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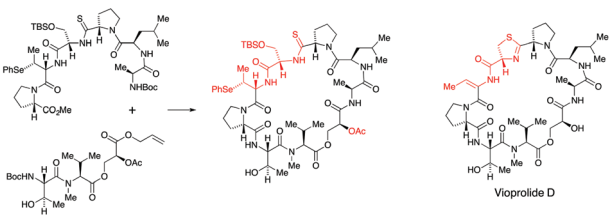
1

Synthesis of macrocyclic precursors of the vioprolides

Eibhlin Butler, Damien Cornut, Gonzalo Gomez-Campillos, Hao Liu, Andrew C. Regan, Lucia F. Rico and Eric J. Thomas*

Convergent syntheses have been developed of macrocycles that may be useful for the synthesis of vioprolide D. Preliminary studies have also been carried out into the introduction of the thiazoline and (*E*)-dehydrobutyrine components.



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Eibhlin	Butler		
Damien	Cornut		
Gonzalo	Gomez-Campillos		
Hao	Liu		
Andrew C.	Regan		
Lucia F.	Rico		
Eric J.	Thomas		0000-0002-5336-8146

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PAPER

Synthesis of macrocyclic precursors of the vioprolides†

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Eibhlin Butler, Damien Cornut, Gonzalo Gomez-Campillos, Hao Liu, Andrew C. Regan, Lucia F. Rico and Eric J. Thomas *

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The vioprolides are novel depsipeptides that have not been synthesized. However, they have been identified as important targets for synthesis because of their novel biological activities and challenging chemical structures. Following early work on the synthesis of a modified tetrapeptide that contained both the (*E*)-dehydrobutyrine and thiazoline components of vioprolide D, problems were encountered in taking an (*E*)-dehydrobutyrine containing intermediate further into the synthesis. A second approach to vioprolides and analogues was therefore investigated in which (*E*)- and (*Z*)-dehydrobutyrines were to be introduced by selenoxide elimination very late in the synthesis. A convergent approach to advanced macrocyclic precursors of the vioprolides was then completed using a modified hexapeptide and a dipeptidyl glycerate. In this work, it was necessary to protect the 2-hydroxyl group of the glycerate as its acetate and not as its 2,2,2-trichloroethoxycarbonate. Preliminary studies were carried out on the introduction of the required dehydrobutyrine and thiazoline components into advanced intermediates.

Introduction

The vioprolides A–D **1–4** comprise a small group of depsipeptides with a range of biological activities that were isolated from the myxobacterium *Cystobacter violaceus* strain Cb vi35.[1] Of the four natural products, vioprolide D **4** was found to be the most active against a variety of fungi and yeasts yet it was the least toxic towards mammalian cells.[1] In a separate study, vioprolide A **1** was found to exhibit a three-fold synergistic effect on the murine type 1 interferon signalling pathway and modulated the NF-κB pathway in cell-based assays thereby showing anti-inflammatory properties.[2] However, the mechanisms of action of the vioprolides are not known. The synthesis of the vioprolides and analogues is therefore of interest in order to provide more material for further biological investigations. We here describe studies that have resulted in the total synthesis of macrocyclic precursors of vioprolide D.[3] A synthesis of the azetidinyl-thiazolinyl fragment of vioprolides A and C is the only other contribution to vioprolide synthesis published to date.[4]

The vioprolides are depsipeptides that comprise eight amino acids, or amino acid derived fragments, together with an (*S*)-glyceric acid unit. The variable positions are occupied by L-homoproline or L-proline and by (2*S*,4*R*)-4-methylazetidinecarboxylic acid or L-proline, see Fig. 1. Atropisomers have been detected across the *N*-methylvaline amide bond. A D-leucine is present in all vioprolides.[1]

It was decided to study a synthesis of vioprolide D **4** first in order to enable a strategy to be developed without the need for the synthesis of the 4-methylazetidinecarboxylic acid. It was envisaged that the same approach could be applied to other members of the series. The introduction of the (*E*)-dehydrobutyrine and the adjacent thiazoline residue was recognised as the most challenging aspect of the synthesis since steric interactions tend to make (*E*)-dehydrobutyrines less stable than their (*Z*)-isomers. Indeed several *anti*-elimination processes are available for the synthesis of (*Z*)-dehydrobutyrines from threonine[5] whereas just one procedure involving a *syn*-dehydration

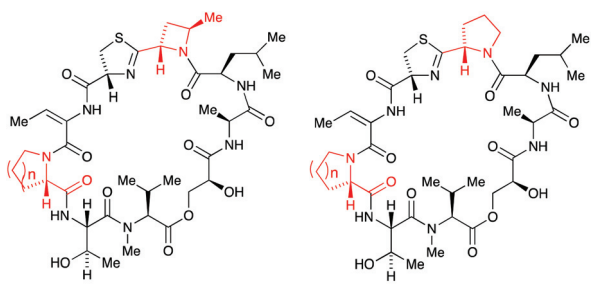


Fig. 1 The structures of the naturally occurring vioprolides.

The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK. E-mail: e.j.thomas@manchester.ac.uk; Tel: +44 (0)161 275 4613

† Electronic supplementary information (ESI) available: copies of all the ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c8ob01756e

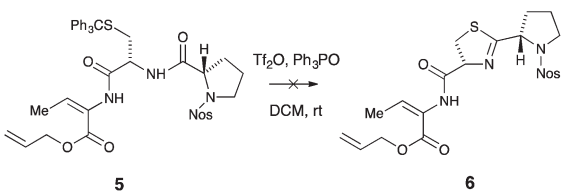
process,[6] is known for the direct synthesis of esters of (*E*)-dehydrobutyrines from threonine. In addition two methods have been reported for the synthesis of esters of (*E*)-dehydrobutyrines by *anti*-elimination from *allo*threonine.[5a,7] Procedures for the introduction of cysteine-derived thiazolines into depsipeptides include the DAST-mediated dehydration of serine-derived thioamides[8] and a biomimetic, one-pot, deprotection–dehydration of *S*-trityl derivatives of cysteine.[9]

Results and discussion

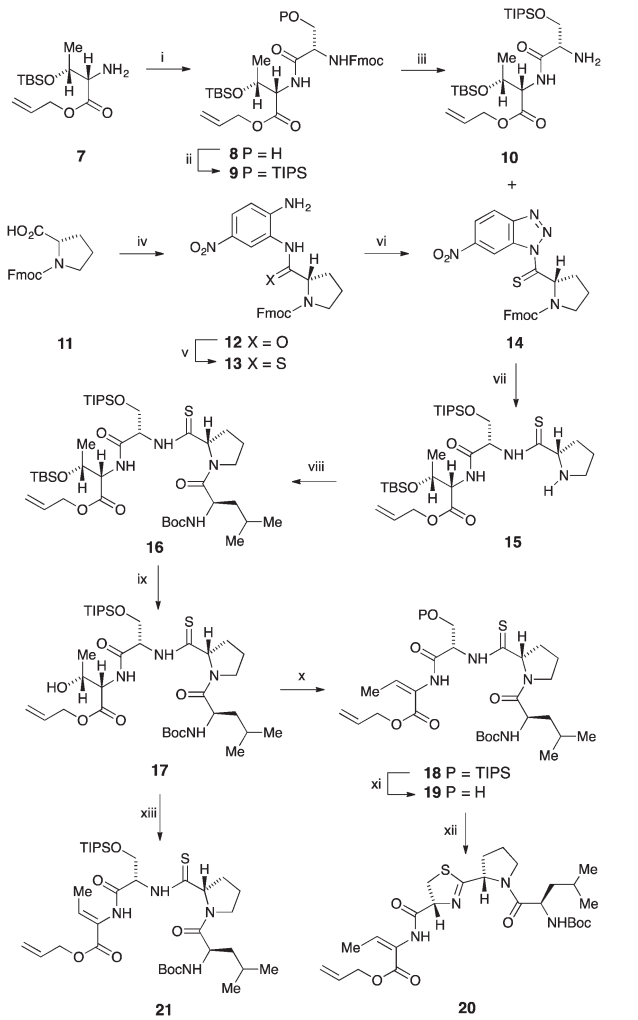
Preliminary studies on the assembly of the (*E*)-dehydrobutyrine-thiazoline component

The epimerisation of amino acid residues adjacent to thiazolines in peptide derivatives is well known[8,9] and so it was decided to introduce the (*E*)-dehydrobutyrine before the thiazoline. However, early studies had shown that attempts to convert the (*E*)-dehydrobutyrine containing tripeptide derivative **5** into the thiazoline **6** by one-pot *S*-deprotection and dehydration following the literature procedure[9] using triphenylphosphine oxide and triflic anhydride gave complex mixtures of products possibly formed by reaction of the intermediate thiol with the double-bond of the dehydrobutyrine, see Scheme 1.[3] It was therefore decided to ascertain whether the introduction of thiazolines by dehydration of serine-derived thioamides was more compatible with the presence of an adjacent (*E*)-dehydrobutyrine.[3]

The *tert*-butyldimethylsilyl ether **7** of L-threonine allyl ester was coupled with Fmoc-protected serine to give the protected dipeptide **8** that was converted into the amino dipeptide **10** *via* the bis-silyl ether **9**. Following the literature procedure for the preparation of the Boc-analogue,[8,10] Fmoc-protected proline was converted into its amide **12** using 2-amino-4-nitroaniline and the amide taken through to the thioamide **13** using phosphorus pentasulfide. Diazotisation gave the benzotriazole **14** that was used to acylate the amino dipeptide **10** to give the thioamide **15** after removal of the Fmoc-protecting group. Coupling the amine **15** with Boc-protected D-leucine then gave the fully protected tetrapeptide **16**. Selective removal of the *tert*-butyldimethylsilyl group in the presence of the tri-isopropylsilyl group proved difficult and so both silyl groups were removed using tetra-*n*-butylammonium fluoride and the primary hydroxyl group of the serine selectively resilylated to give the tetrapeptide derivative **17**, see Scheme 2.



Scheme 1 Unsuccessful introduction of the thiazoline in the presence of an (*E*)-dehydrobutyrine.



Scheme 2 Synthesis of the (*E*)-dehydrobutyrine-thiazoline-L-pro-D-leu fragment **20** of vioprolide D. Reagents and conditions: i, Fmoc-L-ser, HATU, HOBt, $^{i}Pr_2NEt$, DMF, rt, 16 h (97%); ii, TIPSOTf, 2,6-lutidine (2,6-lut.), DCM, rt, 16 h (56%); iii, piperidine (pip.), DMF, rt, 16 h (89%); iv, 2-amino-4-nitroaniline, $^{i}BuOC(O)Cl$, *N*-methyl-morpholine (NMM), THF, −20 °C to rt, 16 h (79%); v, P_4S_{10}, Na_2CO_3, THF, 0 °C, 30 min (71%); vi, $NaNO_2$, glac. AcOH, H_2O, 0 °C, 30 min (86%); vii, (a) **10**, **14**, THF, rt, 6 h (66%) (b) pip., DMF, rt, 16 h (66%); viii, Boc-D-leu, HATU, HOBt, $^{i}Pr_2NEt$, DMF, rt, 16 h (85%); ix, (a) TBAF, THF, rt, 16 h (45%) (b) TIPSCl, imid., THF, rt, 48 h (68%); x, EDC, $CuCl_2$ (cat.), tol., 80 °C, 30 min (65%); xi, TBAF, THF, rt, 16 h (62%); xii, DAST, −15 °C, 1 h (75%); xiii, DAST, py., 0 °C, 2 h (31%).

Dehydration of the tetrapeptide derivative **17** using 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide (EDC) and copper(II) chloride as a catalyst *via* a *syn*-dehydration following the literature procedure,[6] gave the (*E*)-dehydrobutyrine **18** containing about 5% of its (*Z*)-isomer, see Scheme 2. The (*E*)-geometry was assigned to the major product from this reaction by analogy with the literature and by comparison with the (*Z*)-isomer **21** prepared by dehydration of the threonine containing peptide **17** using DAST[5a] [δ_H CH_3CH=; **18**, 1.98; **21**, 1.72].

Desilylation of the protected (*E*)-dehydrobutyrine containing tetrapeptide **18** gave the primary alcohol **19**. Dehydration

using DAST then gave the required thiazoline **20** in which the (*E*)-dehydrobutyrine was still intact, Scheme 2. The ^{1}H NMR spectrum of the thiazoline **20** in DMSO-d_6 at room temperature was complicated by the presence of two rotamers due to the Boc-group, ratio *ca.* 80 : 20. On repeating the NMR spectrum at 100 °C, the peaks of the rotamers coalesced, but they separated out as the solution was cooled back to room temperature. Rotamers were also observed for all the Fmoc-protected amines, *e.g.* the serine derivatives **8** and **9**, prepared during the course of this work and caused broadening of the ^{1}H NMR spectra of these compounds at room temperature.

Yields were not optimised during these preliminary investigations but the assigned structures were consistent with the results of later investigations. The successful synthesis of the modified tetrapeptide **20** that contained both the (*E*)-dehydrobutyrine and the adjacent thiazoline led to the design of the first approach for a convergent synthesis of vioprolide D **4**.

The first approach to vioprolide D; synthesis and chemistry of the modified pentapeptide 22

Based on the preliminary investigations,[3] the synthesis of vioprolide D **4** from the modified pentapeptide **22** and the tripeptide ester **23** shown in Fig. 2 was conceived. At the onset of the work the conversion of allyl esters of (*Z*)-dehydrobutyrines into proline-derived amides was known,[11] and so the formation of the proline to (*E*)-dehydrobutyrine peptide bond was identified as a suitable assembly point since it would avoid α-epimerisation of the acidic component. Macrocyclisation by amide formation between the glyceric acid residue and the L-alanine would then provide a convergent synthesis.[12,13] The thiazoline would have to be introduced as late as possible in the synthesis to avoid epimerisation and so the hydroxyl groups in fragment **23** would need to be protected. The 2,2,2-trichloroethoxycarbonyl (Troc) group was selected for this purpose since conditions were known for its reductive removal in the presence of thiazolines.[8d,14] It was intended to use the allyl ester of the glyceric acid since its palladium(0) catalysed removal should be compatible with the *N*-methylvaline derived ester present in fragment **23**, see Fig. 2.

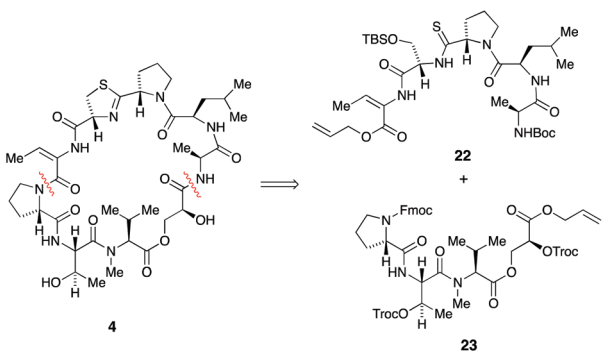
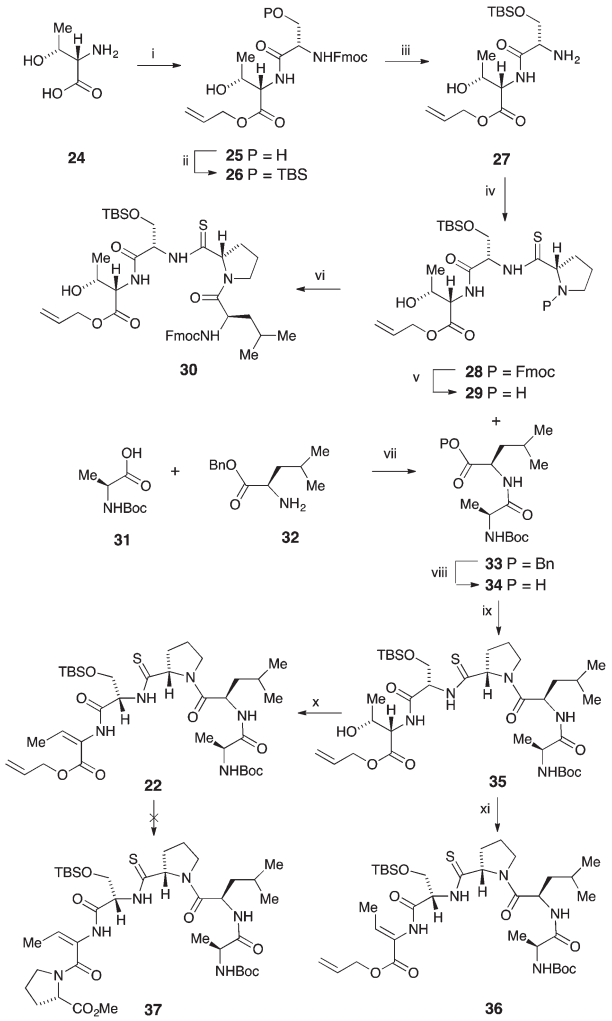


Fig. 2 The convergent strategy conceived initially for a synthesis of vioprolide D 4.



Scheme 3 Synthesis of the (*E*)-dehydrobutyrine **22**. Reagents and conditions: i, (a) allyl alcohol, TsOH, tol., 110 °C, 16 h (b) Fmoc-L-ser, HATU, HOBt, ^{i}Pr$_2$NEt, 0 °C to rt, 16 h (74%); ii, TBSCl, imid., THF, rt, 16 h (79%); iii, pip., THF, rt, 3.5 h (68%); iv, **14**, THF, 0 °C to rt, 16 h (98%); v, pip., THF, rt, 4.75 h (95%); vi, Fmoc-D-leu, HATU, HOBt, rt, 16 h (75%); vii, Et$_3$N, DCM, EDC·HCl, HOBt, rt, 16 h (85%); viii, H$_2$, Pd/C, EtOAc, rt, 16 h (96%); ix, HATU, HOBt, DCM, rt, 16 h (68%); x, EDC, CuCl$_2$ (cat.), tol., 80 °C, 2.5 h (53%); xi, Et$_3$N, MsCl, DCM, 0 °C to rt, 30 m in (58%).

A synthesis of the modified pentapeptide **22** is outlined in Scheme 3. This is based on the chemistry outlined in Scheme 2 but includes improvements. In particular it was found not to be necessary to protect the hydroxyl group of the threonine during the synthesis and the *tert*-butyldimethylsilyl protecting group was preferred for the hydroxyl group of the serine.

L-Threonine **24** was converted into its allyl ester that was coupled with Fmoc-protected serine to provide the dipeptide **25**. This was silylated to give the *tert*-butyldimethylsilyl ether **26**. Following deprotection, the amino-dipeptide **27** was acylated using the benzotriazole **14** to give the thioamide **28** that was deprotected to give the prolinyl peptide **29**. Acylation using Fmoc-protected D-leucine gave the tetrapeptide analogue

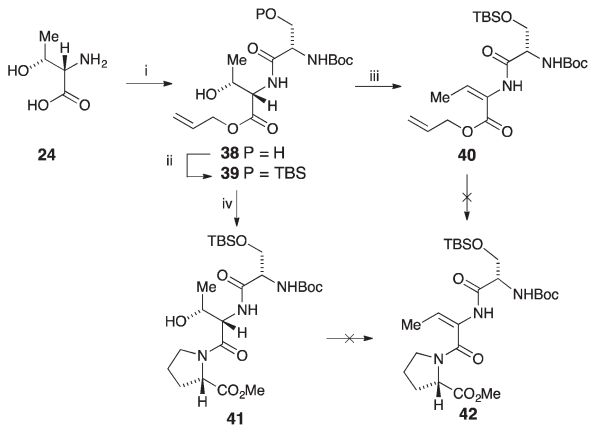
30 but attempts to remove the Fmoc-protecting group led to mixtures of products. It appeared that the free amine derived from the D-leucine had reacted with the thioamide, perhaps to form an amidine, but no product was isolated or characterised (see Experimental). However, the *N*-protected dipeptide **34** was prepared from Boc-protected L-alanine **31** and the benzyl ester **32** of D-leucine, followed by hydrogenolysis of the benzyl ester **33**, and was coupled with the tripeptide derivative **29** to give the modified pentapeptide **35**. Dehydration with EDC and copper(II) chloride then gave the required (*E*)-dehydrobutyrine **22**, see Scheme 3.

Structures were assigned to the products in Scheme 3 by analogy with the literature and from spectroscopic data. Intermediates with Fmoc-protected prolines, *e.g.* the thioamide **28**, were found to have broadened ^{1}H NMR spectra attributed to the presence of rotamers, but following removal of the Fmoc-group the resulting amines, in this case intermediate **29**, had more distinct ^{1}H NMR spectra. For comparison, the threonine-derived pentapeptide **35** was dehydrated using mesyl chloride and triethylamine, to give the (*Z*)-dehydrobutyrine **36**. As before, the (*E*)- and (*Z*)-dehydrobutyrines **22** and **36** were distinguishable by NMR [δ_H CH_3CH═; **22**, 1.99; **36**, 1.84].

This synthesis had provided the required (*E*)-dehydrobutyrine-containing intermediate **22** but the crucial dehydration step was capricious with yields of 20–50% typically obtained and the (*E*) : (*Z*)-selectivity (*ca.* 80 : 20) appeared to be less than had been observed in the earlier study. Moreover, attempts to convert the allyl ester **22** into the corresponding acid by palladium(0) catalysed deallylation,[15] gave only discoloured mixtures of products and the modified hexapeptide **37** was not isolated from attempts to couple the crude deallylated product with methyl L-prolinate, see Scheme 3.

As this work was being carried out, a paper was published that reported difficulties in converting an ester of an (*E*)-dehydrobutyrine into an amide because of isomerisation into the more stable (*Z*)-dehydrobutyrine.[16] It was therefore decided to evaluate the viability of the proposed use of the (*E*)-dehydrobutyrine **22** in the assembly of macrocyclic precursors using simpler (*E*)-dehydrobutyrine containing peptides.

L-Threonine **24** was taken through to the dipeptide **38** [11b] that was monosilylated to give the *tert*-butyldimethylsilyl ether **39**. Boc-protected serine was used in this case to avoid *N*-deprotection in the dehydration step. Dehydration using EDC and copper(II) chloride was now efficient and gave a good yield of the (*E*)-dehydrobutyrine **40**, see Scheme 4. However, the attempted conversion of this dipeptide into the (*E*)-dehydrobutyrine containing tripeptide **42** by palladium catalysed deallylation and coupling the crude product with methyl L-prolinate was discouraging. Only low yields of impure products were isolated that could not be properly characterised. The threonine containing dipeptide **39** was taken through the deallylation and coupling steps to give the protected tripeptide **41** albeit these reactions were not optimised, see Scheme 4. However, the attempted dehydration under the EDC-copper(I) chloride conditions of the threonine containing tripeptide **41** to give the (*E*)-dehydrobutyrine **42** was unsuccessful.



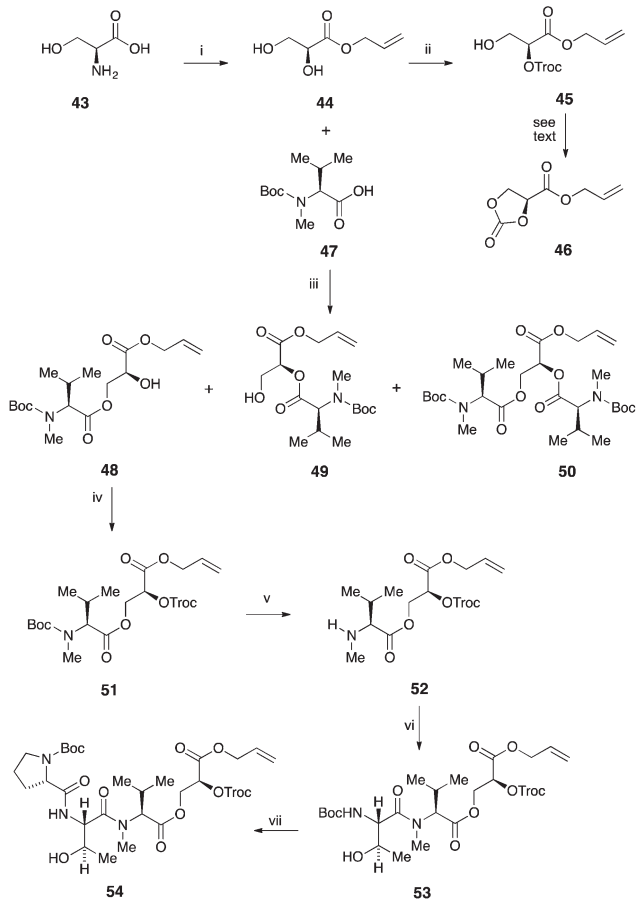
Scheme 4 Synthesis of the (*E*)-dehydrobutyrine **40**. Reagents and conditions: i, (a) allyl alcohol, TsOH, tol., 110 °C, 16 h (b) Boc-L-ser, HATU, HOBt, THF, 0 °C to rt, 16 h; ii, TBSCl, imid., THF, 0 °C to rt, 16 h (72% from **24**); iii, EDC, $CuCl_2$ (cat.), tol., 80 °C, 30 min (82%); iv, (a) $Pd(PPh_3)_4$, $PhSiH_3$, DCM, rt, 1 h (b) methyl L-prolinate, HOBt, PyBOP, NMM, DCM, rt, 16 h (42%).

The EDC-copper(II) chloride procedure for the introduction of the (*E*)-dehydrobutyrine into advanced intermediates was proving troublesome. Moreover, the conversion of the (*E*)-dehydrobutyrine containing esters **22** and **40** into the corresponding prolinyl amides **37** and **42** had not been achieved. It was concluded that assembly of the vioprolides by formation of the (*E*)-dehydrobutyrine-proline peptide bond, as proposed in Fig. 2, was unlikely to be successful.[16]

The first approach to vioprolide D; synthesis and chemistry of modified peptides analogous to the proposed intermediate 23

In parallel with this work, studies were carried out on the synthesis and chemistry of the glyceric acid containing fragment **23**. The selective mono-esterification of the allyl ester of (*S*)-glyceric acid using an *N*-protected *N*-methyl-L-valine was identified as the potentially difficult step in this synthesis.

L-Serine **43** was diazotised following a minor modification of the literature procedure,[17] and esterification of the resulting (*S*)-glyceric acid gave the allyl ester **44**,[17] see Scheme 5. This was taken through into the Troc-protected ester **45** but this ester was found to be unstable during chromatography with respect to cyclisation to the carbonate **46**, and attempts to carry out regioselective mono-esterification of alcohol **45** using a protected *N*-methyl valine[18] were unsuccessful. The direct esterification of the dihydroxy ester **44** using Boc-protected *N*-methylvaline **47** was therefore investigated. Indeed with an excess of the dihydroxyester to minimise bis-esterification, the DCC-DMAP mediated esterification gave an acceptable yield (62%) of the required ester **48** together with its regioisomer **49** (22%) and a minor product provisionally identified as the bis-ester **50** (10%). The structures of these separable products were assigned from spectroscopic data. Further optimisation of this esterification was not studied at this stage.



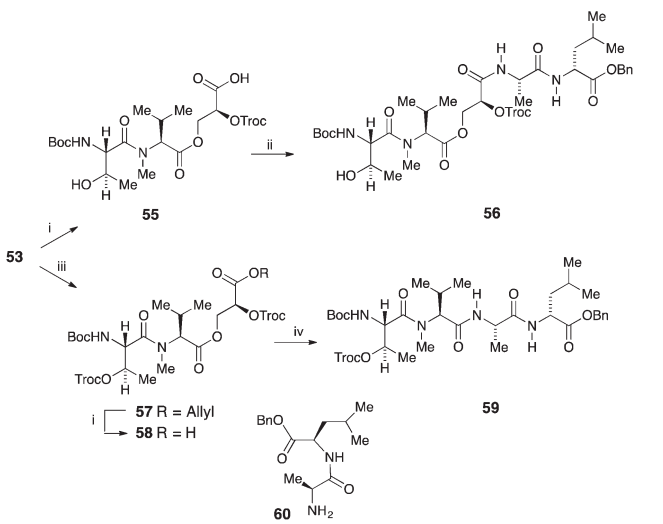
Scheme 5 Synthesis of the glyceric acid containing fragment **54**. Reagents and conditions: i, (a) $NaNO_2$, HCl, H_2O, 0 °C to rt, 24 h (b) $CH_2{=}CHCH_2OH$, $CHCl_3$, $TsOH{\cdot}H_2O$, heat under reflux, 3.5 h (71%); ii, (a) TBSCl, DMAP, Et_3N, DCM, rt, 17 h (56%) (b) TrocCl, DMAP, py., DCM, rt, 17 h (66%) (c) $CuCl_2$, acetone, H_2O, 57 °C, 16 h (87%); iii, DCC, DMAP, DCM, 0 °C to rt, 4 h (**48**, 62%; **49**, 22%; **50**, 10%); iv, TrocCl, DMAP, py., DCM, 0 °C, 3 h (97%); v, TFA, DCM, rt, 1 h (90%); vi, Boc-L-threonine, DMF, DCM, HATU, NMM, rt, 3.5 d (85%); vii, (a) 4 N HCl, dioxane, 0 °C, 4 h (b) Boc-L-proline, NMM, ^{i}BuOC(O)Cl, THF, rt, 15 h (77%).

The hydroxy ester **48** was protected[8d,14] as its Troc-derivative **51** and, after removal of the Boc-group, the *N*-methylamine **52** was coupled with Boc-L-threonine to give the dipeptidyl ester **53**. Using HATU, this coupling was rather slow, 3.5 days, but was efficient, 85%. To complete the synthesis of a fragment that corresponded to the tripeptide derivative **23**, Fig. 2, it remained to remove the Boc-group and to couple the resulting amine with a protected proline. Free amines of dipeptidyl esters with *N*-methylamino acid components can undergo cyclisation to diketopiperazines competitively with *N*-acylation.[19] However, in the present case, removal of the Boc-group from the dipeptide **53** and coupling with Boc-protected L-proline using a mixed anhydride procedure gave the required tripeptidyl glycerate **54** in an acceptable yield of 77%, see Scheme 5.

The tripeptidyl glycerate **54** is the Boc-analogue of the targetted intermediate **23**. Of interest was the relatively efficient construction of the threonine-proline peptide bond in this tripeptide. The formation of this bond may therefore be useful for vioprolide assembly. However, it remained to establish the viability of the other proposed assembly step, *i.e.* formation of the peptide bond between the glyceric acid moiety and a complementary amino peptide as shown in Fig. 2.

Palladium(0) catalysed deallylation of the dipeptidyl glyceride **53** was not very clean although a sample of the hydroxy-acid **55** was isolated after chromatography. However, attempts to couple this acid with the amino dipeptide **60**, prepared by removal of the Boc-group from the previously prepared intermediate **33**, gave rise to complex mixtures of products from which only very low yields of the required amide **56** could be isolated. The amide **56** was identified from ^{1}H and ^{13}C NMR that showed that both fragments were present including the 2,2,2-trichloroethoxy carbonate, and the low resolution MS confirmed the molecular weight. However, this reaction was very capricious and difficult to repeat. To avoid participation of the threonine hydroxyl group, ester **53** was converted into its bis-Troc-derivative **57**. Deallylation now gave the acid **58** in which both of the hydroxyl groups were protected, but attempted coupling of this with the amino-dipeptide **60** surprisingly[20,21] gave the tetrapeptide **59** that had lost the glyceric acid moiety, see Scheme 6. The structure of tetrapeptide **59** was assigned using spectroscopic data.

The formation of the tetrapeptide **59** may have involved participation of the cyclic intermediate **61** derived from the activated acid and the adjacent Troc-protected alcohol.[22] Such an intermediate should be prone to enolisation since its enolate **62** would be stabilised by aromaticity. However, this enolate could also fragment with loss of the carboxylate **63**. The corresponding acid would then be able to couple with the amine **60**,



Scheme 6 Attempted peptide bond formation using Troc-protected glycerides. Reagents and conditions: i, $Pd(Ph_3P)_4$, $PhSiH_3$, DCM, rt, 1–2 h (**55**, 71%; **58**, 55%); ii, (a) **33**, TFA, DCM, rt, 2 h (b) **55**, ^{i}BuOC(O)Cl, NMM, THF, rt, 16 h; iii, TrocCl, py., DCM, 0 °C, 1 h (80%); iv, **60**, PyBOP, NMM, DCM, rt, 16 h (66%).

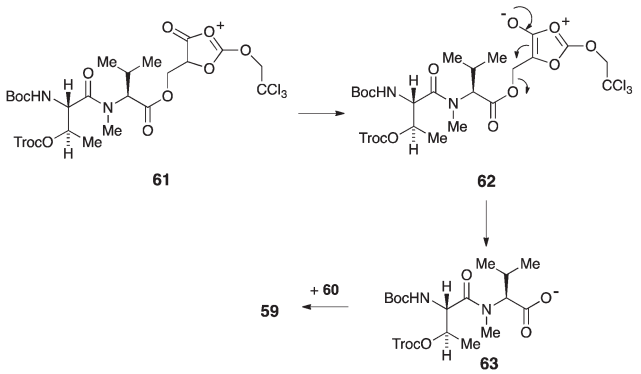


Fig. 3 Possible explanation for loss of the glyceric acid moiety.

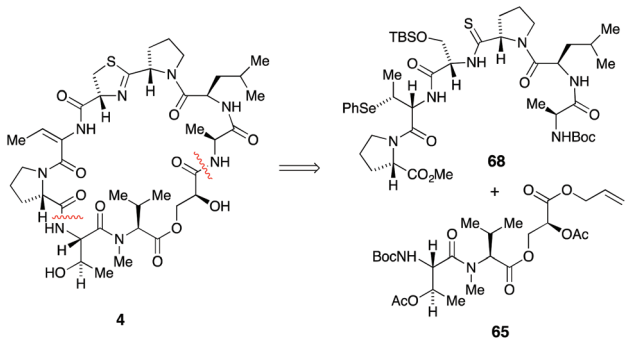


Fig. 4 Revised strategy for a synthesis of vioprolide D 4.

to give the observed tetrapeptide **59**, see Fig. 3. Different reaction conditions might avoid this side-reaction, but it was decided instead to study alternative glycerate protection.

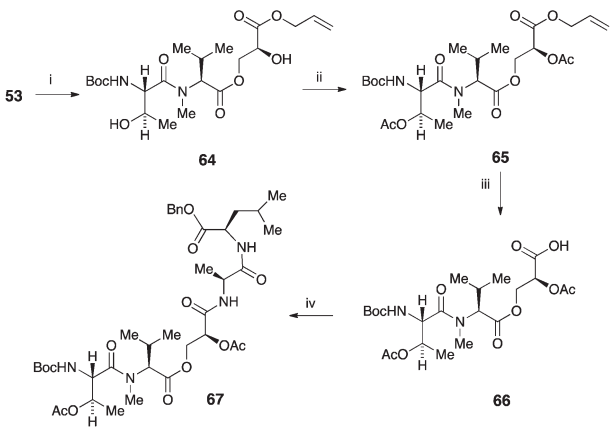
Reductive removal of the Troc-group from the glyceride **53** gave the dihydroxydipeptide glyceride **64** that was converted into the bis-acetate **65**. Following palladium(0) catalysed deallylation, the resulting acid **66** was coupled with the peptide ester **60** to give the required glyceric peptide **67** in a good yield with no side products formed by unwanted participation of the acetates, see Scheme 7. Triethylsilyl protection of the diol **64** was also investigated but some cleavage of the triethylsilyl ethers was observed during the deallylation and coupling steps, and so acetate protection was preferred at this stage.

Revised strategy for synthesis of vioprolide D

At this point it was decided to revise the strategy for a synthesis of vioprolide D **4**, see Fig. 4. The introduction of (*E*)-dehydrobutyrines into advanced intermediates by *syn*-dehydration of threonine-derived peptides was proving difficult even though good yields and stereoselectivities had been observed for simpler substrates. However, a procedure for the introduction of (*E*)-dehydrobutyrines into peptides based on the oxidative elimination of selenides prepared from *allo*-threonines with inversion of configuration, is well known.[23] Indeed an (*E*)-dehydrobutyrine has been introduced into a complex depsipeptide using this procedure.[24] A synthesis of vioprolide D **4** using a selenoxide elimination for introduction of the (*E*)-dehydrobutyrine was therefore considered (Fig. 4).

In this revised approach, the two components were to be the modified hexapeptide **68** and the dipeptide glyceride **65**. Both of the proposed assembly steps have precedents in the studies outlined in Schemes 5 and 7. Protection of the glycerate as its bis-acetate for the peptide bond formation involving the glyceric acid had been established although it was realised that difficulties might arise in saponification of these acetates later in the synthesis in the presence of the glycerate. At the onset of the work, it was not clear that oxidative removal of the selenide would be compatible with the presence of a thioamide, or with the thiazoline, if this were to be introduced first. For these reasons, it was decided to use phenylselenides prepared from threonine for preliminary studies to evaluate the overall strategy even though these would lead to (*Z*)-dehydrobutyrines. There are precedents for isomerisation of (*Z*)-dehydrobutyrines into (*E*)-dehydrobutyrines by benzeneselenol addition-oxidative elimination[23] and so, if necessary, it might be possible to effect such an isomerisation later in the synthesis.

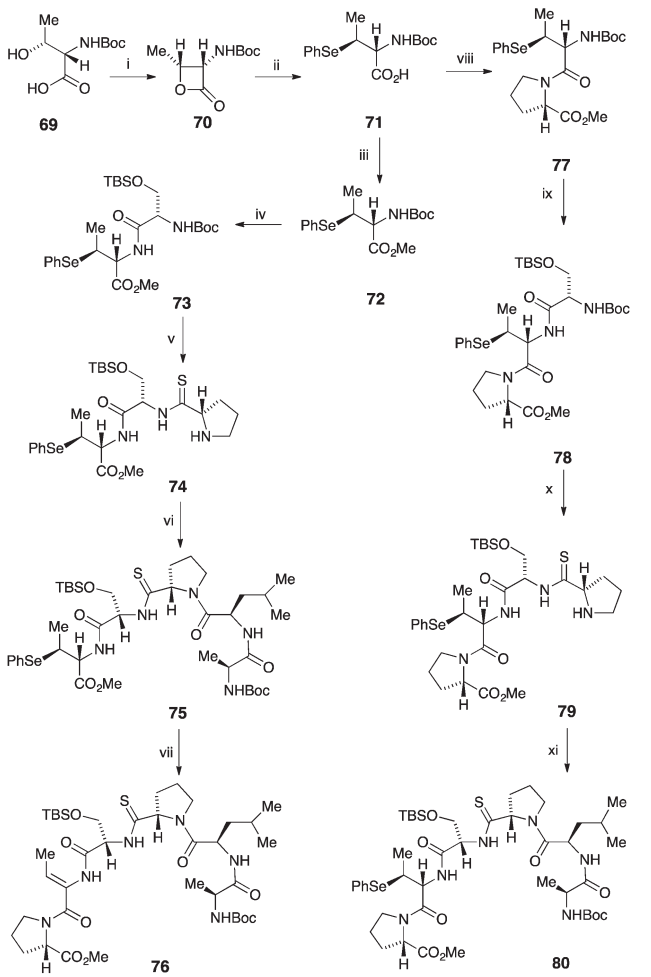
The 3-phenylselanylbutanoic acid **71** was prepared from Boc-protected threonine **69** *via* the oxetane **70** following the literature.[25,26] Esterification gave the methyl ester **72** that was deprotected and the free amine coupled with *O*-TBS-*N*-Boc-protected serine to give the protected dipeptide **73**. Removal of the Boc-group and coupling with the benzotriazole **14** gave the thioamide **74** after removal of the Fmoc-group. This was coupled with the dipeptide acid **34** to give the pentapeptide derivative **75**. Surprisingly, saponification of the methyl ester and coupling the resulting acid with methyl L-prolinate gave the (*Z*)-dehydrobutyrine **76** by loss of benzeneselenol. It may have been possible to tweak the sequence to avoid this elimination, but instead the 3-phenylselanylbutanoic acid **71** was coupled with methyl L-prolinate to give the dipeptide **77**. This was taken through to the tripeptide **78** by removal of the Boc-



Scheme 7 Acetate protection of the glycerate. Reagents and conditions: i, activated Zn, AcOH, Et_2O, rt, 2 h (96%); ii, Ac_2O, DMAP, py., DCM, rt, 17 h (85%); iii, $Pd(PPh_3)_4$, Ph_3SiH, DCM, rt; iv, **60**, PyBOP, NMM, rt (85% from **65**).

protecting group and coupling the resulting free amine with *O*-TBS-*N*-Boc-protected serine. Cleavage of the Boc-group, in this case using trimethylsilyl triflate and 2,6-lutidine to avoid competing loss of the TBS-group, and coupling the amine with the benzotriazole **14** gave the thioamide **79** after removal of the Fmoc-group. The thioamide **79** was then coupled with the dipeptide acid **34** to give the hexapeptide **80**, see Scheme 8.

Structures were assigned to the products in Scheme 8 from spectroscopic data. Oxidative elimination of the phenylselanyl group from the selenide **80** gave the same dehydrobutyrine that had been isolated from the methyl ester **75**, *vide infra*. This was therefore identified as the (*Z*)-isomer **76** (CH_3CH, δ 1.71) formed *via* an apparently *syn*-selective, E1cb elimination process.

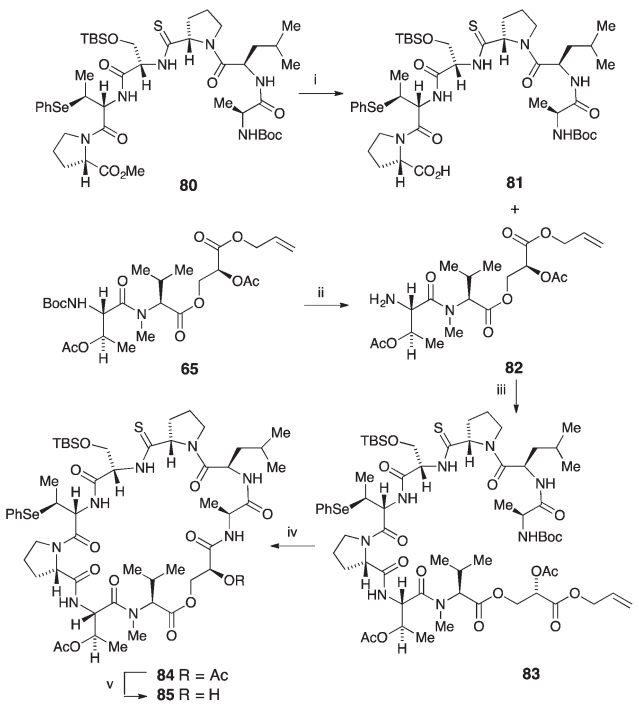


Scheme 8 Synthesis of the modified hexapeptide **80**. Reagents and conditions: i, PyBOP, Et_3N, DCM, rt, 2 h (74%); ii, PhSeH, DMF, 80 °C, 2 h (83%); iii, $TMSCHN_2$, tol., MeOH, rt, 2 h (*ca*. 100%); iv, (a) TFA, DCM, rt, 2 h (b) HATU, HOBt, THF, *O*-TBS-*N*-Boc-L-ser., rt, 16 h (77%); v, (a) TFA, DCM, rt, 2 h (b) **14**, Et_3N, THF, rt, 16 h (c) pip., THF, rt, 4 h (35% from **73**); vi, **34**, HATU, HOBt, DCM, rt, 16 h (85%); vii, (a) NaOH, EtOH, dioxane, rt, 5 h (b) methyl L-prolinate, PyBOP, NMM, DCM, rt, 4.5 h (34%); viii, methyl L-prolinate, PyBOP, NMM, DCM, rt, 4 h (72%); ix, (a) TFA, DCM, rt, 1.5 h (b) *O*-TBS-*N*-Boc-L-ser., HATU, $^iPr_2NEt$, DCM, rt, 32 h (67%); x, (a) TMSOTf, 2,6-lut., DCM, rt, 2 h (b) **14**, $^iPr_2NEt$, DCM, rt, 16 h (66% from **78**) (c) pip., DMF, rt, 10 min (77%); xi, **34**, PyBOP, NMM, DCM, rt, 16 h (61%).

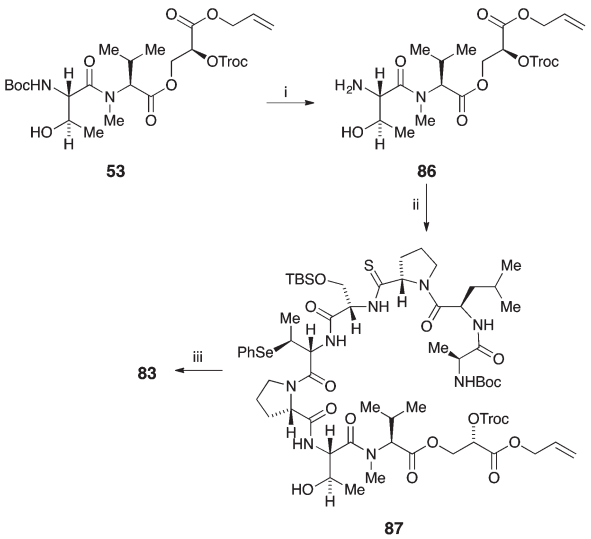
Synthesis of macrocyclic precursors of (*Z*)-iso-vioprolides

Careful saponification of the methyl ester **80** gave the carboxylic acid **81**. This was coupled with the amine **82** that had been prepared by selective deprotection of the glyceride **65** to give the octapeptidyl glyceride **83** in an excellent yield (84%). Palladium(0) catalysed cleavage of the allyl ester and careful acid catalysed removal of the Boc-group then gave the amino-acid that was cyclised to give the macrocyclic intermediate **84** in a yield of 50% over the three steps. At this point attempts were made to remove the acetate protecting groups. In the event, removal of both of the acetates was not achieved. However a careful saponification[27] appeared to remove one of the acetates and gave a modest, 40%, yield of a product that was provisionally identified as the alcohol **85**, see Scheme 9.

Two variations of the synthesis of the macrocyclic compound **84** were investigated. The Troc-protected glyceride **53** was deprotected to give the free amine **86** that was coupled with the acid **81** to give the octapeptidyl glyceride **87**. Removal of the Troc-group gave the corresponding diol that was esterified using acetic anhydride to give the advanced intermediate **83**, see Scheme 10. This synthesis was useful in that it confirmed that coupling of the dipeptidyl glyceride **86**, in which



Scheme 9 Synthesis of a macrocyclic precursor of a (*Z*)-iso-vioprolide. Reagents and conditions: i, LiOH, ^tBuOH, THF, 0 °C to rt, 2 h; ii, 4 N HCl, dioxane, 0 °C, 4 h; iii, $^tBuOC(O)Cl$, NMM, THF, −15 °C to rt, 20 h (84% from **65**); iv, (a) $Pd(PPh_3)_4$, $PhSiH_3$, DCM, 4 h (b) TFA, DCM, 0 °C, 1 h (c) PyBOP, NMM, rt, 3 d (50% from **83**); v, Me_3SnOH, DCM, 70 °C, 1.5 h (40%).



Scheme 10 An alternative synthesis of the octapeptidyl glyceride **83**. Reagents and conditions: i, 4 N HCl, dioxane, 0 °C; ii, **81**, ^{i}BuOC(O)Cl, NMM, THF, −15 °C to rt, 17 h (79% from **53**); iii, (a) activated Zn, AcOH, Et_2O, rt, 16 h (*ca*. 100%) (b) Ac_2O, pyr., DMAP, DCM, 0 °C to rt (59%).

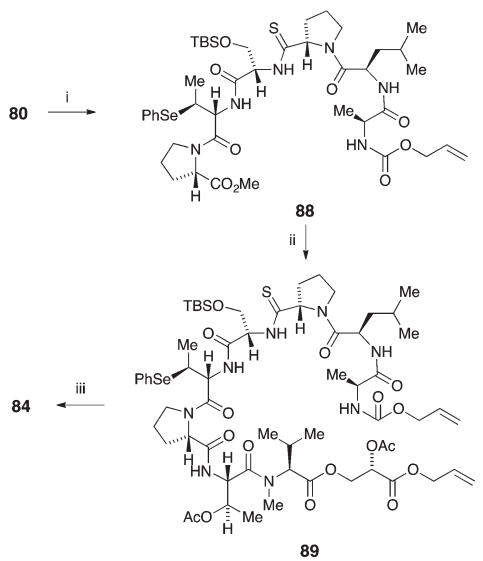
the hydroxyl group of the threonine was unprotected, with the acid **81**, proceeded in a good yield.

In a second variation of the synthesis of the macrocycle **84**, the Boc-group of the hexapeptide **80** was replaced by an alloc-group[28] to give the carbamate **88**, see Scheme 11. This was to avoid the acid-catalysed removal of the Boc-group at the end of the synthesis. Earlier this had been complicated by competing loss of the *tert*-butyldimethyl silyl group. After saponification of the ester moiety in the carbamate **88**, the resulting acid was coupled with the amine **82** to give the octapeptidyl glyceride **89**. This was now taken through to the macrocycle **84** in two steps rather than three.

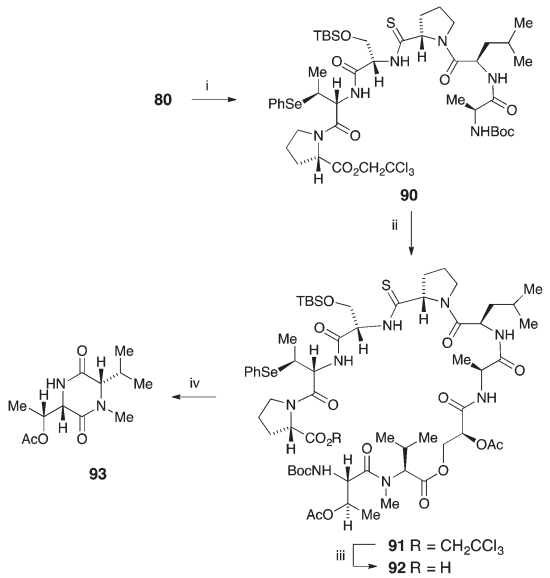
Reversing the assembly steps was also briefly investigated. The acid **81** prepared by saponification of the methyl ester **80** was esterified using 2,2,2-trichlorethanol to give the trichloroethyl ester **90**.[29] Removal of the Boc-group and coupling with the acid **66** now gave the amide **91** that on treatment with activated zinc was converted into the acid **92** without any competing loss of the acetates or cleavage of the glycerate. However, on attempted removal of the Boc-group from the threonine residue and macrocyclisation, the only product that could be isolated was the diketopiperazine **93**, see Scheme 12. The formation of diketopiperazines from esters of *N*-alkylated dipeptides is well known[19] although it hadn't been a problem in the intermolecular coupling of the acid **81** and amine **82**. This approach to the macrocycle **84** was not studied any further.

Synthesis of macrocyclic precursors of vioprolides

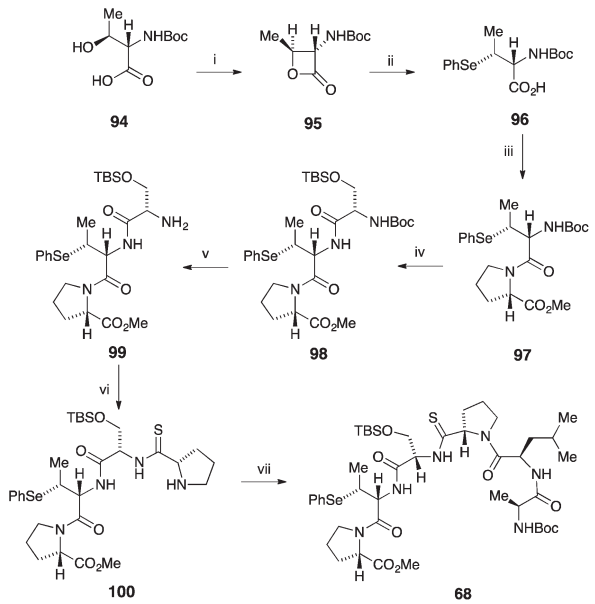
A synthesis of the hexapeptide **68** required for a synthesis of vioprolide D is outlined in Scheme 13. This follows the chemistry developed during the synthesis of its epimer **80** outlined in Scheme 8. In this case, Boc-protected *allo*threonine **94** was cyclised to give the oxetane **95** [30] that on treatment with benzeneselenol gave the selenide **96** with inversion of configuration. Coupling with methyl L-prolinate gave the dipeptide **97** that was converted into the tripeptide **98** by acid catalysed deprotection and coupling with *O*-TBS-*N*-Boc-serine. Deprotection using trimethylsilyl triflate and 2,6-lutidine gave



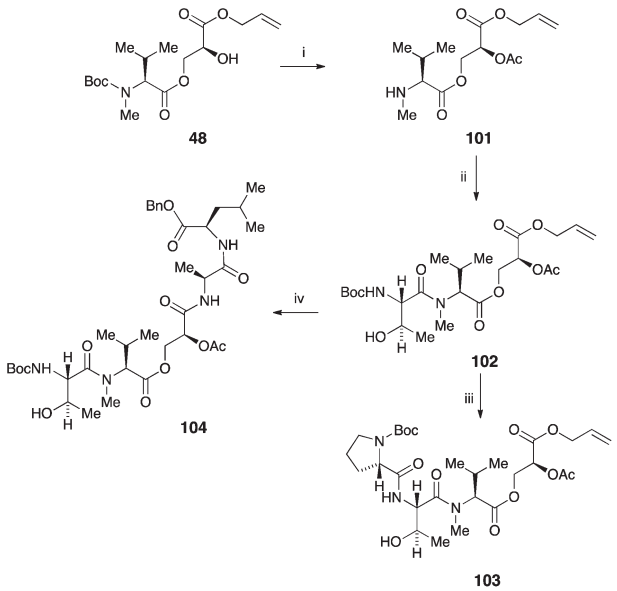
Scheme 11 An alternative synthesis of the macrocycle **84**. Reagents and conditions: i, (a) TMSOTf, 2,6-lut., DCM, rt, 1.5 h (b) $CH_2{=}CHCH_2OC(O)Cl$, $^{i}Pr_2NEt$, DMAP, rt, 16 h (58% from **80**); ii, (a) LiOH, ^{t}BuOH, THF, 0 °C to rt, 2 h (b) **82**, ^{i}BuOC(O)Cl, NMM, THF, −20 °C to rt, 14 h (49%); iii, (a) $Pd(Ph_3P)_4$, $PhSiH_3$, DCM, rt 1 h (b) PyBOP, NMM, DCM, 0 °C to rt, 64 h (**84**, 33%).



Scheme 12 Alternative assembly of the macrocycle from the two components. Reagents and conditions: i, (a) LiOH, ^{t}BuOH : THF (1 : 1), rt, 2 h (b) Cl_3CCH_2OH, EDC.HCl, DMAP, DCM, rt, 16 h (58%); ii, (a) TMSOTf, 2,6-lut., DCM, 2 h, rt (89%) (b) **66**, PyBOP, NMM, rt, 20 h (72%); iii, Zn, NH_4OAc, THF, 0 °C to rt, 16 h; iv, HCl, dioxane, 4 h, 0 °C or TMSOTf, 2,6-lut., DCM.



Scheme 13 Synthesis of the hexapeptide **68**. Reagents and conditions: i, PyBOP, Et_3N, DCM, 0 °C, 1 h, rt, 1 h (95%); ii, PhSeH, DMF, 80 °C, 3 h (93%); iii, methyl L-prolinate, PyBOP, NMM, DCM, rt, 19 h (98%); iv, (a) TFA, DCM, 0 °C, 30 min (b) *O*-TBS-*N*-Boc-L-ser., HATU, $^{i}Pr_2NEt$, DCM, rt, 16 h (71%); v, TMSOTf, 2,6-lut., DCM, rt, 3 h (73%); vi, (a) **14**, $^{i}Pr_2NEt$, DCM, rt, 16 h (93%) (b) pip., DMF, rt, 15 min (83%); vii, **34**, PyBOP, NMM, DCM, rt, 17 h (93%).



Scheme 14 Preliminary studies using the monoacetylated dipeptidyl glycerate **102**. Reagents and conditions: i, (a) Ac_2O, DMAP, py., DCM, rt, 1.5 h (96%) (b) TFA, DCM, rt, 1.5 h (91%); ii, Boc-L-threonine, HATU, NMM, DMF, DCM, rt, 2.5 days (69%); iii, (a) 4 N HCl, dioxane, 0 °C, 4 h (b) Boc-L-proline, $^{i}BuOC(O)Cl$, NMM, THF, rt, 16 h (90%); iv, (a) $Pd(Ph_3P)_4$, $PhSiH_3$, DCM, rt, 45 min (b) **60**, HATU, NMM, DCM, rt, 16 h (66%).

the amine **99** that was acylated using the benzotriazole **14** to give the tetrapeptide **100** after removal of the Fmoc-group using piperidine. The tetrapeptide **100** was then coupled with the acid **34** to give the required hexapeptide **68**, see Scheme 13.

During the synthetic approach to iso-vioprolides, see Scheme 9, it had been found that removal of the acetate from the threonine hydroxyl group was more difficult than selective saponification of the acetate of the glyceric acid, as exemplified by the conversion of bis-acetate **84** into the mono-acetate **85**. Protection of the 2-hydroxyl group of the glyceric acid, *e.g.* as its acetate, was important for formation of the peptide bond of the glycerate, but it was not clear that protection of the hydroxyl group of the threonine was necessary for this step. To clarify this point, the glycerate **48** was acetylated and then deprotected to give the amino-bis-ester **101**. This was coupled with *N*-Boc-L-threonine to give the dipeptidyl glyceride **102**. After removal of the Boc-group, coupling the resulting amine with Boc-protected proline gave the tripeptidyl glyceride **103** as expected from the synthesis of the octapeptidyl glyceride **87**. However, it was also confirmed that the remote hydroxyl group of the threonine did not interfere with peptide formation involving the glycerate now that the 2-hydroxy group of the glycerate is protected as its acetate and not as a Troc-carbonate. Thus following palladium(0) catalysed cleavage of the allyl ester **102**, peptide bond formation using the amino dipeptide **60** gave the glyceric acid amide **104**, see Scheme 14.

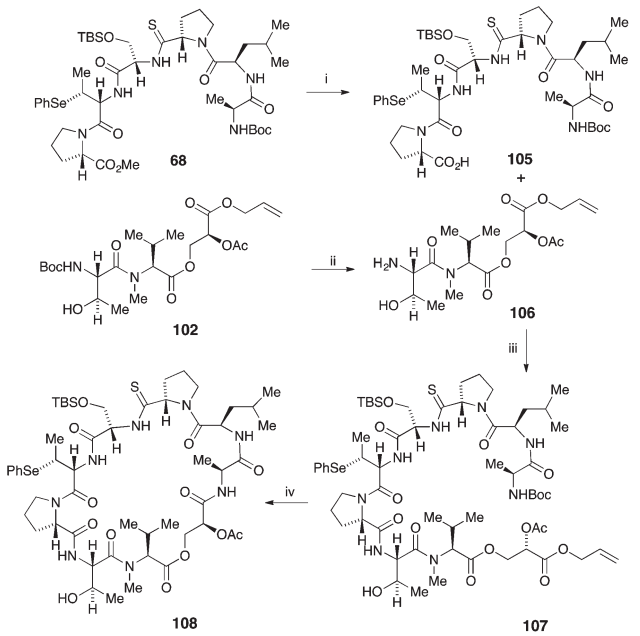
To assemble a macrocyclic precursor of vioprolide D **4**, the acid **105** was prepared by saponification of the hexapeptidyl ester **68**, and was coupled with the amine **106**, that had been prepared from the monoacetylated dipeptidyl glycerate **102**, to give the octapeptidyl glycerate **107**. Stepwise removal of the allyl ester and the Boc-group followed by macrolactamisation then gave the macrocycle **108** as shown in Scheme 15.

The structures shown were assigned to the compounds in Scheme 15 from their spectroscopic data. The methyl group of the acetate in the macrocycle **108** was at δ 2.10 in its ^{1}H NMR spectrum. In the macrocyclic bis-acetate **84**, the two acetate methyl groups were at δ 2.03 and at 2.12. In the mono-acetate prepared by selective saponification, the remaining acetate methyl group was at δ 2.04 with no acetate methyl singlet present at or near to δ 2.12. This is consistent with the selective saponification of the acetate of the glycerate and confirms the monoacetate prepared by saponification as that shown in structure **85** with the remaining acetate being that on the threonine.

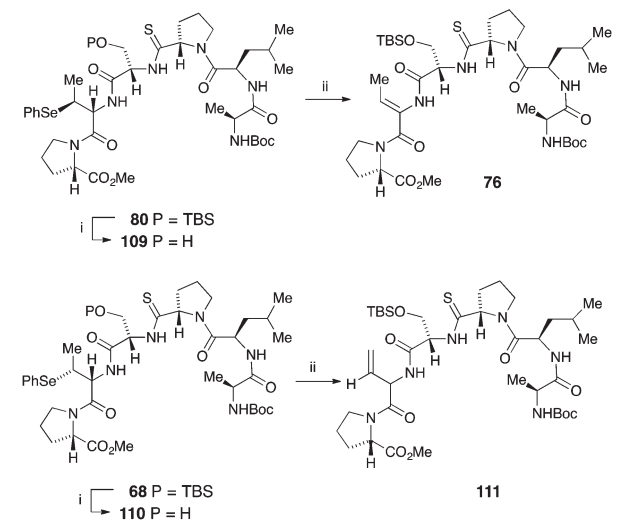
The modified depsipeptide **108** would appear to be a promising intermediate for a synthesis of the (*E*)-dehydrobutyrine-containing vioprolide D **4**. However, it was decided to check the viability of the proposed oxidative and dehydration reactions using substrates prepared from the earlier intermediates **68** and **80** before using valuable macrocyclic intermediates.

Preliminary studies of the oxidative elimination

Oxidative elimination of the phenylselanyl moiety from the hexapeptide **80** gave the (*Z*)-dehydrobutyrine **76**, Scheme 16. The (*Z*)-configuration of the double-bond in this dehydrobutyrine was assigned on the basis of *syn*-elimination of selen-

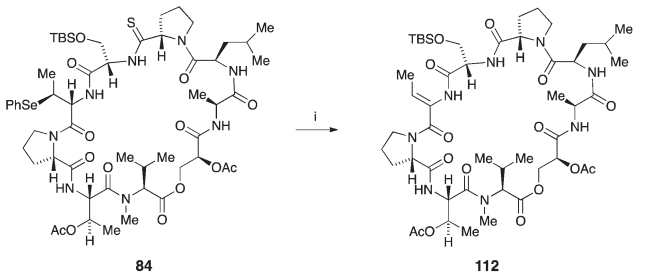


Scheme 15 Synthesis of the macrocycle **108**. Reagents and conditions: i, LiOH, ^{t}BuOH, THF, rt, 2 h (85%); ii, 4 N HCl, dioxane, 0 °C, 4 h; iii, **105**, ^{i}BuOC(O)Cl, NMM, THF, −15 °C, 30 min, add **106**, THF, rt, 16 h (62%); iv, (a) $Pd(Ph_3P)_4$, $PhSiH_3$, DCM, rt, 2 h (b) TFA, DCM, rt, 1 h (88% from **107**) (c) HATU, HOBt, NMM, DCM, rt, 2.5 d (23%).



Scheme 16 Preliminary studies of oxidative elimination. Reagents and conditions: i, TBAF, THF, 0 °C, 5 min, rt, 2 h (**109**, 92%; **110**, 92%); ii, ^{t}BuOOH, DCM, decane, 0 °C, 5 min, rt, 3 h (**76**, 36%; **111** 39%).

oxides. It was also consistent with ^{1}H NMR data (**76**, CH_3CH═, δ 1.71), *cf.* the chemical shifts of the vinylic methyl groups in the dehydrobutyrines (*E*)-**22** (CH_3CH═, δ 1.98) and (*Z*)-**36** (CH_3CH═, δ 1.84). This confirmed the (*Z*)-configuration assigned to the product of coupling and elimination from the phenylselenide **75** as shown in Scheme 8.



Scheme 17 Selenoxide elimination of macrocycle **84**. Reagents and conditions i, ^{t}BuOOH, DCM, decane, 0 °C to rt, 3 h (32%).

Removal of the *tert*-butyldimethylsilyl group from the threonine-derived hexapeptide **80** gave the free alcohol **109** but attempts to take this through to the corresponding (*Z*)-dehydrobutyrine-thiazoline by DAST-mediated dehydration followed by oxidative elimination gave products that were difficult to characterise conclusively because of the presence of rotamers although (*Z*)-alkenes seemed to be present and good yields (75–80%) were obtained (see Experimental).

However, the oxidative elimination of the phenylselanyl group from the epimeric selenide **68** did not give the expected (*E*)-dehydrobutyrine. Instead the terminal alkene **111** was obtained, see Scheme 16. Similarly the alcohol **110** prepared from the hexapeptide **68** gave what appeared to be the terminal alkene containing thiazoline after dehydration and oxidative elimination although again the products were not properly characterised because of the presence of rotamers.

The formation of the terminal alkene **111** on oxidative elimination of the selenide **68** was unexpected and is perhaps indicative of just how sterically hindered (*E*)-double-bonds are in this system when the vinylic methyl group is proximate to a proline residue.

The but-3-enyl containing modified peptide **111** appeared to be predominantly a single epimer. A direct selenoxide elimination to give the terminal alkene would have retained the configuration at C2 of the but-3-enyl residue but this configuration cannot be assumed if the product **111** had been formed by isomerisation of an initially conjugated intermediate and so is not defined in structure **111**. The oxidative elimination was also attempted on the macrocycle **84** (derived from threonine) and gave a (*Z*)-dehydrobutyrine as expected from a *syn*-elimination process (CH_3CH═, δ 1.77). However, the product was shown by ^{13}C NMR and MS to be the amide **112** not the expected thioamide perhaps because of adventitious oxidation due to the excess of oxidant that was used in this one-off, very small scale, reaction, see Scheme 17.

Summary and conclusions

This paper reports progress towards a total synthesis of vioprolide D **4**. The modified depsipeptide **108** would appear to be a promising advanced intermediate since removal of the acetate in the presence of the glycerate is precedented in the conver-

sion of the bis-acetate **84** into the mono-acetate **85**. The diol derived from the acetate **108** could then be protected as its bis-Troc-carbonate and the introduction of the thiazoline and dehydrobutyrine moieties would be studied.

The formation of the terminal alkene **111** rather than the conjugated (*Z*)-dehydrobutyrine on oxidative elimination from the intermediate **68** was unexpected since there are precedents for the introduction of (*E*)-dehydrobutyrines into peptides by selenoxide elimination.[23] The oxidative elimination of selenides to give terminal alkenes can be slow, often being facilitated in synthesis by the use of aryl selenides with electron withdrawing groups in the aromatic ring. Conversely, the 2-acylamino residue in the selenide **68** may be slowing down selenoxide elimination to the conjugated but-2-enoate, although this doesn't appear to be a problem for its epimer **80**. It may be that the adjacent proline residue is providing more steric hindrance towards (*E*)-dehydrobutyrine formation than is present in the other (*E*)-dehydrobutyrine-containing peptides that have been prepared by selenoxide elimination to date.[23] Perhaps this proline is preventing the selenoxides derived from selenide **68** from adopting the preferred conformation for elimination in which H2 would be aligned with the π-orbitals of the carbonyl group as well as being accessible for the periplanar, *syn*-elimination process. However, macrocyclic intermediates derived from *allo*threonine may have very different conformations from those of the simpler intermediate **68**, and so could provide access to (*E*)-dehydrobutyrines on selenoxide elimination. This possibility is well worth investigation.

The iso-vioprolides with (*Z*)-dehydrobutyrines should be much more accessible than their (*E*)-isomers, *cf.* the isolation of the (*Z*)-dehydrobutyrines **76** and **112**. The biological activities of these vioprolide analogues are of interest in their own right. Moreover, several procedures can be envisaged for the conversion of (*Z*)-dehydrobutyrine-containing vioprolides into their (*E*)-isomers in addition to the known benzeneselenol addition – oxidative elimination sequence.[23]

The hexapeptides and dipeptide glycerides, *e.g.* **68** and **102**, are available on multigramme scales and, although the assembly steps have not been optimised, the macrocycles reported here should be relatively accessible for further work. The observations made on the effect of the Troc-carbonate of the 2-hydroxyl group of the glycerate on attempted amide formation are interesting and must be due to fairly subtle effects since the corresponding acetate did not interfere and analogous coupled products have been obtained in similar systems.[21]

Finally, perhaps it is worth concluding that, because of their biological activities, the vioprolides remain challenging yet important targets for synthesis. It is hoped that further work will be carried out in this area, not only on syntheses of the natural products themselves, but also of analogues for biological evaluation. We are unable to continue with our studies on vioprolide synthesis but we very much hope that the investigations reported in this paper will help to encourage further work in this potentially important area.

Experimental

General experimental details

Flash column chromatography was performed using Merck silica gel (60H; 40–60 μ, 230–240 mesh). Light petroleum refers to the fraction boiling between 40 and 60 °C and was redistilled. Tetrahydrofuran was dried over sodium-benzophenone and was distilled under nitrogen. Dichloromethane was dried over CaH_2 and was distilled. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Mass spectra used electron impact ionisation (EI^+), chemical ionisation using ammonia (CI^+), electrospray ionisation in the positive mode (ES^+), atmospheric pressure chemical ionisation in the positive mode ($APCI^+$) and time of flight MS with electrospray ionisation (TOF ES^+). Low resolution and high resolution mass spectra were recorded using a Micromass Trio 200 and a Kratos Concept IS spectrometer, respectively. Characteristic groups of peaks were observed in mass spectra for compounds containing selenium and chlorine atoms. Accurate mass data correspond to compounds with the isotopes ^{80}Se and ^{35}Cl. Infra-red spectra were measured using a Genesis FTIR spectrometer on NaBr plates, either neat or as evaporated films. Nuclear magnetic resonance spectra were recorded using Varian Unity 500 (500 MHz), Varian INOVA 400 (400 MHz) and Varian Unity 300 (300 MHz) spectrometers at *ca.* 25 °C unless otherwise stated. Coupling constants (*J*) are given in hertz (Hz) and chemical shifts are relative to tetramethylsilane. Residual non-deuteriated solvent was used as the internal standard.

Benzyl (*N*-*tert*-butoxycarbonyl-L-alaninyl)-D-leucinate (33). Triethylamine (2.98 mL, 21.34 mmol) was added to D-leucine benzyl ester **32** as its toluene *p*-sulfonate (2.00 g, 5.08 mmol) in DCM (80 mL) and the reaction mixture was stirred at rt for 20 min. Boc-L-alanine (1.05 g, 5.59 mmol), EDC·HCl (1.17 g, 6.10 equiv.) and HOBt (0.69 g, 5.08 mmol) were added and the reaction mixture was stirred at rt for 16 h. DCM (20 mL) was added and the solution was washed with saturated aqueous NH_4Cl (40 mL), H_2O (40 mL) and brine (40 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (3 : 1 light petroleum : EtOAc) gave the title compound **33** as a pale yellow oil (1.70 g, 85%), $[\alpha]_D$ −23.6 (*c* 1.25, $CHCl_3$) (found: M^+ + Na, 415.2192. $C_{21}H_{32}N_2O_5Na$ requires M, 415.2209); ν_{max}/cm^{-1} 3308, 2959, 1715, 1661, 1499, 1455, 1366, 1247, 1167 and 697; δ_H (400 MHz) 0.90–0.92 (6 H, m, leu 5-H_3, 4-CH_3), 1.35 (3 H, d, *J* 7.0, ala 3-H_3), 1.44 [9 H, s, $C(CH_3)_3$], 1.53–1.70 (3 H, m, leu 3-H_2, leu 4-H), 4.21 (1 H, m, ala 2-H), 4.64 (1 H, m, leu 2-H), 5.01 (1 H, br. s, NH), 5.15 and 5.17 (each 1 H, d, *J* 12.0, PhHC*H*), 6.70 (1 H, br. s, NH) and 7.32–7.35 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 18.1, 21.8, 22.8, 24.8, 28.2, 41.3, 50.0, 50.7, 67.0, 128.2, 128.3, 128.5, 135.3, 172.4 and 172.6; *m*/*z* (ES^+) 393.2 (M^+ + 1, 45%), 337.2 (50) and 127.9 (100).

(*N*-*tert*-Butoxycarbonyl-L-alaninyl)-D-leucine (34). A suspension of the benzyl ester **33** (1.70 g, 4.40 mmol) and Pd/C (10%, 0.17 g, 10 wt%) in EtOAc (40 mL) was stirred under H_2 rt for

16 h then filtered through a pad of Celite® washing the Celite with EtOAc (100 mL). Concentration under reduced pressure gave the title compound **34** as a translucent foam (1.27 g, 96%), $[\alpha]_D^{23}$ −17.6 (*c* 1.3, MeOH) (found: M^+ + H, 303.1917. $C_{14}H_{27}N_2O_5$ requires M, 303.1920); ν_{max}/cm^{-1} 3307, 2872, 1717, 1658, 1525, 1368, 1248 and 1166; δ_H (500 MHz, DMSO-d_6) 0.82 and 0.87 (each 3 H, d, *J* 6.5, either leu 5-H_3 or leu 4-CH_3), 1.16 (3 H, d, *J* 7.0, ala 3-H_3), 1.37 [9 H, s, $C(CH_3)_3$], 1.50–1.64 (3 H, m, leu 3-H_2, leu 4-H), 3.99 (1 H, m, ala 2-H), 4.23 (1 H, m, leu 2-H), 6.78 (1 H, d, *J* 7.6, NH) and 7.88 (1 H, d, *J* 8.2, NH); δ_C (100 MHz, DMSO-d_6) 18.5, 21.2, 22.9, 24.3, 28.2, 40.2, 49.7, 50.0, 78.0, 154.9, 172.6 and 174.0; *m*/*z* (ES^+) 325 (M^+ + 23, 50%).

Prop-2-enyl (*N*-*tert*-butoxycarbonyl-L-alaninyl)-D-leucinyl-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)-L-threoninate (35). The tripeptide **29** (0.94 g, 1.98 mmol), HATU (0.83 g, 2.18 mmol) and HOBt (0.13 g, 0.99 mmol) were added to the dipeptide **34** (0.72 g, 2.37 mmol) in DCM (30 mL at 0 °C and the reaction mixture stirred at rt for 16 h. DCM (20 mL) was added and the solution was washed with saturated aqueous NH_4Cl (40 mL), H_2O (40 mL) and brine (40 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (3 : 1 to 1 : 1 light petroleum : EtOAc) gave the title compound **35** as a pale yellow foam (1.02 g, 68%), R_f = 0.3 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{24}$ −126 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 780.3975. $C_{35}H_{63}N_5O_9SSiNa$ requires M, 780.4013); ν_{max}/cm^{-1} 3305, 2956, 1652, 1516, 1451, 1366, 1252, 1166, 1103, 839, 779 and 775; δ_H (400 MHz, $CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.84 [9 H, s, $SiC(CH_3)_3$], 0.92 and 0.96 (each 3 H, d, *J* 6.0, leu 5-H_3 or leu 4-CH_3), 1.17 (3 H, d, *J* 6.8, *threo* 4-H_3), 1.22 (3 H, d, *J* 5.5, ala 3-H_3), 1.44 [9 H, s, $OC(CH_3)_3$], 1.42–1.64 [3 H, m, leu 3-H_2, leu 4-H], 1.98–2.05 (2 H, m, thiopro 4-H_2), 2.30 and 2.43 (each 1 H, m, thiopro 3-H), 3.61 (1 H, t, *J* 8.0, *threo* 3-H), 4.01–4.27 (6 H, m, thiopro 5-H_2, ala 2-H, ser 2-H, ser 3-H_2), 4.35 (1 H, m, leu 2-H), 4.54–4.63 (2 H, m, CO_2CH_2), 5.00 (1 H, dd, *J* 9.0, 3.5, thiopro 2-H), 5.20 (1 H, dd, *J* 10.4, 0.7, CH=CH*H*), 5.33 (2 H, m, CH=CH*H*, *threo* 2-H), 5.88 (1 H, m, C*H*=CH_2), 6.06 (1 H, d, *J* 8.7, NH), 6.84 (1 H, d, *J* 3.7, NH), 7.10 (1 H, d, *J* 5.7, NH) and 8.55 (1 H, d, *J* 7.7, NH); δ_C (100 MHz, $CDCl_3$) −5.4, 17.3, 18.1, 19.6, 21.9, 23.2, 24.0, 24.8, 25.8, 28.3, 33.0, 39.5, 48.5, 49.6, 50.8, 60.6, 60.9, 61.5, 65.9, 67.1, 69.4, 80.2, 118.8, 131.6, 156.1, 168.3, 169.7, 173.5, 174.5 and 202.6; *m*/*z* (ES^+) 780.6 (M^+ + 23, 80%) and 758 (M^+ + 1, 100).

Prop-2-enyl 2-[(*N*-*tert*-butoxycarbonyl-L-alaninyl)-D-leucinyl-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)amino]-(*E*)-but-2-enoate (22). Copper(II) chloride (0.11 g, 0.08 mmol) and EDC (0.05 mL, 0.29 mmol) were added to the pentapeptide **35** (0.10 g, 0.13 mmol) in toluene (5 mL) and the reaction mixture was heated at 80 °C for 2.5 h before being allowed to cool to rt. Water (10 mL) and EtOAc (20 mL) were added and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (6 : 1 light petroleum : EtOAc) gave the title compound **22** as a viscous yellow oil (51 mg, 53%) containing traces of its (*Z*)-isomer **36** (^{1}H NMR), R_f = 0.5 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{22}$ −164 (*c* 0.5, $CHCl_3$) (found: M^+ + Na, 762.3935. $C_{35}H_{61}N_5O_8SSiNa$ requires M, 762.3908); ν_{max}/cm^{-1} 3292, 2955, 2931, 1647, 1511, 1389, 1366, 1166, 1152, 1105, 838, 779 and 754; δ_H (400 MHz, $CDCl_3$) major (*E*)-isomer **22** 0.07 and 0.08 (each 3 H, s, $SiCCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 0.93–0.97 (6 H, m, leu 4-CH_3, leu 5-H_3), 1.26 (3 H, d, *J* 7.5, ala 3-H_3), 1.40 [9 H, s, $OC(CH_3)_3$], 1.40–1.70 [3 H, m, leu 3-H_2, leu 4-H], 1.99 (3 H, d, *J* 7.0, 4-H_3), 1.98–2.42 (4 H, m, thiopro 4-H_2, thiopro 3-H_2), 3.60 (1 H, m, thiopro 5-H), 4.03–4.04 (2 H, m, thiopro 5-H′, ser 3-H), 4.19–4.29 (2 H, m, ser 3-H′, ala 2-H), 4.44 (1 H, m, leu 2-H), 4.71–4.73 (2 H, m, CO_2CH_2), 4.95 (1 H, dd, *J* 8.5, 4.0, thiopro 2-H), 5.13 (1 H, m, ser 2-H), 5.25 (1 H, d, *J* 10.5, CH=CH*H*), 5.36 (1 H, dd, *J* 17.0, 1.0, CH=CH*H*), 5.91–6.00 (2 H, m, C*H*=CH_2, NH), 6.41 (1 H, q, *J* 7.2, 3-H), 7.41 (1 H, d, *J* 3.8, NH), 8.20 (1 H, s, NH) and 8.68 (1 H, d, *J* 7.0, NH); minor (*Z*)-isomer **36** 1.84 (3 H, d, *J* 7.0, 4-H_3); δ_C (100 MHz, $CDCl_3$) −5.4(2), 14.2, 16.0, 18.1, 21.9, 23.2, 24.1, 24.7, 25.7, 28.2, 32.9, 39.9, 48.0, 49.0, 50.1, 61.3, 61.5, 66.1, 69.0, 80.0, 118.9, 126.4, 129.9, 131.6, 156.7, 164.5, 167.6, 172.4, 174.1 and 203.4; *m*/*z* (ES^+) 762.7 (M^+ + 23, 75%), 757.7 (100) and 740.6 (M^+ + 1, 60).

Prop-2-enyl 2-[(*N*-*tert*-butoxycarbonyl-L-alaninyl)-D-leucinyl-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)amino]-(*Z*)-but-2-enoate (36). Triethylamine (34 μL, 0.25 mmol, 1.90 equiv.) and then mesyl chloride (14 μL, 0.18 mmol) were added to the pentapeptide **35** (0.10 g, 0.13 mmol) in DCM (1.20 mL) at 0 °C and the reaction mixture was stirred at rt for 30 min. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (3 : 1 light petroleum : EtOAc) gave the title compound **36** as a pale yellow viscous oil (56 mg, 58%), R_f = 0.6 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{29}$ −164 (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 3292, 2930, 1647, 1511, 838 and 779; δ_H (400 MHz, $CDCl_3$) 0.08 and 0.09 (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 0.95 and 0.98 (each 3 H, d, *J* 7.0, either leu 4-CH_3 or leu 5-H_3), 1.27 (3 H, d, *J* 7.0, ala 3-H_3), 1.40 [9 H, s, $OC(CH_3)_3$], 1.40–1.73 [3 H, m, leu 3-H_2, leu 4-H], 1.84 (3 H, d, *J* 7.0, 4-H_3), 1.99–2.04 (2 H, m, thiopro 4-H_2), 2.29–2.48 (2 H, m, thiopro 3-H_2), 3.62 (1 H, m, thiopro 5-H), 4.07–4.27 (3 H, m, ala 2-H, ser 3-H, thiopro 5-H′), 4.32–4.40 (2 H, m, ser 3-H′, and leu 2-H), 4.60–4.73 (2 H, m, CO_2CH_2), 4.96 1 H, (dd, *J* 8.5, 3.8, thiopro 2-H), 5.23–5.24 (2 H, m, CH=CH*H*, ser 2-H), 5.35 (1 H, d, *J* 17.2, 1.1, CH=CH*H*), 5.93 (1 H, m, C*H*=CH_2), 6.20 (1 H, d, *J* 8.3, NH), 6.75 (1 H, q, *J* 7.0, 3-H), 7.46 (1 H, d, *J* 3.3, NH), 8.01 (1 H, s, NH) and 8.72 (1 H, d, *J* 7.3, NH); δ_C (100 MHz, $CDCl_3$) −5.4(2), 13.9, 15.5, 18.1, 21.9, 23.3, 24.0, 24.8, 25.7, 28.2, 33.0, 39.8, 48.3, 48.7, 50.5, 61.7, 62.3, 66.1, 69.2, 80.0, 118.5, 126.8, 131.7, 135.6, 156.9, 164.8, 166.9, 172.8, 174.4 and 203.4.

Prop-2-enyl (2*S*)-2,3-dihydroxypropanoate (44).[17] Concentrated aqueous HCl (8.1 mL) was added to L-serine (4.20 g, 39.97 mmol) in water (190 mL) and the solution cooled to 0 °C. An aqueous solution of sodium nitrite (5.53 g, 80.14 mmol, 100 mL) was slowly added at 0 °C and the reac-

tion mixture was stirred at rt for 24 h. After concentration under reduced pressure, THF (150 mL) was added and the mixture was filtered. The residue was washed with THF (2 × 20 ml) and the organic solution and washings concentrated under reduced pressure. More THF was added and the solution concentrated under reduced pressure. This was repeated five times (with care not to leave the concentrated dihydroxyacid too long at rt to avoid polymerisation) to give (2*S*)-2,3-dihydroxypropanoic acid as a colourless oil, used directly in the next step (found: $[M - H]^-$, 105.0192. $C_3H_5O_4$ requires M, 105.0193); ν_{max}/cm^{-1} 3318, 3039, 2920, 1614, 1588, 1490, 1462, 1333, 1265, 1245, 1152, 926, 852, 772 and 687; δ_H (400 MHz, DMSO-d_6) 3.51 (1 H, dd, *J* 11.1, 5.1, 3-H), 3.56 (1 H, dd, *J* 11.1, 4.0, 3-H′), 3.95 (1 H, t, *J* 4.6, 2-H) and 7.44 (1 H, br. s, OH); δ_C (100 MHz, DMSO-d_6) 63.7, 71.9 and 174.3; *m*/*z* (ES^-) 104.9 ($[M - 1]^-$, 100%).

Toluene *p*-sulfonic acid (760 mg, 4.0 mmol) was added to this 2,3-dihydroxypropanoic acid in allyl alcohol (54 mL, 794 mmol) and $CHCl_3$ (60 mL) at rt and the mixture was heated under reflux (Dean Stark) for 3.5 h then cooled and concentrated under reduced pressure. Chromatography of the residue (7 : 3 light petroleum : EtOAc) gave the title compound **44** (4.16 g, 71%) as a colourless oil, R_f = 0.40 (7 : 3 light petroleum : EtOAc), $[\alpha]_D^{20}$ −20.9 (*c* 1.2, $CHCl_3$), lit.[17] −21.1 (*c* 1.2, $CHCl_3$) (found: M^+ + Na, 169.0480. $C_6H_{10}O_4Na$ requires M, 169.0477); ν_{max}/cm^{-1} 3417, 1735, 1648, 1379, 1200, 1115, 1067, 932, 771 and 560; δ_H (500 MHz, $CDCl_3$) 3.44 (2 H, br. s, 2 × OH), 3.87 (1 H, dd, *J* 12.0, 3.7, 3-H), 3.93 (1 H, dd, *J* 12.0, 3.1, 3-H′), 4.31 (1 H, t, *J* 3.6, 2-H), 4.71 (2 H, dt, *J* 5.8, 1.4, CO_2CH_2), 5.28 (1 H, dq, *J* 10.5, 1.3, CH═CH*H*), 5.36 (1 H, dq, *J* 17.2, 1.3, CH═CH*H*) and 5.92 (1 H, m, C*H*═CH_2); δ_C (125 MHz, $CDCl_3$) 64.0, 66.5, 71.7, 119.1, 131.2 and 172.7; *m*/*z* (ES^+) 169.0 (M^+ + 23, 100%).

Prop-2-enyl (2*S*)-3-hydroxy-2-(2,2,2-trichloroethoxy-carbonyloxy)propanoate (45). A solution of the propenyl glycerate **44** (100 mg, 0.68 mmol), *tert*-butyldimethylsilyl chloride (144 mg, 0.96 mmol) and imidazole (70 mg, 1.0 mmol) in THF (3 mL) was stirred at rt for 17 h. The reaction mixture was diluted with ether, washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10 : 1 light petroleum : EtOAc) gave prop-2-enyl (2*S*)-2-hydroxy-3-*tert*-butyldimethylsilyloxy-propanoate[17] (100 mg, 56%), R_f = 0.3 (10 : 1 hexane : EtOAc) (found: M^+ + Na, 283.1340. $C_{12}H_{24}O_4SiNa$ requires M, 283.1322); δ_H (500 MHz, $CDCl_3$) 0.03 and 0.05 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 3.07 (1 H, m, OH), 3.86 (1 H, dd, *J* 15.0, 4.1, 3-H), 3.94 (1 H, dd, *J* 15.0, 3.5, 3-H′), 4.23 (1 H, m, 2-H), 4.65–4.80 (2 H, m, CO_2CH_2), 5.25 (1 H, d, *J* 10.5, CH═CH*H*), 5.34 (1 H, d, *J* 17.3, CH═CH*H*) and 5.92 (1 H, m, C*H*═CH_2); δ_C (125 MHz, $CDCl_3$) −5.6, −5.5, 18.2, 25.7, 65.0, 66.0, 71.9, 118.8, 131.5 and 172.4; *m*/*z* (ES^+) 283.2 (M^+ + 23, 100%) and 261.2 (M^+ + 1, 95). Minor amounts of the less polar bis-silylated product and unchanged starting material were also obtained.

A solution of the monosilylated ester (768 mg, 02.95 mmol), 2,2,2-trichloroethoxy chloroformate (496 mL), DMAP (188 mg) and pyridine (0.5 mL) in DCM (25 mL) was stirred at rt for 17 h. Ether was added and the mixture was washed with aqueous hydrogen chloride (1 M), saturated aqueous $NaHCO_3$ and brine. After drying ($MgSO_4$), the organic extracts were concentrated under reduced pressure. Chromatography of the residue (10 : 1 light petroleum : EtOAc) gave prop-2-enyl (2*S*)-3-*tert*-butyldimethylsilyloxy-2-(2,2,2-trichloroethoxycarbonyloxy)-propanoate (706 mg, 66%), R_f = 0.2 (20 : 1 light petroleum : EtOAc), $[\alpha]_D^{23}$ −31 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.08 and 0.10 (each 3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 4.00–4.15 (2 H, m, 3-H_2), 4.65–4.77 (2 H, m, CO_2CH_2), 4.78 and 4.84 (each 1 H, d, *J* 12.5, Cl_3CCH*H*), 5.13 (1 H, m, 2-H), 5.27 (1 H, d, *J* 10.5, CH═CH*H*), 5.35 (1 H, d, *J* 17.2, CH═CH*H*) and 5.90 (1 H, m, C*H*═CH_2); δ_C (100 MHz, $CDCl_3$) −5.5(2), 18.2, 25.7, 62.5, 66.2, 77.6, 94.2, 119.0, 131.2, 153.6 and 166.9.

Copper(II) chloride (12 mg) was added to the fully protected glycerate (370 mg, 0.88 mmol) in water (0.5 mL) and acetone (8 mL) and the reaction mixture stirred at 57 °C for 17 h then cooled to rt. After dilution with DCM and filtration through sand, concentration of the filtrate under reduced pressure gave the title compound **45** (238 mg, 87%), R_f = 0.2 (5 : 1 light petroleum : EtOAc), $[\alpha]_D^{23}$ −32 (*c* 1.05, $CHCl_3$) (found: M^+ + Na, 342.9522. $C_9H_{11}O_6Cl_3Na$ requires M, 342.9519); δ_H (400 MHz, $CDCl_3$) 2.16 (1 H, br. s, OH), 4.05–4.15 (2 H, m, 3-H_2), 4.65–4.80 (2 H, m, CO_2CH_2), 4.83 (2 H, s, Cl_3CCH_2), 5.16 (1 H, m, 2-H), 5.31 (1 H, d, *J* 10.5, CH═CH*H*), 5.33 (1 H, d, *J* 17.5, CH═CH*H*) and 5.90 (1 H, m, C*H*═CH_2); δ_C (100 MHz, $CDCl_3$) 62.0, 66.5, 69.4, 77.2, 94.0, 119.2, 131.0, 153.3 and 166.8; *m*/*z* (ES^+) 345.0 (M^+ + 23, 90%) and 343.1 (M^+ + 23, 100%).

The sample of the monoprotected glycerate **45** contained minor *tert*-butyldimethylsilyl containing residues. However attempts to purify it by chromatography (5 : 1 to 1 : 1 light petroleum : EtOAc) gave a mixture of the Troc-protected glycerate **45** together with the carbonate **46**; δ_H (400 MHz, $CDCl_3$) carbonate **46** 4.56 (1 H, dd, *J* 9.0, 5.0, 3-H), 4.69 (1 H, t, *J* 9.0, 3-H′), 4.73–4.80 (2 H, m, CO_2CH_2), 5.11 (1 H, dd, *J* 9.0, 5.0, 2-H), 5.34 (1 H, d, *J* 10.5, CH═CH*H*), 5.39 (1 H, d, *J* 17.3, CH═CH*H*) and 4.94 (1 H, m, C*H*═CH_2).

Prop-2-enyl (2*S*)-2-hydroxy-3-(*N*-methyl-*N*-*tert*-butoxycarbonyl-L-valinyloxy)propanoate (48), prop-2-enyl (2*S*)-3-hydroxy-2-(*N*-methyl-*N*-*tert*-butoxycarbonyl-L-valinyloxy)propanoate (49) and prop-2-enyl (2*S*)-2,3-bis-(*N*-methyl-*N*-*tert*-butoxycarbonyl-L-valinyloxy)propanoate (50). Dicyclohexyl carbodi-imide (1.18 g, 5.62 mmol) in DCM (10.5 mL) was added to the *N*-methyl-*N*-*tert*-butoxycarbonylvaline (**47**)[18] (1.0 g, 4.32 mmol), 2,3-dihydroxypropanoate **44** (0.98 g, 6.70 mmol) and DMAP (282 mg, 2.31 mmol) in dry DCM (100 mL) dropwise at 0 °C and the solution stirred for 2 h at 0 °C and for 2 h at rt. Ether (50 mL) was added and the mixture filtered. After washing the precipitate with ether (2 × 5 mL) and concentration of the filtrate and washings under reduced pressure, chromatography of the residue (1 : 3 EtOAc : light petroleum) gave a minor product provisionally identified as the title compound **50** (248 mg, 10%) as a colourless oil, ^1H NMR broadened by rotamers, R_f = 0.75 (1 : 3 EtOAc : light petroleum), $[\alpha]_D^{25}$ −55.9 (*c* 1.0, MeOH);

ν_{max}/cm^{-1} 2968, 1748, 1697, 1451, 1391, 1367, 1311, 1254, 1148, 988, 879 and 773; δ_H (500 MHz, DMSO-d_6) 0.85–1.00 (12 H, br. d, J 6.6, 4 × val CH_3), 1.41 and 1.42 [each 9 H, s, $OC(CH_3)_3$], 2.15 (2 H, m, 2 × val 3-H), 2.75 and 2.79 (each 3 H, s, NCH_3), 4.10–4.40 (2 H, br. m, 2 × val 2-H), 4.47 and 4.53 (each 1 H, dd, J 12.3, 3.8, 3-H), 4.30 (2 H, m, CO_2CH_2), 5.25 (1 H, dq, J 10.4, 1.6, CH=CHH), 5.34 (1 H, dq, J 17.3, 1.6, CH=CHH), 5.45 (1 H, m, 2-H) and 5.91 (1 H, m, CH=CH_2); m/z (ES$^+$) 595 (M$^+$ + 23, 100%). The second fraction was the title compound **48** (966 mg, 62%) as a colourless oil, R_f = 0.32 (1 : 3 EtOAc : light petroleum), $[\alpha]_D^{27}$ −66 (c 1.0, $CHCl_3$) (found: M$^+$ + Na, 382.1849. $C_{17}H_{29}NO_7Na$ requires M, 382.1842); ν_{max}/cm^{-1} 3450, 2968, 1741, 1694, 1452, 1367, 1144, 1004, 935 and 773; δ_H (500 MHz, 70 °C, DMSO-d_6) 0.84 and 0.93 (each 3 H, d, J 6.6, either val 3-CH_3 or val 4-H_3), 1.40 [9 H, s, $OC(CH_3)_3$], 2.14 (1 H, m, val 3-H), 2.75 (3 H, s, NCH_3), 4.21 (1 H, dd, J 11.0, 4.5, 3-H), 4.30–4.38 (3 H, m, 2-H, 3-H′, val 2-H), 4.56–4.65 (2 H, m, CO_2CH_2), 5.23 (1 H, dq, J 10.5, 1.5, CH=CHH), 5.33 (1 H, dq, J 17.3, 1.5, CH=CHH), 5.63 (1 H, d, J 6.0, OH) and 5.92 (1 H, m, CH=CH_2); δ_C (125 MHz, 70 °C, DMSO-d_6) 18.4, 19.4, 27.1, 27.7, 30.6, 64.5, 65.3, 68.3, 79.0, 117.6, 132.0, 154.8, 170.0 and 170.5; m/z (ES$^+$) 382.2 (M$^+$ + 23, 70%) and 260.1 (100). The third fraction was the title compound **49** (343 mg, 22%) as a colourless oil, R_f 0.18 (1 : 3 EtOAc : light petroleum), $[\alpha]_D^{25}$ −57 (c 1.0, $CHCl_3$) (found: M$^+$ + Na, 382.1847. $C_{17}H_{29}NO_7Na$ requires M, 382.1842; ν_{max}/cm^{-1} 3429, 2969, 1744, 1695, 1452, 1391, 1368, 1192, 1145, 1070, 986, 938 and 775; δ_H (500 MHz, 100 °C, DMSO-d_6) 0.89 and 1.01 (each 3 H, d, J 6.6, either val 3-CH_3 or val 4-H_3), 1.42 [9 H, s, $OC(CH_3)_3$], 2.24 (1 H, m, val 3-H), 2.81 (3 H, s, NCH_3), 3.80 (2 H, m, 3-H_2), 4.30 (1 H, d, J 9.7, val 2-H), 4.63 (2 H, dt, J 5.4, 1.5, CO_2CH_2), 5.09 (1 H, m, 2-H), 5.23 (1 H, dq, J 10.6, 1.5, CH=CHH), 5.33 (1 H, dq, J 17.3, 1.5, CH=CHH) and 5.90 (1 H, m, CH=CH_2); δ_C (125 MHz, 100 °C, DMSO-d_6) 18.2, 19.0, 27.0, 27.5, 30.4, 60.3, 64.6, 73.7, 79.0, 117.4, 131.6, 154.7, 167.0 and 169.5; m/z (ES$^+$) 382.2 (M$^+$ + 23, 100%).

Prop-2-enyl (2*S*)-2-(2,2,2-trichloroethoxycarbonyloxy)-3-(*N*-methyl-*N*-*tert*-butoxycarbonyl-L-valinyloxy)propanoate (51). Pyridine (0.62 mL, 7.75 mmol) and 2,2,2-trichloroethoxycarbonyl chloride (0.62 mL, 4.4 mmol) were added to the hydroxypropanoate **48** (966 mg, 2.69 mmol) and DMAP (141 mg, 1.16 mmol) in DCM (53 mL) at 0 °C and the reaction mixture stirred for 3 h then diluted with DCM. The solution was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 8 EtOAc : light petroleum) gave the title compound **51** (1.40 g, 97%) as a colourless oil, a mixture of rotamers, R_f = 0.50 (1 : 8 EtOAc : light petroleum), $[\alpha]_D^{24}$ −62 (c 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2967, 1750, 1693, 1445, 1385, 1307, 1199, 1144, 1049, 989, 822, 777 and 734; δ_H (400 MHz, $CDCl_3$) 0.89 and 0.99 (each 3 H, d, J 6.7, either val 3-CH_3 or val 4-H_3), 1.45 [9 H, s, $OC(CH_3)_3$], 2.18 (1 H, m, val 3-H), 2.81 (3 H, s, NCH_3), 4.15 (1 H, br. d, J 7.0, val 2-H), 4.50 and 4.66 (each 1 H, m, 3-H), 4.70 (2 H, d, J 5.7, CO_2CH_2), 4.81 (2 H, br. s, CH_2CCl_3), 5.20–5.40 (3 H, m, CH=CH_2, 2-H) and 5.89 (1 H, m, CH=CH_2); δ_C (100 MHz, $CDCl_3$) 18.9, 19.6, 19.9, 27.7, 28.3, 30.6, 62.1, 62.3, 63.1, 64.9, 66.8, 73.9, 74.1, 77.1, 80.1, 80.4, 93.9, 94.0, 119.5, 130.8, 153.2, 155.3, 156.1, 165.7, 165.8, 170.3 and 170.9; m/z (ES$^+$) 553.3 (M$^+$ + 1, 95%) and 551.4 (M$^+$ + 1, 100).

Prop-2-enyl (2*S*)-2-(2,2,2-trichloroethoxycarbonyloxy)-3-(*N*-methyl-L-valinyloxy)propanoate (52). The Boc protected amine **51** (1.28 g, 2.38 mmol) was stirred in trifluoroacetic acid : DCM (1 : 4, 70 mL) at rt for 1 h. Saturated aqueous $NaHCO_3$ was added until the pH = 9 and the resulting mixture was extracted using ether. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 4 EtOAc : light petroleum) gave the title compound **52** (933 mg, 90%) as a colourless oil, R_f = 0.60 (1 : 1 EtOAc : light petroleum), $[\alpha]_D^{25}$ −15.8 (c 1.0, $CHCl_3$) (found: M$^+$ + H, 434.0528. $C_{15}H_{23}NO_7Cl_3$ requires M, 434.0540); ν_{max}/cm^{-1} 2963, 1741, 1452, 1382, 1247, 1203, 1156, 1049, 820, 780 and 733; δ_H (400 MHz, $CDCl_3$) 0.94 (6 H, d, J 6.9, val 3-CH_3, val 4-H_3), 1.56 (1 H, br. s, NH), 1.91 (1 H, m, val 3-H), 2.34 (3 H, s, NCH_3), 2.94 (1 H, d, J 6.0, val 2-H), 4.54 (1 H, dd, J 12.3, 5.4, 3-H), 4.70 (3 H, m, CO_2CH_2, 3-H′), 4.80 (2 H, s, CH_2CCl_3), 5.28 (2 H, m, CH=CHH, 2-H), 5.35 (1 H, dq, J 17.3, 1.3, CH=CHH) and 5.89 (1 H, m, CH=CH_2); δ_C (100 MHz, $CDCl_3$) 18.4, 19.1, 31.3, 35.1, 61.8, 66.7, 69.1, 74.1, 77.1, 93.9, 119.5, 130.8, 153.2, 165.9 and 174.2; m/z (ES$^+$) 438.2 (M$^+$ + 1, 50%), 436.2 (M$^+$ + 1, 70), 434.3 (M$^+$ + 1, 100).

Prop-2-enyl (2*S*)-3-[(*N*-*tert*-butyloxycarbonyl-L-threoninyl)-*N*-methyl-L-valinyloxy]-2-(2,2,2-trichloroethoxycarbonyloxy)propanoate (53). HATU (136 mg, 0.36 mmol) was added to Boc-L-threonine (135 mg, 0.612 mmol) in DMF : DCM (1 : 1, 3 mL) and the solution stirred at 0 °C for 5 min. The valinyl ester **52** (294 mg, 0.67 mmol) in DCM (1.5 mL) was added followed by *N*-methylmorpholine (0.337 mL, 3.06 mmol) and the mixture was stirred at rt for 3.5 d then concentrated under reduced pressure. EtOAc (10 mL) was added and the solution washed with saturated aqueous NH_4Cl with the aqueous washing re-extracted with EtOAc (10 mL). The organic extracts were washed with brine (10 mL), dried ($MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue (1 : 1 EtOAc : light petroleum) gave the title compound **53** (332 mg, 85%) as a white foam, R_f = 0.75 (1 : 1 EtOAc : light petroleum), $[\alpha]_D^{23}$ −85 (c 1.0, $CHCl_3$) (found: M$^+$ + Na, 657.1351. $C_{24}H_{37}N_2O_{11}Cl_3Na$ requires M, 657.1360); ν_{max}/cm^{-1} 3401, 2974, 1752, 1709, 1635, 1491, 1391, 1248, 1172, 1136, 1090, 1050, 1009, 822, 781 and 733; δ_H (500 MHz, 70 °C, DMSO-d_6) 0.74 and 0.93 (each 3 H, d, J 6.6, val 3-CH_3, val 4-H_3), 1.02 (3 H, d, J 6.3, *threo* 4-H_3), 1.35 [9 H, s, $OC(CH_3)_3$], 2.14 (1 H, m, val 3-H), 3.02 (3 H, s, NCH_3), 3.32 (1 H, br. s, OH), 3.74 (1 H, m, *threo* 3-H), 4.24 (1 H, t, J 7.5, *threo* 2-H), 4.53 (1 H, dd, J 12.5, 4.7, 3-H), 4.58 (1 H, dd, J 12.5, 2.8, 3-H′), 4.66 (2 H, m, CO_2CH_2), 4.77 (1 H, d, J 10.0, val 2-H), 4.97 and 5.02 (each 1 H, d, J 12.0, CHHCCl$_3$), 5.25 (1 H, dq, J 10.5, 1.5, CH=CHH), 5.34 (1 H, dq, J 17.3, 1.5, CH=CHH), 5.44 (1 H, dd, J 4.6, 3.0, 2-H), 5.90 (1 H, m, CH=CH_2) and 6.75 (1 H, br. d, J 8.2, NH); δ_C (125 MHz, 70 °C, DMSO-d_6) 18.3, 19.5, 19.7, 26.8, 28.1, 31.5, 56.5, 61.0, 62.4, 66.0, 66.5, 73.9, 76.4, 78.1, 94.4, 118.5, 131.6,

152.6, 155.4, 165.9, 169.7 and 172.1; *m*/*z* (ES^-) 673.1 ($[M + 35]^-$, 50%), 671.1 ($[M + 35]^-$, 100) and 669.1 ($[M + 35]^-$, 85).

Prop-2-enyl (2*S*)-3-[(*N*-*tert*-butyloxycarbonyl-L-prolinyl)-L-threoninyl-*N*-methyl-L-valinyloxy]-2-(2,2,2-trichloroethoxycarbonyloxy)propanoate (54). Hydrogen chloride in dioxane (4 M, 5.54 mL) was added to the dipeptide ester **53** (260 mg, 0.41 mmol) and the mixture stirred at 0 °C for 4 h then concentrated under reduced pressure to provide the hydrochloride salt of the deprotected dipeptide (237 mg) as a yellow oil. *N*-Methylmorpholine (0.22 mL, 2.04 mmol) and isobutyl chloroformate (0.088 mL, 0.653 mmol) were added to Boc-proline (132 mg, 0.612 mmol) in THF (2 mL) at −20 °C and the mixture was stirred for 20 min at −20 °C. The deprotected dipeptide in THF (2 mL) was added and the mixture was stirred at rt for 15 h then concentrated under reduced pressure. The residue was taken up in EtOAc (10 mL) and the solution washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 EtOAc : light petroleum) gave the title compound **54** (230 mg, 77%) as a colourless oil, R_f = 0.34 (2 : 1 EtOAc : light petrolem); δ_H (500 MHz, 70 °C, DMSO-d_6) 0.77 and 0.95 (each 3 H, d, *J* 6.3, either val 3-CH_3 or val 4-H_3), 1.07 (3 H, d, *J* 6.0, *threo* 4-H_3), 1.38 [9 H, s, $OC(CH_3)_3$], 1.77 (3 H, m, pro 4-H_2, pro 3-H), 2.05 (1 H, m, pro 3-H′), 2.15 (1 H, m, val 3-H), 3.04 (3 H, s, NCH_3), 3.12 (1 H, br. s, OH), 3.30 and 3.37 (each 1 H, m, pro 5-H), 3.88 (1 H, m, *threo* 3-H), 4.19 (1 H, m, *threo* 2-H), 4.51 (1 H, dd, *J* 12.6, 5.3, 3-H), 4.62 (1 H, dd, *J* 12.6, 3.0, 3-H′), 4.62 (1 H, m, pro 2-H), 4.68 (2 H, m, CO_2CH_2), 4.76 (1 H, d, *J* 9.7, val 2-H), 4.95 and 4.99 (each 1 H, d, *J* 12.0, CH*H*CCl_3), 5.26 (1 H, dq, *J* 10.5, 1.3, CH═CH*H*), 5.35 (1 H, dq, *J* 17.3, 1.6, CH═CH*H*), 5.43 (1 H, dd, *J* 5.0, 3.1, 2-H), 5.91 (1 H, m, C*H*═CH_2) and 7.64 (1 H, br. s, NH); δ_C (125 MHz, 70 °C, DMSO-d_6) 18.2, 19.1, 19.3, 22.8, 26.5, 27.8, 31.3, 46.3, 54.2, 59.1, 61.2, 62.0, 65.7, 66.5, 73.8, 76.3, 78.4, 94.2, 118.2, 131.3, 152.2, 153.3, 165.5, 169.3, 171.2 and 171.8.

(2*S*)-3-[(*N*-*tert*-Butyloxycarbonyl-L-threoninyl-*N*-methyl-L-valinyloxy]-2-(2,2,2-trichloroethoxycarbonyloxy)propanoic acid (55). A mixture of the allyl ester **53** (80 mg, 0.13 mmol), phenylsilane (28 μL, 0.25 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.013 mmol) in DCM (7 mL) was stirred at rt for 1.5 h and then concentrated to leave brownish oil. Chromatography (8 : 1 : 1 DCM : MeOH : AcOH) gave a residue that was taken up in EtOAc and chloroform. The solution was concentrated under reduced pressure to leave the title compound **55** (53 mg, 71%) containing a few minor impurities as a pale, yellow foam, R_f = 0.3 (8 : 1 : 1 DCM : MeOH : AcOH) (found: M^+ + Na, 617.1042. $C_{21}H_{33}N_2O_{11}Cl_3Na$ requires M, 617.1042); δ_H (400 MHz, $CDCl_3$) 0.84 and 1.03 (each 3 H, d, *J* 6.5, either val 3-CH_3 or val 4-H_3), 1.23 (3 H, d, *J* 6.2, *threo* 4-H_3), 1.42 [9 H, s, $OC(CH_3)_3$], 2.25 (1 H, m, val 3-H), 3.05 (3 H, s, NCH_3), 4.18 (1 H, m, *threo* 3-H), 4.48 (1 H, m, 3-H), 4.55 (1 H, m, *threo* 2-H), 4.70 (1 H, m, 3-H′), 4.80 and 4.82 (each 1 H, d, *J* 12.0, HC*H*CCl_3), 4.83 (1 H, m, val 2-H), 5.27 (1 H, m, 2-H) and 5.88 (1 H, br. d, *J* 8.0, NH); δ_C (100 MHz, $CDCl_3$) 18.4, 19.0, 19.8, 26.9, 28.2, 31.2, 54.3, 62.2, 63.0, 67.3, 73.8, 80.4, 93.9, 153.2, 156.4, 168.9, 169.6 and 173.0; *m*/*z* (ES^-) 597.3 ($[M - 1]^-$, 40%), 595.3 ($[M - 1]^-$, 100) and 593.3 ($[M - 1]^-$, 95).

The Boc-protected tripeptide **33** (100 mg, 0.26 mmol) was deprotected by stirring in trifluoroacetic acid (1.6 mL) and DCM (6 mL) at rt for 2 h. Concentration under reduced pressure gave the aminodipeptide **60** (61 mg, *ca.* 100%); δ_H (400 MHz, $CDCl_3$) 0.94 (6 H, d, *J* 6.5, leu 5-H_3, 4-CH_3), 1.35 (3 H, d, *J* 7.0, ala 3-H_3), 1.50–1.75 (3 H, m, leu 3-H_2, leu 4-H), 1.79 (2 H, br. s, NH_2), 3.56 (1 H, m, ala 2-H), 4.65 (1 H, m, leu 2-H), 5.15 and 5.18 (each 1 H, d, *J* 12.5, PhHC*H*), 7.30–7.40 (5 H, m, ArH) and 7.69 (1 H, br. d, *J* 7.5, NH). Isobutyl chloroformate (7 μL, 0.05 mmol) and NMM (16.5 μL, 0.15 mmol) were added to the acid **55** (27 mg, 0.045 mmol) in THF (1 mL) at −15 °C and the solution stirred for 10 min. The aminodipeptide **60** (11 mg, 0.04 mmol) was added and the mixture stirred at −20 °C to rt for 16 h. The solution was diluted using EtOAc, filtered through Celite and concentrated under reduced pressure. Chromatography gave the coupled product **56** (28 mg) that contained several impurities; δ_H (400 MHz, $CDCl_3$) 0.93 (6 H, d, *J* 6.5, leu 4-CH_3, leu 5-H_3), 0.99 and 1.21 (each 3 H, d, *J* 6.3, either val 3-CH_3 or val 4-H_3), 1.43 [9 H, s, $OC(CH_3)_3$], 1.50–1.75 (3 H, m, leu 3-H_2, leu 4-H), 1.73 and 1.76 (each 3 H, d, *J* 6.5, either *threo* 4-H_3 or ala 3-H_3), 2.23 (1 H, m, val 3-H), 3.09 (3 H, s, NCH_3), 3.85 (1 H, br. d, *J* 6.3, OH), 4.10 (1 H, m, *threo* 3-H), 4.45–4.85 (7 H, m, *threo* 2-H, val 2-H, 3-H_2, Cl_3CCH_2, ala 2-H), 5.04 (1 H, m, leu 2-H), 5.15 and 5.17 (each 1 H, d, *J* 12.5, PhHC*H*), 5.18 (1 H, m, 2-H), 5.47 (1 H, br. d, *J* 7.0, NH), 6.42 (1 H, m, NH) and 7.30–7.45 (6 H, m, NH, ArH); δ_C (100 MHz, $CDCl_3$) 99.0; *m*/*z* (ES^-) 907.5372 ($[M + Cl]^-$, 75%), 905.5070 ($[M + 35]^-$, 100) and 903.5116 ($[M + Cl]^-$, 80), $C_{37}H_{55}N_4O_{13}Cl_4$ requires M, 903.2520.

Prop-2-enyl (2*S*)-3-{[*N*-*tert*-butyloxycarbonyl-*O*-(2,2,2-trichloroethoxycarbonyl)-L-threoninyl]-*N*-methyl-L-valinyloxy}-2-(2,2,2-trichloroethoxycarbonyloxy)propanoate (57). 2,2,2-Trichloroethyl chloroformate (0.07 mL, 0.51 mmol) and pyridine (0.46 mL, 5.72 mmol) were added to the mono-Troc-protected peptide **53** (90 mg, 0.14 mmol) in DCM (9 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. Water (15 mL) was added, the mixture was extracted with EtOAc (2 × 15 mL), and the organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography (9 : 1 to 2 : 1 light petroleum : EtOAc) gave the title compound **57** as a pale yellow oil (90 mg, 80%), R_f = 0.5 (2 : 1 light petroleum : EtOAc), $[\alpha]_D^{29}$ −32 (*c* 0.8, $CHCl_3$) (found: M^+ + H, 809.0573. $C_{27}H_{39}N_2O_{13}Cl_6$ requires M, 809.0578); ν_{max}/cm^{-1} 2966, 1755, 1712, 1650, 1380, 1248, 1048 and 821; δ_H (500 MHz, $CDCl_3$) 0.86 and 1.04 (each 3 H, d, *J* 6.5, either val 3-CH_3 or val 4-H_3), 1.38 (3 H, d, *J* 6.5, *threo* 4-H_3), 1.42 [9 H, s, $OC(CH_3)_3$], 2.22 (1 H, m, val 3-H), 3.13 (3 H, s, NCH_3), 4.53 (1 H, dd, *J* 10.5, 3-H), 4.66–4.71 (3 H, m, CO_2CH_2, 3-H′), 4.77–4.85 (5 H, m, 2 × CH_2CCl_3, *threo* 3-H), 4.93 (1 H, d, *J* 10.5, val 2-H), 5.16 (1 H, m, *threo* 2-H), 5.28–5.42 (4 H, m, CH═CH_2, 2-H, NH) and 5.91 (1 H, ddt, *J* 17.0, 10.5, 6.0, *CH*═CH_2); δ_C (125 MHz, $CDCl_3$) 16.7, 18.7, 19.7, 27.3, 28.2, 31.7, 53.9, 61.8, 62.4, 66.8, 74.1, 75.0, 76.8, 77.2, 80.2, 94.0, 94.4, 119.6, 130.8, 153.2, 153.6, 155.6, 165.8, 169.7 and 170.6; *m*/*z* (ES^+) 833 (M^+ + 23, 100%).

(2*S*)-3-{[*N*-*tert*-Butyloxycarbonyl-*O*-(2,2,2-trichloroethoxycarbonyl)-L-threoninyl]-*N*-methyl-L-valinyloxy}-2-(2,2,2-trichloroethoxycarbonyloxy)propanoic acid (58). The catalyst $Pd(PPh_3)_4$ (10 mg, 8.9 μmol, 10 mol%) and phenylsilane (22 μL, 0.18 mmol) were added to the allyl ester **57** (70 mg, 0.09 mmol) in DCM (6 mL) and the reaction mixture stirred in the absence of light for 1 h. After concentration under reduced pressure, chromatography of the residue (4 : 1 to 1 : 1 light petroleum : EtOAc) gave the title compound **58** as a yellow viscous oil (38 mg, 55%), R_f = 0.50 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{28}$ −159 (*c* 0.99 in $CHCl_3$) (found: M^+ − H, 767.0101. $C_{24}H_{33}N_2O_{13}Cl_6$ requires M, 767.0108); ν_{max}/cm^{-1} 2968, 1755, 1248, 1169, 1048 and 820; δ_H (400 MHz, DMSO-d_6) 0.73 and 0.95 (each 3 H, d, *J* 7.0, either val 3-CH_3 or val 4-H_3), 1.25 (3 H, d, *J* 6.5, *threo* 4-H_3), 1.35 [9 H, s, $OC(CH_3)_3$], 2.15 (1 H, m, val 3-H), 3.01 (3 H, s, NCH_3), 4.49 (1 H, m, 3-H), 4.56–4.60 (2 H, m, 3-H′, *threo* 2-H), 4.81 (1 H, d, *J* 10.5, val 2-H), 4.86–5.00 (5 H, m, 2 × CH_2CCl_3, *threo* 3-H), 5.32 (1 H, m, 2-H) and 7.54 (1 H, d, *J* 8.0, NH); δ_C (100 MHz, DMSO-d_6) 16.3, 18.3, 19.8, 26.6, 28.0, 31.2, 53.5, 60.9, 62.7, 74.0, 75.2, 75.9, 76.3, 78.5, 94.5, 94.9, 152.7, 155.4, 167.5, 169.5 and 170.5; *m*/*z* (ES^-) 769.3 ($[M - 1]^-$, 100%).

Benzyl [*N*-*tert*-butyloxycarbonyl-*O*-(2,2,2-trichloroethoxycarbonyl)-L-threoninyl]-*N*-methyl-L-valinyl-L-alaninyl-D-leucinate (59). The coupling agent PyBOP (30 mg, 0.07 mmol), the dipeptide **60** (30 mg, 0.10 mmol) and *N*-methylmorpholine (0.02 mL, 0.20 mmol) were added successively to the dipeptidyl glyceric acid **58** (38 mg, 0.05 mmol) in DCM (0.8 mL) at 0 °C and the reaction mixture was stirred at rt for 16 h. DCM (10 mL) was added and the solution washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 light petroleum : EtOAc) gave the title compound **59** as an off white foam (26 mg, 66%), R_f = 0.6 (1 : 1 light petroleum : EtOAc) (found: M^+ + 1, 781.2783. $C_{34}H_{52}N_4O_{10}Cl_3$ requires M, 781.2749); δ_H (400 MHz, $CDCl_3$) 0.80 (3 H, d, *J* 6.5, val 4-H_3), 0.90–0.98 (9 H, m, val 3-CH_3, leu 4-CH_3, leu 5-H_3), 1.35–1.66 (9 H, m, ala 3-H_3, *threo* 4-H_3, leu 4-H, leu 3-H_2), 1.41 [9 H, s, $OC(CH_3)_3$], 2.29 (1 H, m, val 3-H), 3.07 (3 H, s, NCH_3), 4.49 (1 H, m, ala 2-H), 4.59–4.64 (2 H, m, val 2-H, leu 2-H), 4.73–4.83 (3 H, m, *threo* 2-H, CH_2CCl_3), 5.10–5.18 (3 H, m, *threo* 3-H, $PhCH_2$), 5.50 (1 H, d, *J* 9.5, NH), 6.62 (1 H, d, *J* 8.0, NH), 6.69 (1 H, d, *J* 7.5, NH) and 7.32–7.37 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 16.9, 17.4, 18.2, 19.6, 21.9, 22.8, 24.8, 25.6, 28.2, 30.9, 41.4, 48.8, 50.8, 53.3, 62.6, 67.0, 74.7, 80.3, 94.3, 128.2, 128.4, 128.6, 135.3, 153.7, 155.7, 169.5, 170.7, 171.4 and 172.5; *m*/*z* (ES^+) 833.6 (100%) and 803.4 (M^+ + 23, 70).

Prop-2-enyl (2*S*)-3-[(*N*-*tert*-butyloxycarbonyl-L-threoninyl)-*N*-methyl-L-valinyloxy]-2-hydroxypropanoate (64). Activated zinc (92 mg) was added to the Troc-protected glycerate **53** (68 mg, 0.11 mmol) in a mixture of HOAc (0.5 mL) and Et_2O (0.5 mL) cooled in an ice bath and the suspension was stirred at rt for 2 h until the reaction was complete (TLC, 1 : 2 EtOAc : light petroleum). Ether (3 mL) was added, the mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc (3 mL) and concentrated under reduced pressure three times to remove the acetic acid. This process was repeated using $CHCl_3$ and final concentration under reduced pressure gave the title compound **64** (44 mg, 96%) as a white foam (found: M^+ + 1, 461.2472. $C_{21}H_{37}N_2O_9$ requires M, 461.2494); ν_{max}/cm^{-1} 3365, 2975, 1744, 1709, 1598, 1501, 1455, 1393, 1369, 1251, 1164, 1134, 1063, 1010, 884 and 752; δ_H (500 MHz, 20 °C, DMSO-d_6) 0.74 and 0.92 (each 3 H, d, *J* 6.6, either val 3-CH_3 or val 4-H_3), 1.01 (3 H, d, *J* 6.3, *threo* 4-H_3), 1.35 [9 H, s, $OC(CH_3)_3$], 2.13 (1 H, m, val 3-H), 3.02 (3 H, s, NCH_3), 3.76 (1 H, m, *threo* 3-H), 4.19 (1 H, dd, *J* 11.3, 5.3, 3-H), 4.25–4.35 (3 H, m, 3-H′, 2-H, *threo* 2-H), 4.60 (2 H, m, CO_2CH_2), 4.69 (1 H, d, *J* 6.0, *threo* OH), 4.74 (1 H, d, *J* 10.4, val 2-H), 5.23 (1 H, dq, *J* 11.9, 1.5, CH=CH*H*), 5.32 (1 H, dq, *J* 17.2, 1.5, CH=CH*H*), 5.84 (1 H, d, *J* 6.0, 2-OH), 5.90 (1 H, m, C*H*=CH_2) and 6.72 (1 H, d, *J* 7.8, NH); *m*/*z* (ES^-) 495.4 ($[M + 35]^-$, 100%).

Prop-2-enyl (2*S*)-3-[(*O*-acetyl-*N*-*tert*-butyloxycarbonyl-L-threoninyl)-*N*-methyl-L-valinyloxy]-2-acetoxypropanoate (65). Pyridine (0.125, 1.5 mmol) and acetic anhydride (0.14 mL, 1.5 mmol) were added to the diol **64** (195 mg, 0.297 mmol) and DMAP (6 mg, 0.039 mmol) in DCM (6 mL) at 0 °C and the reaction mixture was stirred at rt for 17 h then concentrated under reduced pressure. The residue was taken up in ethyl acetate (10 mL) and the solution washed with aqueous HCl (1 M, 5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 2 to 1 : 1 EtOAc : light petroleum) gave the title compound **65** (137 mg, 85%) as a colourless oil, R_f = 0.37 (1 : 1 EtOAc : light petroleum), $[\alpha]_D^{24}$ −40 (*c* 1.0, $CHCl_3$) (found: M^+ + H, 545.2708. $C_{25}H_{41}N_2O_{11}$ requires M, 545.2705); ν_{max}/cm^{-1} 2970, 1744, 1712, 1652, 1500, 1370, 1234, 1173, 1106, 1061 and 1020; δ_H (400 MHz, $CDCl_3$) 0.83 and 0.99 (each 3 H, d, *J* 6.6, either val 3-CH_3 or val 4-H_3), 1.24 (3 H, d, *J* 6.4, *threo* 4-H_3), 1.41 [9 H, s, $OC(CH_3)_3$], 2.00 and 2.12 (each 3 H, s, CH_3CO_2), 2.18 (1 H, m, val 3-H), 3.09 (3 H, s, NCH_3), 4.42 (1 H, dd, *J* 12.1, 5.5, 3-H), 4.60–4.67 (3 H, m, 3-H′, CO_2CH_2), 4.68 (1 H, m, *threo* 2-H), 4.85 (1 H, d, *J* 10.4, val 2-H), 5.17–5.26 (2 H, m, CH=CH*H*, *threo* 3-H), 5.30–5.35 (2 H, m, CH=CH*H*, 2-H), 5.39 (1 H, d, *J* 9.3, NH) and 5.88 (1 H, m, C*H*=CH_2); δ_C (100 MHz, $CDCl_3$) 16.8, 18.7, 19.5, 20.4, 20.9, 27.3, 28.2, 31.5, 54.0, 61.7, 62.7, 66.3, 69.2, 70.2, 79.9, 119.1, 131.1, 155.7, 166.7, 169.7, 169.8, 170.1 and 170.6; *m*/*z* (ES^+) 545.3 (M^+ + 1, 60%).

Benzyl {(2*S*)-3-[(*O*-acetyl-*N*-*tert*-butoxycarbonyl-L-threoninyl)-*N*-methyl-L-valinyloxy]-2-acetoxypropanoyl}-L-alaninyl-D-leucinate (67). Following the procedure outlined for the preparation of the acid **58**, the allyl ester **65** (40 mg, 0.073 mmol), phenylsilane (16 mg, 0.15 mmol) and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) in DCM (5.8 mL) with stirring in the dark, after concentration under reduced pressure, gave the acid **66**. This acid (15 mg, 0.03 mmol) was coupled with the amine **60** (12 mg, 0.042 mmol) using PyBOP (20 mg, 0.047 mmol) and NMM (0.015 mL, 0.15 mmol) in DCM (8 mL) following the procedure outlined for the synthesis of the peptide **59**, to give the title compound **67** (24 mg, 85%) as a pale yellow oil (found: M^+ + Na, 801.3872. $C_{38}H_{54}N_4O_{13}Na$ requires M, 801.3898); δ_H (500 MHz, DMSO-d_6) 0.74 (3 H, d, *J* 6.5, either val 3-CH_3 or

val 4-H_3), 0.82 and 0.88 (each 3 H, d, *J* 6.5, either leu 4-CH_3 or leu 5-H_3), 0.96 (3 H, d, *J* 6.5, either val 4-H_3 or val 3-CH_3), 1.12 (3 H, d, *J* 7.0, *threo* 4-H_3), 1.24 (3 H, d, *J* 7.0, ala 3-H_3), 1.36 [9 H, s, $OC(CH_3)_3$], 1.45–1.63 [3 H, m, leu 4-H, leu 3-H_2], 1.96 and 2.06 (each 3 H, s, CH_3CO_2), 2.13 (1 H, m, val 3-H), 3.00 (3 H, s, NCH_3), 4.40–4.25 (4 H, m, 3-H_2, ala 2-H, leu 2-H), 4.53 (1 H, t, *J* 7.0, *threo* 2-H), 4.74 (1 H, d, *J* 8.3, val 2-H), 4.93 (1 H, m, *threo* 3-H), 5.12 (2 H, s, $PhCH_2$), 5.20 (1 H, m, 2-H), 7.40 (1 H, d, *J* 7.0, NH), 7.30–7.45 (5 H, m, ArH) and 8.27 and 8.35 (each 1 H, d, *J* 7.0, NH); δ_C (125 MHz, $CDCl_3$) 16.4, 18.4, 18.5, 19.7, 20.6, 21.0, 21.1, 22.7, 24.2, 26.7, 28.0, 31.4, 48.1, 50.2, 53.6, 61.1, 63.3, 66.0, 69.7, 71.1, 78.4, 127.8, 128.1, 128.4, 135.9, 155.5, 165.6, 169.6(2), 169.7, 170.8, 171.9 and 172.2; *m*/*z* (ES^+) 801.5 (M^+ + 23, 100%).

Methyl *N*-[(2*Z*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)aminobut-2-enoyl]-L-prolinate (76). Aqueous NaOH (1 M, 0.2 mL, 0.2 mmol) was added to the pentapeptide ester **75** (60 mg, 0.069 mmol) in EtOH : dioxane (2 : 1, 0.7 mL) and the solution stirred at rt for 5 h. After cooling to 0 °C, the solution was acidified to pH 3 using aqueous HCl (1 M) and extracted using EtOAc (3 × 3 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding acid used without further purification. This acid appeared to have retained the phenyl selanyl group at this stage (^{1}H NMR).

Methyl L-prolinate (10 mg, 0.08 mmol), PyBOP (47 mg, 0.09 mmol) and *N*-methylmorpholine (0.02 mL, 0.18 mmol) were added to the acid derived from the pentapeptide **75** (65 mg, 0.08 mmol) in DCM (1.10 mL) at 0 °C and the reaction mixture was stirred at rt for 4.5 h. DCM (10 mL) was added and the solution washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 light petroleum : EtOAc) afforded the title compound **76** as a pale yellow wax (21 mg, 34%), R_f = 0.4 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{28}$ −211 (*c* 1.0, $CHCl_3$) (found: M^+ + H, 811.4445. $C_{38}H_{67}N_6O_9SSi$ requires M, 811.4454); ν_{max}/cm^{-1} 3281, 2955, 2929, 1746, 1678, 1645, 1628, 1532, 1502, 1436, 1390, 1366, 1329, 1254, 1169, 1106, 839 and 779; δ_H (400 MHz, $CDCl_3$) 0.06 and 0.07 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 0.95 and 1.00 (each H, d, *J* 6.5, either leu 4-CH_3 or leu 5-H_3), 1.25 (3 H, d, *J* 7.0, ala 3-H_3), 1.39 [9 H, s, $OC(CH_3)_3$], 1.39–2.05 (8 H, m, leu 4-H, leu 3-H_2, pro 3-H, pro 4-H_2, thiopro 4-H_2), 1.71 (3 H, d, *J* 7.0, 4-H_3), 2.16–2.23 (2 H, m, pro 3-H′, thiopro 3-H), 2.45 (1 H, m, thiopro 3-H′), 3.46 (1 H, m, pro 5-H), 3.59–3.85 (2 H, m, pro 5-H′, thiopro 5-H), 3.70 (3 H, s, OCH_3), 4.04–4.45 (5 H, m, thiopro 5-H′, ala 2-H, ser 3-H_2, leu 2-H), 4.89 (1 H, m, pro 2-H), 4.97 (1 H, dd, *J* 8.5, 4.0, thiopro 2-H), 5.19–5.32 (2 H, m, ser 2-H, 3-H), 7.99 (1 H, d, *J* 7, NH), 8.16–8.18 (2 H, m, 2 × NH) and 8.87 (1 H, d, *J* 7.5, NH); δ_C (100 MHz, $CDCl_3$) −5.3, 11.9, 14.2, 18.1, 21.2, 22.6, 23.5, 24.1, 24.8, 25.7, 28.2, 30.5, 32.9, 39.6, 45.8, 48.1(2), 50.6, 52.1, 61.6, 62.3, 62.4, 69.4, 79.3, 119.7, 130.4, 158.2, 167.0, 168.6, 173.1, 173.7, 175.2 and 203.6; *m*/*z* (ES^+) 811.5 (M^+ + 1, 100%).

tert-Butyl hydroperoxide in decane (5.5 M, 0.09 mL) was added to the peptide **80** (50 mg, 0.05 mmol) in DCM (0.5 mL) at 0 °C and the reaction mixture stirred at 0 °C for 5 min then at rt for 3 h. Saturated aqueous $Na_2S_2O_3$ (2 mL) was added and the mixture was stirred at rt for 30 min then extracted with EtOAc (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 light petroleum : EtOAc) gave the title compound **76** as a colourless oil (14 mg, 36%), R_f = 0.47 (1 : 1 light petroleum : EtOAc) (found: M^+ + H, 811.4465. $C_{38}H_{67}N_6O_9SSi$ requires M, 811.4454) with spectroscopic data the same as obtained previously; *m*/*z* (ES^-) 809.6 ($[M - 1]^-$, 100%).

Methyl *N*-[(2*R*,3*S*)-2-*tert*-butoxycarbonylamino-3-phenylselanylbutanoyl]-L-prolinate (77). Methyl L-prolinate (20 mg, 0.14 mmol), PyBOP (80 mg, 0.15 mmol) and *N*-methylmorpholine (0.03 mL, 0.31 mmol) were added to the 3-phenylselanylbutanoic acid **71** (50 mg, 0.14 mmol) in DCM (2.2 mL) at 0 °C and the reaction mixture was stirred at rt for 4 h. DCM (10 mL) was added and the solution washed with saturated aqueous NH_4Cl (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 light petroleum : EtOAc) gave the title compound **77** as an off-white foam (47 mg, 72%), R_f = 0.3 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{24}$ −9.8 (*c* 1.0, $CHCl_3$) (found: M^+ + H, 471.1413. $C_{21}H_{31}N_2O_5Se$ requires M, 471.1398); ν_{max}/cm^{-1} 3305, 2975, 1745, 1709, 1645, 1497, 1435, 1391, 1166, 1020 and 743; δ_H (400 MHz, $CDCl_3$) 1.42 (3 H, d, *J* 7.0, 4-H_3), 1.45 [9 H, s, $OC(CH_3)_3$], 1.80–1.96 (3 H, m, pro 3-H, pro 4-H_2), 2.18 (1 H, m, pro 3-H′), 3.28 (1 H, m, pro 5-H), 3.41–3.48 (2 H, m, pro 5-H′, 3-H), 3.69 (3 H, s, OCH_3), 4.48 (1 H, dd, *J* 8.0, 4.5, pro 2-H), 4.67 (1 H, dd, *J* 9.5, 3.5, 2-H), 5.49 (1 H, d, *J* 9.5, NH), 7.24–7.31 (3 H, m, ArH) and 7.68–7.70 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 16.8, 24.8, 28.3, 28.9, 42.0, 46.6, 52.3, 54.8, 58.8, 79.9, 128.0, 129.0, 129.4, 135.8, 155.6, 169.1 and 172.2; *m*/*z* (ES^+) 471.1 (M^+ + 1, 100%) and 469.1 (95).

Methyl *N*-[(2*R*,3*S*)-2-(*N*-*tert*-butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinate (78). Trifluoroacetic acid (1.7 mL) was added to the Boc-protected dipeptide **77** (0.87 g, 1.87 mmol) in DCM (6.8 mL) at 0 °C and the reaction mixture stirred at rt for 1.5 h. DCM (10 mL) was added and the solution washed with saturated aqueous $NaHCO_3$ (30 mL), water (15 mL) and brine (15 mL). The aqueous extracts were re-extracted with DCM (20 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding amine that was then dissolved in DCM (10 mL) and added to *N*-Boc-*O*-TBS-protected L-serine (0.46 g, 2.24 mmol) and HATU (0.68 g, 2.43 mmol) at 0 °C. Di-isopropylethylamine (0.81 mL, 4.68 mmol) was added and the reaction mixture stirred at rt for 32 h. DCM (15 mL) was added and the solution was washed with saturated aqueous NH_4Cl (20 mL), water (20 mL) and brine (20 mL). The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 to 1 : 1 light petroleum : EtOAc) gave the title compound **78** as a pale yellow wax (0.87 g, 67%), R_f = 0.7 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{30}$ −22 (*c* 1.0, $CHCl_3$) (found: M^+ + Na,

694.2405. $C_{30}H_{49}N_3O_7SeSiNa$ requires M, 694.2403,); ν_{max}/cm^{-1} 3302, 2953, 2925, 2856, 1746, 1715, 1681, 1645, 1437, 1345, 1252, 1170, 1112, 837, 779 and 741; δ_H (400 MHz, $CDCl_3$) 0.08 and 0.09 (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.45–1.46 [12 H, m, $OC(CH_3)_3$, 4-H_3], 1.87–2.00 (3 H, m, pro 3-H, pro 4-H_2), 2.15 (1 H, m, pro 3-H′), 3.35 (1 H, m, pro 5-H), 3.43–3.49 (2 H, m, pro 5′-H, 3-H), 3.67–3.73 (4 H, m, OCH_3, ser 3-H), 4.04 (1 H, dd, *J* 10.0, 3.5, ser 3-H′), 4.20 (1 H, m, ser 2-H), 4.47 (1 H, dd, *J* 8.0, 4.5, pro 2-H), 4.97 (1 h, dd, *J* 9.0, 4.5, 2-H), 5.32 (1 H, br. d, *J* 7.0, NH), 7.27–7.37 (4 H, m, ArH, NH) and 7.67–7.70 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −5.6, −5.4, 17.3, 18.3, 24.8, 25.9, 28.3, 28.9, 41.4, 46.7, 52.2, 53.6, 55.8, 58.7, 63.0, 80.2, 128.0, 129.0, 129.4, 135.7, 155.5, 168.2, 170.4 and 172.2; *m*/*z* (ES^+) 672.2 (M^+ + 1, 100%) and 670.2 (M^+ + 1, 50).

Methyl *N*-[(2*R*,3*S*)-2-(L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinate (79). 2,6-Lutidine (2.15 mL, 18.48 mmol) and trimethylsilyl trifluoromethanesulfonate (3.34 mL, 18.48 mmol) were added to the Boc-protected tripeptide **78** (2.10 g, 3.08 mmol) in DCM (45 mL) at 0 °C and the reaction mixture stirred at rt for 2 h. Saturated aqueous $NaHCO_3$ was added until the aqueous phase was at pH 7 and the mixture was extracted with DCM (3 × 20 mL). The organic extracts were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography through a short column (2 : 1 light petroleum : EtOAc to 96 : 4 DCM : MeOH) gave the corresponding amine that was dissolved in DCM (25 mL). Di-isopropylethylamine (0.80 mL, 4.62 mmol) was added and the solution stirred at rt for 5 min and then cooled to 0 °C. Benzotriazole **14** (1.54 g, 3.08 mmol) in DCM (25 mL) was added dropwise, and the solution was stirred at rt for 16 h, diluted with DCM (15 mL), and washed with aqueous HCl (1 M, 15 mL), saturated aqueous $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (2 : 1 to 1 : 1 light petroleum : EtOAc) gave the Fmoc-protected thioamide as a mixture of rotamers (2.0 g, 66%), R_f = 0.7 (1 : 1 light petroleum : EtOAc). Part of this thioamide (0.40 g, 0.44 mmol) was dissolved in DMF (12 mL) and piperidine (0.22 mL, 2.21 mmol) was added. The reaction mixture was stirred for 10 min at rt before saturated aqueous NH_4Cl (10 mL) and water (10 mL) were added. The mixture was extracted with EtOAc (5 × 15 mL) and the organic extracts were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 2 light petroleum : EtOAc to 96 : 4 DCM : MeOH) gave the title compound **79** as a pale yellow wax (0.23 g, 77%), R_f = 0.1 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{27}$ −70 (*c* 1.1, $CHCl_3$) (found: M^+ + H, 685.2361. $C_{30}H_{49}N_4O_5SSeSi$ requires M, 685.2353); ν_{max}/cm^{-1} 3203, 2952, 2857, 1746, 1650, 1511, 1436, 1257, 1196, 1175, 1102, 837, 780 and 742; δ_H (400 MHz, $CDCl_3$) 0.08 (6 H, s, 2 × $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.42 (3 H, d, *J* 7.0, 4-H_3), 1.67–1.73 (2 H, m, thiopro 4-H_2), 1.85–1.98 (4 H, m, pro 3-H, thiopro 3-H, pro 4-H_2), 2.14 (1 H, m, pro 3-H′), 2.34 (1 H, m, thiopro 3-H′), 2.93 and 3.04 (each 1 H, m, thiopro 5-H), 3.29 (1 H, m, pro 5-H), 3.41–3.47 (2 H, m, pro 5-H′, 3-H), 3.66 (3 H, s, OCH_3), 3.76 (1 H, dd, *J* 9.9, ser 3-H), 4.16–4.23 (2 H, m, ser 3-H′, thiopro 2-H), 4.45 (1 H, dd, *J* 8.0, 4.5, pro 2-H), 4.93 (1 H, dd, *J* 9.0, 4.0, 2-H), 5.00 (1 H, dd, *J* 5.5, 4.0, ser 2-H), 7.24–7.30 (4 H, m, ArH, NH), 7.63–7.65 (2 H, m, ArH) and 10.48 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) −5.6, −5.4, 17.1, 18.1, 24.7, 25.7, 25.9, 28.8, 34.4, 40.9, 46.6, 47.3, 52.2, 53.7, 58.5, 58.7, 61.6, 68.1, 128.0, 129.0, 135.7, 168.1, 169.2, 172.1 and 206.6; *m*/*z* (ES^+) 685.4 (M^+ + 1, 100%) and 683.4 (M^+ + 1, 50).

Methyl *N*-[(2*R*,3*S*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinate (80). The dipeptide **34** (0.11 g, 0.38 mmol), PyBOP (0.28 g, 0.53 mmol) and *N*-methylmorpholine (0.17 mL, 1.52 mmol) were added to the tetrapeptide **79** (0.25 g, 0.37 mmol) in DCM (5.6 mL) at 0 °C and the reaction mixture stirred at rt for 16 h. DCM (15 mL) was added and the solution washed with saturated aqueous NH_4Cl (20 mL), water (20 mL) and brine (20 mL). The aqueous extracts were re-extracted with DCM (15 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 to 1 : 2 light petroleum : EtOAc) gave the title compound **80** as a pale yellow foam (0.23 g, 61%), R_f = 0.1 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{23}$ −72 (*c* 0.9, $CHCl_3$) (found: M^+ + Na, 991.3882. $C_{44}H_{72}N_6O_9SSeSiNa$ requires M, 991.3918); ν_{max}/cm^{-1} 3291, 2954, 1747, 1713, 1634, 1511, 1437, 1251, 1170, 1099, 838 and 752; δ_H (500 MHz, $CDCl_3$) 0.10 (6 H s, 2 × $SiCH_3$), 0.88–0.95 [15 H, m, $SiC(CH_3)_3$, leu 4-CH_3, leu 5-H_3], 1.30 (3 H, d *J* 6.5, ala 3-H_3), 1.41 [9 H, s, $OC(CH_3)_3$], 1.45 (3 H, d, *J* 7.0, 4-H_3), 1.51–1.66 (3 H, m, leu 4-H, leu 3-H_2), 1.93–1.97 (5 H, m, pro 4-H_2, thiopro 4-H_2, pro 3-H), 2.12–2.34 (3 H, m, pro 3-H′, thiopro 3-H_2), 3.41–3.69 (4 H, m, 3-H, pro 5-H_2, thiopro 5-H), 3.69 (3 H, s, OCH_3), 3.86–3.92 (2 H, m, thiopro 5-H′, ser 3-H), 4.15–4.22 (2 H, m, ser 3-H′, ala 2-H), 4.48 (1 H, dd, *J* 8.5, 4.5, pro 2-H), 4.63 (1 H, m, leu 2-H), 4.91–5.00 (3 H, m, 2-H, ser 2-H, thiopro 2-H), 5.49 (1 H, d, *J* 8.0, NH), 7.09 (1 H, d, *J* 6.5, NH), 7.25–7.29 (3 H, m, ArH), 7.42 (1 H, d, *J* 8.5, NH), 7.63–7.65 (2 H, m, ArH) and 8.59 (1 H, d, *J* 6.0, NH); δ_C (125 MHz, $CDCl_3$) −5.4, −5.3, 17.7, 18.2, 22.0, 23.2, 24.2, 24.6, 24.8, 25.8, 28.2, 28.9, 32.9, 40.2, 40.4, 46.8, 47.7, 49.6, 49.8, 52.2, 54.5, 59.0, 60.0, 61.4, 68.3, 80.0, 128.0, 128.8, 129.0, 135.7, 155.7, 167.9, 169.2, 171.6, 172.3, 173.4 and 203.1; *m*/*z* (ES^+) 991.4 (M^+ + 23, 100%).

Prop-2-enyl (2*S*)-3-{*N*-[(2*R*,3*S*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl)-D-leucinyl-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinyl-(*O*-acetyl-L-threoninyl)-*N*-methyl-L-valinyloxy}-2-acetoxypropanoate (83). Hydrogen chloride in dioxane (4 M, 8.5 mL) was added to the Boc-protected glycerate **65** (307 mg, 0.56 mmol) and the reaction mixture was stirred for 4 h at 0 °C then concentrated under reduced pressure to give the amine **82** as its ammonium salt, a yellowish oil. Aqueous lithium hydroxide (1 M, 2 mL) and *tert*-butanol (4 mL) were added to the methyl ester **80** (717 mg, 0.74 mmol) in THF (4.0 mL) at 0 °C and the solution was stirred for 2 h at rt. Citric acid was added until the pH = 1 and the solution was extracted with EtOAc. The organic layer was

washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 EtOAc : light petroleum) gave the acid **81** as a yellowish foam. *N*-Methylmorpholine (0.25 mL, 2.26 mmol) and isobutyl chloroformate (0.115 mL, 0.790 mmol) were added dropwise to this acid **81** in THF (10 mL) at −15 °C and the reaction mixture was stirred 10 min at −15 °C. The amine **82** in THF (2 mL) was added and the reaction mixture was stirred at rt for 20 h then concentrated under reduced pressure. EtOAc (10 mL) was added and the solution was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine, then dried over ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 EtOAc : light petroleum) gave the title compound **83** (656 mg, 84%) as a brownish foam, R_f 0.25 (2 : 1 EtOAc : light petroleum), $[\alpha]_D^{25}$ −53 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 1403.5758. $C_{63}H_{100}N_8O_{17}SSeSiNa$ requires M, 1403.5754); ν_{max}/cm^{-1} 3308, 2957, 1746, 1651, 1512, 1438, 1369, 1237, 1101, 1022, 838, 781 and 745; δ_H (500 MHz, 120 °C, DMSO-d_6) 0.08 (6 H, s, 2 × $SiCH_3$), 0.84 (6 H, d, *J* 6.9, val 3-CH_3, leu 4-CH_3), 0.87 (3 H, d, *J* 6.6, leu 5-H_3), 0.89 [9 H, s, $SiC(CH_3)_3$], 0.99 (3 H, d, *J* 6.6, val 4-H_3), 1.20 (3 H, d, *J* 6.3, *threo* 4-H_3), 1.24 (3 H, d, *J* 6.9, ala 3-H_3), 1.41 [9 H, s, $OC(CH_3)_3$], 1.42 (3 H, m, 4′-H_3), 1.54 (2 H, m, leu 3-H_2), 1.62 (1 H, m, leu 4-H), 1.88 (6 H, m), 1.99 (3 H, s, CH_3CO), 2.04 (1 H, m), 2.08 (3 H, s, CH_3CO), 2.22 (2 H, m, val 3-H, pro 3-H), 3.01 (3 H, s, NCH_3), 3.43 and 3.51 (each 1 H, m), 3.61 (3 H, m), 4.03 (3 H, m, ala 2-H, ser 3-H_2), 4.44 (2 H, m, 3-H, thiopro 2-H), 4.45 (1 H, m, leu 2-H), 4.55 (1 H, dd, *J* 12.1, 3.4, 3-H′), 4.66 (2 H, m, CO_2CH_2), 4.69 (1 H, m, val 2-H), 4.93 (1 H, m, 2′-H), 4.96 (1 H, dd, *J* 8.5, 6.6, *threo* 2-H), 5.13 (3 H, m, *threo* 3-H, ser 2-H, pro 2-H), 5.25 (1 H, dq, *J* 10.5, 1.3, CH═CH*H*), 5.34 (2 H, m, CH═CH*H*, 2-H), 5.93 (1 H, m, C*H*═CH_2), 6.15 (1 H, br. d, *J* 7.5, ala NH), 7.31 (3 H, m, ArH), 7.41 (1 H, br. d, *J* 7.8, leu NH), 7.53 (1 H, br. s, *threo* NH), 7.61 (2 H, m, ArH), 7.68 (1 H, br. s, NH′) and 7.53 (1 H, br. d, *J* 7.5, ser NH); δ_C (125 MHz, 120 °C, DMSO-d_6) −6.3(2), 15.8, 16.9, 17.1, 17.5, 18.0, 18.7, 19.2, 19.9, 21.0, 22.2, 23.4, 25.0, 26.4, 27.5, 28.0, 28.1, 30.7, 30.8, 46.1, 46.3, 48.7, 49.6, 51.5, 53.7, 58.9, 59.3, 61.3, 61.9, 64.8, 66.6, 68.9, 69.5, 77.7, 117.4, 126.4, 126.9, 128.1, 128.6, 131.1, 134.1, 154.1, 157.8, 165.8, 167.4, 168.3, 168.6, 168.7, 169.3, 170.2, 171.7 and 203.8; *m*/*z* (ES^-) 1380.3 (M^-, 85%) and 1378.2 (M^-, 100).

{(2*R*,3*S*)-[2-(2*S*)-2-Acetoxy-3-hydroxypropanoyl-L-alaninyl-D-leucinyl-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)amino]-3-phenylselanylbutanoyl}-L-prolinyl-(*O*-acetyl-L-threoninyl)-*N*-methyl-L-valinolactone (84). The catalyst $Pd(PPh_3)_4$ (5 mg, 10 mol%) and $PhSiH_3$ (0.009 mL, 0.075 mmol) were added to the Boc-protected allyl ester **83** (52 mg, 0.038 mmol) in DCM (2 mL) and the reaction mixture was stirred at rt for 4 h. After concentration under reduced pressure, chromatography of the residue (EtOAc) gave the corresponding carboxylic acid (46 mg), R_f = 0.20 (EtOAc), as a brownish foam. Trifluoroacetic acid (0.50 mL) was added to this acid in DCM (2 mL) at 0 °C and the solution stirred at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ was added until pH = 7 and the mixture was extracted with DCM (5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in benzene and the solution concentrated under reduced pressure (water bath at 50 °C). This process was repeated before the residue (33 mg) was taken up in DCM (38 mL). *N*-Methylmorpholine (0.064 mL, 0.56 mmol) and PyBOP (205 mg, 0.38 mmol) were added and the mixture stirred at rt for 3 d. After concentration under reduced pressure, the residue was taken up in EtOAc (10 mL) and the mixture filtered and concentrated under reduced pressure. Chromatography of the brown oily residue (1 : 2 to 1 : 1 acetone : light petroleum, then 10 : 1 DCM : MeOH) gave the title compound **84** (23 mg, 50%) as a brown-yellow foam, R_f 0.75 (1 : 2 acetone : light petroleum).

The catalyst $Pd(PPh_3)_4$ (3 μg, 2.4 μmol, 14 mol%) and $PhSiH_3$ (15 μL, 76 μmol) were added to the bis-allyloxycarbonyl protected peptide **89** (26 mg, 19 μmol) in DCM (0.8 mL) and the reaction mixture was stirred for 1 h before being concentrated under reduced pressure. PyBOP (0.10 g, 0.19 mmol) and *N*-methylmorpholine (0.03 mL, 0.28 mmol) were added to the deprotected peptide in DCM (27 mL) at 0 °C, and the reaction mixture was stirred at rt for 64 h then concentrated under reduced pressure. EtOAc (10 mL) was added, the mixture was filtered, and the filtrate concentrated under reduced pressure. Chromatography of the residue (2 : 1 light petroleum : acetone) followed by preparative TLC (2 : 1 light petroleum : acetone) gave the title compound **84** as a foam (8 mg, 33%), R_f = 0.6 (2 : 1 light petroleum : acetone), $[\alpha]_D^{25}$ −167 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 1245.4811. $C_{55}H_{86}N_8O_{14}SSeSiNa$ requires M, 1245.4811); ν_{max}/cm^{-1} 3307, 2957, 2930, 1744, 1652, 1510, 1438, 1371, 1236, 1188, 1103, 1021, 840, 781 and 746; δ_H (500 MHz, $CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 0.95–1.00 (6 H, m, leu 4-CH_3, val 4-H_3), 1.01 (3 H, d, *J* 6.6, leu 5-H_3), 1.15–1.17 (3 H, m, val 3-CH_3), 1.23–1.38 (9 H, m, 4′-H_3, ala 3-H_3, *threo* 4-CH_3), 1.50 (1 H, m, leu 4-H), 1.60–1.75 (4 H, m, leu 3-H_2, pro or thiopro 4-H_2), 1.93–2.12 (3 H, m, pro or thiopro 3-H, thiopro or pro 4-H_2), 2.03 and 2.12 (each 3 H, s, CH_3CO), 2.26–2.35 (4 H, m, pro or thiopro 3-H_2, thiopro or pro 3-H, val 3-H), 2.67 (3 H, s, NCH_3), 3.36 (1 H, m, 3′-H), 3.49–3.58 (2 H, m, pro or thiopro 5-H_2), 3.67 and 3.85 (each 1 H, m, thiopro or pro 5-H), 3.96 (1 H, dd, *J* 9.0, 3.0, ser 3-H), 4.20–4.33 (3 H, m, ser 3-H′, leu 2-H, 3-H), 4.64 (1 H, d, *J* 10.5, val 2-H), 4.70–4.84 (5 H, m, pro 2-H, thiopro 2-H, ser 2-H, 2′-H, ala 2-H), 4.99–5.14 (3 H, m, 3-H′, 2-H, *threo* 2-H), 5.40 (1 H, m, *threo* 3-H), 6.04 (1 H, d, *J* 7.5, NH), 6.60 (1 H, d, *J* 4.5, NH), 6.94 (1 H, d, *J* 9.0, NH), 7.32–7.34 (3 H, m, ArH), 7.62–7.72 (2 H, m, ArH), 8.37 (1 H, d, *J* 9.0, NH) and 8.61 (1 H, d, *J* 6.0, NH); δ_C (125 MHz, $CDCl_3$) −5.5, −5.4, 15.7, 17.7, 18.0, 18.1, 19.1, 20.2, 20.6, 21.4, 23.6, 23.7, 23.9, 24.8, 25.7(2), 26.8, 29.0(2), 33.1, 39.1, 39.6, 46.9, 47.4, 47.7, 50.8, 52.9, 56.3, 61.4, 61.5, 62.9, 64.0, 65.2, 68.5, 70.5, 74.7, 126.0, 128.6, 129.2, 137.0, 168.2, 168.7, 168.9, 169.8, 169.9, 170.2, 170.8, 171.1, 173.0 and 203.9; *m*/*z* (ES^+) 1223.9 (M^+ + 1, 60%), 1083.0 (65) and 1065.9 (100).

A solution of the diacetate **84** (10 mg, 0.008 mmol) and trimethyltin hydroxide (6 mg, 0.033 mmol) in DCM (0.2 mL) was heated at 70 °C for 1.5 h then cooled and concentrated under

reduced pressure. Preparative TLC (2 : 1 light petroleum : acetone) gave several fractions. The second was identified as the monoacetate **85** (4 mg, 40%); δ_H (400 MHz, $CDCl_3$) 2.04 (3 H, s, CH_3CO) – no peak at δ 2.12; *m*/*z* (ES^+) 1203.7 (M^+ + 23, 100%); (ES^-) 1215.6 ($[M + 35]^-$, 100%).

***N*-*tert*-Butoxycarbonyl-L-*allo*threonine (94).** $NaHCO_3$ (2.17 g, 25.86 mmol) and *tert*-butoxycarbonyl anhydride (5.72 g, 26.19 mmol) in MeOH (34 mL) were added to *allo*-L-threonine (2 g, 16.79 mmol) in water (34 mL) and the reaction mixture was stirred at rt for 24 h. The reaction mixture was acidified to pH 2 using aqueous HCl (0.5 M) and extracted with EtOAc (3 × 100 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **94** as a colourless oil (3.68 g, *ca.* 100%), R_f = 0.25 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{26}$ +12.4 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 242.0989. $C_9H_{17}NO_5Na$ requires M, 242.0999); ν_{max}/cm^{-1} 3345, 2979, 1691, 1512, 1394, 1368, 1252, 1162 and 754; δ_H (400 MHz, $CDCl_3$) 1.27–1.29 (3 H, m, 4-H_3), 1.46 [9 H, s, OC(CH_3)$_3$], 4.15 (1 H, m, 3-H), 4.36 (1 H, m, 2-H) and 5.62 (1 H, dd, *J* 6.0, NH); δ_C (100 MHz, $CDCl_3$) 18.8, 28.2, 59.0, 69.1, 80.9, 156.5 and 173.4; *m*/*z* (ES^-) 218.0 ($[M - 1]^-$, 40%) and 143.9 (100).

(3*S*,4*S*)-3-*tert*-Butoxycarbonylamino-4-methyloxetan-2-one (95).[30] PyBOP (10.5 g, 20.14 mmol) and Et_3N (7.0 mL, 50.4 mmol) were added the Boc-L-*allo*threonine **94** (3.68 g, 16.79 mmol) in dry DCM (245 mL) at 0 °C and the reaction mixture was stirred for 1 h at 0 °C and at rt for 1 h. Saturated aqueous NH_4Cl (100 mL) was added and the organic phase was washed with water (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 light petroleum : EtOAc) gave the title compound **95** as a white semi-solid (3.21 g, 95%), R_f = 0.6 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{26}$ −45.4 (*c* 0.9, $CHCl_3$), lit.[30] −81.7 (*c*, 0.45, MeOH) (found: M^+ + Na, 224.0885. $C_9H_{15}NO_4Na$ requires M, 224.0899); ν_{max}/cm^{-1} 3355, 2992, 1825, 1690, 1537, 1367, 1328, 1292, 1254, 1167, 1131, 1022 and 821; δ_H (400 MHz, $CDCl_3$) 1.46 [9 H, s, OC(CH_3)$_3$], 1.61 (3 H, d, *J* 6.1, 4-CH_3), 4.58 (1 H, dd, *J* 7.5, 4.0, 3-H), 4.75 (1 H, m, 4-H) and 5.22 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) 18.7, 28.2, 64.3, 76.8, 81.3, 154.4 and 168.1; *m*/*z* (ES^+) 240.0 (M^+ + 39, 100%), 224.0 (M^+ + 23, 70).

(2*R*,3*R*)-2-*tert*-Butoxycarbonylamino-3-phenylselanylbutanoic acid (96).[24] Benzeneselenol (7.52 mL, 47.86 mmol) was added dropwise to the oxetanone **95** (3.21 g, 15.95 mmol) in dry, degassed DMF (26 mL) and the reaction mixture was heated to 80 °C for 3 h then cooled to rt. Aqueous NaOH (1 M, 36 mL) and water (72 mL) were added and the reaction mixture was extracted with Et_2O (3 × 90 mL). The aqueous layer was acidified to pH 3 with aqueous HCl (1 M) and washed with EtOAc (3 × 90 mL). The organic extracts were washed with water (2 × 75 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (3 : 1 to 1 : 1 light petroleum : EtOAc) gave the title compound **96**[24] as a pale yellow viscous oil (5.31 g, 93%), R_f = 0.8 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{26}$ +45.8 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 382.0515. $C_{15}H_{21}NO_4SeNa$ requires M, 382.0533); ν_{max}/cm^{-1} 2978, 2928, 1715, 1477, 1394, 1368, 1251, 1160, 1081, 1022 and 741; δ_H (400 MHz, $CDCl_3$) 1.47 [9 H, s, OC(CH_3)$_3$], 1.52 (3 H, d, *J* 7.5, 4-H_3), 3.83 (1 H, m, 3-H), 4.57 (1 H, m, 2-H), 5.35 (1 H, d, *J* 9.5, NH), 7.21–7.30 (3 H, m, ArH), 7.56–7.58 (2 H, m, ArH) and 11.16 (1 H, br. S, OH); *m*/*z* (ES^+) 398.0 (M^+ + 39, 75%), 382.0 (M^+ + 23, 50) and 380.0 (M^+ + 23, 70).

Methyl *N*-[(2*R*,3*R*)-2-*tert*-butoxycarbonylamino-3-phenylselanylbutanoyl]-L-prolinate (97). Methyl L-prolinate (2.48 g, 14.97 mmol), PyBOP (10.02 g, 19.27 mmol) and *N*-methylmorpholine (4.89 mL, 44.46 mmol) were added to the 3-phenylselanylbutanoic acid **96** (5.31 g, 14.82 mmol) in dry DCM (180 mL) at 0 °C and the reaction mixture was stirred at rt for 19 h then diluted with DCM (227 mL). The solution was washed with saturated aqueous NH_4Cl (302 mL), water (302 mL) and brine (302 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (1 : 1 light petroleum : EtOAc) of the residue gave the title compound **97** as an off-white foam (6.82 g, 98%), R_f = 0.3 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{26}$ −58.8 (*c* 1.0, $CHCl_3$) (found: M^+ + H, 471.1375. $C_{21}H_{31}N_2O_5Se$ requires M, 471.1398); ν_{max}/cm^{-1} 3304, 2976, 1746, 1705, 1639, 1514, 1436, 1366, 1245, 1170, 1012 and 743; δ_H (500 MHz, $CDCl_3$) 1.42–1.45 [12 H, m, OC(CH_3)$_3$, 4-H_3], 1.92–1.98 (3 H, m, pro 3-H, pro 4-H_2), 2.15 (1 H, m, pro 3-H′), 3.48 (1 H, m, 3-H), 3.57 (1 H, m, pro 5-H), 3.67 (3 H, s, OCH_3), 3.85 (1 H, m, pro 5-H′), 4.40–4.50 (2 H, m, 2-H, pro 2-H), 5.28 (1 H, d, *J* 8.0, NH), 7.24–7.28 (3 H, m, ArH) and 7.59–7.61 (2 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 18.8, 24.7, 28.2, 29.0, 42.0, 47.2, 52.0, 56.3, 58.8, 79.7, 127.7, 127.8, 128.8, 135.7, 155.1, 170.0 and 172.0; *m*/*z* (ES^+) 471.2 (M^+ + 1, 70%), 469.2 (M^+ + 1, 30) and 258.2 (100).

Methyl *N*-[(2*R*,3*R*)-2-(*N*-*tert*-butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinylamino)-3-phenylselanylbutanoyl]-L-prolinate (98). Trifluoroacetic acid (11 mL) was added to the Boc-protected dipeptide **97** (6.82 g, 14.53 mmol) in dry DCM (52 mL) at 0 °C and the solution was stirred at 0 °C for 30 min and at rt for 30 min. DCM (173 mL) was added and the solution washed with saturated aqueous $NaHCO_3$ (260 mL), water (260 mL) and brine (260 mL). The aqueous extracts were extracted with DCM (2 × 175 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the aminodipeptide that was dissolved in DCM (173 mL) and added to *N*-*tert*-butoxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serine (5.57 g, 17.44 mmol) and HATU (7.18 g, 18.89 mmol) at 0 °C. Di-isopropylethylamine (6.33 mL, 36.32 mmol) was added and the reaction mixture was stirred at rt for 16 h. DCM (260 mL) was added and the solution was washed with saturated aqueous NH_4Cl (346 mL), water (346 mL) and brine (346 mL) then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 to 1 : 1 light petroleum : EtOAc) gave the title compound **98** as a yellow oil (6.92 g, 71%), R_f = 0.7 (1 : 1 light petroleum : EtOAc), $[\alpha]_D^{25}$ −38.6 (*c* 1.0, $CHCl_3$) (found: M^+ + H, 672.2566. $C_{30}H_{50}N_3O_7SeSi$ requires M, 672.2578); ν_{max}/cm^{-1} 3313, 2954, 2929, 2857, 1790, 1748, 1715, 1640, 1472, 1436, 1365, 1252, 1170, 1111, 837, 779 and 743; δ_H (400 MHz, $CDCl_3$) 0.04 (6 H, s, 2 × $SiCH_3$), 0.85 [9 H, s, SiC(CH_3)$_3$], 1.42 [9 H, s, OC(CH_3)$_3$],

1.42 (3 H, d, *J* 7.0, 4-H_3), 1.91–1.96 (3 H, m, pro 3-H, pro 4-H_2), 2.15 (1 H, m, pro 3-H′), 3.51–3.59 (2 H, m, pro 5-H, 3-H), 3.66 (1 H, m, ser 3-H), 3.67 (3 H, s, OCH_3), 3.81 (1 H, m, pro 5-H′), 3.97 (1 H, m, ser 3-H′), 4.12 (1 H, m, ser 2-H), 4.45 (1 H, dd, *J* 8.0, 4.0, pro 2-H), 4.73 (1 H, t, *J* 9.0, 2-H), 5.18 (1 H, d, *J* 7.0, NH), 7.19 (1 H, br. d, *J* 9.5, NH), 7.25–7.28 (3 H, m, ArH) and 7.55–7.58 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −5.6, −5.4, 18.2, 18.5, 24.7, 25.8, 28.2, 29.0, 40.7, 47.4, 52.1, 55.1, 55.6, 58.8, 62.9, 80.1, 127.7, 127.9, 129.0, 135.4, 155.5, 169.0, 170.0 and 172.1; *m*/*z* (ES^+) 672.3 (M^+ + 1, 100%) and 670.3 (M^+ + 1, 60).

Methyl *N*-[(2*R*,3*R*)-2-(*O*-*tert*-butyldimethylsilyl-L-serinylamino)-3-phenylselanylbutanoyl]-L-prolinate (99). 2,6-Lutidine (7.21 mL, 61.92 mmol) and trimethylsilyl trifluoromethanesulfonate (11.21 mL, 61.92 mmol) were added to the Boc-protected tripeptide **98** (6.92 g, 10.32 mmol) in dry DCM (150 mL) at 0 °C and the reaction mixture stirred at rt for 3 h. Saturated aqueous $NaHCO_3$ was added until the solution was at pH 7. Following extraction with DCM (3 × 67 mL), the organic extracts were washed with water (67 mL) and brine (67 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 light petroleum : EtOAc to 95 : 5 DCM : MeOH) gave the title compound **99** as a colourless oil (4.30 g, 73%), R_f = 0.42 (95 : 5 DCM : MeOH), $[\alpha]_D^{27}$ −55.8 (*c* 1.7, $CHCl_3$) (found: M^+ + H, 572.2053. $C_{25}H_{42}N_3O_5SeSi$ requires M, 572.2053); ν_{max}/cm^{-1} 3314, 2952, 2928, 2856, 1746, 1645, 1502, 1435, 1361, 1252, 1195, 1174, 1094, 1021, 839, 777 and 740; δ_H (500 MHz, $CDCl_3$) 0.07 (6 H, s, 2 × $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 1.46 (3 H, d, *J* 6.9, 4-H_3), 1.73 (2 H, br. s, NH_2), 1.92–2.01 (3 H, m, pro 3-H, pro 4-H_2), 2.19 (1 H, m, pro 3-H′), 3.42 (1 H, dd, *J* 6.6, 4.9, ser 2-H), 3.55–3.62 (2 H, m, pro 5-H, 3-H), 3.70 (3 H, s, OCH_3), 3.77 (1 H, dd, *J* 9.9, 6.7, ser 3-H), 3.85 (1 H, dd, *J* 9.9, 4.4, ser 3-H′), 3.91 (1 H, m, pro 5-H′), 4.48 (1 H, dd, *J* 8.6, 4.6, pro 2-H), 4.68 (1 H, t, *J* 9.2, 2-H), 7.27–7.31 (3 H, m, ArH), 7.60 (2 H, dd, *J* 7.3, 1.8, ArH) and 8.11 (1 H, d, *J* 8.6, NH); δ_C (125 MHz, $CDCl_3$) −5.2(2), 18.4, 18.9, 25.0, 26.0, 29.3, 41.0, 47.6, 52.3, 55.0, 56.9, 59.1, 65.1, 127.8, 128.1, 129.2, 135.7, 169.7, 172.4 and 172.7; *m*/*z* (ES^+) 572.2 (M^+ + 1, 100%) and 570.2 (M^+ + 1, 50).

Methyl *N*-[(2*R*,3*R*)-2-(L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinylamino)-3-phenylselanylbutanoyl]-L-prolinate (100). Diisopropylethylamine (1.73 mL, 9.92 mmol) was added to the amine **99** (3.77 g, 6.61 mmol) in DCM (100 mL) and the solution stirred for 5 min. After cooling to 0 °C, benzotriazole **14** (3.63 g, 7.27 mmol) was added dropwise and the reaction mixture was stirred at rt for 16 h. DCM (32 mL) was added and the solution washed with aqueous HCl (1 M, 32 mL), saturated aqueous $NaHCO_3$ (43 mL), water (43 mL) and brine (43 mL). The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2 : 1 to 1 : 1 light petroleum : EtOAc) afforded the Fmoc-protected thioamide as a yellow oil, a mixture of rotamers (5.57 g, 93%), R_f = 0.7 (1 : 1 light petroleum : EtOAc) (found: M^+ + H, 907.3031. $C_{45}H_{59}N_4O_7SSeSi$ requires M, 907.3033); ν_{max}/cm^{-1} 2951, 1746, 1651, 1507, 1435, 1347, 1257, 1174, 1100, 836 and 739; *m*/*z* (ES^+) 929.3 (M^+ + 23, 80%) and 481.1 (100).

Piperidine (3.04 mL, 30.75 mmol) was added to this thioamide (5.57 g, 6.15 mmol) in dry DMF (160 mL) and the reaction mixture was stirred for 15 min at rt. Saturated aqueous NH_4Cl (150 mL) and water (150 mL) were added and the mixture was extracted with EtOAc (10 × 225 mL). The organic extracts were washed with water (150 mL) and brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 2 light petroleum : EtOAc to 95 : 5 DCM : MeOH) gave the title compound **100** as a yellow oil (3.75 g, 83%), R_f = 0.37 (95 : 5 DCM : MeOH), $[\alpha]_D^{27}$ −91.7 (*c* 0.6, $CHCl_3$) (found: M^+ + H, 685.2349. $C_{30}H_{49}N_4O_5SSeSi$ requires M, 685.2353); ν_{max}/cm^{-1} 3208, 2928, 2855, 1746, 1645, 1512, 1435, 1361, 1257, 1173, 1106, 1022, 837, 779 and 740; δ_H (500 MHz, $CDCl_3$) 0.06 and 0.08 (each 3 H, s, $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.42 (3 H, d, *J* 6.8, 4-H_3), 1.60–1.72 (2 H, m, thiopro 4-H_2), 1.92–1.94 (4 H, m, pro 3-H, thiopro 3-H, pro 4-H_2), 2.07 (1 H, br. s, NH), 2.15 (1 H, m, pro 3-H′), 2.35 (1 H, m, thiopro 3-H′), 2.93 and 3.04 (each 1 H, m, thiopro 5-H), 3.48–3.57 (2 H, m, pro 5-H, 3-H), 3.67 (3 H, s, OCH_3), 3.72 (1 H, m, ser 3-H), 3.79 (1 H, m, pro 5-H′), 4.13 (1 H, dd, *J* 9.9, 3.7, ser 3-H′), 4.20 (1 H, dd, *J* 8.6, 5.9, thiopro 2-H), 4.47 (1 H, dd, *J* 8.4, 3.2, pro 2-H), 4.71 (1 H, t, *J* 8.9, 2-H), 4.94 (1 H, d, *J* 4.1, ser 2-H), 7.15 (1 H, d, *J* 8.4, NH), 7.26 (3 H, m, ArH), 7.57 (2 H, d, *J* 7.1, ArH) and 10.44 (1 H, d, *J* 4.2, NH); δ_C (125 MHz, $CDCl_3$) −5.4, −5.2, 18.2, 18.8, 24.9, 25.9, 26.1, 29.2, 34.7, 41.2, 47.5, 52.3, 55.2, 58.5, 59.0, 61.6, 68.5, 127.5, 128.2, 129.2, 135.8, 169.0(2), 172.3 and 206.8; *m*/*z* (ES^+) 685.2 (M^+ + 1, 100%) and 683.2 (M^+ + 1, 50).

Methyl *N*-[(2*R*,3*R*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinylamino)-3-phenylselanylbutanoyl]-L-prolinate (68). The dipeptide **34** (0.81 g, 2.66 mmol) and PyBOP (1.93 g, 3.70 mmol) followed by *N*-methylmorpholine (1.14 mL, 10.36 mmol) were added at 0 °C to the tetrapeptide **100** (1.77 g, 2.59 mmol) in dry DCM (39 mL) and the reaction mixture was stirred at rt for 17 h. DCM (100 mL) was added and the solution was washed with saturated aqueous NH_4Cl (140 mL), water (140 mL) and brine (140 mL). The aqueous washings were extracted with DCM (100 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 to 1 : 2 light petroleum : EtOAc) gave the title compound **68** as a colourless oil (2.36 g, 93%), R_f = 0.48 (1 : 2 light petroleum : EtOAc), $[\alpha]_D^{27}$ −49.3 (*c* 1.2, $CHCl_3$) (found: M^+ + Na, 991.3907. $C_{44}H_{72}N_6O_9SSeSiNa$ requires M, 991.3918); ν_{max}/cm^{-1} 3290, 2954, 1747, 1713, 1634, 1510, 1436, 1364, 1250, 1173, 1097, 1022, 837, 779 and 738; δ_H (500 MHz, $CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.84 [9 H, s, $SiC(CH_3)_3$], 0.93 (6 H, d, *J* 5.9, leu 4-CH_3, leu 5-H_3), 1.31 (3 H, d, *J* 6.7, ala 3-H_3), 1.40 [12 H, br. s, $OC(CH_3)_3$, 4-H_3], 1.53–1.62 (3 H, m, leu 4-H, leu 3-H_2), 1.93–1.94 (5 H, m, pro 4-H_2, thiopro 4-H_2, pro 3-H), 2.15–2.33 (3 H, m, pro 3-H′, thiopro 3-H_2), 3.58 (3 H, m, pro 5-H_2, thiopro 5-H), 3.67 (3 H, s, OCH_3), 3.74 (1 H, m, thiopro 5-H′), 3.83–3.86 (2 H, m, 3-H, ser 3-H), 4.09 (1 H, m, ser 3-H′), 4.22 (1 H, m, ala 2-H), 4.44 (1 H, m, pro 2-H), 4.62 (1 H, br. s, leu 2-H), 4.73–4.78 (2 H, m, 2-H, ser 2-H), 4.93 (1 H, m, thiopro 2-H), 5.50 (1 H, d, *J* 7.6, NH), 7.03 and 7.15 (each 1 H, br. s,

NH), 7.26 (3 H, m, ArH), 7.57 (2 H, m, ArH) and 8.55 (1 H, br. s, NH); δ_C (125 MHz, $CDCl_3$) −5.4, −5.2, 18.2, 18.6, 22.1, 23.3, 24.3, 24.7, 24.9, 25.9, 26.0, 28.4, 29.2, 33.0, 40.4, 40.8, 47.5, 47.9, 49.8, 49.9, 52.3, 55.7, 59.1, 60.3, 61.4, 68.5, 80.0, 128.0, 129.3, 135.3, 155.8, 168.6, 168.9, 171.8, 172.3, 173.5 and 203.0; *m*/*z* (ES^+) 991.4 (M^+ + 23, 100%) and 989.4 (M^+ + 23, 95).

Prop-2-enyl (2*S*)-2-acetoxy-3-(*N*-methyl-L-valinyloxy)propanoate (101). Pyridine (0.69 mL, 8.53 mmol) and acetic anhydride (0.80 mL, 8.46 mmol) were added to the glycerate **48** (1.21 g, 3.36 mmol) and DMAP (62 mg, 0.51 mmol) in DCM (40 mL) at 0 °C and the reaction mixture was stirred at rt for 1.5 h then concentrated under reduced pressure. The residue was dissolved in EtOAc (150 mL) and the solution washed with aqueous HCl (1 M) and brine then dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding acetate (1.29 g, 96%) as a mixture of rotamers; δ_H (400 MHz, DMSO-d_6) 0.75–0.85 (3 H, m, val 4-H_3 or val 3-CH_3), 0.92 (3 H, d, *J* 6.5, val 3-CH_3 or val 4-H_3), 1.36 and 1.40 [each 4.5 H, s, OC$(CH_3)_3$], 2.09 (3 H, s, CH_3CO), 2.10 (1 H, m, val 3-H), 2.72 (3 H, s, NCH_3), 3.99 and 4.27 (each 0.5 H, d, *J* 10.0, val 2-H), 4.35–4.55 (2 H, m, 3-H_2), 4.60–4.65 (2 H, m, CO_2CH_2), 5.25 (1 H, d, *J* 10.0, CH=CH*H*), 5.31 (1 H, d, *J* 17.5, CH=CH*H*), 5.35 (1 H, m, 2-H) and 5.89 (1 H, m, C*H*=CH_2); *m*/*z* (ES^+) 424.2 (M^+ + 23, 100%).

This Boc-protected amine (1.23 g, 3.06 mmol) was dissolved in trifluoroacetic acid : DCM (80 : 20, 114 mL) and the solution was stirred at rt for 1.5 h. After cooling to 0 °C, saturated aqueous $NaHCO_3$ was added until the solution was at pH 9. The mixture was extracted using EtOAc and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **101** (881 mg, 91%) as colourless oil, $[\alpha]_D^{27}$ −26 (*c* 1.0, $CHCl_3$) (found: M^+ + H, 302.1583. $C_{14}H_{24}NO_6$ requires M, 302.1598); ν_{max}/cm^{-1} 2962, 1739, 1579, 1498, 1372, 1198, 1157, 1102, 1022, 988 and 775; δ_H (400 MHz, DMSO-d_6) 0.85 and 0.86 (each 3 H, d, *J* 6.5, val 3-CH_3, val 4-H_3), 1.80 (1 H, hept, *J* 6.9, val 3-H), 2.09 (3 H, s, CH_3CO), 2.19 (3 H, s, NCH_3), 2.81 (1 H, d, *J* 6.3, val 2-H), 4.47 (1 H, dd, *J* 12.3, 4.4, 3-H), 4.54 (1 H, dd, *J* 12.3, 3.0, 3-H′), 4.64 (2 H, m, CO_2CH_2), 5.24 (1 H, d, *J* 10.5, CH=CH*H*), 5.28–5.41 (2 H, m, CH=CH*H*, 2-H) and 5.90 (1 H, ddt, *J* 17.3, 10.5, 5.3, C*H*=CH_2); δ_C (100 MHz, DMSO-d_6) 18.5, 19.1, 20.3, 30.7, 34.5, 62.1, 65.6, 68.6, 70.3, 118.1, 131.8, 166.7, 169.5, 173.8; *m*/*z* (ES^+) 302.2 (M^+ + 1, 70%) and 171.0 (100).

Prop-2-enyl (2*S*)-3-[(*N*-*tert*-butyloxycarbonyl-L-threoninyl)-*N*-methyl-L-valinyloxy]-2-acetoxypropanoate (102). *N*-Boc-L-threonine (2.02 g, 9.21 mmol) in a mixture of DMF : DCM (1 : 1, 8 mL) was stirred at 0 °C for 5 min before HATU (3.50 g, 9.21 mmol), *N*-methylmorpholine (2.50 mL, 22.7 mmol) and the valinylglycerate **101** (1.39 g, 4.60 mmol) in DCM (3.5 mL) were added at 0 °C. The reaction mixture was stirred at rt for 2.5 d then concentrated under reduced pressure. EtOAc was added and the solution was washed with saturated aqueous NH_4Cl and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 EtOAc : light petroleum) gave the title compound **102** (1.59 g, 69%) as a colourless oil, R_f = 0.38 (1 : 1 EtOAc : light petroleum), $[\alpha]_D^{27}$ −90.5 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 525.2407. $C_{23}H_{38}N_2O_{10}Na$ requires M, 525.2419); ν_{max}/cm^{-1} 3392, 2974, 1745, 1708, 1634, 1489, 1367, 1167, 1103, 995, 886 and 736; δ_H (400 MHz, DMSO-d_6) 0.75 and 0.93 (each 3 H, d, *J* 6.7, either val-4-H_3 or val-3-CH_3), 1.02 (3 H, d, *J* 6.3, *threo* 4-H_3), 1.36 [9 H, s, OC$(CH_3)_3$], 2.08 (3 H, s, CH_3CO), 2.14 (1 H, m, val 3-H), 3.02 (3 H, s, NCH_3), 3.75 (1 H, m, *threo* 3-H), 4.26 (1 H, t, *J* 7.4, *threo* 2-H), 4.47 (2 H, d, *J* 3.9, 3-H_2), 4.63 (2 H, dt, *J* 5.4, 1.5, CO_2CH_2), 4.67 (1 H, d, *J* 5.6, OH), 4.75 (1 H, d, *J* 10.3, val 2-H), 5.24 (1 H, dq, *J* 10.5, 1.5, CH=CH*H*), 5.28–5.40 (2 H, m, CH=CH*H*, 2-H), 5.90 (1 H ddt, *J* 17.3, 10.6, 5.4, C*H*=CH_2) and 6.74 (1 H, d, *J* 7.7, NH); δ_C (100 MHz, DMSO-d_6, 25 °C) 18.3, 19.6, 19.7, 20.2, 26.8, 28.1, 31.6, 56.5, 61.1, 62.7, 65.6, 66.5, 70.1, 78.1, 118.2, 131.8, 155.5, 166.6, 169.5, 169.8 and 172.1; *m*/*z* (ES^+) 525.3 (M^+ + 23, 50%), 503.3 (M^+ + 1, 70%) and 403.3 (100).

Prop-2-enyl (2*S*)-3-[(*N*-*tert*-butyloxycarbonyl-L-prolinyl-L-threoninyl)-*N*-methyl-L-valinyloxy]-2-acetoxypropanoate (103). The Boc-protected dipeptidyl glycerate **102** (100 mg, 0.183 mmol) in hydrogen chloride in dioxane (4 M, 1.1 mL) was stirred at 0 °C for 4 h before being concentrated under reduced pressure to give the corresponding ammonium salt. *N*-Methylmorpholine (80 μL, 0.73 mmol) and isobutyl chloroformate (20 μL, 0.15 mmol) were added to Boc-L-proline (32 mg, 0.15 mmol) in THF (2 mL) and the solution was stirred at −20 °C for 15 min. The ammonium salt prepared from the dipeptidyl glycerate **102** in THF (1 mL) was then added dropwise and the reaction mixture stirred at rt for 16 h. EtOAc was added and the solution was washed with saturated aqueous NH_4Cl, water and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (30 : 70 light petroleum : EtOAc) gave the title compound **103** as a colourless oil (68 mg, 90%), R_f = 0.25 (30 : 70 light petroleum : EtOAc), $[\alpha]_D^{27}$ −112 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 622.2944. $C_{28}H_{45}N_3O_{11}Na$ requires M, 622.2946); ν_{max}/cm^{-1} 3366, 2973, 1746, 1677, 1639, 1514, 1479, 1453, 1392, 1368, 1163, 1106, 986 and 753; δ_H (500 MHz, DMSO-d_6, 100 °C) 0.84 and 0.98 (each 3 H, d, *J* 6.6, val 4-H_3 or val 3-CH_3), 1.09 (3 H, d, *J* 6.2, *threo* 4-H_3), 1.41 [9 H, s, OC$(CH_3)_3$], 1.75–1.90 (3 H, m, pro-4-H_2, pro 3-H), 2.07 (1 H, m, pro 3-H′), 2.09 (3 H, s, CH_3CO), 2.20 (1 H, m, val 3-H), 3.03 (3 H, s, NCH_3), 3.31–3.42 (2 H, m, pro 5-H_2), 3.93 (1 H, m, *threo* 3-H), 4.22 (1 H, dd, *J* 8.6, 3.3, pro 2-H), 4.43 and 4.53 (each 1 H, m, 3-H), 4.66 (2 H, d, *J* 5.4, CO_2CH_2), 4.67–4.76 (2 H, m, *threo* 2-H, val 2-H), 5.26 (1 H, d, 11.0, CH=CH*H*), 5.30–5.38 (2 H, m, CH=CH*H*, 2-H), 5.92 (1 H, ddt, *J* 16.4, 10.7, 5.5, C*H*=CH_2) and 7.38 (1 H, d, *J* 7.7, NH); δ_C (125 MHz, DMSO-d_6, 100 °C) 18.1, 18.8, 18.9, 19.4, 22.7, 26.5, 27.5, 29.5, 30.9, 46.0, 53.8, 59.2, 61.5, 62.0, 65.0, 66.4, 69.6, 78.3, 117.6, 131.2, 153.2, 165.9, 168.6, 169.0, 170.9 and 171.4; *m*/*z* (ES^+) 622.4 (M^+ + 23, 80%), 600.5 (M^+ + 1, 100) and 500.3 (60).

Benzyl *N*-{(2*S*)-3-[(*N*-*tert*-butyloxycarbonyl-L-threoninyl)-*N*-methyl-L-valinyloxy]-2-acetoxypropanoyl}-L-alaninyl-D-leucinate (104). The catalyst $Pd(PPh_3)_4$ (21 mg, 0.018 mmol, 15 mol%) and $PhSiH_3$ (60 μL, 0.49 mmol) were added to the prop-2-enyl glycerate **102** (60 mg, 0.12 mmol) in DCM (5 mL) and the reac-

tion mixture was stirred at rt for 45 min then concentrated under reduced pressure to give the corresponding carboxylic acid. HATU (50 mg, 0.13 mmol) and *N*-methylmorpholine (70 μL, 0.64 mmol) were added to this acid in DCM (400 μL) at 0 °C. The aminodipeptide **60** (35 mg, 0.12 mmol) in DCM (0.4 mL) was added at 0 °C and the reaction mixture stirred at rt for 16 h. After concentration under reduced pressure, the residue was dissolved in EtOAc and the solution was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (3 : 7 light petroleum : EtOAc) gave the title compound **104** (57 mg, 66%) as a light brown solid, R_f = 0.41 (1 : 4 light petroleum : EtOAc), $[\alpha]_D^{27}$ −53.8 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 759.3768. $C_{36}H_{56}N_4O_{12}Na$ requires M, 759.3787); ν_{max}/cm^{-1} 3305, 2964, 2935, 1743, 1657, 1516, 1455, 1367, 1221, 1164, 1083, 1018, 945, 885, 745 and 698 δ_H (400 MHz, DMSO-d_6) 0.74 (3 H, d, *J* 6.7, either val 4-H_3 or val 3-CH_3), 0.81 and 0.87 (each 3 H, d, *J* 6.2, either leu 5-H_3 or leu 4-CH_3), 0.93 (3 H, d, *J* 6.7, either val 4-H_3 or val 3-CH_3), 1.01 (3 H, d, *J* 6.3, *threo* 4-H_3), 1.22 (3 H, d, *J* 7.1, ala 3-H_3), 1.35 [9 H, s, $OC(CH_3)_3$], 1.45–1.64 (3 H, m, leu 3-H_2, leu 4-H), 2.06 (3 H, s, CH_3CO), 2.13 (1 H, m, val 3-H), 3.01 (3 H, s, NCH_3), 3.75 (1 H, sext, *J* 6.3, *threo* 3-H), 4.21–4.43 (5 H, m, 3-H_2, *threo* 2-H, ala-2-H, leu-2-H), 4.68 (1 H, d, *J* 5.9, OH), 4.77 (1 H, d, *J* 10.3, val 2-H), 5.12 (2 H, s, $PhCH_2$), 5.18 (1 H, dd, *J* 6.8, 2.8, 2-H), 6.75 (1 H, d, *J* 7.7, *threo* NH), 7.27–7.42 (5 H, m, ArH), 8.28 (1 H, d, *J* 7.7, ala NH) and 8.33 (1 H, d, *J* 8.2, leu NH); δ_C (125 MHz, DMSO-d_6) 18.3, 18.5, 19.6, 19.7, 20.6, 21.1, 22.8, 24.3, 26.7, 28.1, 31.5, 39.4 48.2, 50.2, 56.5, 61.0, 63.2, 66.0, 66.5, 71.2, 78.1, 127.8, 128.1, 128.4, 135.9, 155.5, 165.7, 169.6, 169.8, 171.9, 172.1 and 172.2; *m*/*z* (ES^+) 760.4 (95%), 759.5 (M^+ + 23, 100) and 737.5 (M^+ + 1, 85).

Prop-2-enyl (2*S*)-3-{*N*-[(2*R*,3*R*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinyl-L-threoninyl-*N*-methyl-L-valinyloxy}-2-acetoxypropanoate (107). Hydrogen chloride in dioxane (4 M, 3.7 mL) was added to the Boc-protected dipeptidylglycerate **102** (200 mg, 0.374 mmol) and the reaction mixture was stirred at 0 °C for 4 h. Concentration under reduced pressure then gave the amine **106** as its ammonium salt, a yellowish oil. Aqueous lithium hydroxide (1 M, 1.7 mL) was added to the methyl ester **68** (327 mg, 0.337 mmol) in a mixture of THF and *tert*-butanol (2 : 1, 2.0 mL) and the reaction mixture was stirred at rt for 2 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The aqueous layer was acidified to pH 2 using aqueous HCl (1 M) then saturated using NaCl and extracted with EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the acid **105** as white solid (273 mg, 85%); *m*/*z* (ES^-) 953.6 ($[M^- - 1]^-$, 100%) and 951.7 ($[M - 1]^-$, 50); (ES^+) 993.5 (M^+ + 39, 100%).

N-Methylmorpholine (250 μL, 2.27 mmol) and isobutyl chloroformate (0.45 μL, 0.344 mmol) were added dropwise to this acid **105** (273 mg, 0.286 mmol) in THF (5.2 mL) at −15 °C and the reaction mixture was stirred for 30 min at −15 °C. The amine **106** in THF (2.6 mL) was added and the solution was stirred at rt for 16 h. Saturated aqueous NH_4Cl and EtOAc were added and the aqueous layer was extracted with more EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (1 : 4 DCM : EtOAc) gave the title compound **107** (237 mg, 62%) as a white solid, mp 74–78 °C, R_f = 0.38 (1 : 4 CH_2Cl_2 : EtOAc), $[\alpha]_D^{26}$ −180 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 1361.5682. $C_{61}H_{98}N_8O_{16}SSeSiNa$ requires M, 1361.5648); ν_{max}/cm^{-1} 3314, 2957, 1748, 1631, 1511, 1439, 1367, 1166, 1101, 1022, 837, 780 and 741; δ_H (500 MHz, DMSO-d_6, 100 °C) 0.05 and 0.06 (each 3 H, s, $SiCH_3$), 0.80–0.91 [18 H, m, leu 5-H_3, leu 4-CH_3, val 4-H_3 or val 3-CH_3, $SiC(CH_3)_3$], 0.97 (3 H, d, *J* 6.6, val 4-H_3 or val 3-CH_3), 1.09 (3 H, d, *J* 6.3, *threo* 4-H_3), 1.23 (3 H, d, *J* 7.0, ala 3-H_3), 1.40 [9 H, s, $OC(CH_3)_3$], 1.41 (3 H, d, *J* 7.1, 4′-H_3), 1.51 (2 H, m, leu 3-H_2), 1.60 (1 H, m, leu 4-H), 1.76–2.01 (6 H, m, pro 4-H_2, thiopro 4-H_2, pro 3-H, thiopro 3-H), 2.02–2.11 (4 H, m, pro 3-H′, CH_3CO), 2.19 (1 H, m, val 3-H), 2.26 (1 H, m, thiopro 3-H′), 3.00 (3 H, s, NCH_3), 3.46–3.70 (5 H, m, 3′-H, pro 5-H_2, thiopro 5-H_2), 3.92 (1 H, m, *threo* 3-H), 3.96–4.07 (4 H, m, ser 3-H_2, ala 2-H, thiopro 2-H), 4.26 (1 H, s, OH), 4.43 (1 H, dd, *J* 12.2, 5.5, 3-H), 4.45 (2 H, m, pro 2-H, leu 2-H), 4.52 (1 H, dd, *J* 12.2, 3.6, 3-H′), 4.65 (2 H, d, *J* 5.4, CO_2CH_2), 4.66–4.74 (2 H, m, *threo* 2-H, val 2-H), 4.80 (1 H, t, *J* 8.5, 2′-H), 5.05 (1 H, dt, *J* 7.3, 5.1, ser 2-H), 5.25 (1 H, dq, *J* 10.6, 1.4, CH=CH*H*), 5.29–5.37 (2 H, m, CH=CH*H*, 2-H), 5.91 (1 H, ddt, *J* 17.3, 10.8, 5.5, C*H*=CH_2), 6.26 (1 H, d, *J* 7.5, BocNH), 7.31 (3 H, dd, *J* 5.0, 1.9, ArH), 7.48 (1 H, d, *J* 7.9, leu NH), 7.52–7.61 (3 H, m, ArH, *threo* NH), 8.04 (1 H, s, NH) and 9.11 (1 H, s, thiopro NH); δ_C (125 MHz, DMSO) −6.2 (2), 17.2, 17.7, 18.1, 18.7, 18.9, 19.4, 21.1, 22.4, 23.5, 25.1, 26.5, 27.6, 28.2, 39.5, 40.6, 46.4, 46.7, 48.6, 49.6, 53.9, 54.0, 59.0, 59.2, 61.3, 62.0, 65.0, 66.5, 66.8, 69.6, 77.8, 117.6, 126.9, 128.3, 131.2, 134.1, 154.2, 165.9, 167.3, 168.6, 168.9, 170.3, 170.9, 171.9 and 203.4; *m*/*z* (ES^+) 1361.9 (M^+ + 23, 100%).

{(2*R*,3*R*)-[2-(2*S*)-2-Acetoxy-3-hydroxypropanoyl-L-alaninyl]-D-leucinyl-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-3-phenylselanylbutanoyl}-L-prolinyl-L-threoninyl-*N*-methyl-L-valinolactone (108). The catalyst $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) and $PhSiH_3$ (22 μL, 0.178 mmol) were added to the peptidylglycerate **107** (200 mg, 0.15 mmol) in DCM (7 mL) and the mixture stirred at rt for 2 h then concentrated under reduced pressure to give the corresponding glyceric acid. Trifluoroacetic acid (1.7 mL, 2.20 mmol) was added to this glyceric acid in DCM (8 mL) at 0 °C and the solution stirred for 1 h. After warming to rt, toluene (8 mL) was added and the solution was concentrated under reduced pressure. Ether (8 mL) was added and the solution concentrated under reduced pressure. This process was repeated four times until a light brown solid was obtained. This solid was suspended in ether and the mixture filtered. The solid was then dissolved in DCM and the solution concentrated under reduced pressure to give the *N*-Boc-deprotected peptidylglyceric acid as its trifluoroacetate salt (172 mg, 88%). This was dissolved in DCM

(20 mL), added to HATU (72 mg, 0.189 mmol), HOBt (102 mg, 0.754 mmol) and *N*-methylmorpholine (0.35 mL, 3.14 mmol) in DCM (160 mL), and the reaction mixture stirred at rt for 2.5 d. Saturated aqueous NH_4Cl was added and the aqueous phase was extracted with DCM. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 DCM : EtOAc to DCM to 94 : 6 DCM : MeOH) gave the title compound **108** as pale yellow solid (40 mg, 23%), mp 118–122 °C, $[\alpha]_D^{25}$ −82 (*c* 1.0, $CHCl_3$) (found: M^+ + Na, 1203.4698. $C_{53}H_{84}N_8O_{13}SSeSiNa$ requires M, 1203.4705); ν_{max}/cm^{-1} 3293, 2957, 2929, 2880, 1747, 1634, 1510, 1436, 1258, 1225, 1188, 1096, 837 and 732; δ_H (500 MHz, $CDCl_3$) 0.08 (6 H, s, 2 × $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 0.88 (3 H, d, *J* 6.5, leu 4-CH_3), 0.90–1.00 [9 H, m, leu 5-H_3, val 4-H_3, val 3-CH_3], 1.10 (3 H, d, *J* 6.5, *threo* 4-H_3), 1.28 (3 H, d, *J* 7.0, ala 3-H_3), 1.44 (3 H, d, *J* 6.5, 4′-H_3), 1.30–1.60 (3 H, m, leu 3-H_2, leu 4-H), 1.85–2.01 (6 H, m, pro 4-H_2, thiopro 4-H_2, pro 3-H, thiopro 3-H), 2.10 (3 H, s, CH_3CO), 2.20–2.45 (3 H, m, pro 3-H′, thiopro 3-H′, val 3-H), 2.68 (3 H, s, NCH_3), 3.45–3.55 (2 H, m, pro 5-H, thiopro 5-H), 3.71 (1 H, m, thiopro 5-H′), 3.78 (1 H, m, 3′-H), 3.88 (1 H, m, pro 5-H′), 4.07 (1 H, dd, *J* 9.0, 3.5, ser 3-H), 4.15 (1 H, m, *threo* 3-H), 4.22 (1 H, d, *J* 13.5, 3-H), 4.30–4.35 (3 H, m, ser 3-H′, ala 2-H, thiopro 2-H), 4.57 (1 H, d, *J* 8.0, val 2-H), 4.65–4.75 (3 H, m, leu 2-H, *threo* 2-H, 2′-H), 4.78 (1 H, d, *J* 6.0, OH), 4.82 (2 H, m, pro 2-H, ser 2-H), 4.99 (1 H, dd, *J* 13.5, 7.0, 3-H′), 5.18 (1 H, d, *J* 7.0, 2-H), 6.26 (1 H, d, *J* 6.0, NH), 6.59 (1 H, d, *J* 4.0, NH), 7.12 (1 H, d, *J* 10.1, NH), 7.25–7.30 (3 H, m, ArH), 7.60–7.65 (2 H, m, ArH), 8.16 (1 H, d, *J* 8.0, NH) and 8.76 (1 H, d, *J* 4.0, NH); δ_C (125 MHz, DMSO) −5.2, 15.9, 18.3, 18.6, 18.9, 19.1, 20.2, 20.8, 21.6, 23.7, 24.0, 24.2, 25.0, 25.9, 27.2, 28.3, 29.5, 33.2, 38.8, 39.4, 39.7, 47.2, 47.8, 48.0, 51.0, 51.7, 55.9, 61.4, 61.6, 63.5, 64.0, 65.0, 67.2, 68.4, 74.0, 127.8, 128.2, 129.3, 134.5, 168.1, 168.9, 169.3, 170.3, 171.0, 171.2, 171.4, 173.0, 173.1 and 203.9; *m*/*z* (ES^+) 1205.8 (M^+ + 23, 100%), 1203.8 (M^+ + 23, 95), 1181.9 (M^+ + 1, 50) and 1179.8 (M^+ + 1, 25).

Methyl *N*-[(2*R*,3*S*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinate (109). Tetra-*n*-butylammonium fluoride (1 M in THF, 0.12 mL, 0.12 mmol) was added at 0 °C to the TBS-protected peptide **80** (60 mg, 0.06 mmol) in dry THF (0.9 mL) and the solution was stirred at 0 °C for 5 min then at rt for 2 h. Ethyl acetate (1 mL), saturated aqueous NH_4Cl (1 mL) and brine (1 mL) were added and the aqueous phase was extracted with EtOAc (10 × 1 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 2 light petroleum : EtOAc to 95 : 5 DCM : MeOH) gave the title compound **109** as a yellow oil (48 mg, 92%), R_f = 0.43 (95 : 5 DCM : MeOH) (found: M^+ + Na, 877.3047. $C_{38}H_{58}N_6O_9SSeNa$ requires M, 877.3043); δ_H (500 MHz, $CDCl_3$) 0.93 (6 H, d, *J* 5.8, leu 4-CH_3, leu 5-H_3), 1.10 (3 H, d, *J* 7.1, ala 3-H_3), 1.41 [9 H, s, $OC(CH_3)_3$], 1.49 (3 H, d, *J* 7.1, 4-H_3), 1.59–1.60 (3 H, m, leu 3-H_2, leu 4-H), 1.88–2.01 (5 H, m, pro 3-H, pro 4-H_2, thiopro 4-H_2), 2.17 (1 H, m, pro 3-H′), 2.28 and 2.40 (each 1 H, m, thiopro 3-H), 3.35 (1 H, m, pro 5-H), 3.53–3.63 (3 H, m, 3-H, pro 5-H′, thiopro 5-H), 3.68 (3 H, s, OCH_3), 3.82 (1 H, m, ser 3-H), 3.91 (1 H, m, thiopro 5-H′), 4.04 (1 H, pent, *J* 7.3, ala 2-H), 4.16 (1 H, m, ser 3-H′), 4.37 (1 H, br. s, OH), 4.50 (1 H, dd, *J* 8.4, 3.9, pro 2-H), 4.80 (1 H, m, leu 2-H), 4.86 (1 H, m, 2-H), 4.93 (1 H, dd, *J* 8.5, 3.7, thiopro 2-H), 5.02 (1 H, m, ser 2-H), 5.25 (1 H, d, *J* 8.0, NH), 7.03 (1 H, d, *J* 8.2, NH), 7.25–7.32 (4 H, m, ArH, NH), 7.67–7.69 (2 H, m, ArH) and 8.73 (1 H, d, *J* 7.5, NH); δ_C (125 MHz, $CDCl_3$) 17.9, 18.3, 22.2, 23.2, 24.5, 24.8, 25.0, 28.4, 29.2, 32.2, 40.3, 42.0, 46.9, 48.0, 49.3, 50.1, 52.3, 55.3, 59.2, 60.3, 61.6, 68.1, 80.7, 128.1, 129.2, 129.9, 135.7, 156.6, 167.8, 169.5, 172.2, 172.5, 173.4 and 203.1; *m*/*z* (ES^+) 877.5 (M^+ + 23, 95%), 875.5 (M^+ + 23, 50), 855.5 (M^+ + 1, 100) and 853.5 (M^+ + 1, 50).

Methyl *N*-[(2*R*,3*R*)-2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-L-serinyl)amino-3-phenylselanylbutanoyl]-L-prolinate (110). Following the procedure outlined for the preparation of the alcohol **109**, the TBS-protected peptide **68** (60 mg, 0.06 mmol) in dry THF (0.9 mL) and TBAF (1 M in THF, 0.12 mL, 0.12 mmol), after chromatography (1 : 2 light petroleum : EtOAc to 95 : 5 DCM : MeOH) gave the title compound **110** as a yellow oil (48 mg, 92%), R_f = 0.40 (95 : 5 DCM : MeOH) (found: M^+ + Na, 877.3046. $C_{38}H_{58}N_6O_9SSeNa$ requires M, 877.3043); δ_H (400 MHz, $CDCl_3$) 0.93–0.96 (6 H, m, leu 4-CH_3, leu 5-H_3), 1.14 (3 H, d, *J* 7.1, ala 3-H_3), 1.41 [12 H, br. s, $OC(CH_3)_3$, 4-H_3], 1.53–1.65 (3 H, m, leu 3-H_2, leu 4-H), 1.89–2.02 (5 H, m, pro 3-H, pro 4-H_2, thiopro 4-H_2), 2.21 (1 H, m, pro 3-H′), 2.31 and 2.42 (each 1 H, m, thiopro 3-H), 3.52–3.64 (2 H, m, pro 5-H, thiopro 5-H), 3.66 (3 H, s, OCH_3), 3.81–3.95 (4 H, m, pro 5-H′, thiopro 5-H′, ser 3-H_2), 4.11 (1 H, pent, *J* 7.1, ala 2-H), 4.18–4.24 (2 H, m, 3-H, OH), 4.50 (1 H, dd, *J* 8.7, 4.6, pro 2-H), 4.75 (1 H, t, *J* 9.5, 2-H), 4.82 (1 H, m, leu 2-H), 4.87 (1 H, m, ser 2-H), 4.96 (1 H, dd, *J* 8.5, 3.6, thiopro 2-H), 5.21 (1 H, d, *J* 7.6, NH), 7.01 (1 H, d, *J* 7.5, NH), 7.27–7.33 (3 H, m, ArH), 7.53 (1 H, d, *J* 8.8, NH), 7.60–7.63 (2 H, m, ArH) and 8.61 (1 H, d, *J* 7.0, NH); δ_C (125 MHz, $CDCl_3$) 18.1, 19.0, 22.1, 23.3, 24.5, 24.7, 25.0, 29.3, 32.3, 40.8 (2), 47.5, 48.1, 49.3, 50.1, 52.2, 55.1, 59.1, 60.5, 61.5, 68.1, 80.6, 127.1, 128.3, 129.3, 135.7, 156.5, 168.4, 168.8, 172.3, 172.5, 173.4 and 202.7; *m*/*z* (ES^+) 877.4 (M^+ + 23, 100%) and 875.4 (M^+ + 23, 50).

Methyl *N*-[2-(*N*-*tert*-butoxycarbonyl-L-alaninyl-D-leucinyl-L-thioprolinyl-*O*-*tert*-butyldimethylsilyl-L-serinyl)amino-but-3-enoyl]-L-prolinate (111). *tert*-Butyl hydroperoxide in decane (5.5 M, 0.09 mL) was added to the peptide **68** (50 mg, 0.05 mmol) in DCM (0.5 mL) at 0 °C and the mixture stirred at 0 °C for 5 min and at rt for 3 h. Saturated aqueous $Na_2S_2O_3$ (2 mL) was added and the mixture stirred for 30 min then extracted with EtOAc (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (1 : 1 light petroleum : EtOAc to 1 : 1 EtOAc : CH_3CN) gave the title compound **111** as a colourless oil (16 mg, 39%), some hindered rotation was apparent (^1H NMR), R_f = 0.48 (1 : 1 EtOAc : CH_3CN) (found: M^+ + Na, 833.4260. $C_{38}H_{66}N_6O_9SSiNa$ requires M, 833.4273); δ_H (500 MHz, $CDCl_3$) 0.07 and 0.09 (each 3 H, s, $SiCH_3$),

0.86–0.95 [15 H, m, $SiC(CH_3)_3$, leu 4-CH_3, leu 5-H_3], 1.30 (3 H, d, *J* 6.9, ala 3-H_3), 1.44 [9 H, s, $OC(CH_3)_3$], 1.55–1.63 (3 H, m, leu 4-H, leu 3-H_2), 1.91–2.00 (5 H, m, pro 4-H_2, thiopro 4-H_2, pro 3-H), 2.19–2.32 (3 H, m, pro 3-H′, thiopro 3-H_2), 2.61–2.62 (3 H, m, pro 5-H_2, thiopro 5-H), 3.71 (3 H, s, OCH_3), 3.85–3.90 (2 H, m, thiopro 5-H′, ser 3-H), 4.18 (1 H, m, ser 3-H′), 4.28 (1 H, m, ala 2-H), 4.54 (1 H, m, pro 2-H), 4.71 (1 H, m, leu 2-H), 4.94–5.00 (2 H, m, thiopro 2-H, ser 2-H), 5.14 (1 H, br. s, 2-H), 5.36 (1 H, d, *J* 10.3, 4-H), 5.51 (1 H, d, *J* 16.9, 4-H′), 5.82–5.89 (2 H, m, 3-H, NH), 7.01 (1 H, d, *J* 5.1, NH), 7.45 (1 H, d, *J* 4.6, NH) and 8.47 (1 H, d, *J* 3.2, NH); δ_C (125 MHz, $CDCl_3$) −5.3, −5.2, 18.3, 22.3, 23.3, 24.3, 24.8, 25.0, 25.9, 26.1, 28.5, 29.1, 33.2, 40.7, 46.8, 47.9, 49.5, 49.9, 52.4, 54.0, 59.2, 59.7, 61.6, 68.6, 80.1, 120.0, 131.5, 155.9, 167.6, 169.1, 171.8, 172.5, 173.3 and 203.1; *m*/*z* (ES^+) 833.7 (M^+ + 23, 100%) and 811.7 (M^+ + 1, 60).

{(*Z*)-2-[(2*S*)-(2-Acetoxy-3-hydroxypropanoyl)-L-alaninyl-D-leucinyl-L-thioprolinyl-(*O*-*tert*-butyldimethylsilyl-L-serinyl)aminobut-2-enoyl}-L-prolinyl-(*O*-acetyl-L-threoninyl)-*N*-methyl-L-valinolactone (112). *tert*-Butyl hydroperoxide in decane (5.5 M, 0.03 mL 17 mmol) was added at 0 °C to the selenide **84** (18 mg, 0.02 mmol) in DCM (0.15 mL) and the mixture stirred at 0 °C for 5 min and at rt for 3 h. Saturated aqueous $Na_2S_2O_3$ (2 mL) was added, the mixture was stirred for 30 min, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (100 : 1 DCM : MeOH) gave the title compound **112** as a colourless oil (5 mg, 32%), R_f = 0.33 (100 : 1 DCM : MeOH); δ_H (500 MHz, $CDCl_3$) 0.06 and 0.07 (each 3 H, s, $SiCH_3$), 0.86 (3 H, d, *J* 6.5, leu 4-H_3), 0.87 [9 H, s, $SiC(CH_3)_3$], 0.96, 1.01, 1.11, 1.25 and 1.28 (each 3 H, d, *J* 6.5–7.0, either leu 5-H_3, val 4-H_3, val 3-CH_3, *threo* 4-H_3 or ala 3-H_3), 1.35–1.80 (7 H, m, leu 4-H, leu 3-H_2, 2 × pro 4-H_2), 1.77 (3 H, d, *J* 7.0, 4′-H_3), 1.95–2.10 (2 H, m, 2 × pro 3-H), 2.08 and 2.15 (each 3 H, s, CH_3CO), 2.20 (2 H, m, 2 × pro 3-H′), 2.65 (1 H, m, val 3-H), 2.94 (1 H, d, *J* 8.0, val 2-H), 3.21 (3 H, s, NCH_3), 3.50–3.65 (2 H, m, 2 × pro 5-H), 3.54 (1 H, d, *J* 8.0, 3-H), 3.80 and 4.00 (each 1 H, m, pro 5-H′), 4.05–4.11 (2 H, m, ser 3-H_2), 4.22 (1 H, m, ala 2-H), 4.43 (1 H, m, pro 2-H), 4.45–4.60 (2 H, m, leu 2-H, ser 2-H), 4.85 (1 H, m, pro 2-H), 5.02 (1 H, t, *J* 5.0, *threo* 2-H), 5.17 (1 H, m, *threo* 3-H), 5.29 (1 H, d, *J* 7.0, 3-H′), 5.37 (1 H, dd, *J* 8.0, 7.0, 2-H), 5.69 (1 H, m, 3′-H), 7.33 (1 H, d, *J* 5.5, NH), 7.61 (1 H, d, *J* 4.0, NH), 7.72 (1 H, d, *J* 8.0, NH), 8.35 (1 H, s, NH) and 9.55 (1 H, d, *J* 5.0, NH); δ_C (125 MHz, $CDCl_3$) −5.2, 12.6, 13.4, 18.0, 18.3, 19.3, 21.5, 21.7, 21.9, 22.0, 22.2, 23.6, 24.5, 25.1, 25.9, 28.0, 29.7, 29.9, 31.6, 39.8, 40.0, 46.9, 47.3, 47.9, 51.1, 52.3, 57.1, 61.8, 62.0, 62.6, 64.4, 70.0, 70.6, 70.7, 122.7, 131.1, 167.2, 167.6, 168.3, 168.5, 169.1, 170.2, 171.8, 172.3(2), 173.5 and 173.6; *m*/*z* (ES^+) 1071.9 (M^+ + 23, 100%); (ES^-) 1048.0 (M^-, 100%).

Conflicts of interest

Q3 ■■■■

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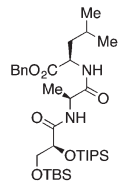

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