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## Note

# A convenient and high-yielding synthesis of 1,2,3,4,6-penta-*O*-acetyl-β-D-[1-$^2$H]-glucopyranose

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Glucosides labelled at the anomeric center with deuterium or tritium have a number of uses ranging from their employment in kinetic isotope-effect measurements in mechanistic studies[1–3] to isotope-tracing experiments[4]. The methods available for synthesis of the necessary labelled precursor to the required glucosides are relatively low-yielding and inconvenient. They include the direct reduction of deuterium oxide solutions of D-glucono-1,5-lactone with sodium amalgam in the presence of phosphoric acid-$d_3$, followed by acetylation[1,3,5], or reduction of the tetrahydropyranyl derivative of D-glucono-1,5-lactone with sodium borodeuteride in tetrahydrofuran, acid-catalyzed hydrolysis, in deuterium oxide, of the protecting groups, and acetylation with acetic anhydride and sodium acetate. The yield for both of these approaches was ~30%.

We now describe an essentially one-flask synthesis of the crystalline title compound in 70% yield from D-gluconolactone, and a simple variation thereof to produce excellent yields of 2,3,4,6-tetra-*O*-acetyl-D-[1-$^2$H]-glucopyranose. The title compound is particularly useful, as it may be readily converted into the tetra-*O*-acetyl-D-glucosyl bromide (with hydrogen bromide in acetic acid) and this used for glycosidation reactions. It may also be used directly in condensation reactions, for example, with phosphoric acid[2,6] or with phenols[7] after isomerization to the α anomer.

Lewis acid-catalyzed acetylation of D-glucono-1,5-lactone (**1**), performed essentially according to Nelson[8] by using acetic anhydride and zinc chloride, gave a good yield of the tetraacetate (**2**) after simple workup and evaporation of the solvent. The resultant gum was dissolved in tetrahydrofuran and treated directly with sodium borodeuteride and additional acetic anhydride in the presence of deuterium oxide. After stirring for 20 h, there was detected a single product which was readily isolated and crystallized, and shown to be 1,2,3,4,6-penta-*O*-acetyl-β-D-[1-$^2$H]-glucopyranose (**3**) by comparison (melting point, t.l.c. mobility, and

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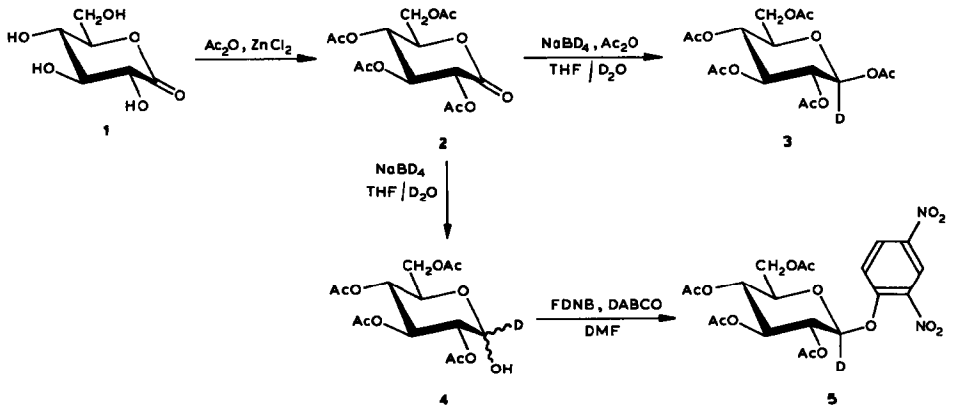


$^1$H-n.m.r. and mass spectra) with authentic penta-*O*-acetyl-β-D-glucopyranose. Both the $^1$H-n.m.r. and the mass-spectral data showed >95% incorporation of deuterium at C-1.

Thus, reduction of the lactone proceeds satisfactorily under these conditions, producing the tetraacetate which is rapidly acetylated by the excess of acetic anhydride under base (borodeuteride) catalysis. Exclusive production of the β anomer is the expected outcome on the basis of the known higher reactivity of the (equatorial) β-anomeric hydroxyl group and the relatively rapid anomerization that occurs under these conditions.

2,3,4,6-Tetra-*O*-acetyl-D-[1-$^2$H]-glucopyranose (**4**) could be readily produced by a minor modification of the aforementioned conditions, made in order to remove traces of acetic anhydride left after acetylation of the lactone. The product was then reduced with sodium borodeuteride as before, but without addition of acetic anhydride, producing a mixture of the α- and β-[1-$^2$H] tetraacetates. Direct treatment of this mixture with 1-fluoro-2,4-dinitrobenzene (FDNB) in *N,N*-dimethylformamide (DMF) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as base[9] gave, after workup, crystalline 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-[1-$^2$H]-glucopyranoside (**5**) in 66% yield from the lactone.

The procedures described thus permit the very convenient and high-yielding synthesis of a number of deuterated glycosides and glycosyl esters, and are readily adapted to synthesis of the tritiated derivatives.

## EXPERIMENTAL

*General procedures.* — Melting points were determined with a Bristoline melting-point apparatus and are uncorrected. T.l.c. separations were performed by using Kieselgel 60 F-254 (Merck) analytical plates; the spots were detected with u.v. light when possible, or by using a 10% methanolic sulfuric acid spray; the solvent system was 1:1 (v/v) ethyl acetate–petroleum ether. $^1$H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal $Me_4Si$) with a Varian XL-300

instrument. Chemical-ionization mass spectra were recorded with a KRATOS MS50 spectrometer.

*1,2,3,4,6-Penta-O-acetyl-β-D-[1-$^2$H]-glucopyranose* (**3**). — 2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone (**2**) was prepared in 92% yield as described by Nelson[8]. The product (3.57 g) was characterized by its $^1$H-n.m.r. spectrum[8].

The acetylated lactone was reduced by the method of Hosie and Sinnott[3], modified as follows. A solution of the syrup in tetrahydrofuran (30 mL) was cooled to 0°, and a cold solution of $NaBD_4$ (0.21 g, 4.81 mmol) in $D_2O$ (1.0 mL) was added dropwise with stirring, followed by dropwise addition of cold acetic anhydride (3.6 mL, 38 mmol). The mixture was stirred for 1 h at 0°, then overnight at room temperature, poured into cold, saturated, $NaHCO_3$ solution (200 mL), and stirred for 1 h, extracted with $CHCl_3$ (2 × 150 mL), and the extract washed with water (2 × 150 mL), dried ($MgSO_4$), and evaporated to a white solid. Crystallization from hot ethanol afforded the pentaacetate **3** (3.18 g, 72% from D-glucono-1,5-lactone); $R_F$ 0.52 ($H_2SO_4$ spray); m.p. 133–134° (lit.[10] m.p. 132°); $^1$H-n.m.r.: δ 5.15–5.29 (m, H-2,3,4), 4.30 (dd, H-6), 4.15 (dd, H-6′), 3.84 (m, H-5), and 2.0–2.1 (4 s, 5 C*H*$_3$CO); no peak due to H-1 at δ 5.75; *m/z* (rel. intensity) 332 {5.51, [$^2$H] ($M^+$ − OAc) = $C_{14}H_{18}DO_9$} and 331 [0.15, ($M^+$ − OAc) = $C_{14}H_{19}O_9$].

*2,3,4,6-Tetra-O-acetyl-β-D-[1-$^2$H]-glucopyranose* (**4**). — The foregoing procedure was modified as follows. A mixture of D-glucono-1,5-lactone (5.0 g, 28 mmol), $ZnCl_2$ (2.5 g, 18 mmol), and acetic anhydride (25 mL) was stirred for 1 h at room temperature, poured into cold, saturated, $NaHCO_3$ (250 mL), stirred for 1 h, extracted with $CHCl_3$ (3 × 100 mL), and the extracts combined, washed with cold water (2 × 100 mL), dried ($MgSO_4$), and evaporated to a colorless syrup. The syrup was dissolved in tetrahydrofuran (60 mL), and cooled to 0°. A cold solution of $NaBD_4$ (0.44 g, 11 mmol) in $D_2O$ (2.1 mL) was added dropwise, with stirring, and the mixture was stirred for 2 h, the base neutralized with Dowex 50-W ($H^+$) ion-exchange resin, the suspension filtered, and the filtrate evaporated *in vacuo*. The resulting syrup was washed with methanol to remove boric acid. The product (**4**) was obtained as a colorless syrup which was a mixture of the anomers (8.01 g, 82%); $R_F$ 0.42 ($H_2SO_4$ spray). Further characterization was provided by derivatization of the syrup with 1-fluoro-2,4-dinitrobenzene by the method of van Boom *et al.*[9]. 2,4-Dinitrophenyl (DNP) 2,3,4,6-tetra-*O*-acetyl-β-D-[1-$^2$H]-glucopyranoside (**5**) was isolated as colorless needles (9.62 g, 66% from the lactone); m.p. 177–178° (lit.[9] m.p. 174–175°); $^1$H-n.m.r.: δ 8.68 (d, H-3 of DNP), 8.40 (dd, H-5 of DNP), 7.49 (d, H-6 of DNP), 5.1–5.4 (m, H-2,3,4), 4.25 (d, H-6,6′), 4.04 (m, H-5), and 2.0–2.2 (4 s, 4 C*H*$_3$CO); peaks at δ 5.1–5.4 integrated for 3 (not 4) protons[9], indicating loss of H-1.

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