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

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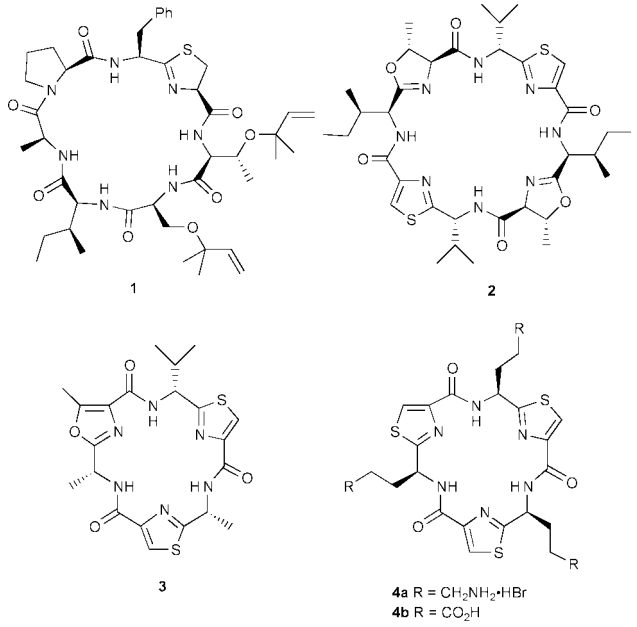
Received (in Cambridge, UK) 13th February 2001, Accepted 8th March 2001
First published as an Advance Article on the web 29th March 2001

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

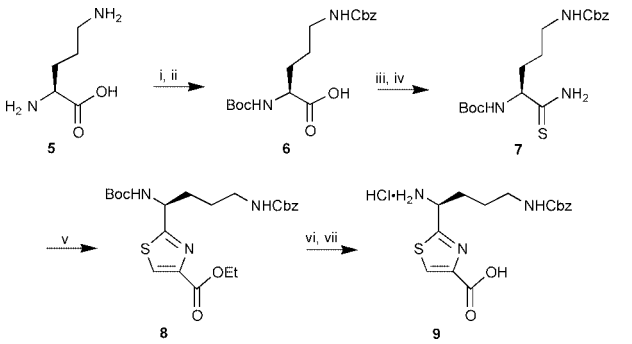


sequence of alternating heterocyclic rings and amino acid units which characterise these structures has led to speculation that the metabolites may have a role to play *in vivo* as metal transport agents, and/or that metals may act as templates in their biological assembly from constituent amino acids/heterocyclic 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]

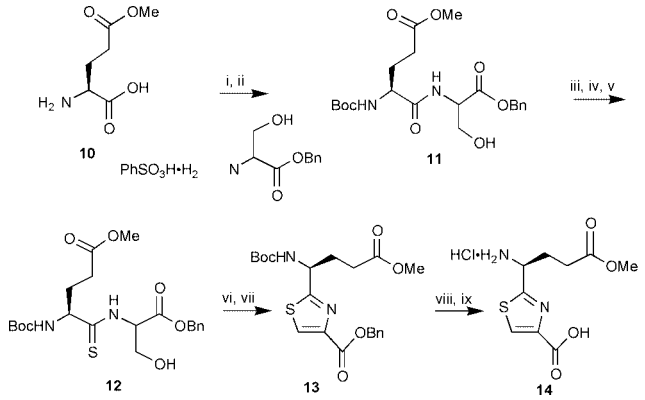
The corresponding L-glutamic acid based thiazole **14** was prepared from L-glutamic acid 5-methyl ester **10** following Boc protection and coupling with DL-serine benzyl ester benzenesulfonate leading to the dipeptide **11**. After conversion of **11** into the thioamide **12**, cyclodehydration in 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

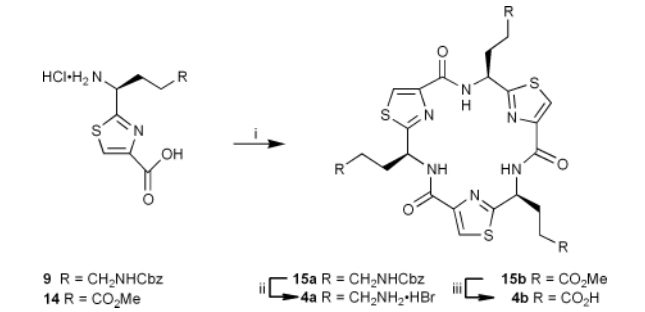


Scheme 1 *Reagents and conditions*: i, $CuCO_3$, H_2O, 30 min, then ZCl, NaOH, 1 h, then EDTA, 2 M HCl, 2 h, 88%; ii, $(Boc)_2O$, NaOH, THF–H_2O, 12 h, 71%; iii, isobutyl chloroformate, NMM (*N*-methylmorpholine), THF, NH_3 (g), −5 °C, 1 h, 99%; iv, Lawesson's reagent, THF, 24 h, 99%; v, ethyl bromopyruvate,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

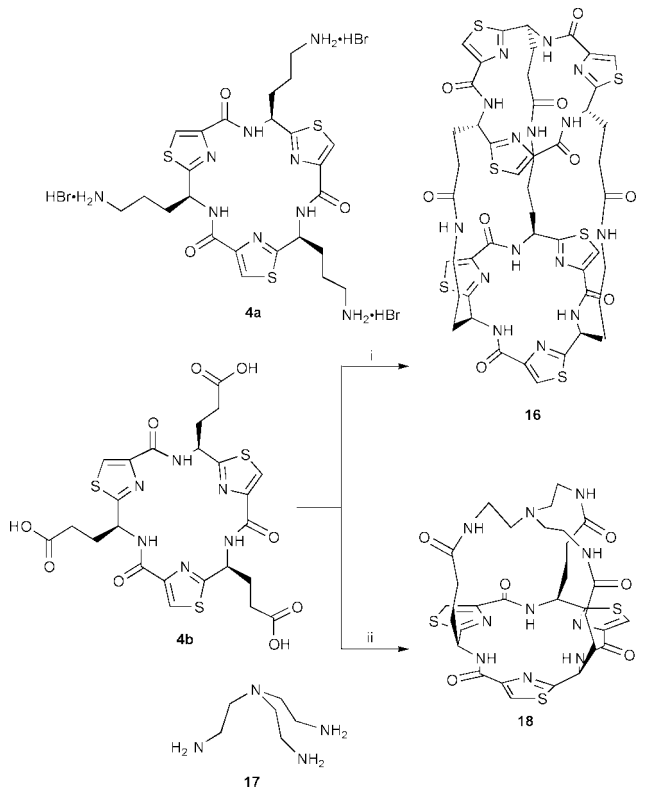
DOI: 10.1039/b101417j



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 δ 8.13 and δ 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 (δ 8.47 and δ 8.43) and the α-carbon protons (δ 5.68 and δ 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 δ 8.89 and δ 8.11 relating to the ring N–H and thiazole protons with a signal at δ 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.

We thank Dr Luis Castro for his interest in this study and Merck Sharp and Dohme for financial assistance. We also thank Dr Kate Jolliffe for preliminary work with the synthesis of the L-ornithine thiazole.

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; δ_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); δ_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; δ_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); δ_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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