Towards the Synthesis of Heterocycle-Containing Natural Products

Hannah Dexter

Thesis submitted to the University of Nottingham

for the degree of Doctor of Philosophy

Abstract

Chapter 1 gives an introduction to ribosomally synthesised and post-translationally modified peptides. The different classes of this group of natural products are described. Examples of linear azol(in)e-containing peptides and cyanobactins are given, along with more detail about these classes of peptides and examples of their chemical synthesis.

Chapter 2 explains the importance of the natural product goadsporin **64**, along with the retrosynthesis and a review of methods to synthese oxazoles, thiazoles and dehydroalanines. The first total synthesis of goadsporin **64** is then reported, demonstrating the use of rhodium catalysis to construct the four oxazole rings. Synthesis of the *N*-terminal fragment **78** validated methods for incorporating the sensitive enamide functionality, and removal of the necessary protecting group. These methods were then applied to the full structure to complete the total synthesis.

Chapter 3 describes work carried out towards the total synthesis of the wewakazole natural products, again using rhodium catalysis methodology. The structures of wewakazole A **65** and wewakazole B **66** share a largely peptidic fragment **267**, differing only by the bis-oxazole fragments **266** and **268**, allowing the synthesis of two natural products via three main fragments. Reported herein is the synthesis of the bis-oxazole fragments **266** and **268** of wewakazole A **65** and B **66**.

Acknowledgements

Firstly, thanks to my supervisor Professor Christopher Moody for providing me with the opportunity to work on this challenging project and for his support along the way. Thanks to all members of C13 for an entertaining three years with rarely a dull moment, but full of cake and tea. Particular thanks to Drs Andrew Nortcliffe, Russ Kitson, Emma Packard, Tim Birkinshaw, Gemma Geary, Alexandre Pradel, Alex Murray and Steve Wales who all provided chemical help and advice. Biggest thanks goes to Dr Martyn Inman for reading this thesis and general support over the last three years, particularly by providing cute baby pictures and custard creams.

Thanks also to all the technical staff in Chemistry who keep the department running. Thanks to Tom Mcinally and Magda Foreiter for help with the LCMS and HPLC. Particular thanks to Dr Huw Williams for all his vital NMR help and knowledge.

Finally, thanks to all my family and friends who have been patient and kind with me over the last three years. Special thanks to my Mum and Dad.

Contents

Abbreviations

Alloc	allyloxycarbonyl
AMP	adenosine monophosphate
BRSM	based on recovered starting materials
Da	daltons
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N,N*-diisopropylethylamine
DMP	Dess-Martin periodinane
DQF	double quantum filtered
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
FDLA	1-fluoro-2,4-dinitrophenyl-5-leucinamide
FMN	flavin mononucleotide
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
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HOOBt	3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one
LAP	linear azol(in)e containing peptide
MeOxz	methyl oxazole
NOE	nuclear Overhauser effect
Oxz	oxazole
p-ABSA	4-(acetamido)benzenesulfonyl azide
pfm	perfluorobutyramide
PG	protecting group
QF	quantum filtered

RiPP	ribosomally synthesised and post-translationally modified peptide
SPPS	solid-phase peptide synthesis
TBAT	tetrabutylammonium difluorotriphenylsilicate
Teoc	trimethylsilylethoxycarbonyl
Thiaz	thiazole
TMSE	trimethylsilylethyl
TOMM	thiazole/oxazole-modified microcin
TosMIC	toluenesulfonylmethyl isocyanide

1. Introduction

1.1 Ribosomally synthesised and post-translationally modified peptides

Natural products have long played an important role in furthering our understanding of the biological world. Studying the structure and role of natural products has led to many medical and agro-chemical developments in the last century.

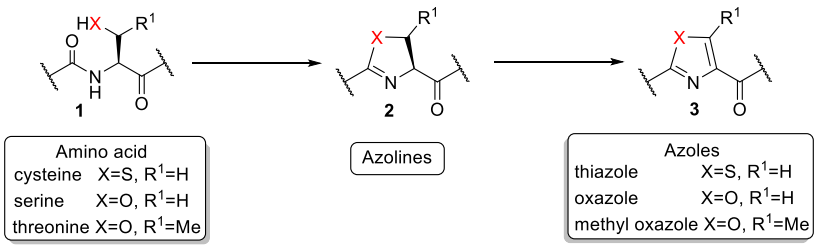
Recent developments in genome mining and sequencing have given rise to a huge increase in the number of known ribosomally synthesised and post-translationally modified peptides (RiPP)s, a class of natural products seen in all domains of life.[1,2] RiPPs cover a vast chemical space due to the diversity of the modifications, all carried out after the ribosomal synthesis of the leader peptide. The ribosomal synthesis of the precursor peptide is the singular uniting factor between all members of this class of natural products. Analogously, non-ribosomal peptides (NRPs) are synthesised by an array of modularly organised non-ribosomal peptide synthetase enzymes in a ribosomally independent pathway.[3]

In comparison to unmodified peptides, post-translational modifications allow for an enhanced chemical stability and biological activity. These features make RiPPs attractive as potential therapeutics.[4]

Members of the RiPPs include but are not limited to lanthipeptides, lasso peptides, bottromycins and microcins. Each class within the group has a characteristic structure or topographical feature. A limit of 10 kDa is given to RiPPs to exclude ribosomally synthesised and post-translationally modified proteins.[1]

1.2 Thiazole/oxazole-modified microcins (TOMMs)

TOMMs are a class of RiPP defined as having azol(in)e containing structure deriving from serine, threonine and cysteine (Scheme 1). These amino acid starting materials **1** are post-translationally modified into azolines **2** and azoles **3**. Both goadsporin 64 and wewakazole A **65** and B **66** fall into the TOMM category as they contain azole features.



Scheme 1. Mechanism of azol(in)e formation in TOMM natural products.

TOMMs all share similar gene clusters that contain an ATP-dependent cyclodehydratase. Non-ribosomally synthesised peptides can also contain the same azol(in)e functionalities, however the enzymatic machinery that carries out these transformations shares no similarity to RiPPs with reference to the

order of amino acids, demonstrating convergent evolution. The classes within TOMMs include, but are not confined to, the bottromycins, thiopeptides, cyanobactins and linear azol(in)e-containing peptides (LAPs).[5]

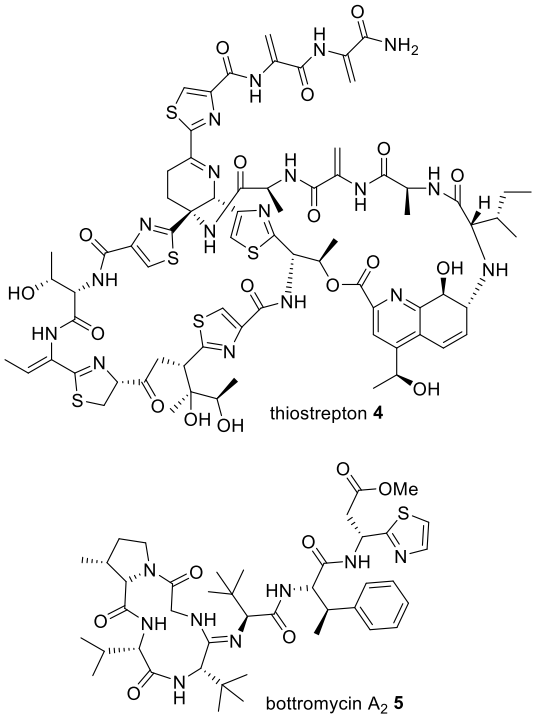


*Figure 1. Structures of thiostrepton **4** and bottromycin A_2 **5**.*

Examples of TOMMs include thiostrepton **4** and bottromycin A_2 **5** (Figure 1). Thiostrepton **4** is a thiopeptide with a wide variety of post-translational modifications including dehydro-amino acids, thiazoles, a thiazoline, a dihydroxylated isoleucine, a tetrahydropyridine ring and a quinaldic acid type functional group. The defining feature of a thiopeptide is the nitrogen-containing six-membered ring. Thiopeptides are of interest due to their anti-bacterial biological activity, allowing them to inhibit protein synthesis in Gram-positive bacteria. The total synthesis of thiostrepton **4** was published in 2005 by Nicolaou *et. al*.[6,7]

Bottromycin A_2 **5** is a member of the bottromycin group, a series of compounds named after *Streptomyces bottropensis DSM 40262* from which they were originally isolated. The bottromycins contain a characteristic macrocyclic amidine with a *C*-terminal decarboxylated thiazole.[1] These compounds are also decorated with additional methyl groups as seen by bottromycin A_2 **5**. The structures of the bottromycins were only definitively assigned following the total synthesis of bottromycin A_2 **5** in 2009.[8] The bottromycins are of interest due to their activity against vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).

1.3 Linear azol(in)e-containing peptides

A LAP is a TOMM which hasn't undergone macrocyclisation. To date there are four examples of LAPs which have had full structure elucidation; microcin B17 **6**, the plantazolicins **15**, the azolemycins **35** and goadsporin **64**. Streptolysin S and trifolitoxin are also thought to belong to the LAP family due to similarities in biosynthetic pathways, but their exact structures have not yet been elucidated.[1,9] There are believed to be other members of the LAP class, the discovery of which is facilitated by mining of genome sequences.[9]

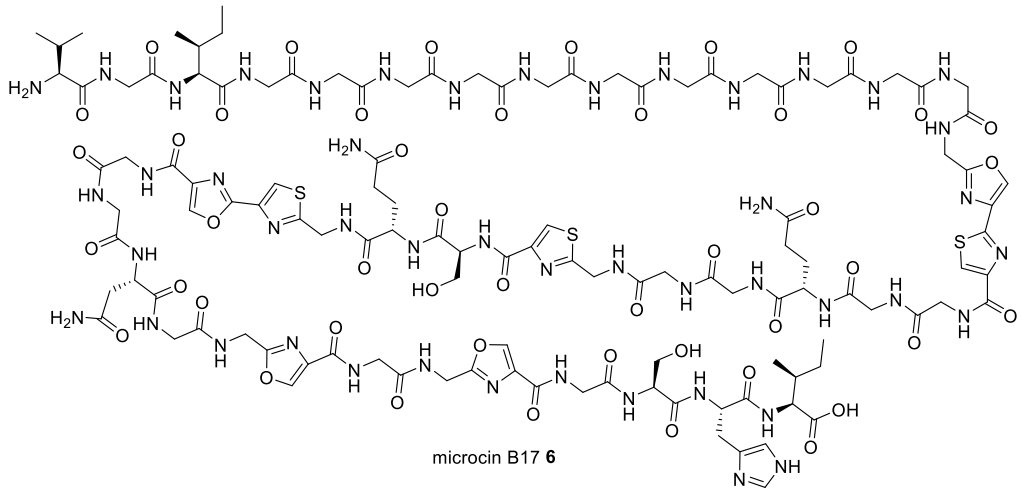
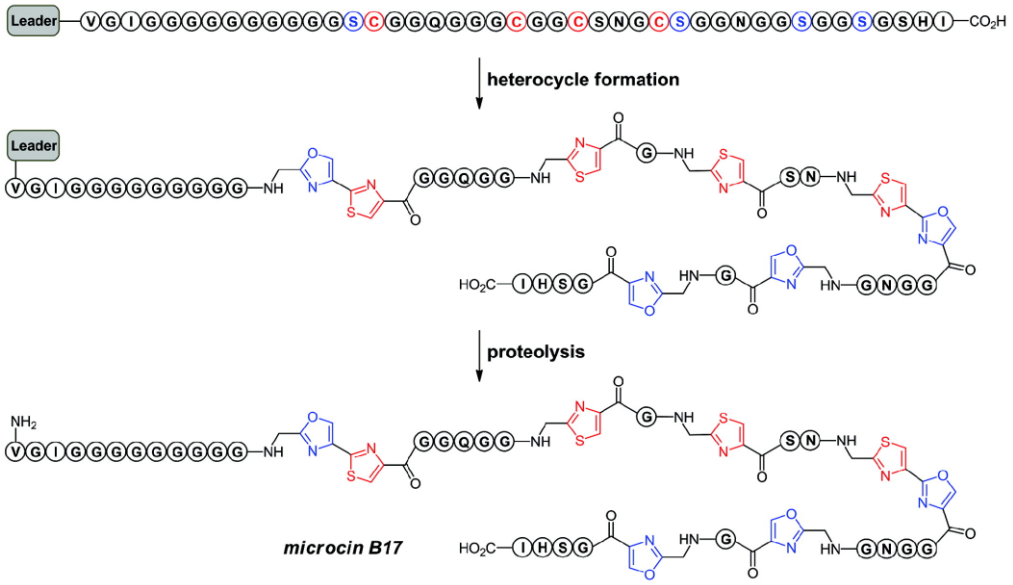


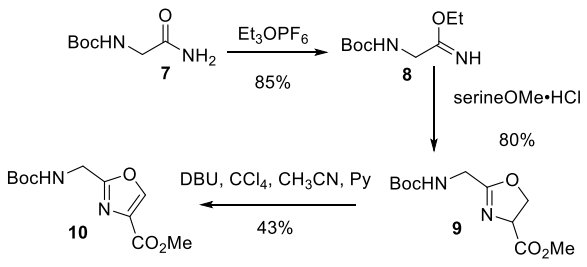
Figure 2. Structure of microcin B17 ***6****.*

Microcin B17 **6** is a LAP produced by multiple *Escherichi coli* strains and demonstrates potent antibiotic activity against Gram-negative bacteria by inhibiting DNA gyrase (Figure 2).[10] The biosynthetic route to microcin B17 **6** was first reported by Walsh *et al*. in 1996. Ribosomal synthesis of a McbA precursor peptide is followed by post-translationally modification by a McbB, McbC and McbD synthase complex to form the heterocycles, before final proteolysis to give microcin B17 **6** (Scheme 2).[11,12] The biosynthesis of other LAPs follows a similar pathway, a further feature shared between natural products in this class.



Scheme 2. Biosynthesis of Microcin B17 ***6****. Reprinted with permission from* (*C. T. Walsh, S. J. Malcolmson, and T. S. Young,* ACS Chem. Biol.*, 2012,* ***7****, 429–442*). *Copyright* (*2012*) *American Chemical Society.*

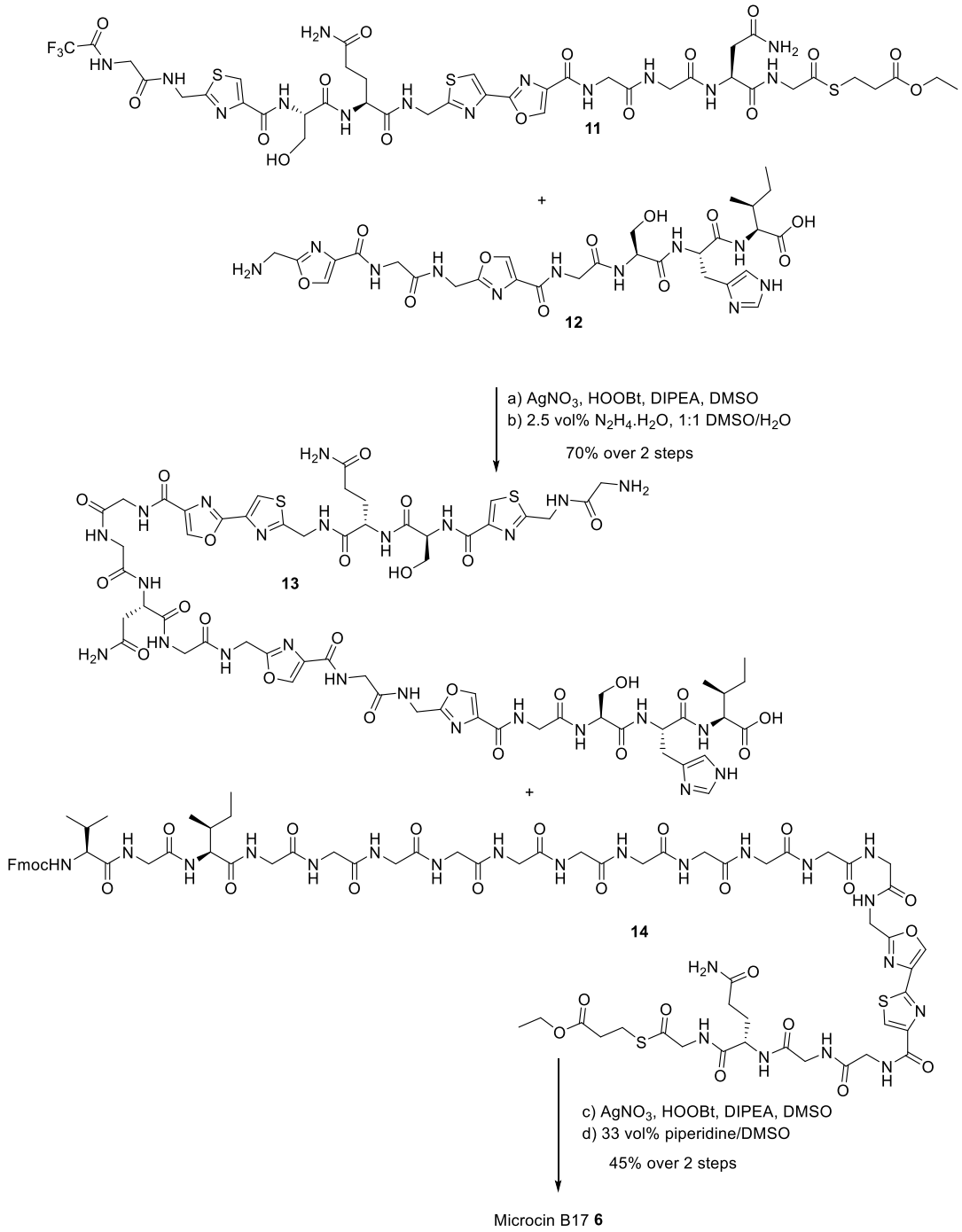
Microcin B17 **6** is a 43 residue peptide containing three thiazoles and four oxazoles. The total synthesis of microcin B17 **6** has been reported twice, by Jung *et al*. in 1996 and by Payne *et. al*. in 2014.[13–15] The first synthesis by Jung utilised solid-phase peptide synthesis (SPPS).[13] The thiazole building blocks were synthesised using the Hantzsch thiazole synthesis. The oxazoles were prepared by treating a carboxamide **7** with triethyloxonium hexafluorophosphate to give imine **8**, followed by the addition of serine to give oxazoline **9**, before final oxidation to oxazole **10** (Scheme 3).



Scheme 3. Synthesis of oxazole ***10*** *by Jung et. al.*

Microcin B17 **6** contains extended residues of glycine, which led to low yields during linear synthesis. Therefore, the authors used building blocks such as Fmoc-Gly-Gly-Gly-OH to access higher yields.

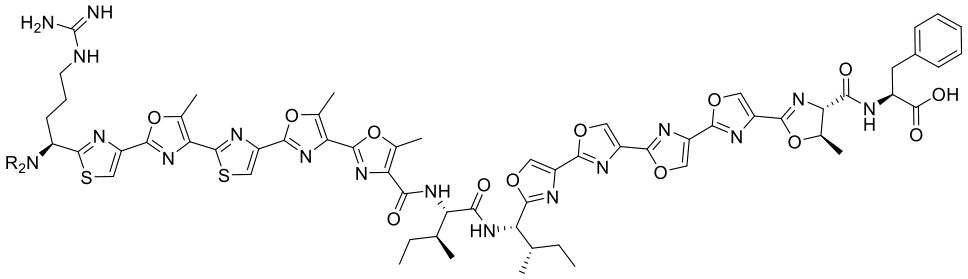
The more recent synthesis by Payne utilised a fragment approach by disconnecting microcin B17 **6** into three fragments **11**, **12** and **14**, each synthesised by SPPS (Scheme 4).[14] The fragments were joined using two solution phase Ag(I) assisted chemical ligation reactions, before final deprotection. The authors were able to extend this work to the synthesis of microcin B17 **6** truncates and analogues; however, these compounds demonstrated reduced activity *in vivo*.[15]



Scheme 4. Synthesis of microcin B17 ***6*** *by Payne et. al.*

Plantazolicins A and B **15** were isolated in 2011 from *Bacillus amyloliquefaciens FZB42* (Figure 3).[16,17] Plantazolicin A **15a** is known to have selective antibiotic activity against nine *Bacillus* strains. The total synthesis of plantazolicin A **15a**

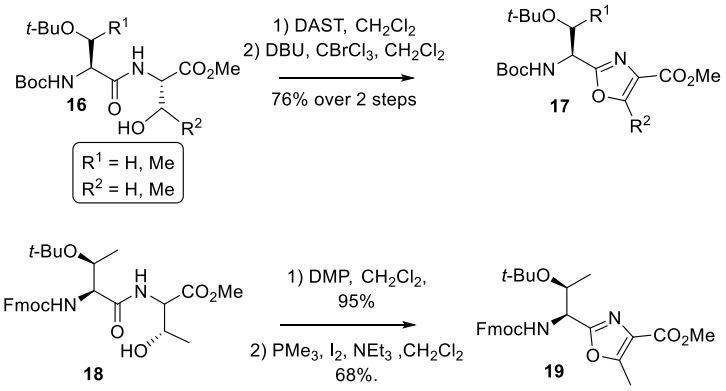
has been completed three times, by Süssmuth, Ley and Moody. The synthesis by Ley included the synthesis of plantazolicin B **15b**.



Plantazolicin A, R= Me **15a**
Plantazolicin B, R=H **15b**

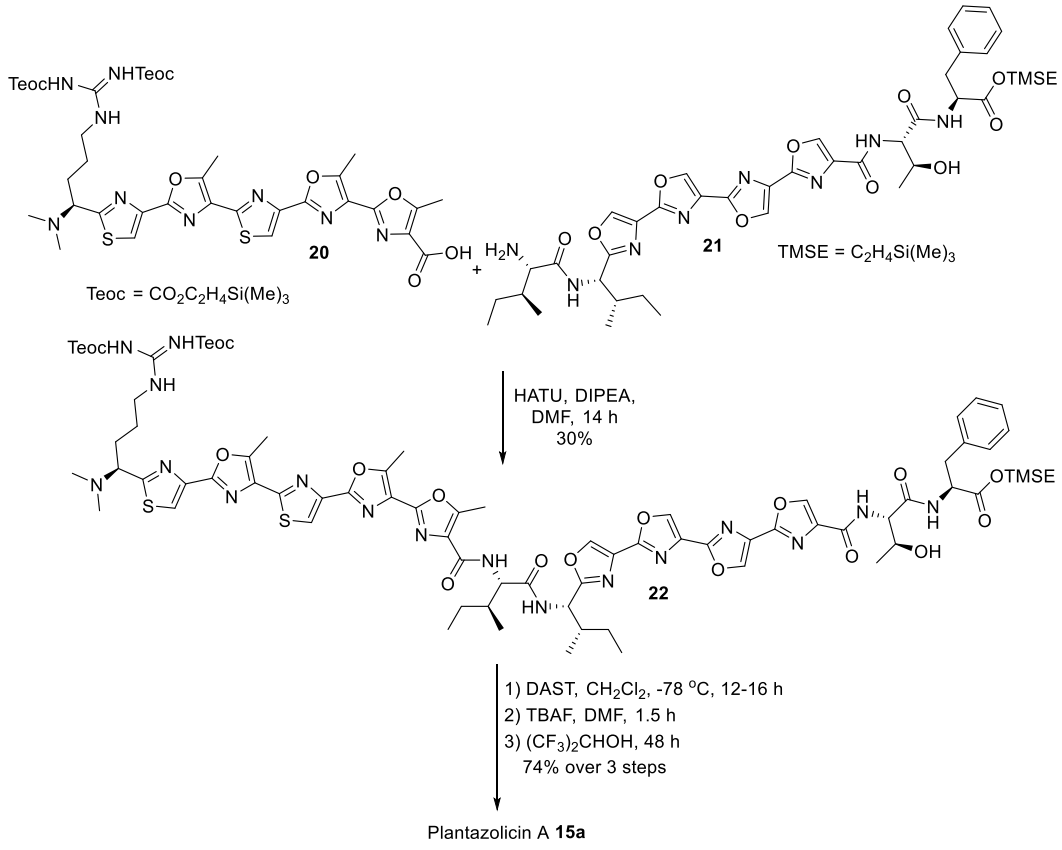
*Figure 3. Structure of the plantazolicins **15**.*

The first synthesis by Süssmuth of plantazolicin A **15a** in 2013 took advantage of the central amide bonds to give two intermediates **20** and **21**.[18] The two intermediates could then be deconstructed into the corresponding heterocyclic building blocks. Both thiazoles were synthesised using the Hantzsch synthesis. In general, the oxazoles were synthesised via cyclodehydration of threonine or serine dipeptides **16** followed by oxidation to give the oxazole **17** (Scheme 5). However, for the synthesis of oxazole **19**, the oxidation step was low yielding, hence they utilised the Gabriel-Robinson oxazole synthesis with Wipf's modification to give the required oxazole **19** in good yield from dipeptide **18**.



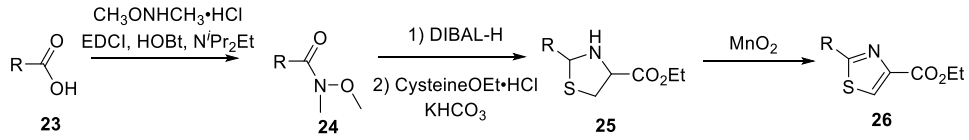
Scheme 5. Synthesis of oxazoles by Süssmuth.

The final steps in the synthesis were amide coupling of **20** and **21** to give peptide **22**, installation of the sensitive oxazoline moiety, and deprotection of the silyl protecting groups to give plantazolicin A **15a** (Scheme 6).



*Scheme 6. Final steps in synthesis of plantazolicin A **15a** by Süssmuth.*

In the synthesis by Ley, the thiazoles were synthesised using a route which avoided the use of sulfurating agents.[19] Thus, both thiazoles were synthesised starting from the carboxylic acid of the preceding amino acid (Scheme 7). The carboxylic acid **23** was transformed to the Weinreb amide **24**, followed by reduction using DIBAL to the corresponding amino aldehyde. This was then immediately condensed with cysteine ethyl ester hydrochloride to give thiazolidine **25**. Oxidation to the required thiazole **26** proceeded with the use of manganese dioxide.

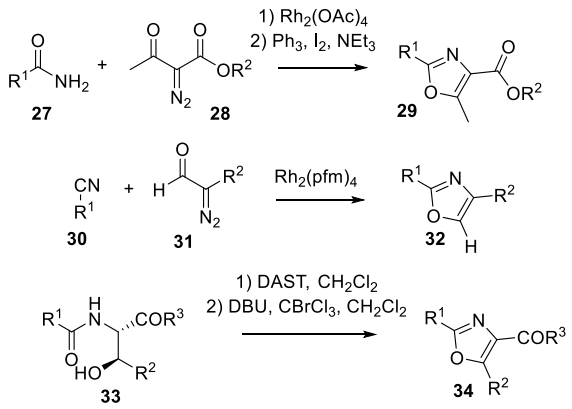


*Scheme 7. Synthesis of thiazoles by Ley during the total synthesis of plantazolicin **15**.*

Ley used the same method for the synthesis of the oxazoles in plantazolicin **15** as shown in Scheme 5 for the conversion of **16** into **17**, however Deoxo-Fluor® was used for the cyclodehydration step rather than DAST.[19]

In the most recent synthesis by Moody, plantazolicin A **15a** was again disconnected at a central amide bond to give two fragments. In this synthesis, the thiazoles were synthesised by Hantzsch reaction. The oxazoles were synthesised by a number of reactions (Scheme 8). Rhodium catalysis was used to give methyl oxazole **29** from amide starting material **27**, and oxazole **32** from nitrile starting material **30** by reaction with diazo compounds **28** and **31** respectively. Oxazoles were also synthesised from serine and threonine

starting materials **33** by cyclisation and oxidation of the intermediate oxazoline to give the desired oxazole **34**.



*Scheme 8. Synthesis of oxazoles in plantazolicin A **15a** by Moody.*

During the synthesis of oxazoles, using the conditions as shown for the conversion of **27** and **28** into **29**, the authors found the oxazole product **29** inseparable from the triphenylphosphine oxide by-product. This was successfully overcome by the use of polymer-supported triphenylphosphine which could simply be filtered from the reaction mixture.

The most recent LAPs to be characterised are the azolemycin family **35** reported in 2015 by Challis *et al* (Figure 4).[20] These LAPs show an additional feature with oxime functionalities which are formed during post-translational modification. Azolemycin B **35b** and C **35c** were shown to have moderate anti-cancer activity, making them an exciting target for total synthesis.

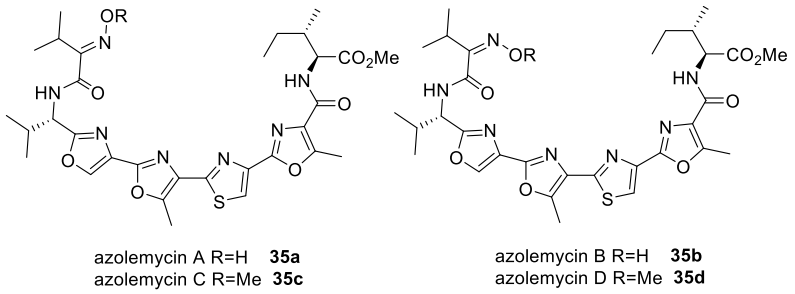
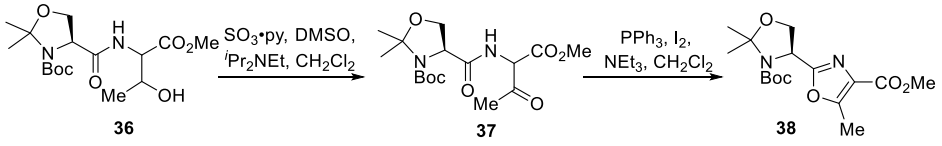


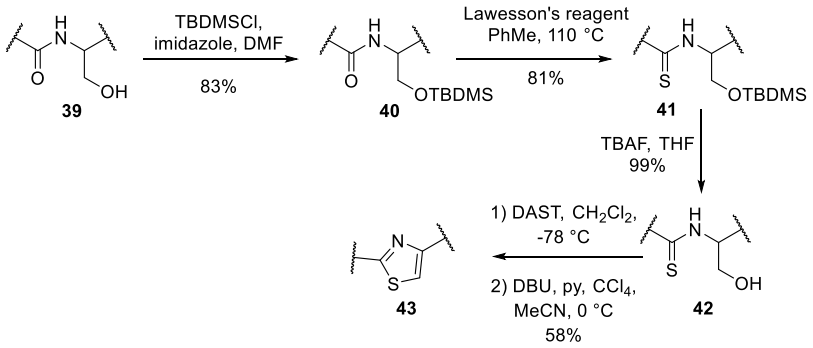
*Figure 4. Structure of the azolemycins **35**.*

The total synthesis of the azolemycins **35** was published in 2016.[21] The synthesis required oxazole **38**, synthesised from alcohol **36**. Compound **36** was oxidised using Parikh–Doering conditions to give ketone **37**, which underwent cyclodehydration to oxazole **38** in a 32% yield over the two steps (Scheme 9).[21,22]



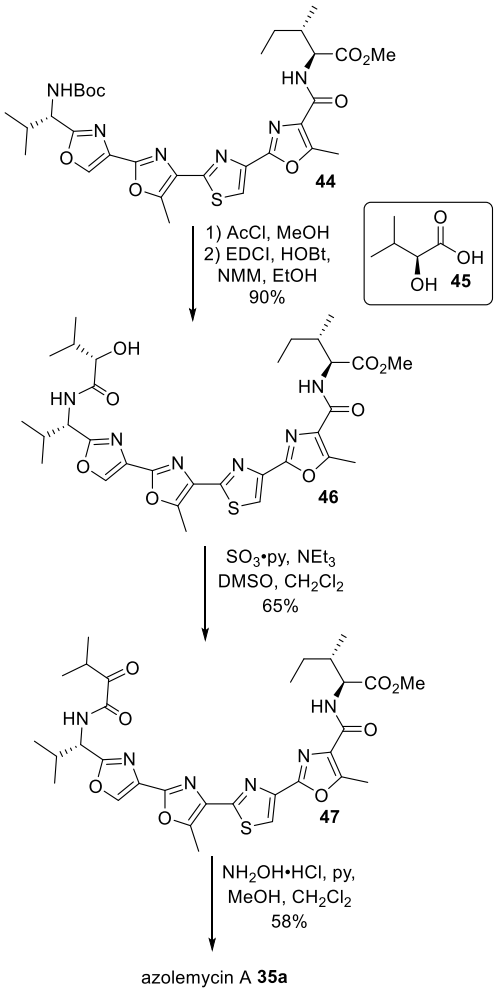
*Scheme 9. Synthesis of oxazole **38** by Fox.*

The thiazole functionality was synthesised via a rather lengthy route (Scheme 10). Firstly, alcohol **39** was protected to give **40**, before the amide could be converted into thioamide **41**. Deprotection gave alcohol **42**, which underwent cyclodehydration and oxidation to give thiazole **43**.



*Scheme 10. Synthesis of thiazole **43** during azolemycin **35** total synthesis.*

The final steps in the total synthesis of azolemycin A **35a** were Boc deprotection of peptide **44** and coupling to 2-hydroxy-3-methylbutyric acid **45** to give **46** (Scheme 11). Alcohol **46** was then oxidised to ketone **47**, followed by reaction with hydroxylamine to give azolemycin A **35a**. Azolemycin D **35d** was synthesised by the same conditions with *O*-methylhydroxylamine replacing hydroxylamine. At this point, the authors found the geometric isomers to be inseparable (mixture of azolemycin A **35a** and B **35b**, and of C **35c** and D **35d**).



Scheme 11. Final steps in the total synthesis of azolemycin A.

1.4 Cyanobactins

Cyanobactins can be classed within the TOMM group in which LAPs also reside. The name cyanobactin denotes a RiPP isolated from a cyanobacterium. In general, cyanobactins are N-C macrocyclic peptides, however genome mining has led to the identification of linear cyanobactins.[23] The cyanobactin family are structurally diverse, including thiazolines, thiazoles, oxazolines, oxazoles,

disulfide bridges, D-amino acids, prenylation, geranylation and occasional *N*-methylation.[24]

The first cyanobactins to be discovered were ulicyclamide **48** and ulithiacyclamide **49**, isolated from the tunicate *Lissoclinum patella* (Figure 5).[25] It was later indentified that the cyanobacterium *Prochloron* was a symbiont of the tunicate, and was itself responsible for the synthesis of the cyanobactins.[26,27] Cyanobacteria are known occupy both aqueous and terrestrial habitats as well as having the ability to survive extreme conditions such as low or high temperatures, low or high salinity and UV radiation.

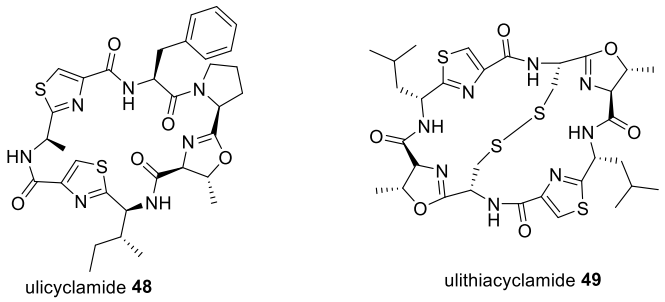
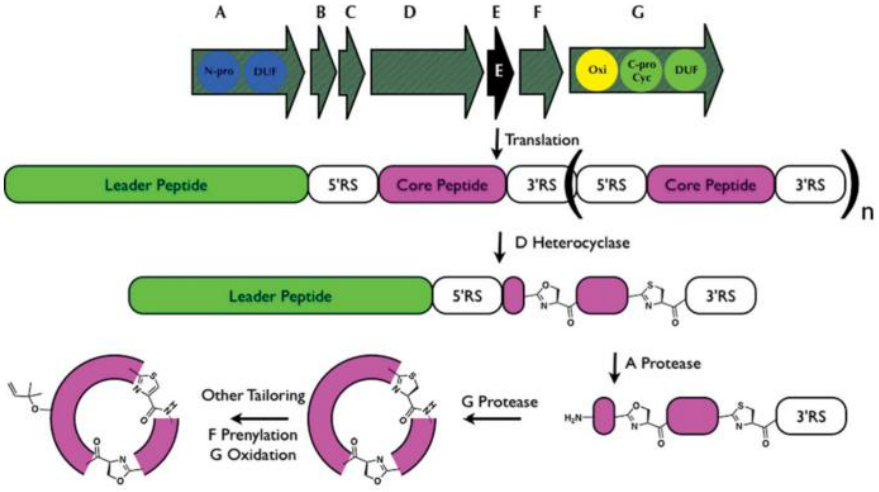


*Figure 5. Structures of ulicyclamide **48** and ulithiacyclamide **49**.*

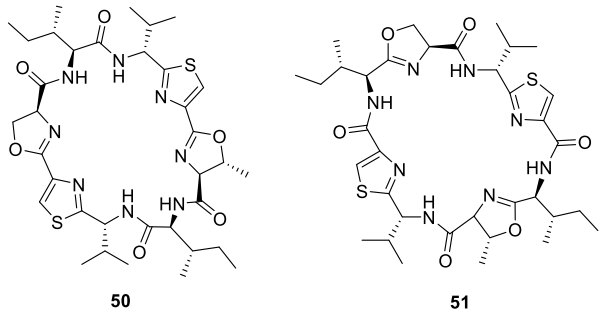
The biosynthesis of cyanobactins is similar to that of LAPs with an additional macrocyclisation step. A precursor peptide, designated the E-peptide, contains the leader peptide, core peptide and both *N*- and *C*-terminal recognition sequences (Scheme 12).[1,28] If present, a D-protein can then modify the E-peptide, by cyclising cysteine, threonine and serine to give thiazoline and oxazoline moieties. An A-protease then removes the *N*-terminal recognition sequence followed by a G-protease removing the *C*-terminal recognitions sequence. The G-protease is then responsible for catalysing macrocyclisation.

At this stage, other modifications can take place, such as prenylation or oxidation of azolines to azoles.



Scheme 12. Biosynthetic pathway for cyanobactins. Reprinted with permission from (W. A. van der Donk et al., Nat. Prod. Rep.*, 2013, **30**, 108–160). Copyright* (*2013*) *The Royal Society of Chemistry.*

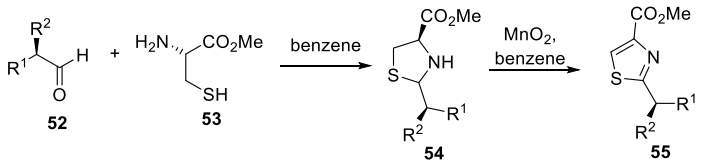
The patellamides and trunkamide are archetypal examples of cyanobactins. Patellamides A-C were first reported in 1982 by Ireland *et al*. as antineoplastic cyclic peptides.[29] In 1985, Hamada *et al.* described the total synthesis of the proposed structure of patellamide A **50**, showing the original structure to be incorrect.[30] Synthesis of a revised structure **51** was shown to match the data for the isolated natural product, by reordering the residues in the original structure **50** (Figure 6).



50 51

*Figure 6. Proposed structure **50** and revised structure **51** of patellamide A.*

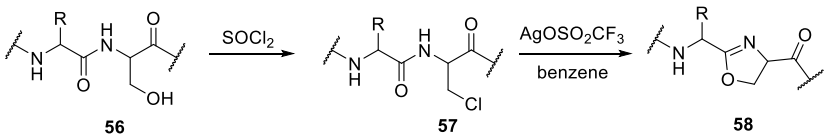
During the synthesis of **50** and **51**, the thiazoles were formed by condensation of an amino aldehyde **52** with cysteine **53** to give thiazolidine **54**, which was oxidised by manganese dioxide to give the thiazole **55** (Scheme 13).[31,32]



52 **53** **54** **55**

*Scheme 13. Synthesis of thiazoles in patellamide A structures **50** and **51** from amino aldehyde **52**.*

Synthesis of the oxazolines in patellamide A **50** and **51** was carried out from a serine-based starting material (Scheme 14). The starting material **56** was treated with thionyl chloride to give alkyl chloride **57** followed by silver trifluoromethanesulfonate to give oxazoline **58**.[30]



56 **57** **58**

*Scheme 14. Synthesis of oxazoline **58** in patellamide A **50** and **51**.*

Trunkamide **59**, a cyanobactin first isolated in 1996, underwent a series of proposed structures before the structure was finally confirmed by Wipf in 2000, showing the thiazoline had D-stereochemistry (Figure 7).[33]

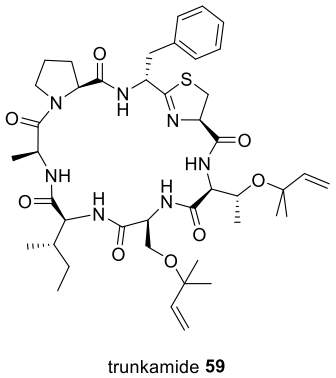
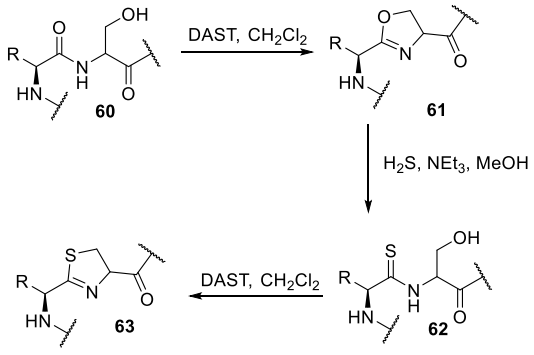


*Figure 7. Structure of trunkamide **59**.*

Wipf made a series of trunkamide stereoisomers before the correct structure was identified. During the synthesis of these stereoisomers, an interesting oxazoline to thiazoline strategy was employed. A serine starting material **60** underwent cyclodehydration to oxazoline **61**, followed by treatment with hydrogen sulfide and base, to give the thioamide **62**. Finally, treatment with DAST gave the desired thiazoline **63** (Scheme 15).[34]



*Scheme 15. Synthesis of thiazoline **63** by Wipf.*

1.5 Project Aims

This Thesis demonstrates the use of rhodium catalysis to facilitate the synthesis of natural products of structural and biological interest. Thus, described herein is the total synthesis of goadsporin **64**,[35,36] and the synthesis of the bis-oxazole fragments in wewakazoles A **65**[37] and B **66**,[38] as shown in boxes (Figure 8). The oxazole heterocycles will be synthesised using rhodium catalysis. Goadsporin **64** is of scientific interest due to its antibacterial activity and unique structure.The wewakazoles A **65** and B **66** are of significance due to their cytotoxic properties, leading to their potential use as anticancer agents.

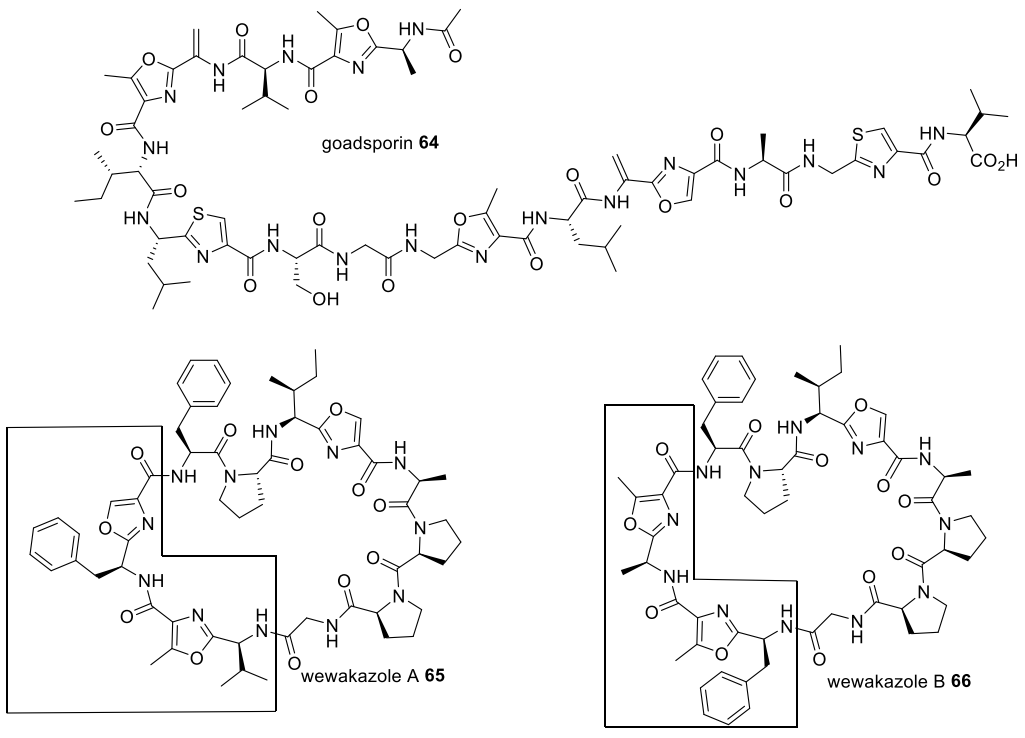


*Figure 8. Structures of goadsporin **64** and the wewakazoles A **65** and B **66**.*

2. Goadsporin

2.1 Goadsporin Biosynthesis and Significance

Goadsporin **64** is a secondary metabolite from the bacterium *Streptomyces sp. TP-A0584,* a soil-derived actinomycete, and was first isolated, purified and characterised in 2001 by Onaka and coworkers.[35,36] It is a linear 19 residue peptide containing two thiazoles, three methyl oxazoles, one oxazole and two dehydroalanine residues.

The isolation chemists were screening streptomycetes for compounds that prompted secondary metabolism when they found an active substance, which they named goadsporin **64** for its ability to encourage sporulation.[35] After fermentation of the producing strain, the culture broth was subjected to purification by reverse phase column chromatography, normal phase silica gel, size exclusion and reverse phase silica chromatography to give pure goadsporin **64**.

The structure determination of goadsporin **64** included several stages.[36] Firstly, extensive NMR spectroscopic analysis was carried out, including 2D analysis to define the amino acids within goadsporin **64**, and give connectivity between residues, thereby providing partial structures. MS/MS analysis was then used to determine the sequence of the partial structures. MS/MS analysis is a useful tool for determining peptide structure as peptides fragment in an ordered

manner.[39] MS/MS analysis was carried out in both the positive and negative modes and a further study functionalised the *C*-terminal with diaminoethane before positive MS/MS analysis. Finally, the stereochemistry of the amino acids was determined using Marfey's method (Figure 9).[40,41] Goadsporin **64** was hydrolysed using acid and derivatised using L- and D/L-FDLA. HPLC analysis of the derivatives confirmed the amino acids in goadsporin **64** to be of L-stereochemistry with no D-isomers detected. This work was also able to confirm the presence of isoleucine rather than *allo*-isoleucine. Therefore, the structure of goadsporin **64** was confirmed to be as shown in Figure 8.

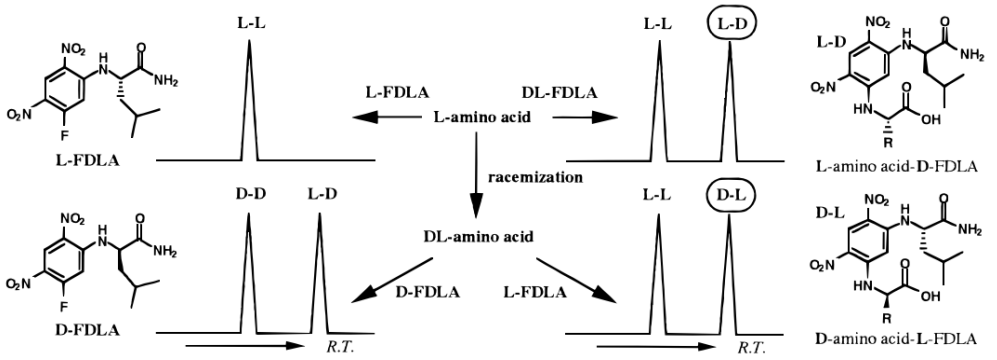
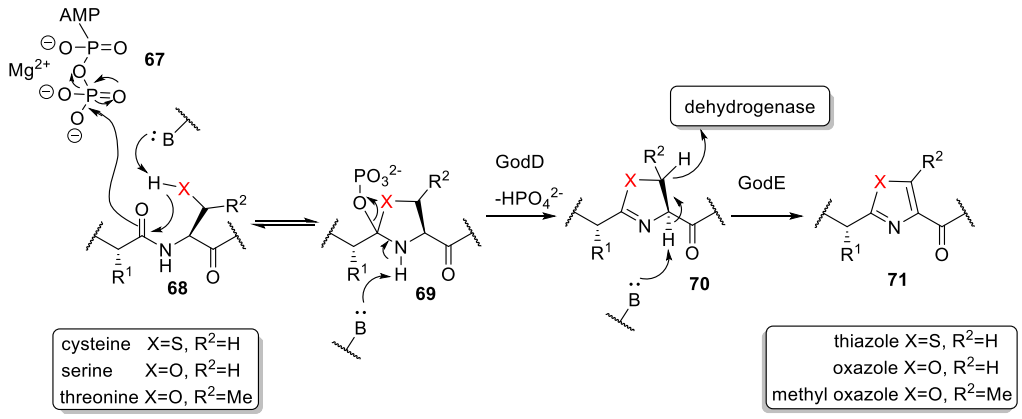


Figure 9. Marfey's method to determine stereochemistry. Reprinted with permission from (*K. Fujii, Y. Ikai, H. Oka, M. Suzuki, and K. Harada,* Anal. Chem.*, 1997, **69**, 5146–5151). Copyright* (*1997*) *American Chemical Society.*

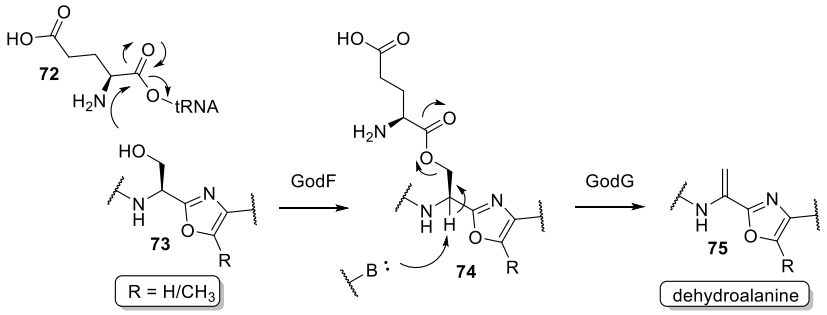
The biosynthesis of goadsporin **64** proceeds by ribosomal synthesis of a parent peptide on which post-translational modifications are carried out by various 'God' genes, which are specific to goadsporin **64**, of which there are GodA to GodH (Scheme 18). These modifications occur to form the methyl oxazoles from threonines, the unsubstituted oxazole from serine and the thiazoles from cysteines (Scheme 16).[12,42,43] Synthesis of the heterocycles begins with

deprotonation of the side chain **68**, followed by addition to the amide carbonyl to give a phosphorylated tetrahedral intermediate **69**.[5,44] The resulting intermediate **69** undergoes a deprotonation-elimination sequence to give the corresponding (methyl) oxazoline or thiazoline **70**. A further deprotonation/elimination gives the desired aromatic heterocycle **71**, assisted by a flavin mononucleotide (FMN) dependent dehydrogenase.[45]



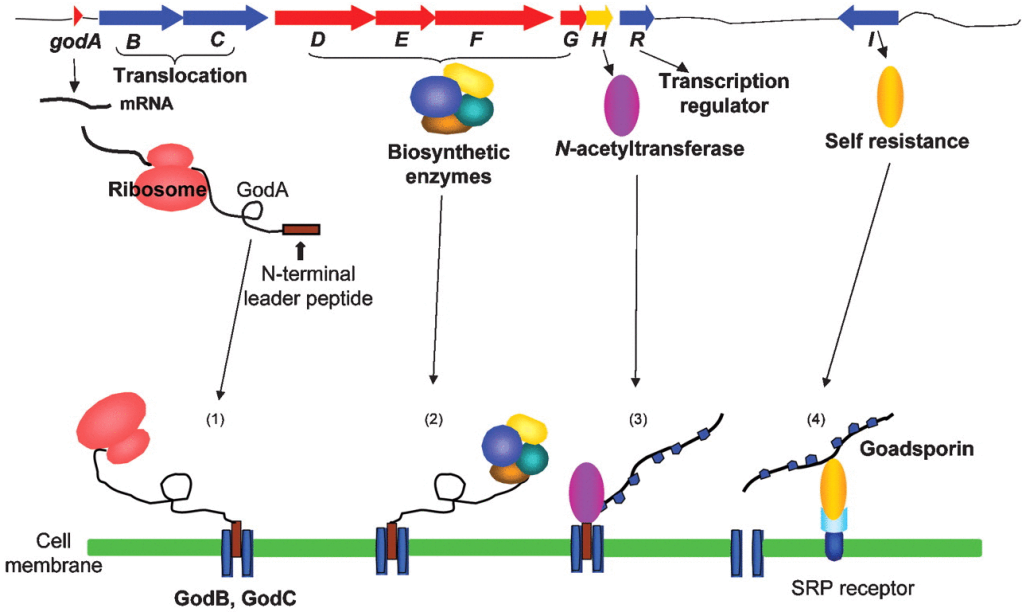
*Scheme 16. Biosynthesis of the heterocycles in goadsporin **64**.*

A recent investigation by Onaka *et al*. provided an insight into the origin of the dehydroalanines in goadsporin **64**.[46] Their work suggests the dehydroalanines are formed through the glutamation of serine **73** by formation of ester **74**, followed by elimination of the glutamate to give dehydroalanine **75** (Scheme 17). The authors also propose the adjacent azole is required for dehydroalanine formation, hence why the serine which is not adjacent to an azole in goadsporin **64** is unaffected by this dehydration process.



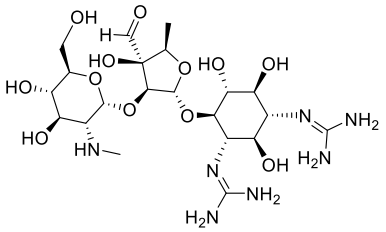
*Scheme 17. Biosynthesis of the dehydroalanines in goadsporin **64**.*

Investigations into the biosynthesis of goadsporin **64** have shown that the synthesis originates with godA, a structural gene, which is translated to give a 49-residue precursor peptide.[47] The leader peptide is transported to the cell membrane and undergoes cyclisation and dehydration, catalysed by GodD, GodE, GodF and GodG genes, to give the heterocycles and dehydroalanines (Scheme 18).[48] The peptide is then degraded by GodB, GodC or other peptidase enzymes, before final *N*-terminal acetylation is carried out by the GodH gene. The biosynthetic machinery which produces goadsporin **64** has also been modified by site-directed mutagenesis and used to produce a series of analogs of goadsporin **64**.[49] This was carried out by modification of the GodA amino acid sequence to give analogues varying from goadsporin **64** by one residue. The authors remark on the biological activity of selected analogues and comment that the biosynthetic machinery could be applied to the heterocyclisation of other peptides.



Scheme 18. Biosynthetic pathway for goadsporin ***64****. Reprinted with permission from* (*H. Onaka, M. Nakaho, K. Hayashi, Y. Igarashi, and T. Furumai,* Microbiology*, 2005, 151, 3923–3933*). *Copyright* (*2005*) *Society for General Microbiology.*

Goadsporin **64** is of scientific interest due to its biological activity. Actinomycetes bacteria, the order from which *Streptomyces sp. TP-A0584* is derived, are of significant interest due to their prevalence for containing biologically active compounds. By 2005, 45% of biologically active microbial metabolites were isolated from actinomycetales and of these >10,000 metabolites, 34% were isolated specifically from the *Streptomyces* genus.[50] In the search for new compounds with biological interest, these bacteria are therefore of particular interest. For example, streptomycin **76** was isolated from *Streptomyces griseus* in 1944, and was the first drug used in the treatment of tuberculosis (Figure 10).[51]



streptomycin **76**

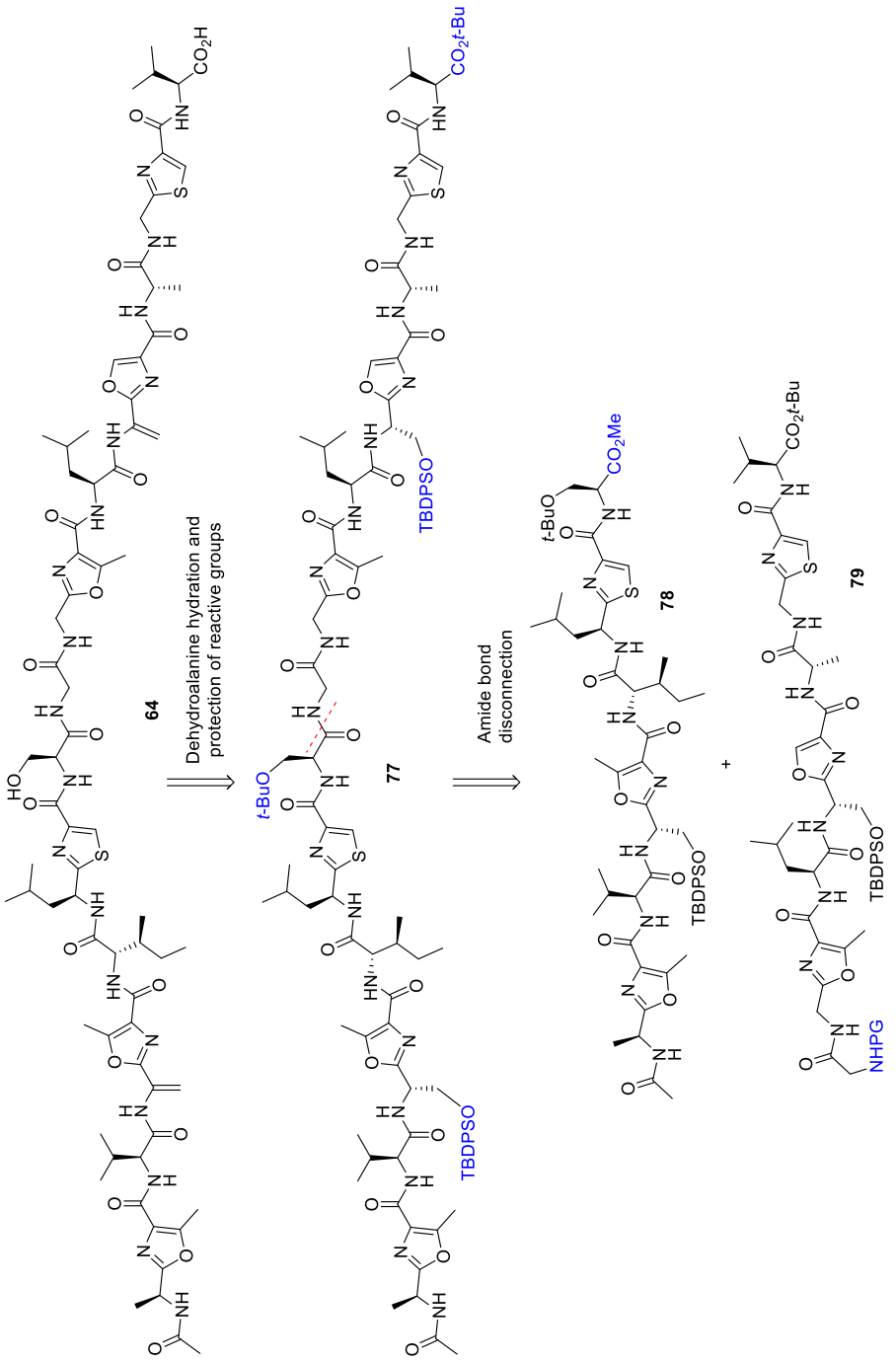
*Figure 10. The structure of streptomycin **76**.*

Goadsporin **64** stimulates secondary metabolism and sporulation in actinomycetes.[35] The molecular target of goadsporin **64** is thought to be specific to streptomycetes, but as yet is unidentified, as the compound does not show activity against mammalian cells or other organisms.[35] Goadsporin **64** interestingly shows no activity against its producing strain. Goadsporin **64** shows a concentration dependent activity on streptomycetes. At low concentrations, goadsporin **64** promotes spore formation in 32 streptomycetes strains and pigment production in 20 out of the 42 strains tested, whereas at high concentrations goadsporin **64** inhibits growth in 32 out of the 42 strains.[35] In the same study Onaka *et al*. suggest that goadsporin **64** may have potential use as an agrochemical due to its antibiotic activity against *Streptomyces scabies*, the bacteria which causes potato scab, against which it has an MIC of 0.2 µg/mL.[35]

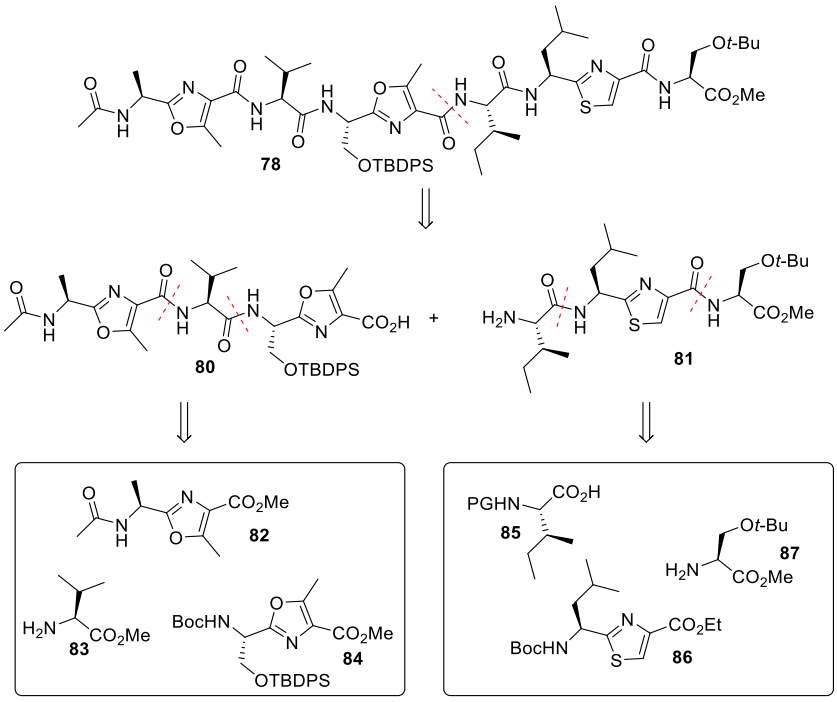
2.2 Proposed Synthetic Route

Our retrosynthetic analysis of goadsporin **64** starts with the hydration of the dehydroalanines to give serine residues (Scheme 19). Late stage introduction of the dehydroalanines was planned due to the potential instability of these enamides. The hydrated dehydroalanines will be protected with silyl protecting groups. The unmodified serine and *C*-terminal carboxylic acid will be orthogonally protected, as a *t*-butyl ether and ester respectively to give protected peptide **77**.

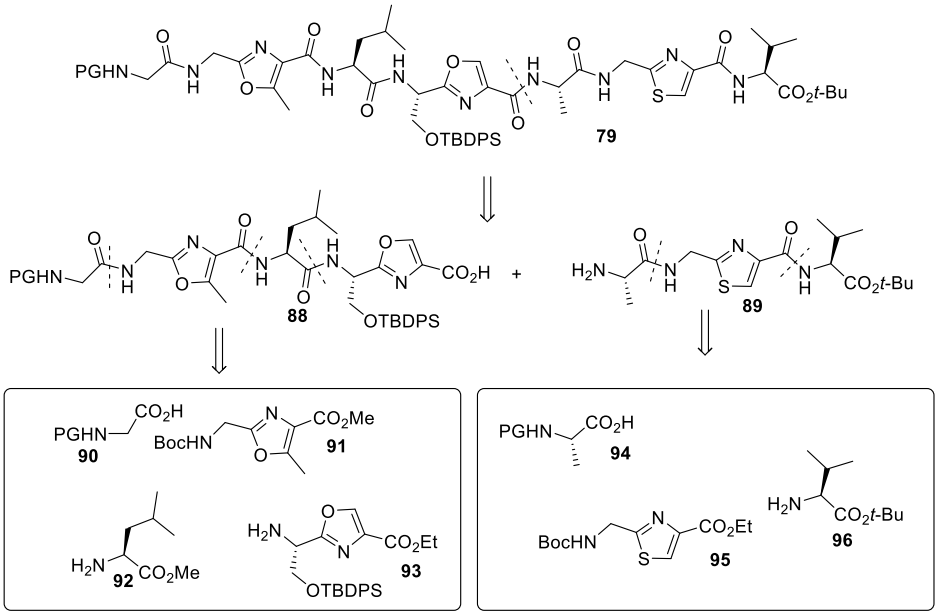
A central amide bond disconnection then gives *N*-terminal fragment **78** and *C*-terminal fragment **79**. Further disconnection as shown for *N*-terminal fragment **78** (Scheme 20) and *C*-terminal fragment **79** (Scheme 21), gives the individual amino acid and heterocyclic derivatives which will be used in the synthesis. The identity of the amino protecting group labelled PG will be discussed in the results and discussion section.



*Scheme 19. Retrosynthesis of goadsporin **64** into N-terminal fragment **78** and C-terminal fragment **79**.*



*Scheme 20. Retrosynthesis of N-terminal fragment **78** into building blocks.*



*Scheme 21. Retrosynthesis of C-terminal fragment **79** into building blocks.*

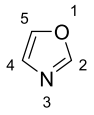
The methods chosen for the synthesis of the heterocycles and the dehydroalanines will be discussed in Section 2.3 that gives a review of the

approaches commonly used in the synthesis of oxazoles, thiazoles and dehydroalanines.

2.3 Synthetic Routes to Oxazoles, Thiazoles and Dehydroalanines

2.3.1 Oxazoles

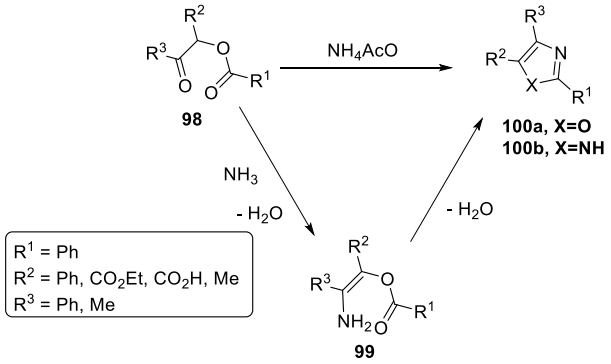
Oxazole **97** is a planar five-membered nitrogen-containing heterocycle (Figure 11). Oxazole **97** contains an O-atom as with furan and a N-atom in the 3 position.[52] The aromaticity of oxazole **97** comes from the delocalisation of the lone pair from the O-atom and the four π-electrons, thereby obeying Hückel's rule.[53] There are myriad established routes to synthesise oxazoles, seven of which will be discussed below.



97

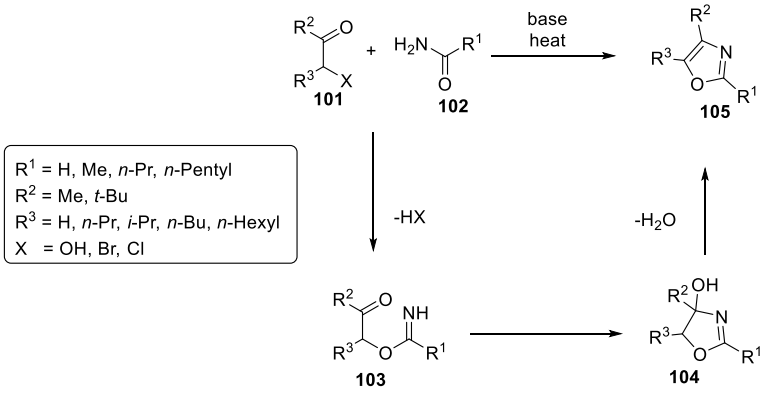
*Figure 11. Structure and numbering of oxazole **97**.*

Oxazoles can be synthesised by treating α-acyloxyketones **98** with an ammonia source, usually ammonium acetate, formed via enamide **99** (Scheme 22). A limitation of this method is the formation of imidazole by-products **100b**.[54]



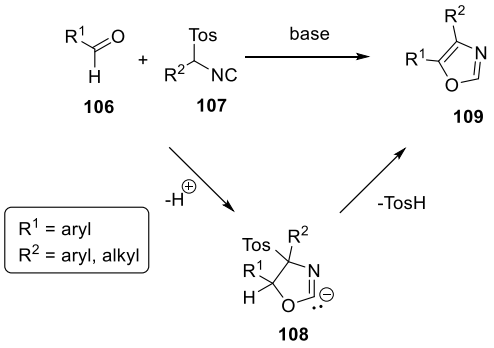
*Scheme 22. Synthesis of oxazoles from α-acyloxyketones **98**.*

The Blümlein-Lewy synthesis of oxazoles involves the condensation and cyclisation of α-halo or α-hydroxyketones **101** with carboxamides **102** (Scheme 23).[55,56] Carboxamide **102** is thought to undergo *O*-alkylation to give intermediate **103,** followed by cyclisation to give **104** and water elimination to give oxazole **105**. Although this method uses relatively simple starting materials, the oxazole products are generally obtained in a low yield.[57] This route is analogous to the Hantzsch thiazole synthesis.[52]



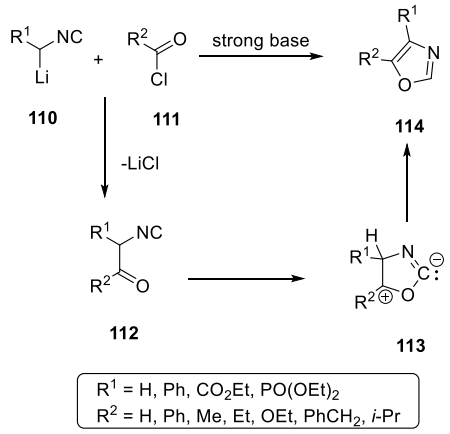
Scheme 23. The Blümlein-Lewy synthesis of oxazoles.

There are several methods in which oxazoles are synthesised from isocyanides.[58,59] One example is the Van Leusen synthesis, where toluenesulfonylmethyl isocyanide (TosMIC) **107** and aldehydes **106** react in the presence of base to give oxazoles **109** (Scheme 24).[52] The Van Leusen synthesis was also developed for use in solid-phase synthesis with functionalised resin acting as the TosMIC equivalent.[60]



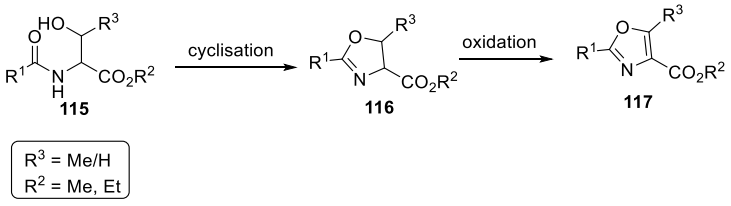
Scheme 24. The Van Leusen oxazole synthesis.

Another method that uses isocyanides is the Schöllkopf synthesis that involves the reaction between α-metalated isocyanides **110** and acid chlorides **111** to form 4,5-subsituted oxazoles **114** (Scheme 25).[61] The α-metalated isocyanide **110** is formed by treatment of the isocyanide with a strong base, for example *n*-butyllithium.[52] The mechanism likely proceeds by acylation of the α-metalated isocyanide **110** to give isocyanide **112,** followed by cyclisation to give intermediate **113**. Finally, proton migration gives oxazole **114**. The need for a strong base limits this method, as sensitive substrates, such as amino acid residues, may be affected.



Scheme 25. Schöllkopf synthesis of oxazoles.

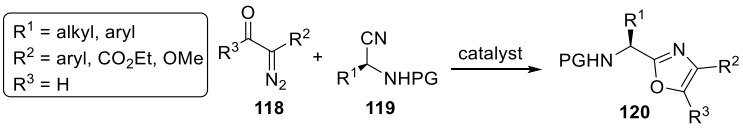
A biomimetic type synthesis of oxazoles is from serine or threonine starting materials (Scheme 26). Here, the alcohol **115** cyclises onto the amide to give the corresponding oxazoline **116**. This cyclisation step can be carried out using a variety of conditions, for example DAST, Burgess reagent, tosyl chloride and Mitsunobu conditions.[62,63] Oxidation of the oxazoline **116** gives the oxazole **117**, for which many conditions have been used, including MnO_2 and DBU/$BrCCl_3$.[64,65]



Scheme 26. Synthesis of oxazoles from serine and threonine.

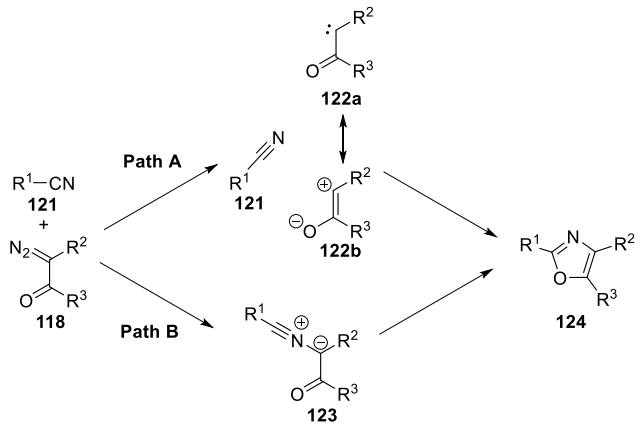
Oxazoles can also be synthesised via the reaction between α-diazocarbonyl compounds **118** and nitriles **119** (Scheme 27).[66,67] These reactions can be carried out under a range of conditions, such as photochemical, thermal, Lewis

acids or metal catalysts, such as copper or rhodium.[68–72] This chemistry has further been developed by Moody *et al*. to allow for the synthesis of chiral oxazoles in low to moderate yields.[73] The required nitrile **119** can be easily synthesised via dehydration of the corresponding amide. This method is ideal for the synthesis of chiral oxazoles that are unsubstituted in the 5-positions, as demonstrated during the synthesis of telomestatin, and thus will be used to synthesise the 5-H oxazole in goadsporin **64**.[74]



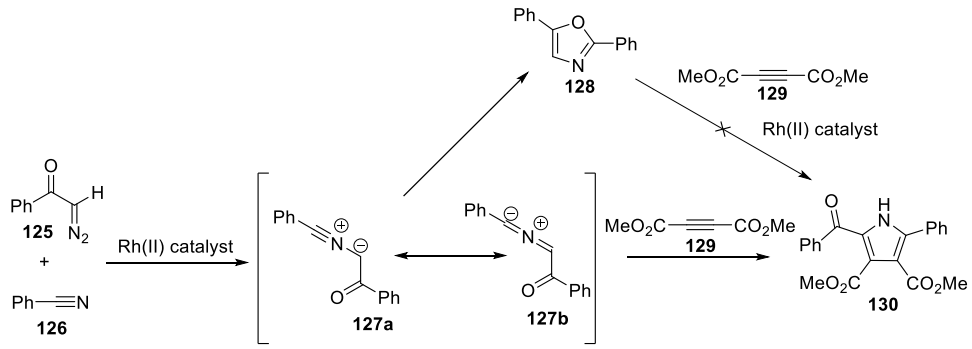
*Scheme 27. Oxazole synthesis from diazo compounds **118** and nitriles **119**.*

The mechanism for this method of oxazole formation is proposed to proceed via one of two pathways (Scheme 28).[73] Pathway A shows a 1,3-dipolar cycloaddition between the nitrile **121** and carbene **122**. Here the carbene **122** may be present as a metal carbenoid if a metal catalyst is used. Pathway B shows formation of an intermediate nitrile ylide **123**, followed by 1,5-cyclisation to give the oxazole **124**.



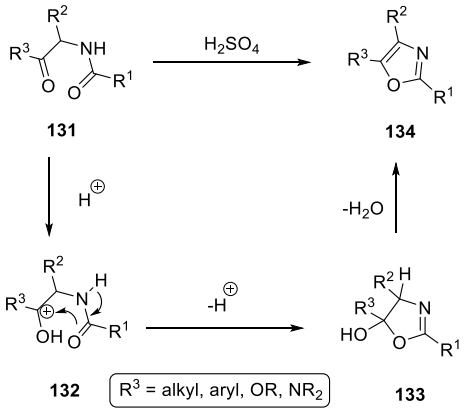
Scheme 28. Proposed mechanisms for oxazole formation.

Further investigation into the mechanism was carried out by Ibata *et al*.[75,76] Reaction of *p*-chlorodiazoacetophenone **125** in benzonitrile **126** in the presence of dimethyl acetylenedicarboxylate (DMAD) **129**, gave 63% of the oxazole product **128**, and 11% of the pyrrole product **130** (Scheme 29). The pyrrole product **130** can be explained by a 1,3-dipolar cycloaddition between nitrile ylide **127** and alkyne **129**, thereby suggesting path B shows the correct mechanism (Scheme 28). To show that the pyrrole product **130** was not generated by a Diels-Alder reaction between oxazole **128** and DMAD **129,** the two were mixed in the presence of the rhodium catalyst, however no pyrrole **130** formation was observed.



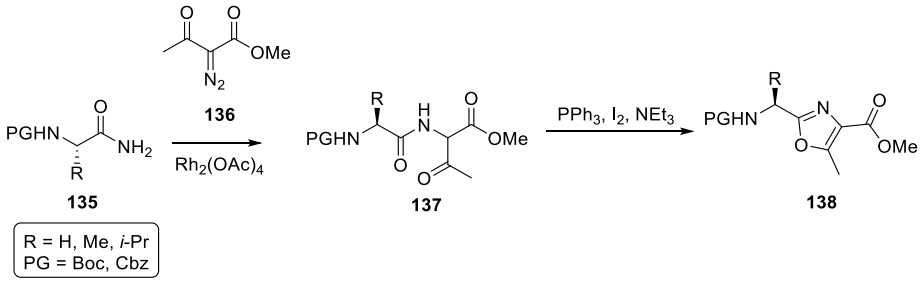
*Scheme 29. Reaction between nitrile ylide **127** and DMAD **129** during mechanistic studies.*

The final method to be discussed is the Robinson-Gabriel synthesis. This method is named after Sir Robert Robinson and Siegmund Gabriel who independently described the dehydrative cyclisation of *N*-acyl 2-aminocarbonyl compounds **131** to give oxazoles **134** (Scheme 30).[77–79] The mechanism of the reaction was deduced using ^{18}O labelled substrates, showing the keto oxygen is not in the resulting oxazole **134**, giving rise to **132** and **133** as intermediates.[52] Originally, the cyclodehydration was carried out with sulfuric acid. However, the development of milder cyclodehydration conditions such as the Wipf modification, which uses iodine, triphenylphosphine and triethylamine, has made the Robinson-Gabriel synthesis suitable for acid sensitive substrates.[80]



Scheme 30. The Robinson-Gabriel oxazole synthesis.

This route to oxazoles has been further developed by Moody *et al*. to easily access the *N*-acyl 2-aminocarbonyl starting materials **137** required for the Robinson-Gabriel reaction. This entails a rhodium catalysed N-H insertion reaction between an α-diazocarbonyl compound **136** and an amino acid carboxamide **135** (Scheme 31).[81] Moody *et al*. then carry out the dehydrative cyclisation using Wipf's mild conditions as previously described to give chiral oxazoles **138**.[80]

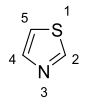


Scheme 31. Oxazole synthesis from amides via N-H insertion and cyclodehydration.

This chemistry using α-diazocarbonyl compounds has been shown to have a wide scope, and its synthetic power has been utilised in the synthesis of natural products such as (+)-nostocyclamide, promothiocin A, telomestatin siphonazole and plantazolicin **15**, as previously discussed.[74,82–86] This methodology will be utilised in our synthesis of the 5-methyl oxazoles in goadsporin **64**.

2.3.2 Thiazoles

Thiazole **139** is a five-membered nitrogen-containing heterocycle (Figure 12). Thiazole **139** contains an S-atom as with thiophene and a N-atom in the 3 position.[52] Compared to oxazole (pKa 0.8), thiazole (pKa 2.5) is more basic and has greater aromaticity, as thiazole has a higher degree of π-electron delocalisation.[52,53] As with oxazoles, there are many synthetic methods for the preparation of thiazoles. Five methods of thiazole synthesis will be discussed herein.

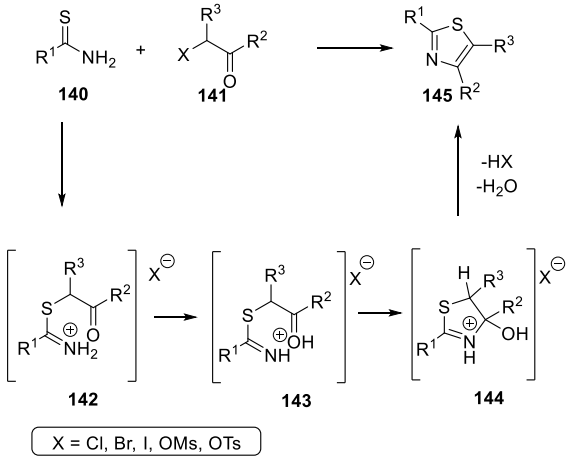


139

*Figure 12. Structure and numbering of thiazole **139**.*

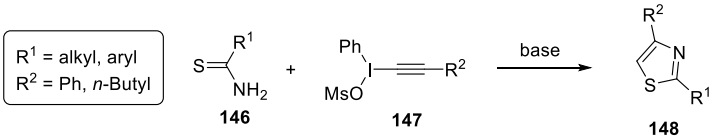
The most widely known thiazole synthesis is the Hantzsch reaction, developed by Rudolf Hantzsch in 1887.[87] This reaction involves the condensation of a thioamide **140** and usually a 2-halocarbonyl **141** (Scheme 32). The sulfur carries out nucleophilic displacement of X, usually a halide, to give an *S*-alkyliminium salt **142**. Intermediate **142** then undergoes proton transfer, cyclisation and water elimination to give thiazole **145**. Originally modified by Holzapfel,[88] by using trifluoroacetic anhydride and pyridine, and further developed by Meyers,[89] switching pyridine for lutidine and lowering the reaction temperature, the modified Hantzsch reaction is routinely used in the synthesis of enantiomerically pure thiazoles.[90] The Hantzsch thiazole synthesis has been

used in the preparation of many thiazole containing fragments in natural products such as amythiamicin D, promothiocin A and nosiheptide.[82,91,92] The synthesis of the two thiazoles in goadsporin **64** will be carried out using the Hantzsch thiazole synthesis.



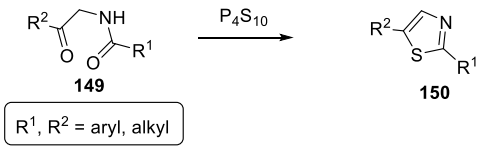
Scheme 32. Hantzsch thiazole synthesis.

Wipf developed a thiazole synthesis using alkynyl(phenyl)iodonium mesylates **147** and thioamides **146**, in the presence triethylamine or carbonate (Scheme 33).[93] The iodonium reagents are synthesised by treatment of iodobenzene diacetate with sodium hydroxide, methanesulfonic anhydride and alkynyl stannanes.[94,95] This method is able to give 2,4-disubstituted thiazoles **148** in moderate to good yield.



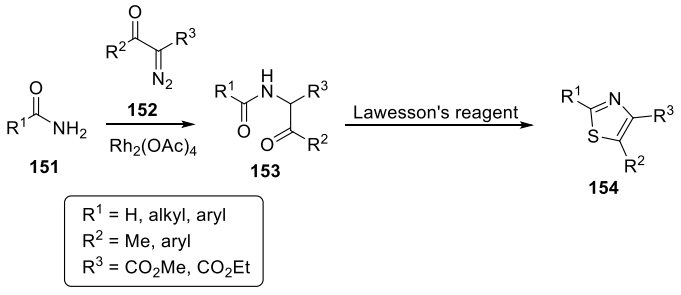
Scheme 33. Thiazole synthesis from thioamides and alkynyl(phenyl)iodonium mesolates.

The Robinson-Gabriel thiazole synthesis involves sulfurisation, for example using phosphorus pentasulfide, and cyclodehydration of α-acylaminoketones **149** to give 2,5-disubstiuted thiazoles **150** (Scheme 34).[52]



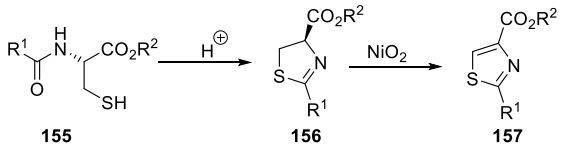
Scheme 34. The Robinson-Gabriel thiazole synthesis.

Moody *et al*. have adapted the rhodium N-H insertion chemistry as described for the synthesis of oxazoles, to synthesise thiazoles.[81] Reaction between amino acid carboxamide **151** and α-diazocarbonyl compound **152**, catalysed by a rhodium(II) complex, gives a ketoamide **153**, as used in the Robinson-Gabriel thiazole synthesis, which upon treatment with Lawesson's reagent, generates the corresponding thiazole **154** (Scheme 35).[96] This method was demonstrated in the synthesis of one of the thiazole fragments of amythiamicin D.[91] Similarly, the reaction can be carried out with a thioamide in place of amide **151** and cyclisation carried out using a previously described Wipf modification.[80,97]



Scheme 35. Thiazole synthesis via N-H insertion and sulfurisation.

Finally, thiazoles can be synthesised by a more biomimetic route from cysteine starting materials **155**, analogous to the route to oxazoles via serine containing starting materials (Scheme 36).[81,98] The sequence involves acid-induced cyclisation to thiazoline **156** followed by oxidation to give the corresponding thiazole **157**. This method was used by Hecht *et al*. during the synthesis of the bisthiazole fragment of bleomycin B_2.[99]



155 **156** **157**

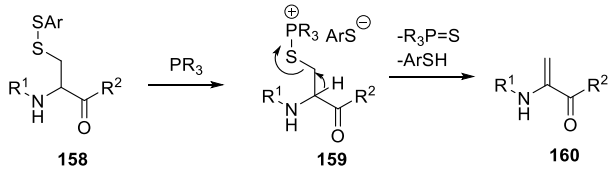
Scheme 36. Synthesis of thiazoles from cysteine starting materials.

2.3.3 Dehydroalanines

Dehydro-amino acids residues are an important feature of post-translationally modified peptides and proteins, providing an electrophilic centre and reducing flexibility, giving conformational control often required for biological activity.[100] These residues can act as starting materials to a range of further post-translational modifications, for example dehydroamino acids act as precursors in the biosynthesis of the pyridine ring in thiopeptides, and the thioether linkages in lanthionines.[101] There are several methods for chemically synthesising dehydroalanine residues, six of which will be discussed herein.

The first of these methods is a reduction-elimination sequence from cysteine disulfides. This involves attack of a phosphine onto the disulfide **158** giving a

thiolate leaving group. The resulting phosphonium salt **159** can then be eliminated to give dehydroalanine **160** (Scheme 37).



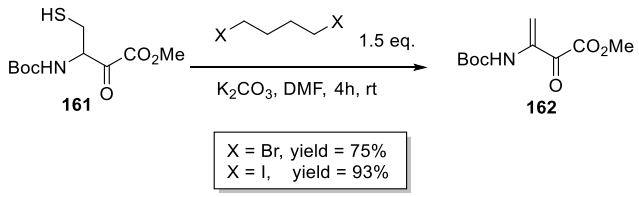
Scheme 37. Synthesis of dehydroalanine from disulfides.

This method has the advantage of being cysteine specific, with cysteine being easily converted into the disulfide, for example using Ellman's reagent, before the reduction-elimination sequence which uses an electron rich phosphine such as tris(dimethylamino)phosphine (HMPT).[102] Although this method has been developed to be a one-pot reaction proceeding with high yields, both HMPT and the oxidised product HMPA are highly toxic.

An alternative method for elimination can be undertaken using a base. This route proceeds via a similar mechanism to the conversion of **158** into **160**, with the disulfide acting as the leaving group under basic conditions to give dehydroalanine.[102] The main limitation of this method is that depending on the disulfide, strong bases may be required to promote the elimination, causing issues such as epimerisation for sensitive substrates.[103]

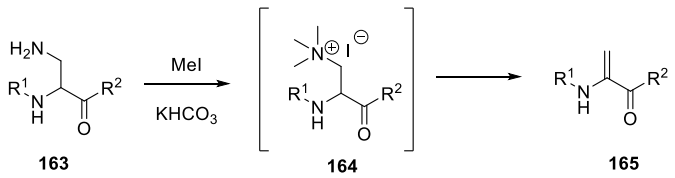
Another method for synthesising dehydroalanine residues is by bis-alkylation of cysteine **161** followed by elimination (Scheme 38). During an investigation by Chalker *et al*. 1,4-bromobutane and 1,4-iodobutanes were used as alkylating agents to generate a bis-alkylated cysteine intermediate.[102] Potassium

carbonate was sufficient to induce elimination, giving the dehydroalanine product **162** in good yield.



Scheme 38. Dehydroalanine synthesis using bis-alkylation/ elimination sequence.

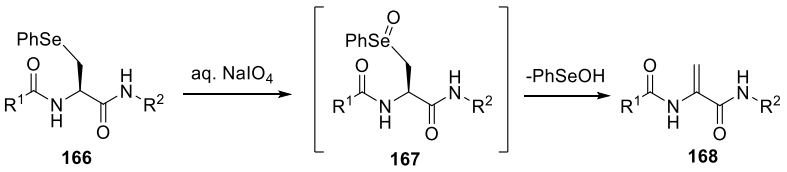
Dehydroalanines can also be formed by the Hofmann degradation of 2,3-diaminopropionic acid **163** (Scheme 39). The reaction proceeds via the bis-alkylation of the amine functionality using methyl iodide, followed by Hofmann elimination to give alkene product **165**.[104] Although this route provided the dehydroalanine-containing product in moderate to good yields, the amine would require protection prior to dehydroalanine formation to withstand other chemical reactions. Additionally, other sensitive groups may not be compatible with the alkylation and elimination conditions used.



Scheme 39. Dehydroalanine formation by bis-alkylation and elimination of a β-amine.

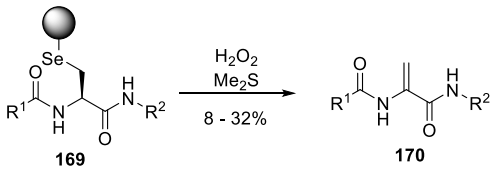
The further method of dehydroalanine synthesis is using selenium derivatives. The use of phenylselenoalanine derivatives was employed in the total synthesis of thiostrepton **4** by Nicolaou *et al*.[6,7] Phenylselenoalanine **166** was used as a

suitable dehydroalanine precursor applying methodology developed by Okeley *et al*., in which the selenium-based precursors were successfully incorporated into peptides. Oxidation of phenylselenoalanine **166** gives the selenoxide **167**, which undergoes syn-elimination to give the alkene product **168** in moderate yields (Scheme 40).



*Scheme 40. Dehydroalanine synthesis from phenylselenoalanine **166**.*

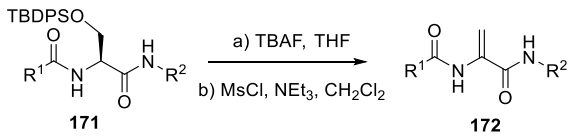
Ayida *et al*. also used selenium based dehydroalanine precursors in the synthesis of thiostrepton side chain analogues, during which the dehydroalanine residues were synthesised from selenoalanine attached to a solid support **169**.[105] This method generally gave low yields, which was attributed to the instability of the dehydroalanine **170** to the oxidative conditions (Scheme 41).



Scheme 41. Use of solid phase selenoalanine to give dehydroalanine.

Finally, dehydroalanines can be prepared from serine precursors. Due to the low yields using the selenium derivative on solid phase, Ayida *et al*. also investigated synthesising dehydroalanine via the deprotection and mesylation

of protected serine **171** (Scheme 42).[105] This method gave access to the desired alkene product **172** in higher yields, although in a substrate with two serines, mono and di-mesylation was observed along with the corresponding elimination products when a one-pot reaction was attempted.[105]



*Scheme 42. Synthesis of dehydroalanine from a TBDPS protected serine **171**.*

The use of protected serine residues to synthesise dehydroalanines has been fairly well reported in the literature. Generally, deprotection of the serine, followed by mesylation or sulfonylation, and treatment with a base gives the alkene elimination product. In 1963, Koshland *et al.* used a method in which serine was subjected to sulfonylation/elimination to give dehydroalanine.[106,107] More recently, the mesylation/elimination strategy was used by Moody *et al.* as the final step in the total synthesis of promothiocin A.[82]

Goadsporin **64** contains two dehydroalanine residues that will be synthesised from serine-based precursors. Ideally, the two serines will be concurrently deprotected, followed by mesylation and base-mediated elimination to give the dehydroalanine residues. The identity of the dehydroalanine precursors is important as goadsporin **64** also contains an unmodified serine which requires orthogonal protection.

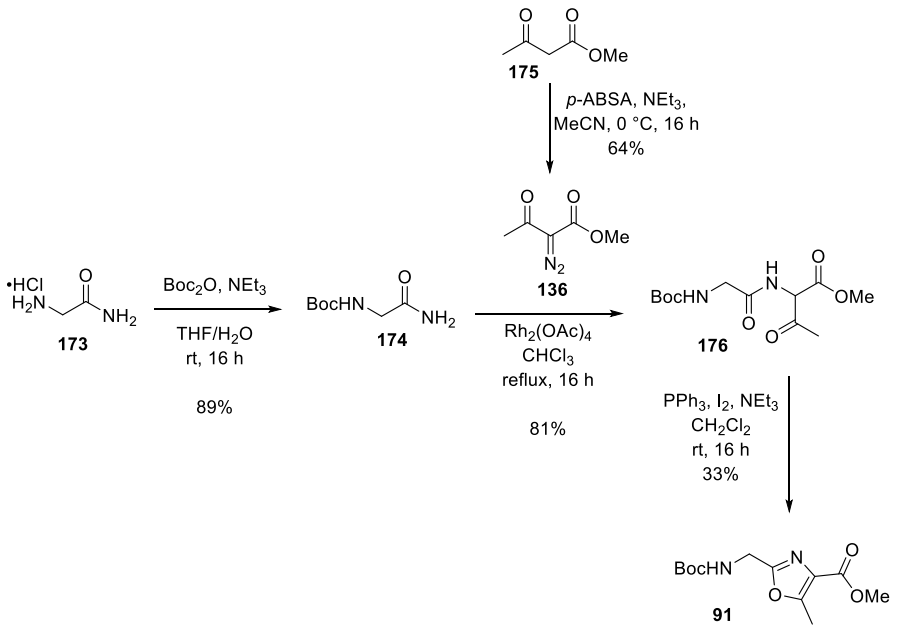
2.4 Synthesis of the Heterocycles

Goadsporin **64** contains three methyl oxazoles derived from alanine, glycine and dehydroalanine, and an oxazole from dehydroalanine. There are also two thiazoles that are derived from glycine and leucine. Synthesis of the oxazole moieties which are based on dehydroalanine utilise an appropriately protected serine precursor to give a suitable building block for use in the total synthesis.

2.4.1 Synthesis of Methyl Oxazoles 91, 182 and 84

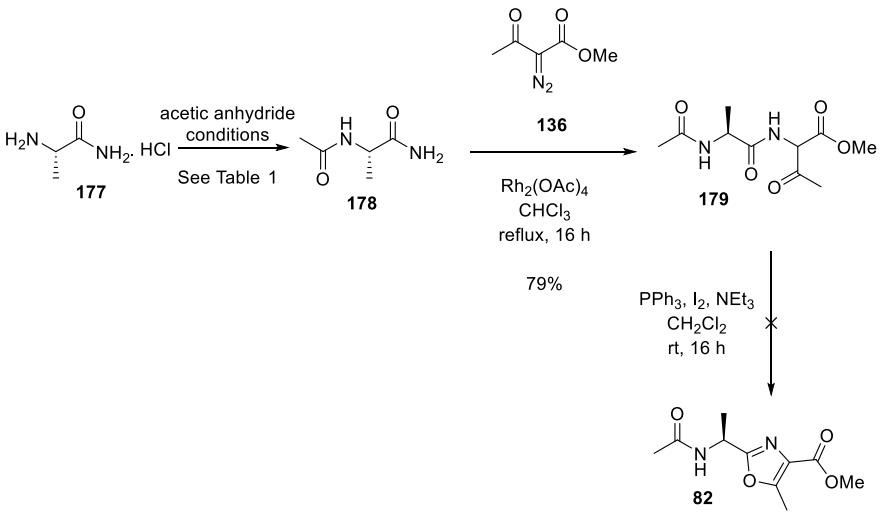
Work towards the synthesis of goadsporin **64** began with the synthesis of methyl oxazoles **91**, **182** and **84**. As mentioned previously, these oxazoles were synthesised using a rhodium catalysed N-H insertion followed by cyclodehydration.

For oxazole **91**, synthesis commenced with Boc protection of glycinamide **173** to give amide **174** (Scheme 43). This amide underwent a rhodium catalysed N-H insertion with diazo compound **136** to give ketoamide **176**. Diazo compound **136** was synthesised from methyl acetoacetate **175** by a diazo transfer reaction using *p*-ABSA. Cyclodehydration of ketoamide **176** using triphenylphosphine, iodine and triethylamine gave oxazole **91** in low yield. The poor yield of this reaction is due to difficult separation of the resulting oxazole from triphenylphosphine oxide.



*Scheme 43. Synthesis of oxazole **91**.*

Initially, synthesis of the alanine oxazole began with acetylation of alaninamide **177** to give **178** (Scheme 44). This seemingly simple transformation was poorly reported in the literature and required trialling several conditions (Table 1). The best acetylation conditions were found to be *N*,*N*-diisopropylethylamine in dichloromethane, giving the desired product as a colourless solid which could be filtered from the reaction mixture (Entry 4). Amide **178** was then subjected to the rhodium catalysis conditions with diazo compound **136** to give ketoamide intermediate **179**. However, cyclodehydration of this species was very low yielding and scale up of this reaction gave none of the desired product oxazole **82**. A potential explanation for this may be the additional acetamide group being involved in the cyclodehydration step, leading to the formation of side products.

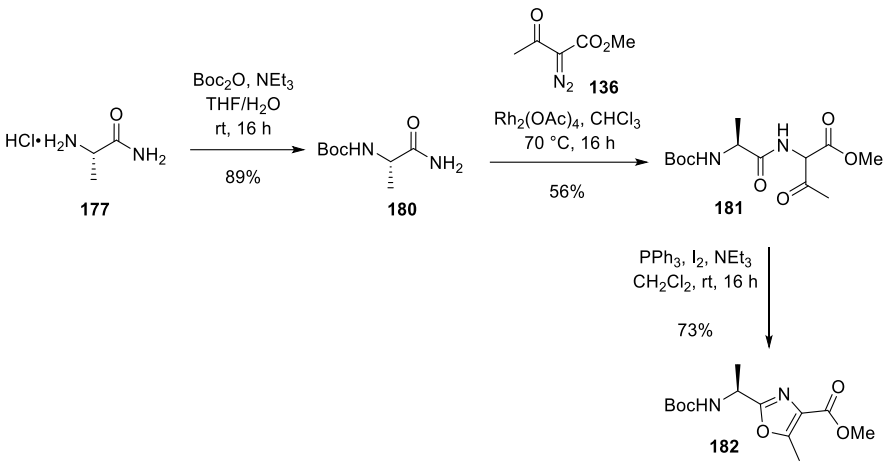


*Scheme 44. Synthesis of oxazole **82** using acetyl as amino protecting group.*

Entry	Solvent	Reagent	Yield
1	chloroform	triethylamine	7%
2	pyridine	-	28%
3	dichloromethane	4-(dimethylamino)pyridine	0%
4	dichloromethane	*N*,*N*-diisopropylethylamine	82%

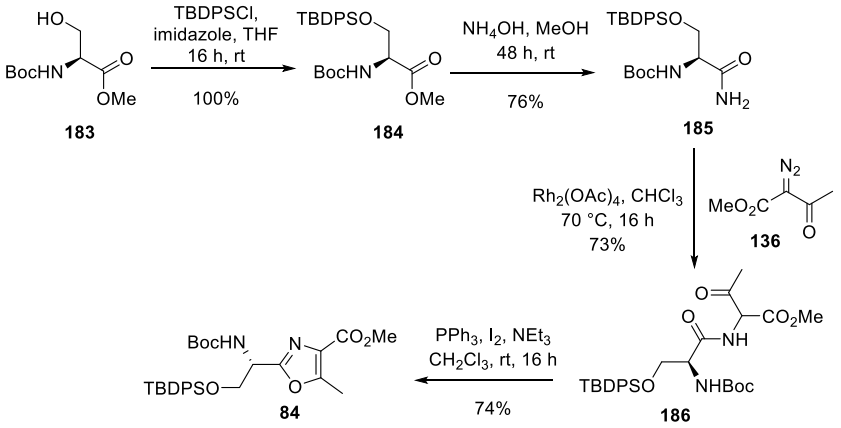
*Table 1. Conditions for acetylation of **177**.*

After poor results with the acetyl group in place, an analogous route was tested with Boc as the amino protecting group (Scheme 45). Boc protection of alaninamide **177** gave amide **180** which underwent the N-H insertion and cyclodehydration to give oxazole **182** in good yield. When scaling up to 40 mmol, the crude mixture from the rhodium N-H insertion can be carried through to the cyclodehydration without purification, giving a yield of 30% of oxazole **182** over the two steps.



*Scheme 45. Synthesis of oxazole **182** using Boc as the amino protecting group.*

The final methyl oxazole **84** was synthesised from Boc-serine methyl ester **183** (Scheme 46). The alcohol **183** was protected using TBDPSCl to give **184** which was converted into the amide **185** using ammonium hydroxide in good yield. The rhodium catalysed N-H insertion with diazo compound **136** and cyclodehydration both proceeded to give oxazole **84** in high yield.

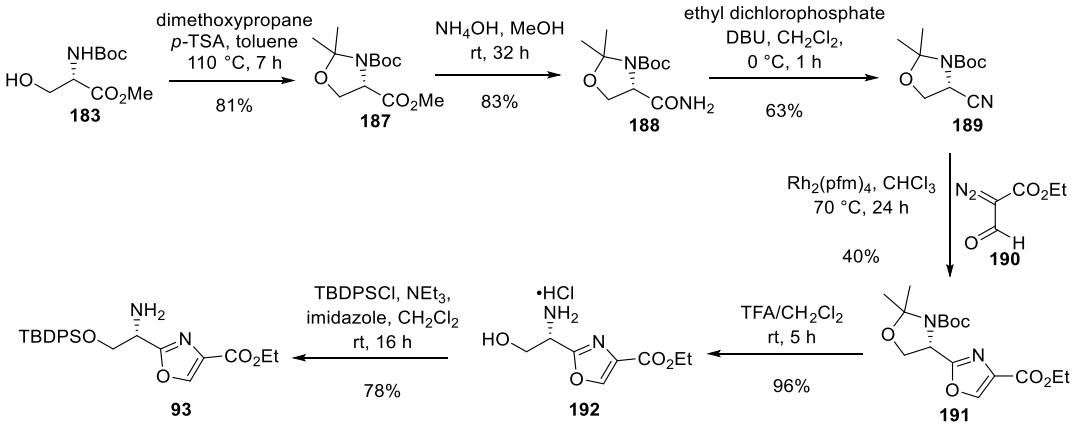


*Scheme 46. Synthesis of oxazole **84**.*

2.4.2 Synthesis of Oxazole 93

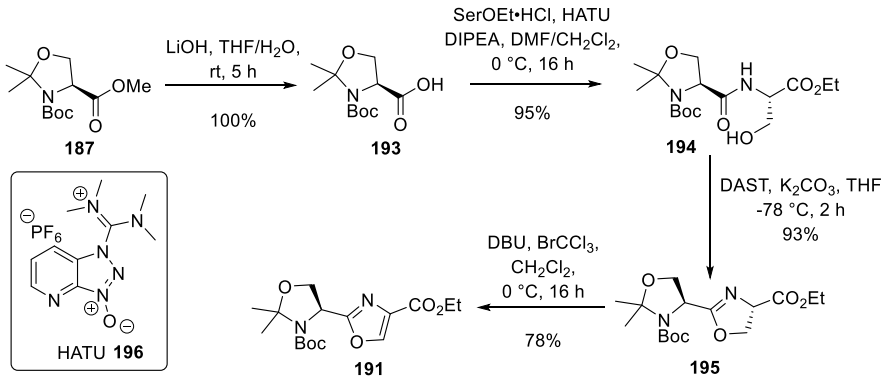
With each of the 5-methyl oxazoles **91**, **182** and **84** in hand, synthesis of the 5-H **93** oxazole was investigated. Synthesis of oxazole **191** has been previously reported by Linder *et al*. during the formal synthesis of telomestatin.[74] Following the procedure reported in the literature, Boc-serine methyl ester **183** was protected using 2,2-dimethyoxypropane to give methyl ester **187** (Scheme 47). Conversion into the amide using ammonium hydroxide gave amide **188** in good yield, dehydration of which with ethyl dichlorophosphate gave nitrile **189** in moderate yield. The nitrile underwent a rhodium catalysed cyclisation with diazo compound **190** to give oxazole **191**.

Global deprotection of **191** with TFA gave amine **192** which could be reprotected using TBDPSCl in good yield to give **93**. For this reprotection it was found that use of dry reagents was vital, with the reaction otherwise being low yielding.



*Scheme 47. Synthesis of oxazole **93**.*

Due to the low yielding rhodium catalysed reaction for the synthesis of oxazole **191** and poor scale up, an alternative route was investigated, following a literature method for synthesis of the methyl ester analogue of oxazole **191**.[108] Hydrolysis of previously synthesised ester **187** gave acid **193**, which was coupled to serine ethyl ester using HATU **196** to give dipeptide **194** (Scheme 48). Cyclisation of alcohol **194** using dichloromethane as the solvent, in accordance with the literature, gave oxazoline **195** in a disappointing 60% yield. Pleasingly, the cyclisation reaction gave oxazoline **195** in higher yield when THF was used as a solvent. Oxazoline **195** was then taken through without purification to the oxidation step, using bromotrichloromethane and DBU to give oxazole **191** in good yield. This route had the advantage of being both amenable to multigram scale-up, and the resulting product being easy to purify, therefore giving access to large quantities of oxazole **191** as required for the total synthesis.

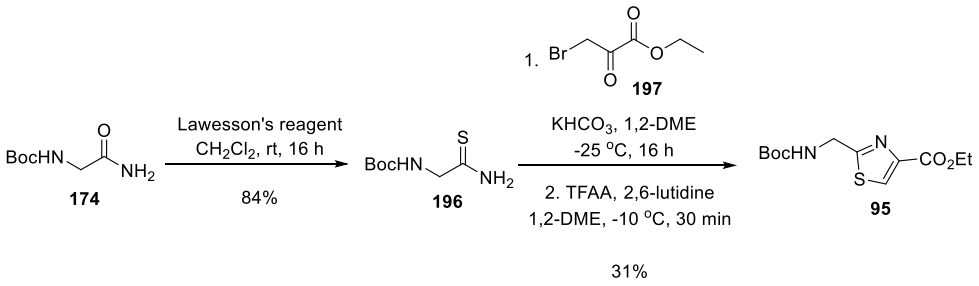


*Scheme 48. Synthesis of oxazole **191** via oxazoline **195**.*

2.4.3 Synthesis of Thiazoles 95 and 86

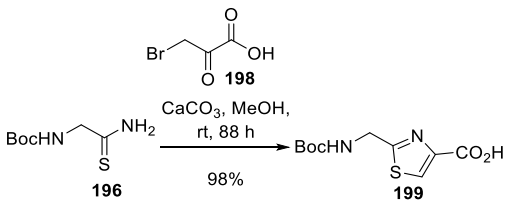
As mentioned in Section 2.3.2, the thiazoles in goadsporin **64** were synthesised using the Hantzsch synthesis.

The synthesis of thiazole **95**, based on glycine, started from the previously synthesised Boc-glycinamide **174** (Scheme 49). This was then converted into thioamide **196** using Lawesson's reagent in high yield. Boc-glycine thioamide **196** was then transformed to the corresponding thiazole **95** by reaction with ethyl bromopyruvate **197** using modified Hantzsch conditions.[84]



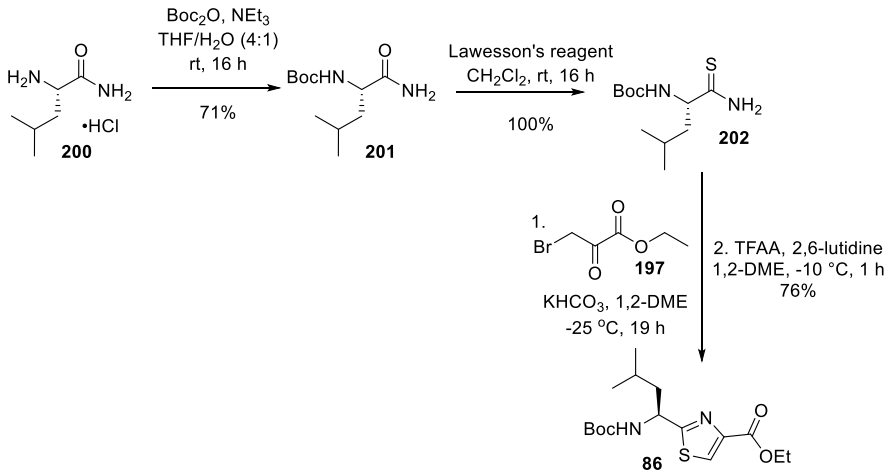
*Scheme 49. Synthesis of thiazole **95**.*

Due to the low yield of thiazole **95**, a variation of the Hantzsch reaction was tested. This method used bromopyruvic acid **198** in replacement of ethyl bromopyruvate **197** to give the thiazole as the carboxylic acid **199** (Scheme 50).[109,110] Pleasingly, the reaction yielded thiazole **199** in high yield, in a single step, without the need for column chromatography. Additionally, generating the carboxylic acid directly eliminates a step from the total synthesis.



*Scheme 50. Synthesis of thiazole **199**.*

The final heterocycle, thiazole **86,** was synthesised starting from commercially available leucinamide hydrochloride **200**. Boc protection followed by conversion into thioamide using Lawesson's reagent gave **202** in high yield (Scheme 51). Thiazole **86** was then synthesised using the modified Hantzsch method in good yield.[84]



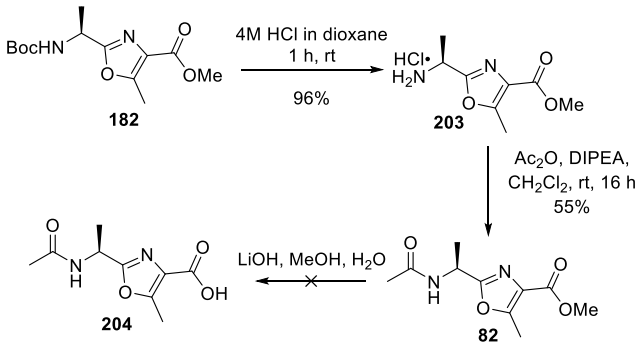
*Scheme 51. Synthesis of thiazole **86**.*

With all the heterocyclic building blocks in hand, synthesis of the *N*-terminal fragment of goadsporin **64** ensued.

2.5 Synthesis of *N*-terminal fragment 78

2.5.1 Synthesis of 1st quarter fragment 80

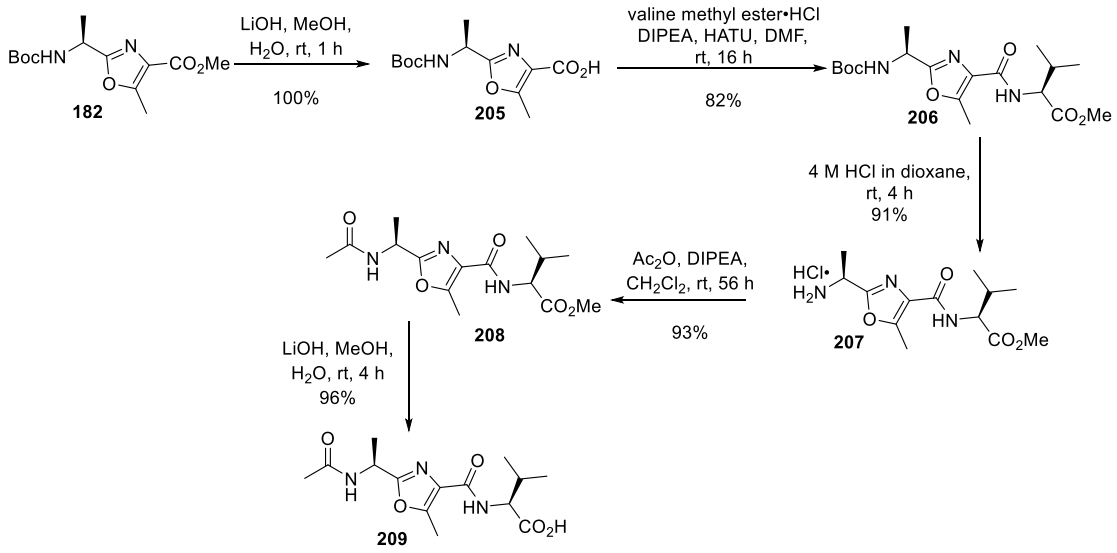
Synthesis of the first quarter fragment **80** began with oxazole **182** (Scheme 52). Boc-deprotection and acetylation gave oxazole **82**. However, ester hydrolysis with lithium hydroxide to access acid **204** proved unsuccessful, with acid **204** isolated only in very low yields after aqueous work-up due to its high aqueous solubility.



*Scheme 52. Attempted synthesis of acid **204**.*

Therefore, the order of steps was altered. Thus oxazole **182** was hydrolysed to give acid **205** in quantitative yield (Scheme 53). Acid **205** underwent amide coupling with valine methyl ester to give dipeptide **206** in high yield. Boc deprotection gave amine **207** which was subjected to acetylation to give methyl ester **208** in good yield. Pleasingly, a single crystal of **208** was grown allowing an X-ray structure to be obtained (Figure 13). This gave confirmation

of the structure and stereochemistry of **208**. Ester hydrolysis gave acid **209** in good yield.



*Scheme 53. Synthesis of acid **209**.*

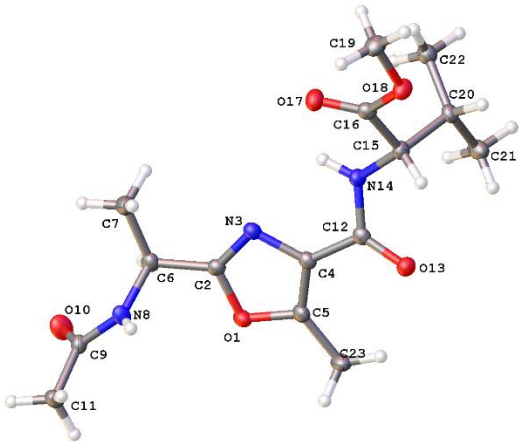
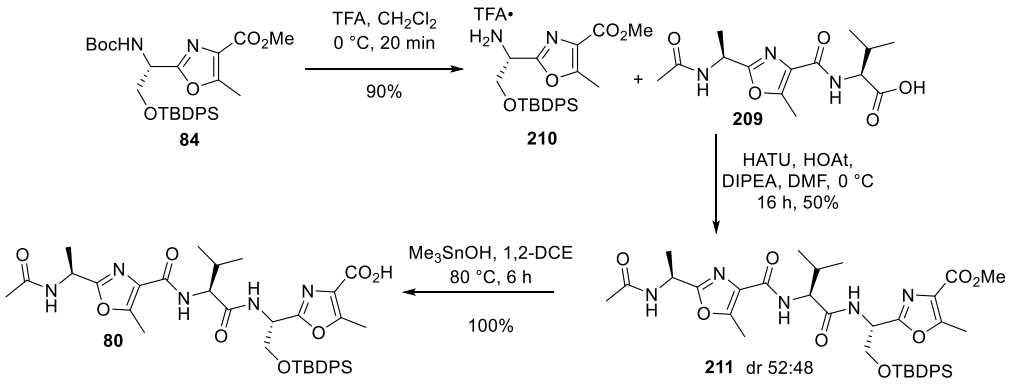


*Figure 13. X-Ray crystal structure of **208**.*

Continuation of the synthesis of the first quarter fragment **80** required selective Boc deprotection of methyl oxazole **84** to give amine **210**, without removal of the silyl protecting group**.** Initial experiments with the standard procedure of HCl in dioxane were low yielding; however, TFA proved to be effective when used at lower temperatures for a short time (Scheme 54).[111] The next stage in

the synthesis was an amide coupling between acid **209** and amine **210** to give peptide **211**. Having completed the coupling under frequently used amide coupling conditions (HATU, HOAt, DIPEA, DMF), it was found that epimerisation had taken place to give a mixture of diastereomers, in a ratio of 52:48, as could be seen by NMR spectroscopy and HPLC (peaks at 3.577 and 3.637 min) (Figure 14).



*Scheme 54. Synthesis of the 1st quarter fragment **80**.*

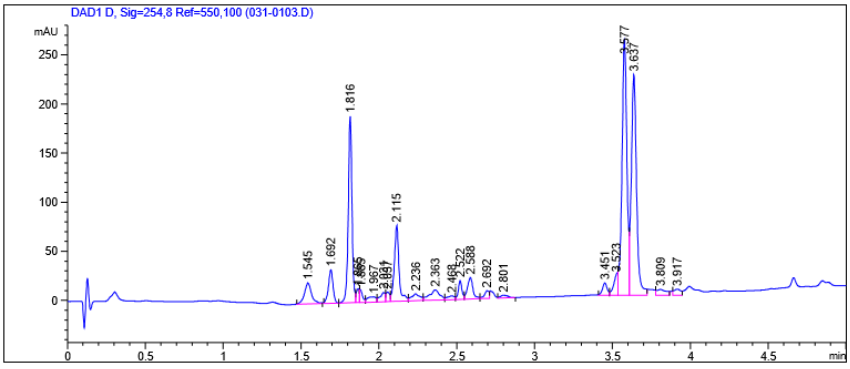
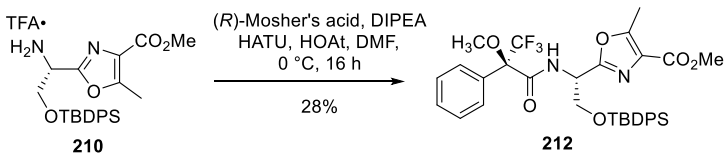


*Figure 14. HPLC of coupling with HATU, HOAt, DIPEA and DMF to give **211** before purification. HPLC using method A (see general information Section 5.1)*

At this point the residue that was undergoing epimerisation needed to be identified, for which there were three options:

- Alanine of **209**
- Valine of **209**
- Serine of **210**

To rule out epimerisation at the TBDPS protected serine methyl oxazole **210**, amine **210** was coupled to (*R*)-Mosher's acid using the same coupling conditions that had previously induced epimerisation (HATU, HOAt, DIPEA, DMF) (Scheme 55). Analysis of the amide product **212** by ^{19}F NMR spectroscopy showed a single peak, suggesting a single diastereomer (Figure 15). This was also reflected in the ^{1}H and ^{13}C NMR spectroscopy, thereby strongly suggesting that the protected serine residue is not undergoing epimerisation during the given conditions.



*Scheme 55. Reaction of amine **210** with (R)-Mosher's acid.*

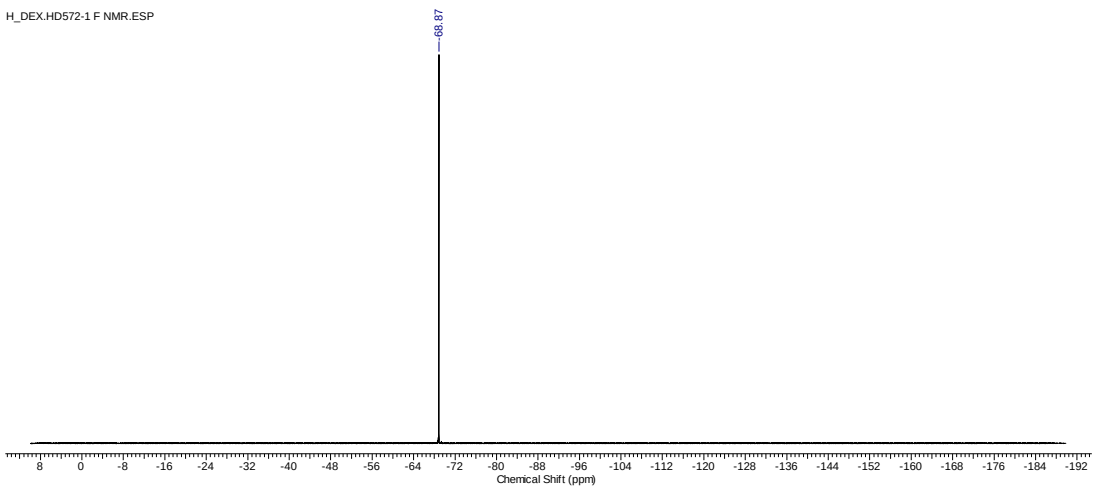
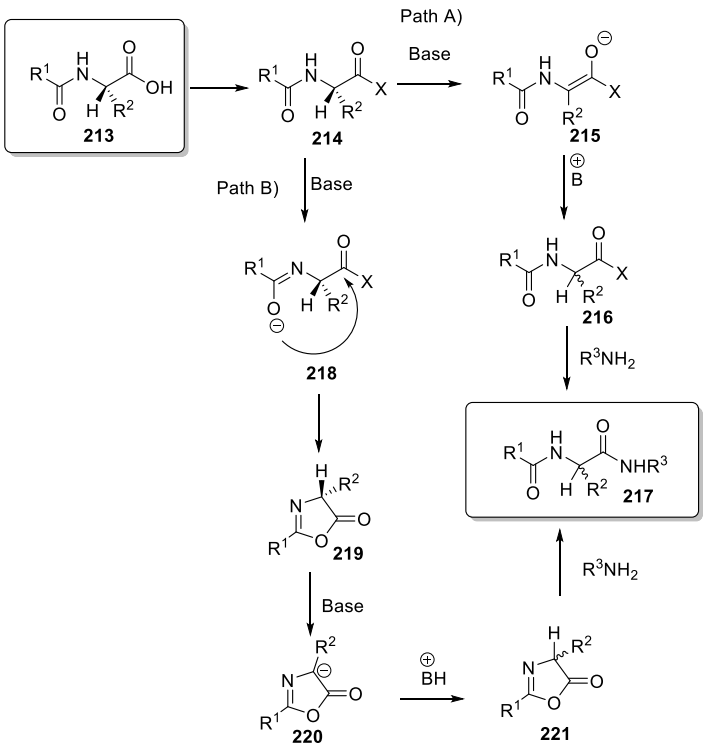


*Figure 15. ^{19}F NMR spectrum of amide **212**.*

Work then moved on to the valine residue. It is known that the αCH of the amino acid residue that is present as the acid can be deprotonated during amide coupling, therefore leading to epimerisation. The two main pathways under which amino acids can lose their chiral integrity are direct enolisation and oxazolone formation (Scheme 56).[103,112] Direct enolisation (path A) involves deprotonation and enolisation of the αCH of the activated *C*-terminal amino acid **214** to give **215**, followed by reprotonation leading to loss of the stereochemical information in **216**. Epimerisation by the oxazolone (path B) proceeds via attack of the enolised oxygen onto the adjacent activated carbonyl to give the intermediate oxazolone **219**. This oxazolone **219** can then be deprotonated (pKa ≈ 9) and reprotonated giving a D/L mixture which can then undergo aminolysis to give **217**.[113]



Scheme 56. Possible mechanisms for epimerisation a) direct enolisation, b) via oxazolone formation.

Epimerisation during amide coupling can be affected by three main factors:[103]

1. The nature of the *N*-protecting group on the amino acid that has a free carboxylic acid to be coupled
2. The identity of the amine base used
3. The coupling reagents used

Therefore, as the protecting group could not be changed without altering the synthetic route, different amide coupling conditions were investigated for the coupling between acid **209** and amine **210** to give peptide **211** (Table 2). As mentioned previously, standard conditions gave high levels of diastereomers (Entry 1). Changing from HATU to HBTU improved the selectivity slightly (Entry 2). Changing the base from DIPEA (pKa 10.8) to pyridine (pKa 5.2), a weaker

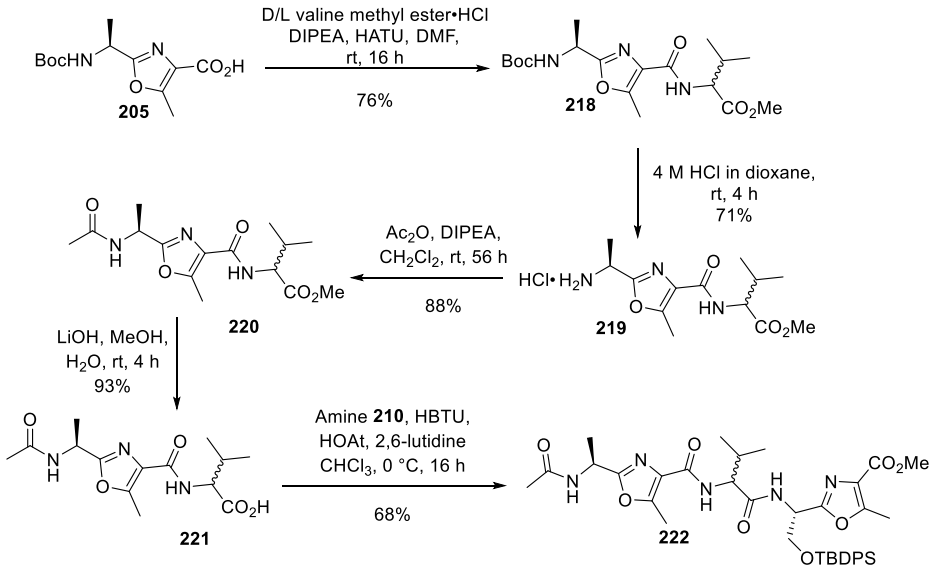
base, (Entry 3) and then to 2,6-lutidine (pKa 6.8) (Entry 4) had dramatic improvements. Lowering the reaction temperature to -25 °C had no effect on the diastereomeric ratio (Entry 5). A base free method of EDC and HOBt gave very poor selectivity (Entry 6).

Optimisation of solvent, equivalents of base and equivalents of both activators gave the highest selectivity of 94:6 (Entry 13). A more hindered pyridine base was tested; 2,6-di-*tert*-butyl-4-methylpyridine (pKa 5.0), giving a 96:4 diastereomeric ratio upon optimisation (Entry 22). This very hindered base is most likely less able to abstract the αCH of the valine residue during amide coupling conditions, thereby supressing epimerisation to acceptable levels (Scheme 56). The addition of copper(II) chloride increased levels of epimerisation in disagreement with some literature precedent (Entry 24).[114]

Entry	Base (equiv)	Coupling agents (equiv)	Solvent	dr
1	DIPEA (5)	HATU (2) HOAt (2)	DMF	52:48
2	DIPEA (5)	HBTU (2) HOAt (2)	DMF	61:39
3	Pyridine (5)	HBTU (2) HOAt (2)	DMF	87:13
4	2,6-lutidine (5)	HBTU (2) HOAt (2)	DMF	91:9
5[a]	2,6-lutidine (5)	HBTU (2) HOAt (2)	DMF	91:9
6		EDC (1.5) HOBt (1.5)	DMF	56:44
7	2,6-lutidine (5)	HBTU (2) HOAt (2)	CH_2Cl_2	92:8
8	2,6-lutidine (5)	HBTU (2) HOAt (2)	$CHCl_3$	93:7
9	2,6-lutidine (4)	HBTU (2) HOAt (2)	$CHCl_3$	93:7
10	2,6-lutidine (4)	HBTU (2) HOAt (2)	CH_2Cl_2	93:7
11[b]	2,6-lutidine (4)	HBTU (2) HOAt (2)	CH_2Cl_2	93:7
12	2,6-lutidine (3)	HBTU (2) HOAt (2)	CH_2Cl_2	91:9
13	2,6-lutidine (4)	HBTU (2) HOAt (1)	CH_2Cl_2	94:6
14	2,6-lutidine (4)	HBTU (2) HOAt (1)	$CHCl_3$	93:7
15	2,6-lutidine (4)	HBTU (1) HOAt (2)	CH_2Cl_2	93:7
16	2,6-lutidine (4)	HBTU (1) HOAt (1)	CH_2Cl_2	91:9
17	2,6-di^{t}Bu,4-Me py (5)	HBTU (2) HOAt (2)	CH_2Cl_2	94:6
18	2,6-di^{t}Bu,4-Me py (4)	HBTU (2) HOAt (1)	CH_2Cl_2	95:5
19	2,6-di^{t}Bu,4-Me py (3)	HBTU (2) HOAt (1)	CH_2Cl_2	93:7
20	2,6-di^{t}Bu,4-Me py (5)	HBTU (2) HOAt (2)	$CHCl_3$	92:8
21[c]	2,6-di^{t}Bu,4-Me py (4)	HBTU (2) HOAt (1)	$CHCl_3$	94:6
22[c]	2,6-di^{t}Bu,4-Me py (4)	HBTU (2) HOAt (1)	CH_2Cl_2	96:4
23[c]	2,6-di^{t}Bu,4-Me py (4)	PyBOP (2) HOAt (1)	CH_2Cl_2	95:5
24[c]	2,6-di^{t}Bu,4-Me py (4)	HBTU (2) HOAt (1) $CuCl_2$ (1.5)	CH_2Cl_2	90:10

*Table 2. Conditions for amide coupling of **209** and **210**. All reactions run at 0 °C apart from [a] at -25 °C and [b] at room temperature. All reactions use TFA salt of **210** apart from [C] entry 21-24 for which the amine was free-based.*

To confirm that epimerisation was occurring at the valine αCH during the amide coupling reaction, the synthesis was carried out with D/L valine to determine whether the same diastereomeric products were identified as had been seen during epimerisation (Scheme 57).



*Scheme 57. Synthesis of **222** with D/L valine.*

Thus, acid **205** was coupled with D/L valine to give amide **218** for which diastereomers could be clearly seen by ^{1}H and ^{13}C NMR spectroscopy. Amide **218** was then Boc-deprotected, acetylated and hydrolysed to give acid **221**. Coupling between acid **221** and amine **210** was then carried out using conditions previously shown to supress epimerisation in comparison to standard conditions (HBTU, HOAt, 2,6-lutidine, $CHCl_3$, Table 2, Entry 9). These conditions gave **222** with a diastereomeric ratio of 46:54 by HPLC, confirming that the valine is the residue undergoing epimerisation, as the product matched that made in Scheme 54 by both HPLC and NMR spectroscopy (Figure 16).

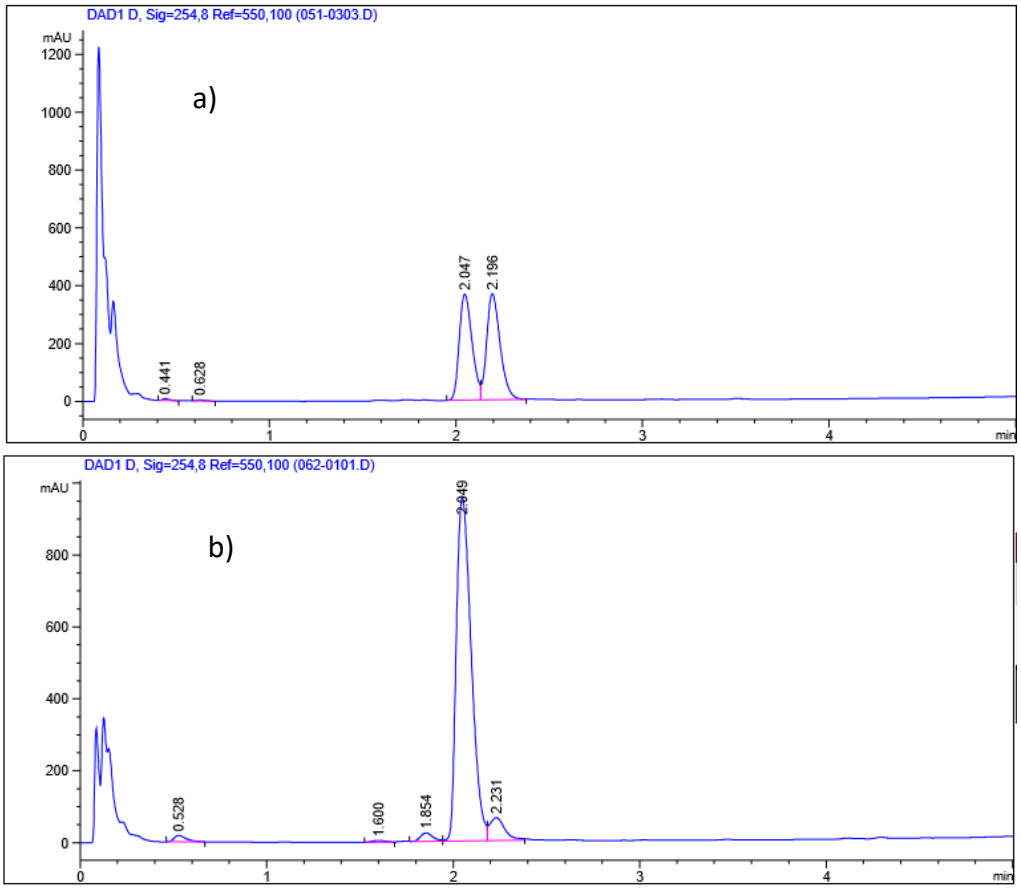
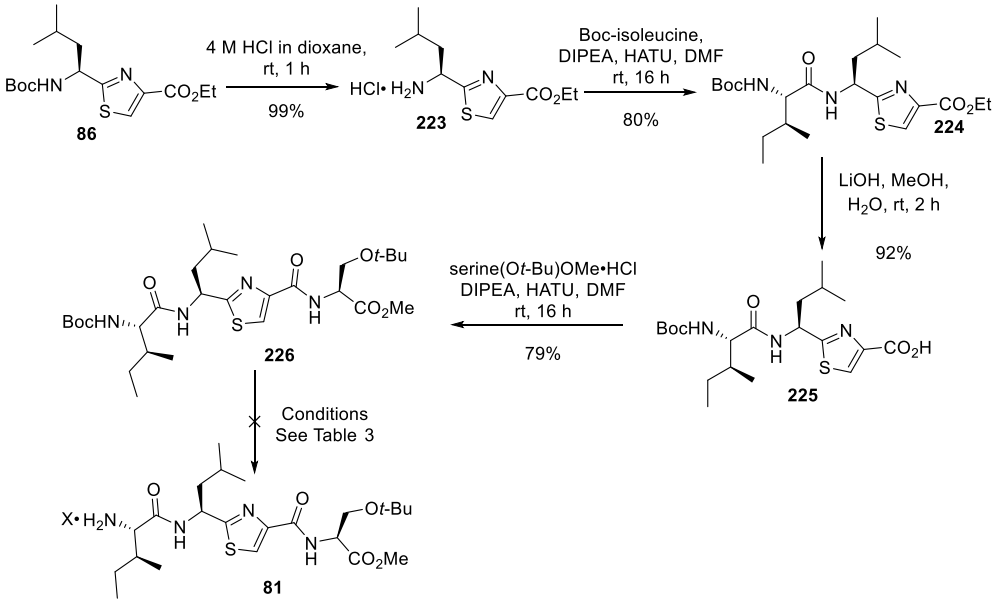


*Figure 16. HPLC traces of a) coupling with D/L valine derivative **221**, b) coupling with L valine derivative **209** both using conditions from Table 2, Entry 9. HPLC using method B (see general information Section 5.1)*

Using the optimum conditions for the aforementioned coupling reaction to complete the synthesis of peptide **211**, a final ester deprotection was carried out using Me_3SnOH in quantitative yield, as advocated by Nicolaou in the synthesis of thiostrepton **4**, to give intermediate **80** in quantitative yield (Scheme 54).[115]

2.5.2 Synthesis of 2nd quarter fragment 81

The synthesis of intermediate **81** began with thiazole **86** (Scheme 58). Boc deprotection gave amine **223,** which was coupled to Boc-isoleucine to give compound **224**. Ester hydrolysis gave acid **225** in moderate yield, which was followed by amide coupling to serine(O*t*-Bu) methyl ester to give compound **226** in good yield. Unfortunately, the Boc group of **226** could not be selectively deprotected in the presence of the *t*-butyl ether to give **81** in high yield using a range of conditions (Table 3).

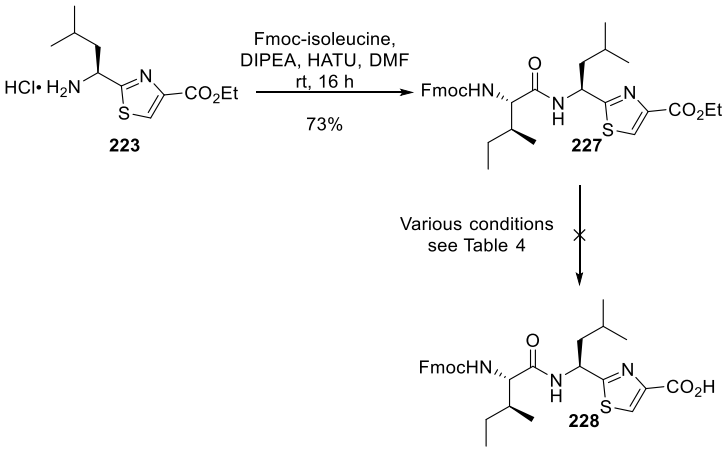


*Scheme 58. Attempted synthesis of **81** using Boc strategy.*

Entry	Solvent/Reagents	Temperature	Time	Yield of 81
1[116]	4M HCl in dioxane	0 °C - rt	25 min	0%
2	CH_2Cl_2/TFA (1:3)	0 °C - rt	50 min	29%
3[117]	Methanesulfonic acid in CH_2Cl_2/*t*-BuOAc (1:4)	0 °C - rt	16 h	0%

*Table 3. Conditions for Boc deprotection of **226**.*

As selective Boc-deprotection proved unsuccessful, Fmoc was tested for the protection of the amino group, hopefully allowing for orthogonal deprotection of the amino group from the *t*-butyl ether (Scheme 59). Amine **223** was therefore coupled to commercially available Fmoc-isoleucine to give compound **227**. A range of conditions were tested for the hydrolysis of compound **227** to give acid **228** (Table 4). Unfortunately, the Fmoc group was unable to withstand hydrolysis conditions and was itself deprotected. The highest yielding conditions were with trimethyltin hydroxide (Entry 3). However, this reaction only gave a moderate yield and when scaled up would require large amounts of the tin reagent.

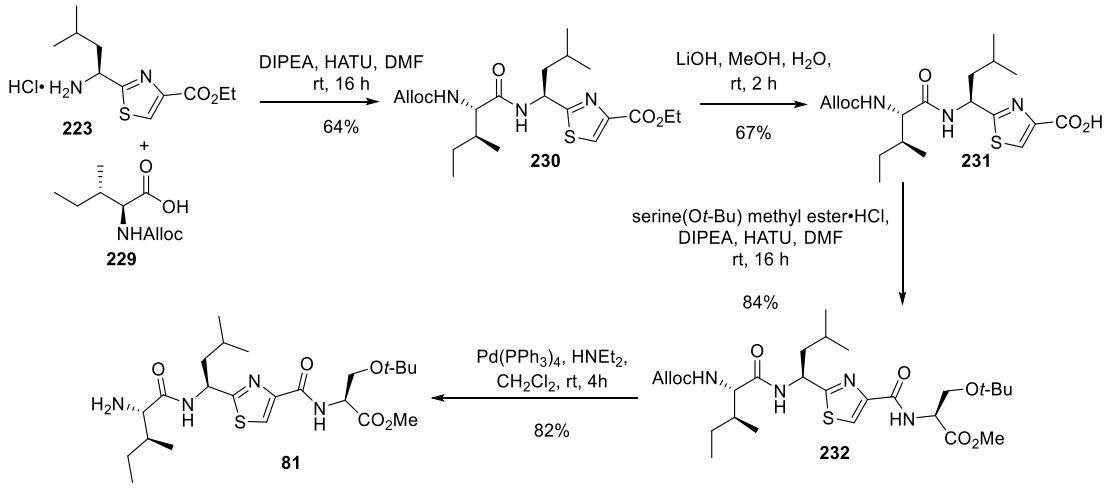


*Scheme 59. Attempted synthesis of **228** using Fmoc strategy.*

Entry	Solvent	Reagent	Time	Yield of 228
1	H_2O/THF (1:5)	LiOH	3 h	0%
2[118]	H_2O/IPA (1:2.3)	NaOH, $CaCl_2$	16 h	0%
3[115]	1,2-DCE	Me_3SnOH	2 h	56%

*Table 4. Conditions for ester hydrolysis of **227**.*

Following limited success using Boc and Fmoc as amino protecting groups, a strategy using Alloc was explored (Scheme 60). It was hoped that the Alloc group would withstand ester hydrolysis with hydroxide, and be selectively deprotected using palladium catalysis without affecting the *t*-butyl ether protecting group. Amine **223** was coupled to the easily synthesised Alloc-isoleucine **229** to give compound **230**. A single crystal of this compound allowed the X-ray structure to be deduced, confirming the structure and stereochemistry of **230** (Figure 17). Ester hydrolysis with lithium hydroxide gave acid **231** in moderate yield. Peptide coupling with serine(O*t*-Bu) methyl ester gave compound **232.** Pleasingly, Alloc deprotection of **232** using $Pd(PPh_3)_4$ gave intermediate **81** in good yield.



*Scheme 60. Synthesis of **81** using Alloc strategy.*

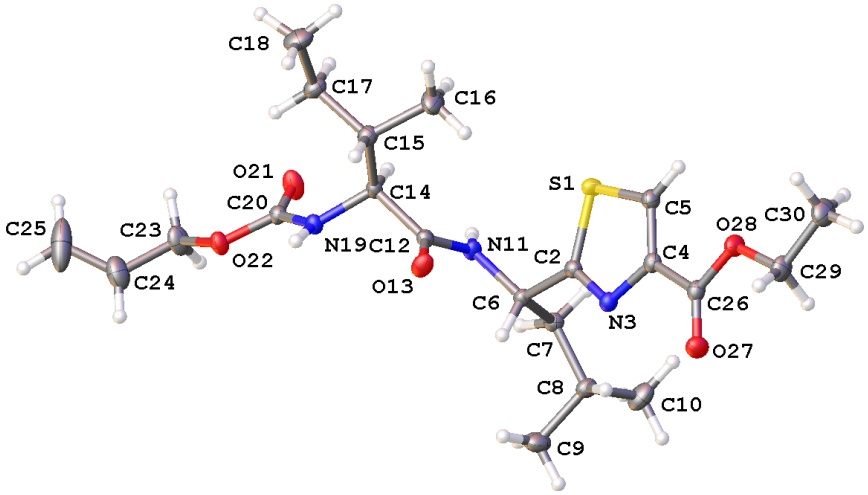


*Figure 17. X-Ray crystal structure of **230**.*

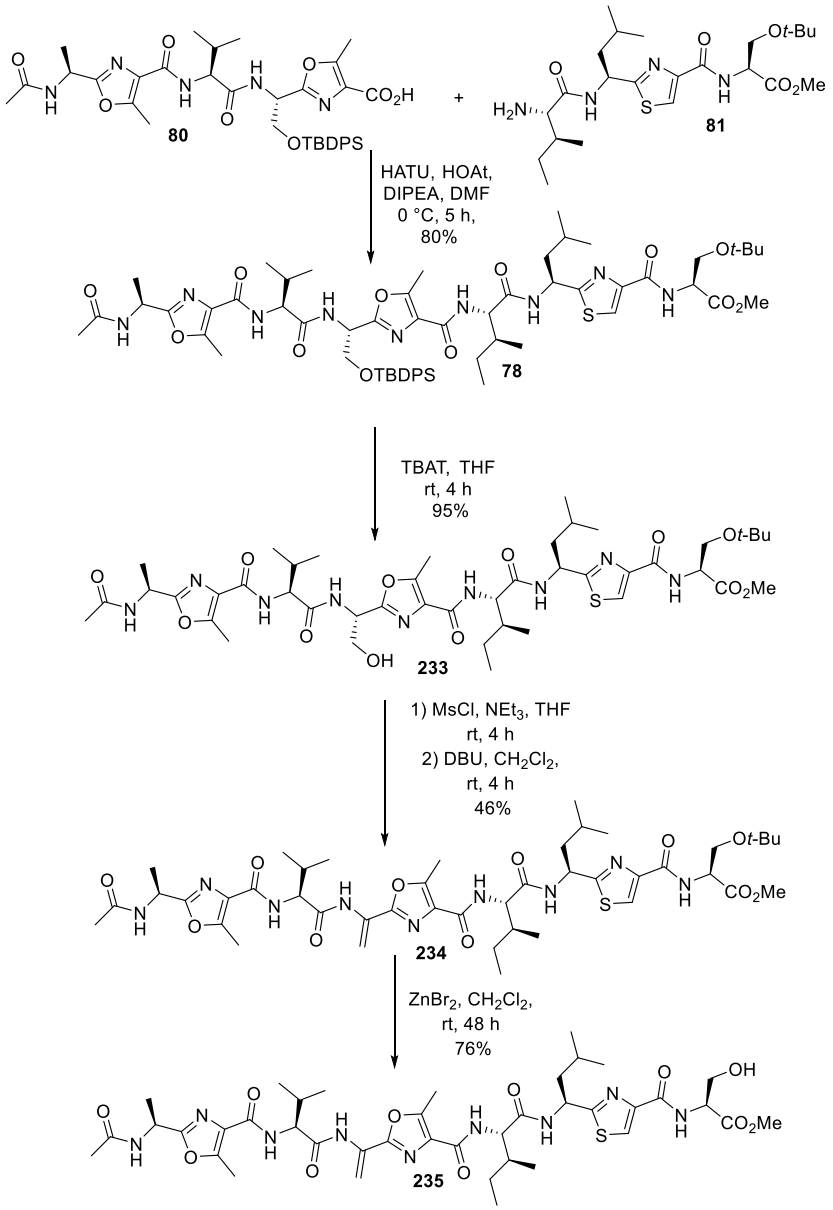
2.5.3 Completion of *N*-terminal fragment 78

With intermediates **80** and **81** in hand, synthesis of the *N*-terminal fragment **78** was carried out, alongside with using the *N*-terminal alkene **235** as a model for the total synthesis. The aim of the synthetic route was to determine

appropriate reaction conditions for the synthesis of the dehydroalanine residue from serine, and deprotection of the *t*-butyl ether protecting group.

Therefore, an amide coupling between **80** and **81** with HATU and HOAt gave compound **78** in high yield (Scheme 61). Silyl group deprotection gave alcohol **233** in good yield using TBAT.[119] The dehydroalanine functionality was installed using a mesylation/elimination strategy. Mesylation was carried out with methanesulfonyl chloride and triethylamine.[82] After concentration and treatment with DBU, dehydroalanine compound **234** was obtained in moderate yield. The final deprotection involved the removal of the *t*-butyl ether to give desired alcohol **235**. This reaction was thought to be problematic due to the instability of the enamide under the acidic conditions usually used for this deprotection.

Pleasingly, several conditions attempted gave the desired product **235** in good yield (Table 5). Initial results with TFA (Entry 1) gave exclusively the enamide hydrolysis products, but at higher concentrations and at lower temperature, the desired product could be isolated in low yield (Entry 2). The use of $TiCl_4$ and $ZnBr_2$ both gave the desired product **235** in good yield. The reaction with $ZnBr_2$ could be easily scaled up, maintaining high yield when allowing the reaction to run for a longer time (48 h) (Entry 5). At this stage, it was encouraging to note that the NMR spectra of the *N*-terminal alcohol **235** in DMSO matched the reported NMR spectroscopic data for goadsporin **64** reasonably well.[36]



*Scheme 61. Synthesis of N-terminal alkene **235**.*

Entry	Conditions	Time	Yield of 235
1	TFA/CH_2Cl_2 (1:1), rt	2.5 h	0%
2	TFA/CH_2Cl_2 (9:1), 0 °C	10 min	46%
3[120]	TMSI, CH_2Cl_2, rt	40 min	0%
4[121]	$TiCl_4$, CH_2Cl_2, -45 °C	1.5 h	100%
5[122]	$ZnBr_2$, CH_2Cl_2, rt	48 h	76%

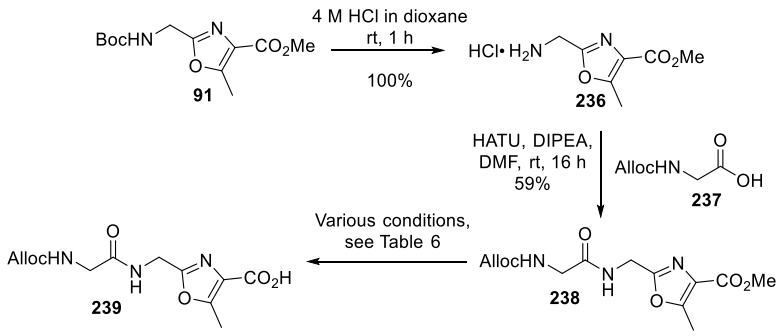
*Table 5. Conditions for synthesis of **235**.*

2.6 Synthesis of *C*-terminal fragment 79

During the synthesis of the *N*-terminal fragment **78**, the nature of the chosen protecting groups was shown to be compatible with the required transformations (see Scheme 61). This knowledge and experience was used to design the synthesis of the *C*-terminal fragment **79** with the appropriate protecting groups in place. To allow for the synthesis of the *C*-terminal fragment **79**, two intermediates **88** and **89** were synthesised (Scheme 66).

2.6.1 Synthesis of 3rd quarter fragment 88

The synthesis of intermediate **88** began with the synthesis of dipeptide **238** (Scheme 62). This was carried out by the Boc-deprotection of methyl oxazole **91** followed by coupling to Alloc-glycine **237** in moderate yield. Unfortunately, the ester hydrolysis of **238** to acid **239** proved to be problematic, with the Alloc group being simultaneously hydrolysed. Various deprotection conditions were tested with limited success (Table 6). Although the reaction with trimethyltin hydroxide proceeded to give acid **239** in moderate yield, it was thought an alternative route may be higher yielding, without the use of such undesirable conditions (Entry 2).

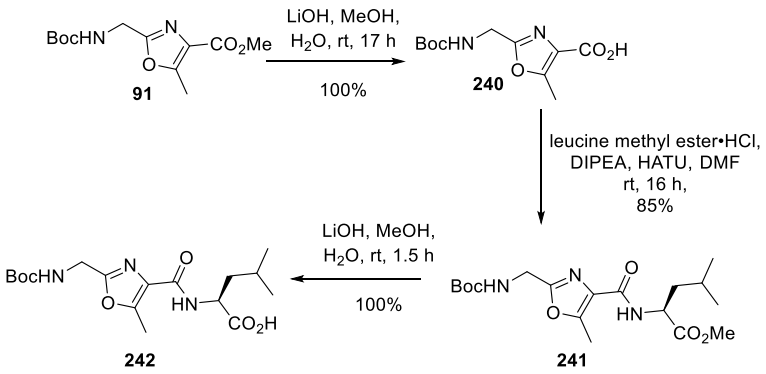


*Scheme 62. Synthesis of acid **239**.*

Entry	Reagent/Solvent	Conditions	Time	Yield of 239
1	LiOH in MeOH/H_2O (4:1)	rt	2 h	20%
2[115]	Me_3SnOH in 1,2-DCE	80 °C	8 h	60%
3[123]	KOH in THF/H_2O/MeOH (1:1:1.5)	0 °C	2 h	16%
4[124]	1M BBr_3 in CH_2Cl_2	-10 °C	2 h	21%
5[125]	BaOH in MeOH	80 °C	2 h	0%

*Table 6. Conditions for hydrolysis of **238**.*

Thus, a different route to intermediate **88** was designed (Scheme 63). Methyl oxazole **91** was hydrolysed to acid **240** that was coupled to leucine methyl ester to give **241**. Dipeptide **241** was then successfully hydrolysed with lithium hydroxide to give acid **242** in quantitative yield, for which a crystal structure confirmed the desired stereochemistry (Figure 18).



*Scheme 63. Synthesis of acid **242**.*

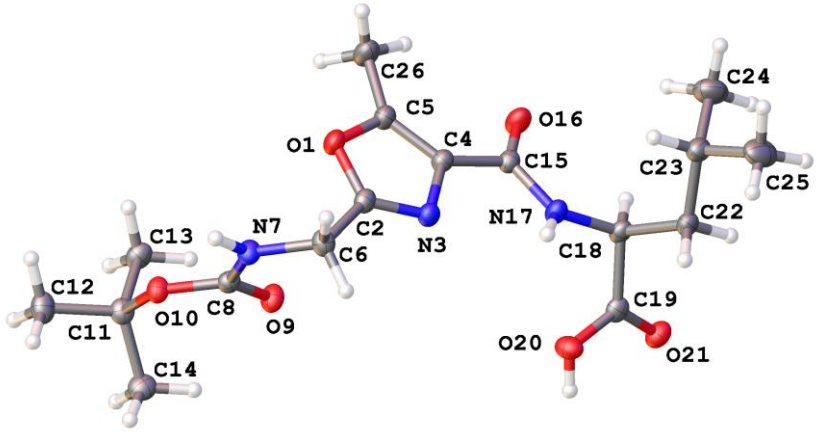
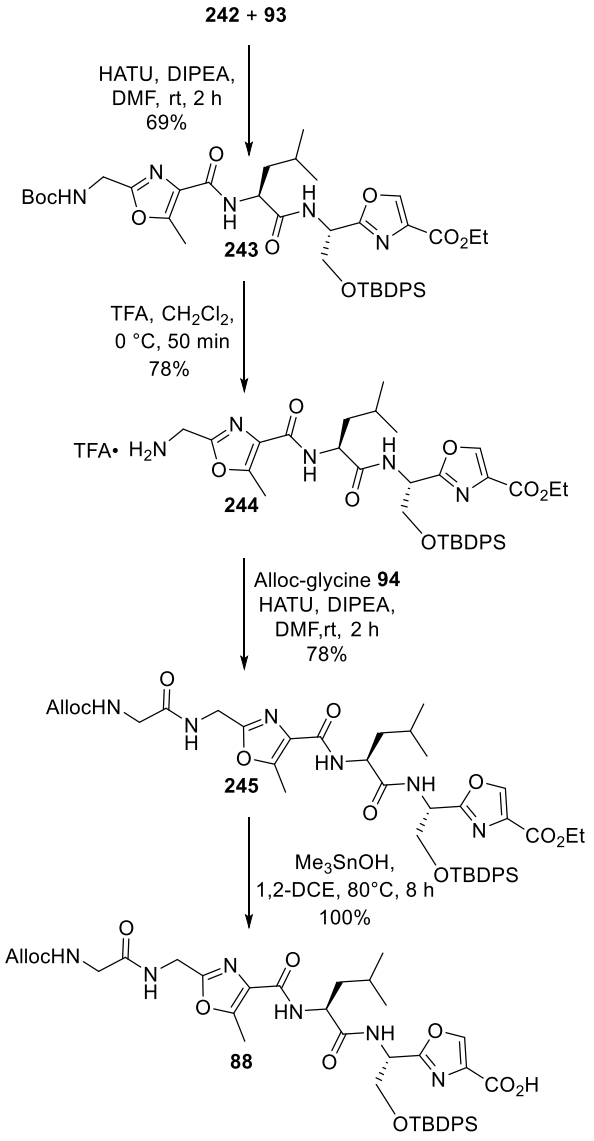


*Figure 18. X-Ray crystal structure of acid **242**.*

Acid **242** was then coupled to oxazole **93** using HATU to give compound **243** in reasonable yield (Scheme 64). Selective Boc-deprotection was carried out using TFA to give amine **244**, which was coupled to Alloc-glycine **237** with HATU to give intermediate **245**, from which ester hydrolysis proceeded in quantitative yield to give desired acid **88**.

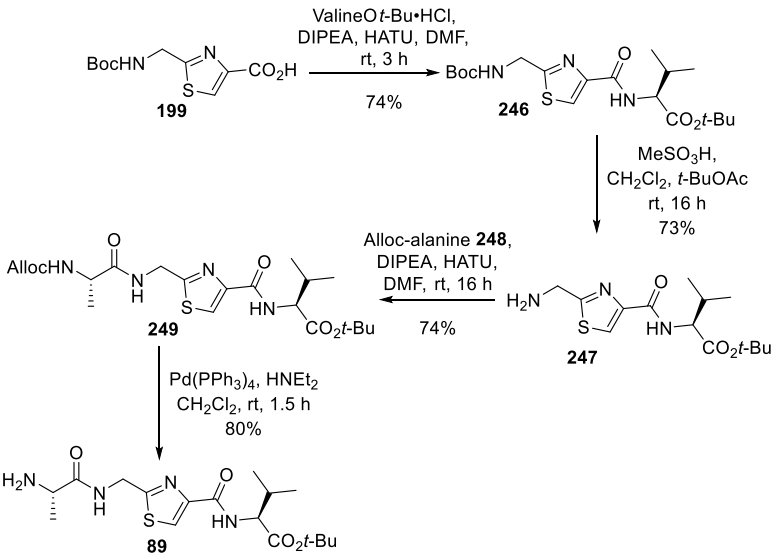


*Scheme 64. Synthesis of intermediate **88**.*

2.6.2 Synthesis of 4th quarter fragment 89

For the synthesis of the final 4th quarter fragment **89**, acid **199** was coupled to valine *t*-butyl ester in good yield to give **246**. Selective Boc-deprotection of **246** was then required (Scheme 65). This transformation could be carried out using methanesulfonic acid with *t*-butyl acetate as a co-solvent with dichloromethane to give amine **247** in good yield.[117] Coupling to Alloc-alanine

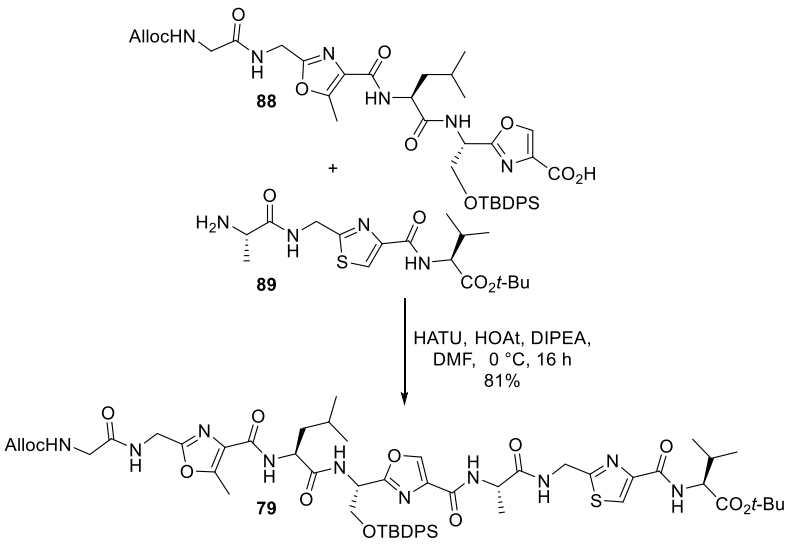
248 gave intermediate **249** in good yield. Deprotection of **249** using palladium tetrakis(triphenylphosphine) and diethylamine gave amine **89** in an 80% yield.



*Scheme 65. Synthesis of amine **89**.*

2.6.3 Completion of *C*-terminal fragment 79

With the 3rd and 4th quarter fragments, acid **88** and amine **89** in hand, synthesis of the *C*-terminal fragment **79** required coupling using HATU and HOAt to give the protected *C*-terminal fragment **79** in good yield (Scheme 66).



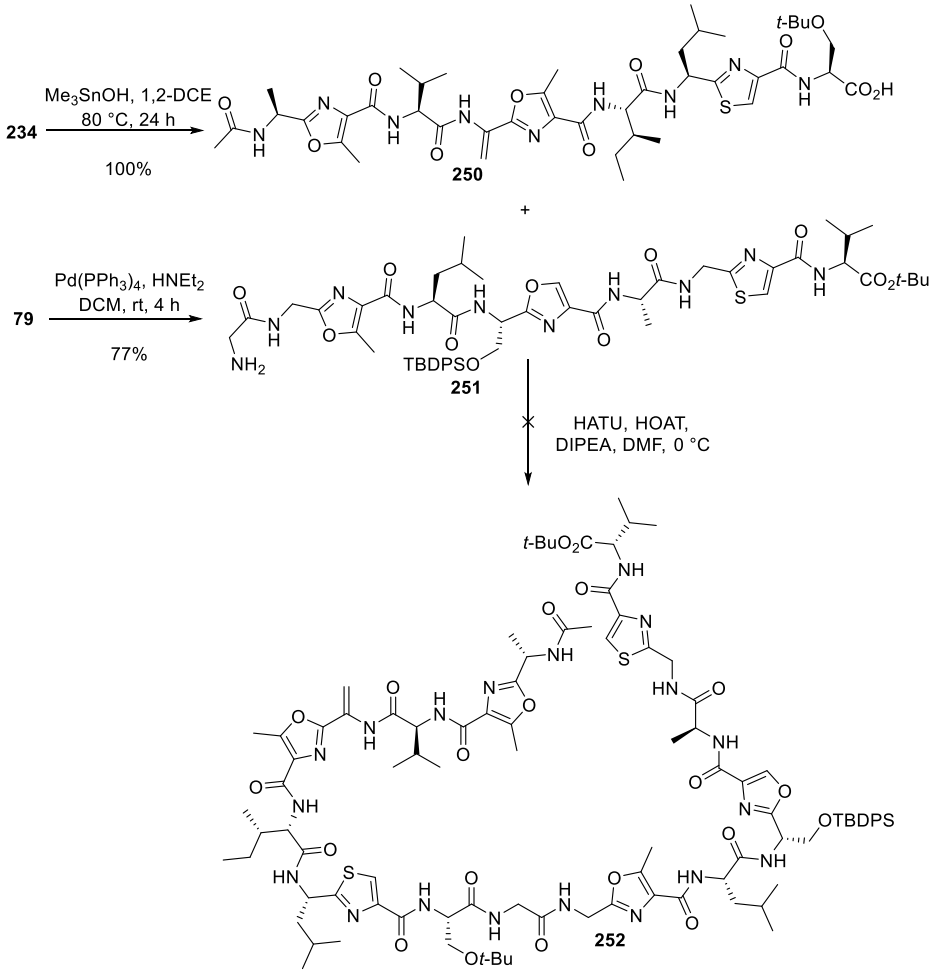
*Scheme 66. Completion of C-terminal fragment **79**.*

2.7 Completion of the Synthesis

To complete the synthesis of goadsporin **64**, all that remained was to couple the *N*- and *C*- terminal fragments together, install the two dehydroalanines and deprotect the remaining protecting groups. Here, there were several options to consider, as the *N*- and *C*-terminal fragments could be coupled together with the dehydroalanines still hydrated and protected, or, the dehydroalanines would be installed first followed by coupling of the two halves.

The first attempt towards a protected analogue of goadsporin **64** proceeded with deprotection of ester **234** to give acid **250**, and peptide **79** to give amine **251** (Scheme 67). At this point, it was thought that having a dehydroalanine already incorporated in the *N*-terminal fragment could potentially be higher yielding overall, as literature evidence for installing two dehydroalanines simultaneously had led to complications.[105] Thus, acid **250** and amine **251** were

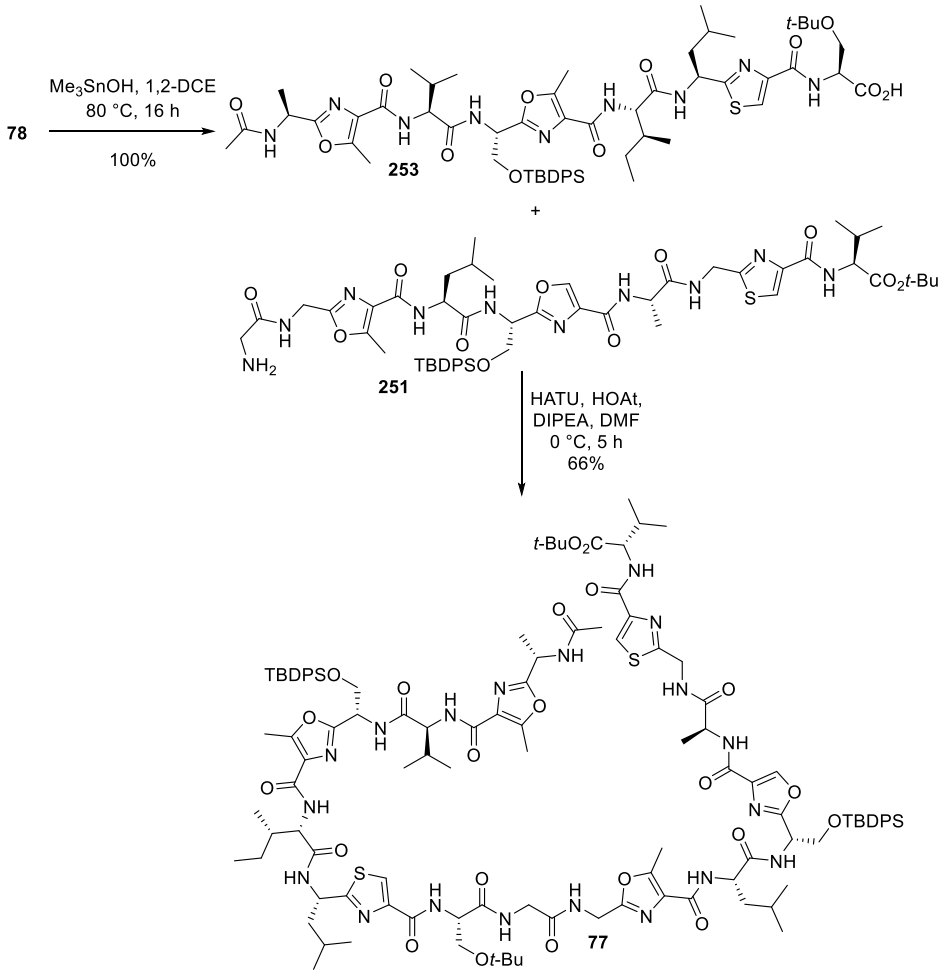
subjected to amide coupling conditions. TLC analysis showed consumption of starting material, and MS of the reaction mixture indicated the correct mass ion. However, the reaction gave a range of products and the desired product **252** could not be successfully isolated from the complex mixture.



*Scheme 67. Attempted synthesis of peptide **252**.*

It was postulated that the numerous products arising from this method may come from the instability of the enamide moiety when subjected to amide coupling conditions. Therefore, a second approach involved coupling of the *N*- and *C*-terminal fragments with both of the dehydroalanines hydrated and

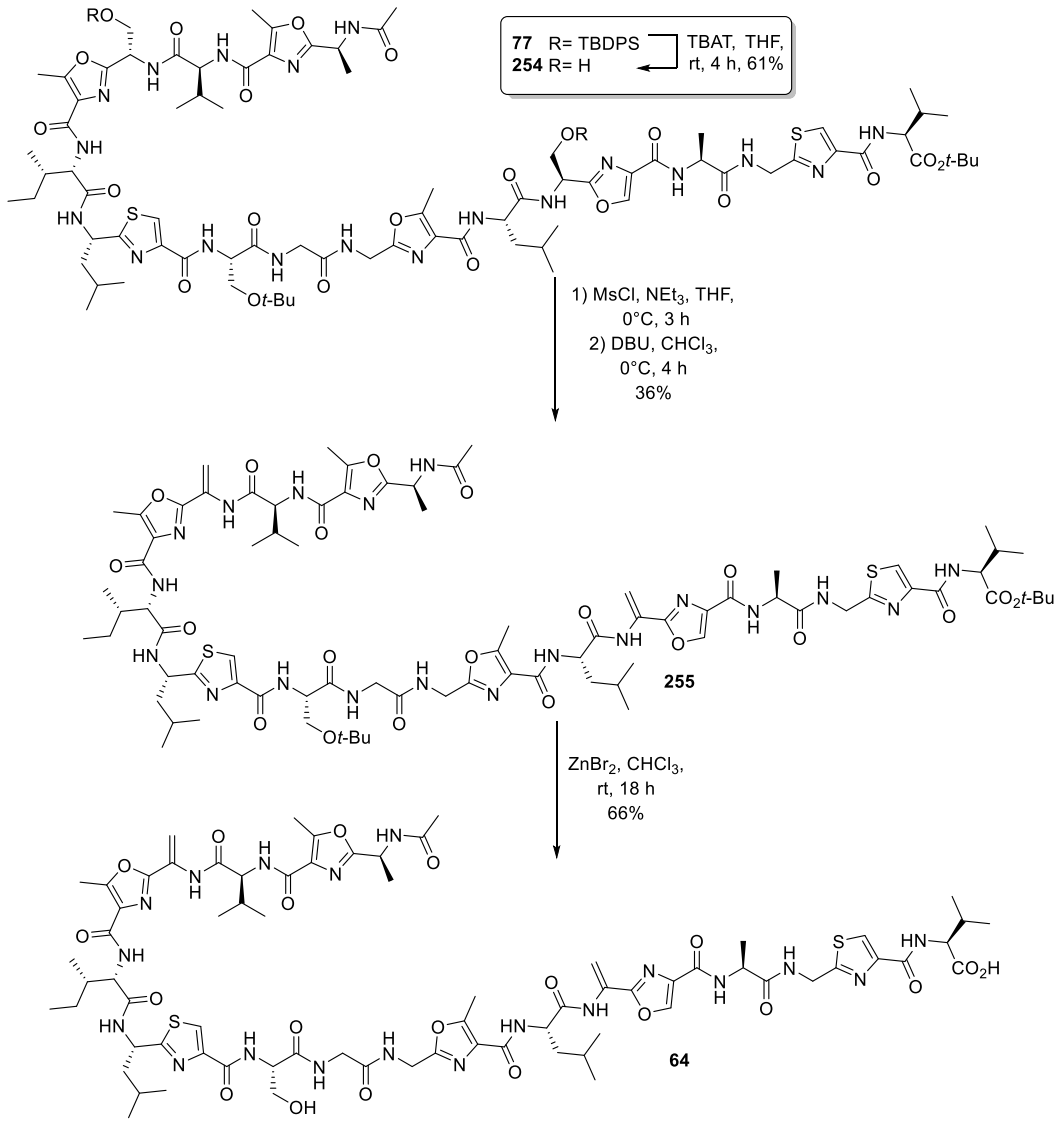
protected (Scheme 68). Consequently, acid **253,** synthesised from peptide **78,** and amine **251** were coupled in moderate yield to give protected peptide **77**.



*Scheme 68. Synthesis of protected peptide **77**.*

Having synthesised protected peptide **77**, the final steps remained (Scheme 69). The two silyl groups were cleanly deprotected using TBAT to give diol **254**. Double mesylation and elimination was carried out in a two-step process, firstly by treatment with methanesulfonyl chloride and triethylamine to give the double mesylate, followed by treatment with DBU in chloroform to give the double enamide product **255**. This desired product was isolated in a moderate yield, often with one mesylate or alcohol side product also being identified

during purification. However, **255** could be separated from other products by column chromatography in a 36% yield. The final step in the synthesis was deprotection of the *t*-butyl ether and ester groups for which conditions had previously been tested on the *N*-terminal fragment **234**. Accordingly, **255** was treated with the Lewis acid zinc bromide in dichloromethane to give goadsporin **64**. Even after being tested on the *N*-terminal fragment **234**, this reaction proved to be difficult, with enamide hydrolysis being observed. Pleasingly, upon changing the solvent from dichloromethane to chloroform with vigorous stirring, goadsporin **64** was isolated after column chromatography in a 66% yield.



*Scheme 69. Synthesis of goadsporin **64**.*

An authentic sample of natural goadsporin **64** was provided thanks to Professor Hiroyasu Onaka and Dr Shumpei Asamizu from the University of Tokyo. Comparison of the natural sample with the synthesised sample by LCMS (Figure 19) and HPLC (Figure 20) along with analysis of a mixed sample containing both natural and synthesised goadsporin **64**, confirmed the total synthesis was complete (see Experimental for LCMS and HPLC details).

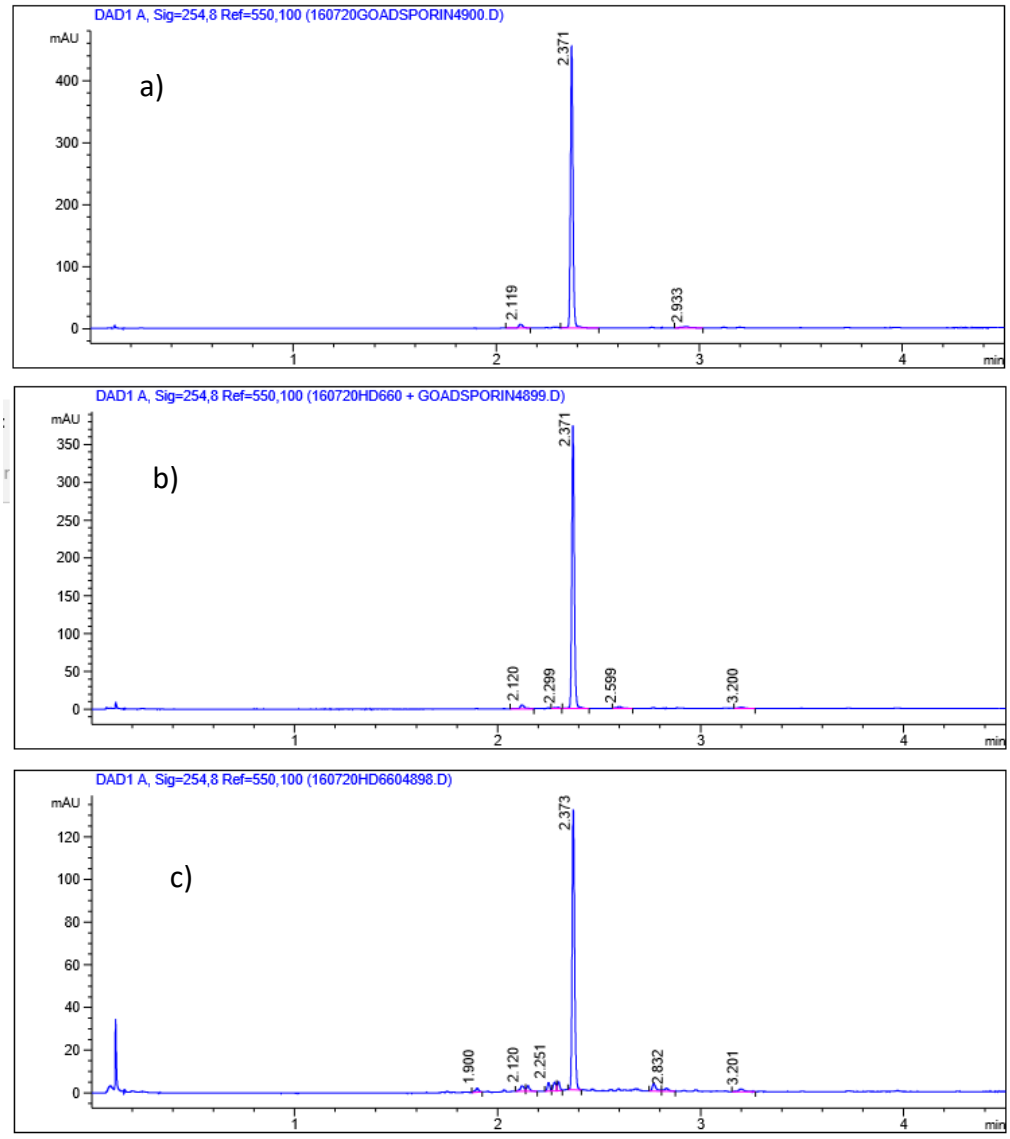


*Figure 19. LCMS analysis of a) natural goadsporin **64**, b) combined sample, c) synthesised goadsporin **64**.*

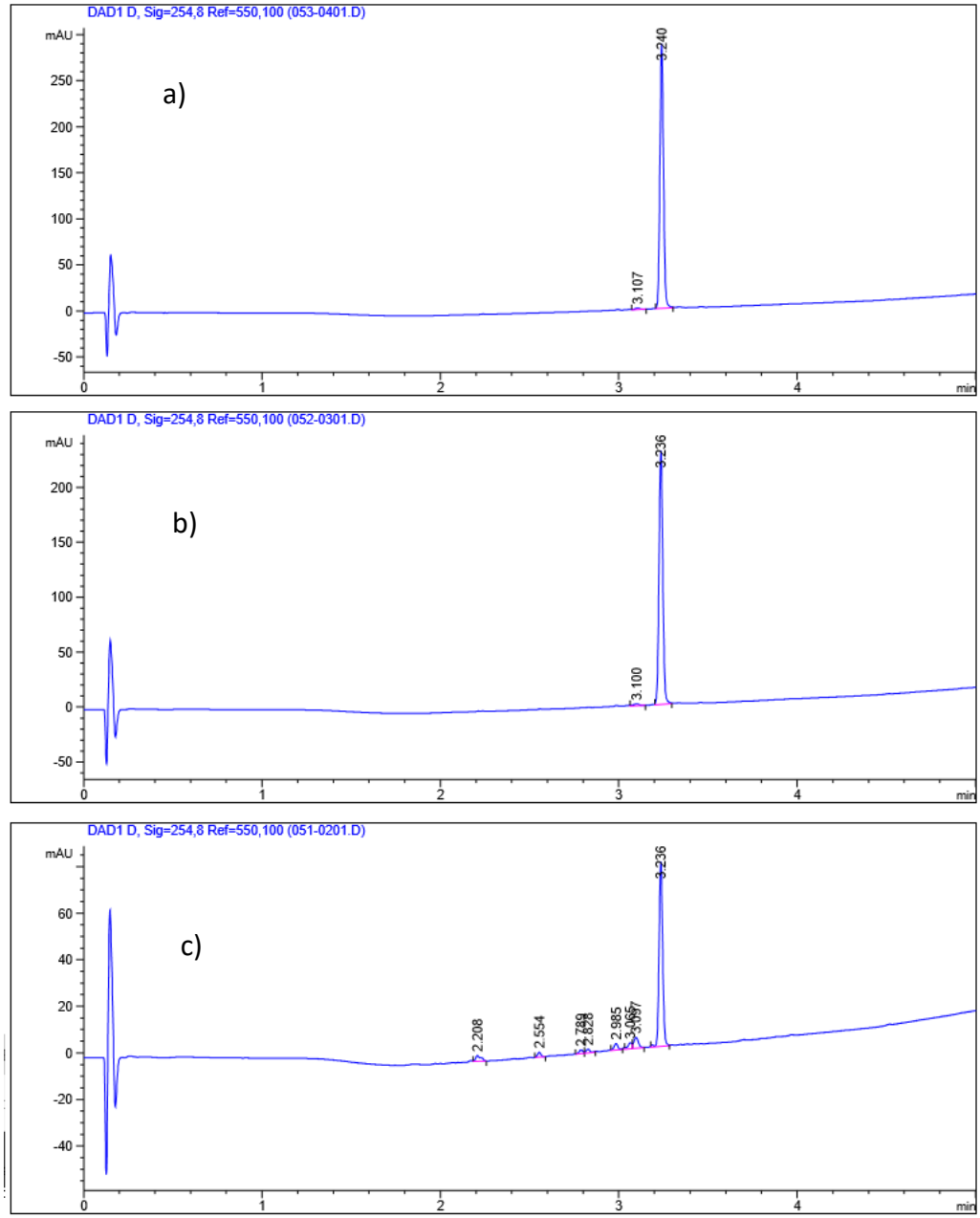


Figure 20. HPLC analysis of a) natural goadsporin ***64****, b) combined sample, c) synthesised goadsporin* ***64****. HPLC using method A (see general information Section 5.1).*

2.8 NMR spectroscopy studies

Having completed the total synthesis, NMR spectroscopic comparison of the synthetic and natural goadsporin **64** was carried out (Table 7). A graph shows this comparison to highlight the differences between the literature and the results from our synthesis (Figure 22).[36] Here, the NH shifts have been highlighted in red. Variation in the shift for these NH protons may be expected due to these protons being labile and exchangeable. This bar charts shows clearly that the two sets of data match well other than the proton signal at number 58 which represents the αCH of the valine at the *C*-terminal.

Residue	Position	Natural δ (^{1}H) (ppm)	Synthetic δ (^{1}H) (ppm)
AcAla[1]	αCH	5.00, 1H, quin 7.3	5.01, 1H, quin 7.4
	βCH_3	1.40, 1H, d 7.1	1.41, 1H, d 7.1
	NH	8.50, 1H, d 7.8	8.53, 1H, d 7.9
	$AcCH_3$	1.83, 3H, s	1.84, 3H, s
MeOxz[2]	5-CH_3	2.51, 3H, s	2.54, 3H, s
Val[3]	αCH	4.62, 1H, m	4.65, 1H, m
	βCH	2.17, 1H, m	2.18, 1H, m
	γCH_3	0.96, 3H, d 6.7	0.96, 3H, m
	γCH_3	0.91, 3H, d, 7.0	0.91, 3H, m
	NH	7.55, 1H, d 9.1	7.57, 1H, d 9.1
DeAla[4]	βCH	5.69, 1H, s	5.70, 1H, s
	βCH	5.83, 1H, s	5.84, 1H, s
	NH	10.01, 1H, s	10.07, 1H, s
MeOxz[5]	5-CH_3	2.58, 3H, s	2.59, 3H, s
Ile[6]	αCH	4.49, 1H, m	4.50, 1H, m
	βCH	1.87, 1H, m	1.88, 1H, m
	γCH	1.06, 1H, m	1.06, 1H, m
	γCH	1.43, 1H, m	1.45, 1H, m
	γCH_3	0.88, 3H, d 5.9	0.87, 3H, d 5.2
	δCH_3	0.82, 3H, t 7.3	0.83, 3H, t 7.4
	NH	7.51, 1H, d 9.3	7.54, 1H, d 9.3
Leu[7]	αCH	5.19, 1H, q 7.7	5.20, 1H, q 7.4

	βCH_2	1.79, 2H, t 7.5	1.80, 2H, t 7.1
	γCH	1.68, 1H, sep 6.7	1.69, 1H, m
	δCH_3	0.92, 3H, d 6.3	0.93, 3H, m
	δCH_3	0.86, 3H, d 6.5	0.87, 3H, m
	NH	9.02, 1H, d, 8.1	9.06, 1H, d 8.4
Thiaz[8]	5-H	8.19, 1H, s	8.21, 1H, s
Ser[9]	αCH	4.50, 1H, m	4.52, 1H, m
	βCH	3.76, 1H, dd, 10.7, 4.9	3.77, 1H, m
	βCH	3.68, 1H, dd, 11.0, 4.5	3.69, 1H, m
	NH	8.07, 1H, d 7.7	8.10, 1H, d 7.6
Gly[10]	αCH	3.82, 1H, dd, 16.9, 5.9	3.83, 1H, dd, 17.0, 5.8
	αCH	3.75, 1H, dd, 16.9, 5.5	3.75, 1H, dd, 16.4, 5.2
	NH	8.46, 1H, t, 5.2	8.55, 1 H, m
Gly[11]	αCH	4.39, 1H, dd, 17.9, 6.0	4.40, 1H, dd, 16.7, 5.5
	αCH	4.37, 1H, dd, 17.4, 5.3	4.37, 1H, dd, 16.7, 5.5
	NH	8.53, 1H, t 5.6	8.59, 1H, t 6.3
MeOxz[12]	5-CH_3	2.53, 3 H, s	2.52, 3H, s
Leu[13]	αCH	4.72, 1H, td, 9.4, 3.8	4.72, 1H, ddd 10.4, 8.4, 4.4
	βCH	1.74, 1H, m	1.75, 1H, m
	βCH	1.58, 1H, m	1.59, 1H, m
	γCH	1.62, 1H, m	1.62, 1H, m
	δCH_3	0.89, 3H, d	0.89, 3H, m
	δCH_3	0.89, 3H, d	0.89, 3H, m
	NH	7.94, 1H, d, 8.6	7.99, 1H, d, 8.2
DeAla[14]	βCH	5.96, 1H, s	5.97, 1H, s
	βCH	5.70, 1H, s	5.71, 1H, s
	NH	9.88, 1H, s	9.90, 1H, s
Oxz[15]	5-H	8.69, 1H, s	8.71, 1H, s
Ala[16]	αCH	4.53, 1H, quin 7.2	4.54, 1H, m
	βCH_3	1.37, 3H, d, 7.1	1.38, 3H, d, 7.1
	NH	8.06, 1H, d 7.6	8.07, 1H, d 7.7
Gly[17]	αCH	4.65, 1H, dd, 16.5, 6.3	4.65, 1H, dd, 17.0, 6.5
	αCH	4.58, 1H, dd, 16.5, 5.7	4.60, 1H, m
	NH	9.06, 1H, t 5.6	9.08, 1H, t 5.5
Thiaz[18]	5-H	8.21, 1H, s	8.18, 1H, s
Val[19]	αCH	4.32, 1H br t, 4.0	4.21, 1H, br s
	βCH	2.18, 1H, m	2.18, 1H, m
	γCH_3	0.90, 3H, d	0.90, 3H, m
	γCH_3	0.89, 3H, d	0.89, 3H, m
	NH	7.86, 1H, d, 8.7	7.94, 1H, br d, 8.5

*Table 7. ^1H NMR spectroscopic comparison of natural and synthetic goadsporin **64**.*

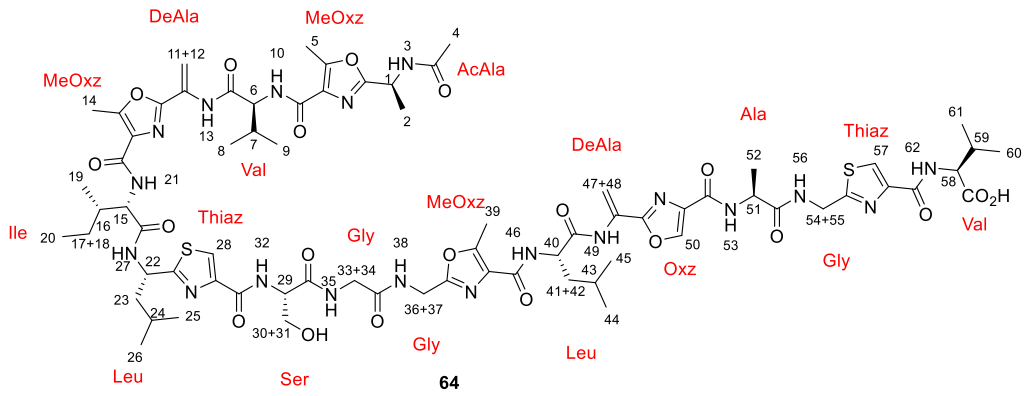


*Figure 21. Goadsporin **64** with proton signals labelled.*

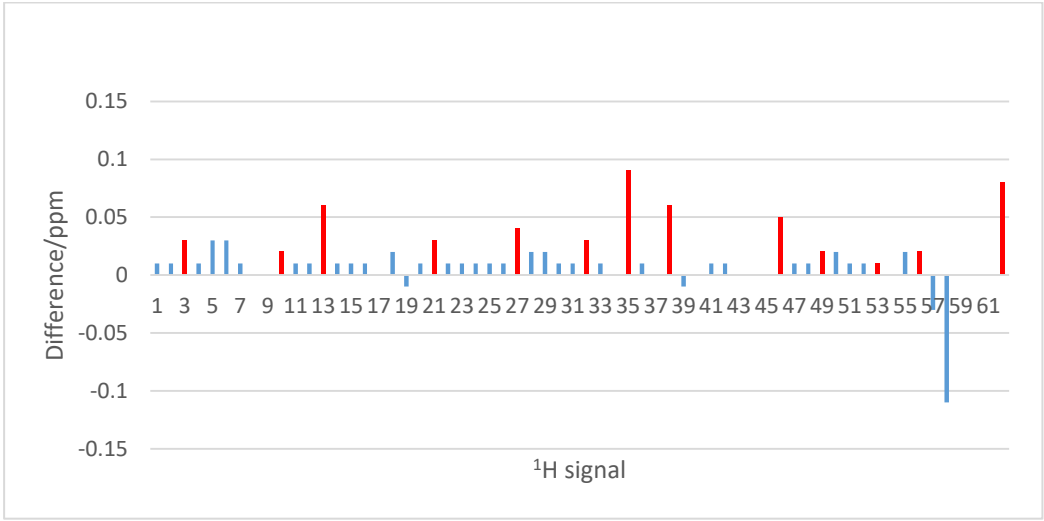


*Figure 22. ^{1}H NMR spectroscopic comparison between natural and synthetic goadsporin **64.** Proton signals labelled as shown in Figure 21.*

This effect of seeing a difference between the synthetic and isolated material was also reflected in the ^{13}C NMR spectroscopic data (Table 8). A bar chart shows this difference in shift more clearly, with signals 68, 69 and 72 showing the highest variation (Figure 24). Signal 68 is the valine αCH, 69 the βCH and 72 is the CO_2H. An explanation for this difference is again due to the exchangeable nature of the *C*-terminal carboxylic acid of goadsporin **64**. If the synthetic material is at a slightly difference pH or contains a different amount of water,

then the rate of exchange of the carboxylic acid may be different, resulting in a different chemical shift of the signals at the *C*-terminal.

Residue	Position	Natural δ (^{13}C) (ppm)	Synthetic δ (^{13}C) (ppm)
AcAla[1]	αCH	42.2	42.2
	βCH_3	18.7	18.8
	AcCO	168.7	168.8
	$AcCH_3$	22.4	22.5
MeOxz[2]	2	162.0	162.1
	4	128.4	128.2
	5	152.8	152.5
	5-CH_3	11.3	11.4
	CO	160.7	160.7
Val[3]	αCH	56.9	57.0
	βCH	31.3	31.4
	γCH_3	19.1	19.2
	γCH_3	17.8	17.9
	CO	170.7	170.7
DeAla[4]	αC	129.0	129.1
	βCH_2	109.2	109.3
MeOxz[5]	2	155.3	155.4
	4	129.3	129.3
	5	153.1	153.2
	5-CH_3	11.4	11.5
	CO	160.3	160.4
Ile[6]	αCH	56.1	56.1
	βCH	37.4	37.4
	γCH_2	24.0	24.1
	γCH_3	15.6	15.6
	δCH_3	10.9	10.9
	CO	170.8	170.8
Leu[7]	αCH	49.3	49.3
	βCH_2	43.1	43.1
	γCH	24.3	24.3
	δCH_3	22.9	23.0
	δCH_3	21.1	21.1
Thiaz[8]	2	174.6	174.7
	4	149.0	149.1
	5	124.1	124.2
	CO	160.0	160.1
Ser[9]	αCH	54.9	54.9
	βCH_2	61.7	61.8

	CO	170.0	170.1
Gly[10]	αCH_2	42.1	42.1
	CO	169.1	169.2
Gly[11]	αCH_2	35.7	35.7
MeOxz[12]	2	158.3	158.3
	4	128.2	128.4
	5	153.1	152.9
	5-CH_3	11.3	11.3
	CO	160.8	160.9
Leu[13]	αCH	51.2	51.2
	βCH_2	40.7	40.7
	γCH	24.4	24.5
	δCH_3	23.0	23.1
	δCH_3	21.5	21.5
	CO	171.8	171.9
DeAla[14]	αC	129.0	129.0
	βCH_2	108.0	108.1
Oxz[15]	2	157.9	157.9
	4	136.2	136.2
	5	142.5	142.6
	CO	159.1	159.1
Ala[16]	αCH	48.0	48.1
	βCH_3	18.3	18.4
	CO	172.4	172.4
Gly[17]	αCH_2	40.5	40.5
Thiaz[18]	2	170.3	170.3
	4	148.7	149.0
	5	124.5	124.1
	CO	160.0	159.8
Val[19]	αCH	57.1	57.8
	βCH	30.3	31.3
	γCH_3	19.1	19.4
	γCH_3	17.9	18.1
	CO	172.6	174.5

*Table 8. ^{13}C NMR spectroscopic comparison of natural and synthetic goadsporin **64**.*

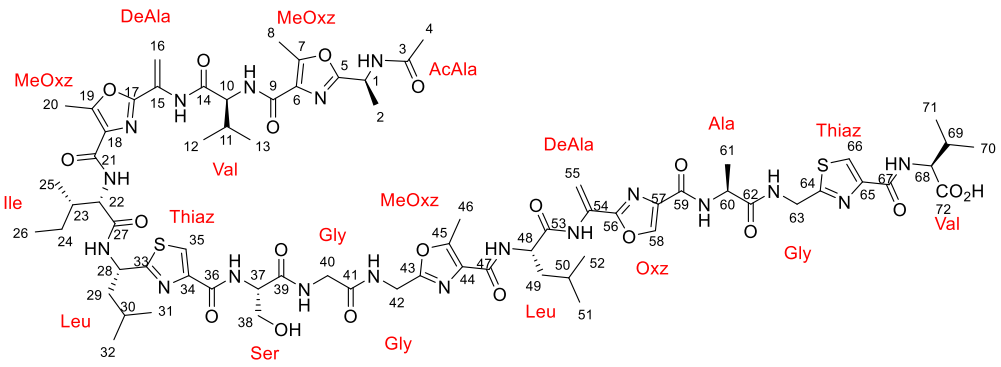


*Figure 23. Goadsporin **64** with carbon signals labelled.*

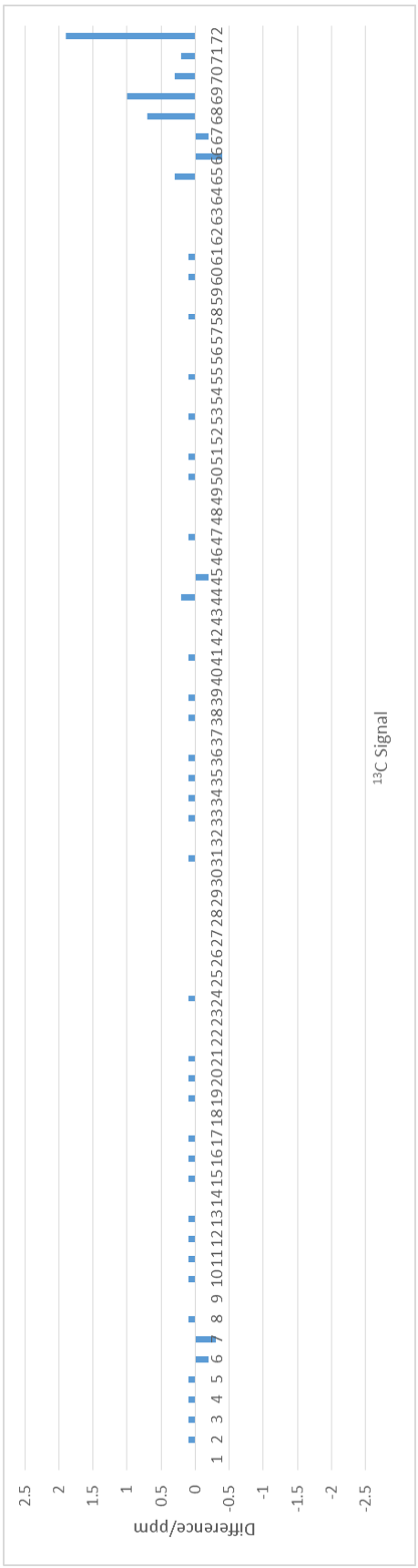


*Figure 24. ^{13}C NMR spectroscopic comparison of natural and synthetic goadsporin **64**. Carbon signals labelled as shown in Figure 23.*

To confirm this hypothesis and rule out epimerisation of the *C*-terminal valine residue, a combined NMR sample containing both natural and synthetic goadsporin **64** was analysed (Figure 25). This shows that although the two samples show two different shifts for the terminal valine αCH (4.32 and 4.21 ppm), in the combined sample only one signal is seen, which is between the other separate shifts (4.31 ppm). The ^{1}H NMR spectra for the combined sample is shown and clearly shows one species is present (Figure 26). This effect is also reflected in the 2D experiments and ^{13}C NMR spectra.

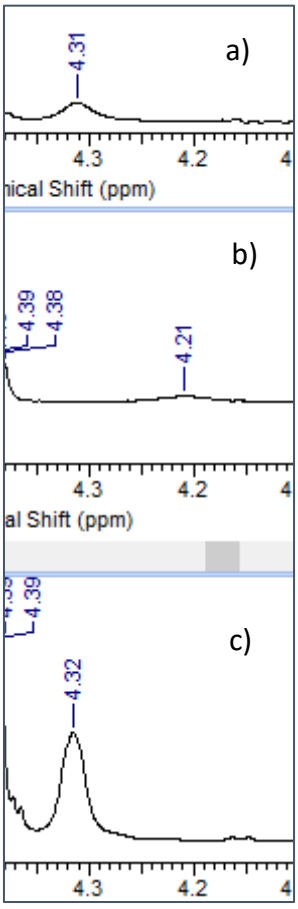


*Figure 25. ^{1}H NMR spectroscopic comparison of the terminal valine αCH of goadsporin **64**; a) combined sample, b) synthetic material, c) natural material.*

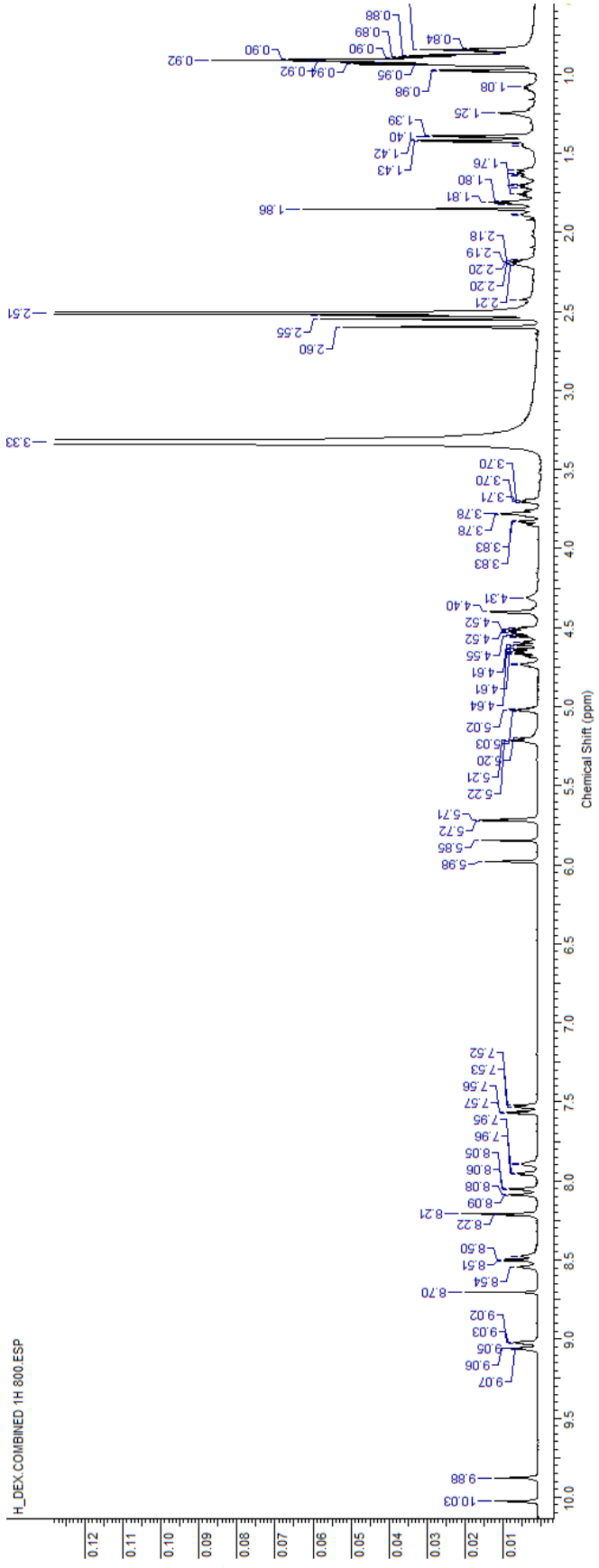


*Figure 26. ^{1}H NMR spectrum of combined sample containing both natural and synthetic goadsporin **64** (DMSO-d_6, 500 MHz).*

Having verified the total synthesis of goadsporin **64** and carried out the NMR spectroscopic comparison, a full NMR spectroscopic assignment was carried out with structural characterisation from first principles using a programme called CCPNMR 2.4. This work was carried out with the help of Dr Huw Williams. The structural analysis was achieved using 2D NMR experiments. HSQC and HMBC experiments were used to link the carbon frame. Other experiments including TOCSY, DQF and QF COSY were used to provide connectivity for the proton framework via ^{1}H J coupling, and NOESY experiments provided through space interactions (see Experimental Section for further information).

Having confirmed the structure, work moved towards elucidating the DMSO conformation of goadsporin **64**. This used a series of NOESY experiments, with different mixing times, which were analysed and for which every NOE signal was accounted for. This work allowed through space distances to be calculated, helping to elucidate the solution structure of goadsporin **64**. Additionally, a map of the interactions between the residues was generated using CCPNMR 2.4, showing no long range interactions (Figure 27). The lines represent interactions as seen from the NOESY experiments. Vertical lines show interactions between different components of the same residue, and lines between residues indicate interactions between residues. The map shows mainly i and i→i+1 interactions, with the exception of a single i→i+2 interaction. The lack of long range interactions suggests a vaguely linear conformation rather than a hairpin-type conformation.

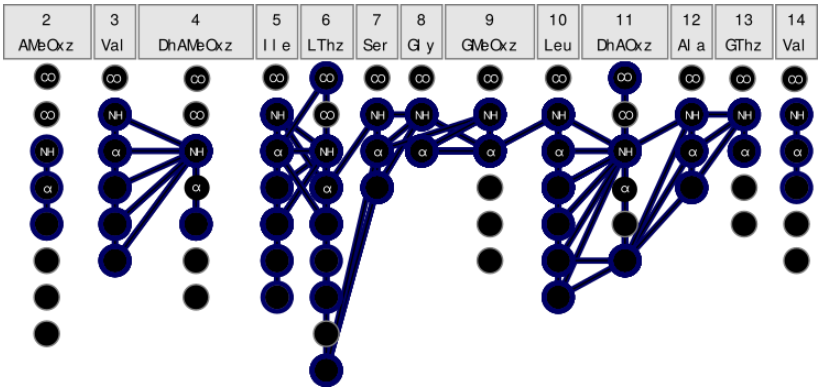


*Figure 27. Connectivity between residues of goadsporin **64** from NOESY experiments. Lines between residues represent through space interactions observed by NMR spectroscopy.*

During analysis of the NOESY data, it was noted that both positive and negative NOEs were seen (Figure 28). This is unusual, as normally small molecules tumble quickly and give positive NOEs, whereas large molecules (such as goadsporin **64**) tumble slowly and give negative NOEs.[126]

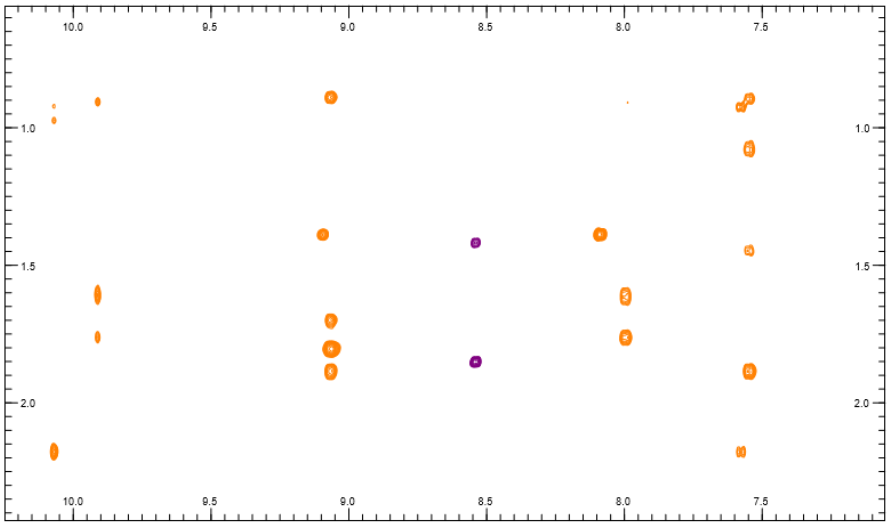


Figure 28. Section of NOESY spectrum showing positive (purple) and negative (orange) NOEs.

The NOE data recorded suggests that the part of the molecule showing positive NOEs is tumbling much faster in comparison to the rest of the molecule. Once

NOEs had been assigned, it was found that the positive NOEs could be attributed to the *N*-terminal section which appears to have increased dynamics compared to the bulk of the molecule (Figure 29).

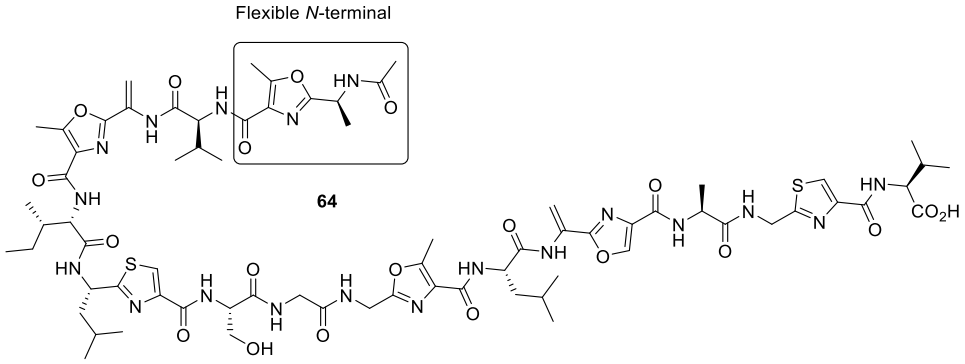


*Figure 29. Structure of goadsporin **64** with flexible N-terminal highlighted.*

To complete the conformational work, molecular modelling of goadsporin **64** was carried out using Spartan 08. Molecular dynamics by means of the Merck Molecular Force Field (MMFF), followed by energy minimisation and optimisation of the geometry gave the structure as shown (Figure 30). This structure was shown to be consistent with the experimental data.

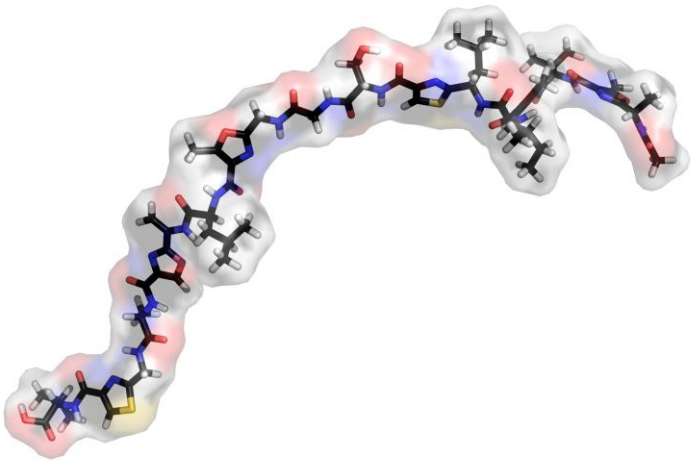
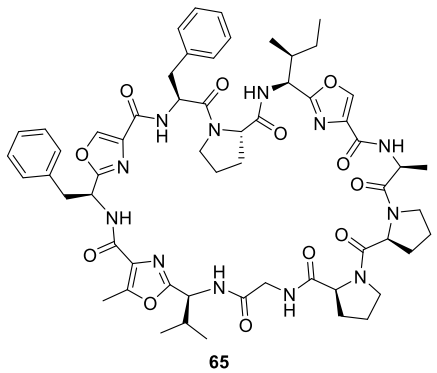


*Figure 30. Model of goadsporin **64** produced using Spartan 08.*

3. Wewakazoles

3.1 Wewakazoles Significance and Previous Synthesis

Wewakazole A **65** was first isolated in 2002 from the cyanobacterium *Lyngbya majuscula*.[37] Gerwick *et al.* described the purification of an extract from the cyanobacteria strain from a coral growth on the coast of Papua New Guinea to give 6.9 mg of wewakazole A **65**. Structure determination using NMR spectroscopy and MS showed the natural product was of peptidic nature with a molecular composition of $C_{59}H_{72}N_{12}O_{12}$ suggesting biosynthesis from twelve amino acid residues. Further NMR analysis using 2D experiments gave rise to several partial structures including two 5-H oxazoles and one 5-Me oxazole. Ultimately NOE studies were used to prove the overall connectivity. The stereochemistry was assigned using Marfey's method, as previously described (Section 2.1), and chiral GCMS analysis with *N*-pentafluoropropyl isopropyl ester derivatives to give the structure shown in Figure 31.



65

*Figure 31. Structure of wewakazole A **65.***

The structure of wewakazole B **66** was published in 2016 by Okino *et al*.[38] Wewakazole B **66** was isolated from *Moorea producens*, a cyanobacterium found in the red sea. After various purification processes, a total of 0.6 mg of wewakazole B **66** was isolated. As with wewakazole A **65**, structure elucidation required thorough NMR spectroscopic analysis in conjunction with MS providing a molecular formula of $C_{58}H_{79}N_{12}O_{12}$ again suggesting origin from twelve amino acids. MS/MS evidence confirmed the proposed structure as similarly to linear peptides, cyclic peptides fragment via known fragmentation pathways.[39] Stereochemical assignment was carried out by ozonolysis and chiral LCMS and HPLC comparison to standards to give the structure of wewakazole B **66** as shown in Figure 32.

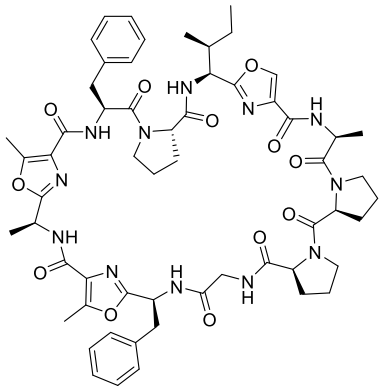


*Figure 32. Structure of wewakazole B **66**.*

The biosynthesis of the wewakazole compounds has not been fully elucidated. This can be attributed to the responsible gene clusters having not yet been characterised.[127] The lack of knowledge in this area highlights the importance of chemical synthesis to access these complex scaffolds, as synthetic biology is

not yet possible, and the natural source provides insufficient amounts of the wewakazoles.

Okino *et al*. also gave an insight into the biological activities of the wewakazoles which they demonstrated to have cytotoxic activity as commonly described for cyanobactins.[24] Wewakazole B **66** was found to have higher cytotoxicity than A with an IC_{50} of 1 μmol against human lung cancer cells compared to 10 μmol.

It is clear to see how the structures of wewakazole A **65** and B **66** are related (Figure 33). The portion shown outside the box for the two compounds is identical in both wewakazole A **65** and B **66**. This portion is mainly peptidic, with the addition of an oxazole, biosynthesised from serine. This section contains three proline residues which are known to induce β-turns, therefore favouring cyclisation.[128] The fragments shown within the boxes differ for wewakazole A **65** and B **66**. In wewakazole A **65**, there is one methyl oxazole with a valine side chain, and one oxazole with a phenylalanine side chain. The fragment contained in the box for for wewakazole B **66** shows two methyl oxazoles biosynthesised from threonine, with phenylalanine and alanine side chains.

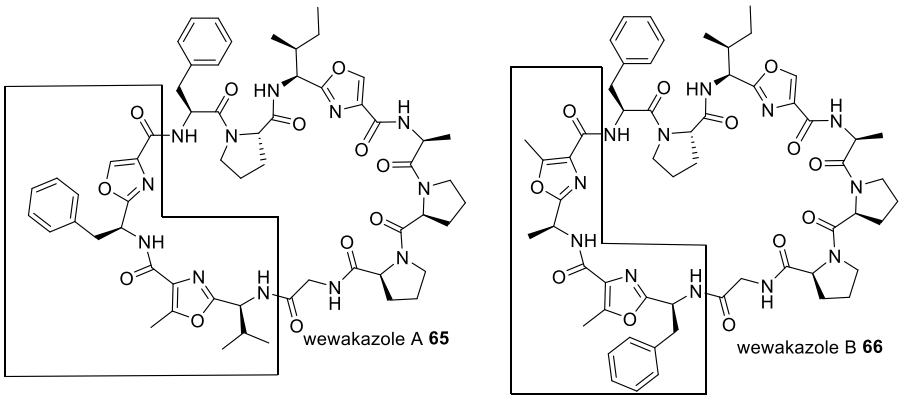
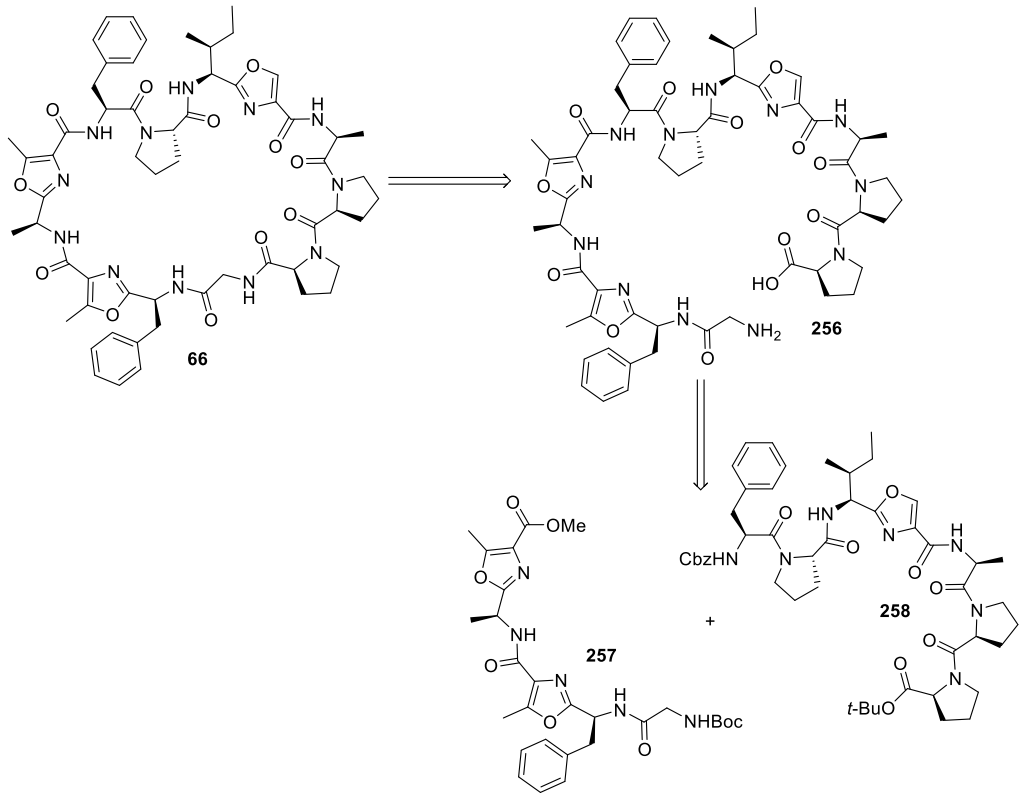


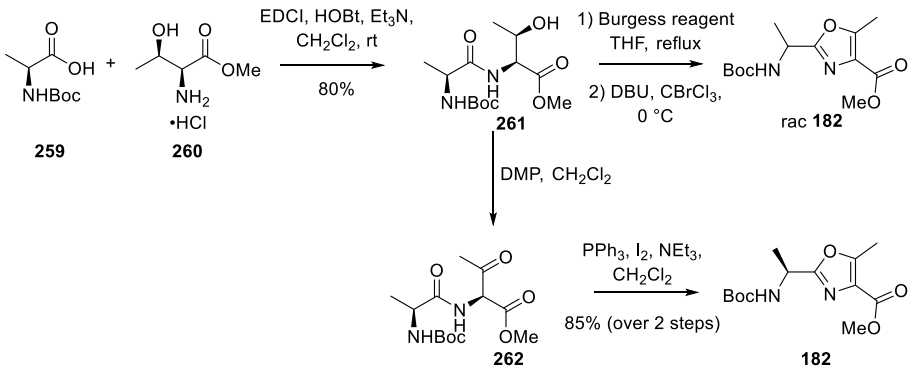
*Figure 33. Structures of wewakazole A **65** and wewakazole B **66**.*

During the course of our work, a synthesis of wewakazole B **66** was reported by Long *et al*.[129] Their retrosynthesis disconnected the cyclic peptide at the Gly-Pro linkage to give linear peptide **256**, followed by a central disconnection of the remaining linear portion to give fragments **257** and **258** (Scheme 70).



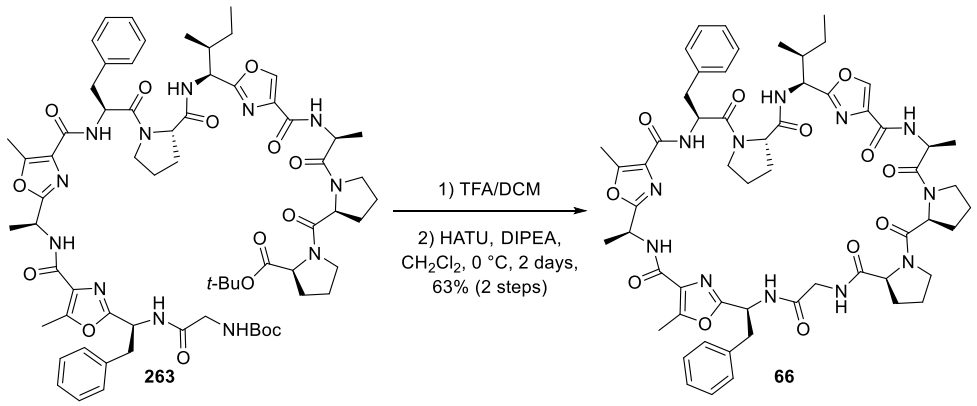
*Scheme 70. Retrosynthetic route of wewakazole B **66** by Long.*

The authors experienced epimerisation during synthesis of the alanine derived oxazole **182** (Scheme 71). Coupling of acid **259** and amine **260** gave dipeptide **261** which was converted into the oxazoline followed by oxidation to the oxazole **182**. Epimerisation was determined using Marfey's analysis, though the authors do not comment on which step induced epimerisation. To avoid epimerisation, an alternative route was followed via ketoamide **262** which was converted into oxazole **182** by Wipf's method for cyclodehydration, for which no epimerisation was observed.[129]



*Scheme 71. Synthesis of oxazole **182** by Long.*

The other 5-Me oxazole in wewakazole B **66** was synthesised using the Burgess reagent/oxidation route as Scheme 71 shows. The 5-H oxazole was also synthesised using this method as the authors found this to be higher yielding than using DAST for synthesis of the intermediate oxazolone. With the heterocyclic building blocks in hand, the relevant amide couplings were carried out to assemble linear fragment **263**. The final steps in the total synthesis were acid mediated deprotection and an amide coupling under high dilution conditions over 2 days to yield wewakazole B **66** on a gram scale in 63% (Scheme 72).

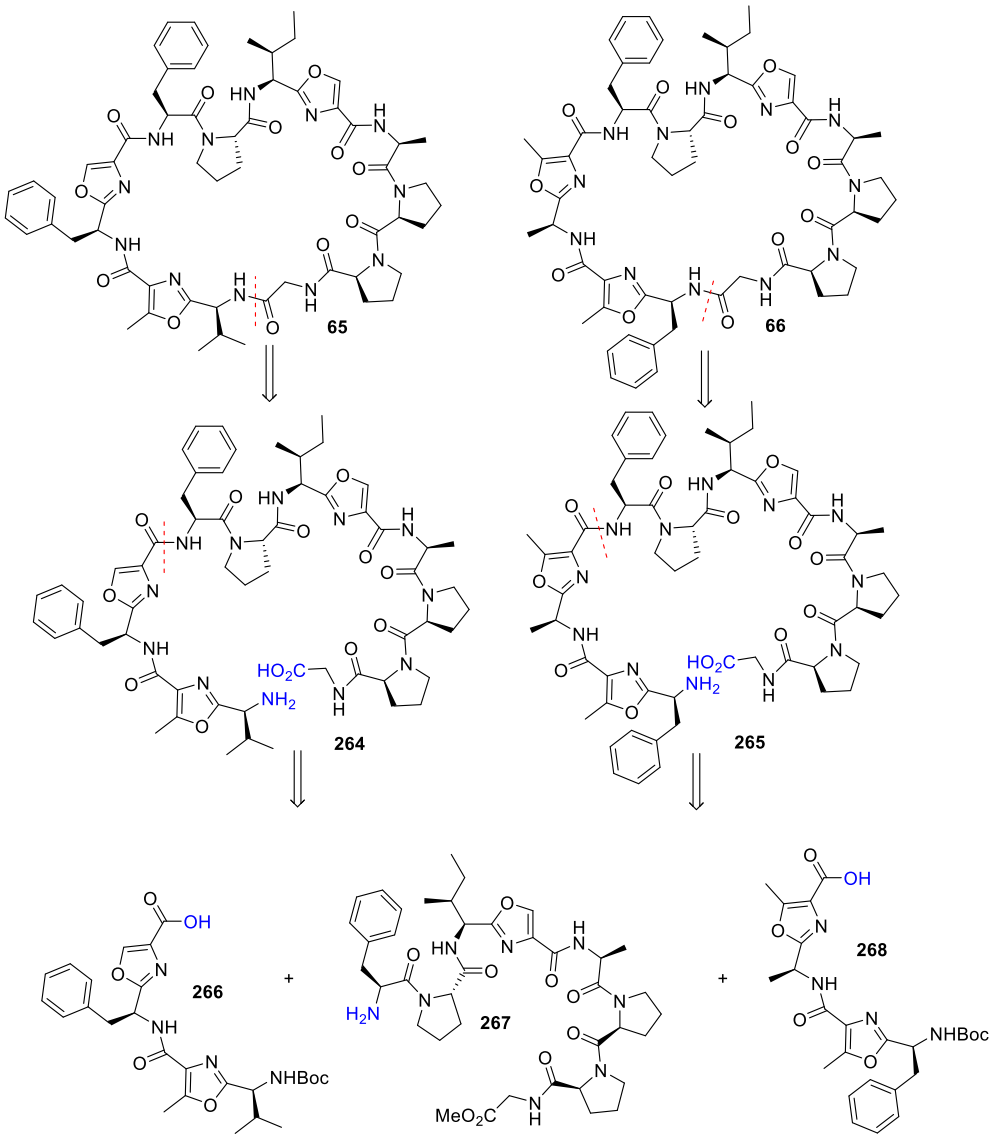


*Scheme 72. Final steps in the synthesis of wewakazole B **66.***

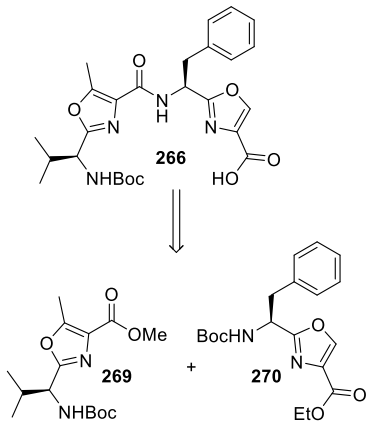
3.2 Proposed Synthetic Route

Our retrosynthesis of wewakazole A **65** and B **66** starts with an amide bond disconnection to give two linear modified peptides **264** and **265** (Scheme 73). Disconnection was chosen at this location as it gives a glycine as the carboxylic acid to undergo the macrocyclisation. Glycine was chosen as it is known that the *C*-terminal residue often undergoes epimerisation during amide coupling macrocyclisation reactions.[130,131]

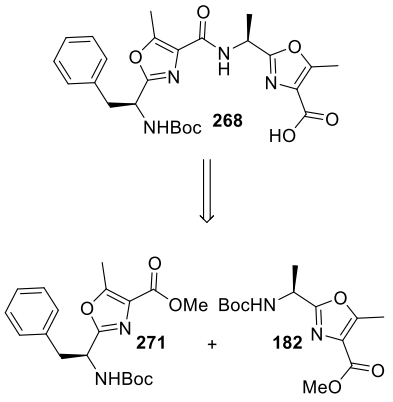
Further disconnection gives two bis-oxazole fragments; **266** and **268**. The remaining fragment **267** containing one oxazole has the same structure for both wewakazole A **65** and B **66**. Therefore construction of both wewakazole natural products can be broken down into three intermediates **266**, **267** and **268**. This work will focus on the synthesis of the two bis-oxazole fragments **266** and **268**. Retrosynthesis of bis-oxazole **266** (Scheme 74) and **268** (Scheme 75) gives the building blocks required for the synthetic route.



*Scheme 73. Retrosynthesis of the wewakazoles to bis-oxazole fragments **266** and **268** and oxazole containing fragment **267**.*



*Scheme 74. Retrosynthesis of bis-oxazole **266**.*

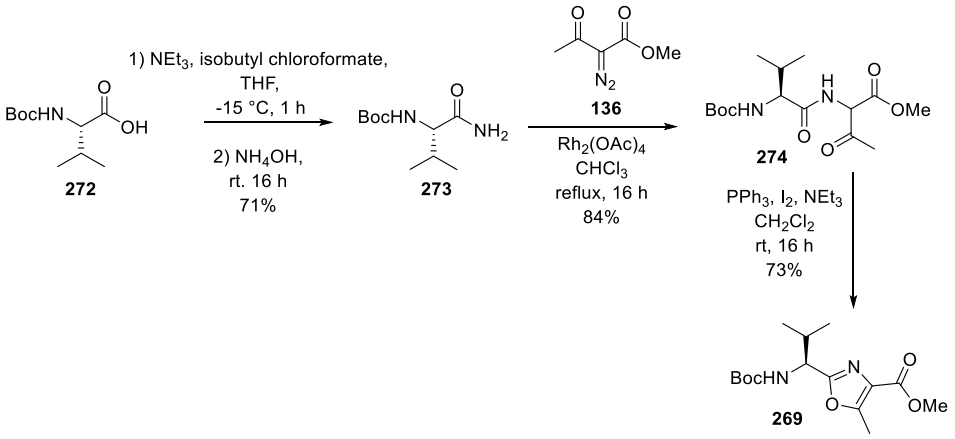


*Scheme 75. Retrosynthesis of bis-oxazole **268**.*

3.3 Synthesis of Fragment 266

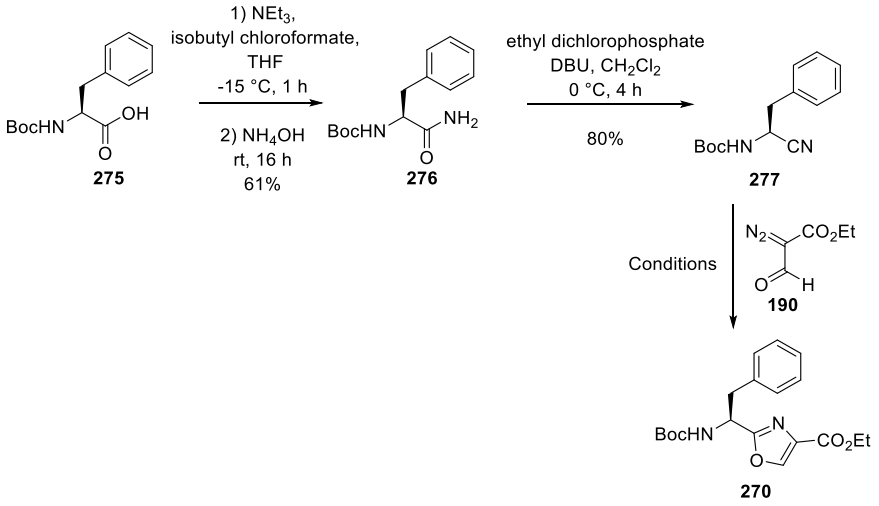
Synthesis of the bis-oxazole fragment of wewakazole A **65** began with the synthesis of oxazole **269** (Scheme 76). Boc-valine **272** was converted into the amide **273** using the mixed anhydride method in good yield. Boc-valinamide **273** was subjected to N-H insertion, with diazo ketoester **136** as analogously

used for the methyl oxazoles in goadsporin **64**, to give ketoamide **274** in good yield. Dehydration of **274** gave oxazole **269** in high yield.



*Scheme 76. Synthesis of oxazole **269**.*

Completion of bis-oxazole **266** required oxazole **270**. This was synthesised analogously to previously synthesised oxazole **191** using the rhodium catalysed reaction between a nitrile and a diazo compound. Boc-phenylalanine **275** was converted into the amide **276** in moderate yield (Scheme 77). Dehydration of amide **276** gave nitrile **277** in good yield. Initially, nitrile **277** was subjected to the conditions previously used with diazo aldehyde **190**, although this gave a low yield of the desired product **270** (Table 9, Entry 1).



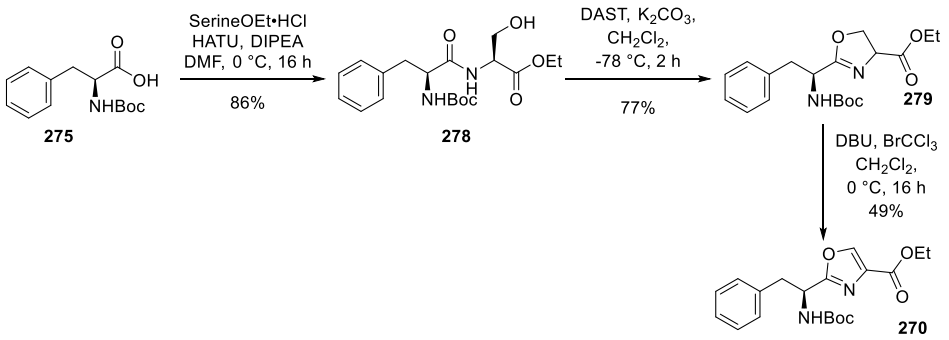
*Scheme 77. Synthesis of oxazole **270**.*

Optimisation of the synthesis of oxazole **270** looked initially at changing the catalyst to rhodium acetate dimer (Table 9, Entry 2). However, this gave a lower yield of the desired oxazole **270**. Work then moved onto changing the solvent from chloroform to 1,2-dichloroethane. A different halogenated solvent was chosen as these are thought to be preferable for rhodium carbenoid type reactions.[132] Switching the solvent to 1,2-dichloroethane gave a slightly higher yield of the oxazole **270** compared to chloroform (Entry 3). It was also found that increasing the reaction temperature when using 1,2-dichloroethane as the solvent gave progressively higher yields of the oxazole **270** (Entries 3,4 and 5). The final conditions, using 1,2-dichloroethane under reflux gave 100% yield based on recovered starting material (Entry 5).

Entry	Catalyst	Solvent	Temp/ °C	Yield of 270 (BRSM)
1	$Rh_2(pfm)_4$	$CHCl_3$	50	23 (36)
2	$Rh_2(OAc)_4$	$CHCl_3$	50	19 (56)
3	$Rh_2(pfm)_4$	1,2-DCE	50	29 (48)
4	$Rh_2(pfm)_4$	1,2-DCE	70	35 (92)
5	$Rh_2(pfm)_4$	1,2-DCE	83	40 (100)

*Table 9. Optimisation of the synthesis of oxazole **270**.*

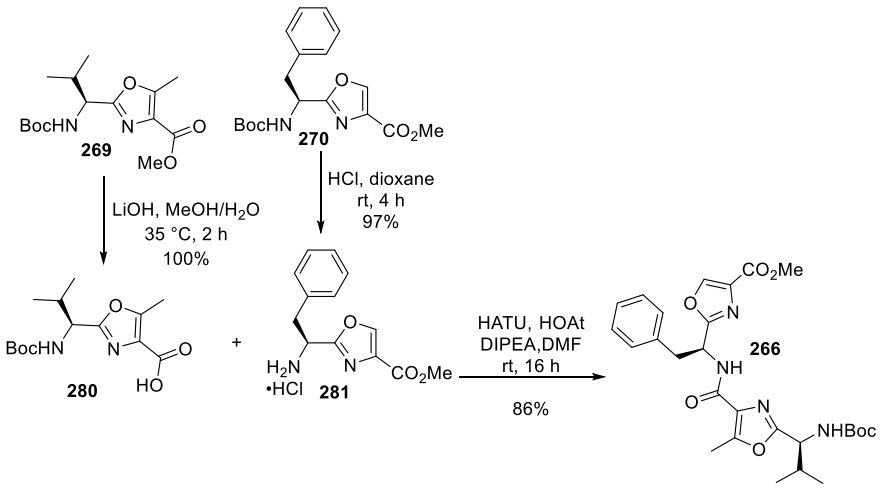
Alternatively, oxazole **270** can be synthesised using a more biomimetic approach from a serine-based starting material (Scheme 78). Boc-phenylalanine **275** was coupled to serine ethyl ester in good yield to give alcohol **278**. Cyclisation was carried out with DAST to give the oxazoline intermediate **279**. Oxidation using $BrCCl_3$ and DBU gave oxazole **270** in moderate yield.



*Scheme 78. Alternative synthesis of oxazole **270**.*

With both required oxazoles in hand, valine oxazole **269** underwent ester hydrolysis to give acid **280**, and phenylalanine oxazole **270** was Boc deprotected to give amine **281** (Scheme 79). Amide coupling of these

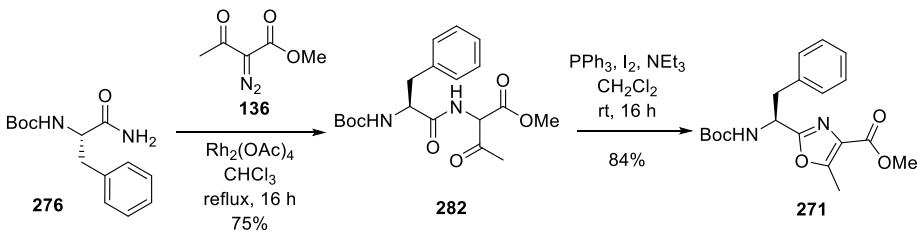
precursors using HATU gave bis-oxazole **266** in 63% yield; pleasingly, using HOAt in addition to HATU gave bis-oxazole **266** in an 86% yield.



*Scheme 79. Synthesis of bis-oxazole **266**.*

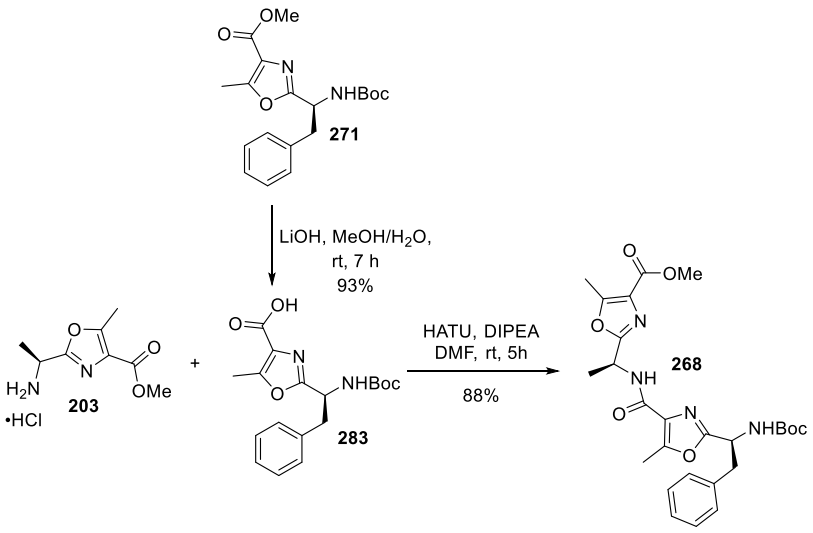
3.4 Synthesis of Fragment 268

Synthesis of the bis-oxazole fragment **268** of wewakazole B **66** required oxazole **271**. The synthesis began with the rhodium catalysed N-H insertion of Boc-phenylalaninamide **276** with diazo compound **136** to give ketoamide **282** in good yield, followed by cyclodehydration to give oxazole **271** in excellent yield (Scheme 80).



*Scheme 80. Synthesis of oxazole **271**.*

Completion of fragment **268** also required oxazole **203** which had previously been synthesised during the work on goadsporin **64**. Therefore, oxazole **271** was hydrolysed to give acid **283** (Scheme 81). Acid **283** underwent amino acid coupling with previously synthesised amine **203** in good yield to give bis-oxazole **268** (Scheme 81). Work to complete the total syntheses of wewakazole A **65** and B **66** has since been achieved in the Moody group by Dr Martyn Inman.



*Scheme 81. Synthesis of bis-oxazole **268**.*

4. Conclusions

The first total synthesis of goadsporin **64** has been completed. Synthesis of the oxazoles was carried out using rhodium catalysis and the thiazoles using the Hantzsch synthesis. Completion of the synthesis utilised a double mesylation and elimination strategy to incorporate the two dehydroalanines simultaneously. Although the final deprotection proved capricious, goadsporin **64** was successfully isolated and compared to the natural form. The synthetic material was shown to co-elute with material from the isolation chemists by LCMS and HPLC. NMR spectroscopic comparison showed differences at the *C*-terminal in the ^{1}H and ^{13}C NMR signals. However, these differences can be accounted for by the presence of exchangeable protons. The total synthesis was unambiguously established by a combined NMR sample, containing both synthetic and natural material, confirming the presence of a single species. Further NMR spectroscopic studies were able to confirm the structure from first principles and gain an insight into the conformation of goadsporin **64** in a DMSO solution.

The same methods utilised in the synthesis of the heterocycles for goadsporin **64** were applied to the synthesis of bis-oxazole fragments **266** and **268** in two other natural products; wewakazole A **65** and wewakazole B **66**. The wewakazoles are cyclic modified peptides which share a mainly peptidic fragment **267** whereas the structures of a bis-oxazole fragments **266** and **268**

vary. Synthesis of bis-oxazole fragments for each of the wewakazoles was successfully completed, with optimisation required for the rhodium catalysed reaction for the synthesis of oxazole **270**. Work towards the total syntheses of wewakazole A **65** and B **66** has been completed in the Moody group, and the anti-cancer activities of the wewakazoles are being evaluated.

5. Experimental Section

5.1 General Information

Anhydrous acetonitrile and dimethylformamide were used as supplied. Chloroform was dried by filtering through neutral alumina and storing under an inert atmosphere. THF was dried by distillation under nitrogen from benzophenone ketyl, and dichloromethane was distilled under nitrogen from calcium hydride. *N,N*-Diisopropylethylamine used was distilled under nitrogen from potassium hydroxide and stored under argon, triethylamine was distilled under nitrogen from calcium hydride and stored under argon. Light petroleum refers to the petroleum fraction with boiling point 40-60 °C and ether denotes diethyl ether.

Solution phase IR were recorded using a Perkin-Elmer 1600 FTIR instrument with the solvent given in each case. ATR solid phase IR were recorded using a Bruker Alpha FTIR instrument. Optical rotations $[\alpha]_{\mathrm{D}}$ were recorded using a ADP440 polarimeter with the reading (average), concentration, temperature and solvent given in each case. High resolution mass spectra were recorded using a Bruker TOF mass spectrometer with electrospray ionisation.

Merck TLC Silica gel 60 F_{254} plates were used for thin-layer chromatography and visualised using basic aqueous potassium permanganate solution, acidic ninhydrin *t*-butanol solution and ultraviolet light. Chromatography on silica

refers to flash chromatography using the specified eluent, with Aldrich technical grade 60 Å 230 – 400 mesh silica gel.

Analytical high performance liquid chromatography was carried out using an Agilent 1200 series with UV analysis at 254 nm, using a Waters XBridge C18 column (2.1 x 30 mm column; particle size: 3.5 µm; pore size: 100 Å). The flow rate was 0.8 mL/min, eluting with acetonitrile containing 0.1% formic acid and water containing 0.1% formic acid. Gradient for HPLC runs used either method A or B.

A) H_2O (95%), MeCN (5%) to H_2O (5%), MeCN (95%) over 3.5 min, then MeCN (100%) between 3.6 and 4.1 min, then coming back to H_2O (95%), MeCN (5%) between 4.2 and 5 min.

B) H_2O (50%), MeCN (50%) to H_2O (5%), MeCN (95%) over 3.5 min, then MeCN (100%) between 3.6 and 4.1 min, then to H_2O (95%), MeCN (5%) between 4.2 and 5 min.

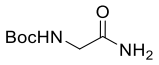
Liquid chromatography-mass spectrometry was run on an Agilent 1200 series with UV analysis at 254 nm, using a Waters XBridge C18 column (2.1 x 30 mm column; particle size: 3.5 µm; pore size: 100 Å) with a flow rate of 0.8 mL/min, eluting with acetonitrile and water containing 0.1% ammonia. The mass detector used was an Agilent 6120 Quadrupole. All LCMS runs carried out using gradient H_2O (95%), MeCN (5%) to H_2O (5%), MeCN (95%) over 3.5 min, then MeCN (100%) between 3.5 and 3.51 min, then coming back to H_2O (95%), MeCN (5%) between 3.51 and 4.5 min.

A range of instruments were used to record NMR spectra; Jeol 270, Bruker DPX400, Bruker AV(III)400, Bruker AV(III)400hd, Bruker AV400, Bruker AV(III)500 and Bruker AV(III)800 at the given frequency. The deuterated solvent used is specified in each case. The Bruker AV400 and Jeol 270 were used to record variable temperature spectra with the temperature and solvent specified in each case. ACD labs was used to process and reference NMR spectra according to residual solvent, with chemical shifts reported in ppm. Peak multiplicity was reported with the following abbreviations: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; and m, multiplet, with coupling constants reported in Hertz. DEPT experiments were used to assign C, CH, CH_2 or CH_3 from the ^{13}C spectra. Complex structure elucidation was carried out using HSQC, COSY and HMBC experiments when needed.

For structural confirmation of goadsporin **64**, 2D ^{1}H and ^{13}C correlation experiments, HMBC, HSQC and HSQC (multiplicity edited) were acquired with 2048 points in t2, and 256 points in t1 with between 16 and 64 transients. ^{1}H homonuclear 2D experiments, TOCSY, NOESY, DQF-COSY and COSY-QF were acquired with 2048 points in t2 and 512 points in t1 with between 16 and 64 transients. NOESY spectra were acquired with mixing times between 100 and 800 ms. Bruker Topspin 3.5 as used to process and reference NMR spectra, before analysis with CCPNMR 2.4.

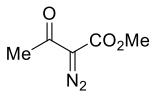
5.2 Synthesis Procedures

N-*tert*-Butoxycarbonylglycinamide 174



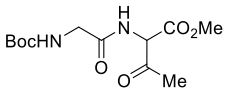
Synthesised according a modified procedure of Videnov.[133] Di-*tert*-butyl dicarbonate (21.0 g, 100.0 mmol) was added to a stirred solution of triethylamine (12.6 mL, 90.5 mmol) and glycinamide hydrochloride **173** (10.0 g, 90.5 mmol) in THF/water (4:1; 150 mL). The reaction was stirred for 16 h at room temperature. The reaction mixture was concentrated *in vacuo* and partitioned between water (200 mL) and ethyl acetate (200 mL). The aqueous layer was acidified to pH 2 using hydrochloric acid (1 M) and washed with ethyl acetate (3 x 70 mL). The combined organic layers were washed with saturated brine (300 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (14.1 g, 89%); mp 97-98 °C (lit.,[134] mp 86-87 °C); (Found: M+Na^+, 197.0915. $C_7H_{14}N_2O_3$ + Na^+ requires 197.0897); ν_{max} ($CHCl_3$)/cm^{-1} 3524, 3452, 2983, 1694, 1593, 1503, 1395, 1369, 1240, 1164; δ_H (400 MHz; $CDCl_3$) 6.07 (1 H, br s, NH), 5.57 (1 H, br s, NH), 5.17 (1 H, br s, NH), 3.83 (2 H, d, *J* 5.6, CH_2), 1.47 (9 H, s, $(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 172.4 (C), 156.4 (C), 80.7 (C), 44.3 (CH_2), 28.6 (CH_3). Data consistent with literature.[133–135]

Methyl 2-diazo-3-oxobutanoate 136



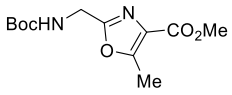
Synthesised according to a modified procedure of Schwartz.[136] Triethylamine (7.00 mL, 50.0 mmol) was added slowly over 15 min to a stirred solution of methyl acetoacetate **175** (6.00 g, 50.0 mmol) and 4-(acetamido)benzenesulfonyl azide (13.0 g, 55.0 mmol) in dry acetonitrile (100 mL) at 0 °C. The mixture was warmed to room temperature over 16 h. The reaction mixture was cooled to -15 °C for 3 h followed by filtration with pentane/ether (4:1, 100 mL) washing. The filtrate was concentrated *in vacuo*, pentane/ether (2:1, 100 mL) added and the solution placed in the freezer for 16 h. The solution was filtered and washed with pentane/ether (3:2; 50 mL). The filtrate was concentrated *in vacuo* to give the *title compound* as a yellow oil (4.55 g, 64%); (Found: M+Na$^+$, 165.0275. $C_5H_6N_2O_3$ + Na$^+$ requires 165.0271); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 2957, 2145, 1719, 1654, 1438, 1367, 1339, 1320, 1254, 1149, 1083; δ_H (400 MHz; $CDCl_3$) 3.85 (3 H, s, $CO_2C\underline{H}_3$), 2.49 (3 H, s, $COC\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 190.4 (C), 162.2 (C), 52.5 (CH_3), 28.5 (CH_3); diazo carbon not observed. Data consistent with literature.[86,136]

Methyl 2-(2-(*tert*-butoxycarbonylaminoacetamido)-3-oxobutanoate 176



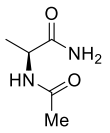
Methyl 2-diazo-3-oxobutanoate **136** (0.42 g, 3.00 mmol) in dry chloroform (3 mL) was added dropwise over 30 min to a solution of *N-tert*-butoxycarbonylglycinamide **174** (0.43 g, 2.5 mmol) and rhodium(II) acetate dimer (0.05 g, 2 mol%) in dry chloroform (38 mL) heated under reflux. The reaction mixture was heated under reflux for a further 16 h. The solution was allowed to cool to room temperature and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (0-4%)-dichloromethane to give the *title compound* as a colourless oil (0.58 g, 81%); (Found: M+Na$^+$, 311.1223. $C_{12}H_{20}N_2O_6$ + Na$^+$ requires 311.1214); ν_{max} ($CHCl_3$)/cm^{-1} 3606, 2983, 1758, 1728, 1496, 1439, 1369, 1278, 1240, 1163; δ_H (400 MHz; $CDCl_3$) 7.16 (1 H, br s, NH), 5.26 (1 H, d, *J* 6.4, NHCH), 5.09 (1 H, br s, NH), 3.89 (2 H, d, *J* 4.6, NHCH_2), 3.83 (3 H, s, CO_2CH_3), 2.40 (3 H, s, $COCH_3$), 1.48 (9 H, s, $C(CH_3)$); δ_C (100 MHz; $CDCl_3$) 198.1 (C), 169.4 (C), 166.3 (C), 156.0 (C), 80.4 (C), 62.8 (CH), 53.4 (CH_3), 43.9 (CH_2), 28.2 (CH_3), 27.9 (CH_3).

Methyl 2-(*tert*-butoxycarbonylaminomethyl)-5-methyloxazole-4-carboxylate 91



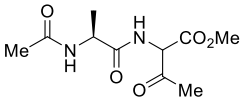
Triethylamine (0.19 mL, 1.37 mmol) and methyl 2-(2-(*tert*-butoxycarbonylaminoacetamido)-3-oxobutanoate **176** (0.096 g, 0.33 mmol) in dry dichloromethane (0.5 mL) were added sequentially to a stirred solution of triphenylphosphine (0.18 g, 0.67 mmol) and iodine (0.17 g, 0.67 mmol) in dry dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica, eluting with ethyl acetate to give the *title compound* as a colourless solid (0.03 g, 33%); mp 102-104 °C; (Found: M+Na^+, 293.1103. $C_{12}H_{18}N_2O_5$ + Na^+ requires 293.1108); ν_{max} ($CHCl_3$)/cm^{-1} 3452, 1983, 2253, 1718, 1624, 1507, 1442, 1393, 1369, 1354, 1247, 1165, 1101, 909, 651; δ_H (400 MHz; $CDCl_3$) 5.15 (1 H, br s, N<u>H</u>), 4.44 (2 H, d, *J* 5.5, NHC<u>H_2</u>), 3.91 (3 H, s, $CO_2C\underline{H_3}$), 2.62 (3 H, s, 5-CH_3), 1.46 (9 H, s, ($C\underline{H_3}$)$_3$); δ_C (100 MHz; $CDCl_3$) 162.4 (C), 159.2 (C), 156.7 (C), 155.4 (C), 127.3 (C), 80.1 (C), 51.8 (CH_3), 37.7 (CH_2), 28.2 (CH_3), 11.8 (CH_3). Data consistent with literature.[82]

(*S*)-*N*-Acetyl alaninamide 178



N,N-Diisopropylethylamine (21.0 mL, 120 mmol) was added to a stirred solution of (*S*)-alaninamide hydrochloride **177** (10.0 g, 80.0 mmol) and acetic anhydride (11 mL, 120 mmol) in dry dichloromethane (360 mL) and the reaction mixture stirred for 16 h at room temperature. The reaction mixture was filtered and washed with cold dichloromethane to give the *title compound* as a colourless solid (9.0 g, 86%); mp 161-162 °C (lit.,[137] mp 162 °C); $[\alpha]_{\mathrm{D}}^{22}$ -37.8 (*c* 1, EtOH) (lit.,[137] $[\alpha]_{\mathrm{D}}^{22}$ -39 (*c* 1, EtOH)); (Found: M+Na$^+$, 153.0635. $C_5H_{10}N_2O_2$ + Na$^+$ requires 153.0634; ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3411, 3011, 1696, 1664, 1592, 158, 1239; δ_H (400 MHz; CD_3OD) 4.33 (1 H, q, *J* 7.3, C<u>H</u>), 1.98 (3 H, s, COC<u>H</u>$_3$), 1.34 (3 H, d, *J* 7.3, CHC<u>H</u>$_3$); δ_C (100 MHz; CD_3OD) 178.1 (C), 173.2 (C), 50.3 (CH), 22.6 (CH_3), 18.4 (CH_3). Data consistent with literature.[137]

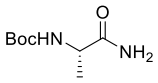
Methyl 2-((*S*)-2-acetamidopropanamido)-3-oxobutanoate 179



Methyl 2-diazo-3-oxobutanoate **136** (3.23 g, 22.8 mmol) in dry chloroform (20 mL) was added dropwise to a solution of (*S*)-*N*-acetyl alaninamide **178** (2.30 g, 17.5 mmol) and rhodium(II) acetate dimer (0.15 g, 4 mol%) in dry chloroform (250 mL) and heated under reflux for 16 h. The solution was cooled to room

temperature and concentrated *in vacuo*. The mixture was purified by chromatography on silica, eluting with methanol (2-5%)-dichloromethane, to give the *title compound,* as an mixture of diastereomers (1:0.8), as a colourless solid (3.38 g, 79%); mp 125-127 °C; (Found: M+Na^+, 267.0943. $C_{10}H_{16}N_2O_5$ + Na^+ requires 267.0951); ν_{max} ($CHCl_3$)/cm^{-1} 3423, 3011, 1758, 1730, 1678, 1502, 1239; major isomer δ_H (400 MHz; $CDCl_3$) 7.38 (1 H, d, *J* 6.5,NH), 6.36 (1 H, d, *J* 7.0 NH), 5.23 (1 H, d, *J* 6.5, CHCO$_2$CH$_3$), 4.65 (1 H, qd, *J* 7.2, 7.0, CHCH$_3$), 3.82 (3 H, s, CO$_2$CH$_3$), 2.37 (3 H, s, COCH$_3$), 2.01 (3 H, s, NHCOCH$_3$), 1.39 (3 H, d, *J* 7.2, CHCH$_3$); δ_C (100 MHz; $CDCl_3$) 198.0 (C), 172.32 (C), 170.06 (C), 166.2 (C), 63.0 (CH), 53.34 (CH_3), 48.46 (CH), 27.9 (CH_3), 23.01 (CH_3), 18.3 (CH_3); minor isomer, the following NMR signals are discernible, the rest overlap with the major isomer δ_H (400 MHz; $CDCl_3$) 4.64 (1 H, qd, *J* 7.2, 7.0, CHCH$_3$), 3.81 (3 H, s, CO$_2$CH$_3$) ; δ_C (100 MHz; $CDCl_3$) 198.1 (C), 172.31 (C), 170.11 (C), 166.2 (C), 62.9 (CH), 53.34 (CH_3), 48.49 (CH), 23.03 (CH_3), 18.2 (CH_3).

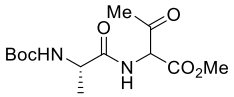
(*S*)-*N*-*tert*-Butoxycarbonylalaninamide 180



Di-*tert*-butyl dicarbonate (9.64 g, 44.2 mmol) was added to a stirred solution of triethylamine (6.72 mL, 48.2 mmol) and (*S*)-alaninamide hydrochloride **177** (5.00 g, 40.1 mmol) in THF/water (4:1; 75 mL). The mixture was stirred for 16 h at room temperature. The reaction mixture was concentrated *in vacuo* and taken into water (150 mL) then acidified to pH 2 with hydrochloric acid (1 M).

The aqueous layer was extracted with ethyl acetate (4 x 60 mL) and the combined organic layers were washed with saturated sodium hydrogen carbonate (150 mL) and saturated brine (150 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (5.5 g, 73%); mp 124-125 °C (lit.,[135] mp 124-125 °C); $[\alpha]_D^{22}$ -1.8 (*c* 1, EtOH) (lit.,[135] $[\alpha]_D^{26}$ -2.7 (*c* 1, EtOH)); (Found: M+Na$^+$, 211.1061. $C_8H_{16}N_2O_3$ + Na$^+$ requires 211.1053); ν_{max} ($CHCl_3$)/cm^{-1} 3672, 3524, 3439, 3009, 2983, 1694, 1592, 1500, 1394, 1369, 1240, 1162; δ_H (400 MHz; MeOD) 4.06 (1 H, q, *J* 7.3, C<u>H</u>), 1.44 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.31 (3 H, d, *J* 7.3, CHC<u>H</u>$_3$); δ_C (100 MHz; MeOD) 178.9 (C), 157.8 (C), 80.7 (C), 51.4 (CH), 28.8 (CH_3), 18.8 (CH_3). Data consistent with literature.[135]

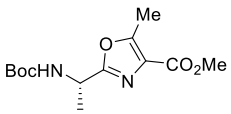
Methyl 2-(*S*)-2-(*tert*-butoxycarbonylamino)propanamido-3-oxobutanoate 181



Methyl 2-diazo-3-oxobutanoate **136** (0.83 g, 5.9 mmol) in dry chloroform (10 mL) was added dropwise over 1 h to a solution of (*S*)-*N*-*tert*-butoxycarbonylalaninamide **180** (0.98 g, 5.3 mmol) and rhodium(II) acetate dimer (47.0 mg, 2 mol%) in dry chloroform (50 mL) heated under reflux. The reaction mixture was heated under reflux for a further 16 h. The reaction mixture was washed with water (2 x 100 mL), saturated sodium hydrogen carbonate (100 mL), saturated brine (100 mL), dried with Na_2SO_4, filtered and

concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (2%)-dichloromethane to give the *title compound,* as an mixture of diastereomers (1:0.7), as a colourless oil (0.90 g, 56%); (Found: M+Na^+, 325.1357. $C_{13}H_{22}N_2O_6$ + Na^+ requires 325.1370); ν_{max} ($CHCl_3$)/cm^{-1} 3420, 3010, 2982, 2934, 1758, 1728, 1683, 1496, 1368, 1240, 1162, 1069; major isomer δ_H (400 MHz; $CDCl_3$) 7.48 - 7.36 (1 H, m, NH), 5.32 - 5.25 (1 H, m, NH), 5.23 - 5.22 (1 H, m, $CHCO_2CH_3$), 4.34 - 4.16 (1 H, m, $CHCH_3$), 3.76 (3 H, s, CO_2CH_3), 2.322 (3 H, s, $COCH_3$), 1.40 (9 H, s, $C(CH_3)_3$), 1.33 (3 H, d, *J* 7.2, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 198.2 (C), 172.8 (C), 166.4 (C), 155.3 (C), 80.3 (C), 62.7 (CH), 53.1 (CH_3), 49.8 (CH), 28.1 (CH_3), 27.8 (CH_3), 18.0 (CH_3); minor isomer, the following NMR signals are discernible, the rest overlap with the major isomer δ_H (400 MHz; $CDCl_3$) 5.21 - 5.20 (1 H, m, $CHCO_2CH_3$), 2.320 (3 H, s, $COCH_3$), 1.32 (3 H, d, *J* 7.2, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 198.4 (C), 166.3 (C), 27.7 (CH_3), 17.9 (CH_3).

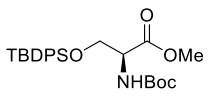
Methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxylate 182



Triethylamine (1.48 mL, 10.6 mmol) and methyl 2-(*S*)-2-(*tert*-butoxycarbonylamino)propanamido-3-oxobutanoate **181** (0.800 g, 2.65 mmol) in dry dichloromethane (20 mL) were added sequentially to a stirred solution of triphenylphosphine (1.39 g, 5.29 mmol) and iodine (1.34 g, 5.29 mmol) in dry

dichloromethane (150 mL). The reaction was stirred at room temperature for 16 h. The reaction mixture was washed with water (200 mL), saturated sodium thiosulfate solution (2 x 200 mL), saturated sodium hydrogen carbonate (200 mL), saturated brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with ethyl acetate (40%)- light petroleum to give the *title compound* as a colourless solid (0.67 g, 73%); mp 92-93 °C (lit.,[82] mp 94-95 °C); $[\alpha]_D^{21}$ -44.9 (*c* 1, $CHCl_3$) (lit.,[82] $[\alpha]_D^{22}$ -44.0 (*c* 1, $CHCl_3$)); (Found: M+Na^+, 307.1264. $C_{13}H_{20}N_2O_5$ + Na^+ requires 307.1264); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3011, 2983, 1714, 1624, 1502, 1443, 1392, 1369, 1318, 1239, 1162, 1102, 1065; δ_H (400 MHz; $CDCl_3$) 5.21 (1 H, br s, NH), 5.02 - 4.78 (1 H, m, CHCH$_3$), 3.88 (3 H, s, CO_2CH_3), 2.59 (3 H, s, 5-CH_3), 1.51 (3 H, d, *J* 7.0, CHCH_3), 1.42 (9 H, s, C(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$) 162.9 (C), 162.6 (C), 156.4 (C), 154.8 (C), 127.2 (C), 80.0 (C), 51.9 (CH_3), 44.6 (CH), 28.2 (CH_3), 20.2 (CH_3), 11.9 (CH_3). Data consistent with literature.[82]

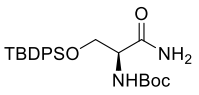
(*S*)-*N*-*tert*-Butoxycarbonylamino-O-(*tert*-butyldiphenylsilyl) serine methyl ester 184



Synthesised according to the procedure of Hughes.[91] To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonylamino serine methyl ester **183** (4.00 g, 18.2 mmol) in dry THF (100 mL) was added imidazole (3.10 g, 45.6 mmol) and *tert*-butyl(chloro)diphenylsilane (5.2 mL, 20.1 mmol). The reaction mixture was

stirred under nitrogen at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate (150 mL) and water (150 mL). The ethyl acetate layer was washed with water (2 x 150 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless oil (8.4 g, 100%); $[\alpha]_D^{23}$ +18.1 (*c* 1, $CHCl_3$) (lit.,[138] $[\alpha]_D^{22}$ +14.2 (*c* 1, $CHCl_3$)); (Found: M+Na^+, 480.2170. $C_{25}H_{35}NO_5Si$ + Na requires 480.2177); ν_{max} ($CHCl_3$)/cm^{-1} 3444, 3011, 2956, 2934, 2860, 1748, 1710, 1502, 1428, 1368, 1351, 1250, 1165, 1113; δ_H (400 MHz; $CDCl_3$) 7.74 - 7.36 (10 H, m, ArH), 5.42 (1 H, d, *J* 8.5, NH), 4.46 - 4.36 (1 H, m, CHNH), 4.08 (1 H, dd, *J* 10.2, 2.5, CHHOTBDPS), 3.90 (1 H, dd, *J* 10.2, 2.6, CHHOTBDPS), 3.75 (3 H, s, CO_2CH_3), 1.47 (9 H, s, $C(CH_3)_3$), 1.04 (9 H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 171.1 (C), 155.2 (C), 135.39 (CH), 135.35 (CH), 132.9 (C), 132.7 (C), 129.77 (CH), 129.75 (CH), 127.68 (CH), 127.66 (CH), 79.7 (C), 64.5 (CH_2), 55.4 (CH), 52.1 (CH_3), 28.2 (CH_3), 26.6 (CH_3), 19.2 (C).

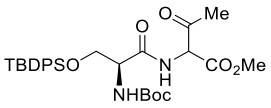
(*S*)-*N*-*tert*-Butoxycarbonylamino-O-(*tert*-butyldiphenylsilyl) serinamide 185



Synthesised according to the procedure of Hughes.[91] To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonylamino-O-(*tert*-butyldiphenylsilyl) serine methyl ester **184** (6.30 g, 13.8 mmol) in methanol (230 mL) was added aqueous ammonium hydroxide (*d* 0.88; 110 mL), and the mixture was stirred for 48 h at room

temperature. The reaction mixture was concentrated *in vacuo* and the remaining residue purified by chromatography on silica, eluting with ethyl acetate (20-30%)-light petroleum to give the *title compound* as a colourless solid (4.6 g, 76%), mp 135-136 °C (lit.,[91] mp 139-141 °C); $[\alpha]_{\mathrm{D}}^{23}$ +27.8 (*c* 1, $CHCl_3$); (Found: M+Na^+, 465.2176. $C_{24}H_{34}N_2O_4Si$ + Na^+ requires 465.2180); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3524, 3410, 3074, 2933, 2889, 1693, 1602, 1490, 1368, 1163, 1113; δ_H (400 MHz; $CDCl_3$) 7.65 (4 H, dt, *J* 8.6, 1.5, ArH), 7.36 - 7.48 (6 H, m, ArH), 6.41 (1 H, br s, CONHH), 5.79 (1 H, br s, CONHH), 5.31 (1 H, d, *J* 7.2, CHNH), 4.36 - 4.21 (1 H, m, CHNH), 4.06 (1 H, dd, *J* 9.9, 4.2, CHHOTBDPS), 3.77 (1 H, dd, *J* 9.9, 6.1, CHHOTBDPS), 1.45 (9 H, s, $CO_2C(CH_3)_3$), 1.07 (9 H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 173.3 (C), 155.4 (C), 135.5 (CH), 135.4 (CH), 132.7 (C), 132.4 (C), 129.8 (CH), 127.7 (CH), 80.0 (C), 64.0 (CH_2), 55.4 (CH), 28.2 (CH_3), 26.7 (CH_3), 19.1 (C). Data consistent with literature.[91]

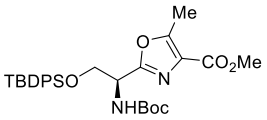
Methyl-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsiloxy-propanamido)-3-oxobutanoate 186



Methyl 2-diazo-3-oxobutanoate **136** (0.58 g, 4.1 mmol) in dry chloroform (10 mL) was added dropwise over 1 h to a solution of (*S*)-*tert*-butoxycarbonylamino-O-(*tert*-butyldiphenylsilyl) serinamide **185** (1.30 g, 2.94 mmol) and rhodium(II) acetate dimer (0.03 g, 2 mol%) in dry chloroform (50 mL) heated under reflux. The reaction mixture was heated under reflux for 16

h. The reaction mixture was cooled, washed with water (2 x 100 mL) and saturated brine solution (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give a brown residue. The residue was purified by chromatography on silica, eluting with ethyl acetate (20-30%)-light petroleum to give the *title compound*, as an mixture of diastereomers (1:0.8), as a colourless solid (1.20 g, 73%); mp 90-91 °C; (Found: M+H$^+$, 557.2671. $C_{29}H_{40}N_2O_7Si$ + H^+ requires 557.2678); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3418, 3011, 2958, 2933, 2860, 1758, 1729, 1680, 1487, 1368, 1161, 1113; major isomer δ_H (400 MHz; $CDCl_3$) 7.66 (4 H, d, *J* 7.3, ArH), 7.60 - 7.53 (1 H, m, NH), 7.47 - 7.34 (6 H, m, ArH), 5.39 - 5.29 (1 H, m, NH), 5.28 (1 H, br s, CHCO$_2$CH$_3$), 4.35 (1 H, br s, CHCH$_2$), 4.14 - 4.00 (1 H, m, CHCHH), 3.84 - 3.79 (1 H, m, CHCHH), 3.76 (3 H, s, CO$_2$CH$_3$), 2.37 (3 H, s, COCH$_3$), 1.45 (9 H, s, CO$_2$C(CH$_3$)$_3$), 1.07 (9 H, s, Si(CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 197.8 (C), 170.20 (C), 166.1 (C), 155.3 (C), 155.3 (CH), 135.5 (CH), 135.4 (CH), 132.7 (C), 132.4 (C), 129.8 (CH), 127.7 (CH), 80.2 (C), 63.8 (CH$_2$), 62.8 (CH), 55.6 (CH), 53.1 (CH$_3$), 28.1 (CH$_3$), 27.8 (CH$_3$), 26.6 (CH$_3$), 19.1 (C); minor isomer, the following NMR signals are discernible, the rest overlap with the major isomer δ_H (400 MHz; $CDCl_3$) 5.27 (1 H, br s, CHCO$_2$CH$_3$), 3.77 (3 H, s, CO$_2$CH$_3$), 2.35 (3 H, s, CO$_2$CH$_3$); δ_C (100 MHz; $CDCl_3$) 170.17 (C), 166.2 (C), 62.9 (CH).

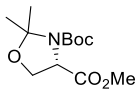
Methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldiphenylsiloxy)-ethyl)-5-methyloxazole-4-carboxylate 84



To a stirred solution of triphenyl phosphine (0.76 g, 2.9 mmol) and iodine (0.73 g, 2.9 mmol) in dry dichloromethane (10 mL) was added triethylamine (0.81 ml, 5.8 mmol) followed by methyl-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldiphenylsiloxy-propanamido)-3-oxobutanoate **186** (0.80 g, 1.44 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 16 h at room temperature. The reaction mixture was partitioned between dichloromethane (100 mL) and water (100 mL). The organic layer was washed with water (100 mL), sodium thiosulfate (3 x 100 mL), saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (5-10%)-light petroleum to give the *title compound* as a pale yellow oil (0.57 g, 74%); $[\alpha]_D^{23}$ 6.35 (*c* 1, $CHCl_3$); (Found: M+Na^+, 561.2407. $C_{29}H_{38}N_2O_6Si$ + Na^+ requires 561.2391); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 3011, 2958, 2933, 1716, 1623, 1502, 1369, 1354, 1249, 1165, 1105; δ_H (400 MHz; $CDCl_3$) 7.58 - 7.49 (4 H, m, ArH), 7.44 - 7.29 (6 H, m, ArH), 5.53 (1 H, d, *J* 8.5, N<u>H</u>), 5.06 - 5.00 (1 H, m, NHC<u>H</u>), 4.02 (1 H, dd, *J* 10.2, 4.4, CHC<u>H</u>H), 3.97 (1 H, dd, *J* 10.2, 4.6, CHCH<u>H</u>), 3.90 (3 H, s, $CO_2C\underline{H}_3$), 2.56 (3 H, s, 5-CH_3), 1.44 (9 H, s, $C(C\underline{H}_3)_3$), 0.99 (9 H, s, $Si(C\underline{H}_3)_3$)); δ_C (100 MHz; $CDCl_3$) 162.5 (C), 160.5 (C), 156.4 (C), 154.9 (C), 135.3 (CH), 132.7 (CH), 132.5 (C), 129.7 (CH),

127.58 (CH), 127.58 (CH), 127.3 (C), 79.9 (C), 65.1 (CH_2), 51.8 (CH_3), 50.7 (CH), 28.2 (CH_3), 26.5 (CH_3), 19.0 (C), 11.8 (CH_3).

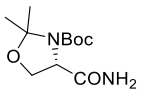
3-*tert*-Butyl-4-methyl-(*S*)-2,2-dimethyloxazolidine-3,4-dicarboxylate 187



Synthesised according to the procedure of Linder.[74] To (*S*)-*N*-(*S*)-*tert*-butoxycarbonylamino-serine methyl ester **183** (10.9 g, 49.6 mmol) in toluene (75 mL) was added 2,2-dimethoxypropane (61.0 mL, 500 mmol) and *p*-toluenesulfonic acid monohydrate (0.189 g, 0.992 mmol) and the reaction mixture was heated under reflux using Dean-Stark conditions for 7 h. The mixture was concentrated *in vacuo* and dissolved in ether (200 mL). The ether was washed with water (200 mL) and saturated sodium hydrogen carbonate (200 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by reduced pressure distillation (5.0 mbar, 97 °C) to give the *title compound* as a colourless oil (10.4 g, 81%); $[\alpha]_D^{23}$ -52.1 (*c* 1, $CHCl_3$) (lit.,[74] $[\alpha]_D^{25}$-51.4 (*c* 1.1, $CHCl_3$)); (Found: M+Na^+, 282.1314. $C_{12}H_{21}NO_5$ + Na^+ requires 282.1317); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2983, 2955, 1755, 1703, 1478, 1456, 1438, 1394, 1368, 1251, 1171, 1096, 1069, 1055; δ_H (270 MHz; 90 °C, DMSO-d_6) 4.40 (1 H, dd, *J* 7.2, 3.2, C<u>H</u>), 4.16 (1 H, dd, *J* 9.1, 7.2, C<u>H</u>H), 3.94 (1 H, dd, *J* 9.1, 3.2, CH<u>H</u>), 3.69 (3 H, s, $CO_2C\underline{H}_3$), 1.56 (3 H, s, C(C<u>H</u>$_3$)(CH_3)), 1.46 (3 H, s, C(CH_3)(C<u>H</u>$_3$)), 1.40 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (100 MHz; 90 °C, DMSO-d_6) 170.7 (C), 150.4 (C), 93.6

(C), 79.2 (C), 65.2 (CH_2), 58.4 (CH), 51.4 (CH_3), 27.5 (CH_3), 24.5 (CH_3), 23.9 (CH_3). Data consistent with literature.[74]

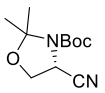
tert-Butyl-(*S*)-4-carbamoyl-2,2-dimethyloxazolidine-3-carboxylate 188



Synthesised according to a modified procedure of Linder.[74] To a stirred solution of 3-*tert*-butyl 4-methyl (*S*)-2,2-dimethyloxazolidine-3,4-dicarboxylate **187** (6.2 g, 24.0 mmol) in methanol (60 mL) was added aqueous ammonium hydroxide (*d* 0.88; 240 mL) and the mixture was stirred at room temperature. After 16 h further aqueous ammonium hydroxide (*d* 0.88; 100 mL) was added and the mixture stirred for a further 16 h, concentrated *in vacuo* and acidified to pH 1 with hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 x 80 mL) and the combined organic layers washed with saturated brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (4.9 g, 83%); mp 108 - 109 °C (lit.,[74] mp 113 - 114 °C); $[\alpha]_D^{24}$ -56.0 (*c* 1.6, $CHCl_3$) (lit.,[74] $[\alpha]_D^{25}$-39.0 (*c* 1.6, $CHCl_3$)); (Found: M+Na^+, 267.1315. $C_{11}H_{20}N_2O_4$ + Na^+ requires 267.1321); ν_{max} ($CHCl_3$)/cm^{-1} 3526, 3410, 3011, 2985, 1694, 1587, 1573, 1478, 1457, 1393, 1369, 1249, 1168, 1094, 1067, 1050, 870, 851; δ_H (270 MHz; 90 °C, DMSO-d_6) 6.83 (2 H, br s, N$\underline{H}_2$), 4.24 (1 H, dd, *J* 7.2, 3.6, C$\underline{H}$), 4.07 (1 H, dd, *J* 8.7, 7.2, C$\underline{H}$H), 3.85 (1 H, dd, *J* 8.7, 3.6, CH$\underline{H}$), 1.56 (3 H, s, C(C$\underline{H}_3$)(CH_3)), 1.46 (3 H, s, C(CH_3)(C$\underline{H}_3$)), 1.41 (9 H, s, C(C$\underline{H}_3$)$_3$);

δ_C (67.5 MHz; 90 °C, DMSO-d_6) 171.5 (C), 151.0 (C), 93.4 (C), 78.9 (C), 66.1 (CH_2), 59.2 (CH), 27.6 (CH_3), 25.0 (CH_3), 24.1 (CH_3). Data consistent with literature.

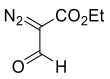
tert-Butyl-(*R*)-4-cyano-2,2-dithyloxazolidine-3-carboxylate 189



Synthesised according to the procedure of Linder.[74] To a stirred solution of *tert*-butyl (*S*)-4-carbamoyl-2,2-dimethyloxazolidine-3-carboxylate 188 (4.85 g, 19.9 mmol) in dichloromethane (10 mL) at 0 °C was added DBU (15.0 mL, 99.0 mmol). The solution was stirred for 10 min then ethyl dichlorophosphate (4.71 mL, 39.7 mmol) was added over 5 min. The mixture was warmed to room temperature and stirred for 1 h. The mixture was cooled to 0 °C and saturated ammonium chloride (50 mL) was added and the mixture was stirred for 10 min. The mixture was extracted with dichloromethane (2 x 100 mL) and the combined organic layers washed with saturated brine (200 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (10%)-light petroleum to give the *title compound* as a colourless solid (2.9 g, 63%); mp 57 - 58 °C (lit.,[74] mp 58 - 59 °C); $[\alpha]_D^{24}$ -101.0 (*c* 1.0, $CHCl_3$) (lit.,[74] $[\alpha]_D^{25}$-74.0 (*c* 1.0, $CHCl_3$)); (Found: M+Na^+, 249.1219. $C_{11}H_{18}N_2O_3$ + Na^+ requires 249.1210); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2985, 2937, 2889, 1709, 1477, 1458, 1371, 1264, 1243, 1165, 1099, 1072, 1056, 821; δ_H (270 MHz; 90 °C, DMSO-d_6) 4.83 (1 H, dd, *J* 5.8, 2.1, C<u>H</u>), 4.18 (1 H, dd, *J* 9.4, 2.1, C<u>H</u>H), 4.11 (1 H, dd, *J* 9.4, 5.8, CH<u>H</u>), 1.56 (3 H,

s, C(C<u>H</u>$_3$)(CH$_3$)), 1.48 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.46 (3 H, s, C(CH$_3$)(C<u>H</u>$_3$)); δ_C (100 MHz; 90 °C, DMSO-d$_6$) 150.1 (C), 118.2 (C), 93.9 (C), 80.6 (C), 65.6 (CH_2), 47.0 (CH), 27.5 (CH_3), 25.6 (CH_3), 23.6 (CH_3). Data consistent with literature.[74]

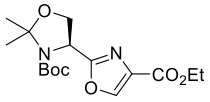
Ethyl 2-diazo-3-oxopropanoate 190



Synthesised according to the procedure of Linder.[74] To a stirred solution of dimethylformamide (7.0 mL, 90 mmol) was added thionyl chloride (6.5 mL, 90 mmol) dropwise and the mixture heated to 40 °C for 2 h. The mixture was concentrated *in vacuo* to give a colourless solid. The solid was dissolved in chloroform (40 mL), cooled to 0 °C and ethyl diazoacetate (18 mL, 180 mmol) was added dropwise over 10 min. The mixture was stirred for 1 h at room temperature. The mixture was concentrated *in vacuo* and ether (50 mL) was added. The precipitate was filtered off and dissolved in aqueous acetic acid (10%; 40 mL) and stirred at room temperature for 16 h. The solution was extracted with ether (2 x 30 mL) and the combined organic layers were washed with saturated sodium hydrogen carbonate (100 mL), sulfuric acid (10%; 100 mL) and saturated brine (100 mL), dried using $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by chromatography on silica, eluting with ethyl acetate (20%)-light petroleum to give the *title compound* as a yellow oil (4.0 g, 31%); (Found: M+Na$^+$, 165.0275. $C_5H_6N_2O_3$ + Na$^+$ requires 165.0276); ν_{max} ($CHCl_3$)/cm^{-1} 2987, 2147, 1713, 1665, 1403, 1387, 1371, 1305,

1242, 1122, 1014; δ_H (400 MHz; $CDCl_3$) 9.58 (1 H, s, C<u>H</u>O), 4.25 (2 H, q, *J* 7.2, C<u>H</u>$_2$), 1.25 (3 H, t, *J* 7.2 C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 181.0 (CH), 160.9 (C), 61.6 (CH_2), 14.0 (CH_3); diazo carbon not observed. Data consistent with literature.[74]

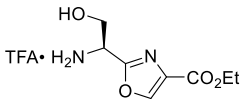
Ethyl (*S*)-2-(3-*tert*-butoxycarbonylamino-2,2-dimethyloxazolidin-4-yl)oxazole-4-carboxylate 191



Synthesised according to the procedure of Linder.[74] Ethyl 2-diazo-3-oxopropanoate **190** (1.89 g, 13.3 mmol) in chloroform (2 mL) was added dropwise over 24 h to a stirred solution of *tert*-butyl (*R*)-4-cyano-2,2-dimethyloxazolidine-3-carboxylate **189** (1.0 g, 4.4 mmol) and dirhodium(II) tetrakis(perfluorobutyramide) (0.11 g, 2.5 mol%) in chloroform (1 mL) at 50 °C. The mixture was concentrated *in vacuo* and purified by chromatography on silica, eluting with ethyl acetate (10%)-light petroleum to give the *title compound* as a colourless solid (0.59 g, 40%); mp 78 - 79 °C (lit.,[74] mp 76 - 78 °C); $[\alpha]_D^{23}$ -67.9 (*c* 1.3, $CHCl_3$) (lit.,[74] $[\alpha]_D^{25}$-75.0 (*c* 1.3, $CHCl_3$)); (Found: M+Na^+, 363.1529. $C_{16}H_{24}N_2O_6$ + Na^+ requires 363.1532); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2984, 2939, 1703, 1584, 1477, 1456, 1380, 1317, 1266, 1244, 1170, 1110, 1062, 1022; δ_H (270 MHz; 90 °C, DMSO-d_6) 8.65 (1 H, s, 5-H), 5.09 (1 H, dd, *J* 6.5, 3.0, C<u>H</u>CH_2), 4.35 - 4.23 (3 H, m, C<u>H</u>$_2$$CH_3$, CHC<u>H</u>H), 4.04 (1 H, dd, *J* 9.2, 3.0, CHCH<u>H</u>), 1.64 (3 H, s, C(C<u>H</u>$_3$)(CH_3)), 1.53 (3 H, s, C(CH_3)(C<u>H</u>$_3$)), 1.33 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.30 (3 H, t, *J* 7.2, CH_2C<u>H</u>$_3$); δ_C (67.5 MHz; 90 °C, DMSO-d_6) 163.2 (C), 160.1 (C), 150.4 (C),

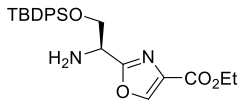
144.4 (CH), 132.5 (C), 93.7 (C), 79.4 (C), 66.3 (CH_2), 59.9 (CH_2), 54.1 (CH), 27.4 (CH_3), 25.1 (CH_3), 23.8 (CH_3), 13.5 (CH_3). Data consistent with literature.[74]

Ethyl (*S*)-2-(1-amino-2-hydroxyethyl)oxazole-4-carboxylate trifluoroacetate 192



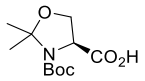
To a stirred solution of ethyl (*S*)-2-(3-*tert*-butoxycarbonylamino-2,2-dimethyloxazolidin-4-yl)oxazole-4-carboxylate 191 (0.11 g, 0.32 mmol) in dichloromethane (0.2 mL) at 0 °C was added trifluoroacetic acid (1.8 mL). The mixture was allowed to warm to room temperature and stirred for 5 h. The mixture was concentrated *in vacuo,* and residual trifluoroacetic acid was removed by azeotrope with toluene, to give the *title compound* as a colourless oil (0.098 g, 96%); $[\alpha]_{\mathrm{D}}^{20}$ -9.4 (*c* 1, $CHCl_3$); (Found: $M+H^+$, 201.0874. $C_8H_{13}N_2O_4$ + H requires 201.0874); ν_{max} (ATR)/cm^{-1} 2987, 1730, 1676, 1375, 1339, 1176, 1076, 1020; δ_H (400 MHz; CD_3OD) 8.50 (1 H, s, 5-H), 4.35 (2 H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$), 4.12 (1 H, t, *J* 5.4, C<u>H</u>CH$_2$), 3.85 (2 H, d, *J* 5.4, CHC<u>H</u>$_2$), 1.36 (3 H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$); δ_c (100 MHz; CD_3OD) 167.8 (C), 162.7 (C), 146.3 (CH), 134.4 (C), 65.6 (CH_2), 62.4 (CH_2), 53.1 (CH), 14.7 (CH_3).

Ethyl (*S*)-2-(1-amino-2-(*tert*-butyldiphenylsiloxy)ethyl)oxazole-4-carboxylate 93



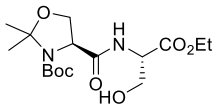
To a stirred solution of ethyl (*S*)-2-(1-amino-2-hydroxyethyl)oxazole-4-carboxylate trifluoroacetate **192** (98 mg, 0.29 mmol) in dry dichloromethane (4.5 mL) at 0 °C was added triethylamine (0.080 mL, 0.58 mmol), imidazole (49 mg, 0.72 mmol) and *tert*-butyl(chloro)diphenylsilane (0.11 mL, 0.43 mmol). The reaction mixture was stirred under nitrogen at room temperature for 16 h. The reaction mixture was taken into water (10 mL) and dichloromethane (10 mL). The aqueous layer was washed with dichloromethane (10 mL), and the combined organic layers were washed with saturated brine (15 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate to give the *title compound* as a yellow oil (98 mg, 78%); $[\alpha]_D^{23}$ +18.0 (*c* 1, $CHCl_3$); (Found: M+H$^+$, 439.2061. $C_{24}H_{30}N_2O_4Si$ + H requires 439.2053); ν_{max} ($CHCl_3$)/cm^{-1} 3053, 2962, 2933, 2860, 1734, 1584, 1472, 1428, 1373, 1319, 1181, 1140, 1112; δ_H (400 MHz; $CDCl_3$) 8.15 (1 H, s, 5-H), 7.63 - 7.52 (4 H, m, ArH), 7.47 - 7.32 (6 H, m, ArH), 4.41 (2 H, q, *J* 7.1. C$\underline{H}_2$CH$_3$), 4.23 (1 H, t, *J* 5.0, C$\underline{H}$CH$_2$), 4.00 (2 H, d, *J* 5.0, CHC$\underline{H}_2$), 1.39 (3 H, t, *J* 7.1, CH$_2$C$\underline{H}_3$), 1.01 (9 H, s, C(C$\underline{H}_3$)$_3$); δ_c (100 MHz, $CDCl_3$) 166.3 (C), 161.2 (C), 143.8 (CH), 135.5 (CH), 133.4 (C), 132.9 (C), 132.8 (C), 129.8 (CH), 127.73 (CH), 127.71 (CH), 66.7 (CH$_2$), 61.2 (CH$_2$), 52.1 (CH), 26.7 (CH$_3$), 19.1 (C), 14.3 (CH$_3$).

(*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidine-4-carboxylic acid 193



Lithium hydroxide monohydrate (2.89 g, 68.9 mmol) was added to 3-*tert*-butyl-4-methyl (*S*)-2,2-dimethyloxazolidine-3,4-dicarboxylate **187** (4.47 g, 17.2 mmol) in THF/water (4:1; 150 mL). The mixture was stirred at room temperature for 5 h. The mixture was concentrated *in vacuo*, taken into water (200 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with saturated brine (300 mL), dried using Na_2SO_4 and concentrated *in vacuo* to give the *title compound* as a colourless solid (4.2 g, 100%); mp 51 - 52 °C; $[\alpha]_D^{22}$ -71.3 (*c* 1, $CHCl_3$); (Found: M+Na^+, 268.1155. $C_{11}H_{19}NO_5$ + Na^+ requires 268.1161); ν_{max} ($CHCl_3$)/cm^{-1} 2983, 2938, 2889, 1765, 1730, 1703, 1477, 1456, 1394, 1369, 1246, 1170, 1097, 1069, 1054; δ_H (400 MHz; 90 °C, DMSO-d_6) 4.30 (1 H, dd, *J* 7.2, 3.1, C<u>H</u>CH_2), 4.14 (1 H, dd, *J* 8.9, 7.2, CHC<u>H</u>H), 3.93 (1 H, dd, *J* 8.9, 3.1, CHCH<u>H</u>), 1.55 (3 H, s, C(C<u>H</u>$_3$)(CH_3)), 1.45 (3 H, s, C(C<u>H</u>$_3$)(CH_3)), 1.41 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (100 MHz; 90 °C, DMSO-d_6) 171.5 (C), 150.7 (C), 93.5 (C), 79.1 (C), 65.6 (CH_2), 58.6 (CH), 27.6 (CH_3), 24.7 (CH_3), 24.2 (CH_3). Data consistent with literature.[108]

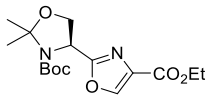
tert-Butyl (_S_)-4-(((_S_)-1-ethoxy-3-hydroxy-1-oxopropan-2-yl)carbamoyl)-2,2-dimethyloxazolidine-3-carboxylate 194



To a stirred solution of ((*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidine-4-carboxylic acid **193** (2.11 g, 8.62 mmol) and (*S*)-*tert*-butoxycarbonylamino-serine ethyl ester hydrochloride (1.84 g, 10.9 mmol) in dimethylformamide/dichloromethane (1:1; 100 mL) at 0 °C, was added *N,N*-diisopropylethylamine (7.66 mL, 43.1 mmol) and HATU (6.56 g, 17.2 mmol). The reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo*, then the residue was taken into water (300 mL) and ethyl acetate (200 mL). The aqueous layer was further extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL), lithium chloride solution (10%; 3 x 200 mL), water (200 mL), saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (30% - 70%)-light petroleum to give the *title compound* as a colourless oil (3.0 g, 95%); $[\alpha]_D^{20}$ -9.1 (*c* 1, $CHCl_3$); (Found: M+Na^+, 383.1800. $C_{16}H_{28}N_2O_7$ + Na^+ requires 383.1794); ν_{max} ($CHCl_3$)/cm^{-1} 3626, 2985, 2939, 2893, 1938, 1681, 1516, 1477, 1464, 1370, 1249, 1168, 1095, 1065; δ_H (270 MHz; 90 °C, DMSO-d_6) 7.72 (1 H, d, *J* 7.4, NH), 4.75 (1 H, t, *J* 4.5, OH), 4.45 - 4.30 (2 H, m, NCH, NHCH), 4.19 - 4.03 (3 H, m, CH_3CH_2, CHHOC), 3.89 (1 H, dd, *J* 8.9, 3.1, CHHOC),

3.77 (1 H, dt, *J* 10.6, 4.5, C<u>H</u>HOH), 3.65 (1 H, dt, *J* 10.6, 4.5, CH<u>H</u>OH), 1.56 (3 H, s, C(C<u>H</u>$_3$)(CH$_3$)), 1.47 (3 H, s, C(CH$_3$)(C<u>H</u>$_3$)), 1.40 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.21 (3 H, t, *J* 7.0, C<u>H</u>$_3$CH$_2$); δ_C (67.5 MHz; 90 °C, DMSO-d$_6$) 169.82 (C), 169.76 (C), 150.9 (C), 93.5 (C), 79.1 (C), 65.9 (CH$_2$), 60.9 (CH$_2$), 60.1 (CH$_2$), 59.1 (CH), 54.3 (CH), 27.6 (CH$_3$), 25.0 (CH$_3$), 24.0 (CH$_3$), 13.5 (CH$_3$).

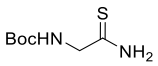
Ethyl (*S*)-2-(3-*tert*-butoxycarbonylamino-2,2-dimethyloxazolidin-4-yl)oxazole-4-carboxylate 191



To a stirred solution of *tert*-butyl (*S*)-4-(((*S*)-1-ethoxy-3-hydroxy-1-oxopropan-2-yl)carbamoyl)-2,2-dimethyloxazolidine-3-carboxylate **194** (1.37 g, 3.81 mmol) in THF (20 mL) at -78 °C was added DAST (0.55 mL, 4.2 mmol) dropwise over 15 min. The reaction mixture was stirred at -78 °C for 2 h. Potassium carbonate (0.735 g, 5.32 mmol) was added and the mixture was warmed to room temperature. The mixture was concentrated *in vacuo* and taken into ethyl acetate (100 mL). The organic solution was washed with saturated sodium hydrogen carbonate (100 mL). The aqueous layer was extracted twice with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with saturated brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the oxazoline **195** as a colourless solid (1.2 g, 93%), which was used immediately without further purification.

To a stirred solution of the oxazoline **195** (0.87 g, 2.6 mmol) in dichloromethane (32 mL) at 0 °C was added DBU (1.52 mL, 10.2 mmol). After 5 min, bromotrichloromethane (1.00 mL, 10.2 mmol) was added dropwise over 10 min. The reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and saturated ammonium chloride (40 mL) was added. The mixture was separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with saturated ammonium chloride (100 mL), saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (10%)-light petroleum to give the *title compound* as a colourless solid (0.68 g, 78%); Data in agreement with previously prepared sample **191** (see page 130).

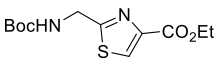
***N*-*tert*-Butoxycarbonyl-glycinethioamide 196**



Synthesised according to a modified procedure of Moody.[84] Lawesson's reagent (3.56 g, 8.81 mmol) was added to a stirred solution of *N*-*tert*-butoxycarbonyl-glycineamide **174** (3.07 g, 17.6 mmol) in dry dichloromethane (220 mL). The solution was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate (150 mL) and water (150 mL). The aqueous layer was washed with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with hydrochloric acid

(1 M; 100 mL) potassium carbonate (10 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (30%)-light petroleum to give the *title compound* as a colourless solid (2.6 g, 84%), mp 122-123 °C (lit.,[84] mp 126-127 °C); (Found: M+Na^+, 213.0670. $C_7H_{14}N_2O_2S$ + Na^+ requires 213.0668); ν_{max} ($CHCl_3$)/cm^{-1} 3446, 2983, 2932, 1708, 1607, 1593, 1505, 1410, 1370, 1240, 1162, 910; δ_H (400 MHz; $CDCl_3$) 7.79 (1 H, br s, NH), 7.46 (1 H, br s, NH), 5.22 (1 H, br s, NH), 4.17 (2 H, d, *J* 6.1, $NHCH_2$), 1.47 (9 H, s, $(CH_3)_3$); δ_C (100 MHz; CD_3OD) 206.7 (C), 158.3 (C), 81.0 (C), 51.7 (CH_2), 28.8 (CH_3). Data consistent with literature.[84]

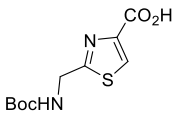
Ethyl 2-((*tert*-butoxycarbonylamino)methyl)thiazole-4-carboxylate 95



Synthesised according to the procedure of Moody.[84] To a stirred solution of *N*-*tert*-butoxycarbonyl-glycinethioamide **196** (0.49 g, 2.59 mmol) in 1,2-dimethyoxyethane (5.5 mL) at -25 °C was added potassium hydrogen carbonate (1.04 g, 10.37 mmol) and ethyl bromopyruvate (1.39 mL, 11.10 mmol). The mixture was allowed to warm to -15 °C for 3 h and further warmed to room temperature over 16 h. The reaction mixture was filtered and washed with ether (10 mL). The filtrate was concentrated *in vacuo* and dissolved in 1,2-dimethyoxyethane (5.5 mL) and cooled to -10 °C. A solution of trifluoroacetic anhydride (1.18 mL, 8.48 mmol) and 2,6-lutidine (2.09 mL, 17.96 mL) in 1,2-dimethyoxyethane (3 mL) was added to the orange solution and the reaction

stirred at -10 °C for 30 min. The reaction mixture was concentrated *in vacuo* and partitioned between chloroform (40 mL) and water (40 mL). The aqueous layer was washed with chloroform (40 mL) and the combined organic layers were washed with water (50 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (20%)-light petroleum to give the *title compound* as a colourless solid (0.23 g, 31%); mp 96-97 °C (lit.,[84] mp 103-104 °C); (Found: M+Na^+, 309.0867. $C_{12}H_{18}N_2O_4S$ + Na^+ requires 309.0879); ν_{max} ($CHCl_3$)/cm^{-1} 3455, 3011, 2984, 1615, 1503, 1370, 1240, 1165; δ_H (400 MHz; $CDCl_3$) 8.08 (1 H, s, 5-H), 5.50 (1 H, br s, NH), 4.61 (2 H, d, *J* 6.1, $NHCH_2$), 4.36 (2 H, q, *J* 7.2, CH_3CH_2), 1.42 (9 H, s, $((CH_3)_3)$), 1.36 (3 H, t, *J* 7.2, CH_3CH_2); δ_C (100 MHz; $CDCl_3$) 170.1 (C), 161.2 (C), 155.6 (C), 146.8 (C), 127.8 (CH), 80.3 (C), 61.4 (CH_2), 44.3 (CH_2), 28.2 (CH_3), 14.2 (CH_3). Data consistent with literature.[84]

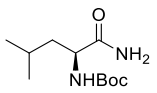
2-((*tert*-Butoxycarbonylamino)methyl)thiazole-4-carboxylic acid 199



To a stirred solution of *N-tert*-butoxycarbonyl-glycinethioamide **196** (1.20 g, 6.29 mmol) in methanol (105 mL) was added calcium carbonate (1.53 g, 15.2 mmol) and bromopyruvic acid (1.23 g, 7.36 mmol). The reaction mixture was stirred at room temperature for 87 h. The reaction mixture was concentrated

in vacuo and residue was taken into water (200 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (4 x 100 mL) and the combined organic extracts were washed with saturated brine (300 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (1.6 g, 98%); mp 172-173 °C (lit.,[139] 178-179 °C); (Found: M-H^+, 257.0598. $C_{10}H_{14}N_2O_4S$ - H^+ requires 257.0596); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 1761, 1715, 1602, 1504, 1369, 1275, 1246, 1193; δ_H (400 MHz; CD_3OD) 8.28 (1 H, s, 5-H), 4.52 (2 H, s, $C\underline{H}_2$), 1.47 (9 H, s, $C(C\underline{H}_3)_3$); δ_C (100 MHz; CD_3OD) 174.1 (C), 164.1 (C), 158.4 (C), 148.3 (C), 129.4 (CH), 81.1 (C), 43.2 (CH_2), 28.2 (CH_3). Data consistent with literature.[139]

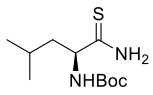
(*S*)-*N*-*tert*-Butoxycarbonyl-leucinamide 201



Di-*tert*-butyl dicarbonate (6.55 g, 30.0 mmol) was added to a stirred solution of triethylamine (3.80 mL, 27.0 mmol) and (*S*)-leucinamide hydrochloride **200** (4.50 g, 27.0 mmol) in THF/water (4:1; 45 mL). After 16 h the organic solvent was evaporated *in vacuo* and the mixture was partitioned between light petroleum (100 mL) and water (100 mL). The aqueous layer was acidified to pH 2 with hydrochloric acid (1 M). The acidified aqueous layer was extracted with ethyl acetate (4 x 100 mL) and the combined organic phases were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with methanol (0-5%)-dichloromethane to

give the *title compound* as a colourless solid (4.44 g, 71%), mp 146-147 °C (lit.,[140] mp 145-146 °C); $[\alpha]_D^{24}$ -11.6 (*c* 1, EtOH) (lit.,[140] $[\alpha]_D^{18}$ -11.1 (*c* 1, EtOH)); (Found: M+Na$^+$, 253.1525. $C_{11}H_{22}N_2O_3$ + Na$^+$ requires 253.1523); ν_{max} ($CHCl_3$)/cm^{-1} 3020, 2963, 2438, 1693, 1500, 1369, 1215, 1163, 800; δ_H (400 MHz; $CDCl_3$) 6.19 (1 H, br s, NH), 5.52 (1 H, br s, NH), 4.90 (1 H, d, *J* 7.7, NH), 4.20 - 4.08 (1 H, m, NHCH), 1.75-1.65 (2 H, m, CH_2), 1.52 - 1.48 (1 H, m, $CH(CH_3)_2$), 1.45 (9 H, s, $C(CH_3)_3$), 0.96 (3 H, d, *J* 6.4, $C(CH_3)(CH_3)$), 0.95 (3 H, d, *J* 6.4, $C(CH_3)(CH_3)$); δ_C (100 MHz; $CDCl_3$) 175.4 (C), 155.8 (C), 80.1 (C), 52.6 (CH), 41.2 (CH_2), 28.3 (CH_3), 24.7 (CH), 22.9 (CH_3), 21.9 (CH_3). Data consistent with literature.[140,141]

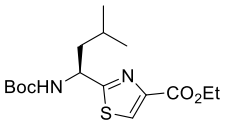
(*S*)-*N*-*tert*-Butoxycarbonyl-leucinethioamide 202



Lawesson's reagent (3.51 g, 8.69 mmol) was added to a stirred solution of (*S*)-*N*-*tert*-butoxycarbonyl-leucinamide **201** (4.00 g, 17.4 mmol) in dry dichloromethane (220 mL). The mixture was stirred at room temperature for 16 h, concentrated *in vacuo* and the residue purified by chromatography on silica, eluting with ethyl acetate (25%)-light petroleum to give the *title compound* **112** as a colourless solid (4.28 g, 100%), mp 157-158 °C (lit.,[142] mp 157.5 °C); $[\alpha]_D^{23}$ -3.8 (*c* 1, $CHCl_3$); (Found: M+Na$^+$, 269.1283. $C_{11}H_{22}N_2O_2S$ + Na$^+$ requires 269.1294); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3481, 3367, 3011, 2963, 1703, 1596, 1496, 1469, 1369, 1240, 1162; δ_H (400 MHz; CD_3OD) 4.39 (1 H, dd, *J* 9.9,

4.3, NHC<u>H</u>), 1.76 - 1.51 (3 H, m, C<u>H</u>$_2$C<u>H</u>(CH$_3$)$_2$, 1.44 (9 H, s, C(C<u>H</u>$_3$)$_3$, 0.95 (6 H, d, *J* 6.4, CH(C<u>H</u>$_3$)$_2$); δ_C (100 MHz; CD_3OD) 212.2 (C), 157.7 (C), 80.8 (C), 60.4 (CH), 45.8 (CH_2), 28.9 (CH_3), 26.3 (CH), 23.7 (CH_3), 22.1 (CH_3).

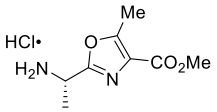
Ethyl (*S*)-2-(1-*tert*-butoxycarbonylamino-3-methylbutyl)thiazole-4-carboxylate 86



To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonyl-leucinethioamide **202** (6.03 g, 24.4 mmol) in 1,2-dimethoxyethane (55 mL) at -40 °C was added potassium hydrogen carbonate (9.75 g, 97.4 mmol) and ethyl bromopyruvate (13.1 mL, 104 mmol). The mixture was allowed to warm to -15 °C for 3 h and warmed to room temperature over 16 h. The reaction mixture was filtered through Celite® and washed with ether (10 mL). The filtrate was concentrated *in vacuo*, dissolved in 1,2-dimethoxyethane (50 mL) and cooled to -40 °C. A solution of trifluoroacetic anhydride (11.2 mL, 80.4 mmol) and 2,6-lutidine (19.9 mL, 170 mmol) in 1,2-dimethoxyethane (20 mL) was added over 5 min and the mixture stirred at -10 °C for 1 h. The reaction mixture was concentrated *in vacuo* and partitioned between chloroform (200 mL) and water (200 mL). The aqueous layer was washed with chloroform (200 mL) and the combined chloroform layers were washed with water (200 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (10%)-light petroleum to

give the *title compound* as a pale yellow oil (6.3 g, 76%). A small portion was recrystallised from pentane to give colourless needles; mp 88-89 °C (lit.,[142] 92 °C); $[\alpha]_D^{20}$ -49.6 (*c* 1.1, $CHCl_3$) (lit.,[143] $[\alpha]_D^{22}$ -51.2 (*c* 1.1, $CHCl_3$)) (Found: M+Na^+, 365.1507. $C_{16}H_{26}N_2O_4S$ + Na^+ requires 365.1505); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3438, 3011, 2982, 2963, 1715, 1602, 1498, 1369, 1242, 1166; δ_H (400 MHz; $CDCl_3$) 8.07 (1 H, s, 5-H), 5.21 - 4.96 (2 H, m, NHCH), 4.42 (2 H, q, *J* 7.2 CH_2CH_3), 1.95 (1 H, m, $CH(CH_3)_2$), 1.73 (2 H, m, $CHCH_2$), 1.45 (9 H, s, $C(CH_3)_3$), 1.40 (3 H, t, *J* 7.2, CH_2CH_3), 0.99 (3 H, d, *J* 6.6, $CH(CH_3)(CH_3)$), 0.98 (3 H, d, *J* 6.6, $CH(CH_3)(CH_3)$); δ_C (100 MHz; DMSO-d_6) 176.6 (C), 160.7 (C), 155.4 (C), 145.8 (C), 128.7 (CH), 78.5 (C), 60.7 (CH_2), 51.2 (CH), 42.9 (CH_2), 28.2 (CH_3), 24.4 (CH), 22.9 (CH_3), 21.2 (CH_3), 14.2 (CH_3). Data consistent with literature.[142–144]

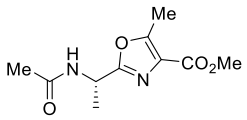
Methyl (*S*)-2-(1-aminoethyl)-5-methyloxazole-4-carboxylate hydrochloride 203



To methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxylate **182** (0.880 g, 3.10 mmol) was added hydrogen chloride in dioxane (4 M; 3.25 mL, 13.0 mmol) and stirred for 1 h at room temperature. The mixture was concentrated *in vacuo* and triturated with ether to give the *title compound* as a pale yellow oil (0.65 g, 96%); $[\alpha]_D^{26}$ 2.0 (*c* 1, $CHCl_3$); (Found: M+H^+, 185.0934. $C_8H_{12}N_2O_3$ + H^+ requires 185.0926); ν_{max} (ATR)/cm^{-1} 3401, 2886, 1721, 1620, 1444, 1388, 1194; δ_H (400 MHz; $CDCl_3$) 9.40 (2 H, br s, NH_2), 4.85 (1 H, q,

J 6.6, C<u>H</u>CH$_3$), 3.88 (3 H, s, CO$_2$C<u>H</u>$_3$), 2.60 (3 H, s, 5-CH$_3$), 1.90 (3 H, d, *J* 6.6, CHC<u>H</u>$_3$); δ_C (100 MHz; CDCl$_3$) 163.1 (C), 158.8 (C), 157.4 (C), 127.5 (C), 52.4 (CH$_3$), 45.2 (CH), 17.5 (CH$_3$), 12.2 (CH$_3$).

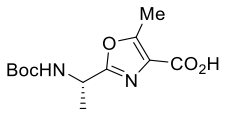
Methyl (*S*)-2-(1-acetamidoethyl)-5-methyloxazole-4-carboxylate 82



To methyl (*S*)-2-(1-aminoethyl)-5-methyloxazole-4-carboxylate hydrochloride **203** (84 mg, 0.38 mmol) in dry dichloromethane (2 mL) was added *N,N*-diisopropylethylamine (0.10 mL, 0.57 mmol) and acetic anhydride (0.05 mL, 0.57 mmol) sequentially. After stirring for 16 h at room temperature, *N,N*-diisopropylethylamine (0.10 mL, 0.57 mmol) and acetic anhydride (0.05 mL, 0.57 mmol) were added. After a further 8 h, the reaction mixture was partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous layer was washed with dichloromethane (5 mL) and the combined organic layers were washed with hydrochloric acid (1M, 10 mL), saturated sodium hydrogen carbonate (10 mL), saturated brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless oil (47 mg, 55%); $[\alpha]_D^{23}$ -51.3 (*c* 1, CHCl$_3$); (Found: M+H$^+$, 227.1032. $C_{10}H_{14}N_2O_4$ + H$^+$ requires 227.1026); ν_{max} (CHCl$_3$)/cm^{-1} 3435, 3009, 1726, 1676, 1511, 1443, 1353, 1190, 1102; δ_H (400 MHz; CDCl$_3$) 6.37 (1 H, d, *J* 7.5, N<u>H</u>), 5.25 (1 H, d q, *J* 7.5, 7.0, C<u>H</u>CH$_3$), 3.91 (3 H, s, CO$_2$C<u>H</u>$_3$), 2.61 (3 H, s, 5-CH$_3$), 2.03 (3 H, s, COC<u>H</u>$_3$),

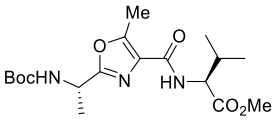
1.53 (3 H, d, *J* 7.0, CHC<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 169.6 (C), 163.0 (C), 162.3 (C), 156.5 (C), 127.0 (C), 51.8 (CH_3), 43.1 (CH), 22.9 (CH_3), 19.8 (CH_3), 11.9 (CH_3).

(*S*)-2-(1-(*tert*-Butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxylic acid 205



Lithium hydroxide monohydrate (0.700 g, 16.7 mmol) was added to methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxylate **182** (0.95 g, 3.3 mmol) in methanol/water (4:1; 35 mL). The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo*, taken into water (20 mL) and acidified to pH 2 with citric acid (10%). The aqueous solution was extracted with ethyl acetate (4 x 30 mL) and the combined organic extracts washed with saturated brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless oil (0.90 g, 100%); $[\alpha]_D^{26}$ -67.2 (*c* 1, $CHCl_3$); (Found: M+Na^+, 293.1095. $C_{12}H_{18}N_2O_5$ + Na^+ requires 293.1113); ν_{max} ($CHCl_3$)/cm^{-1} 3441, 3008, 2983, 2932, 1708, 1630, 1503, 1451, 1393, 1368, 1314, 1241, 1163, 1102, 1065; δ_H (500 MHz; $CDCl_3$) 7.43 (1 H, br s, O<u>H</u>), 6.21 (1 H, d, *J* 8.7, N<u>H</u>), 5.03 - 4.93 (1 H, m, C<u>H</u>CH_3), 2.63 (3 H, s, 5-CH_3), 1.54 (3 H, d, *J* 7.1, CHC<u>H</u>$_3$), 1.39 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (125 MHz; $CDCl_3$) 164.9 (C), 164.3 (C), 157.1 (C), 155.4 (C), 127.0 (C), 79.9 (C), 44.5 (CH), 28.2 (CH_3), 20.1 (CH_3), 11.9 (CH_3). Data consistent with literature.[82]

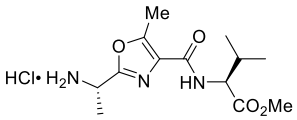
Methyl (*S*)-2-(2-(*S*)-1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate 206



To a stirred solution of (*S*)-2-(1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxylic acid **205** (0.90 g, 3.3 mmol) and (*S*)-valine methyl ester hydrochloride (0.73 g, 4.3 mmol) in dimethylformamide (30 mL) at 0 °C, was added *N,N*-diisopropylethylamine (2.9 mL, 17 mmol) and HATU (3.2 g, 8.3 mmol). The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was taken into water (300 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL), lithium chloride solution (10%; 3 x 200 mL), water (200 mL) and saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (2.5%)-dichloromethane to give the *title compound* as a colourless oil (1.0 g, 82%); $[\alpha]_D^{23}$ -35.3 (*c* 1, $CHCl_3$); (Found: M+Na^+, 406.1963. $C_{18}H_{29}N_3O_6$ + Na^+ requires 406.1954); ν_{max} ($CHCl_3$)/cm^{-1} 3442, 3011, 2973, 1738, 1713, 1668, 1636, 1514, 1439, 1392, 1369, 1240, 1159, 1057; δ_H (400 MHz; $CDCl_3$) 7.32 (1 H, d, *J* 9.2, NH), 5.06 (1 H, br s, NH), 4.99 - 4.84 (1 H, m, NHCHCH$_3$), 4.65 (1 H, dd, *J* 9.2, 5.3, NHCHCH), 3.76 (3 H, s, OCH$_3$), 2.61 (3 H, s, 5-CH$_3$), 2.25 (1 H, d septet, *J* 5.3, 4.9, CHCH(CH$_3$)$_2$), 1.53 (3 H, d, *J* 6.9, CHCH$_3$), 1.48 (9 H, s, C(CH$_3$)$_3$), 1.01 (3 H, d, *J* 4.9, CH(CH$_3$)(CH$_3$)), 0.99 (3 H, d, *J* 4.9, CH(CH$_3$)(CH$_3$)); δ_C (100 MHz;

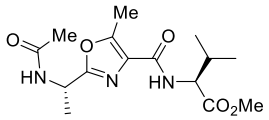
$CDCl_3$) 172.1 (C), 161.6 (C), 161.6 (C), 154.8 (C), 153.2 (C), 128.4 (C), 79.8 (C), 56.5 (CH), 51.9 (CH_3), 44.4 (CH), 31.2 (CH), 28.1 (CH_3), 19.7 (CH_3), 18.9 (CH_3), 17.8 (CH_3), 11.4 (CH_3).

Methyl (*S*)-2-(2-(*S*)-1-aminoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate hydrochloride 207



To methyl (*S*)-2-(2-(*S*)-1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate **206** (0.50 g, 1.3 mmol) was added hydrogen chloride in dioxane (4 M; 1.3 mL, 5.2 mmol) and the mixture was stirred for 4 h at room temperature. The mixture was concentrated *in vacuo* and triturated with ether to give the *title compound* as a colourless oil (0.38 g, 91%); $[\alpha]_{\mathrm{D}}^{23}$ +7.6 (*c* 1, $CHCl_3$); (Found: M+H^+, 284.1602. $C_{13}H_{21}N_3O_4$ + H^+ requires 284.1605); ν_{max} ($CHCl_3$)/cm^{-1} 3407, 2976, 1738, 1671, 1634, 1519, 1439, 1389, 1373, 1155, 1105; δ_H (400 MHz; $CDCl_3$) 9.26 (2 H, br s, N$\underline{H}_2$), 7.55 (1 H, d, *J* 8.8, N$\underline{H}$CH), 4.82 - 4.72 (1 H, m, $NH_2C\underline{H}$), 4.62 (1 H, dd, *J* 8.8, 5.5, NHC$\underline{H}$CH), 3.73 (3 H, s, O$C\underline{H}_3$), 2.62 (3 H, s, 5-CH_3), 2.24 (1 H, d septet, *J* 5.5, 6.6, CHC$\underline{H}(CH_3)_2$), 1.84 (3 H, d, *J* 6.3, CHC$\underline{H}_3$), 1.00 (3 H, d, *J* 6.6, CH(C$\underline{H}_3$)(CH_3)), 0.98 (3 H, d, *J* 6.6, CH(C$\underline{H}_3$)(CH_3)); δ_C (100 MHz; $CDCl_3$) 173.3 (C), 161.3 (C), 157.5 (C), 154.6 (C), 129.1 (C), 56.9 (CH), 52.3 (CH_3), 45.2 (CH), 31.3 (CH), 19.1 (CH_3), 18.2 (CH_3), 17.7 (CH_3), 11.7 (CH_3).

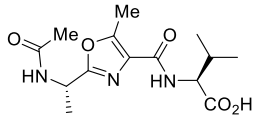
Methyl (*S*)-2-(2-((*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate 208



To methyl (*S*)-2-(2-(*S*)-1-aminoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate hydrochloride 207 (0.57 g, 1.8 mmol) in dry dichloromethane (20 mL) was added *N,N*-diisopropylethylamine (1.5 mL, 8.9 mmol) and acetic anhydride (0.72 mL, 5.3 mmol) sequentially. After stirring for 56 h at room temperature, the reaction mixture was partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous layer was further extracted with dichloromethane (50 mL) and the combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (5%)-dichloromethane to give the *title compound* as a colourless solid (0.53 g, 93%); mp 100-101 °C; $[\alpha]_D^{22}$ -48.1 (*c* 1, $CHCl_3$); (Found: C, 55.4; H, 7.2; N, 13.2. $C_{15}H_{23}N_3O_5$ requires C, 55.4; H, 7.1; N, 12.9%); (Found: M+H^+, 326.1713. $C_{15}H_{23}N_3O_5$ + H^+ requires 326.1710); ν_{max} ($CHCl_3$)/cm^{-1} 3438, 3011, 2970, 2935, 2877, 1739, 1672, 1635, 1513, 1450, 1439, 1338, 1307, 1239, 1153; δ_H (400 MHz; $CDCl_3$) 7.38 (1 H, d, *J* 9.2, CONHCH), 6.58 (1 H, d, *J* 8.0, CH_3CONH), 5.19 (1 H, dq, 8.0, 7.0, NHCHCH_3), 4.61 (1 H, dd, *J* 9.2, 5.4, NHCHCH), 3.73 (3 H, s, CO_2CH_3), 2.54 (3 H, s, 5-CH_3), 2.02 (3 H, s, $COCH_3$), 2.21 (1 H, d septet, *J* 6.9, 5.4, $CH(CH_3)_2$), 1.47 (3 H, d, *J* 7.0, $CHCH_3$), 0.96 (3 H, d, *J* 6.9,

CH(C<u>H</u>$_3$)(CH$_3$)), 0.95 (3 H, d, *J* 6.9, CH(C<u>H</u>$_3$)(CH$_3$)); δ_C (100 MHz; $CDCl_3$) 172.3 (C), 169.5 (C), 161.6 (C), 161.3 (C), 153.5 (C), 128.5 (C), 56.6 (CH), 52.0, (CH_3), 42.9 (CH), 31.3 (CH), 23.1 (CH_3), 19.4 (CH_3), 19.0 (CH_3), 18.0 (CH_3), 11.5 (CH_3).

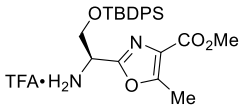
(*S*)-2-(2-((*S*)-1-Acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoic acid 209



Lithium hydroxide monohydrate (0.19 g, 4.5 mmol) was added to methyl (*S*)-2-(2-((*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate **208** (0.29 g, 0.89 mmol) in methanol/water (4:1; 10 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo*, diluted with water (10 mL) and extracted with light petroleum (10 mL). The aqueous solution was acidified to pH 2 with citric acid (10%) and extracted with ethyl acetate (4 x 10 mL). The combined organic extracts were washed with saturated brine (30 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (0.27 g, 96%); mp 103 - 104°C; $[\alpha]_D^{23}$ -44.8 (*c* 1, $CHCl_3$); (Found: M-H$^+$, 310.1414. $C_{14}H_{21}N_3O_5$ - H$^+$ requires 310.1408); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3606, 3436, 3009, 2970, 2935, 2877, 1719, 1671, 1635, 1603, 1516, 1451, 1373, 1240, 1148; δ_H (400 MHz; CD_3OD) 7.75 (1 H, d, *J* 8.9, NH<u>H</u>CHCH), 5.13 (1 H, q, *J* 7.2, C<u>H</u>CH$_3$), 4.52 - 4.45 (1 H, m, NHC<u>H</u>CH), 2.58 (3 H, s, 5-CH$_3$), 2.27 (1 H, d septet, *J* 5.4, 6.8, NHCHC<u>H</u>), 1.99 (3 H, s, C<u>H</u>$_3$CO), 1.53 (3 H, d, *J* 7.2, CHC<u>H</u>$_3$), 1.01 (3 H, d, *J* 6.8,

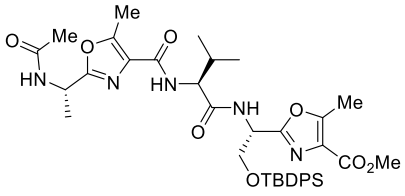
CH(C<u>H</u>$_3$)(CH$_3$)), 1.00 (3 H, d, *J* 6.8, CH(CH$_3$)(C<u>H</u>$_3$)); δ_C (100 MHz; CD$_3$OD) 174.6 (C), 172.9 (C), 163.7 (C), 163.5 (C), 155.2 (C), 129.9 (C), 58.5 (CH), 44.5 (CH), 32.3 (CH), 22.6 (CH$_3$), 19.7 (CH$_3$), 19.0 (CH$_3$), 18.3 (CH$_3$), 11.8 (CH$_3$).

Methyl (*S*)-2-(2-(*tert*-butyldiphenylsiloxy)-1-aminoethyl)-5-methyloxazole-4-carboxylate trifluoroacetate 210



Methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-(*tert*-butyldiphenylsiloxy)-ethyl)-5-methyloxazole-4-carboxylate **84** (0.25 g, 0.46 mmol) was dissolved in trifluoroacetic acid/dichloromethane (95:5; 2 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C, warmed to room temperature for 10 min and concentrated *in vacuo* to give the *title compound* as an orange oil (0.23 g, 90%); $[\alpha]_D^{22}$ +6.3 (*c* 1, CHCl$_3$); (Found: M+H$^+$, 439.2069. C$_{24}$H$_{30}$N$_2$O$_4$Si + H$^+$ requires 439.2048); ν_{max} (ATR)/cm^{-1} 2956, 2931, 2858, 1722, 1676, 1194, 1136, 1112; δ_H (400 MHz; CDCl$_3$) 9.53 (2 H, br s, N<u>H</u>$_2$), 7.69 (2 H, d, *J* 6.8, Ar<u>H</u>), 7.63 (2 H, d, *J* 6.8, Ar<u>H</u>), 7.43 - 7.28 (6 H, m, Ar<u>H</u>), 4.91 - 4.71 (1 H, m, NH$_2$C<u>H</u>), 4.33 - 4.13 (2 H, m, CHC<u>H</u>$_2$), 3.84 (3 H, s, CO$_2$C<u>H</u>$_3$), 2.50 (3 H, s, 5-CH$_3$), 1.06 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (100 MHz; CDCl$_3$) 162.9 (C), 157.7 (C), 156.0 (C), 135.50 (CH), 135.46 (CH), 131.9 (C), 131.7 (C), 130.2 (CH), 130.1 (CH), 127.92 (CH), 127.85 (CH), 127.5 (C) 62.0 (CH$_2$), 52.5 (CH$_3$), 51.0 (CH), 26.4 (CH$_3$), 19.0 (C), 12.0 (CH$_3$).

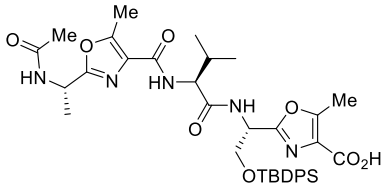
Methyl 2-((*S*)-1-((*S*)-2-(2-((*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanamido)-2-(*tert*-butyldiphenylsiloxy)ethyl)-5-methyloxazole-4-carboxylate 211



Methyl (*S*)-2-(2-(*tert*-butyldiphenylsiloxy)-1-aminoethyl)-5-methyloxazole-4-carboxylate trifluoroacetate **210** (0.66 g, 1.2 mmol) was taken into dichloromethane (10 mL) and washed with saturated sodium hydrogen carbonate (10 mL), saturated sodium carbonate (10 mL) and saturated brine (10 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The concentrated residue was dissolved in dichloromethane (12 mL) and cooled to 0 °C. (*S*)-2-(2-((*S*)-1-Acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoic acid **209** (0.39 g, 1.2 mmol) was added, followed by 2,6-di-*tert*-butyl-4-methylpyridine (0.95 g, 4.6 mmol), HBTU (0.87 g, 2.3 mmol) and HOAt (0.16 g, 1.2 mmol). The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were washed with hydrochloric acid (1 M; 50 mL), saturated sodium hydrogen carbonate (50 mL), water (50 mL) and saturated brine (50 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (1-8%)-dichloromethane to give the *title compound* as a colourless solid (0.64 g, 75%); mp 64-65 °C; $[\alpha]_{\mathrm{D}}^{23}$ -39.1 (*c* 1, $CHCl_3$); (Found:

M+Na$^+$, 754.3244. $C_{38}H_{49}N_5O_8Si$ + Na$^+$ requires 754.3243); ν_{max} (ATR)/cm^{-1} 2860, 2933, 1722, 1656, 1513, 1371, 1351, 1191, 1112, 704; δ_H (400 MHz; $CDCl_3$) 7.56 - 7.47 (4 H, m, ArH), 7.45 - 7.30 (7 H, m, ArH, NHCHCH), 6.80 (1 H, d, *J* 8.0, NHCHCH$_2$), 6.13 (1 H, d, *J* 7.9, NHCHCH$_3$), 5.27 (1 H, ddd, *J* 8.0, 4.6, 4.5, NHCHCH$_2$), 5.22 (1 H, dq, *J* 7.9, 7.0, NHCHCH$_3$), 4.45 (1 H, dd, *J* 9.0, 6.5, NHCHCH), 4.07 (1 H, dd, *J* 10.2, 4.5, NHCHCHH), 3.97 (1 H, dd, *J* 10.2, 4.6, NHCHCHH), 3.91 (3 H, s, CO_2CH_3), 2.59 (3 H, s, 5-CH_3), 2.56 (3 H, s, 5-CH_3), 2.26 (1 H, septet d, *J* 6.8, 6.5, CH(CH$_3$)$_2$), 2.05 (3 H, s, NHCOCH$_3$), 1.51 (3 H, d, *J* 7.0, NHCHCH$_3$), 1.03 (3 H, d, *J* 6.8, CH(CH$_3$)(CH$_3$)), 1.02 (3 H, d, *J* 6.8, CH(CH$_3$)(CH$_3$)), 0.96 (9 H, s, C(CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 170.8 (C), 169.3 (C), 162.5 (C), 161.6 (C), 161.4 (C), 159.8 (C), 156.5 (C), 153.6 (C), 135.4 (CH), 132.5 (C), 132.4 (C), 129.9 (CH), 128.6 (C), 127.79 (CH), 127.75 (CH), 127.6 (C), 64.7 (CH_2), 57.9 (CH), 51.9 (CH_3), 49.5 (CH), 43.2 (CH), 31.1 (CH), 26.6 (CH_3), 23.3 (CH_3), 20.0 (CH_3), 19.2 (CH_3), 19.1 (C), 18.1 (CH_3), 11.9 (CH_3), 11.6 (CH_3).

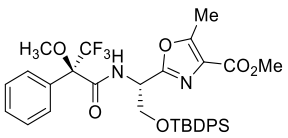
2-((*S*)-1-((*S*)-2-(2-((*S*)-1-Acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanamido)-2-((*tert*-butyldiphenylsiloxy)ethyl)-5-methyloxazole-4-carboxylic acid 80



To methyl 2-((*S*)-1-((*S*)-2-(2-((*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanamido)-2-(*tert*-butyldiphenylsiloxy)ethyl)-5-

methyloxazole-4-carboxylate **211** (0.50 g, 0.69 mmol) in 1,2-dichloroethane (3 mL) was added trimethyltin hydroxide (0.49 g, 2.7 mmol). The mixture was heated under reflux for 16 h, concentrated *in vacuo* and taken into ethyl acetate (50 mL). The organic layer was washed with hydrochloric acid (1 M; 3 x 50 mL) and saturated brine (50 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as colourless solid, which was used without further purification (0.49 g, 100%); (Found: M-H^+, 716.3119. $C_{37}H_{47}N_5O_8Si$ - H^+ requires 716.3121).

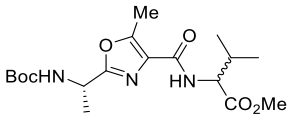
Methyl 2-((3R,6S)-10,10-dimethyl-4-oxo-3,9,9-triphenyl-3-trifluoromethyl-2,8-dioxa-5-aza-9-silaundecan-6-yl)-5-methyloxazole-4-carboxylate 212



To (*R*)-Mosher's acid (0.021, 0.090 mmol) in dimethylformamide (1 mL) at 0 °C was added *N,N*-diisopropylethylamine (0.061 mL, 0.35 mmol), HATU (0.053 g, 0.14 mmol) and HOAt (0.019 g, 0.14 mmol) and the mixture stirred for 10 min. Methyl (*S*)-2-(2-(*tert*-butyldiphenylsiloxy)-1-aminoethyl)-5-methyloxazole-4-carboxylate trifluoroacetate **210** (0.038 g, 0.070 mmol) in dimethylformamide (0.5 mL) was added and the mixture stirred for 16 h. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (4 x 5 mL). The combined organic layers were washed with hydrochloric acid (1 M; 10 mL), saturated sodium hydrogen carbonate (10 mL), water (10 mL), lithium chloride

(10%; 3 x 10 mL) and saturated brine (10 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (1-10%)-dichoromethane to give the *title compound* as a colourless oil (0.013 g, 28%); $[\alpha]_D^{23}$ -45.7 (*c* 1, $CHCl_3$); (Found: M+Na^+, 655.2465. $C_{34}H_{37}F_3N_2O_6Si$ + H^+ requires 655.2451); ν_{max} (ATR) /cm^{-1} 2953, 2931, 2857, 1704, 1620, 1503, 1351, 1267, 1163, 1100, 701; δ_H (400 MHz, $CDCl_3$) 7.94 (1 H, d, *J* 8.3. NH), 7.67 - 7.52 (6 H, m, ArH), 7.48 - 7.33 (9 H, m, ArH), 5.31 (1 H, dt, *J* 8.3, 4.2, NHC<u>H</u>CH_2), 4.16 (1 H, dd, *J* 10.4, 4.2. CHC<u>H</u>H), 4.05 (1 H, dd, *J* 10.4, 4.2, CHCH<u>H</u>), 3.93 (3 H, s, $CO_2C\underline{H}_3$), 3.40 (3 H, q, *J* 1.2, $COC\underline{H}_3$), 2.55 (3 H, s, 5-CH_3), 1.02 (9 H, s, $C(C\underline{H}_3)_3$); δ_C (125 MHz, $CDCl_3$) 166.4 (C), 162.5 (C), 159.5 (C), 156.5 (C), 135.43 (CH), 135.40 (CH), 132.4 (C), 132.3 (C), 131.9 (C), 130.0 (CH), 129.9 (CH), 129.6 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (C), 123.9 (1 C, q, *J* 291.1, $\underline{C}F_3$) 84.2 (1 C, q, *J* 26.8, $\underline{C}(CF_3)$), 64.5 (CH_2), 54.9 (1 C, q, *J* 1.8, $CO\underline{C}H_3$), 51.9 (CH_3), 49.5 (CH), 26.5 (CH_3), 19.2 (C), 11.9 (CH_3); δ_f (376 MHz, $CDCl_3$) -68.9 (3 F, s, CF_3).

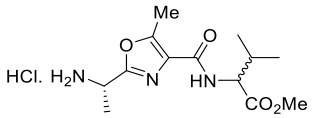
Methyl-2-(2-(*S*)-1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate 218



To a stirred solution of (*S*)-2-(1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxylic acid **205** (0.48 g, 1.8 mmol) and D/L valine methyl ester hydrochloride (0.35 g, 2.1 mmol) in

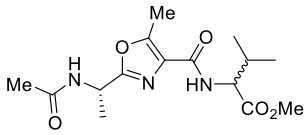
dimethylformamide/dichloromethane (1:1; 30 mL) at 0 °C, was added *N,N*-diisopropylethylamine (1.5 mL, 8.8 mmol) and HATU (1.3 g, 3.5 mmol). The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was taken into water (200 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL), lithium chloride solution (10%; 3 x 200 mL), water (200 mL) and saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (2.5%)-dichloromethane to give the *title compound* as a mixture of diastereomers (1:0.8), as a colourless oil (0.51 g, 76%); (Found: M+Na^+, 384.2133. $C_{18}H_{29}N_3O_6$ + H^+ requires 384.2135); ν_{max} (ATR)/cm^{-1} 2968, 1934, 1741, 1714, 1666, 1634, 1509, 1365, 1246, 1153, 1057, 753; diastereomer A δ_H (400 MHz, $CDCl_3$) 7.29 (1 H, d, *J* 9.0, N<u>H</u>CHCH), 5.15 (1 H, br s, N<u>H</u>CHCH_3), 4.87 (1 H, br s, NHC<u>H</u>CH_3), 4.61 (1 H, dd, *J* 9.0, 5.3, NHC<u>H</u>CH), 3.72 (3 H, s, $CO_2C\underline{H}_3$), 2.57 (3 H, s, 5-CH_3), 2.15 - 2.28 (1 H, d septet, *J* 5.3, 6.9, NHCHC<u>H</u>), 1.49 (3 H, d, *J* 7.0, NHCHC$\underline{H}_3$), 1.43 (9 H, s, C($C\underline{H}_3$)$_3$), 0.98 - 0.83 (6 H, m, CH($C\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 172.21 (C), 161.6 (C), 161.6 (C), 154.8 (C), 153.3 (C), 128.5 (C), 80.0 (C), 56.59 (CH), 52.02 (CH_3), 44.6 (CH), 31.3 (CH), 28.2 (CH_3), 19.87 (CH_3), 19.0 (CH_3), 17.86 (CH_3), 11.5 (CH_3); diastereomer B, the following NMR signals are discernible, the rest overlap with the other diastereomer δ_H (400 MHz, $CDCl_3$) 3.73 (3 H, s, $CO_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 172.16 (C), 161.7 (C), 154.9 (C), 153.4 (C), 56.61 (CH), 52.04 (CH_3), 19.94 (CH_3), 17.91 (CH_3).

Methyl-2-(2-(*S*)-1-aminoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate hydrochloride 219



To methyl-2-(2-(*S*)-1-(*tert*-butoxycarbonylamino)ethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate **218** (0.41 g, 1.1 mmol) was added hydrogen chloride in dioxane (4 M; 1.3 mL, 5.2 mmol) and the mixture was stirred for 4 h at room temperature. The mixture was concentrated *in vacuo* and triturated with ether to give the *title compound* as a mixture of diastereomers (1:1), as a colourless oil (0.24 g, 71%); (Found: M+H$^+$, 284.1604. $C_{13}H_{21}N_3O_4$ + H$^+$ requires 284.1605); ν_{max} (ATR)/cm^{-1} 2963, 2876, 1739, 1666, 1632, 1515, 1438, 1388, 1372, 1266, 1204, 1152, 1107; diastereomer A δ_H (400 MHz, $CDCl_3$) 9.31 (2 H, br s, N$\underline{H}_2$), 7.47 (1 H, d, *J* 7.4, N$\underline{H}$), 4.88 - 4.76 (1 H, m, NHC$\underline{H}$CH$_3$), 4.61 (1 H, br s, NHC$\underline{H}$CH), 3.72 (3 H, s, CO$_2$C$\underline{H}_3$), 2.62 (3 H, s, 5-CH$_3$), 2.23 (1 H, br s, NHCHC$\underline{H}$), 1.86 (3 H, d, *J* 7.7, NHCHC$\underline{H}_3$), 1.00 - 0.95 (6 H, m, CH(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 173.01 (C), 161.3 (C), 157.4 (C), 154.64 (C), 129.13 (C), 56.9 (CH), 52.27 (CH$_3$), 45.3 (CH), 31.2 (CH), 19.0 (CH$_3$), 18.2 (CH$_3$), 17.7 (CH$_3$), 11.7 (CH$_3$); Diastereomer B the following NMR signals are discernible, the rest overlap with the other diastereomer δ_H (400 MHz, $CDCl_3$) 7.49 (1 H, d, *J* 7.4, N$\underline{H}$), 3.71 (3 H, s, CO$_2$C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 172.98 (C), 161.2 (C), 157.2 (C), 154.58 (C), 129.09 (C), 56.8 (CH), 52.25 (CH$_3$), 45.2 (CH), 31.1 (CH), 17.0 (CH$_3$).

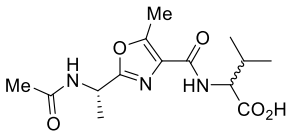
Methyl-2-(2-(*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate 220



To methyl-2-(2-(*S*)-1-aminoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate hydrochloride **219** (0.57 g, 1.8 mmol) in dry dichloromethane (10 mL) was added *N,N*-diisopropylethylamine (1.3 mL, 7.5 mmol) and acetic anhydride (0.21 mL, 2.3 mmol) sequentially. After stirring for 56 h at room temperature, the reaction mixture was partitioned between water (100 mL) and dichloromethane (100 mL). The aqueous layer was further extracted with dichloromethane (50 mL) and the combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate to give the *title compound,* as a mixture of diastereomers (1:1), as a colourless oil (0.21 g, 88%); (Found: M+H$^+$, 326.1721. $C_{15}H_{23}N_3O_5$ + H$^+$ requires 326.1710); ν_{max} (ATR)/cm^{-1} 2964, 2876, 1739, 1656, 1634, 1511, 1436, 1371, 1266, 1202, 1149, 752; diastereomer A δ_H (400 MHz, $CDCl_3$) 7.34 (1 H, d, *J* 9.2, N<u>H</u>), 6.57 (1 H, d, *J* 8.0, N<u>H</u>), 5.19 (1 H, dq, *J* 8.0, 7.0, NHC<u>H</u>CH$_3$), 4.61 (1 H, dd, *J* 9.2, 5.4, NHC<u>H</u>CH), 3.73 (3 H, s, $CO_2C\underline{H}_3$), 2.55 (3 H, s, 5-CH_3), 2.21 (1 H, septet d, *J* 6.8, 5.4, NHCHC<u>H</u>), 2.04 (3 H, s, NHCOC<u>H</u>$_3$), 1.49 (3 H, d, *J* 7.0, NHCHC<u>H</u>$_3$), 0.96 (3 H, d, *J* 6.8, CH(C<u>H</u>$_3$)(CH$_3$)), 0.95 (3 H, *J* 6.8, CH(CH$_3$)(C<u>H</u>$_3$)); δ_C (100 MHz, $CDCl_3$) 172.29 (C), 169.4 (C), 161.6 (C), 161.27 (C),

153.52 (C), 128.5 (C), 56.6 (CH), 52.06 (CH_3), 43.1 (CH), 31.3 (CH), 23.08 (CH_3), 19.6 (CH_3), 19.0 (CH_3), 17.9 (CH_3), 11.5 (CH_3); Diastereomer B, the following NMR signals are discernible, the rest overlap with the diastereomers A δ_H (400 MHz, $CDCl_3$) 7.27 (1 H, d, *J* 9.2, NH), 6.51 (2 H, d, *J* 8.0, NH), 5.18 (1 H, dq, *J* 8.0, 7.0, NHCHCH$_3$), 4.60 (1 H, dd, *J* 9.2, 5.4, NHCHCH), 2.54 (3 H, s, 5-CH_3), 2.03 (3 H, s, NHCOCH$_3$), 1.48 (3 H, d, *J* 7.0, NHCHCH$_3$); δ_C (100 MHz, $CDCl_3$) 172.27 (C), 161.5 (C), 161.26 (C), 153.46 (C), 52.05 (CH_3), 42.9 (CH), 23.06 (CH_3), 19.5 (CH_3).

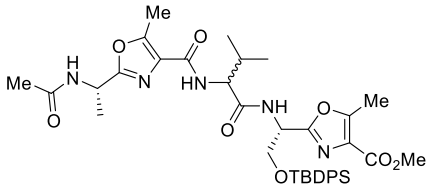
2-(2-(*S*)-1-Acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoic acid 221



Lithium hydroxide monohydrate (0.054 g, 1.2 mmol) was added to methyl-2-(2-(*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoate **220** (0.11 g, 0.32 mmol) in methanol/water (4:1; 3 mL). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo* and diluted with water (10 mL). The aqueous solution was acidified to pH 2 with hydrochloric acid (1 M) and extracted with ethyl acetate (4 x 10 mL). The combined organic extracts were washed with saturated brine (30 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound,* as a mixture of diastereomers (1:1), as a colourless oil (0.094 g, 93%); (Found: M-H^+, 310.1403. $C_{14}H_{21}N_3O_5$ - H^+ requires 310.1408); ν_{max} (ATR)/cm^{-1} 3288, 2964, 2934, 1728,1630, 1515, 1372, 1194, 1142, 750;

diastereomers A δ_H (400 MHz, $CDCl_3$) 8.96 (1 H, br s, O<u>H</u>), 7.33 (1 H, d, *J* 9.0, N<u>H</u>), 6.77 (1 H, d, *J* 8.2, N<u>H</u>), 5.25 (1 H, dq, *J* 8.2, 7.3, NHC<u>H</u>CH_3), 4.67 (1 H, dd, *J* 9.0, 5.1, NHC<u>H</u>CH), 2.60 (3 H, s, 5-CH_3), 2.31 (1 H, m, C<u>H</u>$(CH_3)_2$), 2.08 (3 H, s, NHCOC<u>H</u>$_3$), 1.53 (3 H, d, *J* 7.3, NHCHC<u>H</u>$_3$), 1.06 - 0.98 (6 H, m, CH(C<u>H</u>$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 174.5 (C), 170.3 (C), 161.9 (C), 161.65 (C), 154.1 (C), 128.4 (C), 56.9 (CH), 43.3 (CH), 31.22 (C), 23.0 (CH_3), 19.7 (CH_3), 19.1 (CH_3), 17.9 (CH_3), 11.7 (CH_3); diastereomers B, the following NMR signals are discernible, the rest overlap with the major isomer δ_H (400 MHz, $CDCl_3$) 7.29 (1 H, d, *J* 9.0, NH), 6.69 (1 H, d, *J* 8.2, NH), 5.24 (1 H, dq, *J* 8.2, 7.3, NHC<u>H</u>CH_3), 4.66 (1 H, dd, *J* 9.0, 5.1, NHC<u>H</u>CH), 2.59 (3 H, s, 5-CH_3), 2.07 (3 H, s, NHCOC<u>H</u>$_3$), 1.51 (3 H, d, *J* 7.3, NHCHC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 174.4 (C), 170.2 (C), 161.70 (C), 161.61 (C), 154.0 (C), 128.4 (C), 43.2 (CH), 31.19 (CH), 19.6 (CH_3).

Methyl 2-((*S*)-1-(-2-(2-((*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanamido)-2-(*tert*-butyldiphenylsiloxy)ethyl)-5-methyloxazole-4-carboxylate 222

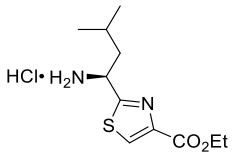


To 2-(2-(*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanoic acid **221** (0.029 g, 0.094 mmol) in chloroform (0.8 mL) at 0 °C was added 2,6-lutidine (0.068 mL, 0.38 mmol) followed by HBTU (0.071 g, 0.19 mmol) and HOAt (0.026 g, 0.19 mmol) and the mixture stirred for 10 min.

Methyl (*S*)-2-(2-(*tert*-butyldiphenylsiloxy)-1-aminoethyl)-5-methyloxazole-4-carboxylate trifluoroacetate **210** (0.052 g, 0.094 mmol) in chloroform (0.2 mL) was added to the mixture and stirred for 16 h. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (4 x 5 mL). The combined organic layers were washed with hydrochloric acid (1 M; 10 mL), saturated sodium hydrogen carbonate (10 mL), water (10 mL) and saturated brine (10 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (1-8%)-dichoromethane to give the *title compound,* as a mixture of diastereomers (1:1), as a colourless oil (0.047 g, 68%); (Found: M+Na^+, 754.3223. $C_{38}H_{49}N_5O_8Si$ + Na^+ requires 754.3243); ν_{max} (ATR)/cm^{-1} 2931, 2876, 2858, 2831, 1722, 1650, 1510, 1370, 1187, 1098, 744, 701; diastereomer A δ_H (400 MHz; $CDCl_3$) 7.56 - 7.45 (4 H, m, Ar<u>H</u>), 7.44 - 7.30 (7 H, m, NH, ArH), 6.99 (1 H, d, *J* 8.3, N<u>H</u>CHCH$_2$), 6.28 (1 H, d, *J* 8.0, N<u>H</u>CHCH$_3$), 5.30 (1 H, dt, *J* 8.3, 4.4, NHC<u>H</u>CH$_2$), 5.22 (1 H, dq, *J* 8.0, 7.0, NHC<u>H</u>CH$_3$), 4.53 (1 H, dd, *J* 9.0, 6.1, NHC<u>H</u>CH), 4.07 (1 H, dd, *J* 9.9, 4.1, CHC<u>H</u>H), 4.00 – 3.94 (1 H, m, CHCH<u>H</u>), 3.91 (3 H, s, $CO_2C\underline{H}_3$), 2.581 (3 H, s, 5-CH_3), 2.56 (3 H, s, 5-CH_3), 2.31 - 2.21 (1 H, m, C<u>H</u>$(CH_3)_2$), 2.07 (3 H, s, NHCOC<u>H</u>$_3$), 1.51 (3 H, d, *J* 7.0, NHCHC<u>H</u>$_3$), 1.02 - 0.99 (6 H, m, CH$(C\underline{H}_3)_2$), 0.96 (9 H, s, C$(C\underline{H}_3)_3$); δ_C (100 MHz; $CDCl_3$) 170.81 (C), 169.4 (C), 162.5 (C), 161.7 (C), 161.5 (C), 159.8 (C), 156.52 (C), 153.7 (C), 135.40 (CH), 135.37 (CH), 132.5 (C), 132.4 (C), 129.93 (CH), 128.6 (C), 127.8 (CH), 127.74 (CH), 127.54 (C), 64.8 (CH_2), 57.9 (CH), 51.9 (CH_3), 49.51 (CH), 43.23 (CH), 31.12 (CH), 26.6 (CH_3), 23.2 (CH_3), 20.0 (CH_3), 19.4 (CH_3), 19.1 (C), 18.1 (CH_3), 11.89 (CH_3), 11.63 (CH_3); diastereomer B δ_H (400 MHz; $CDCl_3$) 6.82 (1 H, d, *J* 8.0, N<u>H</u>CHCH$_2$), 6.19 (1 H, d, *J* 8.0, N<u>H</u>CHCH$_3$),

5.28 (1 H, dt, *J* 8.0, 4.4, NHC<u>H</u>CH_2), 5.21 (1 H, dq, *J* 8.0, 7.0, NHC<u>H</u>CH_3), 4.45 (1 H, dd, *J* 9.0, 6.5, NHC<u>H</u>CH), 4.06 (1 H, dd, *J* 9.9, 4.1, CHC<u>H</u>H), 3.90 (3 H, s, $CO_2C\underline{H}_3$), 2.579 (3 H, s, 5-CH_3), 2.51 (3 H, s, 5-CH_3), 2.05 (3 H, s, NHCOC<u>H</u>$_3$), 1.50 (3 H, d, *J* 7.0, NHCHC<u>H</u>$_3$), 0.95 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 170.75 (C), 169.3 (C), 162.4 (C), 161.6 (C), 161.4 (C), 159.7 (C), 156.45 (C), 153.6 (C), 132.4 (C), 132.3 (C), 128.5 (C), 127.70 (CH), 127.47 (C), 64.6 (CH_2), 57.8 (CH), 49.46 (CH), 43.26 (CH), 31.09 (CH), 26.5 (CH_3), 19.9 (CH_3), 19.2 (CH_3), 19.0 (C), 18.0 (CH_3), 11.86 (CH_3), 11.62 (CH_3).

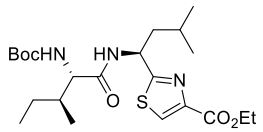
Ethyl (*S*)-2-(1-amino-3-methylbutyl)thiazole-4-carboxylate hydrochloride 223



To ethyl (*S*)-2-(1-*tert*-butoxycarbonylamino-3-methylbutyl)thiazole-4-carboxylate **86** (0.64 g, 1.9 mmol) was added hydrogen chloride in dioxane (4 M; 2.0 mL, 8.0 mmol), and the mixture was stirred for 1 h at room temperature. The mixture was concentrated *in vacuo* and triturated with ether to give the *title compound* as a colourless solid (0.52 g, 99%); mp 139 - 140 °C; (Found: M+H^+, 243.1174. $C_{11}H_{18}N_2O_2S$ + H^+ requires 243.1167); δ_H (400 MHz; DMSO-d_6) 8.92 (2 H, br s, N<u>H</u>$_2$), 8.62 (1 H, s, 5-H), 4.80 (1 H, t, *J* 7.3, $NH_2C\underline{H}$), 4.31 (2 H, q, *J* 7.1, OC<u>H</u>$_2$CH$_3$), 1.88 (2 H, m, CHC<u>H</u>$_2$), 1.49 (1 H, t septet, *J* 7.3, 6.5, $CH_2C\underline{H}(CH_3)_2$), 1.30 (3 H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 0.89 (3 H, d, *J* 6.5, CH(C<u>H</u>$_3$)(CH$_3$), 0.85 (3 H, d, *J* 6.5,

$CH(CH_3)(C\underline{H}_3)$); δ_C (100 MHz; DMSO-d_6) 167.1 (C), 160.6 (C), 145.8 (C), 131.0 (CH), 61.1 (CH_2), 49.9 (CH), 42.7 (CH_2), 24.1 (CH), 22.6 (CH_3), 21.8 (CH_3), 14.3 (CH_3).

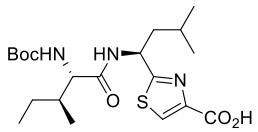
Ethyl 2-((*S*)-1-((2S,3S)-2-(*tert*-butoxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylate 224



To a stirred solution of ethyl (*S*)-2-(1-amino-3-methylbutyl)thiazole-4-carboxylate hydrochloride **223** (1.0 g, 3.6 mmol) and (*S*)-*N*-*tert*-butoxycarbonyl-isoleucine (1.0 g, 4.3 mmol) in dimethylformamide (30 mL) was added *N,N*-diisopropylethylamine (3.1 mL, 18 mmol) and HATU (2.7 g, 7.2 mmol). The reaction was stirred for 16 h. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL), 10% lithium chloride solution (3 x 200 mL), water (200 mL) and saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (2%)-dichloromethane, followed by chromatography on silica, eluting with ethyl acetate (20%)-light petroleum to give the *title compound* as a pale yellow oil (1.3 g, 80%); $[\alpha]_D^{22}$ -49.3 (*c* 1, $CHCl_3$); (Found: M+H^+, 456.2531. $C_{22}H_{37}N_3O_5S$ + H^+ requires 456.2527); ν_{max} ($CHCl_3$)/cm^{-1} 3430, 3010, 1966, 2935, 1714, 1498, 1369, 1240, 1164, 1097, 1020; δ_H (400 MHz; $CDCl_3$) 8.06 (1 H, s, 5-

H), 6.62 (1 H, d, *J* 8.6, CONHCH), 5.41 (1 H, ddd, *J* 9.8, 8.6, 5.4, CONHCH), 5.01 (1 H, d, *J* 7.2 CONHCHCO), 4.41 (2 H, q, *J* 7.1, $COCH_2CH_3$), 3.92 (1 H, dd, *J* 8.6, 7.2, NHCHCH), 2.02 - 1.78 (3 H, m, $NHCHCH_2$, $NHCHCH(CH_3)(CH_2CH_3)$), 1.76 - 1.61 (1 H, m, $CH_2CH(CH_3)_2$), 1.60 - 1.47 (1 H, m, NHCHCHH), 1.43 (9 H, s, $C(CH_3)_3$), 1.39 (3 H, t, *J* 7.1, $COCH_2CH_3$), 1.18 - 1.04 (1 H, m, NHCHCHH), 0.98 - 0.85 (12 H, m, $CH(CH_3)(CH_3)$, $CH(CH_3)(CH_2CH_3)$); δ_C (100 MHz; $CDCl_3$) 173.0 (C), 171.5 (C), 161.3 (C), 155.8 (C), 147.2 (C), 127.0 (CH), 80.1 (C), 61.4 (CH_2), 59.3 (CH), 49.6 (CH), 43.9 (CH_2), 36.6 (CH), 28.2 (CH_3), 24.8 (CH), 24.7 (CH_2), 23.0 (CH_3), 21.6 (CH_3), 15.7 (CH_3), 14.3 (CH_3), 11.2 (CH_3).

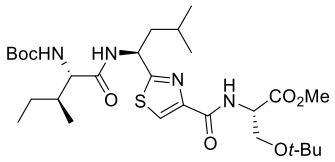
2-((*S*)-1-((2S,3S)-2-(*tert*-Butoxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylic acid 225



Lithium hydroxide monohydrate (0.40 g, 9.6 mmol) was added to ethyl 2-((*S*)-1-((2S,3S)-2-(*tert*-butoxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylate **224** (1.1 g, 2.4 mmol) in methanol/water (5:1; 60 mL). The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*, taken into water (80 mL) and acidified to pH 2 with 10% citric acid. The aqueous solution was extracted with ethyl acetate (4 x 50 mL) and the combined organic extracts washed with saturated brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid, which was used without further

purification (0.94 g, 92%); (Found: M+Na$^+$, 450.2014. $C_{20}H_{33}N_3O_5S$ + Na^+ requires 450.2033).

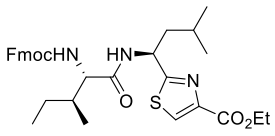
Methyl 3-(*tert*-butoxy)-2-(2-((*S*)-1-((2S,3S)-2-(*tert*-butoxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxamido)-propanoate 226



To a stirred solution of 2-((*S*)-1-((2S,3S)-2-(*tert*-butoxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylic acid **225** (0.24 g, 0.56 mmol) and (*S*)-serine-O-(*tert*-butyl) methyl ester hydrochloride (0.13 g, 0.62 mmol) in dimethylformamide (10 mL) at 0 °C was added *N,N*-diisopropylethylamine (0.49 mL, 2.8 mmol) and HATU (0.64 g, 1.7 mmol). The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (4 x 30 mL). The combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL), 10% lithium chloride solution (3 x 100 mL) and saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (1 - 2%)-dichloromethane, to give the *title compound* as an orange oil (0.26 g, 79%); $[\alpha]_D^{23}$ -56.7 (*c* 1, $CHCl_3$); (Found: M+Na$^+$, 607.3157. $C_{28}H_{48}N_4O_7S$ + Na^+ requires 607.3136); ν_{max} ($CHCl_3$)/cm^{-1}

3417, 3010, 2973, 2936, 2877, 1748, 1672, 1542, 1495, 1392, 1367, 1240, 1162, 1100; δ_H (400 MHz; $CDCl_3$) 8.02 - 7.94 (2 H, m, 5-H, N<u>H</u>CHCH$_2$), 6.88 (1 H, d, *J* 8.8, N<u>H</u>CHCH$_2$), 5.35 (1 H, dt, *J* 8.8, 5.6, C<u>H</u>CH$_2$CH), 5.20 (1 H, d, *J* 8.9, N<u>H</u>CHCH), 4.82 (1 H, dt, *J* 8.5, 3.3, C<u>H</u>CH$_2$O), 3.94 (1 H, dd, *J* 8.9, 7.2, NHC<u>H</u>CH), 3.89 (1 H, dd, *J* 9.2, 3.3, CHC<u>H</u>HO), 3.74 (3 H, s, CO$_2$C<u>H</u>$_3$), 3.63 (1 H, dd, *J* 9.2, 3.3, CHCH<u>H</u>O), 2.03 - 1.91 (1 H, m, CHC<u>H</u>HCH), 1.84 (1 H, m, NHCHC<u>H</u>), 1.79 - 1.63 (2 H, m, CHCH<u>H</u>CH, C<u>H</u>HCH$_3$), 1.59 - 1.45 (1 H, m, CH<u>H</u>CH$_3$), 1.40 (9 H, s, CO$_2$C(C<u>H</u>$_3$)$_3$), 1.19 - 1.03 (9 H, m, OC(C<u>H</u>$_3$)$_3$, C<u>H</u>(CH$_3$)$_2$), 0.93 (3 H, d, *J* 6.5, CH(C<u>H</u>$_3$)(CH$_3$)), 0.92 (3 H, d, *J* 6.5, CH(CH$_3$)(C<u>H</u>$_3$)), 0.89 (3 H, d, *J* 6.8, CHCHC<u>H</u>$_3$), 0.85 (3 H, t, *J* 7.5, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 172.6 (C), 171.7 (C), 170.7 (C), 160.6 (C), 155.8 (C), 149.2, (C), 123.4 (CH), 79.8 (C), 73.4 (C), 61.9 (CH$_2$), 59.2 (CH), 52.6 (CH$_3$), 52.3 (CH), 49.4 (CH), 43.7 (CH$_2$), 36.6 (CH), 28.2 (CH$_3$), 27.2 (CH$_3$), 24.7 (CH$_2$), 24.6 (CH), 22.8 (CH$_3$), 21.7 (CH$_3$), 15.6 (CH$_3$), 11.0 (CH$_3$).

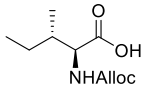
Ethyl 2-((*S*)-1-((2*S*,3*S*)-2-(9-fluorenylmethoxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylate 227



To a stirred solution of ethyl (*S*)-2-(1-amino-3-methylbutyl)thiazole-4-carboxylate hydrochloride **223** (0.51 g, 1.8 mmol) and (*S*)-N-(9-fluorenylmethoxycarbonyl)-isoleucine (0.84 g, 2.4 mmol) in dimethylformamide (20 mL) at 0 °C was added *N,N*-diisopropylethylamine (1.6 mL, 9.2 mmol) and HATU (1.4 g, 3.7 mmol). The mixture was warmed to room

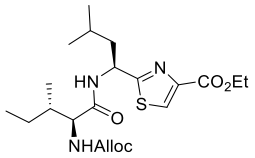
temperature and stirred for 16 h. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL), 10% lithium chloride solution (3 x 200 mL), water (200 mL) and saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (1%)-dichloromethane, followed by chromatography on silica, eluting with ethyl acetate (10-40%)-light petroleum to give the *title compound* as a pale yellow oil (0.77 g, 73%); $[\alpha]_{\mathrm{D}}^{22}$ -57.6 (*c* 1, $CHCl_3$); (Found: M+Na^+, 600.2531. $C_{32}H_{39}N_3O_5S$ + Na^+ requires 600.2503); ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3011, 2965, 2936, 2877, 1721, 1680, 1503, 1451, 1338, 1323, 1097, 1023; δ_H (400 MHz; $CDCl_3$) 8.05 (1 H, s, 5-H), 7.76 (2 H, d, *J* 7.4, Ar<u>H</u>), 7.57 (2 H, d, *J* 7.4, Ar<u>H</u>), 7.39 (2 H, t, *J* 7.4, Ar<u>H</u>), 7.30 (2 H, t, *J* 7.4, Ar<u>H</u>), 6.78 (1 H, d, *J* 8.2, N<u>H</u>CHCH_2), 5.48 (1 H, d, *J* 8.8, N<u>H</u>CHCH), 5.40 (1 H, m, NHC<u>H</u>CH_2), 4.48 - 4.31 (4 H, m, COC<u>H</u>$_2$CH_3, COC<u>H</u>$_2$CH), 4.21 (1 H, t, *J* 6.8, COCH_2C<u>H</u>), 4.07 (1 H, m, NHC<u>H</u>CH), 1.99 - 1.73 (3 H, m, NHCHC<u>H</u>$_2$, NHCHC<u>H</u>), 1.71 - 1.57 (1 H, m, CHCH_2C<u>H</u>), 1.48 (1 H, m, CHC<u>H</u>HCH_3), 1.39 (3 H, t, *J* 7.0, COCH_2C<u>H</u>$_3$), 1.19 - 1.03 (1 H, m, CHCH<u>H</u>CH_3), 0.96 - 0.83 (12 H, m, CH(C<u>H</u>$_3$(C<u>H</u>$_3$), CH(C<u>H</u>$_3$)CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 172.6 (C), 171.1 (C), 161.2 (C), 156.4 (C), 147.1 (C), 143.8 (C), 143.6 (C), 141.24 (C), 141.23 (C), 127.7 (CH), 127.0 (CH), 125.0 (CH), 119.94 (CH), 119.93 (CH), 67.1 (CH_2), 61.4, (CH_2), 59.6 (CH), 49.7 (CH), 47.1 (CH), 43.9 (CH_2), 37.2 (CH), 24.9 (CH), 24.6 (CH_2), 22.8 (CH_3), 21.7 (CH_3), 15.5 (CH_3), 14.3 (CH_3), 11.2 (CH_3).

(*S*)-*N*-Allyloxycarbonyl-isoleucine 229



To a stirred solution of (*S*)-isoleucine (0.50 g, 3.8 mmol) and sodium hydrogen carbonate (0.87 g, 7.6 mmol) in THF/water (3:1; 50 mL) at 0 °C was added allyl chloroformate (0.45 mL, 4.2 mmol) over 5 min. The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo* and water (100 mL) was added. The aqueous solution was acidified with hydrochloric acid (1 M) to pH 2 and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (5%)-dichloromethane, to give the *title compound* as a colourless oil (0.74 g, 91%); $[\alpha]_D^{22}$ +12.7 (*c* 1, $CHCl_3$) (lit.,[145] $[\alpha]_D^{20}$ +2.6 (*c* 0.5, MeOH)); (Found: M+Na^+, 238.1061. $C_{10}H_{17}NO_4$ + Na^+ requires 238.1050); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 2969, 2937, 2880, 1716, 1513, 1462, 1422, 1332, 1240, 1090, 1043, 994, 937; δ_H (400 MHz; $CDCl_3$) 5.93 (1 H, ddt, *J* 17.2, 10.4, 5.4, C<u>H</u>=CHH), 5.33 (1 H, d, *J* 17.2, CH=C<u>H</u>H), 5.26 - 5.19 (2 H, m, CH=CH<u>H</u>, N<u>H</u>), 4.59 (2 H, d, *J* 5.4, OC<u>H</u>$_2$), 4.38 (1 H, dd, *J* 8.8, 4.5, NHC<u>H</u>), 2.05 - 1.81 (1 H, m, NHCHC<u>H</u>), 1.55 - 1.43 (1 H, m, CHC<u>H</u>HCH$_3$), 1.32 - 1.12 (1 H, m, CHCH<u>H</u>CH$_3$), 0.99 (3 H, d, *J* 6.9, CHC<u>H</u>$_3$), 0.95 (3 H, t, *J* 7.4, CH_2C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 176.6 (C), 156.1 (C), 132.5 (CH), 118.0 (CH_2), 66.0 (CH_2), 58.2 (CH), 37.7 (CH), 24.8 (CH_2), 15.5 (CH_3), 11.6 (CH_3). Data consistent with literature.[145,146]

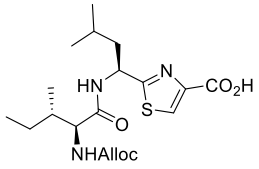
Ethyl 2-((*S*)-1-((2*S*,3*S*)-2-(allyloxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylate 230



To a stirred solution of ethyl (*S*)-2-(1-amino-3-methylbutyl)thiazole-4-carboxylate hydrochloride **223** (0.43 g, 1.5 mmol) and (*S*)-*N*-allyloxycarbonyl-isoleucine **229** (0.37 g, 1.7 mmol) in dimethylformamide (15 mL) at 0 °C was added *N,N*-diisopropylethylamine (1.4 mL, 7.5 mmol) and HATU (1.1 g, 3.0 mmol). The mixture was warmed to room temperature and stirred for 16 h, poured into water (150 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with hydrochloric acid (1 M; 150 mL), saturated sodium hydrogen carbonate (150 mL), lithium chloride solution (10%; 3 x 150 mL), water (150 mL) and saturated brine (150 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (20%)-light petroleum, to give the *title compound* as a colourless solid (0.44 g, 64%); mp 124-125 °C; $[\alpha]_D^{22}$ -57.6 (*c* 1, $CHCl_3$); (Found: C, 57.4; H, 7.6; N, 9.5. $C_{21}H_{33}N_3O_5S$ requires C, 57.4; H, 7.6; N, 9.6%); (Found: M+H$^+$, 440.2215. $C_{21}H_{33}N_3O_5S + H^+$ requires 440.2214); ν_{max} ($CHCl_3$)/cm^{-1} 3426, 3011, 2965, 2936, 2877, 1721, 1679, 1504, 1388, 1370, 1338, 1240, 1097; δ_H (400 MHz; $CDCl_3$) 8.03 (1 H, s, 5-H), 7.14 (1 H, d, *J* 8.2, NHCHCH$_2$), 5.84 (1 H, ddt, *J* 17.2, 10.4, 5.4, CH=CHH), 5.60 (1 H, d, *J* 9.1, NHCHCH), 5.38 - 5.31 (1 H, m, NHCHCH$_2$), 5.23 (1 H, d, *J* 17.2, CH=CHH), 5.14 (1 H, d, *J* 10.4, CH=CHH), 4.50 (2 H, d, *J* 5.4, CHCH$_2$O), 4.35 (2 H, q, *J* 7.1, COCH$_2$CH$_3$),

4.15 - 4.04 (1 H, m, NHC<u>H</u>CH), 1.97 - 1.86 (1 H, m, NHCHC<u>H</u>H), 1.86 - 1.72 (2 H, m, NHCHCH<u>H</u>, NHCHC<u>H</u>), 1.69 - 1.55 (1 H, m, C<u>H</u>$(CH_3)_2$), 1.51 - 1.40 (1 H, m, CHC<u>H</u>HCH$_3$), 1.34 (3 H, t, *J* 7.1, $COCH_2C\underline{H}_3$), 1.09 - 0.98 (1 H, m, CHCH<u>H</u>CH$_3$), 0.90 - 0.78 (12 H, m, CH(C<u>H</u>$_3$)$_2$, CH(C<u>H</u>$_3$)$CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 172.9 (C), 171.3 (C), 161.1 (C), 156.2 (C), 146.9 (C), 132.4 (CH), 127.0 (CH), 117.5 (CH_2), 65.7 (CH_2), 61.2 (CH_2), 59.5 (CH), 49.6 (CH), 43.5 (CH_2), 37.1 (CH), 24.7 (CH), 24.5 (CH_2), 22.8 (CH_3), 21.5 (CH_3), 15.4 (CH_3), 14.2 (CH_3), 11.0 (CH_3).

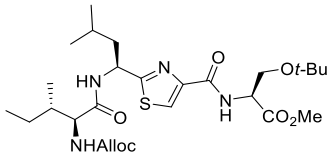
2-((*S*)-1-((2*S*,3*S*)-2-(Allyloxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylic acid 231



Lithium hydroxide monohydrate (0.307 g, 7.31 mmol) was added to ethyl 2-((*S*)-1-((2*S*,3*S*)-2-(allyloxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylate **230** (0.803 g, 1.83 mmol) in methanol/water (5:1; 20 mL). The reaction mixture was stirred at room temperature for 2.5 h. The mixture was concentrated *in vacuo*, taken into water (40 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (4 x 20 mL) and the combined organic extracts washed with saturated brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (0.75 g, 100%); mp 66 – 67 °C; $[\alpha]_D^{22}$ -74.2 (*c* 1, $CHCl_3$); (Found: C, 55.4; H, 7.2; N, 10.2.

$C_{19}H_{29}N_3O_5S$ requires C, 55.5; H, 7.1; N, 10.2%); (Found: M+Na^+, 434.1739. $C_{19}H_{29}N_3O_5S$ + Na^+ requires 434.1720); ν_{max} ($CHCl_3$)/cm^{-1} 3427, 3306, 3011, 2965, 2936, 2877, 1714, 1676, 1509, 1468, 1340, 1240, 1089, 1040, 994, 938; δ_H (400 MHz; $CDCl_3$) 9.12 (1 H, br s, OH), 8.18 (1 H, s, 5-H), 7.54 (1 H, br s, NHCHCH_2), 6.01 - 5.72 (2 H, m, CH=CHH, NHCHCH), 5.40 (1 H, dt, *J* 7.7, 6.8, NHCHCH_2), 5.27 (1 H, d, *J* 17.2, CH=CHH), 5.17 (1 H, d, *J* 10.3, CH=CHH), 4.55 (2 H, d, *J* 4.8, CHCH_2O), 4.12 (1 H, t, *J* 7.6, NHCHCH), 1.96 - 1.80 (3 H, m, NHCHCH_2, NHCHCH), 1.64 (1 H, d septet, *J* 6.6, 6.5, CH(CH_3)$_2$), 1.54 - 1.40 (1 H, m, CHHCH_3), 1.21 - 1.00 (1 H, m, CHHCH_3), 0.99 - 0.72 (12 H, m, CH(CH_3)CH_2(CH_3), CH(CH_3)$_2$); δ_C (100 MHz; $CDCl_3$) 172.8 (C), 171.9 (C), 163.4 (C), 156.5 (C), 146.8 (C), 132.4 (CH), 128.2 (CH), 117.7 (CH_2), 65.9 (CH_2), 59.6 (CH), 49.5 (CH), 43.5 (CH_2), 37.1 (CH), 24.8 (CH), 24.6 (CH_2), 22.7 (CH_3), 21.7 (CH_3), 15.4 (CH_3), 11.0 (CH_3).

Methyl (*S*)-2-(2-((*S*)-1-((2*S*,3*S*)-2-(allyloxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxamido)-3-(*tert*-butoxy)propanoate 232

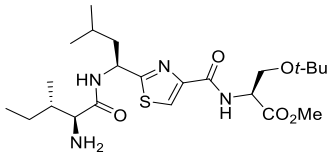


To a stirred solution of 2-((*S*)-1-((2*S*,3*S*)-2-(allyloxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxylic acid **231** (0.208 g, 0.505 mmol) and (*S*)-serine-O-(*tert*-butyl) methyl ester hydrochloride (0.139 g, 0.657 mmol) in dimethylformamide (5 mL) at 0 °C was added *N,N*-

diisopropylethylamine (0.44 mL, 2.5 mmol) and HATU (0.380 g, 1.01 mmol). The mixture was warmed to room temperature and stirred for 16 h, poured into water (50 mL), and extracted with ethyl acetate (4 x 30 mL). The combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL), lithium chloride solution (10%; 3 x 100 mL), water (100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (40%)-light petroleum to give the *title compound* as a colourless oil (0.27 g, 94%); $[\alpha]_D^{23}$ -24.2 (*c* 1, $CHCl_3$); (Found: M+Na^+, 591.2825. $C_{27}H_{44}N_4O_7S$ + Na^+ requires 591.2823); ν_{max} ($CHCl_3$)/cm^{-1} 3422, 3011, 2970, 2936, 2878, 1717, 1672, 1541, 1500, 1438, 1391, 1366, 1240, 1157, 1099, 1043, 992; δ_H (400 MHz; $CDCl_3$) 8.00 - 7.94 (2 H, m, 5-H, NHCHCH_2O), 7.23 (1 H, d, *J* 8.0, NHCHCH_2CH), 5.83 (1 H, ddt, *J* 17.2, 10.5, 5.3, CH=CHH), 5.70 (1 H, d, *J* 9.2, NHCHCH), 5.32 (1 H, dt, *J* 8.0, 6.6, NHCHCH_2CH), 5.22 (1 H, dd, *J* 17.2, 0.9, CH=CHH), 5.13 (1 H, dd, *J* 10.5, 0.9, CH=CHH), 4.79 (1 H, dt, *J* 8.4, 3.2, NHCHCH_2O), 4.49 (2 H, d, *J* 5.3, CH_2=CHCH_2), 4.12 - 4.03 (1 H, m, NHCHCH), 3.86 (1 H, dd, *J* 9.2, 3.2, CHHO*t*-Bu), 3.72 (3 H, s, OCH_3), 3.61 (1 H, dd, *J* 9.2, 3.2, CHHO*t*-Bu), 1.98 - 1.88 (1 H, m, CHHCH(CH_3)$_2$), 1.88 - 1.77 (1 H, m, NHCHCH), 1.76 - 1.58 (2 H, m, CHHCH(CH_3)$_2$), 1.48 (1 H, dqd, *J* 15.1, 7.3, 3.5, CHHCH_3), 1.18 - 1.00 (10 H, m, OC(CH_3)$_3$, CHHCH_3), 0.98 - 0.74 (12 H, m, CH(CH_3)CH_2(CH_3), CH(CH_3)$_2$); δ_C (100 MHz; $CDCl_3$) 172.6 (C), 171.4 (C), 170.6 (C), 160.6 (C), 156.2 (C), 149.1 (C), 132.4 (CH), 123.4 (CH), 117.5 (CH_2), 73.4 (C), 65.6 (CH_2), 61.9 (CH_2), 59.5 (CH), 52.6 (CH), 52.2 (CH_3), 49.4 (CH), 43.6 (CH_2), 37.2

(CH), 27.2 (CH_3), 24.6 (CH), 24.5 (CH_2), 22.6 (CH_3), 21.8 (CH_3), 15.4 (CH_3), 11.0 (CH_3).

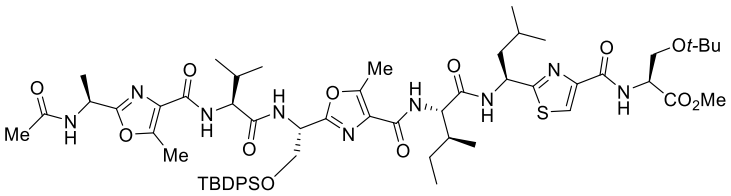
Methyl (*S*)-2-(2-((*S*)-1-((2*S*,3*S*)-2-amino-3-methylpentanamido)-3-methylbutyl)thiazole-4-carbonyl)-(*tert*-butoxycarbonyl)propanoate 81



To a stirred solution of methyl (*S*)-2-(2-((*S*)-1-((2*S*,3*S*)-2-(allyloxycarbonylamino)-3-methylpentanamido)-3-methylbutyl)thiazole-4-carboxamido)-3-(*tert*-butoxycarbonyl propanoate **232** (0.348 g, 0.612 mmol) in dichloromethane (10 mL) was added diethylamine (1.27 mL, 12.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (14 mg, 2 mol%). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo* and the residue purified by chromatography on silica, eluting with methanol (2 - 3%)-dichloromethane to give the *title compound* as a colourless oil (0.30 g, 100%); $[\alpha]_D^{23}$ -43.5 (*c* 1, $CHCl_3$); (Found: M+H^+, 485.2806. $C_{23}H_{40}N_4O_5S$ + H^+ requires 485.2792); ν_{max} ($CHCl_3$)/cm^{-1} 3409, 3341, 3010, 2967, 2935, 2876, 1749, 1666, 1542, 1501, 1438, 1366, 1349, 1240, 1156, 1100; δ_H (400 MHz; $CDCl_3$) 8.03 (1 H, d, *J* 8.4, N<u>H</u>CHCH$_2$O), 7.99 (1 H, s, 5-H), 7.91 (1 H, d, *J* 9.0, CON<u>H</u>CH), 5.35 (1 H, dt, *J* 9.0, 5.8, NHC<u>H</u>CH$_2$CH), 4.84 (1 H, dt, *J* 8.4, 3.1, C<u>H</u>CH$_2$O), 3.91 (1 H, dd, *J* 9.1, 3.1, NHC<u>H</u>HO), 3.76 (3 H, s, CO$_2$C<u>H</u>$_3$), 3.66 (1 H,

dd, *J* 9.1, 3.1, CHHO), 3.33 (1 H, d, *J* 3.8, NH_2CH), 2.08 - 1.99 (1 H, m, NH_2CHCH), 1.96 (1 H, ddd, *J* 14.1, 8.5, 5.8, CHCHHCH), 1.81 (1 H, ddd, *J* 14.1, 8.5, 5.8, CHCHHCH), 1.69 (1 H, d septet, *J* 8.5, 6.3, $CH(CH_3)_2$), 1.39 (1 H, dqd, *J* 14.6, 7.5, 3.8, $CHCHHCH_3$), 1.18 - 1.09 (10 H, m, $C(CH_3)_3$), $CHCHHCH_3$), 1.00 - 0.94 (9 H, m, $CH(CH_3)_2$, $CHCHCH_3$), 0.89 (3 H, t, *J* 7.5, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 174.0 (C), 172.6 (C), 170.9 (C), 160.7 (C), 149.2 (C), 123.3 (CH), 73.5 (C), 62.0 (CH_2), 59.7 (CH), 52.6 (CH), 52.3 (CH_3), 48.9 (CH), 43.9 (CH_2), 37.8 (CH), 27.3 (CH_3), 24.9 (CH), 23.8 (CH_2), 22.9 (CH_3), 21.8 (CH_3), 16.1 (CH_3), 11.9 (CH_3).

Protected *N*-terminal fragment 78

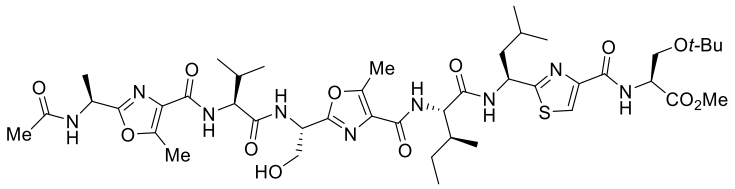


To a stirred solution of 2-((*S*)-1-((*S*)-2-(2-((*S*)-1-acetamidoethyl)-5-methyloxazole-4-carboxamido)-3-methylbutanamido)-2-((*tert*-butyldiphenylsiloxy)ethyl)-5-methyloxazole-4-carboxylic acid **80** (0.321 g, 0.451 mmol) and methyl (*S*)-2-(2-((*S*)-1-((2*S*,3*S*)-2-amino-3-methylpentanamido)-3-methylbutyl)thiazole-4-carbonyl)-(*tert*-butoxycarbonyl)propanoate **81** (0.222 g, 0.459 mmol) in dimethylformamide (5 mL) at 0 °C was added *N,N*-diisopropylethylamine (0.32 mL, 1.8 mmol), HATU (0.343 g, 0.902 mmol) and HOAt (0.123 g, 0.902 mmol). The mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (4 x 20 mL). The

combined organic layers were washed with hydrochloric acid (1 M; 80 mL), saturated sodium hydrogen carbonate (80 mL), lithium chloride solution (10%; 3 x 80 mL), water (80 mL) and saturated brine (80 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (1-3%)-dichloromethane to give the *title compound* as a colourless solid (0.31 g, 80%); mp 104-105 °C; $[\alpha]_D^{23}$ -57.8 (c 1, $CHCl_3$); (Found: M+Na^+, 1206.5683. $C_{60}H_{85}N_9O_{12}SSi$ + Na^+ requires 1206.5700); ν_{max} (ATR)/cm^{-1} 2962, 2932, 2875, 1747, 1652, 1538, 1518, 1193, 1113, 703; δ_H (400 MHz; $CDCl_3$) 8.04 - 7.97 (2 H, m, 5-H, NH), 7.57 - 7.28 (12 H, m, ArH, NH, NH), 6.84 (1 H, d, *J* 8.7, NH), 6.73 (1 H, d, *J* 8.3, NH), 6.13 (1 H, d, *J* 8.0, NH), 5.37 (1 H, t d, *J* 8.7, 5.8, NHCHCH$_2$CH), 5.28 - 5.13 (2 H, m, NHCHCH$_3$, CHCH$_2$OTBDPS), 4.67 (1 H, dt, *J* 8.6, 3.0, CHCH$_2$O*t*-Bu), 4.48 (1 H, dd, *J* 8.9, 6.5, CHCH(CH$_3$)$_2$), 4.37 (1 H, dd, *J* 8.7, 7.9, CHCH(CH$_3$)CH$_2$), 4.04 (1 H, dd, *J* 9.3, 3.1, CHHOTBDPS), 3.99 (1 H, dd, *J* 9.3, 3.1, CHHOTBDPS), 3.93 (1 H, dd, *J* 8.9, 3.0, CHHO*t*-Bu), 3.78 (3 H, s, CO$_2$CH$_3$), 3.68 (1 H, dd, *J* 8.9, 3.0, CHHO*t*-Bu), 2.60 (3 H, s, 5-CH$_3$), 2.56 (3 H, s, 5-CH$_3$), 2.29 (1 H, septet d, *J* 6.7, 6.5, CHCH(CH$_3$)$_2$), 2.09 - 1.93 (5 H, m, NHCOCH$_3$, CHCH(CH$_3$)CH$_2$, CHHCH(CH$_3$)$_2$), 1.82 - 1.72 (1 H, m, CHHCH(CH$_3$)$_2$), 1.72 - 1.62 (1 H, m, CH$_2$CH(CH$_3$)$_2$), 1.62 - 1.54 (1 H, m, CHCHHCH$_3$) 1.53 (3 H, d, *J* 7.0, NHCHCH$_3$), 1.27 - 1.19 (1 H, m, CHCHHCH$_3$), 1.18 (9 H, s, OC(CH$_3$)$_3$), 1.09 (3 H, d, *J* 6.7, CHCH(CH$_3$)(CH$_3$)), 1.08 (3 H, d, *J* 6.7, CHCH(CH$_3$)(CH$_3$)), 0.98 - 0.89 (21 H, m, CH(CH$_3$)CH$_2$CH$_3$, CH$_2$CH(CH$_3$)$_2$, SiC(CH$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 172.5 (C), 170.82 (C), 170.77 (C), 170.7 (C), 169.3 (C), 161.9 (C), 161.6 (C), 161.5 (C), 160.7 (C), 158.9 (C), 153.8 (C), 153.6 (C), 149.4 (C), 135.41 (CH), 135.36 (CH), 132.5 (C), 132.1 (C), 130.0 (CH), 128.7 (C), 128.6 (CH),

127.9 (CH), 127.8 (CH), 123.4 (CH), 73.5 (C), 64.2 (CH_2), 62.0 (CH_2), 58.0 (CH_2), 57.5 (CH), 52.8 (CH), 52.4 (CH_3), 49.6 (CH), 49.5 (CH), 43.9 (CH_2), 43.2 (CH), 36.5 (CH), 31.2 (CH), 27.3 (CH_3), 26.6 (CH_3), 24.81 (CH_2), 24.78 (CH), 23.2 (CH_3), 22.8 (CH_3), 21.9 (CH_3), 20.0 (CH_3), 19.1 (CH_3), 19.0 (C), 18.3 (CH_3), 15.7 (CH_3), 11.7 (CH_3), 11.6 (CH_3), 11.0 (CH_3).

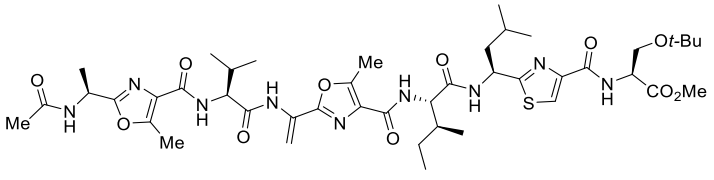
_N_-Terminal alcohol 233



To a stirred solution of protected *N*-terminal fragment **78** (0.182 g, 0.153 mmol) in THF (2 mL) was added tetrabutylammonium difluorotriphenylsilicate (0.166 g, 0.307 mmol) and the mixture stirred at room temperature for 6 h. The mixture was concentrated *in vacuo* and the residue purified by chromatography on silica, eluting with methanol (5%)-chloroform to give the *title compound* as a colourless solid (0.11 g, 77%); mp 130 - 131 °C; $[\alpha]_D^{24}$ -48.1 (*c* 1, CH_3OH); (Found: M+Na^+, 968.4489. $C_{44}H_{67}N_9O_{12}S$ + Na^+ requires 968.4528); ν_{max} (ATR)/cm^{-1} 3403, 3293, 2965, 2937, 2877, 1748, 1654, 1540, 1521, 1154; δ_H (400 MHz; $CDCl_3$) 8.02 (1 H, d, *J* 8.5, NHCH$_2$OC), 8.01 (1 H, s, 5-CH), 7.56 (1 H, d, *J* 8.7, NHCHCH(CH_3)$_2$), 7.51 (1 H, d, *J* 8.4, NHCHCH(CH_3)), 7.47 (1 H, d, *J* 8.2, NHCHCH$_2$OH), 7.04 (1 H, d, *J* 8.3, NHCHCH$_2$C), 6.64 (1 H, d, *J* 8.0, NHCHCH$_3$), 5.33 (1 H, dt, *J* 8.3, 6.3, NHCHCH$_2$C), 5.21 - 5.13 (2 H, m, NHCHCH$_2$OH, NHCHCH$_3$), 4.85 (1 H, ddd, *J* 8.5, 3.5, 3.3, NHCHCH$_2$OC), 4.48 (1 H, dd, *J* 8.7, 7.4,

NHC<u>H</u>CH(CH_3)$_2$), 4.43 (1 H, t, *J* 8.4, NHC<u>H</u>CH(CH_3)C), 3.98 (1 H, dd, *J* 11.0, 3.3, CHC<u>H</u>HOH), 3.92 (1 H, dd, *J* 9.2, 3.1, CHC<u>H</u>HOC), 3.92 - 3.88 (1 H, m, CH<u>H</u>OH), 3.77 (3 H, s, CO_2CH_3), 3.68 (1 H, dd, *J* 9.2, 3.5, CH<u>H</u>OC), 2.56 (3 H, s, 5-CH_3), 2.55 (3 H, s, 5-CH_3), 2.29 - 2.19 (1 H, NHCHC<u>H</u>(CH_3)$_2$), 2.04 (3 H, s, NHCOC<u>H</u>$_3$), 2.01 - 1.92 (2 H, m, NHCHC<u>H</u>CH_3CH_2, NHCHC<u>H</u>HCH), 1.75 (1 H, ddd, *J* 14.7, 8.7, 6.3, NHCHCH<u>H</u>CH), 1.69 - 1.62 (1 H, m, NHCHCH_2C<u>H</u>), 1.62 - 1.53 (1 H, m, NHCHC<u>H</u>HCH_3), 1.49 (3 H, d, *J* 6.9, NHCHC<u>H</u>$_3$), 1.23 - 1.18 (1 H, m, NHCHCH<u>H</u>CH_3), 1.17 (9 H, s, C(CH_3)$_3$), 1.05 (3 H, d, *J* 6.7, NHCHCH(C<u>H</u>$_3$)(CH_3)), 1.04 (3 H, d, *J* 6.7, NHCHCH(CH_3)(C<u>H</u>$_3$)), 0.95 - 0.87 (12 H, m, NHCHCH_2CH(C<u>H</u>$_3$)$_2$, NHCHCH(C<u>H</u>$_3$)CH_2C<u>H</u>$_3$); δ_C (125 MHz; $CDCl_3$) 172.2 (C), 171.7 (C), 171.2 (C), 170.9 (C), 169.8 (C), 162.2 (C), 161.9 (C), 161.6 (C), 160.7 (C), 158.7 (C), 154.0 (C) 153.7 (C), 149.2 (C), 128.8 (C), 128.5 (C), 123.5 (CH), 73.6 (C), 62.7 (CH_2), 62.0 (CH_2), 58.6 (CH), 57.5 (CH), 52.7 (CH), 52.4 (CH_3), 49.59 (CH), 49.58 (CH), 43.7 (CH_2), 43.0 (CH), 36.8 (CH), 31.1 (CH), 27.3 (CH_3), 24.9 (CH_2), 24.7 (CH), 23.1 (CH_3), 22.6 (CH_3), 22.0 (CH_3), 19.5 (CH_3), 19.2 (CH_3), 18.5 (CH_3), 15.6 (CH_3), 11.7 (CH_3), 11.6 (CH_3), 10.9 (CH_3).

_N_-Terminal alkene 234

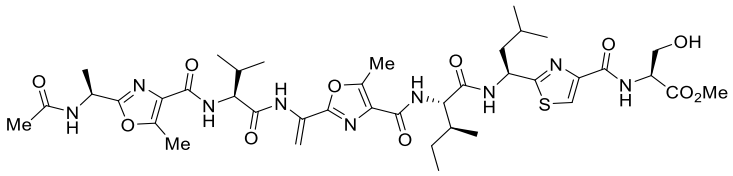


To a stirred solution of *N*-terminal alcohol **233** (77 mg, 0.081 mmol) and triethylamine (0.045 mL, 0.32 mmol) in THF (1 mL) was added methanesulfonyl

chloride (0.016 mL, 0.16 mmol). The mixture was stirred at room temperature for 4 h. The reaction mixture was taken into water (10 mL) and ethyl acetate (10 mL), the aqueous layer was further extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with saturated brine (20 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. To the remaining residue was added dichloromethane (1 mL) and DBU (0.048 mL, 0.32 mmol), and the mixture was stirred at room temperature for 16 h. The reaction mixture was taken into water (10 mL) and ethyl acetate (10 mL). The aqueous layer was further extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with saturated sodium carbonate (20 mL) and saturated brine (20 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (2 - 10%)-chloroform to give the *title compound* as a colourless solid (30 mg, 40%); mp 152 - 153 °C; $[\alpha]_D^{24}$ -16.9 (*c* 1, CH_3OH); (Found: M+Na^+, 950.4390. $C_{44}H_{65}N_9O_{11}S + Na^+$ requires 950.4422); ν_{max} (ATR)/cm^{-1} 3353, 2965, 2832, 2896, 1752, 1641, 1540, 1198; δ_H (400 MHz; CD_3OD) 8.17 (1 H, s, 5-H), 6.12 (1 H, s, C=C<u>H</u>H), 5.80 (1 H, s, C=CH<u>H</u>), 5.36 (1 H, dd, *J* 9.3, 5.9, NHC<u>H</u>CH_2CH), 5.12 (1 H, q, *J* 7.0, NHC<u>H</u>CH_3), 4.77 (1 H, t, *J* 3.4, NHC<u>H</u>CH_2O), 4.63 (1 H, d, *J* 6.8, NHC<u>H</u>CH$(CH_3)_2$), 4.50 (1 H, d, *J* 7.7, NHCHCH(CH_3)), 3.95 (1 H, dd, *J* 9.4, 3.4, NHCHC<u>H</u>HO), 3.77 (3 H, s, $CO_2C\underline{H}_3$), 3.76 (1 H, dd, *J* 9.4, 3.4, NHCHCH<u>H</u>O), 2.64 (3 H, s, 5-CH_3), 2.58 (3 H, s, 5-CH_3), 2.27 (1 H, septet d, *J* 7.0, 6.8, NHCHC<u>H</u>$(CH_3)_3$), 1.99 (3 H, s, NHCOC$\underline{H}_3$), 1.98 - 1.87 (3 H, m, NHCHC$\underline{H}_2$CH, NHCHC<u>H</u>(CH_3)), 1.79 - 1.71 (1 H, m, NHCHCH_2C<u>H</u>), 1.62 - 1.55 (1 H, m, NHCHCHC<u>H</u>H), 1.52 (3 H, d, *J* 7.0, NHCHC$\underline{H}_3$), 1.22 - 1.18 (10 H, m, C($C\underline{H}_3)_3$, NHCHCHCH<u>H</u>), 1.08 (3 H, d, *J*, 7.0,

NHCHCH(C<u>H</u>$_3$)(CH$_3$)), 1.06 (3 H, d, *J*, 7.0, NHCHCH(CH$_3$)(C<u>H</u>$_3$)), 1.01 – 0.86 (12 H, m, NHCHCH(C<u>H</u>$_3$)CH$_2$C<u>H</u>$_3$, NHCHCH$_2$CH(C<u>H</u>$_3$)$_2$); δ_c (100 MHz; CD$_3$OD) 175.0 (C), 173.6 (C), 173.0 (C), 172.9 (C), 172.2 (C), 163.8 (C), 163.5 (C), 163.4 (C), 162.9 (C), 157.1 (C), 155.7 (C), 155.3 (C), 150.2 (C), 130.9 (C), 130.2 (C), 129.9 (C), 125.4 (CH), 108.6 (CH$_2$), 75.0 (C), 63.1 (CH$_2$), 59.8 (CH), 58.6 (CH), 54.4 (CH), 53.1 (CH$_3$), 51.0 (CH), 44.6 (CH$_2$), 44.5 (CH), 39.0 (CH), 32.9 (CH), 27.8 (CH$_3$), 26.1 (CH), 26.0 (CH$_2$), 23.4 (CH$_3$), 22.6 (CH$_3$), 22.3 (CH$_3$), 19.9 (CH$_3$), 19.1 (CH$_3$), 18.7 (CH$_3$), 16.3 (CH$_3$), 11.9 (CH$_3$), 11.8 (CH$_3$), 11.5 (CH$_3$).

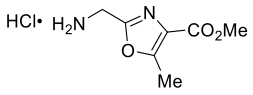
N-Terminal fragment 235



To a solution of *N*-terminal alkene **234** (30 mg, 0.032 mmol) in dichloromethane (0.5 mL) was added zinc bromide (36 mg, 0.16 mmol), and the mixture was stirred at room temperature. After 24 h, zinc bromide (36 mg, 0.16 mmol) was added and the reaction mixture stirred for a further 24 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica, eluting with methanol (5%)-chloroform to give the *title compound* as a colourless oil (21 mg, 76%); $[\alpha]_D^{25}$ +6.1 (*c* 1, CH$_3$OH); (Found: M+Na$^+$, 894.3790. C$_{40}$H$_{57}$N$_9$O$_{11}$S + Na$^+$ requires 894.3796); ν_{max} (ATR)/cm^{-1} 3359, 3121, 2998, 2984, 1704, 1669, 1630, 1519, 1372, 1360, 1340, 1221, 1205, 1053, 935; δ_H (400 MHz; DMSO-d$_6$) 10.01 (1 H, s, N<u>H</u>C=CH$_2$), 9.02 (1 H, d, *J* 7.9, N<u>H</u>CHCH$_2$(CH$_3$)$_2$), 8.51 (1

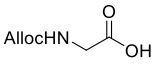
H, d, *J* 7.2, NHCHCH$_3$), 8.22 (1 H, s, 5-H), 8.16 (1 H, d, *J* 9.4, NHCHCH$_2$OH), 7.56 (1 H, d, *J* 9.1, NHCHCH(CH$_3$)$_2$), 7.51 (1 H, d, 9.2, NHCHCH(CH$_3$)), 5.81 (1 H, s, C=CHH), 5.69 (1 H, s, C=CHH), 5.30 (1 H, dd, *J* 6.5, 5.1, OH), 5.19 (1 H, q, *J* 7.9, NHCHCH$_2$CH), 4.99 (1 H, quin, *J* 7.0, NHCHCH$_3$), 4.59 (1 H, dd, *J* 9.1, 6.5, NHCHCH(CH$_3$)$_2$), 4.55 (1 H, ddd, *J* 9.4, 4.5, 3.8, NHCHCH$_2$OH), 4.47 (1 H, dd, *J* 9.2, 6.7, NHCHCH(CH$_3$)CH$_2$), 3.86 (1 H, ddd, *J* 11.1, 6.1, 4.5, CHCHHOH), 3.75 (1 H, ddd, *J* 11.1, 5.1, 3.8, CHCHHOH), 3.65 (3 H, s, CO$_2$CH$_3$), 2.57 (3 H, s, 5-CH$_3$), 2.52 (3 H, s, 5-CH$_3$), 2.15 (1 H, septet d, *J* 6.7, 6.5, NHCHCH(CH$_3$)$_2$), 1.83 (3 H, s, NHCOCH$_3$), 1.82 - 1.65 (3 H, m, CH(CH$_3$)CH$_2$CH$_3$, CH$_2$CH(CH$_3$)$_2$), 1.55 - 1.47 (1 H, m, CH$_2$CH(CH$_3$)$_2$), 1.46 - 1.41 (1 H, m, CH(CH$_3$)CHH), 1.39 (3 H, d, *J* 7.2, NHCHCH$_3$), 1.10 - 1.01 (1 H, m, CH(CH$_3$)CHH), 0.91 - 0.80 (18 H, m, CHCH(CH$_3$)$_2$, CH(CH$_3$)CH$_2$CH$_3$, CH$_2$CH(CH$_3$)$_2$); δ_C (100 MHz; DMSO-d$_6$) 174.8 (C), 171.0 (C), 170.9 (C), 170.8 (C), 169.1 (C), 162.2 (C), 160.9 (C), 160.5 (C), 160.4 (C), 155.5 (C), 153.4 (C), 152.7 (C), 148.8 (C), 129.4 (C), 129.1 (C), 128.3 (C), 124.6 (CH), 109.6 (CH$_2$), 61.2 (CH$_2$), 57.2 (CH), 56.3 (CH), 54.7 (CH), 52.3 (CH3), 49.5 (CH), 43.2 (CH$_2$), 42.4 (CH), 37.5 (CH), 31.4 (CH), 24.5 (CH), 24.2 (CH$_2$), 23.1 (CH$_3$), 22.6 (CH$_3$), 21.3 (CH$_3$), 19.2 (CH$_3$), 18.8 (CH$_3$), 18.0 (CH$_3$), 15.7 (CH$_3$), 11.6 (CH$_3$), 11.5 (CH$_3$), 11.0 (CH$_3$).

Methyl 2-(aminomethyl)-5-methyloxazole-4-carboxylate hydrochloride 236



To methyl 2-(*tert*-butoxycarbonylaminomethyl)-5-methyloxazole-4-carboxylate **91** (0.61 g, 2.3 mmol) was added hydrogen chloride in dioxane (4 M; 2.3 mL, 9.0 mmol) and stirred for 1 h at room temperature. The mixture was concentrated *in vacuo* and triturated with ether to give the *title compound* as a pale yellow solid (0.39, 100%); mp 114 - 145 ^{o}C; (Found: M+H^{+}, 171.0780. $C_7H_{10}N_2O_3$ + H^{+} requires 171.0764); ν_{max} ($CHCl_3$)/cm^{-1} 2985, 1958, 2624, 1724, 1621, 1604, 1506, 1445, 1387, 1375, 1354, 1265, 1193, 1103; δ_H (400 MHz; CD_3OD) 4.33 (2 H, s, C$\underline{H}_2$), 3.89 (3 H, s, OC$\underline{H}_3$), 2.64 (3 H, s, 5-CH_3); δ_c (100 MHz; CD_3OD) 163.8 (C), 159.4 (C), 156.9 (C), 129.0 (C), 52.7 (CH_3), 37.0 (CH_2), 12.2 (CH_3).

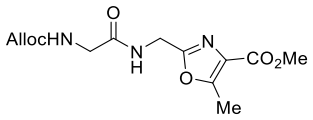
***N*-Allyloxycarbonyl-glycine 237**



To a stirred solution of glycine (4.90 g, 67.0 mmol) in sodium hydroxide (1 M; 67.0 mL) was added allyl chloroformate (8.50 mL, 80.0 mmol). Sodium hydroxide (2 M; 30 mL) was added in portions over 1 h. The mixture was stirred at room temperature for 5 h. The mixture was acidified to pH 1 with hydrochloric acid (1 M) and extracted with ether (3 x 100 mL). The combined

organic layers were washed with saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless solid (7.0 g, 66%); mp 40 - 41 °C (lit.,[147] mp 40 - 42 °C); (Found: M+Na^+, 182.0434. $C_6H_9NO_4$ + Na^+ requires 182.0429); ν_{max} ($CHCl_3$)/cm^{-1} 3453, 3089, 3011, 2048, 1728, 1518, 1434, 1410, 1337, 1242, 1057, 992, 936; δ_H (400 MHz; CD_3OD) 5.94 (1 H, ddt, *J* 17.2, 10.6, 5.4, C<u>H</u>=CHH), 5.32 (1 H, ddt, *J* 17.2, 1.4, 1.4, CH=C<u>H</u>H), 5.19 (1 H, ddt, *J* 10.6, 1.4, 1.4, CH=CHH), 4.55 (2 H, ddd, *J* 5.4, 1.4, 1.4, C<u>H</u>$_2$O), 3.82 (2 H, s, NHC<u>H</u>$_2$); δ_C (100 MHz; CD_3OD) 173.7 (C), 159.1 (C), 134.4 (CH), 117.7 (CH_2), 66.8 (CH_2), 43.2 (CH_2). Data consistent with literature.[147]

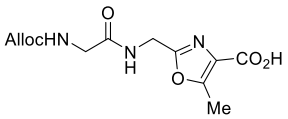
Methyl 2-((2-(allyloxycarbonylamino)acetamido)methyl)-5-methyloxazole-4-carboxylate 238



To a stirred solution of methyl 2-(aminomethyl)-5-methyloxazole-4-carboxylate hydrochloride **236** (0.751 g, 4.41 mmol) and *N*-allyloxycarbonyl-glycine **237** (0.77 g, 4.9 mmol) in dimethylformamide (40 mL) at 0 °C was added *N,N*-diisopropylethylamine (4.07 mL, 22.1 mmol) and HATU (3.36 g, 8.83 mmol). The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was taken into water (400 mL) and extracted with ethyl acetate (4 x 80 mL). The combined organic layers were washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL), lithium chloride solution (10%; 3 x 200 mL) and saturated brine (2 x 200

mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate to give the *title compound* as a colourless solid (0.82 g, 59%); mp 107 - 108 °C; (Found: C, 50.1; H, 5.5; N, 13.4. $C_{13}H_{17}N_3O_6$ requires C, 50.2; H, 5.5; N, 13.4%); (Found: M+Na^+, 334.1022. $C_{13}H_{17}N_3O_6$ + Na^+ requires 334.1010); ν_{max} ($CHCl_3$)/cm^{-1} 3435, 3010, 1725, 1623, 1512, 1443, 1353, 1241, 1102; δ_H (400 MHz; DMSO-d_6) 8.57 (1 H, t, *J* 5.8, NH), 7.45 (1 H, t, *J* 6.3, NH), 5.90 (1 H, ddt, *J* 17.2, 10.5, 5.3, CH_2=CH), 5.29 (1 H, ddt, *J* 17.2, 1.6, 1.4, CHH=CH), 5.17 (1 H, ddt, *J* 10.5, 1.6, 1.4, CHH=CH), 4.47 (2 H, dt, 5.3, 1.4, $CHCH_2$), 4.36 (2 H, d, *J* 5.8, $NHCH_2$), 3.78 (3 H, s, CO_2CH_3), 3.65 (2 H, d, *J* 6.3, $OCONHCH_2$), 2.54 (3 H, s, 5-CH_3); δ_C (100 MHz; DMSO-d_6) 169.5 (C), 162.0 (C), 159.2 (C), 156.3 (C), 156.2 (C), 133.6 (CH), 126.6 (C), 117.0 (CH_2), 64.6 (CH_2), 51.6 (CH_3), 43.3 (CH_2), 35.6 (CH_2), 11.7 (CH_3).

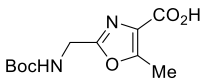
2-((2-(Allyloxycarbonylamino)acetamido)methyl)-5-methyloxazole-4-carboxylic acid 239



To methyl 2-((2-(allyloxycarbonylamino)acetamido)methyl)-5-methyloxazole-4-carboxylate **238** (0.072 g, 0.23 mmol) in 1,2-dichloroethane (1 mL) was added trimethyltin hydroxide (0.14 g, 0.78 mmol). The mixture was heated under reflux for 8 h. The mixture was concentrated *in vacuo* and taken into water (10 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were

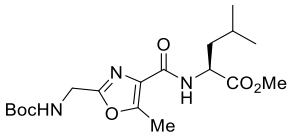
washed with hydrochloric acid (1 M; 10 mL) and saturated brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as colourless solid, which was used without further purification (0.041 g, 60%); (Found: M-H^+, 296.0886. $C_{12}H_{15}N_3O_6$ - H^+ requires 296.0883).

2-(*tert*-Butoxycarbonylaminomethyl)-5-methyloxazole-4-carboxylic acid 240



Lithium hydroxide monohydrate (0.404 g, 9.63 mmol) was added to methyl 2-(*tert*-butoxycarbonylaminomethyl)-5-methyloxazole-4-carboxylate **91** (0.651 g, 2.41 mmol) in methanol/water (4:1; 20 mL). The reaction was stirred at room temperature for 17 h. The mixture was concentrated *in vacuo*, taken into water (100 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (3 x 80 mL). The combined organic extracts were washed with saturated brine (100 mL), dried using Na_2SO_4 and concentrated *in vacuo* to give the *title compound* as a colourless solid (0.62 g, 100%); mp 165-166 °C (lit.,[148] 165-167 °C) ; (Found: M-H^+, 255.0980. $C_{11}H_{16}N_2O_5$ - H^+ requires 255.0981); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3457, 3043, 1756, 1716, 1602, 1505, 1367, 1240, 1165; δ_H (400 MHz; CD_3OD) 4.31 (2 H, s, C$\underline{H}_2$), 2.59 (3 H, s, 5-CH_3), 1.45 (9 H, s, C(C$\underline{H}_3$)$_3$); δ_C (100 MHz; CD_3OD) 165.0 (C), 161.7 (C), 158.3 (C), 158.0 (C), 128.8 (C), 81.0 (C), 38.5 (CH_2), 28.8 (CH_3), 12.1 (CH_3). Data consistent with literature.[148]

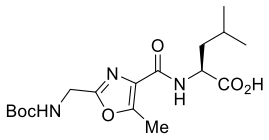
Methyl (2S,3R)-2-(2-((*tert*-butoxycarbonylamino)methyl)-5-methyloxazole-4-carboxamido)-4-methylpentanoate 241



To a stirred solution of 2-(*tert*-butoxycarbonylaminomethyl)-5-methyloxazole-4-carboxylic acid **240** (2.11 g, 8.22 mmol) and (*S*)-leucine methyl ester hydrochloride (1.79 g, 9.86 mmol) in dimethylformamide (80 mL) was added *N,N-d*iisopropylethylamine (7.31 mL, 41.1 mmol) and HATU (6.25 g, 16.4 mmol). The reaction mixture was stirred at room temperature for 16 h, poured into water (500 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic layers were washed with hydrochloric acid (1 M; 300 mL), saturated sodium carbonate (300 mL), lithium chloride solution (10%; 3 x 300 mL) and saturated brine (300 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (30%)-light petroleum to give the *title compound* as a yellow oil (2.7 g, 85%); $[\alpha]_D^{21}$ +2.9 (*c* 1, $CHCl_3$); (Found: M+Na^+, 406.1968. $C_{18}H_{29}N_3O_6$ + Na^+ requires 406.1954); ν_{max} ($CHCl_3$)/cm^{-1} 3453, 3409, 3007, 2961, 2873, 1785, 1740, 1717, 1668, 1509, 1439, 1392, 1369, 1246, 1161; δ_H (400 MHz; $CDCl_3$) 7.23 (1 H, d, *J* 8.7, NHCH), 5.34 (1 H, br s, $NHCH_2$), 4.78 - 4.64 (1 H, m, NHCH), 4.35 (2 H, d, *J* 5.5, $NHCH_2$), 3.72 (3 H, s, CO_2CH_3), 2.56 (3 H, s, 5-CH_3), 1.73 - 1.59 (3 H, m, $NHCHCH_2CH$), 1.44 (9 H, s, $C(CH_3)_3$), 0.93 (6 H, d, *J* 6.1, $CH(CH_3)_2$); δ_C (100 MHz; $CDCl_3$) 173.2 (C), 161.5 (C), 158.1 (C), 155.5 (C), 153.7

(C), 128.6 (C), 80.1 (C), 52.2 (CH_3), 50.0 (CH), 41.4 (CH_2), 37.7 (CH_2), 28.2 (CH_3), 24.7 (CH), 22.7 (CH_3), 21.7 (CH_3), 11.5 (CH_3).

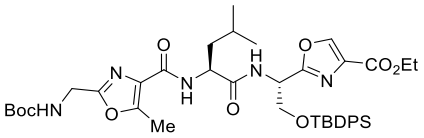
(2*S*,3*R*)-2-(2-(*tert*-Butoxycarbonylaminomethyl)-5-methyloxazole-4-carboxamido)-4-methylpentanoic acid 242



Lithium hydroxide monohydrate (0.733 g, 17.5 mmol) was added to methyl (2*S*,3*R*)-2-(2-((*tert*-butoxycarbonylamino)methyl)-5-methyloxazole-4-carboxamido)-4-methylpentanoate **241** (1.34 g, 3.49 mmol) in methanol/water (4:1; 3 mL). The reaction was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*, taken into water (100 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (3 x 70 mL). The combined aqueous extracts were washed with saturated brine (100 mL), dried using Na_2SO_4 and concentrated *in vacuo* to give the *title compound* as a colourless solid (1.2 g, 93%); mp 61-62 °C; $[\alpha]_D^{21}$ -8.0 (*c* 1, $CHCl_3$); (Found: C, 55.2; H, 7.5; N, 11.2. $C_{17}H_{27}N_3O_6$ requires C, 55.3; H, 7.4; N, 11.4%); (Found: M-H^+, 368.1829. $C_{17}H_{27}N_3O_6$ - H^+ requires 368.1822); ν_{max} ($CHCl_3$)/cm^{-1} 3452, 3407, 3007, 2964, 2934, 2873, 1719, 1666, 1636, 1516, 1394, 1247, 1162; δ_H (270 MHz; 90 °C, DMSO-d_6) 7.61 (1 H, d, *J* 8.5, N<u>H</u>CH), 7.16 (1 H, br s, N<u>H</u>CH_2), 4.46 (1 H, m, NHC<u>H</u>), 4.23 (2 H, d, *J* 5.9 NHC<u>H_2</u>), 2.53 (3 H, s, 5-CH_3), 1.76 - 1.58 (3 H, m, C<u>H_2</u>C<u>H</u>(CH_3)$_2$), 1.40 (9 H, s, C(C<u>H_3</u>)$_3$), 0.91 (3 H, d, *J* 5.9, CH(C<u>H_3</u>)(CH_3)), 0.90 (3 H, d, *J* 5.9, CH(CH_3)(C<u>H_3</u>)); δ_C (67.5 MHz; 90 °C,

DMSO-d_6) 173.1 (C), 160.5 (C), 158.8 (C), 155.1 (C), 152.0 (C), 128.3 (C), 78.2 (C), 49.6 (CH), 40.1 (CH_2), 37.3 (CH_2), 27.8 (CH_3), 24.2 (CH), 22.4 (CH_3), 21.3 (CH_3), 10.8 (CH_3).

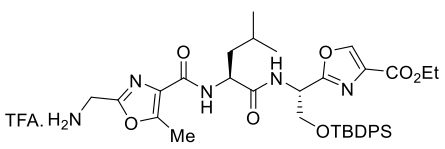
Ethyl 2-((*S*)-1-((*S*)-2-(2-*tert*-butoxycarbonylaminomethyl-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2- *tert*-butyldiphenylsiloxy)-ethyl)oxazole-4-carboxylate 243



To a stirred solution of (2*S*,3*R*)-2-(2-(*tert*-butoxycarbonylaminomethyl)-5-methyloxazole-4-carboxamido)-4-methylpentanoic acid **242** (0.450 g, 1.22 mmol) and ethyl (*S*)-2-(1-amino-2-(*tert*-butyldiphenylsiloxy)ethyl)oxazole-4-carboxylate **93** (0.445 g, 1.02 mmol) in dimethylformamide (6 mL) at 0 °C was added *N,N*-diisopropylethylamine (0.902 mL, 5.07 mmol) and HATU (0.772 g, 2.03 mmol). The mixture was warmed to room temperature and stirred for 16 h, water (60 mL) was added and the mixture was extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL), lithium chloride solution (10%; 3 x 100 mL) and saturated brine (2 x 100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (30%)-light petroleum to give the *title compound* as a colourless oil (0.57 g, 71%); $[\alpha]_D^{19}$ -6.6 (*c* 1, $CHCl_3$);

(Found: M+Na$^+$, 812.3689. $C_{41}H_{55}N_5O_9Si$ + Na^+ requires 812.3667); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2961, 2932, 2859, 1718, 1684, 1666, 507, 1470, 1370, 1318, 1251, 1193, 1161, 1114; δ_H (400 MHz, CD_3OD) 8.48 (1 H, s, 5-H), 7.59 - 7.51 (4 H, m, ArH), 7.44 - 7.31 (6 H, m, ArH), 5.30 (1 H, t, *J* 5.8, NHC<u>H</u>CH_2O), 4.74 - 4.65 (1 H, m, NHC<u>H</u>CH_2CH), 4.35 (2 H, q, *J* 7.2, OC<u>H</u>$_2CH_3$), 4.30 (2 H, s, NHC<u>H</u>$_2$), 4.07 (1 H, dd, *J* 10.3, 5.8, CHC<u>H</u>HO), 4.06 (1 H, dd, *J* 10.3, 5.8, CHCH<u>H</u>O) 2.52 (3 H, s, 5-CH_3), 1.79 - 1.59 (3 H, m, NHCHC<u>H</u>$_2$C<u>H</u>), 1.44 (9 H, s, OC(C<u>H</u>$_3$)$_3$), 1.35 (3 H, t, *J* 7.2, OCH_2C<u>H</u>$_3$), 0.98 - 0.85 (15 H, m, SiC(C<u>H</u>$_3$)$_3$, C(C<u>H</u>$_3$)$_2$); δ_C (100 MHz, CD_3OD) 174.7 (C), 164.6 (C), 163.7 (C), 162.6 (C), 160.8 (C), 158.3 (C), 155.2 (C), 152.9 (C), 146.3 (CH), 136.8 (CH), 134.6 (C), 134.0 (C), 131.2 (CH), 130.0 (C), 129.0 (CH), 80.9 (C), 65.4 (CH_2), 62.4 (CH_2), 52.6 (CH), 51.1 (CH), 42.3 (CH_2), 38.6 (CH_2), 28.9 (CH_3), 27.3 (CH_3), 26.1 (CH), 23.6 (CH_3), 22.2 (CH_3), 20.1 (C), 14.7 (CH_3), 11.8 (CH_3).

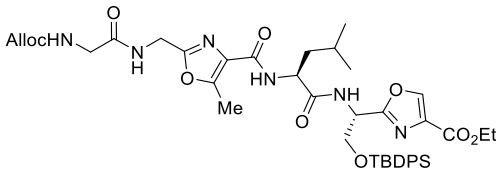
Ethyl 2-((*S*)-1-((*S*)-2-(2-(aminomethyl)-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2-(*tert*-butyldiphenylsilyloxy)ethyl)oxazole-4-carboxylate trifluoroacetate 244



Ethyl 2-((*S*)-1-((*S*)-2-(2-*tert*-butoxycarbonylaminomethyl-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2-*tert*-butyldiphenylsiloxy)-

ethyl)oxazole-4-carboxylate **243** (1.46 g, 1.85 mmol) was dissolved in trifluoroacetic acid/ dichloromethane (95:5; 10 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and then warmed to room temperature for 40 min. The reaction mixture was concentrated *in vacuo* to give the *title compound* as a colourless oil, which was used without further purification (1.60 g, 100%); (Found: M+H$^+$, 690.3328. $C_{24}H_{30}N_2O_4Si$ + H$^+$ requires 690.3323).

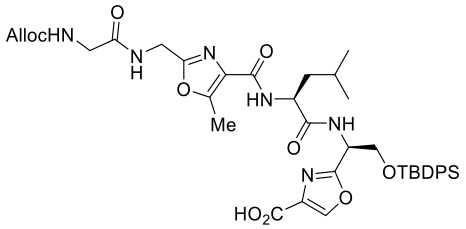
Ethyl 2-((*S*)-1-((*S*)-2-(2-((2-(allyloxycarbonylamino)acetamido)methyl)-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2-(*tert*-butyldiphenylsiloxy)ethyl)oxazole-4-carboxylate 245



To a stirred solution of ethyl 2-((*S*)-1-((*S*)-2-(2-(aminomethyl)-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2-(*tert*-butyldiphenylsilyloxy)ethyl)oxazole-4-carboxylate trifluoroacetate **244** (1.49 g, 1.85 mmol) and *N*-allyloxycarbonyl-glycine **237** (0.354 g, 2.23 mmol) in dimethylformamide (20 mL) at 0 °C was added *N,N*-diisopropylethylamine (1.61 mL, 9.27 mmol), HATU (1.41 g, 3.71 mmol) and HOAt (0.314 g, 2.31 mmol). The mixture was warmed to room temperature and stirred for 2 h. The mixture was taken into water (200 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic layers were washed with hydrochloric acid (1

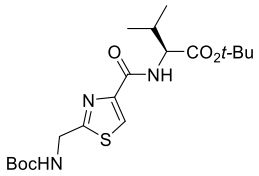
M; 150 mL), saturated sodium hydrogen carbonate (150 mL), lithium chloride solution (10%; 3 x 150 mL) and saturated brine (2 x 150 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (50-80%)-light petroleum to give the *title compound* as a colourless oil (1.2 g, 78%); $[\alpha]_D^{20}$ +3.8 (*c* 0.6, $CHCl_3$); (Found: M+Na^+, 853.3589. $C_{42}H_{54}N_6O_{10}Si$ + Na^+ requires 853.3563); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 3432, 3004, 2961, 2931, 2858, 1730, 1685, 1601, 1511, 1244, 1240, 1113; δ_H (500 MHz; CD_3OD) 8.48 (1 H, s, 5-H), 7.60 - 7.54 (4 H, m, ArH), 7.46 - 7.34 (6 H, m, ArH), 5.94 (1 H, ddt, *J* 16.4, 10.6, 4.7, CH_2=C<u>H</u>), 5.35 - 5.26 (2 H, m, C<u>H</u>H=CH, NHC<u>H</u>CH_2O), 5.18 (1 H, d, *J* 10.6, CH<u>H</u>=CH), 4.71 - 4.65 (1 H, m, NHC<u>H</u>CH_2CH), 4.56 (2 H, dt, *J* 4.7, 1.5, CH_2=CHC<u>H_2</u>), 4.47 (2 H, s, NHC<u>H_2</u>MeOxz), 4.36 (2 H, q, *J* 7.1, CO_2C<u>H_2</u>CH_3), 4.07 (1 H, dd, *J* 15.0, 6.1, CHC<u>H</u>HOSi), 4.05 (1 H, dd, *J* 15.0, 6.1, CHCH<u>H</u>OSi), 3.83 (2 H, s, OCONHC<u>H_2</u>), 2.53 (3 H, s, 5-CH_3), 1.70 - 1.65 (3 H, m, C<u>H_2</u>C<u>H</u>(CH_3)$_2$), 1.37 (3 H, t, *J* 7.1, CO_2CH_2C<u>H_3</u>), 1.00 - 0.85 (15 H, m, C(C<u>H_3</u>)$_3$, CH(C<u>H_3</u>)$_2$); δ_H (125 MHz; CD_3OD) 174.7 (C), 172.8 (C), 164.7 (C), 163.7 (C), 162.6 (C), 159.9 (C), 159.1 (C), 155.4 (C), 146.3 (CH), 136.8 (CH), 134.7 (CH), 134.4 (C), 134.1 (C), 134.0 (C), 131.2 (CH), 130.1 (C), 129.1 (CH), 129.0 (CH) 117.9 (CH_2), 67.0 (CH_2), 65.4 (CH_2), 62.4 (CH_2), 52.7 (CH), 51.2 (CH), 45.0 (CH_2), 42.3 (CH_2), 37.3 (CH_2), 27.3 (CH_3), 26.1 (CH), 23.6 (CH_3), 22.2 (CH_3), 20.1 (C), 14.7 (CH_3), 11.8 (CH_3).

2-((*S*)-1-((*S*)-2-(2-((2-(Allyloxycarbonylamino)acetamido)methyl)-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2-(*tert*-butyldiphenylsiloxy)ethyl)oxazole-4-carboxylic acid 88



To a stirred solution of ethyl 2-((*S*)-1-((*S*)-2-(2-((2-(allyloxycarbonylamino)acetamido)methyl)-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2-(*tert*-butyldiphenylsiloxy)ethyl)oxazole-4-carboxylate **245** (50 mg, 0.61 mmol) in 1,2-dichloroethane (3 mL) was added trimethyltin hydroxide (44 mg, 2.4 mmol). The mixture was heated under reflux for 8 h. The mixture was concentrated *in vacuo* and taken into water (10 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with hydrochloric acid (1 M; 3 x 10 mL) and saturated brine (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as colourless solid, which was used without further purification (49 mg, 100%); (Found: M-H^+, 801.3312. $C_{40}H_{50}N_6O_{10}Si$ - H^+ requires 801.3285).

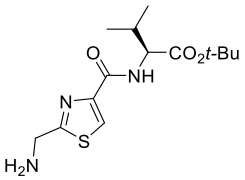
tert-Butyl (_S_)-2-(2-(_tert_-butoxycarbonylaminomethyl)thiazole-4-carboxamido)-3-methylbutanoate 246



To a stirred solution of 2-(*tert*-butoxycarbonylamino)methylthiazole-4-carboxylic acid **199** (1.38 g, 5.34 mmol) and (*S*)-valine *tert*-butyl ester hydrochloride (1.19 g, 6.93 mmol) in dimethylformamide/dichloromethane (1:1; 50 mL) at 0 °C was added *N,N*-diisopropylethylamine (4.75 mL, 26.7 mmol) and HATU (4.06 g, 10.7 mmol). The reaction mixture was stirred at room temperature for 3 h, poured into water (100 mL) and extracted with ethyl acetate (4 x 500 mL). The combined organic layers were washed with hydrochloric acid (1 M, 100 mL), saturated sodium carbonate (100 mL), lithium chloride solution (10%, 3 x 100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (20% - 30%)-light petroleum to give the *title compound* as a colourless solid (2.1 g, 93%); mp 104 - 105 °C; $[\alpha]_D^{19}$ +37.5 (*c* 1, $CHCl_3$); (Found: C, 55.3; H, 7.7; N, 11.1. $C_{19}H_{31}N_3O_5S$ requires C, 55.2; H, 7.6; N, 11.1%); (Found: M+Na^+, 436.1882. $C_{19}H_{31}N_3O_5S$ + Na^+ requires 436.1882); ν_{max} ($CHCl_3$)/cm^{-1} 3455, 3401, 3009, 2980, 2934, 1779, 1720, 1541, 1504, 1370, 1246, 1161; δ_H (400 MHz; $CDCl_3$) 8.04 (1 H, s, 5-H), 7.76 (1 H, d, *J* 9.1, NHCH), 5.25 (1 H, br s, $NHCH_2$), 4.65 - 4.59 (3 H, m, NHCH, $NHCH_2$), 2.28 (1 H, septet d, *J* 6.9, 4.7, $CH(CH_3)_2$), 1.50 (9 H, s, $CHCO_2C(CH_3)_3$), 1.49 (9 H, s, $NHCO_2C(CH_3)_3$), 1.02 (3 H, d, *J* 6.9, $CH(CH_3)(CH_3)$), 0.99 (3 H, d, *J* 6.9,

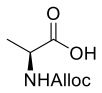
$CH(CH_3)(C\underline{H}_3)$); δ_C (100 MHz; $CDCl_3$) 170.9 (C), 169.1 (C), 160.7 (C), 155.6 (C), 149.6 (C), 123.8 (CH), 82.0 (C), 80.5 (C), 57.3 (CH), 42.3 (CH_2), 31.7 (CH), 28.3 (CH_3), 28.1 (CH_3), 19.1 (CH_3), 17.7 (CH_3).

tert-Butyl (_S_)-2-(2-(aminomethyl)thiazole-4-carboxamido)-3-methylbutanoate 247



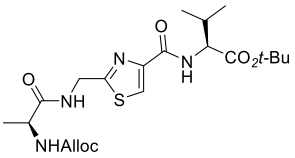
To a stirred solution of *tert*-butyl (*S*)-2-(2-(*tert*-butoxycarbonylaminomethyl)thiazole-4-carboxamido)-3-methylbutanoate **246** (0.488 g, 1.21 mmol) in *tert*-butyl acetate/dichloromethane (12 mL; 1:1) was added methanesulfonic acid (0.16 mL, 2.4 mmol) and the mixture was stirred at room temperature for 5 h. Methanesulfonic acid (0.16 mL, 2.4 mmol) was added and the mixture stirred for a further 2 h. The reaction mixture was cooled to 0 °C and quenched with saturated sodium hydrogen carbonate (50 mL). The solution was diluted with brine (40 mL) and extracted with ethyl acetate (4 x 40 mL). The combined organic layers were washed with brine (100 mL), dried using Na_2SO_4 and concentrated *in vacuo* to give the *title compound* as a yellow oil, which was used without further purification (0.37 g, 100%); (Found: M+Na^+, 336.1339. $C_{14}H_{23}N_3O_3S$ + Na^+ requires 336.1358).

(*S*)-*N*-Allyloxycarbonyl-alanine 248



Synthesised according to the procedure of Sakakura.[149] To a stirred solution of (*S*)-alanine (1.99 g, 22.3 mmol) in sodium hydroxide (1 M; 22.5 mL) was added allyl chloroformate (2.86 mL, 26.9 mmol). Sodium hydroxide (2 M; 10 mL) was added in portions over 1 h. The mixture was stirred at room temperature for 1 h. The mixture was acidified to pH 1 with hydrochloric acid (1 M) and extracted with ether (3 x 50 mL). The combined organic layers were washed with saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless oil (3.8 g, 99%); $[\alpha]_D^{24}$ -11.9 (*c* 1, EtOH) (lit.,[150] $[\alpha]_D^{25}$-19 (*c* 1, EtOH)); (Found: M+Na$^+$, 196.0590. $C_7H_{11}NO_4$ + Na requires 196.0586); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 2990, 2942, 1720, 1511, 1454, 1423, 1410, 1334, 1242, 1060; δ_H (400 MHz; CD_3OD) 5.93 (1 H, ddt, *J* 17.2, 10.5, 5.4, C<u>H</u>=CH_2), 5.31 (1 H, ddt, *J* 17.2, 1.6, 1.6, CH=C<u>H</u>H), 5.18 (1 H, ddt, *J* 10.5, 1.6, 1.6, CH=CH<u>H</u>), 4.54 (2 H, ddd, *J* 5.4, 1.6, 1.6, C<u>H</u>$_2$O), 4.17 (1 H, q, *J* 7.4, C<u>H</u>CH_3), 1.38 (3 H, d, *J* 7.4, CHC<u>H</u>$_3$); δ_C (100 MHz; CD_3OD) 176.6 (C), 158.4 (C), 134.5 (CH), 117.7 (CH_2), 66.6 (CH_2), 50.9 (CH), 18.0 (CH_3). Data consistent with literature.[149,150]

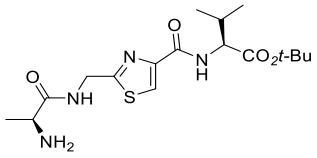
tert-Butyl (_S_)-2-(2-(((_S_)-2-(allyloxycarbonylamino)propanamido)methyl)thiazole-4-carboxamido)-3-methylbutanoate 249



To a stirred solution of *tert*-butyl (*S*)-2-(2-(aminomethyl)thiazole-4-carboxamido)-3-methylbutanoate **247** (0.480 g, 1.53 mmol) and (*S*)-*N*-allyloxycarbonyl-alanine **248** (0.398 g, 2.30 mmol) in dimethylformamide (15 mL) at 0 °C was added *N,N*-diisopropylethylamine (1.36 mL, 7.66 mmol) and HATU (1.16 g, 3.06 mmol). The reaction mixture was stirred at room temperature for 16 h, poured into water (100 mL) and extracted with ethyl acetate (4 x 70 mL). The combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium carbonate (100 mL), lithium chloride solution (10%, 3 x 100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (80%)-light petroleum to give the *title compound* as a yellow oil (0.56 g, 78%); $[\alpha]_D^{21}$ +17.5 (*c* 1, $CHCl_3$); (Found: M+Na^+, 491.1943. $C_{21}H_{32}N_4O_6S$ + Na^+ requires 491.1940); ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2973, 2546, 1723, 1671, 1522, 1496, 1429, 1414, 1370, 1246, 1153; δ_H (500 MHz; CD_3OD) 8.15 (1 H, s, 5-H), 5.93 (1 H, ddt, *J* 17.2, 10.4, 5.2, CH_2=C<u>H</u>), 5.31 (1 H, d, *J* 17.2, C=C<u>H</u>H), 5.18 (1 H, d, *J* 10.4, C=CH<u>H</u>), 4.74 (1 H, d, *J* 16.1, NHC<u>H</u>H), 4.67 (1 H, d, *J* 16.1, NHCH<u>H</u>), 4.59 - 4.48 (2 H, m, $NHCO_2C\underline{H}_2$), 4.45 - 4.40 (1 H, m, NHC<u>H</u>CH), 4.20 (1 H, q, *J* 7.2, NHC<u>H</u>CH_3), 2.26

(1 H, septet d, *J* 6.9, 5.4, NHCHC<u>H</u>), 1.49 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.39 (3 H, d, *J* 7.2, NHCHC<u>H</u>$_3$), 1.00 (3 H, d, *J* 6.9, CH(C<u>H</u>$_3$)(CH$_3$)), 1.00 (3 H, d, *J* 6.9, CH(CH$_3$)(C<u>H</u>$_3$)); δ_C (125 MHz; CD_3OD) 176.3 (C), 172.1 (C), 171.4 (C), 163.0 (C), 158.2 (C), 150.1. (C), 134.4 (CH), 125.8 (CH), 117.8 (CH_2), 83.4 (C), 66.8 (CH_2), 59.5 (CH), 52.2 (CH), 42.0 (CH_2), 32.5 (CH), 28.4 (CH_3), 19.6 (CH_3), 18.5 (CH_3), 18.4 (CH_3).

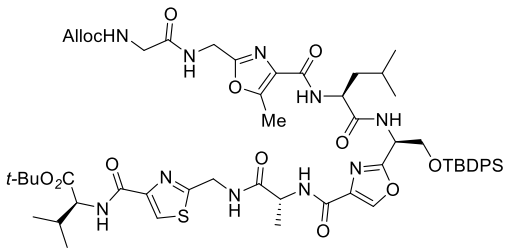
tert-Butyl (_S_)-2-(2-(((_S_)-2-aminopropanamido)methyl)thiazole-4-carboxamido)-3-dimethylbutanoate 89



To a stirred solution *tert*-butyl (*S*)-2-(2-(((*S*)-2-(allyloxycarbonylamino)propanamido)methyl)thiazole-4-carboxamido)-3-methylbutanoate **249** (0.078 g, 0.17 mmol) in dichloromethane (1.5 mL) was added diethylamine (0.35 mL, 3.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (4 mg, 2 mol%). The reaction mixture was stirred at room temperature for 1.5 h. The mixture was concentrated *in vacuo* and the residue purified by chromatography on silica, eluting with methanol (1 - 2%)-chloroform to give the *title compound* as a colourless oil (0.051 g, 80%); $[\alpha]_D^{21}$ +32.0 (*c* 1, $CHCl_3$); (Found: M+H$^+$, 385.1917. $C_{17}H_{28}N_4O_4S$ + H$^+$ requires 385.1904); ν_{max} ($CHCl_3$)/cm^{-1} 3394, 3009, 2972, 2934, 2513, 1726, 1667, 1541, 1518, 1497, 1427, 1371, 1249, 1152; δ_H (400 MHz; CD_3OD) 8.16 (1 H, s, 5-H), 4.77 (1 H, d, *J* 16.2, NHC<u>H</u>H), 4.69 (1 H, d, *J* 16.2, NHCH<u>H</u>), 4.42 (1 H,

d, *J* 5.4, NHC<u>H</u>CH), 3.60 (1 H, q, *J* 7.0, NHC<u>H</u>CH$_3$), 2.26 (1 H, septet d, *J* 6.9, 5.4, NHCHC<u>H</u>), 1.50 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.37 (3 H, d, *J* 7.0, NHCHC<u>H</u>$_3$), 1.01 (3 H, d, *J* 6.9, CH(C<u>H</u>$_3$)(CH$_3$)), 1.00 (3 H, d, *J* 6.9, CH(CH$_3$)(C<u>H</u>$_3$)); δ_C (100 MHz; CD$_3$OD) 177.7 (C), 172.1 (C), 171.2 (C), 163.0 (C), 150.1 (C), 125.8 (CH), 83.5 (C), 59.5 (CH), 51.4 (CH), 41.9 (CH$_2$), 32.5 (CH), 28.4 (CH$_3$), 21.0 (CH$_3$), 19.6 (CH$_3$), 18.5 (CH$_3$).

Protected *C*-terminal 79

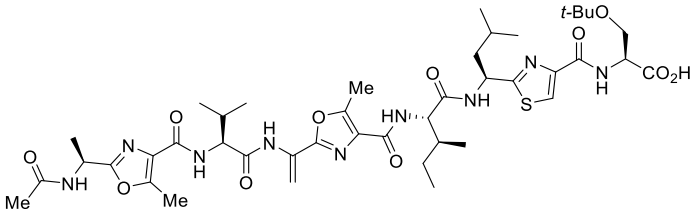


To a stirred solution of 2-((*S*)-1-((*S*)-2-(2-((2-(allyloxycarbonylamino)acetamido)methyl)-5-methyloxazole-4-carboxamido)-4-methylpentanamido)-2-(*tert*-butyldiphenylsiloxy)ethyl)oxazole-4-carboxylic acid **88** (0.314 g, 0.391 mmol) in dimethylformamide (2 mL) at 0 °C, was added *N,N*-diisopropylethylamine (0.321 mL, 1.85 mmol), HATU (0.281 g, 0.738 mmol) and HOAt (0.075 g, 0.55 mmol). The mixture was stirred for 10 min, then *tert*-butyl (*S*)-2-(2-(((*S*)-2-aminopropanamido)methyl)thiazole-4-carboxamido)-3-dimethylbutanoate **89** (0.142 g, 0.369 mmol) in dimethylformamide (2 mL) was added. The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was taken into water (50 mL) and ethyl acetate (50 mL). The aqueous layer was further extracted with ethyl acetate (3 x 30 mL). The

combined organic layers were washed with hydrochloric acid (1 M; 80 mL), saturated sodium hydrogen carbonate (80 mL), lithium chloride solution (10%; 3 x 80 mL), water (80 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (0-10%)-chloroform to give the *title compound* as a colourless oil (0.35 g, 81%); $[\alpha]_D^{21}$ -18.9 (*c* 1, $CHCl_3$); (Found: M+Na^+, 1191.4963. $C_{57}H_{76}N_{10}O_{13}SSi$ + Na requires 1191.4981); ν_{max} ($CHCl_3$)/cm^{-1} 3402, 3263, 3009, 2965, 2934, 1726, 1663, 1600, 1531, 1455, 1428, 1393, 1371, 1240, 1151, 1113; δ_H (400 MHz; CD_3OD) 8.36 (1 H, s, 5-H), 8.16 (1 H, s, 5-H), 7.57 (4 H, m, ArH), 7.48 - 7.34 (6 H, m, ArH), 5.95 (1 H, ddt, *J* 16.1, 10.4, 5.4, CH_2=C<u>H</u>), 5.36 - 5.27 (2 H, m, C<u>H</u>H=CH, C<u>H</u>CH_2OSi), 5.19 (1 H, d, *J* 10.4, CH<u>H</u>=CH), 4.79 (1 H, d, *J* 16.2, NHC<u>H</u>H-Thiaz), 4.75 - 4.67 (2 H, m, NHCH<u>H</u>-Thiaz, NHC<u>H</u>CH_2CH), 4.65 (1 H, q, *J* 7.1, NHC<u>H</u>CH_3), 4.57 (2 H, dt, *J* 5.4, 1.4, CH_2=CHC<u>H_2</u>), 4.48 (2 H, s, NHC<u>H_2</u>-MeOxz), 4.43 (1 H, d, *J* 5.4, NHC<u>H</u>CH), 4.10 (1 H, dt, *J* 16.7, 6.0, C<u>H</u>HOSi), 4.08 (1 H, dt, *J* 16.7, 6.0, CH<u>H</u>OSi), 3.84 (2 H, s, AllocNHC<u>H_2</u>), 2.54 (3 H, s, 5-CH_3), 2.27 (1 H, septet d, *J* 6.7, 5.4, NHCHC<u>H</u>$(CH_3)_2$), 1.79 - 1.63 (3 H, m, NHCHC<u>H_2</u>C<u>H</u>), 1.54 - 1.39 (12 H, m, $CO_2C(C\underline{H_3})_3$, NHCHC<u>$H_3$</u>), 1.02 (3 H, d, *J* 6.7, NHCHCH(C<u>H_3</u>)(CH_3)), 1.01 (3 H, d, *J* 6.7, NHCHCH(CH_3)(C<u>H_3</u>)), 0.98 - 0.93 (15 H, m, $SiC(C\underline{H_3})_3$, $CHCH_2CH(C\underline{H_3})_2$); δ_C (100 MHz; CD_3OD) 175.0 (C), 174.7 (C), 172.8 (C), 172.1 (C), 171.3 (C), 163.8 (C), 163.7 (C), 163.0 (C), 162.4 (C), 159.9 (C), 159.1 (C), 155.4 (C), 150.1 (C), 143.5 (CH), 137.2 (C), 136.8 (CH), 134.4 (CH), 134.1 (C), 134.0 (C), 131.2 (CH), 130.0 (C), 129.09 (CH), 129.07 (CH), 125.9 (CH), 117.9 (CH_2), 83.5 (C), 67.0 (CH_2), 65.2 (CH_2), 59.6 (CH), 52.7 (CH), 51.2 (CH), 50.2 (CH), 45.0 (CH_2), 42.4 (CH_2), 42.1 (CH_2), 37.3 (CH_2), 32.6 (CH),

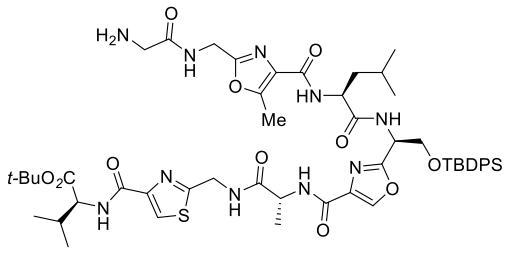
28.5 (CH_3), 27.3 (CH_3), 26.1 (CH), 23.6 (CH_3), 22.2 (CH_3), 20.1 (C), 19.6 (CH_3), 18.8 (CH_3), 18.5 (CH_3), 11.8 (CH_3).

_N_-Terminal acid 250



To a stirred solution of *N*-terminal fragment **234** (20 mg, 0.022 mmol) in 1,2-dichloroethane (0.2 mL) was added trimethyltin hydroxide (16 mg, 0.086 mmol). The mixture was heated at 50 °C for 6 h, after which trimethyltin hydroxide (16 mg, 0.086 mmol) was added. After a further 2 h, trimethyltin hydroxide (16 mg, 0.086 mmol) was again added and the reaction mixture heated at 50 °C for 16 h. The mixture was concentrated *in vacuo* and taken into water (10 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with hydrochloric acid (1 M; 10 mL) and saturated brine (10 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as colourless solid, which was used without further purification (20 mg, 100%); (Found: M+Na^+, 936.4242. $C_{43}H_{63}N_9O_{11}S$ + Na^+ requires 936.4265).

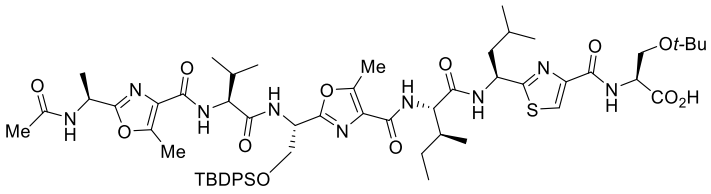
_C_-Terminal amine 251



To a stirred solution of protected *C*-terminal **79** (0.132 g, 0.113 mmol) in dichloromethane (1 mL) was added diethylamine (0.233 mL, 2.26 mmol) and tetrakis(triphenylphosphine)palladium(0) (2.5 mg, 2 mol%). The reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo* and the residue purified by chromatography on silica, eluting with methanol (1 - 5%)-chloroform to give the *title compound* as a colourless solid (0.095 g, 77%); mp 101-102 °C; $[\alpha]_{\mathrm{D}}^{22}$ -18.7 (*c* 1, $CHCl_3$); (Found: $M+H^+$, 1085.4956. $C_{53}H_{72}N_{10}O_{11}SSi$ + H requires 1085.4950); ν_{max} ($CHCl_3$)/cm^{-1} 3402, 3009, 2964, 2934, 1726, 1668, 1600, 1509, 1428, 1371, 1240, 1150, 1113; δ_H (400 MHz; CD_3OD) 8.34 (1 H, s, 5-H), 8.13 (1 H, s, 5-H), 7.58 - 7.50 (4 H, m, ArH), 7.45 - 7.29 (6 H, m, ArH), 5.27 (1 H, t, *J* 6.2, C<u>H</u>CH_2OSi), 4.80 - 4.60 (4 H, m, NHC<u>H</u>$_2$-Thiaz, NHC<u>H</u>CH_3, NHC<u>H</u>CH_2CH), 4.48 (2 H, m, NHC<u>H</u>$_2$-MeOxz), 4.42 (1 H, d, *J* 5.4, NHC<u>H</u>CH), 4.08 (1 H, dd, *J* 15.3, 6.2, C<u>H</u>HOSi), 4.06 (1 H, dd, *J* 15.3, 6.2, CH<u>H</u>OSi), 3.39 (2 H, br s, NH_2C<u>H</u>$_2$), 2.51 (3 H, s, 5-CH_3), 2.24 (1 H, septet d, *J* 6.7, 5.4, NHCHC<u>H</u>$(CH_3)_2$), 1.74 - 1.60 (3 H, m, NHCHC<u>H</u>$_2$C<u>H</u>), 1.50 (3 H, d, *J* 7.3, NHCHC<u>H</u>$_3$), 1.48 (9 H, s, $CO_2C(C$<u>H</u>$_3)_3$), 0.99 (3 H, d, *J* 6.7, NHCHCH(C<u>H</u>$_3$)(CH_3)), 0.98 (3 H, d, *J* 6.7, NHCHCH(CH_3)(C<u>H</u>$_3$)), 0.95 - 0.91 (15 H, m, SiC(C<u>H</u>$_3$)$_3$, $CHCH_2CH(C$<u>H</u>$_3)_2$); δ_C (100 MHz; CD_3OD) 174.9 (C), 174.7 (C), 174.5 (C), 172.1 (C), 171.2 (C), 163.8 (C), 163.6 (C), 163.0 (C), 162.3 (C), 160.0 (C), 155.4 (C), 150.1

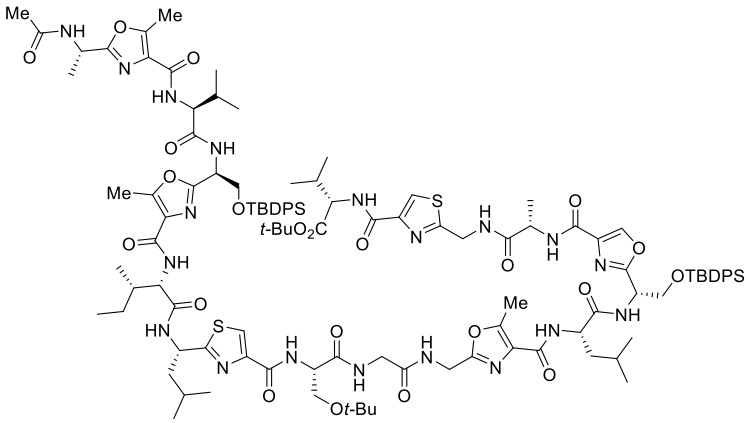
(C), 143.5 (CH), 137.2 (C), 136.7 (CH), 134.1 (C), 134.0 (C), 131.22 (CH), 131.20 (CH), 130.0 (C), 129.07 (CH), 129.05 (CH), 125.9 (CH), 83.4 (C), 65.2 (CH_2), 59.5 (CH), 52.6 (CH), 51.2 (CH), 50.2 (CH), 44.6 (CH_2), 42.4 (CH_2), 42.1 (CH_2), 37.2 (CH_2), 32.5 (CH), 28.5 (CH_3), 27.3 (CH_3), 26.1 (CH), 23.6 (CH_3), 22.3 (CH_3), 20.1 (C), 19.7 (CH_3), 18.9 (CH_3), 18.5 (CH_3), 11.9 (CH_3).

Protected *N*-terminal acid 253



To a stirred solution of protected *N*-terminal **78**(0.223 g, 0.188 mmol) in 1,2-dichloroethane (1 mL) was added trimethyltin hydroxide (0.136 g, 0.753 mmol). The mixture was heated at 70 °C for 16 h. The mixture was concentrated *in vacuo* and taken into water (50 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with hydrochloric acid (1 M; 3 x 60 mL) and saturated brine (2 x 60 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as colourless solid, which was used without further purification (0.22g, 100%); (Found: M-H^+, 1168.5577. $C_{59}H_{83}N_9O_{12}SSi$ - H^+ requires 1168.5573).

Protected peptide 77

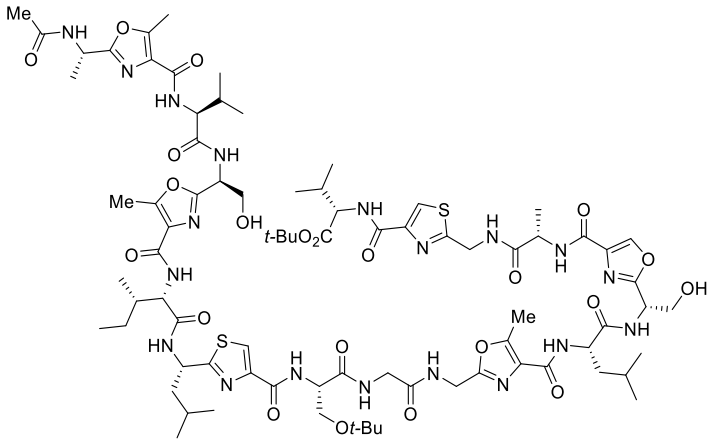


To a stirred solution of protected *N*-terminal acid **253** (0.349 g, 0.298 mmol) and *C*-terminal amine **251** (0.317 g, 0.292 mmol) in dimethylformamide (3 mL) at 0 °C, was added *N,N*-diisopropylethylamine (0.254 mL, 1.46 mmol), HATU (0.222 g, 0.584 mmol) and HOAt (0.060 g, 0.438 mmol). The mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was taken into water (100 mL) and extracted with chloroform/isopropanol (9:1; 3 x 80 mL). The combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL), lithium chloride solution (10%; 3 x 100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with methanol (1-5%)-ethyl acetate to give the *title compound* as a colourless solid (0.43 g, 66%); mp 130-131 °C; $[\alpha]_D^{23}$ -6.5 (*c* 1, CH_3OH); (Found: M+2Na^{2+}, 1141.0073. $C_{112}H_{153}N_{19}O_{22}S_2Si_2$ + 2Na^{2+} requires 1141.0107); ν_{max} (ATR) /cm^{-1} 2962, 2932, 1646, 1524, 1427, 1367, 1111, 750, 701; δ_H (400 MHz; CD_3OD) 8.35 (1 H, s, 5-H), 8.13 (1 H, s, 5-H), 8.06 (1 H, s, 5-H), 7.58 - 7.49 (8 H, m, ArH), 7.42 - 7.31 (12 H, m, ArH), 5.32 (1 H, dd,

J 6.0, 3.8, NHC<u>H</u>$CH_2CH(CH_3)_2$), 5.29 (1 H, t, *J* 6.0, C<u>H</u>CH_2OSi), 5.22 (1 H, t, *J* 5.6, C<u>H</u>CH_2OSi), 5.12 (1 H, q, *J* 7.2, NHC<u>H</u>CH_3), 4.78 (1 H, d, *J* 16.1, NHC<u>H</u>H-Thiaz), 4.74 - 4.61 (2 H, m, NHCH<u>H</u>-Thiaz, NHC<u>H</u>$CH_2CH(CH_3)_2$), 4.64 (1 H, q, *J* 7.2, NHC<u>H</u>CH_3), 4.58 (1 H, t, *J* 5.4, NHC<u>H</u>$CH_2OC(CH_3)_3$), 4.53 - 4.46 (4 H, m, NHC<u>H</u>$CH(CH_3)_2$, NHC<u>H</u>$_2$-Oxaz, NHC<u>H</u>$CH(CH_3)CH_2$), 4.41 (1 H, d, *J* 5.4, NHC<u>H</u>$CH(CH_3)_2$), 4.10 - 4.01 (5 H, m, C<u>H</u>$_2$OSi x 2, NHC<u>H</u>HCO), 3.90 (1 H, d, *J* 16.9, NHCH<u>H</u>CO), 3.83 (1 H, dd, *J* 9.4, 5.4, C<u>H</u>$HOC(CH_3)_3$), 3.76 (1 H, dd, *J* 9.4, 5.4, CH<u>H</u>$OC(CH_3)_3$), 2.55 (3 H, s, 5-CH_3), 2.51 (3 H, s, 5-CH_3), 2.46 (3 H, s, 5-CH_3), 2.24 (1 H, septet d, *J* 6.8, 5.3, NHCHC<u>H</u>$(CH_3)_2$), 2.17 (1 H, septet d, *J* 6.8, 5.4, NHCHC<u>H</u>$(CH_3)_2$), 1.98 (3 H, s, NHCOC<u>H</u>$_3$), 1.96 - 1.80 (3 H, m, NHCHC<u>H</u>$_2CH(CH_3)_2$, NHCHC<u>H</u>$(CH_3)CH_2$), 1.76 - 1.63 (4 H, m, NHCHC<u>H</u>$_2CH(CH_3)_2$, NHCHCH_2C<u>H</u>$(CH_3)_2$ x 2), 1.61 - 1.52 (1 H, m, NHCHCH(CH_3)C<u>H</u>H), 1.50 (6 H, 2 x d, *J* 7.2, NHCHC<u>H</u>$_3$ x 2), 1.48 (9 H, s, CO_2C(C<u>H</u>$_3)_3$), 1.19 (9 H, s, $CH_2OC(CH_3)_3$), 1.16 - 1.10 (1 H, m, NHCHCH(CH_3)CH<u>H</u>), 1.43 - 0.85 (48 H, m, SiC(C<u>H</u>$_3)_3$ x 2, NHCHCH(C<u>H</u>$_3)_2$ x 2, CH(C<u>H</u>$_3)CH_2$C<u>H</u>$_3$, NHCHCH_2CH(C<u>H</u>$_3)_2$ x 2); δ_C (100 MHz; CD_3OD) 174.9 (C), 174.8 (C), 174.7 (C), 173.5 (C), 173.3 (C), 173.0 (C), 172.8 (C), 172.2 (C), 172.1 (C), 171.2 (C), 164.0 (C), 163.63 (C), 163.58 (C), 163.52 (C), 163. 49 (C), 163.38 (C), 163.0 (C), 162.3 (C), 160.8 (C), 159.8 (C), 155.4 (C), 155.13 (C), 155.06 (C), 150.3 (C), 150.2 (C), 143.4 (CH), 137.2 (C), 136.75 (CH), 136.73 (CH), 134.1 (C), 134.04 (C), 134.02 (C), 133.98 (C), 131.24 (CH), 131.21 (CH), 131.18 (CH), 130.1 (C), 130.0 (C), 129.9 (C), 129.12 (CH), 129.08 (CH), 129.05 (CH), 125.9 (CH), 125.3 (CH), 83.4 (C), 75.2 (C), 65.3 (CH_2), 65.2 (CH_2), 62.8 (CH_2), 59.5 (CH), 59.2 (CH), 58.4 (CH), 56.0 (CH), 52.6 (CH), 51.2 (2 x CH), 51.1 (CH), 50.2 (CH), 44.7 (CH_2), 44.5 (CH), 43.9 (CH_2), 42.5 (CH_2), 42.1 (CH_2), 39.2 (CH), 37.3 (CH_2), 33.0 (CH),

32.6 (CH), 28.5 (CH_3), 27.9 (CH_3), 27.37 (CH_3), 27.35 (CH_3), 26.1 (CH x 2), 25.9 (CH_2), 23.6 (CH_3), 23.5 (CH_3), 22.6 (CH_3), 22.4 (CH_3), 22.3 (CH_3), 20.14 (C), 20.08 (C), 19.9 (CH_3), 19.7 (CH_3), 19.2 (CH_3), 19.0 (CH_3), 18.8 (CH_3), 18.5 (CH_3), 16.4 (CH_3), 11.9 (2 x CH_3), 11.8 (CH_3), 11.6 (CH_3).

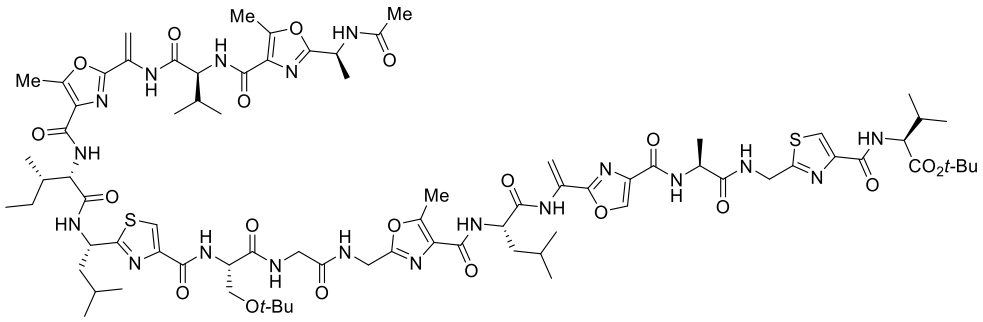
Diol peptide 254



To a stirred solution of protected peptide **77** (0.088 g, 0.039 mmol) in THF (1 mL) was added tetrabutylammonium difluorotriphenylsilicate (0.085 g, 0.16 mmol) and the mixture stirred at room temperature for 4 h. The mixture was concentrated *in vacuo* and the residue purified by chromatography on silica, eluting with methanol (1-8%)-chloroform to give the *title compound* as a colourless solid (42 mg, 61%); mp 173-174 °C; $[\alpha]_D^{23}$ -20.5 (*c* 1, CH_3OH); (Found: M+2Na^{2+}, 902.8947. $C_{80}H_{117}N_{19}O_{22}S_2$ + 2Na^{2+} requires 902.8929); ν_{max} (ATR)/cm^{-1} 3325, 3307, 2965, 1645, 1520, 1368, 1190, 1150, 707; δ_H (400 MHz; CD_3OD) 8.37 (1 H, s, 5-H), 8.15 (1 H, s, 5-H), 8.10 (1 H, s, 5-H), 5.33 (1 H, dd, *J* 9.9, 5.3, NHC<u>H</u>$CH_2CH(CH_3)_2$), 5.21 (1 H, t, *J* 5.6, NHC<u>H</u>CH_2OH), 5.15 (1 H, t, *J* 5.6, NHC<u>H</u>CH_2OH), 5.12 (1 H, q, *J* 7.0, NHC<u>H</u>CH_3), 4.77 (1 H, d, *J* 16.3 NHC<u>H</u>HThiaz),

4.69 (1 H, d, *J* 16.3 NHCHHThiaz), 4.69 - 4.65 (1 H, m, NHCHCH$_2$CH(CH$_3$)$_2$), 4.61 (1 H, q, *J* 7.2, NHCHCH$_3$), 4.59 - 4.56 (1 H, m, NHCHCH$_2$OC), 4.52 - 4.44 (4 H, m, NHCHCH(CH$_3$)$_2$, NHCH$_2$-Oxaz, NHCHCH(CH$_3$)CH$_2$), 4.41 (1 H, d, *J* 5.4, NHCHCH(CH$_3$)$_2$), 4.02 - 3.89 (6 H, m, NHCHCH$_2$OH x 2, NHCH$_2$CO), 3.83 (1 H, dd, *J* 9.4, 4.9, NHCHCHHOC), 3.76 (1 H, dd, *J* 9.4, 5.5, NHCHCHHOC), 2.59 (3 H, s, 5-CH$_3$), 2.58 (3 H, s, 5-CH$_3$), 2.51 (3 H, s, 5-CH$_3$), 2.25 (1 H, septet d, *J* 6.9, 5.4, NHCHCH(CH$_3$)$_2$), 2.17 (1 H, septet d, *J* 6.8, 4.8, NHCHCH(CH$_3$)$_2$), 1.99 (3 H, s, NHCOCH$_3$), 1.96 - 1.83 (3 H, m, NHCHCH$_2$CH(CH$_3$)$_2$, NHCHCH(CH$_3$)CH$_2$), 1.79 - 1.63 (4 H, m, NHCHCH$_2$CH(CH$_3$)$_2$, NHCHCH$_2$CH(CH$_3$)$_2$ x 2), 1.61 - 1.54 (1 H, m, NHCHCH(CH$_3$)CHH), 1.52 (3 H, d, *J* 7.0, NHCHCH$_3$), 1.51 (3 H, d, *J* 7.2, NHCHCH$_3$), 1.49 (9 H, s, CO$_2$C(CH$_3$)$_3$), 1.21 (9 H, s, CH$_2$OC(CH$_3$)$_3$), 1.21 - 1.15 (1 H, m, NHCHCH(CH$_3$)CHH), 1.04 - 0.88 (30 H, m, NHCHCH(CH$_3$)$_2$ x 2, CH(CH$_3$)CH$_2$CH$_3$, NHCHCH$_2$CH(CH$_3$)$_2$ x 2); δ_C (100 MHz; CD$_3$OD) 175.2 (C), 175.1 (C), 174.9 (C), 173.6 (C), 173.5 (C), 173.0 (C), 172.9 (C), 172.2 (C), 172.1 (C), 171.3 (C), 163.9 (C), 163.73 (C), 163.67 (C), 163.55 (2 x C), 163.52 (C), 163.0 (C), 162.5 (C), 161.0 (C), 159.8 (C), 155.4 (C), 155.3 (C), 155.1 (C), 150.2 (C), 150.1 (C), 143.6 (CH), 137.2 (C), 130.1 (C), 130.0 (C), 129.9 (C), 125.9 (CH), 125.4 (CH), 83.5 (C), 75.3 (C), 63.3 (CH$_2$), 63.2 (CH$_2$), 62.8 (CH$_2$), 59.6 (CH), 59.2 (CH), 58.6 (CH), 55.9 (CH), 52.8 (CH), 51.3 (CH), 51.22 (CH), 51.16 (CH), 50.2 (CH), 44.7 (CH$_2$), 44.5 (CH), 43.9 (CH$_2$), 42.6 (CH$_2$), 42.1 (CH$_2$), 39.1 (CH), 37.3 (CH$_2$), 33.1 (CH), 32.6 (CH), 28.5 (CH$_3$), 27.9 (CH$_3$), 26.14 (CH), 26.11 (CH), 25.9 (CH$_2$), 23.7 (CH$_3$), 23.6 (CH$_3$), 22.6 (CH$_3$), 22.20 (CH$_3$), 22.18 (CH$_3$), 19.9 (CH$_3$), 19.6 (CH$_3$), 19.1 (CH$_3$), 18.74 (CH$_3$), 18.67 (CH$_3$), 18.5 (CH$_3$), 16.4 (CH$_3$), 11.83 (CH$_3$), 11.79 (2 x CH$_3$), 11.6 (CH$_3$).

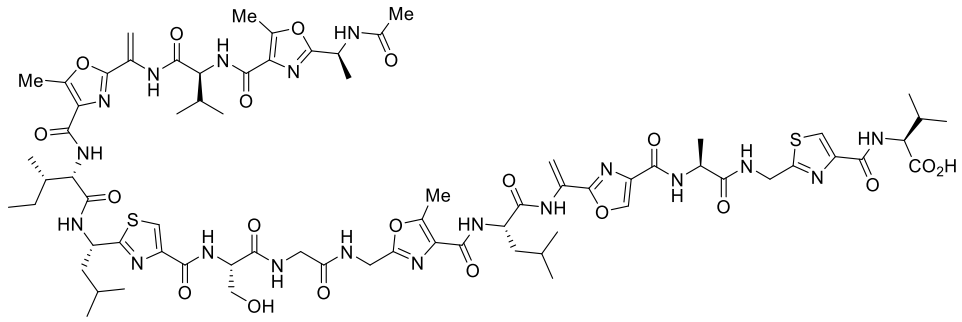
Di-*tert*-butyl protected goadsporin 255



To a stirred solution of diol peptide **254** (0.17 g, 0.096 mmol) in THF (1 mL) at 0 °C, was added triethylamine (0.13 mL, 0.96 mmol) and methanesulfonyl chloride (0.040 mL, 0.38 mmol) and the mixture was stirred for 3 h. The reaction mixture was concentrated *in vacuo* and taken into chloroform (1 mL) and cooled to 0 °C, DBU (0.060 mL, 0.38 mmol) was added and the mixture was stirred for 4 h. The mixture was diluted with water (10 mL) and extracted with chloroform/isopropanol (9:1; 3 x 6 mL). The combined organic extracts were washed with saturated brine (20 mL), dried using Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography eluting with methanol (1-10%)-chloroform to give the *title compound* as a colourless solid (59 mg, 36%); mp 159-160 °C; $[\alpha]_D^{23}$ -69.6 (*c* 1, $CHCl_3$); (Found: M+2Na^{2+}, 884.8841. $C_{80}H_{113}N_{19}O_{20}S_2$ + 2Na^{2+} requires 884.8823); ν_{max} (ATR)/cm^{-1} 3271, 2961, 2873, 16363, 1531, 1425, 1391, 1367, 1193, 1150, 749; δ_H (400 MHz; CD_3OD) 8.28 (1 H, s, 5-H), 8.04 (1 H, s, 5-H), 7.92 (1 H, s, 5-H), 6.33 (1 H, s, C=C<u>H</u>H), 6.26 (1 H, s, C=C<u>H</u>H), 5.72 (1 H, s, C=CH<u>H</u>), 5.66 (1 H, s, C=CH<u>H</u>), 5.28 (1 H, dd, *J* 7.4, 3.4, NHC<u>H</u>CH$_2$CH(CH$_3$)$_2$), 5.14 (1 H, q, *J* 6.9, NHC<u>H</u>CH$_3$), 5.14 (1 H, t, *J* 7.3, NHC<u>H</u>CH$_2$CH(CH$_3$)$_2$), 4.95 (1 H, q, *J* 7.3, NHC<u>H</u>CH$_3$), 4.92 (1 H, d, *J* 7.0, NHC<u>H</u>CH(CH$_3$)$_2$), 4.82 - 4.77 (2 H, m, NHC<u>H</u>CH(CH$_3$)CH$_2$, NHC<u>H</u>H), 4.72 (1 H, d, *J*

16.7, NHC<u>H</u>H), 4.57 (1 H, dd, *J* 6.7, 5.8, NHC<u>H</u>CH_2O), 4.53 (1 H, d, *J* 5.3, NHC<u>H</u>$CH(CH_3)_2$), 4.51 (1 H, d, *J* 15.2, NHCH<u>H</u>), 4.31 (1 H, d, *J* 16.7, NHCH<u>H</u>), 4.15 (1 H, d, *J* 16.9, NHC<u>H</u>H), 4.04 (1 H, dd, *J* 9.2, 6.7, NHCHCH<u>H</u>O), 3.88 (1 H, dd, *J* 9.2, 5.8, NHCHCH<u>H</u>O), 3.83 (1 H, d, *J* 16.9 NHCH<u>H</u>), 2.56 (3 H, s, 5-CH_3), 2.52 (3 H, s, 5-CH_3), 2.43 (3 H, s, 5-CH_3), 2.36 - 2.26 (2 H, m, NHCHC<u>H</u>$(CH_3)_2$ x 2), 2.22 - 2.13 (1 H, m, NHCHCH(CH_3)C<u>H</u>H), 2.02 (3 H, s, NHCOC<u>H_3</u>), 2.00 - 1.85 (3 H, m, NHCHC<u>H_2</u>CH, NHCHC<u>H</u>HCH), 1.81 - 1.69 (2 H, m, NHCHCH<u>H</u>CH, NHCHCH_2C<u>H</u>), 1.64 (3 H, d, *J* 7.3, NHCHC<u>H_3</u>), 1.62 - 1.57 (1 H, m, NHCHCH(CH_3)CH<u>H</u>), 1.52 (3 H, d, *J* 6.9, NHCHC<u>H_3</u>), 1.51 (9 H, s, C(C<u>H_3</u>)$_3$), 1.46 - 1.36 (1 H, m, NHCHCH_2C<u>H</u>), 1.23 (9 H, s, C(C<u>H_3</u>)$_3$), 1.10 (3 H, d, *J* 6.8, NHCHCH(C<u>H_3</u>)(CH_3)), 1.06 (3 H, d, *J* 6.8, NHCHCH(CH_3)(C<u>H_3</u>)), 1.05 - 0.96 (15 H, m, NHCHCH(C<u>H_3</u>)$_2$, NHCHCH_2CH(C<u>H_3</u>)$_2$, NHCHCH(C<u>H_3</u>)CH_2), 0.88 (3 H, t, *J* 7.4, CH$(CH_3)CH_2$C<u>H_3</u>), 0.84 (3 H, d, *J* 6.5, NHCHCH_2CH(C<u>H_3</u>)(CH_3)), 0.71 (3 H, d, *J* 6.5, NHCHCH_2CH(CH_3)(C<u>H_3</u>)); δ_C (125 MHz; CD_3OD) 175.2 (C), 174.9 (C), 174.2 (C), 173.7 (C), 173.5 (C), 173.3 (C), 172.7 (C), 172.1 (C), 171.9 (C), 169.6 (C), 164.5 (C), 164.13 (C), 164.07 (C), 163.9 (C), 163.2 (C), 163.10 (C), 163.07 (C), 159.8 (C), 159.7 (C), 156.9 (C), 155.6 (C), 155.44 (C), 155.37 (C), 150.7 (C), 150.4 (C), 143.8 (CH), 138.7 (C), 131.7 (C), 130.9 (C), 130.5 (C), 129.7 (C), 129.6 (C), 126.3 (CH), 125.3 (CH), 108.1 (CH_2), 107.0 (CH_2), 83.4 (C), 75.1 (C), 62.5 (CH_2), 59.6 (CH), 59.4 (CH), 58.7 (CH), 56.8 (CH), 53.0 (CH), 51.8 (CH), 50.4 (CH), 44.2 (CH), 44.1 (CH_2), 43.7 (CH_2), 43.3 (CH_2), 42.1 (CH_2), 37.7 (CH), 37.2 (CH_2), 33.2 (CH), 32.7 (CH), 28.5 (CH_3), 28.0 (CH_3), 26.27 (CH), 26.26 (CH), 26.2 (CH_2 by HSQC), 24.0 (CH_3), 23.2 (CH_3), 22.7 (CH_3), 22.6 (CH_3), 22.3 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 19.1 (CH_3), 18.9 (CH_3), 18.6 (CH_3), 18.5 (CH_3), 16.3 (CH_3), 12.02 (CH_3), 11.98 (CH_3), 11.85 (CH_3), 10.8 (CH_3).

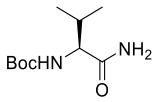
Goadsporin 64



To a stirred solution of di-*tert*-butyl protected goadsporin **255** (13 mg, 0.0075 mmol) in chloroform (0.5 mL) was added zinc(II) bromide (7 mg, 0.030 mmol), and the mixture was stirred for 16 h. Further zinc(II) bromide (7 mg, 0.030 mmol) was added and the mixture heated to 35 °C for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography eluting with methanol (8-12%)-chloroform to give the *title compound* as a colourless solid (8 mg, 66%); mp 196-197 °C (lit.,[36] mp 172-174 °C); $[\alpha]_{\mathrm{D}}^{28}$ 13.2 (*c* 1, MeOH) (lit.,[36] $[\alpha]_{\mathrm{D}}^{22}$ -21 (*c* 1, MeOH)); (Found: M+Na$^+$, 1634.6487. $C_{72}H_{97}N_{19}O_{20}S_2$ + Na$^+$ requires 1634.6491); ν_{max} (ATR)/cm^{-1} 3286, 2960, 1930, 1651, 1538, 1197, 1164, 1115; δ_H (500 MHz; DMSO-d_6) 10.07 (1 H, s, CONHC), 9.90 (1 H, s, CONHC), 9.08 (1 H, t, *J* 6.5, NHCH$_2$), 9.06 (1 H, d, *J* 7.4, NHCH), 8.71 (1 H, s, 5-CH), 8.59 (1 H, t, *J* 5.5, NHCH$_2$), 8.55 (1 H, m, NHCH$_2$), 8.53 (1 H, d, *J* 7.4, NHCH), 8.21 (1 H, s, 5-H), 8.18 (1 H, s, 5-H), 8.10 (1 H, d, *J* 7.6, NHCH), 8.07 (1 H, d, *J* 7.7, NHCH), 7.99 (1 H, d, *J* 10.4, NHCH), 7.94 (1 H, br d, *J* 8.5, NHCH), 7.57 (1 H, d, *J* 9.1, NHCH), 7.54 (1 H, d, *J* 9.3, NHCH), 5.97 (1 H, s, C=CHH), 5.84 (1 H, s, C=CHH), 5.71 (1 H, s, C=CHH), 5.70 (1 H, s, C=CHH), 5.20 (1 H, q, *J* 7.4, NHCHCH$_2$CH), 5.01 (1 H, quin, *J* 7.4, NHCHCH$_3$), 4.72 (1 H, ddd, *J* 10.4, 8.4, 4.4, NHCHCH$_2$CH), 4.65 (1 H, m, NHCHCH(CH$_3$)$_2$), 4.65 (1 H, dd, *J* 17.0, 6.5, NHCHH),

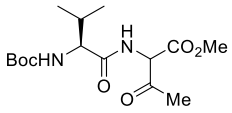
4.60 (1 H, dd, *J* 17.0, 6.5, NHCHH), 4.54 (1 H, m, NHCHCH$_3$), 4.52 (1 H, m, NHCHCH$_2$OH), 4.50 (1 H, m, NHCHCH(CH$_3$)), 4.40 (1 H, dd, *J* 16.7, 5.5, NHCHH), 4.37 (1 H, dd, *J* 16.7, 5.5, NHCHH), 4.21 (1 H, br s, NHCHCH(CH$_3$)$_2$), 3.83 (1 H, dd, *J* 17.0, 5.8, NHCHH), 3.77 (1 H, m, CHCHHOH), 3.75 (1 H, dd, *J* 17.0, 5.8, NHCHH), 3.69 (1 H, m, CHCHHOH), 2.59 (3 H, s, 5-CH$_3$), 2.54 (3 H, s, 5-CH$_3$), 2.52 (3 H, s, 5-CH$_3$), 2.18 (1 H, m, NHCHCH(CH$_3$)$_2$), 2.18 (1 H, m, NHCHCH(CH$_3$)$_2$), 1.88 (1 H, m, NHCHCH(CH$_3$), 1.84 (3 H, s, NHCOCH$_3$), 1.80 (2 H, t, *J* 7.4, NHCHCH$_2$CH), 1.75 (1 H, m, NHCHCHHCH), 1.69 (1 H, m, NHCHCH$_2$CH), 1.62 (1 H, m, NHCHCH$_2$CH), 1.59 (1 H, m, NHCHCHHCH), 1.45 (1 H, m, NHCHCH(CH$_3$)CHH), 1.41 (3 H, d, *J* 7.4, NHCHCH$_3$), 1.38 (3 H, d, *J* 7.1, NHCHCH$_3$), 1.06 (1 H, m, NHCHCH(CH$_3$)CHH), 0.96 (3 H, m, CH$_3$), 0.93 (3 H, m, CH$_3$), 0.91 (3 H, m, CH$_3$), 0.90 (3 H, m, CH$_3$), 0.89 (3 H, m, CH$_3$), 0.89 (3 H, m, CH$_3$), 0.89 (3 H, m, CH$_3$), 0.87 (3 H, m, CH$_3$), 0.87 (3 H, m, CH$_3$), 0.83 (3 H, m, CH$_3$); δ_C (125 MHz; DMSO-d$_6$) 174.7 (C), 174.5 (C), 172.4 (C), 171.9 (C), 170.8 (C), 170.7 (C), 170.3 (C), 170.1 (C), 169.2 (C), 168.8 (C), 162.1 (C), 160.9 (C), 160.7 (C), 160.4 (C), 160.1 (C), 159.8 (C), 159.1 (C), 158.3 (C), 157.9 (C), 155.4 (C), 153.2 (C), 152.9 (C), 152.5 (C), 149.1 (C), 149.0 (C), 142.6 (CH), 136.2 (C), 129.3 (C), 129.1 (C), 129.0 (C), 128.4 (C), 128.2 (C), 124.2 (CH), 124.1 (CH), 109.3 (CH$_2$), 108.1 (CH$_2$), 61.8 (CH$_2$), 57.8 (CH), 57.0 (CH), 56.1 (CH), 54.9 (CH), 51.2 (CH), 49.3 (CH), 48.1 (CH), 43.1 (CH$_2$), 42.2 (CH), 42.1 (CH$_2$), 40.7 (CH$_2$), 40.5 (CH$_2$), 37.4 (CH), 35.7 (CH$_2$), 31.4 (CH), 31.3 (CH), 24.5 (CH), 24.3 (CH), 24.1 (CH$_2$), 23.1 (CH$_3$), 23.0 (CH$_3$), 22.5 (CH$_3$), 21.5 (CH$_3$), 21.1 (CH$_3$), 19.4 (CH$_3$), 19.2 (CH$_3$), 18.8 (CH$_3$), 18.3 (CH$_3$), 18.1 (CH$_3$), 17.9 (CH$_3$), 15.6 (CH$_3$), 11.5 (CH$_3$), 11.4 (CH$_3$), 11.3 (CH$_3$), 10.9 (CH$_3$).

(*S*)-*N*-*tert*-Butoxycarbonylvalinamide 273



To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonylvaline **272** (11.5 g, 52.9 mmol) in dry THF (250 mL) at -15 °C was added triethylamine (8.93 ml, 63.5 mmol) followed by isobutyl chloroformate (8.24 mL, 63.5 mmol) which was added over 10 min. The mixture was stirred for 1 h, after which ammonium hydroxide (d 0.8, 40 mL) was added. The mixture was warmed to room temperature and stirred for 16 h. The mixture was concentrated *in vacuo*, and taken into ethyl acetate (300 mL). The organic layer was washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL) and saturated brine (2 x 200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The resulting solid was recrystallised using ethyl acetate-light petroleum to give the *title compound* as a colourless solid (8.09 g, 71%); mp 153-154 °C (lit.,[142] mp 157 °C); $[\alpha]_D^{25}$ -10.4 (*c* 0.6, $CHCl_3$) (lit.,[151] $[\alpha]_D^{32}$ -5.3 (*c* 0.6, $CHCl_3$)); (Found: M+Na^+, 239.1370. $C_{10}H_{20}N_2O_3$ + Na^+ requires 239.1372); ν_{max} (ATR)/cm^{-1} 3385, 3343, 3197, 2972, 2950, 1683, 1658, 1520, 1172; δ_H (400 MHz; $CDCl_3$) 5.97 (1 H, br s, NH), 5.51 (1 H, br s, NH), 5.05 (1 H, br s, NH), 3.97 (1 H, dd, *J* 8.3, 6.3, NHCH), 2.16 (1 H, septet d, *J* 6.9, 6.3, NHCHCH), 1.46 (9 H, s $C(CH_3)_3$), 1.00 (3 H, d, *J* 6.9, $CH(CH_3)(CH_3)$), 0.95 (3 H, d, *J* 6.9, $CH(CH_3)(CH_3)$); δ_C (125 MHz; $CDCl_3$) 173.9 (C), 155.9 (C), 80.0 (C), 59.4 (CH), 30.6 (CH), 28.3 (CH_3), 19.3 (CH_3), 17.7 (CH_3). Data in agreement with literature.[151]

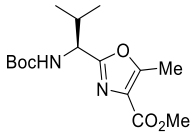
Methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanamido)-3-oxobutanoate 274



Methyl 2-diazo-3-oxobutanoate **136** (0.98 g, 6.94 mmol) in dry chloroform (10 mL) was added dropwise over 2 h to a solution of (*S*)-*N*-*tert*-butoxycarbonylvalinamide **273** (1.01 g, 4.62 mmol) and rhodium(II) acetate dimer (41.0 mg, 2 mol%) in dry chloroform (50 mL) heated under reflux. The reaction mixture was heated under reflux for a further 16 h. The reaction mixture was washed with water (2 x 100 mL), saturated sodium hydrogen carbonate (100 mL) and saturated brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (10-20%)-light petroleum to give the *title compound,* as an mixture of diastereomers (1:0.8), as a colourless solid (1.29 g, 84%); mp 107-108 °C; (Found: M+Na$^+$, 353.1706. $C_{15}H_{26}N_2O_6$ + Na$^+$ requires 353.1689); ν_{max} (ATR)/cm^{-1} 3320, 2958, 1750, 1725, 1686, 1651, 1519, 1269, 1210, 1112; major diastereomer δ_H (500 MHz; $CDCl_3$) 7.19 (1 H, d, *J* 6.1, N<u>H</u>CHCO$_2$CH$_3$), 5.24 (1 H, d, *J* 6.1, NHC<u>H</u>CO$_2$CH$_3$), 5.09 (1 H, d, *J* 5.0, N<u>H</u>CHCH), 4.09 (1 H, dd, *J* 6.6, 5.0, NHC<u>H</u>CH), 3.80 (3 H, s, CO$_2$C<u>H</u>$_3$), 2.38 (3 H, s, COC<u>H</u>$_3$), 2.17 (1 H, septet d, *J* 6.8, 6.6, NHCHC<u>H</u>), 1.44 (9 H, s, C(C<u>H</u>$_3$)$_3$), 0.97 (3 H, d, *J* 6.8, CH(C<u>H</u>$_3$)(CH$_3$)), 0.92 (3 H, d, *J* 6.8 CH(CH$_3$)(C<u>H</u>$_3$)); δ_C (125 MHz; $CDCl_3$) 198.1 (C), 171.5 (C), 166.2 (C), 155.7 (C), 80.0 (C), 62.8 (CH), 59.4 (CH), 53.28 (CH$_3$), 30.7 (CH), 28.2 (CH$_3$), 28.0 (CH$_3$), 19.2 (CH$_3$), 17.2 (CH$_3$); minor diastereomers, the

following signals are discernible δ_H (500 MHz; $CDCl_3$) 7.13 (1 H, d, *J* 6.1, N<u>H</u>CHCO$_2$CH$_3$), 5.07 (1 H, d, *J* 6.5, N<u>H</u>CHCH), 4.07 (1 H, dd, *J* 6.5, 6.0, NHC<u>H</u>CH), 2.20 (1 H, d septet, *J* 6.8, 6.0, NHCHC<u>H</u>), 1.43 (9 H, s, C(C<u>H</u>$_3$)$_3$), 0.90 (3 H, d, *J* 6.8 CH(CH$_3$)(C<u>H</u>$_3$)); δ_C (125 MHz; $CDCl_3$) 198.0 (C), 166.3 (C), 79.9 (C), 62.9 (CH), 59.3 (CH), 53.25 (CH_3), 30.9 (CH), 27.9 (CH_3), 19.1 (CH_3), 17.4 (CH_3).

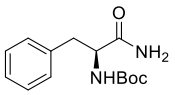
Methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-methylpropyl)-5-methyloxazole-4-carboxylate 269



Triethylamine (1.40 mL, 10.1 mmol) and methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanamido)-3-oxobutanoate **274** (1.21 g, 3.19 mmol) in dry dichloromethane (5 mL) were added sequentially to a stirred solution of triphenylphosphine (1.32 g, 5.02 mmol) and iodine (1.27 g, 5.02 mmol) in dry dichloromethane (20 mL). The mixture was stirred at room temperature for 16 h, washed with water (200 mL), saturated sodium thiosulfate solution (2 x 200 mL), saturated sodium hydrogen carbonate (200 mL) and saturated brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with ethyl acetate (30%)-light petroleum to give the *title compound* as a colourless solid (0.58 g, 73%); mp 83 - 84 °C (lit.,[152] mp 80 - 82 °C);$[\alpha]_D^{25}$ -43.6 (*c* 0.5, $CHCl_3$) (lit.,[152] $[\alpha]_D^{25}$ -28.2 (*c* 0.5, $CHCl_3$)); (Found: M+Na$^+$, 335.1590. $C_{15}H_{24}N_2O_5$ + Na$^+$

requires 335.1583); ν_{max} (ATR)/cm^{-1} 3346, 2968, 2932, 2875, 1716, 1621, 1516, 1366, 1351, 1171, 1099; δ_H (400 MHz; $CDCl_3$) 5.25 (1 H, d, *J* 9.2, NH), 4.72 (1 H, dd, *J* 9.2, 6.2, NHCH), 3.89 (3 H, s, CO_2CH_3), 2.60 (3 H, s, 5-CH_3), 2.16 (1 H, septet d, *J* 6.2, 6.8, NHCHCH), 1.42 (9 H, s, $C(CH_3)_3$), 0.92 (3 H, d, *J* 6.8, $CH(CH_3)(CH_3)$), 0.90 (3 H, s, $CH(CH_3)(CH_3)$); δ_C (125 MHz; $CDCl_3$) 162.7 (C), 162.1 (C), 156.3 (C), 155.3 (C), 127.2 (C), 79.9 (C), 54.0 (CH), 52.0 (CH_3), 32.8 (CH), 28.2 (CH_3), 18.7 (CH_3), 17.9 (CH_3), 12.0 (CH_3). Data in agreement with literature.[152]

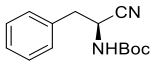
(*S*)-*N*-*tert*-Butoxycarbonylphenylalaninamide 276



To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonylphenylalanine **275** (2.48 g, 9.35 mmol) in dry THF (70 mL) at -15 °C was added triethylamine (1.13 mL, 8.13 mmol) followed by isobutyl chloroformate (1.05 mL, 8.13 mmol) which was added over 10 min. The mixture was stirred for 1 h, after which ammonium hydroxide (d 0.8, 20 mL) was added. The mixture was warmed to room temperature and stirred for 16 h. The mixture was concentrated *in vacuo*, and taken into ethyl acetate (100 mL). The organic layer was washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL) and saturated brine (2 x 100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The resulting solid was recrystallised using ethyl acetate-light petroleum to give the *title compound* as a colourless solid (1.51 g, 61%); mp 142-143 °C (lit.,[142] mp 148 °C); $[\alpha]_D^{25}$ +8.7 (*c* 1, CH_3OH) (lit.,[153] $[\alpha]_D^{20}$

+10.7 (*c* 1, CH_3OH)); (Found: M+Na^+, 287.1345. $C_{14}H_{20}N_2O_3$ + Na^+ requires 287.1372); ν_{max} (ATR)/cm^{-1} 3323, 2978, 2931, 1673, 1367, 1167; δ_H (400 MHz; $CDCl_3$) 7.36 - 7.24 (5 H, m, ArH), 6.08 (1 H, br s, NHH), 5.81 (1 H, br s, NHH), 5.22 (1 H, d, *J* 6.9, NHCH), 4.47 - 4.39 (1 H, m, NHCH), 3.14 - 3.05 (2 H, m, $CHCH_2$), 1.43 (9 H, s, $C(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 173.9 (C), 155.5 (C), 136.6 (C), 129.3 (CH), 128.6 (CH), 126.9 (CH), 80.2 (C), 55.3 (CH), 38.4 (CH_2), 28.2 (CH_3). Data in agreement with literature.[153]

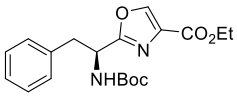
tert-Butyl (*S*)-(1-cyano-2-phenylethyl)carbamate 277



To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonylphenylalaninamide **276** (0.91 g, 3.44 mmol) in dichloromethane (20 mL) at 0 °C was added DBU (2.83 mL, 18.9 mmol). The solution was stirred for 10 min then ethyl dichlorophosphate (1.35 mL, 11.3 mmol) was added over 5 min. The mixture was warmed to room temperature and stirred for 4 h. The mixture was cooled to 0 °C and saturated ammonium chloride (30 mL) was added, and the mixture was stirred for 10 min. The mixture was extracted with dichloromethane (2 x 80 mL) and the combined organic layers washed with saturated brine (200 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (10%)-light petroleum to give the *title compound* as a colourless solid (0.68 g, 80%); mp 112-113 °C (lit.,[141] mp 114-115 °C); $[\alpha]_D^{25}$ -18.0 (*c* 0.5 $CHCl_3$) (lit.,[154] $[\alpha]_D^{25}$ -26.6 (*c* 0.5, $CHCl_3$)); (Found:

M+Na$^+$, 269.1261. $C_{14}H_{18}N_2O_2$ + Na$^+$ requires 269.1266); ν_{max} (ATR)/cm^{-1} 3354, 1689, 1519; δ_H (400 MHz; $CDCl_3$) 7.41 - 7.28 (5 H, m, ArH), 4.83 (2 H, br s, NHCH), 3.12 (1 H, dd, *J* 13.8, 5.5, CHH), 3.06 (1 H, dd, *J* 13.8, 6.9, CHH), 1.45 (9 H, s, C(CH_3)$_3$); δ_C (125 MHz; $CHCl_3$) 154.1 (C), 133.9 (C), 129.5 (CH), 129.0 (CH), 127.9 (CH), 118.3 (C), 81.3 (C), 43.3 (CH), 39.1 (CH_2), 28.2 (CH_3). Data in agreement with literature.[154]

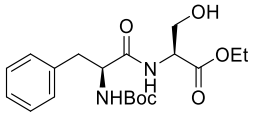
Ethyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-phenylethyl)oxazole-4-carboxylate 270



Ethyl 2-diazo-3-oxopropanoate **190** (0.26 g, 1.8 mmol) in 1,2-dichloroethane (1 mL) was added dropwise over 12 h to a stirred solution of *tert*-butyl (*S*)-(1-cyano-2-phenylethyl)carbamate **277** (0.15 g, 0.61 mmol) and dirhodium (II) tetrakis(perfluorobutyramide) (0.012 g, 2.5 mol%) in 1,2-dichloroethane (0.5 mL) under reflux. The mixture was concentrated *in vacuo* and purified by chromatography on silica, eluting with ethyl acetate (10-20%)-light petroleum to give the *title compound* as a colourless solid (90 mg, 40%); mp 69-70 °C; $[\alpha]_D^{25}$ -18.6 (*c* 1, CH_3OH); (Found: M+H$^+$, 361.1761. $C_{19}H_{24}N_2O_5$ + H$^+$ requires 361.1764); ν_{max} (ATR)/cm^{-1} 3351, 2979, 2934, 1716, 1582, 1516, 1368, 1317, 1170; δ_H (400 MHz; $CDCl_3$) 8.12 (1 H, s, 5-H), 7.28 - 7.19 (4 H, m, ArH, NH), 7.08 - 7.03 (2 H, m, ArH), 5.23 (1 H, br s, NHCH), 4.39 (2 H, q, *J* 7.2, $CO_2CH_2CH_3$), 3.27 - 3.18 (2 H, m, $CHCH_2$), 1.41 (9 H, s, C(CH_3)$_3$), 1.38 (3 H, t, *J* 7.2, $CO_2CH_2CH_3$); δ_C

(100 MHz; $CHCl_3$) 164.6 (C), 161.1 (C), 154.8 (C), 143.7 (CH), 135.6 (C), 133.5 (C), 129.2 (CH), 128.6 (CH), 127.0 (CH), 80.2 (C), 61.3 (CH_2), 50.1 (CH), 40.4 (CH_2), 28.2 (CH_3), 14.3 (CH_3).

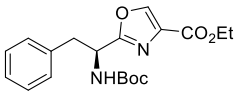
Ethyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanamido)-3-hydroxy-propanoate 278



To a stirred solution of (*S*)-*N*-*tert*-butoxycarbonylphenylalanine **275** (0.98 g, 3.7 mmol) and (*S*)-serine ethyl ester hydrochloride (0.75 g, 4.4 mmol) in dimethylformamide/dichloromethane (1:1; 30 mL) at 0 °C, was added *N,N*-diisopropylethylamine (3.2 mL, 18 mmol) and HATU (2.8 g, 7.4 mmol). The mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was taken into water (300 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with hydrochloric acid (1 M; 200 mL), saturated sodium hydrogen carbonate (200 mL), lithium chloride solution (10%; 3 x 200 mL), water (200 mL) and saturated brine (200 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (40-60%)-light petroleum to give the *title compound* as a colourless solid (1.2 g, 86%); mp 110-111 °C (lit.,[155] mp 112-114 °C); $[\alpha]_D^{24}$ +11.0 (*c* 1, CH_3OH); (Found: M+Na^+, 403.1842. $C_{19}H_{28}N_2O_6$ + Na^+ requires 403.1845); ν_{max} (ATR)/cm^{-1} 3367, 2980, 2937, 1737, 1657, 1526, 1367, 1250, 1168; δ_H (400 MHz; CD_3OD) 7.31 - 7.16 (5 H, m, ArH),

4.51 (1 H, br s C<u>H</u>CH_2OH), 4.38 (1 H, dd, *J* 8.3, 4.9, C<u>H</u>CH_2Ar), 4.19 (2 H, q, *J* 7.2, C<u>H</u>$_2CH_3$), 3.90 (1 H, dd, *J* 11.2, 3.9, C<u>H</u>HOH), 3.81 (1 H, dd, *J* 11.2, 3.4, CH<u>H</u>OH), 3.16 (1 H, dd, *J* 13.3, 4.9, C<u>H</u>HAr), 2.82 (1 H, dd, *J* 13.3, 8.3, CH<u>H</u>Ar), 1.36 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.27 (3 H, t, *J* 7.2, CH_2C<u>H</u>$_3$); δ_C (100 MHz; CD_3OD) 174.6 (C), 171.6 (C), 157.8 (C), 136.8 (C), 130.5 (CH), 129.5 (CH), 127.8 (CH), 80.8 (C), 63.0 (CH_2), 62.7 (CH_2), 57.4 (CH), 56.4 (CH), 39.3 (CH_2), 28.8 (CH_3), 14.6 (CH_3). Data in agreement with literature.[156]

Ethyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-phenylethyl)oxazole-4-carboxylate 270

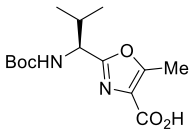


To a stirred solution of ethyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanamido)-3-hydroxy-propanoate **278** (0.67 g, 1.8 mmol) in THF (20 mL) at -78 °C was added DAST (0.26 mL, 1.9 mmol) dropwise over 15 min. The reaction mixture was stirred at -78 °C for 2 h. Potassium carbonate (0.735 g, 5.32 mmol) was added and the mixture was warmed to room temperature. The mixture was concentrated *in vacuo* and taken into ethyl acetate (100 mL). The organic solution was washed with saturated sodium hydrogen carbonate (100 mL). The aqueous layer was extracted twice with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with saturated brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the oxazoline **279** as a

colourless solid (0.49 g, 77%), which was used immediately without further purification.

To a stirred solution of the oxazoline **279** (0.49 g, 1.4 mmol) in dichloromethane (20 mL) at 0 °C was added DBU (0.43 mL, 2.9 mmol) then after 5 min, bromotrichloromethane (0.29 mL, 2.9 mmol) was added dropwise over 10 min. The reaction was warmed to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and saturated ammonium chloride (40 mL) was added. The mixture was separated and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic layers were washed with saturated ammonium chloride (100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (10-20%)-light petroleum to give the *title compound* as a colourless solid (0.24 g, 49%). Data in agreement with previously prepared sample **270** (see page 215).

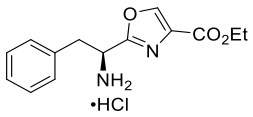
(*S*)-2-(1-(*tert*-Butoxycarbonylamino)-2-methylpropyl)-5-methyloxazole-4-carboxylic acid 280



Lithium hydroxide monohydrate (0.504 g, 12.01 mmol) was added to methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-methylpropyl)-5-methyloxazole-4-carboxylate **269** (0.938 g, 3.00 mmol) in methanol/water (4:1; 30 mL). The

reaction mixture was stirred at 35 °C for 2 h. The mixture was concentrated *in vacuo*, taken into water (50 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (4 x 30 mL) and the combined organic extracts washed with saturated brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless oil (0.90 g, 100%); mp 61 - 62 °C; $[\alpha]_D^{25}$ -65.1 (*c* 1, CH_3OH); (Found: M-H^+, 297.1459. $C_{14}H_{22}N_2O_5$ - H^+ requires 297.1451); ν_{max} (ATR)/cm^{-1} 3304, 2969, 2932, 2877, 1700, 1628, 1523, 1392, 1163; δ_H (400 MHz; $CDCl_3$) 6.40 (1 H, d, *J* 9.6, NH), 4.75 (1 H, dd, *J* 9.6, 6.6, NHCH), 2.65 (3 H, s, 5-CH_3), 2.20 (1 H, septet d, *J* 6.8, 6.6, NHCHCH), 1.41 (9 H, s, $C(CH_3)_3$), 0.98 (3 H, d, *J* 6.8, $CH(CH_3)(CH_3)$), 0.92 (3 H, d, *J* 6.8, $CH(CH_3)(CH_3)$); δ_C (100 MHz; $CDCl_3$) 164.8 (C), 163.6 (C), 157.1 (C), 155.1 (C), 126.9 (C), 79.7 (C), 54.3 (CH), 32.8 (CH), 28.3 (CH_3), 18.9 (CH_3), 18.2 (CH_3), 11.9 (CH_3). Data in agreement with literature.[157]

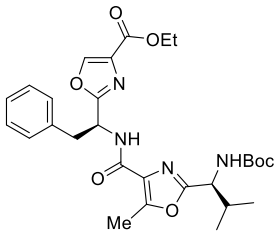
Ethyl (*S*)-2-(1-amino-2-phenylethyl)oxazole-4-carboxylate hydrochloride 281



To ethyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-phenylethyl)oxazole-4-carboxylate **270** (0.44 g, 1.2 mmol) was added hydrogen chloride in dioxane (4 M; 1.2 mL, 4.8 mmol) and the mixture was stirred for 4 h at room temperature. The mixture was concentrated *in vacuo* and triturated with ether to give the *title compound* as a colourless solid (0.35 g, 97%); mp 50 - 51 °C; $[\alpha]_D^{26}$ +91.8 (*c*

1, $CHCl_3$); (Found: M+H$^+$, 261.1236. $C_{14}H_{16}N_2O_3$ + H$^+$ requires 261.1239); ν_{max} (ATR)/cm^{-1} 2980, 2866, 1721, 1579, 1497, 1374, 1338, 1112; δ_H (400 MHz; $CDCl_3$) 9.43 (2 H, br s, N<u>H</u>$_2$), 8.07 (1 H, s, 5-CH), 7.19 (5 H, s, ArH), 5.05 (1 H, dd, *J* 9.4, 4.1, NH$_2$C<u>H</u>), 4.21 (2 H, q, *J* 6.8, C<u>H</u>$_2$CH$_3$), 3.68 (1 H, dd, *J* 13.2, 4.1, CHC<u>H</u>H), 3.51 (1 H, dd, *J* 13.2, 9.4, CHCH<u>H</u>), 1.27 (3 H, t, *J* 6.8, CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 161.5 (C), 160.4 (C), 144.7 (CH), 134.1 (C), 133.1 (C), 129.5 (CH), 128.7 (CH), 127.4 (CH), 61.7 (CH_2), 50.7 (CH), 38.1 (CH_2), 14.1 (CH_3).

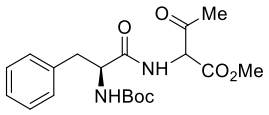
Ethyl 2-((*S*)-1-(2-((*S*)-1-(*tert*-butoxycarbonylamino)-2-methylpropyl)-5-methyloxazole-4-carboxamido)-2-phenylethyl)oxazole-4-carboxylate 266



To a stirred solution of (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-methylpropyl)-5-methyloxazole-4-carboxylic acid **280** (0.406 g, 1.36 mmol) and ethyl (*S*)-2-(1-amino-2-phenylethyl)oxazole-4-carboxylate hydrochloride **281** (0.404 g, 1.37 mmol) in dimethylformamide (14 mL), was added *N,N*-diisopropylethylamine (1.01 mL, 5.44 mmol) and HATU (1.03 g, 2.63 mmol) and HOAt (0.18 g, 1.36 mmol) and the mixture was stirred for 16 h. The reaction mixture was taken into water (150 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated

sodium hydrogen carbonate (100 mL), lithium chloride solution (10%; 3 x 100 mL), water (100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (20 - 40%)-light petroleum to give the *title compound* as a colourless oil (0.63 g, 86%); $[\alpha]_D^{26}$ -37.4 (*c* 1, $CHCl_3$); (Found: M+Na^+, 563.2482. $C_{28}H_{36}N_4O_7$ + Na^+ requires 563.2482); ν_{max} (ATR)/cm^{-1} 3304, 2974, 2932, 2875, 1742, 1714, 1668, 1514, 1368, 1172, 1111; δ_H (400 MHz; $CDCl_3$) 8.09 (1 H, s, 5-H), 7.47 (1 H, d, *J* 8.6, N<u>H</u>CHCH_2), 7.26 - 7.20 (3 H, m, ArH), 7.15 - 7.11 (2 H, m, ArH), 5.61 (1 H, ddd, *J* 8.6, 7.2, 7.0, NHC<u>H</u>CH_2), 5.10 (1 H, d, *J* 8.7, N<u>H</u>CHCH), 4.70 (1 H, dd, *J* 8.7, 6.0, NHC<u>H</u>CH), 4.39 (2 H, q, *J* 7.1, OC<u>H</u>$_2$CH_3), 3.37 (1 H, dd, *J* 13.7, 7.2, CHC<u>H</u>H), 3.33 (1 H, dd, *J* 13.7, 7.0, CHCH<u>H</u>), 2.58 (3 H, s, 5-CH_3), 2.51 (1 H, septet d, *J* 6.8, 6.0, NHCHC<u>H</u>), 1.46 (9 H, s, C(C<u>H</u>$_3$)$_3$), 1.38 (3 H, t, *J* 7.1, OCH$_2$C<u>H</u>$_3$), 0.93 (3 H, d, *J* 6.8, CH(C<u>H</u>$_3$)(CH$_3$), 0.92 (3 H, d, *J* 6.8, CH(CH$_3$)(C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 164.2 (C), 161.3 (C), 161.1 (C), 160.8 (C), 155.3 (C), 153.4 (C), 143.7 (CH), 135.7 (C), 133.7 (C), 129.2 (CH), 128.6 (CH), 128.3 (C), 127.1 (CH), 80.1 (C), 61.3 (CH_2), 53.9 (CH), 48.2 (CH), 40.1 (CH_2), 32.6 (CH), 28.3 (CH_3), 18.6 (CH_3), 17.9 (CH_3), 14.3 (CH_3), 11.6 (CH_3).

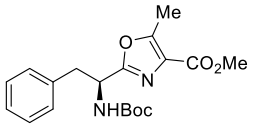
Methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanamido)-3-oxobutanoate 282



Methyl 2-diazo-3-oxobutanoate **136** (1.21 g, 8.51 mmol) in dry chloroform (15 mL) was added dropwise over 3 h to a solution of (*S*)-*N*-*tert*-butoxycarbonylphenylalaninamide **276** (1.54 g, 5.83 mmol) and rhodium(II) acetate dimer (50.0 mg, 2 mol%) in dry chloroform (60 mL) heated under reflux. The reaction mixture was heated under reflux for a further 16 h. The reaction mixture was washed with water (2 x 100 mL), saturated sodium hydrogen carbonate (100 mL) and saturated brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (10-20%)-light petroleum to give the *title compound,* as an mixture of diastereomers (1:0.8), as a colourless oil (1.61 g, 75%); (Found: M+Na^+, 401.1684. $C_{19}H_{26}N_2O_6$ + Na^+ requires 401.1689); ν_{max} (ATR)/cm^{-1} 3325, 2978, 2932, 1752, 1725, 1659, 1497, 1366, 1159; major diastereomer δ_H (400 MHz; $CDCl_3$) 7.44 - 7.38 (1 H, m, N<u>H</u>CHCO$_2$CH$_3$), 7.36 - 7.30 (2 H, m, ArH), 7.29 - 7.24 (3 H, m, ArH), 5.33 – 5.27 (2 H, m, N<u>H</u>CHCH$_2$, C<u>H</u>CO$_2$CH$_3$), 4.59 (1 H, br s, NHC<u>H</u>CH$_2$), 3.83 (3 H, s, CO$_2$C<u>H</u>$_3$), 3.19 (1 H, dd, *J* 14.2, 6.3, CHC<u>H</u>H), 3.12 - 3.03 (1 H, m, CHCH<u>H</u>), 2.39 (3 H, s, COC<u>H</u>$_3$), 1.440 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 197.9 (C), 171.4 (C), 166.1 (C), 155.3 (C), 137.4 (C), 129.2 (CH), 128.40 (CH), 126.71 (CH), 80.0 (C), 62.67 (CH), 55.1 (CH), 53.09 (CH_3), 37.88 (CH_2), 28.0 (CH_3), 27.7 (CH_3); minor diastereomer, the

following signals are discernible δ_H (400 MHz; $CDCl_3$) 3.82 (3 H, s, $CO_2C\underline{H}_3$), 2.35 (3 H, s, $COC\underline{H}_3$), 1.436 (9 H, s, $C(C\underline{H}_3)_3$); δ_C (100 MHz; $CDCl_3$) 198.3 (C), 166.3 (C), 136.3 (C), 129.1 (CH), 128.37 (CH), 126.68 (CH), 79.9 (C), 62.71 (CH), 53.11 (CH_3), 37.85 (CH_2), 27.6 (CH_3).

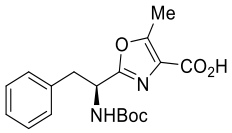
Methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-phenylethyl)-5-methyloxazole-4-carboxylate 271



Triethylamine (1.85 mL, 12.8 mmol) and methyl 2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanamido)-3-oxobutanoate **282** (1.21 g, 3.19 mmol) in dry dichloromethane (8 mL) were added sequentially to a stirred solution of triphenylphosphine (1.68 g, 6.39 mmol) and iodine (1.63 g, 6.39 mmol) in dry dichloromethane (30 mL). The mixture was stirred at room temperature for 16 h. The reaction mixture was washed with water (200 mL), saturated sodium thiosulfate solution (2 x 200 mL), saturated sodium hydrogen carbonate (200 mL) and saturated brine (200 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica eluting with ethyl acetate (20%)-light petroleum to give the *title compound* as a colourless solid (0.97 g, 84%); mp 108-109 °C (lit.,[158] mp 98-99 °C); $[\alpha]_D^{25}$ -38.0 (*c* 1, $CHCl_3$); (Found: M+H$^+$, 361.1757. $C_{19}H_{24}N_2O_5$ + H$^+$ requires 361.1764); ν_{max} (ATR)/cm^{-1} 3340, 2978, 1718, 1689, 1522, 1367, 1351, 1170, 1099; δ_H (400 MHz; $CDCl_3$) 7.26 - 7.18 (3 H, m, ArH), 7.08 - 7.03 (2 H, m, ArH),

5.22 - 5.10 (2 H, m, NHCH), 3.90 (3 H, s, CO_2CH_3), 3.22 (1 H, dd, *J* 13.8, 6.1, CHCHH), 3.16 (1 H, dd, *J* 13.8, 6.4, CHCHH), 2.56 (3 H, s, 5-CH_3), 1.39 (9 H, s, $C(CH_3)_3$); δ_C (125 MHz; $CDCl_3$) 162.8 (C), 161.7 (C), 156.4 (C), 154.8 (C), 135.7 (C), 129.2 (CH), 128.5 (CH), 127.3 (CH), 126.9 (C), 80.0 (C), 52.0 (CH_3), 49.9 (CH), 40.3 (CH_2), 28.2 (CH_3), 11.9 (CH_3).Data in agreement with literature .[158]

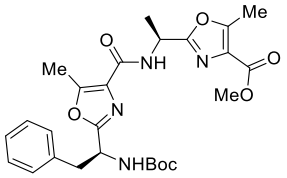
(*S*)-2-(1-(*tert*-Butoxycarbonylamino)-2-phenylethyl)-5-methyloxazole-4-carboxylic acid 283



Lithium hydroxide monohydrate (0.176 g, 4.21 mmol) was added to methyl (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-phenylethyl)-5-methyloxazole-4-carboxylate **271** (0.379 g, 1.05 mmol) in methanol/water (4:1; 10 mL). The reaction mixture was stirred at room temperature for 7 h. The mixture was concentrated *in vacuo*, taken into water (20 mL) and acidified to pH 2 with hydrochloric acid (1 M). The aqueous solution was extracted with ethyl acetate (4 x 30 mL) and the combined organic extracts washed with saturated brine (100 mL), dried with Na_2SO_4, filtered and concentrated *in vacuo* to give the *title compound* as a colourless oil (0.34 g, 93%); mp 172-173 °C; $[\alpha]_D^{26}$ -36.4 (*c* 1, $CHCl_3$); (Found: M-H^+, 345.1447. $C_{18}H_{22}N_2O_5$ - H^+ requires 345.1451); ν_{max} (ATR)/cm^{-1} 3320, 2977, 1700, 1367, 1167; δ_H (400 MHz; $CDCl_3$) 7.30 - 7.20 (3 H, m, ArH), 7.14 – 7.10 (2 H, m, ArH), 6.11 (1 H, d, *J* 6.9, NH), 5.18 (1 H, ddd, *J* 7.4, 7.0, 6.9, NHCH), 3.23 (1 H, dd, *J* 13.6, 7.0, CHCHH), 3.22 - 3.19 (1 H, m, CHCHH),

2.59 (3 H, s, 5-CH_3), 1.38 (9 H, s, C($C\underline{H}_3$)$_3$); δ_C (100 MHz; $CDCl_3$) 164.9 (C), 163.1 (C), 157.2 (C), 155.3 (C), 135.9 (C), 129.3 (CH), 128.5 (CH), 126.99 (CH), 126.97 (C), 80.0 (C), 50.1 (CH), 40.5 (CH_2), 28.2 (CH_3), 11.9 (CH_3).

Methyl 2-((*S*)-1-(2-((*S*)-1-(*tert*-butoxycarbonylamino)-2-phenylethyl)-5-methyloxazole-4-carboxamido)ethyl)-5-methyloxazole-4-carboxylate 268



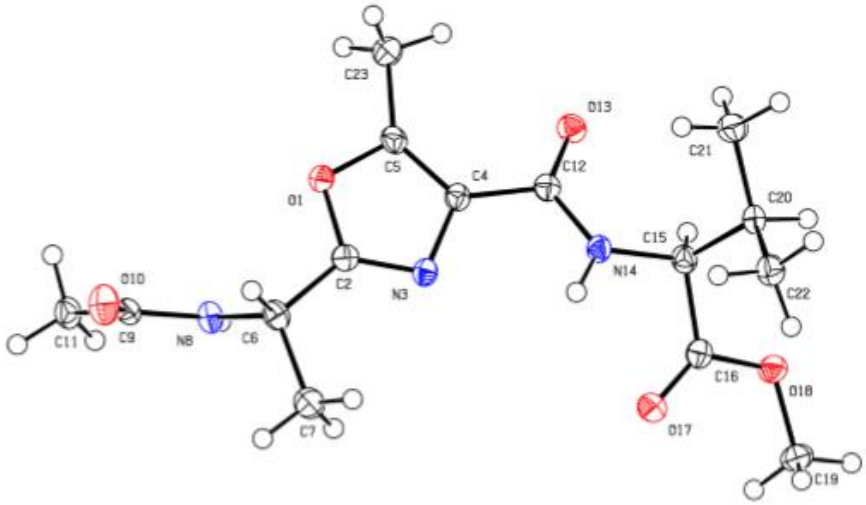
To a stirred solution of (*S*)-2-(1-(*tert*-butoxycarbonylamino)-2-phenylethyl)-5-methyloxazole-4-carboxylic acid **283** (0.14 g, 0.039 mmol) and methyl (*S*)-2-(1-aminoethyl)-5-methyloxazole-4-carboxylate hydrochloride **203** (0.086 g, 0.39 mmol) in dimethylformamide (4 mL), was added *N,N*-diisopropylethylamine (0.27 mL, 1.6 mmol) and HATU (0.29 g, 0.78 mmol and the mixture was stirred for 5 h. The reaction mixture was taken into water (100 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic layers were washed with hydrochloric acid (1 M; 100 mL), saturated sodium hydrogen carbonate (100 mL), lithium chloride solution (10%; 3 x 100 mL), water (100 mL) and saturated brine (100 mL), dried using Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica, eluting with ethyl acetate (50%)-light petroleum to give the *title compound* as a colourless solid (0.18 g, 88%); mp 153-154 °C; $[\alpha]_D^{25}$ -19.4 (*c* 1, $CHCl_3$); (Found: C, 60.9; H, 6.3; N, 10.8.

$C_{26}H_{32}N_4O_7$ requires C, 60.9; H, 6.3; N, 10.9%); (Found: M+Na^+, 535.2167. $C_{26}H_{32}N_4O_7$ + Na^+ requires 535.2169); ν_{max} (ATR)/cm^{-1} 3293, 2978, 2930, 1717, 1667, 1650, 1629, 1516, 1172; δ_H (400 MHz; $CDCl_3$) 7.34 - 7.28 (2 H, m, ArH, NHCHCH_3), 7.26 - 7.20 (2 H, m, ArH), 7.07 - 7.02 (2 H, m, ArH), 5.40 (1 H, dq, *J* 8.5, 7.2, NHC<u>H</u>CH_3), 5.15 - 5.01 (2 H, m, N<u>H</u>C<u>H</u>CH_2), 3.90 (3 H, s, CO_2C<u>H</u>$_3$), 3.23 (1 H, dd, *J* 13.7, 5.8, CHC<u>H</u>H), 3.14 (1 H, dd, *J* 13.7, 4.4, CHCH<u>H</u>), 2.61 (3 H, s, 5-CH_3), 2.59 (3 H, s, 5-CH_3), 1.64 (3 H, d, *J* 7.2, NHCHC<u>H</u>$_3$), 1.42 (9 H, s, C(C<u>H</u>$_3$)$_3$); δ_C (125 MHz; $CDCl_3$) 162.6 (C), 162.4 (C), 161.1 (C), 160.4 (C), 156.6 (C), 154.8 (C), 153.7 (C), 135.7 (C), 129.3 (CH), 128.48 (CH), 128.46 (C), 127.3 (C), 127.0 (CH), 80.2 (C), 52.0 (CH_3), 49.8 (CH), 42.3 (CH), 40.0 (CH_2), 28.3 (CH_3), 19.7 (CH_3), 12.0 (CH_3), 11.6 (CH_3).

5.3 X-Ray Crystal Structures

X-Ray crystal structure of compound 208 and experimental detail

ref. CCDC 1519990

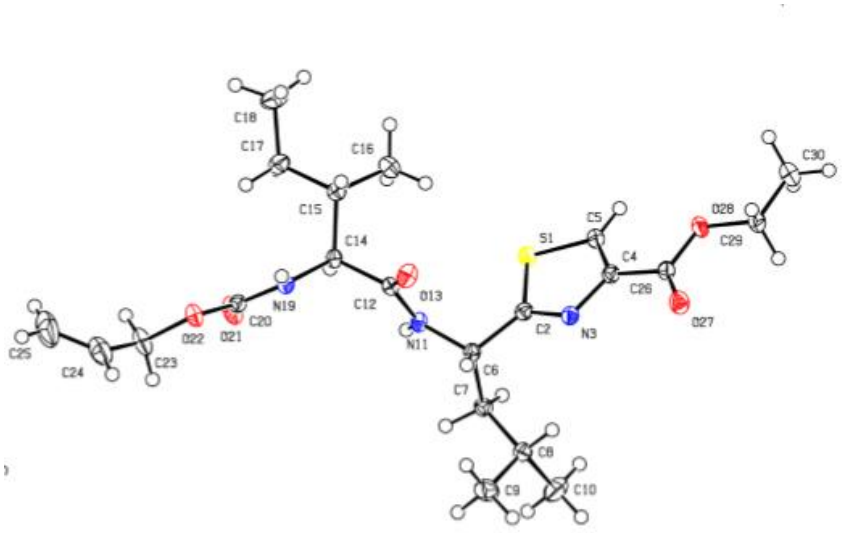


Empirical formula	$C_{15}H_{23}N_3O_5$
Formula weight	325.36
Temperature/K	120
Crystal system, space group	Monoclinic, $P2_1$
a, b, c/Å	4.9861(4), 16.7793(14), 10.0491(9)
α, β, γ/°	90, 92.768(8), 90
Volume/$Å^3$	839.76(12)
Z	2
$\rho_{calc}g/cm^3$	1.287
μ/mm^{-1}	0.810
F(000)	348.0
Crystal size/mm^3	0.851 × 0.1015 × 0.0517
Radiation	CuKα (λ = 1.54184)

2Θ range for data collection/°	8.81 to 148.812
Index ranges	-6 ≤ h ≤ 5, -20 ≤ k ≤ 20, -11 ≤ l ≤ 12
Reflections collected	5884
Independent reflections	3304 [R_{int} = 0.0384, R_{sigma} = 0.0456]
Data/restraints/parameters	3304/1/220
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0386, wR_2 = 0.0984
Final R indexes [all data]	R_1 = 0.0403, wR_2 = 0.1016
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.26
Flack parameter	-0.07(13)
Diffractometer	SuperNova, Dual, Atlas diffractometer

X-Ray crystal structure of compound 230 and experimental detail

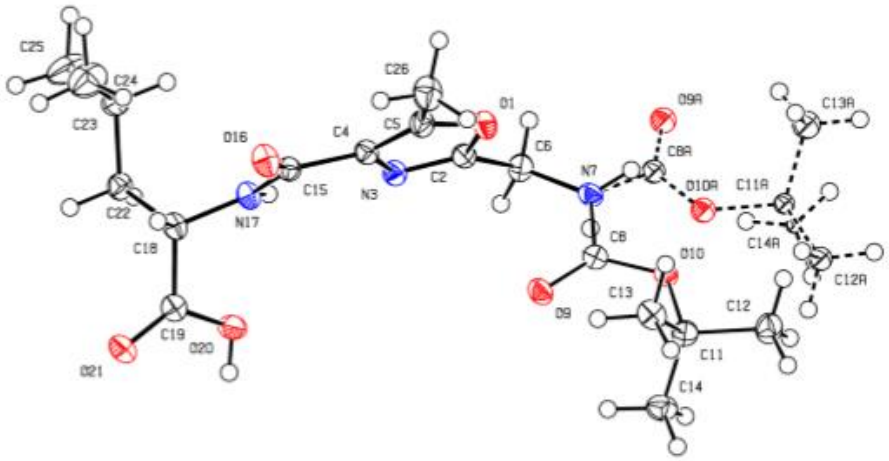
ref. CCDC 1519991



Empirical formula	$C_{21}H_{33}N_3O_5S$
Formula weight	439.56
Temperature/K	120

Crystal system, space group	Monoclinic, $P2_1$
a, b, c/Å	16.3748(6), 4.85200(13), 16.9489(6)
α, β, γ /°	90, 118.852(5), 90
Volume/Å^3	1179.44(8)
Z	2
ρ_{calc}g/cm^3	1.238
μ/mm^{-1}	1.512
F(000)	472.0
Crystal size/mm^3	0.4491 × 0.0443 × 0.0304
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.954 to 148.552
Index ranges	-20 ≤ h ≤ 16, -5 ≤ k ≤ 5, -18 ≤ l ≤ 21
Reflections collected	10066
Independent reflections	4467 [R_{int} = 0.0194, R_{sigma} = 0.0250]
Data/restraints/parameters	4467/1/282
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1 = 0.0250, wR_2 = 0.0621
Final R indexes [all data]	R_1 = 0.0259, wR_2 = 0.0628
Largest diff. peak/hole / e Å^{-3}	0.18/-0.22
Flack parameter	0.007(7)
Diffractometer	GV1000, Atlas diffractometer

X-Ray crystal structure of compound 242 and experimental detail



Empirical formula	$C_{19}H_{33}N_3O_7S$
Formula weight	447.54
Temperature/K	120
Crystal system, space group	Monoclinic, $P2_1$
a, b, c/Å	5.17746(8), 19.9553(3), 11.0102(2)
α, β, γ /°	90, 94.3799(16), 90
Volume/Å^3	1134.23(3)
Z	2
ρ_{calc}g/cm^3	1.310
μ/mm^{-1}	1.648
F(000)	480.0
Crystal size/mm^3	0.7806 × 0.0927 × 0.0385
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.054 to 148.7
Index ranges	-6 ≤ h ≤ 6, -24 ≤ k ≤ 24, -11 ≤ l ≤ 13
Reflections collected	16503
Independent reflections	4600 [R_{int} = 0.0528, R_{sigma} = 0.0366]
Data/restraints/parameters	4600/56/312
Goodness-of-fit on F^2	1.022

Final R indexes [I>=2σ (I)]	R_1 = 0.0393, wR_2 = 0.1060
Final R indexes [all data]	R_1 = 0.0404, wR_2 = 0.1068
Largest diff. peak/hole / e Å^{-3}	0.24/-0.33
Flack parameter	0.005(11)
Diffractometer	GV1000, TitanS2 diffractometer

6. References

1. P. G. Arnison, M. J. Bibb, G. Bierbaum, A. A. Bowers, T. S. Bugni, G. Bulaj, J. A. Camarero, D. J. Campopiano, G. L. Challis, J. Clardy, P. D. Cotter, D. J. Craik, M. Dawson, E. Dittmann, S. Donadio, P. C. Dorrestein, K.-D. Entian, M. A. Fischbach, J. S. Garavelli, U. Göransson, C. W. Gruber, D. H. Haft, T. K. Hemscheidt, C. Hertweck, C. Hill, A. R. Horswill, M. Jaspars, W. L. Kelly, J. P. Klinman, O. P. Kuipers, J. A. Link, W. Liu, M. A. Marahiel, D. A. Mitchell, G. N. Moll, B. S. Moore, R. Müller, S. K. Nair, I. F. Nes, G. E. Norris, B. M. Olivera, H. Onaka, M. L. Patchett, J. Piel, M. J. T. Reaney, S. Rebuffat, P. R. Ross, H.-G. Sahl, E. W. Schmidt, M. E. Selsted, K. Severinov, B. Shen, K. Sivonen, L. Smith, T. Stein, R. D. Süssmuth, J. R. Tagg, G.-L. Tang, A. W. Truman, J. C. Vederas, C. T. Walsh, J. D. Walton, S. C. Wenzel, J. M. Willey, and W. A. van der Donk, *Nat. Prod. Rep.*, 2013, **30**, 108–160.

2. C. L. Cox, J. R. Doroghazi, and D. A. Mitchell, *BMC Genomics*, 2015, **16**, 778.

3. M. A. Marahiel, *J. Pept. Sci.*, 2009, **15**, 799–807.

4. P. Vlieghe, V. Lisowski, J. Martinez, and M. Khrestchatisky, *Drug Discov. Today*, 2010, **15**, 40–56.

5. M. V. Metelev and D. A. Ghilarov, *Mol. Biol.*, 2014, **48**, 29–45.

6. K. C. Nicolaou, B. S. Safina, M. Zak, S. H. Lee, M. Nevalainen, M. Bella, A. A. Estrada, C. Funke, F. J. Zécri, and S. Bulat, *J. Am. Chem. Soc.*, 2005, **127**,

11159–11175.

7. K. C. Nicolaou, M. Zak, B. S. Safina, A. A. Estrada, S. H. Lee, and M. Nevalainen, *J. Am. Chem. Soc.*, 2005, **127**, 11176–11183.

8. H. Shimamura, H. Gouda, K. Nagai, T. Hirose, M. Ichioka, Y. Furuya, Y. Kobayashi, S. Hirono, T. Sunazuka, and S. Omura, *Angew. Chem. Int. Ed.*, 2009, **48**, 914–917.

9. A. J. Scupham and E. W. Triplett, *J. Appl. Microbiol.*, 2006, **100**, 500–507.

10. A. Buyer, S. Freund, G. Nicholson, and G. Jung, *Angew. Chem. Int. Ed.*, 1993, **32**, 1336–1339.

11. Y. M. Li, J. C. Milne, L. L. Madison, R. Kolter, and C. T. Walsh, *Science*, 1996, **274**, 1188–1193.

12. J. O. Melby, N. J. Nard, and D. A. Mitchell, *Curr. Opin. Chem. Biol.*, 2011, **15**, 369–378.

13. G. Videnov, D. Kaiser, M. Brooks, and G. Jung, *Angew. Chem. Int. Ed.*, 1996, **35**, 1506–1508.

14. R. E. Thompson, K. A. Jolliffe, and R. J. Payne, *Org. Lett.*, 2011, **13**, 680–683.

15. R. E. Thompson, F. Collin, A. Maxwell, K. A. Jolliffe, and R. J. Payne, *Org. Biomol. Chem.*, 2014, **12**, 1570–1578.

16. R. Scholz, K. J. Molohon, J. Nachtigall, J. Vater, A. L. Markley, R. D. Süssmuth, D. A. Mitchell, and R. Borriss, *J. Bacteriol.*, 2011, **193**, 215–

224.

17. K. J. Molohon, J. O. Melby, J. Lee, B. S. Evans, K. L. Dunbar, S. B. Bumpus, N. L. Kelleher, and D. A. Mitchell, *ACS Chem. Biol.*, 2011, **6**, 1307–1313.

18. S. Banala, P. Ensle, and R. D. Süssmuth, *Angew. Chem. Int. Ed.*, 2013, **52**, 9518–9523.

19. Z. E. Wilson, S. Fenner, and S. V. Ley, *Angew. Chem. Int. Ed.*, 2015, **54**, 1284–1288.

20. N. Liu, L. Song, M. Liu, F. Shang, Z. Anderson, D. J. Fox, G. L. Challis, and Y. Huang, *Chem. Sci.*, 2016, **7**, 482–488.

21. Z. J. Anderson and D. J. Fox, *Org. Biomol. Chem.*, 2016, **14**, 1450–4.

22. J. R. Parikh and W. V. E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505–5507.

23. N. Leikoski, L. Liu, J. Jokela, M. Wahlsten, M. Gugger, A. Calteau, P. Permi, C. A. Kerfeld, K. Sivonen, and D. P. Fewer, *Chem. Biol.*, 2013, **20**, 1033–1043.

24. J. Martins and V. Vasconcelos, *Mar. Drugs*, 2015, **13**, 6910–6946.

25. C. Ireland and P. Scheuer, *J. Am. Chem. Soc.*, 1980, **102**, 5688–5691.

26. M. R. Prinsep, R. E. Moore, I. A. Levine, and G. M. Patterson, *J. Nat. Prod.*, 1992, **55**, 140–142.

27. P. F. Long, W. C. Dunlap, C. N. Battershill, and M. Jaspars, *ChemBioChem*, 2005, **6**, 1760–1765.

28. E. W. Schmidt, J. T. Nelson, D. A. Rasko, S. Sudek, J. A. Eisen, M. G.

Haygood, and J. Ravel, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 7315–7320.

29. C. M. Ireland, A. R. Durso, R. A. Newman, and M. P. Hacker, *J. Org. Chem.*, 1982, **47**, 1807–1811.

30. Y. Hamada, M. Shibata, and T. Shioiri, *Tetrahedron Lett.*, 1985, **26**, 6501–6504.

31. Y. Hamada, K. Kohda, and T. Shioiri, *Tetrahedron Lett.*, 1984, **25**, 5303–5306.

32. Y. Hamada, S. Kato, and T. Shioiri, *Tetrahedron Lett.*, 1985, **26**, 3223–3226.

33. P. Wipf and Y. Uto, *J. Org. Chem.*, 2000, **65**, 1037–1049.

34. P. Wipf and P. C. Fritch, *J. Am. Chem. Soc.*, 1996, **118**, 12358–12367.

35. H. Onaka, H. Tabata, Y. Igarashi, Y. Sato, and T. Furumai, *J. Antibiot.*, 2001, **54**, 1036–1044.

36. Y. Igarashi, Y. Kan, K. Fujii, T. Fujita, K. Harada, H. Naoki, H. Tabata, H. Onaka, and T. Furumai, *J. Antibiot.*, 2001, **54**, 1045–1053.

37. L. M. Nogle, B. L. Marquez, and W. H. Gerwick, *Org. Lett.*, 2003, **5**, 3–6.

38. J. A. V. Lopez, S. S. Al-Lihaibi, W. M. Alarif, A. Abdel-Lateff, Y. Nogata, K. Washio, M. Morikawa, and T. Okino, *J. Nat. Prod.*, 2016, 1213–1218.

39. B. Paizs and S. Suhai, *Mass Spectrom. Rev.*, 2005, **24**, 508–548.

40. K. Fujii, Y. Ikai, T. Mayumi, H. Oka, M. Suzuki, and K. I. Harada, *Anal.*

Chem., 1997, **69**, 3346–3352.

41. K. Fujii, Y. Ikai, H. Oka, M. Suzuki, and K. Harada, *Anal. Chem.*, 1997, **69**, 5146–5151.

42. U. Mocek, Z. Zeng, D. O'Hagan, P. Zhou, L. D. G. Fan, J. M. Beale, and H. G. Floss, *J. Am. Chem. Soc.*, 1993, **115**, 7992–8001.

43. U. Mocek, A. R. Knaggs, R. Tsuchiya, T. Nguyen, J. M. Beale, and H. G. Floss, *J. Am. Chem. Soc.*, 1993, **115**, 7557–7568.

44. K. L. Dunbar, J. O. Melby, and D. A. Mitchell, *Nat. Chem. Biol.*, 2012, **8**, 569–575.

45. C. T. Walsh, S. J. Malcolmson, and T. S. Young, *ACS Chem. Biol.*, 2012, **7**, 429–442.

46. T. Ozaki, Y. Kurokawa, S. Hayashi, N. Oku, S. Asamizu, Y. Igarashi, and H. Onaka, *ChemBioChem*, 2016, **17**, 218–223.

47. H. Onaka, *Biosci. Biotechnol. Biochem.*, 2009, **73**, 2149–2155.

48. H. Onaka, M. Nakaho, K. Hayashi, Y. Igarashi, and T. Furumai, *Microbiology*, 2005, **151**, 3923–3933.

49. H. Onaka, *Actinomycetologica*, 2006, **20**, 62–71.

50. J. Bérdy, *J. Antibiot.*, 2005, **58**, 1–26.

51. S. A. Waksman, *Science*, 1953, **118**, 259–266.

52. T. Eicher, S. Hauptmann, and A. Speicher, *The Chemistry of Heterocycles*, Wiley-VCH, Third., 2012.

53. D. T. Davies, *Aromatic Heterocyclic Chemistry*, OUP Oxford, 1994.

54. P. P. E. Strzybny, T. van Es, and O. G. Backeberg, *J. Org. Chem.*, 1963, **28**, 3381–3383.

55. M. Lewy, *Chem. Ber.*, 1887, **20**, 2576–2580.

56. F. O. Blümlein, *Chem. Ber.*, 1884, **17**, 2485–2497.

57. R. H. Wiley, *Chem. Rev.*, 1945, **37**, 401–442.

58. A. V Lygin and A. de Meijere, *Angew. Chem. Int. Ed.*, 2010, **49**, 9094–9124.

59. O. Possel and A. M. van Leusen, *Heterocycles*, 1977, **7**, 77–80.

60. B. A. Kulkarni and A. Ganesan, *Tetrahedron: Asymmetry*, 1999, **40**, 5633–5636.

61. U. Schöllkopf and F. Gerhart, *Angew. Chem. Int. Ed.*, 1968, **7**, 805–806.

62. D. A. Evans, G. S. Peterson, J. S. Johnson, D. M. Barnes, K. R. Campos, and K. A. Woerpel, *J. Org. Chem.*, 1998, **63**, 4541–4544.

63. P. Wipf and G. B. Hayes, *Tetrahedron*, 1998, **54**, 6987–6998.

64. C. Shin, Y. Nakamura, and K. Okumura, *Chem. Lett.*, 1993, 1405–1408.

65. D. R. Williams, P. D. Lowder, Y. G. Gu, and D. A. Brooks, *Tetrahedron Lett.*, 1997, **38**, 331–334.

66. R. Huisgen, G. Binsch, and L. Ghosez, *Chem. Ber.*, 1965, **97**, 2628–2639.

67. R. Huisgen, H. J. Strum, and G. Binsch, *Chem. Ber.*, 1964, **97**, 2864–2867.

68. M. P. Doyle, M. Oppenhuizen, C. E. Elliot, and M. R. Boelkins, *Tetrahedron Lett.*, 1978, **26**, 2247–2250.

69. T. Ibata and Y. Isogami, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 618–620.

70. G. Moniotte P, H, J. Hubert, A, and H. Teyssie, P, *J. Organomet. Chem.*, 1975, **88**, 115–120.

71. N. T. Buu and J. T. Edward, *Can. J. Chem.*, 1972, **50**, 3730–3737.

72. Y.-C. Kuo, T. Aoyama, and T. Shioiri, *Chem. Pharm. Bull.*, 1982, **30**, 526–533.

73. K. J. Doyle and C. J. Moody, *Tetrahedron*, 1994, **50**, 3761–3772.

74. J. Linder, T. P. Garner, H. E. L. Williams, M. S. Searle, and C. J. Moody, *J. Am. Chem. Soc.*, 2011, **133**, 1044–1051.

75. T. Ibata and K. Fukushima, *Chem. Lett.*, 1992, 2197–2200.

76. K. Fukushima and T. Ibata, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 3469–3481.

77. R. Robinson, *J. Chem. Soc.*, 1909, **95**, 2167–2174.

78. S. Gabriel, *Eur. J. Inorg. Chem.*, 1910, **43**, 134–138.

79. S. Gabriel, *Eur. J. Inorg. Chem.*, 1910, **43**, 1283–1287.

80. P. Wipf and C. P. Miller, *J. Org. Chem.*, 1993, **58**, 3604–3606.

81. R. A. Hughes and C. J. Moody, *Angew. Chem. Int. Ed.*, 2007, **46**, 7930–7954.

82. M. C. Bagley, K. E. Bashford, C. L. Hesketh, and C. J. Moody, *J. Am. Chem.*

Soc., 2000, **122**, 3301–3313.

83. J. Linder and C. J. Moody, *Chem. Commun.*, 2007, **21**, 1508–1509.

84. C. J. Moody and M. C. Bagley, *J. Chem. Soc. Perkin Trans. 1*, 1998, 601–607.

85. M. C. Bagley, R. T. Buck, S. L. Hind, and C. J. Moody, *J. Chem. Soc. Perkin Trans. 1*, 1998, 591–600.

86. H. Wada, H. E. L. Williams, and C. J. Moody, *Angew. Chem. Int. Ed.*, 2015, **54**, 15147–15151.

87. A. Hantzsch and J. H. Weber, *Chem. Ber.*, 1887, **20**, 3118–3132.

88. M. W. Bredenkamp, C. W. Holzapfel, and W. J. van Zyl, *Synth. Commun.*, 1990, **20**, 2235–2249.

89. E. Aguilar and A. I. Meyers, *Tetrahedron Lett.*, 1994, **35**, 2473–2476.

90. K. C. Majumdar and S. K. Chattopadhyay, *Heterocycles in Natural Product Synthesis*, Wiley VCH, 2011.

91. R. A. Hughes, S. P. Thompson, L. Alcaraz, and C. J. Moody, *J. Am. Chem. Soc.*, 2005, **127**, 15644–15651.

92. K. Umemura, T. Tate, M. Yamaura, J. Yoshimura, Y. Yonezawa, and C. Shin, *Synthesis*, 1995, 1423–1426.

93. P. Wipf and S. Venkatraman, *J. Org. Chem.*, 1996, **61**, 8004–8005.

94. M. D. Bachi, N. Bar-Ner, C. M. Crittell, P. J. Stang, and B. L. Williamson, *J. Org. Chem.*, 1991, **56**, 3912–3915.

95. V. V. Zhdankin, C. M. Crittell, P. J. Stang, and N. S. Zefirov, *Tetrahedron Lett.*, 1990, **31**, 4821.

96. J. R. Davies, P. D. Kane, and C. J. Moody, *Tetrahedron*, 2004, **60**, 3967–3977.

97. B. Shi, A. J. Blake, W. Lewis, I. B. Campbell, B. D. Judkins, and C. J. Moody, *J. Org. Chem.*, 2010, **75**, 152–161.

98. E. Riego, D. Hernández, F. Albericio, and M. Álvarez, *Synthesis*, 2005, **2005**, 1907–1922.

99. D. A. McGowan, U. Jordis, D. K. Minster, and M. Hecht, S, *J. Am. Chem. Soc.*, 1977, **99**, 8078–8079.

100. E. Palmer D, C. Pattaroni, K. Numani, K. Chadha, R, M. Goodman, T. Wakamiya, K. Fukase, S. Horimoto, M. Kitazawa, H. Fujita, A. Kubo, and T. Shiba, *J. Am. Chem. Soc.*, 1992, **114**, 5634–5642.

101. C. T. Walsh, S. Garneau-Tsodikova, and G. J. Gatto, *Angew. Chem. Int. Ed.*, 2005, **44**, 7342–7372.

102. J. M. Chalker, S. B. Gunnoo, O. Boutureira, S. C. Gerstberger, M. Fernández-González, G. J. L. Bernardes, L. Griffin, H. Hailu, C. J. Schofield, and B. G. Davis, *Chem. Sci.*, 2011, **2**, 1617–1868.

103. A. El-Faham and F. Albericio, *Chem. Rev.*, 2011, **111**, 6557–6602.

104. Nomoto, S, A. Sano, and T. Shiba, *Tetrahedron Lett.*, 1979, 521–522.

105. B. K. Ayida, K. B. Simonsen, D. Vourloumis, and T. Hermann, *Bioorg. Med.*

Chem. Lett., 2005, **15**, 2457–2460.

106. D. H. Strumeyer, W. N. White, and D. E. Koshland, *Proc. Natl. Acad. Sci. U. S. A.*, 1963, **50**, 931–935.

107. I. Photaki, *J. Am. Chem. Soc.*, 1963, **85**, 1123–1126.

108. S. K. Chattopadhyay, S. Biswas, and B. K. Pal, *Synthesis*, 2006, 1289–1294.

109. C. Bailly, R. Houssin, and J.-L. Bernier, *Tetrahedron*, 1988, **44**, 5833–5843.

110. C. Kelly, R, I. Gebhard, and N. Wicnienski, *J. Org. Chem.*, 1986, **51**, 4590–4594.

111. J. S. Davies, C. L. Higginbotham, E. J. Treemer, C. Brown, and R. C. Treadgold, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3043–3048.

112. M. Bodanszky, *Principles in Peptide Synthesis*, Springer-Verlag Berlin, 1984.

113. J. De Jersey and B. Zerner, *Biochemistry*, 1969, **8**, 1967–1974.

114. M. G. Ryadnov, L. V Klimenko, and Y. V Mitin, *J. Pept. Res.*, 1999, **53**, 322–8.

115. K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, and B. S. Safina, *Angew. Chem. Int. Ed.*, 2005, **44**, 1378–1382.

116. M. Tamaki and V. J. Hruby, *J. Pept. Res.*, 2001, **58**, 338–341.

117. L. S. Lin, T. Lanza, S. E. de Laszlo, Q. Truong, T. Kamenecka, and W. K. Hagmann, *Tetrahedron Lett.*, 2000, **41**, 7013–7016.

118. R. Pascal and R. Sola, *Tetrahedron Lett.*, 1998, **39**, 5031–5034.

119. K. P. Reber, S. D. Tilley, C. A. Carson, and E. J. Sorensen, *J. Org. Chem.*, 2013, **78**, 9584–9607.

120. M. E. Jung and M. A. Lyster, *J. Org. Chem.*, 1977, **42**, 3761–3764.

121. M. Valencic, T. van der Does, and E. de Vroom, *Tetrahedron Lett.*, 1998, **39**, 1625–1628.

122. R. Kaul, Y. Brouillette, Z. Sajjadi, K. A. Hansford, and W. D. Lubell, *J. Org. Chem.*, 2004, **69**, 6131–6133.

123. A. Sakakura, S. Umemura, and K. Ishihara, *Synlett*, 2009, 1647–1650.

124. A. M. Felix, *J. Org. Chem.*, 1974, **39**, 1427–1429.

125. M. O. Anderson, J. Moser, J. Sherrill, and R. K. Guy, *Synlett*, 2004, 2391–2393.

126. N. E. Jacobsen, *NMR Data Interpretation Explained: Understanding 1D and 2D NMR Spectra of Organic Compounds and Natural Products*, John Wiley & Sons, 2016.

127. M. S. Donia and E. W. Schmidt, *Chem. Biol.*, 2011, **18**, 508–519.

128. H. Fu, G. R. Grimsley, A. Razvi, J. M. Scholtz, and C. N. Pace, *Proteins Struct. Funct. Bioinforma.*, 2009, **77**, 491–498.

129. B. Long, J. Zhang, X. Tang, and Z. Wu, *Org. Biomol. Chem.*, 2016, **14**, 9712–9715.

130. C. J. White and A. K. Yudin, *Nat. Chem.*, 2011, **3**, 509–24.

131. A. Ehrlich, H. Heyne, R. Winter, M. Beyermann, H. Haber, L. A. Carpino, and M. Bienert, *J. Org. Chem.*, 1996, **61**, 8831–8838.

132. D. Connell, R, M. Tebbe, A. R. Gangloff, P. Helquist, and B. Akermark, *Tetrahedron*, 1993, **49**, 5445–5459.

133. G. Videnov, D. Kaiser, C. Kempter, and G. Jung, *Angew. Chem. Int. Ed.*, 1996, **108**, 1604–1607.

134. S. T. Chen, S. H. Wu, and K. T. Wang, *Synthesis*, 1988, 37–38.

135. S. Nozaki and I. Muramatsu, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2647–2648.

136. B. D. Schwartz, J. R. Denton, Y. Lian, H. M. L. Davies, and C. M. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 8329–8332.

137. G. M. Blackburn, T. H. Lilley, E. Walmsley, and H. Lilley, *J. Chem. Soc. Faraday Trans. 1 Phys. Chem. Condens. Phases*, 1980, **76**, 915–922.

138. R. Dave and N. A. Sasaki, *Org. Lett.*, 2004, **6**, 15–18.

139. J. A. Souto, E. Vaz, I. Lepore, A. C. Pöppler, G. Franci, R. Álvarez, L. Altucci, and Á. R. De Lera, *J. Med. Chem.*, 2010, **53**, 4654–4667.

140. V. F. Pozdnev, *Tetrahedron Lett.*, 1995, **36**, 7115–7118.

141. A. Boeijen and R. M. J. Liskamp, *Eur. J. Org. Chem.*, 1999, **1999**, 1991–2443.

142. R. Houssin, M. Lohez, J.-L. Bernier, and J.-P. Henichart, *J. Org. Chem.*, 1985, **50**, 2787–2788.

143. U. Schmidt, P. Gleich, H. Griesser, and R. Urz, *Synthesis*, 1986, 992–998.

144. M. R. Davis, E. K. Singh, H. Wahyudi, L. D. Alexander, J. B. Kunicki, L. A. Nazarova, K. A. Fairweather, A. M. Giltrap, K. A. Jolliffe, and S. R. McAlpine, *Tetrahedron*, 2012, **68**, 1029–1051.

145. A. Bianco, C. Zabel, P. Walden, and G. Jung, *J. Pept. Sci.*, 1998, **4**, 471–478.

146. Y. E. Jad, G. A. Acosta, T. Naicker, M. Ramtahal, A. El-Faham, T. Govender, H. G. Kruger, B. G. De La Torre, and F. Albericio, *Org. Lett.*, 2015, **17**, 6182–6185.

147. T. S. Ibrahim, S. R. Tala, S. A. El-Feky, Z. K. Abdel-Samii, and A. R. Katritzky, *Synlett*, 2011, 2013–2016.

148. M. O. Cox, R. H. Prager, and C. E. Svensson, *Aust. J. Chem.*, 2004, **57**, 747–758.

149. A. Sakakura and Y. Hayakawa, *Tetrahedron*, 2000, **56**, 4427–4435.

150. R. Chincilla, D. J. Dodsworth, C. Nájera, and J. M. Soriano, *Synlett*, 2003, **6**, 809–812.

151. D. J. Bentley and C. J. Moody, *Org. Biomol. Chem.*, 2004, **2**, 3545–3547.

152. A. Bertram, N. Maulucci, O. M. New, S. M. Mohd Nor, and G. Pattenden, *Org. Biomol. Chem.*, 2007, **5**, 1541–53.

153. D. Tessaro, L. Cerioli, S. Servi, F. Viani, and P. D'Arrigo, *Adv. Synth. Catal.*, 2011, **353**, 2333–2338.

154. X. De An and S. Yu, *Org. Lett.*, 2015, **17**, 5064–5067.

155. R. S. Dhiman, L. G. Opinska, and R. Kluger, *Org. Biomol. Chem.*, 2011, **9**, 5645–5647.

156. G. Priem, L. Rocheblave, C. De Michelis, J. Courcambeck, and J. L. Kraus, *J. Chem. Soc. Perkin Trans. 1*, 2000, 819–824.

157. M. Schnopp, S. Ernst, and G. Haberhauer, *Eur. J. Org. Chem.*, 2009, 213–222.

158. P. M. T. Ferreira, E. M. S. Castanheira, L. S. Monteiro, G. Pereira, and H. Vilaça, *Tetrahedron*, 2010, **66**, 8672–8680.