Studies towards the synthesis of complex amino acids derived from microsclerodermins

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by

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For Ma and Papa

Declaration

I hereby declare that this submission is my own work and, to the best of my knowledge, it contains no materials previously published or written by another person, except where mentioned. No portion of the work referred to in this thesis been submitted in support of an application for another qualification of the University of Oxford or any other University or Institute of learning. Any contribution made to the research by others, with whom I have worked at the University of Oxford, is explicitly acknowledged in the thesis.

Akshat Rathi

Trinity 2012

Abstract

Studies towards the synthesis of complex amino acids derived from microsclerodermins

This thesis describes the studies towards the synthesis of β-amino acids found in the microsclerodermins, a family of complex macrocyclic hexapeptides. These β-amino acids have four or five contiguous stereocentres and an aliphatic side-chain. The synthetic route utilised an aminohydroxylation reaction to install the most challenging moiety in the structure - the 1,2-amino alcohol. The work aimed to construct the core structure (five contiguous stereocentres) of the β-amino acids and install the side-chain later to enable the synthesis of multiple members (A, B, F, G, H and I) of the microsclerodermin family.

The synthesis started with Roche ester, which contained the first methyl stereocentre. It was converted to the diene precursor in four high yielding steps. The next two stereocentres were installed *via* a Sharpless asymmetric dihydroxylation. With the appropriate protecting groups in place, the remaining two stereocentres were to be installed *via* a Sharpless asymmetric aminohydroxylation. Various reported reagents and conditions were used to effect the transformation, but the attempts were unsuccessful. This forced us to alter our synthetic plans, and the revised synthetic route involved the use of the tethered aminohydroxylation (TA) reaction developed by the Donohoe group. After the development of an efficient protocol to prepare the TA-precursor, the alkene, with three stereocentres already in place, was successfully converted to the desired stereopentad *via* the TA-reaction (10 steps, 11% overall yield).

With the stereopentad in hand, installation of the side-chain of the β-amino acids through an alkenyl or alkyl linkage was investigated. For alkenyl-linked side-chains, the appropriate aldehyde was synthesised, but attempts to effect the transformation *via* a Horner-Wadsworth-Emmons reaction or a Witting reaction failed. With lessons learnt from those, we then focused our efforts on installing an alkyl-linked side-chain. In this case, we were able to install a side-chain *via* a copper-mediated displacement reaction, which gave us a protected form of the precursor of the β-amino acid of microsclerodermin B. Finally, various efforts to study the reactivity of the stereopentad and the investigations into finding the most effective set of protecting groups have been used to propose a synthetic route for the incorporation of the β-amino acid into the macrocycle.

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Trinity 2012

Acknowledgements

"I don't believe in fate, my friend", a wise man once said, "But the complex chain of events that have enabled this to happen make me doubt myself sometimes."

My experience as a DPhil student hasn't been far from these words of the wise man. This thesis is a scientific record of my efforts towards a goal, and, unfortunately, it leaves unsaid a large part of what went into enabling me to reach this point. The few hundred words that will fit on this page then deserve to be dedicated to the people whose contributions have made this possible.

Foremost, I'd like to express my gratitude to my parents, whose invisible support has enabled me to set myself challenges that I could not imagine achieving. Their continuous presence in my life has helped me focus on what is important.

I'd like to thank Prof Tim Donohoe for being a wonderful supervisor, and for believing in me and my abilities. The longest conversations that we had were those when I was ready to give up on a reaction. If it wasn't for his encouragement, support and openness, this project would not have been half as complete as it is now.

Research is as much a human endeavour as it is a scientific one, and not many outside of the scientific community appreciate that. I'd like to thank the TJD group for being a great bunch to work with. Each one of you deserves a mention for multiple reasons, but as that's not possible - here's a big thank you. All through my time I remained stationed in F9, and it had some of the most fun people to work with (Mike, Alex, Ishy, Manuel, Ali, Darren, Di, Anne, Christian, Luiz and Mikhail).

A special mention to my proof-readers Dr Christian Winter, Dr Rob Pullin and Anne Kornahrens, and to Dr Adam Lacy, Dr Mikhail Kabeshov and Prof Luiz Claudio Barbosa for their support and mentoring. Also, special thanks to Amber Thompson for teaching me to use the X-ray machine, and allowing me to appreciate a whole new world of crystals.

If the Chemistry Research Laboratory was my first home (for the sheer number of hours spent), then Exeter College could be called my second home. It is not hard for me to admit that, without the friends I made at Exeter, my life in Oxford would've been half as much fun. I learnt as much outside of lab as much I did inside its four walls, and it was my friends at Exeter who were the source of much of that learning - for that another big thank you.

A special mention to Deeksha Sharma, who probably understood chemists more than I did, for her unwavering support and for those regular pushes to achieve my goals, to Alex Flint for some of the greatest conversations and for all those mini-projects that helped me learn, and to Frances Cairncross, the Rector of Exeter College, for her mentorship.

Finally, all this would not have been possible without funding from the Narotam Sekhsaria Foundation, the JN Tata Foundation, Exeter College and Tim Donohoe - for that a big thank you. Your investment has enabled me to experience some of the most fruitful years of my life.

Abbreviations

AA	asymmetric aminohydroxylation
AD	asymmetric dihydroxylation
Ac	acetyl
AETD	3-amino-10-(*p*-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid
AIBN	azobisisobutyronitrile
AMMTD	(2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-6-methyl-12-(*p*-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid
AMPTD	(2*S*,3*R*,4*S*,5*S*,6*S*,7*E*,9*E*,11*E*)-3-amino-6-methyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid
APTO	(2*S*,3*R*,4*S*,5*S*,7*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid
app.	apparent
aq.	aqueous
AQN	anthraquinone
Ar	aromatic group
BAIB	[bis(acetoxy)iodo]benzene
Boc_2O	di-*tert*-butyl dicarbonate
Bn	benzyl group
br.	broad
BTCA	benzyltrichloroacetimidate
Bu	butyl group
Bz	benzoyl
C	Celsius
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclo
DBB	4,4'-di-*tert*-butylbiphenyl
DBDM	1,3-dibromo-2,2-dimethyl (hydantoin)
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DCDM	1,3-dichloro-2,2-dimethyl (hydantoin)

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMB	dimethoxybenzyl
1,2-DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
2,2-DMP	2,2-dimethoxypropane
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
eq.	equivalents
Et	ethyl
GABOB	γ-amino-β-hydroxybutyric acid
HCT	human colon tumour
Hex	hexyl
HMBC	heteronuclear multiple-bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMRS	high resolution mass spectrometry
HPLC	high-performance liquid chromatography
Hz	hertz
i	iso
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
Im	imidazole
IR	infra-red
K	Kelvin
liq.	liquid
LDA	lithium diisopropylamide
LG	leaving group
Me	methyl

MOM	methoxymethyl ether
MP	melting point
Ms	methanesulfonyl
MS	mass spectrometry
M. S.	molecular sieves
m/z	mass-to-charge ratio
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PFP	pentafluorophenyl
PCC	pyridinium chlorochromate
Ph	phenyl
PHAL	phthalazine
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PT	5-phenyltetrazole
PTSA	*p*-toluenesulfonic acid
Py	pyridine
R	generic alkyl group
ROESY	rotating-frame nOe spectroscopy
rsm	recovered starting material
Su	succinimide
t	tertiary
TA	tethered aminohydroxylation
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl
TMSI	trimethylsilyl iodide
TPAP	tetrapropylammonium perruthenate
Ts	tosyl
wt.	weight

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Chapter 1

The microsclerodermin family

Chapter 1

1.1 General Introduction

Isolated from marine sponges, the microsclerodermins are biologically active and structurally complex natural products. The β-amino acids found in microsclerodermins are the most complex of the six amino acids that constitute any microsclerodermin. They contain four or five contiguous stereocentres and an unsaturated side chain terminating in an aromatic ring. This thesis concerns efforts towards the synthesis of these β-amino acids. The challenge of synthesising such a complex structure and the potential of this work to generate new methodologies for organic synthesis has drawn the attention of many synthetic chemists. Despite the similarity of the core stereocentre sequence amongst the series, general methods for preparing these amino acids are lacking. This thesis contains studies aimed at developing a novel route in a bid to build the β-amino acids for any of the nine members of the microsclerodermin family.

Section 1.2 will provide a general overview of microsclerodermins and related natural products, focussing on their occurrence in nature, biological activity, and structural complexities. Section 1.3 will look at previous syntheses of microsclerodermins with particular attention paid to work done on the β-amino acid residues.

1.2 The microsclerodermin family

1.2.1 Introduction

Sponges of the order *Lithistida* produce some of the most bioactive and complex marine natural products known,[1] including discodermolide,[2] theonellamide[3] and swinholide A,[4] all of which have attracted the attention of synthetic organic chemists. One such family of natural products

produced by *Lithistida* sponge are the microsclerodermins, isolated by D. John Faulkner and co-workers of the Scripps Institution of Oceanography, USA, between 1994 and 2000 (Figure 1).

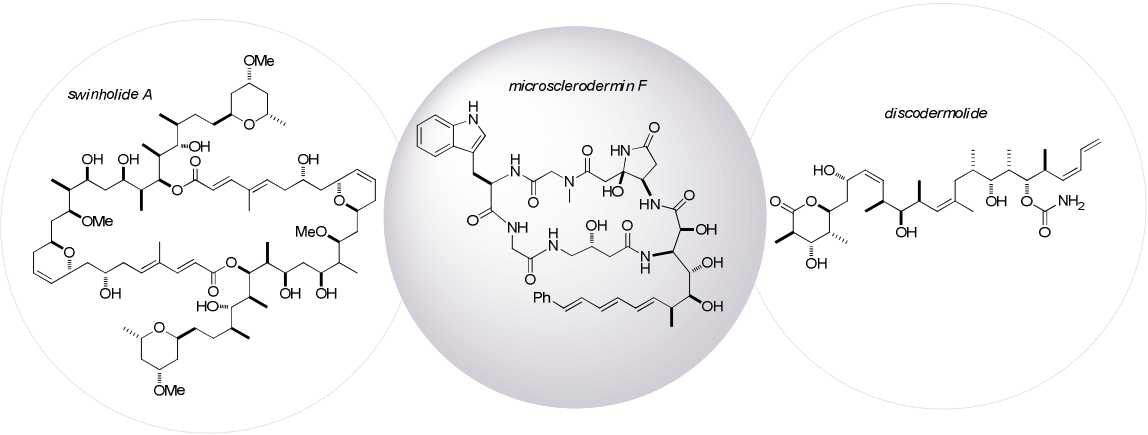


Figure 1: Select natural products isolated from sponges of the order Lithistida

The microsclerodermin family is comprised of nine cyclic hexapeptides, microsclerodermin A through I. Microsclerodermins A and B were isolated from a specimen of *Microscleroderma* sponge found in New Caledonia.[5] Microsclerodermins C-E were isolated from sponge species found in the Philippines - *Theonella cupola* contained microsclerodermins C and D[6] and *Microscleroderma* sponge contained microsclerodermins D and E.[6] Microsclerodermins F-I were isolated from a deep-water specimen of *Microscleroderma* sponge found in Palau.[7] Some members of the microsclerodermins family were also recently isolated from sponges in the related *Lithistida* genus *Amphibleptula* and from the family *Pachastrellidae*.[8]

The biological production of the microsclerodermins is not yet completely understood as *Lithistida* sponges often harbour a large number of symbiotic organisms. Faulkner speculated that microsclerodermins may be produced by these symbiotic bacteria, and isolated structurally-related theopalauamide (Figure 2) from symbiotic bacteria in *Theonella* sponges.[9]

In 2008, his theory received further support when pedein A and B (Figure 2) were isolated from self-sustaining bacteria called myxobacteria.[10] Only small quantities of microsclerodermins have ever been isolated (0.001-0.190% dry weight). Consequently, investigations into the association between sponges and their bacterial flora have been hampered.

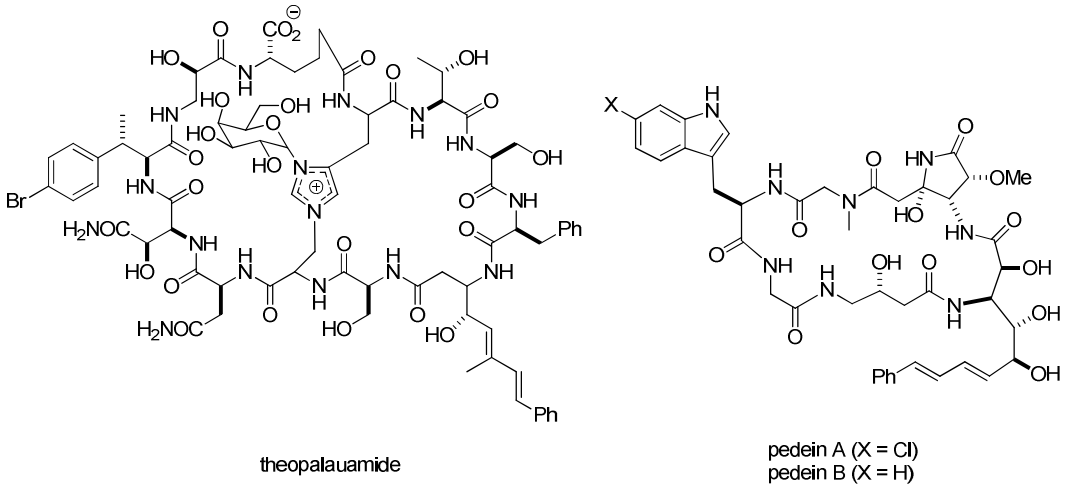


Figure 2: Natural products resembling microsclerodermins derived from bacteria

The biological activity of the family has been tested, and it has produced promising leads. Microsclerodermins F-I were tested for cytotoxicity against the human colorectal carcinoma cell line HCT-116 and were found to have low IC_{50} values ranging from 1.0 to 2.4 μg per mL. The entire family displays potent anti-fungal activity with microsclerodermin F being the most active against *Candida albicans* at 1.5 μg per paper disk assay,[5] followed by microsclerodermins A and B at 2.5 μg per paper disk assay.[7] An ever-increasing resistance to standard 'azole' antifungal drugs, such as itrazole and fluconazole,[11] has powered the search for novel anti-fungal treatments. This has led to the discovery that several complex cyclic peptides possess potent fungicidal properties, amongst which are the microsclerodermins. However, further investigation into their promising biological activities has been affected by their relative scarcity.

1.2.2 General structure of the microsclerodermins

All nine members of the family share the same core structure - a 23-membered cyclic hexapeptide. The six constituent amino acids are a tryptophan derivative, a glycine fragment, a γ-hydroxy-γ-lactam residue, a sarcosine fragment, the γ-amino-β-hydroxybutanoic acid (GABOB), and a chiral polyhydroxylated β-amino acid with an aliphatic chain (Figure 3).

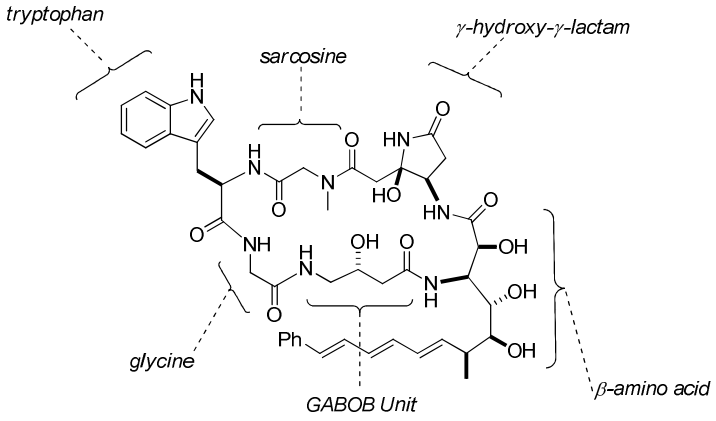


Figure 3: The constituent amino acids of microsclerodermin F

1.2.3 Microsclerodermins A-D

Microsclerodermins A (**1**) and B (**2**) share a tryptophan-2-carboxylic acid residue and a polyhydroxylated β-amino acid. The β-amino acid has an additional methyl group branching from C-6 and terminates with a *para*-methoxy-*trans*-styrene moiety. Microsclerodermins A and B differ only in the substitution about the γ-hydroxy-γ-lactam unit, where microsclerodermin A has an extra hydroxyl group adjacent to the carbonyl at C-46 (Figure 4). Microsclerodermins C (**3**) and D (**4**) are similar to **2** but they share a different polyhydroxylated β-amino acid that terminates in a *trans*-styrene moiety (known as APTO). Moreover, their tryptophan units both lack the carboxylic acid group, which is instead chlorinated at the 6' position, and the nitrogen of the indole of microsclerodermin C forms part of a urea group. They also have the opposite *syn* stereochemistry on the γ-hydroxy-γ-lactam unit (Figure 4).

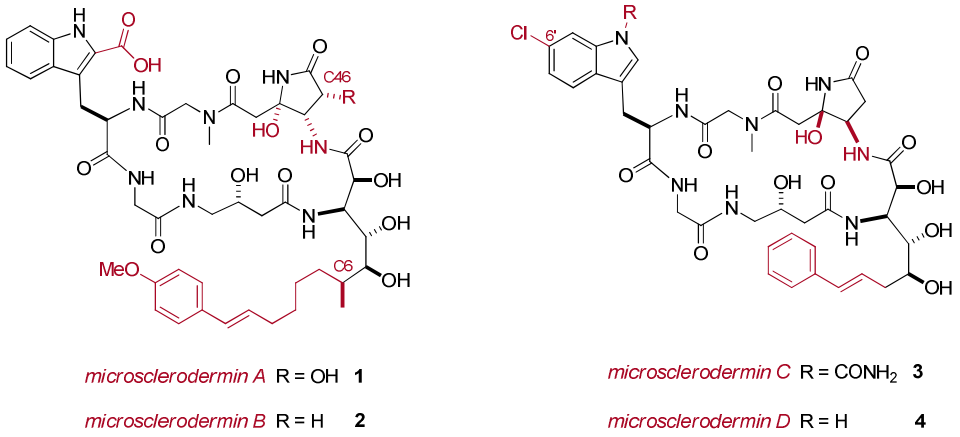


Figure 4: Microsclerodermins A-D

1.2.4 Microsclerodermin E

Microsclerodermin E (**5**) shares the tryptophan-2-carboxylic acid residue found in microsclerodermins A and B (Figure 5), but its polyhydroxylated β-amino acid terminates with a diene conjugated to a *para*-ethoxy phenyl group (known as AETD). Intriguingly, **5** is the only member of the microsclerodermin family to be isolated as a dehydromicrosclerodermin, with an α,β-unsaturated amide instead of the γ-hydroxy-γ-lactam functionality. Faulkner was confident that dehydration did not occur during isolation and subsequent separation because key signals identifying the dehydrated form were present in the NMR spectra of the crude peptide mixtures before treatment with acid or base. Furthermore, microsclerodermin E was isolated after HPLC separation from a mixture also containing microsclerodermin D.

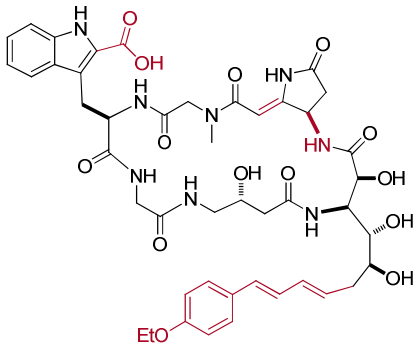


Figure 5: Microsclerodermin E

1.2.5 Microsclerodermins F-I

Microsclerodermins F (**6**) and G (**7**) have a β-amino acid with a methyl group at C-6 that terminates with a triene conjugated to a phenyl group (known as AMPTD). Microsclerodermin F features an unsubstituted tryptophan while microsclerodermin G has the corresponding 2,3-dehydrotryptophan (Figure 6). Microsclerodermins H (**8**) and I (**9**) are identical to F and G, respectively, with the addition of a methyl group at C-10 of the polyene.

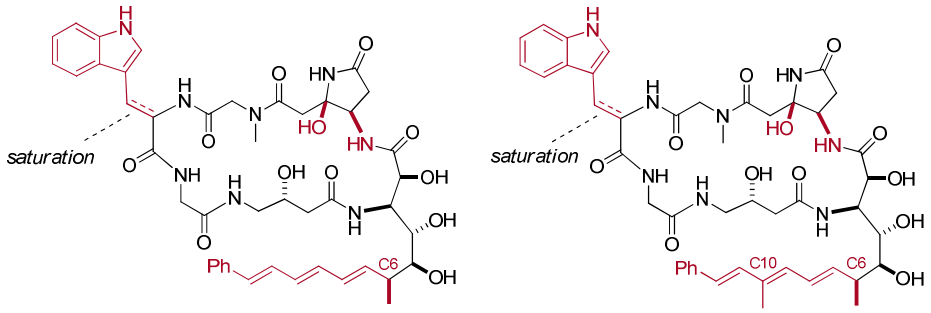


Figure 6: Microsclerodermins F-I

1.2.6 Points of note on isolation and structure

Some general points to note about the isolation and structure of the microsclerodermins are as follows:

- Less than 30 mg of each microsclerodermin have been isolated from collected sponge samples, except for microsclerodermin C (73 mg).
- The freeze-dried sponge samples were extracted multiple times with organic and aqueous solvents and the residues thus obtained were further purified by reversed-phase column chromatography and HPLC to yield the microsclerodermins.
- All of the microsclerodermins, apart from microsclerodermin E (**5**), readily lose one molecule of water, to form the corresponding dehydromicrosclerodermin. Treating microsclerodermins under dehydrating conditions, such as treatment with TFA, will effect this loss of water from the γ-hydroxy-γ-lactam unit.
- The relative *syn* stereochemistry of the γ-hydroxy-γ-lactam of the microsclerodermins was established using ROESY data, specifically a correlation between the H-2 and H-4 protons, thus requiring OH and NH to be on the same face of the pyrrolidinone ring (Figure 7).

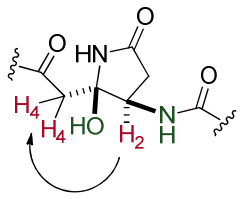


Figure 7: *Key ROESY correlation establishing a syn relationship*

1.3 Synthesis of microsclerodermins

The only total synthesis of a microsclerodermin to date was reported by Dawei Ma,[12] but the microsclerodermins' structural complexity and biological activity has attracted the work of a number of other synthetic chemists. This work is reviewed here, with focus placed on the synthesis of the β-amino acid units (Figure 8). In this section, the first four syntheses are those of the β-amino acid residues with 4 stereogenic centres (*viz*. APTO and AETD) and the remaining three syntheses are those of the β-amino acid residues with 5 stereogenic centres (*viz*. AMMTD and AMPTD).

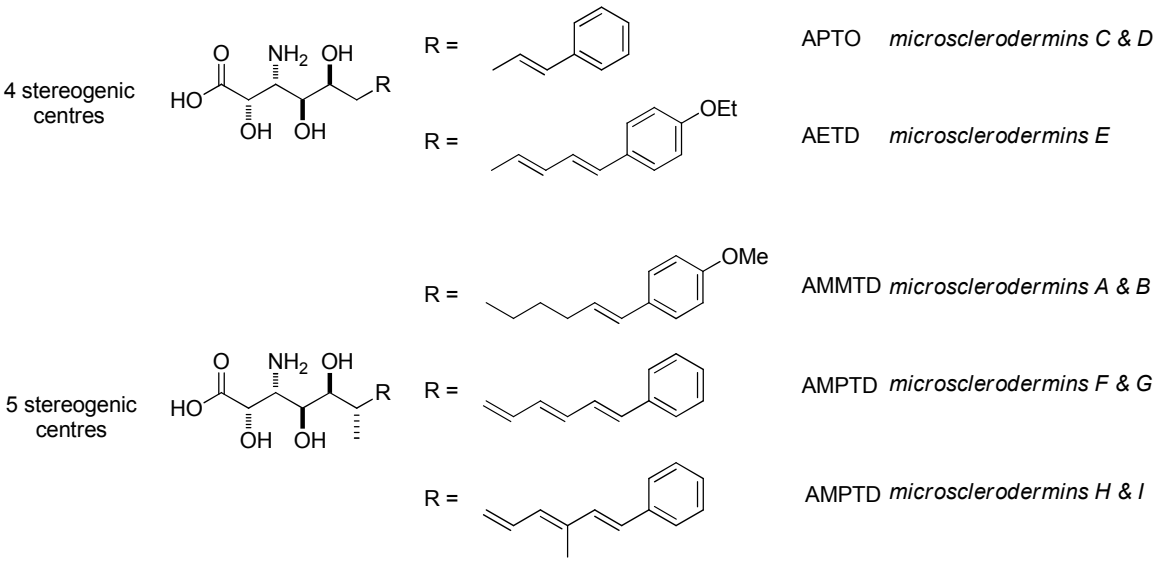
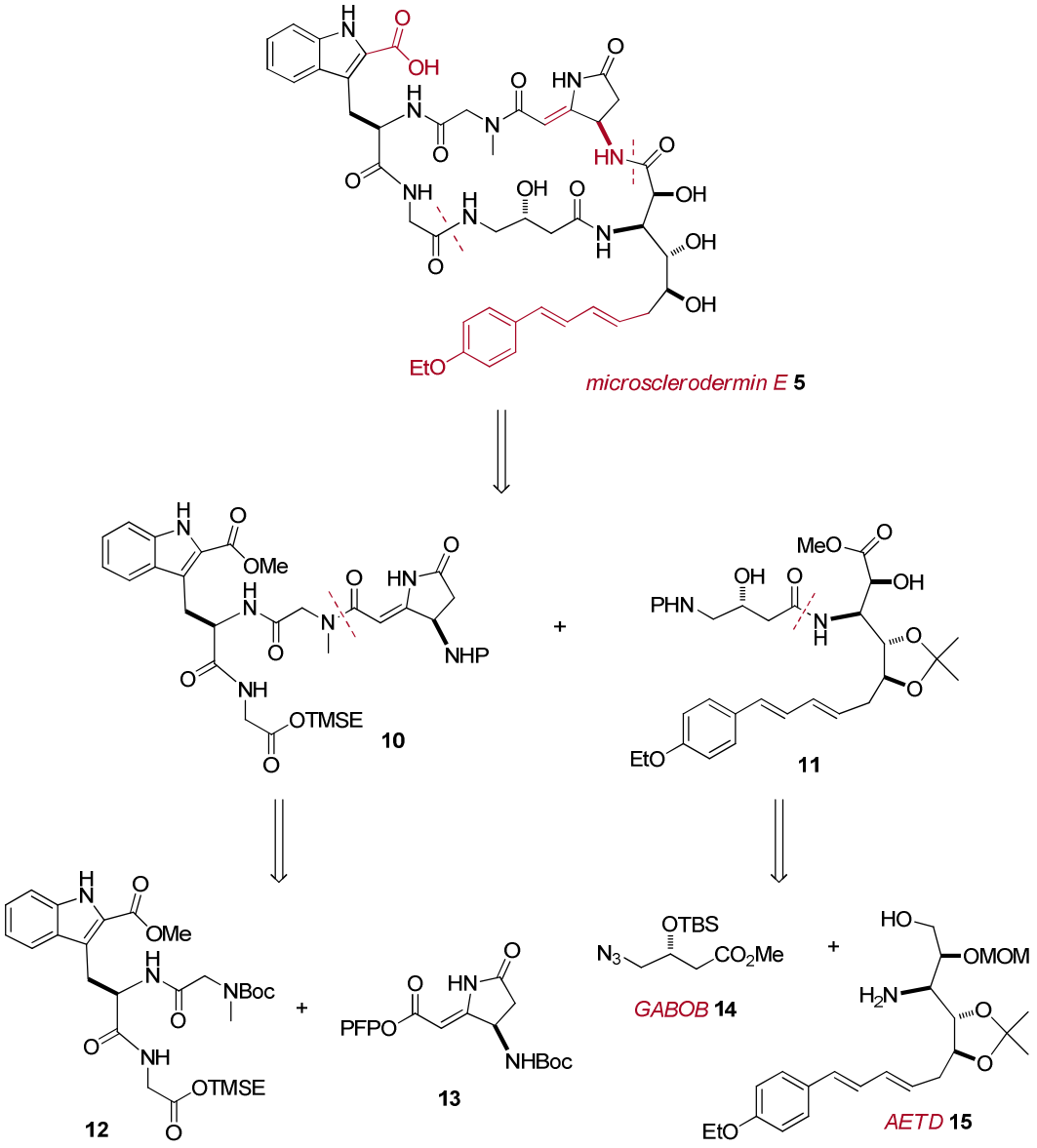


Figure 8: Structures of the β-amino acid residues of microsclerodermins

1.3.1 Ma's total synthesis of microsclerodermin E

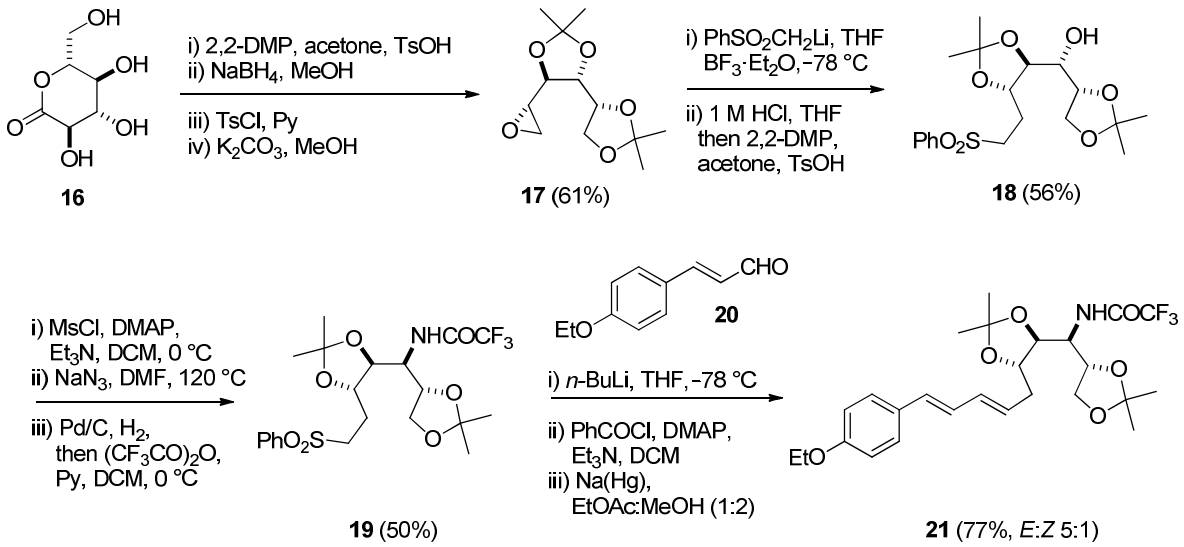
Dawei Ma and a co-worker at the Shanghai Institute of Organic Chemistry, China reported an asymmetric total synthesis of microsclerodermin E, the simplest member of the family, lacking the hemiaminal and the methyl group in the β-amino acid (see Figure 5).[12] In the initial retrosynthetic disconnection the macrocycle was split into a tetrapeptide **10** and a dipeptide **11** (Scheme 1). Further disconnections of the dipeptide led to the GABOB unit **14** and polyhydroxylated compound **15**, known as the AETD fragment. The tetrapeptide was disconnected into tripeptide **12** and pyrrolidinone **13**.



Scheme 1: Ma's retrosynthesis of microsclerodermin E

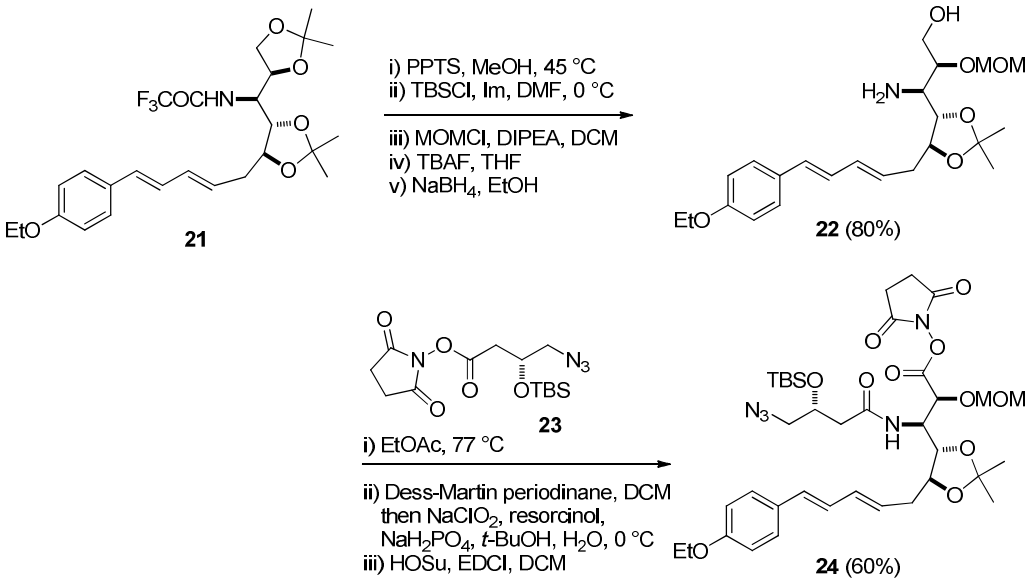
Ma began the synthesis of AETD from δ-gluconolactone (**16**), which contains all four stereocentres (Scheme 2). Compound **16** was doubly acetonide protected, and it was then reduced to a diol. Tosylation of the primary alcohol and treatment with base gave epoxide **17**. It was then opened with the lithium salt of methylphenyl sulfone and the acetonide groups were removed and re-installed to form **18**. Mesylation of the hydroxyl group and displacement with azide followed, consequent azide reduction and treatment with trifluoroacetic anhydride

afforded amide **19**. With all the stereocentres in place, Julia olefination with aldehyde **20** installed the diene side chain to give **21** as a 5:1 separable mixture of alkene isomers.



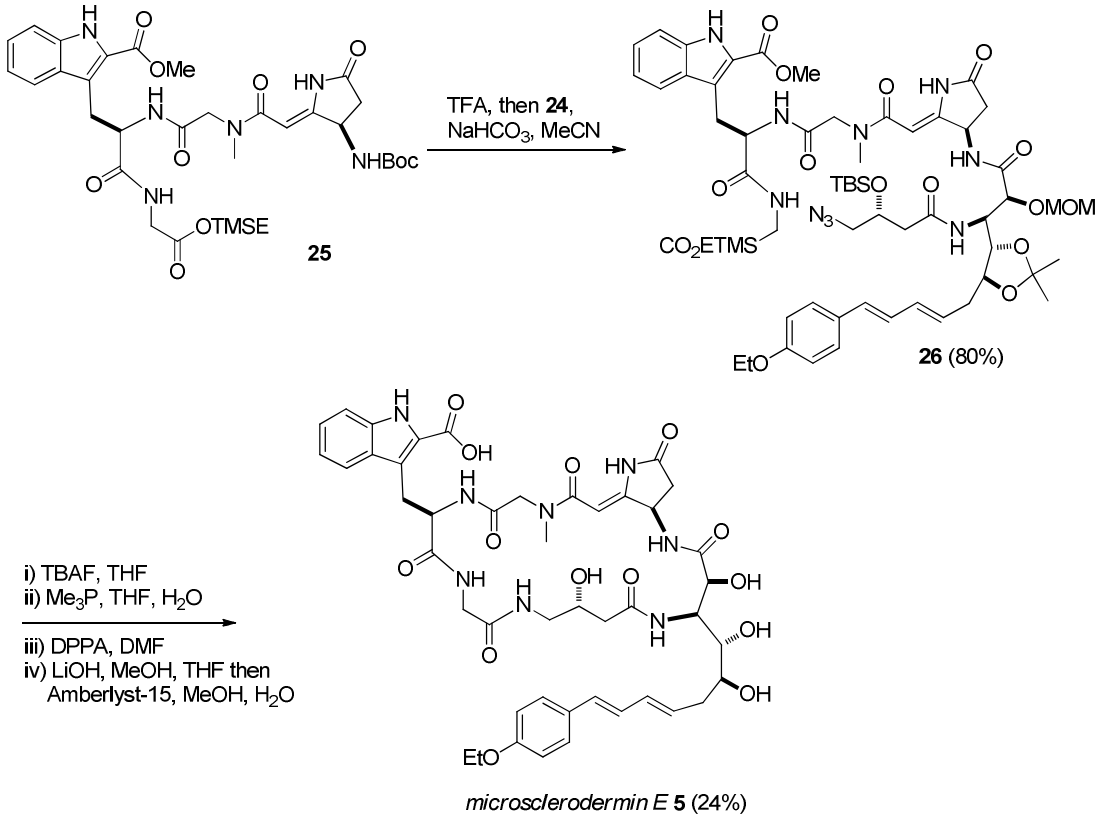
Scheme 2: Ma's synthesis of protected form of AETD

Selective removal of the terminal acetonide and TBS protection of the primary alcohol allowed MOM protection of the secondary diol (Scheme 3). Removal of the TBS group and reductive cleavage of the trifluoroacetate gave amino alcohol **22**. It was then coupled with the activated GABOB derivative **23** to give compound **24**, followed by which the primary alcohol was oxidised and treated with N-hydroxysuccinimide to prepare an activated ester **24** for further coupling.



Scheme 3: Ma's synthesis of compound 24

To prepare the linear hexapeptide precursor **26**, the Boc group of compound **25** was removed, and it was treated with the activated compound **24** (Scheme 4).

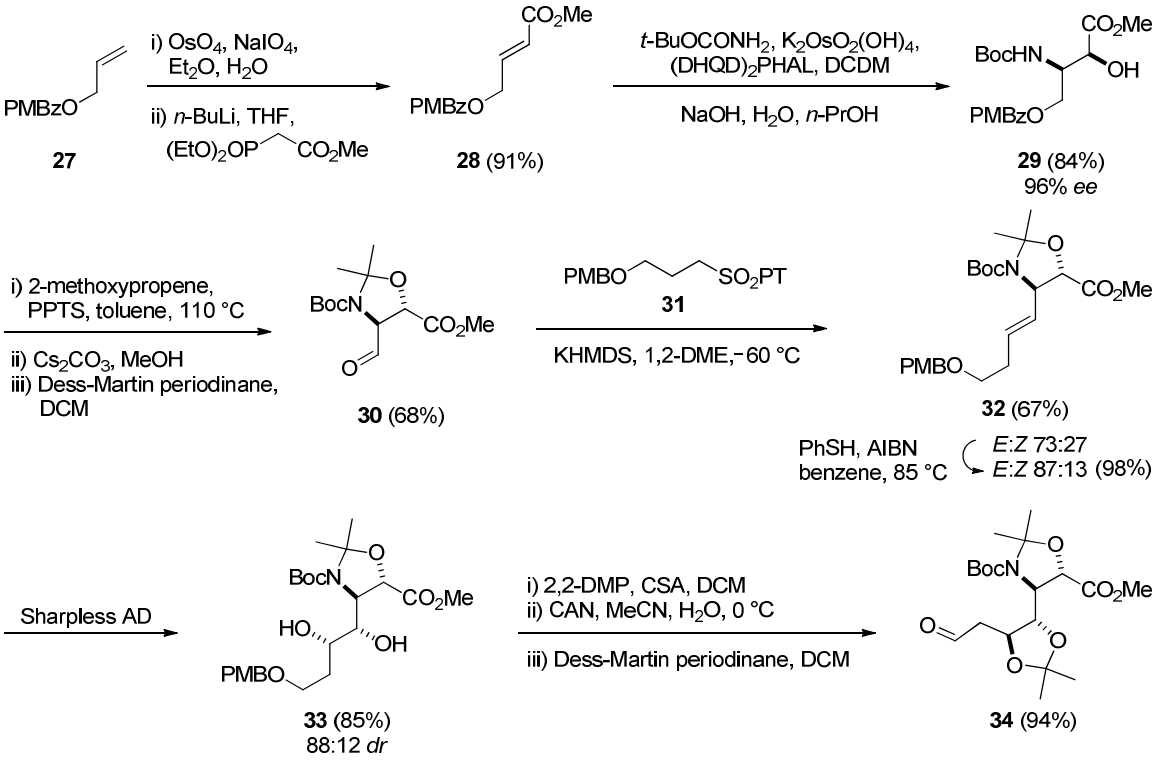


Scheme 4: Ma's synthesis of hexapeptide 26 and macrocyclization

Treatment with TBAF removed both the TMSE ester and the TBS group, and Staudinger reduction of the azide gave an amino acid (Scheme 4). Macrocyclization with DPPA in DMF required two weeks to achieve a yield of 40% of desired product over three steps with 9% of separable isomer, which resulted from the partial racemization during assembly of the pyrrolidinone fragment. Finally, hydrolysis of the indole ester and removal of the acid-sensitive protecting groups with mildly acidic resin gave microsclerodermin E (**5**) in 1% yield over 26 linear steps.

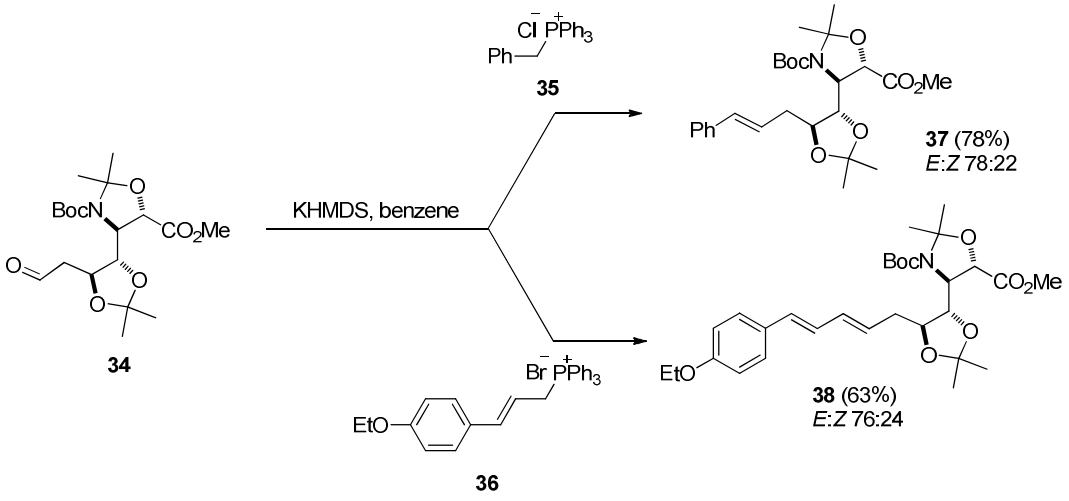
1.3.2 McLeod's synthesis of APTO and AETD

Malcolm McLeod and co-workers at the University of Sydney, Australia completed asymmetric syntheses of the protected forms of the β-amino acids APTO from microsclerodermins C (**3**) and D (**4**) and AETD from microsclerodermin E (**5**).[13]



Scheme 5: McLeod's synthesis of APTO and AETD core

One-pot dihydroxylation and periodate cleavage of allyl 4-methoxybenzoate (**27**) allowed olefination of the resultant aldehyde *via* the Horner-Wadsworth-Emmons reaction to give α,β-unsaturated ester **28** as a separable mixture of diastereomers (Scheme 5). Using the aromatic benzoate as a directing group, the Sharpless asymmetric aminohydroxylation of the alkene with 1,3-dichloro-5,5-dimethylhydantoin (DCDM) as the reoxidant gave the β-amino alcohol **29** as a single regioisomer in good yield and enantioselectivity. Formation of the *N,O*-acetonide and removal of the benzoate with mild base allowed Dess-Martin oxidation of the resulting alcohol to the aldehyde **30**. Modified Julia olefination with **31** gave alkene **32** as a mixture of isomers, with the *E* alkene as majority. Further treatment with phenylthiol radical isomerized some of the undesired *Z* alkene to the desired *E* alkene over 10 days. Sharpless asymmetric dihydroxylation gave diol **33** as an inseparable mixture of diastereomers, which were carried through and separated at the conclusion of the synthesis. Formation of the acetonide and oxidative removal of the PMB group allowed oxidation to the key aldehyde **34**.

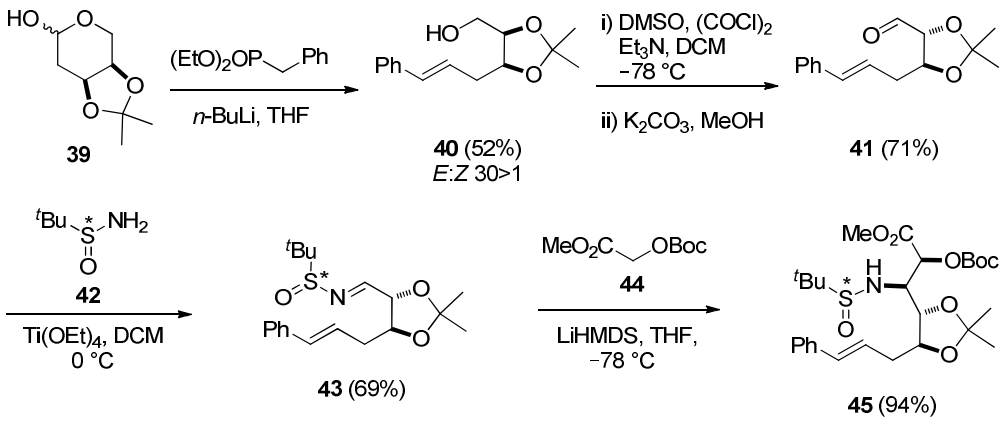


Scheme 6: McLeod's synthesis of protected form of APTO and AETD

Aldehyde **34** provided a common intermediate for the completion of AETD and APTO derivatives (Scheme 6). Wittig reaction with benzyltriphenylphosphonium chloride **35** and KHMDS gave APTO derivative **37** in an overall yield of 12% over 13 steps, while the conjugated phosphonium bromide **36** gave AETD derivative **38** in 9% yield over 13 steps.

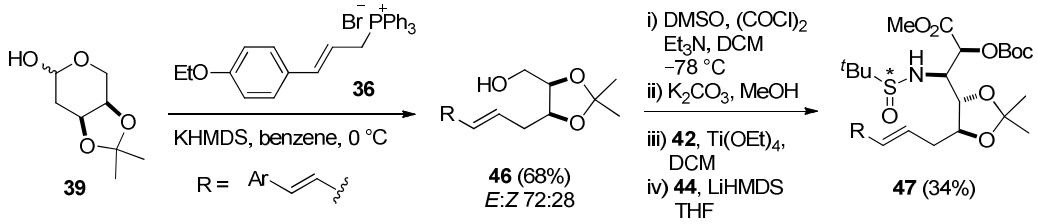
1.3.3 Aitken's synthesis of APTO and AETD

David Aitken and co-workers at the University of Paris-sud, France completed concise syntheses of protected forms of APTO from microsclerodermins C (**3**) and D (**4**) and AETD from microsclerodermin E (**5**).[14] Starting with commercially available 2-deoxy-D-ribose acetonide (**39**), homologation was achieved *via* the Horner-Wadsworth-Emmons reaction to give alkene **40** (Scheme 7).



Scheme 7: Aitken's synthesis of protected form of APTO

Swern oxidation followed by treatment with base, allowed complete epimerization of the adjacent carbinol to give aldehyde **41**. Condensation with (*S*)-*tert*-butylsulfinamide (**42**) gave sulfinimine **43**. Reaction with the enolate of *O*-Boc methyl glycolate (**44**) gave protected APTO **45** as a single diastereomer in 23% yield over five steps.

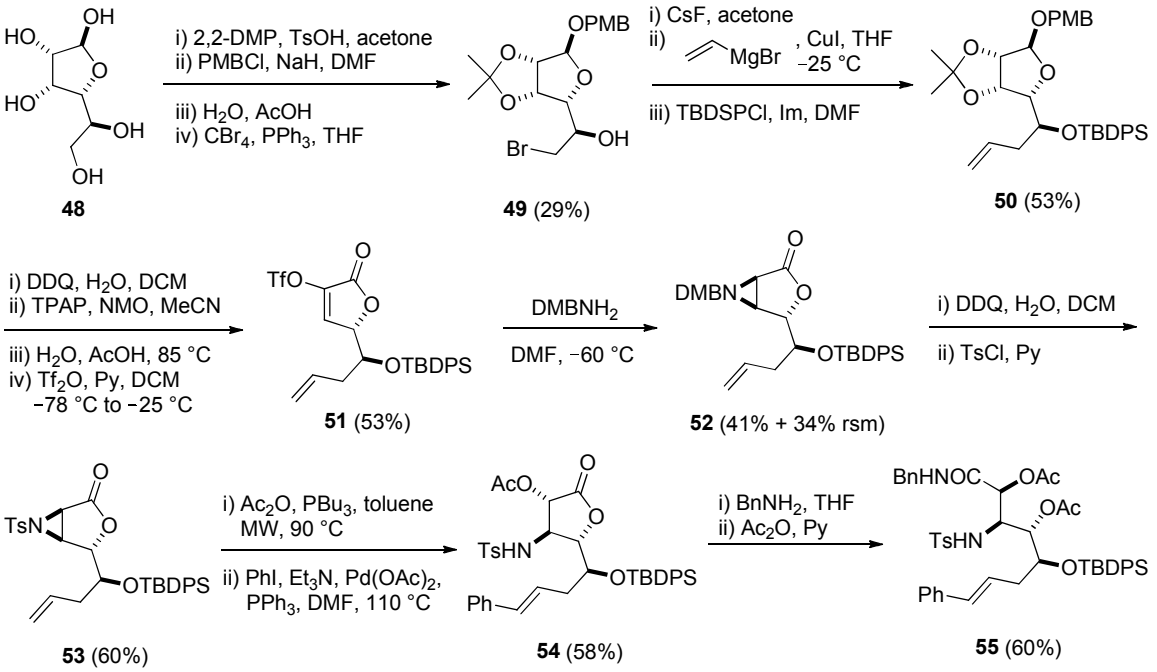


Scheme 8: Aitken's synthesis of protected form of AETD

After failed attempts to optimize the olefination reaction, Aitken was forced to use McLeod's conditions for installation of the AETD diene side chain. Reaction of **39** with phosphonium salt **36** gave the diene **46** as a separable mixture of diastereomers (Scheme 8). After separation, the alcohol was oxidized and epimerized as before. Condensation with **42** gave sulfinimine, which on reaction with the enolate of **44**, gave **47** as a single diastereomer in 16% yield over five steps.

1.3.4 Dauban and Dodd's synthesis of APTO

The group of Philippe Dauban and Robert Dodd from CNRS, France reported the synthesis of protected APTO *via* their aziridino-γ-lactone methodology.[15] Conversion of L-gulose (**48**) to its diacetonide and protection of the remaining free hydroxyl group as a PMB ether was followed by selective removal of one acetonide to give a diol, which was converted to the terminal bromide **49** (Scheme 9). Treatment with base converted the bromide to an epoxide, which was subsequently opened with vinyl cuprate. TBDPS protection of the alcohol afforded **50**.

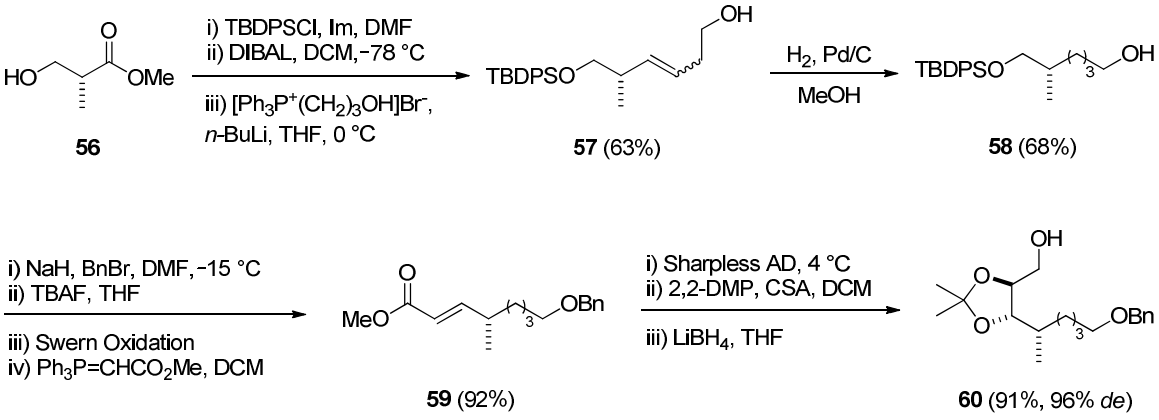


Scheme 9: Dauban and Dodd's synthesis of protected form of APTO

Oxidative cleavage of the PMB ether and subsequent Ley oxidation yielded a lactone. Treatment with triflic anhydride and pyridine gave the mono triflate **51** resulting from elimination of the triflate beta to the carbonyl. Treatment with dimethoxybenzylamine gave protected key aziridine **52**. The benzyl group was removed oxidatively and the amine reprotected with the electron-withdrawing tosyl group to give **53**. Opening of the activated aziridine with tri-*n*-butylphosphine and acetic anhydride[16] under microwave conditions gave the fully protected lactone containing all the stereocentres of APTO (Scheme 9). Heck coupling with iodobenzene gave the conjugated aromatic alkene **54**. Treatment with benzylamine opened the lactone to yield the secondary amide as a mixture of monoacetates (which occurred due to the migration of the acetate group in this step), and acetylation of the mixture gave the diacetate **55** in 0.43% yield over 16 steps.

1.3.5 Shioiri's studies towards microsclerodermin B

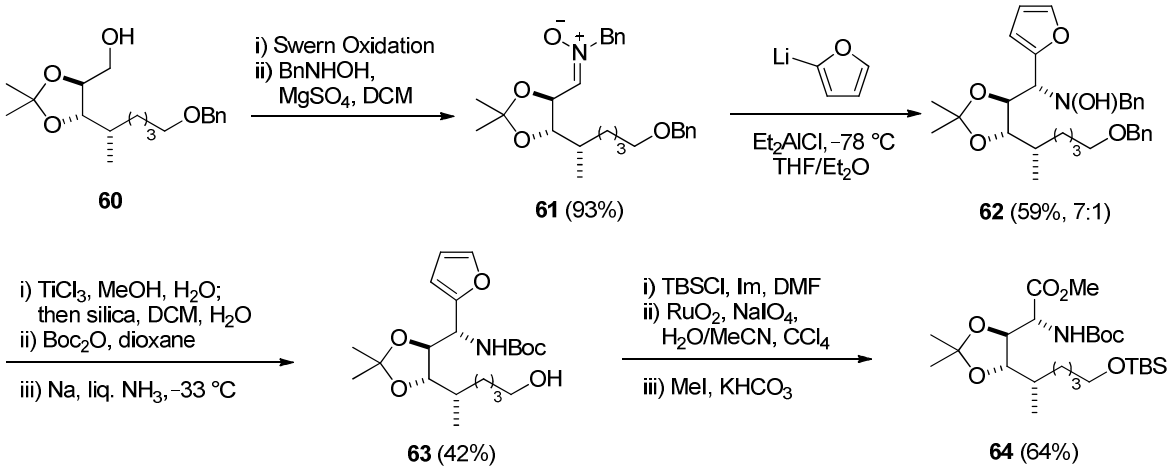
Takayuki Shioiri and co-workers at Nagoya City University, Japan have reported studies towards the synthesis of microsclerodermin B (**2**) culminating in the synthesis of protected forms of the β-amino acid, GABOB unit and the γ-hydroxy-γ-lactam precursor. Their route starts with the modification of commercially available (*R*)-Roche ester **56**, which contains the C6 methyl stereocentre already set up for the carbon framework of the side chain (Scheme 10).[17] Partial reduction of TBDPS protected Roche ester gave an aldehyde, which under Wittig conditions yielded alkene **57**. Hydrogenation of the double bond gave **58**. Benzylation of the primary alcohol was followed by removal of the TBDPS protecting group, allowing oxidation to the aldehyde and subsequent Wittig reaction to yield α,β-unsaturated ester **59**. A Sharpless asymmetric dihydroxylation reaction was used to set two more stereocentres (96% *de*) and acetonide protection of the diol allowed ester reduction to alcohol **60**.



Scheme 10: Shioiri's efforts towards the synthesis of AMMTD

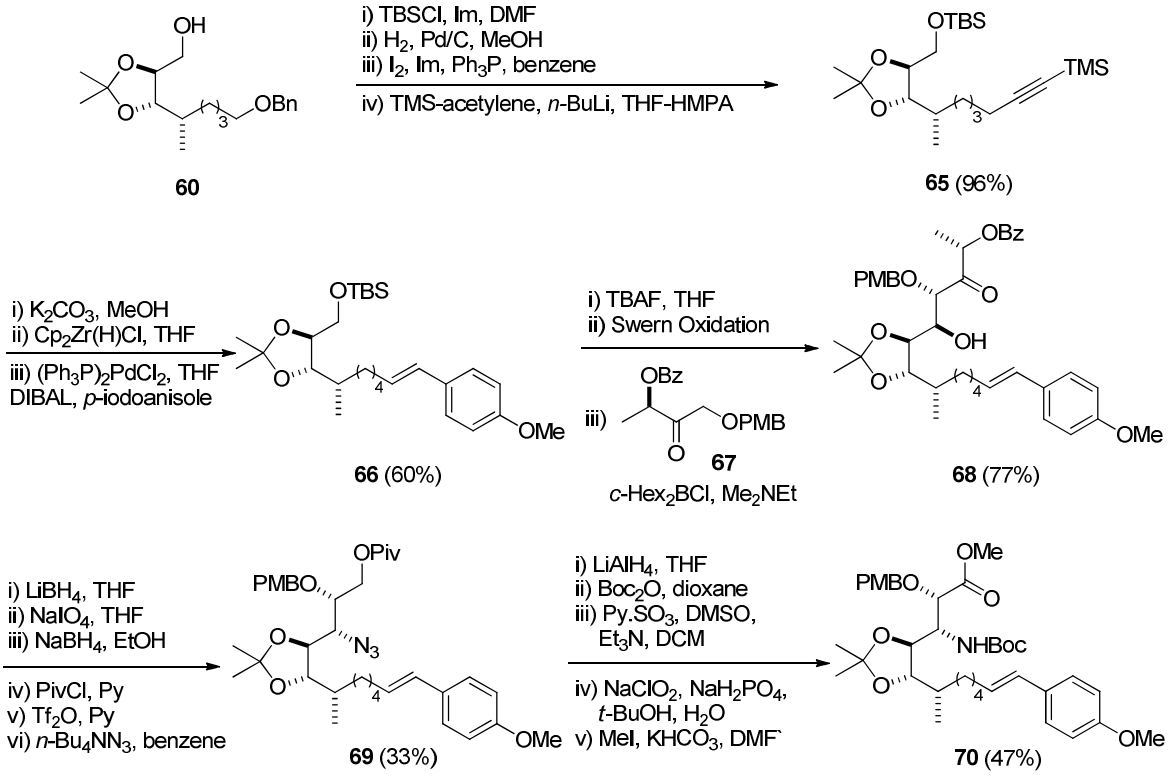
The next stereogenic centre was introduced using methodology developed by the Dondoni group.[18] Oxidation to the aldehyde and subsequent condensation with *N*-benzylhydroxylamine gave nitrone **61**, to which 2-furyllithium was added to give a mixture of adducts as an inseparable diastereomeric mixture (7:1) in favour of desired isomer **62** (Scheme 11). A one-

pot *N*-debenzylation and *N*-dehydroxylation was achieved by treatment with titanium trichloride and silica to give the amine, which was then Boc protected. Removal of the *O*-benzyl group *via* the Birch reaction and separation of diastereomers by chromatography gave **63**. TBS protection of the primary alcohol allowed cleavage of the furan to give the carboxylic acid, which on esterification completed the synthesis of **64** in 5.3% yield over 20 steps.



Scheme 11: Shioiri's attempts to install the nitrogen stereocentre of AMMTD

Fragment **64** however, lacks one stereocentre next to the protected amine, and additionally also lacks the phenylalkene side chain for the synthesis of the β-amino acid unit (compare **2** in Figure 4). Shioiri and co-workers then reported another route starting from **60** (derived from **59** in Scheme 10) to prepare the appropriately protected β-amino acid unit known as AMMTD (Scheme 12).[19] TBS protection of **60**, removal of the benzyl group, conversion to the iodide, and subsequent displacement with lithium TMS-acetylide gave **65**. Treatment with potassium carbonate led to the removal of the TMS group giving an alkyne, and subsequent hydrozirconation and Negishi coupling with *p*-iodoanisole gave **66**.

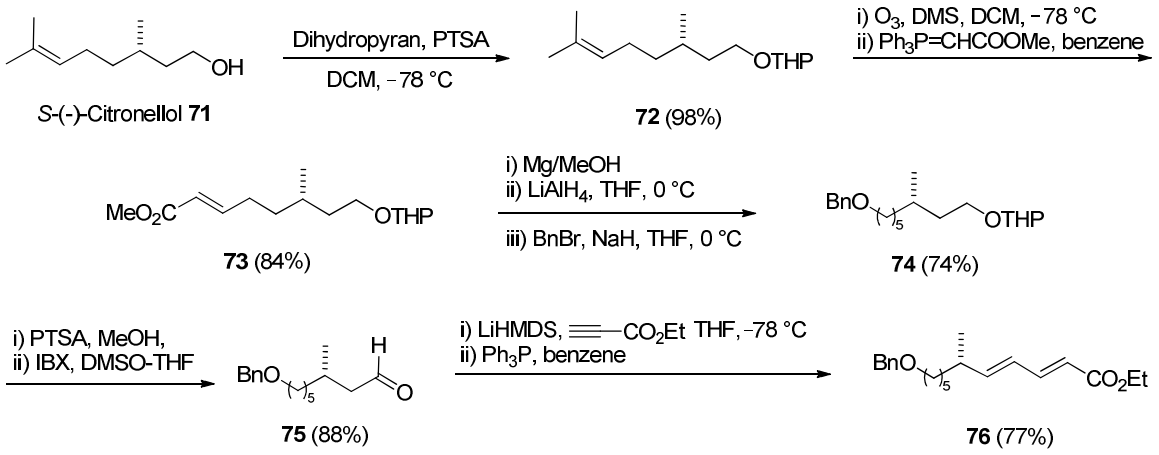


Scheme 12: Shioiri's synthesis of the protected form of AMMTD.

The TBS group was removed, the alcohol was oxidized to the aldehyde, followed by *anti*-aldol addition of **67** under Paterson's conditions[20] to afford the aldol product **68** as a single diastereomer, with the correct stereochemistry at the β-carbon for an S_N2 azide displacement. Lithium borohydride reduced the ketone and removed the benzoate to allow periodate oxidation. The resultant aldehyde was reduced to a diol and selectively protected at the primary hydroxyl group as its pivaloate, allowing conversion of the secondary alcohol to the corresponding triflate and displacement with azide to yield **69**. Treatment with lithium aluminium hydride removed the pivaloate and also reduced the azide. Boc-protection of the amine followed by a two-step oxidation to the acid and esterification gave **70** in 2.7% yield over 32 steps. Shioiri and co-workers subsequently built the other building blocks of microsclerodermin B,[21] but a total synthesis has not yet been reported.

1.3.6 Chandrashekhar's studies towards AMMTD

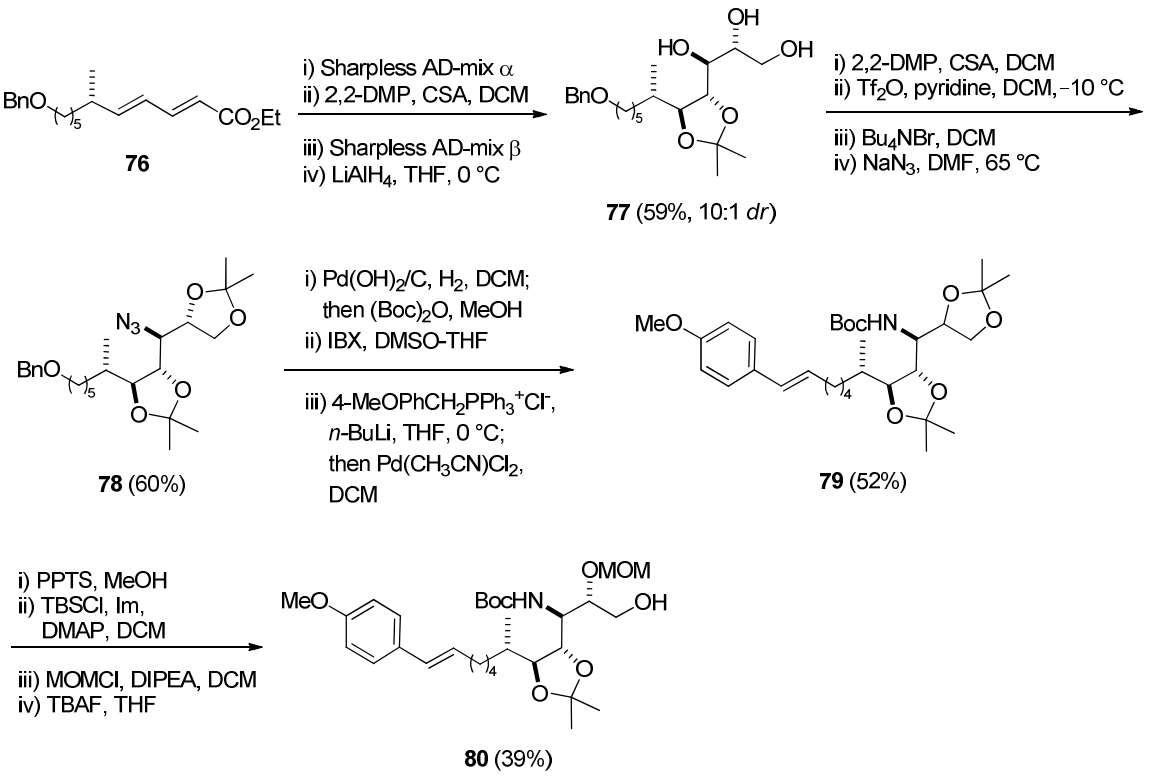
Srivari Chandrashekhar and a co-worker at the Indian Institute of Chemical Technology, India synthesized a protected precursor of AMMTD.[22] *S*-(−)-citronellol (**71**), which contained the necessary methyl stereocentre, was THP protected to yield **72** (Scheme 13). Ozonolysis of the alkene and chain extension by a Wittig reaction gave **73**. Treatment with magnesium in methanol effected conjugate reduction of the alkene and lithium aluminium hydride reduction of the ester was followed by benzyl protection to give **74**.



Scheme 13: Chandrashekhar's synthesis of the carbon framework for AMMTD

Removal of the THP group and IBX oxidation gave aldehyde **75** (Scheme 13). Treatment with lithiated ethyl propiolate formed an intermediate propargylic alcohol as a mixture of diastereomers, consequent treatment with triphenylphosphine effected alcohol elimination *via* an allene, which rearranged to the desired conjugated diene **76**. The diene **76** underwent a regioselective Sharpless asymmetric dihydroxylation reaction at the distal double bond, followed by protection of the diol as the acetonide. Attempts to introduce the 1,2-amino alcohol *via* the Sharpless asymmetric aminohydroxylation reaction at the α,β-unsaturated ester were unsuccessful, therefore an indirect approach was taken (Scheme 14). A second Sharpless asymmetric dihydroxylation reaction was performed to afford a diol ester, which was reduced

with lithium aluminium hydride to afford **77**. The triol was then acetonide protected to form the less hindered product. The remaining secondary alcohol that possessed the correct stereochemistry, was triflated and then brominated with inversion. Azide displacement then re-inverted the stereocentre to give **78**, with all five stereocentres as desired.



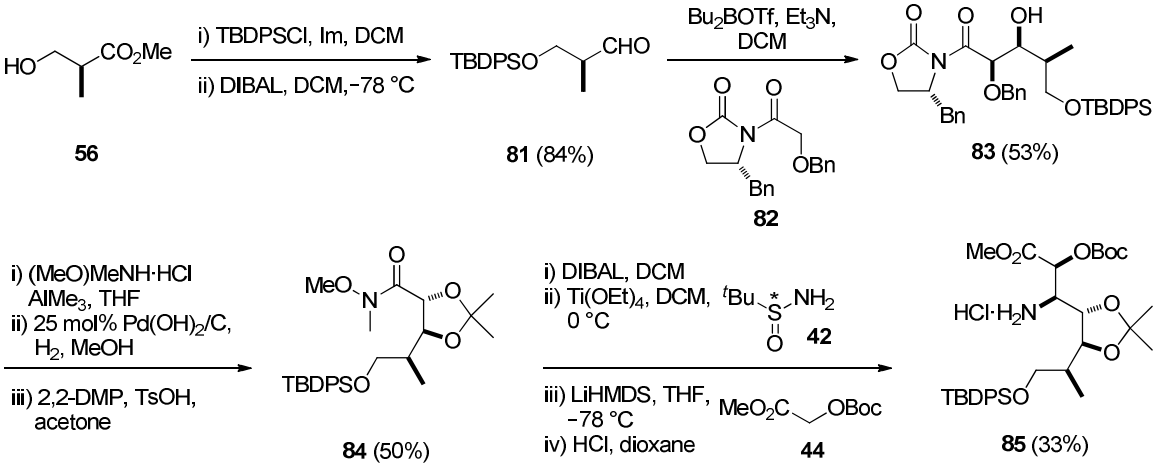
Scheme 14: Chandrashekhar's synthesis of protected form of AMMTD

Removal of the benzyl protecting group and reduction of the azide to an amine was achieved in one pot, followed by Boc protection of the amine. The primary alcohol was then oxidized to the aldehyde and Wittig olefination installed the alkene and aromatic ring of the side chain with a 3:2 *E*:Z ratio. Treatment of the mixture with bis(acetonitrile)palladium(II) chloride gave the pure *E* alkene **79** in excellent yields. Selective removal of terminal acetonide and TBS masking of the primary alcohol allowed MOM protection of the secondary alcohol. Finally, the TBS

group was removed by treatment with TBAF to give alcohol **80** in 3% yield over 26 steps. Oxidation of the primary alcohol would give the protected form of AMMTD.

1.3.7 Williams's studies towards AMPTD

Robert Williams and a co-worker at Colorado State University, USA reported their efforts towards the synthesis of AMPTD.[23] Starting with Roche ester (**56**), on TBDPS protection and partial reduction, aldehyde **81** was obtained (Scheme 15). An aldol reaction with Evans' oxazolidinone **82** gave compound **83** in moderate yield and as a single diastereomer. Attempts to cleave the benzyl group in the presence of the oxazolidinone gave poor yields. Hence, compound **83** was transaminated to the Weinreb amide and subjected to reductive removal of the benzyl group. The diol thus formed was protected as an acetonide to give compound **84**. Treatment with DIBAL converted the Weinreb amide to the corresponding aldehyde, which was treated with (*S*)-*tert*-butylsulfinamide (**42**) under Aitken's conditions to yield a sulfinimine. Reaction with the enolate of *O*-Boc methyl glycolate (**44**) and subsequent acidic removal of the sulfur group afforded the protected amino acid **85** in an overall yield of 7% over 10 steps. The Williams group went on to synthesise other amino acids of microsclerodermin G but a total synthesis has not yet been reported.



Scheme 15: Williams's synthesis of the core of AMPTD

1.3.8 Summary

In the preceding sections we looked at the past synthetic efforts towards the synthesis of microsclerodermins and, in particular, the challenge of synthesising the β-amino acid fragment. The main difficulties faced were installation of the 1,2-amino alcohol moiety and the attachment of the side-chain.

In synthesising β-amino acid with four stereocentres, we observed that it was possible to add a side chain after the core stereocentres were built but higher yields were obtained when the side chain was incorporated early on in the synthesis. Amongst the reported examples, Aitken's synthesis is the shortest and the most effective synthesis of the β-amino acids APTO and AETD.

For the β-amino acids with five contiguous stereocentres, both Shioiri and Chandrashekhar's synthesis of AMMTD had the side chain attached early on, limiting their methodology to microsclerodermins A and B. Williams's route that builds the core five stereocentres first using Aitken's conditions seems most effective, but their synthesis remains incomplete without the inclusion of the side chain.

1.4 Project aim

Due to the notable structural commonalities in the β-amino acids of all microsclerodermins, we decided to install the crucial four stereocentres to first build up the core stereocentre framework, common to the β-amino acids in all microsclerodermins, and then, either through a displacement or an olefination reaction, install the diverse side chains.

Starting our synthesis with an additional methyl stereocentre in place would give access to a concise route to the β-amino acid fragment of six of the nine microsclerodermins (A, B, F, G, H and I). If the route proves successful, then it can be envisioned that we could analogously prepare the β-amino acid fragment of the remaining three microsclerodermins (C, D and E), which only have four contiguous stereocentres.

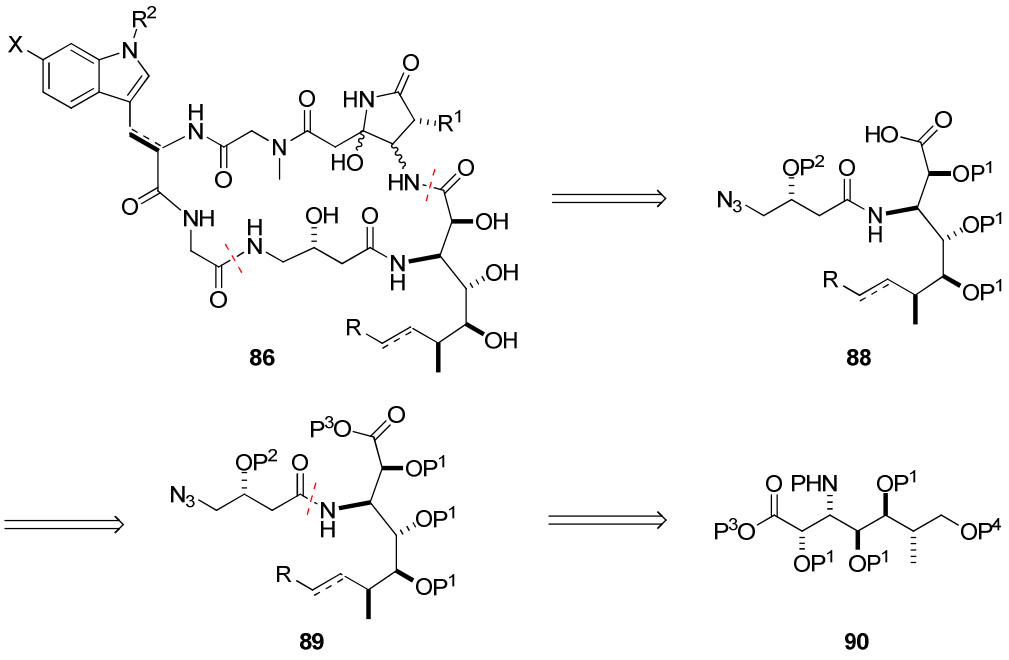
Chapter 2

Trial by aminohydroxylation

Chapter 2

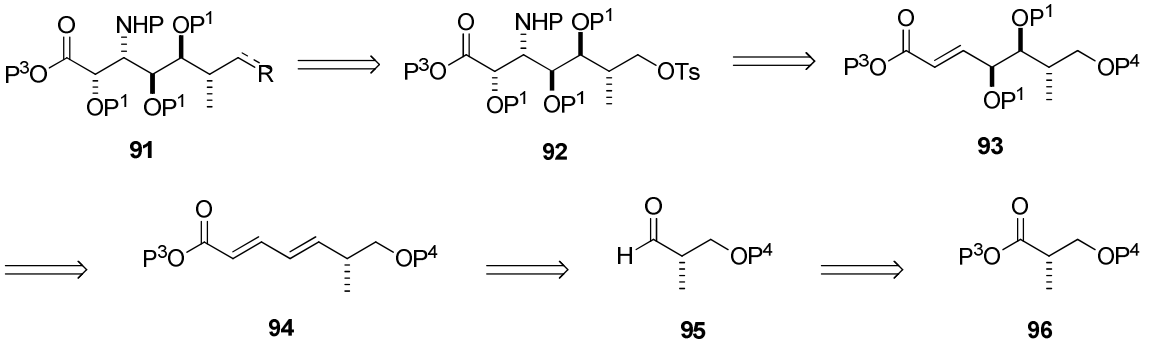
2.1 Proposed retrosynthetic analysis of the β-amino acid unit

As part of an on-going project within the Donohoe group towards the synthesis of a member of the microsclerodermin family, the synthesis of the β-amino acid plays a vital role. Based on precedence from the total synthesis of microsclerodermin E by the Ma group,[12] it was decided to disconnect the microsclerodermins into compound **87** and compound **88** (Scheme 16, similar to Ma' disconnection in Scheme 1). The protected compound **89** can be formed by coupling the protected GABOB unit with the amine **90**. Compound **89** on hydrolysis of the ester would give acid **88** ready for the first coupling to the tetrapeptide. The macrocyclisation would be achieved upon Staudinger reduction of the azide, and subsequent removal of protecting groups will give the desired microsclerodermin **86**.



Scheme 16: Our proposed retrosynthesis of microsclerodermins

The presence of a structural commonality in the β-amino acid unit contained in all microsclerodermins aided the development of a retrosynthetic strategy to enable syntheses of this fragment for multiple members of the family. We envisaged that by starting with (*S*)-Roche ester (**56**), which contains the methyl stereocentre, we could build β-amino acids for microsclerodermins A, B, F, G, H and I that contain five contiguous stereocentres. The other four common stereocentres could be installed *via* a Sharpless asymmetric dihydroxylation reaction followed by an aminohydroxylation reaction.

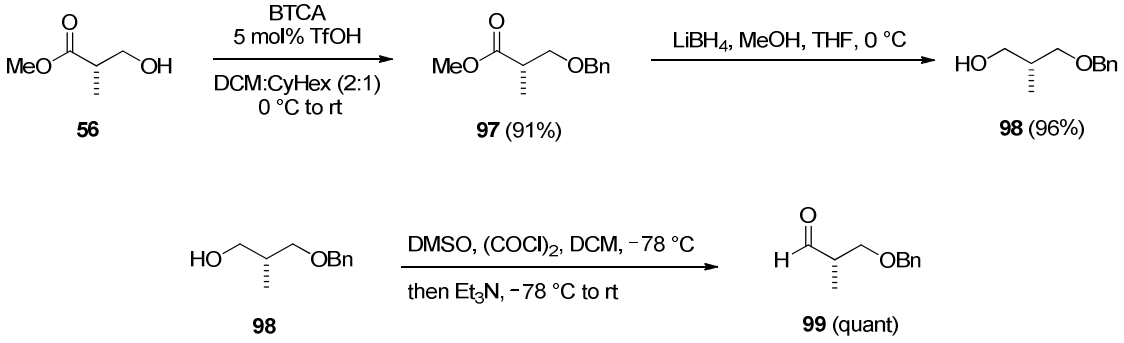


Scheme 17: Our proposed retrosynthesis of the β-amino acid

To install the side chain on the β-amino acid, removal of protecting group P^4 will give a primary alcohol that could be converted to a leaving group such as tosylate **92**, and displaced with various nucleophiles (Scheme 17). Alternatively, it could be oxidised to an aldehyde and olefinated depending on the target β-amino acid **91**. An aminohydroxylation reaction on suitably protected diol **93** will install the last two stereocentres. A Sharpless asymmetric dihydroxylation (AD) reaction will install two more stereocentres on the distal double bond of diene **94**. To prepare the diene **94**, Roche ester (**56**) provides a good starting point as it contains the methyl stereocentre, and it can be converted to aldehyde **95**, which can further undergo olefination reactions.

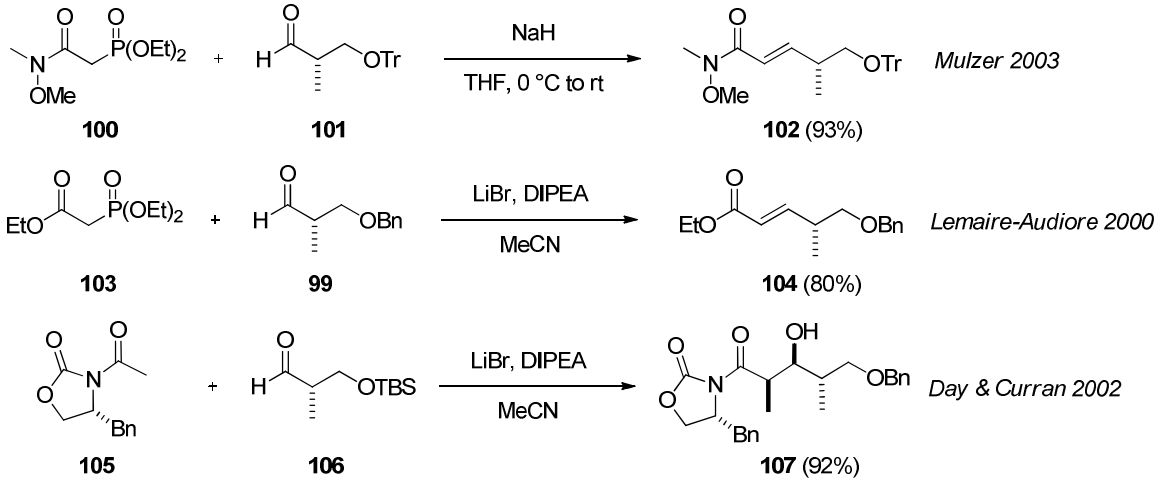
2.2 Synthesis of diene

We envisaged that diene **94** could be obtained through a highly *trans*-selective Horner-Wadsworth-Emmons reaction of aldehyde **95** derived from Roche ester (**56**) and the corresponding phosphonate. Thus, we proceeded with the synthesis of the aldehyde by first protecting the primary alcohol with a benzyl group.[24] The alcohol was treated with 2,2-benzyltrichloroacetimidate (BTCA) and sub-stoichiometric quantities of triflic acid to give **97** in 91% yield (Scheme 18). Then in a two-step procedure, compound **97** was reduced to alcohol **98** with lithium borohydride and oxidised using Swern conditions to give desired aldehyde **99** in 96% yield over two steps. A direct, selective reduction of ester **97** to aldehyde **99** was attempted with a minimal amount of diisobutylaluminium hydride at low temperature of either −78 °C or −90 °C, but over reduction was observed in both cases.[25]



Scheme 18: Synthesis of aldehyde 99

Literature examples for the use of the aldehyde derived from Roche ester indicated to us that it was reasonably stable to racemisation under a variety of strongly basic conditions. All products in Scheme 19 were isolated as single enantiomers.[26]



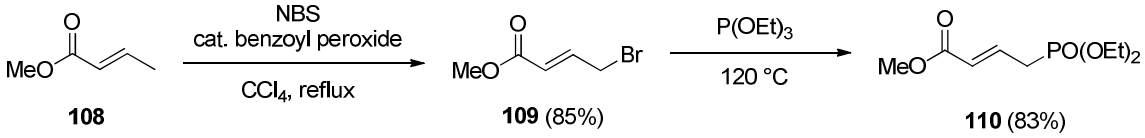
100 **101** **102** (93%)

103 **99** **104** (80%)

105 **106** **107** (92%)

Scheme 19: Literature precedent for the use of aldehyde derived from Roche ester (56)

With aldehyde **99** in hand, we set out to prepare the corresponding phosphonate. Methyl crotonate (**108**) was treated with *N*-bromosuccinimide in the presence of sub-stoichiometric quantity of benzoyl peroxide to give bromide **109** in 85% yield (Scheme 20).[27] Then under the Michaelis-Arbuzov reaction conditions, the bromide was converted to the desired phosphonate **110** in 83% yield.[28]

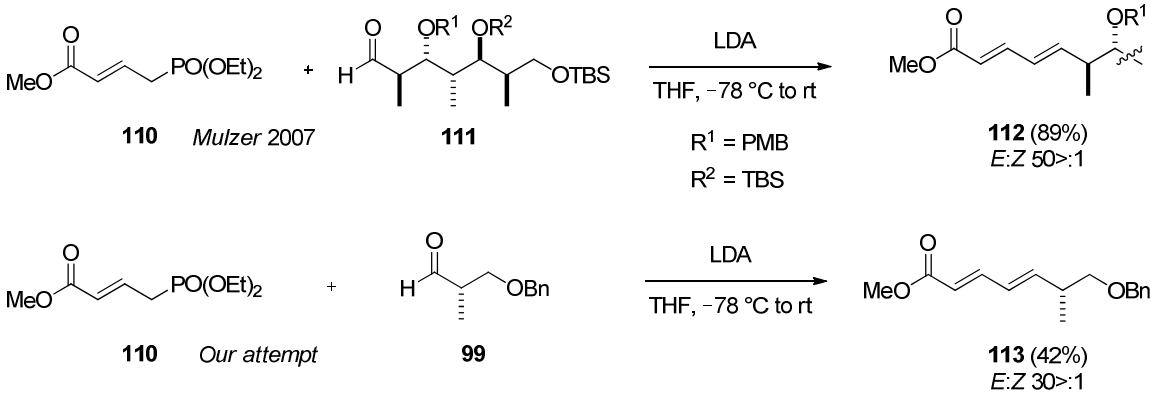


108 **109** (85%) **110** (83%)

Scheme 20: Synthesis of phosphonate 110

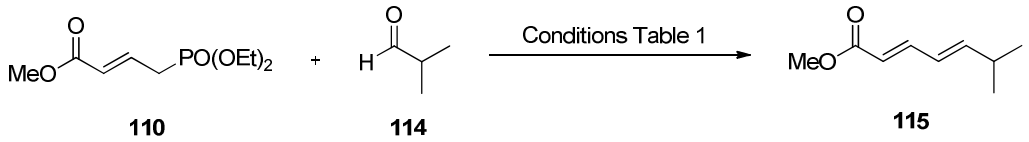
In 2007, Johann Mulzer and co-workers from the University of Vienna completed the synthesis of efomycine M by using phosphonate **110** in a Horner-Wadsworth-Emmons olefination as one of the key steps (Scheme 21).[29] With both the phosphonate **110** and aldehyde **99** in hand, we attempted to use the conditions reported by Barth and Mulzer, who converted aldehyde **111** into diene **112** with high selectivity. Pleasingly, in our case too, we obtained the *E* isomer **113**

exclusively, with a *trans* coupling constant of 15.4 Hz. But unfortunately, the yield of 42% was unsatisfyingly low.



Scheme 21: Synthesis of diene 113

In order to improve the olefination yield, isobutyraldehyde (**114**) was chosen as a model aldehyde and, based on literature precedents,[29 - 32] a number of conditions were studied for optimisation (Table 1). Using methyl magnesium bromide as the base only traces of the model diene were obtained (Entry 1). Using DBU as a base with lithium chloride (Entries 2 and 3) as an additive gave similar results to the initial LDA conditions (Entry 4). Increasing the number of equivalents of phosphonate and LDA gave improved yields (Entries 5 and 6). The best results were obtained with $LiOH \cdot H_2O$ as the base, under reflux and in the presence of molecular sieves (Entries 7 and 8).



Entry [a]	*Phosphonate (eq.)*	*Base (eq.)*	*Additive*	*Temp. (ºC)*	*Yield (115)*
1	1	MeMgBr (1) [30]	-	Reflux	Traces
2	1	DBU (1) [31]	LiCl	rt	47%
3	2	DBU (2)	LiCl	rt	55%
4	1	LDA (1.5)	-	−78 ºC to rt	42%
5	2	LDA (2.5)	-	−78 ºC to rt	74%
6	3	LDA (3.5)	-	−78 ºC to rt	79%
7	1	$LiOH \cdot H_2O$ (1.2) [32]	M. S. [b]	Reflux	82%
8	2	$LiOH \cdot H_2O$ (2.4)	M. S.	Reflux	88%

[a] *All reactions were carried out using 1 eq. of isobutyraldehyde*; [b] *M. S. stands for molecular sieves.*

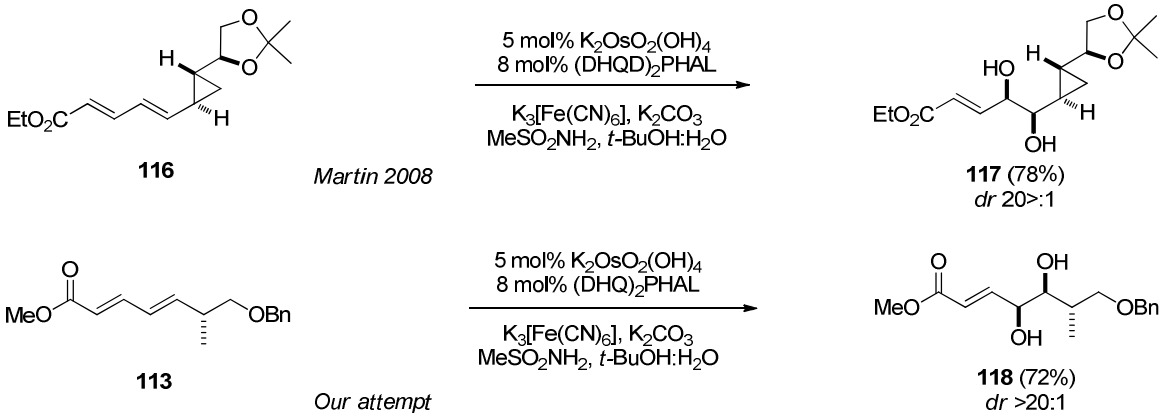
Table 1: Horner-Wadsworth-Emmons olefination optimisation

By applying the optimised conditions (Entry 8) to aldehyde **99**, we obtained a good yield of **113** (74%) on 100 mg scale. But scaling up the reaction to gram scale led to a much lower yield of 49%. We then applied the next best set of conditions (Entry 6) and obtained a yield of 69% with complete *E*-selectivity even on a gram scale. Despite discrepancies in yield, with the diene in hand, we proceeded to synthesise the desired diol **93**.

2.3 Synthesis of diol

Exploiting preferential osmylation of α,β,γ,δ-unsaturated esters at the more electron-rich double bond,[33] we treated diene **113** with classic Sharpless AD conditions using the α-mix (0.1 mol% potassium osmate and 0.2 mol% $(DHQ)_2PHAL$ ligand) in the presence of methane sulfonamide

in a hope that the dihydroxylation will occur from the top face of the alkene according to the Sharpless mnemonic. However using these conditions, even after 24 hours, no dihydroxylated product was observed by TLC analysis or mass spectrometry. The catalyst and ligand loading were then increased to 1 mol% and 2 mol% respectively, but no dihydroxylation occurred after a further 24 hours. In 2008, Stephen Martin of the University of Texas-Austin used a 'super' AD-mix (5 mol% potassium osmate and 8% ligand) to selectively dihydroxylate α,β,γ,δ-unsaturated ester **116** to give diol **117** towards the synthesis of solandelactone E (Scheme 22).[34] Using the same conditions with $(DHQ)_2PHAL$ as the ligand, we were pleased to isolate the desired diol **118** in 72% yield as a single diastereomer.



Scheme 22: Synthesis of diol 118

Furthermore for comparison, we also dihydroxylated the diene using the same conditions but with diastereomeric ligand $(DHQD)_2PHAL$ giving the diol with undesired stereochemistry in 54% yield again as a single diastereomer. The stereochemistry of both diols was assigned according to the Sharpless mnemonic.[33] Interestingly, the two compounds could be differentiated by the ^1H NMR signals of their respective benzylic protons. A singlet was observed at δ = 4.54 ppm in spectra of diol **118** and two doublets (AB system) were observed at δ = 4.50 ppm and 4.54 ppm in spectra of the undesired diastereomer (Figure 9).

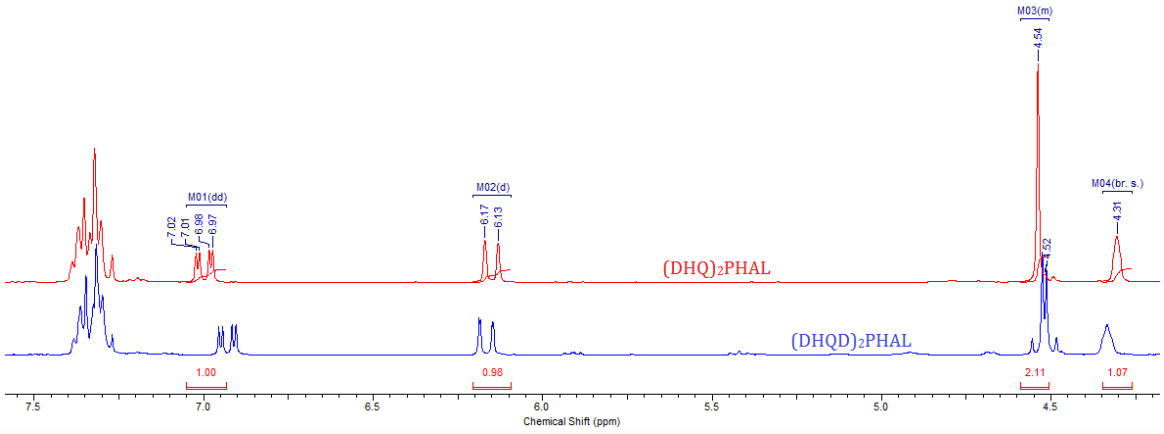


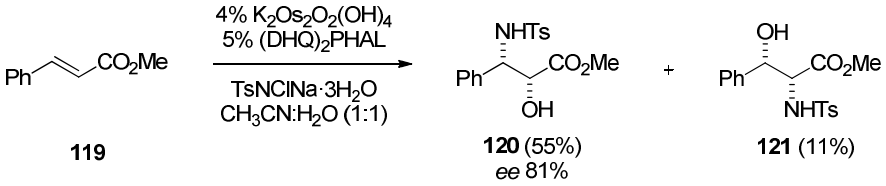
Figure 9: Comparing ^{1}H NMR spectra of diols derived from (DHQ)$_2$PHAL and (DHQD)$_2$PHAL

A multi-gram scale synthesis of diol **118** gave a slightly lower yield (67%) and selectivity (15:1), possibly due to ineffective stirring that may have caused pockets of higher temperature within the large round bottom flask. Fortunately, the diastereomers could be separated by column chromatography. With diol **118** in hand, we looked to investigate an aminohydroxylation reaction. The Sharpless asymmetric aminohydroxylation (AA) remains the most powerful reaction to install the key 1,2-amino alcohol motif in the desired *syn*-fashion. However, the pioneering reaction has suffered from a lack of general conditions to effect high regio- and enantioselectivity in the oxidation of all classes of olefins. Before proceeding to our experimental results, in the next section, I will review the Sharpless AA literature with particular focus on the reaction of α,β-unsaturated esters.

2.4 Introduction to the Sharpless asymmetric aminohydroxylation reaction

First reported in 1996,[35] the Sharpless asymmetric aminohydroxylation reaction remains one of the most powerful methods for direct, catalytic, and enantioselective synthesis of vicinal amino alcohols directly from alkenes.[36, 37] It transforms a range of alkenes in to their corresponding amino alcohols on exposure to sub-stoichiometric loadings of potassium osmate,

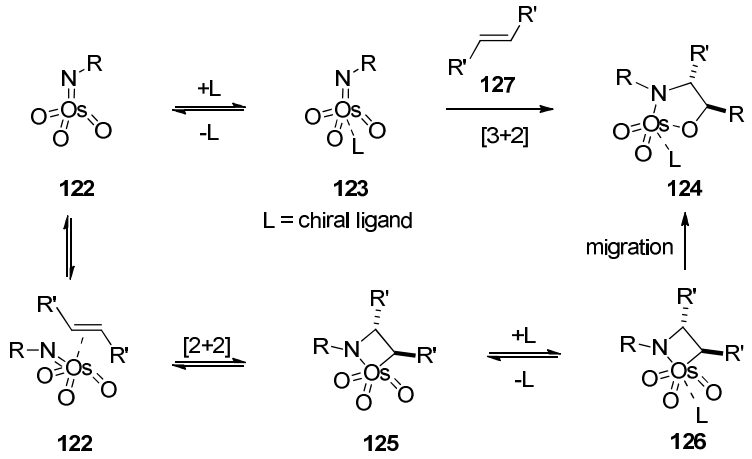
$K_2OsO_2(OH)_4$, in the presence of a stoichiometric nitrogen source that also acts as a reoxidant. The regio- and stereoselectivity is controlled by the addition of *cinchona* alkaloid ligands such as $(DHQ)_2PHAL$ (Scheme 23).



Scheme 23: The first reported example of the Sharpless AA reaction

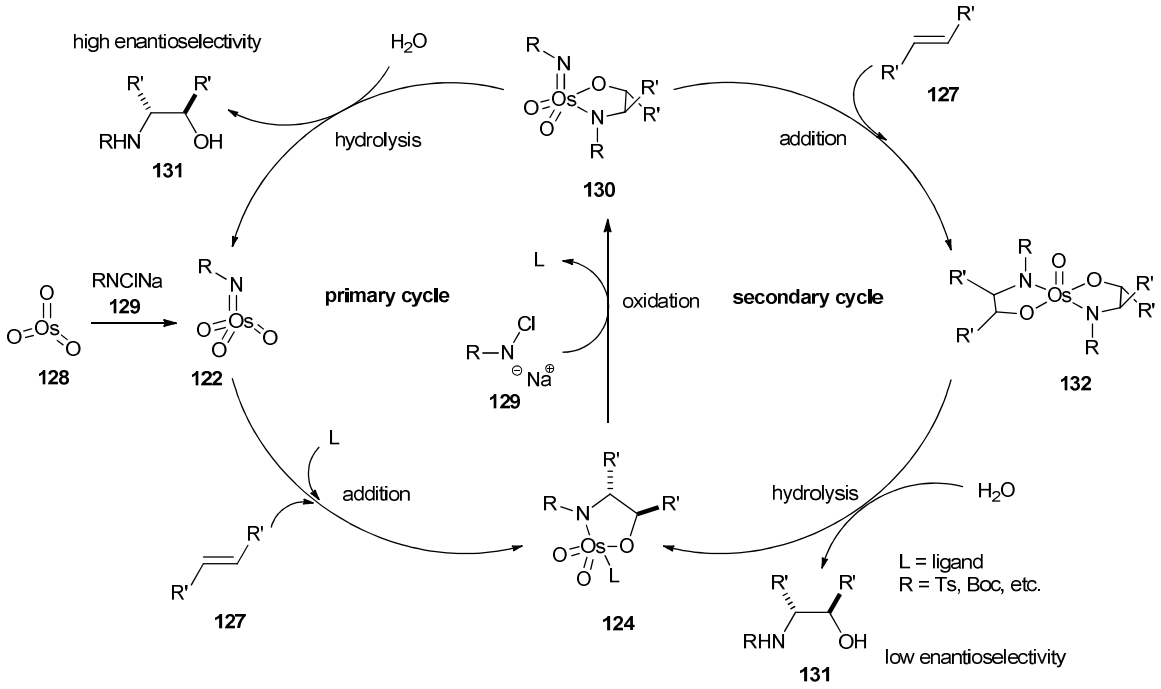
2.4.1 Mechanism

The proposed mechanism of the AA reaction closely resembles that of its forerunner, the AD reaction. The intermediate believed to be involved in the key bond forming step is the imidotrioxoosmium (VIII) species **122**, which adds with *syn*-stereospecificity to the alkene **127** to give the azaglycolate complex **124** (Scheme 24). Two pathways have been suggested for this process. The first, proposed by Sharpless, involves a formal [2+2] cycloaddition of the alkene to the imidotrioxoosmium species **122** to give the osmaazetidine **125**, followed by ligand coordination to form **126** and 1,2-migration of the carbon-osmium bond to give the osmium azaglycolate addition product **124**.[38] The second, which was recently shown by a computational study to be the more likely route,[39] involves the [3+2] cycloaddition of ligand-bound complex **123** to the alkene to give **124**.



Scheme 24: Addition of osmium to the alkene

It is postulated that the reaction proceeds by two simultaneous catalytic cycles (Scheme 25).



Scheme 25: Mechanism of the AA reaction

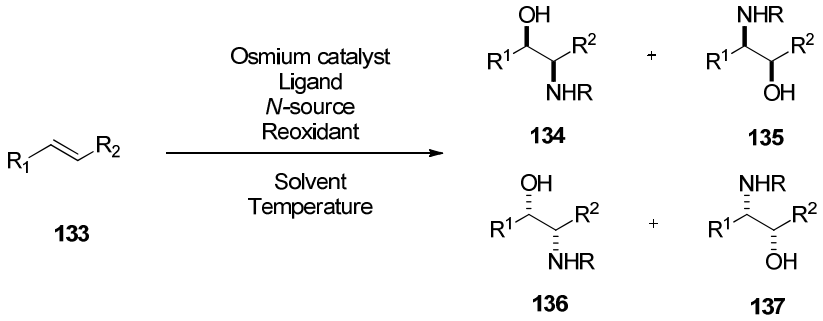
The primary cycle begins with the oxidation of the Os^{VI} species **128** by the nitrogen oxidising agent to deliver the imidotrioxoosmium (VIII) species **122**, which undergoes a cycloaddition

reaction to the alkene **127** to generate the azaglycolate complex **124**, with regio- and enantioselectivity enforced by the chiral ligand (Scheme 25). Reoxidation of this species gives **130**, which can then be hydrolysed to give the amino alcohol **131**, and the initial osmium species which re-enters the catalytic cycle. Alternatively, the oxidised azaglycolate species **130** may enter the ligand-free secondary cycle if it undergoes addition to a second alkene **127** to give the bis(azaglycolate)osmium species **132** before hydrolysis (Scheme 25). In this catalytic cycle, low regio- and enantioselectivities are obtained as the ligand does not coordinate to osmium during the reaction.

Ligands have been observed to increase the catalytic turnover of the reaction favouring the primary cycle. The hydrolysis steps, which can be accelerated by the use of aqueous solvent mixtures, allow the primary cycle to dominate.[36]

2.4.2 Regioselectivity

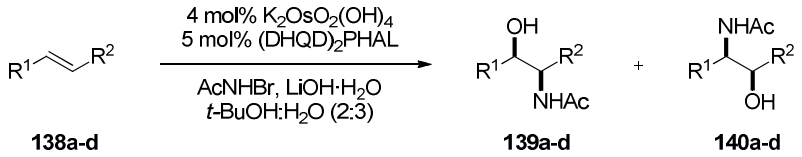
The AA reaction mechanism dictates that the addition must occur in a *syn* fashion, where both groups add to the same face of the alkene with four possible products (Scheme 26). For this reaction to be synthetically useful both the regio- and enantioselectivity must be controlled to favour the desired product.



Scheme 26: Possible products of an AA reaction

The three main factors that affect regioselectivity are alkene substitution, alkene polarisation, and ligand-substrate interactions:

Alkene substitution: From studies on the AA of homoallylic alcohol derivatives, it was shown that the nitrogen preferably adds to the less substituted end of the alkene (Scheme 27, **138a** *vs.* **138b**).[40] In the case of 1,2-disubstituted alkenes regioselectivity also depends on the nature of the protecting group on the homoallylic alcohol (**138c** *vs*. **138d**).

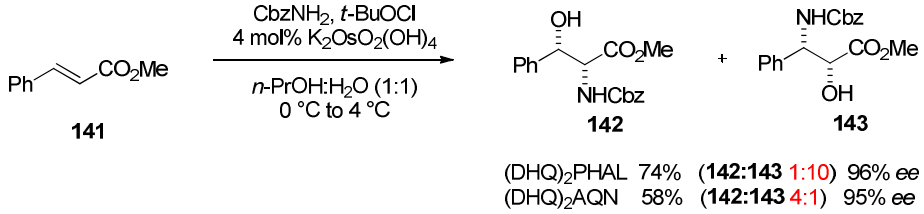


Substrate	R^1	R^2	**139:140**
138a	$TBDPSOCH_2CH_2$	H	>20:1
138b	$p\text{-}MeOC_6H_4OCH_2CH_2$	H	1.2:1
138c	$TBDPSOCH_2CH_2$	Et	2.0:1
138d	$p\text{-}MeOC_6H_4OCH_2CH_2$	Et	1:3.5

Scheme 27: Effect of allylic alcohol protecting group on regioselectivity

Alkene polarisation: Polarisation of the alkene leads to preferential formation of the β-amino product when α,β-unsaturated esters undergo the AA reaction. It is postulated that the β-amino isomer predominates due to the greater nucleophilic character of the imidoosmium grouping (Os=NR), which favours nitrogen addition to the more electrophilic carbon of the alkene.

Ligand-substrate interaction: It has been observed in several examples that changing the aromatic linker of the chiral ligand to an anthraquinone unit (see Figure 10 for ligands) results in reversal of regioselectivity to favour α-amino products (Scheme 28).[41] This may point to the strength of ligand-substrate interactions, which can overcome the strong electronic bias created by the ester group in α,β-unsaturated esters.



Scheme 28: The effect of ligands on regio- and enantioselectivity

2.4.3 Enantioselectivity

The enantioselectivity and, to a certain extent the regioselectivity, is induced in the product by the presence of chiral ligands in the reaction mixture. The ligands (Figure 10) are made up of an aromatic spacer group, for example phthalazine (PHAL) or anthraquinone (AQN), and a chiral *cinchona* alkaloid moiety, either dihydroquinine (DHQ) or the pseudoenantiomeric dihydroquinidine (DHQD).

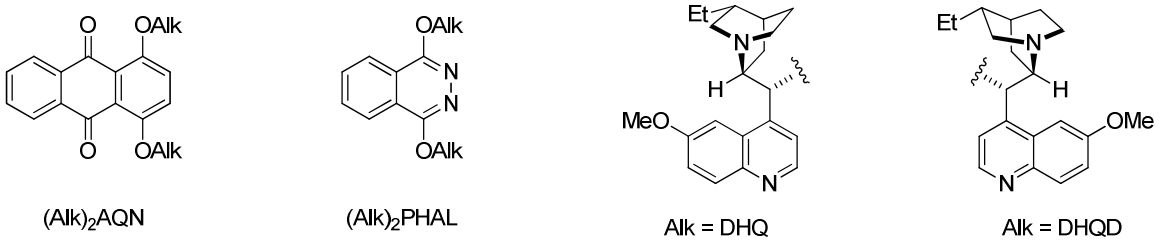


Figure 10: Sharpless AA and AD ligands

As a general rule, the asymmetric induction is of the same sense as that of the AD reaction for related substrates. Thus, the AD mnemonic, which is briefly discussed here (Figure 11), can be used for predicting the sense of enantioselectivity.[33] The substrate pocket, formed due to the catalyst-ligand complex, sets steric constraints on the mnemonic. To predict the outcome, the alkene must be positioned according to these constraints, such that the small substituents of the alkene point towards the sterically congested southeast and/or northwest quadrants. Once that is done, the mnemonic predicts that DHQD-derived ligands attack from the top (β) face of the

alkene, while DHQ-derived ligands attack from the bottom (α) face of the alkene. The magnitude of enantioselectivity is highly dependent on the alkene substitution pattern.

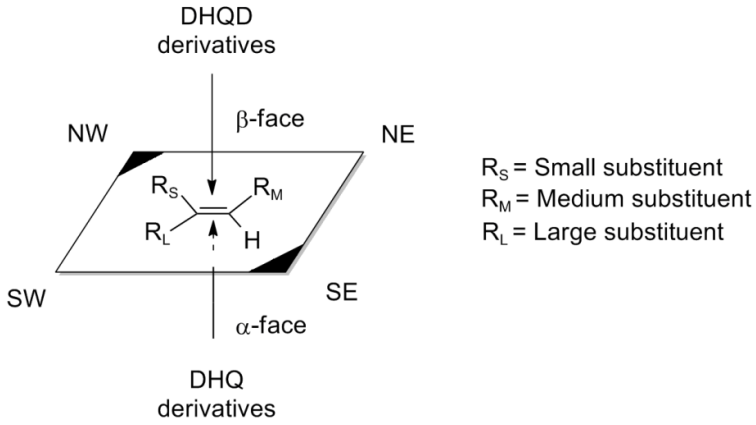
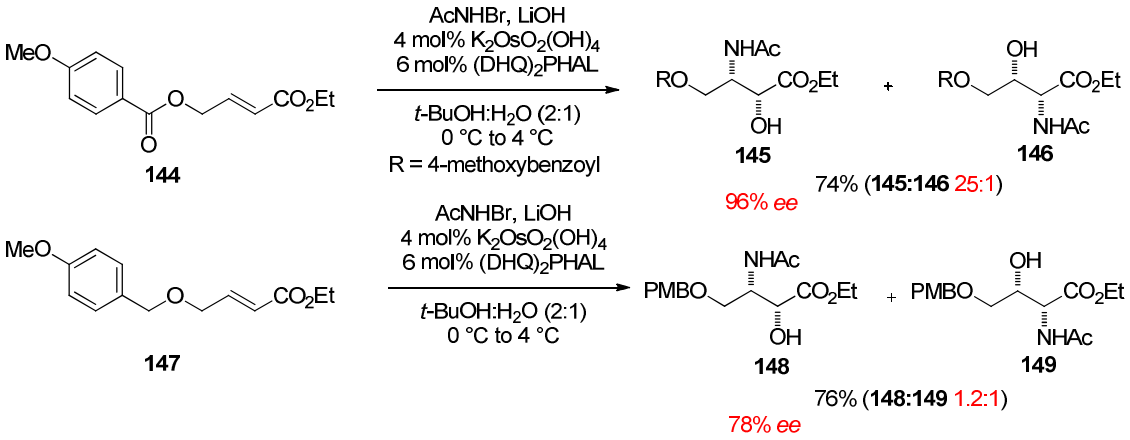


Figure 11: The Sharpless AD mnemonic

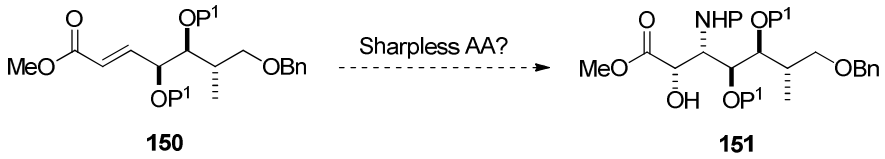
Effect of protecting groups: In 2002, Iwao Ojima and co-workers from SUNY-Stony Brook, USA showed that the presence of a 4-methoxybenzoyl as protecting group on an allylic alcohol enhanced the regio- and enantioselectivity of the Sharpless AA reaction.[42] The effect was so significant that removal of only the carbonyl group in **144** led to a drastic reduction in regio- and enantioselectivity in aminohydroxylation of **147** (Scheme 29). It was reasoned that the aryloxy group on the allylic alcohol led to favourable π-stacking interactions with the ligand giving higher regio- and enantioselectivity.



Scheme 29: The effect of protecting group on regio- and enantioselectivity

2.5 Synthesis of amino-alcohol 151

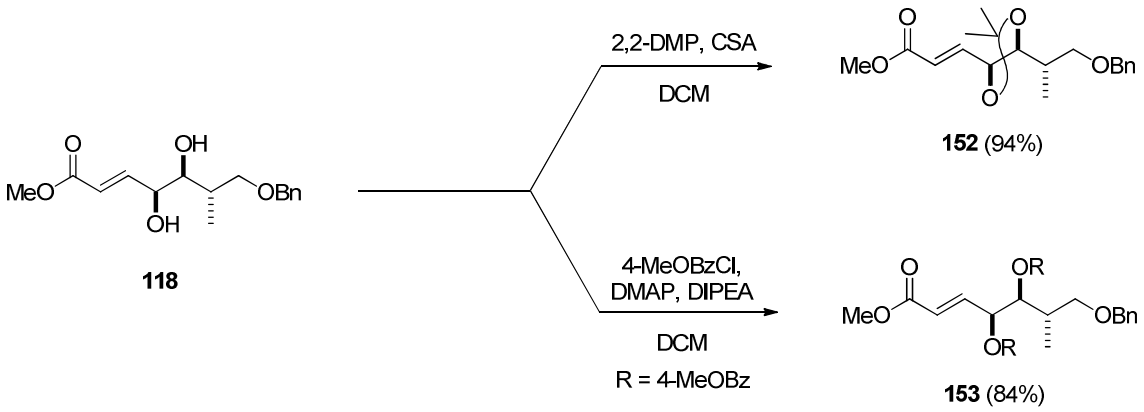
Having reviewed the AA literature, we were able to draw some conclusions to help strategise the synthesis of the target molecule **151** (Scheme 30). To date, no one has reported a successful Sharpless AA reaction on a γ,δ-dihydroxyl-α,β-unsaturated ester substrate. Despite the lack of direct precedent, we wanted to try effecting a Sharpless AA reaction to enable the shortest route to our target molecule..



Scheme 30: The desired Sharpless AA

The presence of an α,β-unsaturated ester in substrate **118** (see Scheme 22) bodes well with the preference for the β-amino product. According to the AD mnemonic,[33] $(DHQD)_2PHAL$ ligand would be predicted to give the desired selectivity, but the magnitude of selectivity was uncertain. Taking example from Ojima's work, we chose 4-methoxybenzoyl as protecting group P^1 in a hope to enhance the regio- and enantioselectivity. As an alternative protecting

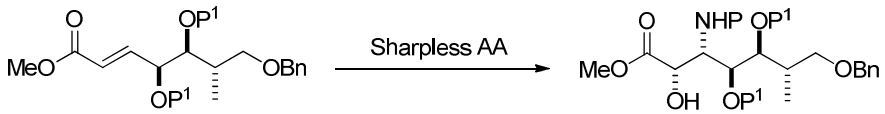
group, an acetonide may be able to provide the steric bulk on one face of the alkene to force the aminohydroxylation to occur on the opposite and desired face. As drawn With these insights, we proceeded to synthesise the protected diol substrates for the Sharpless AA reaction (Scheme 31). Acetonide **152** was synthesised in 94% yield and 4-methoxybenzoyl protected diol **118** in 84% yield from diol **153**, using 2,2-dimethoxypropane in the presence of catalytic camphor sulfonic acid and 4-methoxybenzoyl chloride in the presence of dimethylaminopyridine and diisopropylethylamine, respectively.



Scheme 31: Synthesis of protected diol substrates

With the desired substrates in hand we proceeded to try a range of conditions to effect the Sharpless AA reaction on diols **152** and **153** (Table 2). We attempted to use the original set of conditions reported by Sharpless using chloramine-T (Entry 1), which was found to be successful with methyl cinammate. For substrate **152**, despite complete consumption of the starting material not even a trace amount of product was observed. Similar results were obtained when benzyl carbamate was used as the *N*-source, with *tert*-butyl hypochlorite as reoxidant and sodium hydroxide as base, for both substrates **152** and **153** (Entries 2 and 3). Rapid consumption (2 h to 6 h) of the starting material in both these cases indicated that, since none of the AA product was being formed, the powerful chlorinating agents may have, in some

way, caused the degradation of the alkene. It has previously been reported that side reactions leading to chlorination of the alkene may occur under these conditions.[43]



152 or **153** **151**

No [a]	*Substrate*	*Nitrogen Source*	*Oxidant*	*Base*	*Solvent*	*Result*
1	**152**	chloramine-T[44]	-	-	$CH_3CN:H_2O$	SM consumed No product
2	**152**, **153**	benzyl carbamate[45]	*t*-BuOCl	NaOH	$CH_3CN:H_2O$	SM consumed No product
3	**152**, **153**	benzyl carbamate[45]	*t*-BuOCl	NaOH	$PrOH:H_2O$	SM consumed No product
4[b]	**153**	AcNHBr[46]	-	LiOH	$^tBuOH:H_2O$	20% SM recovered 20% dihydroxylation[f]
5[c]	**153**	AcNHBr[46]	-	LiOH	$^tBuOH:H_2O$	SM consumed 40% dihydroxylation[f]
6[d]	**152**, **153**	*tert*-butylcarbamate[47]	DCDM	NaOH	$PrOH:H_2O$	SM consumed No product
7[e]	**153**	*tert*-butylcarbamate[47]	DCDM	NaOH	$PrOH:H_2O$	SM consumed No product
8[d]	**152**, **153**	*tert*-butylcarbamate[47]	DBDM	NaOH	$^tBuOH:H_2O$	SM consumed No product
9	**153**	benzyl 4-chlorobenzoyl-oxycarbamate[49]	-	-	$CH_3CN:H_2O$	30% SM recovered trace dihydroxylation

[a] All experiments, except where mentioned, were carried out with 4 mol% $K_2OsO_2(OH)_4$ and 5 mol% $(DHQD)_2PHAL$. [b] T = 4 °C, t = 24 h. [c] T = 4 °C, t = 48 h. [d] 5 mol% $K_2OsO_2(OH)_4$ and 7 mol% $(DHQD)_2PHAL$. [e] 5 mol% $K_2OsO_2(OH)_4$ and 7 mol% $(DHQ)_2PHAL$. [f] Dihydroxylation product was observed by ^1H NMR, HRMS analysis.

DCDM = 1,3-dichloro-5,5-dimethylhydantoin

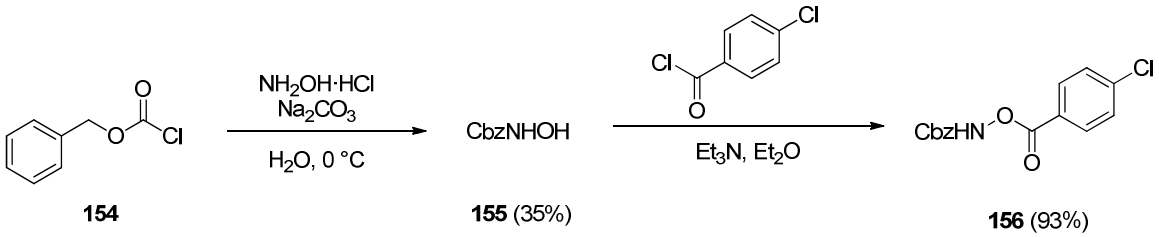
Table 2: Reagents and conditions employed in attempted Sharpless AA reactions

To resolve the issue, we chose milder conditions by employing *N*-bromoacetamide (which was easily synthesised by treating acetamide with bromine[48]) as the nitrogen source (Entries 4 and 5) at lower temperature. This time we found that, even after 24 hours, the starting material was not consumed. On work up, approximately 20% starting material and 20% of dihydroxylated product (as detected by ^{1}H NMR and MS analysis) was recovered, but no AA product was found. If the reaction is left to run for a further 24 hours then complete consumption of the starting material occurred, but it only yielded more dihydroxylated product without a trace of the AA product. Indeed, Sharpless had previously reported that AD can occur under AA reaction conditions, which occurs due to the hydrolysis of the imidoosmium species to osmium tetroxide. The presence of ligand accelerates the catalysis to form dihydroxylated product even further.[36]

He further reported that diol formation can be reduced by using a high ligand to osmium ratio. A literature search for such conditions led us to those used by McLeod (previously discussed in Scheme 5), which used a higher catalyst (5 mol%) and ligand loadings (7 mol%) with slightly higher ligand to osmium ratio (1.4:1 instead of 1.25:1). Additionally, McLeod's alkene substrate **28** (see Scheme 5), which had successfully undergone a Sharpless AA reaction, was the closest reported substrate to our starting material **153**.

Thus, according to McLeod's conditions, we proceeded to use *tert*-butyl carbamate as the nitrogen source, 1,3-dichloro-5,5-dimethylhydantoin (DCDM) as the reoxidant, and sodium hydroxide as base (Entries 6 and 7). Despite complete consumption of the starting material for both substrates **152** and **153**, no AA product was obtained. Keeping in mind the sensitivity of the alkene towards chlorinating agents, we used the bromine variant of DCDM (Entry 8) but were still unsuccessful in effecting the desired transformation.

In 2011, Andreas Luxenburger and co-workers reported improved Sharpless AA conditions with an alternate class of nitrogen source.[49] They used alkyl 4-chlorobenzyloxycarbamates to effect base-free Sharpless AA with high regio- and enantioselectivities, where the leaving group on the nitrogen is an arylcarboxylate instead of a halogen atom. We synthesised the nitrogen source **156** in a two-step, albeit low-yielding, procedure by first protecting the nitrogen on hydroxylamine hydrochloride with the carboxybenzyl group and then attaching the 4-chlorobenzoyloxy group on the hydroxyl group (Scheme 32).



Scheme 32: Synthesis of a new class of nitrogen source

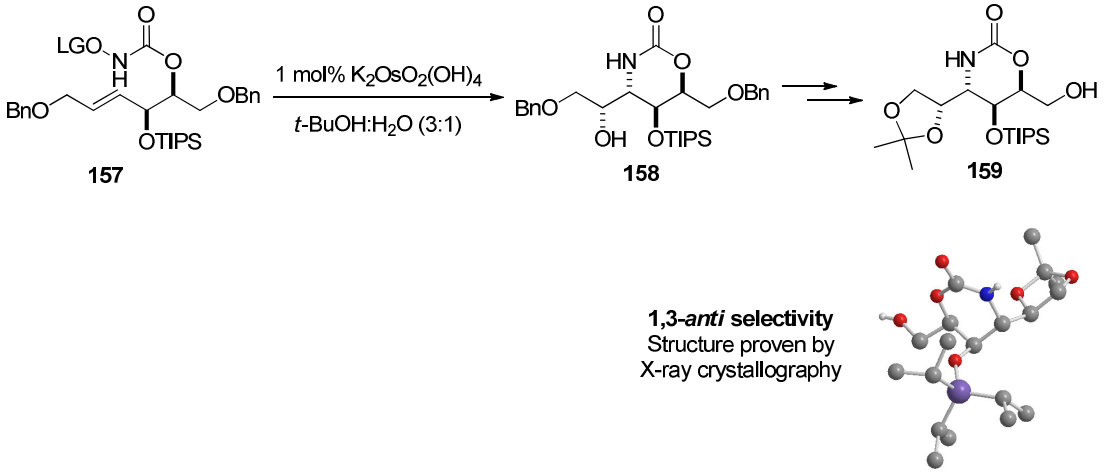
With the new *N*-source in hand, we proceeded to treat protected diol **153** with Luxenburger's conditions (Entry 9). Unfortunately, even after 24 hours, there was a significant amount of starting material present with traces of dihydroxylated product (as detected by mass spectrometry), but no AA product.

We believe that we may not have reaped the full benefits of using a 4-methoxybenzoyl protected allylic alcohol substrate because the additional protected homoallylic alcohol may have disrupted the desired π-stacking. The greater steric demand of the catalytic species involved in the AA reactions may be one of the reasons for the limited substrate scope for the AA reaction as opposed to the AD reaction (imidotrioxoosmium complex **122** relative to osmium tetroxide). The greater size of the imidosubstituent (consider Os=NR *vs.* Os=O) would

render approach of the nitrogen to a disubstituted olefinic carbon more difficult. Our substrates, protected diol **153** or acetonide **152**, could have suffered from this difficulty due to the presence of bulky protecting groups. Thus, we hoped that if traces of AA product were formed when naked diol **118** was treated to some of the AA conditions discussed, then we might conclude that steric hindrance had indeed caused the Sharpless AA to fail on desired substrates **152** and **153**. Under Luxenburger's conditions, the reaction of diol **118** was very sluggish with starting material present even after 7 days. On working up the reaction, we recovered 40% of the starting material and traces of dihydroxylated and aminohydroxylated product, detected by mass spectrometry and crude ^{1}H NMR spectroscopy, rendering support to our hypothesis.

2.6 An alternative aminohydroxylation

The failure of the Sharpless AA reaction to effect the desired transformation made us consider other methods to install the key 1,2-aminoalcohol motif. In 2006, the Donohoe group developed an adaptation of the Sharpless AA conditions, the tethered aminohydroxylation (TA), which maintains the complete *syn*-stereospecificity of the AA reaction, while guaranteeing full regiocontrol by tethering the nitrogen source to the olefin.[43] This reaction seemed particularly attractive because co-workers in the Donohoe group have previously established that systems such as **157** afford high 1,3-*anti* diastereoselectivity in favour of product **158** (Scheme 33), which closely resembles our target molecule **151**, with four of the five stereocentres in the right place.[50] In this case, the relative stereochemistry of TA product **158** was confirmed by the X-ray crystal structure of its derivative **159**.[51]



Scheme 33: Examples of the TA reaction that closely resemble desired product

Incorporating the TA reaction would require slight adaptations to the current synthetic route, which will be discussed in detail in the next chapter.

Chapter 3

Success through tethering

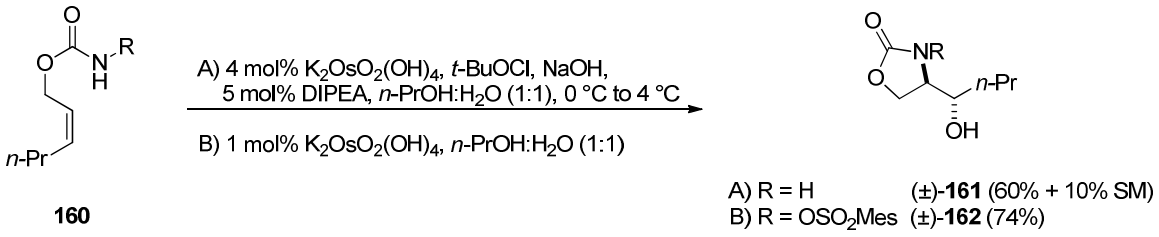
Chapter 3

3.1 Introduction to the tethered aminohydroxylation reaction

Before proceeding with the application of the tethered aminohydroxylation (TA) methodology to our target molecule, in this section a review of the TA literature with particular focus on homoallylic substrates is given.

3.1.1 Development of the TA reaction

First reported in 2001,[52] the TA reaction enforces complete regioselectivity of the osmium-mediated aminohydroxylation product by tethering the *N*-source to one end of the alkene. Among the first few substrates disclosed was alkene **160**, which had the nitrogen source tethered on the allylic alcohol. These early reported examples relied on generating an *N*-chlorocarbamate prior to the introduction of the osmium catalyst (analogous to the Sharpless AA),[52] but it was soon observed that *N*-chlorocarbamates, formed *in situ* in the presence of *t*-BuOCl, were unstable to the reaction conditions resulting in low yields and incomplete conversions (Scheme 34, Conditions A). In 2006, the Donohoe group demonstrated that the use of *N*-sulfonylcarbamates could avoid the aforementioned problems. This carbamate functionality was capable of oxidising the osmium (VI) catalyst to the active osmium (VIII) species leading to higher yields even at lower catalyst loadings (Scheme 34, Conditions B).

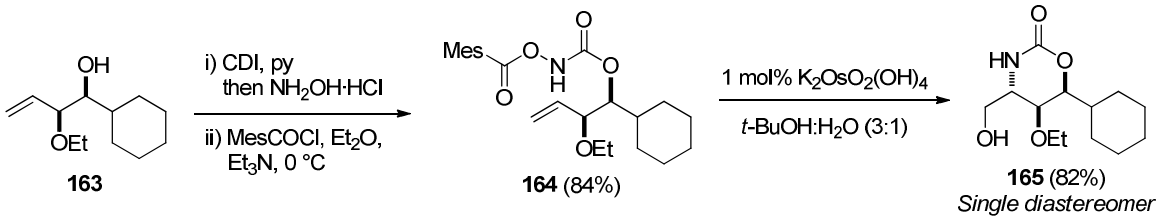


160

A) R = H (±)-**161** (60% + 10% SM)
B) R = OSO_2Mes (±)-**162** (74%)

Scheme 34: The tethered aminohydroxylation reaction

Furthermore, the addition of base, which was previously necessary in order to deprotonate the *N*-chlorocarbamate precursor prior to oxidation of the osmium species, was no longer required under these conditions. However, *N*-sulfonylcarbamate could not be stored for long periods of time. Despite notable improvements over *t*-BuOCl, these 2nd generation reoxidants gave lower yields on substrates such as acyclic homoallylic alcohols. Further optimisation revealed that *O*-aryloxycarbamates increased yields in all substrate classes, including acyclic homoallylic alcohols (Scheme 35). Screening experiments showed that pentafluorobenzoyl or 2,4,6-trimethylbenzoyl derivatives lead to the highest TA yields. In addition, both derivatives are stable and can be stored at room temperature for several weeks without any decomposition. Both *O*-aryloxycarbamate (3rd generation) and *N*-sulfonylcarbamates (2nd generation) can be prepared by sequential reaction of the parent alcohol with *N*,*N'*-carbonyldiimidazole and hydroxylamine followed by aroylation or sulfonylation respectively to yield desired compounds (Scheme 35).

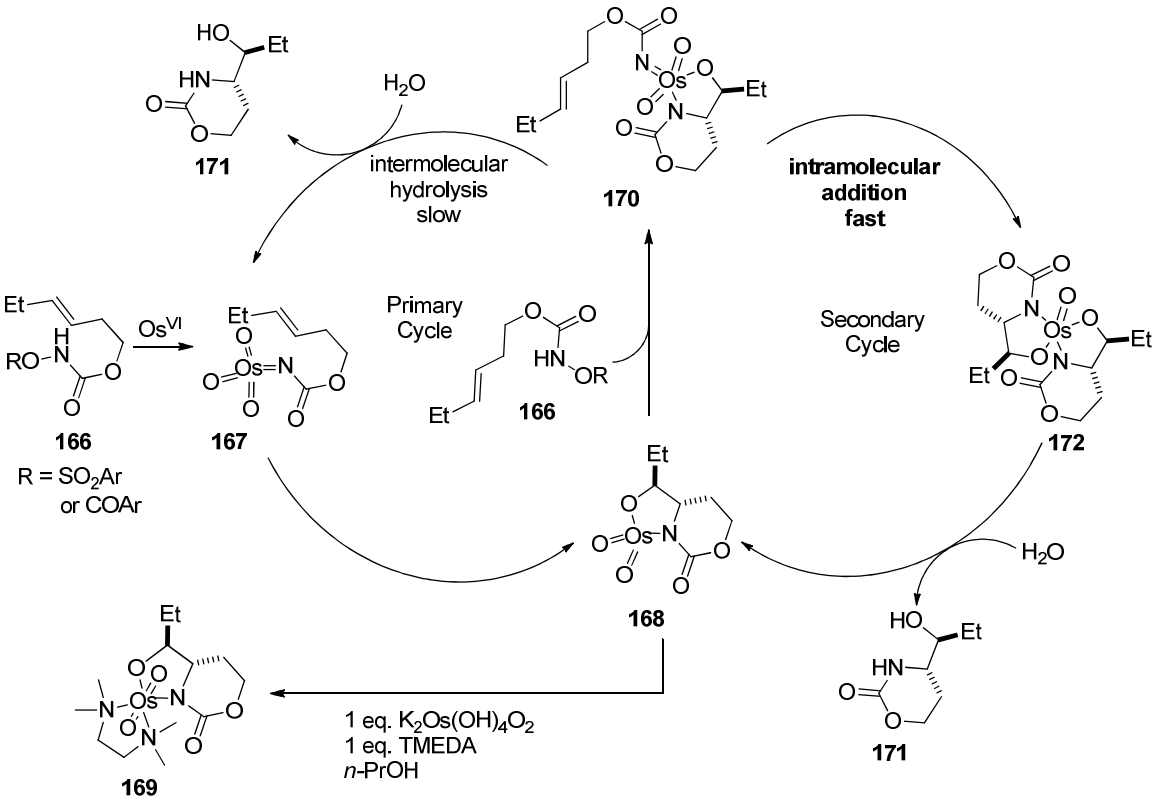


Scheme 35: The 3rd generation TA reaction

3.1.2 Mechanism of the TA reaction

The mechanism for this transformation is in accordance with that of the corresponding Sharpless asymmetric aminohydroxylation and dihydroxylation reaction. It is depicted for a typical 2nd or 3rd generation carbamate reoxidant system (Scheme 36). The **167** species is thought to undergo a [3+2] cycloaddition onto the alkene to generate osmium(VI) azaglycolate

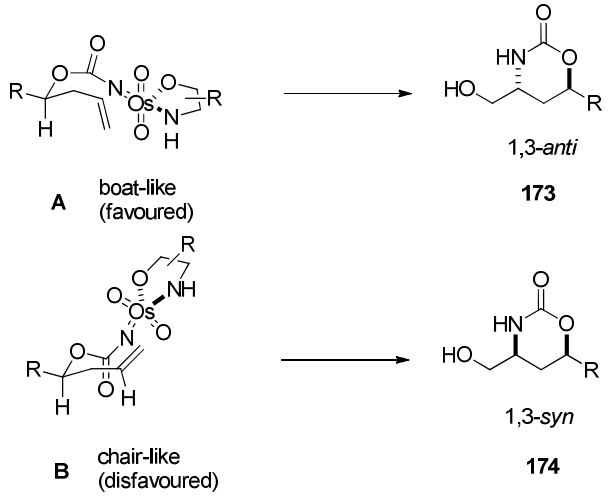
168, as evidenced by the isolation and characterisation of **169** by X-ray crystallography. The osmium(VI) azaglycolate **169** was trapped when the reaction was performed with stoichiometric amounts of osmium in the presence of tetramethyldiethylamine (TMEDA), which has strong affinity for osmium.



Scheme 36: Mechanism of the TA reaction

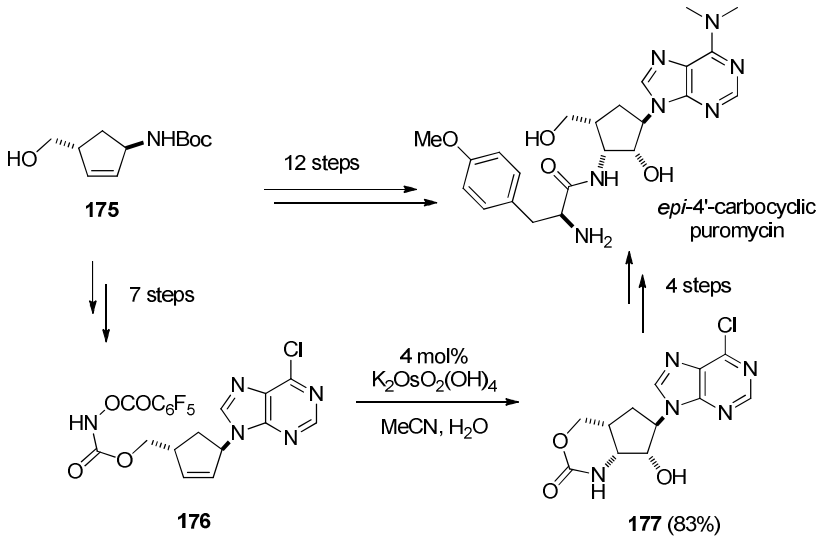
Enantioselectivity in the TA reaction was not induced by the addition of chiral ligands to the reaction mixtures. This indicates that the TA reaction of allylic or homoallylic carbamates is in fact a secondary catalytic cycle process, in which an intramolecular cycloaddition reaction with the tethered olefin is more rapid than the hydrolysis of the osmium(VIII) intermediate **170**. This crowding of the osmium centre during the crucial bond forming step thus prevents binding of asymmetric ligands.

Understanding the 1,3-*anti* selectivity displayed by TA reactions of homoallylic substrates is crucially important for our synthetic target. In 2007, Donohoe and co-workers proposed a simple model to explain the diastereoselectivity (Scheme 37).[50] By assuming that the Os=N−C linkage is linear and remains reasonably so in the transition state, it can be noted that the boat-like conformation **A**, with an equatorial R group, allows the best overlap between the oxidant and the π-bonds of the alkene giving rise to the 1,3-*anti* product **173**. The corresponding chair-like conformation **B**, which would give the 1,3-*syn* product **174**, is less favourable because this arrangement puts a larger distance between the orbitals of the alkene and the imido-osmium complex.



Scheme 37: Transition state model for 1,3-anti diastereoselectivity of the TA reaction

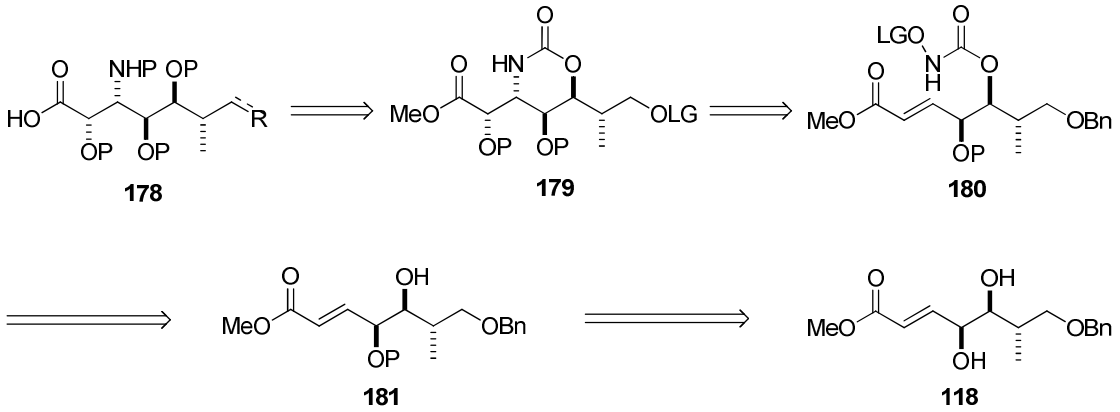
Borne out of the need to overcome the low regioselectivity displayed by the Sharpless AA reaction,[53] the tethered aminohydroxylation has demonstrated its potential and generality by application in the synthesis of several natural products.[54] For example, in 2010, Marvin Miller and co-workers at the University of Notre Dame, USA used the 3rd generation TA reoxidant on a homoallylic alcohol substrate towards an efficient synthesis of *epi*-4'-carbocyclic puromycin (Scheme 38). The TA reaction gave the desired diastereomer in a good yield of 83%.



Scheme 38: Application of the TA methodology to natural product synthesis

3.2 Modified synthetic strategy

Having failed to effect aminohydroxylation to install the key 1,2-aminoalcohol *via* the Sharpless AA, we turned our attention to the tethered aminohydroxylation reaction developed in the Donohoe group.[54] Our modified strategy to incorporate this methodology involves the synthesis of the β-amino acid **178** by the displacement of a leaving group (such as tosylate) with a nucleophile (Scheme 39). This is in line with our previous retrosynthesis for installation of the aliphatic side chain (see Scheme 17). Finally, hydrolysis of the ester would yield acid **178**. Compound **179** with all five stereocentres in place could be obtained by the TA reaction of **180**, which could come from **181** by a two-step procedure developed by the Donohoe group.[50] To prepare **181**, we could selectively protect diol **118** by taking advantage of the more reactive allylic alcohol position compared to the homoallylic alcohol. These minor changes will enable tethering of the *N*-source for a successful TA reaction.

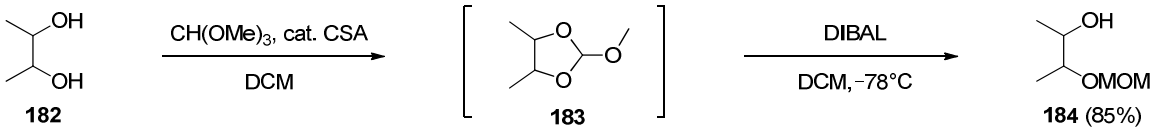


Scheme 39: The revised retrosynthesis

3.3 Selective protection of diol 118

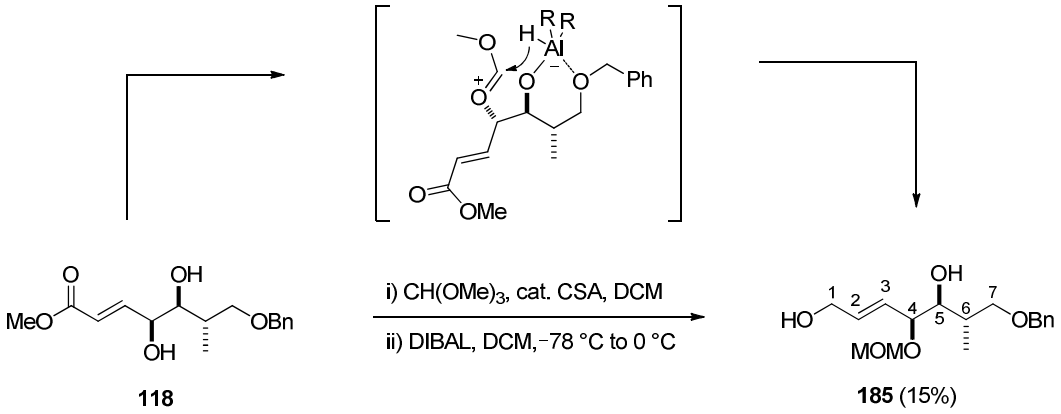
In order to proceed with the revised strategy, we first needed to selectively mono-protect previously prepared diol **118** (see Scheme 22). Although the selective mono-TIPS protection of an allylic alcohol over a homoallylic alcohol has been reported in literature,[55] submission of diol **118** to the reported reaction conditions (1 eq. of TIPSOTf and 2 eq. of 2,6-lutidine) gave an inseparable mixture of mono-protected diols. Similarly, reaction of diol **118** with MOM-Cl (1 eq.) in the presence of Hünig's base after 48 h gave an unidentifiable mixture with 60% starting material recovered.[56]

It was therefore proposed that we use the Yamamoto protocol[57] to achieve the desired selectivity. According to the protocol diol **182** is treated with trimethyl orthoformate (2 eq.) in presence of sub-stoichiometric amounts of CSA to form orthoformate **183**, which is opened with a hydride source such as DIBAL (10 eq.) to give mono-protected diol **184**.



Scheme 40: The Yamamoto protocol

Using unsymmetrical diols gives 1:1 mixture of mono-protected diols, but we postulated (despite any literature precedent) that the adjacent benzyl ether might enable the chelation of the Lewis acid and ensure regioselective opening of the acetal. The hydride is then delivered in a manner such that we would obtain the desired product **181**. On subjecting diol **118** to the Yamamoto protocol, we were pleased to obtain the desired mono-protected diol **185**, albeit in only 15% yield but with 52% recovered starting material (Scheme 41). The regioisomer was confirmed by COSY correlations (distinct ^{1}H NMR signals from H-6 were correlated to H-5, which had direct correlation to the OH signal at 3.33 ppm) and HMBC correlations (the CH_2 protons of the MOM group had direct correlation to C4 but not to C5).

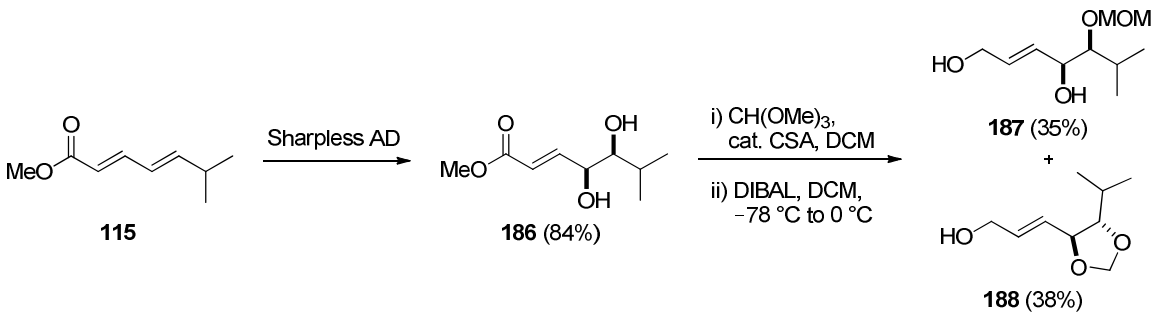


Scheme 41: The Yamamoto Protocol and its application to substrate 185

At this point we were aware that using the Yamamoto protocol would mean that the ester in diol **118** would be reduced concomitantly, and as such we proceeded to optimise the transformation. The Yamamoto protocol requires large excess of DIBAL (10 eq.), which, in our

case, caused a number of issues. The original paper reported a basic work up (2 M NaOH), but this led to the precipitation of aluminium hydroxide, which made it difficult to ensure that all of the product was transferred to the organic layer. Mass spectrometry indicated the presence of product in the aqueous layer even after five washings with ethyl acetate. Instead, when we did an acidic work up (1 M HCl) we were ensured that no product remained in the aqueous layer, but we were able to observe (by mass spectrometry) traces of the triol side product. This indicated, unsurprisingly, that even mild acid causes cleavage of the MOM group. Eventually, we were able to increase the yield by using aqueous solution of Rochelle's salt (sodium potassium tartrate) in the work up, which readily complexed with the aluminium salts and made the extraction with organic solvents more efficient. Our optimised conditions used 20 equivalents of DIBAL and Rochelle's salt in the work up of the reaction and increased the yield of the desired product **185** to 45%.

In order to investigate our chelation hypothesis and further optimise the reaction we designed model substrate **186**, which did not have the additional oxygen atom to chelate with DIBAL. It was proposed that in the absence of chelation we would obtain a 1:1 mixture of mono-protected diols. Model substrate **186** was obtained in 84% yield by treating diene **115** to the Sharpless AD conditions (Scheme 42). On subjecting diol **186** to the Yamamoto protocol, to our surprise, we obtained only a single regioisomer of the mono-protected diol **187** in 35% yield along with methylene acetal **188** in 38% yield.

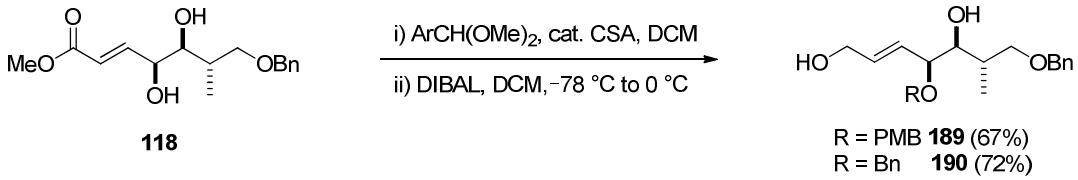


Scheme 42: Mechanistic investigation of selective protection

The opposite selectivity may be attributed to the steric hindrance created by the isopropyl group, which may have biased the aluminium to chelate more with the allylic oxygen atom rather than the homoallylic oxygen atom and thus deliver the hydride in an opposite fashion to that we noted with the desired substrate **185** in Scheme 41.

The side-product **188**, a methylene acetal, was obtained in a comparable yield indicating that the aluminium chelation to the exocyclic methoxy group of the orthoformate intermediate also occurs. This indicated to us that the low yield of the desired mono-protected alcohol **185** may be due to the formation of an analogous methylene acetal. This high selectivity in Scheme 41 and Scheme 42 suggests that aluminium chelation is indeed a strong factor that determines the position of hydride transfer but also that steric hindrance, in absence of the extra chelating oxygen atom, plays an important role.[58]

The possibility of chelation to the methoxy group prompted the use of an alternative acetal to trimethyl orthoformate, which does not possess the exocyclic methoxy group. We therefore attempted to use the Yamamoto protocol on diol **118** by treating it first with anisaldehyde dimethylacetal or benzaldehyde dimethylacetal in the presence of CSA, and then upon completion by TLC treating it with DIBAL (20 eq.) to deliver the hydride in a selective fashion (Scheme 43). We were pleased to obtain the desired regioisomers **189** and **190** in higher yields, with the regioselectivity confirmed by COSY correlations (as previously discussed with compound **185**).

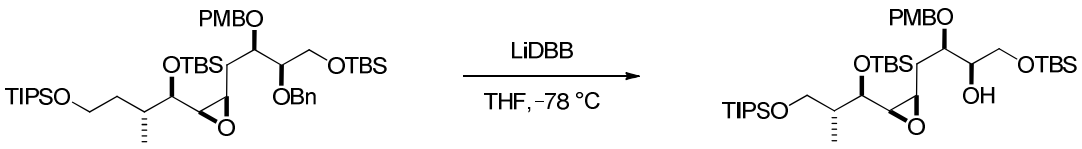


118

R = PMB **189** (67%)
R = Bn **190** (72%)

Scheme 43: Selective PMB / Bn protection of 118

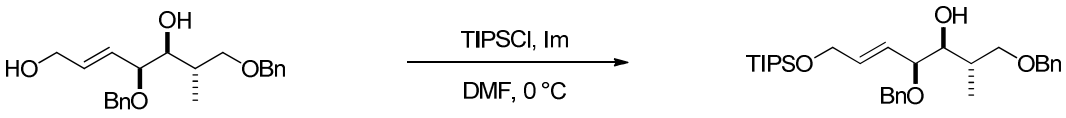
Our choice to selectively mono-protect the diol with a PMB group instead of a MOM group was supported by precedent that a benzyl group could be selectively cleaved in the presence of a PMB ether. In their synthesis of fragments of pectenotoxin-4, David Evans and co-workers had shown that by using Li/DBB at a low temperature they could selectively remove the benzyl group (Scheme 44).[59]



191 **192** (79%)

Scheme 44: David Evans' selective cleavage of benzyl ether over PMB ether

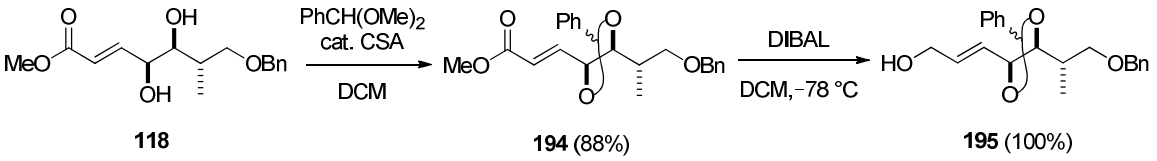
Unfortunately, subjecting **190** to the same deprotection conditions lead to recovery of most of the starting material and with no traces of the desired product. Thus, we proceeded to use Bn-derivative **190**, which was synthesised in slightly higher yield than the PMB-derivative **189**, to continue the synthesis of the TA-precursor. Following a one-pot ester reduction and selective diol protection we needed to mono-protect **190** at the primary hydroxyl group. Attempts to use triisopropylsilyl trifluoromethanesulfonate in the presence of triethylamine gave a mixture of mono- and bis-protected silyl ethers, as observed by ^{1}H NMR and mass spectrometry analysis. However, when compound **190** was treated with chlorotriisopropylsilane in the presence of imidazole in DMF, we obtained the desired product **193** in 81% yield (Scheme 45).



190 **193** (81%)

Scheme 45: Selective TIPS protection of primary alcohol 190

Although we were able to obtain alcohol **190** from diol **118** (see Scheme 43) in a satisfactory yield of 72% over two steps, this methodology posed scalability issues. To drive the selective opening of the acetal to completion required a large excess of DIBAL. On small scales, by using Rochelle's salt to complex with the aluminium salts, we were able to effectively extract the desired product from the aqueous layer. Unfortunately, on a gram-scale, the large volume of saturated Rochelle's salt solution needed to completely complex the aluminium residues required significant volumes of organic solvent to extract the product from the aqueous solution. Since using large excess of reagents at such scales proved to be impractical, we considered carrying out the procedure in a step-wise fashion. Accordingly, diol **118** was treated with benzaldehyde dimethylacetal in the presence of CSA to form acetal **194**, which was further reduced by using 2 equivalents of DIBAL to furnish alcohol **195** in 88% yield over two steps (Scheme 46).

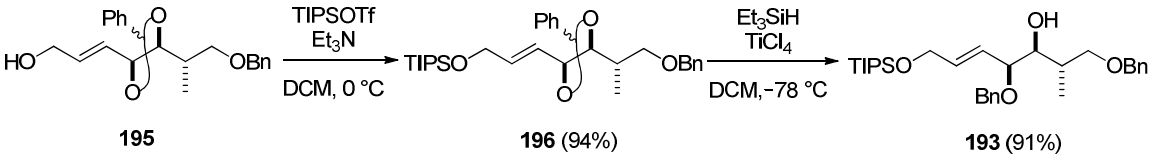


118 **194** (88%) **195** (100%)

Scheme 46: Scaling up the synthesis of 195

With no selectivity issues, the installation of the TIPS protecting group on the primary hydroxyl group proceeded smoothly to give acetal **196** in an excellent yield of 94% using triisopropyl trifluoromethanesulfonate in the presence of triethylamine (Scheme 47). However, we found that opening acetal **196** selectively to give alcohol **193** still required 10 equivalents of DIBAL to drive the reaction to completion, which led to the same extraction difficulties in the work up. A literature search on the opening of benzaldehyde acetals led us to work published by Hiyoshizo Kotsuki at Kochi University, Japan that reported the use of titanium tetrachloride

as a Lewis acid and triethylsilane as a hydride source to open a symmetric acetal furnishing a mono-benzyl protected diol.[60] We postulated that the extra chelating oxygen atom in our system would help open the acetal in a regioselective manner (as evidenced by our work with the Yamamoto protocol). Indeed when the acetal **196** was subjected to Kotsuki's conditions, we obtained the desired alcohol **193** (the data were identical to compound synthesised in Scheme 45) in an excellent yield of 91% (Scheme 47). To our further delight, this reaction worked at gram scales and gave repeatable results.

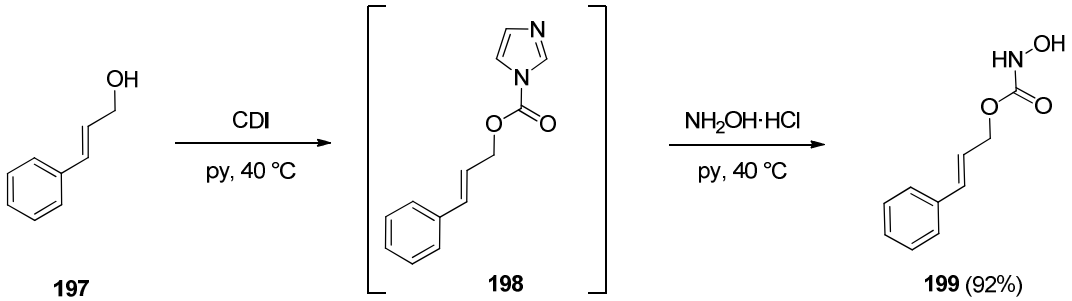


195 **196** (94%) **193** (91%)

Scheme 47: Scaling up the synthesis of 193

3.4 Synthesis of the TA-precursor

With the desired alcohol **193** in hand, we looked to tether the nitrogen source on to the homoallylic alcohol in order to prepare the TA precursor. Previously reported work showed that cinnamyl alcohol (**197**) can be converted to hydroxycarbamate **199** in a one-pot procedure (Scheme 48).[50] Exposure to *N,N'*-carbodiimidazole (CDI) generates imidazole **198**, which yielded the desired product in 92% yield on treatment with hydroxylamine hydrochloride salt.

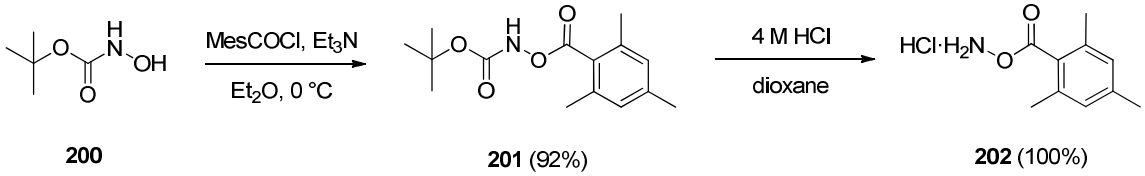


197 **198** **199** (92%)

Scheme 48: Previously reported tethering of the N-source to 197

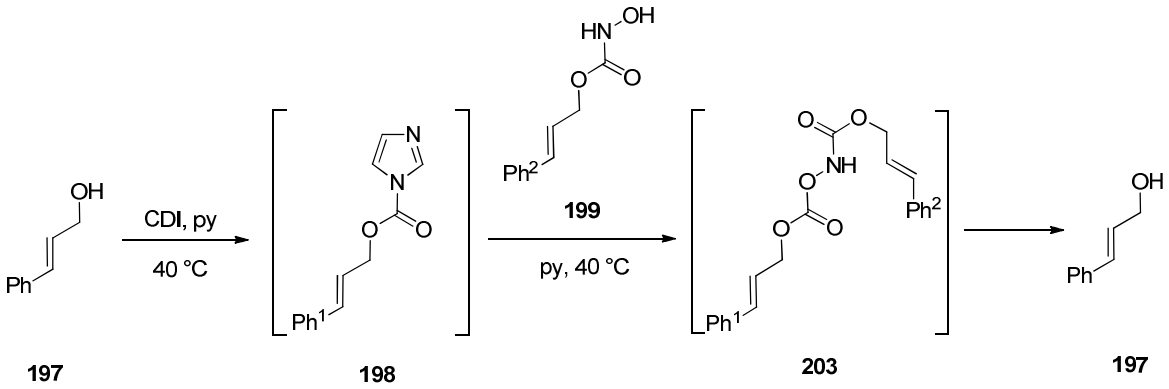
However, in our hands, treating **193** to the reported conditions only gave a yield of 35% for desired compound, with significant amounts of recovered starting material. To understand the lower yield obtained we repeated the reaction reported using cinnamyl alcohol (**197**). As TLC and NMR analysis of the reaction mixture after addition of *N,N*-carbodiimidazole indicated that complete consumption of the starting material had occurred, it was concluded that the addition of the hydroxylamine hydrochloride salt thus caused the starting material to be returned. To ensure that an impurity in the reagents wasn't leading to the unexpected results, the reaction was repeated with freshly distilled pyridine, new *N,N*-carbodiimidazole, and recrystallized hydroxylamine hydrochloride salt, but this did not result in any appreciable improvement in yield or conversion. Additionally, experiments showed that the scale at which the reaction was run was not important.

It was postulated that the application of the hydrochloride salt of hydroxylamine may be interfering with the reaction. Therefore, triethylamine was added to the reaction mixture to form the free base of hydroxylamine *in situ*, before adding the free base to the imidazole carboxylate intermediate. As no improvement in the outcome was observed, we proceeded to try alternative hydroxylamine sources. Both the commercially available *O*-trimethylsilylhydroxylamine and the mesitoyl protected analogue **202** (prepared in a high-yielding two-step procedure, Scheme 49) failed to give any improvement in yields or conversion.



Scheme 49: Synthesis of O-mesitoyl protected hydroxylamine hydrochloride 202

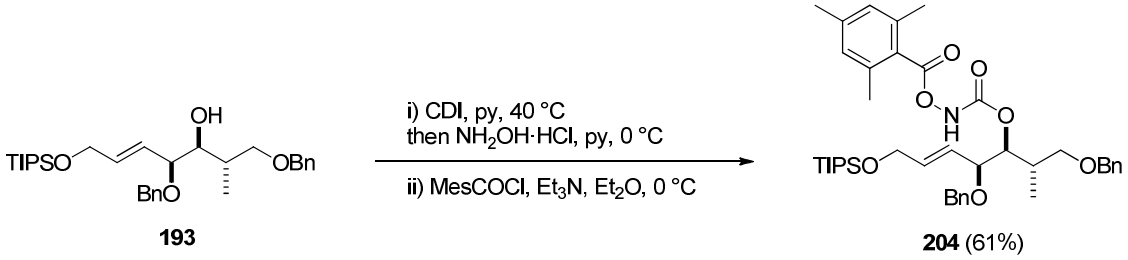
Our attempts to substitute phosgene for *N,N*-carbodiimidazole resulted in very poor yields of the desired hydroxycarbamate. It was hypothesised that the use of excess hydroxylamine hydrochloride may be leading to the decomposition of the hydroxycarbamate **199**. To test this, we subjected the hydroxycarbamate **199** to the eaction conditions for 24 h with hydroxylamine hydrochloride (5 eq.). The resultant mixture was analysed by ^{1}H NMR spectroscopy and no further reaction was observed. Thus, the low yields and returned starting material are not the result of decomposition of the hydroxycarbamate **199**.



Scheme 50: Understanding the cause for returned starting material

It was then suggested that if the hydroxycarbamate does not decompose by reacting with hydroxylamine, it may instead be reacting with the imidazole carboxylate intermediate **198**. To test this, we added the hydroxycarbamate **199** to *in situ* formed imidazole carboxylate intermediate **198** (Scheme 50). Indeed, a reaction occurred that delivered alcohol **197** and an unidentified product. Thus, the nucleophilic attack of the oxygen of hydroxycarbamate **199** on the intermediate **198** leads to formation of an unstable carbonate **203**, which leads to returning of the starting alcohol. To overcome this deleterious process, the reaction was repeated at higher dilution so that the hydroxycarbamate product **199** will be less likely to encounter and react with the intermediate. As such, compound **197** was subjected to the reaction conditions by

reducing the concentration of both the alcohol (from 0.3 mmol/mL to 0.05 mmol/mL) and the hydroxylamine (1 mmol/mL to 0.1 mmol/mL). To our surprise, this led to a decrease in the product to starting material ratio in the reaction mixture. It was then postulated that this side reaction may be curbed by increasing the concentration of hydroxylamine (from 1 mmol/mL to 5 mmol/mL) to ensure that the intermediate reacts much more rapidly with hydroxylamine than with the hydroxycarbamate **199**. To our delight, under these conditions, we observed an increase in the yield and conversion. Further lowering the temperature at which hydroxylamine was added to the reaction mixture to 0 °C helped improve the overall yield to 72% with only traces of cinnamyl alcohol recovered. Applying these optimised conditions to our starting material **193** improved the yield of the hydroxycarbamate formation. Acylation of the hydroxycarbamate subsequently proceeded in quantitative yield to furnish the TA-precursor **204** in 61% yield over two steps (Scheme 51).

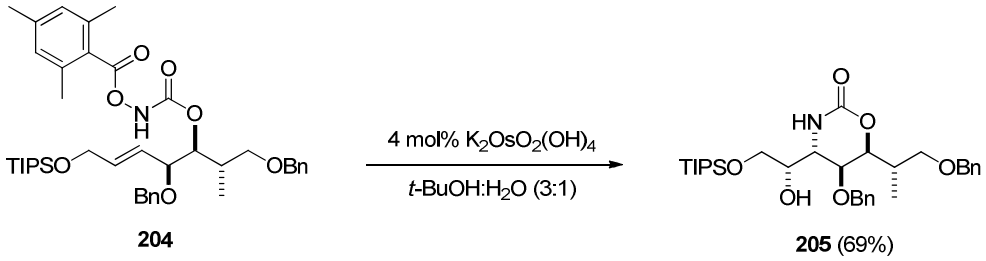


Scheme 51: The optimised conditions for preparation of the TA-precursor 204

3.5 The TA reaction

With the TA-precursor in hand, we subjected **204** to the conditions developed by the Donohoe group that used 1 mol% potassium osmate. After stirring overnight, TLC analysis showed a significant amount of starting material. Thus, further 1 mol% of the catalyst was added. However, after further 16 hours, there was still some starting material present with a more polar spot, possibly product. To push the reaction to completion, a further 2 mol% of the catalyst was

added. After stirring overnight, there was no remaining starting material as indicated by TLC analysis. Following chromatographic purification, the desired oxidation product **205** was isolated as a single diastereomer in 69% yield.



Scheme 52: The TA reaction on 204

The stereochemistry of the TA-product was confirmed by nOe studies on a related compound **205a** (Figure 12). Robert Pullin, a postdoc in the Donohoe group, synthesised **205a** by treating **205** with TBS triflate in presence of 2,6-lutidine (see Appendix for details).

Enhancements were observed between H^3 and H^4, H^3 and H^{10} and H^4 and H^5, which are consistent with the proposed *anti*-configuration (see Section 3.1.2 and Scheme 33). A strong enhancement would have been expected between H^3 and H^5 in the *syn*-configuration but this was not observed.

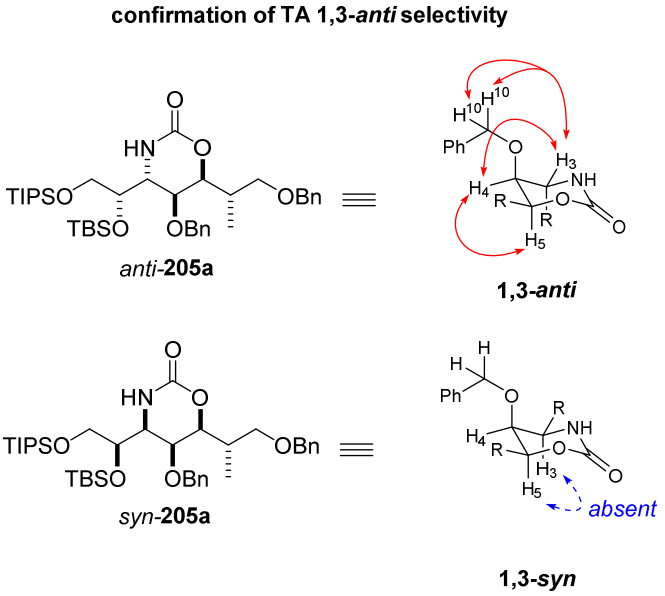


Figure 12: nOe enhancements present in stereopentad 205

Starting from Roche ester (**56**), we have prepared the desired core structure of microsclerodermins' β-amino acids with five stereocentres in 10 steps with an overall yield of 11% (or *via* a longer route in 12 steps with an overall yield of 15%). Now we looked to attach the side chain to complete the synthesis.

Chapter 4

The side-chain saga

Chapter 4

4.1 Introduction of the side-chain

With the five stereogenic centres of the core β-amino acid in place, we looked to install the alkyl/alkenyl side-chain towards completion of the synthesis of the amino acid. Amongst those β-amino acids with five stereocentres (Figure 13), the side-chain was envisaged to be attached *via* an olefination reaction (for microsclerodermins F, G, H and I) or *via* a displacement reaction (for microsclerodermins A and B).

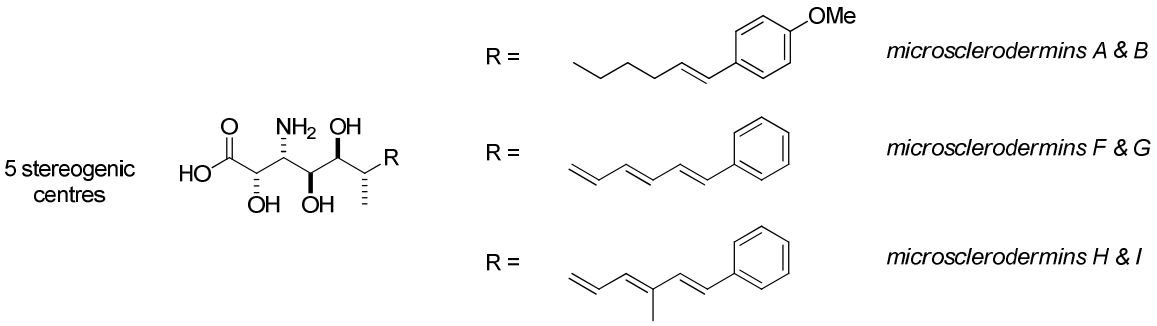
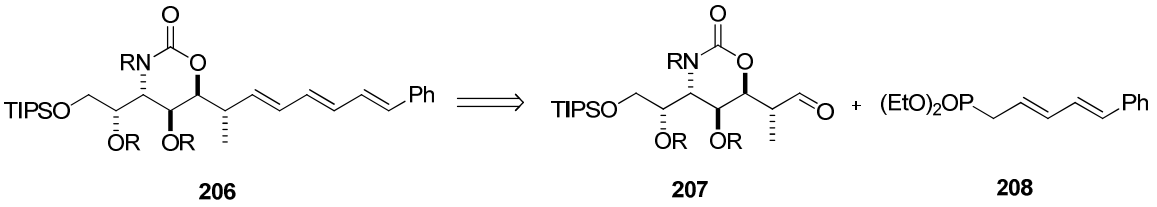


Figure 13: Structures of the β-amino acid residues of microsclerodermins

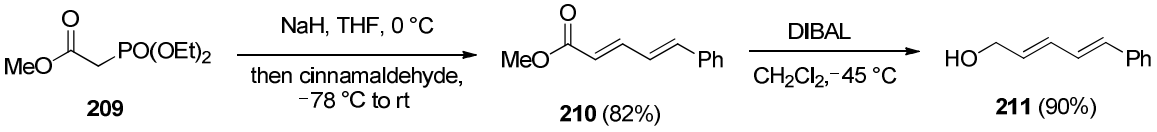
At first we aimed to install the side-chain, which constitutes a triene with a terminal phenyl ring, to enable the synthesis of microsclerodermin F and G. If we were successful, then we could analogously prepare the β-amino acids for microsclerodermins H and I, which has an extra methyl substituent. It was envisaged that an olefination reaction between aldehyde **207** and phosphonate **208** would be an effective way to prepare **206** (Scheme 53).



Scheme 53: Proposed introduction of the alkenyl side-chain

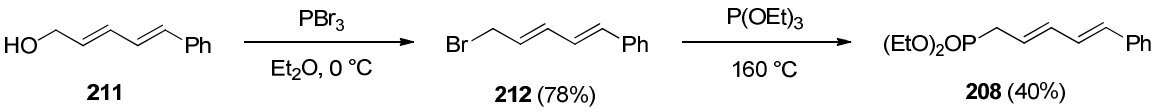
4.2 Synthesis of phosphonate 208

To prepare the required phosphonate, we first synthesised diene **210** from commercially available methyl 2-(diethoxyphosphoryl)acetate (**209**). On treating phosphonate **209** with cinnamaldehyde in the presence of sodium hydride (Scheme 54), diene **210** was obtained in 82% yield with complete *E*-selectivity (confirmed by a *trans* coupling constant of 15.3 Hz, X-Ray crystal structure obtained, see Appendix). It was then reduced to alcohol **211** by treating with DIBAL in a yield of 90%.92



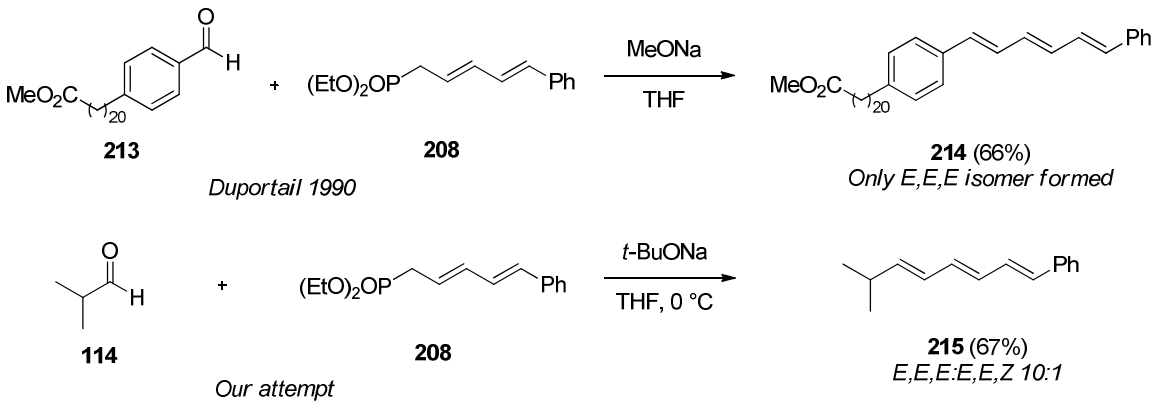
Scheme 54: Synthesis of alcohol 211

Alcohol **211** was converted to bromide **212** by treating it with phosphorus tribromide in a good yield of 78% (Scheme 55). The Michaelis-Arbuzov reaction on bromide **212** furnished the desired phosphonate **208** in a moderate yield of 40%.[96]



Scheme 55: Synthesis of phosphonate 208

In 1990, Guy Duportail and co-workers at the Université Louis Pasteur, France used phosphonate **208** to synthesise **214** (with only the *E,E,E*-isomer formed) by using sodium methoxide as the base (Scheme 56).[61] We tested phosphonate **208** by treating it with sodium *tert*-butoxide followed by isobutyraldehyde to give alkene **215** in 54% yield (*E*,*E*,*E*:*E*,*E*,*Z* = 10:1). Lowering the temperature of the reaction mixture to 0 °C before addition of isobutyraldehyde improved the yield to 67% with similar *E*:*Z* selectivity.



Scheme 56: Phosphonate 208 in action

4.3 Protecting-group strategies

With a successful model for the proposed olefination in hand, we assessed the protecting groups on the heteroatoms of the desired aldehyde **207** that were needed for the olefination reaction (Scheme 53). The most critical of those protecting groups is the one on the hydroxyl group at C4 (Figure 14). If the protecting group at C4 and C7 were not orthogonal, then both would have to be removed to enable oxidation of the primary hydroxyl group at C7. There was a fear that on selective oxidation to the aldehyde **216** (which we hoped would occur efficiently given the literature precedent for oxidation of primary over secondary) the free hydroxyl group

at C4 could lead to the formation of a lactol. Although a lactol could be opened to effect an olefination reaction, a survey of the literature showed that such a transformation is usually difficult, and if it occurs then it is usually a less efficient reaction.

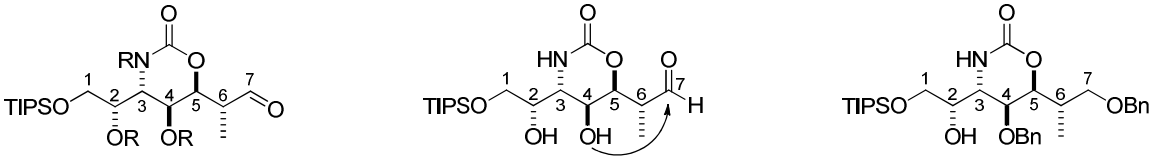
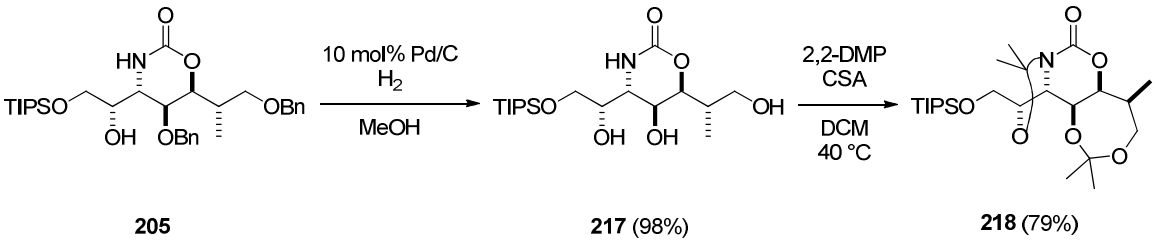


Figure 14: Assessing the protecting groups on proposed aldehyde 216

The previously synthesised TA-product **205** (see Section 3.5) possessed benzyl protected hydroxyl groups at both C4 and C7, which may make it an unsuitable substrate to prepare the desired aldehyde. We envisaged that on removal of both the benzyl groups, we could protect the hydroxyl groups at C2 and C4 by tying them together as an acetonide group. We believed that a 6 membered-acetonide ring with two secondary hydroxyl groups (C2 and C4) would be thermodynamically more favoured to the 7 membered-acetonide with one primary and one secondary hydroxyl group (C4 and C7). To that effect, we hydrogenated TA product **205** to remove both the benzyl groups to give triol **217** in an excellent yield of 98% (Scheme 57). It was then treated with 2,2-dimethoxypropane in the presence of a sub-stoichiometric amount of CSA. At room temperature the reaction was very sluggish, so it was heated to 30 °C in a sealed vial. After 4 h, there was still significant starting material present so it was further heated to 40 °C and stirred for a further 6 h when complete conversion was obtained. On purification, we obtained carbamate **218** in a good yield of 79%. Although it had both hydroxyl groups at C2 and C4 protected, they were tied to different acetonide groups. We were surprised that despite the reduced nucleophilicity of the nitrogen atom (induced by the carbamate group), the acetonide group favoured five-membered ring with the nitrogen atom and the hydroxyl group at

C2. We attempted to run the reaction at a lower temperature to try to alter the selectivity of acetonide formation, despite the potential cost of longer reaction time, but we were unsuccessful in making any difference to the selectivity; moreover the reaction did not proceed to completion.

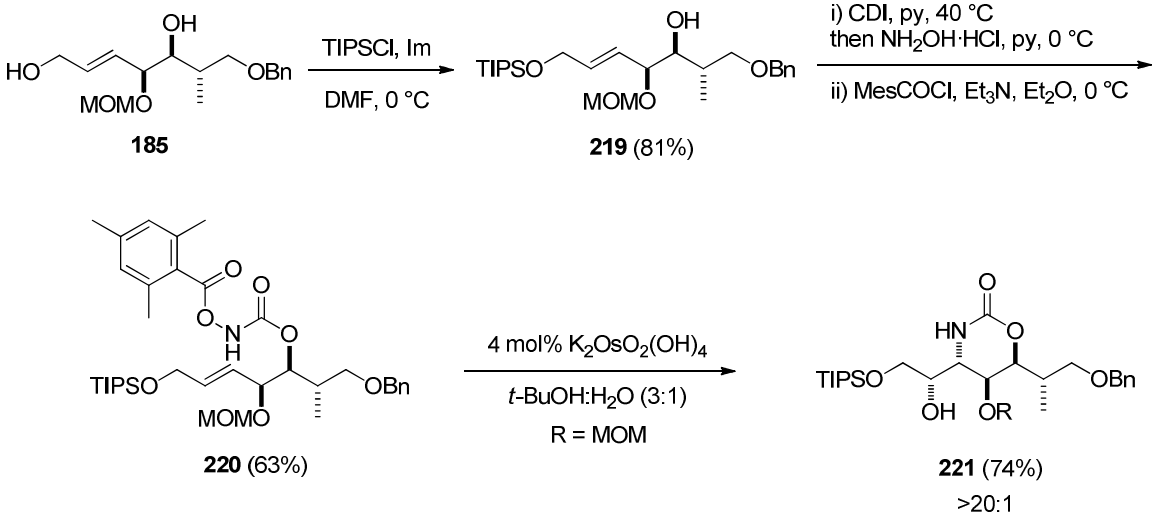


Scheme 57: Installing the acetonide protecting group

At this point, we envisaged that if the nitrogen on the carbamate was protected then the acetonide formation may be forced to occur across the hydroxyl groups at C2 and C4 (6-membered v/s 7-membered). To that end, we treated alcohol **205** with di-*tert*-butyl dicarbonate (1.2 eq.) in presence of DMAP in the hope that the carbamate would be selectively Boc protected. Unfortunately, we obtained a mixture of *O*-protected and *N*,*O*-bisprotected carbamates. A reduction in the number of equivalents of di-*tert*-butyl dicarbonate (0.9 eq.) and the absence of DMAP slowed down the reaction, but still gave a mixture of products. These results showed that the hydroxyl group at C2 was much more nucleophilic than the carbamate. If the Boc protecting group prefers to add to the hydroxyl group first, we concluded that other carbamate protecting groups would react in a similar manner and would not allow for selective protection at the carbamate.

However, we have shown previously that instead of a benzyl protecting group we could install the MOM protecting group on the hydroxyl at C4, albeit in a lower yielding route (see Scheme

41). To that end we selectively protected diol **185** to give silylether **219** in a good yield of 81% (Scheme 58). It was then subjected to the optimised conditions to prepare the TA precursor **220** in a yield of 63%, which underwent the TA reaction to furnish the desired TA product **221** in a good yield of 74% as a single diastereomer.

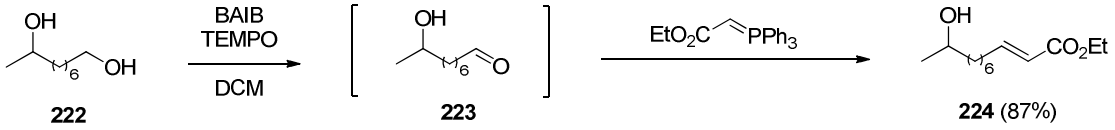


Scheme 58: Synthesis of MOM-protected TA product

4.4 Olefination reactions

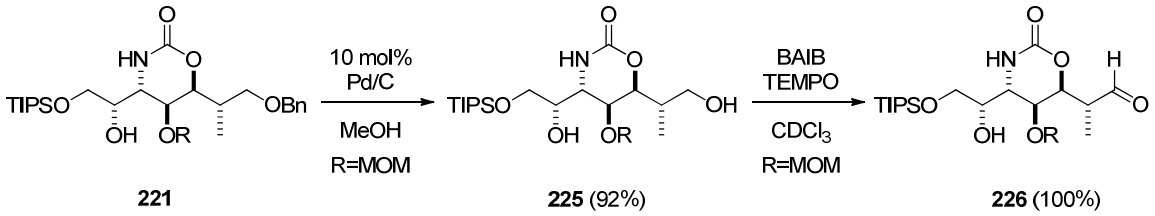
Now with an orthogonal protecting group installed at C4 and C7, we looked to selectively oxidise a primary alcohol (C7) in the presence of a secondary alcohol (C2) to enable the synthesis of the target aldehyde **207**. In 2006, Jean-Michel Vatèle at the Université Claude Bernard, France reported the use of TEMPO (2,2,6,6-tetramethyl-1-piperdinyloxy) and BAIB (bis(acetoxy)iodobenzene) to enable such an oxidation (Scheme 59).[62] Vatèle showed that the oxidation conditions were compatible for an *in situ* olefination reaction. The mild conditions needed to effect the transformation and its compatibility with many protecting groups made it an attractive option to synthesise aldehyde **207**. Additionally, the ability to use the intermediate

aldehyde without a work up or purification meant that even sensitive aldehydes could be made and used for further olefination reactions through this methodology.



Scheme 59: Vatèle's one pot oxidation/olefination reaction

Thus, we proceeded to remove the benzyl group from carbamate **221** to afford alcohol **225** in a yield of 92% (Scheme 60). It was then oxidised by using Vatèle's procedure to give aldehyde **226** (confirmed by the appearance of a doublet at 9.86 ppm in the ^{1}H NMR spectrum and a singlet at 201.9 ppm in the ^{13}C NMR spectrum). The oxidation was carried out in deuterated chloroform instead of dichloromethane, which enabled us to monitor the progress of the reaction by NMR spectroscopy.

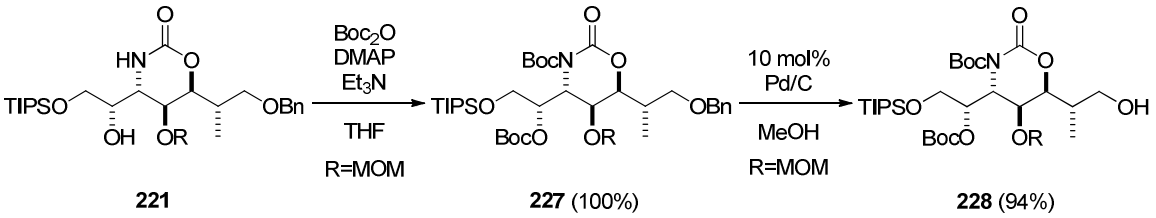


Scheme 60: Synthesis of aldehyde 226

The aldeyhyde was then treated to the conditions used to effect the model olefination of phosphonate **208**. We ensured that an excess of phosphonate (5 eq.) and sodium *tert*-butoxide (5 eq.) was added to compensate for the naked hydroxyl group at C2 and the unprotected nitrogen on the carbamate. Unfortunately, no reaction occurred as analysed by crude NMR and mass spectrometry. The aldehyde was detected by TLC analysis for about 2 h after addition,

but after work up no aldehyde was recovered, which may indicate decomposition over the course of the reaction.

It was proposed that if the heteroatoms (C2-OH and C3-NH) were protected, then fewer equivalents of phosphonate **208** and base would be needed, and that may perhaps help curb side reactions and/or reduce decomposition of the aldehyde. Accordingly, we looked to protect the hydroxyl group at C2 and the carbamate. The protecting group of choice, which can be efficiently installed and removed, was the Boc group. From our previous experience, we knew that it would prefer to protect the hydroxyl group on C2 first before protecting the carbamate. Thus, we added an excess of di-*tert*-butyl dicarbonate (3 eq.) to form the *N*,*O*-bisprotected carbamate **227** in quantitative yield (Scheme 61). Compound **227** was then hydrogenated to remove the benzyl group to give alcohol **228** in 94% yield.

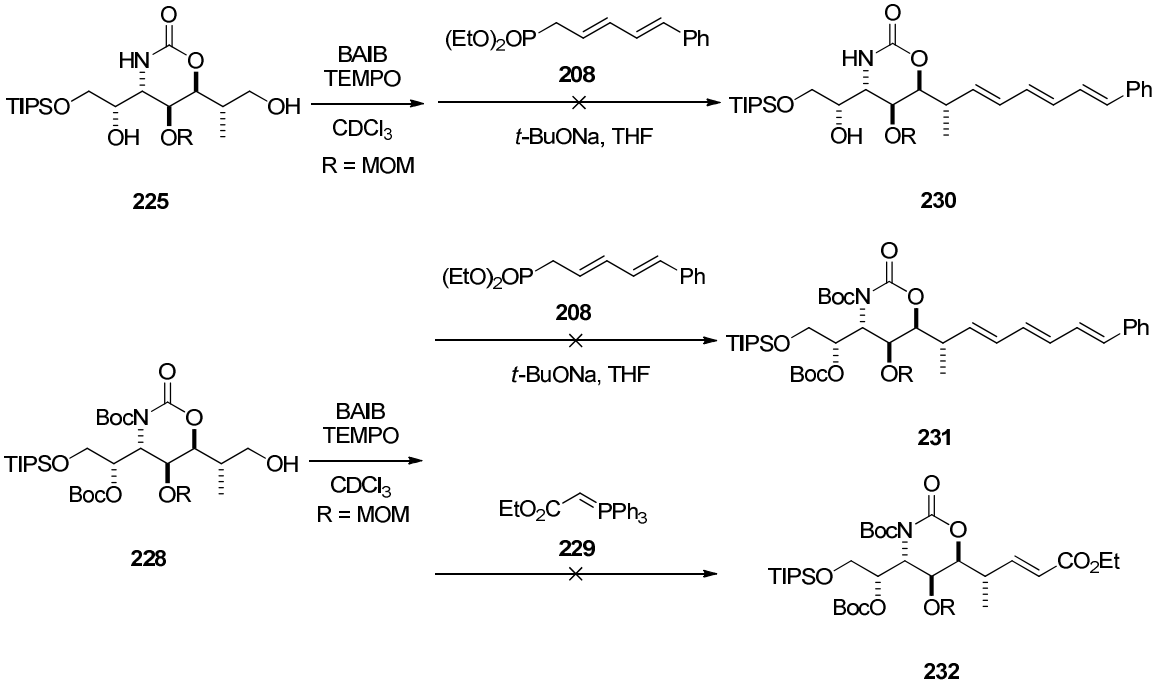


221 **227** (100%) **228** (94%)

Scheme 61: Adding protecting groups

Oxidation of **228** was carried out by Vatèle's procedure to give the desired aldehyde (detected by the appearance of a doublet at 9.84 ppm in the ^{1}H NMR spectrum). On evaporation of the solvent, the aldehyde was redissolved in THF and added to a solution of phosphonate **208** (2 eq.) and sodium *tert*-butoxide (2 eq.) in THF. This time the aldehyde could be detected by TLC analysis upto 6 h after addition, but again no trace of product was observed by crude NMR or mass spectrometry (Scheme 62). To ensure that the slightly less reactive phosphonate **208** was not causing the reaction to fail, we subjected the phosphonate to the conditions reported in

Scheme 56, which resulted in a successful reaction. We also attempted the one-pot olefination/oxidation as reported by Vatèle by adding (carbethoxymethylene)triphenylphosphorane (**229**) upon oxidation of alcohol **228** but found no trace of the expected alkene **232**.



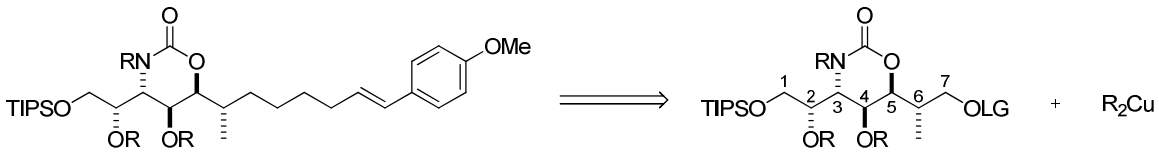
Scheme 62: Failed attempts at the olefination of aldehydes 225 and 228

Vatèle's procedure used stoichiometric amount of BAIB as the reoxidant, which gives iodobenzene and acetate anion as by-products. Although Vatèle showed that the by-products were compatible for further Wittig olefination, we wanted to ensure that they were not interfering with our olefination reactions. Thus, we used Dess-Martin periodinane to oxidise alcohol **228** and, following an aqueous work up acquired byproduct-free aldehyde. Unfortunately, on subjecting it to the previously used olefination reaction conditions (phosphonate **208** (2 eq.) and sodium *tert*-butoxide (2 eq.)), we were still unable to detect conversion to the desired alkene.

At this point in the project, the microsclerodermin team in the Donohoe group, based on previous work, had chosen microsclerodermin B as the target for total synthesis. Having failed to effect the olefination reaction and with little time in our hands, we focussed our efforts on synthesising the constituent β-amino acid of microsclerodermin B (see Figure 13, page 79), which required an alkyl linkage at C7-C8 instead of an alkene linkage chain.

4.5 Displacement reactions

The side-chain of microsclerodermin B's β-amino acid consists of six carbon atoms with an alkene at the end attached to a *p*-methoxyphenyl ring (Scheme 63). For the installation of the side-chain (as in **233**) through an alkyl linkage, we needed to effect a displacement reaction at C7. To do that we needed to turn the hydroxyl group at C7 into a good leaving group (as in **234**) and find conditions that would enable an alkyl displacement, potentially *via* the use of a cuprate.



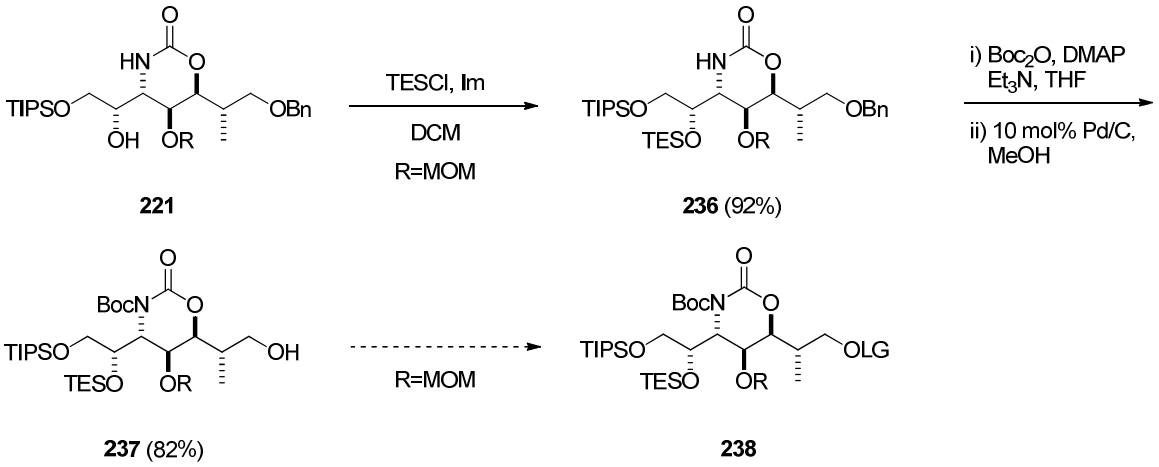
233 **234** **235**

Scheme 63: Potential way to introduce an alkyl side-chain on to the stereopentad

4.5.1 Protecting group strategy for substrate 234

To prepare substrate **234**, we reconsidered our protecting group strategy. In the face of failed olefination reactions, we were unsure about the stability of carbonates such as **228** (see Scheme 62). Thus, we decided to instead silyl protect hydroxyl group at C2. Accordingly, we treated alcohol **221** with chlorotriethylsilane in the presence of imidazole to give silyl ether **236** in a yield of 92%. Compound **236** was then treated with di-*tert*-butyl dicarbonate in the presence of

DMAP and triethylamine to give the Boc-protected carbamate, which was subsequently, without further purification, hydrogenated in the presence of palladium on activated charcoal to give alcohol **237** in 82% yield over two steps.



221 **236** (92%)

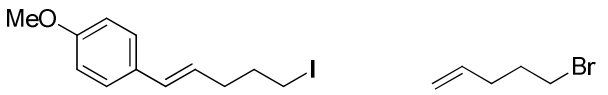
237 (82%) **238**

Scheme 64: Preparing an appropriately protected substrate

With the appropriately protected alcohol **237** in our hands, which would later be transformed to a suitable electrophile **238**, we now needed to choose the corresponding alkyl halide, which on treatment with *tert*-butyllithium would give the desired alkyllithium to prepare the desired cuprate.

4.5.2 Choosing the alkyl halide

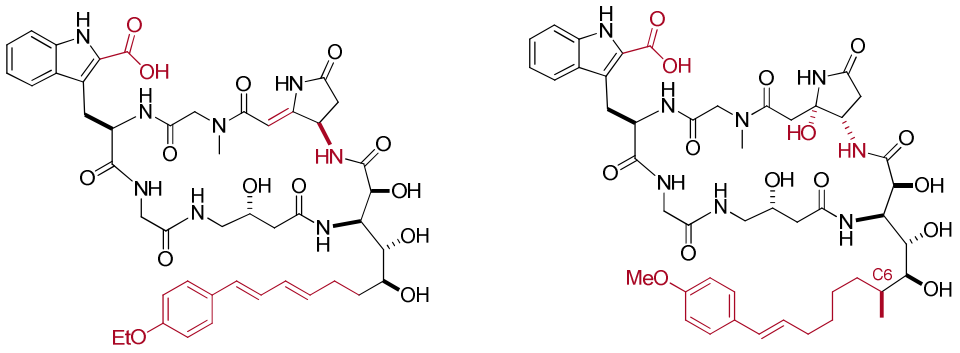
Given that we were interested in building the constituent β-amino acid of microsclerodermin B, the obvious choice for an alkyl halide should have been **239** (Figure 15). But prior work in the Donohoe group towards the total synthesis of the target molecule made 5-bromopent-1-ene the appropriate choice, which will now be discussed in the context of the end-game for the planned total synthesis.



239 **240**

Figure 15: Potential alkyl halides for introduction of the side chain

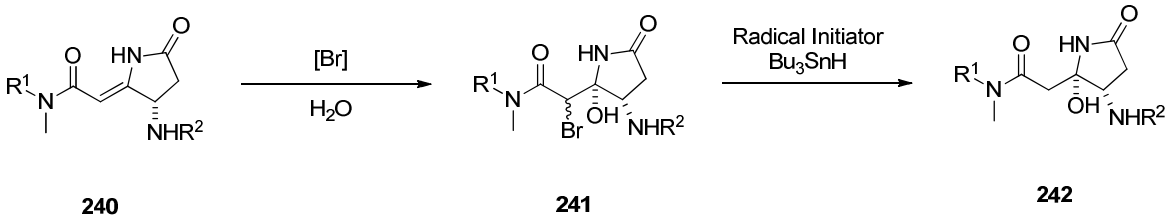
The only previously reported total synthesis of a microsclerodermin was that of microsclerodermin E by Dawei Ma (Figure 16). It is the simplest member of the family as it lacked the hemiaminal and the methyl group at C6 in the β-amino acid. Our target molecule microsclerodermin B possessed both these moieties, and the work described in this thesis has focused on the synthesis of the β-amino acid with the extra methyl stereocentre.



microsclerodermin E **5** *microsclerodermin B* **2**

Figure 16: Microsclerodermins B and E

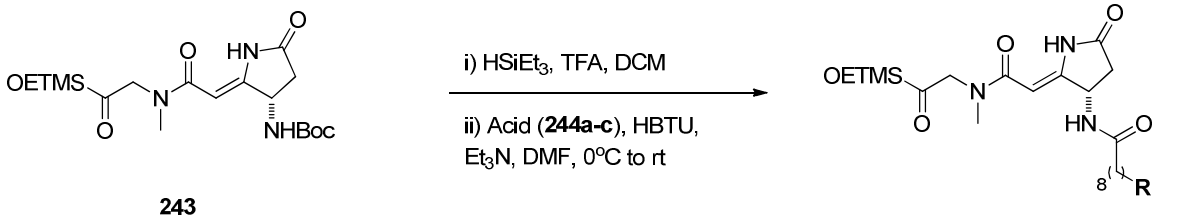
Work on the synthesis of the hemiaminal and the other constituent amino acids has been carried out by co-workers in the Donohoe group, Robert Pullin, Christian Winter and Jessica Kershaw.[63] Their work has shown that the hemiaminal moiety is very sensitive and cannot tolerate acidic or basic reaction conditions, which cause spontaneous elimination. They found that one way to introduce this moiety was be *via* hydroxybromination of **240**, followed by radical debromination of compound **241** to form desired hemiaminal **242** (Scheme 65).



240 **241** **242**

Scheme 65: Synthesis of the sensitive hemiaminal 242

Relevant to the synthesis of the β-amino acid - the focus of this thesis - is the fact that the sensitivity of the hemiaminal moiety dictated that the hydroxybromination-debromination sequence would have to occur in the very last few steps of the total synthesis. At this point in the synthesis, R^1 and R^2 would be connected to each other through five peptide bonds forming a macrocycle and R^2 would be the β-amino acid with the five stereocentres and the side-chain attached to it. Thus, it is important to understand whether the side-chain would be able to tolerate the proposed end-game. To that end, Robert Pullin prepared **245a-c** from **243** as model systems to test the end-game. In these model systems he included a terminal double bond (**245a**), a double bond with a *p*-methoxyphenyl ring (**245b**, microsclerodermin B mimic), and a terminal alkyne (**245c**).[64]

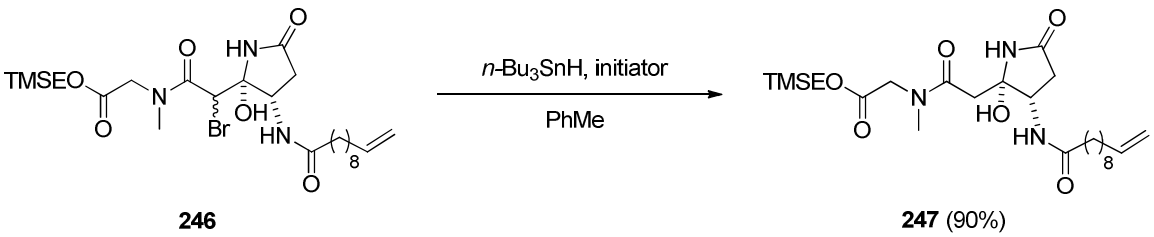


243

245a R = CH=CH_2 (81 %)
245b R = CH=CHPhOMe (76 %)
245c R = C≡CH (63 %)

Scheme 66: Synthesis of model systems to test end-game

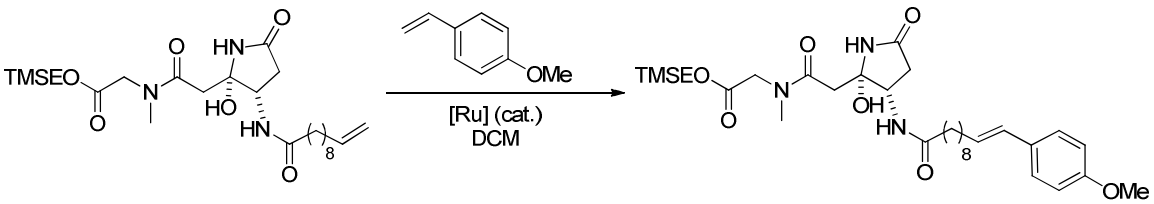
On subjecting these model systems to a brominating agent in the presence of water, Pullin found that the desired hydroxybromination occurred in **245a** and **245c** in moderate yields. However, in the case of **245b** bromination of the *p*-methoxyphenyl ring and hydroxybromination of the adjacent double bond was observed by ^{1}H NMR and mass spectrometry instead of hydroxybromination at the desired alkene. Furthermore, when the hydroxybromination product of **245a** was treated with dehalogenation conditions (triethylborane and tributyltin hydride in the presence of air at 0 °C) the desired debrominated product **247** was obtained in an excellent yield of 90% (Scheme 67).



246 **247** (90%)

Scheme 67: Radical debromination of 246

The use of **247** for the end-game was then completed since it was found that a metathesis reaction could attach the aromatic ring to the terminal double bond. Pullin showed that **247** could be converted to **248** in 80% yield without affecting the sensitive hemiaminal moiety (Scheme 68).



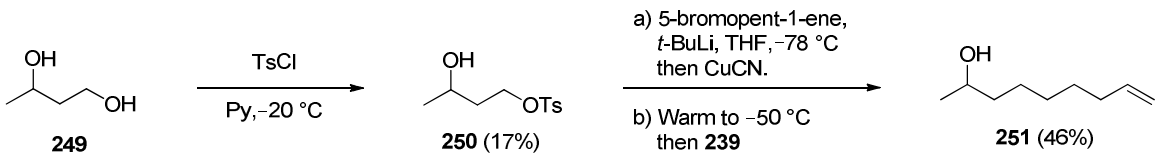
247 **248** (80%)
E-selective
no dehydration of RSM or product

Scheme 68: Metathesis reaction used to attach aromatic ring to 247

These experiments with model systems have helped us to devise the last few steps of the potential total synthesis. It also indicated to us that installing the aromatic ring on the side chain early on will be incompatible with the reagents to be used later in the synthesis and showed that the appropriate alkyl halide would be one with the right number of carbon atoms and a terminal double bond instead. Thus, our choice was 5-bromopent-1-ene.

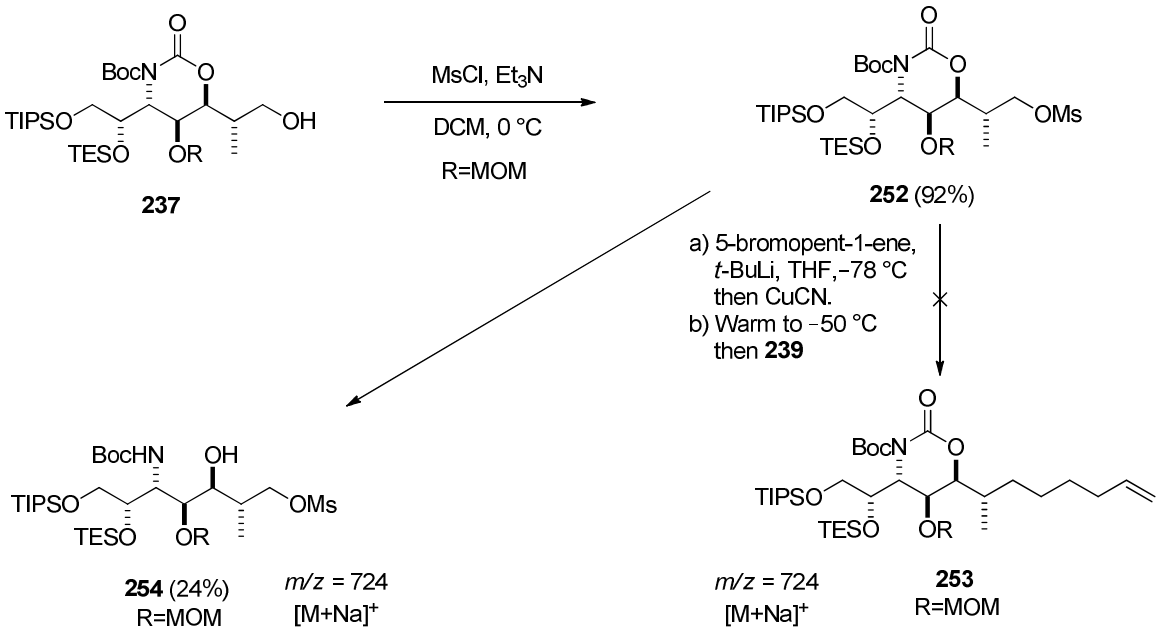
4.5.3 Cuprate displacements

With the precursor for cuprate displacements **237** and the alkyl halide ready, we looked for precedents for the copper-mediated alkyl installations. Among the numerous examples in the literature we decided to first test the cyanocuprates ($R_2Cu(CN)Li_2$), also known as Lipshutz cuprates. These cuprates are known to be more reactive and less thermally labile than the standard Gilman reagent (R_2CuLi).[65] For a test reaction, we synthesised a model tosylate **250** from 1,3-butanediol (**249**), albeit in a yield of 17% (Scheme 69). We used 5-bromopent-1-ene as the alkyl bromide to prepare the Lipshutz cuprate. The procedure involved *in situ* preparation of the desired alkyllithium from the alkyl halide by treatment with *tert*-butyllithium at −78 °C. The mixturewas then warmed to a suitable temperature and copper cyanide was added to it to allow the formation of the Lipshutz cuprate. The substrate with the leaving group was then added to the reaction mixture and the mixture was allowed to warm to room temperature. In our case, on subjecting tosylate **250** to these reaction conditions we were pleased to obtained 8-nonen-2-ol (**251**) in an acceptable yield of 46%.



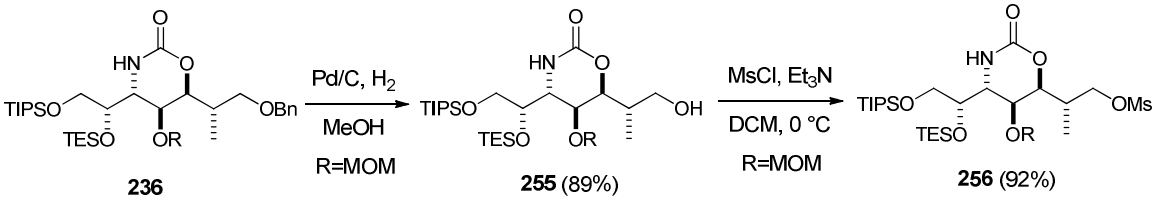
Scheme 69: Testing the Lipshutz cuprate

With limited time at our hands, instead of optimising the reaction on a model compound, we focused our efforts to effect the displacement on the desired substrate. Accordingly, we treated alcohol **237** with mesyl chloride in the presence of triethylamine to deliver mesylate **252** in a yield of 92% (Scheme 70). Moreover, mesylation reactions generally proceed smoothly and deliver clean products. This allowed us to use mesylate **252** without the need for further purification by silica gel column chromatography. On treating mesylate **252** to the Lipshutz cuprate that we had previously used in Scheme 69, we found complete conversion after stirring the mixture at room temperature for 12 h. We were pleased to find a peak at m/z = 724 in the mass spectra, which corresponded to the $[M+Na]^+$ ion of the product **253**. On purification though, the product showed no alkene-type peaks in ^1H NMR spectra or ^{13}C spectra. Furthermore, ^{13}C spectra indicated only a single peak in the carbonyl region at 157.7 ppm indicating the loss of one carbonyl group. A complete analysis indicated that, instead of the displacement of the mesylate, the opening of the activated carbamate had occurred to give alcohol **254** in a poor yield of 24%.



Scheme 70: First attempt to displace mesylate 252

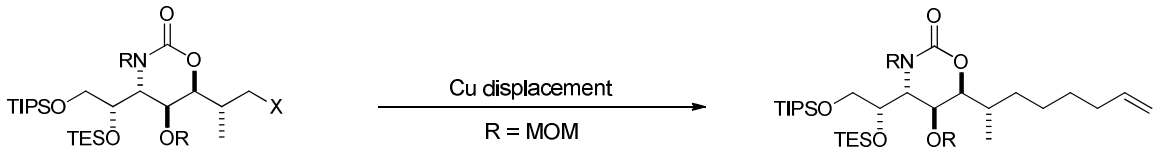
Although opening of an activated carbamate under strongly basic conditions is not an uncommon occurrence, we were surprised that the mesylate was stable enough to survive these conditions. To avoid the opening of the carbamate, we prepared carbamate **236** which lacked the Boc group and thus hoped that the cyclic carbamate would be less reactive. Carbamate **236** (see Scheme 64) was then hydrogenated to alcohol **255** in 89% yield (Scheme 71). This was then subjected to the mesylation conditions to furnish mesylate **256** in a good yield of 92%.



236 **255** (89%) **256** (92%)

Scheme 71: Preparation of an alternative mesylate 256

We were aware that, without the Boc protecting group, the cyclic carbamate would bear an acidic proton which will be deprotonated kinetically quicker than the displacement would take place. Accordingly, the use of an excess of the $R_2Cu(CN)Li_2$ species would be crucial. Unfortunately, on treating mesylate **256** with an excess of the Lipshutz cuprate (10 eq.) we only recovered starting material and found no trace of product. In the light of this result, we decided to investigate the various other conditions reported in the literature to effect the displacement (Table 3).



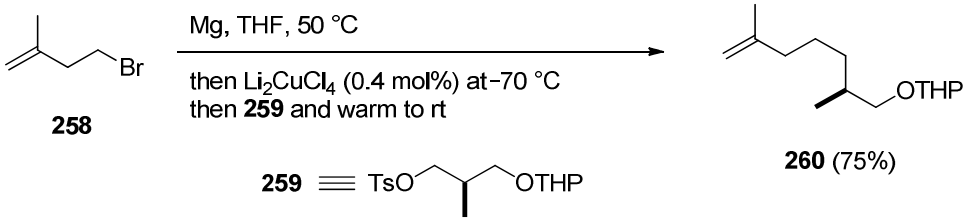
X = OMs R = Boc **252**
X = OMs R = H **256**

R = Boc **253**
R = H **257**

No	*Substrate*	*Copper Source*	*Alkyl lithium or Grignard reagent*	*Temperature*	*Result*
1	**252**	CuCN (7.5 eq.)	*t*-BuLi (30 eq.) / bromopentene (15 eq.)	−78 °C to −50 °C then to rt	SM consumed **254** obtained
2	**256**	CuCN (10 eq.)	*t*-BuLi (40 eq.) / bromopentene (20 eq.)	−78 °C to −50 °C then to rt	No reaction
3	**256**	Li_2CuCl_4 (0.1 eq.)	Mg / bromopentene (5 eq.)	−70 °C then to rt	No reaction
4	**256**	Li_2CuCl_4 (1 eq.)	Mg / bromopentene (10 eq.)	−70 °C then to rt	No reaction
5	**256**	$CuBr{\cdot}SMe_2$ (1.5 eq.)	Mg / bromopentene (3 eq.)	−20 °C then to rt	No reaction
6	**262**	CuCN (10 eq.)	*t*-BuLi (40 eq.) / bromopentene (20 eq.)	−78 °C to −50 °C then to rt	SM consumed No product
7	**262**	Li_2CuCl_4 (1 eq.)	Mg / bromopentene (10 eq.)	−70 °C then to rt	No reaction

Table 3: Reagents and conditions employed in attempted displacement reactions

In 2006, Ulrich Klar and co-workers of Schering AG showed that they could displace tosylate **259** in the presence of catalytic amount of dilithium tetrachlorocuprate to give **260** in a yield of 75% (Scheme 72).[66]

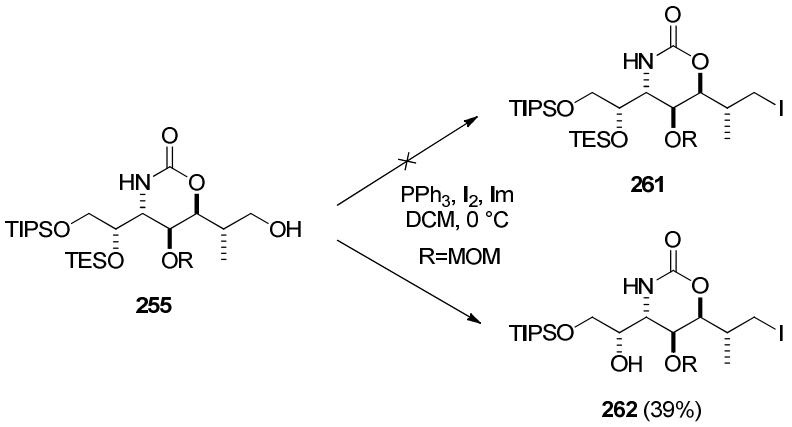


Scheme 72: The use of catalytic dilithium tetrachlorocuprate to synthesise 260

Accordingly, we prepared the required Grignard reagent by adding 5-bromopent-1-ene to magnesium turnings (dibromoethane was used as an initiator). The Grignard reagent, after titration, was carefully added to a solution of dilithium tetrachlorocuprate (freshly prepared) and mesylate **256** in THF at −70 °C. After stirring the mixture at rt for 12 h, we found significant amount of starting material still present and no trace of product by TLC analysis and mass spectrometry (Table 3, Entry 3). Moving from a sub-stoichiometric amount of copper, we also used stoichiometric quantity (Entry 4), but this made no difference to the outcome of the reaction. With the required Grignard reagent in hand, we attempted to use conditions reported by Scott Nelson at the University of Pittsburgh, USA who used copper bromide to effect the displacement of a tosylate (Entry 5),[67] but again found that a significant amount of the starting material was returned.

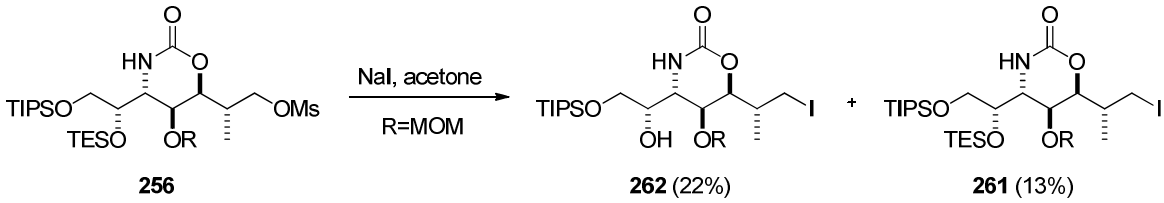
The lack of conversion of mesylate **256** indicated that it might be unreactive under these conditions. It was proposed that use of better leaving group such as an iodide might enable the reaction to occur. Accordingly, we treated alcohol **255** with triphenylphosphine (1.0 eq.) and iodine (1.1 eq.) in the presence of imidazole (1.5 eq.). After stirring the mixture for 12 h, mass

spectrometry indicated the presence of the product and the starting material (Scheme 73). Thus, more triphenylphosphine (0.3 eq.) and iodine (0.3 eq.) was added to the mixture and stirred for 6 h when TLC analysis indicated complete consumption of the starting material. However, instead of the desired product **261**, we only obtained iodide **262** in a poor yield of 39%.



Scheme 73: The synthesis of iodide 262

Alternatively, subjecting mesylate **256** (see Scheme 71) to the Finkelstein reaction conditions (sodium iodide in acetone) led to the formation of mixture of iodides **261** and **262** (with and without the TES group) in a poor combined yield of 35% (Scheme 74).

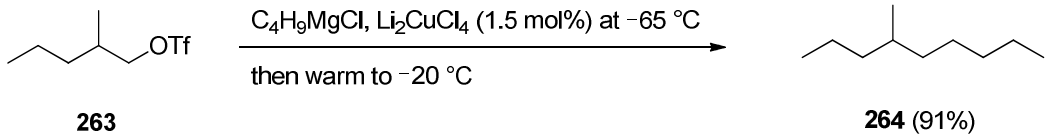


Scheme 74: Alternative method for synthesising iodide 262

Although the loss of TES group was undesirable, it was postulated that it would not hamper the displacement reaction if excess of the cuprate was used. Accordingly iodide **262** was subjected

to the Lipshutz cuprate (Table 3, Entry 6). The starting material was consumed but no trace of product was observed. Whereas when iodide **262** was treated to dilithium tetrachlorocuprate and the alkyl Grignard (Entry 7) no reaction occurred.

To further increase the reactivity of the leaving group, we looked at the use of primary triflates in the displacement reaction. We found precedent in work by Shifa Wang and co-worker at Virginia Polytechnic Institute, USA, who displaced alkyl triflates with primary alkyl Grignard reagents in the presence of dilithium tetrachlorocuprate (Scheme 75) to effect a number of displacements in very high yields.[68]



263 **264** (91%)

Scheme 75: Alkyl triflate 263 displaced by butyl Grignard

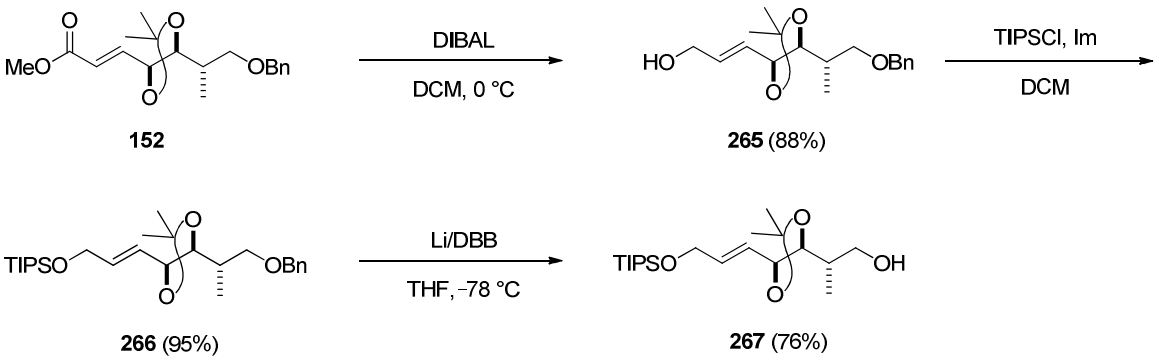
Accordingly we treated alcohol **255** to triflic anhydride in the presence of pyridine at −20 °C and slowly warmed the reaction to 0 °C. At this point, all of the starting material was consumed as shown by TLC analysis. The reaction mixture was then diluted with dichloromethane and passed through a pad of Celite. The crude product obtained was an unidentifiable mixture indicating decomposition of the starting material. Repeating this reaction with freshly distilled reagents did not make any difference to the outcome. This indicated that the triflate, if formed, was too unstable to be isolated.

Whilst we were unsuccessful in effecting the displacement reaction, these experiments had given us a better understanding of the reactivity of the stereopentad. The potential steric hindrance may have resulted in the inability of a nucleophile to effect the displacement. We

also learnt the right combination of protecting groups that could be used. At this point in time, with very little material available, I started writing up my thesis and Christian Winter, a co-worker in the Donohoe group, investigated the displacement reaction with the use of a model substrate. His work is included in this thesis for completeness.

4.5.4 Work by Christian Winter

The model substrate **267** was synthesised from acetonide **152** (see Scheme 31) in three steps. Ester **152** was reduced to alcohol **265** with DIBAL in a yield of 88%, followed by TIPS protection to furnish silyl ether **266** in 95% yield (Scheme 76). The benzyl group was then removed by Birch reduction to give alcohol **267** in 76% yield.



152 **265** (88%) **266** (95%) **267** (76%)

Scheme 76: Synthesis of model substrate 267

With the model alcohol **267** in hand, Winter looked to synthesise substrates with different leaving groups and subject them to displacement conditions (Table 4). First, mesylate **268** was synthesised in an excellent yield of 94% and subjected to a premixed solution of CuCN and hexylmagnesium bromide (Entry 1). Unfortunately, no reaction occurred and the starting material was recovered quantitatively.

X = Ms **268**
X = I **269**

No [a]	*Substrate*	*Copper Source*	*Alkyl lithium or Grignard reagent*	*Temperature*	*Result*
1	**268**	CuCN (3 eq.)	HexMgBr (6 eq.)	−40 °C to −15 °C then to rt	100% RSM
2	**269**	CuCN (2 eq.)	HexMgBr (4 eq.)	−40 °C to −15 °C then to rt	50% RSM no product
3	**269**	$CuBr{\cdot}SMe_2$ (2 eq.)	HexMgBr (4 eq.)	−60 °C to −40 °C then to 10 °C	63% RSM trace product
4	**269**	Li_2CuCl_4 (1 eq.)	HexMgBr (10 eq.)	−60 °C to rt	decomposition
5	**269**	CuCN (2 eq.)	*n*-BuLi (4 eq.)	−40 °C to −15 °C	35% RSM 35% product
6	**269**	CuCN (5 eq.)	*t*-BuLi (20 eq.) / bromopentene (10 eq.)	−78 °C to rt then −25 °C	decomposition
7 [b]	**269**	CuCN (6.5 eq.)	*t*-BuLi (26 eq.) / iodopentene (13 eq.)	−78 °C to rt then −25 °C to −15 °C	23% product 20% side product

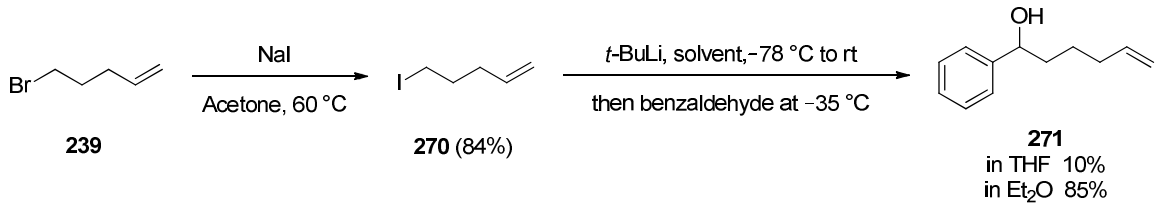
[a] All experiments, except where mentioned, were carried out in THF; [b] The halogen-metal exchange was carried out in Et_2O instead of THF.

Table 4: Reagents and conditions employed in attempted displacement reactions

Given the low reactivity of mesylates, the next substrate to be synthesised was iodide **269**. Following the same procedure as used in Scheme 73, iodide **269** was obtained, but in a similarly poor yield of 24%. The reaction was then repeated by first allowing triphenylphosphine and iodine to react in the presence of imidazole and then adding alcohol **267** to the solution at 0 °C. This helped improve the reaction yield to 74%. Iodide **269** was then treated to the same conditions as in Entry 1, but again no trace of the desired product was detected (Table 4, Entry 2). The use of $CuBr{\cdot}SMe_2$, instead of CuCN, also returned significant amount of the starting material but mass spectrometric analysis showed a peak at m/z = 463 corresponding to the $[M+Na]^+$ ion of the desired product (with hexyl side-chain attached) (Entry 3). Purification by column chromatography only gave a low product yield, but it was the first time that a displacement product, albeit only in trace amounts, was observed. When dilithium tetrachlorocuprate was used as the copper source, no product was formed despite complete consumption of the starting material, possibly because of the decomposition of the iodide (Entry 4).

It is worth noting that an excess of alkyllithium or alkyl Grignard reagents in the reaction mixture seemed to cause the decomposition of the starting material. Hence, cyano-cuprates seemed a better option than dilithium tetrachlorocuprate. Thus, iodide **269** was subjected to a cyanocuprate prepared with *n*-BuLi (Table 4, Entry 5). We were pleased when the desired product with the attached side chain (*n*-Bu) was isolated in 35% yield with 35% recovered starting material. With this promising result, 5-bromopent-1-ene (the desired alkyl source) was converted to corresponding alkyllithium by treatment with *t*-BuLi and iodide **269** was treated with the corresponding Lipshutz cuprate (Entry 6). Unfortunately, no product or returned starting material was obtained. It was hypothesised that perhaps the halogen-metal exchange to form the alkyllithium was not occurring as was hoped.

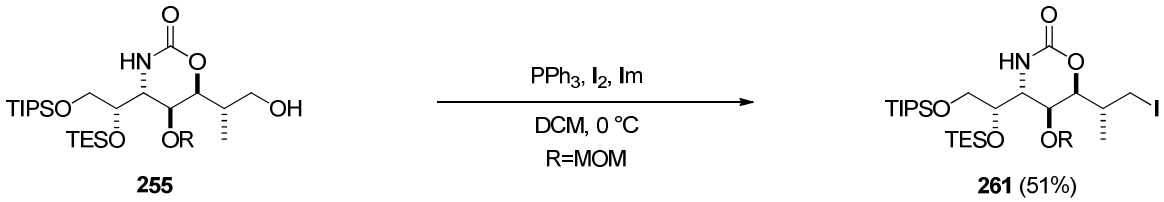
To ensure that complete halogen-metal exchange with 5-bromopent-1-ene occurs, the more reactive 5-iodopent-1-ene (**270**) was prepared in 84% yield *via* the Finkelstein reaction.[69] Formation of the desired alkyllithium by treatment of 5-iodopent-1-ene (**270**) with *tert*-butyllithium was observed by trapping it with benzaldehyde (Scheme 77). To our surprise, in THF, the solvent used up to this point for the formation of cyano cuprates, we obtained a very poor yield of 10% for benzylic alcohol **271**. It was hypothesised that the reason for the poor yield in THF could be because of its susceptibility to decomposition at higher temperatures with *tert*-butyllithium.[70] Thus, diethyl ether was employed as the solvent for the reaction and we were pleased that the yield improved to 85%, thus confirming efficient halogen-metal exchange.



Scheme 77: Trapping of benzaldehyde with desired alkyllithium

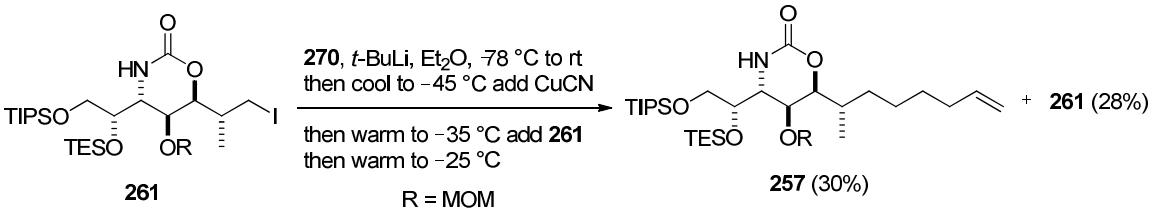
With this improved procedure for halogen-metal exchange, Winter treated iodide **269** with the Lipshutz cuprate derived from 5-iodopent-1-ene (**270**) and *tert*-butyllithium in diethyl ether. We were pleased that, for the first time, we had successfully attached the desired side-chain (pent-1-enyl), albeit in only 23% yield (Table 4, Entry 7). However, along with the desired product, 20% of a side-product was also isolated. ^{1}H NMR analysis of this side-product indicated a large number of alkene protons and the absence of the TIPS and the acetonide protecting group, which meant that under strongly basic conditions an elimination may have occurred.

Given that in the real system there was a more robust protecting group in the form of a carbamate group (*vs.* the acetonide group in the model system), it was proposed that the same optimised conditions were to be applied on the real system. Accordingly, alcohol **255** was subjected to iodination to yield iodide **261** in a moderate yield of 51% (Scheme 78).



Scheme 78: Synthesis of iodide 261

Winter then subjected iodide **261** to the previously successful cyanocuprate conditions: To a solution of 5-iodopent-1-ene in diethyl ether was added *tert*-butyllithium at −78 °C. The mixture was warmed to rt and stirred for 1 h to allow completion of halogen-metal exchange. At this point, it was added to cooled (−45 °C) solution of copper cyanide in THF. The mixture was then warmed to −35 °C, stirred for 15 mins before the addition of iodide **261** (Scheme 79). On purification, delightfully, compound **257** was obtained in 30% yield (as evidenced by the occurrence of the non-terminal olefinic proton in the ^{1}H NMR spectrum at 5.80 ppm as doublet of doublet of triplets with 17.0, 10.2 and 6.7 Hz as the respective coupling constants). As hoped no degradation products were observed, but 28% starting material was recovered indicating the clear possibility of further optimisation. It is also important to note that the reaction was conducted on a small scale.



Scheme 79: Synthesis of 257

4.6 Summary

Starting from Roche ester (**56**) we have synthesised alcohol **255** in 12 steps with an overall yield of 6%, and in two further unoptimised steps **261** has then been converted to **257**, which has all the five stereocentres in place and the desired side-chain attached to it. In the next chapter, we look at how **257** could be incorporated into the total synthesis of microsclerodermin B and the lessons we have learnt along the way which could help its successful incorporation.

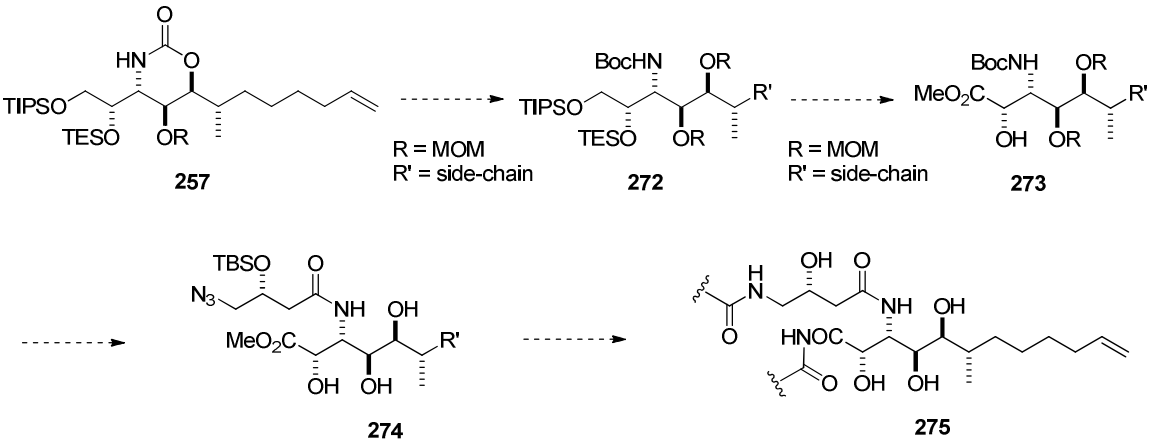
Chapter 5

The road ahead

Chapter 5

5.1 Proposed synthetic sequence for incorporation of β-amino acid in the macrocycle

With **257** in hand, we propose a synthetic sequence (Scheme 80) that may be used to convert **257** into the desired β-amino acid and incorporated into the macrocycle **275**. Following Boc-protection and opening of the cyclic carbamate (by the use of Cs_2CO_3 in MeOH), the free hydroxyl group is MOM protected to yield **272**. Both the silyl protecting groups are then removed and the primary alcohol is selectively oxidised to the acid, which is protected as its methyl ester **273**.

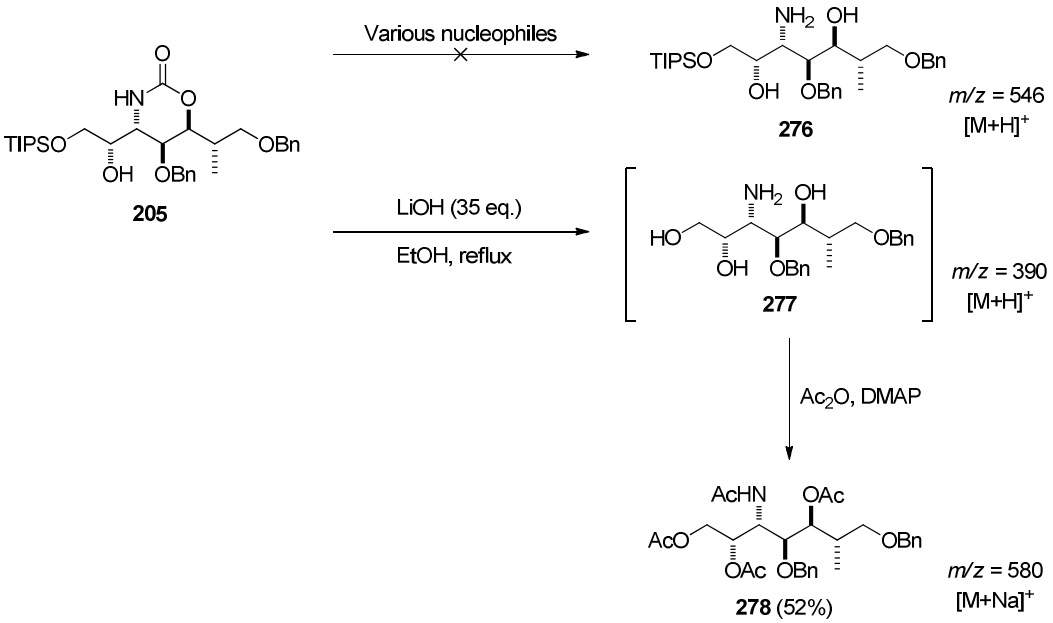


Scheme 80: Proposed incorporation of β-amino acid into the macrocycle

Compound **273** is then treated with TFA to remove the Boc and the MOM protecting groups. It is then reacted with activated ester **23** (see Scheme 3) to yield **274**, which is now ready for further peptide coupling at either the acid (protected as an ester) or the amine (masked as an azide). Further peptide couplings will enable the incorporation of the β-amino acid into the macrocycle **275**. This proposed synthetic sequence is based on prior work done on the stereopentad and other literature precedent, which will now be discussed.

5.1.1 Carbamate opening

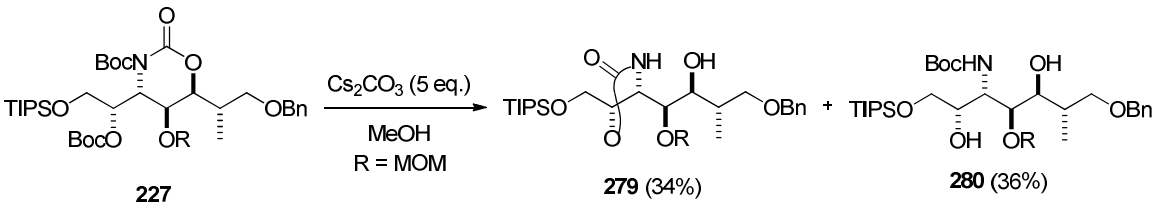
One of the features of the tethered aminohydroxylation reaction is the formation of the cyclic carbamate in the TA product. It is a robust protecting group that can sometimes prove to be a disadvantage. Carbamate opening usually requires more than one step - activation by Boc protection followed by cleavage of the less sterically hindered carbamate with a nucleophile.[71] To reduce the number of steps in the overall synthetic sequence, I have attempted to open the cyclic carbamate **205** in one step with various nucleophiles such as Cs_2CO_3, LiOH, KOH, $Ba(OH)_2$, but those attempts, without preactivation of the carbamate, proved ineffective. Only under extreme conditions (30 eq. of LiOH, reflux in ethanol) we observed the opening of the carbamate (Scheme 81), but along with the loss of the TIPS protecting group as indicated by mass spectrometry (*m/z* = 390 for the $[M+H]^+$ ion of **277**).



Scheme 81: Opening unactivated cyclic carbamate 205

Isolation of **277** was attempted with the use of ion-exchange resins, but given the large excess of LiOH it proved to be unsuccessful. We then looked to recover the product by treating the reaction mixture with acetic anhydride in an attempt to both neutralise the base and then acylate all positions (Scheme 81). We were successful at isolating acetamide **278** in 52% yield, but attempts to improve the yield of this reaction, such as the use of microwave (instead of reflux for ~16 h in step 1), proved fruitless. Moreover, the protecting groups now installed on **278** were not compatible with the planned synthetic strategy and hence this route was abandoned.

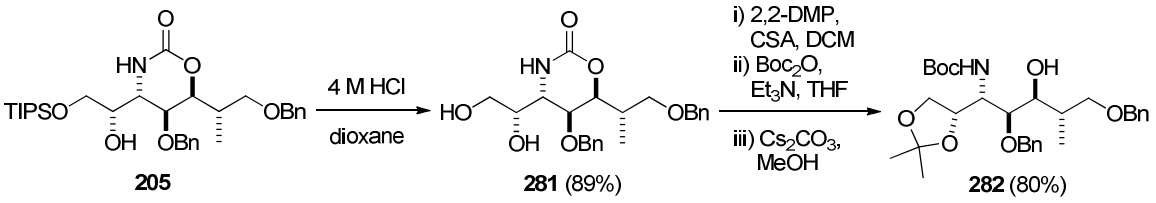
Going back to the two-step methodology used for opening cyclic carbamates,[71] we treated bis-Boc protected compound **227** (see Scheme 61) with Cs_2CO_3 in methanol. However, instead of the expected product, we isolated **280** in which the desired opening of the carbamate had occurred but also the loss of the Boc group at C2 has occurred. We also isolated **279** in 34% yield which, to our surprise, had a rearranged cyclic carbamate (as confirmed by COSY correlations and the downfield shift of the carbonyl to 160.7 ppm, which is typical for an unsubstituted 5-membered cyclic carbamate[72]). The occurrence of **279** can be attributed to cleavage of the carbonate at C2 under basic conditions, which allowed the resulting free hydroxyl group to attack the Boc-carbonyl attached to the nitrogen atom at C3 (leading to the loss of butoxide and) resulting in the five-membered cyclic carbamate. Compound **279** is inert to further reactions.



227 **279** (34%) **280** (36%)

Scheme 82: Cs_2CO_3 mediated opening of the activated carbamate 227

This result indicated the need for a robust protecting group at C2. Before settling on the TES group (see Scheme 64), we attempted to synthesise a compound where C1 and C2 were tied together with an acetonide group. Thus, TA-product **205** was treated with 4 M HCl to furnish diol **281** in 89% yield (Scheme 83). It was then treated with 2,2-dimethoxypropane in the presence of catalytic CSA to give the desired acetonide, which was subsequently Boc protected. It was then treated with Cs_2CO_3 (5 eq.) and pleasingly alcohol **282** was formed in a good yield (80% over 3 steps). Thus, we had shown that, with a robust protecting group at C2 and N-Boc activation of the carbonyl, the desired carbamate opening can indeed be effected in higher yields.



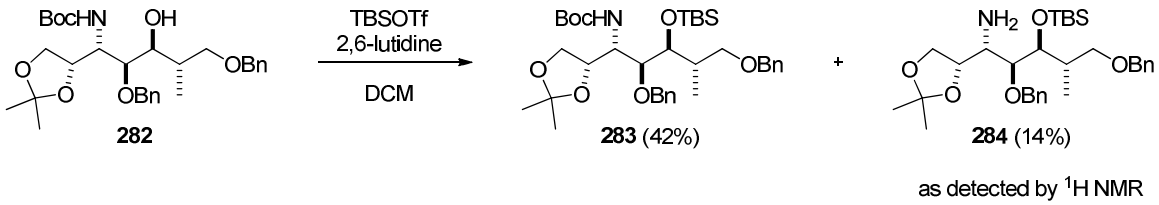
Scheme 83: Installing a more robust protecting group at C2

Eventually, we settled on using the TES protecting group at C2 (see Scheme 64) instead of the acetonide (that ties C1 and C2) because fewer number of steps were needed in the overall synthetic sequence to install the TES, and it proved to be equally effective (undergoing displacement reaction in strongly basic condition).

5.1.2 Protecting group at C5

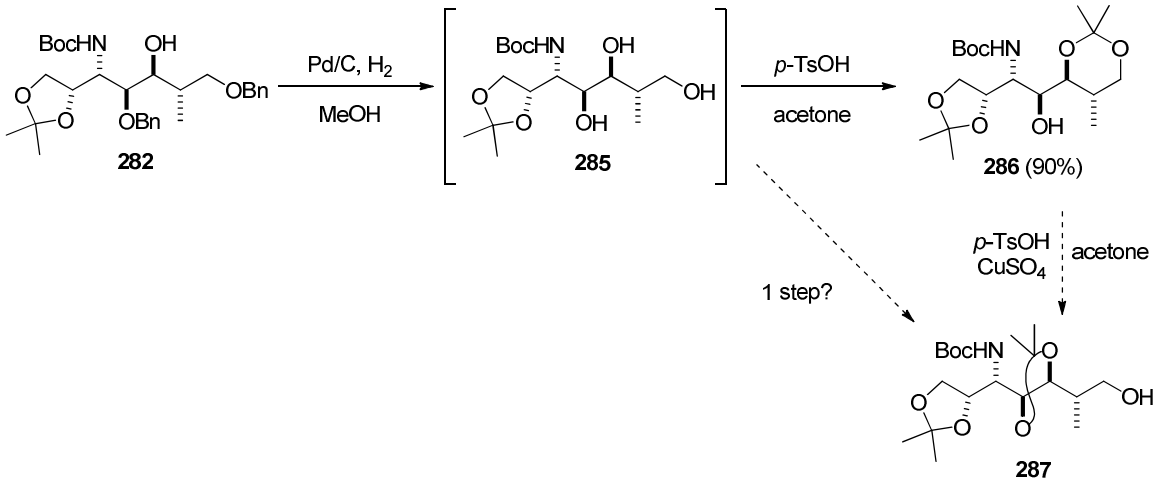
Our suggestion to install a MOM protecting group at C5 (see Scheme 80) after the opening of the carbamate comes from brief studies done on **282**. In our attempts to install a TBS group at C5 (Scheme 84), we were able to obtain carbamate **283** in a yield of only 42%. The low yield could be attributed to the formation of a side-product **284**, which indicated that loss of the Boc

group had occurred (as observed by mass spectrometry and ^{1}H NMR spectroscopy) despite the presence of excess 2,6-lutidine (5 eq.).



Scheme 84: Installation of TBS at C5 of compound 282

We also looked at installing an acetonide group across C4 and C5 by first hydrogenating **282** to give an intermediate triol **285**, which upon treatment with acetone in the presence of *p*-toluenesulfonic acid yields acetonide **286** (Scheme 85). Preliminary studies at converting **286** to **287** (the thermodynamically favoured product) by the use of $CuSO_4$ were successful but further optimisation will be needed to use this route.

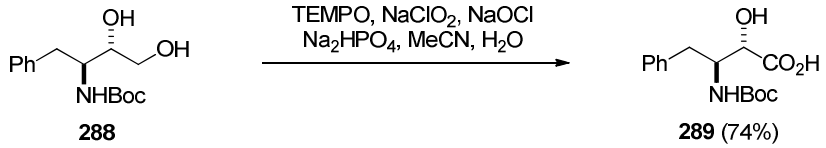


Scheme 85: Installing an acetonide across C4 and C5 of compound 282

Thus, if the protecting group at C4 of the stereopentad is a benzyl group then the route in Scheme 85 could be undertaken to give alcohol **287**, which could be further iodinated and displaced to attach the side-chain. But if the protecting group at C4 is a MOM group then it is better to have a MOM group at C5 too, which would enable a global deprotection to yield the desired amine for further coupling with the GABOB unit (see Scheme 80).

5.1.3 Selective oxidation

Fortunately for our synthetic strategy, the protecting groups at C1 and C2 need not be orthogonal because there is much literature precedent for the selective oxidation of primary alcohols in presence of secondary alcohols (including α to the primary alcohol). One of the most commonly used method was reported by Mangzhu Zhao and co-workers at Merck Research Laboratories, USA,[73] who used a TEMPO-catalysed oxidation (with sodium hypochlorite as the stoichiometric oxidant) to convert primary alcohols to the corresponding acid. The use of the method is illustrated in the work of Masaya Ikunaka and co-workers of Nagase & Co., Japan, who converted 1,2-diol **288** to hydroxy-acid **289** in 74% yield without glycol oxidative cleavage (Scheme 86).[74]



288 **289** (74%)

Scheme 86: Selective oxidation of the 1,2-diol 288 to the hydroxy-acid 289

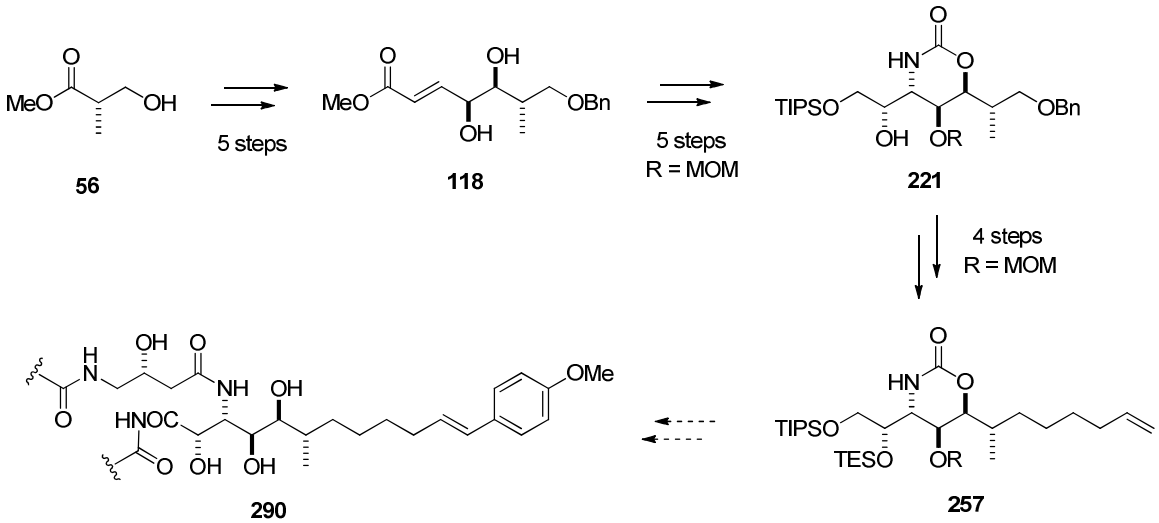
5.1.4 Dipeptide 274

The proposed synthetic strategy (Scheme 80) involves the formation of compound **274** before forming peptide bonds with the other tetrapeptide of microsclerodermin B. This recommendation follows from the work done by Dawei Ma in the total synthesis of

microsclerodermin E (Scheme 1),[12] who coupled compound **11** with tetrapeptide **10** at the tail-end of the synthesis. Our proposed end-game (see Section 4.5.2) would involve a similar coupling followed by reduction of the azide to the amine. The amine can then undergo the macrocyclization peptide coupling and the last step of the total synthesis would involve a metathesis reaction to attach the aromatic ring to the side chain of the β-amino acid.

5.2 Conclusion

The synthesis of **257**, appropriate to the synthesis of microsclerodermin B, was completed in fourteen steps starting from commercially available Roche ester (**56**). Compound **56** was first converted to (*E*,*E*)-diene **113** following a Horner-Wadsworth-Emmons olefination with phosphonate **110**. The first two stereocentres were introduced selectively on the distal double bond *via* a Sharpless asymmetric dihydroxylation reaction to give diol **118**. Whilst attempts to install the next two stereocentres *via* the Sharpless asymmetric aminohydroxylation failed, this led us to use the tethered aminohydroxylation (TA), which successfully introduced the remaining two stereocentres of the target molecule, thus furnishing stereopentad **221**.



Scheme 87: Summary of the work done towards the synthesis of 290

Stereopentad **221**, following attachment of appropriate protecting groups, was subjected to a number of olefination reactions in a bid to install the olefinic side-chain appropriate to microsclerodermins F, G, H and I, but attempts proved unsuccessful. In line with work done by co-workers in the Donohoe group, the aim of the project was then narrowed to the synthesis of the β-amino acid appropriate to microsclerodermin B (and A). This involved the attachment of an alkyl side-chain with a terminal double bond (in line with our proposed end-game), and was accomplished by Winter in the Donohoe group *via* a copper-mediated displacement reaction of iodide **261** to give compound **257**.

In conjunction with literature precedent for the final few steps for incorporation of the β-amino acid into the microsclerodermin macrocycle, work conducted on the opening of cyclic carbamates, during manipulation of stereopentad **221**, has resulted in a proposed synthetic sequence (Scheme 80) for the final completion of the β-amino acid and the synthesis of microsclerodermin B **2**.

Chapter 6

Experimental

Chapter 6

6.1 Experimental Techniques

Solvents & reagents: Tetrahydrofuran was purified by filtration through two columns of activated alumina (grade DD-2) as supplied by Alcoa, employing the method of Grubbs *et al.*;[75] dichloromethane (DCM) and toluene were purified by filtration through two columns of basic activated aluminium oxide (Brockmann I, standard grade, ~150 mesh, 58 angstrom) as supplied by Aldrich. Other solvents were used as supplied without purification. Light petroleum or petrol refers to the fraction of petroleum ether, which boils in the range 40-60 ˚C. Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used as supplied or purified according to the procedures outlined by Perrin and Amarego.[76] Alkyl halides were filtered through a plug of potassium carbonate and anhydrous magnesium sulfate prior to use.

Chromatography: Column fractions and reactions were monitored by thin-layer chromatography (TLC). TLC was performed on Merck DC-Alufolien 60 F_{254} 0.2 mm pre-coated aluminium backed silica plates. Compounds were visualised with UV light and/or by staining with basic potassium permanganate solution, DNPH solution or vanillin solution as appropriate. Column chromatography was carried out according to the method described by Still *et al.* [77] using ICN Silica Gel (32-63 60 Å), the solvent system used is quoted in parentheses.

NMR Spectroscopy: ^{1}H NMR and ^{13}C NMR spectra were recorded using a DQX400 (400 MHz, and 100.16 MHz), a DPX 400 (400 MHz), an AVC500 (500 MHz and 125.7 MHz) or a

DPX200 (200 MHz) spectrometer at room temperature. Chemical shifts (δ) are quoted in parts per million (ppm) relative to an internal standard, tetramethylsilane ($SiMe_4$). Coupling constants (*J*) are given to the nearest 0.1 Hz.

The abbreviations for the spin multiplicity in ^{1}H-NMR spectra are the following:

(s) singlet	(d) doublet	(t) triplet	(q) quartet
(quin) quintet	(m) multiplet	(b) broad	(app) apparent

Assignments of both ^{1}H and ^{13}C NMR were aided by COSY (correlated spectroscopy), HMQC (heteronuclear multiple-quantum correlation) and HMBC (heteronuclear multiple-bond correlation). Protons of OH groups are missing in some spectra due to proton exchange.

IR Spectroscopy: Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Compounds were analysed as thin films on NaCl plates or pressed onto a KBr disk. Absorption maxima are quoted in wavenumbers (cm^{-1}).

Mass Spectrometry: Mass spectra (*m/z*) were recorded on a Fisons Platform II instrument and accurate mass (HRMS) on a Micromass 500 LCT under the conditions of electrospray ionization (ESI). *m/z* values are reported in Daltons.

Melting Points: Melting points were determined using a Leica Galen III heated-stage microscope and are uncorrected.

6.2 General Procedures

Procedure A: *Horner-Wadsworth-Emmons olefination with LDA as base* [29]

A solution of lithium diisopropylamide (LDA) was prepared by adding a solution of *n*-BuLi (1.5 eq.) to a solution of DIPA (1.5 eq.) in THF (3 mL/mmol) under argon at 0 °C and stirring for 0.5 h. The freshly prepared solution of LDA was added dropwise to a solution of phosphonate **110** (1.0 eq.) in THF (7 mL/mmol) at −78 °C and the reaction mixture was allowed to warm to −20 °C over 3 hours. The reaction mixture was then re-cooled to −78 °C and a solution of aldehyde (1.0 eq.) in THF (1 mL/mmol) was added *via* cannula. The reaction mixture was allowed to warm up to room temperature overnight and was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL/mmol). The organic layer was separated and the aqueous layer was extracted three times with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification was carried out using flash column chromatography as specified.

Procedure B: *Horner-Wadsworth-Emmons olefination with DBU as base* [31]

To a stirred suspension of LiCl (1.2 eq.) in dry acetonitrile (10 mL/mmol) under nitrogen at rt were added (*E*)-methyl-4-(diethoxyphosphoryl)but-2-enoate (1.2 eq.) and DBU (1.2 eq.). After 10 min, aldehyde (1.0 eq.) was added and the mixture stirred overnight. The reaction was quenched by addition of 1 M HCl (2 mL/mmol) and brine (10 mL/mmol). The organic layer was separated and the aqueous layer was extracted three times with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification was carried out using flash column chromatography as specified.

Procedure C: *Horner-Wadsworth-Emmons olefination with LiOH·H_2O as base* [32]

A suspension of the aldehyde (1.0 eq.), (*E*)-methyl-4-(diethoxyphosphoryl)but-2-enoate (1.1 eq.), LiOH·H_2O (1.1 eq.), and activated 4Å molecular sieves (beads, 4-8 mesh, 1.5 g/mmol of aldehyde) in THF (10 mL/mmol) was heated at reflux under a nitrogen atmosphere for about 12 h. The crude reaction mixture was then filtered through a short plug of silica gel eluting with Et_2O. The mixture was concentrated *in vacuo*, and the crude product was purified by flash column chromatography as specified.

Procedure D: *Sharpless asymmetric dihydroxylation* [34]

To a solution of $K_3Fe(CN)_6$ (3.0 eq.), K_2CO_3 (3.0 eq.) and ligand (as specified) in a 1:1 mixture of *t*-BuOH and water (10 mL/mmol) was added $K_2OsO_4·2H_2O$ (as specified) and $MeSO_2NH_2$ (3.0 eq.). After stirring at rt for 10 min, a solution of the olefin in *t*-BuOH was added to the reaction vessel. The mixture was stirred at rt for 20 h and quenched with Na_2SO_3 (1.5 g/mmol). It was extracted with EtOAc and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Purification was carried out using flash column chromatography as specified.

Procedure E: *Yamamoto Protocol* [57]

A solution of diol (1.0 eq.), $CH(OMe)_3$ (2.0 eq.) and CSA (0.1 eq.) in CH_2Cl_2 (15 mL/mmol) was stirred at rt for 45 min. The solution was cooled to −78 °C, and neat DIBAL-H (10.0 eq.) was added dropwise. The mixture was stirred at this temperature for 1 h and then placed in an ice bath. After 10 min, 2 M NaOH (10 mL/mmol) was added and the mixture was extracted with EtOAc. The organics were washed with 2 M NaOH (2 × 10 mL/mmol) and brine (10

mL/mmol), dried (Na_2SO_4), and concentrated under reduced pressure. Purification was performed using flash column chromatography as specified.

Procedure F: *Sharpless asymmetric aminohydroxylation with benzyl carbamate* [45]

Benzyl carbamate (3 eq.) was dissolved in *n*-propyl alcohol (4 mL/mmol) in a vial equipped for magnetic stirring. To this stirred solution was added a freshly prepared solution of 2 M NaOH (3 eq.) in water (7.5 mL/mmol), followed by a freshly prepared solution of *tert*-butyl hypochlorite (3.05 eq.). Then a solution of the ligand (5 mol%) in *n*-propyl alcohol (3.5 mL/mmol) was added. The vial with a homogenous reaction mixture was then immersed in a room-temperature water bath, and stirred for a few minutes. The olefin (1 eq.) was added, followed by the osmium catalyst $K_2OsO_4 \cdot 2H_2O$ (4 mol%) and the reaction stirred at rt. After TLC analysis confirmed the absence of the starting material, ethyl acetate (7 mL/mmol) was added and the phases were separated. The combined organic layers were washed with brine (20 mL/mmol), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude product. Purification was performed by flash column chromatography as specified.

Procedure G: *Sharpless asymmetric aminohydroxylation with Chloramine-T* [44]

To a stirred solution of ligand (5 mol%) in acetonitrile (20 mL/mmol) and water (20 mL/mmol) at rt, were added alkene (1 eq.), Chloramine-T trihydrate (3 eq.) and $K_2OsO_4 \cdot 2H_2O$ (4 mol%). The reaction was stirred at rt until disappearance of the SM was observed by TLC analysis. Then, Na_2SO_3 (1 g/mmol) was added and the reaction was stirred for 1 h. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (20 mL/mmol), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude product. Purification was performed by flash column chromatography as specified.

Procedure H: *Sharpless asymmetric aminohydroxylation with N-bromoacetamide* [46]

To a solution of $K_2OsO_4 \cdot 2H_2O$ (4 mol%) and $LiOH \cdot H_2O$ (1.3 eq.) in water (6 mL/mmol), was added a solution of the alkene (1 eq.) and ligand (5 mol%) in *t*-BuOH (4 mL/mmol) and the reaction was stirred until homogeneity was achieved. The solution was cooled to 4 °C and *N*-bromoacetamide (1.4 eq.) was added in one portion. The reaction was stirred at 4 °C until disappearance of the SM was observed by TLC analysis. Then, Na_2SO_3 (1 g/mmol) was added and the reaction was stirred for 1 h. The combined organic layers were washed with brine (20 mL/mmol), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude product. Purification was performed by flash column chromatography as specified.

Procedure I: *Sharpless asymmetric aminohydroxylation with N-Boc Carbamate* [47]

To a solution of *tert*-butyl carbamate (3.0 eq.) in propanol (20 mL/mmol) at rt, was added a solution of NaOH in water and 1,3-dichloro-5,5-dimethylhydantoin (2.0 eq.). The suspension was stirred until a homogenous solution was obtained, then a solution of ligand (7 mol%) in propanol (15 mL/mmol) was added. Finally, a solution of alkene (1.0 eq.) in propanol (15 mL/mmol) was added followed by $K_2OsO_4 \cdot 2H_2O$ (5 mol%) and reaction was stirred at room temperature until disappearance of the SM was observed by TLC analysis. A saturated aqueous solution of Na_2SO_3 (10 mL/mmol) was then added and the reaction was stirred for 1 h. Brine (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a crude product. The excess of *tert*-butyl carbamate was removed by sublimation under high vacuum. Purification was performed by flash column chromatography as specified.

Procedure J: *Boc protection of Carbamate*

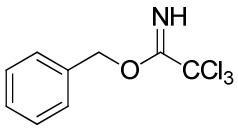
To a solution of carbamate in CH_2Cl_2 (10 mL/mmol) at rt, was added anhydrous triethylamine (1.1 eq.) and DMAP (0.1 eq.). The solution was stirred until all the DMAP had dissolved, and then di-*tert*-butyl dicarbonate (1.5 eq.) was added. The reaction was stirred at room temperature until disappearance of the SM was observed by TLC analysis. On completion the reaction mixture was concentrated *in vacuo* and redissolved in Et_2O (10 mL). Water (10 mL/mmol) was then added and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. Purification was performed by flash column chromatography as specified.

Procedure K: *Removal of benzyl protecting group by hydrogenation in presence of Pd/C*

To a solution of the benzyl protected alcohol in MeOH (10 mL/mmol) was added Pd/C (106 mg/mmol, 10% Pd by weight). Hydrogen was introduced into the reaction flask *via* a balloon. After purging the reaction flask for 5 min, the reaction was left stirring at rt until disappearance of the SM was observed by TLC analysis. On completion, the reaction mixture was filtered over an appropriately sized pad of Celite. The Celite pad was then washed with MeOH (10 mL/mmol) and CH_2Cl_2 (10 mL/mmol). On removal of solvent *in vacuo*, crude product was obtained. Purification was performed by flash column chromatography as specified.

6.3 Experimental Procedures

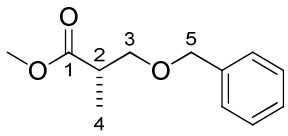
2,2,2-Benzyltrichloroacetimidate [78]



50% aqueous potassium hydroxide (92 mL) and tetra-*N*-butylammonium hydrogen sulfate (140 mg, 0.4 mmol) were added to a solution of benzyl alcohol (8.7 mL, 84 mmol) in CH_2Cl_2 (92 mL) at −15 °C and stirred vigorously. After 5 minutes, trichloroacetonitrile (10 mL, 101 mmol) was added dropwise. The resulting mixture was stirred at the same temperature for 0.5 h and then allowed to warm to rt. The organic layer was separated, and the aqueous later was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to 1/3 the volume, then filtered through a Celite pad (2 cm thick). The pad was further washed with CH_2Cl_2 (100 mL). Concentration of combined filtrates under reduced pressure gave the title compound as a yellow oil (20.65 g, 97%).

^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (1H, br. s, NH), 7.66 - 7.29 (5H, m, Ph), 5.36 (2H, s, C$\underline{H}_2$Ph) ppm. The spectroscopic data were consistent with those reported in literature.[78]

(*S*)-Methyl 3-(benzyloxy)-2-methylpropanoate (97)

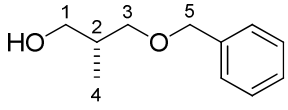


Benzyl 2,2,2-trichloroacetimidate (2.00 mL, 10.80 mmol) was added dropwise to a stirred solution of (*S*)-3-hydroxy-2-methyl propionic acid methyl ester (1.00 mL, 9.00 mmol) in cyclohexane and CH_2Cl_2 (13.5 mL, 2:1) at 0 °C. Trifluoromethanesulfonic acid (60 µL, 0.54

mmol) was then added dropwise and the reaction mixture was allowed warm to rt. After stirring for 5h, it was observed by TLC analysis that the starting material was not consumed, thus the reaction mixture was cooled again to 0 °C and benzyl 2,2,2-tricholoracetimidate (0.85 mL, 4.50 mmol) and trifluoromethanesulfonic acid (20 μL, 0.23 mmol) were added dropwise. The reaction was allowed to warm to rt. After stirring for 16 h, at which point complete consumption of the starting material was seen by TLC analysis, the reaction mixture was filtered over a 2 cm thick pad of Celite. To the filtrate were added saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), and then extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) before being concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol:diethyl ether, 96:4) to afford ester **97** (1.62 g, 87%) as a colourless oil.

$[\alpha]_D^{21}$ +12.1 (*c* = 3.00, $CHCl_3$) {lit.[24] $[\alpha]_D^{20}$ +10.2 (*c* = 3.00, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 - 7.23 (5H, m, Ph), 4.54 (2H, s, C$\underline{H_2}$Ph), 3.71 (3H, s, OCH_3), 3.67 (1H, dd, *J* = 9.9, 7.3 Hz, H-3), 3.51 (1H, dd, *J* = 9.9, 5.9 Hz, H-3'), 2.85 - 2.75 (1H, m, H-2), 1.19 (3H, d, *J* = 7.1 Hz, H-4) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 175.3 (C=O), 138.2 (*ipso*-ArC), 128.4 (ArC), 127.7 (ArC), 127.6 (ArC), 73.1 (C5), 72.0 (C3), 51.8 (OCH_3), 40.2 (C2), 14.0 (C4) ppm. The spectroscopic data were consistent with those reported in literature.[24]

(*R*)-3-(Benzyloxy)-2-methylpropan-1-ol (98)

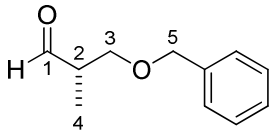


$LiBH_4$ (10 mL, 20 mmol) was added dropwise to a stirred solution of ester **97** (1.38 g, 6.64 mmol) in THF (40 ml) at 0 °C. MeOH (0.90 mL) was added and the reaction mixture was

allowed to warm to rt. After stirring for 2h, a solution of 1.0 M NaOH (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petrol:diethyl ether, 75:25) to afford alcohol **98** (1.07g, 90%) as a colourless oil.

$[\alpha]_D^{21}$ +14.2 (*c* = 1.0, $CHCl_3$) {lit.[79] $[\alpha]_D^{20}$ +12.9 (*c* = 1.01, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.39 - 7.28 (5H, m, Ph), 4.53 (2H, s, C<u>H</u>$_2$Ph), 3.67 - 3.59 (2H, m, H-3), 3.56 (1H, dd, *J* = 9.0, 8.0 Hz, H-1), 3.44 (1H, dd, *J* = 9.0, 8.0 Hz, H-1'), 2.66 (1H, br. s, OH), 2.15 - 2.04 (1H, m, H-2), 0.90 (3H, d, *J* = 7.0 Hz, H-4) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.0 (*ipso*-ArC), 128.4 (ArC), 127.7 (ArC), 127.6 (ArC), 75.4 (C3), 73.3 (C5), 67.8 (C1), 35.5 (C2), 13.4 (C4) ppm. The spectroscopic data were consistent with those reported in literature.[79]

(*S*)-3-(Benzyloxy)-2-methylpropanal (99)

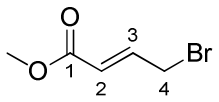


Dimethyl sulfoxide (0.85 mL, 12 mmol) was added dropwise to a solution of oxalyl chloride (0.52 mL, 3.60 mmol) in CH_2Cl_2 (12.5 mL) at –78 °C. After stirring for 30 min, a solution of alcohol **98** (540 mg, 0.3 mmol) in CH_2Cl_2 (2.5 mL) was added *via* cannula. Stirring was continued for further 1 h at –78 °C, then triethylamine (2.09 mL, 15 mmol) was added dropwise and the reaction mixture was allowed to warm to rt (*ca.* 1h). A saturated aqueous solution of NH_4Cl (24 mL) was then added and the phases were separated. The organic phase

was washed with additional NH_4Cl solution (5 × 15 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford aldehyde **99** as a yellow oil (523 mg, 98%), which was used without further purification.

$[\alpha]_D^{21}$ +21.4 (*c* = 1.0, $CHCl_3$) {lit.[80] $[\alpha]_D^{20}$ +29.0 (*c* = 1.16, $CHCl_3$)}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.74 (1H, d, *J* = 1.5 Hz, CHO), 7.40 - 7.28 (5H, m, Ph), 4.54 (2H, s, C<u>H</u>$_2$Ph), 3.73 - 3.63 (2H, m, H-3), 2.74 - 2.63 (1H, m, H-2), 1.15 (3H, d, *J* = 7.2 Hz, H-4) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 203.9 (C=O), 137.9 (*ipso*-ArC), 128.4 (ArC), 127.8 (ArC), 127.6 (ArC), 73.3 (C5), 70.1 (C3), 46.8 (C2), 10.8 (C4) ppm. The spectroscopic data were consistent with those reported in literature.[81]

(*E*)-Methyl 4-bromobut-2-enoate (109)

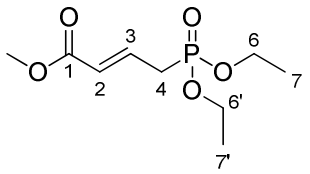


To a solution of methyl crotonate **108** (10.60 mL, 0.10 mol) and *N*-bromosuccinimide (17.80 g, 0.10 mol) in CCl_4 was added a few crystals of benzoyl peroxide and the mixture was heated at reflux for 16 h. The reaction mixture was cooled and filtered. The filtrate was dried (Na_2SO_4) and the oily residue was distilled under reduced pressure to give **109** as a yellow oil (15.37g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.94 (1H, dt, *J* = 15.2, 7.5 Hz, H-3), 5.98 (1H, dt, *J* = 15.2, 1.2 Hz, H-2), 3.96 (2H, dd, *J* = 7.5, 1.2 Hz, H-4), 3.69 (3H, s, OCH_3) ppm; **^{13}C NMR** (100

MHz, $CDCl_3$) δ = 165.8 (C=O), 142.0 (C3), 124.1 (C2), 51.8 (OCH_3), 29.2 (C4) ppm. The spectroscopic data were consistent with those reported in literature.[82]

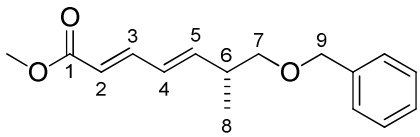
(*E*)-Methyl 4-(diethoxyphosphoryl)but-2-enoate (110)



Freshly prepared bromide **109** (7.69 g, 42.70 mmol) and triethylphosphite (8.51 g, 51.20 mmol) were heated at 120 °C for 3 h. The product was isolated by distillation at 175 °C under vacuum (1 mbar) and gave **110** as a colourless oil (8.36 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (1H, dt, *J* = 15.5, 7.7 Hz, H-3), 5.92 (1H, dd, *J* = 15.5, 4.9, Hz, H-2), 4.13 - 4.02 (4H, m, H-6 and H-6'), 3.69 (3H, s, OCH_3), 2.76 - 2.65 (2H, m, H-4), 1.28 (6H, t, *J* = 7.1 Hz, H-7 and H-7') ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.0 (C=O), 137.9 (C3), 125.3 (C2), 62.3 (C6), 62.2 (C6'), 51.6 (OCH_3), 31.3 (C7), 29.9 (C7'), 16.4 (C4) ppm. The spectroscopic data were consistent with those reported in literature.[83]

(*R*,2*E*,4*E*)-Methyl 7-(benzyloxy)-6-methylhepta-2,4-dienoate (113)

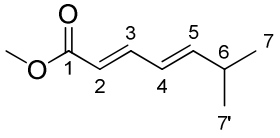


(*S*)-3-(Benzyloxy)-2-methylpropanal **99** (89 mg, 0.50 mmol) was subjected to the general procedure **A** (3 eq of **110** and 3.50 eq. of LDA was used), affording olefin **113**. Purification by

flash column chromatography (petrol:ethyl acetate, 94:6) gave the product as a colourless oil (87 mg, 67%, 4*E*:4*Z* = 8:1, by ^{1}H NMR spectroscopy).

$[\alpha]_D^{25}$ +1.2 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2960, 2855, 1720, 1644, 1496, 1454, 1361 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 - 7.23 (6H, m, Ph and H-3), 6.23 (1H, dd, *J* = 15.4, 9.9 Hz, H-4), 6.11 (1H, dd, *J* = 15.4, 7.1 Hz, H-5), 5.83 (1H, d, *J* = 15.4 Hz, H-2), 4.52 (2H, s, C$\underline{H_2}$Ph), 3.75 (3H, s, OCH_3), 3.40 (1H, dd, *J* = 9.1, 1.8 Hz, H-7), 3.36 (1H, dd, *J* = 9.1, 1.3 Hz, H-7), 2.70 - 2.58 (1H, m, H-6), 1.09 (3H, d, *J* = 6.7 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.7 (C=O), 146.7 (C5), 145.2 (C3), 138.5 (*ipso*-ArC), 128.4, 127.8, 127.6 (ArC), 127.5 (C4), 119.5 (C2), 74.4 (C7), 73.1 (C9), 51.5 (OCH_3), 37.4 (C6), 16.5 (C8) ppm. **MS** *m/z* (ESI^+) 283 $[M+Na]^+$; **HRMS** (ESI^+) $C_{16}H_{20}NaO_3^+$ $[M+Na]^+$ required 283.1305, found 283.1305.

(2*E*,4*E*)-Methyl 6-methylhepta-2,4-dieonate (115)

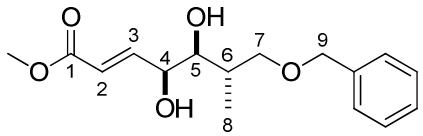


Isobutyraldehyde **114** (91 μL, 1.00 mmol) was subjected to the general procedure **A** (3.00 eq. of phosphonate and 3.50 eq. of LDA was used), affording olefin **115**. Purification by flash column chromatography (petrol:ethyl acetate, 95:5) gave the product (122 mg, 79%, 4*E*:4*Z* > 30:1) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31-7.22 (1H, m, H-3), 6.14-6.09 (2H, m, H-4 and H-5), 5.81 (1H, d, *J* = 15.4 Hz, H-2), 3.74 (3H, s, OCH_3), 2.49-2.36 (1H, m, H-6), 1.05 (6H, d, *J* = 6.8 Hz,

H-7 and H-7') ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.7 (C=O), 151.4 (C5), 145.6 (C3), 125.4 (C4), 118.9 (C2), 51.5 (OCH_3), 31.5 (C6), 21.8 (C7, C7') ppm. The spectroscopic data were consistent with those reported in literature.[84]

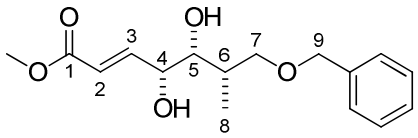
(4*S*,5*S*,6*S*,*E*)-Methyl 7-(benzyloxy)-4,5-dihydroxy-6-methylhept-2-enoate (118)



Unsaturated ester **113** was subjected to the general procedure **D** using $K_2OsO_4 \cdot 2H_2O$ (5 mol%) and $(DHQ)_2PHAL$ (8 mol%) as ligand to yield **118** as a colourless oil (26 mg, 71%) after purification by flash column chromatography (petrol:ethyl acetate, 80:20).

$[\alpha]_D^{25}$ +7.7 (*c* = 1.1, $CHCl_3$); **IR** ν_{max} (neat): 3435, 3030, 2922, 1723, 1658, 1364 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.42 - 7.28 (5H, m, Ph), 7.00 (1H, dd, *J* = 15.7, 4.3 Hz, H-3), 6.15 (1H, d, *J* = 15.7 Hz, H-2), 4.54 (s, 2H, C$\underline{H}_2$Ph), 4.31 (1H, m, H-4), 3.74 (3H, s, OCH_3), 3.64 - 3.59 (1H, m, H-7), 3.58 - 3.51 (2H, m, H-7 and H-5), 3.13 (1H, br s, 4-OH), 2.18 (1H, br s, 5-OH), 2.19 - 2.07 (1H, m, H-6), 0.99 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.8 (C=O), 148.5 (C3), 137.0 (*ipso*-ArC), 128.6 (ArC), 128.1 (ArC), 127.8 (ArC), 121.3 (C2), 78.2 (C5), 74.2 (C9), 73.7 (C7), 71.7 (C4), 51.6 (OCH_3), 35.5 (C6), 14.5 (C8) ppm; **MS** *m/z* (ESI^+) 353 $[M+CH_3CN+NH_4]^+$; **HRMS** (ESI^+) $C_{16}H_{22}NaO_5^+$ $[M+Na]^+$ required 317.1359, found 317.1356.

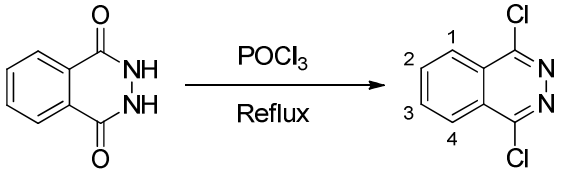
(4*R*,5*R*,6*S*,*E*)-Methyl 7-(benzyloxy)-4,5-dihydroxy-6-methylhept-2-enoate



Unsaturated ester **113** was subjected to the general procedure **D** using $K_2OsO_4 \cdot 2H_2O$ (5 mol%) and $(DHQD)_2PHAL$ (8 mol%) as ligand to yield title compound as a colourless oil (38 mg, 52%) after purification by flash column chromatography (petrol:ethyl acetate, 80:20).

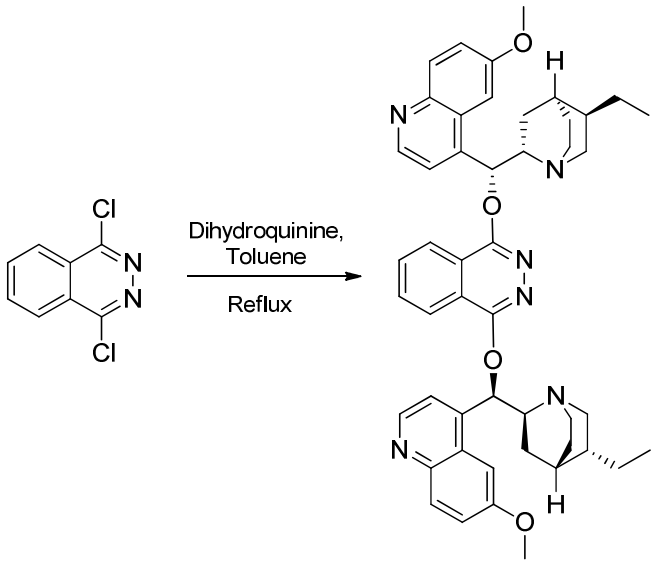
$[\alpha]_D^{26}$ –2.7 (*c* = 1.1, $CHCl_3$); **IR** ν_{max} (neat): 3428, 3030, 2924, 1724, 1659, 1363 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 - 7.28 (5H, m, Ph), 6.93 (1H, dd, *J* =15.7, 4.8 Hz, H-3), 6.17 (1H, dd, *J* =15.7, 1.8 Hz, H-2), 4.54 (1H, d, *J* = 11.4 Hz, H-9), 4.50 (1H, d, *J* = 11.4 Hz, H-9), 4.36 - 4.31 (1H, m, H-4), 3.74 (3H, s, OCH_3), 3.65 - 3.54 (2H, m, H-5 and H-7), 3.47 (1 H, dd, *J* = 9.4, 6.3 Hz, H-7), 3.34 (1H, br. s, 4-OH), 2.88 (1H, br. s, 5-OH), 2.03-1.93 (1H, m, H-6), 1.03 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.8 (C=O), 146.9 (C3), 137.5 (*ipso*-ArC), 128.5 (ArC), 127.9 (ArC), 127.8 (ArC), 121.9 (C2), 76.1 (C5), 73.6 (C7 or C9), 73.3 (C7 or C9), 71.3 (C4), 51.7 (OCH_3), 36.1 (C6), 12.1 (C8) ppm; **MS** *m/z* (ESI^+) 353 $[M+CH_3CN+NH_4]^+$; **HRMS** (ESI^+) $C_{16}H_{22}NaO_5^+$ $[M+Na]^+$ required 317.1359, found 317.1359.

$(DHQ)_2PHAL$



To a flame-dried flask containing phosphorus oxychloride (45 mL) was added 2,3-dihydrophthalazine -1,4-dione (8.5 g, 52.5 mmol). The reaction mixture was stirred under reflux for 4 h. Phosphorus oxychloride was then removed by distillation under mild vacuum. The residue was dissolved in CH_2Cl_2 (200 mL) and stirred rapidly as the solution was neutralized by careful addition of solid and aqueous sodium hydrogen carbonate. When effervescence had ceased, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (petrol : ethyl acetate, 85:15) and afforded a white solid (6.4 g, 61% yield).

MP 193-195 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.94 - 7.90 (2H, m, H-2 and H-3), 7.59 (2H, d, *J* = 7.9 Hz, H-1 and H-4) ppm. The spectroscopic data were consistent with those reported in literature.[85]

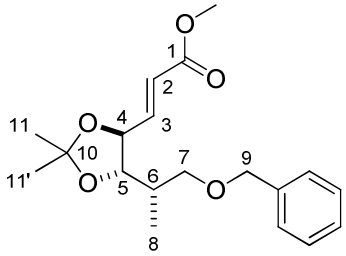


To a 100 mL flame-dried flask was added dihydroquinine (4.0 g, 123 mmol), 1,4-dichlorophthalazine (1.23 g, 62 mmol), K_2CO_3 (2.56 g, 186 mmol) and 50 mL anhydrous

toluene. The flask was equipped with a Dean-Stark condenser and the solution was refluxed in an oil bath at 135 ^{o}C for 2 h under a nitrogen atmosphere. Then, KOH pellets (9.9 g, 0.186 mmol, 86% purity) were added and the mixture was refluxed for azeotropic removal of water. The reaction was followed by TLC (CH_2Cl_2 : MeOH, 95:5) and reflux was stopped after 8 h. The solution was allowed to cool to room temperature and diluted with water (15 mL) and then extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was washed with water (15 mL) and brine (20 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was recrystallised from EtOAc to give a white fluffy solid (2.05 g, 42 % yield).

MP 177-179 °C. The spectroscopic data were consistent with those reported in literature.[86]

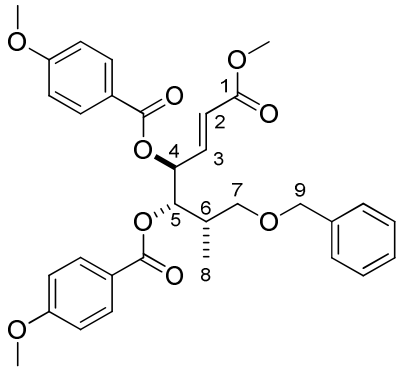
(4*S*,5*S*,6*S*,*E*)-Methyl 7-*O*-benzyl-4,5-*O*-isopropylidene-6-methylhept-2-enoate (152)



To a stirred solution of diol **118** (29 mg, 0.10 mmol) in 1 mL CH_2Cl_2 at room temperature was added 2,2-dimethoxypropane (0.19 mL, 1.5 mmol) and CSA (2 mg, 0.01 mmol). The reaction was stirred for 3 h and then quenched with saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). After removal of solvents *in vacuo*, flash chromatography on silica gel using a gradient of petroleum ether and ethyl acetate (100:0 → 95:5) afforded **152** as a colourless oil (31 mg, 93%).

$[\alpha]_D^{26}$ –9.9 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3064, 2968, 2858, 1727, 1661, 1454, 1437, 1371 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 - 7.22 (5H, m, Ph), 6.93 (1H, dd, *J* = 15.4, 6.0 Hz, H-3), 6.15 (1H, d, *J* = 15.4 Hz, H-2), 4.51 (2H, s, C$\underline{H}_2$Ph), 4.46 (1H, dd, *J* = 6.8, 6.0 Hz, H-4), 3.80 (1H, dd, *J* = 6.8, 6.4 Hz, H-5), 3.75 (3H, s, OCH_3), 3.59 (1H, dd, *J* = 9.3, 5.7 Hz, H-7), 3.42 (1H, dd, *J* = 9.3, 5.7 Hz, H-7), 2.16 - 2.04 (1H, m, H-6), 1.42 (3H, s, H-11), 1.40 (3H, s, H-11'), 1.03 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.6 (C=O), 145.6 (C3), 138.4 (*ipso*-ArC), 128.4 (ArC), 127.6 (ArC), 127.5 (ArC), 122.1 (C2), 109.2 (C10), 82.2 (C4), 77.9 (C5), 73.2 (C9), 71.9 (C8), 51.7 (OCH_3), 36.3 (C6), 27.1 (C11), 26.7 (C11'), 13.9 (C7) ppm; **MS** *m/z* (ESI^+) 357 $[M+Na]^+$; **HRMS** (ESI^+) $C_{19}H_{26}NaO_5^+$ $[M+Na]^+$ required 357.1672, found 357.1672.

(4*S*,5*S*,6*S*,*E*)-Methyl-7-*O*-benzyl-4,5-bis-*O*-(4-methoxybenzoate)-6-methylhept-2-enoate (153)



To a stirred solution of diol **118** (88 mg, 0.30 mmol) in CH_2Cl_2 (10 mL) were added *p*-methoxybenzoyl chloride (337 mg, 1.98 mmol), DMAP (2 mg, 0.016 mmol) and diisopropylethyl amine (0.60 mL, 3.60 mmol) at rt. The mixture was stirred overnight and the resulting heterogeneous mixture was poured into water and then extracted with ether. The combined organic extracts were washed with 1 M HCl, brine and saturated aqueous solution of $NaHCO_3$, and dried ($MgSO_4$). After concentration *in vacuo*, the residue was subjected to flash

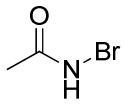
column chromatography on silica gel (petroleum ether, ethyl acetate, 95:5 → 90:10) affording **153** as a yellow oil (142 mg, 84%).

$[\alpha]_D^{25}$ –234.7 (*c* = 0.45, $CHCl_3$); **IR** ν_{max} (neat): 3087, 3029, 2965, 2860, 1719, 1638, 1511 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.02 - 7.98 (4H, m, PhOMe), 7.38 -7.25 (5H, m, Ph), 7.08 (1 H, dd, *J* = 15.9, 5.1 Hz, H-3), 6.93 - 6.82 (4H, m, PhOMe), 6.15 (1H, t, *J* = 5.6 Hz, H-4), 6.08 (1H, d, *J* = 15.9, H-2), 5.48 (1H, t, *J* = 5.8 Hz, H-5), 4.54 (1H, d, *J* = 11.9 Hz, H-9), 4.49 (1H, d, *J* = 11.9 Hz, H-9), 3.84 (6H, s, *J* = 3.3 Hz, $PhOCH_3$), 3.69 (3H, s, OCH_3), 3.65 - 3.58 (1H, m, H-7), 3.44 - 3.34 (1H, m, H-7), 2.45 - 2.29 (1H, m, H-6), 1.06 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.1 (C=O), 165.5 (C=O), 165.0 (C=O), 163.7 (ArC PhOMe), 163.5 (ArC PhOMe), 142.5 (C3), 138.1 (*ipso*-ArC), 131.9 (ArC PhOMe), 131.8 (ArC PhOMe), 128.4 (ArC), 127.8 (ArC), 127.6 (ArC), 123.2 (C2), 122.0 (ArC PhOMe), 121.7 (ArC PhOMe), 113.8 (ArC PhOMe), 113.7 (ArC PhOMe), 75.3 (C5), 73.4 (C9), 72.5 (C4), 71.3 (C7), 55.5 ($PhOCH_3$), 51.7 ($C(O)OCH_3$), 34.9 (C6), 14.7 (C8) ppm; **MS** *m/z* (ESI^+) 585 $[M+Na]^+$; **HRMS** (ESI^+) $C_{32}H_{34}NaO_9^+$ $[M+Na]^+$ required 585.2095, found 585.2094.

tert-Butyl hypochlorite (^{t}BuOCl) [87]

^{t}BuOH (18 mL) in AcOH (12 mL) was slowly added to a solution of 12% NaOCl (100 mL) in water (150 mL) at 0 °C, in the dark. After stirring for 3 min, the mixture was separated and the organic layer washed with 10% aqueous Na_2CO_3 (25 mL). The organic phase was dried ($CaCl_2$) and stored at 4 °C over $CaCl_2$.

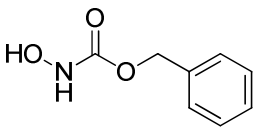
_N_-Bromoacetamide [88]



Acetamide (5 g, 85 mmol) was dissolved in bromine (13.5 g, 85 mmol) contained in a 250 mL conical flask, and the solution was cooled to 0 °C in an ice bath. An ice-cold aqueous 50% potassium hydroxide solution (15 mL) was added in small portions with swirling and cooling until the solution became light yellow. The nearly solid reaction mixture was allowed to stand at 0 °C for 3 h. The mixture was treated with NaCl (10 g) and chloroform (50 mL) and warmed on a water bath with vigorous swirling. After a few minutes the clear red chloroform layer was decanted from the semisolid lower layer, and the aqueous layer extracted with chloroform (2 × 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and then to it was added hexane (150 mL) slowly and with swirling. White needles of N-bromoacetamide began to form at once. The solution was allowed to stand at 0 °C for a further 2 h, and then the crystals (7.51 g, 64%) were collected with suction, washed with hexane, and air-dried.

MP 103-104 °C (lit.[88] MP 103-104 °C); **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 5.93 (1H, br. s, NH), 2.22 (3H, s, CH_3) ppm. The spectroscopic data were consistent with those reported in literature.[88]

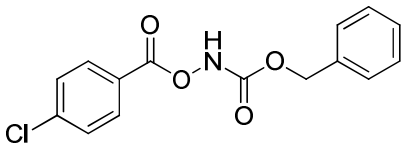
Benzyl hydroxycarbamate (155)



Benzyl chloroformate **154** (4.6 mL, 32.1 mmol) was added dropwise to a solution of hydroxylamine hydrochloride (2.22 g, 32.1 mmol) and sodium carbonate (5.11 g, 48.2 mmol) in water (14.6 mL) while maintaining the temperature below 30 °C with an ice-bath. The ice bath was removed and replaced by a water bath to warm the reaction to rt but allow for absorption of any heat evolved during the reaction. The reaction was stirred for 1 h. The reaction was then quenched by the addition of concentrated HCl until pH 1 was attained. Then it was extracted with CH_2Cl_2 (2 × 50 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a residue that was purified by flash column chromatography (petrol:ethyl acetate, 80:20 → 70:30) to yield benzyl hydroxycarbamate **155** (1.90 g, 35%) as an off-white solid.

MP 62-63 °C (lit.[49] MP 62-64 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.81 (2H, br. s, NH and OH), 7.26 (5H, m, Ph), 5.06 (2H, s, CH_2) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.4 (C=O), 135.5 (*ipso*-ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 67.8 (CH_2) ppm. The spectroscopic data were consistent with those reported in literature.[49]

Benzyl 4-chlorobenzoyloxycarbamate (156)

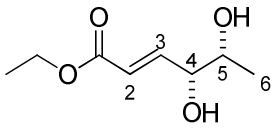


4-Chlorobenzoyl chloride (1.31 mL, 10.2 mmol) was added dropwise to a solution of benzyl hydroxycarbamate **155** (1.90 g, 11.4 mmol) and triethylamine (1.44 mL, 10.4 mmol) in diethyl ether (50 mL) at 0 °C. The reaction was stirred at room temperature for 1 h. Then it was quenched with 1 M HCl solution (10 mL). The separated organic layer was washed with water (2 × 40 mL) and saturated $NaHCO_3$ solution (10 mL), dried ($MgSO_4$), and the solvent was

removed under reduced pressure to give carbamate **156** (3.24 g, 93%) as a colourless crystalline solid, which was used without further purification.

MP 96-98 °C (lit.[49] MP 97-98 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.38 (1H, s, NH), 8.04-8.01 (2H, m, Ph-Cl), 7.48-7.45 (2H, m, Ph-Cl), 7.39-7.32 (5H, m, Ph), 5.25 (2H, s, CH_2) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 165.0 (C=O), 156.3 (C=O), 141.0 (*ipso*-ArC), 134.9 (*ipso*-ArC), 131.3 (ArC), 129.2 (ArC), 128.7 (ArC), 128.3 (ArC), 125.1 (ArC), 68.5 (CH_2) ppm. The spectroscopic data were consistent with those reported in literature.[49]

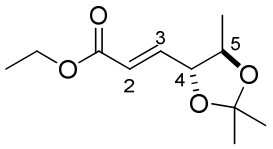
(4*R*,5*R*,*E*)-Ethyl 4,5-dihydroxyhex-2-enoate



Ethyl sorbate (980 mg, 7 mmol) was subjected to the general procedure **D** using $K_2OsO_4 \cdot 2H_2O$ (5 mol%) and $(DHQD)_2PHAL$ (8 mol%) as ligand to yield title compound as a colourless oil (950 mg, 78%) after purification by flash column chromatography (petrol:ethyl acetate, 7:3).

$[\alpha]_D^{26}$ +54.8 (*c* = 1.10, EtOH) {lit.[89] $[\alpha]_D^{24}$ +64.0 (*c* = 1.10, EtOH)}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.90 (1H, dd, *J* = 15.7, 5.3 Hz, H-3), 6.11 (1H, dd, *J* = 15.7, 1.52 Hz, H-2), 4.18 (2H, q, *J* = 7.2 Hz, $C\underline{H}_2CH_3$), 4.06 – 3.99 (1H, m, H-4), 3.74 – 3.65 (1H, m, H-5), 3.50 (1H, br. s, 4-OH), 3.19 (1H, br. s, 5-OH), 1.27 (3H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_3$), 1.21 (3H, d, *J* = 6.3 Hz, H-6) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.6 (C=O), 146.7 (C3), 122.4 (C2), 75.6 (C4), 70.3 (C5), 60.7 ($\underline{C}H_2CH_3$), 19.0 (C6), 14.2 ($CH_2\underline{C}H_3$) ppm. The spectroscopic data were consistent with those reported in literature.[89]

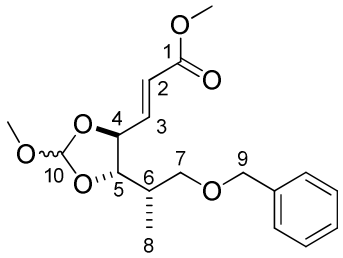
(*E*)-Ethyl 3-((4*R*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acrylate



To a stirred solution of (4*R*,5*R*,*E*)-Ethyl 4,5-dihydroxyhex-2-enoate (174 mg, 1.0 mmol) in 1 mL CH_2Cl_2 at room temperature was added 2,2-dimethoxypropane (0.19 mL, 1.5 mmol) and CSA (23 mg, 0.1 mmol). The reaction was stirred for 3 h and quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). After removal of solvents *in vacuo*, flash chromatography on silica gel using a gradient of petroleum ether and ethyl acetate (100:0 → 95:5) afforded title compound as a colourless oil (193 mg, 91%).

$[\alpha]_D^{25}$ –2.8 (*c* = 1.10, EtOH); {lit.[90] $[\alpha]_D^{20}$ –2.45 (*c* = 1.10, EtOH)}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.87 (1H, dd, *J* = 15.7, 5.8 Hz, H-3), 6.13 (1H, dd, *J* = 15.7, 1.2 Hz, H-2), 4.22 (2H, q, *J* = 7.2 Hz, C$\underline{H}_2$CH$_3$), 4.09 (1H, qd, *J* = 6.0, 2.4 Hz, H-5), 3.85 (1H, ddd, *J* = 8.4, 5.8, 2.4 Hz, H-4), 1.45 (3H, s, C(C$\underline{H}_3$)$_a$), 1.42 (3H, s, C(C$\underline{H}_3$)$_b$), 1.25 - 1.37 (6H, m, CH$_2$C$\underline{H}_3$ and H-6) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = 165.9 (C=O), 143.4 (C3), 122.8 (C2), 119.2 ($\underline{C}$(CH$_3$)$_2$), 81.6 (C5), 76.4 (C4), 60.6 ($\underline{C}$H$_2$CH$_3$), 27.2 (C($\underline{C}$H$_3$)$_2$), 26.6 (C($\underline{C}$H$_3$)$_2$), 16.6 (C6), 14.2 (CH$_2\underline{C}$H$_3$) ppm. The spectroscopic data were consistent with those reported in literature.[91]

(4*S*,5*S*,6*S*,*E*)-7-*O*-Benzyl-4,5-*O*-(methoxymethylene)-6-methylhept-2-enoate

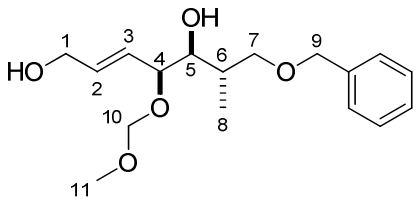


Diol **118** (29 mg, 0.10 mmol) was treated with trimethyl orthoformate (22 μL, 0.20 mmol) and CSA (2 mg, 0.01 mmol) in CH_2Cl_2 (1 mL). After 1h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried ($MgSO_4$). After concentration *in vacuo*, the residue was subjected to flash column chromatography on silica gel (petrol:ethyl acetate, 100:0 → 90:10) affording title compound as a colourless oil (34 mg, 100%) as a 1.2:1 inseparable mixture of diastereomers.

$[\alpha]_D^{25}$ –19.0 (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 2918, 1727, 1665, 1453, 1304 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.38 - 7.27 (5H, m, Ph), 6.98 - 6.91 (1H, m, *Major* H-3), 6.90 - 6.83 (1H, m, *Minor* H-3), 6.16 (1H, app t, *J* = 15.2 Hz, H-2), 5.80 (1H, s, *Minor* H-10), 5.77 (1H, s, *Major* H-10), 4.68 (1H, t, *J* = 6.6 Hz, *Minor* H-4), 4.57-4.52 (1H, m, *Major* H-4), 4.51 (2H, s, *Minor* H-9), 4.50 (2H, s, *Major* H-9), 4.02 (1H, t, *J* = 7.2 Hz, *Major* H-5), 3.81 (1H, t, *J* = 7.6 Hz, *Minor* H-5), 3.76 (3H, s, OCH_3), 3.64 -3.42 (2H, m, H-7), 3.35 (3H, s, *Major* OCH_3), 3.34 (3H, s, *Minor* OCH_3), 2.18 - 2.07 (1H, m, H-6), 1.07 - 1.01 (3H, m, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.3 (C=O), 145.2 (*Major* C3), 143.6 (*Minor* C3), 138.4 (*Minor ipso*-ArC), 138.2 (*Major ipso*-ArC), 128.8 (ArC), 128.4 (ArC), 127.7 (ArC), 127.6 (ArC), 126.4 (ArC), 122.8 (*Minor* C2),122.6 (*Major* C2), 115.9 (*Minor* C10), 116.1 (*Major* C10), 82.9 (*Minor* C5), 81.4 (*Major* C5), 78.2 (C4), 73.2 (C9), 71.7 (C7), 51.8 and 51.7 (OCH_3), 37.3 (*Minor* C6), 36.4

(*Major* C6), 13.9 (*Minor* C8), 13.4 (*Major* C8) ppm; **MS** *m/z* (ESI^+) 359 $[M+Na]^+$; **HRMS** (ESI^+) $C_{18}H_{24}NaO_6^+$ $[M+Na]^+$ required 359.1465, found 359.1465.

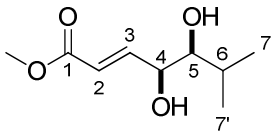
(4*S*,5*S*,6*S*,*E*)-7-(Benzyloxy)-4-(methoxymethoxy)-6-methylhept-2-ene-1,5-diol (185)



Diol **118** (29 mg, 0.10 mmol) was subjected to general procedure **E**, affording the MOM ether **185**. Purification by flash column chromatography (petrol:ethyl acetate, 90:10) gave the product (10 mg, 32%) as a colourless oil.

$[\alpha]_D^{20}$ +81.4 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3424, 3061, 3029, 2954, 2851, 1649, 1571 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 - 7.28 (5H, m, Ph), 5.87 (1H, dt, *J* = 15.5, 5.0 Hz, H-2), 5.75 (1H, ddt, *J* = 15.5, 7.0, 1.0 Hz, H-3), 4.73 (1H, d, *J* = 6.8 Hz, H-10), 4.57 (1H, d, *J* = 6.8 Hz, H-10), 4.52 (2H, s, C$\underline{H}_2$Ph), 4.22 - 4.11 (3H, m, H-4 and H-1), 3.57 (2H, m, H-7), 3.52 - 3.46 (1H, m, H-5), 3.40 (3H, s, OCH_3), 3.33 (1 H, d, *J* = 4.0 Hz, 5-OH), 2.21 - 2.08 (1H, m, H-6), 1.01 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.0 (*ipso*-ArC), 134.0 (C2), 128.4 (ArC), 128.3 (ArC), 127.7 (ArC) 127.7 (C3), 93.9 (C10), 77.9 (C5), 77.2 (C4), 73.7 (C9), 73.4 (C7), 62.9 (C1), 55.9 (OCH_3), 35.1 (C6), 14.4 (C8) ppm; **MS** *m/z* (ESI^+) 333 $[M+Na]^+$; **HRMS** (ESI^+) $C_{17}H_{26}NaO_5^+$ $[M+Na]^+$ required 333.1673, found 333.1671.

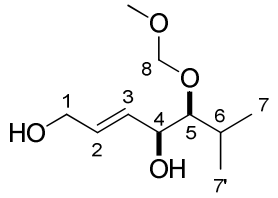
(4*S*,5*S*,*E*)-Methyl 4,5-dihydroxy-6-methylhept-2-enoate (186)



Unsaturated ester **115** was subjected to the general procedure **D** using $K_2OsO_4 \cdot 2H_2O$ (5 mol%) $(DHQ)_2PHAL$ (8 mol%) as ligand. After flash chromatography on silica gel (petrol:ethyl acetate, 100:0 → 95:5) **186** was obtained as a colourless oil (158 mg, 84%).

$[\alpha]_D^{25}$ –27.2 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3420, 2960, 2872, 1722, 1652, 1369 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.95 (1H, ddd, *J* =15.7, 6.4, 5.0 Hz, H-3), 6.15 (1H, dd, *J* = 15.7, 5.0 Hz, H-2), 4.36 - 4.28 (1H, m, H-4), 3.75 (3H, s, OCH_3), 3.34 - 3.25 (1H, m, H-5), 2.70 (1H, br s, 4-OH), 2.31 (1H, br. s, 5-OH), 1.92 - 1.75 (1H, m, H-6), 1.05 - 0.95 (6H, m, H-7 and H-7') ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.8 (C=O), 147.8 (C3), 121.8 (C2), 78.7 (C5), 71.8 (C4), 51.8 (OCH_3), 30.0 (C6), 19.7 (C7), 17.0 (C7') ppm; **MS** *m/z* (ESI^+) 189 $[M+H]^+$; **HRMS** (ESI^+) $C_9H_{16}NaO_4$ $[M+Na]^+$ required 211.0941, found 211.0943.

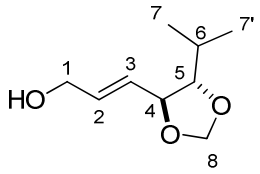
(4*S*,5*S*,*E*)-5-(Methoxymethoxy)-6-methylhept-2-ene-1,4-diol (187)



Diol **186** (30 mg, 0.16 mmol) was subjected to general procedure **E**, affording the MOM ether **187**. Purification by flash column chromatography (petrol:ethyl acetate, 4:1) gave the product (11 mg, 35%) as a colourless oil.

$[\alpha]_D^{26}$ –15.1 (*c* = 0.9, $CHCl_3$); **IR** ν_{max} (neat): 3432, 3058, 2959, 2874, 1658, 1354 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.99 (1H, dt, *J* = 15.4, 4.6 Hz, H-2), 5.71 (1 H, dd, *J* = 15.5, 6.7 Hz, H-3), 4.79 (1 H, d, *J* = 6.6 Hz, H-8), 4.64 (1H, d, *J* = 6.6 Hz, H-8), 4.19 (2H, d, *J* = 4.6 Hz, H-1), 4.20 - 4.07 (1H, m, H-4), 3.60 (1H, br. s, OH-4), 3.45 (3H, s, OCH_3), 3.16 (1H, dd, *J* = 6.8, 3.0 Hz, H-5), 1.87 (1H, m, H-6), 0.96 (3H, d, *J* = 6.8 Hz, H-7), 0.88 (3H, d, *J* = 6.8 Hz, H-7') ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 131.8 (C3), 130.3 (C2), 99.0 (C8), 90.2 (C5), 72.6 (C4), 63.1 (C1), 56.0 (OCH_3), 29.7 (C6), 20.1 (C7), 15.9 (C7') ppm; **MS** *m/z* (ESI^+) 227 $[M+Na]^+$; **HRMS** (ESI^+) $C_{10}H_{20}NaO_4^+$ $[M+Na]^+$ required 227.1254, found 227.1251.

(*E*)-3-((4*S*,5*S*)-5-Isopropyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (188)

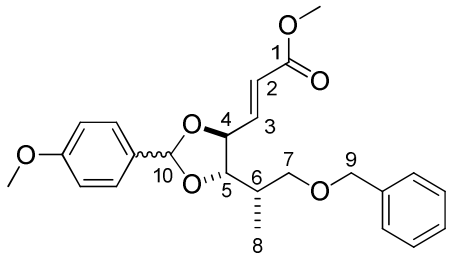


Diol **186** (30 mg, 0.16 mmol) was subjected to general procedure **E**, affording the methylene acetal **188**. Purification by flash column chromatography (petrol:ethyl acetate, 90:10) gave the product (10 mg, 38%) as a colourless oil.

$[\alpha]_D^{26}$ +47.5 (*c* = 0.6, $CHCl_3$); **IR** ν_{max} (neat): 3421, 3062, 2961, 2876, 1649, 1453, 1315 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.04 - 5.93 (1H, m, H-3), 5.75 (1H, dt, *J* = 15.4, 4.6 Hz, H-2), 5.01 (1H, d, *J* = 11.9 Hz, H-8), 4.97 (1H, d, *J* = 11.9 Hz, H-8), 4.20 (2H, d, *J* = 4.6 Hz, H-1), 4.17 - 4.09 (1H, m, H-4), 3.40 (1H, t, *J* = 6.8 Hz, H-5), 1.91 - 1.80 (1H, m, H-6), 1.49 (1H, br. s, 1-OH), 1.02 (3H, d, *J* = 6.8 Hz, H-7), 0.95 (3H, d, *J* = 6.8 Hz, H-7') ppm; **^{13}C NMR** (100

MHz, $CDCl_3$) δ = 133.1 (C3), 128.7 (C2), 94.5 (C8), 86.3 (C5), 79.3 (C4), 62.8 (C1), 30.6 (C6), 18.8 (C7), 18.7 (C7') ppm; **MS** *m/z* (ESI^+) 195 $[M+Na]^+$; **HRMS** (ESI^+) $C_9H_{16}NaO_3^+$ $[M+Na]^+$ required 195.0992, found 195.0991.

(4*S*,5*S*,6*S*,*E*)-7-*O*-Benzyl-4,5-*O*-(4-methoxybenzylidene)-6-methylhept-2-enoate

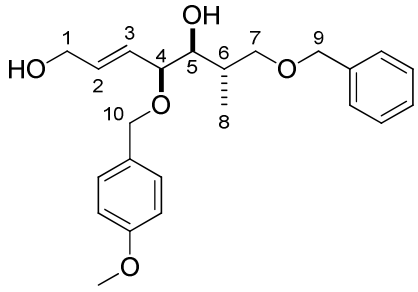


Diol **118** (29 mg, 0.10 mmol) was treated with *p*-anisaldehyde dimethyl acetal (34 μL, 0.20 mmol) in presence of CSA (2 mg, 0.01 mmol) in CH_2Cl_2 (1 mL). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried ($MgSO_4$). After concentration *in vacuo*, the residue was subjected to flash column chromatography on silica gel (petrol: ethyl acetate, 100:0 → 90:10) affording title compound as a colourless oil (41 mg, 100%) as a 2:1 inseparable mixture of diastereomers.

$[\alpha]_D^{25}$ +2.2 (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 2905, 1725, 1661, 1615, 1496, 1454, 1436, 1304 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 - 7.25 (H, m, Ph and *Ph*OMe), 6.98 (1H, ddd, *J* = 15.7, 5.0, 2.6 Hz, H-3), 6.92 (2H, d, *J* = 8.6 Hz, *Ph*OMe), 6.20 (1H, d, *J* = 15.7 Hz, H-2), 5.92 (1H, s, *Minor* H-10), 5.84 (1H, s, *Major* H-10), 4.66 (1H, app q, *J* = 6.0 Hz, H-4), 4.52 (2H, s, H-9), 3.95 (1H, td, *J* = 6.6, 1.5 Hz, *Major* H-5), 3.89 (1H, app t, *J* = 7.3 Hz, *Minor* H-5), 3.83 (3H, s, OCH_3), 3.77 (3H, s, *Major* OCH_3), 3.75 (3H, s, *Minor* OCH_3), 3.60 (1H, dd, *J* = 8.8, 5.4

Hz, *Major* H-7), 3.55 - 3.45 (1H, m, *Minor* H-7), 3.52 (1H, dd, *J* = 8.8, 5.8 Hz, H-7'), 2.30 - 2.20 (1H, m, H-6), 1.11 (3H, d, *J* = 6.8 Hz, *Major* H-8), 1.07 (3H, d, *J* = 6.8 Hz, *Minor* H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.6 (*Major* C=O), 166.4 (*Minor* C=O), 160.5 (*Minor* ArC PhOMe), 160.6 (*Major* ArC PhOMe), 145.5 (*Major* C3), 144.4 (*Minor* C3), 138.3 (*ipso*-ArC), 129.0 (ArC), 128.4 (ArC), 128.2 (ArC), 128.1 (ArC), 127.6 (ArC), 121.5 (*Major* C2), 121.3 (*Minor* C2), 113.8 (ArC PhOMe), 103.7 (*Minor* C10), 103.2 (*Major* C10), 83.6 (*Major* C5), 82.7 (*Minor* C5), 79.3 (*Minor* C4), 77.6 (*Major* C4), 73.3 (C9), 72.0 (*Minor* C7), 71.9 (*Major* C7), 55.3 and 55.7 (OCH_3), 36.6 (*Minor* C6), 36.5 (*Major* C6), 13.7 (*Minor* C8), 13.6 (*Major* C8) ppm; **MS** *m/z* (ESI^+) 435 $[M+Na]^+$; **HRMS** (ESI^+) $C_{24}H_{28}NaO_6^+$ $[M+Na]^+$ required 435.1778, found 435.1776.

(4*S*,5*S*,6*S*,*E*)-7-(Benzyloxy)-4-(4-methoxybenzyloxy)-6-methylhept-2-ene-1,5-diol (189)

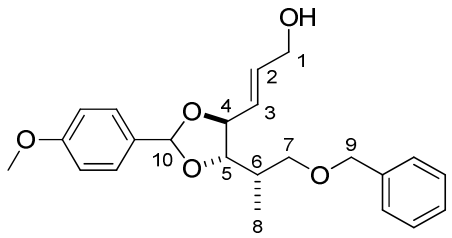


Diol **118** (29 mg, 0.10 mmol) was subjected to general procedure **E** (using *p*-anisaldehyde dimethyl acetal and 20 eq. of DIBAL-H, instead of trimethyl orthoformate and 10 eq. of DIBAL-H) to afford alcohol **189**. Purification by flash column chromatography (petrol:ethyl acetate, 90:10) gave the product as a colourless oil (25 mg, 67%).

$[\alpha]_D^{25}$ +26.8 (*c* = 0.9, $CHCl_3$); **IR** ν_{max} (neat): 3435, 3064, 3029, 2962, 2858, 1651, 1517 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.38 - 7.21 (7H, m, Ph and *Ph*OMe), 6.87 (2H, d, *J* = 8.6 Hz,

*Ph*OMe), 5.88 (1H, dt, *J* = 15.7, 5.0 Hz, H-2), 5.77 (1H, dd, *J* = 15.7, 7.6 Hz, H-3), 4.57 (1H, d, *J* = 11.5 Hz, H-10), 4.48 (2H, s, H-9), 4.28 (1H, d, *J* = 11.5 Hz, H-10), 4.21 (2H, d, *J* = 5.0 Hz, H-1), 3.91 (1H, dd, *J* = 7.5, 5.2 Hz, H-4), 3.81 (3H, s PhOC$\underline{H}_3$), 3.58 (1H, dd, *J* = 9.1, 6.6 Hz, H-5), 3.48 - 3.42 (2H, m, H-7), 3.09 (1H, d, *J* = 3.5 Hz, 5-OH), 2.15 - 2.03 (1H, m, H-6), 0.90 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.4 (ArC PhOMe), 138.3 (*ipso*-ArC), 133.8 (C2), 129.6, 128.9, 128.3, 128.1 and 127.6 (ArC and C3); 113.7 (ArC PhOMe), 102.8 (C10), 79.2 (C4 or C5), 77.6 (C5 or C4), 73.2 (C9), 73.1 (C7), 70.0 (C10), 63.0 (C1), 55.3 (OCH_3), 35.2 (C6), 14.7 (C8) ppm; **MS** *m/z* (ESI^+) 409 $[M+Na]^+$; **HRMS** (ESI^+) $C_{23}H_{30}NaO_4^+$ $[M+Na]^+$ required 409.1985, found 409.1985.

(4*S*,5S,6*S*,*E*)-7-*O*-Benzyl-4,5-*O*-(4-methoxybenzylidene)-6-methylhept-2-enol

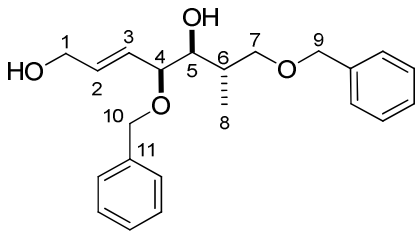


Diol **118** (29 mg, 0.10 mmol) was subjected to general procedure **E** (using *p*-anisaldehyde dimethyl acetal (34 μL, 0.2 mmol), instead of trimethyl orthoformate. Also, the reaction was quenched with saturated aqueous Rochelle's salt solution instead of 2 M NaOH solution) to afford title compound. Purification by flash column chromatography (petrol:ethyl acetate, 90:10) gave the product as a colourless oil (30 mg, 74%). (NB: Data for only the major diastereomer is reported for clarity.)

$[\alpha]_D^{25}$ –11.2 (*c* = 1.3, $CHCl_3$); **IR** ν_{max} (neat): 3435, 3064, 3029, 2962, 2858, 1651, 1517 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 - 7.32 (7H, m, Ph and *Ph*OMe), 6.91 (2H, d, *J* = 8.5 Hz,

*Ph*OMe), 6.01 (1H, dd, *J* = 15.4, 4.7 Hz, H-2), 5.87 (1H, s, H-10), 5.83 (1H, m, H-3), 4.54 - 4.47 (3H, m, C$\underline{H}_2$Ph and H-4), 4.22 - 4.13 (2H, m, C$\underline{H}_2$OH), 3.99 (H, t, *J* = 6.8 Hz, H-5), 3.68 (3H, s, OCH_3), 3.63 (1H, dd, *J* = 9.2, 5.1 Hz, H-7), 3.50 (1H, dd, *J* = 9.2, 6.1 Hz, H-7), 2.22 - 2.15 (1H, m, H-6), 1.45 (1H, t, *J* = 5.8 Hz, OH), 1.08 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 160.4 (ArC), 138.5 (*ipso*-ArC), 137.6 (*ipso*-ArC), 132.9 (C2), 129.8 (ArC), 128.9 (ArC), 128.3 (ArC), 128.1 (ArC), 127.5 (C3); 113.7 (ArC), 102.8 (C10), 83.7 (C5), 79.2 (C4), 73.1 (C9), 72.2 (C7), 62.8 (C1), 55.3 (OCH_3), 36.5 (C6), 13.9 (C8) ppm; **MS** *m/z* (ESI^+) 407 $[M+Na]^+$; **HRMS** (ESI^+) $C_{23}H_{28}NaO_4^+$ $[M+Na]^+$ required 407.1829, found 407.1826.

(4*S*,5*S*,6*S*,*E*)-4,7-Bis(benzyloxy)-6-methylhept-2-ene-1,5-diol (190)

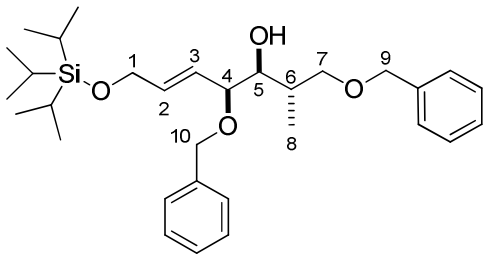


Diol **118** (29 mg, 0.10 mmol) was subjected to general procedure **E** (using 2.0 eq benzaldehyde dimethyl acetal and 20 eq. of DIBAL-H, instead of trimethyl orthoformate and 10 eq. of DIBAL-H. Also, the reaction was quenched with saturated aqueous Rochelle's salt solution instead of 2 M NaOH solution) to afford alcohol **190**. Purification by flash column chromatography (petrol:ethyl acetate, 90:10) gave the product as a colourless oil (26 mg, 72%).

$[\alpha]_D^{20}$ +41.5 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3405, 3030, 2923, 2856, 1497, 1454, 1364 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.38 - 7.28 (10H, m, Ph), 5.87 (1H, dt, *J* = 15.7, 5.0, H-2), 5.77 (1H, dd, *J* = 15.7, 7.5 Hz, H-3), 4.64 (1H, d, *J* = 11.9 Hz, H-10), 4.48 (2H, s, H-9), 4.35

(1H, d, *J*=11.9 Hz, H-10'), 4.18 (2H, d, *J* = 5.0 Hz, H-1), 3.93 (1H, dd, *J* = 7.5, 5.0 Hz, H-4), 3.58 (1H, dd, *J* = 9.1, 6.6 Hz, H-7), 3.51 - 3.44 (2H, m, H-7' and H-5), 3.17 (1H, br. s, OH), 2.14 - 2.08 (1H, m, H-6), 0.91 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.2 (*ipso*-ArC), 138.2 (*ipso*-ArC), 134.0 (C2), 128.7 (ArC), 128.4 (ArC), 128.0 (ArC), 127.7 (ArC), 127.6 (C3), 127.6 (ArC), 80.0 (C4), 77.6 (C5), 73.3 (C7 or C9), 73.1 (C7 or C9), 70.4 (C10), 62.9 (C1), 35.2 (C6), 14.7 (C8) ppm; **MS** *m/z* (ESI^+) 379 $[M+Na]^+$; **HRMS** (ESI^+) $C_{22}H_{28}NaO_4^+$ $[M+Na]^+$ required 379.1880, found 379.1884.

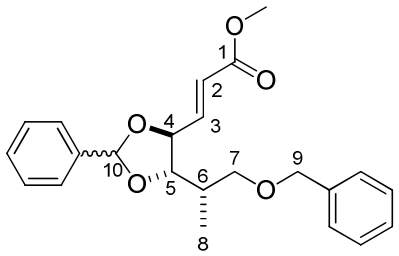
(2*S*,3*S*,4*S*,*E*)-1,4-Bis(benzyloxy)-2-methyl-7-((triisopropylsilyl)oxy)hept-5-en-3-ol (193)



To a solution of alcohol **196** (820 mg, 1.61 mmol) in CH_2Cl_2 (16 mL) was added triethylsilane (1.1 mL, 6.44 mmol) at –78 °C. Then titanium tetrachloride (0.27 mL, 2.41 mmol) was added dropwise. The solution then turned yellow and was kept stirring at the same temperature. On complete consumption of the starting material (~5 h), water is added dropwise and reaction warmed to rt. The mixture was extracted with EtOAc (3 × 10 mL). The organic layer was sequentially washed with saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by flash column chromatography (petrol : ethyl acetate, 90:10) to yield compound **193** as a colourless oil (749 mg, 91%).

$[\alpha]_D^{26}$ +28.8 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3431, 2943, 2865, 1461, 1381 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 - 7.27 (10H, m, Ph), 5.90 - 5.75 (2H, m, H-2 and H-3), 4.66 (1H, d, *J* = 11.6 Hz, H-10), 4.49 (2H, s, H-9), 4.37 - 4.30 (3H, m, H-10' and C<u>H</u>$_2$OH), 3.95 (1H, t, *J* = 6.3 Hz, H-4), 3.61 (1H, dd, *J* = 9.1, 6.3 Hz, H-7), 3.51 - 3.43 (2H, m, H-5 and H-7'), 3.00 (1H, br. s, 5-OH), 2.17 - 2.05 (1H, m, H-6), 1.13 - 1.07 (21H, m, Si(C<u>H</u>$(CH_3)_2)_3$ and Si(CH(C<u>H</u>$_3)_2)_3$), 0.96 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.5 (*ipso*-ArC), 138.3 (*ipso*-ArC), 134.9 (C3), 128.4 (ArC), 128.3 (ArC), 128.0 (ArC), 127.6 (ArC), 127.6 (ArC), 127.5 (ArC), 126.8 (C2), 80.4 (C4), 77.4 (C5), 70.1 (C10), 73.1 (C9), 72.8 (C7), 63.3 (C1), 35.1 (C6), 18.0 (Si(CH(<u>C</u>$H_3)_2)_3$), 14.9 (C8), 12.0 (Si(<u>C</u>$H(CH_3)_2)_3$) ppm; **MS** *m/z* (ESI$^+$) 535 $[M+Na]^+$; **HRMS** (ESI$^+$) $C_{31}H_{48}NaO_4Si^+$ $[M+Na]^+$ required 535.3214, found 535.3212.

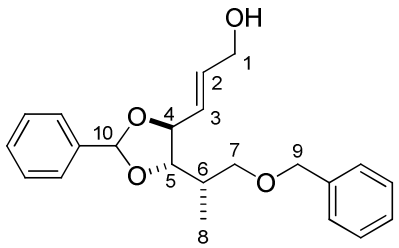
(4*S*,5S,6*S*,*E*)-Methyl-7-*O*-benzyl-4,5-*O*-benzylidene-6-methylhept-2-enoate (194)



To a mixture of diol **118** (990 mg, 3.37 mmol) and CSA (79 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at rt was added benzaldehyde dimethyl acetal (1 mL, 6.74 mmol) dropwise. The mixture was stirred until completion (~3 h) as judged by TLC analysis. On completion water (1 mL) was added to the solution and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture purified by column chromatography (petrol : ethyl acetate, 95:5) to afford the acetal **194** (1.13 g, 88%) as a colourless oil and as a 1.8:1 inseparable mixture of diastereomers.

$[\alpha]_D^{25}$ –7.2 (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 2951, 2887, 1726, 1661, 1603, 1588, 1496, 1457, 1436 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.55 – 7.27 (10H, m, Ph), 7.03 – 6.95 (1H, m, H-3), 6.26 – 6.17 (1H, m, H-2), 5.98 (1H, s, *Minor* H-10), 5.90 (1H, s, *Major* H-10), 4.73 – 4.66 (1H, m, H-4), 4.57 - 4.48 (2H, m, H-9), 3.98 (1H, t, *J* = 6.7 Hz, *Major* H-5), 3.91 (1H, t, *J* = 7.3 Hz, *Minor* H-5), 3.78 (3H, s, *Major* OCH_3), 3.76 (3H, s, *Minor* OCH_3), 3.69 (1H, dd, *J* = 9.1, 4.8 Hz, *Minor* H-7), 3.62 (1H, dd, *J* = 9.2, 5.2 Hz, *Major* H-7), 3.56 – 3.49 (1H, m, H-7'), 2.31 – 2.14 (1H, m, H-6), 1.12 (3H, d, *J* = 7.1 Hz, *Major* H-8), 1.09 (3H, d, *J* = 6.8 Hz, *Minor* H-8) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 166.5 (*Major* C=O), 166.4 (*Minor* C=O), 145.3 (*Major* C3), 144.3 (*Minor* C3), 138.4 (*Minor ipso*-ArC), (138.3 *Major ipso*-ArC), 137.6 (*Minor ipso*-ArC), 136.9 (*Major ipso*-ArC), 129.6 (ArC), 129.4 (ArC), 128.4 (ArC), 127.6 (ArC), 126.8 (ArC), 126.6 (ArC), 122.3 (*Minor* C2), 121.6 (*Major* C2), 103.7 (*Minor* C10), 103.3 (*Major* C10), 83.7 (*Major* C5), 82.8 (*Minor* C5), 79.8 (*Minor* C4), 77.7 (*Major* C4), 73.3 (*Major* C9), 73.2 (*Minor* C9), 72.0 (*Minor* C7), 71.9 (*Major* C7), 51.7 (OCH_3), 36.6 (*Minor* C6), 36.5 (*Major* C6), 13.7 (*Minor* C8), 13.6 (*Major* C8) ppm; **MS** *m/z* (ESI^+) 405 $[M+Na]^+$; **HRMS** (ESI^+) $C_{23}H_{26}NaO_5^+$ $[M+Na]^+$ required 405.1672, found 405.1678.

(4*S*,5*S*,6*S*,*E*)-7-*O*-Benzyl-4,5-*O*-benzylidene-6-methylhept-2-enol (195)

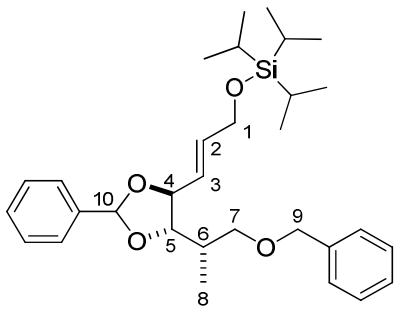


To a solution of **194** (836 mg, 2.25 mmol) in CH_2Cl_2 (22.5 mL) at −78 °C was added DIBAL (4.5 mL, 1M in DCM) dropwise. The solution was stirred until the starting material was

consumed and then the reaction was quenched with saturated aqueous Rochelle's salt solution (5 mL) at −78 °C. The reaction mixture was warmed to rt and more Rochelle's salt solution was added (20 mL). It then stirred for further 30 mins at rt until the cloudy white solution became clear. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (petrol : ethyl acetate, 90:10) to afford the alcohol **195** (794 mg, 100%) as a colourless oil. (NB: Data for only the major diastereomer is reported for clarity.)

$[\alpha]_D^{25}$ –3.5 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2858, 1661, 1455, 1454, 1406 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.55 - 7.28 (10H, m, Ph), 6.01 (1H, dt, *J* = 15.4, 4.8 Hz, H-2), 5.92 (1H, s, H-10), 5.83 (1H, ddt, *J* = 15.4, 6.8, 1.4 Hz, H-3), 4.53 (1H, app t, *J* = 6.8 Hz, H-4), 4.52 (2H, s, C$\underline{H}_2$Ph), 4.25 - 4.10 (2H, m, H-1), 3.92 (1H, t, *J* = 6.8 Hz, H-5), 3.62 (1H, dd, *J* = 9.2, 5.2 Hz, H-7), 3.50 (1H, dd, *J* = 9.2, 5.8 Hz, H-7), 2.32 - 2.10 (1H, m, H-6), 1.52 (1H, br. s, OH), 1.08 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.5 (*ipso*-ArC), 137.6 (*ipso*-ArC), 133.1 (C2), 129.4 (ArC), 128.8 (ArC), 128.4 (ArC), 127.6 (ArC), 126.7 (ArC and C3), 102.9 (C10), 83.8 (C5), 79.3 (C4), 73.2 (C9), 72.2 (C7), 62.8 (C1), 36.5 (C6), 13.9 (C8) ppm; **MS** *m/z* (ESI^+) 377 $[M+Na]^+$; **HRMS** (ESI^+) $C_{22}H_{26}NaO_4^+$ $[M+Na]^+$ required 377.1723, found 377.1719.

(4*S*,5*S*,6*S*,*E*)-7-*O*-benzyl-4,5-*O*-benzylidene-6-methyl-1-(triisopropylsilyloxy)hept-2-enol (196)

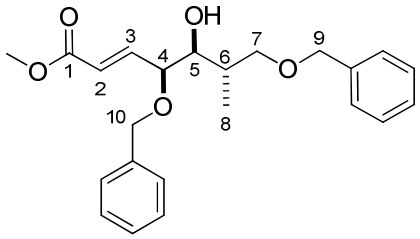


Triethylamine (0.43 mL, 3.05 mmol) was added to a stirred solution of alcohol **195** (720 mg, 2.03 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was cooled to 0 °C, and then triisopropylsilyl trifluoromethanesulfonate (0.65 mL, 2.44 mmol) was added dropwise. After stirring for 30 min, following the consumption of the starting material, saturated aqueous solution of $NaHCO_3$ (15 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography to yield **196** (970 mg, 94%) as a clear oil. (NB: Data for only the major diastereomer is reported for clarity.)

$[\alpha]_D^{20}$ –4.7 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2924, 2865, 1461, 1381 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.56 - 7.47 (2H, m, Ph), 7.44 - 7.24 (8H, m, Ph), 6.00 - 5.92 (1H, m, H-2), 5.88 (1H, dd, *J* = 15.5, 6.6 Hz, H-3), 4.52 (3H, m, H-9 and H-5), 4.32 (2H, d, *J* = 3.3 Hz, H-1), 3.90 (1H, t, *J* = 6.8 Hz, H-4), 3.66 (1H, dd, *J* = 9.1, 4.8 Hz, H-7), 3.51 (1H, dd, *J* = 9.1, 6.3 Hz, H-7'), 2.26 - 2.15 (1H, m, H-6), 1.20 - 1.04 (21H, m, Si(C<u>H</u>$(CH_3)_2)_3$ and Si(CH(C<u>H</u>$_3)_2)_3$), 0.96 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.6 (*ipso*-ArC), 137.9 (*ipso*-ArC), 133.4 (C3), 129.2 (ArC), 128.3 (ArC), 127.5 (ArC), 127.5 (ArC), 127.0 (ArC),

126.7 (C2), 102.8 (C10), 84.0 (C4), 79.7 (C5), 73.1 (C9), 72.83 (C7), 63.0 (C1), 36.6 (C6), 18.0 ($Si(CH(\underline{C}H_3)_2)_3$), 14.0 (C8), 12.0 ($Si(\underline{C}H(CH_3)_2)_3$); **MS** *m/z* ($ESI^+$) 533 $[M+Na]^+$; **HRMS** (ESI^+) $C_{31}H_{46}NaO_4Si^+$ $[M+Na]^+$ required 533.3058, found 533.3049.

(4*S*,5*S*,6*S*,*E*)-Methyl-4,7-bis(benzyloxy)-5-hydroxy-6-methylhept-2-enoate

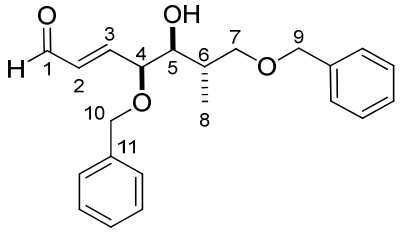


To a solution of acetal **194** (19 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C was added triethylsilane (32 µL, 0.2 mmol). After stirring for a few minutes, $TiCl_4$ (9 µL, 0.075 mmol) was added dropwise. The reaction mixture was stirred at that temperature until complete consumption of the starting material was observed (~ 2 h). Then the reaction was quenched with water (1 mL) and warmed to rt. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to yield crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 90:10 → 85:15) to yield title compound (14 mg, 73%) as a colourless oil.

$[\alpha]_D^{25}$ +38.7 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2931, 2861, 1724, 1666, 1521, 1497, 1454, 1395 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.38 - 7.27 (10H, m, Ph), 7.01 (1H, dd, *J* = 15.9, 6.5 Hz, H-3), 6.09 (1H, d, *J* = 15.9 Hz, H-2), 4.65 (1H, d, *J* = 11.7 Hz, H-10), 4.48 (2H, s, H-9), 4.35 (1H, d, *J* = 11.7 Hz, H-10'), 4.14 (1H, t, *J* = 5.4 Hz, H-4), 3.77 (3H, s, OCH_3), 3.60 - 3.55 (1H, m, H-7), 3.54 (1H, t, *J* = 5.4 Hz, H-5), 3.47 (1H, dd, *J* = 9.1, 4.7 Hz, H-7'), 3.20 (1H, br.

s, 5-OH), 2.13 - 2.03 (1H, m, H-6), 0.88 (3H, d, J = 6.9 Hz, H-8) ppm; **^{13}C NMR** (125MHz, $CDCl_3$) δ = 166.4 (C=O), 145.7 (C3), 138.0 (*ipso*-ArC), 137.6 (*ipso*-ArC), 128.5 (ArC), 128.4 (ArC), 128.0 (ArC), 127.9 (ArC), 127.6 (ArC), 123.5 (C2), 79.3 (C4), 77.2 (C5), 73.3 (C9), 73.1 (C7), 71.4 (C10), 51.7 (OCH_3), 35.2 (C6), 14.6 (C8) ppm; **MS** *m/z* (ESI^+) 407 $[M+Na]^+$; **HRMS** (ESI^+) $C_{23}H_{28}NNaO_5^+$ $[M+Na]^+$ required 407.1829, found 407.1833.

(4*S*,5*S*,6*S*,*E*)-4,7-bis(benzyloxy)-5-hydroxy-6-methylhept-2-enal

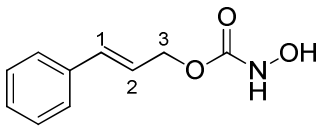


To a solution of (4*S*,5*S*,6*S*,*E*)-Methyl-4,7-bis(benzyloxy)-5-hydroxy-6-methylhept-2-enoate (42 mg, 0.108 mmol) in CH_2Cl_2 (1 mL) at −78°C was added DIBAL (0.22 mL, 1 M in CH_2Cl_2). The reaction was stirred at that temperature until complete consumption of the starting material had occurred (~1 h, as observed by TLC analysis). The reaction was then quenched with a saturated aqueous solution of Rochelle's salt and warmed to rt. After stirring at rt, the milky solution became clear. The organic layer was then separated and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product, which on purification by column chromatography (petrol:ethyl acetate, 90:10 → 80:20) yielded alcohol **190** (31 mg, 76%) and a side-product (title compound, 8 mg, 21%) as colourless oils.

$[\alpha]_D^{20}$ +13.7 (c = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 3403, 3020, 2925, 2856, 1691, 1455 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.62 (1H, d, J = 7.8 Hz, CHO), 7.40 - 7.28 (10H, m, Ph), 6.94

(1H, dd, *J* = 15.9, 6.1 Hz, H-3), 6.34 (1H, ddd, *J* = 15.9, 7.8, 1.0 Hz, H-2), 4.66 (1H, d, *J* = 11.6 Hz, H-10), 4.49 (2H, s, H-9), 4.39 (1H, d, *J* = 11.6 Hz, H-10'), 4.24 (1H, ddd, *J* = 5.9, 4.5, 1.1 Hz, H-4), 3.62 - 3.54 (2H, m, H-7 and H-5), 3.51 (1H, dd, *J* = 9.4, 4.3 Hz, H-7'), 3.39 (1H, d, *J* = 3.8 Hz, OH), 2.11 (1H, m, H-6), 0.86 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 193.4 (C=O), 154.5 (C3), 137.8 (*ipso*-ArC), 137.3 (*ipso*-ArC), 133.8 (C2), 128.5 (ArC), 128.5 (ArC), 128.1 (ArC), 127.8 (ArC), 127.7 (ArC), 79.3 (C4), 77.5 (C5), 73.6 (C7 or C9), 73.4 (C7 or C9), 71.8 (C10), 35.3 (C6), 14.2 (C8) ppm; **MS** *m/z* (ESI^+) 377 $[M+Na]^+$; **HRMS** (ESI^+) $C_{22}H_{28}NaO_4^+$ $[M+Na]^+$ required 377.1723, found 377.1720.

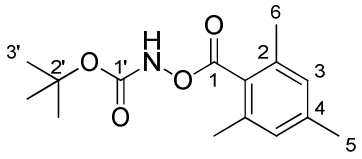
Cinnamyl hydroxycarbamate (199)



To a solution of cinnamyl alcohol **197** (268 mg, 2 mmol) in dry pyridine (4 mL) at rt was added *N,N*-carbonyldiimidazole (810 mg, 5 mmol). The reaction mixture was heated to 40 °C and stirred. After complete consumption of alcohol was observed by TLC analysis (~2 h), the reaction mixture was cooled down to 0 °C and hydroxylamine hydrochloride (1.38 g, 20 mmol) was added. The reaction was then slowly warmed to rt and stirred until the intermediate carbonyl imidazole disappeared by TLC analysis (~4 h). The reaction was quenched with water (10 mL), and the separated aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by column chromatography (petrol:ethyl acetate, 90:10 → 40:60) to give cinnamyl hydroxycarbamate **199** (278 mg, 72%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (1H, br. s., NH), 7.44 - 7.24 (5H, m, Ph), 6.65 (1H, d, *J* = 15.7 Hz, H-1), 6.26 (1H, dt, *J* = 15.7, 6.5 Hz, H-2), 4.80 (2H, d, *J* = 6.5 Hz, H-3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 159.3 (C=O), 136.0 (C1), 134.8 (*ipso*-ArC), 128.6 (ArC), 128.2 (ArC), 126.7 (ArC), 122.6 (C2), 66.7 (C3) ppm. The spectroscopic data were consistent with those reported in literature.[92]

***tert*-Butyl (2,4,6-trimethylbenzoyl)oxycarbamate (201)**

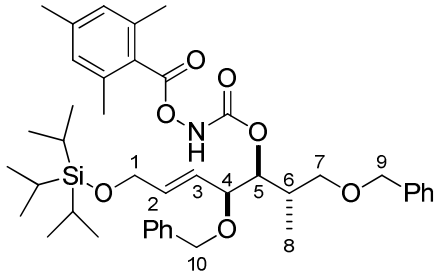


N-Boc hydroxylamine **200** (5.0 g, 37.5 mmol) was dissolved in Et_2O and the mixture was cooled to 0 °C. Triethylamine (5.68 g, 7.8 mL, 56.2 mmol) was added to the mixture, followed by drop wise addition of 2,4,6-trimethylbenzoylchloride. The colourless solution became milky white. Upon completion, as shown by TLC analysis (~6 h), the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was washed with Et_2O (3 × 30 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. *In vacuo* removal of solvents gave the crude mixture which was purified by flash column chromatography (petrol:ethyl acetate, 99:1 → 90:10) to afford **201** (9.7g, 34.6 mmol, 92%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (1H, s, NH), 6.89 (2H, s, H-4), 2.38 (6H, s, PhC$\underline{H}_3$), 2.30 (3H, s, PhC$\underline{H}_3$), 1.54 (9H, s, H-3') ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.3 (C=O), 155.6 (C=O), 140.8 (*ipso*-ArC), 136.7 (ArC), 128.7 (ArC), 126.7 (ArC), 83.3 (C2'), 28.1 (C3'), 21.4

($Ph\underline{C}H_3$), 20.0 ($Ph\underline{C}H_3$) ppm. The spectroscopic data were consistent with those reported in literature.[93]

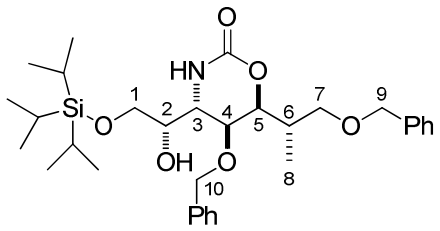
(2*S*,3*S*,4*S*,*E*)-1,4-Bis(benzyloxy)-2-methyl-7-((triisopropylsilyl)oxy)hept-5-en-3-yl(2,4,6-trimethylbenzoyl)oxycarbamate (204)



To a solution of alcohol **193** (600 mg, 1.18 mmol) in dry pyridine (2.5 mL) at rt was added *N,N*-carbonyldiimidazole (478 mg, 2.95 mmol). The reaction mixture was heated to 40 °C and stirred. After complete consumption of alcohol was observed by TLC analysis (~2 h), it was cooled down to 0 °C and hydroxylamine hydrochloride (826 mg, 11.8 mmol) was added. The reaction was then slowly warmed to rt and stirred until the intermediate carbonyl imidazole could not be observed by TLC analysis (~4 h). The reaction was quenched with water (10 mL), and the separated aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product, which was redissolved in Et_2O (12 mL). To this solution was added triethylamine (0.25 mL, 1.8 mmol), and the solution cooled to 0 °C. Mesitoyl chloride (0.24 mL, 1.4 mmol) was then added dropwise and the mixture stirred overnight (~12 h). The reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product, which was purified by column chromatography (petrol:ethyl acetate, 90:10) to give TA pre-cursor **204** (517 mg, 61%).

$[\alpha]_D^{26}$ +2.1 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2865, 1752, 1612, 1455 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.35 (1H, s, NH), 7.37 - 7.25 (10H, m, Ph), 6.89 (2H, s, $PhMe_3$), 5.90 (1H, dt, *J* = 15.4, 4.4 Hz, H-2), 5.74 (1H, dd, *J* = 15.4, 7.6 Hz, H-3), 4.99 (1H, dd, *J* = 6.6, 5.1 Hz, H-5), 4.65 (1H, d, *J* = 11.9 Hz, H-10), 4.48 (1H, d, *J* = 11.9 Hz, H-9), 4.44 (1H, d, *J* = 11.9 Hz, H-9'), 4.35 (1H, d, *J* = 11.9 Hz, H-10'), 4.32 (2H, d, *J* = 3.3 Hz, H-1), 4.12 (1H, dd, *J* = 7.3, 5.3 Hz, H-4), 3.54 (1H, dd, *J* = 9.3, 5.1 Hz, H-7), 3.35 (1H, dd, *J* = 9.3, 6.3 Hz, H-7'), 2.41 - 2.32 (10H, m, $Ph(C\underline{H}_3)_3$ and H-6), 1.10 - 1.07 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 0.99 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 168. 9 ($Ar\underline{C}$=O), 156.5 (NHC=O), 140.7 (ArC), 138.5 (ArC), 138.1 (ArC), 136.8 (ArC), 135.9 (ArC) 135.5 (C3), 128.3 (ArC), 128.3 (ArC), 128.0 (ArC), 127.7 (ArC), 127.5 (ArC), 127.4 (ArC), 126.6 (ArC), 125.2 (C2), 80.1 (C5), 78.0 (C4), 73.1 (C9), 71.5 (C7), 70.2 (C10), 63.2 (C1), 34.4 (C6), 21.2 ($Ar\underline{C}H_3$), 20.2 ($Ar\underline{C}H_3$), 18.0 ($Si(CH(\underline{C}H_3)_2)_3$), 14.4 (C8), 12.0 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 740 $[M+Na]^+$; **HRMS** (ESI^+) $C_{42}H_{59}NNaO_7Si^+$ $[M+Na]^+$ required 740.3953, found 740.3954.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-1-hydroxy-2-((triisopropylsilyl)oxy)ethyl)-1,3-oxazinan-2-one (205)

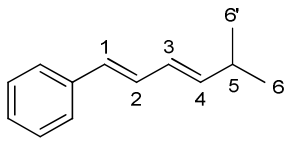


A solution of $K_2OsO_4{\cdot}2H_2O$ (24 mg, 0.064 mmol) in water (2 mL) was added to a stirred solution of carbamate **204** (1.15 g, 1.6 mmol) in ^{t}BuOH (24 mL) and water (6 mL). The stirring

was continued for 40 h, at which point complete consumption of the starting material was observed by TLC analysis. Na_2SO_3 (316 mg) was then added and stirring was continued for a further 30 min. ^{t}BuOH was removed *in vacuo*, then toluene was added, and the water was removed *via* azeotropic distillation. The crude product was purified by flash column chromatography (petrol:ethyl acetate, 80:20 → 60:40) to afford TA product **205** (630 mg, 69%) as a clear oil.

$[\alpha]_D^{25}$ −34.0 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3335, 2942, 2866, 1704, 1456 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 - 7.22 (10H, m, Ph), 6.09 (1H, br. s, NH), 4.70 (1H, d, *J* = 11.9 Hz, H-10), 4.57 - 4.41 (3H, m, H-9 and H-10'), 4.36 (1H, d, *J* = 9.9 Hz, H-5), 3.81 - 3.71 (4H, m, H-1, H-3 and H-4), 3.64 (2H, d, *J* = 4.3, Hz, H-7), 3.57 (1H, d, *J* = 4.0 Hz, H-2), 2.45 - 2.33 (1H, m, H-6), 1.15 - 1.04 (21H, m, Si(C<u>H</u>$(CH_3)_2)_3$ and Si(CH(C<u>H</u>$_3)_2)_3$), 0.91 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 154.7 (C=O), 138.7 (*ipso*-ArC), 137.0 (*ipso*-ArC), 135.4 (C3), 128.5 (ArC), 128.4 (ArC), 128.1 (ArC), 127.9 (ArC), 127.5 (ArC), 127.4 (C2), 78.2 (C5), 73.2 (C9), 72.3 (C2), 71.3 (C7 or C10), 71.2 (C7 or C10), 70.3 (C4), 65.1 (C1), 54.7 (C3), 34.0 (C6), 18.0 (Si(CH(<u>C</u>$H_3)_2)_3$), 13.3 (C8), 11.8 (Si(<u>C</u>$H(CH_3)_2)$) ppm; **MS** *m/z* (ESI^+) 594 $[M+Na]^+$; **HRMS** (ESI^+) $C_{32}H_{49}NNaO_6Si^+$ $[M+Na]^+$ required 594.3221, found 594.3220.

(1*E*,3*E*) 1-Phenyl-5-methylhexa-1,3-diene

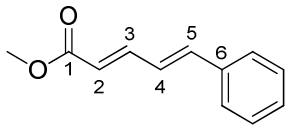


Diethyl cinnamyl phosphonate (508 mg, 2 mmol) and isobutyraldehyde **114** (0.18 mL, 2 mmol) were used in general procedure A. The crude mixture was purified by flash column

chromatography (petrol : diethyl ether, 95:5) to yield the desired product as a colourless oil (186 mg, 54%).

MP 68-70 °C (lit.[96] 69-70 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 - 7.15 (5H, m, Ph), 6.77 (1H, dd, *J* = 15.7, 10.4 Hz, H-2), 6.48 (1H, d, *J* = 15.7 Hz, H-1), 6.20 (1H, dd, *J* = 15.2, 10.6 Hz, H-3), 5.83 (1H, dd, *J* = 15.3, 6.7 Hz, H-4), 2.50 - 2.35 (1H, m, H-5), 1.07 (6H, d, *J* = 6.8 Hz, H-6) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 142.8 (C1), 137.7 (*ipso*-ArC), 130.1 (C3), 129.6 (C2), 128.5 (ArC), 127.5 (ArC), 127.0 (ArC), 126.1 (C4), 31.3 (C5), 22.3 (C6) ppm. The spectroscopic data were consistent with those reported in literature.[94]

(2*E*,4*E*)-Methyl 5-phenylpenta-2,4-dienoate (210)



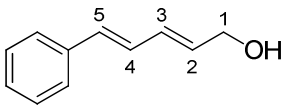
Procedure 1: Benzaldehyde (86 µL, 0.84 mmol) was subjected to general procedure **B**, affording unsaturated diene **210**. Purification by flash column chromatography (petrol:ethyl acetate, 95:5) gave the product (110 mg, 69%, 4*E*:4*Z* > 30:1) as a yellow solid.

Procedure 2: To an ice-cooled suspension of hexane-washed sodium hydride (60% dispersion; 4 g, 0.1 mol) in THF (150 mL) was slowly added methyl diethylphosphonoacetate (19 mL, 0.1 mol) and the mixture was then stirred for 15 min. The mixture was cooled to –78 °C and after the dropwise addition of cinnamaldehyde (12.6 mL, 0.1 mol) stirring was continued for a further 20 min and then the mixture was allowed to warm up to room temperature. The resulting mixture was quenched with saturated aqueous NH_4Cl (100 mL) and then extracted with diethyl ether (2 × 100 mL). The organic phase was washed with brine (50 mL), dried

($MgSO_4$) and concentrated under reduced pressure to give the crude product as an off-white solid. Purification by flash silica chromatography (petrol:ethyl acetate, 90:10) gave the dienoate as a yellow solid (17.5 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 - 7.45 (3H, m, Ph and H-3), 7.38 - 7.30 (3H, m, Ph), 6.92 - 6.85 (2H, m, H-4 and H-5), 6.02 (1H, d, *J* = 15.3 Hz, H-2), 3.78 (3H, s, OCH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 167.3 (C=O), 144.6 (C3), 140.3(C5), 135.8 (*ipso*-ArC), 128.8 (ArC), 128.6 (ArC), 127.0 (ArC), 126.0 (C4), 120.7 (C2), 51.3 (OCH_3) ppm. The spectroscopic data were consistent with those reported in literature.[32]

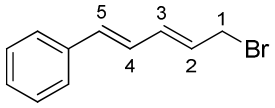
(2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-ol (211)



(*E,E*)-Methyl 5-phenylpenta-2,4-dienoate (**210**, 0.94 g, 5 mmol) was dissolved in dry toluene (10 mL) under an atmosphere of nitrogen, and then diisobutylaluminum hydride (1 M solution in hexane, 10 mL) was added slowly over 1 h. The reaction mixture was then heated to 45 °C for 3 h until no starting material remained. The mixture was then cooled to 0 °C and MeOH (1 mL) was added, followed by addition of water (0.5 mL). The white gel formed was repeatedly washed with MeOH and the combined organic washings were concentrated *in vacuo.* Purification by flash column chromatography (petrol:ethyl acetate, 95:5) gave the product (655 mg, 82%, 2*E*,4*E*: 2*E*,4*Z* > 18:1) as a white solid.

MP 77 - 79 °C (lit. MP 79.5 - 81.5 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 - 7.23 (5H, m, Ph), 6.82 (1H, dd, *J* = 15.7, 10.9 Hz, H-4), 6.58 (1H, d, *J* = 15.7 Hz, H-5), 6.44 (1H, dd, *J* = 14.9, 10.9 Hz, H-3), 5.98 (1H, dt, *J* = 14.9, 5.3 Hz, H-2), 4.26 (2H, d, *J* = 5.3 Hz, H-1) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 137.5 (*ipso*-ArC), 133.1 (C2 or C3), 133.0 (C2 or C3), 131.9 (C4), 129.1 (ArC), 128.6 (ArC), 128.1 (ArC), 126.8 (C5), 63.7 (C1) ppm. The spectroscopic data were consistent with those reported in literature.[95]

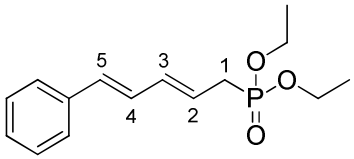
(2*E*,4*E*)-1-bromo-5-phenyl-2,4-pentadiene (212)



(2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-ol (**211**, 2.4 g, 15 mmol) was dissolved in Et_2O (20 mL) and cooled to 0 °C. Phosphorus tribromide (1.5 mL, 16 mmol) was added and the reaction mixture was stirred for 1.5 h. It was then poured onto ice, extracted with ether, washed with $NaHCO_3$ and dried over $MgSO_4$. The combined organic extracts were concentrated *in vacuo* to afford a yellow solid (2.5 g, 75%, 2*E*,4*E*: 2*E*,4*Z* > 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 - 7.20 (5H, m, Ph), 6.78 (1H, dd, *J* = 15.6, 10.5 Hz, H-4), 6.60 (1H, d, *J* = 15.6 Hz, H-5), 6.46 (1H, dd, *J* = 14.9, 10.5 Hz, H-3), 6.00 (1H, dt, *J* = 14.9, 8.2 Hz, H-2), 4.11 (2H, d, *J* = 8.2 Hz, H-1) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 136.6 (*ipso*-ArC), 135.0 (C2 or C3), 134.4 (C4), 128.8 (C2 or C3), 128.5 (ArC), 127.9 (ArC), 127.1 (ArC), 126.4 (C5), 33.4 (C1) ppm. The spectroscopic data were consistent with those reported in literature.[96]

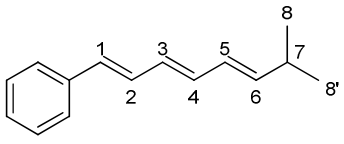
Diethyl ((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)phosphonate (208)



(2*E*,4*E*)-1-Bromo-5-phenyl-2,4-pentadiene (**212**, 3.48 g, 15.6 mmol) was heated to 160 °C with triethyl phosphite (3.0 mL, 17.5 mmol) for 20h. The reaction mixture was purified by flash column chromatography (petrol:ethyl acetate 70:30) to afford the product as a white solid (2.93 g, 67%, 2*E*,4*E*: 2*E*,4*Z* > 20:1).

MP 141-143 °C (lit.[97] 142-145 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 - 7.17 (5H, m, Ph), 6.77 (1H, dd, *J* = 15.5, 10.5 Hz, H-4), 6.50 (1H, dd, *J* = 15.8, 1.6 Hz, H-5), 6.34 (1H, ddd, *J*=15.2, 10.4, 4.8 Hz, H-3), 5.76 (1H, dq, *J* = 15.2, 7.6 Hz, H-2), 4.20 - 4.04 (4H, m, $OC\underline{H}_2CH_3$), 2.70 (2H, dd, *J* = 22.9, 7.6 Hz, H-1), 1.32 (6H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 137.1 (*ipso*-ArC), 135.1 (C3), 132.0 (C5), 128.6 (ArC), 128.3 (C4), 127.6 (ArC), 126.3 (ArC), 122.6 (C2), 62.1 ($O\underline{C}H_2CH_3$), 62.0 ($O\underline{C}H_2CH_3$), 31.7 ($OCH_2\underline{C}H_3$), 30.3 ($OCH_2\underline{C}H_3$), 16.4 (C1) ppm. The spectroscopic data were consistent with those reported in literature.[95]

((1*E*,3*E*,5*E*)-7-Methylocta-1,3,5-trien-1-yl)benzene (215)

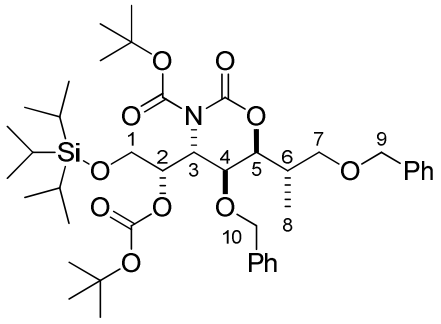


To a solution of phosphonate **208** (100 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C was added sodium *tert*-butoxide (34 mg, 0.36 mmol). The reaction mixture was warmed to rt and stirred

for 30 minutes. It was then re-cooled to 0 °C and isobutyraldehyde (30 μL, 0.3 mmol) was added to the solution. The reaction was allowed to warm to room temperature and stirred overnight (~12 h). Saturated aqueous NH_4Cl solution (3 mL) was then added, the organic layer separated and the aqueous extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by column chromatography (petrol:diethyl ether, 95:5) to give alkene **215** (40 mg, 67%, 1*E*,3*E*,5*E*: 1*E*,3*E*,5*Z* = 10:1) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 - 7.17 (5H, m, Ph), 6.88 - 6.78 (1H, m), 6.61 - 6.48 (1H, m), 6.44 - 6.26 (2H, m), 6.18 - 6.05 (1H, m), 5.78 (1H, dd, *J* = 15.2, 6.8 Hz, H-6), 2.55 - 2.31 (1H, m, H-7), 1.07 (6H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 142.9, 137.6 (*ipso*-ArC), 134.0, 131.4, 130.9, 129.3, 128.6 (ArC), 127.6 (ArC), 127.3 (ArC), 126.2, 31.4 (C7), 22.3 (C8) ppm.

(4*S*,5*S*,6*S*)-*tert*-Butyl 5-(benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-3,3-diisopropyl-2,10,10-trimethyl-8-oxo-4,7,9-trioxa-3-silaundecan-6-yl)-2-oxo-1,3-oxazinane-3-carboxylate

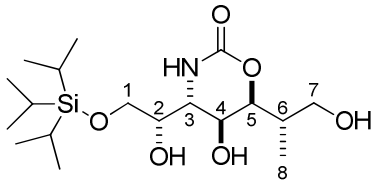


To a solution of carbamate **205** (33 mg, 0.058 mmol) in THF (0.6 mL) at rt was added triethylamine (18 μL, 0.06 mmol) and 4-(dimethylamino)pyridine (1 mg, 0.008 mmol), and the

mixture was cooled to 0 °C. After stirring for a few minutes, di-*tert*-butyl dicarbonate (35 mg, 0.18 mmol) was added to the solution. It was stirred until all the starting material was consumed (~4 h). On completion, the reaction mixture was concentrated *in vacuo* and redissolved in Et_2O (5 mL). Water (5 mL) was then added and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. Purification was performed by flash column chromatography (petrol:ethyl acetate, 95:5) to give title compound (42 mg, 94%) as colourless oil.

$[\alpha]_D^{20}$ –17.3 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2867, 1796, 1744, 1497, 1456 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.37 - 7.27 (10H, m, Ph), 5.11 (1H, dd, *J* = 8.7, 2.7 Hz, H-3), 4.77 (1H, d, *J* = 11.4 Hz, C$\underline{H}_a$H$_b$Ph), 4.67 - 4.61 (1H, m, H-4), 4.55 (1H, d, *J* = 12.1 Hz, C$\underline{H}_a$H$_b$Ph), 4.48 (1H, d, *J* = 12.1 Hz, CH$_a\underline{H}_b$Ph), 4.43 (1H, d, *J* = 11.4 Hz, CH$_a\underline{H}_b$Ph), 4.45 - 4.40 (1H, m, H-5), 3.96 (1H, app. t, *J* = 2.5 Hz, H-2), 3.98 - 3.90 (1H, m, H-1), 3.82 (1H, dd, *J* = 11.5, 4.2 Hz, H-1'), 3.70 (1H, dd, *J* = 9.1, 5.1 Hz, H-7), 3.58 (1H, dd, *J* = 9.1, 3.0 Hz, H-7'), 2.42 - 2.32 (1H, m, H-6), 1.53 (9H, s, C$\underline{H}_3$C) 1.46 (9H, s, C$\underline{H}_3$C), 1.11 - 1.05 (21H, m, Si(C$\underline{H}$(CH$_3$)$_2$)$_3$ and Si(CH(C$\underline{H}_3$)$_2$)$_3$), 0.94 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 152.8 (C=O), 151.8 (C=O), 147.9 (C=O), 138.6 (*ipso*-ArC), 136.9 (*ipso*-ArC), 128.5 (ArC), 128.3 (ArC), 128.0 (ArC), 127.7 (ArC), 127.6 (ArC), 127.4 (ArC), 83.6 (C$\underline{C}$(CH$_3$)$_2$), 82.8 (C$\underline{C}$(CH$_3$)$_2$), 78.9 (C5) 75.6 (C4) 73.2 (CH_2Ph), 70.9 (CH_2Ph or C7), 70.8 (CH_2Ph or C7), 69.0 (C2), 63.2 (C1), 54.5 (C3), 34.6 (C6), 27.8 C($\underline{C}$H$_3$)$_3$), 27.7 (C($\underline{C}$H$_3$)$_3$), 17.9 (Si(CH($\underline{C}$H$_3$)$_2$)$_3$), 13.0 (C8), 11.8 (Si(C$\underline{H}$(CH$_3$)$_2$)$_3$) ppm; **MS** *m/z* (ESI$^+$) 794 [M+Na]$^+$; **HRMS** (ESI$^+$) $C_{42}H_{65}NNaO_{10}Si^+$ [M+Na]$^+$ required 794.4270, found 794.4262.

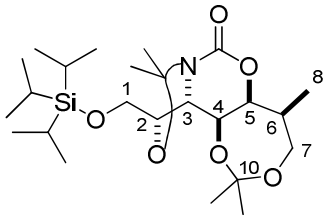
(4*S*,5*S*,6*S*)-5-hydroxy-4-((*S*)-1-hydroxy-2-((triisopropylsilyl)oxy)ethyl)-6-((*S*)-1-hydroxypropan-2-yl)-1,3-oxazinan-2-one (217)



To a solution of carbamate **205** (80 mg, 0.14 mmol) in MeOH (1.4 mL) was added Pd on activated charcoal (10% by wt., 15 mg). The reaction was stirred overnight at rt. On complete consumption of the starting material (~16 h), MeOH was evaporated *in vacuo* and the crude product was redissolved in CH_2Cl_2. The solution was then filtered over a pad of Celite and the pad was washed with CH_2Cl_2 (3 × 5 mL). The combined filtrate was evaporated *in vacuo* to yield **217** as a colourless oil (54 mg, 98%).

$[\alpha]_D^{25}$ −24.0 (*c* = 0.4, $CHCl_3$); **IR** ν_{max} (neat): 3348, 2943, 2867, 1716, 1462 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 6.73 - 6.53 (1H, s, NH), 4.34 (1H, d, *J* = 7.8 Hz, H-5), 4.00 (1H, s, H-4), 3.80 - 3.72 (3H, m, H-1 and H-7), 3.63 (1H, dd, *J* = 10.9, 3.5 Hz, H-7'), 3.60 - 3.49 (2H, m, H-3 and H-2), 2.22 - 2.08 (1H, m, H-6), 1.09 - 1.04 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 1.02 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 154.2 (C=O), 80.2 (C5), 72.4 (C2), 65.4 (C1), 64.2 (C4), 63.6 (C7), 59.7 (C3), 36.5 (C6), 17.9 ($Si(CH(C\underline{H}_3)_2)_3$), 14.0 (C8), 11.8 ($Si(C\underline{H}(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 414 $[M+Na]^+$; **HRMS** (ESI^+) $C_{18}H_{37}NNaO_6Si^+$ $[M+Na]^+$ required 414.2288, found 414.2294.

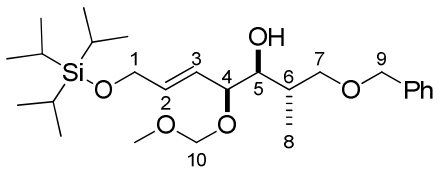
(5*S*,5a*S*,11*R*,11a*R*,11b*S*)-2,2,5,9,9-Pentamethyl-11-(((triisopropylsilyl)oxy)methyl)hexahydro-[1,3]dioxepino[4,5-e]oxazolo[3,4-c][1,3]oxazin-7(4H)-one (218)



To a solution of alcohol **217** (25 mg, 0.064 mmol) in CH_2Cl_2 (0.7 mL) was added CSA (3 mg, 0.013 mmol) and 2,2-dimethoxypropane (80 μL, 0.65 mmol). The reaction mixture was sealed and warmed to 30 °C. After stirring for 4 h, very little conversion had occurred. Thus, the reaction was warmed to 40 °C and stirred for another 6 h, after which complete consumption of the starting material was observed. The solvent was evaporated *in vacuo* and the crude product was redissolved in EtOAc (3 mL). Saturated aqueous solution of $NaHCO_3$ (2 mL) was then added, the aqueous phase extracted with EtOAc (3 × 3 mL) and the combined organic phases dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product was purified by flash column chromatography (petrol:ethyl acetate, 90:10) to yield compound **218** as a colourless oil (24 mg, 79%).

$[\alpha]_D^{25}$ −30.4 (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2867, 1712, 1461, 1424 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.33 (1H, m, H-5), 3.94 - 3.84 (2H, m, H-4 and H-7), 3.67 - 3.58 (3H, m, H-2, H-3 and H-7'), 3.30 (2H, dd, *J* = 12.1, 3.3 Hz, H-1), 2.02 - 1.90 (1H, m, H-6), 1.64 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.12 - 1.03 (24H, m, H-8, Si(C<u>H</u>$(CH_3)_2)_3$ and Si(CH(C<u>H</u>$_3)_2)_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 152.1 (C=O), 101.2 (<u>C</u>$(CH_3)_2$), 93.4 (<u>C</u>$(CH_3)_2$), 77.9 (C5), 77.2 (C2.), 67.0 (C1), 63.2 (C4), 62.8 (C7), 62.4 (C3), 38.9 (C6), 26.5 (C(<u>C</u>$H_3)_2$), 25.3 (C(<u>C</u>$H_3)_2$), 24.9 (C(<u>C</u>$H_3)_2$), 24.6 (C(<u>C</u>$H_3)_2$), 17.9 (Si(CH(C<u>H</u>$_3)_2)_3$), 12.4 (C8), 11.8 (Si(C<u>H</u>$(CH_3)_2)_3$) ppm; **MS** *m/z* (ESI$^+$) 496 $[M+Na]^+$; **HRMS** (ESI$^+$) $C_{24}H_{45}NNaO_6Si^+$ $[M+Na]^+$ required 496.3065, found 496.3061.

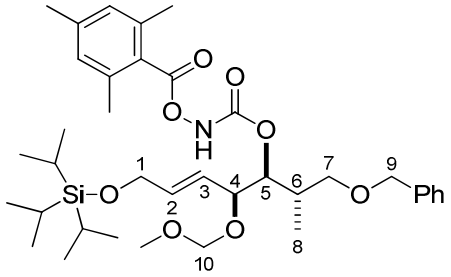
(2*S*,3*S*,4*S*,*E*)-1-(Benzyloxy)-4-(methoxymethoxy)-2-methyl-7-((triisopropylsilyl)oxy)hept-5-en-3-ol (219)



Imidazole (142 mg, 2.1 mmol) and then chlorotriisopropylsilane (0.22 mL, 1 mmol) were added to a stirred solution of diol **185** (320 mg, 2.1 mmol) in DMF (10 mL). After stirring for 20 h, the reaction mixture was diluted with petrol, and then washed with saturated aqueous $NaHCO_3$ (20 mL). The combined aqueous phases were extracted with Et_2O (3 × 15 mL), then the combined organic extracts were dried over Na_2SO_4. Upon filtration and concentrated *in vacuo* crude product was obtained, which was purified by flash column chromatography (petrol:ethyl acetate, 95:5 → 80:20) to afford **219** (705 mg, 72%) as a clear oil.

$[\alpha]_D^{25}$ +60.3 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3484, 2931, 2884, 1474 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.37 - 7.28 (5H, m, Ph), 5.82 (1H, dt, *J* = 15.5, 4.0 Hz, H-2), 5.73 (1H, ddt, *J* = 15.5, 7.5, 1.5 Hz, H-3), 4.75 (1H, d, *J* = 7.0 Hz, H-10), 4.56 (1H, d, *J* = 7.0 Hz, H-10'), 4.52 (2H, s, H-9), 4.29 - 4.25 (2H, m, H-1), 4.19 (1H, dd, *J* = 7.5, 5.0 Hz, H-4), 3.60 (1H, dd, *J* = 9.0, 6.5 Hz, H-7), 3.53 (1H, dd, *J* = 9.0, 5.5 Hz, H-7'), 3.48 (1H, m, H-5), 3.40 (3H, s, OCH_3), 3.13 (1H, br. s, 5-OH), 2.13 - 2.03 (1H, m, H-6), 1.16 - 1.04 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 1.03 (3H, d, *J* = 7.0 Hz, H-8) ppm; **^{13}C NMR** (125MHz, $CDCl_3$) δ = 138.2 (*ipso*-ArC), 134.8 (C2), 128.3 (ArC), 127.6 (ArC), 127.5 (ArC), 126.1 (C3), 93.7 (C10), 77.6 (C4), 77.3 (C5), 73.3 (C7 or C9), 73.2 (C7 or C9), 63.1 (C1), 55.8 (OCH_3), 35.0 (C6), 18.0 ($Si(CH(\underline{C}H_3)_2)_3$) 14.5 (C8), 12.0 ($Si(\underline{C}H(CH_3)_2)$) ppm; **MS** *m/z* ($ESI^+$) 489 $[M+Na]^+$; **HRMS** (ESI^+) $C_{26}H_{46}NaO_5Si^+$ $[M+Na]^+$ required 489.3007, found 489.3005.

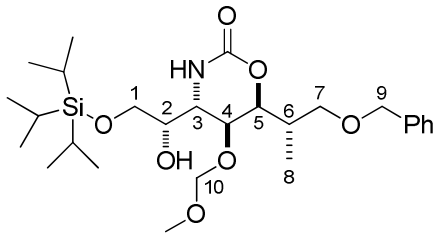
(2*S*,3*S*,4*S*,*E*)-1-(benzyloxy)-4-(methoxymethoxy)-2-methyl-7-((triisopropylsilyl)oxy)hept-5-en-3-yl (2,4,6-trimethylbenzoyl)oxycarbamate (220)



To a solution of alcohol **219** (466 mg, 1.07 mmol) in dry pyridine (2.2 mL) at rt was added *N,N*-carbonyldiimidazole (434 mg, 2.68 mmol). The reaction mixture was heated to and stirred at 40 °C. After complete consumption of alcohol was observed by TLC analysis (~2 h), the reaction mixture was cooled down to 0 °C and hydroxylamine hydrochloride (744 mg, 10.7 mmol) was added. The reaction was then slowly warmed to rt and stirred until the intermediate carbonyl imidazole had disappeared by TLC analysis (~4 h). The reaction was quenched with water (10 mL), and the separated aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was redissolved in Et_2O (12 mL). To this solution was added triethylamine (0.14 mL, 0.96 mmol) and it was cooled to 0 °C. Mesitoyl chloride (0.16 mL, 0.96 mmol) was then added dropwise and the mixture stirred overnight (~12 h). The reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product, which was purified by column chromatography (petrol:ethyl acetate, 90:10) to afford TA pre-cursor **220** (452 mg, 63%).

$[\alpha]_D^{25}$ +25.0 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3265, 2940, 2865, 1775, 1755 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.32 (1H, br. s, NH), 7.37 - 7.25 (5H, m, Ph), 6.89 (2H, s, Ar), 5.87 (1H, dt, *J* = 15.5, 4.0 Hz, H-2), 5.66 (1H, ddt, *J* = 15.5, 7.5, 1.5 Hz, H-3), 4.99 (1H, app t, *J* = 6.0 Hz, H-5), 4.73 (1H, d, *J* = 7.0 Hz, H-10), 4.54 (1H, d, *J* = 7.0 Hz, H-10'), 4.49 - 4.47 (2H, m, H-9), 4.41 (1H, dd, *J* = 7.5, 6.0 Hz, H-4), 4.27 (2H, dd, *J* = 4.0, 1.5 Hz, H-1), 3.57 (1H, dd, *J* = 9.0, 5.0 Hz, H-7), 3.40 (3H, s, OCH_3), 3.36 (1H, dd, *J* = 9.0, 6.5 Hz, H-7'), 2.37 (6H, s, *o*-Ar$C\underline{H}_3$), 2.36 (1H, m, H-6), 2.30 (3H, s, *p*-Ar$C\underline{H}_3$), 1.17 - 1.10 (24H, m, H-8, Si($C\underline{H}(CH_3)_2)_3$ and Si($CH(C\underline{H}_3)_2)_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.0 (Ar$\underline{C}$=O), 156.5 (NHC=O), 140.8 (ArC), 138.4 (ArC), 136.8 (ArC), 135.8 (C3), 128.7 (ArC), 128.6 (ArC), 128.2 (ArC), 127.6 (ArC), 127.4 (ArC), 124.4 (C2), 93.5 (C10), 80.1 (C5), 75.5 (C4), 73.1 (C7 or C9), 71.1 (C7 or C9), 62.9 (C1), 55.8 (OCH_3), 34.3 (C6), 21.2 ($ArCH_3$), 20.0 ($ArCH_3$), 18.0 ($Si(CH(\underline{C}H_3)_2)_3$), 14.5 (C8), 11.9 ($Si(\underline{C}H(CH_3)_2)$) ppm; **MS** *m*/*z* ($ESI^+$) 694 $[M+Na]^+$; **HRMS** (ESI^+) $C_{37}H_{57}NNaO_8Si$ $[M+Na]^+$ required 694.3746, found 694.3751.

(5*S*,6*S*)-6-((*S*)-1-(Benzyloxy)propan-2-yl)-4-((*S*)-1-hydroxy-2-((triisopropylsilyl)oxy)ethyl)-5-(methoxymethoxy)-1,3-oxazinan-2-one (221)

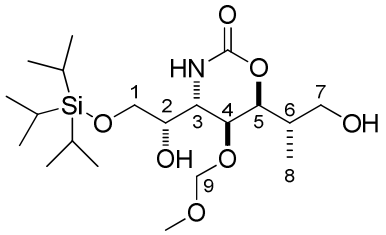


A solution of $K_2OsO_4 \cdot 2H_2O$ (6 mg, 0.016 mmol) in water (0.5 mL) was added to a stirred solution of carbamate **220** (268 mg, 0.4 mmol) in ^{t}BuOH (6 mL) and water (1.5 mL). The stirring was continued for 48 h when complete consumption of the starting material was observed by TLC analysis. Na_2SO_3 (75 mg) was then added and stirring was continued for a

further 30 min. ^{t}BuOH was removed *in vacuo*, toluene was added and the water was removed *via* azeotropic distillation. The crude product was purified by flash column chromatography (petrol:ethyl acetate, 80:20) to afford TA product **221** (155 mg, 74%)

$[\alpha]_D^{20}$ −31.3 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3360, 2942, 2866, 1710, 1464 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.35 - 7.25 (5H, m, Ph), 5.73 (1H, br. s, NH), 4.77 (1H, d, *J* = 7.0 Hz, H-10), 4.67 (1H, d, *J* = 7.0 Hz, H-10'), 4.55 (1H, d, *J* = 12.0 Hz, H-9), 4.50 (1H, d, *J* = 12.0 Hz, H-9'), 4.38 (1H, dd, *J* = 10.0, 1.5 Hz, H-5), 3.98 - 3.93 (1H, m, H-4), 3.81 - 3.75 (2H, m, H-1), 3.75 - 3.71 (1H, m, H-3), 3.68 (1H, dd, *J* = 9.0, 3.0 Hz, H-7), 3.64 (1H, dd, *J* = 9.0, 6.0 Hz, H-7'), 3.62 - 3.58 (1H, m, H-2), 3.40 (3H, s, OCH_3), 2.72 (1H, br. s, OH), 2.36 - 2.30 (1H, m, H-6), 1.21 - 1.02 (24H, m, H-8, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 154.1 (NHC=O), 138.7 (ipso-ArC), 128.3 (ArC), 127.5 (ArC), 127.4 (ArC), 95.6 (C10), 78.0 (C5), 73.2 (C2), 72.0 (C9), 71.2 (C7), 69.4 (C4), 65.3 (C1), 56.5 (C3 or OCH_3), 56.2 (C3 or OCH_3), 33.9 (C6), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 13.1 (C8), 11.9 ($Si(\underline{C}H(CH_3)_2)$) ppm; **MS** *m/z* (ESI) 548 $[M+Na]^+$; **HRMS** (ESI^+) $C_{27}H_{47}NNaO_7Si$ $[M+Na]^+$ required 548.3014, found 548.3017.

(5*S*,6*S*)-4-((*S*)-1-Hydroxy-2-((triisopropylsilyl)oxy)ethyl)-6-((*S*)-1-hydroxypropan-2-yl)-5-(methoxymethoxy)-1,3-oxazinan-2-one (225)

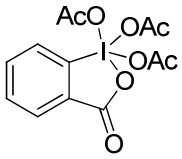


To a solution of carbamate **221** (45 mg, 0.086 mmol) in MeOH (0.86 mL) was added Pd on activated charcoal (10% by wt., 9 mg). The reaction was stirred overnight at room temperature. On complete consumption of the starting material (~21 h, as observed by TLC analysis),

MeOH was evaporated *in vacuo* and the crude product was redissolved in CH_2Cl_2. The solution was then filtered over a pad of Celite and the pad was washed with CH_2Cl_2 (3 × 5 mL). The combined filtrate was evaporated *in vacuo* to yield **225** as a colourless oil (34 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.89 (1H, d, *J* = 2.3 Hz, NH), 4.77 (1H, d, *J* = 7.1 Hz, H-9), 4.66 (1H, d, *J* = 7.1 Hz, H-9'), 4.47 (1H, d, *J* = 10.1 Hz, H-5), 4.05 (1H, br. s., OH), 4.00 - 3.92 (2H, m, H-4 and H-7), 3.83 - 3.69 (3H, m, H-1, H-2 and H-3), 3.62 (2H, m, H-1' and H-7'), 3.39 (3H, s, OCH3), 2.24 - 2.13 (1H, m, H-6), 1.14 - 1.04 (21H, m, $Si(CH(CH_3)_2)_3$ and $Si(CH(CH_3)_2)_3$), 1.01 (3H, d, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 153.5 (C=O), 95.5 (C9), 78.9 (C5), 72.1 (C2), 69.4 (C4) 64.9 (C7) 63.8 (C1), 56.2 (C3 or OCH_3), 55.9 (C3 or OCH_3), 32.8 (C6), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 12.7 (C8), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 458 $[M+Na]^+$; **HRMS** (ESI^+) $C_{20}H_{41}NNaO_7Si^+$ $[M+Na]^+$ required 458.2545, found 458.2544.

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess Martin periodinane)



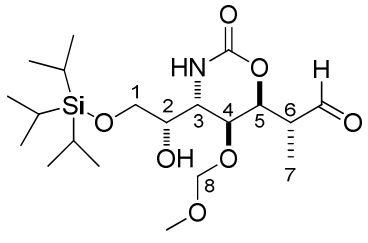
Potassium bromate (8.0 g, 48 mmol) was added to a 2M sulfuric acid solution (75 mL). The resulting clear solution was heated to 60°C in an oil bath and 2-iodobenzoic acid (8.0 g, 32.3 mmol) was added portion-wise over 40 min. The solution became red-orange, bromine vapor was evolved, and a white solid began to separate. After the addition was complete, the reaction mixture then was maintained at an internal temperature of 65 °C for 2.5 h. The reaction mixture was cooled to 2-3 °C in an ice-water bath, and the resulting solids are collected by vacuum filtration. The filter cake was thoroughly washed with cold deionized water (2 × 50 mL), and

absolute ethanol (2 × 10 mL) to afford the iodinane oxide (1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide, 8.82 g).

The iodinane oxide (8.82 g) was added to a solution of glacial acetic acid (15 mL), and acetic anhydride (30 mL). The flask was flushed with argon, and maintained under an inert atmosphere. Magnetic stirring was commenced, and the mixture was heated to 85°C (internal temperature) over 30 min, and kept at this temperature until all the solids dissolved to afford a yellow solution . Heating and stirring were discontinued and the reaction mixture was allowed to cool slowly to rt in the oil bath over 24 h. A large quantity of colourless crystals separated out during this time. The resulting crystalline solids were isolated by careful vacuum filtration in the reaction vessel under argon and were washed with diethyl ether (2 × 10 mL). Residual solvent was removed under vacuum affording Dess Martin periodinane (10.1 g, 74% yield over 2 steps) as a white, crystalline solid.

MP: 231-233 °C (lit.[98] 232-233 °C). The spectroscopic data were consistent with those reported in literature.[99]

(2*R*)-2-((5*S*,6*S*)-4-((*S*)-1-Hydroxy-2-((triisopropylsilyl)oxy)ethyl)-5-(methoxymethoxy)-2-oxo-1,3-oxazinan-6-yl)propanal (226)

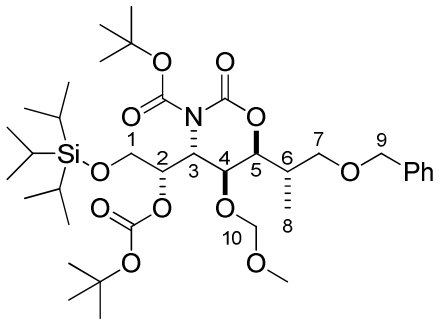


To a solution of alcohol **225** (14 mg, 0.032 mmol) in $CDCl_3$ (0.4 mL) at rt was added [bis(acetoxy)-iodo)]benzene (11 mg, 0.036 mmol) and TEMPO (1 mg, 0.004 mmol) and the mixture was stirred until all of the starting material was consumed (~2 h). The reaction mixture

was then concentrated in vacuo to give the crude product, which was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 9.86 (1H, d, *J* = 2.4 Hz, CHO), 6.00 (1H, br. s., NH), 4.90 - 4.61 (3H, m, H-5 and H-8), 4.07 - 3.60 (5H, m, H-1, H-2, H-3 and H-4), 3.40 (3H, s, OCH_3) 2.94 - 2.73 (1H, m, H-6) 1.21 (3H, d, *J* = 7.2 Hz), 1.15 - 0.97 (21 H, m, $Si(CH(CH_3)_2)_3$ and $Si(CH(CH_3)_2)_3$) ppm; **^{13}C NMR** (50 MHz, CDCl3) δ = 201.9 (CHO), 153.3 (NHCO), 95.5 (C8), 78.1 (C5), 71.5 (C2), 70.1 (C4), 64.9 (C1), 56.0 (C3 or OCH_3), 55.7 (C3 or OCH_3), 46.3 (C6), 17.5 ($Si(CH(CH_3)_2)_3$), 11.3 ($Si(CH(CH_3)_2)_3$), 10.5 (C7) ppm.

(4*S*,5*S*,6*S*)-*tert*-Butyl 6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-3,3-diisopropyl-2,10,10-trimethyl-8-oxo-4,7,9-trioxa-3-silaundecan-6-yl)-5-(methoxymethoxy)-2-oxo-1,3-oxazinane-3-carboxylate (227)

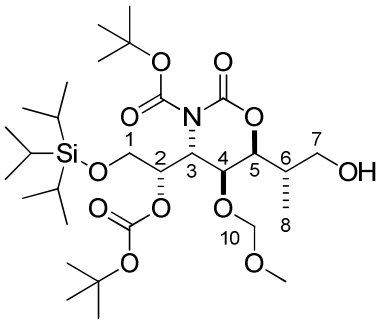


To a solution of carbamate **221** (85 mg, 0.16 mmol) in THF (0.8 mL) at rt was added triethylamine (55 μL, 0.18 mmol) and 4-(dimethylamino)pyridine (2.5 mg, 0.02 mmol), and the mixture was cooled to 0 °C. After stirring for a few minutes, di-*tert*-butyl dicarbonate (106 mg, 0.48 mmol) was added to the solution, which was stirred until all the starting material was consumed (~6 h). On completion, the reaction mixture was concentrated *in vacuo* and redissolved in Et_2O (5 mL). Water (5 mL) was then added and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. Purification was performed by

flash column chromatography (petrol:ethyl acetate, 95:5) to give carbamate **227** (116 mg, 100%) as colourless oil.

$[\alpha]_D^{20}$ –24.4 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2867, 1796, 1744, 1459 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.38 - 7.24 (5H, m, Ph), 4.89 (1H, dd, *J* = 8.6, 2.5 Hz, H-3), 4.80 (1H, d, *J* = 7.3 Hz, H-10), 4.65 (1H, d, *J* = 7.3 Hz, H-10'), 4.62 - 4.58 (1H, m, H-2), 4.57 (1H, d, *J* = 12.2 Hz, H-9), 4.51 (1H, d, *J* = 12.2 Hz, H-9'), 4.47 (1H, dd, *J* = 9.9, 1.3 Hz, H-5), 4.12 (1H, app t, *J* = 2.5 Hz, H-4), 3.904 (1H, dd, *J* = 11.1, 4.5 Hz, H-1), 3.82 (1H, dd, *J* = 11.1, 4.3, H-1'), 3.70 (1H, dd, *J* = 9.0, 5.5 Hz, H-7) 3.62 (1H, dd, *J* = 9.0, 2.7 Hz, H-7'), 3.38 (3H, s, OCH_3), 2.37 - 2.25 (1H, m, H-6), 1.54 (9H, s, $C\underline{H}_3C$) 1.45 (9H, s, $C\underline{H}_3C$) 1.11 - 1.05 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$) 1.03 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 152.9 (C=O), 151.9 (C=O), 148.1 (C=O), 138.7 (*ipso*-ArC), 128.3 (ArC), 127.6 (ArC), 127.4 (ArC), 95.3 (C10), 83.6 ($\underline{C}(CH_3)_3$), 82.8 ($\underline{C}(CH_3)_3$), 78.2 (C5), 75.6 (C2), 73.2 (C9), 70.8 (C7), 67.5 (C4), 63.5 (C1), 56.7 (C3 or $O\underline{C}H_3$), 56.3 (C3 or $O\underline{C}H_3$), 34.3 (C6), 27.8 ($C(\underline{C}H_3)_3$), 27.6 ($C(\underline{C}H_3)_3$), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 12.8 (C8), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 748 $[M+Na]^+$; **HRMS** (ESI^+) $C_{37}H_{63}NNaO_{11}Si^+$ $[M+Na]^+$ required 748.4063, found 748.4065.

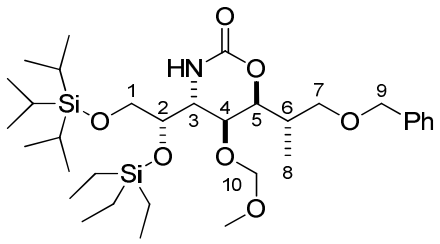
(4*S*,5*S*,6*S*)-*tert*-Butyl 4-((*S*)-3,3-diisopropyl-2,10,10-trimethyl-8-oxo-4,7,9-trioxa-3-silaundecan-6-yl)-6-((*S*)-1-hydroxypropan-2-yl)-5-(methoxymethoxy)-2-oxo-1,3-oxazinane-3-carboxylate (228)



To a solution of carbamate **227** (36 mg, 0.05 mmol) in MeOH (0.5 mL) was added Pd on activated charcoal (10% by wt., 5 mg). The reaction was stirred overnight at room temperature. On complete consumption of the starting material (~21 h, as observed by TLC analysis), MeOH was evaporated *in vacuo* and the crude product was redissolved in CH_2Cl_2. The solution was then filtered over a pad of Celite and the pad was washed with CH_2Cl_2 (3 × 3 mL). The combined filtrate was evaporated *in vacuo* to yield **228** as a colourless oil (29 mg, 94%).

$[\alpha]_D^{20}$ +2.1 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3450, 2942, 2866, 1790, 1743, 1462 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.90 (1H, dd, *J* = 8.6, 2.5 Hz, H-3), 4.81 (1H, d, *J* = 7.3 Hz, H-10), 4.66 (1 H, d, *J* = 7.3 Hz, H-10'), 4.62 - 4.56 (1H, m, H-2), 4.43 (1H, dd, *J* = 10.1, 2.5 Hz, H-5), 4.13 (1H, app t, *J* = 2.5 Hz, H-4), 3.94 (1H, dd, *J* = 11.1, 4.8 Hz, H-1), 3.90 - 3.86 (1H, m, H-7), 3.83 (1H, dd, *J* = 11.1, 4.6 Hz, H-1'), 3.79 - 3.73 (1H, m, H-7'), 3.39 (3H, s, OCH_3), 2.33 - 2.20 (1H, m, H-6), 1.92 - 1.83 (1H, br. s, OH), 1.54 (9H, s, C$\underline{H}_3$C), 1.45 (9H, s, C$\underline{H}_3$C), 1.09 - 1.03 (21H, m, Si(C$\underline{H}$(CH$_3$)$_2$)$_3$ and Si(CH(C$\underline{H}_3$)$_2$)$_3$), 0.99 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 153.5 (C=O), 152.9 (C=O), 147.8 (C=O), 95.3 (C10), 83.7 (C(CH$_3$)$_3$), 83.0 (C(CH$_3$)$_3$), 79.6 (C5), 75.5 (C2), 67.5 (C4), 64.4 (C7), 63.6 (C1), 56.7 (C3 or OCH_3), 56.4 (C3 or OCH_3), 35.6 (C6), 27.8 (C(C$\underline{H}_3$)$_3$), 27.6 (C(C$\underline{H}_3$)$_3$), 17.9 (Si(CH(C$\underline{H}_3$)$_2$)$_3$), 12.5 (C8), 11.8 (Si(C$\underline{H}$(CH$_3$)$_2$)$_3$) ppm; **MS** *m/z* (ESI$^+$) 672 $[M+Na]^+$; **HRMS** (ESI$^+$) $C_{30}H_{57}NNaO_{11}Si^+$ $[M+Na]^+$ required 658.3593, found 658.3590.

(4*R*,5*S*,6*S*)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-3,3-diethyl-8,8-diisopropyl-9-methyl-4,7-dioxa-3,8-disiladecan-5-yl)-5-(methoxymethoxy)-1,3-oxazinan-2-one (236)

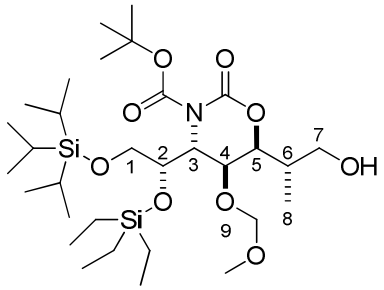


To a solution of alcohol **221** (51 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) at rt was added imidazole (34 mg, 0.5 mmol). After imidazole dissolved, the mixture was cooled to 0 °C and chlorotriethylsilane (59 µL, 0.3 mmol) was added dropwise. The solution was stirred till complete consumption of the starting material was observed by TLC analysis (~3 h) and then water (1 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 90:10 →80:20) to give carbamate **236** (59 mg, 92%) as a colourless oil.

$[\alpha]_D^{25}$ −44.7 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2943, 2868, 1715, 1458 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = ^{1}H NMR ($CDCl_3$) δ ppm 7.34 - 7.24 (5H, m, Ph), 5.09 (1H, d, *J* = 3.3 Hz, NH), 4.77 (1H, d, *J* = 7.2 Hz, H-10), 4.68 (1 H, d, *J* = 7.2 Hz, H-10'), 4.55 (1H, d, *J* = 11.9 Hz, H-9), 4.49 (2 H, d, *J* = 11.9 Hz, H-9'), 4.39 (1H, d, *J* = 10.1 Hz, H-5), 4.02 (1H, app. S, H-4), 3.85 (2H, app. t, *J* = 3.8 Hz, H-3), 3.78 - 3.59 (5H, m, H-1, H-2 and H-7), 3.39 (3H, s, OCH_3), 2.38 - 2.27 (1H, m, H-6) 1.12 - 1.01 (24H, m, H-8, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 0.95 - 0.89 (9H, m, $Si(CH_2C\underline{H}_3)_3$), 0.58 (6H, q, *J* = 7.7 Hz, $Si(C\underline{H}_2CH_3)_3$) ppm; **^{13}C NMR** (100 MHz,

$CDCl_3$) δ = 153.9 (C=O), 138.8 (*ipso*-ArC), 128.2 (ArC), 127.5 (ArC), 127.3 (ArC), 95.7 (C10), 78.1 (C5), 73.5 (C2), 73.1 (C9), 71.1 (C7), 69.3 (C4), 64.4 (C1), 56.2 (C3), 55.9 (OCH_3), 34.1 (C6), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 13.2 (C8), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 5.0 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 662 $[M+Na]^+$; **HRMS** (ESI^+) $C_{33}H_{61}NNaO_7Si_2^+$ $[M+Na]^+$ required 662.3879, found 662.3884.

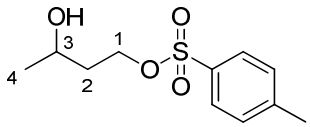
(4*R*,5*S*,6*S*)-*tert*-Butyl 4-((*S*)-3,3-diethyl-8,8-diisopropyl-9-methyl-4,7-dioxa-3,8-disiladecan-5-yl)-6-((*S*)-1-hydroxypropan-2-yl)-5-(methoxymethoxy)-2-oxo-1,3-oxazinane-3-carboxylate (237)



To a solution of carbamate **236** (64 mg, 0.1 mmol) in THF (1 mL) at rt was added triethylamine (30 μL, 0.25 mmol) and dimethylaminopyridine (2 mg). Then to the homogenous solution was added di-*tert*-butyl dicarbonate (44 mg, 0.2 mmol) and the reaction was stirred till complete consumption of the starting material was observed by TLC analysis (~16 h). The reaction was then concentrated *in vacuo* to give the crude product. Following purification by column chromatography (petrol:ethyl acetate, 95:5), the intermediate was dissolved in methanol (1 mL). To the solution was added Pd on activated charcoal (10% by wt., 10 mg). The reaction was stirred overnight at room temperature. On complete consumption of the starting material (~16 h), MeOH was evaporated *in vacuo* and the crude redissolved in CH_2Cl_2. The solution was then filtered over a pad of Celite and the pad was washed with CH_2Cl_2 (3 × 5 mL). The combined filtrate was evaporated *in vacuo* to yield **237** as a colourless oil (46 mg, 82%).

$[\alpha]_D^{25}$ +5.1 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2944, 2869, 1790, 1734, 1461 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.83 - 4.76 (2H, m, H-3 and H-10), 4.61 (1H, d, *J* = 7.1 Hz, H-10'), 4.35 (1H, dd, *J* = 9.9, 2.5 Hz, H-5), 4.09 (1H, app. t, *J* = 2.5 Hz, H-4), 3.85 (1H, dd, *J* = 11.0, 4.4 Hz, H-7), 3.75 (1 H, dd, *J* = 11.0, 4.4 Hz, H-7'), 3.71 - 3.67 (3H, m, H-1 and H-2), 3.38 (3H, s, OCH_3), 2.33 - 2.23 (1H, m, H-6), 1.52 (9H, s, $C(CH_3)_3$), 1.15 - 1.04 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 1.01 - 0.91 (12 H, m, H-8 and $Si(CH_2C\underline{H}_3)_2$), 0.62 (6H, q, *J* = 8.00 Hz, $Si(C\underline{H}_2CH_3)_2$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 152.7 (C=O), 148.4 (C=O), 95.1 (C9), 83.2 ($\underline{C}(CH_3)_3$), 80.7 (C5), 72.1 (C2), 68.5 (C4), 66.2 (C1), 64.8 (C7), 58.5 (C3), 56.3 (OCH_3), 35.5 (C6), 27.9 ($C(\underline{C}H_3)_3$), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 12.6 (C8), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 4.9 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 672 $[M+Na]^+$; **HRMS** (ESI^+) $C_{31}H_{63}NNaO_9Si_2^+$ $[M+Na]^+$ required 672.3934, found 672.3930.

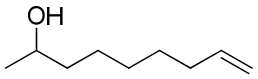
3-Hydroxybutyl 4-methylbenzenesulfonate (250)



p-Toluenesulfonyl chloride (1 g, 5.25 mmol) in pyridine (15 mL) was added dropwise to a solution of 1,3-butanediol **249** (450 mg, 5 mmol) in pyridine (2 mL) at −20 °C. The mixture was stirred at −20 °C for 1 h, before the pyridine was removed *in vacuo*. The reaction mixture was redissolved in CH_2Cl_2 (30 mL) and washed successively with water (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic layer was dried over anhydrous $NaSO_4$ and the solvent was removed *in vacuo*. The crude oil was purified by flash column chromatography (petrol:ethyl acetate, 80:20 → 70:30) to afford **250** as a yellow oil (210 mg, 17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (2H, d, *J* = 7.6 Hz, Ar), 7.35 (2H, d, *J* = 8.8 Hz, Ar), 4.27 - 4.09 (2H, m, H-1), 3.96 - 3.94 (1H, m, H-3), 2.45 (3H, s, ArC<u>H</u>$_3$), 1.84-1.67 (2H, m, H-2), 1.19 (3H, d, *J* = 6.4 Hz, H-4) ppm. The spectroscopic data were consistent with those reported in literature.[100]

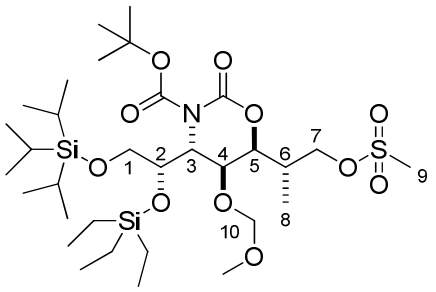
Non-8-en-2-ol



To a solution of 5-bromopent-1-ene **239** (606 mg, 4.07 mmol) in THF (4 mL) at −78 °C was added *tert*-butyllithium (4.3 mL, 1.9 M in hexane) dropwise. The reaction was then stirred for 30 mins and then CuCN (167 mg, 1.85 mmol) was added. After warming to −50 °C, tosylate **250** (90 mg, 0.37 mmol) in THF (0.5 mL) was added dropwise. The reaction was allowed to warm to rt and stirred till complete consumption of the starting material had occurred (~2 h,by TLC analysis). A saturated aqueous NH_4Cl solution (3 mL) was added, followed by Et_2O (5 mL) and the reaction stirred for a further 15 minutes. The organic phase was separated and the aqueous phase extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude product, which on purification by flash column chromatography (petrol:ethyl acetate, 95:5) gave non-8-en-2-ol **251** (24 mg, 46%) as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 5.84 - 5.66 (1H, m, C<u>H</u>=CH_2), 5.02 - 4.86 (2H, m, CH=C<u>H</u>$_2$), 3.81 - 3.68 (1H, m, C<u>H</u>OH), 2.10 - 1.98 (2H, m, CH_2), 1.50-1.23 (7H, m, CH_2), 1.67 - 1.56 (1H, m, CH_2), 1.17 (3H, d, *J* = 6.0Hz, CH_3) ppm. The spectroscopic data were consistent with those reported in literature.[101]

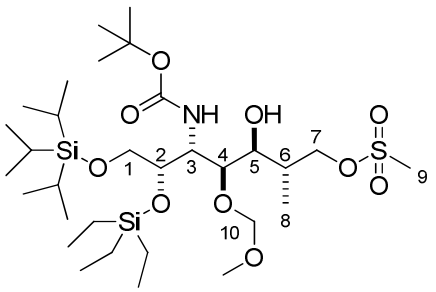
(4*R*,5*S*,6*S*)-*tert*-Butyl 4-((*S*)-3,3-diethyl-8,8-diisopropyl-9-methyl-4,7-dioxa-3,8-disiladecan-5-yl)-5-(methoxymethoxy)-6-((*S*)-1-((methylsulfonyl)oxy)propan-2-yl)-2-oxo-1,3-oxazinane-3-carboxylate (252)



To a solution of alcohol **237** (10 mg, 0.015 mmol) in DCM (0.3 mL) at rt was added triethylamine (6 μL, 0.043 mmol). The mixture was cooled to 0 °C and then mesylchloride (3 μL, 0.039 mmol) was added to it. The solution was stirred till the starting material was consumed (~3 h, by TLC analysis) and then saturated aqueous $NaHCO_3$ solution (0.3 mL) was added. The reaction was filtered over Celite and the pad washed with CH_2Cl_2 (3 × 3 mL). The organic layers were evaporated *in vacuo* to give mesylate **252** (10 mg, 92%) as a colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 4.91 (1H, m, H-3), 4.86 (1H, d, *J* = 7.0 Hz, H-10), 4.67 (1H, d, *J* = 7.0 Hz, H-10), 4.55 (1H, m, H-4), 4.47 - 4.35 (2H, m, H-7), 4.15 (1H, m, H-5), 3.83 - 3.67 (3H, m, H-1 and H-2), 3.44 (3H, s, OCH_3), 3.09 (3H, s, H-9), 2.62 - 2.46 (1H, m, H-6), 1.58 (9H, s, $C(CH_3)_3$), 1.18 - 1.09 (24H, m, H-8 and $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 1.07 - 0.95 (9H, m, $Si(CH_2C\underline{H}_3)_3$), 0.68 (6H, q, *J* = 7.7 Hz, $Si(C\underline{H}_2CH_3)_3$) ppm; **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 153.2 (C=O), 95.7 (C10), 83.3 ($\underline{C}(CH_3)_3$), 78.3 (C5), 73.3 (C2), 71.6 (C7), 68.2 (C4), 66.2 (C1), 58.2 (C3), 56.3 (OCH_3), 36.7 (C6), 33.4 (C9), 27.8 ($C(\underline{C}H_3)_3$) 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 12.4 (C8), 11.7 ($Si(\underline{C}H(CH_3)_2)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 4.9 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 750 $[M+Na]^+$; **HRMS** (ESI^+) $C_{32}H_{65}NNaO_{11}SSi_2^+$ $[M+Na]^+$ required 750.3709, found 750.3705.

(2*S*,3*S*,4*S*,5*R*,6*S*)-5-((*tert*-Butoxycarbonyl)amino)-3-hydroxy-4-(methoxymethoxy)-2-methyl-6-((triethylsilyl)oxy)-7-((triisopropylsilyl)oxy)heptyl methanesulfonate (254)

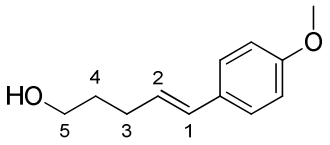


A solution of 5-bromopent-1-ene **239** (28 mg, 0.19 mmol) in THF (0.2 mL) was cooled to −78 °C, then *tert*-butyllithium (0.2 mL, 1.9M in pentane, 0.38 mmol) was added. The solution turned pale yellow and it was stirred for 1 h to give the desired organolithium. To this was added copper(I) cyanide (8 mg, 0.086 mmol) and the reaction was warmed to −45 °C and stirred for 2 h. Then mesylate **252** (9 mg, 0.012 mmol) in THF (0.1 mL) was added. The reaction was warmed to −25 °C and stirred for 1 h. Due to the remaining starting material, the reaction mixture was warmed to rt and stirred overnight (~10 h). Then a saturated aqueous NH_4Cl solution (1 mL) was added, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 90:1 → 80:20) to give **254** (2 mg, 24%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.09 (1H, d, *J* = 8.8 Hz, NH), 4.84 (1H, d, *J* = 6.3 Hz, H-10), 4.78 (1H, d, *J* = 6.3 Hz, H-10'), 4.69 (1H, d, *J* = 3.8 Hz, OH), 4.56 (1H, dd, *J* = 8.8, 4.4 Hz, H-7), 4.32 (1H, dd, *J* = 8.8, 2.2 Hz, H-7'), 4.23 (1H, dd, *J* = 8.8, 5.0 Hz, H-4), 4.07 (1H, t, *J* = 9.3 Hz, H-3), 3.68 - 3.44 (4H, m, H-1, H-2 and H-5), 3.42 (3H, s, OCH_3), 2.98 (3H, s, H-9), 2.22 - 2.14 (1H, m, H-6) 1.45 (9 H, s) 1.08 - 1.03 (24H, m, H-8 and $Si(C\underline{H}(CH_3)_2)_3$ and

$Si(CH(C\underline{H}_3)_2)_3$), 0.98 (9H, t, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$) 0.69 - 0.62 (6H, m, $Si(C\underline{H}_2CH_3)_3$) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 157.7 (C=O), 97.4 (C10), 80.5 ($\underline{C}(CH_3)_3$), 78.1 (H5), 73.7 (C7), 70.7 (C2 or C4), 70.4 (C2 or C4), 63.6 (C1), 56.1 (OCH_3), 50.7 (C3), 36.4 (C6), 34.4 (C9), 28.2 ($C(\underline{C}H_3)_3$), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 13.6 (C8), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$), 6.9 ($Si(CH_2\underline{C}H_3)_3$), 5.1 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 724 $[M+Na]^+$; **HRMS** (ESI^+) $C_{31}H_{67}NNaO_{10}SSi_2^+$ $[M+Na]^+$ required 724.3916, found 724.3910.

(*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol

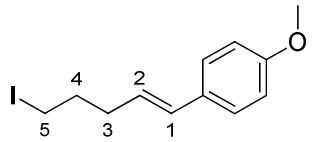


To a solution of 1,1,3,3-tetramethyldisiloxane (482 mg, 3.6 mmol) and 4-pentyn-1-ol (604 mg, 7.2 mmol) in THF (2 mL) was added platinum(0)-1,3-divinyl-1,1,3,3-tetradimethylsiloxane complex (100 μL) dropwise at rt. The reaction mixture was stirred for 30 min before adding a solution of TBAF (8 mL, 1M in THF), followed by sequential addition of $Pd(dba)_2$ (115 mg, 0.2 mmol) and 4-iodoanisole (936 mg, 4 mmol). The reaction mixture was stirred for a further 60 min. Ether (20 mL) was added; then the mixture was filtered through a short column of SiO_2, eluted with ether (100 mL) and then was concentrated. The crude mixture was then purified by flash column chromatography (petrol:ethyl acetate 90:10 → 70:30) to afford the desired compound as a white solid (455 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (2H, d, *J* = 8.6 Hz, $\underline{Ph}OCH_3$), 6.84 (2H, d, *J* = 8.6 Hz, $PhOCH_3$), 6.37 (1H, d, *J* = 15.7 Hz, H-1), 6.09 (1H, dt, *J* = 15.7, 7.0 Hz, H-2), 3.80 (3H, s, OCH_3), 3.69 (2H, t, *J* = 6.4 Hz, H-5), 2.33 - 2.24 (2H, m, H-4), 2.16 (1H, br. s, OH), 1.72 - 1.69

(2H, m, H-3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.7 (ArC), 130.5 (C1), 130.3 (ArC), 129.7 (ArC), 127.9 (ArC), 127.0 (C2), 113.9 (ArC), 62.3 (C5), 55.3 (PhO*Me*), 32.4 (C3), 29.3 (C4) ppm. The spectroscopic data were consistent with those reported in literature.[102]

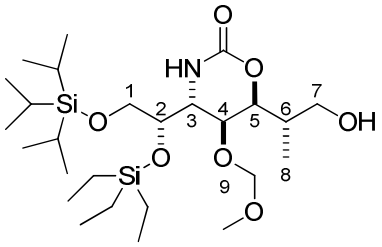
(*E*)-1-(5-Iodopent-1-en-1-yl)-4-methoxybenzene (270)



To a solution of (*E*)-5-(4-methoxyphenyl)pent-4-en-1-ol (230 mg, 1.2 mmol) in CH_2Cl_2 (2.5 mL) was added sequentially imidazole (98 mg, 1.4 mmol), iodine (321 mg, 1.2 mmol) and triphenylphosphine (312 mg, 1.19 mmol) at rt. The mixture was stirred overnight and the crude was dry loaded on silica for purification by flash column chromatography (petrol:diethyl ether, 100:1), which afforded the title compound as a colourless oil (345 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (2H, d, *J* = 8.6 Hz, PhOCH_3), 6.85 (2H, d, J = 8.6 Hz, PhOCH_3), 6.41 (1H, d, *J* = 15.9 Hz, H-1), 6.01 (1 H, dt, J=15.9, 7.0 Hz, H-2), 3.81 (3H, s, PhOCH_3), 3.24 (2H, t, *J* = 7.0 Hz, H-3), 2.32 (2H, q, *J* = 7.0 Hz, H-4), 1.99 (2H, quin, *J* = 7.0 Hz, H-5) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.9 (ArC), 130.7 (C1), 130.3 (ArC), 127.1 (ArC), 126.1 (C2), 114.1 (ArC), 55.3 (PhO*Me*), 33.5 (C3), 33.0 (C4), 6.5 (C5) ppm. The spectroscopic data were consistent with those reported in literature.[103]

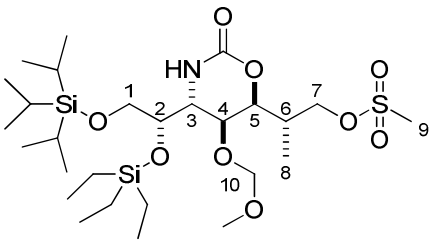
(4*R*,5*S*,6*S*)-4-((*S*)-3,3-Diethyl-8,8-diisopropyl-9-methyl-4,7-dioxa-3,8-disiladecan-5-yl)-6-((*S*)-1-hydroxypropan-2-yl)-5-(methoxymethoxy)-1,3-oxazinan-2-one (255)



To a solution of carbamate **236** (32 mg, 0.051 mmol) in MeOH (0.51 mL) was added Pd on activated charcoal (10% by wt., 5 mg). The reaction was stirred overnight at room temperature. On complete consumption of the starting material (~21 h, by TLC and MS analysis), MeOH was evaporate *in vacuo* and the crude redissolved in CH_2Cl_2. The solution was then filtered over a pad of Celite and the pad was washed with CH_2Cl_2 (3 × 5 mL). The combined filtrate was evaporated *in vacuo* to yield **255** as a colourless oil (24 mg, 89%).

$[\alpha]_D^{25}$ −21.3 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3450, 2944, 2870, 1716, 1459 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.15 (1H, d, *J* = 2.8 Hz, NH), 4.78 (2H, d, *J* = 7.1 Hz, H-9), 4.68 (1 H, d, *J* = 7.1 Hz, H-9'), 4.37 (1H, d, *J* = 10.1 Hz, H-5), 4.02 (1H, app s, H-4), 3.85 (1H, app t, *J* = 3.8 Hz, H-7), 3.80 - 3.56 (5H, m, H-1, H-2, H-3 and H-7'), 3.40 (3H, s, OCH_3), 2.32 - 2.19 (1H, m, H-6), 1.99 (1H, br. s., OH), 1.09 - 1.04 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 0.98 - 0.92 (12H, m, H-8 and $Si(CH_2C\underline{H}_3)_3$), 0.68 - 0.58 (6H, m, $Si(C\underline{H}_2CH_3)_3$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 153.6 (C=O), 95.6 (C9), 79.5 (C5), 73.5 (C2), 69.1 (C4), 64.7 (C1 or C7), 64.4 (C1 or C7), 56.2 (C3 or OCH_3), 55.9 (C3 or OCH_3), 35.4 (C6), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 12.9 (C8), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 5.1 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 572 $[M+Na]^+$; **HRMS** (ESI^+) $C_{26}H_{55}NNaO_7Si_2^+$ $[M+Na]^+$ required 572.3409, found 572.3410.

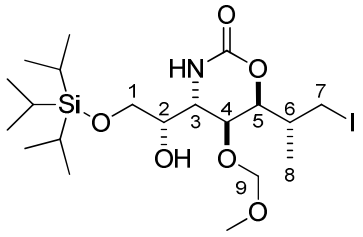
(*S*)-2-((4*R*,5*S*,6*S*)-4-((*S*)-3,3-Diethyl-8,8-diisopropyl-9-methyl-4,7-dioxa-3,8-disiladecan-5-yl)-5-(methoxymethoxy)-2-oxo-1,3-oxazinan-6-yl)propyl methanesulfonate (256)



To a solution of alcohol **255** (22 mg, 0.04 mmol) in dry CH_2Cl_2 (0.8 mL) was added triethylamine (17 μL, 0.12 mmol) and mesyl chloride (4 μL, 0.05 mmol) at rt. The reaction mixture was stirred for 1 h and then quenched with a saturated aqueous $NaHCO_3$ solution (0.5 mL). The reaction was filtered over Celite and the pad washed with CH_2Cl_2 (3 × 3 mL). The combined organic layers were evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 85:15) to give mesylate **256** (23 mg, 92%) as a colourless oil.

$[\alpha]_D^{25}$ −42.9 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2866, 1715, 1454 cm^{-1}; **^{1}H NMR** (250 MHz, $CDCl_3$) δ = 5.21 (1H, d, *J* = 3.0 Hz, NH), 4.83 (1H, d, *J* = 7.3 Hz, H-10), 4.73 (1H, d, *J* = 7.3 Hz, H-10'), 4.54 (1H, dd, *J* = 9.5, 4.6 Hz, H-7), 4.43 (1H, dd, *J* = 9.50, 2.4 Hz, H-7'), 4.09 - 4.02 (1H, m, H-5), 3.97 - 3.92 (1H, m, H-4), 3.87 - 3.58 (4H, m, H-1, H-2 and H-3), 3.45 (3H, s, OCH_3), 3.07 (3H, s, H-9), 2.59 - 2.46 (1H, m, H-6), 1.19 - 1.08 (24H, m, H-8, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 1.06 - 0.94 (9H, m, $Si(C\underline{H}_2CH_3)_3$), 0.73 - 0.58 (6H, m, $Si(CH_2C\underline{H}_3)_3$) ppm; **^{13}C NMR** (63 MHz, $CDCl_3$) δ = 153.2 (C=O), 95.7 (C10), 77.3 (C5), 73.3 (C2), 71.6 (C7), 68.9 (C4), 64.2 (C1), 56.3 (C3), 55.5 (OCH_3), 36.8 (C6), 33.3 (C9), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 12.6 (C8), 11.7 ($Si(\underline{C}H(CH_3)_2)_3$), 6.8 ($Si(CH_2\underline{C}H_3)_3$), 5.1 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 650 $[M+Na]^+$; **HRMS** (ESI^+) $C_{27}H_{57}NNaO_9SSi_2^+$ $[M+Na]^+$ required 650.3185, found 650.3187.

(4*S*,5*S*,6*S*)-4-((*S*)-1-Hydroxy-2-((triisopropylsilyl)oxy)ethyl)-6-((*R*)-1-iodopropan-2-yl)-5-(methoxymethoxy)-1,3-oxazinan-2-one (262)



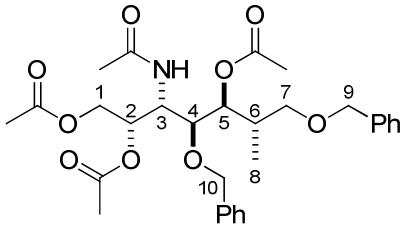
To a solution of imidazole (4 mg, 0.06 mmol) in dry CH_2Cl_2 (0.4 mL) was added triphenylphosphine (10 mg, 0.04 mmol) at rt. The solution was then cooled to 0 °C and iodine (11 mg, 0.04 mmol) was added, followed by solution of alcohol **255** (21 mg, 0.038 mmol) in CH_2Cl_2 (0.4 mL). The reaction mixture was warmed to rt and stirred for 16 h. As TLC indicated that starting material was still present more triphenylphosphine (5 mg, 0.02 mmol) and iodine (6 mg, 0.02 mmol) were added and the reaction mixture was stirred until all the starting material had disappeared (~4 h). Then a solution of saturated aqueous sodium thiosulfate (1 mL) was added and stirred for 5 min. The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to give the crude reaction mixture. On purification by flash column chromatography (petrol:ethyl acetate, 95:5) iodide **262** (8 mg, 39%) was obtained as a colourless oil.

$[\alpha]_D^{25}$ −13.1 (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 3336, 2926, 2866, 1712, 1463 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.51 (1H, d, *J* = 2.5 Hz, NH), 4.78 (1 H, d, *J* = 7.2 Hz, H-9), 4.68 (1H, d, *J* = 7.2 Hz, H-9'), 4.28 (1H, dd, *J* = 9.5, 1.2 Hz, H-5), 3.95 (1H, d, *J* = 1.2 Hz, H-4), 3.80 (2H, m, H-1), 3.76 - 3.72 (1 H, m, H-3), 3.68 - 3.60 (1H, m, H-2) 3.59 - 3.53 (1H, m, H-7), 3.51 - 3.46 (1H, m, H-7'), 3.41 (3H, s, OCH_3), 2.63 (1 H, d, *J* = 7.6 Hz, OH), 1.96 - 1.87 (1H, m, H-6), 1.11 - 1.05 (21H, m, Si(C<u>H</u>$(CH_3)_2)_3$ and Si(CH(C<u>H</u>$_3)_2)_3$), 1.03 (3H, d, *J* = 6.6 Hz, H-8) ppm;

^{13}C NMR (63 MHz, $CDCl_3$) δ = 153.5 (C=O), 95.7 (C9), 80.0 (C5), 71.9 (C2), 69.6 (C4), 65.5 (C1), 56.5 (C3), 56.3 (OCH_3), 33.6 (C6), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$) 16.5 (C7) 14.6 (C8) 11.7 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 568 $[M+Na]^+$; **HRMS** (ESI^+) $C_{20}H_{40}INNaO_6Si_2^+$ $[M+Na]^+$ required 568.1562, found 568.1583.

Please see Appendix for Christian Winter's experimental results

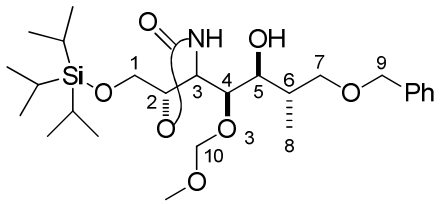
(2*S*,3*S*,4*S*,5*S*,6*S*)-3-Acetamido-4,7-bis(benzyloxy)-6-methylheptane-1,2,5-triyl triacetate (278)



To a solution of carbamate **205** (6 mg, 0.01 mmol) dissolved in 1 mL EtOH was added LiOH (7.5 mg, 0.30 mmol). The reaction mixture was then refluxed in a sealed vial till all the starting material was consumed (~16 h, as observed by mass spectrometry). The solvent was then evaporated *in vacuo* and the redissolved in chloroform. To this added acetic anhydride (1 mL, 11 mmol) and DMAP (1 mg, 0.8 mmol) and the reaction mixture was stirred till completion (~12 h, as observed by mass spectrometry). The solution was then evaporated *in vacuo* and the crude mixture was subjected to purification by flash column chromatography (petro:ethyl acetate, 2:1) to yield **278** (3 mg, 52%) as a colourless oil.

$[\alpha]_D^{23}$ +10.5 (*c* = 0.2, $CHCl_3$); **IR** ν_{max} (neat): 2924, 2866, 1701, 1691, 1674, 1457 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.39 - 7.28 (10H, m, Ph), 5.56 (1H, d, *J* = 9.9 Hz, NH), 5.45 (1H, ddd, *J* = 7.3, 5.0, 2.2 Hz, H-2), 5.14 (1H, dd, *J* = 7.3, 4.7 Hz, H-4), 4.64 (2H, d, *J* = 11.0 Hz, H-10), 4.55 (2H, ddd, *J* = 9.9, 7.3, 2.2 Hz, H-3), 4.46 - 4.40 (3H, m, H-9 and H-10'), 4.19 (2H, dd, *J* = 11.8, 5.0 Hz, H-1), 4.03 (2H, dd, *J* = 11.8, 7.3 Hz, H-1'), 3.74 (1H, dd, *J* = 6.9, 4.7 Hz, H-5), 3.50 (1H, dd, *J* = 9.5, 6.0 Hz, H-7), 3.30 (1H, dd, *J* = 9.3, 6.0 Hz, H-7'), 2.33 - 2.26 (1H, m, H-6), 2.04 (3H, s, $COCH_3$), 2.02 (3H, s, $COCH_3$), 2.02 (3H, s, $COCH_3$), 1.88 (3H, s, $COCH_3$), 1.03 (3H, d, *J* = 6.9 Hz, H-8) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 170.5 (C=O),170.5 (C=O), 169.7 (C=O), 169.5 (C=O), 138.2 (*ipso*-ArC), 137.6 (*ipso*-ArC), 128.6 (ArC), 128.3 (ArC), 128.0 (ArC), 127.7 (ArC), 127.6 (ArC), 78.1 (C5), 74.7 (C4), 74.0 (C9 or C10), 73.2 (C9 or C10), 71.8 (C7), 69.8 (C2), 63.0 (C1), 48.5 (C3), 34.6 (C6), 23.2 ($CO\underline{C}H_3$), 21.1 ($CO\underline{C}H_3$), 20.9 ($CO\underline{C}H_3$), 20.7 ($CO\underline{C}H_3$), 14.8 (C8) ppm; **MS** *m/z* (ESI^+) 580 $[M+Na]^+$; **HRMS** (ESI^+) $C_{30}H_{39}NaNO_9^+$ $[M+Na]^+$ required 580.2517, found 580.2522.

(4*S*,5*S*)-4-((1*S*,2*S*,3*S*)-4-(Benzyloxy)-2-hydroxy-1-(methoxymethoxy)-3-methylbutyl)-5-(((triisopropylsilyl)oxy)methyl)oxazolidin-2-one (279)

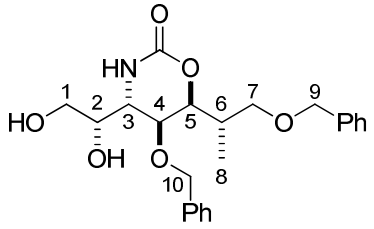


To a solution of carbamate **227** (52 mg, 0.1 mmol) in MeOH (1 mL) at rt was added cesium carbonate (211 mg, 0.65 mmol) and the reaction mixture was stirred till all the starting material was consumed. The reaction was then quenched with saturated aqueous NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated

in vacuo to give the crude product, which was purified by flash column chromatography to give carbamate **279** (18 mg, 34%) as a colourless oil

$[\alpha]_D^{23}$ −7.4 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3339, 2943, 2866, 1742, 1463 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 - 7.21 (5H, m, Ph), 5.08 (1H, s, NH), 4.84 - 4.65 (3H, m, H-2 and H-10), 4.51 (2H, s, H-9), 4.10 - 4.04 (1H, m, H-3), 3.94 (1H, dd, *J* = 10.7, 3.7 Hz, H-1), 3.84 (1H, dd, *J* = 11.1, 2.8 Hz, H-1'), 3.74 (1H, d, *J* = 3.0 Hz, H-4), 3.72 - 3.67 (11H, m, H-7), 3.60 - 3.49 (2H, m, H-5 and H-7'), 3.42 (3H, s, OCH_3), 2.61 (1H, br. s, OH), 2.17 - 2.06 (1H, m, H-6) 1.10 - 1.03 (21H, m, $Si(CH(CH_3)_2)_3$ and $Si(CH(CH_3)_2)_3$) 0.93 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, CDCl3) δ = 160.8 (C=O), 137.6 (*ipso*-ArC), 128.6 (ArC), 128.0 (ArC), 127.7 (ArC), 98.3 (C10), 81.2 (C2), 78.6 (C2), 75.8 (C5), 74.9 (C4), 73.5 (C9), 64.2 (C1), 56.4 (C3 or OCH_3), 55.3 (C3 or OCH_3), 43.2 (s) 35.0 (C6), 17.9 ($Si(CH(CH_3)_2)_3$), 14.0 (C8), 11.9 ($Si(CH(CH_3)_2)_3$) ppm; **MS** *m*/*z* (ESI) 548 $[M+Na]^+$; **HRMS** (ESI^+) $C_{27}H_{47}NNaO_7Si$ $[M+Na]^+$ required 548.3014, found 548.3016.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-1,2-dihydroxyethyl)-1,3-oxazinan-2-one (281)

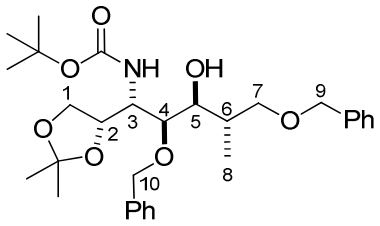


To a solution of carbamate **205** (118 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at rt was added 4 M HCl in dioxane (0.13 mL, 0.52 mmol). The reaction was stirred till completion (~ 12 h, by TLC analysis) then the solvent was evaporated *in vacuo* and the crude product is purified by flash

column chromatography (CH_2Cl_2:methanol, 100:0 → 95:5) to yield **281** as a colourless oil (78 mg, 89%).

$[\alpha]_D^{23}$ −7.4 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3339, 2943, 2866, 1742, 1463 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 - 7.19 (10H, m, Ph), 6.99 (1H, d, *J* = 2.8 Hz, NH), 4.68 (1H, d, *J* = 11.6 Hz, H-10), 4.49 (1H, d, *J* = 12.1 Hz, H-9), 4.44 (1H, d, *J* = 12.1 Hz, H-9'), 4.39 (1H, d, *J* = 11.6 Hz, H-10'), 4.32 (1H, d, *J* = 10.1, Hz, H-5), 3.78 (1H, s, H-3), 3.64 (1H, dd, *J* = 11.6, 4.0 Hz, H-7), 3.65 - 3.53 (4H, m, H-1, H-4 and H-7'), 3.44 (1H, d, *J* = 4.3 Hz, H-2), 2.40 - 2.27 (1H, m, H-6), 0.80 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 155.7 (C=O), 138.5 (*ipso*-ArC), 137.0 (*ipso*-ArC), 128.5 (ArC), 128.3 (ArC), 128.2 (ArC), 128.1 (ArC), 127.6 (ArC), 127.5 (ArC), 78.4 (C5), 73.2 (C9), 72.3 (C2), 71.3 (C1), 71.2 (C10), 69.4 (C4), 63.8 (C1), 53.9 (C3), 33.9 (C6), 13.1 (C8); **MS** *m/z* (ESI^+) 438 $[M+Na]^+$; **HRMS** (ESI^+) $C_{23}H_{29}NNaO_6^+$ $[M+Na]^+$ required 438.1887, found 438.1891.

***tert*-Butyl ((1*S*,2*S*,3*S*,4*S*)-2,5-bis(benzyloxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-4-methylpentyl)carbamate (282)**

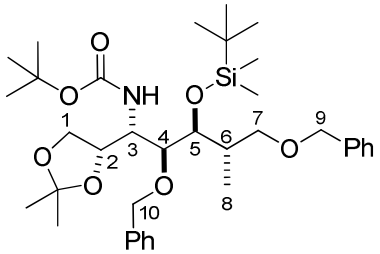


To a stirred solution of carbamate **281** (68 mg, 0.12 mmol) in dry methanol (1.2 mL) was added caesium carbonate (239 mg, 0.735 mmol) at room temperature. The reaction was monitored by TLC and on completion (~6 h) the solvent was evaporated under reduced pressure. The reaction mixture was dissolved in CH_2Cl_2 (5 mL) and water (1 mL) was added. The layers were

separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic layer was concentrated under reduced pressure and purified using flash column chromatography (petrol : ethyl acetate, 80:20) to afford compound **282** (55 mg, 85%) as a colourless oil.

$[\alpha]_D^{25}$ −19.1 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3334, 2942, 2867, 1724, 1461 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.15 (1H, d, *J* = 9.9 Hz, NH), 4.76 (1H, d, *J* = 11.1 Hz, H-10), 4.63 (1H, d, *J* = 11.1 Hz, H-10'), 4.52 (2H, s, H-9), 4.51 - 4.48 (1H, m, H-2), 4.09 - 4.01 (2H, m, H-3 and H-1), 3.72 (1H, t, *J* = 7.8 Hz, H-1), 3.68 (1H, dd, *J* = 9.0, 4.8 Hz, H-7), 3.60 (1H, dd, *J* = 9.0, 5.7 Hz, H-7'), 3.53 - 3.47 (2H, m), 2.24 - 2.11 (1H, m, H-6), 1.48 (3H, s, $C(C\underline{H}_3)_2$), 1.44 (9H, s, $C(C\underline{H}_3)_3$), 1.37 (3H, s, $C(C\underline{H}_3)_2$), 0.97 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 156.9 (C=O), 138.7 (*ipso*-ArC), 138.0 (*ipso*-ArC), 128.4 (ArC), 128.3 (ArC), 128.0 (ArC), 127.8 (ArC), 127.5 (ArC), 127.4 (ArC), 109.2 ($\underline{C}(CH_3)_2$), 80.1 ($\underline{C}(CH_3)_3$), 78.5 (CH), 73.9 (CH), 73.6 (CH_2), 73.3 (CH), 73.1 (CH_2), 66.3 (CH_2), 50.4 (C3), 35.6 (C6), 28.3 ($C(\underline{C}H_3)_3$), 26.3 ($C(\underline{C}H_3)_2$), 25.1 ($C(\underline{C}H_3)_2$), 14.5 (C8) ppm; **MS** *m/z* (ESI^+) 552 $[M+Na]^+$; **HRMS** (ESI^+) $C_{30}H_{43}NNaO_7^+$ $[M+Na]^+$ required 552.2935, found 552.2932.

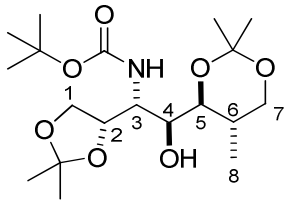
***tert*-Butyl ((1*S*,2*S*,3*S*,4*S*)-2,5-bis(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methylpentyl)carbamate (283)**



To a solution of alcohol **282** (19 mg, 0.036 mmol) in CH_2Cl_2 (0.4 mL) at rt was added 2,6-lutidine (21 μL, 0.18 mmol) and TBSOTf (16 μL, 0.072 mmol). The reaction was stirred until the starting material was consumed and then the solution was diluted with ethyl acetate (2 mL) and passed through a Celite pad. It was then evaporated *in vacuo* and the crude product was purified by flash column chromatography (petrol:ethyl acetate, 95:5 → 90:10) to give carbamate **283** (10 mg, 43%) as a colourless oil

$[\alpha]_D^{23}$ −72.6 (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 2944, 2868, 1727, 1454 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.37 - 7.25 (10H, m, Ph), 5.04 (1H, d, *J* = 9.1 Hz, NH), 4.71 (1H, d, *J* = 11.4 Hz, H-9 or H-10), 4.54 (1H, d, *J* = 10.7 Hz, H-10 or H-9), 4.52 (1H, d, *J* = 11.4 Hz, H-9 or H-10), 4.50 - 4.41 (2H, m, H-9 or H-10 and H-2), 3.97 (1H, t, *J* = 7.6 Hz, H-1), 3.90 (1 H, dd, *J* = 8.2, 2.8 Hz, H-5), 3.83 (1H, t, *J* = 9.30 Hz, H-3), 3.72 (1H, t, *J* = 7.9 Hz, H-1'), 3.65 (1H, dd, *J* = 9.8, 2.8 Hz, H-4), 3.51 (1H, dd, *J* = 8.9, 4.0 Hz, H-7) 3.45 (1H, dd, *J* = 8.9, 6.0 Hz, H-7'), 2.09 - 1.95 (1H, m, H-6), 1.41 (9H, s, $OC(C\underline{H}_3)_3$), 1.40 (3H, s, $C(C\underline{H}_3)_2$) 1.32 (3H, s, $C(C\underline{H}_3)_2$) 1.12 (3H, d, *J* = 6.9 Hz, H-8), 0.92 (9H, s, $SiC(C\underline{H}_3)_3$), 0.10 (3H, s, $Si(C\underline{H}_3)_2$) 0.04 (3H, s, $Si(C\underline{H}_3)_2$) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 156.0 (C=O), 138.8 (*ipso*-ArC), 138.4 (*ipso*-ArC), 128.3 (ArC), 128.2 (ArC), 127.6 (ArC), 127.5 (ArC), 127.5 (ArC), 127.3 (ArC), 108.5 ($\underline{C}(CH_3)_2$), 80.4 (C4), 79.1 ($\underline{C}(CH_3)_3$), 74.8 (C2), 73.2 (C9 or C10 or C7), 73.1 (C5), 72.8 (C7 or C9 or C10), 72.7 (C10 or C9 or C7), 65.9 (C1), 51.7 (C3), 36.6 (C6), 28.3 ($C(\underline{C}H_3)_3$), 26.2($C(\underline{C}H_3)_2$), 25.9 ($SiC(\underline{C}H_3)_3$), 25.4 ($C(\underline{C}H_3)_2$), 18.1 ($SiCH_3$), 14.8 (C8), -4.0 ($Si(CH)_3)_2$), -5.1 ($Si(CH)_3)_2$) ppm; **MS** *m/z* (ESI^+) 666 $[M+Na]^+$; **HRMS** (ESI^+) $C_{36}H_{57}NNaO_7Si^+$ $[M+Na]^+$ required 666.3797, found 666.3803.

***tert*-Butyl ((1*R*,2*S*)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxy-2-((4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)carbamate (286)**



To a solution of carbamate **282** (39 mg, 0.074 mmol) in MeOH (0.74 mL) was added Pd on activated charcoal (10% by wt., 7 mg). The reaction was stirred overnight at room temperature. On complete consumption of the starting material (~21 h, by TLC analysis), MeOH was evaporate *in vacuo* and the crude redissolved in CH_2Cl_2. The solution was then filtered over a pad of Celite and the pad was washed with CH_2Cl_2 (3 × 5 mL). The combined filtrate was evaporated *in vacuo* and redissolved in acetone (1 mL). To the solution was added *p*-toluenesulfonic acid (3 mg) and the reaction stirred until full consumption of the intermediate triol (~6 h). The solvent was then evaporated *in vacuo* and the crude product purified by flash column chromatography (petrol:ethyl acetate, 90:10 → 80:20) to yield **286** (26 mg, 90%) as a colourless oil.

$[\alpha]_D^{23}$ +20.7 (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2866, 1729, 1462 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 4.82 (1H, d, *J* = 10.1 Hz, NH), 4.65 (1H, t, *J* = 7.20 Hz, H-2), 4.03 (1H, dd, *J* = 8.08, 7.2 Hz, H-1), 3.82 - 3.71 (2H, m, H-1' and H-3), 3.65 - 3.47 (4H, m, H-7, H-4 and H-5), 2.41 (2H, d, *J* = 10.6 Hz, OH), 2.14 - 2.05 (1H, m, H-6), 1.46 - 1.43 (15H, s, $C(C\underline{H}_3)_3$ and CH_3), 1.42 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.36 (3H, s, CH_3), 0.79 (3H, d, *J* = 6.6 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 155.9 (C=O), 109.0 ($\underline{C}(CH_3)_2$), 98.6 ($\underline{C}(CH_3)_2$), 79.49 ($\underline{C}(CH_3)_3$), 73.89 (C2), 73.2 (C5), 69.9 (C4), 66.2 (C1 or C7), 65.8 (C7 or C1), 51.0 (C3), 29.5 (C6), 29.1 (CH_3), 28.27 ($C(\underline{C}H_3)_3$), 26.23 (CH_3), 25.0 (CH_3), 18.8 (CH_3), 12.4 (C8) ppm; **MS**

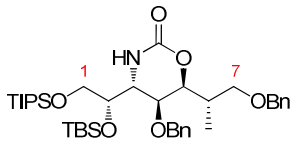
m/z (ESI$^+$) 412 [M+Na]$^+$; **HRMS** (ESI$^+$) $C_{19}H_{35}NNaO_7^+$ [M+Na]$^+$ required 412.2306, found 412.2301.

Appendix
&
References

Appendix:

Data from Robert Pullin

(4*R*,5*S*,6*S*)-5-(benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-8,8-diisopropyl-2,2,3,3,9-pentamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (205a)

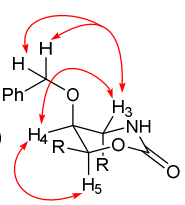


tert-Butyldimethylsilyl trifluoromethanesulfonate (1.34 mL, 5.83 mmol) was added dropwise to a solution of alcohol **205** (0.47 g, 0.83 mmol) and 2,6-lutidine (1.34 mL, 11.62 mmol) in CH_2Cl_2 (8.3 mL) at 0 ^oC. The reaction was slowly warmed to room temperature over 16 h and then quenched by the slow addition of water. The aqueous layer was separated and extracted with CH_2Cl_2, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol:ethyl acetate, 90:10) afforded silyl ether **205a** (0.50 g, 87%) as a colorless oil

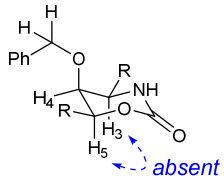
$[\alpha]^{20}_D$ –38.8 (*c* 1.21, $CHCl_3$); **IR** ν_{max} (neat): 2941, 2864, 1713, 1462, 1362, 1310 cm^{-1} ; **^{1}H NMR** (500 MHz, $CDCl_3$) 7.36-7.24 (10H, m, 10 x Ph*H*), 5.12 (1H, br d, *J* 3.1, N*H*), 4.70 (1H, d, *J* 11.6, 4-(OC*H*HPh)), 4.52 (1H, d, *J* 12.0, 7-(OC*H*HPh)), 4.47 (1H, d, *J* 12.0, 7-(OCH*H*Ph)), 4.47 (1H, d, *J* 11.7, 4-(OCH*H*Ph)), 4.33 (1H, dd, *J* 9.9 and 1.3, 5-*H*), 3.92 (1H, t, *J* 3.5, 3-*H*), 3.82 (1H, d, *J* .1.1, 4-*H*), 3.75 (1H, m, 1-*H*H), 3.68 (1H, dd, *J* 9.0 and 5.4, 7-*H*H), 3.65-3.59 (3H, m, 2-*H*, 1-H*H* and 7-H*H*) 2.39 (1H, m, 6-*H*), 1.14-1.06 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 0.94 (3H, d, *J* 7.0, 6- (CH_3)), 0.84 (9H, s, SiC(CH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) 153.8 (*C*(O)), 138.7 ($C_{(Ar)}$), 137.2 ($C_{(Ar)}$), 128.5 (*C*H$_{(Ar)}$), 128.2 (*C*H$_{(Ar)}$), 127.9 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 127.3 (*C*H$_{(Ar)}$), 78.0 (5-*C*), 75.5 (2-*C*), 73.1 (7-(O*C*H_2Ph)), 71.2 (7-*C*), 70.9 (4-(O*C*H_2Ph)), 70.1 (4-*C*), 64.7 (1-*C*), 54.3 (3-*C*), 34.3 (6-*C*), 25.7 (SiC(*C*H)$_3$), 18.0 (Si(CH(*C*H_3)$_2$), 17.9 (Si(*C*(CH_3)$_3$), 13.4 (6-(*C*H_3)), 11.8 (Si*C*H(CH_3)$_2$), –4.3 (Si*C*H_3), –4.4 (Si*C*H_3) ppm; **MS** *m/z* (ESI$^+$) 708 [M+Na]$^+$; *m/z* **HRMS** (ESI$^+$) $C_{38}H_{63}NO_6Si_2Na$ [M+Na]$^+$ required 708.4086, calculated 708.4087.

confirmation of TA 1,3-*anti* selectivity:

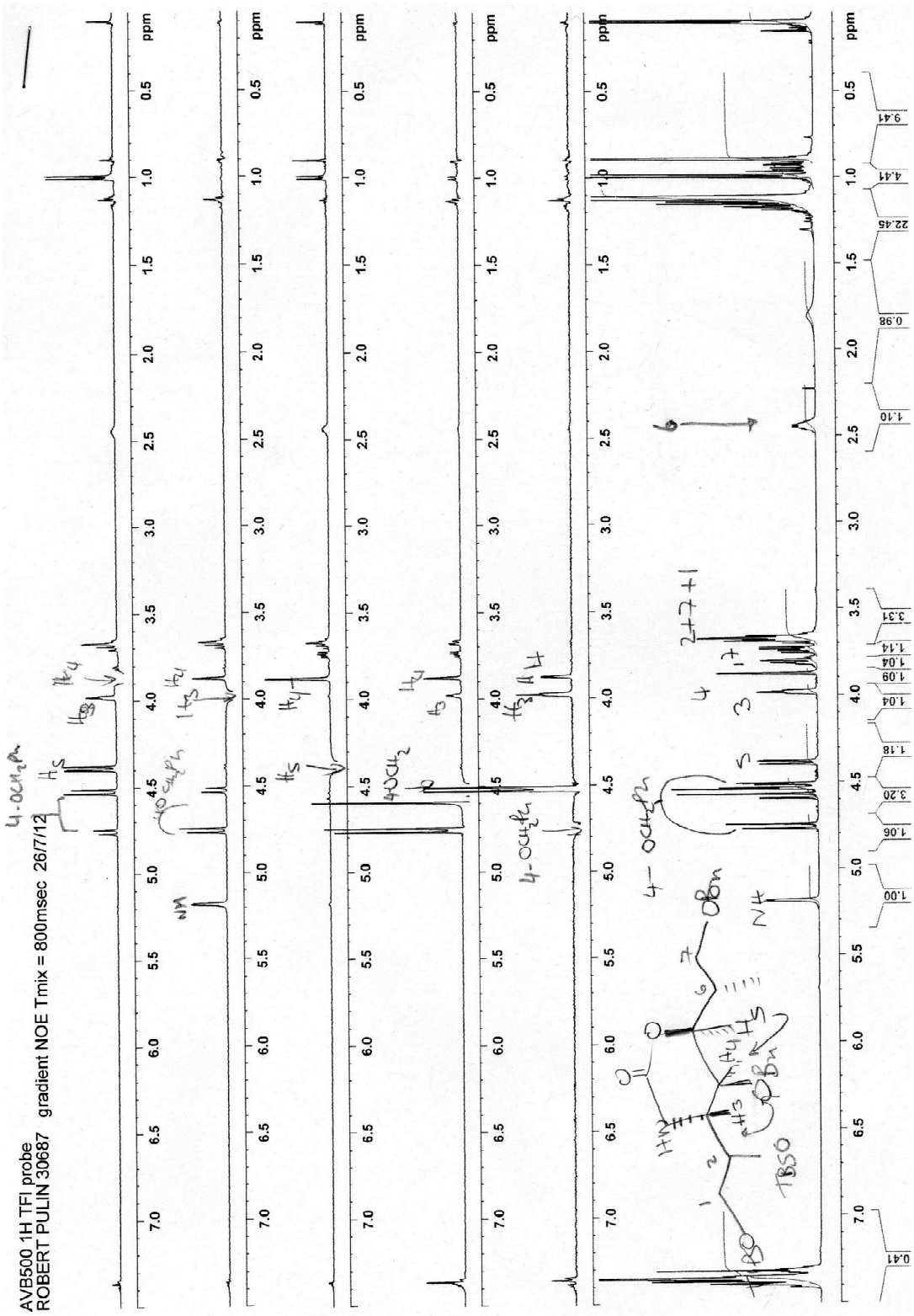
key nOe interactions: (compound 205a)



1,3-*anti*

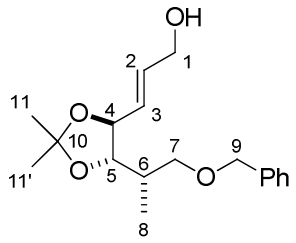


1,3-*syn*



Experimental work carried out by Christian Winter is included in this thesis for completeness.

(*E*)-3-((4*S*,5*S*)-5-((*S*)-1-(Benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (265)

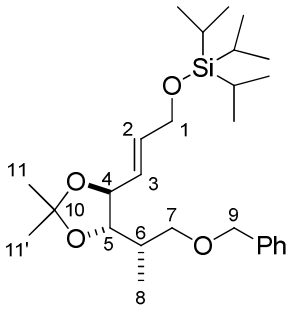


To a solution of ester **152** (176 mg, 0.53 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C was added DIBAL solution (1.6 mL, 1 M in DCM, 1.6 mmol) dropwise. The reaction was stirred at 0 °C for 1 h and then MeOH (2 mL) was added dropwise. The reaction was warmed to rt and then saturated aqueous Rochelle's solution (10 mL) was added. It was stirred for a further 30 mins till the cloudy white solution became clear. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 67:33) to give alcohol **265** (142 mg, 88%) as a colourless oil.

IR ν_{max} (neat): 3414, 2985, 2933, 2861, 1497 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.42 - 7.23 (5H, m, Ph), 5.95 (1 H, dt, *J* = 15.4, 5.0 Hz, H-2) 5.77 - 5.61 (1H, m, H-3), 4.49 (2H, s, H-9), 4.30 (1H, t, *J* = 7.8 Hz, H-4), 4.11 (2H, dd, *J* = 4.8, 1.0 Hz, H-1), 3.72 (1H, dd, *J* = 8.2, 6.4 Hz, H-5), 3.59 (1H, dd, *J* = 9.2, 5.3 Hz, H-7), 3.39 (1H, dd, *J* = 9.2, 6.4 Hz, H-7'), 2.14 - 2.05 (1H, m, H-6), 2.02 (1H, br. s., OH), 1.39 (6H, s, H-11), 1.00 (3H, d, *J* = 6.9 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.6 (*ipso*-ArC), 134.1 (C3), 128.9 (C2), 128.4 (ArC), 127.6

(ArC), 108.4 (C10), 82.2 (C5), 79.6 (C4), 73.1 (C7 or C9), 72.3 (C7 or C9), 62.7 (C1), 36.3 (C6), 27.1 (C11), 27.1 (C11'), 14.2 (C8) ppm; **MS** *m/z* (ESI^+) 329 $[M+Na]^+$; **HRMS** (ESI^+) $C_{18}H_{26}NaO_4^+$ $[M+Na]^+$ required 329.1723, found 329.1713.

(((*E*)-3-((4*S*,5S)-5-((S)-1-(Benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)oxy)triisopropylsilane (266)

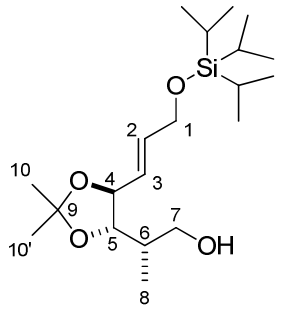


To a solution of alcohol **265** (470 mg, 1.53 mmol) in dry CH_2Cl_2 (15 mL) at rt was added imidazole (157 mg, 2.30 mmol) and triisopropylchlorosilane (0.42 mL, 2 mmol). The solution was stirred for 8 h, and then it was diluted with ethyl acetate (15 mL). It was then successively washed with water (10 mL) and brine (2 × 10 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated *in vacuo* to give the crude product. It was purified by flash column chromatography (petrol:ethyl acetate, 98:2) to give silyl ether **266** (670 mg, 95%) as a colourless oil.

IR ν_{max} (neat): 3030, 2941, 2892, 2865, 1496 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.39 - 7.22 (5H, m, Ph), 5.92 (1H, dt, *J* = 15.2, 4.0 Hz, H-2), 5.77 (1H, m, H-3), 4.54 (1H, d, *J* = 12.4 Hz, H-9), 4.49 (1H, d, *J* = 12.4 Hz, H-9'), 4.33 (1H, t, *J* = 7.7 Hz, H-4), 4.28 (2H, dd, *J* = 4.2, 1.6 Hz, H-1), 3.71 (1H, dd, *J* = 8.0, 6.7 Hz, H-5), 3.63 (1H, dd, *J* = 9.1, 5.1 Hz, H-7), 3.40 (1H, dd, *J* = 9.1, 6.8 Hz, H-7'), 2.14 - 2.01 (1H, m, H-6), 1.41 (6H, s, H-11), 1.15 - 1.05 (21H, m,

Si(C<u>H</u>$(CH_3)_2)_3$ and Si(CH(C<u>H</u>$_3)_2)_3$), 1.02 (3H, d, J = 7.1 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 138.8 (*ipso*-ArC), 134.2 (C2), 128.4 (ArC), 127.6 (ArC), 127.6 (ArC), 127.4 (C3), 108.3 (C10), 82.5 (C5), 79.9 (C4), 73.2 (C9), 72.5 (C7), 63.2 (C1), 36.6 (C6), 27.2 (C11), 27.1 (C11'), 18.1 (Si(CH(C<u>H</u>$_3)_2)_3$), 14.2 (C8), 12.1 (Si(C<u>H</u>$(CH_3)_2)_3$) ppm; **MS** *m/z* (ESI^+) 485 $[M+Na]^+$; **HRMS** (ESI^+) $C_{27}H_{46}ClNaO_4Si^+$ $[M+Na]^+$ required 485.3508, found 485.3507.

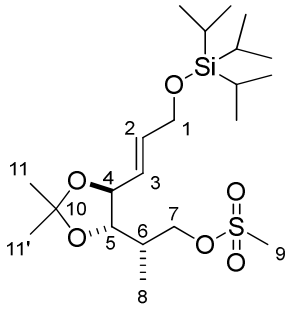
(*S*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-((*E*)-3-((triisopropylsilyl)oxy)prop-1-en-1-yl)-1,3-dioxolan-4-yl)propan-1-ol (267)



To dry THF (40 mL) was added di-*tert*-butyl biphenyl (DBB, 1.53 g, 5.76 mmol), and the solution was cooled to 0 °C. To this solution were added small pieces of lithium (596 mg, 86.4 mmol) and the dark green mixture was stirred for 2 h. Then in a separate flask was prepared a solution of benzyl ether **266** (668 mg, 1.44 mmol) in THF (20 mL), and it was cooled to −78 °C. To this was added the Li/DBB solution dropwise (green solution turns brown and as the reaction progresses becomes deep red) and stirred for 3 h at −78 °C. Then saturated aqueous NH_4Cl solution (20 mL) was added, and the reaction mixture allowed to warm to rt. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 88:12 → 80:20) to give alcohol **267** (406 mg, 76%) as a colourless oil.

$[\alpha]_D^{23}$ −2.8 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 3447, 2942, 2866, 1463 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.93 (1H, dt, *J* = 14.9, 4.0 Hz, H-2), 5.76 (1H, m, H-3), 4.29 - 4.23 (3H, m, H-1 and H-4), 3.66 - 3.60 (3H, m, H-5 and H-7), 2.74 (1H, br. s, OH), 1.97 - 1.85 (1H, m, H-6), 1.43 (3H, s, H-10), 1.41 (3H, s, H-10'), 1.10 - 1.01 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 0.89 (3H, d, *J* = 6.8 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 134.9 (C2), 127.0 (C3), 108.9 (C9), 85.6 (C5), 81.4 (C4), 67.5 (C7), 63.0 (C1), 38.5 (C6), 27.2 (C10), 27.1 (C10'), 18.1 ($Si(CH(\underline{C}H_3)_2)_3$), 13.7 (C8), 12.1 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** $C_{20}H_{40}NaO_4Si^+$ *m/z* (ESI^+) 395 $[M+Na]^+$

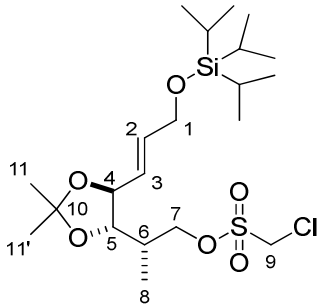
(*S*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-((*E*)-3-((triisopropylsilyl)oxy)prop-1-en-1-yl)-1,3-dioxolan-4-yl)propyl methanesulfonate (268)



To a solution of alcohol **267** (28 mg, 0.075 mmol) in dry CH_2Cl_2 (1 mL) was added triethylamine (41 µL, 0.3 mmol) and mesyl chloride (17 µL, 0.22 mmol) at rt. The reaction mixture was stirred for 1 h and then quenched with a saturated aqueous $NaHCO_3$ solution (1 mL). The reaction was filtered over Celite and the pad washed with CH_2Cl_2 (3 × 3 mL). The organic layers were evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 85:15) to give mesylate **268** (32 mg, 94%) as a colourless oil.

$[\alpha]_D^{23}$ −14.2 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2866, 1464 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.93 (2 H, dt, *J* = 15.2, 3.8 Hz) 5.76 (1 H, m, *J* = 15.2, 7.6 Hz), 4.34 (1H, dd, *J* = 9.6, 3.8 Hz, H-1), 4.30 - 4.18 (4H, m, H-1', H-7 and H-4), 3.60 (1H, t, *J* = 8.0 Hz, H-5), 3.01 (3H, s, H-9), 2.14 - 2.02 (1H, m, H-6), 1.40 (3H, s, H-11), 1.39 (3H, s, H-11'), 1.11 - 1.00 (24H, m, $Si(C\underline{H}(CH_3)_2)_3$, $Si(CH(C\underline{H}_3)_2)_3$ and H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 135.0 (C2), 126.8 (C3), 108.9 (C10), 81.3 (C4 or C5), 80.9 (C4 or C5), 72.4 (C7), 63.0 (C1), 37.2 (C6), 36.9 (C9), 27.2 (C11), 27.1 (C11'), 18.1 ($Si(CH(\underline{C}H_3)_2)_3$), 13.7 (C8), 12.1 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** $C_{21}H_{42}NaO_6SSi^+$ *m/z* (ESI^+) 473 $[M+Na]^+$

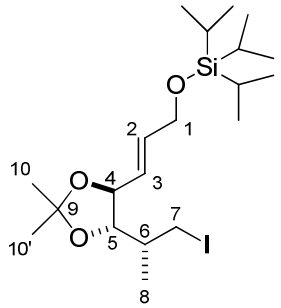
(*S*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-((*E*)-3-((triisopropylsilyl)oxy)prop-1-en-1-yl)-1,3-dioxolan-4-yl)propyl chloromethanesulfonate



To a solution of alcohol **267** (14 mg, 0.036 mmol) in dry CH_2Cl_2 (0.75 mL) at rt was added triethylamine (20 μL, 0.15 mmol) and chloromesyl chloride (10 μL, 0.11 mmol). The reaction mixture was stirred for 1.5 h and then a solution of saturated aqueous $NaHCO_3$ (0.3 mL) was added. The solution was filtered over Celite and the pad washed with CH_2Cl_2 (3 × 3 mL). The solution was evaporated *in vacuo* to yield crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 90:10) to give title compound (14 mg, 80%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.94 (1H, dt, *J* = 15.2, 4.0 Hz, H-2), 5.76 (1H, m, H-3), 4.64 (1H, d, *J* = 12.4 Hz, H-9), 4.59 (1H, d, *J* = 12.4 Hz, H-9'), 4.52 - 4.47 (1H, m, H-7), 4.43 - 4.36 (1H, m, H-7'), 4.29 - 4.21 (3H, m, H-1 and H-3), 3.62 (1H, t, *J* = 8.0 Hz, H-5), 2.16 - 2.04 (1H, m, H-6) 1.40 (6H, s, H-11) 1.11 - 1.02 (24H, m, $Si(C\underline{H}(CH_3)_2)_3$, $Si(CH(C\underline{H}_3)_2)_3$ and H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 135.1 (C2), 126.7 (C3), 109.0 (C10), 81.2 (C4 or C5), 81.0 (C4 or C5), 75.8 (C7), 63.0 (C1), 53.4 (C9), 37.3 (C6), 27.2 (C11), 27.1 (C11'), 18.1 ($Si(CH(\underline{C}H_3)_2)_3$), 13.7 (C8), 12.1 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 507 $[M+Na]^+$; **HRMS** (ESI^+) $C_{21}H_{41}ClNaO_6SSi^+$ $[M+Na]^+$ required 507.1974, found 507.1968.

(((*E*)-3-((4*S*,5*S*)-5-((*R*)-1-Iodopropan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)oxy)triisopropylsilane (269)

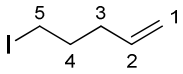


To a solution of imidazole (20 mg, 0.29 mmol) in dry CH_2Cl_2 (0.5 mL) was added triphenylphosphine (28 mg, 0.11 mmol) at rt. The solution was then cooled to 0 °C and iodine (28 mg, 0.11 mmol) was added. After stirring for 10 mins the solution turns orange to which was added alcohol **267** (27 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred at 0 °C for 2 h, and then it was slowly warmed to rt and stirred for further 8 h. Then a solution of saturate sodium thiosulfate (1 mL) was added and stirred for 5 mins. The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined

organic layers were dried over anhydrous Na_2SO_4 and evaporated to give the crude reaction mixture. On purification by flash column chromatography (petrol:ethyl acetate, 95:5) iodide **269** (26 mg, 74%) was obtained as a colourless oil.

$[\alpha]_D^{23}$ −10.3 (*c* = 0.74, $CHCl_3$); **IR** ν_{max} (neat): 2942, 2891, 2866, 1461 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 5.92 (1H, dt, *J* = 15.4, 4.1 Hz, H-2), 5.78 (1H, m, H-3), 4.31 - 4.22 (3H, m, H-1 and H-4), 3.55 (1H, t, *J* = 7.8 Hz, H-5), 3.43 (1H, dd, *J* = 9.6, 3.3 Hz, H-7), 3.26 (1H, dd, *J* = 9.6, 7.1 Hz, H-7'), 1.74 - 1.61 (1H, m, H-6), 1.41 (6H, s, H-10), 1.14 - 1.03 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 0.99 (3H, d, *J* = 6.6 Hz, H-8) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 134.6 (C2), 127.3 (C3), 108.7 (C9), 83.6 (C5), 80.5 (C4), 63.1 (C1), 38.8 (C6), 27.3 (C10), 27.0 (C10'), 18.1 ($Si(CH(\underline{C}H_3)_2)_3$),, 17.5 (C8), 14.0 (C7), 12.1 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 505 $[M+Na]^+$; **HRMS** (ESI^+) $C_{20}H_{39}INaO_3Si^+$ $[M+Na]^+$ required 505.1605, found 505.1595.

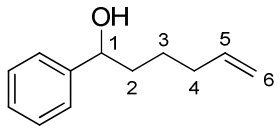
5-Iodopent-1-ene (270)



To a solution of sodium iodide (2 g, 13.3 mmol) in acetone (22 mL) at rt was added 5-bromopent-1-ene **239** (1 g, 6.7 mmol). The reaction mixture was heated to 60 °C and stirred for 2 h. The solution was then cooled to rt and water (5 mL) was added, which was then extracted with pentane (3 × 20 mL). Combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and evaporated *in vacuo* (200 mbar, 40 °C, 30 min) to give the 5-iodopent-1-ene **270** (1.1 g, 84%).

^{1}H NMR (200 MHz, $CDCl_3$) δ = 5.76 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, H-2), 5.16 - 4.96 (2H, m, H-1), 3.19 (2H, t, *J* = 6.9 Hz, H-5), 2.24 - 2.09 (2H, m, H-3), 2.00 - 1.82 (2H, m, H-4). The spectroscopic data were consistent with those reported in literature.[104]

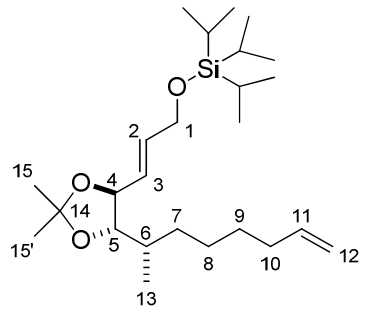
1-Phenylhex-5-en-1-ol (271)



To a solution of iodide **270** (88 mg, 0.45 mmol) in diethyl ether (1 mL) at −78 °C was added *tert*-butyllithium (0.57 mL, 1.6 M in pentane, 0.91 mmol). The reaction is warmed to rt and stirred for 1 h. Then it was cooled to −35 °C and benzaldehyde (0.15 mL, 0.47 mmol) was added. The reaction was then quenched with saturated aqueous solution of NH_4Cl (1 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 2 mL). The combined organic layers are dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 90:10) to give alcohol **271** (64 mg, 82%) as a colourless oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.40 - 7.27 (5H, m, Ph), 5.87 - 5.73 (1H, m, H-5), 5.05 - 4.93 (2H, m, H-6), 4.70 - 4.61 (1H, m, H-1), 2.17 (1H, d, *J* = 3.1 Hz, OH), 2.16 - 2.03 (2H, m, H-2), 1.85 - 1.66 (2H, m, H-3 or H-4), 1.57 - 1.22 (2H, m, H-3 or H-4). The spectroscopic data were consistent with those reported in literature.[105]

(((*E*)-3-((4*S*,5*S*)-2,2-Dimethyl-5-((*S*)-oct-7-en-2-yl)-1,3-dioxolan-4-yl)allyl)oxy)triisopropylsilane

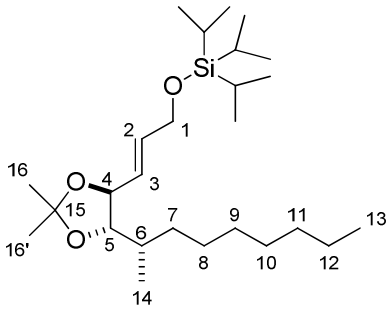


A solution of 5-iodopent-1-ene **270** (157 mg, 0.8 mmol) in Et_2O (1.6 mL) was cooled to −78 °C, then *tert*-butyllithium (1.0 mL, 1.6 M in pentane, 1.6 mmol). It was then warmed to rt and stirred for 1 h to give the desired organolithium. In a separate flask copper(I) cyanide (19 mg, 0.21 mmol) was suspended in THF (0.5 mL) and cooled to −40 °C. To this flask was added 1.3 mL of the previously prepared organolithium solution. (Note: On addition, precipitation is observed.) The reaction was then slowly warmed to −25 °C, then iodide **269** (15 mg, 0.03 mmol) in THF (0.2 mL) was added. The reaction was warmed to −15 °C and stirred for 3.5 h (over this period precipitation slowly disappeared). Then a saturated aqueous NH_4Cl solution (1 mL) was added and the reaction mixture warmed to rt. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 98:2 → 97:3) to give title compound (4.5 mg, 34%) as a colourless oil.

$[\alpha]_D^{23}$ −10.1 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2933, 2866, 1641, 1464 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.89 (1H, dt, *J* = 15.2, 4.0 Hz, H-2), 5.86 - 5.72 (2H, m, H-3 and H-11), 5.03 - 4.91 (2H, m, H-12), 4.27 (2H, dd, *J* = 4.1, 1.3 Hz, H-1), 4.21 (1H, t, *J* = 7.6 Hz, H-4), 3.59 (1H, dd, *J* = 8.0, 6.5 Hz, H-5), 2.08 - 2.01 (2H, m, H-10), 1.77 - 1.67 (1H, m, H-6), 1.56 - 1.51

(1H, m, H-7 or H-8 or H-9), 1.41 (9H, m, H-15 and H7 or H8 or H9), 1.39 - 1.33 (2H, m, H7 or H8 or H9), 1.13 - 1.04 (21H, m, Si(C<u>H</u>$(CH_3)_2)_3$ and Si(CH(C<u>H</u>$_3)_2)_3$), 0.91 (3H, d, J = 6.9 Hz, H-13) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 139.2 (C11), 133.9 (C3), 127.9 (C2), 114.4 (C12), 108.1 (C14), 85.0 (C5), 79.6 (C4), 63.2 (C1), 35.7 (C6), 33.9 (C10), 32.9 (C7 or C8 or C9), 29.2 (C7 or C8 or C9), 27.3 (C15), 27.1 (C15'), 26.6 (C7 or C8 or C9), 18.1 (Si(CH(<u>C</u>$H_3)_2)_3$), 15.6 (C13), 12.1 (Si(<u>C</u>$H(CH_3)_2)_3$) ppm; **MS** *m/z* (ESI^+) 447 $[M+Na]^+$; **HRMS** (ESI^+) $C_{25}H_{48}NaO_3Si^+$ $[M+Na]^+$ required 447.3265, found 447.3259.

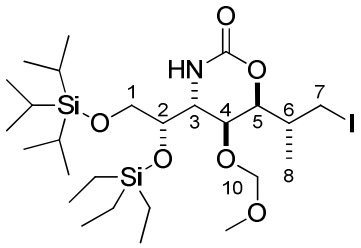
(((*E*)-3-((4*S*,5*S*)-2,2-Dimethyl-5-((*S*)-octan-2-yl)-1,3-dioxolan-4-yl)allyl)oxy)triisopropylsilane



To a suspension of copper(I) iodide (6.5 mg, 0.034 mmol) in dry THF (0.7 mL) at −40 °C was added hexyl magnesium bromide (70 µL, 0.138 mmol) and stirred for 30 mins. Then to this solution was added iodide **269** (15 mg, 0.031 mmol) in THF (0.5 mL) at −40 °C. The reaction mixture was then warmed to −20 °C over 3 h and then to rt overnight. Then saturated aqueous NH_4Cl solution (1 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was washed with ethyl acetate (2 × 3 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 97:3) to give title compound (3 mg, 22%).

$[\alpha]_D^{23}$ −14.2 (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (neat): 2934, 2866, 1464 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.88 (1H, dt, *J* = 15.2, 4.1 Hz, H-2), 5.75 (1H, m, H-3), 4.26 (2H, dd, *J* = 3.9, 1.4 Hz, H-1), 4.21 (1H, t, *J* = 7.6 Hz, H-4), 3.59 (1H, dd, *J* = 7.9, 6.3 Hz, H-5), 1.74 - 1.65 (1H, m, H-6), 1.41 (3H, s, H-16), 1.40 (3H, s, H-16'), 1.22 - 1.32 (12H, m, H-7, H-8, H-9, H-10, H-11 and H-12), 1.10 - 1.03 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 0.92 - 0.86 (6H, m, H-13 and H-14) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 133.8 (C3), 127.9 (C2), 108.0 (C15), 85.2 (C5), 79.4 (C4), 63.2 (C1), 35.8 (C6), 33.1 (C7-C12), 32.1 (C7-C12), 29.9 (C7-C12), 29.8 (C7-C12), 29.5 (C7-C12), 27.3 (C7-C12), 27.2 (C16), 27.1 (C16'), 18.1 ($Si(CH(\underline{C}H_3)_2)_3$), 15.6 (C14), 14.3 (C13), 12.1 ($Si(\underline{C}H(CH_3)_2)_3$) ppm; **MS** *m/z* ($ESI^+$) 463 $[M+Na]^+$; **HRMS** (ESI^+) $C_{26}H_{52}NaO_3Si^+$ $[M+Na]^+$ required 463.3578, found 463.3584.

(4*R*,5*S*,6*S*)-4-((*S*)-3,3-Diethyl-8,8-diisopropyl-9-methyl-4,7-dioxa-3,8-disiladecan-5-yl)-6-((*R*)-1-iodopropan-2-yl)-5-(methoxymethoxy)-1,3-oxazinan-2-one (261)

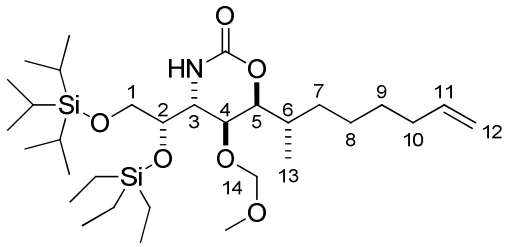


To a solution of imidazole (13 mg, 0.19 mmol) in dry CH_2Cl_2 (0.34 mL) was added triphenylphosphine (19 mg, 0.07 mmol) at rt. The solution was then cooled to 0 °C and iodine (18 mg, 0.07 mmol) was added. After stirring for 10 mins the solution turns orange to which was added alcohol **255** (24 mg, 0.047 mmol) in CH_2Cl_2 (0.34 mL). The reaction was stirred at 0 °C for 16 h then slowly warmed to rt and stirred for a further 6 h. Then a solution of saturated aqueous sodium thiosulfate (1 mL) was added and stirred for 5 mins. The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined

organic layers were dried over anhydrous Na_2SO_4 and evaporated to give the crude reaction mixture. On purification by flash column chromatography (petrol:ethyl acetate, 95:5) iodide **261** (16 mg, 51%) was obtained as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.10 (1H, d, *J* = 2.8 Hz, NH), 4.76 (1H, d, *J* = 7.1 Hz, H-10), 4.66 (1H, d, *J* = 7.1 Hz, H-10'), 4.16 (1H, d, *J* = 9.5 Hz, H-5), 4.04 (1H, app s, H-4), 3.84 (1H, app t, *J* = 3.9 Hz, H-7), 3.53 - 3.80 (4H, m, H-1, H-2 and H-7'), 3.49 (1H, dd, *J* = 9.80, 2.8 Hz, H-3) 3.39 (3H, s, OCH_3), 2.02 - 1.86 (1H, m, H-6), 1.13 - 1.04 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 1.02 (3H, d, *J* = 6.7 Hz, H-8), 1.00 - 0.91 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.69 - 0.68 (9H, m, $Si(CH_2C\underline{H}_3)_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 153.4 (C=O), 95.7 (C10), 80.0 (C5), 73.5 (C2), 69.1 (C4), 64.6 (C1), 56.2 (C3), 33.8 (C6), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 16.6 (C7 or C8), 14.7 (C7 or C8), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$), 6.9 ($Si(CH_2\underline{C}H_3)_3$), 5.2 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 682 $[M+Na]^+$; **HRMS** (ESI^+) $C_{26}H_{54}INNaO_6Si_2^+$ $[M+Na]^+$ required 682.2427, found 682.2421.

(4*R*,5*S*,6*S*)-4-((*S*)-3,3-Diethyl-8,8-diisopropyl-9-methyl-4,7-dioxa-3,8-disiladecan-5-yl)-5-(methoxymethoxy)-6-((*S*)-oct-7-en-2-yl)-1,3-oxazinan-2-one (257)

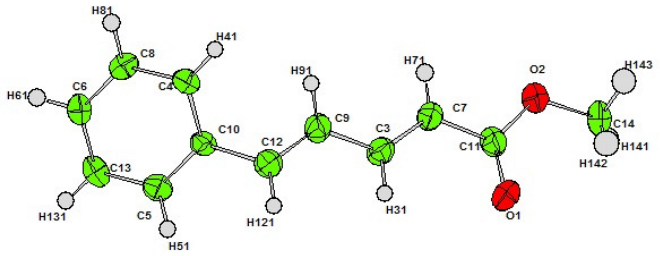


A solution of 5-iodopent-1-ene **270** (135 mg, 0.68 mmol) in Et_2O (0.9 mL) was cooled to −78 °C, then *tert*-butyllithium (0.74 mL, 1.9 M in pentane, 1.4 mmol). It was then warmed to rt and stirred for 1 h to give the desired organolithium. In a separate flask copper(I) cyanide (15 mg,

0.17 mmol) was suspended in THF (0.6 mL) and cooled to −45 °C. To this flask was added 0.85 mL of the previously prepared organolithium solution. (Note: On addition, precipitation is observed.) The reaction was then slowly warmed to −35 °C, then iodide **261** (15 mg, 0.022 mmol) in THF (0.2 mL) was added. The reaction was warmed to −25 °C and stirred for 1 h. Then a saturated aqueous NH_4Cl solution (1 mL) was added and the reaction mixture warmed to rt. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to give crude product, which was purified by flash column chromatography (petrol:ethyl acetate, 80:20 → 75:25) to give alkene **257** (4 mg, 30%) as a colourless oil.

$[\alpha]_D^{23}$ −65.6 (*c* = 0.25, $CHCl_3$); **IR** ν_{max} (neat): 2940, 2866, 1716, 1463 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 5.80 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, H-11), 5.05 (1H, d, *J* = 2.8 Hz, NH), 5.02 - 4.90 (2H, m, H-12), 4.76 (1H, d, *J* = 7.2 Hz, H-14), 4.67 (1H, d, *J* = 7.2 Hz, H-14'), 4.07 (1H, d, *J* = 10.1 Hz, H-5), 4.03 (1H, app. s, H-4), 3.83 (1H, app. t, *J* = 3.6 Hz, H-3), 3.77 - 3.72 (1H, m, H-1), 3.69 (1 H, dt, *J* = 8.4, 3.6 Hz, H-2), 3.63 - 3.59 (1H, m, H-1), 3.39 (3H, s, OCH_3), 2.09 - 2.01 (3H, m, H-10, H-6), 1.92 - 1.84 (1H, m, H-7 or H-8 or H-9), 1.40 (3H, m, H-7 or H-8 or H-9), 1.30 - 1.24 (2H, m, H-7 or H-8 or H-9), 1.10 - 1.04 (21H, m, $Si(C\underline{H}(CH_3)_2)_3$ and $Si(CH(C\underline{H}_3)_2)_3$), 0.96 (9H, t, *J* = 7.9 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.91 (3H, d, *J* = 6.9 Hz, H-13), 0.60 (6H, q, *J* = 7.9 Hz, $Si(CH_2C\underline{H}_3)_3$) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ = 154.2 (C=O), 139.1 (C11), 114.2 (C12), 95.7 (C14), 81.2 (C5), 73.6 (C2), 69.4 (C4), 64.4 (C1), 56.2 (C3), 55.8 (OCH_3), 33.8 (C7-C10), 32.9 (C6), 32.0 (C7-C10), 29.1 (C7-C10), 25.9 (C7-C10), 17.9 ($Si(CH(\underline{C}H_3)_2)_3$), 14.6 (C13), 11.8 ($Si(\underline{C}H(CH_3)_2)_3$) 6.9 ($Si(CH_2\underline{C}H_3)_3$), 5.1 ($Si(\underline{C}H_2CH_3)_3$) ppm; **MS** *m/z* ($ESI^+$) 624 $[M+Na]^+$; **HRMS** (ESI^+) $C_{31}H_{63}NNaO_6Si_2^+$ $[M+Na]^+$ required 624.4086, found 624.4081.

X-Ray crystal structure of compound **210** [(2*E*,4*E*)-methyl 5-phenylpenta-2,4-dienoate]



To prove the *trans*-selectivity of Horner-Wadsworth-Emmons olefination, benzaldehyde was subjected to general procedure B and the product was crystallised. Crystals of 001aki09 were grown by Akshat Rathi from ethyl acetate. A single crystal having dimensions approximately 0.2 x 0.32 x 0.4 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, λ = 0.71073 A). Intensity data were processed using the DENZO-SMN package.[106]

Examination of the systematic absences of the intensity data showed the space group to be *P n a 21*. The structure was solved in this space group using the direct-methods program SIR92,[107] which located all non-hydrogen atoms. The hydrogen atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. Subsequent full-matrix least-squares refinement was carried out against F^2 using the CRYSTALS program suite.[108] Coordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms, and the hydrogen atoms were refined with riding constraints. A modified statistical weighting scheme was applied. Refinement converged satisfactorily to give R = 0.0549, Rw = 0.0763.

Attached is a thermal ellipsoid plot (CAMERON) at 50% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning hydrogen atoms..

Crystal data

$C_{12}H_{12}O_2$	F_{000} = 400
Mr = 188.23	Dx = 1.219 Mg m−3
Orthorhombic, *Pna*2$_1$	Mo *K*α radiation, λ = 0.71073 Å
Hall symbol: P 2c -2n	Cell parameters from 342 reflections
a = 6.0964 (9) Å	θ = 5–27º
b = 7.1283 (13) Å	μ = 0.08 mm−1
c = 23.601 (3) Å	T = 150 K
V = 1025.6 (3) Å^3	Block, yellow
Z = 4	0.10 × 0.10 × 0.10 mm

Data collection

Area diffractometer	532 reflections with I > 2.0σ(I)
Monochromator: graphite	R_{int} = 0.000
T = 150 K	θ_{max} = 27.3º
ω scans	θ_{min} = 5.1º
Absorption correction: multi-scan	
DENZO/SCALEPACK (Otwinowski & Minor, 1997)	*h* = −7→7
Tmin = 0.99, Tmax = 0.99	*k* = −8→8
2758 measured reflections	*l* = −29→30
680 independent reflections	

Refinement

Refinement on F^2

Primary atom site location: structure-invariant direct methods

Least-squares matrix: full

Hydrogen site location: inferred from neighbouring sites

$R[F^2 > 2\sigma(F^2)] = 0.057$

H-atom parameters constrained

$wR(F^2) = 0.145$

Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.1P)^2 + 0.0P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$

S = 1.04 (Δ/σ)

max = 0.0001

680 reflections Δρ

max = 0.38 e Å^{-3}

127 parameters Δ

ρmin = −0.39 e Å^{-3}

1 restraint

Extinction correction: None

Fractional atomic coordinates & isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	Uiso*/Ueq
O1	0.6137 (7)	0.5386 (7)	0.7368 (2)	0.0568
O2	0.2866 (7)	0.4539 (6)	0.7045 (2)	0.0542
C3	0.7725 (9)	0.4940 (8)	0.6226 (3)	0.0379
C4	1.0157 (9)	0.4189 (7)	0.4453 (2)	0.0363
C5	1.3374 (9)	0.5781 (8)	0.4770 (3)	0.0381
C6	1.2998 (9)	0.5006 (8)	0.3783 (3)	0.0397
C7	0.5720 (10)	0.4543 (8)	0.6397 (2)	0.0400
C8	1.1018 (9)	0.4196 (8)	0.3905 (3)	0.0393
C9	0.8473 (10)	0.4655 (8)	0.5646 (3)	0.0401
C10	1.1337 (8)	0.4990 (7)	0.4893 (3)	0.0329

C11 0.4982 (10) 0.4866 (8) 0.6983 (3) 0.0408

C12 1.0476 (10) 0.5127 (9) 0.5473 (3) 0.0383

C13 1.4198 (9) 0.5795 (8) 0.4228 (3) 0.0392

C14 0.1937 (10) 0.4803 (11) 0.7609 (3) 0.0609

H31 0.8738 0.5451 0.6490 0.0460*

H41 0.8752 0.3648 0.4521 0.0443*

H51 1.4204 0.6284 0.5077 0.0487*

H61 1.3555 0.5051 0.3409 0.0465*

H71 0.4696 0.4047 0.6145 0.0483*

H81 1.0207 0.3614 0.3609 0.0527*

H91 0.7497 0.4097 0.5379 0.0475*

H121 1.1442 0.5597 0.5754 0.0458*

H131 1.5580 0.6335 0.4160 0.0496*

H141 0.0604 0.4092 0.7642 0.1012*

H142 0.2991 0.4363 0.7882 0.1011*

H143 0.1675 0.6116 0.7676 0.1013*

Atomic displacement parameters (Å^2)

U^{11} U^{22} U^{33} U^{12} U^{13} U^{23}

O1 0.052 (3) 0.086 (3) 0.032 (2) −0.010 (2) 0.0015 (17) −0.007 (2)

O2 0.040 (2) 0.082 (3) 0.041 (3) −0.006 (2) 0.0043 (19) −0.013 (2)

C3 0.037 (3) 0.045 (3) 0.032 (3) 0.007 (3) −0.003 (2) 0.000 (3)

C4 0.033 (3) 0.035 (3) 0.041 (3) −0.004 (2) 0.001 (2) 0.002 (3)

C5 0.034 (3) 0.038 (4) 0.042 (4) 0.002 (2) −0.003 (2) 0.001 (3)

C6 0.040 (3) 0.044 (4) 0.035 (3) 0.008 (3) 0.004 (2) 0.001 (3)

C7 0.038 (3) 0.051 (3) 0.031 (3) 0.002 (2) 0.001 (2) −0.003 (2)

C8 0.039 (3) 0.038 (3) 0.041 (3) 0.004 (2) −0.003 (2) 0.001 (2)

C9 0.040 (3) 0.043 (3) 0.037 (3) 0.002 (2) 0.001 (2) 0.005 (3)

C10 0.026 (3) 0.033 (3) 0.040 (3) 0.003 (2) −0.0016 (19) −0.004 (3)

C11 0.037 (3) 0.051 (4) 0.034 (3) 0.001 (3) 0.005 (2) 0.001 (3)

C12 0.036 (3) 0.040 (3) 0.039 (3) 0.006 (2) −0.003 (3) −0.001 (2)

C13 0.033 (3) 0.039 (3) 0.045 (4) 0.001 (2) 0.005 (2) 0.003 (3)

C14 0.047 (4) 0.093 (6) 0.043 (4) −0.004 (3) 0.015 (3) −0.014 (3)

Geometric parameters (Å, °)

O1—C11 1.208 (8) C6—C13 1.398 (9)

O2—C11 1.318 (7) C6—H61 0.947

O2—C14 1.459 (8) C7—C11 1.472 (7)

C3—C7 1.318 (8) C7—H71 0.932

C3—C9 1.458 (8) C8—H81 0.951

C3—H31 0.950 C9—C12 1.331 (8)

C4—C8 1.395 (7) C9—H91 0.953

C4—C10 1.387 (7) C10—C12 1.469 (8)

C4—H41 0.953 C12—H121 0.949

C5—C10 1.394 (8) C13—H131 0.940

C5—C13 1.374 (8) C14—H141 0.961

C5—H51 0.953 C14—H142 0.962

C6—C8 1.369 (8) C14—H143 0.963

C11—O2—C14 117.2 (5) C3—C9—H91 118.9

C7—C3—C9 123.2 (5) C12—C9—H91 118.4

C7—C3—H31 119.0 C5—C10—C4 118.2 (5)

C9—C3—H31 117.8 C5—C10—C12 119.0 (5)

C8—C4—C10 119.9 (5) C4—C10—C12 122.7 (5)

C8—C4—H41 119.8 C7—C11—O2 112.0 (5)

C10—C4—H41 120.3 C7—C11—O1 125.2 (6)

C10—C5—C13 121.4 (5) O2—C11—O1 122.8 (6)

C10—C5—H51 117.9 C10—C12—C9 126.7 (5)

C13—C5—H51 120.7 C10—C12—H121 116.9

C8—C6—C13 118.3 (6) C9—C12—H121 116.4

C8—C6—H61 121.7 C6—C13—C5 120.3 (5)

C13—C6—H61 120.0 C6—C13—H131 120.3

C3—C7—C11 122.5 (5) C5—C13—H131 119.4

C3—C7—H71 120.4 O2—C14—H141 109.5

C11—C7—H71 117.0 O2—C14—H142 108.0

C4—C8—C6 121.8 (6) H141—C14—H142 109.9

C4—C8—H81 119.0 O2—C14—H143 109.8

C6—C8—H81 119.2 H141—C14—H143 111.0

C3—C9—C12 122.7 (5) H142—C14—H143 108.5

Hydrogen-bond geometry (Å, °)

D—H···A	D—H	H···A	D···A	D—H···A
C6—H61···O1^{i}	0.95	2.48	3.393	161

Symmetry codes: (i) −x+2, −y+1, z−1/2.

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