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# Design and synthesis of novel tubular and cage structures based on thiazole-containing macrolactams related to marine cyclopeptides

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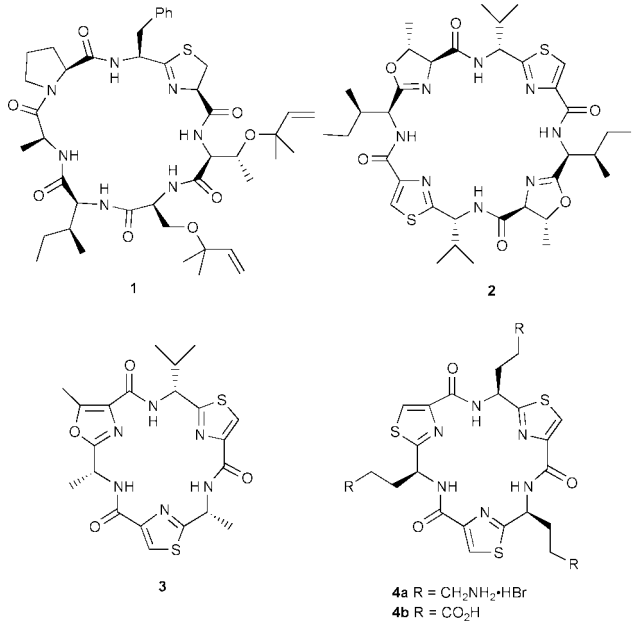
**Tubular and cage structures, *i.e.* 16 and 18, have been synthesised from modified cyclic peptides following selective cyclotrimerisations of L-ornithine and L-glutamic acid thiazole amino acids under high dilution conditions.**

Marine organisms, especially sea-squirts, have delivered an astonishing variety of novel cyclopeptide alkaloids which accommodate thiazole and oxazole rings derived from unusual amino acids, *e.g.* trunkamide **1**,[1] ascidiacyclamide **2**.[2] The

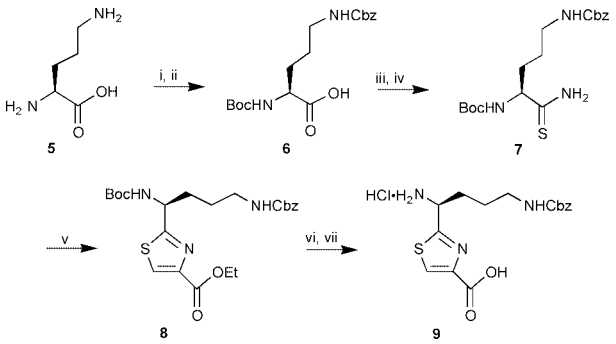



sequence of alternating heterocyclic rings and amino acid units which characterise these structures has led to speculation that the metabolites may have a role to play *in vivo* as metal transport agents, and/or that metals may act as templates in their biological assembly from constituent amino acids/heterocyclic rings.[3] In previous studies we have examined the self assembly and metal-templated cyclooligomerisations of amino acid based thiazoles and oxazoles, culminating in the syntheses of novel cyclotetramers and cyclotrimers,[4] and also in the total synthesis of the natural cyclopeptide dendroamide A **3**.[5] In a continuation of this work we have now investigated the syntheses of the cyclopeptide scaffolds **4a** and **4b**, containing additional amino and carboxylic acid functionality respectively, with a view to examining their applications in the synthesis of 'cage-' and 'tube-' like structures for possible use as membrane ion channel mimics and for the development of macromolecular devices and scaffolds for protein mimics. Thus, in this *Communication* we describe concise syntheses of **4a** and **4b**[6] and their conversion into the tubular polyamide **16** and into the cage structure **18**.[7,8]

Each of the substituted thiazoles **4a** and **4b** was prepared by routes developed in our laboratories and based on well-established literature precedent. Thus, protection of the C-5 amino group of L-ornithine **5** as its *Z*-carbamate followed by Boc protection of the C-2 amino function first led to the carboxylic acid **6**. Amidation of **6** followed by treatment with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfate] next produced the thioamide **7**. A Hantzsch thiazole ring forming reaction between **7** and ethyl bromopyruvate[9] then gave the substituted thiazole **8** which, on saponification of the ethyl ester and removal of the Boc protection, gave the L-ornithine based thiazole amino acid **9** with ≥95% ee (Scheme 1).[10]

The corresponding L-glutamic acid based thiazole **14** was prepared from L-glutamic acid 5-methyl ester **10** following Boc protection and coupling with DL-serine benzyl ester benzenesulfonate leading to the dipeptide **11**. After conversion of **11** into the thioamide **12**, cyclodehydration in the presence of Burgess' reagent [methyl(carboxysulfamoyl)triethylammonium hydroxide, inner salt][11] next produced the corresponding thiazoline which was immediately converted into the thiazole **13** upon treatment with $BrCCl_3$–DBU at 0 °C.[12] Debenzylation of **13** under catalytic transfer hydrogenation conditions[13] and Boc deprotection finally gave the free thiazole amino acid **14** with ≥95% ee (Scheme 2).

When the L-ornithine amino acid thiazole **9** was treated with pentafluorophenyl diphenylphosphinate (FDPP) in the presence of *i*-$Pr_2NEt$ in DMF under high dilution, selective cyclooligomerisation took place to give the cyclic trimer **15a** in 11% yield. In a similar manner, cyclooligomerisation of the L-glutamic acid based thiazole **14** under the same conditions led cleanly to the $C_3$-symmetric cyclic trimer **15b** in 41% yield (Scheme 3). After removal of the amine protection in **15a** and saponification of the methyl ester groups in **15b**, activation of the tris-carboxylic acid **4b** with FDPP and *i*-$Pr_2NEt$ followed by treatment with the tris-amine **4a** under high dilution in DMF led to the formation of the tubular structure **16** as a powder in 30% yield (Scheme 4).† Mass spectometry indicated the presence of a monomeric product. This was reinforced by the NMR spectroscopic data for




**Scheme 1** *Reagents and conditions*: i, $CuCO_3$, $H_2O$, 30 min, then ZCl, NaOH, 1 h, then EDTA, 2 M HCl, 2 h, 88%; ii, $(Boc)_2O$, NaOH, THF–$H_2O$, 12 h, 71%; iii, isobutyl chloroformate, NMM (*N*-methylmorpholine), THF, $NH_3$ (g), −5 °C, 1 h, 99%; iv, Lawesson's reagent, THF, 24 h, 99%; v, ethyl bromopyruvate, $KHCO_3$, DME, −15 °C, then TFAA, collidine, DME, −15 °C, 79%; vi, NaOH, THF–$H_2O$, 18 h, 97%; vii, 4 M HCl, dioxane, 12 h, 98%.

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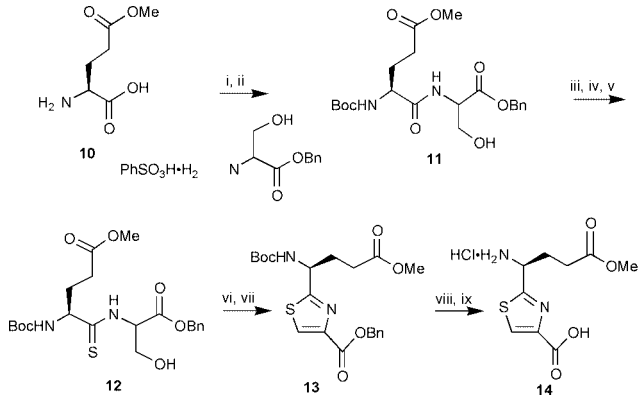
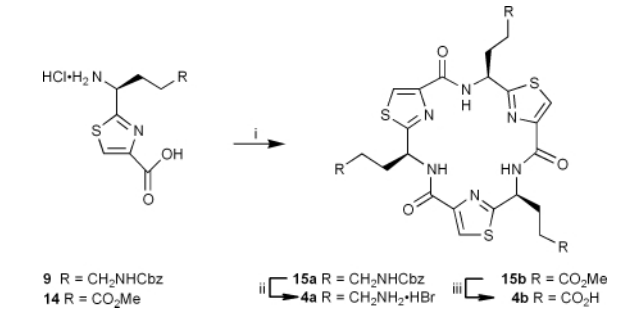
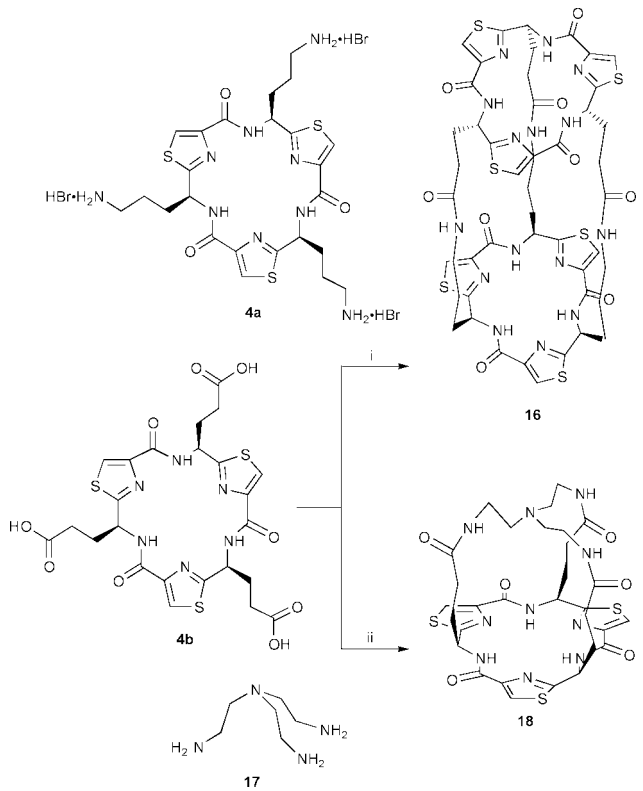


**Scheme 2** *Reagents and conditions*: i, $(Boc)_2O$, $Et_3N$, THF–$H_2O$, 24 h, 90%; ii, HOBt, EDCI·HCl, NMM, $CH_2Cl_2$, 0 °C, 30 min, then DL-serine benzyl ester benzenesulfonate, NMM, 0 °C → RT, 48 h, 94%; iii, TBDMSCl, $Et_3N$, DMAP, $CH_2Cl_2$, 14 h, 86%; iv, Lawesson's reagent, $C_6H_6$, 80 °C, 14 h, 94%; v, TBAF, THF, 0 °C, 3 h, 91%; vi, Burgess' reagent, THF, 65 °C, 30 min; vii, $CBrCl_3$, DBU, $CH_2Cl_2$, 0 °C, 4 h, 63% over two steps; viii, $NH_4HCO_2$, 10% Pd/C, EtOH, 78 °C, 24 h, 70%; ix, 2 M HCl, dioxane, 24 h, 60%.



**Scheme 3** *Reagents and conditions*: i, FDPP, *i*-$Pr_2NEt$, DMF, (**15a** 3 d, 11%; **15b** 9 d, 41%); ii, 33% HBr–AcOH, 6 h, 77%; iii, NaOH, THF–$H_2O$, 12 h, 98%.



**Scheme 4** *Reagents and conditions*: i, FDPP, *i*-$Pr_2NEt$, **4a**, DMF, 10 d, 30%; ii, FDPP, *i*-$Pr_2NEt$, **17**, DMF, 3 d, 40%.

**16** which were consistent with those expected for a $C_3$-symmetric polymacrocycle. Most notably, two singlet peaks at $\delta$ 8.13 and $\delta$ 8.11 were observed in the $^1$H NMR spectrum corresponding to the two sets of thiazole protons. Additionally, NMR signals were observed relating to the amide N–H ($\delta$ 8.47 and $\delta$ 8.43) and the α-carbon protons ($\delta$ 5.68 and $\delta$ 5.58) within the macrocyclic rings.

A corresponding condensation between the L-glutamic acid trimer **4b** and tris(aminoethyl)amine **17** in the presence of FDPP–$Pr_2NEt$ led to isolation of the cage structure **18**, also as a solid, in 40% yield.‡ Again, mass spectrometry established that formation of the desired monomer had occurred. Additionally, the $^1$H NMR spectrum confirmed the structure of **18** as $C_3$-symmetric with peaks at $\delta$ 8.89 and $\delta$ 8.11 relating to the ring N–H and thiazole protons with a signal at $\delta$ 6.26 corresponding to the three side-chain amide protons. The applications of the $C_3$-symmetric cyclic trimers **4a** and **4b** and their relatives in asymmetric and library synthesis, and also in molecular recognition phenomena, will be described in future publications.

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## Notes and references

† **16**: mp 236–237 °C (decomp.) (from $CHCl_3$–MeOH–$Et_2O$); $[\alpha]_D^{294}$ −38.4° [*c* = 0.5, ($CHCl_3$–MeOH 3:1)]; IR ($cm^{-1}$): 3401, 3007, 2930, 1668, 1541; $\delta_H$ (500 MHz, $CDCl_3$) 8.47 (3H, m), 8.43 (3H, dd, *J* = 8.1 and 3.0 Hz), 8.13 (3H, s), 8.11 (3H, s), 5.68 (3H, m), 5.58 (3H, m), 3.67–3.01 (6H, m), 2.68–2.32 (9H, m), 2.31–2.12 (9H, m), 2.02–1.91 (3H, m), 1.57–1.51 (3H, m); $\delta_C$ [125 MHz, ($CDCl_3$)] 173.2 (s), 169.7 (s), 159.7 (s), 159.6 (s), 148.8 (s), 148.7 (s), 124.4 (d), 124.3 (d), 51.4 (d), 50.4 (d), 39.7 (t), 35.9 (t), 34.3 (t), 32.0 (t), 25.9 (t); HRMS (ES) *m/z* 1196.2198; calcd. for $C_{48}H_{51}S_6N_{15}O_9Na$ ([M + Na]$^+$): 1196.2216.

‡ **18**: mp 281–282 °C (decomp.) (from $CHCl_3$–MeOH–$Et_2O$); $[\alpha]_D^{294}$ −26.4° [*c* = 0.5, ($CHCl_3$–MeOH 3:1)]; IR ($cm^{-1}$): 3399, 3007, 1672, 1543; $\delta_H$ (360 MHz, $CDCl_3$) 8.89 (3H, d, *J* = 9.5 Hz), 8.11 (3H, s), 6.26 (3H, br s), 5.94 (3H, d, *J* = 9.1 Hz), 3.40 (3H, m), 3.12 (3H, m), 2.67–2.41 (12H, m), 2.32–2.24 (3H, m), 2.18–2.08 (3H, m); $\delta_C$ [90.5 MHz, ($CDCl_3$–$CD_3OD$ 9:1)] 173.0 (s), 167.8 (s), 159.3 (s), 148.8 (s), 123.8 (d), 53.0 (t), 48.5 (d), 37.0 (t), 31.8 (t), 28.9 (t); HRMS (ES) *m/z* 751.1917; calcd. for $C_{30}S_3N_{10}O_6H_{36}Na$ ([M + Na]$^+$): 751.1879.


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