Total synthesis and stereochemical reassignment of dehydromicrosclerodermin B and microsclerodermin J

A thesis submitted to the
Board of the Faculty of the Mathematical, Physical and Life Sciences
Division for the degree of

Doctor of Philosophy
in the
University of Oxford

by

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Hilary 2016

Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source. Text taken from another source will be enclosed in quotation marks and a reference given.

Ekaterina Melikhova

Oxford, Hilary 2016

Contents

Declaration 1
Contents 2
Abstract 4
Acknowledgements 5
Abbreviations 6
Chapter 1 The microsclerodermin family 9
1.1 Isolation and structure determination of the microsclerodermins 9
1.1.1 Microsclerodermins A and B 10
1.1.2 Microsclerodermins C-E 14
1.1.3 Microsclerodermins F-I 15
1.1.4 Microsclerodermins J and K 16
1.1.5 Microsclerodermins L and M 18
1.2 Synthetic studies on the microsclerodermins 20
1.2.1 Total synthesis of microsclerodermin E by Ma 20
1.2.2 Studies towards microsclerodermin B by Shioiri 27
1.2.3 Studies towards synthesis of the β-amino acid residues 31
1.3 Project aims and retrosynthetic analysis of microsclerodermin B 39
Chapter 2 Synthesis of the AMMTD β-amino acid 42
2.1 Retrosynthetic analysis of the AMMTD β-amino acid 42
2.2 Synthesis of diol **158** 43
2.3 Development of the key TA reaction 46
2.4 Installation of the AMMTD side-chain *via* cuprate displacement 56
2.5 Completion of the synthesis of AMMTD 60
Chapter 3 First generation approach to the protected cyclic peptide 67
3.1 Preparation of the AMMTD amino alcohol for coupling 67
3.2 Synthesis of the AMMTD-GABOB dipeptide 70
3.3 Synthesis of the linear hexapeptide 75
3.4 Synthesis of the cyclic hexapeptide 78
3.5 Attempts to cleave the methyl ester of cyclic peptide **299** 89

Chapter 4 Synthesis and stereochemical reassignment of dehydromicrosclerodermin B 94
4.1 Revised route to tryptophan-2-carboxylate 94
4.2 Synthesis of the TMSE containing Gly-Trp-Sar-Pyrr tetrapeptide 101
4.3 Synthesis of the TMSE containing cyclic peptide and attempts to apply the "end-game strategy 105
4.4 Synthesis and spectral analysis of dehydromicrosclerodermin B 112
4.5 Synthesis and data analysis of reassigned dehydromicrosclerodermin B (*epi*-**358**) 124
Chapter 5 Synthesis and stereochemical reassignment of microsclerodermin J . 133
Chapter 6 Studies towards the total synthesis of dehydromicrosclerodermin A . 139
6.1 Introduction 139
6.2 Retrosynthetic analysis and hydroxylation of an aspartic acid derivative 140
6.3 Synthesis of the Blaise reaction precursor 145
6.4 The Blaise reaction and determination of product enantiopurity 147
Chapter 7 Conclusions 152
Chapter 8 Experimental 156
8.1 Experimental techniques 156
8.2 Experimental procedures 158
8.3 Supplementary CIF data for compound **202** 355
References 371

Abstract

Total synthesis and stereochemical reassignment of dehydromicrosclerodermin B and microsclerodermin J

This thesis describes research towards the total synthesis of two marine natural products, dehydromicrosclerodermin B and microsclerodermin J. The synthesis of the most complex subunit of these peptides, AMMTD, was accomplished in a longest linear sequence of 21 steps starting from (*S*)-Roche ester. Preliminary results conducted by other group members were improved; the key cuprate displacement reaction and the final steps of the synthetic sequence were developed. Subsequently, AMMTD-GABOB dipeptide was synthesised and coupled with the northern hemisphere. An appropriate protecting group strategy was developed such that macrolactamisation and subsequent protecting group removal could be achieved. This required the design of a new approach to the synthesis of the tryptophan-2-carboxylic acid. An "end-game" strategy, which had previously been developed on model substrates, failed on late-stage cyclic or linear hexapeptides. Because of this, studies turned to the completion of a synthesis of dehydromicrosclerodermin B. Comparison of the data for synthetic and natural dehydromicrosclerodermin B revealed a mistake in the assignment of the (45*S*)-configuration. The corresponding (45*R*)-epimer was synthesised and its data were in a good agreement with those of dehydromicrosclerodermin B. Based on the reassignment of the C45 stereocentre of dehydromicrosclerodermin B, the total synthesis of microsclerodermin J containing a reassigned (*R*)-configured pyrrolidinone unit was accomplished. NMR data for synthetic and natural microsclerodermin J were in complete agreement, confirming that the initial stereochemical assignment of this natural product was incorrect.

Acknowledgements

First I would like to thank my supervisor, Prof. Timothy J. Donohoe, for giving me the opportunity to work in his group and, particularly, for allowing me to research total syntheses of the microsclerodermins. I am very grateful for his help and encouragement in difficult moments, and for his teaching and support throughout the whole of my DPhil.

Many thanks go to the past members of "team microsclerodermin": Dr Robert Pullin for supervising me in the first few months of my DPhil, Dr Christian Winter, Dr Akshat Rathi and Hang Xu for their contributions to the project.

I am very grateful to my boyfriend, who has always been helpful and attentive to my problems, and who also gave me advice without which the project would not have been finished. Many thanks to him for spending so many hours proof reading my thesis and helping me to make it as good as it could possibly be.

Dr Thomas Parsons from the Ben Davis group deserves great acknowledgement, as he helped me hugely with HPLC purification of the natural products – he did this with understanding and care. I would like to mention the NMR and MS staff, particularly Dr Barbara Odell, who always gave priority to my precious samples!

I would particularly like to thank the Hill Foundation for providing my main DPhil funding – without this scholarship I would have never been able to study at Oxford. I hope that they will keep supporting Russian students at Oxford and expand the number of scholars. I am also grateful to the Society of Chemical Industry for recognising my work and awarding me a Messel scholarship; the funding this provided was of great help while I was writing my thesis.

I reserve the most thanks for my family, who have always believed in me and have supported me through the whole of my studies.

Abbreviations

AETD	3-amino-10-(p-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid
AD	asymmetric dihydroxylation
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
APTD	(2*S*,3*R*,4*S*,5*S*)-3-amino-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
BAIB	[bis(acetoxy)iodo]benzene
BCB	*B*-bromocatecholborane
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BTCA	benzyltrichloroacetimidate
CDI	1,1'-carbonyldiimidazole
CLSI	clinical and laboratory standards institute
COMU	(1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
CSA	camphorsulfonic acid
CSO	(10-camphorsulfonyl)oxaziridine
dba	dibenzylideneacetone
de	diastereoisomeric excess
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIC	*N*,*N*′-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMB	dimethoxybenzyl
DMP	Dess-Martin periodinane

2,2-DMP	2,2-dimethoxypropane
DPPA	diphenylphosphoryl azide
EDCI (EDC)	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
ee	enantiomeric excess
FCC	flash column chromatography
FDPP	pentafluorophenyl diphenylphosphinate
Fm	9-fluorenylmethyl
GABOB	γ-amino-β-hydroxybutyric acid
Gly	glycine
Grubbs I	Grubbs Catalyst 1st Generation
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	*N,N,N′,N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HCT	human colon tumour
HMDS	hexamethyldisilazide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	*N*-hydroxybenzotriazole
Hoveyda-Grubbs II	Hoveyda-Grubbs Catalyst 2nd Generation
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
Im	imidazole
LG	leaving group
MIC	minimum inhibitory concentration
MPM	*para*-methoxybenzyl
NMM	*N*-methylmorpholine
Pfp	pentafluorophenyl
PHAL	phthalazine
PMP	*para*-methoxyphenyl
PTSA	*para*-toluenesulfonic acid
PyAOP	(7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

PyBOP	(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
Pyrr	pyrrolidinone
QPHOS	1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
(*R*,*R*)-Et-DUPHOS	(−)-1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)benzene
Sar	sarcosine
Su	succinimide
TA	tethered aminohydroxylation
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBCD	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBDPS	*tert*-butyldiphenylsilyl
TMSE	2-(trimethylsilyl)ethyl
TOCSY	total correlation spectroscopy
Trp	tryptophan

Standard abbreviations are not specified here.

Chapter 1 The microsclerodermin family

1.1 Isolation and structure determination of the microsclerodermins

Microsclerodermins A-M are a family of thirteen macrocyclic hexapeptides, isolated from the marine sponges *Microscleroderma* and *Theonella*, and terrestrial myxobacteria *Jahnella*, *Chondromyces* and *Sorangium*. The microsclerodermins were isolated as white powders after extraction and reverse phase HPLC purification. All members of the family consist of a 23-membered macrocycle, which is constructed from six amino acid units: a tryptophan derivative (Trp), sarcosine (Sar), a substituted pyrrolidinone (Pyrr), a polyhydroxylated β-amino acid, γ-amino-β-hydroxybutanoic acid (GABOB) and glycine (Gly).

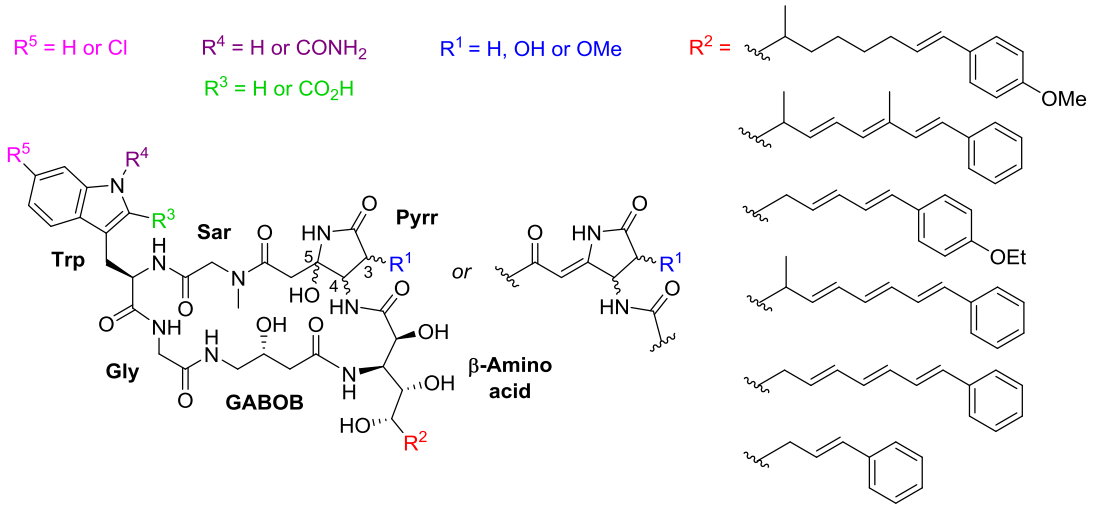


Figure 1. Structural overview of the microsclerodermin natural products.

Throughout the family, the tryptophan fragment differs in substitution on the indole nitrogen and at the 2- and 6-positions of the indole ring (R^3, R^4 and R^5, Figure 1). For

example, some members are chlorinated at R^5 and some have a carboxylic acid at R^3. For most of the members, the pyrrolidinone unit possesses a C5 (pyrrolidinone numbering) hydroxyl group, as shown in Figure 1, but others are unsaturated at this position. The pyrrolidinone unit is also reported to have different stereochemistry at C3 and C4, depending on the member of the family. The polyhydroxylated β-amino acid unit contains four or five contiguous stereocentres with the same configuration, but differs in the structure of the R^2 side-chain. The GABOB, Gly and Sar residues are common to all members of the family. A more detailed structural overview for each member of the family is provided below.

1.1.1 Microsclerodermins A and B

Microsclerodermins A and B, the first two members of the family, were reported by Faulkner and co-workers in 1994.[1] These were isolated from the lithistid sponge *Microscleroderma*, which was collected at a depth of 1000 feet off Norfolk Rise near New Caledonia. The sponge contains only 0.005% (dry weight) of microsclerodermin A and 0.001% (dry weight) of microsclerodermin B. Both natural products were found to inhibit the growth of *Candida albicans* at a loading of 2.5 μg/disk.

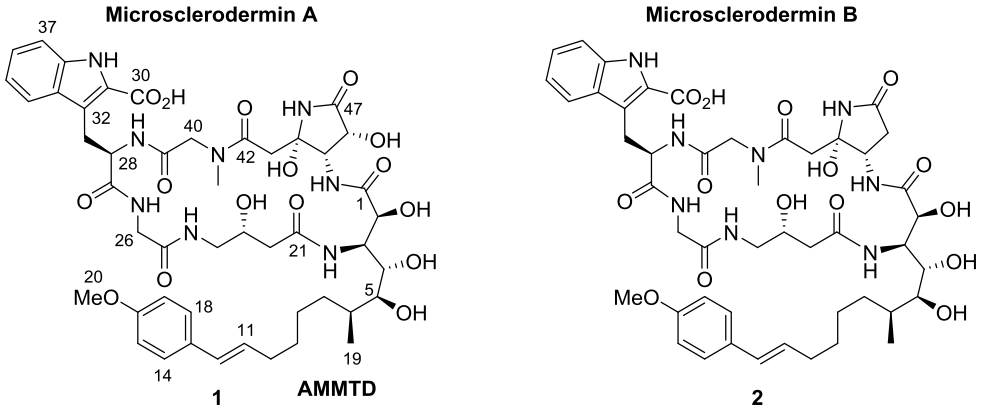
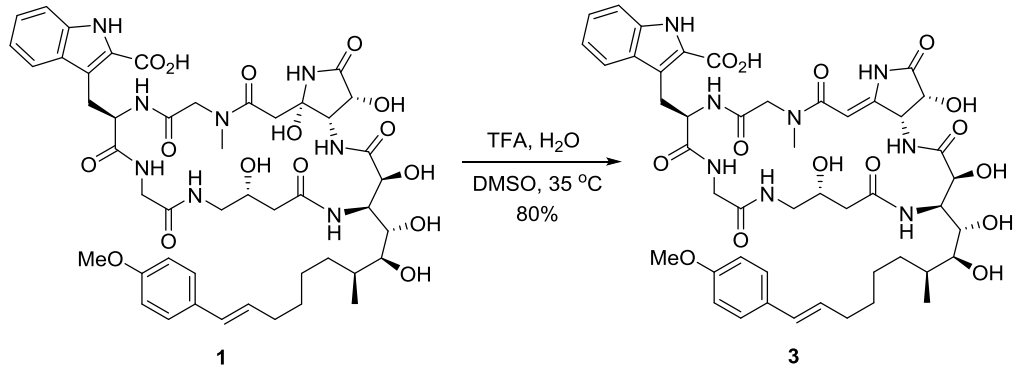


Figure 2. Reported structures of microsclerodermins A and B.

It was observed that the hydroxylated pyrrolidinone unit of microsclerodermin A is readily dehydrated upon exposure to mild acid or desiccants to afford dehydromicrosclerodermin A **3** (Scheme 1). This facile dehydration has also been reported for other members of the family that contain the C44 aminal moiety (microsclerodermin A numbering, see later).



Scheme 1. Dehydration of microsclerodermin A.

The connectivity of microsclerodermin A was assigned on the basis of detailed NMR analysis (^{1}H, ^{13}C, COSY, TOCSY, HMQC, HMBC, and ROESY) and derivatisation experiments. The natural product contains a C31 carboxylated tryptophan unit, a sarcosine linker, a C44/C46 dihydroxylated pyrrolidinone, a polyhydroxylated β-amino acid named AMMTD, and GABOB and glycine residues. The relative stereochemistry was assigned by NOE analysis and by comparison of peptide degradation products to authentic samples of amino acids; this latter approach also enabled the assignment of the absolute stereochemistry. Degradation experiments were performed on **3** and indicated the following:

(i) The GABOB unit has the (*R*)-configuration based on analysis of a GABOB acid degradation product (Scheme 2).

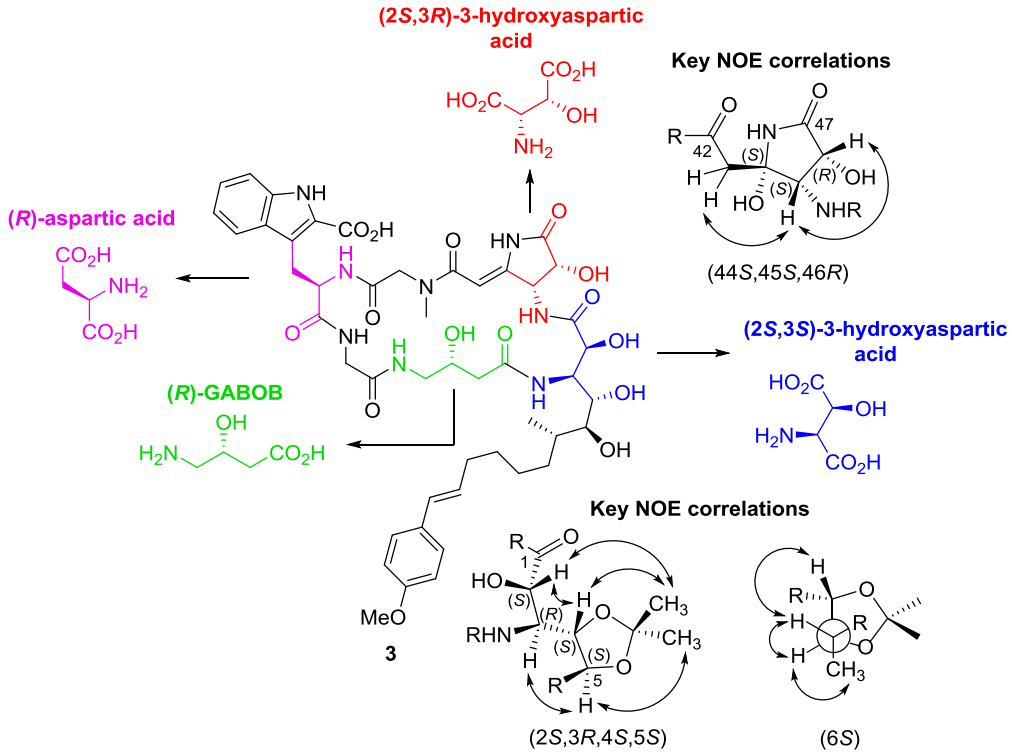
(ii) The tryptophan unit has the (*R*)-configuration by analysis of an (*R*)-aspartic acid degradation product (Scheme 2).

(iii) The pyrrolidinone has the (45*S*,46*R*)-configuration by analysis of a (2*S*,3*R*)-3-hydroxyaspartic acid degradation product. The pyrrolidinone of dehydromicrosclerodermin A was therefore assigned as having the same relative stereochemistry (45*R*,46*R*) (Scheme 2).

(iv) C44 has the (*S*)-configuration on the basis of ROESY correlations observed between H43, H45 and H46 (Scheme 2).

(v) The AMMTD unit has the (2*S*,3*R*)-configuration by analysis of a (2*S*,3*S*)-3-hydroxyaspartic acid obtained in a different manner to (iii) (Scheme 2).

(vi) The configurations of the AMMTD C4-C6 stereocentres were assigned as (4*S*,5*S*,6*S*) by ROESY analysis of dehydromicrosclerodermin A acetonide (Scheme 2).



Scheme 2. Key studies used in the stereochemical assignment of microsclerodermin A **1**.

The proposed structure of microsclerodermin B was based on the very strong similarity of its NMR data to microsclerodermin A, with only the C46 signal differing significantly. It is important to note that microsclerodermins A and B are the only members of the family with the proposed (44*S*,45*S*)-configuration, whereas microsclerodermins J and K are the only others with the (45*S*)-configuration. In all additional members, C45 has been assigned as having the (*R*)-configuration. The assignments of the C45 stereocentre of microsclerodermins B, J and K was made by analogy to microsclerodermin A and additional degradation experiments were not performed. Subsequently, Li also identified microsclerodermins A and B during isolation of microsclerodermins J and K from the deep-water sponge *Microscleroderma herdmani*.[2]

1.1.2 Microsclerodermins C-E

Four years later, in 1998, Faulkner reported studies on the isolation of microsclerodermins C **4**, D **5** and E **6** (Figure 3).[3] These members of the family were found in the *Theonella* and *Microscleroderma* sponges, collected from the Visayan Islands in the Philippines.

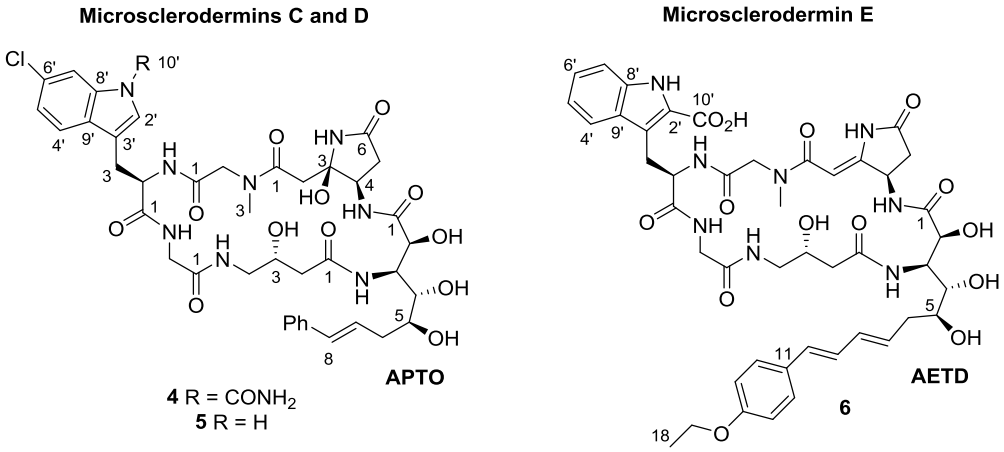


Figure 3. Microsclerodermins C-E.

The fact that these compounds were found in different genera of sponges led Faulkner to suggest that the microsclerodermins originate from the symbiosis of these sponges with filamentous microorganisms. Indeed, such organisms were found in the *Theonella* sponge.[3] In 2013, Muller detected microsclerodermin D in the terrestrial myxobacteria *Jahnella* and *Chondromyces* (see later).[4] Thus, Faulkner's assumption about the potential symbiotic origin of these natural products appears well founded.

The structures of microsclerodermins C-E were proposed using a combination of NMR techniques and derivatisation and degradation experiments. The tryptophan residue in microsclerodermins C and D is chlorinated at C6', and for microsclerodermin C the

indole nitrogen is part of a urea. The pyrrolidinone unit of microsclerodermins C and D is present as the C3 hydroxylated form, but this stereocentre was proposed to have the opposite configuration to that previously assigned for microsclerodermins A and B; no comment was made on this difference in pyrrolidinone stereochemistry. The β-amino acid fragment of microsclerodermins C and D contains four stereocentres and is named APTO. Microsclerodermin E was proposed to contain a tryptophan-2-carboxylic acid residue, an unsaturated (*R*)-pyrrolidinone unit and a β-amino acid named AETD. All three of these peptides were reported to be active against *Candida albicans* in a paper disk assay (microsclerodermin C: inhibition at 5 μg/disk; microsclerodermin E: 10 μg/disk; microsclerodermin D: 100 μg/disk).

1.1.3 Microsclerodermins F-I

In 2000, microsclerodermins F-I were isolated by the Faulkner group from a deep-water specimen of the *Microscleroderma* sponge, collected at Short Dropoff near Koror, Palau.[5] The sponge contained 0.002% (wet weight) of microsclerodermin F **7**, 0.001% (wet weight) of G **9**, 0.004% (wet weight) of H **8** and 0.002% (wet weight) of I **10**. Microsclerodermins F-I were found to inhibit the growth of *Candida albicans* using a paper disk diffusion assay. Peptide **7** was the most active at 1.5 μg/disk, followed by **9** at 3 μg/disk, **8** at 12 μg/disk and **10** at 25 μg/disk. All four microsclerodermins showed very similar cytotoxicity against the HCT-116 cell line, with IC_{50} values of 1.0 μg/mL (**8**), 1.1 μg/mL (**10**), 1.8 μg/mL (**7**) and 2.4 μg/mL (**9**).

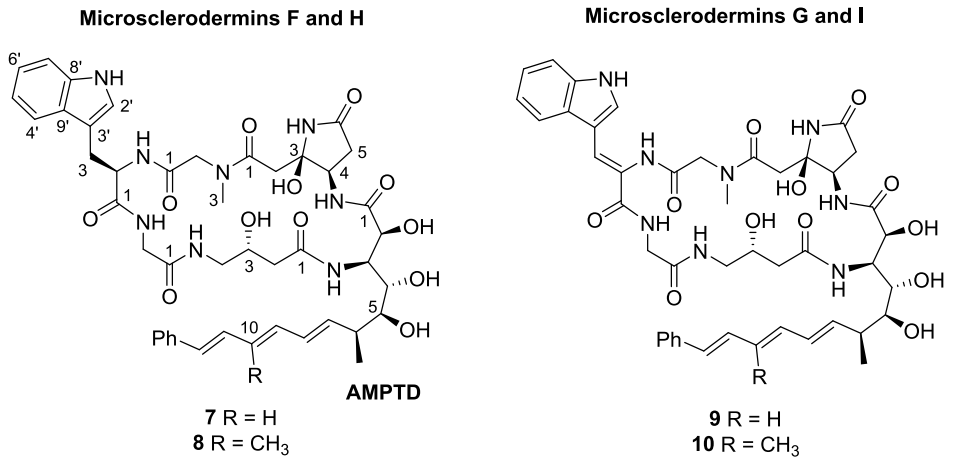


Figure 4. Microsclerodermins F-I.

Microsclerodermins F-I contain a hydroxylated (*R*,*R*)-pyrrolidinone and a β-amino acid named AMPTD. Microsclerodermins F and H possess a (*R*)-tryptophan residue, whereas microsclerodermins G and I have a 2,3-dehydrotryptophan. AMPTD comprises a conjugated (*E*,*E*,*E*)-triene, which, for microsclerodermins H and I, is methylated at C10. In common with previously isolated microsclerodermins, the GABOB, Gly and Sar units are also present in microsclerodermins F-I. The hydroxylated pyrrolidinone unit of these natural products was readily dehydrated under acidic conditions to furnish the corresponding C2-C3 dehydro derivatives. Structural assignments of microsclerodermins F-I were based on NMR analysis and supporting chemical derivatisations and degradations conducted in a similar fashion to those outlined earlier (see Section 1.1.1).

1.1.4 Microsclerodermins J and K

In 2012, the Li group reported the structures of microsclerodermins J **11** and K **12**, which were isolated from the deep-water sponge *Microscleroderma herdmani*, collected in Mauritius.[2] Microsclerodermins J and K were tested for antifungal activity against

Candida albicans using the CLSI broth microdilution method. IC_{50} values for microsclerodermin J and K were found to be 9.0 and 5.3 μg/mL respectively.

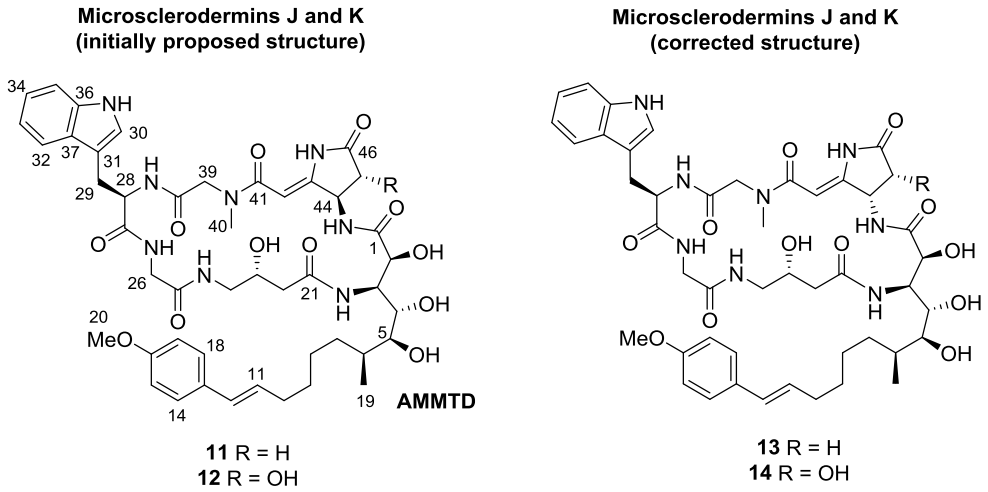


Figure 5. Microsclerodermins J and K.

The structures of these two new members were assigned by comparison of their NMR data to dehydromicrosclerodermin C and dehydromicrosclerodermin A. Only the (*R*)-tryptophan amino acid unit was rigorously assigned by degradation experiments. In the initial report, Li assigned the pyrrolidinone unit of both natural products as having the (44*R*)-configuration. This assertion was based on comparison of the NMR data of microsclerodermin J to that of dehydromicrosclerodermin C; it was speculated that microsclerodermin K shared the same stereochemistry at the pyrrolidinone unit. Subsequently, the Li group published a corrigendum, which stated that both natural products have the C44 (*S*)-configuration (structures **13** and **14**).[6] This reassignment was made by comparison of the NMR data of microsclerodermin K to that of dehydromicrosclerodermin A. However, no degradation experiments were conducted to provide further support for the absolute stereochemistry of the pyrrolidinone unit.

1.1.5 Microsclerodermins L and M

Microsclerodermins L and M *are not of marine origin* and were isolated by the Muller group from terrestrial myxobacteria.[4] Microsclerodermin L **15** was found in *Jahnella* and *Chondromyce*s myxobacteria, whereas microsclerodermin M **16** was isolated from *Sorangium* myxobacteria. Microsclerodermins L and M were tested against *Candida albicans* and showed MIC values of 18 μg/mL and 0.16 μg/mL respectively.

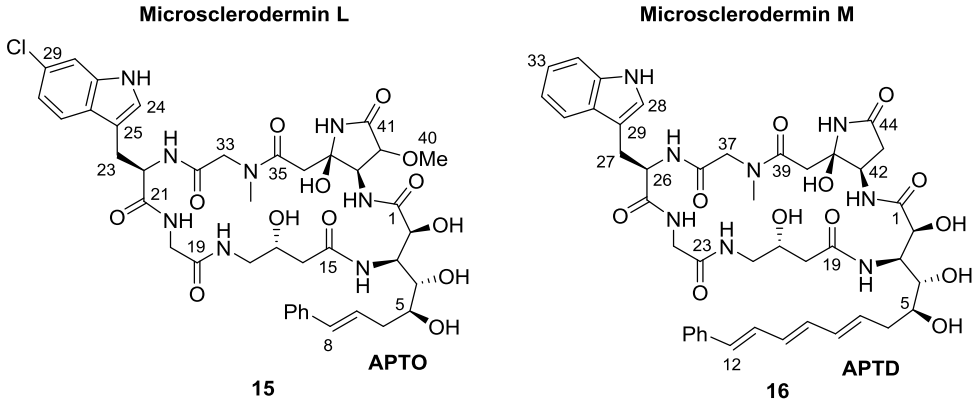


Figure 6. Microsclerodermins L and M.

The structures of both natural products were assigned based on NMR data and associated derivatisation and degradation experiments. The relative stereochemistry of the pyrrolidinone and β-amino acid units was supported by ROESY correlations, whereas the absolute configurations of each subunit were determined by degradation experiments and advanced Marfey analysis.[7] The structure of microsclerodermin L is very similar to microsclerodermin D except that it contains an additional methoxy group on the pyrrolidinone ring at C39. Notably, microsclerodermin D was also found in the same terrestrial myxobacteria species of *Jahnella* and *Chondromyces*. The configuration of the C39 stereocentre was not assigned because suitable enantiomerically pure reference

compounds could not be obtained for comparison to the degradation products. Microsclerodermin M contains amino acid residues that are common to previously reported members, apart from the β-amino acid residue (APTD), which in this case lacks a methyl group at the C6 position.

The discovery that microsclerodermins are present in terrestrial microorganisms was pre-dated by the isolation of two structurally similar natural products, pedeins A **17** and B **18**. These have a peptidic core that is identical to the microsclerodermins and were found in the terrestrial myxobacterium *Chondromyce*s *pediculatus*. Note that the structures in Figure 7 were taken from Muller's report[4] as, in the original isolation paper, the reported pyrrolidinone stereochemistry was unclear.[8]

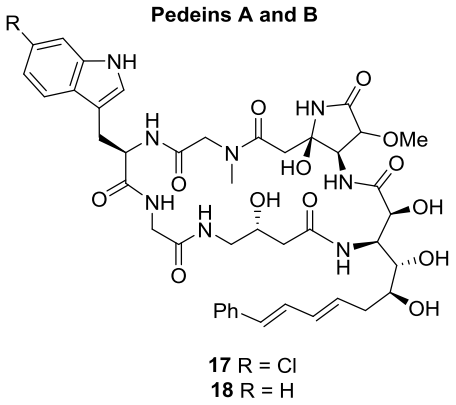


Figure 7. Pedeins A and B.

The discovery of microsclerodermins and pedeins in several myxobacteria is one of the few instances where the same family of natural products has been found in marine organisms and terrestrial bacteria. Moreover, the discovery of a group of terrestrial myxobacteria producing *exactly* the same compound as found in lithistid sponges (microsclerodermin D) fuels speculation about the actual biosynthetic origin of marine

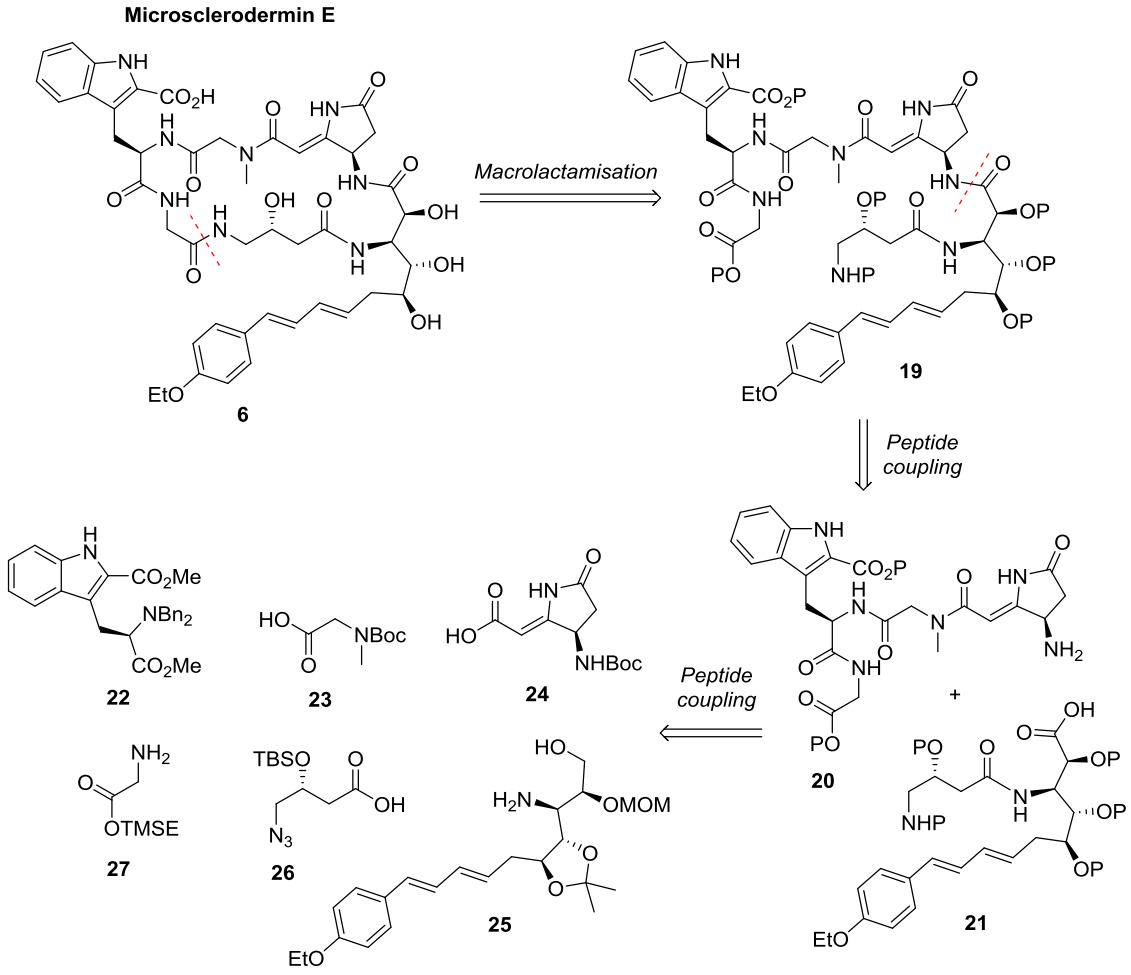
microsclerodermins. Muller proposed that the marine microsclerodermins actually originate from a myxobacterium phylogenetically related to the *Jahnella*, *Chondromyces* or *Sorangium* taxa living in symbiosis with the sponges from which the microsclerodermins were previously isolated.[3] In support of this hypothesis, studies of sponge metagenomes recently identified δ-proteobacteria in the sponge holobiont.[9] The phylogenetic tree presented in that work lists a clade containing nine myxobacterial species of terrestrial origin, including *Sorangium cellulosum* and *Chondromyces pediculatus*. These data underpin Muller's assumption that an evolutionary link exists between microsclerodermin biosynthesis in terrestrial and marine producers. The identification of an isolated *Jahnella* species from a soil sample collected from the same Philippine island where the *Microscleroderma* sponge was initially found suggests that the myxobacteria are washed into the ocean and adapt to symbiosis with the sponge. Based on these observations and the identification of two slightly different microsclerodermin biosynthetic gene clusters from two myxobacteria (*Jahnella* and *Sorangium*), the Muller group proposed a coherent model for microsclerodermin biosynthesis. To date, this is the only biosynthetic study reported on the microsclerodermins.[4]

1.2 Synthetic studies on the microsclerodermins

1.2.1 Total synthesis of microsclerodermin E by Ma

At the outset of the work described later, there was only one total synthesis of any microsclerodermin – microsclerodermin E **6**, as reported by the Ma group in 2003.[10] Ma's retrosynthesis involved disconnection of the macrocycle at the least hindered amide bond, which connects the Gly and GABOB units. The linear hexapeptide was constructed from two major fragments **20** and **21** (Scheme 3). Ma devised new approaches to the synthesis

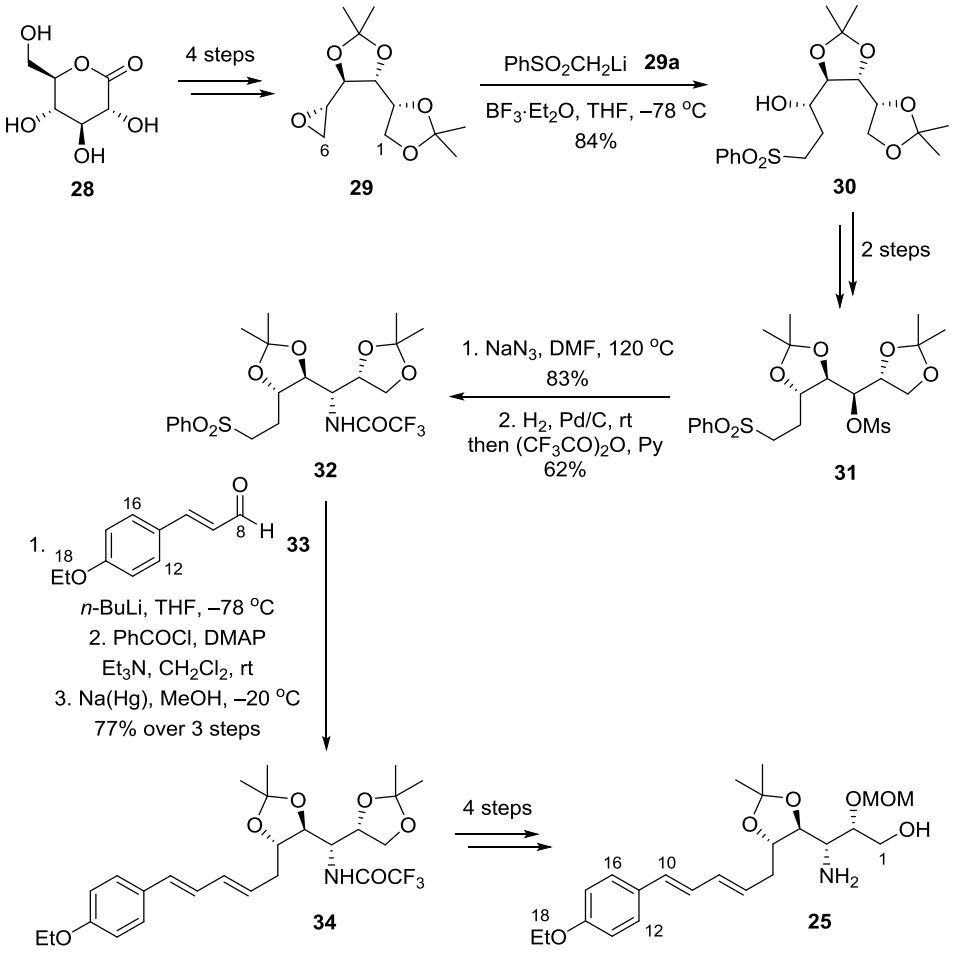
of the three amino acids that are not available from commercial sources: tryptophan-2-carboxylate **22**, pyrrolidinone **24** and AETD **25**. The synthesis of GABOB unit **26** was based on previous studies reported by Shioiri.[11]



Scheme 3. Retrosynthetic analysis of microsclerodermin E by Ma and co-workers.

The AETD amino acid was constructed from δ-gluconolactone **28** (Scheme 4), which contains all the required stereochemical information. The synthesis commenced with a four step conversion to epoxide **29**, which was opened with organolithium **29a** to afford sulfone **30**. Further transformations provided mesylate **31**, which was converted to

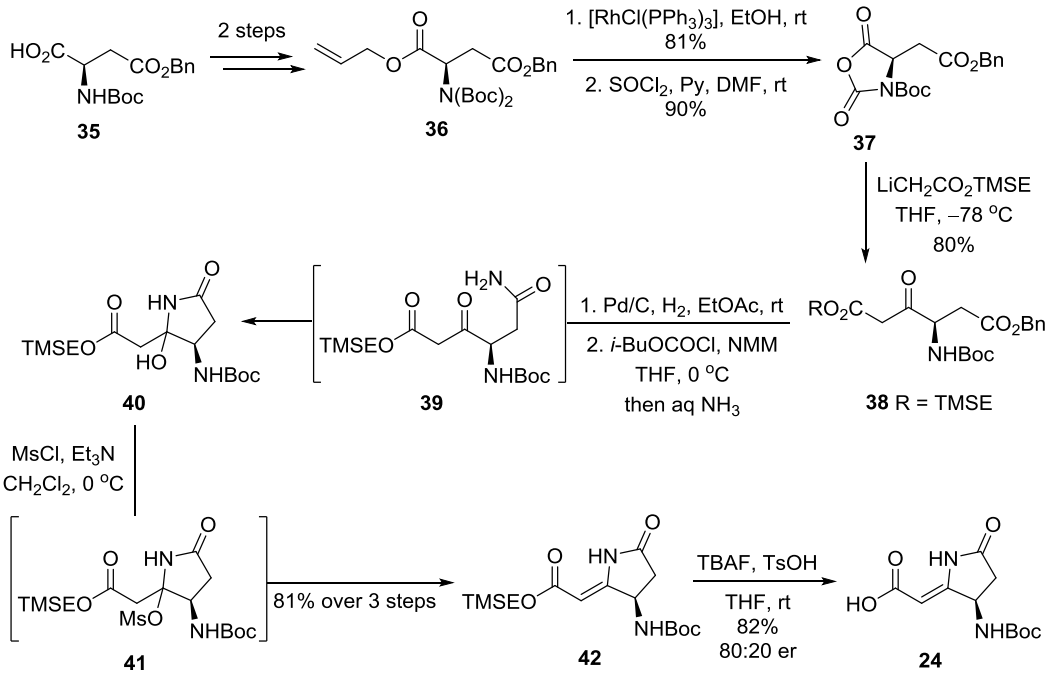
amide **32** by a sequence of S_N2 substitution with sodium azide, hydrogenation and acylation. Julia olefination of **32** with aldehyde **33** installed the C7-C18 diene moiety of **34**. A sequence of protecting group manipulations provided amino alcohol **25**, which was in the correct form for later steps in the total synthesis.



Scheme 4. Synthesis of AETD by Ma and co-workers.

Ma's synthesis of the pyrrolidinone unit **24** was based on a formal intramolecular condensation of the amide of **39** onto the ketone (Scheme 5). To enable this, aspartic acid derivative **35** was converted into urethane *N*-carboxyanhydride **37** *via* a four step sequence. Compound **37** was treated with the lithium enolate of 2-trimethylsilylethyl

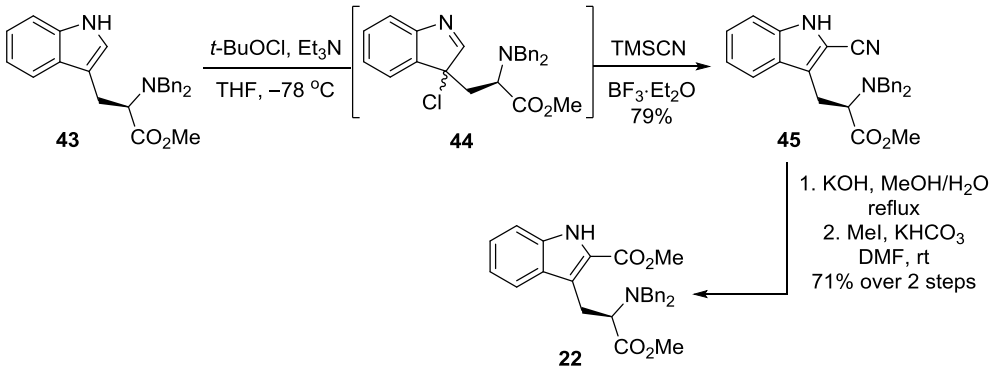
acetate to give β-keto ester **38**. Hydrogenolytic cleavage of the benzyl ester of **38** was followed by formation of amide **39** and spontaneous cyclisation to hydroxypyrrolidinone **40**. At this stage, elimination to **42** was achieved *via* the formation of mesylate **41**. Ma noted that pyrrolidinone **42** was susceptible to epimerisation when exposed to basic reagents, including TBAF, which was used to remove the TMSE group. For this step, racemisation was partially suppressed by buffering with TsOH, and, in this way, **24** could be isolated as a 4:1 mixture of (*R*)- and (*S*)-enantiomers.



Scheme 5. Synthesis of pyrrolidinone **24** by Ma and co-workers.

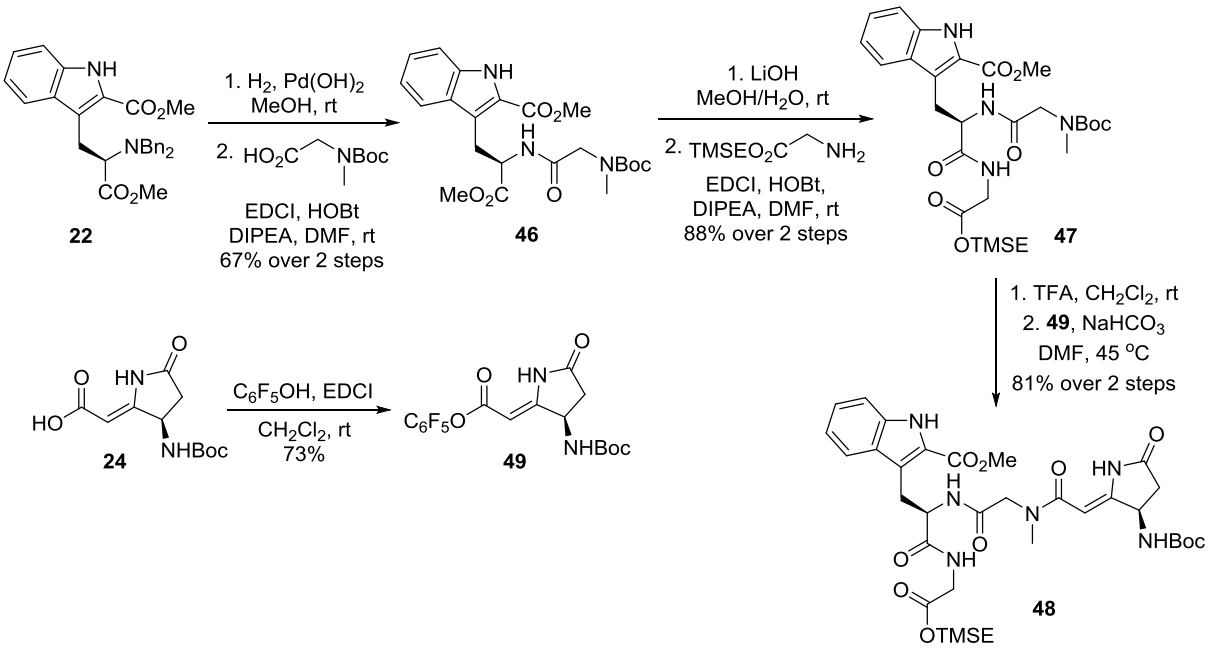
Tryptophan-2-carboxylic acid **22** was synthesised according to a protocol reported by Danishefsky (Scheme 6).[12] This involved treatment of D-tryptophan derivative **43** with *tert*-butyl hypochlorite to generate **44**. This was treated *in situ* with trimethylsilylcyanide

to install the nitrile group at the indole C2 position. Nitrile **45** was then hydrolysed under basic conditions and the resulting acid was converted into methyl ester **22**.



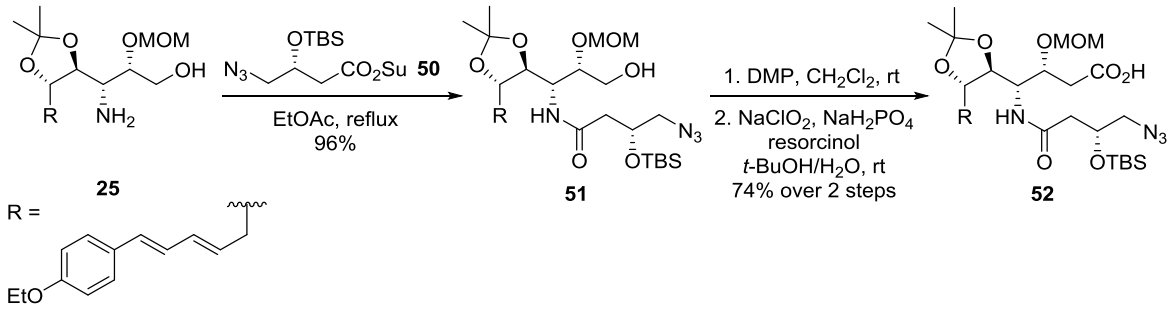
Scheme 6. Synthesis of tryptophan-2-carboxylate **22** by Ma and co-workers.

At this stage, tryptophan derivative **22** was coupled to the sarcosine and glycine units to afford **47**. Both amide bond formations were accomplished using EDCI and HOBt as activating reagents (Scheme 7). The pyrrolidinone amino acid was transformed into pentafluorophenol activated ester **49** for further connection with the Gly-Trp-Sar tripeptide **47**. This was readily achieved to afford the northern hemisphere **48** of microsclerodermin E in 81% yield over two steps.



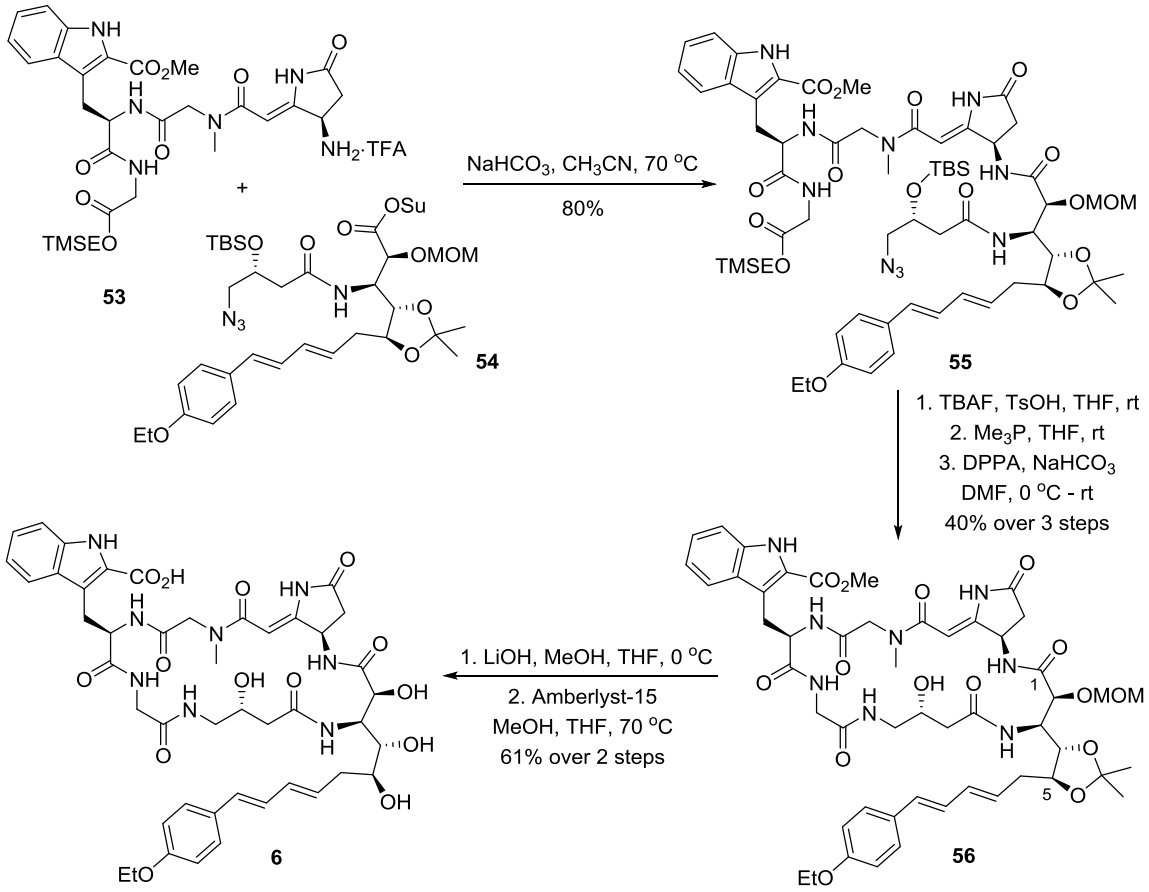
Scheme 7. Synthesis of tetrapeptide **48** by Ma and co-workers.

AETD amino alcohol **25** was coupled with the GABOB fragment *via* formation of GABOB-OSu activated ester **50**. Conversion of the primary alcohol of **51** to AETD-GABOB acid **52** was achieved by initial formation of the aldehyde (Dess-Martin) and subsequent oxidation under Pinnick conditions (Scheme 8).



Scheme 8. Synthesis of AETD-GABOB dipeptide **52** by Ma and co-workers.

The northern hemisphere of microsclerodermin E **53** was connected with the AETD-GABOB dipeptide *via* OSu activated ester **54** (Scheme 9). The resulting adduct **55** was treated with TBAF/TsOH in order to liberate the *C*-terminus and the GABOB hydroxyl group; during this process, partial epimerisation (4:1 dr) of the pyrrolidinone stereocentre took place (*cf.* **42** in Scheme 5). The amine group of the GABOB fragment had been masked through the synthetic sequence as an azide; reduction of this was achieved with trimethylphosphine and subsequent macrolactamisation, using DPPA, furnished macrocyclic peptide **56** in 40% over three steps. At this stage, the minor diastereoisomer that arose from the TBAF reaction was separated by column chromatography.



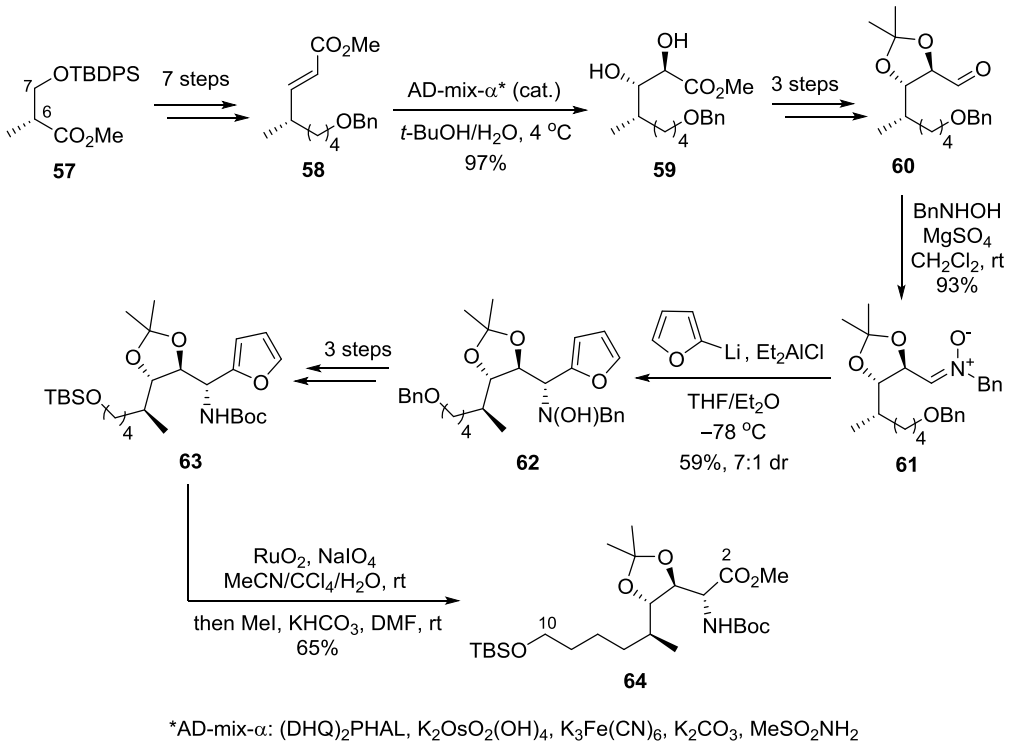
Scheme 9. Completion of the synthesis of microsclerodermin E by Ma and co-workers.

Hydrolysis of the methyl ester of **56** to the indole-2-carboxylic acid (LiOH) proceeded smoothly and, surprisingly, epimerisation of the pyrrolidinone unit was not observed under these conditions. The final step, which involved concomitant cleavage of the C2 methoxymethyl ether and the C4-C5 acetonide using Amberlyst-15, afforded microsclerodermin E **6** in 62% yield from **56** (two steps). The data of the synthetic material was in good agreement with that of the natural product.

1.2.2 Studies towards microsclerodermin B by Shioiri

The Shioiri group has reported several studies towards the synthesis of microsclerodermin B. These include two approaches to the construction of the AMMTD fragment,[13,14] a synthesis of a protected form of tryptophan-2-carboxylic acid,[15,11] and routes to the pyrrolidinone unit[15,11] and the GABOB fragment.[15,11]

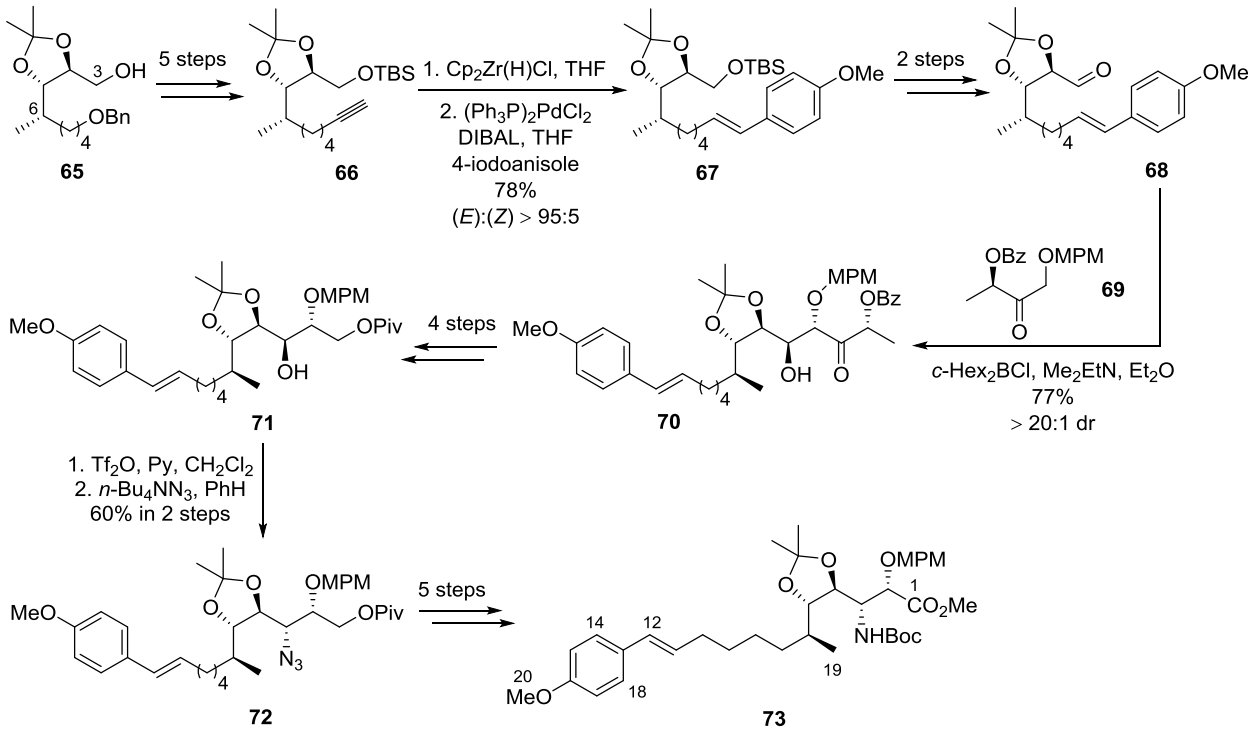
The Shioiri group's initial studies on the synthesis of AMMTD C2-C10 building block **64** are shown on Scheme 10. The key steps in the sequence are: 1) Sharpless asymmetric dihydroxylation of acrylate **58** and 2) Dondoni diastereoselective furan addition to nitrone derivative **61**. Acrylate **58** was synthesised in seven steps from Roche ester derivative **57**, which bears the requisite C6 stereocentre. Sharpless asymmetric dihydroxylation, using AD-mix-α, proceeded smoothly to afford diol **59** in high diastereopurity. This was protected and advanced to nitrone **61** over four steps. Addition of 2-lithiofuran generated adduct **62**, with the anticipated stereochemistry for the C3 stereocentre.[16] Three step conversion to *N*-Boc carbamate **63** was followed by oxidative cleavage of the furan moiety (cat. RuO_4, $NaIO_4$) and methylation of the incipient carboxylic acid to afford ester **64** in good overall yield.



*AD-mix-α: $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$

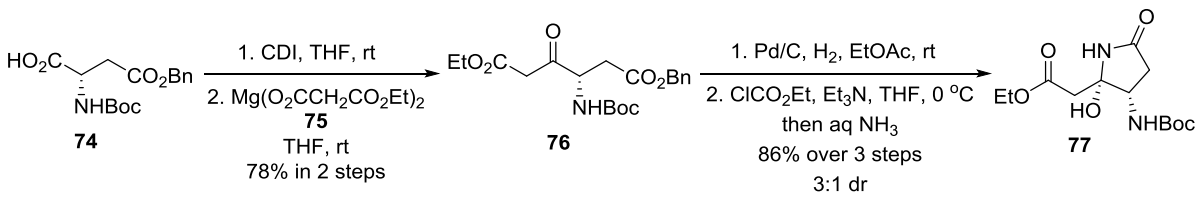
Scheme 10. Shioiri's initial studies towards AMMTD.

Subsequent work from the Shioiri group outlined a strategy to introduce the C11-C20 styrenic moiety. Intermediate **65**, which had previously been prepared from **59**, was converted into alkyne **66** *via* a five step sequence. Regioselective hydrozirconation using the Schwartz reagent was followed by Pd-catalysed Negishi cross-coupling[17] with 4-iodoanisole to afford **67**, which contains the C11-C20 styrenic moiety. Advancement to aldehyde **68** was followed by an aldol reaction with the boron enolate of **69**, which installed the C2 hydroxyl group of **70** with the correct stereochemistry. Subsequent steps generated secondary alcohol **71**, which was converted to azide **72** *via* the corresponding triflate. At this stage, a series of oxidation level adjustments and protecting group manipulations afforded AMMTD precursor **73** in five further steps (Scheme 11).



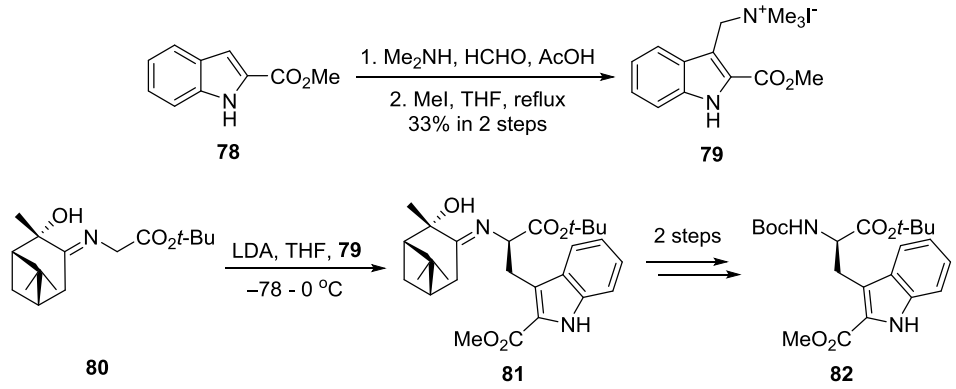
Scheme 11. Shioiri's synthesis of protected AMMTD.

For the synthesis of the pyrrolidinone unit **77** of microsclerodermin B Shioiri employed an intramolecular aminal formation strategy (*cf.* **40** in Ma's synthesis, Scheme 5).[15,11] For this, aspartic acid derivative **74** was transformed into ketoester **76** in two steps *via* activation of the carboxylate with CDI and subsequent displacement with the magnesium enolate of malonic acid monoester **75** (Scheme 12). Subsequent steps, which are similar to those developed by Ma (Scheme 5), involved benzyl ester cleavage (H_2, Pd/C), primary amide formation and spontaneous cyclisation to furnish aminal **77** in 3:1 dr.



Scheme 12. Shioiri's synthesis of the pyrrolidinone unit **77**.

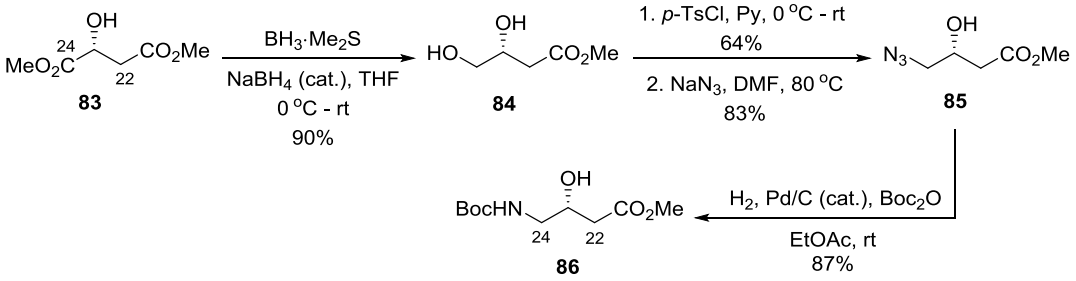
Asymmetric alkylation of chiral Schiff base **80** with ammonium salt **79**, derived from indole-2-carboxylic acid methyl ester **78**,[15,11] was employed as a key step in the synthesis of tryptophan-2-carboxylate **82** (Scheme 13). Here, the approach of electrophile **79** to the enolate of **80** is controlled by the chiral auxiliary to afford adduct **81** with high diastereoselectivity.[18] Subsequent advancement to carbamate **82** was achieved by a sequence of imine hydrolysis and carbamate formation (Boc_2O).



Scheme 13. Synthesis of tryptophan-2-carboxylate **82** by Shioiri and co-workers.

Shioiri's synthesis of the GABOB unit used (*R*)-dimethyl malate **83** as a starting material.[15,11] Directed reduction of di-ester **83** with $BH_3 \cdot Me_2S$ generated mono-ester **84** with high selectivity. Selective mono-tosylation of the primary alcohol and displacement with sodium azide delivered product **85** in good overall yield (Scheme 14). Conversion of

azide **85** to Boc-carbamate **86** was achieved using a one-pot hydrogenation/Boc-protection protocol. Compound **86** is a protected form of GABOB.



Scheme 14. Synthesis of GABOB **86** by Shioiri and co-workers.

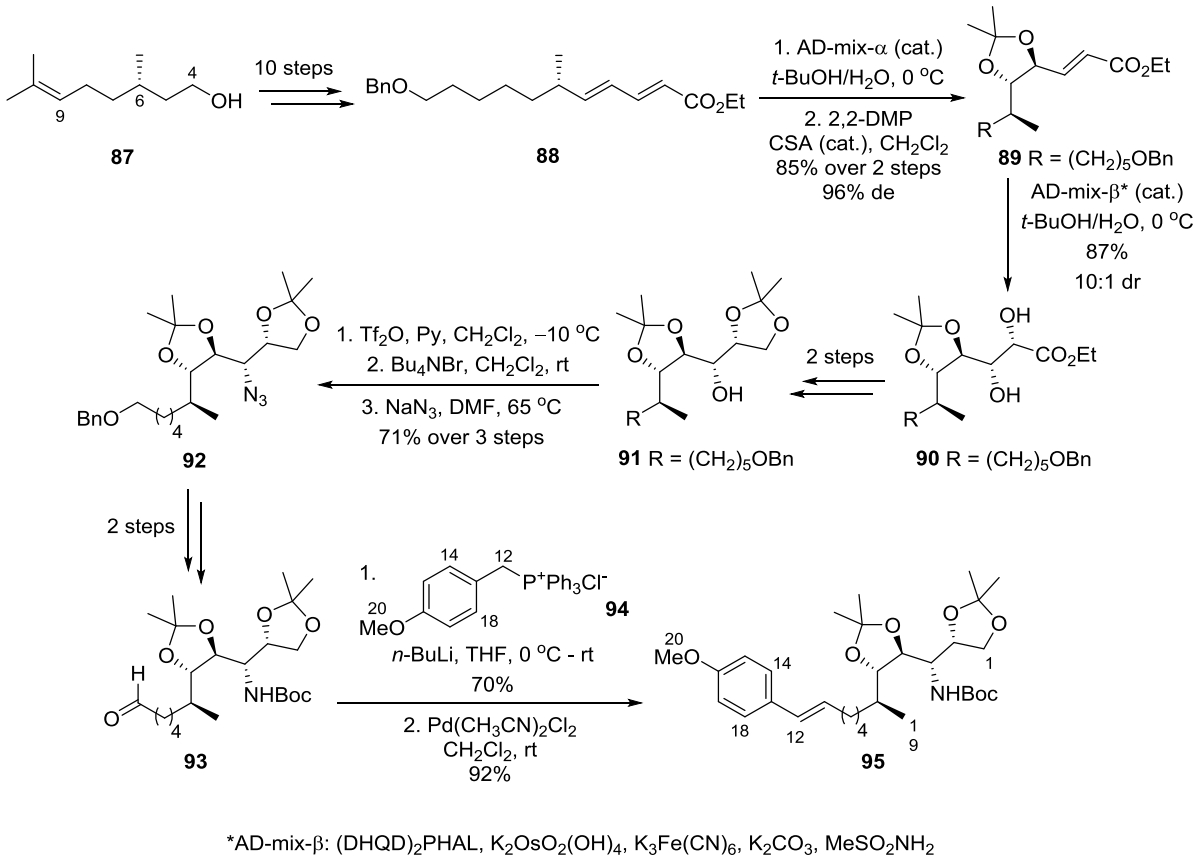
To date, the Shioiri group has published syntheses of all the non-commercial amino acids of microsclerodermin B (**73**, **77**, **82** and **86**). Nevertheless, they have not yet reported the total synthesis of this natural product.

1.2.3 Studies towards synthesis of the β-amino acid residues

The most challenging unit to prepare of any microsclerodermin is the polyhydroxylated β-amino acid residue, as this possesses four or five contiguous stereocentres. Several groups have reported their studies towards the synthesis of these amino acids, where various methodologies have been employed to introduce the diol and amino alcohol moieties.

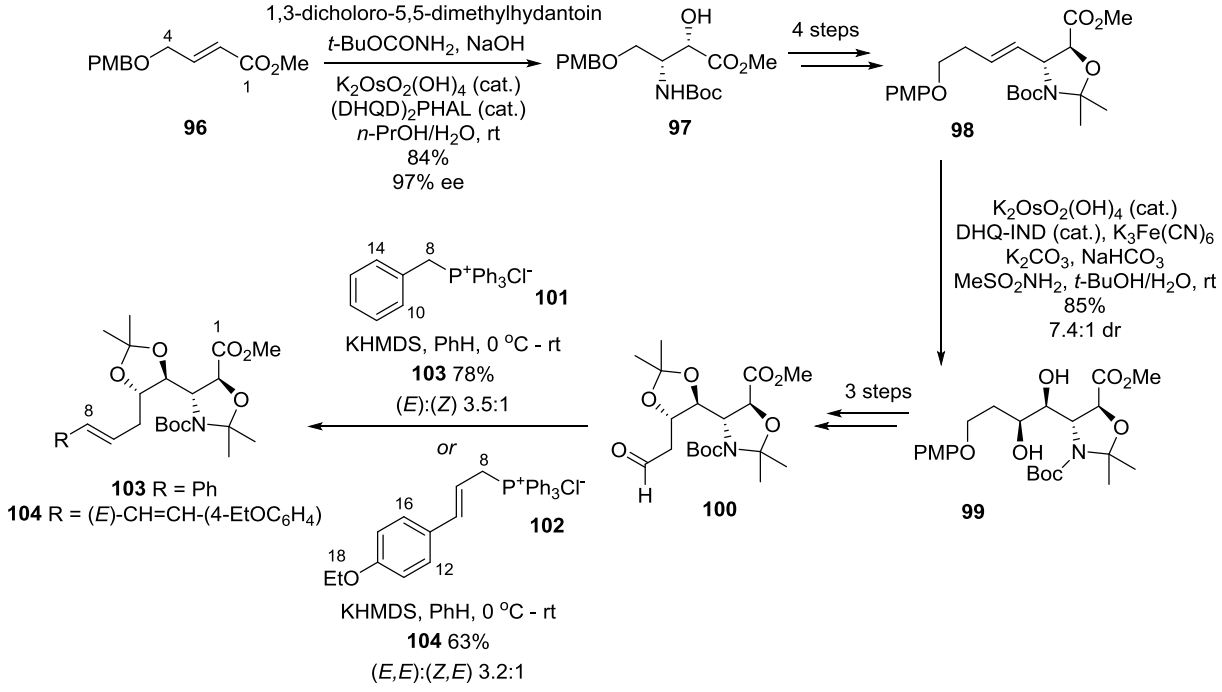
One of the earliest reports was by Chandrasekhar in 2006, who developed a synthesis of the AMMTD fragment, which is present in microsclerodermins A **1**, B **2**, J **13** and K **14**.[19] (*S*)-(−)-Citronellol **87**, which bears the requisite C6 stereocentre, was chosen as the starting point (Scheme 15). This was converted to diene **88** in ten steps. Subsequently, an iterative Sharpless

dihydroxylation/protection strategy was employed to generate **90**. Each dihydroxylation was under catalyst control, using AD-mix-α for the first and AD-mix-β for the second. Subsequent steps involved triflation of secondary alcohol **91** to facilitate nucleophilic amination with overall stereoretention. This was achieved *via* S_N2 displacement of the triflate by bromide (Bu_4NBr) and subsequent S_N2 displacement of the bromide with azide (NaN_3). An alternative approach to installing the amino-substituent by Sharpless asymmetric aminohydroxylation of acrylate **89** was unsuccessful. The C11-C20 styrenic moiety was introduced using a two-step procedure, which employed a (*Z*)-selective Wittig reaction on aldehyde **93** with the ylide derived from **94**. Subsequent isomerisation of the (*Z*)-alkene to the desired (*E*)-isomer **95** was achieved using a palladium catalyst.[20]



Scheme 15. Synthesis of AMMTD by Chandrasekhar and co-workers.

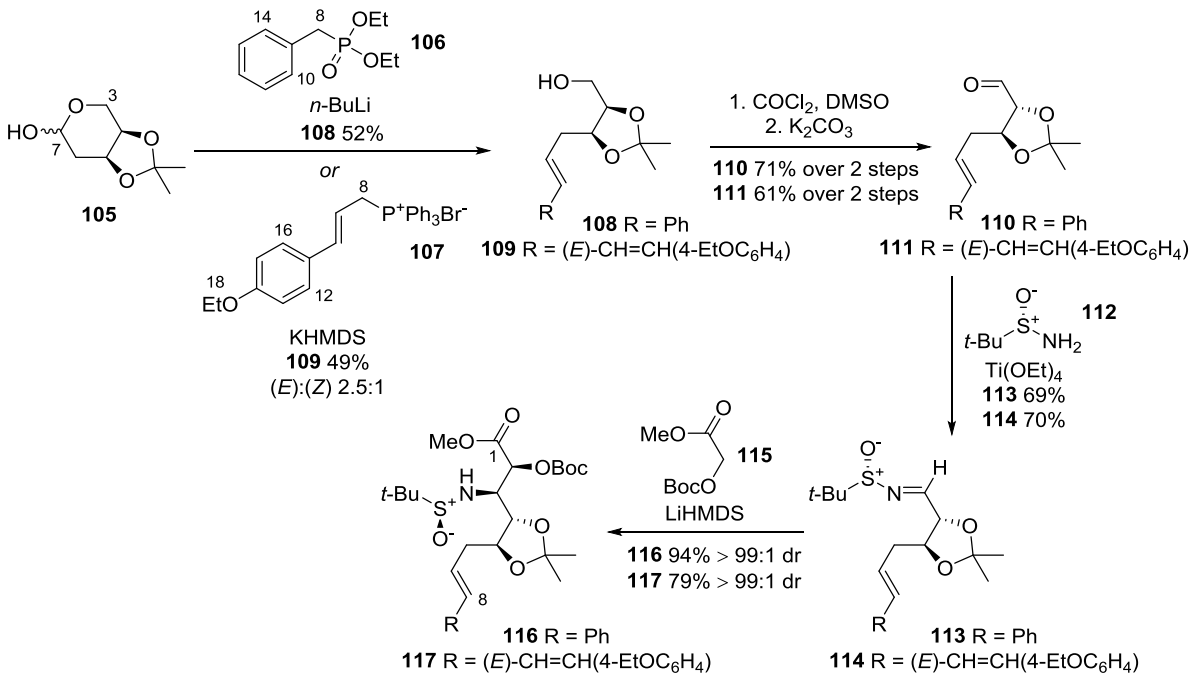
The APTO and AETD β-amino acids have been subject of greater synthetic attention, perhaps because they contain four stereocentres rather than the five present in AMMTD and AMPTD. The first synthesis of APTO and AETD was published by McLeod in 2007.[21] The key steps to build the core of these amino acids were based on Sharpless aminohydroxylation and dihydroxylation methodologies. The aminohydroxylation protocol was applied to acrylate **96** and provided product **97** with excellent regio- and stereoselectivity (Scheme 16). Further steps involved formation of alkene **98**, which was the precursor for the Sharpless dihydroxylation reaction. This process was conducted using rarely employed alkaloid ligand DHQ-IND to obtain diol **99** in 85% yield and 7.4:1 dr. Advancement to aldehyde **100** was followed by *trans*-selective Wittig olefinations to install either the C7-C14 styrene of APTO **103** and or the C7-C18 diene of AETD **104**.



Scheme 16. Synthesis of protected APTO and AETD by McLeod and co-workers.

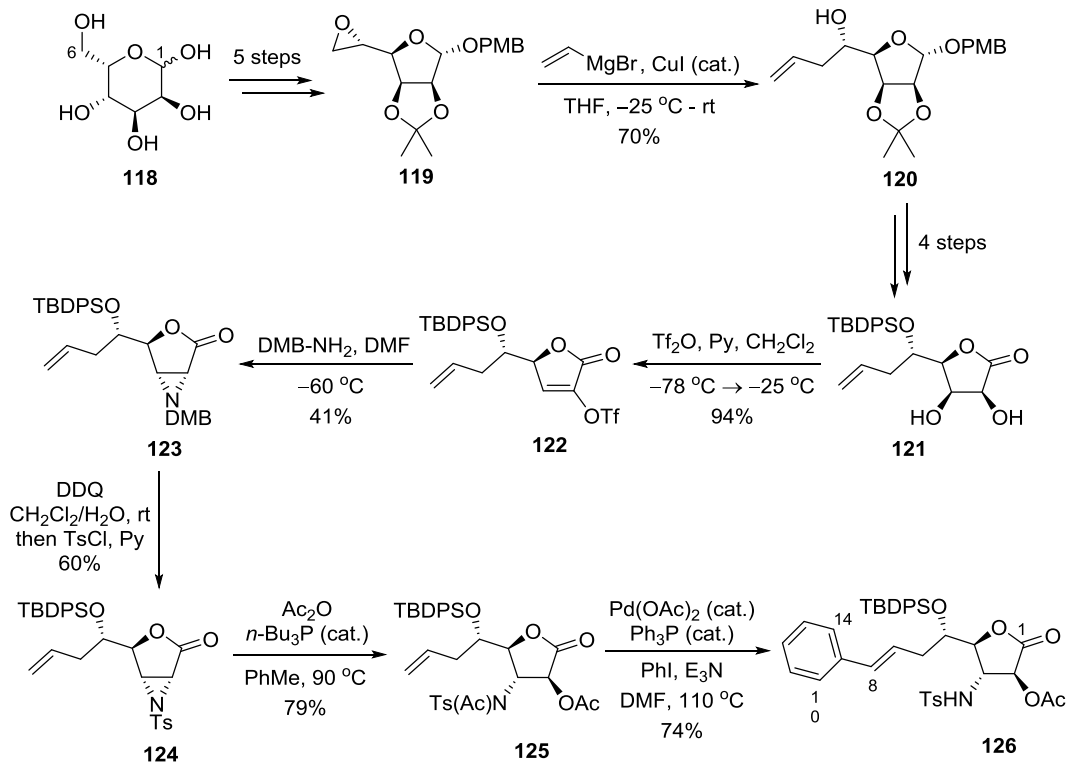
In 2008 Aitken published a concise route to the APTO and AETD amino acids using, as a key step, Mannich addition of α-hydroxyester **115** to Ellman sulfinimines **113** and **114**.[22] Using this approach, APTO **116** and AETD **117** were synthesised in just five steps from the readily available 2-deoxy-D-ribose acetonide **105** (Scheme 17). Lactol **105** was treated with the anion of either phosphonate **106** (for APTO) or phosphonium salt **107** (for AETD) to install the C8-C14 or C8-C18 side-chains. Swern oxidation of the primary alcohols of **108** and **109** was followed by base induced inversion of the C2 stereocentre to obtain diastereoisomers **110** and **111**. Condensation with chiral sulfinamide **112** was promoted using $Ti(OEt)_4$[23] to afford chiral sulfinimes **113** and **114**, which were then reacted with enolate of hydroxyester **115** to obtain fully protected forms of APTO **116** and AETD **117** in high yield. Studies on the latter step showed that the highest dr and yield required the *tert*-butyl group on sulfur, in combination with a methyl ester and *O*-Boc group on **115**.

Another synthesis of the APTO unit was reported by Dodd in 2009.[24] The strategy was based on regioselective opening of the aziridine of **124** by acetate to build the 1,2-amino alcohol moiety at C2-C3 (Scheme 18). The key aziridine **124** was constructed from commercially available sugar L-gulose **118**, which bears the correct stereochemistry at C4 and C5. Compound **118** was converted into epoxide **119** in five steps and this was opened with the organocuprate generated from vinyl magnesium bromide to install the alkene of **120**.



Scheme 17. Synthesis of APTO and AETD by Aitken and co-workers.

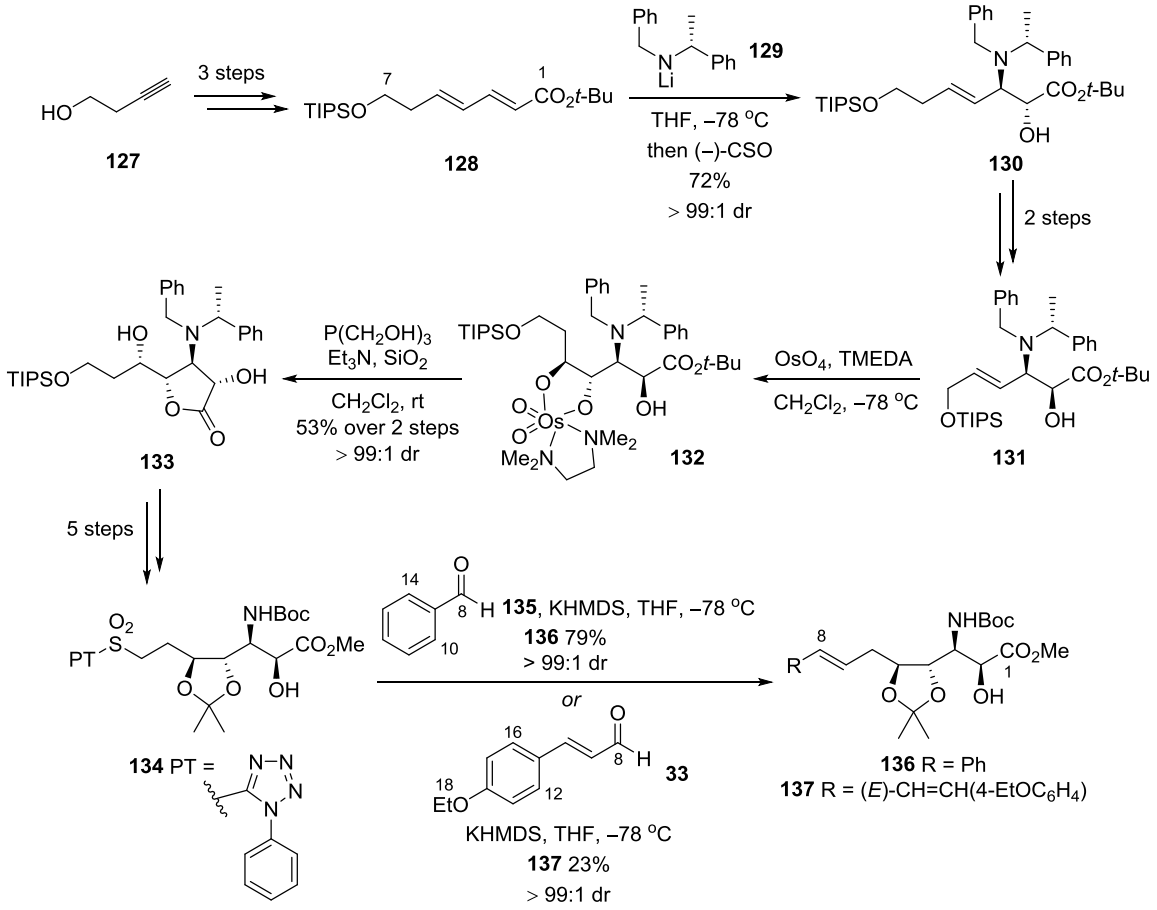
Further steps generated lactone **121**, which was subjected to an aziridination protocol previously developed in the Dodd group.[25] Accordingly, bis-triflation of diol **121** was followed by β-elimination to the cyclic acrylate. Conjugate addition of DMB-NH_2 was then followed by intramolecular displacement of the C2 triflate to generate aziridine **123**. At this stage, replacement of the electron rich *N*-dimethoxybenzyl moiety with an electron-withdrawing *N*-tosyl group was required. C2 selective opening of the resulting aziridine **124** with acetate was achieved in high regioselectivity using catalytic tri-*n*-butylphosphine and excess acetic anhydride. Installation of the terminal phenyl moiety onto product **125** was performed using a Heck reaction with iodobenzene. Styrene **126** is a protected form of APTO, which may be appropriate for direct peptide bond formation in subsequent steps towards, for example, microsclerodermins C, D and L.



Scheme 18. Synthesis of APTO by Dodd and co-workers.

Recently, in 2013, the Davies group published syntheses of the APTO and AETD amino acids.[26] Their approach to the construction of the core was based on a diastereoselective conjugate addition/enolate oxidation cascade to install the C2-C3 amino alcohol functionality (Scheme 19). Key diene **128** was obtained in three steps from commercially available 3-butyn-1-ol **127**. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **129** to diene **128** was followed by oxidation of the *in situ* generated lithium β-amino enolate with (−)-CSO to afford amino alcohol **130** in good yield and excellent diastereoselectivity. The configuration of the C2 hydroxyl group was inverted *via* a two-step procedure to generate diastereoisomer **131**. *Syn*-dihydroxylation of the C4-C5 olefin was accomplished using the Donohoe protocol,[27] which involved initial cycloaddition with OsO_4/TMEDA to generate osmate ester-TMEDA

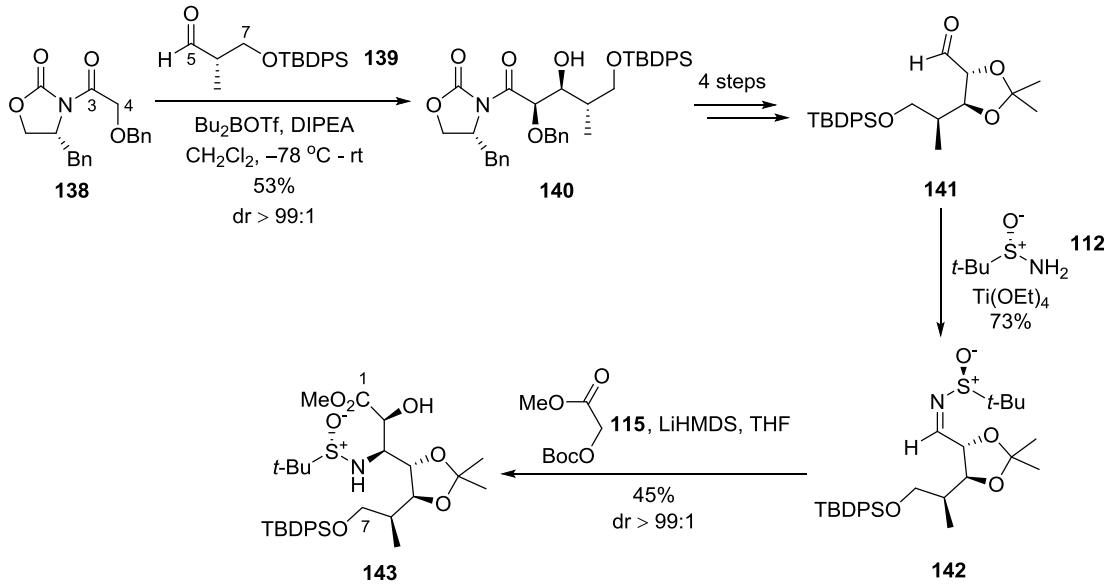
complex **132**. This was cleaved to the diol, which afforded lactone **133** by cyclisation of the C4 hydroxyl onto the *tert*-butyl ester. Adduct **133** was converted to Julia-Kocienski precursor **134** to enable the installation of the C7-C14 styrenic unit or C7-C18 diene. Reaction of the potassium anion of **134** with aldehyde **135** or **33** provided protected forms of APTO **136** and AETD **137**.



Scheme 19. Synthesis of protected APTO and AETD by Davies and co-workers.

In 2009 Williams reported studies towards the AMPTD fragment of microsclerodermins H and I.[28] In this work, the synthesis of the C2-C6 stereopentad core of AMPTD was accomplished, albeit without introduction of the triene side-chain

(Scheme 20). The key steps in this synthesis were: 1) a *syn*-aldol reaction of Evans oxazolidinone **138** with aldehyde **139** to install the C4-C5 diol and 2) Mannich addition of glycolate **115** to imine **142** to build the C2-C3 amino alcohol; this latter step is analogous to that previously reported by Aitken.[22]



Scheme 20. Synthesis of the AMPTD stereopentad by Williams and co-workers.

The synthetic studies summarised above highlight several key issues. Significantly, there is only one reported total synthesis of any microsclerodermin – microsclerodermin E.[10] This member contains an unsaturated pyrrolidinone core, which makes it inherently less challenging than those that contain sensitive hydrated variants (e.g. microsclerodermins A-D, F-I, L and M). Thus, methodology that enables the introduction of the aminal moiety onto the pyrrolidinone unit would be valuable. Furthermore, to date, there are only two reported routes to AMMTD. One was developed by Shioiri and proceeded in a longest sequence of 31 steps,[14] and the other was reported by Chandrasekhar.[19] This latter synthesis proceeds in fewer steps (26 in the longest linear

sequence), but the final compound was at the wrong C1 oxidation level for further assembly steps. Therefore the development of shorter and more efficient routes to the synthesis of microsclerodermin β-amino acids containing five stereocentres (AMMTD and AMPTD) is also of interest.

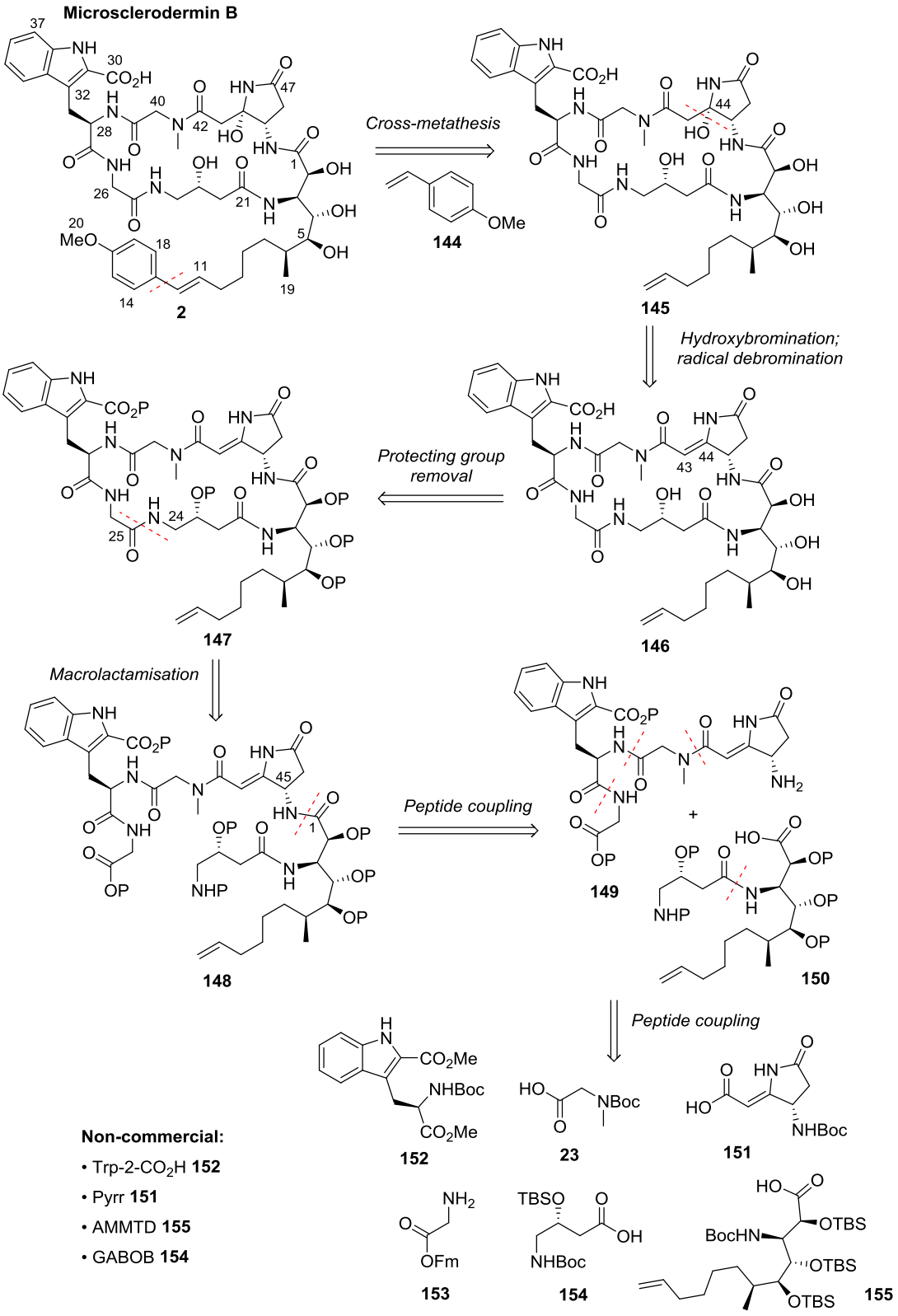
1.3 Project aims and retrosynthetic analysis of microsclerodermin B

Studies towards the synthesis of the microsclerodermins have been ongoing in the Donohoe group since 2007, with the main target being microsclerodermin B **2**. The first aim of the project described here was completion of the synthesis of the AMMTD unit. Preliminary studies on the synthesis of the AMMTD fragment were performed by Dr Akshat Rathi, but major improvements to the efficiency of the sequence were required, and the final steps had not been developed. The northern hemisphere **149** of microsclerodermin B can be derived from a pyrrolidinone unit with unsaturation at C43-C44; a route to this, which provides material ready for coupling, had been developed by Dr Robert Pullin and Dr Christian Winter. Thus, the second major aim was connection of the northern hemisphere **149** to the rest of the amino acid units and subsequent elaboration to the target using an "end-game" strategy outlined below.

The retrosynthetic analysis of microsclerodermin B begins by considering installation of the pyrrolidinone C44 hydroxyl group. As discussed earlier, this functionality is extremely sensitive to acidic or basic conditions, and, as such, should be introduced at a late stage. For this, a hydration methodology had been developed on model systems, which involved hydroxybromination of an alkylidene pyrrolidinone double bond and subsequent radical debromination (for more details see Chapter 4). In order to perform this process selectively, it was decided that the electron rich styrenic moiety should be

installed after hydration of the pyrrolidinone unit to avoid competing hydroxybromination of the styrene double bond. It was proposed that this could be introduced under neutral conditions using Ru-catalysed alkene cross-metathesis of **144** and **145**. With these considerations in mind, the "end-game" strategy required cyclic deprotected peptide **146**, which contains a terminal alkene on the AMMTD unit and unsaturation at the pyrrolidinone core (Scheme 21).

"End-game" precursor **146** could be obtained from protected cyclic peptide **147** by cleavage of the hydroxyl and ester protecting groups. Macrolactamisation at the least hindered C25-N24 site could be performed on linear substrate **148**. Disconnection of linear hexapetide **148** at C1-N45 reveals two major fragments: tetrapeptide **149** and AMMTD-GABOB dipeptide **150**. These fragments can be disconnected further at the amide bonds to provide single amino acids: tryptophan-2-carboxylate **152**, sarcosine **23**, pyrrolidinone **151**, AMMTD **155**, GABOB **154** and glycine **153**. Four of these amino acids, namely tryptophan **152**, pyrrolidinone **151**, AMMTD **155** and GABOB **154** are not commercially available. The synthetic approach to the AMMTD subunit is outlined in Chapter 2. Synthesis of the other three non-commercial amino acids is described in Chapters 3 and 4.



Scheme 21. Retrosynthetic analysis of microsclerodermin B.

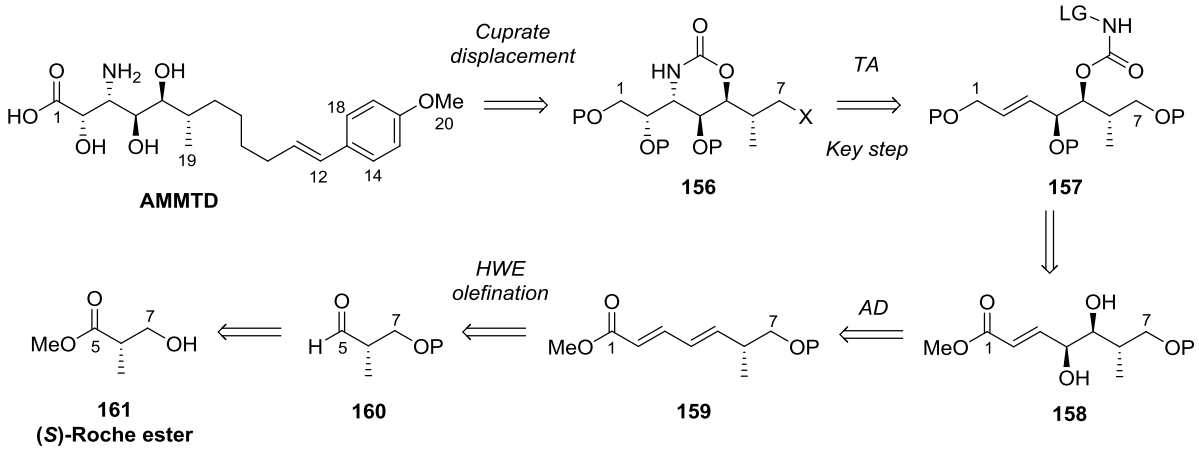
Chapter 2 Synthesis of the AMMTD β-amino acid

2.1 Retrosynthetic analysis of the AMMTD β-amino acid

The polyhydroxylated β-amino acid residue AMMTD is present in four members of the microsclerodermin family, namely microsclerodermins A, B, J and K. It constitutes the C1-C20 region of these natural products and represents the most challenging motif, consisting of five contiguous stereocentres and an aliphatic side-chain. Of particular interest was the 1,2-aminoalcohol moiety at C2 and C3, as this could potentially be accessed using group methodology based on the tethered aminohydroxylation reaction (TA).[29] Thus the retrosynthetic strategy for AMMTD was designed to incorporate the TA as one of the key steps.

The most important aspect of the retrosynthetic analysis was late-stage installation of the aliphatic C8-C20 side-chain, such that modification of the AMMTD core could be exploited for the synthesis of different members of the microsclerodermin family (see Figure 4 for the structure of the AMPTD amino acid in microsclerodermins F-I). Additionally, this approach removed the complication of carrying the C11-C20 styrenic moiety through a series of olefin 1,2-difunctionalisations, which were planned as earlier steps in the synthesis. It was envisaged that introduction of the C8-C12 side-chain could be achieved by organocuprate displacement of electrophile **156** (Scheme 22). The key step in construction of AMMTD – installation of the 1,2-aminoalcohol moiety at C2 and C3 – could be performed *via* a regio- and stereoselective TA reaction involving alkene **157**. This in turn would arise from selective installation of the requisite carbamate onto diol **158**. For this intermediate, installation of the two hydroxyl groups at C4 and C5 would exploit the

Sharpless asymmetric dihydroxylation method (AD). This could be performed regioselectively on diene **159**, which would be generated by (*E*)-selective Horner-Wadsworth-Emmons olefination of aldehyde **160**. Aldehyde **160** would arise from commercially available (*S*)-Roche ester **161**, which incorporates the C6 methyl-substituted stereocentre.

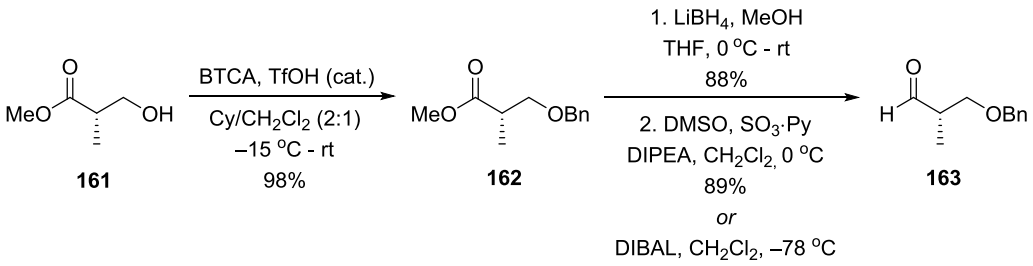


Scheme 22. Retrosynthetic analysis of AMMTD.

2.2 Synthesis of diol 158

The synthesis of AMMTD was pursued according to the retrosynthetic plan outlined in Scheme 22, and was guided further by preliminary results obtained by Dr Akshat Rathi.[30] The first step towards the key diene **167** involved *O*-benzylation of (*S*)-Roche ester **161** using benzyl 2,2,2-trichloroacetimidate (BTCA) under acid catalysed conditions (TfOH); basic conditions were avoided to mitigate issues associated with methyl ester hydrolysis.[31] Reduction of methyl ester **162** to aldehyde **163** could be achieved by two different approaches. A two-step procedure involved reduction of **162** to alcohol using $LiBH_4$, followed by Parikh-Doering oxidation, which delivered aldehyde **163**

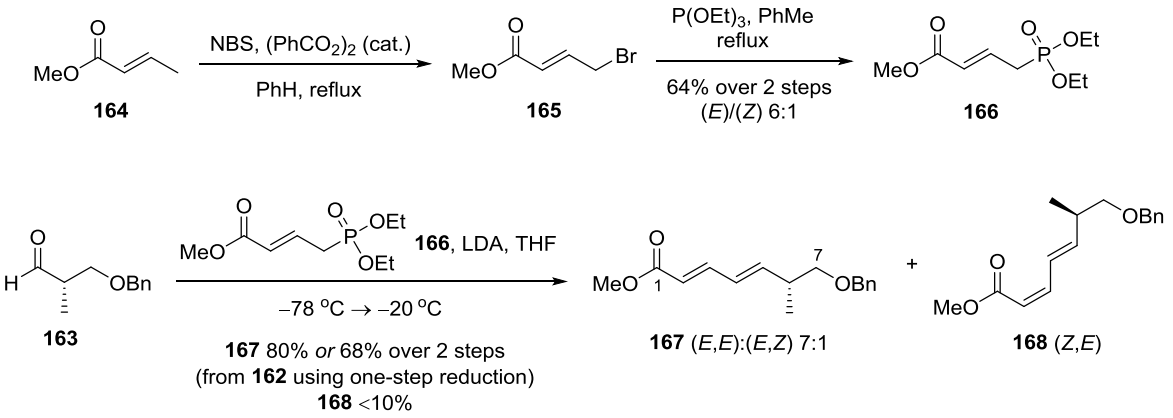
in 78% yield (two steps). Alternatively, low temperature reduction of **162** with 1.0 equivalent of DIBAL afforded **163** directly and in acceptable purity for advancement to subsequent steps (Scheme 23).[32]



Scheme 23. Synthesis of aldehyde **163**.

Mulzer and co-workers have reported high (*E*)-selectivity for the synthesis of a diene analogous to **167** under Horner-Wadsworth-Emmons olefination conditions, using phosphonate **166**.[33] The requisite phosphonate **166** was synthesised in two steps by Wohl-Ziegler bromination (NBS, cat. $(PhCO_2)_2$) of methyl crotonate, and Arbuzov reaction of the resulting allylic bromide (Scheme 24).[34] Treatment of **163** with the lithium enolate of **166** afforded **167** in 80% yield and as a 7:1 mixture of (*E*,*E*) ($^3J_{H4\text{-}H5}$ = 15.4 Hz) and (*E*,*Z*) ($^3J_{H4\text{-}H5}$ = 10.8 Hz) geometric isomers. Interestingly, during purification of the desired diene **167** (as an inseparable mixture of (*E*,*E*) and (*E*,*Z*) isomers) a small amount of a side-product (*Z*,*E*)-**168** was also isolated. This presumably forms from (*Z*)-**166**, which is likely generated by double bond isomerisation during the radical bromination. In initial studies, a key issue was partial epimerisation of the C6 stereocentre of **163** under the olefination conditions, however, it was found that this could be suppressed by performing the reaction at −20 °C (Scheme 24). Using these conditions, the enantiopurity of diene **167**

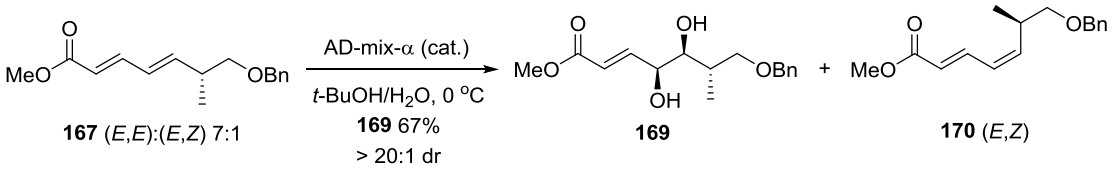
was >95% ee; this was determined by a sequence of *O*-debenzylation (to the primary alcohol) and derivatisation to the Mosher's esters (see the Experimental section).



Scheme 24. Synthesis of diene **167**.

Installation of the hydroxyl groups at the C4 and C5 positions of **167** was achieved *via* catalyst controlled diastereoselective Sharpless *syn*-dihydroxylation. As expected, the process was selective for the more electron rich alkene[35] and the requisite diastereoselectivity was achieved by selecting the appropriate (pseudo-)enantiomer of the catalyst (AD-mix-α, Scheme 25). The reaction mixture was extremely viscous, and so Rathi's previously developed procedure[30] was improved by (a) using a mechanical stirrer (in place of a magnetic one) and (b) employing slow addition of diene **167** (one hour, syringe pump). In this manner, diol **169** was obtained in 67% yield and >20:1 dr (as determined by ^{1}H NMR), with the stereochemical outcome as predicted by the Sharpless mnemonic and later confirmed by X-ray analysis.[36] Note that previously Dr Akshat Rathi had performed the dihydroxylation reaction using the other (pseudo-)enantiomer of the catalyst (AD-mix-β) in order to confirm the chemical shifts in the ^{1}H NMR for the other

diastereoisomer.[30] Additionally, at this stage, (*E*,*Z*)-diene **170**, which was the minor product from the Horner-Wadsworth-Emmons olefination, was removed due to preferential dihydroxylation (approximately 11-fold) of the (*E*)-double bond (i.e. (*E*,*Z*)-**170** remained intact and was recovered during flash column chromatography).[37]



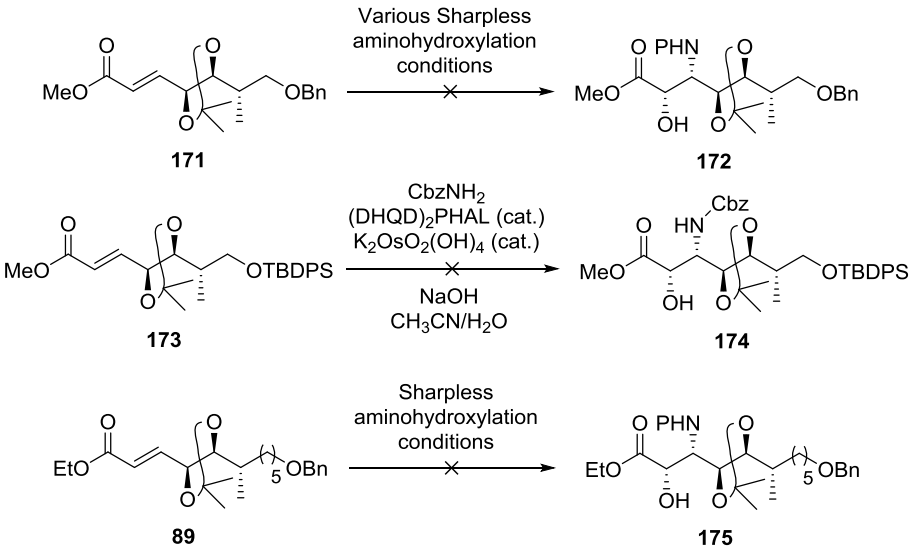
167 (*E*,*E*):(*E*,*Z*) 7:1 — **169** — **170** (*E*,*Z*)

Scheme 25. Sharpless dihydroxylation of diene **167**.

2.3 Development of the key TA reaction

Further modifications of diol **169** aimed to introduce the 1,2-aminoalcohol moiety onto the C2 and C3 positions. Previous studies[30] on protected diol **171** showed that the Sharpless asymmetric aminohydroxylation method failed to provide any desired product (Scheme 26). This outcome was unsurprising, as this methodology is highly dependent on the nature of the alkene substrate; attempted Sharpless aminohydroxylations of related alkenes **173** and **89** were reported to be unsuccessful by Williams[28] and Chandrasekhar.[19] These limitations provided an opportunity to showcase the complementarity of the tethered aminohydroxylation methodology developed in the Donohoe group.[29] In this approach, regiocontrol is guaranteed because the nitrogen source is tethered to the olefinic substrate and reactivity is enhanced because the reaction is intramolecular.

At this point it is pertinent to give a brief overview of the development of the TA reaction. The Donohoe group has developed three generations of TA substrates, which differ in the nature of the *N*-based leaving group (oxidant).

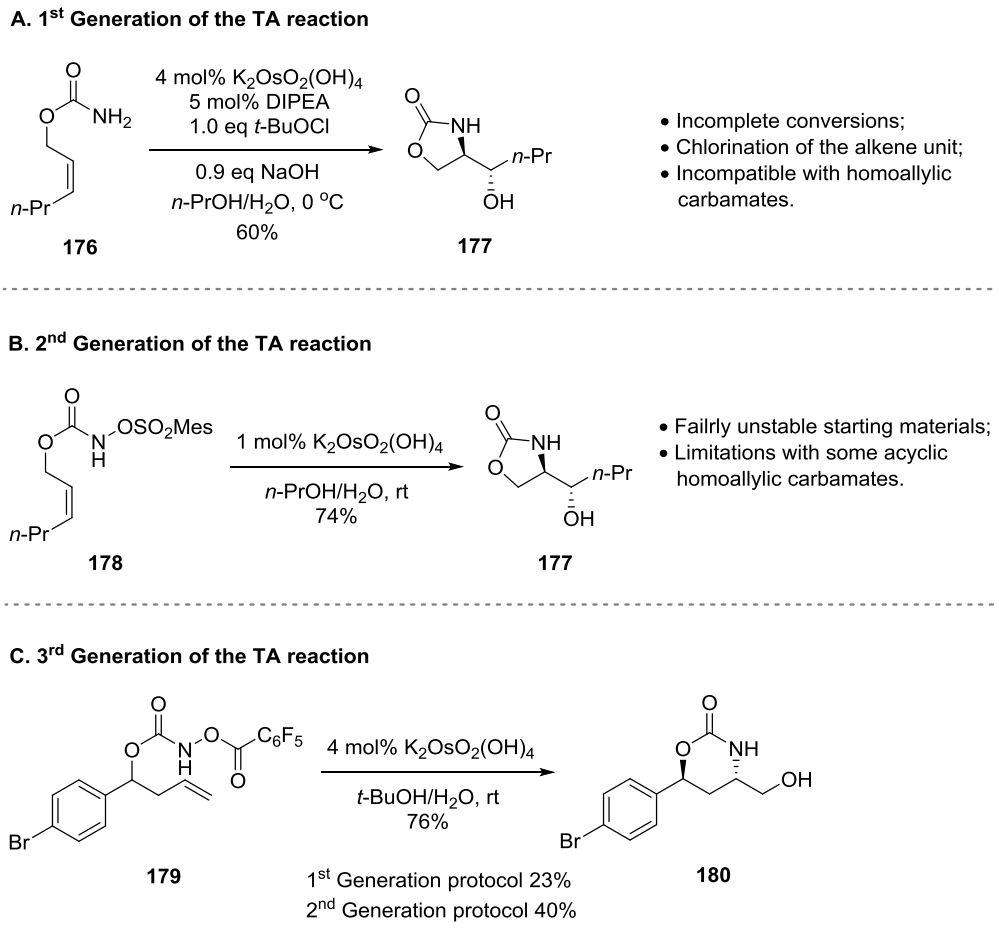


Scheme 26. Attempted Sharpless aminohydroxylation of alkenes **171**, **173** and **89**.

The 1st generation approach was reported in 2002[38] and relied on *in situ* generation of *N*-chlorocarbamates using *tert*-butyl hypochlorite as the stoichiometric oxidant under basic conditions (Scheme 27A). In simple cases, this approach works well, however, the use of *tert*-butyl hypochlorite and NaOH leads to the formation of side-products in more complex settings. Competitive chlorination of the alkene unit was a competing side-reaction, particularly with homoallylic carbamates. It was also found that the *in situ* generated *N*-chlorocarbamates were unstable under the reaction conditions, resulting in incomplete conversions and lower yields.

A 2nd generation approach was developed, which avoids the use of *tert*-butyl hypochlorite by exploiting *N*-sulfonyloxycarbamates **178** as the *internal* oxidant; these substrates can be prepared from the corresponding alcohols in two steps.[39] The 2nd generation TA procedure does not require a strong base and employs low catalyst loadings (often 1 mol% [Os]) to give higher yields of the products (Scheme 27B). The most important improvement to the reaction scope was its tolerance to certain homoallylic

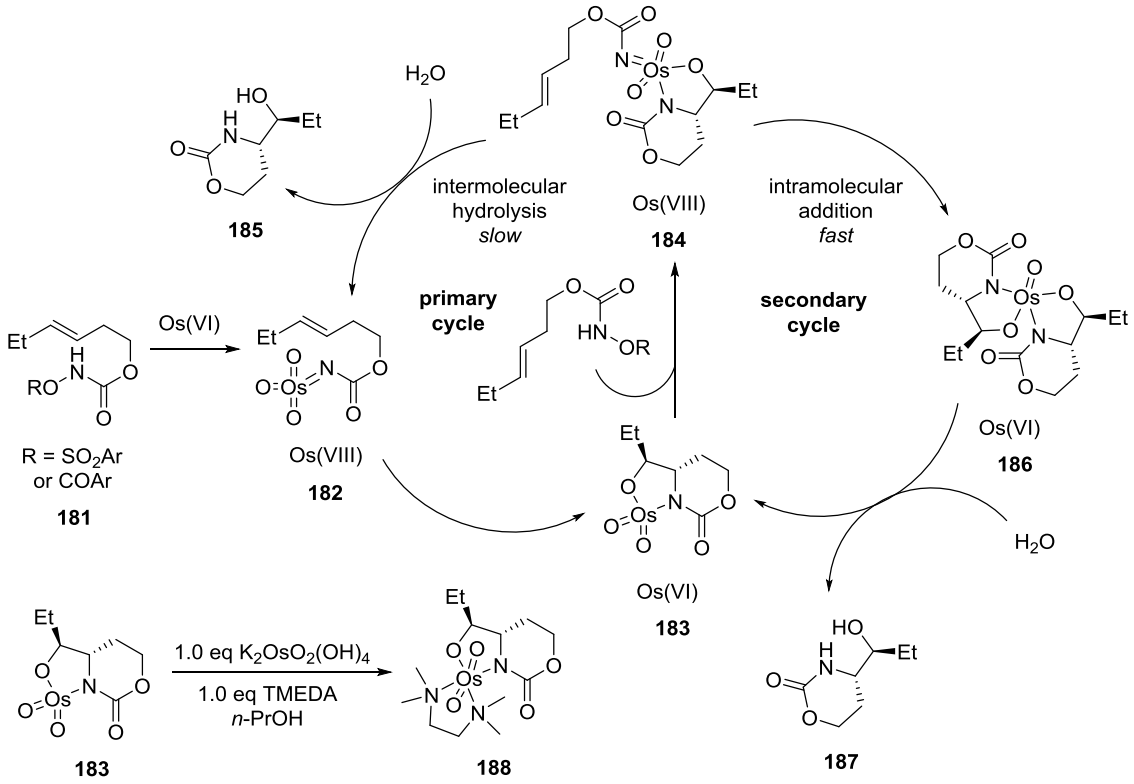
alcohol derived substrates; these were not compatible with the 1st generation TA protocol (see above).



Scheme 27. Development of the TA reaction.

One issue with *N*-sulfonylcarbamates is that they are not particularly stable and so for some substrates that react slowly, such as acyclic homoallylic variants, good yields could still not be achieved. This problem was addressed by developing a 3rd generation of the TA protocol that uses aroyloxycabamates **179** as internal oxidants.[29] Pentafluorobenzoyl and 2,4,6-trimethylbenzoyl carbamates are bench stable substrates and were shown to provide the TA products in high yields. Using this approach, higher yields

were obtained for allylic carbamate substrates and the scope was broadened to encompass even acyclic homoallylic alcohol derivatives (Scheme 27C). In all cases, high *syn*-diastereoselectivity was observed and the processes were completely regioselective.

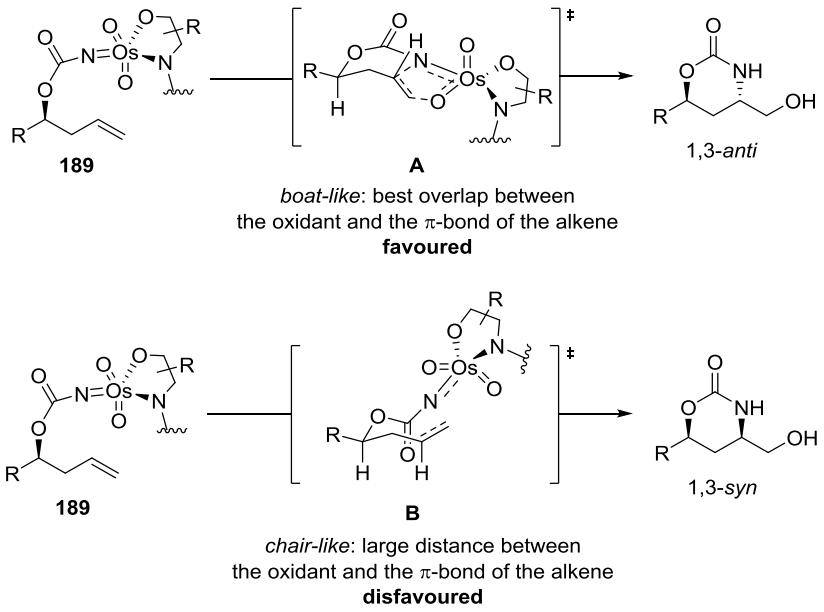


Scheme 28. Proposed mechanism of the TA reaction.

The mechanism for the 2nd and 3rd generations of the TA reaction is based on the same principles as for Sharpless aminohydroxylation. Oxidation of osmium(VI) to trioxoimido osmium(VIII) is achieved by reaction with the *N*-oxycarbamate **181** (Scheme 28). This complex then undergoes intramolecular (3+2) cycloaddition onto the alkene to afford **183**; this is supported by X-ray analysis of stoichiometrically generated TMEDA adduct **188**.[39] Oxidation of osmium azaglycolate **183** by a second molecule of **181** leads to the formation of osmium(VIII) species **184**. This can either undergo

hydrolysis to form **185** (primary cycle) or intramolecular (3+2) cycloaddition to form **186** (secondary cycle). One important observation made during investigations into the TA reaction of allylic carbamates was that enantioselectivity could not be induced by addition of chiral ligands. This suggests that the process likely proceeds *via* the secondary catalytic cycle where the osmium centre is hindered, such that chiral ligands are unable to ligate efficiently (Scheme 28).

TA reactions of homoallylic carbamates derived from secondary alcohols afford products with a 1,3-*anti* relationship between the oxygen atom to which reoxidant moiety is attached and the newly installed C-N bond (Scheme 29). This aspect of selectivity makes the TA reaction well suited to the AMMTD stereopentad, which embodies this stereorelationship between C3-amino and C5-hydroxyl moieties. The high 1,3-*anti* selectivity observed in TA reactions can be explained by considering possible transition states **A** and **B** (Scheme 29).[29] Assuming the Os=N−C linkage is linear, a boat-like conformation **A**, which leads to the 1,3-*anti* product, is favoured as it allows the best overlap between the oxidant and the π-bond of the alkene. Access, to the alternative 1,3-*syn* diastereoisomer requires access to the alternative chair-like conformation **B**, however, this results in a larger distance between the oxidant and the alkene, such that this pathway is disfavoured.

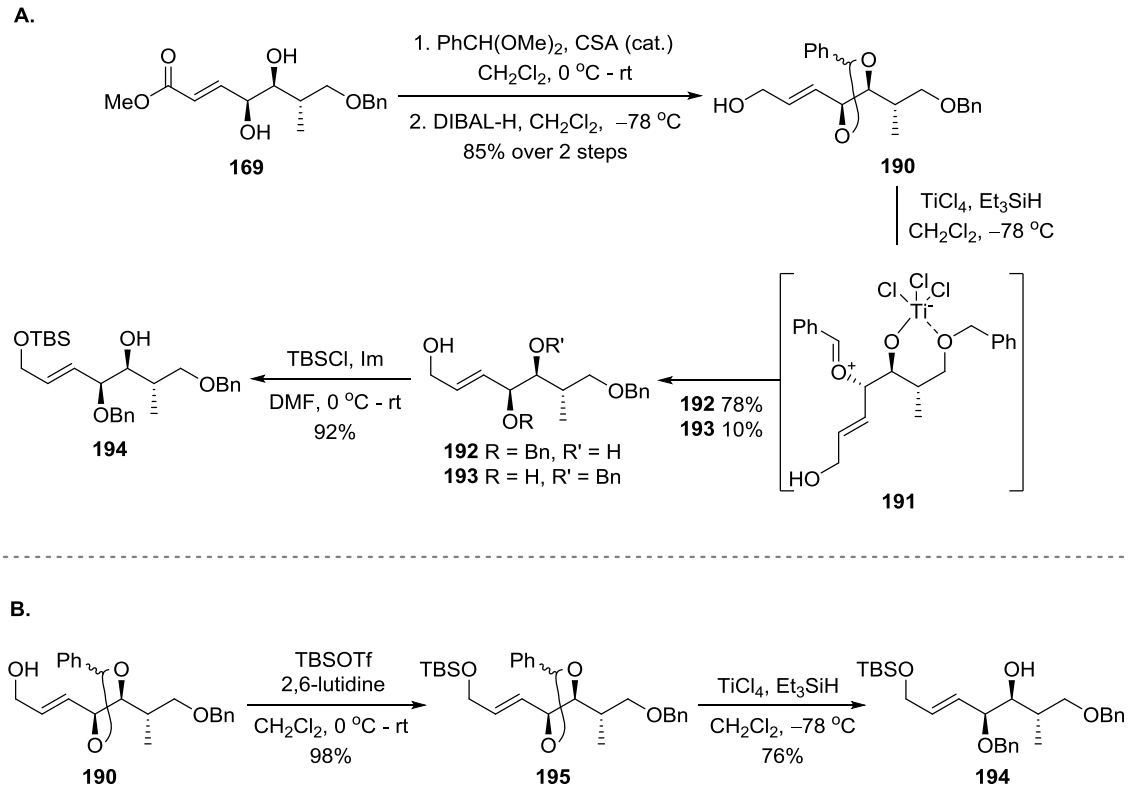


Scheme 29. Explanation for 1,3-*anti* diastereoselectivity in TA reactions of secondary homoallylic alcohol derived carbamates.

Thus, studies were undertaken to convert Sharpless dihydroxylation product **169** into a suitable "3rd generation" TA precursor **197** (Schemes 30, 31). In early work it was found that acrylates were not suitable for aminohydroxylation because competitive C-N bond forming conjugate addition (instead of aminohydroxylation) occurred under the TA conditions. Accordingly, the diol of **169** was protected as a benzylidene acetal and then the ester was reduced (DIBAL-H) to the primary alcohol **190** in 85% yield. It was possible to combine these two steps into a one-pot procedure and obtain product **190** in similar yield, but this necessitated an excess of DIBAL-H for the reduction step (6.0 *vs*. 2.0 equivalents); this modification presented work-up difficulties on large scale and so the two-step approach was favoured.

For the construction of homoallylic carbamate moiety, selective protection of the C4 hydroxyl group was required. This was achieved by regioselective reductive acetal

cleavage using $TiCl_4$ as the Lewis acid and Et_3SiH as the hydride source (Scheme 30A). Similar conditions were reported by Kotsuki for the opening of a symmetrical acetal to furnish a mono-benzylated diol.[40] In the present case, regioselectivity is likely controlled by chelation of the Ti-centre to the oxygen of the benzyl ether of **190**. This results in opening to intermediate **191**, which undergoes ionic reduction to the target **192**. The regiochemical outcome of this process was confirmed by HMBC analysis of **192**. Small quantities (approximately 10%) of alternate regioisomer **193** were also observed.

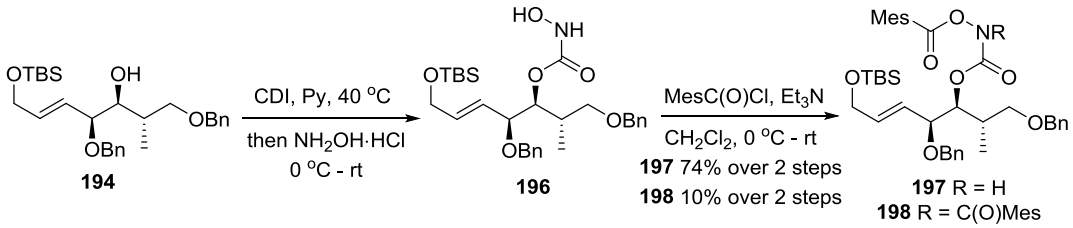


Scheme 30. Synthesis of alcohol **194** by a chelation controlled mono-benzylation strategy.

In previous "Donohoe" studies towards the AMMTD amino acid, Dr Akshat Rathi and co-workers had employed a TIPS protecting group for the C1-hydroxyl.[30] It was envisaged that a TBS group might be more suitable in the present case, as it is less

hindered and hence easier to remove selectively from the primary alcohol later in the synthesis. Thus, mono-protection of the primary alcohol of **192** was achieved in 92% yield using 1.0 equivalent of TBSCl, and this left the C5-hydroxyl of product **194** free for subsequent installation of the carbamate moiety, as required for the pivotal TA step (Scheme 30A).

It was found that alcohol **194** could be also obtained *via* an inverted sequence of steps (Scheme 30B). Here, TBS protection of **190**, using TBSOTf rather than TBSCl, was followed by regioselective reductive acetal opening ($TiCl_4$, Et_3SiH) to afford **194** in a very similar overall yield of 76% (*vs.* 78% in Scheme 30A). However, because TBSCl is cheaper and easier to handle than TBSOTf, the route outlined in Scheme 30A was preferred.



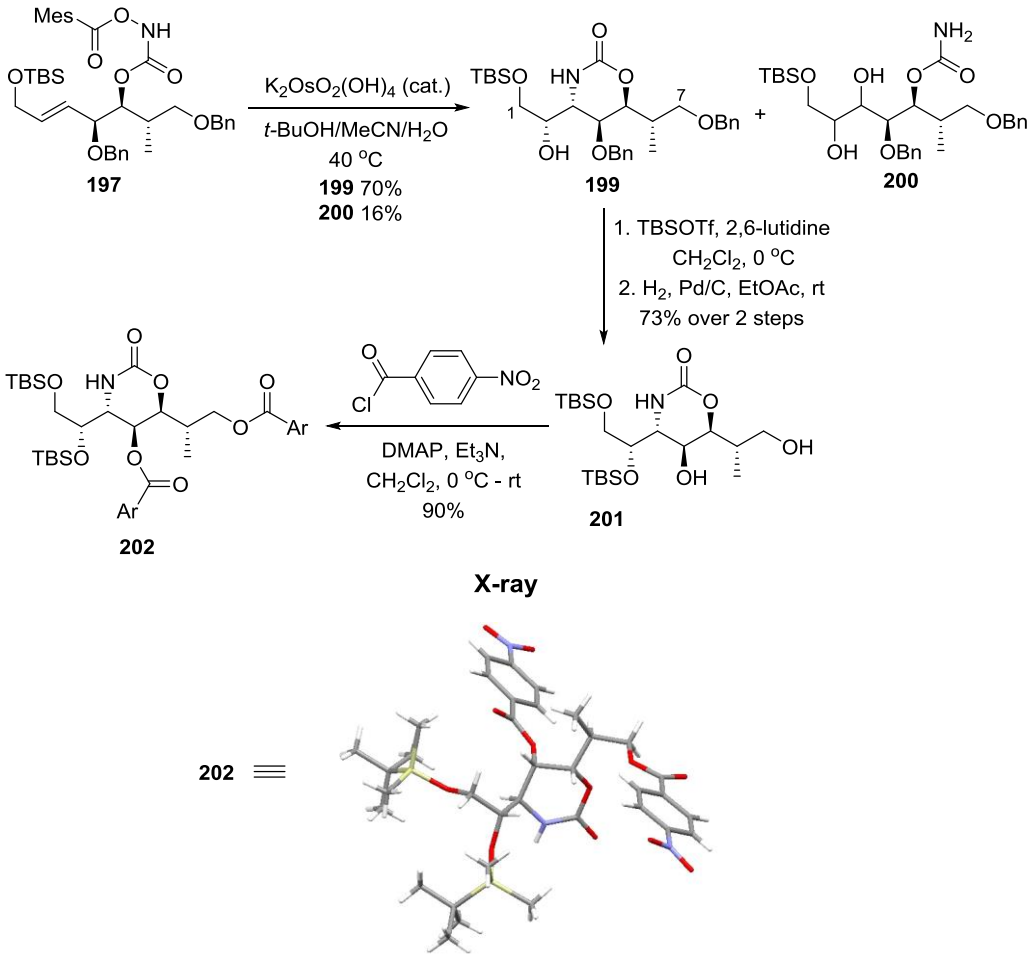
Scheme 31. Synthesis of the TA precursor.

Conversion of the C5 hydroxyl of **194** to the *N*-aroyloxycarbamate, as required for the proposed "3rd generation" TA reaction, was accomplished by adaptation of a two-step procedure reported for the TA methodology.[29] Treatment of **194** with CDI and hydroxylamine generated intermediate **196**, which was acylated directly with 2,4,6-trimethylbenzoyl chloride to afford TA precursor **197** in good overall yield. Small quantities of side-product **198**, in which acylation had also occurred at nitrogen, were

observed; this side-product was readily removed by flash column chromatography. Attempts to prevent the formation of **198** by reducing the equivalents of MesC(O)Cl were unsuccessful, as in these cases, intermediate **196** was not fully consumed.

With precursor **197** in hand, the key TA step was pursued. Pleasingly, previously developed conditions[30] (5 mol% $K_2OsO_2(OH)_4$, *t*-BuOH/H_2O, rt, 48 h) provided TA product **199** in 60% yield and as a single diastereoisomer. However, the reaction was slow and did not progress to completion. These issues were resolved by heating the reaction to 40 ^oC and changing the solvent system to *t*-BuOH/MeCN/H_2O. Under these conditions, **199** was isolated in 70% yield and the reaction time was decreased to 24-30 hours (Scheme 32). In addition to desired product **199**, diol **200**, in which the mesitoyl group had been cleaved, was isolated in 16% yield. Careful analysis of NMR spectra of crude reaction mixtures revealed that the TA reaction was completely diastereoselective as no traces of the alternative 1,3-*syn* diastereoisomer could be detected (the stereochemistry of **199** was assigned based on literature precedent[29] and was later confirmed by X-ray analysis, see below). Protection of the C2-hydroxyl of **199** as its TBS ether and *O*-debenzylation of C4 and C7 hydroxyls (H_2, Pd/C, EtOAc) provided diol **201** in 73% yield for the two steps. When the hydrogenolysis reaction was carried out in MeOH/EtOAc (1:1), a triol side-product, resulting from concomitant loss of the primary TBS group of **201**, was obtained in 35% yield (see the Experimental section); this side-product was not observed using solely EtOAc as solvent. A TBS group was chosen to protect the C2 hydroxyl (rather than a TES group as employed in model studies by Dr Christian Winter) to allow selective cleavage of the primary C1-OTBS later in the synthesis. The 1,3-*anti* relationship embedded within the cyclic carbamate of **199**, as well as the *syn* addition of N and O across the double bond were confirmed by single crystal

X-ray diffraction analysis of benzoylated derivative **202**. At this stage, all five contiguous stereocentres of the AMMTD fragment had been introduced, with the route to **199** proceeding in 13% overall yield over a longest linear sequence of 10 steps. Research into the sequence up to this stage was pursued in collaboration with post-doctoral researcher Dr Robert Pullin.

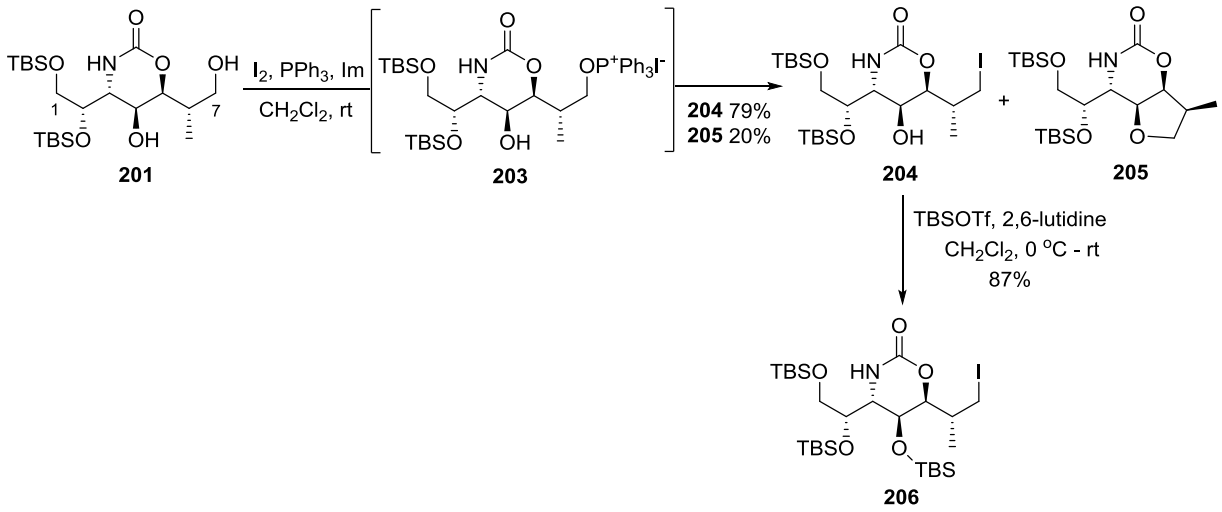


Scheme 32. The TA reaction and confirmation of relative stereochemistry by X-ray analysis of **202**.

2.4 Installation of the AMMTD side-chain *via* cuprate displacement

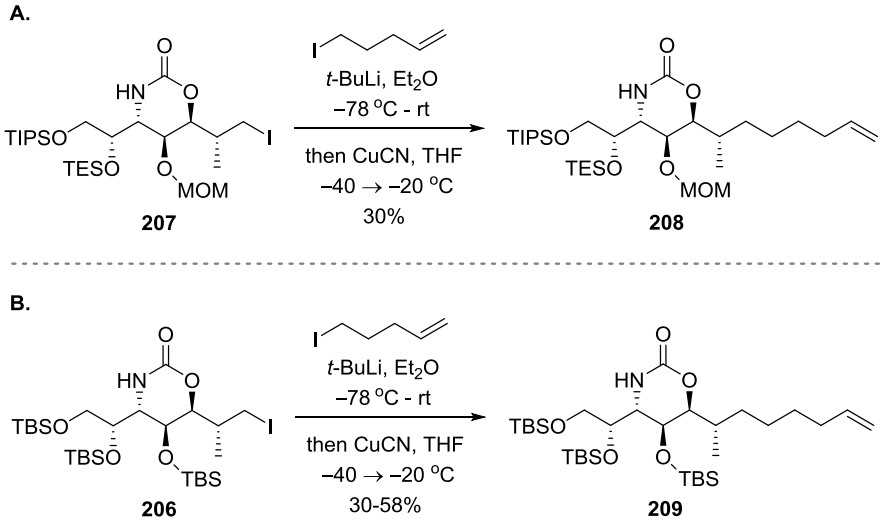
The next key transformation in the synthesis of the AMMTD fragment was installation of the aliphatic side-chain. For this, the C7 hydroxyl group of **201** had to be converted into a suitable leaving group for displacement by an organocuprate nucleophile. Investigations by Dr Christian Winter[41] had found that an alkyl iodide was the only suitable electrophile for the cuprate reaction; other leaving groups were not reactive enough or gave significant amounts of side-products. Accordingly, an Appel reaction was used to convert alcohol **201** into iodide **204**. In early investigations, this process proved to be capricious and required optimisation to provide good reproducibility. Ultimately, it was found that using dry CH_2Cl_2 as solvent and conducting the reaction at room temperature provided **204** in 79% yield and with acceptable levels of reproducibility (Scheme 33). A THF side-product **205** was also isolated in 20% yield, and this likely results from intramolecular attack of the free C4 hydroxyl group onto activated alcohol **203**.

Next, the C4 hydroxyl group was protected as its TBS ether; this silyl group was chosen to allow subsequent selective cleavage of the primary TBS group (see later). Note that in previous studies,[41] a MOM protecting group was employed at C4, however, it was considered that this would be difficult to cleave at a late stage of the synthesis due to the acid sensitive nature of the microsclerodermins.



Scheme 33. Synthesis of iodide **206**.

With substantial quantities of iodide **206** in hand, investigations into the cuprate displacement were undertaken. This process appeared to be one of the most challenging steps in the synthetic sequence towards AMMTD. Indeed, it had previously been found by Dr Christian Winter[41] that only a higher order Lipshutz cuprate[42] was reactive enough to displace the iodide of analogue **207**, albeit in modest yield (Scheme 34A).



Scheme 34. Studies on cuprate displacement of A) iodide **207** and B) iodide **206.**

Unfortunately, the conditions outlined in Scheme 34A were not suitable for iodide **206** as they led to low and irreproducible yields of target **209** (Scheme 34B). Accordingly, significant improvements were required and this necessitated an in-depth optimisation study. Based on preliminary results, CuCN was chosen as the copper source and optimisation focused on two key, interlinked issues: (a) incomplete conversion of starting material **206** and (b) the identification of a method for the problematic separation of unreacted iodide **206** from cuprate product **209**. This latter aspect meant that, at this stage, it was not possible to carry material further through the sequence unless full conversion of iodide **206** could be achieved.

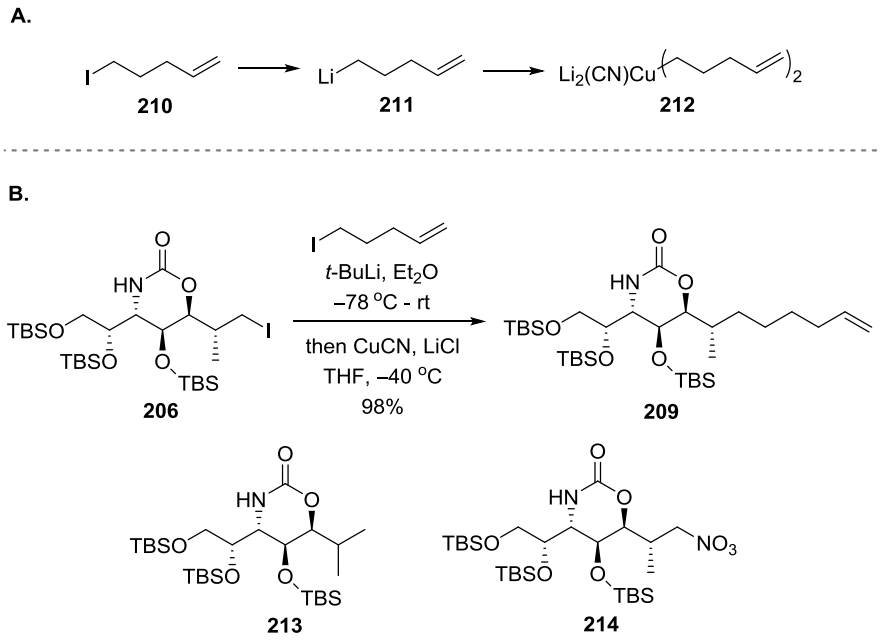
Preliminary investigations sought efficient methods for accessing organolithium reagent **211** (Scheme 35A). Using lithium wire and 1-bromo-4-pentene to generate the organolithium species[43] did not give reproducible results, whereas lithiation of 1-bromo-4-pentene with *t*-BuLi, followed by transmetallation with CuCN failed to give any product **209**. The most reliable method involved lithiation of freshly prepared 1-iodo-4-pentene[44] **210** with a fresh solution of *t*-BuLi. The second important observation was the dependence of the organocuprate stability upon the reaction solvent. THF has been reported to be the best solvent for forming higher order Lipshutz cuprates.[41] However, organolithium reagent **211** was best prepared in Et_2O, as THF degrades relatively rapidly when exposed to *t*-BuLi.[45] Extensive experimentation led to the following observations: the formation of organolithium **211** must be performed in Et_2O at a concentration of 0.90 M, whereas subsequent transmetallation to the cuprate was best accomplished in THF at a CuCN concentration of 0.30 M. Careful control of reaction temperature was also essential. The cuprate reagent **212** was most stable at −40 °C, and this temperature was optimal for the transmetallation and displacement steps. It had previously been reported

that warming of the reaction mixture to −20 °C was necessary for the displacement;[41] however, reinvestigation found that this was detrimental and led to decomposition of the cuprate.

Although the key points listed above played a significant role in reaction optimisation, the most important aspect was the addition of LiCl to stabilise the cuprate species. This modification also provided a substantial enhancement to reaction reproducibility. The role of LiCl is not entirely understood, however, studies involving Grignard reagents[46] suggest that it breaks down oligomeric species, thereby releasing active components into solution; it is assumed that a similar effect may be operative in the current scenario. Additionally, it was observed that the solubility of CuCN in THF increased when LiCl was added; this may lead to more efficient transmetallation with organolithium **211**.

Taking all of the above into account, the best results were obtained when the organolithium solution was added at a rate of 2 mL/min to a suspension of CuCN and LiCl in THF. These conditions proved to be robust and the reaction was scaled up to 1.0 g of **206** to provide **209** in 98% isolated yield (Scheme 35B). Under non-optimised conditions, proto-deiodination side product **213** was often observed (Scheme 35B). This presumably forms if transmetallation of organolithium **211** to cuprate **212** does not proceed to completion. The residual organolithium **211** can promote lithium halogen exchange of **206** and protonation (during work-up) then affords **213**. Under the optimised conditions outlined in Scheme 35B this side-product was never observed. However, even under these conditions, on occasion, the reaction did not go to completion. Fortunately, it was found that, in these cases, product **209** could be separated from starting material **206**

using silver nitrate impregnated silica gel. This served to convert iodide **206** into corresponding nitrate **214**, which was easily separable from **209** (Scheme 35B).



Scheme 35. The cuprate displacement reaction.

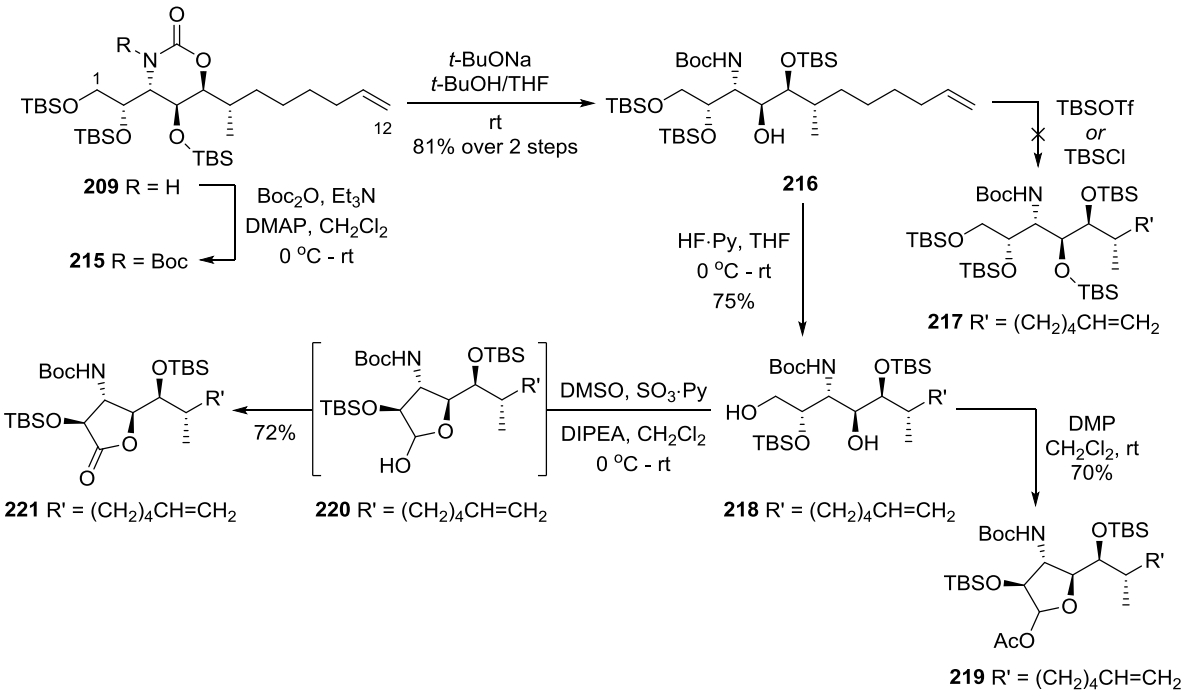
2.5 Completion of the synthesis of AMMTD

The next steps towards the AMMTD amino acid involved cleavage of the carbamate protecting group, removal of the primary TBS ether and oxidation of the C1 hydroxyl back to the carboxylic acid. Attempts to cleave the unactivated cyclic carbamate of **209** failed, and so activation of this moiety by installation of a Boc group on nitrogen was pursued. Initial attempts to install the *N*-Boc-group resulted primarily in recovered starting material. However, use of a large excess of Boc_2O (30 equivalents) and stoichiometric DMAP resulted in complete conversion of **209** to target **215** (Scheme 36).[47] Even with the Boc-group in place, carbamate hydrolysis proved to be non-trivial. Typical

conditions for cleavage of six-membered carbamates, such as Cs_2CO_3/MeOH, LiOH/MeOH/H_2O, LiOH/EtOH, LiOH/*i*-PrOH or Cs_2CO_3/*i*-PrOH,[48] at room temperature or with heating, resulted in mixtures of products or cleavage of the *N*-Boc-group. Conditions that are known to effect cleavage of five-membered carbamates (LiOH/H_2O_2) returned only starting material, whereas attempted reductive cleavage with DIBAL-H resulted in a complex mixture of side-products. After extensive experimentation, it was found that the desired hydrolysis could be accomplished at room temperature using sodium *tert*-butoxide in *t*-BuOH/THF to provide **216** in 81% yield over two steps from **209** (Scheme 36). It is assumed that, under these conditions, traces of water release metastable (non-aggregated) and highly reactive NaOH; this rationale has been proposed by Lloyd-Jones for hydroxide promoted cleavage of *tert*-butyl benzoates.[49] Notably, migration of the C4 TBS-ether to the incipient C5 hydroxyl occurred under the reaction conditions, resulting in a mixture of regioisomers with **216** as the major one (>10:1 ratio). In addition to the desired cyclic carbamate cleavage, competitive removal of the *N*-Boc-group was observed, resulting in a 9% yield of carbamate **209**, which could be recycled.

Further advancement of **216** required protection of the C-4 hydroxyl group. Attempts to install a TBS group using TBSOTf resulted in cleavage of the *N*-Boc moiety, whereas the use of TBSCl led only to recovery of starting material (Scheme 36). Difficulties encountered here likely reflect the sterically hindered nature of the secondary alcohol. With this in mind, oxidation of the primary alcohol to the acid was pursued in the presence of a free hydroxyl group at C4. Selective cleavage of the primary TBS ether at C1 in the presence of two secondary *O*-TBS groups was investigated. Several conditions (AcOH/H_2O/THF, CSA/MeOH, HF·Py/THF)[50] were tested and a good yield of **218** (75%)

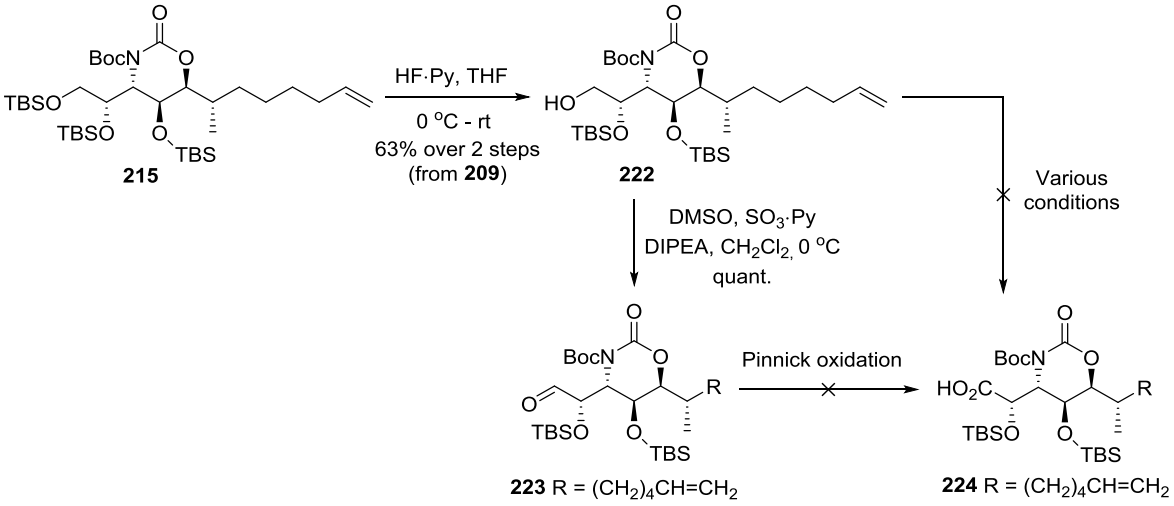
was obtained using HF·pyridine (Scheme 36); under these conditions less than 10% of bis-deprotected material was observed. Oxidation of the primary alcohol of **218** under Parikh-Doering conditions resulted in formation of five-membered lactone **221** rather than the initially targeted carboxylic acid (Scheme 36). Initial oxidation to the aldehyde presumably triggers cyclisation to lactol **220**, which is then oxidised to lactone **221**. Interestingly, oxidation of **218** using the Dess-Martin reagent led predominantly to undesired side-product **219**, where acylation of the lactol hydroxyl had occurred.



Scheme 36. Cleavage of the carbamate moiety and oxidation to lactone **221**.

Concurrent studies focused on preventing cyclisation during the oxidation step. Accordingly, the primary TBS ether of **215** was cleaved to afford alcohol **222**, which was then exposed to several oxidation protocols (Scheme 37). Direct oxidation to acid **224** was investigated using a variety of conditions ($NaClO_2$/TEMPO/NaClO, PDC/DMF,

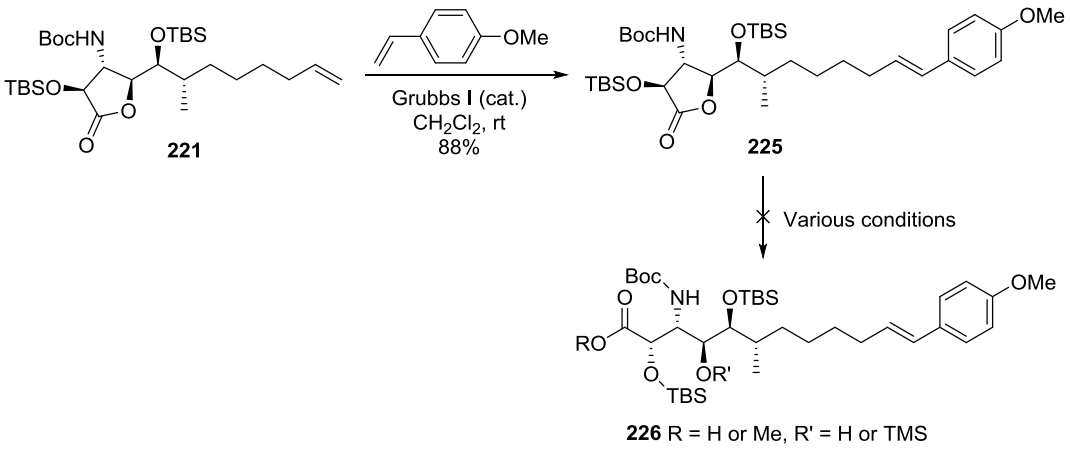
IBX/DMSO/*N*-hydroxysuccinimide), but none were successful. In some cases, ^{1}H NMR spectra of crude material indicated the presence of aldehyde **223**, along with other unidentified side-products. Attempts to develop a two-step procedure, involving Parikh-Doering oxidation to aldehyde **223** and subsequent Pinnick oxidation to acid **224**, led to the decomposition during the latter step. Due to the failure of this approach, lactone **221** was chosen for advancement to subsequent steps.



Scheme 37. Attempted C1 oxidation of **222** to acid **224**.

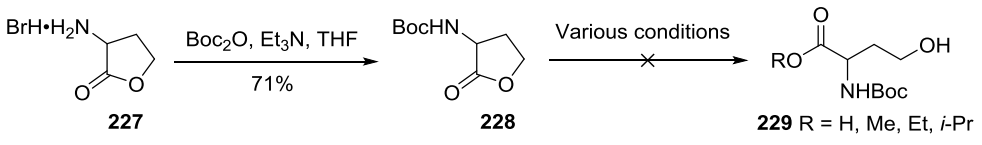
At this stage, to complete the synthesis of the AMMTD fragment,[51] the styrene moiety was introduced *via* cross-metathesis of **221** with 4-vinylanisole using conditions developed by Dr Robert Pullin. This provided proof-of-concept for this method, however, in the envisaged total synthesis of microsclerodermin B this step would be incorporated into the end-game strategy (see later). Opening of the lactone of **225** proved to be challenging. Hydrolysis to acid **226** using LiOH in THF/MeOH/H_2O led to the formation of the carboxylate salt, but, upon acidifiation and chromatographic purification, cyclisation back to lactone **225** occurred. Treatment of **225** with freshly prepared MeONa in MeOH

did not give the desired methyl ester **226** and led only to decomposition products. Attempts to hydrolyse lactone **225** to the corresponding carboxylate and effect either *in situ* methyl ester formation (with MeI) or protection of the C4 hydroxyl group (with TMSCl) also failed.



Scheme 38. Cross-metathesis and attempts to obtain acid or methyl ester **226**.

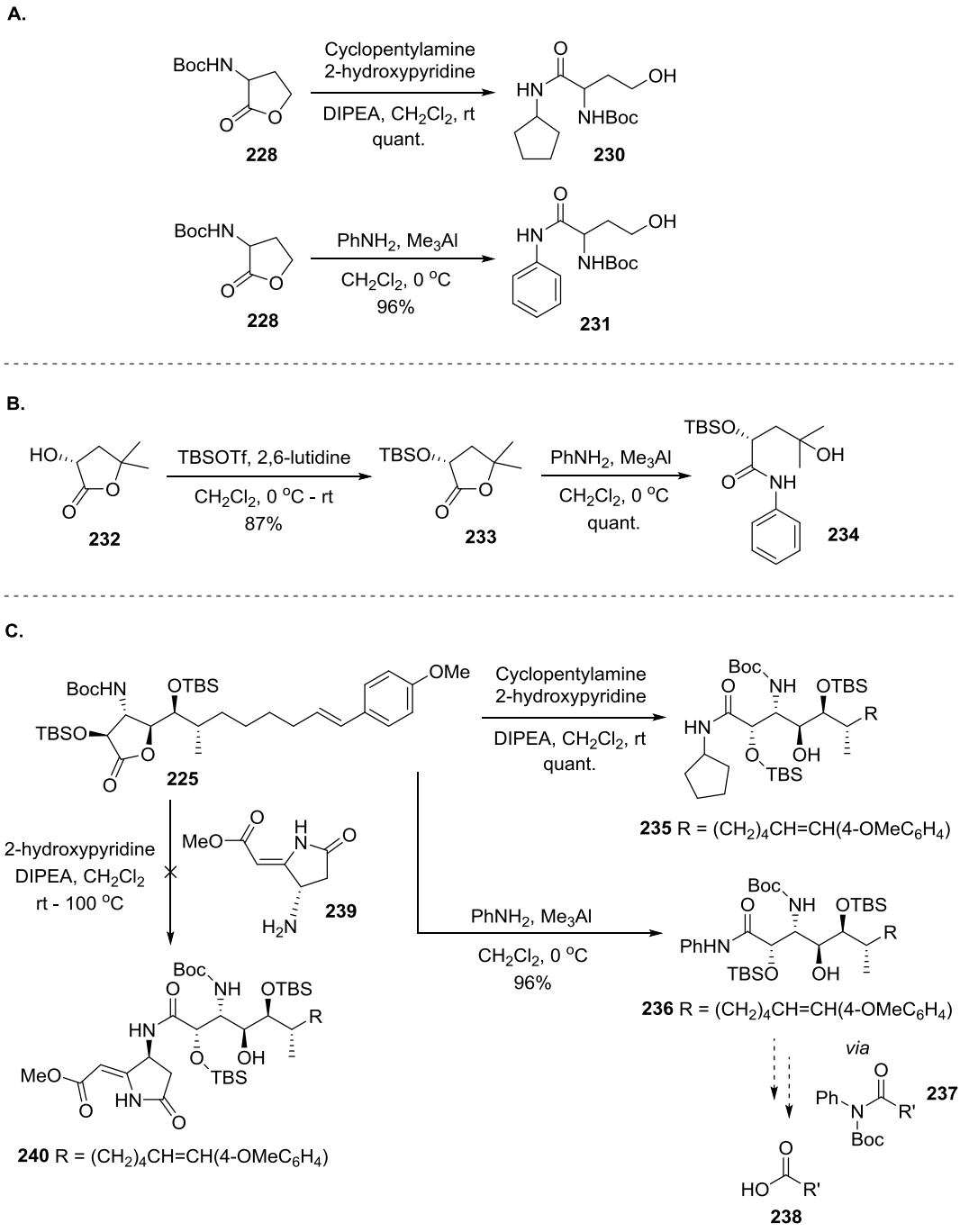
At this stage, further conditions were tested using model lactone **228** (Scheme 39). Attempted alcoholysis of this using a variety of bases (Na_2CO_3, Cs_2CO_3, NaOH, EtONa, *i*-PrONa) in combination with different alcohols (MeOH, EtOH, *i*-PrOH) as solvents failed, even under forcing conditions. In some cases the corresponding acid **229** was isolated in very low yield, but mainly starting lactone **228** was observed.



Scheme 39. Attempts to convert model lactone **228** into acid or esters **229**.

The total synthesis of microsclerodermin B requires amide bond formation at C1. Accordingly, it was envisaged that direct opening of the lactone of **225** with an amine or aniline could provide a strategy for coupling with the pyrrolidinone core (see Figure 2). Opening of model lactones **228** and **233** with cyclopentylamine and aniline was investigated to evaluate the stability of *N*-Boc-groups and TBS-ethers under the reaction conditions. Amide formation between **228** and cyclopentylamine proceeded smoothly using 2-hydroxypyridine as an activating agent (Scheme 40A).[52] Me_3Al was required as a Lewis acid to promote reaction of the less nucleophilic aniline and this generated **231** and **234** in 96% and 100% yield, respectively (Scheme 40A and 40B). Aniline was investigated because aniline amides have been shown to undergo facile hydrolysis to carboxylic acids *via* the corresponding *N*-Boc phenylcarbamates **237**.[53] Gratifyingly, application of both amide formation procedures to AMMTD precursor **225** generated amides **235** and **236** in good yield (Scheme 40C). Unfortunately, extension of the cyclopentylamine conditions to amine containing pyrrolidinone **239**, which is present in the northern hemisphere of microsclerodermin B, was unsuccessful. More forcing conditions, employing a large excess of **239** or an increased temperature of 100 ^{o}C also failed to yield target amide **240**, with starting lactone **225** remaining intact.

At this stage the AMMTD subunit of microsclerodermin B had been synthesised in protected form **236** *via* a longest linear sequence of 21 steps.[51] As efforts to convert lactone **225** to the free acid had been unsuccessful, further investigations were required to prepare this fragment in a form that would be amenable to late stage amide coupling.

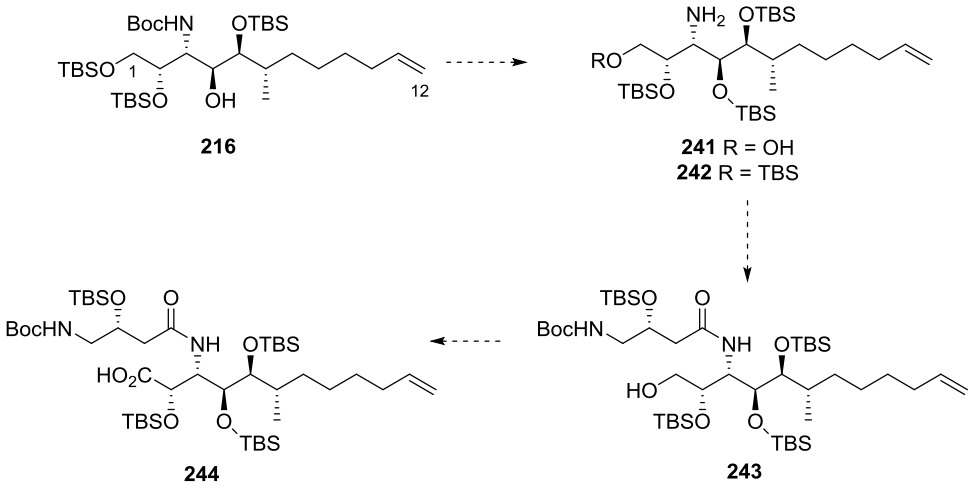


Scheme 40. Opening of model and "real" lactones **228**, **233** and **225** with cyclopentylamine and aniline.

Chapter 3 First generation approach to the protected cyclic hexapeptide

3.1 Preparation of the AMMTD amino alcohol for coupling

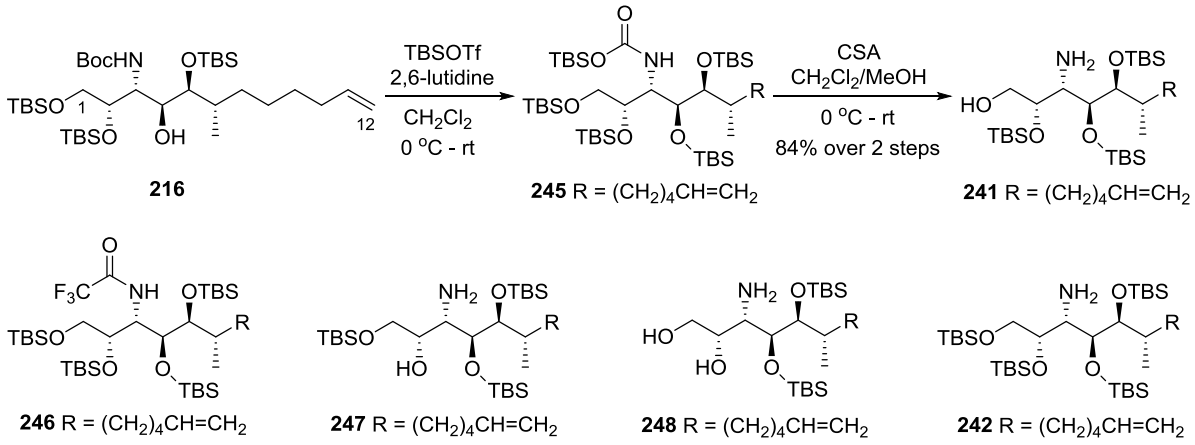
The studies in Chapter 2 had provided efficient access to lactone **225**. However, it was found that direct peptide bond formation using this was not feasible in the context of an eventual synthesis of microsclerodermin B. Thus, studies were pursued that might allow C1 oxidation to be performed at a later stage. In Ma's synthesis of microsclerodermin E this oxidation was accomplished after the AMMTD unit had been coupled to GABOB (see Scheme 8, Chapter 1).[10] It was decided that a similar approach might be beneficial in the current scenario. Thus, it was envisaged that protection of the C4 hydroxyl group of **216**, using TBSOTf, could be combined with intentional removal of the *N*-Boc group.[54] In the studies outlined in Scheme 36, retention of this protecting group had been sought and so TBSOTf could not be employed. Selective cleavage of the primary TBS ether of **242** could then be performed either before or after coupling with the GABOB unit. With the C4 hydroxyl protected, oxidation of primary alcohol **243** to acid **244** would occur without the problematic lactonisation (Scheme 41). Additionally, the styrenic unit of AMMTD would not be installed until the microsclerodermin B "end game" (see Chapter 4); this decision was made to allow prior selective modifications of the electron rich pyrrolidinone double bond.



Scheme 41. Revised approach for C1 oxidation.

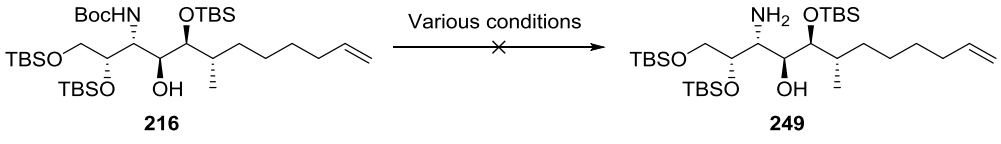
Simultaneous cleavage of the *N*-Boc group and protection of the C4 hydroxyl group of **216** was attempted using TBSOTf in the presence of 2,6-lutidine (Scheme 42). Surprisingly, direct formation of TBS ether **242** did not occur and instead silyl carbamate **245** was formed, as confirmed by ^{1}H NMR and MS analysis. This intermediate was stable and did not decompose to the free amine when exposed to silica gel, aqueous saturated ammonium chloride solution, AcOH/MeOH or K_2CO_3/MeOH. These observations suggested that harsher acidic or basic conditions were required and it was envisaged that this could be combined with simultaneous cleavage of the primary C1 TBS ether. Accordingly, subjection of silyl carbamate **245** to TFA provided amino alcohol **241** in 40% yield, however, this was formed as a 1:1 mixture with trifluoroacetamide **246**. Treatment of carbamate **245** with HF·pyridine successfully released the C3 amine and the C1 hydroxyl, but migration of the TBS-group from the C2 to the C1 alcohol occurred to afford a mixture of alcohol **247** and diol **248**. Notably, the same migration took place when the target amino alcohol **241** was stored at room temperature or 5 ^{o}C for a few days. It is possible that the C3 amine assists in the migration of the secondary silyl group.[55]

Eventually, it was found that using an excess of CSA (2.0 equivalents) in CH_2Cl_2/MeOH provided target **241** cleanly in 84% overall yield (two steps) from **216** (Scheme 42). When only 1.0 equivalent of CSA was employed and the reaction was stopped after one hour, it was possible to isolate intermediate amine **242**. Cleavage of the primary TBS group required longer reaction times (48 hours) and 2.0 equivalents of CSA.



Scheme 42. Synthesis of amino alcohol **241**.

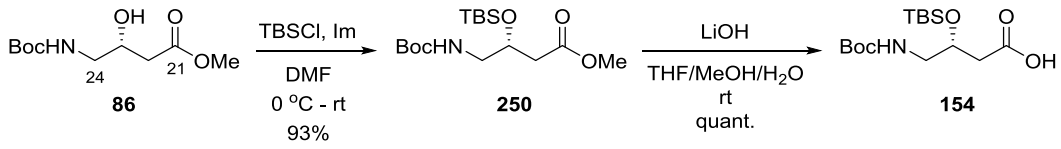
Attempts to cleave the *N*-Boc group of **216** without first forming the C4 silyl ether failed to provide amino alcohol **249** (Scheme 43). For example, treatment of **216** with dry TFA effected selective cleavage of the primary TBS group in 79% yield, but left the *N*-Boc group untouched. Exposure of **216** to Lewis acids that are reported for *N*-Boc deprotection, such as $AlCl_3$ or $ZnBr_2$,[56] gave a complex mixture of side-products.



Scheme 43. Attempts to cleave selectively the *N*-Boc-group of carbamate **216**.

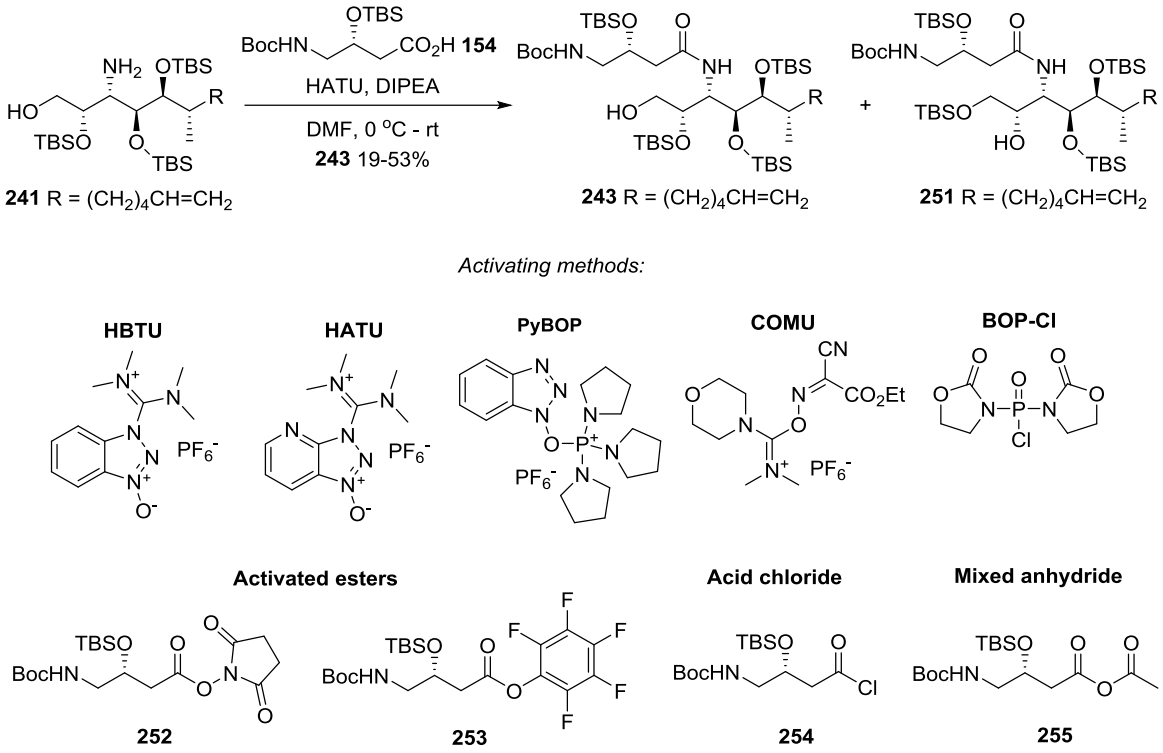
3.2 Synthesis of the AMMTD-GABOB dipeptide

The synthesis of the GABOB unit of microsclerodermin B was based on the route previously developed by Shioiri.[11] A Boc protecting group was selected for the GABOB C24 amine, as it was assumed that this could be removed under mild conditions prior to the key macrolactamisation step (Scheme 44). Compound **86** was prepared according to Shioiri's method outlined in Scheme 14 (see Chapter 1 and the Experimental section). The C23 hydroxyl of **86** was converted into silyl ether **250** using TBSCl. Subsequent methyl ester hydrolysis with LiOH afforded target carboxylic acid **154** in quantitative yield (Scheme 44).



Scheme 44. Synthesis of the GABOB amino acid.

The next key transformation towards the assembly of the hexapeptide of microsclerodermin B involved coupling of the AMMTD and GABOB fragments (Scheme 45). In Ma's synthesis of microsclerodermin E, this bond formation was accomplished by activating the GABOB amino acid as its OSu ester in EtOAc at reflux (see Chapter 1).[10] Since this report in 2003, methods for amide bond formation have developed significantly, such that milder procedures were now available.[57] Accordingly, high generality coupling reagents, such as HATU, HBTU, PyBOP, COMU and BOP-Cl were selected initially for investigation. These represent the most widely used uranium- and phosphonium-based activating agents.

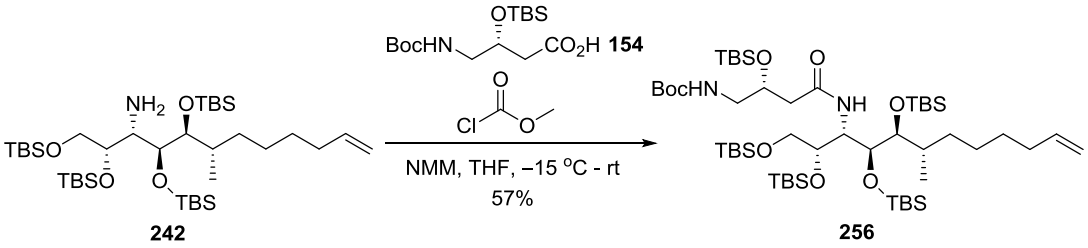


Scheme 45. Coupling of the AMMTD and GABOB amino acids.

Amino alcohol **241** was found to be a challenging substrate for amide coupling. A key issue was migration of the TBS-group from the C2 to the C1 hydroxyl under basic conditions, which led to side-product **251**. Initial attempts to unite **241** and **154** using the aforementioned coupling reagents resulted in low mass recovery and multiple side-products, which were not readily identified. Other peptide bond forming methodologies were also investigated such as amidation *via* acid chloride **254**, mixed anhydride **255** and activated esters **252** and **253**. After extensive studies, which also evaluated reaction temperature, solvent (DMF, CH_2Cl_2 and THF) and concentration, an acceptable yield (53%) of **243** was achieved on 20 mg scale using 1.2 equivalents of GABOB, 1.3 equivalents of HATU and 3.0 equivalents of DIPEA in DMF at 0 °C. Unfortunately, this procedure was capricious and on larger scale (150 mg), **243** was

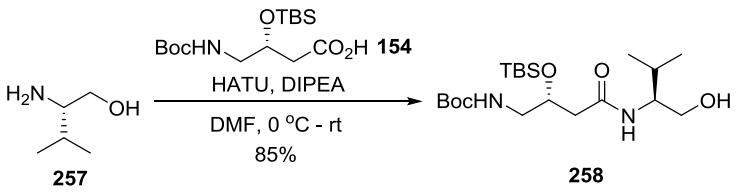
formed in only 19% yield. As a reproducible procedure could not be identified, further studies were conducted to circumvent this issue.

Based on the observation that facile migration of the C2 *O*-TBS group of **243** occurred to afford side-product **251**, amide formation was evaluated on systems with a protected C1 hydroxyl. As previously mentioned, amine **242** could be accessed from **245** using 1.0 equivalent of CSA. A range of peptide bond formations were explored on this substrate and, by activating the GABOB acid as a mixed anhydride, it was found that dipeptide **256** could be formed in 57% yield (Scheme 46). However, this approach was abandoned because of the modest yield and issues associated with selective cleavage of the primary TBS ether of **256**.



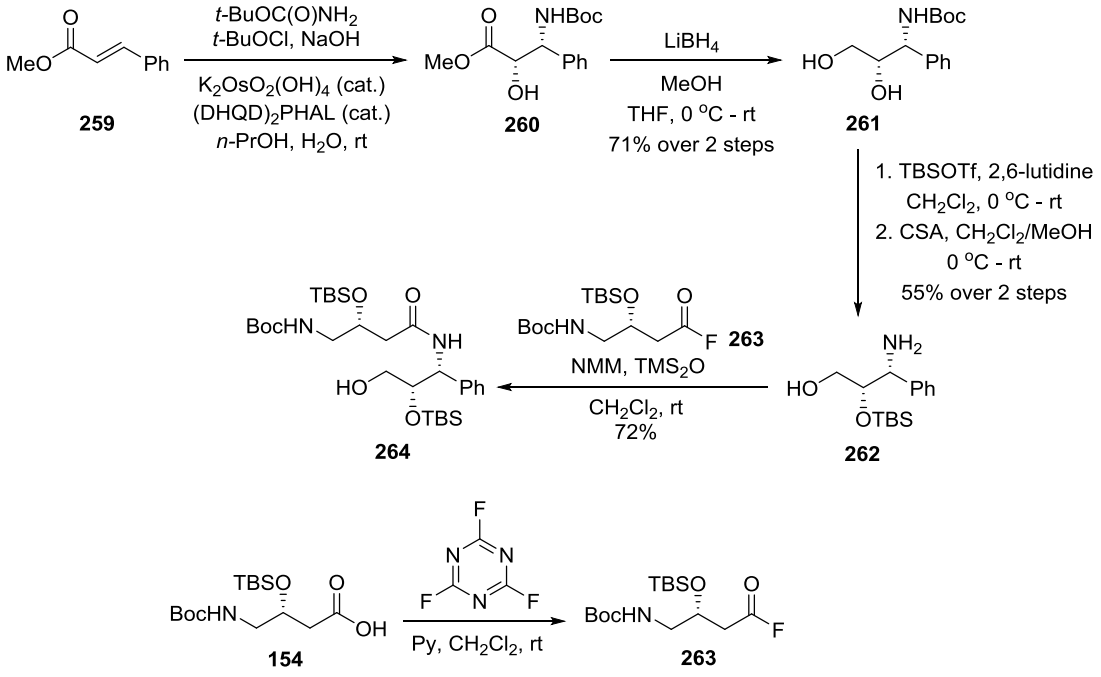
Scheme 46. Coupling of amine **242** with GABOB.

Further investigations into the coupling of AMMTD with GABOB were guided by studies on simple model substrates **257** and **262**. GABOB acid **154** was coupled to L-valinol **257** using HATU to establish whether the GABOB unit contained incompatible functionality (Scheme 47). No side-reactions were observed and dipeptide **258** was formed in 85% yield. Thus, the issue appeared to lie with the amino alcohol moiety of AMMTD unit **241** and studies were undertaken to elucidate this.



Scheme 47. Coupling of amine **257** with GABOB.

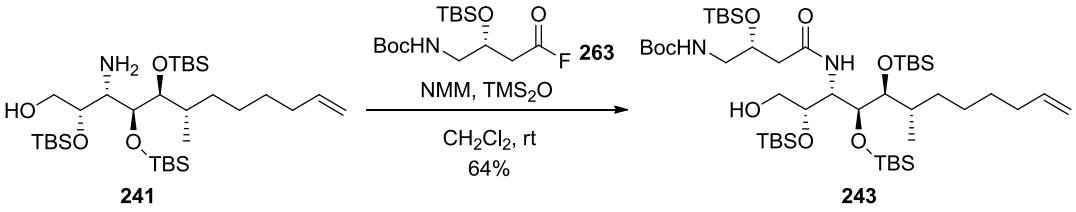
Model substrate **262** was prepared in four steps from methyl cinnamate **259**, using the Sharpless asymmetric aminohydroxylation method as the key step (Scheme 48). When model amino alcohol **262** was subjected to the previously developed amide formation conditions, which used HATU in combination with DIPEA and DMF, only a 27% yield of **264** was observed, with the mass balance consisting of multiple unidentified side-products. Interestingly, **264** could be accessed in an increased yield of 43% by changing the solvent to CH_3CN and avoiding an aqueous work-up.



Scheme 48. Synthesis of model substrate **262** and its coupling with GABOB.

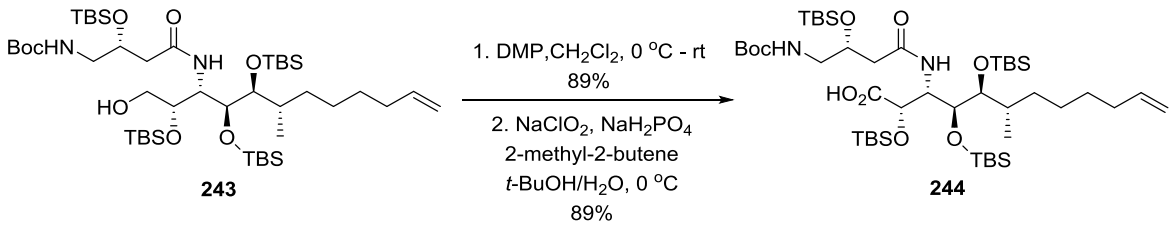
Further conditions were screened, and it was found coupling *via* acid fluoride **263** provided the desired product **264** in high yield (72%) and with excellent reproducibility (Scheme 48).[58] Of the bases explored for this reaction, NMM was found to be the best. TMS_2O is an important additive in this reaction as it sequesters the released fluoride, which otherwise led to partial cleavage of the *O*-TBS groups.

Use of these optimised conditions on AMMTD amino alcohol **241** furnished dipeptide **243** in 64% yield and with good reproducibility (Scheme 49). Subsequent application to an *N*-Fmoc protected GABOB variant resulted in even higher yields (75-80%) (see Section 3.4).



Scheme 49. Coupling AMMTD and GABOB *via* acid fluoride **263**.

At this stage, a two-step procedure was employed to oxidise the C1 alcohol to the carboxylic acid required for coupling with the northern hemisphere of microsclerodermin B. Oxidation of **243** with Dess-Martin periodinane provided the corresponding aldehyde, which underwent smooth Pinnick oxidation to afford acid **244** in high yield (Scheme 50). An alternative one-step protocol using TEMPO/BAIB[59] did not provide any acid **244**; here, formation of the aldehyde was observed, but starting material remained unreacted. Acid **244** was highly unstable and consequently was advanced immediately to the next step.



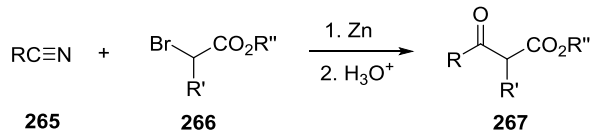
Scheme 50. Oxidation of alcohol **243** to acid **244**.

3.3 Synthesis of the linear hexapeptide

With the AMMTD-GABOB fragment in hand, synthesis of linear hexapeptide **274**, which contains all of the six required amino acids, was pursued. The northern hemisphere **273** of microsclerodermin B was prepared by Dr Rob Pullin and Dr Christian Winter; this contains two non-commercial amino acids, namely a 2-tryptophan carboxylate **22** and the pyrrolidinone unit **151**. The 2-tryptophan carboxylate **22** was prepared using Ma's method, where the carboxylate group is installed by treatment of a commercially available D-tryptophan amino acid derivative with *tert*-butyl hypochlorite and trimethylsilyl cyanide (see Scheme 6, Chapter 1).[10] The methyl ester of **22** was chosen because Ma had demonstrated that this could be hydrolysed with lithium hydroxide during the end-game of his synthesis. This was surprising, as, in the same report, epimerisation of the pyrrolidinone stereocentre occurred using TBAF; this issue was not noted during lithium hydroxide promoted methyl ester hydrolysis.

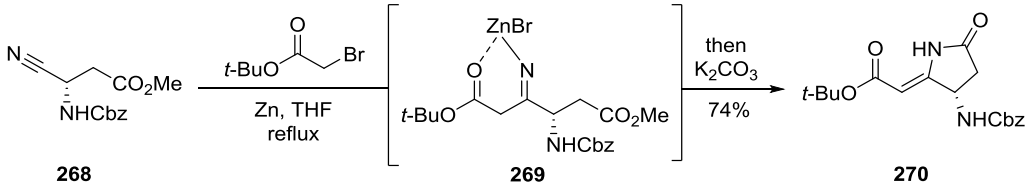
For the construction of the pyrrolidinone unit, a Blaise reaction was employed as the key step. This process was discovered in 1901 and involves the reaction of a nitrile **265** with a bromoacetate **266** derived zinc enolate to generate, after acidic work-up, the

corresponding β-keto ester **267** (Scheme 51).[60] The process is similar to the Reformatsky reaction, in which the nitrile electrophile is replaced by a carbonyl compound.



Scheme 51. General scheme for the Blaise reaction.

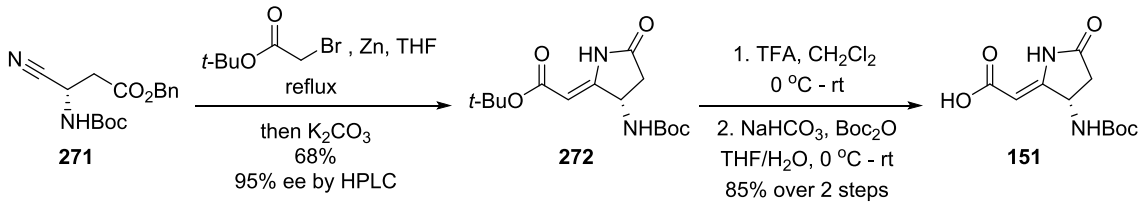
In 2009 Kouklovsky reported a study on the homologation of amino acids using the Blaise reaction, and this gave concise access to chiral pyrrolidinones.[61] One of the examples was a protected version of the pyrrolidinone amino acid **270** of interest (Scheme 52).



Scheme 52. The Blaise reaction in the synthesis of pyrrolidinone **270**.

The mechanism for the formation of the pyrrolidinone **270** involves attack of the *tert*-butyl bromoacetate derived organozinc reagent onto nitrile **268**. Upon basic work-up (aq. K_2CO_3), isomerisation to the corresponding enamine is followed by lactamisation to target **270**. This method was adapted by Dr Christian Winter for the preparation of unsaturated pyrrolidinone amino acid **151**, as required for the synthesis of microsclerodermin B. *N*-Boc protected nitrile **271** was selected because its removal could be achieved using conditions that are compatible with the double bond and other protecting

groups used on the northern hemisphere. Nitrile **271** was readily synthesised in two steps from a commercially available aspartic acid derivative (see the Experimental section). Exposure of this to the requisite bromoacetate derived zinc enolate afforded pyrrolidinone **272** in 68% yield and 95% ee, as determined by chiral HPLC analysis. NOE studies on compound **272** were performed by Hang Xu and confirmed the expected *Z*-geometry of the pyrrolidinone double bond (observed NOE correlations: H43-H45, H43-NH45). Conversion of **272** to **151** was then accomplished *via* a two-step procedure, which involved deprotection of the ester and amino moieties, and subsequent reinstallation of the *N*-Boc group (Scheme 53).

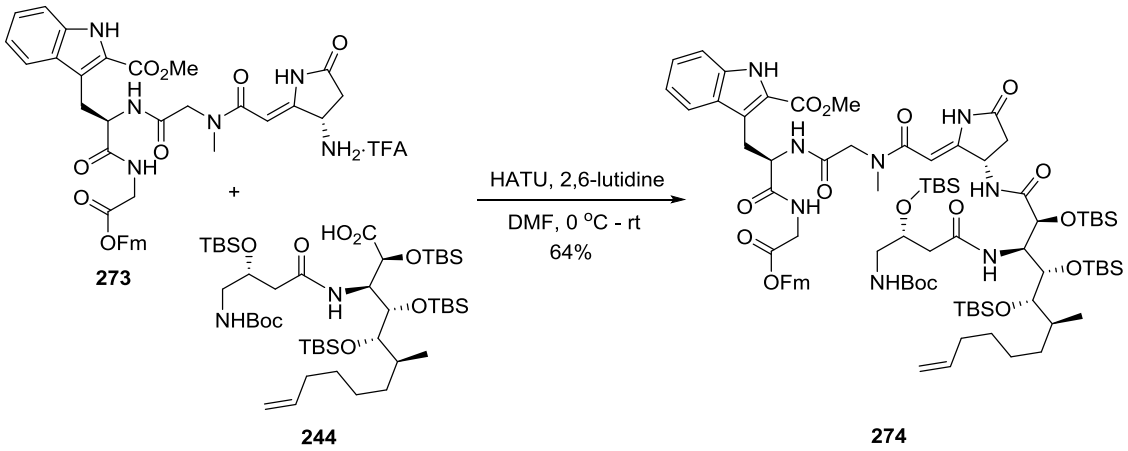


Scheme 53. Synthesis of pyrrolidinone amino acid **151**.

With all four of the amino acids (Gly, 2-Trp-CO_2Me, Sar and pyrrolidinone) of the northern hemisphere of microsclerodermin B in hand, Dr Robert Pullin prepared tetrapeptide **273** using standard procedures. This material was then available for coupling with AMMTD-GABOB dipeptide **244**.

The coupling of **273** and **244** was readily achieved, and, on the first attempt, the target linear hexapeptide **274** was formed in a good yield of 64%. The procedure used 1.5 equivalents of amine **273**, HATU, 2,6-lutidine and DMF as solvent (Scheme 54). A weak base was chosen to avoid cleavage of the Fm-ester of the glycine residue of **273**. Lower equivalents of amine **273**, other coupling reagents such as PyBOP or COMU and

other solvents gave lower yields of **274**. Thus, the conditions outlined in Scheme 54 were retained for further studies.

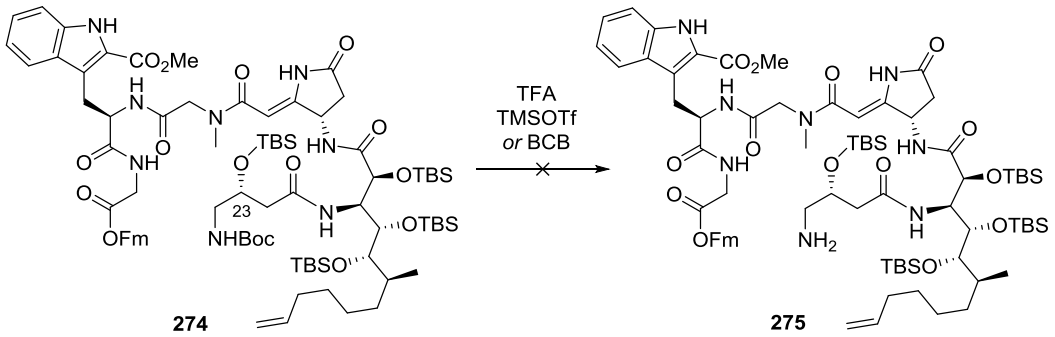


Scheme 54. Synthesis of linear hexapeptide **274**.

3.4 Synthesis of the cyclic hexapeptide

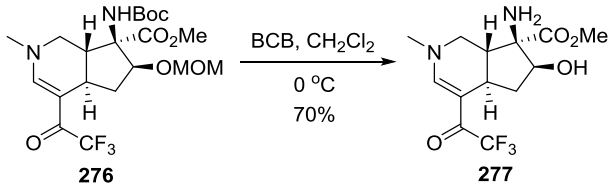
The next key step in the synthetic sequence towards microsclerodermin B was macrolactamisation. Initially, it was planned to (a) deprotect the *N*-terminus using TFA, (b) deprotect the *C*-terminus using piperidine and (c) promote cyclisation of the resulting linear hexapeptide using an appropriate activating reagent. Unfortunately, sequential treatment of linear hexapeptide **274** with TFA, piperidine and HATU resulted in a complex mixture of products (Scheme 55). When PyBOP was used instead of HATU, LCMS indicated that low yielding macrocyclisation did occur, but this only afforded products containing two or three TBS-groups, rather than the expected four. It was evident that partial cleavage of the TBS ethers occurred when hexapeptide **274** was exposed to TFA. Accordingly, alternative conditions were investigated to effect clean removal of the *N*-Boc group of **274**. Silyl triflates are one of the most useful reagents for *N*-Boc cleavage in the

presence of acid labile functionalities,[54] however, exposure of **274** to TMSOTf led primarily to decomposition. *B*-Bromocatecholborane (BCB) has been reported as a very mild Lewis acid for *N*-Boc cleavage.[62] However, when three equivalents of this reagent were used, only cleavage of the *O*-TBS groups of hexapeptide **274** was observed and the *N*-Boc remained untouched. Increasing the amount of BCB led to decomposition of hexapeptide **274**, thereby highlighting its sensitivity to even mild Lewis acids.



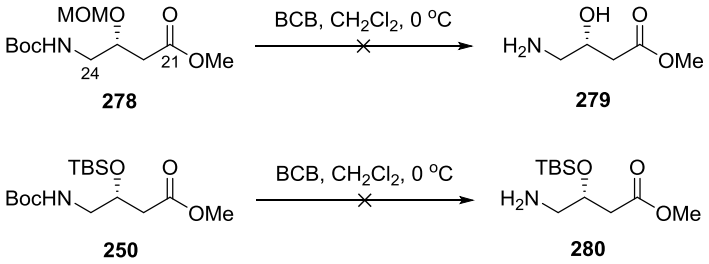
Scheme 55. Attempts to cleave the *N*-Boc group of **274**.

A key consideration for the macrolactamisation step was whether the C23 hydroxyl of the GABOB unit needed to be protected or not for cyclisation to occur. In Ma's synthesis of microsclerodermin E, cleavage of the protecting group at this position was specifically undertaken prior to cyclisation.[10] This suggested that a free hydroxyl group may be beneficial for macrocyclisation; this issue was investigated at the same time as studies on *N*-Boc cleavage of substrate **274**. Initially, TES or MOM protecting groups were considered ideal for selective liberation of the C23 hydroxyl in the presence of the AMMTD *O*-TBS ethers. This choice was guided further by studies from Kende and co-workers, who demonstrated concomitant removal of the *N*-Boc and MOM groups of compound **276** under mild conditions (BCB) (Scheme 56).[63]



Scheme 56. Concomitant cleavage of *N*-Boc and MOM protecting groups using BCB.

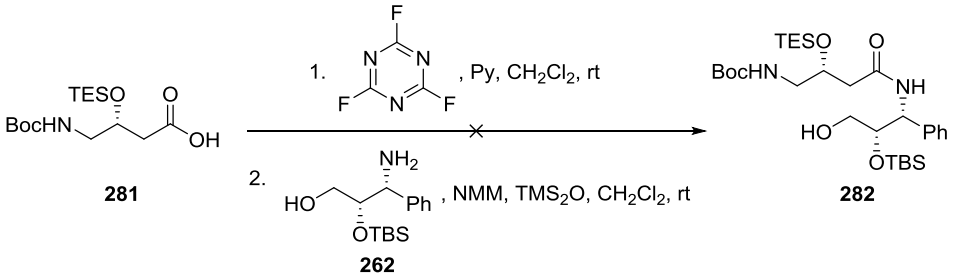
GABOB substrate **278** was prepared and used as a model system to study simultaneous cleavage of the Boc- and MOM-groups, whereas analogue **250** was used to check the stability of TBS ethers under the reaction conditions (Scheme 57). Unfortunately, in both cases only decomposition of the substrates was observed. Consequently, further studies on protection of the C23 hydroxyl of **278** as its MOM ether were abandoned, and, additionally, no further studies were conducted with *B*-bromocatecholborane.



Scheme 57. Model studies on concomitant cleavage of *N*-Boc and MOM ethers using BCB.

An *O*-TES group was considered as an alternative for protection of the C23 hydroxyl. These are less bulky than TBS ethers and there is literature precedent for the selective cleavage of secondary TES protected alcohols in the presence of secondary TBS protected hydroxyls.[50] However, because *O*-TES groups are more labile than TBS ethers,

potential issues were anticipated during the preceding acid fluoride promoted amide bond formation (Scheme 58). Accordingly, *O*-TES protected GABOB **281** was prepared and tested under these coupling conditions with model amino alcohol **262** (Scheme 58). Unsurprisingly, the reaction did not lead to amide **282** and only the formation of undefined side-products was observed, possibly as a result of *O*-TES cleavage.

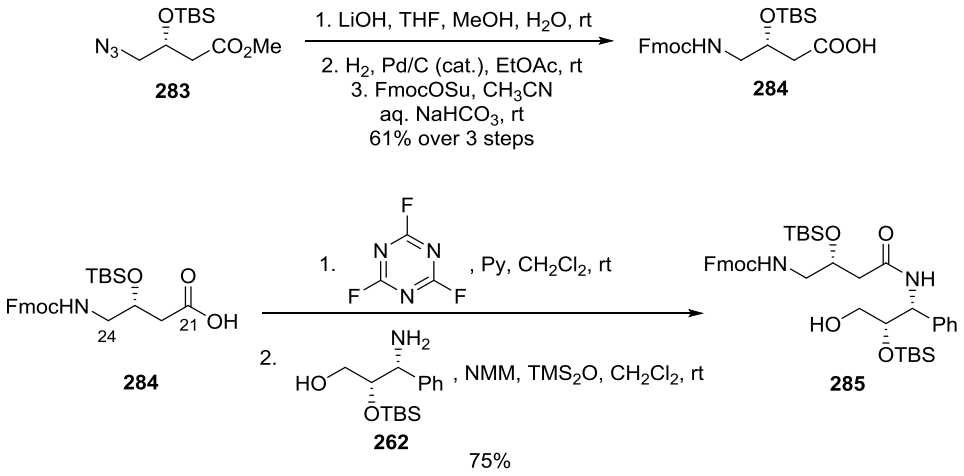


Scheme 58. Attempted acid fluoride coupling of *O*-TES protected GABOB **281** with a model amine.

Because of the observations outlined above, the "free C23 hydroxyl strategy" was not pursued further and a TBS ether was retained at this position. The inability to cleave the *N*-Boc carbamate at C24 of **274**, prompted a revision of this protecting group to one that could be cleaved selectively under mild conditions. Extensive literature research was undertaken into the compatibilities of potential alternative protecting groups, leading to the conclusion that an Fmoc carbamate would be suitable. Cleavage of these employs mild amine bases such as piperidine, diethylamine, DBU and, less commonly, Et_3N or DIPEA.[64] In the proposed synthetic sequence it was anticipated that this approach might enable concomitant deprotection of the *C*- and *N*-termini of the linear hexapeptide.

Fmoc carbamates are sensitive to fluoride,[65] and so compatibility studies on acid fluoride formation and subsequent coupling to AMMTD were undertaken using model

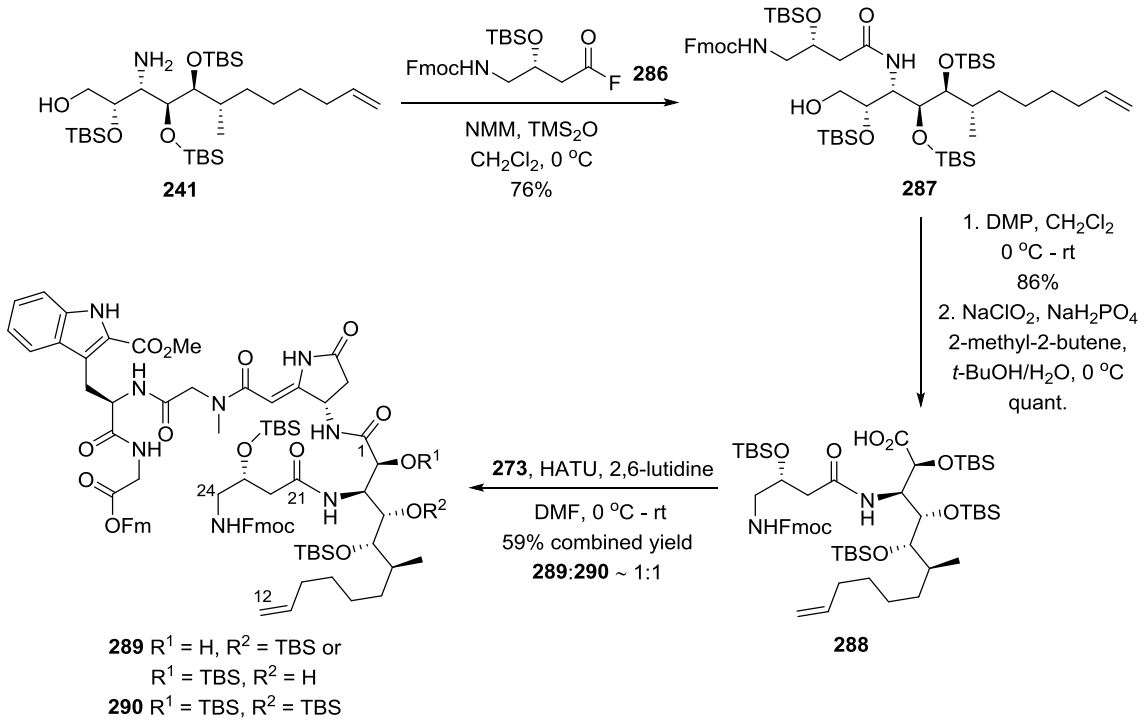
substrate **262** (Scheme 59). *N*-Fmoc protected GABOB **284** was prepared from azide **283** in three steps, using literature procedures.[10,11] Pleasingly, conversion to the corresponding acid fluoride and subsequent amide bond formation with amine **262** proceeded smoothly and no cleavage of the *N*-Fmoc group was detected.



Scheme 59. Coupling of *N*-Fmoc, *O*-TBS protected GABOB with the model amine.

Based on these studies, *N*-Fmoc protected GABOB **284** was incorporated into the synthesis of AMMTD-GABOB dipeptide **287**. Adoption of previously developed conditions then allowed conversion of **288** to a mixture of linear hexapeptides **289** and **290**, which both possess a Fm ester at the *C*-terminus and a Fmoc carbamate at the *N*-terminus (Scheme 60). For **289**, unexpected cleavage of C2 or C4 *O*-TBS ether had occurred; due to the complexity of the NMR data, it was not possible to identify unambiguously which hydroxyl group had been liberated. This issue appeared to arise because of the instability of acid **288**, which decomposed slowly on standing and so was best used immediately. Amide bond formation between **288** and **273** was reasonably slow, presumably because both coupling partners are bulky, and this allowed competitive

de-silylation of acid **288** to occur in solution to generate linear hexapeptide **289**. Despite this complication, it was found that linear hexapeptides **289** and **290** could be separated by flash column chromatography and carried through further steps (see below) and so the *O*-TBS cleavage was not a major concern.



Scheme 60. Synthesis of *N*-Fmoc protected linear hexapeptides **289** and **290**.

Formation of macrocyclic amides is not a trivial transformation because high conformational entropic penalties must be overcome, whilst avoiding competing pathways such as dimerisation and oligomerisation. Additionally, macrolactamisation precursors contain both nucleophilic and electrophilic sites, and so selective activation of the carboxylate must occur in the presence of a more nucleophilic amine. Consequently, not all methods for conventional peptide coupling are transferable to the formation of cyclic systems.

An extensive literature survey on macrolactamisation methods identified four predominant protocols. The first involves phosphonium reagents, such as BOP, PyBOP and PyAOP, which have a key advantage over uronium variants, as they do not react with amines (Figure 8A).[57] This is because P−N bonds are comparatively weak and so selective reaction with carboxylates can be achieved. Reagents containing a pyrrolidine moiety instead of a dimethylamine unit circumvent the generation of highly toxic HMPA and so PyBOP and PyAOP are most commonly used.[66] Of these, PyAOP is considered superior, because the pyridine moiety assists with amide formation (Figure 8A). Often, these reagents are used in the combination with HOAt or HOBt additives, which suppress epimerisation and/or facilitate activation of the carboxylic acid.[67]

A second important macrolactamisation protocol uses phosphorus-based reagents such as DPPA, BOP-Cl and DEPBT (Figure 8B). The most widely used reagent of this class is DPPA, and, indeed, this was employed by Ma for macrolactamisation *en route* to microsclerodermin E, albeit in low yield.[10,68] As with phosphonium-based approaches, this method has the advantage of selectively activating the carboxylate terminus, thereby preventing undesired reaction with the amine moiety.

A third common protocol employs pentafluorophenol activated esters. These can be accessed from the carboxylic acid using either FDPP or a combination of pentafluorophenol and EDC (Figure 8C).[69] Generally, this method does not provide high reactivity and so is not suitable for challenging macrocyclisations.

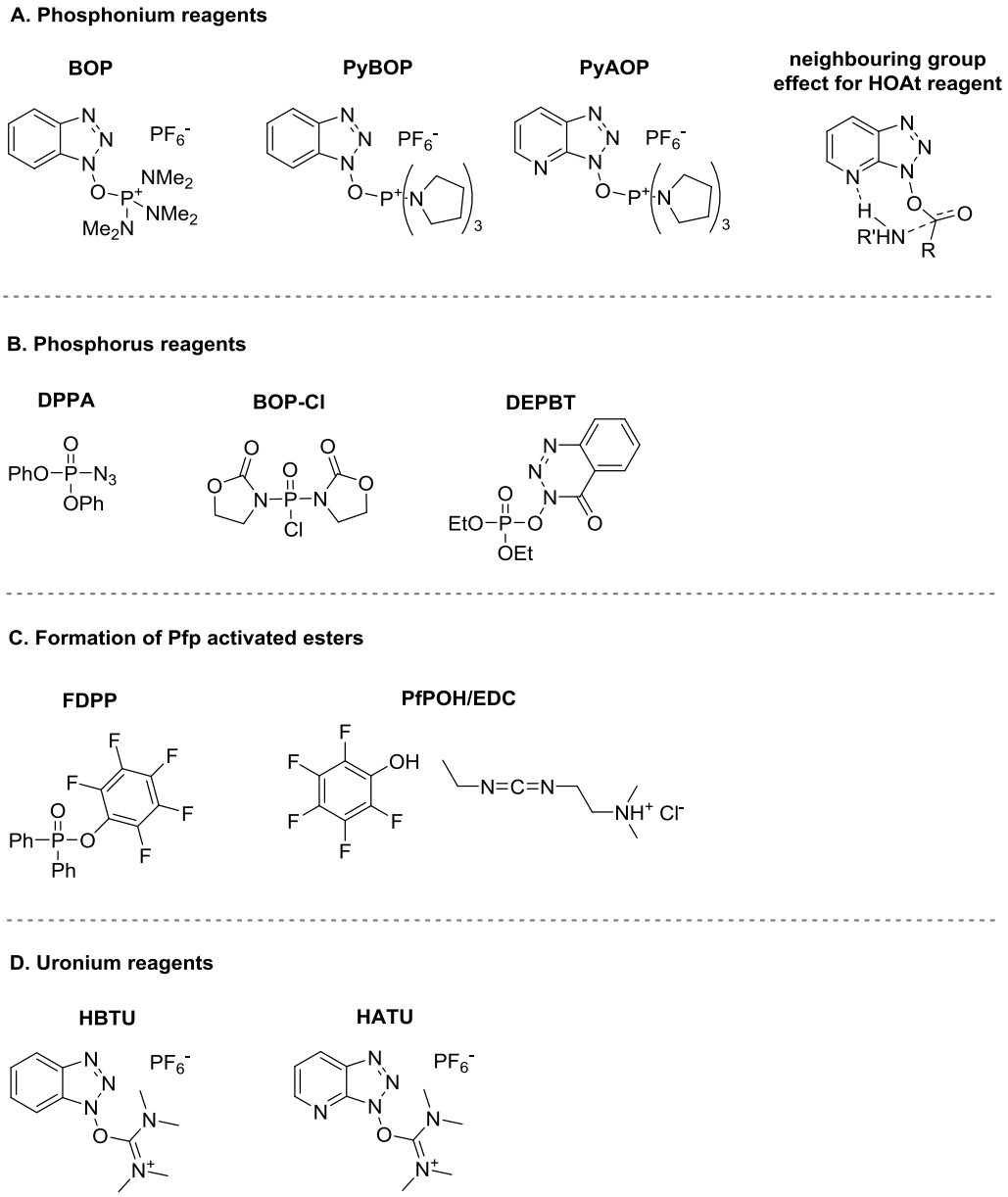


Figure 8. Reagents for macrolactamisation.

Despite potential side-reactions between the amine functionality and the activating agent, uronium coupling reagents are widely used for the formation of macrolactams. HATU and HBTU are regarded as the most reactive, with HATU often considered to be the "golden standard" (Figure 8D).[70] The main drawback with uronium reagents is that they are incompatible with hindered substrates, and, in these cases, reaction with the amino

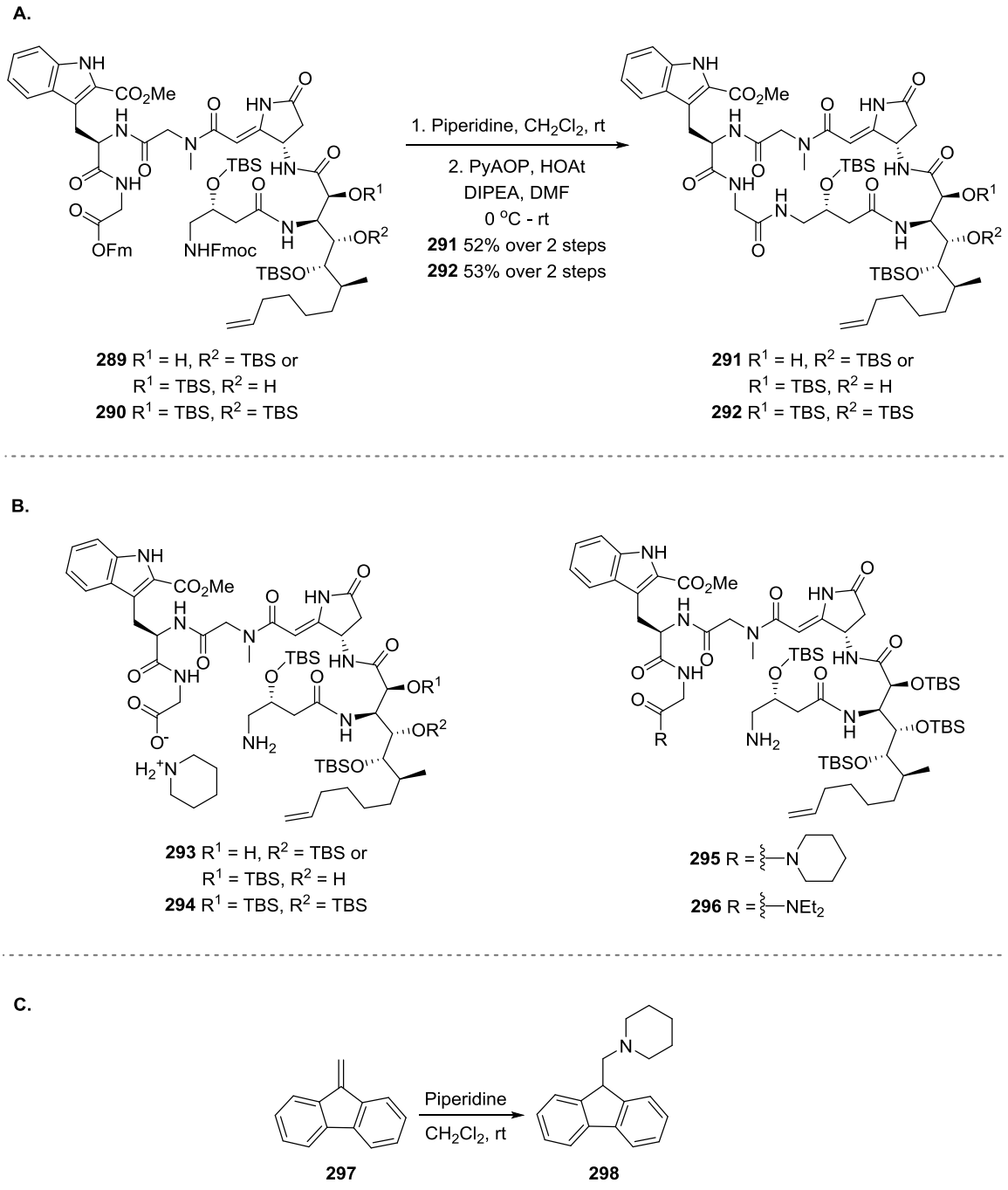
moiety often proceeds faster. Another issue is that an excess of the activating reagent is usually employed and, again, this can lead to detrimental reaction with the amine.

Based on the considerations outlined above, a PyAOP/HOAt activating system was chosen for macrocyclisation of linear substrates **289** and **290**. The first attempt at this involved initial treatment of **289** or **290** with piperidine to cleave the Fm ester and Fmoc carbamate. The crude amino acid was then exposed to PyAOP, HOAt and DIPEA in DMF under high dilution (2 μM), and, pleasingly, the desired cyclised product **291** was observed in low yield (24%). However, a major side-product was amide **295**, in which piperidine (from the *N*-Fmoc and Fm ester cleavage step) had coupled with the *C*-terminus; note that an analytically pure sample of **295** could not be obtained (Scheme 61B). Consequently, removal of all piperidine was required prior to macrolactamisation. However, this was considered challenging as it would require de-salting of carboxylate **293**/**294** in the presence of a free amino group.

To eliminate the problematic formation of piperidine amide **295**, Et_3N and DBU were investigated for deprotection of **289** and **290**, as it was anticipated that these two bases should easily perform the required deprotection. However, the key disadvantage of tertiary amine bases is their inability to trap debenzofulvene **297**, a by-product that can react further with the liberated amine or other nucleophilic groups.[64] Consequently, it is more common to use piperidine or diethylamine for the cleavage of Fmoc carbamates. When linear hexapeptide **289** was subjected to Et_3N or DBU, and then submitted to cyclisation conditions, only traces of the desired cyclic peptide **291** were obtained. Treatment of **289** with diethylamine allowed subsequent macrolactamisation to proceed in 20% yield, but this was accompanied by formation of the expected diethyl amide side-product **296** and other undefined impurities. Surprisingly, in this case, TLC analysis

indicated that debenzofulvene was not scavenged by diethylamine. This observation suggested that one of the issues associated with Fm and Fmoc cleavage was side-reaction between the released amine and debenzofulvene. In earlier attempts using piperidine, debenzofulvene had been scavenged successfully (Scheme 61C), and so studies turned back to the use of this base. After extensive investigation, the two-step procedure was improved by drying crude amino acid **293** or **294** under high vacuum at 40 ^{o}C for four hours and then subjecting it to flash column chromatography (2-5-25% MeOH/$CHCl_3$) to remove excess piperidine and by-products from the fluorenylmethoxy moiety. Piperidine salts **293** or **294** prepared in this fashion underwent macrocyclisation using PyAOP at high dilution (1 μM) to provide cyclic products **291** and **292** in good yields (Scheme 61A). The highly polar nature of the intermediates meant that it was difficult to monitor these reactions by TLC and so a prolonged reaction time of approximately one week was used to ensure complete conversion.

A surprising observation in the NMR spectra of cyclic peptides **291** and **292** was duplicated signals for protons and carbons near the tertiary amide bond. NMR experiments in DMSO-D_6 showed a 1:1 ratio of rotamers, whereas in CD_3OD a 4:1 ratio was observed; this latter solvent allowed full assignment of the ^{1}H and ^{13}C NMR spectra. The fact that cyclic peptides **291** and **292** were rotameric was concerning, as this feature is not present in any reported spectra of a microsclerodermin. At this stage, the synthesis was continued, because it was envisaged that the protecting groups may have been responsible for rendering **291** and **292** rotameric.

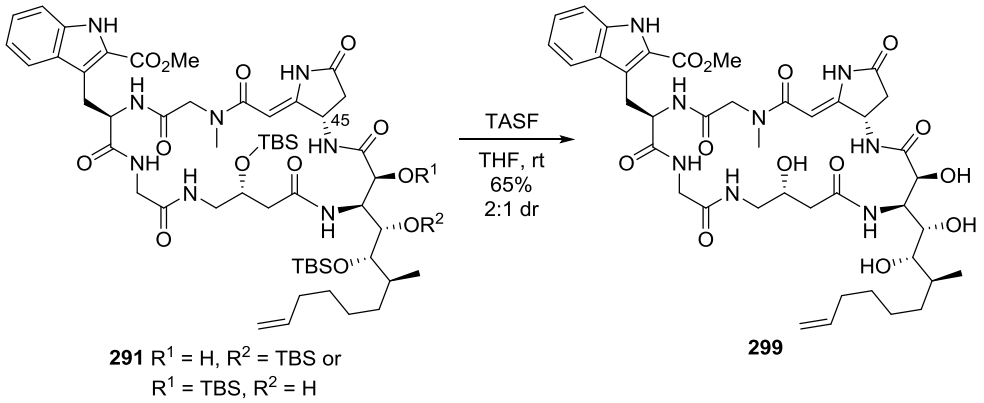


Scheme 61. Macrolactamisation studies.

3.5 Attempts to cleave the methyl ester of cyclic peptide 299

In accord with the retrosynthetic analysis presented in Scheme 21, further steps required transformation of protected cyclic peptides **291** and **292**, which contain an unsaturated pyrrolidinone core and a terminal double bond on the AMMTD residue, into "end-game" precursor **146**. To accomplish this, cleavage of the silyl ethers and the methyl ester was required.

Ma reported that the C45 stereocentre of substrates related to **291**, which contain an unsaturated pyrrolidinone unit, were susceptible to epimerisation when treated with TBAF (Scheme 5, Chapter 1).[10] TASF is regarded as one of the mildest fluoride sources for silyl ether cleavage,[71] and, accordingly, cyclic peptide **291** was treated with this reagent in THF in the hope of obtaining tetraol **299**. However, even using TASF, epimerisation of the C45 stereocentre took place to provide product **299** as a 2:1 mixture of diastereoisomers, fortunately, it was possible to separate the major and minor diastereoisomers by column chromatography (Scheme 62) (it was assumed that epimerisation took place at the C45 stereocentre based on Ma's report,[10] in the current case the diastereoisomers of **299** were not fully characterised due to contamination with minor impurities).

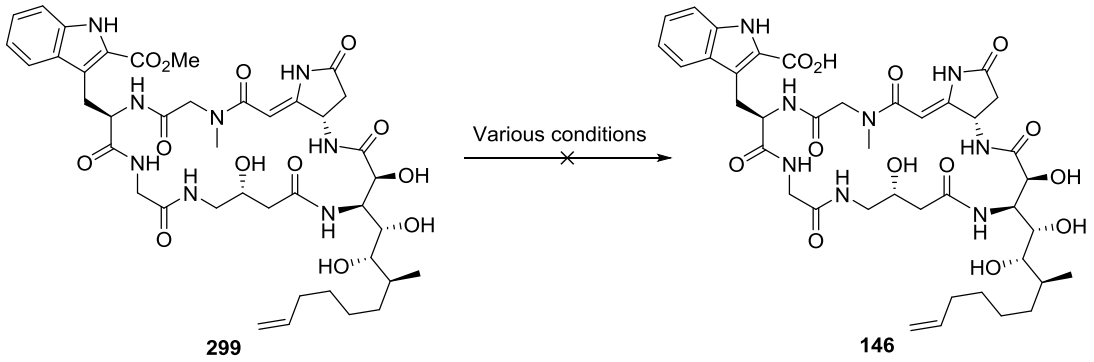


Scheme 62. Cleavage of the TBS groups of **291**.

The next challenge was cleavage of the methyl ester of the indole-2-carboxylate unit of **299**. Adaptation of a procedure reported by Ma, which used excess LiOH in THF/H_2O/MeOH at 0 ^oC and subsequent acidification with 1M HCl, gave a mixture of unidentified products.[10] Ma had noted the very sensitive nature of a similar substrate to acidic conditions. Nevertheless, it was reported that, after removal of solvent, microsclerodermin E was obtained under these conditions (see Scheme 9). Because of the very polar nature of the microsclerodermins, standard extraction procedures cannot be employed after the acidification step. In the case of **299**, TLC analysis after the LiOH step indicated one major component, which led to the false assumption (*vide infra*) that the issue lay in the acidification procedure. An alternative approach also failed, which involved acidification of the mixture with Amberlyst-15, such that the acid could be removed by filtration rather than concentration. Attempts to modify the "Ma conditions" by employing stoichiometric quantities of LiOH and HCl (rather than an excess) led to similar results. LCMS indicated the formation of a highly polar side-product where the mass had increased by 32 units. However, due to the scale of reaction and lack of material, the structure of this component could not be determined. The observed increase in mass could be attributed to incorporation of a molecule of MeOH, however, when MeOH free conditions were evaluated this side-product was still formed.

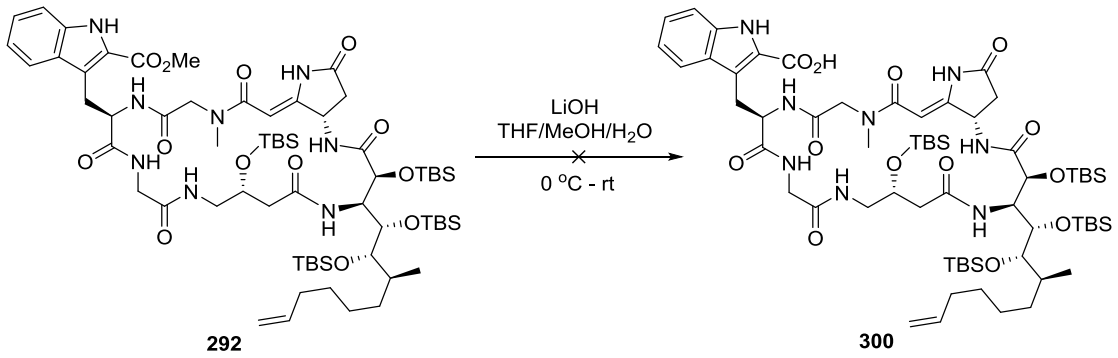
An extensive evaluation of the literature identified Me_3SnOH as a reagent for mild methyl ester hydrolysis, as first reported by Nicolaou.[72] This method has been employed on a range of substrates that are sensitive to epimerisation or prone to other side-reactions. Indeed, the protocol is widely used in total synthesis and seemed well suited to the case in hand. Accordingly, methyl ester **299** was heated in 1,2-dichloroethane at 60 or 80 ^oC with an excess of Me_3SnOH. However, only traces of desired product **146** were observed by

MS, with the mass balance consisting of starting material and a complex mixture of unidentified side-products. Full conversion of **299** could not be achieved, even with 25 equivalents of Me_3SnOH at 80 °C for three days.



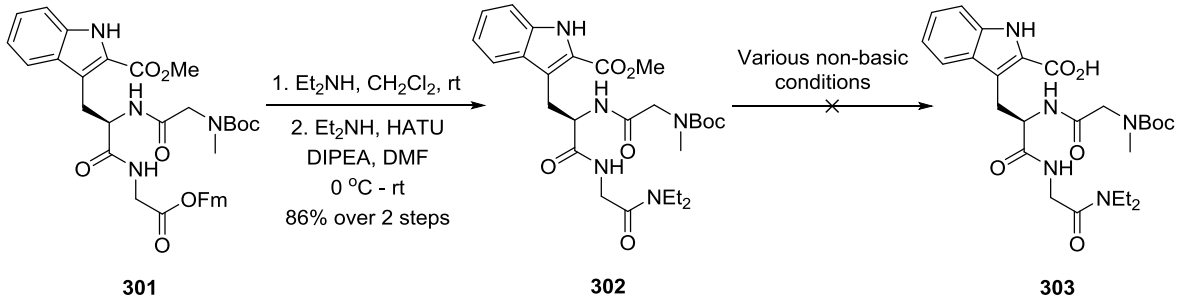
Scheme 63. Attempts to hydrolyse the methyl ester of substrate **299**.

Methyl ester hydrolysis was also investigated on protected cyclic peptide **292**. Treatment of this with 1.2 equivalents of LiOH resulted in no conversion of starting material, which was surprising, as under similar conditions tetraol **299** was fully consumed. Addition of further LiOH led to the formation of several side-products and, when the reaction mixture was acidified (as previously), partial cleavage of the TBS ethers was observed to provide a complex mixture of inseparable components (Scheme 64).



Scheme 64. Attempt to hydrolyse the methyl ester of substrate **292**.

Cyclic peptides **299** and **292** were available in small quantities and consequently were extremely precious. Further conditions for methyl ester hydrolysis were therefore explored on model substrate **302** (Scheme 65). This was easily prepared in two steps from intermediate tripeptide **301** by cleavage of the Fm ester and subsequent coupling with diethylamine.



Scheme 65. Attempts to hydrolyse the methyl ester of substrate **302**.

Model methyl ester **302** was subjected to a variety of non-basic hydrolysis protocols, such as LiI in DMF at 60 °C,[73] TMSI in CH_3CN at 60 °C[74] and pig liver esterase in acetone/phosphate buffer.[75] However, none of these conditions provided the corresponding acid. In the case of LiI and pig liver esterase, starting material remained

intact, whereas decomposition was observed using TMSI. The use of *excess* LiOH was the only procedure found that could effect hydrolysis. Because an excess of LiOH was required for model substrate **302**, it was assumed that the earlier attempt to hydrolyse the methyl ester of cyclic peptide **299** with 1.1 equivalents of LiOH had not resulted in reaction at the methyl ester moiety (the formation of an unidentified side-product had been observed).

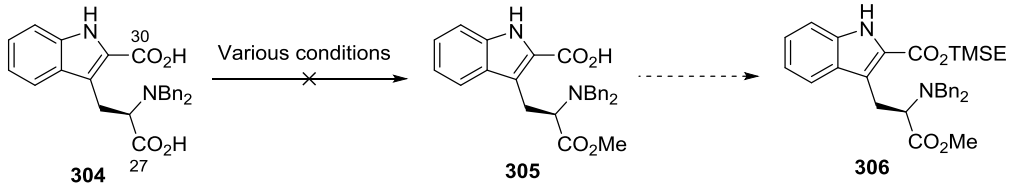
Based on these studies, use of a methyl ester as the protecting group for the indole carboxylic acid was abandoned. Clearly, a different protecting group was required for this position, but this choice had to be carefully considered because the late-stage hexapeptide was extremely sensitive to both basic and acidic conditions.

Chapter 4 Synthesis and stereochemical reassignment of dehydromicrosclerodermin B

4.1 Revised route to tryptophan-2-carboxylate

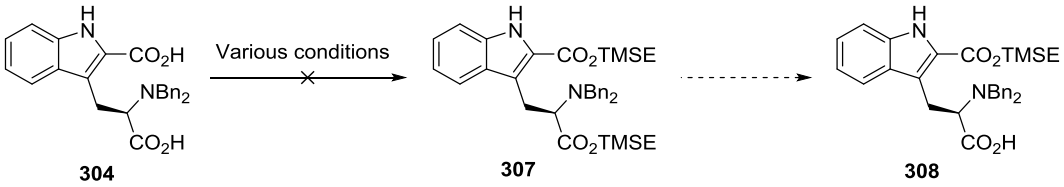
As mentioned at the end of Chapter 3, a new protecting group for the indole carboxylic acid was required. After extensive consideration, a trimethylsilylethyl (TMSE) ester was selected in place of the incompatible methyl ester. The main reason for this choice was the ability to cleave the TMSE group using TASF, a reagent that earlier studies had shown was compatible with late-stage substrates, albeit with partial epimerisation of the C45 stereocentre (Scheme 62). Another important consideration for the use of a TMSE group was that it would avoid the need to acidify with strong acids. This approach seemed promising and it was hoped that conditions could be developed that would avoid C45 epimerisation. Consequently, a synthetic sequence to a TMSE protected cyclic peptide was pursued.

Initial studies on the synthesis of a TMSE protected tryptophan-2 carboxylic acid derivative focused on intermediate **304**; this diacid was prepared by Dr Robert Pullin using protocols previously developed by Ma.[10] One of the strategies for installing protecting groups onto **304** involved initial mono-methylation of the C27 carboxylate, followed by esterification of the indole-2-carboxylic acid with trimethylsilylethanol. Unfortunately, selective mono-methylation of the C27 acid, with $TMSCHN_2$ or MeI, could not be achieved, as in all cases mixtures of starting material, monomethylated and bismethylated products were formed (Scheme 66).



Scheme 66. Attempts to perform monomethylation of diacid **304**.

Another approach for the installation of the protecting groups onto substrate **304** involved double protection of the diacid with TMSE groups (Scheme 67). In previous studies by Ma, selective monocleavage of the C27 methyl ester in the presence of one at C30 was possible,[10] (Scheme 7, Chapter 1) and so it was hoped that the corresponding TMSE analogue **307** would behave similarly. Bisesterificated product **307** had never previously been synthesised, so several esterification methods were explored in order to install the two TMSE groups. Activation of **304** in the presence of TMSE-OH using Steglich esterification conditions (DCC or EDC), MsCl, CDI or HATU was not successful. An alternate approach involving *O*-alkylation with excess commercially available trimethylsilylethylbromide was also ineffective. In all cases, either mixtures of side-products were observed or starting material was not consumed.

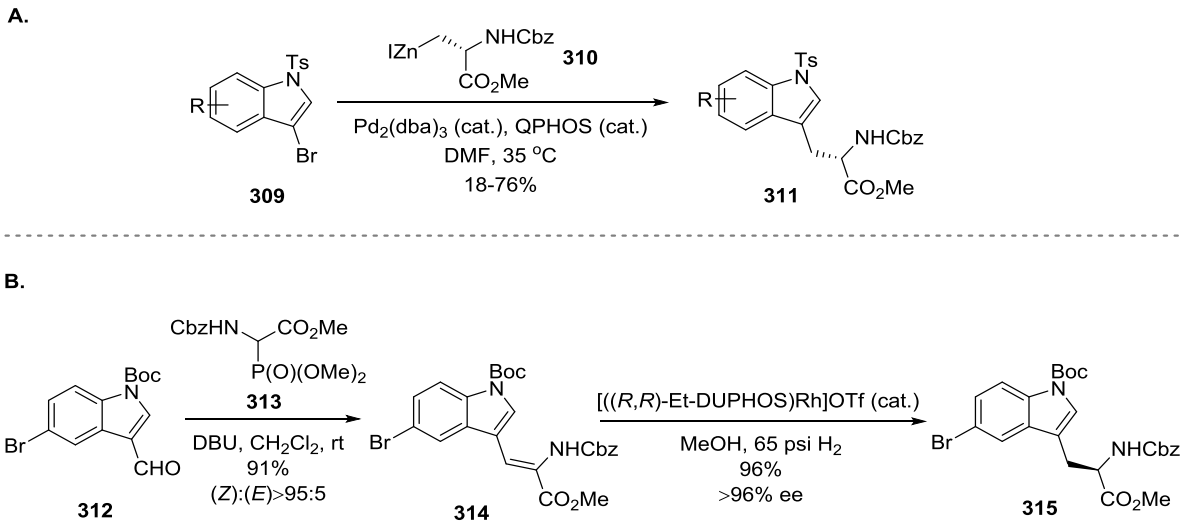


Scheme 67. Attempts to bisesterify diacid **304**.

Because installation of the required TMSE group onto intermediate **304** failed, a revised approach to the target amino acid was devised. Several methods for the synthesis

of tryptophan derivatives exist.[76] Of particular interest were those that employ 2-indole carboxylic acid as a starting material. This would enable the problematic TMSE ester formation to be performed at the earliest possible stage. Two known methodologies appeared to be attractive.

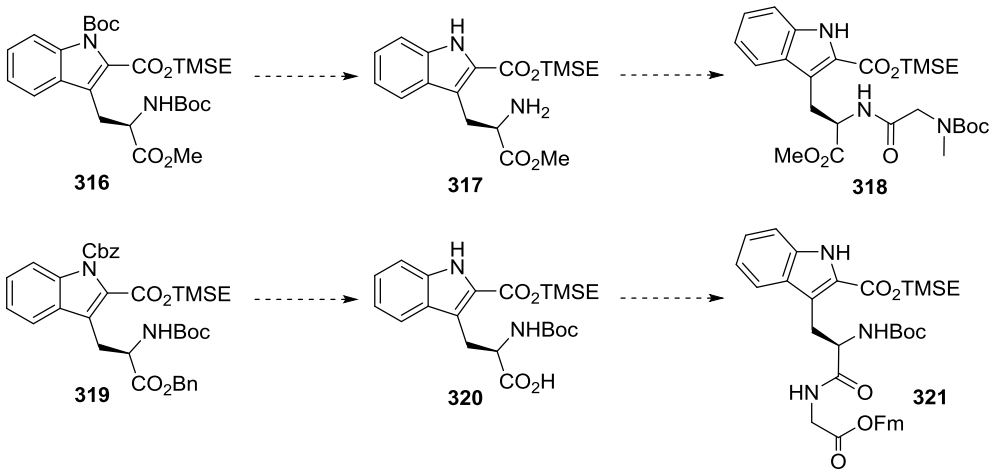
The first of these, reported in 2011 by Yokoyama, was based on Negishi coupling between *N*-protected 3-indole bromides **309** and organozinc reagent **310,** which is derived from an iodoalanine derivative (Scheme 68A).[77] The zinc reagent can be prepared *in situ* using catalytic amounts of 1,2-dibromoethane and trimethylsilyl chloride with gentle heating. The efficiency of the approach is highly dependent on the indole *N*-protecting group, with sulfonamides providing superior results to carbamates. C2 substituted indoles were not viable substrates under the reported conditions.



Scheme 68. (A) Negishi coupling and (B) HWE-enantioselective hydrogenation approaches in the synthesis of tryptophan derivatives.

The second promising methodology, reported by Hruby in 2001, employed Horner-Wadsworth-Emmons olefination between 3-indole carbaldehyde **312** and phosphonate **313**, followed by enantioselective hydrogenation (Scheme 68B).[78] A Boc group was chosen to protect the indole nitrogen and an orthogonal *N*-Cbz was chosen for phosphonate **313**, which can be prepared in four steps from benzyl carbamate.[79] Note that outcomes of processes involving other protecting group combinations were not disclosed. However, an important aspect of this methodology was its applicability to C2-substituted indoles.

The Negishi coupling approach appeared more attractive as it would take four steps from 2-indole carboxylic acid, which was one less than the olefination-hydrogenation strategy. Additionally, it seemed highly likely that a TMSE ester would survive the sequence and iodoalanine derivative **310** is much easier to prepare than phosphonate **313**. However, two aspects of this approach were concerning, with the first regarding the indole protecting group. For the envisaged synthesis of microsclerodermin B, it was desirable to perform cleavage of the indole protecting group at the same time as liberation of the *C*- or *N*-terminus of **316** or **319** (Scheme 69). Therefore, a Boc- or Cbz-carbamate was most suitable rather than an *N*-Ts, which was reported as most effective for the Negishi coupling.[77] The second key issue was the presence of an electron withdrawing ester substituent at the 2-position of the indole ring; substitution at this position was not tolerated in the original Negishi coupling report.

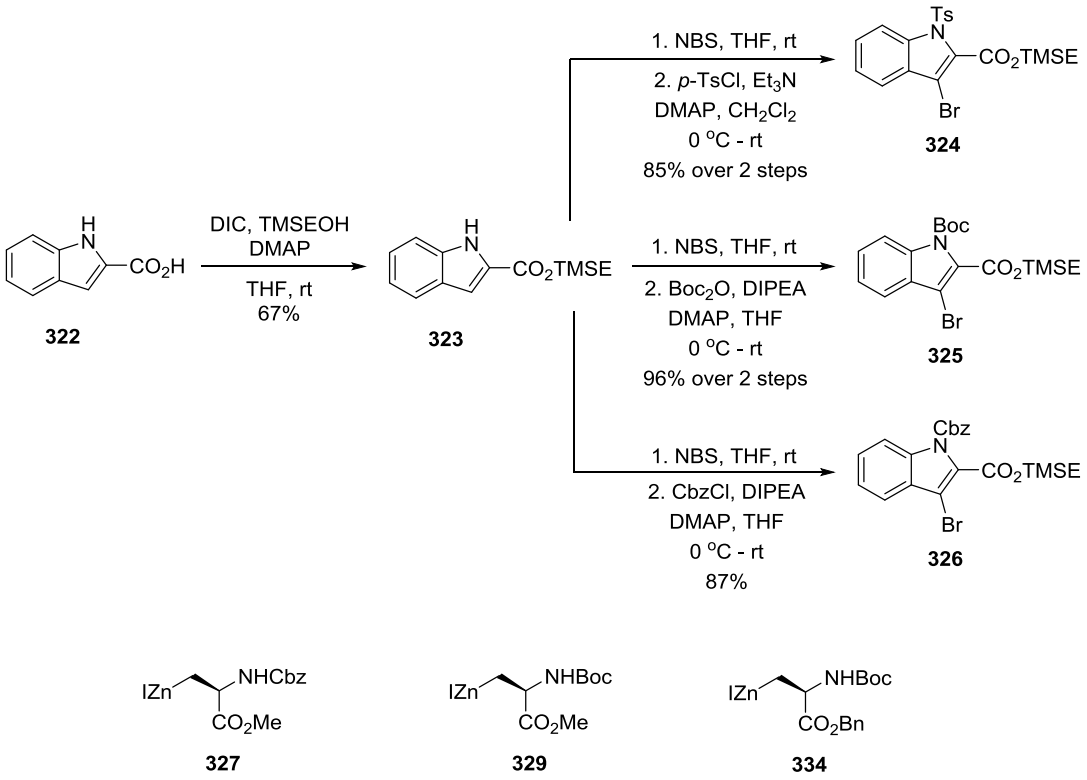


Scheme 69. Protecting group strategy for tryptophan-2-carboxylic acid.

Despite the issues outlined above, studies were undertaken to develop a Negishi-based approach to ester **316**/**319**. The first step in the sequence involved esterification of indole-2-carboxylic acid **322** to provide **323**, which somewhat surprisingly was not a known compound (Scheme 70). An initial attempt to install the TMSE group of **323** using the Steglich esterification procedure (EDC) provided only 12% yield of ester **323**. By switching from EDC to DCC, an increased yield (59%) of **323** could be achieved, but purification was extremely challenging. However, changing the activating agent to DIC enabled the clean isolation of **323** in 67% yield, with the mass balance consisting of an unidentified side-product. Attempts to esterify the carboxylic acid of **322** using trimethylsilylethylbromide or Mitsunobu conditions failed.

Bromination of the 3-position of **323** using NBS was followed by protection of the indole nitrogen, with TsCl, Boc_2O or CbzCl, to furnish Negishi precursors **324**, **325** and **326**. A range of differentially protected substrates was targeted so as the impact of the *N*-substituent on the Negishi reaction could be examined. The requisite organozinc reagents **327**, **329** and **334** were prepared from iodoalanine precursors,[77]

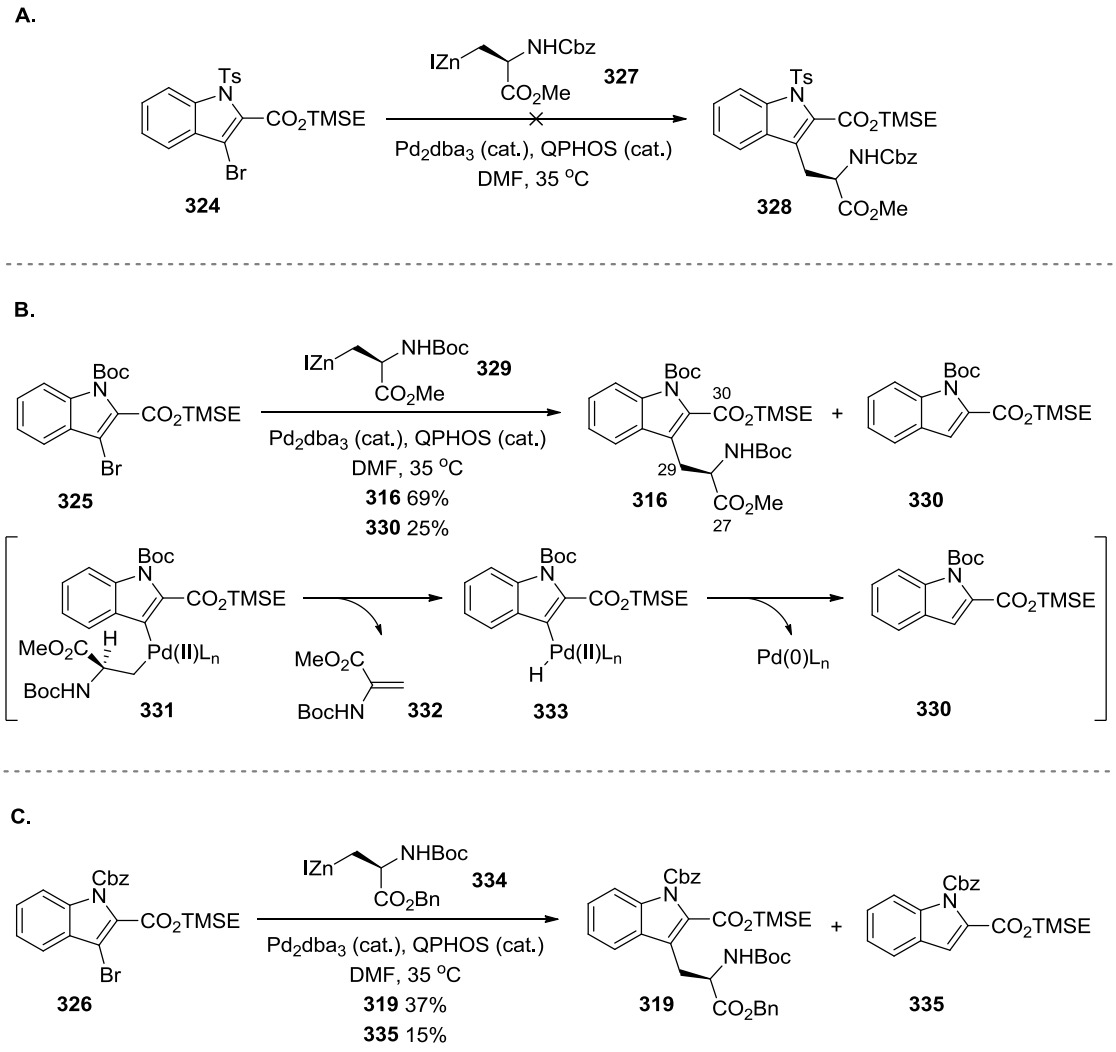
which, in turn, were generated by Appel iodination of the corresponding D-alanine derivative.[80]



Scheme 70. Synthesis of the Negishi coupling partners.

As expected, when substrates **324**, **325** and **326** were subjected to the reported Negishi conditions,[77] different outcomes were observed in each case (Scheme 71). *N*-Ts indole bromide **324** afforded a complex mixture, from which none of desired product **328** could be isolated (Scheme 71A). This result was concerning as in Yokoyama's report, *N*-sulfonamides provided the best results.[77] Fortunately, coupling of Boc protected indole bromide **325** with the organozinc reagent **329** derived from Boc protected iodoalanine provided the desired product **316** in 69% yield (Scheme 71B). This set of protecting groups was preferred, because concomitant cleavage of both Boc-groups could be

achieved later in the sequence (see Scheme 69). The main side-product of this reaction was proto-depalladation adduct **330**, which likely arises *via* reductive elimination of palladium hydride **333**, itself generated by β-hydride elimination from intermediate **331**. Indeed, aminoacrylate side-product **332** was also observed. The conversion of **325** to **316** was robust and could be conducted readily on multi-gram scale. Additionally, the enantiopurity of **316** was confirmed by formation and analysis of the corresponding Mosher's amides (see the Experimental section).



Scheme 71. The Negishi coupling in the synthesis of Trp-2-CO_2TMSE.

Additional studies established that coupling of *N*-Cbz protected indole bromide **326** with organozinc reagent **334** provided Negishi adduct **319** in moderate yield (37%) (Scheme 71C). Here, significant quantities of proto-depalladation product **335** formed, and a dimeric indole side-product was also observed. Compound **319** was suitably protected to allow concomitant cleavage of the *N*-Cbz carbamate and the benzyl ester (Scheme 69). This was important, as subsequent studies showed that cleavage of the *N*-Boc group and methyl ester of **316** was not trivial. Consequently, substrate **319** could have been a viable alternative, however, due to the low yield of the Negishi reaction (which could not be optimised) this option was abandoned.

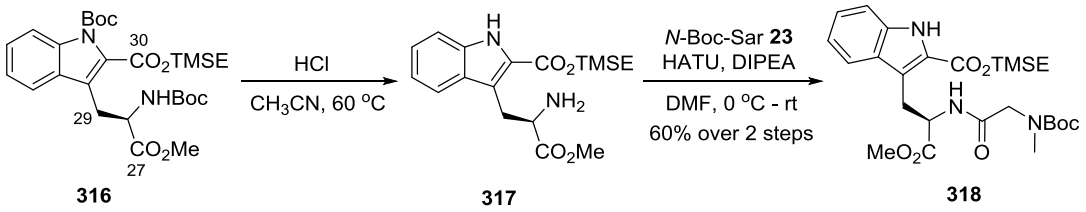
4.2 Synthesis of the TMSE containing Gly-Trp-Sar-Pyrr tetrapeptide

Having obtained tryptophan-2-carboxylate in a viable protected form (**316**), its incorporation into the northern hemisphere of microsclerodermin B was pursued. This required the identification of conditions for the removal of the protecting groups and for subsequent peptide coupling of the deprotected terminus.

Studies were undertaken to enable simultaneous deprotection of the C28 nitrogen and indole moiety of **316**. Removal of *N*-Boc groups from indoles tends to require much harsher conditions than primary amine derived variants.[56,81] A complication was that the TMSE group of **316** needed to be retained, but this functionality is known to be acid sensitive.[82,83] Unsurprisingly, typical conditions for Boc-group cleavage from **316** using TFA resulted in mixtures of mono- and bis-deprotected substrates, and low mass recovery, likely due to competing TMSE ester cleavage. The use of silyl triflates (TBSOTf and TMSOTf) resulted in selective deprotection of the C28 amino-carbamate and left the indole *N*-Boc group intact. Attempted thermolytic cleavage (180 ^{o}C) of the *N*-Boc groups

was successful, but also facilitated subsequent attack of the liberated C28 amine onto the C30 ester.

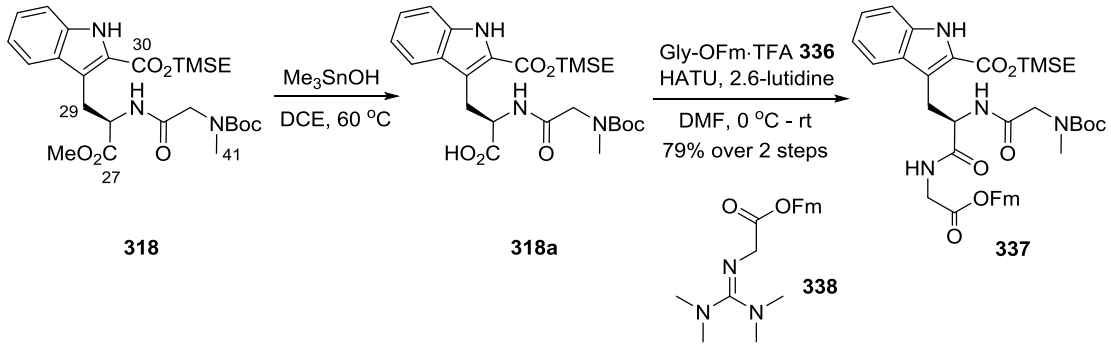
It has been reported that selective cleavage of *N*-Boc groups in the presence of TMSE esters can be achieved using dry HCl in organic solvent.[82] Ultimately, it was this approach that enabled access to free amine **317**. After an extensive evaluation of reaction temperature, equivalents of HCl and reaction solvents, it was found that treatment of **316** with 8-10 equivalents of HCl (as a 4M solution in dioxane) in CH_3CN at 60 ^oC provided the best results. Very careful monitoring of the reaction (by TLC and MS) was required for optimal yields of **317**. The crude amine **317** was then coupled with the sarcosine unit **23** to provide dipeptide **318** in 60% yield over two steps (Scheme 72).



Scheme 72. Synthesis of dipeptide **318**.

Previous studies by Ma[10] and Dr Robert Pullin showed that selective cleavage of the C27 methyl ester of **46** in the presence of the C30 ester could be achieved using 1.05 equivalents of LiOH (see Scheme 7, Chapter 1). Unfortunately, when dipeptide **318** was subjected to these conditions hydrolysis of the TMSE ester was the predominant reaction pathway. It is likely that this is facilitated by nucleophilic attack of hydroxide onto the silicon centre rather than onto the C27 carbonyl. As outlined in Section 3.5, trimethyltin hydroxide is a mild reagent for the selective hydrolysis of methyl esters in the presence of base sensitive functionality.[72] Indeed functional groups such as *N*-Fmoc, *N*-Ac

and more hindered esters (e.g. isopropyl and ethyl) remain intact when heated with an excess of this reagent.[72] Pleasingly, this protocol provided excellent selectivity for the hydrolysis of **318** and competitive cleavage of the TMSE ester was not observed. To achieve full conversion, 7.8 equivalents of trimethyltin hydroxide were employed at a temperature of 60 °C.[72] After optimisation, subsequent coupling of acid **318a** with a protected glycine derivative **366** proceeded smoothly using common peptide bond formation conditions (Scheme 73). The success of this transformation took into account two key issues. Firstly, only 1.05 equivalents of Gly-OFm·TFA **366** and 1.1 equivalents of HATU were used, since excess amine and activating reagent led to the formation of side-product **338**, which results from attack of the amine of **336** onto the uronium moiety of HATU. Compound **338** was inseparable from tripeptide **337** and so its formation had to be minimised. Secondly, 2,6-lutidine was used as a weak hindered base to avoid cleavage of the Fm group; this pathway was problematic when Et_3N or DIPEA were employed.



318 **318a** **338** **337**

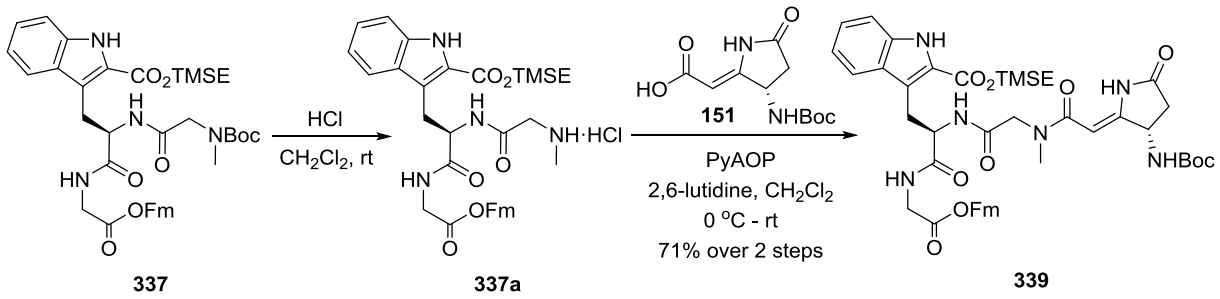
Scheme 73. Synthesis of tripeptide **337**.

A notable feature of the NMR spectra of tripeptide **337** was that most of the signals were duplicated due to restricted rotation around the tertiary carbamate bond. High temperature NMR experiments were conducted in DMSO-D_6 at 90 °C, and, under these

conditions, convergence of the two sets of signals was observed, thereby supporting a rotameric relationship (see the Experimental section). Note that in the NMR spectra of dipeptide **318** the signals were broad, but two distinct sets were not observed.

At this stage, completion of the northern hemisphere of microsclerodermin B required *N*-Boc group cleavage from the sarcosine unit of **337** and subsequent coupling with the pyrrolidinone unit. The former step was readily accomplished using HCl in dioxane at room temperature and no cleavage of the TMSE ester was observed. Coupling of deprotected tripeptide **337a** with pyrrolidinone amino acid **151** proved to be challenging due to the hindered nature of the nucleophile. Optimisation of this reaction was performed with co-worker Hang Xu, and this involved the exploration of several peptide bond formation methods. Addition of a variety of coupling reagents to a solution of deprotected tripeptide **337a** and carboxylic acid **151** did not afford **339** in yields above 50%, regardless of the activator employed. Pre-activation of **151** as the corresponding pentafluorophenol ester, an approach that had been used by Ma,[10] gave **339** in 58% yield, but the pre-activation step was very low yielding and so this protocol was abandoned. In all of these initial efforts, the formation of multiple unidentified side-products accounted for the inefficiencies observed. It was reasoned that this was due either to the low reactivity of the amine of deprotected **337a** or sluggish activation of the acid of **151**. Accordingly, prior activation of pyrrolidinone amino acid **151** was performed by exposure to PyAOP for two hours at 0 ^{o}C and this was followed by addition of amine **337a** to yield target **339**. For this process, CH_2Cl_2 was used as solvent to (a) mitigate potential side-products that might arise using DMF as solvent, and (b) to avoid the requirement of performing an aqueous work-up on polar product **339**. Under these optimised conditions the yield of **339** was increased to 71% over two steps (Scheme 74). Room temperature NMR spectra of tetrapeptide **339**

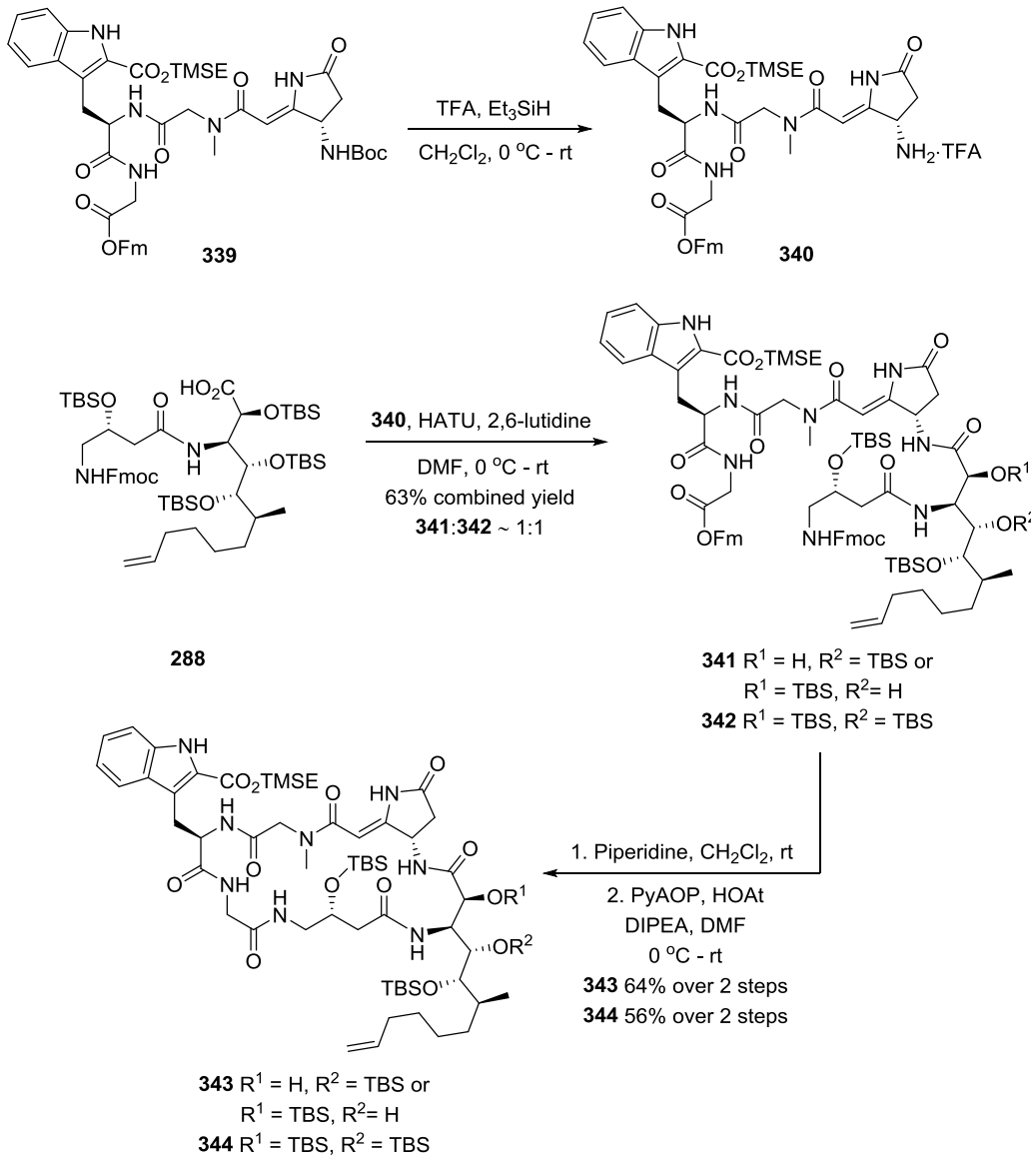
showed two rotameric forms likely due to restricted rotation about the tertiary amide bond; convergence of these signals was observed at 90 ^{o}C (see the Experimental section).



Scheme 74. Synthesis of tetrapeptide **339**.

4.3 Synthesis of the TMSE containing cyclic peptide and attempts to apply the "end-game" strategy

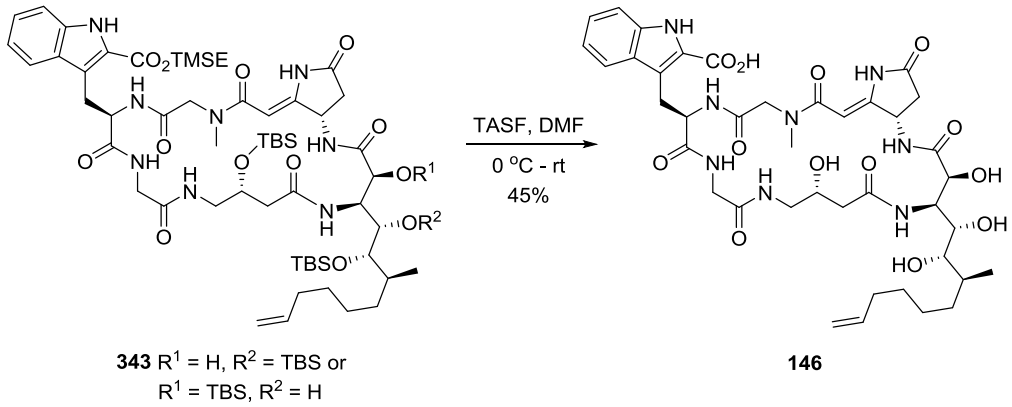
Having accessed the northern hemisphere with a TMSE protecting group on the indole-2-carboxylic acid unit and with ample AMMTD-GABOB dipeptide in hand, linear hexapeptides **341** and **342** were synthesised (Scheme 75). *N*-Boc deprotection of tetrapeptide **339** using TFA/Et_3SiH provided amine **340** cleanly, with no complications resulting from the acid sensitivity of the TMSE group. However, the pyrrolidinone unit of **339** was unstable and other acids such as HCl were not suitable. Coupling of a slight excess of TFA salt **340** with acid **288** was achieved using HATU and 2,6-lutidine in DMF to furnish a 1:1 mixture of linear hexapeptides **341** and **342** in 63% yield. For the latter, spontaneous loss of one of the TBS groups had occurred, however, **341** and **342** were readily separable by column chromatography. Gratifyingly, macrocyclisation of **341** and **342**, using the previously developed procedure (see Scheme 61, Chapter 3), furnished cyclic peptides **343** and **344** in good yields.



Scheme 75. Synthesis of cyclic hexapeptides **343** and **344**.

The "end-game strategy" now required global cleavage of the protecting groups of **343**/**344** using TASF. Previously, deprotection of substrate **291** using TASF had resulted in the formation of a minor and separable C45 epimer (Scheme 62, Chapter 3). It was anticipated that an analogous result would be obtained during the deprotection of **343**/**344** and it was hoped that separation of the epimers would not be problematic. To this end, **343** was exposed to excess TASF (15.0 equivalents) in DMF and this effected

global deprotection, accompanied by partial C45 epimerisation. Pleasingly, the major product **146** could be isolated from this mixture in 45% yield (Scheme 76). A similar result was obtained for deprotection of **344**. It was difficult to determine the exact ratio of epimers formed during deprotection due to the presence of other impurities and a clean sample of the minor product could not be obtained. Nevertheless, this result was encouraging because cleavage of indole ester had finally been achieved and the procedure was efficient enough to provide useful quantities of product **146**.



Scheme 76. Synthesis of the precursor for the "end-game".

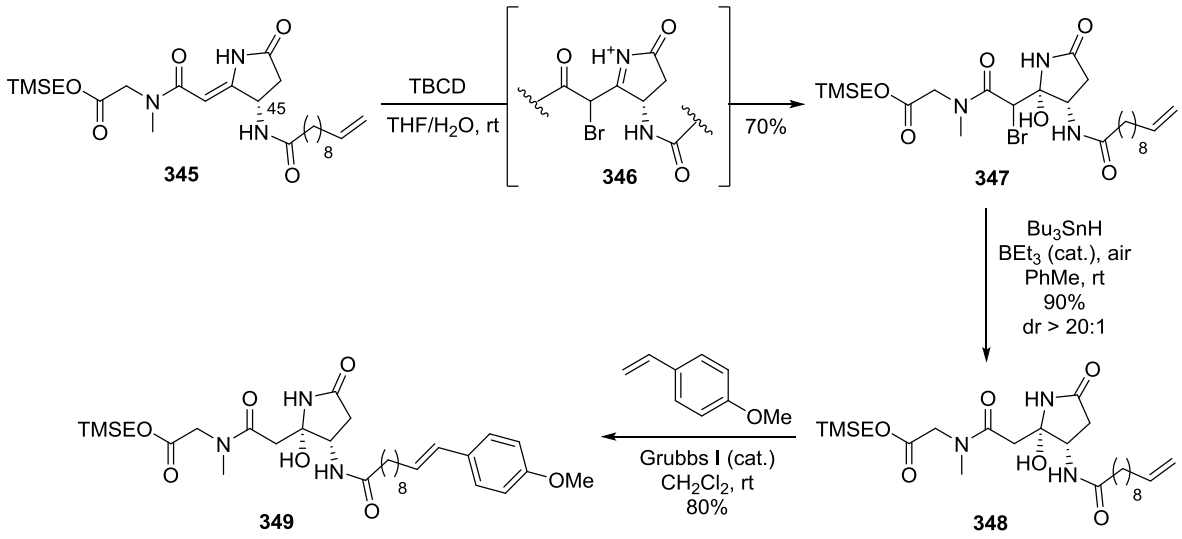
The NMR spectra of compound **146** were surprising as most of the signals were duplicated and ROESY experiments confirmed that this was a result of rotamers. The exact ratio was solvent dependent: in DMSO-D_6 a 1:1 ratio was observed, whereas in DMF-D_7 this ratio was approximately 5:1. This observation was a major concern as no members of the microsclerodermin family exhibit rotameric behaviour in their NMR data. NMR spectra of natural dehydromicrosclerodermin B were obtained from Li,[2] who had isolated this alongside microsclerodermins A, B, J and K, and rotameric behaviour was not evident. The structure of compound **146** is very similar to the reported structure of

dehydromicrosclerodermin B, differing only in the absence of the styrenic moiety. Consequently, the duplication of signals in the synthetic material (**146**) led to some concern about the structural assignment of **2**. Nevertheless, at this stage, the exact cause of the discrepancy was not evident and so it was decided to pursue the "end-game" strategy on **146**.

As outlined in Chapter 1, the retrosynthetic analysis of microsclerodermin B involved late-stage hydration of the unsaturated pyrrolidinone unit and subsequent metathetic installation of the styrene moiety onto the AMMTD side-chain. The former step was left to near the very end of the synthesis because of the highly sensitive nature of the pyrrolidinone hydroxyl group. Indeed, model studies had indicated that this functionality would not survive acidic conditions[41] or phosphonium peptide coupling reagents. Introduction of the styrene moiety was planned as the final step so as selective hydration of the electron rich pyrrolidinone double bond could be performed beforehand.

Dr Robert Pullin and Dr Christian Winter had developed the "end game" on model substrate **345**, which bears the key functionalities present in the "real" system. Several methodologies for hydration of the pyrrolidinone double bond of **345** were studied, and it was found that a sequence of hydroxybromination and subsequent radical debromination gave the desired aminal **348** in good yield and excellent regio- and diastereoselectivity (Scheme 77). Optimised conditions employed NBS in THF/H_2O and this afforded **347** in 70% yield. The *syn*-diastereorelationship between the newly installed hydroxyl and the C45 amino group of **347** was assumed to originate from thermodynamic control during hydroxybromination, although an exact mechanistic rationale for this was unclear. Repetition of this process revealed that reactions conducted with NBS exhibited a high degree of batch dependence and so the brominating agent was changed to TBCD

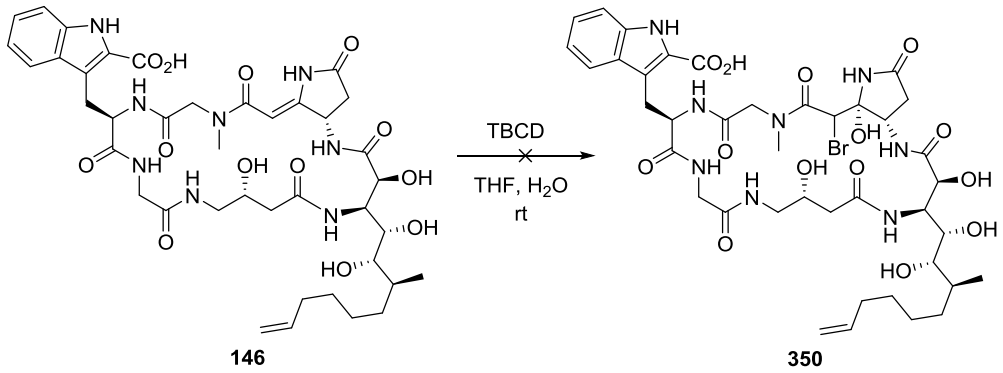
(2,4,4,6-tetrabromo-2,5-cyclohexadienone), which gave much better reproducibility. High yielding radical debromination of **347** could be achieved under very mild conditions using triethylborane as an initiator and tributyltin hydride as the reductant.[84] Introduction of the styrene moiety was achieved by cross-metathesis of **348** with 4-methoxystyrene. For this step, highest conversions and selectivity were achieved using the Grubbs 1st generation system, which provided **349** in 80% yield (Scheme 77).



Scheme 77. Model studies for the "end-game".

The validated "end-game" protocol was now applied to advanced intermediate **146**. Exposure of this to the hydroxybromination procedure resulted in full conversion of starting material after one hour but, unfortunately, a complex mixture of products formed and no desired bromohydrin **350** was observed by TLC or MS (Scheme 78). Extensive efforts were undertaken to identify the main products from the reaction, but unfortunately challenges associated with purification meant that no conclusive structural data could be secured. Consequently, a rationale for the failure of this step could not be advanced,

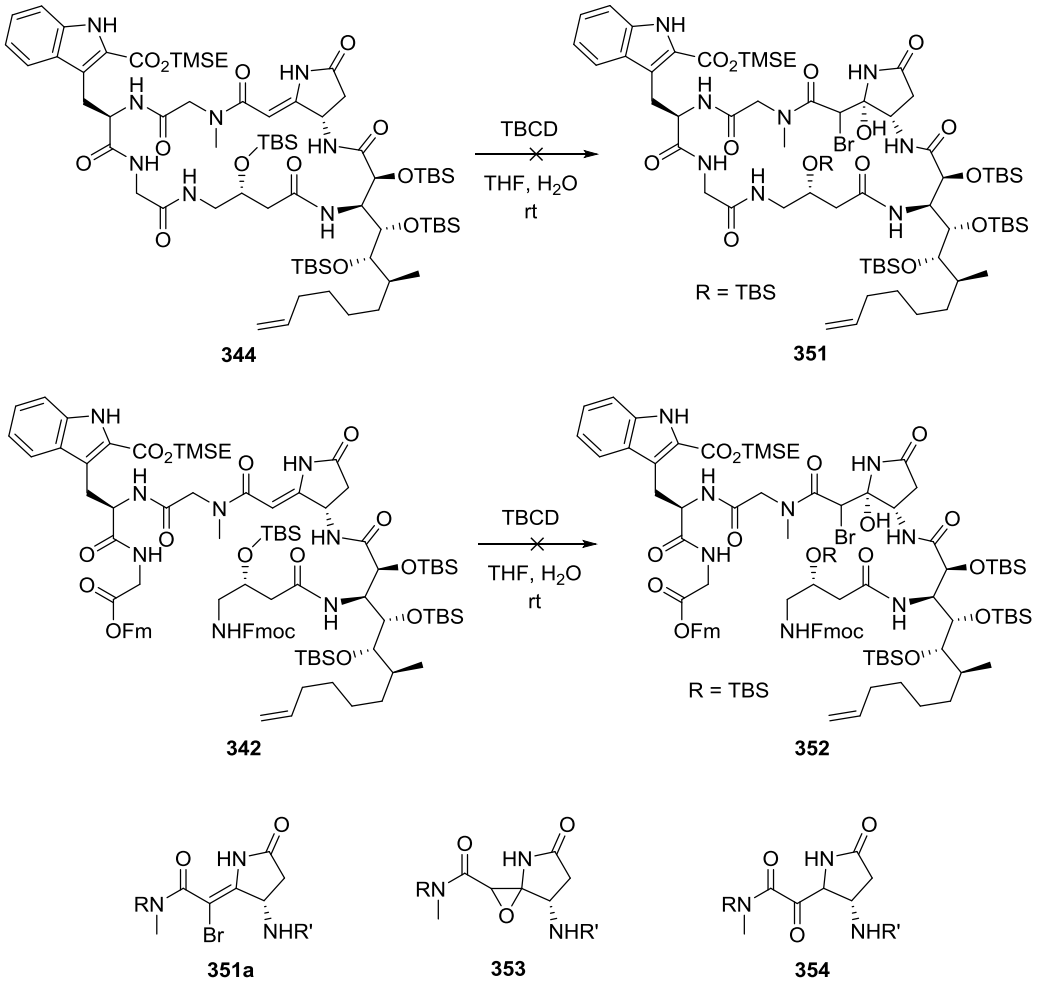
however likely key factors considered were the greater complexity of hexapeptide **146** (*vs.* model system **345**) and the conformational constraints of the macrocyclic ring system.



Scheme 78. Attempted hydroxybromination of substrate **146**.

To test whether functional groups in substrate **146** or its cycle conformation restricted installation of the bromohydrin moiety, the methodology was investigated on fully protected cyclic peptide **344** and on protected linear hexapeptide **342** (Scheme 79). Unfortunately, these experiments also did not provide any of the desired products. In both reactions starting material was consumed, but no bromohydrin was obtained. In the case of cyclic substrate **344** formation of three products was observed by TLC. When the crude mixture was purified by FCC, two major fractions were isolated. In the mass spectrum of the minor fraction a peak corresponding to the starting material plus a bromine atom was detected (potentially vinylbromide **351a**). The major isolated fraction contained two products, and the mass spectrum of this corresponded to the starting material plus an oxygen atom. Analysis of the NMR spectra of these fractions was quite difficult due to the complexity of the structures, lack of material and contamination with impurities; although disappearance of the pyrrolidinone double bond singlet at 5.66 ppm was observed, confirming that a reaction did take place at the correct site, but led only to side-products.

The side-products with the mass of starting material plus and oxygen atom could have the structures of epoxide **353** or rearranged ketone **354**. Formation of a similar epoxide side-product was also observed in the hydroxybromination reaction with model substrate **345**, but in small quantities. Consequently, it is probable that this undesired pathway took place in "real" system **344**.



Scheme 79. Attempts to perform hydroxybromination on substrates **344** and **342**.

A similar outcome was obtained in case of linear protected hexapeptide **342**. A few unidentified and inseparable side-products were isolated, with the major peak in the mass

spectrum of this mixture corresponding to starting material plus an oxygen atom. However, due to difficulties with separation it was not possible to characterise the side-products.

The observations made during these attempts to apply the planned "end-game" strategy to late-stage substrates **146**, **344** and **342** led to the abandonment of this bromohydrin-based route. Thus, based on the availability of advanced intermediates and with time considerations in mind, attention was switched to the completion of a synthesis of dehydromicrosclerodermin B **358**.

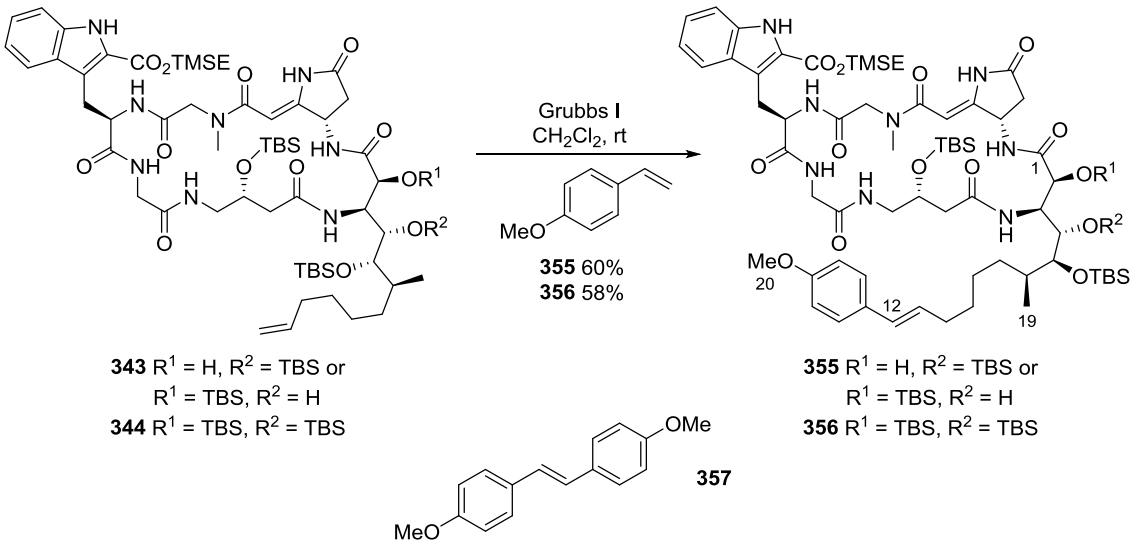
4.4 Synthesis and spectral analysis of dehydromicrosclerodermin B

To complete the synthesis of dehydromicrosclerodermin B (the dehydrated version of microsclerodermin B) two transformations were required on protected cyclic hexapeptide **343/344**. First, installation of the C13-C20 aromatic moiety onto the AMMTD side-chain would be achieved *via* cross-metathesis with 4-methoxystyrene. This would be followed by global deprotection to afford the proposed structure of dehydromicrosclerodermin B. At this stage, a detailed comparison of spectral data with that of the natural isolate would be undertaken.

Studies on cross-metathesis between **343** and 4-methoxystyrene were commenced using conditions developed previously on a model system.[51] Unfortunately, exposure of **343** to Grubbs I catalyst (3 × 5.0 mol% over 48 hours) in the presence of excess styrene (5.0 equivalents) in CH_2Cl_2 at room temperature resulted only in 69% recovery of starting material. Notably, homodimerisation of the styrene partner (to form **357**) was not observed, despite this being a significant side-reaction when these conditions were applied to simpler substrates (for example **221** and **348**). This suggested that the Ru-catalyst was

being inhibited, perhaps by ligation to the amide groups of cyclic peptide **343**. Indeed, this problem has been noted in other scenarios where substrates possess functional groups that can coordinate to the Ru-centre.[85] To validate this assertion, the reaction was repeated using 1.5 equivalents of the "catalyst", and, pleasingly, some conversion to product **355** was observed (1.7:1.0 **343**:**355**). Separation of target **355** from starting material **343** was challenging and so further studies were conducted to push the reaction to completion. Accordingly, portionwise addition of excess Grubbs I "catalyst" (2 × 2.0 equivalents over 48 hours) and a large excess of 4-methoxystyrene (2 × 10.0 equivalents over 48 hours) was employed. Under these conditions, no starting material remained and product **355** was isolated in 60% yield, with some losses attributed to difficulties associated with purification of the product from the catalyst (Scheme 80). A similar yield (58%) was achieved for fully protected substrate **344**.

Evidently further optimisation of this step would be desirable. However, investigations into the use of other catalysts were not fruitful, with the Hoveyda-Grubbs II system leading only to the formation of unidentified side-products. Several studies have highlighted the benefits of using mild Lewis acidic additives, such as $Ti(O\textit{i}\text{-}Pr)_4$,[85] aluminum tris(2,6-diphenylphenoxide)[86] and $MgCl_2$,[87] to chelate polar groups and mitigate catalyst deactivation. It would be interesting to explore this approach in the cross-metathesis of substrate **343**, but, due to the limited amount of material available, this was not feasible during the present study.

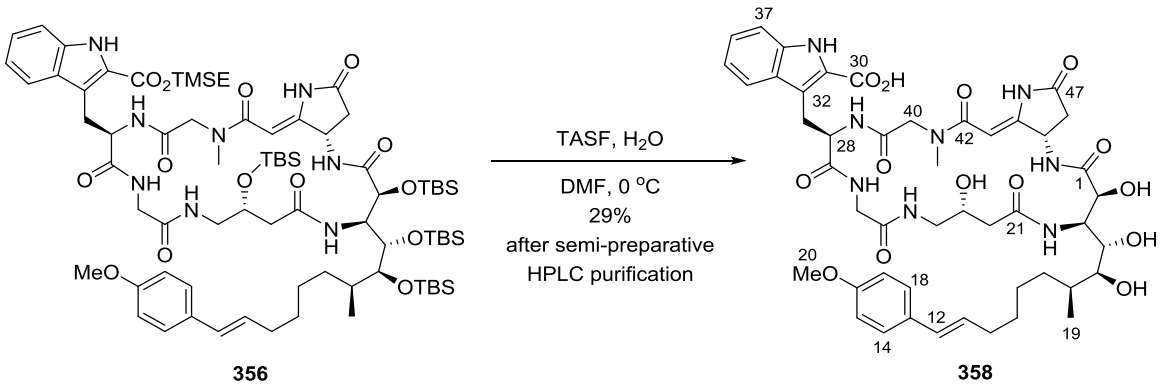


Scheme 80. Cross-metathesis on cyclic protected peptides **343** and **344**.

The last step in the synthetic sequence towards dehydromicrosclerodermin B was global cleavage of the protecting groups. When cross-metathesis product **356** was subjected to conditions developed previously (excess TASF in DMF, Section 4.3) clean formation of product **358** was not observed. Although the protecting groups were removed, substantial epimerisation of the C45 stereocentre took place to deliver a 1:1 mixture of diastereoisomers, which could not be separated. The extent of epimerisation was concerning (*cf*. substrate **343**, Scheme 76, Section 4.3) and was attributed to the quality of the TASF reagent. Indeed, it was later confirmed that the basicity of this hygroscopic fluoride source is influenced by the amount of water present (*vide infra*).

With the aim of preventing epimerisation, further conditions were investigated on substrate **356**. These reactions were monitored by LCMS as NMR analysis was challenging due to amide resonance and the high structural complexity of the product(s). The basicity of TASF was examined in a variety of solvents, including THF, THF/H_2O and DMF/H_2O. Use of either THF or THF/H_2O was not successful; the former resulted in

substantial epimerisation (to three products) whereas the latter did not enable full deprotection, resulting in selective cleavage of one *O*-silyl group. Fortunately, employment of DMF wetted with 2.0 equivalents of H_2O (relative to TASF) resulted in the formation of a single product (**358**) by LCMS. Excess TASF was quenched by addition of TMS_2O and a high vacuum centrifuge was used to enable removal of DMF at room temperature, thereby avoiding the need to heat the potentially sensitive crude product on a conventional rotary evaporator. Further purification required standard FCC and subsequent semi-preparative reverse phase HPLC, with lyophilisation to evaporate the $TFA/CH_3CN/H_2O$ solvent mixture. Using this procedure **358** was isolated in 29% yield and as a single diastereoisomer; the low yield of this transformation can be attributed to losses during semi-preparative HPLC (Scheme 81).



Scheme 81. Completion of the synthesis of the proposed structure of dehydromicrosclerodermin B.

The ability of water to moderate the basicity of TASF has been observed by other research groups.[71] This effect likely arises *via* solvation of the fluoride anion, however, water could not be used as the solvent, perhaps because TASF decomposes under these

conditions. Note that attempted deprotection of **356** under acidic conditions (aqueous TFA or HF) was not successful and only decomposition products were observed.

Analysis of the NMR data for **358** provided unexpected results as two rotameric forms were present in a ratio of approximately 3:1 (Figure 9). Room temperature NMR data for natural dehydromicrosclerodermin B are not rotameric, and no member of the microsclerodermin family exhibits rotameric NMR data.

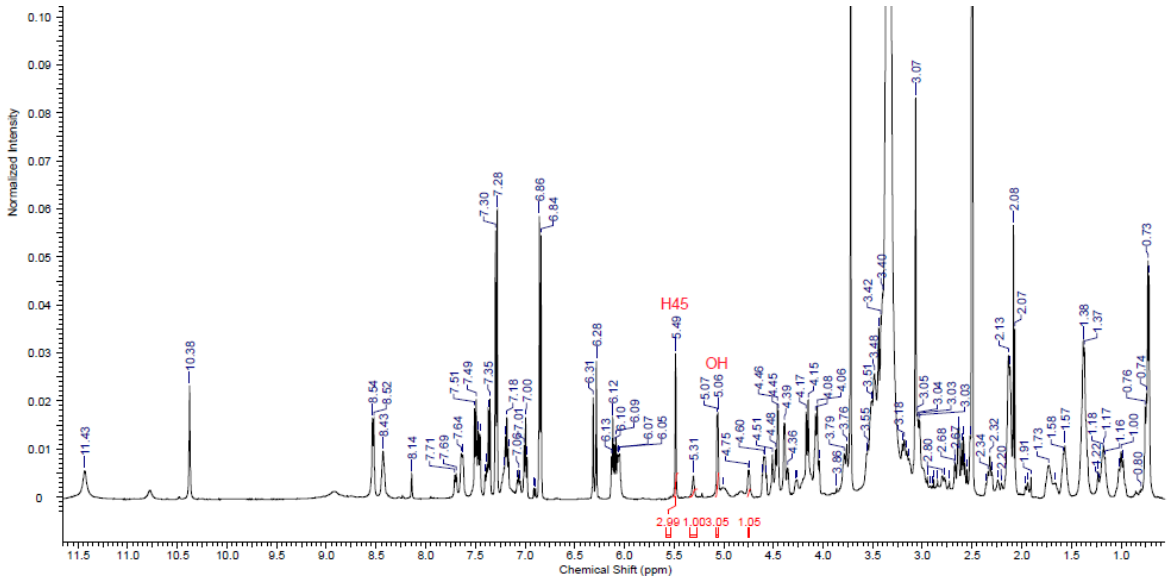


Figure 9. ^{1}H NMR spectrum at room temperature of **358**.

ROESY experiments on **358** showed exchange between the two sets of signals, thereby confirming that they belonged to rotamers rather than diastereoisomers (Figure 10). For example, strong correlations were observed between the major (5.49 ppm, s) and minor (5.31 ppm, s) signals for H45 and between the two signals for one of the hydroxyl groups (5.07 ppm, d, major; 4.75 ppm, d, minor).

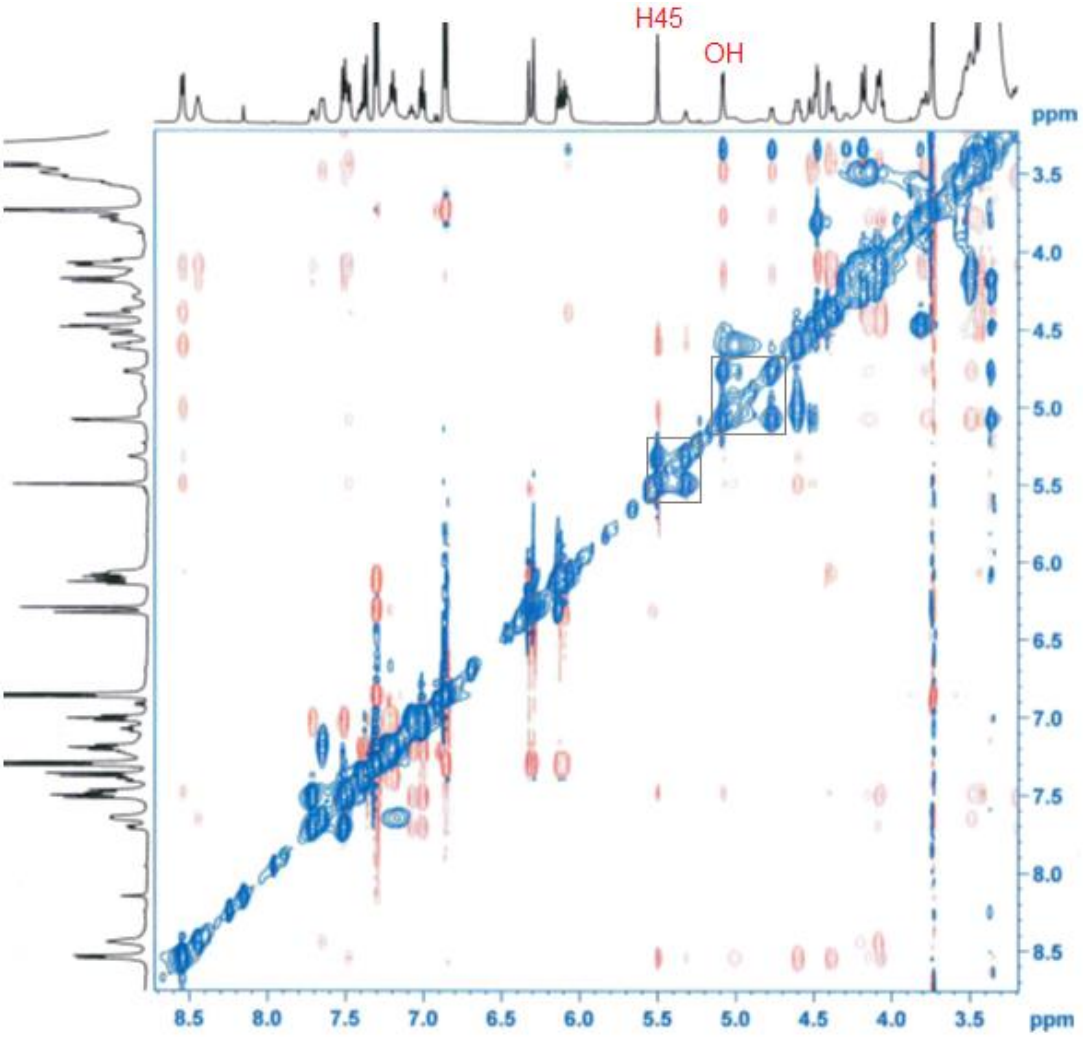


Figure 10. ROESY spectrum of **358**.

Complete coalescence of the two sets of signals was observed when ^{1}H NMR analysis was performed at 90 ^{o}C (Figure 11). The effect of concentration on the rotameric ratio was also investigated and it was found the ^{1}H NMR data were essentially identical at both 0.05 mg/μL and 0.01 mg/μL. Thus, the presence of two rotameric forms in the NMR spectra was not due to the amount of material in the NMR sample.

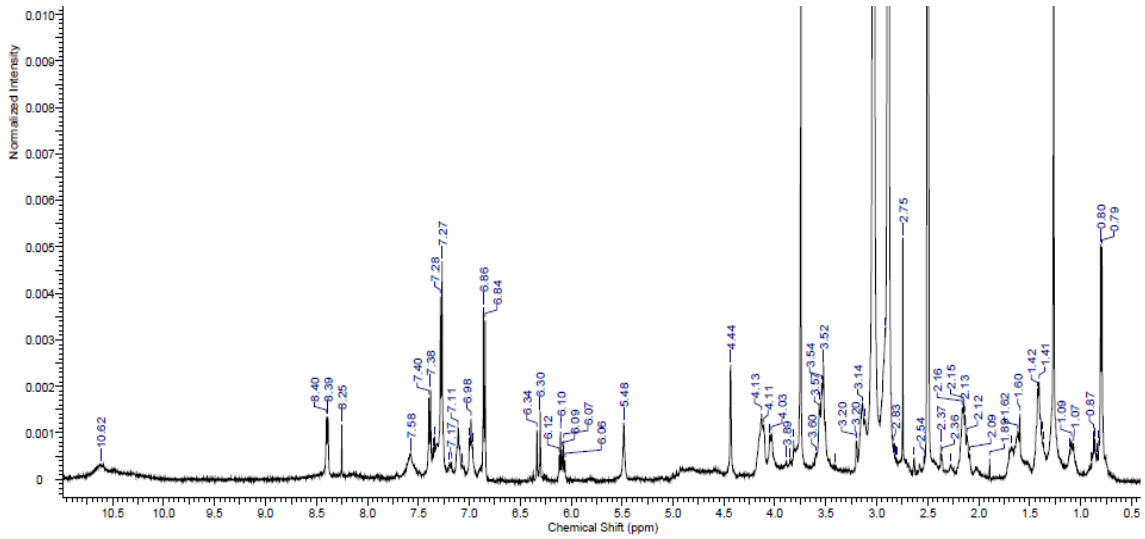
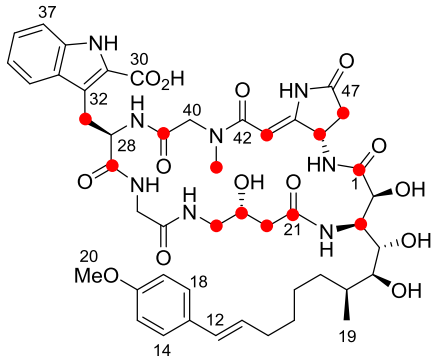


Figure 11. ^{1}H NMR spectrum at 90 ^{o}C of **358**.

^{1}H NMR data for peptidic compounds often have a dependence on sample concentration, the amount of H_2O present and other parameters, such as temperature. Consequently, comparison of the data for synthetic **358** to that of natural dehydromicrosclerodermin B was best achieved using ^{13}C NMR data. A comparison chart, outlining the difference in chemical shifts (δ_C) for each signal is shown in Figure 12; in this analysis C30-32 are not included as these signals could not be resolved in the ^{13}C NMR of natural dehydromicrosclerodermin B. Two obvious regions of the molecule show a large discrepancy in the data (δ_C up to 2.3 ppm); these are the pyrrolidinone core and the GABOB unit. Faulkner reported a detailed assignment of dehydromicrosclerodermin A where it was found that the pyrrolidinone and GABOB units have weak NOE correlations (H43-H22, H43-H23, H43-H24, NH24-NH45) which shows that they are close in space.[1] Because the structure of dehydromicrosclerodermin B is very similar to dehydromicrosclerodermin A, a similar spatial arrangement might be expected. Consequently, stereochemical misassignment of either the pyrrolidinone C45 or GABOB

C23 could result in the large discrepancy observed in the ^{13}C NMR data. Furthermore, inversion of either stereocentre would be expected to influence strongly the conformation of the macrocycle, which might result in two rotameric forms as observed in the NMR spectra of synthetic **358**. Unfortunately, detailed NOE analysis of synthetic **358** was not possible due to the presence of the two rotamers.



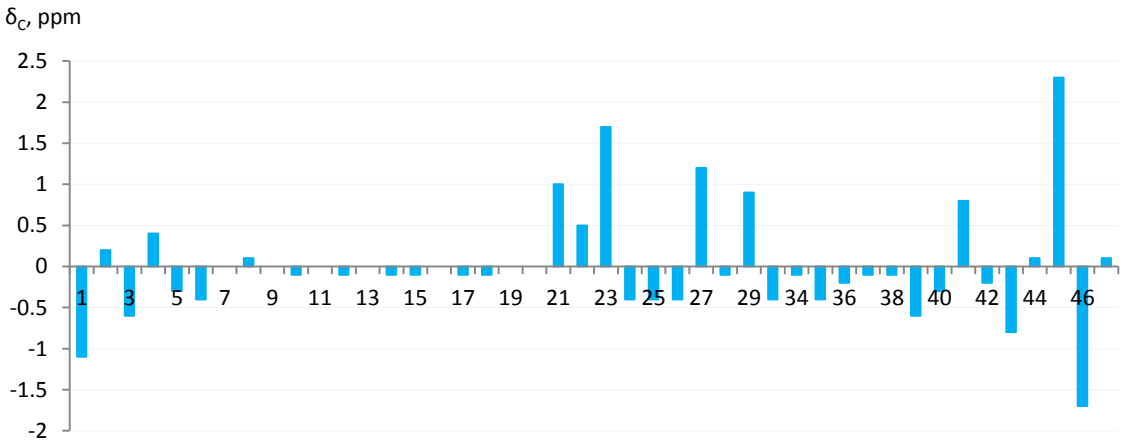
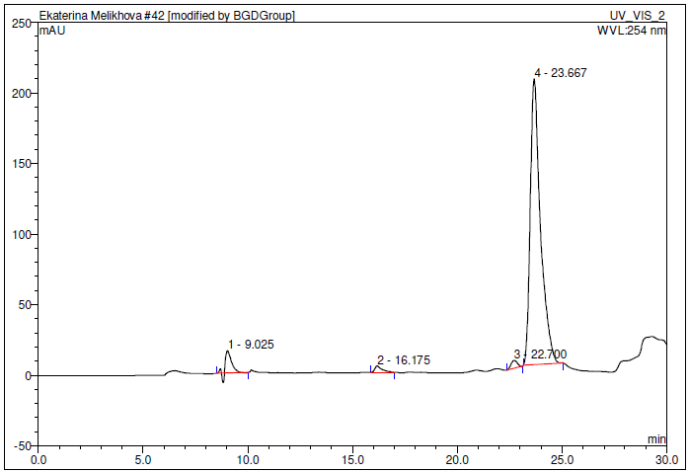
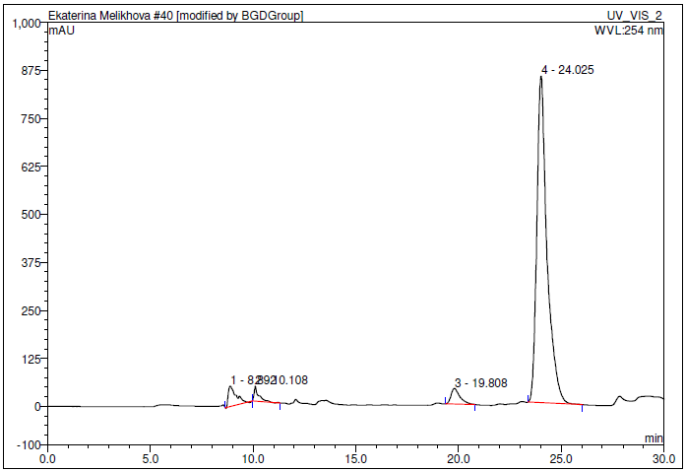


Figure 12. Comparison of ^{13}C NMR of **358** and natural dehydromicrosclerodermin B.

A.



B.



C.

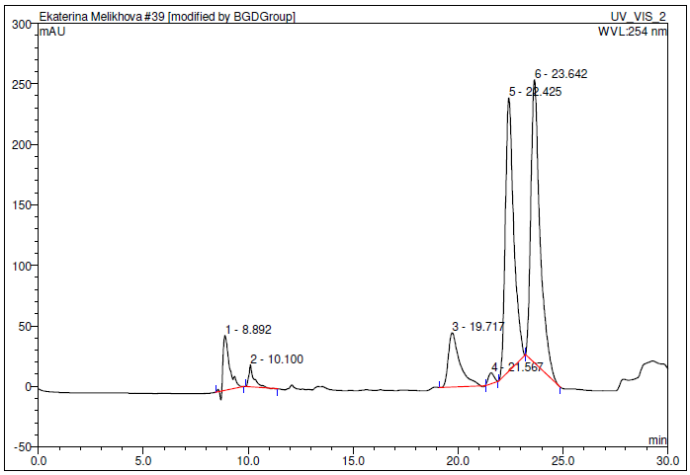
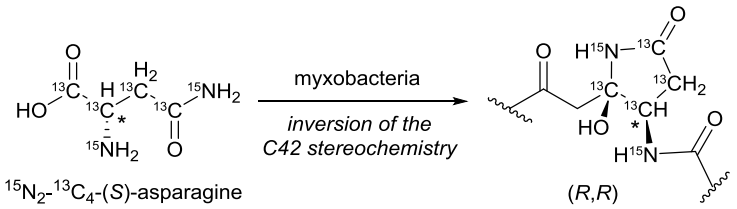


Figure 13. HPLC traces of (A) synthetic **358**, (B) natural dehydromicrosclerodermin B and (C) a 1:1 mixture.

Confirmation that synthetic **358** was different to natural dehydromicrosclerodermin B was achieved by comparison to an authentic sample of the natural product kindly provided by the Li group.[2] HPLC studies clearly revealed that these were two different compounds, possessing similar but distinct retention times (Figure 13).

At this stage, it was important to evaluate whether the incorrect structural assignment of dehydromicrosclerodermin B was due to misassignment of the C45 or C23 stereocentre. It was noted that only two members of the microsclerodermin family, microsclerodermins A and B, have been assigned as having the (45*S*)-configuration.[1] Why should these two natural products be distinct from the rest of the family? Furthermore, the assignment of microsclerodermin B was made solely by analogy to microsclerodermin A. Accordingly, an incorrect assignment of microsclerodermin A would lead to the incorrect assignment of microsclerodermin B, and, in turn, dehydromicrosclerodermin B. By contrast, the GABOB C23 stereocentre possesses the (*R*)-configuration in all microsclerodermins isolated to date.

Another interesting observation that supported an incorrect assignment of the C45 stereocentre was the observation that the stereochemistry of this position inverts during the biosynthesis of microsclerodermin M **16**.[4] When *Sorangium cellulosum* was fed with fully labelled $^{15}N_2$-$^{13}C_4$-(*S*)-asparagine **359**, inversion of the C42 stereochemistry resulted in the formation of (*R*,*R*)-pyrrolidinone **360**, not the (*S*,*S*)-diastereoisomer, as would be expected from (*S*)-asparagine **359** (Scheme 82).[4] This indicates that the most stable configuration of the pyrrolidinone unit is the (*R*)-configuration.



$^{15}N_2$-$^{13}C_4$-(*S*)-asparagine
359

360

Scheme 82. Inversion of the asparagine derived stereochemistry in the biosynthesis of microsclerodermin M.

The ^{13}C NMR data for synthetic **358** and natural dehydromicrosclerodermin B were compared to structurally similar dehydromicrosclerodermin C **361**, which is reported as having the (45*R*)-stereochemistry (Figure 14);[3] in this analysis signals for the structurally distinct tryptophan residue and AMMTD side-chain were not included. Interestingly, for synthetic **358**, the difference in the pyrrolidinone and GABOB regions is similar to that highlighted in Figure 12. This shows that synthetic **358** has very similar discrepancies with the data for the two structures, one of which was proposed as having the (45*S*)-configuration (dehydromicrosclerodermin B **358**), with the other proposed to have the (45*R*)-configuration (dehydromicrosclerodermin C **361**). Comparison of the ^{13}C NMR data for natural dehydromicrosclerodermin B and natural dehydromicrosclerodermin C showed little difference for the pyrrolidinone and GABOB units (< 0.2 ppm, Figure 14B). This suggests that natural dehydromicrosclerodermin B and dehydromicrosclerodermin C **361** share the same (*R*)-pyrrolidinone.

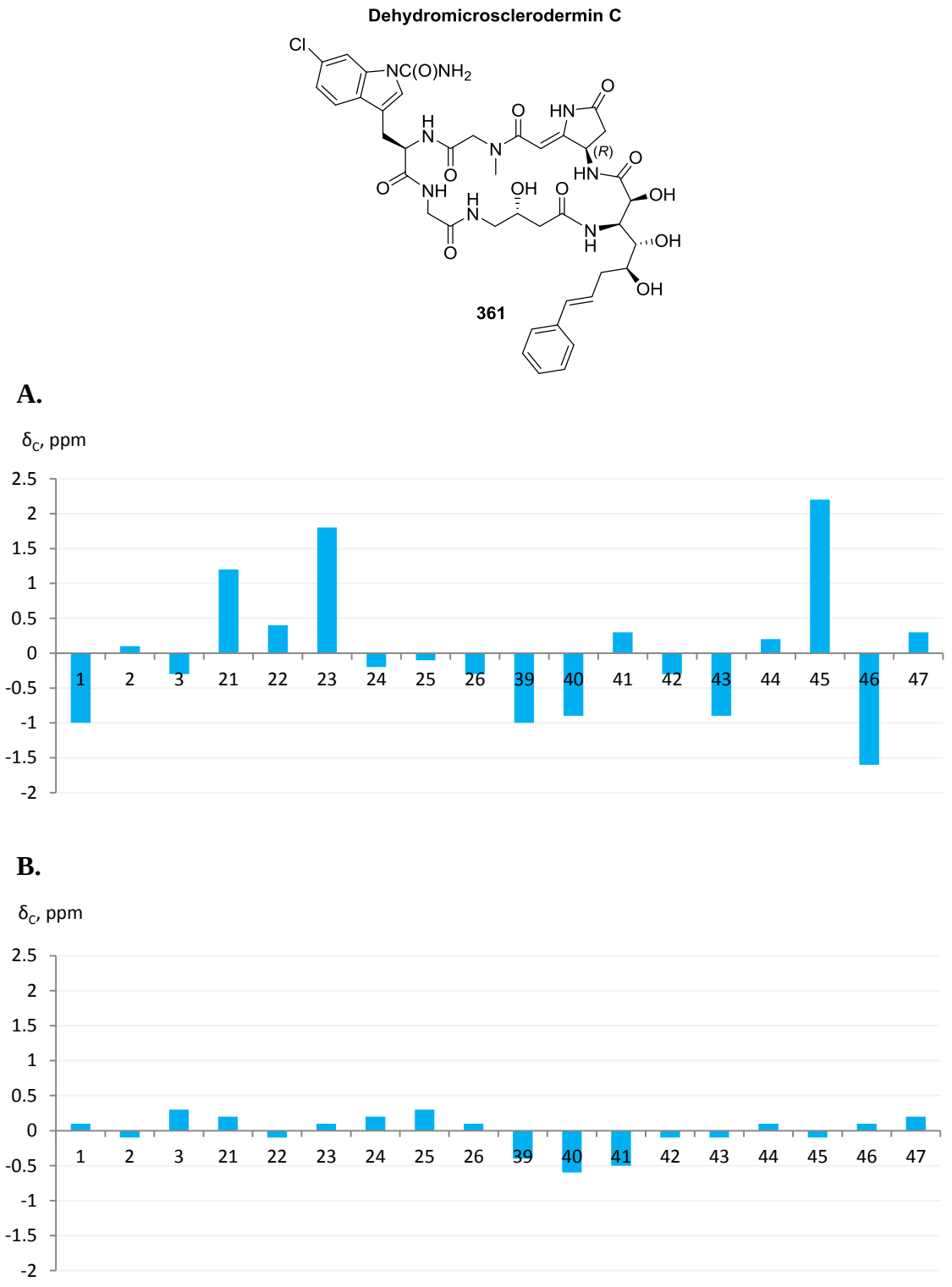


Figure 14. Comparison of ^{13}C NMR data of (A) synthetic **358** and (B) natural dehydromicrosclerodermin B with natural dehydromicrosclerodermin C (numbering as in dehydromicrosclerodermin B).

At this stage, the configurations of all commercially sourced enantiopure compounds used *en route* to synthetic **358** were rechecked and found to be correct. Based on this, and the considerations outlined above, the structure of dehydromicrosclerodermin B was tentatively reassigned from **358** to *epi*-**358** (Figure 15). This proposed reassignment also has implications for the configuration of C45 stereocentre of microsclerodermins A and B. In order to validate this hypothesis, the synthesis of the C45 epimer, *epi*-**358**, was now pursued.

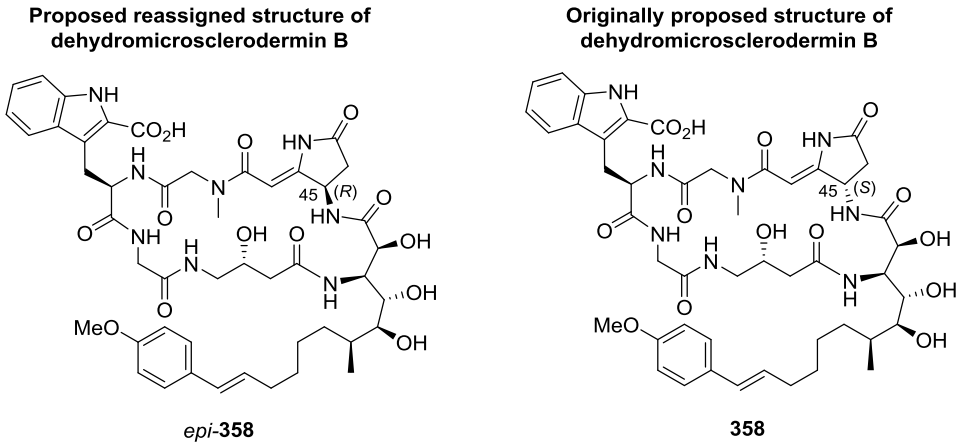
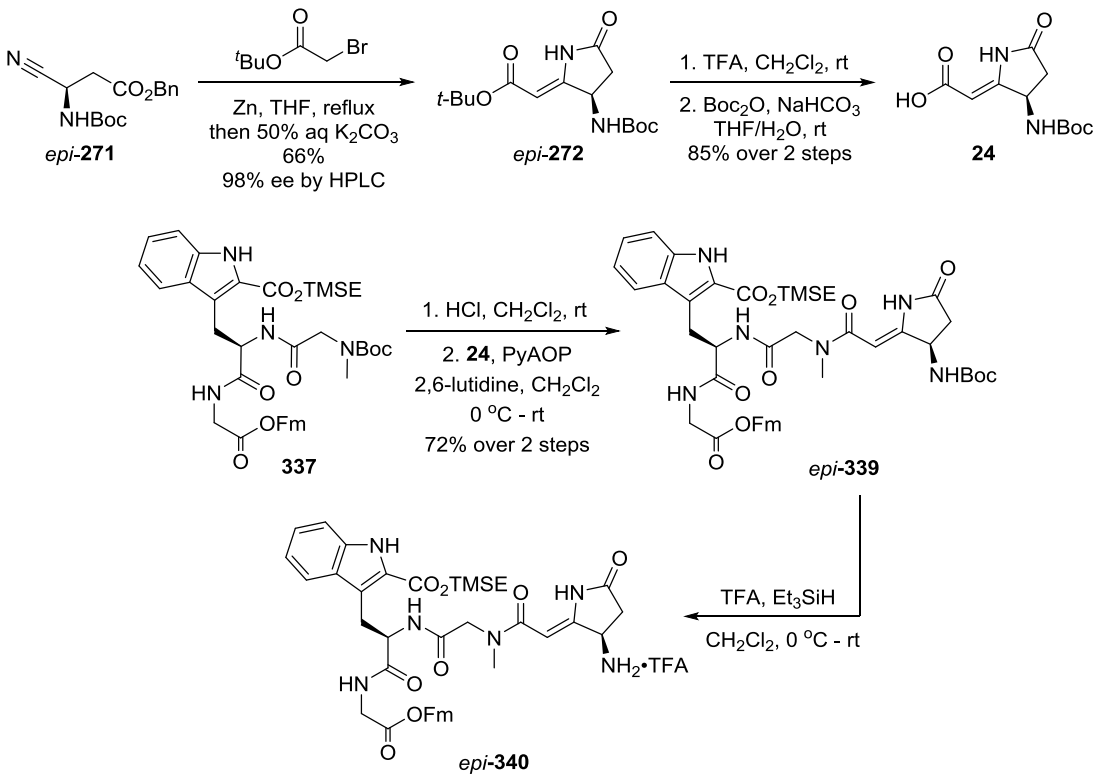


Figure 15. Proposed reassignment of dehydromicrosclerodermin B (*epi*-**358**).

4.5 Synthesis and data analysis of reassigned dehydromicrosclerodermin B (*epi*-358)

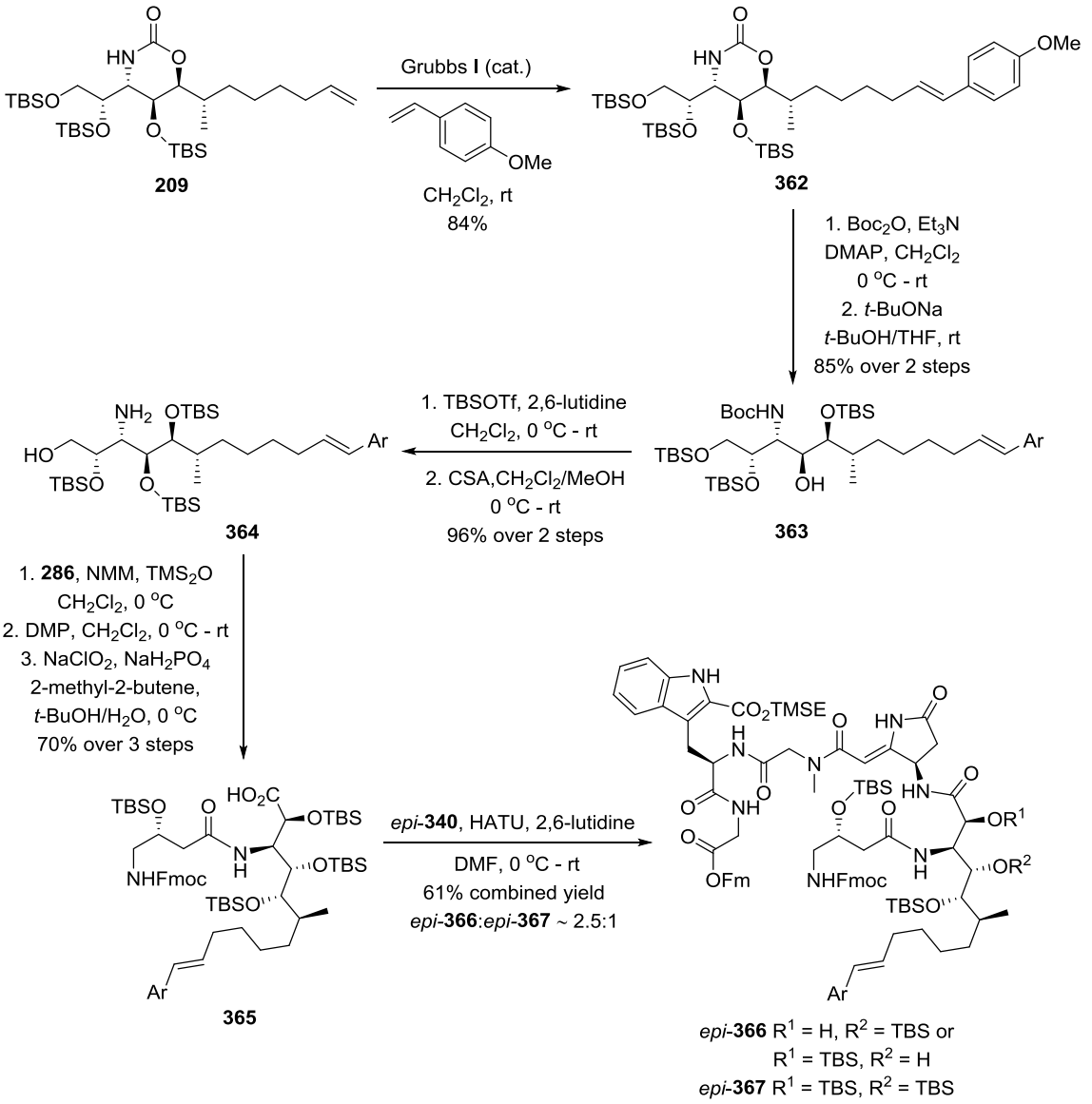
For the synthesis of *epi*-**358**, (*R*)-pyrrolidinone amino acid **24** was prepared using the same protocol as developed for the (*S*)-enantiomer (Scheme 83). The enantiopurity of compound **24** was determined to be 98% ee by chiral HPLC analysis of the corresponding methyl ester **24a** (obtained by treatment of **24** with $TMSCHN_2$; see the Experimental

section). Pyrrolidinone unit **24** was then incorporated into the synthesis of the northern hemisphere, *epi*-**340**, by adaptation of the previously developed sequence (Scheme 83).



Scheme 83. Synthesis of tetrapeptide *epi*-**340**.

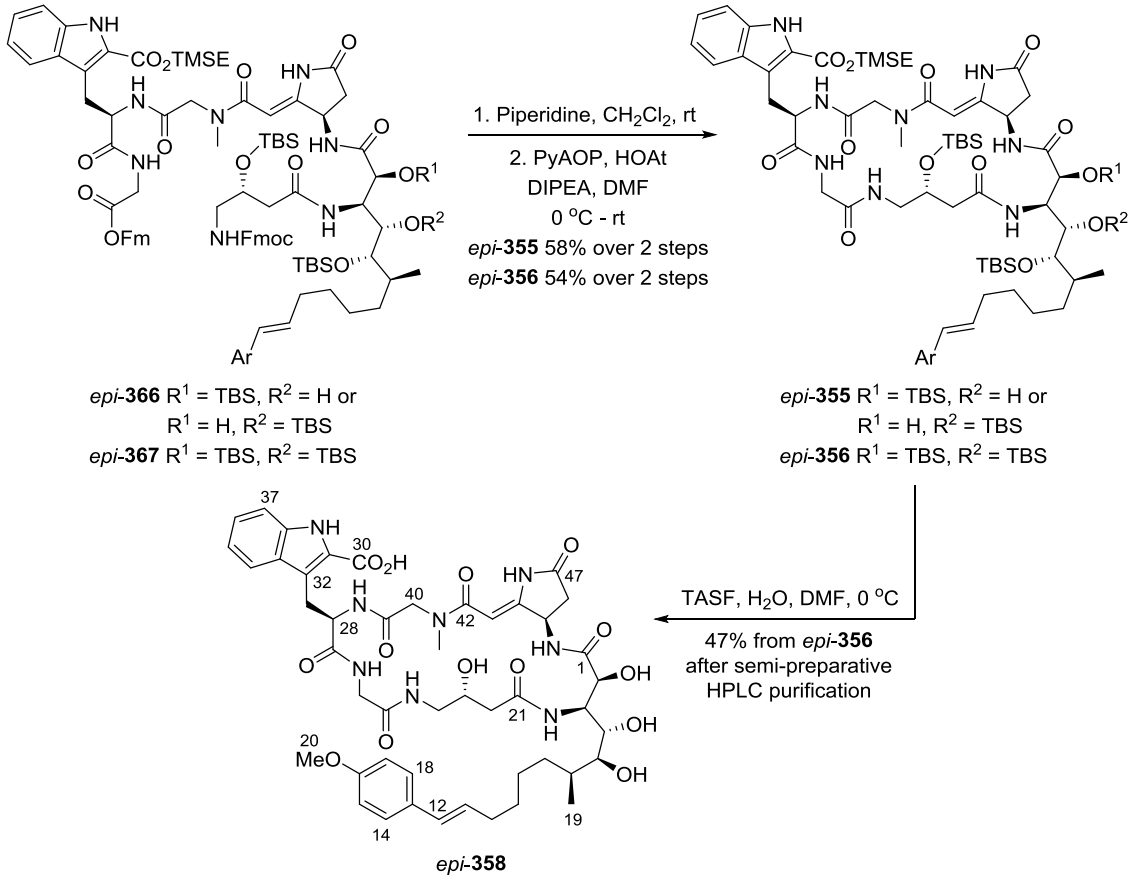
As the route involving late-stage selective hydroxybromination of the pyrrolidinone double bond had been discarded (Section 4.3), the styrene moiety of the AMMTD unit was introduced earlier in the synthesis to avoid the problematic late stage cross-metathesis (see Scheme 80, Section 4.4). This transformation was readily performed on cuprate reaction product **209**, using the Grubbs I catalyst system, to generate **362** in 84% yield (Scheme 84). Fully elaborated AMMTD fragment **362**, containing the aromatic ring, was advanced to linear hexapeptides *epi*-**366** and *epi*-**367** *via* adaptation of the synthetic sequence described in Section 4.3 (see the Experimental section for details).



Scheme 84. Synthesis of linear hexapeptides *epi*-**366** and *epi*-**367**.

Next, linear hexapeptides *epi*-**366** and *epi*-**367** were subjected to previously developed macrolactamisation conditions and, gratifyingly, this furnished protected cyclic peptides *epi*-**355** and *epi*-**356** in good yields (Scheme 85). Encouragingly, the NMR spectra of *epi*-**355** and *epi*-**356** consisted of a single set of peaks; previously, cyclic peptides **355** and **356**, containing the alternate (45*S*)-pyrrolidinone, exhibited two rotameric forms. This provided tentative evidence that the (45*R*)-configured macrolactams

epi-**355** and *epi*-**356** might possess the correct stereochemistry. Global cleavage of the protecting groups from *epi*-**356**, using TASF/H_2O/DMF and subsequent semi-preparative HPLC purification, furnished *epi*-**358** in 47% yield and as a single diastereoisomer (Scheme 85). Deprotection of *epi*-**355** proceeded with similar levels of efficiency but an accurate isolated yield was not obtained due to limited access to HPLC instrumentation.



Scheme 85. Completion of the synthesis of reassigned dehydromicrosclerodermin B, *epi*-**358**.

The NMR data for synthetic *epi*-**358** were compared to data obtained by Li for natural dehydromicrosclerodermin B and showed positive results. Mixtures of rotamers were not observed, which indicated that this epimer prefers one stable rotameric form

(Figure 16). Certain signals exhibited a dependence on concentration and possibly on the carboxylic acid protonation state, such that it was difficult to compare directly the ^{1}H NMR spectrum for *epi*-**358** with that of the natural product. Nevertheless, the key pyrrolidinone H43 (5.25 ppm, s) and H45 (5.21 ppm, m) signals of the synthetic material had the same chemical shifts as the natural isolate.

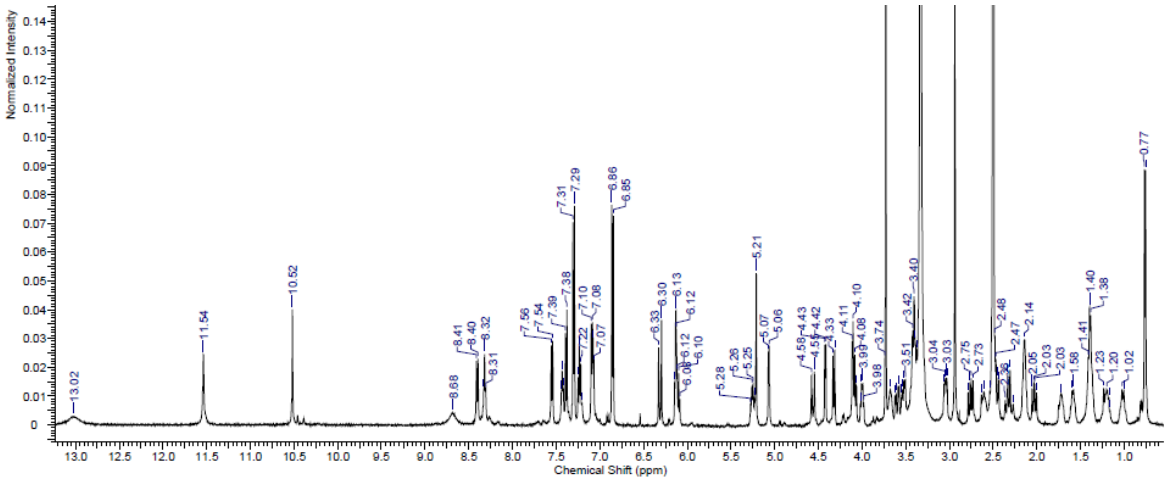


Figure 16. ^{1}H NMR spectrum of synthetic *epi*-**358**.

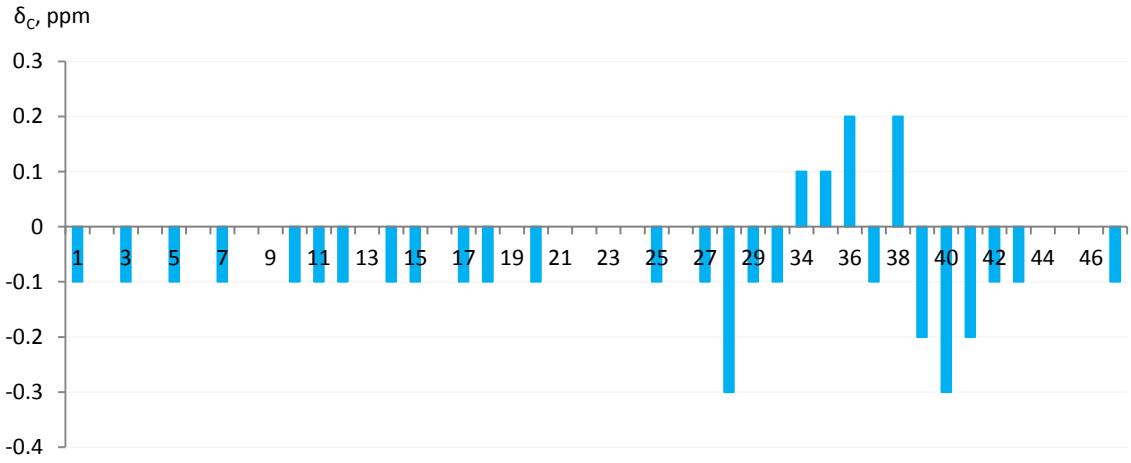


Figure 17. Comparison of ^{13}C NMR data of synthetic *epi*-**358** with natural dehydromicrosclerodermin B.

Comparison of the ^{13}C NMR data provided strong evidence that the structure of synthetic *epi*-**358** matches dehydromicrosclerodermin B, with all signals in good agreement (Figure 17). For most of the signals the difference in chemical shifts does not exceed 0.1 ppm. Some signals, such as C28, C36, C38, C39, C40 and C41 differ by 0.2-0.3 ppm. The chemical shifts of these signals may depend on the protonation state of indole-2-carboxylic acid. For the isolation of synthetic *epi*-**358**, 0.01% TFA was employed in the solvent used for HPLC purification; this solvent system was adopted because it was used by Faulkner for the isolation of microsclerodermins A and B.[1] It is possible, that the NMR data obtained by Li for natural dehydromicrosclerodermin B are not of the fully protonated form; information on the purification procedure used is not available. Nevertheless, the strong correlation observed for the ^{13}C NMR data appeared to validate the proposed reassignment of the C45 stereocentre.

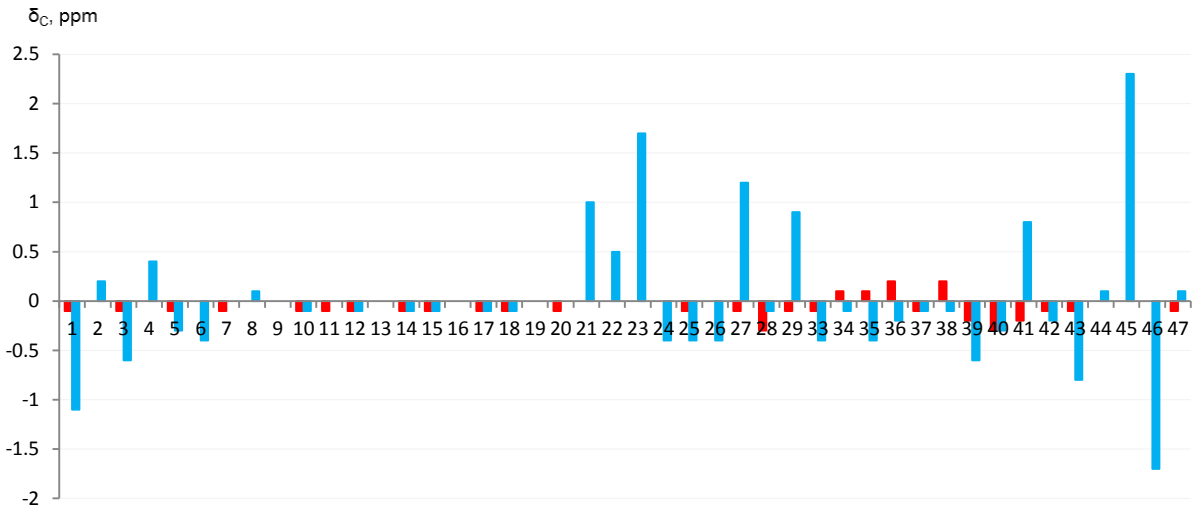


Figure 18. Comparison of ^{13}C NMR data of synthetic *epi*-**358** (red) and synthetic **358** (blue) with natural dehydromicrosclerodermin B.

Figure 18 compares the ^{13}C NMR data for natural dehydromicrosclerodermin B with synthetic **358** (blue) and *epi*-**358** (red); the latter shows a much stronger correlation. Further evidence that synthetic *epi*-**358** matched natural dehydromicrosclerodermin B was secured by ^{1}H NMR and HPLC analysis of 1:1 mixtures of the two samples. The ^{1}H NMR spectrum showed a single set of peaks (Figure 19) and the HPLC trace revealed only one major component (Figure 20).

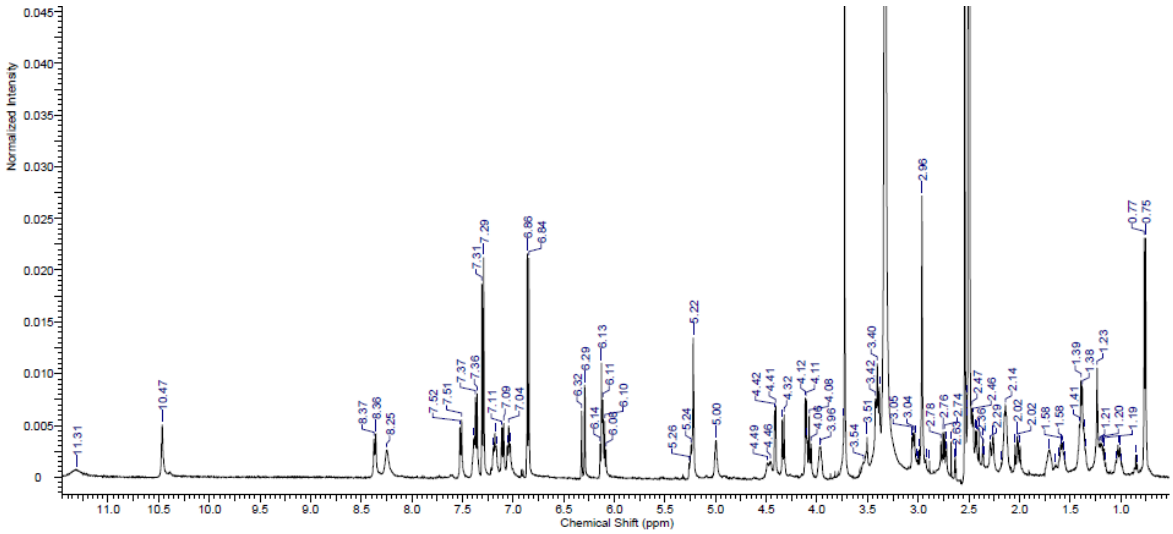


Figure 19. ^{1}H NMR spectrum of 1:1 mixture of synthetic *epi*-**358** and natural dehydromicrosclerodermin B.

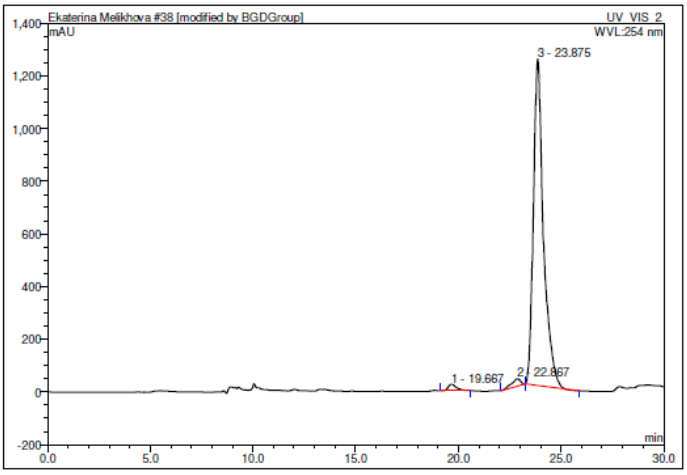


Figure 20. HPLC trace of 1:1 mixture of synthetic *epi*-**358** and natural dehydromicrosclerodermin B.

Based upon the data analysis outlined above, it was concluded that the initially proposed structure **358** of dehydromicrosclerodermin B, and, by extension, that of microsclerodermin B are incorrect, with both natural isolates instead having the (*R*)-configured C45 stereocentre. Indeed, it is tempting to conclude that every member of the microsclerodermin family contains an (*R*)-configured pyrrolidinone, however, definitive structural reassignment of microsclerodermin A is not possible at the present time. Microsclerodermin B was assigned by Faulkner on the basis of degradation studies conducted on microsclerodermin A **1**. Microsclerodermin A is either unique in having an (*S*)-configured pyrrolidinone, or the C45 stereocentre was incorrectly assigned due to a mistake during degradation studies. However, the incorrect assignment of microsclerodermin B mandates reassignment of the C44 stereocentre of microsclerodermin J **13** (Figures 21, 5); the stereochemistry of this compound was originally assigned, in part, by comparison to the incorrect structure of microsclerodermin B.[2,6]

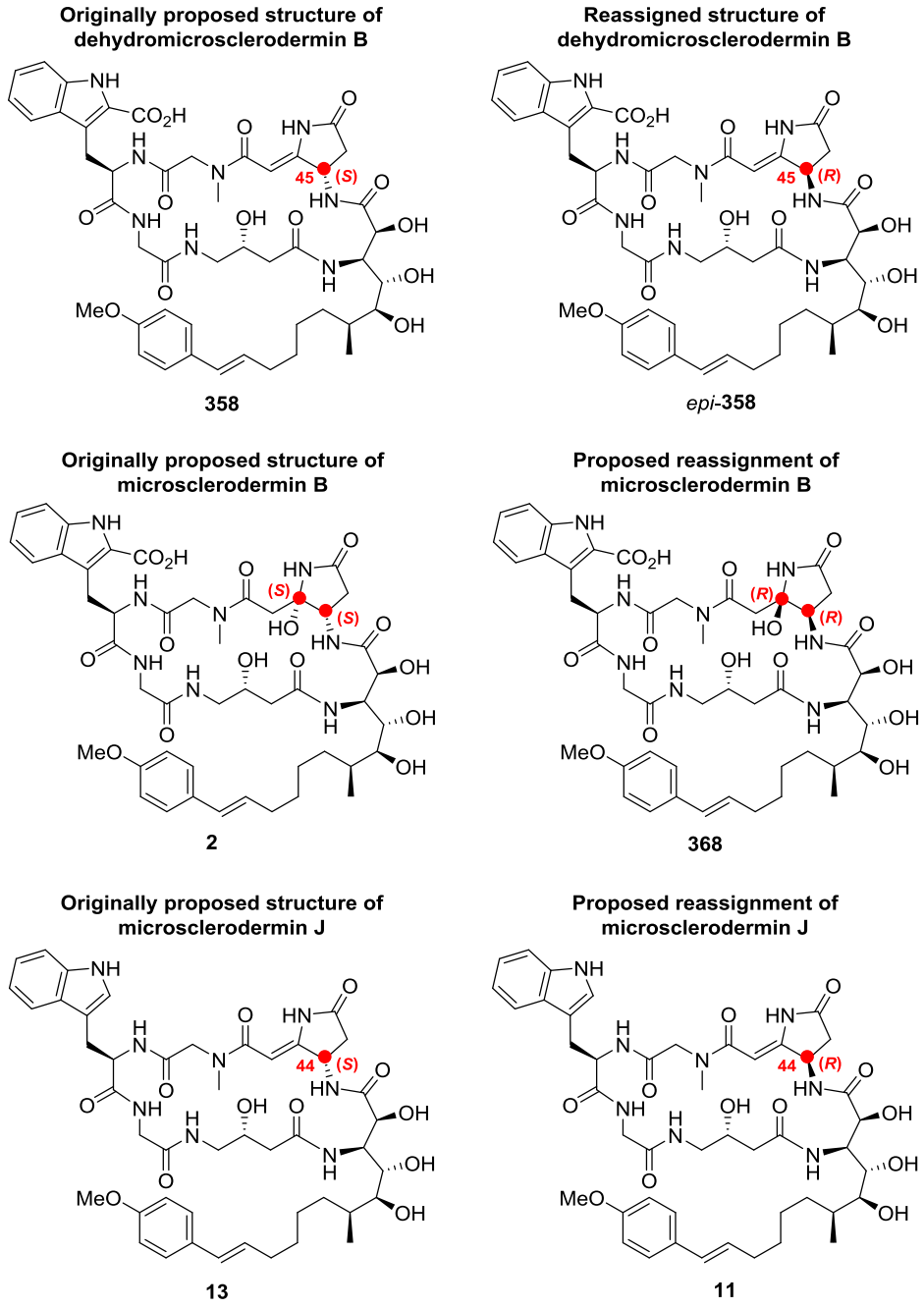


Figure 21. Conclusions from the data analysis of synthetic **358**, synthetic *epi*-**358** and natural dehydromicrosclerodermin B.

Chapter 5 Synthesis and stereochemical reassignment of microsclerodermin J

The stereochemical reassignment of dehydromicrosclerodermin B prompted studies to confirm the configuration of the pyrrolidinone stereocentre of microsclerodermin J **13**, a similar member of the microsclerodermin family, possessing a different tryptophan unit (Figure 22). In the initial isolation report, it was proposed that this natural product contained a (*R*)-configured pyrrolidinone amino acid,[2] but subsequently a correction was issued, which reassigned this to the (*S*)-configured variant.[6]

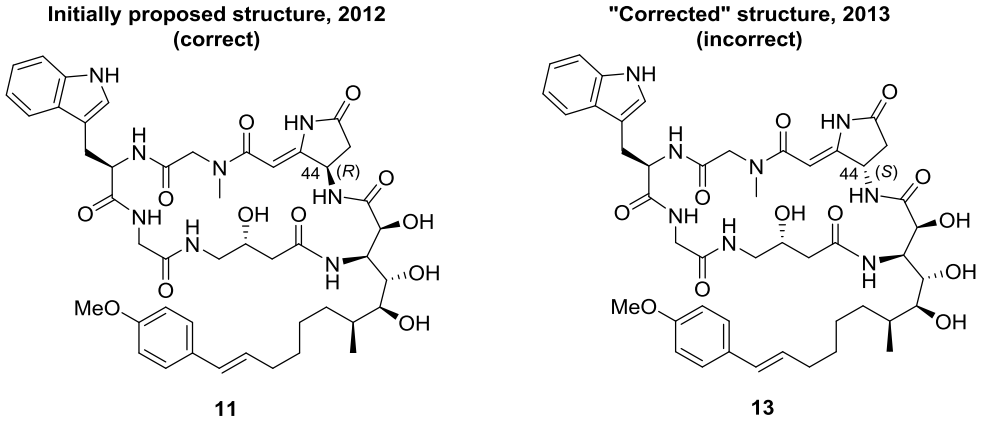
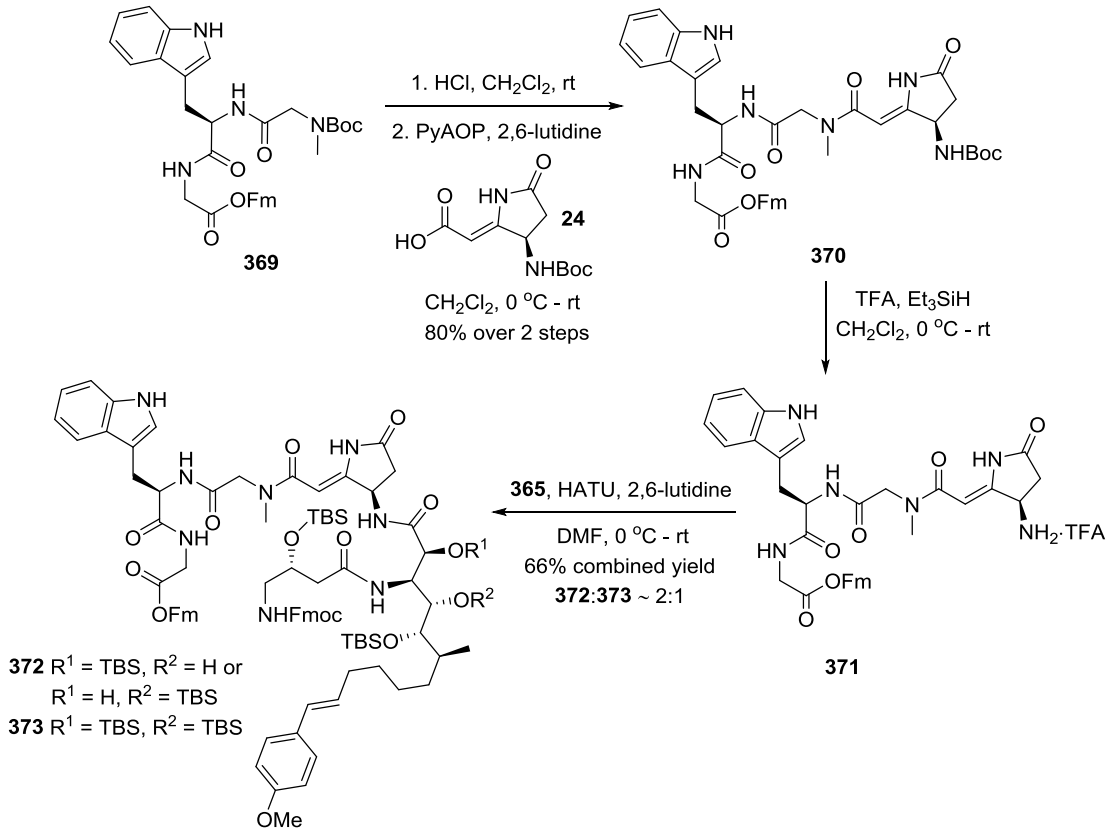


Figure 22. Microsclerodermin J.

The initial assignment was based on comparison to dehydromicrosclerodermin C **361**, which was proposed to have a (*R*)-configured pyrrolidinone, although this had not been confirmed synthetically. For microsclerodermin J, no degradation experiments were conducted to confirm the absolute stereochemistry of any amino acids apart from the tryptophan unit. Thus, the basis for the

correction of stereochemistry at C44 was unclear and, at best, was considered tentative. Based on the hypothesis that all microsclerodermins actually contain a (*R*)-configured pyrrolidinone unit, it was proposed that the correct structure of microsclerodermin J is actually **11** (Figure 22).

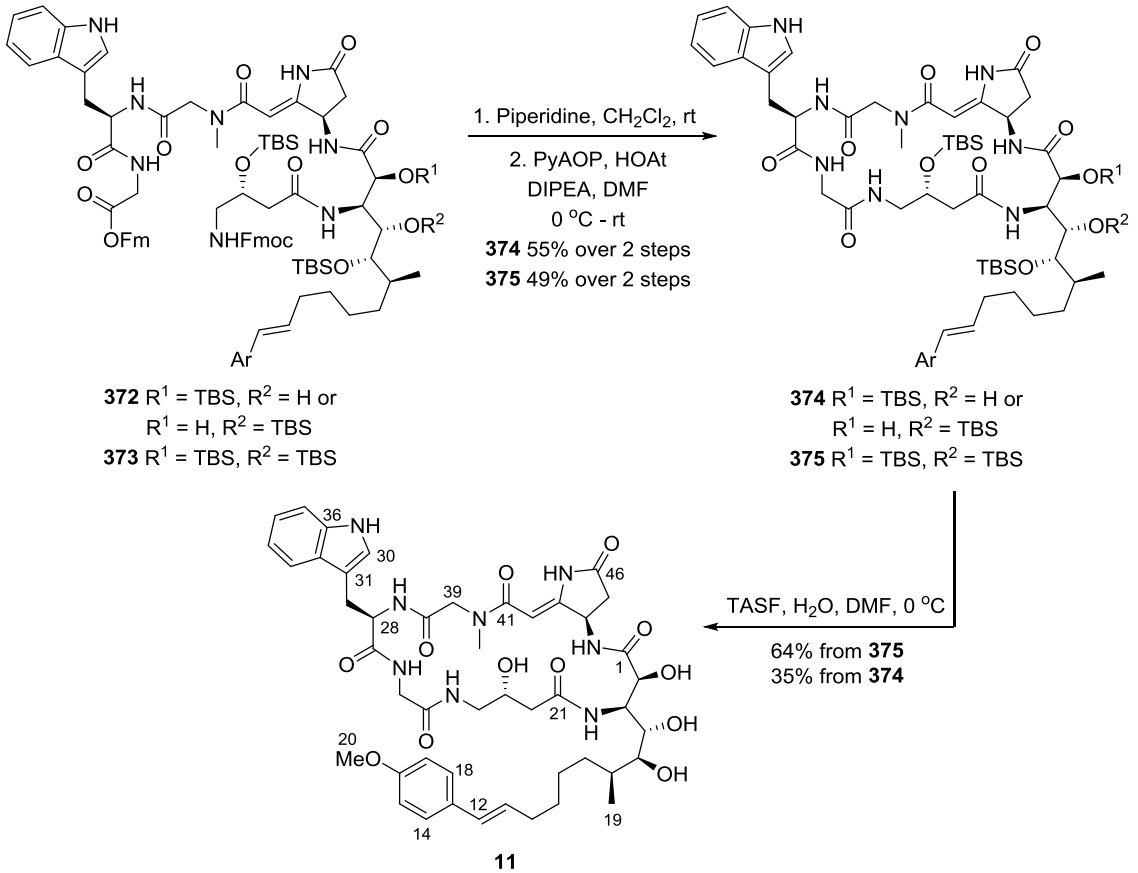
The proposed synthesis of microsclerodermin J **11** involved a very similar sequence to that used for dehydromicrosclerodermin B, with the requisite tryptophan fragment being commercially available. Thus, with all of the amino acids in hand, the synthetic sequence towards microsclerodermin J was pursued.



Scheme 86. Synthesis of linear hexapeptides **372** and **373**.

Tripeptide **369** was prepared in collaboration with Hang Xu, a postgraduate student in the group. This was then advanced to tetrapeptide **370** according to procedures developed for the northern hemisphere of dehydromicrosclerodermin B. Compound **371** was then converted into linear hexapeptides **372** and **373** by coupling with AMMTD-GABOB dipeptide **365** (Scheme 86).

Macrolactamisation of **372/373** and cleavage of the silyl ethers using previously developed conditions afforded the proposed structure **11** of microsclerodermin J in good yield (Scheme 87). Purification of **11** did not require semi-preparative HPLC as the compound could be obtained cleanly after standard chromatography.



Scheme 87. Completion of the synthesis of microsclerodermin J.

Pleasingly, only one set of signals was evident in the NMR spectra of **11** (Figure 23), indicating that the structure possessed one dominant rotameric form; this was in agreement with isolation report on microsclerodermin J.[2] Direct comparison of the data of **11** to that of microsclerodermin J was aided by copies of the isolation NMR spectra provided by the Li group. This was critical as there were inaccuracies in the data listings given in the isolation paper.[2] Table 1 outlines these errors, which were revealed by comparing the original copy of Li's ^{13}C NMR spectrum with the published ^{13}C NMR data listings. The published ^{1}H NMR data listing for microsclerodermin J was largely correct, with the exception of the signals for H7; the correct chemical shifts are 1.71 ppm (1H, m) and 1.02 ppm (1H, m) instead of 2.16 ppm (2H, br s), as confirmed by personal communication with Dr Li.

The ^{1}H NMR spectrum of **11** matched perfectly with that of the natural product, with the exception of the OH and NH protons, the shifts of which are dependent on sample concentration. Comparison of the ^{13}C NMR data showed a complete match between the spectra of synthetic and natural material, with the differences in chemical shift not exceeding 0.1 ppm (Figure 24). Based on this data, it was confirmed that microsclerodermin J has the (*R*)-configuration at the C44 pyrrolidinone stereocentre. Accordingly, the structure originally proposed by the Li group was correct and no corrigendum was needed.

Carbon №	δ_C published (incorrect),[2] ppm	δ_C original (correct), ppm
1	**174.1**	**173.7**
2	69.4	69.5
4	68.4	68.5
5	72.8	72.9
6	**34**	**34.5**
8	25.9	26
9	29.5	29.6
11	128.4	128.5
12	128.9	129
15	113.9	114
17	113.9	114
19	**15.9**	**15.5**
23	**67.1**	**66.6**
24	**45.7**	**45.2**
25	168.9	169
27	171.5	171.6
29	25.7	25.8
37	**127.5**	**127.1**
39	**50**	**50.5**
41	168.1	168.2
44	45.9	46
45	**34.5**	**34.1**
46	174.9	175

Table 1. Inaccuracies in the published ^{13}C NMR data for natural microsclerodermin J.

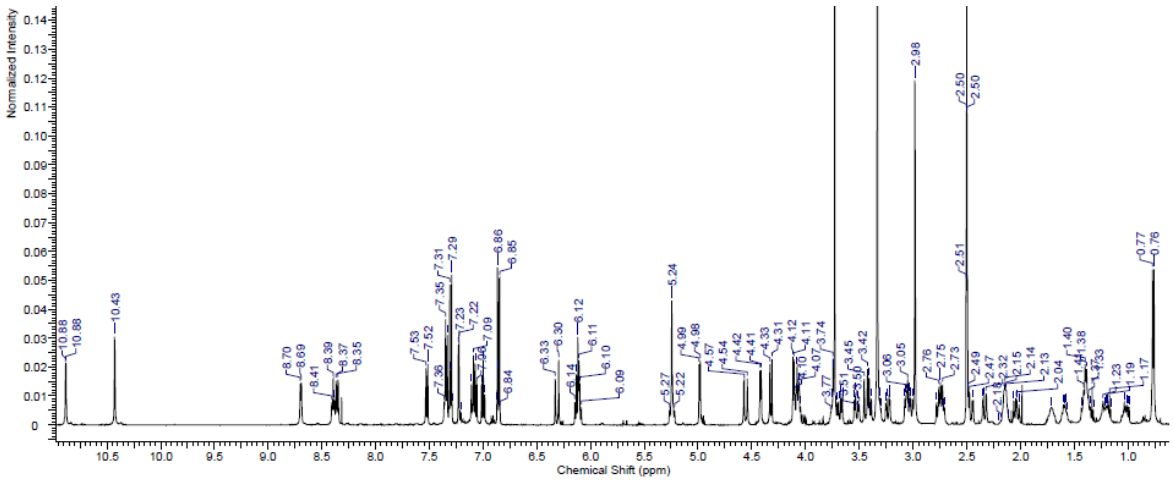


Figure 23. ^{1}H NMR spectrum of synthetic microsclerodermin J.

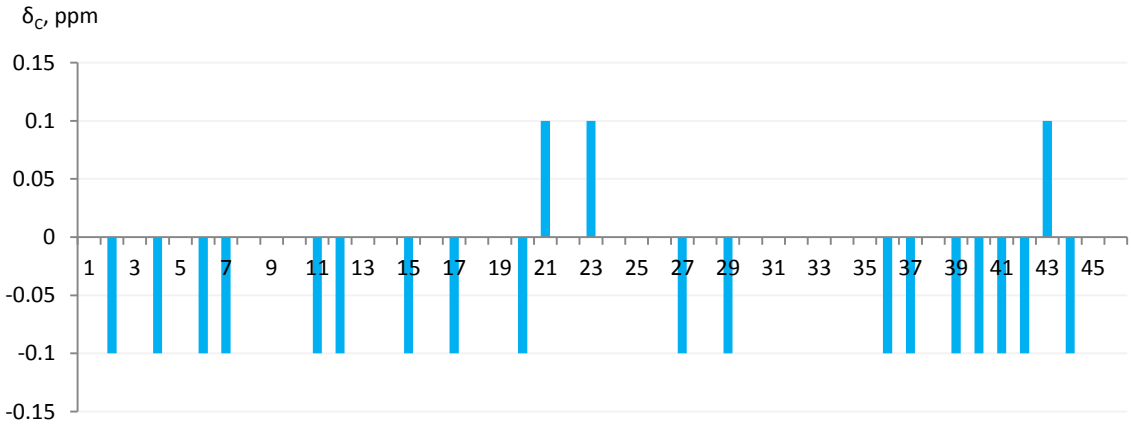


Figure 24. Comparison of ^{13}C NMR of synthetic and natural microsclerodermin J.

Chapter 6 Studies towards the total synthesis of dehydromicrosclerodermin A

6.1 Introduction

At this stage, dehydromicrosclerodermin A **3** became an attractive synthetic target as this would enable the stereochemical assignment of the pyrrolidinone residue to be either confirmed or corrected (Figure 25). Compared to dehydromicrosclerodermin B, **3** contains an additional hydroxyl group at the C46 position of the pyrrolidinone ring. Based on degradation studies, Faulkner proposed that this residue has the (45*R*,46*R*)-configuration.[1]

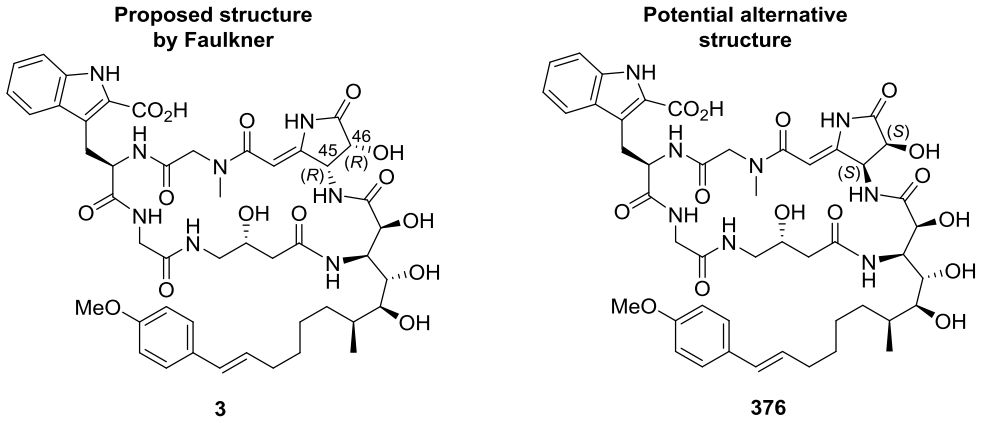
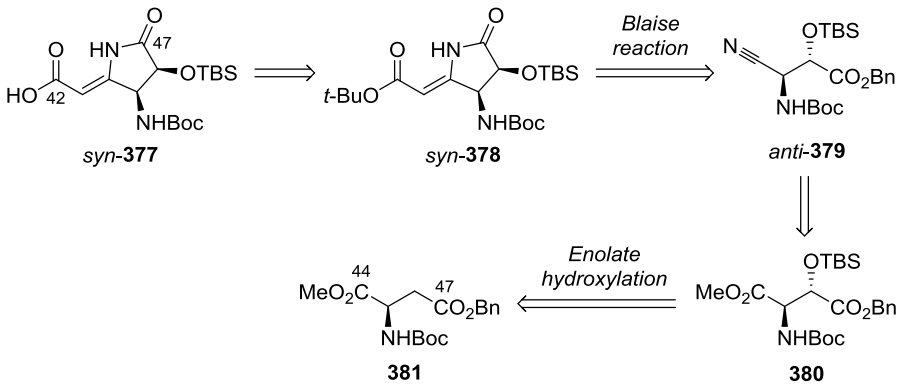


Figure 25. Dehydromicrosclerodermin A.

However, the stereochemical reassignments of dehydromicrosclerodermin B **358** and microsclerodermin J **13** suggested that dehydromicrosclerodermin A might also have the (*S*)-configuration at C45. Faulkner had used NOE correlations to assign a *syn*

relationship between H45 and H46 of microsclerodermin A **1**. Thus, it was considered that either the proposed structure (**3**) is correct and this natural product has a distinct C45 configuration, or an assignment error had been made such that alternate diastereoisomer **376** is the correct structure.

6.2 Retrosynthetic analysis and hydroxylation of an aspartic acid derivative

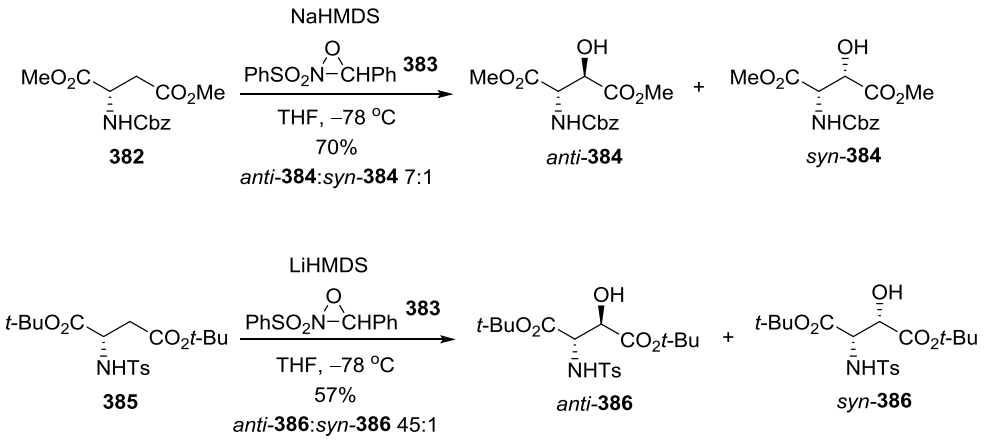


Scheme 88. Retrosynthetic analysis of pyrrolidinone amino acid *syn*-**377**.

Initial studies targeted the (45*S*)-configured diastereoisomer **376**. The synthesis of *syn*-**377** requires a stereocontrolled strategy to introduce a hydroxyl group onto the C46 position of the pyrrolidinone. In earlier work, a Blaise reaction had been used as the key step in the construction of the pyrrolidinone amino acid, and it was decided to adapt this approach by using an *anti*-hydroxyaspartic acid derivative for the synthesis of nitrile *anti*-**379**. Thus, the retrosynthetic plan for pyrrolidinone amino acid *syn*-**377** involved a Blaise reaction on nitrile *anti*-**379**, which, in turn, would be generated by (a) selective hydrolysis of the methyl ester of **380**, (b) formation of the primary amide and

(c) elimination of water. It was envisaged that *anti*-amino alcohol derivative **380** would arise *via* α-hydroxylation of aspartic acid derivative **381** (Scheme 88).

Only one relevant study was found in the literature on the selective α-hydroxylation of aspartic acid derivatives.[88] Here, treatment of Cbz-carbamate **382** with excess NaHMDS generated the corresponding dianion, which was then treated with Davis oxaziridine **383** (Scheme 89). This generated products *anti*-**384** and *syn*-**384** in 70% yield with 7:1 *anti*:*syn* selectivity. Interestingly, it was found that the use of other bases, such as LiHMDS, KHMDS and LDA, led to lower diastereoselectivity. The diastereoisomeric ratio of the process was also dependent on the choice of nitrogen and carboxylic acid protecting groups. In the event, further improvements were made by switching to sulfonamide **385**, which also possesses bulky *tert*-butyl esters. This substrate provided product *anti*-**386** in 45:1 dr when LiHMDS was used as base.

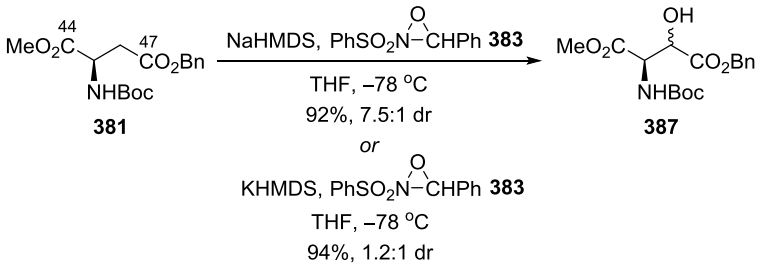


Scheme 89. Hydroxylation of aspartic acid derivatives **382** and **385**.

Inspired by this literature precedent, substrate **381** was studied for the proposed hydroxylation reaction based on the following considerations (Scheme **90**). A benzyl ester

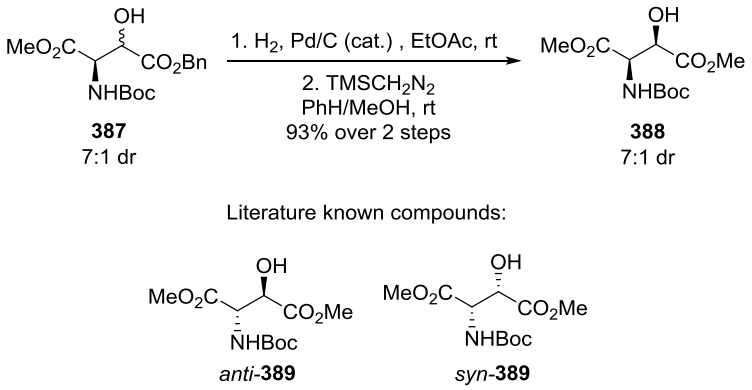
was selected for C47 because this protecting group had been used in the synthesis of the pyrrolidinone unit **151** of dehydromicrosclerodermin B. The C44 carboxylate was protected as its methyl ester as there is ample precedent for the selective hydrolysis of these in the presence of benzyl esters (for example, using trimethyltin hydroxide).[72] Finally, a Boc-carbamate was employed to mask the C45 nitrogen, because, again, this approach had been successful in the synthesis of dehydromicrosclerodermin B.

Extensive studies were undertaken to develop the proposed hydroxylation process. It was found that the reaction outcome was dependent on several parameters, including: (a) the choice and equivalents of base (e.g. LiHMDS, NaHMDS, KHMDS), (b) the equivalents of oxaziridine, and (c) the order and rate of addition of these reagents. These observations led to two sets of conditions which were employed to provide access to either diastereoisomer of the targets (*vide infra*). Use of 1.1 equivalents of oxaziridine **383** and 3.0 equivalents of NaHMDS provided **387** in 92% yield and 7.5:1 dr (inseparable) if the oxaziridine was added directly after the base. Conversely, preformation of the dianion over two hours using KHMDS (2 equivalents) provided adduct **387** in 94% yield and 1.2:1 dr. In this case, slow addition of the oxaziridine as a solution in THF was required to ensure complete conversion of the starting material.



Scheme 90. Hydroxylation of substrate **381**.

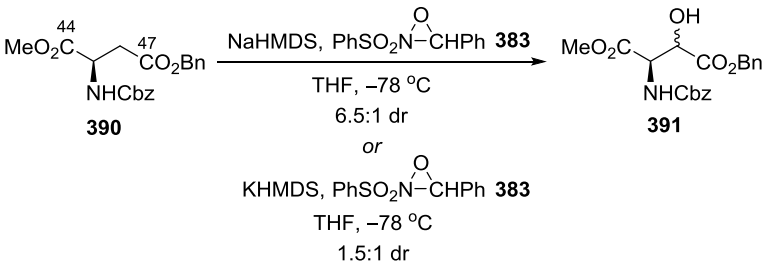
Product **387** was converted into methyl ester **388** so as the relative stereochemistry of each diastereoisomer could be determined by comparison to literature data (Scheme 91).[89] This study indicated that the major diastereoisomer of **387** was the *syn*-isomer, meaning that optimised α-hydroxylation conditions led predominantly to the undesired diastereoisomer of the product. This was surprising as it contrasted completely the reported results obtained using similar aspartic acid derivatives (Scheme 91). Thus, relying on the stereochemical assignment of literature compounds *anti*-**389** and *syn*-**389**, it seemed that the hydroxylation reaction using KHMDS provided the highest selectivity for the desired *anti*-amino alcohol of **387** (1.2:1 *syn:anti*). Attempts to improve this result using chiral oxaziridines ((+)-CSO or (−)-CSO) resulted in low conversions and diastereoselectivities.



Scheme 91. Determination of the relative stereochemistry of **387**.

It seemed that the choice of *N*-Boc group on **381** was critical to the observed inversion in hydroxylation diastereoselectivity relative to literature studies (*cf.* Scheme 89). To investigate this, *N*-Cbz protected substrate **390** was prepared (see Experimental section) and evaluated under the optimised hydroxylation protocols

(Scheme 92); these reactions were analysed by ^{1}H NMR of the crude reaction mixture and product **391** was not isolated. Assignment of the relative stereochemistry of **391** was based on its similarity to *N*-Boc protected hydroxylation product **387**. In both products, the ^{1}H NMR spectra are diagnostic, with a signal for the methyl ester at 3.81 ppm for the minor (*anti*) diastereoisomer and 3.60 ppm for the major (*syn*) one. This analysis suggested that the outcomes of the hydroxylation reactions involving **390** were very similar to results obtained using *N*-Boc variant **381** (NaHMDS 6.5:1 *syn*:*anti*; KHMDS 1.5:1 *syn*:*anti*). *N*-Cbz substrate **390** differs from "literature" variant **382** only by the presence of a benzyl ester at C47 (instead of a methyl or *tert*-butyl ester). Taken together, these results suggest that either there is an error in the reported assignments of hydroxyaspartic acid derivatives *anti*-**389** and *syn*-**389** or the reported stereochemical outcomes for the hydroxylation of **382** and **385** are incorrect.



Scheme 92. Hydroxylation of substrate **390**.

At this stage, time was extremely limited and so it was decided to carry KHMDS product **387** (with 1.2:1 dr) through the synthetic sequence. This decision was made in the hope that separation of the two diastereoisomers might be possible at a later stage and also because this approach would provide both diastereoisomers of the pyrrolidinone core.

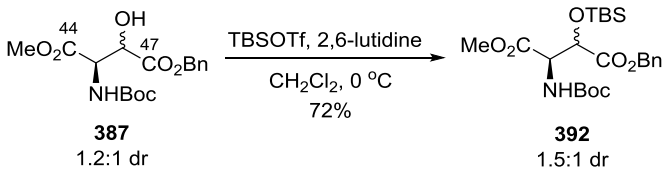
Comparative NOE studies on these cyclic compounds (*syn*-**378** and *anti*-**378**) would provide strong support for their relative stereochemistry.

Studies were also conducted to determine the enantiopurity of hydroxylation product **387**. Chiral HPLC analysis was not suitable as conditions could not be found to provide separation for both enantiomers of each diastereoisomer of racemic material. Analysis of the corresponding Mosher's esters was also problematic due to signal overlap in the ^{19}F NMR spectrum. However, even though it was not possible to measure the ee accurately, it was obvious that **387** was not racemic and had high levels of enantioenrichment.

6.3 Synthesis of the Blaise reaction precursor

Conversion of **387** to Blaise precursor *anti*-**379** involved formation of an *O*-TBS ether, selective cleavage of the methyl ester, amidation and formation of the nitrile (see Schemes 93, 94). However, the seemingly simple task of installing a TBS ether on the C46 hydroxyl of **387** proved challenging. When TBSCl and imidazole were employed for this transformation no reaction was observed. Replacement of imidazole with DBU did afford target **392**, but epimerisation of the C45 or C46 stereocentre took place; substrate **392** was highly sensitive to basic conditions. At the outset, the use of TBSOTf was deemed unsuitable because it can also effect deprotection of *N*-Boc carbamates. However, in the end, this reagent became the only choice for installation of the requisite TBS ether. An initial attempt, using 1.1 equivalents of TBSOTf, gave product **392** in 52% yield. The efficiency of the process was improved by prolonging the TBSOTf addition time to 15 minutes and this modification afforded **392** in 72% yield (Scheme 93). Over the course of the reaction a marginal enrichment of dr occurred, with **392** being isolated in 1.5:1 dr

from starting material (**387**) of 1.2:1 dr. This observation suggests that one of the diastereoisomers of **387** reacts faster than the other, although further evidence to support this assertion was not obtained. The mass balance of the reaction consisted predominantly of recovered **387**, but attempts to increase conversion using additional TBSOTf were complicated by competing cleavage of the *N*-Boc group.



387
1.2:1 dr

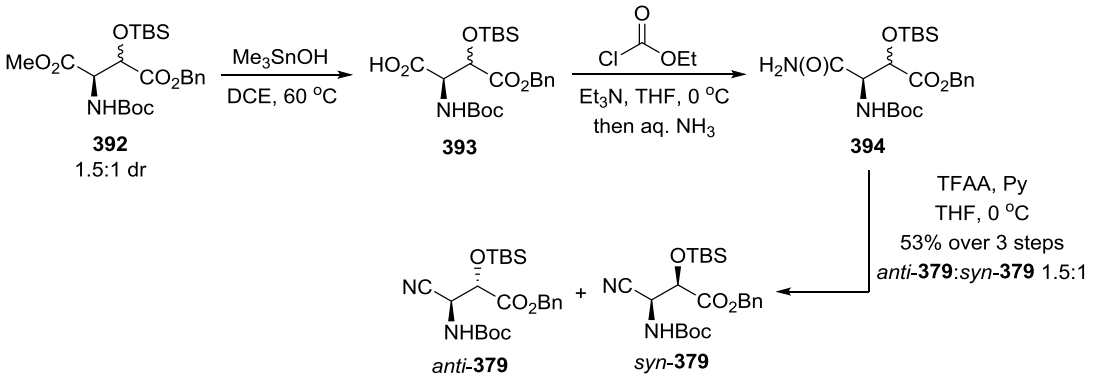
392
1.5:1 dr

Scheme 93. TBS protection of the C46 hydroxyl group.

Selective hydrolysis of the methyl ester of **392** was achieved using trimethyltin hydroxide, which provided **393** with high regioselectivity. Subsequent steps to nitrile *anti*-**379** used conditions developed for the pyrrolidinone unit **151** of dehydromicrosclerodermin B. Accordingly, treatment of **393** with ethyl chloroformate generated the corresponding mixed anhydride which was treated with aqueous ammonia to afford primary amide **394**. Dehydration of **394** was accomplished using TFAA to provide *anti*-**379** and *syn*-**379** in 53% overall yield from **392** (Scheme 94). At this stage, separation of the *anti* and *syn* diastereoisomers could be achieved by flash column chromatography; the relative stereochemistry of each was assigned by analysis of derivatives described later. Note that purification of acid **393** and amide **394** was not trivial, such that full characterisation was not pursued and their intermediacy is inferred.

Attempts to measure the ee of the diastereoisomers of nitrile by derivatisation to the corresponding Mosher's ester/amide were thwarted because conditions could not be

found to cleave either the *N*-Boc or *O*-TBS groups. For example, exposure of *anti*-**379** to either TBSOTf (to remove the *N*-Boc group) or TASF/H_2O/DMF (to remove the *O*-TBS group) led to complex mixtures of products. Thus, verification of enantiointegrity of the sequence was postponed until the stage of the Blaise reaction product (*vide infra*).

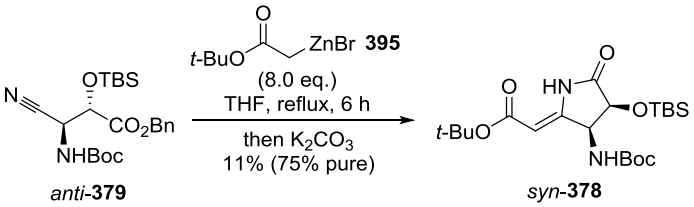


Scheme 94. Synthesis of nitriles *anti*-**379** and *syn*-**379**.

6.4 The Blaise reaction and determination of product enantiopurity

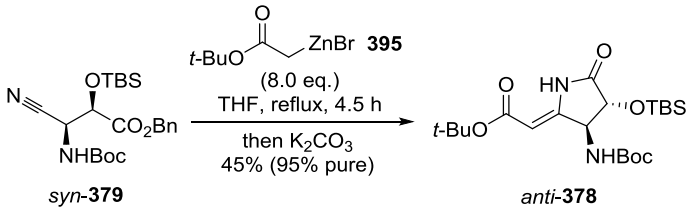
With single diastereoisomers of precursors *anti*-**379** and *syn*-**379** in hand, studies on the key Blaise reaction were pursued. Initially, cyclisation of desired diastereoisomer *anti*-**379** was explored using conditions developed previously for the dehydromicrosclerodermin B pyrrolidinone unit (Scheme 53). Thus, nitrile *anti*-**379** was heated at reflux in the presence of 4.0 equivalents of organozinc reagent **395** (prepared by exposure of *tert*-butyl bromoacetate to acid activated Zn). After one hour low conversion was observed, whereas a 2:1 ratio of product to starting material was obtained when the reaction was left for four hours; in both cases low mass recoveries were obtained. The best result was achieved using 8.0 equivalents of organozinc reagent **395** and a reaction time of six hours. These conditions ensured complete conversion but provided *syn*-**378** in only

11% yield and 75% purity after column chromatography (Scheme 95). The mass balance of the process consisted of multiple side-products, indicating competitive decomposition of starting material *anti*-**379** and/or product *syn*-**378**. Alternate methods for zinc activation (TMSCl,[90] Zn/Cu couple, iodine[91]) were also explored but none offered any benefits.



Scheme 95. The Blaise reaction on nitrile *anti*-**379**.

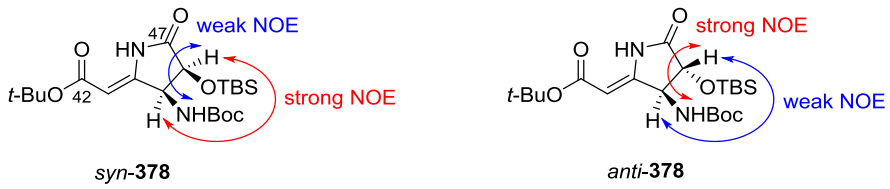
The undesired nitrile *syn*-**379** preformed slightly better in the Blaise reaction (Scheme 96). A survey of conditions, including equivalents of organozinc reagent **395**, reaction time and zinc activation method, led to the conditions outlined in Scheme 96, which provided *anti*-**378** in 45% yield and with acceptable purity.



Scheme 96. The Blaise reaction on nitrile *syn*-**379**.

The relative stereochemistry of Blaise products *syn*-**378** and *anti*-**378** was determined by NOESY experiments (Figure 26). Both compounds showed a 1,2-correlation between H45 and H46 but with different intensities. For pyrrolidinone

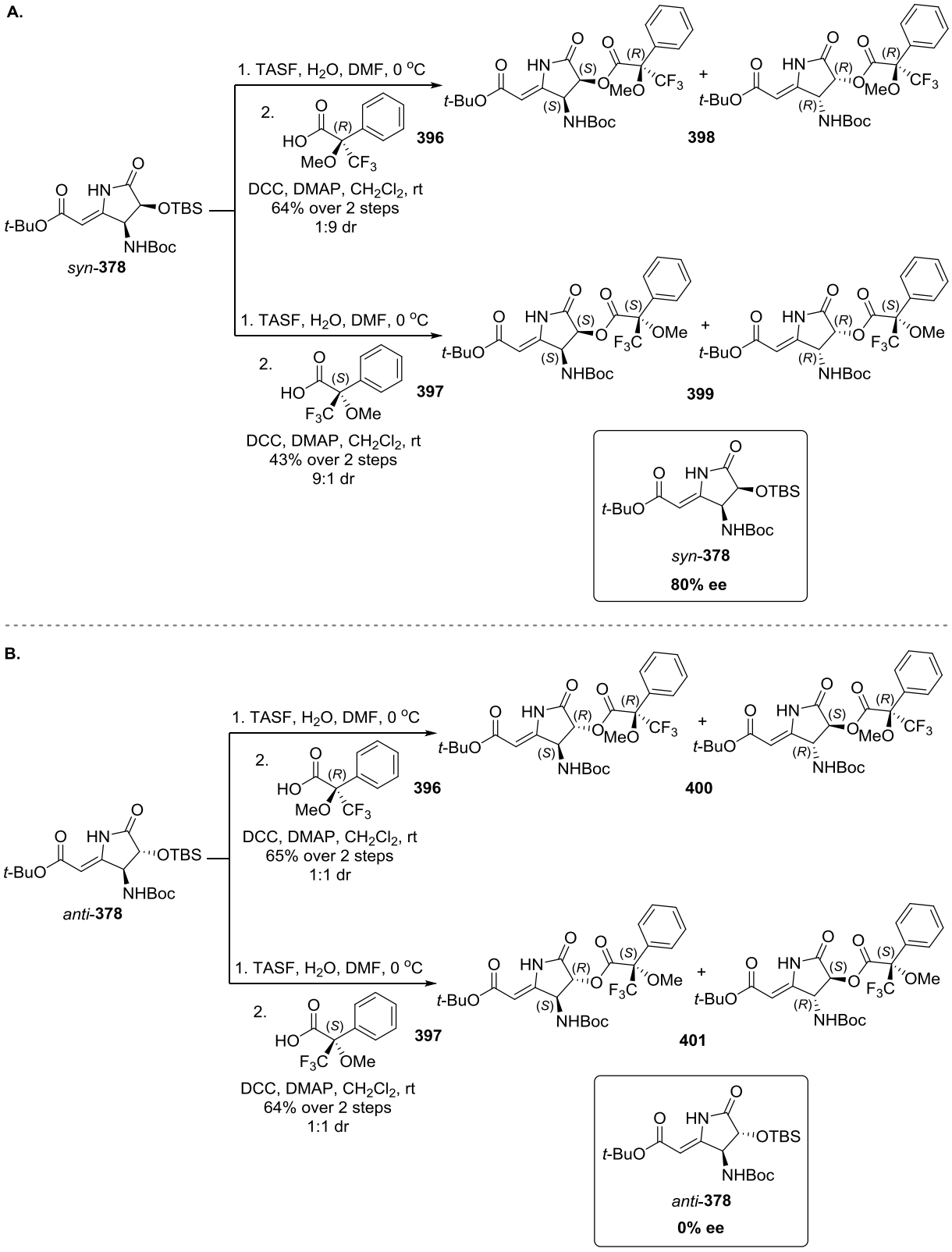
syn-**378** strong H45-H46 and weak NH45-H46 correlations were observed, whereas pyrrolidinone *anti*-**378** had a strong NH45-H46 correlation and a weak H45-H46 correlation. These data also support the stereochemistry of earlier intermediates, including nitriles *anti*-**379** and *syn*-**379**.



syn-**378** *anti*-**378**

Figure 26. Determination of the relative stereochemistry of Blaise products *syn*-**378** and *anti*-**378.**

In addition to studies on the relative stereochemistry of Blaise products *syn*-**378** and *anti*-**378**, the enantiopurity of each of compound was examined by Mosher's ester analysis. In both cases, TBS ether cleavage was readily achieved using TASF/H_2O/DMF. The resulting free alcohol was then esterified using either enantiomer of Mosher's acid. For *syn*-**378**, Mosher's esters **398** and **399** were both formed in 9:1 dr, which indicates an enantiopurity of approximately 80% ee (Scheme 97A). For *anti*-**378**, Mosher's esters **400** and **401** were both formed in 1:1 dr, indicating that complete racemisation had occurred (Scheme 97B).



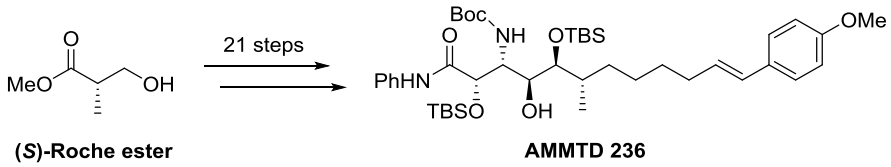
Scheme 97. Determination of the enantiopurity of Blaise products *syn*-**378** and *anti*-**378**.

The results in Scheme 97 were surprising and raised two key questions. First, at which step does epimerisation occur? And second, why is one of the diastereoisomers of the Blaise reaction racemic (*anti*-**378**) and the other only partially epimerised (*syn*-**378**)? At the present time, it is only possible to speculate at which stage epimerisation may have occurred because of the aforementioned difficulties in measuring the ee of earlier intermediates. However, the ^{19}F NMR spectra of Mosher's esters derived from hydroxylation reaction product **387** indicated that reasonable levels of enantiopurity had been maintained. Epimerisation during the Blaise reaction seems unlikely as nitriles *anti*-**379** and *syn*-**379** appeared to undergo stereospecific conversion to pyrrolidinones *syn*-**378** and *anti*-**378**. Any epimerisation would manifest in lower diastereospecificities for these processes (i.e. in each case, the alternate diastereoisomer would also be observed). Thus, the most likely stage seems to be during trimethyltin hydroxide promoted hydrolysis of the methyl ester of **392** (Scheme 94). This may involve epimerisation of one or both of the stereocentres of *syn*-**392**. The fact that *anti*-**392** does not undergo complete epimerisation is intriguing and suggests that it is kinetically more inert to racemisation under the reaction conditions. Nevertheless, these suggestions must be viewed with caution and further experimental evidence is required to reach firm conclusions.

Because of the low yield of Blaise reaction product *syn*-**378**, the level of enantiopurity, and time constraints, this route towards the pyrrolidinone unit of dehydromicrosclerodermin A was not pursued further. Future work in the Donohoe group will be required to develop a method for accessing pyrrolidinone *syn*-**378**.

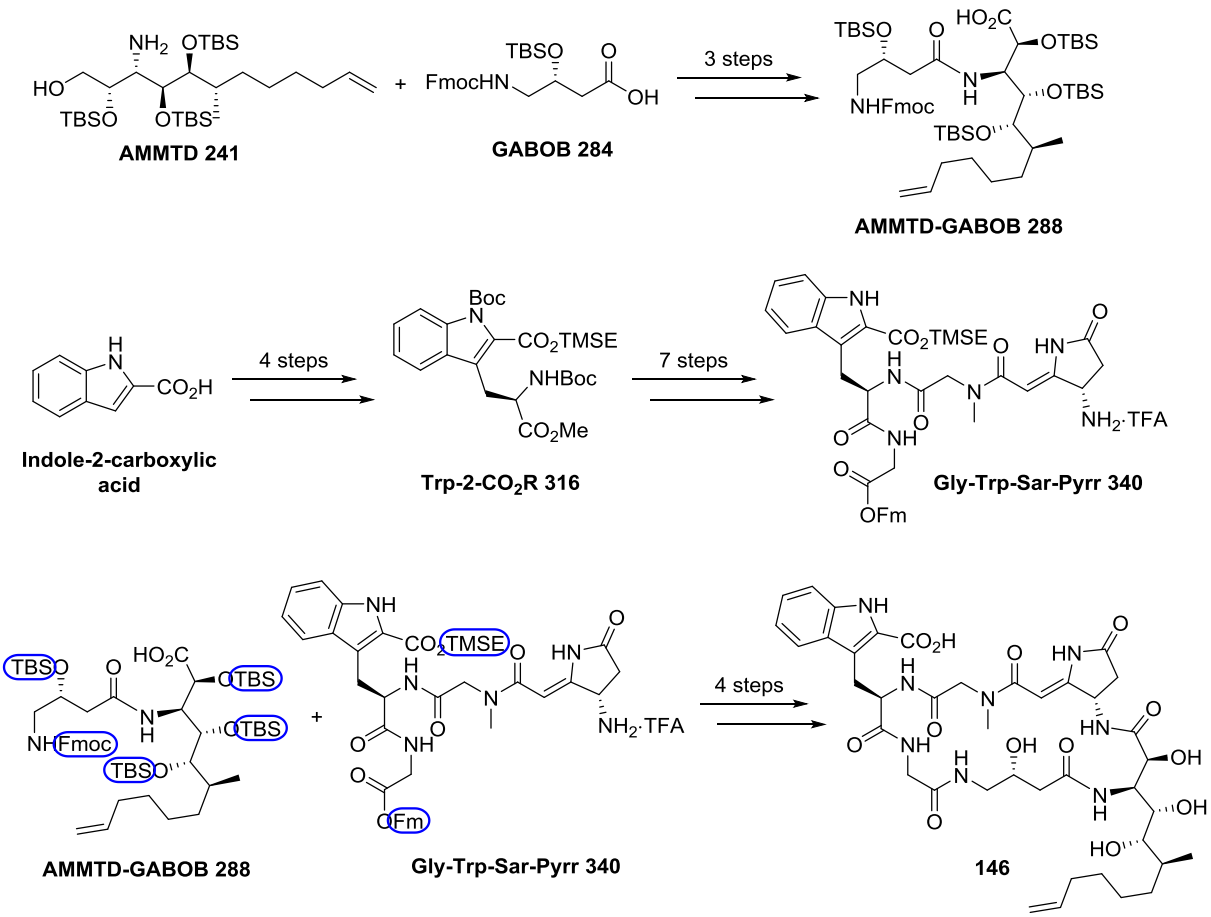
Chapter 7 Conclusions

In conclusion, the synthesis of the AMMTD subunit **236** of microsclerodermins A, B, J and K has been accomplished in a longest linear sequence of 21 steps starting from (*S*)-Roche ester. Building on prior studies from the group, the overall synthetic sequence was optimised, the key cuprate displacement reaction was dramatically improved and the final steps of the AMMTD synthesis were developed.



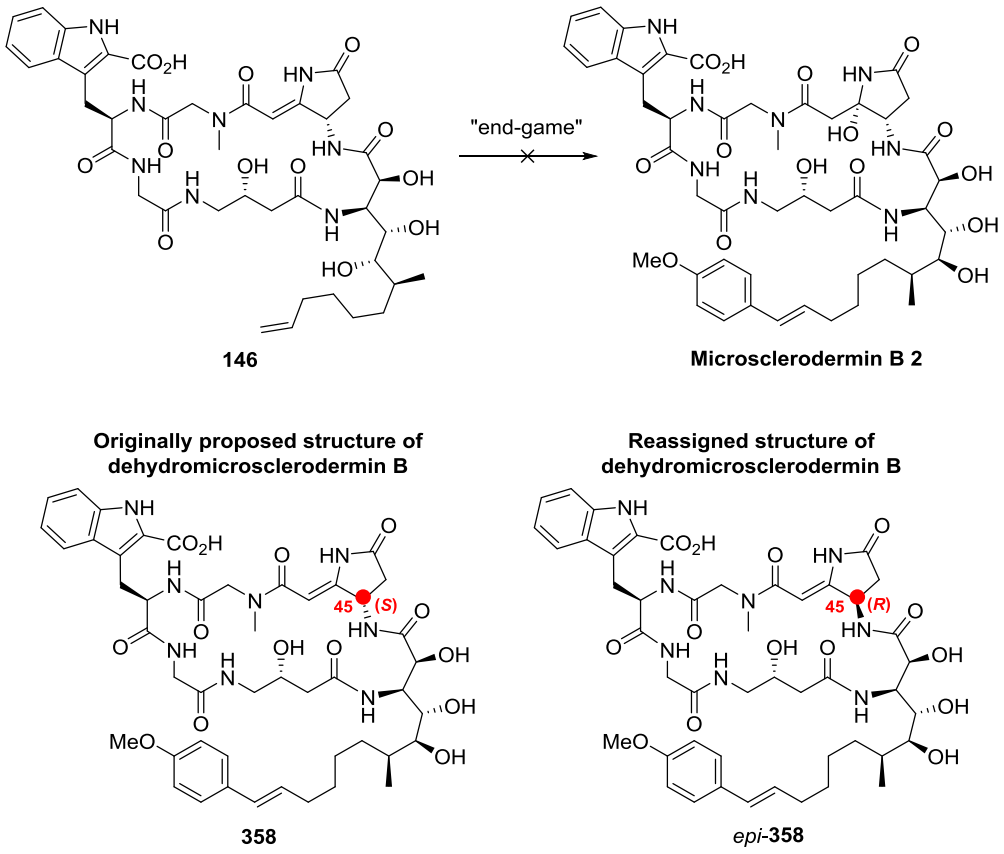
Scheme 98. Synthesis of AMMTD subunit **236**.

AMMTD-GABOB dipeptide **288** was synthesised and coupled with the northern hemisphere **340** of the proposed structure of dehydromicrosclerodermin B. An appropriate protecting group strategy was developed such that macrolactamisation and subsequent protecting group removal could be achieved. These endeavours required the development of a new approach to the synthesis of tryptophan-2-carboxylic acid derivative **316**.



Scheme 99. Synthesis of deprotected cyclic peptide **146**.

Initially, a synthesis of microsclerodermin B **2** was pursued but application of a previously developed "end-game" strategy for introduction of the sensitive C44 hydroxyl group was unsuccessful. Consequently, the proposed structure **358** of dehydromicrosclerodermin B was prepared instead. Analysis of the data for **358** suggested a mistake in the stereochemical assignment of the C45 stereocentre, and this hypothesis was confirmed by synthesising *epi*-**358**, the data of which was in good agreement with that of dehydromicrosclerodermin B.



Scheme 100. Unsuccessful "end-game" strategy and stereochemical reassignment of dehydromicrosclerodermin B.

Having corrected the C45 stereochemical assignment of dehydromicrosclerodermin B, studies moved towards a synthesis of microsclerodermin J **11**, because there has also been confusion over the configuration of the C44 stereocentre of this natural product. In the event, it was shown that the pyrrolidinone unit of **11** has the same configuration as in dehydromicrosclerodermin B. NMR data for synthetic and natural **11** were in complete agreement and thus the configuration of the C44 stereocentre of this natural product has also been corrected. This correction is also most likely applicable to microsclerodermins A and K, although synthetic studies have yet to confirm this.

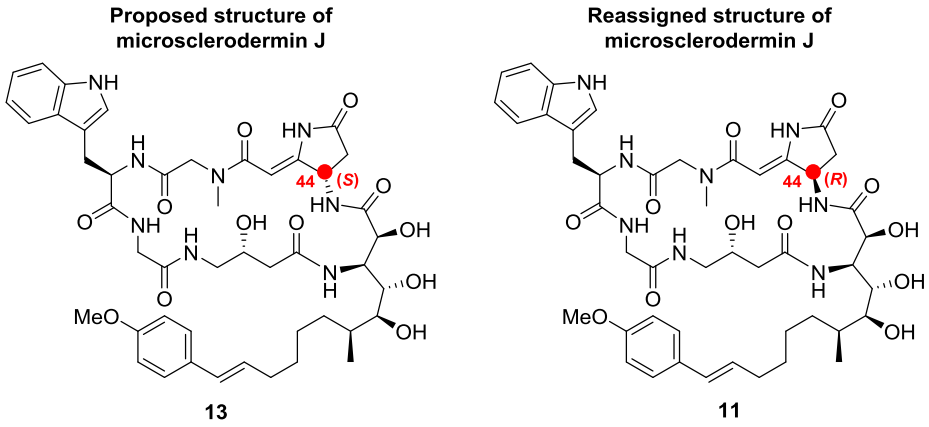
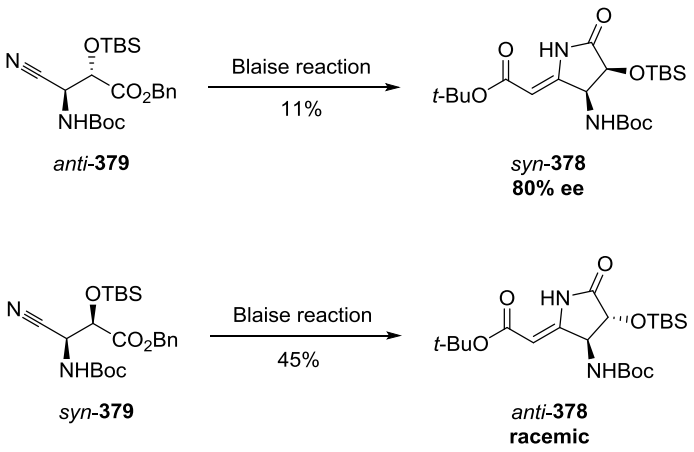


Figure 27. Stereochemical reassignment of microsclerodermin J.

Preliminary studies have been conducted towards the synthesis of the proposed reassigned structure of dehydromicrosclerodermin A. This natural product contains a more complex, hydroxylated pyrrolidinone unit and it has been shown that, at the present stage, the Blaise reaction is poorly suited to its synthesis. Further issues associated with maintaining the enantiopurity of intermediates *en route* to the Blaise reaction were also highlighted. As such, further studies are required to complete a synthesis of *syn*-**378** and confirm or reassign the pyrrolidinone stereochemistry of dehydromicrosclerodermin A.



Scheme 101. Studies towards dehydromicrosclerodermin A.

Chapter 8 Experimental

8.1 Experimental techniques

General: All non-aqueous reactions were carried out under an argon atmosphere in flame dried glassware unless otherwise stated. All reactions were followed by analytical thin layer chromatography (TLC) and procedure times represent reaction completion as judged accordingly. Reaction temperatures (unless otherwise stated) represent bath temperatures.

Solvents: Anhydrous DMF and 1,2-dichloroethane were used as commercially supplied. CH_2Cl_2, Et_2O, MeCN, MeOH, THF and toluene were purified by filtration through two activated alumina purification columns. In cases where mixtures of solvents were used, the ratios refer to the component volumes. Petrol refers to petroleum ether in the boiling range 30-60 °C.

Reagents: All reagents were used as supplied commercially unless otherwise stated.

Chromatography: Flash column chromatography was carried out using silica gel 40-63 μm unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using aluminium backed pre-coated silica gel 60 F_{254} plates and visualised under UV radiation at 254 nm and staining with phosphomolybdic acid in ethanol, potassium permanganate in water or vanillin in ethanol.

Optical Rotation: Specific rotations (α') were recorded on a Perkin Elmer 341 Polarimeter, with a cell pathlength (l) of 1.0 dm, at the stated temperature (°C) and

concentration (c) (measured in units of g/100 mL); specific rotations were converted to optical rotations, $[\alpha]_D$, *via* the equation: $[\alpha]_D = (100 \cdot \alpha')/(l \cdot c)$.

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

Mass Spectrometry: Mass spectrometry was carried out using CI^+ (NH_3), ES^+ or EI^+ and recorded using a Brucker MicroTof or Fisons Platform II spectrometer. Only molecular ions and fragments from molecular ions are reported with relative intensities of peaks quoted as a percentage value. Accurate mass (HRMS) were recorded on a Brucker MicroTof spectrometer under conditions of electrospray ionisation (ESI).

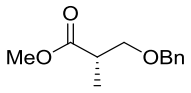
NMR Spectroscopy: ^1H NMR spectra were recorded at 200, 400 and 500 MHz in $CDCl_3$, CD_2Cl_2, D_6-DMSO or D_4-MeOD, on a Bruker Advance 200, 250, 300, 400 or 500 spectrometer respectively, at the stated temperature, and reported as follows; chemical shift (δ) (reported to the nearest 0.01 ppm), (number of protons, multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and/or broad (br)), coupling constant, *J* (reported in Hertz (Hz) to the nearest 0.1 Hz), assignment). Residual protic solvent was used as the internal reference: $CDCl_3$ (δ_H = 7.26 ppm), D_6-DMSO (δ_H = 2.50 ppm), D_4-MeOD (δ_H = 3.31 ppm). ^{13}C NMR spectra were recorded at 75, 100 and 126 MHz, with complete proton decoupling, in $CDCl_3$, D_6-DMSO or D_4-MeOD, on a Bruker Advance 400 or 500 spectrometer respectively with the chemical shift, δ, reported to the nearest 0.1 ppm. The internal reference used: $CDCl_3$ (δ_C = 77.0 ppm), D_6-DMSO (δ_C = 39.5 ppm), D_4-MeOD (δ_C = 49.1 ppm). ^{19}F NMR spectra were recorded at 376 MHz on a Bruker Advance 400 spectrometer with the chemical shift reported to the nearest 0.1 ppm. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ_H = 0.00 ppm). Assignments were based upon COSY, DEPT, HSQC and HMBC

experiments, NOE enhancement experiments where appropriate, and by comparison to related compounds.

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

8.2 Experimental procedures

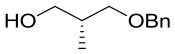
Methyl (*S*)-3-(benzyloxy)-2-methylpropanoate (162)[31]



Freshly prepared benzyl 2,2,2-trichloroacetimidate[92] (10.0 mL, 53.8 mmol) was added to a solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate **161** (5.00 mL, 45.3 mmol) in cyclohexane/CH_2Cl_2 (75 mL, 2:1) at −15 °C. Trifluoromethanesulfonic acid (0.40 mL, 4.5 mmol) was then added dropwise, resulting in the formation of a white suspension. The solution was stirred at this temperature for 2 h before being warmed to room temperature and stirred for 16 h. Benzyl 2,2,2-trichloroacetimidate (10.4 mL, 56.0 mmol) and trifluoromethanesulfonic acid (0.67 mL, 7.5 mmol) were subsequently added in five equal portions over a 24 h period. The solution was then filtered through Celite, washed with petrol, and then concentrated *in vacuo*. The residue was then dissolved in ethyl acetate and sequentially washed with saturated aqueous $NaHCO_3$ and brine solutions, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded benzyl ether **162** (9.20 g, 98%) as a colourless oil;

R_f: 0.50 (10% EtOAc/petrol); $[\alpha]_D^{20}$ +9.0 (*c* 1.42, $CHCl_3$) (lit.[31] $[\alpha]_D^{20}$ +10.2 (*c* 3.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.29-7.18 (5H, m, 5 x Ph*H*), 4.45 (2H, s, OC*H*$_2$Ph), 3.62 (3H, s, OC*H*$_3$), 3.59 (1H, dd, *J* 9.2 and 7.3, 3-*H*H), 3.42 (1H, dd, *J* 9.2 and 5.9, 3-H*H*), 2.72 (1H, m, 2-*H*), 1.11 (3H, d, *J* 7.1, 2-(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 175.3 (*C*(O)), 138.2 (*C*$_{(Ar)}$), 128.4 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 73.1 (O*C*H$_2$Ph), 72.0 (3-*C*), 51.8 (O*C*H$_3$), 40.2 (2-*C*), 14.0 (2-(*C*H$_3$)). All data were in agreement with those previously reported.[31]

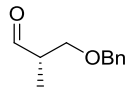
(*R*)-3-(Benzyloxy)-2-methylpropan-1-ol (162a)[31]



Lithium borohydride (2.60 mL of a 4.0 M solution in THF, 10.3 mmol) was added slowly to a solution of ester **162** (0.70 g, 3.40 mmol) in THF (23 mL) at 0 °C. Methanol (0.50 mL, 11.3 mmol) was then added slowly and once the exothermic reaction had subsided (approx. 15 minutes), the mixture was warmed to room temperature and stirred for 1 h. Aqueous NaOH (15 mL of a 1 M solution) was added slowly and the aqueous layer was then separated and extracted with EtOAc. The organic extracts were washed with brine solution, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-20% EtOAc/petrol) afforded alcohol **162a** (0.54 g, 88%) as a colourless oil; R_f: 0.20 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +13.8 (*c* 1.62, $CHCl_3$) (lit.[31] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +11.3 (*c* 4.9, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.39-7.24 (5H, m, 5 x Ph*H*), 4.53 (2H, s, OC*H*$_2$Ph), 3.63-3.61 (2H, m, 1-*H*), 3.56 (1H, dd, *J* 9.1 and 4.6, 3-*H*H), 3.42 (1H, dd, *J* 9.1 and 7.8, 3-H*H*), 2.64 (1H, br s, O*H*), 2.09 (1H, m, 2-*H*), 0.90 (3H, d, *J* 6.8, 2-(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 138.0 (*C*$_{(Ar)}$), 128.4 (*C*H$_{(Ar)}$), 127.7 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 75.4 (3-*C*), 73.3

(O*C*H_2Ph), 35.5 (2-*C*), 13.4 (2-(*C*H_3)). All data were in agreement with those previously reported.[31]

(*S*)-3-(Benzyloxy)-2-methylpropanal (163)[32]

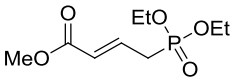


*Method A (reduction of ester **161**)*: Diisobutylaluminum hydride (24.0 mL of a 1 M solution in toluene, 24.0 mmol) was added dropwise to a solution of ester **161** (5.00 g, 24.0 mmol) in CH_2Cl_2 (60.0 mL) at −78 °C. The mixture was stirred for 1 h. MeOH (12.0 mL) was then added slowly at −78 °C and the mixture was stirred for 10 minutes before being warmed to room temperature and quenched with a saturated aqueous salt of Rochelle's. The solution was stirred vigorously for 30 minutes before separation of the aqueous layer, which was extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford aldehyde **163** (4.50 g (yield reported for diene **167** over two steps)) as a yellow oil. The compound was used immediately and without further purification in the subsequent step; R_f: 0.40 (15% EtOAc/petrol); δ_H (200 MHz, $CDCl_3$) 9.74 (1H, d, *J* 1.5, C*H*O), 7.40-7.23 (5H, m, 5 x Ph*H*), 4.54 (2H, s, OC*H*$_2$Ph), 3.75-3.61 (2H, m, 3-*H*), 2.68 (1H, m, 2-*H*), 1.15 (3H, d, *J* 7.1, 2-(C*H*$_3$)). Data was in agreement with those previously reported.[93]

*Method B (oxidation of alcohol **162a**)*: Dimethyl sulfoxide (25.7 mL, 362 mmol), *N*,*N*-diisopropylethylamine (25.2 mL, 145 mmol) and sulfur trioxide pyridine complex (17.3 g, 109 mmol) were added sequentially to a solution of alcohol **162a** (6.50 g, 36.2 mmol) in CH_2Cl_2 (181 mL) at 0 °C and the mixture was stirred for 1.5 h. Saturated

aqueous $NaHCO_3$ was then added and the aqueous layer was separated and extracted with CH_2Cl_2. The organic layer was then washed sequentially with saturated aqueous copper sulfate (x 2), ammonium chloride (x 2) and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford aldehyde **163** (5.70 g, 89%) as a light orange oil. The compound was used immediately and without further purification in the subsequent step.

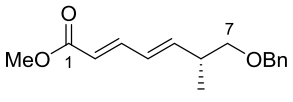
Methyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate (166)[34]



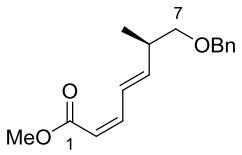
Benzoyl peroxide (274 mg, 1.10 mmol) was added portionwise to a solution of methyl crotonate **164** (6.00 mL, 57.0 mmol) and *N*-bromosuccinimide (10.6 g, 59.4 mmol) in benzene (57.0 mL). The mixture was then heated at reflux for 20 h. After cooling to room temperature, Na_2SO_4 was added and the solution was filtered through Celite, washing with petrol. The filtrate was then concentrated *in vacuo* to afford methyl (*E*)-4-bromobut-2-enoate **165** (10.1 g) as an orange oil; δ_H (200 MHz, $CDCl_3$) 7.02 (1H, dt, *J* 15.3 and 7.3, 3-*H*), 6.04 (1H, dt, *J* 15.3 and 1.3, 2-*H*), 4.02 (2H, dd, *J* 7.3 and 1.3, C*H*$_2$Br), 3.77 (3H, s, CO_2CH_3).[34] Triethyl phosphite (11.0 mL, 63.9 mmol) was added to a solution of freshly prepared allyl bromide **165** (10.1 g) in toluene (30 mL). The mixture was then heated at reflux for 20 h. The solution was cooled to room temperature and concentrated *in vacuo*. The residue was then redissolved CH_2Cl_2, concentrated onto SiO_2 and purified by flash column chromatography (20-50-100% EtOAc/petrol) to afford phosphonate **166** (8.60 g, 64%, (2 steps)) as an orange oil, with an (*E*)/(*Z*) isomeric ratio of 6:1; R_f: 0.20 (50% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$ (chemical shifts reported for the major (*E*)-isomer only)) 6.84 (1H, ddt, *J* 15.6, 7.9 and 7.9, 3-*H*), 5.92 (1H, ddt, *J* 15.6, 5.0

and 1.4, 2-*H*), 4.19-4.04 (4H, m, 2 x OC*H*$_2$CH$_3$), 3.73 (3H, s, CO$_2$C*H*$_3$), 2.70 (2H, ddd, *J* 23.0, 7.9 and 1.4, 4-*H*), 1.32 (6H, t, *J* 7.1, 2 x OCH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major (*E*)-isomer only)) 166.0 (d, $^4J_{C\text{-}P}$ 2.4, *C*(O)), 137.8 (d, $^2J_{C\text{-}P}$ 11.2, 3-*C*), 125.3 (d, $^3J_{C\text{-}P}$ 13.6, 2-*C*), 62.2 (d, $^2J_{C\text{-}P}$ 7.2, O*C*H$_2$CH$_3$), 51.6 (CO$_2$*C*H$_3$), 30.6 (d, $^1J_{C\text{-}P}$ 139.0, 4-*C*), 16.4 (d, $^3J_{C\text{-}P}$ 6.4, OCH$_2$*C*H$_3$). All data were in agreement with those previously reported.[34]

Methyl (*R*,2*E*,4*E*)-7-(benzyloxy)-6-methylhepta-2,4-dienoate (167) and methyl (*R*,2*Z*,4*E*)-7-(benzyloxy)-6-methylhepta-2,4-dienoate (168)[30]



167 (*E*,*E*):(*E*,*Z*) 7:1



168 (*Z*,*E*)

General procedure: n-Butyllithium (2.05 eq. of a 2.5 M solution in hexanes) was added slowly to a solution of diisopropylamine (2.05 eq.) in THF (0.4 M) at 0 ºC and the mixture was stirred for 30 minutes. The LDA solution was then added slowly to a solution of phosphonate **166** (2.00 eq.) in THF (0.4 M) at −78 ºC. The solution was warmed to −20 ºC and stirred for 2.5 h, before being recooled to −78 ºC. Aldehyde **163** (1.00 eq.) in THF (1.0 M) was then added slowly to the phosphonate solution, which was warmed to −20 ºC slowly and stirred for 3 h. Saturated aqueous ammonium chloride solution was then added and the solution was warmed to room temperature. The aqueous layer was then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2-5% EtOAc/petrol) afforded diene **167** with an (*E*,*E*)/(*E*,*Z*) isomeric ratio of 7:1 and (*Z*,*E*)-diene **168**. Data for

diene **167**: colourless oil; R_f: 0.50 (15% EtOAc/petrol); $[\alpha]_D^{20}$ +1.2 (*c* 0.86, $CHCl_3$) (lit.[30] $[\alpha]_D^{25}$ +1.2 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$ (chemical shifts reported for the major (*E*,*E*)-isomer only)) 7.29-7.16 (6H, m, 5 x Ph*H* and 3-*H*), 6.14 (1H, dd, *J* 15.4 and 10.8, 4-*H*), 6.03 (1H, dd, *J* 15.4 and 7.1, 5-*H*), 5.74 (1H, d, *J* 15.2, 2-*H*), 4.43 (2H, s, OCH_2Ph), 3.66 (3H, s, CO_2CH_3), 3.30 (2H, dd, *J* 6.9 and 1.7, 7-*H*), 2.55 (1H, m, 6-*H*), 1.00 (3H, d, *J* 6.9, 6-(CH_3)); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major (*E*,*E*)-isomer only)) 167.6 (*C*(O)), 146.6 (5-*C*), 145.2 (3-*C*), 138.2 ($C_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 127.8 (4-*C*), 127.6 (2 x $CH_{(Ar)}$), 119.4 (2-*C*), 74.4 (7-*C*), 73.0 (OCH_2Ph), 51.4 (OCH_3), 37.3 (6-*C*), 16.5 (6-(*C*H_3)). All data were in agreement with those previously reported.[30]

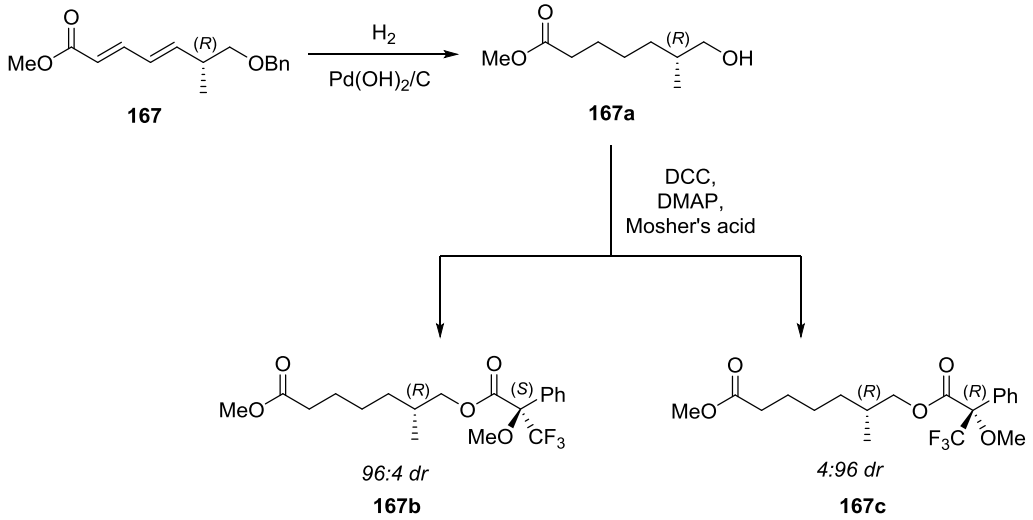
Method A (aldehyde **163**, obtained by reduction of **162**): 3.84 g scale, **167** in 68% yield from **162**.

Method B (aldehyde **163**, obtained by oxidation of **162a**): 1.15 g scale, **167** in 80% yield for the olefination step; **168** in <10% yield.

Data for diene **168**: colourless oil; R_f: 0.55 (15% EtOAc/petrol); $[\alpha]_D^{20}$ −5.0 (*c* 0.22, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2859, 1716, 1640, 1454, 1267, 1196, 1176, 1094, 1001, 819, 736, 698; δ_H (400 MHz, $CDCl_3$) 7.43 (1H, dd, *J* 15.4 and 11.3, 4-*H*), 7.37-7.29 (5H, m, 5 x Ph*H*), 6.58 (1H, dd, *J* 11.5 and 11.5, 3-*H*), 6.08 (1H, dd, *J* 15.4 and 7.1, 5-*H*), 5.62 (1H, d, *J* 11.5, 2-*H*), 4.53 (2H, s, OCH_2Ph), 3.65 (3H, s, CO_2CH_3), 3.43 (1H, dd, *J* 9.3 and 6.9, 7-H*H*), 3.38 (1H, dd, *J* 9.3 and 6.6, 7-*H*H), 2.70 (1H, m, 6-*H*), 1.12 (3H, d, *J* 6.9, 6-(CH_3)); δ_C (100 MHz, $CDCl_3$) 166.9 (*C*(O)), 147.6 (5-*C*), 145.5 (3-*C*), 138.4 ($C_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 127.5 ($CH_{(Ar)}$), 126.2 (4-*C*), 115.7 (2-*C*), 74.6 (7-*C*), 73.0

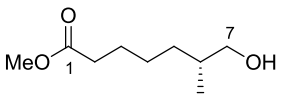
(O*C*H$_2$Ph), 51.1 (O*C*H$_3$), 37.6 (6-*C*), 16.6 (6-(*C*H$_3$)); *m/z* (ES$^+$) 283 (MNa$^+$, 100%); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{16}H_{20}O_3Na$ 283.1305, observed 283.1305.

The enantiopurity of diene **167** was confirmed by removal of the benzyl group under catalytic hydrogenation (with concomitant reduction of the olefins) and formation of the corresponding Mosher's esters:



Scheme 102. Confirmation of the enantiopurity of diene **167.**

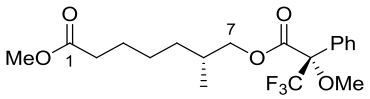
Methyl (*R*)-7-hydroxy-6-methylheptanoate (167a)



EtOAc (HPLC grade) (7.70 mL) was added to diene **167** (200 mg, 0.77 mmol) and Pd(OH)$_2$ on carbon (50.0 mg, 25% wt.) and the mixture was stirred under an atmospheric (balloon) pressure of hydrogen for 24 h. The solution was then filtered through Celite, washed with EtOAc and concentrated *in vacuo* to afford alcohol **167a** (130 mg) as a

colourless oil. The compound was used without further purification in the subsequent step; R_f: 0.20 (15% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, CO_2CH_3), 3.50 (1H, dd, *J* 10.5 and 5.9, 7-*H*H), 3.43 (1H, dd, *J* 10.5 and 6.4, 7-H*H*), 2.33 (2H, t, *J* 7.6, 2-*H*), 1.67-1.59 (3H, m, 6-*H* and 3-*H*), 1.47-1.29 (4H, m, 4-*H*, 5-*H*H and O*H*), 1.13 (1H, m, 5-H*H*), 0.92 (3H, d, *J* 6.9, 6-(CH_3)).

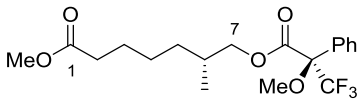
Methyl (*R*)-6-methyl-7-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)heptanoate (167b)



(*S*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (100 mg, 0.43 mmol), *N*,*N*′-dicyclohexylcarbodiimide (97.0 mg, 0.47 mmol) and DMAP (11.0 mg, 0.09 mmol) were added sequentially to a solution of alcohol **167a** (65.0 mg, 0.37 mmol) in CH_2Cl_2 (4.00 mL) at 0 °C. The mixture was slowly warmed to room temperature stirred for 4 h. The solution was then filtered through Celite, washing with CH_2Cl_2, and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded ester **167b** (124 mg, 82% over 2 steps) as a colourless oil; R_f: 0.50 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −15.6 (*c* 0.41, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2951, 1740, 1452, 1243, 1166, 1121, 1082, 1021, 766, 719, 698; δ_H (400 MHz, $CDCl_3$) 7.53-7.50 (2H, m, 2 x Ph*H*), 7.42-7.38 (3H, m, 3 x Ph*H*), 4.17 (1H, dd, *J* 10.5 and 6.4, 7-H*H*), 4.12 (1H, dd, *J* 10.5 and 5.9, 7-*H*H), 3.66 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 2.28 (2H, t, *J* 7.3, 2-*H*), 1.84 (1H, m, 6-*H*), 1.57 (2H, tt, *J* 7.6 and 7.6, 3-*H*), 1.38-1.12 (4H, m, 5-*H* and 4-*H*), 0.91 (3H, d, *J* 6.6, 6-(CH_3)); δ_C (100 MHz, $CDCl_3$) 174.0 (*C*(O)), 166.6 (*C*(O)), 132.3

($C_{(Ar)}$), 129.5 ($CH_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 127.3 ($CH_{(Ar)}$), 123.3 (q, $^{1}J_{C\text{-}F}$ 288.5, CF_3), 84.6 (q, $^{2}J_{C\text{-}F}$ 27.8, $C(OCH_3)(CF_3)Ph$), 70.9 (7-*C*), 55.3 (OCH_3), 51.4 (OCH_3), 33.8 (2-*C*), 32.6 (5-*C*), 32.2 (6-*C*), 26.1 (4-*C*), 24.9 (3-*C*), 16.6 (6-(CH_3)); δ_F (376 MHz, $CDCl_3$) −71.58; *m/z* (ES^+) 413 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{19}H_{25}O_5F_3Na$ 413.1546, observed 413.1532.

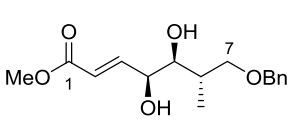
Methyl (*R*)-6-methyl-7-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)heptanoate (167c)



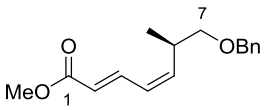
(*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (100 mg, 0.43 mmol), *N*,*N*′-dicyclohexylcarbodiimide (97.0 mg, 0.47 mmol) and DMAP (11.0 mg, 0.09 mmol) were added sequentially to a solution of alcohol **167a** (65.0 mg, 0.37 mmol) in CH_2Cl_2 (4.00 mL) at 0 °C. The mixture was slowly warmed to room temperature stirred for 4 h. The solution was then filtered through Celite, washing with CH_2Cl_2, and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded ester **167c** (127 mg, 85% over 2 steps) as a colourless oil; R_f: 0.50 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +37.2 (*c* 0.43, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2951, 1740, 1452, 1242, 1166, 1121, 1082, 1021, 766, 719, 698; δ_H (400 MHz, $CDCl_3$) 7.52-7.50 (2H, m, 2 x Ph*H*), 7.41-7.38 (3H, m, 3 x Ph*H*), 4.22 (1H, dd, *J* 10.8 and 5.6, 7-H*H*), 4.07 (1H, dd, *J* 10.8 and 6.4, 7-*H*H), 3.65 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 2.28 (2H, t, *J* 7.6, 2-*H*), 1.84 (1H, m, 6-*H*), 1.62-1.54 (2H, m, 3-*H*), 1.39-1.13 (4H, m, 5-*H* and 4-*H*), 0.90 (3H, d, *J* 6.6, 6-(CH_3)); δ_C (100 MHz, $CDCl_3$) 174.0 (*C*(O)), 166.6 (*C*(O)), 132.3 ($C_{(Ar)}$),

129.5 (*C*H$_{(Ar)}$), 128.3 (*C*H$_{(Ar)}$), 127.3 (*C*H$_{(Ar)}$), 123.3 (q, $^{1}J_{C\text{-}F}$ 288.5, *C*F$_3$), 84.6 (q, $^{2}J_{C\text{-}F}$ 27.8, *C*(OCH$_3$)(CF$_3$)Ph), 71.0 (7-*C*), 55.3 (O*C*H$_3$), 51.4 (O*C*H$_3$), 33.8 (2-*C*), 32.6 (5-*C*), 32.2 (6-*C*), 26.1 (4-*C*), 24.9 (3-*C*), 16.6 (6-(*C*H$_3$)); δ_F (376 MHz, CDCl$_3$) −71.57; *m/z* (ES$^+$) 413 (MNa$^+$, 100%); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{19}H_{25}O_5F_3Na$ 413.1546, observed 413.1527.

Methyl (4*S*,5*S*,6*S*,*E*)-7-(benzyloxy)-4,5-dihydroxy-6-methylhept-2-enoate (169) and methyl (*R*,2*E*,4*Z*)-7-(benzyloxy)-6-methylhepta-2,4-dienoate (170)[30]



169



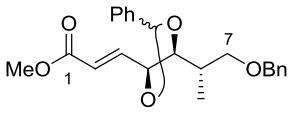
170 (*E*,*Z*)

Potassium osmate(VI) dihydrate (127 mg, 0.40 mmol), was added in one portion to a solution of potassium carbonate (7.20 g, 51.8 mmol), methanesulfonamide (4.90 g, 51.8 mmol), potassium hexacyanoferrate(III) (17.1 g, 51.8 mmol) and (DHQ)$_2$PHAL (453 mg of a 95% purity mixture, 0.55 mmol) in *tert*-butanol/water (173 mL, 1:1) at 0 °C. The mixture was vigorously stirred (mechanical stirrer) for 20 minutes. Diene **167** (4.50 g, 17.3 mmol, in 15 mL of MeCN) was then added *via* syringe pump (20 mL/hr) to the solution and stirring was maintained at 0 °C for 16 h. Saturated aqueous sodium sulfite solution was then added and the mixture was stirred for 20 minutes. The aqueous layer was then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (20-25% EtOAc/petrol) afforded diol **169** (3.41 g, 67%) as a single diastereoisomer and unreacted (*E*,*Z*)-diene **170**. Data for diol **169**: colourless oil; R_f: 0.25

(30% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +8.5 (*c* 1.16, $CHCl_3$) (lit.[30] $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +7.7 (*c* 1.1, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.31-7.19 (5H, m, 5 x Ph*H*), 6.92 (1H, dd, *J* 15.7 and 4.4, 3-*H*), 6.07 (1H, dd, *J* 15.7 and 2.0, 2-*H*), 4.46 (2H, s, OC*H*$_2$Ph), 4.23 (1H, m, 4-*H*), 3.66 (3H, s, CO_2CH_3), 3.53 (1H, dd, *J* 9.3 and 3.9, 7-H*H*), 3.49-3.45 (2H, m, 7-*H*H and 5-*H*), 2.04 (1H, m, 6-*H*), 0.90 (3H, d, *J* 7.1, 6-(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 166.7 (*C*(O)), 148.4 (3-*C*), 137.0 ($C_{(Ar)}$), 128.6 ($CH_{(Ar)}$), 128.0 ($CH_{(Ar)}$), 127.8 ($CH_{(Ar)}$), 121.2 (2-*C*), 78.1 (5-*C*), 74.0 (7-*C*), 73.6 (O*C*H$_2$Ph), 71.6 (4-*C*), 51.5 (O*C*H$_3$), 35.4 (6-*C*), 14.4 (6-(*C*H$_3$)). All data were in agreement with those previously reported.[30]

Data for diene **170**: colourless oil; R_f: 0.50 (15% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ –7.7 (*c* 0.33, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2954, 1721, 1453, 1272, 1174, 1096, 980, 739, 699; δ_H (400 MHz, $CDCl_3$) 7.55 (1H, ddd, *J* 15.4, 11.7and 0.98, 3-*H*), 7.27-7.16 (5H, m, 5 x Ph*H*), 6.06 (1H, dd, *J* 10.8 and 10.8, 4-*H*), 5.81 (1H, d, *J* 15.4, 2-*H*), 5.63 (1H, dd, *J* 10.8 and 10.8, 5-*H*), 4.42 (2H, s, OC*H*$_2$Ph), 3.66 (3H, s, CO_2CH_3), 3.27 (2H, dd, *J* 6.4 and 3.2, 7-*H*), 3.04 (1H, m, 6-*H*), 0.96 (3H, d, *J* 6.9, 6-(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 167.5 (*C*(O)), 143.8 (5-*C*), 139.7 (3-*C*), 138.3 ($C_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 127.4 ($CH_{(Ar)}$), 127.4 ($CH_{(Ar)}$), 126.5 (4-*C*), 121.3 (2-*C*), 74.5 (7-*C*), 72.9 (O*C*H$_2$Ph), 51.4 (O*C*H$_3$), 33.3 (6-*C*), 17.5 (6-(*C*H$_3$)); *m/z* (ES^+) 261 (MH^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{16}H_{20}O_3Na$ 283.1305, observed 283.1316.

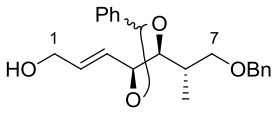
Methyl (*E*)-3-((4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2-phenyl-1,3-dioxolan-4-yl)acrylate (171)[30]



Benzaldehyde dimethyl acetal (15.5 mL, 105 mmol) was added dropwise to a solution of diol **169** (15.5 g, 52.7 mmol) and (±)-camphor 10-sulfonic acid (1.2 g, 5.3 mmol) in CH_2Cl_2 (300 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 2 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer was then separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded acetal **171** (18.55 g, 92%) as a colourless oil, as 3:1 mixture of diastereoisomers; R_f: 0.60 (35% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −8.9 (*c* 1.58, $CHCl_3$) (lit.[30] $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −7.2 (*c* 0.5, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$ (*denotes the major diastereoisomer)) 7.42-7.18 (10H, m, 10 x Ph*H*), 6.90* and 6.89 (1H, dd, *J* 15.6 and 5.2, 3-*H*), 6.12* and 6.11 (1H, dd, *J* 15.6 and 1.5, 2-*H*), 5.88 and 5.80* (1H, s, $(RO)_2CHPh$), 4.60 (1H, m, 4-*H*), 4.46-4.40 (2H, s, OCH_2Ph), 3.88* and 3.81 (1H, dd, *J* 6.9* and 6.9*, 7.1 and 7.1, 5-*H*), 3.69* and 3.67 (3H, s, CO_2CH_3), 3.59 and 3.52* (1H, dd, *J* 9.0 and 4.9, 9.3* and 5.4*, 7-H*H*), 3.44* and 3.41 (1H, dd, *J* 9.3* and 5.4*, 9.0 and 4.9, 7-*H*H), 2.16 (1H, m, 6-*H*), 1.03* and 0.99 (3H, d, *J* 6.9* and 7.1, 6-(CH_3)); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 166.5 (*C*(O)), 145.3 (3-*C*), 138.2 ($C_{(Ar)}$), 136.8 ($C_{(Ar)}$), 129.6 ($CH_{(Ar)}$), 128.4 ($CH_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 126.7 ($CH_{(Ar)}$), 121.5 (2-*C*), 103.3 ($(RO)_2CHPh$), 83.7 (5-*C*), 77.7 (4-*C*),

73.2 (O*C*H$_2$Ph), 71.9 (7-*C*), 51.7 (O*C*H$_3$), 36.5 (6-*C*), 13.6 (6-(*C*H$_3$)). All data were in agreement with those previously reported.[30]

(*E*)-3-((4*S*,5*S*)-5-((*S*)-1-(Benzyloxy)propan-2-yl)-2-phenyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (190)[30]

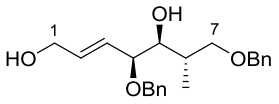


*Method A (one-pot acetal protection and reduction of diol **169**)*: Benzaldehyde dimethyl acetal (5.60 mL, 40.8 mmol) was added dropwise to a solution of diol **169** (6.00 g, 20.4 mmol) and (±)-camphor 10-sulfonic acid (474 mg, 2.00 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 1.5 h. Then the reaction mixture was cooled to −78 °C and diisobutylaluminum hydride (102.0 mL of a 1.2 M solution in toluene, 122.4 mmol) was added dropwise. The mixture was stirred for 3.5 h at −78 °C. Then MeOH (51 mL) was added slowly at −78 °C and the mixture was stirred for 10 minutes before being warmed to room temperature and quenched with Rochelle salt. The solution was stirred vigorously for 30 minutes. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-20-30% EtOAc/petrol) afforded alcohol **190** (6.00 g, 83%) as a colourless oil, as a 3:1 mixture of diastereoisomers; R_f: 0.40 (40% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −12.3 (*c* 1.12, $CHCl_3$) (lit.[30] $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −3.5 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$ (*denotes the major diastereoisomer)) 7.51-7.49 (2H, m, 2 x Ph*H*), 7.41-7.27 (8H, m, 8 x Ph*H*), 6.04 and 6.00* (1H, dt, *J* 15.4 and 5.1, 2-*H*), 5.93 (1H, s, (RO)$_2$C*H*Ph), 5.83 (1H, m, 3-*H*), 4.55-4.49 (3H,

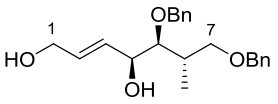
m, 4-*H* and OC*H*$_2$Ph), 4.18-4.15 (2H, m, 1-*H*), 3.92* and 3.84 (1H, dd, *J* 6.8* and 6.8*, 7.3 and 7.3, 5-*H*), 3.70 and 3.63* (1H, dd, *J* 9.1 and 4.8, 9.4* and 5.1*, 7-H*H*), 3.52* and 3.49 (1H, dd, *J* 9.1* and 5.8*, 9.1 and 6.3, 7-*H*H), 2.21 (1H, m, 6-*H*), 1.77 (1H, br s, O*H*), 1.09* and 1.06 (3H, d, *J* 7.1* and 6.8, 6-(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 138.4 (*C*$_{(Ar)}$), 137.6 (*C*$_{(Ar)}$), 133.0 (2-*C*), 129.3 (*C*H$_{(Ar)}$), 128.7 (*C*H$_{(Ar)}$), 128.3 (*C*H$_{(Ar)}$ and 3-*C*), 127.5 (*C*H$_{(Ar)}$), 126.6 (*C*H$_{(Ar)}$), 126.6 (*C*H$_{(Ar)}$), 102.8 ((RO)$_2$*C*HPh), 83.7 (5-*C*), 79.3 (4-*C*), 73.1 (O*C*H$_2$Ph), 72.1 (7-*C*), 62.7 (1-*C*), 36.4 (6-*C*), 13.8 (6-(*C*H$_3$)). All data were in agreement with those previously reported.[30]

*Method B (reduction of acetal **171**)*: Diisobutylaluminum hydride (97.0 mL of a 1 M solution in toluene, 97.0 mmol) was added dropwise to a solution of ester **171** (18.6 g, 48.5 mmol), in CH_2Cl_2 (300 mL) at −78 ºC. The mixture was stirred then for 2 h at −78 ºC before the addition of saturated aqueous Rochelle's salt. The solution was warmed to room temperature and stirred vigorously for 30 minutes. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-30% EtOAc/petrol) afforded alcohol **190** (15.84 g, 92%) as a colourless oil, as a 3:1 mixture of diastereoisomers.

(4*S*,5*S*,6*S*,*E*)-4,7-Bis(benzyloxy)-6-methylhept-2-ene-1,5-diol (192) and (4*S*,5*S*,6*S*,*E*)-5,7-bis(benzyloxy)-6-methylhept-2-ene-1,4-diol (193)[30]



192



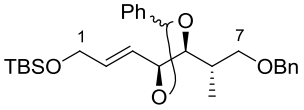
193

Titanium(IV) chloride (3.4 mL of a 1 M solution in CH_2Cl_2, 3.4 mmol) was added dropwise to a solution of acetal **190** (0.80 g, 2.3 mmol) and triethylsilane (1.4 mL, 9.0 mmol) in CH_2Cl_2 (23 mL) at −78 °C, resulting in the formation of a bright yellow solution. The reaction was stirred for 3 h and quenched by the addition of water at −78 °C. The solution was then warmed to room temperature and the aqueous layer was separated and extracted with EtOAc. The organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-10-30% EtOAc/petrol) afforded diol **192** (0.63 g, 78%) and a side-product – another regioisomer diol **193** (82 mg, 10%). Data for diol **192**: colourless oil; R_f: 0.25 (40% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +23.6 (*c* 0.31, $CHCl_3$) (lit.[30] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +41.5 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.38-7.29 (10H, m, 10 x Ph*H*), 5.90 (1H, dt, *J* 15.7 and 4.7, 2-*H*), 5.79 (1H, dd, *J* 15.7 and 7.6, 3-*H*), 4.66 (1H, d, *J* 11.7, 4-(OC*H*HPh)), 4.50 (2H, s, 7-(OCH_2Ph)), 4.37 (1H, d, *J* 11.7, 4-(OCH*H*Ph)), 4.21 (2H, d, *J* 4.7, 1-*H*), 3.95 (1H, dd, *J* 7.6 and 5.1, 4-*H*), 3.60 (1H, dd, *J* 9.1 and 6.9, 7-H*H*), 3.51-3.47 (2H, m, 7-*H*H and 5-*H*), 3.14 (1H, br s, O*H*), 2.13 (1H, m, 6-*H*), 1.58 (1H, br s, O*H*), 0.93 (3H, d, *J* 7.1, 6-(CH_3)); δ_C (100 MHz, $CDCl_3$) 138.2 (2 x $C_{(Ar)}$), 134.0 (2-*C*), 128.8 (3-*C*), 128.4 (2 x $CH_{(Ar)}$), 128.0 ($CH_{(Ar)}$), 127.7 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 80.0 (4-*C*), 77.6 (5-*C*), 73.3

(7-(O*C*H$_2$Ph)), 73.1 (7-*C*), 70.4 (4-(O*C*H$_2$Ph)), 63.0 (1-*C*), 35.2 (6-*C*), 14.7 (6-(*C*H$_3$)). All data were in agreement with those previously reported.[30]

Data for diol **193**: colourless oil; R_f: 0.20 (40% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +7.5 (*c* 2.25, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3422 (br), 2855, 1453, 1362, 1207, 1090, 1061, 971, 733, 697; δ_H (400 MHz, $CDCl_3$) 7.35-7.29 (10H, m, 10 x Ph*H*), 5.91 (1H, dt, *J* 15.1 and 4.7, 2-*H*), 5.77 (1H, dd, *J* 15.1 and 5.7, 3-*H*), 4.64-4.58 (2H, m, 5-(OC*H*$_2$Ph)), 4.50 (2H, s, 7-(OC*H*$_2$Ph)), 4.25 (1H, m, 4-*H*), 4.12 (2H, d, *J* 4.7, 1-*H*), 3.58-3.51 (2H, m, 7-*H*), 3.44 (1H, m, 5-*H*), 2.19 (1H, m, 6-*H*), 1.08 (3H, d, *J* 6.9, 6-(C*H*$_3$)); δ_C (100 MHz, $CDCl_3$) 138.2 (*C*$_{(Ar)}$), 138.2 (*C*$_{(Ar)}$), 132.0 (3-*C*), 130.6 (2-*C*), 128.4 (*C*H$_{(Ar)}$), 128.4 (*C*H$_{(Ar)}$), 127.9 (*C*H$_{(Ar)}$), 127.8 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 83.8 (5-*C*), 74.8 (5-(O*C*H$_2$Ph)), 73.1 (7-(O*C*H$_2$Ph)), 71.9 (7-*C*), 71.9 (4-*C*), 63.0 (1-*C*), 35.9 (6-*C*), 15.0 (6-(*C*H$_3$)). *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{22}H_{28}O_4Na$ 379.1885, observed 379.1854.

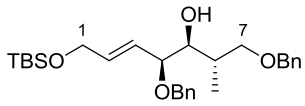
(((*E*)-3-((4*S*,5*S*)-5-((*S*)-1-(Benzyloxy)propan-2-yl)-2-phenyl-1,3-dioxolan-4-yl)allyl)oxy)(*tert*-butyl)dimethylsilane (195)



tert-Butyldimethylsilyl trifluoromethanesulfonate (0.16 mL, 0.69 mmol) was added dropwise to a solution of alcohol **190** (0.22 g, 0.63 mmol) and 2,6-lutidine (0.17 mL, 1.5 mmol) in CH_2Cl_2 (6.3 mL) at 0 °C. The reaction was slowly warmed to room temperature over 1.5 h and then quenched by the slow addition of water. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4),

filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-5% EtOAc/petrol) afforded silyl ether **195** (0.29 g, 98%) as a colourless oil, as a 3:1 mixture of diastereoisomers; R_f: 0.65 (5% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −6.9 (*c* 1.59, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3033, 2955, 2929, 2883, 2856, 1456, 1405, 1379, 1362, 1310, 1290, 1253, 1218, 1093, 1063, 1027, 972, 835, 776, 734, 696, 666; δ_H (400 MHz, $CDCl_3$ (*denotes the major diastereoisomer)) 7.51-7.49 (2H, m, 2 x Ph*H*), 7.41-7.27 (8H, m, 8 x Ph*H*), 6.01-5.91 (2H, m, 2-*H* and $(RO)_2CHPh$), 5.82 (1H, ddt, *J* 15.4, 7.1 and 1.8, 3-*H*), 4.54-4.49 (3H, m, 4-*H* and OCH_2Ph), 4.24-4.20 (2H, m, 1-*H*), 3.90* and 3.81 (1H, dd, *J* 6.8* and 6.8*, 7.3 and 7.3, 5-*H*), 3.72 and 3.65* (1H, dd, *J* 9.1 and 4.8, 9.4* and 5.1*, 7-H*H*), 3.51* and 3.48 (1H, dd, *J* 9.1* and 6.1*, 9.1 and 6.6, 7-*H*H), 2.19 (1H, m, 6-*H*), 1.10* and 1.06 (3H, d, *J* 7.1* and 6.8, 6-(CH_3)), 0.94* and 0.93 (9H, s, $SiC(CH_3)_3$), 0.10 and 0.08 (6H, s, 2 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 138.5 ($C_{(Ar)}$), 137.8 ($C_{(Ar)}$), 133.3 (2-*C*), 129.2 ($CH_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 127.5 ($CH_{(Ar)}$), 127.5 ($CH_{(Ar)}$), 127.2 (3-C), 126.7 ($CH_{(Ar)}$), 126.7 ($CH_{(Ar)}$), 102.8 ($(RO)_2CHPh$), 83.9 (5-*C*), 79.6 (4-*C*), 73.1 (OCH_2Ph), 72.2 (7-*C*), 62.9 (1-*C*), 36.5 (6-*C*), 25.9 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 14.0 (6-(CH_3)), −5.3 (2 x $SiCH_3$). *m/z* HRMS (ES^+) MNa^+ calculated for $C_{28}H_{40}O_4SiNa$ 491.2575, observed 491.2588.

(2*S*,3*S*,4*S*,*E*)-1,4-Bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-methylhept-5-en-3-ol (194)

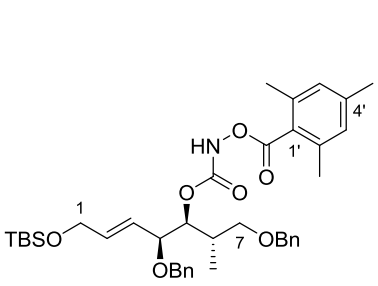


*Method A (TBS protection of **192**)*: *tert*-Butyldimethylsilyl chloride (4.00 g, 26.6 mmol) was added to a solution of alcohol **192** (9.00 g, 25.3 mmol) and imidazole (3.80 g, 55.7 mmol) in DMF (200 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 6 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride and diluted with EtOAc. The organic layer was separated and washed with brine (x 3), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-5-10% EtOAc/petrol) afforded silyl ether **194** (10.92 g, 92%) as a colourless oil; R_f: 0.80 (50% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +28.7 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3479 (br), 2955, 2929, 2856, 1497, 1455, 1378, 1362, 1253, 1208, 1093, 1068, 1028, 975, 835, 776, 733, 696; δ_H (400 MHz, $CDCl_3$) 7.30-7.21 (10H, m, 10 x Ph*H*), 5.76 (1H, dt, *J* 15.7 and 4.4, 2-*H*), 5.68 (1H, dd, *J* 15.7 and 7.6, 3-*H*), 4.59 (1H, d, *J* 11.7, 4-(OC*H*HPh)), 4.42 (2H, s, 7-(OCH_2Ph)), 4.27 (1H, d, *J* 11.7, 4-(OCH*H*Ph)), 4.17 (2H, d, *J* 4.4, 1-*H*), 3.87 (1H, dd, *J* 7.6 and 5.6, 4-*H*), 3.54 (1H, dd, *J* 9.3 and 6.4, 7-H*H*), 3.43-3.37 (2H, m, 7-*H*H and 5-*H*), 2.92 (1H, br s, O*H*), 2.04 (1H, m, 6-*H*), 0.87 (9H, s, SiC(CH_3)$_3$), 0.87 (3H, d, *J* 6.9, 6-(CH_3)), 0.04 (6H, s, 2 x SiCH_3); δ_C (100 MHz, $CDCl_3$) 138.4 ($C_{(Ar)}$), 138.3 ($C_{(Ar)}$), 134.7 (2-*C*), 128.3 ($CH_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 128.0 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 127.5 ($CH_{(Ar)}$), 127.1 ($CH_{(Ar)}$), 127.1 (3-*C*), 80.2 (4-*C*), 77.3 (5-*C*), 73.1 (7-(OCH_2Ph)), 72.8 (7-*C*), 70.1 (4-(OCH_2Ph)), 63.2 (1-*C*), 35.1 (6-*C*), 25.9 (SiC(CH_3)$_3$), 18.4 (Si*C*(CH_3)$_3$), 14.8 (6-(*C*H_3)), −5.2 (2 x Si*C*H_3). *m/z* (ES^+) 493 (MNa^+,

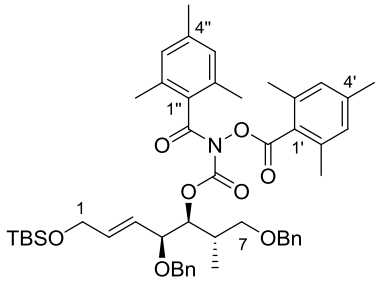
100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{28}H_{42}O_4SiNa$ 493.2745, observed 493.2741.

*Method B (opening of acetal **195**)*: Titanium(IV) chloride (2.60 mL of a 1 M solution in CH_2Cl_2, 2.60 mmol) was added dropwise to a solution of acetal **195** (610 mg, 1.30 mmol) and triethylsilane (0.83 mL, 5.2 mmol) in CH_2Cl_2 (13.0 mL) at −78 ºC, resulting in the formation of a bright yellow solution. The reaction was stirred for 2 h and quenched by the addition of water at −78 ºC. The solution was then warmed to room temperature and the aqueous layer was separated and extracted with EtOAc. The organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-5-10% EtOAc/petrol) afforded alcohol **194** (465 mg, 76%) as a colourless oil.

(2*S*,3*S*,4*S*,*E*)-1,4-Bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-methylhept-5-en-3-yl (2,4,6-trimethylbenzoyl)oxycarbamate (197) and (2*S*,3*S*,4*S*,*E*)-1,4-bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-2-methylhept-5-en-3-yl (2,4,6-trimethylbenzoyl)((2,4,6-trimethylbenzoyl)oxy)carbamate (198)



197



198

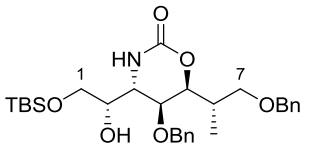
1,1'-Carbonyldiimidazole (4.00 g of ca. 95% purity, 23.4 mmol) was added to a solution of alcohol **194** (1.8 g, 3.9 mmol) in pyridine (26.0 mL) and was subsequently heated at 40 ^{o}C for 4 h. The solution was then cooled to 0 ^{o}C and hydroxylamine hydrochloride (5.40 g, 78.0 mmol) was added in one portion. The mixture was slowly warmed to room temperature and stirred for 20 h. Water was then added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-30% EtOAc/petrol) afforded hydroxamic acid **196** (1.93 g, approx. 90% purity) and returned starting material alcohol **194** (287 mg, 16%). Data for hydroxamic acid **196**: colourless oil; R_f: 0.70 (15% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 7.68 (1H, br s, N*H*), 7.37-7.22 (10H, m, 10 x Ph*H*), 6.84 (1H, br s, O*H*), 5.82 (1H, dt, *J* 15.5 and 4.4, 2-*H*), 5.62 (1H, dd, *J* 15.5 and 6.8, 3-*H*), 4.88 (1H, dd, *J* 7.6 and 4.1, 5-*H*), 4.60 (1H, d, *J* 11.9, 4-(OC*H*HPh)), 4.43 (2H, s, 7-(OCH_2Ph)), 4.29 (1H, d, *J* 11.9, 4-(OCH*H*Ph)), 4.26-4.17 (2H, m, 1-*H*), 4.05 (1H, dd, *J* 6.8 and 4.1, 4-*H*), 3.45 (1H, dd, *J* 9.1 and 5.0, 7-H*H*), 3.27 (1H, dd, *J* 9.1 and

6.6, 7-*H*H), 2.31 (1H, m, 6-*H*), 0.94-0.91 (12H, m, 6-(CH_3) and SiC(CH_3)$_3$), 0.09 (6H, s, 2 x SiCH_3). Triethylamine (1.0 mL, 7.3 mmol) and 2,4,6-trimethylbenzoylchloride (0.60 mL, 3.7 mmol) were added sequentially to the hydroxamic acid (1.9 g, 3.7 mmol) in CH_2Cl_2 (37 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 16 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-5-10% EtOAc/petrol) afforded *O*-benzoyl hydroxamate **197** (1.95 g, 74% over 2 steps) and a side-product – acylated on nitrogen carbamate **198** (304 mg, 10% over 2 steps). Data for *O*-benzoyl hydroxamate **197**: colourless oil; R_f: 0.75 (30% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +1.4 (*c* 0.58, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2954, 2928, 2883, 2856, 1753, 1619, 1497, 1471, 1454, 1380, 1361, 1314, 1250, 1158, 1093, 1070, 1005, 979, 950, 835, 814, 777, 736, 967; δ_H (400 MHz, $CDCl_3$) 8.22 (1H, s, N*H*), 7.34-7.26 (10H, m, 10 x Ph*H*), 6.88 (2H, s, 3'/5'-H), 5.87 (1H, dt, *J* 15.7 and 4.7, 2-*H*), 5.68 (1H, ddt, *J* 15.7, 7.6 and 1.5, 3-*H*), 4.96 (1H, dd, *J* 7.1 and 4.9, 5-*H*), 4.64 (1H, d, *J* 11.7, 4-(OC*H*HPh)), 4.47 (1H, d, *J* 11.7, 7-(OC*H*HPh)), 4.42 (1H, d, *J* 11.7, 7-(OCH*H*Ph)), 4.33 (1H, d, *J* 11.7, 4-(OCH*H*Ph)), 4.22 (2H, dd, *J* 4.7 and 1.5, 1-*H*), 4.09 (1H, dd, *J* 7.6 and 4.9, 4-*H*), 3.51 (1H, dd, *J* 9.3 and 5.1, 7-H*H*), 3.34 (1H, dd, *J* 9.3 and 6.4, 7-*H*H), 2.35 (6H, s, 2'- and 6'-CH_3), 2.33 (1H, m, 6-*H*), 2.31 (3H, s, 4'-CH_3), 0.96 (3H, d, *J* 7.1, 6-(CH_3)), 0.92 (9H, s, SiC(CH_3)$_3$), 0.08 (6H, s, 2 x SiCH_3); δ_C (100 MHz, $CDCl_3$) 169.0 (*C*(O)), 156.4 (*C*(O)), 140.8 ($C_{(Ar)}$), 138.5 ($C_{(Ar)}$), 138.1 ($C_{(Ar)}$), 136.8 ($C_{(Ar)}$), 135.3 (2-*C*), 128.6 (*C*H$_{(Ar)}$), 128.3 (*C*H$_{(Ar)}$), 128.3 (*C*H$_{(Ar)}$), 128.0 (*C*H$_{(Ar)}$), 127.7 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 127.4 (*C*H$_{(Ar)}$), 126.6 ($C_{(Ar)}$), 125.5 (3-*C*), 80.1 (5-*C*), 78.1 (4-*C*), 73.1 (7-(O*C*H$_2$Ph)), 71.4 (7-*C*), 70.3 (4-(O*C*H$_2$Ph)), 63.1 (1-*C*), 34.4 (6-*C*), 25.9 (SiC(*C*H$_3$)$_3$), 21.2 (4'-(*C*H$_3$)), 20.0 (2'- and 5'-(*C*H$_3$)), 18.4

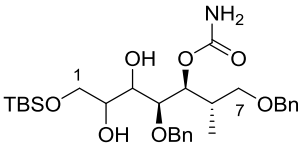
(Si*C*$(CH_3)_3$), 14.4 (6-(*C*H_3)), −5.3 (2 x Si*C*H_3). *m/z* (ES^+) 698 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{39}H_{53}NO_7SiNa$ 698.3484, observed 698.3474.

Data for acylated on nitrogen carbamate **198**: colourless oil; R_f: 0.75 (15% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −6.3 (*c* 3.28, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2927, 2856, 1758, 1710, 1455, 1309, 1226, 1096, 1028, 994, 836, 734, 697, 616; δ_H (400 MHz, $CDCl_3$) 7.35-7.25 (10H, m, 10 x Ph*H*), 6.91 (2H, s, 3'/5'-H), 6.84-6.75 (2H, m, 3''/5''-H), 5.82 (1H, m, 2-*H*), 5.58 (1H, m, 3-*H*), 5.01 (1H, m, 5-*H*), 4.55 (1H, dd, *J* 11.0 and 11.0, 4-(OC*H*HPh)), 4.39 (2H, s, 7-(OC*H*$_2$Ph)), 4.24 (1H, dd, *J* 11.0 and 11.0, 4-(OCH*H*Ph)), 4.20 (2H, d, *J* 4.4, 1-*H*), 3.96 (1H, m, 4-*H*), 3.30 (1H, m, 7-H*H*), 3.13 (1H, m, 7-*H*H), 2.50 (6H, s, 2 x C*H*$_3$), 2.43 (3H, s, C*H*$_3$), 2.35 (3H, s, C*H*$_3$), 2.28 (3H, s, C*H*$_3$), 2.19-2.12 (4H, m, C*H*$_3$ and 6-*H*), 0.93 (9H, s, SiC(C*H*$_3$)$_3$), 0.92 (3H, d, *J* 6.6, 6-(C*H*$_3$)), 0.09 (6H, s, 2 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 166.5 (2 x *C*(O)), 150.1 (*C*(O)), 140.8 ($C_{(Ar)}$), 138.8 ($C_{(Ar)}$), 138.4 ($C_{(Ar)}$), 138.1 ($C_{(Ar)}$), 137.7 ($C_{(Ar)}$), 136.3 ($C_{(Ar)}$), 135.5 (2-*C*), 134.3 ($C_{(Ar)}$), 133.0 ($C_{(Ar)}$), 128.8 (*C*H$_{(Ar)}$), 128.3 (2 x *C*H$_{(Ar)}$), 128.2 (2 x *C*H$_{(Ar)}$), 127.8 (*C*H$_{(Ar)}$), 127.4 (2 x *C*H$_{(Ar)}$), 125.3 (3-*C*), 81.6 (5-*C*), 78.2 (4-*C*), 73.0 (7-(O*C*H$_2$Ph)), 71.1 (7-*C*), 70.3 (4-(O*C*H$_2$Ph)), 62.9 (1-*C*), 34.2 (6-*C*), 25.9 (SiC(*C*H$_3$)$_3$), 21.2 (*C*H$_3$), 20.0 (*C*H$_3$), 19.1 (*C*H$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 14.3 (6-(*C*H$_3$)), −5.3 (2 x Si*C*H$_3$). *m/z* (ES^+) 844 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{49}H_{63}NO_8SiNa$ 844.4215, observed 844.4188.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyethyl)-1,3-oxazinan-2-one (199) and (2*S*,3*S*,4*S*)-1,4-bis(benzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-5,6-dihydroxy-2-methylheptan-3-yl carbamate (200)



199



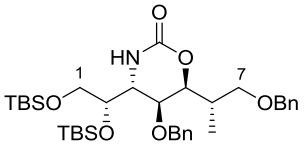
200

Potassium osmate(VI) dihydrate (9.0 mg, 26 μmol) was added in one portion to a solution of *O*-benzoyl hydroxamate **197** (347 mg, 0.51 mmol) in *t*-BuOH/MeCN/H_2O (10.3 mL, 4:4:1) and heated at 40 ºC for 30 h. After which saturated aqueous sodium sulfite was added to quench the reaction and the solution was stirred at room temperature for 20 minutes. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-50-100% EtOAc/petrol) afforded amino alcohol **199** (190 mg, 70%) as a single diastereoisomer and a side-product – diol **200** (45 mg, 16%). Data for aminoalcohol **199**: colourless foam; R_f: 0.25 (40% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −37.4 (*c* 0.49, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3318 (br), 3031, 2928, 2856, 1697, 1497, 1455, 1361, 1309, 1253, 1209, 1100, 1067, 1028, 939, 907, 835, 779, 733, 696, 669; δ_H (400 MHz, $CDCl_3$) 7.37-7.27 (10H, m, 10 x Ph*H*), 5.68 (1H, d, *J* 2.5, N*H*), 4.69 (1H, d, *J* 11.7, 4-(OC*H*HPh)), 4.54 (1H, d, *J* 12.0, 7-(OC*H*HPh)), 4.48 (1H, d, *J* 12.0, 7-(OCH*H*Ph)), 4.48 (1H, d, *J* 11.7, 4-(OCH*H*Ph)), 4.30 (1H, dd, *J* 10.0 and 1.5, 5-*H*), 3.75 (1H, m, 4-*H*), 3.73 (1H, m, 3-*H*), 3.68 (2H, dd, *J* 4.7 and 4.7, 1-*H*), 3.64-3.61 (2H, m, 7-*H*), 3.53 (1H, dd,

J 9.1 and 4.7, 2-*H*), 2.37 (1H, m, 6-*H*), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 0.90 (3H, d, *J* 7.1, 6-(C*H*$_3$)), 0.11 (6H, s, 2 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 154.1 (*C*(O)), 138.7 (*C*$_{(Ar)}$), 137.1 (*C*$_{(Ar)}$), 128.6 (*C*H$_{(Ar)}$), 128.3 (*C*H$_{(Ar)}$), 128.2 (*C*H$_{(Ar)}$), 128.0 (*C*H$_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 127.4 (*C*H$_{(Ar)}$), 78.0 (5-*C*), 73.2 (7-(O*C*H$_2$Ph)), 72.0 (2-*C*), 71.3 (7-*C*), 71.2 (4-(O*C*H$_2$Ph)), 70.3 (4-*C*), 65.1 (1-*C*), 55.2 (3-*C*), 34.1 (6-*C*), 25.9 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 13.3 (6-(*C*H$_3$)), −5.4 (2 x Si*C*H$_3$). *m/z* (ES$^+$) 552 (MNa$^+$, 100%), 530 (MH$^+$, 25); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{29}H_{43}NO_6SiNa$ 552.2752, observed 552.2754.

Data for diol **200**: colourless oil; R_f: 0.50 (40% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −26.5 (*c* 0.23, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3505 (br), 3392, 2955, 2856, 1690, 1454, 1390, 1332, 1254, 1094, 1042, 835, 778, 732, 697; δ_H (400 MHz, $CDCl_3$) 7.32-7.20 (10H, m, 10 x Ph*H*), 5.07 (2H, br s, N*H*), 4.93 (1H, dd, *J* 9.8 and 1.5, 5-*H*), 4.76 (1H, d, *J* 11.0, 4-(OC*H*HPh)), 4.63 (1H, d, *J* 11.0, 4-(OCH*H*Ph)), 4.40 (2H, s, 7-(OC*H*$_2$Ph)), 3.97 (1H, d, *J* 4.9, 3-(O*H*)), 3.88-3.84 (2H, m, 2-*H* and 4-*H*), 3.75 (1H, dd, *J* 9.8 and 6.4, 1-*H*H), 3.67 (1H, dd, *J* 9.8 and 6.1, 1-H*H*), 3.57 (1H, dd, *J* 8.6 and 4.9, 3-*H*), 3.43 (1H, dd, *J* 8.8 and 3.4, 1-*H*H), 3.36 (1H, dd, *J* 8.8 and 5.9, 1-H*H*), 2.63 (1H, d, *J* 5.6, 2-(O*H*)), 2.27 (1H, m, 6-*H*), 1.01 (3H, d, *J* 6.9, 6-(C*H*$_3$)), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), 0.03 (6H, s, 2 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 158.1 (*C*(O)), 138.3 (*C*$_{(Ar)}$), 137.8 (*C*$_{(Ar)}$), 128.3 (*C*H$_{(Ar)}$), 128.2 (*C*H$_{(Ar)}$), 127.9 (*C*H$_{(Ar)}$), 127.8 (*C*H$_{(Ar)}$), 127.5 (*C*H$_{(Ar)}$), 127.3 (*C*H$_{(Ar)}$), 77.4 (4-*C*), 76.1 (5-*C*), 74.6 (4-(O*C*H$_2$Ph)), 73.1 (7-(O*C*H$_2$Ph)), 71.8 (7-*C*), 70.0 (2-*C*), 68.5 (3-*C*), 64.7 (1-*C*), 34.2 (6-*C*), 25.8 (SiC(*C*H$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 14.7 (6-(*C*H$_3$)), −5.5 (Si*C*H$_3$), −5.5 (Si*C*H$_3$). *m/z* (ES$^+$) 570 (MNa$^+$, 30%), 548 (MH$^+$, 100); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{29}H_{45}NO_7SiNa$ 570.2858, observed 570.2836.

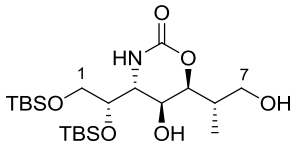
(4*R*,5*S*,6*S*)-5-(Benzyloxy)-6-((*S*)-1-(benzyloxy)propan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (199a)



tert-Butyldimethylsilyl trifluoromethanesulfonate (1.0 mL, 4.4 mmol) was added dropwise to a solution of amino alcohol **199** (0.90 g, 1.8 mmol) and 2,6-lutidine (1.0 mL, 8.8 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The solution was then stirred at this temperature for 3 h before being quenched with *i*-PrOH. Water was then added and aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-10-20% EtOAc/petrol) afforded silyl ether **199a** (1.00 g, 87%) as a viscous colourless oil; R_f: 0.75 (50% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −34.3 (*c* 0.54, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3247, 3136, 2952, 2929, 2884, 2857, 1714, 1462, 1423, 1361, 1309, 1254, 1103, 1071, 912, 832, 777, 733, 696; δ_H (400 MHz, $CDCl_3$) 7.32-7.20 (10H, m, 10 x Ph*H*), 5.12 (1H, s, N*H*), 4.66 (1H, d, *J* 11.7, 4-(OC*H*HPh)), 4.49 (1H, d, *J* 12.0, 7-(OC*H*HPh)), 4.43 (1H, d, *J* 12.0, 7-(OCH*H*Ph)), 4.42 (1H, d, *J* 11.7, 4-(OCH*H*Ph)), 4.20 (1H, dd, *J* 10.0 and 1.0, 5-*H*), 3.82 (1H, d, *J* 1.0, 4-*H*), 3.78 (1H, dd, *J* 5.1 and 5.1, 3-*H*), 3.67-3.61 (2H, m, 1-H*H* and 7-H*H*), 3.58-3.51 (2H, m, 1-*H*H and 7-*H*H), 3.49 (1H, m, 2-*H*), 2.34 (1H, m, 6-*H*), 0.87 (3H, d, *J* 6.4, 6-(C*H*$_3$)), 0.87 (9H, s, SiC(C*H*$_3$)$_3$), 0.83 (9H, s, SiC(C*H*$_3$)$_3$), 0.04 (6H, s, 2 x SiC*H*$_3$), 0.03 (6H, s, 2 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 153.6 (*C*(O)), 138.7 ($C_{(Ar)}$), 137.2 ($C_{(Ar)}$), 128.5 ($CH_{(Ar)}$), 128.2 ($CH_{(Ar)}$), 127.9 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$), 127.5 ($CH_{(Ar)}$), 127.3 ($CH_{(Ar)}$), 77.7 (5-*C*), 73.7 (2-*C*), 73.1 (7-(O*C*H$_2$Ph)), 71.2 (7-*C*), 70.9 (4-(O*C*H$_2$Ph)), 69.4

(4-*C*), 64.8 (1-*C*), 55.2 (3-*C*), 34.2 (6-*C*), 25.9 (SiC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 13.4 (6-(*C*H_3)), −4.3 (Si*C*H_3), −4.5 (Si*C*H_3), −5.4 (Si*C*H_3). *m/z* (ES^+) 644 (MH^+, 100%), 530 (MH^+, 25); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{35}H_{57}NO_6Si_2Na$ 666.3617, observed 666.3620.

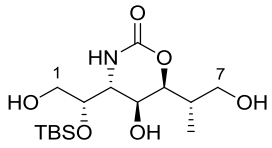
(4*R*,5*S*,6*S*)-5-Hydroxy-6-((*S*)-1-hydroxypropan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (201)



EtOAc (HPLC grade) (22 mL) was added to benzyl ether **199a** (1.4 g, 2.1 mmol) and palladium on carbon (280 mg, 20% wt.) and the mixture was stirred under an atmospheric (balloon) pressure of hydrogen for 20 h. The solution was then filtered through Celite, washing with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) afforded diol **201** (0.80 g, 85%) as a colourless solid; R_f: 0.30 (80% EtOAc/petrol); m. p. 178-180 ºC; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −62.6 (*c* 0.53, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3369 (br), 3254 (br), 2929, 2857, 1697, 1677, 1472, 1318, 1254, 1099, 1069, 874, 834, 767, 745, 665; δ_H (500 MHz, $CDCl_3$) 5.43 (1H, s, N*H*), 4.29 (1H, d, *J* 5.7, 5-*H*), 4.04 (1H, s, 4-*H*), 3.90 (1H, dd, *J* 11.0 and 7.3, 7-H*H*), 3.65-3.55 (5H, m, 1-*H*, 2-*H*, 3-*H* and 7-*H*H), 2.15 (1H, m, 6-*H*), 1.07 (3H, d, *J* 6.9, 6-(C*H*$_3$)), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.09 (6H, s, 2 x SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 154.5 (*C*(O)), 79.9 (5-*C*), 73.6 (2-*C*), 64.8 (1-*C*), 64.5 (4-*C*), 63.2 (7-*C*), 60.0 (3-*C*), 37.2 (6-*C*), 25.9 (SiC(*C*H_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 17.9

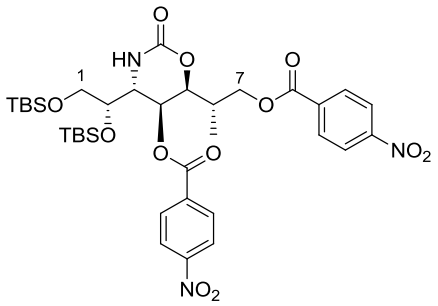
(Si*C*(CH_3)$_3$), 14.8 (6-(*C*H_3)), −4.4 (Si*C*H_3), −4.5 (Si*C*H_3), −5.5 (Si*C*H_3); *m/z* (ES^+) 464 (MH^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{21}H_{45}NO_6Si_2Na$ 486.2678, observed 486.2678.

(4*R*,5*S*,6*S*)-4-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxyethyl)-5-hydroxy-6-((*S*)-1-hydroxypropan-2-yl)-1,3-oxazinan-2-one (201a)



Colourless oil; R_f: 0.30 (100% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −35.8 (*c* 0.76, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3289 (br), 2931, 2174, 1688, 1462, 1313, 1255, 1109, 1049, 910, 836, 777; δ_H (400 MHz, $CDCl_3$) 4.28 (1H, dd, *J* 9.5 and 1.2, 5-*H*), 4.09 (1H, dd, *J* 1.2 and 1.2, 4-*H*), 3.77-3.52 (6H, m, 7-*H*, 1-*H*, 2-*H* and 3-*H*), 2.11 (1H, m, 6-*H*), 1.05 (3H, d, *J* 7.1, 6-(C*H*$_3$)), 0.93 (9H, s, SiC(C*H*$_3$)$_3$), 0.14 (6H, s, 2 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 157.0 (*C*(O)), 80.3 (5-*C*), 75.3 (2-*C* or 3-*C*), 64.4 (1-*C*), 64.0 (7-*C*), 63.9 (4-*C*), 60.8 (2-*C* or 3-*C*), 37.7 (6-*C*), 26.6 (SiC(*C*H$_3$)$_3$), 19.1 (Si*C*(CH$_3$)$_3$), 13.5 (6-(*C*H$_3$)), −4.0 (Si*C*H$_3$), −4.1 (Si*C*H$_3$); *m/z* (ES^+) 721 (M_2Na^+, 100%), 372 (MNa^+, 15); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{15}H_{31}NO_6SiNa$ 372.1813, observed 372.1809.

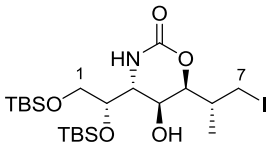
(*S*)-2-((4*R*,5*S*,6*S*)-5-((4-Nitrobenzoyl)oxy)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-2-oxo-1,3-oxazinan-6-yl)propyl 4-nitrobenzoate (202)



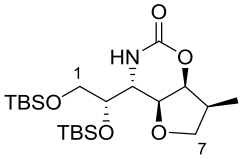
Triethylamine (24.0 µl, 172 µmol), DMAP (5.3 mg, 43 µmol) and 4-nitrobenzoyl chloride (22.0 mg, 116 µmol) were added sequentially to a solution of diol **201** (20 mg, 43 µmol) in CH_2Cl_2 (0.4 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 24 h before being quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-10-20% EtOAc/petrol) afforded benzoylate **202** (29.6 mg, 90%) as a colourless solid; R_f: 0.30 (20% EtOAc/petrol); m. p. 178-180 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −24.6 (*c* 0.24, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2930, 1710, 1607, 1522, 1348, 1270, 1097, 1015, 943, 831, 778, 718, 694; δ_H (400 MHz, $CDCl_3$) 8.33 (2H, d, *J* 9.1, 2 x Ph*H*), 8.29-8.24 (4H, m, 4 x Ph*H*), 8.18 (2H, d, *J* 9.1, 2 x Ph*H*), 5.67 (1H, s, 4-*H*), 5.43 (1H, br s, N*H*), 4.70 (1H, dd, *J* 11.3 and 3.7, 7-H*H*), 4.54-4.50 (2H, m, 7-*H*H and 5-*H*), 3.89 (1H, m, 2-*H*), 3.77-3.67 (3H, m, 1-*H* and 3-*H*), 2.47 (1H, m, 6-*H*), 1.10 (3H, d, *J* 7.1, 6-(C*H*$_3$)), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 0.15 (3H, s, SiC*H*$_3$), 0.14 (3H, s, SiC*H*$_3$), 0.10 (3H, s, SiC*H*$_3$), 0.10 (3H, s, SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 164.5 (*C*(O)), 163.9 (*C*(O)), 152.8 (*C*(O)), 151.0 ($C_{(Ar)}$), 150.5 ($C_{(Ar)}$), 135.4 ($C_{(Ar)}$), 134.0 ($C_{(Ar)}$), 131.1 ($CH_{(Ar)}$), 130.7 ($CH_{(Ar)}$), 123.8 ($CH_{(Ar)}$), 123.5 ($CH_{(Ar)}$), 76.9

(5-*C*), 73.4 (2-*C*), 66.8 (4-*C*), 66.6 (7-*C*), 64.6 (1-*C*), 58.3 (3-*C*), 34.0 (6-*C*), 25.8 (SiC(CH_3)$_3$), 25.7 (SiC(CH_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 13.1 (6-(*C*H_3)), −4.3 (Si*C*H_3), −4.3 (Si*C*H_3), −5.4 (2 x Si*C*H_3); *m/z* (ES^+) 784 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{35}H_{51}N_3O_{12}Si_2Na$ 784.2903, observed 784.2909.

(4*R*,5*S*,6*S*)-5-Hydroxy-6-((*R*)-1-iodopropan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (204) and (4*R*,4a*S*,7*S*,7a*S*)-7-methyl-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)hexahydro-2*H*-furo[2,3-*e*][1,3]oxazin-2-one (205)



204



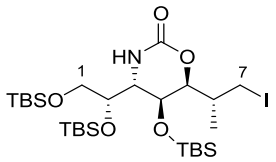
205

Iodine (284 mg, 1.11 mmol) was added in one portion to a solution of imidazole (237 mg, 3.40 mmol) and triphenylphosphine (300 mg, 1.11 mmol) in CH_2Cl_2 (4.0 mL) and the mixture was stirred for 10 minutes. A portion of diol **201** (394 mg, 0.850 mmol) in CH_2Cl_2 (4.5 mL) was then added dropwise to the solution and the mixture was stirred for 3 h. Saturated aqueous Na_2SO_3 was then added and the solution stirred for 10 mins. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30-60% EtOAc/petrol) afforded iodide **204** (387 mg, 79%) and a side-product – tetrahydrofuran **205** (76 mg, 20%). Data for iodide **204**: colourless foam; R_f: 0.60 (80% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −59.6 (*c* 1.41, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3356 (br), 3247 (br), 2953, 2929, 2884, 2857, 1714, 1463, 1445, 1422, 1312, 1252, 1102, 1067, 1006, 961,

937, 832, 776, 669; δ_H (400 MHz, $CDCl_3$) 5.40 (1H, br s, N*H*), 4.12 (1H, s, 4-*H*), 4.02 (1H, dd, *J* 9.5 and 0.7, 5-*H*), 3.68-3.55 (4H, m, 1-*H*, 2-*H* and 3-*H*), 3.52-3.50 (2H, m, 7-*H*), 1.93 (1H, m, 6-*H*), 1.06 (3H, d, *J* 6.6, 6-(CH_3)), 0.91 (18H, s, 2 x SiC(CH_3)$_3$), 0.12 (3H, s, SiCH_3), 0.11 (3H, s, SiCH_3), 0.09 (3H, s, SiCH_3), 0.09 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 153.6 (*C*(O)), 80.7 (5-*C*), 73.5 (2-*C*), 65.3 (1-*C*), 63.4 (4-*C*), 61.0 (3-*C*), 34.3 (6-*C*), 25.9 (2 x SiC(*C*H_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 18.0 (Si*C*(CH_3)$_3$), 16.8 (6-(*C*H_3)), 14.6 (7-*C*), −4.2 (Si*C*H_3), −4.4 (Si*C*H_3), −5.4 (Si*C*H_3), −5.4 (Si*C*H_3); *m/z* (ES^+) 574 (MH^+, 100%), 1147 (M_2H^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{21}H_{44}INO_5Si_2Na$ 596.1695, observed 596.1713.

Data for tetrahydrofuran **205**: colourless oil; R_f: 0.70 (80% EtOAc/petrol); $[\alpha]_D^{20}$ −26.6 (*c* 0.99, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2928, 2856, 1716, 1462, 1429, 1333, 1294, 1138, 1115, 831, 775, 710, 667; δ_H (400 MHz, $CDCl_3$) 5.16 (1H, br s, N*H*), 4.65 (1H, dd, *J* 3.7 and 3.7, 5-*H*), 4.15 (1H, s, 4-*H*), 4.01 (1H, dd, *J* 8.1 and 8.1, 7-*H*H), 3.73-3.54 (5H, m, 1-*H*, 7-H*H*, 2-*H* and 3-*H*), 2.50 (1H, m, 6-*H*), 1.19 (3H, d, *J* 6.9, 6-(CH_3)), 0.90 (9H, s, SiC(CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.09 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 153.6 (*C*(O)), 80.3 (5-*C*), 75.7 (4-*C*), 72.9 (2-*C*), 72.1 (7-*C*), 63.9 (1-*C*), 55.5 (3-*C*), 40.0 (6-*C*), 25.8 (SiC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 18.1 (Si*C*(CH_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 9.7 (6-(*C*H_3)), −4.3 (Si*C*H_3), −4.6 (Si*C*H_3), −5.5 (Si*C*H_3), −5.5 (Si*C*H_3); *m/z* HRMS (ES^+) MH^+ calculated for $C_{21}H_{44}NO_5Si_2$ 446.2758, observed 446.2756.

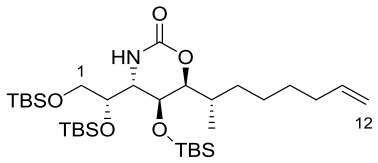
(4*S*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((*R*)-1-iodopropan-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (206)



tert-Butyldimethylsilyl trifluoromethanesulfonate (1.34 mL, 5.83 mmol) was added dropwise to a solution of alcohol **204** (474 mg, 0.830 mmol) and 2,6-lutidine (1.34 mL, 11.6 mmol) in CH_2Cl_2 (8.3 mL) at 0 ºC. The solution was then stirred at this temperature for 16 h before being quenched with *i*-PrOH. Water was then added and aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-5-10% EtOAc/petrol) afforded silyl ether **206** (497 mg, 87%) as a colourless solid; R_f: 0.30 (10% EtOAc/petrol); m. p. 134-137 ºC; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −51.4 (*c* 0.35, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3447, 2954, 2927, 2884, 2855, 1698, 1454, 1419, 1360, 1303, 1252, 1109, 1074, 980, 935, 911, 876, 836, 810, 777, 724, 667; δ_H (400 MHz, $CDCl_3$) 5.09 (1H, br s, N*H*), 4.17 (1H, s, 4-*H*), 3.99 (1H, d, *J* 9.3, 5-*H*), 3.66 (1H, m, 1-*H*H), 3.58-3.52 (3H, m, 1-H*H*, 7-*H*H and 2-*H*), 3.51-3.47 (2H, m, 7-H*H* and 3-*H*), 1.84 (1H, m, 6-*H*), 0.99 (3H, d, *J* 6.9, 6-(C*H*$_3$)), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.12 (6H, s, 2 x SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.11 (3H, s, SiC*H*$_3$), 0.09 (6H, s, 2 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 153.1 (*C*(O)), 80.4 (5-*C*), 73.6 (2-*C*), 64.9 (1-*C*), 63.8 (4-*C*), 60.3 (3-*C*), 34.1 (6-*C*), 26.0 (SiC(*C*H$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 25.6 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 16.9 (6-(*C*H$_3$)), 14.8 (7-*C*), −4.0 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.4 (Si*C*H$_3$), −4.6 (Si*C*H$_3$), −5.3 (Si*C*H$_3$), −5.4 (Si*C*H$_3$);

m/z (ES^+) 688 (MH^+, 100%), 710 (MNa^+, 30); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{27}H_{58}INO_5Si_3Na$ 710.2560, observed 710.2548.

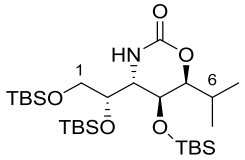
(4*S*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((*S*)-oct-7-en-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (209)



tert-Butyllithium (22.2 mL of a 1.7 M solution in pentane, 37.8 mmol) was added to a solution of freshly prepared 5-iodo-1-pentene[44] **210** (3.71 g, 18.9 mmol) in diethyl ether (20.3 mL) at −78 °C. The solution was then warmed to room temperature and stirred for 1 h. The organolithium solution was then transferred dropwise to a Schlenk tube, held at −40 °C, which was pre-loaded with copper(I) cyanide (846 mg, 9.45 mmol) and lithium chloride (801 mg, 18.9 mmol) (*note*: the lithium chloride has previously been dried under high vacuum in the Schlenk tube for 16 h at 120 °C) in THF (31.5 mL) (*note*: the copper(I) cyanide and lithium chloride THF solution had previously been sonicated for three minutes to ensure solubilisation of copper cyanide). The organocuprate (pale yellow-to-milky white in appearance) was then allowed to stir for 30 minutes at −40 °C. Iodide **206** (1.00 g, 1.45 mmol) in THF (6.00 mL) was then added dropwise to the organocuprate and the reaction was stirred at −40 °C for 6 h. The reaction was quenched by the cautious addition of saturated aqueous ammonium chloride solution. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-5-10% EtOAc/petrol)

afforded alkene **209** (896 mg, 98%) as a colourless solid; R_f: 0.30 (10% EtOAc/petrol); m. p. 85-88 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −52.9 (*c* 0.51, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2955, 2927, 2855, 1692, 1457, 1389, 1361, 1309, 1253, 1111, 1069, 968, 937, 907, 875, 809, 728; δ_H (400 MHz, $CDCl_3$) 5.80 (1H, m, 11-*H*), 5.04 (1H, d, *J* 2.9, N*H*), 5.02-4.91 (2H, m, 12-*H*), 4.14 (1H, d, *J* 0.7, 4-*H*), 3.90 (1H, d, *J* 9.8, 5-*H*), 3.63 (1H, m, 1-*H*H), 3.56-3.49 (3H, m, 1-H*H*, 2-*H* and 3-*H*), 2.08-2.03 (2H, m, 10-*H*), 1.96 (1H, m, 6-*H*), 1.88 (1H, m, 7-H*H*), 1.44-1.34 (3H, m, 9-*H* and 8-*H*H), 1.23 (1H, m, 8-H*H*), 1.14 (1H, m, 7-*H*H), 0.89-0.86 (30H, m, 6-(C*H*$_3$) and 3 x SiC(C*H*$_3$)$_3$), 0.11, 0.10, 0.09, 0.09, 0.08, 0.07 (6 x 3H, s, SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 154.0 (*C*(O)), 139.1 (11-*C*), 114.2 (12-*C*), 81.6 (5-*C*), 73.6 (2-*C*), 64.6 (1-*C*), 64.1 (4-*C*), 59.9 (3-*C*), 33.8 (10-*C*), 32.9 (6-*C*), 31.9 (7-*C*), 29.1 (9-*C*), 26.0 (8-*C*), 25.9 (SiC(*C*H$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 25.6 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 14.9 (6-(*C*H$_3$)), −4.0 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.4 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), −5.4 (2 x Si*C*H$_3$); *m/z* (ES^+) 630 (M^+, 100%), 631 (MH^+, 30); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{32}H_{67}NO_5Si_3Na$ 652.4219, observed 652.4195.

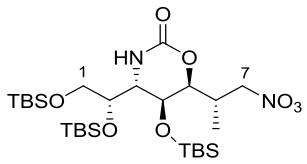
(4*S*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-isopropyl-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (213)



Colourless solid; R_f: 0.25 (10% EtOAc/petrol); m. p. 125-128 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −47.9 (*c* 0.39, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2956, 2929, 2856, 1695, 1450, 1254, 1104, 1081, 928, 838, 809, 776, 723, 691; δ_H (400 MHz, $CDCl_3$) 5.04 (1H, d, *J* 2.5, N*H*), 4.15 (1H, d, *J* 0.6, 4-*H*),

3.84 (1H, d, *J* 9.5, 5-*H*), 3.64 (1H, d, *J* 6.0, 1-*H*H), 3.57-3.50 (3H, m, 1-H*H*, 2-*H* and 3-*H*), 2.10 (1H, m, 6-*H*), 1.11 (3H, d, *J* 6.6, 6-(CH_3)), 0.91 (3H, d, *J* 8.5, 6-(CH_3)), 0.90 (18H, s, 2 x SiC(CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.12, 0.11, 0.10, 0.10, 0.09, 0.08 (6 x 3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 154.0 (*C*(O)), 83.1 (5-*C*), 73.6 (2-*C*), 64.6 (1-*C*), 64.0 (4-*C*), 60.0 (3-*C*), 28.2 (6-*C*), 25.9 (SiC(*C*H_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 25.6 (SiC(*C*H_3)$_3$), 19.2 (6-(*C*H_3)), 18.4 (Si*C*(CH$_3$)$_3$), 18.3 (6-(*C*H_3)), 18.0 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), −4.1 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.4 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), −5.4 (2 x Si*C*H$_3$); *m/z* (ES$^+$) 562 (MH$^+$, 100%), 584 (MNa$^+$, 60); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{27}H_{59}NO_5Si_3Na$ 584.3593, observed 584.3579.

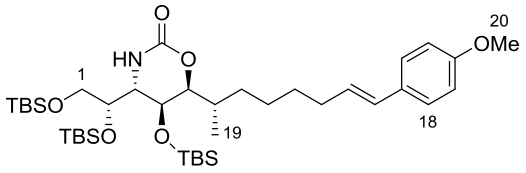
(*S*)-2-((4*S*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-2-oxo-1,3-oxazinan-6-yl)propyl nitrate (214)



Colourless solid; R_f: 0.25 (10% EtOAc/petrol); m. p. 98-101 ºC; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −42.3 (*c* 0.52, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2956, 2929, 2857, 1700, 1633, 1473, 1361, 1277, 1256, 1109, 1086, 992, 926, 837, 777, 665; δ_H (400 MHz, $CDCl_3$) 5.15 (1H, br s, N*H*), 4.70-4.63 (2H, m, 7-*H*), 4.23 (1H, d, *J* 10.0, 5-*H*), 4.11 (1H, s, 4-*H*), 3.65-3.49 (4H, m, 1-*H*, 2-*H* and 3-*H*), 2.43 (1H, m, 6-*H*), 1.04 (3H, d, *J* 6.9, 6-(CH_3)), 0.89 (18H, s, 2 x SiC(CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.12, 0.11, 0.11, 0.10, 0.08, 0.08 (6 x 3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 153.1 (*C*(O)), 77.8 (5-*C*), 73.8 (7-*C*), 73.3 (2-*C*), 64.2 (1-*C*), 64.0 (4-*C*), 59.4 (3-*C*), 32.4 (6-*C*), 25.9 (SiC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 25.6 (SiC(*C*H_3)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 18.0

(Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 12.9 (6-(*C*H$_3$)), −4.1 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.4 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), −5.4 (Si*C*H$_3$), −5.4 (Si*C*H$_3$); *m/z* (ES$^+$) 623 (MH$^+$, 30%), 645 (MNa$^+$, 100); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{27}H_{58}N_2O_8Si_3Na$ 645.3393, observed 645.3379.

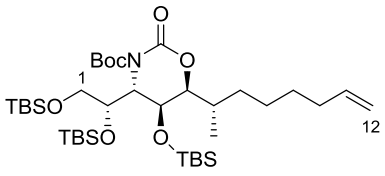
(4*S*,5*S*,6*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-1,3-oxazinan-2-one (362)



Alkene **209** (300 mg, 0.48 mmol) and 4-vinylanisole (0.32 mL, 2.38 mmol) were added to dry degassed CH_2Cl_2 (1.60 mL). Grubbs I catalyst (12.0 mg, 14.3 μmol) was then added to the solution and the reaction was stirred at room temperature for a total period of 48 h. Four additional injections of Grubbs I catalyst (12.0 mg, 14.3 μmol (per injection)) were made at regular intervals over this period. After which DMSO (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The mixture was then concentrated *in vacuo* and purified by flash column chromatography (5-10-15% EtOAc/petrol) to afford styrene **362** (293 mg, 84%) as a colourless solid; R_f: 0.25 (10% EtOAc/petrol); m. p. 94-96 ^oC; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −48.7 (*c* 1.04, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2952, 2928, 2856, 1714, 1695, 1511, 1462, 1452, 1362, 1303, 1249, 1173, 1108, 1080, 926, 836, 777; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.8, 14- and 18-*H*), 6.83 (2H, d, *J* 8.8, 15- and 17-*H*), 6.32 (1H, d, *J* 15.7, 12-*H*), 6.07 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 5.07 (1H, d, *J* 2.9, N*H*), 4.15 (1H, d, *J* 0.7, 4-*H*), 3.91 (1H, d, *J* 9.8, 5-*H*), 3.80 (3H, s, 20-*H*), 3.63 (1H,

d, *J* 6.4, 1-*H*H), 3.57-3.49 (3H, m, 1-H*H*, 2-*H* and 3-*H*), 2.22-2.17 (2H, m, 10-*H*),1.99-1.89 (2H, m, 6-*H* and 7-*H*H), 1.49-1.42 (3H, m, 9-*H* and 8-*H*H), 1.28 (1H, m, 8-H*H*), 1.18 (1H, m, 7-H*H*), 0.90-0.88 (30H, m, 6-(C*H*$_3$) and 3 x SiC(C*H*$_3$)$_3$), 0.11, 0.10, 0.09, 0.09, 0.08, 0.08 (6 x 3H, s, SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 158.5 (16-*C*), 153.9 (*C*(O)), 130.8 (13-*C*), 129.0 (12-*C*), 128.9 (11-*C*), 126.9 (14- and 18-*C*), 113.8 (15- and 17-*C*), 81.6 (5-*C*), 73.6 (2-*C*), 64.6 (1-*C*), 64.1 (4-*C*), 59.9 (3-*C*), 55.2 (20-*C*), 33.0 (10-*C*), 32.9 (6-*C*), 31.9 (7-*C*), 29.6 (9-*C*), 26.0 (8-*C*), 25.9 (SiC(*C*H$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 25.6 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 14.9 (6-(*C*H$_3$)), −4.1 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.4 (Si*C*H$_3$), −4.7 (Si*C*H$_3$), −5.4 (2 x Si*C*H$_3$); *m/z* (ES^+) 658 (MNa^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{39}H_{74}NO_6Si_3$ 736.4818, observed 736.4816.

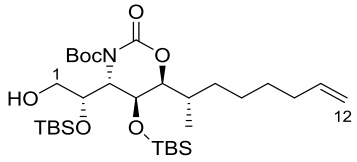
(4*S*,5*S*,6*S*)-*tert*-Butyl 5-((*tert*-butyldimethylsilyl)oxy)-6-((*S*)-oct-7-en-2-yl)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-2-oxo-1,3-oxazinane-3-carboxylate (215)



Triethylamine (170 µl, 1.23 mmol), di-*tert*-butyl dicarbonate (1.68 mL, 7.34 mmol) and DMAP (60 mg, 0.49 mmol) were added sequentially to a solution of carbamate **209** (154 mg, 0.250 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 24 h. Water was added and aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and

concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-2% EtOAc/petrol) afforded *N*-Boc-carbamate **215** (218 mg) as a viscous colourless oil (in mixture with Boc_2O, which was inseparable from the desired product); R_f 0.50 (2% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 5.80 (1H, m, 11-*H*), 5.01-4.91 (2H, m, 12-*H*), 4.55 (1H, dd, *J* 5.1 and 3.3, 3-*H*), 4.12 (1H, dd, *J* 2.3 and 2.3, 4-*H*), 3.91 (1H, dd, *J* 9.6 and 2.3, 5-*H*), 3.66-3.59 (2H, m, 1-*H*), 3.56 (1H, m, 2-*H*), 2.07-2.02 (2H, m, 10-*H*), 1.95 (1H, m, 6-*H*), 1.87 (1H, m, 7-*H*H), 1.45-1.34 (3H, m, 9-*H* and 8-*H*H), 1.50 (9H, s, $CO_2C(CH_3)_3$), 1.23-1.08 (2H, m, 8-H*H* and 7-H*H*), 0.90, 0.87 and 0.86 (3 x $SiC(CH_3)_3$), 0.84 (3H, d, *J* 6.8, 6-(CH_3)), 0.13 ($SiCH_3$), 0.09-0.07 (15H, m, 5 x $SiCH_3$).

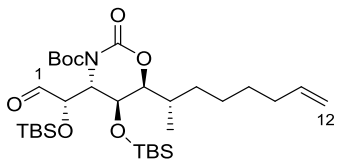
(4*S*,5*S*,6*S*)-*tert*-Butyl 5-((*tert*-butyldimethylsilyl)oxy)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)-2-hydroxyethyl)-6-((*S*)-oct-7-en-2-yl)-2-oxo-1,3-oxazinane-3-carboxylate (222)



Hydrogen fluoride pyridine (69 μL of a 70% solution, 2.7 mmol) was added to a solution of silyl ether **215** (100 mg, 0.140 mmol) in THF (1.4 mL) at 0 °C. The mixture was then slowly warmed to room temperature and stirred for 16 h. The reaction was quenched by the cautious addition of saturated aqueous $NaHCO_3$. The solution was then diluted with EtOAc and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (20-50% EtOAc/petrol) afforded alcohol **222**

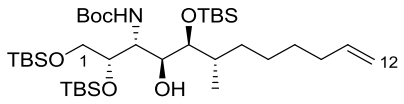
(54.8 mg, 65% over 2 steps from alkene **209**) as a colourless solid; R_f: 0.75 (20% EtOAc/petrol); m. p. 92-94 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −23.0 (*c* 0.20, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3521 (br), 2928, 2857, 1772, 1678, 1472, 1367, 1252, 1210, 1159, 1091, 995, 832, 776; δ_H (400 MHz, $CDCl_3$) 5.80 (1H, m, 11-*H*), 5.01-4.91 (2H, m, 12-*H*), 4.51 (1H, dd, *J* 2.7 and 2.7, 4-*H*), 4.12 (1H, dd, *J* 10.0 and 2.7, 5-*H*), 3.98 (1H, dd, *J* 2.7 and 2.7, 3-*H*), 3.77 (1H, m, 2-*H*), 3.58 (1H, m, 1-*H*H), 3.42-3.37 (2H, m, 1-H*H* and 1-O*H*), 2.07-1.86 (4H, m, 10-*H*, 6-*H* and 7-*H*H), 1.52 (9H, s, $CO_2C(CH_3)_3$), 1.42-1.33 (3H, m, 9-*H* and 8-*H*H), 1.23 (1H, m, 8-H*H*), 1.07 (1H, m, 7-H*H*), 0.88 (9H, s, $SiC(CH_3)_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.85 (3H, d, *J* 6.9, 6-(CH_3)), 0.12, 0.11, 0.09, 0.09 (4 x 3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 155.2 (*C*(O)), 148.2 (*C*(O)), 139.0 (11-*C*), 114.2 (12-*C*), 84.1 ($CO_2C(CH_3)_3$), 83.7 (5-*C*), 72.3 (2-*C*), 65.6 (3-*C*), 62.8 (1-*C*), 59.1 (4-*C*), 33.8 (10-*C*), 32.9 (6-*C*), 31.7 (7-*C*), 29.0 (9-*C*), 27.9 ($CO_2C(CH_3)_3$), 26.1 (8-*C*), 25.8 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 18.0 (2 x $SiC(CH_3)_3$), 14.9 (6-(CH_3)), −3.8 ($SiCH_3$), −4.2 ($SiCH_3$), −4.4 ($SiCH_3$), −5.1 ($SiCH_3$); *m/z* (ES^+) 638 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{31}H_{61}NO_7Si_2Na$ 638.3879, observed 638.3861.

(4*R*,5*S*,6*S*)-*tert*-Butyl 5-((*tert*-butyldimethylsilyl)oxy)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)-2-oxoethyl)-6-((*S*)-oct-7-en-2-yl)-2-oxo-1,3-oxazinane-3-carboxylate (223)



Dimethyl sulfoxide (17 μL, 0.24 mmol), *N*,*N*-diisopropylethylamine (17 μL, 0.10 mmol) and sulfur trioxide pyridine complex (12 mg, 0.073 mmol) were added sequentially to a solution of alcohol **222** (15 mg, 0.024 mmol) in CH_2Cl_2 (0.24 mL) at 0 °C. The mixture was slowly warmed to room temperature stirred for 1 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer was separated and extracted with CH_2Cl_2. The organic layer was then washed sequentially with saturated aqueous copper sulfate (x 2), ammonium chloride (x 2) and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford aldehyde **223** (14.7 mg, 100%) as a colourless oil. The compound was used immediately and without further purification in the subsequent step; R_f: 0.80 (20% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 9.56 (1H, s, 1-*H*), 5.81 (1H, m, 11-*H*), 5.03-4.92 (2H, m, 12-*H*), 4.35 (1H, dd, *J* 3.1 and 3.1, 3-*H*), 4.05 (1H, m, 4-*H*), 3.87-3.84 (2H, m, 2-*H* and 5-*H*), 2.09-1.86 (4H, m, 10-*H*, 6-*H* and 7-*H*H), 1.51 (9H, s, $CO_2C(CH_3)_3$), 1.45-1.37 (3H, m, 9-*H* and 8-*H*H), 1.30 (1H, m, 8-H*H*), 1.11 (1H, m, 7-H*H*), 0.94 (9H, s, $SiC(CH_3)_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.85 (3H, d, *J* 8.3, 6-(CH_3)), 0.13 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$).

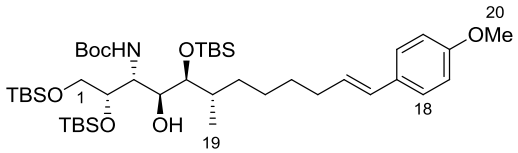
tert-Butyl ((5*S*,6*S*,7*R*,8*S*)-8-((_tert_-butyldimethylsilyl)oxy)-6-hydroxy-2,2,3,3,11,11,12,12-octamethyl-5-((*S*)-oct-7-en-2-yl)-4,10-dioxa-3,11-disilatridecan-7-yl)carbamate (216)



Sodium *tert*-butoxide (357 mg, 3.71 mmol) was added in one portion to a stirred solution of *N*-Boc-carbamate **215** (542 mg, 0.740 mmol) in *t*-BuOH/THF (14.8 mL, 1:1) at room temperature. The reaction was stirred for 45 minutes before the addition of saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-1-2% EtOAc/petrol) afforded silyl ether **216** (isolated with small amounts of the regioisomeric 5-(OTBS) silyl ether) (425 mg, 81% over 2 steps) and a side-product – carbamate **209** (41 mg, 9%). Data for silyl ether **216**: viscous colourless oil; R_f: 0.55 (1% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 3530 br, 3460, 2929, 2857, 1718, 1472, 1493, 1365, 1253, 1170, 1068, 1005, 937, 832, 776, 675; δ_H (400 MHz, $CDCl_3$ (chemical shifts reported for the major compound only)) 5.81 (1H, m, 11-*H*), 5.02-4.90 (2H, m, 12-*H*), 4.63 (1H, d, *J* 10.0, N*H*), 4.22 (1H, t, *J* 6.8, 2-*H*), 3.80 (1H, d, *J* 3.3, 5-*H*), 3.55 (1H, dd, *J* 10.0 and 10.0, 3-*H*), 3.47-3.43 (2H, m, 1-*H*), 3.24 (1H, m, 4-*H*), 3.15 (1H, d, *J* 8.5, O*H*), 2.07-2.02 (2H, m, 10-*H*), 1.56 (1H, m, 6-*H*), 1.43 (9H, s, $CO_2C(CH_3)_3$), 1.39-1.27 (4H, m, 9-*H* and 8-*H*), 1.21 (1H, m, 7-*H*H), 1.08 (1H, m, 7-H*H*), 0.91-0.88 (30H, m 3 x $SiC(CH_3)_3$ and 6-(CH_3)), 0.21, 0.14, 0.12 and 0.10 (4 x 3H, s, $SiCH_3$), 0.03 (6H, s, 2 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major compound only)) 156.6 (*C*(O)), 139.0 (11-*C*), 114.3 (12-*C*), 78.6

($CO_2C(CH_3)_3$), 72.3 (5-*C*), 70.7 (2-*C*), 67.0 (4-*C*), 64.1 (1-*C*), 53.2 (3-*C*), 39.6 (6-*C*), 33.6 (10-*C*), 32.7 (7-*C*), 29.2 (9-*C*), 28.4 ($CO_2C(CH_3)_3$), 26.8 (8-*C*), 26.1 ($SiC(CH_3)_3$), 26.0 (2 x $SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 14.6 (6-(CH_3)), −4.2 ($SiCH_3$), −4.3 ($SiCH_3$), −5.0 ($SiCH_3$), −5.1 ($SiCH_3$), −5.4 ($SiCH_3$), −5.6 ($SiCH_3$); *m/z* (ES^+) 726 (MNa^+, 100%), 604 ($(M-Boc)H^+$, 10); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{36}H_{77}NO_6Si_3Na$ 726.4930, observed 726.4951.

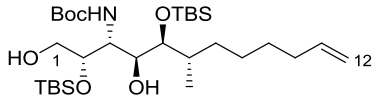
tert-Butyl ((5*S*,6*S*,7*R*,8*S*)-8-((_tert_-butyldimethylsilyl)oxy)-6-hydroxy-5-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecan-7-yl)carbamate (363)



Triethylamine (2.50 ml, 18.1 mmol), di-*tert*-butyl dicarbonate (16.6 mL, 72.4 mmol) and DMAP (442 mg, 3.62 mmol) were added sequentially to a solution of carbamate **362** (2.66 g, 3.62 mmol) in CH_2Cl_2 (24.0 mL) at 0 ^oC. The mixture was then warmed to room temperature and stirred for a total period of 40 h. Two additional injections of di-*tert*-butyl dicarbonate (8.30 mL, 36.2 mmol (per injection)) and DMAP (442 mg, 3.62 mmol (per injection)) were made at regular intervals over this period. Water was added and aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded the *N*-Boc-carbamate as a viscous colourless oil (in mixture with Boc_2O, which was inseparable from the desired product).

Sodium *tert*-butoxide (1.74 g, 18.1 mmol) was added in one portion to a stirred solution of the *N*-Boc-carbamate in *t*-BuOH/THF (72.0 mL, 1:1) at room temperature. The reaction was stirred for 2.5 h before the addition of saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1-2% EtOAc/petrol) afforded silyl ether **363** (2.49 g, 85% over 2 steps), as a viscous colourless oil; R_f: 0.40 (2% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −4.6 (*c* 1.78, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3445 br, 2954, 2929, 2857, 1718, 1493, 1472, 1366, 1292, 1249, 1173, 1145, 1068, 937, 905, 834, 777, 676; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.8, 14- and 18-*H*), 6.84 (2H, d, *J* 8.8, 15- and 17-*H*), 6.34 (1H, d, *J* 15.7, 12-*H*), 6.09 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 4.68 (1H, d, *J* 9.8, N*H*), 4.27 (1H, t, *J* 6.9, 2-*H*), 3.85 (1H, d, *J* 3.2, 5-*H*), 3.80 (3H, s, 20-*H*), 3.60 (1H, dd, *J* 9.8 and 9.8, 3-*H*), 3.48 (2H, d, *J* 6.9, 1-*H*), 3.28 (1H, dd, *J* 8.8 and 8.8, 4-*H*), 3.17 (1H, d, *J* 8.8, O*H*), 2.23-2.18 (2H, m, 10-*H*), 1.60 (1H, m, 6-*H*), 1.49-1.44 (13H, m, $CO_2C(CH_3)_3$, 9- and 8-*H*), 1.28 (1H, m, 7-*H*H), 1.15 (1H, m, 7-H*H*), 0.94-0.91 (30H, m 3 x $SiC(CH_3)_3$ and 19-*H*), 0.25, 0.17, 0.16 and 0.13 (4 x 3H, s, $SiCH_3$), 0.06 (6H, s, 2 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 158.6 (16-*C*), 156.6 (*C*(O)), 130.7 (13-*C*), 129.2 (12-*C*), 128.6 (11-*C*), 126.9 (14- and 18-*C*), 113.8 (15- and 17-*C*), 78.6 ($CO_2C(CH_3)_3$), 72.3 (5-*C*), 70.7 (2-*C*), 67.0 (4-*C*), 64.1 (1-*C*), 55.1 (20-*C*), 53.2 (3-*C*), 39.5 (6-*C*), 32.8 (10-*C*), 32.7 (7-*C*), 29.9 (9-*C*), 27.8 ($CO_2C(CH_3)_3$), 26.9 (8-*C*), 26.0 ($SiC(CH_3)_3$), 25.9 (2 x $SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 14.6 (19-*C*), −4.3 ($SiCH_3$), −4.3 ($SiCH_3$), −5.0 ($SiCH_3$), −5.1 ($SiCH_3$), −5.5 ($SiCH_3$), −5.7 ($SiCH_3$); *m/z* (ES^+) 833 (MNa^+, 100%), 811 (MH^+, 25); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{43}H_{84}NO_7Si_3$ 810.5550, observed 810.5543.

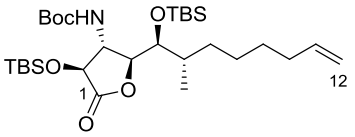
***tert*-Butyl ((5*S*,6*R*,7*S*,8*S*)-7-hydroxy-5-(hydroxymethyl)-2,2,3,3,10,10,11,11-octamethyl-8-(*S*)-oct-7-en-2-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)carbamate (218)**



Hydrogen fluoride pyridine (304 μL of a 70% solution, 3.02 mmol) was added to a solution of silyl ether **216** (425 mg, 0.600 mmol) in THF (6.0 mL) at 0 °C. The mixture was then slowly warmed to room temperature and stirred for 30 h. The reaction was quenched by the cautious addition of saturated aqueous $NaHCO_3$. The solution was then diluted with EtOAc and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded alcohol **218** (267 mg, 75%) as a colourless oil, where the minor regioisomeric 5-(OTBS) silyl ether had been removed upon purification by flash column chromatography; R_f: 0.25 (5% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +23.9 (*c* 0.93, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3553, 2928, 2856, 1673, 1537, 1471, 1277, 1173, 1042, 939, 896, 775, 679; δ_H (400 MHz, $CDCl_3$) 5.81 (1H, m, 11-*H*), 5.03-4.94 (2H, m, 12-*H*), 4.44 (1H, d, *J* 10.6, N*H*), 4.27 (1H, dd, *J* 8.9 and 5.9, 2-*H*), 3.76 (1H, d, *J* 3.8, 5-*H*), 3.60 (1H, dd, *J* 10.6 and 10.6, 3-*H*), 3.51 (1H, dd, *J* 11.4 and 5.9, 1-*H*H), 3.35 (1H, dd, *J* 9.5 and 9.5, 4-*H*), 3.25 (1H, dd, *J* 11.4 and 9.6, 1-H*H*), 3.15 (1H, br, O*H*), 2.29 (1H, d, *J* 9.2, 1-O*H*)), 2.09-2.04 (2H, m, 10-*H*), 1.63 (1H, m, 6-*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$), 1.41-1.35 (4H, m, 9-*H* and 8-*H*H), 1.31-1.21 (2H, m, 8-H*H*, 7-*H*H), 1.12 (1H, m, 7-H*H*), 0.93 (3H, d, *J* 6.9, 6-(CH_3)), 0.91 (9H, s, SiC(CH_3)$_3$), 0.89 (9H, s, SiC(CH_3)$_3$), 0.13 (3H, s, SiCH_3), 0.12 (3H, s, SiCH_3), 0.09 (6H, s, 2 x SiCH_3); δ_C (100 MHz, $CDCl_3$) 157.4 (*C*(O)), 138.9 (11-*C*), 114.4 (12-*C*), 80.1 ($CO_2C(CH_3)_3$), 72.5

(5-*C*), 69.8 (2-*C*), 66.4 (4-*C*), 63.1 (1-*C*), 52.9 (3-*C*), 39.1 (6-*C*), 33.6 (10-*C*), 33.1 (7-*C*), 29.1 (9-*C*), 28.3 ($CO_2C(CH_3)_3$), 26.8 (8-*C*), 25.9 (2 x $SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 14.7 (6-(CH_3)), −4.5 ($SiCH_3$), −4.5 ($SiCH_3$), −4.8 ($SiCH_3$), −5.0 ($SiCH_3$); *m/z* (ES^+) 612 (MNa^+, 60%), 590 (MH^+, 40), 490 ($(M–Boc)H^+$, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{30}H_{63}NO_6Si_2Na$ 612.4086, observed 612.4067.

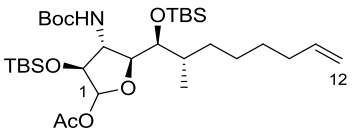
tert-Butyl ((2*S*,3*R*,4*S*)-4-((_tert_-butyldimethylsilyl)oxy)-2-((1*S*,2*S*)-1-((_tert_-butyldimethylsilyl)oxy)-2-methyloct-7-en-1-yl)-5-oxotetrahydrofuran-3-yl)carbamate (221)



Dimethyl sulfoxide (0.28 mL, 4.0 mmol), *N*,*N*-diisopropylethylamine (0.28 mL, 1.6 mmol) and sulfur trioxide pyridine complex (191 mg, 1.19 mmol) were added sequentially to a solution of diol **218** (236 mg, 0.400 mmol) in CH_2Cl_2 (4.0 mL) at 0 °C. The mixture was slowly warmed to room temperature stirred for 2.5 h. Additional portions of dimethyl sulfoxide (0.28 mL, 4.0 mmol), *N*,*N*-diisopropylethylamine (0.28 mL, 1.6 mmol) and sulfur trioxide pyridine complex (191 mg, 1.19 mmol) were then added, and the mixture was stirred for 1 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded lactone **221** (169 mg, 72%) as a colourless solid; R_f: 0.60 (5% EtOAc/petrol); m. p. 81-83 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −21.3 (*c* 0.08, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3334, 2929, 2857, 1777, 1704, 1531, 1463, 1389, 1281, 1151, 1067, 837, 775, 661;

δ_H (400 MHz, $CDCl_3$) 5.80 (1H, m, 11-*H*), 5.02-4.93 (2H, m, 12-*H*), 4.79 (1H, d, *J* 8.3, N*H*), 4.70 (1H, d, *J* 8.8, 2-*H*), 4.44 (1H, dd, *J* 8.6 and 5.1, 4-*H*), 3.84 (1H, ddd, *J* 8.8, 8.6 and 8.3, 3-*H*), 3.60 (1H, dd, *J* 5.1 and 3.2, 5-*H*), 2.07-2.02 (2H, m, 10-*H*), 1.68 (1H, m, 6-*H*), 1.44 (9H, s, $CO_2C(CH_3)_3$), 1.41-1.17 (6H, m, 9-*H*, 8-*H* and 7-*H*), 0.97 (3H, d, *J* 6.9, 6-(CH_3)), 0.91 (9H, s, $SiC(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.17 (3H, s, $SiCH_3$), 0.12 (6H, s, 2 x $SiCH_3$), 0.07 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 172.9 (1-*C*), 154.5 (*C*(O)), 138.9 (11-*C*), 114.4 (12-*C*), 80.4 ($CO_2C(CH_3)_3$), 78.4 (4-*C*), 76.5 (5-*C*), 71.7 (2-*C*), 57.6 (3-*C*), 36.0 (6-*C*), 33.8 (10-*C*), 31.4 (8-*C*), 29.2 (9-*C*), 28.3 ($CO_2C(CH_3)_3$), 26.9 (7-*C*), 26.0 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 16.6 (6-(CH_3)), −4.3 (2 x $SiCH_3$), −4.7 ($SiCH_3$), −5.4 ($SiCH_3$); *m/z* (ES^+) 608 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{30}H_{59}NO_6Si_2Na$ 608.3773, observed 608.3762.

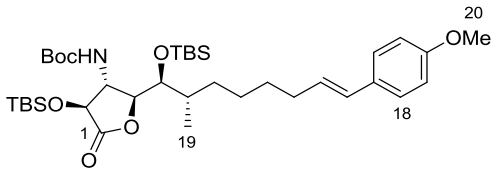
(3*S*,4*R*,5*S*)-4-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-5-((1*S*,2*S*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methyloct-7-en-1-yl)tetrahydrofuran-2-yl acetate (219)



Dess-Martin periodinane (142 mg, 0.330 mmol) was added to the solution of diol **218** (44 mg, 0.08 mmol) in CH_2Cl_2 (0.75 mL) at room temperature. The mixture was stirred for 5 h. Saturated aqueous $NaHCO_3$ was then added. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-2-5% EtOAc/petrol) afforded acylated lactol **219** (35.3 mg, 70%) as a colourless

oil; R_f: 0.40 (5% EtOAc/petrol); $[\alpha]_D^{20}$ +23.9 (*c* 0.28, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2930, 2858, 1720, 1501, 1472, 1367, 1252, 1111, 1007, 939, 836, 776, 671; δ_H (400 MHz, $CDCl_3$) 6.00 (1H, s, 1-*H*), 5.80 (1H, m, 11-*H*), 5.01-4.91 (2H, m, 12-*H*), 4.83 (1H, d, *J* 10.0, N*H*), 4.02-3.92 (3H, m, 2-*H*, 3-*H* and 4-*H*), 3.62 (1H, d, *J* 9.1, 5-*H*), 2.10 (3H, s, C*H*$_3$CO$_2$), 2.06-2.03 (2H, m, 10-*H*), 1.72 (1H, m, 6-*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.40-1.30 (4H, m, 9-*H*, 8-*H*H and 7-*H*H), 1.29-1.17 (2H, m, 8-H*H* and 7-H*H*), 0.96 (3H, d, *J* 6.9, 6-(C*H*$_3$)), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.13 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.03 (3H, s, SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 169.3 (*C*(O)), 154.5 (*C*(O)), 139.2 (11-*C*), 114.1 (12-*C*), 102.4 (1-*C*), 89.1 (4-*C*), 81.0 (2-*C*), 79.8 ($CO_2C(CH_3)_3$), 78.7 (5-*C*), 58.6 (3-*C*), 35.3 (6-*C*), 33.9 (10-*C*), 29.4 (9-*C*), 28.3 ($CO_2C(CH_3)_3$), 27.1 (7-*C*), 26.2 ($SiC(CH_3)_3$), 26.0 (8-*C*), 25.6 ($SiC(CH_3)_3$), 21.3 (CH_3CO_2), 18.6 ($SiC(CH_3)_3$), 18.2 (6-(CH_3)), 17.9 ($SiC(CH_3)_3$), −3.8 ($SiCH_3$), −4.8 ($SiCH_3$), −5.1 ($SiCH_3$), −5.1 ($SiCH_3$); *m/z* (ES^+) 652 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{32}H_{63}NO_7Si_2Na$ 652.4035, observed 652.4026.

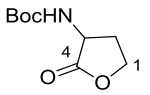
tert-Butyl ((2*S*,3*R*,4*S*)-4-((_tert_-butyldimethylsilyl)oxy)-2-((1*S*,2*S*,*E*)-1-((_tert_-butyldimethylsilyl)oxy)-8-(4-methoxyphenyl)-2-methyloct-7-en-1-yl)-5-oxotetrahydrofuran-3-yl)carbamate (225)



Alkene **221** (71.0 mg, 0.12 mmol) and 4-vinylanisole (81 μL, 0.61 mmol) were added to dry degassed CH_2Cl_2 (0.4 mL). Grubbs I catalyst (5.0 mg, 6.0 μmol) was then added to the

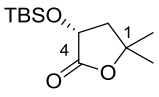
solution and the reaction was stirred at room temperature for a total period of 48 h. Two additional injections of Grubbs I catalyst (5.0 mg, 6.0 μmol (per injection)) were made at regular intervals over this period. After which DMSO (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The mixture was then concentrated *in vacuo* onto silica gel and purified by flash column chromatography (petrol-2-5% EtOAc/petrol) to afford styrene **225** (73.3 mg, 88%) as a colourless oil; R_f: 0.25 (5% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −19.2 (*c* 0.13, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3393, 2929, 2857, 1788, 1719, 1510, 1463, 1366, 1249, 1153, 835, 777, 669; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 9.3, 14- and 18-*H*), 6.85 (2H, d, *J* 9.3, 15- and 17-*H*), 6.33 (1H, d, *J* 15.9, 12-*H*), 6.08 (1H, dt, *J* 15.9 and 6.9, 11-*H*), 4.68 (1H, d, *J* 8.3, N*H*), 4.58 (1H, d, *J* 8.8, 2-*H*), 4.39 (1H, dd, *J* 8.6 and 4.9, 4-*H*), 3.38-3.81 (4H, m, 3-*H* and 20-*H*), 3.61 (1H, dd, *J* 4.9 and 3.2, 5-*H*), 2.23-2.18 (2H, m, 10-*H*), 1.69 (1H, m, 6-*H*), 1.50-1.39 (12H, m, $CO_2C(CH_3)_3$, 9-*H* and 7-*H*H), 1.34-1.22 (3H, m, 8-*H* and 7-H*H*), 0.98 (3H, d, *J* 6.9, 19-*H*), 0.91 (18H, s, 2 x $SiC(CH_3)_3$), 0.17 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 172.9 (1-*C*), 158.7 (16-*C*), 154.5 (*C*(O)), 130.5 (13-*C*), 129.2 (12-*C*), 128.7 (11-*C*), 126.9 (14- and 18-*C*), 113.9 (15- and 17-*C*), 80.4 ($CO_2C(CH_3)_3$), 78.4 (4-*C*), 76.4 (5-*C*), 71.8 (2-*C*), 57.4 (3-*C*), 55.2 (20-*C*), 36.0 (6-*C*), 33.0 (10-*C*), 31.3 (8-*C*), 29.6 (9-*C*), 28.3 ($CO_2C(CH_3)_3$), 26.9 (7-*C*), 26.0 ($SiC(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 16.6 (19-*C*), −4.3 ($SiCH_3$), −4.7 ($SiCH_3$), −5.4 ($SiCH_3$); *m/z* (ES^+) 714 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{37}H_{65}NO_7Si_2Na$ 714.4192, observed 714.4180.

***tert*-Butyl (2-oxotetrahydrofuran-3-yl)carbamate (228)[94]**



Triethylamine (0.84 ml, 6.0 mmol) and di-*tert*-butyl dicarbonate (1.4 mL, 6.0 mmol) were added sequentially to a solution of 3-aminodihydrofuran-2(3*H*)-one hydrobromide **227**(1.0 g, 5.5 mmol) in THF (10 mL) at 0 ºC. The mixture was then warmed to room temperature and stirred for 16 h. Water was added, then aqueous layer was adjusted to pH ≈ 5 with 10% aqueous citric acid and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-100% EtOAc/petrol) afforded *N*-Boc-lactone **228** (0.79 g, 71%) as a colourless solid; R_f: 0.60 (EtOAc); m.p. 120-122 ºC (lit.[95] m.p. 124-126 ºC); δ_H (400 MHz, $CDCl_3$) 5.26 (1H, br s, N*H*), 4.43-4.32 (2H, m, 1-*H*H and 3-*H*), 4.22 (1H, m, 1-H*H*), 2.76 (1H, m, 2-*H*H), 2.20 (1H, m, 2-H*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 175.4 (4-*C*), 155.4 (*C*(O)), 80.4 ($CO_2C(CH_3)_3$), 65.6 (1-*C*), 50.0 (3-*C*), 30.2 (2-*C*), 28.1 ($CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[95]

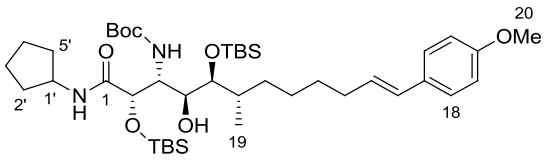
(*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-5,5-dimethyldihydrofuran-2(3*H*)-one (233)



tert-Butyldimethylsilyl trifluoromethanesulfonate (1.56 mL, 6.92 mmol) was added dropwise to a solution of (*R*)-3-hydroxy-5,5-dimethyldihydrofuran-2(3*H*)-one **232**

(300 mg, 2.31 mmol) and 2,6-lutidine (1.61 mL, 13.8 mmol) in CH_2Cl_2 (23.1 mL) at 0 °C. The solution was warmed to room temperature and stirred for 3 h before being quenched with *i*-PrOH. Water was then added and aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-25% EtOAc/petrol) afforded silyl ether **233** (556 mg, 87%) as a colourless solid; R_f: 0.50 (50% EtOAc/petrol); m. p. 87-90 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +26.7 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2930, 1792, 1461, 1360, 1247, 1211, 1134, 1028, 861, 836, 778, 671; δ_H (400 MHz, $CDCl_3$) 4.01-3.99 (2H, m, 2-*H*H and 3-*H*), 3.89 (1H, d, *J* 8.8, 2-H*H*), 1.15 (3H, s, 1-(C*H*$_3$)), 1.06 (3H, s, 1-(C*H*$_3$)), 0.94 (9H, s, SiC(C*H*$_3$)$_3$), 0.21 (3H, s, SiC*H*$_3$), 0.14 (3H, s, SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 160.7 (4-*C*), 77.2 (3-*C*), 75.8 (2-*C*), 40.9 (1-*C*), 25.6 (SiC(*C*H$_3$)$_3$), 23.1 (1-(*C*H$_3$)), 19.1 (1-(*C*H$_3$)), 18.3 (Si*C*(CH$_3$)$_3$), −4.5 (Si*C*H$_3$), −5.4 (Si*C*H$_3$); *m/z* (ES$^+$) 267 (MNa$^+$, 100%); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{12}H_{24}O_3SiNa$ 267.1387, observed 267.1390.

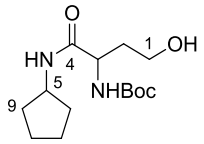
***tert*-Butyl ((5*S*,6*R*,7*S*,8*S*)-5-(cyclopentylcarbamoyl)-7-hydroxy-8-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecan-6-yl)carbamate (235)**



N,*N*'-Diisopropylethylamine (5.0 μL, 30 μmol), 2-hydroxypyridine (1.4 mg, 15 μmol) and cyclopentylamine (4.0 μL, 38 μmol) were added sequentially to a solution of lactone **225** (11 mg, 15 μmol) in CH_2Cl_2 (0.15 mL) at room temperature. The mixture was stirred for

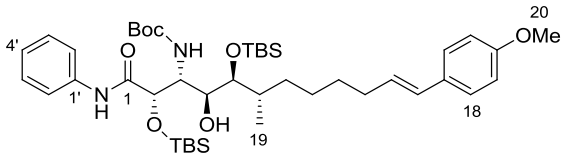
48 h, then concentrated *in vacuo* onto silica gel and purified by flash column chromatography (petrol-5-10% EtOAc/petrol) to afford amide **235** (10.7 mg, 92%) as a colourless oil; R_f: 0.30 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −7.9 (*c* 0.14, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3432, 2954, 2929, 2857, 1722, 1683, 1511, 1492, 1365, 1249, 1173, 1073, 964, 836, 779, 676; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.3, 14- and 18-*H*), 6.84 (2H, d, *J* 8.3, 15- and 17-*H*), 6.37 (1H, d, *J* 8.1, N*H*), 6.32 (1H, d, *J* 15.7, 12-*H*), 6.08 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 4.62 (1H, s, 2- or 4-*H*), 4.51 (1H, d, *J* 10.3, N*H*), 4.25 (1H, m, 1'-*H*), 3.88 (1H, dd, *J* 10.3 and 10.3, 3-*H*), 3.81 (3H, s, 20-*H*), 3.74 (1H, d, *J* 3.4, 5-*H*), 3.22-3.14 (2H, m, 4- or 2-*H* and 4-O*H*), 2.19 (2H, dt, *J* 6.9 and 6.9, 10-*H*), 1.99-1.91 (2H, m, 2'-*H*H and 5'-*H*H), 1.68-1.61 (5H, m, 6-*H*, 4'-*H* and 3'-*H*), 1.46-1.08 (17H, m, $CO_2C(CH_3)_3$, 7-*H*, 8-*H*, 9-*H*, 2'-H*H* and 5'-H*H*), 0.97 (9H, s, $SiC(CH_3)_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.91 (3H, d, *J* 7.1, 19-*H*), 0.26 (3H, s, $SiCH_3$), 0.19 (3H, s, $SiCH_3$), 0.12 (6H, s, 2 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 171.6 (1-*C*), 158.6 (16-*C*), 154.8 (*C*(O)), 130.6 (13-*C*), 129.2 (12-*C*), 128.6 (11-*C*), 127.0 (14- and 18-*C*), 113.9 (15- and 17-*C*), 79.2 ($CO_2C(CH_3)_3$), 72.1 (2- or 4-*C*), 72.1 (5-*C*), 67.0 (4- or 2-*C*), 55.7 (3-*C*), 55.3 (20-*C*), 50.5 (1'-*C*), 39.3 (6-*C*), 33.5, 32.9, 32.9, 32.7, (10-*C*, 7-*C* or 8-*C*, 2'-*C* and 5'-*C*), 29.8 (9-*C*), 28.4 ($CO_2C(CH_3)_3$), 26.9 (7-*C* or 8-*C*), 25.9 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 23.6 (4'-*C*), 23.6 (3'-*C*), 18.2 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 14.6 (19-*C*), −4.3 ($SiCH_3$), −5.0 ($SiCH_3$), −5.1 ($SiCH_3$), −5.2 ($SiCH_3$); *m/z* (ES^+) 799 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{42}H_{76}N_2O_7Si_2Na$ 799.5083, observed 799.5106.

***tert*-Butyl (1-(cyclopentylamino)-4-hydroxy-1-oxobutan-2-yl)carbamate (230)**



N,*N*'-Diisopropylethylamine (86 μL, 0.50 mmol), 2-hydroxypyridine (24 mg, 0.25 mmol) and cyclopentylamine (37 μL, 0.37 mmol) were added sequentially to a solution of lactone **228** (50 mg, 0.25 mmol) in CH_2Cl_2 (2.5 mL) at room temperature. The mixture was stirred for 48 h, then concentrated *in vacuo* and purified by flash column chromatography (50-100% EtOAc/petrol) to afford amide **230** (71.6 mg, 100%) as a colourless oil; R_f: 0.40 (EtOAc); m. p. 123-125 ^oC; ν_{max}/cm^{-1} (neat) 3455, 3261, 2963, 1690, 1635, 1540, 1391, 1288, 1252, 1165, 1054, 994, 872, 674; δ_H (400 MHz, $CDCl_3$) 6.82 (1H, d, *J* 6.4, N*H*), 5.73 (1H, d, *J* 7.3, N*H*), 4.26 (1H, m, 3-*H*), 4.15 (1H, m, 5-*H*), 3.99 (1H, br s, 1-O*H*), 3.67 (1H, br s, 1-*H*), 1.98-1.92 (3H, m, 2-*H*H, 6-*H*H and 9-*H*H), 1.73-1.52 (5H, m, 2-H*H*, 8-*H* and 7-*H*), 1.42-1.35 (11H, m, $CO_2C(CH_3)_3$, 6-H*H* and 9-H*H*); δ_C (100 MHz, $CDCl_3$) 171.4 (4-*C*), 156.6 (*C*(O)), 80.1 ($CO_2C(CH_3)_3$), 58.4 (1-*C*), 51.2 (3-*C*), 51.2 (5-*C*), 36.4 (2-*C*), 32.8 (6-*C*), 32.8 (9-*C*), 28.2 ($CO_2C(CH_3)_3$), 23.7 (7-*C* or 8-*C*), 23.6 (7-*C* or 8-*C*); *m/z* (ES^+) 595 (M_2Na^+, 100%), 287 (MH^+, 70); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{14}H_{26}N_2O_4Na$ 309.1785, observed 309.1778.

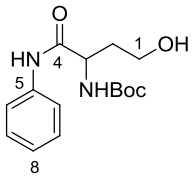
***tert*-Butyl ((5*S*,6*R*,7*S*,8*S*)-7-hydroxy-8-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,10,10,11,11-octamethyl-5-(phenylcarbamoyl)-4,9-dioxa-3,10-disiladodecan-6-yl)carbamate (236)**



Aniline (8.0 μL, 83 μmol), trimethylaluminium (42 μL of a 2.0 M solution in hexanes, 83 μmol) were added sequentially to a solution of lactone **225** (23 mg, 33 μmol) in dry CH_2Cl_2 (0.33 mL) at 0 °C. The mixture was stirred for 3 h before being quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (hexane-2-5% EtOAc/hexane) afforded amide **236** (20.2 mg, 78%) as a colourless oil; R_f: 0.30 (5% EtOAc/hexane); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −60.0 (*c* 0.08, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3404, 2954, 2929, 1722, 1603, 1511, 1442, 1248, 1172, 1075, 962, 836, 780, 691; δ_H (400 MHz, $(CD_3)_2SO$) 9.07 (1H, s, N*H*), 7.51 (2H, d, *J* 7.6, 2'- and 6'-*H*), 7.32-7.27 (4H, m, 3'- and 5'-*H* and 14- and 18-*H*), 7.05 (1H, dd, *J* 7.3 and 7.3, 4'-*H*), 6.85 (2H, d, *J* 8.8, 15- and 17-*H*), 6.31-6.27 (2H, m, 12-*H* and N*H*), 6.10 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 4.52 (1H, d, *J* 2.2, 2- or 4-*H*), 3.75-3.73 (4H, m, 3-*H* and 20-*H*), 3.68 (1H, d, *J* 3.9, 5-*H*), 3.48 (1H, d, *J* 8.6, 4-O*H*), 3.36 (1H, m, 4- or 2-*H*), 2.15 (2H, dt, *J* 6.9 and 6.9, 10-*H*), 1.59 (1H, m, 6-*H*), 1.39-1.29 (5H, m, 7-H*H*, 8-*H* and 9-*H*), 1.22 (9H, s, $CO_2C(CH_3)_3$), 1.11 (1H, m, 7-*H*H), 0.93 (9H, s, $SiC(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.88 (3H, d, *J* 6.9, 19-*H*), 0.14 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); δ_C (100 MHz, $(CD_3)_2SO$) 170.4 (1-*C*), 158.3 (16-*C*), 155.4

(*C*(O)), 138.2 (1'-*C*), 129.9 (13-*C*), 129.0 (12-*C*), 128.6 (3'- and 5'-*C* or 14- and 18-*C*), 128.1 (11-*C*), 126.9 (3'- and 5'-*C* or 14- and 18-*C*), 123.6 (4'-*C*),119.7 (2'- and 6'-*C*), 113.9 (15- and 17-*C*), 77.9 ($CO_2C(CH_3)_3$), 73.0 (2- or 4-*C*), 72.1 (5-*C*), 67.0 (4- or 2-*C*), 55.5 (3-*C*), 55.0 (20-*C*), 38.4 (6-*C*), 32.4 (10-*C* and 7-*C*), 29.4 (9-*C*), 28.0 ($CO_2C(CH_3)_3$), 26.4 (8-*C*), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), 15.0 (19-*C*), −4.4 ($SiCH_3$), −5.1 ($SiCH_3$), −5.1 ($SiCH_3$), −5.2 ($SiCH_3$); *m/z* (ES^+) 808 (MNa^+, 100%), 685 ($(M-Boc)H_2^+$, 50); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{43}H_{72}N_2O_7Si_2Na$ 807.4770, observed 807.4773.

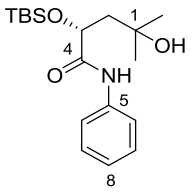
tert-Butyl (4-hydroxy-1-oxo-1-(phenylamino)butan-2-yl)carbamate (231)



Aniline (27 μL, 0.30 mmol), trimethylaluminium (150 μL of a 2.0 M solution in hexanes, 0.298 mmol) were added sequentially to a solution of lactone **228** (30 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The mixture was stirred for 3 h before being quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-100% EtOAc/petrol) afforded amide **231** (42.1 mg, 96%) as a colourless oil; R_f: 0.60 (EtOAc); ν_{max}/cm^{-1} (neat) 3304, 2978, 1669, 1601, 1499, 1444, 1367, 1249, 1163, 1052, 908, 866, 753, 732, 691; δ_H (400 MHz, $CDCl_3$) 8.86 (1H, br s, N*H*), 7.55 (2H, d, *J* 7.8, 6- and 10-*H*), 7.32 (2H, dd, *J* 7.8 and 7.8, 7- and 9-*H*), 7.12 (1H, t, *J* 7.3, 8-*H*), 5.78 (1H, br s, N*H*), 4.55 (1H, br s, 3-*H*), 3.84 (2H, br s, 1-*H*), 2.17

(1H, br s, 2-*H*H), 1.85 (1H, br s, 2-H*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $(CD_3)_2SO$) 170.3 (4-*C*), 156.9 (*C*(O)), 137.7 (5-*C*), 129.0 (7- and 9-*C*), 124.5 (8-*C*), 120.0 (6- and 10-*C*), 80.7 ($CO_2C(CH_3)_3$), 58.6 (1-*C*), 52.0 (3-*C*), 36.2 (2-*C*), 28.3 ($CO_2C(CH_3)_3$); *m/z* (ES^+) 317 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{15}H_{22}N_2O_4Na$ 317.1472, observed 317.1467.

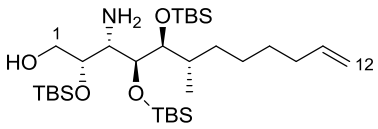
(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-methyl-*N*-phenylpentanamide (234)



Aniline (25 μL, 0.27 mmol), trimethylaluminium (140 μL of a 2.0 M solution in hexanes, 0.270 mmol) were added sequentially to a solution of lactone **233** (30 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C. The mixture was stirred for 2 h before being quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-10-20% EtOAc/petrol) afforded amide **234** (41.5 mg, 100%) as a colourless oil; R_f: 0.40 (20% EtOAc/hexane); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +109.6 (*c* 0.27, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3396, 2930, 1672, 1601, 1524, 1472, 1442, 1312, 1255, 1077, 875, 837, 780, 754, 691; δ_H (400 MHz, $CDCl_3$) 8.25 (1H, br s, N*H*), 7.53 (2H, d, *J* 7.6, 6- and 10-*H*), 7.36 (2H, dd, *J* 7.6 and 7.6, 7- and 9-*H*), 7.16 (1H, t, *J* 7.6, 8-*H*), 4.15 (1H, s, 3-*H*), 3.55 (1H, d, *J* 11.7, 2-*H*H), 3.42 (1H, d, *J* 11.7, 2-H*H*), 3.15 (1H, br s, 1-O*H*), 1.09 (3H, s, 1-(CH_3)), 1.03 (9H, s, $SiC(CH_3)_3$), 0.89 (3H, s, 1-(CH_3)), 0.18 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 171.6 (4-*C*), 136.7 (5-*C*), 129.2 (7- and 9-*C*), 124.7 (8-*C*),

119.6 (6- and 10-*C*), 78.3 (3-*C*), 70.1 (2-*C*), 40.8 (1-*C*), 25.8 (SiC(CH_3)$_3$), 23.4 (1-(CH_3)), 19.0 (1-(CH_3)), 18.0 (SiC(CH_3)$_3$), −5.2 (SiCH_3), −5.3 (SiCH_3); *m/z* (ES^+) 338 (MH^+, 100%), 360 (MNa^+, 30); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{18}H_{31}NO_3SiNa$ 360.1965, observed 360.1958.

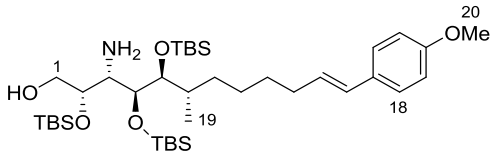
(2*S*,3*S*,4*S*,5*S*,6*S*)-3-Amino-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-6-methyldodec-11-en-1-ol (241)



tert-Butyldimethylsilyl trifluoromethanesulfonate (3.20 mL, 14.1 mmol) was added dropwise to a solution of **216** (994 mg, 1.41 mmol) and 2,6-lutidine (3.20 mL, 28.2 mmol) in CH_2Cl_2 (15.0 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h before being quenched with saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with CH_2Cl_2. The organic layers were then washed with 1M HCl (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2/MeOH (15.0 mL, 1:1) and (±)-camphor 10-sulfonic acid (657 mg, 2.80 mmol) was added in one portion at 0 °C. The mixture was then warmed to room temperature and stirred for 48 h. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was then separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded aminoalcohol **241** (686 mg, 84% over 2 steps) as a colourless oil; R_f: 0.30 (10% EtOAc/hexane); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −38.8 (*c* 0.08, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2955, 2929, 2858, 1472, 1253, 1066, 909, 834, 775, 669; δ_H (400 MHz,

$CDCl_3$) 5.82 (1H, m, 11-*H*), 5.03-4.93 (2H, m, 12-*H*), 4.04 (1H, m, 2-*H*), 3.89 (1H, dd, *J* 11.7 and 2.7, 1-*H*H), 3.80 (1H, dd, *J* 11.7 and 2.0, 1-H*H*), 3.64 (1H, dd, *J* 9.5 and 2.9, 4-*H*), 3.53 (1H, dd, *J* 7.6 and 2.9, 5-*H*), 3.10 (1H, d, *J* 9.5, 3-*H*), 2.09-2.04 (2H, m, 10-*H*), 1.86-1.58 (4H, m, 6-*H*, 7-*H*H and NH_2), 1.46-1.33 (3H, m, 9-*H* and 8-*H*H), 1.21 (1H, m, 8-H*H*), 1.02 (1H, m, 7-H*H*), 0.98 (3H, d, *J* 6.6, 6-(CH_3)), 0.93-0.87 (28H, m, 3 x SiC(CH_3)$_3$ and 7-H*H*), 0.21, 0.13, 0.11, 0.11, 0.10 and 0.08 (6 x 3H, s, 6 x SiCH_3); δ_C (100 MHz, $CDCl_3$) 139.0 (11-*C*), 114.3 (12-*C*), 79.6 (5-*C*), 74.5 (4-*C*), 69.7 (2-*C*), 69.0 (1-*C*), 58.5 (3-*C*), 34.8 (6-*C*), 33.8 (10-*C*), 33.1 (7-*C*), 29.2 (9-*C*), 26.4 (8-*C*), 26.0 (SiC(*C*H_3)$_3$), 26.0 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 17.4 (6-(*C*H$_3$)), −2.6 (Si*C*H$_3$), −3.3 (Si*C*H$_3$), −3.7 (Si*C*H$_3$), −4.3 (Si*C*H$_3$), −4.6 (Si*C*H$_3$), −4.8 (Si*C*H$_3$); *m/z* (ES^+) 604 (MH^+, 100%), 605 ((MH_2^+, 15); *m/z* HRMS (ES^+) MH^+ calculated for $C_{31}H_{70}NO_4Si_3$ 604.4607, observed 604.4607.

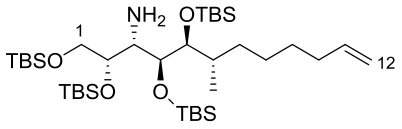
(2*S*,3*S*,4*S*,5*S*,6*S*,*E*)-3-Amino-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-12-(4-methoxyphenyl)-6-methyldodec-11-en-1-ol (364)



tert-Butyldimethylsilyl trifluoromethanesulfonate (7.00 mL, 30.5 mmol) was added dropwise to a solution of **363** (2.47 g, 3.05 mmol) and 2,6-lutidine (7.10 mL, 61.0 mmol) in CH_2Cl_2 (30.0 mL) at 0 ºC. The mixture was warmed to room temperature and stirred for 16 h before being quenched with saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with CH_2Cl_2. The organic layers were then washed with

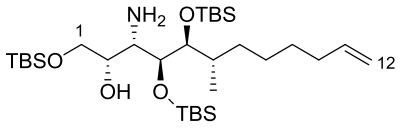
1M HCl (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2/MeOH (15.0 mL, 1:1) and (±)-camphor 10-sulfonic acid (1.42 g, 6.10 mmol) was added in one portion at 0 °C. The mixture was then warmed to room temperature and stirred for 46 h. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was then separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-7.5-10-20% EtOAc/petrol) afforded aminoalcohol **364** (2.07 g, 96% over 2 steps) as a colourless oil; R_f: 0.30 (20% EtOAc/hexane); $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −24.5 (*c* 2.58, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2954, 2929, 2857, 1511, 1464, 1249, 1065, 939, 879, 833, 774, 671; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, d, *J* 8.5, 14- and 18-*H*), 6.84 (2H, d, *J* 8.5, 15- and 17-*H*), 6.33 (1H, d, *J* 15.7, 12-*H*), 6.09 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 4.05 (1H, br s, 2-*H*), 3.90 (1H, dd, *J* 11.8 and 2.4, 1-*H*H), 3.83-3.81 (4H, m, 1-H*H* and 20-*H*), 3.65 (1H, dd, *J* 9.6 and 2.9, 4-*H*), 3.55 (1H, dd, *J* 7.5 and 2.9, 5-*H*), 3.11 (1H, d, *J* 9.6, 3-*H*), 2.23-2.18 (2H, m, 10-*H*), 1.80-1.69 (2H, m, 6-*H* and 7-*H*H), 1.50-1.41 (3H, m, 9-*H* and 8-*H*H), 1.25 (1H, m, 8-H*H*), 1.05 (1H, m, 7-H*H*), 0.99 (3H, d, *J* 6.6, 19-*H*), 0.94-0.87 (28H, m, 3 x SiC(C*H*$_3$)$_3$ and 7-H*H*), 0.22, 0.14, 0.12, 0.12, 0.11 and 0.09 (6 x 3H, s, 6 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 158.6 (16-*C*), 130.8 (13-*C*), 129.2 (12-*C*), 128.9 (11-*C*), 127.0 (14- and 18-*C*), 113.9 (15- and 17-*C*), 79.7 (5-*C*), 74.5 (4-*C*), 69.8 (2-*C*), 69.1 (1-*C*), 58.6 (3-*C*), 55.3 (20-*C*), 34.8 (6-*C*), 33.1 (10- or 7-*C*), 33.0 (10- or 7-*C*), 29.8 (9-*C*), 26.5 (8-*C*), 26.0 (SiC(*C*H$_3$)$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 17.5 (6-(*C*H$_3$)), −2.6 (Si*C*H$_3$), −3.3 (Si*C*H$_3$), −3.7 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.5 (Si*C*H$_3$), −4.8 (Si*C*H$_3$); *m/z* (ES$^+$) 711 (MH$^+$, 100%); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{38}H_{76}NO_5Si_3$ 710.5026, observed 710.5003.

(5*S*,6*S*,7*S*,8*S*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,11,11,12,12-octamethyl-5-((*S*)-oct-7-en-2-yl)-4,10-dioxa-3,11-disilatridecan-7-amine (242)



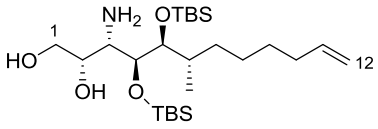
Colourless oil; R_f: 0.70 (5% EtOAc/hexane); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −12.6 (*c* 0.19, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2929, 2858, 2360, 2342, 1472, 1257, 1077, 835, 775, 669; δ_H (400 MHz, $CDCl_3$) 5.81 (1H, m, 11-*H*), 5.02-4.91 (2H, m, 12-*H*), 4.09 (1H, dd, *J* 6.4 and 6.4, 2- or 4-*H*), 3.69-3.57 (4H, m, 5-, 3- and 1-*H*), 2.99 (1H, d, *J* 9.5, 2- or 4-*H*), 2.08-2.03 (2H, m, 10-*H*), 1.82 (1H, m, 6-*H*), 1.73-1.65 (3H, m, 7-*H*H and NH_2), 1.45-1.29 (4H, m, 9- and 8-*H*), 1.20 (1H, m, 7-H*H*), 0.96 (3H, d, *J* 6.6, 6-(CH_3)), 0.90-0.88 (36H, m, 4 x SiC(CH_3)$_3$), 0.13, 0.12, 0.12, 0.11, 0.11, 0.08, 0.06 and 0.05 (8 x 3H, s, 8 x SiCH_3); δ_C (100 MHz, $CDCl_3$) 139.2 (11-*C*), 114.1 (12-*C*), 79.9 (5- or 3-*C*), 74.7 (5- or 3-*C*), 72.5 (2- or 4-*C*), 65.2 (1-*C*), 54.2 (2- or 4-*C*), 34.5 (6-*C*), 33.9 (10-*C*), 32.8 (7-*C*), 29.3 (9-*C*), 26.6 (8-*C*), 26.1 (SiC(*C*H_3)$_3$), 26.0 (SiC(*C*H_3)$_3$), 26.0 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 17.6 (6-(*C*H$_3$)), −2.6 (Si*C*H$_3$), −3.1 (Si*C*H$_3$), −3.3 (Si*C*H$_3$), −4.3 (Si*C*H$_3$), −4.8 (Si*C*H$_3$), −5.4 (Si*C*H$_3$), −5.4 (Si*C*H$_3$); *m/z* (ES$^+$) 718 (MH$^+$, 100%), 719 ((MH$_2^+$, 50); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{37}H_{84}NO_4Si_4$ 718.5472, observed 718.5477.

(6*S*,7*S*,8*S*,9*S*)-7-Amino-8-((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,11,11,12,12-octamethyl-9-((*S*)-oct-7-en-2-yl)-4,10-dioxa-3,11-disilatridecan-6-ol (247)



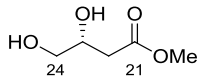
Colourless oil; R_f: 0.40 (10% EtOAc/hexane); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −36.4 (*c* 0.22, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2955, 2929, 2858, 1472, 1253, 1064, 909, 833, 774, 668; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, m, 11-*H*), 5.03-4.92 (2H, m, 12-*H*), 3.74 (1H, t, *J* 5.9, 2-*H*), 3.67-3.62 (2H, m, 4-*H* and 1-*H*H), 3.54-3.50 (2H, m, 5-*H* and 1-H*H*), 3.19 (1H, d, *J* 9.5, 3-*H*), 2.09-2.03 (2H, m, 10-*H*), 1.87-1.67 (4H, m, 6-*H*, 7-*H*H and NH_2), 1.45-1.33 (3H, m, 9-*H* and 8-*H*H), 1.21 (1H, m, 8-H*H*), 1.04 (1H, m, 7-H*H*), 0.98 (3H, d, *J* 6.6, 6-(CH_3)), 0.91, 0.89 and 0.89 (3 x 9H, s, 3 x SiC(CH_3)$_3$), 0.15, 0.13, 0.11, 0.09 and 0.06 (6 x 3H, s, 6 x SiCH_3); δ_C (100 MHz, $CDCl_3$) 139.1 (11-*C*), 114.2 (12-*C*), 80.3 (5-*C*), 73.7 (4-*C*), 68.2 (2-*C*), 65.5 (1-*C*), 53.0 (3-*C*), 34.6 (6-*C*), 33.9 (10-*C*), 33.0 (7-*C*), 29.4 (9-*C*), 26.5 (8-*C*), 26.0 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 18.2 (Si*C*$(CH_3)_3$), 18.1 (Si*C*$(CH_3)_3$), 18.0 (Si*C*$(CH_3)_3$), 17.6 (6-(*C*H_3)), −3.5 (Si*C*H_3), −3.5 (Si*C*H_3), −4.9 (Si*C*H_3), −5.3 (Si*C*H_3), −5.4 (Si*C*H_3), −5.4 (Si*C*H_3); *m/z* (ES^+) 604 (MH^+, 100%), 719 ((MH_2^+, 40); *m/z* HRMS (ES^+) MH^+ calculated for $C_{31}H_{70}NO_4Si_3$ 604.4607, observed 604.4628.

(2*S*,3*S*,4*S*,5*S*,6*S*)-3-Amino-4,5-bis((*tert*-butyldimethylsilyl)oxy)-6-methyldodec-11-ene-1,2-diol (248)



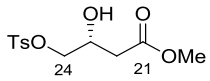
Colourless oil; R_f: 0.50 (50% EtOAc/hexane); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −9.6 (*c* 0.23, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2928, 2857, 1471, 1252, 1063, 968, 835, 774, 701; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, m, 11-*H*), 5.02-4.92 (2H, m, 12-*H*), 3.82-3.79 (2H, m, 2- and 3- or 4-*H*), 3.72 (1H, dd, *J* 12.0 and 3.2, 1-*H*H), 3.59 (1H, dd, *J* 12.0 and 2.5, 1-H*H*), 3.36 (1H, dd, *J* 7.3 and 4.1, 3- or 4-*H*), 3.30 (1H, d, *J* 9.5, 5-*H*), 2.91-2.51 (2H, m, 2 x O*H* or N*H*), 2.09-2.03 (2H, m, 10-*H*), 1.81 (1H, m, 7-*H*H), 1.73 (1H, m, 6-*H*), 1.47-1.34 (3H, m, 9-*H* and 8-*H*H), 1.23 (1H, m, 8-H*H*), 1.05 (1H, m, 7-H*H*), 0.94 and 0.93 (2 x 9H, s, 2 x SiC(C*H*$_3$)$_3$), 0.79 (3H, d, *J* 6.6, 6-(C*H*$_3$)), 0.16, 0.16, 0.14 and 0.12 (6 x 3H, s, 6 x SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 139.3 (11-*C*), 114.0 (12-*C*), 77.0 (5-*C*), 73.2 (2-*C*), 70.1 (3-*C*), 64.7 (1-*C*), 58.2 (4-*C*), 35.0 (6-*C*), 33.8 (10-*C*), 32.0 (7-*C*), 29.3 (9-*C*), 26.4 (8-*C*), 25.9 (SiC(*C*H$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 15.5 (6-(*C*H$_3$)), −4.2 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.5 (Si*C*H$_3$), −4.6 (Si*C*H$_3$); *m/z* (ES^+) 490 (MH^+, 100%), 491 ((MH_2^+, 35); *m/z* HRMS (ES^+) MH^+ calculated for $C_{25}H_{56}NO_4Si_2$ 490.3742, observed 490.3740.

Methyl (*R*)-3,4-dihydroxybutanoate (84)[11]



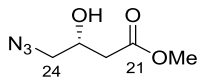
Neat borane dimethyl sulfide complex (3.18 mL, 33.6 mmol) was added dropwise to a solution of (*R*)-dimethyl malate **83** (5.18 g, 31.9 mmol) in THF (68 mL) at room temperature. The mixture was stirred at room temperature until evolution of hydrogen gas ceased (approx. 30 minutes). Then the mixture was cooled to 0 ºC and stirred for further 30 minutes. Sodium borohydride (60.0 mg, 1.60 mmol) was added in one portion and once the exothermic reaction had subsided (approx. 15 minutes), the mixture was warmed to room temperature and stirred for 30 minutes. Methanol (11.0 mL) and *p*-Toluenesulfonic acid (304 mg) were added, the reaction mixture was stirred for 1.5 h and then concentrated *in vacuo*. The residue was dissolved in benzene and methanol, and the resulting solution was concentrated again; this operation was repeated. Benzene was added to the residue and the solution was concentrated, which was repeated to eliminate methanol and $B(OMe)_3$. Purification by flash column chromatography (5-100% EtOAc/petrol) afforded diol **84** (2.89 g, 68%) as a colourless oil; R_f: 0.25 (EtOAc); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +25.7 (*c* 0.40, $CHCl_3$) (lit.[96] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +13.8 (*c* 2.27, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 4.13 (1H, m, 23-*H*), 3.71 (3H, s, OC*H*$_3$), 3.66 (1H, m, 24-*H*H), 3.53 (1H, m, 24-H*H*), 2.60-2.45 (2H, m, 22-*H*); δ_C (100 MHz, $CDCl_3$) 173.0 (21-*C*), 68.5 (23-*C*), 65.7 (24-*C*), 51.9 (O*C*H$_3$), 37.5 (22-*C*). All data were in agreement with those previously reported.[11]

Methyl (*R*)-3-hydroxy-4-(tosyloxy)butanoate (84a)[11]



p-Toluenesulfonyl chloride (4.31 g, 22.6 mmol) was added to a solution of **84** (2.89 g, 21.5 mmol) in pyridine (57.0 mL) at 0 °C. The mixture was warmed slowly to room temperature, stirred for 12 h and then concentrated *in vacuo* with toluene (x 2). Purification by flash column chromatography (30-50% EtOAc/petrol) afforded alcohol **84a** (4.60 g, 74%) as a colourless solid; R_f: 0.50 (50% EtOAc); m. p. 79-81 °C (lit.[11] m. p. 81-82 °C); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +0.6 (*c* 1.92, $CHCl_3$) (lit.[11] $[\alpha]_{\mathbf{D}}^{\mathbf{26}}$ +6.8 (*c* 1.10, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.3, Ph*H*), 7.33 (2H, d, *J* 8.3, Ph*H*), 4.23 (1H, m, 23-*H*), 4.01 (2H, d, *J* 5.1, 24-*H*), 3.66 (3H, s, OCH_3), 3.26 (1H, d, *J* 5.0, O*H*), 2.51 (2H, dd, *J* 5.1 and 3.8, 22-*H*), 2.42 (3H, s, ArCH_3); δ_C (100 MHz, $CDCl_3$) 171.7 (21-*C*), 145.0 ($C_{(Ar)}$), 132.3 ($C_{(Ar)}$), 129.8 ($CH_{(Ar)}$), 127.8 ($CH_{(Ar)}$), 72.0 (24-*C*), 65.8 (23-*C*), 51.9 (OCH_3), 37.1 (22-*C*), 21.5 (ArCH_3). All data were in agreement with those previously reported.[11]

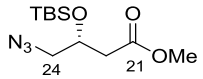
Methyl (*R*)-4-azido-3-hydroxybutanoate (85)[11]



Sodium azide (5.20 g, 79.8 mmol) was added to a solution of **85** (4.60 g, 15.9 mmol) in DMF (45.0 mL) at room temperature. The mixture was heated at 80 °C for 3 h. Then it was diluted with EtOAc and washed with brine (x 3), dried (Na_2SO_4), filtered and concentrated

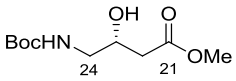
in vacuo. Purification by flash column chromatography (30% EtOAc/petrol) afforded azide **85** (1.64 g, 65%) as a colourless oil; R_f: 0.50 (30% EtOAc); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +13.9 (*c* 0.26, $CHCl_3$) (lit.[11] $[\alpha]_{\mathbf{D}}^{\mathbf{26}}$ +19.6 (*c* 1.03, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 4.22 (1H, m, 23-*H*), 3.74 (3H, s, OCH_3), 3.66 (2H, dd, *J* 6.3 and 6.3, 24-*H*), 3.17 (1H, m, O*H*), 2.58-2.55 (2H, m, 22-*H*); δ_C (100 MHz, $CDCl_3$) 172.5 (21-*C*), 67.3 (23-*C*), 55.5 (24-*C*), 52.0 (OCH_3), 38.1 (22-*C*). All data were in agreement with those previously reported.[11]

Methyl (*R*)-4-azido-3-((*tert*-butyldimethylsilyl)oxy)butanoate (283)[10]



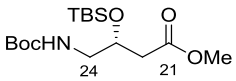
tert-Butyldimethylsilyl chloride (3.66 g, 24.3 mmol) was added to a solution of **85** (1.93 g, 12.1 mmol) and imidazole (3.30 g, 48.5 mmol) in DMF (40.0 mL) at 0 ^oC. The solution was then warmed to room temperature and stirred for 16 h. The reaction was diluted with EtOAc and washed with brine (x 3), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol-2% EtOAc/petrol) afforded silyl ether **283** (3.24 g, 98%) as a colourless oil; R_f: 0.80 (30% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +3.4 (*c* 0.70, $CHCl_3$) (lit.[10] not reported); δ_H (400 MHz, $CDCl_3$) 4.26 (1H, m, 23-*H*), 3.68 (3H, s, OCH_3), 3.37 (1H, dd, *J* 12.5 and 4.4, 24-*H*H), 3.23 (1H, dd, *J* 12.5 and 5.4, 24-H*H*), 2.56 (2H, dd, *J* 6.1 and 3.2, 22-*H*), 0.89 (9H, s, SiC(CH_3)$_3$), 0.13 (3H, s, SiCH_3), 0.09 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 171.3 (21-*C*), 68.7 (23-*C*), 56.4 (24-*C*), 51.7 (OCH_3), 39.9 (22-*C*), 25.6 (SiC(*C*H_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), −4.7 (Si*C*H_3), −5.1 (Si*C*H_3). All data were in agreement with those previously reported.[10]

Methyl (*R*)-4-((*tert*-butoxycarbonyl)amino)-3-hydroxybutanoate (86)[11]



EtOAc (HPLC grade) (20 mL) and di-*tert*-butyl dicarbonate (4.03 mL, 17.5 mmol) were added sequentially to azide **85** (1.64 g, 10.3 mmol) and palladium on carbon (500 mg, 10% wt.). The mixture was stirred under an atmospheric (balloon) pressure of hydrogen for 24 h. The solution was then filtered through Celite, washing with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (30-50% EtOAc/petrol) afforded protected amine **86** (2.33 g, 97%) as a colourless oil; R_f: 0.25 (30% EtOAc); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +6.4 (*c* 0.13, $CHCl_3$) (lit.[11] $[\alpha]_{\mathbf{D}}^{\mathbf{26}}$ +5.4 (*c* 1.06, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 5.01 (1H, br s, N*H*), 4.12 (1H, m, 23-*H*), 3.72 (3H, s, OCH_3), 3.51 (1H, br s, O*H*), 3.32 (1H, m, 24-*H*H), 3.13 (1H, ddd, *J* 13.9, 13.9 and 6.9, 24-H*H*), 2.51-2.49 (2H, m, 22-*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 172.9 (21-*C*), 156.6 (*C*(O)), 79.7 ($CO_2C(CH_3)_3$), 67.7 (23-*C*), 51.9 (OCH_3), 45.5 (24-*C*), 38.4 (22-*C*), 28.3 ($CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[11]

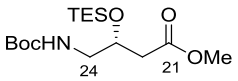
Methyl (*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate (250)



tert-Butyldimethylsilyl chloride (759 mg, 5.04 mmol) was added to a solution of alcohol **86** (522 mg, 2.24 mmol) and imidazole (763 mg, 11.2 mmol) in DMF (6.5 mL) at

0 °C. The solution was then warmed to room temperature and stirred for 16 h. The reaction was diluted with EtOAc and washed with brine (x 3), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded silyl ether **250** (721 mg, 93%) as a colourless oil; R_f: 0.25 (10% EtOAc/petrol); $[\alpha]_D^{20}$ +5.5 (*c* 0.80, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2931, 1718, 1509, 1437, 1366, 1252, 1169, 1114, 1006, 836, 779; δ_H (400 MHz, $CDCl_3$) 4.75 (1H, m, N*H*), 4.23 (1H, m, 23-*H*), 3.68 (3H, s, OC*H*$_3$), 3.25-3.18 (2H, m, 24-*H*), 2.47 (2H, d, *J* 6.1, 22-*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.09 (3H, s, Si*CH*$_3$), 0.06 (3H, s, Si*CH*$_3$); δ_C (100 MHz, $CDCl_3$) 171.6 (21-*C*), 155.9 (*C*(O)), 79.3 ($CO_2C(CH_3)_3$), 68.4 (23-*C*), 51.6 (OCH_3), 46.0 (24-*C*), 40.1 (22-*C*), 28.4 ($CO_2C(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), −4.7 ($SiCH_3$), −5.0 ($SiCH_3$); *m/z* (ES^+) 370 (MNa^+, 100%), 248 ($(M-Boc)H^+$, 90); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{16}H_{33}O_5NSiNa$ 370.2020, observed 370.2015.

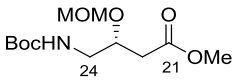
Methyl (*R*)-4-((*tert*-butoxycarbonyl)amino)-3-((triethylsilyl)oxy)butanoate (250a)



Triethylchlorosilane (0.82 mL, 4.88 mmol) was added to a solution of alcohol **86** (454 mg, 1.95 mmol) and imidazole (664 mg, 9.75 mmol) in DMF (5.60 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 16 h. The reaction was diluted with EtOAc and washed with brine (x 3), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-15-25% EtOAc/petrol) afforded silyl ether **250a** (451 mg, 67%) as a colourless oil; R_f: 0.80 (50% EtOAc/petrol); $[\alpha]_D^{20}$ +14.0

(*c* 0.49, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2955, 1718, 1508, 1437, 1366, 1246, 1167, 1115, 1005, 859, 727; δ_H (400 MHz, $CDCl_3$) 4.79 (1H, m, N*H*), 4.24 (1H, m, 23-*H*), 3.68 (3H, s, OC*H*$_3$), 3.23-3.20 (2H, m, 24-*H*), 2.48 (2H, d, *J* 6.3, 22-*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$), 0.95 (9H, t, *J* 7.9, $Si(CH_2CH_3)_3$), 0.61 (6H, q, *J* 7.9, $Si(CH_2CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.6 (21-*C*), 155.9 (*C*(O)), 78.7 ($CO_2C(CH_3)_3$), 68.2 (23-*C*), 51.6 (OCH_3), 46.1 (24-*C*), 40.1 (22-*C*), 28.4 ($CO_2C(CH_3)_3$), 6.7 ($Si(CH_2CH_3)_3$), 4.7 ($Si(CH_2CH_3)_3$); *m/z* (ES^+) 370 (MNa^+, 100%), 248 ($(M-Boc)H^+$, 50); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{16}H_{33}O_5NSiNa$ 370.2020, observed 370.2021.

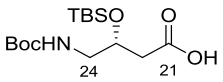
Methyl (*R*)-4-((*tert*-butoxycarbonyl)amino)-3-(methoxymethoxy)butanoate (278)



Iodomethyl methyl ether (40.0 μL, 46.4 μmol) was added to a solution of alcohol **86** (54.0 mg, 23.2 μmol) and Proton-sponge® (150 mg, 69.5 μmol) in THF (2.00 mL) at 0 ºC. The solution was then warmed to room temperature and stirred for 5 h. The solution was filtered through Celite, washing with EtOAc, and concentrated *in vacuo*. Purification by flash column chromatography (30-40-50% EtOAc/petrol) afforded methoxymethyl ether **278** (57.9 mg, 90%) as a colourless oil; R_f: 0.60 (50% EtOAc/petrol); $[\alpha]_D^{20}$ +1.4 (*c* 0.28, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2976, 1739, 1714, 1519, 1439, 1367, 1250, 1169, 1103, 1034, 919; δ_H (400 MHz, $CDCl_3$) 5.02 (1H, br s, N*H*), 4.64 (2H, m, OCH_2OCH_3), 4.04 (1H, m, 23-*H*), 3.66 (3H, s, OC*H*$_3$), 3.33 (3H, s, OCH_2OCH_3), 3.29-3.22 (2H, m, 24-*H*), 2.52 (2H, dd, *J* 9.9 and 7.5, 22-*H*), 1.41 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.3 (21-*C*), 155.9 (*C*(O)), 96.5 (OCH_2OCH_3), 79.2 ($CO_2C(CH_3)_3$), 74.4 (23-*C*), 55.6

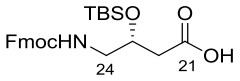
(OCH_2OCH_3), 51.7 (OCH_3), 43.9 (24-*C*), 37.9 (22-*C*), 28.3 ($CO_2C(CH_3)_3$); *m/z* (ES^+) 300 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{12}H_{23}O_6NNa$ 300.1418, observed 300.1414.

(*R*)-4-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanoic acid (154)



Lithium hydroxide (71.0 mg, 2.96 mmol) was added to a solution of ester **250** (517 mg, 1.49 mmol) in THF/MeOH/H_2O (15 mL, 2:2:3) at room temperature. The mixture was stirred for 3 h and then acidified to pH 3-4 by the slow addition of aqueous solution of citric acid (10%). The aqueous layer was then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid **154** (502 mg, quant.) as a colourless solid; R_f: 0.50 (50% EtOAc/petrol); m. p. 78-81 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +26.8 (*c* 0.42, MeOH); ν_{max}/cm^{-1} (neat) 2931, 1712, 1658, 1396, 1268, 1169, 1098, 950, 830, 776; δ_H (400 MHz, CD_3OD) 5.00 (2H, br s, N*H* and O*H*), 4.20 (1H, m, 23-*H*), 3.14 (1H, dd, *J* 13.7 and 6.1, 24-*H*H), 3.04 (1H, dd, *J* 13.7 and 6.1, 24-H*H*), 2.48 (1H, dd, *J* 14.9 and 4.2, 22-*H*H), 2.30 (1H, dd, *J* 14.9 and 8.1, 22-*H*H), 1.44 (9H, s, $CO_2C(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); δ_C (100 MHz, CD_3OD) 173.6 (21-*C*), 158.5 (*C*(O)), 80.3 ($CO_2C(CH_3)_3$), 70.3 (23-*C*), 47.5 (24-*C*), 41.8 (22-*C*), 28.9 ($CO_2C(CH_3)_3$), 26.5 ($SiC(CH_3)_3$), 19.0 ($SiC(CH_3)_3$), −4.2 ($SiCH_3$), −4.6 ($SiCH_3$); *m/z* (ES^+) 356 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{15}H_{31}NO_5SiNa$ 356.1864, observed 356.1864.

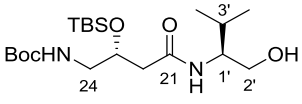
(*R*)-4-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanoic acid (284)



Lithium hydroxide (168 mg, 7.02 mmol) was added to a solution of ester **283** (640 mg, 2.34 mmol) in THF/MeOH/H_2O (23.4 mL, 2:2:3) at room temperature. The mixture was stirred for 2 h and then acidified to pH 3-4 by the slow addition of aqueous HCl (1 M) solution. The aqueous layer was then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. EtOAc (HPLC grade) (10 mL) was added to the crude carboxylic acid and palladium on carbon (170 mg, 25% wt.), and the mixture was stirred under an atmospheric (balloon) pressure of hydrogen at room temperature for 48 h. The solution was then filtered through Celite, washing with $CHCl_3$/MeOH (1:1), and concentrated *in vacuo*. Fmoc *N*-hydroxysuccinimide ester (829 mg, 2.46 mmol) was added to a solution of the crude amino acid in CH_3CN/saturated aqueous $NaHCO_3$ (12.0 mL, 1:1) at room temperature. The mixture was stirred for 16 h and then acidified to pH 3-4 by the slow addition of aqueous HCl (1 M) solution. The aqueous layer was then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-30-60-100% EtOAc/petrol) afforded acid **284** (650 mg, 61% over 3 steps) as a colourless foam; R_f: 0.50 (EtOAc); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +3.2 (*c* 0.28, MeOH); ν_{max}/cm^{-1} (neat) 2929, 1710, 1520, 1450, 1252, 1109, 1004, 835, 777, 740; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 7.6, 2 x Ar*H*), 7.61-7.58 (2H, m, 2 x Ar*H*), 7.41 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 7.32 (2H, d, *J* 7.6, 2 x Ar*H*), 5.04 (1H, t, *J* 5.9, N*H*), 4.43 (2H, d, *J* 6.9,

OC*H*$_2$CH), 4.26-4.21 (2H, m, OCH$_2$C*H* and 23-*H*), 3.34-3.30 (2H, m, 24-*H*), 2.51 (2H, d, *J* 5.9, 22-*H*), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.10 (3H, s, SiC*H*$_3$), 0.09 (3H, s, SiC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 175.4 (21-*C*), 156.6 (*C*(O)), 143.8 ($C_{(Ar)}$), 141.3 ($C_{(Ar)}$), 127.7 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 125.0 ($CH_{(Ar)}$), 120.0 ($CH_{(Ar)}$), 68.00 (OCH$_2$*C*H or 23-*C*), 66.8 (O*C*H$_2$CH), 47.2 (OCH$_2$*C*H or 23-*C*), 46.2 (24-*C*), 39.8 (22-*C*), 26.7 (SiC(*C*H$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), −4.8 (Si*C*H$_3$), −4.9 (Si*C*H$_3$); *m/z* (ES^+) 456 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{25}H_{34}NO_5Si$ 456.2201, observed 456.2195.

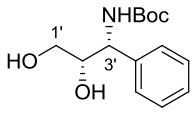
tert-Butyl ((_R_)-2-((_tert_-butyldimethylsilyl)oxy)-4-(((_S_)-1-hydroxy-3-methylbutan-2-yl)amino)-4-oxobutyl)carbamate (258)



HOBt (17.0 mg, 0.13 mmol) was added to a solution of acid **154** (39.0 mg, 0.12 mmol) in DMF (0.50 mL) at room temperature and the mixture was cooled to 0 °C. EDAC (24.0 mg, 0.13 mmol) was added, and the mixture was stirred for 10 minutes. *N*,*N*-diisopropylethylamine (68.0 μL, 0.39 mmol) and a solution of (*S*)-(+)-2-amino-3-methyl-1-butanol **257** (10.0 mg, 0.10 mmol) in DMF (0.50 mL) were then added sequentially. The mixture was warmed slowly to room temperature and stirred for 16 h. The solution was then diluted with EtOAc, washed with citric acid (10%) and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-100% EtOAc/petrol) afforded amide **258** (721 mg, 93%) as a colourless oil; R_f: 0.60 (EtOAc); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −7.6 (*c* 0.25, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3320 (br), 2958, 2929, 2857, 1694, 1647, 1531, 1472, 1390, 1366, 1252, 1171,

1083, 1005, 978, 955, 832, 777, 667; δ_H (400 MHz, $CDCl_3$) 6.68 (1H, d, *J* 7.1, N*H*), 4.94 (1H, m, N*H*), 4.14 (1H, m, 23-*H*), 3.75-3.62 (3H, m, 1'- and 2'-*H*), 3.31 (1H, ddd, *J* 13.7, 7.1 and 5.4, 24-*H*H), 3.11 (1H, ddd, *J* 13.7, 13.7 and 5.4, 24-H*H*), 2.47 (1H, dd, *J* 14.2 and 6.4, 22-*H*H), 2.40 (1H, dd, *J* 14.2 and 4.4, 22-H*H*), 1.92 (1H, m, 3'-*H*), 1.44 (9H, s, $CO_2C(CH_3)_3$), 0.97 (6H, dd, *J* 6.6 and 6.6, 2 x 3'-(CH_3)), 0.90 (9H, s, $SiC(CH_3)_3$), 0.11 (6H, s, 2 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 171.4 (21-*C*), 156.4 (*C*(O)), 79.7 ($CO_2C(CH_3)_3$), 68.7 (23-*C*), 64.2 (2'-*C*), 57.7 (1'-*C*), 45.2 (24-*C*), 42.0 (22-*C*), 29.0 (3'-*C*), 28.4 ($CO_2C(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 19.5 (3'-(CH_3)), 18.8 (3'-(CH_3)), 18.0 ($SiC(CH_3)_3$), −4.8 ($SiCH_3$), −4.9 ($SiCH_3$); *m/z* (ES^+) 419 (MH^+, 100%), 441 (MNa^+, 30); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{20}H_{42}N_2O_5SiNa$ 441.2755, observed 441.2744.

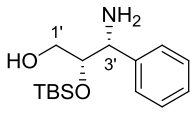
tert-Butyl ((1*R*,2*S*)-2,3-dihydroxy-1-phenylpropyl)carbamate (261)



A solution of sodium hydroxide (75.0 mg, 1.88 mmol) in H_2O (4.60 mL) was added to a solution of *tert*-butyl carbamate (224 mg, 1.91 mmol) in *n*-PrOH (2.50 mL) at room temperature, followed by a freshly prepared[97] solution of *tert*-butyl hypochlorite (0.21 mL, 1.88 mmol). A solution of $(DHQD)_2PHAL$ (24.0 mg, 30.0 μmol) in *n*-PrOH (2.10 mL) was then added and the mixture was stirred until homogeneous. Methyl cinnamate **259** (100 mg, 0.62 mmol) and potassium osmate(VI) dihydrate (9.00 mg, 25.0 μmol) were added sequentially to the mixture. The reaction mixture was stirred for 2 h. After which saturated aqueous sodium sulfite was added to quench the reaction and the solution was stirred at room temperature for 20 minutes. The aqueous layer was separated and extracted

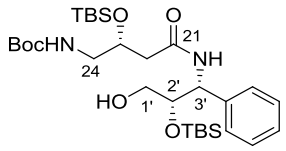
with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-30% EtOAc/petrol) afforded amino alcohol **260** as a colourless solid. Lithium borohydride (0.46 mL of a 4 M solution in THF, 1.85 mmol) was added slowly to a solution of amino alcohol **260** in THF (6.10 mL) at 0 °C. Methanol (82.0 μL, 2.04 mmol) was then added slowly and once the exothermic reaction had subsided (approx. 15 minutes), the mixture was warmed to room temperature and stirred for 1 h. Aqueous sodium hydroxide (5.0 mL of a 1 M solution) was added slowly and the aqueous layer then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (60-90% EtOAc/petrol) afforded alcohol **261** (117 mg, 71% over 2 steps) as a colourless solid; R_f: 0.25 (60% EtOAc/petrol); m. p. 63-65 °C (lit.[98] m. p. 74 °C); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −0.3 (*c* 0.27, $CHCl_3$) (lit.[98] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −19.9 (*c* 0.40, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.39-7.28 (5H, m, Ph*H*), 5.74 (1H, br s, N*H* or O*H*), 4.77 (1H, br s, N*H* or O*H*), 3.89-3.70 (3H, m, 2'-, 3'-*H* and O*H*), 3.53-3.52 (2H, m, 1'-*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.5 (*C*(O)), 140.0 ($C_{(Ar)}$), 128.5 ($CH_{(Ar)}$), 127.4 ($CH_{(Ar)}$), 126.7 ($CH_{(Ar)}$), 80.0 ($CO_2C(CH_3)_3$), 74.8 (2'- or 3'-*C*), 63.6 (1'-*C*), 55.7 (2'- or 3'-*C*), 28.2 ($CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[98]

(2*S*,3*R*)-3-Amino-2-((*tert*-butyldimethylsilyl)oxy)-3-phenylpropan-1-ol (262)



tert-Butyldimethylsilyl trifluoromethanesulfonate (0.60 mL, 2.63 mmol) was added dropwise to a solution of **261** (117 mg, 0.44 mmol) and 2,6-lutidine (0.61 mL, 5.26 mmol) in CH_2Cl_2 (4.40 mL) at 0 ºC. The mixture was warmed to room temperature and stirred for 12 h before being quenched with saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with CH_2Cl_2. The organic layer was then washed with 1M HCl (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2/MeOH (4.40 mL, 1:1) and (±)-camphor 10-sulfonic acid (204 g, 0.88 mmol) was added in one portion at 0 ºC. The mixture was then warmed to room temperature and stirred for 22 h. Saturated aqueous $NaHCO_3$ was added and the aqueous layer was then separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (60-80-100% EtOAc/petrol) afforded aminoalcohol **262** (68 mg, 55% over 2 steps) as a colourless oil; R_f: 0.20 (60% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +20.2 (*c* 0.27, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2928, 2857, 1739, 1471, 1362, 1253, 1058, 834, 775, 700; δ_H (400 MHz, $CDCl_3$) 7.36-7.26 (5H, m, Ph*H*), 4.21 (1H, d, *J* 4.2, 3'-*H*), 3.82 (1H, dt, *J* 4.2 and 4.2, 2'-*H*), 3.68-3.65 (2H, m, 1'-*H*), 2.53 (3H, br s, NH_2 and O*H*), 0.90 (9H, s, SiC(CH_3)$_3$), 0.00 (3H, s, SiCH_3), −0.19 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 143.3 ($C_{(Ar)}$), 128.2 ($CH_{(Ar)}$), 127.2 ($CH_{(Ar)}$), 126.9 ($CH_{(Ar)}$), 76.4 (2'-*C*), 65.4 (1'-*C*), 58.2 (3'-*C*), 25.8 (SiC(CH_3)$_3$), 18.1 (Si*C*(CH_3)$_3$), −4.7 (SiCH_3), −5.3 (SiCH_3); *m/z* (ES^+) 282 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{15}H_{28}NO_2Si$ 282.1884, observed 282.1887.

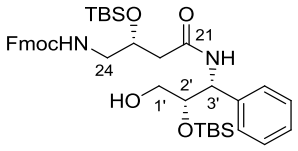
***tert*-Butyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((1*R*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-1-phenylpropyl)amino)-4-oxobutyl)carbamate (264)**



Cyanuric fluoride (24.0 μL, 0.28 mmol) was added dropwise to a solution of **154** (79.0 mg, 0.24 mmol) and pyridine (19.0 μL, 0.24 mmol) in CH_2Cl_2 (2.30 mL) at room temperature. The mixture was stirred for 3 h. The reaction was diluted with CH_2Cl_2 and washed with ice-cold water (x 1), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid fluoride **263** as an orange oil, which was used without further purification in the subsequent step. 4-Methylmorpholine (32.0 μL, 0.29 mmol), hexamethyldisiloxane (41.0 μL, 0.19 mmol), a solution of freshly prepared acid fluoride **263** in CH_2Cl_2 (0.50 mL) were added sequentially to a solution of **262** (27.0 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) at room temperature. The mixture was stirred for 20 minutes and then concentrated *in vacuo*. Purification by flash column chromatography (20-30% EtOAc/petrol) afforded amide **264** (43.0 mg, 72%) as a colourless solid; R_f: 0.20 (30% EtOAc/petrol); m. p. 135-137 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +17.5 (*c* 0.11, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3303, 2952, 2887, 1712, 1638, 1537, 1365, 1249, 1171, 1099, 1053, 967, 829, 777, 699; δ_H (400 MHz, $CDCl_3$) 7.86 (1H, d, *J* 9.3, N*H*), 7.43-7.29 (5H, m, Ph*H*), 5.41 (1H, d, *J* 9.3, 3'-*H*), 4.96 (1H, m, N*H* or O*H*), 4.26 (1H, m, N*H* or O*H*), 4.19 (1H, m, 23-*H*), 3.95 (1H, dt, *J* 5.1 and 5.1, 2'-*H*), 3.68-3.59 (2H, m, 1'-*H*H and 24-*H*H), 3.32 (1H, dd, *J* 9.3 and 9.3, 1'-H*H*), 3.15 (1H, ddd, *J* 14.2, 14.2 and 4.7, 24-H*H*), 2.64 (1H, dd, *J* 13.5 and 7.8,

22-*H*H), 2.43 (1H, dd, *J* 13.5 and 3.7, 22-H*H*), 1.52 (9H, s, $CO_2C(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.81 (9H, s, $SiC(CH_3)_3$), 0.15 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$), −0.14 (3H, s, $SiCH_3$), −0.51 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 171.4 (21-*C*), 156.8 (*C*(O)), 139.2 ($C_{(Ar)}$), 128.2 ($CH_{(Ar)}$), 127.3 ($CH_{(Ar)}$), 127.2 ($CH_{(Ar)}$), 79.9 ($CO_2C(CH_3)_3$), 76.0 (2'-*C*), 69.3 (23-*C*), 63.2 (1'-*C*), 53.5 (3'-*C*), 44.8 (24-*C*), 42.1 (22-*C*), 28.4 ($CO_2C(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), −4.8 (2 x $SiCH_3$), −5.0 ($SiCH_3$), −5.9 ($SiCH_3$); *m/z* (ES^+) 597 (MH^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{30}H_{56}N_2O_6Si_2Na$ 619.3569, observed 619.3576.

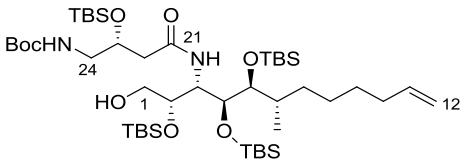
(9*H*-Fluoren-9-yl)methyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((1*R*,2*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-1-phenylpropyl)amino)-4-oxobutyl) carbamate (285)



Cyanuric fluoride (10.0 μL, 103 μmol) was added dropwise to a solution of **284** (39.0 mg, 86.0 μmol) and pyridine (7.00 μL, 86.0 μmol) in CH_2Cl_2 (0.80 mL) at room temperature. The mixture was stirred for 3 h. The reaction was diluted with CH_2Cl_2 and washed with ice-cold water (x 1), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid fluoride **286** as a yellow solid, which was used without further purification in the subsequent step. 4-Methylmorpholine (12.0 μL, 105 μmol), hexamethyldisiloxane (15.0 μL, 70.0 μmol), a solution of freshly prepared acid fluoride **286** in CH_2Cl_2 (0.30 mL) were added sequentially to a solution of **262** (11.0 mg, 39.0 μmol) in CH_2Cl_2 (0.20 mL) at room temperature. The mixture was stirred for 30 minutes and then concentrated *in vacuo*.

Purification by flash column chromatography (20-30% EtOAc/petrol) afforded amide **285** (18.8 mg, 75%) as a colourless foam; R_f: 0.20 (30% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +9.8 (*c* 1.25, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3306, 2929, 1726, 1631, 1539, 1450, 1362, 1248, 1118, 1049, 989, 833, 778, 758, 741, 699, 623; δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 7.5, 2 x Ar*H*), 7.61 (2H, d, *J* 7.5, 2 x Ar*H*), 7.42 (2H, dd, *J* 7.5 and 7.5, 2 x Ar*H*), 7.36-7.24 (8H, m, 7 x Ar*H* and N*H*), 5.38 (1H, d, *J* 9.4, 3'-*H*), 4.47-4.42 (2H, m, OCH_2CH), 4.28-4.19 (2H, m, 23-*H* and OCH_2CH), 3.96-3.92 (2H, m, 2'-*H* and O*H*), 3.66-3.59 (2H, m, 1'-*H*H and 24-*H*H), 3.36 (1H, dd, *J* 10.5 and 10.5, 1'-H*H*), 3.22 (1H, ddd, *J* 13.9, 13.9 and 5.0, 24-H*H*), 2.54 (1H, dd, *J* 14.0 and 6.9, 22-*H*H), 2.41 (1H, dd, *J* 14.0 and 4.2, 22-H*H*), 0.88 (9H, s, SiC(CH_3)$_3$), 0.77 (9H, s, SiC(CH_3)$_3$), 0.12 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3), −0.51 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 171.2 (21-*C*), 157.1 (*C*(O)), 143.9 ($C_{(Ar)}$), 141.3 ($C_{(Ar)}$), 139.2 ($C_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 127.7 ($CH_{(Ar)}$), 127.3 ($CH_{(Ar)}$), 127.1 ($CH_{(Ar)}$), 127.1 ($CH_{(Ar)}$), 125.0 ($CH_{(Ar)}$), 120.0($CH_{(Ar)}$), 76.0 (2'-*C*), 68.9 (23-*C*), 66.9 (O*C*H_2CH), 63.3 (1'-*C*), 53.5 (3'-*C*), 47.3 (OCH_2CH), 45.3 (24-*C*), 42.0 (22-*C*), 25.8 (SiC(*C*H_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), −4.8 (2 x Si*C*H$_3$), −5.0 (Si*C*H$_3$), −5.7 (Si*C*H$_3$); *m/z* (ES$^+$) 719 (MH$^+$, 100%); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{40}H_{59}N_2O_6Si_2$ 719.3906, observed 719.3891.

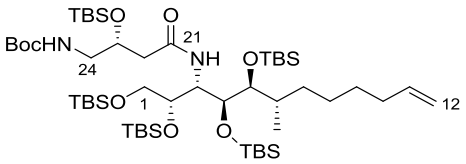
***tert*-Butyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((5*S*,6*S*,7*S*,8*S*)-7-((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2,2,3,3,10,10,11,11-octamethyl-8-((*S*)-oct-7-en-2-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)amino)-4-oxobutyl)carbamate (243)**



Cyanuric fluoride (33.0 μL, 0.38 mmol) was added dropwise to a solution of **154** (89.0 mg, 0.27 mmol) and pyridine (22.0 μL, 0.27 mmol) in CH_2Cl_2 (2.60 mL) at room temperature. The mixture was stirred for 3 h. The reaction was diluted with CH_2Cl_2 and washed with ice-cold water (x 1), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid fluoride **263** as an orange oil, which was used without further purification in the subsequent step. 4-Methylmorpholine (29.0 μL, 0.26 mmol), hexamethyldisiloxane (37.0 μL, 0.17 mmol), a solution of freshly prepared acid fluoride **263** in CH_2Cl_2 (0.45 mL) were added sequentially to a solution of **241** (52.4 mg, 0.09 mmol) in CH_2Cl_2 (0.45 mL) at room temperature. The mixture was stirred for 20 minutes and then concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded amide **243** (50.7 mg, 64%) as a colourless oil; R_f: 0.20 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −22.5 (*c* 0.04, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3428, 2954, 2929, 1720, 1658, 1516, 1471, 1365, 1170, 1090, 1058, 938, 832, 774, 671; δ_H (400 MHz, $CDCl_3$) 6.28 (1H, br s, N*H*), 5.79 (1H, m, 11-*H*), 5.01-4.92 (2H, m, 12-*H*), 4.84 (1H, m, N*H*), 4.36 (1H, dd, *J* 10.0 and 4.9, O*H*), 4.21-4.14 (2H, m, 23- and 3-*H*), 4.08-4.00 (2H, m, 4- and 2-*H*), 3.58 (1H, ddd, *J* 10.0, 10.0 and 5.4, 1-*H*H), 3.48 (1H, dd, *J* 9.3 and 2.5, 5-*H*), 3.25-3.14 (3H, m, 24-*H* and 1-H*H*), 2.48-2.27 (2H, m, 22-*H*), 2.06-2.01 (2H, m, 10-*H*),

1.62 (1H, m, 6-*H*), 1.52 (1H, m, 7-*H*H), 1.43 (9H, s, $CO_2C(CH_3)_3$), 1.41-1.25 (3H, m, 9-*H* and 8-*H*H), 1.10 (1H, m, 8-H*H*), 0.99 (3H, d, *J* 6.6, 6-(CH_3)), 0.94, 0.89, 0.88 and 0.87 (4 x 9H, s, 4 x $SiC(CH_3)_3$), 0.84 (1H, m, 7-H*H*), 0.16, 0.14, 0.13, 0.10, 3 x 0.09 and 0.07 (8 x 3H, s, 8 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 171.2 (21-*C*), 155.8 (*C*(O)), 138.9 (11-*C*), 114.3 (12-*C*), 79.5 (5-*C*), 79.0 ($CO_2C(CH_3)_3$), 72.6 (4- or 23-*C*), 71.3 (4- or 23-*C*), 68.0 (2- or 3-*C*), 62.7 (1-*C*), 52.8 (2- or 3-*C*), 45.7 (24-*C*), 42.0 (22-*C*), 35.1 (6-*C*), 34.0 (7-*C*), 33.9 (10-*C*), 29.4 (9-*C*), 28.4 ($CO_2C(CH_3)_3$), 26.5 (8-*C*), 26.2 (2 x $SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.0 (2 x $SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), 17.0 (6-(CH_3)), −2.4 ($SiCH_3$), −3.1 ($SiCH_3$), −3.4 ($SiCH_3$), −3.7 ($SiCH_3$), −4.6 ($SiCH_3$), −4.6 ($SiCH_3$), −4.7 ($SiCH_3$), −4.9 ($SiCH_3$); *m/z* (ES^+) 920 ((MH_2^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{46}H_{98}N_2O_8Si_4Na$ 941.6292, observed 941.6267.

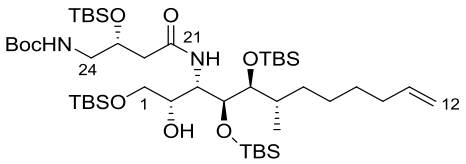
tert-Butyl ((*R*)-4-(((5*S*,6*S*,7*S*,8*S*)-6,8-bis((_tert_-butyldimethylsilyl)oxy)-2,2,3,3,11,11,12,12-octamethyl-5-((*S*)-oct-7-en-2-yl)-4,10-dioxa-3,11-disilatridecan-7-yl)amino)-2-((_tert_-butyldimethylsilyl)oxy)-4-oxobutyl)carbamate (256)



4-Methylmorpholine (11.0 μL, 0.10 mmol), methyl chloroformate (84.0 μL, 0.06 mmol) were added sequentially to a solution of **154** (20.6 mg, 0.06 mmol) in THF (0.15 mL) at −15 ºC. The mixture was stirred for 15 minutes. Amine **242** (20.0 mg, 0.03 mmol) in THF (0.15 mL) was then added dropwise to the reaction. The mixture was warmed to −10 ºC, stirred for 20 minutes and then concentrated *in vacuo* onto SiO_2. Purification by flash

column chromatography (2-5% EtOAc/petrol) afforded amide **256** (16.6 mg, 57%) as a colourless oil; R_f: 0.30 (5% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −15.0 (*c* 0.06, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3459, 2954, 2929, 1724, 1505, 1471, 1364, 1252, 1171, 1089, 938, 832, 774, 670; δ_H (400 MHz, $CDCl_3$) 5.85-5.72 (2H, m, 11-*H* and N*H*), 5.01-4.90 (2H, m, 12-*H*), 4.86 (1H, br s, N*H*), 4.20-4.13 (2H, m, 23- and 3-*H*), 4.04 (1H, dd, *J* 6.1 and 6.1, 2-*H*), 3.82 (1H, dd, *J* 10.0 and 2.5, 4-*H*), 3.53-3.46 (2H, m, 1-*H*), 3.40 (1H, dd, *J* 9.5 and 2.2, 5-*H*), 3.29-3.18 (2H, m, 24-*H*), 2.40 (1H, dd, *J* 15.2 and 3.7, 22-H*H*), 2.20 (1H, dd, *J* 15.2 and 8.8, 22-*H*H), 2.05-2.00 (2H, m, 10-*H*), 1.62-1.60 (2H, m, 6-*H* and 7-*H*H), 1.43 (9H, s, $CO_2C(CH_3)_3$), 1.35-1.04 (4H, m, 8- and 9-*H*), 0.95 (3H, d, *J* 6.6, 6-(CH_3)), 0.92, 0.89, 0.89, 0.89 and 0.88 (5 x 9H, s, 5 x $SiC(CH_3)_3$), 0.88 (1H, m, 7-H*H*), 0.14, 0.14, 0.12, 0.12, 0.11, 0.09, 0.08, 0.07, 0.07 and 0.05 (10 x 3H, s, 10 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 168.4 (21-*C*), 155.8 (*C*(O)), 139.1 (11-*C*), 114.2 (12-*C*), 79.0 ($CO_2C(CH_3)_3$), 78.8 (5-*C*), 73.7 (2- and 4-*C*), 68.3 (23-*C*), 65.8 (1-*C*), 52.6 (3-*C*), 45.8 (24-*C*), 42.4 (22-*C*), 34.6 (6-*C*), 34.1 (7-*C*), 33.9 (10-*C*), 29.4 (9-*C*), 28.4 ($CO_2C(CH_3)_3$), 26.4 (8-*C*), 26.2 ($SiC(CH_3)_3$), 26.1 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.4 (2 x $SiC(CH_3)_3$), 18.0 (3 x $SiC(CH_3)_3$), 16.8 (6-(CH_3)), −2.3 ($SiCH_3$), −3.2 ($SiCH_3$), −3.3 ($SiCH_3$), −4.2 ($SiCH_3$), −4.6 ($SiCH_3$), −4.7 ($SiCH_3$), −4.8 ($SiCH_3$), −4.8 ($SiCH_3$), −5.4 ($SiCH_3$), −5.5 ($SiCH_3$).

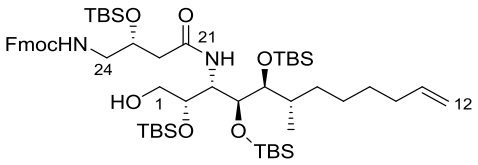
***tert*-Butyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((5*S*,6*S*,7*S*,8*S*)-6-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-2,2,3,3,11,11,12,12-octamethyl-5-((*S*)-oct-7-en-2-yl)-4,10-dioxa-3,11-disilatridecan-7-yl)amino)-4-oxobutyl)carbamate (251)**



Colourless oil; R_f: 0.40 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −8.0 (*c* 0.10, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3456, 2954, 2929, 1722, 1509, 1472, 1365, 1253, 1171, 1089, 910, 833, 774, 668; δ_H (400 MHz, $CDCl_3$) 6.08 (1H, br s, N*H*), 5.81 (1H, m, 11-*H*), 5.05 (1H, br s, N*H*), 5.01-4.92 (2H, m, 12-*H*), 4.18 (1H, m, 23-*H*), 4.05-4.04 (2H, m, 3- and 4-*H*), 3.93 (1H, m, 2-*H*), 3.61 (1H, dd, *J* 10.1 and 4.7, 1-*H*H), 3.52-3.42 (3H, m, 1-H*H*, 24-*H*H and 5-*H*), 3.00 (1H, m, 24-H*H*), 2.87 (1H, br s, O*H*), 2.38 (1H, dd, *J* 13.9 and 3.2, 22-H*H*), 2.25 (1H, dd, *J* 13.9 and 6.9, 22-*H*H), 2.06-2.02 (2H, m, 10-*H*), 1.64-1.58 (2H, m, 6-*H* and 7-*H*H), 1.44 (9H, s, $CO_2C(CH_3)_3$), 1.39-1.28 (3H, m, 8-*H*H and 9-*H*), 1.17 (1H, m, 8-H*H*), 0.96 (3H, d, *J* 6.3, 6-(CH_3)), 0.94, 0.92, 0.89 and 0.88 (4 x 9H, s, 4 x $SiC(CH_3)_3$), 0.78 (1H, m, 7-H*H*), 0.16, 0.14, 0.13, 0.11, 0.10, 0.09, 0.05 and 0.04 (8 x 3H, s, 8 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 169.2 (21-*C*), 156.2 (*C*(O)), 139.1 (11-*C*), 114.2 (12-*C*), 79.3 (5-*C*), 79.2 ($CO_2C(CH_3)_3$), 74.0 (3- or 4-*C*), 71.1 (2-*C*), 68.3 (23-*C*), 64.9 (1-*C*), 51.7 (3- or 4-*C*), 44.7 (24-*C*), 42.0 (22-*C*), 35.1 (6-*C*), 33.9 (10-*C*), 33.5 (7-*C*), 29.2 (9-*C*), 28.4 ($CO_2C(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 26.1 (8-*C*), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), 16.8 (6-(CH_3)), −3.2 ($SiCH_3$), −3.4 ($SiCH_3$), −3.6 ($SiCH_3$), −4.8 ($SiCH_3$), −4.8 ($SiCH_3$), −5.3 ($SiCH_3$), −5.3

(Si*C*H$_3$), −5.4 (Si*C*H$_3$); *m/z* (ES$^+$) 942 ((MNa$^+$, 100); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{46}H_{98}N_2O_8Si_4Na$ 941.6292, observed 941.6287.

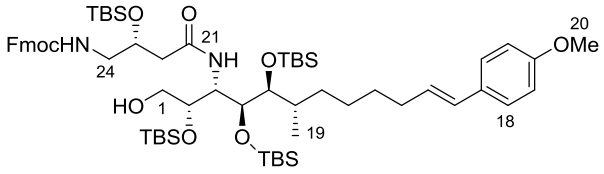
(9*H*-Fluoren-9-yl)methyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((5*S*,6*S*,7*S*,8*S*)-7-((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-2,2,3,3,10,10,11,11-octamethyl-8-((*S*)-oct-7-en-2-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)amino)-4-oxobutyl)carbamate (287)



Cyanuric fluoride (0.14 mL, 1.67 mmol) was added dropwise to a solution of **284** (634 mg, 1.39 mmol) and pyridine (0.11 mL, 1.39 mmol) in CH_2Cl_2 (13.0 mL) at room temperature. The mixture was stirred for 3 h. The reaction was diluted with CH_2Cl_2 and washed with ice-cold water (x 1), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid fluoride **286** as a yellow solid, which was used without further purification in the subsequent step. 4-Methylmorpholine (0.24 mL, 2.18 mmol), hexamethyldisiloxane (0.46 mL, 2.18 mmol), a solution of freshly prepared acid fluoride **286** in CH_2Cl_2 (4.20 mL) were added sequentially to a solution of **241** (453 mg, 0.73 mmol) in CH_2Cl_2 (3.00 mL) at room temperature. The mixture was stirred for 20 minutes and then concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded amide **287** (576 mg, 76%) as a colourless solid; R_f: 0.20 (10% EtOAc/petrol); m.p. 46-49 ^oC; $[\alpha]_D^{20}$ −3.6 (*c* 0.08, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2956, 2929, 2857, 1658, 1518, 1471, 1406, 1254, 1089, 1058, 938, 876, 833, 775, 740, 674;

δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 7.3, 2 x Ar*H*), 7.61 (2H, d, *J* 7.3, 2 x Ar*H*), 7.41 (2H, dd, *J* 7.3 and 7.3, 2 x Ar*H*), 7.32 (2H, dd, *J* 7.3 and 7.3, 2 x Ar*H*), 6.31 (1H, br s, N*H*), 5.79 (1H, m, 11-*H*), 5.17 (1H, t, *J* 5.6, N*H*), 5.01-4.93 (2H, m, 12-*H*), 4.44 (1H, dd, *J* 9.8 and 6.9, OC*H*HCH), 4.34-4.17 (5H, m, OCH*H*CH, OCH_2C*H*, O*H*, 23- and 3-*H*), 4.10-4.01 (2H, m, 4- and 2-*H*), 3.61 (1H, ddd, *J* 11.0, 11.0 and 5.6, 1-*H*H), 3.50 (1H, dd, *J* 9.3 and 2.2, 5-*H*), 3.37 (2H, dd, *J* 5.4 and 5.4, 24-*H*), 3.23 (1H, ddd, *J* 11.0, 11.0 and 4.9, 1-H*H*), 2.46 (1H, dd, *J* 15.4 and 3.9, 22-*H*H), 2.35 (1H, dd, *J* 15.4 and 8.6, 22-H*H*), 2.07-2.02 (2H, m, 10-*H*), 1.64 (1H, m, 7-*H*H), 1.54 (1H, m, 6-*H*), 1.44-1.27 (3H, m, 9-*H* and 8-*H*H), 1.11 (1H, m, 8-H*H*), 1.01 (3H, d, *J* 6.6, 6-(CH_3)), 0.95, 0.91, 0.91 and 0.87 (4 x 9H, s, 4 x $SiC(CH_3)_3$), 0.82 (1H, m, 7-H*H*), 0.17, 0.16, 0.15, 0.12, 0.11, 0.11, 0.10, 0.10 (8 x 3H, s, 8 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 171.0 (21-*C*), 156.4 (*C*(O)), 144.1 ($C_{(Ar)}$), 144.0 ($C_{(Ar)}$), 141.3 (2 x $C_{(Ar)}$), 138.9 (11-*C*), 127.6 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 125.1 ($CH_{(Ar)}$), 119.9 ($CH_{(Ar)}$), 114.4 (12-*C*), 79.6 (5-*C*), 72.6 (4-*C*), 71.3 (2-*C*), 68.0 (23-*C*), 66.8 (OCH_2CH), 62.7 (1-*C*), 52.9 (3-*C*), 47.2 (OCH_2CH), 46.1 (24-*C*), 41.9 (22-*C*), 35.0 (6-*C*), 33.9 (7-*C*), 33.9 (10-*C*), 29.3 (9-*C*), 26.5 (8-*C*), 26.1 (2 x $SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.0 (2 x $SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), 17.0 (6-(CH_3)), −2.4 ($SiCH_3$), −3.1 ($SiCH_3$), −3.4 ($SiCH_3$), −3.7 ($SiCH_3$), −4.4 ($SiCH_3$), −4.6 ($SiCH_3$), −4.7 ($SiCH_3$), −4.9 ($SiCH_3$); *m/z* (ES^+) 1064 ((MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{56}H_{100}N_2O_8Si_4Na$ 1063.6449, observed 1063.6455.

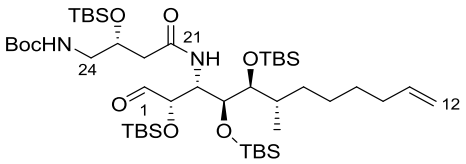
(9*H*-Fluoren-9-yl)methyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((5*S*,6*S*,7*S*,8*S*)-7-((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)-8-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecan-6-yl)amino)-4-oxobutyl)carbamate (364a)



Cyanuric fluoride (0.60 mL, 6.98 mmol) was added dropwise to a solution of **284** (2.26 g, 4.97 mmol) and pyridine (0.40 mL, 4.97 mmol) in CH_2Cl_2 (50.0 mL) at room temperature. The mixture was stirred for 3 h. The reaction was diluted with CH_2Cl_2 and washed with ice-cold water (x 1), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid fluoride **286** as a yellow solid, which was used without further purification in the subsequent step. 4-Methylmorpholine (0.94 mL, 8.57 mmol), hexamethyldisiloxane (1.82 mL, 8.57 mmol), a solution of freshly prepared acid fluoride **286** in CH_2Cl_2 (17.0 mL) were added sequentially to a solution of **364** (2.03 g, 2.86 mmol) in CH_2Cl_2 (12.0 mL) at 0 °C. The solution was stirred for 20 minutes at 0 °C and then concentrated *in vacuo*. Purification by flash column chromatography (7.5-10-20% EtOAc/petrol) afforded amide **364a** (2.63 g, 80%) as a colourless solid; R_f: 0.30 (10% EtOAc/petrol); m.p. 44-46 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −4.1 (*c* 3.00, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2929, 2856, 1730, 1657, 1511, 1470, 1249, 1092, 1056, 876, 834, 775, 740, 676; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 7.3, 2 x Ar*H*), 7.61 (2H, d, *J* 7.3, 2 x Ar*H*), 7.41 (2H, dd, *J* 7.3 and 7.3, 2 x Ar*H*), 7.32 (2H, dd, *J* 7.3 and 7.3, 2 x Ar*H*), 7.26 (2H, d, *J* 8.2, 14- and 18-*H*), 6.83 (2H, d, *J* 8.2, 15- and 17-*H*), 6.31 (1H, d, *J* 15.7, 12-*H*), 6.31 (1H, m,

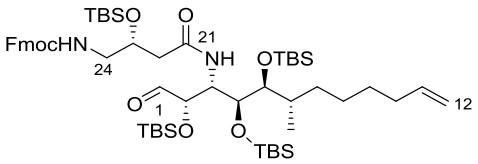
N*H*), 6.06 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 5.17 (1H, m, N*H*), 4.43 (1H, dd, *J* 9.5 and 9.5, OC*H*HCH), 4.30-4.18 (5H, m, OCH*H*CH, OCH_2C*H*, O*H*, 23- and 3-*H*), 4.08 (1H, m, 2-*H*), 4.03 (1H, d, *J* 9.6, 4-*H*), 3.80 (3H, s, 20-*H*), 3.62 (1H, m, 1-*H*H), 3.51 (1H, dd, *J* 9.2 and 1.8, 5-*H*), 3.38-3.36 (2H, m, 24-*H*), 3.23 (1H, m, 1-H*H*), 2.47 (1H, dd, *J* 15.1 and 3.1, 22-*H*H), 2.35 (1H, dd, *J* 15.1 and 8.5, 22-H*H*), 2.20-2.15 (2H, m, 10-*H*), 1.66 (1H, m, 7-*H*H), 1.55 (1H, m, 6-*H*), 1.49-1.35 (3H, m, 9-*H* and 8-*H*H), 1.15 (1H, m, 8-H*H*), 1.02 (3H, d, *J* 6.6, 19-*H*), 0.95-0.87 (37H, m, 7-H*H* and 4 x $SiC(CH_3)_3$), 0.17, 0.16, 0.15, 0.12, 0.10, 0.10, 0.09, 0.08 (8 x 3H, s, 8 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 171.0 (21-*C*), 158.6 (16-*C*), 156.4 (*C*(O)), 144.1 ($C_{(Ar)}$), 144.0 ($C_{(Ar)}$), 141.3 (2 x $C_{(Ar)}$), 130.7 (13-*C*), 129.2 (12-*C*), 128.7 (11-*C*), 127.6 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$ or 14- and 18-*C*), 126.9 ($CH_{(Ar)}$ or 14- and 18-*C*), 125.1 ($CH_{(Ar)}$), 119.9 ($CH_{(Ar)}$), 113.9 (15- and 17-*C*), 79.6 (5-*C*), 72.7 (4-*C*), 71.3 (2-*C*), 68.0 (23-*C*), 66.8 (OCH_2CH), 62.7 (1-*C*), 55.3 (20-*C*), 52.9 (3-*C*), 47.2 (OCH_2CH), 46.1 (24-*C*), 41.8 (22-*C*), 35.0 (6-*C*), 34.0 (7-*C*), 33.1 (10-*C*), 30.0 (9-*C*), 26.6 (8-*C*), 26.2 (2 x $SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.0 (3 x $SiC(CH_3)_3$), 17.1 (19-*C*), −2.4 ($SiCH_3$), −3.1 ($SiCH_3$), −3.4 ($SiCH_3$), −3.7 ($SiCH_3$), −4.4 ($SiCH_3$), −4.5 ($SiCH_3$), −4.7 ($SiCH_3$), −4.9 ($SiCH_3$); *m/z* (ES^+) 1148 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{63}H_{107}N_2O_9Si_4$ 1147.7048, observed 1147.7024.

***tert*-Butyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((5*S*,6*R*,7*S*,8*S*)-7-((*tert*-butyldimethylsilyl)oxy)-5-formyl-2,2,3,3,10,10,11,11-octamethyl-8-((*S*)-oct-7-en-2-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)amino)-4-oxobutyl)carbamate (243a)**



Dess-Martin periodinane (69.0 mg, 0.16 mmol) was added to a solution of alcohol **243** (50.0 mg, 0.05 mmol) in wet CH_2Cl_2 (0.50 mL) at 0 ^oC. The solution was then warmed to room temperature and stirred for 3 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer was then separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc/petrol) afforded aldehyde **243a** (44.3 mg, 89%) as a colourless oil; R_f: 0.50 (10% EtOAc/petrol); δ_H (400 MHz, $CDCl_3$) 9.52 (1H, s, 1-*H*), 6.91 (1H, br s, N*H*), 5.79 (1H, m, 11-*H*), 5.01-4.92 (2H, m, 12-*H*), 4.81 (1H, m, N*H*), 4.28 (1H, s, 2- or 3-*H*), 4.16 (1H, m, 23-*H*), 4.00-3.89 (2H, m, 2- or 3-*H* and 4-*H*), 3.55 (1H, dd, *J* 9.3 and 2.5, 5-*H*), 3.20 (2H, br s, 24-*H*), 2.28 (1H, d, *J* 6.1, 22-*H*), 2.06-2.01 (2H, m, 10-*H*), 1.77-1.62 (2H, m, 6-*H* and 7-*H*H), 1.44 (9H, s, $CO_2C(CH_3)_3$), 1.40-1.29 (3H, m, 9-*H* and 8-*H*H), 1.13 (1H, m, 8-H*H*), 1.00 (3H, d, *J* 6.6, 6-(CH_3)), 0.96, 0.91, 0.90 and 0.86 (4 x 9H, s, 4 x SiC(CH_3)$_3$), 0.81 (1H, m, 7-H*H*), 0.17, 0.17, 0.13, 0.12, 0.12, 0.07, 0.07 and 0.03 (8 x 3H, s, 8 x SiCH_3). The compound was used immediately in the subsequent step.

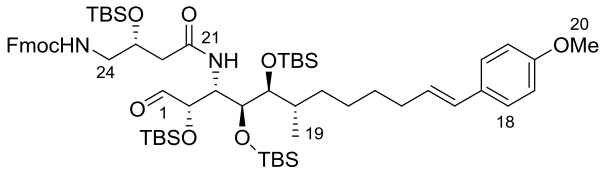
(9*H*-Fluoren-9-yl)methyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((5*S*,6*R*,7*S*,8*S*)-7-((*tert*-butyldimethylsilyl)oxy)-5-formyl-2,2,3,3,10,10,11,11-octamethyl-8-((*S*)-oct-7-en-2-yl)-4,9-dioxa-3,10-disiladodecan-6-yl)amino)-4-oxobutyl)carbamate (287a)



Dess-Martin periodinane (352 mg, 0.83 mmol) was added to a solution of alcohol **287** (246 mg, 0.24 mmol) in wet CH_2Cl_2 (2.40 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 3 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer was then separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOAc/petrol) afforded aldehyde **287a** (212 mg, 86%) as a colourless solid; R_f: 0.50 (10% EtOAc/petrol); m.p. 42-44 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −9.0 (*c* 0.1, $CHCl_3$); ν_{max} /cm^{-1} (neat) 2953, 2929, 2857, 1673, 1515, 1471, 1390, 1252, 1097, 1005, 938, 872, 832, 813, 775, 758, 674; δ_H (400 MHz, $CDCl_3$) 9.55 (1H, s, 1-*H*), 7.77 (2H, d, *J* 7.6, 2 x Ar*H*), 7.62 (2H, d, *J* 7.6, 2 x Ar*H*), 7.41 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 7.32 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 6.87 (1H, d, *J* 4.9, N*H*), 5.80 (1H, m, 11-*H*), 5.22 (1H, t, *J* 5.4, N*H*), 5.01-4.93 (2H, m, 12-*H*), 4.41 (1H, dd, *J* 10.3 and 7.3, OC*H*HCH), 4.31-4.20 (4H, m, OCH*H*CH, OCH_2CH, 2- and 23-*H*), 4.02 (1H, dd, *J* 9.5 and 5.4, 3-*H*), 3.91 (1H, dd, *J* 9.5 and 2.0, 4-*H*), 3.56 (1H, dd, *J* 9.1 and 2.0, 5-*H*), 3.32-3.31 (2H, m, 24-*H*), 2.35 (2H, d, *J* 6.1, 22-*H*), 2.07-2.02 (2H, m, 10-*H*), 1.74 (1H, m, 6-*H*), 1.63 (1H, m, 7-*H*H), 1.42-1.27 (3H, m, 9-*H* and 8-*H*H), 1.13 (1H, m, 8-H*H*), 1.01 (3H, d, *J* 6.9, 6-(CH_3)), 0.96, 0.91, 0.91 and 0.88 (4 x 9H, s, 4 x SiC(CH_3)$_3$), 0.95 (1H, m, 7-H*H*), 0.18, 0.17, 0.14, 0.13,

0.13, 0.09, 0.08, 0.06 (8 x 3H, s, 8 x SiCH_3); δ_C (100 MHz, $CDCl_3$) 200.0 (1-*C*), 169.3 (21-*C*), 156.4 (*C*(O)), 144.1 ($C_{(Ar)}$), 144.0 ($C_{(Ar)}$), 141.3 ($C_{(Ar)}$), 141.2 ($C_{(Ar)}$), 138.9 (11-*C*), 127.6 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 125.2 ($CH_{(Ar)}$), 119.9 ($CH_{(Ar)}$), 114.4 (12-*C*), 79.3 (5-*C*), 76.9 (2-*C*), 73.2 (4-*C*), 68.0 (23-*C*), 66.8 (OCH_2CH), 55.3 (3-*C*), 47.2 (OCH_2CH), 46.7 (24-*C*), 42.1 (22-*C*), 35.1 (6-*C*), 33.9 (7- or 10-*C*), 33.8 (7- or 10-*C*), 29.4 (9-*C*), 26.3 (8-*C*), 26.1 (2 x SiC(CH_3)$_3$), 25.8 (2 x SiC(CH_3)$_3$), 18.4 (Si*C*(CH_3)$_3$), 18.0 (3 x Si*C*(CH_3)$_3$), 16.9 (6-(CH_3)), −2.4 (SiCH_3), −3.4 (SiCH_3), −3.5 (SiCH_3), −4.0 (SiCH_3), −4.6 (SiCH_3), −4.6 (SiCH_3), −4.7 (SiCH_3), −4.9 (SiCH_3); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{56}H_{98}N_2O_8Si_4Na$ 1061.6292, observed 1061.6294.

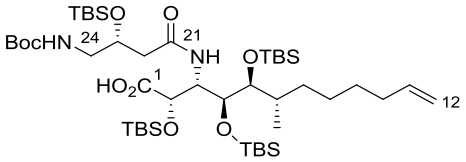
(9*H*-Fluoren-9-yl)methyl ((*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(((5*S*,6*R*,7*S*,8*S*)-7-((*tert*-butyldimethylsilyl)oxy)-5-formyl-8-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecan-6-yl)amino)-4-oxobutyl)carbamate (364b)



Dess-Martin periodinane (4.79 g, 11.3 mmol) was added to a solution of alcohol **364a** (2.59 g, 2.26 mmol) in wet CH_2Cl_2 (22.6 mL) at 0 ºC. The solution was then warmed to room temperature and stirred for 5 h. Saturated aqueous $NaHCO_3$ was then added and the aqueous layer was then separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5-7.5-10% EtOAc/petrol) afforded aldehyde **364b** (2.26 g, 87%) as a

colourless solid; R_f: 0.40 (10% EtOAc/petrol); m.p. 48-50 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +13.3 (*c* 2.58, $CHCl_3$); ν_{max} /cm^{-1} (neat) 2953, 2929, 2856, 1730, 1511, 1464, 1249, 1103, 1041, 1005, 873, 833, 776, 758, 740, 673; δ_H (400 MHz, $CDCl_3$) 9.55 (1H, s, 1-*H*), 7.77 (2H, d, *J* 7.3, 2 x Ar*H*), 7.62 (2H, d, *J* 7.3, 2 x Ar*H*), 7.41 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 7.32 (2H, dd, *J* 7.3 and 7.3, 2 x Ar*H*), 7.27 (2H, d, *J* 8.8, 14- and 18-*H*), 6.89 (1H, d, *J* 4.2, N*H*), 6.84 (2H, d, *J* 8.8, 15- and 17-*H*), 6.31 (1H, d, *J* 15.7, 12-*H*), 6.06 (1H, dt, *J* 15.7 and 6.9, 11-*H*), 5.23 (1H, t, *J* 5.9, N*H*), 4.41 (1H, dd, *J* 10.3 and 7.1, OC*H*HCH), 4.31-4.19 (4H, m, OCH*H*CH, OCH_2C*H*, 2- and 23-*H*), 4.02 (1H, dd, *J* 9.5 and 5.6, 3-*H*), 3.91 (1H, d, *J* 8.8, 4-*H*), 3.80 (3H, s, 20-*H*), 3.57 (1H, dd, *J* 8.8 and 2.5, 5-*H*), 3.32-3.31 (2H, m, 24-*H*), 2.35 (2H, d, *J* 6.1, 22-*H*), 2.20-2.15 (2H, m, 10-*H*), 1.77 (1H, m, 6-*H*), 1.65 (1H, m, 7-*H*H), 1.47-1.35 (3H, m, 9-*H* and 8-*H*H), 1.17 (1H, m, 8-H*H*), 1.02 (3H, d, *J* 6.6, 19-*H*), 0.96, 0.91, 0.91 and 0.87 (4 x 9H, s, 4 x $SiC(CH_3)_3$), 0.95 (1H, m, 7-H*H*), 0.18, 0.17, 0.14, 0.14, 0.13, 0.08, 0.07, 0.04 (8 x 3H, s, 8 x $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 200.0 (1-*C*), 169.4 (21-*C*), 158.6 (16-*C*), 156.4 (*C*(O)), 144.1 ($C_{(Ar)}$), 144.0 ($C_{(Ar)}$), 141.3 (2 x $C_{(Ar)}$), 130.6 (13-*C*), 129.2 (12-*C*), 128.6 (11-*C*), 127.6 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$ or 14- and 18-*C*), 127.0 ($CH_{(Ar)}$ or 14- and 18-*C*), 125.2 ($CH_{(Ar)}$), 119.9 ($CH_{(Ar)}$), 113.9 (15- and 17-*C*), 79.4 (5-*C*), 76.8 (2-*C*), 73.2 (4-*C*), 68.0 (23-*C*), 66.8 (OCH_2CH), 55.2 (20- and 3-*C*), 47.2 (OCH_2CH), 46.7 (24-*C*), 42.1 (22-*C*), 35.0 (6-*C*), 33.8 (7-*C*), 33.1 (10-*C*), 30.1 (9-*C*), 26.4 (8-*C*), 26.1 (2 x $SiC(CH_3)_3$), 25.8 (2 x $SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 18.0 (3 x $SiC(CH_3)_3$), 16.9 (19-*C*), −2.4 ($SiCH_3$), −3.4 ($SiCH_3$), −3.5 ($SiCH_3$), −4.0 ($SiCH_3$), −4.6 ($SiCH_3$), −4.6 ($SiCH_3$), −4.7 ($SiCH_3$), −5.0 ($SiCH_3$); *m/z* (ES^+) 1146 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{63}H_{105}N_2O_9Si_4$ 1145.6892, observed 1145.6882.

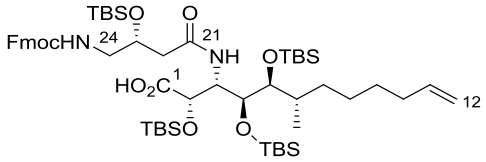
(2*S*,3*R*,4*S*,5*S*,6*S*)-3-((*R*)-4-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-6-methyldodec-11-enoic acid (244)



2-Methyl-2-butene (16.0 μL, 0.14 mmol), NaH_2PO_4 (23.0 mg, 0.19 mmol) and $NaClO_2$ (5.70 mg, 0.06 mmol) were added sequentially to a solution of aldehyde **243a** (44.3 mg, 0.05 mmol) in *t*-BuOH/H_2O (0.35 mL, 2.5:1) at 0 °C. The solution was slowly warmed to room temperature and stirred for 2 h. The solution was then diluted with EtOAc, water was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-20-40% EtOAc/petrol) afforded acid **244** (39.8 mg, 89%) as a colourless oil; R_f: 0.30 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −37.7 (*c* 0.06, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2929, 2858, 1686, 1514, 1471, 1366, 1252, 1088, 832, 775, 671; δ_H (400 MHz, CD_2Cl_2) 5.81 (1H, m, 11-*H*), 5.00-4.90 (2H, m, 12-*H*), 4.44-4.16 (3H, m, 2-, 3- and 23-*H*), 3.89 (1H, m, 4-*H*), 3.50-3.13 (3H, m, 24- and 5-*H*), 2.62-2.22 (2H, m, 22-*H*), 2.04-2.02 (2H, m, 10-*H*), 1.72-1.59 (2H, m, 6-*H* and 7-*H*H), 1.43 (9H, s, $CO_2C(CH_3)_3$), 1.39-1.27 (3H, m, 8-*H*H and 9-*H*), 1.12 (1H, m, 8-H*H*), 0.99-0.87 (40H, m, 6-(CH_3), 4 x $SiC(CH_3)_3$ and 7-H*H*), 0.17, 0.17, 0.17, 0.14, 0.10, 0.08, 0.08 and 0.08 (8 x 3H, s, 8 x $SiCH_3$); δ_C (100 MHz, CD_2Cl_2) 174.6 (1-*C*), 171.6 (21-*C*), 155.3 (*C*(O)), 139.8 (11-*C*), 114.5 (12-*C*), 79.9 (5-*C*), 77.3 ($CO_2C(CH_3)_3$), 74.7 (4-*C*), 72.7 (2- or 3- or 23-*C*), 70.2 (2- or 3- or 23-*C*), 69.2 (2- or 3- or 23-*C*), 44.9 (24-*C*), 42.5 (22-*C*), 35.7 (6-*C*), 34.5 (10-*C*), 34.4

(7-*C*), 30.3 (9-*C*), 28.9 ($CO_2C(CH_3)_3$), 26.7 (8-*C*), 26.6 ($SiC(CH_3)_3$), 26.3 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 18.6 ($SiC(CH_3)_3$), 18.6 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), 17.2 (6-(CH_3)), −3.3 ($SiCH_3$), −3.9 ($SiCH_3$), −4.3 ($SiCH_3$), −4.4 ($SiCH_3$), −4.5 ($SiCH_3$), −4.6 ($SiCH_3$), −5.0 ($SiCH_3$), −5.3 ($SiCH_3$); *m/z* (ES^+) 933 ((MH^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{46}H_{96}N_2O_9Si_4Na$ 955.6086, observed 955.6091.

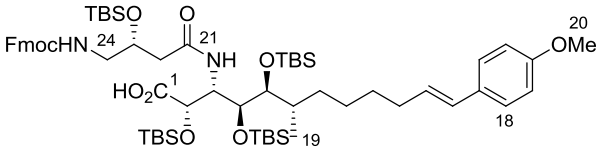
(2*S*,3*R*,4*S*,5*S*,6*S*)-3-((*R*)-4-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-6-methyldodec-11-enoic acid (288)



2-Methyl-2-butene (64.0 μL, 0.61 mmol), NaH_2PO_4 (97.0 mg, 0.81 mmol) and $NaClO_2$ (24.0 mg, 0.26 mmol) were added sequentially to a solution of aldehyde **287a** (212 mg, 0.20 mmol) in *t*-BuOH/H_2O (1.44 mL, 2.5:1) at 0 ^oC. The solution was slowly warmed to room temperature and stirred for 2.5 h. The solution was then diluted with EtOAc, water was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude acid **288** (217 mg, quant.) as a colourless solid. R_f: 0.50 (30% EtOAc/petrol); δ_H (400 MHz, CD_2Cl_2) 7.76 (2H, d, *J* 7.3, 2 x Ar*H*), 7.61 (2H, d, *J* 7.6, 2 x Ar*H*), 7.38 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 7.31-7.26 (2H, m, 2 x Ar*H*), 6.51 (1H, br s, N*H*), 5.80 (1H, m, 11-*H*), 5.37 (1H, m, N*H*), 5.01-4.89 (2H, m, 12-*H*), 4.53-4.21 (6H, m, OCH_2CH,

OCH_2CH, 2-, 3- and 23-*H*), 3.90 (1H, dd, *J* 9.8 and 2.0, 4-*H*), 3.52 (1H, dd, *J* 8.8 and 2.2, 5-*H*), 3.36-3.21 (2H, m, 24-*H*), 2.41 (1H, dd, *J* 15.4 and 4.7, 22-*H*H), 2.26 (1H, dd, *J* 15.4 and 9.5, 22-H*H*), 2.05-2.00 (2H, m, 10-*H*), 1.69-1.58 (2H, m, 6-*H* and 7-*H*H), 1.43-1.29 (3H, m, 9-*H* and 8-*H*H), 1.14 (1H, m, 8-H*H*), 1.01 (3H, d, *J* 6.6, 6-(CH_3)), 0.93, 0.93, 0.91 and 0.86 (4 x 9H, s, 4 x SiC(CH_3)$_3$), 0.88 (1H, m, 7-H*H*), 0.19, 0.18, 0.17, 0.16, 0.11, 0.11, 0.07, 0.06 (8 x 3H, s, 8 x SiCH_3). The compound was used immediately and without further purification in the subsequent step.

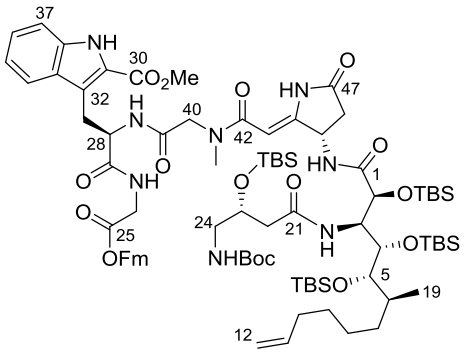
(2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-((*R*)-4-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-12-(4-methoxyphenyl)-6-methyldodec-11-enoic acid (365)



2-Methyl-2-butene (0.82 mL, 7.74 mmol), NaH_2PO_4 (933 mg, 7.78 mmol) and $NaClO_2$ (308 mg, 2.72 mmol) were added sequentially to a solution of aldehyde **364b** (2.23 g, 1.95 mmol) in *t*-BuOH/H_2O (16.0 mL, 3:1) at 0 °C. The solution was slowly warmed to room temperature and stirred for 2.5 h. The solution was then diluted with EtOAc, water was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude acid **365** (2.26 g, quant.) as a colourless solid. R_f: 0.60 (50% EtOAc/petrol); 7.76 (2H, d, *J* 7.2, 2 x Ar*H*), 7.60 (2H, d, *J* 7.5, 2 x Ar*H*), 7.39 (2H, dd, *J* 7.5 and 7.5, 2 x Ar*H*), 7.31-7.25 (4H, m, 2 x Ar*H*, 14- and 18-*H*), 6.83 (2H, d, *J* 8.4, 15- and 17-*H*), 6.30 (1H, d, *J* 15.7,

12-*H*), 6.06 (1H, dt, *J* 15.7 and 7.0, 11-*H*), 5.33 (1H, br s, N*H*), 4.55-4.20 (6H, m, OC*H*$_2$CH, OCH$_2$C*H*, 2-, 3- and 23-*H*), 3.91 (1H, m, 4-*H*), 3.80 (3H, s, 20-*H*), 3.52 (1H, d, *J* 9.2, 5-*H*), 3.34 (2H, br s, 24-*H*), 2.41 (1H, dd, *J* 15.3 and 4.1, 22-*H*H), 2.28 (1H, dd, *J* 15.3 and 9.0, 22-H*H*), 2.19-2.14 (2H, m, 10-*H*), 1.72-1.61 (2H, m, 6-*H* and 7-*H*H), 1.49-1.35 (3H, m, 9-*H* and 8-*H*H), 1.19 (1H, m, 8-H*H*), 1.00 (3H, d, *J* 6.7, 19-*H*), 0.94-0.87 (37H, m, 7-H*H* and 4 x SiC(C*H*$_3$)$_3$), 0.18, 0.17, 0.16, 0.16, 0.10, 0.10, 0.06, 0.06 (8 x 3H, s, 8 x SiC*H*$_3$). The compound was used immediately and without further purification in the subsequent step.

(2-((*R*)-2-(2-((*Z*)-2-((*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*)-3-((*R*)-4-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-(2-(methoxycarbonyl)-1*H*-indol-3-yl)propanamido)acetoxy)fermium (274)

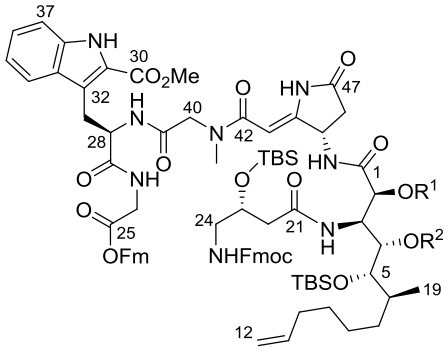


HATU (10.4 mg, 27.0 μmol), 2,6-lutidine (10.0 μL, 84.0 μmol) and amine salt **273** (21.0 mg, 26.0 μmol) were added sequentially to a solution of carboxylic acid **244** (20.0 mg, 21.0 μmol) in DMF (0.21 mL) at 0 °C. The mixture was warmed slowly to room temperature and stirred for 16 h. The solution was then diluted with EtOAc and washed

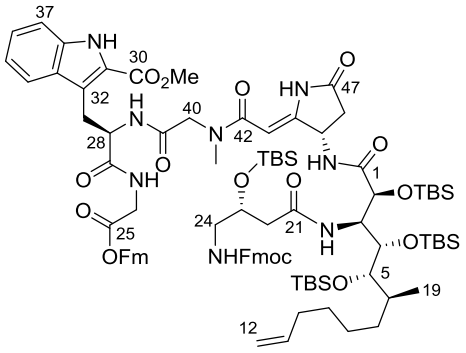
with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-80% EtOAc/petrol) afforded a linear hexapeptide **274** (21.8 mg, 64%) as a colourless solid; R_f 0.50 (EtOAc); m.p. 93-95 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −10.0 (*c* 0.04, EtOAc); ν_{max} /cm^{-1} (neat) 2985, 1738, 1373, 1235, 1044, 938, 847, 634; δ_H (500 MHz, D_6-DMSO) 11.60 (1H, s, N*H*), 10.33(1H, s, N*H*), 8.40 (1H, t, *J* 5.2, N*H*), 8.32 (1H, d, *J* 6.8, N*H*), 7.98 (1H, d, *J* 8.2, N*H*), 7.89 (2H, d, *J* 7.6, 2 x Ar*H*), 7.78 (1H, d, *J* 7.6, 34-*H*), 7.69 (2H, d, *J* 7.6, 2 x Ar*H*), 7.43-7.32 (5H, m, 37-*H* and 4 x Ar*H*), 7.22 (1H, dd, *J* 7.6 and 7.6, 36-*H*), 7.05 (1H, dd, *J* 7.6 and 7.6, 35-*H*), 6.52 (1H, br s, N*H*), 5.74 (1H, m, 11-*H*), 5.59 (1H, s, 43-*H*), 5.34 (1H, d, *J* 6.2, N*H*), 5.06 (1H, m, 45-*H*), 4.97-4.89 (2H, m, 12-*H*), 4.65 (1H, m, 28-*H*), 4.35 (2H, d, *J* 7.3, OC*H*$_2$CH), 4.28-4.24 (2H, m, OCH$_2$C*H* and 4- or 2-*H*), 4.17 (1H, d, *J* 6.2, 3-*H*), 3.98-3.81 (8H, m, CO_2CH_3, 40-*H*H, 26-, 23- and 4- or 2-*H*), 3.71 (1H, d, *J* 15.8, 40-H*H*), 3.49 (1H, dd, *J* 14.0 and 5.5, 29-*H*H), 3.32 (1H, m, 5-*H*), 3.28 (1H, dd, *J* 14.0 and 9.5, 29-H*H*), 3.02 (1H, m, 24-*H*H), 2.84 (1H, m, 24-H*H*), 2.69 (3H, s, 41-*H*), 2.65 (1H, m, 46-*H*H), 2.26-2.12 (3H, m, 46-H*H* and 22-*H*), 1.99-1.95 (2H, m, 10-*H*), 1.67-1.59 (2H, m, 6-*H* and 7-*H*H), 1.34 (9H, s, $CO_2C(CH_3)_3$), 1.30-1.23 (3H, m, 8-*H*H and 9-*H*), 1.07 (1H, m, 8-H*H*), 0.90-0.81 (40H, m, 4 x $SiC(CH_3)_3$, 19-*H* and 7-H*H*), 0.14, 0.11, 0.10, 0.05, 0.05, 0.02, 0.01 and 0.01 (8 x 3H, s, 8 x $SiCH_3$); δ_C (126 MHz, D_6-DMSO) 174.7 (47-*C*), 172.7 (1-*C*), 171.5 (27-*C*), 169.6 (25-*C*), 167.9 (21-*C*), 167.7 (39-*C*), 164.6 (42-*C*), 162.3 (30-*C*), 156.7 (44-*C* or *C*(O)), 155.6 (44-*C* or *C*(O)), 143.5 ($C_{(Ar)}$), 143.5 ($C_{(Ar)}$), 140.7 ($C_{(Ar)}$), 138.7 (11-*C*), 136.2 (38-*C*), 127.8 ($CH_{(Ar)}$), 127.5 (33-*C*), 127.2 ($CH_{(Ar)}$), 125.2 ($CH_{(Ar)}$), 124.7 (36-*C*), 123.8 (32-*C*), 120.7 (34-*C*), 120.2 ($CH_{(Ar)}$), 119.5 (35-*C*), 118.7 (31-*C*), 114.6 (12-*C*), 112.3 (37-*C*), 88.3 (43-*C*), 78.3 ($CO_2C(CH_3)_3$), 77.4 (5-*C*), 72.9 (2- or 4-*C*), 69.9 (3-*C*), 68.2 (23-*C*), 66.2 (OCH_2CH), 53.7 (28-*C*), 52.8 (2- or 4-*C*), 51.6 (CO_2CH_3), 49.8 (40-*C*), 46.7 (45-*C*), 46.1

(OCH$_2$*C*H), 45.0 (24-*C*), 42.2 (22-*C*), 40.8 (26-*C*), 38.2 (41-*C*), 35.0 (46-*C*), 34.6 (6-*C*), 33.2 (10-*C*), 32.8 (7-*C*), 28.5 (9-*C*), 28.2 (CO$_2$C(*C*H$_3$)$_3$), 27.6 (29-*C*), 26.1 (SiC(*C*H$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 25.4 (8-*C*), 18.0 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 17.7 (Si*C*(CH$_3$)$_3$), 17.7 (Si*C*(CH$_3$)$_3$), 16.2 (19-*C*), −3.2 (Si*C*H$_3$), −3.4 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −5.0 (Si*C*H$_3$), −5.0 (Si*C*H$_3$), −5.3 (Si*C*H$_3$); *m/z* (ES$^+$) 1644 ((MNa$^+$, 100); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{84}H_{132}N_8O_{16}Si_4Na$ 1643.8731, observed 1643.8777.

Methyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (289) and methyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (290)



289 R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H



290

HATU (220 mg, 0.57 mmol), 2,6-lutidine (0.27 mL, 2.31 mmol) and amine salt **273** (475 mg, 0.57 mmol) were added sequentially to a solution of carboxylic acid **288** (428 mg, 0.41 mmol) in DMF (4.50 mL) at 0 ^{o}C. The mixture was warmed slowly to room temperature and stirred for 16 h. The solution was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-60-70% EtOAc/petrol) afforded linear hexapeptides **289**

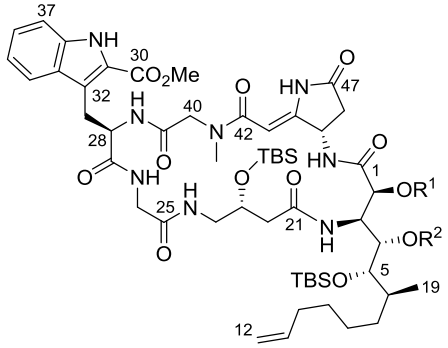
(182 mg, 27%) and **290** (220 mg, 32%). Data for linear hexapeptide **289**: colourless solid; R_f 0.25 (70% EtOAc/petrol); m.p. 54-56 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −10.7 (*c* 0.92, EtOAc); ν_{max} /cm^{-1} (neat) 3271, 2929, 2856, 1658, 1526, 1450, 1324, 1255, 1197, 1096, 1051, 1025, 1006, 878, 835, 776, 760, 742; δ_H (500 MHz, D_6-DMSO) 11.60 (1H, s, N*H*), 10.34 (1H, s, N*H*), 8.40-8.34 (2H, m, 2 x N*H*), 7.99 (1H, d, *J* 7.9, N*H*), 7.87 (4H, dd, *J* 7.4 and 7.4, 4 x Ar*H*), 7.79 (1H, d, *J* 8.0, 34-*H*), 7.68 (4H, dd, *J* 6.6 and 6.6, 4 x Ar*H*), 7.42-7.26 (9H, m, 37-*H* and 8 x Ar*H*), 7.22 (1H, dd, *J* 7.3 and 7.3, 36-*H*), 7.14 (1H, m, N*H*), 7.05 (1H, dd, *J* 7.3 and 7.3, 35-*H*), 6.64 (1H, br s, O*H*), 5.73 (1H, m, 11-*H*), 5.62 (1H, s, 43-*H*), 5.33 (1H, d, *J* 5.4, N*H*), 5.04 (1H, m, 45-*H*), 4.96-4.88 (2H, m, 12-*H*), 4.66 (1H, m, 28-*H*), 4.35 (2H, d, *J* 7.1, OC*H*$_2$CH), 4.29-4.23 (3H, m, 2-*H*, OC*H*HCH and OCH$_2$C*H*), 4.20-4.12 (3H, m, 3-*H*, OCH*H*CH and OCH$_2$C*H*), 4.03 (1H, m, 23-*H*), 3.95 (1H, d, *J* 15.9, 40-*H*H), 3.88-3.82 (6H, m, CO$_2$C*H*$_3$, 26- and 4-*H*), 3.71 (1H, d, *J* 15.9, 40-H*H*), 3.50 (1H, dd, *J* 13.4 and 4.9, 29-*H*H), 3.32 (1H, m, 5-*H*), 3.29 (1H, dd, *J* 13.4 and 9.1, 29-H*H*), 3.08 (1H, m, 24-*H*H), 2.98 (1H, m, 24-H*H*), 2.76 (3H, s, 41-*H*), 2.64 (1H, m, 46-*H*H), 2.31-2.15 (3H, m, 46-H*H* and 22-*H*), 1.98-1.95 (2H, m, 10-*H*), 1.64-1.59 (2H, m, 6-*H* and 7-*H*H), 1.30-1.22 (3H, m, 8-*H*H and 9-*H*), 1.07 (1H, m, 8-H*H*), 0.87-0.76 (31H, m, 3 x SiC(C*H*$_3$)$_3$, 19-*H* and 7-H*H*), 0.14, 0.10, 0.10, 0.04, −0.02 and −0.02 (6 x 3H, s, 6 x SiC*H*$_3$); δ_C (126 MHz, D_6-DMSO) 174.8 (47-*C*), 172.6 (1-*C*), 171.5 (27-*C*), 169.6 (25-*C*), 168.2 (21-*C*), 167.9 (42-*C*), 167.7 (39-*C*), 162.3 (30-*C*), 156.7 (44-*C*), 156.3 (*C*(O)), 143.9 (*C*$_{(Ar)}$), 143.8 (*C*$_{(Ar)}$), 143.5 (2 x *C*$_{(Ar)}$), 140.7 (2 x *C*$_{(Ar)}$), 138.7 (11-*C*), 137.0 (2 x *C*$_{(Ar)}$), 136.2 (38-*C*), 128.7 (*C*H$_{(Ar)}$), 128.4 (*C*H$_{(Ar)}$), 127.7 (*C*H$_{(Ar)}$), 127.6 (33-*C*), 127.2 (*C*H$_{(Ar)}$), 126.5 (*C*H$_{(Ar)}$), 125.2 (*C*H$_{(Ar)}$), 124.7 (36-*C*), 123.8 (32-*C*), 120.7 (34-*C*), 120.2 (*C*H$_{(Ar)}$), 120.1 (*C*H$_{(Ar)}$), 119.4 (35-*C*), 118.7 (31-*C*), 114.6 (12-*C*), 112.3 (37-*C*), 88.4 (43-*C*), 78.1 (5-*C*), 72.8 (4-*C*), 69.8 (3-*C*), 68.1 (23-*C*), 66.2 (O*C*H$_2$CH), 65.5 (O*C*H$_2$CH), 53.7 (28-*C*),

52.9 (2-*C*), 51.6 (CO_2CH_3), 49.8 (40-*C*), 46.7 (45-*C* and OCH_2CH), 46.1 (OCH_2CH), 45.6 (24-*C*), 42.1 (22-*C*), 40.8 (26-*C*), 35.8 (41-*C*), 35.1 (46-*C*), 34.6 (6-*C*), 33.2 (10-*C*), 32.9 (7-*C*), 28.5 (9-*C*), 27.7 (29-*C*), 26.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 25.4 (8-*C*), 18.0 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), 17.7 ($SiC(CH_3)_3$), 16.2 (19-*C*), −3.2 ($SiCH_3$), −3.4 ($SiCH_3$), −4.9 ($SiCH_3$), −4.9 ($SiCH_3$), −4.9 ($SiCH_3$), −5.2 ($SiCH_3$); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{88}H_{120}N_8O_{16}Si_3Na$ 1652.8056, observed 1652.8094.

Data for linear hexapeptide **290**: colourless solid; R_f 0.50 (70% EtOAc/petrol); m.p. 119-121 °C; $[\alpha]_D^{20}$ −2.4 (*c* 0.25, EtOAc); ν_{max} /cm^{-1} (neat) 2954, 2932, 1663, 1526, 1451, 1360, 1254, 1210, 1101, 831, 777, 741, 673; δ_H (500 MHz, D_6-DMSO) 11.61 (1H, s, N*H*), 10.42 (1H, s, N*H*), 8.41 (1H, br s, N*H*), 8.00 (1H, d, *J* 7.4, N*H*), 7.86 (4H, dd, *J* 7.6 and 7.6, 4 x Ar*H*), 7.79 (1H, d, *J* 7.9, 34-*H*), 7.69-7.67 (3H, m, N*H* and 2 x Ar*H*), 7.63 (1H, d, *J* 7.4, Ar*H*), 7.57 (1H, d, *J* 7.6, Ar*H*), 7.42-7.25 (11H, m, 37-*H*, 2 x N*H* and 8 x Ar*H*), 7.20 (1H, dd, *J* 7.6 and 7.6, 36-*H*), 7.04 (1H, dd, *J* 7.6 and 7.6, 35-*H*), 5.75 (1H, m, 11-*H*), 5.44 (1H, s, 43-*H*), 5.11 (1H, br s, 45-*H*), 4.97-4.89 (2H, m, 12-*H*), 4.67 (1H, m, 28-*H*), 4.36-4.32 (3H, m, 2- or 4-*H* and OCH_2CH), 4.26-4.12 (6H, m, OCH_2CH, 2 x OCH_2CH, 3-*H* and 40-*H*H), 4.03 (1H, m, 23-*H*), 3.88-3.86 (5H, m, CO_2CH_3 and 26-*H*), 3.77 (1H, d, *J* 8.8, 4- or 2-*H*), 3.51-3.50 (2H, m, 29-*H*H and 5-*H*), 3.40 (1H, m, 40-H*H*), 3.28-3.19 (2H, m, 29-H*H* and 24-*H*H), 2.96 (1H, m, 24-H*H*), 2.65-2.63 (4H, m, 46-*H*H and 41-*H*), 2.40-2.26 (2H, m, 46-H*H* and 22-*H*H), 2.13 (1H, m, 22-H*H*), 1.98-1.97 (2H, m, 10-*H*), 1.63-1.54 (2H, m, 6-*H* and 7-*H*H), 1.33-1.22 (3H, m, 8-*H*H and 9-*H*), 1.06 (1H, m, 8-H*H*), 0.89-0.76 (40H, m, 4 x $SiC(CH_3)_3$, 19-*H* and 7-H*H*), 0.20-0.02 (24H, m, 8 x $SiCH_3$); δ_C (126 MHz, D_6-DMSO) 175.1 (47-*C*), 171.6 (1- and 27-*C*), 169.7 (25-*C*), 168.3 (21-*C*), 167.8 (42-*C*), 167.7 (39-*C*), 162.3 (30-*C*),

156.7 (44-*C* and *C*(O)), 143.9 ($C_{(Ar)}$), 143.7 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.8 ($C_{(Ar)}$), 140.7 (3 x $C_{(Ar)}$), 138.6 (11-*C*), 136.2 (38-*C*), 127.8 ($CH_{(Ar)}$), 127.6 ($CH_{(Ar)}$ and 33-*C*), 127.2 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 125.3 ($CH_{(Ar)}$), 125.1 ($CH_{(Ar)}$), 125.0 ($CH_{(Ar)}$), 124.7 (36-*C*), 123.8 (32-*C*), 120.7 (34-*C*), 120.2 ($CH_{(Ar)}$), 120.1 ($CH_{(Ar)}$), 119.5 (35-*C*), 118.8 (31-*C*), 114.7 (12-*C*), 112.4 (37-*C*), 87.7 (43-*C*), 73.2 (4- or 2-*C*), 71.9 (4- or 2-*C*), 69.8 (5-*C*), 68.4 (23-*C*), 66.2 (OCH_2CH), 65.4 (OCH_2CH), 54.1 (3-*C*), 53.8 (28-*C*), 51.6 (CO_2CH_3), 49.9 (40-*C*), 46.9 (45-*C*), 46.6 (OCH_2CH), 46.1 (OCH_2CH), 45.8 (24-*C*), 42.2 (22-*C*), 40.9 (26-*C*), 35.5 (41-*C*), 34.7 (46-*C*), 33.3 (10-*C*), 33.2 (7-*C*), 28.6 (9-*C*), 27.9 (6- and 29-*C*), 26.2 (8-*C* and $SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), 17.8 ($SiC(CH_3)_3$), 16.0 (19-*C*), −2.5 ($SiCH_3$), −2.9 ($SiCH_3$), −3.3 ($SiCH_3$), −3.5 ($SiCH_3$), −4.1 ($SiCH_3$), −4.8 ($SiCH_3$), −4.9 ($SiCH_3$), −5.1 ($SiCH_3$); *m/z* (ES^+) 1767 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{94}H_{134}N_8O_{16}Si_4Na$ 1766.8913, observed 1766.8937.

Methyl 3-(((3a*S*,6*S*,7*R*,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((1*S*,2*S*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-3-methylnon-8-en-1-yl)-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (291)



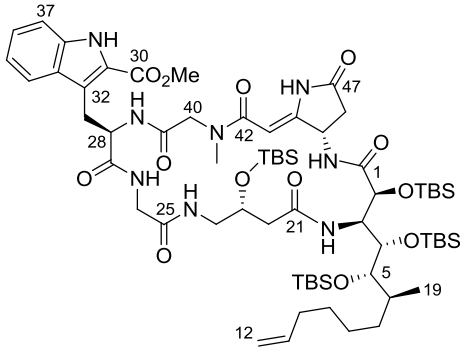
R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H

Piperidine (0.50 mL, 6.06 mmol) was added to a solution of linear hexapeptide **289** (182 mg, 112 μmol) in CH_2Cl_2 (10.0 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried under high vacuum for 4 h at 40 °C. Purification by flash column chromatography (2-5-25% MeOH/$CHCl_3$) afforded piperidine salt of linear amino acid **293** as a colourless solid. The piperidine salt of amino acid **293** was dissolved in DMF (111 mL) and cooled to 0 °C. PyAOP (582 mg, 1.12 mmol), HOAt (152 mg, 1.12 mmol) and *N*,*N*-diisopropylethylamine (0.19 mL, 1.12 mmol) were then added sequentially. The mixture was warmed slowly to room temperature, stirred for 9 days and concentrated *in vacuo*. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed with water, dried

(Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography ($CHCl_3$-1-2-3% MeOH/$CHCl_3$) afforded cyclic hexapeptide **291** (70.2 mg, 52% over 2 steps) as a colourless solid; R_f 0.20 (EtOAc); m.p. 114-117 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −6.0 (*c* 0.08, $CHCl_3$); ν_{max} /cm^{-1} (neat) 3338, 2924, 2854, 2361, 2341, 1655, 1523, 1255, 1098, 835, 777, 745, 669; δ_H (500 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 7.68 (1H, d, *J* 8.0, 34-*H*), 7.41 (1H, d, *J* 8.2, 37-*H*), 7.28 (1H, ddd, *J* 8.0, 8.0 and 0.8, 36-*H*), 7.10 (1H, dd, *J* 8.0 and 8.0, 35-*H*), 5.79 (1H, m, 11-*H*), 5.70 (1H, d, *J* 0.8, 43-*H*), 5.08 (1H, dd, *J* 9.1 and 2.8, 45-*H*), 5.00-4.89 (3H, m, 28- and 12-*H*), 4.45 (1H, m, N*H* or O*H*), 4.40-4.35 (3H, m, 26-*H*H, 2- and 4-*H*), 4.06 (1H, m, 3-*H*), 4.00-3.94 (5H, m, CO_2CH_3, 29-*H*H and 23-*H*), 3.93-3.86 (2H, m, 40-*H*), 3.60-3.56 (2H, m, 26-H*H* and 5-*H*), 3.27 (1H, dd, *J* 14.0 and 11.5, 29-H*H*), 3.22 (3H, s, 41-*H*), 3.05 (2H, d, *J* 15.6, 24-*H*), 2.86 (1H, dd, *J* 18.6 and 9.1, 46-*H*H), 2.48 (1H, dd, *J* 18.6 and 3.3, 46-H*H*), 2.37-2.29 (2H, m, 22-*H*), 2.06-2.02 (2H, m, 10-*H*), 1.74-1.66 (2H, m, 6-*H* and 7-*H*H), 1.41-1.29 (3H, m, 8-*H*H and 9-*H*), 1.20 (1H, m, 8-H*H*), 1.03 (3H, d, *J* 6.6, 19-*H*), 0.99-0.90 (28H, m, 3 x $SiC(CH_3)_3$ and 7-H*H*), 0.24, 0.22, 0.22, 0.16, 0.14, 0.14 (18H, 6 x s, 6 x $SiCH_3$); δ_C (126 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 178.3 (47-*C*), 176.2 (1-*C*), 173.7 (27-*C*), 172.4 (25-*C*), 171.9 (39-*C*), 171.4 (42-*C*), 170.9 (21-*C*), 164.2 (30-*C*), 158.4 (44-*C*), 140.1 (11-*C*), 138.0 (38-*C*), 129.6 (33-*C*), 126.4 (36-*C*), 125.3 (32-*C*), 121.2 (34-*C*), 121.0 (35-*C*), 121.0 (31-*C*), 115.1 (12-*C*), 113.6 (37-*C*), 91.2 (43-*C*), 81.1 (5-*C*), 74.8 (3-*C*), 71.6 (2- or 4-*C*), 71.1 (23-*C*), 56.8 (2- or 4-*C*), 55.2 (40-*C*), 54.9 (24-*C*), 54.7 (28-*C*), 52.3 (CO_2CH_3), 49.5 (45-*C*), 45.1 (22-*C*), 42.8 (26-*C*), 38.7 (41-*C*), 37.0 (46-*C*), 36.4 (6-*C*), 35.1 (10-*C*), 34.9 (7-*C*), 30.4 (9-*C*), 27.4 (8-*C*), 27.1 (29-*C*), 27.0 ($SiC(CH_3)_3$), 26.6 ($SiC(CH_3)_3$), 26.6 ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$), 19.2 ($SiC(CH_3)_3$), 19.0 ($SiC(CH_3)_3$), 17.7 (19-*C*), −2.3 ($Si(CH_3)_3$),

−3.0 (Si*C*H$_3$), −4.0 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.5 (Si*C*H$_3$), −4.9 (Si*C*H$_3$); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{61}H_{97}N_8O_{13}Si_3$ 1233.6477, observed 1233.6473.

Methyl 3-(((3a*S*,6*S*,7*R*,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-22-methyl-7-((5*S*,6*S*)-2,2,3,3,8,8,9,9-octamethyl-6-((*S*)-oct-7-en-2-yl)-4,7-dioxa-3,8-disiladecan-5-yl)-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (292)

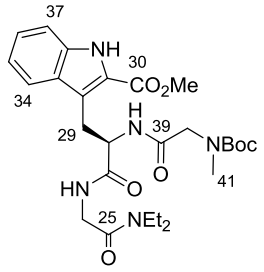


Piperidine (0.50 mL, 6.06 mmol) was added to a solution of linear hexapeptide **290** (210 mg, 120 μmol) in CH_2Cl_2 (10.0 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried under high vacuum for 4 h at 40 °C. Purification by flash column chromatography (2-5-25% MeOH/$CHCl_3$) afforded piperidine salt of linear amino acid **294** as a colourless solid. The piperidine salt of amino acid **294** was dissolved in DMF (120 mL) and cooled to 0 °C. PyAOP (420 mg, 0.81 mmol), HOAt (163 mg, 1.20 mmol) and *N*,*N*-diisopropylethylamine (0.21 mL, 1.20 mmol) were then added sequentially. The mixture was warmed slowly to room temperature, stirred for 13 days and concentrated

in vacuo. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (70-80-90% EtOAc/petrol) afforded cyclic hexapeptide **292** (84.2 mg, 53% over 2 steps) as a colourless solid; R_f 0.50 (EtOAc); m.p. 167-169 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −38.3 (*c* 0.83, EtOAc); ν_{max} /cm^{-1} (neat) 2929, 2857, 1652, 1519, 1439, 1312, 1253, 1099, 834, 777, 744, 673; δ_H (500 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 7.74 (1H, d, *J* 8.2, 34-*H*), 7.41 (1H, d, *J* 8.4, 37-*H*), 7.30 (1H, dd, *J* 7.4 and 7.4, 36-*H*), 7.13 (1H, dd, *J* 7.4 and 7.4, 35-*H*), 6.25 (1H, d, *J* 7.1, N*H*), 5.78 (1H, m, 11-*H*), 5.66 (1H, s, 43-*H*), 5.27 (1H, m, 45-*H*), 4.99-4.90 (2H, m, 12-*H*), 4.69 (1H, m, 28-*H*), 4.52 (1H, br s, 2-*H*), 4.36 (1H, dd, *J* 9.0 and 9.0, 3-*H*), 4.27 (1H, d, *J* 16.6, 26-*H*H), 4.06-3.98 (5H, m, CO_2CH_3, 40-*H*H and 23-*H*), 3.91 (1H, m, 4-*H*), 3.78 (1H, dd, *J* 14.0 and 3.2, 29-H*H*), 3.71 (1H, m, 24-*H*H), 3.63 (1H, m, 5-*H*), 3.47-3.39 (3H, m, 29-, 26- and 40-H*H*), 3.31 (3H, s, 41-*H*), 2.84-2.77 (3H, m, 24-H*H* and 46-*H*), 2.34 (1H, m, 22-*H*H), 2.17 (1H, m, 22-H*H*), 2.04-2.01 (2H, m, 10-*H*), 1.68-1.61 (2H, m, 6-*H* and 7-*H*H), 1.43-1.33 (3H, m, 8-*H*H and 9-*H*), 1.16 (1H, m, 8-H*H*), 1.04 (3H, d, *J* 5.4, 19-*H*), 0.99-0.86 (37H, m, 4 x SiC(CH_3)$_3$ and 7-H*H*), 0.25, 0.23, 0.21, 0.16, 0.15, 0.14, 0.12, 0.11 (24H, 8 x s, 8 x SiCH_3); δ_C (126 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 178.8 (47-*C*), 175.2 (1-*C*), 173.0 (27-*C*), 172.7 (39-*C*), 171.7 (42-*C*), 170.6 (21-*C*), 170.3 (25-*C*), 165.0 (30-*C*), 159.6 (44-*C*), 140.0 (11-*C*), 138.2 (38-*C*), 128.5 (33-*C*), 127.0 (36-*C*), 125.2 (32-*C*), 121.5 (34-*C*), 121.1 (31-*C*), 120.9 (35-*C*), 115.2 (12-*C*), 113.7 (37-*C*), 91.3 (43-*C*), 80.6 (5-*C*), 76.6 (4-*C*), 74.5 (2-*C*), 70.6 (23-*C*), 57.7 (3-*C*), 56.3 (28-*C*), 55.5 (40-*C*), 52.7 (CO_2CH_3), 49.0 (45-*C*), 47.0 (24-*C*), 45.4 (22-*C*), 43.3 (26-*C*), 38.6 (41-*C*), 36.1 (46-*C*), 35.6 (6-*C*), 35.2 (7-*C*), 35.1 (10-*C*), 30.6 (9-*C*), 27.5 (8-*C*), 27.1 (29-*C*), 27.2 (SiC(CH_3)$_3$), 27.0 (SiC(CH_3)$_3$), 27.0 (SiC(CH_3)$_3$), 26.6 (SiC(CH_3)$_3$), 19.6

(Si*C*$(CH_3)_3$), 19.5 (Si*C*$(CH_3)_3$), 19.3 (Si*C*$(CH_3)_3$), 19.0 (Si*C*$(CH_3)_3$), 17.9 (19-*C*), −2.0 (Si*C*H_3), −2.1 (Si*C*H_3), −2.7 (Si*C*H_3), −3.5 (Si*C*H_3), −3.7 (Si*C*H_3), −4.0 (Si*C*H_3), −4.2 (Si*C*H_3), −4.5 (Si*C*H_3); *m/z* HRMS (ES^+) MH^+ calculated for $C_{65}H_{113}N_8O_{13}Si_4$ 1325.7499, observed 1325.7496.

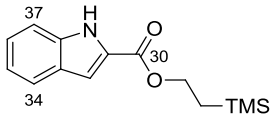
Methyl (*R*)-3-(2-(2-((*tert*-butoxycarbonyl)(methyl)amino)acetamido)-3-((2-(diethylamino)-2-oxoethyl)amino)-3-oxopropyl)-1*H*-indole-2-carboxylate (302)



Diethylamine (0.75 ml, 7.25 mmol) was added to a solution of tripeptide **301** (250 mg, 0.37 mmol) in CH_2Cl_2 (3.70 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* to afford the corresponding carboxylic acid salt as a colourless solid, which was used directly in the subsequent step. The acid was dissolved in DMF (3.70 mL) and cooled to 0 °C. *N*,*N*-Diisopropylethylamine (0.13 mL, 0.75 mmol), HATU (185 mg, 0.49 mmol) and diethylamine (50.0 μL, 0.49 mmol) were then added sequentially. The mixture was warmed slowly to room temperature and stirred for 16 h. The solution was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-70-100% EtOAc/petrol-5%MeOH/EtOAc) afforded model tripeptide **302** (175 mg, 86% over 2 steps) as a colourless solid; R_f: 0.50 (60% EtOAc/petrol); m.p. 68-70 °C; $[\alpha]_D^{20}$ +7.8 (*c* 0.27, MeOH); ν_{max}/cm^{-1} (neat) 3310,

2985, 2362, 1636, 1525, 1451, 1385, 1367, 1250, 1150, 1098, 843, 746, 608; δ_H (400 MHz, D_4-MeOD (* denotes major rotamer)) 7.79 (1H, d, *J* 7.6, 34-*H*), 7.44 (1H, d, *J* 8.1, 37-*H*), 7.30 (1H, dd, *J* 8.1 and 8.1, 36-*H*), 7.13 (1H, dd, *J* 7.6 and 7.6, 35-*H*), 4.84 (1H, m, 28-*H*), 4.06-3.96 (5H, m, 26-*H* and CO_2CH_3), 3.87-3.58 (4H, m, 40- and 29-*H*), 3.41-3.29 (4H, m, 2 x NCH_2CH_3), 2.75* and 2.67 (3H, br s, 41-*H*), 1.48 and 1.33* (9H, br s, $CO_2C(CH_3)_3$), 1.20 (3H, t, *J* 7.1, NCH_2CH_3), 1.13 (3H, t, *J* 7.1, NCH_2CH_3); δ_C (126 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 173.7 (*C*(O)), 171.8 (*C*(O)), 168.9 (*C*(O)), 164.9 (*C*(O)), 157.3 (*C*(O)), 137.9 ($C_{(Ar)}$), 129.0 ($C_{(Ar)}$), 126.5 (36-*C*), 125.3 ($C_{(Ar)}$), 121.4 (34-*C*), 121.2 (35-*C*), 120.2 ($C_{(Ar)}$), 113.5 (37-*C*), 81.6 ($CO_2C(CH_3)_3$), 56.5 (28-*C*), 53.4 (40-*C*), 52.7 (CO_2CH_3), 42.5 (NCH_2CH_3), 42.0 (26-*C*), 41.8 (NCH_2CH_3), 35.9 (41-*C*), 28.6 ($CO_2C(CH_3)_3$), 28.4 (29-*C*), 14.3 (NCH_2CH_3), 13.3 (NCH_2CH_3); *m/z* (ES^+) 746 (MH^+, 100%), 568 (MNa^+, 90%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{27}H_{39}O_7N_5Na$ 568.2742, observed 568.2722.

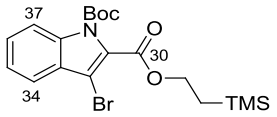
2-(Trimethylsilyl)ethyl 1*H*-indole-2-carboxylate (323)



N,*N*′-Diisopropylcarbodiimide (0.60 mL, 3.90 mmol), DMAP (79.0 mg, 0.65 mmol) and 2-(trimethylsilyl)ethanol (0.56 mL, 3.90 mmol) were added sequentially to a solution of indole-2-carboxylic acid **322** (524 mg, 3.25 mmol) in THF (32.0 mL) at room temperature. The mixture was stirred for 2 h. Additional portions of *N*,*N*′-diisopropylcarbodiimide (0.50 mL, 3.25 mmol), DMAP (40.0 mg, 0.33 mmol) and 2-(trimethylsilyl)ethanol (0.47 mL, 3.25 mmol) were then added, and the mixture was stirred for 16 h. The solution

was then filtered through Celite, washing with CH_2Cl_2, and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (5% EtOAc/petrol) afforded ester **323** (571 mg, 67%) as a colourless solid; R_f: 0.40 (10% EtOAc/petrol); m.p. 122-124 °C; ν_{max}/cm^{-1} (neat) 3340, 1686, 1531, 1454, 1364, 1314, 1251, 1198, 1167, 1040, 978, 839, 771, 739, 703, 645; δ_H (400 MHz, $CDCl_3$) 9.22 (1H, br s, N*H*), 7.75 (1H, d, *J* 7.8, 34-*H*), 7.49 (1H, d, *J* 8.1, 37-*H*), 7.38 (1H, dd, *J* 7.8 and 7.8, 36-*H*), 7.27 (1H, s, 32-*H*), 7.21 (1H, dd, *J* 7.8 and 7.8, 35-*H*), 4.53 (2H, t, *J* 8.3, $TMSCH_2C\mathit{H}_2$), 1.22 (2H, t, *J* 8.3, $TMSC\mathit{H}_2CH_2$), 0.16 (9H, s, $Si(C\mathit{H}_3)_3$); δ_C (100 MHz, $CDCl_3$) 162.3 (30-*C*), 136.8 ($\mathit{C}_{(Ar)}$), 127.7 ($\mathit{C}_{(Ar)}$), 127.5 ($\mathit{C}_{(Ar)}$), 125.2 (36-*C*), 122.6 (34-*C*), 120.7 (35-*C*), 111.9 (37-*C*), 108.4 (32-*C*), 63.4 ($TMSCH_2\mathit{C}H_2$), 17.5 ($TMS\mathit{C}H_2CH_2$), −1.4 ($Si(\mathit{C}H_3)_3$); *m/z* (ES^+) 284 (MNa^+, 100%); *m/z* HRMS (ES^-) M−H calculated for $C_{14}H_{18}O_2NSi$ 260.1112, observed 260.1114.

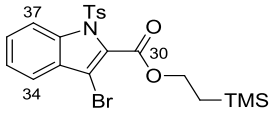
1-*tert*-Butyl 2-(2-(trimethylsilyl)ethyl) 3-bromo-1*H*-indole-1,2-dicarboxylate (325)



N-Bromosuccinimide (3.13 g, 17.6 mmol) was added in one portion to a solution of ester **323** (2.00 g, 7.66 mmol) in THF (76.0 mL) at room temperature. The mixture was stirred for 2.5 h. Saturated aqueous Na_2SO_3 was then added, the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. *N*,*N*-Diisopropylethylamine (2.70 mL, 15.3 mmol), DMAP (468 mg, 3.83 mmol) and di-*tert*-butyl dicarbonate (8.80 mL, 38.3 mmol) were added sequentially to a solution of the crude bromide in THF (51.0 mL) at 0 °C. The solution was

then warmed to room temperature and stirred for 16 h. Water was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-1% EtOAc/petrol) afforded bromide **325** (3.25 g, 96% over 2 steps) as a viscous colourless oil, which solidified in the freezer; R_f: 0.40 (5% EtOAc/petrol); m.p. 44-46 ^oC; ν_{max}/cm^{-1} (neat) 2950, 1727, 1558, 1448, 1363, 1326, 1250, 1230, 1151, 1114, 1074, 973, 858, 835, 740, 697, 642; δ_H (400 MHz, $CDCl_3$) 8.11 (1H, d, *J* 8.3, 34-*H*), 7.59 (1H, d, *J* 7.6, 37-*H*), 7.46 (1H, ddd, *J* 8.3, 7.6 and 1.5, 35-*H*), 7.35 (1H, ddd, *J* 8.3, 7.6 and 1.0, 36-*H*), 4.50-4.46 (2H, m, $TMSCH_2CH_2$), 1.64 (9H, s, $CO_2C(CH_3)_3$), 1.21-1.16 (2H, m, $TMSCH_2CH_2$), 0.10 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 161.6 (30-*C*), 148.5 (*C*(O)), 135.5 ($C_{(Ar)}$), 127.9 (2 x $C_{(Ar)}$), 127.4 (35-*C*), 123.8 (36-*C*), 120.7 (37-*C*), 115.1 (34-*C*), 102.4 ($C_{(Ar)}$), 85.3 ($CO_2C(CH_3)_3$), 64.4 ($TMSCH_2CH_2$), 27.9 ($CO_2C(CH_3)_3$), 17.4 ($TMSCH_2CH_2$), −1.5 ($Si(CH_3)_3$); *m/z* (ES^+) 462 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{19}H_{26}O_4NSiBrNa$ 462.0707, observed 462.0697.

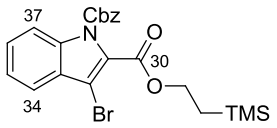
2-(Trimethylsilyl)ethyl 3-bromo-1-tosyl-1*H*-indole-2-carboxylate (324)



N-Bromosuccinimide (503 mg, 2.83 mmol) was added in one portion to a solution of ester **323** (369 mg, 1.41 mmol) in THF (14.0 mL) at room temperature. The mixture was stirred for 1.5 h. Saturated aqueous Na_2SO_3 was then added, the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered

and concentrated *in vacuo*. Triethylamine (1.58 ml, 11.3 mmol), DMAP (172 mg, 1.42 mmol) and *p*-toluenesulfonyl chloride (1.61 g, 8.46 mmol) were added sequentially to a solution of the crude bromide in CH_2Cl_2 (9.40 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 16 h. Water was added and the aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-1-2-5% EtOAc/petrol) afforded bromide **324** (595 mg, 85% over 2 steps) as a viscous colourless oil; R_f: 0.50 (10% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 2954, 1727, 1446, 1378, 1327, 1252, 1175, 1147, 1089, 1056, 928, 858, 836, 752, 703, 660; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, *J* 8.3, 34-*H*), 7.85 (2H, d, *J* 8.6, Ph*H*), 7.51 (1H, d, *J* 8.1, 37-*H*), 7.44 (1H, ddd, *J* 8.3, 7.3 and 1.2, 35-*H*), 7.33 (1H, ddd, *J* 8.1, 7.3 and 1.0, 36-*H*), 7.23 (2H, d, *J* 8.6, Ph*H*), 4.59-4.54 (2H, m, $TMSCH_2C\mathit{H_2}$), 2.35 (3H, s, $ArCH_3$), 1.27-1.22 (2H, m, $TMSCH_2CH_2$), 0.11 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 161.3 (30-*C*), 145.4 ($C_{(Ar)}$), 135.3 ($C_{(Ar)}$), 134.2 ($C_{(Ar)}$), 129.7 ($CH_{(Ar)}$), 128.8 (2 x $C_{(Ar)}$), 127.4 ($CH_{(Ar)}$ and 35-*C*), 124.7 (36-*C*), 120.9 (37-*C*), 114.9 (34-*C*), 103.7 ($C_{(Ar)}$), 65.3 ($TMSCH_2CH_2$), 21.6 ($ArCH_3$), 17.3 ($TMSCH_2CH_2$), −1.5 ($Si(CH_3)_3$); *m/z* (ES^+) 516 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{21}H_{24}O_4NSiBrSNa$ 516.0271, observed 516.0263.

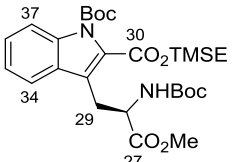
1-Benzyl 2-(2-(trimethylsilyl)ethyl) 3-bromo-1*H*-indole-1,2-dicarboxylate (326)



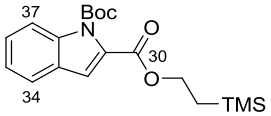
N,*N*-Diisopropylethylamine (0.29 ml, 1.67 mmol), DMAP (46.0 mg, 0.38 mmol) and benzyl chloroformate (0.14 mL, 0.98 mmol) were added sequentially to a solution of purified 2-(trimethylsilyl)ethyl 3-bromo-1*H*-indole-2-carboxylate (258 mg, 0.76 mmol) in THF (7.50 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 15 h. Water was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (petrol-1-2% EtOAc/petrol) afforded bromide **326** (313 mg, 87%) as a viscous colourless oil; R_f: 0.40 (5% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 2954, 1731, 1449, 1389, 1321, 1250, 1208, 1117, 1076, 1042, 987, 935, 858, 835, 751, 696, 633; δ_H (400 MHz, $CDCl_3$) 8.12 (1H, d, *J* 8.6, 34-*H*), 7.60 (1H, m, 37-*H*), 7.48-7.35 (7H, m, 35-, 36-*H* and 5 x Ar*H*), 5.43 (2H, s, OC*H*$_2$Ph), 4.26-4.22 (2H, m, TMSCH$_2$C*H*$_2$), 1.06-1.01 (2H, m, TMSC*H*$_2$CH$_2$), 0.06 (9H, s, Si(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 161.3 (30-*C*), 149.9 (*C*(O)), 135.5 ($C_{(Ar)}$), 134.1 ($C_{(Ar)}$), 128.9 (*C*H$_{(Ar)}$), 128.7 (2 x *C*H$_{(Ar)}$), 128.6 ($C_{(Ar)}$), 128.0 ($C_{(Ar)}$), 127.6 (*C*H$_{(Ar)}$), 124.2 (*C*H$_{(Ar)}$), 120.8 (37-*C*), 115.2 (34-*C*), 103.3 ($C_{(Ar)}$), 69.8 (O*C*H$_2$Ph), 64.5 (TMSCH$_2$*C*H$_2$), 17.2 (TMS*C*H$_2$CH$_2$), −1.5 (Si(*C*H$_3$)$_3$); *m/z* (ES$^+$) 496 (MNa$^+$, 100%); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{22}H_{24}O_4NSiBrNa$ 496.0550, observed 496.0536.

(*R*)-1-*tert*-Butyl 2-(2-(trimethylsilyl)ethyl) 3-(2-((*tert*-butoxycarbonyl)amino)-3-metho xy-3-oxopropyl)-1*H*-indole-1,2-dicarboxylate (316) and

1-*tert*-butyl 2-(2-(trimethylsilyl)ethyl) 1*H*-indole-1,2-dicarboxylate (330)



316



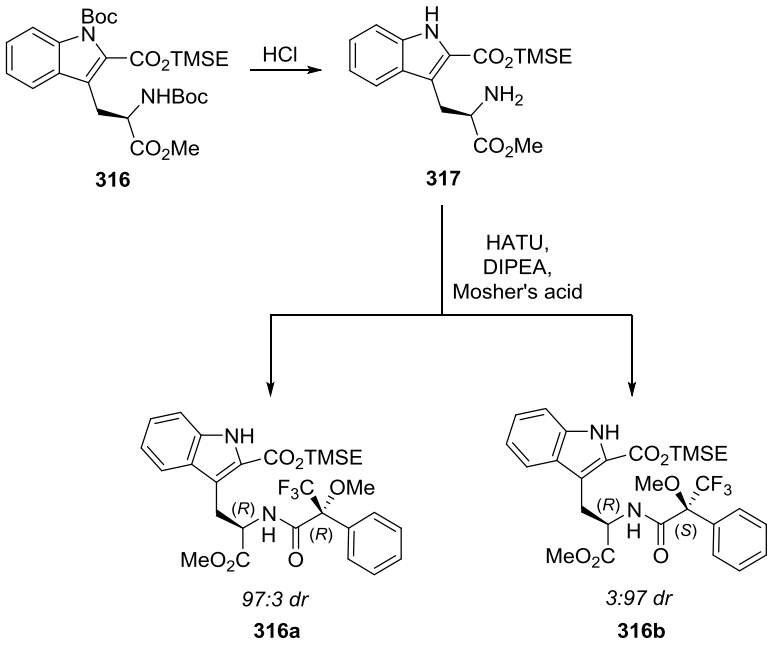
330

1,2-Dibromoethane (0.16 mL, 1.82 mmol) was added to a suspension of zinc dust (2.32 g, 35.4 mmol) in DMF (8.00 mL) at room temperature. The mixture was heated at 50 °C for 30 minutes. Then the reaction mixture was allowed to cool to room temperature after which chlorotrimethylsilane (50.0 μL, 0.36 mmol) was added, and the mixture was stirred for further 30 minutes. *N*-(*tert*-Butoxycarbonyl)-3-iodo-D-alanine methyl ester (1.94 g, 5.90 mmol) in DMF (8.00 mL) was added and the mixture was then stirred for 2 h at room temperature. The reaction mixture was left standing for 30 minutes, and the supernatant liquid was transferred to a solution of bromide **325** (2.00 g, 4.54 mmol), $Pd_2(dba)_3$ (208 mg, 0.23 mmol) and QPhos (260 mg, 0.37 mmol) in DMF (2.00 mL). The resultant mixture was heated at 35 °C for 2 h and then concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (2-5-10% EtOAc/petrol) afforded protected amino acid **316** (1.76 g, 69%) and a side-product – indole **330** (456 mg, approx. 25%, 90% purity). Data for amino acid **316**: colourless foam; R_f: 0.30 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +4.0 (*c* 0.48, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2978, 1716, 1502, 1453, 1366, 1328, 1247, 1215, 1154, 1103, 1061, 939, 837, 748, 697; δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* 8.6, 34-*H*), 7.66 (1H, d, *J* 7.8, 37-*H*), 7.42 (1H, dd, *J* 7.8 and 7.8, 35-*H*), 7.30 (1H, dd,

J 7.8 and 7.8, 36-*H*), 5.77 (1H, d, *J* 7.1, N*H*), 4.51 (1H, m, 28-*H*), 4.46-4.40 (2H, m, TMSCH$_2$C*H$_2$*), 3.69 (3H, s, CO$_2$C*H$_3$*), 3.30 (1H, dd, *J* 13.9 and 5.9, 29-*H*H), 3.23 (1H, dd, *J* 13.9 and 8.3, 29-H*H*), 1.64 (9H, s, CO$_2$C(C*H$_3$*)$_3$), 1.40 (9H, s, CO$_2$C(C*H$_3$*)$_3$), 1.16 (2H, t, *J* 9.5, TMSC*H$_2$*CH$_2$), 0.09 (9H, s, Si(C*H$_3$*)$_3$); δ_C (100 MHz, $CDCl_3$) 172.5 (27-*C*), 162.6 (30-*C*), 155.4 (*C*(O)), 149.2 (*C*(O)), 136.5 ($C_{(Ar)}$), 128.7 ($C_{(Ar)}$), 128.3 ($C_{(Ar)}$), 126.9 (35-*C*), 123.3 (36-*C*), 121.3 ($C_{(Ar)}$), 120.2 (37-*C*), 115.0 (34-*C*), 84.6 (CO$_2$*C*(CH$_3$)$_3$), 79.7 (CO$_2$*C*(CH$_3$)$_3$), 64.3 (TMSCH$_2$*C*H$_2$), 53.8 (28-*C*), 52.3 (CO$_2$*C*H$_3$), 28.3 (CO$_2$C(*C*H$_3$)$_3$), 28.0 (CO$_2$C(*C*H$_3$)$_3$), 27.2 (29-*C*), 17.3 (TMS*C*H$_2$CH$_2$), −1.6 (Si(*C*H$_3$)$_3$); *m/z* (ES$^+$) 585 (MNa$^+$, 100%); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{28}H_{42}O_8N_2SiNa$ 585.2603, observed 585.2596.

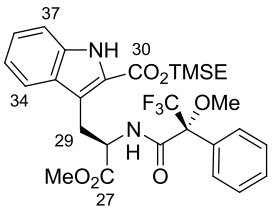
Data for indole **330**: colourless oil; R_f: 0.40 (5% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 2954, 1727, 1543, 1476, 1449, 1369, 1323, 1229, 1195, 1154, 1135, 1115, 1069, 932, 836, 746, 696; δ_H (400 MHz, $CDCl_3$) 8.09 (1H, d, *J* 8.6, 34-*H*), 7.61 (1H, d, *J* 7.8, 37-*H*), 7.42 (1H, ddd, *J* 8.6, 7.3 and 1.2, 35-*H*), 7.27 (1H, ddd, *J* 7.8, 7.3 and 0.7, 36-*H*), 7.09 (1H, s, 32-*H*), 4.44-4.40 (2H, m, TMSCH$_2$C*H$_2$*), 1.64 (9H, s, CO$_2$C(C*H$_3$*)$_3$), 1.16-1.12 (2H, m, TMSC*H$_2$*CH$_2$), 0.10 (9H, s, Si(C*H$_3$*)$_3$); δ_C (100 MHz, $CDCl_3$) 162.0 (30-*C*), 149.3 (*C*(O)), 137.8 ($C_{(Ar)}$), 131.0 ($C_{(Ar)}$), 127.6 ($C_{(Ar)}$), 126.6 (35-*C*), 123.2 (36-*C*), 122.1 (37-*C*), 114.8 (34-*C*), 114.4 (32-*C*), 84.5 (CO$_2$*C*(CH$_3$)$_3$), 63.7 (TMSCH$_2$*C*H$_2$), 27.8 (CO$_2$C(*C*H$_3$)$_3$), 17.3 (TMS*C*H$_2$CH$_2$), −1.5 (Si(*C*H$_3$)$_3$); *m/z* (ES$^+$) 384 (MNa$^+$, 100%); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{19}H_{27}O_4NSiNa$ 384.1602, observed 384.1592.

The enantiopurity of amino acid **316** was confirmed by removal of the Boc groups and formation of the corresponding Mosher's amides:



Scheme 103. Confirmation of the enantiopurity of amino acid **316.**

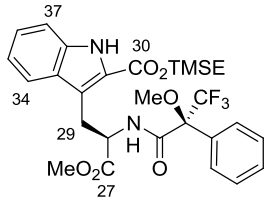
2-(Trimethylsilyl)ethyl 3-((*R*)-3-methoxy-3-oxo-2-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)propyl)-1*H*-indole-2-carboxylate (316a)



Hydrogen chloride (0.17 mL of a 4 M solution in dioxane, 0.68 mmol) was added to a solution of protected amino acid **316** (38.5 mg, 68.4 μmol) in CH_3CN (0.5 mL) at room temperature. The mixture was heated at 60 ^oC for 1 h. After this time the reaction was

cooled to room temperature and slowly quenched with saturated aqueous $NaHCO_3$. EtOAc was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude amine **317** as a pale yellow oil. Amine **317** was dissolved in DMF (0.5 mL) and the solution was cooled to 0 °C. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (16.5 mg, 70.4 μmol), HATU (30.2 mg, 79.0 μmol) and *N*,*N*-diisopropylethylamine (31.0 μL, 0.18 mmol) were then added sequentially. The mixture was warmed slowly to room temperature and stirred for 16 h. The reaction was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/petrol) afforded amide **316a** (14.5 mg, 37% over 2 steps) as a colourless oil; R_f: 0.40 (20% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −7.5 (*c* 1.13, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3333, 2954, 1747, 1687, 1520, 1438, 1319, 1249, 1165, 1120, 1098, 996, 942, 837, 744, 720, 696; δ_H (400 MHz, $CDCl_3$) 8.53 (1H, s, N*H*), 7.71 (1H, d, *J* 8.1, 34-*H*), 7.64 (1H, d, *J* 8.1, N*H*), 7.40-7.36 (2H, m, 37-*H* and Ar*H*), 7.29 (1H, dd, *J* 7.1 and 7.1, 36-*H*), 7.18 (1H, ddd, *J* 8.1, 8.1 and 1.7, 35-*H*), 7.15-7.06 (4H, m, 4 xAr*H*), 4.93 (1H, m, 28-*H*), 4.35-4.23 (2H, m, $TMSCH_2CH_2$), 3.78 (3H, s, CO_2CH_3), 3.59-3.56 (2H, m, 29-*H*), 3.52 (3H, d, *J* 1.7, OCH_3), 1.16-1.11 (2H, m, $TMSCH_2CH_2$), 0.11 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.8 (27-*C*), 166.6 (*C*(O)), 161.9 (30-*C*), 135.5 ($C_{(Ar)}$), 133.1 ($C_{(Ar)}$), 128.9 ($CH_{(Ar)}$), 128.0 ($CH_{(Ar)}$), 127.4 ($C_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 126.1 (36-*C*), 124.3 ($C_{(Ar)}$), 123.5 (q, $^1J_{C\text{-}F}$ 290.9, CF_3), 120.9 (35-*C*), 120.2 (34-*C*), 118.1 ($C_{(Ar)}$), 111.8 (37-*C*), 84.0 (q, $^2J_{C\text{-}F}$ 26.2, *C*(OCH_3)(CF_3)Ph), 63.7 ($TMSCH_2CH_2$), 55.2 (OCH_3), 53.2 (28-*C*), 52.5 (CO_2CH_3), 26.5 (29-*C*), 17.5 ($TMSCH_2CH_2$), −1.5 ($Si(CH_3)_3$); δ_F (376 MHz, $CDCl_3$) −69.2; *m/z* (ES^+) 579 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{28}H_{34}O_6N_2F_3Si$ 579.2133, observed 579.2120.

2-(Trimethylsilyl)ethyl 3-((*R*)-3-methoxy-3-oxo-2-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)propyl)-1*H*-indole-2-carboxylate (316b)

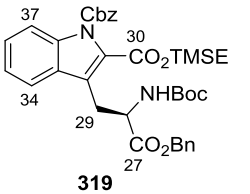


Hydrogen chloride (0.17 mL of a 4 M solution in dioxane, 0.68 mmol) was added to a solution of protected amino acid **316** (38.5 mg, 68.4 μmol) in CH_3CN (0.5 mL) at room temperature. The mixture was heated at 60 °C for 1 h. After this time the reaction was then cooled to room temperature and slowly quenched with saturated aqueous $NaHCO_3$. EtOAc was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude amine **317** as a pale yellow oil. Amine **317** was dissolved in DMF (0.5 mL) and the solution was cooled to 0 °C. (*S*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (16.5 mg, 70.4 μmol), HATU (30.2 mg, 79.0 μmol) and *N*,*N*-diisopropylethylamine (31.0 μL, 0.18 mmol) were then added sequentially. The mixture was warmed slowly to room temperature and stirred for 16 h. The reaction was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/petrol) afforded amide **316b** (15.1 mg, 38% over 2 steps) as a colourless oil; R_f: 0.40 (20% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −35.5 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3337, 2953, 1745, 1686, 1515, 1439, 1318, 1249, 1164, 1120, 1098, 993, 947, 837, 744, 721, 696; δ_H (400 MHz, $CDCl_3$) 8.82 (1H, s, N*H*), 7.84 (1H, d, *J* 6.9, N*H*), 7.74 (1H, d, *J* 8.1, 34-*H*), 7.56-7.54 (2H, m, 2 x Ar*H*), 7.41-7.36 (5H, m, 3 x Ar*H*,

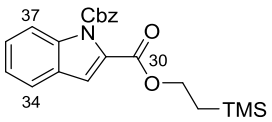
36- and 37-*H*), 7.20 (1H, ddd, *J* 8.1, 8.1 and 1.5, 35-*H*), 4.81 (1H, m, 28-*H*), 4.51-4.38 (2H, m, $TMSCH_2CH_2$), 3.70 (3H, s, CO_2CH_3), 3.66-3.64 (2H, m, 29-*H*), 3.16 (3H, d, *J* 1.2, OCH_3), 1.22-1.08 (2H, m, $TMSCH_2CH_2$), 0.10 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.7 (27-*C*), 166.6 (*C*(O)), 162.3 (30-*C*), 135.7 ($C_{(Ar)}$), 132.3 ($C_{(Ar)}$), 129.4 ($CH_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 128.1 ($CH_{(Ar)}$), 127.5 ($C_{(Ar)}$), 126.1 (36-*C*), 124.4 ($C_{(Ar)}$), 123.6 (q, $^1J_{C\text{-}F}$ 289.3, CF_3), 120.9 (35-*C*), 120.3 (34-*C*), 118.2 ($C_{(Ar)}$), 111.9 (37-*C*), 83.9 (q, $^2J_{C\text{-}F}$ 27.0, $C(OCH_3)(CF_3)Ph$), 63.9 ($TMSCH_2CH_2$), 54.6 (OCH_3), 53.9 (28-*C*), 52.4 (CO_2CH_3), 26.4 (29-*C*), 17.5 ($TMSCH_2CH_2$), −1.6 ($Si(CH_3)_3$); δ_F (376 MHz, $CDCl_3$) −69.4; *m/z* (ES^+) 579 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{28}H_{34}O_6N_2F_3Si$ 579.2133, observed 579.2125.

(*R*)-1-Benzyl 2-(2-(trimethylsilyl)ethyl) 3-(3-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)-3-oxopropyl)-1*H*-indole-1,2-dicarboxylate (319) and

1-benzyl 2-(2-(trimethylsilyl)ethyl) 1*H*-indole-1,2-dicarboxylate (335)



319



335

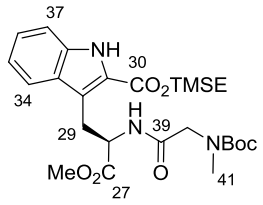
1,2-Dibromoethane (4.00 μL, 42.0 μmol) was added to a suspension of zinc dust (54.0 mg, 0.82 mmol) in DMF (0.20 mL) at room temperature. The mixture was heated at 50 °C for 30 minutes. Then the reaction mixture was allowed to cool to room temperature after which chlorotrimethylsilane (1.00 μL, 8.40 μmol) was added, and the mixture was stirred for further 30 minutes. *N*-(*tert*-Butoxycarbonyl)-3-iodo-D-alanine benzyl ester (56.0 mg, 0.14 mmol) in DMF (0.20 mL) was added and the mixture was then stirred for 2 h at room

temperature. The reaction mixture was left standing for another 30 minutes, and the supernatant liquid was transferred to a solution of bromide **326** (50.0 mg, 0.11 mmol), $Pd_2(dba)_3$ (5.00 mg, 5.30 μmol) and QPhos (8.00 mg, 10.5 μmol) in DMF (0.10 mL). The resultant mixture was heated at 35 °C for 4.5 h and then concentrated *in vacuo* onto silica gel. Purification by flash column chromatography (2-5-10% EtOAc/petrol) afforded protected amino acid **319** (26.1 mg, 37%) and a side-product – indole **335** (6.0 mg, 15%). Data for amino acid **319**: colourless oil; R_f: 0.25 (10% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +5.5 (*c* 2.08, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2955, 1739, 1713, 1499, 1454, 1389, 1328, 1249, 1219, 1170, 1104, 1061, 1025, 938, 858, 836, 748, 696; δ_H (400 MHz, $CDCl_3$) 8.07 (1H, d, *J* 8.3, 34-*H*), 7.67 (1H, d, *J* 7.8, 37-*H*), 7.46-7.38 (6H, m, 6 x Ar*H*), 7.33-7.29 (4H, m, 4 x Ar*H*), 7.22-7.20 (2H, m, 2 x Ar*H*), 5.78 (1H, d, *J* 7.1, N*H*), 5.40 (2H, s, OCH_2Ph), 5.10 (2H, d, *J* 5.9, OCH_2Ph), 4.59 (1H, m, 28-*H*), 4.23-4.16 (2H, m, $TMSCH_2CH_2$), 3.32-3.22 (2H, m, 29-*H*), 1.39 (9H, s, $CO_2C(CH_3)_3$), 1.01-0.96 (2H, m, $TMSCH_2CH_2$), 0.03 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 171.8 (27-*C*), 162.3 (30-*C*), 155.3 (*C*(O)), 150.6 (*C*(O)), 136.4 ($C_{(Ar)}$), 135.3 ($C_{(Ar)}$), 134.5 ($C_{(Ar)}$), 128.8 ($C_{(Ar)}$), 128.7 (2 x $CH_{(Ar)}$), 128.5 ($CH_{(Ar)}$), 128.4 ($CH_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 128.1 ($C_{(Ar)}$), 127.9 ($CH_{(Ar)}$), 127.2 ($CH_{(Ar)}$), 123.7 ($CH_{(Ar)}$), 122.4 ($C_{(Ar)}$), 120.3 (37-*C*), 115.2 (34-*C*), 79.7 ($CO_2C(CH_3)_3$), 69.5 (OCH_2Ph), 67.1 (OCH_2Ph), 64.4 ($TMSCH_2CH_2$), 53.9 (28-*C*), 28.3 ($CO_2C(CH_3)_3$), 27.2 (29-*C*), 17.2 ($TMSCH_2CH_2$), −1.6 ($Si(CH_3)_3$); *m/z* (ES^+) 695 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{37}H_{44}O_8N_2SiNa$ 695.2759, observed 695.2734.

Data for indole **335**: colourless oil; R_f: 0.40 (5% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 2954, 1724, 1545, 1450, 1390, 1320, 1264, 1220, 1197, 1153, 1135, 1114, 1065, 982, 938, 836, 748, 697; δ_H (400 MHz, $CDCl_3$) 8.08 (1H, dd, *J* 8.6 and 0.7, 34-*H*), 7.61 (1H, d, *J* 7.6,

37-*H*), 7.48-7.37 (6H, m, 35-*H* and 5 x Ar*H*), 7.28 (1H, m, 36-*H*), 7.13 (1H, d, *J* 0.7, 32-*H*), 5.43 (2H, s, OC*H*$_2$Ph), 4.28-4.24 (2H, m, TMSCH$_2$C*H*$_2$), 1.03-1.09 (2H, m, TMSC*H*$_2$CH$_2$), 0.05 (9H, s, Si(C*H*$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 161.9 (30-*C*), 150.8 (*C*(O)), 134.5 ($C_{(Ar)}$), 131.0 ($C_{(Ar)}$), 128.9 ($C_{(Ar)}$), 128.8 ($CH_{(Ar)}$), 128.7 (2 x $CH_{(Ar)}$), 127.7 ($C_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 123.6 (36-*C*), 122.2 (37-*C*), 115.4 (32-*C*), 115.0 (34-*C*), 69.6 (O*C*H$_2$Ph), 63.9 (TMSCH$_2$*C*H$_2$), 17.2 (TMS*C*H$_2$CH$_2$), −1.5 (Si(*C*H$_3$)$_3$); *m/z* (ES^+) 418 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{22}H_{25}O_4NSiNa$ 418.1445, observed 418.1429.

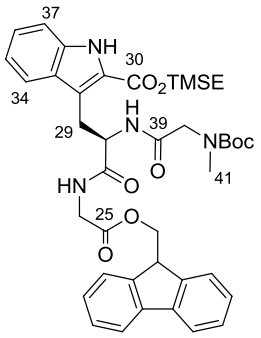
2-(Trimethylsilyl)ethyl (*R*)-3-(2-(2-((*tert*-butoxycarbonyl)(methyl)amino)acetamido)-3-methoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (318)



Hydrogen chloride (3.00 mL of a 4 M solution in dioxane, 12.0 mmol) was added to a solution of protected amino acid **316** (0.83 g, 1.47 mmol) in CH_3CN (10.0 mL) at room temperature. The mixture was heated at 60 °C for 1 h 40 minutes. After this time the reaction was then cooled to room temperature and slowly quenched with saturated aqueous $NaHCO_3$. EtOAc was added and the aqueous layer separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude amine **317** as a pale yellow oil. Amine **317** was dissolved in DMF (10.0 mL) and cooled to 0 °C. *N*-Boc-Sar **23** (324 mg, 1.71 mmol), HATU (732 mg, 1.93 mmol) and *N*,*N*-diisopropylethylamine (0.75 mL, 4.28 mmol) were then added sequentially. The mixture was warmed slowly to room temperature and stirred for 3 h. The reaction was then

diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (25-40% EtOAc/petrol) afforded dipeptide **318** (471 mg, 60% over 2 steps) as a colourless foam; R_f: 0.50 (50% EtOAc/petrol); m.p. 43-45 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −13.5 (*c* 0.43, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3335, 3066, 2955, 1747, 1699, 1670, 1544, 1526, 1446, 1394, 1383, 1322, 1247, 1145, 1095, 1053, 935, 867, 837, 747, 697; δ_H (400 MHz, $CDCl_3$) 9.03 (1H, br s, N*H*), 7.69 (1H, d, *J* 8.1, 34-*H*), 7.37 (1H, d, *J* 8.1, 37-*H*), 7.31 (1H, dd, *J* 7.8 and 7.8, 36-*H*), 7.16 (1H, dd, *J* 7.8 and 7.8, 35-*H*), 4.82 (1H, br s, 28-*H*), 4.48 (2H, br s, $TMSCH_2CH_2$), 3.86-3.82 (2H, m, 40-*H*), 3.68 (3H, br s, CO_2CH_3), 3.60 (2H, d, *J* 5.6, 29-*H*), 2.73 (3H, s, 41-*H*), 1.38 (9H, s, $CO_2C(CH_3)_3$), 1.17 (2H, t, *J* 8.8, $TMSCH_2CH_2$), 0.10 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 172.0 (27-*C*), 169.6 (39-*C*), 162.3 (30-*C*), 155.1 (*C*(O)), 135.6 ($C_{(Ar)}$), 127.8 ($C_{(Ar)}$), 125.8 (36-*C*), 124.4 ($C_{(Ar)}$), 120.7 (35-*C*), 120.2 (34-*C*), 118.4 ($C_{(Ar)}$), 111.9 (37-*C*), 80.3 ($CO_2C(CH_3)_3$), 63.8 ($TMSCH_2CH_2$), 53.8 (28-*C*), 53.0 (40-*C*), 52.2 (CO_2CH_3), 35.2 (41-*C*), 28.1 ($CO_2C(CH_3)_3$), 26.5 (29-*C*), 17.6 ($TMSCH_2CH_2$), −1.6 ($Si(CH_3)_3$); *m/z* (ES^+) 534 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{26}H_{40}O_7N_3Si$ 534.2630, observed 534.2613.

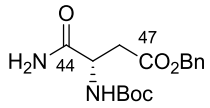
2-(Trimethylsilyl)ethyl (*R*)-3-(3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*tert*-butoxycarbonyl)(methyl)amino)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (337)



Trimethyltin hydroxide (1.00 g, 5.53 mmol) was added to a solution of dipeptide **318** (378 mg, 0.71 mmol) in 1,2-DCE (7.00 mL) at room temperature. The mixture was heated at 60 ^{o}C for 5.5 h. After this time the reaction was cooled to room temperature, diluted with EtOAc, washed with 1M aqueous $KHSO_4$ (x 3), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude acid **318a** as a colourless foam. Acid **318a** was dissolved in DMF (7.00 mL) and the solution was cooled to 0 ^{o}C. 2,6-Lutidine (0.25 mL, 2.12 mmol), HATU (296 mg, 0.78 mmol) and Gly-OFm·TFA **336** (273 mg, 0.74 mmol) were then added sequentially. The mixture was warmed slowly to room temperature and stirred for 16 h. The reaction was then diluted with EtOAc and washed with brine solution (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30-50% EtOAc/petrol) afforded tripeptide **337** (423 mg, 79% over 2 steps) as a colourless solid; R_f: 0.50 (60% EtOAc/petrol); m.p. 112-114 ^{o}C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +5.3 (*c* 0.68, MeOH); ν_{max}/cm^{-1} (neat) 2949, 1748, 1669, 1543, 1448, 1396, 1320, 1249, 1152, 1098, 1039, 839, 744; δ_H (400 MHz, D_4-MeOD (* denotes major rotamer)) 7.75-7.74 (3H, m, 3 x Ar*H*), 7.61 (2H, d, *J* 7.3, 2 x Ar*H*), 7.41 (1H, d, *J* 8.3, Ar*H*), 7.37-7.24 (5H, m,

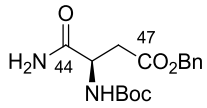
5 x Ar*H*), 7.10 (1H, dd, *J* 7.6 and 7.6, Ar*H*), 4.82 (1H, m, 28-*H*), 4.52-4.47 (2H, m, TMSCH$_2$C*H$_2$*), 4.43-4.39 (2H, m, OC*H$_2$*CH), 4.20 (1H, t, *J* 6.9, OCH$_2$C*H*), 3.96* and 3.95 (2H, s, 26-*H*), 3.78-3.44 (4H, m, 40- and 29-*H*), 2.67* and 2.59 (3H, s, 41-*H*), 1.41 and 1.22* (9H, s, CO$_2$C(C*H$_3$*)$_3$), 1.27-1.22 (2H, m, TMSC*H$_2$*CH$_2$), 0.09 (9H, s, Si(C*H$_3$*)$_3$); δ_C (126 MHz, D$_4$-MeOD (chemical shifts reported for the major rotamer only)) 174.4 (27-*C*), 171.1 (25- and 39-*C*), 164.4 (30-*C*), 157.3 (*C*(O)), 145.1 (2 x *C*$_{(Ar)}$), 142.7 (*C*$_{(Ar)}$), 138.0 (*C*$_{(Ar)}$), 129.0 (*C*H$_{(Ar)}$), 128.4 (*C*H$_{(Ar)}$ and *C*$_{(Ar)}$), 126.5 (*C*H$_{(Ar)}$), 126.3 (*C*H$_{(Ar)}$), 125.9 (*C*$_{(Ar)}$), 121.4 (*C*H$_{(Ar)}$), 121.3 (*C*H$_{(Ar)}$), 121.1 (*C*H$_{(Ar)}$), 120.0 (*C*$_{(Ar)}$), 113.5 (*C*H$_{(Ar)}$), 81.7 (CO$_2$*C*(CH$_3$)$_3$), 68.2 (O*C*H$_2$CH), 64.6 (TMSCH$_2$*C*H$_2$), 56.6 (28-*C*), 53.5 (40-*C*), 48.0 (OCH$_2$*C*H), 42.3 (26-*C*), 36.2 (41-*C*), 28.8 (CO$_2$C(*C*H$_3$)$_3$), 28.6 (29-*C*), 18.8 (TMS*C*H$_2$CH$_2$), −1.3 (Si(*C*H$_3$)$_3$); δ_H (500 MHz, D$_6$-DMSO, 363 K) 11.21 (1H, s, N*H*), 8.01 (1H, m, N*H*), 7.85 (2H, d, *J* 7.6, 2 x Ar*H*), 7.79 (1H, d, *J* 8.2, 34-*H*), 7.67 (2H, d, *J* 7.6, 2 x Ar*H*), 7.53 (1H, d, *J* 7.9, N*H*), 7.44-7.39 (3H, m, 2 x Ar*H* and 37-*H*), 7.33 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 7.23 (1H, dd, *J* 7.9 and 7.9, 36-*H* or 35-*H*), 7.06 (1H, dd, *J* 7.9 and 7.9, 35-*H* or 36-*H*), 4.73 (1H, m, 28-*H*), 4.46-4.42 (2H, m, TMSCH$_2$C*H$_2$*), 4.38 (2H, d, *J* 7.3, OC*H$_2$*CH), 4.25 (1H, t, *J* 7.0, OCH$_2$C*H*), 3.91 (1H, dd, *J* 17.3 and 6.0, 26-*H*H), 3.85 (1H, dd, *J* 17.3 and 5.7, 26-H*H*), 3.72 (1H, d, *J* 16.4, 40-*H*H), 3.56 (1H, d, *J* 16.4, 40-H*H*), 3.53 (1H, dd, *J* 13.6 and 4.7, 29-*H*H), 3.38 (1H, dd, *J* 13.6 and 9.1, 29-H*H*), 2.54 (3H, s, 41-*H*), 1.32 (9H, s, CO$_2$C(C*H$_3$*)$_3$), 1.21-1.17 (2H, m, TMSC*H$_2$*CH$_2$), 0.08 (9H, s, Si(C*H$_3$*)$_3$); *m/z* (ES$^+$) 756 (MH$^+$, 100%), 777 (MNa$^+$, 75%); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{41}H_{51}O_8N_4Si$ 755.3471, observed 755.3454.

Benzyl (*S*)-4-amino-3-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate (271a)[41]



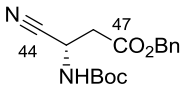
Ethyl chloroformate (0.57 mL, 6.01 mmol) was slowly added to a solution of triethylamine (0.84 mL, 6.01 mmol) and (*S*)-4-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoic acid (1.62 g, 5.01 mmol) in THF (25.0 mL) at 0 °C and the solution was stirred for 2 h at this temperture. The resulting suspension was treated with ammonia (4.00 mL of a 35% aqueous solution) and stirred for 30 minutes at 0 °C. The aqueous phase was then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford amide **271a** (1.62 g, quant.) as a colourless solid; R_f: 0.40 (50% EtOAc/petrol); m.p. 163-165 °C (lit.[41] m.p. 161-162 °C); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +15.4 (*c* 0.41, $CHCl_3$) (lit.[41] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +38.5 (*c* 0.13, $CHCl_3$)); δ_H (400 MHz, D_6-DMSO) 7.37-7.30 (5H, m, 5 x Ph*H*), 7.27 (1H, br s, N*H*), 7.10 (1H, br s, N*H*), 7.05 (1H, d, *J* 8.6, N*H*), 5.08 (2H, d, *J* 2.7, OCH_2Ph), 4.29 (1H, m, 45-*H*), 2.76 (1H, dd, *J* 16.1 and 5.4, 46-*H*H), 4.58 (1H, dd, *J* 16.1 and 8.8, 46-H*H*), 1.37 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, D_6-DMSO) 172.6 (44- or 47-*C*), 170.3 (44- or 47-*C*), 155.2 (*C*(O)), 136.1 ($C_{(Ar)}$), 128.4 (C$H_{(Ar)}$), 127.9 (C$H_{(Ar)}$), 127.8 (C$H_{(Ar)}$), 78.2 ($CO_2C(CH_3)_3$), 65.6 (OCH_2Ph), 50.8 (45-*C*), 36.4 (46-*C*), 28.2 ($CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[41]

Benzyl (*R*)-4-amino-3-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate (*epi*-271a)



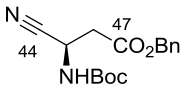
Ethyl chloroformate (1.74 mL, 18.2 mmol) was slowly added to a solution of triethylamine (2.53 mL, 18.2 mmol) and (*R*)-4-(benzyloxy)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoic acid (4.89 g, 15.1 mmol) in THF (75.0 mL) at 0 °C and the solution was stirred for 2 h at this temperature. The resulting suspension was treated with ammonia (12.0 mL of a 35% aqueous solution) and stirred for 30 minutes at 0 °C. The aqueous phase was then separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford amide *epi*-**271a** (4.88 g, quant.) as a colourless solid; R_f: 0.40 (50% EtOAc/petrol); m.p. 146-148 ºC; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −8.5 (*c* 0.58, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2359, 2174, 2103, 1976, 1915, 1734, 1673, 1637, 1518, 1295, 1161, 982, 754, 724, 663, 626; δ_H (400 MHz, D_6-DMSO) 7.37-7.32 (5H, m, 5 x Ph*H*), 7.25 (1H, br s, N*H*), 7.09 (1H, br s, N*H*), 7.03 (1H, d, *J* 8.4, N*H*), 5.08 (2H, d, *J* 2.0, OC*H*$_2$Ph), 4.29 (1H, m, 45-*H*), 2.77 (1H, dd, *J* 16.0 and 5.3, 46-*H*H), 4.58 (1H, dd, *J* 16.0 and 8.7, 46-H*H*), 1.38 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, D_6-DMSO) 172.6 (44- or 47-*C*), 170.3 (44- or 47-*C*), 155.1 (*C*(O)), 136.1 ($C_{(Ar)}$), 128.4 (C*H*$_{(Ar)}$), 127.9 (C*H*$_{(Ar)}$), 127.7 (C*H*$_{(Ar)}$), 78.2 ($CO_2C(CH_3)_3$), 65.6 (O*C*H$_2$Ph), 50.8 (45-*C*), 36.4 (46-*C*), 28.1 ($CO_2C(CH_3)_3$); *m/z* (ES^+) 345 (MNa^+, 50%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{16}H_{23}O_5N_2$ 323.1602, observed 323.1602.

Benzyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-cyanopropanoate (271)[41]



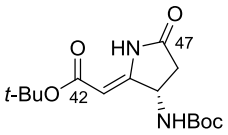
Pyridine (2.02 mL, 25.0 mmol) and freshly distilled trifluoroacetic anhydride (1.39 mL, 10.0 mmol) were added sequentially to a solution of amide **271a** (1.62 g, 5.01 mmol) in THF (25.0 mL) at 0 °C. The resulting red solution was stirred for 2 h at 0 °C and then diluted with EtOAc. After warming to room temperature the solution was washed with aqueous saturated $NaHCO_3$ (x 2), 1 M HCl and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/petrol) afforded nitrile **271** (1.33 g, 87%) as a pale yellow oil; R_f: 0.30 (20% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ –22.6 (*c* 1.58, $CHCl_3$) (lit.[41] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ –26.1 (c 1.00, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 7.38-7.32 (5H, m, 5 x Ph*H*), 5.86 (1H, d, *J* 8.8, N*H*), 5.17 (2H, s, OCH_2Ph), 4.94 (1H, br s, 45-*H*), 2.91 (1H, dd, *J* 17.1 and 5.6, 46-*H*H), 2.85 (1H, dd, *J* 17.1 and 6.1, 46-H*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 168.8 (47-*C*), 154.0 (*C*(O)), 134.7 ($C_{(Ar)}$), 128.4 ($CH_{(Ar)}$), 128.3 ($CH_{(Ar)}$), 128.1 ($CH_{(Ar)}$), 117.7 (44-*C*), 81.0 ($CO_2C(CH_3)_3$), 67.1 (OCH_2Ph), 38.2 (45-*C*), 37.1 (46-*C*), 27.9 ($CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[41]

Benzyl (*R*)-3-((*tert*-butoxycarbonyl)amino)-3-cyanopropanoate (*epi*-271)



Pyridine (6.12 mL, 75.7 mmol) and freshly distilled trifluoroacetic anhydride (4.21 mL, 30.3 mmol) were added sequentially to a solution of amide *epi*-**271a** (4.88 g, 15.1 mmol) in THF (76.0 mL) at 0 °C. The resulting red solution was stirred for 45 minutes at 0 °C and then diluted with EtOAc. After warming to room temperature the solution was washed with aqueous saturated $NaHCO_3$ (x 2), 1 M HCl and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% EtOAc/petrol) afforded nitrile *epi*-**271** (4.69 g, quant.) as a pale yellow oil, which then solidified in the freezer; R_f: 0.30 (20% EtOAc/petrol); m.p. 43-45 ºC; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +25.0 (*c* 0.92, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3337, 2362, 2334, 1735, 1689, 1519, 1253, 1226, 1186, 1152, 1053, 1030, 971, 753, 695, 668, 650, 634, 612; δ_H (400 MHz, $CDCl_3$) 7.42-7.36 (5H, m, 5 x Ph*H*), 5.60 (1H, d, *J* 6.9, N*H*), 5.21 (2H, s, OCH_2Ph), 4.95 (1H, br s, 45-*H*), 2.94 (1H, dd, *J* 17.4 and 5.1, 46-*H*H), 2.86 (1H, dd, *J* 17.4 and 5.4, 46-H*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.1 (47-*C*), 154.1 (*C*(O)), 134.8 ($C_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 128.5 ($CH_{(Ar)}$), 117.7 (44-*C*), 81.5 ($CO_2C(CH_3)_3$), 67.5 (OCH_2Ph), 38.3 (45-*C*), 37.4 (46-*C*), 28.2 ($CO_2C(CH_3)_3$); *m/z* (ES^+) 327 (MNa^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{16}H_{21}O_4N_2$ 305.1496, observed 305.1495.

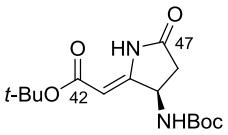
***tert*-Butyl (*S*,*Z*)-2-(3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetate (272)[41]**



Activated zinc was prepared by washing zinc powder with 3 M HCl, water, ethanol and diethyl ether. After drying under reduced pressure, activated zinc powder (3.22 g, 49.3 mmol) was suspended in THF (43.0 mL) and heated to reflux. Following the reported procedure by Kishi,[99] four drops of *tert*-butyl bromoacetate and two drops of 1,2-dibromoethane were added and the mixture was stirred at reflux for 15 minutes. After addition of a solution of nitrile **271** (3.00 g, 9.86 mmol) in THF (21.0 mL) in one portion, a solution of *tert*-butyl bromoacetate (5.82 mL, 39.4 mmol) in THF (21.0 mL) was added over a 40 minutes period *via* syringe pump. The black coloured reaction mixture was stirred for further 10 minutes at reflux and then cooled to room temperature. After the addition of THF (43.0 mL) and K_2CO_3 (14.0 mL of a 50% aqueous solution), the mixture was vigorously stirred for 15 minutes, filtered through Celite, washing with diethyl ether. The solution was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (15-20% EtOAc/petrol) afforded pyrrolidinone **272** (2.08 g, 68%) as a colourless foam; R_f: 0.25 (20% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ –66.0 (*c* 0.62, $CHCl_3$) (lit.[41] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ –70.2 (*c* 1.00, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 9.74 (1H, s, N*H*), 5.10 (1H, d, *J* 1.5, 43-*H*), 5.08 (1H, d, *J* 8.6, N*H*), 4.94 (1H, m, 45-*H*), 2.90 (1H, dd, *J* 17.9 and 9.1, 46-*H*H), 2.37 (1H, dd, *J* 17.9 and 5.9, 46-H*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 174.0 (47-*C*), 167.4 (42-*C*), 156.6 (44-*C*), 155.0

(*C*(O)), 92.5 (43-*C*), 80.7 (2 x $CO_2C(CH_3)_3$), 48.7 (45-*C*), 36.4 (46-*C*), 28.2 (2 x $CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[41]

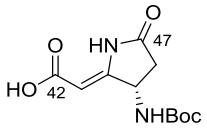
***tert*-Butyl (*R*,*Z*)-2-(3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetate (*epi*-272)**



Activated zinc was prepared by washing zinc powder with 3 M HCl, water, ethanol and diethyl ether. After drying under reduced pressure, activated zinc powder (4.95 g, 75.7 mmol) was suspended in THF (66.0 mL) and heated to reflux. Following the reported procedure by Kishi,[99] four drops of *tert*-butyl bromoacetate and two drops of 1,2-dibromoethane were added and the mixture was stirred at reflux for 15 minutes. After addition of a solution of nitrile *epi*-**271** (4.67 g, 15.1 mmol) in THF (33.0 mL) in one portion, a solution of *tert*-butyl bromoacetate (8.94 mL, 60.6 mmol) in THF (33.0 mL) was added over a 40 minutes period *via* syringe pump. The black coloured reaction mixture was stirred for further 10 minutes at reflux and then cooled to room temperature. After the addition of THF (44.0 mL) and K_2CO_3 (22.0 mL of a 50% aqueous solution), the mixture was vigorously stirred for 15 minutes, filtered through Celite, washing with diethyl ether. The solution was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (15-20% EtOAc/petrol) afforded pyrrolidinone *epi*-**272** (3.11 g, 66%) as a colourless foam; R_f: 0.25 (20% EtOAc/petrol); m.p. 53-55 ^oC; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +69.8 (*c* 1.65, $CHCl_3$); ν_{max}/cm^{-1} (neat) 1756, 1679, 1643, 1518, 1367, 1270, 1253,1208, 1165, 1138, 816, 755, 675, 654, 627, 608; δ_H (400 MHz, $CDCl_3$) 9.74 (1H, s,

N*H*), 5.11 (1H, d, *J* 1.0, 43-*H*), 5.01-4.94 (2H, m, N*H* and 45-*H*), 2.91 (1H, dd, *J* 18.1 and 9.1, 46-*H*H), 2.37 (1H, dd, *J* 17.9 and 5.6, 46-H*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 173.9 (47-*C*), 167.5 (42-*C*), 156.6 (44-*C*), 155.1 (*C*(O)), 92.5 (43-*C*), 80.8 (2 x $CO_2C(CH_3)_3$), 48.8 (45-*C*), 36.5 (46-*C*), 28.3 ($CO_2C(CH_3)_3$), 28.2 ($CO_2C(CH_3)_3$); *m/z* (ES^+) 335 (MNa^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{15}H_{25}O_5N_2$ 313.1758, observed 313.1754; Assay of enantiomeric excess (conditions: 90:10 heptane/*i*-PrOH, 1.0 mL/min.): 98% ee (t_R (minor) = 28.8 min., t_R (major) = 18.5 min.).

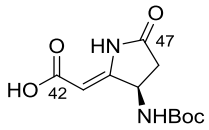
(*S*,*Z*)-2-(3-((*tert*-Butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetic acid (151)[41]



Trifluoroacetic acid (5.00 mL, 65.3 mmol) was added to a solution of pyrrolidinone **272** (800 mg, 2.56 mmol) in CH_2Cl_2 (25.0 mL) at room temperature. The reaction was stirred for 4 h. The solution was concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 3) to afford the corresponding free amino acid salt as an orange foam. The amino acid was dissolved in THF/H_2O (18.0 mL, 1:1), $NaHCO_3$ (1.20 g, 14.3 mmol) and di-*tert*-butyl dicarbonate (1.20 mL, 5.12 mmol) were added at 0 ^oC. The mixture was warmed to room temperature and stirred for 48 h. The solution was acidified to pH 2-3 with aqueous HCl solution (1 M) and then diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid **151** (557 mg, 85% over 2 steps) as a colourless solid; R_f: 0.25 (5% MeOH/EtOAc); m.p. 132-134 ^oC

(lit.[41] m.p. 128-131 °C); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ –123.2 (*c* 1.25, EtOAc) (lit.[41] $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ –71.2 (*c* 0.13, EtOAc)); δ_H (400 MHz, D_6-DMSO) 9.96 (1H, s, N*H*), 7.48 (1H, d, *J* 8.3, N*H*), 4.88 (1H, s, 43-*H*), 4.78 (1H, m, 45-*H*), 2.74 (1H, dd, *J* 17.4 and 9.5, 46-*H*H), 2.33 (1H, dd, *J* 17.4 and 5.9, 46-H*H*), 1.40 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, D_6-DMSO) 174.6 (47-*C*), 168.6 (42-*C*), 160.0 (44-*C*), 155.2 (*C*(O)), 89.0 (43-*C*), 78.7 ($CO_2C(CH_3)_3$), 48.3 (45-*C*), 34.4 (46-*C*), 28.1 ($CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[41]

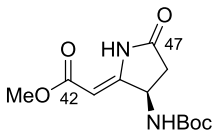
(*R*,*Z*)-2-(3-((*tert*-Butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetic acid (24)



Trifluoroacetic acid (9.50 mL, 124 mmol) was added to a solution of pyrrolidinone *epi*-**272** (1.87 g, 5.99 mmol) in CH_2Cl_2 (50.0 mL) at room temperature. The reaction was stirred for 4 h. The solution was then concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 3) to afford the corresponding free amino acid salt as an orange foam. The amino acid was dissolved in THF/H_2O (41.0 mL, 1:1), $NaHCO_3$ (1.76 g, 21.0 mmol) and di-*tert*-butyl dicarbonate (2.75 mL, 12.0 mmol) were added at 0 °C. The mixture was warmed to room temperature and stirred for 20 h. The solution was acidified to pH 2-3 with aqueous HCl solution (1 M) and then diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford acid **24** (1.31 g, 85% over 2 steps) as a colourless solid; R_f: 0.25 (5% MeOH/EtOAc); m.p. 95-97 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +102.7 (*c* 2.33, EtOAc); ν_{max}/cm^{-1} (neat) 2362, 2035, 1682, 1515, 1258, 1165, 753, 712, 661; δ_H (400 MHz, D_6-DMSO) 12.08 (1H, br s, CO_2H), 9.98 (1H, s, N*H*), 7.49 (1H, d, *J* 8.6,

N*H*), 4.88 (1H, s, 43-*H*), 4.78 (1H, m, 45-*H*), 2.73 (1H, dd, *J* 17.4 and 9.5, 46-*H*H), 2.32 (1H, dd, *J* 17.4 and 5.9, 46-H*H*), 1.40 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, D_6-DMSO) 174.7 (47-*C*), 168.8 (42-*C*), 160.0 (44-*C*), 155.3 (*C*(O)), 89.1 (43-*C*), 78.7 ($CO_2C(CH_3)_3$), 48.3 (45-*C*), 34.4 (46-*C*), 28.2 ($CO_2C(CH_3)_3$). *m/z* (ES^-) 255 (M-H, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{11}H_{17}O_5N_2$ 257.1132, observed 257.1143.

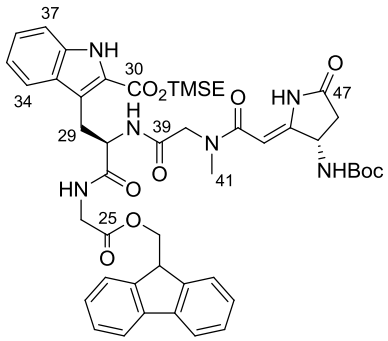
Methyl (*R,Z*)-2-(3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)acetate (24a)



Carboxylic acid **24** (100 mg, 0.39 mmol) was dissolved in toluene (6.50 mL) and methanol (1.63 mL) and treated with trimethylsilyl diazomethane (0.39 mL of a 2 M solution in hexanes, 0.78 mmol) at room temperature. After stirring the mixture for 1 h acetic acid (10.0 mL of 2 M aqueous solution) was added. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30-50% EtOAc/petrol) afforded methyl ester **24a** (64.3 mg, 61%) as a colourless solid; R_f: 0.50 (50% EtOAc/petrol); m.p. 178-180 ^oC; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ +123.9 (*c* 2.00, EtOAc); ν_{max} /cm^{-1} (neat) 2362, 2162, 2065, 2014, 1689, 1524, 1173, 691, 667, 633, 612; δ_H (400 MHz, $CDCl_3$) 9.72 (1H, br s, N*H*), 5.22 (1H, d, *J* 7.9, N*H*), 5.18 (1H, s, 43-*H*), 4.94 (1H, m, 45-*H*), 3.70 (3H, s, CO_2CH_3), 2.89 (1H, dd, *J* 18.0 and 9.3, 46-*H*H), 2.41 (1H, dd, *J* 18.0 and 5.3, 46-H*H*), 1.43 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 174.1 (47-*C*), 168.2 (42-*C*), 157.9 (44-*C*), 155.0 (*C*(O)), 90.2 (43-*C*), 80.7 (*C*(CH_3)$_3$), 51.3 (CO_2CH_3,), 48.7 (45-*C*), 36.0 (46-*C*), 28.2

($CO_2C(CH_3)_3$); *m/z* (ES^+) 293 (MNa^+, 100%); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{12}H_{18}N_2O_5Na$ 293.1108, observed 293.1108; Assay of enantiomeric excess (conditions: 80:20 heptane/*i*-PrOH, 1.0 mL/min.): 98% ee (t_R (major) = 11.6 min., t_R (minor) = 21.3 min.).

2-(Trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (339)

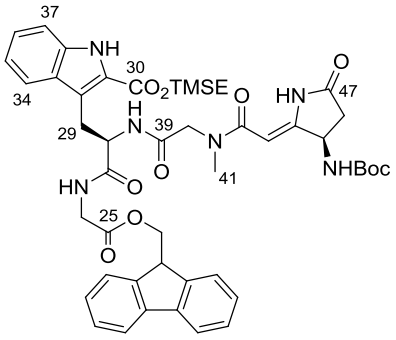


Hydrogen chloride (0.58 mL of a 4 M solution in dioxane, 2.33 mmol) was added to a solution of protected tripeptide **337** (117 mg, 0.16 mmol) in CH_2Cl_2 (1.82 mL) at room temperature. The mixture was stirred for 4 h, concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 2) to afford amine salt **337a** as an amorphous colourless solid, which was used directly in the subsequent step. Carboxylic acid **151** (47.8 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (1.00 mL) and the solution was cooled to 0 ^oC. 2,6-Lutidine (72.0 µL, 0.62 mmol) and PyAOP (97.5 mg, 0.19 mmol) were then added sequentially. The mixture was stirred at 0 ^oC for 2 h. Amine salt **337a** in CH_2Cl_2 (1.10 mL) was added to the solution. The mixture was warmed slowly to room temperature, stirred for 16 h and then concentrated *in vacuo*. Purification by flash column

chromatography (60-70-80-100% EtOAc/petrol) afforded tetrapeptide **339** (98.4 mg, 71% over 2 steps) as a colourless solid; R_f: 0.30 (80% EtOAc/petrol); m.p. 124-126 ^oC; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −20.1 (*c* 1.00, acetone); ν_{max}/cm^{-1} (neat) 3279, 2951, 1745, 1654, 1515, 1451, 1367, 1333, 1248, 1168, 1130, 1058, 943, 839, 759, 741; δ_H (500 MHz, D_6-DMSO (* denotes major rotamer)) 11.52 (1H, s, N*H*), 10.35 and 10.24* (1H, br s, N*H*), 8.37 (1H, t, *J* 5.4, N*H*), 8.17 and 8.02* (1H, d, *J* 7.3, N*H*), 7.89 (2H, d, *J* 7.6, 2 x Ar*H*), 7.79 (1H, d, *J* 7.7, 34-*H*), 7.69 (2H, d, *J* 7.4, 2 x Ar*H*), 7.48 (1H, d, *J* 7.3, N*H*), 7.43-7.32 (5H, m, 37-*H* and 4 x Ar*H*), 7.22 (1H, dd, *J* 7.4 and 7.4, 36-*H*), 7.05 (1H, dd, *J* 7.7 and 7.7, 35-*H*), 5.30* and 5.16 (1H, s, 43-*H*), 4.78-4.69 (2H, m, 28- and 45-*H*), 4.40-4.34 (4H, m, OCH_2CH and TMSCH_2CH_2), 4.25 (1H, t, *J* 7.1, OCH_2C*H*), 4.02 (1H, d, *J* 16.4, 40-*H*H), 3.92-3.83 (2H, m, 26-*H*), 3.74-3.53 (2H, m, 40-H*H* and 29-*H*H), 3.26 (1H, m, 29-H*H*), 2.73 (1H, m, 46-*H*H), 2.56* and 2.38 (3H, br s, 41-*H*), 2.29 (1H, m, 46-H*H*), 1.40* and 1.32 (9H, s, $CO_2C(CH_3)_3$), 1.16-1.13 (2H, m, TMSCH_2CH_2), 0.04 (9H, s, Si(CH_3)$_3$); δ_C (126 MHz, D_6-DMSO (chemical shifts reported for the major rotamer only)) 174.5 (47-*C*), 171.6 (27-*C*), 169.6 (25-*C*), 167.8 (42- or 39-*C*), 167.5 (42- or 39-*C*), 162.3 (30-*C*), 157.8 (*C*(O)), 155.4 (44-*C*), 143.9 ($C_{(Ar)}$), 140.7 ($C_{(Ar)}$), 136.1 ($C_{(Ar)}$), 127.8 ($CH_{(Ar)}$), 127.7 ($C_{(Ar)}$), 127.2 ($CH_{(Ar)}$), 125.3 ($CH_{(Ar)}$), 124.6 (36-*C*), 124.2 ($C_{(Ar)}$), 120.7 (34-*C*), 120.2 ($CH_{(Ar)}$), 119.4 (35-*C*), 118.5 ($C_{(Ar)}$), 112.3 (37-*C*), 87.2 (43-*C*), 78.6 ($CO_2C(CH_3)_3$), 66.2 (OCH_2CH), 62.4 (TMSCH_2CH_2), 53.7 (28-*C*), 49.8 (40-*C*), 48.4 (45-*C*), 46.1 (OCH_2CH), 40.9 (26-*C*), 35.5 (41-*C*), 34.3 (46-*C*), 28.1 ($CO_2C(CH_3)_3$), 27.4 (29-*C*), 17.2 (TMSCH_2CH_2), −1.6 (Si(CH_3)$_3$); δ_H (500 MHz, D_6-DMSO, 363 K) 11.19 (1H, s, N*H*), 10.22 (1H, s, N*H*), 7.97 (1H, m, N*H*), 7.86 (2H, d, *J* 7.6, 2 x Ar*H*), 7.78 (1H, d, *J* 7.9, 34-*H*), 7.67 (2H, d, *J* 7.6, 2 x Ar*H*), 7.67 (1H, m, N*H*), 7.43-7.40 (3H, m, 2 x Ar*H* and 37-*H*), 7.34 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 7.23 (1H, dd, *J* 7.9 and 7.9, 36-*H*), 7.07

(1H, m, N*H*), 7.06 (1H, dd, *J* 7.9 and 7.9, 35-*H*), 5.32 (1H, s, 43-*H*), 4.73-4.72 (2H, m, 28- and 45-*H*), 4.45-4.38 (4H, m, OCH_2CH and TMSCH_2CH_2), 4.26 (1H, t, *J* 6.9, OCH_2C*H*), 3.96-3.88 (3H, m, 40-*H*H and 26-*H*), 3.71 (1H, d, *J* 16.4, 40-H*H*), 3.56 (1H, dd, *J* 13.9 and 5.4, 29-*H*H), 3.36 (1H, dd, *J* 13.9 and 9.1, 29-H*H*), 2.72 (1H, m, 46-*H*H), 2.65 (3H, s, 41-*H*), 2.34 (1H, dd, *J* 17.7 and 5.7, 46-H*H*), 1.40 (9H, s, $CO_2C(CH_3)_3$), 1.20-1.17 (2H, m, TMSCH_2CH_2), 0.08 (9H, s, Si(CH_3)$_3$); *m/z* (ES^+) 893 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{47}H_{57}O_{10}N_6Si$ 893.3899, observed 893.3869.

2-(Trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*R*)-3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (*epi*-339)



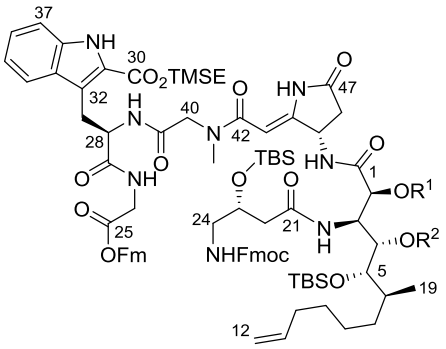
Hydrogen chloride (0.99 mL of a 4 M solution in dioxane, 3.98 mmol) was added to a solution of protected tripeptide **337** (200 mg, 0.27 mmol) in CH_2Cl_2 (3.12 mL) at room temperature. The mixture was stirred for 4 h, concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 2) to afford amine salt **337a** as an amorphous colourless solid, which was used directly in the subsequent step. Carboxylic acid **24** (81.5 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and the solution was cooled to 0 ^oC. 2,6-Lutidine (0.15 mL, 1.27 mmol) and PyAOP (166 mg, 0.32 mmol) were

then added sequentially. The mixture was stirred at 0 °C for 2 h. Amine salt **337a** in CH_2Cl_2 (2.0 mL) was added to the solution. The mixture was warmed slowly to room temperature, stirred for 16 h and then concentrated *in vacuo*. Purification by flash column chromatography (60-70-80-100% EtOAc/petrol) afforded tetrapeptide *epi*-**339** (170 mg, 72% over 2 steps) as a colourless solid; R_f: 0.30 (80% EtOAc/petrol); m.p. 118-120 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +49.0 (*c* 0.61, acetone); ν_{max}/cm^{-1} (neat) 3656, 2978, 2890, 2363, 1466, 1386, 1252, 1154, 1076, 956, 668; δ_H (500 MHz, D_6-DMSO (* denotes major rotamer)) 11.52 (1H, s, N*H*), 10.35 and 10.29* (1H, br s, N*H*), 8.50 and 8.37* (1H, br s, N*H*), 8.06 (1H, d, *J* 8.2, N*H*), 7.89 (2H, d, *J* 7.6, 2 x Ar*H*), 7.79 (1H, d, *J* 7.9, 34-*H*), 7.69 (2H, d, *J* 7.6, 2 x Ar*H*), 7.48 (1H, d, *J* 8.0, N*H*), 7.43-7.33 (5H, m, 37-*H* and 4 x Ar*H*), 7.22 (1H, dd, *J* 7.1 and 7.1, 36-*H*), 7.05 (1H, dd, *J* 7.1 and 7.1, 35-*H*), 5.30* and 5.07 (1H, s, 43-*H*), 4.81-4.69 (2H, m, 28- and 45-*H*), 4.40-4.35 (4H, m, OC*H*$_2$CH and TMSCH$_2$C*H*$_2$), 4.26 (1H, t, *J* 6.9, OCH$_2$C*H*), 4.01 (1H, m, 40-*H*H), 3.93-3.83 (2H, m, 26-*H*), 3.64-3.49 (2H, m, 40-H*H* and 29-*H*H), 3.26 (1H, m, 29-H*H*), 2.73 (1H, dd, *J* 18.0 and 10.3, 46-*H*H), 2.50* and 2.43 (3H, br s, 41-*H*), 2.29 (1H, dd, *J* 18.0 and 4.9, 46-H*H*), 1.40* and 1.29 (9H, s, $CO_2C(CH_3)_3$), 1.16-1.13 (2H, m, TMSC*H*$_2$CH$_2$), 0.04 (9H, s, Si(C*H*$_3$)$_3$); δ_C (126 MHz, D_6-DMSO (chemical shifts reported for the major rotamer only)) 174.5 (47-*C*), 171.5 (27-*C*), 169.6 (25-*C*), 167.7 (42- or 39-*C*), 167.5 (42- or 39-*C*), 162.0 (30-*C*), 157.8 (*C*(O)), 155.5 (44-*C*), 143.5 ($C_{(Ar)}$), 140.7 ($C_{(Ar)}$), 136.1 ($C_{(Ar)}$), 127.8 ($CH_{(Ar)}$), 127.8 ($C_{(Ar)}$), 127.2 ($CH_{(Ar)}$), 125.3 ($CH_{(Ar)}$), 124.6 (36-*C*), 124.1 ($C_{(Ar)}$), 120.7 (34-*C*), 120.2 ($CH_{(Ar)}$), 119.4 (35-*C*), 118.6 ($C_{(Ar)}$), 112.3 (37-*C*), 87.3 (43-*C*), 79.2 ($CO_2C(CH_3)_3$), 66.2 (O*C*H$_2$CH), 62.4 (TMSCH$_2$*C*H$_2$), 53.6 (28-*C*), 49.8 (40-*C*), 48.4 (45-*C*), 46.1 (OCH$_2$*C*H), 40.9 (26-*C*), 35.4 (41-*C*), 34.3 (46-*C*), 28.1 ($CO_2C(CH_3)_3$), 27.5 (29-*C*), 17.1 (TMS*C*H$_2$CH$_2$), −1.6 (Si(*C*H$_3$)$_3$); δ_H (500 MHz, D_6-DMSO, 363 K) 11.21 (1H, s, N*H*),

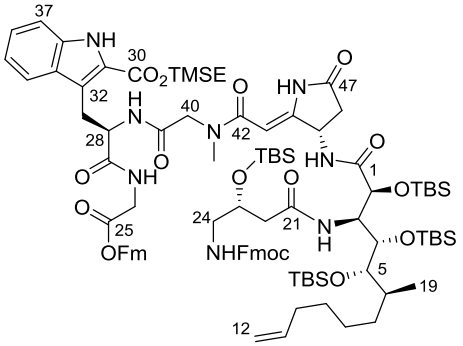
10.24 (1H, s, N*H*), 8.01 (1H, br s, N*H*), 7.86 (2H, d, *J* 7.6, 2 x Ar*H*), 7.79 (1H, d, *J* 8.2, 34-*H*), 7.68-7.67 (3H, m, N*H* and 2 x Ar*H*), 7.43-7.40 (3H, m, 2 x Ar*H* and 37-*H*), 7.34 (2H, dd, *J* 7.6 and 7.6, 2 x Ar*H*), 7.23 (1H, dd, *J* 7.9 and 7.9, 36-*H*), 7.11 (1H, br s, N*H*), 7.06 (1H, dd, *J* 7.9 and 7.9, 35-*H*), 5.29 (1H, s, 43-*H*), 4.75-4.68 (2H, m, 28- and 45-*H*), 4.45-4.38 (4H, m, OCH_2CH and TMSCH_2CH_2), 4.26 (1H, t, *J* 7.3, OCH_2C*H*), 3.94-3.90 (3H, m, 40-*H*H and 26-*H*), 3.74 (1H, d, *J* 16.4, 40-H*H*), 3.56 (1H, dd, *J* 13.6 and 5.0, 29-*H*H), 3.36 (1H, dd, *J* 13.6 and 9.1, 29-H*H*), 2.73 (1H, dd, *J* 17.3 and 9.5, 46-*H*H), 2.63 (3H, s, 41-*H*), 2.33 (1H, dd, *J* 17.3 and 5.4, 46-H*H*), 1.39 (9H, s, $CO_2C(CH_3)_3$), 1.20-1.17 (2H, m, TMSCH_2CH_2), 0.08 (9H, s, $Si(CH_3)_3$); *m/z* (ES^+) 729 (50%), 751 (100%), 893 (MH^+, 100%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{47}H_{57}O_{10}N_6Si$ 893.3899, observed 893.3907.

2-(Trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (341) and

2-(trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (342)



341 R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H



342

Trifluoroacetic acid (0.32 mL, 4.18 mmol) and triethylsilane (0.14 mL, 0.88 mmol) were added sequentially to a solution of tetrapeptide **339** (382 mg, 0.43 mmol) in CH_2Cl_2 (4.30 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 2 h. The solution was then concentrated *in vacuo* and the residue dissolved in toluene and again concentrated *in vacuo* (x 2) to afford amine salt **340** as a colourless solid, which was used

directly in the subsequent step. HATU (137 mg, 0.36 mmol), 2,6-lutidine (0.13 mL, 1.11 mmol) and amine salt **340** (328 mg, 0.36 mmol) were added sequentially to a solution of carboxylic acid **288** (293 mg, 0.28 mmol) in DMF (2.80 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 16 h. The solution was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (40-50-70% EtOAc/petrol) afforded linear hexapeptides **341** (160 mg, 34%) and **342** (148 mg, 29%). Data for linear hexapeptide **341**: colourless solid; R_f 0.50 (70% EtOAc/petrol); m.p. 91-93 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −15.4 (*c* 1.08, EtOAc); ν_{max} /cm^{-1} (neat) 3324, 2927, 2855, 1659, 1528, 1470, 1323, 1249, 1196, 1096, 941, 835, 777, 741, 671; δ_H (500 MHz, D_6-DMSO) 11.51 (1H, s, N*H*), 10.34 (1H, s, N*H*), 8.35 (2H, br s, 2 x N*H*), 8.03 (1H, d, *J* 7.9, N*H*), 7.87 (4H, dd, *J* 7.4 and 7.4, 4 x Ar*H*), 7.78 (1H, d, *J* 7.9, 34-*H*), 7.67 (4H, d, *J* 7.4, 4 x Ar*H*), 7.42-7.37 (5H, m, 37-*H* and 4 x Ar*H*), 7.34-7.27 (4H, m, 4 x Ar*H*), 7.21 (1H, dd, *J* 7.4 and 7.4, 36-*H*), 7.14 (1H, m, N*H*), 7.04 (1H, dd, *J* 7.4 and 7.4, 35-*H*), 6.63 (1H, br s, O*H*), 5.73 (1H, m, 11-*H*), 5.60 (1H, s, 43-*H*), 5.33 (1H, d, *J* 6.3, N*H*), 5.03 (1H, m, 45-*H*), 4.96-4.88 (2H, m, 12-*H*), 4.66 (1H, m, 28-*H*), 4.39-4.23 (7H, m, 2-*H*, OC*H*$_2$CH, OC*H*HCH, OCH$_2$C*H* and TMSCH$_2$C*H*$_2$), 4.19-4.14 (3H, m, 3-*H*, OCH*H*CH and OCH$_2$C*H*), 4.05-3.81 (5H, m, 40-*H*H, 26-, 23- and 4-*H*), 3.67 (1H, d, *J* 16.1, 40-H*H*), 3.53 (1H, m, 29-*H*H), 3.32-3.24 (2H, m, 29-H*H* and 5-*H*), 3.07 (1H, m, 24-*H*H), 2.96 (1H, m, 24-H*H*), 2.71 (3H, s, 41-*H*), 2.63 (1H, dd, *J* 17.5 and 10.1, 46-*H*H), 2.30-2.15 (3H, m, 46-H*H* and 22-*H*), 1.99-1.94 (2H, m, 10-*H*), 1.65-1.56 (2H, m, 6-*H* and 7-*H*H), 1.30-1.23 (3H, m, 8-*H*H and 9-*H*), 1.16-1.12 (2H, m, TMSC*H*$_2$CH$_2$), 1.06 (1H, m, 8-H*H*), 0.87-0.79 (31H, m, 3 x SiC(C*H*$_3$)$_3$, 19-*H* and 7-H*H*), 0.13-−0.02 (27H, m, 6 x SiC*H*$_3$ and Si(C*H*$_3$)$_3$); δ_C (126 MHz, D_6-DMSO) 174.8 (47-*C*), 172.7 (1-*C*), 171.5 (27-*C*), 169.6 (25-*C*), 168.2 (21-*C*), 167.8 (42-*C*), 167.7 (39-*C*), 162.0 (30-*C*), 156.7

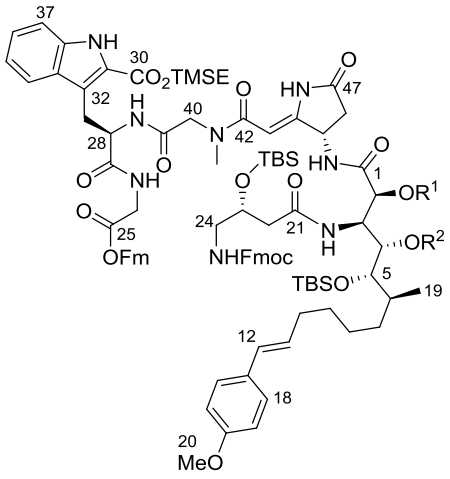
(44-*C*), 156.3 (*C*(O)), 143.9 ($C_{(Ar)}$), 143.9 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.7 (4 x $C_{(Ar)}$), 138.7 (11-*C*), 136.1 (38-*C*), 127.8 ($CH_{(Ar)}$), 127.7 (33-*C*), 127.6 ($CH_{(Ar)}$), 127.2 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 125.2 ($CH_{(Ar)}$), 125.2 ($CH_{(Ar)}$), 124.6 (36-*C*), 124.2 (32-*C*), 120.7 (34-*C*), 120.2 ($CH_{(Ar)}$), 120.1 ($CH_{(Ar)}$), 119.4 (35-*C*), 118.4 (31-*C*), 114.6 (12-*C*), 112.3 (37-*C*), 88.5 (43-*C*), 78.1 (5-*C*), 72.8 (4-*C*), 69.9 (3-*C*), 68.2 (23-*C*), 66.2 (OCH_2CH), 65.5 (OCH_2CH), 62.4 ($TMSCH_2CH_2$), 53.8 (28-*C*), 52.9 (2-*C*), 49.7 (40-*C*), 46.7 (45-*C* and OCH_2CH), 46.1 (OCH_2CH), 45.6 (24-*C*), 42.1 (22-*C*), 40.9 (26-*C*), 35.7 (41-*C*), 35.1 (46-*C*), 34.7 (6-*C*), 33.2 (10-*C*), 32.9 (7-*C*), 28.5 (9-*C*), 27.6 (29-*C*), 26.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 25.4 (8-*C*), 18.0 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), 17.7 ($SiC(CH_3)_3$), 17.2 ($TMSCH_2CH_2$), 16.2 (19-*C*), −1.5 ($Si(CH_3)_3$), −3.1 ($SiCH_3$), −3.3 ($SiCH_3$), −4.9 ($SiCH_3$), −4.9 ($SiCH_3$), −4.9 ($SiCH_3$), −5.2 ($SiCH_3$); *m/z* (ES^+) 1717 (MH^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{92}H_{130}N_8O_{16}Si_4Na$ 1737.8533, observed 1737.8532.

Data for linear hexapeptide **342**: colourless solid; R_f 0.60 (70% EtOAc/petrol); m.p. 138-140 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −9.4 (*c* 0.83, EtOAc); ν_{max} /cm^{-1} (neat) 2951, 2931, 1739, 1661, 1523, 1450, 1365, 1251, 1230, 1096, 834, 777, 741, 620; δ_H (500 MHz, D_6-DMSO) 11.51 (1H, s, N*H*), 10.39 (1H, s, N*H*), 8.38 (1H, br s, N*H*), 8.03 (1H, d, *J* 8.2, N*H*), 7.87 (4H, dd, *J* 11.4 and 7.6, 4 x Ar*H*), 7.79 (1H, d, *J* 8.0, 34-*H*), 7.68-7.67 (3H, m, N*H* and 2 x Ar*H*), 7.63 (1H, d, *J* 7.6, Ar*H*), 7.57 (1H, d, *J* 7.6, Ar*H*), 7.42-7.25 (11H, m, 37-*H*, 2 x N*H* and 8 x Ar*H*), 7.19 (1H, dd, *J* 7.3 and 7.3, 36-*H*), 7.03 (1H, dd, *J* 7.3 and 7.3, 35-*H*), 5.75 (1H, m, 11-*H*), 5.42 (1H, s, 43-*H*), 5.09 (1H, br s, 45-*H*), 4.97-4.90 (2H, m, 12-*H*), 4.67 (1H, m, 28-*H*), 4.39-4.31 (5H, m, 2- or 4-*H*, OCH_2CH and $TMSCH_2CH_2$), 4.26-4.17 (3H, m, $OCHHCH$, OCH_2CH and 40-*H*H), 4.14-4.08 (3H, m, $OCHHCH$, OCH_2CH and 3-*H*), 4.01 (1H, m, 23-*H*), 3.86 (2H, dd, *J* 5.0 and 5.0, 26-*H*), 3.76 (1H, d,

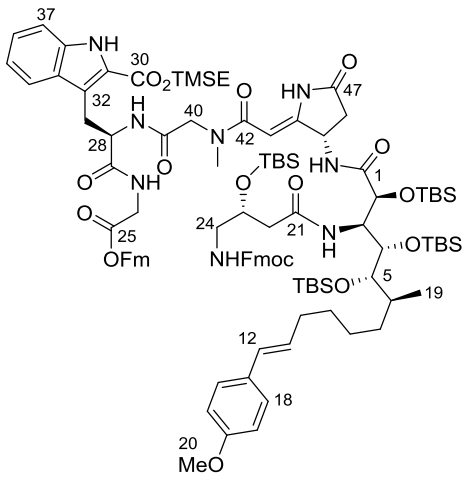
J 9.5, 4- or 2-*H*), 3.55-3.51 (2H, m, 29-*H*H and 5-*H*), 3.38 (1H, m, 40-H*H*), 3.26-3.16 (2H, m, 29-H*H* and 24-*H*H), 2.95 (1H, br s, 24-H*H*), 2.65-2.60 (4H, m, 46-*H*H and 41-*H*), 2.36-2.29 (2H, m, 46-H*H* and 22-*H*H), 2.11 (1H, d, *J* 11.8, 22-H*H*), 1.99-1.97 (2H, m, 10-*H*), 1.58-1.54 (2H, m, 6-*H* and 7-*H*H), 1.32-1.23 (3H, m, 8-*H*H and 9-*H*), 1.15-1.12 (2H, m, TMSCH_2CH_2), 1.05 (1H, m, 8-H*H*), 0.89-0.75 (40H, m, 4 x SiC(CH_3)$_3$, 19-*H* and 7-H*H*), 0.20-0.02 (33H, m, 8 x SiCH_3 and Si(CH_3)$_3$); δ_C (126 MHz, D_6-DMSO) 175.0 (47-*C*), 171.5 (1- and 27-*C*), 169.6 (25-*C*), 168.3 (21-*C*), 167.7 (42- and 39-*C*), 162.0 (30-*C*), 157.0 (44-*C*), 156.7 (*C*(O)), 143.9 ($C_{(Ar)}$), 143.6 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.8 ($C_{(Ar)}$), 140.7 (3 x $C_{(Ar)}$), 136.1 (11-*C*), 136.1 (38-*C*), 127.7 (C$H_{(Ar)}$), 127.5 (C$H_{(Ar)}$ and 33-*C*), 127.2 (C$H_{(Ar)}$), 126.9 (C$H_{(Ar)}$), 125.2 (C$H_{(Ar)}$), 125.1 (C$H_{(Ar)}$), 124.9 (C$H_{(Ar)}$), 124.5 (36-*C*), 124.2 (32-*C*), 120.7 (34-*C*), 120.2 (C$H_{(Ar)}$), 120.0 (C$H_{(Ar)}$), 119.4 (35-*C*), 118.5 (31-*C*), 114.7 (12-*C*), 112.3 (37-*C*), 87.7 (43-*C*), 71.8 (4- or 2-*C*), 70.3 (5-*C*), 68.3 (23-*C*), 66.2 (O*C*H_2CH), 65.4 (O*C*H_2CH), 62.3 (TMSCH_2*C*H_2), 54.0 (3-*C*), 53.7 (28-*C*), 51.7 (4- or 2-*C*), 49.7 (40-*C*), 46.9 (45-*C*), 46.5 (OCH_2*C*H), 46.1 (OCH_2*C*H), 45.7 (24-*C*), 42.2 (22-*C*), 40.8 (26-*C*), 35.4 (41-*C*), 34.6 (46-*C*), 33.3 (10- and 7-*C*), 28.5 (9-*C*), 27.6 (6- and 29-*C*), 26.2 (8-*C* and SiC(*C*H_3)$_3$), 26.0 (SiC(*C*H_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 18.2 (2 x Si*C*(CH_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 17.7 (Si*C*(CH_3)$_3$), 17.1 (TMS*C*H_2CH_2), 16.0 (19-*C*), −1.6 (Si(*C*H_3)$_3$), −2.5 (Si*C*H_3), −3.4 (Si*C*H_3), −4.2 (Si*C*H_3), −4.4 (Si*C*H_3), −4.8 (2 x Si*C*H_3), −4.9 (Si*C*H_3), −5.1 (Si*C*H_3); *m/z* (ES^+) 1830 (MH^+, 100), 1853 (MNa^+, 80); *m/z* HRMS (ES^+) MH^+ calculated for $C_{98}H_{145}N_8O_{16}Si_5$ 1830.9653, observed 1830.9620.

2-(Trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-12-(4-methoxyphenyl)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (366) and

2-(trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-12-(4-methoxyphenyl)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (367)



366 R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H



367

HATU (962 mg, 2.53 mmol), 2,6-lutidine (0.91 mL, 7.78 mmol) and amine salt **340** (2.29 g, 2.53 mmol) were added sequentially to a solution of carboxylic acid **365** (2.03 g, 1.75 mmol) in DMF (19.0 mL) at 0 ^{o}C. The mixture was warmed to room temperature and

stirred for 16 h. The solution was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (40-50-60-70% EtOAc/petrol) afforded linear hexapeptides **366** (1.16 g, 36) and **367** (161 mg, 5%). Data for linear hexapeptide **366**: colourless solid; R_f 0.30 (60% EtOAc/petrol); m.p. 100-102 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −32.6 (*c* 0.78, EtOAc); ν_{max} /cm^{-1} (neat) 2932, 2399, 2297, 1659, 1510, 1450, 1249, 1177, 1099, 835, 777, 741, 671; δ_H (500 MHz, D_6-DMSO) 11.51 (1H, s, N*H*), 10.32 (1H, s, N*H*), 8.35 (2H, br s, 2 x N*H*), 8.03 (1H, d, *J* 8.0, N*H*), 7.87 (4H, dd, *J* 7.4 and 7.4, 4 x Ar*H*), 7.78 (1H, d, *J* 8.0, 34-*H*), 7.67 (4H, d, *J* 7.4, 4 x Ar*H*), 7.42-7.37 (5H, m, 37-*H* and 4 x Ar*H*), 7.34-7.28 (4H, m, 4 x Ar*H*), 7.25 (2H, d, *J* 8.8, 14- and 18-*H*), 7.21 (1H, dd, *J* 7.6 and 7.6, 36-*H*), 7.14 (1H, m, N*H*), 7.04 (1H, dd, *J* 7.6 and 7.6, 35-*H*), 6.83 (2H, d, *J* 8.8, 15- and 17-*H*), 6.65 (1H, br s, O*H*), 6.26 (1H, d, *J* 15.9, 12-*H*), 6.05 (1H, dt, *J* 15.9 and 6.9, 11-*H*), 5.60 (1H, s, 43-*H*), 5.33 (1H, d, *J* 6.0, N*H*), 5.02 (1H, m, 45-*H*), 4.66 (1H, m, 28-*H*), 4.39-4.22 (7H, m, 2-*H*, OCH_2CH, OC*H*HCH, OCH_2C*H* and $TMSCH_2CH_2$), 4.19-4.14 (3H, m, 3-*H*, OCH*H*CH and OCH_2C*H*), 4.02 (1H, m, 23-*H*), 3.94 (1H, d, *J* 16.6, 40-*H*H), 3.87-3.81 (3H, m, 26- and 4-*H*), 3.71 (3H, s, 20-*H*), 3.67 (1H, m, 40-H*H*), 3.53 (1H, dd, *J* 13.4 and 4.7, 29-*H*H), 3.33 (1H, m, 5-*H*), 3.26 (1H, dd, *J* 13.4 and 9.3, 29-H*H*), 3.05 (1H, m, 24-*H*H), 2.97 (1H, m, 24-H*H*), 2.71 (3H, s, 41-*H*), 2.63 (1H, dd, *J* 17.7 and 9.3, 46-*H*H), 2.30-2.15 (3H, m, 46-H*H* and 22-*H*), 2.11-2.07 (2H, m, 10-*H*), 1.67-1.58 (2H, m, 6-*H* and 7-*H*H), 1.34-1.27 (3H, m, 8-*H*H and 9-*H*), 1.16-1.12 (2H, m, $TMSCH_2CH_2$), 1.09 (1H, m, 8-H*H*), 0.87-0.77 (31H, m, 3 x $SiC(CH_3)_3$, 19-*H* and 7-H*H*), 0.13-−0.05 (27H, m, 6 x $SiCH_3$ and $Si(CH_3)_3$); δ_C (126 MHz, D_6-DMSO) 174.7 (47-*C*), 172.6 (1-*C*), 171.5 (27-*C*), 169.6 (25-*C*), 168.3 (21-*C*), 167.8 (42-*C*), 167.7 (39-*C*), 162.0 (30-*C*), 158.3 (16-*C*), 156.7 (44-*C*), 156.3 (*C*(O)), 143.9 ($C_{(Ar)}$), 143.8 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.7 (4 x $C_{(Ar)}$), 136.1 (38-*C*), 130.0

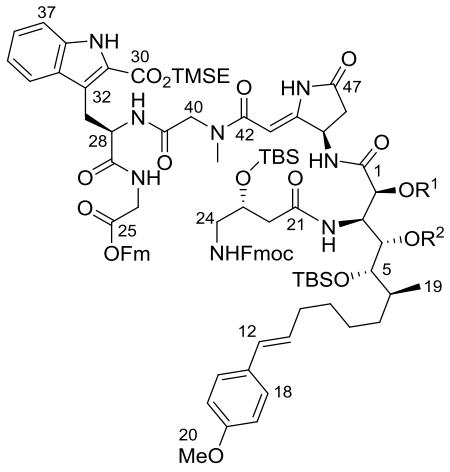
(13-*C*), 129.0 (12-*C*), 128.1 (11-*C*), 127.8 (*C*H$_{(Ar)}$), 127.7 (33-*C*), 127.6 (*C*H$_{(Ar)}$), 127.2 (*C*H$_{(Ar)}$), 127.0 (*C*H$_{(Ar)}$), 126.9 (14- and 18-*C*), 125.2 (*C*H$_{(Ar)}$), 125.2 (*C*H$_{(Ar)}$), 124.6 (36-*C*), 124.2 (32-*C*), 120.7 (34-*C*), 120.2 (*C*H$_{(Ar)}$), 120.1 (*C*H$_{(Ar)}$), 119.4 (35-*C*), 118.4 (31-*C*), 113.9 (15- and 17-*C*), 112.3 (37-*C*), 88.4 (43-*C*), 78.1 (5-*C*), 72.9 (4-*C*), 69.9 (3-*C*), 68.1 (23-*C*), 66.2 (O*C*H$_2$CH), 65.5 (O*C*H$_2$CH), 62.4 (TMSCH$_2$*C*H$_2$), 55.0 (20-*C*), 53.8 (28-*C*), 52.9 (2-*C*), 49.7 (40-*C*), 46.7 (45-*C* and OCH$_2$*C*H), 46.1 (OCH$_2$*C*H), 45.6 (24-*C*), 42.1 (22-*C*), 40.8 (26-*C*), 35.7 (41-*C*), 35.1 (46-*C*), 34.8 (6-*C*), 33.0 (7-*C*), 32.5 (10-*C*), 29.3 (9-*C*), 27.6 (29-*C*), 26.1 (SiC(*C*H$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 25.5 (8-*C*), 18.0 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 17.7 (Si*C*(CH$_3$)$_3$), 17.1 (TMS*C*H$_2$CH$_2$), 16.2 (19-*C*), −1.6 (Si(*C*H$_3$)$_3$), −3.2 (Si*C*H$_3$), −3.4 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −5.2 (Si*C*H$_3$); *m/z* (ES$^+$) 1822 (MH$^+$, 100); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{99}H_{137}N_8O_{17}Si_4$ 1822.9196, observed 1822.9207.

Data for linear hexapeptide **367**: colourless solid; R_f 0.50 (60% EtOAc/petrol); m.p. 94-96 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −7.2 (*c* 0.43, EtOAc); ν_{max} /cm^{-1} (neat) 2953, 2929, 2859, 2388, 2291, 1748, 1661, 1512, 1463, 1250, 1176, 1098, 835, 777, 741, 627; δ_H (500 MHz, D$_6$-DMSO) 11.51 (1H, s, N*H*), 10.39 (1H, s, N*H*), 8.39 (1H, br s, N*H*), 8.03 (1H, d, *J* 7.6, N*H*), 7.87 (4H, dd, *J* 11.5 and 7.7, 4 x Ar*H*), 7.87 (1H, m, N*H*), 7.79 (1H, d, *J* 8.2, 34-*H*), 7.68-7.67 (3H, m, N*H* and 2 x Ar*H*), 7.63 (1H, d, *J* 7.6, Ar*H*), 7.56 (1H, d, *J* 7.4, Ar*H*), 7.42-7.26 (12H, m, 8 x Ar*H*, N*H*, 14-, 18- and 37-*H*), 7.19 (1H, dd, *J* 7.3 and 7.3, 36-*H*), 7.03 (1H, dd, *J* 7.3 and 7.3, 35-*H*), 6.84 (1H, d, *J* 8.7, 15 and 17-*H*), 6.28 (1H, d, *J* 15.8, 12-*H*), 6.07 (1H, dt, *J* 15.8 and 6.6, 11-*H*), 5.41 (1H, br s, 43-*H*), 5.08 (1H, br s, 45-*H*), 4.67 (1H, m, 28-*H*), 4.39-4.30 (5H, m, 2- or 4-*H*, OC*H*$_2$CH and TMSCH$_2$C*H*$_2$), 4.24 (1H, t, *J* 7.1, OCH$_2$C*H*), 4.13-4.08 (2H, m, OC*H*HCH and 40-*H*H), 4.15-4.07 (3H, m, OCH*H*CH,

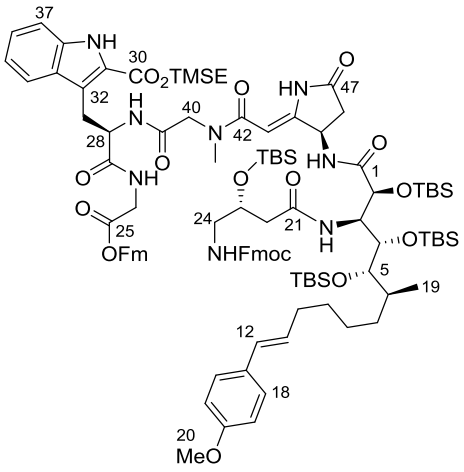
OCH_2CH and 3-*H*), 4.01 (1H, m, 23-*H*), 3.86 (2H, dd, *J* 5.2 and 5.2, 26-*H*), 3.76 (1H, d, *J* 9.6, 4- or 2-*H*), 3.71 (3H, s, 20-*H*), 3.55-3.51 (2H, m, 29-*H*H and 5-*H*), 3.38 (1H, m, 40-H*H*), 3.24 (1H, dd, *J* 13.2 and 9.3, 29-H*H*), 3.15 (1H, m, 24-*H*H), 2.96 (1H, m, 24-H*H*), 2.66-2.59 (4H, m, 46-*H*H and 41-*H*), 2.36-2.27 (2H, m, 46-H*H* and 22-*H*H), 2.11-2.10 (3H, m, 10-*H* and 22-H*H*), 1.58-1.54 (2H, m, 6-*H* and 7-*H*H), 1.37-1.29 (3H, m, 8-*H*H and 9-*H*), 1.16-1.11 (2H, m, TMSCH_2CH_2), 1.08 (1H, m, 8-H*H*), 0.89-0.75 (40H, m, 4 x SiC(CH_3)$_3$, 19-*H* and 7-H*H*), 0.20-−0.05 (33H, m, 8 x SiCH_3 and Si(CH_3)$_3$); δ_C (126 MHz, D_6-DMSO) 175.0 (47-*C*), 171.5 (1- and 27-*C*), 169.6 (25-*C*), 168.3 (21-*C*), 167.7 (42- and 39-*C*), 162.0 (30-*C*), 158.3 (16-*C*), 157.1 (44-*C*), 156.7 (*C*(O)), 143.9 ($C_{(Ar)}$), 143.6 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.8 ($C_{(Ar)}$), 140.7 (3 x $C_{(Ar)}$), 136.1 (38-*C*), 129.9 (13-*C*), 129.1 (12-*C*), 128.0 (11-*C*), 127.7 ($CH_{(Ar)}$), 127.5 ($CH_{(Ar)}$ and 33-*C*), 127.2 ($CH_{(Ar)}$), 126.9 ($CH_{(Ar)}$), 126.9 (14- and 18-*C*), 125.2 ($CH_{(Ar)}$), 125.1 ($CH_{(Ar)}$), 124.9 ($CH_{(Ar)}$), 124.5 (36-*C*), 124.2 (32-*C*), 120.7 (34-*C*), 120.2 ($CH_{(Ar)}$), 120.1 ($CH_{(Ar)}$), 119.4 (35-*C*), 118.5 (31-*C*), 113.9 (15- and 17-*C*), 112.3 (37-*C*), 87.6 (43-*C*), 71.8 (4- or 2-*C*), 70.0 (5-*C*), 68.3 (23-*C*), 66.2 (OCH_2CH), 65.4 (OCH_2CH), 62.3 ($TMSCH_2CH_2$), 55.0 (20-*C*), 54.0 (3-*C*), 53.8 (28-*C*), 51.8 (4- or 2-*C*), 49.7 (40-*C*), 46.9 (45-*C*), 46.5 (OCH_2CH), 46.1 (OCH_2CH), 45.6 (24-*C*), 42.1 (22-*C*), 40.8 (26-*C*), 35.4 (41-*C*), 34.6 (46-*C*), 33.3 (7-*C*), 32.5 (10-*C*), 29.3 (9-*C*), 27.5 (6- and 29-*C*), 26.1 (8-*C*), 25.9 (SiC(CH_3)$_3$), 25.8 (SiC(CH_3)$_3$), 25.7 (2 x SiC(CH_3)$_3$), 18.1 (2 x Si*C*(CH_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 17.7 (Si*C*(CH_3)$_3$), 17.1 (TMSCH_2CH_2), 16.0 (19-*C*), −1.6 (Si(CH_3)$_3$), −2.5 (SiCH_3), −3.1 (SiCH_3), −3.2 (SiCH_3), −3.4 (SiCH_3), −4.2 (SiCH_3), −4.4 (SiCH_3), −4.9 (SiCH_3), −5.2 (SiCH_3); *m/z* (ES^+) 1936 (MH^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{105}H_{151}N_8O_{17}Si_5Na$ 1958.9936, observed 1958.9841.

2-(Trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*R*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-12-(4-methoxyphenyl)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (*epi*-366) and

2-(trimethylsilyl)ethyl 3-((*R*)-3-((2-((9*H*-fluoren-9-yl)methoxy)-2-oxoethyl)amino)-2-(2-((*Z*)-2-((*R*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-12-(4-methoxyphenyl)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-oxopropyl)-1*H*-indole-2-carboxylate (*epi*-367)



epi-**366** R^1 = H, R^2 = TBS or R^1 = TBS, R^2 = H



epi-**367**

HATU (55.9 mg, 0.15 mmol), 2,6-lutidine (53.0 μL, 0.45 mmol) and amine salt *epi*-**340** (121 mg, 0.15 mmol) were added sequentially to a solution of carboxylic acid **365** (118 mg, 0.10 mmol) in DMF (1.13 mL) at 0 °C. The mixture was warmed to room

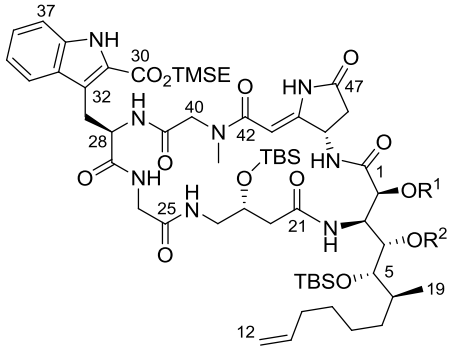
temperature and stirred for 16 h. The solution was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (40-50-60-70-80% EtOAc/petrol) afforded linear hexapeptides *epi*-**366** (85.1 mg, 46%) and *epi*-**367** (30.2 mg, 15%). Data for linear hexapeptide *epi*-**366**: colourless solid; R_f 0.30 (60% EtOAc/petrol); m.p. 97-99 ^oC; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −3.8 (*c* 3.19, EtOAc); ν_{max} /cm^{-1} (neat) 2974, 2361, 2297, 1660, 1512, 1468, 1246, 1031, 1005, 779, 760, 741, 668; δ_H (500 MHz, D_6-DMSO) 11.51 (1H, s, N*H*), 10.33 (1H, s, N*H*), 8.34-8.31 (2H, m, 2 x N*H*), 8.07 (1H, d, *J* 8.2, N*H*), 7.87 (4H, dd, *J* 8.0 and 8.0, 4 x Ar*H*), 7.80 (1H, d, *J* 7.9, 34-*H*), 7.69-7.67 (5H, m, N*H* and 4 x Ar*H*), 7.42-7.25 (11H, m, 14-, 18-, 37-*H* and 8 x Ar*H*), 7.21 (1H, dd, *J* 7.4 and 7.4, 36-*H*), 7.10 (1H, br s, N*H*), 7.04 (1H, dd, *J* 7.4 and 7.4, 35-*H*), 6.83 (2H, d, *J* 8.7, 15- and 17-*H*), 6.26 (1H, d, *J* 15.9, 12-*H*), 6.05 (1H, dt, *J* 15.9 and 6.8, 11-*H*), 5.60 (1H, br s, O*H*), 5.26 (1H, s, 43-*H*), 4.76-4.69 (2H, m, 45- and 28-*H*), 4.39-4.16 (9H, m, 2-*H*, 2 x OCH_2CH, 2 x OCH$_2$C*H* and TMSCH$_2$CH_2), 4.10 (1H, m, 3-*H*), 3.98 (1H, m, 23-*H*), 3.87-3.81 (4H, m, 40-*H*H, 26- and 4-*H*), 3.71 (3H, s, 20-*H*), 3.71 (1H, m, 40-H*H*), 3.58 (1H, m, 29-*H*H), 3.33 (1H, m, 5-*H*), 3.28 (1H, m, 29-H*H*), 3.02-2.96 (2H, m, 24-*H*), 2.62 (1H, m, 46-*H*H), 2.53 (3H, s, 41-*H*), 2.50 (1H, m, 46-H*H*), 2.25 (1H, m, 22-*H*H), 2.15-2.10 (3H, m, 22-H*H* and 10-*H*), 1.60-1.54 (2H, m, 6-*H* and 7-*H*H), 1.35-1.22 (3H, m, 8-*H*H and 9-*H*), 1.15-1.11 (2H, m, TMSCH_2CH$_2$), 1.09 (1H, m, 8-H*H*), 0.87-0.77 (31H, m, 3 x SiC(CH_3)$_3$, 19-*H* and 7-H*H*), 0.13-−0.05 (27H, m, 6 x SiCH_3 and Si(CH_3)$_3$); δ_C (126 MHz, D_6-DMSO) 175.4 (47-*C*), 172.9 (1-*C*), 171.5 (27-*C*), 169.6 (25-*C*), 168.2 (21-*C*), 167.8 (42-*C*), 167.8 (39-*C*), 162.0 (30-*C*), 158.3 (16-*C*), 157.1 (44-*C*), 156.4 (*C*(O)), 143.9 ($C_{(Ar)}$), 143.8 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.7 (4 x $C_{(Ar)}$), 136.1 (38-*C*), 130.0 (13-*C*), 129.1 (12-*C*), 128.1 (11-*C*), 127.8 (*C*H$_{(Ar)}$), 127.6 (33-*C*), 127.6 (*C*H$_{(Ar)}$), 127.2 (*C*H$_{(Ar)}$), 127.0 (*C*H$_{(Ar)}$), 126.9 (14- and 18-*C*), 125.3

(*C*H$_{(Ar)}$), 125.1 (*C*H$_{(Ar)}$), 124.6 (36-*C*), 124.1 (32-*C*), 120.8 (34-*C*), 120.2 (*C*H$_{(Ar)}$), 120.1 (*C*H$_{(Ar)}$), 119.5 (35-*C*), 118.6 (31-*C*), 113.9 (15- and 17-*C*), 112.3 (37-*C*), 87.9 (43-*C*), 78.3 (5-*C*), 72.7 (4-*C*), 70.2 (3-*C*), 68.0 (23-*C*), 66.2 (O*C*H$_2$CH), 65.6 (O*C*H$_2$CH), 62.4 (TMSCH$_2$*C*H$_2$), 55.0 (20-*C*), 53.7 (28-*C*), 52.9 (2-*C*), 49.8 (40-*C*), 47.4 (45-*C*), 46.7 (OCH$_2$*C*H), 46.1 (OCH$_2$*C*H), 45.6 (24-*C*), 42.0 (22-*C*), 40.9 (26-*C*), 35.8 (41-*C*), 33.5 (46-*C*), 33.3 (7-*C*), 32.5 (10-*C*), 29.4 (9-*C*), 27.5 (29- and 6-*C*), 26.1 (SiC(*C*H$_3$)$_3$), 25.9 (8-*C*), 25.7 (2 x SiC(*C*H$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 17.6 (Si*C*(CH$_3$)$_3$), 17.1 (TMS*C*H$_2$CH$_2$), 16.4 (19-*C*), −1.6 (Si(*C*H$_3$)$_3$), −3.3 (2 x Si*C*H$_3$), −4.9 (Si*C*H$_3$), −5.0 (2 x Si*C*H$_3$), −5.3 (Si*C*H$_3$); *m/z* (ES$^+$) 1845 (MNa$^+$, 100), 1823 (MH$^+$, 90); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{99}H_{136}N_8O_{17}Si_4Na$ 1844.9026, observed 1844.8948.

Data for linear hexapeptide *epi*-**367**: colourless solid; R_f 0.50 (60% EtOAc/petrol); m.p. 88-90 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +27.2 (*c* 1.27, EtOAc); ν_{max} /cm^{-1} (neat) 3022, 2930, 2857, 2362, 1701, 1679, 1659, 1512, 1249, 1196, 1179, 1101, 1035, 1007, 856, 835, 777, 759, 741, 623; δ_H (500 MHz, D$_6$-DMSO) 11.51 (1H, s, N*H*), 10.42 (1H, s, N*H*), 8.26 (1H, br s, N*H*), 8.00 (1H, d, *J* 8.7, N*H*), 7.87 (4H, dd, *J* 7.9 and 7.9, 4 x Ar*H*), 7.87 (1H, m, N*H*), 7.77 (1H, d, *J* 7.9, 34-*H*), 7.68-7.64 (5H, m, N*H* and 4 x Ar*H*), 7.42-7.26 (12H, m, 8 x Ar*H*, N*H*, 14-, 18- and 37-*H*), 7.19 (1H, dd, *J* 7.4 and 7.4, 36-*H*), 7.03 (1H, dd, *J* 7.4 and 7.4, 35-*H*), 6.84 (1H, d, *J* 8.4, 15 and 17-*H*), 6.28 (1H, d, *J* 15.9, 12-*H*), 6.07 (1H, dt, *J* 15.9 and 6.8, 11-*H*), 5.20 (1H, br s, 43-*H*), 4.79-4.68 (2H, m, 45- and 28-*H*), 4.39-4.19 (9H, m, , 2 x OC*H*$_2$CH, 2 x OCH$_2$C*H* and TMSCH$_2$C*H*$_2$), 4.13 (1H, dd, *J* 9.9 and 9.9, 3-*H*), 4.01 (1H, m, 23-*H*), 3.90-3.85 (3H, m, and 26-*H*), 3.74-3.71 (5H, m, 40-H*H*, 2- or 4-*H* and 20-*H*), 3.55 (1H, m, 29-*H*H), 3.46 (1H, m, 5-*H*), 3.28 (1H, m, 29-H*H*), 3.10 (1H, m, 24-*H*H), 2.96 (1H, m, 24-H*H*), 2.63-2.52 (5H, m, 46- and 41-*H*), 2.30 (1H, m, 22-*H*H), 2.12-2.10 (3H, m, 10-*H*

and 22-H*H*), 1.58-1.53 (2H, m, 6-*H* and 7-*H*H), 1.37-1.30 (3H, m, 8-*H*H and 9-*H*), 1.16-1.12 (2H, m, TMSC*H*$_2$CH$_2$), 1.09 (1H, m, 8-H*H*), 0.86-0.70 (40H, m, 4 x SiC(C*H*$_3$)$_3$, 19-*H* and 7-H*H*), 0.17-−0.05 (33H, m, 8 x SiC*H*$_3$ and Si(C*H*$_3$)$_3$); δ_C (126 MHz, D$_6$-DMSO) 175.1 (47-*C*), 171.5 (1- and 27-*C*), 169.6 (25-*C*), 167.8 (42-, 21- and 39-*C*), 162.0 (30-*C*), 158.3 (16-*C*), 157.0 (44-*C* and *C*(O)), 143.8 (*C*$_{(Ar)}$), 143.7 (*C*$_{(Ar)}$), 143.5 (2 x *C*$_{(Ar)}$), 140.8 (*C*$_{(Ar)}$), 140.7 (3 x *C*$_{(Ar)}$), 136.1 (38-*C*), 129.9 (13-*C*), 129.1 (12-*C*), 128.0 (11-*C*), 127.7 (*C*H$_{(Ar)}$), 127.5 (*C*H$_{(Ar)}$ and 33-*C*), 127.2 (*C*H$_{(Ar)}$), 126.9 (*C*H$_{(Ar)}$), 126.9 (14- and 18-*C*), 125.3 (*C*H$_{(Ar)}$), 125.2 (*C*H$_{(Ar)}$), 125.1 (*C*H$_{(Ar)}$), 124.6 (36-*C*), 124.2 (32-*C*), 120.7 (34-*C*), 120.1 (2 x *C*H$_{(Ar)}$), 119.4 (35-*C*), 118.5 (31-*C*), 113.9 (15- and 17-*C*), 112.3 (37-*C*), 87.6 (43-*C*), 72.2 (4- or 2-*C*), 70.0 (5-*C*), 68.2 (23-*C*), 66.2 (O*C*H$_2$CH), 65.8 (O*C*H$_2$CH), 62.4 (TMSCH$_2$*C*H$_2$), 55.0 (20-*C*), 53.7 (3- and 28-*C*), 52.0 (4- or 2-*C*), 50.0 (40-*C*), 47.6 (45-*C*), 46.6 (OCH$_2$*C*H), 46.1 (OCH$_2$*C*H), 45.3 (24-*C*), 41.7 (22-*C*), 40.9 (26-*C*), 35.5 (41-*C*), 33.5 (7-*C*), 33.3 (46-*C*), 32.6 (10-*C*), 29.4 (9-*C*), 27.3 (6- and 29-*C*), 26.1 (8-*C*), 25.8 (2 x SiC(*C*H$_3$)$_3$), 25.7 (2 x SiC(*C*H$_3$)$_3$), 17.9 (2 x Si*C*(CH$_3$)$_3$), 17.7 (2 x Si*C*(CH$_3$)$_3$), 17.1 (TMS*C*H$_2$CH$_2$), 16.1 (19-*C*), −1.6 (Si(*C*H$_3$)$_3$), −2.3 (Si*C*H$_3$), −3.2 (Si*C*H$_3$), −3.5 (Si*C*H$_3$), −3.5 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −4.9 (Si*C*H$_3$), −5.2 (Si*C*H$_3$); *m/z* (ES$^+$) 1936 (MH$^+$, 100); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{105}H_{151}N_8O_{17}Si_5$ 1937.0072, observed 1937.0034.

2-(Trimethylsilyl)ethyl 3-(((3a*S*,6*S*,7*R*,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((1*S*,2*S*,3*S*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-3-methylnon-8-en-1-yl)-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (343)

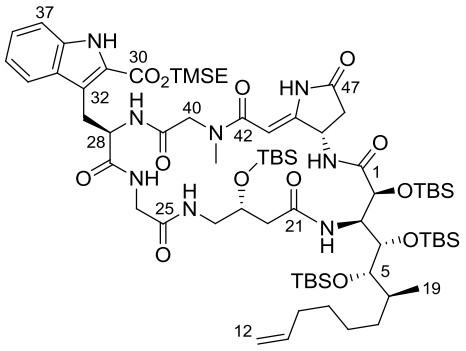


Piperidine (1.00 mL, 10.1 mmol) was added to a solution of linear hexapeptide **341** (153 mg, 89.0 μmol) in CH_2Cl_2 (15.0 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried under high vacuum for 4 h at 40 °C. Purification by flash column chromatography (2-5-25% MeOH/$CHCl_3$) afforded the piperidine salt of linear amino acid as a colourless solid. The piperidine salt of amino acid was dissolved in DMF (89.0 mL) and the solution was cooled to 0 °C. PyAOP (464 mg, 0.89 mmol), HOAt (121 mg, 0.89 mmol) and *N*,*N*-diisopropylethylamine (0.16 mL, 0.89 mmol) were then added sequentially. The mixture was warmed slowly to room temperature, stirred for 7 days and concentrated *in vacuo*. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed with water, dried

(Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (80-90% EtOAc/petrol) afforded cyclic hexapeptide **343** (74.2 mg, 64% over 2 steps) as a colourless solid; R_f 0.30 (EtOAc); m.p. 180-182 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −44.6 (*c* 0.83, EtOAc); ν_{max} /cm^{-1} (neat) 2930, 2857, 2360, 2341, 1654, 1541, 1250, 1099, 835, 777, 746, 668; δ_H (500 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 7.66 (1H, d, *J* 8.2, 34-*H*), 7.41 (1H, d, *J* 8.4, 37-*H*), 7.27 (1H, dd, *J* 8.0 and 8.0, 36-*H*), 7.10 (1H, dd, *J* 8.0 and 8.0, 35-*H*), 5.78 (1H, m, 11-*H*), 5.68 (1H, s, 43-*H*), 5.04 (1H, dd, *J* 9.0 and 3.3, 45-*H*), 4.99-4.90 (3H, m, 28- and 12-*H*), 4.47 (2H, t, *J* 8.7, $TMSCH_2CH_2$), 4.40-4.34 (3H, m, 26-*H*H, 2- and 4-*H*), 4.05 (1H, d, *J* 9.5, 3-*H*), 4.00-3.95 (2H, m, 29-*H*H and 23-*H*), 3.88 (2H, d, *J* 16.2, 40-*H*), 3.61-3.55 (2H, m, 26-H*H* and 5-*H*), 3.24 (1H, dd, *J* 13.7 and 11.5, 29-H*H*), 3.21 (3H, s, 41-*H*), 3.04-2.93 (2H, m, 24-*H*), 2.84 (1H, dd, *J* 18.6 and 9.0, 46-*H*H), 2.47 (1H, dd, *J* 18.6 and 3.3, 46-H*H*), 2.36-2.26 (2H, m, 22-*H*), 2.06-2.01 (2H, m, 10-*H*), 1.72-1.66 (2H, m, 6-*H* and 7-*H*H), 1.40-1.32 (3H, m, 8-*H*H and 9-*H*), 1.24-1.17 (3H, m, $TMSCH_2CH_2$ and 8-H*H*), 1.02 (3H, d, *J* 6.6, 19-*H*), 0.98-0.92 (28H, m, 3 x $SiC(CH_3)_3$ and 7-H*H*), 0.23-0.10 (27H, m, 6 x $SiCH_3$ and $Si(CH_3)_3$); δ_C (126 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 178.2 (47-*C*), 176.2 (1-*C*), 173.6 (27-*C*), 172.4 (25-*C*), 171.9 (39-*C*), 171.3 (42-*C*), 171.0 (21-*C*), 164.0 (30-*C*), 158.2 (44-*C*), 140.0 (11-*C*), 137.9 (38-*C*), 129.7 (33-*C*), 126.3 (36-*C*), 125.7 (32-*C*), 121.1 (34-*C*), 121.0 (35-*C*), 120.7 (31-*C*), 115.1 (12-*C*), 113.6 (37-*C*), 91.2 (43-*C*), 81.0 (5-*C*), 74.8 (3-*C*), 71.6 (2- or 4-*C*), 70.9 (23-*C*), 64.1 ($TMSCH_2CH_2$), 56.7 (2- or 4-*C*), 55.2 (24-*C*), 55.0 (40-*C*), 54.7 (28-*C*), 49.2 (45-*C*), 45.1 (22-*C*), 42.8 (26-*C*), 38.8 (41-*C*), 36.9 (46-*C*), 36.4 (6-*C*), 35.0 (10-*C*), 34.8 (7-*C*), 30.4 (9-*C*), 27.1 (8-*C*), 27.0 ($SiC(CH_3)_3$), 26.6 ($SiC(CH_3)_3$), 26.6 ($SiC(CH_3)_3$), 26.8 (29-*C*), 19.4 ($SiC(CH_3)_3$), 19.2 ($SiC(CH_3)_3$), 19.0 ($SiC(CH_3)_3$), 18.8 ($TMSCH_2CH_2$), 17.7 (19-*C*), −1.3

(Si(CH_3)$_3$), −2.4 (SiCH_3), −2.4 (SiCH_3), −4.1 (SiCH_3), −4.2 (SiCH_3), −4.5 (SiCH_3), −4.9 (SiCH_3); *m/z* (ES$^+$) 1297 (MH$^+$, 100), 1319 (MNa$^+$, 80%); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{63}H_{109}N_8O_{13}Si_4$ 1297.7186, observed 1297.7163.

2-(Trimethylsilyl)ethyl 3-(((3a*S*,6*S*,7R,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-22-methyl-7-((5*S*,6*S*)-2,2,3,3,8,8,9,9-octamethyl-6-((*S*)-oct-7-en-2-yl)-4,7-dioxa-3,8-disiladecan-5-yl)-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (344)

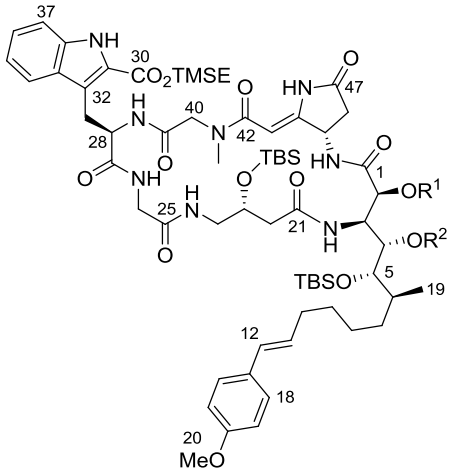


Piperidine (0.50 mL, 5.05 mmol) was added to a solution of linear hexapeptide **342** (87.0 mg, 47.5 μmol) in CH_2Cl_2 (10.0 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried under high vacuum for 4 h at 40 °C. Purification by flash column chromatography (2-5-25% MeOH/$CHCl_3$) afforded the piperidine salt of linear amino acid as a colourless solid. The piperidine salt of amino acid was dissolved in DMF (50.0 mL) and the solution was cooled to 0 °C. PyAOP (248 mg, 0.48 mmol), HOAt (65.0 mg, 0.48 mmol) and *N*,*N*-diisopropylethylamine (83.0 μL, 0.48 mmol) were then added sequentially. The

mixture was warmed slowly to room temperature, stirred for 7 days and concentrated *in vacuo*. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (70-80-90% EtOAc/petrol) afforded cyclic hexapeptide **344** (37.2 mg, 56% over 2 steps) as a colourless solid; R_f 0.60 (EtOAc); m.p. 188-190 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −38.2 (*c* 2.50, EtOAc); ν_{max} /cm^{-1} (neat) 3021, 2933, 2857, 1657, 1518, 1427, 1312, 1249, 1196, 1098, 834, 777, 746, 670; δ_H (500 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 7.74 (1H, d, *J* 8.2, 34-*H*), 7.43 (1H, d, *J* 8.4, 37-*H*), 7.30 (1H, dd, *J* 7.9 and 7.9, 36-*H*), 7.12 (1H, dd, *J* 7.9 and 7.9, 35-*H*), 5.78 (1H, m, 11-*H*), 5.66 (1H, s, 43-*H*), 5.27 (1H, m, 45-*H*), 4.99-4.88 (2H, m, 12-*H*), 4.67 (1H, d, *J* 11.7, 28-*H*), 4.60 (1H, m, $TMSCH_2CHH$), 4.52 (1H, s, 2-*H*), 4.42 (1H, m, $TMSCH_2CHH$), 4.37-4.29 (2H, m, 26-*H*H and 3-*H*), 4.02 (1H, m, 23-*H*), 4.01 (1H, d, *J* 15.8, 40-*H*H), 3.92 (1H, d, *J* 8.2, 4-*H*), 3.77 (1H, dd, *J* 14.0 and 3.0, 29-*H*H), 3.71 (1H, d, *J* 13.6, 24-*H*H), 3.63 (1H, d, *J* 9.0, 5-*H*), 3.46-3.39 (3H, m, 29-, 26- and 40-H*H*), 3.33 (3H, s, 41-*H*), 2.86-2.75 (3H, m, 24-H*H* and 46-*H*), 2.33 (1H, m, 22-*H*H), 2.16 (1H, m, 22-H*H*), 2.05-2.01 (2H, m, 10-*H*), 1.64-1.55 (2H, m, 6-*H* and 7-*H*H), 1.40-1.32 (3H, m, 8-*H*H and 9-*H*), 1.25-1.21 (2H, m, $TMSC\mathit{H_2}CH_2$), 1.14 (1H, m, 8-H*H*), 1.04-0.86 (40H, m, 19-*H*, 4 x $SiC(C\mathit{H_3})_3$ and 7-H*H*), 0.24-0.09 (33H, m, 8 x $SiC\mathit{H_3}$ and $Si(C\mathit{H_3})_3$); δ_C (126 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 178.8 (47-*C*), 175.2 (1-*C*), 173.0 (27-*C*), 172.9 (39-*C*), 171.6 (42-*C*), 170.6 (21-*C*), 170.1 (25-*C*), 164.8 (30-*C*), 159.5 (44-*C*), 140.0 (11-*C*), 138.1 (38-*C*), 128.5 (33-*C*), 126.9 (36-*C*), 125.7 (32-*C*), 121.5 (34-*C*), 120.8 (31-*C*), 120.7 (35-*C*), 115.1 (12-*C*), 113.7 (37-*C*), 91.4 (43-*C*), 80.5 (5-*C*), 76.6 (4-*C*), 74.5 (2-*C*), 70.6 (23-*C*), 64.6 ($TMSCH_2\mathit{C}H_2$), 57.7 (3-*C*), 56.4 (28-*C*), 55.6 (40-*C*), 49.0 (45-*C*), 46.9 (24-*C*), 45.4 (22-*C*), 43.2 (26-*C*), 38.7 (41-*C*), 36.1 (46-*C*), 35.6 (6-*C*), 35.1 (7-*C*),

35.1 (10-*C*), 30.9 (9-*C*), 27.5 (8-*C*), 27.1 (29-*C*), 27.2 (SiC(CH_3)$_3$), 27.0 (SiC(CH_3)$_3$), 26.6 (2 x SiC(CH_3)$_3$), 19.5 (Si*C*(CH_3)$_3$), 19.3 (Si*C*(CH_3)$_3$), 19.1 (Si*C*(CH_3)$_3$), 19.0 (Si*C*(CH_3)$_3$), 18.9 (TMSCH_2CH_2), 17.9 (19-*C*), −1.3 (Si(CH_3)$_3$), −1.9 (SiCH_3), −2.7 (SiCH_3), −3.5 (SiCH_3), −3.6 (SiCH_3), −3.6 (SiCH_3), −4.1 (SiCH_3), −4.2 (SiCH_3), −4.6 (SiCH_3); *m/z* (ES^+) 1413 (MH^+, 100), 1435 (MNa^+, 30%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{69}H_{123}N_8O_{13}Si_5$ 1411.8050, observed 1411.8053.

2-(Trimethylsilyl)ethyl 3-(((3a*S*,6*S*,7*R*,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((1*S*,2*S*,3*S*,*E*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-9-(4-methoxyphenyl)-3-methylnon-8-en-1-yl)-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (355)



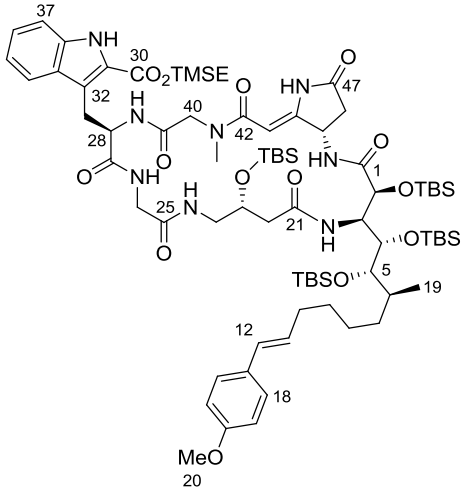
R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H

Alkene **343** (64.5 mg, 49.7 μmol) and 4-vinylanisole (70.0 μL, 0.50 mmol) were added to dry degassed CH_2Cl_2 (1.00 mL). Grubbs I catalyst (80.0 mg, 0.10 mmol) was then added

to the solution and the reaction was stirred at room temperature for a total period of 48 h. One additional injection of 4-vinylanisole (70.0 μL, 0.50 mmol) and Grubbs I catalyst (80.0 mg, 0.10 mmol) was made after 24 h. After which DMSO (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The mixture was then concentrated *in vacuo* and purified by flash column chromatography (50-80-100% EtOAc/petrol) to afford styrene **355** (41.8 mg, 60%) as a colourless solid; R_f 0.30 (EtOAc); m.p. 119-121 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −27.2 (*c* 1.65, EtOAc); ν_{max} /cm^{-1} (neat) 3022, 2933, 2856, 2390, 2348, 2286, 1659, 1445, 1326, 1249, 1098, 835, 776, 749; δ_H (500 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 7.67 (1H, d, *J* 8.0, 34-*H*), 7.42 (1H, d, *J* 8.4, 37-*H*), 7.28-7.21 (3H, m, 36-, 14- and 18-*H*), 7.09 (1H, dd, *J* 7.6 and 7.6, 35-*H*), 6.82 (2H, d, *J* 8.8, 15- and 17-*H*), 6.30 (1H, d, *J* 15.8, 12-*H*), 6.05 (1H, dt, *J* 15.8 and 6.9, 11-*H*), 5.69 (1H, s, 43-*H*), 5.07 (1H, dd, *J* 8.4 and 3.5, 45-*H*), 4.92 (1H, dd, *J* 10.7 and 3.5, 28-*H*), 4.47 (2H, t, *J* 8.7, TMSCH_2C*H*$_2$), 4.40-4.24 (3H, m, 26-*H*H, 2- and 4-*H*), 4.05 (1H, d, *J* 9.0, 3-*H*), 3.99-3.95 (2H, m, 29-*H*H and 23-*H*), 3.85 (2H, d, *J* 17.2, 40-*H*), 3.76 (3H, s, 20-*H*), 3.62-3.56 (2H, m, 26-H*H* and 5-*H*), 3.24 (1H, dd, *J* 13.7 and 11.5, 29-H*H*), 3.20 (3H, s, 41-*H*), 3.06-3.01 (2H, m, 24-*H*), 2.84 (1H, dd, *J* 18.4 and 9.0, 46-*H*H), 2.46 (1H, dd, *J* 18.4 and 2.5, 46-H*H*), 2.35-2.29 (2H, m, 22-*H*), 2.17-2.13 (2H, m, 10-*H*), 1.72-1.68 (2H, m, 6-*H* and 7-*H*H), 1.45-1.38 (3H, m, 8-*H*H and 9-*H*), 1.26-1.20 (3H, m, TMSC*H*$_2$CH$_2$ and 8-H*H*), 1.03 (3H, d, *J* 6.5, 19-*H*), 0.97-0.86 (28H, m, 3 x SiC(C*H*$_3$)$_3$ and 7-H*H*), 0.23-0.09 (27H, m, 6 x SiC*H*$_3$ and Si(C*H*$_3$)$_3$); δ_C (126 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 178.1 (47-*C*), 176.1 (1-*C*), 173.7 (27-*C*), 172.4 (25-*C*), 171.9 (39-*C*), 171.4 (42-*C*), 170.9 (21-*C*), 164.0 (30-*C*), 160.4 (16-*C*), 158.2 (44-*C*), 137.9 (38-*C*), 132.1 (13-*C*), 130.9 (12-*C*), 129.8 (33-*C*), 129.4 (11-*C*), 128.3 (14- and 18-*C*), 126.3 (36-*C*), 125.8 (32-*C*),

121.2 (34-*C*), 121.0 (35-*C*), 120.6 (31-*C*), 115.0 (15- and 17-*C*), 113.6 (37-*C*), 91.2 (43-*C*), 81.1 (5-*C*), 74.9 (3-*C*), 71.6 (2-*C*), 70.9 (23-*C*), 64.1 ($TMSCH_2\mathit{C}H_2$), 56.7 (4-*C*), 55.8 (20-*C*), 55.1 (24-*C*), 55.1 (40-*C*), 54.9 (28-*C*), 49.2 (45-*C*), 45.0 (22-*C*), 42.8 (26-*C*), 38.8 (41-*C*), 37.0 (46-*C*), 36.2 (6-*C*), 34.9 (7-*C*), 34.4 (10-*C*), 31.0 (9-*C*), 27.5 (8-*C*), 27.0 ($SiC(\mathit{C}H_3)_3$), 26.7 ($SiC(\mathit{C}H_3)_3$), 26.6 ($SiC(\mathit{C}H_3)_3$), 26.8 (29-*C*), 19.4 ($Si\mathit{C}(CH_3)_3$), 19.2 ($Si\mathit{C}(CH_3)_3$), 19.0 ($Si\mathit{C}(CH_3)_3$), 18.8 ($TMS\mathit{C}H_2CH_2$), 17.8 (19-*C*), −1.3 ($Si(\mathit{C}H_3)_3$), −2.3 ($Si\mathit{C}H_3$), −3.0 ($Si\mathit{C}H_3$), −4.0 ($Si\mathit{C}H_3$), −4.2 ($Si\mathit{C}H_3$), −4.4 ($Si\mathit{C}H_3$), −4.8 ($Si\mathit{C}H_3$); *m/z* (ES^+) 1404 (MH^+, 100), 1426 (MNa^+, 30%); *m/z* HRMS (ES^+) MH^+ calculated for $C_{70}H_{115}N_8O_{14}Si_4$ 1404.7638, observed 1404.7682.

2-(Trimethylsilyl)ethyl 3-(((3a*S*,6*S*,7*R*,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((5*S*,6*S*)-6-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (356)

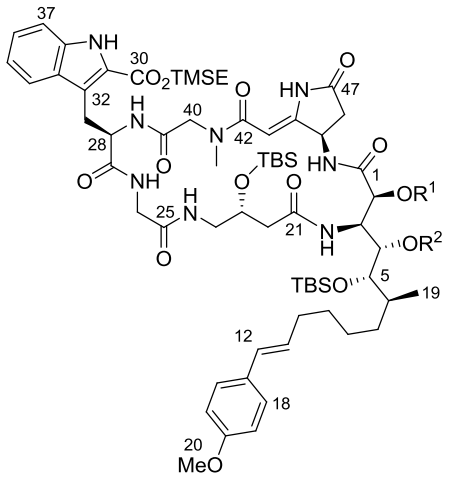


Alkene **344** (50.0 mg, 35.0 μmol) and 4-vinylanisole (45.0 μL, 0.35 mmol) were added to dry degassed CH_2Cl_2 (2.00 mL). Grubbs I catalyst (58.0 mg, 71.0 μmol) was then added to the solution and the reaction was stirred at room temperature for a total period of 48 h. One additional injection of 4-vinylanisole (45.0 μL, 0.35 mmol) and Grubbs I catalyst (58.0 mg, 71.0 μmol) was made after 24 h. After which DMSO (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The mixture was then concentrated *in vacuo* and purified by flash column chromatography (50-60-70-80-100% EtOAc/petrol) to afford styrene **356** (30.5 mg, 58%) as a colourless solid; R_f 0.30 (80% EtOAc/petrol); m.p. 162-164 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −24.0 (*c* 1.53, EtOAc);

ν_{max} /cm^{-1} (neat) 2953, 2929, 2856, 1657, 1511, 1316, 1250, 1097, 834, 776, 745, 673; δ_H (500 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 7.74 (1H, d, *J* 8.0, 34-*H*), 7.43 (1H, d, *J* 8.4, 37-*H*), 7.30 (1H, dd, *J* 7.6 and 7.6, 36-*H*), 7.25 (2H, d, *J* 8.7, 14- and 18-*H*), 7.12 (1H, dd, *J* 7.6 and 7.6, 35-*H*), 6.83 (2H, d, *J* 8.7, 15- and 17-*H*), 6.30 (1H, d, *J* 15.9, 12-*H*), 6.06 (1H, dt, *J* 15.9 and 6.9, 11-*H*), 5.65 (1H, s, 43-*H*), 5.26 (1H, m, 45-*H*), 4.68 (1H, d, *J* 11.2, 28-*H*), 4.60 (1H, m, TMSCH$_2$C*H*H), 4.52 (1H, s, 2-*H*), 4.43-4.35 (2H, m, 3-*H* and TMSCH$_2$CH*H*), 4.26 (1H, dd, *J* 10.7 and 10.7, 26-*H*H), 4.02-3.96 (2H, m, 23-*H* and 40-*H*H), 3.91 (1H, d, *J* 6.8, 4-*H*), 3.78 (1H, m, 29-*H*H), 3.76 (3H, s, 20-*H*), 3.71 (1H, m, 24-*H*H), 3.64 (1H, d, *J* 9.0, 5-*H*), 3.46-3.41 (3H, m, 29-, 26- and 40-H*H*), 3.31 (3H, s, 41-*H*), 2.80-2.78 (3H, m, 24-H*H* and 46-*H*), 2.34 (1H, m, 22-*H*H), 2.19-2.15 (3H, m, 22-H*H* and 10-*H*), 1.72-1.62 (2H, m, 6-*H* and 7-*H*H), 1.45-1.34 (3H, m, 8-*H*H and 9-*H*), 1.24-1.20 (3H, m, 8-H*H* and TMSC*H*$_2$CH$_2$), 1.04 (3H, d, *J* 5.4, 19-*H*), 0.99-0.86 (37H, m, 4 x SiC(C*H*$_3$)$_3$ and 7-H*H*), 0.40-0.09 (33H, m, 8 x SiC*H*$_3$ and Si(C*H*$_3$)$_3$); δ_C (126 MHz, D_4-MeOD (chemical shifts reported for the major rotamer only)) 178.7 (47-*C*), 175.2 (1-*C*), 173.0 (27-*C*), 172.8 (39-*C*), 171.6 (42-*C*), 170.6 (21-*C*), 170.3 (25-*C*), 164.7 (30-*C*), 160.4 (16-*C*), 159.6 (44-*C*), 138.1 (38-*C*), 132.1 (13-*C*), 131.0 (12-*C*), 129.3 (11-*C*), 128.5 (33-*C*), 128.3 (14- and 18-*C*), 126.9 (36-*C*), 125.7 (32-*C*), 121.5 (34-*C*), 120.9 (31-*C*), 120.8 (35-*C*), 115.1 (15- and 17-*C*), 113.7 (37-*C*), 91.4 (43-*C*), 80.7 (5-*C*), 76.6 (4-*C*), 74.5 (2-*C*), 70.6 (23-*C*), 64.6 (TMSCH$_2$*C*H$_2$), 57.7 (3-*C*), 56.4 (28-*C*), 55.8 (20-*C*), 55.5 (40-*C*), 49.2 (45-*C*), 47.0 (24-*C*), 45.3 (22-*C*), 43.3 (26-*C*), 38.6 (41-*C*), 36.1 (46-*C*), 35.4 (6-*C*), 35.1 (7-*C*), 34.4 (10-*C*), 30.9 (9-*C*), 27.6 (8-*C*), 27.1 (29-*C*), 27.2 (SiC(*C*H$_3$)$_3$), 27.0 (SiC(*C*H$_3$)$_3$), 26.6 (2 x SiC(*C*H$_3$)$_3$), 19.6 (Si*C*(CH$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$), 19.1 (Si*C*(CH$_3$)$_3$), 19.0 (Si*C*(CH$_3$)$_3$), 18.9 (TMS*C*H$_2$CH$_2$), 18.0 (19-*C*), −1.3 (Si(*C*H$_3$)$_3$), −0.7 (Si*C*H$_3$), −1.9 (Si*C*H$_3$), −2.7 (Si*C*H$_3$), −3.5 (Si*C*H$_3$),

−3.6 (Si*C*H$_3$), −4.0 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −4.5 (Si*C*H$_3$); *m/z* (ES$^+$) 1517 (MH$^+$, 100); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{76}H_{129}N_8O_{14}Si_5$ 1517.8469, observed 1517.8535.

2-(Trimethylsilyl)ethyl 3-(((3a*R*,6*S*,7*R*,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((1*S*,2*S*,3*S*,*E*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-9-(4-methoxyphenyl)-3-methylnon-8-en-1-yl)-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (*epi*-355)



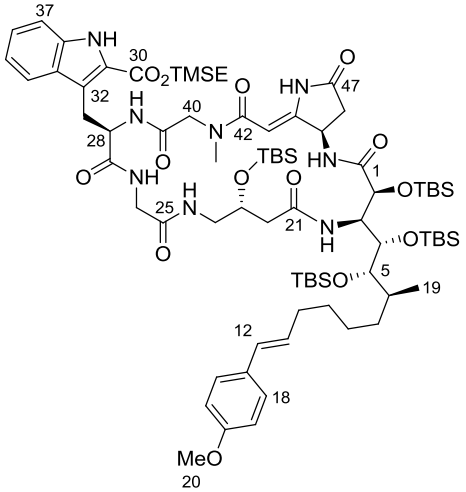
R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H

Piperidine (0.25 mL, 2.53 mmol) was added to a solution of linear hexapeptide *epi*-**366** (35.0 mg, 19.2 μmol) in CH_2Cl_2 (5.00 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried under high vacuum for 4 h at 40 °C. Purification by flash column chromatography (2-5-25% MeOH/$CHCl_3$) afforded the piperidine salt of linear amino acid as a colourless solid. The piperidine salt of amino acid was dissolved in DMF (19.2 mL) and the solution

was cooled to 0 °C. PyAOP (100 mg, 0.19 mmol), HOAt (26.1 mg, 0.19 mmol) and *N*,*N*-diisopropylethylamine (33.0 μL, 0.19 μmol) were then added sequentially. The mixture was warmed slowly to room temperature, stirred for 6 days and concentrated *in vacuo*. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (60-100% EtOAc/petrol) afforded cyclic hexapeptide *epi*-**355** (15.7 mg, 58% over 2 steps) as a colourless solid; R_f 0.25 (80% EtOAc/petrol); m.p. 170-172 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −42.1 (*c* 1.40, EtOAc); ν_{max} /cm^{-1} (neat) 2929, 2858, 2157, 1659, 1528, 1511, 1250, 1096, 836, 776, 669; δ_H (500 MHz, D_4-MeOD) 7.73 (1H, d, *J* 8.2, 34-*H*), 7.44 (1H, d, *J* 8.4, 37-*H*), 7.30 (1H, ddd, *J* 8.2, 8.2 and 0.8, 36-*H*), 7.22 (2H, d, *J* 8.7, 14- and 18-*H*), 7.11 (1H, ddd, *J* 8.2, 8.2 and 0.8, 35-*H*), 6.76 (2H, d, *J* 8.7, 15- and 17-*H*), 8.37 (1H, d, *J* 9.3, N*H* or O*H*), 6.27 (1H, d, *J* 15.8, 12-*H*), 6.04 (1H, dt, *J* 15.8 and 6.9, 11-*H*), 5.61 (1H, d, *J* 1.4, 43-*H*), 5.24 (1H, ddd, *J* 9.5, 6.3 and 1.1, 45-*H*), 4.56-4.20 (5H, m, $TMSCH_2CH_2$, 23-, 28- and 4-*H*), 4.35 (1H, s, 2-*H*), 4.29 (1H, d, *J* 17.7, 29-*H*H), 4.16 (1H, d, *J* 14.7, 40-*H*H), 4.01 (1H, dd, *J* 9.5 and 2.1, 3-*H*), 3.66 (3H, s, 20-*H*), 3.62 (2H, d, *J* 6.8, 26-*H*), 3.51 (1H, dd, *J* 9.3 and 2.5, 5-*H*), 3.32-3.27 (5H, m, 41-*H*, 29-H*H* and 40-H*H*), 3.09 (1H, m, 24-*H*H), 2.76-2.70 (2H, m, 46-*H*H and 24-H*H*), 2.63 (1H, dd, *J* 18.0 and 6.5, 46-H*H*), 2.48 (1H, dd, *J* 14.5 and 4.7, 22-*H*H), 2.21-2.12 (2H, m, 10-*H*), 2.08 (1H, dd, *J* 14.5 and 2.1, 22-H*H*), 1.72-1.67 (2H, m, 6-*H* and 7-*H*H), 1.45-1.39 (2H, m, 9-*H*H and 8-*H*H), 1.33 (1H, m, 9-H*H*), 1.27-1.24 (3H, m, 8-H*H* and $TMSCH_2CH_2$), 0.99 (3H, d, *J* 6.6, 19-*H*), 0.97 (9H, s, $SiC(CH_3)_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 0.94 (1H, m, 7-H*H*), 0.82 (9H, s, $SiC(CH_3)_3$), 0.22, 0.18, 0.16, 0.13 (4 x 3H, s, 4 x $SiCH_3$), 0.11 (9H, s, $Si(CH_3)_3$), 0.10, 0.06 (2 x 3H, s, 2 x $SiCH_3$); δ_C (126 MHz, D_4-MeOD) 177.3 (47-*C*), 177.3 (1-*C*), 174.5 (39-*C*), 173.3 (27-*C*), 172.8 (25-*C*), 171.0 (42-*C*), 169.8 (21-*C*), 165.2 (30-*C*),

160.3 (16-*C*), 157.7 (44-*C*), 138.1 (38-*C*), 132.2 (13-*C*), 130.8 (12-*C*), 129.5 (11-*C*), 129.0 (33-*C*), 128.3 (14- and 18-*C*), 126.9 (36-*C*), 126.0 (32-*C*), 121.4 (34-*C*), 121.4 (35-*C*), 119.5 (31-*C*), 115.0 (15- and 17-*C*), 113.6 (37-*C*), 91.5 (43-*C*), 81.1 (5-*C*), 75.4 (3-*C*), 71.8 (2-*C*), 68.1 (23-*C*), 64.9 (TMSCH$_2$*C*H$_2$), 59.1 (4-*C*), 55.8 (20-*C*), 55.2 (28-*C*), 54.8 (40-*C*), 48.7 (45-*C*), 48.1 (24-*C*), 46.3 (22-*C*), 43.1 (29-*C*), 39.9 (41-*C*), 35.8 (6-*C*), 35.0 (7-*C*), 34.7 (10- or 46-*C*), 34.6 (10- or 46-*C*), 31.0 (9-*C*), 27.5 (8-*C*), 27.1 (SiC(*C*H$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 26.6 (SiC(*C*H$_3$)$_3$), 26.6 (26-*C*), 19.4 (Si*C*(CH$_3$)$_3$), 19.1 (Si*C*(CH$_3$)$_3$), 19.0 (Si*C*(CH$_3$)$_3$), 18.9 (TMS*C*H$_2$CH$_2$), 17.5 (19-*C*), −1.3 (Si(*C*H$_3$)$_3$), −2.4 (Si*C*H$_3$), −2.8 (Si*C*H$_3$), −3.7 (Si*C*H$_3$), −4.0 (Si*C*H$_3$), −4.2 (Si*C*H$_3$), −5.1 (Si*C*H$_3$); *m/z* (ES$^+$) 1404 (MH$^+$, 100), 1426 (MNa$^+$, 80%); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{70}H_{115}N_8O_{14}Si_4$ 1404.7638, observed 1404.7606.

2-(Trimethylsilyl)ethyl 3-(((3a*R*,6*S*,7*R*,11*R*,18*R*,*Z*)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((5*S*,6*S*)-6-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylate (*epi*-356)

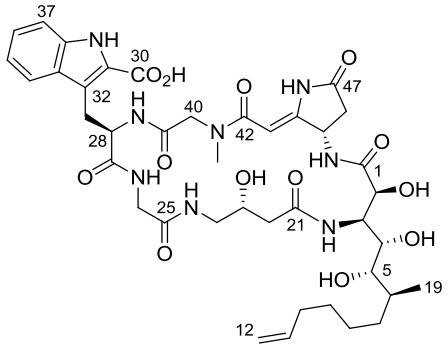


Piperidine (0.25 mL, 2.53 mmol) was added to a solution of linear hexapeptide *epi*-**367** (15.0 mg, 7.74 μmol) in CH_2Cl_2 (5.00 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried under high vacuum for 4 h at 40 °C. Purification by flash column chromatography (2-5-25% MeOH/$CHCl_3$) afforded the piperidine salt of linear amino acid as a colourless solid. The piperidine salt of amino acid was dissolved in DMF (7.80 mL) and the solution was cooled to 0 °C. PyAOP (40.4 mg, 77.4 μmol), HOAt (10.5 mg, 77.4 μmol) and *N*,*N*-diisopropylethylamine (14.0 μL, 77.4 μmol) were then added sequentially. The mixture was warmed slowly to room temperature, stirred for 6 days and concentrated

in vacuo. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-70% EtOAc/petrol) afforded cyclic hexapeptide *epi*-**356** (6.4 mg, 54% over 2 steps) as a colourless solid; R_f 0.50 (60% EtOAc/petrol); m.p. 141-143 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −40.4 (*c* 0.70, EtOAc); ν_{max} /cm^{-1} (neat) 2542, 2200, 2158, 2117, 2084, 2050, 2007, 1975, 1948, 1658, 1521, 1251, 1101, 833, 772, 690, 674, 648, 622; δ_H (500 MHz, D_4-MeOD) 7.71 (1H, d, *J* 8.2, 34-*H*), 7.44 (1H, d, *J* 8.4, 37-*H*), 7.30 (1H, ddd, *J* 8.0, 8.0 and 0.8, 36-*H*), 7.21 (2H, d, *J* 8.7, 14- and 18-*H*), 7.11 (1H, dd, *J* 8.0 and 8.0, 35-*H*), 6.75 (2H, d, *J* 8.7, 15- and 17-*H*), 6.27 (1H, d, *J* 15.8, 12-*H*), 6.04 (1H, dt, *J* 15.8 and 7.1, 11-*H*), 5.66 (1H, s, 43-*H*), 5.30 (1H, dd, *J* 7.9 and 1.4, 45-*H*), 4.59-4.40 (6H, m, $TMSCH_2CH_2$, 23-, 28-, 4- and 2-*H*), 4.23 (1H, d, *J* 17.2, 29-*H*H), 4.18 (1H, d, *J* 14.9, 40-*H*H), 3.84 (1H, dd, *J* 9.8 and 2.4, 3-*H*), 3.68 (3H, s, 20-*H*), 3.63-3.60 (3H, m, 26- and 5-*H*), 3.29 (3H, s, 41-*H*), 3.18 (1H, d, *J* 17.2, 29-*H*H), 3.11-3.06 (2H, m, 24-*H*H and 40-H*H*), 2.80-2.74 (2H, m, 46-*H*H and 24-H*H*), 2.54 (1H, dd, *J* 19.6 and 4.4, 22-*H*H), 2.48 (1H, dd, *J* 17.5 and 7.9, 46-H*H*), 2.19-2.07 (3H, m, 22-H*H* and 10-*H*), 1.71-1.67 (2H, m, 6-*H* and 7-*H*H), 1.46-1.39 (2H, m, 9-*H*H and 8-*H*H), 1.33 (1H, m, 9-H*H*), 1.28-1.24 (3H, m, 8-H*H* and $TMSCH_2CH_2$), 1.02 (9H, s, $SiC(CH_3)_3$), 1.00 (3H, d, *J* 6.2, 19-*H*), 0.96 (9H, s, $SiC(CH_3)_3$), 0.96 (9H, s, $SiC(CH_3)_3$), 0.94 (1H, m, 7-H*H*), 0.84 (9H, s, $SiC(CH_3)_3$), 0.23-0.07 (33H, m, 8 x $SiCH_3$ and $Si(CH_3)_3$); δ_C (126 MHz, D_4-MeOD) 176.3 (47-*C*), 175.3 (1-*C*), 174.0 (25-*C*), 173.3 (27-*C*), 172.3 (39-*C*), 170.8 (42-*C*), 169.4 (21-*C*), 165.2 (30-*C*), 160.4 (16-*C*), 156.4 (44-*C*), 138.1 (38-*C*), 132.1 (13-*C*), 130.9 (12-*C*), 129.5 (11-*C*), 129.1 (33-*C*), 128.3 (14- and 18-*C*), 126.9 (36-*C*), 126.0 (32-*C*), 121.4 (34- and 35-*C*), 119.4 (31-*C*), 115.0 (15- and 17-*C*), 113.5 (37-*C*), 91.6 (43-*C*), 80.6 (5-*C*), 76.9 (3-*C*), 73.7 (2- or 4-*C*), 68.2 (23-*C*), 64.9 ($TMSCH_2CH_2$),

59.1 (2- or 4-*C*), 56.0 (28-*C*), 55.8 (20-*C*), 54.3 (40-*C*), 48.7 (45-*C*), 47.9 (24-*C*), 45.3 (22-*C*), 43.0 (29-*C*), 39.7 (41-*C*), 35.5 (46-*C*), 34.9 (7- and 6-*C*), 34.8 (10-*C*), 30.9 (9-*C*), 27.8 (8-*C*), 27.1 (SiC(*C*H_3)$_3$), 27.0 (SiC(*C*H_3)$_3$), 26.7 (2 x SiC(*C*H_3)$_3$), 26.6 (26-*C*), 19.4 (Si*C*(CH_3)$_3$), 19.3 (Si*C*(CH_3)$_3$), 19.0 (Si*C*(CH_3)$_3$), 18.9 (Si*C*(CH_3)$_3$), 18.9 (TMS*C*$H_2$$CH_2$), 17.6 (19-*C*), −0.9 (Si*C*H_3), −1.3 (Si*C*H_3 and Si(*C*H_3)$_3$), −2.5 (Si*C*H_3), −3.1 (Si*C*H_3), −3.7 (Si*C*H_3), −3.7 (Si*C*H_3), −4.0 (Si*C*H_3), −4.1 (Si*C*H_3); *m/z* (ES^+) 1518 (MH^+, 100); *m/z* HRMS (ES^+) MH^+ calculated for $C_{76}H_{129}N_8O_{14}Si_5$ 1517.8469, observed 1517.8457.

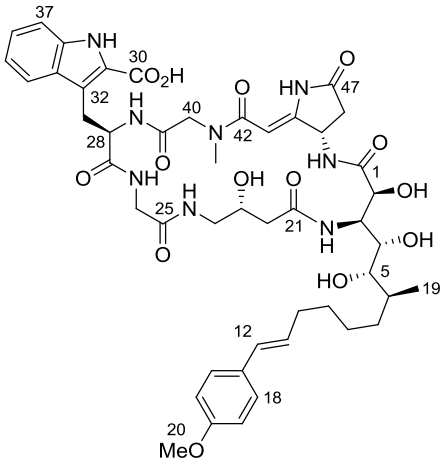
3-(((3a*S*,6*S*,7*R*,11*R*,18*R*,*Z*)-7-((1*S*,2*S*,3*S*)-1,2-Dihydroxy-3-methylnon-8-en-1-yl)-6,11-dihydroxy-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylic acid (146)



TASF (78.0 mg, 284 μmol) was added to a solution of cyclic peptide **343** (24.6 mg, 18.9 μmol) in DMF (1.00 mL) at 0 °C. The mixture was warmed slowly to room temperature, stirred for 16 h and concentrated *in vacuo*. Purification by flash column chromatography (20-25-33% MeOH/$CHCl_3$) and further reverse phase column chromatography (20-25-30% CH_3CN/H_2O) afforded deprotected cyclic peptide **146**

(7.3 mg, 45%) as a colourless solid; R_f 0.30 (30% MeOH/$CHCl_3$); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −20.4 (*c* 0.23, 0.1 M NH_4HCO_3, pH 7); ν_{max} /cm^{-1} (neat) 3309, 2925, 2423, 2144, 1641, 1586, 1535, 1442, 1334, 1293, 1226, 1107, 1026, 845, 744, 645; δ_H (500 MHz, D_7-DMF (chemical shifts reported for the major rotamer only)) 11.60 (1H, br s, N*H*), 10.73 (2H, s, 2 x N*H*), 8.87 (1H, br s, N*H*), 8.73 (1H, d, *J* 7.7, N*H*), 7.74 (1H, d, *J* 9.5, N*H*), 7.69 (1H, d, *J* 7.9, 34-*H*), 7.50 (1H, d, *J* 9.5, N*H*), 7.44 (1H, d, *J* 8.4, 37-*H*), 7.17 (1H, dd, *J* 7.6 and 7.6, 36-*H*), 7.02 (1H, dd, *J* 7.6 and 7.6, 35-*H*), 5.82 (1H, m, 11-*H*), 5.55 (1H, s, 43-*H*), 5.37 (1H, br s, O*H*), 5.06 (1H, m, 45-*H*), 5.01-4.90 (3H, m, 12-*H* and O*H*), 4.67 (1H, s, 2-*H*), 4.52 (1H, d, *J* 7.3, O*H*), 4.47-4.43 (2H, m, 23- and 3-*H*), 4.23 (1H, d, *J* 11.2, 28-*H*), 4.14 (1H, d, *J* 4.9, O*H*), 3.94 (1H, m, 26-*H*H), 3.80 (1H, dd, *J* 11.2 and 11.2, 29-*H*H), 3.72-3.64 (5H, m, 24-*H*H, 26-H*H*, 40-*H* and 4-*H*), 3.33 (1H, m, 5-*H*), 3.14 (1H, m, 29-H*H*), 3.08 (3H, s, 41-*H*), 3.01 (1H, m, 46-*H*H), 2.89 (1H, m, 24-H*H*), 2.49 (1H, dd, *J* 17.7 and 5.0, 46-H*H*), 2.38 (1H, d, *J* 12.5, 22-*H*H), 2.15 (1H, dd, *J* 12.5 and 10.6, 22-H*H*), 2.05-2.02 (2H, m, 10-*H*), 1.75-1.69 (2H, m, 6-*H* and 7-*H*H), 1.39-1.29 (3H, m, 8-*H*H and 9-*H*), 1.19 (1H, m, 8-H*H*), 1.08 (1H, m, 7-H*H*), 0.81 (3H, d, *J* 6.5, 19-*H*); δ_C (126 MHz, D_7-DMF (chemical shifts reported for the major rotamer only)) 173.8 (*C*(O)), 173.7 (*C*(O)), 173.5 (*C*(O)), 171.6 (*C*(O)), 169.6 (*C*(O)), 169.4 (*C*(O)), 169.2 (*C*(O)), 168.8 (*C*(O)), 156.6 (44-*C*), 139.6 (11-*C*), 135.4 (38-*C*), 134.0 (31- or 32-*C*), 129.1 (31- or 32-*C*), 128.6 (33-*C*), 122.8 (36-*C*), 119.5 (34-*C*), 118.8 (35-*C*), 114.2 (12-*C*), 112.0 (37-*C*), 89.7 (43-*C*), 73.5 (5-*C*), 70.2 (2-*C*), 69.2 (4-*C*), 66.9 (23-*C*), 59.8 (28-*C*), 54.4 (3-*C*), 53.9 (40-*C*), 48.5 (45-*C*), 44.8 (24-*C*), 43.2 (26-*C*), 41.4 (22-*C*), 38.1 (41-*C*), 36.5 (46-*C*), 34.9 (6-*C*), 34.0 (10-*C*), 33.3 (7-*C*), 29.4 (9-*C*), 26.4 (8-*C*), 25.5 (29-*C*), 15.5 (19-*C*); *m/z* (ES^+) 855 (MH^+, 100); *m/z* HRMS (ES^+) MH^+ calculated for $C_{40}H_{55}N_8O_{13}$ 855.3883, observed 855.3865.

3-(((3a*S*,6*S*,7*R*,11*R*,18*R*,*Z*)-7-((1*S*,2*S*,3*S*,*E*)-1,2-Dihydroxy-9-(4-methoxyphenyl)-3-methylnon-8-en-1-yl)-6,11-dihydroxy-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylic acid (358)

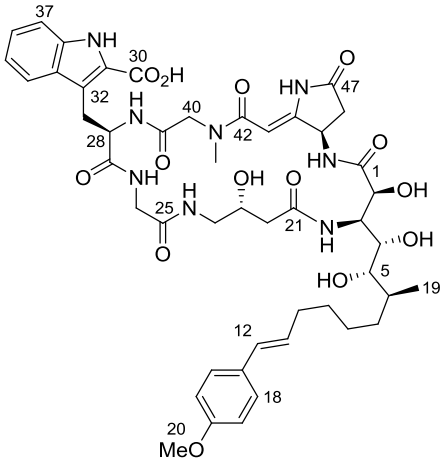


H_2O (11 μL, 0.58 mmol) and TASF (100 μL of a 2.9 M solution in DMF, 0.29 mmol) were added sequentially to a solution of protected cyclic peptide **356** (29.0 mg, 19.1 μmol) in DMF (0.50 mL) at 0 °C. The reaction was stirred for 10 h at 0 °C. After which TMS_2O (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The solution was then concentrated using high vacuum centrifugal evaporator. Purification by flash column chromatography (10-20-25% MeOH/$CHCl_3$) and further semi-preparative reverse phase HPLC (XBridge Prep C18 5.0 μm 10 mm x 250 mm column, at 4.4 mL/min with UV detection 214 nm: 2 mins – 5% CH_3CN in 0.05% aqueous TFA, linear increase; 3 mins – 42% CH_3CN in 0.05% aqueous TFA, isocratic; 23 mins – 42% CH_3CN in 0.05% aqueous TFA, linear increase; 24 mins – 95% CH_3CN in 0.05% aqueous TFA, isocratic) with subsequent lyophilisation afforded deprotected cyclic peptide **358** (5.3 mg,

29%) as a colourless solid; R_f 0.30 (30% MeOH/$CHCl_3$); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −26.4 (*c* 0.23, 0.1 M NH_4HCO_3, pH 7); ν_{max} /cm^{-1} (neat) 3299, 2926, 2853, 1651, 1537, 1511, 1339, 1246, 1201, 1177, 1132, 1025, 968, 839, 800, 745, 720, 664; δ_H (500 MHz, D_6-DMSO (chemical shifts reported for the major conformer only)) 11.44 (1H, br s, N*H*), 10.38 (1H, s, N*H*), 8.53 (1H, d, *J* 6.9, N*H*), 8.43 (1H, br s, N*H*), 7.64 (1H, d, *J* 6.0, N*H*), 7.50 (1H, d, *J* 8.2, 34-*H*), 7.47 (1H, d, *J* 9.0, N*H*), 7.36 (1H, d, *J* 8.4, 37-*H*), 7.29 (2H, d, *J* 8.7, 14- and 18-*H*), 7.18 (1H, dd, *J* 7.4 and 7.4, 36-*H*), 6.99 (1H, dd, *J* 7.4 and 7.4, 35-*H*), 6.85 (2H, d, *J* 8.7, 15- and 17-*H*), 6.30 (1H, d, *J* 15.8, 12-*H*), 6.10 (1H, dt, *J* 15.8 and 6.8, 11-*H*), 6.05 (1H, m, N*H*), 5.49 (1H, s, 43-*H*), 5.07 (1H, d, *J* 4.3, O*H*), 4.59 (1H, m, 45-*H*), 4.49 (1H, d, *J* 16.6, 40-*H*H), 4.46 (1H, d, *J* 3.8, O*H*), 4.39 (1H, s, 2-*H*), 4.17 (1H, d, *J* 9.9, O*H*), 4.07-4.04 (2H, m, 28- and 3-*H*), 3.76 (1H, m, 24-*H*H), 3.72 (3H, s, 20-*H*), 3.56-3.35 (5H, m, 26-*H*H, 29-*H*H, 40-H*H*, 23- and 4-*H*), 3.18 (1H, m, 29-H*H*), 3.07 (3H, s, 41-*H*), 3.07-3.03 (2H, m, 26-H*H* and 5-*H*), 2.66 (1H, dd, *J* 17.8 and 5.2, 46-*H*H), 2.58 (1H, dd, *J* 17.8 and 9.6, 46-H*H*), 2.50 (1H, m, 22-*H*H), 2.32 (1H, m, 24-H*H*), 2.14-2.07 (3H, m, 22-H*H* and 10-*H*), 1.73 (1H, m, 7-*H*H), 1.58 (1H, m, 6-*H*), 1.38-1.37 (3H, m, 8-*H*H and 9-*H*), 1.17 (1H, m, 8-H*H*), 1.00 (1H, m, 7-H*H*), 0.72 (3H, d, *J* 6.6, 19-*H*); δ_C (126 MHz, D_6-DMSO (chemical shifts reported for the major conformer only), 31- and 32-*C* were not identified) 175.1 (47-*C*), 173.6 (21-*C*), 172.5 (1-*C*), 172.3 (27-*C*), 169.9 (39-*C*), 168.7 (25-*C*), 167.8 (42-*C*), 163.7 (30-*C*), 158.3 (16-*C*), 157.7 (44-*C*), 135.6 (38-*C*), 130.1 (13-*C*), 128.9 (12-*C*), 128.5 (11-*C*), 127.6 (33-*C*), 126.9 (14- and 18-*C*), 124.1 (36-*C*), 120.1 (34-*C*), 119.1 (35-*C*), 113.9 (15- and 17-*C*), 112.2 (37-*C*), 86.9 (43-*C*), 72.7 (5-*C*), 69.6 (2-*C*), 68.8 (4-*C*), 68.6 (23-*C*), 56.4 (28-*C*), 55.1 (20-*C*), 53.2 (3-*C*), 49.7 (40-*C*), 48.2 (45-*C*), 45.0 (24-*C*), 42.5 (26-*C*), 41.9 (22-*C*), 37.3 (41-*C*), 34.0 (6-*C*), 32.8 (7-*C*), 32.5 (10- and 46-*C*), 29.6 (9-*C*), 26.2 (8-*C*), 26.0 (29-*C*), 15.5 (19-*C*);

m/z (ES^+) 962 (MH^+, 100), 984 (MNa^+, 30), 1923 (M_2H^+, 30), 1945 (M_2Na^+, 10); *m/z* HRMS (ES^-) M-H^- calculated for $C_{47}H_{59}N_8O_{14}$ 959.4156, observed 959.4150.

3-(((3a*R*,6*S*,7*R*,11*R*,18*R*,*Z*)-7-((1*S*,2*S*,3*S*,*E*)-1,2-dihydroxy-9-(4-methoxyphenyl)-3-methylnon-8-en-1-yl)-6,11-dihydroxy-22-methyl-2,5,9,14,17,20,23-heptaoxo-1,2,3,3a,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23-tetracosahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosin-18-yl)methyl)-1*H*-indole-2-carboxylic acid (*epi*-358)

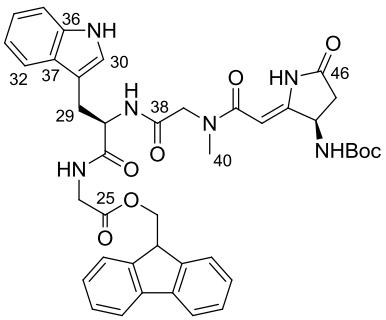


H_2O (1.00 μL, 55.6 μmol) and TASF (79.0 μL of a 0.25 M solution in DMF, 19.8 μmol) were added sequentially to a solution of protected cyclic peptide *epi*-**356** (2.00 mg, 1.32 μmol) in DMF (0.10 mL) at 0 ºC. The reaction was stirred for 8 h at 0 ºC. After which TMS_2O (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The solution was then concentrated using high vacuum centrifugal evaporator. Purification by flash column chromatography (10-20-25% MeOH/$CHCl_3$) and further semi-preparative reverse phase HPLC (XBridge Prep C18 5.0 μm 10 mm x 250 mm column, at 4.4 mL/min with UV detection 214 nm: 2 mins – 5% CH_3CN in 0.05% aqueous

TFA, linear increase; 3 mins – 42% CH_3CN in 0.05% aqueous TFA, isocratic; 23 mins – 42% CH_3CN in 0.05% aqueous TFA, linear increase; 24 mins – 95% CH_3CN in 0.05% aqueous TFA, isocratic) with subsequent lyophilisation afforded deprotected cyclic peptide *epi*-**358** (0.6 mg, 47%) as a colourless solid; R_f 0.30 (30% MeOH/$CHCl_3$); $[\alpha]_{\mathbf{D}}^{\mathbf{20}}$ −48.4 (*c* 0.23, 0.1 M NH_4HCO_3, pH 7); ν_{max} /cm^{-1} (neat) 3301, 2923, 2852, 1737, 1531, 1335, 1292, 1247, 1203, 1174, 1024, 997, 824, 763, 692; δ_H (500 MHz, D_6-DMSO) 13.02 (1H, br s, CO_2*H*), 11.54 (1H, s, N*H*), 10.52 (1H, s, N*H*), 8.68 (1H, br s, N*H*), 8.40 (1H, d, *J* 8.8, N*H*), 8.32 (1H, t, *J* 5.2, N*H*), 7.55 (1H, d, *J* 8.0, 34-*H*), 7.43 (1H, t, *J* 6.2, N*H*), 7.39 (1H, d, *J* 8.2, 37-*H*), 7.30 (2H, d, *J* 8.7, 14- and 18-*H*), 7.23 (1H, dd, *J* 7.3 and 7.3, 36-*H*), 7.10-7.07 (2H, m, 35-*H* and N*H*), 6.85 (2H, d, *J* 8.7, 15- and 17-*H*), 6.31 (1H, d, *J* 15.9, 12-*H*), 6.14-6.08 (2H, m, 11-*H* and O*H*), 5.25 (1H, m, 45-*H*), 5.21 (1H, s, 43-*H*), 5.07 (1H, d, *J* 4.7, O*H*), 4.56 (1H, d, *J* 16.1, 40-*H*H), 4.42 (1H, d, *J* 5.4, 2-*H*), 4.32 (1H, d, *J* 9.5, O*H*), 4.11-4.06 (2H, m, 3-*H* and O*H*), 4.00 (1H, m, 28-*H*), 3.73 (3H, s, 20-*H*), 3.68 (1H, m, 23-*H*), 3.60 (1H, dd, *J* 17.0 and 6.3, 26-*H*H), 3.53 (1H, dd, *J* 13.6 and 5.7, 29-*H*H), 3.42-3.37 (3H, m, 24-*H*H, 29-H*H* and 4-*H*), 3.31-3.25 (2H, m, 26-H*H* and 40-H*H*), 3.04 (1H, m, 5-*H*), 2.94 (3H, s, 41-*H*), 2.76 (1H, dd, *J* 17.7 and 9.9, 46-*H*H), 2.60 (1H, m, 24-H*H*), 2.46 (1H, dd, *J* 17.7 and 5.4, 46-H*H*), 2.32 (1H, d, *J* 13.6, 22-*H*H), 2.17-2.12 (2H, m, 10-*H*), 2.03 (1H, dd, *J* 13.7 and 10.9, 22-H*H*), 1.72 (1H, m, 7-*H*H), 1.59 (1H, m, 6-*H*), 1.41-1.38 (3H, m, 8-*H*H and 9-*H*), 1.20 (1H, m, 8-H*H*), 1.01 (1H, m, 7-H*H*), 0.76 (3H, d, *J* 6.6, 19-*H*); δ_C (126 MHz, D_6-DMSO) 174.9 (47-*C*), 173.5 (1-*C*), 172.6 (21-*C*), 171.0 (27-*C*), 170.3 (39-*C*), 169.0 (25-*C*), 167.9 (42-*C*), 163.5 (30-*C*), 158.3 (16-*C*), 157.6 (44-*C*), 135.9 (38-*C*), 130.1 (13-*C*), 128.9 (12-*C*), 128.4 (11-*C*), 127.9 (33-*C*), 126.9 (14- and 18-*C*), 124.8 (32-*C*), 124.5 (36-*C*), 120.3 (34-*C*), 119.6 (35-*C*), 118.1 (31-*C*), 113.9 (15- and 17-*C*), 112.2 (37-*C*), 87.6 (43-*C*), 72.9 (5-*C*), 69.4 (2-*C*),

68.4 (4-*C*), 66.9 (23-*C*), 56.2 (28-*C*), 55.0 (20-*C*), 53.7 (3-*C*), 49.7 (40-*C*), 45.9 (45-*C*), 45.4 (24-*C*), 42.9 (26-*C*), 41.4 (22-*C*), 36.3 (41-*C*), 34.4 (6-*C*), 34.2 (46-*C*), 32.7 (7-*C*), 32.5 (10-*C*), 29.6 (9-*C*), 26.1 (8-*C*), 25.0 (29-*C*), 15.5 (19-*C*); *m/z* (ES^+) 962 (MH^+, 100), 984 (MNa^+, 10); *m/z* HRMS (ES^+) MH^+ calculated for $C_{47}H_{61}N_8O_{14}$ 961.4302, observed 961.4308.

(9*H*-Fluoren-9-yl)methyl 2-((*R*)-2-(2-((*Z*)-2-((*R*)-3-((*tert*-butoxycarbonyl)amino)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-(1*H*-indol-3-yl)propanamido)acetate (370)



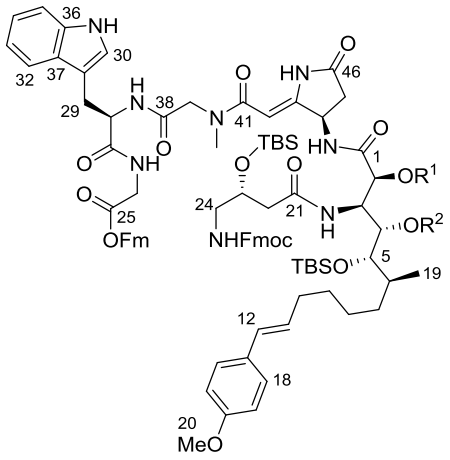
Hydrogen chloride (1.20 mL of a 4 M solution in dioxane, 4.92 mmol) was added to a solution of tripeptide **369** (200 mg, 1.47 mmol) in CH_2Cl_2 (1.64 mL) at room temperature. The mixture was stirred for 2 h, concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 2) to afford the corresponding amine salt as an amorphous colourless solid, which was used directly in the subsequent step. Carboxylic acid **24** (88.3 mg, 0.34 mmol) was dissolved in CH_2Cl_2 (1.50 mL) and the solution was cooled to 0 ^oC. 2,6-Lutidine (153 μL, 1.31 mmol) and PyAOP (179 mg, 0.34 mmol) were then added sequentially. The mixture was stirred at 0 ^oC for 2 h. The amine salt in CH_2Cl_2 (2.64 mL) was added to the solution. The mixture was warmed slowly to room

temperature, stirred for 16 h and then concentrated *in vacuo*. Purification by flash column chromatography (100% EtOAc-2% MeOH/ EtOAc) afforded tetrapeptide **370** (196 mg, 80% over 2 steps) as a colourless solid; R_f: 0.30 (EtOAc); m.p. 85-87 ^oC; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +59.1 (*c* 0.43, acetone); ν_{max}/cm^{-1} (neat) 3299, 2056, 1960, 1741, 1656, 1549, 1492, 1366, 1342, 1249, 1205, 1166, 758, 738, 641, 618; δ_H (500 MHz, D_6-DMSO (* denotes major rotamer)) 10.80 (1H, s, N*H*), 10.38 and 10.34* (1H, s, N*H*), 8.62 and 8.56* (1H, br s, N*H*), 8.24 and 8.15* (1H, d, *J* 7.9, N*H*), 7.90 (2H, d, *J* 7.6, 2 x Ar*H*), 7.71 (2H, d, *J* 7.4, 2 x Ar*H*), 7.60 (1H, d, *J* 7.7, 32-*H*), 7.42 (1H, d, *J* 8.2, N*H*), 7.43 (2H, dd, *J* 7.4 and 7.4, 2 x Ar*H*), 7.34 (2H, dd, *J* 7.4 and 7.4, 2 x Ar*H*), 7.31 (1H, d, *J* 8.0, 35-*H*), 7.14 (1H, s, 30-*H*), 7.05 (1H, ddd, *J* 7.9, 7.9 and 0.8, 34-*H*), 6.97 (1H, ddd, *J* 7.9, 7.9 and 0.6, 33-*H*), 5.36* and 5.25 (1H, s, 42-*H*), 4.79 (1H, m, 44-*H*), 4.63 (1H, m, 28-*H*), 4.39 (2H, d, *J* 7.3, OCH_2CH), 4.27 (1H, t, *J* 7.3, OCH_2CH), 4.02-3.97 (3H, m, 26-*H* and 39-*H*H), 3.88 (1H, d, *J* 15.9, 39-H*H*), 3.20 (1H, dd, *J* 14.3 and 3.5, 29-*H*H), 2.95 (1H, dd, *J* 14.3 and 9.6, 29-H*H*), 2.77* and 2.62 (3H, br s, 40-*H*), 2.73 (1H, m, 45-*H*H), 2.30 (1H, dd, *J* 17.5 and 5.2, 45-H*H*), 1.40* and 1.30 (9H, s, $CO_2C(CH_3)_3$); δ_C (126 MHz, D_6-DMSO (chemical shifts reported for the major rotamer only)) 174.6 (46-*C*), 172.1 (38- or 27-*C*), 169.8 (38- or 27-*C*), 168.2 (41-*C*), 162.3 (25-*C*), 157.8 (43-*C*), 155.4 (*C*(O)), 143.5 ($C_{(Ar)}$), 140.7 ($C_{(Ar)}$), 136.0 ($C_{(Ar)}$), 127.8 ($CH_{(Ar)}$), 127.3 ($C_{(Ar)}$), 127.2 ($CH_{(Ar)}$), 125.3 ($CH_{(Ar)}$), 123.7 (30-*C*), 120.8 (34-*C*), 120.2 ($CH_{(Ar)}$), 118.4 (32-*C*), 118.2 (33-*C*), 111.3 (35-*C*), 110.0 ($C_{(Ar)}$), 87.4 (42-*C*), 78.7 ($CO_2C(CH_3)_3$), 66.2 (OCH_2CH), 53.2 (28-*C*), 49.9 (39-*C*), 48.4 (44-*C*), 46.1 (OCH_2CH), 40.8 (26-*C*), 36.0 (40-*C*), 34.3 (45-*C*), 28.1 ($CO_2C(CH_3)_3$), 27.8 (29-*C*); δ_H (500 MHz, D_6-DMSO, 363 K) 10.54 (1H, s, N*H*), 10.26 (1H, s, N*H*), 8.14 (1H, m, N*H*), 7.87 (2H, d, *J* 7.6, 2 x Ar*H*), 7.73 (1H, d, *J* 7.6, N*H*), 7.68 (2H, d, *J* 7.6, 2 x Ar*H*), 7.57 (1H, d, *J* 7.8, 32-*H*), 7.42 (2H, dd, *J* 7.5, 2 x Ar*H*), 7.36-7.32 (3H, m,

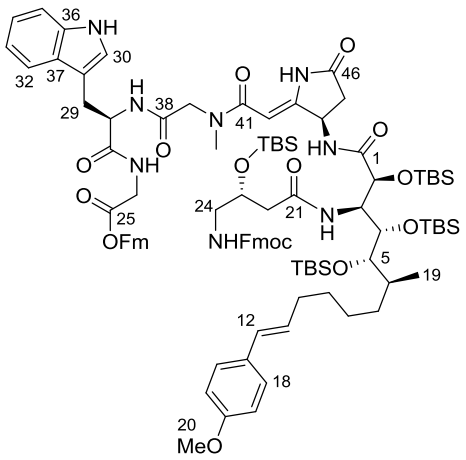
2 x Ar*H* and 35-*H*), 7.13-7.12 (2H, m, 30-*H* and N*H*), 7.05 (1H, dd, *J* 7.8, 34-*H*), 6.97 (1H, dd, *J* 7.8, 33-*H*), 5.37 (1H, s, 42-*H*), 4.75 (1H, m, 44-*H*), 4.67 (1H, m, 28-*H*), 4.42-4.39 (2H, m, OC*H*$_2$CH), 4.27 (1H, t, *J* 7.0, OCH$_2$C*H*), 3.99-3.91 (4H, m, 26- and 39-*H*), 3.24 (1H, dd, *J* 14.8 and 5.3, 29-*H*H), 3.04 (1H, m, 29-H*H*), 2.79 (3H, s, 40-*H*), 2.73 (1H, dd, *J* 17.6 and 7.8, 45-*H*H), 2.34 (1H, dd, *J* 17.6 and 5.5, 45-H*H*), 1.40 (9H, s, CO$_2$C(C*H*$_3$)$_3$); *m/z* (ES$^+$) 749 (MH$^+$, 100%), 766 (MNa$^+$, 50%); *m/z* HRMS (ES$^+$) MH$^+$ calculated for $C_{41}H_{45}O_8N_6$ 749.3293, observed 749.3289.

(9*H*-Fluoren-9-yl)methyl 2-((*R*)-2-(2-((*Z*)-2-((*R*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-12-(4-methoxyphenyl)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-(1*H*-indol-3-yl)propanamido)acetate (372) and

(9*H*-fluoren-9-yl)methyl 2-((*R*)-2-(2-((*Z*)-2-((*R*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-((*R*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanamido)-2,4,5-tris((*tert*-butyldimethylsilyl)oxy)-12-(4-methoxyphenyl)-6-methyldodec-11-enamido)-5-oxopyrrolidin-2-ylidene)-*N*-methylacetamido)acetamido)-3-(1*H*-indol-3-yl)propanamido)acetate (373)



372 R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H



373

Trifluoroacetic acid (0.38 mL, 4.90 mmol) and triethylsilane (0.16 mL, 0.98 mmol) were added sequentially to a solution of tetrapeptide **370** (367 mg, 0.49 mmol) in CH_2Cl_2 (5.00 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 2 h. The solution was then concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 2) to afford amine salt **371** as a colourless solid, which was

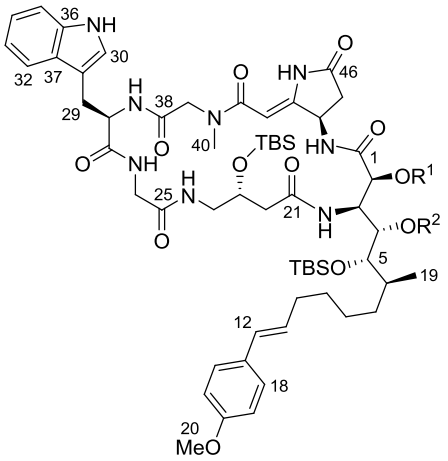
used directly in the subsequent step. HATU (81.0 mg, 0.21 mmol), 2,6-lutidine (76.0 μL, 0.65 mmol) and amine salt **371** (162 mg, 0.21 mmol) were added sequentially to a solution of carboxylic acid **365** (174 mg, 0.15 mmol) in DMF (1.63 mL) at 0 ^{o}C. The mixture was warmed to room temperature and stirred for 16 h. The solution was then diluted with EtOAc and washed with brine (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (60-70-80-100% EtOAc/petrol) afforded linear hexapeptides **372** (112 mg, approx. 45%) and **373** (54.1 mg, 21). Data for linear hexapeptide **372** (contaminated with traces of *N*,*N*′-dimethylurea): colourless solid; R_f 0.60 (EtOAc); m.p. 93-95 ^{o}C; ν_{max} /cm^{-1} (neat) 3314, 2930, 2856, 1657, 1511, 1451, 1382, 1249, 1198, 1100, 877, 834, 777, 759, 740, 669; δ_H (500 MHz, D_6-DMSO) 10.81 (1H, s, N*H*), 10.38 (1H, s, N*H*), 8.56 (1H, br s, N*H*), 8.38 (1H, d, *J* 5.5, N*H*), 8.16 (1H, d, *J* 7.4, N*H*), 7.88 (2H, d, *J* 7.6, 2 x Ar*H*), 7.86 (2H, d, *J* 7.7, 2 x Ar*H*), 7.71 (2H, d, *J* 7.6, 2 x Ar*H*), 7.68 (2H, dd, *J* 7.6 and 3.9, 2 x Ar*H*), 7.60 (1H, d, *J* 7.6, 32-*H*), 7.43-7.25 (12H, m, N*H*, 14-, 18-, 35-*H* and 8 x Ar*H*), 7.16 (1H, s, 30-*H*), 7.11 (1H, br s, N*H*), 7.04 (1H, dd, *J* 7.3 and 7.3, 34-*H*), 6.97 (1H, dd, *J* 7.6 and 7.6, 33-*H*), 6.83 (2H, d, *J* 8.7, 15- and 17-*H*), 6.27 (1H, d, *J* 15.8, 12-*H*), 6.06 (1H, dt, *J* 15.8 and 6.6, 11-*H*), 5.59 (1H, br s, O*H*), 5.33 (1H, s, 42-*H*), 4.83 (1H, m, 44-*H*), 4.65 (1H, m, 28-*H*), 4.39-4.37 (2H, m, OCH_2CH), 4.30 (1H, d, *J* 3.6, OC*H*HCH), 4.28-4.23 (2H, m, 2-*H* and OCH_2C*H*), 4.21-4.17 (2H, m, OCH*H*CH and OCH_2C*H*), 4.12 (1H, m, 3-*H*), 3.98-3.89 (5H, m, 23-, 26- and 39-*H*), 3.82 (1H, m, 4-*H*), 3.71 (3H, s, 20-*H*), 3.33 (1H, m, 5-*H*), 3.22 (1H, d, *J* 11.5, 29-*H*H), 3.02-2.95 (3H, m, 29-H*H* and 24-*H*), 2.82 (3H, s, 40-*H*), 2.63 (1H, m, 45-*H*H), 2.54 (1H, m, 45-H*H*), 2.27 (1H, m, 22-*H*H), 2.17-2.10 (3H, m, 22-H*H* and 10-*H*), 1.65-1.56 (2H, m, 6-*H* and 7-*H*H), 1.41-1.30 (3H, m, 8-*H*H and 9-*H*), 1.12 (1H, m, 8-H*H*), 0.88-0.78 (31H, m, 3 x SiC(CH_3)$_3$, 19-*H* and 7-H*H*), 0.14, 0.10, 0.10, 0.05, 0.03, 0.03 (6 x 3H, s,

6 x SiCH_3); δ_C (126 MHz, D_6-DMSO) 175.3 (46-*C*), 172.9 (1-*C*), 172.0 (27-*C*), 169.8 (25-*C*), 168.3 (38-*C*), 168.1 (21-*C*), 167.9 (41-*C*), 158.3 (16-*C*), 157.1 (43-*C*), 156.4 (*C*(O)), 143.9 ($C_{(Ar)}$), 143.8 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.7 (4 x $C_{(Ar)}$), 136.0 (36-*C*), 130.0 (13-*C*), 129.1 (12-*C*), 128.1 (11-*C*), 127.8 ($CH_{(Ar)}$), 127.6 (2 x $CH_{(Ar)}$), 127.4 (37-*C*), 127.2 ($CH_{(Ar)}$), 127.0 ($CH_{(Ar)}$), 126.9 (14- and 18-*C*), 125.3 (2 x $CH_{(Ar)}$), 125.2 ($CH_{(Ar)}$), 125.1 ($CH_{(Ar)}$), 123.7 (30-*C*), 120.8 (34-*C*), 120.2 ($CH_{(Ar)}$), 120.1 ($CH_{(Ar)}$), 118.4 (32-*C*), 118.2 (33-*C*), 113.9 (15- and 17-*C*), 111.3 (35-*C*), 110.0 (31-*C*), 88.0 (42-*C*), 78.4 (5-*C*), 72.8 (4-*C*), 70.1 (3-*C*), 68.0 (23-*C*), 66.2 (O*C*H_2CH), 65.6 (O*C*H_2CH), 55.0 (20-*C*), 53.3 (28-*C*), 52.9 (2-*C*), 50.0 (39-*C*), 47.3 (44-*C*), 46.7 (OCH_2*C*H), 46.1 (OCH_2*C*H), 45.6 (24-*C*), 42.1 (22-*C*), 40.8 (26-*C*), 36.1 (40-*C*), 33.6 (45-*C*), 33.0 (7-*C*), 32.6 (10-*C*), 29.4 (9- and 6-*C*), 27.8 (29-*C*), 26.1 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 25.7 (8-*C*), 18.0 (Si*C*(CH_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 17.6 (Si*C*(CH_3)$_3$), 16.4 (19-*C*), −3.2 (Si*C*H_3), −3.3 (Si*C*H_3), −4.9 (Si*C*H_3), −5.0 (2 x Si*C*H_3), −5.3 (Si*C*H_3); *m/z* HRMS (ES^+) MH^+ calculated for $C_{93}H_{125}N_8O_{15}Si_3$ 1678.8600, observed 1678.8595.

Data for linear hexapeptide **373**: colourless solid; R_f: 0.80 (EtOAc); m.p. 107-109 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +32.3 (*c* 1.50, EtOAc); ν_{max}/cm^{-1} (neat) 2928, 2856, 1657, 1511, 1463, 1359, 1250, 1176, 1100, 834, 776, 759, 740, 671, 619; δ_H (500 MHz, D_6-DMSO) 10.81 (1H, s, N*H*), 10.46 (1H, s, N*H*), 8.54 (1H, br s, N*H*), 8.10 (1H, d, *J* 7.6, N*H*), 7.89-7.84 (5H, m, N*H* and 4 x Ar*H*), 7.71-7.65 (5H, m, N*H* and 4 x Ar*H*), 7.59 (1H, d, *J* 7.7, 32-*H*), 7.43-7.25 (12H, m, N*H*, 14-, 18-, 35-*H* and 8 x Ar*H*), 7.15 (1H, s, 30-*H*), 7.03 (1H, dd, *J* 7.4 and 7.4, 34-*H*), 6.96 (1H, dd, *J* 7.4 and 7.4, 33-*H*), 6.84 (2H, d, *J* 8.7, 15- and 17-*H*), 6.28 (1H, d, *J* 15.8, 12-*H*), 6.07 (1H, dt, *J* 15.8 and 6.8, 11-*H*), 5.21 (1H, br s, 42-*H*), 4.72 (1H, m, 44-*H*), 4.64 (1H, m, 28-*H*), 4.38-4.34 (2H, m, OCH_2CH), 4.31-4.25 (3H, m, 2- or 4-*H*,

OC*H*HCH and OCH_2C*H*), 4.22-4.17 (2H, m, OCH*H*CH and OCH_2C*H*), 4.15-4.12 (2H, m, 39-*H*H and 3-*H*), 4.02 (1H, m, 23-*H*), 3.97 (2H, d, *J* 4.7, 26-*H*), 3.74 (1H, m, 39-H*H*), 3.72 (1H, m, 2- or 4-*H*), 3.71 (3H, s, 20-*H*), 3.48 (1H, m, 5-*H*), 3.21 (1H, d, *J* 11.0, 29-*H*H), 3.10 (1H, m, 24-*H*H), 2.99-2.94 (2H, m, 29-H*H* and 24-H*H*), 2.79 (3H, s, 40-*H*), 2.63-2.52 (2H, m, 45-*H*), 2.25 (1H, m, 22-*H*H), 2.12-2.08 (3H, m, 22-H*H* and 10-*H*), 1.61-1.56 (2H, m, 6-*H* and 7-*H*H), 1.42-1.31 (3H, m, 8-*H*H and 9-*H*), 1.10 (1H, m, 8-H*H*), 0.86-0.78 (40H, m, 4 x SiC(CH_3)$_3$, 19-*H* and 7-H*H*), 0.17, 0.12, 0.07, 0.03, 0.03, 0.02, −0.02, −0.04 (8 x 3H, s, 8 x SiCH_3); δ_C (126 MHz, D_6-DMSO) 175.3 (46-*C*), 172.1 (27-*C*), 171.6 (1-*C*), 169.8 (25-*C*), 168.2 (38-*C*), 167.8 (41- and 21-*C*), 158.3 (16-*C*), 157.0 (*C*(O) and 43-*C*), 143.8 ($C_{(Ar)}$), 143.7 ($C_{(Ar)}$), 143.5 (2 x $C_{(Ar)}$), 140.7 (4 x $C_{(Ar)}$), 136.0 (36-*C*), 130.0 (13-*C*), 129.1 (12-*C*), 128.0 (11-*C*), 127.8 ($CH_{(Ar)}$), 127.6 (2 x $CH_{(Ar)}$), 127.4 (37-*C*), 127.2 ($CH_{(Ar)}$), 126.9 ($CH_{(Ar)}$, 14- and 18-*C*), 125.3 (2 x $CH_{(Ar)}$), 125.2 ($CH_{(Ar)}$), 125.1 ($CH_{(Ar)}$), 123.7 (30-*C*), 120.8 (34-*C*), 120.2 (2 x $CH_{(Ar)}$), 118.4 (32-*C*), 118.2 (33-*C*), 113.9 (15- and 17-*C*), 111.3 (35-*C*), 110.0 (31-*C*), 87.6 (42-*C*), 72.3 (2- or 4-*C*), 69.7 (5-*C*), 68.0 (23-*C*), 66.2 (OCH_2CH), 65.8 (OCH_2CH), 55.0 (20-*C*), 53.7 (3-*C*), 53.2 (28-*C*), 51.9 (2- or 4-*C*), 50.1 (39-*C*), 47.7 (44-*C*), 46.6 (OCH_2*C*H), 46.1 (OCH_2*C*H), 45.3 (24-*C*), 41.6 (22-*C*), 40.9 (26-*C*), 35.9 (40-*C*), 33.5 (7-*C*), 33.2 (45-*C*), 32.6 (10-*C*), 29.4 (9-*C*), 29.1 (6-*C*), 27.7 (29-*C*), 26.1 (8-*C*), 25.8 (SiC(CH_3)$_3$), 25.8 (SiC(CH_3)$_3$), 25.7 (SiC(CH_3)$_3$), 18.1 (Si*C*(CH_3)$_3$), 17.9 (Si*C*(CH_3)$_3$), 17.7 (Si*C*(CH_3)$_3$), 16.1 (19-*C*), −2.2 (SiCH_3), −3.5 (SiCH_3), −4.2 (SiCH_3), −4.9 (3 x SiCH_3), −5.2 (2 x SiCH_3); *m/z* HRMS (ES^+) MH^+ calculated for $C_{99}H_{139}N_8O_{15}Si_4$ 1792.9465, observed 1792.9447.

(3a*R*,6*S*,7*R*,11*R*,18*R*,*Z*)-18-((1*H*-Indol-3-yl)methyl)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((1*S*,2*S*,3*S*,*E*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-9-(4-methoxyphenyl)-3-methylnon-8-en-1-yl)-22-methyl-3a,4,7,8,10,11,12,13,15,16,18,19,21,22-tetradecahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosine-2,5,9,14,17,20,23(1*H*,3*H*,6*H*)-heptaone (374)



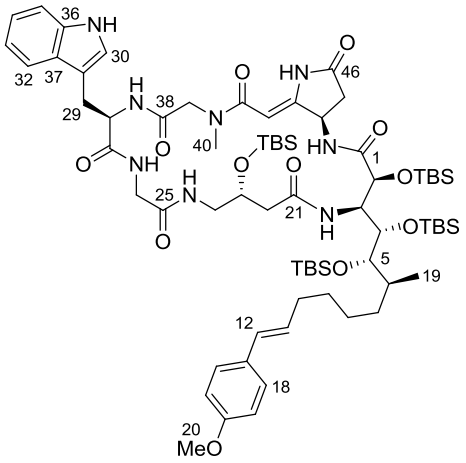
R^1 = H, R^2 = TBS or
R^1 = TBS, R^2 = H

Piperidine (0.25 mL, 2.53 mmol) was added to a solution of linear hexapeptide **372** (111 mg, 66.0 μmol) in CH_2Cl_2 (5.00 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried under high vacuum for 2 h at 40 °C. Purification by flash column chromatography (5-10-20-25-30% MeOH/$CHCl_3$) afforded the piperidine salt of linear amino acid as a colourless solid. The piperidine salt of amino acid was dissolved in DMF (66.0 mL) and the solution was cooled to 0 °C. PyAOP (344 mg, 0.66 mmol), HOAt (90.0 mg, 0.66 mmol) and *N*,*N*-diisopropylethylamine (115 μL, 0.66 mmol) were then added sequentially. The mixture was warmed slowly to room temperature, stirred for 5 days and concentrated *in vacuo*. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed

with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc-2% MeOH/EtOAc) afforded cyclic hexapeptide **374** (45.6 mg, 55% over 2 steps) as a colourless solid; R_f 0.30 (2% MeOH/EtOAc); m.p. 156-158 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −18.6 (*c* 3.25, EtOAc); ν_{max} /cm^{-1} (neat) 2981, 2889, 1658, 1512, 1462, 1382, 1250, 1148, 1081, 955, 877, 833, 776, 743, 668; δ_H (500 MHz, D_4-MeOD) 7.62 (1H, d, *J* 8.0, 32-*H*), 7.36 (1H, d, *J* 8.0, 35-*H*), 7.22 (1H, s, 30-*H*), 7.20 (2H, d, *J* 8.7, 14- and 18-*H*), 7.11 (1H, dd, *J* 8.0 and 8.0, 34-*H*), 7.02 (1H, dd, *J* 7.3 and 7.3, 33-*H*), 6.72 (2H, d, *J* 8.7, 15- and 17-*H*), 6.39 (1H, d, *J* 9.0, N*H* or O*H*), 6.26 (1H, d, *J* 15.8, 12-*H*), 6.03 (1H, dt, *J* 15.8 and 7.1, 11-*H*), 5.60 (1H, d, *J* 1.3, 42-*H*), 5.24 (1H, m, 44-*H*), 4.54 (1H, dd, *J* 10.4 and 3.2, 28-*H*), 4.50-4.42 (3H, m, 26-*H*H, 23- and 4-*H*), 4.36 (1H, s, 2-*H*), 4.25 (1H, d, *J* 14.8, 39-*H*H), 4.02 (1H, dd, *J* 9.6 and 2.1, 3-*H*), 3.59 (3H, s, 20-*H*), 3.51 (1H, dd, *J* 9.1 and 2.1, 5-*H*), 3.45 (1H, m, 26-H*H*), 3.42 (1H, m, 29-H*H*), 3.26 (3H, s, 40-*H*), 3.15 (1H, d, *J* 14.8, 39-H*H*), 3.13-3.08 (2H, m, 29-H*H* and 24-*H*H), 2.78 (1H, d, *J* 14.2, 24-H*H*), 2.73 (1H, dd, *J* 18.0 and 9.6, 45-*H*H), 2.64 (1H, dd, *J* 18.0 and 6.5, 45-H*H*), 2.50 (1H, dd, *J* 14.3 and 4.7, 22-*H*H), 2.18-2.08 (3H, m, 22-H*H* and 10-*H*), 1.73-1.64 (2H, m, 6-*H* and 7-*H*H), 1.45-1.42 (2H, m, 9-*H*H and 8-*H*H), 1.34 (1H, m, 9-H*H*), 1.23 (1H, m, 8-H*H*), 0.99 (3H, d, *J* 6.6, 19-*H*), 0.97 (9H, s, SiC(C*H*$_3$)$_3$), 0.94 (9H, s, SiC(C*H*$_3$)$_3$), 0.91 (1H, m, 7-H*H*), 0.85 (9H, s, SiC(C*H*$_3$)$_3$), 0.22, 0.18, 0.17, 0.14, 0.13, 0.07 (6 x 3H, s, 6 x SiC*H*$_3$); δ_C (126 MHz, D_4-MeOD) 177.3 (1- or 47-*C*), 177.2 (1- or 47-*C*), 175.1 (38-*C*), 174.1 (27-*C*), 172.8 (25-*C*), 170.9 (41-*C*), 169.8 (21-*C*), 160.3 (16-*C*), 157.6 (43-*C*), 138.4 (36-*C*), 132.1 (13-*C*), 130.8 (12-*C*), 129.5 (11-*C*), 128.4 (37-*C*), 128.3 (14- and 18-*C*), 124.8 (30-*C*), 122.8 (34-*C*), 120.0 (33-*C*), 119.5 (32-*C*), 115.0 (15- and 17-*C*), 112.6 (35-*C*), 111.2 (31-*C*), 91.5 (42-*C*), 81.1 (5-*C*), 75.4 (3-*C*), 71.8 (2-*C*), 68.1 (23-*C*), 57.8 (28-*C*), 55.7 (20-*C*), 55.2 (4-*C*), 54.4 (39-*C*), 48.6 (44-*C*),

48.3 (24-*C*), 46.4 (22-*C*), 43.1 (26-*C*), 39.9 (40-*C*), 35.7 (6-*C*), 35.0 (7-*C*), 34.7 (45-*C*), 34.6 (10-*C*), 31.0 (9-*C*), 27.8 (29-*C*), 27.5 (8-*C*), 27.1 (SiC(*C*H_3)$_3$), 26.8 (SiC(*C*H_3)$_3$), 26.6 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH_3)$_3$), 19.1 (Si*C*(CH_3)$_3$), 19.0 (Si*C*(CH_3)$_3$), 17.6 (19-*C*), −2.3 (Si*C*H_3), −2.8 (Si*C*H_3), −3.7 (Si*C*H_3), −3.9 (Si*C*H_3), −4.2 (Si*C*H_3), −5.1 (Si*C*H_3); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{64}H_{102}N_8O_{12}Si_3Na$ 1281.6817, observed 1281.6798.

(3a*R*,6*S*,7*R*,11*R*,18*R*,*Z*)-18-((1*H*-Indol-3-yl)methyl)-6,11-bis((*tert*-butyldimethylsilyl)oxy)-7-((5*S*,6*S*)-6-((*S*,*E*)-8-(4-methoxyphenyl)oct-7-en-2-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-22-methyl-3a,4,7,8,10,11,12,13,15,16,18,19,21,22-tetradecahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosine-2,5,9,14,17,20,23(1*H*,3*H*,6*H*)-heptaone (375)

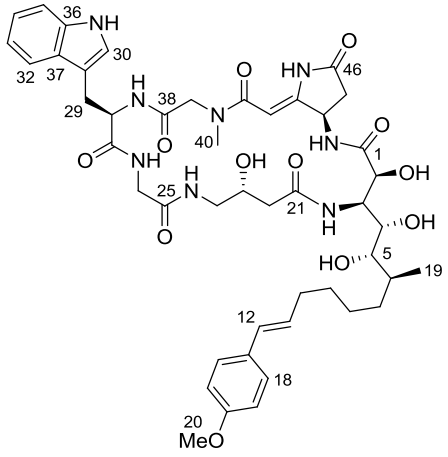


Piperidine (0.25 mL, 2.53 mmol) was added to a solution of linear hexapeptide **373** (54.0 mg, 30.0 μmol) in CH_2Cl_2 (5.00 mL) at room temperature. The reaction was stirred for 2 h. The solution was then concentrated *in vacuo* and the crude mixture was dried

under high vacuum for 2 h at 40 °C. Purification by flash column chromatography (5-10-20-25-30% MeOH/$CHCl_3$) afforded the piperidine salt of linear amino acid as a colourless solid. The piperidine salt of amino acid was dissolved in DMF (30.0 mL) and the solution was cooled to 0 °C. PyAOP (156 mg, 0.30 mmol), HOAt (40.8 mg, 0.30 mmol) and *N*,*N*-diisopropylethylamine (52.0 μL, 0.30 mmol) were then added sequentially. The mixture was warmed slowly to room temperature, stirred for 5 days and concentrated *in vacuo*. The residue was then redissolved in 2% MeOH/$CHCl_3$, washed with water, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc-2% MeOH/EtOAc) afforded cyclic hexapeptide **375** (20.2 mg, 49% over 2 steps) as a colourless solid; R_f 0.50 (2% MeOH/EtOAc); m.p. 165-167 °C; $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −12.9 (*c* 1.67, EtOAc); ν_{max} /cm^{-1} (neat) 2930, 2857, 1740, 1656, 1511, 1462, 1250, 1176, 1099, 834, 776, 741, 671; δ_H (500 MHz, D_4-MeOD) 7.63 (1H, d, *J* 7.9, 32-*H*), 7.36 (1H, d, *J* 8.0, 35-*H*), 7.22 (1H, s, 30-*H*), 7.18 (2H, d, *J* 8.5, 14- and 18-*H*), 7.12 (1H, dd, *J* 8.0 and 8.0, 34-*H*), 7.03 (1H, dd, *J* 7.9 and 7.9, 34-*H*), 6.89 (2H, d, *J* 8.5, 15- and 17-*H*), 6.26 (1H, d, *J* 15.8, 12-*H*), 6.03 (1H, dt, *J* 15.8 and 7.1, 11-*H*), 5.90 (1H, br s, N*H*), 5.66 (1H, s, 42-*H*), 5.32 (1H, dd, *J* 7.4 and 7.4, 44-*H*), 4.56-4.46 (4H, m, 23-, 28-, 4- and 2-*H*), 4.40 (1H, d, *J* 17.3, 26-*H*H), 4.24 (1H, d, *J* 14.8, 39-*H*H), 3.85 (1H, dd, *J* 9.9 and 2.4, 3-*H*), 3.61 (1H, m, 5-*H*), 3.59 (3H, s, 20-*H*), 3.43 (1H, dd, *J* 15.1 and 3.0, 29-*H*H), 3.37 (1H, d, *J* 17.3, 26-H*H*), 3.26 (3H, s, 40-*H*), 3.12 (1H, dd, *J* 15.1 and 10.4, 29-H*H*), 3.07 (1H, m, 24-*H*H), 2.97 (1H, m, 39-H*H*), 2.82 (1H, m, 24-H*H*), 2.79 (1H, dd, *J* 17.3 and 9.6, 45-*H*H), 2.56 (1H, dd, *J* 15.1 and 4.6, 22-*H*H), 2.50 (1H, dd, *J* 17.3 and 7.4, 45-H*H*), 2.21-2.01 (3H, m, 22-H*H* and 10-*H*), 1.74-1.68 (2H, m, 6-*H* and 7-*H*H), 1.42-1.39 (2H, m, 9-*H*H and 8-*H*H), 1.33 (1H, m, 9-H*H*), 1.23 (1H, m, 8-H*H*), 1.03 (9H, s, SiC(CH_3)$_3$), 1.00 (3H, d, *J* 6.6, 19-*H*), 0.96 (9H, s, SiC(CH_3)$_3$), 0.96

(9H, s, SiC(C*H*$_3$)$_3$), 0.90 (1H, m, 7-H*H*), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), 0.23, 0.23, 0.22, 0.20, 0.16, 0.15, 0.13, 0.09 (8 x 3H, s, 8 x SiC*H*$_3$); δ_C (126 MHz, D$_4$-MeOD) 176.3 (46-*C*), 175.3 (1-*C*), 174.7 (38-*C*), 174.1 (27-*C*), 172.4 (25-*C*), 170.8 (41-*C*), 169.3 (21-*C*), 160.3 (16-*C*), 156.3 (44-*C*), 138.5 (36-*C*), 132.1 (13-*C*), 130.9 (12-*C*), 129.4 (11-*C*), 128.5 (37-*C*), 128.3 (14- and 18-*C*), 124.8 (30-*C*), 122.8 (34-*C*), 120.0 (33-*C*), 119.5 (32-*C*), 115.0 (15- and 17-*C*), 112.6 (35-*C*), 111.1 (31-*C*), 91.6 (42-*C*), 80.5 (5-*C*), 76.9 (3-*C*), 73.7 (2- or 4-*C*), 68.3 (23-*C*), 57.8 (2- or 4-*C*), 55.9 (28-*C*), 55.7 (20-*C*), 54.1 (39-*C*), 48.3 (44-*C*), 48.1 (24-*C*), 45.5 (22-*C*), 43.2 (26-*C*), 39.7 (40-*C*), 35.5 (45-*C*), 35.0 (7-*C*), 34.8 (6- and 10-*C*), 30.9 (9-*C*), 27.9 (8- or 29-*C*), 27.8 (8- or 29-*C*), 27.1 (SiC(*C*H$_3$)$_3$), 27.0 (SiC(*C*H$_3$)$_3$), 26.8 (SiC(*C*H$_3$)$_3$), 26.7 (SiC(*C*H$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 19.0 (Si*C*(CH$_3$)$_3$), 17.6 (19-*C*), −0.9 (Si*C*H$_3$), −2.5 (Si*C*H$_3$), −3.1 (Si*C*H$_3$), −3.5 (Si*C*H$_3$), −3.7 (Si*C*H$_3$), −3.8 (Si*C*H$_3$), −3.9 (Si*C*H$_3$), −4.1 (Si*C*H$_3$); *m/z* (ES$^+$) 1396 (MNa$^+$, 100); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{70}H_{116}N_8O_{12}Si_4Na$ 1395.7682, observed 1395.7639.

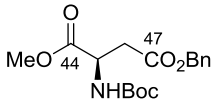
(3a*R*,6*S*,7*R*,11*R*,18*R*,*Z*)-18-((1*H*-Indol-3-yl)methyl)-7-((1*S*,2*S*,3*S*,*E*)-1,2-dihydroxy-9-(4-methoxyphenyl)-3-methylnon-8-en-1-yl)-6,11-dihydroxy-22-methyl-3a,4,7,8,10,11,12,13,15,16,18,19,21,22-tetradecahydropyrrolo[2,3-*m*][1,4,7,10,15,19]hexaazacyclotricosine-2,5,9,14,17,20,23(1*H*,3*H*,6*H*)-heptaone (11)



H_2O (8.40 μL, 0.47 mmol) and TASF (100 μL of a 2.35 M solution in DMF, 0.23 mmol) were added sequentially to a solution of protected cyclic peptide **375** (20.0 mg, 14.6 μmol) in DMF (0.80 mL) at 0 °C. The reaction was stirred for 7 h at 0 °C. After which TMS_2O (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The solution was then concentrated using high vacuum centrifugal evaporator. Purification by flash column chromatography (5-10-15% MeOH/$CHCl_3$) afforded deprotected cyclic peptide **11** (8.5 mg, 64%) as a colourless solid; R_f 0.50 (15% MeOH/$CHCl_3$); $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −55.5 (*c* 0.12, 1/5 0.1 M NH_4HCO_3/MeOH) (lit.[2] $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −57.3 (*c* 0.12, 1/5 0.1 M NH_4HCO_3/MeOH)); δ_H (500 MHz, D_6-DMSO) 10.88 (1H, d, *J* 1.9, N*H*), 10.43 (1H, s, N*H*), 8.70 (1H, d, *J* 5.2, N*H*), 8.39 (1H, t, *J* 6.2, N*H*), 8.36 (1H, d, *J* 8.8, N*H*), 7.52 (1H, d, *J* 7.9, 32-*H*), 7.36-7.33 (2H, m, 35-*H* and N*H*), 7.30 (2H, d, *J* 8.8, 14- and 18-*H*), 7.23 (1H, d, *J* 2.4, 30-*H*), 7.11-7.06 (2H, m, 34-*H* and N*H*), 7.00 (1H, ddd, *J* 7.9, 7.9 and 0.8,

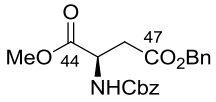
33-*H*), 6.86 (2H, d, *J* 8.8, 15- and 17-*H*), 6.31 (1H, d, *J* 15.9, 12-*H*), 6.14-6.09 (2H, m, 11-*H* and O*H*), 5.27-5.22 (2H, m, 42- and 44-*H*), 4.98 (1H, d, *J* 5.0, O*H*), 4.56 (1H, d, *J* 16.1, 39-*H*H), 4.42 (1H, d, *J* 5.4, 2-*H*), 4.32 (1H, d, *J* 9.5, O*H*), 4.12-4.05 (3H, m, O*H*, 28- and 3-*H*), 3.74 (1H, m, 23-*H*), 3.73 (3H, s, 20-*H*), 3.68 (1H, dd, *J* 16.9 and 6.5, 26-*H*H), 3.52 (1H, dd, *J* 16.9 and 6.0, 26-H*H*), 3.44 (1H, d, *J* 16.1, 39-H*H*), 3.41 (1H, m, 4-*H*), 3.31 (1H, m, 24-*H*H), 3.23 (1H, dd, *J* 14.8 and 4.6, 29-*H*H), 3.08-3.00 (2H, m, 29-H*H* and 5-*H*), 2.98 (3H, s, 40-*H*), 2.78-2.71 (2H, m, 24-H*H* and 45-*H*H), 2.46 (1H, dd, *J* 17.8 and 5.5, 45-H*H*), 2.33 (1H, dd, *J* 14.3 and 1.9, 22-*H*H), 2.20-2.11 (2H, m, 10-*H*), 2.04 (1H, dd, *J* 14.3 and 10.4, 22-H*H*), 1.71 (1H, m, 7-*H*H), 1.59 (1H, m, 6-*H*), 1.43-1.35 (3H, m, 8-*H*H and 9-*H*), 1.21 (1H, m, 8-H*H*), 1.02 (1H, m, 7-H*H*), 0.77 (3H, d, *J* 6.6, 19-*H*); δ_C (126 MHz, D_6-DMSO) 175.0 (46-*C*), 173.7 (1-*C*), 172.5 (21-*C*), 171.5 (27-*C*), 170.9 (38-*C*), 169.0 (25-*C*), 168.1 (41-*C*), 158.3 (16-*C*), 157.5 (43-*C*), 136.1 (36-*C*), 130.1 (13-*C*), 128.9 (12-*C*), 128.4 (11-*C*), 127.0 (37-*C*), 126.9 (14- and 18-*C*), 123.9 (30-*C*), 121.0 (34-*C*), 118.4 (33-*C*), 118.1 (32-*C*), 113.9 (15- and 17-*C*), 111.4 (35-*C*), 110.0 (31-*C*), 87.8 (42-*C*), 72.9 (5-*C*), 69.4 (2-*C*), 68.4 (4-*C*), 66.7 (23-*C*), 55.7 (28-*C*), 55.0 (20-*C*), 53.7 (3-*C*), 50.4 (39-*C*), 45.9 (44-*C*), 45.2 (24-*C*), 42.8 (26-*C*), 41.4 (22-*C*), 36.8 (40-*C*), 34.4 (6-*C*), 34.1 (45-*C*), 32.7 (7-*C*), 32.5 (10-*C*), 29.6 (9-*C*), 26.0 (8-*C*), 25.7 (29-*C*), 15.5 (19-*C*); *m/z* HRMS (ES^+) MH^+ calculated for $C_{46}H_{61}N_8O_{12}$ 917.4404, observed 917.4397. All data were in agreement with those previously reported.[2]

4-Benzyl 1-methyl (*R*)-2-((*tert*-butoxycarbonyl)amino)succinate (381)



(*R*)-4-(Benzyloxy)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoic acid (5.00 g, 15.5 mmol) was dissolved in toluene (154 mL) and methanol (64.0 mL) and treated with trimethylsilyl diazomethane (15.5 mL of a 2 M solution in hexanes, 31.0 mmol) at room temperature. After stirring the mixture for 1 h acetic acid (200 mL of 2 M aqueous solution) was added. The aqueous layer was separated and extracted with EtOAc. The organic layers were then washed with saturated aqueous $NaHCO_3$ (x 3), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford ester **381** (5.23 g, quant.) as a colourless solid. The compound was used without further purification in the subsequent step. R_f: 0.25 (20% EtOAc/petrol); m.p. 62-64 ^oC (lit.[100] m.p. 64-66 ^oC); $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ +9.1 (*c* 1.00, MeOH) (lit.[100] $[\alpha]_{\mathbf{D}}^{\mathbf{23}}$ +8.1 (*c* 1.00, MeOH)); δ_H (400 MHz, $CDCl_3$**)** 7.39-7.33 (5H, m, 5 x Ph*H*), 7.50 (1H, d, *J* 8.6, N*H*), 5.13 (2H, d, *J* 3.7, OCH_2Ph), 4.60 (1H, m, 45-*H*), 3.71 (3H, s, CO_2CH_3), 3.05 (1H, dd, *J* 16.9 and 4.4, 46-*H*H), 2.88 (1H, dd, *J* 16.9 and 4.9, 46-H*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$**)** 171.5 (44- or 47-*C*), 170.8 (44- or 47-*C*), 155.3 (*C*(O)), 135.3 ($C_{(Ar)}$), 128.6 (C$H_{(Ar)}$), 128.4 (C$H_{(Ar)}$), 128.3 (C$H_{(Ar)}$), 80.1 ($CO_2C(CH_3)_3$), 66.8 (OCH_2Ph), 52.6 (CO_2CH_3,), 49.9 (45-*C*), 36.9 (46-*C*), 28.2 ($CO_2C(CH_3)_3$). All data were in agreement with those previously reported.[100]

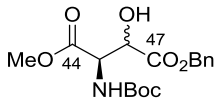
4-Benzyl 1-methyl (*R*)-2-(((benzyloxy)carbonyl)amino)succinate (390)



Trifluoroacetic acid (1.00 mL, 13.1 mmol) was added to a solution of ester **381** (210 mg, 0.62 mmol) in CH_2Cl_2 (3.00 mL) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. The solution was then concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 2) to afford the corresponding amine salt, which was used directly in the subsequent step. *N*,*N*-Diisopropylethylamine (0.65 ml, 3.73 mmol), DMAP (38.0 mg, 0.31 mmol) and benzyl chloroformate (0.18 mL, 1.24 mmol) were added sequentially to a solution of the amine salt in CH_2Cl_2 (6.20 mL) at 0 °C. The solution was then warmed to room temperature and stirred for 1 h. Water was added and the aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-20% EtOAc/petrol) afforded carbamate **390** (213 mg, 92% over 2 steps) as a viscous colourless oil; R_f: 0.15 (20% EtOAc/petrol); $[\alpha]_{\mathbf{D}}^{\mathbf{25}}$ −16.5 (*c* 0.40, $CHCl_3$); ν_{max} /cm^{-1} (neat) 3358, 2954, 1722, 1509, 1455, 1340, 1211, 1174, 1042, 1001, 738, 696; δ_H (400 MHz, $CDCl_3$) 7.38-7.32 (10H, m, 10 x Ph*H*), 7.78 (1H, d, *J* 8.3, N*H*), 5.16-5.09 (4H, m, 2 x OCH_2Ph), 4.67 (1H, m, 45-*H*), 3.71 (3H, s, CO_2CH_3), 3.09 (1H, dd, *J* 17.1 and 4.7, 46-*H*H), 2.91 (1H, dd, *J* 17.1 and 4.7, 46-H*H*); δ_C (100 MHz, $CDCl_3$**)** 171.1 (44- or 47-*C*), 170.6 (44- or 47-*C*), 155.9 (*C*(O)), 136.1 ($C_{(Ar)}$), 135.2 ($C_{(Ar)}$), 128.6 (C$H_{(Ar)}$), 128.5 (C$H_{(Ar)}$), 128.4 (C$H_{(Ar)}$), 128.3 (C$H_{(Ar)}$), 128.2 (C$H_{(Ar)}$), 128.1 (C$H_{(Ar)}$), 67.1 (O*C*H_2Ph), 66.9 (O*C*H_2Ph), 52.8 (CO_2CH_3,), 50.3 (45-*C*), 36.7 (46-*C*); *m/z* (ES^+) 372

(MH^+, 100), 394 (MNa^+, 90); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{20}H_{21}NO_6Na$ 394.1261, observed 394.1256.

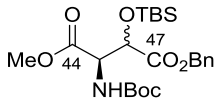
1-Benzyl 4-methyl (3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-hydroxysuccinate (387)



Potassium bis(trimethylsilyl)amide (37.4 mL of a 1 M solution in THF, 37.4 mmol) was added slowly to a solution of ester **381** (6.30 g, 18.7 mmol) in THF (125 mL) at −78 °C and the mixture was stirred for 2 h. A solution of freshly prepared 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine[101] **383** (5.37 g, 20.6 mmol) in THF (62.0 mL) was added dropwise to the reaction over a 40 minutes period *via* syringe pump. After stirring the mixture for 3 h at −78 °C, (±)-camphor 10-sulfonic acid (75.0 mL of 1 M solution in THF) was added. The solution was warmed to room temperature and diluted with EtOAc. The organic layer was then washed with 1M HCl (x 1), saturated aqueous $NaHCO_3$ (x 1) and brine (x 1), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-25-30% EtOAc/petrol) afforded aminoalcohol **387** (6.22 g, 94%) as a viscous colourless oil, as a 1.2:1.0 mixture of diastereoisomers; R_f: 0.40 (30% EtOAc/petrol); ν_{max} /cm^{-1} (neat) 3391, 2979, 1744, 1716, 1501, 1456, 1393, 1250, 1215, 1162, 1114, 1060, 1016, 753, 699; δ_H (400 MHz, $CDCl_3$ (*denotes the major diastereoisomer)) 7.44-7.37 (5H, m, 5 x Ph*H*), 5.51* (1H, d, *J* 6.4, N*H*), 5.33 (1H, m, N*H*), 5.33-5.16 (2H, m, OCH_2Ph), 4.87 (1H, d, *J* 8.6, 45-*H*), 4.75 (1H, dd, *J* 5.6 and 2.0, 46-*H*), 4.58* (1H, dd, *J* 5.1 and 2.0, 46-*H*), 3.81 and 3.60* (3H, s, CO_2CH_3), 3.57* and 3.32 (1H, m, O*H*), 1.47* and 1.46 (9H, s, $CO_2C(CH_3)_3$);

δ_C (100 MHz, $CDCl_3$ (*denotes the major diastereoisomer)) 171.9 and 171.3* (44- or 47-*C*), 169.9 and 169.0* (44- or 47-*C*), 155.6 (*C*(O)), 134.7 ($C_{(Ar)}$), 128.8 ($CH_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 128.6 ($CH_{(Ar)}$), 80.6* and 80.3 ($CO_2C(CH_3)_3$), 72.2* and 71.1 (46-*C*), 68.4 and 68.0* (OCH_2Ph), 57.0* and 56.1 (45-*C*), 52.9 and 52.5* (CO_2CH_3), 28.2* and 28.1 ($CO_2C(CH_3)_3$); *m/z* (ES^+) 376 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{17}H_{23}NO_7Na$ 376.1367, observed 376.1360.

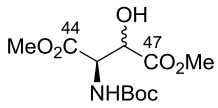
1-Benzyl 4-methyl (3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)succinate (392)



tert-Butyldimethylsilyl trifluoromethanesulfonate (4.86 mL, 21.1 mmol) was added dropwise to a solution of alcohol **387** (6.22 g, 17.6 mmol, as 1.2:1.1 mixture of diastereoisomers) and 2,6-lutidine (4.93 mL, 42.3 mmol) in CH_2Cl_2 (176 mL) at 0 °C. The solution was then warmed to room temperature for 3.5 h before being quenched with *i*-PrOH. Water was then added and aqueous layer was separated and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc/petrol) afforded silyl ether **392** (5.92 g, 72%) as a colourless oil, as a 1.5:1.0 mixture of diastereoisomers; R_f: 0.50 (10% EtOAc/petrol); ν_{max} /cm^{-1} (neat) 3446, 2955, 2931, 2858, 1754, 1716, 1498, 1364, 1251, 1161, 1142, 1063, 1019, 837, 780, 752, 697; δ_H (400 MHz, $CDCl_3$ (*denotes the major diastereoisomer)) 7.41-7.33 (5H, m, 5 x Ph*H*), 5.42* (1H, d, *J* 7.6, N*H*), 5.27 (1H, m, N*H*), 5.29-5.11 (2H, m, OCH_2Ph), 4.87 (1H, m, 45-*H*), 4.83 (1H, m, 46-*H*), 4.63* (1H,

d, *J* 2.5, 46-*H*), 3.74 and 3.53* (3H, s, CO_2CH_3), 1.45* and 1.44 (9H, s, $CO_2C(CH_3)_3$), 0.88* and 0.86 (9H, s, $SiC(CH_3)_3$), 0.08 and 0.06* (3H, s, $SiCH_3$), 0.04* and 0.02 (3H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$ (*denotes the major diastereoisomer)) 170.2 and 170.1* (44- or 47-*C*), 169.2 (44- or 47-*C*), 155.5 and 154.8* (*C*(O)), 135.4* and 135.2 ($C_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 128.6 ($CH_{(Ar)}$), 128.4 ($CH_{(Ar)}$), 128.4* ($CH_{(Ar)}$), 128.4* ($CH_{(Ar)}$), 128.3* ($CH_{(Ar)}$), 80.1 ($CO_2C(CH_3)_3$), 72.8* and 72.6 (46-*C*), 67.3 and 66.9* (OCH_2Ph), 57.5* and 57.1 (45-*C*), 52.5 and 52.3* (CO_2CH_3,), 28.3* and 28.2 ($CO_2C(CH_3)_3$), 25.5* and 25.5 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.8 ($SiCH_3$), −5.0* ($SiCH_3$), −5.6* ($SiCH_3$), −5.9 ($SiCH_3$); *m/z* (ES^+) 490 (MNa^+, 100), 368 ($(M\text{-}Boc)H^+$, 95); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{23}H_{37}NO_7SiNa$ 490.2232, observed 490.2223.

Dimethyl (2*R*)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxysuccinate (388)



EtOAc (HPLC grade) (1.50 mL) was added to benzyl ester **387** (42.0 mg, 0.12 mmol, as 7.0:1.0 mixture of diastereoisomers) and palladium on carbon (20.0 mg, 50% wt.) and the mixture was stirred under an atmospheric (balloon) pressure of hydrogen for 16 h. The solution was then filtered through Celite, washing with EtOAc, and concentrated *in vacuo*. The crude carboxylic acid was dissolved in toluene (2.50 mL) and methanol (0.50 mL) and treated with trimethylsilyl diazomethane (0.12 mL of a 2 M solution in hexanes, 0.24 mmol) at room temperature. After stirring the mixture for 1 h acetic acid (5.00 mL of 2 M aqueous solution) was added. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to

afford methyl ester **388** (30.6 mg, 93% over 2 steps) as a colourless oil, as a 7.0:1.0 mixture of diastereoisomers; R_f: 0.20 (30% EtOAc/petrol); ν_{max} /cm^{-1} (neat) 3388, 2979, 1744, 1714, 1506, 1439, 1367, 1218, 1161, 1119, 1059, 1017, 854, 779, 759, 691; δ_H (400 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 5.55 (1H, d, *J* 8.1, N*H*), 4.85 (1H, dd, *J* 8.1 and 1.7, 45-*H*), 4.53 (1H, d, *J* 1.7, 46-*H*), 3.83 (3H, s, CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 172.0 (44- or 47-*C*), 169.1 (44- or 47-*C*), 155.5 (*C*(O)), 80.6 ($CO_2C(CH_3)_3$), 72.1 (46-*C*), 57.0 (45-*C*), 52.8 (CO_2CH_3), 52.7 (CO_2CH_3), 28.2 ($CO_2C(CH_3)_3$); *m/z* (ES^+) 300 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{11}H_{19}NO_7Na$ 300.1054, observed 300.1052.

Benzyl (2*R*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-3-cyanopropanoate (*syn*-379) and benzyl (2*S*,3*S*)-3-((*tert*-butoxycarbonyl)amino)-2-((*tert*-butyldimethylsilyl)oxy)-3-cyanopropanoate (*anti*-379)



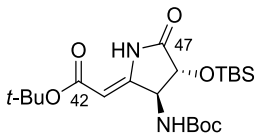
syn-**379** *anti*-**379**

Trimethyltin hydroxide (3.40 g, 18.8 mmol) was added to a solution of ester **392** (5.92 g, 12.7 mmol, as 1.0:1.5 mixture of diastereoisomers) in 1,2-DCE (7.00 mL) at room temperature. The mixture was heated at 60 °C for 14 h. After this time the reaction was cooled to room temperature, diluted with EtOAc, washed with 1M aqueous $KHSO_4$ (x 3), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10-20-50-100% EtOAc/petrol) afforded acid **393** as a colourless oil.

Ethyl chloroformate (0.99 mL, 10.3 mmol) was slowly added to a solution of triethylamine (1.44 mL, 10.3 mmol) and acid **393** (3.89 g, 8.59 mmol) in THF (43.0 mL) and the solution was stirred for 2 h at 0 °C. The resulting suspension was treated with ammonia (7.00 mL of a 35% aqueous solution) and stirred for 30 minutes at 0 °C. The aqueous phase was then separated and extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford amide **394** as a colourless oil. Pyridine (3.47 mL, 42.9 mmol) and freshly distilled trifluoroacetic anhydride (2.39 mL, 17.2 mmol) were added sequentially to a solution of amide **394** in THF (43.0 mL) at 0 °C. The resulting red solution was stirred for 1 h at 0 °C and then diluted with EtOAc. After warming to room temperature the solution was washed with aqueous saturated $NaHCO_3$ (x 2), 1 M HCl and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3-6-10% EtOAc/petrol) afforded nitriles *syn*-**379** (1.22 g, 22% over 3 steps) and *anti*-**379** (1.73 g, 31% over 3 steps). Data for nitrile *syn*-**379**: pale yellow oil; R_f: 0.50 (10% EtOAc/petrol); ν_{max} /cm^{-1} (neat) 2932, 2859, 1761, 1723, 1487, 1393, 1368, 1255, 1157, 1132, 1056, 1005, 947, 838, 782, 746, 697; δ_H (400 MHz, $CDCl_3$) 7.40-7.35 (5H, m, 5 x Ph*H*), 5.27 (1H, d, *J* 9.5, N*H*), 5.17 (2H, d, *J* 9.5, OC*H*$_2$Ph), 5.09 (1H, d, *J* 9.5, 45-*H*), 4.52 (1H, d, *J* 2.5, 46-*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$), 0.95 (9H, s, $SiC(CH_3)_3$), 0.14 (6H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 168.7 (47-*C*), 154.1 (*C*(O)), 134.6 ($C_{(Ar)}$), 128.7 (C*H*$_{(Ar)}$), 128.7 (C*H*$_{(Ar)}$), 128.6 (C*H*$_{(Ar)}$), 117.0 (44-*C*), 81.5 ($CO_2C(CH_3)_3$), 72.1 (46-*C*), 67.9 (OCH_2Ph), 46.4 (45-*C*), 28.1 ($CO_2C(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), −5.0 ($SiCH_3$), −5.6 ($SiCH_3$); *m/z* (ES$^+$) 457 (MNa$^+$, 100); *m/z* HRMS (ES$^+$) MNa$^+$ calculated for $C_{22}H_{34}N_2O_5SiNa$ 457.2129, observed 457.2130.

Data for *anti*-nitrile **379**: pale yellow oil; R_f: 0.40 (10% EtOAc/petrol); ν_{max} /cm^{-1} (neat) 2932, 2859, 1724, 1498, 1393, 1368, 1253, 1153, 1011, 839, 782, 750, 697; δ_H (400 MHz, $CDCl_3$) 7.39-7.37 (5H, m, 5 x Ph*H*), 5.22 (2H, d, *J* 9.1, OC*H*$_2$Ph), 5.11 (1H, m, N*H*), 5.04 (1H, m, 45-*H*), 4.43 (1H, d, *J* 4.7, 46-*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $SiCH_3$); δ_C (100 MHz, $CDCl_3$) 168.6 (47-*C*), 153.9 (*C*(O)), 134.5 ($C_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 115.9 (44-*C*), 81.5 ($CO_2C(CH_3)_3$), 72.4 (46-*C*), 67.9 (OCH_2Ph), 46.1 (45-*C*), 28.1 ($CO_2C(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), −5.0 ($SiCH_3$), −5.5 ($SiCH_3$); *m/z* (ES^+) 457 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{22}H_{34}N_2O_5SiNa$ 457.2129, observed 457.2125.

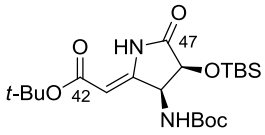
(*Z*)-*tert*-Butyl 2-((3*S*,4*R*)-3-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-5-oxopyrrolidin-2-ylidene)acetate (*anti*-378)



Activated zinc was prepared by washing zinc powder with 3 M HCl, water, ethanol and diethyl ether. After drying under reduced pressure, activated zinc powder (1.46 g, 22.3 mmol) was suspended in THF (22.0 mL) and heated to reflux. Following the reported procedure by Kishi,[99] four drops of *tert*-butyl bromoacetate and two drops of 1,2-dibromoethane were added and the mixture was stirred at reflux for 15 minutes. After addition of a solution of nitrile *syn*-**379** (970 mg, 2.23 mmol) in THF (11.0 mL) in one portion, a solution of *tert*-butyl bromoacetate (2.63 mL, 17.8 mmol) in THF (11.0 mL) was added over a 1 h period *via* syringe pump. The green coloured reaction mixture was stirred for further 4.5 h at reflux and then cooled to room temperature. After the addition of THF

(20.0 mL) and K_2CO_3 (6.80 mL of a 50% aqueous solution), the mixture was vigorously stirred for 30 minutes, filtered through Celite, washing with diethyl ether. The solution was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3-5% EtOAc/petrol) afforded pyrrolidinone *anti*-**378** (441 mg, 45%, approx. 95% purity) as a colourless foam; R_f: 0.50 (10% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 3336, 2931, 2858, 1763, 1721, 1683, 1654, 1527, 1367, 1271, 1253, 1208, 1134, 1050, 866, 839, 782, 756, 689, 671; δ_H (400 MHz, C_6D_6) 9.66 (1H, s, N*H*), 4.96 (1H, d, *J* 1.2, 43-*H*), 4.60 (1H, dd, *J* 9.3 and 9.3, 45-*H*), 4.20 (1H, d, *J* 9.3, N*H*), 3.93 (1H, d, *J* 7.1, 46-*H*), 1.38 (18H, s, 2 x $CO_2C(CH_3)_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 0.28 (3H, s, $SiCH_3$), 0.19 (3H, s, $SiCH_3$); δ_C (100 MHz, C_6D_6) 172.0 (47-*C*), 168.1 (42-*C*), 155.3 (*C*(O)), 153.9 (44-*C*), 91.8 (43-*C*), 80.6 ($CO_2C(CH_3)_3$), 80.3 ($CO_2C(CH_3)_3$), 74.8 (46-*C*), 58.4 (45-*C*), 28.6 (2 x $CO_2C(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 18.9 ($SiC(CH_3)_3$), −3.9 ($SiCH_3$), −4.7 ($SiCH_3$); *m/z* (ES^+) 465 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{21}H_{38}N_2O_6SiNa$ 465.2391, observed 465.2389.

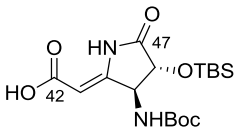
(*Z*)-*tert*-Butyl 2-((3*S*,4*S*)-3-((*tert*-butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-5-oxopyrrolidin-2-ylidene)acetate (*syn*-378)



Activated zinc was prepared by washing zinc powder with 3 M HCl, water, ethanol and diethyl ether. After drying under reduced pressure, activated zinc powder (141 mg, 2.16 mmol) was suspended in THF (1.90 mL) and heated to reflux. Following the reported procedure by Kishi,[99] four drops of *tert*-butyl bromoacetate and two drops of

1,2-dibromoethane were added and the mixture was stirred at reflux for 15 minutes. After addition of a solution of nitrile *anti*-**379** (96.0 mg, 0.22 mmol) in THF (0.94 mL) in one portion, a solution of *tert*-butyl bromoacetate (0.26 mL, 1.73 mmol) in THF (0.94 mL) was added over a 1 h period *via* syringe pump. The green coloured reaction mixture was stirred for further 6 h at reflux and then cooled to room temperature. After the addition of THF (1.90 mL) and K_2CO_3 (0.62 mL of a 50% aqueous solution), the mixture was vigorously stirred for 30 minutes, filtered through Celite, washing with diethyl ether. The solution was then dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3-5% EtOAc/petrol) afforded pyrrolidinone *syn*-**378** (11.1 mg, 10%, approx. 75% purity) as a colourless foam; R_f: 0.50 (10% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 3343, 2931, 2858, 1756, 1717, 1682, 1650, 1503, 1367, 1252, 1215, 1208, 1136, 1058, 941, 863, 836, 781, 698; δ_H (400 MHz, C_6D_6) 9.84 (1H, s, N*H*), 5.29 (1H, s, 43-*H*), 4.87 (1H, d, *J* 9.1, N*H*), 4.72 (1H, dd, *J* 9.1 and 9.1, 45-*H*), 3.68 (1H, d, *J* 7.3, 46-*H*), 1.38 (9H, s, $CO_2C(CH_3)_3$), 1.35 (9H, s, $CO_2C(CH_3)_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.16 (3H, s, $SiCH_3$), 0.12 (3H, s, $SiCH_3$); δ_C (100 MHz, C_6D_6) 172.8 (47-*C*), 168.3 (42-*C*), 156.3 (*C*(O)), 155.8 (44-*C*), 93.7 (43-*C*), 80.6 ($CO_2C(CH_3)_3$), 80.2 ($CO_2C(CH_3)_3$), 67.9 (46-*C*), 52.0 (45-*C*), 28.6 (2 x $CO_2C(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 18.9 ($SiC(CH_3)_3$), −4.2 ($SiCH_3$), −5.0 ($SiCH_3$); *m/z* (ES^+) 465 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{21}H_{38}N_2O_6SiNa$ 465.2391, observed 465.2391.

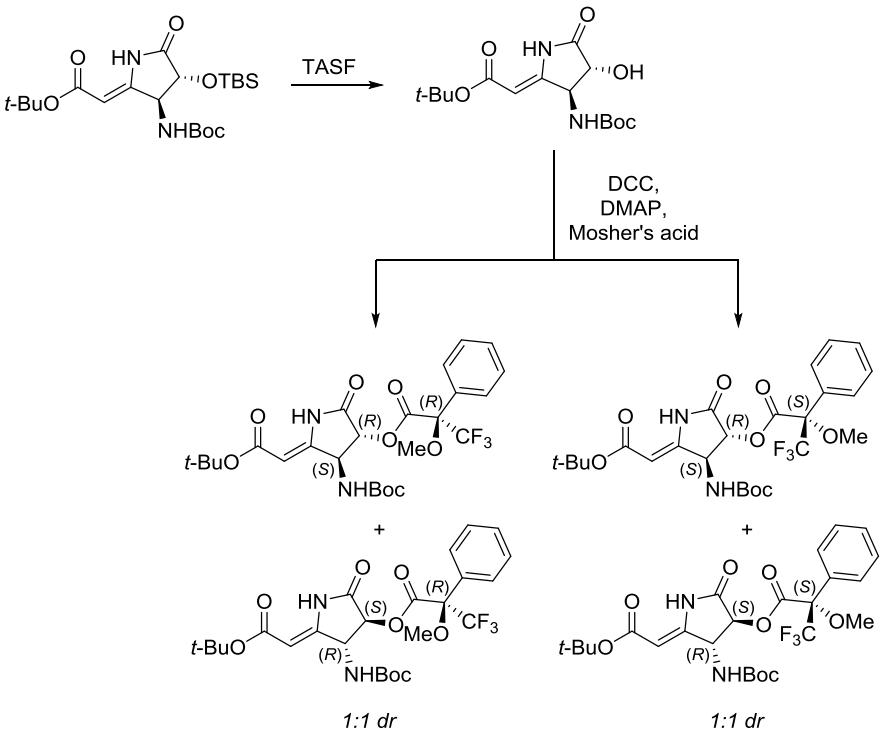
(*Z*)-2-((3*S*,4*R*)-3-((*tert*-Butoxycarbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-5-oxopyrrolidin-2-ylidene)acetic acid (*anti*-377)



Trifluoroacetic acid (0.21 mL, 2.74 mmol) was added to a solution of ester *anti*-**378** (48.0 mg, 0.11 mmol) in CH_2Cl_2 (1.10 mL) at 0 °C. The reaction was warmed slowly to room temperature and stirred for 3 h. The solution was concentrated *in vacuo* and the residue then dissolved in toluene and again concentrated *in vacuo* (x 3) to afford the corresponding free amino acid salt as an orange foam. The amino acid was dissolved in THF/H_2O (1.00 mL, 1:1), $NaHCO_3$ (27.2 mg, 0.32 mmol) and di-*tert*-butyl dicarbonate (28.0 μL, 0.12 mmol) were added at room temperature. The mixture was stirred for 14 h. The solution was acidified to pH 2-3 with aqueous HCl solution (1 M) and then diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50-100% EtOAc/petrol-5% MeOH/EtOAc) afforded acid *anti*-**377** (19.4 mg, 47% over 2 steps) as an orange foam; R_f: 0.50 (EtOAc); m.p. 134-136 ^oC; ν_{max}/cm^{-1} (neat) 3306, 2932, 2859, 1676, 1532, 1444, 1368, 1346, 1253, 1189, 1141, 1052, 838, 782, 723, 667; δ_H (400 MHz, D_6-DMSO): 10.28 (1H, br s, N*H*), 7.51 (1H, d, *J* 8.4, N*H*), 4.78 (1H, d, *J* 1.0, 43-*H*), 4.50-4.46 (2H, m, 45- and 46-*H*), 1.40 (9H, s, $CO_2C(CH_3)_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); δ_C (100 MHz, D_6-DMSO) 172.2 (47-*C*), 169.6 (42-*C*), 155.4 (*C*(O)), 151.8 (44-*C*), 92.5 (43-*C*), 78.7 ($CO_2C(CH_3)_3$), 73.2 (46-*C*), 57.5 (45-*C*), 28.1 ($CO_2C(CH_3)_3$), 25.6

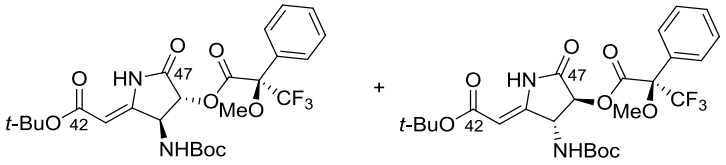
(SiC(CH_3)$_3$), 18.0 (SiC(CH_3)$_3$), −4.6 (SiCH_3), −5.2 (SiCH_3); *m/z* (ES^-) 385 (M-H, 100%); *m/z* HRMS (ES^-) M-H calculated for $C_{17}H_{29}O_6N_2Si$ 385.1800, observed 385.1805.

The enantiopurity of pyrrolidinone *anti*-**378** was confirmed by removal the TBS group and formation of the corresponding Mosher's esters:



Scheme 104. Confirmation of the enantiopurity of pyrrolidinone *anti*-**378**.

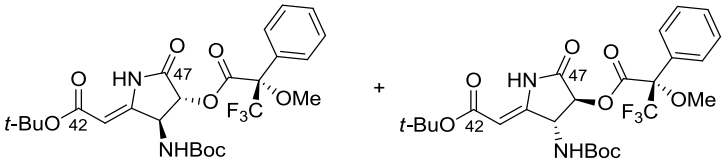
Mixture of (*R*)-(3*R*,4*S*,*Z*)-5-(2-(*tert*-butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate and (*R*)-(3*S*,4*R*,*Z*)-5-(2-(*tert*-butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (400)



H_2O (7.0 μL, 0.36 mmol) and TASF (100 μL of a 1.18 M solution in DMF, 0.12 mmol) were added sequentially to a solution of pyrrolidinone *anti*-**378** (17.5 mg, 0.04 mmol) in DMF (0.50 mL) at 0 °C. The reaction was stirred for 3 h at 0 °C. After which TMS_2O (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The solution was then diluted with EtOAc and washed with saturated aqueous ammonium chloride (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. *N*,*N*′-Dicyclohexylcarbodiimide (9.80 mg, 47.4 μmol), DMAP (2.40 mg, 19.8 μmol) and a solution of the deprotected pyrrolidinone in CH_2Cl_2 (0.50 mL) were added sequentially to a solution of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (9.20 mg, 39.5 μmol) in CH_2Cl_2 (0.50 mL) at room temperature. The mixture was stirred for 16 h, filtered through Celite, washing with CH_2Cl_2, and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/petrol) afforded 1:1 mixture of esters **400** (14.0 mg, 65% over 2 steps) as a colourless oil; R_f: 0.40 (10% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 3330, 2981, 1760, 1686, 1657, 1517, 1369, 1272, 1255, 1166, 1141, 1049, 971, 815, 724, 697; δ_H (500 MHz, $CDCl_3$) 9.94 and 9.91 (1H, s, N*H*), 7.62-7.61 (2H, m, 2 x Ar*H*), 7.43-7.42

(3H, m, 3 x Ar*H*), 5.68 and 5.58 (1H, d, *J* 6.6 and 6.9, 46-*H*), 5.17 and 5.15 (1H, d, *J* 1.7, 43-*H*), 5.13 and 4.93 (1H, m, 45-*H*), 4.98 (1H, d, *J* 8.8, N*H*), 3.65 and 3.62 (3H, s, CO_2CH_3), 1.49 and 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.48 and 1.46 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 167.5 and 167.2 (47-*C*), 167.0 (42-*C*), 166.1 (*C*(O)), 154.7 (*C*(O)), 151.0 (44-*C*), 131.7 and 131.6 ($C_{(Ar)}$), 129.8 ($CH_{(Ar)}$), 128.5 ($CH_{(Ar)}$), 127.6 and 127.5 ($CH_{(Ar)}$), 123.0 (q, $^1J_{C\text{-}F}$ 289.0, CF_3), 93.7 and 93.6 (43-*C*), 84.9 and 84.8 (q, $^2J_{C\text{-}F}$ 28.6 and 27.7, *C*(OCH_3)(CF_3)Ph), 81.4 (2 x $CO_2C(CH_3)_3$), 75.1 and 74.6 (46-*C*), 55.9 (OCH_3), 54.8 and 54.4 (45-*C*), 28.2 (2 x $CO_2C(CH_3)_3$); δ_F (376 MHz, $CDCl_3$) −71.97 and 72.02; *m/z* (ES^+) 567 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{25}H_{31}O_8N_2F_3Na$ 567.1925, observed 567.1922.

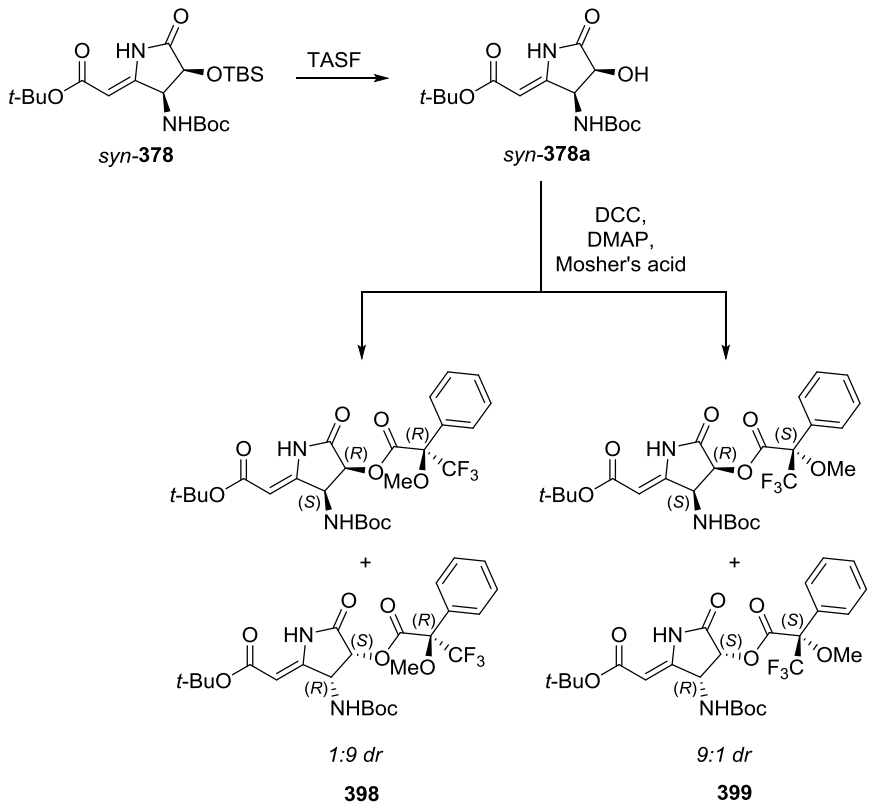
Mixture of (*S*)-(3*R*,4*S*,*Z*)-5-(2-(*tert*-butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate and (*S*)-(3*S*,4*R*,*Z*)-5-(2-(*tert*-butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (401)



H_2O (7.0 μL, 0.36 mmol) and TASF (100 μL of a 1.18 M solution in DMF, 0.12 mmol) were added sequentially to a solution of pyrrolidinone *anti*-**378** (17.5 mg, 0.04 mmol) in DMF (0.50 mL) at 0 °C. The reaction was stirred for 3 h at 0 °C. After which TMS_2O (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The

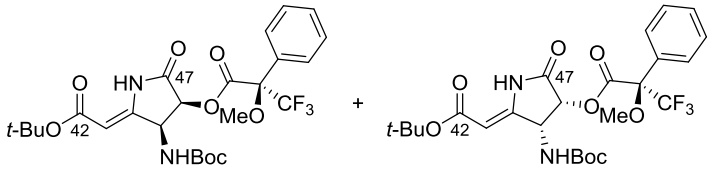
solution was then diluted with EtOAc and washed with saturated aqueous ammonium chloride (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. *N*,*N*′-Dicyclohexylcarbodiimide (9.80 mg, 47.4 μmol), DMAP (2.40 mg, 19.8 μmol) and a solution of the deprotected pyrrolidinone in CH_2Cl_2 (0.50 mL) were added sequentially to a solution of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (9.20 mg, 39.5 μmol) in CH_2Cl_2 (0.50 mL) at room temperature. The mixture was stirred for 16 h, filtered through Celite, washing with CH_2Cl_2, and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/petrol) afforded 1:1 mixture of esters **401** (13.8 mg, 64% over 2 steps) as a colourless oil; R_f: 0.40 (10% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 3332, 2980, 1760, 1686, 1657, 1517, 1369, 1272, 1255, 1166, 1141, 1049, 973, 814, 724, 698; δ_H (500 MHz, $CDCl_3$) 9.94 and 9.90 (1H, s, N*H*), 7.62-7.61 (2H, m, 2 x Ar*H*), 7.43-7.42 (3H, m, 3 x Ar*H*), 5.68 and 5.58 (1H, d, *J* 6.6 and 6.9, 46-*H*), 5.17 and 5.15 (1H, d, *J* 1.4 and 1.6, 43-*H*), 5.15 and 4.93 (1H, m, 45-*H*), 4.99 (1H, m, N*H*), 3.65 and 3.62 (3H, s, CO_2CH_3), 1.49 and 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.48 and 1.46 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 167.5 and 167.2 (47-*C*), 167.0 (42-*C*), 166.1 (*C*(O)), 154.6 (*C*(O)), 151.0 (44-*C*), 131.6 ($C_{(Ar)}$), 129.8 ($CH_{(Ar)}$), 128.5 ($CH_{(Ar)}$), 127.5 and 127.4 ($CH_{(Ar)}$), 123.0 (q, $^1J_{C\text{-}F}$ 289.0, CF_3), 93.6 and 93.5 (43-*C*), 84.9 and 84.8 (q, $^2J_{C\text{-}F}$ 28.6, $C(OCH_3)(CF_3)Ph$), 81.3 (2 x $CO_2C(CH_3)_3$), 75.0 and 74.6 (46-*C*), 55.8 (OCH_3), 54.8 and 54.4 (45-*C*), 28.2 (2 x $CO_2C(CH_3)_3$); δ_F (376 MHz, $CDCl_3$) −71.97 and 72.02; *m/z* (ES^+) 567 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{25}H_{31}O_8N_2F_3Na$ 567.1925, observed 567.1920.

The enantiopurity of pyrrolidinone *syn*-**378** was confirmed by removal the TBS group and formation of the corresponding Mosher's esters:



Scheme 105. Confirmation of the enantiopurity of pyrrolidinone *syn*-**378**.

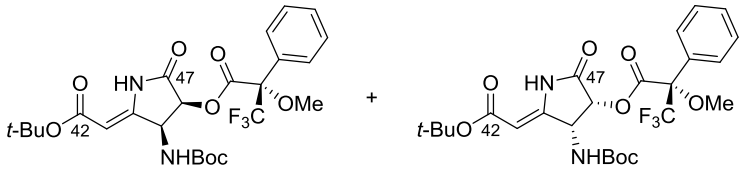
Mixture of (*R*)-(3*S*,4*S*,*Z*)-5-(2-(*tert*-butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate and (3*R*,4*R*,*Z*)-5-(2-(*tert*-butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (398)



H_2O (4.00 μL, 0.22 mmol) and TASF (60.0 μL of a 0.22 M solution in DMF, 67.5 μmol) were added sequentially to a solution of pyrrolidinone *syn*-**378** (10.0 mg, 22.5 μmol) in DMF (0.28 mL) at 0 °C. The reaction was stirred for 3 h at 0 °C. After which TMS_2O (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The solution was then diluted with EtOAc and washed with saturated aqueous ammonium chloride (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. *N*,*N*′-Dicyclohexylcarbodiimide (5.60 mg, 27.0 μmol), DMAP (1.40 mg, 11.2 μmol) and a solution of the deprotected pyrrolidinone in CH_2Cl_2 (0.50 mL) were added sequentially to a solution of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (5.30 mg, 22.5 μmol) in CH_2Cl_2 (0.10 mL) at room temperature. The mixture was stirred for 16 h, filtered through Celite, washing with CH_2Cl_2, and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/petrol) afforded 1:9 mixture of esters **398** (7.80 mg, 64% over 2 steps) as a colourless oil; R_f: 0.40 (10% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 3342, 2978, 2932, 2360, 1770, 1687, 1654, 1523, 1369, 1274, 1256, 1170, 1143, 1014, 829, 723, 697, 642; δ_H (500 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer

only)) 10.01 (1H, s, N*H*), 7.59-7.57 (2H, m, 2 x Ar*H*), 7.46-7.43 (3H, m, 3 x Ar*H*), 5.48 (1H, d, *J* 8.4, 46-*H*), 5.28 (1H, dd, *J* 8.4 and 8.4, 45-*H*), 5.23 (1H, d, *J* 1.4, 43-*H*), 4.81 (1H, d, *J* 9.5, N*H*), 3.50 (3H, s, CO_2CH_3), 1.49 (9H, s, $CO_2C(CH_3)_3$), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 168.6 (47-*C*), 167.1 (42-*C*), 165.8 (*C*(O)), 154.7 (*C*(O)), 153.0 (44-*C*), 130.8 ($C_{(Ar)}$), 130.0 ($CH_{(Ar)}$), 128.6 ($CH_{(Ar)}$), 127.8 ($CH_{(Ar)}$), 122.9 (q, $^1J_{C\text{-}F}$ 288.0, CF_3), 94.6 (43-*C*), 85.0 (q, $^2J_{C\text{-}F}$ 27.7, $C(OCH_3)(CF_3)Ph$), 81.3 ($CO_2C(CH_3)_3$), 81.2 ($CO_2C(CH_3)_3$), 68.4 (46-*C*), 55.5 (OCH_3), 49.6 (45-*C*), 28.2 ($CO_2C(CH_3)_3$), 28.1 ($CO_2C(CH_3)_3$); δ_F (376 MHz, $CDCl_3$) −72.06; *m/z* (ES^+) 567 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{25}H_{31}O_8N_2F_3Na$ 567.1925, observed 567.1923.

Mixture of (*S*)-(3*S*,4*S*,*Z*)-5-(2-(*tert*-Butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate and (3*R*,4*R*,*Z*)-5-(2-(*tert*-butoxy)-2-oxoethylidene)-4-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidin-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (399)



H_2O (4.00 μL, 0.22 mmol) and TASF (60.0 μL of a 0.22 M solution in DMF, 67.5 μmol) were added sequentially to a solution of pyrrolidinone *syn*-**378** (10.0 mg, 22.5 μmol) in DMF (0.28 mL) at 0 °C. The reaction was stirred for 3 h at 0 °C. After which TMS_2O (100 μL) was added and the solution was stirred at room temperature for 10 minutes. The

solution was then diluted with EtOAc and washed with saturated aqueous ammonium chloride (x 2), dried (Na_2SO_4), filtered and concentrated *in vacuo*. *N*,*N*′-Dicyclohexylcarbodiimide (5.60 mg, 27.0 μmol), DMAP (1.40 mg, 11.2 μmol) and a solution of the deprotected pyrrolidinone in CH_2Cl_2 (0.50 mL) were added sequentially to a solution of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (5.30 mg, 22.5 μmol) in CH_2Cl_2 (0.10 mL) at room temperature. The mixture was stirred for 16 h, filtered through Celite, washing with CH_2Cl_2, and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/petrol) afforded 9:1 mixture of esters **399** (5.30 mg, 43% over 2 steps) as a colourless oil; R_f: 0.40 (10% EtOAc/petrol); ν_{max}/cm^{-1} (neat) 2981, 2936, 1764, 1687, 1656, 1512, 1369, 1273, 1257, 1170, 1143, 1017, 820, 720, 698, 650; δ_H (500 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 10.01 (1H, s, N*H*), 7.56-7.55 (2H, m, 2 x Ar*H*), 7.45-7.43 (3H, m, 3 x Ar*H*), 5.59 (1H, d, *J* 8.0, 46-*H*), 5.27 (1H, dd, *J* 8.0 and 8.0, 45-*H*), 5.17 (1H, s, 43-*H*), 4.56 (1H, d, *J* 9.5, N*H*), 3.59 (3H, s, CO_2CH_3), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.47 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$ (chemical shifts reported for the major diastereoisomer only)) 168.6 (47-*C*), 167.0 (42-*C*), 165.6 (*C*(O)), 154.7 (*C*(O)), 152.9 (44-*C*), 131.5 ($C_{(Ar)}$), 130.0 ($CH_{(Ar)}$), 128.7 ($CH_{(Ar)}$), 127.3 ($CH_{(Ar)}$), 123.0 (q, $^1J_{C\text{-}F}$ 289.0, CF_3), 94.7 (43-*C*), 84.7 (q, $^2J_{C\text{-}F}$ 28.6, $C(OCH_3)(CF_3)Ph$), 81.3 ($CO_2C(CH_3)_3$), 81.3 ($CO_2C(CH_3)_3$), 67.8 (46-*C*), 55.7 (OCH_3), 49.7 (45-*C*), 28.2 ($CO_2C(CH_3)_3$), 28.1 ($CO_2C(CH_3)_3$); δ_F (376 MHz, $CDCl_3$) −71.78; *m/z* (ES^+) 567 (MNa^+, 100); *m/z* HRMS (ES^+) MNa^+ calculated for $C_{25}H_{31}O_8N_2F_3Na$ 567.1925, observed 567.1924.

8.3 Supplementary CIF data for compound 202

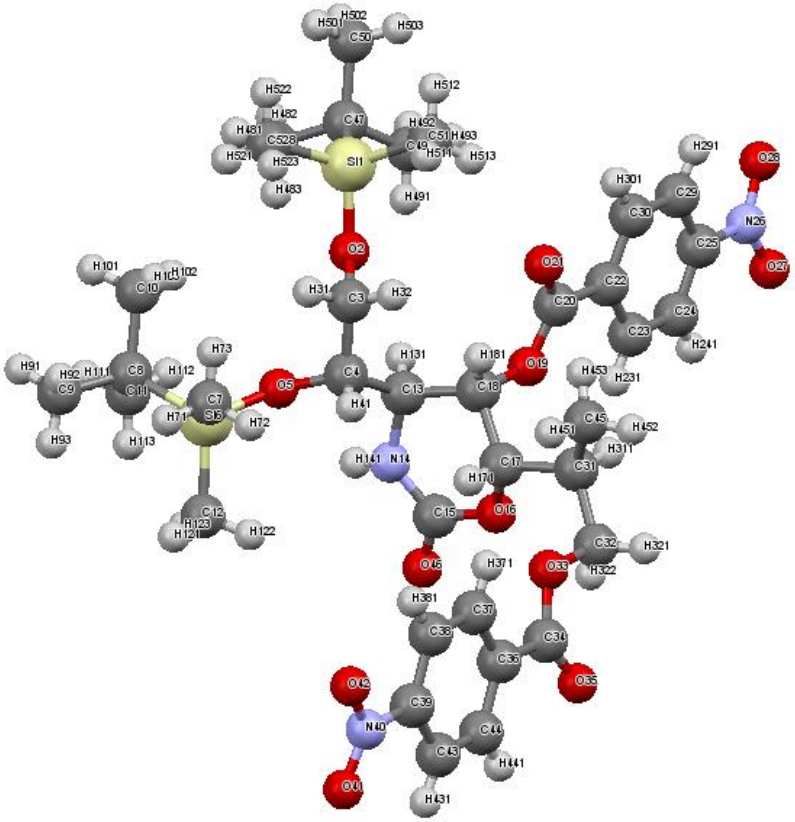


Figure 28. X-ray crystal structure of 202.

Title: (*S*)-2-((4*R*,5*S*,6*S*)-5-((4-Nitrobenzoyl)oxy)-4-((*S*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-2-oxo-1,3-oxazinan-6-yl)propyl 4-nitrobenzoate (**202**)

Computing details:

Data collection: *CrystalClear*-SM Expert 2.0 r4 (Rigaku, 2009); cell refinement: CrysAlis, (Oxford Diffraction, 2002); data reduction: CrysAlis, (Oxford Diffraction, 2002); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge et al., 2003); molecular graphics:

CAMERON (Watkin et al., 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge et al., 2003).

Experimental:

Crystal data

$C_{35}H_{51}N_3O_{12}Si_2$	$F(000) = 1624$
$M_r = 761.97$	$D_x = 1.243$ Mg m^{-3}
Monoclinic, $C2$	Melting point: not measured K
Hall symbol: C 2y	Synchrotron radiation, $\lambda = 0.68890$ Å
$a = 23.9112$ (12) Å	Cell parameters from 5021 reflections
$b = 6.4920$ (9) Å	$\theta = 2–27°$
$c = 26.346$ (2) Å	$\mu = 0.15$ mm^{-1}
$\beta = 95.462$ (6)°	$T = 100$ K
$V = 4071.2$ (7) Å^3	Needle, clear_pale_colourless
$Z = 4$	0.02 × 0.01 × 0.01 mm

Data collection

Rigaku Saturn724+ (2x2 bin mode) diffractometer	2417 reflections with $I > 2.0\sigma(I)$
Synchrotron monochromator	$R_{int} = 0.135$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 1.8°$
Absorption correction: multi-scan CrysAlis, (Oxford Diffraction, 2002)	$h = -31\rightarrow30$
$T_{min} = 0.55$, $T_{max} = 1.00$	$k = -7\rightarrow4$
14518 measured reflections	$l = -33\rightarrow33$
4586 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.096$	H-atom parameters constrained
$wR(F^2) = 0.223$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 0.576E + 04 0.872E + 04 0.518E + 04 0.237E + 04 611.
S = 1.01	$(\Delta/\sigma)_{max} = 0.0002$
3140 reflections	$\Delta\rho_{max} = 0.59$ e Å^{-3}
469 parameters	$\Delta\rho_{min} = -0.61$ e Å^{-3}

Special details

Refinement

On initial data reduction, it became apparent that the sample had suffered significant radiation damage. This was demonstrated by the progressively increasing interframe scale-factor and elevated *R*-indices. Only the first four runs were acceptable and an *R*(int) frame filter was applied to remove the worst outlying reflections. This meant the final dataset was noisy and incomplete, however, crystals were scarce and of poor quality, so despite best efforts it was not possible to augment this dataset.

On refinement, some of the atomic displacement parameters did not satisfy the Hirshfeld condition, so vibrational restraints and thermal similarity restraints were included in the refinement.

Initial unrestrained refinement of the Flack *x* parameter gave a value of −0.458 (44), suggesting that the absolute configuration could not be reliably determined (Flack, 1983; Flack & Bernardinelli, 2000). Analysis of the Bijvoet differences using *CRYSTALS* gave the Hooft *y* parameter as −0.54 (28), however the probability the configuration is correct assuming the material is enantiopure was determined to be >99.9% (99.35% allowing for the racemate; Hooft *et al.*, 2008; Thompson *et al.* 2008; Thompson & Watkin 2009; Thompson & Watkin 2011). Refinement of the Flack *x* parameter with the application of difference restraints (Thompson & Watkin 2011) gave a final value of 0.021 (26). In the absence of significant anomalous scattering (FRIEDIF = 43.02; Flack and Shmueli, 2007), Friedel pairs were merged for the final refinement.

Hooft, *R*. W. W.; Straver, *L*. H.; Spek, A. *L*. *J. Appl. Cryst*. **2008**, 41, 96–103.

Thompson, A. *L*.; Watkin, D. J.; Gal, *Z*. A.; Jones, *L*.; Hollinshead, J.; Jenkinson, *S. F*.; Fleet, G. W. J.; Nash, *R*. J. *Acta Cryst*. **2008**, C64, o649-o652.

Thompson, A. *L*.; Watkin, D. J. *Tetrahedron: Asymmetry*. **2009**, 20, 712–717.

Thompson, A. *L*.; Watkin, D. J. *J. Appl. Cryst*. **2011**, 44, 1017–1022.

Flack, H. D.; Shmueli, U. *Acta Crystallogr., Sect. A*. **2007**, 63, 257–265.

Flack, H. D. *Acta Cryst*. **1983**, A39, 876–881.

Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst*. **2000**, 33, 1143–1148.

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

	x	*y*	*z*	U_{iso}*/U_{eq}
Si1	*0.59400 (13)*	*0.8898 (7)*	*0.85855 (14)*	*0.0720*
O2	*0.6375 (3)*	*0.7296 (14)*	*0.8318 (3)*	*0.0660*
C3	*0.6781 (4)*	*0.809 (2)*	*0.8000 (5)*	*0.0641*

C4	*0.7142 (4)*	*0.639 (2)*	*0.7831 (4)*	*0.0561*
O5	*0.7493 (3)*	*0.5555 (14)*	*0.8259 (3)*	*0.0648*
Si6	*0.81281 (12)*	*0.6318 (7)*	*0.84760 (14)*	*0.0683*
C7	*0.8244 (5)*	*0.897 (2)*	*0.8273 (6)*	*0.0783*
C8	*0.8177 (4)*	*0.606 (2)*	*0.9185 (5)*	*0.0728*
C9	*0.8740 (5)*	*0.693 (3)*	*0.9436 (6)*	*0.0947*
C10	*0.7700 (5)*	*0.732 (3)*	*0.9410 (6)*	*0.1016*
C11	*0.8108 (7)*	*0.370 (3)*	*0.9337 (6)*	*0.1019*
C12	*0.8650 (5)*	*0.469 (2)*	*0.8188 (5)*	*0.0775*
C13	*0.6812 (4)*	*0.4588 (19)*	*0.7573 (4)*	*0.0527*
N14	*0.7184 (3)*	*0.2819 (17)*	*0.7495 (4)*	*0.0575*
C15	*0.7222 (4)*	*0.173 (2)*	*0.7068 (5)*	*0.0547*
O16	*0.6968 (2)*	*0.2504 (13)*	*0.6634 (3)*	*0.0499*
C17	*0.6812 (3)*	*0.4670 (17)*	*0.6622 (4)*	*0.0457*
C18	*0.6471 (3)*	*0.5169 (18)*	*0.7074 (4)*	*0.0468*
O19	*0.5959 (2)*	*0.3999 (11)*	*0.7004 (2)*	*0.0438*
C20	*0.5490 (4)*	*0.4983 (19)*	*0.7035 (4)*	*0.0486*
O21	*0.5449 (3)*	*0.6827 (13)*	*0.7117 (4)*	*0.0667*
C22	*0.4978 (3)*	*0.3650 (17)*	*0.6955 (4)*	*0.0414*
C23	*0.5017 (3)*	*0.1645 (17)*	*0.6771 (4)*	*0.0412*
C24	*0.4545 (3)*	*0.0434 (18)*	*0.6707 (4)*	*0.0461*
C25	*0.4042 (3)*	*0.1217 (17)*	*0.6826 (4)*	*0.0402*
N26	*0.3535 (3)*	*−0.0097 (16)*	*0.6774 (4)*	*0.0515*
O27	*0.3566 (3)*	*−0.1802 (14)*	*0.6583 (4)*	*0.0737*
O28	*0.3103 (2)*	*0.0532 (15)*	*0.6932 (4)*	*0.0780*
C29	*0.3989 (3)*	*0.3199 (17)*	*0.7001 (4)*	*0.0437*
C30	*0.4462 (3)*	*0.4407 (18)*	*0.7064 (4)*	*0.0494*
C31	*0.6509 (4)*	*0.5091 (19)*	*0.6103 (4)*	*0.0517*

C32	*0.6863 (4)*	*0.4401 (19)*	*0.5684 (4)*	*0.0537*
O33	*0.7373 (2)*	*0.5608 (12)*	*0.5734 (2)*	*0.0469*
C34	*0.7798 (4)*	*0.4890 (18)*	*0.5480 (4)*	*0.0439*
O35	*0.7778 (3)*	*0.3261 (13)*	*0.5241 (3)*	*0.0569*
C36	*0.8294 (3)*	*0.6249 (17)*	*0.5526 (3)*	*0.0393*
C37	*0.8277 (3)*	*0.8285 (16)*	*0.5713 (4)*	*0.0419*
C38	*0.8750 (3)*	*0.9484 (18)*	*0.5754 (4)*	*0.0446*
C39	*0.9249 (3)*	*0.8702 (18)*	*0.5597 (4)*	*0.0421*
N40	*0.9755 (3)*	*0.9949 (16)*	*0.5639 (3)*	*0.0531*
O41	*1.0202 (2)*	*0.9166 (15)*	*0.5565 (3)*	*0.0682*
O42	*0.9713 (3)*	*1.1822 (14)*	*0.5757 (4)*	*0.0768*
C43	*0.9269 (4)*	*0.6678 (18)*	*0.5403 (4)*	*0.0470*
C44	*0.8796 (3)*	*0.5501 (18)*	*0.5365 (4)*	*0.0457*
C45	*0.6353 (4)*	*0.740 (2)*	*0.6045 (4)*	*0.0592*
O46	*0.7487 (3)*	*0.0114 (16)*	*0.7056 (3)*	*0.0769*
C47	*0.5516 (5)*	*0.721 (3)*	*0.8976 (5)*	*0.0779*
C48	*0.5911 (6)*	*0.618 (3)*	*0.9402 (7)*	*0.1098*
C49	*0.5233 (7)*	*0.559 (3)*	*0.8625 (8)*	*0.1203*
C50	*0.5058 (6)*	*0.851 (3)*	*0.9208 (6)*	*0.1089*
C51	*0.5488 (5)*	*1.029 (2)*	*0.8076 (5)*	*0.0718*
C52	*0.6370 (6)*	*1.085 (3)*	*0.8980 (6)*	*0.0926*
H31	*0.7014*	*0.9089*	*0.8193*	*0.0769**
H32	*0.6584*	*0.8735*	*0.7702*	*0.0770**
H41	*0.7383*	*0.6976*	*0.7586*	*0.0670**
H71	*0.8615*	*0.9413*	*0.8400*	*0.1179**
H73	*0.7970*	*0.9853*	*0.8408*	*0.1180**
H72	*0.8203*	*0.9070*	*0.7906*	*0.1178**
H91	*0.8760*	*0.6774*	*0.9802*	*0.1420**

H93	*0.9050*	*0.6204*	*0.9310*	*0.1420**
H92	*0.8768*	*0.8373*	*0.9355*	*0.1421**
H101	*0.7799*	*0.7532*	*0.9769*	*0.1519**
H103	*0.7654*	*0.8631*	*0.9241*	*0.1520**
H102	*0.7354*	*0.6556*	*0.9360*	*0.1520**
H111	*0.8183*	*0.3538*	*0.9701*	*0.1530**
H113	*0.8368*	*0.2861*	*0.9169*	*0.1531**
H112	*0.7730*	*0.3253*	*0.9234*	*0.1530**
H121	*0.9001*	*0.5411*	*0.8193*	*0.1160**
H123	*0.8703*	*0.3428*	*0.8377*	*0.1160**
H122	*0.8512*	*0.4392*	*0.7842*	*0.1160**
H131	*0.6544*	*0.4133*	*0.7806*	*0.0631**
H171	*0.7156*	*0.5495*	*0.6660*	*0.0546**
H181	*0.6384*	*0.6648*	*0.7074*	*0.0559**
H231	*0.5357*	*0.1114*	*0.6692*	*0.0488**
H241	*0.4567*	*−0.0916*	*0.6587*	*0.0547**
H291	*0.3642*	*0.3704*	*0.7072*	*0.0520**
H301	*0.4437*	*0.5759*	*0.7182*	*0.0588**
H311	*0.6162*	*0.4277*	*0.6069*	*0.0619**
H322	*0.6952*	*0.2950*	*0.5721*	*0.0638**
H321	*0.6661*	*0.4627*	*0.5350*	*0.0637**
H371	*0.7945*	*0.8811*	*0.5809*	*0.0500**
H381	*0.8740*	*1.0808*	*0.5888*	*0.0528**
H431	*0.9604*	*0.6156*	*0.5305*	*0.0559**
H441	*0.8810*	*0.4174*	*0.5227*	*0.0549**
H452	*0.6200*	*0.7660*	*0.5702*	*0.0889**
H451	*0.6680*	*0.8241*	*0.6124*	*0.0889**
H453	*0.6076*	*0.7737*	*0.6273*	*0.0890**

H482	*0.5690*	*0.5440*	*0.9629*	*0.1650**
H481	*0.6130*	*0.7211*	*0.9589*	*0.1651**
H483	*0.6157*	*0.5231*	*0.9253*	*0.1650**
H492	*0.4993*	*0.4743*	*0.8812*	*0.1810**
H491	*0.5510*	*0.4734*	*0.8489*	*0.1810**
H493	*0.5010*	*0.6248*	*0.8349*	*0.1809**
H502	*0.4887*	*0.7705*	*0.9457*	*0.1640**
H501	*0.5230*	*0.9718*	*0.9367*	*0.1640**
H503	*0.4777*	*0.8920*	*0.8941*	*0.1640**
H512	*0.5190*	*1.0987*	*0.8224*	*0.1081**
H511	*0.5713*	*1.1276*	*0.7914*	*0.1080**
H513	*0.5330*	*0.9318*	*0.7828*	*0.1081**
H522	*0.6122*	*1.1707*	*0.9155*	*0.1389**
H521	*0.6627*	*1.0164*	*0.9227*	*0.1389**
H523	*0.6577*	*1.1693*	*0.8764*	*0.1390**
H141	*0.7300*	*0.2173*	*0.7770*	*0.0689**

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Si1	0.0485 (17)	0.078 (3)	0.090 (2)	0.0077 (17)	0.0093 (14)	−0.005 (2)
O2	0.034 (3)	0.068 (5)	0.098 (5)	0.001 (3)	0.016 (3)	0.007 (4)
C3	0.032 (4)	0.069 (6)	0.091 (7)	−0.012 (3)	0.008 (3)	0.003 (5)
C4	0.028 (4)	0.070 (5)	0.070 (5)	−0.013 (3)	0.007 (2)	0.008 (4)
O5	0.047 (3)	0.074 (5)	0.072 (4)	−0.009 (3)	−0.002 (3)	0.005 (4)
Si6	0.0387 (14)	0.082 (3)	0.083 (2)	−0.0036 (17)	0.0011 (13)	0.001 (2)
C7	0.036 (5)	0.085 (4)	0.113 (9)	−0.011 (5)	0.002 (6)	0.007 (6)

C8	0.042 (5)	0.091 (7)	0.083 (3)	0.013 (5)	−0.007 (4)	−0.001 (5)
C9	0.056 (5)	0.124 (12)	0.101 (7)	0.006 (7)	−0.012 (6)	−0.033 (10)
C10	0.062 (5)	0.146 (12)	0.099 (7)	0.025 (9)	0.020 (7)	−0.005 (10)
C11	0.087 (9)	0.111 (7)	0.108 (10)	0.000 (7)	0.012 (8)	0.031 (8)
C12	0.049 (4)	0.091 (8)	0.093 (7)	−0.003 (6)	0.004 (5)	−0.011 (7)
C13	0.028 (4)	0.064 (5)	0.067 (4)	−0.012 (3)	0.008 (3)	0.012 (4)
N14	0.038 (4)	0.068 (5)	0.066 (4)	−0.002 (4)	0.003 (4)	0.017 (4)
C15	0.029 (5)	0.058 (5)	0.077 (4)	−0.005 (4)	0.010 (4)	0.013 (3)
O16	0.023 (3)	0.057 (3)	0.071 (3)	−0.003 (3)	0.007 (3)	0.001 (3)
C17	0.018 (4)	0.052 (4)	0.067 (3)	−0.012 (4)	0.004 (2)	0.007 (4)
C18	0.025 (3)	0.046 (5)	0.070 (3)	−0.008 (3)	0.007 (2)	0.004 (4)
O19	0.020 (2)	0.040 (4)	0.073 (4)	−0.003 (2)	0.009 (2)	0.003 (3)
C20	0.025 (2)	0.047 (4)	0.074 (6)	0.003 (2)	0.007 (4)	0.003 (5)
O21	0.024 (3)	0.047 (4)	0.129 (7)	0.000 (3)	0.009 (4)	−0.004 (5)
C22	0.022 (2)	0.041 (4)	0.061 (6)	0.006 (3)	0.009 (4)	0.004 (4)
C23	0.019 (3)	0.044 (4)	0.062 (6)	0.007 (3)	0.014 (4)	0.001 (5)
C24	0.025 (3)	0.048 (5)	0.067 (6)	0.003 (3)	0.009 (4)	−0.008 (5)
C25	0.020 (2)	0.043 (4)	0.059 (5)	0.003 (3)	0.007 (3)	0.008 (4)
N26	0.023 (3)	0.056 (4)	0.076 (6)	−0.003 (3)	0.008 (3)	0.009 (4)
O27	0.036 (4)	0.060 (5)	0.127 (7)	−0.015 (4)	0.019 (4)	−0.010 (5)
O28	0.018 (3)	0.076 (6)	0.141 (7)	0.003 (3)	0.015 (3)	0.003 (5)
C29	0.017 (3)	0.049 (4)	0.066 (6)	0.010 (3)	0.010 (4)	0.003 (5)
C30	0.026 (3)	0.042 (5)	0.081 (7)	0.007 (3)	0.012 (4)	−0.002 (5)
C31	0.026 (4)	0.063 (5)	0.066 (4)	−0.015 (4)	0.003 (3)	0.008 (4)
C32	0.032 (4)	0.059 (7)	0.070 (4)	−0.018 (4)	0.003 (4)	−0.003 (5)
O33	0.026 (2)	0.057 (5)	0.058 (4)	−0.012 (3)	0.006 (2)	−0.001 (3)
C34	0.025 (3)	0.047 (5)	0.059 (6)	−0.001 (3)	−0.001 (3)	0.005 (4)
O35	0.034 (3)	0.052 (5)	0.085 (5)	−0.008 (3)	0.007 (3)	−0.007 (4)

C36	0.026 (3)	0.045 (4)	0.047 (5)	−0.001 (3)	0.004 (3)	0.002 (4)
C37	0.023 (3)	0.045 (4)	0.059 (6)	0.001 (3)	0.011 (4)	0.001 (4)
C38	0.029 (3)	0.049 (5)	0.055 (5)	−0.006 (3)	0.005 (4)	−0.004 (5)
C39	0.021 (3)	0.053 (4)	0.051 (5)	−0.006 (3)	−0.002 (3)	0.001 (5)
N40	0.027 (2)	0.062 (4)	0.071 (5)	−0.014 (3)	0.008 (4)	0.001 (5)
O41	0.023 (2)	0.078 (5)	0.103 (6)	−0.013 (3)	0.003 (3)	−0.015 (5)
O42	0.033 (4)	0.061 (4)	0.139 (8)	−0.019 (3)	0.020 (4)	−0.006 (5)
C43	0.024 (3)	0.056 (5)	0.062 (6)	0.000 (3)	0.006 (4)	−0.003 (5)
C44	0.028 (3)	0.044 (5)	0.065 (6)	0.001 (3)	0.006 (4)	−0.003 (5)
C45	0.041 (5)	0.074 (5)	0.063 (6)	0.008 (5)	0.005 (4)	0.011 (5)
O46	0.051 (4)	0.075 (5)	0.105 (6)	0.018 (4)	0.013 (4)	0.017 (4)
C47	0.045 (5)	0.093 (8)	0.098 (7)	0.018 (4)	0.021 (3)	0.003 (4)
C48	0.079 (8)	0.111 (14)	0.141 (10)	0.037 (8)	0.020 (6)	0.042 (8)
C49	0.091 (10)	0.116 (13)	0.158 (13)	−0.033 (9)	0.035 (8)	−0.018 (9)
C50	0.065 (7)	0.141 (15)	0.126 (11)	0.049 (8)	0.036 (6)	0.011 (9)
C51	0.050 (6)	0.071 (8)	0.096 (7)	0.013 (5)	0.009 (4)	−0.008 (5)
C52	0.067 (7)	0.105 (10)	0.104 (9)	−0.001 (6)	0.001 (5)	−0.021 (7)

Geometric parameters (Å, º)

Si1—O2	1.673 (8)	C24—C25	1.369 (12)
Si1—C47	1.869 (15)	C24—H241	0.935
Si1—C51	1.873 (13)	C25—N26	1.479 (12)
Si1—C52	1.881 (16)	C25—C29	1.377 (15)
O2—C3	1.435 (13)	N26—O27	1.221 (12)
C3—C4	1.491 (17)	N26—O28	1.220 (10)
C3—H31	0.971	C29—C30	1.373 (13)

C3—H32	0.972	C29—H291	0.926
C4—O5	1.446 (13)	C30—H301	0.934
C4—C13	1.536 (15)	C31—C32	1.518 (15)
C4—H41	0.981	C31—C45	1.548 (18)
O5—Si6	1.647 (7)	C31—H311	0.982
Si6—C7	1.832 (16)	C32—O33	1.445 (11)
Si6—C8	1.867 (14)	C32—H322	0.969
Si6—C12	1.852 (14)	C32—H321	0.975
C7—H71	0.960	O33—C34	1.354 (11)
C7—H73	0.963	C34—O35	1.229 (13)
C7—H72	0.964	C34—C36	1.473 (13)
C8—C9	1.548 (17)	C36—C37	1.413 (15)
C8—C10	1.565 (19)	C36—C44	1.399 (12)
C8—C11	1.60 (3)	C37—C38	1.368 (13)
C9—H91	0.966	C37—H371	0.923
C9—H93	0.962	C38—C39	1.395 (13)
C9—H92	0.965	C38—H381	0.931
C10—H101	0.963	C39—N40	1.451 (12)
C10—H103	0.962	C39—C43	1.412 (16)
C10—H102	0.964	N40—O41	1.216 (11)
C11—H111	0.965	N40—O42	1.261 (13)
C11—H113	0.965	C43—C44	1.359 (13)
C11—H112	0.964	C43—H431	0.929
C12—H121	0.961	C44—H441	0.937
C12—H123	0.961	C45—H452	0.957
C12—H122	0.959	C45—H451	0.961
C13—N14	1.479 (15)	C45—H453	0.960
C13—C18	1.526 (14)	C47—C48	1.55 (2)

C13—H131	0.973	C47—C49	1.52 (2)
N14—C15	1.342 (15)	C47—C50	1.554 (18)
N14—H141	0.860	C48—H482	0.961
C15—O16	1.339 (13)	C48—H481	0.958
C15—O46	1.225 (14)	C48—H483	0.960
O16—C17	1.455 (14)	C49—H492	0.962
C17—C18	1.541 (14)	C49—H491	0.960
C17—C31	1.510 (14)	C49—H493	0.959
C17—H171	0.979	C50—H502	0.963
C18—O19	1.438 (10)	C50—H501	0.961
C18—H181	0.982	C50—H503	0.963
O19—C20	1.299 (11)	C51—H512	0.960
C20—O21	1.222 (14)	C51—H511	0.962
C20—C22	1.497 (14)	C51—H513	0.959
C22—C23	1.395 (15)	C52—H522	0.962
C22—C30	1.386 (12)	C52—H521	0.959
C23—C24	1.373 (13)	C52—H523	0.961
C23—H231	0.924		
O2—Si1—C47	105.0 (6)	C24—C23—H231	119.3
O2—Si1—C51	109.7 (5)	C23—C24—C25	119.3 (10)
C47—Si1—C51	111.9 (6)	C23—C24—H241	120.3
O2—Si1—C52	108.8 (5)	C25—C24—H241	120.4
C47—Si1—C52	112.8 (7)	C24—C25—N26	119.7 (10)
C51—Si1—C52	108.6 (7)	C24—C25—C29	122.4 (9)
Si1—O2—C3	120.4 (8)	N26—C25—C29	118.0 (8)
O2—C3—C4	110.7 (10)	C25—N26—O27	118.7 (8)
O2—C3—H31	108.7	C25—N26—O28	119.2 (9)

C4—C3—H31	109.2	O27—N26—O28	122.1 (9)
O2—C3—H32	109.0	C25—C29—C30	118.2 (8)
C4—C3—H32	109.2	C25—C29—H291	120.7
H31—C3—H32	110.0	C30—C29—H291	121.0
C3—C4—O5	110.8 (9)	C22—C30—C29	120.8 (10)
C3—C4—C13	113.9 (8)	C22—C30—H301	119.2
O5—C4—C13	107.1 (9)	C29—C30—H301	120.0
C3—C4—H41	107.8	C17—C31—C32	110.7 (8)
O5—C4—H41	108.9	C17—C31—C45	110.8 (10)
C13—C4—H41	108.2	C32—C31—C45	111.1 (10)
C4—O5—Si6	127.2 (7)	C17—C31—H311	108.3
O5—Si6—C7	110.0 (5)	C32—C31—H311	107.5
O5—Si6—C8	106.8 (5)	C45—C31—H311	108.4
C7—Si6—C8	112.3 (7)	C31—C32—O33	107.3 (8)
O5—Si6—C12	108.7 (5)	C31—C32—H322	110.3
C7—Si6—C12	106.9 (7)	O33—C32—H322	110.0
C8—Si6—C12	112.2 (6)	C31—C32—H321	110.5
Si6—C7—H71	109.9	O33—C32—H321	110.0
Si6—C7—H73	108.9	H322—C32—H321	108.7
H71—C7—H73	109.4	C32—O33—C34	115.9 (8)
Si6—C7—H72	110.6	O33—C34—O35	123.8 (9)
H71—C7—H72	109.3	O33—C34—C36	112.9 (9)
H73—C7—H72	108.8	O35—C34—C36	123.3 (9)
Si6—C8—C9	111.4 (10)	C34—C36—C37	122.7 (8)
Si6—C8—C10	110.7 (9)	C34—C36—C44	118.3 (10)
C9—C8—C10	106.4 (12)	C37—C36—C44	119.0 (9)
Si6—C8—C11	109.9 (11)	C36—C37—C38	120.6 (8)
C9—C8—C11	110.4 (12)	C36—C37—H371	119.8

C10—C8—C11	108.0 (13)	C38—C37—H371	119.6
C8—C9—H91	110.3	C37—C38—C39	119.5 (10)
C8—C9—H93	109.9	C37—C38—H381	120.3
H91—C9—H93	108.9	C39—C38—H381	120.2
C8—C9—H92	109.6	C38—C39—N40	120.3 (10)
H91—C9—H92	108.9	C38—C39—C43	120.3 (9)
H93—C9—H92	109.1	N40—C39—C43	119.3 (9)
C8—C10—H101	109.1	C39—N40—O41	119.6 (10)
C8—C10—H103	110.1	C39—N40—O42	118.1 (9)
H101—C10—H103	109.5	O41—N40—O42	122.3 (9)
C8—C10—H102	109.2	C39—C43—C44	119.6 (9)
H101—C10—H102	109.6	C39—C43—H431	120.0
H103—C10—H102	109.4	C44—C43—H431	120.5
C8—C11—H111	110.0	C36—C44—C43	120.9 (10)
C8—C11—H113	109.9	C36—C44—H441	119.9
H111—C11—H113	109.2	C43—C44—H441	119.2
C8—C11—H112	109.5	C31—C45—H452	109.4
H111—C11—H112	109.1	C31—C45—H451	110.2
H113—C11—H112	109.1	H452—C45—H451	109.3
Si6—C12—H121	109.8	C31—C45—H453	109.6
Si6—C12—H123	109.5	H452—C45—H453	109.2
H121—C12—H123	109.7	H451—C45—H453	109.1
Si6—C12—H122	108.8	Si1—C47—C48	109.1 (9)
H121—C12—H122	109.3	Si1—C47—C49	107.8 (10)
H123—C12—H122	109.7	C48—C47—C49	110.5 (16)
C4—C13—N14	111.3 (7)	Si1—C47—C50	109.5 (11)
C4—C13—C18	113.7 (9)	C48—C47—C50	110.8 (12)
N14—C13—C18	110.5 (9)	C49—C47—C50	109.1 (12)

C4—C13—H131	107.1	C47—C48—H482	109.4
N14—C13—H131	106.9	C47—C48—H481	109.6
C18—C13—H131	106.8	H482—C48—H481	109.6
C13—N14—C15	128.2 (9)	C47—C48—H483	109.5
C13—N14—H141	114.3	H482—C48—H483	109.4
C15—N14—H141	114.0	H481—C48—H483	109.4
N14—C15—O16	117.0 (11)	C47—C49—H492	109.7
N14—C15—O46	123.4 (11)	C47—C49—H491	110.1
O16—C15—O46	119.6 (12)	H492—C49—H491	109.1
C15—O16—C17	118.6 (9)	C47—C49—H493	109.6
O16—C17—C18	109.9 (8)	H492—C49—H493	109.1
O16—C17—C31	107.2 (9)	H491—C49—H493	109.1
C18—C17—C31	114.9 (8)	C47—C50—H502	109.5
O16—C17—H171	108.3	C47—C50—H501	109.2
C18—C17—H171	107.8	H502—C50—H501	109.7
C31—C17—H171	108.6	C47—C50—H503	109.5
C17—C18—C13	109.6 (7)	H502—C50—H503	109.5
C17—C18—O19	107.2 (8)	H501—C50—H503	109.4
C13—C18—O19	111.0 (8)	Si1—C51—H512	109.6
C17—C18—H181	109.4	Si1—C51—H511	109.3
C13—C18—H181	109.8	H512—C51—H511	109.4
O19—C18—H181	109.8	Si1—C51—H513	109.6
C18—O19—C20	117.5 (9)	H512—C51—H513	109.2
O19—C20—O21	125.3 (9)	H511—C51—H513	109.7
O19—C20—C22	113.9 (10)	Si1—C52—H522	109.0
O21—C20—C22	120.8 (9)	Si1—C52—H521	110.1
C20—C22—C23	120.5 (8)	H522—C52—H521	109.2
C20—C22—C30	119.9 (10)	Si1—C52—H523	110.0

C23—C22—C30	119.6 (9)	H522—C52—H523	109.1
C22—C23—C24	119.7 (8)	H521—C52—H523	109.4
C22—C23—H231	121.0		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C4—H41···O46^{i}	0.98	2.50	3.318 (17)	141
C17—H171···O28^{ii}	0.98	2.31	3.168 (17)	146
C31—H311···O41^{iii}	0.98	2.54	3.361 (17)	141
C38—H381···O27^{iv}	0.93	2.46	3.310 (17)	151
C51—H513···O21	0.96	2.51	3.376 (17)	150

Symmetry codes: (i) *x*, *y*+1, *z*; (ii) *x*+1/2, *y*+1/2, *z*; (iii) *x*−1/2, *y*−1/2, *z*; (iv) *x*+1/2, *y*+3/2, *z*.

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