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Note

Acetylated methyl glucopyranuronate trichloroacetimidate as a glycosyl donor for efficient synthesis of disaccharides

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Dedicated to Professor H. El Khadem on the occasion of his 80th birthday

Abstract

Allyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl uronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**4**) and benzyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl uronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**5**) have been efficiently synthesized by coupling allyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**2**) or benzyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**3**) with methyl (2,3,4-tri-*O*-acetyl-1-*O*-trichloroacetimidoyl)-α-D-glucopyranuronate (**1**), respectively, using trimethylsilyl triflate as promoter.

Keywords: Uronic acid; Glycosylation; Trichloroacetimidate; Disaccharides

Glycosides of D-glucuronic acid are widely known as components of oligo- and poly-saccharides of biological significance.[1–4] We report here the synthesis of the selectively protected disaccharides glycosides **4** and **5**, which are required for further conversion into glycosyl donors for block synthesis of more extended oligosaccharides. Selection of the target disaccharides **4** and **5** as proposed to use allyl or benzyl β-glycosides, access permitted to compounds with a free 1-OH group, the propyl glycoside, and various spacered derivatives, by functionalizing the aglycon. Thus, the allyl group in compound **4** is useful as an affinity ligand,[5,6] and the benzyl group in compound **5** is useful for its ease of selective deprotection, and it can serve as a lipid tail.

Glycosylation of the acceptors, allyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**2**)[7] and benzyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**3**),[8] with methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate bromide[9] under the Helferich reaction conditions was unsuccessful, because the 1,2-orthoester was formed as a major primary product.[10,11]

In choosing a strategy for synthesizing the target disaccharides, the key question was the selection of the glucosyluronic donor. We chose methyl (2,3,4-tri-*O*-acetyl-1-*O*-trichloroacetimidoyl)-α-D-glucopyranuronate (**1**),[12] which was synthesized by selective O-deacetylation of methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glycopyranuronate[13] using hydrazinium acetate according to the procedure of Dullenkopf and co-workers[14] to give methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate, followed by treatment with trichloroacetonitrile and 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) to form the crystalline imidate **1** in good yield.

As shown in Scheme 1, the coupling of compound **1** with **2**, in the presence of trimethylsilyl triflate as the glycosyl promoter and molecular sieves 4 Å in dichloromethane for 2 h at −30 °C, gave the desired disaccharide glycoside **4** in moderate yield, after separation from some accompanying transesterification[15] product of the acceptor, namely allyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**6**).[16] The ^{1}H NMR spectrum of the resulting crystalline disaccharide glycoside **4** showed two doublets for β-anomeric protons at δ 5.19 and 4.60 ppm, $J_{1,2}$ 8.4 and 8.0 Hz for H-1 and

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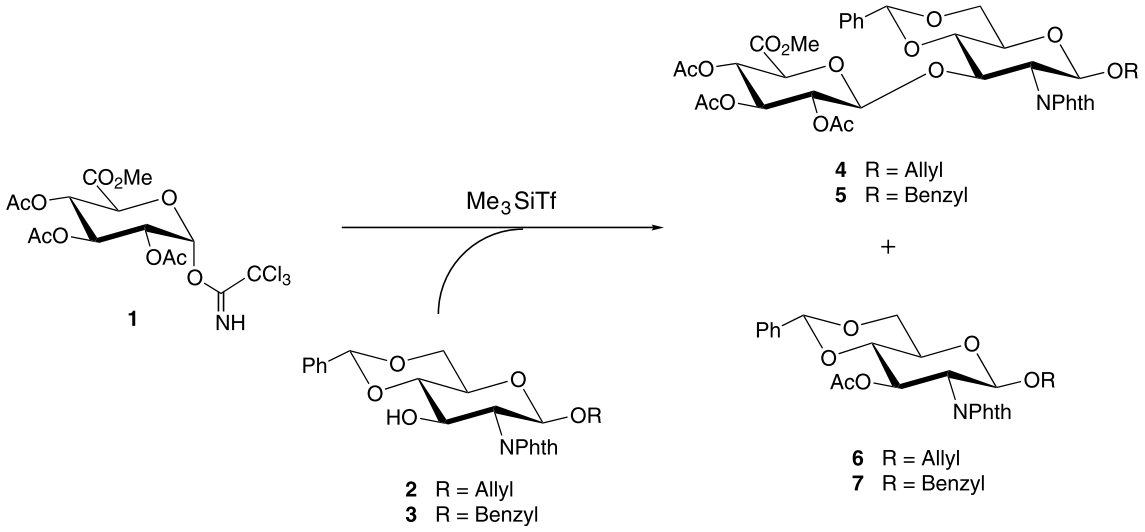

Scheme 1.

H-1′, respectively, but no signals for α-anomeric protons were visible. Also observed were signals for three acetyl groups, and the expected ratios of aromatic protons to acetyl methyl protons. The ^{13}C NMR spectrum included lines for two β-anomeric carbons at δ 97.89 and 100.04 ppm for C-1 and C-1′, respectively, and no signals attributable to α-anomeric carbon atoms were found.

Similarly, coupling of compound **1** to **3** by the standard procedure used for the allyl analogue afforded the crystalline disaccharide glycoside **5** in good yield, after separation from some accompanying transesterification product of the acceptor, namely benzyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**7**), whose ^1H NMR spectrum showed a doublet of doublets at δ 5.88 ppm (having spacings 10.0, 9.2 Hz) for H-3. The formation of the coupling product as the disaccharide glycoside **5** was supported by its ^1H NMR spectrum, which showed two doublets for β-anomeric protons at δ 5.14 and 4.57 ppm, $J_{1,2}$ 8.0 and 7.6 Hz for H-1 and H-1′, respectively, and the ^{13}C NMR spectrum included lines for two β-anomeric carbons at δ 97.77 and 100.07 ppm for C-1 and C-1′, respectively.

1. Experimental

1.1. General methods

Melting points (mp) were measured with a gallenkamp melting point apparatus and are uncorrected. ^1H NMR spectra were recorded at Sugen, Inc. with a Varian Mercury 400 MHz spectrometer at ambient temperature, and ^{13}C NMR spectra with a Varian Mercury 400 MHz instrument operating at 100.60 MHz. Chemical shifts are referenced to Me_4Si as the internal standard. COSY spectra were used to trace connectivity. Assignments were based on homo- and hetero-nuclear correlation using the supplier's software. Mass spectra were obtained on a Finnigan LCQ-Deca instrument at Sugen, Inc., USA. Separations were accomplished by open-column chromatography on silica gel 60 (70–230 mesh, Merck). Thin layer chromatography (TLC) was performed on silica gel plates (250 μm, Merck). Elemental analyses were performed at Galbraith Laboratories, Inc., Knoxville, TN 37821, USA.

1.2. Methyl (2,3,4-tri-*O*-acetyl-1-*O*-trichloroacetimidoyl)-α-D-glucopyranuronate (1)

The title compound **1** was prepared from methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate, as described before, and then purified by passing through a flash chromatography of silica gel using 3:97 acetone–$CHCl_3$, and crystallized from diethyl ether–petroleum ether to give 4.75 g, (83%), mp 102–104 °C, lit.[14] 106–107 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1 H, D_2O-exchangeable N*H*); 6.64 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1α); 5.63 (t, 1 H, $J_{2,3}$ 9.8 Hz, $J_{3,4}$ 9.2 Hz, H-3); 5.27 (t, 1 H, $J_{3,4}$ 9.8 Hz, $J_{4,5}$ 10.2 Hz, H-4); 5.15 (dd, 1 H, $J_{1,2}$ 3.9 Hz, $J_{2,3}$ 10.1 Hz, H-2); 4.50 (d, 1 H, $J_{4,5}$ 10.6 Hz, H-5); 3.75 (s, 3 H, OCH_3); 2.05, 2.04, 2.03 (3 s, 9 H, 3 × CH_3CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.88, 169.83, 169.58 (3 C, 3 × $OCOCH_3$); 167.24 (C-6); 160.65 (*C*=N); 92.84 (C-1); 70.75 (C-5); 69.75 (C-2); 69.38 (C-4); 69.22 (C-3); 53.44 (OCH_3); 21.13, 20.95, 20.86 (3 C, 3 × $OCOCH_3$).

1.3. General procedure for coupling

For β-glycosidic couplings by the trichloroacetimidate method, the glycosyl acceptor was placed in a dry round-bottomed flask, along with a magnetic stirring

bar, glycosyl trichloroacetimidate, and powdered 4 Å activated molecular sieves. After these additions, the reactor was closed at the neck (rubber septum) and dried by keeping the system under vacuum for 3–4 h. Next, dry CH_2Cl_2 is injected with a dry syringe and the mixture was stirred for 15 min at room temperature (rt) and then cooled to −30 °C. Trimethylsilyl triflate was added and the mixture was stirred below −30 °C for 1 h and then allowed to warm up gradually to rt. The mixture was kept overnight at rt with stirring, at which time TLC (3:7:10 EtOAc–petroleum ether–toluene) showed disappearance of the starting material and two new spots (a high mobility spot; above the donor and low mobility spot; below the donor and above the acceptor). A few drops of Et_3N was added to quench the reaction, and the solid was filtered off over a bed of Celite and washed with CH_2Cl_2. The combined filtrate and washings were evaporated to dryness under diminished pressure. The resulting residue was subjected to column chromatography on silica gel using 1:3:10 EtOAc–petroleum ether–toluene and then 3:7:10 as the eluent afforded a fast-moving fraction as a result of transesterification of the acceptor. In the present work, the proportions of reagents, with respect to glycosyl acceptor were; trichloroacetimidate donor, 1.5 mol; trimethylsilyl triflate, 0.49 mol; CH_2Cl_2, 12 mL/g and 4 Å molecular sieves 2 g/g.

1.3.1. Allyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (4). Compound **2** was prepared as described by El-Sokkary and co-workers;[7] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.84, 7.76–7.72 (2 m, 4 H, C_6H_4–); 7.48–7.44, 7.38–7.34 (2 m, 5 H, Ph–*H*); 5.75–5.65 (m, 1 H, –C*H*=); 5.55 (s, 1 H, Ph–C*H*); 5.48 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 5.17–5.05 (4 q, 2 H, =CH_2); 4.63 (dd, 1 H, *J* 8.8, 9.2 Hz, H-3); 4.42 (q, 1 H, *J* 4.8, 10.8 Hz, H-6$_a$); 4.36–4.26 (m, 2 H, H-6$_b$ and –OC*H*H–CH=); 4.08–4.02 (m, 1 H, –OCH*H*–CH=); 3.86 (t, 1 H, *J* 10.0, 10.0 Hz, H-4); 3.79 (t, 1 H, $J_{2,3}$ 9.6 Hz, $J_{1,2}$ 8.4 Hz, H-2); 3.77–3.70 (m, 1 H, H-5). A mixture of **2** (250 mg, 0.57 mmol) and imidate **1** (410 mg, 0.86 mmol) were subjected to the procedure for β-glycosidic coupling just described. The resulting residue was subjected to column chromatography of silica gel using 1:3:10 EtOAc–petroleum ether–toluene, then 3:7:10 as the eluent afforded a fast-moving fraction; allyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**6**);[16] as a result of transesterification of the acceptor, which was isolated and crystallized from EtOAc–petroleum ether to give 54 mg of **4**, mp 156 °C. The ^{1}H NMR (400 MHz, $CDCl_3$) was similar to that of **2** excepts for the downfield shift of H-3 to δ 5.89 (dd, 1 H, *J* 8.8, 9.2 Hz), loss of the OH signal and appearance of OCOCH_3 at δ 1.90 (s, 3 H).

The second fraction from the chromatography compound **4** was isolated by evaporation of the solvent under diminished pressure and the residual syrup crystallized from EtOAc–petroleum ether giving **4** (232 mg; 54%); mp 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.84, 7.78–7.74 (2 m, 4 H, C_6H_4–); 7.46–7.42, 7.40–7.36 (2 m, 5 H, Ph–*H*); 5.70–5.59 (m, 1 H, –C*H*=); 5.52 (s, 1 H, Ph–C*H*); 5.19 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1β); 5.14–5.04 (4 q, 2 H, =CH_2); 5.00 (t, 1 H, $J_{4',5'}$ 9.6 Hz, $J_{3',4'}$ 10.0 Hz, H-4′); 4.99 (t, 1 H, $J_{3',4'}$ 10.8 Hz, $J_{2',3'}$ 9.2 Hz, H-3′); 4.79 (t, 1 H, $J_{2',3'}$ 8.4 Hz, $J_{1',2'}$ 8.0 Hz, H-2′); 4.74 (dd, 1 H, *J* 9.2, 8.4 Hz, H-3); 4.60 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1′β); 4.42–4.33 (m, 2 H, H-2 and H-6$_b$); 4.24 and 4.01 (2 q, 2 H, –OCH_2–CH=); 3.91–3.83 (m, 2 H, H-4 and H-6$_a$); 3.67–3.61 (m, 1 H, H-5); 3.57 (s, 3 H, COOCH_3); 3.55 (d, 1 H, $J_{4',5'}$ 9.6 Hz, H-5′); and 1.92, 1.87, 1.46 (3 s, 9 H, 3 × OCOCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.13, 169.38, 168.71 (3 C, 3 × O*C*OCH$_3$); 166.87 (*C*OOCH$_3$); 137.00–126.22 (aromatic carbons and –*C*H=); 117.94 (=*C*H$_2$); 101.89 (Ph–*C*H–); 100.04 (C-1′); 97.89 (C-1); 81.30 (C-4); 76.14 (C-3); 72.49 (C-3′); 72.20 (C-5′); 71.65 (C-2′); 70.31–96.07 (3 C, C-6$_{a,b}$ and C-4′); 66.63 (C-5); 55.43 (C-2); 53.00 (COO*C*H$_3$); 20.93, 20.89, 20.30 (3 C, 3 × OCO*C*H$_3$). MS (m/z) = 753.6 (M^+), (m/z) = 771.9 $(M+H_2O)^+$. Anal. Calcd for $C_{37}H_{39}NO_{16}\cdot 1.5\ H_2O$: C, 56.92; H, 5.42; N, 1.79. Found: C, 56.69; H, 5.17; N, 1.75.

1.3.2. Benzyl (methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl uronate)-(1→3)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (5). Compound **3** was prepared as described by Lemieux and co-workers;[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.71 (m, 4 H, C_6H_4–); 7.48–7.44, 7.38–7.34 (2 m, 5 H, Ph–*H*); 7.10–7.00 (m, 5 H, C_6H_5–CH_2); 5.55 (s, 1 H, Ph–C*H*); 5.44 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1); 4.85–4.53 (AB, 2 H, J_{AB} 12.0 Hz, Ph–CH_2); 4.66–4.57 (m, 1 H, H-3); 4.44 (q, 1 H, *J* 4.4, 10.4 Hz, H-6$_a$); 4.34 (dd, 1 H, $J_{1,2}$ 8.4 Hz, $J_{2,3}$ 10.4 Hz, H-2); 3.92–3.72 (m, 3 H, H-4, H-5 and H-6$_b$); 2.78 (bs, 1 H, O*H*-3). A mixture of **3** (250 mg, 0.51 mmol), imidate **1** (370 mg, 0.77 mmol) was subjected to the procedure for β-glycosidic coupling. The resulting residue was subjected to column chromatography on silica gel using 1:3:10 EtOAc–petroleum ether–toluene, then 3:7:10 as eluent afforded a fast-moving fraction, benzyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**7**); as a result of transesterification of the acceptor, which was isolated and crystallized from EtOAc–petroleum ether to yield 65 mg, mp 172 °C. The ^{1}H NMR (400 MHz, $CDCl_3$) was similar to that of **3** except for the downfield shift of H-3 to δ 5.88 (dd, 1 H, *J* 10.0, 9.2 Hz), loss of the OH signal, and appearance of OCOCH_3 at δ 1.89 (s, 3 H). MS (m/z) = 529.2 (M^+).

The second fraction from the chromatography was compound **5**, obtained by evaporation of the solvent and crystallization of the syrup from EtOAc–petroleum ether yield **5** 243 mg (59%); mp 98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.72 (m, 4 H, C_6H_4–); 7.45–7.36 (m, 5 H, Ph–*H*); 7.10–6.98 (m, 5 H, C_6H_5–CH_2); 5.53 (s, 1 H, Ph–C*H*); 5.14 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1β); 5.02 (t, 1 H, $J_{4',5'}$ 9.2 Hz, $J_{3',4'}$ 9.6 Hz, H-4′); 4.97 (t, 1 H, $J_{3',4'}$ 9.6 Hz, $J_{2',3'}$ 8.8 Hz, H-3′); 4.82–4.48 (AB, 2 H, J_{AB} 12.0 Hz, Ph–CH_2); 4.78 (t, 1 H, $J_{2',3'}$ 8.8 Hz, $J_{1',2'}$ 8.4 Hz, H-2′); 4.71 (dd, 1 H, *J* 8.8 Hz, *J* 8.4 Hz, H-3); 4.57 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1′β); 4.39 (q, 1 H, *J* 4.8, 10.4 Hz, H-6_b); 4.35 (dd, 1 H, $J_{1,2}$ 8.4 Hz, $J_{2,3}$ 8.8 Hz, H-2); 3.92–3.84 (m, 2 H, H-4 and H-6_a); 3.67–3.60 (m, 1 H, H-5); 3.66 (s, 3 H, COOCH_3); 3.54 (d, 1 H, $J_{4',5'}$ 9.6 Hz, H-5′); and 1.91, 1.86, 1.43 (3 s, 9 H, 3 × OCOCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.13, 169.38, 168.70 (3 C, 3 × O*C*OCH$_3$); 166.86 (*C*OOCH$_3$); 137.24, 136.86 (2 C, 2 × *C*=O of phthalimido group); 129.43–126.22 (aromatic carbons), 101.86 (C_6H_5–*C*H–); 100.07 (C-1′); 97.77 (C-1); 81.20 (C-4); 76.08 (C-3); 72.46 (C-5′); 72.20 (C-2′); 71.62, 71.43 (2 C, C-3′ and C-4′); 69.50, 69.06 (2 C, C-$6_{a,b}$); 66.60 (C-5); 55.48 (C-2); 53.00 (COO*C*H$_3$); 20.92, 20.89, 20.27 (3 C, 3 × OCO*C*H$_3$). MS $(m/z) = 803.8$ (M^+), $(m/z) = 821.9$ $(M+H_2O)^+$. Anal. Calcd for $C_{41}H_{41}NO_{16}\cdot$ 1.5 H_2O: C, 60.59; H, 5.21; N, 1.72. Found: C, 60.58; H, 5.60; N, 1.58.

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