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Synthesis and characterization of acetylated sept-D-glucopyranose carbamate as an oligosaccharide donor

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ABSTRACT

An oligosaccharide donor, acetylated sept-D-glucopyranose tetradecyl carbamate, was designed and synthesized. This compound could be easily linked to hydroxyl-containing compounds through an *O*-glycosidic bond. Characterization of all the oligosaccharide intermediates and the final product was thoroughly discussed.

1. Introduction

Glycosyl carbamates were reported as glycosyl donors whose carbamate moiety could be displaced by the hydroxyl group in hydroxyl-containing acceptors and form an *O*-glycosidic bond, which constituted a kind of glycosylation reaction [1,2]. Compared to glycose, oligosaccharides showed more interesting properties. For example, they could be used to form glycocluster and glycodendrimer, which might lead to cluster effect [3,4]. Besides, polyanionic polysaccharides constitute a large family of anti-HIV chemotherapeutic agents [5]. These polyanionic polysaccharides, such as heparin sulfate (HS) and dextran sulfate (DS), though have strong affinity to the basic regions of gp120, unfortunately are also anticoagulants. They can hardly achieve therapeutic anti-HIV drug levels without affecting blood clotting [5,6]. And, DS was poorly absorbed when dosed orally, and when given intravenously, it resulted in toxicity before it could produce a therapeutic effect based on HIV biomarker levels [5,7,8]. The fact that sulfated oligosaccharides with attached alkyl chains yielded good anti-HIV activity and low toxicities encouraged studies using analogous alkylated oligosaccharides [5,9]. Rather than using the Koenigs–Knorr stepwise oligosaccharide synthesis method [10], in this article, we tried to introduce a cheap, short-routed, and straightforward process to produce oligosaccharide donors. Compound **1** is comprised of an acetylated sept-D-glucopyranose and a tetradecyl alkyl chain, as well as the carbamate moiety between them, which could be easily linked to hydroxyl-containing supporters through an *O*-glycosidic bond (Fig. 1) [1]. Hexa- and octa-D-glucopyranose donors could be obtained similarly using α- and γ-cyclodextrin.

2. Experimental

β-Cyclodextrin **2** was acetylated with acetic anhydride in pyridine and cleaved with concentrated perchloric acid to give per-acetylated maltoheptaose **4**, whose anomeric hydroxyl group was then selectively deprotected using ethylenediamine (EDA) and acetic acid to give the anomeric hydroxyl containing acetylated oligosaccharide **5** (Scheme 1) [9,11–16]. Compound **5** was then connected to tetradecylamine by phosgene to give the oligosaccharide donor acetylated sept-D-glucopyranose tetradecyl carbamate **1** [17,18]. Experimental details description as well as the MS and NMR spectra of compounds **3**, **4**, **5**, **1** are listed in Supporting information, and spectral data of the products are as follows.

*Heptakis (2,3,6-tri-O-acetyl)-β-cyclodextrin (**3**)*: yield 83%; white solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5. 21 (t, 7H, J = 8 Hz, C3-H), 5.06 (s 7H, C1-H), 4.74–4.71 (m, 7H, C5-H), 4.42–4.39, 4.26–4.22 (m, 14H, C6-H, C6-H′), 4.10 (s, 7H, C2-H), 3.85 (t, 7H, J = 8 Hz, C4-H), 2.09–1.95 (m, 63H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.03, 169.31 (–CO–), 96.57 (C1), 76.54 (C4), 69.98 (C3, C5), 69.38 (C2), 62.34 (C6), 20.43 ($-CH_3$); MALDI-FTMS (m/z): calcd. for $[M+Na]^+$: 2039.6, found: 2039.6, calcd. for $[M+K]^+$: 2055.6, found: 2055.5.

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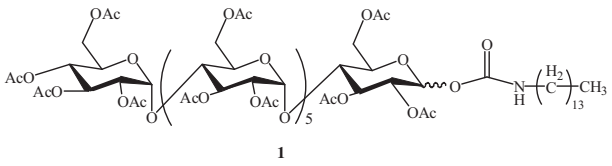

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Fig. 1. Chemical structure of sept-D-glucopyranose tetradecyl carbamate **1**.

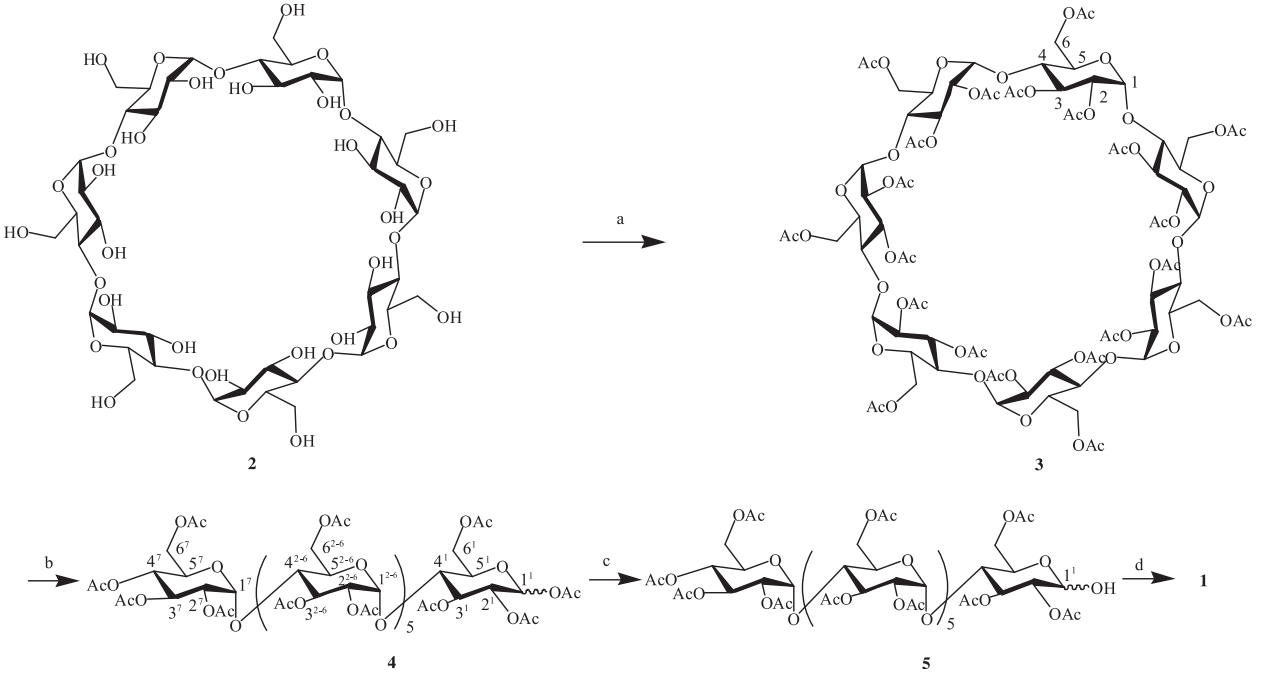
*2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl-[(1 → 4)-2,3,6-tri-O-acetyl-α-D-glucopyranosyl]$_5$-(1 → 4)-1,2,3, 6-tetra-O-acetyl-α, β-D-glucopyranosyl (**4**):* Yield 12%; white solid; ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.10 (s, 1H, C1^1-H), 5.40–5.36, 5.30–5.18 (m, 7H, C3-H), 5.28–5.15 (m, 6H, C1$^{2-7}$-H), 5.02–4.70 (m, 7H, C5-H), 4.15–4.10, 4.03–3.93 (m, 7H, C2-H), 4.37–4.10, 4.03–3.96 (m, 14H, C6-H, C6-H′), 4.10–4.05, 4.00–3.90 (m, 7H, C4-H), 2.19–1.95 (m, 69H, –CH$_3$); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 170.02–169.06 (–CO–), 95.84, 95.53 (C1$^{2-7}$), 88.12 (C1^1), 74.00, 73.66 (C4), 71.15, 70.90, 68.86 (C3), 69.86, 68.86, 68.76 (C2), 69.40, 69.17, 67.72 (C5), 62.75, 62.39, 61.33 (C6), 20.98–20.21 (–CH$_3$); MALDI-FTMS (*m*/*z*): calcd. for [M+Na]$^+$: 2141.6, found: 2141.6, calcd. for [M+K]$^+$: 2157.6, found: 2157.5.

*2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl-[(1 → 4)-2,3,6-tri-O-acetyl-α-D-glucopyranosyl]$_5$-(1 → 4)-2,3,6-tri-O-acetyl-α, β-D-glucopyranose (**5**):* Yield 37%; white solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.45–5.35, 5.30–5.15 (m, 7H, C3-H), 5.25–5.10 (m, 6H, C1$^{2-7}$-H), 5.13–5.08 (m, 1H, C1^1-H), 5.05–4.55 (m, 7H, C5-H), 4.38–4.10, 4.12, 4.00 (m, 14H, C6-H, C6-H′), 4.12–3.90 (m, 7H, C2-H), 4.00–3.82 (m, 7H, C4-H), 2.08–1.91 (m, 66H, –CH$_3$); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 170.10–169.14 (–CO–), 95.54 (C1$^{2-7}$), 88.00 (C1^1), 74.21, 74.03 (C4), 71.35, 70.87, 68.65 (C3), 71.30, 69.82, 69.41, 68.00 (C5), 68.88, 68.00 (C2), 62.77, 61.35 (C6), 20.57–20.25 (–CH$_3$); MALDI-FTMS (*m*/*z*): calcd. for [M+Na]$^+$: 2099.6, found: 2099.6, calcd. for [M+K]$^+$: 2115.6, found: 2115.6.

*2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl-[(1 → 4)-2,3,6-tri-O-acetyl-α-D-glucopyranosyl]$_5$-(1 → 4)-2,3,6-tri-O-acetyl-α, β-D-glucopyranose tetradecyl carbamate (**1**):* Yield 85%; white solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.79–5.77 (m, 1H, C1^1-H), 5.48–5.13 (m, 7H, C3-H), 5.30–5.10 (m, 6H, C1$^{2-7}$-H), 5.04–4.90, 4.90–4.67 (m, 7H, C5-H), 4.40–4.10, 4.07–3.97 (m, 14H, C6-H, C6-H′), 4.13–3.90 (m, 7H, C2-H), 4.15–3.87 (m, 7H, C4-H), 3.04–2.87, 1.24 (m, 26H, –CH$_2$–), 2.10–1.94 (m, 66H, Ac-CH$_3$), 0.87–0.84 (t, *J* = 7 Hz, 3H, R-CH$_3$); ^{13}C NMR (100 MHz, DMSO-***d*$_6$**): δ 170.07–169.18 (–CO–), 153.62 (–CONH–), 95.56 (C1$^{2-7}$), 91.00 (C1^1), 74.02 (C4), 70.90, 69.43 (C3), 69.89, 68.02 (C5), 69.43, 68.68 (C2), 62.80, 61.00 (C6), 40.12, 31.28–22.09 (–CH$_2$–), 20.53–20.26 (Ac-CH$_3$), 13.93 (R-CH$_3$); MALDI-FTMS (*m*/*z*): calcd. for [M+Na]$^+$: 2338.8, found: 2338.8, calcd. for [M+K]$^+$: 2354.8, found: 2354.8.

3. Results and discussion

Chemical shift changes of the oligosaccharides **3**, **4**, **5**, **1** could be observed clearly in the HSQC NMR spectra (Fig. S1, in Supporting information). For per-acetylated β-cyclodextrin **3**, the seven acetylated monosaccharide units have exactly identical structures whose chemical shifts in the same glucose ring are all the same in ^{1}H NMR and ^{13}C NMR. Since the two protons in C6 (C6-H, C6-H′) are not chemically equivalent, their chemical shifts are 4.42–4.39 and 4.26–4.22, respectively (Fig. S1a). When the cyclic structure of compound **3** was transformed into an open chain oligo-glucose structure (maltoheptaose **4**), the chemical environment of the seven acetylated monosaccharide units changed accordingly: The original identical proton and ^{13}C chemical shifts turned into chemical shift clusters around the original positions. The largest deviation of proton and ^{13}C chemical shift were generated in C1^1-H and C1^1, which moved from 5.06 and 96.57 to 6.10 and 88.12 respectively. These signals were far from the proton and ^{13}C chemical shifts of C1$^{2-7}$-H and C1$^{2-7}$, which were at 5.28–5.15 and 95.84, 95.53 ppm, respectively (Fig. S1b). The possible reason for proton chemical shift alterations was the change of the shielding effect of the carbonyl group on the C1^1 anomeric hydroxy group. The C1^1-H was in the deshielding zone of the carbonyl group and when the acetyl group on the C1^1 anomeric hydroxyl was selectively removed (compound **5**), the chemical shift of C1^1-H was moved upfield from 6.10 to 5.13–5.08 ppm (Fig. S1c). When the C1^1 anomeric hydroxyl was converted into a carbamate, the



Scheme 1. Synthesis of sept-D-glucopyranose tetradecyl carbamate **1**. Reagents and conditions: (a) Ac_2O, pyridine, 50 °C, 10 h, 83%; (b) 70% aq. $HClO_4$, Ac_2O, 0 °C, 20 h, then 23 °C, 2 h, 12%; (c) EDA, acetic acid, dry THF, 30 °C, 39 h, 70% and (d) tetradecyl isocyanate, TEA, toluene, 80 °C, 6 h, 85%.

new carbonyl group in the carbamate exerts its deshielding effect on $C1^1$-H, whose chemical shift moved downfield from 5.13–5.08 to 5.79–5.77 ppm. In contrast, the chemical shifts of its counterpart $C1^{2-7}$-H, stayed at 5.30–5.10 ppm (Fig. S1d). ^{13}C chemical shifts of $C1^1$ in compounds **4**, **5** and **1**, were at 88.12, 88.00 and 91.00 ppm respectively, which were not remarkably altered, but all far from the corresponding ^{13}C chemical shifts of their $C1^{2-7}$ counterparts in compounds **4**, **5**, and **1**. They were of course also differed from the ^{13}C chemical shift in compound **3**.

4. Conclusion

In conclusion, oligosaccharide donor acetylated sept-D-glucopyranose carbamate **1** was synthesized and thorough discussion of the characterization data of the obtained complex molecule supports the conclusion. The procedure introduced here might be helpful for the oligosaccharide involved processes.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.10.025.

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