Synthesis of libraries of thiazole, oxazole and imidazole-based cyclic peptides from azole-based amino acids. A new synthetic approach to bistratamides and didmolamides†

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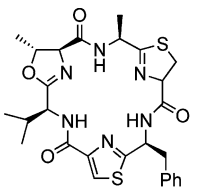
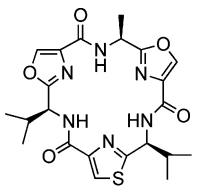
Treatment of a 1 : 1 mixture of the thiazole-based amino acids **8a** and **8b** with FDPP–*i*-Pr_2NEt in CH_3CN gave a mixture of the cyclic trimers **14**, **15**, **16** and **17** and the cyclic tetramers **19** and **23** in the ratio 2 : 7 : 5 : 8 : 1 : 1 and in a combined yield of 70%. Separate coupling reactions between the bisimidazole amino acid **45** and the thiazole/oxazole amino acids **43a** and **42a** in the presence of FDPP–*i*-Pr_2NEt led to the bisimidazole based cyclic trimers **55** and **57** respectively (54–57%) and to the cyclic tetramer **56** (8–11%). Similar coupling reactions involving the bisthiazole and bisoxazole amino acids **49** and **47** with the imidazole/oxazole/thiazole amino acids **41a**, **42a** and **43a** gave rise to the library of oxazole, thiazole and imidazole-based cyclic peptides **58**, **59**, **60**, **61**, **62**, **63**, **64** and **65**. A coupling reaction between the bisthiazole amino acid **49** and the oxazole amino acid **73** led to an efficient (36% overall) synthesis of bistratamide H (**67**) found in the ascidian *Lissoclinum bistratum*. Coupling reactions involving oxazolines with thiazole amino acids were less successful. Thus, a coupling reaction between the phenylalanine-based oxazoline amino acid **71a** and either the thiazole amino acid **8a** or the bisthiazole amino acid **74** gave only a 2% yield of the cyclic hexapeptide didmolamide A (**4**) found in the ascidian *Didemnum molle*. Didmolamide B (**68**) was obtained in 9% yield from a coupling reaction between **74** and the phenylalanine threonine amino acid **72**, using either FDPP or DPPA.

Introduction

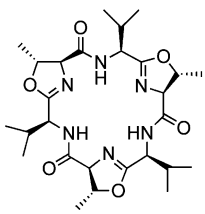
The past decade has seen rapid progress in the isolation and characterisation of a plethora of azole-based cyclic peptides from marine organisms, fungi and algae.[1] Furthermore, many of these secondary metabolites show useful biological properties, including antibacterial and antiviral activities and cytotoxicity.[2] Prominent amongst these cyclic peptides are the "bistratamides", *e.g.* **1** and **2**, which are oxazole, oxazoline, thiazole, thiazoline-based hexapeptides, isolated from the Great Barrier Reef and from the Philippine ascidian ("sea squirt") *Lissoclinum bistratum*.[3] The bistratamides are related to the C_3-symmetric trisoxazoline westiellamide **3** which is also found in *L. bistratum*,[4] and to the bisthiazole based "didmolamides", *e.g.* **4**, isolated more recently from the ascidian *Didemnum molle* collected off the coast of Madagascar.[5] Structures similar to the bistratamides and didmolamides, are the dendroamides and nostocyclamides, *e.g.* **5** and **6** respectively, which have been isolated from cyanobacteria.[6] The interesting antitumor and antidrug resistance properties, in particular, and their potential for acting as metal ion chelators, have combined to make azole-based cyclic hexapeptides of the type represented by structures **1**–**6** attractive targets for total synthesis and biological evaluation.[7]



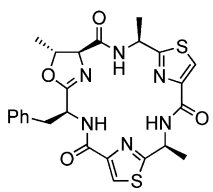
1, Bistratamide B



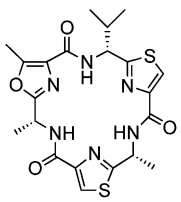
2, Bistratamide G



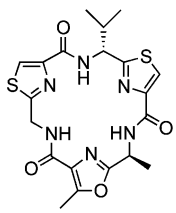
3, Westiellamide



4, Didmolamide A



5, Dendroamide A



6, Nostocyclamide

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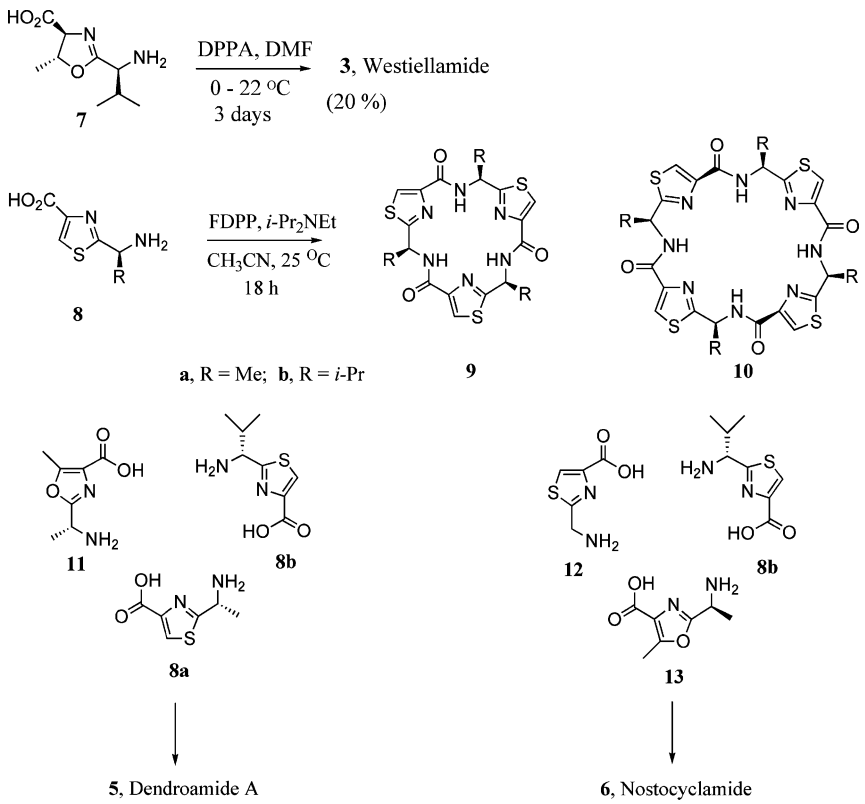
The overwhelming majority of the published syntheses of azole-based cyclic hexapeptides have used a straightforward strategy involving the iterative coupling of enantiopure azole amino acids to produce a linear hexapeptide, followed by macrolactamisation of an appropriate ω-amino acid intermediate.[7] Several years ago, Wipf and Miller[8] demonstrated that the 18-membered cyclic hexapeptide westiellamide **3** could be obtained in 20% yield by cyclooligomerisation of the *trans*-oxazoline **7** in the presence of the coupling agent DPPA. In later studies, our own research group showed that similar cyclooligomerisations could be carried out with thiazole-based amino acids, *e.g.* **8a** and **8b**, in the presence of FDPP–*i*-Pr_2NEt, leading to high yields (approx. 70%) of the cyclic trimers **9** together with smaller amounts of the corresponding cyclic tetramers **10**.[9] Somewhat remarkably, we also showed that acceptable yields, *i.e.* approx. 22–26%, of the natural products dendroamide A (**5**) and nostocyclamide **6**, were produced when mixtures of their constituent azole-based amino acids, *i.e.* **8a**, **8b**, **11**, and **8b**, **12**, **13** respectively, were treated similarly with FDPP–*i*-Pr_2NEt.[10] In continuation of these studies of the assembly of cyclic peptides, we have now evaluated the scope for the formation of other, mixed, azole-based structures, including those from imidazoles and oxazolines. These studies are described here, alongside an approach to bisthiazole oxazoline-based cyclic hexapeptides, *e.g.* didmolamide A (**4**).

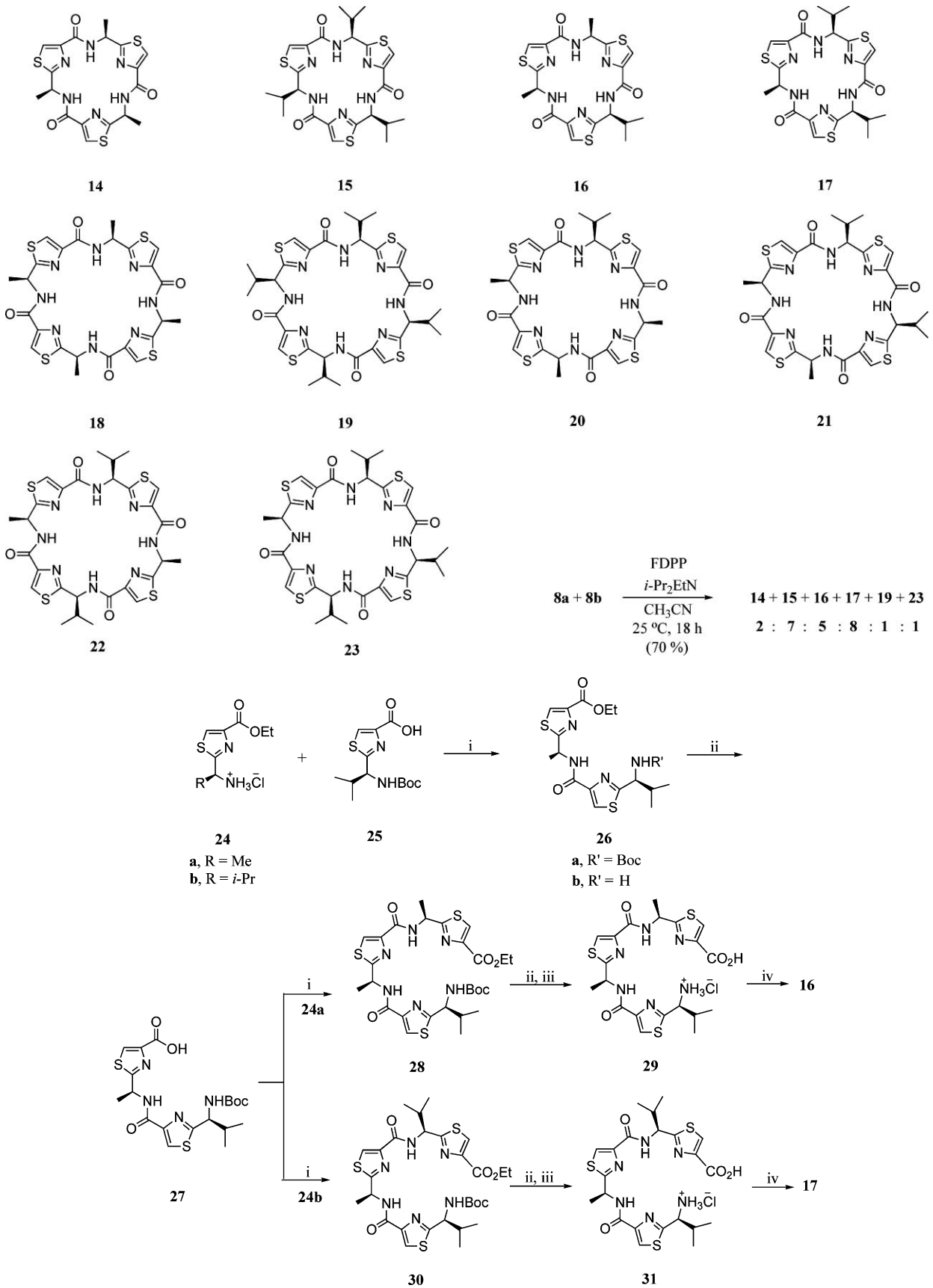
Mixed cyclooligomerisation of the alanine and valine-based thiazole amino acids 8a and 8b

To gain some insight into the factors which might control the selectivity of cyclooligomerisations of azole-based amino acids, we first decided to study the outcome of treating a 1 : 1 mixture of the alanine and valine-based thiazoles, **8a** and **8b** respectively, with FDPP-*i*-Pr_2NEt. Earlier, we had shown that when the thiazoles **8a** and **8b** are treated separately with FDPP–*i*-Pr_2NEt at room temperature under high dilution in CH_3CN, they each led to the cyclic trimers **9** and the cyclic tetramers **10**, in ratios of 9 : 2 and 5 : 2 respectively, in very good overall yields.[9] Only minute amounts of higher cyclic oligomers could be detected by HPLC-MS from these reactions. Treatment of a 1 : 1 mixture of **8a** and **8b** with FPPP–*i*–Pr_2NEt under the same reaction conditions *a priori*, would be expected to lead to four possible cyclic trimers, *i.e.* **14**, **15**, **16**, **17**, and to six possible cyclic tetramers, *i.e.* **18**, **19**, **20**, **21**, **22**, **23**.

In reality, treatment of a solution of a 1 : 1 mixture of **8a** and **8b** in CH_3CN, with FDPP–*i*-Pr_2NEt, produced all the cyclic trimers **14**, **15**, **16** and **17**, but only two cyclic tetramers,*i.e.* **19** and **23**, in the ratio 2 : 7 : 5 : 8 : 1 : 1 and in a combined yield of 70%. The ratio of the cyclic peptide products was determined by HPLC analysis and comparison of retention time data with those of authentic compounds prepared by more conventional linear routes starting from the enantiopure thiazole amino acids **8a** and **8b**.

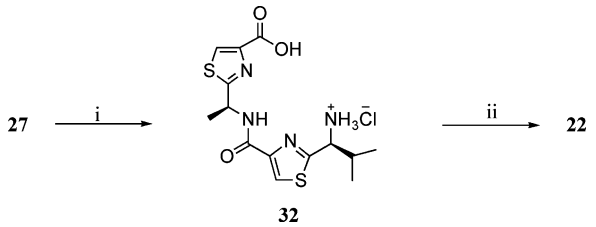
The symmetrical cyclic trimers **14** and **15** and cyclic tetramers **18** and **19** were enantiomers of compounds from our earlier studies.[9] The cyclic trimers **16** and **17** were both elaborated from the same bisthiazole **26a** produced from a coupling reaction between the thiazole amine **24a** and the thiazole carboxylic acid **25**, using EDCI–HOBt–NMM (Scheme 1). Saponification of the ethyl ester group in **26a** next led to the bisthiazole carboxylic acid **27**. A second coupling reaction between **27** and **24a** then gave the tristhiazole **28** which, by sequential deprotection of the ethyl ester and Boc groups gave the ω-amino acid **29**. Macrolactamisation of **29**, using FDPP–*i*-Pr_2NEt, finally gave the cyclic peptide **16**. In a similar manner, the bisthiazole **27** was elaborated to the tristhiazole **30**, *en route* to the cyclic peptide **17** (Scheme 1).





Scheme 1 *Reagents and conditions*: i, EDCI (1.0 mole eq.), HOBt (1.0 mole eq.), NMM (1.0 mole eq.), CH_2Cl_2, DMF, *ca.* 70%; ii, NaOH (10 mole eq.), THF–H_2O 9 : 1, rt, 18 h; iii, 4 M HCl in dioxane, rt, 6 h; iv, FDPP (1.5 mole eq.), *i*-Pr_2NEt (3 mole eq.), CH_3CN, rt, 2 h, *ca.* 60%.

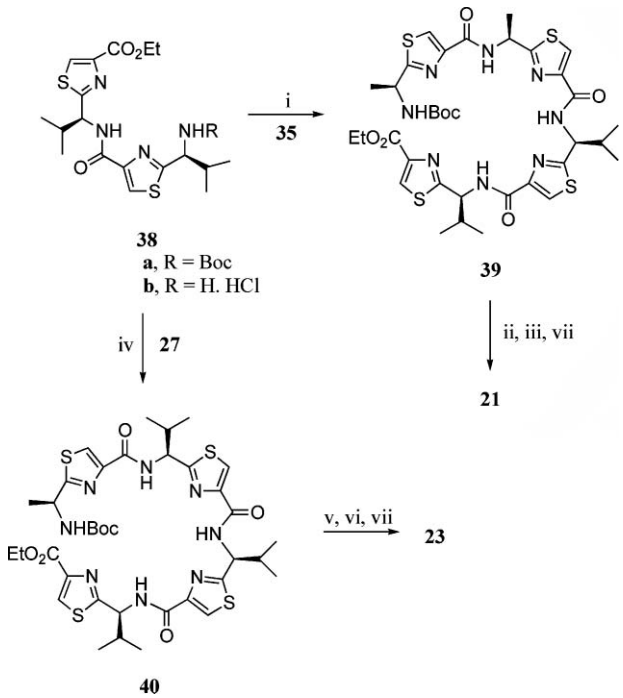
The bisthiazole carboxylic acid **27** was also used to prepare the cyclic tetramer **22**, following removal of the Boc-protection and 'dimerisation' of the resulting bisthiazole ω-amino acid **32** in the presence of FDPP–*i*-Pr_2NEt (Scheme 2).



Scheme 2 *Reagents and conditions*: i, 4 M HCl in dioxane, rt, 6 h, 95%; ii, FDPP (1.5 mole eq.), *i*-Pr_2NEt (3 mole eq.), CH_3CN, rt, 2 h, 50%.

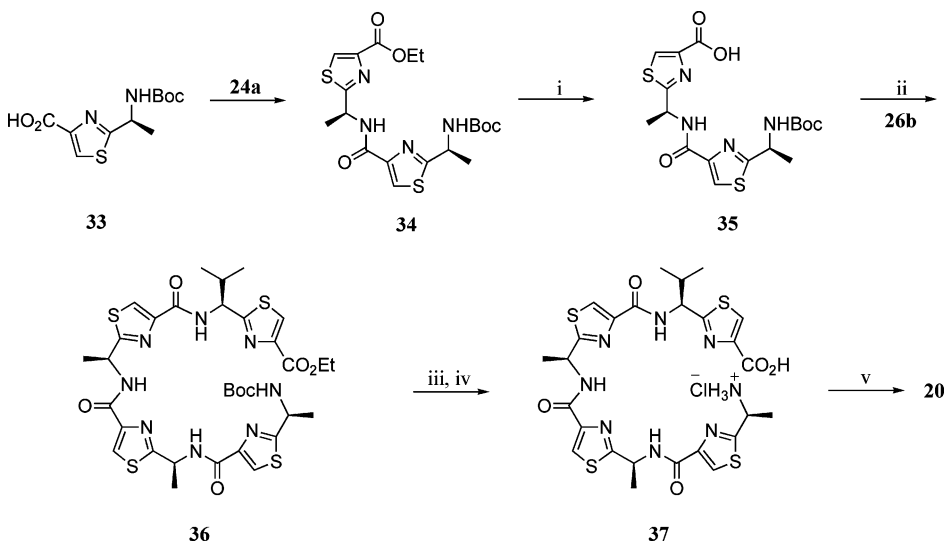
The three remaining cyclic tetramers **20**, **21**, and **23** were each synthesised in an iterative manner from appropriately substituted and protected bisthiazole intermediates prepared from straightforward coupling reactions between appropriately functionalised alanine and valine-based thiazoles. Thus, a coupling reaction between **24a** and the thiazole carboxylic acid **33** first gave the bisthiazole **34** which was saponified to the carboxylic acid **35**. A coupling reaction between **35** and the free amine **26b** produced after Boc-deprotection of **26a**, next led to the tetrathiazole **36**. Removal of the protecting groups from **36**, followed by macrolactamisation of the resulting ω-amino acid **37** finally gave the cyclic tetramer **20** (Scheme 3).

In a similar straightforward manner, the unsymmetrical cyclic tetramer **21** was prepared from a coupling reaction between the bisthiazole carboxylic acid **35** and the bisthiazole amine **38b**, followed by sequential deprotection of the Boc and ethyl ester groups in the product **39** and macrolactamisation of the resulting ω-amino acid (Scheme 4). A corresponding coupling reaction between **38b** and the bisthiazole carboxylic acid **27** led to the tetrathiazole **40** which, using similar chemistry, was converted into the cyclic tetramer **23**.



Scheme 4 *Reagents and conditions*: i, EDCI (1.5 mole eq.), HOBt (1.5 mole eq.), NMM (1.5 mole eq.), CH_2Cl_2, 0 °C, 75%; ii, NaOH (10 mole eq.), THF–H_2O 9 : 1, rt, 2.5 h; iii, 4 M HCl in dioxane, rt, 1 h, 57% (over 2 steps); iv, EDCI (1.5 mole eq.), HOBt (1.5 mole eq.), NMM (1.5 mole eq.), CH_2Cl_2, 0 °C, 63%; v, NaOH (10 mole eq.), THF–H_2O 9 : 1, rt, 3 h; vi, 4 M HCl in dioxane, rt, 1 h; vii, FDPP, *i*-Pr_2NEt, CH_3CN, rt, 23 °C; 53% (over 3 steps for **23**), 57% (over 3 steps for **21**).

The ease of formation of cyclic trimers, *i.e.* **14**–**17**, over cyclic tetramers during the cyclooligomerisation of a 1 : 1 mixture of **8a** and **8b** is consistent with the observations made earlier when the same thiazoles were treated separately with FDPP–*i*-Pr_2NEt. Perhaps more surprising was the observation that the unsymmetrical cyclic trimers **16** and **17** were produced in amounts similar to

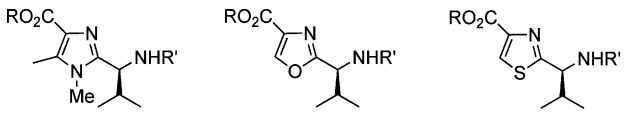


Scheme 3 *Reagents and conditions*: i, NaOH (10 mole eq.), THF–H_2O 9 : 1, rt, 18 h, 86%; ii, **26b**, EDCI (1.5 mole eq.), HOBt (1.5 mole eq.), NMM (3.0 mole eq.), CH_2Cl_2, DMF, 61%; iii, NaOH (10 mole eq.), THF–H_2O 9 : 1, rt, 3.5 h; iv, 4 M HCl in dioxane, rt, 2 h; v, FDPP (1.0 mole eq.), *i*-Pr_2NEt (1.0 mole eq.), CH_3CN, rt, 24 h, 60%.

15, and that relatively small amounts of the alanine-based cyclic trimer **14** were obtained. Of course we have no information on the order in which the thiazole amino acids **8a** and **8b** are coupled to each other to form a linear tristhiazole, and hence the amide bond which is formed last in the macrolactamisations. On the basis of minimisation of transannular non-bonding interactions between the alkyl side chains in the transition states during the macrocyclisations, we might expect the bulkier isopropyl groups to favour formation of the cyclic trimers **14** and **16** containing the smaller methyl group substituents, but this is not the case. What needs to be taken into account, however, is the greater solubility of the valine-based thiazole **8b**, and possibly any isopropyl-substituted acylic intermediates, which may be responsible for the increased formation of the cyclic trimers **15** and **17**. It is perhaps also significant that the only two cyclic tetramers produced in the mixed cyclooligomerisation of **8a** and **8b**, *i.e.* **19** and **23**, also contain only (in the case of **19**), or largely, isopropyl group side chains.

Synthesis of mixed imidazole, oxazole and thiazole-based cyclic peptides

Imidazole-containing cyclic peptides have not yet been found in nature, but there are a few alkaloids, *e.g.* pilocarpine,[11] derived from the imidazole ring-containing amino acid histidine that are known, and imidazoles commonly act as ligands in several important metalloenzymes.[12] In view of their special properties, it was decided to extend the scope of our synthetic studies and prepare a range of imidazole ring-based cyclic peptides[13] linked to oxazoles and thiazoles for biological evaluation and possible exploitation in asymmetric synthesis. We therefore prepared the enantiopure valine-based imidazole,[13] oxazole[9] and thiazole[9] amino acids, **41a**, **42a** and **43a** respectively, and their various carboxylic acid and amine derivatives, using methods which are well-precedented in the literature.[9,10,14] The mono-azole derivatives **41a/b**, **42a/b** and **43a/b** were then used in separate coupling reactions to elaborate the corresponding valine-based bisazole amino acids **45**,[13] **47** and **49** (Scheme 5), in readiness for further coupling reactions to elaborate mixed imidazole/oxazole/thiazole-based cyclic peptides.

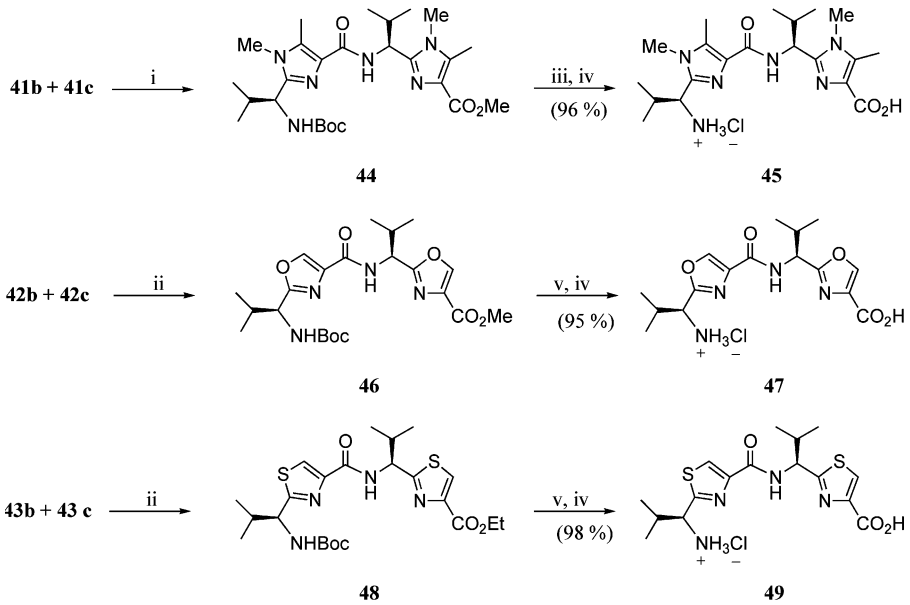


41 **42** **43**

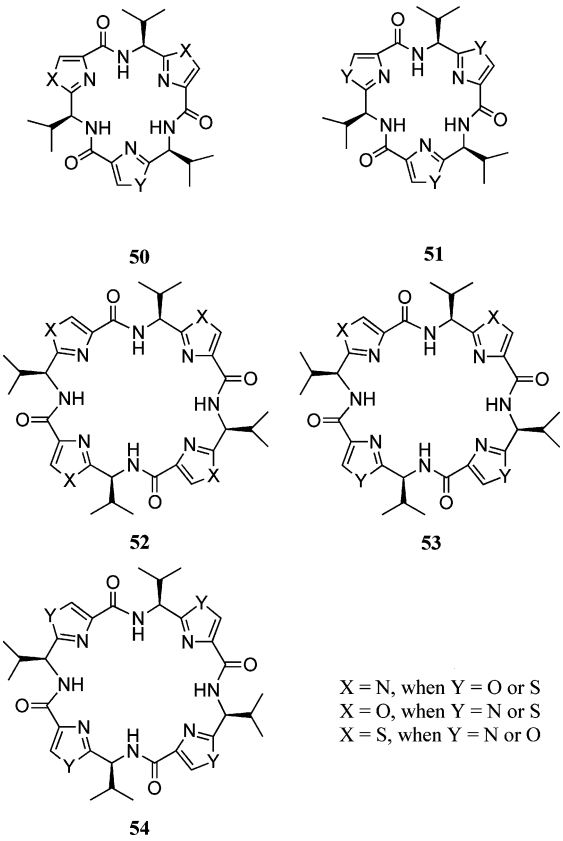
a, R = H, R' = H
b, R = H, R' = Boc
c, R = Me, R' = H
d, R = Me, R' = Boc

Our earlier studies had demonstrated that cyclooligomerisations of homogeneous, and even cyclisations of mixed, thiazole amino acids favoured the formation of cyclic trimers and cyclic tetramers, with only minute amounts of higher oligomers being produced concurrently.[9] In principle then, we would expect largely the formation of only two cyclic trimers, *i.e.* **50** and **51**, and three cyclic tetramers *i.e.* **52**, **53** and **54**, from any cyclisation reaction involving one of the bisazole amino acids **45**, **47** and **49** with one of the mono-azole amino acids **41a**, **42a** and **43a** (Scheme 6). Furthermore, bearing in mind the relative number of amide bond-forming reactions involved, we would expect that the aforementioned cyclisations would favour the production of the cyclic trimer **50** and the cyclic tetramer **52** where only two amide bond forming reactions are involved.

As expected, therefore, a coupling reaction between the bisimidazole amino acid **45**[13] and the thiazole amino acid **43a**, in CH_3CN, in the presence of FDPP–Pr_2NEt at room temperature for three days, produced only the expected cyclic trimer **55** and the cyclic tetramer **56** which were obtained in the ratio 5 : 1 and in a combined yield of 68%. A corresponding reaction between **45** and the oxazole amino acid **42a**, led to a similar yield and similar



Scheme 5 *Reagents and conditions*: i, DPPA, DIPEA, DMF, 70%; ii, EDCI, HOBt, NMM, DCM, 85–97%; iii, LiOH, THF–MeOH–H_2O 2 : 2 : 1, 0 °C; iv, 4 M HCl in 1,4-dioxane; v, aq. NaOH, MeOH–1,4-dioxane.



Scheme 6

ratio of the analogous cyclic trimer **57** and the cyclic tetramer **56** (Scheme 7). Interestingly, when a 1 : 1 : 1 mixture of the azole amino acids **42a**, **43a** and **45** was treated with FDPP–Pr_2NEt only the two cyclic trimers **55** and **57** were obtained, and in equal amounts in a combined yield of 62%. Only minute amounts (<1%) of the cyclic tetramer **56** could be detected by HPLC analysis.

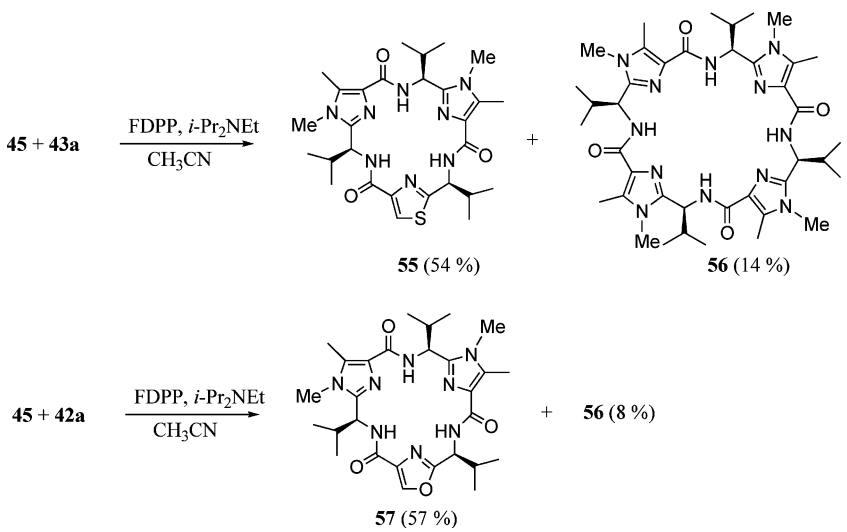
In other investigations of cyclisations of mixtures of mono and bisazole amino acids, the bisthiazole amino acid **49** and the oxazole amino acid **42a** produced a 4 : 1 mixture of the cyclic trimer **58** and the symmetrical cyclic tetramer **11b** (combined 50% yield), and **49** reacted with the imidazole amino acid **41a** leading to a similar 4 : 1 mixture of the cyclic trimer **60** and the tetramer **9b** in 50% yield (Scheme 8). A small amount of the trisoxazole based cyclic trimer **59** (3%) was also obtained from the former cyclisation and the thiazole-imidazole based cyclic tetramer **61** was a significant product (9%) produced in the cyclisation between **49** and **41a** (Scheme 8).

Cyclisations involving the bisoxazole amino acid **47** and the azole amino acids **41a** and **43a** were less selective and resulted in reduced yields of modified cyclic peptides due to the poorer solubility of **47** in acetonitrile (Scheme 9). The bisoxazole-based cyclic trimers **62** and **64** were the major products produced in each of the reactions (23–30%), alongside smaller amounts, *i.e.* 8–12%, of the corresponding bisoxazole based cyclic tetramers **63** and **65** respectively.

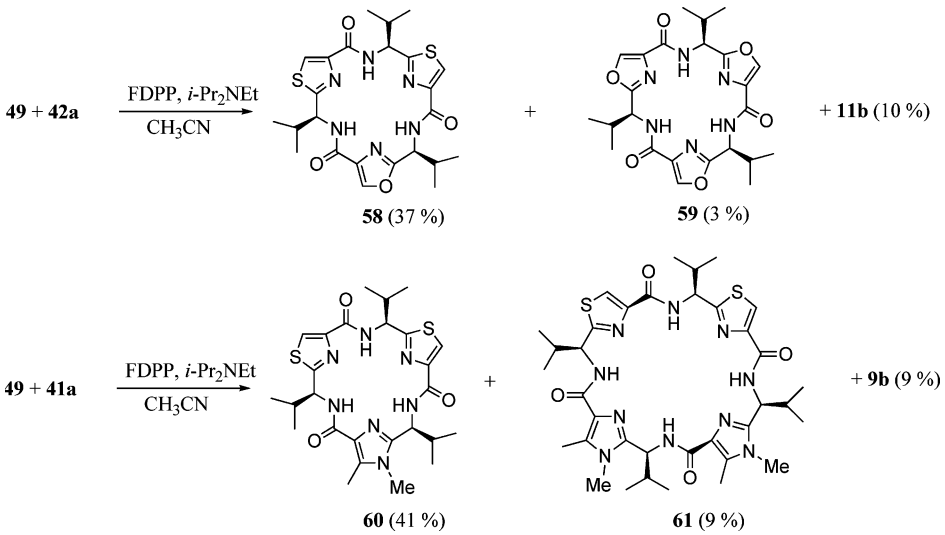
Synthesis of oxazoline-containing cyclic peptides; Didmolamides A and B

As a corollary to our studies of the synthesis of mixed oxazole, imidazole and thiazole-based cyclic peptides from the assembly of azole amino acids, we also evaluated the scope for similar assemblies involving *oxazoline* amino acids which might, hopefully, lead to oxazoline-based cyclic hexapeptides, *e.g.* bistratamide E (**66**) and didmolamide A (**4**).

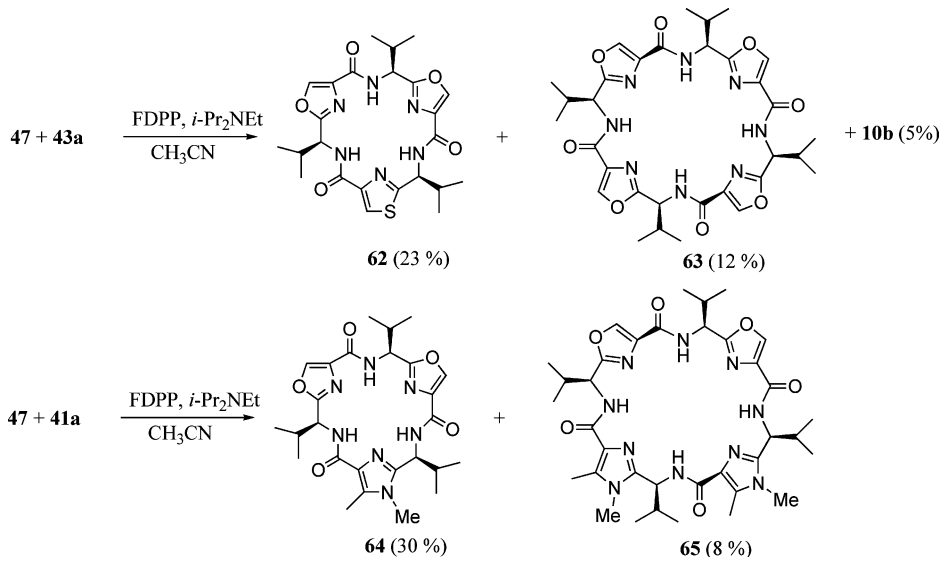
Bistratamide E (**66**) is the oxazoline analogue of bistratamide H (**67**), and both metabolites were isolated in 2003 by Faulkner and Perez[15] from the ascidian *L. bistratum* collected in the southern Philippines. The bistratamides show modest activity, *i.e.* IC_{50} 1.7–7.9 μg ml^{-1} against human colon tumour (HCT-116) cell lines. Didmolamide A (**4**) together with didmolamide B (**68**) were also isolated in 2003, but from the ascidian *Didemnum mole* collected in Madagascar.[5] These metabolites are also mildly toxic to several cultured tumour cell lines, with IC_{50} values of 10–20 μg ml^{-1}. Both the bistratamide and the didmolamide families of cyclic peptides have attracted a great deal of interest within the synthetic chemistry community and several of their members have been synthesised, including the metabolites **1**, **2**, **66**, **67** and **68**.[7] All



Scheme 7

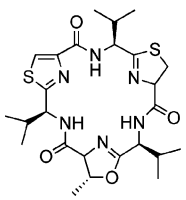


Scheme 8

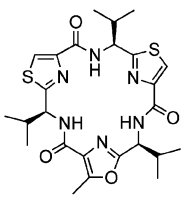


Scheme 9

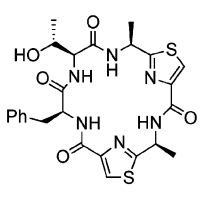
of these syntheses have used a conventional linear approach, building up a linear azole-based peptide chain, followed by a macrocyclisation mediated by pyBOP–DMAP.



66, Bistratamide E



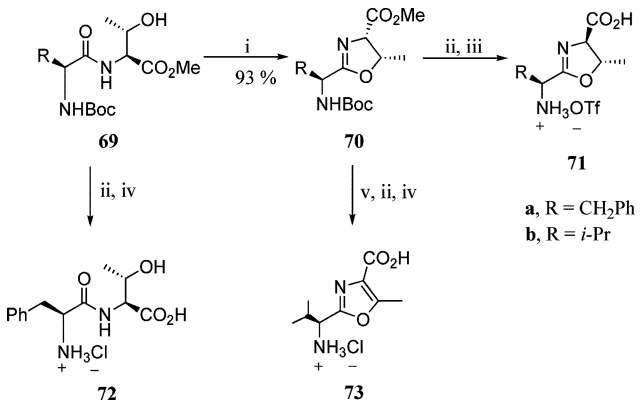
67, Bistratamide H



68, Didmolamide B

In the majority of our cyclooligomerisation and assembly studies leading to cyclic peptides from azole-based amino acids, we had found that optimum yields were obtained using FDPP and *i*-Pr_2NEt as coupling agents in acetonitrile at room temperature for 3–5 days.[9] Previously however, other researchers had concluded that DPPA was the best coupling reagent for the synthesis of cyclic peptides, and particularly for those compounds containing oxazoline rings.[16] Indeed, Wipf and Miller[8] showed that the cyclooligomerisation of the oxazoline amino acid **7**, leading to westiellamide **3**, was best carried out in the presence of DPPA at 0–22 °C over 4 days. We therefore examined both FDPP and DPPA in our attempted assemblies of didmolamide A (**4**) and bistratamide E (**66**) from the oxazoline-based amino acids **71a** and **71b** respectively. The oxazolines **71a** and **71b**, were both synthesised from the corresponding dipeptides **69** following: i) cyclodehydration using Deoxo-Fluor, ii) careful saponification of the resulting oxazoline esters **70**, and iii) Boc-deprotection (Scheme 10).[17]

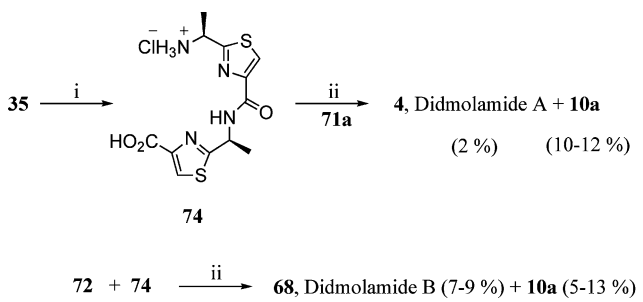
When a solution of the phenylalanine-based oxazoline **71a** and the bisthiazole amino acid **74** produced after Boc-deprotection of **35** in CH_3CN was treated with FDPP in DMF with added NMM for 4 days at room temperature, work up and chromatography gave didmolamide A (**4**) in a disappointing 2% yield. The structure and



Scheme 10 *Reagents and conditions*: i, Deoxo-Fluor, DCM, −20 °C; ii, LiOH, H_2O, MeOH, 78%; iii, TMSOTf, DCM, 0 °C, 85%; iv 4 M HCl, 1,4-dioxane, rt; v, $BrCCl_3$, DBU, DCM, 0 °C to rt, 90% over 3 steps.

stereochemistry of **4** followed from comparison of its spectroscopic and other data with those of an authentic sample prepared in a linear fashion according to the method of Kelly and You.[7g] The major product isolated from the reaction was the cyclic tetramer **10a** (10–12%), accompanied by trace amounts of higher oligomers. The same outcome was observed when the two substrates **71a** and **74** were reacted in the presence of DPPA, DMF, NMM at 0–5 °C for 4.5 days. Likewise, when the oxazoline **71a** was reacted with two equivalents of the thiazole amino acid **8a**, using either FDPP or DPPA as coupling agents, didmolamide A (**4**) was still only produced in 2% yield. In these instances however, the major product was the cyclic trimer **9a** (12%), accompanied by the corresponding cyclic tetramer **10a** (2%).

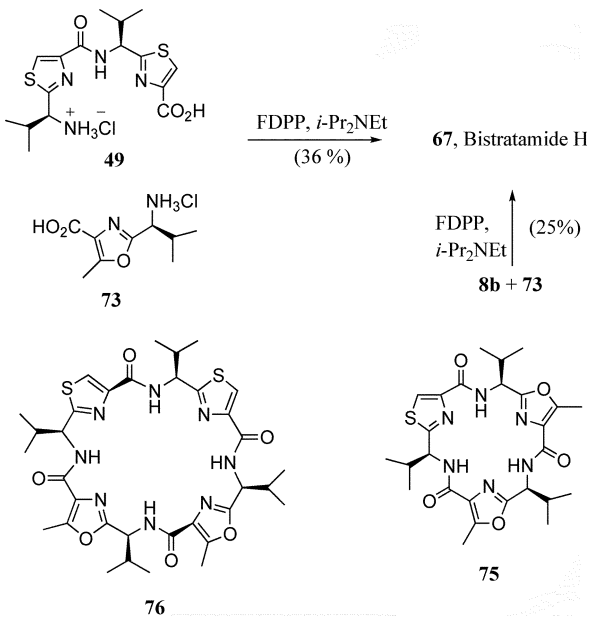
To our disappointment, the cyclic tetramer **10b** was the only product isolated when the valine-based oxazoline **71b** and the bisthiazole amino acid **49** were treated with FDPP–*i*-Pr_2NEt, *i.e.* no bistratamide E (**66**) could be detected in the crude reaction product. More interesting perhaps, was the observation that when a 1 : 1 mixture of the dipeptide amino acid **72** and the bisthiazole amino acid **74** was exposed to DPPA or to FDPP (with added *i*-Pr_2NEt in DMF), didmolamide B (**68**) was produced in 7–9% yield (Scheme 11), accompanied by the cyclic tetramer **10a** (5–13%).



Scheme 11 *Reagents and conditions*: i, 4 M HCl, 1,4-dioxane, 25 °C, 4 h; ii, FDPP, DMF, NMM, 25 °C or DPPA, DMF, NMM, 0–25 °C, 4.5 d.

Synthesis of bistratamide H and concluding remarks

To further demonstrate the scope and advantages of our one step synthesis of azole-based cyclic hexapeptides from their azole-constituent amino acids, we prepared the oxazole amino acid **73** from the corresponding oxazoline **70**, and reacted it with the bisthiazole amino acid **49** in the presence of FDPP–*i*-Pr_2NEt and isolated bistratamide H (**67**)[15] in a very agreeable 36% yield (Scheme 12). A small amount (~9%) of the cyclic tetramer **10b** was produced concurrently. Bistratamide H (**67**) could also be produced in 25% yield when the oxazole amino acid **73** (1 eq.) was reacted with 2 equivalents of the monothiazole amino acid **8b** in the presence of FDPP–*i*-Pr_2NEt. Small amounts of the thiazole-based cyclic trimer (**9b**, 8%) and tetramer (**10b**, 4%), together with the bisoxazole-based cyclic trimer (**75**, 9%) and tetramer (**76**, 8%) were also produced in the reaction. A comparison of this approach to bistratamide H with that described by Kelly and You,[7i] showed that our mixed azole amino acid approach involved 8 steps and gave the target in 24% overall yield, whereas the linear approach used 12 steps and led to bistratamide H in 13% overall yield.



Scheme 12

Experimental

General details

Nuclear magnetic resonance spectra (NMR) were recorded on Bruker DPX (270, 360 and 500 MHz for ^1H, and 67.5, 90.5 and 125 MHz for ^{13}C) spectrometers as dilute solutions in deuterated solvents as specified. Deuterochloroform was deacidified over anhydrous potassium carbonate. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane (TMS) or referenced to residual protonated solvent: chloroform (δ_H 7.27, δ_C 77.0) or residual methanol (δ_H 3.31, δ_C 49.0), as internal standard. Signal multiplicities are designated by the following abbreviations: ^1H spectra: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, br = broad. In ^{13}C spectra the multiplicities were determined using a DEPT sequence with secondary pulses at 90° and 135° where appropriate. Signal multiplicities are designated by: s = quaternary, d = tertiary methine, t = secondary methylene, q = primary methyl. ^{19}F NMR spectra were recorded on a Bruker DPX 300 (282 MHz) spectrometer and are referenced to residual protonated solvent, *i.e.* chloroform. All coupling constants (J) are quoted to the nearest 0.1 Hz.

Ultraviolet spectra were recorded on a Phillips PU 8700 spectrophotometer as solutions in spectroscopic grade ethanol and are given in nm, with ε in $dm^3\ mol^{-1}\ cm^{-1}$ in parentheses.

Infrared (IR) spectra were obtained using a Perkin Elmer 1600 series FT-IR or Avatar 320 FT-IR instrument as dilute solutions in spectroscopic grade solvents or as liquid films. Absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}).

Mass spectra were recorded on either a VG Autospec, MM-701CF or Micromass LCT spectrometer using electrospray (ES) or fast atom bombardment (FAB) techniques. Due to the soft nature of these techniques, little fragmentation of the compounds occurred and hence nominal mass and fragmentation data have not been included. High-resolution mass spectra are calculated to 4 decimal places from the molecular formula corresponding to the observed signal using the most abundant isotopes of each element.

Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser, and melting points (which are uncorrected) were recorded on a Stuart Scientific SMP3 melting point apparatus.

Optical rotations were measured on a JASCO DIPA-370 polarimeter, and solutions were prepared using spectroscopic grade solvents, $[\alpha]_D$ values are recorded in units of 10^{-1} deg $cm^2\ g^{-1}$. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) and the solvents employed were either of analytical grade or were distilled before use according to the technique of Still *et al.*[18]

All HPLC analyses were performed using either a Hewlett Packard series 1100 system with a reverse phase Waters-Associates 440, or a Nova-Pak® C_{18} column (3.9 × 300 mm internal diameter). Simultaneous detections of the products were carried out at several wavelengths using a Hewlett Packard 1100 Diode Array UV detector, and also using a refractometer detector. The solvent flow was kept at 1 ml min^{-1}, and 10 μL samples were injected. The solvent mixture was varied depending on the compounds being analysed.

All reactions were monitored by thin layer chromatography (TLC) using Merck Dc-Alufolien silica gel $60F_{254}$ 0.2 mm precoated aluminium plates. TLC plates were visualised by quenching of UV fluorescence (λ_{max} = 254 nm) light and were subsequently developed using either acidic ninhydrin solution, acidic alcoholic vanillin solution or a basic potassium permanganate solution as appropriate.

Routinely, organic extracts were dried over anhydrous magnesium sulfate or sodium sulfate. Solvents were removed *in vacuo* using a Büchi rotary evaporator. Anhydrous organic solvents were stored under an atmosphere of nitrogen and/or over sodium wire. Other organic solvents were dried by distillation as follows: THF and dimethyl ethylene glycol (sodium benzophenone ketyl), dichloromethane and methanol (calcium hydride), acetonitrile (K_2CO_3), under an inert atmosphere. Other organic solvents and reagents were purified according to accepted literature procedures. Where necessary, reactions requiring anhydrous conditions were performed in flame or oven dried apparatus under a nitrogen atmosphere.

(1′*S*)-2-(1-{[2-(1′-*tert*-Butoxycarbonylamino-2′-methylpropyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid ethyl ester 26a. General Procedure A

4-Methylmorpholine (60 μL, 0.6 mmol) was added dropwise to a stirred solution of the L-valine thiazole acid **25** (181 mg, 0.6 mmol) in anhydrous CH_2Cl_2 (3 ml) at 0 °C under a nitrogen atmosphere. 1-Hydroxybenzotriazole (82 mg, 0.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (116 mg, 0.6 mmol) were added consecutively in one portion. The mixture was stirred at 0 °C for 40 minutes and then a precooled solution of L-alanine thiazole amine **24a** (128 mg, 0.6 mmol) and 4-methylmorpholine (60 μL, 0.6 mmol) in dichloromethane (3 ml) was added dropwise over 1 min. The mixture was stirred at 0 °C for 4 h and then allowed to warm to room temperature over 15 h. Water (*ca.* 20 ml) was added and the aqueous layer was separated and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (3 × 20 ml), 10% aqueous citric acid (3 × 10 ml), and brine (3 × 10 ml), then dried ($MgSO_4$) and evaporated *in vacuo.* The residue was purified by chromatography on silica gel, eluting with pentane–ethyl acetate (1 : 1) to give the *dipeptide* (208 mg, 72%) as a colourless solid, mp 165–167 °C (from petroleum 40–60 °C–diethyl ether); $[\alpha]_D^{23}$ −35.9 (*c* 1.0 in $CHCl_3$); ν_{Max} (soln: $CHCl_3$)/cm^{-1} 3442, 1719, 1602; δ_H (360 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.10 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.41 (3H, t, *J* 6.8, OCH_2CH_3), 1.47 (9H, s, Bu*t*), 1.81 (3H, d, *J* 6.8, CH_3CH), 2.84 (1H, m, $CHCH(CH_3)_2$), 4.30 (2H, q, *J* 6.8, OCH_2CH_3), 5.32 (1H, m, N*H*Boc), 5.43 (1H, m, $CHCH(CH_3)_2$), 5.51 (1H, dq, *J* 6.8, 2.4, $CHCH_3$), 7.88 (1H, d, *J* 6.8, N*H*CO), 8.03 (1H, s, C*H*S), 8.07 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 14.4 (q), 18.1 (q), 22.3 (q), 28.3 (q), 33.0 (d), 48.8 (d), 56.5 (t), 61.4 (d), 127.1 (d), 149.2 (s), 161.3 (s), 171.8 (s), 174.7 (s); *m/z* (FAB) found 505.1502 ([M + Na]$^+$ $C_{21}H_{30}N_4NaO_5S_2$ requires 505.1555).

(1′*S*)-2-(1-{[2-(1′-*tert*-Butoxycarbonylamino-2′-methylpropyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid 27. General Procedure B

Sodium hydroxide (40 mg, 0.9 mmol) was added to a stirred solution of the thiazole ester **26a** (60 mg, 0.12 mmol) in THF–H_2O (9 : 1) (1.5 ml) at room temperature, and the mixture was stirred at room temperature for a further 3 h. The separated aqueous layer was acidified to pH 4 with citric acid (*ca.* 50 mg) and then extracted with ethyl acetate (3 × 5 ml). The combined organic extracts were washed with water (3 × 15 ml) and brine (3 × 10 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *thiazole acid* (49 mg, 90%) which crystallised as a colourless solid, mp 172–173 °C (from petroleum 40–60 °C–diethyl ether); $[\alpha]_D^{23}$ −22.9 (*c* 1.0 in $CHCl_3$); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3433, 3244, 3090, 2961, 1715, 1513; δ_H (360 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.05 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.40 (9H, s, Bu*t*), 1.58 (3H, d, *J* 6.7, CH_3CH), 2.86 (1H, m, $CHCH(CH_3)_2$), 5.23 (1H, m, $CHCH(CH_3)_2$), 5.32 (1H, m, N*H*Boc), 5.58 (1H, m, $CHCH_3$), 7.75 (1H, d, *J* 7.4, N*H*CO), 8.10 (1H, s, C*H*S), 8.21 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 16.8 (q), 17.2 (q), 23.3 (q), 28.7 (q), 34.3 (d), 50.3 (d), 61.7 (d), 70.6 (s), 119.6 (d), 143.2 (s), 165.0 (s), 166.3 (s), 167.9 (s), 172.0 (s); *m/z* (FAB) found 455.1440 ([M + H]$^+$ $C_{19}H_{27}N_4O_5S_2$ requires 455.1423).

(1′*S*)-2-(1′*S*-{[2-(1-{[2-(1′-*tert*-Butoxycarbonylamino-2′-methylpropyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid ethyl ester 28

Using General Procedure A, the bisthiazole carboxylic acid **27** (88 mg, 0.24 μmol) was coupled to the thiazole hydrochloride

salt **24**[9b] (50 mg, 0.24 mmol) to give the *tripeptide* (62 mg, 68%) as a colourless solid, mp 236–238 °C (from petroleum 40–60 °C–diethyl ether); $[\alpha]_D^{23}$ −15.7 (*c* 0.1 in $CHCl_3$); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3400, 2874, 1738, 1651; δ_H (360 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.05 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.40 (3H, t, *J* 7.1, OCH_2CH_3), 1.45 (9H, s, Bu*t*), 1.62 (3H, d, *J* 6.8, CH_3CH), 1.80 (3H, d, *J* 6.9, CH_3CH), 2.65 (1H, app quintet, *J* 6.8, $CH(CH_3)_2$), 4.42 (2H, q, *J* 7.1, OCH_2CH_3), 5.06–5.10 (1H, m, $CHCH_3$), 5.10–5.18 (1H, m, NHBoc), 5.34 (1H, dd, *J* 6.8, 9.2, $CHCH(CH_3)_2$), 5.59 (1H, dq, *J* 6.9, 6.9, $CHCH_3$), 7.79 (1H, d, *J* 8.4, NHCO), 7.97 (1H, d, *J* 9.3, NHCO), 8.06 (1H, s, CHS), 8.07 (1H, s, CHS), 8.08 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 14.2 (q), 17.9 (q), 19.6 (q), 21.0 (q), 21.2 (q), 28.2 (q), 32.9 (d), 47.0 (d), 56.4 (d), 61.3 (t), 80.2 (s), 123.9 (d), 124.0 (d), 126.9 (d), 147.3 (s), 148.9 (s), 149.0 (s), 160.4 (s), 160.6 (s), 161.2 (s), 171.6 (s), 172.9 (s), 175.0 (s), 179.8 (s); *m*/*z* (FAB) found 659.1722 ($[M + Na]^+$ $C_{27}H_{36}N_6NaO_6S_3$ requires 659.1756).

(1′*S*)–(1-{[2-(1-{[2-(1-Amino-2-methyl-propyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid hydrochloride 29

Using General Procedure B, the tristhiazole ethyl ester **28** (50 mg, 79 μmol) was converted into the corresponding carboxylic acid, which was obtained as a yellow oil. The thiazole carboxylic acid was then stirred with a solution of hydrogen chloride in 1,4-dioxane (1.6 ml, 4 M) at room temperature for 2 h under an atmosphere of nitrogen. The solvent was removed *in vacuo* by azeotroping with toluene to leave the *carboxylic acid hydrochloride* (32 mg, 75%) as a viscous oil, $[\alpha]_D^{23}$ −76.4 (*c* 0.1 in CH_3CN); δ_H (360 MHz, CD_3OD) 1.01 (3H, d, *J* 6.7, $CHCH_3CH_3$), 1.13 (3H, d, *J* 6.7, $CHCH_3CH_3$), 1.83 (3H, d, *J* 6.9, CH_3CH), 1.84 (3H, d, *J* 6.9, CH_3CH), 2.50–2.60 (1H, m, $CH(CH_3)_2$), 4.99–5.13 (1H, m, $CHCH_3$), 5.28 (1H, d, *J* 8.0, $CHCH(CH_3)_2$), 5.62–5.65 (1H, m, $CHCH_3$), 8.25 (1H, s, CHS), 8.37 (1H, s, CHS), 8.43 (1H, s, CHS); δ_C (90.5 MHz, CD_3OD) 19.1 (q), 20.0 (q), 20.3 (q), 21.1 (q), 34.3 (d), 58.3 (d), 74.1 (d), 125.9 (d), 127.4 (d), 129.4 (d), 148.0 (s), 149.8 (s), 149.9 (s), 162.3 (s), 162.9 (s), 163.9 (s), 168.9 (s), 173.4 (s), 176.8 (s).

Cyclic-bis-(*S*)-alaninethiazole-(*S*)-valinetristhiazole 16. General Procedure C[9b,10b]

N,*N*-Diisopropylethylamine (17 μL, 74 μmol) was added to a stirred solution of the ω-amino acid **29** (20 mg, 37 μmol) in anhydrous acetonitrile (7 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 min, then pentaflurophenyldiphenylphosphinate (FDPP, 28 mg, 74 μmol) was added and the mixture was stirred at room temperature for a further 30 h. The solvent was evaporated *in vacuo* and the residue was partitioned between dichloromethane (15 ml) and water (5 ml). The separated aqueous layer was extracted with dichloromethane (3 × 10 ml) and the combined organic extracts were then washed successively with saturated aqueous K_2CO_3 (3 × 5 ml) and brine (2 × 5 ml), dried ($MgSO_4$) and evaporated *in vacuo.* The residue was purified by chromatography on silica gel, eluting with light petroleum 40–60 °C–ethyl acetate (1 : 1) to give the *cyclic peptide* (11 mg, 59%) as a colourless powder, mp 263–264 °C (from CH_2Cl_2–diethyl ether); $[\alpha]_D^{23}$ −28.3 (*c* 0.1 in CH_3CN); λ_{max} (CH_3CN)/nm 231 (ε/dm^3 mol^{-1} cm^{-1} 19 600); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3698, 3404, 2927, 1665, 1601, 1543; δ_H (500 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.09 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.75 (3H, d, *J* 6.8, CH_3CH), 1.75 (3H, d, *J* 6.7, CH_3CH), 2.26–2.35 (1H, m, $CH(CH_3)_2$), 5.46 (1H, dd, *J* 5.6, 9.1, ($CHCH(CH_3)_2$), 5.58–5.71 (2H, m, ($CHCH_3$)$_2$), 8.13 (2H, s, (3 × CHS)), 8.17 (1H, s, CHS), 8.53 (1H, d, *J* 9.1, NHCO), 8.64 (2H, d, *J* 7.8, (2 × NHCO)); δ_C (125 MHz, $CDCl_3$) 18.4 (q), 18.8 (q), 29.7 (q), 35.5 (q), 47.2 (d), 47.3 (d), 55.8 (d), 123.6 (d), 123.8 (d), 124.1 (d), 148.7 (s), 149.0 (s), 149.1 (s), 159.5 (s), 159.6 (s), 159.7 (s), 168.6 (s), 171.0 (s), 171.4 (s); *m*/*z* (FAB) found 513.0763 ($[M + Na]^+$ $C_{20}H_{22}N_6NaO_3S_3$ requires 513.0813).

(1′*S*)-2-(1-{[2-(1′-Amino-2′-methylpropyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid hydrochloride 32. General Procedure D

A solution of hydrogen chloride in 1,4-dioxane (0.1 ml, 4 M) was added to the Boc amine **27** (25 mg, 55 μmol), and the mixture was stirred at room temperature for 6 h under a nitrogen atmosphere. The dioxane was evaporated *in vacuo*, using toluene (*ca.* 0.5 ml) as an azeotrope to leave the *amine hydrochloride* (20 mg, 97%) which crystallised as a hygroscopic solid, mp 83–84 °C (from dichloromethane); $[\alpha]_D^{21}$ −28.0 (*c* = 0.1, MeOH); δ_H (360 MHz, CD_3OD) 0.97 (3H, d, *J* 7.2, $CHCH_3CH_3$), 1.01 (3H, d, *J* 7.2, $CHCH_3CH_3$), 1.58 (3H, d, *J* 7.4, CH_3CH), 2.56 (1H, m, $CHCH(CH_3)_2$), 3.89 (1H, m, $CHCH(CH_3)_2$), 5.05 (1H, m, $CHCH_3$), 7.91 (1H, s, CHS), 8.11 (1H, s, CHS); δ_C (90.5 MHz, CD_3OD) 16.4 (q), 16.8 (q), 23.3 (q), 36.8 (d), 50.3 (d), 63.1 (d), 119.8 (d), 144.5 (s), 166.4 (s), 167.9 (s), 172.0 (s); *m*/*z* (FAB) found: 355.0869 ($[MH - Cl]^+$, $C_{14}H_{19}N_4O_3S_2$ requires 355.0899).

Cyclic-(*S*)-alaninethiazole-(*S*)-valinetetrathiazole 22 and hexathiazole

Using General Procedure C, the thiazole amino acid hydrochloride **32** (30 mg, 77 μmol) was dimerised to give the *cyclic tetramer* (eluted first) (13 mg, 50%) as a colourless powder, mp 272–275 °C (CH_3CN–diethyl ether); $[\alpha]_D^{23}$ −90.3 (*c* 0.1 in CH_3CN); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3441, 3396, 3123, 2965, 1759, 1709, 1673, 1539; δ_H (360 MHz, $CDCl_3$) 0.89 (6H, d, *J* 6.7, (2 × $CHCH_3CH_3$)), 0.92 (6H, d, *J* 6.7, (2 × $CHCH_3CH_3$)), 1.38 (6H, d, *J* 6.8, (2 × $CHCH_3$)), 2.10 (2H, m, $CHCH$ (2 × CH_3)), 5.40 (2H, m, (2 × $CHCHNH$)), 5.67 (2H, m, (2 × $CHCH_3$)), 7.89 (2H, s, (2 × CHS)), 7.91 (2H, s, (2 × CHS)), 8.16 (2H, d, *J* 8.4, (2 × NHCO)), 8.22 (2H, d, *J* 9.2, (2 × NHCO)); δ_C (90.5 MHz, $CDCl_3$) 17.3 (q), 21.2 (q), 27.8 (d), 46.2 (d), 53.1 (d), 135.2 (d), 152.6 (d), 154.9 (d), 160.1 (s), 160.8 (s), 170.8 (s), 171.6 (s); *m*/*z* (FAB) found 673.1536 ($[M + H]^+$ $C_{28}H_{33}N_8O_4S_4$ requires 673.1508). The corresponding *cyclic hexamer* (3 mg, 12%) (eluted second) was also produced as a colourless powder, $[\alpha]_D^{23}$ −212.8 (*c* 0.05 in CH_3CN); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3688, 3244, 3123, 3008, 2963, 2873, 1728, 1665, 1515, 1501; δ_H (270 MHz, $CDCl_3$) 1.02 (9H, d, *J* 7.0, (3 × $CHCH_3CH_3$)), 1.21 (9H, d, *J* 7.0, (3 × $CHCH_3CH_3$)), 1.91 (9H, d, *J* 6.8 CH (2 × CH_3)), 2.45 (3H, m, (3 × $CHCH(CH_3)_2$)), 5.29 (3H, m, (3 × $CHCHNH$)), 5.32 (3H, m, (3 × $CHCH_3$)), 8.05 (6H, d, *J* 8.2, (6 × NHCO)), 8.06 (3H, s, (3 × CHS)), 8.08 (3H, s, (3 × CHS)); δ_C (67.5 MHz, $CDCl_3$) 19.7 (q), 19.9 (q), 21.2 (q), 34.0 (d), 41.9 (d), 45.8 (d), 53.4 (d), 55.5 (d), 60.5 (d), 67.2 (d), 124.3 (d),

125.1 (d), 148.3 (d), 148.8 (s), 160.2 (s), 160.3 (s), 169.8 (s); *m/z* (FAB) found 1031.2020 ([M + Na]$^+$ $C_{42}H_{48}N_{12}NaO_6S_6$ requires 1031.2042).

Cyclic-tris-(*S*)-alaninethiazole-(*S*)-valinetetrathiazole 20

1 M sodium hydroxide solution (0.3 ml, 0.30 mmol) was slowly added to a stirred solution of the tetrapeptide **36** (30 mg, 28 μmol) in THF–H_2O (9 : 1) (1.5 ml) at room temperature, and the mixture was stirred for a further 3.5 h. The mixture was partitioned between ethyl acetate (5 ml) and water (1 ml), and the separated aqueous layer was then acidified to pH 4 with citric acid (*ca.* 40 mg) and extracted with ethyl acetate (3 × 5 ml). The combined organic extracts were washed with brine (3 × 10 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the corresponding carboxylic acid as a colourless solid which was used immediately. The carboxylic acid was stirred with a solution of hydrogen chloride in 1,4-dioxane (80 μL, 4 M) at room temperature under an atmosphere of nitrogen for 2 h. The dioxane was evaporated *in vacuo*, using toluene (*ca.* 1 ml) as an azeotrope to leave the amine hydrochloride **37**. The ω-amino acid **37** was suspended in acetonitrile (8 ml), and then *N*,*N*-diisopropylethylamine (15 μL, 87 μmol), and pentaflurophenyldiphenylphosphinate (31 mg, 87 μmol) were added at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 24 h, and then the acetonitrile was evaporated *in vacuo.* The residue was partitioned between dichloromethane (5 ml) and water (0.5 ml), and the separated aqueous layer was extracted with dichloromethane (3 × 5 ml). The combined organic extracts were washed successively with saturated aqueous K_2CO_3 (3 × 10 ml) and brine (2 × 10 ml), then dried over (Na_2SO_4) and evaporated *in vacuo.* The residue was purified by chromatography on silica gel, eluting with pentane–ethyl acetate (1 : 1) to give the *cyclic peptide* (10 mg, 60%) as a colourless powder, mp 251–252 °C (CH_3CN–diethyl ether), $[\alpha]_D^{23}$ −168 (*c* 0.1 in CH_3CN); λ_{max} (CH_3CN)/nm 235, 237 (ε/dm^3 mol^{-1} cm^{-1} 227 976, 228 500); δ_H (360 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.19 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.79 (9H, d, *J* 7.2 (3 × $CHCH_3$)), 2.57 (1H, m, $CH(CH_3)_2$), 5.18 (1H, m, $CHCH(CH_3)_2$), 5.65 (3H, m, (3 × $CHCH_3$)), 8.07 (1H, s, CHS), 8.19 (3H, s, (3 × CHS)), 8.68 (4H, m, (4 × NHCO)); δ_C (90.5 MHz, $CDCl_3$) 17.3 (q), 21.2 (q), 27.8 (d), 46.0 (d), 52.0 (d), 135.2 (d), 149.4 (d), 154.9 (d), 160.3 (s), 161.4 (s), 171.2 (s), 171.8 (s); *m/z* (FAB) found 645.1197 ([M + H]$^+$ $C_{26}H_{29}N_8O_4S_4$ requires 645.1195).

Cyclic-bis-(*S*)-valinethiazolebis-(*S*)-alaninetetrathiazole 21

1 M sodium hydroxide solution (0.2 ml, 0.20 mmol) was added slowly to a stirred solution of the tetrapeptide **39** (23 mg, 28 μmol) in THF–H_2O (9 : 1) (1.0 ml) at room temperature, and the mixture was stirred for a further 2.5 h. The mixture was partitioned between ethyl acetate (5 ml) and water (0.5 ml), and the separated aqueous layer was then acidified to pH 4 with citric acid (*ca.* 25 mg) and extracted with ethyl acetate (3 × 5 ml). The combined organic extracts were washed with brine (3 × 10 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the thiazole carboxylic acid as a colourless solid. The acid was used immediately and stirred with a solution of hydrogen chloride in 1,4-dioxane (59 μL, 4 M) at room temperature under a nitrogen atmosphere for 1 h. The dioxane was evaporated *in vacuo*, using toluene (*ca.* 1 ml) as an azeotrope to leave the ω-amino acid. The residue was suspended in acetonitrile (6 ml), and then *N*,*N*-diisopropylethylamine (11 μL, 64 μmol) and pentaflurophenyldiphenylphosphinate (23 mg, 64 μmol) were added at 23 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 30 h, and then the acetonitrile was evaporated *in vacuo.* The residue was partitioned between dichloromethane (5 ml) and water (0.5 ml), and the separated aqueous layer was extracted with dichloromethane (3 × 5 ml). The combined organic extracts were washed successively with saturated aqueous K_2CO_3 (3 × 10 ml) and brine (2 × 10 ml), then dried over (Na_2SO_4) and evaporated *in vacuo.* The residue was purified by chromatography on silica gel, eluting with pentane–ethyl acetate (1 : 1) to give the *cyclic peptide* (11 mg, 57%) as a colourless powder, $[\alpha]_D^{23}$ −35.4 (*c* 1.0 in $CHCl_3$); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3082, 2860, 1710, 1681; δ_H (500 MHz, $CDCl_3$) 0.90 (6H, d, *J* 7.0, (CH_3CH_3CH)), 0.95 (6H, d, *J* 7.0, (2 × CH_3CH_3CH)), 1.68–170 (6H, d, *J* 6.8, (2 × CH_3CH)), 2.66–2.68 (2H, m, (2 × $CH(CH_3)_2$), 5.38–5.42 (2H, m, (2 × $CHCH(CH_3)_2$), 5.35–5.49 (2H, br m, (2 × $CHCH_3$)), 7.86 (2H, d, *J* 8.8, (2 × NHCO)), 7.92 (2H, d, *J* 8.5, (2 × NHCO)), 8.07 (2H, s, (2 × CHS)), 8.11 (2H, s, (2 × CHS)); δ_C (125 MHz, $CDCl_3$) 17.7 (q), 17.9 (q), 27.2 (q), 27.9 (q), 33.5 (d), 56.4 (d), 68.3 (d), 123.8 (d), 126.9 (d), 147.4 (s), 149.3 (s), 160.8 (s), 161.2 (s), 171.6 (s), 171.7 (s); *m/z* (FAB) found 673.1515 ([M + H]$^+$ $C_{28}H_{33}N_8O_4S_4$ requires 673.1508).

Cyclic-tris-(*S*)-valinethiazole-(*S*)-alaninetetrathiazole 23

1 M sodium hydroxide solution (0.2 ml, 0.20 mmol) was added slowly to a stirred solution of the tetrapeptide **40** (20 mg, 24 μmol) in THF–H_2O (9 : 1) (1.0 ml) at room temperature, and the mixture was stirred for a further 3 h. The mixture was partitioned between ethyl acetate (5 ml) and water (0.5 ml), and the separated aqueous layer was then acidified to pH 4 with citric acid (*ca.* 25 mg) and extracted with ethyl acetate (3 × 5 ml). The combined organic extracts were washed with brine (3 × 10 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the thiazole carboxylic acid, as a colourless solid which was used immediately. The carboxylic acid was stirred with a solution of hydrogen chloride in 1,4-dioxane (50 μL, 4 M) at room temperature under an atmosphere of nitrogen for 1 h. The dioxane was evaporated *in vacuo*, using toluene (*ca.* 1 ml) as an azeotrope, to give the corresponding ω-amino acid. The residue was suspended in acetonitrile (5 ml), and then *N*,*N*-diisopropylethylamine (9 μL, 55 μmol) and pentaflurophenyldiphenylphosphinate (20 mg, 55 μmol) were added at 23 °C under an atmosphere of nitrogen. The solution was stirred at room temperature for 24 h, and then the acetonitrile was evaporated *in vacuo.* The residue was partitioned between dichloromethane (5 ml) and water (0.5 ml), and the separated aqueous fraction was then extracted with dichloromethane (3 × 5 ml). The combined organic extracts were washed successively with saturated aqueous K_2CO_3 (3 × 10 ml) and brine (2 × 10 ml), then dried over (Na_2SO_4) and evaporated *in vacuo.* The residue was purified by chromatography on silica gel, eluting with pentane–ethyl acetate (1 : 1) to give the *cyclic peptide* (8 mg, 53%) as a colourless powder, $[\alpha]_D^{23}$ −83.2 (*c* 1.0 in $CHCl_3$); ν_{Max} (soln: $CHCl_3$)/cm^{-1} 3019, 1785, 1681; δ_H (500 MHz, $CDCl_3$) 0.97 (9H, d, *J* 7.2, (3 × CH_3CH_3CH)), 0.99 (9H, d, *J* 7.2, (3 × CH_3CH_3CH)),

1.72 (3H, d, *J* 6.8, C*H*$_3$CH), 2.58–2.63 (3H, br m, (3 × C*H*(CH$_3$)$_2$), 5.39–5.47 (3H, m, (3 × C*H*CH(CH$_3$)$_2$)), 5.52 (1H, m, C*H*CH$_3$), 7.93 (3H, d, *J* 9.8, (3 × NHCO)), 7.97 (1H, br s, N*H*CO), 7.99 (3H, s, (3 × C*H*S)), 8.07 (1H, s, C*H*S); δ_C (125 MHz, CDCl$_3$) 18.2 (q), 27.7 (q), 34.7 (d), 57.4 (d), 67.3 (d), 124.1 (d), 127.2 (d), 147.3 (s), 148.9 (s), 161.8 (s), 162.4 (s), 171.7 (s), 172.3 (s); *m/z* (FAB) found 723.1610 ([M + Na]$^+$ $C_{30}H_{36}N_8NaO_4S_4$ requires 723.1640).

Oxazole/bisimidazole-based cyclic trimer 57

Using General Procedure C, the bisimidazole **45** (83 mg, 0.183 mmol) was reacted with the oxazole **42a** (40 mg, 0.183 mmol) to give i) the *cyclic trimer* (58 mg, 57%); mp 111–113 °C; $[a]_D^{25}$ −90.2 (*c* 1, CHCl$_3$); δ_H (360 MHz, CDCl$_3$) 0.99–1.09 (9H, m, (3 × –CH(C*H*$_3$)(CH$_3$)) overlapped), 0.99–1.09 (9H, m, (3 × –CH(CH$_3$)(C*H*$_3$)) overlapped), 2.03–2.23 (2H, m, (2 × –C*H*(CH$_3$)$_2$) overlapped), 2.27 (1H, m, –C*H*(CH$_3$)$_2$), 2.52 (3H, s, Imid-C*H*$_3$), 2.53 (3H, s, Imid-C*H*$_3$), 3.48 (3H, s, –NC*H*$_3$), 3.50 (3H, s, –NC*H*$_3$), 5.05 (1H, dd, *J* 8.4, 5.6 Hz, Het-C*H*), 5.08–5.18 (2H, m, 2 × Het-C*H*), 8.12 (1H, s, Oxaz-*H*), 8.30 (1H, d, *J* 9.3 Hz, –C(O)N*H*), 8.36 (1H, d, *J* 8.7 Hz, –C(O)N*H*), 8.39 (1H, d, *J* 8.4 Hz, –C(O)N*H*); δ_C (90 MHz, CDCl$_3$) 9.7 (×2), 17.9, 18.2 (×2), 18.7, 19.4, 19.5, 30.3, 30.4, 33.9, 34.9, 35.0, 49.6, 50.6, 52.3, 129.5 (×2), 132.5, 132.8, 135.5, 140.8, 145.9, 147.1, 159.8, 163.2, 163.7, 164.5; HRMS [M + H]$^+$ *m/z* 553.3261 (calcd for $C_{28}H_{41}N_8O_4$ 553.3270), and ii) the known cyclic tetramer **56** (8%).[13]

Imidazole/bisthiazole-based cyclic trimer 60

Using General Procedure C, the bisthiazole **49** (44.0 mg, 0.105 mmol) reacted with the imidazole **41a** (26.0 mg, 0.105 mmol) to give i) the *cyclic trimer* (24 mg, 41%): δ_H (360 MHz, CDCl$_3$) 1.02–1.09 (9H, m, (3 × –CH(C*H*$_3$)(CH$_3$)) overlapped), 1.02–1.09 (9H, m, (3 × –CH(CH$_3$)(C*H*$_3$)) overlapped), 2.18 (1H, m, –C*H*(CH$_3$)$_2$), 2.21 (1H, m, –C*H*(CH$_3$)$_2$), 2.56 (3H, s, Imid-C*H*$_3$), 2.58 (1H, m, –C*H*(CH$_3$)$_2$), 3.53 (3H, s, –NC*H*$_3$), 5.20 (1H, dd, *J* 9.5, 5.7 Hz, Het-C*H*), 5.37 (1H, dd, *J* 9.4, 5.7 Hz, Het-C*H*), 5.42 (1H, dd, *J* 9.5, 6.1 Hz, Het-C*H*), 8.05 (2H, s, 2 × Thiaz-*H*), 8.42 (1H, d, *J* 9.4 Hz, –C(O)N*H*), 8.48 (2H, br d, *J* 9.5 Hz, –C(O)N*H*); δ_C (90 MHz, CDCl$_3$) 9.7, 17.9, 18.4, 18.5, 19.0, 19.1, 19.4, 29.8, 30.4, 34.9, 35.5, 50.4, 55.0, 55.5, 123.0, 123.3, 124.3, 146.2, 149.1, 149.5, 160.0, 160.4, 163.0, 168.5, 169.4, 169.6. HRMS [M + H]$^+$ *m/z* 558.2314 (calcd for $C_{26}H_{36}N_7O_3S_2$ 558.2321), ii) the *cyclic tetramer* **61** (6.9 mg, 9%): δ_H (360 MHz, CDCl$_3$) 0.90–1.06 (12H, m, (4 × –CH(C*H*$_3$)(CH$_3$)) overlapped), 0.90–1.06 (12H, m, (4 × –CH(CH$_3$)(C*H*$_3$)) overlapped), 2.44 (1H, m, –C*H*(CH$_3$)$_2$), 2.50 (3H, s, Imid-C*H*$_3$), 2.51 (3H, s, Imid-C*H*$_3$), 2.55 (2H, m, (2 × –C*H*(CH$_3$)$_2$)), 2.63 (1H, m, –C*H*(CH$_3$)$_2$), 3.64 (6H, s, (2 × –NC*H*$_3$)), 4.92 (1H, app t, *J* 10.2 Hz, Het-C*H*), 4.98 (1H, app t, *J* 9.6 Hz, Het-C*H*), 5.13 (1H, m, Het-C*H*), 5.37 (1H, m, Het-C*H*), 7.98 (2H, s, 2 × Thiaz-*H*), 8.02–8.11 (4H, m, 4 × –C(O)N*H* overlapped); δ_C (90 MHz, CDCl$_3$) 9.8, 9.9, 17.8, 17.9, 18.1, 18.3 (×2), 18.5, 18.7, 18.8, 30.1, 31.3, 33.8, 34.2, 35.1, 35.4, 49.9, 50.3, 54.2, 55.0, 122.9, 123.4, 128.9, 130.0, 131.7, 133.0, 145.9, 146.3, 158.9, 159.3, 160.0, 160.2, 163.1, 163.4, 167.7, 168.2; HRMS [M + H]$^+$ *m/z* 751.3462 (calcd for $C_{36}H_{51}N_{10}O_4S_2$ 751.3468), and iii) the cyclic tetramer **9b** (9%).

Didmolamide A (4)

N-Methylmorpholine (0.05 mL, 0.46 mmol) was added to a stirred solution of the oxazoline **71a** (19 mg, 0.077 mmol) and the bisthiazole **74** (28 mg, 0.077 mmol) in dry DMF (3.85 ml) at room temperature under a nitrogen atmosphere. The stirred mixture was cooled to 0 °C and then DPPA (0.05 mL, 0.23 mmol) was added. The yellow solution was stirred at 0 °C for 1 hour and then allowed to warm to room temperature where it was stirred for 4.5 days. The mixture was evaporated *in vacuo* to leave a residue which was dissolved in ethyl acetate (15 ml). The solution was washed with H_2O (2 × 10 ml) and the organic extract was then dried (Na_2SO_4) and evaporated *in vacuo.* The residue was purified by chromatography eluting with DCM–EA–MeOH (75 : 25 : 3) to give i) didmolamide A (**4**) (0.85 mg, 2%) as a colourless solid, $[a]_D^{29}$ −37.0 (*c* 1.0, MeOH) (lit.[5] $[a]_D^{25}$ −35.7 (*c* 0.59, MeOH)); ν_{max} (soln, CHCl$_3$) 3706, 2967, 1660 cm^{-1}; δ_H (360 MHz, CDCl$_3$) 1.39 (3H, d, *J* 10.5, C*H*$_3$CHO), 1.44 (3H, d, *J* 6.8, CHC*H*$_3$), 1.76 (3H, d, *J* 6.8, C*H*$_3$CH), 3.25 (1H, dd, *J* 14.0, 4.1, C*H*$_2$Ph), 3.41 (1H, dd, *J* 14.0, 4.1, C*H*$_2$Ph), 4.65 (1H, dd, *J* 10.5, 2.3, C*H*CH(O)), 5.13–5.20 (1H, m, C*H*(O)), 5.20–5.29 (1H, m, C*H*CH$_2$Ph), 5.38–5.46 (1H, m, C*H*CH$_3$), 5.46–5.60 (1H, m, C*H*CH$_3$), 7.20–7.31 (5H, m, Ar*H*), 7.69 (1H, app d, *J* 7.1, N*H*-ala), 8.10 (1H, s, C*H*S), 8.17 (1H, s, C*H*S), 8.27 (1H, app d, *J* 7.7, N*H*-ala), 8.64 (1H, app d, *J* 6.5, N*H*-phe); δ_C (90.5 MHz, CDCl$_3$) 16.5 (q), 24.2 (q), 25.0 (q), 37.4 (t), 46.2 (d), 48.0 (d), 48.1 (d), 70.4 (d), 80.8 (d), 123.8 (d), 123.9 (d), 127.3 (d), 128.2 (d), 130.0 (d), 135.6 (s), 148.4 (s), 149.1 (s), 159.4 (s), 159.8 (s), 167.7 (s), 168.3 (s), 170.8 (s), 171.2 (s); *m/z* (EI) 539.1535 ([M$^+$ + H], $C_{25}H_{26}O_4N_2S_2$ + H requires 539.1530), and ii) the cyclic tetramer **10a** (5.6 mg, 12%) as a colourless solid, mp 272–273 °C (DCM–ethyl acetate–MeOH) (lit.[9] mp 270–271 °C (CH$_3$CN–Et$_2$O)); $[a]_D^{25}$ −148.0 (*c* 0.3, CHCl$_3$) (lit.[9] $[a]_D^{23}$ −160.2 (*c* 1.0, CH$_3$CN)); ν_{max} (soln, CHCl$_3$) 3696, 3370, 2962, 1666, 1602 cm^{-1}; δ_H (360 MHz, CDCl$_3$) 1.85 (12H, d, *J* 6.9, (4 × C*H*$_3$CH)), 5.60 (4H, app quintet, *J* 6.9, (4 × C*H*CH$_3$)), 8.06 (4H, d, *J* 7.9, 4 × NHCO), 8.12 (4H, s, 4 × C*H*S); δ_C (90.6 MHz, CDCl$_3$) 170.9 (s), 160.0 (s), 148.4 (s), 124.9 (d), 46.1 (d), 21.3 (q).

Didmolamide B (68)

a) Using General Procedure C, the phenylalanine threonine **72** (30 mg, 0.11 mmol) was coupled with the bisthiazole amino acid **74** (40 mg, 0.11 mmol) and the crude product was purified by chromatography on silica eluting with DCM–EA–MeOH (75 : 25 : 2–5) to give i) didmolamide B (5.5 mg, 9%) as a colourless foam: $[a]_D^{25}$ −225.0 (*c*, 0.008, MeOH) (lit.[5] $[a]_D^{25}$ −216 (*c*, 0.11, MeOH); ν_{max} (soln, CHCl$_3$), 3685, 2925, 1668 cm^{-1}; δ_H (360 MHz, CDCl$_3$CD$_3$OD) 0.85 (3H, d, *J* 6.5, C*H*$_3$CHOH), 1.54 (3H, d, *J* 7.0, C*H*$_3$CH-thz), 1.65 (3H, d, *J* 6.8, C*H*$_3$CH-thz), 3.18 (1H, dd, *J* 7.6, 14.2, C*H*$_2$Ph), 3.31 (1H, dd, *J* 7.5, 10.7, C*H*$_2$Ph), 4.01 (1H, t, *J* 7.2, C*H*CHOH), 4.22–4.31 (1H, m, C*H*OH), 4.98–5.07 (1H, m, C*H*CH$_2$Ph), 5.30–5.39 (1H, m, C*H*CH$_3$), 5.39–5.48 (1H, m, C*H*CH$_3$), 7.15–7.31 (5H, m, Ar*H*), 7.50 (1H, d, *J* 6.9, N*H*-ala), 8.02 (1H, s, C*H*S), 8.03 (1H, s, C*H*S), 8.17 (1H, d, *J* 7.8, N*H*-ala), 8.44 (1H, d, *J* 7.2, N*H*-thr), 8.57 (1H, d, *J* 8.5, N*H*-phe); δ_C (90 MHz, CDCl$_3$–CD$_3$OD) 18.7 (q), 22.1 (q), 23.7 (q), 37.4 (t), 46.4 (d), 47.4 (d), 54.4 (d), 60.5 (d), 66.0 (d), 123.6 (d), 123.9 (d), 127.2 (d), 128.8 (d), 129.3 (d), 136.2 (s), 148.2 (s), 149.0 (s), 160.0 (s), 160.6 (s), 169.9 (s), 170.4 (s), 171.5 (s), 171.6 (s); HRMS:

$[M + H]^+$ *m/z* 557.1565 (calcd for $C_{25}H_{28}N_6O_5S_2$ 557.1642), and ii) the cyclic tetramer **10a** (5%).

b) A coupling reaction between **72** and **74**, using DPPA–*i*-Pr_2NEt in DMF, gave didmolamide B (7%) and the cyclic tetramer **10a** (12%).

Bistratamide H (67)

Using General Procedure C, the bisthiazole **49** (77.0 mg, 0.18 mmol) was coupled with the oxazole **73** (43.1 mg, 0.18 mmol) to give the cyclic peptide (36 mg, 36%) as a solid: $[a]_D^{25}$ −94.8 (*c* 1, MeOH); [lit[19]: −92.2 (*c* 1, MeOH)]; δ_H (360 MHz, DMSO-d_6) 0.94 (3H, d, *J* 6.8 Hz, –CH(CH_3)(CH_3)), 0.96 (3H, d, *J* 6.8 Hz, –CH(CH_3)(CH_3)), 0.98 (3H, d, *J* 6.8 Hz, –CH(CH_3)(CH_3)), 0.99 (3H, d, *J* 6.8 Hz, –CH(CH_3)(CH_3)), 1.01 (3H, d, *J* 6.8 Hz, –CH(CH_3)(CH_3)), 1.03 (3H, d, *J* 6.8 Hz, –CH(CH_3)(CH_3)), 2.25 (3H, m, 3 × –CH(CH_3)$_2$ overlapped), 2.63 (3H, s, Oxaz-CH_3), 5.10 (1H, dd, *J* 8.5, 5.2 Hz, Het-CH), 5.38 (1H, dd, *J* 8.5, 5.5 Hz, Het-CH), 5.47 (1H, dd, *J* 9.7, 6.6 Hz, Het-CH), 8.37 (1H, s, Thiaz-H), 8.39 (1H, s, Thiaz-H), 8.40 (1H, d, *J* 10.5 Hz, –C(O)NH), 8.54 (1H, d, *J* 9.0 Hz, –C(O)NH), 8.56 (1H, d, *J* 11.0 Hz, –C(O)NH); δ_C (90 MHz, DMSO-d_6) 12.2, 18.9, 19.0, 19.1, 19.2, 19.5, 19.9, 33.7, 35.3, 35.5, 53.2, 55.5, 55.7, 125.7, 126.2, 128.7, 148.7, 149.2, 154.2, 159.9, 160.4, 160.7, 161.4, 169.4, 169.9; HRMS $[M + Na]^+$ *m/z* 567.1777 (calcd for $C_{25}H_{32}N_6NaO_4S_2$ 567.1819).

Abbreviations

Boc: *N*-*tert*-Butoxycarbonyl; BOP: (benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate; DIPEA: *i*-Pr_2NEt (Hünigs Base); DMF: $HCON(CH_3)_2$; DPPA: $(PhO)_2$-$P(O)N_3$; EDCI: (dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; FDPP: $Ph_2P(O)OC_6F_5$; NMM: *N*-methylmorpholine; Py BOP: benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate.

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