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Huge (14-, 21-, 28-, 35-, 56- and 70-membered ring) macrocyclic lactams—a novel family of carbopeptoid-cyclodextrins

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Abstract—Hydrogenation of linear ω-azido-pentafluorophenyl esters gives cyclic peptides containing 14-, 21-, 28-, 35-, 56- and 70-membered ring lactams from oligomers derived from ε-amino acids in excellent to moderate yields with a lack of racemisation during the cyclisation step.

The predilection towards constrained structure of large macrocycles derived from carbohydrates and peptides has been used by Nature for many purposes.[1] Kessler and co-workers[2] has pioneered the incorporation of sugar amino acids (SAAs)[3] into cyclic peptides[4,5] and indicated the confluence of structure between cyclodextrins and cyclic peptides in such structures to give a novel carbopeptoid-cyclodextrin[6] class of biomaterial.[7] Cyclic peptides containing SAAs[8,9] have been used in tissue engineering of cartilage[10] and have provided a set of novel integrin inhibitors.[11]

Cyclic peptides also have potential applications in nanotube technology[12–15] although they are most widely known as antibiotics[16] and for other chemotherapeutic purposes. Accordingly, there has been much interest in their chemical[17] and enzymatic[18] synthesis. The two most widely used cyclic peptides—gramicidin and cyclosporine are 30- and 33-membered rings; significant activity was found in a 42-ring analogue of gramicidin.[19] Even bigger cyclic peptides have biological activity; a 54-membered ring has been used as a foot-and-mouth disease viral epitope,[20] and an 87-membered ring is in pharmaceutical development as an antibiotic.[21] Easy access to a new set of cyclic peptides with some of the structural features of carbohydrates should provide biomaterials with useful properties.

Polymerisation of a further class of SAAs [6-amino-6-deoxyaldonic acids (ε-amino acids)] may provide fully hydroxylated analogues of nylon 6 as a family of new biomaterials. Although analogues of nylon 6,6—in which one of the components is a carbohydrate[22–24]—have been studied for some time,[25] the first example of a fully hydroxylated analogue of nylon 6 has only recently been reported.[26]

In a project designed to make homogeneous oligomers of fully hydroxylated nylon 6 **2** as a new class of biopolymer,[27] a fully protected form **3**[28] of 6-amino-6-deoxygalactonic acid **1** was converted by standard peptide coupling methods to a series of protected oligomeric azido methyl esters **4**–**7** (Scheme 1). This paper reports the conversions of the methyl esters to the corresponding pentafluorophenyl (PFP) esters; their subsequent hydrogenation leads to very high yields of large (up to 70-membered ring) protected macrocyclic lactams. Initial studies are also reported on the deprotection to form 14 **8** and 28 **9**—but not completely deprotected 56 **10**—ring carbopeptoid analogues of cyclodextrins. These materials constitute a novel class of biomacrocycle, the properties of which may have a number of interesting features (Scheme 1).

Keywords: cyclic peptide; cyclodextrin; sugar amino acid; macrocyclic lactam; biopolymer.
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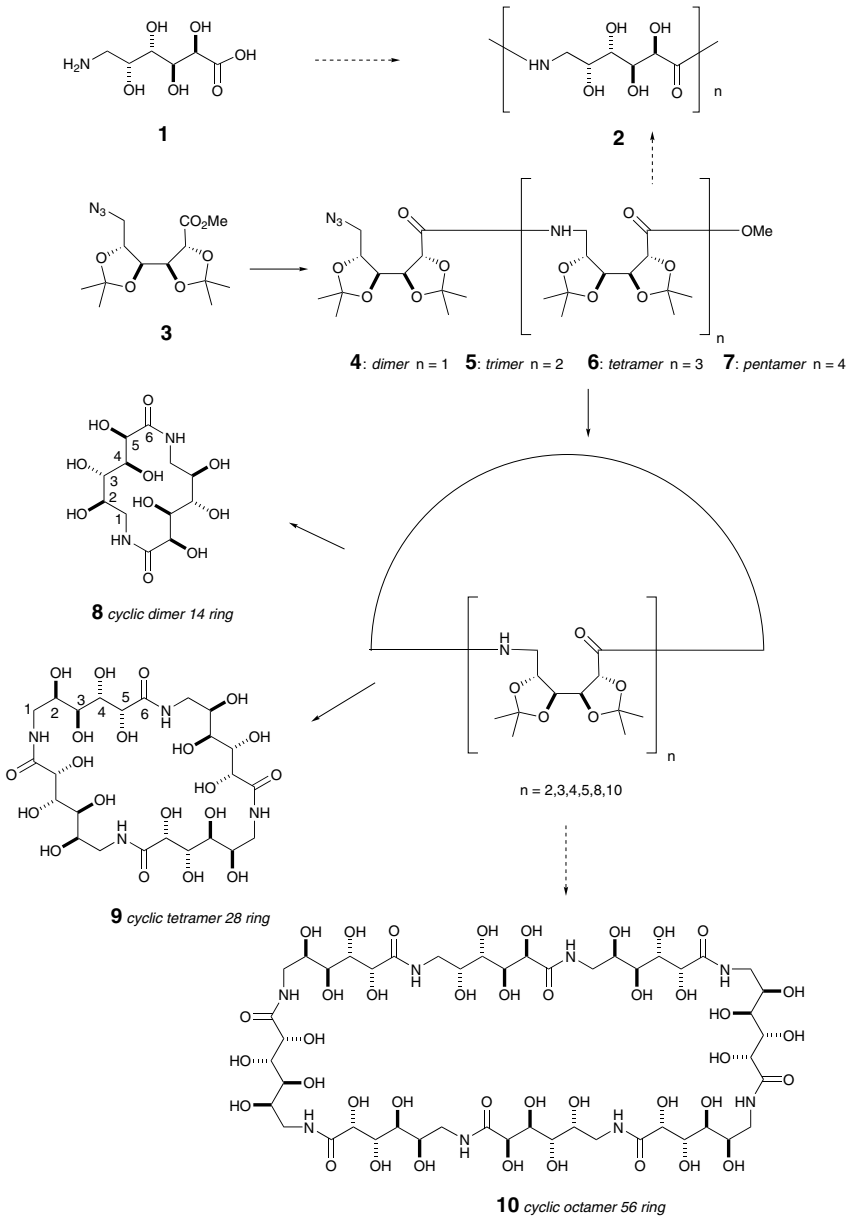
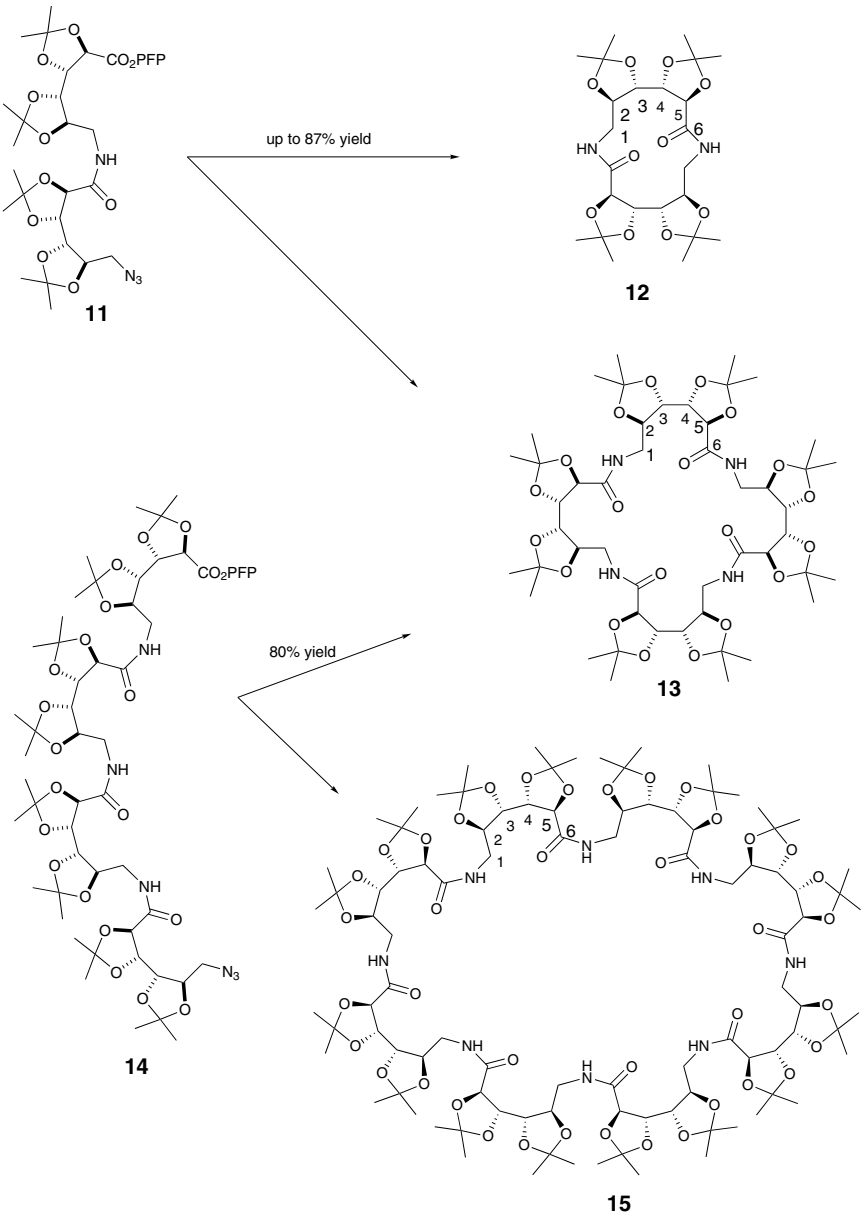


Scheme 1.

Hydrogenation of the linear dimeric azido PFP ester **11**[29] in the presence of palladium black at 10.2 mg/mL (13.8 mM) gave an easily separable mixture of the cyclic dimer **12** (30% yield) and the cyclic tetramer **13** (30% yield), together with some 16% of higher oligomers (Scheme 2); all hydrogenations in this paper were carried out at room temperature and pressure with dioxane as the solvent. When the hydrogenation was carried out at 1.0 mg/mL (1.38 mM) up to 87% of the cyclic dimer of **12**[30] was formed; in some experiments at the same concentration yields of around 75% of **12** together with about 10% of **13**[31] were isolated. Differences in these yields may arise from different degrees of aggregation of the catalyst during the reduction, or for other reasons; nonetheless, high yields of the dimer **12** can be obtained at low concentration. Deprotection of the dimer **12** by treatment with acid ion exchange resin gave the crystalline 14-membered ring lactam **8**[32] in 65% yield, the structure of which was firmly established by X-ray crystallographic analysis (Fig. 1).[33]

It was just possible that a catenane structure, rather than the monocyclic 28-membered ring structure **13**, had been formed. This ambiguity was resolved by experiments on the hydrogenation of the linear tetramer PFP ester **14**, which at 10 mg/mL (8.0 mM) formed the same cyclic tetramer **13** in 80% yield, together with 17% of the cyclic octamer **15**, isolated in 17% yield, giving a total yield of cyclic materials of 97%. When the hydrogenation was performed at a concentration of 50 mg/mL (4.0 mM) a 57% yield of the tetramer **13** was obtained together with 31% of the octamer **15**[34]—again a high combined yield of the two macrocyclic lactams of 88%.

A low yield of the tetramer has also been obtained by in situ activation of the pre-formed linear amino acid as its



Scheme 2. Products from hydrogenation of linear dimer **11** and linear tetramer **14**.

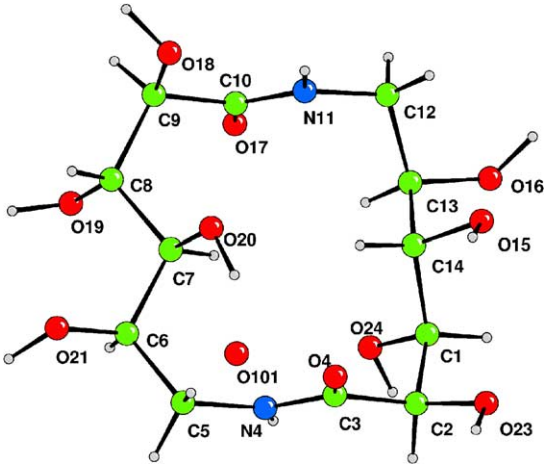
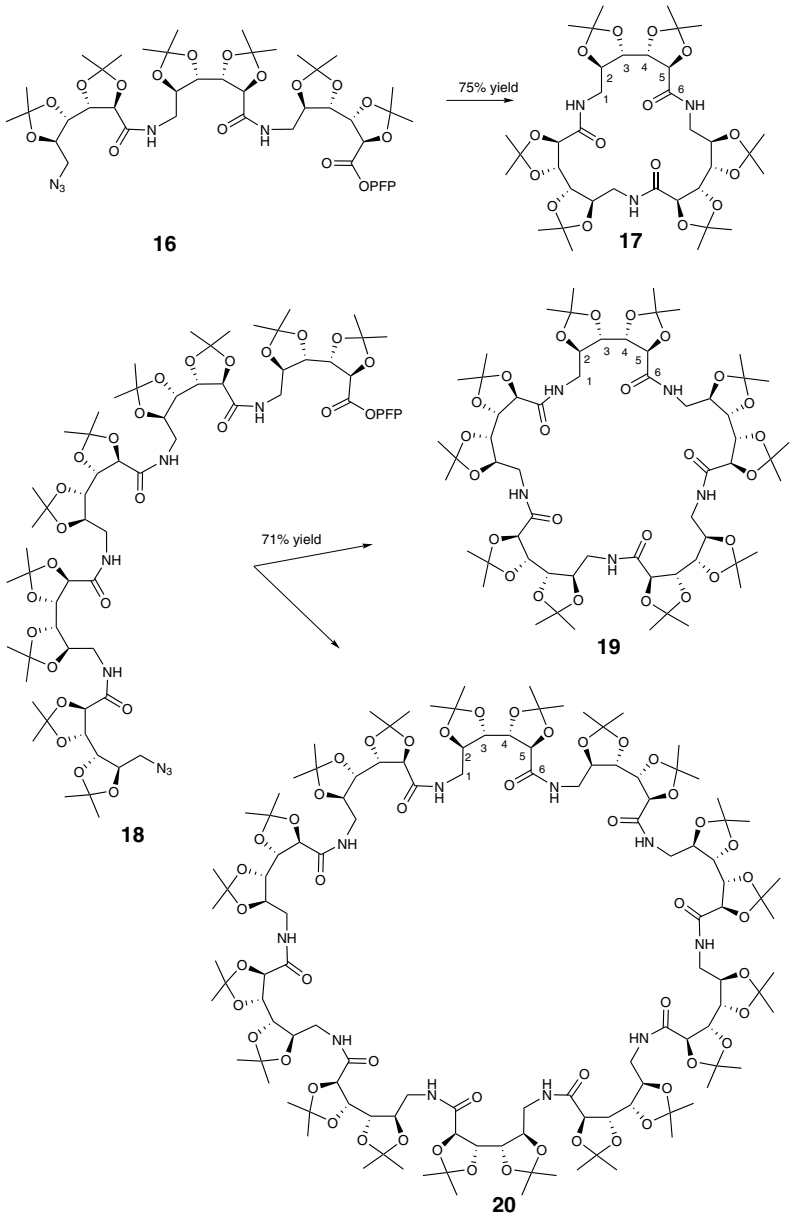


Figure 1. X-ray crystal structure of deprotected dimer **8** with crystallographic numbering.

PFP ester;[35] however, the present procedure provides far superior and more convenient access to reasonable amounts of material. The cyclic tetramer **13** was successfully deprotected by treatment with aqueous trifluoroacetic acid to give **9**[36] in quantitative yield; longer treatment with acid gave rise to other products. It has not been possible so far to achieve complete deprotection of the octamer **15** to give the unprotected 56-ring lactam **10**.

The potential for the cyclisation of further linear oligomers was investigated (Scheme 3). Thus hydrogenation of the linear trimer PFP ester **16** at 1 mg/mL afforded the cyclic trimer **17**[37] in 75% isolated yield; no significant amount of the cyclic hexamer was found in the reaction mixture, although mass spectrometry of the residue indicated that traces had been formed. In contrast, hydrogenation of the PFP ester of linear pentamer **18** at



Scheme 3. Products from hydrogenation of linear trimer **16** and linear pentamer **18**.

1 mg/mL gave 71% of the cyclic pentamer **19**[38] together with a small amount (9%) of the cyclic decamer **20**.[39]

The ease of separation of the different cyclic products by chromatography has been crucial in establishing the structures of the cyclic materials. As CHN microanalysis of all the products is identical, the structural assignments rely on mass spectroscopic analysis, including accurate mass measurements for the smaller macrocycles and a comparison for the larger molecules of the calculated and observed isotope distributions. The symmetry of the galactose repeating unit for all the protected cyclic compounds considerably simplifies both the ^{1}H (Table 1) and ^{13}C (Table 2) NMR spectra.

Again the octamer **15** and the decamer **20** may have catenane rather than monocyclic structures. The very similar NMR data for all of the oligomers—effectively identical for the larger rings—is consistent with a monocyclic structure. This dichotomy will be resolved by synthesis and attempted closure of the linear octamer and decamer in due course.

The predisposition for cyclisation of the linear amino-PFP esters in excellent yields was unexpected. As yet, no limit to the size of ring formed has been established. It is not clear at present if the high cyclisation yields are specific to the case of *galacto*-isomers or will prove to be a general method for the generation of a wide range of huge ring macrolactams. It is noteworthy that high yields of homogeneous material indicated that little if any epimerisation at C-2 of the activated species takes place. It may be that these large ring lactams—in deprotected, partially protected or fully protected forms—will have biological and/or structural properties of interest. The following paper describes further cyclisations of mixed

Table 1. Comparison of chemical shifts of selected protons in *galacto* cyclooligomers (in CD_3CN, 500 or 400 MHz)

	^{1}H NMR analysis of protected oligomers						
	H-1 δ (ppm)	H-1′ δ (ppm)	H-2 δ (ppm)	H-3 δ (ppm)	H-4 δ (ppm)	H-5 δ (ppm)	CON*H* δ (ppm)
Dimer **12**	2.87	3.79	4.30	4.15	3.86	4.50	7.32
Trimer **17**	3.45	3.45	4.31	4.18	4.24	4.52	7.33
Tetramer **13**	3.52	3.59	4.39	4.08	4.34	4.46	7.15
Pentamer **19**	3.48	3.54	4.29	4.03	4.32	4.43	7.20
Octamer **15**	3.52	3.52	4.27	3.99	4.31	4.45	7.19
Decamer **20**	3.51	3.51	4.25	3.98	4.31	4.45	7.20

The carbon atoms have been numbered in each case starting with the carbon attached to N terminal end of the compound.

Table 2. Comparison of chemical shifts of selected carbons in *galacto* cyclooligomers (in CD_3CN, 125 or 100 MHz)

	^{13}C NMR analysis of protected oligomers					
	C-1 δ (ppm)	C-2 δ (ppm)	C-3 δ (ppm)	C-4 δ (ppm)	C-5 δ (ppm)	*C*ONH δ (ppm)
Dimer **12**	41.73	71.78	80.17	79.84	74.89	170.44
Trimer **17**	40.10	75.56	79.55	78.65	74.95	171.52
Tetramer **13**	39.00	75.05	77.41	78.51	74.71	171.31
Pentamer **19**	40.65	76.10	78.59	78.99	76.03	171.16
Octamer **15**	40.65	76.85	78.40	79.15	76.58	171.10
Decamer **20**	40.68	76.85	78.00	79.19	76.67	171.15

linear oligomers derived from an amino aldonic acid and 6-amino hexanoic acid in a attempt to further delineate the scope of the efficient cyclisation reactions.[40,41]

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29. The procedure for the conversion of methyl esters to PFP esters is exemplified by the preparation of the dimeric azido PFP ester **11**. Aqueous sodium hydroxide (1 M, 2.2 mL) was added to a stirred solution of the methyl ester **4** (1.17 g,

2.04 mmol) in 1,4-dioxane (15 mL). The reaction mixture was stirred for 4 h at room temperature. TLC (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of starting material (R_f 0.6) to one product (R_f 0.0–0.1). Amberlite IR-120 (H+) resin was added to the solution, which was then stirred for 15 min. The resin was removed by filtration and the filtrate was concentrated in vacuo to give the crude azido acid (1.09 g, 95%), which was dissolved in 1,4-dioxane (7 mL). Pentafluorophenol (718 mg, 3.90 mmol) and EDCI.HCl (449 mg, 2.34 mmol) were added and the reaction mixture was stirred at room temperature under an atmosphere of argon. After 16 h, TLC (ethyl acetate/cyclohexane, 1:1) indicated complete conversion of the starting material (R_f 0.0–0.1) to a major UV active product (R_f 0.65). The solvent was removed in vacuo and the residue was dissolved in dichloromethane (75 mL). The resulting solution was washed with aqueous sodium bicarbonate solution (5% w/v, 30 mL × 2) and the aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were washed with citric acid solution (5% w/v, 40 mL). The organic layer was dried (magnesium sulfate), filtered and the solvent removed. The residue was purified by flash column chromatography (ethyl acetate/cyclohexane, 1:4) to yield the dimeric PFP ester **11** (1.32 g, 94%) as a colourless oil, $[\alpha]_D^{25}$ +2.8 (*c* 1.3, $CDCl_3$); ν_{max} (thin film): 3428 cm^{-1} (N–H), 2105 cm^{-1} (N_3 stretch), 1797 cm^{-1} (C=O, CO_2Pfp), 1681 cm^{-1} (C=O, amide I), 1520 cm^{-1} (C=O, amide II); MS *m/z* (ES+): 725.25 ($M+H^+$, 100%), 747.23 ($M+Na^+$, 85%); HRMS: $C_{30}H_{37}N_4O_{11}F_5Na$ ($M+Na^+$) calcd 747.2282, found 747.2277; $C_{30}H_{37}N_4O_{11}F_5$ calcd: C 49.73%, H 5.15%, N 7.73%, found C 49.35%, H 4.97%, N 7.25%.

30. Selected data for protected cyclic dimer **12**: oil, $[\alpha]_D^{24}$ +6.35 (*c* 3.1, $CHCl_3$); ν_{max} (thin film): 3349 cm^{-1} (N–H), 1682 cm^{-1} (C=O, amides I), 1520 cm^{-1} (C=O, amides II); ^1H and ^{13}C NMR are given in Tables 1 and 2. MS *m/z* (ES+): 515.26 ($M+H^+$, 100%); HRMS: $C_{24}H_{39}N_2O_{10}$ ($M+H^+$) calcd 515.2605, found 515.2603.
31. Selected data for protected cyclic tetramer **13**: $[\alpha]_D^{24}$ −35.2 (*c* 1.3, $CHCl_3$); mp: >210 °C; ν_{max} (thin film): 3429 cm^{-1} (N–H), 1682 cm^{-1} (C=O, amides I), 1525 cm^{-1} (C=O, amides II); ^1H and ^{13}C NMR are given in Tables 1 and 2. MS *m/z* (ES+): 1029.60 ($M+H^+$, 20%), 1051.55 ($M+Na^+$, 100%); MS *m/z* Isotope distribution (ES+): $C_{48}H_{76}N_4O_{20}Na$ ($M+Na^+$) calcd 1051.50, 100%; 1052.50, 60%; 1053.50, 20%; 1054.50, 5%, measured 1051.55, 100%; 1052.51, 60%; 1053.53, 20%; 1054.61, 5%; $C_{48}H_{76}N_4O_{20}$ calcd C 56.02%, H 7.44%, N 5.44%, found C 55.52%, H 7.91%, N 5.04%.
32. Data for deprotected cyclic dimer **8**: $[\alpha]_D^{24}$: −45.2 (*c* 0.65, H_2O); mp: >220 °C; fine, white solid darkened on heating; ν_{max} (thin film, Ge plate): 3348 cm^{-1} (O–H, N–H), 1644 cm^{-1} (C=O, amides I), 1544 cm^{-1} (C=O, amides II); ^1H NMR δ_H (500 MHz, D_2O): 3.15 (2H, dd, $J_{1,1'}$ 12.8, $J_{1,2}$ 3.8, 2×H-1), 3.32 (2H, a-br d, $J_{3,4}$ 8.6, 2×H-3), 3.52–3.55 (2H, br m, 2×H-1′), 3.87 (2H, dd, $J_{4,3}$ 8.6, $J_{4,5}$ 4.9, 2×H-4), 3.97 (2H, br m, 2×H-2), 4.22 (2H, d, $J_{5,4}$ 4.9, 2×H-5); ^{13}C NMR δ_C (125 MHz, D_2O): 39.98 (2×C-1), 67.50 (2×C-2), 69.92 (2×C-3), 70.46 (2×C-4), 74.90 (2×C-5), 174.07 (2×*C*ONH); MS *m/z* (ES−): 353.12 ($[M-H]^-$, 100%); HRMS: $C_{12}H_{21}N_2O_{10}$ ($[M-H]^-$) calcd 353.1196, found 353.1193.
33. Crystallographic data deposited at CCDC, reference no: CCDC 218823. Crystal data: Size: 0.30 × 0.40 × 0.40, Crystal system: Trigonal, Space group: $P3_121$, *a*: 9.2689(1), *b*: 9.2689(1), *c*: 28.9539(6), Volume: 2154.24(6), Density: 1.65, $2\theta_{max}$: 60.04, Radiation type: Mo Kα, Wavelength: 0.710730 Å, Diffractometer type: Nonius KappaCCD, Scan type: Omega, Temperature (K): 150, Reflections measured: 6990, Independent reflections: 2416, Rint: 0.0004, Reflections used: 1887, sigma(I) limit: 3.00, μ: 0.145, Absorption type: multi-scan, Transmission range: 0.94–0.96, Structure solution: Sir92, Structure refinement: CRYSTALS, Refined on *F* squared, Hydrogen on carbon: riding, others: refined, Partially occupied water of solvation: 0.30, some disorder, $\Delta\rho_{min}$: −0.35, $\Delta\rho_{max}$: 0.36, *R*-factor: 0.039, Weighted *R*-factor: 0.094, Number of parameters: 249, Goodness of fit: 1.118.
34. Selected data for protected cyclic octamer **15**: $[\alpha]_D^{22}$ +0.83 (*c* 0.6, CD_3CN); ν_{max} (thin film): 3428 cm^{-1} (N–H), 1677 cm^{-1} (C=O, amides I), 1527 cm^{-1} (C=O, amides II); ^1H and ^{13}C NMR are given in Tables 1 and 2 MS *m/z* (ES+): 2075.1 ($M+NH_4^+$, 100%), 2080.0 ($M+Na^+$, 95%); MS *m/z* (ES+): 1040.2 ($[M+H+Na]^{2+}$, 50%), 1051.2 ($[M+NH_4+Na]^{2+}$, 100%); MS *m/z* Isotope distribution (ES+): $C_{96}H_{152}N_8O_{40}Na$ ($M+Na^+$) calcd 2080.0, 90%; 2081.0, 100%; 2082.0, 65%; 2083.0, 30%; 2084.0, 6%, measured 2079.0, 90%; 2080.0, 100%; 2081.0, 55%; 2082.0, 25%; 2083.0, 5%; 2084.0, 3%; MS *m/z* Isotope distribution (ES+): $C_{96}H_{156}N_9O_{40}$ ($M+NH_4^+$) calcd 2075.0, 90%; 2076.0, 100%; 2077.1, 65%; 2078.1, 30%; 2079.1, 6%, measured 2074.1, 80%; 2075.1, 95%; 2076.1, 55%; 2077.1, 30%; 2078.1, 7%.
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36. Data for deprotected cyclic tetramer **9**: $[\alpha]_D^{25}$ +3.0 (*c* 0.2, D_2O); mp: >220 °C, white solid darkened on heating above 160 °C; ^1H NMR δ_H (500 MHz, D_2O): 3.32 (4H, dd, $J_{1,1'}$ 13.6, *J* 7.5, 4×H-1), 3.56 (4H, dd, $J_{1',1}$ 13.6, *J* 5.8, 4×H-1′), 3.63 (4H, dd, $J_{3,4}$ 9.5, $J_{3,2}$ 1.9, 4×H-3), 3.93 (4H, dd, $J_{4,3}$ 9.5, $J_{4,5}$ 1.8, 4×H-4), 3.94 (4H, m, 4×H-2), 4.41 (4H, d, $J_{5,4}$ 1.8, 4×H-5); ^{13}C NMR δ_C (125 MHz, D_2O): 41.83 (4×C-1), 68.86 (4×C-2), 69.87 (4×C-3), 71.47 (4×C-4), 71.77 (4×C-5), 176.21 (4×*C*ONH); MS *m/z* (ES−): 707.25 ($[M-H]^-$, 19%), 708.25 ($[M-H]^-$, 58%), 709.26 ($[M-H]^-$, 100%); HRMS: $C_{24}H_{43}N_4O_{20}$ ($[M-H]^-$) calcd 707.2471, found 707.2492.
37. Selected data for protected cyclic trimer **17**: $[\alpha]_D^{21}$ +3.2 (*c* 2.0, $CDCl_3$); ν_{max} (thin film): 3352 cm^{-1} (N–H), 1673 cm^{-1} (C=O, amides I), 1531 cm^{-1} (C=O, amides II); ^1H and ^{13}C NMR are given in Tables 1 and 2; MS *m/z* (ES+): 794.30 ($[M+Na]^+$, 100%); HRMS: $C_{36}H_{57}N_3O_{15}Na$ ($[M+Na]^+$) calcd 794.3687, found 794.3693.
38. Selected data for protected cyclic pentamer **19**: $[\alpha]_D^{24}$ −15.6 (*c* 1.0, $CHCl_3$); mp: sinters 118–119 °C, melts 120–121 °C; ν_{max} (thin film): 3429 cm^{-1} (N–H), 1682 cm^{-1} (C=O, amides I), 1528 cm^{-1} (C=O, amides II); ^1H and ^{13}C NMR are given in Tables 1 and 2, MS *m/z* (ES+): 1308.10 ($[M+Na]^+$, 100%); MS *m/z* Isotope distribution (ES+): $C_{60}H_{95}N_5O_{25}Na$ ($[M+Na]^+$) calcd 1308.6, 100%; 1309.6, 70%; 1310.6, 30%; 1311.6, 10%; 1312.6, 3%, measured 1308.9, 100%; 1309.9, 70%; 1310.9, 18%; 1311.9, 4%; 1312.9, 2%.
39. Selected data for protected cyclic decamer **20**: $[\alpha]_D^{25}$ +0.55 (*c* 0.55, CD_3CN); ν_{max} (thin film): 3429 cm^{-1} (N–H), 1682 cm^{-1} (C=O, amides I), 1520 cm^{-1} (C=O, amides II); ^1H and ^{13}C NMR are given in Tables 1 and 2. MS *m/z* (ES+): 2591.3 ($[M+NH_4]^+$, 100%); MS *m/z* Isotope distribution (ES+): $C_{120}H_{194}N_{11}O_{50}$ ($[M+NH_4]^+$) calcd 2589.3, 70%; 2590.3, 100%; 2591.3, 80%; 2592.3, 40%; 2593.3, 20%; 2594.3, 8%, measured 2590.3, 68%; 2591.3, 100%; 2592.3, 80%; 2593.3, 38%; 2594.3, 8%; 2595.3, 5%.
40. Mayes, B. A.; Cowley, A. R.; Ansell, C. W. G.; Fleet, G. W. J. *Tetrahedron Lett.* **2003**, *45*. See: doi:10.1016/j.tetlet.2003.10.105.
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