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Cyclo[(6-amino-6-deoxy-D-galactonic acid)$_4$]: a new class of carbopeptoid-cyclodextrin

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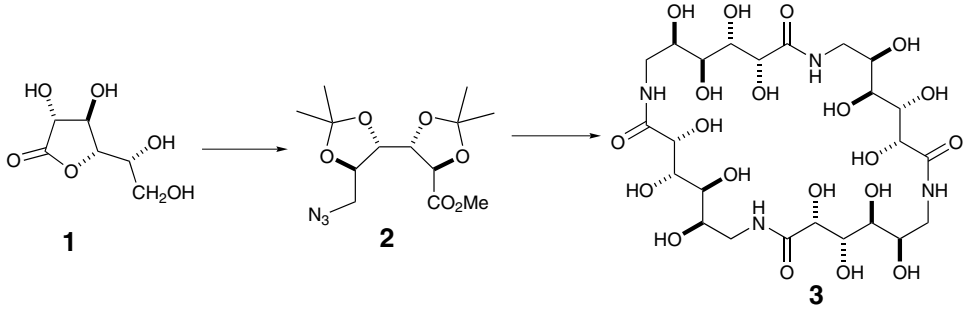
Abstract—The formation of the 28-membered ring cyclo[(6-amino-6-deoxy-D-galactonic acid)$_4$] by cyclisation of a protected open chain fully hydroxylated nylon 6 linear tetramer in modest yield provides the first example of a new class of carbopeptoid-cyclodextrin.

Peptides and oligosaccharides are attractive targets for mimicry due to their involvement in many complex biological processes.[1] The importance of sugar amino acids (SAAs) as components for peptidomimetics was recognised by Paulsen[2] in 1955 but it is only in recent years that their potential has been developed.[3,4] Linear oligomers of conformationally locked[5,6] SAAs provide many examples for predisposition towards secondary structures in relatively small molecules.[7–10] Substitution of tetrahydropyran-[11] and tetrahydrofuran-[12,13] dipeptide isosteres in natural peptides have led to biologically active analogues[14] with greater stability to peptide cleavage. Cyclic peptides containing SAAs have provided a set of novel integrin inhibitors.[15] Cyclic SAAs[16,17] may also provide an array of desired ring size and defined secondary structure; such a carbopeptoid equivalent of cyclodextrins (CPCD) may lead to exquisite specificity of recognition and catalysis. The control of formation of cyclodextrin (CD) inclusion complexes[18,19] provides the basis for CD's main industrial uses in drugs, foods and cosmetics.[20]

A further class of SAA—6-amino-6-deoxyaldonic acids—should provide fully hydroxylated analogues of nylon 6 as a family of new biomaterials. Although mimics of nylon 6,6—in which one of the components is a carbohydrate[21–23]—have been studied for some time,[24] the first example of a carbohydrate analogue of fully hydroxylated nylon 6 has only recently been reported.[25] This paper reports the synthesis from



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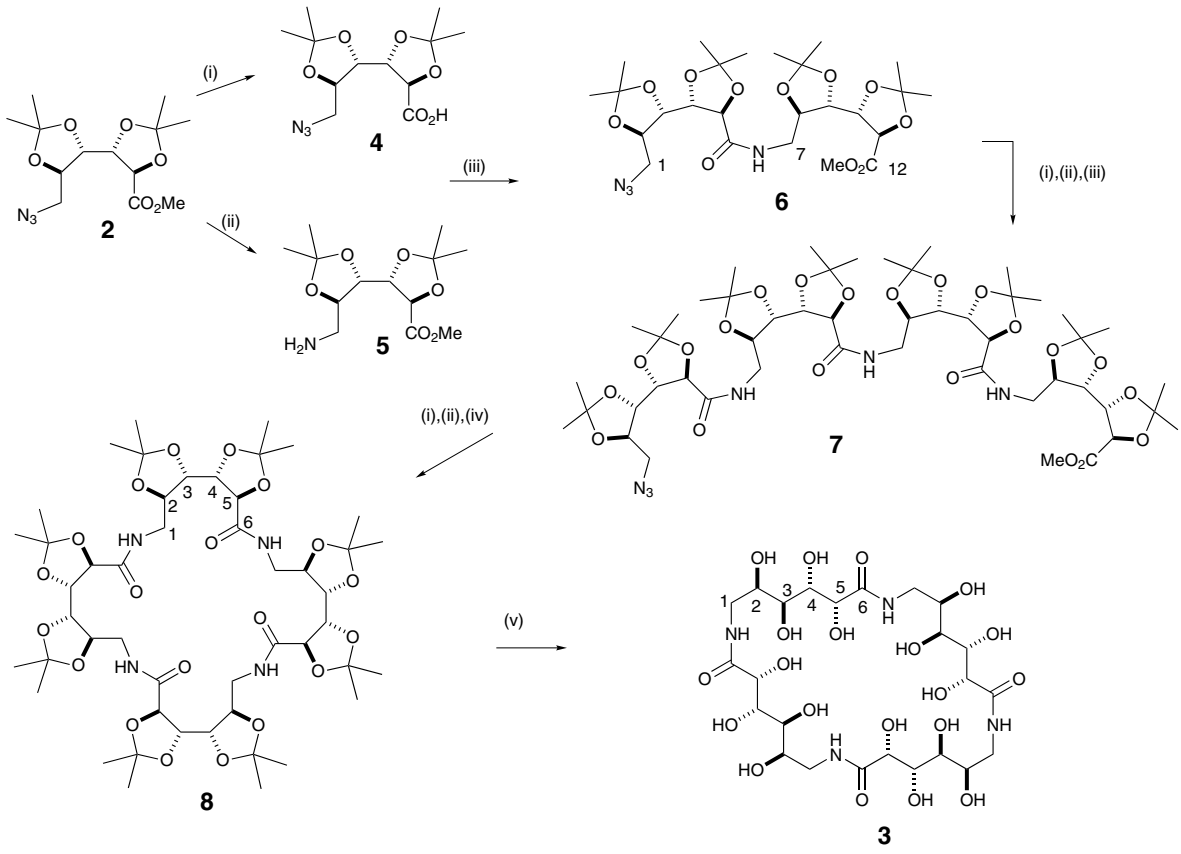

Scheme 1. Reagents and conditions: (i) NaOH, H_2O, dioxane; (ii) H_2, Pd black, dioxane; (iii) DIPEA, TBTU, DMF; (iv) DIPEA, FDPP, MeCN; (v) CF_3CO_2H–H_2O, 3:1.

D-galactonolactone **1** of a protected linear tetramer of a fully hydroxylated nylon 6 equivalent **7** and its subsequent cyclisation and deprotection to a 28-membered ring carbopeptide **3**; subsequent deprotection afforded the first example of a new class of carbopeptoid-cyclodextrins (CPCD).

D-Galactonolactone **1** was converted to the key intermediate azido galactonate **2** as previously described.[26] Treatment of **2** with sodium hydroxide in aqueous dioxane gave the acid **4**, whilst hydrogenation of **2** in the presence of palladium black formed the corresponding amine **5** (Scheme 1). The acid **4** was activated in the presence of the amine **5** by sequential treatment with diisopropylethylamine (DIPEA) and *O*-(1*H*-benzotriazol-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) to form the dimer **6** in an overall yield of 77%.[27] The dimeric azidoester **6** was subjected to the same iterative procedure of hydrolysis, reduction and peptide coupling to give the linear tetrameric ester **7** in an overall yield of 89%.[28]

Hydrolysis of the azidoester **7** by sodium hydroxide followed by hydrogenation in the presence of palladium black gave the corresponding tetrameric amino acid, which was treated with DIPEA and pentafluorophenyl diphenyl phosphinate (FDPP) in acetonitrile[29,30] to afford the protected cyclic tetramer **8** in 30% overall yield.[31] Successful removal of all the acetonides was achieved by the treatment of **8** with aqueous trifluoroacetic acid to give the 28-membered ring unprotected cyclic peptide **3** in quantitative yield.[32]

In summary, although the yield for the cyclisation step of the linear tetramer is modest, the sequence allowed the preparation of the first example of a CPCD based on a hydroxylated nylon 6 monomer. If a general high yield procedure were to be found for the cyclisation of the linear oligomers, an interesting new class of biodegradable macrocycles will be available for study; the following papers describe unexpectedly high yield cyclisations to large rings.[33–35]

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27. *Data for dimer* **6**: $[\alpha]_D^{25}$ +12.4 (*c* 0.95, $CHCl_3$); colourless oil; ν_{max} (thin film): 3427 cm^{-1} (N–H, br), 2104 cm^{-1} (N_3 stretch), 1755 cm^{-1} (C=O, CO_2Me), 1680 cm^{-1} (C=O, amide I), 1530 cm^{-1} (C=O, amide II); ^1H NMR δ_H (500 MHz, $CDCl_3$): 1.38, 1.41, 1.42, 1.45, 1.47, 1.48 (24H, 6×s, 4×C(CH_3)$_2$), 3.33 (1H, dd, $J_{1,1'}$ 13.2, $J_{1,2}$ 4.7, H-1), 3.53–3.62 (2H, m, H-7, H-7′), 3.66 (1H, dd, $J_{1',1}$ 13.2, $J_{1',2}$ 3.5, H-1′), 3.75 (1H, a-t, *J* 7.0, H-9), 3.80 (3H, s, CO_2CH_3), 4.10–4.14 (2H, m, H-3, H-8), 4.29 (1H, a-t, *J* 5.6, H-4), 4.33 (1H, m, H-2), 4.36 (1H, dd, $J_{10,9}$ 7.0, $J_{10,11}$ 5.6, H-10), 4.50 (1H, d, $J_{5,4}$ 6.0, H-5), 4.56 (1H, d, $J_{11,10}$ 5.6, H-11), 6.97 (1H, t, $J_{amide,7}$ 5.6, CONH); ^{13}C NMR δ_C (125 MHz, $CDCl_3$): 25.85, 25.95, 26.63, 26.78, 26.85, 27.05, 27.14 (4×C(C_3)$_2$), 40.64 (C-7), 51.56 (C-1), 52.44 (CO_2C_3), 76.70 (C-5), 77.10 (C-11), 77.24 (C-2), 77.48, 77.88 (C-3, C-8), 78.89 (C-9), 78.94 (C-4), 79.35 (C-10), 109.86, 110.17, 111.22, 112.26 (4×*C*(CH_3)$_2$), 170.66 (*C*ONH), 171.08 (C_2CH_3); MS *m*/*z* (APCI+): 572.51 ($M+H^+$, 70%), 594.56 ($M+Na^+$, 100%); HRMS: $C_{25}H_{41}N_4O_{11}$ ($M+H^+$) calcd 573.2772, found 573.2775; $C_{25}H_{40}N_4O_{11}$ requires: C, 52.49; H, 7.08; N, 9.74. Found: C, 52.44; H, 7.04; N, 9.78.
28. *Data for linear tetramer* **7**: $[\alpha]_D^{21}$ +1.1 (*c* 0.8, $CDCl_3$); mp 59 °C (sinters), 60–61 °C (melts); ν_{max} (thin film): 3428 cm^{-1} (N–H), 2104 cm^{-1} (N_3 stretch), 1754 cm^{-1} (C=O, CO_2Me), 1678 cm^{-1} (C=O, amides I), 1527 cm^{-1} (C=O, amides II); ^1H NMR δ_H (500 MHz, $CDCl_3$): 1.38, 1.42, 1.43, 1.45, 1.47, 1.48 (48H, 6×s, 8×C(CH_3)$_2$), 3.33 (1H, dd, $J_{1,1'}$ 13.4, $J_{1,2}$ 4.7, H-1), 3.51–3.63 (6H, m, H-7, H-7′, H-13, H-13′, H-19, H-19′), 3.65 (1H, dd, $J_{1',1}$ 13.4, $J_{1',2}$ 3.2, H-1′), 3.75 (1H, a-t, *J* 7.3, H-21), 3.80 (3H, s, CO_2CH_3), 3.89 (2H, m, H-9, H-15), 4.10–4.13 (2H, m, H-3, H-20), 4.26–4.35 (6H, m, H-2, H-8, H-14, H-4, H-10, H-16), 4.35 (1H, dd, $J_{22,21}$ 7.4, $J_{22,23}$ 5.5, H-22), 4.49, 4.50, 4.51 (3H, 3×d, *J* 5.2, *J* 5.4, *J* 5.9, H-5, H-11, H-17), 4.56 (1H, d, $J_{23,22}$ 5.5, H-23), 6.95–7.00 (3H, m, C(6)ON*H* C(12)ON*H*, C(18)ON*H*); ^{13}C NMR δ_C (125 MHz, $CDCl_3$): 25.89, 25.99, 26.02, 26.65, 26.79, 26.83, 26.87, 27.08, 27.15, 27.17 (8×C(C_3)$_2$), 40.12, 40.26, 40.77 (C-7, C-13, C-19), 51.56 (C-1), 52.39 (CO_2C_3), 76.46, 76.55, (C-8, C-14), 76.63, 76.70, 76.88 (C-5, C-11, C-17), 77.14 (C-2), 77.19 (C-23), 77.50, 77.97 (C-3, C-20), 78.28, 78.43 (C-9, C-15), 78.81, 78.85, 78.96 (C-4, C-10, C-16), 79.05 (C-21), 79.41 (C-22), 109.56, 109.64, 109.87, 110.13, 111.26, 112.27 (8×*C*(CH_3)$_2$), 170.57, 170.59, 170.66 (*C*(6)ONH, *C*(12)ONH, *C*(18)ONH), 171.04 (C_2CH_3); MS *m*/*z* (ES+): 1109.35 ($M+Na^+$, 100%); MS *m*/*z* Isotope distribution (ES+): $C_{49}H_{78}N_6O_{21}Na$ ($M+Na^+$) calcd 1109.51, 100%; 1110.52, 60%; 1111.52, 20%; 1112.52, 7%, measured 1109.50, 100%; 1110.50, 45%; 1111.52, 12%; 1112.53, 4%; $C_{49}H_{78}N_6O_{21}$ requires: C, 54.13; H, 7.23; N, 7.73. Found: C, 53.96; H, 7.30; N, 7.89.
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31. *Data for cyclic tetramer* **8**: $[\alpha]_D^{24}$ −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 NMR δ_H (500 MHz, $CDCl_3$): 1.42, 1.47, 1.48 (48H, 3×s, 8×C(CH_3)$_2$), 3.25 (4H, a-br-d, *J* 15.0, 4×H-1), 4.08–4.14 (8H, m, 4×H-1′, 4×H-3), 4.39 (4H, a-d, *J* 8.4, 4×H-5), 4.44 (4H, a-d, *J* 8.7, 4×H-4), 4.55 (4H, a-d, *J* 8.7, 4×H-2), 7.00 (4H, a-d, *J* 9.0, 4×CONH); ^{13}C NMR δ_C (125 MHz, $CDCl_3$): 26.20, 26.40, 26.70, 27.15 (8×C(C_3)$_2$), 37.60 (4×C-1), 73.41 (4×C-2), 74.60 (4×C-5), 75.40 (4×C-3), 77.80 (4×C-4), 108.28, 110.27 (8×*C*(CH_3)$_2$), 170.04 (4×*C*ONH); ^1H NMR δ_H (500 MHz, C_6D_6): 1.16, 1.33, 1.36, 1.44 (48H, 4×s, 8×C(CH_3)$_2$), 3.05 (4H, dd, *J* 12.4, *J* 2.5, 4×H-1), 4.37 (4H, dd, *J* 13.6, *J* 10.5, 4×H-1′), 4.43 (4H, a-d, *J* 9.3, 4×H-3), 4.68 (4H, a-d, *J* 8.3, 4×H-5), 4.75 (4H, a-d, *J* 8.6, 4×H-4), 4.79 (4H, a-d, *J* 8.1, 4×H-2), 7.97 (4H, a-d, *J* 8.2, 4×CONH); ^1H NMR δ_H (500 MHz, CD_3CN): 1.40, 1.41, 1.44, 1.46 (48H, 4×s, 8×C(CH_3)$_2$), 3.31 (4H, a-dt, $J_{1,1'}$ 14.2, $J_{1,2}$ 4.2, 4×H-1), 3.83 (4H, ddd, $J_{1',1}$ 14.2, $J_{1',CONH}$ 8.2, $J_{1',2}$ 3.1, 4×H-1′), 4.08 (4H, dd, $J_{3,2}$ 8.9, $J_{3,4}$ 1.4, 4×H-3), 4.41 (4H, dd, $J_{4,5}$ 7.7, $J_{4,3}$ 1.4, 4×H-4), 4.40-4.46 (8H, m, 4×H-2, 4×H-5), 7.13-7.16 (4H, m, 4×CONH); ^{13}C NMR δ_C (125 MHz, CD_3CN): 25.77, 26.39, 26.43, 27.04 (8×C(C_3)$_2$), 39.00 (4×C-1), 74.71, 75.05 (4×C-2, 4×C-5), 77.41 (4×C-3), 78.51 (4×C-4), 108.94, 110.72 (8×*C*(CH_3)$_2$), 171.31 (4×*C*ONH); 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%; $C_{48}H_{76}N_4O_{20}$ requires: C, 56.02; H, 7.44; N, 5.44. Found: C, 55.52; H, 7.91; N, 5.04.

32. *Data for unprotected cyclic tetrapeptide* **3**: $[\alpha]_D^{25}$ +3.0 (*c* 0.2, D_2O); mp >220 °C, fine, 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.

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