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Concise synthesis of stereodefined, thiazole—containing cyclic hexa- and octapeptide relatives of the *Lissoclinums*, via cyclooligomerisation reactions

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Abstract—The synthesis of a range of thiazole containing cyclic peptides using cyclooligomerisation reactions of amino acid substituted thiazole monomers and by macrolactamisation procedures is reported. The synthetic approaches lead to high yields of novel 18- and 24-membered ring analogues of the naturally occurring *Lissoclinum* families of cyclic peptides found in marine organisms and algae.
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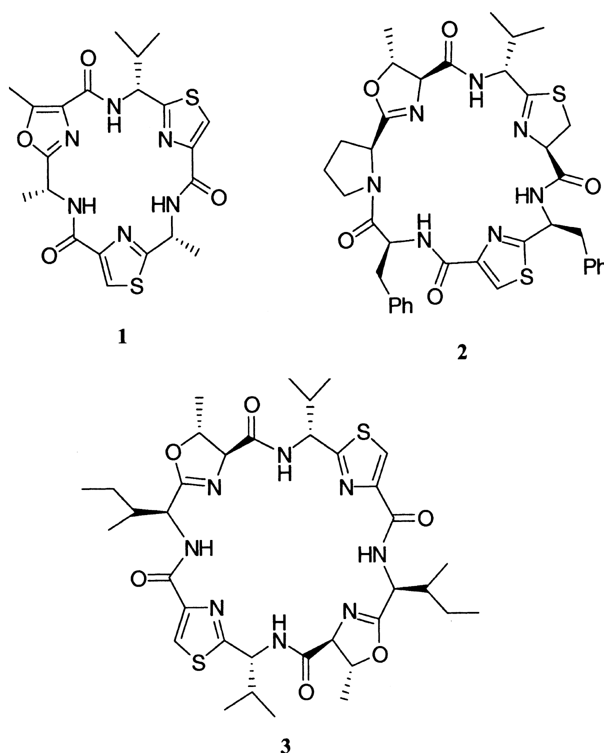
1. Introduction

A large number of cyclic peptides containing 'unnatural' D-amino acids, together with modified amino acids in the form of azole heterocycles, have been isolated from ascidians, cyanobacteria and other sources in recent years. Many of these secondary metabolites possess significant biological activity, including cytotoxic, immunoregulatory and antibiotic activities. However, relatively small quantities of cyclic peptides are available from natural sources and, in general, little is known about the biological mode of action of these compounds.

The *Lissoclinum* cyclic peptides e.g. dendroamide A (**1**),[1] lissoclinamide 4 (**2**)[2] and ascidiacyclamide **3**[3] represent a group of cyclic peptides, characterised by the presence of oxazoline/oxazole/thiazoline/thiazole heterocycles alternating with proteinogenic amino acid residues.[4]



The size and conformations of these macrocycles, and the nature of the functional groups they possess, have led to speculation that they have potential for metal ion chelation and transport in vivo, and that these features may contribute to their biological activity.[5] A number of recent studies have indicated that these natural products and their analogues do, indeed, form complexes with a variety of metal ions.[6] With the aim of further investigating the capacity of *Lissoclinum*-type cyclic peptides to bind metal ions, we have developed a concise, high-yielding cyclooligomerisation procedure which leads to novel thiazole-based analogues of natural cyclic peptides from appropriate amino acid substituted thiazole precursors. These studies are now described in detail.[7]

Keywords: Lissoclinum; cyclooligomerisation; thiazole.
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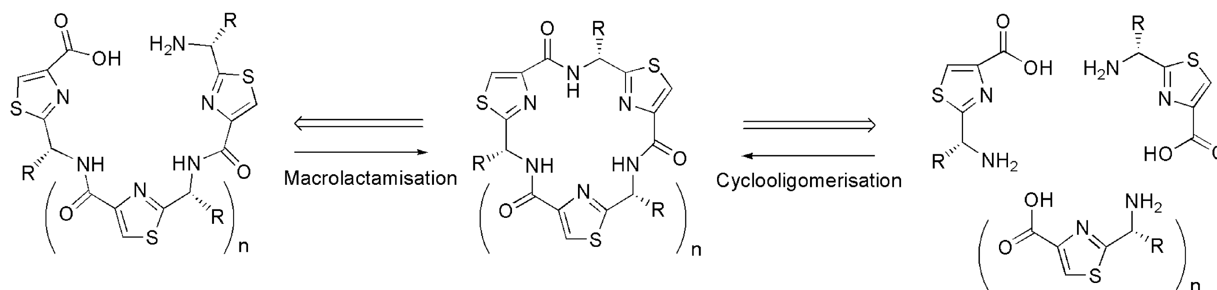


Figure 1. Cyclooligomerisation and macrocyclisation approaches to thiazole-containing cyclic peptides.

2. Results and discussion

The azole heterocycles present in the *Lissoclinum* peptides are derived from cyclodehydrations of cysteine, serine and threonine residues linked to adjacent amino acids in a peptide sequence.[8] The presence of these modified peptide bonds has been found to induce 'turn' structures that facilitate ring closure of the linear peptide chains.[9] We therefore, became interested in investigating the cyclooligomerisation reactions of thiazole amino acid derivatives, and the macrolactamisations of linear oligomers of these modified dipeptides (Fig. 1).

The syntheses of thiazole based amino acids have been reported previously and we prepared the known thiazole derivatives **4a–c** using a modified Holpfazel–Hantzsch procedure.[10] Analysis of the Mosher amide derivatives[11] of these compounds indicated that the valine and alanine derived thiazoles, **4a** and **4b** respectively, were both optically pure (ee≥95%). However, despite further modification of the synthetic procedure, in our hands the phenylalanine derived thiazole **4c** could not be obtained in >70% ee using this method of synthesis.

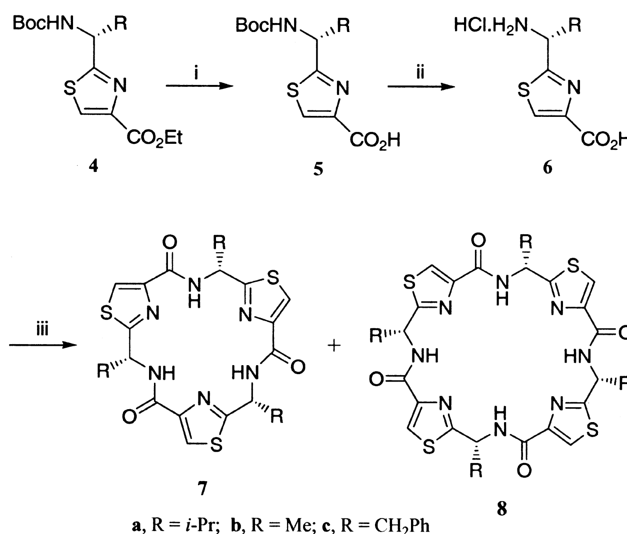
2.1. One-pot cyclooligomerisation reactions

Saponification of each of the thiazole esters **4a–c** gave the corresponding carboxylic acids **5a–c** which were immediately subjected to treatment with a 4 M solution of HCl in dioxane, leading to the heterocyclic amino acids **6**, as their hydrochloride salts, in essentially quantitative yields. Treatment of the amino acids **6** with the peptide coupling reagent, pentafluorophenyl diphenylphosphinate (FDPP),[12] resulted in smooth cyclooligomerisation and the formation of mixtures of cyclic peptide products in good overall yield (Scheme 1).[7]

Thus, cyclooligomerisation of the homochiral thiazoles **6a** and **6b** led to the cyclic trimers **7a** and **7b** and the cyclic tetramers **8a** and **8b**, respectively as the major products, albeit in differing ratios depending upon the amino acid derivative.[13] In both cases, the reactions could be carried out on a gram scale and the enantiomerically pure cyclic trimers and tetramers could be separated by routine column chromatography on silica gel (Table 1).

Trace amounts of higher oligomers (cyclic pentamers, hexamers, heptamers, octamers and nonamers) were detected by FAB mass spectrometry from **6a** and **6b**, but these compounds were not isolated, separated and/or characterised.

The ^{1}H NMR spectra of the cyclic trimers, **7a** and **7b**, and the corresponding cyclic tetramers **8a** and **8b**, in $CDCl_3$ at 22°C were similar, showing only a single set of signals for each type of proton, thereby indicating that the compounds are C_3 and C_4 symmetric, respectively. In both cases the resonance signals attributable to the amide protons of the cyclic trimers (**7a** and **7b**) lie downfield (by 0.6–0.7 ppm) from those of the corresponding cyclic tetramers (**8a** and **8b**, respectively), indicating that intramolecular hydrogen bond networks of the tetramers are not as strong as those of the corresponding trimers. The temperature dependence of the chemical shifts of the peptide NH signals of the D-valine derived trimer **7a** (0.02 ppb per degree) and tetramer **8a** (2.4 ppb per degree) in $CDCl_3$ also indicate that intramolecular H-bonding is stronger in the trimer than the tetramer.[14] The vicinal $^3J_{NHCH}$ values of 9.3 Hz and 9.1 Hz



Scheme 1. *Reagents and conditions*: (i) NaOH (10 mol equiv.), THF/H_2O, 9:1, rt, 18 h; (ii) 4 M HCl in dioxane, rt, 6 h; (iii) FDPP (1.5 mol equiv.), *i*-Pr_2NEt (3 mol equiv.), CH_3CN, rt, 18 h.

Table 1. Cyclooligomerisation reactions of thiazole amino acids **6**

Amino acid	Yield of cyclic products[a] (%)	Trimer to tetramer ratio[b]
6a	91	5:2
6b	55	9:2
6c	63	1:3[c]
rac-**6a**	75	1:1[d]

[a] Yields of cyclised products prior to separation.
[b] Determined by HPLC.
[c] Ratio of **9c**:**8c**.
[d] Diastereomeric mixtures of trimers and tetramers.

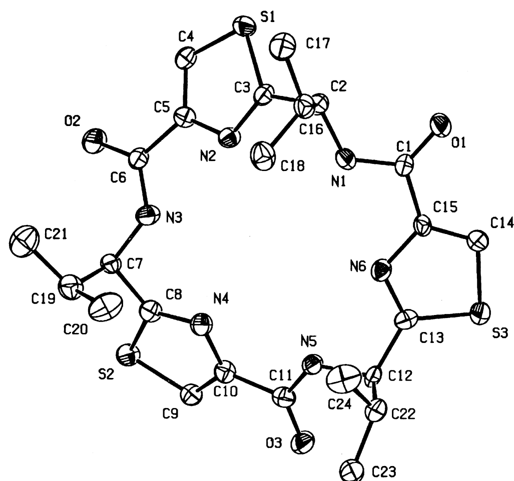


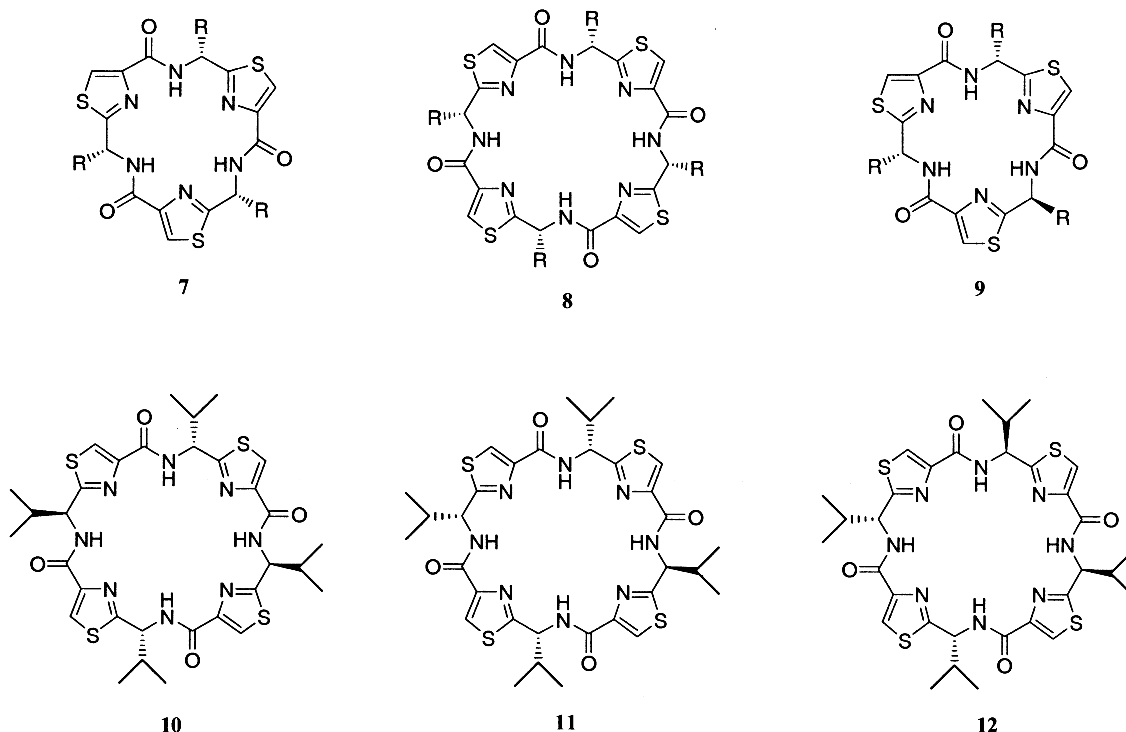
Figure 2. ORTEP plot of compound **7a** derived from X-ray crystallographic data.

for **7a** and **8a**, respectively correspond to dihedral angles of 150°<θ<180°, suggesting that the conformations of both macrocycles are similar.[15]

X-ray quality crystals of **7a** were obtained by slow diffusion of diethyl ether into a dichloromethane solution of the cyclic peptide. The X-ray structure indicates that the 18 membered macrocycle has a nearly planar structure in which all of the amide NH and thiazole nitrogen atoms are oriented towards the centre of the macrocycle, forming a network of bifurcated hydrogen bonds which rigidifies the molecule (Fig. 2). As a result of this rigidification, all of the isopropyl side chains lie on the same face of the molecule and are forced to adopt pseudoaxial orientations. The NHαCH dihedral angles of the three amide linkages in **7a** were found to lie between 159 and 167°, which is consistent with the values determined by ^{1}H NMR spectroscopy. This correlation suggests that the cyclic tetramer **8a** adopts a similar conformation in which the thiazole units form the corners of a square with all side chains on the same face of the molecule.[16]

Comparing the cyclooligomerisation reactions of the thiazoles **6a** and **6b**, it is clear that the ratio of cyclic trimer to cyclic tetramer (as measured by ^{1}H NMR and HPLC) decreases as the steric bulk of the side chains increases. This may be attributed to the steric congestion imposed upon the cyclic trimers **7a** and **7b**, in which all side chains adopt pseudoaxial conformations. As the size of the side chains increases, unfavourable transannular interactions in the cyclic trimers will increase and we postulate that this situation must also be reflected in the conformations of the linear precursors immediately prior to cyclisation. As such, linear tris-thiazoles with bulkier side chain substituents might be expected to adopt conformations such that the rate of addition of a monomer to the linear tris-thiazole would be comparable to, or faster than, that of cyclisation, leading to the formation (and subsequent cyclisation) of higher oligomers.

Interestingly, none of the expected cyclic trimer **7c** was obtained upon treatment of the enantiomerically enriched phenylalanine derived thiazole **6c** with FDPP. In this case, the diastereomeric trimer **9c**, together with the tetramer **8c** were the major products isolated. The formation of **9c** can be attributed to the contamination of the thiazole amino acid **6c** with its enantiomer [ee of the protected thiazole **6c**=70%]. Whilst benzyl groups are generally considered



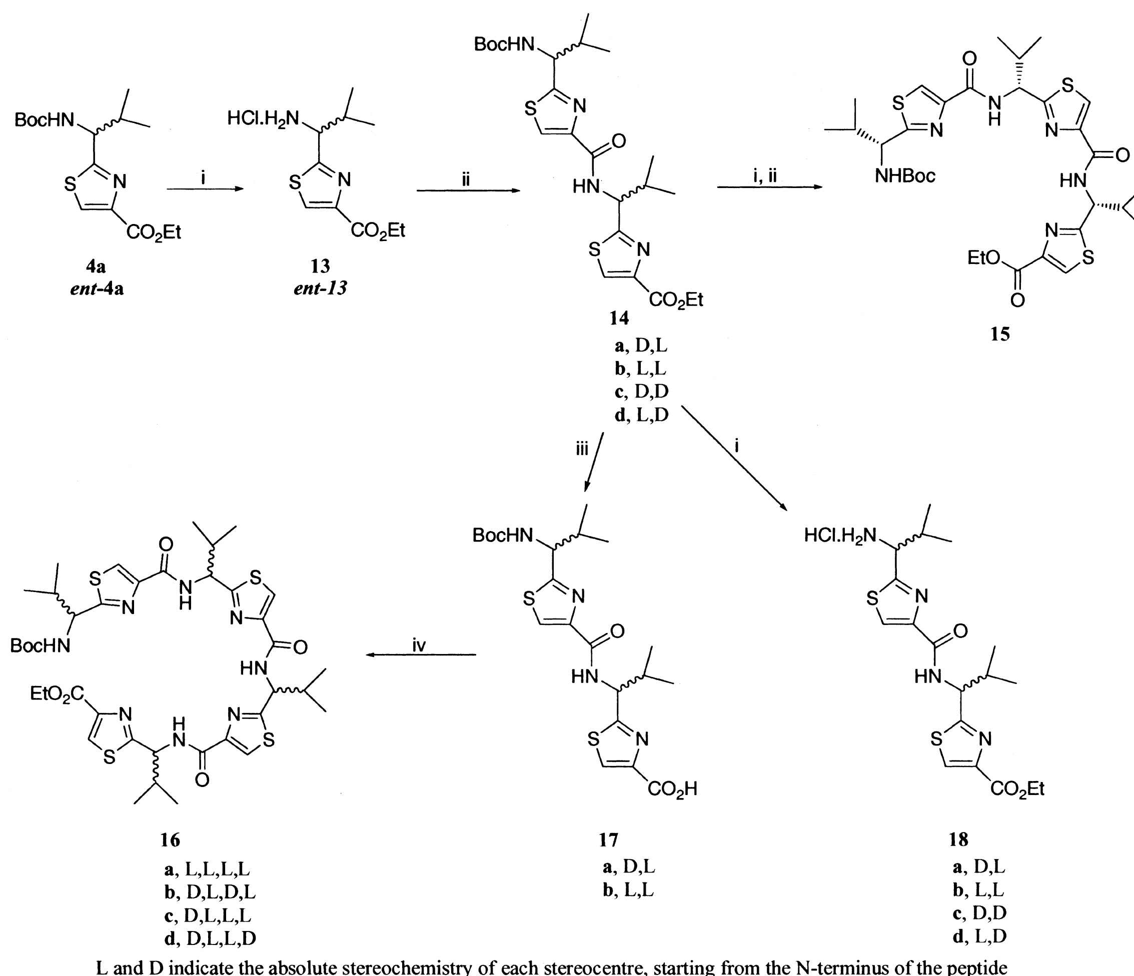
a, R = *i*-Pr; **b**, R = Me; **c**, R = CH_2Ph

to be less sterically demanding than isopropyl groups, in the case of the transannular interactions involved in the cyclic trimers, it might be expected that those involving benzyl groups would be greater than those involving isopropyl groups since the 'reach' of a benzyl group across the ring will be greater than that of an isopropyl group. Presumably, in the case of the thiazole **6c**, the repulsive transannular interactions in the linear tris-thiazole precursor to **7c** slow down the rate of cyclisation to such an extent that the rate of addition of a monomer is much faster than that of cyclisation, so that none of the cyclic trimer **7c** is actually obtained. Fewer transannular interactions would be present in the linear precursor leading to the diastereoisomer **9c**, and cyclisation of this linear tris-thiazole of mixed stereochemistry must be favourable, since no cyclic tetramer with mixed stereochemistry was obtained from this particular cyclooligomerisation reaction.[17]

Our initial cyclooligomerisation studies with the enantiomerically enriched phenylalanine derived thiazole **6c** indicated that somewhat different results might be expected upon cyclooligomerisation of any racemic thiazole amino acid from those obtained using a homochiral thiazole amino acid. In the case of a racemic amino acid, the formation of two diastereomeric cyclic trimers together with four diastereomeric cyclic tetramers might be expected and any repulsive transannular interactions should be minimised in cyclic compounds containing one or more stereocentres of the opposite chirality. Therefore we examined the cyclooligomerisation of the racemic thiazole amino acid *rac*-**6a**.

Upon treatment of *rac*-**6a** with FDPP in the presence of Hünig's base, a mixture of diastereomeric cyclic peptides was obtained in 75% yield. This mixture was found to contain the cyclic trimers *rac*-**7a** and *rac*-**9a** and the cyclic tetramers *rac*-**8a**, **10**, *rac*-**11** and **12**.

No higher cyclic oligomers were observed. Separation of this mixture was achieved by preparative HPLC and the overall cyclic trimer: cyclic tetramer ratio was found to be 1:1 in contrast to the 5:2 ratio observed for the homochiral thiazole **6a**. As expected, the majority of the products contained stereocentres of both configurations, although small amounts of both cyclic trimer *rac*-**7a** and cyclic tetramer *rac*-**8a**, in which all side chains are of the same configuration, were also isolated. Interestingly, a higher proportion of cyclic tetramers was obtained upon cyclooligomerisation of *rac*-**6a** compared to that obtained upon cyclooligomerisation of homochiral **6a**, indicating that factors other than transannular interactions influence the



Scheme 2. *Reagents and conditions*: (i) 4 M HCl in dioxane, rt, 6 h; (ii) **5a** or *ent*-**5a** (1 mol equiv.); EDCI (1.5 mol equiv.), HOBt (1.5 mol equiv.), NMM (3.0 mol equiv.), CH_2Cl_2, DMF; (iii) NaOH (10 mol equiv.), THF/H_2O, 9:1, rt, 18 h; (iv) **18a-d** (1 mol equiv.), EDCI (1.5 mol equiv.), HOBt (1.5 mol equiv.), NMM (3.0 mol equiv.), CH_2Cl_2, DMF.

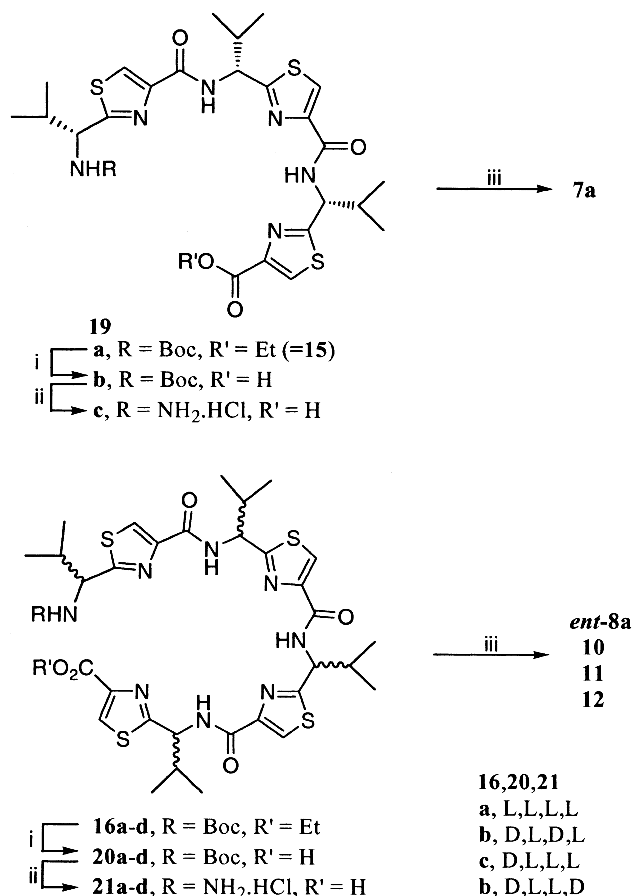
cyclooligomerisation reaction. One contributing factor may be the relative ease of cyclisation of linear peptides containing mixtures of D and L amino acid residues.[2d,e]

Whilst *rac*-**8a** was identified by comparison with the optically pure material obtained previously, the relative stereochemistries of the diastereomeric cyclic tetramers, **10–12**, were assigned on the basis of their symmetry as determined by ^{1}H NMR spectroscopy. The unsymmetrical cyclic tetramer *rac*-**11** was easily identified, since four signals were observed in the ^{1}H NMR spectrum for each type of proton present in this molecule, as expected for a molecule having C_1 symmetry. The cyclic tetramers **10** and **12** are both *meso*-compounds having C_2 and C_i symmetry, respectively. The ^{1}H NMR spectrum of one of these compounds exhibits only a single set of signals for each type of proton in the molecule, whilst two sets of signals are observed for each type of proton in the ^{1}H NMR spectrum of the other tetramer. Since the cyclic tetramer **10** possesses a higher element of symmetry than **12**, the structure in which the side chains have alternate configurations was assigned to the compound which exhibited fewer signals in the ^{1}H NMR spectrum. This assignment was subsequently confirmed following its synthesis via the macrolactamisation of linear peptide amino acids of known relative stereochemistry (see below).

2.2. Macrolactamisation approach

The cyclooligomerisation approach described above is an efficient route to the synthesis of large quantities of *Lissoclinum* cyclic peptide analogues in which all side chains lie on the same face of the molecule. However, the synthesis of compounds with mixed stereochemistry via the cyclooligomerisation approach results in the formation of racemates and requires the separation of diastereomers as illustrated by the cyclooligomerisation of *rac*-**6a**. Since mixtures of D and L stereocentres are commonly found in the naturally occurring cyclic peptides of interest to us, an alternative route to such compounds utilising a macrocyclisation approach was investigated.

To date, the majority of syntheses of naturally occurring *Lissoclinum* cyclic peptides have relied on the synthesis of a linear peptide, followed by a macrolactamisation step and subsequent installation of some or all of the azole heterocycles.[4,18] However, since the azole heterocycles induce a turn structure in a linear peptide that should promote cyclisation,[9] we chose to reverse the normal sequence of the latter two steps and prepared the enantiomerically pure linear thiazole-containing peptides **15** and **16** prior to performing the macrocyclisation step. Thus, the amines **13** and *ent*-**13** were prepared following Boc-deprotection of the thiazoles **4a** and *ent*-**4a**, respectively. Each of these amines were then coupled with each of the carboxylic acids **5a** and *ent*-**5a** using standard peptide coupling techniques[19] leading to the four possible diastereomeric bis-thiazoles **14** in good yield (Scheme 2). Hydrolysis of the ethyl esters of the bis-thiazoles **14a** and **14b** and Boc-deprotection of the bis-thiazoles **14a–d** next led to the acids **17a** and **17b** and the amines **18a–d**, respectively.



Scheme 3. *Reagents and conditions*: (i) NaOH (10 mol equiv.), EtOH/H_2O, rt, 14 h; (ii) 4 M HCl in dioxane, rt, 18 h; (iii) FDPP (1.5 mol equiv.), *i*-Pr_2NEt (3 mol equiv.), CH_3CN, rt, 2 h.

The fully protected tris-thiazole **15** was then prepared on reacting the carboxylic acid **5a** with the bis-thiazole amine **18c**, again using standard peptide coupling techniques. Similarly, the enantiomerically pure linear tetra-thiazoles **16** were prepared in good yield upon coupling the appropriate bis-thiazole acids **17a** and **17b** with the bis-thiazole amines **18a–d**. Saponification of the linear tris- and tetra-thiazole esters **15** and **16**, respectively, gave the corresponding carboxylic acids **19b** and **20** which were immediately subjected to treatment with a 4 M solution of HCl in dioxane, to give the peptides **19c** and **21** as their hydrochloride salts in essentially quantitative yields. Treatment of these salts with FDPP in the presence of Hünigs base finally gave the cyclic peptides (**7a**, *ent*-**8a** and **10–12**) in yields ranging from 58–85% (Scheme 3).

These macrolactamisation yields are considerably higher than most of those obtained in previously reported syntheses of the *Lissoclinum* natural products, in which the heterocycles were incorporated after macrocyclisation.[4,18] This suggests that incorporation of the turn-inducing thiazoles in the linear precursor does indeed favour the macrocyclisation reactions.

3. Conclusions

The synthesis of analogues of the *Lissoclinum* cyclic

peptides has been achieved in high yield via both cyclooligomerisation and macrocyclisation approaches. The cyclooligomerisation approach is favoured for the synthesis of cyclic peptides in which all side chains are identical and of the same stereochemistry, since it provides rapid access to large amounts of novel cyclic peptides. However, the more traditional stepwise approach allows easy access to cyclic peptides containing side chains that have different stereochemistry, as this circumvents the need to separate mixtures of diastereomers. This stepwise approach is also applicable to the synthesis of compounds having side chains with different functional groups.[20] The synthesis of such compounds, together with an investigation of their metal complexation behaviour is underway in our laboratories, and will be reported at a later date.

4. Experimental

4.1. General

Optical rotations were recorded in spectroscopic grade chloroform on a Jasco DIP-370 polarimeter, $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Proton NMR spectra were recorded on either a Bruker DPX 360 (360 MHz) or a Bruker DPX 500 (500 MHz) spectrometer as dilute solutions in deuterochloroform, d_6-dimethyl sulfoxide or d_4-methanol. Chemical shifts are quoted in parts per million (ppm) relative to residual chloroform (δ 7.26), dimethylsulfoxide (δ 2.50) or methanol (δ 3.35) as internal standard and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. All coupling constants, *J*, are quoted in Hertz. Carbon-13 NMR spectra were recorded using the instruments indicated above, at frequencies of 90 MHz or 125 MHz, respectively. Chemical shifts are reported relative to internal chloroform (δ 77.0) as standard on a broad band decoupled mode, and the multiplicities were determined using a DEPT sequence. Mass Spectra were recorded on a VG Autospec, MM-701 CF, a VG Micromass 7070E or a Micromass LCT using electron ionisation (EI), fast atom bombardment (FAB) or electrospray (ES) techniques. Microanalytical data were obtained on a Perkin–Elmer 240B elemental analyser at the University of Nottingham. Flash chromatography was performed on Merck silica gel 60 as the stationary phase and the solvents employed were either of analytical grade or were distilled before use. Analytical HPLC was performed using either a Waters-Associates 440 or a Hewlett Packard series 1100 machine with a Nova-Pak® C_{18} column (3.9×300 mm internal diameter). Preparative HPLC was performed using a Waters-Associates 440 machine with a Dynamax Silica Gel Cartridge Column (30 cm×10 mm internal diameter).

The protected thiazoles **4a–c** were prepared according to literature procedures.[10]

4.2. General procedure 1 for the *C*-deprotection of thiazole amino acid derivatives

Sodium hydroxide (10 equiv.) was added to a solution of the thiazole in a mixture of THF and H_2O (9:1 (v/v), 0.5 M in thiazole) and the mixture was stirred at room temperature for 18 h. The solution was washed with ethyl acetate, then the separated aqueous layer was acidified to pH 4 by the addition of an aqueous solution of citric acid (10% w/v). The mixture was extracted with ethyl acetate and the organic extracts were combined and washed with H_2O and brine. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure to leave the carboxylic acid.

4.3. General procedure 2 for the *N*-deprotection of thiazole amino acid derivatives

A solution of HCl in dioxane (4 M) was added to the protected amino acid (1 mL/mmol) and the mixture was stirred at room temperature under a nitrogen atmosphere for 6 h. The solvent was removed under reduced pressure, then toluene (10 mL/mmol) was added to the residue and the solvent was again removed under reduced pressure to leave the amine as the hydrochloride salt, which was purified by trituration with diethyl ether.

4.4. General procedure 3 for the linear peptide coupling of thiazole amino acid units

N-Methylmorpholine (1.5 equiv.) was added to a suspension of the carboxylic acid (0.25 M) in CH_2Cl_2. The mixture was cooled to 0°C, and then HOBt (1.5 equiv.) followed by EDCI (1.5 equiv.) were added. The solution was stirred at 0°C for 10 min, then a precooled solution of the amino acid (1.1 equiv.) in DMF and NMM (1.5 equiv.) was added. The mixture was warmed to room temperature and stirred at this temperature for 15 h. The solution was partioned between ethyl acetate and aq. citric acid (10% w/v) and the separated aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed sequentially with saturated aq. $NaHCO_3$, H_2O and brine, then dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give the required amide.

4.5. General procedure 4 for the cyclooligomerisation of thiazole amino acids

Diisopropylethylamine (3 equiv.) and FDPP (1.5 equiv.) were added to a suspension of the amino acid in anhydrous acetonitrile (21 mL/mmol), and the mixture was stirred at ambient temperature for 18 h and then evaporated to dryness in vacuo. The residue was partitioned between ethyl acetate (50 mL) and aq. HCl (2 M, 50 mL) and the separated organic layer was washed with aq. HCl (2 M, 50 mL). The combined aqueous solutions were back extracted with ethyl acetate (50 mL) and then the organic solutions were combined and washed successively with aq. NaOH (1 M, 2×50 mL), H_2O (50 mL) and brine (50 mL). The solution was dried ($MgSO_4$) and the solvent was then removed under reduced pressure to leave a mixture of cyclic peptide products, which were separated by column chromatography (silica gel) or by preparative HPLC (Dynamax Silica Gel Cartridge Column, 30 cm×10 mm internal diameter).

4.6. General procedure 5 for macrocyclisation of linear peptides

An aqueous solution of NaOH (1 M, 10 equiv.) was added to a solution of the linear oligomer in ethanol (0.02 g/mL) and the mixture was stirred at room temperature for 14 h. The ethanol was removed under reduced pressure and the aqueous residue was acidifed to pH 2 by the addition of aq. HCl (2 M). The mixture was extracted with CH_2Cl_2 (3×25 mL) and then the combined organic extracts were washed with H_2O (2×25 mL) and brine (25 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. A solution of HCl in dioxane (4 M, 1 mL/mmol) was added to the residue and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 18 h. The solvent was removed under reduced pressure, then toluene (15 mL) was added to the residue and the solvent was again removed under reduced pressure. The residue was suspended in CH_3CN (2 mL per 0.01 mmol of compound), and then diisopropylethylamine (3 equiv.) and FDPP (1.5 equiv.) were added. The mixture was stirred at room temperature under a nitrogen atmosphere for 2 h and then the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate (50 mL) and aq. HCl (2 M, 50 mL) and the separated organic layer was washed with aq. HCl (2 M, 50 mL). The combined aqueous extracts were back extracted with ethyl acetate (50 mL) and then the organic solutions were combined and washed successively with aq. NaOH (1 M, 2×50 mL), H_2O (50 mL) and brine (50 mL). The solution was dried ($MgSO_4$) and the solvent was then removed under reduced pressure. The residue was purified by chromatography on silica gel to give the required cyclic peptide.

4.7. Amino acid 6a

The thiazole **4a** (1.0 g, 3.0 mmol) was treated according to general procedure 1 and gave the carboxylic acid **5a** as a pale yellow solid. This material was not purified, but was immediately treated according to general procedure 2 leading to the amino acid (0.7 g, 97%) as a colourless solid, which was used without purification.

4.8. Amino acid 6b

The thiazole **4b** (0.4 g, 1.3 mmol) was treated according to general procedure 1 and gave the carboxylic acid **5b** as a pale brown solid. This material was not purified, but was immediately treated according to general procedure 2 leading to the amino acid (0.26 g, 94%) as a colourless solid, which was used without purification.

4.9. Amino acid 6c

The thiazole **4c** (100 mg, 0.27 mmol) was treated according to general procedure 1 and gave the carboxylic acid **5c** as a pale brown solid. This material was not purified, but was immediately treated according to general procedure 2 leading to the amino acid (72 mg, 95%) as a colourless solid, which was used without purification.

4.10. Amino acid *rac*-6a

Thiazole *rac*-**4a** (0.99 g, 3.0 mmol) was treated according to general procedure 1 and gave the carboxylic acid *rac*-**5a** as a pale yellow solid. This material was not purified, but was immediately treated according to general procedure 2 leading to the amino acid *rac*-**6a** (0.69 g, 96%) as a colourless solid, which was used without purification.

4.10.1. Cyclic trimer 7a and cyclic tetramer 8a. The thiazole amino acid **6a** (0.12 g, 0.51 mmol) was treated according to general procedure 4 and the crude product was purified by column chromatography (ethyl acetate/hexane; 7:3) to give the cyclic trimer (0.064 g, 70%) as a colourless solid; mp 258–260°C (from Et_2O); $[\alpha]_D^{23}=+126.8$ (*c* 0.53, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.45 (d, J=9.3 Hz, 3H), 8.09 (s, 3H), 5.43 (dd, J=9.3, 5.8 Hz, 3H), 2.30 (m, 3H), 1.10 (d, J=6.8 Hz, 9H), 1.05 (d, J=6.8 Hz, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.6 (C), 159.7 (C), 149.1 (C), 123.4 (CH), 55.4 (CH), 35.3 (CH), 18.8 (CH_3), 18.3 (CH_3); *m/z* (FAB) 547.1582, ($C_{24}H_{31}N_6O_3S_3$ requires 547.1620, $[M+H]^+$); Found C, 52.5; H, 5.6; N, 15.0. $C_{24}H_{30}N_6O_3S_3$ requires C, 52.7; H, 5.5; N, 15.0%. Further elution gave the cyclic tetramer (0.023 g, 25%) as a colourless solid; mp 152–154°C (from Et_2O); $[\alpha]_D^{23}=+204.6$ (*c* 0.57, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.06 (s, 4H), 7.84 (d, J=9.1 Hz, 4H), 5.22 (dd, J=9.1, 8.2 Hz, 4H), 2.59 (m, 4H), 1.17 (d, J=6.7 Hz, 12H), 1.04 (d, J=6.6 Hz, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.3 (C), 160.3 (C), 148.9 (C), 124.2 (CH), 55.3 (CH), 32.6 (CH), 19.6 (CH_3), 18.9 (CH_3); *m/z* (FAB) 729.2152, ($C_{32}H_{41}N_8O_4S_4$ requires 729.2134, $[M+H]^+$); Found C, 50.9; H, 5.5; N, 14.6. $C_{32}H_{40}N_8O_4S_4$.0.5 H_2O requires C, 50.9; H, 5.7; N, 14.8%.

4.11. Crystal structure determination of compound 7a

Single crystals of compound **7a** suitable for X-ray diffraction were obtained upon slow diffusion of diethyl ether into a solution of **7a** in dichloromethane. A crystal was encapsulated in a film of RS3000 perfluoropolyether oil and mounted on a dual-stage glass fibre before transfer to the diffractometer.

4.11.1. Crystal data†. $C_{24}H_{30}N_6O_3S_3$, M=546.72, monoclinic, a=18.926(5), b=7.961(2), c=19.455(5) Å, β=106.89(2)°, U=2804.8(13) Å^3, T=150(2) K, space group *I*2 (Alt. *C*2, No. 5), Z=4, D_c=1.295 g cm^{-3}, μ(Mo–*K*a)=0.300 mm^{-1}, 4094 unique reflections measured and used in all calculations. Final R_1 [3639 F>4s(F)]=0.0572 and wR(all F^2) was 0.141.

4.11.2. Cyclic trimer 7b and cyclic tetramer 8b. The thiazole amino acid **6b** (0.19 g, 0.92 mmol) was treated according to general procedure 4 and the crude product was purified by column chromatography (ethyl acetate/hexane; 7:3 to 9:1) to give the cyclic trimer (0.058 g, 41%) as a colourless solid; mp 298–300°C (CH_2Cl_2/Et_2O);

† Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 153184 and 204593. Copies of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or email: deposit@ccdc.cam.ac.uk].

$[\alpha]_D^{28}$=+48.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.68 (d, *J*=6.8 Hz, 3H), 8.17 (s, 3H), 5.64 (app. quintet, *J*=6.8 Hz, 3H), 1.74 (d, *J*=6.8 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 171.2 (C), 159.5 (C), 148.8 (C), 124.0 (CH), 47.4 (CH), 25.0 (CH_3); *m/z* (FAB) 485.0512 ($C_{18}H_{18}O_3N_6S_3Na$ requires 485.0500, $[M+Na]^+$). Further elution gave the cyclic tetramer (0.018 g, 13%) as a colourless solid; mp 268–271°C; $[\alpha]_D^{23}$=+17.1 (*c* 0.7, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.12 (s, 4H), 7.99 (d, *J*=8.1 Hz, 4H), 5.61 (app. quintet, *J*=6.9 Hz, 4H), 1.86 (d, *J*=6.9 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (C), 159.9 (C), 148.2 (C), 124.8 (CH), 46.0 (CH), 21.2 (CH_3); *m/z* (FAB) 639.0666 ($C_{24}H_{24}O_4N_8S_4Na$ requires 639.0701, $[M+Na^+]$).

4.11.3. Cyclic trimer 9c and cyclic tetramer 8c. The thiazole amino acid **6c** (50 mg, 0.18 mmol) was treated according to general procedure 4 and the crude product was purified by column chromatography (ethyl acetate/hexane; 7:3) to give the cyclic trimer (4.0 mg, 10%) as a colourless solid; mp 248–249°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{28}$=−0.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.57 (d, *J*=4.6 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.69 (d, *J*=5.8 Hz, 1H), 8.14 (s, 1H), 8.04 (s, 1H), 8.01 (s, 1H), 7.18–7.31 (m, 9H), 7.02–7.05 (m, 6H), 5.86–5.87 (m, 1H), 5.65–5.66 (m, 1H), 5.46–5.48 (m, 1H), 3.74 (dd, *J*=4.2, 12.9 Hz, 1H), 3.57 (dd, *J*=4.2, 12.9 Hz, 1H), 3.55 (dd, *J*=4.2, 12.9 Hz, 1H), 3.21 (dd, *J*=8.4, 13.7 Hz, 1H), 2.90 (dd, *J*=9.1, 12.8 Hz, 1H), 2.89 (dd, *J*=9.1, 12.8 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.1 (C), 168.1 (C), 168.0 (C), 160.0 (C), 159.9 (C), 159.5 (C), 149.1 (C), 148.5 (C), 148.3 (C), 130.1 (CH), 129.9 (CH), 129.7 (CH), 129.3 (CH), 128.7 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 124.9 (CH), 123.9 (CH), 123.5 (CH), 120.3 (CH), 54.1 (CH), 53.8 (CH), 52.9 (CH), 43.6 (CH_2), 43.3 (CH_2), 43.1 (CH_2), 9 signals obscured or overlapping; *m/z* (FAB) 713.1450 ($C_{36}H_{30}O_3N_6S_3Na$ requires 713.1439, $[M+Na]^+$). Further elution gave the cyclic tetramer (17 mg, 41%) as a colourless solid; mp 250–254°C; $[\alpha]_D^{28}$=−5.79 (*c* 1.5, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.99 (s, 4H), 7.95–7.98 (d, *J*=8.5 Hz, 4H), 7.15–7.30 (m, 20H), 5.68–5.74 (m, 4H), 3.49–3.57 (m, 8H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.4 (C), 148.6 (C), 135.9 (C), 130.0 (CH), 129.6 (CH), 127.2 (CH), 123.9 (CH), 52.7 (CH), 43.9 (CH_2), 3 signals obscured or overlapping; *m/z* (FAB) 920.2004, ($C_{48}H_{40}O_4N_8S_4$ requires 920.2055, M^+).

4.11.4. Cyclooligomerisation of *rac*-6a. The thiazole amino acid *rac*-**6a** (0.50 g, 2.1 mmol) was treated according to general procedure 4 and the crude product was separated by preparative HPLC (ethyl acetate/hexane; 62:48; flow rate 1 mL/min) producing 6 fractions A-F (combined yield 75%) in the ratio 38:12:6:18:21:5.

Concentration of fraction A (retention time: 9 min) gave the cyclic trimer *rac*-**9a** as a colourless solid, mp 150–155°C (CH_2Cl_2/Et_2O). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.52 (d, *J*=9.3 Hz, 1H), 8.50 (d, *J*=8.1 Hz, 1H), 8.46 (d, *J*=6.9 Hz, 1H), 8.20 (s, 1H), 8.12 (s, 2H), 5.70 (dd, *J*=3.0, 9.3 Hz, 1H), 5.52 (dd, *J*=3.8, 8.1 Hz, 1H), 5.25 (dd, *J*=5.6, 6.9 Hz, 1H), 2.56–2.48 (m, 1H), 2.42–2.28 (m, 2H), 1.10 (d, *J*=6.7 Hz, 3H), 1.08 (d, *J*=6.7 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.8 Hz, 3H), 0.85 (d, *J*=6.8 Hz, 3H), 0.81 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.5 (C), 167.5 (C), 167.1 (C), 160.3 (C), 160.2 (C), 160.1 (C), 149.6 (C), 148.9 (C), 148.7 (C), 124.9 (CH), 123.5 (CH), 123.0 (CH), 57.0 (CH), 56.5 (CH), 55.7 (CH), 37.2 (CH), 35.4 (CH), 33.5 (CH), 19.6 (CH_3), 19.4 (CH_3), 18.2 (CH_3), 18.0 (CH_3), 17.3 (CH_3), 16.1 (CH_3); MS (EI) *m/z* 569.1432, ($C_{24}H_{30}N_6O_3S_3Na$ requires 569.1433, $[M+Na]^+$).

Concentration of fraction B (retention time: 14 min) gave the cyclic tetramer **10** as a colourless solid, mp 330–335°C (CH_2Cl_2/Et_2O). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.31 (d, *J*=9.7 Hz, 4H), 8.11 (s, 4H), 5.39 (dd, *J*=6.9, 9.7 Hz, 4H), 2.24 (m, 4H), 1.03 (d, *J*=6.9 Hz, 12H), 0.94 (d, *J*=6.9 Hz, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.1 (C), 159.9 (C), 149.7 (C), 123.5 (CH), 55.3 (CH), 35.1 (CH), 19.1 (CH_3), 18.7 (CH_3); MS (EI) *m/z* 751.1912, ($C_{32}H_{40}O_4N_8S_4Na$ requires 751.1953, $[M+Na]^+$).

Concentration of fraction C (retention time: 15.5 min) gave the cyclic trimer *rac*-**7a** as a colourless solid, which was identical in all respects other than optical rotation, to the compound obtained upon cyclooligomerisation of amino acid **6a**.

Concentration of fraction D (retention time: 16.5 min) gave the cyclic tetramer **12** as a colourless solid, mp 312–315°C (CH_2Cl_2/Et_2O). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.16 (s, 2H), 8.11 (s, 2H), 8.03 (d, *J*=8.8 Hz, 2H), 7.92 (d, *J*=9.2 Hz, 2H), 5.26 (m, 4H), 2.75–2.68 (m, 2H), 2.56–2.51 (m, 2H), 1.08 (d, *J*=6.7 Hz, 6H), 1.04 (d, *J*=6.8 Hz, 6H), 0.97 (d, *J*=6.7 Hz, 6H), 0.89 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.4 (C), 170.2 (C), 161.1 (C), 160.6 (C), 148.6 (C), 148.5 (C), 124.7 (CH), 124.6 (CH), 57.4 (CH), 56.0 (CH), 33.8 (CH), 31.9 (CH), 19.72 (CH_3), 19.68 (CH_3), 17.65 (CH_3), 17.45 (CH_3); MS (EI) *m/z* 751.1957, ($C_{32}H_{40}O_4N_8S_4Na$ requires 751.1953, $[M+Na]^+$).

Concentration of fraction E (retention time: 19 min) gave the cyclic tetramer *rac*-**11** as a colourless solid mp 110–114°C (CH_2Cl_2/Et_2O). ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.48 (d, *J*=8.9 Hz, 1H), 8.23 (d, *J*=8.7 Hz, 1H), 8.12 (s, 1H), 8.09 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 7.98 (d, *J*=7.8 Hz, 1H), 7.88 (d, *J*=9.9 Hz, 1H), 5.47 (dd, *J*=4.9, 8.9 Hz, 1H), 5.32 (dd, *J*=9.9, 9.9 Hz, 1H), 5.23 (dd, *J*=6.7, 8.7 Hz, 1H), 5.00 (d, *J*=7.8, 8.3 Hz, 1H), 2.71–2.86 (m, 1H), 2.43–2.37 (m, 2H), 2.25–2.22 (m, 1H), 1.21 (d, *J*=6.6 Hz, 3H), 1.15 (d, *J*=6.8 Hz, 3H), 1.09 (d, *J*=6.6 Hz, 3H), 1.04 (d, *J*=6.8 Hz, 3H), 1.00–0.95 (m, 9H), 0.84 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.3 (C), 169.5 (C), 169.0 (C), 168.3 (C), 160.6 (C), 160.2 (C), 160.1 (C), 160.0 (C), 150.0 (C), 149.6 (C), 149.1 (C), 148.7 (C), 124.4 (CH), 124.1 (CH), 124.0 (CH), 123.8 (CH), 56.7 (CH), 55.7 (CH), 55.0 (CH), 34.9 (CH), 34.8 (CH), 33.3 (CH), 32.6 (CH), 20.0 (CH_3), 19.8 (CH_3), 19.4 (CH_3), 19.2 (CH_3), 19.1 (CH_3), 18.9 (CH_3), 18.4 (CH_3), 18.2 (CH_3) (1 signal overlapping); MS (EI) *m/z* 751.1936, ($C_{32}H_{40}O_4N_8S_4Na$ requires 751.1953, $[M+Na]^+$).

Concentration of fraction F (retention time: 31 min) gave the cyclic tetramer *rac*-**8a** as a colourless solid, which was identical in all respects, other than optical rotation, to the compound obtained upon cyclooligomerisation of amino acid **6a**.

4.12. Amine 13

The thiazole **4a** (5.0 g, 15 mmol) was treated according to general procedure 2 to give the amine (3.9 g, 97%) as the hydrochloride salt which was used without purification.

4.13. Amine *ent*-13

The thiazole *ent*-**4a** (5.0 g, 15 mmol) was treated according to general procedure 2 to give the amine (4.0 g, 99%) as the hydrochloride salt which was used without purification.

4.13.1. Bis-thiazole 14a. The amine *ent*-**13** (0.50 g, 1.9 mmol) and the acid **5a** (0.57 g, 1.9 mmol) were coupled according to general procedure 3. The crude product was purified by column chromatography (ethyl acetate/petroleum ether; 1:1) to give the dithiazole (0.83 g, 86%) as a colourless foam; mp 61–64°C; $[\alpha]_D^{23}=+31.4$ (*c* 1.7, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.03 (s, 1H), 7.95 (d, J=9.2 Hz, 1H), 5.31 (dd, J=6.8, 9.2 Hz, 1H), 5.21 (d, J=8.1 Hz, 1H), 4.88 (bs, 1H), 4.41 (q, J=7.1 Hz, 2H), 2.64 (m, 1H), 2.37 (m, 1H), 1.46 (s, 9H), 1.39 (t, J=7.1 Hz, 3H), 1.03 (d, J=6.8 Hz, 3H), 1.00 (d, J=6.8 Hz, 3H), 0.99 (d, J=6.8 Hz, 3H), 0.93 (d, J=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.1 (C), 171.7 (C), 161.3 (C), 160.8 (C), 155.4 (C), 149.2 (C), 147.5 (C), 127.0 (CH), 123.4 (CH), 80.2 (C), 61.3 (CH_2), 58.0 (CH), 56.5 (CH), 33.2 (CH), 33.0 (CH), 28.3 (CH_3), 19.7 (CH_3), 19.3 (CH_3), 18.0 (CH_3), 17.3 (CH_3), 14.3 (CH_3); MS (EI) *m/z* 533.1837 ($C_{23}H_{34}N_4O_5S_2Na$ requires: 533.1868, $[M+Na]^+$); Found: C, 53.9; H, 6.3; N, 11.05. $C_{23}H_{34}N_4O_5S_2$ requires: C, 54.1; H, 6.7; N, 11.0%.

4.13.2. Bis-thiazole 14b. The amine *ent*-**13** (0.50 g, 1.9 mmol) and the acid *ent*-**5a** (0.57 g, 1.9 mmol) were coupled according to general procedure 3. The crude product was purified by column chromatography (ethyl acetate/petroleum ether; 1:1) to give the dithiazole (0.78 g, 81%) as a colourless foam; mp 91–93°C; $[\alpha]_D^{23}=-5.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.00 (bs, 1H), 7.93 (d, J=9.2 Hz, 1H), 5.31–5.22 (m, 2H), 4.86 (bs, 1H), 4.38 (q, J=7.1 Hz, 2H), 2.60 (m, 1H), 2.35 (m, 1H), 1.42 (s, 9H), 1.37 (t, J=7.1 Hz, 3H), 1.00 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.9 (C), 171.6 (C), 161.2 (C), 160.8 (C), 155.3 (C), 149.3 (C), 147.4 (C), 126.9 (CH), 123.3 (CH), 80.2 (C), 61.3 (CH_2), 57.8 (CH), 56.4 (CH), 33.1 (CH), 32.9 (CH), 28.2 (CH_3), 19.6 (CH_3), 19.2 (CH_3), 18.0 (CH_3), 17.3 (CH_3), 14.3 (CH_3); *m/z* (ES) 533.1822 ($C_{23}H_{34}N_4O_5S_2Na$ requires: 533.1868, $[M+Na]^+$); Found: C, 54.2; H, 6.6; N, 11.3. $C_{23}H_{34}N_4O_5S_2$ requires: C, 54.1; H, 6.7; N, 11.0%.

4.13.3. Bis-thiazole 14c. The amine **13** (0.67 g, 2.5 mmol) and the acid **5a** (0.7 g, 2.3 mmol) were coupled according to general procedure 3. The crude product was purified by column chromatography (ethyl acetate/petroleum ether; 1:1) to give the dithiazole (1.2 g, 90%) as a colourless foam; mp 93–94°C; $[\alpha]_D^{23}=+5.6$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.02 (bs, 1H), 7.92 (d, J=9.2 Hz, 1H), 5.31 (dd, J=9.2, 7.0 Hz, 1H), 5.18 (bs, 1H), 4.85 (bs, 1H), 4.42 (q, J=7.2 Hz, 2H), 2.63–2.54 (bm, 1H), 2.38–2.29 (bm, 1H), 1.40 (s, 9H), 1.34 (t, J=7.2 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.94 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.7 (C), 171.6 (C), 161.2 (C), 160.7 (C), 155.3 (C), 149.2 (C), 147.4 (C), 126.9 (CH), 123.3 (CH), 80.1 (C), 61.3 (CH_2), 56.4 (CH), 56.3 (CH), 33.0 (CH), 32.9 (CH), 28.2 (CH_3), 19.6 (CH_3), 19.2 (CH_3), 17.9 (CH_3), 17.3 (CH_3), 14.2 (CH_3); *m/z* (ES) 533.1813 ($C_{23}H_{34}N_4O_5S_2Na$ requires: 533.1868, $[M+Na]^+$); Found: C, 53.9; H, 6.7; N, 10.8. $C_{23}H_{34}N_4O_5S_2$ requires: C, 54.1; H, 6.7; N, 11.0%.

4.13.4. Bis-thiazole 14d. The amine **13** (0.50 g, 1.9 mmol) and the acid *ent*-**5a** (0.57 g, 1.9 mmol) were coupled according to general procedure 3. The crude product was purified by column chromatography (ethyl acetate/petroleum ether; 1:1) to give the dithiazole (0.76 g, 79%) as a colourless foam; mp 60–63°C; $[\alpha]_D^{22}=-28.6$ (*c* 1.8, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.01 (s, 1H), 7.95 (d, J=9.2 Hz, 1H), 5.28 (m, 1H), 5.25 (d, J=8.1 Hz, 1H), 4.86 (bs, 1H), 4.38 (q, J=7.1 Hz, 2H), 2.61 (m, 1H), 2.35 (m, 1H), 1.43 (s, 9H), 1.37 (t, J=7.1 Hz, 3H), 1.00 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H), 0.97 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.1 (C), 171.7 (C), 161.2 (C), 160.8 (C), 155.4 (C), 149.2 (C), 147.4 (C), 126.9 (CH), 123.4 (CH), 80.2 (C), 61.3 (CH_2), 57.9 (CH), 56.4 (CH), 33.1 (CH), 32.9 (CH), 28.2 (CH_3), 19.6 (CH_3), 19.2 (CH_3), 18.0 (CH_3), 17.3 (CH_3), 14.3 (CH_3); MS (EI) *m/z* 533.1819 ($C_{23}H_{34}N_4O_5S_2Na$ requires: 533.1868, $[M+Na]^+$); Found: C, 54.2; H, 6.7; N, 11.1. $C_{23}H_{34}N_4O_5S_2$ requires: C, 54.1; H, 6.7; N, 11.0%).

4.13.5. Bis-thiazole amine 18a. The carbamate **14a** (0.20 g, 0.39 mmol) was treated according to general procedure 2 and gave the hydrochloride salt of the amine (0.16 g, 91%) as a colourless solid; mp 137–140°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{23}=+10$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, CD_3OD) δ 8.62 (d, J=8.7 Hz, 1H), 8.42 (s, 1H), 8.41 (s, 1H), 5.33 (dd, J=8.7, 6.8 Hz, 1H), 4.76 (d, J=6.8 Hz, 1H), 4.43 (q, J=7.1 Hz, 2H), 2.85–2.23 (m, 2H), 1.43 (t, J=7.1 Hz, 3H), 1.16 (d, J=6.9 Hz, 3H), 1.12 (d, J=6.7 Hz, 3H), 1.07 (d, J=6.8 Hz, 3H), 1.02 (d, J=6.8 Hz, 3H), signals due to amino group protons not observed; ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.4 (C), 164.0 (C), 161.4 (C), 160.7 (C), 148.8 (C), 146.5 (C), 128.2 (CH), 125.2 (CH), 61.5 (CH_2), 58.3 (CH), 57.8 (CH), 32.3 (CH), 32.2 (CH), 19.8 (CH_3), 19.1 (CH_3), 18.6 (CH_3), 18.0 (CH_3), 14.3 (CH_3); *m/z* (ES) 843.2788 ($C_{36}H_{52}N_8O_6S_4Na$ requires: 843.2795, $[2M+Na]^+$).

4.13.6. Bis-thiazole amine 18b. The carbamate **14b** (0.40 g, 0.78 mmol) was treated according to general procedure 2 and gave the hydrochloride salt of the amine (0.34 g, 99%) as a colourless solid; mp 120–123°C; $[\alpha]_D^{23}=+35.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, d_6-DMSO) δ 8.95 (br s, 4H), 8.46 (s, 1H), 8.42 (s, 1H), 5.10 (dd, J=8.5, 8.4 Hz, 1H), 4.72 (m, 1H), 4.29 (q, J=7.1 Hz, 2H), 2.60–2.45 (m, 1H), 2.39–2.30 (m, 1H), 1.29 (t, J=7.1 Hz, 3H), 1.02 (d, J=6.6 Hz, 3H), 1.00 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.9 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H); *m/z* (ES) 821.2908 ($C_{36}H_{53}N_8O_6S_4$ requires 821.2971, $[2M+H]^+$).

4.13.7. Bis-thiazole amine 18c. The carbamate **14c** (0.40 g, 0.78 mmol) was treated according to general procedure 2 and gave the hydrochloride salt of the amine (0.32 g, 91%)

as a colourless solid; mp 121–123°C; $[\alpha]_D^{24}=-42.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, d_6-DMSO) δ 8.92 (br s, 4H), 8.46 (s, 1H), 8.42 (s, 1H), 5.10 (dd, *J*=8.5, 8.4 Hz, 1H), 4.73 (m, 1H), 4.29 (q, *J*=7.1 Hz, 2H), 2.60–2.45 (m, 1H), 2.39–2.30 (m, 1H), 1.29 (t, *J*=7.1 Hz, 3H), 1.02 (d, *J*=6.6 Hz, 3H), 0.99 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.9 Hz, 3H), 0.89 (d, *J*=6.8 Hz, 3H); *m/z* (ES) 821.2921 ($C_{36}H_{53}N_8O_6S_4$ requires 821.2971, $[2M+H]^+$).

4.13.8. Bis-thiazole amine 18d. The carbamate **14d** (0.20 g, 0.39 mmol) was treated according to general procedure 2 and gave the hydrochloride salt of the amine (0.15 g, 86%) as a colourless solid; mp 140–143°C; $[\alpha]_D^{23}=-0.3$ (*c* 1.5, $CHCl_3$); ^1H NMR (360 MHz, CD_3OD) δ 8.62 (d, *J*=8.7 Hz, 1H), 8.42 (s, 2H), 5.33 (dd, *J*=8.7, 6.8 Hz, 1H), 4.76 (d, *J*=6.3 Hz, 1H), 4.43 (q, *J*=7.1 Hz, 2H), 2.47 (m, 2H), 1.43 (t, *J*=7.1 Hz, 3H), 1.16 (d, *J*=6.9 Hz, 3H), 1.11 (d, *J*=6.7 Hz, 3H), 1.07 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H), signals due to amino group protons not observed; ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.4 (C), 164.0 (C), 161.4 (C), 160.7 (C), 148.8 (C), 146.5 (C), 128.2 (CH), 125.2 (CH), 61.5 (CH_2), 58.3 (CH), 57.8 (CH), 32.3 (CH), 32.2 (CH), 19.8 (CH_3), 19.1 (CH_3), 18.6 (CH_3), 18.0 (CH_3), 14.3 (CH_3); *m/z* (ES) 433.1822 ($C_{18}H_{26}N_4O_3S_2Na$ requires: 433.1868, $[M+Na]^+$).

4.13.9. Bis-thiazole acid 17a. The ester **14a** (0.60 g, 1.2 mmol) was treated according to general procedure 1 and gave the acid (0.54 g, 96%) as a colourless solid; mp 105–108°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{24}=+20.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.99 (br s, 1H), 8.17 (s, 1H), 8.10 (s, 1H), 8.03 (d, *J*=8.6 Hz, 1H), 6.59 (br s, 1H), 5.30 (dd, *J*=7.4, 8.6 Hz, 1H), 4.86 (m, 1H), 2.58 (m, 1H), 2.32 (m, 1H), 1.42 (br s, 9H), 1.05–0.86 (m, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.1 (C), 171.9 (C), 163.9 (C), 161.9 (C), 155.6 (C), 149.0 (C), 147.0 (C), 128.3 (CH), 123.9 (CH), 80.3 (C), 56.5 (CH), 58.0 (CH), 33.2 (CH), 32.9 (CH), 28.3 (CH_3), 19.7 (CH_3), 19.3 (CH_3), 18.1 (CH_3), 17.4 (CH_3); *m/z* (ES) 505.1548 ($C_{21}H_{30}N_4O_5S_2Na$ requires: 505.1555, $[M+Na]^+$).

4.13.10. Bis-thiazole acid 17b. The ester **14b** (0.20 g, 0.39 mmol) was treated according to general procedure 1 and gave the acid (0.15 g, 79%) as a colourless solid; mp 102–106°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{24}=-26.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.08 (s, 1H), 7.94 (bs, 1H), 5.36–5.31 (m, 1H), 5.18 (bs, 1H), 4.90 (bs, 1H), 2.65–2.50 (m, 1H), 2.41–2.26 (m, 1H), 1.45 (s, 9H), 1.06–1.00 (m, 9H), 0.95 (d, *J*=6.2 Hz, 3H), signal due to carboxylic acid group proton not observed; *m/z* (ES) 505.1588 ($C_{21}H_{30}N_4O_5S_2Na$ requires 505.1555, $[M+Na]^+$).

4.13.11. Linear tris-thiazole 15. The amine **18c** (0.87 g, 1.9 mmol) and the acid **5a** (0.52 g, 1.7 mmol) were coupled according to general procedure 3 and the crude product was purified by column chromatography (silica; ethyl acetate/petroleum ether; 2:3) to give the tristhiazole (1.0 g, 85%) as a colourless foam; m.p. 104–106°C, $[\alpha]_D^{21}=+7.3$ (*c* 0.8, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.05 (s, 1H), 8.03 (s, 1H), 7.95 (d, *J*=9.2 Hz, 1H), 7.84 (d, *J*=9.2 Hz, 1H), 5.35 (dd, *J*=5.9, 9.2 Hz, 1H), 5.33 (dd, *J*=6.7, 9.2 Hz, 1H), 5.20 (d, *J*=8.7 Hz, 1H), 4.89 (bs, 1H), 4.39 (q, *J*=7.1 Hz, 2H), 2.66–2.53 (m, 2H), 2.41–2.30 (m, 1H), 1.43 (s, 9H), 1.38 (t, *J*=7.1 Hz, 3H), 1.05 (d, *J*=7.1 Hz, 3H), 1.03 (d, *J*=7.1 Hz, 3H), 1.02 (d, *J*=7.0 Hz, 3H), 1.00 (d, *J*=6.8 Hz, 3H), 0.98 (d, *J*=6.4 Hz, 3H), 0.91 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.5 (C), 171.9 (C), 171.8 (C), 161.3 (C), 160.9 (C), 160.8 (C), 155.4 (C), 149.3 (C), 149.2 (C), 147.4 (C), 126.9 (CH), 123.5 (CH), 80.3 (C), 61.4 (CH_2), 57.9 (CH), 56.5 (CH), 56.2 (CH), 32.9 (CH), 32.9 (CH), 28.2 (CH_3), 19.6 (CH_3), 19.5 (CH_3), 19.3 (CH_3), 17.8 (CH_3), 17.6 (CH_3), 17.4 (CH_3), 14.3 (CH_3), 2 signals obscured or overlapping; *m/z* (ES) 693.2629 ($C_{31}H_{45}N_6O_6S_3$ requires 693.2563 $[M+H]^+$); Found: C, 53.4; H, 6.3; N, 12.1. $C_{31}H_{44}N_6O_6S_3$ requires: C, 53.75; H, 6.4; N, 11.8%.

4.13.12. Linear tetra-thiazole 16a. The amine **18b** (0.15 g, 0.31 mmol) and the acid **17b** (0.17 g, 0.31 mmol) were coupled according to general procedure 3, and the crude product was purified by column chromatography (ethyl acetate/petroleum ether (7:3) to give the tetramer (0.24 g, 92%) as a colourless solid; mp 107–108°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{28}=+28.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.03 (s, 1H), 8.02 (s, 1H), 8.01 (br s, 1H), 7.99 (s, 1H), 7.90 (d, *J*=9.1 Hz, 1H), 7.82 (d, *J*=9.2 Hz, 1H), 7.80 (d, *J*=9.2 Hz, 1H), 5.35–5.24 (m, 4H), 4.82 (bs, 1H), 4.35 (q, *J*=7.2 Hz, 2H), 2.64–2.43 (bm, 3H), 2.28 (m, 1H), 1.38 (s, 9H), 1.33 (t, *J*=7.1 Hz, 3H), 1.03–0.91 (m, 21H), 0.85 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7 (C), 172.0 (C), 171.8 (C), 161.1 (C), 160.7 (C), 160.6 (C), 155.3 (C), 149.3 (C), 149.1 (C), 147.3 (C), 126.8 (CH), 123.6 (CH), 123.5 (CH), 123.4 (CH), 80.3 (C), 61.2 (CH_2), 57.9 (CH), 56.4 (CH), 56.3 (CH), 56.2 (CH), 32.9 (CH), 32.8 (CH), 32.7 (CH), 28.1 (CH_3), 19.5 (CH_3), 19.4 (CH_3), 19.3 (CH_3), 19.1 (CH_3), 17.6 (CH_3), 17.5 (CH_3), 17.4 (CH_3), 17.2 (CH_3), 14.2 (CH_3), 4 signals obscured or overlapping; *m/z* (ES) 897.2871 ($C_{39}H_{54}N_8O_7S_4Na$ requires 897.2896, $[M+Na]^+$); Found: C, 52.9; H, 6.2; N, 12.4. $C_{39}H_{54}N_8O_7S_4 \cdot 0.5H_2O$ requires: C, 53.0; H, 6.3; N, 12.7%.

4.13.13. Linear tetrathiazole 16b. The amine **18a** (0.15 g, 0.31 mmol) and the acid **17a** (0.17 g, 0.31 mmol) were coupled according to general procedure 3, and the crude product was purified by column chromatography (ethyl acetate/petroleum ether (7:3) to give the tetramer (0.20 g, 77%) as a colourless solid, mp 79–83°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{25}=+23.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.06 (s, 2H), 8.04 (s, 1H), 7.98 (d, *J*=9.0 Hz, 1H), 7.89 (d, *J*=9.0 Hz, 1H), 7.85 (d, *J*=9.0 Hz, 1H), 5.38–5.30 (m, 3H), 5.14 (d, *J*=7.8 Hz, 1H), 4.88 (d, *J*=7.8 Hz, 1H), 4.42 (q, *J*=7.1 Hz, 2H), 2.72–2.53 (m, 4H), 1.44 (br s, 9H), 1.39 (t, *J*=7.1 Hz, 3H), 0.92–1.06 (d, *J*=6.8 Hz, 24H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.7 (C), 172.0 (C), 171.9 (C), 171.8 (C), 161.2 (C), 160.9 (C), 160.8 (C), 160.7 (C), 155.4 (C), 149.4 (C), 149.3 (C), 147.4 (C), 127.0 (CH), 123.7 (CH), 123.6 (CH), 80.3 (C), 61.4 (CH_2), 56.5 (CH), 56.3 (CH), 32.9 (CH), 28.2 (CH_3), 19.7 (CH_3), 19.5 (CH_3), 19.2 (CH_3), 18.9 (CH_3), 17.9 (CH_3), 17.8 (CH_3), 17.4 (CH_3), 17.3 (CH_3), 8 signals obscured or overlapping; m/z (ES) 897.2904, ($C_{39}H_{54}N_8O_7S_4Na$ requires 897.2896, $[M+Na]^+$).

4.13.14. Linear tetra-thiazole 16c. The amine **18b** (0.15 g, 0.31 mmol) and the acid **17a** (0.17 g, 0.31 mmol) were coupled according to general procedure 3, and the crude

product was purified by column chromatography (ethyl acetate/petroleum ether (7:3) to give the tetramer (0.15 g, 57%) as a colourless solid, mp 80–84°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{24}$=+31.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.03–8.09 (s, 4H), 7.80–7.96 (d *J*=10.8 Hz, 4H), 5.29–5.46 (m, 2H), 5.12 (d, *J*=7.8 Hz, 1H), 4.88 (d, *J*=7.8 Hz, 1H), 4.42 (q, *J*=7.1 Hz, 2H), 2.53–2.67 (m, 4H), 1.44 (br s, 9H), 1.39 (t, *J*=7.1 Hz, 3H), 0.92–1.09 (d, *J*=6.8 Hz, 24H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.0 (C), 171.9 (C), 161.1 (C), 160.7 (C), 149.2 (C), 147.3 (C), 123.5 (CH), 80.3 (C), 61.3 (CH_2), 61.2 (C), 60.2 (CH), 56.4 (CH), 56.2 (CH), 32.8 (CH), 28.1 (CH_3), 20.7 (CH_3), 19.5 (CH_3), 19.3 (CH_3), 19.1 (CH_3), 17.6 (CH_3), 17.5 (CH_3), 17.3 (CH_3), 14.2 (CH_3), 14.0 (CH_3), 13 signals obscured or overlapping; *m*/*z* (ES) 897.2876 ($C_{39}H_{54}N_8O_7S_4Na$ requires 897.2896, $[M+Na]^+$); Found C, 51.0; H, 5.9; N, 12.3. $C_{39}H_{54}N_8O_7S_4.2(H_2O)$ requires: C, 51.4; H, 6.4; N, 12.3%).

4.13.15. Linear tetra-thiazole 16d. The amine **18d** (0.15 g, 0.31 mmol) and the acid **17a** (0.17 g, 0.31 mmol) were coupled according to general procedure 3, and the crude product was purified by column chromatography (ethyl acetate/petroleum ether (7:3) to give the tetramer (0.15 g, 57%) as a colourless solid, mp 94–96°C (CH_2Cl_2/Et_2O); $[\alpha]_D^{26}$=+23.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.06 (s, 2H), 8.03 (s, 1H), 7.93 (d, *J*=9.1 Hz, 1H), 7.88 (d, *J*=9.3 Hz, 1H), 7.84 (d, *J*=9.0 Hz, 1H), 5.39–5.30 (m, 3H), 5.12 (d, *J*=8.7 Hz, 1H), 4.88 (br s, 1H), 4.42 (q, *J*=7.1 Hz, 2H), 2.72–2.52 (m, 4H), 1.45 (s, 9H), 1.39 (t, *J*=7.1 Hz, 3H), 1.08–0.90 (m, 24H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.8 (C), 172.3 (C), 172.1 (C), 172.0 (C), 171.7 (C), 161.3 (C), 161.0 (C), 160.9 (C), 155.4 (C), 149.5 (C), 149.3 (C), 149.2 (C), 147.5 (C), 127.1 (CH), 123.8 (CH), 123.7 (CH), 123.6 (CH), 80.4 (C), 61.34 (CH_2), 58.1 (CH), 56.6 (CH), 56.5 (CH), 56.4 (CH), 33.1 (CH), 33.0 (CH_3), 32.9 (CH), 28.0 (CH_3), 19.8 (CH_3), 19.6 (CH_3), 19.5 (CH_3), 19.3 (CH_3), 17.9 (CH_3), 17.8 (CH_3), 17.6 (CH_3), 17.4 (CH_3), 14.4 (CH_3), 1 signal obscured or overlapping; *m*/*z* (ES) 897.2910 ($C_{39}H_{54}N_8O_7S_4Na$ requires 897.2896, $[M+Na]^+$).

4.14. Macrocyclisation of compound 15

The tristhiazole **15** (0.1 g, 0.14 mmol) was treated according to general procedure 5, and the crude product was purified by column chromatography (silica; ethyl acetate/petroleum ether; 7:3) to give **7a** (0.07 g, 84%) as a colourless solid, which was identical, in all respects, to the product obtained upon cyclooligomerisation of **6a**.

4.15. Macrocyclisation of compound 16a

The tetrathiazole **16a** (0.2 g, 0.2 mmol) was treated according to general procedure 5, and the crude product was purified by column chromatography (silica; ethyl acetate) to give *ent*-**8a** (0.15 g, 87%) as a colourless solid, which was identical, in all respects, apart from optical rotation, to the product obtained upon cyclooligomerisation of *rac*-**6a**, $[\alpha]_D^{22}$=−200.3 (*c* 0.65, $CHCl_3$).

4.16. Macrocyclisation of compound 16b

The tetrathiazole **16b** (10 mg, 0.012 mmol) was treated according to general procedure 5, and the crude product was purified by column chromatography (silica; ethyl acetate) to give **10** (6 mg, 68%) as a colourless solid, which was identical, in all respects, to the product obtained upon cyclooligomerisation of *rac*-**6a**.

4.17. Macrocyclisation of compound 16c

The tetrathiazole **16c** (10 mg, 0.012 mmol) was treated according to general procedure 5, and the crude product was purified by column chromatography (silica; ethyl acetate) to give **11** (5 mg, 58%) as a colourless solid, which was identical, in all respects apart from optical rotation, to the product obtained upon cyclooligomerisation of *rac*-**6a**, $[\alpha]_D^{26}$=+63.2 (*c* 1.0, $CHCl_3$).

4.18. Macrocyclisation of compound 16d

The tetrathiazole **16d** (10 mg, 0.012 mmol) was treated according to general procedure 5, and the crude product was purified by column chromatography (silica; ethyl acetate) to give **12** (6 mg, 68%) as a colourless solid, which was identical, in all respects, to the product obtained upon cyclooligomerisation of *rac*-**6a**.

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