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Preparation of new amide-linked pseudodisaccharides by the carboxymethylglycoside lactone (CMGL) strategy

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Abstract—6-Aminodeoxy sugars react with carboxymethyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside 2-*O*-lactone (α-CMGL) to provide the corresponding new amide-linked glucose/glucose or glucose/galactose pseudodisaccharides in good yields. The strategy is extended to the synthesis of an amide-linked sugar/nucleoside adduct.
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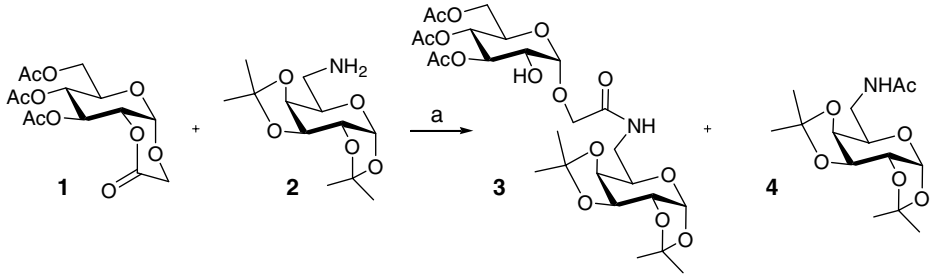
In recent years, considerable interest has been devoted to the design and synthesis of amide-linked polysaccharidic structures.[1–4] The assembly of modified carbohydrates bearing both an amino and a carboxylate function, called sugar amino acids (SAAs), using carbohydrate and peptide chemistry has provided compounds of biological interest. For example, antiviral activity against HIV and inhibition of sialyl Lewis x-dependant cell adhesion have been found for some sulfated amide-linked oligomers.[5,6] SAAs oligomers have also been used for their ability to mimic peptides and, in some cases, have shown to adopt well-defined secondary conformations.[7–9]

We have recently reported that the readily available carboxymethyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside 2-*O*-lactone **1** (α-CMGL) was a useful synthon for anchoring a carbohydrate moiety on several alcohols and amines via the selective opening of the lactone ring.[10,11] We report here, the synthesis of new amide-linked pseudodisaccharides such as **3** using the opening of α-CMGL by various aminodeoxy sugars (Scheme 1). The length of the four-atom inter-glycosidic linkage being close to that of a monosaccharide unit, such derivatives can also be considered as trisaccharides mimetics. In the literature, such oligosaccharide analogues having non-glycosidic spacers have been reported. For example,



Scheme 1. Reagents and conditions: THF, rt, 18 h, 90% (**3**).

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linear or cyclic oligosaccharides with a four-carbon rigid connection were constructed,[12–15] and a compound bearing a six-atom acyclic spacer between two glucose residues has been synthesized and was found to be a competitive inhibitor of the hydrolysis of *p*-nitrophenyl α-maltotriose by porcine alpha-amylase.[16]

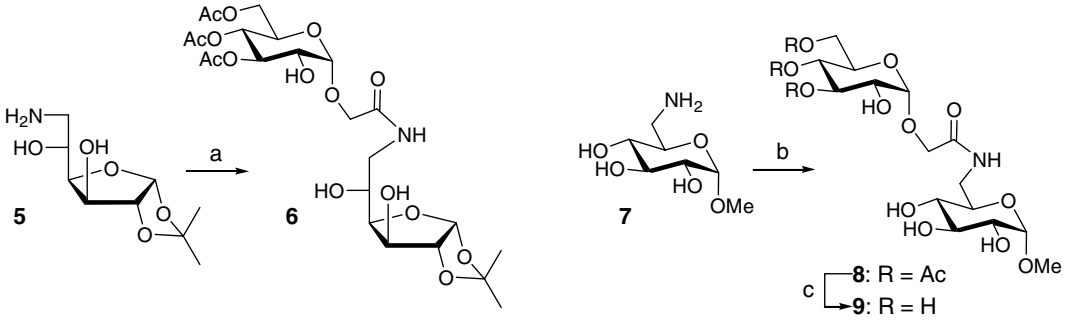
The ring opening of lactone **1** was first studied using the protected 6-aminodeoxy galactopyranose **2**[17] as a nucleophile for obtaining compound **3** (Scheme 1). NMR spectroscopy showed the typical pattern of carboxymethylglycoside adducts, including H(2) and H(3), respectively, at 3.83 and 5.33 ppm.[18] Different reaction conditions were employed varying solvent, concentration and relative stoichiometry of the reactants. Unlike what is observed for the opening of α-CMGL **1** with alcohols,[11] it was noted that the reaction with amine **2** did not require the presence of DMAP. On the contrary, it was shown that its use led to an increase in the yield of the undesired N-acetylated derivative **4**[19] arising from competitive intermolecular O-to-N acetyl exchange. The obtained yields showed that the best result is achieved when the reactants are placed in THF with a slight excess of lactone **1**. In these conditions, only trace amounts of **4** were detected by TLC.

The reaction of lactone **1** with two partially protected 6-aminodeoxy sugars **5**[20] and **7**[21] was then studied (Scheme 2). For solubility reasons, reaction with compound **7** was performed in anhydrous DMF. Reactions yielded the partially protected pseudodisaccharides **6** and **8**, with the expected selectivity for the amine versus the alcohol functions. Deprotection of the obtained amide-linked pseudodisaccharide **8** was carried out using standard Zemplén conditions leading to the free pseudodisaccharide **9** (Scheme 2).

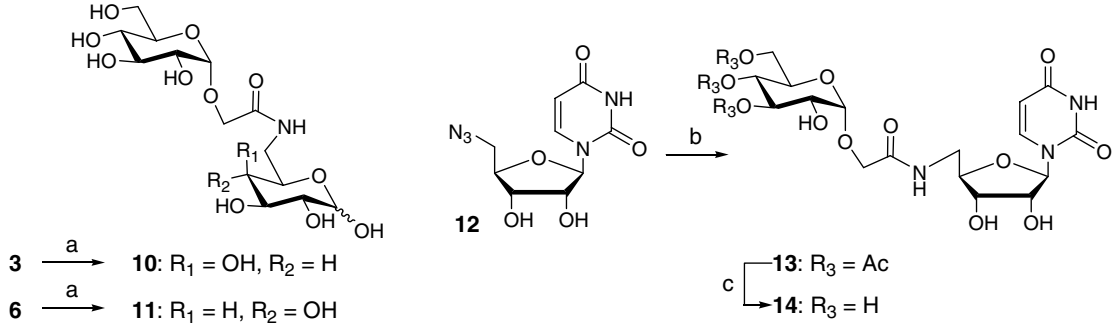
In the case of compounds **3** and **6**, both isopropylidene and acetyl groups were removed simultaneously using a 0.5 M HCl solution at 50 °C to give access to the corresponding fully unprotected compounds **10** and **11** (Scheme 3),[23] showing the reasonably good stability of the α-carboxymethyl linkage of such derivatives under acidic conditions.

The same strategy was finally applied to the synthesis of an amide-linked sugar/nucleoside adduct. Thus, 5′-deoxy-5′-azidouridine **12**[24] was reduced (H_2, Pd/C) to the corresponding 5′-deoxyamino analogue, which was reacted without further purification with lactone **1** in DMF to furnish, after removal of the acetyl groups, the amide **14** (Scheme 3). No protection of the uracil moiety was needed.

In summary, we have demonstrated that the opening of carboxymethyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside 2-*O*-lactone (α-CMGL) with deoxyamino sugars constitutes an efficient strategy for constructing amide-linked pseudodisaccharides. This reaction has been applied to the synthesis of new glucose–glucose, glucose–galactose and glucose–uridine adducts. We are now studying the scope of this reaction with respect to other nucleophilic species in order to obtain more elaborated glycoconjugate analogues similar to compound **14**, which could potentially mimic the glucosyltransferases substrate (UDP-Glc). Extension to carboxymethyl glycoside



Scheme 2. Reagents and conditions: (a) THF, rt, 18 h, 90%; (b) DMF, rt, 15 h, 87%; (c) MeONa/MeOH, rt, 1 h, 83%.[22]



Scheme 3. Reagents and conditions: (a) 0.5 M HCl, dioxane/H_2O, 50 °C, 12 h, 80%; (b) (i) H_2, Pd/C, EtOH, rt, 15 h, (ii) **1**, DMF, rt, 70% overall; (c) MeONa/MeOH, rt, 1 h, 82%.[25]

lactones derived from other mono or oligosaccharides is also under investigation.

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18. Compound **3**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, $J = 7.3$ Hz, 1H), 5.55 (d, $J = 5$ Hz, 1H), 5.33 (t, $J = 9.9$ Hz, 1H), 5.01 (t, $J = 9.4$ Hz, 1H), 4.81 (d, $J = 3.6$ Hz, 1H), 4.58 (dd, $J = 7.9$ Hz, $J = 2.4$ Hz, 1H), 4.34 (dd, $J = 5.0$ Hz, $J = 2.4$ Hz, 1H), 4.22–4.34 (m, 3H), 4.05–4.12 (m, 2H), 3.94 (ddd, $J = 13.9$ Hz, $J = 9.2$ Hz, $J = 2.0$ Hz, 1H), 3.83 (dd, $J = 9.9$ Hz, $J = 3.6$ Hz, 1H), 3.79 (m, 1H), 3.16 (ddd, $J = 12.6$ Hz, $J = 7.1$ Hz, $J = 2.0$ Hz, 1H), 2.07 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.46 (s, 3H), 1.42 (s, 6H), 1.32 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 171.1, 170.2, 169.5, 110.2, 109.5, 99.8, 96.7, 72.7, 71.9, 70.9, 70.9, 70.2, 68.5, 68.4, 68.4, 67.9, 62.3, 39.6, 26.4, 26.3, 25.2, 24.7, 21.3, 21.1, 21.0 $[\alpha]_D^{20}$ +78 (*c* 1.0, CH_2Cl_2). HRMS (ES) calcd for $[M+Na]^+$ 628.2217, found 628.2225. Anal. Calcd for $C_{26}H_{39}NO_{15}$: C, 51.57; H, 6.49; N, 2.31. Found: C, 51.27; H, 6.68; N, 2.22.
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22. Compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (t, $J = 8.3$ Hz, 1H), 5.92 (d, $J = 3.0$ Hz, 1H), 5.30 (t, $J = 9.6$ Hz, 1H), 5.01 (t, $J = 9.9$ Hz, 1H), 4.93 (d, $J = 3.3$ Hz, 1H), 4.54 (d, $J = 3.4$ Hz, 1H), 4.34 (m, 3H), 4.06–3.93 (m, 5H), 3.80–3.60 (m, 1H), 3.74 (dd, $J = 9.6$, $J = 3.3$ Hz, 1H), 3.33–3.28 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 171.7, 171.5, 171.1, 170.1, 111.9, 105.4, 99.9, 85.5, 81.1, 75.2, 73.2, 70.5, 69.5, 69.5, 68.4, 67.8, 62.3, 43.8, 27.0, 26.4, 21.3, 21.2, 21.1. $[\alpha]_D^{20}$ +95 (*c* 1.0, CH_2Cl_2). HRMS (ES) calcd for $[M+Na]^+$ 588.1904, found 588.1909. Anal. Calcd for $C_{23}H_{35}NO_{15}$: C, 48.85; H, 6.24; N, 2.48. Found: C, 48.55; H, 6.35; N, 2.41.
Compound **8**: ^{1}H NMR (300 MHz, MeOD): δ 5.23 (t, $J = 9.8$ Hz, 1H), 4.95 (t, $J = 9.8$ Hz, 1H), 4.94 (d, $J = 3.9$ Hz, 1H), 4.68 (d, $J = 3.7$ Hz, 1H), 4.26 (d, $J = 15.5$ Hz, 1H), 4.25 (dd, $J = 12.2$ Hz, $J = 4.8$ Hz, 1H), 4.09 (d, $J = 15.5$ Hz, 1H), 4.07 (dd, $J = 12.2$ Hz, $J = 2.3$ Hz, 1H), 4.02 (ddd, $J = 10.3$ Hz, $J = 4.8$ Hz, $J = 2.3$ Hz, 1H), 3.76 (dd, $J = 9.8$ Hz, $J = 3.9$ Hz, 1H), 3.66–3.56 (m, 4H), 3.42 (dd, $J = 9.6$ Hz, $J = 3.7$ Hz, 1H), 3,16 (t, $J = 8.9$ Hz, 1H), 3.40 (s, 3H), 2.05 (s, 6H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, MeOD): 172.4, 172.2, 172.0, 171.5, 101.3, 100.6, 74.9, 74.3, 73.5, 73.3, 71.3, 71.0, 70.0, 69.4, 68.0, 63.3, 55.8, 41.1, 20.9, 20.7, 20.7. $[\alpha]_D^{20}$ +119 (*c* 1.0, MeOH). HRMS (ES) calcd for $[M+Na]^+$ 562.1748, found 562.1749. Anal. Calcd for $C_{21}H_{33}NO_{15}$: C, 46.75; H, 6.17; N, 2.60. Found: C, 46.30; H, 6.52; N, 2.51.
Compound **9**: ^{1}H NMR (500 MHz, MeOD): δ 4.83 (d, $J = 3.7$ Hz, 1H), 4.67 (d, $J = 3.7$ Hz, 1H), 4.23 (d, $J = 15.7$ Hz, 1H), 4.04 (d, $J = 15.7$ Hz, 1H), 3.81 (dd, $J = 11.9$ Hz, $J = 2.3$ Hz, 1H), 3.68 (dd, $J = 11.9$ Hz, $J = 5.4$ Hz, 1H), 3.67 (t, $J = 9.5$ Hz, 1H), 3.63–3.52 (m, 5H), 3.48 (dd, $J = 9.7$ Hz, $J = 3.7$ Hz, 1H), 3.42 (dd, $J = 9.6$ Hz,$J = 3.7$ Hz, 1H), 3.40 (s, 3H), 3.32 (t, $J = 9.3$ Hz, 1H), 3.17 (t, $J = 9.2$ Hz, 1H); ^{13}C NMR (75 MHz, MeOD): 172.6, 101.2, 101.0, 74.9, 74.8, 74.4, 73.5, 73.2, 73.2, 71.5, 71.4, 67.7, 62.5, 55.8, 41.1. $[\alpha]_D^{20}$ +155 (*c* 1.0, MeOH). HRMS (ES) calcd for $[M+Na]^+$ 436.1431, found 436.1432.
23. Compounds **10** and **11** were identified by mass spectroscopy and characteristic ^{1}H NMR patterns have been assigned. Compound **10**: ^{1}H NMR (300 MHz, D_2O): δ 5.24 (d, $J = 3.6$ Hz, H-1′α), 4.98 (d, $J = 3.6$ Hz, H-1), 4.56 (d, $J = 7.8$ Hz, H-1′β), 4.28 and 4.13 (d, $J = 15.6$ Hz, AB system, H-7), α:β = 4:6. $[\alpha]_D^{20}$ +102 (*c* 1.0, H_2O); HRMS-LSIMS calcd for $[M+H]^+$ 400.1455, found 400.1457.
Compound **11**: ^{1}H NMR (500 MHz, D_2O): δ 5.25 (d, $J = 3.9$ Hz, H-1′α), 5.02 (d, $J = 3.8$ Hz, H-1), 4.68 (d, $J = 8.1$ Hz, H-1′β), 4.33 and 4.18 (d, $J = 15.6$ Hz, AB system, H-7), α:β = 3:7. $[\alpha]_D^{20}$ +90 (*c* 0.7, H_2O); HRMS-LSIMS calcd for $[M+H]^+$ 400.1455, found 400.1459.
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25. Compound **13**: ^{1}H NMR (300 MHz, CD_3OD): δ 7.66 (d, $J = 8.1$ Hz, 1H), 5.76 (d, $J = 8.1$ Hz, 1H), 5.75 (d, $J = 4.4$ Hz, 1H), 5.33 (t, $J = 9.6$ Hz, 1H), 4.96 (t, $J = 9.7$ Hz, 1H), 4.95 (d, $J = 3.7$ Hz, 1H), 4.31–4.22 (m, 3H), 4.13–4.02 (m, 5H), 3.77 (dd, $J = 9.7$ Hz, $J =$

3.7 Hz, 1H), 3.68 (dd, $J = 14.1$ Hz, $J = 6.0$ Hz, 1H), 3.57 (dd, $J = 14.1$ Hz, $J = 3.6$ Hz, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (50 MHz, CD_3OD): 172.4, 172.4, 172.1, 171.4, 166.0, 152.3, 143.2, 103.1, 100.6, 92.3, 83.8, 74.5, 74.3, 72.3, 70.9, 69.9, 69.2, 68.3, 63.3, 41.7, 20.9, 20.7, 20.7. $[\alpha]_D^{20}$ +80 (*c* 1.0, MeOH). LSIMS $[M+H]^+$ 590, $[M+Na]^+$ 612. Anal. Calcd for $C_{23}H_{31}NO_{15}\cdot 0.33H_2O$: C, 46.39; H, 5.36; N, 7.06. Found: C, 46.39; H, 5.55; N, 7.44. Compound **14**: ^{1}H NMR (300 MHz, D_2O): δ 7.69 (d, $J = 8.1$ Hz, 1H), 5.89 (d, $J = 8.1$ Hz, 1H), 5.79 (d, $J = 4.2$ Hz, 1H), 4.96 (t, $J = 3.6$ Hz, 1H), 4.39 (t, $J = 4.2$ Hz, 1H), 4.28 (d, $J = 15.6$ Hz, 1H), 4.16–4.08 (m, 3H), 3.86–3.63 (m, 6H), 3.60 (dd, $J = 9.9$, $J = 3.6$ Hz, 1H); 3.42 (t, $J = 9.0$ Hz, 1H); ^{13}C NMR (50 MHz, D_2O): 172.8, 166.7, 152.0, 142.9, 102.8, 99.4, 91.3, 82.2, 73.5, 73.3, 72.8, 71.6, 71.0, 69.9, 66.9, 60.9, 40.7. $[\alpha]_D^{20}$ +82 (*c* 1.0, MeOH). HRMS-LSIMS calcd for $[M+H]^+$ 464.1517, found 464.1513.