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Towards hydroxylated nylon 6: linear and cyclic oligomers from a protected 6-amino-6-deoxy-D-galactonate—a novel class of carbopeptoid-cyclodextrin (CPCD)

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Abstract—Circular dichroism studies on a series of linear oligomers derived from a protected 6-amino-6-deoxy-D-galactonate (an ε-amino acid) indicated a predisposition to form a rigid structure in solution, which is comparable to a β-sheet composed of L-amino acids; in contrast, a diastereomeric allonate series provided no evidence for secondary structure. A linear tetramer was cyclised to a 28-membered ring lactam in modest yield, which on deprotection formed a class of macrocycle with structural features of both a cyclic peptide and a cyclodextrin.

1. Introduction

Sugar amino acids[1,2] (SAA) are currently exploited as peptidomimetics and as scaffolds for the construction of new biomaterials.[3,4] Hydroxylated nylons 6,6[5] in which the hexanedioic acid component has been replaced by an aldaric acid provide a class of biodegradable polymers,[6] which has attracted considerable attention with respect to their synthesis[7–10] and structure.[11,12] In contrast, the first synthesis of a fully hydroxylated nylon 6 oligomer in which the monomeric unit was a 6-amino-6-deoxy-D-allonic acid has only recently been described.[13] Herein we report the synthesis of a set of linear oligomers derived from 6-amino-6-deoxy-D-galactonic acid. Linear oligomers of conformationally locked[14,15] SAA, including those which possess tetrahydropyran,[16] tetrahydrofuran[17–19] and oxetane[20] rings provide examples of relatively small molecules predisposed towards formation of secondary structures.[21,22] The β-sheet structures of the *galacto*-oligomers indicated by circular dichroism herein extend the range of SAA, which appear to adopt secondary structures in solution.

Cyclic carbohydrates (cyclodextrins) and cyclic peptides have a multitude of proven applications in both therapeutic and structural areas; this is reflected in the number of papers in 2002, which have cyclodextrin [1139] or cyclic peptide [108] as key words. Although there have been extensive studies on a wide range of carbohydrate macrocycles,[23] the vast bulk of publications are confined to the basic glucoside structure. The inclusion complexes formed by cyclodextrins[24,25] account for their industrial uses in drugs, foods and cosmetics[26] and in stabilising the structures of nanotubes.[27–29] The range of cyclic peptides—both in terms of ring size and structural components—is far greater. Their applications are diverse,[30] extending from antibiotics[31] to nanotubes[32–35] and much effort has been devoted to their chemical[36] and enzymatic[37] synthesis. Cyclic peptides containing SAA have provided a set of novel cyclic structures;[38,39] some cyclic RGD analogues, which contain a furanoid SAA have been shown to be integrin inhibitors.[40] Herein we also describe the cyclisation of the tetramer **6** followed by deprotection to afford the 28-membered ring macrocyclic lactam **3** (Scheme 1). The macrocycle has structural features in common with both cyclodextrins and cyclic peptides and is an example of a novel class of biomaterial, which may be described as carbopeptoid-cyclodextrins (CPCD). Some of this work has already been the subject of a preliminary report.[41]

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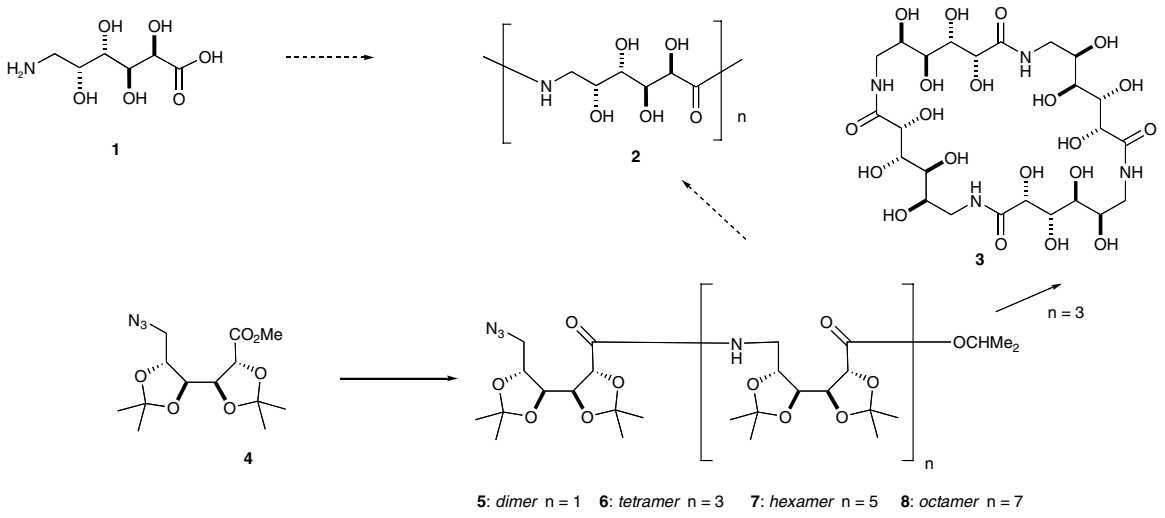


Scheme 1.

2. Results and discussion

2.1. Synthesis of defined linear oligomers

The *galacto*-stereochemistry was selected for the synthesis of the series of fully hydroxylated nylon 6 oligomers **5**–**8** because (i) the building block **4** can be made on a reasonable scale, (ii) the *trans*,*trans*-acetonides in **4** preclude the easy formation of a seven ring lactam and (iii) this would allow comparison with the all *cis*,*cis*-acetonide series **23**–**26** previously prepared.[13]

A practical synthesis of the building block **4** was developed from D-galactonolactone **9** by modification of the previously published procedure (Scheme 2).[42] Thus, reaction of **9** with dimethoxypropane in acetone in the presence of *p*-toluenesulfonic acid (TSA) gave the required diacetonide **11** with the C-6 hydroxyl group free in a 76% yield. The diacetonide **10** with the C-4 hydroxyl free was also isolated in 18% yield. Subsequent esterification of the primary alcohol **11** with mesyl chloride in pyridine in the presence of 4-(dimethylamino)pyridine (DMAP) gave the crystalline mesylate **12** (95% yield). Treatment of **12** with sodium azide in dimethyl formamide (DMF) gave the azido methyl ester **4** in 90% yield. The overall yield from D-galactonolactone **9** to produce 14 g of **4** was 65%.

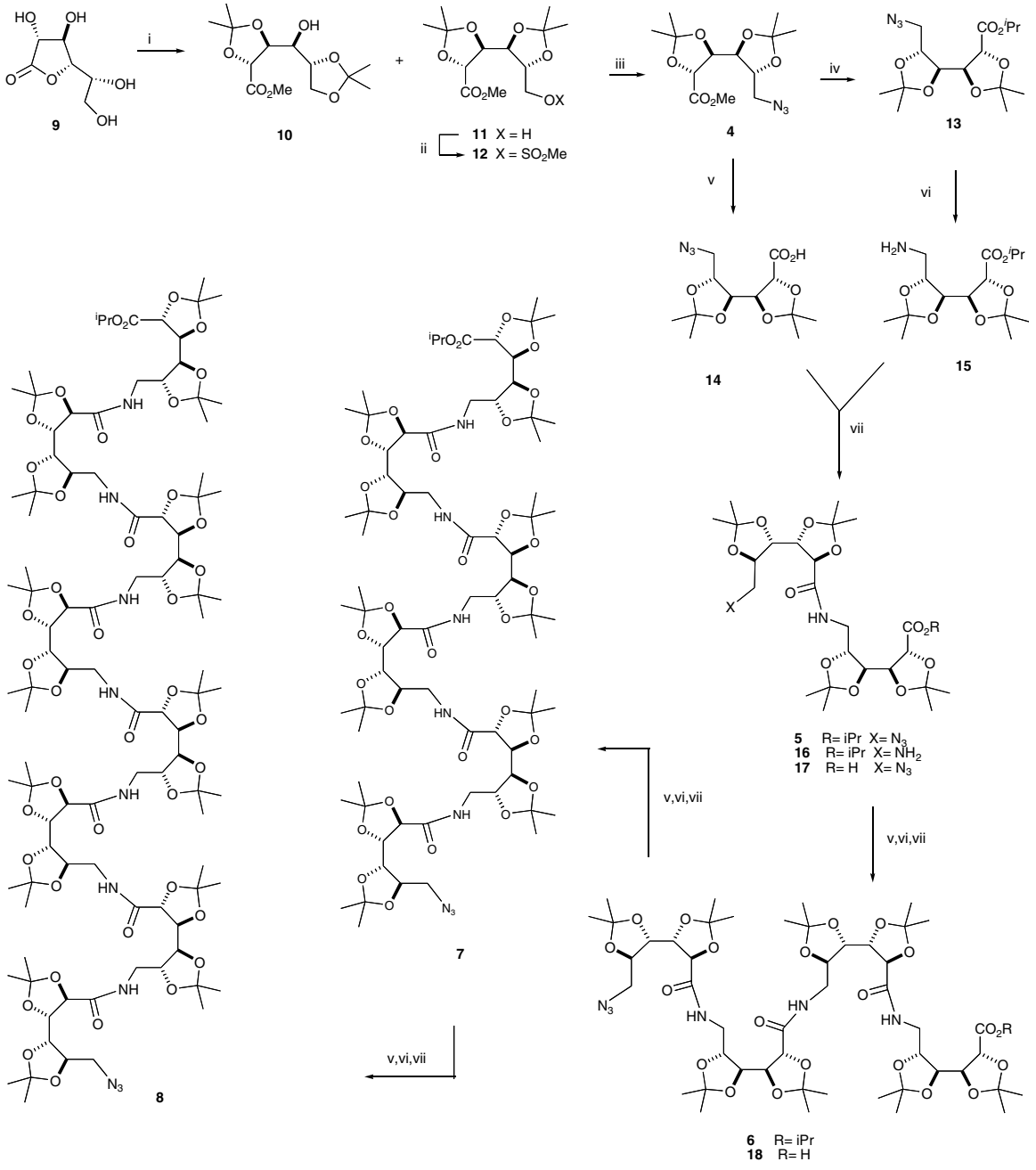
The more hindered isopropyl ester **13** was prepared in order to prevent the possible self-condensation of the amino methyl ester. Accordingly the methyl group in **4** was exchanged by treatment with potassium carbonate in isopropanol to give the isopropyl ester **13** in 83% yield; no epimerisation at C-2 occurred in this ester exchange. The synthesis of the linear oligomers was undertaken by standard iterative peptide coupling procedures. The isopropyl azide **13** was reduced to the amine **15** by hydrogenation in the presence of palladium black and the methyl ester treated with sodium hydroxide in aqueous dioxane to afford the acid **14**. Activation of the acid by 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide (EDCI) in the presence of hydroxybenzotriazole (HOBt) and diisopropylethylamine (DIPEA), followed by addition of the amine **15** gave the dimer **5** in 74% yield.

For the linear tetramer, dimer **5** was reduced to the amino ester **16** and separately hydrolysed to the acid **17**. Compound **17** was subjected to sequential treatment with HOBt, DIPEA, EDCI and the crude amine **16** to afford the linear tetramer **6** in 73% yield. Iteration by treatment of the activated ester derived from the tetramer acid **18** with the amine dimer **16** produced the hexamer **7** in 62% yield. Finally, further iteration from the activated acid from the hexamer with the dimeric amine **16** gave the linear octamer **8** in 63% yield.

2.2. Synthesis of cyclic oligomers

Attempts were made to generate oligomers and polymers from both monomeric **19** and dimeric **20** amino acids, derived by catalytic hydrogenation of the azides, **14** and **17**, respectively (Scheme 3). A number of peptide activating agents were investigated, which gave intractable mixtures; it is well recognised that pentafluorophenyl (PFP) esters generally give the highest yields in the preparation of cyclic peptides.[35] Accordingly, when the amino acid **19** was activated by DIPEA and pentafluorophenyl diphenylphosphinate (FDPP) to provide an in situ PFP ester, analysis of this reaction mixture by MALDI TOF (LD+) mass spectrometry revealed the formation of macrocyclic species. Molecular ions corresponding to the cyclic trimer ($M+Na^+$, 794.6), cyclic tetramer ($M+Na^+$, 1051.7), cyclic pentamer ($M+Na^+$, 1309.1), cyclic hexamer ($M+Na^+$, 1566.9) and cyclic heptamer ($M+Na^+$, 1824.5) were observed in a ratio of approximately 12:6:5:3:2, respectively. However, it was not possible to isolate any of the cyclic compounds in a pure form.

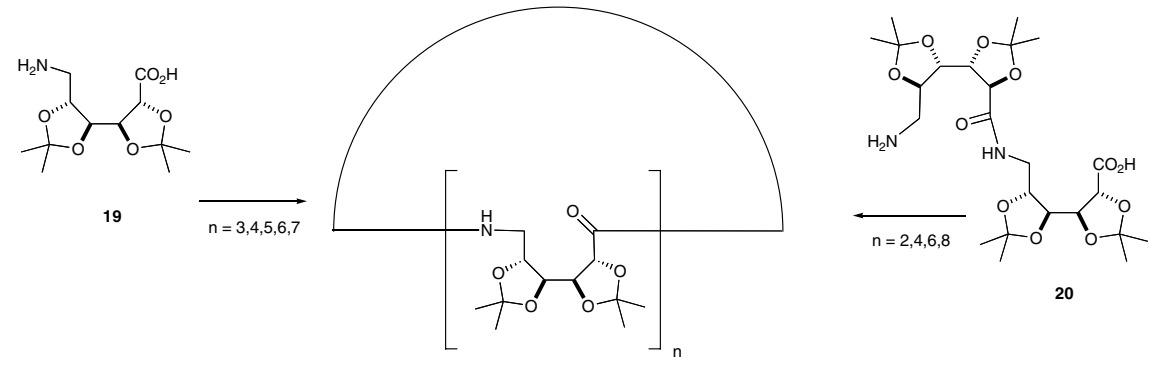
It was considered that the dimeric amino acid would provide a better opportunity for the isolation of pure cyclic species in the cyclisation experiments. Thus, the



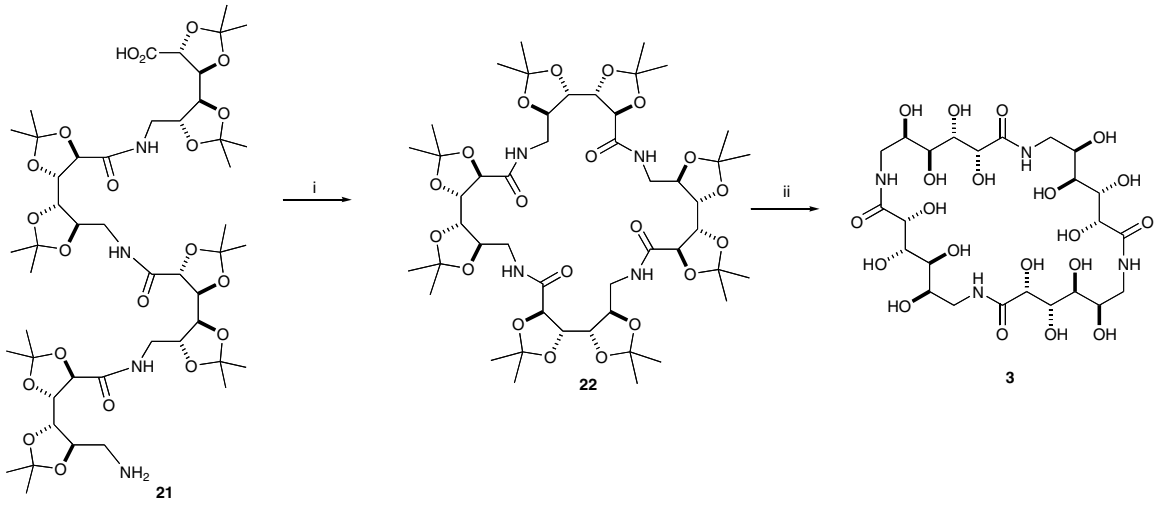
Scheme 2. Reagents and conditions: (i) $Me_2C(OMe)_2$, Me_2CO, TSA; (ii) $MeSO_2Cl$, DMAP, pyridine; (iii) NaN_3, DMF; (iv) Me_2CHOH, K_2CO_3; (v) NaOH (aq), dioxane, then Amberlite IR-120 H^+; (vi) H_2, Pd black, EtOAc; (vii) EDCI, HOBt, DIPEA, CH_2Cl_2.

dimeric amino acid **20** was treated with DIPEA and FDPP and the reaction mixture analysed by MALDI TOF (LD+) mass spectrometry. Formation of the cyclic dimer ($M+Na^+$, 537.5), cyclic tetramer ($M+Na^+$, 1051.7), cyclic hexamer ($M+Na^+$, 1566.9) and cyclic octamer ($M+Na^+$, 2080.9) in a ratio of approximately 5:20:5:1, respectively, was observed. Again pure samples of the individual macrocycles were not isolated.

Due to the relative abundance of the cyclic tetramer in the reaction of the dimeric amino acid **20**, the conversion of the tetrameric azidoacid **18** to the cyclic tetramer **22** was investigated on a preparative scale via its PFP ester (Scheme 4). Hydrogenation of the azidoacid **18** afforded the amino acid **21**, a suspension of which in acetonitrile was treated with DIPEA and FDPP. This allowed the isolation of the macrocyclic lactam **22** in 30% yield over the three steps. This yield has not been optimised but is consistent with reported yields for macrocyclisation by FDPP activation and related reagents.[43–45] Careful treatment of the protected 28-ring macrocyclic lactam **22** with aqueous trifluoroacetic acid gave the unprotected cyclic tetramer **3** in a quantitative yield. The cyclic tetramer **3** was not stable under strongly acidic conditions and slowly gave rise to a complex mixture of products. Although the NMR spectra of the linear oligomers are highly complex, those of the protected **22** and unprotected **3** cyclic tetramers are simple, having only 10



Scheme 3. Random cyclooligomerisations.



Scheme 4. Reagents and conditions: (i) DIPEA, FDPP, MeCN; (ii) CF_3COOH, H_2O.

different ^{13}C resonances for **22** and six different ^{13}C resonances for **3**; the ^{1}H NMR spectra of the compounds also showed the symmetry of the materials.

2.3. Circular dichroism (CD) studies

The *galacto*-oligomers **5**, **6**, **7** and **8** possess adjacent *trans*,*trans*-acetonides whereas the corresponding *allo*-oligomers **23**, **24**, **25** and **26** have adjacent *cis*,*cis*-acetonides (Fig. 1). The NMR spectra of neither series provided any evidence of structural organisation in a wide range of solvents.

CD spectroscopy is a widely used technique in structural studies of proteins, peptides and peptidomimetic compounds;[46] it is unclear as to whether open-chain carbopeptoids display characteristic CD spectra analogous to peptidic compounds, although tentative comparisons may be drawn.[47] CD spectroscopic investigations were performed on the *trans–trans* and *cis–cis* acetonide oligomers to identify any propensity for the adoption of ordered structures in solution (Fig. 2). The CD spectra were recorded in 2,2,2-trifluoroethanol (TFE) at 293 K.

The *trans–trans* oligomers, with *galacto* stereochemistry displayed CD spectra (Fig. 2a), which were analogous to

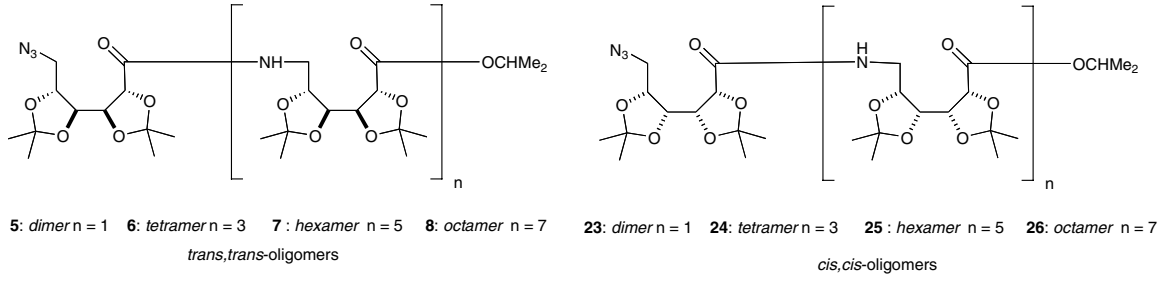


Figure 1.

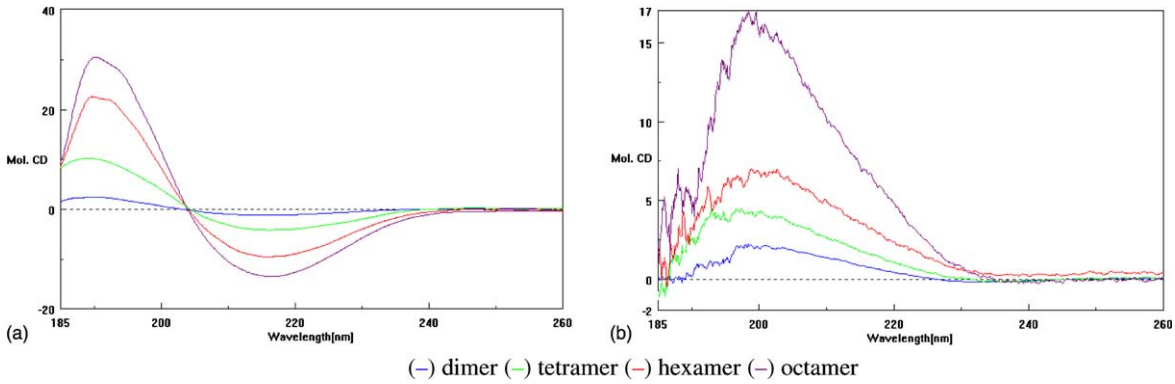


Figure 2. CD spectra of the *cis–cis* and *trans–trans* oligomers: (a) the *trans,trans-galacto*-oligomers **5**–**8**; (b) the *cis,cis-allo*-oligomers **23**–**26**. The CD spectra were normalised for compound concentration and path length.

that of a β-sheet peptidic structure composed of L-amino acid residues. No major changes in the spectra, over and above that attributable to increasing number of amide linkages, were observed with increasing the chain length. This suggests that the individual amides did not partake in exciton coupling to any great extent.[48] When the *trans–trans* oligomer CD spectra were normalised for mean amide concentration, a very subtle change with increased chain length was observed (Fig. 3). The *trans–trans* dimer **5** appeared to adopt a subtly different conformation to the hexamer **7** (crossing the *x*-axis at 203 nm and at 204 nm, respectively). Subsequent extension from the hexamer **7** to the octamer **8** no longer altered the conformational preference of the system. It could be suggested that the spectrum of the tetramer **6** was intermediate between the conformations adopted by the dimer **5** and hexamer **7**. In contrast to the β-sheet appearance of the *trans–trans* oligomers, the *cis–cis* oligomers displayed CD spectra, which were similar to an irregular structure composed of D-amino acid residues (Fig. 2b). Again, the growth of CD intensity was related to increasing chain length, which suggested that the observed conformational preference was inherent to dimer **23**.

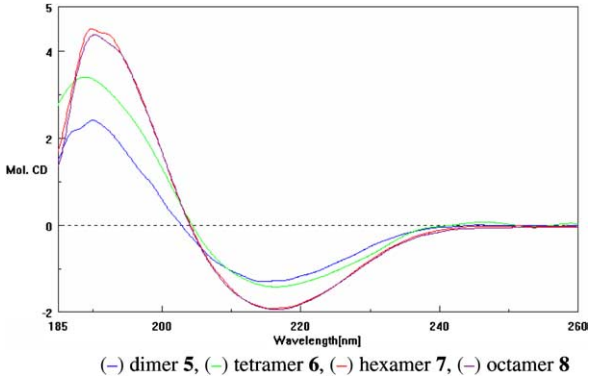


Figure 3. CD spectra of the *trans–trans* oligomers using the mean amide concentration. The CD spectra were normalised for mean amide concentration and path length and the resulting spectra Fourier transform noise reduced.

Despite the current uncertainty of the structural interpretation of CD data in the study of the conformational preference of open-chain carbopeptoids, which is under further investigation, it was clear that the *trans–trans* and *cis–cis* oligomers adopted significantly different conformations in TFE. These two conformations appeared to be analogous to two distinct conformations well characterised in proteins, peptides and peptidomimetics. The value of CD in establishing solution secondary structural preferences in carbopeptoids is worthy of further study.

3. Conclusion

Herein we have reported the synthesis of a series of linear oligomers **5**–**8** as examples of a fully hydroxylated nylon 6. The CD spectra of **5**–**8** in which all the acetonides on the backbone are *trans* showed that in solution a β-sheet structure may be adopted. In contrast, random coils were indicated by the CD spectra of the series **23**–**26** in which the backbone acetonides are all *cis*. We have also reported the formation of the 28-membered ring lactam **22** in modest yield by cyclisation of the linear tetramer. Deprotection of **22** gave a novel macrocycle **3**, which has some of the structural features of both a cyclodextrin and a cyclic peptide, and is an example of a novel class of carbopeptoid-cyclodextrin. If convenient preparations of such macrocycles are developed, they may well have properties of both structural and biological importance.

4. Experimental

Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl or purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride and stored over dried 3 Å molecular sieves; hexane refers to 60–80 °C petroleum ether; water was

distilled. *N*,*N*-Dimethylformamide was purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Reactions performed under an atmosphere of nitrogen or hydrogen gas were maintained by an inflated balloon. Buffer (pH 7) was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 mL). All other reagents were used as supplied, without prior purification. Thin layer chromatography (TLC) was performed on aluminium or plastic sheets coated with 60 F_{254} silica. Sheets were visualised using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid or 0.5% ninhydrin in methanol (particularly for amines). Flash column chromatography was performed on Sorbsil C60 40/60 silica, acidic ion-exchange chromatography was performed on Amberlite® IR-120 (H^+). Melting points were recorded on a Köfler hot block and are corrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 500 or AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) or where stated on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in deuterated solvent. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference and ^{13}C NMR spectra in D_2O were referenced to 1,4-dioxane (δ_C 67.4). ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform, or Perkin–Elmer Paragon 1000 spectrophotometer using thin films on NaCl plates (thin film) or KBr discs. Only the characteristic peaks are quoted. Low resolution mass spectra (m/z) were recorded on VG MassLab 20–250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers and high resolution mass spectra (HRMS m/z) on a Micromass Autospec 500 OAT spectrometer. Techniques used were electrospray (ES), matrix assisted laser desorption ionisation (MALDI), chemical ionisation (CI, NH_3), or atmospheric pressure chemical ionisation (APCI) using partial purification by HPLC with 40:40:20 methanol–acetonitrile–water as eluant, as stated. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 mL.

Circular dichroism (CD) spectra were recorded in the Centre for Biospectroscopy, Imperial College London on a JASCO J600 circular dichroism spectrometer fitted with a bespoke thermostated cell holder. The sample cell was a quartz Suprasil cylindrical cell with a path length of 1.0 cm (except for the *trans–trans* tetramer **6** where 0.1 cm was used). Sample spectra were measured at 293 K in TFE, and at the following compound concentrations: **6** at 198.7, **7** at 125.7, **8** at 38.3, **9** at 28.7, **23** at 200, **24** at 66.7, **25** at 40 and **26** at 30.7 μM. The following acquisition parameters were used: scan speed = 10 nm/min, time constant = 4 s, spectral band width = 1 nm, data interval = 0.1 nm, scan range = 260–185 nm. A baseline spectrum of the solvent was recorded in the same cell at a proximal time and subtracted from the sample spectra. The resultant spectra were normalised for path length and for compound (Fig. 2) or mean amide (Fig. 3) concentration. The spectra shown in Figure 3 were Fourier transform noise reduced and compared to the original spectrum to ensure that smoothing gave a representative spectrum.

4.1. Methyl 2,3:4,5-di-*O*-isopropylidene-D-galactonate 11 and methyl 2,3:5,6-di-*O*-isopropylidene-D-galactonate 10

p-Toluenesulfonic acid monohydrate (5.38 g, 28.3 mmol) was added to a stirred suspension of D-galactono-1,4-lactone **9** (10.07 g, 56.5 mmol) in 2,2-dimethoxypropane (200 mL) and acetone (15 mL). The reaction was stirred at 40 °C for 18 h under an atmosphere of nitrogen after which TLC (3:2 ethyl acetate–hexane) indicated complete conversion of starting material (R_f 0.0) to three products (R_f 0.9, R_f 0.6, R_f 0.5). Sodium carbonate was added to neutralise and the mixture filtered through Celite®. The solvent was removed in vacuo and the residue dissolved in dichloromethane (200 mL) and extracted with water (2×75 mL). The aqueous phase was extracted with dichloromethane (50 mL) and the combined organic extracts dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by repeated flash column chromatography (3:8 ethyl acetate–hexane) gave methyl 2,3:5,6-di-*O*-isopropylidene-D-galactonate **10** (2.95 g, 18%) (R_f 0.6, 3:2 ethyl acetate–hexane) as a colourless oil:[42] $[\alpha]_D^{23} = -22.2$ (c 1.03, $CHCl_3$) {lit.[42] $[\alpha]_D^{20} = -10.8$ (c 1.16, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 4.60 (1H, d, H-2, $J_{2,3}$ 5.9 Hz), 4.28 (1H, dd, H-3, $J_{3,2}$ 5.9 Hz, $J_{3,4}$ 7.3 Hz), 4.24 (1H, ddd, H-5, $J_{5,4}$ 3.9 Hz, $J_{5,6}$ 6.8 Hz, $J_{5,6'}$ 6.7), 4.07 (1H, dd, H-6′, $J_{6',5}$ 6.7 Hz, $J_{6',6}$ 8.3 Hz), 3.90 (1H, dd, H-6, $J_{6,5}$ 6.8 Hz, $J_{6,6'}$ 8.3 Hz), 3.79 (3H, s, CO_2CH_3), 3.57 (1H, br dd, H-4, $J_{4,3}$ 7.3 Hz, $J_{4,5}$ 3.9 Hz), 2.51 (1H, br s, OH-4), 1.45, 1.43, 1.40, 1.36 (12H, 4×s, 2×C(CH_3)$_2$). Methyl 2,3:4,5-di-*O*-isopropylidene-D-galactonate **11** (5.96 g) (R_f 0.5, 3:2 ethyl acetate–hexane) and a hemiacetal intermediate (≈17 g) (R_f 0.9, 3:2 ethyl acetate–hexane), which was not characterised was stirred in 7:3 acetic acid–water (40 mL) at room temperature for 2 min. The solvent was removed in vacuo (co-evaporation with toluene) and purification by flash column chromatography (3:8 ethyl acetate–hexane) gave a further amount of methyl 2,3:4,5-di-*O*-isopropylidene-D-galactonate **11** (6.51 g; 12.47 g in total, 76%) as a colourless oil: $[\alpha]_D^{23} = -20.5$ (c 1.24, $CHCl_3$) {lit.[42] $[\alpha]_D^{20} = -15.0$ (c 1.13, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 4.57 (1H, d, H-2, $J_{2,3}$ 5.4 Hz), 4.38 (1H, dd, H-3, $J_{3,2}$ 5.4 Hz, $J_{3,4}$ 7.5 Hz), 4.11 (1H, m, H-5), 3.95 (1H, a-t, H-4, J 7.6 Hz), 3.86 (1H, m, H-6′), 3.81 (3H, s, CO_2CH_3), 3.74 (1H, ddd, H-6, $J_{6,5}$ 4.3 Hz, $J_{6,6'}$ 11.9 Hz, $J_{OH,6}$ 8.2 Hz), 2.09 (1H, dd, OH-6, $J_{OH,6}$ 8.2 Hz, $J_{OH,6'}$ 4.7 Hz), 1.48, 1.43, 1.42, 1.41 (12H, 4×s, 2×C(CH_3)$_2$).

4.2. Methyl 2,3:4,5-di-*O*-isopropylidene-6-*O*-methanesulfonyl-D-galactonate 12

Methanesulfonyl chloride (4.1 mL, 53.0 mmol) was added to a stirred solution of methyl 2,3:4,5-di-*O*-iso-

propylidene-D-galactonate **10** (15.00 g, 51.7 mmol) and 4-(dimethylamino)pyridine (380 mg) in pyridine (100 mL) at 0 °C. The reaction mixture was stirred for 2.5 h at room temperature. TLC (1:2 ethyl acetate–hexane) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.3). The solvent was removed in vacuo (co-evaporation with toluene). The residue was dissolved in dichloromethane (650 mL) and washed with water (250 mL) and brine (150 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was pre-adsorbed onto silica and purified by flash column chromatography (1:2 ethyl acetate–hexane) to yield methyl 2,3:4,5-di-*O*-isopropylidene-6-*O*-methanesulfonyl-D-galactonate **12** (18.08 g, 95%) as a crystalline solid, mp 99 °C (ethyl acetate/hexane); $[\alpha]_D^{24} = -5.1$ (*c* 0.9, $CHCl_3$) {lit.[42] mp 98–99 °C (diethyl ether/hexane); $[\alpha]_D^{23} = -6.1$ (*c* 1.00, $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$) 4.55 (1H, d, H-2, $J_{2,3}$ 5.3 Hz), 4.49 (1H, dd, H-6′, $J_{6',5}$ 2.7 Hz, $J_{6',6}$ 11.1 Hz), 4.37 (1H, dd, H-3, $J_{3,2}$ 5.3 Hz, $J_{3,4}$ 7.6 Hz), 4.32 (1H, dd, H-6, $J_{6,5}$ 5.3 Hz, $J_{6,6'}$ 11.1 Hz), 4.26 (1H, ddd, H-5, $J_{5,4}$ 7.7 Hz, $J_{5,6}$ 5.3 Hz, $J_{5,6'}$ 2.7 Hz), 3.93 (1H, a-t, H-4, *J* 7.7 Hz), 3.81 (3H, s, CO_2CH_3), 3.08 (3H, s, SO_2CH_3), 1.47, 1.44, 1.42 (12H, 3×s, 2×C(CH_3)$_2$).

4.3. Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate 4

Sodium azide (3.63 g, 55.8 mmol) was added to a stirred solution of the mesylate **12** (18.06 g, 49.0 mmol) in DMF (150 mL). The reaction mixture was stirred for 36 h at 85 °C. TLC (1:2 ethyl acetate–hexane) indicated complete conversion of the starting material (R_f 0.3) to a single product (R_f 0.6). The solvent was removed in vacuo (co-evaporation with toluene). The residue was dissolved in ethyl acetate (500 mL) and washed with water (2×150 mL). The aqueous phase was extracted with ethyl acetate (150 mL) and the combined organic extracts washed with brine (150 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (1:6 ethyl acetate–hexane) to yield methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate **4** (13.88 g, 90%) as a colourless oil, $[\alpha]_D^{25} = +31.3$ (*c* 0.8, $CHCl_3$) {lit.[42] $[\alpha]_D^{23} = +30.9$ (*c* 2.13, $CHCl_3$)}; δ_H (200 MHz, $CDCl_3$) 4.57 (1H, d, H-2, $J_{2,3}$ 5.2 Hz), 4.35 (1H, dd, H-3, $J_{3,2}$ 5.2 Hz, $J_{3,4}$ 7.5 Hz), 4.18 (1H, m, H-5), 3.95 (1H, a-t, H-4, *J* 7.6 Hz), 3.81 (3H, s, CO_2CH_3), 3.66 (1H, dd, H-6′, $J_{6',5}$ 3.1 Hz, $J_{6',6}$ 13.1 Hz), 3.33 (1H, dd, H-6, $J_{6,5}$ 5.0 Hz, $J_{6,6'}$ 13.1 Hz), 1.47, 1.46, 1.41 (12H, 3×s, 2×C(CH_3)$_2$).

4.4. Isopropyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate 13

Potassium carbonate (435 mg, 3.12 mmol) was added to a stirred solution of the azide **4** (829 mg, 2.63 mmol) in isopropanol (34 mL). The reaction mixture was stirred under an atmosphere of nitrogen at 60 °C for 48 h. TLC (1:2 ethyl acetate–hexane) indicated conversion of the starting material (R_f 0.5) to a single product (R_f 0.6). The reaction mixture was allowed to cool to room temperature, filtered and the solvent removed in vacuo. The residue was purified by flash column chromatography (1:6 ethyl acetate–hexane) to yield isopropyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate **13** (746 mg, 83%) as a colourless oil: $[\alpha]_D^{23} = +29.0$ (*c* 1.12, $CHCl_3$); ν_{max} (thin film): 2103 (N_3), 1749 (C=O, ester) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.10 (1H, sept, C*H*(CH_3)$_2$, *J* 6.3 Hz), 4.46 (1H, d, H-2, $J_{2,3}$ 5.4 Hz), 4.27 (1H, dd, H-3, $J_{3,2}$ 5.4 Hz, $J_{3,4}$ 7.6 Hz), 4.16 (1H, ddd, H-5, $J_{5,4}$ 7.8 Hz, $J_{5,6}$ 5.1 Hz, $J_{5,6'}$ 3.1 Hz), 3.92 (1H, a-t, H-4, *J* 7.7 Hz), 3.63 (1H, dd, H-6′, $J_{6',5}$ 3.1 Hz, $J_{6',6}$ 13.2 Hz), 3.31 (1H, dd, H-6, $J_{6,5}$ 5.1 Hz, $J_{6,6'}$ 13.2 Hz), 1.45, 1.43, 1.40, 1.39 (12H, 4×s, 2×C(CH_3)$_2$), 1.28, 1.27 (6H, 2×d, CH(CH_3)$_2$, *J* 6.3 Hz); δ_C (100.6 MHz, $CDCl_3$) 170.2 (s, *C*=O), 112.2, 110.5 (2×s, 2×*C*(CH_3)$_2$), 79.9, 78.9, 77.9, 77.8 (4×d, C-2, C-3, C-4, C-5), 69.2 (d, *C*H(CH_3)$_2$), 51.9 (t, C-6), 27.2, 26.9, 26.8, 26.0 (4×q, 2×C(*C*H_3)$_2$), 21.6 (q, CH(*C*H_3)$_2$); *m*/*z* (APCI+) 316.1 (M−N_2+H^+; 100%); HRMS *m*/*z* (CI+) found 344.1826 (M+H^+), $C_{15}H_{26}N_3O_6$ requires 344.1822.

4.5. Isopropyl 6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-galactonate (dimer) 5

A solution of isopropyl azide **13** (666 mg, 1.94 mmol) in isopropanol (34 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (26 mg). After 4.5 h TLC (1:2 ethyl acetate–hexane) indicated complete conversion of the starting material (R_f 0.6) to baseline material. The reaction mixture was filtered through Celite® (eluted with isopropanol) and the solvent removed in vacuo to give the amine **15**.

Aqueous sodium hydroxide (1.94 mL, 1 M) was added to a stirred solution of the methyl ester **4** (611 mg, 1.94 mmol) in dioxane (13 mL). The reaction mixture was stirred at room temperature for 2 h after which TLC (1:2 ethylacetate–hexane) indicated complete conversion of the starting material (R_f 0.5) to a baseline material. The solvent was removed in vacuo (co-evaporation with toluene) after which the residue was dissolved in water (15 mL) and stirred with an Amberlite® IR-120 (H^+) resin for 1 min. The resin was removed by filtration and the filtrate concentrated in vacuo to give crude 6-azido acid **14**.

1-(3-Dimethyl-aminopropyl)-3-ethylcarbodiimide (558 mg, 2.91 mmol) was added to a stirred solution of the crude 6-azido acid **14**, 1-hydroxybenzotriazole (393 mg, 2.91 mmol) and diisopropylethylamine (0.51 mL, 2.91 mmol) in dichloromethane (6 mL) at 0 °C. The mixture was stirred for 30 min under an atmosphere of nitrogen and a solution of the crude isopropyl amine **15** in dichloromethane (2×2 mL) added. The reaction mixture was allowed to warm to room temperature and stirred for 20 h, after which TLC (1:1 ethyl acetate–hexane) indicated the formation of a major product (R_f 0.5). The reaction mixture was diluted with dichloromethane (220 mL) and washed with 1 M hydrochloric acid (110 mL). The aqueous layer was extracted with

dichloromethane (55 mL) and the combined organic layers washed with pH 7 buffer (110 mL) and brine (110 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography (1:3 ethyl acetate–hexane increasing polarity to 1:2 ethyl acetate–hexane) yielded the dimer **5** (864 mg, 74%) as a colourless oil: $[\alpha]_D^{23} = +10.0$ (*c* 1.59, $CHCl_3$); ν_{max} (thin film): 3429, 3371 (NH), 2104 (N_3), 1748 (C=O, ester), 1682 and 1526 (C=O, amide) cm^{-1}; δ_H (400 MHz, benzene-d_6) 6.84 (1H, dd, N*H*, $J_{NH,6B}$ 5.1 Hz, $J_{NH,6'B}$ 6.7 Hz), 4.98 (1H, sept, C*H*(CH_3)$_2$, *J* 6.3 Hz), 4.66 (1H, d, H-2B, $J_{2B,3B}$ 5.6 Hz), 4.60 (1H, d, H-2A, $J_{2A,3A}$ 6.0 Hz), 4.52 (1H, dd, H-3B, $J_{3B,2B}$ 5.6 Hz, $J_{3B,4B}$ 7.3 Hz), 4.42 (1H, dd, H-3A, $J_{3A,2A}$ 6.0 Hz, $J_{3A,4A}$ 4.3 Hz), 4.40 (1H, ddd, H-5A, $J_{5A,4A}$ 8.2 Hz, $J_{5A,6A}$ 4.5 Hz, $J_{5A,6'A}$ 3.5 Hz), 4.23 (1H, dd, H-4A, $J_{4A,3A}$ 4.3 Hz, $J_{4A,5A}$ 8.2 Hz), 4.05 (1H, ddd, H-5B, $J_{5B,4B}$ 7.5 Hz, $J_{5B,6B}$ 4.5 Hz, $J_{5B,6'B}$ 5.5 Hz), 3.74 (1H, a-t, H-4B, *J* 7.4 Hz), 3.66 (1H, ddd, H-6′B, $J_{6'B,5B}$ 5.5 Hz, $J_{6'B,6B}$ 14.0 Hz, $J_{6'B,NH}$ 6.7 Hz), 3.45 (1H, a-dt, H-6B), 3.18 (1H, dd, H-6′A, $J_{6'A,5A}$ 3.5 Hz, $J_{6'A,6A}$ 13.3 Hz), 2.93 (1H, dd, H6A, $J_{6A,5A}$ 4.5 Hz, $J_{6A,6'A}$ 13.3 Hz), 1.45, 1.41, 1.37, 1.34, 1.29, 1.26, 1.24 (24H, 7×s, 4×C(C*H*$_3$)$_2$), 0.99, 0.99 (6H, 2×d, 2×CH(C*H*$_3$)$_2$, *J* 6.3 Hz); δ_C (100.6 MHz, benzene-d_6) 171.0, 170.6 (2×s, 2×*C*=O), 112.8, 111.5, 110.4, 110.1 (4×s, 4×*C*(CH_3)$_2$), 80.6, 79.8, 79.7, 79.0, 78.7, 78.2, 77.7, 77.0 (8×d, C-2A, C-3A, C-4A, C-5A, C-2B, C-3B, C-4B, C-5B), 69.2 (d, *C*H(CH_3)$_2$), 51.8 (t, C-6A), 41.1 (t, C-6B), 27.6, 27.6, 27.4, 27.3, 27.1, 26.6, 26.5 (7×q, 4×C(*C*H$_3$)$_2$) 21.8 (q, CH(*C*H$_3$)$_2$); *m/z* (APCI+) 601.8 (M+H$^+$; 100%), 623.7 (M+Na$^+$; 53%), 573.4 (M−N_2+H$^+$; 38%). Found: C, 54.01; H, 7.43; N, 9.24. $C_{27}H_{44}N_4O_{11}$ requires C, 53.99; H, 7.38; N, 9.33.

4.6. Isopropyl 6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonate (linear tetramer) 6

A solution of dimer **5** (420 mg, 0.7 mmol) in isopropanol (20 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (10 mg). After 18 h TLC (1:1 ethyl acetate–hexane) indicated conversion of starting material (R_f 0.7) to baseline material. The reaction mixture was filtered through Celite® (eluted with isopropanol) and the solvent removed to give the crude dimer amine **16**.

Aqueous sodium hydroxide (0.70 mL, 1 M) was added to a stirred solution of dimer **5** (432 mg, 0.70 mmol) in dioxane (20 mL) and the reaction mixture stirred at room temperature. After 18 h aqueous sodium hydroxide (0.29 mL, 1 M) and water (8 mL) were added and the reaction mixture stirred at room temperature for a further 18 h. TLC (1:1 ethyl acetate–hexane) indicated conversion of the starting material (R_f 0.7) to a baseline material. The solvent was removed in vacuo (co-evaporation in toluene) and the residue dissolved in water (15 mL) and stirred with Amberlite® IR-120 (H$^+$) resin for 1 min. The resin was removed by filtration and the filtrate concentrated in vacuo to give the crude dimer acid **17**.

1-(3-Dimethyl-aminopropyl)-3-ethylcarbodiimide (208 mg, 1.10 mmol) was added to a stirred solution of crude dimer acid **17**, 1-hydroxybenzotriazole (147 mg, 1.10 mmol) and diisopropylethylamine (0.19 mL, 1.10 mmol) in dichloromethane (3 mL) at 0 °C. The mixture was stirred for 30 min under an atmosphere of nitrogen and a solution of crude dimer amine **16** in dichloromethane (3×1 mL) added. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. TLC (1:1 ethyl acetate–hexane) indicated formation of a major product (R_f 0.2). The reaction mixture was diluted with dichloromethane (120 mL) and washed with 1 M hydrochloric acid (60 mL), pH 7 buffer (60 mL) and brine (60 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography (2:3 ethyl acetate–hexane increasing polarity to 1:1 ethyl acetate–hexane) yielded tetramer **6** (568 mg, 73%) as an amorphous solid: $[\alpha]_D^{23} = +1.5$ (*c* 1.05, $CHCl_3$); ν_{max} (thin film): 3430, 3372 (NH), 2102 (N_3), 1746 (C=O, ester), 1678 and 1530 (C=O, amide) cm^{-1}; δ_H (400 MHz, benzene-d_6)[†] 6.95 (2H, a-dd, N*H*-B, N*H*-C, *J* 4.9 Hz, *J*′ 7.0 Hz), 6.93 (1H, dd, N*H*-D, $J_{NH,6D}$ 5.1 Hz, $J_{NH,6'D}$ 6.5 Hz) 4.98 (1H, sept, C*H*(CH_3)$_2$, *J* 6.3 Hz), 4.69 (1H, d, H-2B/C′, $J_{2,3}$ 4.7 Hz), 4.67 (1H, d, H-2B/C, $J_{2,3}$ 5.0 Hz), 4.66 (1H, d, H-2D, $J_{2D,3D}$ 5.6 Hz), 4.59 (1H, m, H-3B/C′), 4.58 (1H, d, H-2A, $J_{2A,3A}$ 6.5 Hz), 4.56 (1H, m, H-3B/C), 4.54 (1H, m, H-5B/C), 4.51 (1H, m, H-3D), 4.46 (2H, m, H-5A, H-5B/C′), 4.41 (1H, m, H-3A), 4.24 (1H, dd, H-4A, $J_{4A,3A}$ 4.0 Hz, $J_{4A,5A}$ 8.3 Hz), 4.14 (1H, dd, H-4B/C, $J_{4,3}$ 3.4 Hz, $J_{4,5}$ 8.4 Hz), 4.11 (1H, dd, H-4B/C′, $J_{4,3}$ 3.8 Hz, $J_{4,5}$ 8.3 Hz), 4.05 (1H, ddd, H-5D, $J_{5D,4D}$ 7.4 Hz, $J_{5D,6D}$ 4.7 Hz, $J_{5D,6'D}$ 5.6 Hz), 3.76 (1H, m, H-6′B/C), 3.75 (1H, a-t, H-4D, *J* 7.4 Hz), 3.73 (1H, m, H-6′B/C′), 3.65 (1H, ddd, H-6′D, $J_{6'D,5D}$ 5.6 Hz, $J_{6'D,6D}$ 13.9 Hz, $J_{6'D,NH}$ 6.5 Hz), 3.50 (1H, a-dt, H-6D, $J_{6D,5D}$ 4.7 Hz,$J_{6D,6'D}$ 13.9 Hz), 3.44 (1H, m, H-6B/C), 3.42 (1H, m, H-6B/C′), 3.25 (1H, dd, H-6′A, $J_{6'A,5A}$ 3.3 Hz, $J_{6'A,6A}$ 13.4 Hz), 2.97 (1H, dd, H-6A, $J_{6A,5A}$ 4.6 Hz, $J_{6A,6'A}$ 13.4 Hz), 1.46, 1.43, 1.41, 1.39, 1.38, 1.37, 1.36, 1.35, 1.34, 1.34, 1.30, 1.27, 1.24 (48H, 13×s, 8×C(C*H*$_3$)$_2$), 0.99, 0.99 (6H, 2×d, 2×CH(C*H*$_3$)$_2$, *J* 6.3 Hz); δ_C (100.6 MHz, benzene-d_6) 171.3, 171.1, 170.6 (3×s, 4×*C*=O), 112.8, 111.5, 111.4, 111.3, 110.4, 110.1, 109.6, 109.6 (8×s, 8×*C*(CH_3)$_2$), 80.6, 80.0, 79.7, 79.6, 79.5, 79.1, 78.7, 78.6, 78.1, 77.6, 76.9, 76.8, 76.6, 76.5 (14×d, C-2A, C-3A, C-4A, C-5A, C-2B, C-3B, C-4B, C-5B, C-2C, C-3C, C-4C, C-5C, C-2D, C-3D, C-4D, C-5D), 69.2 (d, *C*H(CH_3)$_2$), 51.7 (t, C-6A), 41.3 (t, C-6D), 40.4 (t, C-6B, C-6C), 27.7, 27.7, 27.6, 27.4, 27.3, 27.3, 27.1, 27.1, 26.7, 26.6, 26.4, 26.4 (12×q, 8×C(*C*H$_3$)$_2$), 21.8 (q, CH(*C*H$_3$)$_2$); *m/z* (APCI+) 1115.9 (M+H$^+$; 100%), 1137.9 (M+Na$^+$; 50%); *m/z* (ES+) Found 1115.58 (M+H$^+$; 100%), 1116.55 (M+H$^+$; 60%), 1117.53 (M+H$^+$; 20%), 1118.56 (M+H$^+$; 5%) $C_{51}H_{83}N_6O_{21}$

[†] Note that although the proton spin systems within each residue of **6** were identified via TOCSY, it was not possible to distinguish between the residues B and C and so they are labelled B/C and B/C′.

[M+H$^+$] calculated isotopic distribution: 1115.56 (M+H$^+$; 100%), 1116.56 (M+H$^+$; 56%), 1117.57 (M+H$^+$; 20%), 1118.57 (M+H$^+$; 5%); *m/z* (ES+) Found 1132.63 (M+NH_4^+; 100%), 1133.59 (M+NH_4^+; 56%), 1134.58 (M+NH_4^+; 20%) $C_{51}H_{86}N_7O_{21}$[M+NH_4^+] calculated isotopic distribution: 1132.59 (M+NH_4^+; 100%), 1133.59 (M+ NH_4^+; 56%), 1134.59 (M+NH_4^+; 20%).

4.7. Isopropyl 6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonate (linear hexamer) 7

A solution of dimer **5** (40 mg, 67 μmol) in isopropanol (1 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (6 mg). After 16 h TLC (1:1 ethyl acetate–hexane) indicated conversion of the starting material (R_f 0.7) to baseline material. The reaction mixture was filtered through Celite® (eluted with isopropanol) and the solvent removed in vacuo to give the crude dimer amine **16**.

Aqueous sodium hydroxide (75 μL, 1 M) was added to a stirred solution of tetramer **6** (76 mg, 68 μmol) in dioxane (0.4 mL) and water (0.15 mL). The reaction mixture was stirred for 16 h at room temperature then aqueous sodium hydroxide (7 μL) and water (70 μL) added. After 4 h TLC (2:1 ethyl acetate–hexane) indicated conversion of the starting material (R_f 0.6) to a baseline material. The solvent was removed in vacuo (co-evaporation with toluene) and the residue dissolved in dioxane (2 mL) and water (2 mL) and stirred with Amberlite® IR-120 (H$^+$) resin for 1 min. The resin was removed by filtration and the filtrate concentrated in vacuo to give the crude tetramer acid **18** (65 mg, 61 μmol).

1-(3-Dimethyl-aminopropyl)-3-ethylcarbodiimide (18 mg, 92 μmol) was added to a stirred solution of the crude tetramer acid **18**, 1-hydroxybenzotriazole (12.4 mg, 92 μmol) and diisopropylethylamine (16 μL, 92 μmol) in dichloromethane (0.2 mL) at 0 °C. The mixture was stirred for 30 min under an atmosphere of nitrogen and a solution of crude dimer amine **16** in dichloromethane (3×0.2 mL) added. The reaction mixture was allowed to warm to room temperature and stirred for 48 h after which TLC (4:1 ethyl acetate–hexane) indicated the formation of a major product (R_f 0.5). The reaction mixture was diluted with dichloromethane (20 mL) and washed with 1 M hydrochloric acid (10 mL), pH 7 buffer (10 mL) and brine (10 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography (4:3 ethyl acetate–hexane increasing polarity to 3:2 ethyl acetate–hexane then to 2:1 ethyl acetate–hexane) yielded hexamer **7** (62 mg, 62%) as an amorphous solid: $[\alpha]_D^{23} = -3.5$ (*c* 0.84, $CHCl_3$); ν_{max} (thin film): 3428, 3358 (NH), 2104 (N_3), 1742 (C=O, ester), 1683 and 1526 (C=O, amide) cm^{-1}; δ_H (400 MHz, benzene-d_6) 7.05 (1H, dd, N*H*, *J* 4.9 Hz, *J′* 7.0 Hz), 7.04 (1H, dd, N*H*, *J* 4.9 Hz, *J′* 7.0 Hz), 6.99 (1H, dd, N*H*, *J* 4.9 Hz, *J′* 7.1 Hz), 6.98 (1H, dd, N*H*, *J* 4.8 Hz, *J′* 7.0 Hz), 6.95 (1H, dd, N*H*-F, $J_{NH,6F}$ 5.0 Hz, $J_{NH,6'F}$ 6.5 Hz), 4.99 (1H, sept, C*H*(CH_3)$_2$, *J* 6.3 Hz), 4.71–4.66 (5H, m, H-2B, H-2C, H-2D, H-2E, H-2F), 4.64–4.42 (12H, m, H-2A, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-5A, H-5B, H-5C, H-5D, H-5E), 4.26 (1H, dd, H-4A, $J_{4A,3A}$ 4.0 Hz, $J_{4A,5A}$ 8.3 Hz), 4.17–4.12 (4H, m, H-4B, H-4C, H-4D, H-4E), 4.06 (1H, ddd, H-5F, $J_{5F,4F}$ 7.4 Hz, $J_{5F,6F}$ 4.7 Hz, $J_{5F,6'F}$ 5.6 Hz), 3.81–3.72 (4H, m, H-6′B, H-6′C, H-6′D, H-6′E), 3.76 (1H, a-t, H-4F, *J* 7.4 Hz), 3.66 (1H, ddd, H-6′F, $J_{6'F,5F}$ 5.6 Hz, $J_{6'F,6F}$ 13.9 Hz, $J_{6'F,NH}$ 6.5 Hz), 3.54–3.43 (5H, m, H-6B, H-6C, H-6D, H-6E, H-6F), 3.27 (1H, dd, H-6′A, $J_{6'A,5A}$ 3.3 Hz, $J_{6'A,6A}$ 13.4 Hz), 2.99 (1H, dd, H-6A, $J_{6A,5A}$ 4.6 Hz, $J_{6A,6'A}$ 13.4 Hz), 1.47, 1.45, 1.42, 1.41, 1.39, 1.38, 1.37, 1.37, 1.36, 1.35, 1.32, 1.31, 1.29 1.25 (72H, 14×s, 12×C(CH_3)$_2$), 1.00, 1.00 (6H, 2×d, CH(C*H*$_3$)$_2$, *J* 6.3 Hz); δ_C (100.6 MHz, benzene-d_6) 171.3, 171.1, 171.0, 170.6 (4×s, 6×*C*=O), 112.8, 111.5, 111.4, 111.4, 111.4, 111.3, 110.4, 110.1, 109.7, 109.6, 109.6 (11×s, 12×*C*(CH_3)$_2$), 80.6, 80.0, 79.7, 79.6, 79.1, 78.8, 78.7, 78.7, 78.0, 78.0, 77.6, 77.2, 76.9, 76.8, 76.7, 76.6 (16×d, C-2A, C-3A, C-4A, C-5A, C-2B, C-3B, C-4B, C-5B, C-2C, C-3C, C-4C, C-5C, C-2D, C-3D, C-4D, C-5D, C-2E, C-3E, C-4E, C-5E, C-2F, C-3F, C-4F, C-5F), 69.2 (d, *C*H(CH_3)$_2$), 51.8 (t, C-6A), 41.3 (t, C-6F), 40.6, 40.6, 40.5, 40.4 (4×t, C-6B, C-6C, C-6D, C-6E), 28.0, 27.9, 27.7, 27.7, 27.6, 27.5, 27.3, 27.2, 27.1, 26.7, 26.6, 26.5, 26.5, 26.4 (14×q, 12×C(*C*H$_3$)$_2$), 21.8, 21.8 (2×q, CH(*C*H$_3$)$_2$); *m/z* (ES+) 815.52 ([M+2H]$^{2+}$, 100%), 816.03 ([M+2H]$^{2+}$, 90%), 816.47 ([M+2H]$^{2+}$, 55%). *m/z* (ES+) Found 1651.85 (M+Na$^+$; 100%), 1652.81 (M+Na$^+$; 80%), 1653.75 (M+Na$^+$; 40%), 1654.76 (M+Na$^+$; 15%) $C_{75}H_{120}N_8O_{31}Na$ [M+Na$^+$] calculated isotopic distribution: 1651.80 (M+Na$^+$; 100%), 1652.80 (M+Na$^+$; 80%), 1653.80 (M+Na$^+$; 40%), 1654.80 (M+Na$^+$; 15%).

4.8. Isopropyl 6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonate (linear octamer) 8

A solution of dimer **5** (25 mg, 42 μmol) in isopropanol (1 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (3 mg). After 16 h TLC (1:1 ethyl acetate–hexane) indicated conversion of starting material (R_f 0.7) to baseline material. The reaction mixture was filtered through Celite® (eluted with isopropanol) and the solvent was removed in vacuo to give the crude dimer amine **16**.

Aqueous sodium hydroxide (70 μL, 1 M) was added to a stirred solution of hexamer **7** (57 mg, 35 μmol) in dioxane (0.5 mL) and water (0.1 mL). The reaction mixture

was stirred at room temperature for 4.5 h after which TLC (4:1 ethyl acetate–hexane) indicated conversion of the starting material (R_f 0.5) to a baseline material. The solvent was removed in vacuo (co-evaporation with toluene) and the residue dissolved in dioxane (2 mL) and water (2 mL) and stirred with Amberlite® IR-120 (H^+) resin for 1 min. The resin was removed by filtration and the filtrate concentrated in vacuo to give the crude hexamer acid.

1-(3-Dimethyl-aminopropyl)-3-ethylcarbodiimide (10 mg, 53 μmol) was added to a stirred solution of hexamer acid, 1-hydroxybenzotriazole (7 mg, 53 μmol) and diisopropylethylamine (9 μL, 53 μmol) in dichloromethane (0.3 mL) at 0 °C. The mixture was stirred for 30 min under an atmosphere of nitrogen and a solution of crude dimer amine **16** in dichloromethane (3 × 0.25 mL) added. The reaction mixture was allowed to warm to room temperature and stirred for 24 h after which TLC (4:1 ethyl acetate–hexane) indicated the formation of a major product (R_f 0.3). The reaction mixture was diluted with dichloromethane (20 mL) and washed with 1 M hydrochloric acid (5 mL), pH 7 buffer (5 mL) and brine (5 mL). The organic phase was dried (magnesium sulfate), filtered and concentrated in vacuo. Purification by flash column chromatography (2:1 ethyl acetate–hexane) yielded octamer **8** (47 mg, 63%) as an amorphous solid: $[\alpha]_D^{23} = -5.3$ (*c* 0.88, $CHCl_3$); ν_{max} (thin film): 3429, 3368 (NH), 2104 (N_3), 1745 (C=O, ester), 1680 and 1527 (C=O, amide) cm^{-1}; δ_H (400 MHz, benzene-d_6) 7.08–7.04 (4H, m, 4 × N*H*), 7.00 (1H, dd, N*H*, *J* 4.7 Hz, *J′* 6.9 Hz), 6.99 (1H, dd, N*H*, *J* 4.7 Hz, *J′* 7.0 Hz), 6.96 (1H, dd, N*H*-H, $J_{NH,6H}$ 5.0 Hz, $J_{NH,6'H}$ 6.5 Hz), 4.99 (1H, sept, C*H*$(CH_3)_2$, *J* 6.3 Hz), 4.73–4.68 (7H, m, H-2B, H-2C, H-2D, H-2E, H-2F, H-2G, H-2H), 4.64–4.44 (16H, m, H-2A, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-3H, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-5G), 4.28 (1H, dd, H-4A, $J_{4A,3A}$ 4.0 Hz, $J_{4A,5A}$ 8.3 Hz), 4.19–4.14 (6H, m, H-4B, H-4C, H-4D, H-4E, H-4F, H-4G), 4.07 (1H, ddd, H-5H, $J_{5H,4H}$ 7.5 Hz, $J_{5H,6H}$ 4.7 Hz, $J_{5H,6'H}$ 5.6 Hz), 3.83–3.73 (6H, m, H-6′B, H-6′C, H-6′D, H-6′E, H-6′F, H-6′G), 3.78 (1H, a-t, H-4H, *J* 7.4 Hz), 3.67 (1H, ddd, H-6′H, $J_{6'H,5H}$ 5.6 Hz, $J_{6'H,6H}$ 13.9 Hz, $J_{6'H,NH}$ 6.5 Hz), 3.55–3.44 (7H, m, H-6B, H-6C, H-6D, H-6E, H-6F, H-6G, H-6H), 3.27 (1H, dd, H-6′A, $J_{6'A,5A}$ 3.3 Hz, $J_{6'A,6A}$ 13.4 Hz), 2.99 (1H, dd, H-6A, $J_{6A,5A}$ 4.6 Hz, $J_{6A,6'A}$ 13.4 Hz), 1.49, 1.46, 1.44, 1.44, 1.44, 1.42, 1.40, 1.40, 1.39, 1.38, 1.38, 1.37, 1.34, 1.34, 1.32, 1.32, 1.32, 1.30 1.26 (96H, 19 × s, 16 × C(CH_3)$_2$), 1.01, 1.01 (6H, 2 × d, CH(CH_3)$_2$, *J* 6.3 Hz); δ_C (100.6 MHz, benzene-d_6) 171.3, 171.1, 170.6 (3 × s, 8 × *C*=O), 112.9, 111.5, 111.5, 111.4, 111.4, 110.4, 110.2, 109.7, 109.7, 109.6 (10 × s, 16 × *C*$(CH_3)_2$), 80.6, 80.0, 79.7, 79.1, 78.9, 78.8, 78.7, 78.7, 78.1, 77.6, 76.9, 76.8, 76.7, 76.6 (14 × d, C-2A, C-3A, C-4A, C-5A, C-2B, C-3B, C-4B, C-5B, C-2C, C-3C, C-4C, C-5C, C-2D, C-3D, C-4D, C-5D, C-2E, C-3E, C-4E, C-5E, C-2F, C-3F, C-4F, C-5F, C-2G, C-3G, C-4G, C-5G, C-2H, C-3H, C-4H, C-5H), 69.2 (d, *C*H$(CH_3)_2$), 51.8 (t, C-6A), 41.3 (t, C-6H), 40.6, 40.6, 40.5, 40.4 (4 × t, C-6B, C-6C, C-6D, C-6E, C-6F, C-6G), 28.2, 27.8, 27.7, 27.6, 27.5, 27.4, 27.2, 27.1, 26.7, 26.6, 26.5, 26.4 (12 × q, 16 × C(CH_3)$_2$), 21.8 (q, CH(CH_3)$_2$); *m*/*z* (ES+) Found 2166.17 ($M+Na^+$, 90%), 2167.15 ($M+Na^+$, 100%), 2168.15 ($M+Na^+$, 65%), 2169.14 ($M+Na^+$, 30%), 2170.16 ($M+Na^+$, 12%), 2171.18 ($M+Na^+$, 4%) $C_{99}H_{158}N_{10}O_{41}Na$ [$M+Na^+$] calculated isotopic distribution 2166.05 ($M+Na^+$, 90%), 2167.05 ($M+Na^+$, 100%), 2168.05 ($M+Na^+$, 65%), 2169.06 ($M+Na^+$, 30%), 2170.06 ($M+Na^+$, 12%).

4.9. Cyclo 6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonyl)-D-galactonyl)-D-galactonyl)-D-galactonic acid (cyclic tetramer) 22

Aqueous sodium hydroxide (38 μL, 1.2 equiv, 1 M) was added to a stirred solution of tetramer **6** (37 mg, 33 μmol) in dioxane (0.5 mL) and water (73 μL). After 18 h aqueous sodium hydroxide (6 μL, 0.2 equiv, 1 M) and water (73 μL) were added and the reaction mixture stirred at room temperature for a further 5 h after which TLC (2:1 ethyl acetate–hexane) indicated conversion of the starting material (R_f 0.6) to baseline material. The solvent was removed in vacuo (co-evaporation with toluene) and the residue dissolved in dioxane (2 mL) and water (2 mL) and stirred with Amberlite® IR-120 (H^+) resin for 1 min. The resin was removed by filtration and the filtrate concentrated in vacuo to give the crude tetramer azidoacid **18**.

A solution of **18** (34 mg) in dioxane (1 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (5 mg). After 18 h, mass spectrometry showed complete conversion of starting material [*m*/*z* (APCI+) 1095.8 ($M+Na^+$; 89%), 1073.9 ($M+H^+$; 45%)] to product [(*m*/*z* (APCI+) 1069.9 ($M+Na^+$; 89%), 1047.6 ($M+H^+$; 90%)]. The reaction mixture was filtered through Celite® (eluted with dioxane) and the solvent removed to give the crude tetramer amino acid **21**.

Diisopropylethylamine (18 μL, 99 μmol) and pentafluorophenyl diphenylphosphinate (FDPP) (19 mg, 50 μmol) were added to a suspension of the crude tetramer amino carboxylic acid **21** in anhydrous acetonitrile (1.6 mL) and the solution stirred at room temperature for 72 h. TLC (3:1 ethyl acetate–hexane) indicated conversion of baseline material to a major product (R_f 0.6). The solvent was removed in vacuo (co-evaporation with toluene) and the residue dissolved in ethyl acetate (10 mL) and washed with 2 M hydrochloric acid (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL) and the combined organic extracts washed with 0.5 M NaOH (10 mL), pH 7 buffer (10 mL) and brine (10 mL). The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash column chromatography (1:1 ethyl acetate–hexane increasing polarity to 2:1 ethyl acetate–hexane) yielded the fully protected cyclic tetramer **22** (10 mg, 30%) as an amorphous solid: $[\alpha]_D^{22} = -27.9$ (*c* 0.14, $CHCl_3$); ν_{max} (thin film): 3405, 3357 (NH), 1686 and 1535 (C=O, amide) cm^{-1}; δ_H (500 MHz, benzene-d_6) 7.09 (4H, m, 4 × N*H*), 4.93 (4H, br d, 4 × H-

5, J 8.7 Hz), 4.88 (4H, d, 4×H-3, J 8.2 Hz), 4.80 (4H, d, 4×H-2, J 8.4 Hz), 4.56 (4H, a-d, 4×H-4, J 9.1 Hz), 4.50 (4H, br dd, 4×H-6′, J 10.7 Hz, J' 13.5 Hz), 3.16 (4H, br d, 4×H-6′, J 14.8 Hz), 1.57, 1.48, 1.46, 1.28 (48H, 4×s, 8×C(CH_3)$_2$); δ_C (125.7 MHz, benzene-d_6) 170.7 (s, 4×C=O), 110.5, 108.5 (2×s, 8×C(CH_3)$_2$), 78.8, 76.5, 75.4, 74.4 (4×d, 4×C-2, 4×C-3, 4×C-4, 4×C-5), 38.0 (t, 4×C-6), 27.7, 27.1, 27.0, 26.3 (4×q, 8×C(CH_3)$_2$); m/z (MALDI TOF LD+) Found 1067.7 ($M+K^+$, 100%), 1068.6 ($M+K^+$, 52%), 1069.6 ($M+K^+$, 32%), 1070.6 ($M+K^+$, 10%) C_{48} $H_{76}N_4O_{20}K^+$ [$M+K^+$] calculated isotopic distribution: 1067.5 ($M+K^+$, 100%), 1068.5 ($M+K^+$, 52%), 1069.5 ($M+K^+$, 32%), 1070.5 ($M+K^+$, 10%).

4.10. Cyclo[–(6-amino-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonic acid)$_4$–] 3

The protected cyclic tetramer **22** (19 mg, 0.018 mmol) was dissolved in trifluoroacetic acid (TFA)–water, 3:1 (1 mL) and stirred for 0.5 h. The solvent was removed in vacuo to give a white solid (20 mg), which was re-dissolved in TFA–H_2O 3:1 (1 mL); the solution was stirred for a further 0.5 h. The solvent was removed in vacuo to give a colourless glass. Acetonide hydrolysis was confirmed by the lack of methyl protons in the ^{1}H NMR spectrum. The residue was dissolved in water (2 mL) and acetonitrile (50 mL) added. The reaction mixture was left to stand for 15 h, allowing a precipitate to form, which was then separated from the solution by centrifugation to give the deprotected cyclic tetramer **3** (13 mg, quantitative) as a white solid: mp >220 °C darkened on heating above 160 °C; $[\alpha]_D^{25} = +3.0$ (c 0.2, D_2O); ν_{max} (KBr disc): 3402 (br, O–H), 2522, 2462 (w, N–H), 1647 (C=O, amides I), 1542 (C=O, amides II) cm^{-1}; δ_H (500 MHz, D_2O) 4.41 (4H, d, 4×H-2, $J_{2,3}$ 1.8), 3.94 (4H, m, 4×H-5), 3.93 (4H, dd, 4×H-3, $J_{3,4}$ 9.5, $J_{3,2}$ 1.8), 3.63 (4H, dd, 4×H-4, $J_{4,3}$ 9.5, $J_{4,5}$ 1.9), 3.56 (4H, dd, 4×H-6′, $J_{6',6}$ 13.6, J 5.8), 3.32 (4H, dd, 4×H-6, $J_{6,6'}$ 13.6, J 7.5); δ_C (125.7 MHz, D_2O) 176.21 (s, 4×C=O), 71.77 (d, 4×C-2), 71.47 (d, 4×C-3), 69.87 (d, 4×C-4), 68.86 (d, 4×C-5), 41.83 (t, 4×C-6); m/z (ES-) 707.25 ([M−H]$^-$, 19%), 708.25 ([M−H]$^-$, 58%), 709.26 ([M−H]$^-$, 100%); HRMS m/z: Found 707.2492 $C_{24}H_{43}N_4O_{20}$ ([M−H]$^-$) requires 707.2471.

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