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Note

An efficient synthesis of methyl 1,2,3,4-tetra-*O*-acetyl-β-L-idopyranuronate

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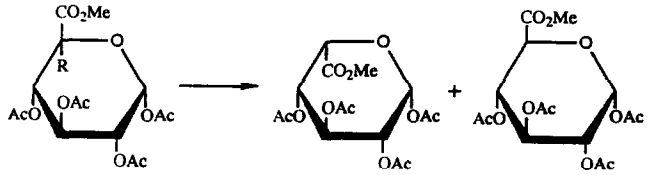
L-Iduronic acid is a constituent of heparin, dermatan sulfate, and a type-specific polysaccharide of *Clostridium perfringens*[1]. The ready availability of L-iduronic acid and its derivatives is important for the synthesis of various heparin fragments. Sinaÿ et al.[2] reported the preparation of methyl 1,2,3,4-tetra-*O*-acetyl-α-L-idopyranuronate starting from methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranuronate, which was isomerized by bromination at C-5, then reduction with tributyltin hydride. The ratio of L-*ido* to D-*gluco* product in the reduction step was 1:3, so that the yield of L-iduronic derivative was only ~ 27%. The present Note describes a highly efficient conversion of the readily available α anomer of methyl tetra-*O*-acetyl-D-glucopyranuronate[3] to the corresponding β-L-idopyranuronate. Conducting the hydride reduction at a lower temperature resulted in a higher yield of the desired product with less decomposition. Also, the choice of starting compound was the key in determining the higher yield of desired product.

Methyl 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranuronate (**1**) on treatment with *N*-bromosuccinimide[4] gave the 5-bromo derivative **2** in 65% yield. Reduction of **2** with tributyltin hydride in boiling benzene[5] (in lieu of toluene) gave a mixture of the β-L-idopyranuronate (**3**) and the starting material **1**. The ratio of L-*ido* to D-*gluco* isomers was 3:1, and the two compounds were easily separated by short column chromatography to give **3** in 67% yield.



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EXPERIMENTAL

General methods.—Optical rotations were measured at 20–25°C with a Perkin–Elmer model 241 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were determined with a Varian Gemini 300 MHz spectrometer at ambient temperature, the ^{13}C spectra being recorded at 75.50 MHz. Chemical shifts are referenced to $(CH_3)_4Si$ as the internal standard. Irradiation was with standard 110 V, 150 W bulbs. Separations were accomplished by open-column chromatography on Silica Gel 60 (70–230 mesh, Merck), with mixtures of toluene and EtOAc or hexane and EtOAc. TLC was performed on Silica Gel 60F 254 (Merck) with detection by UV light and by charring with H_2SO_4. Elemental analyses were performed by the Galbraith Laboratories Inc., (Knoxville, TN).

*Methyl 1,2,3,4-tetra-*O*-acetyl-5-*C*-bromo-α-*D*-glucopyranuronate* (**2**).—A suspension of methyl 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranuronate (**1**; 5.0 g, 13.3 mmol) and *N*-bromosuccinimide (2.8 g, 15.7 mmol) in dry CCl_4 (200 mL) was stirred at 60°C for 2 h under irradiation[4]. The mixture was cooled to room temperature and filtered, and the solvent was evaporated. Short column chromatography (9:1 toluene–EtOAc) of the residue gave amorphous compound **2** (3.92 g, 65%); $[\alpha]_D$ + 4.7° (*c* 0.7, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 89.1 (C-1), 87.1 (C-5), and 54.1 (OCH_3); ^{1}H NMR: δ 6.54 (d, 1 H, $J_{1,2}$ 4.09 Hz, H-1). Anal. Calcd for $C_{15}H_{19}BrO_{11}$ (454.01): C, 39.69; H, 4.22; Br, 17.60. Found: C, 39.89; H, 4.34; Br, 17.61.

*Methyl 1,2,3,4-tetra-*O*-acetyl-β-L-idopyranuronate* (**3**).—A mixture of **2** (7.54 g, 16.60 mmol) and tributyltin hydride (11.6 mL) in dry benzene was boiled under reflux for 1 h with stirring. The solvent was evaporated and the residue applied to a silica gel column (7:3 → 6:4 hexane–EtOAc) to give **3** (4.18 g, 67%); $[\alpha]_D$ + 12.3° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.05 (d, 1 H, $J_{1,2}$ 1.83 Hz, H-1), 3.75 (s, 3 H, CO_2CH_3), and 2.10 (4 s, 12 H, Ac). Anal. Calcd for $C_{15}H_{20}O_{11}$: C, 47.87; H, 5.35. Found: C, 48.11; H, 5.32.

The D-gluco product **1**, which can be used as starting material for repeating the reaction, was also isolated (1.2 g, ~20%); $[\alpha]_D$ + 97° (*c* 0.73, $CHCl_3$), lit.[3] $[\alpha]_D$ + 98° ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.45 (d, 1 H, $J_{1,2}$ 3.60 Hz, H-1), 3.75 (s, 3 H, CO_2CH_3), and 2.10 (4 s, 12 H, Ac).

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