layer; extracting the mixture with diethyl ether several times until complete decolouration of the aqueous layer. Eventually a 1:1 mixture of **3.17** to benzaldehyde without other impurities was obtained. Fortunately, the benzaldehyde did not interfere in the next step, thus further purification was avoided. *Bis* protection of the diol as the corresponding TBS ethers yielded **3.18** in 78% over two steps (Scheme 3.8)



Scheme 3.8: Preparation of Weinreb amides **3.18** and **3.16** from **3.15**

By slightly tweaking the reaction conditions when changing the order of which the reagents were added, isolation of Weinreb amide **3.16** was possible in 37% yield (Scheme 3.8). In this case, stirring **3.15** with *N,O*-dimethoxyhydroxylamine in dichloromethane at 0° was followed by dropwise addition of a 2 M toluene solution of $AlMe_3$. The reaction was monitored by TLC and quenched accordingly.

Even though the optimised conditions for the transformation of benzylidene acetal **3.15** to Weinreb amide **3.18** (Scheme 3.8) were reliable and consistently high yielding on small scale (≈0.25 mmol), it was found that when trying to increase the scale of the reaction it became progressively more sluggish giving **3.18** in lower yields accompanied by an undesired lactone **3.19** that had not been previously observed (Figure 3.1).

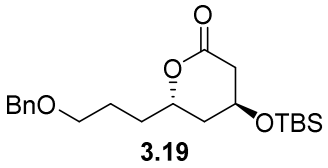
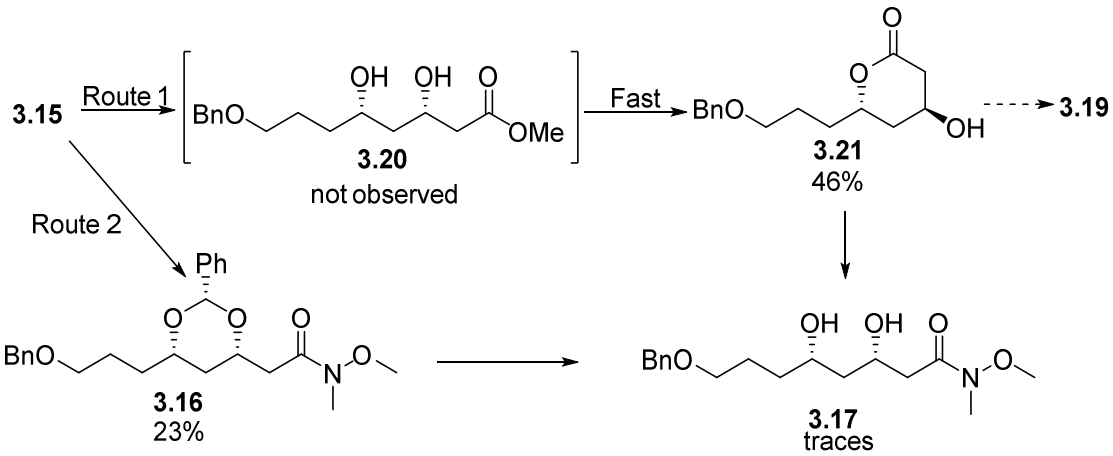


Figure 3.1: Structure of undesired lactone **3.19**

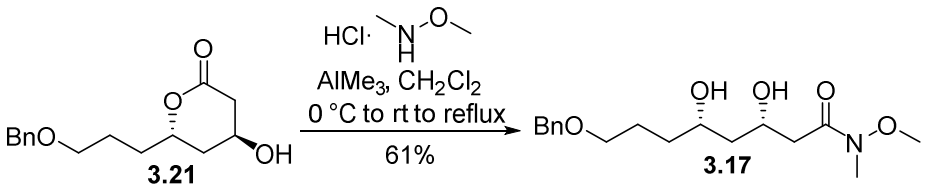
In attempt to understand the possible reaction pathways involved, we used the conditions mentioned earlier to convert benzylidene acetal **3.15** to Weinreb amide **3.17** on a 16 mmol scale reaction and then quenched it after 24h. Lactone **3.21** and protected Weinreb amide **3.16** where isolated after purification in 46% and 23% yield respectively. Traces of desired Weinreb amide **3.17** as well as 13% of the starting material were also observed. With this results in hands, we propose two different pathways for the reaction (Scheme 3.9).



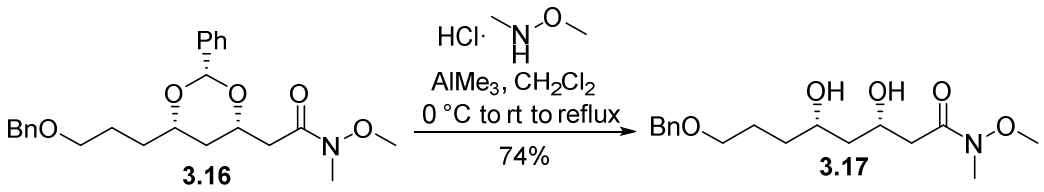
Scheme 3.9: Attempt to prepare **3.17** on larger scale

The obtained results suggest that Weinreb amide formation in **3.15** is in competition with the benzylidene acetal cleavage. If the benzylidene acetal is cleaved first (route 1) it would lead to the syn-β,δ-dihydroxy ester **3.20**, which under the reaction conditions would quickly cyclise to form δ-lactone **3.21**. Formation of lactone **3.19** can be explained by this route after the protection of the alcohol. Alternatively, the dimethylaluminium amide species can attack **3.21** once again to give the desired Weinreb amide **3.17**. On the other hand, in the case that **3.16** is formed first the subsequent benzylidene acetal cleavage would directly lead to **3.17**.

Isolation of both intermediates **3.21** and **3.16** suggest that both pathways are possible. Re-submitting **3.21** (Scheme 3.10) and **3.16** (Scheme 3.11) to the same conditions gave once again the desired product **3.17** in 61% and 74% respectively.

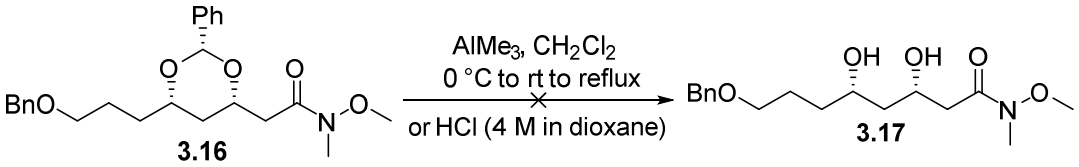


Scheme 3.10: Synthesis of **3.17** from **3.21**



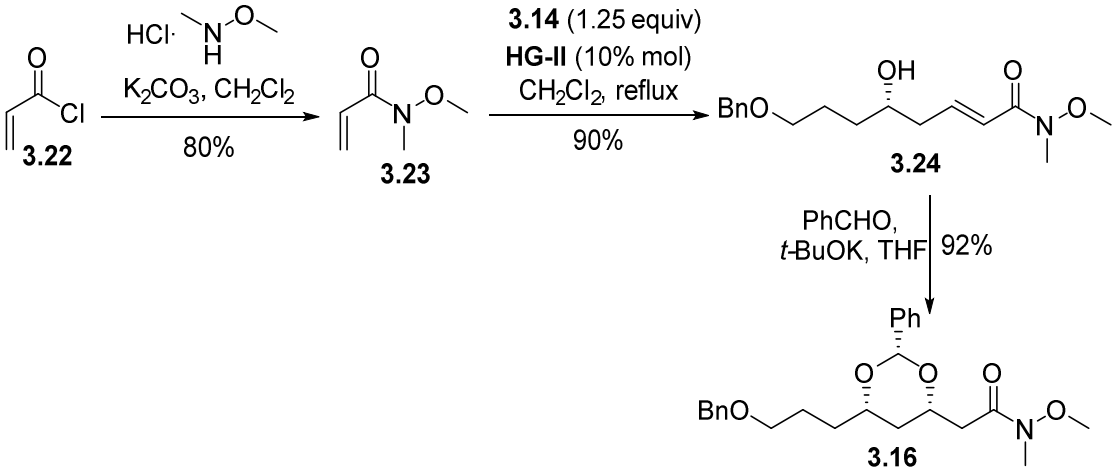
Scheme 3.11: Synthesis of **3.17** from **3.16**

Intrigued by these results we were also inclined into trying other conditions for the benzylidene acetal moiety cleavage of amide **3.16.** Using 4 M HCl in dioxane led primarily to the recovery of the starting material **3.16** along with a few unidentified decomposition products; sadly no trace of desired diol **3.17** was observed (Scheme 3.12). $AlMe_3$ without any amine was also tested; however, as expected no reaction took place. This led us to the conclusion that the dimethylaluminium amide species is required in order to cleave the benzylidene acetal.



Scheme 3.12: Synthesis of **3.16** from **3.17**

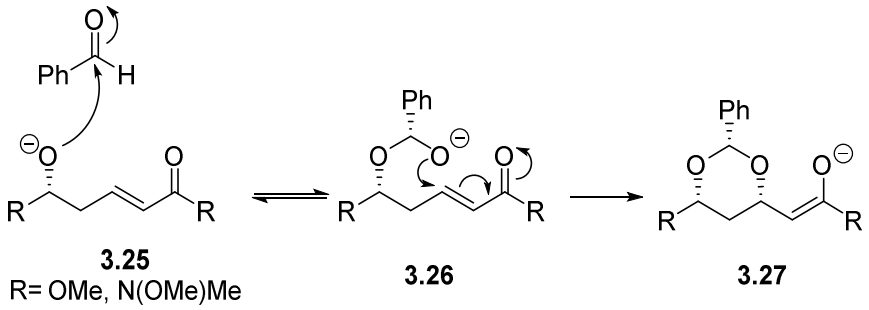
We next investigated an alternative slightly more convergent route using **3.23**, which already bears the Weinreb amide functionality. Preparation of **3.23** from the corresponding chloride **3.22** was easily performed (Scheme 3.13). Coupling of **3.23** with type I olefin **3.14** afforded the desired alcohol **3.24** in 90% yield. It is worth mentioning that **3.23** has to be freshly distilled before the reaction and **HG-II** catalyst must be used in higher loading compared to previous metathesis reactions performed.



Scheme 3.13: Alternative route for the synthesis of **3.16**

Conjugate addition to hydroxy amide **3.24** gave the corresponding benzylidene acetal **3.16** in excellent yield and as a single diastereomer. This route (Scheme 3.13) is slightly higher yielding and originally had one fewer step comparing with the route utilising ester **3.10** (Table 3.1 and scheme 3.6). However, since we found conditions to form Weinreb amide **3.17** with concomitant removal of benzylidene acetal (Scheme 3.8) the same number of steps are needed. Additionally, the use large amount of **HGII** catalyst as well as excess of valuable precursor **3.14** made this route practically costly and therefore less efficient.

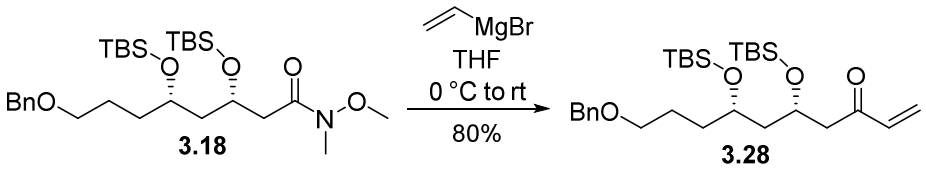
The mechanism of the oxa-Michael reaction on unsaturated hydroxy ester or unsaturated hydroxy amide systems is shown in Scheme 3.14.



Scheme 3.14: Oxa-Michael reaction

Formation of the 1,3-*syn* product is favoured due to all substituents being in the equatorial position. Since the reaction is under thermodynamic control any 1,3-*anti* diol formed can undergo a retro-Michael addition thus isomerizing to the more stable *syn* isomer.

The final step of the synthesis was the vinylation of **3.18**, which proceeded smoothly, thus furnishing the C6-C14 fragment **3.28** in 80% yield (Scheme 3.15).

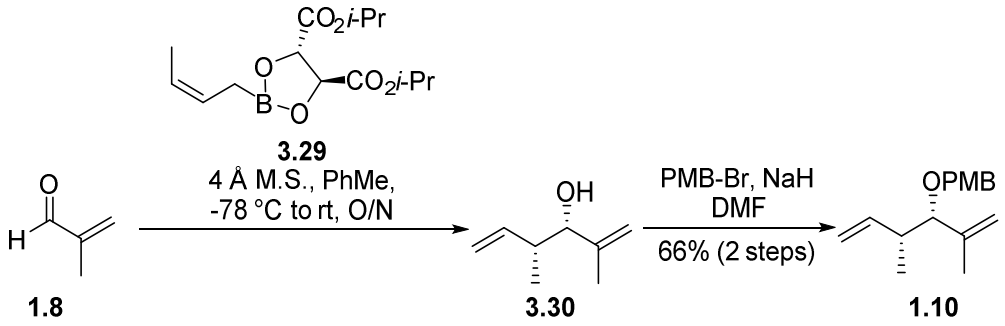


Scheme 3.15: Synthesis of the C6-C14 fragment **3.28**

Overall, the C6-C14 fragment **3.28** was prepared in 45.7% yield from alkene **1.185** over 8 steps.

3.1.2 Synthesis of the unfunctionalized C1-C5 fragment

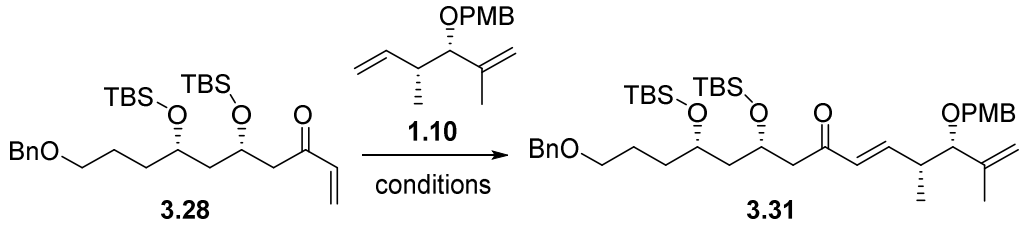
Diene **1.10** has been synthesised before by Leighton *et al.*[5] starting from methacrolein **1.8** and reagent **1.12** (Scheme 1.2). We used crotyl boronate **3.29** instead, thus obtaining alcohol **3.30**, which was subsequently protected as its PMB ether giving **1.10** in 66% yield for the two steps. By comparing the specific rotation of **1.10** to the literature value, we determined the enantioselectivity being er ≈ 6:1. This value is slightly inferior compared to the one obtained by Leighton.



Scheme 3.16: Synthesis of diene **1.10** using crotyl boronate **4.29**

3.1.3 Cross metathesis of the two fragments and further functionalisation attempts

With both fragments in hand, we started investigating coupling conditions using cross metathesis for the formation of **3.31** The results obtained are presented in Table 3.2.

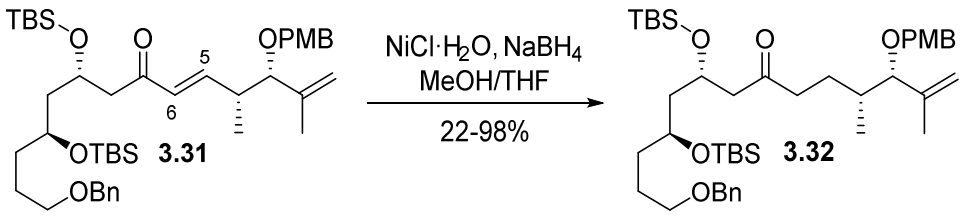


Entry	Equivalents (3.28: 1.10)	Scale (mmol)	Catalyst (mol%)	Solvent	Time	Temp	Yield
1	1: 1.4	0.48	**G-II** (10)	CH_2Cl_2	3 days	reflux	39%
2	1: 1.2	0.19	**HG-II** (5)	CH_2Cl_2	3 days	reflux	57%
3	1: 1.4	0.48	**HG-II** (10)	CH_2Cl_2	3 days	reflux	68%
4	1: 1.3	0.31	**HG-II** (7.5)	toluene	3 days	60 °C	64%
5	1: 1.4	1.34	**HG-II** (7.5)	toluene	2 days	60 °C	66%
6	2: 1	0.26	**HG-II** (10)	CH_2Cl_2	16 h	reflux	86%

Table 3.2: Cross metathesis of enone **3.28** with diene **1.10**

Refluxing in dichloromethane for 3 days using 10 mol% **G-II** catalyst gave the desired product **3.31** in 39% yield (entry 1), whereas using similar conditions but switching to **HG-II** instead furnished **3.31** in 57% yield with just 5 mol% catalyst loading (entry 2). Doubling the catalyst amount slightly increased the yield (entry 3), while changing the solvent to toluene gave similar results (entries 4 and 5). Using two equivalents of the type II olefin **3.28** was found to be the best conditions decreasing the reaction time to 16 h and giving **3.31** in 86% yield (entry 6). The only drawback with these conditions was that they did not allow the recovery of the excess of valuable enone **3.28** used.

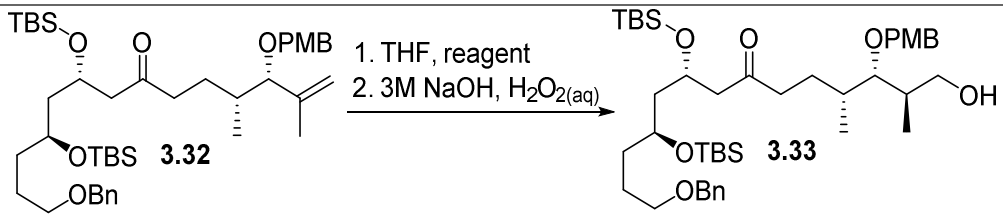
We next attempted the selective reduction of the C5-C6 double bond, which was achieved using $NiCl_2{\cdot}H_2O/NaBH_4$, giving the desired ketone **3.32** in almost quantitative yield when first attempted (Scheme 3.17). Unfortunately, this reaction was not reproducible giving mixed results especially when increasing the scale. The use of Stryker's reagent instead was also attempted with no luck.



Scheme 3.17: Selective reduction of the C5-C6 double bond

We continued the synthesis with the small amount of material we had in hand to determine if it was worth bringing forward more material. The hydroboration of **3.32** was investigated first. Several conditions are presented in table 4.3. However, after several attempts using

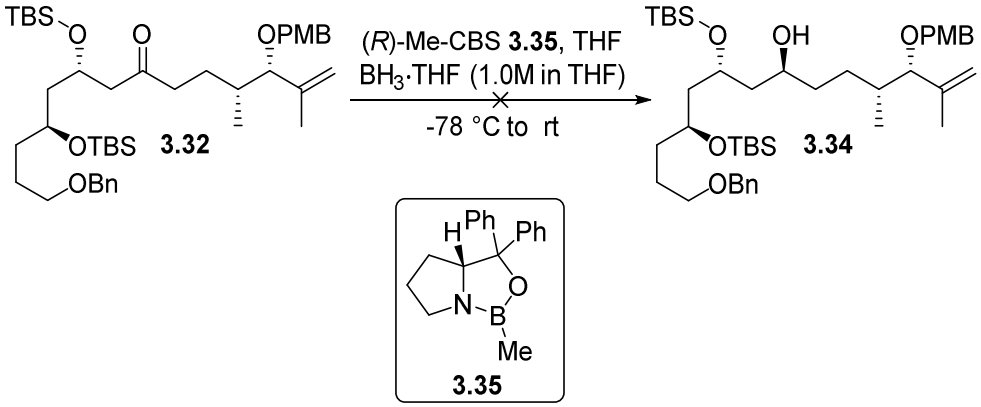
9-BBN (entries 1 and 2) or its corresponding dimer (entries 3, 4 and 5), it was not possible to generate the desired terminal alcohol **3.33**.



Entry	Reagent	C (M)	Scale (mmol)	T (C°)	Outcome
1	2 eq. 9-BBN (0.5 M in THF)	0.20	0.16	-78 to rt	SM recovered
2	4 eq. 9-BBN (0.5 M in THF)	0.13	0.27	-78 to rt	SM recovered
3	1.25 eq. 9-BBN dimer	0.27	0.27	rt	SM recovered
4	2.5 eq. 9-BBN dimer	0.27	0.27	rt	Decomposition
5	1.6 eq. 9-BBN dimer	0.27	0.20	rt	SM recovered

Table 3.3: Hydroboration attempts of **3.32**

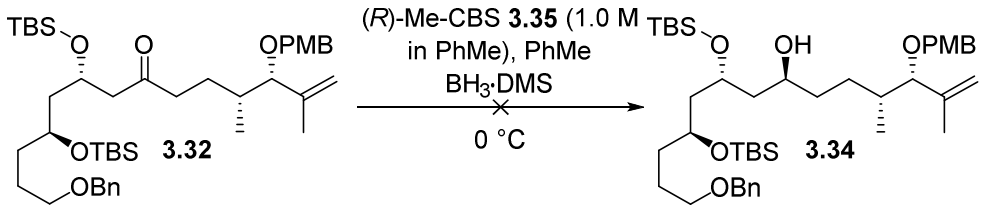
With the hydroboration being unsuccessful, we sought to change the order of the following steps. Thus, the diastereoselective reduction of ketone **3.32** using (*R*)-Me-CBS **3.35** with BH_3·THF complex was attempted to form alcohol **3.34**. (Scheme 3.18)



Scheme 3.18: Attempt to diastereoselectivly reduce ketone **4.23**

When trying the reaction using one equivalent of each **3.35** and BH_3·THF complex, even after prolonged reaction times no product was observed. Conveniently the starting material could be recovered. When increasing the amounts of **3.35** and BH_3·THF complex, only decomposition was observed.

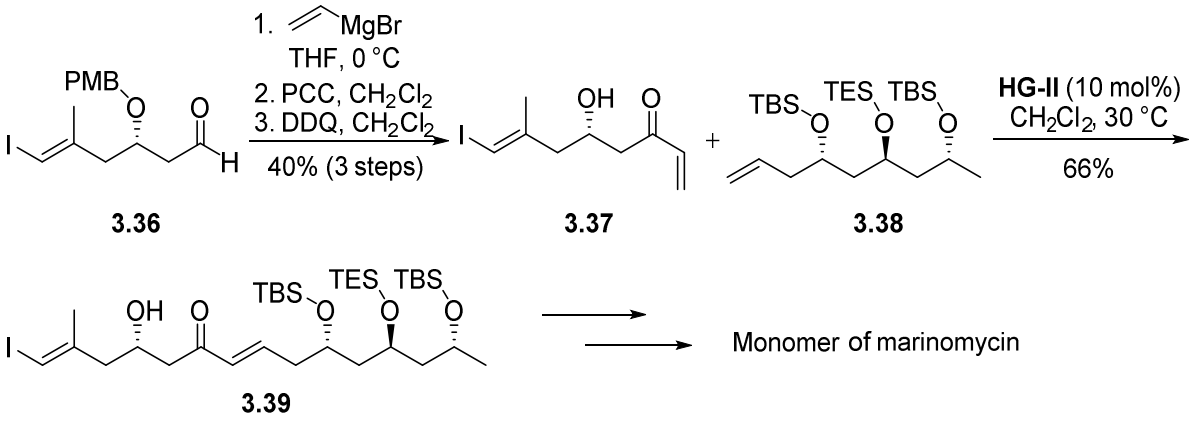
A final attempt for the CBS reduction of enone **3.32** using slightly different conditions was made. The solvent of the reaction was switched to toluene, while a solution of **3.35** in toluene instead of solid **3.35** was employed. Also, the previously used BH_3·THF complex was replaced with BH_3·DMS (Scheme 3.19). Disappointingly, the desired compound **3.34** was not formed.



Scheme 3.19: Attempt to diastereoselectivly reduce ketone **3.32**

3.2 Approach 2: Coupling of the C6-C15 and functionalised C1-C5 fragments by cross metathesis

After the unsuccessful attempts to further functionalise **3.32**, we opted for functionalising at an earlier stage, specifically before the cross metathesis reaction. Initially, we believed that a vinyl iodide moiety was deemed to be very unstable. However, we came across an example in the literature by Cossy *et al*.[66] in their synthesis of the monomeric counterpart of marinomycin A (Scheme 3.20). Starting from aldehyde **3.36**, which bears a vinyl iodide moiety, enone **3.37** was prepared using vinylmagnesium bromide in 40% yield after three steps. Enone **3.37** was subsequently coupled with homoallylic protected **3.38** alcohol by cross metathesis to give desired intermediate **3.39** in 66% yield.



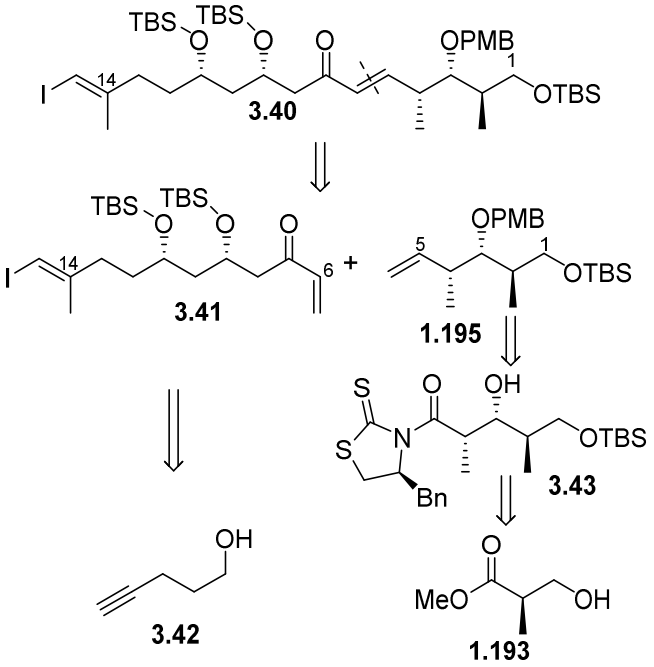
Scheme 3.20: Use of a vinyl iodide moiety in the synthesis of marinomycin A

Digging further in the literature revealed numerous reactions under various conditions where vinyl iodides were used while keeping the vinyl iodide functionality intact.[67,68] This, in combination with the structural resemblance of our substrates to the intermediates used by Cossy *et al*. led us to investigate a new possible route to synthesise the C6-C15 fragment. The vinyl iodide moiety would be installed at an earlier stage of the synthesis, which would

[66] Amans, D.; Bareille, L.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2009**, *74*, 7665.
[67] Xiao-Bo, D.; Margaret, B. A.; Furkert, D. P. *J. Org. Chem.* **2018**, *83*, 12460
[68] Jokin, C.; Gómez, A.; Costa, A. M.; Fernández, P.; Isart, C.; Sidera, M.; Vilarrasa, J. *Tetrahedron Lett.* **2014**, *55*, 4623.

also significantly reduce the number of steps used to prepare the C6-C15 fragment (Scheme 3.21).

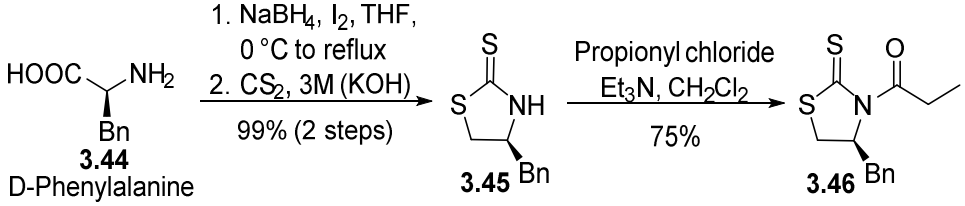
Regarding the C1-C5 fragment, **1.193** would be used as the starting material. This compound had been previously prepared in the group. Unfortunately, we could not acquire *Z*-butene that was needed to prepare the crotyl boronate **3.29**, which was used in the previous synthesis of **1.193**. Therefore it was decided to use a Crimmins aldol to set the required C3,C4-*syn* stereochemistry instead. The C2 stereocentre could already be set in place starting with Roche ester **1.193** (Scheme 3.21).



Scheme 3.21: Revised retrosynthesis

3.2.1 Synthesis of the functionalized C1-C5 fragment

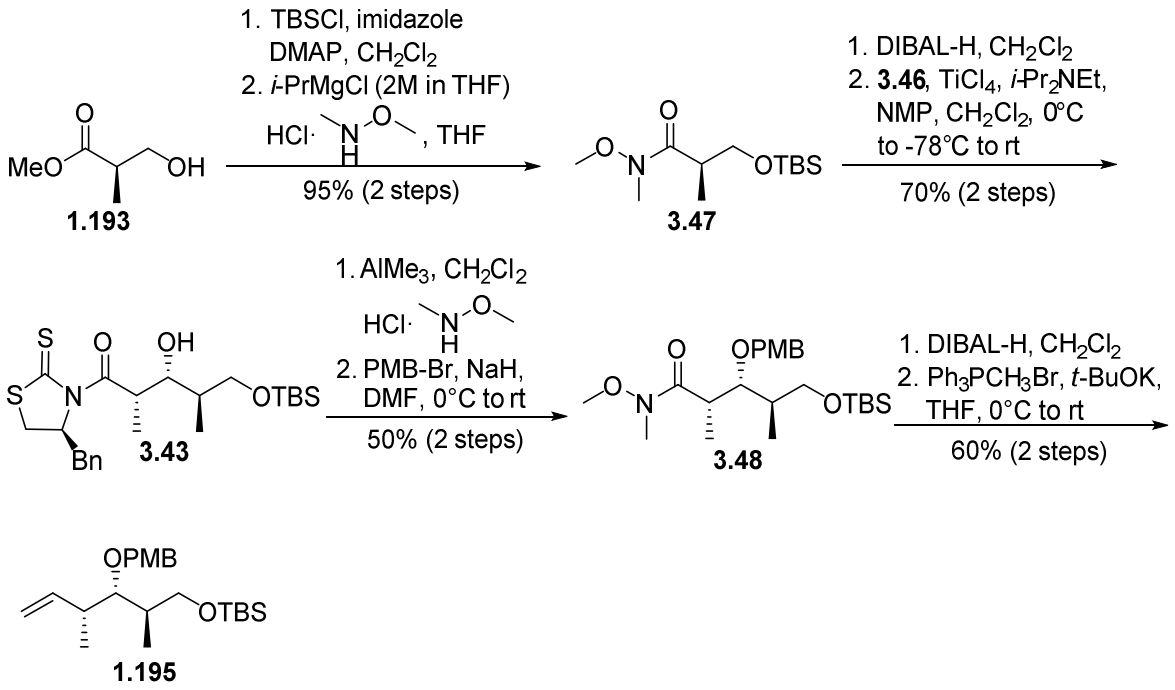
At first, the Crimmins acylated auxiliary **3.46** was prepared by reduction of D-Phenylalanine to the amino alcohol and subsequently treated with carbon disulfide in the presence of 3M KOH giving thiazolidinethione **3.45** (Scheme 3.22). Crude thiazolidinethione **3.45** was then *N*-propionylated furnishing **3.46** in 75% yield.



Scheme 3.22: Acylated crimmins auxiliary **3.46** preparation

With **3.46** in hand, the forward synthesis of the C1-C5 fragment commenced from (*R*)-Roche ester **1.193** that was protected as the corresponding TBS ether and subsequently converted into Weinreb amide **3.47** (Scheme 3.23). Direct conversion of ester **1.193** to its corresponding aldehyde was preferred, however this often led to racemization and we anticipated avoiding this risk by going via the Weireb amide. DIBAL-H reduction of Weinreb amide **3.47** gave the corresponding aldehyde that was immediately used in the Crimmins aldol reaction using NMP and *i*-Pr_2NEt[69] thus forming aldol **3.43** that was obtained as a single diastereomer in 70% yield after purification.

The next step in the synthesis was the alcohol protection of **3.43** that was initially unsuccessfully attempted using PMB trichloroacetimidate under acidic conditions. Auxiliary cleavage using $AlMe_3$ and *N,O*-hydroxylamine transformed **3.43** into the corresponding Weinreb amide, which allowed its subsequent protection using PMB-Br under basic conditions thus furnishing **3.48** in 50% for the two steps. Amide **3.48** was then treated with DIBAL-H and the resulting aldehyde underwent a Wittig olefination using the required phosphonium salt to yield **1.195** in 60% yield for the two steps. Overall, the C1-C5 functionalized fragment **1.195** was prepared in 20% yield over 8 steps from (*R*)-Roche ester **1.193.**

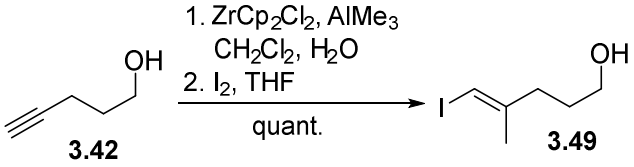


Scheme 3.23: Synthesis of the C1-C5 fragment **1.195**

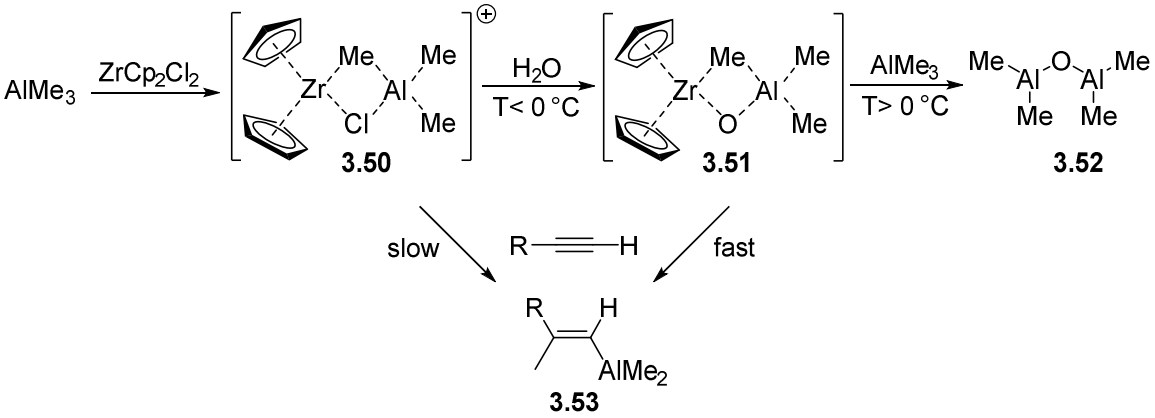
[69] Crimmins, M. T.; She, J. *Synlett* **2004**, 1371

3.2.2 Synthetic efforts to prepare the C6-C15 fragment starting from 4-pentyn-1-ol

We also thought of installing the vinyl iodide moiety at the start of the synthesis. Negishi carboalumination of 4-pentyn-1-ol (Scheme 3.24) was performed using water to accelerate the reaction by forming the more reactive species **3.51** (Scheme 3.25) as suggested by Wipf *et al.*[70] Trapping of the alkenylalane intermediate **3.53** with iodine gave the desired vinyl iodide **3.49** in quantitative yield.



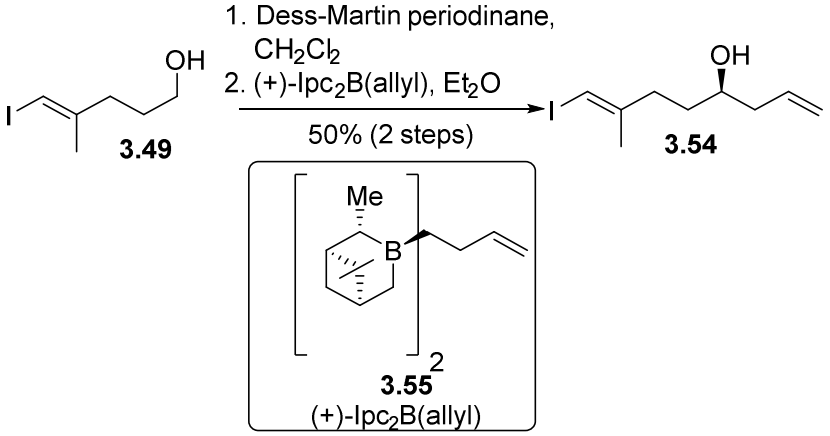
Scheme 3.24: Water-accelerated Negishi carboalumination of 4-pentyn-1-ol



Scheme 3.25: Mechanism of the water-accelerated Negishi carboalumination

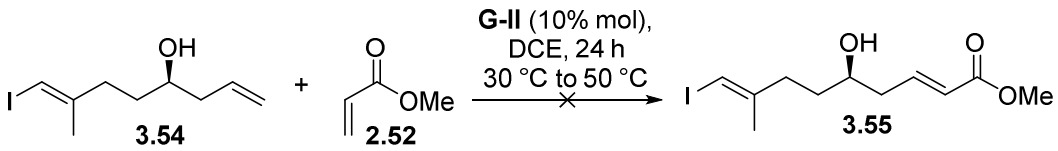
Since we had a sealed ampule of (+)-Ipc$_2$B(allyl) **3.55** in hand, we continued the synthesis of the enantiomer of compound **3.41**. Thus, alcohol **3.49** was oxidised using Dess-Martin periodinane to give the corresponding aldehyde that was subsequently subjected to an allylation reaction using (+)-Ipc$_2$B(allyl) **3.55** furnishing allylic alcohol **3.54** in 50% yield over two steps.

[70] Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* **1993**, *32*, 1068.



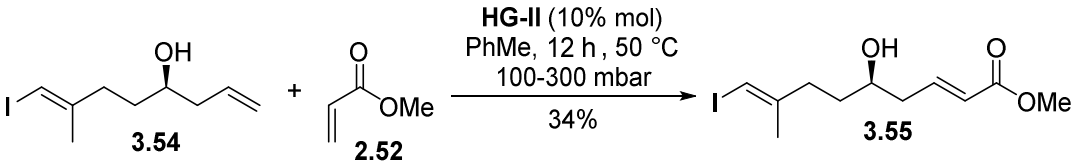
Scheme 3.26: Preparation of homoallyl alcohol **3.54**

When first trying the cross metathesis reaction between **3.54** and methyl acrylate **2.52** using **G-II** catalyst (Scheme 3.27) at 30 °C after 12 h, TLC analysis showed only starting material, thus we decided to heat the reaction to 50 °C and left to stir for a further 12 h period. Unfortunately, no desired product **3.55** was observed whereas by this time other decomposition products had started appearing.



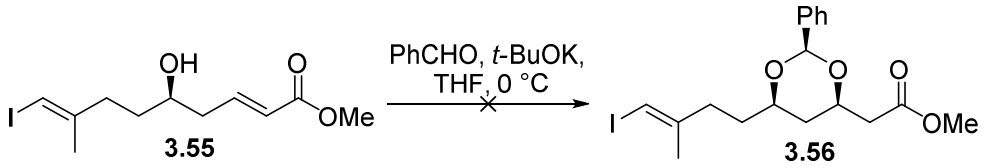
Scheme 3.27: Unsuccessful cross metathesis attempt to prepare **3.55**

We next attempted using the more active **HG-II** catalyst as well as running the reaction under reduced pressure in a Schlenk tube (Scheme 3.28). The crude reaction mixture proved to contain **3.55**. Tedious purification finally provided the desired conjugate ester **3.55** in 34% yield.



Scheme 3.28: Successful cross metathesis attempt to prepare **3.55**

Although cross metathesis between vinyl iodide **3.54** and methyl acrylate **2.52** was rather low yielding, no further attempts to optimise were perused. Since the main priority at this stage was to determine if the oxa-Michael conjugate addition using conjugate ester **3.55** was feasible. Unfortunately, only the decomposition of vinyl iodide **3.54** was observed (Scheme 3.29).

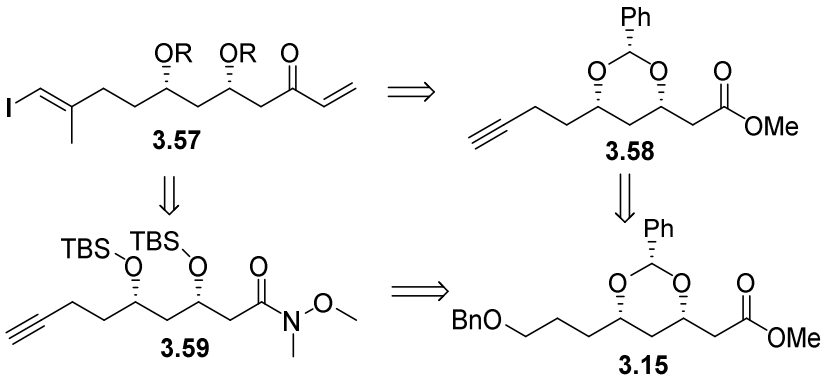


Scheme 3.29: Oxa-Michael conjugate addition in **3.56**

To add to this unfortunate result, trying to prepare more conjugate ester **3.55** from **3.54** by cross metathesis was not reproducible, therefore we decided to abandon this route.

3.2.3 Efforts to install the vinyl iodide moiety after the oxa-Michael conjugate addition reaction

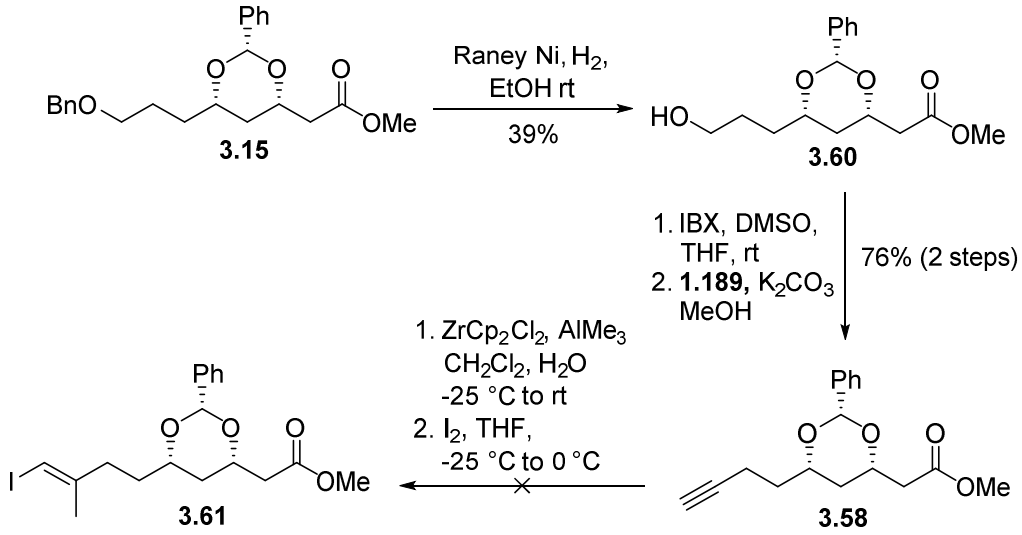
After these disappointing albeit rather expected results, we envisaged testing the Negishi carboalumination on either ester **3.58** or amide **3.59** (Scheme 68). Both of these substrates could be synthesised starting from **3.15,** which we had already prepared earlier.



Scheme 3.30: Plausable retrosynthetic paths to prepare **4.50** from **4.51** or **4.52**

Selective deprotection of the benzyl ether in the presence of the benzylidene acetal **3.15**[71] was sluggish and only gave moderate yield of free alcohol **3.60** (Scheme 3.31). Despite this result and since enough material was obtained, we focused on carrying on with the synthesis. Oxidation of **3.60** using IBX gave the crude aldehyde that was employed in the subsequent step without any further putification. The Seyferth-Gilbert homologation reaction was performed using Ohira-Bestman reagent **1.189** to furnish the required alkyne **3.58** in 76% yield for the two steps.

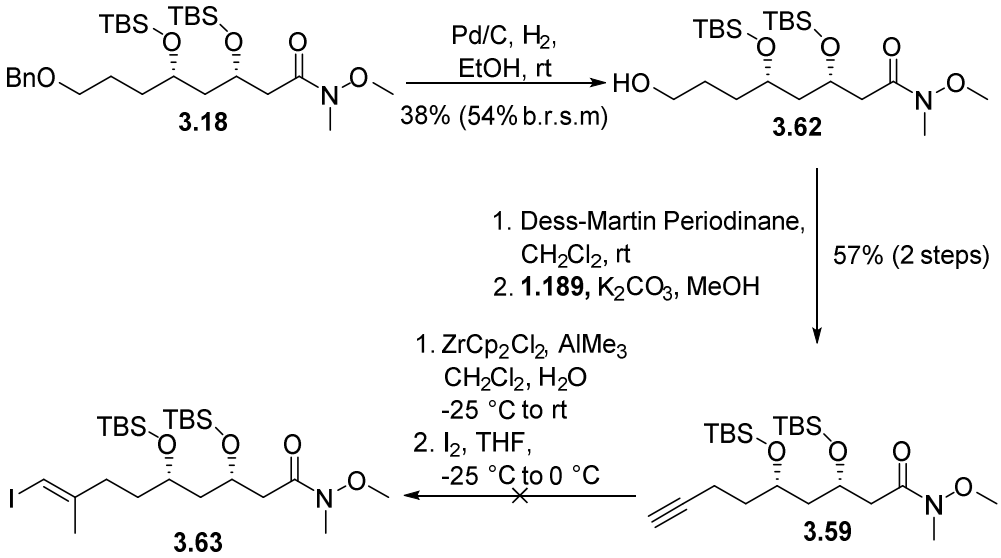
[71] Vincent, A.; Prunet, J. *Tetrahedron Lett.* **2006**, *47,* 4075.



Scheme 3.31: Negishi carboalumination attempt with ester **3.15**

Subjection of alkyne **3.58** to the Negishi carboalumination using the same conditions as those used previously for 4-pentyn-1-ol only gave a complex mixture of by-products.

We then turned our attention to the *bis*-TBS protected Weinreb amide **3.18** that was hydrogenated using Pd/C at atmospheric pressure to give free alcohol **3.62** in 38% yield, while partially recovering the starting material (Scheme 3.32). Oxidation of **3.62** to the aldehyde was initially anticipated by using IBX; however, Dess-Martin periodinane gave slightly better yields as well as avoiding the purification that was necessary in order to remove the DMSO when performing the reaction with IBX. Alkyne **3.59** was obtained in 57% yield over two steps from alcohol **3.62** and was then subjected to the Negishi carboalumination reaction.



Scheme 3.32: Negishi carboalumination attempt with amide 3.63

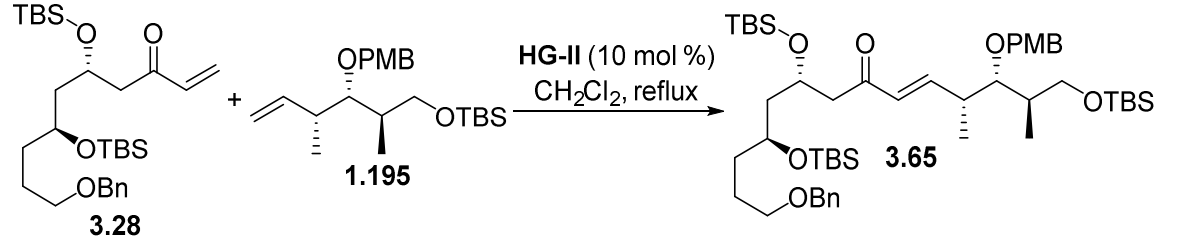
Unfortunately, once again a complicated mixture with no sign of the desired vinyl iodide **3.63** was observed.

3.3 Approach 3: Coupling of the C6-C14 and functionalised C1-C5 fragments by cross metathesis

3.3.1 Cross metathesis reaction between C6-C14 and functionalised C1-C5 fragments

Since all attempts to install the vinyl iodide moiety at an earlier stage of the synthesis were ineffective, we reverted to our initial plan that involved the late stage homologation and subsequent functionalisation.

In our last approach to arrive to our target, the key cross metathesis step was used to couple the C6-C14 segment **3.28** with the functionalised C1-C5 segment **1.195** to give the desired enone **3.65** (Table 3.2). When an excess of **1.11** is employed, compound **3.65** is obtained in 71% yield (entry 1). The use of **4.4** in excess resulted in the reduction of the reaction time from 48 h to 24 h and a slightly increase in the yield (entry 2).



Entry	Equivalents (4.4 : 1.11)	Time	Outcome
1	1 : 1.6	48 h	71%*
2	2 : 1	24 h	89%**

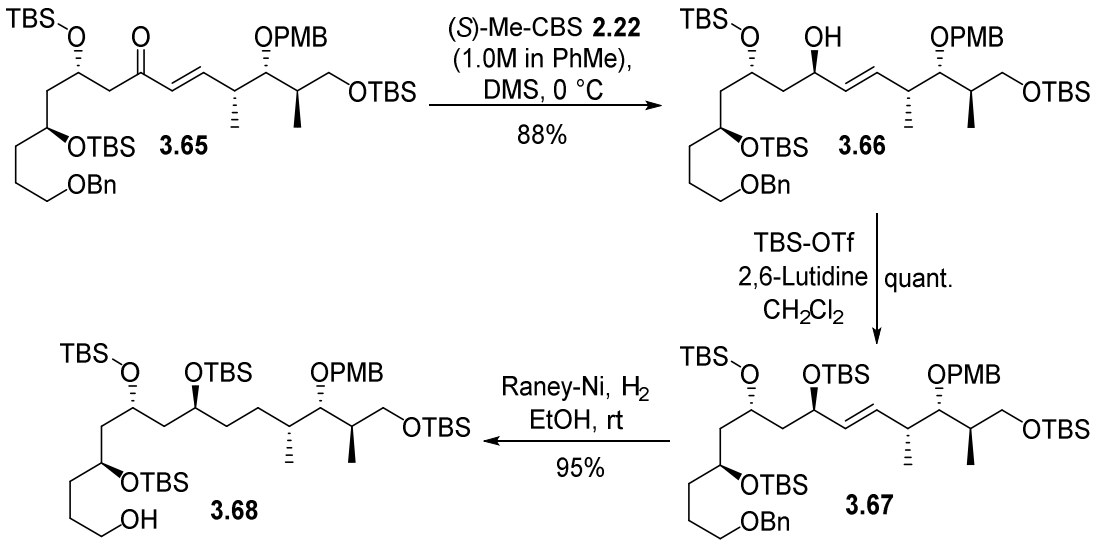
* As well as 100% recovery of excess **1.195** ** Also recovered 14% of enone **3.28**

Table 3.4: Cross metathesis of enone **3.28** with diene **1.195**

3.3.2 Further functionalisation of the C1-C14 fragment and end game of the synthesis

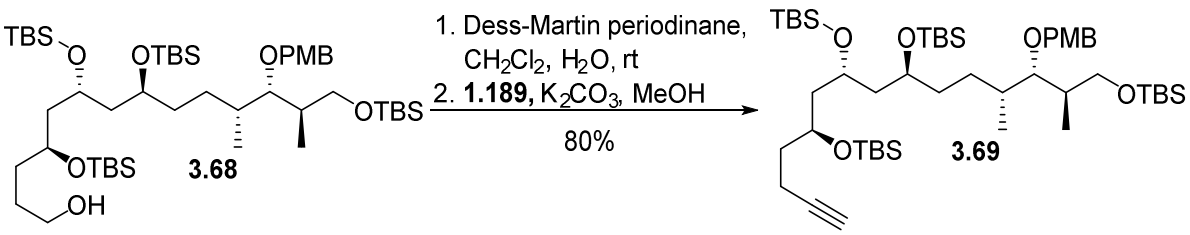
The final stereogenic centre of the molecule was installed by the reduction of enone **3.65** using (*S*)-(-)-2-Me-CBS-oxazaborolidine **2.22,** successfully providing **3.66** in good yield and as a single diastereomer after purification (Scheme 3.33). Subsequent protection of allylic alcohol **3.66** as its *t*-butyldimethylsilyl ether proceeded in quantitative yield and was followed

by the selective hydrogenation of the alkene and benzyl ether functionalities over the PMB ether in **3.67** using Raney-Ni.



Scheme 3.33: Synthesis of **3.68**

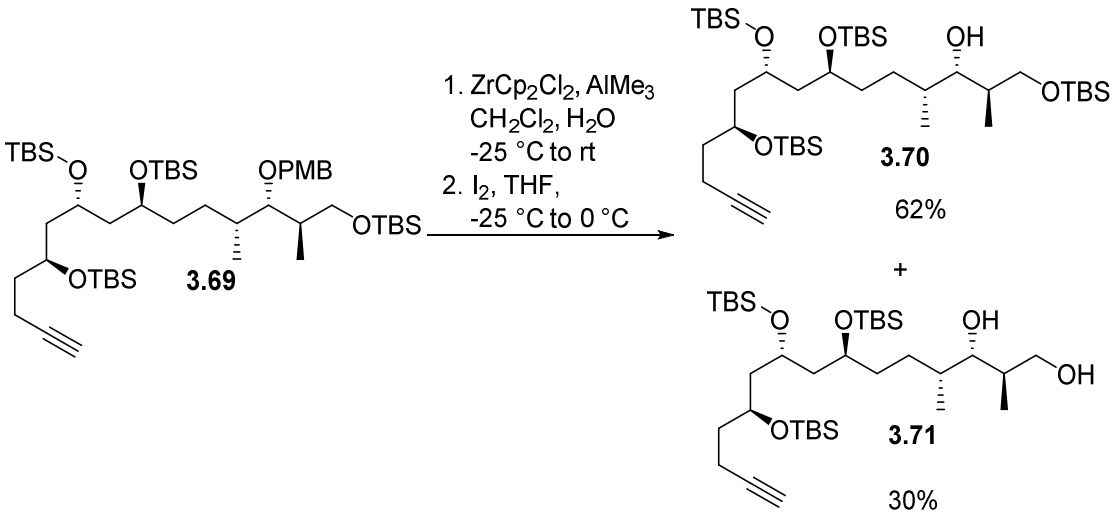
Although managing to obtain **3.68** from **3.67** in good yield eventually, this step proved to be much more challenging and time-consuming that what we first thought. Several different batches of commercially available Raney-Ni catalyst were tested in freshly distilled ethanol under 1 atm of hydrogen and were found to be extremely sluggish. The debenzylation alone took 10 days whereas leaving the reaction for another week had little difference with alkene still being intact. Attempts to try and warm the reaction (up to 60 °C) resulted in non-selective product mixtures with the alkene and/or PMB ether still intact while benzyl ether was cleaved. Finally, triturating the Raney-Ni catalyst a dozen of times with freshly distilled H_2O followed by ethanol and carefully monitoring the reaction by NMR was necessary to assure obtaining the desired product in high yields.



Scheme 3.34: Synthesis of **3.69** using Dess-Martin periodinane

Alcohol **3.68** was then converted to its corresponding aldehyde by oxidation with Dess-Martin periodinane (Scheme 3.34). Using CH_2Cl_2 that had been saturated in H_2O as the solvent was found to increase the yield of product while reducing the reaction time. The aldehyde obtained was then subjected to a Seyferth-Gilbert homologation reaction using Ohira-Bestman reagent once again, giving alkyne **3.69** in 80% yield over 2 steps.

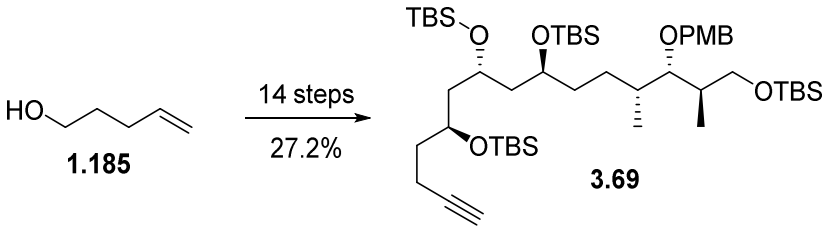
With alkyne **3.69** in hand the notorious Negishi carboalumination was tested using similar conditions as previously (Scheme 3.35). Surprisingly we observed no carboalumination taking place with the alkyne remaining intact (Scheme 3.35). The deprotected alcohol **3.70** and *bis* deprotected diol **3.71** were formed in 62% and 30% yield respectively. Unfortunately, due to time limitation and the lack of material no further attempts were made.



Scheme 3.35: Negishi reaction in **3.69**

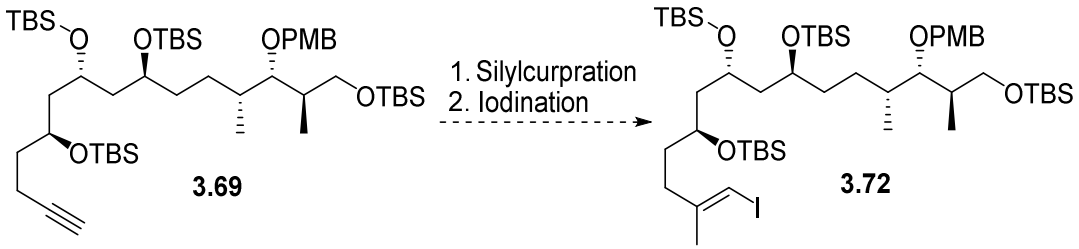
3.4 Conclusion and future work

As shown in Scheme 3.36 a high yielding reliable route to construct advanced intermediate alkyne **3.69** enantioselectivity was found starting from 4-penten-1-ol **1.185** (27.2% yield over 14 steps).



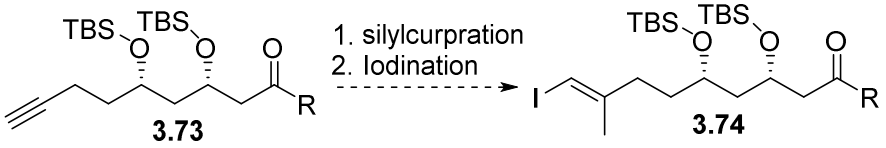
Scheme 3.36: Summary of the synthesis of alkyne **3.69**

Unfortunately, the vinyl iodide moiety could not be installed by a Negishi carboalumination. In the future it would be interesting to try a silylcupration reaction instead in order to obtain **3.72** (Scheme 3.37).



Scheme 3.37: Alternative method to prepare vinyl iodide **3.72**

Testing the silylcupration reaction at an earlier stage of the synthesis would also be desirable (Scheme 3.38).

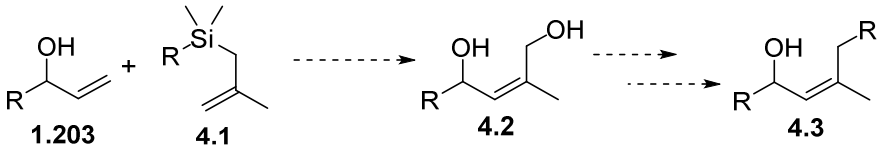


Scheme 3.38: Installing the vinyl iodide moiety at an early stage of the synthesis

Chapter 4: Synthesis of *Z*-olefin

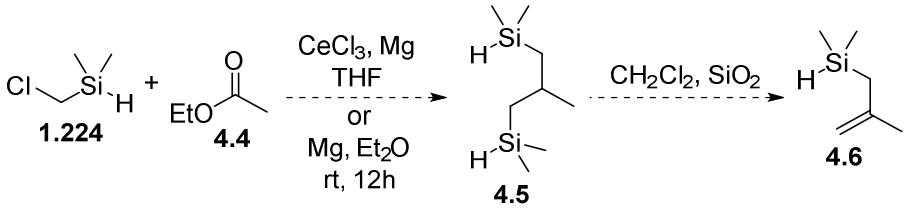
4.1 Synthesis of *Z*-olefins

Following the successful development of the silicon tether RCM methodology to prepare trisubstituted *E*-olefins selectively from allylic and homoallylic alcohols (Chapter 1.4.4), it has been long desired in the group to prepare *Z*-olefins selectively also (Scheme 4.1).



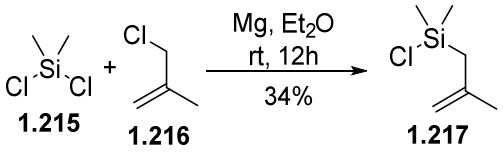
Scheme 4.1: Preparation of trisubstituted *Z*-olefins

Initially we investigated using the novel Peterson olefination to prepare hydrosilane **4.6** from EtOAc **4.4** (Scheme 4.2). Unfortunately, due to the high volatility of **4.6**, the THF could not be separated from the reaction mixture and interfered with the silane dehydrogenative coupling. A few attempts were also made to isolate intermediate **4.5** that was thought to have a higher boiling point, however, isolation of **4.5** was unsuccessful. Lastly, a final attempt was made to run the reaction without the use of cerium trichloride, thus by passing the use of THF, but as expected only starting material was recovered.



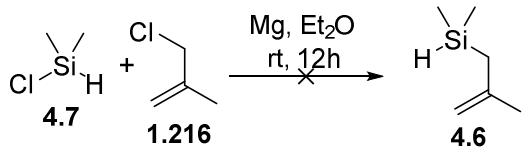
Scheme 4.2: Peterson olefination of EtOAc **4.4**

Following the work initially carried out by Mehdi Boumediene, we managed to prepare allyl chlorosilane **1.217** from the Grignard reaction of **1.215** with **1.216** in moderate yield (Scheme 4.3).



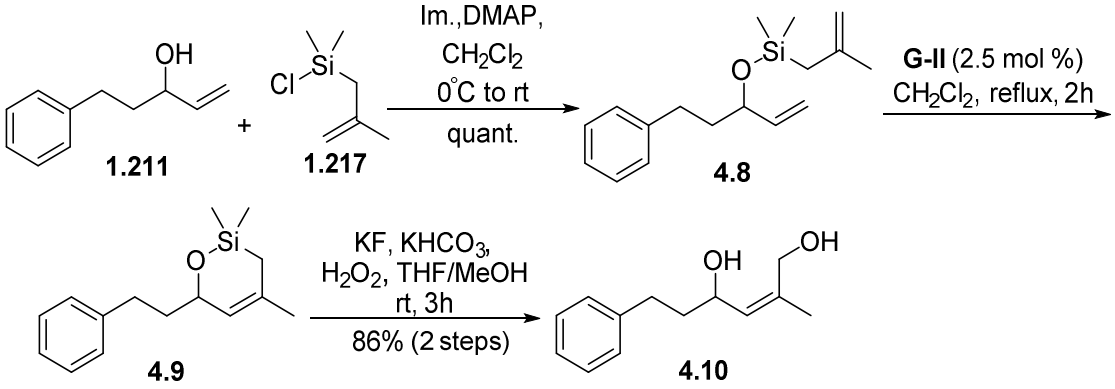
Scheme 4.3: Preparation of allyl chlorosilane **1.217**

However, when trying these reaction conditions to prepare hydrosilane **4.6** via Grignard reaction of **4.7** with **1.216,** the desired compound **4.6** was not observed (Scheme 4.4).



Scheme 4.4: Unsuccessful attempt to prepare hydrosilane **4.3**

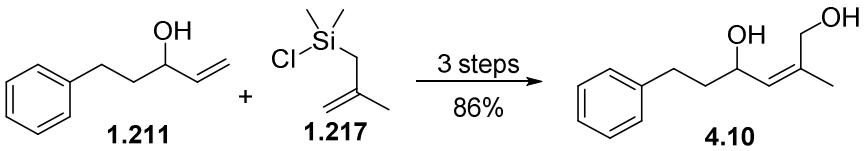
With allyl chlorosilane **1.217** in hand, we proceeded our studies towards the synthesis of *Z*-olefins selectively (Scheme 4.5). Silylation of **1.211** afforded alkoxysilane **4.8** in quantitative yield. Subjection of diene **4.8** to RCM using **G-II** furnished the desired six-membered silacycle **4.9** in just 2 h. The reduction in the reaction time is attributed to the steric hindrance of the substrate employed. It is believed that diene **4.8** encompasses a reduced steric demand compared to the more bulky silanes synthesised previously due to their larger side chains. Silacycle **4.9** was found to be very unstable, therefore it was used immediately in the next step following a quick filtration through a pad of celite to remove the **G-II** catalyst. Diol **4.10** was then prepared by the Tamao-Fleming oxidation[72] of **4.9** in 86% yield over two steps.



Scheme 4.5: Preparation of *Z*-olefin **4.10**

4.2 Conclusion and future work

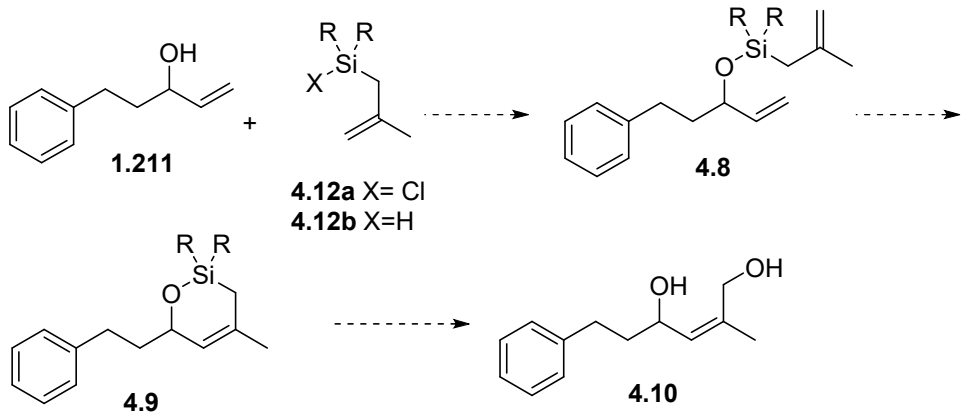
In summary *Z*-olefin **4.10** was prepared in 86% yield over three steps from allylic alcohol **1.211** and chlorosilane **1.217** (Scheme 4.6).



Scheme 4.6: Summary of the synthesis of *Z*-olefin **4.10**

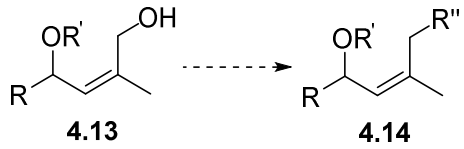
[72] Fujiwara, T.; Yanai, K.; Shimane, K.; Takamori, M.; Takeda, T. *Eur. J. Org. Chem.* **2001**, 155

Despite the high yielding synthesis of **4.10**, the synthesis and handling of the chlorosilane **1.217** was problematic due to its high volatility and low yield; furthermore, silacycle **4.9** is highly unstable (Scheme 4.7). Having this in mind, an efficient route for preparation of chlorosilanes **4.12a** or hydrosilanes **4.12b** is envisioned. The presence of larger SiR_2 groups may result in a less volatile and more stable analogues **4.9** that can be converted in **4.10**.



Scheme 4.7: Synthesis of **4.10** from **4.12**

As shown in Scheme 4.8, this methodology could be applied in the synthesis of functionalized *Z*-trisubstitueted olefins **4.14**.



Scheme 4.8: Synthesis of **4.14** from **4.13**

Chapter 5: Experimental

5.1 General

Apparatus:

NMR spectra were recorded on either a Bruker AVI DPX-400 spectrometer, a Bruker AVIII DPX-400 spectrometer (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz) or on a Bruker DPX-500 spectrometer (^{1}H NMR: 500 MHz, ^{13}C NMR: 126 MHz). Deuterated chloroform ($CDCl_3$) was used as the solvent for both ^{1}H and ^{13}C NMR, with residual solvent peak δ 7.26 being used for calibration of ^{1}H NMR and $CDCl_3$ peak at δ 77.0 for ^{13}C. Signal splitting patterns are described as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), octet (oct), nonet (non), multiplet (m), broad singlet, or any combination of the above. Two dimensional experiments (COSY, NOESY, HSQC, HMBC, and HMQC) were recorded, where necessary, for assignment. IR spectra were recorded using a Shimadzu FTIR-8400 Golden Gate™ attachment, utilizing a type IIa diamond as a single reflection element, allowing for the direct reading of powder and oil samples. High resolution mass spectra were recorded under ESI and CI conditions by the University of Glasgow analytical service. Optical rotations were recorded on an Autopol V polarimeter. Ozonolysis was carried out using a Degremont Technologies Triogen ozone generator.

Chromatography:

Flash chromatography was executed under forced flow conditions, using HPLC graded solvents and silica gel 60 (Fluorochem silica gel 60, 40 - 63 or Merck silica gel 60, 40 – 63). Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 covered alumina plates F254.

Both silica and TLC plates were oven dried and subsequently kept in air sealed pyrex containers.

Visualization of TLC plates was carried out under UV light and stained using $KMnO_4$, *p*-anisaldehyde, vanillin or cerium ammonium molybdate followed by heating.

Solvents and reagents:

Dry solvents such as THF, CH_2Cl_2, Et_2O, MeCN and toluene were collected from an in-house Pure-SolvTM 500 Solvent Purification System. Dry ethanol, methanol, DMF, DMSO, EtOAc, 1,2-dichoromethane were used from commercial bottles. All reagents were used directly from supplier, unless stated otherwise.

General conditions:

Air or moisture sensitive reactions were carried out in pre-dried glassware by flame drying under vacuum and subsequently flushing with argon. Solvents were degassed using the freeze and thaw method.

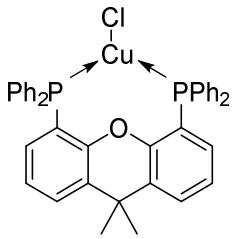
Nomenclature

IUPAC nomenclature was used for all compounds (determined by ChemDraw Professional 15.0).

For the description of NMR spectra, the numbering used follows the chain extension as described on the formula, not the IUPAC numbering.

5.2 Preparation of reagents

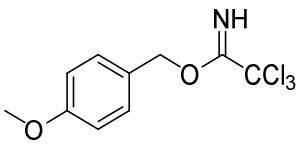
(Xantphos)CuCl 1.231[40]



Chemical Formula: $C_{39}H_{32}ClCuOP_2$
Molecular Weight: 677.63

To a suspension of dry CuCl (300 mg, 3.03 mmol, 1.12 equiv) in CH_2Cl_2 (10 mL) was added Xantphos (1.56 g, 2.70 mmol) and the resultant clear solution was stirred for 30 min. The solvent was removed *in vacuo* and the precipitated solid was triturated in dry and degassed acetonitrile (15 mL). The suspension was vigorously stirred for 4 h and filtered under Argon atmosphere. The wet cake was washed with acetonitrile (3 x 5 mL) and dried *in vacuo* to afford an off-white powder (1.38 g, 2.03 mmol, 75%).

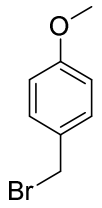
4-Methoxybenzyl 2,2,2-trichloroacetimidate[54]



Chemical Formula: $C_{10}H_{10}Cl_3NO_2$
Molecular Weight: 282.55

A solution of 4-methoxybenzyl alcohol (2.80 g, 20.2 mmol) in ether (3.5 mL) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 200 mg, 5.00 mmol, 0.25 equiv) in ether (4 mL). After stirring for 30 min, the solution was cooled to 0 °C and freshly distilled trichloroacetonitrile (2.10 mL, 20.9 mmol, 1.03 equiv) was added dropwise over a period of 1 h. The solution was then allowed to warm to 20°C over 1 h, pumped down to a viscous oil, and subsequently treated with 5 mL of pentane containing 0.6 mL of methanol and shaken vigorously. The resulting brown precipitate was filtered off and the filtrate was concentrated. This sequence was repeated once more before concentrating *in vacuo* and subsequently backfilling the flask with argon, and 4-methoxybenzyl benzyl 2,2,2-trichloroacetimidate (4.50 g, 15.9 mmol, 80%) was obtained as a pale-yellow liquid that was used immediately.

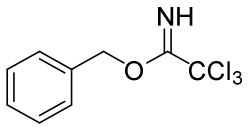
PMB-Br[73]



Chemical Formula: C_8H_9BrO
Molecular Weight: 201.06

A solution of PMB-OH (20.0 g, 144 mmol) in diethyl ether (80 mL) was shaken with HBr (47% w/w in water, 20 mL) in a separatory funnel. The organic phase was then washed with 80 mL of a saturated aqueous NaBr solution, dried over K_2CO_3, filtered and concentrated *in vacuo* to afford PMB-Br (22.0 g, 109 mmol, 76%) as a clear liquid that was used immediately after its preparation.

Benzyl 2,2,2-trichloroacetimidate[74]



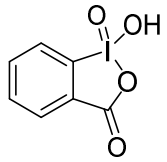
Chemical Formula: $C_9H_8Cl_3NO$
Molecular Weight: 252.52

Sodium hydride (60% dispersion in mineral oil, 300 mg, 7.5 mmol, 0.15 equiv) was suspended in ether (6 mL) and a solution of benzyl alcohol (5.2 mL, 50 mmol) in ether (5

[73] Ruder, S. M.; Ronald, R. C. *Tetrahedron Lett.* **1987**, *28*, 135.
[74] Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. I* **1985**, 2247.

mL) was added dropwise. After stirring 20 min, the solution was cooled to 0 °C and freshly distilled trichloroacetonitrile (5.0 mL, 10 mmol) was added dropwise during 1 h. The solution was allowed to warm to 20 °C over 1 h, concentrated to a syrup, treated with 5 mL of pentane containing 0.6 mL of methanol, shaken vigorously and filtered. The filtrate and pentane washings were concentrated. This sequence was repeated twice to remove a precipitate. After concentrating *in vacuo*, the resultant benzyl 2,2,2-trichloroacetimidate (10.9 g, 43 mmol, 86%) was used directly.

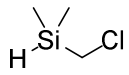
IBX[75]



Chemical Formula: $C_7H_5IO_4$
Molecular Weight: 280.02

To a stirred suspension of oxone (74.4 g, 242 mmol, 6.00 equiv) in H_2O (400 mL) was added 2-iodobenzoic acid (10.0 g, 40.3 mmol) in one portion. The reaction mixture was heated to 70 °C and stirred at this temperature for 2 h. After cooling to room temperature, the reaction vessel was placed in the fridge for 3 h and the reaction mixture was then filtered. The white solid was washed with H_2O (200 mL) and acetone (200 mL), giving pure IBX (7.93 g, 28.3 mmol, 70%).

(Chloromethyl)dimethylsilane 1.224[76]



Chemical Formula: C_3H_9ClSi
Molecular Weight: 108.64

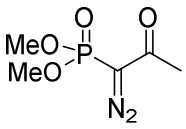
To a mixture of lithium aluminium hydride (3.5 g, 92 mmol, 0.53 equiv) in Et_2O (140 mL) at 0 °C was added dropwise (over 4 h) chloro(chloromethyl)dimethylsilane (23.0 mL, 175 mmol, 1.90 equiv). The mixture was warmed to RT and left to stir for a further 3 h. The reaction was quenched with a 1 M aqueous solution of hydrochloric acid (16.5 mL) and left to stir for 1 h, then the layers were separated. The aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over magnesium sulfate, filtered

[75] Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

[76] Thibon, J.; Latxague, L.; Déléris, G. *J. Org. Chem.* **1997**, *62*, 4635.

and carefully concentrated *in vacuo* (25 °C, 180 mbar). The crude was purified by distillation (81–83 °C) to furnish (chloromethyl)dimethylsilane (10.3 g, 94.4 mmol, 54%) as a colourless liquid.

Dimethyl-1-diazo-2-oxopropylphosphonate 1.189



Chemical Formula: $C_5H_9N_2O_4P$
Molecular Weight: 192.11

A solution of dimethyl (2-oxopropyl)-phosphonate (1.1 mL, 8.0 mmol) and *p*-acetamidobenzenesulfonyl azide[77] (2.12 g, 8.80 mmol, 1.10 equiv) in acetonitrile (40 mL) at 0 °C was treated with potassium carbonate (1.33 g, 9.60 mmol, 1.20 equiv) and stirred for 2 h. It was then filtered (removal of potassium carbonate) and the filtrate concentrated *in vacuo*. After dilution in chloroform and stirring for 30 min, the solution was filtered (removal of *N*-(4-sulfamoylphenyl)-acetamide) and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc 1:1) to afford dimethyl (1-diazo-2-oxopropyl)-phosphonate **1.189** (1.34 g, 6.98 mmol, 87%) as pale-yellow oil oil. The reagent was kept under argon in the freezer

(*S,S*)-Diisopropyl (*E*)-crotylboronate 2.15[47]

trans-2-butene (16.0 mL, 178 mmol, 1.06 equiv) was condensed from a gass lecture bottle into a rubber sealed 25.0 mL volumetric cylinder that was immersed in a dry ice/acetone bath (-78 °C) and then transfered *via* cannula to a 500 mL 3-neck round bottom flask that was equipped with a -100 °C thermometer and contained a stirred solution of potassium *tert*-butoxide (18.8 g, 168 mmol, 1.00 equiv) in THF (160 mL) at -78 °C. *n*-BuLi (2.2 M solution in hexane, 76.0 mL, 167 mmol, 1.00 equiv) was then added dropwise using a syringe pump at a rate such that the internal temperature did not exceed -65 °C. After the addition was complete (approximately 45 min on this scale), the resulting bright yellow suspension was allowed to warm to 50 °C and maintained at this temperature for 25 min before re-cooling back to -78 °C. Freshly distilled triisopropyl borate (38.8 mL, 168 mmol, 1.00 equiv) was then added dropwise using a syringe pump at a rate such that the internal temperature did not exceed -65 °C and the reaction mixture was stirred for a further 30 min at -78 °C. The reaction mixture was then poured into a 1-L extractor funnel containing 1 M

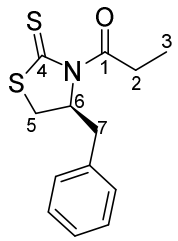
[77] Davies, H. M. L.; Cantrell, W. R.; Romines, K. R.; Baum, J. S. *Org. Synth*. **1992**, *70*, 93.

aqueous HCl solution saturated with NaCl (300 mL) and the aqueous layer was adjusted to pH 1 using more of the above solution as required. Then a solution of (-)-diisopropyl D-tartrate (46.3 g, 109 mmol, 1.18 equiv) in diethyl ether (50 mL) was added and the mixture shaken vigourously for 10 min. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), vacuum filtered under an argon blanket and the filtrate was concentrated *in vacuo* to give (*S,S*)-diisopropyl (*E*)-crotylboronate **2.15** (31.0 g, 104 mmol, 58%) as a thick colourless oil. The freshly prepared reagent was then subsequently handled and stored as a 0.24 - 0.48 M solution in toluene over 4 Å molecular sieves under argon and kept in the freezer for up to several months without deterioration.

(*R,R*)-Diisopropyl (*Z*)-Crotylboronate 3.29[47]

cis-2-butene (8.50 mL, 97.1 mmol, 1.04 equiv) was condensed into a volumetric cylinder immersed in a dry ice/acetone cooling bath (-78 °C) and was added *via* cannula to a stirred suspension of potassium *tert*-butoxide (10.5 g, 93.5 mmol, 1.00 equiv) in THF (80 mL) at -78 °C. *n*-BuLi (2.2 M solution in hexane, 42.5 mL, 93.5 mmol, 1.00 equiv) was then added dropwise at a rate such that the internal temperature did not exceed -65 °C. After completion of the addition, the resulting bright yellow solution was stirred at -50 °C for 40 min then warmed to -20 °C and stirred for a further 10 min before cooling back to -78 °C. Triisopropyl borate (21.6 mL, 93.6 mmol, 1.00 equiv) was then added dropwise at a rate such that the internal temperature did not exceed -65 °C and the reaction mixture was stirred for a further 30 min at -78 °C. The reaction mixture was then poured onto 1 M aqueous HCl solution (saturated with NaCl, 160 mL) and shaken vigorously. A solution of L-(+)-diisopropyl tartrate (25.50 g, 109 mmol, 1.17 equiv) in diethyl ether (50 mL) was added and the mixture shaken vigorously for 10 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give (*R,R*)-diisopropyl (*Z*)-crotylboronate **3.29** (18.3 g, 62.3 mmol, 65%) as a colourless oil. The freshly prepared reagent was stored as solution in toluene over 4 Å molecular sieves and kept in the freezer for several months without deterioration.

(*S*)-6-(4-benzyl-2-thioxothiazolidin-3-yl)propan-1-one 3.46[45]



Chemical Formula: $C_{13}H_{15}NOS_2$
Molecular Weight: 265.39

In a 3-necked flask, sodium borohydride (6.90 g, 182 mmol, 2.43 equiv) was dissolved in THF (200 mL). (*L*)-Phenylalanine **3.44** (12.5 g, 75.0 mmol) was added in one portion then the mixture was cooled to 0 °C. A solution of iodine (19.0 g, 75.0 mmol, 1.00 equiv) in THF (100 mL) was added dropwise via the addition funnel (over 30 min). After the addition was complete the flask was heated to reflux and left to stir overnight. The flask was then allowed to cool down and methanol was added cautiously until the mixture became clear. The solvent was then removed under vacuum giving a white paste, which was dissolved in a 20% aqueous solution of potassium hydroxide (150 mL). The crude mixture was left to stir at RT for 3 h, then the aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum giving (*L*)-phenylalaninol as a white solid, which was used in the next step without purification.

Crude (*L*)-phenylalaninol was dissolved in a 3 M aqueous solution of potassium hydroxide (200 mL) and left to stir for 30 min. Carbon disulfide (22.5 mL, 372 mol, 5.0 equiv) was then added dropwise, the mixture was warmed to 110 °C and stirred overnight. The flask was then cooled to RT and the reaction mixture was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The crude product **3.45** (15.5 g, 99% over 2 steps) was then used in the next step without further purification.

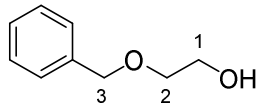
(The aqueous phase was diluted and the glassware rinsed with a solution of bleach and potassium hydroxide to remove any traces of carbon sulfide).

(*S*)-4-Benzylthiazolidine-2-thione **3.45** (4.05 g, 20.0 mmol) was dissolved in CH_2Cl_2 (100 mL) followed by addition of freshly distilled triethylamine (7.0 mL, 50 mmol, 2.5 equiv). The reaction was cooled to 0 °C followed by addition of propionyl chloride (2.8 mL, 30 mmol, 1.5 equiv) over 5 min. The reaction was left to stir at RT overnight, after which the mixture was diluted with CH_2Cl_2 (100 mL) and water (200 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the organic layer was dried over magnesium sulfate, filtered and

concentrated under vacuum. The crude product was purified by recrystallisation from acetonitrile to furnish **3.46** (4.00 g, 75%) as a bright yellow solid.

5.3 Procedures and products characterization

2-Benzyloxyethanol 2.7[78]



Chemical Formula: $C_9H_{12}O_2$
Molecular Weight: 152.19

To a stirred suspension of NaH (60% dispersion in mineral oil, 7.40 g, 185 mmol, 1.80 equiv) in THF (250 mL), ethylene glycol **2.6** (50.0 mL, 894 mmol, 8.60 equiv) was added and reaction mixture was stirred for 1 h. After this benzyl bromide (17.8 g, 104 mmol) was added dropwise and the reaction was heated to reflux for 24 h. Then the reaction was quenched using saturated aqueous NH_4Cl (300 mL), concentrated *in vacuo* and the residue was extracted with EtOAc (3 x 250 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (250 mL), brine (250 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to afford **2.7** (15.8 g, 104 mmol, quant) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 5H, ***H***-Ar), 4.58 (s, 2H, C***H***-3), 3.77 (m, 2H, C***H***-2), 3.62 (t, *J* = 4.7 Hz, 2H, C***H***-2), 2.20 (br s, 1H, CH_2O***H***).

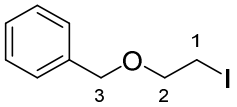
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (C-Ar), 128.5 (C-Ar), 127.8 (C-Ar), 127.6 (C-Ar), 73.3 (C-3), 71.4 (C-2), 62.0 (C-1).

IR (neat, cm^{-1}) 2862, 1450, 1358, 1211, 1103, 1065.

In agreement with literature data.

[78] Puebla, A.; Esteve, F. R.; Rico, M. F.; Rodriguez, M. I.; Rodriguez, A. S.; Xiang, Y.; Romero, C.; Wolfgang, J. P.; Leal, V.; Gil, R. P. Patent WO2015/177340 *A1*, **2015**.

2-Benzyloxyethyl iodide 2.8[79]



Chemical Formula: $C_9H_{11}IO$
Molecular Weight: 262.09

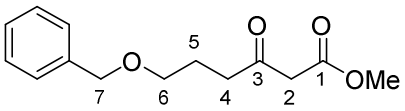
To a stirred solution of **2.7** (16.50 g, 108.0 mmol) in a mixture of ether (200 mL) and acetonitrile (50 mL) were added triphenylphosphine (63.0 g, 240 mmol, 2.22 equiv) and imidazole (18.6 g, 273 mmol, 2.52 equiv). After cooling the mixture to 0 °C iodine (55.1 g, 217 mmol, 2.00 equiv) was added and the reaction was stirred overnight at room temperature. It was then diluted with petroleum ether (500 mL) and filtered. The filtrate was washed with a 10% aqueous solution of $CuSO_4$ (400 mL) then brine (500 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **2.8** (27.42 g, 105.0 mmol, 97%) as a yellow liquid, which was used for the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H, ***H***-Ar), 4.61 (s, 2H, C***H***-3), 3.72 (t, *J* = 7.0 Hz, 2H, C***H***-2), 3.35 (t, *J* = 6.8 Hz, 2H, C***H***-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8 (C-Ar), 133.6 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 72.9 (C-3), 70.7 (C-2), 2.9 (C-1).

In agreement with literature data.

Methyl 6-benzyloxy-3-oxohexanoate 2.10[46]



Chemical Formula: $C_{14}H_{18}O_4$
Molecular Weight: 250.29

To a stirred suspension of NaH (60% dispersion in mineral oil, 13.8 g, 344 mmol, 1.81 equiv) in THF (310 mL) at 0 °C, methyl acetoacetate **2.9** (24.0 mL, 223 mmol, 1.17 equiv) was added dropwise. After 5 min, *n*-butyllithium (2.0 M in hexane, 150 mL, 300 mmol, 1.57 equiv) was added at a flow rate of 40 mL/h. After stirring the mixture for a further 10 min, a solution of **2.8** (50.0 g, 190 mmol) in THF (165 mL) was added dropwise. The solution was stirred for 2 h at room temperature then was quenched with a saturated aqueous NH_4Cl solution, extracted with ether and the organic layer was washed with brine, dried over $MgSO_4$, filtered

[79] Tokoroyama, T.; Aoto, T. *J. Org. Chem*. **1998**, *12*, 4151

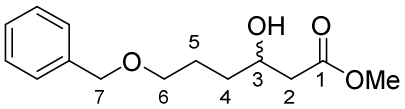
and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 4:1) to give **2.10** (36.5 g, 146 mmol, 77%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H, ***H***-Ar), 4.52 (s, 2H, C***H***-7), 3.77 (s, 3H, OC***H$_3$***), 3.54 (t, *J* = 6.3 Hz, 2H, C***H***-6), 3.50 (s, 2H, C***H***-2), 2.71 (t, *J* = 7.0 Hz, 2H, C***H***-4), 1.97 (tt, *J* = 7.2, 6.2 Hz, 2H, C***H***-5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4 (C-3), 167.6 (C-1), 138.4 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 72.9 (C-7), 69.0 (C-6), 52.3 (OCH_3), 49.1 (C-2), 39.8 (C-4), 23.7 (C-5).

In agreement with literature data.

Methyl 6-benzyloxy-3-hydroxyhexanoate (±) 2.11[46]



Chemical Formula: $C_{14}H_{20}O_4$
Molecular Weight: 252.31

To a solution of **2.10** (0.10 g, 0.40 mmol) in ethanol (6 mL) was added $NaBH_4$ (16 mg, 0.42 mmol, 1.0 equiv) and the resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with a 1 M aqueous solution of HCl (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 1:1) furnished **(±) 2.11** (60 mg, 0.24 mmol, 60 %) as a yellow oil.

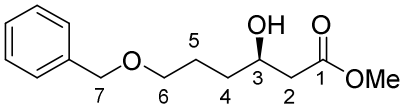
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H, ***H***-Ar), 4.52 (s, 2H, C***H***-7), 4.09-4.04 (m, 1H, C***H***-3), 3.72 (s, 3H, OC***H$_3$***), 3.52 (t, *J* = 6.2 Hz, 2H, C***H***-6), 3.28 (d, *J* = 4.0 Hz, 1H, C3-***OH***), 2.52 (dd, *J* = 16.2, 4.1 Hz, 1H, C***H***-2), 2.45 (dd, *J* = 16.2, 4.1 Hz, 1H, C***H***-2), 1.81-1.69 (m, 2H, C***H***-4), 1.68-1.47 (m, 2H, C***H***-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1 (C-1), 138.2 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 72.9 (C-7), 70.1 (C-6), 67.8 (C-3), 51.2 (OC*H$_3$*), 41.3 (C-2), 33.6 (C-4), 25.8 (C-5).

IR (neat, cm^{-1}) 3449, 2970, 2859, 1721, 1437, 1366, 1206, 1094.

In agreement with literature data.

Methyl (*R*)-6-benzyloxy-3-hydroxyhexanoate 2.11[46]



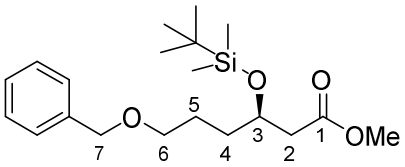
Chemical Formula: $C_{14}H_{20}O_4$
Molecular Weight: 252.31

To prepare the catalyst, benzeneruthenium dichloride (156 mg, 0.31 mmol, 0.007 equiv) and (*R*)-BINAP (297 mg, 0.048 mmol, 0.011 equiv) were dissolved in anhydrous DMF (24 mL) and stirred at 105 °C for 20 min. A solution of **2.10** (11.2 g, 44.8 mmol) in degassed methanol (35 mL) was added to the catalyst solution. The resulting mixture was transferred to a hydrogenation reactor, where it was stirred for 48 h under 10 bar hydrogen at 95 °C. After concentrating *in vacuo* the dark red solution was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to afford **2.11** (10.5 g, 41.6 mmol, 93%), *er* > 99:1. The enantiomeric purity of the compound was determined by chiral HPLC (chiral OD cel column with a flow rate of 1 mL/min and solvent system of 10% isopropanol/hexane) t_r = 15.1 min (Major), t_r = 17.0 min (Minor).

[α]$^{25}_D$ -8.1 (*c* 1.0, $CHCl_3$).

In agreement with literature data.

Methyl (*R*)-6-benzyloxy-3-butyldimethylsilyloxyhydroxyhexanoate 2.12[46]



Chemical Formula: $C_{20}H_{34}O_4Si$
Molecular Weight: 366.57

To a stirred solution of **2.11** (7.60 g, 30.1 mmol) in DCM (280 mL) at -78 °C was added Et_3N (12.8 mL, 91.8 mmol, 3.05 equiv) and TBSOTf (10.3 mL, 44.8 mmol, 1.49 equiv) dropwise, and the reaction mixture was stirred for 1 h. After that, it was quenched with saturated aqueous NH_4Cl (300 mL) and extracted with ether (3 x 300 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered and then concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to afford **2.12** (11.0 g, 30.0 mmol, quant.) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H, ***H***-Ar), 4.51 (s, 2H, C***H***-7), 4.18 (dq, *J* = 6.6, 5.4 Hz, 1H, C***H***-3), 3.67 (s, 3H, OC***H₃***), 3.48 (t, *J* = 6.8 Hz, 2H, C***H***-6), 2.49 (dd, *J* = 14.6, 7.2 Hz, 1H, C***H***-2), 2.43 (dd, *J* = 14.6, 5.7 Hz, 1H, C***H***-2), 1.68-1.63 (m, 2H, C***H***-4), 1.61-1.58 (m, 2H, C***H***-5), 0.87 (s, 9H, -SiC(C***H₃***)$_3$-), 0.07 (s, 3H, -SiC(C***H₃***)$_2$-), 0.04 (s, 3H, -SiC(C***H₃***)$_2$-).

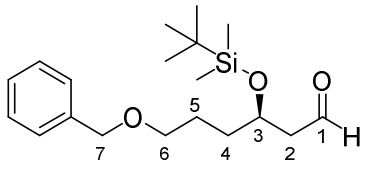
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2 (C-1), 138.6 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 72.8 (C-7), 70.3 (C-6), 69.2 (C-3), 51.5 (OCH_3), 42.5 (C-2), 34.2 (C-4), 25.8 (-SiC(***C***H_3)$_3$-), 25.2 (C-5), 18.0 (-Si***C***$(CH_3)_3$-), -4.5 (-SiC(***C***H_3)$_2$-), -4.9 (-SiC(***C***H_3)$_2$-).

IR (neat, cm^{-1}) 2952, 2858, 1769, 1447, 1369, 1261, 1096.

[α]$^{25}_D$ -13.2 (*c* 1.0, $CHCl_3$).

In agreement with literature data.

(*R*)-6-(Benzyloxy)-3-(*tert*-butyldimethylsiloxy)hexanal 2.13[46]



Chemical Formula: $C_{19}H_{32}O_3Si$
Molecular Weight: 336.55

To a stirred solution of **2.12** (5.50 g, 15.0 mmol) in CH_2Cl_2 (40 mL) was added DIBAL-H (1.0 M solution in hexanes, 17.5 mL, 17.5 mmol, 1.17 equiv) dropwise at – 78 °C. The reaction mixture was stirred for 2.5 h before adding EtOAc (40 mL) followed by silica. The resultant reaction mixture was stirred at room temperature for 2 h, filtered and the filtrate concentrated *in vacuo* to furnish aldehyde **2.13** as a clear oil (5.00 g, 15.0 mmol, quant.) that was used in next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.5 Hz, 1H, C***H***-1), 7.35-7.27 (m, 5H, ***H***-Ar), 4.51 (s, 2H, C***H***-7), 4.23 (quint, *J* = 6.0 Hz, 1H, C***H***-3), 3.49 (t, *J* = 6.0 Hz, 2H, C***H***-6), 2.59-2.48 (m, 2H, C***H***-2), 1.67-1.61 (m, 4H, C***H***-4, C***H***-5), 0.90 (s, 9H, -SiC(C***H₃***)$_3$-), 0.08 (s, 3H, -SiC(C***H₃***)$_2$-), 0.07 (s, 3H, -SiC(C***H₃***)$_2$-).

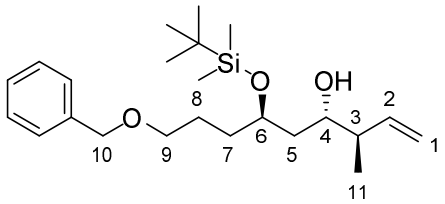
^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1 (C-1), 138.5 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 72.9 (C-7), 70.2 (C-6), 68.0 (C-3), 50.8 (C-2), 34.5 (C-4), 25.8 (-SiC(***C***H_3)$_3$-), 25.5 (C-5), 18.0 (-Si***C***$(CH_3)_3$-), -4.4 (-SiC(***C***H_3)$_2$-), -4.7 (-SiC(***C***H_3)$_2$-).

IR (neat, cm^{-1}) 2947, 2932, 2855, 1736, 1458, 1366,1250, 1211, 1096.

$[\alpha]^{29}_D$ -4.4 (*c* 1.5, $CHCl_3$)

In agreement with literature data.

(3*R*,4*S*,6*R*)-9-(Benzyloxy)-6-(*tert*-butyldimethylsiloxy)-3-methylnon-1-en-4-ol 2.16[41]



Chemical Formula: $C_{23}H_{40}O_3Si$
Molecular Weight: 392.66

To a stirred suspension of 4 Å molecular sieves (5.0 g) and (*S,S*)-diisopropyl-(*E*)-crotylboronate (0.24 M in toluene, 116 mL, 28.0 mmol, 1.75 equiv) at -78 °C was added aldehyde **2.13** (5.3 g, 15.7 mmol) at a flow rate of 0.1 mL/min. The reaction mixture was stirred at -78 °C for 7 h and allowed to warm to room temperature overnight. The reaction was then quenched with a 0.5 M aqueous solution of NaOH (100 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 3:1) to afford **2.16** (5.85 g, 14.9 mmol, 95%) as a clear oil and as a 6:1 mixture of diastereomers.

The major diastereomer is described below:

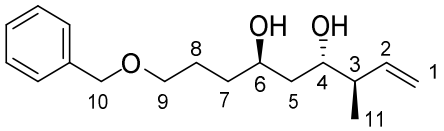
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 5H, ***H***-Ar), 5.86-5.77 (m, 1H, C***H***-2), 5.86-5.05 (m, 2H, C***H***-1), 4.51 (s, 2H, C***H***-10), 4.05-4.00 (m, 1H, C***H***-6), 3.81 (ddd, *J* = 9.9, 5.1, 2.1 Hz, 1H C***H***-4), 3.48 (t, *J* = 6.0 Hz, 2H, C***H***-9), 3.10 (d, *J* = 2.1 Hz, 1H, C4-O***H***), 2.26-2.16 (m, 1H, C***H***-3), 1.70-1.50 (m, 6H, C***H***-5, C***H***-7, C***H***-8), 1.04 (d, *J* = 5.0 Hz, 3H, C***H***-11), 0.90 (s, 9H, SiC(C***H*****$_3$**$)_3$), 0.10 (s, 3H, SiC(C***H*****$_3$**$)_2$), 0.08 (s, 3H, SiC(C***H*****$_3$**$)_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (C-2), 138.6 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 115.3 (C-1), 72.9 (C-10), 71.3 (C-4), 71.2 (C-6), 70.4 (C-9), 44.1 (C-3), 38.6 (C-5), 33.0 (C-7), 25.9 (C-8), 25.9 (SiC(***C***$H_3)_3$), 18.0 (Si***C***$(CH_3)_3$), 15.7 (C-11), -4.5 (SiC(***C***$H_3)_2$), -4.7 (SiC(***C***$H_3)_2$).

IR (neat, cm^{-1}) 3065, 2928, 2855, 1495, 1462, 1362, 1256, 1099, 1074.

HRMS (ESI, *m/z*) calcd for $(C_{23}H_{40}O_3SiNa)^+$ 415.2644, found 414.2627.

(3*R*, 4*S*, 6*R*)-9-(Benzyloxy)-3-methylnon-1-ene-4,6 diol 2.18



Chemical Formula: $C_{17}H_{26}O_3$
Molecular Weight: 278.39

Method A

To a stirred suspension of homoallylic alcohol **2.16** (5.70 g, 14.5 mmol, *dr*: 6:1) in THF (31 mL) was added dropwise a 1 M solution of TBAF in THF (28.5 mL, 28.5 mmol, 1.97 equiv) at 0 °C. After the addition was complete, the ice bath was removed and the reaction mixture was stirred for 4 h at room temperature. The solution was then quenched with a saturated aqueous solution of ammonium chloride (30 mL) and extracted with ether (3 x 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification by column chromatography on silica gel (EtOAc: ether: petroleum ether 1.5:1.5:1) gave the desired diol **2.18** (3.15 g, 11.3 mmol, 78%) as a clear oil and as a 42:1 mixture of diastereomers.

Method B

Homoallylic alcohol **2.16** (400 mg, 1.02 mmol, *dr*: 6:1) was dissolved in a 5:95 solution of HF/acetonitrile (22 mL) and the resulting solution was stirred for 4 h at room temperature. The reaction mixture was quenched by the addition of a saturated aqueous solution of calcium chloride (25 mL). The solution was then extracted with ether (3 x 20 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification by column chromatography on silica gel (EtOAc: ether: petroleum ether 1.5:1.5:1) gave the desired diol **2.18** (160 mg, 0.57 mmol, 56%) as a clear oil and as a 16:1 mixture of diastereomers.

The major diastereomer is described below:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H, ***H***-Ar), 5.79-5.72 (m, 1H, C***H***-2), 5.13-5.09 (m, 2H, C***H***-1), 4.52 (s, 2H, C***H***-10), 3.97-3.91 (m, 1H, C***H***-6), 3.76-3.72 (m, 1H, C***H***-4), 3.55-3.50 (m, 2H, C***H***-9), 3.27 (d, *J* = 4.0 Hz, 1H, C6-O***H***), 2.46-2.43 (m, 1H, C4-O***H***), 2.29-2.20 (m, 1H, C***H***-3), 1.80-1.72 (m, 2H, C***H***-8), 1.65-1.55 (m, 4H, C***H***-5, C***H***-7), 1.01 (d, *J* = 6.8 Hz, 3H, C***H***-11).

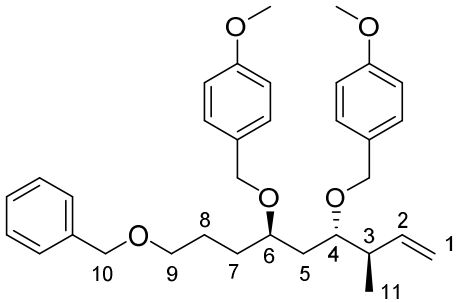
^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6 (C-2), 138.1 (C-Ar), 128.5 (C-Ar), 127.8 (C-Ar), 122.8 (C-Ar), 116.4 (C-1), 73.1 (C-10), 72.0 (C-4), 70.6 (C-9), 69.1 (C-6), 44.4 (C-3), 39.6 (C-5), 34.9 (C-7), 26.6 (C-8), 16.1 (C-11).

IR (neat, cm^{-1}) 3379, 2909, 1450, 1311, 1288, 1157, 1096, 1072.

HRMS (ESI, *m/z*) calcd for $(C_{17}H_{26}O_3Na)^+$ 301.1774, found 301.1760

[α]$^{25}_D$ -17.9 (*c* 1.0, $CHCl_3$).

4,4'-((3*R*,4*S*,6*R*)-9-(Benzyloxy)-3-methylnon-1-ene-4,6-diyl)*bis*(methoxybenzene) 2.19



Chemical Formula: $C_{33}H_{42}O_5$
Molecular Weight: 518.69

To a stirred solution of diol **2.18** (9.00 g, 32.3 mmol) in DMF (90 mL) at 0 °C was added dropwise PMBBr (22.0 g, 109 mmol, 3.35 equiv), followed by NaH (60% dispersion in mineral oil 5.00 g, 125 mmol, 3.87 equiv). The reaction mixture was stirred for 4 h at 0 °C and for a further 36 h at room temperarure. The reaction was then quenched by the addition of water. The mixture was extracted with ether (3 x 50 mL) and the organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 9:1 then 4:1) gave the protected alcohol **2.19** (16.7 g, 32.2 mmol, quant.) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H, ***H***-Ar), 7.25-7.17 (m, 4H, ***H***-Ar (PMB)), 6.88-6.81 (m, 4H, ***H***-Ar (PMB)), 5.80 (ddd, *J* = 16.9, 10.9, 6.8 Hz, 1H, C***H***-2), 5.07-5.03 (m, 2H, C***H***-1), 4.50 (s, 2H, C***H***-10), 4.49 (d, *J* = 11.1 Hz, 1H, C***H$_2$***-PMB), 4.47 (m, 1H, C***H$_2$***-PMB) 4.45 (d, *J* = 11.1 Hz, 1H, C***H$_2$***-PMB), 4.25 (d, 1H, *J* = 11.0, C***H$_2$***-PMB), 3.78 (s, 3H, PMB-OC***H$_3$***), 3.77 (s, 3H, PMB-OC***H$_3$***), 3.63-3.58 (m, 2H, C***H***-4, C***H***-6), 3.47 (t, 2H, *J* = 6.2 Hz, C***H***-9), 2.60-2.54 (m, 1H, C***H***-3), 1.71-1.51 (m, 6H, C***H***-5, C***H***-7, C***H***-8), 1.02 (d, 3H, *J* = 6.9 Hz, C***H***-11).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 159.0 (C-Ar), 140.8 (C-2), 138.6 (C-Ar), 131.2 (C-Ar), 131.1, (C-Ar), 129.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 114.6 (C-1),

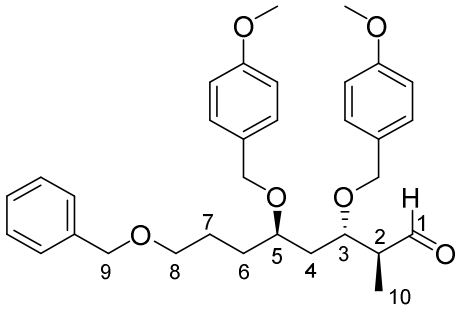
113.7 (C-Ar), 78.8 (C-4), 75.2 (C-6), 72.8 (C-10), 71.3 (C-9), 70.5 (**C**H_2-PMB), 70.2 (**C**H_2-PMB), 55.2 (O**C**H_3-PMB), 40.0 (C-3), 36.0 (C-5), 30.5 (C-7), 25.2 (C-8), 13.7 (C-11).

IR (neat, cm^{-1}) 2854, 2839, 1612, 1512, 1304, 1250, 1173, 1080, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{33}H_{42}O_5Na)^+$ 541.2924, found 541.2903.

[α]$^{25}_D$ -37.4 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*,5*R*)-8-(Benzyloxy)-3, 5-*bis*(4-methoxybenzyloxy)-2-methyloctanal 2.20



Chemical Formula: $C_{32}H_{40}O_6$
Molecular Weight: 520.67

To a stirred solution of **2.19** (3.85 g, 7.42 mmol) and 2,6-lutidine (1.54 mL, 13.2 mmol, 1.78 equiv) in a mixture of water (36 mL) and dioxane (102 mL) was added osmium tetroxide (0.12 M aqueous solution, 1.5 mL, 0.22 mmol, 0.03 equiv) followed by sodium periodate (6.40 g, 30.0 mmol, 4.04 equiv). The mixture was stirred for 5 h at room temperature, then was quenched with a saturated aqueous solution of sodium sulfite (15 mL) and left to stir for a further 20 min. The solution was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with brine (50 mL), dried over $NaSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to afford aldehyde **2.20** (2.20 g, 4.23 mmol, 57%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, 1H, *J* = 1.7 Hz, C***H***-1), 7.39-7.30 (m, 5H, ***H***-Ar), 7.25 (d, 2H, *J* = 8.6 Hz, ***H***-Ar (PMB)), 7.20 (d, 2H, *J* = 8.6 Hz, ***H***-Ar (PMB)), 6.89-6.86 (m, 4H, ***H***-Ar (PMB)), 4.52 (s, 2H, C***H***-9), 4.50-4.43 (m, 2H, C***H$_2$***-PMB), 4.32 (d, 1H, *J* = 10.8 Hz, C***H$_2$***-PMB), 4.28 (d, 1H, *J* = 10.9 Hz, C***H$_2$***-PMB), 4.03 (ddd, 1H, *J* = 9.3, 4.6, 2.8 Hz, C***H***-3), 3.80 (s, 6H, PMB-OC***H$_3$***), 3.69-3.66 (m, 1H, C***H***-5), 3.51-3.48 (m, 2H, C***H***-8), 2.79-2.72 (m, 1H, C***H***-2), 1.72-1.55 (m, 6H, C***H***-4, C***H***-6, C***H***-7), 1.12 (d, 3H, *J* = 6.9 Hz, C***H***-10).

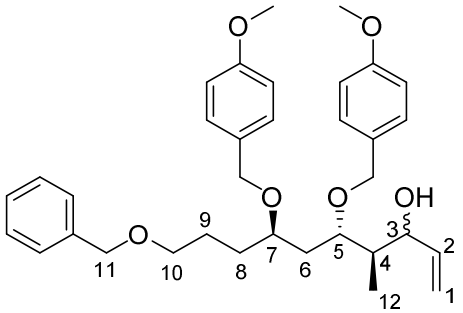
^{13}C NMR (126 MHz, $CDCl_3$) δ 204.0 (C-1), 159.2 (C-Ar), 159.1 (C-Ar), 138.6 (C-Ar), 130.9 (C-Ar), 130.3 (C-Ar), 129.3 (C-Ar), 129.3 (C-Ar),128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 113.8 (C-Ar), 113.8 (C-Ar), 75.7 (C-3), 74.7 (C-5), 72.9 (C-9), 71.7 (**C**H_2-PMB), 70.4 (C-8),

70.2 (**C**H_2-PMB), 55.3 (O**C**H_3-PMB), 55.1 (O**C**H_3-PMB) 49.9 (C-2), 37.5 (C-4), 30.3 (C-6), 25.1 (C-7), 9.1 (C-10).

IR (neat, cm^{-1}) 2936, 2863, 1721, 1613, 1512, 1454, 1302, 1246, 1067, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{32}H_{40}O_6Na)^+$ 543.2725, found 543.2705.

(4*R*,5*S*,7*R*)-10-(Benzyloxy)-5, 7-*bis*(4-methoxybenzyloxy)-4-methyldec-1-en-3-ol 2.21



Chemical Formula: $C_{34}H_{44}O_6$
Molecular Weight: 548.72

To a stirred suspension of aldehyde **2.20** (2.00 g, 3.84 mmol) in THF (50 mL) at -78 °C was added vinylmagnesium bromide (0.5 M in THF, 30 mL, 15 mmol, 3.9 equiv). The solution was stirred for 4 h at -78 °C and then allowed to warm to room temperature overnight. The reaction was then quenched by the addition of a saturated aqueous solution of ammonium chloride (40 mL). The mixture was then extracted with ether (3 x 40 mL) and the combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude product was purified by column chromatography on silica gel (petroleum ether: ether 3:1) to give **2.21** (1.54 g, 2.81 mmol, 73%) as a clear oil and as a 1:1 mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.39 (m, 5H, ***H***-Ar), 7.26-7.19 (m, 4H, ***H***-Ar (PMB)), 6.89-6.85 (m, 4H, ***H***-Ar (PMB)), 5.91-5.78 (m, 1H, C***H***-2), 5.29-5.13 (m, 2H, C***H***-1), 4.53 (s, 2H, C***H***-11), 4.51-4.21 (m, 4.5H, C***H***-3, C***H$_2$***-PMB), 3.93-3.90 (m, 0.5H, C***H***-3), 3.80 (s, 1.5H, PMB-OC***H$_3$***), 3.80 (s, 1.5H, PMB-OC***H$_3$***), 3.79 (s, 1.5H, PMB-OC***H$_3$***), 3.79 (s, 1.5H, PMB-OC***H$_3$***), 3.71-3.68 (m, 1H, C***H***-5 or C***H***-7), 3.63-3.59 (m, 1H, C***H***-5 or C***H***-7), 3.58-3.52 (m, 2H, C***H***-10), 3.07 (d, 0.5H, *J* = 3.1 Hz C3-***OH***), 2.63 (d, 0.5H, *J* = 3.3 Hz C3-***OH***), 2.02-1.13 (m, 7H, C***H***-4, C***H***-6, C***H***-8, C***H***-9), 0.99 (d, 1.5H, *J* = 7.1 Hz, C***H***-12), 0.99 (d, 1.5H, *J* = 7.1 Hz, C***H***-12).

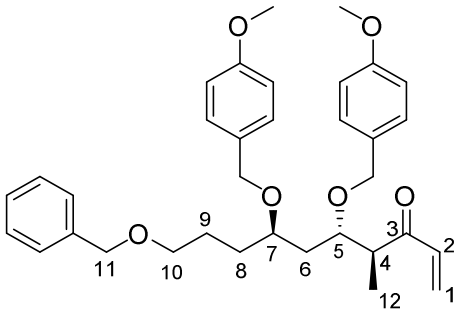
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C-Ar), 139.8 (C-Ar), 139.6 (C-2), 130.8 (C-Ar), 130.4 (C-Ar), 129.5 (C-Ar), 129.4 (C-Ar), 129.4 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar),

116.0 (C-1), 114.6 (C-1), 113.8 (C-Ar), 113.8 (C-Ar), 83.1 (C-5 or C-7), 80.3 (C-3), 76.0, 75.7, 75.3 (C-5 or C-7), 72.9 (C-11), 72.3 (C-3), 70.9 (**C**H_2-PMB), 70.4 (C-10), 70.1 (**C**H_2-PMB), 55.3 (O**C**H_3-PMB), 41.7 (C-4), 40.6 (C-4), 37.9 (C-6), 30.3 (C-8), 25.1 (C-9), 11.5 (C-12), 11.1 (C-12).

IR (neat, cm^{-1}) 2398, 2862, 1613, 1514, 1362, 1302, 1248, 1173, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{34}H_{44}O_6Na)^+$ 571.3030, found 571.3016.

(4*S*,5*S*,7*R*)-10-(Benzyloxy)5-7-*bis*(4-methoxybenzyloxy)-4-methyldec-1-en-3-one 2.1



Chemical Formula: $C_{34}H_{42}O_6$
Molecular Weight: 546.70

To a stirred suspension of alcohol **2.21** (200 mg, 0.36 mmol) in DMSO (13 mL) and THF (7 mL) was added IBX (350 mg, 1.2 mmol, 3.5 equiv) at room temperature and the reaction mixture was stirred overnight. Then, water was added (30 mL) and the solution was extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine (60 mL), dried over $MgSO_4$ filtered and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (petroleum ether: ether 3:1) to give **2.1** (175 mg, 0.32 mmol, 89%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H, ***H***-Ar), 7.23 (d, 2H, *J* = 8.6 Hz, ***H***-Ar (PMB)), 7.17 (d, 2H, *J* = 8.6 Hz, ***H***-Ar (PMB)), 6.86-6.83 (m, 4H, ***H***-Ar (PMB)), 6.46 (dd, 1H, *J* = 17.4, 10.4 Hz, C***H***-2), 6.25 (dd, 1H, *J* = 17.3, 1.2 Hz, C***H***-1_{trans}), 5.76 (dd, 1H, *J* = 10.3, 1.2 Hz, C***H***-1_{cis}), 4.51 (s, 2H, C***H***-11), 4.48 (d, 1H, *J* = 11.1 Hz, C***H₂***-PMB), 4.43 (d, 1H, *J* = 11.1 Hz, C***H₂***-PMB), 4.27-4.25 (m, 2H, C***H₂***-PMB), 4.01-3.97 (m, 1H, C***H***-5), 3.80 (s, 3H, PMB-OC***H₃***), 3.79 (s, 3H, PMB-OC***H₃***), 3.67-3.64 (m, 1H, C***H***-7), 3.50-3.47 (m, 2H, C***H***-10), 3.22-3.17 (app quint, 1H, *J* = 6.7 Hz, C***H***-4), 1.77-1.55 (m, 6H, C***H***-6, C***H***-8, C***H***-9), 1.09 (d, 3H, *J* = 6.8 Hz, C***H***-12).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.3 (C-3), 159.2 (C-Ar), 159.1 (C-Ar), 138.6 (C-Ar), 135.8 (C-2), 131.0 (C-Ar), 130.5 (C-Ar), 129.4 (C-Ar), 129.3 (C-Ar), 128.4 (C-Ar), 128.0 (C-1),

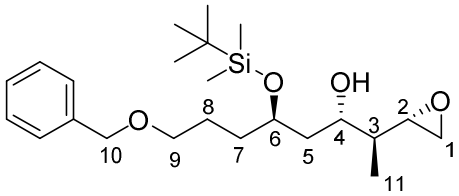
127.6 (C-Ar), 127.5 (C-Ar), 113.8 (C-Ar), 113.7 (C-Ar), 76.7 (C-5), 74.7 (C-7), 72.9 (C-11), 72.0 (**C**H_2-PMB), 70.4 (C-10), 69.9 (**C**H_2-PMB), 55.3 (O**C**H_3-PMB), 47.5 (C-4), 37.0 (C-6), 30.4 (C-8), 25.2 (C-9), 11.1 (C-12)

IR (neat, cm^{-1}) 2973, 2864, 1676, 1612, 1514, 1402, 1302, 1248, 1173, 1067, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{34}H_{42}O_6Na)^+$ 569.2879, found 569.2864.

[α]$^{25}_D$ -24.9 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*,5*R*)-8-(Benzyloxy)-5-((*tert*-butyldimethylsilyl)oxy)-2-((*S*)-oxiran-2-yl)octan-3-ol 2.24



Chemical Formula: $C_{23}H_{40}O_4Si$
Molecular Weight: 408.65

Method 1:

To a stirred suspension of homoallylic alcohol **2.16** (40 mg, 0.1 mmol, *dr* 6:1) in dichloromethane (1 mL) was added $VO(acac)_2$ (1 mg, 0.004 mmol, 0.04 equiv) at 0 °C. After 15 min, TBHP (5.5 M solution in decane, 40 µL, 0.22 mol, 2.2 equiv) was added and solution was stirred for 4 h at 0 °C and 19 h at room temperature. Then a saturated aqueous solution of sodium thiosulfate (1.5 mL) was added and the solution was extracted with dichloromethane (3 x 2 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 3:1) gave epoxy alcohol **2.24** (3 mg, 0.007 mmol, 9%) as a yellow oil and as 2:1 mixture of diastereomers.

Method 2:

To a stirred solution of homoallylic alcohol **2.16** (120 mg, 0.30 mmol, *dr*: 6:1) in THF (3 mL) at -78 °C was added *n*BuLi (1.9 M solution in hexanes, 0.30 mL, 0.57 mmol, 1.9 equiv). After 30 min. CO_2 was bubbled through the reaction mixture, then after a further 30 min freshly sublimed I_2 (280 mg, 1.1 mmol, 3.7 equiv) in THF (3 mL) was added. After a further 1 h, CO_2 bubbling was stopped, the reaction was warmed to room temperature and the solvent was removed *in vacuo.* Then the solution was cooled to -78 °C and MeOH (7 mL)

followed by K_2CO_3 (300 mg, 2.2 mmol, 7.3 equiv) was added. After stirring for 2 h at -78 °C and 4 h at room temperature, water was added (7 mL) and the mixture was extracted with dichloromethane (3 x 7 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium thiosulfate (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 3:1) gave epoxy alcohol **2.24** (2 mg, 0.006 mmol, 2%) as a yellow oil and as a 10:1 mixture of diastereomers.

The major diastereomer is described below:

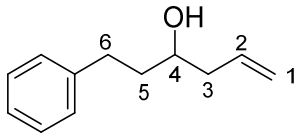
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H, ***H***-Ar), 4.50 (s, 2H, C***H***-10), 4.09-4.03 (m, 1H, C***H***-4), 4.03-3.98 (m, 1H, C***H***-6), 3.64 (d, *J* = 1.5 Hz, 1H, C4-O***H***), 3.48-3.45 (m, 2H, C***H***-9), 3.02 (ddd, *J* = 7.3, 4.0, 2.9 Hz, 1H, C***H***-2), 2.76-2.71 (m, 1H, C***H***-1), 2.45 (dd, *J* = 5.0, 2.8 Hz, 1H, C***H***-1), 1.88-1.82 (m, 1H, C***H***-3), 1.72-1.59 (m, 6H, C***H***-5, C***H***-7, C***H***-8), 0.97 (d, 3H, *J* = 7.1 Hz, C***H***-11), 0.90 (s, 9H, SiC(C***H₃***)$_3$), 0.11 (s, 3H, SiC(C***H₃***)$_2$), 0.08 (s, 3H, SiC(C***H₃***)$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 72.9 (C-10), 71.5 (C-6), 71.0 (C-4), 70.3 (C-9), 53.5 (C-2), 44.9 (C-1), 42.3 (C-3), 38.7 (C-5), 32.6 (C-7), 26.2 (C-8), 25.8 (SiC(***C***H$_3$)$_3$), 18.0 (Si***C***(CH$_3$)$_3$), 12.6 (C-11), -4.6 (SiC(***C***H$_3$)$_2$), -4.7 (SiC(***C***H$_3$)$_2$).

IR (neat, cm^{-1}) 2951, 2926, 2855, 1470, 1454, 1360, 1252, 1196, 1098, 1069.

HRMS (ESI, *m/z*) calcd for $(C_{23}H_{40}O_4SiNa)^+$ 431.2594, found 431.2600.

1-Phenylhex-5-en-3-ol 2.35[80]



Chemical Formula: $C_{12}H_{16}O$
Molecular Weight: 176.26

Zinc (400 mg, 6.1 mmol, 2.1 equiv) was added to a stirred suspension of hydrocinnamaldehyde (400 mg, 3.00 mmol) in THF (3.0 mL). Then the solution was cooled to 0 °C and allyl bromide (0.50 mL, 5.8 mmol, 1.9 equiv) was added followed by dropwise

[80] Ghadigaonkar, S.; Koli, M. R.; Gamre, S. S.; Choudhary, M. K.; Chattopadhyay, S.; Sharma, A. *Tetrahedron: Asymmetry* **2012**, *23,* 1093.

addition of a saturated solution of ammonium chloride (12 mL). After addition was complete, the reaction mixture was warmed to room temperature and stirred overnight. 1 M aqueous HCl (25 mL) was then added and the solution was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography on silica gel (petroleum ether: ether 3:1) furnished homoallylic alcohol **2.35** (365 mg, 2.07 mmol, 70%) as a clear oily liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H, ***H***-Ar), 5.90-5.80 (m, 1H, C***H***-2), 5.20-5.14 (m, 2H, C***H***-1), 3.74-3.67 (m, 1H, C***H***-4), 2.88-2.68 (m, 2H, C***H***-3), 2.39-2.17 (m, 2H, C***H***-6), 1.85-1.79 (m, 2H, C***H***-5).

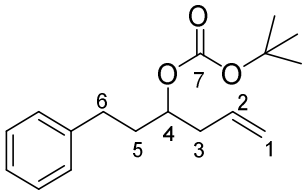
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.1 (C-2), 134.6 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 125.8 (C-Ar), 118.3 (C-1), 69.9 (C-4), 42.1 (C-3), 38.5 (C-6), 32.1 (C-5).

IR (neat, cm^{-1}) 3026, 2978, 2930, 2861, 1641, 1603, 1495, 1454.

LRMS (CI, *m/z*) (MH^+-H_2O) 159.1.

In agreement with literature data

***tert*-Butyl-(1-phenylhex-5-en-3-yl)carbonate 2.36** [81]



Chemical Formula: $C_{17}H_{24}O_3$
Molecular Weight: 276.38

To a stirred solution of **2.35** (350 mg, 2.00 mmol) in THF (7 mL) at 0 °C was added a 2M solution of NaHDMS in THF (1.50 mL, 3.0 mmol, 1.5 equiv) followed by di-*tert*-butyl dicarbonate (650 mg, 3.0 mmol, 1.5 equiv). The reaction was stirred for 2 h and then brine (5 mL) was added and the mixture was extracted with ether (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude product was purified by column chromatography on silica gel (petroleum ether: ether 3:1) to give **2.36** (533 mg, 1.90 mmol, 97%) as a clear oil.

[81] Gadakh, S. K.; Sudalai, A. *Tetrahedron: Asymmetry* **2015**, *26*, 118.

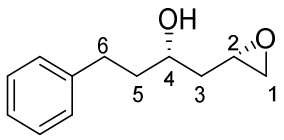
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H, ***H***-Ar), 7.21-7.15 (m, 2H, ***H***-Ar), 5.78 (ddt, *J* = 17.3, 10.2, 6.3 Hz, 1H, C***H***-2), 5.14-5.04 (m, 2H, C***H***-1), 4.78-4.69 (m, 1H, C***H***-4), 2.73 (ddd, *J* = 13.8, 10.4, 6.3 Hz, 1H, C***H***-3) 2.63 (ddd, *J* = 13.8, 10.2, 6.3 Hz, C***H***-3, 1H), 2.42-2.34 (m, 2H, C***H***-6), 1.99-1.81 (m, 2H, C***H***-5), 1.50 (s, 9H, OC(C***H*****$_3$**)$_3$.

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4 (C-7), 141.5 (C-2), 133.4 (C-Ar), 128.4 (C-Ar), 128.4 (C-Ar), 126.0 (C-Ar), 118.0 (C-1), 81.8 (O**C**$(CH_3)_3$), 76.0 (C-4), 38.8 (C-3), 35.5 (C-6), 31.7 (C-5), 27.8 (OC(**C**$H_3)_3$).

IR (neat, cm^{-1}) 1735, 1457, 1369,1276, 1253, 1161, 1119, 1071.

HRMS (ESI, *m/z*) calcd for $(C_{17}H_{24}O_3Na)^+$ 299.1623, found 299.1633.

1-(Oxiran-2-yl)-4-phenylbutan-2-ol 2.37



Chemical Formula: $C_{12}H_{16}O_2$
Molecular Weight: 192.26

To a stirred suspension of allylic carbonate **2.36** (180 mg, 0.650 mmol) in toluene (16 mL) at -78 °C, was added slowly iodine monochloride (0.07 mL, 1.4 mmol, 1.9 equiv). After 2 h, the reaction mixture was warmed to room temperature and the solvent was evaporated to give a viscous dark red oil. This oil was then redissolved in methanol (16 mL) and potassium carbonate (300 mg, 2.2 mmol, 3.0 equiv) was added and the reaction mixture was stirred for 1 day at room temperature. The solution was then quenched by the addition of saturated aqueous solution of sodium thiosulfate (16 mL) and was extracted with ether (3 x 15 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether: methanol 10:10:1) gave epoxy alcohol **2.37** (104 mg, 0.540 mmol, 75%) as a pale-yellow liquid and as a 98:2 mixture of diastereomers.

The major diastereomer is described below:

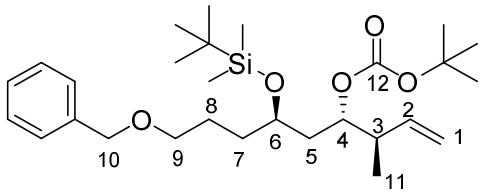
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.19 (m, 5H, ***H***-Ar), 3.94-3.93 (m, 1H, C***H***-4), 3.11-3.07 (m, 1H, C***H***-2), 2.84-2.77 (m, 2H, C***H***-1, C***H***-3), 2.71 (dt, *J* = 13.8, 8.0 Hz, 1H, C***H***-1), 2.50 (dd, *J* = 4.8, 2.7 Hz, 1H, C***H***-3), 2.13 (br s, 1H, C4-O***H***),1.93-1.82 (m, 3H, C***H***-5, C***H***-6), 1.53 (dt, *J* = 14.6, 8.1 Hz, 1H, C***H***-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8 (C-Ar), 128.4 (C-Ar), 125.9 (C-Ar), 69.9 (C-4), 50.6 (C-2), 46.6 (C-1), 39.8 (C-3), 39.1 (C-6), 31.8 (C-5).

IR (neat, cm^{-1}) 2920, 1495, 1454, 1410, 1260, 1117, 1094, 1047, 1030.

HRMS (ESI, *m/z*) calcd for $(C_{12}H_{16}O_2Na)^+$ 215.1048, found 215.1048.

(3*R*,4*S*,6*R*)-9-(Benzyloxy)-6-((*tert*-butyldimethylsil)oxy)-3-methylnon-1-en-4-yl *tert*-butylcarbonate 2.38



Chemical Formula: $C_{28}H_{48}O_5Si$
Molecular Weight: 492.77

To a stirred solution of **2.16** (200 mg, 0.51 mmol, *dr*: 6:1) in toluene (6 mL) was added DMAP (48 mg, 0.38 mmol, 0.74 equiv) and di-*tert*-butyl dicarbonate (160 mg, 0.73 mmol, 1.40 equiv) and reaction mixture was stirred for 2 days at room temperature. Then the reaction was quenched with a 1 M aqueous solution of HCl (5 mL), the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic extracts where washed with a saturated aqueous solution of sodium hydrogen carbonate (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude product was purified by column chromatography on silica gel (petroleum ether: ether 3:1) to give **2.38** (245 mg, 0.50 mmol, 98%) as a clear oil and as a 6:1 mixture of diastereomers.

The major diastereomer is described below:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, ***H***-Ar), 5.79-5.70 (m, 1H, C***H***-2), 5.09-5.03 (m, 2H, C***H***-1), 4.79-4.74 (m, 1H, C***H***-4), 4.50 (s, 2H, C***H***-10), 3.83-3.77 (m, 1H, C***H***-6), 3.47-3.45 (m, 2H, C***H***-9), 2.58-2.55 (m, 1H, C***H***-3), 1.66-1.53 (m, 6H, C***H***-5, C***H***-7, C***H***-8), 1.48 (s, 9H, OC(C***H*****$_3$**$)_3$), 1.01 (d, 3H, *J* = 6.9 Hz, C***H***-11), 0.89 (s, 9H, SiC(C***H*****$_3$**$)_3$), 0.05 (s, 3H, SiC(C***H*****$_3$**$)_2$), 0.04 (s, 3H, SiC(C***H*****$_3$**$)_2$).

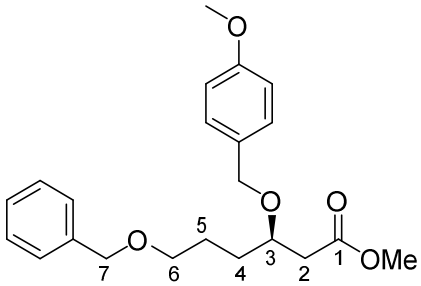
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (C-12), 139.4 (C-2), 138.6 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.4 (C-Ar), 115.4 (C-1), 81.5 (O**C**$(CH_3)_3$), 77.2 (C-4), 72.8 (C-10), 70.6 (C-9), 68.4

(C-6), 41.5 (C-3), 37.6 (C-5), 34.3 (C-7), 27.8 (OC(**C**H_3)$_3$), 25.9 (SiC(***C***H_3)$_3$), 24.6 (C-8), 18.0 (Si***C***$(CH_3)_3$), 14.5 (C-11), -4.1 (SiC(***C***H_3)$_2$), -4.9 (SiC(***C***H_3)$_2$).

IR (neat, cm^{-1}) 2929, 2857, 1738, 1368, 1276, 1253, 1163, 1095.

HRMS (ESI, *m/z*) calcd for $(C_{28}H_{48}O_5SiNa)^+$ 515.3169, found 515.3150.

Methyl (*R*)-6-(benzyloxy)-3-((4-methoxybenzyl)oxy)hexanoate 2.39



Chemical Formula: $C_{22}H_{28}O_5$
Molecular Weight: 372.46

To a stirred solution of alcohol **2.11** (1.00 g, 3.96 mmol) in 1,2-dichloroethane (10 mL) was added 4-methoxybenzyl alcohol (750 mg, 5.43 mmol, 1.37 equiv) in 1,2-dichloroethane (5 mL) followed by Amberlyst 15 hydrogen resin (200 mg, 20% *w/w*) and reaction mixture was stirred at reflux for one day. Three more portions of 4-methoxybenzyl alcohol (250 mg, 1.81 mmol, 0.46 equiv) in 1,2-dichloroethane (2 mL) were added every two days. After final addition mixture was left to stir at reflux for 1 day and then filtered, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to give **2.39** (1.14 g, 3.06 mmol, 77%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H, ***H***-Ar), 7.28-7.22 (m, 2H, ***H***-Ar (PMB)), 6.88 (d, *J* = 8.7 Hz, 2H, ***H***-Ar (PMB)), 4.51 (s, 2H, C***H***-7), 4.49-4.48 (m, 2H, C***H$_2$***-PMB), 3.93-3.90 (m, 1H, C***H***-3), 3.82 (s, 3H, PMB-OC***H$_3$***), 3.70 (s, 3H, OC***H$_3$***), 3.50 (t, 2H, *J* = 5.2 Hz, C***H***-6), 2.64 (dd, *J* = 15.1, 7.2 Hz, 1H, C***H***-2), 2.49 (dd, *J* = 15.1, 5.5 Hz, 1H, C***H***-2), 1.80-1.64 (m, 4H, C***H***-5, C***H***-4).

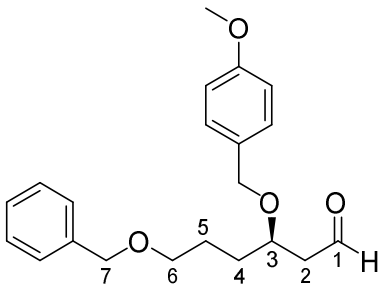
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1 (C-1), 159.2 (C-Ar), 138.6 (C-Ar), 130.6 (C-Ar), 129.4 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 113.8 (C-Ar), 75.4 (C-3), 72.9 (C-7), 71.2 (C-6 or **C**H_2-PMB), 70.2 (C-6 or **C**H_2-PMB), 55.3 (O**C**H_3-PMB), 51.6 (O**C**H_3), 39.7 (C-2), 31.1 (C-4), 25.5 (C-5).

IR (neat, cm^{-1}) 2997, 1754, 1611, 1510, 1454, 1360, 1244, 1172, 1032.

HRMS (ESI, *m/z*) calcd for $(C_{22}H_{28}O_5Na)^+$ 395.1829, found 395.1819.

[α]$^{25}_D$ -20.3 (*c* 1.0, $CHCl_3$).

(*R*)-6-(Benzyloxy)-3-((4-methoxybenzyl)oxy)hexanal 2.40



Chemical Formula: $C_{21}H_{26}O_4$
Molecular Weight: 342.44

To a stirred solution of **2.39** (1.11 g, 2.98 mmol) in CH_2Cl_2 (13 mL) was added DIBAL-H (1.2 M CH_2Cl_2 solution, 4.0 mL, 4.8 mmol, 1.6 equiv) dropwise at – 78 °C. The reaction mixture was stirred for 1.5 h before adding EtOAc (1 mL) and a saturated aqueous Rochelle's salt solution (1 mL) then the aqueous phase was extracted with ether (3 x 2 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude mixture was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to give aldehyde **2.40** (776 mg, 2.27 mmol, 76%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (app. t, *J* = 2.1 Hz 1H, C***H***-1), 7.39-7.31 (m, 5H, ***H***-Ar), 7.22 (d, *J* = 8.6 Hz, 2H, ***H***-Ar (PMB)), 6.86 (d, *J* = 8.6 Hz, 2H, ***H***-Ar (PMB)), 4.49 (s, 2H, C***H***-7), 4.46 (d, *J* = 11.0 Hz, 2H, C***H$_2$***-PMB), 3.97-3.94 (m, 1H, C***H***-3), 3.80 (s, 3H, PMB-OC***H$_3$***), 3.48 (t, 2H, *J* = 6.1 Hz, C***H***-6), 2.67 (ddd, *J* = 16.3, 7.2, 2.6 Hz, 1H, C***H***-2), 2.55 (ddd, *J* = 16.3, 4.8, 1.9 Hz, 1H, C***H***-2), 1.73-1.64 (m, 4H, C***H***-5, C***H***-4).

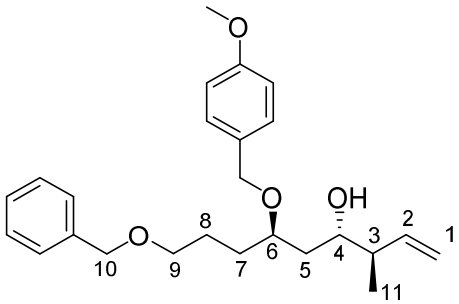
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.6 (C-1), 159.3 (C-Ar), 138.6 (C-Ar), 130.8 (C-Ar), 129.4 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 113.9 (C-Ar), 73.7 (C-3), 73.0 (C-7), 70.9 (C-6 or **C**H_2-PMB), 70.1 (C-6 or **C**H_2-PMB), 55.3 (O**C**H_3-PMB), 48.3 (C-2), 31.0 (C-4), 25.4 (C-5).

IR (neat, cm^{-1}) 2997, 2835, 1722, 1611, 1510, 1454, 1302, 1248, 1177, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{21}H_{26}O_4Na)^+$ 365.1731, found 365.1723.

[α]$^{25}_D$ -6.4 (*c* 1.0, $CHCl_3$).

(3*R*,4*S*,6*R*)-9-(Benzyloxy)-6-(4-(methoxybenzyl)oxy)-3-methylnon-1-en-4-ol 2.41



Chemical Formula: $C_{25}H_{34}O_4$
Molecular Weight: 398.54

Homoallylic alcohol **2.41** was obtained from the corresponding aldehyde **2.40** according to the procedure described for **2.16**. Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave **2.40** as clear oil.

Scale: 2.04 mmol

Yield: 60% (11:1:1 mixture of diastereomers)

The major diastereomer is described below:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H, ***H***-Ar), 7.26-7.23 (m, 2H, ***H***-Ar (PMB)), 6.88-6.85 (m, 2H, ***H***-Ar (PMB)), 5.80 (ddd, 1H, *J* = 16.8, 10.7, 8.1 Hz, C***H***-2), 5.09-5.02 (m, 2H, C***H***-1), 4.50 (s, 2H, C***H***-10), 4.48-4.47 (m, 2H, C***H$_2$***-PMB), 3.80 (s, 3H, PMB-OC***H$_3$***), 3.76-3.75 (m, 2H, C***H***-6, C***H***-4), 3.47 (t, 2H, *J* = 6.2 Hz, C***H***-9), 2.54 (d, 1H, *J* = 3.3 Hz, C4-O***H***), 2.23-2.14 (m, 1H, C***H***-3), 1.79-1.56 (m, 6H, C***H***-5, C***H***-7, C***H***-8), 1.02 (d, 3H, *J* = 7.0 Hz, C***H***-11).

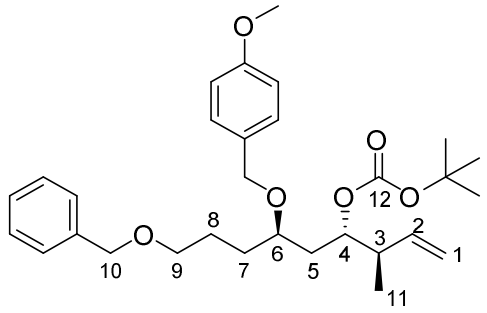
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C-Ar), 140.6 (C-2), 138.6 (C-Ar), 130.6 (C-Ar), 129.5 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 115.5 (C-1), 113.8 (C-Ar), 76.4 (C-6), 72.9 (C-10), 71.4 (C-4), 71.0 (**C**H_2-PMB), 70.3 (C-9), 55.3 (O**C**H_3-PMB), 44.2 (C-3), 37.3 (C-5), 30.3 (C-7), 25.8 (C-8),16.0 (C-11).

IR (neat, cm^{-1}) 2933, 2836, 1613, 1512, 1454, 1442 1302, 1246, 1075, 1033.

HRMS (ESI, *m/z*) calcd for $(C_{25}H_{34}O_4Na)^+$ 421.2349, found 421.2333.

[α]$^{25}_D$ -20.3 (*c* 1.0, $CHCl_3$).

(3*R*,4*S*,6*R*)-9-(Benzyloxy)-6-((4-methoxybenzyl)oxy)-3-methylnon-1-en-4-yl *tert*-butyl carbonate 2.42



Chemical Formula: $C_{30}H_{42}O_6$
Molecular Weight: 498.66

Carbonate **2.42** was obtained from the corresponding homoallylic alcohol **2.41** according to the procedure described for **2.36**. Purification by column chromatography on silica gel (petroleum ether: EtOAc 3:1) gave **2.42** as clear oil.

Scale: 1.2 mmol

Yield: 87%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 7H, ***H***-Ar, ***H***-Ar (PMB)), 6.86 (d, 2H, *J* = 8.7 Hz, ***H***-Ar (PMB)), 5.76 (ddd, 1H, *J* = 17.3, 10.4, 8.0 Hz, C***H***-2), 5.09-4.93 (m, 3H, C***H***-1, C***H***-4), 4.51 (s, 2H, C***H***-10), 4.49-4.33 (m, 2H, C***H$_2$***-PMB), 3.80 (s, 3H, PMB-OC***H$_3$***), 3.48-3.42 (m, 3H, C***H***-6, C***H***-9, C***H***-6), 2.48-2.34 (m, 1H, C***H***-3), 1.72-1.58 (m, 6H, C***H***-5, C***H***-7, C***H***-8), 1.53 (s, 9H, OC(C***H$_3$***)$_3$), 1.02 (d, 3H, *J* = 6.9 Hz, C***H***-11).

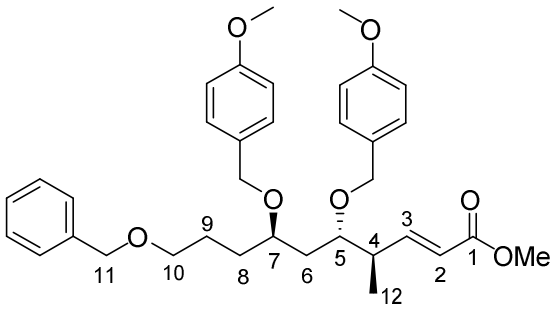
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C-Ar), 153.6 (C-12), 139.4 (C-2), 138.6 (C-Ar), 130.9 (C-Ar), 129.7 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 115.7 (C-1), 113.8 (C-Ar), 85.2 (O**C**$(CH_3)_3$), 81.6 (C-4), 75.3 (C-6), 72.9 (C-10), 71.5 (**C**H_2-PMB), 70.5 (C-9), 55.3 (O**C**H_3-PMB), 42.4 (C-3), 36.6 (C-5), 29.7 (C-7), 27.4 (OC(**C**$H_3)_3$), 25.2 (C-8), 15.6 (C-11).

IR (neat, cm^{-1}) 3001, 1736, 1273, 1250, 1211, 1165, 1179, 1065, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{30}H_{42}O_6Na)^+$ 521.2871, found 521.2852.

[α]$^{25}_D$ -30.1 (*c* 1.0, $CHCl_3$).

Methyl-(4*R*,5*S*,7*R*,*E*)-10-(benzyloxy)-5,7-*bis*((4-methoxybenzyl)oxy)-4-methyldec-2-enoate 2.47



Chemical Formula: $C_{35}H_{44}O_7$
Molecular Weight: 576.73

A general procedure for the cross metathesis of alkene **2.18** with methyl acrylate **2.52** is described below while the conditions, solvent and quantities of reagents and catalysts used are summarized in Table 2.4.

To a stirred suspension of alkene **2.18** (500 mg, 0.96 mmol) and methyl acrylate **2.52** (0.50 mL, 5.5 mmol, 5.7 mmol, 5.19 equiv) in dichloromethane (7 mL) was added **HG-II** catalyst (69 mg, 0.11 mmol, 0.11 equiv) and the reaction mixture was heated to reflux and left to stir overnight. Then the mixture was concentrated *in vacuo* and purified by column chromatography on silica gel (petroleum ether: EtOAc 3:1) to give ester **2.47** (550 mg, 0.95 mmol, 99%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, ***H***-Ar), 7.22-7.17 (m, 4H, ***H***-Ar (PMB)), 6.97 (dd, 1H, *J* = 15.8, 7.2 Hz C***H***-3), 6.87-6.83 (m, 4H, ***H***-Ar (PMB)), 5.83 (dd, 1H, *J* = 15.8, 1.4 Hz, C***H***-2), 4.49 (s, 2H, C***H***-11), 4.47-4.43 (m, 2H, C***H$_2$***-PMB), 4.26-4.21 (m, 2H, C***H$_2$***-PMB), 3.78 (s, 6H, PMB-OC***H$_3$***), 3.73 (s, 3H, OC***H$_3$***), 3.67-3.59 (m, 2H, C***H***-5, C***H***-7), 3.47 (t, 2H, *J* = 5.8 Hz C***H***-10), 2.69-2.64 (m, 1H, C***H***-4), 1.67-1.58 (m, 4H, C***H***-6, C***H***-8), 1.55-1.50 (m, 2H, C***H***-9), 1.07 (d, 3H, *J* = 6.8 Hz, C***H***-12).

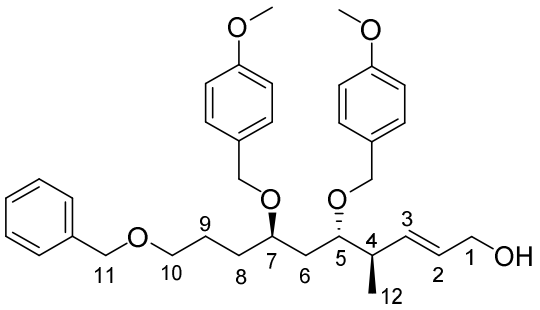
^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0 (C-1), 159.1 (C-Ar), 159.1 (C-Ar), 151.1 (C-3), 138.6 (C-Ar), 131.0 (C-Ar), 130.7 (C-Ar), 129.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 121.1 (C-2), 113.8 (C-Ar), 78.3 (C-5), 74.9 (C-7), 72.9 (C-11), 71.8 (C-10), 70.4 (**C**H_2-PMB), 70.2 (**C**H_2-PMB), 55.3 (O**C**H_3-PMB), 51.4 (CO**C**H_3), 39.7 (C-4), 36.8 (C-6), 30.4 (C-8), 25.1 (C-9), 13.8 (C-12).

IR (neat, cm^{-1}) 2949, 2860, 1721, 1655, 1613, 1586, 1512, 1454, 1435, 1302, 1246, 1173, 1150, 1067, 1034, 1013.

HRMS (ESI, *m/z*) calcd for $(C_{35}H_{44}O_7Na)^+$ 599.2979, found 599.2956.

[α]$^{25}_D$ -28.9 (*c* 1.0, $CHCl_3$).

(4*R*,5*S*,7*R*,*E*)-10-(Benzyloxy)-5,7-*bis*((4-methoxybenzyl)oxy)-4-methyldec-2-en-1-ol 2.45



Chemical Formula: $C_{34}H_{44}O_6$
Molecular Weight: 548.72

Method 1

To a stirred solution of **2.47** (1.80 g, 3.12 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added DIBAL-H (1 M solution in hexanes, 7.00 mL, 7.00 mmol, 2.24 equiv) dropwise. The reaction mixture was then allowed to warm to room temperature overnight and EtOAc (10 mL) was added, followed by silica. The resulting suspension was stirred for 40 min and was the filtered and concentrated *in vacuo.* Purification by column chromatography on silica gel (petroleum ether: diethyl ether 1:1) gave allylic alcohol **2.45** (1.40 g, 2.55 mmol, 82%) as a clear oil.

Method 2

To a stirred solution of acetate **2.46** (59.0 mg, 0.10 mmol) in ethanol (0.75 mL) and H_2O (0.15 mL) was added NaOH (14.5 mg, 0.36 mmol, 3.6 equiv) at room temperature. The reaction mixture was stirred overnight and then concentrated *in vacuo.* The residue was dissolved in EtOAc (1 mL) and the resulting solution was washed with brine (3 x 0.5 mL), dried over $MgSO_4$, filtered and concentrated in *vacuo.* Purification by column chromatography on silica gel (petroleum ether: diethyl ether 1:1) gave allylic alcohol **2.45** (49 mg, 0.09 mmol, 89%) as a clear oil.

Method 3

Allylic alcohol **2.45** was obtained from alkene **2.18** and alcohol **2.48** according to the procedure described for **2.47**. Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave **2.45** as clear oil.

Scale: 0.24 mmol

Yield: 7% (9% b.r.s.m)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, ***H***-Ar), 7.22-7.19 (m, 4H, ***H***-Ar (PMB)), 6.86-6.83 (m, 4H, ***H***-Ar (PMB)), 5.66-5.64 (m, 2H, C***H***-2, C***H***-3), 4.50 (s, 2H, C***H***-11), 4.44-4.49 (m, 2H, C***H$_2$***-PMB), 4.27-4.23 (m, 2H, C***H$_2$***-PMB), 4.08 (m, 2H, C***H***-1), 3.78 (s, 3H, PMB-OC***H$_3$***), 3.77 (s, 3H, PMB-OC***H$_3$***), 3.63-3.56 (m, 2H, C***H***-5, C***H***-7), 3.47 (t, 2H, *J* = 6.0 Hz C***H***-10), 2.59-2.55 (m, 1H, C***H***-4), 1.68-1.53 (m, 6H, C***H***-6, C***H***-8, C***H***-9), 1.02 (d, 3H, *J* = 6.6 Hz, C***H***-12).

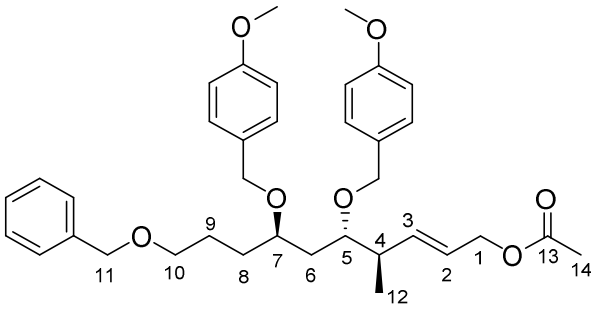
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C-Ar), 138.6 (C-Ar), 134.8 (C-3 or C-2), 131.0 (C-3 or C-2), 131.0 (C-Ar), 129.4 (C-Ar), 129.4 (C-Ar), 129.3 (C-Ar), 129.3 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 113.7 (C-Ar), 78.9 (C-5), 75.2 (C-7), 72.9 (C-11), 71.4 (C-10), 70.5 (**C**H_2-PMB), 70.4 (**C**H_2-PMB), 63.8 (C-1), 55.3 (O**C**H_3-PMB), 38.8 (C-4), 36.2 (C-6), 30.5 (C-8), 25.2 (C-9), 14.3 (C-12).

IR (neat, cm^{-1}) 2872, 1514, 1456, 1302, 1248, 1086, 1032.

HRMS (ESI, *m/z*) calcd for $(C_{34}H_{44}O_6Na)^+$ 571.3037, found 571.3053.

[α]$^{25}_D$ -36.7 (*c* 1.0, $CHCl_3$).

(4*R*,5*S*,7*R*,*E*)-10-(Benzyloxy)-5,7-*bis*((4-methoxybenzyl)oxy)-4-methyldec-2-en-1-yl acetate 2.46



Chemical Formula: $C_{36}H_{46}O_7$
Molecular Weight: 590.76

Allyl aceate **2.46** was obtained from alkene **2.18** and acetate **2.52** according to the procedure described for **2.47**. Purification by column chromatography on silica gel (petroleum ether: ether 3:1) gave **2.46** as clear oil.

Scale: 0.19 mmol

Yield: 76% (83% b.r.s.m)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H, ***H***-Ar), 7.23-7.18 (m, 4H, ***H***-Ar (PMB)), 6.86-6.83 (m, 4H, ***H***-Ar (PMB)), 5.74 (dd, *J* = 15.5, 7.0 Hz, 1H, C***H***-3), 5.59 (dtd, *J* = 15.5, 6.3, 1.0 Hz, 1H, C***H***-2), 4.52 (d, *J* = 6.3 Hz, 2H, C***H***-1), 4.50 (s, 2H, C***H***-11), 4.47 (d, 1H, *J* = 11.0 Hz C***H$_2$***-PMB), 4.44 (d, 1H, *J* = 10.9 Hz C***H$_2$***-PMB), 4.26-4.23 (m, 2H, C***H$_2$***-PMB), 3.78 (s, 3H, PMB-OC***H$_3$***), 3.78 (s, 3H, PMB-OC***H$_3$***), 3.64-3.55 (m, 2H, C***H***-5, C***H***-7), 3.47 (t, 2H, *J* = 5.9 Hz C***H***-10), 2.60-2.52 (m, 1H, C***H***-4), 2.04 (s, 3H, C***H***-14), 1.71-1.59 (m, 4H, C***H***-8, C***H***-9), 1.58-1.46 (m, 2H, C***H***-6), 1.02 (d, 3H, *J* = 6.7 Hz, C***H***-12).

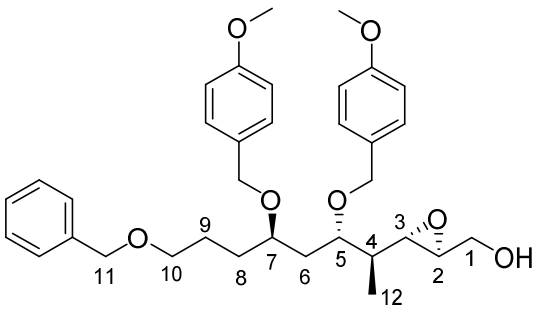
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8 (C-13), 159.1 (C-Ar), 159.1 (C-Ar), 138.6 (C-Ar), 138.0 (C-3), 131.0 (C-Ar), 130.9 (C-Ar), 129.3 (C-Ar), 129.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 124.2 (C-2), 113.7 (C-Ar), 113.7 (C-Ar), 78.8 (C-5), 75.1 (C-7), 72.8 (C-11), 71.5 (C-10), 70.5 (**C**H_2-PMB), 70.5 (**C**H_2-PMB), 65.3 (C-1), 55.2 (O**C**H_3-PMB), 39.2 (C-4), 36.3 (C-6), 30.5 (C-8), 25.2 (C-9), 21.0 (C-14), 14.3 (C-12).

IR (neat, cm^{-1}) 2951, 2855, 1704, 1615, 1522, 1455, 1437, 1240, 1168, 1015.

HRMS (ESI, *m/z*) calcd for $(C_{36}H_{46}O_7Na)^+$ 613.3136, found 613.3113.

[α]$^{25}_D$ -31.4 (*c* 0.5, $CHCl_3$).

((2*S*,3*S*)-3-((2*S*,3*S*,5*R*)-8-(Benzyloxy)-3,5-*bis*((4-methoxybenzyl)oxy)octan-2-yl)oxiran-2-yl)methanol 2.44



Chemical Formula: $C_{34}H_{44}O_7$
Molecular Weight: 564.72

To a stirred solution of freshly distilled titanium isopropoxide (280 µL, 0.93 mmol, 0.20 equiv) and 4Å molecular sieves (1.70 g) in dichloromethane (20 mL) at -23 °C was added freshly distilled (*L*)-(+)-diisopropyl tartrate (240 µL, 1.10 mmol, 0.23 equiv). After 10 min, allylic alcohol **2.45** (2.60 g, 4.74 mmol) in dichloromethane (12 mL) was slowly added. After a further 30 min of stirring, *tert*-butyl hydroperoxide (5.5 M solution in decane, 2.07 mL, 11.4 mmol, 2.4 equiv) in 6 mL of dichloromethane was added dropwise. Stirring continued for 36 h at -23 °C and then H_2O (15 mL) and a 30% aqueous NaOH solution (15 mL) were added

and the reaction mixture was warmed to 0 °C and stirred for another 3 h. Then methanol (5 mL) and petroleum ether (5 mL) were added and the solution was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: EtOAc 3:2) gave epoxy alcohol **2.44** (2.46 g, 4.36 mmol, 92%) as a clear oil and as a 12:1 mixture of diastereomers.

The major diastereomer is described below:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H, ***H***-Ar), 7.24-7.19 (m, 4H, ***H***-Ar (PMB)), 6.86-6.83 (m, 4H, ***H***-Ar (PMB)), 4.50 (s, 2H, C***H***-11), 4.49-4.41 (m, 2H, C***H$_2$***-PMB), 4.27 (d, 1H, *J* = 11.0 Hz C***H$_2$***-PMB), 4.24 (d, 1H, *J* = 11.0 Hz C***H$_2$***-PMB), 3.78(s, 3H, PMB-OC***H$_3$***), 3.77 (s, 3H, PMB-OC***H$_3$***), 3.76-3.69 (m, 2H, C***H***-1), 3.66-3.59 (m, 2H, C***H***-5, C***H***-7), 3.48 (t, 2H, *J* = 6.0 Hz C***H***-10), 2.94-2.91 (m, 1H, C***H***-2), 2.90-2.87 (m, 1H, C***H***-3), 1.85-1.81 (m, 1H, C***H***-4), 1.75-1.63 (m, 6H, C***H***-6, C***H***-8, C***H***-9), 0.92 (d, 3H, *J* = 7.1 Hz, C***H***-12).

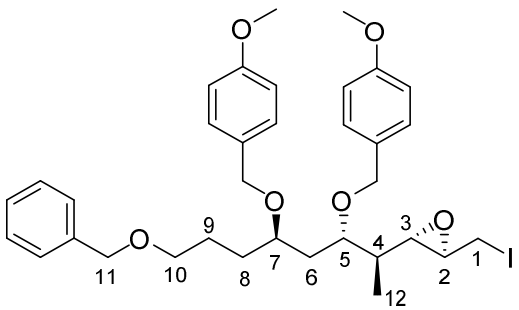
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C-Ar), 138.6 (C-Ar), 130.9 (C-Ar), 130.9 (C-Ar), 129.5 (C-Ar), 129.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 113.8 (C-Ar), 113.7 (C-Ar), 77.4 (C-5), 75.4 (C-7), 72.9 (C-11), 71.6 (C-10), 70.4 (**C**H_2-PMB), 70.4 (**C**H_2-PMB), 62.0 (C-1), 57.3 (C-2), 56.3 (C-3), 55.3 (O**C**H_3-PMB), 38.2 (C-4), 36.8 (C-6), 30.5 (C-8), 25.2 (C-9), 11.0 (C-12).

IR (neat, cm^{-1}) 2945, 2862, 1613, 1512, 1360, 1302, 1246, 1173, 1067, 1032.

HRMS (ESI, *m/z*) calcd for $(C_{34}H_{44}O_7Na)^+$ 587.2985, found 587.2954.

[α]$^{25}_D$ -50.6 (*c* 1.0, $CHCl_3$).

(2*R*,3*S*,4*S*,5*S*,7*R*)-10-(Benzyloxy)-5,7-bis((4-methoxybenzyl)oxy)-4-methyldec-3-yl)-2-(iodomethyl)oxirane



Chemical Formula: $C_{34}H_{43}IO_6$
Molecular Weight: 674.62

Method 1

Iodine (450 mg, 1.77 mmol, 2.50 equiv) was added to a stirred suspension of imidazole (155 mg, 0.88 mmol, 1.24 equiv) and triphenylphosphine (515 mg, 1.96 mmol, 2.77 equiv) and epoxide **2.44** (400 mg, 0.71 mmol) in a mixture of ether (1.2 mL) and acetonitrile (0.5 mL) at 0 °C. The solution was left to warm to room temperature and stirred overnight. Then the reaction mixture was diluted with petroleum ether (2 mL) and diethyl ether (2 mL). The resultant solution was washed with a saturated aqueous solution of sodium thiosulfate, a saturated aqueous solution of copper sulfate and brine, dried ($MgSO_4$) filtered and concentrated *in vacuo*.

Method 2

To a stirred solution of epoxide **2.44** (340 mg, 0.60 mmol) in CH_2Cl_2 at 0°C was added triethylamine (0.12 mL, 0.86 mmol, 1.4 equiv) followed by MsCl (0.07 mL, 0.90 mmol, 1.5 equiv). After 30 min a saturated aqueous solution of citric acid (3 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$ filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: EtOAc 2:1) gave the mesylate intermediate as a clear oil that was dissolved in methyl ethyl ketone (10 mL) and NaI (141 mg, 0.94 mmol, 1.6 equiv) was added. The resulting mixture was refluxed for 1 h and then cooled to room temperature and concentrated *in vacuo.* The resulting viscous oil was dissolved in EtOAc (15 mL) and washed with brine (15 mL), dried over $MgSO_4$ filtered and concentrated *in vacuo.*

The crude 2,3-epoxy iodide was used in the next step without further purification regardless of the preparation method used. For analysis a sample was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to give 2,3-epoxy iodide as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H, ***H***-Ar), 7.25-7.19 (m, 4H, ***H***-Ar (PMB)), 6.85 and 6.84 (2d, 4H, *J* = 8.5 Hz, ***H***-Ar (PMB)), 4.50-4.46 (m, 3H, C***H***-11, C***H$_2$***-PMB), 4.42 (d, 1H, *J* = 11.0 Hz, C***H$_2$***-PMB), 4.27 (d, 1H, *J* = 11.0 Hz, C***H$_2$***-PMB), 4.26 (d, 1H, *J* = 11.1 Hz, C***H$_2$***-PMB), 3.78 (s, 3H, PMB-OC***H$_3$***), 3.77 (s, 3H, PMB-OC***H$_3$***), 3.72-3.68 (m, 1H, C***H***-5), 3.64-3.60 (m, 1H, C***H***-7), 3.47 (t, 2H, *J* = 6.1 Hz, C***H***-10), 3.27-3.24 (m, 1H, C***H***-2), 3.04-2.96 (m, 2H, C***H***-1), 2.78 (dd, 1H, *J* = 7.7, 1.8 Hz, C***H***-3), 1.72-1.63 (m, 7H, C***H***-4, C***H***-6, C***H***-8, C***H***-9), 1.00 (d, 3H, *J* = 7.1 Hz, C***H***-12).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C-Ar), 159.1 (C-Ar), 138.6 (C-Ar), 131.0 (C-Ar), 130.9 (C-Ar), 129.4 (C-Ar), 129.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 113.7 (C-Ar), 113.7 (C-Ar), 77.4 (C-5), 75.0 (C-7), 72.8 (C-11), 71.8 (C-10), 70.4 (**C**H_2-PMB), 70.1 (**C**H_2-

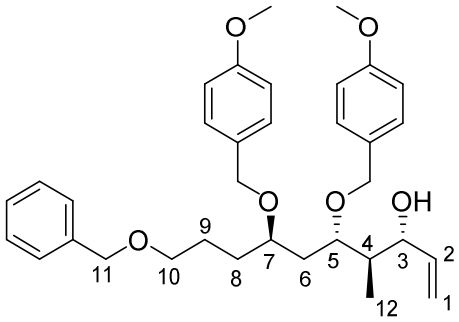
PMB), 63.4 (C-2), 57.0 (C-3), 55.3 (O**C**H_3-PMB), 39.2 (C-4), 36.9 (C-6), 30.4 (C-8), 25.1 (C-9), 12.1 (C-12), 5.0 (C-1).

IR (neat, cm^{-1}) 2932, 2862, 1612, 1512, 1458, 1358, 1304, 1242, 1173, 1065, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{34}H_{43}IO_6Na)^+$ 697.1997, found 697.1997.

[α]$^{25}_D$ -26.0 (*c* 1.0, $CHCl_3$).

(3*R*,4*R*,5*S*,7*R*)-10-(Benzyloxy)-5,7-*bis*((4-methoxybenzyl)oxy)-4-methyldec-1-en-3-ol 2.4



Chemical Formula: $C_{34}H_{44}O_6$
Molecular Weight: 548.72

Method 1

Crude 2,3-epoxy iodide obtained from Method 1 was dissolved in dry MeOH (2.5 mL) and zinc (235 mg, 3.59 mmol, 5.1 equiv) was added. The reaction mixture was stirred at reflux for 3 h, after which it was cooled to room temperature and filtered through a pad of celite, washed with diethyl ether and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: EtOAc 3:1) gave allylic alcohol **2.4** (337 mg, 0.61 mmol, 88%) as a clear oil.

Method 2

Crude 2,3-epoxy iodide obtained from Method 2 was dissolved in MeOH (10 mL) and zinc (740 mg, 11.3 mmol, 20 equiv) was added followed by Iodine (10 mg, 0.08 mmol, 0.14 equiv). The resulting mixture was refluxed for 2 h and cooled to room temperature, filtered through celite and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: EtOAc 3:1) gave allylic alcohol **2.4** (300 mg, 0.55 mmol, 92%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H, ***H***-Ar), 7.22-7.19 (m, 4H, ***H***-Ar (PMB), 6.85-6.83 (m, 4H, ***H***-Ar (PMB)), 5.89-5.82 (m, 1H, C***H***-2), 5.23-5.13 (m, 2H, C***H***-1), 4.50 (s, 2H, C***H***-11), 4.46 (d, 1H, *J* = 11.0 Hz, C***H$_2$***-PMB), 4.44 (d, 1H, *J* = 11.0 Hz, C***H$_2$***-PMB), 4.24 (d, 1H, *J* = 11.0 Hz, C***H$_2$***-PMB), 4.21 (d, 1H, *J* = 11.0 Hz, C***H$_2$***-PMB), 3.91-3.86 (m, 2H, C***H***-3, C***H***-5), 3.77 (s, 3H, PMB-OC***H$_3$***), 3.77 (s, 3H, PMB-OC***H$_3$***), 3.59-3.56 (m, 1H, C***H***-7), 3.48 (t, 2H, *J* = 6.0 Hz, C***H***-10), 2.59 (br s, 1H, C3-***OH***), 2.00-1.93 (m, 1H, C***H***-4), 1.73-1.52 (m, 6H, C***H***-6, C***H***-8, C***H***-9), 0.82 (d, 3H, *J* = 7.0 Hz, C***H***-12).

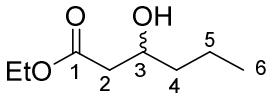
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C-Ar), 159.1 (C-Ar), 139.8 (C-2), 138.6 (C-Ar), 130.9 (C-Ar), 130.7 (C-Ar), 129.5 (C-Ar), 129.4 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 116.0 (C-1), 113.8 (C-Ar), 77.1 (C-5), 75.9 (C-7), 75.6 (C-3), 72.9 (C-11), 70.9 (C-10), 70.4 (**C**H_2-PMB), 70.4 (**C**H_2-PMB), 55.3 (O**C**H_3-PMB), 55.2 (O**C**H_3-PMB), 40.6 (C-4), 36.1 (C-6), 30.4 (C-8), 25.1 (C-9), 11.1 (C-12).

IR (neat, cm^{-1}) 3028, 2953, 2932, 2866, 1612, 1585, 1512, 1497, 1454, 1360, 1302, 1246, 1171, 1063, 1036.

HRMS (ESI, *m/z*) calcd for $(C_{34}H_{44}O_6Na)^+$ 571.3000, found 571.3015.

[α]$^{25}_D$ -41.9 (*c* 1.0, $CHCl_3$).

Ethyl 3-hydroxyhexanoate



Chemical Formula: $C_8H_{16}O_3$
Molecular Weight: 160.21

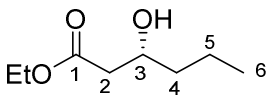
To a solution of ethyl caproate (100 mg, 0.60 mmol) in ethanol (5 mL) was added $NaBH_4$ (24 mg, 0.60 mmol, 1.0 equiv) and the resulting solution was stirred for 1 h at 0 °C. The reaction mixture was quenched with a 1 M aqueous solution of HCl (3 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum to give the desired compound (87 mg, 0.55 mmol, 91 %) as a clear oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, 2H, *J* = 7.0 Hz, C***H$_2$***-ethyl ester), 4.07-4.00 (m, 1H, C***H***-3), 2.94 (broad s, 1H, C-O***H***), 2.53 (dd, 1H, *J* = 16.5, 3.0 Hz, C***H***-2), 2.42 (dd, 1H, *J* = 16.5, 9.0 Hz, C***H***-2), 1.59-1.36 (m, 4H, C***H***-4, C***H***-5), 1.30 (t, 3H, *J* = 7.0, C***H$_3$***-ethyl ester), 0.96 (t, 3H, *J* = 7.1, C***H***-6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2 (C-1), 67.8 (C-3), 60.6 (***C***H_2-ethyl ester), 41.3 (C-2), 38.6 (C-4), 18.7 (C-5), 14.2 (C-6 or ***C***H_3-ethyl ester), 14.2 (C-6 or ***C***H_3-ethyl ester).

IR (neat, cm^{-1}) 2962, 1713, 1466, 1404, 1304, 1258, 1173, 1096, 1018.

(*R*) Ethyl 3-hydroxyhexanoate 2.59[40]



Chemical Formula: $C_8H_{16}O_3$
Molecular Weight: 160.21

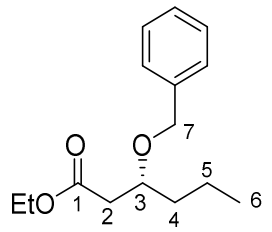
β-Hydroxyketoester **2.59** was obtained from the corresponding β-ketoester **1.82** according to the procedure described for **2.11** using *R*-tol-BINAP as the ligand. Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave **2.59** as clear oil. The enantiomeric purity of the compound was determined by chiral HPLC (chiral OD cel column with a flow rate of 0.5 mL/min and solvent system of 2% isopropanol/hexane) t_r = 12.5 min (Major), t_r = 16.4 min (Minor).

Scale: 27.7 mmol

Yield: 94% (*er* 98:2)

$[\alpha]^{25}_D$ -23.0 (*c* 1.0, $CHCl_3$).

Ethyl 3-(benzyloxy)hexanoate 2.60[40]



Chemical Formula: $C_{15}H_{22}O_3$
Molecular Weight: 250.34

To a stirred suspension of β-Hydroxyketoester **2.59** (1.45 g, 9.05 mmol) and freshly prepared benzyl 2,2,2-trichloroacetimidate (6.86 g, 27.7 mmol, 3.00 equiv) in dichloromethane (15 mL) was added slowly triflic acid (0.10 mL, 1.1 mmol, 0.12 equiv). The reaction mixture was stirred at room temperature for 2 days and was then quenched by the addition of a saturated aqueous solution of sodium bicarbonate (20 mL). The mixture was

extracted with ether (3 x 20 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave benzylated alcohol **2.60** (2.09 g, 8.33 mmol, 92%) as a pale-yellow oil.

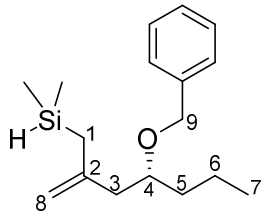
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H, ***H***-Ar), 4.58 (d, 1H, *J* = 11.3 Hz, C***H***-7), 4.54 (d, 1H, *J* = 11.3 Hz, C***H***-7), 4.18 (q, 1H, *J* = 7.0 Hz, C***H*****$_2$**-ethyl ester), 4.15 (q, 1H, *J* = 7.0 Hz, C***H*****$_2$**-ethyl ester), 3.96-3.89 (m, 1H, C***H***-3), 2.64 (dd, 1H, *J* = 15.0, 7.0 Hz, C***H***-2), 2.49 (dd, 1H, *J* = 15.0, 5.5 Hz, C***H***-2), 1.66-1.37 (m, 4H, C***H***-4, C***H***-5), 1.26 (t, 3H, *J* = 7.1, C***H*****$_3$**-ethyl ester), 0.96 (t, 3H, *J* = 7.1, C***H***-6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9 (C-1), 138.6 (C-Ar), 128.3 (C-Ar), 127.8 (C-Ar), 127.5 (C-Ar), 76.0 (C-3), 71.6 (C-7), 60.4 (***C***H_2-ethyl ester), 40.1 (C-2), 36.7 (C-4), 18.5 (C-5), 14.2 (C-6 or ***C***H_3-ethyl ester), 14.1 (C-6 or ***C***H_3-ethyl ester).

HRMS (ESI, *m/z*) calcd for $(C_{15}H_{22}O_3Na)^+$ 273.1467, found 273.1464.

[α]$^{25}_D$ -3.0 (*c* 1.0, $CHCl_3$).

(*R*)-(4-(Benzyloxy)-2-methyleneheptyl)dimethylsilane 1.253



Chemical Formula: $C_{17}H_{28}OSi$
Molecular Weight: 276.50

Cerium(III) chloride heptahydrate (15.0 g, 40.3 mmol, 4.94 equiv) was dried under vacuum at 80 °C for 12 h, 120 °C for 2 h, 140 °C for 2 h and then 160°C for 2 h. After allowing flask to cool to room temperature, dry THF (145 mL) was slowly added. The mixture was stirred for 16 h at room temperature to give the cerium(III) chloride-THF complex as a white precipitate.

To a stirred suspension of magnesium (900 mg, 37 mmol, 4.6 equiv) and 1,2-dibromoethane (2 drops) in THF (36 mL) at reflux was added dropwise chloromethyldimethylsilane **1.224** (3.50 mL, 28.7 mmol, 3.52 equiv) and the resulting solution was stirred for 3 h.

The above black solution was cooled to room temperature and was then added dropwise (over 1.5 h) at -78 °C to the cerium(III) chloride-THF complex. The resulting grey suspension was stirred for 30 min, and then ethyl caproate (1.35 mL, 8.10 mmol) in dry THF (15 mL) was added. The reaction mixture was stirred for 3 h at -78 °C and then stirred overnight at room temperature. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (200 mL) at 0 °C, water was added and the mixture was extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with water and brine (2 x 250 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was stirred with silica gel in dichloromethane for 3 days. The mixture was then filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 98:2) to give silane **1.253** (1.05 g, 6.10 mmol, 75%) as a clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H, ***H***-Ar), 4.70-4.69 (m, 1H, C***H***-8), 4.66-4.65 (m, 1H, C***H***-8), 4.58 (d, *J* = 11.6 Hz, 1H, C***H***-9), 4.50 (d, *J* = 11.6 Hz, 1H, C***H***-9), 3.93 (non, *J* = 3.6 Hz, 1H, Si-***H***), 3.58-3.52 (m, 1H, C***H***-4), 2.37 (ddd, *J* = 14.1, 6.1, 0.8 Hz, 1H, C***H***-3), 2.15 (ddd, *J* = 14.1, 6.6, 0.9 Hz, 1H, C***H***-3), 1.62-1.61 (m, 2H, C***H***-1), 1.52-1.31 (m, 4H, C***H***-5, C***H***-6), 0.91 (t, *J* = 7.1 Hz, 3H, C***H***-7), 0.11 (d, *J* = 3.6 Hz, 3H, -Si(C***H***$_3$)$_2$-), 0.10 (d, *J* = 3.6 Hz, 3H, -Si(C***H***$_3$)$_2$-).

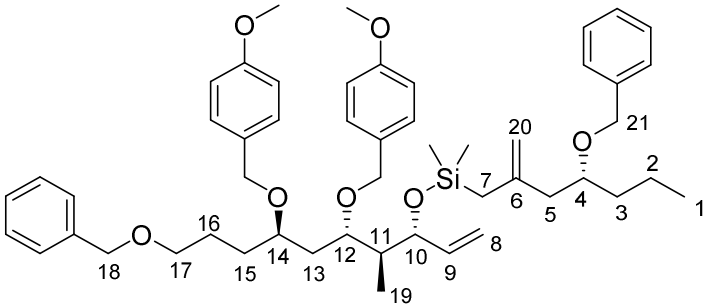
^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3 (***C***-2), 139.0 (***C***-Ar), 128.3 (***C***-Ar), 127.8 (***C***-Ar), 127.4 (***C***-Ar), 110.3 (***C***-8), 77.5 (***C***-4), 71.0 (***C***-9), 42.7 (***C***-3), 36.4 (***C***-5), 24.6 (***C***-1), 18.7 (***C***-6), 14.2 (***C***-7), -4.4 (-Si(***C***H3)2-).

IR (neat, cm^{-1}) 2957, 2932, 2872, 2114, 1634, 1497, 1454, 1248, 1092, 1067, 1028, 885, 839, 733, 696.

HRMS (ESI, *m/z*) calcd for $C_{17}H_{28}OSiNa$ $[M+Na]^+$: 299.1802, found: 299.1787.

$[\alpha]^{25}_D$ +15.2 (*c* 1.0, $CHCl_3$).

(3*R*,10*S*,11*S*,13*R*)-11,13-*bis*(4-methoxybenzyloxy)-7,7,10-trimethyl-5-methylene-1,18-diphenyl-3-propyl-9-vinyl-2,8,17-trioxa-7-silaoctadecane 2.3



Chemical Formula: $C_{51}H_{70}O_7Si$
Molecular Weight: 823.20

To a stirred suspension of allylic alcohol **2.4** (450 mg, 0.82 mmol), silane **1.253** (450 mg, 1.63 mmol, 2.0 equiv) and xanthphos copper chloride (50.0 mg, 0.086 mmol, 0.10 equiv) in toluene (20 mL) at 85 °C was added lithium *tert*-butoxide (2.2 M in THF, 0.40 mL, 0.88 mmol, 1.1 equiv) in toluene (4 mL) via syringe pump at a flow rate of 0.40 mL/min. After completion of the addition, the reaction was left to stir overnight. The reaction mixture was then cooled to room temperature and quenched by addition of a saturated solution of ammonium chloride (50 mL). The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic layer where washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 4:1) gave **2.3** (567 mg, 0.69 mmol, 84%) as a pale-yellow oil, as well as silane **1.253** (214 mg, 0.77 mmol, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.25 (m, 10H, ***H***-Ar), 7.21-7.17 (m, 4H, ***H***-Ar (PMB), 6.83-6.80 (m, 4H, ***H***-Ar (PMB)), 5.76 (ddd, *J* = 17.3, 10.3, 7.2 Hz 1H, C***H***-9), 5.14-5.09 (m, 2H, C***H***-8), 4.68-4.63 (m, 2H, C***H***-20), 4.56-4.53 (m, 1H, C***H***-21), 4.49 (s, 2H, C***H***-18), 4.47-4.41 (m, 3H, C***H₂***-PMB, C***H***-21), 4.23 (d, 1H, *J* = 11.0 Hz, C***H₂***-PMB), 4.19 (d, 1H, *J* = 11.1 Hz, C***H***-10), 3.97 (t, 1H, *J* = 7.5 Hz, C***H***-10), 3.89-3.86 (m, 1H, C***H***-12), 3.77 (s, 3H, PMB-OC***H₃***), 3.75 (s, 3H, PMB-OC***H₃***), 3.66-3.62 (m, 1H, C***H***-4), 3.56-3.51 (m, 1H, C***H***-14), 3.46 (t, 2H, *J* = 6.2 Hz, C***H***-17), 2.34 (dd, 1H, *J* = 14.3, 6.3 Hz, C***H***-5), 2.11 (dd, 1H, *J* = 14.0, 6.5 Hz, C***H***-5), 2.03-1.99 (m, 1H, C***H***-11), 1.70-1.59 (m, 7H, C***H***-7, C***H***-13, C***H***-15, C***H***-16), 1.51-1.46 (m, 4H, C***H***-2, C***H***-3, C***H***-13), 1.31-1.38 (m, 1H, C***H***-13), 0.91-0.87 (m, 3H, C***H***-1), 0.78 (d, 3H, *J* = 7.0 Hz, C***H***-19), 0.09 (s, 3H, Si(C***H₃***)$_2$), 0.09 (s, 3H, Si(C***H₃***)$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 158.9 (C-Ar), 143.6 (C-6), 140.2 (C-9), 139.0 (C-Ar), 138.7 (C-Ar), 131.4 (C-Ar), 131.3 (C-Ar), 129.3 (C-Ar), 129.2 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 127.8 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 115.7 (C-8), 113.7 (C-Ar), 113.6 (C-Ar), 110.6 (C-20), 77.6 (C-4), 76.3 (C-10), 75.6 (C-12), 75.0 (C-14), 72.8 (C-18), 71.0 (C-21), 70.6 (C-17), 70.4 (**C**H$_2$-PMB), 70.3 (**C**H$_2$-PMB), 55.2 (O**C**H$_3$-PMB), 55.2

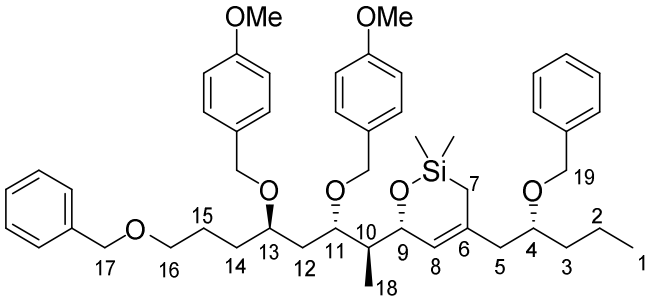
(O**C**H_3-PMB), 43.2 (C-5), 41.1 (C-11), 36.4 (C-3), 35.4 (C-13), 30.6 (C15), 27.5 (C-7), 25.1 (C-16), 18.7 (C-2), 14.2 (C-1), 10.3 (C-19), -1.1 (Si(***C***H_3)$_2$), -1.2 (Si(***C***H_3)$_2$).

IR (thin film, cm^{-1}) 3028, 2953, 2932, 2866, 1612, 1585, 1512, 1497, 1454, 1360, 1302, 1246, 1171, 1063, 1036.

HRMS (ESI, *m/z*) calcd for $(C_{51}H_{70}O_7SiNa)^+$ 845.4789, found 845.4743.

[α]$^{25}_D$ -30.3 (*c* 1.0, $CHCl_3$).

(*R*)-6-((2*S*,3*S*,5*R*)-8-(Benzyloxy)-3,5-*bis*((4-methoxybenzyl)oxy)octan-2-yl)-4-((*R*)-2-(benzyloxy)pentyl)-2,2-dimethyl-3,6-dihydro-2H-1,2-oxasiline 2.61



Chemical Formula: $C_{49}H_{66}O_7Si$
Molecular Weight: 795.15

To a solution of oxysilane **2.3** (200 mg, 0.24 mmol) in the solvent indicated (0.5 mL) was added ruthenium metathesis catalyst (10 mol%) under argon. The reaction was stirred for 1 day at 70 °C and 5 mol% of catalyst was added. The sequence addition/stirring was repeated for 1 more day. After 24 h the reaction mixture was loaded on silica gel and purified by column chromatography to give silacycle **2.61**, as well as oxysilane **2.3** as clear oils.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 14H, ***H***-Ar), 6.87-6.83 (m, 4H, ***H***-Ar (PMB)), 5.45 (br s, 1H, C***H***-8), 4.59-4.51 (m, 4H, C***H***-17, C***H***-19), 4.46-4.42 (m, 2H, C***H$_2$***-PMB), 4.27-4.28 (m, 1H, C***H***-9), 4.24-4.20 (m, 2H, C***H$_2$***-PMB), 4.01-3.98 (m, 1H, C***H***-11), 3.78 (s, 3H, PMB-OC***H$_3$***), 3.76 (s, 3H, PMB-OC***H$_3$***), 3.67-3.64 (m, 1H, C***H***-4), 3.58-3.56 (m, 1H, C***H***-13), 3.49 (t, 2H, *J* = 6.5 Hz, C***H***-16), 2.42 (dd, 1H, *J* = 13.4, 6.1 Hz, C***H***-5), 2.19 (dd, 1H, *J* = 13.4, 6.1 Hz, C***H***-5), 2.09-2.05 (m, 1H, C***H***-10), 1.76-1.64 (m, 5H, C***H***-12, C***H***-14, C***H***-15), 1.57-1.49 (m, 3H, C***H***-12, C***H***-3), 1.43-1.22 (m, 4H, C***H***-2, C***H***-7), 0.94-0.90 (m, 6H, C***H***-1, C***H***-18), 0.20 (s, 3H, Si(C***H$_3$***)$_2$), 0.11 (s, 3H, Si(C***H$_3$***)$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9 (C-Ar), 158.8 (C-Ar), 138.9 (C-Ar), 138.6 (C-Ar), 133.5 (C-6), 131.4 (C-Ar), 131.2 (C-Ar), 129.3 (C-Ar), 129.1 (C-Ar), 128.3 (C-Ar), 128.2 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 127.3 (C-Ar), 127.0 (C-8), 113.6 (C-Ar), 113.5 (C-

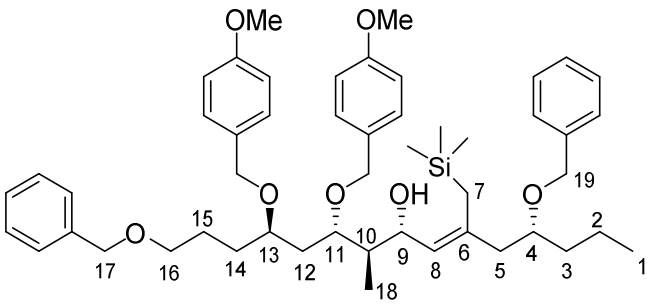
Ar), 76.9 (C-4), 75.8 (C-11), 75.3 (C-13), 73.9 (C-9), 72.7 (C-17), 70.7 (C-19), 70.5 (**C**H_2-PMB), 70.3 (**C**H_2-PMB), 69.9 (C-16), 55.2 (O**C**H_3-PMB), 55.1 (O**C**H_3-PMB), 46.6 (C-5), 42.1 (C-10), 36.2 (C-12), 35.4 (C-3), 30.9 (C-14), 25.4 (C-7), 18.6 (C-15), 16.3 (C-2) 14.2 (C-1), 10.1 (C-18), -0.10 (Si(***C***H_3)$_2$), -0.90 (Si(***C***H_3)$_2$).

IR (thin film, cm^{-1}) 2955, 2929, 2861, 1612, 1513, 1454, 1361, 1246, 1172, 1067, 1036.

HRMS (ESI, *m/z*) calcd for $(C_{49}H_{66}O_7SiNa)^+$ 817.4470, found 817.4433.

[α]$^{25}_D$ -14.7 (*c* 1.0, $CHCl_3$).

(4*R*,8*R*,9*R*,10*S*,12*R*,*Z*)-4,15-bis(Benzyloxy)-10,12-*bis*((4-methoxybenzyl)oxy)-9-methyl-6-((trimethylsilyl)methyl)pentadec-6-en-8-ol 2.62



Chemical Formula: $C_{50}H_{70}O_7Si$
Molecular Weight: 811.19

Oxasilane **2.61** (59 mg, 0.074 mmol) was dissolved in Et_2O (3 mL) and cooled to -78°C. MeLi (1 M in Et_2O, 0.19 mL, 0.19 mmol, 2.6 equiv) was then added dropwise and the resulting mixture was stirred for 1 h at -78°C and 1h at room temperature. Then a saturated aqueous solution of NH_4Cl (3 mL) was added and the mixture was extracted with Et_2O (3 x 3 mL). The combined organic phases were washed with H_2O (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a clear oil (60.0 mg, 0.074 mmol, quant.). For best results the crude was used in the next step without further purification due to its rapid decomposition. For analysis a sample was purified by column chromatography on silica gel (petroleum ether: ether 2:1) giving **2.62** as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.20 (m, 14H, ***H***-Ar), 6.84-6.82 (m, 4H, ***H***-Ar (PMB)), 5.15 (d, 1H, *J* = 9.0 Hz, C***H***-8), 4.56-4.46 (m, 6H, C***H***-16, C***H***-19, C***H$_2$***-PMB), 4.24-4.20 (m, 2H, C***H$_2$***-PMB), 4.04-4.00 (m, 1H, C***H***-9), 3.95-3.92 (m, 1H, C***H***-11), 3.76 (s, 6H, C***H$_3$***-PMB), 3.60-3.53 (m, 2H, C***H***-4, C***H***-13), 3.48 (t, *J* = 5.5 Hz, 2H, C***H***-16), 2.33 (dd, *J* = 13.6, 5.9 Hz, 1H, C***H***-5), 2.33 (dd, *J* = 13.6, 7.0 Hz, 1H, C***H***-5), 1.96-2.01 (m, 1H, C***H***-10), 1.47-1.72 (m,

12H, C***H***-2, C***H***-3, C***H***-7, C***H***-12, C***H***-14, C***H***-15), 0.90 (t, *J* = 6.6 Hz, 3H, C***H***-1), 0.78 (d, *J* = 6.9 Hz, 3H, C***H***-18), 0.05 (s, 9H, -Si(C***H₃***)₃-).

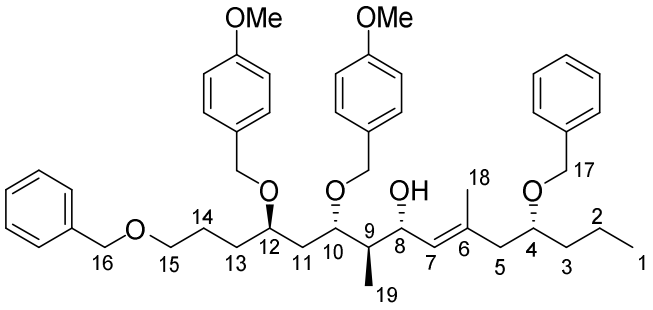
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C-Ar), 159.0 (C-Ar), 138.9 (C-6 or C-Ar), 138.8 (C-6 or C-Ar), 138.6 (C-Ar), 131.0 (C-Ar), 130.8 (C-Ar), 129.4 (C-Ar), 129.4 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 127.7 (C-Ar), 127.5 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 126.7 (C-8), 113.7 (C-Ar), 113.7 (C-Ar), 78.0 (C-4), 76.7 (C-11), 75.7 (C-13), 72.8 (C-17), 71.0 (C-9), 70.5 (C-19), 70.4 (C-16), 70.4 (**C**H_2-PMB), 70.4 (**C**H_2-PMB), 55.2 (O**C**H_3-PMB), 55.2 (O**C**H_3-PMB), 44.0 (C-5), 41.3 (C-10), 36.2 (C-3), 35.7 (C-12), 30.6 (C-14), 25.2 (C-15), 22.2 (C-7), 18.4 (C-2), 14.2 (C-1), 10.6 (C-18), -0.7 (Si(***C***H_3)$_2$).

IR (thin film, cm^{-1}) 3470, 2953, 2934, 2869, 1612, 1513, 1454, 1246, 1172, 1065, 1036.

HRMS (ESI, *m/z*) calcd for $(C_{50}H_{70}O_7SiNa)^+$ 833.4783, found 833.4768.

[α]$^{25}_D$ -46.6 (*c* 1.0, $CHCl_3$).

(4*R*,8*R*,9*R*,10*S*,12*R*,*E*)-4,15-*bis*(Benzyloxy)-10,12-*bis*((4-methoxybenzyl)oxy)-6,9-dimethylpentadec-6-en-8-ol 1.258



Chemical Formula: $C_{47}H_{62}O_7$
Molecular Weight: 739.01

To a stirred suspension of **2.62** (60.0 mg, 0.0740 mmol) in DMF (1.6 mL) at 0 °C was added tetrabutylammonium fluoride trihydrate (60.0 mg, 0.19 mmol, 2.60 equiv) in one portion. The reaction mixture was then left to stirred for 30 min at 0 °C and was then quenched by addition of a saturated solution of ammonium chloride (2 mL). The mixture was extracted with diethyl ether (3 x 5 mL) and the combined organic layers where washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 3:2) gave **1.258** (43.5 mg, 0.0600 mmol, 79%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10H, ***H***-Ar), 7.24-7.21 (m, 4H, ***H***-Ar (PMB)), 6.85 (d, *J* = 8.6 Hz, 4H, (PMB)), 5.27 (d, *J* = 8.9 Hz, 1H, C***H***-7), 4.57-4.45 (m, 6H, C***H***-16, C***H***-17, C***H₂***-PMB), 4.24-4.13 (m, 3H, C***H***-8, C***H₂***-PMB), 3.96-3.93 (m, 1H, C***H***-10), 3.77 (s, 6H,

PMB-OC***H*₃**), 3.61-3.54 (m, 2H, C***H***-4, C***H***-12), 3.49 (t, *J* = 5.0 Hz, 2H, C***H***-15), 2.40 (dd, *J* = 13.6, 5.9 Hz, 1H, C***H***-5), 2.19 (dd, *J* = 13.6, 6.8 Hz, 1H, C***H***-5), 2.03-1.98 (m, 1H, C***H***-9), 1.72-1.65 (m, 8H, C***H***-3, C***H***-11, C***H***-13, C***H***-18), 1.52-1.47 (m, 3H, C***H***-3, C***H***-14), 1.27-1.26 (m, 2H, C***H***-2), 0.90 (t, *J* = 6.9 Hz, 3H, C***H***-1), 0.75 (d, *J* = 7.0 Hz, 3H, C***H***-19).

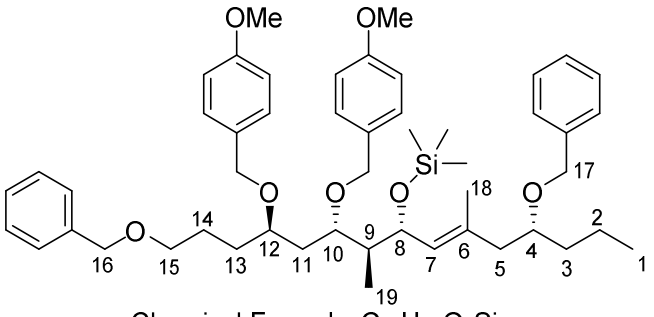
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (C-Ar), 159.1 (C-Ar), 138.9 (C-Ar), 138.6 (C-Ar), 136.1 (C-6), 131.0 (C-Ar), 130.7 (C-Ar), 129.5 (C-Ar or C-7), 129.5 (C-Ar or C-7), 129.4 (C-Ar or C-7), 128.3 (C-Ar), 128.3 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 113.7 (C-Ar), 113.7 (C-Ar), 77.2 (C-4), 75.6 (C-10, C12), 72.9 (C-16), 70.8 (C-17, C-8), 70.6 (C-15), 70.5 (**C**H_2-PMB), 55.2 (O**C**H_3-PMB), 55.2 (O**C**H_3-PMB), 44.6 (C-5), 41.0 (C-9), 36.1 (C-3), 35.7 (C-11), 30.5 (C-13), 25.2 (C-14), 18.4 (C-2), 17.4 (C-18), 14.2 (C-1), 10.5 (C-19).

IR (thin film, cm^{-1}) 3441, 2932, 2862, 1612, 1512, 1458, 1358, 1304, 1242, 1034.

HRMS (ESI, *m*/*z*) calcd for $(C_{47}H_{62}O_7Na)^+$ 761.4388, found 761.4358.

[α]$^{23}_D$ -33.2 (*c* 1.0, $CHCl_3$).

(((4*R*,8*R*,9*S*,10*S*,12*R*,*E*)-4,15-*bis*(Benzyloxy)-10,12-*bis*((4-methoxybenzyl)oxy)-6,9-dimethylpentadec-6-en-8-yl)oxy)trimethylsilane 2.65



Chemical Formula: $C_{50}H_{70}O_7Si$
Molecular Weight: 811.19

To a stirred solution of allylic alcohol **1.258** (60.0 mg, 0.0800 mmol) in CH_2Cl_2 (0.8 mL) at -78 °C were added TMS-OTf (20 µL, 0.11 mmol, 1.4 equiv) and 2,6-lutidine (30 µL, 0.26 mmol, 3.3 equiv) and the mixture was left to warm to room temperature and stirred for 1 h. Then the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (1 mL) and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 4:1) to furnish **2.65** (65.0 mg, 0.0800 mmol, quant.) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 10H, ***H***-Ar), 7.21-7.18 (m, 4H, ***H***-Ar (PMB)), 6.83 (d, *J* = 8.6 Hz, 2H, (PMB)), 6.81 (d, *J* = 8.5 Hz, 2H, (PMB)), 5.18 (d, *J* = 9.1 Hz, 1H, C***H***-7),

4.57-4.55 (m, 1H, C***H***-17), 4.50-4.44 (m, 4H, C***H***-16, C***H***-17, C***H₂***-PMB), 4.40 (d, 1H, *J* = 11.2 Hz, C***H₂***-PMB), 4.19-4.16 (m, 2H, C***H₂***-PMB), 4.16-4.13 (m, 1H, C***H***-10), 4.03-4.01 (m, 1H, C***H***-8), 3.77 (s, 6H, PMB-OC***H₃***), 3.65-3.61 (m, 1H, C***H***-4), 3.56-3.51 (m, 1H, C***H***-12), 3.46 (t, *J* = 6.1 Hz, 2H, C***H***-15), 2.38 (dd, *J* = 13.6, 5.3 Hz, 1H, C***H***-5), 2.16 (dd, *J* = 13.7, 7.4 Hz, 1H, C***H***-5), 2.09-2.01 (m, 1H, C***H***-9), 1.70-1.61 (m, 7H, C***H***-3, C***H***-11, C***H***-13, C***H***-18), 1.55-1.44 (m, 5H, C***H***-2, C***H***-3, C***H***-13, C***H***-14), 1.38-1.32 (m, 1H, C***H***-2), 0.89 (t, *J* = 6.9 Hz, 3H, C***H***-1), 0.73 (d, *J* = 7.0 Hz, 3H, C***H***-19), 0.02 (s, 9H, -Si(C***H₃***)$_3$-).

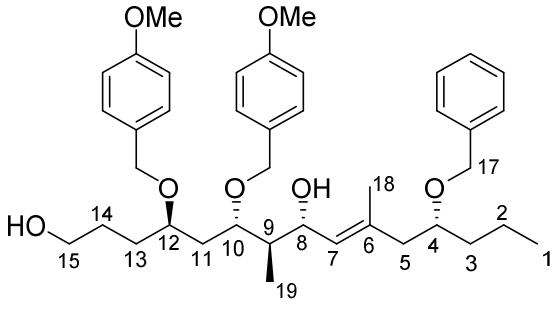
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C-Ar), 158.9 (C-Ar), 138.9 (C-Ar), 138.7 (C-Ar), 133.5 (C-6), 131.5 (C-Ar), 131.4 (C-Ar), 130.7 (C-Ar), 129.4 (C-Ar or C-7), 129.2 (C-Ar or C-7), 128.3 (C-Ar), 128.3 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 113.7 (C-Ar), 113.5 (C-Ar), 77.7 (C-4), 75.2 (C-10), 75.1 (C-12), 72.8 (C-16), 70.9 (C-17 or C-8), 70.8 (C-17 or C-8), 70.7 (C-15), 70.4 (**C**H_2-PMB), 70.0 (**C**H_2-PMB), 55.2 (O**C**H_3-PMB), 55.2 (O**C**H_3-PMB), 44.2 (C-5), 41.0 (C-9), 36.0 (C-3), 34.6 (C-11), 30.7 (C-13), 25.1 (C-14), 18.4 (C-2), 17.6 (C-18), 14.2 (C-1), 9.8 (C-19), 0.4 (SiC(***C***H_3)$_3$).

IR (thin film, cm^{-1}) 2951, 2932, 2858, 1612, 1512, 1496, 1454, 1360, 1301, 1245, 1207, 1172, 1055, 1036.

HRMS (ESI, *m/z*) calcd for $(C_{50}H_{70}O_7SiNa)^+$ 833.4783, found 833.4751.

[α]$^{23}_D$ -39.3 (*c* 1.0, $CHCl_3$).

(4*R*,6*S*,7*R*,8*R*,12*R*,*E*)-12-(Benzyloxy)-4,6-*bis*((4-methoxybenzyl)oxy)-7,10-dimethylpentadec-9-ene-1,8-diol 2.66



Chemical Formula: $C_{40}H_{56}O_7$
Molecular Weight: 648.88

Lithium wire (diameter 3.2 mm, 5 cm, ≈43 mg/cm) in mineral oil was transferred into a beaker containing petroleum ether and cut into small pieces (≈5 mm) and subsequently flattened to increase the surface area. These pieces were then dipped one at a time in MeOH until shiny and then Et_2O to rinse before being transferred into a stirring suspension of 4,4'-di-*tert*-butylbiphenyl (267 mg, 1.0 mmol) in degassed THF (5.0 mL). After adding all the lithium pieces, the resulting mixture was sonicated for 10 min. until a deep blue-green

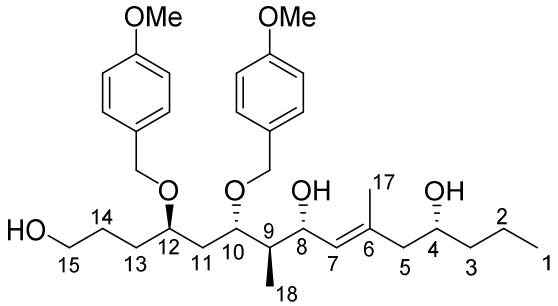
solution was observed, and subsequently stirred for 2 h at 0°C. This LiDBB solution was then added dropwise to a stirred mixture of **2.65** (50.0 mg, 62.0 µmol) in degassed THF (0.75 mL) until the deep blue-green colouration persisted in the mixture. More LiDBB solution was added when decolouration of the reaction mixture was observed (maroon colour) while the reaction was carefully monitored by TLC until the starting material spot disappeared. The reaction mixture was then quenched by the addition of a saturated aqueous solution of ammonium chloride (1.0 mL), extracted with Et_2O (3 x 1 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel (petroleum ether: EtOAc 1:1) to furnish **2.66** (23.0 mg, 35.0 µmol, 57%) as well as triol **2.67** (10.0 mg, 18.0 µmol, 29%) as clear oils.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.20 (m, 9H, ***H***-Ar), 6.86-6.84 (m, 4H, ***H***-Ar (PMB)), 5.26 (d, *J* = 8.4 Hz, 1H, C***H***-7), 4.55-4.40 (m, 4H, C***H***-17, C***H$_2$***-PMB), 4.25-4.21 (m, 2H, C***H$_2$***-PMB), 4.17-4.12 (m, 1H, C***H***-10), 3.96-3.93 (m, 1H, C***H***-8), 3.77 (s, 6H, PMB-OC***H$_3$***), 3.63-3.53 (m, 4H, C***H***-4, C***H***-12, C***H***-15), 2.38 (dd, *J* = 13.6, 6.0 Hz, 1H, C***H***-5), 2.18 (dd, *J* = 13.7, 6.7 Hz, 1H, C***H***-5), 2.03-1.98 (m, 1H, C***H***-9), 1.68-1.59 (m, 9H, C***H***-3, C***H***-11, C***H***-13, C***H***-14, C***H***-18), 1.55-1.44 (m, 3H, C***H***-2, C***H***-3, C***H***-13), 1.35-1.30 (m, 1H, C***H***-2), 0.89 (t, *J* = 6.8 Hz, 3H, C***H***-1), 0.75 (d, *J* = 7.0 Hz, 3H, C***H***-19).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C-Ar), 159.1 (C-Ar), 138.9 (C-Ar), 136.2 (C-Ar), 135.8 (C-6), 131.0 (C-Ar), 130.5 (C-Ar), 129.6 (C-Ar or C-7), 129.5 (C-Ar or C-7), 128.3 (C-Ar), 127.7 (C-Ar), 125.5 (C-Ar), 113.8 (C-Ar), 113.8 (C-Ar), 77.2 (C-4), 75.7 (C-10), 70.9 (C-17 or C-8 or C12), 70.6 (C-17 or C-8 or C12), 70.6 (C-17 or C-8 or C12), 70.4 (**C**H_2-PMB), 63.1 (C-15), 55.3 (O**C**H_3-PMB), 44.6 (C-5), 40.9 (C-9), 36.2 (C-3), 34.2 (C-11), 30.3 (C-13), 28.1 (C-14), 18.5 (C-2), 17.4 (C-18), 14.2 (C-1), 10.5 (C-19).

HRMS (ESI, *m/z*) calcd for $(C_{40}H_{56}O_7Na)^+$ 671.3918, found 671.3905.

(4*R*,6*S*,7*R*,8*R*,12*R*,*E*)-4,6-*bis*((4-Methoxybenzyl)oxy)-7,10-dimethylpentadec-9-ene-1,8,12-triol 2.67



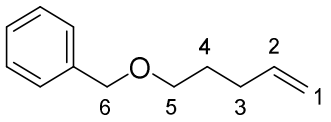
Chemical Formula: $C_{33}H_{50}O_7$
Molecular Weight: 558.76

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.20 (m, 4H, ***H***-Ar), 6.85-6.84 (m, 4H, ***H***-Ar (PMB)), 5.28 (d, *J* = 8.4 Hz, 1H, C***H***-7), 4.47-4.44 (m, 2H, C***H$_2$***-PMB), 4.25-4.11 (m, 4H, C***H$_2$***-PMB, C***H***-10, C***H***-8), 3.76 (s, 6H, PMB-OC***H$_3$***), 3.63-3.60 (m, 4H, C***H***-4, C***H***-12, C***H***-15), 2.19-2.16 (m, 1H, C***H***-5), 2.06-2.01 (m, 2H, C***H***-5, C***H***-9), 1.73-1.50 (m, 9H, C***H***-3, C***H***-11, C***H***-13, C***H***-14, C***H***-17), 1.44-1.28 (m, 4H, C***H***-2, C***H***-3, C***H***-13), 0.92 (t, *J* = 6.9 Hz, 3H, C***H***-1), 0.77 (d, *J* = 7.0 Hz, 3H, C***H***-18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (C-Ar), 159.1 (C-Ar), 135.9 (C-6), 130.9 (C-Ar), 130.3 (C-Ar), 129.7 (C-Ar or C-7), 129.5 (C-Ar or C-7), 128.7 (C-Ar), 113.8 (C-Ar), 113.7 (C-Ar), 75.6 (C-10), 70.6 (C12 or **C**H_2-PMB), 70.6 (C12 or **C**H_2-PMB), 70.2 (C12 or **C**H_2-PMB), 68.7 (C-4 or C8), 68.2 (C-4 or C8), 63.1 (C-15), 55.2 (O**C**H_3-PMB), 48.0 (C-5), 40.8 (C-9), 39.4 (C-3), 38.7 (C-11), 29.7 (C-13), 28.9 (C-14), 18.9 (C-2), 17.0 (C-17), 14.1 (C-1), 10.9 (C-18).

HRMS (ESI, *m/z*) calcd for $(C_{33}H_{50}O_7Na)^+$ 581.3449 found 581.3449.

((Pent-4-enyloxy)methyl)benzene 3.11[82]



Chemical Formula: $C_{12}H_{16}O$
Molecular Weight: 176.26

To a stirring suspension of NaH (60% dispersion in mineral oil, 1.05 g, 43.7 mmol, 1.90 equiv) in THF (70 mL), tetrabutylammonium iodide (0.89 g, 0.23 mmol, 0.010 equiv) was added. Then the reaction mixture was cooled to 0 °C and 4-penten-1-ol **1.185** (2.00 g, 23.0 mmol) was added dropwise and left to stir for 30 min. Benzyl bromide (6.29 g, 36.8 mmol, 1.60 equiv) was then added dropwise at 0 °C and the reaction mixture was left to stir at room temperature for 5 h. After which, the reaction was quenched by addition of crushed ice and extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated under vacuum to give a yellow oil. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 9:1) to afford **3.11** (4.05 g, 23.0 mmol, quant.) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.43 (m, 5H, ***H***-Ar), 5.85 (ddt, *J* = 16.9, 10.2, 7.0 Hz, 1H, C***H***-2), 5.05 (dq, *J* = 17.0, 1.6 Hz, 1H, C***H***-1_{trans}), 5.00 (ddt, *J* = 10.1, 2.0, 1.3 Hz, 1H, C***H***-1_{cis}), 4.53 (s, 2H, C***H***-6), 3.51 (t, *J* = 6.4 Hz, 2H, C***H***-5), 2.18 (qt, *J* = 6.9, 1.2 Hz, 2H, C***H***-3), 1.75 (app quint, *J* = 6.4 Hz, 2H, C***H***-4).

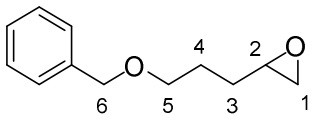
[82] Srihary, P.; Kumaraswamy, B.; Somaiah, R.; Yadav, J. S. *Synthesis* **2010**, *6*, 1039.

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (C-Ar), 138.3 (C-2), 128.4 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 114.7 (C-1), 72.9 (C-6), 69.7 (C-5), 30.4 (C-3), 29.0 (C-4).

IR (neat, cm^{-1}) 3017, 2970, 2940, 2866, 1730, 1366, 1211, 1103.

In agreement with literature data.

2-(3-(Benzyloxy)propyl)oxirane 3.12



Chemical Formula: $C_{12}H_{16}O_2$
Molecular Weight: 192.26

m-CPBA (30.8 g, 178 mmol, 1.40 equiv) was added to a stirred suspension of alkene **3.11** (20.0 g, 113 mmol) in CH_2Cl_2 (480 mL) and the reaction was stirred overnight at room temperature. The solution was then filtered and washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 480 mL), a saturated aqueous solution of sodium bicarbonate (480 mL), brine (480 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to give a pale-yellow oil. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to give **3.12** (21.7 g, 113 mmol, quant.) as a clear oil.

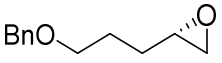
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.38 (m, 5H, ***H***-Ar), 4.54 (s, 2H, C***H***-6), 3.50-3.58 (m, 2H, C***H***-5), 2.95-2.97 (m, 1H, C***H***-2), 2.77 (ddd, *J* = 5.1, 3.9, 0.5 Hz, 1H, C***H***-1), 2.50 (dd, *J* = 5.3, 2.9 Hz, 1H, C***H***-1), 1.67-1.82 (m, 4H, C***H***-3, C***H***-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 72.9 (C-6), 69.8 (C-1), 52.1 (C-2), 47.1 (C-5), 29.3 (C-3), 26.2 (C-4).

IR (neat, cm^{-1}) 2924, 2955, 1730, 1450, 1366, 1258, 1096.

HRMS (ESI, *m/z*) calcd for $(C_{12}H_{16}O_2Na)^+$ calcd for 215.1048, found 215.1041.

(*R*)-2-(3-(Benzyloxy)propyl)oxirane (+) 3.13

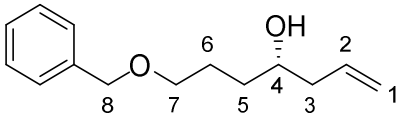


Chemical Formula: $C_{12}H_{16}O_2$
Molecular Weight: 192.26

To a solution of (*S,S*)-Jacobsen's catalyst (240.0 mg, 0.398 mmol, 5.0 x 10^{-3} equiv) in toluene (0.9 mL) was added acetic acid (0.09 mL, 1.57 mmol, 0.20 equiv) and the reaction mixture was stirred for 1 h open to air at room temperature. After this time reaction mixture was concentrated under vacuum and then put under high vacuum for another 1 h. Racemic epoxide **3.11** (14.00 g, 72.8 mmol) was then added followed by the dropwise addition of deionized H_2O (0.80 mL, 44 mmol, 0.57 equiv) at 0 °C. The reaction mixture was then stirred for 24 h at room temperature and purified by column chromatography on silica gel (petroleum ether: ether 3:2) to give **3.13** (7.00 g, 36.4 mmol, quant.) as a clear oil, *er* = 97:3. The enantiomeric purity of the compound was determined by chiral HPLC (chiral OJ cel column with a flow rate of 1.0 mL/min and solvent system of 1% isopropanol/hexane) t_r = 24.1 min (Major), t_r = 26.5 min (Minor).

$[\alpha]^{19}_D$ -8.0 (*c* 2.08, $CHCl_3$)

(*R*)-7-(Benzyloxy)hept-1-en-4-ol (+) 3.14



Chemical Formula: $C_{14}H_{20}O_2$
Molecular Weight: 220.31

CuI (400 mg, 4.73 mmol, 0.500 equiv) was dissolved in THF (15 mL) followed by the dropwise addition of vinylmagnesium bromide (1.0 M, 21.0 mL, 21.0 mmol, 5.05 equiv) at -30 °C while stirring. After 30 min, epoxide **3.13** (800 mg, 4.16 mmol) in THF (5 mL) was slowly added and the reaction mixture was stirred overnight at -30 °C. After that it was quenched with saturated aqueous NH_4Cl (20 mL), filtered and extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 1:1) to afford **3.14** (907 mg, 4.12 mmol, 99%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.44 (m, 5H, ***H***-Ar), 5.81-5.90 (m, 1H, C***H***-2), 5.15-5.18 (m, 1H, C***H***-1_{trans}), 5.13 (m, 1H, C***H***-1_{cis}), 4.54 (s, 2H, C***H***-8), 3.66-3.73 (m, 1H, C***H***-4), 3.54 (t, *J* = 6.0 Hz, 2H, C***H***-7), 2.37 (d, *J* = 4.0 Hz, 1H, C4-***OH***), 2.27-2.34 (m, 1H, C***H***-3), 2.17-2.25 (m, 1H, C***H***-3), 1.73-1.82 (m, 2H, C***H***-6), 1.64-1.72 (m, 1H, C***H***-5), 1.46-1.57 (m, 1H, C***H***-5).

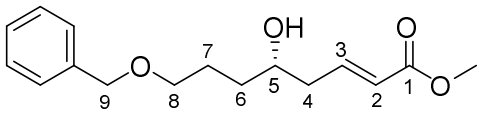
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 (C-Ar), 135.1 (C-2), 128.4 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 117.7 (C-1), 73.0 (C-8), 70.6 (C-4), 70.5 (C-7), 42.0 (C-3), 34.0 (C-5), 26.2 (C-6).

IR (neat, cm^{-1}) 2916, 2855, 1643,1450, 1358, 1204, 1096, 1026.

HRMS (ESI, *m/z*) calcd for $(C_{14}H_{20}O_2Na)^+$ calcd for 243.1356, found 243.1353.

$[\alpha]^{23}_D$ -8.7 (*c* 1.0, $CHCl_3$).

Methyl (*S*,*E*)-8-(benzyloxy)-5-hydroxyoct-2-enoate 3.10



Chemical Formula: $C_{16}H_{22}O_4$
Molecular Weight: 278.35

Homoallylic alcohol **3.14** (3.00 g, 13.6 mmol), methyl acrylate **2.52** (3.91 mL, 43.1 mmol, 3.17 equiv) and GII catalyst (265 mg, 0.32 mmol, 0.024 equiv) were suspended in dry, degassed dichloromethane (80 mL). The mixture was heated to reflux and stirred for 24 h, then after cooling to room temperature, silica was added, and the solvent was removed by concentrating *in vacuo.* Dry loading onto column chromatography on silica gel (petroleum ether: ether 1:1) gave pure conjugated ester **3.10** (3.78 g, 12.4 mmol, 92%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H, ***H***-Ar), 7.00 (dt, *J* = 15.3, 7.4 Hz, 1H, C***H***-3), 5.90 (dt, *J* = 15.3, 1.5 Hz, 1H, C***H***-2), 4.52 (s, 2H, C***H***-9), 3.79-3.74 (m, 1H, C***H***-5), 3.73 (s, 3H, OC***H$_3$***), 3.54-3.50 (m, 2H, C***H***-8), 2.75 (d, *J* = 4.1, 1H, C5-***OH***), 2.39-2.36 (m, 2H, C***H***-4), 1.77-1.72 (m, 2H, C***H***-7), 1.71-1.65 (m, 1H, C***H***-6), 1.55-1.48 (m, 1H, C***H***-6).

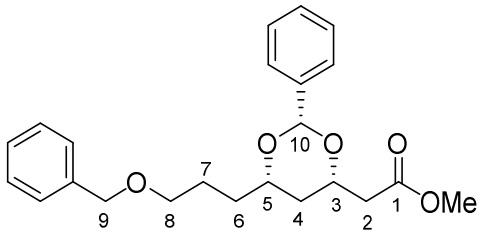
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (C-1), 145.8 (C-3), 137.9 (C-Ar), 128.5 (C-Ar), 127.8 (C-Ar), 123.2 (C-2), 73.2 (C-9), 70.4 (C-8), 70.3 (C-5), 51.5 (O**C**H_3), 40.2 (C-4), 34.7 (C-6), 26.3 (C-7).

IR (neat, cm^{-1}) 2940, 2855, 1721, 1651, 1453, 1319, 1273, 1165, 1096, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{16}H_{22}O_4Na)^+$ 301.1416, found 301.1408.

$[\alpha]^{23}_D$ -2.0 (*c* 1.0, $CHCl_3$).

Methyl-1-((3*S*,5*S*,10*S*)-5-(8-(benzyloxy)propyl)-10-phenyl-1,3-dioxan-9-yl)acetate (*S*,*E*)-8-(benzyloxy)-5-hydroxy-N-methoxy-N-methyloct-2-enamide 3.15



Chemical Formula: $C_{23}H_{28}O_5$
Molecular Weight: 384.47

To a stirred suspension of conjugated ester **3.10** (1.20 g, 4.31 mmol) in THF (26 mL) at 0 °C was added freshly distilled benzaldehyde (0.44 mL, 4.3 mmol, 1.0 equiv) followed by *t*-BuOK (1.0 M solution in THF 0.38 mL, 0.38 mmol, 0.09 equiv). The sequence of addition was repeated 3 more times in 15 min intervals. After the final addition the reaction mixture was stirred for a further 10 min and was quenched with a saturated aqueous solution of ammonium chloride (25 mL). The mixture was extracted with diethyl ether (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 4:1) gave **3.15** (1.23 g, 3.19 mmol, 74%) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.28 (m, 10H, ***H***-Ar), 5.55 (s, 1H, C***H***-10), 4.52 (s, 2H, C***H***-9), 4.31 (dtd, *J* = 11.1, 6.7, 2.4 Hz, 1H, C***H***-3), 3.89-3.84 (m, 1H, C***H***-5), 3.72 (s, 3H, OC***H$_3$***), 3.57-3.48 (m, 2H, C***H***-8), 2.75 (dd, *J* = 15.6, 6.7 Hz, 1H, C***H***-2), 2.53 (dd, *J* = 15.6, 6.7 Hz, 1H, C***H***-2), 1.89-1.66 (m, 5H, C***H***-4, C***H***-6, C***H***-7), 1.49-1.42 (m, 1H, C***H***-4).

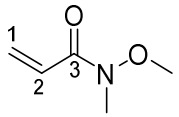
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C-1), 138.6 (C-Ar), 138.5 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 126.1 (C-Ar), 100.6 (C-10), 76.4 (C-3), 73.2 (C-5), 72.9 (C-9), 70.1 (C-8), 51.8 (O**C**H$_3$), 40.8 (C-2), 36.5 (C-4), 32.5 (C-6), 25.4 (C-7).

IR (neat, cm^{-1}) 2847, 1754, 1443, 1358, 1211, 1096, 1018.

HRMS (ESI, *m/z*) calcd for $(C_{23}H_{28}O_5Na)^+$ 407.1829, found 407.1823.

[α]$^{23}_D$ -6.0 (*c* 1.0, $CHCl_3$).

***N*-Methoxy-*N*-methylacrylamide 3.23**



Chemical Formula: $C_5H_9NO_2$
Molecular Weight: 115.13

Acroyl chloride **3.22** (8.0 mL, 99 mmol) was added dropwise to a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (11.6 g, 119 mmol, 1.20 equiv) and $NaHCO_3$ (20.8 g, 248 mmol, 2.50 equiv) in CH_2Cl_2 (80 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight. The reaction was then quenched by the slow addition of a 1.0 M aqueous solution HCl (60 mL) and the biphasic mixture separated. The aqueous layer was then extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* using a room temperature water-bath. The crude product was then purified by vacuum distillation (bp: 80 °C, 83 mbar) to afford **3.23** (9.12 g, 79.1 mmol, 80%) as a colourless liquid.

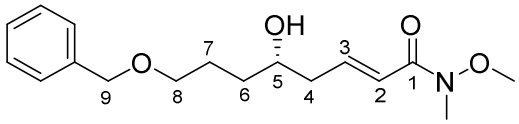
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 17.1, 10.4 Hz, 1H, C***H***-2), 6.41 (dd, *J* = 17.1, 1.9 Hz, 1H, C***H***-1_{trans}), 5.73 (dd, *J* = 10.4, 2.0 Hz, 1H, C***H***-1_{cis}), 3.69 (s, 3H, OC***H*****$_3$**), 3.24 (s, 3H, NC***H*****$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5 (C-3), 129.0 (C-2), 125.9 (C-1), 61.8 (NO**C**H_3), 32.3 (N**C**H_3).

IR (neat, cm^{-1}) 2940, 1652, 1620, 1420, 1358, 1180, 988, 787.

HRMS (ESI, *m/z*) calcd for $(C_5H_9NO_2Na)^+$ 138.0525, found 138.0524.

(*S*,*E*)-8-(Benzyloxy)-5-hydroxy-*N*-methoxy-*N*-methyloct-2-enamide 3.24



Chemical Formula: $C_{17}H_{25}NO_4$
Molecular Weight: 307.39

Homoallylic alcohol **3.14** (100 mg, 0.45 mmol, 1.25 equiv), amide **3.23** (42.0 mg, 0.36 mmol) and HG-II catalyst (12.0 mg, 0.0190 mmol, 0.0530 equiv) were suspended in degassed dichloromethane (8 mL). The mixture was heated to reflux and stirred for 24 h, then HG-II

catalyst (12.0 mg, 0.0190 mmol, 0.0530 equiv) was added and stirring at reflux continued for a further 24 h. After cooling to room temperature, silica was added, and the solvent was removed by concentrating *in vacuo.* Dry loading onto column chromatography on silica gel (EtOAc) gave pure conjugated amide **3.24** (100 mg, 0.33 mmol, 90%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H, ***H***-Ar), 7.00-6.94 (m, 1H, C***H***-3), 6.48 (d, *J* = 15.0 Hz, 1H, C***H***-2), 4.51 (s, 2H, C***H***-9), 3.79-3.74 (m, 1H, C***H***-5), 3.68 (s, 3H, OC***H₃***), 3.51 (t, *J* = 6.0 Hz, 2H, C***H***-8), 3.23 (s, 3H, NC***H₃***), 2.42-2.39 (m, 2H, C***H***-4), 1.78-1.64 (m, 3H, C***H***-6, C***H***-7), 1.55-1.48 (m, 1H, C***H***-6).

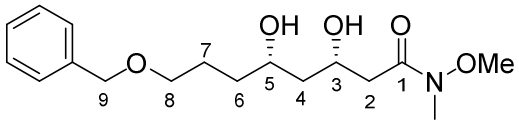
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7 (C-1), 143.8 (C-3), 138.1 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 127.7 (C-Ar), 121.2 (C-2), 73.1 (C-9), 70.4 (C-8), 70.4 (C-5), 61.7 (NO**C**H_3), 40.6 (C-4), 34.4 (C-6), 32.4 (N**C**H_3), 26.2 (C-7).

IR (neat, cm^{-1}) 2932, 2855, 1721, 1659, 1620, 1420, 1381, 1180, 1096.

HRMS (ESI, *m/z*) calcd for $(C_{17}H_{25}NO_4Na)^+$ 330.1681, found 330.1672.

$[\alpha]^{23}_D$ -13.1 (*c* 1.0, $CHCl_3$).

(3*S*,5*S*)-8-(Benzyloxy)-3,5-dihydroxy-*N*-methoxy-*N*-methyloctanamide 3.17



Chemical Formula: $C_{17}H_{27}NO_5$
Molecular Weight: 325.41

A stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (1.53 g, 25.0 mmol, 5.34 equiv) in CH_2Cl_2 (18 mL) was cooled to 0 °C followed by the dropwise addition of $AlMe_3$ (2.0 M solution in toluene, 8.1 mL, 16.2 mmol, 3.5 equiv) (Caution! Exothermic reaction with release of methane). After the addition was complete the mixture was stirred at room temperature for 2 h before adding a solution of ester **3.15** (1.80 g, 4.68 mmol) in CH_2Cl_2 (18 mL) dropwise. The reaction mixture was heated to reflux and stirred for a further 3 days. Then the reaction mixture was cooled to room temperature and was quenched by the careful addition of a 2M aqueous solution of HCl (20 mL) and was extracted with EtOAc (5 x 20 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Crude **3.17** was obtained as a yellow oil and used in the next step without further

purification. For analysis a sample was purified by column chromatography on silica gel (EtOAc) giving **5** as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H, ***H***-Ar), 4.51 (s, 2H, C***H***-9), 4.38 (br s, 1H, C3-O***H***), 4.33-4.25 (m, 1H, C***H***-3), 4.00 (d, *J* = 1.4 Hz, 1H, C5-O***H***), 3.95-3.87 (m, 1H, C***H***-3), 3.68 (s, 3H, N-***OMe***), 3.52 (t, *J* = 6.1 Hz, 2H, C***H***-8), 3.19 (s, 3H, N-C***H₃***), 2.68-2.48 (m, 2H, C***H***-2), 1.81-1.67 (m, 2H, C***H***-4), 1.64-1.51 (m, 4H, C***H***-6, C***H***-7).

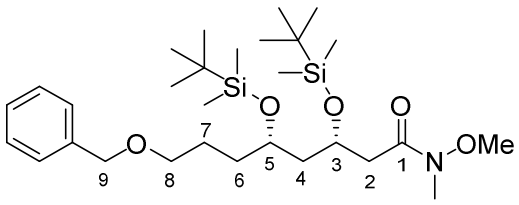
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C-1), 138.3 (C-Ar), 128.4 (C-Ar), 127.7 (C-Ar), 127.6 (C-Ar), 73.0 (C-9), 71.7 (C-5), 70.5 (C-8), 69.1 (C-3), 61.3 (NO**C**H_3), 42.5 (C-2), 38.6 (C-4), 34.8 (C-6), 31.8 (N**C**H_3), 25.9 (C-7).

IR (neat, cm^{-1}) 2940, 1736, 1612, 1513, 1450, 1366, 1219, 1072, 1034.

HRMS (ESI, *m/z*) calcd for $(C_{17}H_{27}NO_5Na)^+$ 348.1787, found 348.1789.

[α]$^{23}_D$ +58.5 (*c* 0.5, $CHCl_3$).

(3*S*,5*S*)-8-(Benzyloxy)-3,5-*bis*((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methyloctanamide 3.18



Chemical Formula: $C_{29}H_{55}NO_5Si_2$
Molecular Weight: 553.93

Crude **3.17** obtained from the reaction described above was dissolved in CH_2Cl_2 (36 mL) and cooled to -78 °C. Then TBS-OTf (2.60 mL, 15.2 mmol, 3.25 equiv) and pyridine (1.51 mL, 19.5 mmol, 4.16 equiv) were simultaneously added and the reaction was left to warm to room temperature overnight. The reaction mixture was poured into a 250 mL extractor funnel containing an aqueous saturated solution of NH_4Cl (40 mL). The aqueous layer was then extracted with ether (3 x 40 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 4:1) gave **3.18** (2.03 g, 3.65 mmol, 78%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, ***H***-Ar), 4.51 (s, 2H, C***H***-9), 4.35-4.29 (m, 1H, C***H***-3), 3.80-3.84 (m, 1H, C***H***-5), 3.68 (s, 3H, N-***OMe***), 3.48 (t, *J* = 6.0 Hz, 2H, C***H***-8), 3.17

(s, 3H, N-C***H₃***), 2.72-2.68 (m, 1H, C***H***-2), 2.47 (dd, *J* = 15.0, 5.0 Hz, 1H, C***H***-2), 1.78-1.60 (m, 5H, C***H***-4, C***H***-6, C***H***-7), 1.53-1.46 (m, 1H, C***H***-7) 0.91, 0.88 (2s, 18H,-SiC(C***H₃***)$_3$-), 0.10, 0.08, 0.06, 0.05 (4s, 12H, -SiC(C***H₃***)$_2$-).

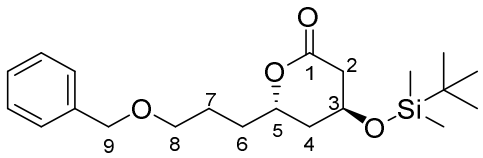
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1 (C-1), 138.6 (C-Ar), 128.2 (C-Ar), 127.5 (C-Ar), 127.3 (C-Ar), 72.7 (C-9), 70.5 (C-8), 69.1 (C-3), 67.0 (C-5), 61.2 (NO**C**H_3), 45.5 (C-2), 39.9 (C-4), 33.4 (C-6), 31.8 (N**C**H_3), 25.9 (Si(***C***$(CH_3)_3$), 25.8 (Si(***C***$(CH_3)_3$), 25.3 (C-7), 17.9 (Si(C(***C***$H_3)_3$), 17.9 (Si(C(***C***$H_3)_3$), -4.4, -4.5, -4.6, -4.7 (Si(***C***$H_3)_2$).

IR (neat, cm^{-1}) 2932, 2855, 1744, 1667, 1366, 1250, 1088, 1003.

HRMS (ESI, *m/z*) calcd for $(C_{29}H_{55}NO_5Si_2Na)^+$ 576.3511, found 576.3487.

[α]$^{23}_D$ +34.4 (*c* 0.5, $CHCl_3$).

(4*S*,6*S*)-6-(3-(Benzyloxy)propyl)-4-((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-one 3.19



Chemical Formula: $C_{21}H_{34}O_4Si$
Molecular Weight: 378.58

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H, ***H***-Ar), 4.72-4.67 (m, 1H, C***H***-5), 4.50 (s, 2H, C***H***-9), 4.29 (dt, *J* = 7.2, 3.8 Hz, 1H, C***H***-3), 3.61-3.38 (m, 2H, C***H***-8), 2.62-2.53 (m, 2H, C***H***-2), 1.87-1.64 (m, 6H, C***H***-4, C***H***-6, C***H***-7), 0.87 (1s, 9H,-SiC(C***H₃***)3-), -0.06, -0.07 (2s, 6H, -SiC(C***H₃***)$_2$ -).

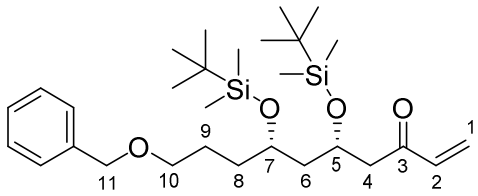
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4 (C-1), 138.4 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.6 (C-Ar), 75.8 (C-5), 72.9 (C-9), 69.8 (C-8), 63.5 (C-3), 39.3 (C-2), 36.5 (C-4), 32.3 (C-6), 25.7 (Si(***C***$(CH_3)_3$), 25.2 (C-7), 17.9 (Si(C(***C***$H_3)_3$), -4.9, -4.9 (Si(***C***$H_3)_2$).

IR (thin film, cm^{-1}) 2953, 2857, 1734, 1472, 1362, 1252, 1159, 1082, 1028.

HRMS (ESI, *m/z*) calcd for $(C_{21}H_{34}NO_4SiNa)^+$ calcd for 401.2119, found 401.2114.

[α]$^{23}_D$ -10.0 (*c* 2.0, $CHCl_3$).

(5*S*,7*S*)-10-(Benzyloxy)-5,7-*bis*((*tert*-butyldimethylsilyl)oxy)dec-1-en-3-one 3.28



Chemical Formula: $C_{29}H_{52}O_4Si_2$
Molecular Weight: 520.90

To a stirred suspension of **3.18** (500 mg, 0.90 mmol) in THF (8 mL) at 0°C was added dropwise vinyl magnesium bromide (4.50 mL, 4.50 mmol, 5.00 equiv). The reaction mixture was then heated to reflux and monitored by TLC. When the complete consumption of staring material was observed, the reaction mixture was cooled to room temperature and quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was then extracted with ether (3 x 10 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 9:1) gave **3.28** (373 mg, 0.72 mmol, 80%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, ***H***-Ar), 6.36 (dd, *J* = 17.6, 10.6 Hz, 1H, C***H***-2), 6.20 (dd, *J* = 17.6, 0.9 Hz, 1H, C***H***-1$_{trans}$), 5.81 (dd, *J* = 10.6, 0.9 Hz, 1H, C***H***-1$_{cis}$), 4.50 (s, 2H, C***H***-11), 4.33-4.28 (m, 1H, C***H***-5), 3.82-3.77 (m, 1H, C***H***-7), 3.47 (t, *J* = 6.5 Hz, 2H, C***H***-10), 2.76 (dd, *J* = 15.2, 7.0 Hz, 1H, C***H***-4), 2.66 (dd, *J* = 15.2, 4.9 Hz, 1H, C***H***-4), 1.72-1.55 (m, 5H, C***H***-6, C***H***-8, C***H***-9), 1.52-1.46 (m, 1H, C***H***-9) 0.89, 0.84 (2s, 18H,-SiC(C***H$_3$***)$_3$-), 0.06, 0.05, 0.04, 0.01 (4s, 12H, -SiC(C***H$_3$***)$_2$ -).

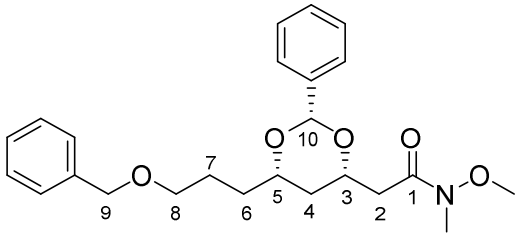
^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4 (C-3), 138.6 (C-Ar), 137.5 (C-2), 128.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-1), 72.8 (C-11), 70.6 (C-10), 69.1 (C-5), 67.8 (C-7), 47.3 (C-4), 45.3 (C-6), 33.6 (C-8), 25.9 (Si(***C***(CH$_3$)$_3$), 25.9 (Si(***C***(CH$_3$)$_3$), 25.3 (C-9), 18.0 (Si(C(***C***H$_3$)$_3$), 18.0 (Si(C(***C***H$_3$)$_3$), 4.3, 4.4, 4.5, 4.6 (Si(***C***H$_3$)$_2$).

IR (neat, cm^{-1}) 2928, 2855, 1684, 1614, 1472, 1400, 1360, 1252, 1094, 1069.

HRMS (ESI, *m/z*) calcd for $(C_{29}H_{52}O_4Si_2Na)^+$ 543.3296, found 576.3277.

[α]$^{23}_D$ +13.1 (*c* 1.0, $CHCl_3$).

2-((2*S*,4*S*,6*S*)-6-(3-(benzyloxy)propyl)-2-phenyl-1,3-dioxan-4-yl)-*N*-methoxy-*N*-methylacetamide 3.16



Chemical Formula: $C_{24}H_{31}NO_5$
Molecular Weight: 413.51

Benzylidene acetal **3.16** was obtained from the corresponding conjugate amide **3.24** according to the procedure described for **3.15**. Purification by column chromatography on silica gel (petroleum ether: EtOAc 1:1) gave **3.24** as clear oil.

Scale: 0.87 mmol

Yield: 92%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.44 (m, 2H, ***H***-Ar), 7.38-7.26 (m, 8H, ***H***-Ar), 5.55 (s, 1H, C***H***-10), 4.51 (s, 2H, C***H***-9), 4.42-4.35 (m, 1H, C***H***-3), 3.90-3.85 (m, 1H, C***H***-5), 3.67 (s, 3H, N-***OMe***), 3.55-3.48 (m, 2H, C***H***-8), 3.20 (s, 3H, N-C***H₃***), 2.98 (dd, *J* = 15.3, 5.7 Hz, 1H, C***H***-2), 2.55 (dd, *J* = 15.6, 6.2 Hz, 1H, C***H***-2), 1.89-1.62 (m, 5H, C***H***-4, C***H***-6, C***H***-7), 1.45 (dd, *J* = 24.1, 11.2 Hz, 1H, C***H***-4).

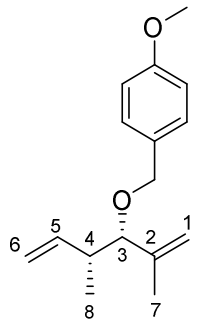
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4 (C-1), 138.7 (C-Ar), 138.6 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 126.1 (C-Ar), 100.6 (C-10), 76.4 (C-3), 73.5 (C-3), 72.8 (C-9), 70.1 (C-8), 61.4 (NO**C**H_3), 38.2 (C-4), 36.9 (C-2), 32.5 (N**C**H_3), 32.0 (C-7), 25.4 (C-6).

IR (neat, cm^{-1}) 2940, 2855, 1736, 1659, 1450, 1366, 1211, 1102, 1018.

HRMS (ESI, *m/z*) calcd for $(C_{24}H_{31}NO_5Na)^+$ 413.2202, found 436.2204.

[α]$^{23}_D$ -18.2 (*c* 1.0, $CHCl_3$).

1-((((3*S*,4*R*)-2,4-Dimethylhexa-1,5-dien-3-yl)oxy)methyl)-4-methoxybenzene 1.10



Chemical Formula: $C_{16}H_{22}O_2$
Molecular Weight: 246.35

Diene **3.30** was obtained from methacrolein **1.8** (222 mg, 3.17 mmol) according to the procedure used for **2.16** employing a 0.5 M solution of (*R,R*)-Diisopropyl-(*Z*)-crotylboronate in toluene. The crude product obtained was dissolved in DMF (13 mL) and cooled to 0 °C. Then PMB-Br (1.15 g, 5.72 mmol, 1.80 equiv) was added followed by NaH (60% dispersion in mineral oil, 215 mg, 5.38 mmol, 1.70 equiv) and the resultant mixture was left to warm to room temperature and stirred for a further 3 h after addition. The reaction was quenched using a saturated aqueous solution of NH_4Cl (15 mL), extracted with Et_2O (3 x 15 mL), washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (petroleum ether: ether 95:5) to afford **1.10** (650 mg, 2.64 mmol, 66% over 2 steps) as a clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H, ***H***-Ar), 6.87 (d, *J* = 8.6 Hz, 2H, ***H***-Ar), 5.67-5.56 (m, 1H, C***H***-5), 5.04-4.95 (m, 2H, C***H***-1, C***H***-6), 4.92 (dd, *J* = 10.3, 1.4 Hz, 1H, C***H***-6_{cis}), 4.86 (s, 1H, C***H***-1), 4.45 (d, *J* = 11.4 Hz, 1H, C***H*$_2$**-PMB), 4.16 (d, *J* = 11.4 Hz, 1H, C***H*$_2$**-PMB), 3.81 (s, 3H, PMB-OC***H*$_3$**), 3.39 (d, *J* = 8.8 Hz, 1H, C***H***-3), 2.43-2.33 (m, 1H, C***H***-4), 1.68 (s, 3H, C***H***-8), 1.09 (d, *J* = 6.6 Hz, 3H, C***H***-6).

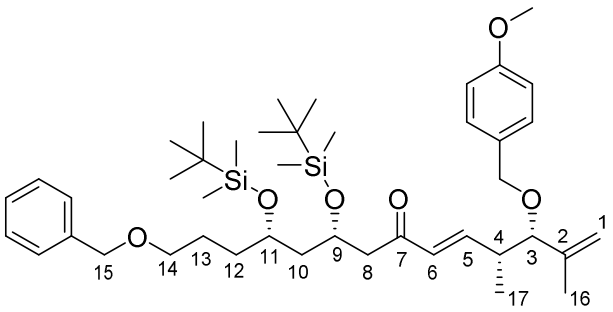
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 143.5 (C-2), 140.7 (C-5), 130.9 (C-Ar), 129.4 (C-Ar), 114.9 (C-Ar), 113.7 (C-6 or C-1), 113.6 (C-6 or C-1), 87.1 (C-3), 69.7 (**C**H_2-PMB), 55.3 (O**C**H_3-PMB), 40.7 (C-4), 17.0 (C-8), 16.8 (C-7).

IR (neat, cm^{-1}) 2970, 1736, 1643, 1450, 1373, 1227, 1018.

HRMS (ESI, *m/z*) calcd for $(C_{16}H_{22}O_2Na)^+$ 269.1512, found 269.1500.

[α]$^{23}_D$ -38.7 (*c* 1.0, CH_2Cl_2) (*Lit.*: **[α]$^{25}_D$** -45.2 (*c* 1.0, CH_2Cl_2)).[5]

(3*S*,4*R*,9*S*,11*S*,*E*)-14-(Benzyloxy)-9,11-*bis*((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethyltetradeca-1,5-dien-7-one 3.31



Chemical Formula: $C_{43}H_{70}O_6Si_2$
Molecular Weight: 739.20

A general procedure for the cross metathesis of enone **3.28** with diene **1.10** is described below while the conditions, solvent and quantities of reagents and catalysts used are summarized in Table 3.2.

A 0.1 M solution of enone **3.28** and diene **1.10** in the solvent indicated for each experiment was degassed using the freeze-pump-thaw method. Ruthenium metathesis catalyst was then added in portions of 2.5 mol%. After the time indicated, the reaction mixture was cooled to room temperature and subsequently dry loaded on silica gel and purified by column chromatography (petroleum ether: ether 95:5) to afford **3.31** as a clear oil and as a 6:1 mixture of diastereomers.

The major diastereomer is described below:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, ***H***-Ar), 7.24 (d, *J* = 8.6 Hz, 2H, ***H***-Ar(PMB)), 6.87 (d, *J* = 8.6 Hz, 2H, ***H***-Ar(PMB)), 6.61 (dd, *J* = 15.9, 8.0 Hz, 1H, C***H***-5), 6.06 (dd, *J* = 15.9, 0.9 Hz, 1H, C***H***-6), 5.00 (s, 1H, C***H***-1), 4.90 (s, 1H, C***H***-1), 4.50 (s, 2H, C***H***-15), 4.46 (d, *J* = 11.5 Hz, 1H, C***H$_2$***-PMB), 4.29-4.24 (m, 1H, C***H***-9), 4.17 (d, *J* = 11.4 Hz, 1H, C***H$_2$***-PMB), 3.81-3.77 (m, 4H, PMB-OC***H$_3$***, C***H***-11), 3.50-3.45 (m, 3H, C***H***-3, C***H***-14), 2.66 (dd, *J* = 15.2, 6.9 Hz, 1H, C***H***-8), 2.62-2.50 (m, 2H, C***H***-4, C***H***-8), 1.71-1.53 (m, 9H, C***H***-10, C***H***-12, C***H***-13, C***H***-16), 1.12 (d, *J* = 6.6 Hz, 3H, C***H***-17) 0.88, 0.84 (2s, 18H, -SiC(C***H$_3$***)3-), 0.05, 0.04, 0.04, 0.03 (4s, 12H, -SiC(C***H$_3$***)$_2$-).

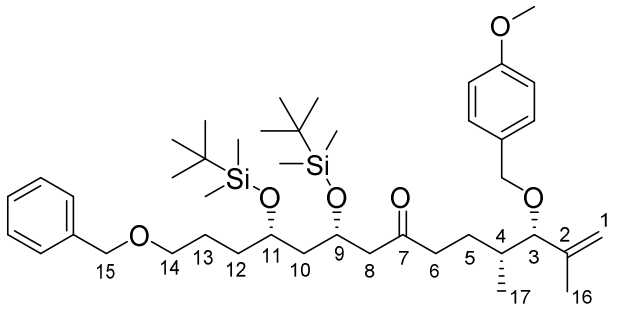
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9 (C-7), 159.1 (C-Ar), 148.6 (C-5), 142.7 (C-2), 138.7 (C-Ar), 130.4 (C-6), 130.4 (C-Ar), 129.4 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.4 (C-Ar), 115.6 (C-1), 113.7 (C-Ar), 86.0 (C-3), 72.8 (C-15), 70.6 (C-14), 69.7 (**C**H$_2$-PMB), 69.1 (C-9), 66.8 (C-11), 55.3 (O**C**H$_3$-PMB), 48.0 (C-8), 45.3 (C-10), 39.6 (C-4), 33.5 (C-12), 25.9 (Si(***C***(CH$_3$)$_3$), 25.9 (Si(***C***(CH$_3$)$_3$), 25.3 (C-13), 18.0 (Si(C(***C***H$_3$)$_3$), 17.9 (Si(C(***C***H$_3$)$_3$), 17.0 (C-17), 16.1 (C-16), -4.4 (Si(***C***H$_3$)$_2$), -4.6 (Si(***C***H$_3$)$_2$).

IR (thin film, cm^{-1}) 2950, 2854, 1694, 1613, 1513, 1462, 1361, 1247, 1065, 1036.

HRMS (ESI, *m/z*) calcd for $(C_{43}H_{70}O_6Si_2Na)^+$ 761.4603, found 761.4578.

$[\alpha]^{23}_D$ -16.3 (*c* 1.0, $CHCl_3$).

(3*S*,4*R*,9*S*,11*S*)-14-(Benzyloxy)-9,11-*bis*((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethyltetradec-1-en-7-one 3.32



Chemical Formula: $C_{43}H_{72}O_6Si_2$
Molecular Weight: 741.21

Enone **3.31** (50.0 mg, 0.0680 mmol) was dissolved in a mixture of THF (0.4 mL) and MeOH (0.2 mL) and the resultant solution was cooled to 0 °C. Then $NiCl_2 \cdot 6H_2O$ (8.2 mg, 0.060 mmol 0.90 equiv) was added and the mixture was stirred for 15 min before adding $NaBH_4$ (5.1 mg, 0.13 mmol, 1.9 equiv) in two portions over 30 min. The reaction was then monitored by TLC and when indicated that the starting material was completely consumed (apprx. 10 min after last addition of $NaBH_4$) it was concentrated *in vacuo.* The resulting mixture was dissolved in Et_2O, filtered through celite and concentrated *in vacuo* giving the crude product as a clear oil that was further purified by column chromatography on silica gel (petroleum ether: ether 9:1) to afford **3.32** (49.0 mg, 0.066 mmol, 98%) as a clear liquid and as 9:1 mixture of diastereomers.

The major diastereomer is described below:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (m, 7H, ***H***-Ar), 6.86 (d, *J* = 8.6 Hz, 2H, ***H***-Ar(PMB)), 5.03 (s, 1H, C***H***-1), 4.91 (s, 1H, C***H***-1), 4.50 (s, 2H, C***H***-15), 4.45 (d, *J* = 11.4 Hz, 1H, C***H₂***-PMB), 4.24 (dt, *J* = 12.0, 6.0 Hz, 1H, C***H***-9), 4.15 (d, *J* = 11.4 Hz, 1H, C***H₂***-PMB), 3.79 (s, 3H, PMB-OC***H₃***), 3.77-3.73 (m, 2H, C***H***-11), 3.46 (t, *J* = 6.5 Hz, 2H, C***H***-14), 3.34 (d, *J* = 7.9 Hz, 1H, C***H***-3), 2.54-2.28 (m, 5H, C***H***-4, C***H***-6, C***H***-8), 1.67-1.48 (m, 10H, C***H***-5, C***H***-10, C***H***-12, C***H***-13, C***H***-16), 10.94 (d, *J* = 6.4 Hz, 3H, C***H***-17) 0.89, 0.85 (2s, 18H, -SiC(C***H₃***)$_3$-), 0.05, 0.05, 0.04, -0.01 (4s, 12H, -SiC(C***H₃***)$_2$-).

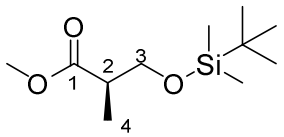
^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6 (C-7), 159.0 (C-Ar), 143.2 (C-2), 138.7 (C-Ar), 131.0 (C-Ar), 129.4 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 115.1 (C-1), 113.7 (C-Ar), 87.3 (C-3), 72.8 (C-15), 70.6 (C-14), 69.8 (**C**H_2-PMB), 69.1 (C-9), 66.8 (C-11), 55.3 (O**C**H_3-PMB), 50.2 (C-6), 45.0 (C-8),42.3 (C-10), 34.6 (C-4), 33.8 (C-12), 26.6 (C-5), 25.9 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 25.2 (C-13), 18.0 (Si(C(***C***$H_3)_3$), 17.9 (Si(C(***C***$H_3)_3$), 17.2 (C-17), 15.6 (C-16), -4.3 (Si(***C***$H_3)_2$), -4.4 (Si(***C***$H_3)_2$), -4.5 (Si(***C***$H_3)_2$), -4.7 (Si(***C***$H_3)_2$).

IR (thin film, cm^{-1}) 2955, 2857, 1715, 1612, 1514, 1462, 1302, 1275, 1057

HRMS (ESI, *m/z*) calcd for $(C_{43}H_{72}O_6Si_2Na)^+$ 763.4760, found 763.4738.

[α]$^{23}_D$ -8.3 (*c* 0.132, $CHCl_3$).

Methyl (*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate[83]



Chemical Formula: $C_{11}H_{24}O_3Si$
Molecular Weight: 232.40

To a stirred solution of (*R*)-(-)-Roche ester (2.00 g, 16.9 mmol) in dichloromethane (15 mL) at 0 °C was added imidazole (1.84 g, 27.2 mmol, 1.60 equiv) and DMAP (20.5 mg, 0.17 mmol, 1.0 mol%) followed by the dropwise addition of a solution of *tert*-butyldimethylsilyl chloride (2.70 g, 17.6 mmol, 1.05 equiv) in dichloromethane (8 mL). The reaction mixture was then allowed to warm to room temperature and stirred overnight. Water (25 mL) was then added and the mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Mg_2SO_4), filtered and concentrated *in vacuo.* Purification by column chromatography on silica gel (petroleum ether: ether 9:1) afforded **102** (3.93 g, quant.) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (dd, *J* = 9.7, 6.9 Hz, 1H, C***H***-3), 3.68 (s, 3H, -OC***H***$_3$), 3.66 (dd, *J* = 9.9, 6.1 Hz, 1H, C***H***-3), 2.66 (m, 1H, C***H***-2), 1.14 (d, *J* = 7.1 Hz, 3H, C***H***-4), 0.88 (s, 9H, -SiC(C***H***$_3)_3$-), 0.05 (s, 3H, -Si(C***H***$_3)_2$-), 0.04 (s, 3H, -Si(C***H***$_3)_2$-).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (C-1), 65.2 (C-3), 51.5 (O***C***H_3), 42.5 (C-2), 25.8 (-SiC(***C***$H_3)_3$-), 18.2 (-Si***C***$(CH_3)_3$-), 13.4 (C-4), -5.5 (-Si(***C***$H_3)_2$-).

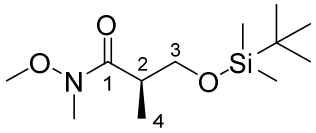
HRMS (ESI, *m*/*z*) calcd for $(C_{11}H_{24}O_3SiNa)^+$ 255.1387, found 255.1377.

[83] Cooksey, J. P.; Ford, R.; Kocienski, P. J.; Pelotier, B.; Pons, J.-M. *Tetrahedron* **2010**, *66*, 6462

[α]$^{24}_{D}$ -18.6 (*c* 1.0, $CHCl_3$) (*Lit.*: **[α]$^{25}_{D}$** -20.5 (*c* 1.0, $CHCl_3$))

In agreement with literature data.

(*R*)-3-((tert-butyldimethylsilyl)oxy)-N-methoxy-N,2-dimethylpropanamide 3.47



Chemical Formula: $C_{12}H_{27}NO_3Si$
Molecular Weight: 261.44

To a stirred solution of ester **1.193** (3.80 g, 16.4 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.40 g, 24.6 mmol, 1.50 equiv) in THF (45 mL) at -15 °C was added isopropylmagnesium bromide (2.0 M in 2-Me THF, 24.0 mL, 48.0 mmol, 2.93 equiv) dropwise. The solution was stirred for 3 h at -15 °C and the reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (100 mL) and extracted with diethyl ether (3 x 75 mL). The combined organic layers were dried (Mg_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 4:1) afforded Weinreb amide **3.47** (4.08 g, 95%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (dd, 1H, *J* = 9.5, 8.2 Hz, C***H***-3), 3.71 (s, 3H, N-***OMe***), 3.53 (dd, 1H, *J* = 9.5, 6.1 Hz, C***H***-3), 3.22-3.11 (m, 1H, C***H***-2), 3.19 (s, 3H, N-C***H$_3$***), 1.07 (d, 3H, *J* = 6.9 Hz, C***H***-4), 0.87 (s, 9H, -SiC(C***H$_3$***)$_3$-), 0.04 (s, 3H, -Si(C***H$_3$***)$_2$-), 0.03 (s, 3H, -Si(C***H$_3$***)$_2$-).

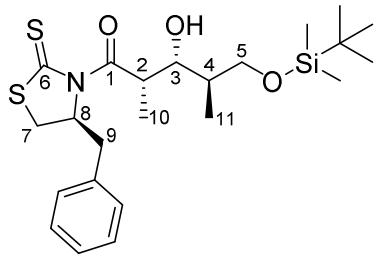
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1 (C-1), 65.7 (C-3), 61.5 (NO**C**H_3), 38.1 (N**C**H_3), 32.0 (C-2), 25.8 (-SiC(*C*H_3)$_3$-), 18.2 (-Si*C*(CH_3)$_3$-), 13.4 (C-4), -5.5 (-Si(*C*H_3)$_2$-), -5.5 (-Si(*C*H_3)$_2$-).

IR (neat, cm^{-1}) 2959, 2927, 2857, 1666, 1470, 1463, 1388, 1260, 1097.

HRMS (ESI, *m*/*z*) calcd for $(C_{12}H_{27}NO_3SiNa)^+$ 284.1652, found 284.1649.

[α]$^{25}_{D}$ -19.3 (*c* 1.0, $CHCl_3$).

(2*S*,3*R*,4*R*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,4-dimethylpentan-1-one 3.43



Chemical Formula: $C_{23}H_{37}NO_3S_2Si$
Molecular Weight: 467.76

To a stirred suspension of Weinreb amide **3.47** (525 mg, 2.00 mmol) in CH_2Cl_2 (18 mL) was added DIBAL-H (1.0 M CH_2Cl_2 solution, 2.10 mL, 2.10 mmol, 1.05 equiv) dropwise at -78 °C. The reaction mixture was stirred for 1 h before adding EtOAc (15 mL) and a saturated aqueous Rochelle's salt solution (15 mL), and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo* to give the crude aldehyde that was used in the next step without further purification.

To a solution of (*L*)-4-benzyl-3-proponylthiazolidin-2-thione **3.46** (478 mg, 1.80 mmol, 0.90 equiv) in CH_2Cl_2 (6 mL) at 0 °C was added titanium tetrachloride (0.22 mL, 1.80 mmol, 0.90 equiv). The mixture was stirred 15 min at 0 °C then diisopropylethylamine (0.35 mL, 1.80 mmol, 0.90 equiv) was added. The reaction was stirred for 1 h then cooled to -78 °C and *N*-methyl-2-pyrrolidinone (0.19 mL, 1.80 mmol, 0.90 equiv) was added. The reaction was stirred for 1 h followed by dropwise addition of a solution of the crude aldehyde prepared above in CH_2Cl_2 (3 mL). The reaction was stirred for 1 h at -78 °C then warmed to room temperature over 1 h. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by flash chromatrography on silica gel (petroleum ether: ether 3:1) to furnish a yellow oil **3.47** as a single diastereomer (588 mg, 1.25 mmol, 70% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H, ***H***-Ar), 5.28-5.23 (m, 1H, C***H***-8), 4.78 (qd, *J* = 6.9, 3.6 Hz, 1H, C***H***-2), 4.15 (d, *J* = 1.3 Hz, 1H, C3-O***H***), 3.96-3.93 (m, 1H, C***H***-3), 3.77 (dd, *J* = 10.0, 4.1 Hz, 1H, C***H***-5), 3.62 (dd, *J* = 10.0, 4.1 Hz, 1H, C***H***-5), 3.40-3.32 (m, 2H, C***H***-7, C***H***-9), 3.06 (dd, *J* = 13.1, 10.8 Hz, 1H, C***H***-7), 2.87 (d, *J* = 11.4 Hz, 1H, C***H***-9), 1.82-1.72 (m, 1H, C***H***-4), 1.24 (d, *J* = 6.7 Hz, 3H, C***H***-10), 0.88 (s, 9H, -SiC(C***H***$_3$)$_3$-), 0.85 (d, *J* = 6.9 Hz, 3H, C***H***-11), 0.07, 0.07 (2s, 6H, -Si(C***H***$_3$)$_2$-).

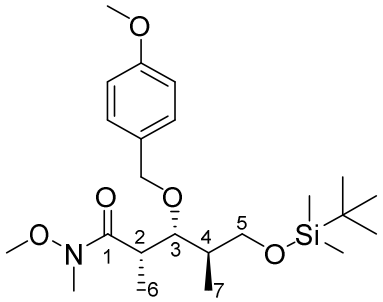
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2 (C-6), 177.3 (C-1), 136.6 (C-Ar), 129.4 (C-Ar), 128.8 (C-Ar), 127.1 (C-Ar), 76.7 (C-3), 70.0 (C-5), 68.7 (C-8), 42.4 (C-2), 37.3 (C-4), 36.5 (C-7), 32.0 (C-9), 25.8 (-Si*C*$(CH_3)_3$-), 18.1 (-SiC(*C*$H_3)_3$-), 13.1 (C-10), 9.1 (C-11), -5.6 (-Si(*C*$H_3)_2$-), -5.7 (-Si(*C*$H_3)_2$-).

IR (thin film, cm^{-1}) 2926, 1701, 1605, 1456, 1341, 1258, 1165, 1057

HRMS (ESI, *m*/*z*) calcd for $(C_{23}H_{37}NO_3SiNa)^+$ 490.1876, found 490.1863.

[α]$^{25}_D$ +9.7 (*c* 0.38, $CHCl_3$).

(2*S*,3*R*,4*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-3-((4-methoxybenzyl)oxy)-N,2,4-trimethylpentanamide 3.48[84]



Chemical Formula: $C_{23}H_{41}NO_5Si$
Molecular Weight: 439.67

N,*O*-dimethylhydroxylamine hydrochloride (345 mg, 3.54 mmol, 3.00 eqiuv.) was dissolved in CH_2Cl_2 (6 mL) and after cooling the reaction mixture to 0 °C, $AlMe_3$ (2.0 M in toluene, 1.77 mL, 3.54 mmol, 3.00 equiv) was added dropwise. The resulting mixture was stirred for 1 h at room temperature before cooling to 0 °C at which point thiazolidine **3.43** (550 mg, 1.18 mmol) in CH_2Cl_2 (6 mL) was added dropwise. The stirred suspension was allowed to warm to room temperature overnight. Then the reaction was quenched by the dropwise addition of a 1.0 M aqueous solution of HCl (3.0 mL, 3.0 mmol, 1.0 equiv). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo*.

The crude yellow oil obtained was dissolved in DMF (7 mL) and cooled to 0 °C. Then PMB-Br (474 mg, 2.36 mmol, 2.00 equiv) in DMF (2 mL) was added followed by NaH (60% dispersion in mineral oil, 71.0 mg, 1.77 mmol, 1.50 equiv) and the resultant mixture was left to warm to room temperature and stirred overnight. The reaction was then quenched using a saturated aqueous solution of NH_4Cl (10 mL), extracted with Et_2O (3 x 10 mL), washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was

[84] Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878

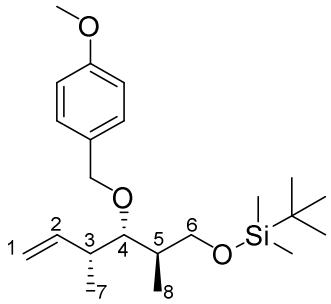
purified by column chromatography on silica gel (petroleum ether: ether 4:1) to afford **3.48** (259 mg, 0.59 mmol, 50% over 2 steps) as a clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H, ***H***-Ar (PMB)), 6.86 (d, *J* = 8.7 Hz, 2H, ***H***-Ar (PMB)), 4.50 (d, *J* = 10.4 Hz, 1H, C***H*****$_2$**-PMB), 4.43 (d, *J* = 10.4 Hz, 1H, C***H*****$_2$**-PMB), 3.79 (s, 3H, PMB-OC***H*****$_3$**), 3.74-3.67 (m, 2H, C***H***-5), 3.69 (s, 3H, N-***OMe***), 3.55 (dd, *J* = 9.7, 6.9 Hz, 1H, C***H***-3), 3.19 (s, 3H, N-C***H*****$_3$**), 3.14-3.11 (m, 1H, C***H***-2), 1.83-1.74 (m, 1H, C***H***-4), 1.20 (d, *J* = 6.9 Hz, 3H, C***H***-6), 0.99 (d, *J* = 6.9 Hz, 3H, C***H***-7), 0.89 (s, 9H, -SiC(C***H*****$_3$**)$_3$-), 0.03, 0.02 (2s, 6H, -Si(C***H*****$_3$**)$_2$-).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0 (C-1), 159.1 (C-Ar), 131.0 (C-Ar), 129.6 (C-Ar), 113.7 (C-Ar), 81.6 (C-3), 74.3 (**C**H_2-PMB), 64.7 (C-5), 61.2 (NO**C**H_3), 55.3 (O**C**H_3-PMB), 39.5 (C-2), 38.2 (N**C**H_3), 32.4 (C-4), 25.9 (-SiC(*C*H_3)$_3$-), 18.3 (-Si*C*(CH_3)$_3$-), 14.9 (C-6), 12.5 (C-7), -5.4 (-Si(*C*H_3)$_2$-), -5.4 (-Si(*C*H_3)$_2$-).

In agreement with literature data.

tert-Butyl((2*R*,3*S*,4*R*)-3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-enyloxy) dimethylsilane 1.195



Chemical Formula: $C_{22}H_{38}O_3Si$
Molecular Weight: 378.63

Weinreb amide **3.48** (250 mg, 0.57 mmol) was dissolved in CH_2Cl_2 (5 mL) and the stirred solution was cooled to -78 °C. Then DIBAL-H (1.0 M in hexanes 0.66 mL, 0.66 mmol, 1.2 equiv) was dropwise added and stirred until complete conversion judged by TLC. At that point EtOAc (5 mL), Et_2O (5 mL) and a saturated aqueous Rochelle's salt solution (7 mL) were added and the mixture was stirred for a further 1 h while allowing it to warm to room temperature. Then the two phases were separated, and the aqueous phase was further extracted with ether (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product obtained as a colourless liquid was used in the next step without further purification.

At 0 °C *t*-BuOK (717 mg, 2.01 mmol, 3.53 equiv) and methyltriphenylphosphonium bromide (226 mg, 2.01 mmol, 3.53 equiv) were dissolved in THF (2.7 mL) and stirred for 90 min.

Then a solution of crude aldehyde prepared above in THF (3 mL) was added dropwise and the resultant stirred suspension was left to warm to room temperature overnight. The reaction mixture was then poured into a 50 mL extractor funnel containing an aqueous saturated solution of NH_4Cl (6 mL). The aqueous layer was extracted with ether (3 x 40 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 9:1) gave **1.195** (130 mg, 0.34 mmol, 60% over 2 steps) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H, ***H***-Ar (PMB)), 6.86 (d, *J* = 8.7 Hz, 2H, ***H***-Ar (PMB)), 5.93 (ddd, *J* = 17.5, 10.3, 7.5 Hz, 1H, C***H***-2), 5.07 (dt, 1H, *J* = 17.5, 1.6 Hz, C***H***-1$_{trans}$), 5.01-4.98 (m, 1H, C***H***-1$_{cis}$), 4.50 (d, 1H, *J* = 10.7 Hz, C***H$_2$***-PMB), 4.45 (d, 1H, *J* = 10.7 Hz, C***H$_2$***-PMB), 3.80 (s, 3H, C***H$_3$***-PMB), 3.68-3.61 (m, 2H, C***H***-6), 3.28 (dd, 1H, *J* = 7.4, 4.4 Hz, C***H***-4), 2.47-2.41 (m, 1H, C***H***-3), 1.89-1.81 (m, 1H, C***H***-5), 1.04 (d, 3H, *J* = 6.8 Hz, C***H***-7), 0.95 (d, 3H, *J* = 6.9 Hz, C***H***-8), 0.90 (s, 9H, -SiC(C***H$_3$***)$_3$-), 0.04, 0.03 (2s, 6H, -Si(C***H$_3$***)$_2$-).

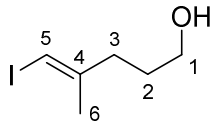
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 143.1 (C-2), 131.4 (C-Ar), 129.2 (C-Ar), 113.7 (C-Ar), 113.6 (C-1), 84.1 (C-4), 74.3 (***C***H$_2$-PMB), 64.8 (C-6), 55.3 (***C***H$_3$-PMB), 40.1 (C-3), 38.6 (C-5), 26.0 (-SiC(***C***H$_3$)$_3$-), 18.3 (-Si***C***(CH$_3$)$_3$-), 14.6 (C-7), 14.0 (C-8), -5.3 (-Si(***C***H$_3$)$_2$-), -5.4 (-Si(***C***H$_3$)$_2$-).

IR (neat, cm^{-1}) 2955, 2929, 2857, 1611, 1513, 1460, 1247, 1085.

HRMS (ESI, *m*/*z*) calcd for $(C_{22}H_{38}O_3SiNa)^+$ 401.2482, found 401.2470.

[α]$^{23}_D$ +20.1 (*c* 1.0, $CHCl_3$).

(*E*)-5-Iodo-4-methylpent-4-en-1-ol 3.49[85]



Chemical Formula: $C_6H_{11}IO$
Molecular Weight: 226.06

Zirconocene dichloride (3.51 g, 12.0 mmol, 2.00 equiv) was weighed out into a flame dried, argon flushed 100 mL round bottom flask containing a magnetic stirrer bar in a glovebox. The flask was then sealed and subsequently removed. Degassed CH_2Cl_2 (2.0 mL) was added and the heterogenous mixture was cooled to -25 °C while stirring. Then $AlMe_3$ (2.0 M solution in toluene 14.4 mL, 28.8 mmol, 4.80 equiv) was added dropwise and the solution

[85] Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, *12*, 1089

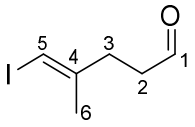
stirred for a further 20 min after the addition was complete. At this point the reaction mixture was homogenous with pale-yellow colouration and freshly distilled H_2O (216 µL, 12.0 mmol, 2.0 equiv) was then cautiously added. The mixture was then stirred for a further 30 min before the dropwise addition of a degassed solution of alkyne **3.42** (560 µL, 6.00 mmol) in CH_2Cl_2 (7.0 mL + 3.0 mL rinse) that had been pre-treated with $AlMe_3$ (2.0 M solution in toluene 3.6 mL, 7.2 mmol, 1.2 equiv). The mixture was then stirred for 6 h at -25 °C and 12 h at room temperature before re-cooling back to -25 °C. A solution of iodine (7.61 g, 30.0 mmol, 5.00 equiv) in THF (18.0 mL) was then added and stirring continued for 1 h at -25 °C and 1 h at 0 °C. A saturated aqueous solution of K_2CO_3 (7.0 mL) was then slowly added followed by $MgSO_4$ while leaving the mixture to warm to room temperature over 30 min. The resultant mixture was then filtered through a pad of celite and rinsed with CH_2Cl_2. The filtrate was then washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 20 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave vinyl iodide **3.49** (1.36 g, 5.99 mmol, quant.) as a colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.92 (m, 1H, C***H***-5), 3.66-3.61 (m, 2H, C***H***-1), 2.30 (t, *J* = 7.6 Hz, 2H, C***H***-3), 1.85 (s, 3H, C***H***-6), 1.71 (tt, *J* = 7.5, 6.4 Hz, 2H, C***H***-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4 (C-4), 74.9 (C-5), 62.0 (C-1), 35.7 (C-3), 30.5 (C-2), 23.8 (C-6).

In agreement with literature data.

(*E*)-5-Iodo-4-methylpent-4-enal



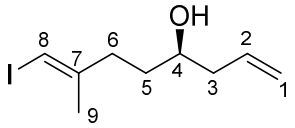
Chemical Formula: C_6H_9IO
Molecular Weight: 224.04

To a stirred solution of **3.49** (565 mg, 2.50 mmol) in CH_2Cl_2 (10.0 mL) was added Dess-Martin periodinane (1.27 g, 2.99 mmol, 1.20 equiv) at room temperature. The resultant mixture was monitored by TLC until disappearance of the starting material, at which point ether (15 mL) followed by a saturated aqueous solution of $NaHCO_3$ (20 mL) were added. The mixture was then extracted with ether (3 x 10 mL) and the combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$ (2 x 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude aldehyde as a colourless liquid that was immediately used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H, C***H***-1), 5.98 (m, 1H, C***H***-5), 2.61-2.52 (m, 4H, C***H***-2, C***H***-3), 1.86 (s, 3H, C***H***-6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.8 (C-1), 145.8 (C-4), 76.0 (C-5), 41.8 (C-3), 31.4 (C-2), 24.0 (C-6).

(*R,E*)-8-Iodo-7-methylocta-1,7-dien-4-ol 3.54



Chemical Formula: $C_9H_{15}IO$
Molecular Weight: 266.12

The above crude aldehyde was dissolved in Et_2O (20.0 mL) and the stirred solution was cooled to -78 °C. Then (+)-*B*-allyldiisopinocampheylborane (1.0 M solution in pentane 5.0 mL, 5.0 mmol, 2.0 equiv) from a sealed ampule was added dropwise. The reaction mixture was stirred for 6 h at ambient temperature and subsequently poured into a saturated aqueous solution of NH_4Cl (20 mL). The mixture was then separated, and the aqueous phase was extracted with Et_2O (3 x 15 mL), washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product obtained was purified by column chromatography on silica gel (petroleum ether: ether 2:1) give homoallylic alcohol **3.54** (330 mg, 1.24 mmol, 50% over 2 steps) as a colourless oil.

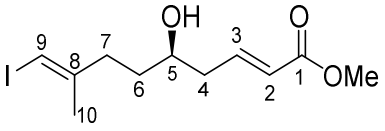
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (m, 1H, C***H***-8), 5.84-5.77 (m, 1H, C***H***-2), 5.16-5.13 (m, 2H, C***H***-1), 3.63-3.61 (m, 1H, C***H***-4), 2.42-2.36 (m, 1H, C***H***-3), 2.33-2.27 (m, 2H, C***H***-6), 2.19-2.13 (m, 1H, C***H***-3), 1.85 (s, 3H, C***H***-9), 1.63-1.58 (m, 2H, C***H***-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7 (C-7), 134.4 (C-2), 118.6 (C-1), 74.9 (C-8), 69.8 (C-4), 42.1 (C-3), 35.7 (C-6), 34.7 (C-5), 23.9 (C-9).

IR (thin film, cm^{-1}) 3370, 2918, 1618, 1265, 1130, 1053, 1009.

HRMS (ESI, *m*/*z*) calcd for $(C_9H_{15}IONa)^+$ 289.0060, found 289.0065.

Methyl (*R*,2*E*,8*E*)-5-hydroxy-9-iodo-8-methylnona-2,8-dienoate 3.55



Homoallylic alcohol **3.54** (120 mg, 0.45 mmol), methyl acrylate **2.52** (120 µL, 1.35 mmol, 3 equiv) and toluene (5.0 mL) were dispensed in a Schlenk bomb and subsequently degassed using the freeze-pump-thaw method. **HG-II** catalyst (28 mg, 0.045 mmol, 0.10 equiv) was then added, the bomb was evacuated (≈ 100 mbar), sealed and the resultant mixture was heated to 50 °C and stirred for 12 h. At this stage the reaction mixture was cooled to room temperature and the pressure in the bomb measured (≈ 300 mbar) before filling with argon. The mixture was transferred to a round bottom flask (rinsed with toluene 3 x 2 mL) and concentrated *in vacuo.* Purification by column chromatography on silica gel (petroleum ether: ether 3:1) gave conjugated ester **3.55** (49.0 mg, 0.15 mmol, 34%) as a colourless oil.

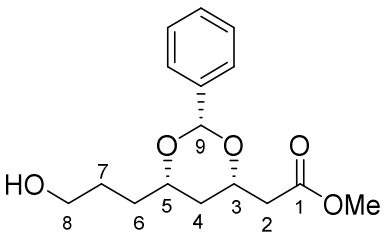
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 15.1, 7.4 Hz, 1H, C***H***-3), 5.93-5.89 (m, 2H, C***H***-2, C***H***-9), 3.74-3.69 (m, 1H, C***H***-5), 3.73 (s, 3H, OC***H*****$_3$**), 2.40-2.25 (m, 4H, C***H***-4, C***H***-7), 1.83 (s, 3H, C***H***-10), 1.65-1.58 (m, 2H, C***H***-6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6 (C-1), 147.3 (C-8), 144.9 (C-3), 123.7 (C-2), 75.2 (C-9), 69.7 (C-5), 51.5 (O**C**H_3), 40.3 (C-4), 35.6 (C-7), 34.9 (C-6), 23.9 (C-10).

IR (thin film, cm^{-1}) 3568, 2855, 1721, 1655, 1437, 1269, 1117, 1007.

HRMS (ESI, *m*/*z*) calcd for $(C_{11}H_{17}IO_3Na)^+$ 347.0115, found 347.0114.

Methyl 3-((3*S*,5*S*,9*S*)-9-(3-hydroxypropyl)-3-phenyl-3,5-dioxan-5-yl)acetate 3.60



Chemical Formula: $C_{16}H_{22}O_5$
Molecular Weight: 294.35

Raney nickel (7.0 mL) (W.R. Grace and Co. Raney® 2800, ≈ 50% w/w slurry in H_2O) was transferred to a flame dried, argon flushed round bottom flask and the H_2O was removed. Ethanol (10 mL) was added and the mixture was stirred for 5 min before removing the ethanol. This cycle of addition/stirring/removal was repeated 3 more times. Then a solution of **3.15** (1.00 g, 2.60 mmol) in ethanol (7 mL + 3 mL rinse) was added and a 3-way tap was fitted onto the flask that was connected to a high vacuum pump and a balloon of hydrogen. The round bottom flask was then evacuated and subsequently filled with hydrogen several times. The reaction mixture was then left to stir at room temperature for 5 days before filtering through a pad of celite and the round bottom flask was cautiously rinsed with Et_2O (3 x 15 mL). The filtrate was concentrated *in vacuo* and subsequently purified by column

chromatography on silica gel (petroleum ether: EtOAc 1:1) to give free alcohol **3.60** (300 mg, 1.02 mmol, 39%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 6.7 Hz, 2H, ***H***-Ar), 7.36-7.26 (m, 3H, ***H***-Ar), 5.55 (s, 1H, C***H***-9), 4.31 (dtd, *J* = 11.1, 6.8, 2.3 Hz, 1H, C***H***-3), 3.90-3.87 (m, 1H, C***H***-5), 3.69 (s, 3H, OC***H₃***), 3.64 (t, *J* = 5.8 Hz, 2H, C***H***-8), 2.73 (dd, *J* = 15.7, 7.0 Hz, 1H, C***H***-2), 2.52 (dd, *J* = 15.7, 6.1 Hz, 1H, C***H***-2), 2.31 (br s, 1H, C8-O***H***), 1.77-1.64 (m, 5H, C***H***-4, C***H***-6, C***H***-7), 1.50-1.42 (m, 1H, C***H***-4).

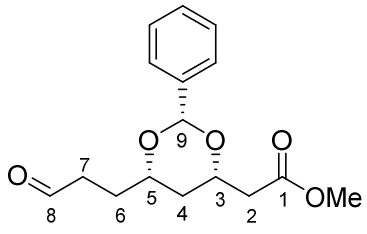
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (C-1), 138.2 (C-Ar), 128.7 (C-Ar), 128.1 (C-Ar), 126.0 (C-Ar), 100.6 (C-10), 76.5 (C-3), 73.1 (C-5), 62.5 (C-8), 51.7 (O**C**H_3), 40.6 (C-2), 36.4 (C-4), 32.3 (C-6), 28.4 (C-7).

IR (thin film, cm^{-1}) 3672, 2961, 1736, 1406, 1395, 1344, 1260, 1078, 1057.

HRMS (ESI, *m*/*z*) calcd for $(C_{16}H_{22}O_5Na)^+$ 317.1359, found 317.1348.

[α]$^{23}_D$ -16.0 (*c* 0.1, $CHCl_3$).

Methyl 2-((2*S*,4*S*,6*S*)-6-(3-oxopropyl)-2-phenyl-1,3-dioxan-4-yl)acetate



Chemical Formula: $C_{16}H_{20}O_5$
Molecular Weight: 292.33

To a stirred suspension of alcohol **3.60** (40.0 mg, 0.136 mmol) in a mixture of DMSO (0.36 mL) and DMF (0.24 mL) was added IBX (57.0 mg, 0.200 mmol, 1.47 equiv) at room temperature. The reaction mixture was stirred overnight and then Et_2O (1.0 mL) and H_2O (1.0 mL) were added. Stirring continued for 2 h and the mixture was subsequently filtered, the filtrate was extracted with Et_2O (3 x 1 mL) and the combined organic extracts were washed with H_2O (3 x 2 mL), brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The aldehyde (39.0 mg, 0.133 mmol, 98%) was obtained as colourless oil that was used in the next step without any further purification.

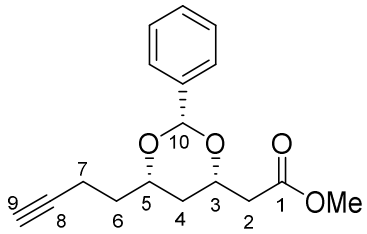
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H, C***H***-8), 7.48-7.34 (m, 5H, ***H***-Ar), 5.54 (s, 1H, C***H***-9), 4.32-4.30 (m, 1H, C***H***-3), 3.89-3.87 (m, 1H, C***H***-5), 3.71 (s, 3H, OC***H₃***), 2.75 (dd, *J* = 15.6, 6.8 Hz, 1H, C***H***-2), 2.65 (m, 2H, C***H***-7), 2.53 (dd, *J* = 15.6, 5.9 Hz, 1H, C***H***-2), 1.97-1.84 (m, 2H, C***H***-6), 1.76-1.71 (m, 1H, C***H***-4), 1.51-1.46 (m, 1H, C***H***-4).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0 (C-8), 171.0 (C-1), 138.2 (C-Ar), 128.7 (C-Ar), 128.1 (C-Ar), 126.0 (C-Ar), 100.6 (C-9), 75.4 (C-3), 73.0 (C-5), 51.7 (O**C**H_3), 40.6 (C-2), 39.6 (C-7), 36.3 (C-4), 28.1 (C-6).

HRMS (ESI, *m*/*z*) calcd for $(C_{16}H_{20}O_5Na)^+$ 315.1203, found 315.1194.

Fully characterised at the next step.

Methyl 2-((2*S*,4*S*,6*S*)-6-(but-3-yn-1-yl)-2-phenyl-1,3-dioxan-4-yl)acetate



Chemical Formula: $C_{17}H_{20}O_4$
Molecular Weight: 288.34

A stirred solution of crude above aldehyde (35.0 mg, 0.120 mmol) in methanol (1.2 mL) was cooled to 0 °C. K_2CO_3 (67.0 mg, 0.480 mmol, 4.00 equiv) and dimethyl-1-diazo-2-oxopropylphosphonate (57.0 mg, 0.300 mmol, 2.50 equiv) were then added. The reaction mixture was left to warm to room temperature and stirred overnight before it was diluted with Et_2O (3 mL), quenched with H_2O (3 mL) and a saturated aqueous solution of NH_4Cl (3 mL). The aqueous phase was extracted with Et_2O (3 x 3 mL) and the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude was purified by column chromatography on silica gel (petroleum ether: ether 4:1) to afford alkyne **3.58** (27.0 mg, 0.0900 mmol, 78%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.48 (m, 2H, ***H***-Ar), 7.37-7.32 (m, 3H, ***H***-Ar), 5.58 (s, 1H, C***H***-10), 4.34 (dtd, *J* = 11.1, 6.7, 2.3 Hz, 1H, C***H***-3), 4.04-3.99 (m, 1H, C***H***-5), 3.71 (s, 3H, OC***H$_3$***), 2.75 (dd, *J* = 15.7, 7.0 Hz, 1H, C***H***-2), 2.54 (dd, *J* = 15.7, 6.2 Hz, 1H, C***H***-2), 2.45-2.34 (m, 2H, C***H***-7), 1.97 (t, *J* = 2.6 Hz, 1H, C***H***-9), 1.91-1.84 (m, 1H, C***H***-6), 1.79-1.73 (m, 2H, C***H***-4, C***H***-6), 1.50-1.43 (m, 1H, C***H***-4).

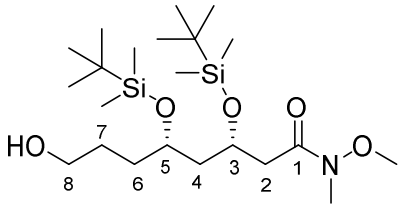
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1 (C-1), 138.3 (C-Ar), 128.7 (C-Ar), 128.1 (C-Ar), 126.0 (C-Ar), 100.5 (C-10), 83.8 (C-8), 74.8 (C-3), 73.1 (C-5), 68.6 (C-9), 51.7 (O**C**H_3), 40.7 (C-2), 36.2 (C-6), 34.4 (C-6), 14.3 (C-7).

IR (thin film, cm^{-1}) 2990, 2922, 1738, 1437, 1346, 1202, 1134, 1057.

HRMS (ESI, *m*/*z*) calcd for $(C_{17}H_{20}O_4Na)^+$ 311.1254, found 311.1244.

$[\alpha]^{23}_D$ -64.0 (*c* 0.05, $CHCl_3$).

(3*S*,5*S*)-3,5-*bis*((*tert*-Butyldimethylsilyl)oxy)-8-hydroxy-*N*-methoxy-*N*-methyloctanamide 3.62



Chemical Formula: $C_{22}H_{49}NO_5Si_2$
Molecular Weight: 463.81

Palladium on carbon (214 mg, 32% w/w) was suspended into a 25 mL round-bottom flask that contained a stirred solution of Weinreb amide **3.18** (665 mg, 1.20 mmol) in ethanol (6.5 mL). A 3-way adaptor tap connected to a high vacuum pump and a balloon filled with H_2 was then fitted onto the flask and the vessel was flushed with H_2 10 times. The reaction mixture was then left to stir at room temperature for 4 days before filtering through a pad of celite. The round-bottom flask was rinsed with Et_2O (3 x 10 mL) and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: EtOAc 1:1) afforded the desired deprotected alcohol **3.62** (210 mg, 0.45 mmol, 39%) as a colourless oil as well as recovered starting material **3.18** (200 mg, 0.36 mmol, 30%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30-4.22 (m, 1H, C***H***-3), 3.95-3.85 (m, 1H, C***H***-5), 3.69 (s, 3H, N-***OMe***), 3.66-3.59 (m, 2H, C***H***-8), 3.17 (s, 3H, N-C***H*****$_3$**), 2.66 (dd, *J* = 14.7, 5.6 Hz, 1H, C***H***-2), 2.50 (dd, *J* = 15.1, 5.9 Hz, 1H, C***H***-2), 2.04 (t, *J* = 5.5 Hz, 1H, C8-***OH***), 1.72-1.55 (m, 6H, C***H***-4, C***H***-6, C***H***-7), 0.90, 0.87 (2s, 18H,-SiC(C***H*****$_3$**)3-), 0.09, 0.07, 0.07, 0.04 (4s, 12H, -SiC(C***H*****$_3$**)$_2$ -).

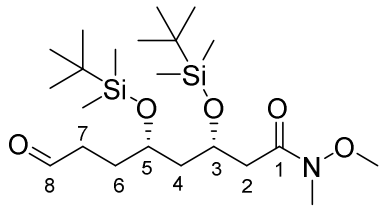
^{13}C NMR (126 MHz, $CDCl_3$) δ 181.0 (C-1), 69.0 (C-3), 66.9 (C-5), 63.2 (C-8), 61.3 (NO**C**H_3), 44.8 (C-2), 40.2 (C-4), 32.9 (C-6), 30.3 (N**C**H_3), 27.9 (C-7), 25.9 (Si(***C***$(CH_3)_3$), 25.8 (Si(***C***$(CH_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), -4.5, -4.5, -4.5, -4.7 (Si(***C***$H_3)_2$).

IR (thin film, cm^{-1}) 2928, 2857, 1661, 1645, 1472, 1462, 1362, 1254, 1180, 1055.

HRMS (ESI, *m*/*z*) calcd for $(C_{22}H_{49}O_5Si_2Na)^+$ 486.3041, found 486.3028.

[α]$^{23}_D$ -6.0 (*c* 0.1, $CHCl_3$).

(3*S*,5*S*)-3,5-*bis*((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methyl-8-oxooctanamide



Chemical Formula: $C_{22}H_{47}NO_5Si_2$
Molecular Weight: 461.79

The aldehyde was obtained from the corresponding alcohol **3.62** according to the procedure described for (*E*)-5-iodo-4-methylpent-4-enal. The colourless oily crude product obtained was used in the following step without further purification.

Scale: 0.41 mmol

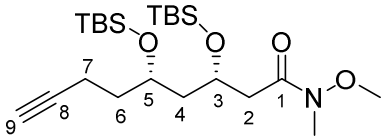
Yield: 90%

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.6 Hz, 1H, C***H***-8), 4.29-4.20 (m, 1H, C***H***-3), 3.90 (dt, *J* = 15.1, 4.7 Hz, 1H, C***H***-5), 3.69 (s, 3H, N-***OMe***), 3.17 (s, 3H, N-C***H₃***), 2.68 (dd, *J* = 15.0, 6.2 Hz, 1H, C***H***-2), 2.53-2.44 (m, 2H, C***H***-2, C***H***-7), 1.99-1.90 (m, 1H, C***H***-7), 1.78-1.61 (m, 4H, C***H***-4, C***H***-6), 0.88, 0.87 (2s, 18H,-SiC(C***H₃***)3-), 0.07, 0.07, 0.04, 0.04 (4s, 12H, -SiC(C***H₃***)$_2$ -).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6 (C-8), 181.0 (C-1), 68.1 (C-3), 66.8 (C-5), 61.3 (NO**C**H_3), 45.0 (C-2), 40.1 (C-4), 39.3 (C-7), 29.7 (N**C**H_3), 28.6 (C-6), 25.9 (Si(***C***$(CH_3)_3$), 25.8 (Si(***C***$(CH_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 17.9 (Si(C(***C***$H_3)_3$), -4.4, -4.5, -4.6, -4.7 (Si(***C***$H_3)_2$).

Fully characterised at the next step.

(3*S*,5*S*)-3,5-*bis*((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylnon-8-ynamide 3.59



Chemical Formula: $C_{23}H_{47}NO_4Si_2$
Molecular Weight: 457.80

Alkyne **3.59** was obtained from the above aldehyde according to the procedure described for **3.58**. Purification by column chromatography on silica gel (petroleum ether: ether 3:1) gave **3.59** as a clear oil.

Scale: 0.41 mmol

Yield: 57% (over 2 steps, from alcohol **3.62**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33-4.24 (m, 1H, C***H***-3), 3.96-3.89 (m, 1H, C***H***-5), 3.69 (s, 3H, N-***OMe***), 3.17 (s, 3H, N-C***H$_3$***), 2.69 (dd, *J* = 14.2, 6.0 Hz, 1H, C***H***-2), 2.48 (dd, *J* = 14.7, 5.9 Hz, 1H, C***H***-2), 2.26 (td, *J* = 7.3, 2.4 Hz, 2H, C***H***-7), 1.92 (t, *J* = 2.6 Hz, 1H, C***H***-9), 1.85-1.59 (m, 4H, C***H***-4, C***H***-6,), 0.89, 0.87 (2s, 18H,-SiC(C***H$_3$***)3-), 0.09, 0.07, 0.04 (3s, 12H, -SiC(C***H$_3$***)$_2$ -).

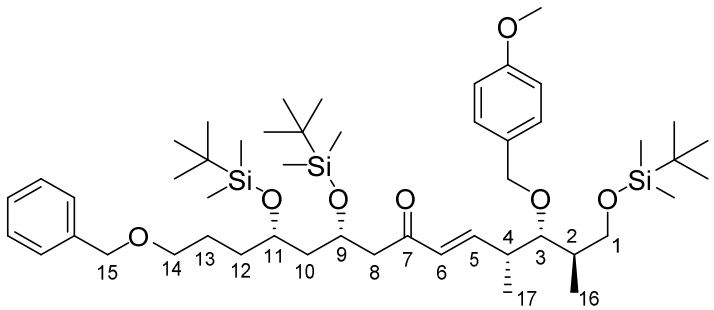
^{13}C NMR (126 MHz, $CDCl_3$) δ 181.1 (C-1), 84.6 (C-8), 68.4 (C-3), 67.9 (C-9), 66.8 (C-5), 61.3 (NO***C***H_3), 45.5 (C-2), 40.1 (C-4), 35.6 (C-6), 31.9 (N***C***H_3), 25.9 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 17.9 (Si(C(***C***$H_3)_3$), 14.3 (C-7), -4.3, -4.5, -4.6 (Si(***C***$H_3)_2$).

IR (thin film, cm^{-1}) 2953, 2857, 1661, 1472, 1385, 1256, 1090.

HRMS (ESI, *m*/*z*) calcd for $(C_{23}H_{47}O_4Si_2Na)^+$ 480.2936, found 480.2937.

[α]$^{23}_D$ -10.7 (*c* 0.1, $CHCl_3$).

(5*S*,7*S*,12*R*,13*S*,14*R*,*E*)-5-(3-(benzyloxy)propyl)-7-((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadec-10-en-9-one 3.65



Chemical Formula: $C_{49}H_{86}O_7Si_3$
Molecular Weight: 871.48

A general procedure for the cross metathesis of enone **3.28** with diene **1.195** is described below while the conditions and quantities of reagents and catalysts used are summarized in Table 3.4.

A 0.1 M solution of enone **3.28** and alkene **1.195** in the CH_2Cl_2 for each experiment was degassed using the freeze-pump-thaw method. **HG-II** metathesis catalyst was then added in two portions of 5 mol%. After the time indicated the reaction mixture was cooled to room temperature and subsequently dry loaded on silica gel and purified by column chromatography (petroleum ether: ether 95:5) to afford **3.65** as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H, ***H***-Ar), 7.22 (d, *J* = 8.6 Hz, 2H, ***H***-Ar(PMB)), 6.93 (dd, *J* = 16.0, 7.5 Hz, 1H, C***H***-5), 6.85 (d, *J* = 8.6 Hz, 2H, ***H***-Ar(PMB)), 6.16 (d, *J* = 15.9, 1H, C***H***-6), 4.50 (s, 2H, C***H***-15), 4.45 (d, *J* = 10.7 Hz, 1H, C***H₂***-PMB), 4.40 (d, *J* = 10.7 Hz, 1H, C***H₂***-PMB), 4.31 (m, 1H, C***H***-9), 3.81-3.77 (m, 4H, PMB-OC***H₃***, C***H***-11), 3.68 (dd, *J* = 9.7, 5.3 Hz, 1H, C***H***-1), 3.61 (dd, *J* = 9.7, 3.8 Hz, 1H, C***H***-1), 3.46 (t, *J* = 6.5 Hz, 2H, C***H***-14), 3.38 (dd, *J* = 7.9, 3.8 Hz, 1H, C***H***-3), 2.70 (dd, *J* = 15.2, 6.9 Hz, 1H, C***H***-8), 2.65-2.57 (m, 2H, C***H***-8, C***H***-4), 1.87-1.81 (m, 1H, C***H***-2), 1.73-1.54 (m, 6H, C***H***-10, C***H***-12, C***H***-13), 1.08 (d, *J* = 6.8 Hz, 3H, C***H***-17), 0.94 (d, *J* = 6.9 Hz, 3H, C***H***-16) 0.90, 0.88, 0.84 (3s, 27H, -SiC(C***H₃***)$_3$-), 0.06, 0.05, 0.04, 0.04, -0.01 (5s, 18H, -SiC(C***H₃***)$_2$-).

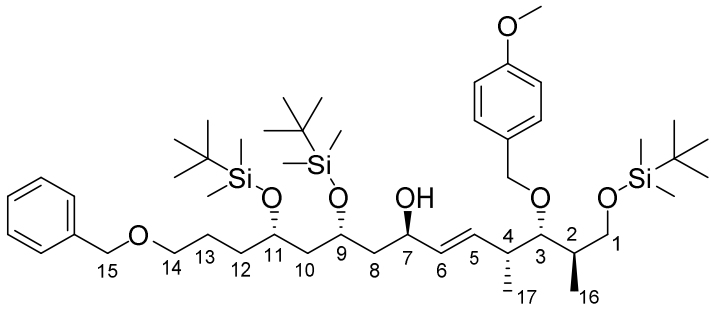
^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9 (C-7), 159.1 (C-Ar), 151.3 (C-5), 138.7 (C-Ar), 130.8 (C-Ar or C-6), 130.1 (C-Ar or C-6), 129.3 (C-Ar), 128.3 (C-Ar), 127.6 (C-Ar), 127.4 (C-Ar), 113.8 (C-Ar), 83.2 (C-3), 74.4 (***C***H$_2$-PMB), 72.8 (C-15), 70.6 (C-14), 69.1 (C-9), 66.8 (C-11), 64.6 (C-1), 55.2 (O***C***H$_3$-PMB), 48.0 (C-8), 45.4 (C-10), 39.0 (C-4), 38.7 (C-2), 33.5 (C-12), 26.0 (Si(***C***(CH$_3$)$_3$), 25.9 (Si(***C***(CH$_3$)$_3$), 25.9 (Si(***C***(CH$_3$)$_3$), 25.3 (C-13), 18.3 (Si(C(***C***H$_3$)$_3$), 18.0 (Si(C(***C***H$_3$)$_3$), 18.0 (Si(C(***C***H$_3$)$_3$), 14.5 (C-17), 13.1 (C-16), -4.4 (Si(***C***H$_3$)$_2$), -4.4 (Si(***C***H$_3$)$_2$), -4.5 (Si(***C***H$_3$)$_2$), -4.6 (Si(***C***H$_3$)$_2$), -5.3 (Si(***C***H$_3$)$_2$), -5.4 (Si(***C***H$_3$)$_2$), .

IR (thin film, cm^{-1}) 2953, 2855, 1612, 1514, 1462, 1362, 1302, 1250, 1173, 1059, 1007.

HRMS (ESI, *m/z*) calcd for $(C_{49}H_{86}O_7Si_3Na)^+$ 893.5574, found 893.5533.

[α]$^{23}_D$ -11.6 (*c* 0.336, $CHCl_3$).

(5*S*,7*R*,9*R*,12*R*,13*S*,14*R*,*E*)-5-(3-(Benzyloxy)propyl)-7-((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadec-10-en-9-ol 3.66



Chemical Formula: $C_{49}H_{88}O_7Si_3$
Molecular Weight: 873.49

(*S*)-(-)-2-Methyl-CBS-oxazaborolidine **2.22** (1.0 M in toluene 0.36 mL, 0.36 mmol, 1.3 equiv) was cooled to 0 °C at which point $BH_3{\cdot}SMe_2$ (36 µL, 0. 38 mmol, 1.4 equiv) was added and the mixture was stirred for 3 h while keeping the temperature constant. Then a solution of

enone **3.65** (240 mg, 0.275 mmol) in toluene (1.8 mL) was added dropwise over 5 min and the resultant suspension was left to stir for a further 4 h at 0 °C. The reaction was then quenched by the slow and cautious addition of methanol (2 mL) giving off H_2 evolution. Once bubbling had ceased, a saturated aqueous NH_4Cl solution (4 mL) was added and the mixture was extracted with ether (3 x 2 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (petroleum ether: ether 4:1) to give **3.66** (210 mg, 0.240 mmol, 88%) as a colourless oil and as a single diastereomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (m, 7H, ***H***-Ar, ***H***-Ar(PMB)), 6.86 (d, *J* = 8.7 Hz, 2H, ***H***-Ar(PMB)), 5.77 (dd, *J* = 15.5, 7.6 Hz, 1H, C***H***-6), 5.51 (dd, *J* = 15.5, 6.3 Hz, 1H, C***H***-5), 4.50-4.44 (m, 4H, C***H***-15, C***H$_2$***-PMB), 4.39-4.36 (m, 1H, C***H***-7), 4.12 (m, 1H, C***H***-9), 3.79 (s, 3H, PMB-OC***H$_3$***), 3.74-3.70 (m, 1H, C***H***-11), 3.67-3.62 (m, 2H, C***H***-1), 3.47 (t, *J* = 6.6 Hz, 2H, C***H***-14), 3.35 (br s, 1H, C7-O***H***), 3.28 (dd, *J* = 7.7, 4.2 Hz, 1H, C***H***-3), 2.47-2.41 (m, 1H, C***H***-4), 1.86-1.47 (m, 9H, C***H***-2, C***H***-8, C***H***-10, C***H***-12, C***H***-13), 1.03 (d, *J* = 6.8 Hz, 3H, C***H***-17), 0.94 (d, *J* = 6.9 Hz, 3H, C***H***-16) 0.91, 0.90, 0.88 (3s, 27H, -SiC(C***H$_3$***)$_3$-), 0.11, 0.09, 0.05, 0.04, 0.04, 0.03 (6s, 18H, -SiC(C***H$_3$***)$_2$-).

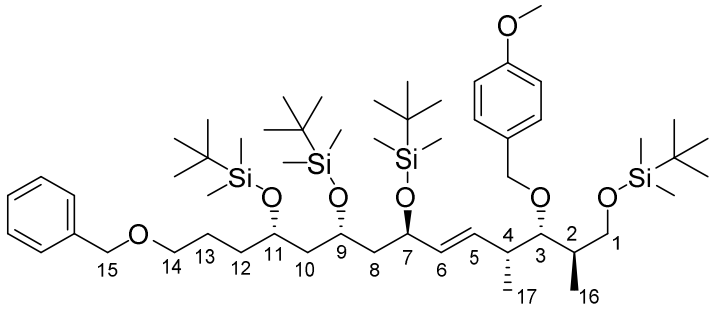
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 (C-Ar), 138.6 (C-Ar), 134.9 (C-6), 132.0 (C-5), 131.3 (C-Ar), 129.2 (C-Ar), 128.3 (C-Ar), 127.5 (C-Ar), 127.5 (C-Ar), 113.7 (C-Ar), 84.1 (C-3), 74.3 (***C***H$_2$-PMB), 72.8 (C-15), 70.5 (C-14), 69.4 (C-9), 69.2 (C-7), 68.7 (C-11), 64.8 (C-1), 55.2 (O***C***H$_3$-PMB), 43.3 (C-10), 42.0 (C-8), 38.7 (C-4), 38.6 (C-2), 34.1 (C-12), 26.0 (Si(***C***(CH$_3$)$_3$), 25.9 (Si(***C***(CH$_3$)$_3$), 25.8 (Si(***C***(CH$_3$)$_3$), 25.1 (C-13), 18.3 (Si(C(***C***H$_3$)$_3$), 18.0 (Si(C(***C***H$_3$)$_3$), 17.9 (Si(C(***C***H$_3$)$_3$), 14.6 (C-17), 14.1 (C-16), -4.2 (Si(***C***H$_3$)$_2$), -4.5 (Si(***C***H$_3$)$_2$), -4.6 (Si(***C***H$_3$)$_2$), -4.7 (Si(***C***H$_3$)$_2$), -5.3 (Si(***C***H$_3$)$_2$), -5.4 (Si(***C***H$_3$)$_2$), .

IR (thin film, cm^{-1}) 2953, 2928, 1612, 1514, 1362, 1250, 1055.

HRMS (ESI, *m/z*) calcd for $(C_{49}H_{88}O_7Si_3Na)^+$ 895.5730, found 895.5700.

[α]$^{23}_D$ -16.5 (*c* 0.20, $CHCl_3$).

(6*R*,7*S*,8*R*,11*R*,13*S*,15*S*,*E*)-15-(3-(Benzyloxy)propyl)-11,13-*bis*((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadec-9-ene 3.67



Chemical Formula: $C_{55}H_{102}O_7Si_4$
Molecular Weight: 987.75

Protected alcohol **3.67** was obtained from alcohol **3.66** according to the procedure described for **2.12**. Purification by column chromatography on silica gel (petroleum ether: ether 95:5) gave **3.67** as a clear oil.

Scale: 0.18 mmol

Yield: quant.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 3H, ***H***-Ar), 7.27-7.26 (m, 2H, ***H***-Ar), 7.24 (d, *J* = 8.7 Hz, 2H, ***H***-Ar(PMB)), 6.86 (d, *J* = 8.7 Hz, 2H, ***H***-Ar(PMB)), 5.63 (dd, *J* = 15.5, 8.1 Hz, 1H, C***H***-6), 5.43 (dd, *J* = 15.5, 7.5 Hz, 1H, C***H***-5), 4.50-4.43 (m, 4H, C***H***-15, C***H$_2$***-PMB), 4.15-4.11 (m, 1H, C***H***-7), 3.85-3.81 (m, 1H, C***H***-9), 3.79 (s, 3H, PMB-OC***H$_3$***), 3.76-3.71 (m, 1H, C***H***-11), 3.63 (m, 2H, C***H***-1), 3.47-3.40 (m, 2H, C***H***-14), 3.25 (dd, *J* = 7.6, 4.1 Hz, 1H, C***H***-3), 2.45-2.38 (m, 1H, C***H***-4), 1.85-1.80 (m, 1H, C***H***-2), 1.75-1.55 (m, 8H, C***H***-8, C***H***-10, C***H***-12, C***H***-13), 1.00 (d, *J* = 6.8 Hz, 3H, C***H***-17), 0.93 (d, *J* = 6.9 Hz, 3H, C***H***-16) 0.90, 0.89, 0.88, 0.87 (4s, 36H, -SiC(C***H$_3$***)$_3$-), 0.07, 0.06, 0.05, 0.04, 0.04, 0.03, 0.02, 0.02 (8s, 24H, -SiC(C***H$_3$***)$_2$-).

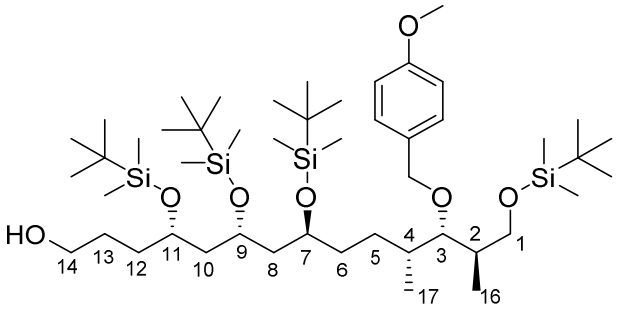
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C-Ar), 138.7 (C-Ar), 134.8 (C-6), 132.9 (C-5), 131.3 (C-Ar), 129.1 (C-Ar), 128.3 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 113.7 (C-Ar), 84.2 (C-3), 74.5 (***C***H$_2$-PMB), 72.7 (C-15), 71.5 (C-7), 70.7 (C-14), 69.3 (C-9), 67.1 (C-11), 64.7 (C-1), 55.3 (O***C***H$_3$-PMB), 47.6 (C-10 or C-8), 45.9 (C-10 or C-8), 39.1 (C-4), 38.6 (C-2), 33.1 (C-12), 26.0 (Si(***C***(CH$_3$)$_3$), 26.0 (Si(***C***(CH$_3$)$_3$), 26.0 (Si(***C***(CH$_3$)$_3$), 25.9 (Si(***C***(CH$_3$)$_3$), 25.7 (C-13), 18.3 (Si(C(***C***H$_3$)$_3$), 18.2 (Si(C(***C***H$_3$)$_3$), 18.1 (Si(C(***C***H$_3$)$_3$), 18.0 (Si(C(***C***H$_3$)$_3$), 14.8 (C-17), 14.5 (C-16), -3.8 (Si(***C***H$_3$)$_2$), -3.9 (Si(***C***H$_3$)$_2$), -4.1 (Si(***C***H$_3$)$_2$), -4.2 (Si(***C***H$_3$)$_2$), -4.3 (Si(***C***H$_3$)$_2$), -4.5 (Si(***C***H$_3$)$_2$), -5.4 (Si(***C***H$_3$)$_2$), -5.4 (Si(***C***H$_3$)$_2$), .

IR (thin film, cm^{-1}) 2926, 2855, 1742, 1464, 1258, 1119.

HRMS (ESI, *m/z*) calcd for $(C_{55}H_{102}O_7Si_4Na)^+$ 1009.6595, found 1009.6579.

$[\alpha]^{23}_D$ -11.0 (*c* 0.10, $CHCl_3$).

(4*S*,6*R*,8*S*,11*R*,12*S*,13*R*)-4,6,8,14-tetrakis((*tert*-Butyldimethylsilyl)oxy)-12-((4-methoxybenzyl)oxy)-11,13-dimethyltetradecan-1-ol 3.68



Chemical Formula: $C_{48}H_{98}O_7Si_4$
Molecular Weight: 899.65

Raney nickel (2.5 mL) (W.R. Grace and Co. Raney® 2800, ≈ 50% w/w slurry in H_2O) was transferred to a flame dried, argon flushed round bottom flask and the H_2O was removed. Freshly distilled H_2O (5 mL) was added and the mixture was stirred for 5 min before removing the ethanol. This cycle of addition/stirring/removal was repeated 20 more times. Freshly distilled ethanol (10 mL) was then added and the mixture was stirred for 5 min before removing the ethanol. This cycle of addition/stirring/removal was repeated 5 more times. Then a solution of **3.67** (170 mg, 0.172 mmol) in ethanol (1.5 mL + 0.5 mL rinse) was added and a 3-way tap was fitted onto the flask that was connected to a high vacuum pump and a balloon of hydrogen. The round-bottom flask was then evacuated and subsequently filled with hydrogen several times. The reaction mixture was then left to stir at room temperature for 5 days before filtering through a pad of celite and the round bottom flask was cautiously rinsed with Et_2O (3 x 15 mL). The filtrate was concentrated *in vacuo* and subsequently purified by column chromatography on silica gel (petroleum ether: ether 1:1) to give free alcohol **3.68** (148 mg, 0.164 mmol, 95%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H, ***H***-Ar(PMB)), 6.86 (d, *J* = 8.6 Hz, 2H, ***H***-Ar), 4.53-4.48 (m, 2H, C***H*$_2$**-PMB), 3.97-3.90 (m, 1H, C***H***-9), 3.80 (s, 3H, PMB-OC***H*$_3$**), 3.77-3.56 (m, 6H, C***H***-1, C***H***-7, C***H***-11, C***H***-14), 3.27 (dd, *J* = 8.7, 1.9 Hz, 1H, C***H***-3), 1.83-1.79 (m, 1H, C***H***-2), 1.68-1.50 (m, 10H, C***H***-4, C***H***-6, C***H***-8, C***H***-10, C***H***-12, C***H***-13), 1.41-1.33 (m, 2H, C***H***-5, C***H***-6), 1.25 (m, 1H, C***H***-5), 0.91-0.88 (m, 42 H, C***H***-16, C***H***-17, -SiC(C***H*$_3$**)$_3$-), 0.08-0.04 (m, 24H, -SiC(C***H*$_3$**)$_3$-).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C-Ar), 131.6 (C-Ar), 129.0 (C-Ar), 113.7 (C-Ar), 83.9 (C-3), 74.6 (***C***H_2-PMB), 70.2 (C-7), 69.2 (C-9), 67.7 (C-11), 65.0 (C-1), 63.2 (C-14), 55.3

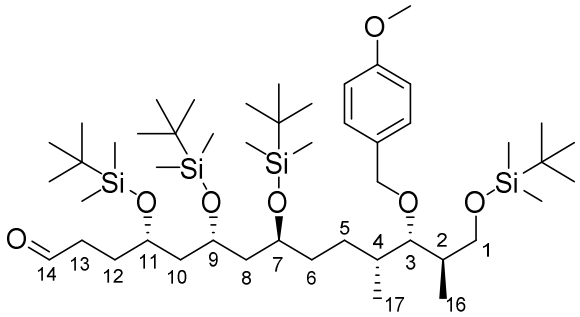
(O***C***H_3-PMB), 46.6 (C-10 or C-8), 45.1 (C-10 or C-8), 38.6 (C-2), 35.9 (C-6), 35.8 (C-4) 32.7 (C-13), 30.6 (C-5), 28.2 (C-12), 26.0 (Si(***C***$(CH_3)_3$), 26.0 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 18.3 (Si(C(***C***$H_3)_3$), 18.1 (Si(C(***C***$H_3)_3$), 18.1 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 14.8 (C-17), 13.4 (C-16), -3.7 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.3 (Si(***C***$H_3)_2$), -4.5 (Si(***C***$H_3)_2$), -5.3 (Si(***C***$H_3)_2$), -5.4 (Si(***C***$H_3)_2$).

IR (thin film, cm^{-1}) 3381, 2953, 1626, 1614, 1248, 1126, 1053.

HRMS (ESI, *m/z*) calcd for $(C_{48}H_{98}O_7Si_4Na)^+$ 921.6282, found 921.6252.

[α]$^{23}_D$ -5.8 (*c* 0.10, $CHCl_3$).

(4*S*,6*R*,8*S*,11*R*,12*S*,13*R*)-4,6,8,14-tetrakis((*tert*-Butyldimethylsilyl)oxy)-12-((4-methoxybenzyl)oxy)-11,13-dimethyltetradecanal



Chemical Formula: $C_{48}H_{96}O_7Si_4$
Molecular Weight: 897.63

Dichloromethane (5 mL) and distilled H_2O (5 mL) were mixed in a separatory funnel and the two layers were separated. This CH_2Cl_2 (0.40 mL) was added to a mixture of alcohol **3.68** (18.8 mg, 20.0 μmol) and Dess-Martin periodinane (17.0 mg, 40.0 μmol, 2.00 equiv) and the resultant suspension was stirred for 2 h. The reaction mixture was then concentrated *in vacuo* and subsequently dissolved in Et_2O (1 mL), washed with a saturated aqueous solution of sodium thiosulfate (3 x 1 mL), a saturated aqueous solution of $NaHCO_3$ (1 mL), H_2O (1 mL) and brine (1 mL). The combined aqueous phases were then back extracted with Et_2O (1 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (pentane: ether 10:1) to give the aldehyde (16.7 mg, 18.6 μmol, 93%) as a colourless oil.

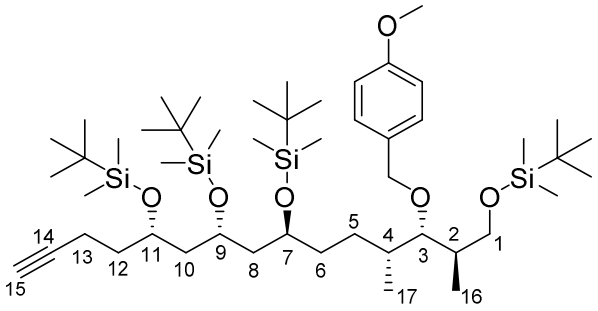
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H, C***H***-14), 7.25 (d, *J* = 8.0 Hz, 2H, ***H***-Ar(PMB)), 6.85 (d, *J* = 8.4 Hz, 2H, ***H***-Ar), 4.51 (s, 2H, C***H$_2$***-PMB), 3.92 (m, 1H, C***H***-9), 3.79 (s, 3H, PMB-OC***H$_3$***), 3.76-3.66 (m, 3H, C***H***-1, C***H***-7, C***H***-11), 3.62 (dd, *J* = 9.4, 2.4 Hz, 1H, C***H***-1), 3.28-3.26 (m, 1H, C***H***-3), 2.50-2.45 (m, 2H, C***H***-13), 1.92-1.91 (m, 1H, C***H***-2), 1.80 (m, 1H, C***H***-

4), 1.68-1.57 (m, 8H, C***H***-6, C***H***-8, C***H***-10, C***H***-12), 1.36-1.29 (m, 2H, C***H***-5), 0.91-0.88 (m, 42H, C***H***-16, C***H***-17, -SiC(C***H₃***)₃-), 0.07-0.04 (m, 24H, -SiC(C***H₃***)₃-).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4 (C-14), 159.0 (C-Ar), 131.6 (C-Ar), 129.0 (C-Ar), 113.7 (C-Ar), 83.8 (C-3), 74.5 (***C***H_2-PMB), 70.2 (C-7), 68.4 (C-9), 67.6 (C-11), 65.0 (C-1), 55.3 (O***C***H_3-PMB), 46.5 (C-10 or C-8), 45.5 (C-10 or C-8), 39.7 (C-13), 38.6 (C-2), 35.9 (C-6), 35.7 (C-4), 30.6 (C-5), 28.5 (C-12), 26.0 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 25.8 (Si(***C***$(CH_3)_3$), 18.3 (Si(C(***C***$H_3)_3$), 18.1 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 14.8 (C-17), 13.4 (C-16), -3.8 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.2 (Si(***C***$H_3)_2$), -4.6 (Si(***C***$H_3)_2$). -5.3 (Si(***C***$H_3)_2$), -5.4 (Si(***C***$H_3)_2$).

Fully characterised at the next step

(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-5-(But-3-yn-1-yl)-7,9-*bis*((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadecane 3.69



Chemical Formula: $C_{49}H_{96}O_6Si_4$
Molecular Weight: 893.64

Alkyne **3.69** was obtained from the above aldehyde according to the procedure described for **3.58**. Purification by column chromatography on silica gel (petroleum ether: ether 97:3) gave **3.69** as a clear oil.

Scale: 39 µmol

Yield: 80% (over 2 steps, from alcohol **3.68**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H, ***H***-Ar(PMB)), 6.85 (d, *J* = 8.6 Hz, 2H, ***H***-Ar), 4.54-5.48 (s, 2H, C***H₂***-PMB), 3.97-3.91 (m, 1H, C***H***-9), 3.80 (s, 3H, PMB-OC***H₃***), 3.77-3.71-3.69 (m, 3H, C***H***-1, C***H***-7, C***H***-11), 3.63 (dd, *J* = 9.6, 3.0 Hz, 1H, C***H***-1), 3.27 (dd, *J* = 8.7, 1.3 Hz, 1H, C***H***-1), 2.28-2.23 (m, 2H, C***H***-13), 1.91 (t, *J* = 2.5 Hz, 1H, C***H***-15), 1.82-1.74 (m, 2H, C***H***-2, C***H***-4), 1.72-1.52 (m, 8H, C***H***-6, C***H***-8, C***H***-10, C***H***-12), 1.36-1.29 (m,

2H, C***H***-5), 0.91-0.88 (m, 42H, C***H***-16, C***H***-17, -SiC(C***H₃***)₃-), 0.08-0.04 (m, 24H, -SiC(C***H₃***)₃-).

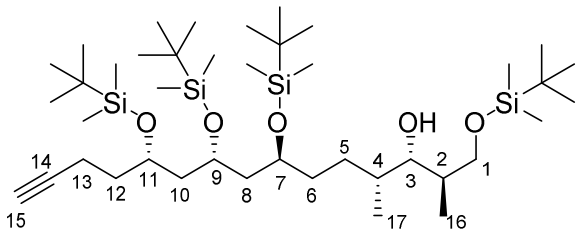
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C-Ar), 131.6 (C-Ar), 129.0 (C-Ar), 113.7 (C-Ar), 84.6 (C-14), 83.9 (C-3), 74.6 (***C***H_2-PMB), 70.3 (C-7), 68.4 (C-9), 68.1 (C-15), 67.6 (C-11), 65.0 (C-1), 55.3 (O***C***H_3-PMB), 46.6 (C-10 or C-8), 45.9 (C-10 or C-8), 38.6 (C-2), 35.9 (C-6), 35.7 (C-4), 35.4 (C-12), 30.6 (C-5), 26.0 (Si(***C***$(CH_3)_3$), 26.0 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 18.3 (Si(C(***C***$H_3)_3$), 18.1 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 14.8 (C-17), 14.4 (C-13), 13.4 (C-16), -3.8 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.2 (Si(***C***$H_3)_2$), -4.6 (Si(***C***$H_3)_2$). -5.3 (Si(***C***$H_3)_2$), -5.4 (Si(***C***$H_3)_2$).

IR (thin film, cm^{-1}) 2928, 2857, 1462, 1383, 1250, 1142, 1072.

HRMS (ESI, *m/z*) calcd for $(C_{49}H_{96}O_6Si_4Na)^+$ 915.6176, found 915.6140.

[α]$^{23}_D$ -5.8 (*c* 0.50, $CHCl_3$).

(6*R*,7*S*,8*R*,11*S*,13*R*,15*S*)-15-(But-3-yn-1-yl)-11,13-*bis*((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,6,8,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadecan-7-ol 3.70



Chemical Formula: $C_{41}H_{88}O_5Si_4$
Molecular Weight: 773.49

Alcohol **3.70** and diol **3.71** were obtained from alkyne **3.69** (45 mg, 50 µmol) according to the procedure described for **3.49.** Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave **3.70** (24 mg, 31 µmol, 62%) and **3.71** (10 mg, 15 µmol, 30%) as clear oils.

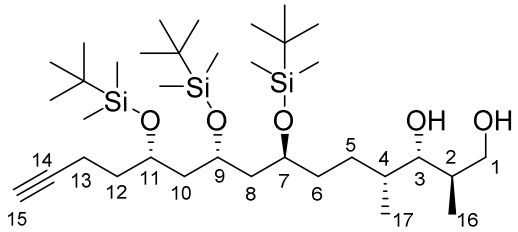
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97-3.88 (m, 1H, C***H***-9), 3.78-3.70 (m, 2H, C***H***-1, C***H***-7 or C***H***-11), 3.64-3.57 (m, 2H, C***H***-1, C***H***-7 or C***H***-11), 3.40-3.38 (m, 1H, C***H***-3), 2.30-2.21 (m, 2H, C***H***-13), 1.91 (t, *J* = 2.6 Hz, 1H, C***H***-15), 1.81-1.49 (m, 12H, C***H***-2, C***H***-4, C***H***-5, C***H***-6, C***H***-8, C***H***-10, C***H***-12), 0.90-0.83 (m, 39 H, C***H***-16, -SiC(C***H₃***)₃-), 0.79 (d, *J* = 6.9 Hz, 3H, C***H***-17), 0.08-0.05 (m, 24H, -SiC(C***H₃***)₃-).

^{13}C NMR (126 MHz, $CDCl_3$) δ 84.6 (C-14), 79.2 (C-3), 70.0 (C-7), 69.2 (C-1), 68.3 (C-9), 68.0 (C-15), 67.5 (C-11), 46.4 (C-10 or C-8), 45.8 (C-10 or C-8), 37.3 (C-2), 35.6 (C-6), 35.4

(C-4), 35.3 (C-12), 30.3 (C-5), 26.0 (Si(***C***$(CH_3)_3$), 26.0 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 18.2 (Si(C(***C***$H_3)_3$), 18.1 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 14.4 (C-17), 13.4 (C-13), 12.7 (C-16), -3.8 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.2 (Si(***C***$H_3)_2$), -4.6 (Si(***C***$H_3)_2$). -5.6 (Si(***C***$H_3)_2$), -5.6 (Si(***C***$H_3)_2$).

HRMS (ESI, *m/z*) calcd for $(C_{41}H_{88}O_5Si_4Na)^+$ 795.5507, found 795.5463.

(2*R*,3*S*,4*R*,7*S*,9*R*,11*S*)-7,9,11-*tris*((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylpentadec-14-yne-1,3-diol 3.71



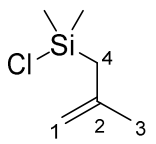
Chemical Formula: $C_{35}H_{74}O_5Si_3$
Molecular Weight: 659.23

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95-3.90 (m, 1H, C***H***-9), 3.78-3.63 (m, 4H, C***H***-1, C***H***-7, C***H***-11), 3.46 (dd, *J* = 8.8, 2.7 Hz, 1H, C***H***-3), 2.33-2.20 (m, 2H, C***H***-13), 1.92 (t, *J* = 2.6 Hz, 1H, C***H***-15), 1.88-1.49 (m, 12H, C***H***-2, C***H***-4, C***H***-5, C***H***-6, C***H***-8, C***H***-10, C***H***-12), 0.89-0.88 (m, 30 H, C***H***-16, -SiC(C***H***$_3$)$_3$-), 0.81 (d, *J* = 6.9 Hz, 3H, C***H***-17), 0.07-0.06 (m, 18H, -SiC(C***H***$_3$)$_3$-).

^{13}C NMR (126 MHz, $CDCl_3$) δ 84.6 (C-14), 80.1 (C-3), 70.0 (C-7), 68.8 (C-1), 68.4 (C-9), 68.0 (C-15), 67.4 (C-11), 46.4 (C-10 or C-8), 45.7 (C-10 or C-8), 37.4 (C-2), 35.3 (C-6), 35.0 (C-4), 31.9 (C-12), 30.3 (C-5), 25.9 (Si(***C***$(CH_3)_3$), 25.9 (Si(***C***$(CH_3)_3$), 18.1 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 18.0 (Si(C(***C***$H_3)_3$), 14.4 (C-17), 13.6 (C-13), 12.5 (C-16), -3.8 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.1 (Si(***C***$H_3)_2$), -4.2 (Si(***C***$H_3)_2$), -4.2 (Si(***C***$H_3)_2$), -4.6 (Si(***C***$H_3)_2$).

HRMS (ESI, *m/z*) calcd for $(C_{35}H_{74}O_5Si_3Na)^+$ 681.4742, found 681.4737.

Chlorodimethyl(2-methylallyl)silane 1.217[44]



Chemical Formula: $C_6H_{13}ClSi$
Molecular Weight: 148.71

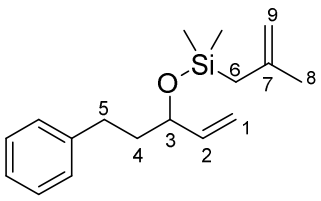
To a 3-neck flask fitted with a reflux condenser was added pre-dried magnesium turnings (4.86 g, 200 mmol, 2.00 equiv), diethyl ether (230 mL) and 3 drops of 1,2-dibromoethane. Then, a mixture of dimethyldichlorosilane **1.215** (12.1 mL, 100 mmol) and 3-chloro-2-methyl-1-propene **1.216** (14.7 mL, 150 mmol, 1.50 equiv) in diethyl ether (20 mL) was added dropwise over 4 h, maintaining gentle reflux. The reaction mixture was stirred for a further 12 h at room temperature at which point a white precipitate had formed. After filtering off the white solid, the filtrate was concentrated at 20 °C, 250 mbar. The crude product was then purified by vacuum distillation at 50 °C, 20 mbar furnishing **1.217** (4.99 g, 34 mmol, 34%) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 1H, C***H***-1), 4.50 (s, 1H, C***H***-1), 1.73 (m, 3H, C***H***-3), 1.57 (s, 2H, C***H***-4), 0.10 (2s, 6H, -SiC(C***H$_3$***)$_2$-).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0 (C-2), 108.6 (C-1), 30.4 (C-4), 25.1 (C-3), 0.4 (-SiC(***C***H_3)$_2$-).

IR (neat, cm^{-1}) 3075, 2957, 2913, 2160, 1638, 1373, 1254, 1059.

Dimethyl(7-methylallyl)((5-phenylpent-1-en-3-yl)oxy)silane 4.8



Chemical Formula: $C_{17}H_{26}OSi$
Molecular Weight: 274.48

To a stirred solution of allylic alcohol **1.211** (500 mg, 3.08 mmol) and chlorodimethyl(2-methylallyl)silane **1.217** (687 mg, 4.62 mmol, 1.50 equiv) in dichloromethane (6 mL) at 0 °C was added imidazole (630 mg, 9.25 mmol, 3.00 equiv) and DMAP (10 mg, 0.08 mmol, 0.025 equiv). The reaction mixture was then left to warm to room temperature and stirred for a further 2 h. Then, water (5 mL) was added and the mixture was extracted with diethyl ether (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 99:1) gave **4.8** (845 mg, 3.08 mmol, quant.) as a colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 3H, ***H***-Ar), 7.21-7.18 (m, 2H, ***H***-Ar), 5.85 (ddt, *J* = 16.9, 10.3, 6.4 Hz, 1H, C***H***-2), 5.19 (dd, *J* = 17.1, 0.9 Hz, 1H, C***H***-1$_{trans}$), 5.10 (dd, *J* = 10.3, 0.8 Hz, 1H, C***H***-1$_{cis}$), 4.64 (s, 1H, C***H***-9), 4.55 (s, 1H, C***H***-9), 4.18-4.14 (m, 1H, C***H***-3),

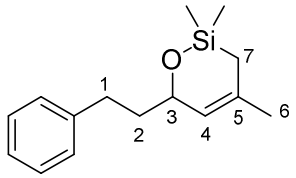
2.73-2.60 (m, 2H, C***H***-5), 1.90-1.80 (m, 2H, C***H***-4), 1.78 (s, 3H, C***H***-8), 1.66 (s, 2H, C***H***-6), 0.16 and 0.15 (2s, 6H, -SiC(C***H₃***)$_2$-).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.8 (C-7), 142.2 (C-2), 141.2 (C-Ar), 128.4 (C-Ar), 128.3 (C-Ar), 125.7 (C-Ar), 114.4 (C-1), 108.9 (C-8), 73.6 (C-3), 39.5 (C-5), 31.6 (C-4), 28.9 (C-6), 25.3 (C-8), -1.1 (-SiC(***C***H$_3$)$_2$-), -1.4. (-SiC(***C***H$_3$)$_2$-).

HRMS (ESI, *m/z*) calcd for $(C_{17}H_{26}OSiNa)^+$ 297.1651, found 297.1637.

IR (neat, cm^{-1}) 2959, 2914, 2940, 1638, 1454, 1252, 1078.

5,8,8-Trimethyl-3-phenethyl-3,9-dihydro-2*H*-8,9-oxasiline 4.9



Chemical Formula: $C_{15}H_{22}OSi$
Molecular Weight: 246.43

Diene **4.8** (260 mg, 0.95 mmol) and **G-II** (20 mg, 0.024 mmol, 0.025 equiv) in degassed dichloromethane (9.5 mL) were refluxed for 2 h. The solvent was then removed by concentrating *in vacuo*. Petroleum ether (5 mL) and diethyl ether (5 mL) were then added and the diethyl ether was removed by concentrating *in vacuo*. The resultant solution that had traces of dark solid was passed through a plug of silica and rinsed with petroleum ether, thus giving the desired silacycle **4.9** as colourless oil that was immediately used in the next step without further purification.

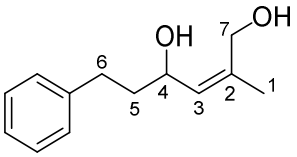
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H, ***H***-Ar), 7.24-7.14 (m, 3H, ***H***-Ar), 5.35-5.34 (m, 1H, C***H***-4), 5.19 (ddd, *J* = 9.1, 4.5, 2.2 Hz, 1H, C***H***-3), 2.80-2.64 (m, 2H, C***H***-1), 1.89-1.73 (m, 5H, C***H***-2, C***H***-6), 1.27-1.11 (m, 2H, C***H***-7), 0.19 (s, 3H, -SiC(C***H₃***)$_2$-), 0.16 (s, 3H, -SiC(C***H₃***)$_2$-).

^{13}C NMR (101MHz, $CDCl_3$) δ 142.6 (C-Ar), 132.4 (C-5), 128.5 (C-Ar), 128.2 (C-Ar), 126.0 (C-4), 125.6 (C-Ar), 71.4 (C-3), 40.2 (C-1), 31.4 (C-2), 28.2 (C-7), 17.6 (C-6), 0.3 (-SiC(***C***H$_3$)$_2$-), -0.8 (-SiC(***C***H$_3$)$_2$-).

HRMS (ESI, *m/z*) calcd for $(C_{15}H_{22}OSiNa)^+$ 269.1338, found 269.1328.

IR (neat, cm^{-1}) 3028, 2959, 1715, 1454, 1250, 1140, 1030.

(Z)-2-Methyl-6-phenylhex-2-ene-1,4-diol 4.10



Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.29

The above silacycle **4.9** was dissolved in a mixture of MeOH (9.5 mL) and THF (9.5 mL), then KF (275 mg, 4.75 mmol, 5.00 equiv) and $KHCO_3$ (219 mg, 2.19 mmol, 2.30 equiv) were added, followed by the dropwise addition of a 30% aqueous solution of H_2O_2 (4.6 mL, 35 mmol, 37 equiv). The reaction mixture was left to stir at room temperature for 16 h and was quenched with a saturated aqueous solution of sodium thiosulfate (20 mL). NaCl was then added until the mixture became saturated followed by extraction of the product with EtOAc (5 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (petroleum ether: ether 1:1) gave diol **4.10** (168 mg, 0.81 mmol, 86% over 2 steps) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H, ***H***-Ar), 7.22-7.15 (m, 3H, ***H***-Ar), 5.40 (d, *J* = 8.3 Hz, 1H, C***H***-3), 4.46-4.41 (m, 1H, C***H***-4), 4.22 (d, *J* = 12.3 Hz, 1H, C***H***-7), 4.00 (d, *J* = 12.3 Hz, 1H, C***H***-7), 2.74-2.63 (m, 2H, C***H***-6), 2.04-1.90 (m, 3H, C***H***-5, C4-O***H***, C7-O***H***), 1.83 (m, 3H, C***H***-1) 1.81-1.76 (m, 1H, C***H***-5).

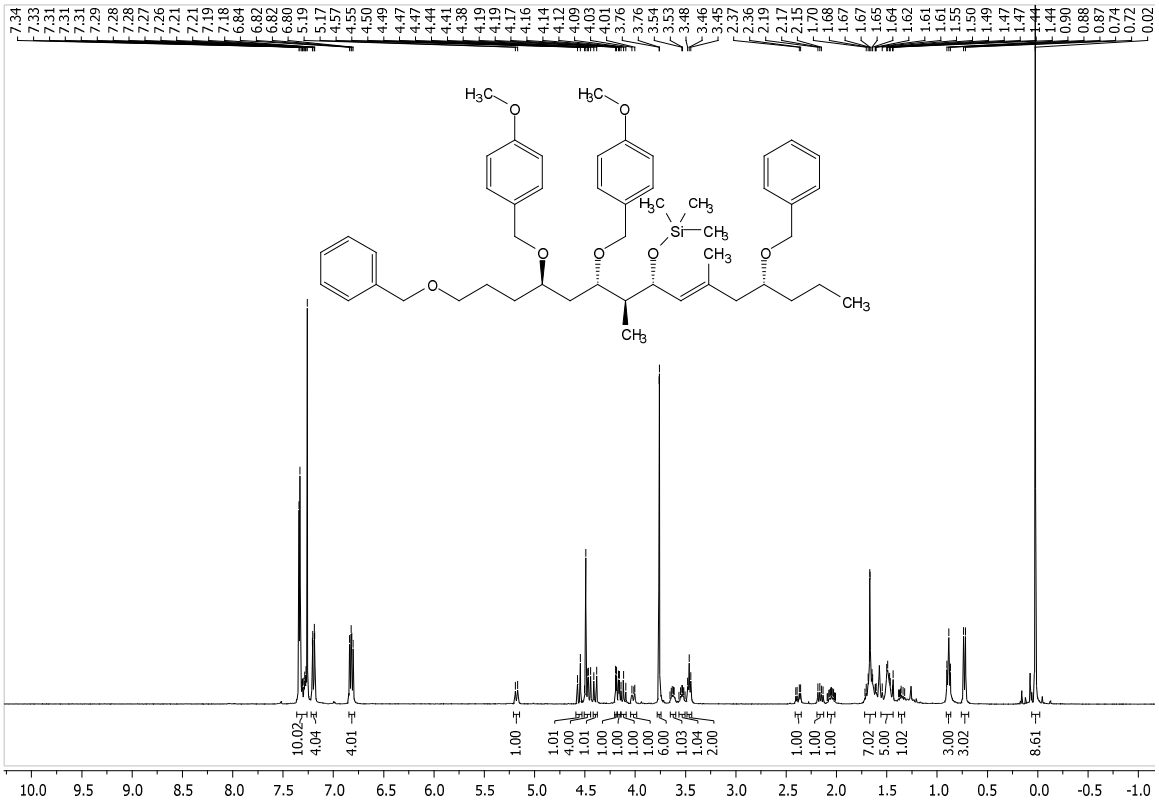
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7 (C-2), 138.7 (C-Ar), 130.9 (C-Ar), 128.4 (C-Ar), 128.4 (C-Ar), 125.9 (C-3), 67.3 (C-4), 62.1 (C-7), 39.1 (C-6), 31.7 (C-5), 21.8 (C-1).

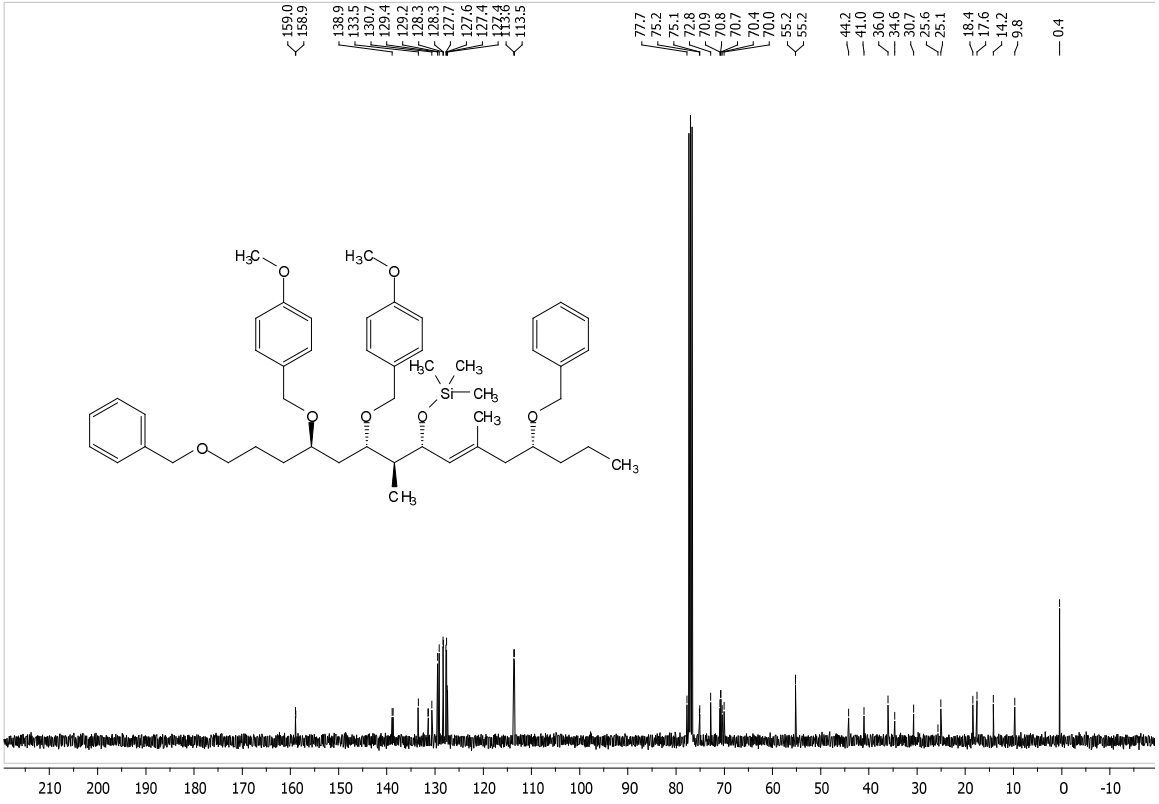
HRMS (ESI, *m/z*) calcd for $(C_{13}H_{18}OSiNa)^+$ 269.1199, found 269.1190.

IR (neat, cm^{-1}) 3024, 2920, 2851, 1724, 1601, 1493, 1454, 1373, 1261, 1072.

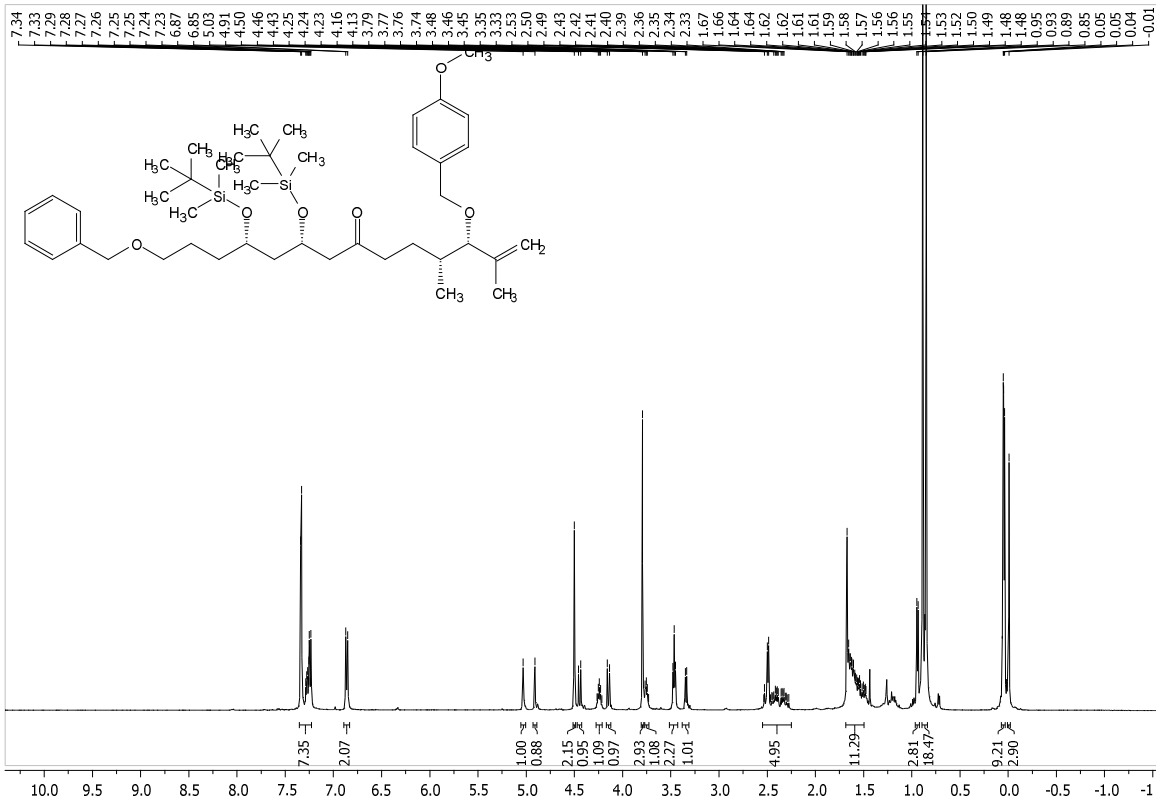
Appendices

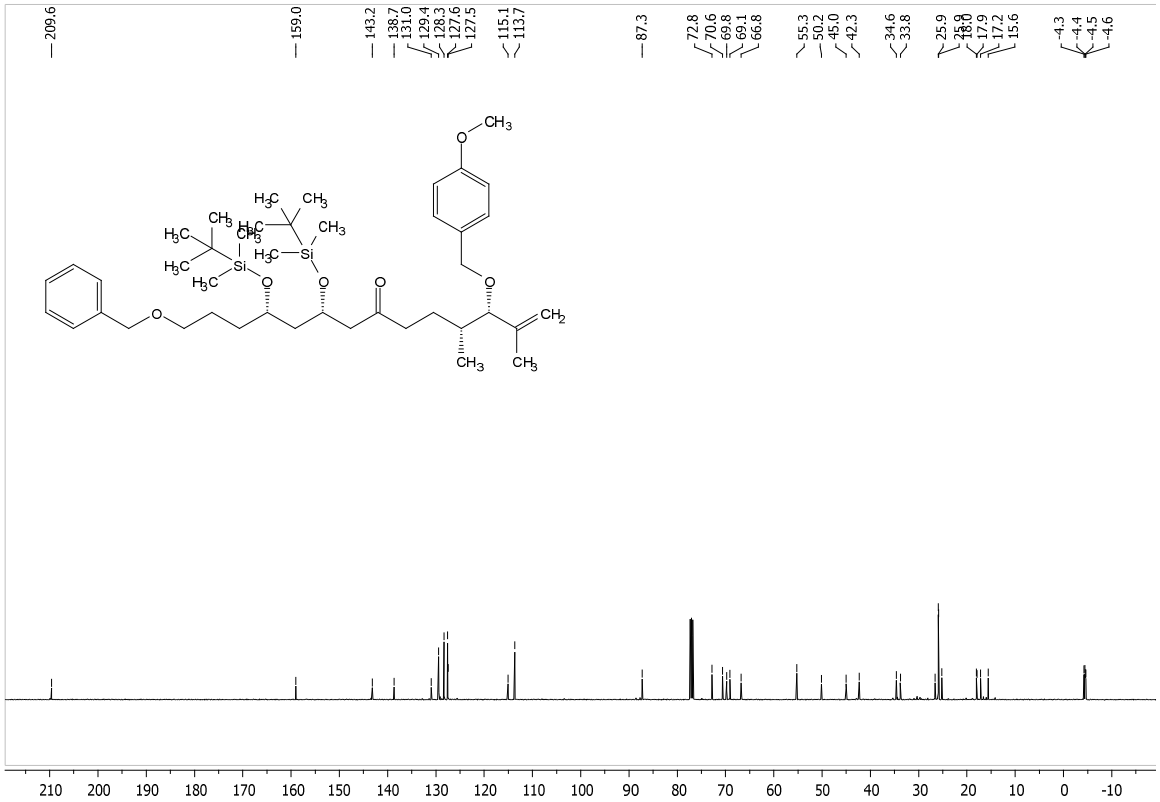
(((4*R*,8*R*,9*S*,10*S*,12*R*,*E*)-4,15-*bis*(Benzyloxy)-10,12-*bis*((4-methoxybenzyl)oxy)-6,9-dimethylpentadec-6-en-8-yl)oxy)trimethylsilane 2.65



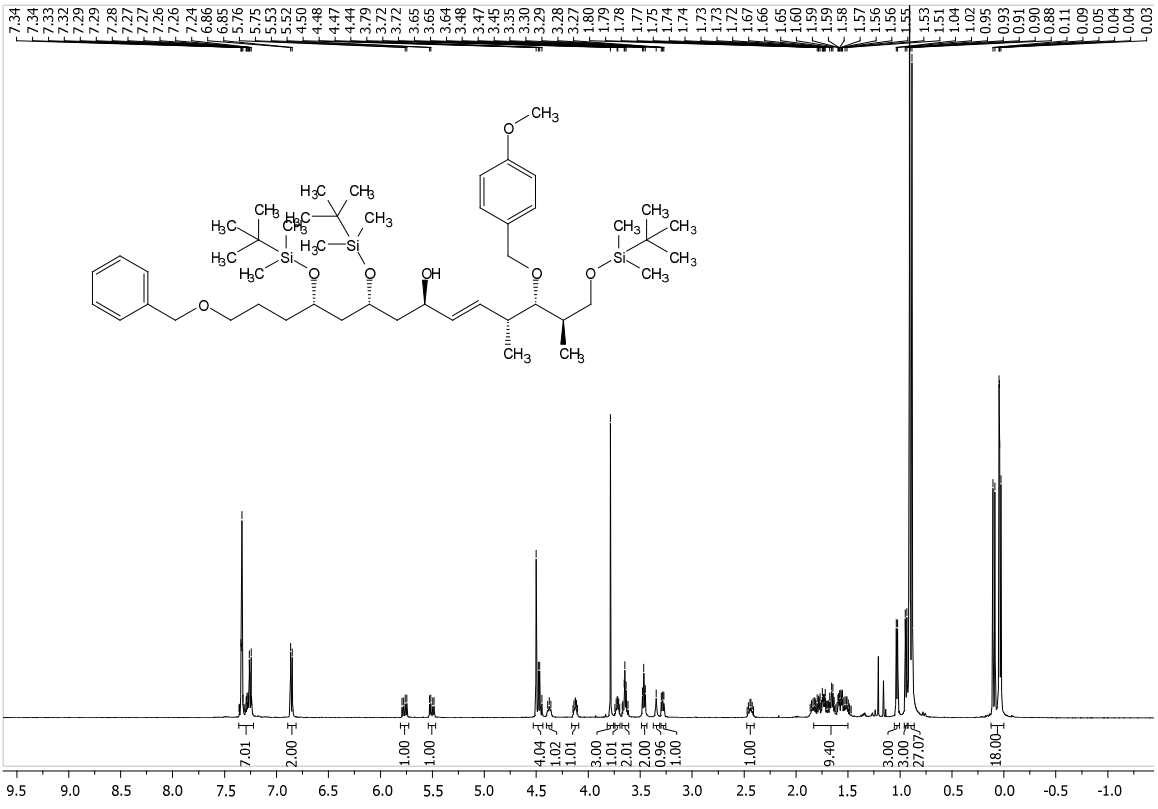


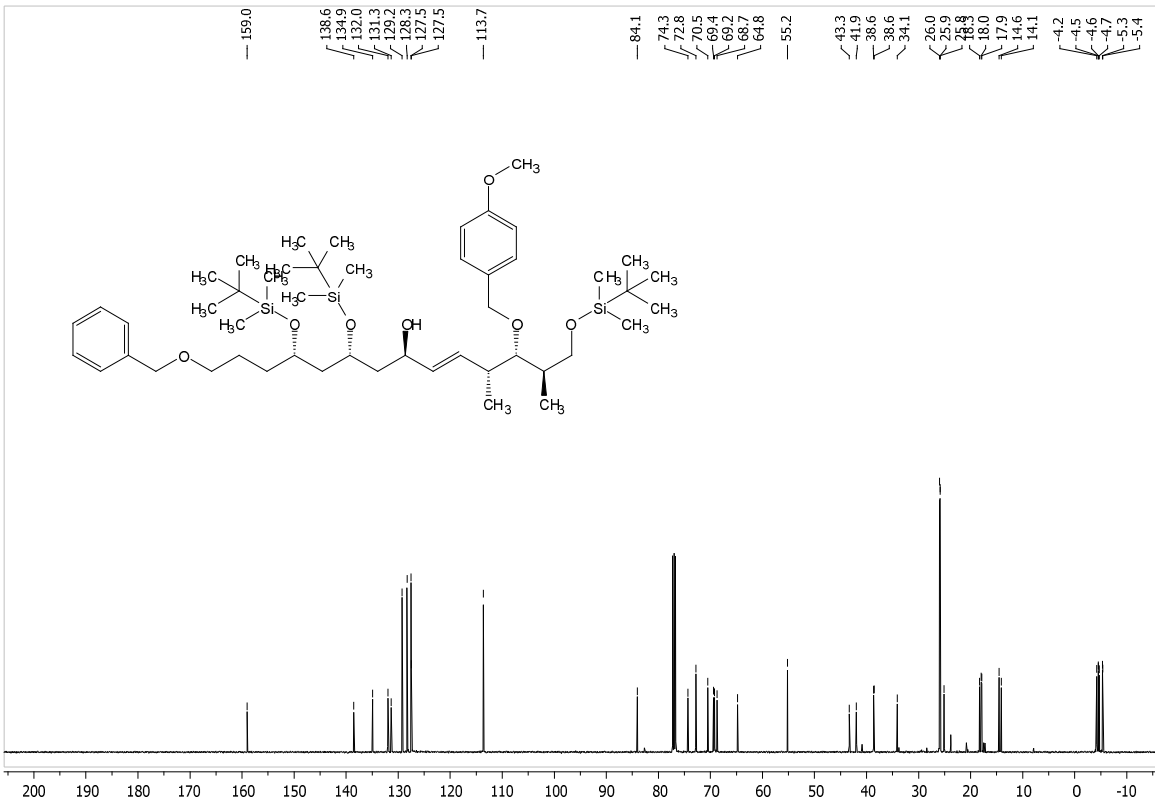
(3*S*,4*R*,9*S*,11*S*)-14-(Benzyloxy)-9,11-*bis*((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-dimethyltetradec-1-en-7-one 3.32





(5*S*,7*R*,9*R*,12*R*,13*S*,14*R*,*E*)-5-(3-(Benzyloxy)propyl)-7-((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadec-10-en-9-ol 3.66





(5*S*,7*R*,9*S*,12*R*,13*S*,14*R*)-5-(But-3-yn-1-yl)-7,9-*bis*((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,12,14,17,17,18,18-decamethyl-4,16-dioxa-3,17-disilanonadecane 3.69