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Note

A practical synthesis of methyl 4-*O*-methyl-α-D-glucopyranosiduronic acid

Kaichang Li, Richard F. Helm *

Department of Wood Science and Forest Products, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061-0323, USA

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The principal hemicellulose of temperate zone hardwoods is *O*-acetyl-(4-*O*-methylglucurono)xylan, constituting 15–30% of the weight of these woods [1]. The (1 → 4)-β-D-xylopyranosyl backbone carries occasional substitutions at the 2-position by 4-*O*-methyl-α-D-glucopyranosiduronic acid, as well as randomly distributed acetyl groups. The overall structure of xylan in temperate zone hardwoods is quite conserved [2]. This implies that the chemical characteristics of this hemicellulose play an integral role in hardwood cell-wall composite structure. As part of our efforts to more fully understand woody cell-wall structure and function, a simple, high yielding route to alkyl 4-*O*-methyl-α-D-glucopyranosiduronic acids from D-glucose was desired.

Several methods have been developed to synthesize methyl 4-*O*-methyl-α-D-glucopyranosiduronic acid and methyl (methyl 4-*O*-methyl-α-D-glucopyranosid)uronate, [3–6] and a chromatographic/chemical method has been used to isolate 4-*O*-methyl-D-glucuronic acid from wood [7]. Since all reported methods involved several steps, the exploration of alternative strategies was deemed worthwhile. We now report a four-step synthesis of methyl 4-*O*-methyl-α-D-glucopyranosiduronic acid (**7**) from methyl α-D-glucopyranoside (**1**).

* Corresponding author.

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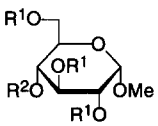
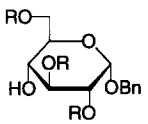
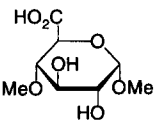
1. Results and discussion

Methyl α-D-glucopyranoside (**1**) was activated by bis(tributyltin) oxide and subsequently tribenzoylated to give methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside. Slight modifications of the original procedure [8] have improved the yield of **2** from 63 to 90% (see Experimental section). Furthermore, benzyl α-D-glucopyranoside (**5**) was also tribenzoylated to afford benzyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (**6**) in 83% yield. Compound (**6**) is an excellent precursor for the synthesis of compounds in which the anomeric protecting group needs to be easily removed.







	R^1	R^2
1	H	H
2	Bz	H
3	Bz	Me
4	H	Me

5 R = H
6 R = Bz

7

Compound (**2**) was methylated with methyl triflate in dichloromethane with 2,6-di-*tert*-butyl-4-methylpyridine [9] to yield methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methyl-α-D-glucopyranoside (**3**) (92% yield). This procedure is only suitable for small-scale reactions (for example, ^{13}C-labeled compounds) since it requires a large excess of 2,6-di-*tert*-butyl-4-methylpyridine. Large-scale methylation reactions were performed with iodomethane and silver oxide in DMF, which afford **3** in 80% yield [10,11]. Subsequent debenzoylation of **3** in methanol with catalytic amount of sodium methoxide quantitatively gave **4**.

The selective oxidation of **4** to **7** was achieved after investigation into several oxidation procedures. It has recently been reported that methyl α-D-glucopyranoside can be oxidized with Pt/C, O_2 to give sodium(methyl α-D-glucopyranosid)uronate in very high yield [12]. However, in our hands, the oxidation of **4** with Pt/C, O_2 gave **7** in only about 50% yield. It should be noted that the conversion of **4** to **7** with Pt/C, O_2 has previously been reported to be ineffective [6]. This suggests that the 4-*O*-methyl group changes the reactivity of methyl α-D-glucopyranoside towards oxidation of the primary hydroxyl group. The oxidation of **4** with nitrogen dioxide [3] also gave a low yield of **7**.

Our attention was then turned to reports that TEMPO-catalyzed (TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) oxidations are very effective for selective oxidation of the hydroxyl groups of carbohydrate [13,14]. The reaction of **4** with TEMPO, sodium bromide, and sodium hypochlorite in water at pH 10–11 quickly produced **7** in 90% yield [14].

Thus, in conclusion, methyl 4-*O*-methyl-α-D-glucopyranosiduronic acid can conveniently be prepared from **1** in four steps (74% overall yield). The use of benzyl α-D-glucopyranoside (**5**) allows entry into the 4-*O*-alkyl-D-glucopyranoses and D-gluco-

ronic acid, and the oxidation methodology should also be suitable for the synthesis of glucosyluronic containing oligosaccharides.

2. Experimental

General.—Melting points were uncorrected and optical rotations were obtained at ambient temperatures. Evaporations were performed under diminished pressure at temperatures not exceeding 42°C (unless otherwise stated). All reactions were performed under an atmosphere of dry nitrogen. NMR spectra were recorded on a 400 MHz instrument operated at 27°C. Chemical shifts (ppm) are relative to the central solvent peak of acetone-d_6 (^{13}C, 29.8 ppm ^{1}H, 2.04 ppm). Assignments are based on standard one-(^{1}H, ^{13}C, DEPT) and two-dimensional (homo- and hetero-nuclear) NMR experiments. Thin-layer chromatography was performed with Alugram Sil-G/UV_{254} plates (Macherey-Nagel) with visualization either with UV light or by charring (5% H_2SO_4 in 95% EtOH). Column chromatography was with Silica Gel 60 (230–400 mesh, Whatman) using a standard flash chromatography apparatus (Ace Glass).

*Methyl 2,3,6-tri-*O*-benzoyl-α-*D*-glucopyranoside* (**2**).—A mixture of methyl α-D-glucopyranoside (**1**) (1.00 g, 5.15 mmol), bis(tributylin) oxide (4.61 g, 7.73 mmol) and toluene (50 mL) was placed in an oil-bath (140°C) and refluxed overnight with a Dean–Stark trap (side arm prefilled with toluene). Subsequently, the side-arm was emptied and an additional amount of toluene was distilled over (~ 25 mL). The mixture was then cooled under nitrogen atmosphere to about 22°C, and a solution of benzoyl chloride (3.62 g, 25.75 mmol) in toluene (5mL) was added dropwise with stirring during 5 min. The reaction was continued for 5 h at 20–25°C, at which time the mixture was concentrated at 50°C. Purification by silica gel chromatography (toluene, 200 mL then 10:1 toluene–EtOAc) gave methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (**2**) (2.35 g, 4.64 mmol, 90.1%). Crystals from ethyl ether–hexane; mp 129–130°C, $[\alpha]_D$ + 147.8° (*c* 0.50, $CHCl_3$); lit. [8] mp 127–129°C, $[\alpha]_D$ + 149.4° (*c* 0.49, $CHCl_3$). NMR (acetone-d_6): δ_H (consistent with reported data [7]); δ_C: 55.44 (1-OCH_3), 64.45 (C-6), 69.57 (C-4), 70.82 (C-5), 73.02 (C-2), 74.12 (C-3), 97.85 (C-1), 166.19, 166.48, 166.62 (C = O)

*Benzyl 2,3,6-tri-*O*-benzoyl-α-*D*-glucopyranoside* (**6**).—Compound **5** was tribenzoylated, as described for methyl α-D-glucopyranoside (**1**), to give **6** in 83% yield which could be crystallized from ethyl ether–hexane; mp 100–101°C, $[\alpha]_D$ + 144.1° (*c* 0.50, $CHCl_3$). NMR (acetone-d_6): δ_H 4.21 (t, 1 H, $J_{4,5} = J_{3,4}$ 9.6 Hz, H-4), 4.35 (m, 1 H, H-5), 4.66 (d, 1 H, J_{gem} 12.4 Hz, CH_2Ph), 4.68 (dd, 1 H, $J_{5,6b}$ 5.3, $J_{6a,6b}$ 11.9 Hz, H-6b), 4.77 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 11.9 Hz, H-6a), 4.91 (d, 1 H, J_{gem} 12.2 Hz, CH_2Ph), 5.28 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.2 Hz, H-2), 5.39 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 6.00 (dd, 1 H, $J_{3,4}$ 9.2, $J_{2,3}$ 10.2 Hz, H-3); δ_C: 64.36 (Bn), 69.51 (C-4), 69.99 (C-6), 71.20 (C-5), 72.89 (C-2), 74.12 (C-3), 96.08 (C-1), 166.11, 166.43, 166.61 (C=O). Anal. Calcd for $C_{34}H_{30}O_9$: C, 70.09; H, 5.19. Found: C, 69.97; H, 5.26.

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methyl-α-*D*-glucopyranoside* (**3**).—Compound **3** was prepared by two different routes. For small-scale reactions, methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (**2**) was methylated with methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 [9] for 3 days, which gave **3** as a foam (92% yield).

Large-scale reactions were based on the Kuhn methylation procedure [10,11]. Silver oxide (7.73 g, 33.37 mmol) was added to a solution of **2** (3.38 g, 6.67 mmol) and MeI (4.74 g, 33.37 mmol) in DMF (25 mL). The mixture was stirred in the dark. When TLC (19:1 $CHCl_3$–EtOAc) indicated that **2** had almost disappeared, the reaction was diluted with $CHCl_3$. The mixture was filtered and washed with $CHCl_3$. The filtrate was washed with water four times and processed in standard fashion to afford a syrup which was purified by silica gel chromatography (19:1 $CHCl_3$–EtOAc) to give **3** (2.78 g, 80%). Compound **3** has been reported in the literature previously [15], but without physical data: $[\alpha]_D$ + 132.1° (*c* 1 1.0, $CHCl_3$). NMR (acetone-d_6): δ_H 3.45 (s, 3 H, 1-OCH_3), 3.50 (s, 3 H, 4-OCH_3), 3.90 (t, 1 H, $J_{3,4}$ 9.7 Hz, H-4), 4.13 (m, 1 H, H-5), 4.59 (dd, 1 H, $J_{5,6b}$ 5.1, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.71 (dd, 1 H, $J_{5,6a}$ 2.3, $J_{6a,6b}$ 12.1 Hz, H-6a), 5.15 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.19 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 10.2 Hz, H-2), 5.94 (dd, 1 H, $J_{3,4}$ 9.2, $J_{2,3}$ 10.2 Hz, H-3); δ_C: 55.52 (1-OCH_3), 60.66 (4-OCH_3), 64.08 (C-6), 69.66 (C-5), 73.00 (C-2), 73.54 (C-3), 78.91, (C-4), 97.72 (C-1), 166.16, 166.23, 166.52 (C=O). Anal. Calcd for $C_{29}H_{28}O_9$: C, 66.92; H, 5.42. Found: C, 66.96; H, 5.16.

*Methyl 4-*O*-methyl-α-*D*-glucopyranoside* (**4**).—The solution of compound **3** (1.00 g, 1.92 mmol), $NaOCH_3$ (30 mg) and MeOH (30 mL) was stirred at room temperature. When TLC (6:1 $CHCl_3$–MeOH) showed that the reaction was complete, the mixture was neutralized with ion-exchange resin (H^+ form), filtered, and the filtrate was concentrated to give a syrup. The syrup was dissolved in water and evaporated to a syrup, and this operation was repeated three times. The syrup was dried under vacuum to give **4** quantitatively, which could be crystallized from EtOAc; mp 95–96°C, $[\alpha]_D$ + 158° (*c* 1.21, water); lit. [16] mp 94–95°C, $[\alpha]_D$ + 165° (*c* 1.2, water); lit. [17] mp 97–98°C, $[\alpha]_D$ + 167° (*c* 1.17, water). NMR (9:1 acetone-d_6–D_2O): δ_H 3.06 (dd, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 10.0 Hz, H-4), 3.30 (s, 3 H, 1-OCH_3), 3.37 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 9.7 Hz, H-2), 3.43 (m, 1 H, H-5), 3.48 (s, 3 H, 4-OCH_3), 3.61 (dd, 1 H, $J_{5,6b}$ 4.7 $J_{6a,6b}$ 11.9 Hz, H-6b), 3.68 (t, 1 H, $J_{3,4} = J_{2,3}$ = 9.2 Hz, H-3), 3.70 (dd, 1 H, $J_{5,6a}$ 2.3, $J_{6a,6b}$ 11.9 Hz, H-6a), 4.61 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1); δ_C: 55.21 (1-OCH_3), 60.30 (4-OCH_3), 60.90 (C-6), 71.18 (C-5), 71.97 (C-2), 73.53 (C-3), 79.75 (C-4), 99.68 (C-1).

Compound **4** could also be obtained from **2** without the purification of **3**. According to the foregoing procedures Ag_2O-MeI and debenzoylation, crude **4** was obtained as a syrup which was purified with silica gel chromatography (6:1 $CHCl_3$–MeOH) to give **4** (78% yield based on **2**).

*Methyl 4-*O*-methyl-α-*D*-glucopyranosiduronic acid* (**7**).—The solution of compound **4** (1.00 g, 4.80 mmol), TEMPO (7.5 mg, 0.048 mmol), NaBr (0.25 g, 2.4 mmol) and de-ionized water (15 mL) was cooled to 0°C in an ice-water bath. Sodium hypochlorite (5% solution, 0.79 g, 10.56 mmol, 14.3 mL) was added dropwise to the mixture. The pH value was kept at 10–11 by dropwise addition of 0.5 N NaOH. TLC (6:1 $CHCl_3$–MeOH) showed that the starting material (**4**) disappeared in 30 min. After a reaction time of 60 min, MeOH (10 mL) was added to quench the reaction, and the mixture was evaporated to a solid which was extracted with MeOH. The extract was evaporated to a solid which was purified by silica gel (3:1:0.25 $CHCl_3$–MeOH–HOAc) to give methyl 4-*O*-methyl α-D-glucopyranosiduronic acid (**7**) in 90% yield; $[\alpha]_D$ + 129.3° (c 1.27, water); lit. [3] $[\alpha]_D$ + 47° (*c* 1.02, water) NMR (9:1, acetone-d_6–D_2O): δ_H 3.26 (dd, 1 H, $J_{3,4}$ 9.0, $J_{4,5}$ 9.9 Hz, H-4), 3.32 (s, 3 H, 1-OCH_3), 3.42 (s, 3 H, 4-OCH_3), 3.45 (dd, 1 H, $J_{1,2}$

3.8, $J_{2,3}$ 9.7 Hz, H-2), 3.67 (t, 1 H, $J_{3,4} = J_{2,3} = 9.3$ Hz, H-3), 3.89 (d, 1 H, $J_{4,5}$ 10.1 Hz, H-5), 4.67 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1); δ_C 55.65 (1-OCH_3), 60.35 (4-OCH_3), 70.60 (C-5), 72.15 (C-2), 73.56 (C-3), 81.83 (C-4), 100.69 (C-1), 171.89 (C-6).

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