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SYNTHESIS OF A NEW CARBOHYDRATE MIMETICS: "CARBOPEPTOID" CONTAINING A *C*-1 CARBOXYLATE AND *C*-2 AMINO GROUP

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Abstract: Readily access to a new class of carbohydrate mimetics has been demonstrated from a D-glucosamine derivative by the synthesis of a tetrameric carbopeptoid in which the glycosidic bonds are replaced with amido linkages.

An interesting polysaccharide analogue was first proposed by Lehmann[1] in 1975 in which the glycosidic bonds were replaced with amido linkages. This analogue was later re-proposed and named "carbopeptoid" by Nicolaou et al.;[2] however, no experimental and physical data have thus far been provided for such a compound. An application of carbohydrate as an amino acid analogue has been recently reported: Tietze et al. has prepared a glucose homolog with both an amino and a carboxyl group and incorporated it into peptide synthesis to mimic a proline β-turn residue.[3] As part of our ongoing efforts in designing new carbohydrate mimetics, we report herein the first synthesis of such a tetrameric analogue in which D-glucosamine derivatives are linked via the *C*-1 β-carboxylate and the *C*-2 α-amino groups (**1**, Figure 1).

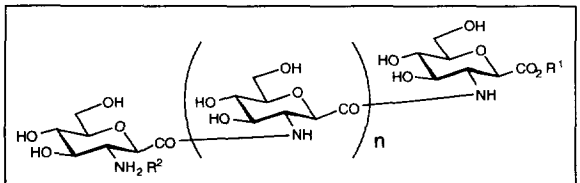
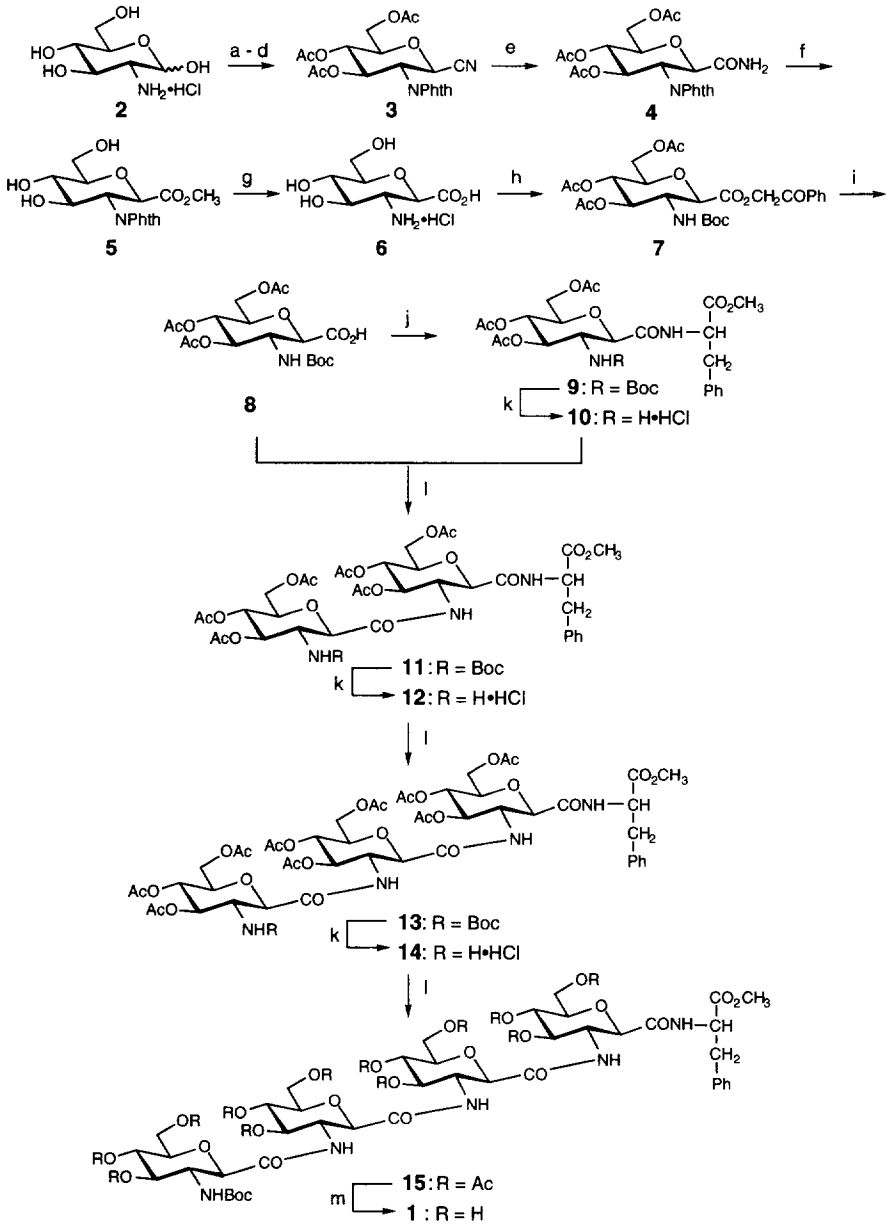


Figure 1. General structure of carbopeptoid **1**

For the preparation of a monomeric component (**8**) that is suitable for solid-phase chain elongation,[4] D-glucosamine hydrochloride (**2**) was first converted to a known 1-cyano-2-phthalimido derivative (**3**) according to the published procedure.[5] The *C*-1 CN group of **3** was hydrated with 30% HBr-AcOH[6] treatment to a $CONH_2$ group (**4**) in 85% yield; this product was subsequently treated with Dowex 50W-X8 [H^+] in refluxing MeOH to give the methyl ester derivative (**5**) in 97% yield. Removal of the phthaloyl group was accomplished by the successive treatment of **5** with aqueous LiOH and 3N HCl to give an amine derivative (**6**) as a HCl salt in 95% overall yield. tButoxycarbonylation of the amino group of **6** with BOC-ON,[7] followed by esterification of the *C*-1 carboxylate with 2-bromoacetophenone gave **7** in 73% overall yield after *O*-acetylation. Hydrogenolysis of **7** over Pd-C afforded **8**[8] in 90% yield.

For *C*-terminal modification, the monomeric component (**8**) was first linked to L-phenylalanine methyl ester, which has the potential for further replacement by a polymer support to permit the solid-phase assembly of oligo- and polysaccharide mimetics. Coupling of **8** with L-phenylalanine methyl ester using diethylphosphoryl cyanide (DEPC)[9] and Et_3N gave **9**[8] in 86% yield. The BOC group of **9** was removed with 2N HCl/EtOAc to give **10**[8] in 95% yield. The elongation reaction of **10** with **8** was carried out smoothly with



Scheme 1. Synthesis of a carbopeptoid tetramer 1. Reagents and conditions: a)-d) ref. 4, 46% overall; e) 30% HBr-AcOH, 3h, 0 °C to r.t., 85%; f) Dowex 50W-X8 [H^+], MeOH, 16h, 80 °C, 97%; g) (i) 6eq of LiOH, MeOH/H_2O (3:1), 16h, 60 °C, (ii) 3N HCl, 3h, reflux, 95% overall; h) (i) 2eq of BOC-ON, Et_3N, dioxane/H_2O (1:1), 12h, r.t., (ii) 2-bromoacetophenone, Et_3N, DMF, 4h, r.t., (iii) Ac_2O, pyridine, 12h, r.t., 73% overall; i) H_2, Pd/C, AcOEt/EtOH (2:1), 16h, r.t., 90%; j) L-phenylalanine methyl ester, DEPC, Et_3N, 16h, 0 °C to r.t., 86%; k) 2N HCl in EtOAc, 3h, 0 °C to r.t., 95%; l) 1.2 eq of **8**, BOP, DIEA, DMF, 16h, r.t., 59%; (m) MeONa in MeOH (pH 11), 2h, r.t., 68%

BOP reagent[10] and diisopropylethylamine (DIEA) in DMF to give the coupling product in 59% yield. Repetition of the same synthetic manipulation: (i) removal of the BOC group and (ii) coupling with the monomeric component (**8**), easily produced the trimer[8] (**13**) and the tetramer[8] (**15**). The tetramer (**15**) was *O*-deacetylated with NaOMe in MeOH to give **1**[8] in 68% yield.

The assembly of such oligosaccharide analogues is equivalent to a peptide bond formation, and the stereochemistry of the linkages is completely controlled by the choice of building blocks. These "carbopeptoid" would be resistant to glycosidases and may have an interesting biological activities as carbohydrate or peptide mimetics. In fact, the carbopeptoid **1**, after *O*-sulfation, has been found to show a strong inhibitory potency against HIV infection to CD4 cell[11] although it is composed of only four glucose units:[12] at 50 μM concentration, the sulfated **1** completely blocked the syncytium formation caused by HIV infection to CD4 cells.[13] This methodology can be further extended to a solid-phase synthesis of a new oligo- and polysaccharide analogue.

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8. Selected ^{1}H and ^{13}C NMR data: **4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-*tert*-butoxycarbonylamino-D-glycero-D-gulo-heptonic acid (8)**: ^{1}H NMR (300 MHz, CD_3OD): δ 5.17 (t, 1H, *J*= 9.4 Hz, H-4), 4.99 (t, 1H, *J*= 9.6 Hz, H-5), 4.29 (q, 1H, *J*= 5.0, 12.4 Hz, H-7a), 4.10 (q, 1H, *J*= 2.0, 12.3 Hz, H-7b), 3.97-3.86 (m, 2H, H-2,3), 3.79 (3.75 (m, 1H, H-6), 2.04, 2.00, 1.99 (3s, 3H each, 3×CH_3CO), 1.40 (s, 9H, $NHCO_2tBu$); ^{13}C NMR (72.5 Hz, CD_3OD): δ 172.5 (C-1), 171.9, 171.4 (3×CH_3CO), 157.6 ($NHCO_2tBu$), 80.9, 76.9, 75.9, 70.3, 63.8, 54.4 (C-2,3,4,5,6,7), 28.7 (tBu), 20.7, 20.68, 20.61 (3×CH_3CO).

   4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-*tert*-butoxycarbonylamido-D-glycero-D-gulo-heptur-onyl L-phenylalanine methyl ester (9): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.12 (m, 5H, Ph), 6.87 (d, 1H, *J*= 8.1 Hz, NH), 5.27 (m, 2H, H-2, 4), 5.03 (t, 1H, *J*= 9.7 Hz, H-5), 4.80 (m, 1H, $CHCO_2CH_3$ of L-Phe), 4.21 (q, 1H, *J*= 5.0, 12.4 Hz, H-7a), 4.14 (q, 1H, *J*= 1.2, 11.9 Hz, α-proton of L-Phe), 4.03 (d, 1H, *J*= 9.9 Hz, H-7b), 4.03 (d, 1H, *J*= 9.9 Hz, NH), 3.81-3.70 (m, 5H, H-2, 5, CO_2CH_3 of L-Phe), 3.18-3.02 (2H, CH_2Ph of L-Phe), 2.07, 2.06, 2.02 (3s, 3H each, 3×CH_3CO), 1.39 (s, 9H, $NHCO_2tBu$); ^{13}C NMR (72.5 MHz, $CDCl_3$): δ 171.1, 170.4, 169.2 (3×CH_3CO), 170.2 (CO_2CH_3), 166.8 (NHCO), 154.9 (NHOCOtBu), 135.6, 129.0, 128.2, 126.9 (Ph), 79.5, 76.8, 75.2, 73.1, 68.4, 62.0 (C-2,3,4,5,6,7), 52.6 ($CHCO_2CH_3$ of L-Phe), 52.0 (CO_2CH_3 of L-Phe), 37.6 (CH_2Ph of L-Phe), 27.9 (tBu), 20.44, 20.38, 20.33 (3×CH_3CO).

   Dimer: 4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-*tert*-butoxycarbonylamino-D-glycero-D-gulo-hepturonyl β(1,3) 4,5,7-tri-*O*-acetyl-3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl L-phenylalanine methyl ester (11): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.11 (m, 5H, Ph), 7.01

(d, 1H, *J*= 7.9 Hz, NH), 6.70 (d, 1H, *J*= 7.1 Hz, NH), 5.38 (t, 1H, *J*= 9.7 Hz, H-4), 5.21 (t, 1H, *J*= 9.5 Hz, H-4'), 5.07-4.98 (m, 3H, H-2,5, H-5'), 4.72 (q, 1H, *J*= 6.3, 14.0 Hz, C<u>H</u>CO_2CH_3 of L-Phe), 4.29-4.08 (m, 5H, H-7a, 7b, H-2', 7'a, 7'b), 3.97-3.87 (m, 2H, H-3, 6), 3.77-3.55 (m, 5H, H-3',6', $CO_2C\underline{H}_3$ of L-Phe), 3.18-3.06 (2H, C$\underline{H}_2$Ph of L-Phe), 2.08, 2.06, 2.05, 2.02 (3H each, 6×C$\underline{H}_3$CO), 1.39 (s, 9H, NHCO_2t<u>Bu</u>); ^{13}C NMR (72.5 MHz, $CDCl_3$): δ 171.1, 170.9, 170.6, 170.5, 169.30, 169.25 (6×$CH_3\underline{C}O$), 170.1 ($\underline{C}O_2CH_3$), 167.7, 166.8 (NH$\underline{C}$O), 155.2 (NHO$\underline{C}$OtBu), 135.8, 129.0, 128.4, 126.9 (Ph), 79.8, 76.3, 76.2, 75.5, 73.3, 72.3, 68.4, 68.3, 62.1, 61.9, 52.9 ($\underline{C}HCO_2CH_3$ of L-Phe), 52.2 ($CO_2\underline{C}H_3$), 37.4 (C$\underline{H}_2$Ph of L-Phe), 28.0 (tBu), 20.6, 20.5, 20.4 (6×$\underline{C}H_3CO$).

Trimer: 4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-*tert*-butoxycarbonylamino-D-glycero-D-gulo-hepturonyl β(1,3) 4,5,7-tri-*O*-acetyl-3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl β(1,3) 4,5,7-tri-*O*-acetyl-3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl L-phenylalanine methyl ester (13): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.11 (m, 5H, Ph), 6.94 (d, 1H, *J*= 6.9 Hz, NH), 5.25 (t, *J*= 8.7 Hz, 2H), 5.14-4.98 (m, 4H), 4.77 (q, 1H, *J*= 5.5, 12.1 Hz, C<u>H</u>CO_2CH_3 of L-Phe), 4.35-4.00 (m, 10H), 3.78-3.72 (m, 6H), 3.55 (q, 1H, *J*= 8.8,15.5 Hz), 3.22-3.08 (2H, C$\underline{H}_2$Ph of L-Phe), 2.07-1.99 (3H each, 9×C$\underline{H}_3$CO), 1.45 (s, 9H, NHCO_2t<u>Bu</u>); ^{13}C NMR (72.5 MHz, $CDCl_3$): δ 170.9, 170.4, 170.3, 170.2, 170.1, 169.9, 169.3, 169.2, 169.1 (9×$CH_3\underline{C}O$, $\underline{C}O_2CH_3$), 168.2, 167.9, 166.8 (NH$\underline{C}$O), 156.2 (NHO$\underline{C}$OtBu), 135.5, 129.0, 128.7, 126.9 (Ph), 80.4, 77.2, 77.1, 75.3, 75.2, 74.9, 73.4, 73.3, 72.7, 68.9, 68.4, 62.4, 62.1, 62.0, 52.7 ($\underline{C}HCO_2CH_3$ of L-Phe), 52.0 ($CO_2\underline{C}H_3$ of L-Phe), 37.3 (C$\underline{H}_2$Ph of L-Phe), 27.9 (tBu), 20.3, 20.26, 20.18 (9×$\underline{C}H_3CO$).

Tetramer: 4,5,7-Tri-*O*-acetyl-2,6-anhydro-3-*tert*-butoxycarbonylamino-D-glycero-D-gulo-hepturonyl β(1,3) 4,5,7-tri-*O*-acetyl-3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl β(1,3) 4,5,7-tri-*O*-acetyl-3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl β(1,3) 4,5,7-tri-*O*-acetyl-3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl L-phenylalanine methyl ester (15): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.14 (m, 5H, Ph), 7.09 (d, 1H, *J*= 7.5 Hz, NH), 7.00 (d, 1H, *J*= 7.7 Hz, NH), 5.46 (m, 1H), 5.37-5.28 (m, 3H), 5.10-4.99 (m, 4H), 4.73 (q, 1H, *J*= 6.0,13.6 Hz, C<u>H</u>CO_2CH_3 of L-Phe), 4.30-4.10 (m, 13H), 3.94-3.83 (m, 2H), 3.73-3.61 (m, 8H), 3.21-3.07 (2H, C$\underline{H}_2$Ph of L-Phe), 2.11-2.00 (3H each, 12×C$\underline{H}_3$CO), 1.41 (s, 9H, NHCO_2t<u>Bu</u>); ^{13}C NMR (72.5 MHz, $CDCl_3$): δ 171.0, 170.7, 170.6, 170.5, 170.4, 170.2, 169.5, 169.4, 169.3, 169.1 (12×$CH_3\underline{C}O$, $\underline{C}O_2CH_3$ of L-Phe), 168.7, 168.0, 167.7, 167.1 (NH$\underline{C}$O), 156.1 (NHO$\underline{C}$OtBu), 135.6, 129.2, 128.9, 127.1 (Ph), 79.8, 76.7, 75.4, 75.2, 75.0, 74.7, 72.3, 68.6, 68.4, 68.2, 62.2, 62.1, 62.0, 53.0 ($\underline{C}HCO_2CH_3$ of L-Phe), 52.3 ($CO_2\underline{C}H_3$ of L-Phe), 37.5 ($\underline{C}H_2$Ph of L-Phe), 28.3 (tBu), 20.8, 20.6, 20.5, 20.4, 20.3 (12×$\underline{C}H_3CO$).

Tetramer: 2,6-Anhydro-3-*tert*-butoxycarbonylamino-D-glycero-D-gulo-hepturonyl β(1,3) 2,6-anhydro-3-amino-D-glycero-D-gulo-hepturonyl β(1,3) 3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl β(1,3) 3-amino-2,6-anhydro-D-glycero-D-gulo-hepturonyl L-phenylalanine methyl ester (1): ^{1}H NMR (300 MHz, D_2O): δ 7.32-7.17 (m, 5H, Ph), 4.57 (q, 1H, *J*= 6.5, 8.2 Hz, C<u>H</u>CO_2CH_3 of L-Phe), 3.87-3.58 (m, 21H), 3.50-3.32 (m, 10H), 3.10 (q, 1H, *J*= 8.2,14.0 Hz, C$\underline{H}_2$Ph of L-Phe), 2.95 (q, 1H, *J*= 6.5,14.0 Hz, C$\underline{H}_2$Ph of L-Phe), 1.35 (s, 9H, NHCO_2t<u>Bu</u>); ^{13}C NMR (72.5 MHz, D_2O): δ 173.5($\underline{C}O_2CH_3$ of L-Phe), 171.8, 171.5, 171.1, 170.5 (NH$\underline{C}$O), 158.3 (NHO$\underline{C}$OtBu), 136.7, 129.6, 129.2, 127.7 (Ph of L-Phe), 81.8, 79.6, 79.5, 79.4, 78.1, 77.1, 77.0, 75.1, 74.9, 74.7, 74.4, 70.0, 69.7, 69.6, 61.0, 60.9, 60.7, 55.8, 54.3, 54.2, 54.1, 53.5, 53.3 ($CO_2\underline{C}H_3$ of L-Phe), 37.0 ($\underline{C}H_2$Ph of L-Phe), 28.1 (tBu).

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