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Carbonucleotoids and Carbopeptoids: New Carbohydrate Oligomers

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Abstract: *Carbonucleotoids (phosphate-bond linked carbohydrates) and carbopeptoids (peptide-bond linked carbohydrates) are proposed as new oligosaccharide ligands. The ready access to these analogues is demonstrated by the facile synthesis of the tetrameric carbonucleotoid* ***1.***

Oligonucleotides, peptides and oligosaccharides are three classes of oligomers whose chemical synthesis has been extensively studied.[1,2,3] Such molecules can now be routinely synthesized both in solution and in the solid phase, manually or on automated systems with the exception of oligosaccharides whose construction is considerably less efficient. This state of affairs reflects the availability of techniques for the construction of the phosphate and peptide bonds in nearly quantitative yields and the absence of stereocenters associated with these linkages. In contrast, the relatively lower yields and the complication of two isomeric glycosidation products in glycoside bond forming reactions renders the synthesis of conventional oligosaccharides rather problematic.

The rapidly growing importance of carbohydrates in biology[4] and the emergence of chemical libraries[5] as potential tools for ligand lead and drug discovery prompted us to design two groups of carbohydrate-based oligomers **I** and **II** (Figure 1), using the nucleotide and peptide bond, respectively, to link component units.

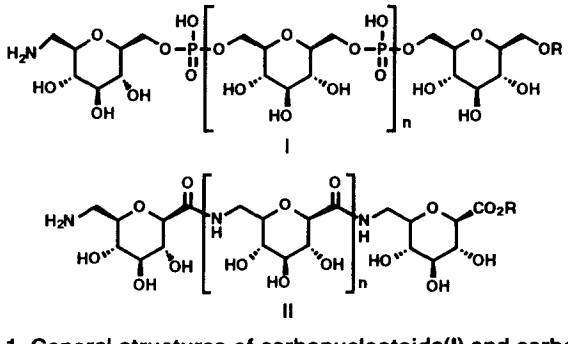

Figure 1. General structures of carbonucleotoids(I) and carbopeptoids (II)

Several advantages were envisioned for these molecules termed "carbonucleotoids" (**I**) and "carbopeptoids" (**II**), respectively, including: (a) ease of formation; (b) possibility of library generation; (c) choice of solution or solid phase synthesis; and (d) polyfunctionality. In this communication, we demonstrate the validity of these concepts by the synthesis of the tertrameric carbonucleotoid **1** from readily available starting materials.

Scheme 1 summarizes the synthesis of the tetrameric compound **1** starting with glucose pentaacetate (**2**). Thus, manipulation of **2** by a known sequence afforded methylester **3** in large quantities.[6] The latter compound was then selectively silylated at the primary position, benzylated at the three secondary positions,[7] and reduced under standard conditions to afford key intermediate **4** in 51% overall yield.[8] Compound **4** served as a common intermediate to prepare the two requisite carbohydrate units **6** and **7**.[9] The naphthoyl group on **7** was chosen to serve as a convenient UV-detectable marker for chromatographic analysis of subsequent intermediates and to mimic potential solid phase chemistry. The conversion of **4** to the targeted *N,N*-diisopropyl-aminophosphoramidite (**6**) was accomplished using 2-cyanoethyl-*N,N*-diisopropylchloro-phosphoramidite **5**[10] in the presence of diisopropylethylamine (DIPEA) in methylene chloride under strictly anhydrous conditions. Purification of the crude product, formed in a few minutes in essentially quantitative yield, could be carried out by quick filtration through a short silica gel column using petroleum ether: ethylacetate: triethylamine (75: 20: 5) as eluent.

The hydroxy component **7** was prepared in 90% overall yield from **4** by esterification with 2-naphthoyl chloride in the presence of dimethylaminopyridine (DMAP), followed by acid-induced desilylation. Coupling of the two intermediates **6** and **7** proceeded smoothly under anhydrous conditions in methylene chloride in the presence of 1*H*-tetrazole. Upon completion of the reaction as indicated by TLC, addition of *m*-CPBA to the reaction mixture resulted in oxidation of phosphorus as judged by a lower R_f value. Standard work-up with aqueous $NaHCO_3$ solution, followed by flash chromatography afforded pure dimer **8** in 97% yield.[9] Removal of the silyl group from **8** under acid conditions gave the hydroxy compound **9** in 95% yield which was now ready for further extension via coupling with another molecule of **6**.[9]

Repetition of the sequence allowed the preparation of the trimeric compounds **10** and **11** and the tetrameric compounds **12** and **13** in similarly high yields (Scheme 1). Removal of the cyanoethylene group under mildly basic conditions (NH_4OH), followed by hydrogenolysis (Pd/C-H_2) of the benzyl ethers led to the naphthoate ester **1** in 80% overall yield.

It is envisioned that the described chemistry could be used to produce higher homologs of a variety of carbonucleotoid structures (**I**) similar to **1**, and that extensions in the corresponding carbopeptoid area would generate structures of type **II**. Mixing different component units in these reactions may, of course, result in a variety of chemical libraries of predesigned molecular structures. The latter are expected to find applications in ligand-receptor binding studies and biological screening assays.

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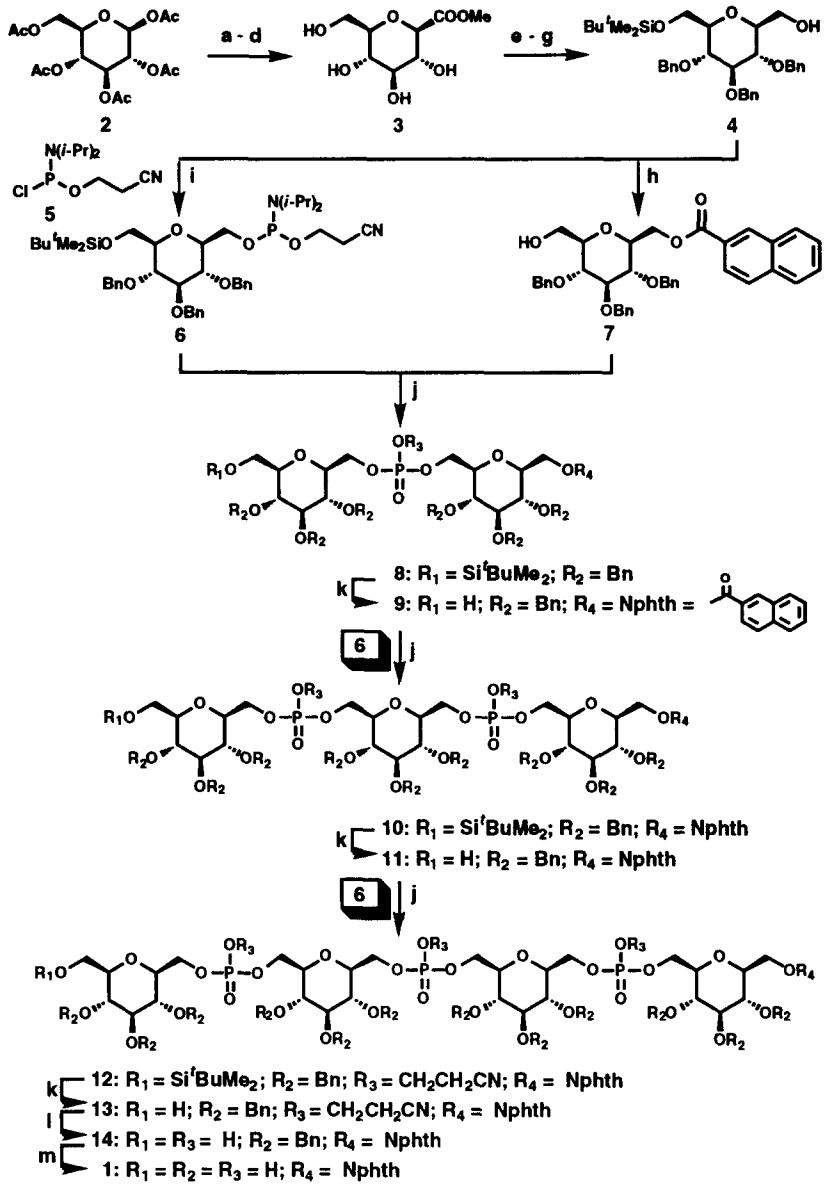
Scheme 1. Synthesis of Carbonucleotoid 1[a]



[a]Reagents and conditions: (a)-(d) ref. 6, 41% overall; (e) 1.2 equiv of $^{t}BuMe_2SiCl$, 2.5 equiv of imid., DMF, 2 h, 0 °C, 93%; (f) 9 equiv of BnBr, 6 equiv of Ag_2O, DMF, 20 h, 25 °C, 83%; (g) 3 equiv of DIBALH, THF, 1 h, 0 °C, 66%; (h) i. 3 equiv of naphthoyl chloride, 10 equiv of pyr., 45 min., 25 °C; ii. AcOH/THF/H_2O (3:1:1) 15 h, 25 °C, 90 % overall; (i) 1.5 equiv of 5, 4 equiv of $^{i}Pr_2EtN$, CH_2Cl_2, 5 min, 25 °C, 95%; (j) 3-5 equiv of 6 (0.1M solution in CH_2Cl_2), 10 equiv of 1*H*-tetrazole, CH_2Cl_2, 20 min., 25 °C, then 4.5-7.5 equiv of *m*-CPBA, 5 min, 97%; (k) AcOH/THF/H_2O (3:1:1), 18 h, 25 °C, 95%; (l) 1:1 conc. aq. NH_4OH / CH_3CN, 2 h, 50 °C, 88%; (m) H_2, Pd/C, EtOH/THF/AcOH (2:1:1),25 °C, 72 h, 78%.

References and Notes

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7. (a) Kuhn, R.; Löw, I.; Trischmann, H. *Chem. Ber.* **1957**, *90*, 203; (b) Helferich, B.; Klein, W. *Ann. Chem.* **1926**, *450*, 219.
8. All compounds exhibited satisfactory analytical and spectroscopic data. Yields refer to homogeneous materials.
9. **Phosphoramidate 6** (2 diastereomers): IR, (neat) cm^{-1}: 3089, 2964, 2927, 2856, 2253, 1497, 1455, 1396, 1363, 1253, 1184, 1156, 1094, 1028, 978, 876, 836, 779, 735; ^{1}H-NMR (400 MHz, C_6D_6): δ 7.34 (m, 5 H, Ph), 7.14 (m, 10 H, Ph), 4.97 (m, 4 H, CH_2Ph), 4.78 (m, 2 H, CH_2Ph), 4.07-3.24 (m, 13 H, OCH, OCH_2, CH_2CN), 1.81 (m, 2 H, $CH(CH_3)_2$), 1.16 (m, 12 H, CH_3CH), 1.03 , 1.02 (2 s, 9 H, ^{t}BuSi), 0.20, 0.18, 0.16, 0.15 (4 *s*, 6 H, Me_2Si); HRMS: $C_{43}H_{63}O_7N_2PSi$, Calc. (M+Cs^+): 911.3197; found: 911.3185.

   Naphthoylester 7: IR, (neat) cm^{-1}: 3494, 3062, 2919, 1716, 1630, 1600, 1454, 1355, 1284, 1228, 1197, 1091,779, 736; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 8.58 (s, 1 H, Ar), 8.00 (m, 2 H, Ar), 7.89 (m, 2 H, Ar), 7.59 (m, 2 H, Ar), 7.32 (m, 15 H, Ph), 4.95 (m, 3 H), 4.90 (d, *J*=4.5 Hz, 1 H), 4.69 (m, 3 H), 4.52 (dd, *J* = 3.9, 12.0 Hz, 1 H), 3.91 (dd, *J* = 2.6, 12.0, 1 H), 3.83 (d, *J*= 8.3, 1 H), 3.70 (m, 4 H), 3.96 (m, 1 H), 2.25 (s, 1 H, OH). HRMS: $C_{39}H_{38}O_7$ Calc. (M+Cs^+): 751.1672; found: 751.1668.

   Dimer 9: IR, (neat) cm^{-1}: 3397, 3030, 2923, 2254, 1718, 1653, 1629, 1497, 1453, 1355, 1284, 1227, 1197, 1094, 1029, 780.^{1}H-NMR (400 MHz, C_6D_6): δ 8.82 (s, 1 H, Ar), 8.26 (d, 1 H, Ar), 7.72 (m, 1 H, Ar), 7.61 (m, 1 H, Ar), 7.48 (m, 1 H, Ar), 7.37-6.95 (m, 32 H, Ar, Ph), 4.89-4.18 (m, 21 H, CH_2Ph, CH_2-Ar, -CH_2CH_2CN, $CHCH_2$-Ar and CH_2OH), 3.95-3.45 (m, 13 H, CH- and CH_2-sugar), 1.71 (s, 1 H, OH); HRMS: $C_{170}H_{72}O_5NP$ calc. (M+H^+): 1198.4718; found: 1198.4715.

   Tetramer 13: IR, (neat) cm^{-1}: 3420, 3064, 2924, 2255, 1721, 1497, 1455, 1357, 1278, 1028, 737. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1 H, Ar), 8.00 (m, 2 H, Ar), 7.91 (m, 2 H, Ar), 7.55 (m, 2 H, Ar), 7.30 (m, 60 H, Ph), 4.93-4.05 (m, 39 H, CH_2Ph, CH_2-Ar, CH_2CH_2CN and CH_2OH), 3.88-3.27 (m, 23 H, CH- and CH_2-sugar), 2.58 (s, 1 H, OH). HRMS: $C_{132}H_{140}O_{31}N_3P_3$ Calc. (M+Cs^+): 2488.7738; found: 2488.7758.

   Tetramer 1: IR, (neat) cm^{-1}: 3376, 2934, 1450, 1244, 1110, 1088. ^{1}H-NMR (400 MHz, D_2O): δ 8.41 (s, 1 H, Ar), 8.00 (m, 2 H, Ar), 7.91 (m, 2 H, Ar), 7.55 (m, 2 H, Ar), 4.93-4.05 (m, 4 H, CH_2-Ar and CH_2OH), 3.88-3.27 (m, 32 H, CH- and CH_2-sugar); HRMS: $C_{39}H_{59}O_{31}P_3$ Calc. (M+H^+):1117.2331; found: 1117.2350.
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