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DENDROAMIDE A, NOSTOCYCLAMIDE AND RELATED CYCLOPEPTIDES FROM CYANOBACTERIA. TOTAL SYNTHESIS, TOGETHER WITH ORGANISED AND METAL-TEMPLATED ASSEMBLY FROM OXAZOLE AND THIAZOLE-BASED AMINO ACIDS†

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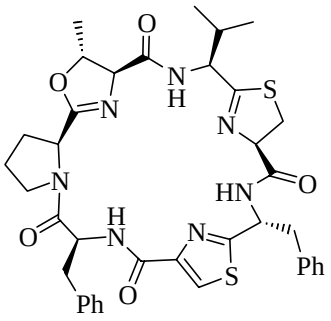
Abstract - Oxazole and thiazole-based amino acids (**15**-**18**) are shown to undergo organised and metal-templated assemblies leading to novel cyclic peptides. Thus, a 1:1:1 mixture of the amino acids (**15**, **16** and **17**) undergo cyclisation in the presence of FDPP producing the natural hexapeptide dendroamide A (**4**), together with its positional isomer (**33**) and other cyclic trimers in a combined yield of 75%. Likewise, a mixture of **15**, **16** and **18** cyclised to nostocyclamide (**6**), isolated from a cyanobacterium, and equal amounts of the analogues (**36**, **37** and **38**) in a combined yield of 65%. The proportions of the cyclopeptide products produced in these novel cyclooligomerisations varied when the cyclisations were carried out in the presence of various metal ions, *e.g.* Cu^{2+}, Ca^{2+}, Na^{+}, K^{+}, Ag^{+}. A brief discussion of the influence of metals in controlling the outcome of some of these reactions is given.

Nature has presented us with a prodigious variety of oxazole/oxazoline and thiazole/thiazoline-based secondary metabolites in recent years, many of which are based on macrocyclic structures, and include lissoclinamide 4 (**1**),[1] mollamide (**2**)[2] and ascidiacyclamide (**3**)[3] from ascidians (sea squirts),[4] and dendroamide A (**4**),[5] raocyclamide (**5**)[6] and nostocyclamide (**6**)[7] from cyanobacteria. The characteristic sequence of alternating cysteine/serine-derived heterocycles and amino acids in these compounds is highly reminiscent of macrocyclic ligands such as porphyrins and aza crown ethers, which seems to suggest that they are tailor-made for metal complexation and ion transport *in vivo*.[8] Indeed, metal binding data have now been determined for a variety of marine cyclopeptides and they seem particularly prone to

† This paper is dedicated to A.I. Meyers on the occasion of his 70th birthday. Professor Meyers carried out distinguished research in the area of oxazole-based natural products over several decades, including the synthesis of the cyclopeptide bistratamide D, (-)-madumycin II, and griseoviridin.

binding to Cu^{2+}, Zn^{2+} and Ca^{2+}.[9] Furthermore, Fairlie *et al.*[10] have described crystal structures for novel bridged Cu^{2+} complexes of patellamide D and ascidiacyclamide (**7** and **8**).



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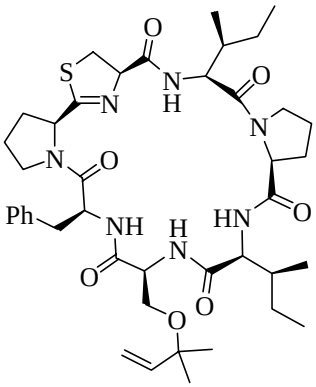

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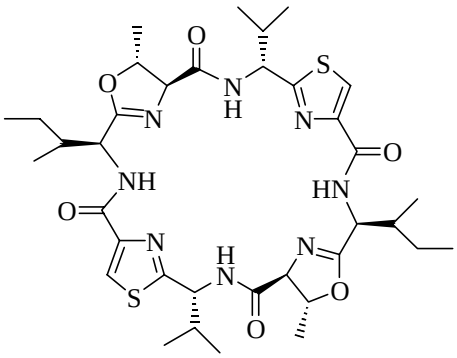

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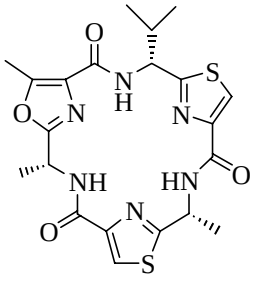

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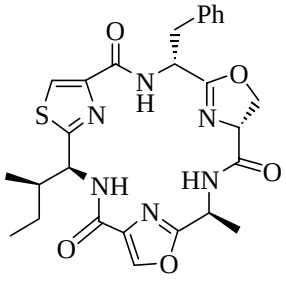

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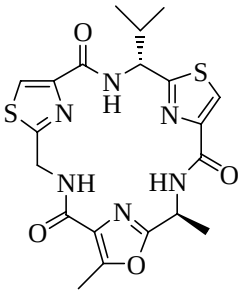

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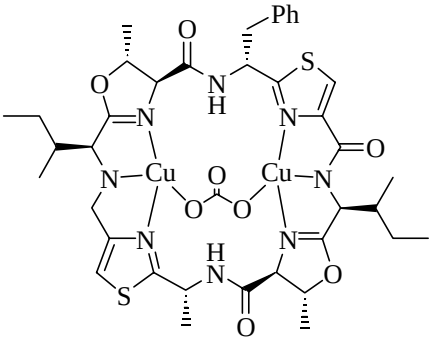

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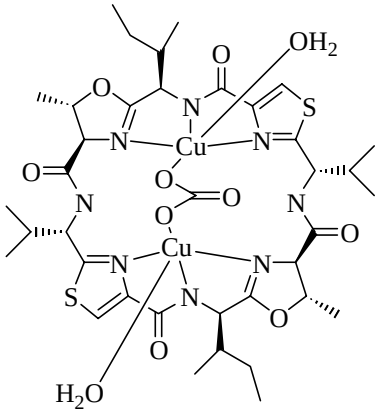
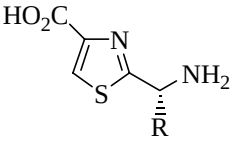


8

The incidence of cyclopeptide – metal conjugates *in vivo* also begs the question – do metal ions perhaps provide a template for the biological assembly of these compounds in the marine melieu? If so, is this part of their *modus operandum* in nature, and could this cyclopeptide – metal congruence account for the

striking and diverse biological activities observed for these natural products? In addition, what is the biosynthesis pathway followed to heterocyclic cyclopeptide structures of the types (**1**-**3** and **4**-**6**)? Are the heterocyclic rings produced late in the biosynthesis, as seems likely, or are there some cases where the heterocyclic amino acids (**9** and **10**) are formed first and then linked with 'regular' amino acids, *e.g.* proline, phenylalanine, valine, in an ordered fashion to ultimately produce the natural product?



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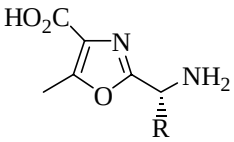

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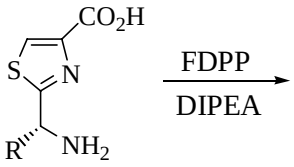
a, R = Me; **b**, R = ^{i}Pr; **c**, R = CH_2Ph; **d**, R = H.



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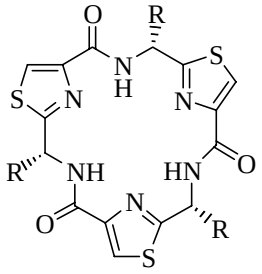
FDPP
DIPEA



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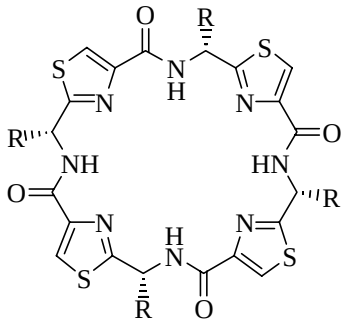

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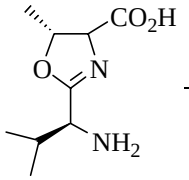
a, R = Me; **b**, R = ^{i}Pr; **c**, R = CH_2Ph



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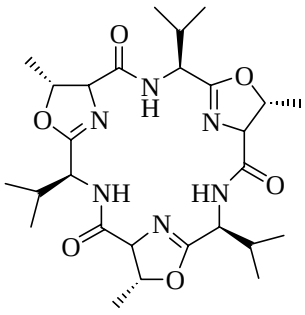

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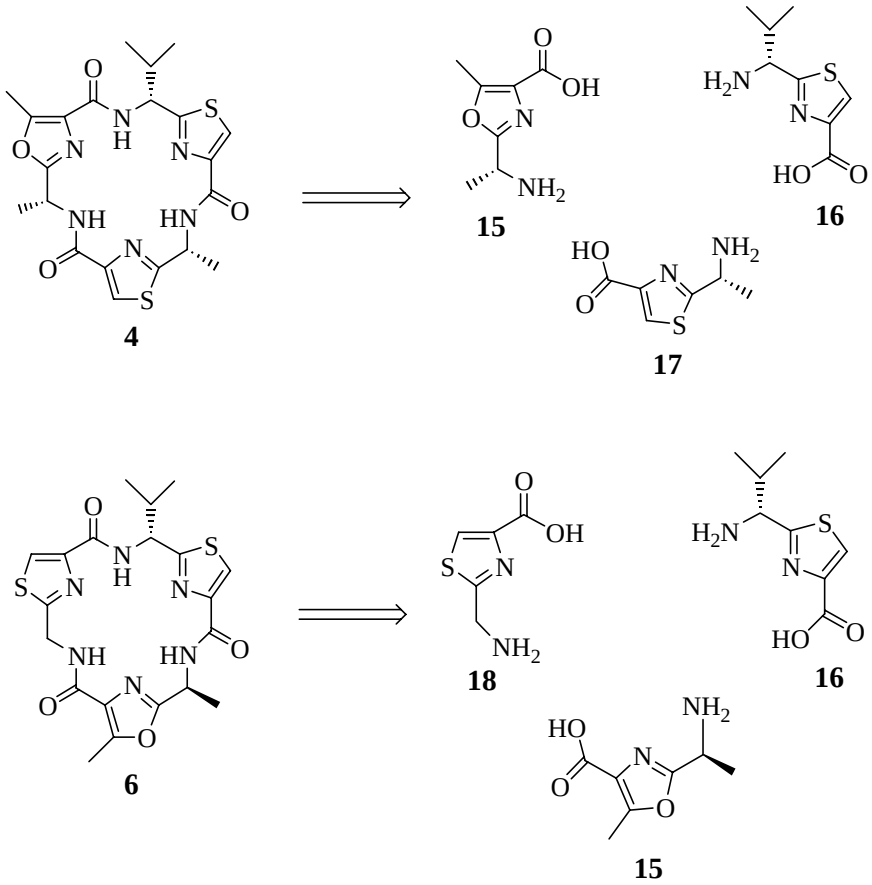
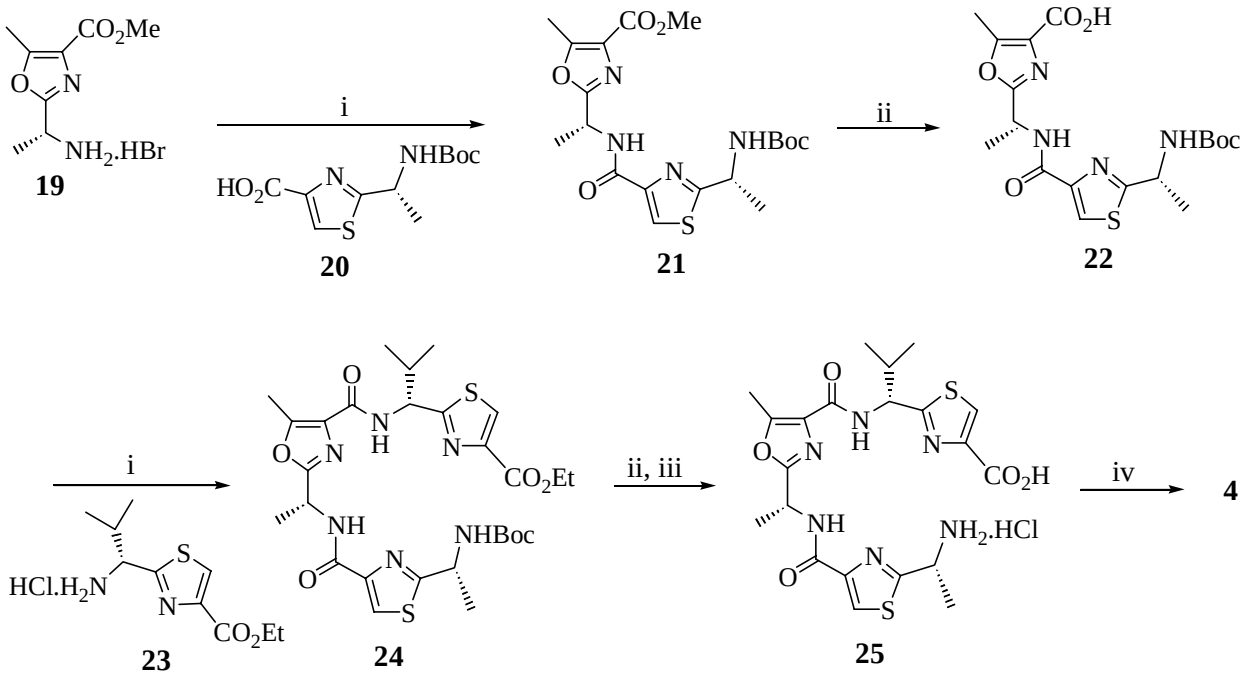
It was against this background, and with the aforementioned questions in mind, that we earlier examined the cyclooligomerisations of several valine, phenylalanine and alanine-based thiazole amino acids (**9a-c**) (as their HCl or HBr salts), which were found to lead to the formation of the cyclic trimers (**11**) and tetramers (**12**) in remarkable high yields, *i.e.* 80-90%.[11] Wipf *et al.*[12] had also studied the cyclooligomerisation of the oxazoline (**13**) leading to a concise synthesis of westiellamide (**14**), and some

complementary investigations of cyclooligomerisations of heterocyclic-based amino acids were described contemporaneously by Fairlie *et al.*[13] Following inspection of the structures of dendroamide A (**4**) and nostocyclamide (**6**), we asked ourselves whether it was possible to assemble these cyclopeptides by simply mixing the oxazole and thiazole-based amino acids (**15**, **16**, and **17**) for **4** and (**15**, **16**, and **18**) for **6**, in the presence of an appropriate peptide coupling agent. The outcome of this speculation, and the influence of various metal ion additives in determining the ratios of cyclopeptide products in the reactions studied, are now presented in this paper.[14]



Dendroamide A (**4**) was isolated from the cyanobacterium *Stigonema dendroideum* in 1996, and has been shown to exhibit multidrug resistance reversing activity.[5] Its cyclopeptide structure is made up of the three heterocyclic units (**15**) (from *D*-alanine and threonine), (**16**) (from *D*-valine and cysteine) and (**17**) (from *D*-alanine and cysteine). As a prelude to our investigations of the 'organised' and metal-templated assembly of dendroamide A from these heterocyclic units, we decided first to synthesise the cyclopeptide totally, and in a linear fashion, from the methyl ester (**19**), the Boc amine (**20**), and the ethyl ester (**23**). Each of these heterocyclic-based amino acid derivatives can be produced enantiomerically pure, *i.e.* homochiral, using methods that are now well-developed in many laboratories (see EXPERIMENTAL).[15] A coupling reaction between the oxazole amine salt (**19**) and the thiazole acid (**20**) in the presence of 1-

(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), and *N*-hydroxybenzotriazole (HOBt) and *N*-methylmorpholine (NMM) first led to the linear oxazole-thiazole (**21**) in 80% yield. Saponification of **21**, followed by a coupling reaction between the resulting carboxylic acid (**22**) and the thiazole amine (**23**) in the presence of EDC, HOBt and NMM next gave the linear thiazole-oxazole-thiazole (**24**). Saponification of **24**, and deprotection of the Boc group then led to the amino acid macrocyclisation precursor (**25**). When a solution of **25** in acetonitrile containing diisopropylethylamine (DIPEA) was stirred in the presence of pentafluorophenyl diphenyl phosphinate (FDPP) at rt for 2 h, work up and chromatography finally gave dendroamide A (**4**) as a white solid, whose spectroscopic and chiroptical data were found to be identical to those reported for the natural product isolated from *S. dendroideum*.[5] Following the preliminary publication of our synthesis of dendroamide A,[14a] Xia and Smith described an alternative synthesis of this cyclopeptide.[16]

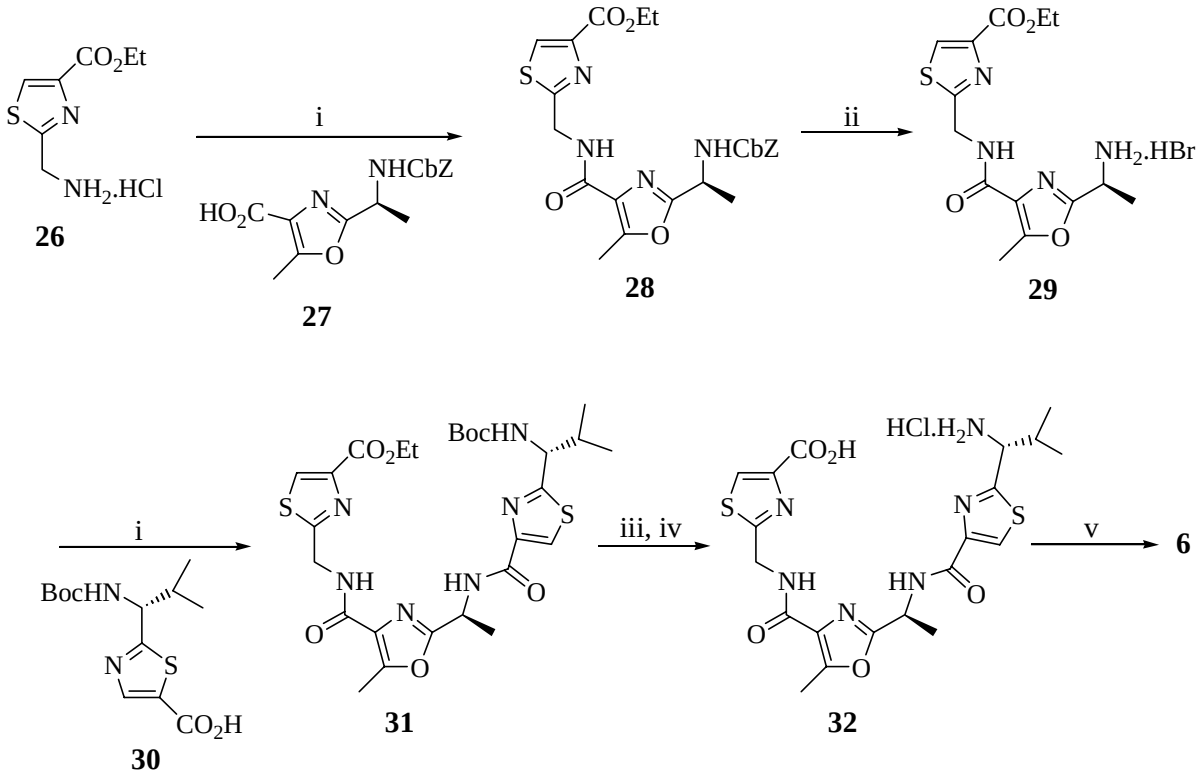


Reagents: i, EDC, HOBt, NMM, DCM, 0 °C, 80 %; ii, NaOH, THF, H_2O, rt, 97 %; iii, 4M HCl, dioxane, rt, 70 %; iv, FDPP, DIPEA, MeCN, rt, 91 %.

Scheme 1

Following an identical strategy, and using the thiazole amine salt (**26**), the oxazole acid (**27**), and the thiazole acid (**30**), likewise, we were able to secure a total synthesis of nostocyclamide (**6**) (Scheme 2), whose spectroscopic data were identical to those described for the natural product isolated from the cyanobacterium *Nostoc* sp.[7] Hitherto, Moody and Bagley[17] had reported a different linear synthesis of

nostocyclamide, and our material showed an identical optical rotation to that measured by these authors for their synthetic material.

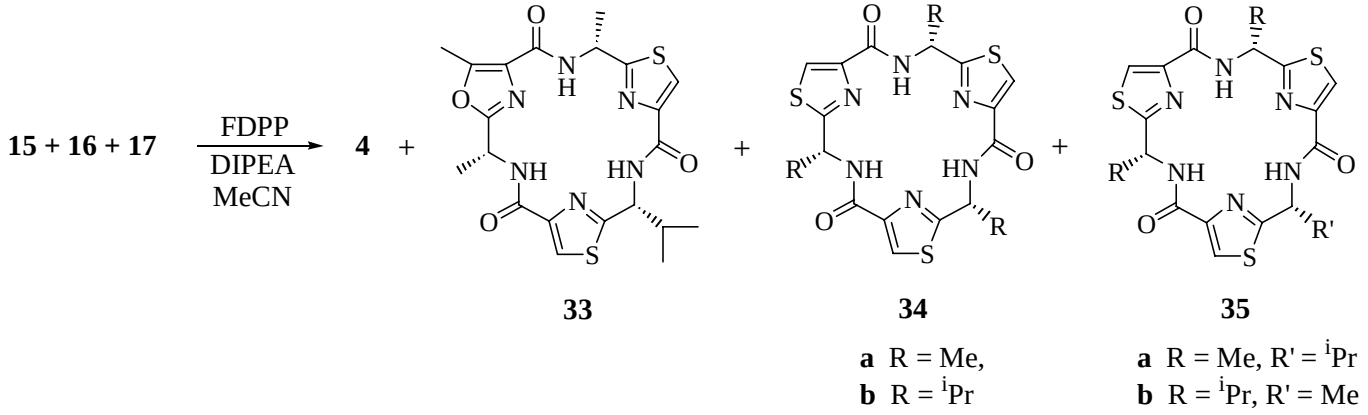


Reagents: i, EDC, HOBt, NMM, DCM, 0 °C, 60 % and 21 %; ii, 33 % HBr in acetic acid, 91 %; iii, NaOH, THF, H_2O, rt; iv, 4M HCl, dioxane, rt; v, FDPP, DIPEA, MeCN, 10 %.

Scheme 2

With authentic samples of dendroamide A (**4**) and nostocyclamide (**6**) in hand, we now set about examining the outcome of simply mixing their heterocyclic amino acid components in the presence of FDPP-DIPEA. In our earlier 'homo' oligomerisation studies with the thiazoles (**9a**, **9b**, and **9c**)[11] we had found that the use of FDPP-DIPEA as coupling reagent offered several practical advantages over alternatives such as DPPA, DPPCl and EDC. From the coupling of the hydrochloride/hydrobromide salts of the three heterocyclic amino acids (**15**, **16** and **17**) we would expect to form eleven symmetrical and unsymmetrical thiazole/oxazole cyclopeptides *cf* (**11**), one of which should be dendroamide A (**4**), *i.e.* the statistical yield of each cyclopeptide product would be approximately 9% based on a quantitative overall yield. Furthermore, taking into account the possibility of the formation of cyclotetramers, *cf.* (**12**), there was the likelihood of forming forty-nine cyclic peptide trimers and tetramers from a mixed cyclooligomerisation of the amino acids (**15**, **16** and **17**). It was to our surprise and pleasure, therefore, to find that when a solution of a 1:1:1 mixture of the amino acids (**15**, **16** and **17**) in acetonitrile was mixed with FDPP-DIPEA at rt for 3 days, work up and chromatography separated dendroamide A (**4**) (23%) together with its positional isomer (**33**) (22%) and the four *tris*-thiazoles (**34a**, **34b**, **35a** and **35b**), in a

combined yield of 30%, *i.e.* a total yield of 75% of cyclic peptide trimers. No cyclopeptide tetramer products could be detected by chromatography or by HPLC - MS. The structures of the aforementioned cyclic peptide trimers were confirmed following their independent syntheses using linear strategies similar to that used to synthesise authentic dendroamide A (**4**), *viz* Scheme 1; see EXPERIMENTAL.

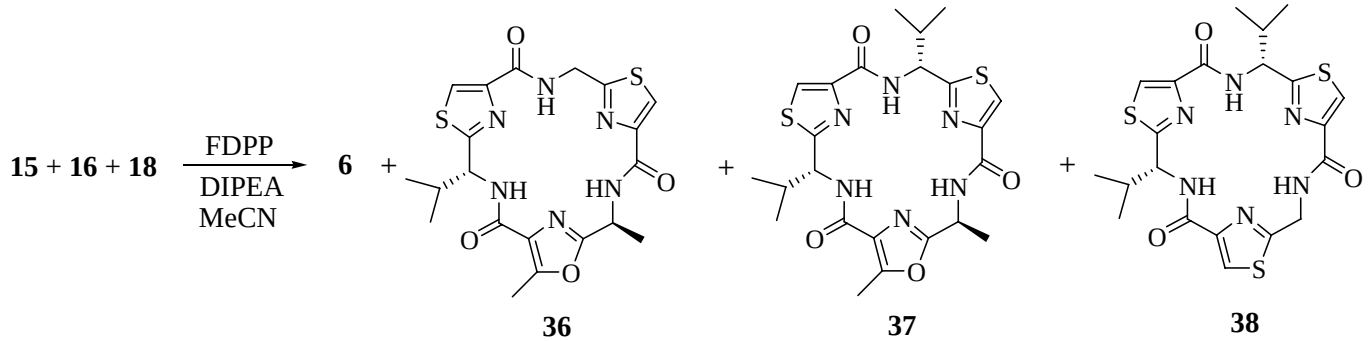


33 **34** **35**

a R = Me, **b** R = ^{i}Pr

a R = Me, R' = ^{i}Pr **b** R = ^{i}Pr, R' = Me

In a precisely similar manner, when a solution containing equal amounts of the three synthetic amino acids (**15**, **16** and **18**) in acetonitrile was stirred in the presence of FDPP-DIPEA at rt for 3 days, work up and chromatography separated approximately equal amounts of nostocyclamide (**6**) and the cyclic peptide trimer analogues (**36**, **37** and **38**) in a combined yield of 65%. Once again, the structures of each of these analogues followed from their independent syntheses, which were carried out in a linear fashion using Boc-amine protected and methyl ester derivatives of the corresponding heterocyclic amino acids, *cf.* Schemes 1 and 2.

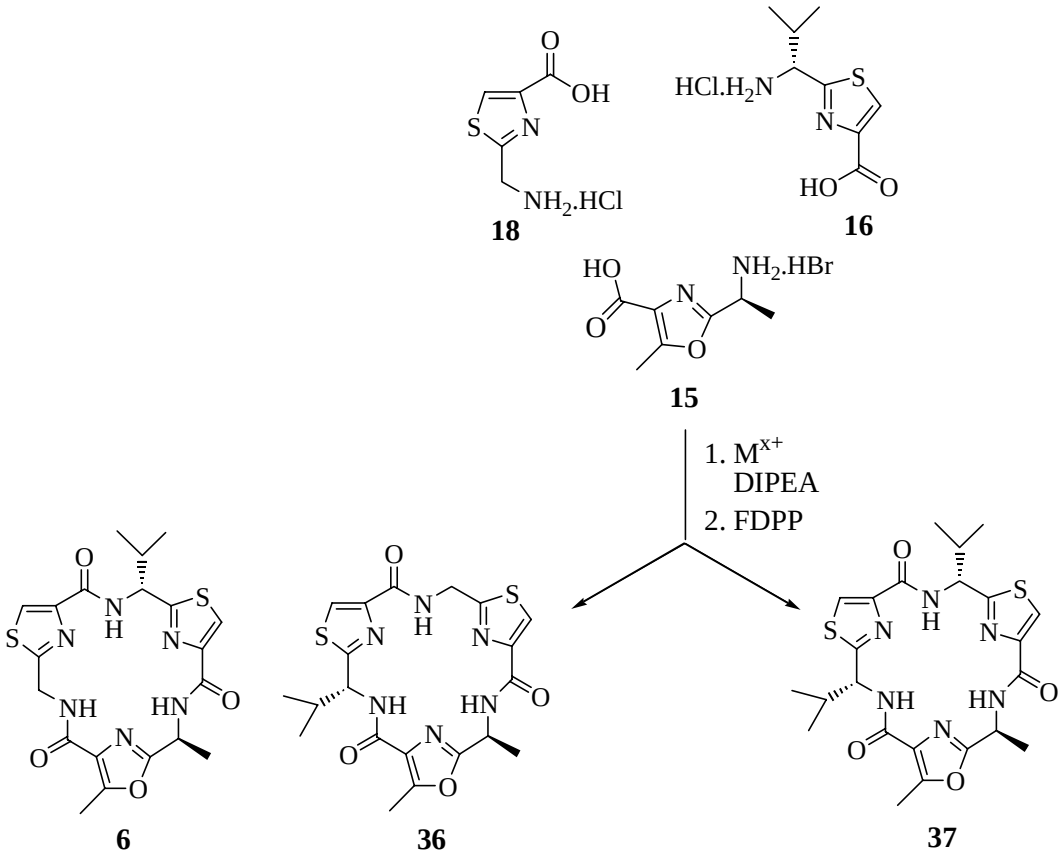


36 **37** **38**

We now turned to examining the templating effects of metal ions in determining the outcomes of the cyclooligomerisations involving the thiazole and oxazole based amino acids (**15-18**). In earlier investigations involving the 'homo' cyclooligomerisation of the valine thiazole amino acid (**9b**), to the cyclotrimer (**11b**), and the cyclotetramer (**12b**), we found that the presence of smaller alkali metal ions favoured the formation of **11b**, whereas the presence of larger metal ions (*e.g.* Cu^{2+}) enhanced the formation of the tetramer (**12b**).[11] We concluded that these differences were associated with the

templating effect of the metal ions, with the size of the cyclic peptide formed being related to the ionic radius of the metal template.

It was revealing to find then that when a solution of a 1:1:1 mixture of the heterocyclic amino acids (**15**, **16** and **18**) in acetonitrile and DIPEA was stirred in the presence of either $LiBF_4$ or $Ca(BF_4)_2$ at rt for 6 h, prior to the addition of FDPP, only nostocyclamide A (**6**) and its cyclic trimer positional isomer (**36**) were produced (as 3:1 and 5:3 mixtures respectively), albeit in a diminished yield of 26-28%. In the presence of $Cu(BF_4)_2$ the proportion of natural nostocyclamide (**6**) was enhanced even further, *i.e.* 2:1, (**6**:**36**), but at the expense of an even lower overall yield of 11%.



			Percentage Composition of Cyclic Products	
Metal Salt	Ionic Radius / Å	Overall yield / %	**6**	**36**
no metal	-	71	21	23
$Cu(BF_4)_2$	0.71	9	66	34
$LiBF_4$	0.73	26	45	13
$Ca(BF_4)_2$	1.14	28	48	29

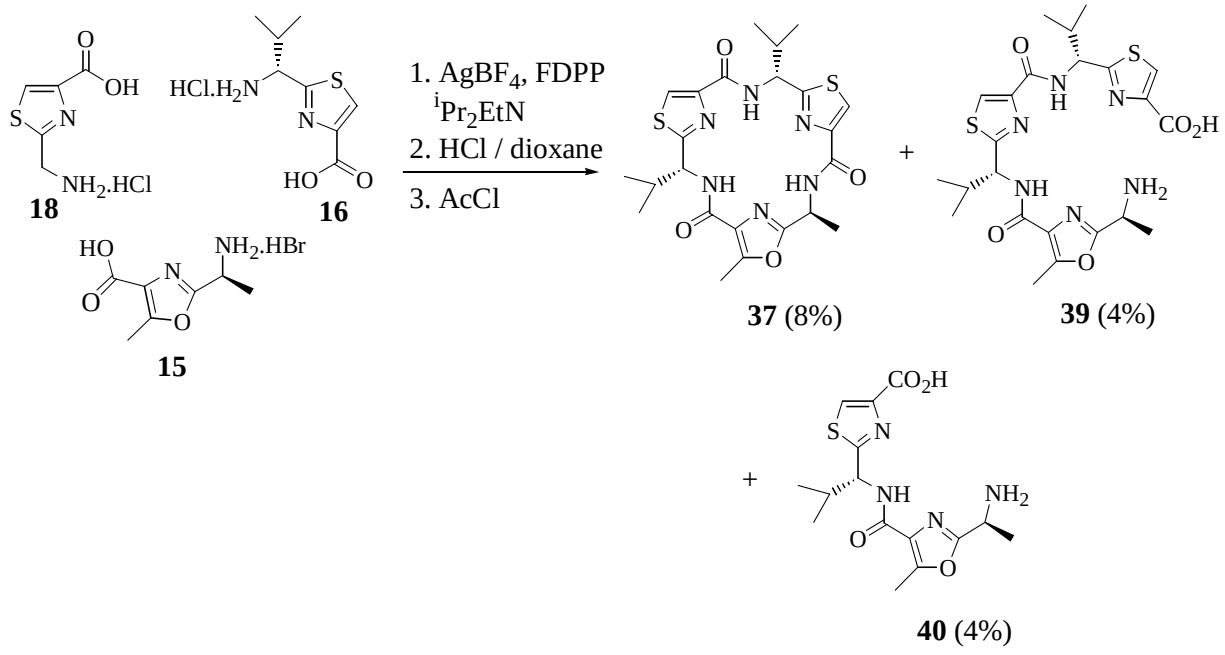
Table 1 : Ratios of cyclic peptide products (**6**) and (**36**) formed from mixing the amino acids (**15**, **16** and **18**) in the presence of Li^+, Ca^{2+} and Cu^{2+} tetrafluoroborate salts.

Perhaps even more revealing was the observation that when the same three amino acids (**15**, **16** and **18**) were mixed with FDPP-DIPEA in the presence of the tetrafluoroborate salts of either Zn, Na or K, a significant enhancement in the formation of **37** resulted, in addition to nostocyclamide and its positional isomer (**36**) (see Table 2). Indeed, in the presence of $AgBF_4$ the cyclic trimer (**37**) was the only product of the reaction (14%)!

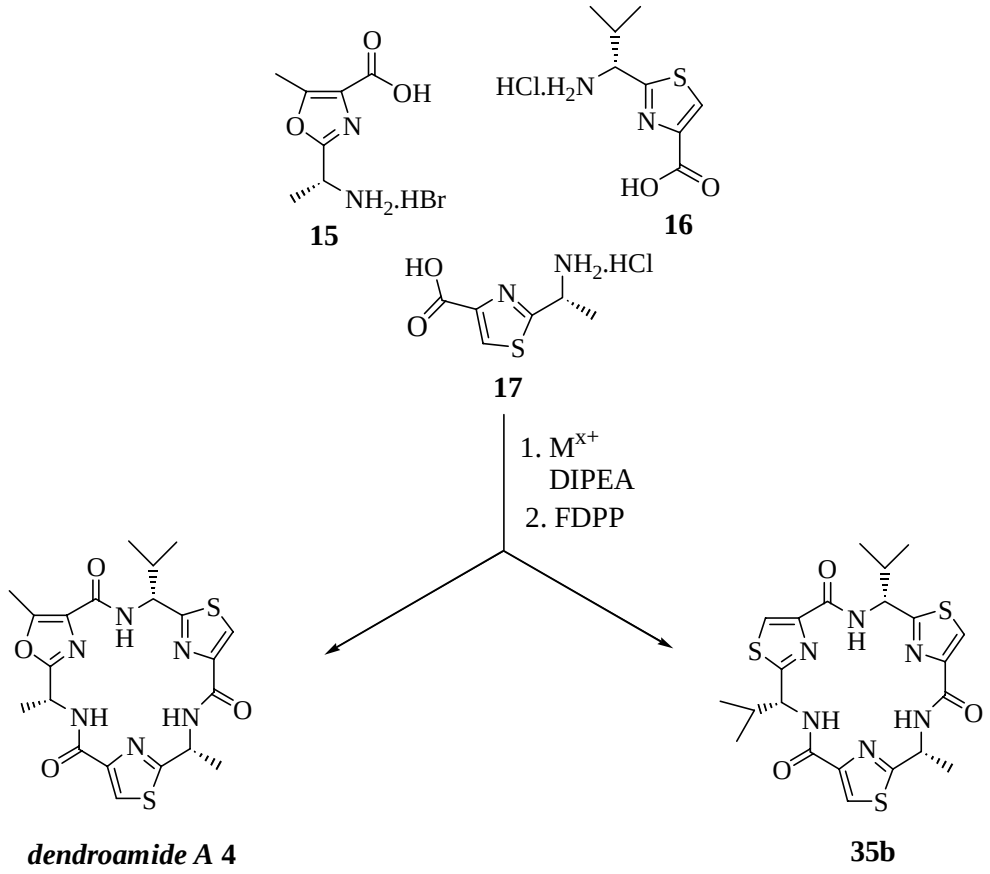
			Percentage Composition of Cyclic Products		
Metal Salt	Ionic Radius / Å	Overall yield / %	**6**	**36**	**37**
no metal	-	71	21	23	21
$Zn(BF_4)_2$	0.74	23	25	38	36
$AgBF_4$	0.81	14	-	-	100
$NaBF_4$	1.13	34	28	28	44
KBF_4	1.51	40	26	26	48

Table 2 : Ratios of cyclic peptide products (**6**, **36** and **37**) formed from mixing the amino acids (**15**, **16** and **18**) in the presence of Zn^{2+}, Ag^{+}, Na^{+} and K^{+} tetrafluoroborate salts

The poor yields of cyclic peptides resulting from the metal-templated reactions led us to examine the cyclooligomerisation of **15**, **16** and **18** in the presence of Ag^{+} in more detail. Thus, when the crude product was stirred in the presence of 4M HCl in dioxane to remove any silver residues, as AgCl, and then treated with acetyl chloride – DIPEA, the recovered material was shown to contain the expected cyclic peptide (**37**) but also its linear trimer (**39**) and linear dimer (**40**) precursors in a combined yield of 16 %.



Parallel metal-templating reactions were carried out with the three amino acids (**15**, **16** and **17**) leading to dendroamide A (**4**) and to its isomers and cyclotrimer analogues. To our astonishment, when the amino acids were coupled in the presence of fluoroborate salts of either Cu, Li, Zn, or K the proportion of the cyclic peptide analogue (**35b**) of dendroamide A increased markedly from 29% (in the absence of metal) to as high as 59%; indeed in the presence of $AgBF_4$, **35b** was the only trimeric cyclic peptide product to be observed. Finally, in this series, we found that when $Ca(BF_4)_2$ acted as a template in the assembly of trimeric cyclic peptides from **15**, **16** and **17**, the proportion of dendroamide A amongst the products increased to 52% with only 23% of the analogue (**35b**) being produced concurrently (Table 3).



Metal Salt	Ionic Radius / Å	Overall yield / %	Percentage Composition of Cyclic Products	
			35b	**4**
$Cu(BF_4)_2$	0.71	12	61	
$LiBF_4$	0.73	38	59	
$Zn(BF_4)_2$	0.74	38	59	
$NaBF_4$	1.13	55	48	
KBF_4	1.51	33	29	
No Metal	-	75	29	23
$AgBF_4$	0.81	13	100	
$Ca(BF_4)_2$	1.14	28	23	52

Table 3 : Ratios of cyclic peptide products (**4** and **35b**) formed from mixing the amino acids (**15**, **16** and **17**) in the presence of various metal tetrafluoroborate salts.

Clearly, the size of the metal, its oxidation state, the nature of the counter ions, the affinity of the metal for the nitrogen, sulphur and oxygen heteroatoms in the amino acids (**15-18**), alongside solubility, solvent effects, metal aggregation, and a number of additional issues, combine to influence the ratios of cyclic peptide products resulting from the aforementioned cyclooligomerisations. We are a long way from understanding these factors, and clearly other detailed studies will need to be carried out before we are able to obtain a full appreciation, and thereby use, these potentially useful assemblies in the synthesis of designed heterocyclic-based cyclic peptides.

EXPERIMENTAL

General. All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were recorded in spectroscopic grade chloroform or ethanol on a Jasco DIP-370 polarimeter and $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. UV spectra were recorded on a Phillips PU 8700 spectrophotometer as solutions in spectroscopic grade ethanol and ε values are recorded in units of dm^3 mol^{-1} cm^1. IR spectra were obtained using Perkin-Elmer 1600 series FT-IR instrument or a Nicolet Magna 550 instrument as liquid films or as dilute solutions in spectroscopic grade chloroform. NMR spectra were recorded at 360 or 500 MHz for ^1H, and at 90.5 or 125 MHz for ^{13}C on either a Bruker DPX 360, or a Bruker DPX 500 spectrometer as dilute solutions in deuterochloroform unless otherwise stated. The chemical shifts are quoted in parts per million (ppm) relative to residual chloroform (δ_H 7.27, δ_C 77.0) or residual methanol (δ_H 3.35, δ_C 77.0) as internal standard and the multiplicity of each signal is

designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; br, broad; m, multiplet; app., apparent; obs., obscured. All coupling constants are quoted in Hertz. MS spectra were recorded on a VG Autospec, a MM-701CF, a VG Micromass 7070E or a Micromass LCT. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Flash chromatography was performed on Merck silica gel 60 F_{254} precoated aluminium backed plates which were visualised with UV light and were developed using either acidic ninhydrin solution, acidic ethanol vanillin solution or a basic potassium permanganate solution. All air-sensitive reactions were carried out under nitrogen using flame-dried glassware. Dichloromethane and acetonitrile were freshly distilled from calcium hydride, and tetrahydrofuran was freshly distilled from sodium. All other reagents were used without further purification.

1'(*R*)-2-(1-Amino-ethyl)-5-methyl-oxazole-4-carboxylic acid methyl ester hydrobromide (19)

N-Methylmorpholine (2.6 mL, 23.7 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.5 g, 23.7 mmol) and *N*-hydroxybenzotriazole (3.2 g, 23.7 mmol) were added to a stirred solution of CbZ-protected (*D*)-alanine[18] (4.8 g, 21.5 mmol) at 0 °C under an atmosphere of nitrogen. The resulting mixture was stirred for 20 min and then a precooled solution of (*D, L*) - threonine methyl ester hydrochloride (3.6 g, 21.5 mmol) deprotonated with *N*-methylmorpholine (2.6 mL, 23.7 mmol) in DMF (5 mL) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and then at rt for 14 h. Water (*ca.* 50 mL) was added and the aqueous layer was separated and extracted with ethyl acetate (6 x 50 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (3 x 40 mL), 10 % aqueous citric acid solution (3 x 40 mL), and brine (3 x 40 mL), and then dried ($MgSO_4$) and evaporated *in vacuo*. The yellow residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to give 2'(*R*)-2-(2-benzyloxy-carbonylaminopropionylamino)-3-hydroxybutyric acid methyl ester[18] (5.75 g, 79 %) as a viscous oil; υ_{max} ($CHCl_3$)/cm^{-1} 3429, 2954, 1730, 1682; δ_H (360 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.4 Hz, C*H*$_3$CHOH), 1.44 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 3.76 (3H, s, C*H*$_3$O), 4.34-4.37 (1H, br m, C*H*(OH)CH_3), 4.34-4.37 (1H, m, C*H*CH_3), 4.58 (1H, dd, *J* 2.4, 8.9 Hz, C*H*CO_2Me), 5.13 (2H, s, C*H*$_2$Ph), 5.40-5.47 (1H, br s, N*H*CbZ), 6.83 (1H, d, *J* 8.9 Hz, N*H*CO), 7.30-7.39 (5H, m, ArH); δ_C (90.5 MHz, CD_3OD) 18.7 (q), 19.5 (q), 50.5 (d), 52.3 (q), 57.3 (d), 66.6 (t), 67.3 (d), 127.7 (d), 127.9 (d), 128.1 (d), 155.8 (s), 171.3 (s), 173.5 (s); *m/z* (FAB) Found: 361.1377 (M^++Na^+, $C_{16}H_{22}N_2O_6Na$ requires 361.1376).

Dess Martin periodinane[19] (17.6 g, 41.5 mmol) was added in one portion to a solution of the dipeptide (10.8 g, 31.9 mmol) in anhydrous dichloromethane (100 mL) at rt under an atmosphere of nitrogen. The resulting brown solution was stirred at rt for 4 h, the volatiles were then removed *in vacuo* leaving a solid yellow residue. The residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to give the corresponding ketone (9.2 g, 86 %) as a colourless solid; mp 117-118 °C (from dichloromethane); υ_{max} ($CHCl_3$)/cm^{-1} 3422, 2957, 1757, 1729, 1682; δ_H (360 MHz, $CDCl_3$) 1.42 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 2.38 (3H, s, C*H*$_3$COCH), 3.81 (3H, s, C*H*$_3$OCO), 4.36-4.40 (1H, m, C*H*CH_3), 5.13 (2H, s, C*H*$_2$Ph), 5.24 (1H, d, *J* 6.3 Hz, C*H*CO_2Me), 5.36 (1H, d, *J* 6.9 Hz, N*H*CbZ), 7.15-7.20 (1H, br s, N*H*CO), 7.31-7.36 (5H, m, Ar*H*); δ_C (90.5 MHz, CD_3OD) 18.2 (q), 27.5 (q), 50.0 (d), 52.1 (q), 62.6 (d), 66.6 (t), 127.7 (d), 127.8 (d), 128.2 (d), 155.8 (s), 166.3 (s), 172.6 (s), 198.4 (s); *m/z* (FAB) Found: 359.1219 (M^++Na^+, $C_{16}H_{20}N_2O_6Na$ requires 359.1219).

A solution of the ketone (1.2 g, 3.6 mmol) in anhydrous THF (3.5 mL) at -78 °C under an atmosphere of nitrogen was added dropwise, over 5 min, to a solution of triphenylphosphine (2.1 g, 7.85 mmol), iodine (0.9 g, 7.14 mmol) and triethylamine (1.8 mL, 12.96 mmol) in anhydrous THF (12 mL) at -78 °C. The resulting yellow solution was allowed to stir at -78 °C for 4 h and at rt for a further 14 h. Water (*ca*. 50 mL) was added and the separated aqueous layer was extracted with dichloromethane (4 x 40 mL). The combined organic extracts were washed successively with a saturated solution of sodium hydrogen carbonate (2 x 40 mL), 2M hydrochloric acid solution (2 x 40 mL) and brine (2 x 40 mL), and then were dried ($MgSO_4$) and evaporated *in vacuo*. The solid yellow residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to give 1'(*R*)-2-(1-benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carboxylic acid methyl ester (960 mg, 84 %) as a colourless solid; mp 126-128 °C (from dichloromethane) (lit.,[20] mp 125-126 °C); $[\alpha]_D$ +29.4° (c = 1.0, $CHCl_3$); Anal. Calcd for $C_8H_{13}N_2O_3Br$ + $2H_2O$: C, 37.5; H, 6.7; N, 10.9; Found: C, 37.8; H, 6.5; N, 11.0. υ_{max} ($CHCl_3$)/cm^{-1} 3433, 2954, 1722, 1624; δ_H (360 MHz, $CDCl_3$) 1.57 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 2.62 (3H, s, C*H*$_3$CO), 3.91 (3H, s, C*H*$_3$O), 5.03-5.09 (1H, m, C*H*CH_3), 5.12-5.13 (2H, m, C*H*$_2$Ar), 5.31 (1H, br s, N*H*CbZ), 7.30-7.35 (5H, m, Ar*H*); δ_C (90.5 MHz, $CDCl_3$); 11.9 (q), 20.0 (q), 45.0 (d), 51.9 (q), 67.0 (t), 128.0 (d), 128.1 (d), 128.4 (d), 136.1 (s), 155.4 (s), 156.6 (s), 162.5 (s), 167.1 (s); *m/z* (FAB) Found: 341.1086 (M^++Na^+, $C_{16}H_{18}N_2O_5Na$ requires 341.1113).

A solution of 33 % hydrobromic acid (1 mL) in acetic acid was added dropwise over 5 min to a solution of the above oxazole (570 mg, 1.6 mmol) in glacial acetic acid (2 mL) at rt under and atmosphere of nitrogen. The resulting yellow solution was stirred for 2 h and the volatiles were removed *in vacuo* to

give 5-methyloxazole-4-carboxylic acid methyl ester hydrobromide (**19**) (400 mg, 94 %) as a yellow hygroscopic foam; $[\alpha]_D$ +18.8° (c = 1.2, EtOH); δ_H (360 MHz, CD_3OD); 1.73 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 2.69 (3H, s, C*H*$_3$CO), 3.93 (3H, s, C*H*$_3$OCO), 4.70-4.74 (1H, m, C*H*CH$_3$); δ_C (90.5 MHz, CD_3OD); 12.6 (q), 17.5 (q), 45.7 (d), 53.0 (q), 139.2 (s), 158.8 (s), 159.5 (s), 163.4 (s); *m/z* (FAB) Found: 184.0832 (M^+- HBr, $C_8H_{12}N_2O_3$ requires 184.0848).

1'-(*R*)-2-(1-*tert*-Butoxycarbonylaminoethyl)-thiazole-4-carboxylic acid (20)

N-Methylmorpholine (3.5 mL, 31.5 mmol) and *iso*butyl chloroformate (4.1 mL, 31.5 mmol) were added to a stirred solution of Boc-(*D*)-alanine (6.0 g, 31.5 mmol) in anhydrous THF (85 mL) at -5 °C under a nitrogen atmosphere. The solution was stirred at -5 °C for 15 min, and then ammonia was bubbled through the solution for 5 min at –5 °C and for 20 min at rt. The resulting mixture was stirred at rt for 20 min and then water (*ca*. 30 mL) was added. The separated aqueous layer was extracted with dichloromethane (4 x 30 mL), the combined organic extracts were then washed successively with saturated sodium hydrogen carbonate solution (3 x 30 mL), and brine (3 x 30 mL), and then dried ($MgSO_4$) and evaporated *in vacuo* to leave 2-(*R*)-(1-carbamoylethyl)carbamic acid *tert*-butyl ester (5.5 g, 92 %) as a colourless powder; mp 90-93 °C (from dichloromethane) (lit.,[20] mp 95-96 °C); υ_{max} ($CHCl_3$)/cm^{-1} 3482, 3436, 1704; δ_H (360 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 1.40 (9H, s, Bu^t), 4.22 (1H, br m, C*H*CH$_3$), 5.53 (1H, br m, N*H*Boc), 6.41 (1H, br s, N*H*$_2$), 6.74 (1H, br s, N*H*$_2$).

Lawesson's reagent[21] (5.82 g, 14.4 mmol) was added as one portion to a stirred solution of the amide (5.46 g, 28.8 mmol) in anhydrous THF (70 mL) at rt under an atmosphere of nitrogen. The resulting solution was stirred at rt for 14 h and concentrated *in vacuo* to leave a green oil. The residue was purified by chromatography on silica using 30 % ethyl acetate in light petroleum as eluant to give the corresponding thioamide (5 g, 85 %) as a pale green/yellow solid; mp 83-84 °C (from dichloromethane) (lit.,[22] mp 85-87 °C); υ_{max} ($CHCl_3$)/cm^{-1} 3524, 3437, 2978, 1697; δ_H (360 MHz, $CDCl_3$) 1.33 (9H, s, Bu^t), 1.36-1.39 (3H, m, C*H*$_3$CH), 4.53 (1H, br, C*H*CH$_3$), 5.66 (1H, br, N*H*Boc); δ_C (90.5MHz, $CDCl_3$) 20.8 (q), 21.7 (d), 28.1 (q), 79.9 (s), 155.2 (s), 210.2 (s).

A solution of the above thioamide (1.4 g, 6.6 mmol) in DMF (9 mL) was stirred with potassium hydrogen carbonate (5.3 g, 52.6 mmol) at rt for 10 min. The solution was cooled to -15 °C and then ethyl bromopyruvate (2.5 mL, 19.7 mmol) was added dropwise over 5 min. The resulting yellow solution was stirred at -15 °C for 10 min and then a precooled mixture of collidine (7.4 mL, 55.9 mmol) and trifluoroacetic anhydride (3.7 mL, 26.3 mmol) in dry DME (9 mL) was then added dropwise over 15 min.

This solution was stirred at -15 °C for a further 15 min and then poured onto ice cold water (40 mL). The separated aqueous layer was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were then washed successively with 10% aqueous citric acid solution (3 x 30 mL), 15 % copper sulfate solution (3 x 30 mL), and brine (3 x 30 mL), and then dried ($MgSO_4$) and evaporated *in vacuo* to leave a brown residue. This residue was purified by chromatography on silica using 30 % ethyl acetate in light petroleum as eluant to give 1'-(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carboxylic acid ethyl ester (1.41 g, 71 %) as a pale yellow solid; mp 88-90 °C (from petroleum ether/ether) (lit.,[23] mp 89.5 °C); $[\alpha]_D$ +34.4° (c = 1.20, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3440, 2980, 2935, 1715, 1488; δ_H (360 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1Hz, C*H*$_3$CH$_2$), 1.33 (9H, s, Bu^t), 1.51 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 4.29 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 4.99-5.01 (1H, m, C*H*CH$_3$), 5.47 (1H, d, *J* 7.2 Hz, N*H*Boc), 7.99 (1H, s, C*H*S); δ_C (90.5MHz, $CDCl_3$) 14.0 (q), 21.3 (q), 27.9 (q), 48.7 (d), 61.1 (t), 79.8 (s), 126.9 (d), 146.8 (s), 154.7 (s), 161.0 (s), 174.9 (s); *m/z* (FAB) Found: 323.1046 (MH^++Na^+, $C_{13}H_{20}N_2O_4NaS$ requires 323.1041).

Sodium hydroxide (416 mg, 10.4 mmol) was added in one portion to a stirred solution of the thiazole ester (390 mg, 1.3 mmol) in THF:H_2O (9:1) (7 mL) at rt, and the mixture was stirred for 2.5 h. The separated aqueous layer was acidified to pH 4 with citric acid and then extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with water (3 x 20 mL) and brine (3 x 20 mL), then dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the thiazole-4-carboxylic acid (291 mg, 82 %) as a colourless solid; mp 127-129 °C (from ethyl acetate/petroleum ether) (lit.,[23] mp 128-129 °C); $[\alpha]_D$ +36.0° (c = 1.0, $CHCl_3$); Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.5; H, 5.9; N, 10.3%; Found: C, 48.3; H, 6.1; N, 9.8. υ_{max} ($CHCl_3$)/cm^{-1} 3440, 2934, 2614, 1711, 1491; δ_H (360 MHz, $CDCl_3$) 1.46 (9H, s, Bu^t), 1.64 (3H, d, *J* 6.7 Hz, C*H*$_3$CH), 5.10-5.12 (1H, m, C*H*CH$_3$ and N*H*Boc), (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 21.5 (q), 28.3 (q), 48.7 (d), 80.4 (s), 128.5 (d), 146.4 (s), 155.0 (s), 164.2 (s).

1'(*R*)-(1-{[1'(*R*)-(-*tert*-Butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)-5-methyl-oxazolecarboxylic acid methyl ester (21)

N-Methylmorpholine (0.19 mL, 1.76 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (338 mg, 1.76 mmol) and *N*-hydroxybenzotriazole (238 mg, 1.76 mmol) were added to a stirred solution of 1'-(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carboxylic acid (**20**) (436 mg, 1.6 mmol) in anhydrous dichloromethane (20 mL) at 0 °C under an atmosphere of nitrogen. The resulting solution was stirred at 0 °C for a further 15 min and then a precooled solution of 1'(*R*)-2-(1-aminoethyl)-

5-methyloxazole-4-carboxylic acid methyl ester hydrobromide (**19**) (353 mg, 1.6 mmol) deprotonated with *N*-methylmorpholine (0.19 mL, 1.76 mmol) in DMF (3 mL) was added dropwise over 5 min. The orange/opaque solution was stirred at 0 °C for 1 h and then at rt for 15 h . 10 % Aqueous citric acid solution (30 mL) was added and the separated aqueous layer was extracted with dichloromethane (5 x 30 mL). The combined organic extracts were washed successively with a saturated solution of sodium hydrogen carbonate (3 x 30 mL), water (3 x 30 mL), and brine (3 x 30 mL), and then dried ($MgSO_4$) and evaporated *in vacuo*. The brown residue was purified by chromatography on silica using 60 % ethyl actetate in light petroleum as eluant to give the thiazole-oxazole (560 mg, 80 %) as a colourless foam; $[\alpha]_D$ +29.6° (c = 1.0, $CHCl_3$); Anal. Calcd for $C_{19}H_{25}N_4O_6S$ + 0.5 H_2O: C, 51.1; H, 5.9; N, 12.6; Found: C, 50.6; H, 5.9; N, 12.6. υ_{max} ($CHCl_3$)/cm^{-1} 3688, 3872, 3606, 1716, 1672, 1622; δ_H (360 MHz, $CDCl_3$) 1.46 (9H, s, Bu^t), 1.60 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 1.68 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 2.62 (3H, s, C*H*$_3$CCO), 3.90 (3H, s, C*H*$_3$CO), 5.06-5.14 (1H, br m. C*H*CH$_3$), 5.06-5.14 (1H, br. m. N*H*Boc), 5.41-5.50 (1H, m, C*H*CH$_3$), 7.74 (1H, d, *J* 8.5 Hz, N*H*CO), 8.03 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 11.3 (q), 18.7 (q), 20.4 (q), 27.7 (d), 30.7 (d), 42.5 (q), 51.1 (q), 79.6 (s), 124.3 (d), 126.7 (s), 148.3 (s), 155.1 (s), 160.1 (s), 161.8 (s), 161.9 (s), 162.2 (s), 162.3 (s); *m/z* (FAB) Found: 473.1471 (M^++ Na^+, $C_{20}H_{26}N_4NaO_6S$ requires 473.1492).

1'(*R*)-2-1'(*R*)-2-(1-{[2-(-*tert*-Butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)-5-methyl-oxazolecarboxylic acid (22)

Sodium hydroxide (365 mg, 9.12 mmol) was added to a stirred solution of the ester (**21)** (500 mg, 1.14 mmol) in THF:H_2O (5:4) (11 mL) at rt and the mixture was stirred at rt for 14 h. The separated aqueous layer was acidified to pH 4 with citric acid and then extracted with ethyl acetate (5 x 20 mL). The combined organic extracts were washed with brine (3 x 20 mL), dried ($MgSO_4$) and then evaporated *in vacuo* to leave the carboxylic acid (470 mg, 97%) as a foam which crystallised as a cream powder; mp 76-78 °C (from ether); $[\alpha]_D$ +36.4° (c = 1.0, $CHCl_3$); Anal. Calcd for $C_{18}H_{24}N_4O_6S$ + H_2O: C, 48.8; H, 5.9; N, 12.6; Found : C, 48.4; H, 5.6; N, 12.0. υ_{max} ($CHCl_3$)/cm^{-1} 3441, 3399, 3206, 1706, 1668, 1622; δ_H (360 MHz, $CDCl_3$) 1.45 (9H, s, Bu^t), 1.57 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 1.70 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 2.63 (3H, s, C*H*$_3$CO), 5.06-5.13 (1H, br s, C*H*CH$_3$), 5.18-5.33 (1H, br s, N*H*Boc), 5.42-5.50 (1H, m, C*H*CH$_3$), 7.95-7.98 (1H, br s, N*H*CO), 8.06 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 11.6 (q), 18.7 (q), 20.8 (q), 27.9 (q), 42.7 (d), 48.2 (d), 79.7 (s), 124.0 (d), 126.9 (s), 148.1 (s), 154.9 (s), 156.0 (s), 160.6 (s), 162.4 (s), 164.0 (s), 172.7 (s); *m/z* (FAB) Found: 447.1275 (MH^++Na^+, $C_{18}H_{24}N_4O_6NaS$ requires 447.1314).

1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-Butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)-5-methyl-oxazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid ethyl ester (24)

N-Methylmorpholine (0.14 mL, 1.26 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (242 mg, 1.26 mmol) and *N*-hydroxybenzotriazole (170 mg, 1.26 mmol) were added to a stirred solution of the oxazole-thiazole carboxylic acid (**22**) (470mg, 1.10 mmol) in anhydrous dichloromethane (12 mL) at 0 °C under an atmosphere of nitrogen. The solution was stirred at 0 °C for 15 min and then a precooled solution of the thiazole amine hydrochloride (**23**) (304 mg, 1.15 mmol) deprotonated with *N*-methylmorpholine (0.14 mL, 1.26 mmol) in DMF (3 mL) was added dropwise over 5 min. The resulting orange solution was stirred at 0 °C for 1 h and then at rt for 16 h. 10% Aqueous citric acid solution (20 mL) was added, and the separated aqueous layer was then extracted with dichloromethane (4 x 30 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (3 x 20 mL), water (3 x 20 mL), and brine (3 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo.* The orange residue was purified by chromatography on silica using 50 % ethyl actetate in light petroleum as eluant to give the hexapeptide (497 mg, 70 %) as a colourless foam; $[\alpha]_D$ +46.4° (c = 1.0, $CHCl_3$); Anal. Calcd for $C_{26}H_{34}N_6O_7S_2 + 2H_2O$: C, 48.6; H, 5.7; N, 10.9; Found: C, 48.0; H, 5.2; N, 11.2. υ_{max} ($CHCl_3$)/cm^{-1} 3400, 2979, 1714, 1668, 1635; δ_H (360 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8 Hz, $(CH_3)_2CH$), 1.02 (3H, d, *J* 6.8 Hz, $(CH_3)_2CH$), 1.39 (3H, t, *J* 7.0 Hz, CH_3CH_2), 1.45 (9H, s, Bu^t), 1.63 (3H, d, *J* 6.9 Hz, CH_3CH), 1.68 (3H, d, *J* 7.0 Hz, CH_3CH), 2.55-2.64 (1H, m, $CH(CH_3)_2$), 2.62 (3H, s, CH_3CO), 4.41 (2H, q, *J* 7.0 Hz, CH_2CH_3), 5.01-5.11 (1H, br s, $CHCH_3$), 5.11-5.26 (1H, br s, NHBoc), 5.29 (1H, dd, *J* 6.7, 9.2 Hz, $CHCHCH_3$), 5.42 (1H, dt, *J* 7.1, 15.4 Hz, $CHCH_3$), 7.57 (1H, d, *J* 9.2 Hz, NHCO), 7.76 (1H, d, *J* 8.4 Hz, NHCO), 8.06 (1H, s, CHS), 8.06 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 11.1 (q), 13.8 (q), 17.4 (q), 18.7 (q), 19.1 (q), 20.2 (q), 27.7 (t), 32.4 (d), 42.4 (d), 48.2 (d), 55.4 (d), 60.7 (q), 79.2 (s), 123.4 (d), 126.6 (s), 127.9 (d), 146.7 (s), 148.3 (s), 153.3 (s), 154.2 (s), 159.9 (s), 160.6 (s), 160.8 (s), 160.9 (s), 171.2 (s), 174.5 (s); *m/z* (FAB) Found: 657.2186 (MH^++Na^+, $C_{28}H_{34}N_6NaO_7S_2$ requires 657.2141).

1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[2-(1-Aminoethyl)thiazole-4-carbonyl]amino}ethyl)-5-methyloxazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid hydrochloride (25)

Sodium hydroxide (247 mg, 6.2 mmol) was added to a solution of the oxazole–*bis*-thiazole ester (**24)** (480 mg, 0.77 mmol) in THF:H_2O (5:4) (8 mL) at rt and the reaction was stirred for 15 h. The separated aqueous layer was acidified to pH 4 with citric acid and the aqueous layer was extracted with dichloromethane (5 x 20 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to leave 1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)-

5-methyloxazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid (446 mg, 0.75 mmol, 97 %) as a colourless foam which crystallised as a colourless powder; mp 108-110 °C (from dichloromethane); $[\alpha]_D$ +42.8° (c = 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3401, 1714, 1667, 1634; δ_H (360 MHz, $CDCl_3$) 0.96-1.06 (6H, m, $(CH_3)_2CH$), 1.47 (9H, s, Bu^t), 1.60-1.62 (3H, m, CH_3CH), 1.68 (3H, d, *J* 7.1 Hz, CH_3CH), 2.51-2.55 (1H, m, $CH(CH_3)_2$), 2.62 (3H, s, CH_3CO), 5.02-5.10 (1H, br m, $CHCH_3$), 5.22-5.28 (1H, br m, $CHCH(CH_3)_2$), 5.22-5.28 (1H, br m, NHBoc), 5.44-5.47 (1H, m, $CHCH_3$), 7.70-7.79 (1H, br. s, NHCO), 7.87-7.91 (1H, br. s, NHCO), 8.07 (1H, s, CHS), 8.09 (1H, CHS); δ_C (90.5 MHz, $CDCl_3$) 11.6 (q), 18.1 (q), 19.2 (q), 19.5 (q), 21.1 (q), 28.1 (q), 32 .7 (d), 43.0 (d), 48.7 (d), 55.9 (d), 80.2 (s), 121.1 (s), 124.6 (d), 128.3 (d), 146.7 (s), 148.4 (s), 154.2 (s), 155.2 (s), 160.8 (s), 161.2 (s), 161.6 (s), 163.5 (s), 173.2 (s), 175.9 (s); *m/z* (FAB) Found: 629.1823 (MH^++Na^+, $C_{26}H_{34}N_6O_7NaS_2$ requires 629.1828).

The Boc amine (400 mg, 0.67 mmol) was stirred with a solution of hydrochloric acid in dioxane (3 mL, 4 M) at rt for 2 h under an atmosphere of nitrogen. The mixture was diluted with ether and the resulting precipitate was filtered to give the amino acid hydrochloride (348 mg, 96 %) as a colourless solid; mp 72-74 °C (from dichloromethane); $[\alpha]_D$ +24.4° (c = 1.0, EtOH); δ_H (360 MHz, CD_3OD) 0.99 (3H, d, *J* 6.7 Hz, $(CH_3)_2CH$), 1.10 (3H, d, *J* 6.7 Hz, $(CH_3)_2CH$), 1.74 (3H, d, *J* 7.0 Hz, CH_3CH), 1.82 (3H, d, *J* 6.9 Hz, CH_3CH), 2.46-2.52 (1H, m, $CH(CH_3)_2$), 2.62 (3H, s, CH_3CO), 4.93-4.98 (1H, m, $CHCH_3$), 5.24 (1H, d, *J* 7.8 Hz, $CHCH(CH_3)_2$), 5.42 (1H, q, *J* 7.0 Hz, $CHCH_3$), 8.36 (1H, s, CHS), 8.42 (1H, s, CHS); δ_C (90.5 MHz, CD_3OD) 18.3 (q), 19.0 (q), 19.9 (q), 20.5 (q), 33.9 (q), 44.4 (d), 49.1 (d), 57.5 (d), 58.1 (d)127.5 (d), 129.3 (s), 129.6 (d), 147.4 (s), 149.6 (s), 153.3 (s), 161.7 (s), 162.6 (s), 163.1 (s), 163.3 (s), 168.6 (s), 173.7 (s); *m/z* (FAB) Found: 507.1451 (MH^+-Cl^-, $C_{21}H_{27}N_6O_5S_2$ requires 507.1484).

(+)-Dendroamide A (4)

Diisopropylethylamine (0.15 mL, 0.84 mmol) was added to a stirred suspension of the amino acid hydrochloride **25** (150 mg, 0.28 mmol) in anhydrous acetonitrile (6 mL) at rt under a nitrogen atmosphere. The solution was stirred for 5 min, and then FDPP (160 mg, 0.42 mmol) was added and the mixture was stirred at rt for 2 h. Water (*ca*. 20 mL) was added and the separated aqueous layer was extracted with dichloromethane (5 x 20 mL). The combined organic extracts were washed successively with 2M sodium hydroxide solution (3 x 20 mL), 2M hydrochloric acid solution (3 x 20 mL), and brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave an orange residue. The residue was purified by chromatography on silica using 80 % ethyl acetate in light petroleum as eluant to give *dendroamide A* (125 mg, 91 %) as a colourless solid; mp 146-148 °C (from dichloromethane) (lit.,[6] no

mp given); $[\alpha]_D$ +66.9° (c = 0.7, $CHCl_3$) (lit.,[6] $[\alpha]_D$ +40.5° (c = 3.5, CH_2Cl_2); λ_{max} (MeOH)/nm 224 (ε/dm^3 mol^{-1}cm^{-1} 279136); υ_{max} ($CHCl_3$)/cm^{-1} 3396, 1716, 1666, 1639; δ_H (360 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.08 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.71 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 1.74 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 2.28-2.37 (1H, m, C*H*(CH$_3$)$_2$), 2.68 (3H, s, C*H*$_3$CO), 5.21 (1H, app. quintet, *J* 6.4 Hz, C*H*CH$_3$), 5.32 (1H, dd, *J* 4.8, 8.2 Hz, C*H*CH(CH$_3$)$_2$), 5.72 (1H, dq, *J* 6.8, 8.2 Hz, C*H*CH$_3$), 8.14 (1H, s, C*H*S), 8.15 (1H, s, C*H*S), 8.49 (1H, d, *J* 8.2 Hz, N*H*CO), 8.56 (1H, d, *J* 8.2 Hz, N*H*CO), 8.65 (1H, d, *J* 6.4 Hz, N*H*CO); δ_C (125 MHz, CD_2Cl_2); 11.7 (q), 18.3 (q), 18.5 (q), 21.1 (q), 25.1 (q), 35.6 (d), 44.6 (d), 47.4 (d), 56.2 (d), 123.8 (d), 124.1 (d), 128.9 (s), 149.2 (s), 149.3 (s), 154.0 (s), 159.7 (s), 160.0 (s), 160.7 (s), 162.2 (s), 168.9 (s), 171.8 (s); *m/z* (FAB) Found: 511.1169 (MH^++Na^+, $C_{21}H_{24}N_6O_4NaS_2$ requires 511.1198).

1'(*S*)-2-(1-Benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carboxylic acid (27)

N-Methylmorpholine (3.4 mL, 31.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.0 g, 31.2 mmol) and *N* - hydroxybenzotriazole (4.2 g, 31.2 mmol) were added to a stirred solution of CbZ-protected (*L*)-alanine[18] (6.3 g, 28.4 mmol) in anhydrous dichloromethane (400 mL) at 0 °C under an atmosphere of nitrogen. The resulting mixture was stirred for 20 min at 0 °C and then a precooled solution of (*D, L*) - threonine methyl ester hydrochloride (4.8 g, 28.4 mmol) deprotonated with *N*-methylmorpholine (3.4 mL, 31.2 mmol) in DMF (4 mL) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and then at rt for 14 h. Water (*ca*. 40 mL) was added, the aqueous layer separated and extracted with ethyl acetate (4 x 40 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (3 x 40 mL), water (3 x 40 mL), and brine (3 x 40 mL), then dried ($MgSO_4$) and evaporated *in vacuo*. The yellow residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to give 2'(*S*)-2-(2-benzyloxycarbonylamino-propionylamino)-3-hydroxybutyric acid methyl ester (7.88 g, 82 %) as a viscous oil; υ_{max} ($CHCl_3$)/cm^{-1} 3428, 2541, 1715, 1682; δ_H (360 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.4 Hz, C*H*$_3$CHOH), 1.40 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 3.73 (3H, s, C*H*$_3$O), 4.31-4.41 (1H, br m, C*H*(OH)CH$_3$), 4.31-4.41 (1H, m, C*H*CH$_3$), 4.58-4.61 (1H, m, C*H*CO$_2$Me), 5.03-5.08 (2H, m, C*H*$_2$Ph), 5.84 (1H, d, *J* 7.8 Hz, N*H*CbZ), 7.22 (1H, d, *J* 8.9 Hz, N*H*CO), 7.29-7.40 (5H, m, ArH); δ_C (90.5 MHz, CD_3OD) 16.3 (q), 18.2 (q), 49.8 (q), 50.8 (d), 56.9 (d), 65.5 (t), 66.3 (d), 126.7 (d), 126.8 (d), 127.3 (d), 155.8 (s), 171.3 (s), 173.5 (s); *m/z* (FAB) Found: 361.1336 (M^+ + Na^+, $C_{16}H_{22}N_2O_6Na$ requires 361.1376).

Dess-Martin periodinane[19] (7.8 g, 18.4 mmol) was added in one portion to a solution of the above 3-hydroxy ester (5.0 g, 14.2 mmol) in anhydrous dichloromethane (80 mL) at rt under an atmosphere of

nitrogen. The resulting mixture was stirred for 4 h at rt, and then the volatiles were removed *in vacuo* to leave a solid orange residue. The residue was purified by chromatography on silica using 50 % ethyl acetate in light petroleum as eluant to give 2'(*S*)-2-(2-benzyloxycarbonylaminopropionylamino)-3-oxobutyric acid methyl ester (3.1 g, 9.1 mmol, 64 %) as a colourless solid; mp 118-119 °C (from dichloromethane) (lit.,[20] mp 122-123 °C); υ_{max} ($CHCl_3$)/cm^{-1} 3423, 2957, 1757, 1729, 1685; δ_H (360 MHz, $CDCl_3$) 1.42 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 2.39 (3H, s, C*H*$_3$COCH), 3.82 (3H, s, C*H*$_3$OCO), 4.35-4.40 (1H, m, C*H*CH$_3$), 5.14 (2H, s, C*H*$_2$Ph), 5.24 (1H, d, *J* 6.5 Hz, C*H*CO$_2$Me), 5.31 (1H, d, *J* 7.6 Hz, N*H*CbZ), 7.15-7.21 (1H, br s, N*H*CO), 7.32-7.46 (5H, m, Ar*H*); δ_C (90.5 MHz, $CDCl_3$) 18.3 (q), 27.7 (q), 50.1 (d), 53.1 (q), 62.7 (d), 66.8 (t), 127.8 (d), 127.9 (d), 128.3 (d), 155.8 (s), 166.3 (s), 172.6 (s), 198.3 (s); *m/z* (FAB) Found: 359.1219 (M^++Na^+, $C_{16}H_{20}N_2O_6Na$ requires 359.1219).

A solution of the 3-oxomethyl ester (3.1 g, 9.3 mmol) in anhydrous THF (9 mL) at -78 °C was added dropwise over 5 min to a solution of triphenylphosphine (5.4 g, 20.5 mmol), iodine (2.4 g, 18.6 mmol) and triethylamine (4.7 mL, 33.5 mmol) in anhydrous THF (32 mL) at -78 °C under an atmosphere of nitrogen. The resulting mixture was allowed to stir at -78 °C for 5 h and at rt for 15 h. Water (*ca.* 50 mL) was added and the separated aqueous layer was then extracted with dichloromethane (4 x 40 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (2 x 40 mL), 2M hydrochloric acid solution (2 x 40 mL) and brine (2 x 40 mL), were then dried ($MgSO_4$) and evaporated *in vacuo*. The solid yellow residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to leave 1'(*S*)-2-(1-benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carboxylic acid methyl ester (2.2 g, 75 %) as a colourless solid; mp 126-128 °C (from dichloromethane) (lit.,[20] mp 125.5-126 °C); $[\alpha]_D$ -33.6° (c = 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3433, 2954, 1722, 1624; δ_H (360 MHz, $CDCl_3$) 1.57 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 2.61 (3H, s, C*H*$_3$CO), 3.91 (3H, s, C*H*$_3$O), 5.02 (1H, dq, *J* 5.5, 7.9 Hz, C*H*CH$_3$), 5.12-5.13 (2H, m, C*H*$_2$Ar), 5.42 (1H, d, *J* 7.9 Hz, N*H*CbZ), 7.29-7.37 (5H, m, Ar*H*); δ_C (90.5 MHz, $CDCl_3$); 11.9 (q), 19.7(q), 44.8 (d), 51.7 (q), 66.7 (t), 127.8 (d), 127.9 (d), 128.2 (d), 135.9 (s), 155.3 (s), 156.3 (s), 162.3 (s), 162.3 (s); *m/z* (FAB) Found: 341.1118 (M^++Na^+, $C_{16}H_{18}N_2O_5Na$ requires 341.1113).

A solution of sodium hydroxide (900 mg, 22.6 mmol) in water (9 mL) was added to a solution of the above oxazole methyl ester (0.9 g, 2.83 mmol) in ethanol (27 mL) at rt. The solution was stirred for 3 h, and then the volatiles were removed *in vacuo* and the residue was diluted with hydrochloric acid solution (20 mL, 2M). The precipitated oxazole-4-carboxylic acid (792 mg, 92 %) was collected by suction filtration and recrystallised as a colourless solid; mp. 166-168 °C (from ether); $[\alpha]_D$ -68.7° (c = 1.0,

$CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3441, 2998, 1723; δ_H (360 MHz, CD_3OD) 1.55 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 2.61 (3H, s, C*H*$_3$CO), 4.91-4.97 (1H, m, C*H*CH$_3$), 5.12 (2H, br s, C*H*$_2$Ar), 6.48-6.55 (1H, br s, N*H*CbZ) 7.31-7.39 (5H, m, Ar*H*); δ_C (125 MHz, CD_3OD); 13.0 (q), 20.2 (q), 47.3 (d), 68.7 (t), 129.9 (d), 130.1 (d), 130.2 (d), 139.2 (s), 158.3 (s), 159.1 (s), 165.3 (s), 166.5 (s); *m/z* (FAB) Found: 327.0952 (M^++Na^+, $C_{15}H_{16}N_2O_5Na$ requires 327.0957).

1'(*R*)-2-({[1'(*R*)-2-(1-Benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carbonyl]amino}-methyl)thiazole-4-carboxylic acid ethyl ester (28)

N-Methylmorpholine (0.08 mL, 0.76 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (146 mg, 0.76 mmol) and *N*-hydroxybenzotriazole (103 mg, 0.76 mmol) were added to a solution of the oxazole-4-carboxylic acid (**27**) (210 mg, 0.7 mmol) in anhydrous dichloromethane (8 mL) at 0 °C under an atmosphere of nitrogen. The resulting solution was stirred for 20 min and then a precooled solution of the thiazole amine hydrochloride (**26**)[15j] (183 mg, 0.82 mmol) deprotonated with *N*-methylmorpholine (0.08 mL, 0.76 mmol) in DMF (1 mL) was added dropwise over 5 min. This solution was stirred at 0 °C for 1 h and at rt for 18 h. Water (*ca*. 20 mL) was added and the separated aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed successively with 10 % aqueous citric acid solution (3 x 10 mL), saturated sodium hydrogen carbonate solution (3 x 10 mL) and brine (3 x 10 mL), was then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 40 % ethyl acetate in light petroleum as eluant to give the thiazole-oxazole amine CbZ (208 mg, 60 %) as a cream foam; $[\alpha]_D$ -231.7° (c = 0.53, CH_3Cl); υ_{max} ($CHCl_3$): 3422, 2983, 2938, 1715, 1668; δ_H (360 MHz, $CHCl_3$) 1.36 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 1.49 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 2.57 (3H, s, C*H*$_3$CO), 4.38 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 4.85 (2H, d, *J* 6.5 Hz, C*H*$_2$NH), 4.86-4.95 (1H, m, C*H*CH$_3$), 5.08 (2H, s, C*H*$_2$Ph), 5.62 (1H, br s, N*H*CbZ), 7.28-7.31 (5H, m, Ar*H*), 8.09 (1H, s, C*H*S); δ_C (90.5 MHz, $CHCl_3$) 11.1 (q), 13.8 (q), 18.9 (q), 30.8 (d), 39.9 (t), 60.9 (t), 66.3 (d), 127.5 (d), 127.6 (d), 127.6 (d), 127.9 (d), 135.9 (s), 146.3 (s), 153.3 (s), 155.3 (s), 160.7 (s), 161.3 (s), 161.6 (s), 168.7 (s); *m/z* (FAB) Found: 473.1517 ($M^+ + H^+$, $C_{22}H_{25}N_4O_6S$ requires 473.1495).

1'(*R*)-2-({[1'(*R*)-2-(1-Aminoethyl)-5-methyloxazole-4-carbonyl]amino}methyl)thiazole-4-carboxylic acid ethyl ester hydrobromide (29)

A solution of the amine CbZ (**28**) (208 mg, 0.44 mmol) in 33 % hydrobromic acid in acetic acid (1 mL) and glacial acetic acid (0.6 mL) was stirred at rt for 3 h under an atmosphere of nitrogen. The volatiles were removed *in vacuo* to leave the free amine hydrobromide (168 mg, 91 %) as a brown, highly

hygroscopic powder; $[\alpha]_D$ -18.0° (c = 0.4, EtOH); δ_H (360 MHz, CD_3OD) 1.44 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 1.77 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 2.69 (3H, s, C*H*$_3$CO), 4.45 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 4.69-4.87 (1H, m, C*H*CH$_3$), 4.97-5.01 (2H, m, C*H*$_2$NH), 8.51 (1H, s, C*H*S); δ_C (90.5 MHz, CD_3OD) 12.1 (q), 14.5 (q), 17.8 (q), 40.0 (t), 45.5 (d), 63.9 (t), 129.1 (s), 131.8 (d), 140.0 (s), 156.4 (s), 158.5 (s), 158.6 (s), 163.3 (s), 177.2 (s); *m/z* (FAB) Found: 361.0948 (M^+ - HBr + Na^+, $C_{14}H_{18}N_4O_4NaS$ requires 361.0946).

1'(*R*)-2-({[1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-Butoxycarbonylamino-2-methylpropyl)thiazole-4-carbonyl]-amino}ethyl)-5-methyloxazole-4-carbonyl]amino}methyl)thiazole-4-carboxylic acid ethyl ester (31)

N-Methylmorpholine (0.06 mL, 0.53 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (102 mg, 0.53 mmol) and *N*-hydroxybenzotriazole (72 mg, 0.53 mmol) were added to a solution of the thiazole-4-carboxylic acid (**30**)[24] (143 mg, 0.48 mmol) in anhydrous dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 20 min and then a precooled solution of the amine hydrobromide (**29**) (200 mg, 0.48 mmol), deprotonated with *N*-methylmorpholine (0.06 mL, 0.53 mmol) in DMF (1 mL), was added dropwise over 5 min. This solution was stirred at 0 °C for 1 h and then at rt for 15 h. Water (*ca*. 20 mL) was added and the separated aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed successively with 10 % aqueous citric acid solution (3 x 20 mL), saturated sodium hydrogen carbonate solution (3 x 20 mL) and brine (2 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica using 70 % ethyl acetate in light petroleum as eluant gave the oxazole-*bis*-thiazole-4-carboxylic acid ethyl ester (20 mg, 26 %) as a colourless foam; $[\alpha]_D$ +5.0° (c = 0.4, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3408, 2929, 1716, 1669; δ_H (360 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.00 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.40 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 1.46 (9H, s, Bu^t), 1.66 (3H, s, C*H*$_3$CO), 4.43 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 4.80-4.87 (1H, m, C*H*CH$_3$), 4.92 (2H, d, *J* 6.5 Hz, C*H*$_2$NH), 5.14 (1H, d, *J* 8.2 Hz, N*H*Boc), 5.38-5.43 (1H, m, C*H*CH(CH$_3$)$_2$), 7.61-7.65 (1H, m, N*H*CO), 7.61-7.65 (1H, m, N*H*CO), 8.05 (1H, s, C*H*S), 8.13 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 11.7 (q), 14.4 (q), 17.4 (q), 19.4 (q), 28.3 (q), 33.2 (q), 40.4 (d), 42.3 (d), 58.1 (d), 61.5 (d), 123.5 (d), 128.1 (d), 128.4 (s), 134.3 (s), 138.2 (s), 146.9 (s), 154.1 (s), 155.4 (s), 160.3 (s), 161.3 (s), 162.0 (s); *m/z* (FAB) Found: 643.1928 (M^+ + Na^+, $C_{27}H_{36}N_6O_7NaS_2$ requires 643.1985).

Nostocyclamide (6)

Sodium hydroxide (12 mg, 0.26 mmol) was added to a solution of the oxazole-*bis*-thiazolecarboxylic acid ester (**31**) (40 mg, 0.06 mmol) in THF:H_2O (5:3) (2 mL) at rt. The solution was stirred for 15 h, then

ethyl acetate (*ca*. 1 mL) was added and the separated aqueous layer was acidified to pH 4 with citric acid. The aqueous layer was extracted with ethyl acetate (5 x 20 mL) and the combined organic extracts were then washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated *in vacuo* to leave the carboxylic acid as a pale yellow foam. The residue was stirred with a 4M solution of hydrochloric acid in dioxane (1 mL) at rt for 1 h under an atmosphere of nitrogen and then the dioxane was removed *in vacuo,* using toluene as an azeotrope to leave the oxazole-*bis*-thiazole amino acid (**32**) as a highly hygroscopic yellow solid, which was used immediately.

Diisopropylethylamine (0.02 mL, 0.12 mmol), and FDPP (23 mg, 0.06 mmol) were added to a solution of the macrocyclic precursor (**32**) in anhydrous acetonitrile (1.5 mL) at rt under an atmosphere of nitrogen. The solution was stirred for 14 h, then water (*ca*. 10 mL) was added and the separated aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic extracts were washed successively with 10 % aqueous citric acid solution (3 x 10 mL), saturated sodium hydrogen carbonate solution (3 x 10 mL) and brine (2 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a colourless solid residue. The residue was purified by chromatography on silica using 80 % ethyl acetate in light petroleum as eluant to give nostocyclamide (3 mg, 10 %) as a colourless solid; mp 255-257 °C (lit.,[7] mp 259-260 °C); $[\alpha]_D$ +46.4° (c = 0.2, $CHCl_3$) (lit.,[17] $[\alpha]_D$ +51.3° (0.84, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3396, 3125, 3006, 2966, 2929, 1666, 1642; δ_H (360 MHz, $CDCl_3$) 0.95 (3H, d, *J* 7.1 Hz, (CH_3)$_2$CH), 0.97 (3H, d, *J* 7.1 Hz, (CH_3)$_2$CH), 1.70 (3H, d, *J* 6.6 Hz, CH_3CH), 2.31-2.35 (1H, m, CH(CH_3)$_2$), 2.71 (3H, s, CH_3O), 4.79 (1H, d, *J* 17.6, CH_2NH), 4.99 (1H, d, *J* 17.6 CH_2NH), 5.10-5.14 (1H, m, $CHCH_3$), 5.65 (1H, d, *J* 3.3 Hz, CHCH(CH_3)$_2$), 7.53 (1H, d, *J* 6.1 Hz, NHCO), 7.81 (1H, d, *J* 7.1 Hz, NHCO), 7.84 (1H, d, *J* 7.1 Hz, NHCO), 8.16 (1H, s, CHS), 8.19 (1H, s, CHS); *m/z* (FAB) Found: 497.1042 ($M^+ + Na^+$, $C_{20}H_{22}N_6O_4NaS_2$ requires 497.1046).

Synthesis of the structural isomer (33) of dendroamide A

N-Methylmorpholine (0.1 mL, 0.9 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (173 mg, 0.9 mmol) and *N*-hydroxybenzotriazole (122 mg, 0.9 mmol) were added to a solution of the thiazole-4-carboxylic acid (**30**)[24] (235 mg, 0.82 mmol) in anhydrous dichloromethane (10 mL) at 0 °C under an atmosphere of nitrogen. The solution was stirred at 0 °C for 15 min, and then a precooled solution of the oxazole amine hydrobromide (**19**) (218 mg, 0.82 mmol) deprotonated with *N*-methylmorpholine (0.1 mL, 0.9 mmol) in DMF (2 mL) was added dropwise over 5 min. The resulting solution was stirred at 0 °C for 1 h, and then at rt for 16 h. Water (*ca*. 30 mL) was added and the separated aqueous layer was then extracted with dichloromethane (4 x 20 mL). The combined organic

extracts were washed with 10% aqueous citric acid solution (3 x 20 mL), and saturated aqueous sodium hydrogen carbonate solution (3 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 30 % ethyl acetate in light petroleum as eluant to give 1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-butoxycarbonylamino-2-methylpropyl)thiazole-4-carbonyl]amino}ethyl)-5-methyloxazole-4-carboxylic acid methyl ester (244 mg, 64 %) as a colourless foam; $[\alpha]_D$ +19.6° (c = 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3696, 3605, 1715, 1669, 1622; δ_H (500 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.9 Hz, (CH_3)$_2$CH), 1.00 (3H, d, *J* 6.9 Hz, (CH_3)$_2$CH), 1.47 (9H, s, Bu^t), 1.70 (3H, d, *J* 7.1 Hz, CH_3CH), 2.34-2.41 (1H, m, (C*H*(CH_3)$_2$), 2.63 (3H, s, CH_3CO), 3.91 (3H, s, CH_3OCO), 4.84-4.88 (1H, m, C*H*CH(CH_3)$_2$), 5.16 (1H, d, *J* 8.4 Hz, N*H*Boc), 5.46 (1H, dq, *J* 7.1, 8.6 Hz, C*H*CH_3), 7.69 (1H, d, *J* 8.6 Hz, N*H*CO), 8.04 (1H, s, C*H*S); δ_C (125 MHz, $CDCl_3$) 11.8 (q), 17.5 (q), 19.3 (q), 19.4 (q), 28.1 (q), 32.7 (d), 42.8 (q), 51.7 (d), 57.7 (d), 79.9 (s), 123.3 (d), 127.2 (s), 149.1 (s), 155.2 (s), 156.3 (s), 160.3 (s), 162.3 (s), 162.4 (s), 172.4 (s); *m/z* (FAB) Found: 489.1759 ($MH^+ + Na^+$, $C_{21}H_{31}N_4O_6NaS$ requires 489.1784).

A 4M solution of hydrochloric acid in dioxane (2 mL) was added to 1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-butoxycarbonylamino-2-methylpropyl)thiazole-4-carbonyl]amino}ethyl)-5-methyl-oxazole-4-carboxylic acid methyl ester at rt under an atmosphere of nitrogen. The solution was stirred for 1 h and then the dioxane was removed *in vacuo* using toluene as an azeotrope to leave the amine hydrochloride salt (225 mg, 98 %) as a pale yellow foam: $[\alpha]_D$ +2.4° (c = 0.5, EtOH); δ_H (360 MHz, CD_3OD) 1.07 (3H, d, *J* 6.4 Hz, (CH_3)$_2$CH), 1.18 (3H, d, *J* 6.4 Hz, (CH_3)$_2$CH), 1.73 (3H, d, *J* 6.9 Hz, CH_3CH), 2.45-2.48 (1H, m, C*H*(CH_3)$_2$), 2.64 (3H, s, CH_3CO), 3.91 (3H, s, CH_3OCO), 4.77-4.79 (1H, m, C*H*CH_3), 5.38-5.40 (1H, m, C*H*(CH_3)$_2$), 8.41 (1H, s, C*H*S), 8.75 (1H, br s, N*H*CO); δ_C (90.5 MHz, CD_3OD) 10.1 (q), 16.5 (q), 16.7 (q), 16.9 (q), 31.5 (q), 42.6 (d), 50.4 (d), 56.8 (d), 125.3 (d), 126.1 (s), 147.7 (s), 156.0 (s), 160.1 (s), 161.7 (s), 162.0 (s), 164.1 (s); *m/z* (FAB) Found: 367.1459 (MH^++Na^+, $C_{16}H_{23}N_4O_4S$ requires 367.1440).

N-Methylmorpholine (0.06 mL, 0.57 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (110 mg, 0.57 mmol) and *N*-hydroxybenzotriazole (77 mg, 0.57 mmol) were added to a stirred solution of 1'-(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carboxylic acid (**20**) (142 mg, 0.52 mmol) in anhydrous dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred for 20 min at 0 °C, and then a precooled solution of the above amine (210 mg, 0.52 mmol) deprotonated with *N*-methylmorpholine (0.06 mL, 0.57 mmol) in DMF (2 mL) was then added dropwise over 5 min. The solution was stirred at 0 °C for 1 h, and then at rt for 16 h. Water (*ca*. 20 mL) was added

and the separated aqueous layer was then extracted with dichloromethane (4 x 20 mL). The combined organic extracts were washed with 10% aqueous citric acid solution (3 x 10 mL), and saturated aqueous sodium hydrogen carbonate solution (3 x 10 mL), and then dried ($MgSO_4$) and evaporated *in vacuo* . The residue was purified by chromatography on silica using 60 % ethyl acetate in light petroleum as eluant to give 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carbonyl]amino}ethyl)-5-methyloxazole-4-carboxylic acid methyl ester (207 mg, 62 %) as a colourless foam which crystallised as a colourless powder; mp 78-84 °C (from dichloromethane); $[\alpha]_D$ +6.4° (c = 0.5, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3401, 2970, 1716, 1672, 1622; δ_H (360 MHz, $CDCl_3$) 1.05 (6H, d, *J* 6.4 Hz, (CH_3)$_2$CH), 1.46 (9H, s, Bu^t), 1.63 (3H, d, *J* 6.5 Hz, CH_3CH), 1.70 (3H, d, *J* 7.1 Hz, CH_3CH), 2.52-2.62 (1H, m, CH(CH_3)$_2$), 2.62 (3H, s, CH_3CO), 3.90 (3H, s, CH_3OCO), 5.11 (1H, br s, NHBoc), 5.11 (1H, br s, $CH$$CH_3$), 5.33 (1H, dd, *J* 6.4, 9.1 Hz, CHCH(CH_3)$_2$), 5.41-5.49 (1H, m, $CH$$CH_3$), 7.71 (1H, d, *J* 8.3 Hz, NHCO), 7.83 (1H, d, *J* 9.1 Hz, NHCO), 8.04 (1H, s, CHS), 8.06 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 11.8 (q), 17.7 (q), 19.4 (q), 19.5 (q), 28.1 (d), 32.6 (d), 42.8 (d), 51.7 (q), 56.1 (d), 79.9 (s), 123.5 (d), 123.7 (d), 127.2 (s), 148.8 (s), 149.1 (s), 154.8 (s), 154.9 (s), 156.3 (s), 160.2 (s), 160.6 (s), 162.3 (s), 171.4 (s), 175.0 (s); *m/z* (FAB) Found: 643.1958 (MH^++Na^+, $C_{27}H_{36}N_6O_7NaS_2$ requires 643.1985).

Sodium hydroxide (51 mg, 1.28 mmol) was added to a solution of 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carbonyl]amino}ethyl)-5-methyloxazole-4-carboxylic acid methyl ester (207 mg, 0.32 mmol) in THF:H_2O (5:4) (4 mL) at rt. The solution was stirred for 5 h, and the separated aqueous layer was then acidified to pH4 with citric acid and then extracted with dichloromethane (4 x 15 mL). The combined organic extracts were washed with water (2 x 10 mL) and brine (2 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow oil. The oil was stirred with a 4M solution of hydrochloric acid in dioxane (4 mL) at rt for 2 h under an atmosphere of nitrogen. The dioxane was removed *in vacuo* using toluene as an azeotrope to leave 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[1'(*R*)-(1-aminoethyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carbonyl]amino}ethyl)-5-methyloxazole-4-carboxylic acid hydrochloride (115 mg, 82 %) as a hygroscopic cream solid; $[\alpha]_D$ -129.1° (c = 0.37, EtOH); δ_H (360 MHz, CD_3OD) 1.05 (3H, d, *J* 6.5 Hz, (CH_3)$_2$CH), 1.14 (3H, d, *J* 6.5 Hz, (CH_3)$_2$CH), 1.72 (3H, d, *J* 6.9 Hz, CH_3CH), 1.84 (3H, d, *J* 6.8 Hz, CH_3CH), 2.46-2.60 (1H, m, CH(CH_3)$_2$), 2.65 (3H, s, CH_3CO), 4.95-5.03 (1H, m, $CH$$CH_3$), 5.22-5.25 (1H, m, CHCH(CH_3)$_2$), 5.38-5.42 (1H, m, $CH$$CH_3$), 8.25 (1H, s, CHS), 8.41 (1H, s, CHS); *m/z* (FAB) Found: 507.1455 (M^+-Cl^-, $C_{21}H_{27}N_6O_5S_2$ requires 507.1484).

Diisopropylethylamine (0.1 mL, 0.6 mmol) and FDPP (115 mg, 0.3 mmol) were added to a suspension of 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[1'(*R*)-(1-aminoethyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carbonyl]amino}ethyl)-5-methyloxazole-4-carboxylic acid hydrochloride (100 mg, 0.3 mmol) in anhydrous acetonitrile (3 mL) at rt under an atmosphere of nitrogen. The solution was stirred at rt for 14 h, water (*ca.* 20 mL) was then added and the separated aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic extracts were washed with 2M hydrochloric acid solution (3 x 10 mL) and saturated sodium hydrogen carbonate solution (3 x 10 mL), then dried ($MgSO_4$), and evaporated *in vacuo* to leave a colourless solid residue. The residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to give the *cyclic peptide* (68 mg, 76 %) as a colourless powder; mp 145-147 °C (from dichloromethane); $[\alpha]_D$ +61.1° (c = 0.7, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3395, 2969, 1687, 1640; δ_H (360 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.09 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.69 (3H, d, *J* 6.8 Hz, CH_3CH), 1.73 (3H, d, *J* 6.8 Hz, CH_3CH), 2.29 (1H, dq, *J* 6.8, 13.5 Hz, CH(CH_3)$_2$), 2.69 (3H, s, CH_3CO), 5.24-5.31 (1H, m, CHCH$_3$), 5.39-5.49 (1H, m, CHCH$_3$), 5.39-5.49 (1H, m, CHCH(CH_3)$_2$), 8.11 (1H, s, CHS), 8.15 (1H, s, CHS), 8.44 (1H, d, *J* 9.1 Hz, NHCO), 8.60-8.65 (1H, m, NHCO); δ_C (90.5 MHz, $CDCl_3$) 11.6 (q), 18.5 (q), 18.8 (q), 20.8 (q), 24.9 (q), 35.5 (d), 43.9 (d), 47.5 (d), 55.7 (d), 123.2 (d), 124.2 (d), 131.6 (s), 148.6 (s), 149.2 (s), 153.9 (s), 159.6 (s), 159.8 (s), 160.5 (s), 161.6 (s), 168.3 (s), 171.3 (s); *m/z* (FAB) Found: 511.1231 (M^++Na^+, $C_{21}H_{24}N_6O_4NaS_2$ requires 511.1198).

Synthesis of the (*R*),(*R*),(*R*)-alanine *tris*-thiazole Cyclopeptide (34a)

A 4M solution of hydrochloric acid in dioxane (2 mL) was added to 1'-(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carboxylic acid (**20**) (291 mg, 1.07 mmol) at rt under an atmosphere of nitrogen, and the mixture was then stirred for 2 h. The dioxane was removed *in vacuo* by azeotroping with toluene to leave 1'-(*R*)-2-(1'-aminoethyl)thiazole-4-carboxylic acid hydrochloride (190 mg, 86 %) as a hygroscopic cream solid; mp 262-264 °C (from ethanol ether) (lit.,[25] mp 265-267 °C); $[\alpha]_D$ +0.4° (c = 1, EtOH); Anal. Calcd for $C_6H_9N_2O_2ClS$: C, 34.6; H, 4.4; N, 13.5; Found : C, 34.1; H, 4.2; N, 13.1. δ_H (360 MHz, CD_3OD) 1.79 (3H, d, *J* 6.9 Hz, CH_3CH), 4.94 (1H, app q, *J* 6.9 Hz, CHCH$_3$), 8.52 (1H, s, CHS); δ_C (125 MHz, CD_3OD); 20.2 (q), 48-50 (d) (obs., by CD_3OD), 130.9 (d), 148.4 (s), 163.9 (s) ; *m/z* (FAB) Found: 485.0512 (MH^++Na^+, $C_{18}H_{18}N_6O_3NaS_3$ requires 485.0500).

Diisopropylethylamine (0.48 mL, 2.76 mmol) was added dropwise over 5 min to a stirred solution of 1'-(*R*)-2-(1'-aminoethyl)thiazole-4-carboxylic acid (190 mg, 0.92 mmol) in anhydrous acetonitrile (18 mL) at rt under a nitrogen atmosphere. The solution was stirred at rt for 5 min, then FDPP (530 mg, 1.38

mmol) was added in one portion and the mixture was stirred at rt for 3 days. The solvent was removed *in vacuo* to leave a yellow residue which was taken up in dichloromethane (*ca.* 30 mL) and washed successively with 2M hydrochloric acid solution (4 x 20 mL), 2M sodium hydroxide solution (3 x 20 mL), and brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum to 90 % ethyl acetate in light petroleum (40-60°C) as eluants to give: i) the *cyclic peptide* (58 mg, 0.38 mmol, 41%) as a colourless powder; mp 298-300 °C (from dichloromethane); $[\alpha]_D$ +48.1° (c = 1, $CHCl_3$); Anal. Calcd for $C_{18}H_{18}N_6O_3S_3$ requires: C, 46.8; H, 3.9; Found : C, 46.8; H, 4.1. λ_{max} (EtOH)/nm 228 (ε/dm^3 mol^{-1}cm^{-1} 1916); υ_{max} ($CHCl_3$)/cm^{-1} 3402, 2977, 1663; δ_H (360 MHz, $CDCl_3$) 1.74 (9H, d, *J* 6.8 Hz, C*H*$_3$CH), 5.64 (3H, app. quintet, *J* 6.8 Hz, C*H*CH$_3$), 8.17 (3H, s, C*H*S), 8.68 (3H, d, *J* 6.8 Hz, N*H*CO); δ_C (125 MHz, $CDCl_3$); 25.0 (q), 47.4 (d), 124.0 (d), 148.8 (s), 159.5 (s), 171.2 (s) ; *m/z* (FAB) Found: 485.0512 (MH^++Na^+, $C_{18}H_{19}N_6O_3NaS_3$ requires 485.0500), and ii) the corresponding *cyclic octa-peptide* (18 mg, 0.09 mmol, 10 %) as a colourless powder; mp 268-271 °C (from dichloromethane); $[\alpha]_D^{293}$ +17.1° (c = 0.7°, $CHCl_3$); λ_{max} (EtOH)/nm 225 (ε/dm^3 mol^{-1}cm^{-1} 55593); υ_{max} ($CHCl_3$)/cm^{-1} 3632, 3402, 2928, 2856, 1715, 1665, 1543, 1462, 1297, 1016; δ_H (360 MHz, $CDCl_3$) 1.86 (12H, d, *J* 6.9 Hz, C*H*$_3$CH), 5.61 (4H, app. quintet, *J* 6.9 Hz, C*H*CH$_3$), 7.99 (4H, d, *J* 8.1 Hz, N*H*CO*)*, 8.12 (4H, s, C*H*S); δ_C (125 MHz, $CDCl_3$) 21.2 (q), 46.0 (d), 124.8 (d), 148.2 (s), 159.9 (s), 170.8 (s); *m/z* (FAB) Found: 639.0666 (MH^+,+ Na^+, $C_{24}H_{25}N_8O_4NaS_4$ requires 639.0701).

Synthesis of the (*R*),(*R*),(*R*)-valine *tris*-thiazole Cyclopeptide (34b)

Diisopropylethylamine (0.48 mL, 0.51 mmol) was added dropwise over 5 min to a stirred solution of 1'-(*R*)-2-(1'-aminoethyl)thiazole-4-carboxylic acid hydrochloride[25] (120mg, 0.51 mmol) in anhydrous acetonitrile (18 mL) at rt under a nitrogen atmosphere. The solution was stirred at rt for 5 min, then FDPP (268 mg, 0.75 mmol) was added in one portion and the mixture was stirred at rt for 3 days. The solvent was removed *in vacuo* to leave a yellow residue which was taken up in dichloromethane (*ca.* 30 mL) and washed successively with 2M hydrochloric acid solution (4 x 20 mL), 2M sodium hydroxide solution (3 x 20 mL), and brine (2 x 20 mL), and then dried ($MgSO_4$) and evaporated *in vacuo*. The colourless residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum to 90 % ethyl acetate in light petroleum (40-60%) as eluants to give; i) the *cyclic peptide* (**34a**) (58 mg, 41%) as a colourless powder; mp 152-154 °C (from dichloromethane); $[\alpha]_D$ +126.3° (c = 1, $CHCl_3$); Anal. Calcd for $C_{24}H_{30}N_6O_3S_3$ requires C, 52.7; H, 5.5; N, 15.0; Found C, 52.5; H, 5.6; N, 15.0. δ_H (360 MHz, $CDCl_3$) 1.05 (9H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.10 (9H, d, *J* 6.8 Hz, 5.64, (C*H*$_3$)$_2$CH), 2.30 (3H, m,

C*H*(CH_3)$_2$), 5.43 (3H, dd, *J* 5.8, 9.3 Hz, C*H*CH(CH_3)$_2$), 8.09 (3H, s, C*H*S), 8.45 (3H, d, *J* 9.3 Hz, N*H*CO); δ_C (90 MHz, $CDCl_3$); 18.3 (q), 18.8 (q), 35.3 (d), 55.4 (d), 123.4 (d), 149.1 (s), 159.7 (s), 168.6 (s); *m/z* (FAB) Found: 547.1582 ($M+H^+$, $C_{24}H_{31}N_6O_3S_3$ requires 547.1620), and ii) the corresponding *cyclic octa-peptide* (18 mg, 10 %) as a colourless powder; mp 152-154 ˚C (from ether); $[\alpha]_D^{297}$ +204.6° (c = 0.57, $CHCl_3$); Anal. Calcd for $C_{32}H_{40}N_8O_4S_4.0.5\ H_2O$ requires C, 50.9; H, 5.7; N, 14.8; Found C, 50.9; H, 5.5; N, 14.6. δ_H (360 MHz, $CDCl_3$), 1.04 (12H, d, *J* 6.6Hz, (C*H*$_3$)$_2$), 1.17 (12H, d, *J* 6.7 Hz, (C*H*$_3$)$_2$), 2.59 (4H, m, C*H*(CH_3)$_2$), 5.22 (4H, dd, *J* 8.2, 9.1Hz, C*H*CH(CH_3)$_2$), 7.84 (4H, d, *J* 9.1 Hz, N*H*CO), 8.06 (4H, s, C*H*S); δ_C (90 MHz, $CDCl_3$) 18.9 (q), 19.6 (q), 32.6 (d), 55.3 (d), 124.2 (d), 148.9 (s), 160.3 (s), 169.3 (q); *m/z* (FAB) Found: 729.2152, ($M+H^+$, $C_{32}H_{41}N_8O_4S_4$ requires 729.2134).

Synthesis of the *bis* -(*R*)-alanine-thiazole-(*R*)-valine-*tris*-thiazole Cyclopeptide (35a)

N-Methylmorpholine (0.07 mL, 0.66 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (127 mg, 0.66 mmol) and *N*-hydroxybenzotriazole (89 mg, 0.66 mmol) were added to a stirred solution of the alanine thiazole acid (**20**) (163 mg, 0.6 mmol) in anhydrous dichloromethane (7 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 20 min and then a precooled solution of 1'-(*R*)-2-(1'-aminoethyl)thiazole-4-carboxylic acid ethyl ester hydrochloride[25] (142 mg, 0.6 mmol) deprotonated with *N*-methylmorpholine (0.07 mL, 0.66 mmol) in DMF (1 mL) was added dropwise over 5 min. The solution was stirred at 0 °C for 1 h, and then at rt for 17 h. 10 % Aqueous citric acid solution (20 mL) was added, and the separated aqueous layer was extracted with ethyl acetate (5 x 20 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (3 x 15 mL), 10 % aqueous citric acid solution (3 x 15 mL), and brine (2 x 15 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica using 50 % ethyl acetate in light petroleum as eluant gave 1'(*R*)-2-(1-{[1'(*R*)-2-(1'-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)thiazole-4-carboxylic acid ethyl ester (119 mg, 50 %) as a pale yellow foam; $[\alpha]_D$ +30.0° (c = 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3442, 1716, 1668; δ_H (360 MHz, $CDCl_3$) 1.41 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$CO$_2$), 1.47 (9H, s, Bu^t), 1.62 (3H, d, *J* 6.6 Hz, C*H*$_3$CH), 1.81 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 4.43 (2H, q, *J* 7.1 Hz, CH$_3$C*H*$_2$CO$_2$), 5.61 (1H, br s, N*H*Boc), 5.61 (1H, br s, C*H*CH$_3$), 5.62 (1H, dq, *J* 7.0, 7.0 Hz, C*H*CH$_3$), 7.85 (1H, d, *J* 7.9 Hz, N*H*CO), 8.05 (1H, s, C*H*S), 8.10 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 14.2 (q), 20.8 (q), 21.2 (q), 28.2 (q), 47.0 (d), 48.6 (d), 61.3 (t), 80.1 (s), 123.8 (d), 127.3 (d), 146.9 (s), 148.8 (s), 154.8 (s), 160.4 (s), 161.1 (s), 172.9 (s), 174.6 (s); *m/z* (FAB) Found: 477.1200 (MH^++Na^+, $C_{19}H_{26}N_4O_5NaS_2$ requires 477.1242).

Sodium hydroxide (96 mg, 2.4 mmol) was added in one portion to a solution of the above ethyl ester (119 mg, 0.3 mmol) in THF:H_2O (6:3) (5 mL) at rt. The solution was stirred at rt for 6 h, and the separated aqueous layer was then acidified to pH 4 with citric acid and was extracted with dichloromethane (5 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL), and brine (3 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave 1'(*R*)-2-(1-{[1'(*R*)-2-(1'-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)thiazole-4-carboxylic acid (100 mg, 84 %) as a pale yellow foam; $[\alpha]_D$ +30.4° (c = 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3440, 3398, 1758, 1712, 1668; δ_H (360 MHz, $CDCl_3$) 1.46 (9H, s, Bu^t), 1.62 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 1.81 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 5.09 (2H, br d, *J* 6.9, C*H*CH_3 and C*H*CH_3), 7.87 (1H, br s, N*H*CO), 8.09 (1H, s, C*H*S), 8.10 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 20.7 (q), 21.4 (q), 28.2 (q), 46.9 (d), 47.1 (d), 80.3 (s), 124.2 (d), 128.7 (d), 146.5 (s), 148.6 (s), 160.7 (s), 164.0 (s), 173.1 (s), 174.2 (s),176.4 (s); *m/z* (FAB) Found: 449.0915 ($MH^+ + Na^+$, $C_{17}H_{22}N_4O_5NaS_2$ requires 449.0929).

N-Methylmorpholine (0.03 mL, 0.27 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (52 mg, 0.27 mmol) and *N*-hydroxybenzotriazole (37 mg, 0.27 mmol) were added to a solution of 1'(*R*)-2-(1-{[1'(*R*)-2-(1'-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)-thiazole-4-carboxylic acid (94 mg, 0.24 mmol) in anhydrous dichloromethane (4 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 20 min and then a precooled solution of the valine thiazole amine (**23**) (64 mg, 0.24 mmol) deprotonated with *N*-methylmorpholine (0.03 mL, 0.27 mmol) in DMF (1 mL) was added dropwise over 5 min. The solution was stirred at 0 °C for 1 h, and then at rt for 15 h. 10 % Aqueous citric acid solution (20 mL) was added, and the separated aqueous layer was extracted with ethyl acetate (5 x 20 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (3 x 20 mL), 10 % aqueous citric acid solution (3 x 20 mL), and brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a residue. The residue was purified by chromatography on silica using 50 % ethyl acetate in light petroleum (40-60 °C) as eluant to give 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[1'-(1'-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}ethyl)-thiazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid ethyl ester (97 mg, 63 %) as a pale yellow foam; $[\alpha]_D$ +28.0° (c = 2.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3399, 1716, 1668; δ_H (360 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.05 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.40 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.45 (9H, s, Bu^t), 1.62 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 1.80 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 2.65 (1H, app. quintet, *J* 6.8Hz, C*H*(CH$_3$)$_2$), 4.42 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 5.06-5.10 (1H, m, C*H*CH_3), 5.10-5.18 (1H, br s, N*H*Boc), 5.34 (1H, dd, *J* 6.8, 9.2 Hz, C*H*CH(CH$_3$)$_2$), 5.59 (1H, dq, *J* 6.9, 6.9 Hz, C*H*CH_3), 7.79 (1H, d, *J* 8.4 Hz, N*H*CO), 7.97 (1H, d, *J* 9.3 Hz, N*H*CO), 8.06 (1H, s, C*H*S), 8.07 (1H, s, C*H*S), 8.08 (1H,

s, C*H*S); 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: 659.1773 ($MH^+ + Na^+$, $C_{27}H_{36}N_6O_6NaS_3$ requires 659.1756).

Sodium hydroxide (48 mg, 1.2 mmol) was added in one portion to a solution of the *tris*-thiazole ester (97 mg, 0.15 mmol) in THF:H_2O (5:4) (3 mL) at rt. The solution was stirred for 5 h, and the separated aqueous layer was then acidified to pH 4 with citric acid and extracted with ethyl acetate (6 x 15 mL). The combined organic extracts were washed with water (3 x 10 mL) and brine (3 x 10 mL), and then dried ($MgSO_4$) and evaporated *in vacuo*. The yellow residue was stirred with a 4M solution of hydrochloric acid in dioxane (1 mL) for 4 h at rt under an atmosphere of nitrogen. The solvent was removed *in vacuo* by azeotroping with toluene to leave 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[2-(1'-aminoethyl)thiazole-4-carbonyl]amino}ethyl)thiazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid hydrochloride (63 mg, 73 %) as a viscous oil; $[\alpha]_D$ +2.0° (c = 0.8, EtOH); δ_H (360 MHz, CD_3OD) 1.01 (3H, d, *J* 7.7 Hz, C*H*$_3$CH), 1.13 (3H, d, *J* 6.7 Hz, C*H*$_3$CH), 1.83 (3H, d, *J* 6.9 Hz, (C*H*$_3$)$_2$CH), 1.84 (3H, d, *J* 6.9 Hz, (C*H*$_3$)$_2$CH), 2.50-2.60 (1H, m, C*H*(CH$_3$)$_2$), 4.99-5.13 (1H, m, C*H*CH$_3$), 5.28 (1H, d, *J* 8.0 Hz, C*H*CH(CH$_3$)$_2$), 5.62-5.65 (1H, m, C*H*CH$_3$), 8.25 (1H, s, C*H*S), 8.37 (1H, s, C*H*S), 8.43 (1H, s, C*H*S); δ_C (90.5 MHz, CD_3OD) 19.1 (q), 20.0 (q), 20.3 (q), 21.1 (q), 34.3 (d), 43.8 (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); *m/z* (FAB) Found: 509.1102 (MH^+-Cl^-, $C_{20}H_{25}N_6O_4S_3$ requires 509.1099).

Diisopropylethylamine (0.03 mL, 0.17 mmol) was added to a solution of 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[2-(1'-aminoethyl)thiazole-4-carbonyl]amino}ethyl)thiazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid hydrochloride (30 mg, 0.055 mmol) in anhydrous acetonitrile (3 mL) at rt under an atmosphere of nitrogen. The solution was stirred for 5 min and then FDPP (32 mg, 0.08 mmol) was added in one portion. The resulting mixture was stirred at rt for 3 days, then water (*ca*. 10 mL) was added and the separated aqueous layer was extracted with dichloromethane (5 x 15 mL). The combined organic extracts were washed successively with 2M hydrochloric acid solution (3 x 10 mL), 2M sodium hydroxide solution (3 x 10 mL) and brine (2 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica using 80 % ethyl acetate in light petroleum as eluant to give the *cyclic peptide* (22 mg, 82 %) as a colourless powder; mp. 254-256 °C (from dichloromethane); $[\alpha]_D$ +36.0° (c = 0.4, $CHCl_3$); λ_{max} (MeOH)/nm 231 (ε/dm^3 mol^{-1}cm^{-1} 19510);

υ_{max} ($CHCl_3$)/cm^{-1} 3403, 2930, 1665, 1544; δ_H (360 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.8 Hz, $(CH_3)_2CH$), 1.09 (3H, d, *J* 6.8 Hz, $(CH_3)_2CH$), 1.75 (3H, d, *J* 6.8 Hz, CH_3CH), 1.75 (3H, d, *J* 6.7 Hz, CH_3CH), 2.26-2.35 (1H, m, $CH(CH_3)_2$), 5.46 (1H, dd, *J* 5.6, 9.1 Hz, $CHCH(CH_3)_2$), 5.58-5.71 (2H, m, $CHCH_3$ and $CHCH_3$), 8.13 (1H, s, CHS), 8.13 (1H, s, CHS), 8.17 (1H, s, CHS), 8.53 (1H, d, *J* 9.1 Hz, NHCO), 8.64 (2H, d, *J* 7.8 Hz, NHCO and NHCO); δ_C (125 MHz, $CDCl_3$); 18.4 (q), 18.8 (q), 24.9 (q), 29.7 (q), 35.5 (d), 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: 513.0890 ($MH^+ + Na^+$, $C_{20}H_{22}N_6O_3NaS_3$ requires 513.0813).

Synthesis of the *bis*-(*R*)-Valine-thiazole-(*R*)-alanine-*tris*-thiazole Cyclopeptide (35b)

N-Methylmorpholine (0.07 mL, 0.63 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (121 mg, 0.63 mmol) and *N*-hydroxybenzotriazole (85 mg, 0.63 mmol) were added to a solution of the thiazole-4-carboxylic acid (**30**)[24] (171 mg, 0.57 mmol) in anhydrous dichloromethane (6 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 20 min and then a precooled solution of the valine thiazole amine (**23**) (152 mg, 0.57 mmol) deprotonated with *N*-methylmorpholine (0.07 mL, 0.63 mmol) in DMF (1 mL) was added dropwise over 5 min. The solution was stirred at 0 °C for 1 h, and then at rt for 15 h. 10 % Aqueous citric acid solution (20 mL) was added, and the separated aqueous layer was extracted with ethyl acetate (5 x 20 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (3 x 20 mL), 10 % aqueous citric acid solution (3 x 20 mL), and brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a residue. The residue was purified by chromatography on silica using 50 % ethyl acetate in light petroleum as eluant to give the *bis*-thiazole (117 mg, 46 %) as a pale yellow foam.

A 4M solution of hydrochloric acid in dioxane (1 mL) was added to the *bis*-thiazole (117 mg, 0.26 mmol) at rt and the solution was stirred for 8 h under an atmosphere of nitrogen. The solvent was removed *in vacuo* using toluene as an azeotrope to give 1'(*R*)-2-(1'-{[1'(*R*)-2-(1,2-dimethylpropyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carboxylic acid ethyl ester (93 mg, 93 %) as a viscous oil; $[\alpha]_D$ +5.6° (c = 1.5, EtOH); δ_H (360 MHz, CD_3OD) 1.02-1.04 (3H, m, $CH(CH_3)_2$), 1.06-1.10 (3H, m, $CH(CH_3)_2$), 1.12 (3H, d, *J* 6.8 Hz, $CH(CH_3)_2$), 1.16-1.19 (3H, m, $CH(CH_3)_2$), 1.43 (3H, t, *J* 7.1 Hz, $CH_3CH_2CO_2$), 2.41-2.49 (1H, m, $CH(CH_3)_2$), 2.41-2.49 (1H, m, $CH(CH_3)_2$), 4.43 (2H, q, *J* 7.1 Hz, $CO_2CH_2CH_3$), 4.78 (1H, dd, *J* 2.4, 6.2 Hz, $CHCH(CH_3)_2$), 5.33 (1H, dd, *J* 4.7, 7.5 Hz, $CHCH(CH_3)_2$, 8.42 (2H, s, CHS and CHS); δ_C (90.5 MHz, CD_3OD) 14.6 (q), 18.4 (q), 18.6 (q), 19.1 (q), 19.8 (q), 33.6

(d), 34.4 (d), 58.3 (d), 58.6 (d), 62.8 (t), 127.4 (d), 129.8 (d), 146.4 (s), 149.7 (s), 162.0 (s), 162.4 (s), 166.3 (s), 174.4 (s); *m/z* (FAB) Found: 411.155 ($MH^+ + Na^+$, $C_{18}H_{27}N_4O_2NaS_2$ requires 411.1525).

N-Methylmorpholine (0.03 mL, 0.22 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (942 mg, 0.22 mmol) and *N*-hydroxybenzotriazole (30 mg, 0.22 mmol) were added to a stirred solution of 1'-(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carboxylic acid **(20**) (55 mg, 0.2 mmol) in anhydrous dichloromethane (4 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 20 min and a precooled solution of the above *bis*-thiazole hydrochloride salt (77 mg, 0.2 mmol) deprotonated with *N*-methylmorpholine (0.024 mL, 0.22 mmol) in DMF (1 mL) was then added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, and at rt for 14 h. 10 % Aqueous citric acid solution (20 mL) was added, and the separated aqueous layer was extracted with ethyl acetate (5 x 20 mL). The combined organic extracts were washed successively with saturated sodium hydrogen carbonate solution (3 x 20 mL), 10 % aqueous citric acid solution (3 x 20 mL), and brine (2 x 20 mL), and then dried ($MgSO_4$) and evaporated *in vacuo* to leave a residue. Purification by chromatography on silica using 50 % ethyl acetate in light petroleum as eluant gave 1'(*R*)-2-(1'-{[1'(*R*)-2-(1-{[1'(*R*)-2-(1-*tert*-butoxycarbonylaminoethyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carboxylic acid ethyl ester (97 mg, 63 %) as a pale yellow foam; $[\alpha]_D$ +31.3° (c = 0.6, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3398, 1721, 1682, 1666,; δ_H (360 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.05 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.06 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.08 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.40 (3H, t, *J* 7.1 Hz, $CH_3CH_2CO_2$), 1.47 (9H, s, Bu^t), 1.64 (3H, d, *J* 6.7 Hz, CH_3CH), 2.53-2.69 (2H, m, CH(CH_3)$_2$, and CH(CH_3)$_2$) 4.42 (2H, q, *J* 7.1 Hz, CH_2CH_3), 5.02-5.12 (1H, m, CHCH$_3$), 5.13-5.18 (1H, br s, NHBoc), 5.35 (1H, dd, *J* 6.0, 11.8 Hz, CHCH(CH_3)$_2$), 5.37 (1H, dd, *J* 6.0, 11.8 Hz, CHCH(CH_3)$_2$), 7.89 (1H, d, *J* 8.9 Hz, NHCO), 7.94 (1H, d, *J* 9.2 Hz, NHCO), 8.05 (1H, s, CHS), 8.07 (1H, s, CHS), 8.07 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 14.3 (q), 17.7 (q), 17.9 (q), 19.4 (q), 19.6 (q), 21.0 (q), 28.2 (q), 29.6 (d), 32.9 (d), 33.1 (d), 56.1 (d), 56.4 (d), 61.3 (t), 80.3 (s), 123.6(d), 123.8 (d), 126.9 (d), 147.4 (s), 149.1 (s), 149.3 (s), 154.9 (s), 160.7 (s), 160.8 (s), 161.2 (s), 171.6 (s), 171.7 (s), 175.1 (s); *m/z* (FAB) Found: 687.2012 ($MH^+ + Na^+$, $C_{29}H_{40}N_6O_6NaS_3$ requires 687.2069).

Sodium hydroxide (51 mg, 1.28 mmol) was added in one portion to a stirred solution of the above *tris*-thiazole ethyl ester (105 mg, 0.16 mmol) in THF:H_2O (5:4) (3 mL) at rt. The solution was stirred for 9 h, and the separated aqueous layer acidified to pH 4 with citric acid, the acidified aqueous layer was then extracted with ethyl acetate (5 x 20 mL). The combined organic extracts were washed with water (3 x 10 mL) and brine (3 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo*. The yellow oil was

subsequently stirred with a 4M solution of hydrochloric acid in dioxane (1 mL) at rt under an atmosphere of nitrogen for 3 h. The solvent was removed *in vacuo* by azeotroping with toluene to give 1'(*R*)-2-(1'-{[1'(*R*)-2-(1-{[2-(1-aminoethyl)thiazole-4-carbonyl]amino}2-methylpropyl)thiazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid hydrochloride (52 mg, 56 %) as a viscous oil; $[\alpha]_D$ +8.4° (c = 1.0, EtOH); δ_H (360 MHz, CD_3OD) 1.01 (3H, d, *J* 6.7 Hz, (C*H*$_3$)$_2$CH), 1.08 (3H, d, *J* 6.7 Hz, (C*H*$_3$)$_2$CH), 1.12-1.15 (6H, m, (C*H*$_3$)$_2$CH), 1.82 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 2.50-2.63 (1H, m, C*H*(CH$_3$)$_2$), 2.50-2.63 (1H, m, C*H*(CH$_3$)$_2$), 5.00-5.06 (1H, m, C*H*CH$_3$), 5.28-5.39 (1H, m, C*H*CH(CH$_3$)$_2$), 5.28-5.39 (1H, m, C*H*CH(CH$_3$)$_2$), 8.27 (1H, s, C*H*S), 8.27 (1H, s, C*H*S), 8.36 (1H, s, C*H*S); δ_C (90.5 MHz, CD_3OD) 18.8(q), 19.1 (q), 19.8 (q), 19.9 (q), 20.3 (q), 34.4 (d), 34.5 (d), 34.6 (d), 58.1 (d), 58.3 (d), 125.8 (d), 127.5 (d), 129.5 (d), 147.2 (s), 149.9 (s), 150.0 (s), 162.4 (s), 162.8 (s), 167.2 (s), 169.1 (s), 172.4 (s), 172.6 (s).

Diisopropylethylamine (0.04 mL, 0.26 mmol) and then FDPP (50 mg, 0.13 mmol) were added to a suspension of 1'(*R*)-2-(1'-{[1'(*R*)-2-(1-{[2-(1-aminoethyl)thiazole-4-carbonyl]amino}-2-methylpropyl)-thiazole-4-carbonyl]amino}-1'(*R*)-2-methylpropyl)thiazole-4-carboxylic acid hydrochloride (50 mg, 0.09 mmol) in anhydrous acetonitrile (3 mL) at rt under an atmosphere of nitrogen. This solution was stirred at rt for 2 days, then water (*ca.* 10 mL) was added and the separated aqueous layer was then extracted with dichloromethane (4 x 20 mL). The combined organic extracts were washed successively with 2M hydrochloric acid solution (2 x 10 mL), saturated sodium hydrogen carbonate solution (2 x 10 mL) and brine (2 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a solid residue. The residue was purified by chromatography using 80 % ethyl acetate in light petroleum as eluant to give the *cyclic peptide* (37 mg, 79 %) as a colourless powder; $[\alpha]_D$ +34.0° (c = 0.2, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3292, 2926, 1666; δ_H (360 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.06 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.12 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.75 (3H, d, *J* 6.8 Hz, (C*H*$_3$CH), 2.24-2.37 (1H, m, C*H*(CH$_3$)$_2$), 2.24-2.37 (1H, m, C*H*(CH$_3$)$_2$), 5.38-5.42 (1H, m, C*H*(CH$_3$)$_2$), 5.40 (1H, dd, *J* 6.1, 8.9 Hz, C*H*CH(CH$_3$)$_2$), 5.51 (1H, dd, *J* 5.3, 9.4 Hz, C*H*CH(CH$_3$)$_2$), 5.61-5.69 (1H, m, C*H*CH$_3$), 8.10 (1H, s, C*H*S), 8.13 (1H, s, C*H*S), 8.13 (1H, s, C*H*S), 8.47 (1H, d, *J* 8.9 Hz, N*H*CO), 8.51 (1H, d, *J* 9.4 Hz, N*H*CO), 8.59 (1H, d, *J* 7.6 Hz, N*H*CO); δ_C (90.5 MHz, $CDCl_3$) 20.3 (q), 27.3 (q), 28.6 (q), 28.8 (q), 29.7 (q), 30.3 (d), 30.7 (d), 35.2 (d), 35.3 (d), 36.0 (d), 123.4 (d), 128.6 (d), 130.5 (d), 136.3 (s), 144.2 (s), 149.5 (s), 155.7 (s), 159.8 (s), 159.9 (s), 169.1 (s), 177.0 (s), 180.9 (s); *m/z* (FAB) Found: 541.111 ($MH^+ + Na^+$, $C_{22}H_{26}N_6O_3NaS_3$ requires 541.1126).

Synthesis of the structural isomer (36) of nostocyclamide

N-Methylmorpholine (0.084 mL, 0.76 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (146 mg, 0.76 mmol) and *N*-hydroxybenzotriazole (103 mg, 0.76 mmol) were added to a solution of the 1'(*S*)-2-(1-benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carboxylic acid (**27**) (210 mg, 0.7 mmol) in anhydrous dichloromethane (8 mL) at 0 °C under an atmosphere of nitrogen. This mixture was stirred at 0 °C for 20 min and then a precooled solution of the valine thiazole amine hydrochloride (**23**) (279 mg, 1.06 mmol) deprotonated with *N*-methylmorpholine (0.084 mL, 0.76 mmol) in DMF (1 mL) was added dropwise over 5 min. The resulting solution was stirred at 0 °C for 1 h and at rt for 16 h. Water (*ca.* 20 mL) was added and the separated aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with 10 % aqueous citric acid solution (3 x 10 mL) and a saturated solution of sodium hydrogen carbonate (3 x 10 mL), and then dried ($MgSO_4$) and evaporated *in vacuo* to leave the tetrapeptide (240 mg, 77 %) as a colourless foam; $[\alpha]_D$ -101.9° (c = 0.5, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3402, 2965, 1723, 1668, 1634; δ_H (360 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.01 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.39 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$O), 1.55 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 2.55-2.65 (1H, m, C*H*(CH$_3$)$_2$), 2.60 (3H, s, C*H*$_3$CO), 4.41 (2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 4.94-5.01 (1H, m, C*H*CH$_3$), 5.15 (2H, s, Ar*H*), 5.28 (1H, dd, *J* 6.8, 9.2 Hz, C*H*CH(CH$_3$)$_2$), 5.41 (1H, br s, N*H*CbZ), 7.32-7.37 (5H, m, Ar*H*), 7.51 (1H, d, *J* 9.2 Hz, N*H*CO), 8.07 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 11.4 (q), 14.1 (q), 17.8 (q), 19.4 (q), 32.7 (d), 44.9 (d), 55.7 (d), 61.1 (t), 66.7 (t), 126.7 (d), 127.8 (d), 127.9 (d), 128.2 (d), 136.0 (s), 147.2 (s), 153.5 (s), 155.4 (s), 161.0 (s), 161.2 (s), 161.3 (s), 171.6 (s); *m/z* (FAB) Found: 515.1946 ($M^+ + H^+$, $C_{25}H_{30}N_4O_6S$ requires 515.1964).

A 33 % solution of hydrobromic acid in acetic acid (1 mL) and glacial acetic acid (0.6 mL) were added to the above tetrapeptide at rt under an atmosphere of nitrogen. The resulting solution was stirred for 3 h and the volatiles were removed *in vacuo* to give the thiazoleoxazole amine hydrobromide (250 mg, 99 %) as a brown foam; $[\alpha]_D$ +218.4° (c = 0.5, EtOH); δ_H (360 MHz, CD_3OD) 0.99 (3H, d, *J* 6.5 Hz, (C*H*$_3$)$_2$CH), 1.09 (3H, d, *J* 6.4 Hz, (C*H*$_3$)$_2$CH), 1.20 (3H, t, *J* 7.0 Hz, C*H*$_3$CH$_2$O), 1.77 (3H, d, *J* 6.4 Hz, C*H*$_3$CH), 2.50-2.58 (1H, m, C*H*(CH$_3$)$_2$), 2.65 (3H, s, C*H*$_3$CO), 3.64 (2H, q, *J* 7.0 Hz, C*H*$_2$CH$_3$), 4.79-4.81 (1H, m, C*H*CH$_3$), 5.19-5.25 (1H, m, C*H*CH(CH$_3$)$_2$), 8.45 (1H, s, C*H*S); δ_C (90.5 MHz, CD_3OD) 12.1 (q), 17.6 (q), 18.0 (q), 18.9 (q), 19.8 (q), 33.6 (q), 45.6 (d), 57.2 (d), 58.0 (t), 129.2 (d), 138.8 (s), 144.5 (s), 156.0 (s), 158.4 (s), 161.2 (s), 162.4 (s); *m/z* (FAB) Found: 381.1597 ($M^+ - Br^-$, $C_{17}H_{25}N_4O_4S$ requires 381.1597).

N-Methylmorpholine (0.07 mL, 0.59 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (114 mg, 0.59 mmol) and *N*-hydroxybenzotriazole (80 mg, 0.59 mmol) were added to a solution of thethiazole-4-carboxylic acid (**30**)[24] (140 mg, 0.54 mmol) in anhydrous dichloromethane (6 mL) at 0°C under an atmosphere of nitrogen. This mixture was stirred for 20 min and a solution of the thiazoleoxazole amine hydrochloride (250 mg, 0.54 mmol) deprotonated with *N*-methylmorpholine (0.07 mL, 0.59 mmol) in DMF (1 mL) was then added dropwise over 5 min. The resulting solution was stirred at 0 °C for 1 h and at rt for 15 h. Water (*ca.* 30 mL) was added and the separated aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with a 10 % aqueous citric acid solution (2 x 30 mL) and a saturated solution of sodium hydrogen carbonate (2 x 30 mL), and were then dried ($MgSO_4$) and evaporated *in vacuo*. Purification by chromatography on silica using 70 % ethyl acetate in light petroleum led to the isolation of the oxazole-*bis*-thiazole (235 mg, 70 %) as a cream foam; $[\alpha]_D$ +5.1° (c = 0.7, $CHCl_3$); δ_H (360 MHz, $CHCl_3$) 1.01 (3H, d, *J* 6.7 Hz, $(CH_3)_2CH$), 1.06 (3H, d, *J* 6.7 Hz, $(CH_3)_2CH$), 1.50 (9H, s, Bu^t), 1.70 (3H, d, *J* 7.0 Hz, CH_3CH), 2.65 (3H, s, CH_3CO), 4.65 (2H, d, *J* 5.7 Hz, CH_2NH), 5.30 (1H, dd, *J* 7.0, 9.1 Hz, $CHCH(CH_3)_2$), 5.43-5.50 (1H, m, $CHCH_3$), 7.62 (1H, d, *J* 8.7 Hz, NHCO), 7.77 (1H, d, *J* 8.2 Hz, CHS), 8.13 (1H, s, CHS); δ_C (90.5 MHz, $CHCl_3$) 11.7 (q), 18.0 (q), 19.3 (q), 19.7 (q), 29.3 (q), 29.7 (q), 31.9 (d), 43.0 (d), 56.0 (d), 124.3 (d), 127.2 (q), 128.6 (s), 147.1 (s), 149.1 (s), 154.0 (s), 155.6 (s), 160.2 (s), 161.1 (s), 161.6 (s), 161.8 (s), 169.6 (q), 172.1 (s); *m/z* (FAB) Found: 643.1913 ($M^+ + Na^+$, $C_{27}H_{36}N_6O_7S_2$ requires 643.1985).

Sodium hydroxide (60 mg, 1.42 mmol) was added to a solution of the oxazole-*bis*-thiazole carboxylic acid ethyl ester (215 mg, 0.38 mmol) in THF:H_2O (5:3) (4 mL) at rt. The solution was stirred for 15 h and the separated aqueous layer was then acidified to pH 4 with citric acid. The aqueous layer was then extracted with ethyl acetate (5 x 20 mL) and the combined organic extracts washed with brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the carboxylic acid as a pale yellow foam.

The Boc-oxazole-*bis*-thiazole was stirred with a 4M solution of hydrochloric acid in dioxane (1 mL) at rt for 1 h under an atmosphere of nitrogen. The dioxane was removed *in vacuo* using toluene as an azeotrope to leave a highly hygroscopic yellow solid which was immediately subjected to the coupling conditions.

Diisopropylethylamine (0.05 mL, 0.28 mmol) and FDPP (54 mg, 0.14 mmol) were added to a suspension of the macrocyclic precursor (50 mg, 0.095 mmol) in anhydrous acetonitrile (4 mL) at rt under an atmosphere of nitrogen. This solution was stirred for 1 day and then water (*ca.* 10 mL) was added and the

separated aqueous layer was extracted with dichloromethane (5 x 10 mL). The combined organic extracts were washed with 2M hydrochloric acid solution (2 x 10 mL), a saturated solution of sodium hydrogen carbonate (2 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a solid colourless residue. This residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to give the *cyclic peptide* (23 mg, 0.049 mmol, 52 %) as a colourless powder; mp 263-264 °C (from dichloromethane); $[\alpha]_D$ +21.1 (c = 1.0° $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3394, 1667, 1639; δ_H (360 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.7 Hz, (CH_3)$_2$CH), 1.04 (3H, d, *J* 6.7 Hz, (CH_3)$_2$CH), 1.68 (3H, d, *J* 6.7 Hz, CH_3CH), 2.33-2.38 (1H, m, CH(CH_3)$_2$), 2.70 (3H, s, CH_3CO), 4.88 (1H, dd, *J* 3.1, 18.2 Hz, CH_2NH), 5.17 (1H, dd, *J* 5.4, 18.2 Hz, CH_2NH), 5.23 (1H, app. quintet, *J* 6.7 Hz, $CH$$CH_3$), 5.32 (1H, dd, *J* 4.5, 7.7 Hz, CHCH(CH_3)$_2$), 8.17 (1H, s, CHS), 8.18 (1H, s, CHS), 8.43 (1H, br s, N$H$$CH_2$), 8.52 (1H, d, *J* 7.7 Hz, NHCHCH(CH_3)$_2$), 8.69 (1H, d, *J* 6.7 Hz, NHCHCH_3); δ_C (125 MHz, $CDCl_3$) 11.7 (q), 17.8 (q), 18.5 (q), 19.7 (q), 34.7 (d), 41.6 (t), 44.5 (d), 56.2 (d), 123.7 (d), 123.8 (d), 128.5 (s), 148.5 (s), 149.0 (s), 154.2 (s), 159.7 (s), 160.5 (s), 160.6 (s), 161.2 (s), 165.0 (s), 167.9 (s); *m/z* (FAB) Found: 497.1033 ($M^+ + Na^+$, $C_{20}H_{22}N_6O_4S_2$ requires 497.1042).

Synthesis of the *bis*-(*R*)-valine-thiazole-(*S*)-alanine-oxazole Cyclopeptide (37)

N-Methylmorpholine (0.08 mL, 0.73 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (139 mg, 0.73 mmol) and *N*-hydroxybenzotriazole (99 mg, 0.73 mmol) were added to a solution of the oxazole-4-carboxylic acid **(27)** (200 mg, 0.66 mmol) in anhydrous dichloromethane (7 mL) at 0 °C under an atmosphere of nitrogen. This solution was stirred at 0 °C for 20 min and then a precooled solution of the valine thiazole amine (**23**) (175 mg, 0.66 mmol) deprotonated with *N*-methylmorpholine (0.08 mL, 0.73 mmol) in anhydrous DMF (3 mL) was added dropwise over 5 min. The resulting solution was stirred at 0 °C for 1 h and at rt for 15 h. Water (*ca.* 30 mL) was added and the separated aqueous layer was extracted with dichloromethane (4 x 25 mL). The combined organic extracts were washed successively with 10 % aqueous citric acid solution (3 x 20 mL), saturated sodium hydrogen carbonate solution (3 x 20 mL) and brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo.* The yellow residue was purified by chromatography on silica using 60 % ethyl acetate in light petroleum as eluant to give 1'(*R*)-2-(1-{[1'(*S*)-2-(1-benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carboxylic acid ethyl ester (260 mg, 77 %) as a cream foam which crystallised to give a colourless powder; $[\alpha]_D$ +32.8° (c = 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3438, 1723, 1668, 1635; δ_H (360 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.03 (3H, d, *J* 6.8 Hz, (CH_3)$_2$CH), 1.40 (3H, t, *J* 7.1 Hz, CH_3CH_2O), 1.57 (3H, d, *J* 7.0 Hz, CH_3CH), 2.59-2.66 (1H, m, CH(CH_3)$_2$), 2.61 (3H, s, CH_3CO), 4.42 (2H, q, *J* 7.1 Hz, CH_2CH_3), 4.99-5.09 (1H, m, $CH$$CH_3$), 5.16 (2H, m, CH_2Ph),

5.29 (1H, dd, *J* 6.7, 9.2 Hz, C*H*NH), 5.34-5.36 (1H, br m, N*H*CbZ), 7.35-7.38 (5H, m, Ar*H*), 7.52 (1H, d, *J* 8.9 Hz, N*H*CO), 8.07 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 11.4 (q), 14.1 (q), 17.8 (q), 19.4 (q), 19.6 (q), 32.7 (d), 44.9 (d), 55.7 (d), 61.1 (t), 66.8 (t), 126.7 (d), 127.8 (d), 127.9 (d), 128.2 (d), 136.0 (s), 147.2 (s), 153.5 (s), 155.5 (s), 161.0 (s), 161.2 (s), 161.3 (s), 171.7 (s); *m/z* (FAB) Found: 537.1725 ($M^+ + Na^+$, $C_{25}H_{30}N_4O_6NaS$ requires 537.1784).

Sodium hydroxide (82 mg, 2.07 mmol) was added to a solution of the above oxazole-thiazolecarboxylic acid ethyl ester (260 mg, 0.51 mmol) in THF:H_2O (5:3) (5 mL) at rt. The solution was stirred for 14 h, ethyl acetate (*ca.* 30 mL) was added and the separated aqueous layer was acidified to pH 4 with citric acid. The aqueous layer was then extracted with ethyl acetate (5 x 20 mL) and the combined organic extracts washed with brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to give 1'(*R*)-2-(1-{[1'(*S*)-2-(1-benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carboxylic acid (2.06 mg, 83 %) as a pale yellow solid: mp 70-73 °C (from dichloromethane); $[\alpha]_D$ +50.4° (c = 1.0°, EtOH); υ_{max} ($CHCl_3$)/cm^{-1} 3437, 1723, 1667; δ_H (360 MHz, CD_3OD) 1.00 (3H, d, *J* 6.7 Hz, (C*H*$_3$)$_2$CH), 1.08 (3H, d, *J* 6.7 Hz, (C*H*$_3$)$_2$CH), 1.58 (3H, d, *J* 7.2 Hz, C*H*$_3$CH), 2.47-2.57 (1H, m, C*H*(CH$_3$)$_2$), 2.60 (3H, s, C*H*$_3$CO), 4.91-4.95 (1H, m, C*H*CH$_3$), 5.14 (2H, br s, C*H*$_2$Ph), 5.21-5.26 (1H, m, C*H*CH(CH$_3$)$_2$), 7.28-7.38 (5H, m, Ar*H*), 8.34 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 11.7 (q), 18.8 (q), 19.2 (q), 19.9 (q), 34.1 (d), 43.8 (t), 46.2 (d), 57.8 (d), 128.8 (d), 129.0 (d), 129.1 (d), 129.4 (d), 138.0 (s), 148.3 (s), 155.4 (s), 158.0 (s), 163.6 (s), 163.9 (s), 176.7 (s); *m/z* (FAB) Found: 509.1509 ($M^+ + Na^+$, $C_{23}H_{26}N_4O_6NaS$ requires 509.1471).

N-Methylmorpholine (0.03 mL, 0.23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol) and *N*-hydroxybenzotriazole (31 mg, 0.23 mmol) were added to a solution of the oxazole-thiazole acid (100 mg, 0.21 mmol) in anhydrous dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen. The solution was stirred for 20 min at 0 °C and then a precooled solution of the thiazole amine (**23**) deprotonated with *N*-methylmorpholine (0.03 mL, 0.23 mmol) in DMF (1 mL) was added dropwise over 5 min. The resulting solution was stirred at 0 °C for 1 h and then at rt for 17 h. Water (*ca.* 20 mL) was added and the separated aqueous layer was extracted with dichloromethane (4 x 20 mL). The combined organic extracts were washed with 10 % aqueous citric acid solution (3 x 20 mL) and brine (2 x 20 mL), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 50 % ethyl acetate in light petroleum as eluant to give 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[1'(*S*)-2-(1-benzyloxycarbonylaminoethyl)-5-methyloxazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carboxylic acid ethyl ester (96

mg, 66 %) as a cream foam; $[\alpha]_D$ +34.6° (c = 0.9, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3399, 1722, 1668, 1635; δ_H (360 MHz, $CDCl_3$) 1.00-1.06 (6H, m, (CH_3)$_2$CH), 1.00-1.06 (6H, m, (CH_3)$_2$CH), 1.37 (3H, t, *J* 7.1 Hz, CH_3CH_2O), 1.59 (3H, d, *J* 7.0 Hz, CH_3CH), 2.48-2.55 (1H, m, CH(CH_3)$_2$), 2.57-2.66 (1H, m, CH(CH_3)$_2$), 2.62 (3H, s, CH_3CO), 4.39 (2H, q, *J* 7.1 Hz, CH_2CH_3), 5.02-5.09 (1H, m, $CHCH_3$), 5.12-5.14 (2H, m, CH_2Ph), 5.30-5.36 (1H, m, CHCH(CH_3)$_2$), 5.30-5.36 (1H, m, CHCH(CH_3)$_2$), 5.48 (1H, d, *J* 8.3 Hz, NHCbZ), 7.35-7.39 (5H, m, ArH), 7.48 (1H, d, *J* 9.4 Hz, NHCO), 7.98 (1H, d, *J* 9.3 Hz, NHCO), 8.03 (1H, s, CHS), 8.04 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 11.6 (q), 14.3 (q), 17.8 (q), 17.9 (q), 19.4 (q), 19.6 (q), 19.7 (q), 33.0 (d), 33.1 (d), 45.0 (d), 55.8 (d), 56.4 (d), 61.3 (t), 67.1 (t), 123.5 (d), 126.9 (d), 128.1 (d), 128.2 (d), 128.5 (d), 136.1 (s), 147.4 (s), 149.3 (s), 153.9 (s), 160.7 (s), 161.2 (s), 161.4 (s), 161.5 (s), 171.6 (s), 171.7 (s); *m/z* (FAB) Found: 719.2368 ($M^+ + Na^+$, $C_{33}H_{40}N_6O_7NaS_2$ requires 719.2297).

A solution of sodium hydroxide (20 mg, 0.5 mmol) in water (0.5 mL) was added to a solution of the oxazole *bis*-thiazole carboxylic acid ethyl ester (88 mg, 0.13 mmol) in ethanol (2 mL) and the mixture was stirred for 4 h. The volatiles were removed *in vacuo* and the residue was acidified with 2M hydrochloric acid solution (30 mL), the amine was then collected by suction filtration as a colourless solid.

The carboxylic acid was immediately stirred with a 33 % solution of hydrobromic acid in acetic acid (1 mL) and glacial acetic acid (0.6 mL) for 3 h at rt under an atmosphere of nitrogen. The volatiles were removed *in vacuo* to give 1'(*R*)-2-(1-{[1'(*R*)-2-(1-{[1'(*S*)-2-(1-aminoethyl)-5-methyloxazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carbonyl]amino}-2-methylpropyl)thiazole-4-carboxylic acid hydrobromide (65 mg, 0.1 mmol, 77 %) as a brown foam; $[\alpha]_D$ +4.0° (c = 0.7, EtOH); δ_H (360 MHz, CD_3OD) 1.00-1.04 (3H, m, (CH_3)$_2$CH), 1.00-1.04 (3H, m, (CH_3)$_2$CH), 1.09-1.13 (3H, m, (CH_3)$_2$)CH), 1.09-1.13 (3H, m, (CH_3)$_2$CH), 1.76 (3H, d, *J* 7.0 Hz, CH_3CH), 2.51-2.60 (1H, m, CH(CH_3)$_2$), 2.51-2.60 (1H, m, CH(CH_3)$_2$), 2.67 (3H, s, CH_3CO), 4.76-4.80 (1H, m, $CHCH_3$), 5.15-5.28 (1H, m, CHCH(CH_3)$_2$), 5.15-5.28 (1H, m, CHCH(CH_3)$_2$), 8.26 (1H, s, CHS), 8.41 (1H, s, CHS); δ_C (90.5 MHz, CD_3OD) 14.9 (q), 15.1 (q), 20.7 (q), 21.5 (q), 21.7 (q), 22.3 (q), 35.6 (q), 48.4 (d), 59.3 (d), 60.0 (d), 60.7 (d), 128.8 (d), 131.5 (d), 133.2 (s), 147.6 (s), 147.8 (s), 158.1 (s), 158.2 (s), 160.4 (s), 164.2 (s), 164.3 (s), 164.4 (s), 176.2 (s); *m/z* (FAB) Found: 552.1777 (M^+ - HBr + H_2O, $C_{23}H_{32}N_6O_6S_2$ requires 552.1825).

Diisopropylethylamine (0.4 mL, 0.3 mmol) and FDPP (576 mg, 0.15 mmol) were added to a suspension of the above macrocyclic precursor (65 mg, 0.1 mmol) in anhydrous acetonitrile …mL at rt under an atmosphere of nitrogen. This solution was stirred for 24 h, and then water (*ca.* 10 mL) was added and the

separated aqueous layer was extracted with dichloromethane (4 x 15 mL). The combined organic extracts were washed successively with 2M hydrochloric acid solution (3 x 10 mL), saturated sodium hydrogen carbonate solution (3 x 10 mL), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a solid colourless residue. This residue was purified by chromatography on silica using 70 % ethyl acetate in light petroleum as eluant to give the *cyclic peptide* (35 mg, 68 %) as a colourless foam; $[\alpha]_D$ +46.0° (c = 0.3, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3396, 2928, 1668; δ_H (360 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.06 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CH), 1.08 (3H, d, *J* 7.2 Hz, (C*H*$_3$)$_2$CH), 1.10 (3H, d, *J* 7.2 Hz, (C*H*$_3$)$_2$CH), 1.70 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 2.28-2.38 (1H, m, C*H*(CH$_3$)$_2$), 2.28-2.38 (1H, m, C*H*(CH$_3$)$_2$), 2.67 (3H, s, C*H*$_3$O), 5.21-5.31 (1H, m, C*H*CH$_3$), 5.21-5.31 (1H, m, C*H*CH(CH$_3$)$_2$), 5.52 (1H, dd, *J* 5.7, 9.5 Hz, C*H*CH(CH$_3$)$_2$), 8.11 (1H, s, C*H*S), 8.11 (1H, s, C*H*S), 8.44 (1H, d, *J* 5.7 Hz, N*H*CO), 8.45 (1H, d, *J* 9.0 Hz, N*H*CO), 8.60 (1H, d, *J* 6.6 Hz, N*H*CO); δ_C (90.5 MHz, $CDCl_3$) 11.7 (q), 18.3 (q), 18.6 (q), 19.0 (q), 21.0 (q), 34.9 (q), 35.6 (d), 44.1 (d), 55.4 (d), 55.9 (d), 77.3 (d), 123.4 (d), 123.7 (d), 128.4 (s), 128.5 (s), 148.9 (s), 149.0 (s), 153.8 (s), 159.9 (s), 160.6 (s), 161.7 (s), 168.1 (s), 168.7 (s); *m/z* (FAB) Found: 517.1703 ($M^+ + H^+$, $C_{23}H_{29}N_6O_4S_2$ requires 517.1692).

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REFERENCES

1. a) B. M. Degnan, C. J. Hawkins, M. F. Lavin, E. J. McCaffrey, D. L. Parry, A. L. van den Brenk, and D. J. Watters, *J. Med. Chem.*, 1989, **32**, 1349; b) F. J. Schimtz, M. B. Ksebati, J. S. Chang, J. L. Wang, M. B. Hossain, and D. van der Helm, *J. Org. Chem.*, 1989, **54**, 3463; c) C. D. J. Boden and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 2000, 875.
2. a) B. F. Bowden, A. R. Carroll, J. C. Coll, D. C. R. Hockless, B. W. Skelton, and A. H. White, *Aust. J. Chem.*, 1994, **47**, 61; b) B. McKeever and G. Pattenden, *Tetrahedron Lett.*, 1999, **40**, 9317.
3. Y. Hamamoto, M. Endo, M. Nakagawa, T. Nakanishi, and K. Mizukawa, *J. Chem. Soc., Chem. Commun.*, 1983, 323.
4. For reviews, see: a) D. J. Faulkner, *J. Nat. Prod.*, 2002, **19**, 1 and earlier reviews in this series; b) B. S. Davidson, *Chem. Rev.*, 1993, **93**, 1771.
5. R. E. Moore, J. Ogino, G. M. I. Patterson, and C. D. Smith, *J. Nat. Prod.*, 1996, **59**, 581.
6. a) V. Admi, U. Afek, and S. Carmeli, *J. Nat. Prod.*, 1996, **59**, 396; b) D. J. Freeman and G. Pattenden, *Tetrahedron Lett.*, 1998, **39**, 3251.

7. T. Plüss, F. Jüttner, W. von Philipsborn, and A. Linden, *J. Org. Chem.*, 1995, **60**, 7891.
8. For a discussion on this topic see: J. P. Michael and G. Pattenden, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1.
9. a) A. L. van den Brenk, K. A. Byriel, D. P. Fairlie, L. R. Gahan, G. R. Hanson, C. J Hawkins, A. Jones, C. H. L. Kennard, B. Moubaraki, and K. S. Murray, *Inorg. Chem.*, 1994, **33**, 3549; b) P. Wipf, S. Venkatraman, C. P. Miller, and S. J. Geib, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1516; c) A. L. van den Brenk, D. P. Fairlie, L. R. Gahan, G. R. Hanson, and T. W. Hambley, *Inorg. Chem.*, 1996, **35**, 1095; d) D. J. Freeman, G. Pattenden, A. F. Drake, and G. Siligardi, *J. Chem. Soc., Perkin Trans. 2*, 1998, 129; e) L. Grøndahl, N. Sokolenko, G. Abbenante, D. P. Fairlie, G. R. Hanson, and L. R. Gahan, *J. Chem. Soc., Dalton Trans.*, 1999, 1227; f) R. M. Cusack, L. Grøndahl, G. Abbenante, D. P. Fairlie, L. R. Gahan, G. R. Hanson, and T. W. Hambley, *J. Chem. Soc., Perkin Trans. 2*, 2000, 323; g) L. A. Morris, M. Jaspars, J. J. Kettenes-van den Bosch, K. Versluis, A. J. R. Heck, S. M. Kelly, and N. C. Price, *Tetrahedron*, 2001, **57**, 3185; h) R. M. Cusack, L. Grøndahl, D. P. Fairlie, L. R. Gahan, and G. R. Hanson, *J. Chem. Soc., Perkin Trans. 2*, 2002, 556.
10. a) A. L. van den Brenk, D. P. Fairlie, L. R. Gahan, G. R. Hanson, C. J. Hawkins, and A. Jones, *Inorg. Chem.*, 1994, **33**, 2280; b) References 9a and 9c; c) Reference 9e.
11. A. Bertram, J. S. Hannam, K. A. Jolliffe, and G. Pattenden, *Synlett*, 1999, 1723; A. J. Blake, J. S. Hannam, K. A. Jolliffe, and G. Pattenden, *Synlett*, 2000, 1515.
12. P. Wipf and C. P. Miller, *J. Am. Chem. Soc.*, 1992, **114**, 10975.
13. N. Sokolenko, G. Abbenante, M. J. Scanlon, A. Jones, L. R. Gahan, G. R. Hanson, and D. P. Fairlie, *J. Am. Chem. Soc.*, 1999, **121**, 2603.
14. Preliminary communications: a) A. Bertram and G. Pattenden, *Synlett*, 2000, 1519; b) A. Bertram and G. Pattenden, *Synlett*, 2001, 1873.
15. For recent publications see: a) D. R. Williams, P. D. Lowder, Y-G. Gu, and D. A. Brooks, *Tetrahedron Lett.*, 1997, **38**, 331; b) A. I. Meyers and F. X. Tavares, *J. Org. Chem.*, 1996, **61**, 8207; c) P. Larfargue, P. Guenot, and J-P. Lellouche, *Synlett*, 1995, 171; d) P. Wipf, C. P. Miller, S. Venkatraman, and P. C. Fritch, *Tetrahedron Lett.*, 1995, **36**, 6395; e) E. Anguilar and A. I. Meyers, *Tetrahedron Lett.*, 1994, **35**, 2473; f) P. Wipf and C. P. Miller, *J. Org. Chem.*, 1993, **58**, 3604; g) M. North and G. Pattenden, *Tetrahedron*, 1990, **46**, 8267; h) C. W. Holzapfel, M. W. Bredankemp, and W. J. Vanzyl, *Syn. Commun.*, 1990, **20**, 2235; i) Y. Hamada, M. Shibata, T. Sugiura, S. Kata, and T. Shioiri, *J. Org. Chem.*, 1987, **52**, 1252; j) R. C. Kelly, I. Gebhard, and N. Wicnienski, *J. Org. Chem.*, 1986, **51**, 4590; k) C. W. Holzapfel and G. R. Pettit, *J. Org. Chem.*, 1985, **50**, 2323; l) R. Houssain,

M. Lohez, J-L. Bernier, and J-P. Hénichart, *J. Org. Chem.*, 1985, **50**, 2787; m) D. L. Evans, D. K. Minster, U. Jordis, S. M. Hecht, A. L. Mazzu, and A. I. Meyers, *J. Org. Chem*., 1979, **44**, 497.

16. C. D. Smith and Z. Xia, *J. Org. Chem*., 2001, **66**, 3459.
17. C. J. Moody and M. C. Bagley, *J. Chem. Soc., Perkin Trans. 1*, 1998, 601.
18. S. V. Downing, E. Anguilar, and A. I. Meyers, *J. Org. Chem.*, 1999, **64**, 826.
19. D. B. Dess and J. C. Martin, *J. Am. Chem. Soc*., 1991, **113**, 7277; R. E. Ireland and L. Liu, *J. Org. Chem.*, 1993, **58**, 2899.
20. M. C. Bagley, R. T. Buck, S. L. Hind, and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1998, 591.
21. S. O. Lawesson, B. S. Peterson, and S. Scheibye, *Bull. Soc. Chim. Belg.*, 1978, **87**, 229.
22. U. Schmidt, H. Griesser, P. Gleich, and R. Utz, *Synthesis*, 1986, 992; H. Kigoshi and S. Yamada, *Tetrahedron*, 1999, **42**, 1230.
23. K. Okamura, A. Ito, H. Saito, Y. Nakamura, and C.G. Shin, *Bull. Chem. Soc. Jpn*., 1996, **69**, 2309.
24. A. I. Meyers and E. Aguilar, *Tetrahedron Lett*., 1994, **35**, 2477.
25. D. F. W Cross, *J. Chem. Soc.*, 1963, 2143.