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The controlled assembly of modified cyclopeptide cages via scaffolded cyclooligomerisations

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Abstract—Novel thiazole- and oxazole-containing modified cyclopeptide C_3-symmetric cages have been synthesised utilising a trimeric linker to control the assembly and cyclooligomerisation of heterocyclic amino acids.

A wide variety of unusual and biologically important thiazole- and oxazole-containing cyclopeptide alkaloids have been isolated from the marine environment in recent years; typical examples include ascidiacyclamide **1** and raocyclamide A **2**.[1,2] The presence of alternating amino acid residues and heterocyclic rings in these secondary metabolites, with heteroatom lone pairs directed towards the macrocyclic cavity, has led to speculation that they may function as metal complexation and transport agents in vivo.[3] It has also been postulated that certain relatives of these marine natural products, which present multiple functional groups in one direction e.g. **3**, could have applications in the field of molecular recognition.[4] In addition to total synthesis, self-assembly and metal-templated cyclooligomerisation studies of thiazole- and oxazole-containing amino acids, we have recently reported the design and synthesis of some cyclopeptide scaffolds, i.e. **3a** and **3b**, containing additional functionality on the amino acid side-chains, and their subsequent conversion into novel tubular polyamides and cage structures, e.g. **4** (Fig. 1).[5]

In continuation of these studies, we now describe a concise and flexible approach to C_3-symmetric molecular cages viz. **5**, using the tris-carboxylic acid linker **6** to control the assembly and cyclooligomerisation of heterocyclic amino acids (Scheme 1).

Thus, the L-ornithine-derived thiazole **7**, which was prepared via an established synthetic route, was first reacted as its amine salt with the known tris-carboxylic acid **6** in the presence of pentafluorophenyl diphenylphosphinate (FDPP) and diisopropylethylamine (i-Pr_2NEt) in DMF, to produce the tris-amide **8** in 87% yield.[5,6] Saponification of the three ethyl esters

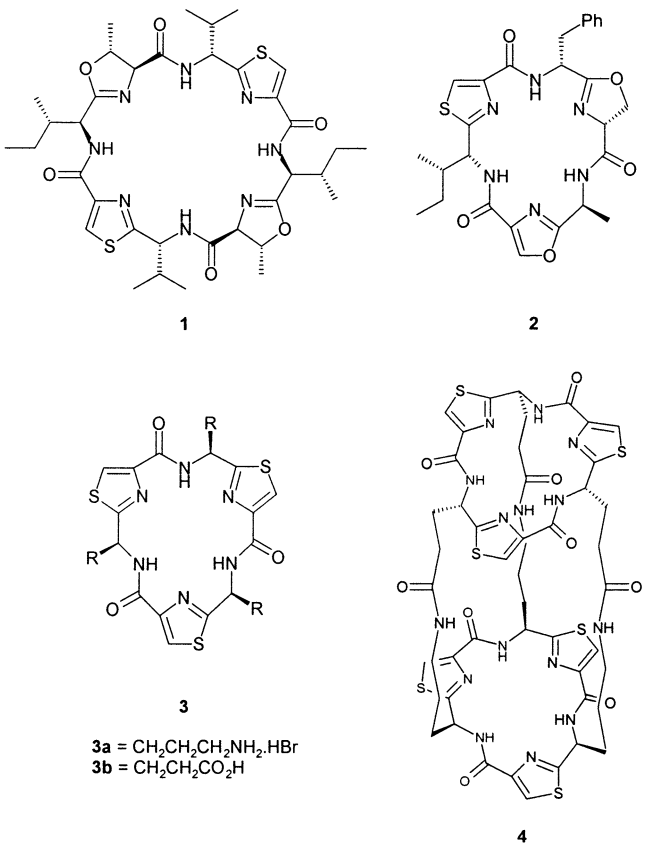

Figure 1.

Keywords: cyclopeptide; cyclooligomerisation; cage; thiazole; oxazole; amino acid.

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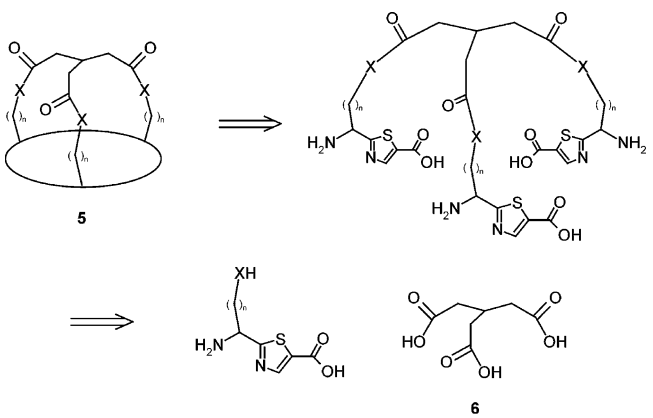
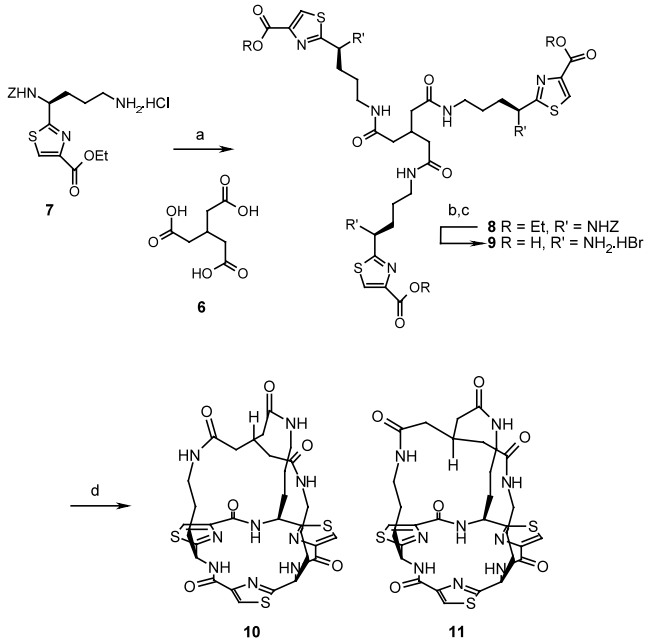
in **8** and removal of the *Z*-carbamates next led to the fully deprotected trimeric thiazole amino acid **9**. When a solution of **9** in DMF at high dilution (2.5 mM) was reacted with FDPP and DBU over 7 days, a controlled cyclooligomerisation took place, resulting in the formation of the isomeric cage cyclopeptides **10** and **11** (ratio 2:3; in a combined yield of 19%) which were separated by preparative TLC (Scheme 2). The spectroscopic data for each of the cage compounds were characteristic for C_3-symmetric structures and their ^{1}H NMR spectra showed typical absorptions at δ 8.39 /δ 8.07 and δ 8.41/δ 8.11 (**10** and **11**) relating to their two sets of ring NH and thiazole protons.[7,8]

We next extended our study to the synthesis of oxazole-containing cyclopeptide cages and examined the effect of a shortened amino acid side-chain on the composition of the cyclooligomerisation products. Thus, the L-serine-derived oxazole **14** was first synthesised from Boc-L-serine **12** involving (i) protection of the alcohol **12** as the TBDMS ether; (ii) coupling with L-serine benzyl ester benzenesulfonate to yield dipeptide **13**; (iii) conversion of the β-hydroxyamide **13** into the corresponding oxazole **14** following treatment at −78°C with diethylamino sulfurtrifluoride (DAST) and oxidation of the resulting oxazoline with $BrCCl_3$–DBU; this sequence produced the oxazole with ≥95% e.e.[9] After deprotection of the silyl ether in **14**, the resulting alcohol was coupled with the tris-carboxylic acid **6** leading to tris-ester **15** in 88% yield. Hydrogenolysis of the three benzyl esters in **15** and subsequent deprotection of the amino groups then afforded the cyclooligomerisation precursor **16**.

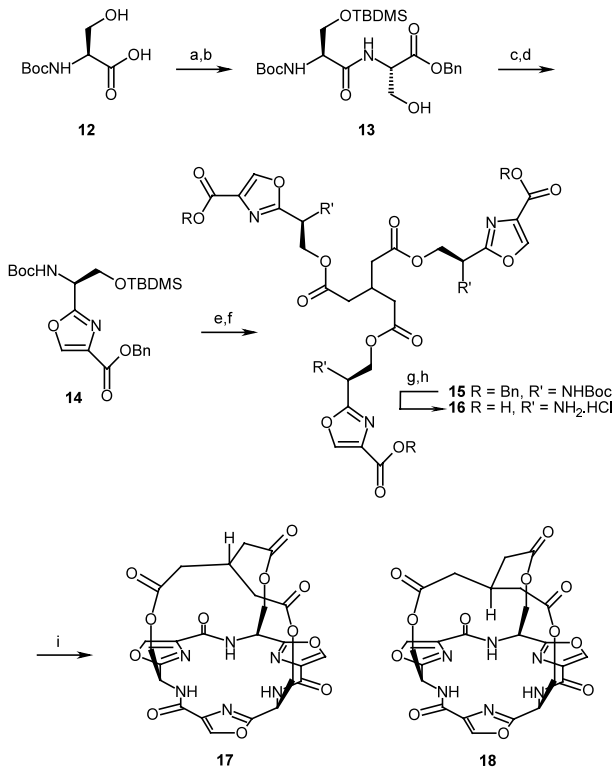
We were pleased to find that the scaffolded cyclooligomerisation of the tris-amino acid **16** in the presence of FDPP and 4-DMAP, in DMF at high dilution, led to the formation of two trimeric cage cyclopeptides, i.e. **17** and **18** (ratio 9:5), in a combined yield of 19% (Scheme 3). Mass spectrometry and NMR spectroscopic studies confirmed that the two cage cyclopeptides were monomeric and variable temperature ^{1}H NMR studies in DMSO-d_6 demonstrated the clear presence of both 'inside' and 'outside' tertiary



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) FDPP, *i*-Pr_2NEt, DMF, 24 h, 87%; (b) NaOH, THF/H_2O, 24 h; (c) 33% HBr/AcOH, 18 h, 81% (two steps); (d) FDPP, DBU, DMF, 7 days, 19% (ratio 2:3).



Scheme 3. *Reagents and conditions*: (a) TBDMSCl, imidazole, CH_2Cl_2, 12 h, 69%; (b) L-serine benzyl ester benzenesulfonate, EDCI·HCl, NMM, HOBt, CH_2Cl_2, 0°C, 12 h, 91%; (c) DAST, CH_2Cl_2, −78°C, 2 h; (d) $BrCCl_3$, DBU, CH_2Cl_2, 0°C, 8 h, 47% (two steps); (e) TBAF, THF, 0°C, 1 h, 84%; (f) **6**, EDCI·HCl, 4-DMAP, NMM, CH_2Cl_2, 0°C, 12 h, 88%; (g) H_2, 10% Pd/C, MeOH, 48 h, 94%; (h) 4 M HCl/dioxane, 3 h, 73%; (i) FDPP, 4-DMAP, DMF, 5 days, 19% (ratio 9:5).

hydrogen cyclopeptide diastereoisomers.[10,11] No coalescence of signals was observed in the ^{1}H NMR spectrum upon heating the mixture to 100°C and the two sets of amide protons (δ 8.42 and δ 8.36) were clearly visible at elevated temperatures. The presence of diastereoisomers was further reinforced in the ^{13}C NMR spectrum which showed differing sets of absorptions for the two cyclopeptides. The spectroscopic data for the cage cyclopeptides synthesised in this study, by themselves, did not allow an unambiguous distinction between the two sets of 'inside' and 'outside' diastereoisomers, i.e. **10** and **11** and also **17** and **18**.[12] Further studies are underway to resolve the stereochemical assignments and also to investigate the ion-binding and transport properties of these novel cyclopeptides.

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7. Data for **10**: mp 273–274°C (decomp.) (from $CHCl_3$–Et_2O); $[\alpha]_D^{301}$ 4.80 ($c=0.5$, $CHCl_3$); IR (cm^{-1}): 3435, 3400, 2960, 1672, 1549; δ_H (360 MHz, $CDCl_3$) 8.39 (d, 3H, $J=9.6$ Hz, 3×NHCH), 8.07 (s, 3H, 3×NC=CHS), 6.69, (t, 3H, $J=5.9$ Hz, 3×CH_2NH), 5.59 (m, 3H, 3×NHCHCH$_2$), 3.42 (m, 3H, 3×$CH_2CH_aH_bNH$), 3.19 (m, 3H, 3×$CH_2CH_aH_bNH$), 2.61 (m, 1H, $HC(CH_2CONH)_3$), 2.39 (m, 6H, $HC(CH_2CONH)_3$), 2.08 (m, 3H, 3×NHCHCH_aH_b), 1.92–1.71 (9H, m, 3×NHCHCH_aH_b, 3×CH_2); δ_C (90 MHz, $CDCl_3$) 171.8 (s), 169.9 (s), 159.5 (s), 149.2 (s), 123.4 (d), 49.2 (d), 39.3 (t), 38.4 (t), 36.4 (t), 31.5 (d), 26.1(t); HRMS (ES) m/z 728.2108; calcd for $C_{31}S_3N_9O_6H_{38}$ ([M+H]$^+$): 728.2107.
8. Data for **11**: mp 252–253°C (decomp.) (from $CHCl_3$–Et_2O); $[\alpha]_D^{300}$ −44.0 [$c=0.5$, $CHCl_3$]; IR (cm^{-1}): 3402, 2927, 2855, 1729, 1666, 1549; δ_H (360 MHz, $CDCl_3$) 8.49 (d, 3H, $J=9.1$ Hz, 3×NHCH), 8.11 (s, 3H, 3×NC=CHS), 6.84 (br m, 3H, 3×CH_2NH), 5.70 (m, 3H, 3×NHCHCH$_2$), 3.57 (m, 3H, 3×$CH_2CH_aH_bNH$), 3.01 (m, 3H, 3×$CH_2CH_aH_bNH$), 2.47 (m, 3H, $HC(CH_aH_bCONH)_3$), 2.38 (m, 1H, $HC(CH_aH_b)_3$), 2.29 (m, 3H, $HC(CH_aH_b)_3$), 2.11 (m, 3H, 3×NHCHCH_aH_b), 1.97 (m, 3H, 3×NHCHCH$_aH_b$), 1.69 (m, 6H, 3×CH_2); δ_C (90 MHz, $CDCl_3$) 172.4 (s), 169.8 (s), 159. 6 (s), 149.2 (s), 123.7 (d), 49.9 (d), 40.7 (t), 38.8 (t), 35.9 (d), 35.3 (t), 24.8 (t); HRMS (ES) m/z 728.2101; calcd for $C_{31}S_3N_9O_6H_{38}$ ([M+H]$^+$): 728.2107.
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10. Data for **17**/**18**: mp 290–291°C (decomp.) (from $CHCl_3$); $[\alpha]_D^{293}$ 184.4 [$c=1.0$, $CHCl_3$]; IR (cm^{-1}): 3388, 1742, 1688, 1600; δ_H (360 MHz, $CDCl_3$) 8.59 (6H, m, 3×NHCH, 3×NHCH), 8.33 (s, 3H, 3×NC=CHO), 8.32 (s, 3H, 3×NC=CHO), 5.49–5.42 (m, 9H, 3×NHCH, 3×CHCH_aH_b, 3×NHCH), 5.24 (dd, 3H, $J=11.5$, 1.5 Hz, 3×CHCH_aH_b), 4.01 (dd, 3H, $J=11.5$, 1.9 Hz, 3×CHCH$_aH_b$), 3.93 (dd, 3H, $J=11.8$, 2.4 Hz, 3×CHCH$_aH_b$), 2.43–1.86 (m, 14H, $HC(CH_2)_3$, $HC(CH_2)_3$, $HC(CH_2)_3$, $HC(CH_2)_3$); δ_C (90 MHz, $CDCl_3$) 171.0 (s), 170.6 (s), 160.1 (s), 159.8 (s), 158.9 (s), 158.8 (s), 142.4 (d), 142.1 (d), 135.1 (s), 135.1 (s), 64.0 (t), 62.2 (t), 48.8 (d), 48.6 (d), 38.2 (t), 37.2 (t), 34.1 (d), 28.4 (d); HRMS (ES) m/z 621.1239; calcd for $C_{25}N_6O_{12}H_{22}Na$ ([M+Na]$^+$): 621.1193.
11. Variable temperature ^{1}H NMR data for **17**/**18**: δ_H (360 MHz, DMSO-d_6, 298 K) 9.00 (s, 3H, 3×NC=CHO), 8.97 (s, 3H, 3×NC=CHO), 8.38 (d, 6H, $J=7.5$ Hz, 3×NHCH, 3×NHCH), 5.66 (d, 3H, $J=7.4$ H, 3×NHCH), 5.60 (d, 3H, $J=7.2$ Hz, 3×NHCH), 5.17 (d, 3H, $J=11.5$ Hz, 3×CHCH_aH_b), 5.00 (d, 3H, $J=10.5$ Hz, 3×CHCH_aH_b), 4.09 (d, 3H, $J=10.0$ Hz, 3×CHCH$_aH_b$), 4.01 (d, 3H, $J=11.5$ Hz, 3×CHCH$_aH_b$), 3.30 (d, 6H, $J=8.6$ Hz, $HC(CH_2CO_2)_3$), 2.70 (d, 3H, $J=13.3$ Hz, $HC(CH_aH_bCO_2)_3$), 2.46–2.10 (m, 2H, $HC(CH_2CO_2)_3$, $HC(CH_aH_bCO_2)_3$), 2.00 (m, 3H, $HC(CH_aH_bCO_2)_3$); δ_H (360 MHz, DMSO-d_6, 373 K) 8.71 (s, 3H, 3×NC=CHO), 8.67 (s, 3H, 3×NC=CHO), 8.42 (m, 3H, 3×NHCH), 8.36 (m, 3H, 3×NHCH), 5.56 (m, 6H, 3×NHCH, 3×NHCH), 5.05 (d, 3H, $J=11.4$ Hz, 3×CHCH_aH_b), 4.97 (d, 3H, $J=11.8$ Hz, 3×CHCH_aH_b), 4.17 (d, 3H, $J=11.2$ Hz, 3×CHCH$_aH_b$), 4.12 (d, 3H, $J=11.4$ Hz, 3×CHCH$_aH_b$), 2.68 (m, 9H, $HC(CH_2CO_2)_3$, $HC(CH_aH_b)_3$), 2.45 (m, 2H, $HC(CH_2CO_2)_3$, $HC(CH_aH_bCO_2)_3$), 2.06 (dd, 3H, $J=$ 14.6, 11.0 Hz, $HC(CH_aH_bCO_2)_3$).
12. In an attempt to resolve these issues, we carried out energy minimisation and Monte Carlo conformational searches on the diastereoisomers **10**/**11** and **17**/**18** using the MacroModel 5.5 implementation of the AMBER* force field. These data could be interpreted, based on the assumption that the observed ratios of diastereomeric products reflected the relative ease of the final cyclisation steps, to indicate that structures **11** and **17** would be the major products resulting from the cyclooligomerisations of **9** and **16**, respectively, i.e. the minimum energy conformers were calculated to have the following values: **10**: $E=-67.0$ kJ mol^{-1}, **11**: $E=-77.4$ kJ mol^{-1}, **17**: $E=57.82$ kJ mol^{-1}, **18**: $E=-122.62$ kJ mol^{-1}.