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Note

A practical synthesis of 1,2,3,6-tetra-*O*-acetyl-α- and β-D-glucopyranose, and their use to prepare trisaccharides

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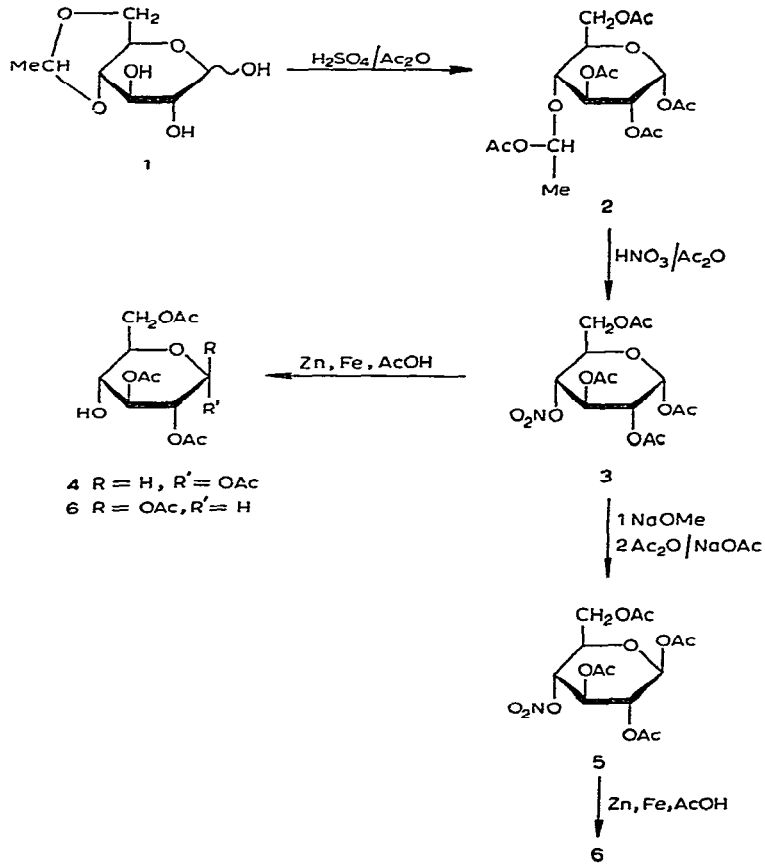
Reactions designed to give derivatives of D-glucose having a free hydroxyl group at C-4 are somewhat complicated and laborious, and often start with a methyl D-glucopyranoside or depend upon migration from O-4 to O-6 of a pyranoid ester to leave this hydroxyl group free[1–3]. We have found that a reaction scheme starting with the readily prepared 4,6-*O*-ethylidene-D-glucose[5] constitutes a simpler route. The key reaction involves replacement of the labile 4-*O*-(1-acetoxyethyl) group with the more-stable nitro group; this allows the preparation of either the crystalline 1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose (**6**), heretofore difficult to obtain, or the previously unknown α anomer (**4**) which, like most tetraacetates of α-D-glucose, was obtained only as an oil. Unlike the behavior of the corresponding acetylated methyl D-glucosides[2], acetyl migration from O-4 to O-6 occurs under alkaline conditions with both anomers during attempts to prepare higher D-glucose oligomers *via* Koenigs–Knorr reactions. Consequently, it is preferable to prepare (1→6)-linked D-gluco-oligosaccharides from the more readily prepared α anomer.

A reaction scheme similar to that employed by Bell and Synge[4] for the D-glucosides was employed for replacing the 1-acetoxyethyl group on O-4 by hydrogen to give the heretofore unreported[3] α-acetyl derivative **4**. The intermediate 4-nitrate **3** is a syrup that need not be isolated or purified prior to removal of the nitric ester group by treatment with acetic acid–zinc dust–iron filings to give **4**. Furthermore, the nitric ester group in **3** is stable to 1M sodium methoxide, and hence affords a more practical route to the difficultly obtainable β anomer **5**, accomplished by deacetylation followed by reacetylation with acetic anhydride–sodium acetate. Denitration gave the known 1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose (**6**). Unlike the α anomers **3** and **4**, the β anomers **5** and **6** are crystalline.

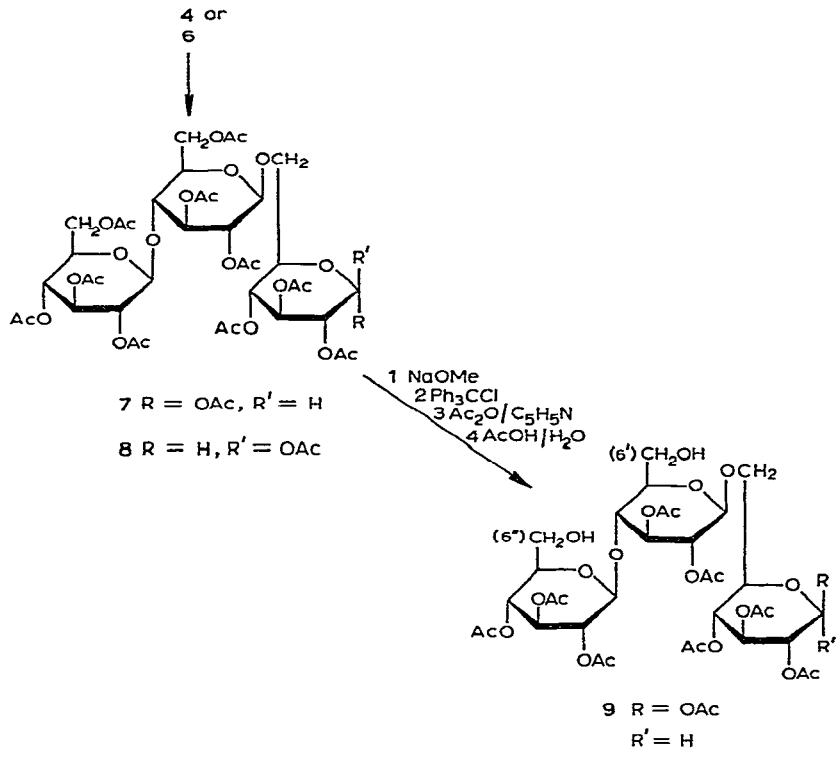
Attempts to prepare cellotriose by coupling at the 4-hydroxyl group of **4** or **6** with cellobiosyl bromide *via* the Koenigs–Knorr reaction gave products **7** and **8**, different from the α- and β-cellotriosides expected. The compounds could be interconverted by deacetylation followed by reacetylation with the appropriate acetylating reagent; hence, compounds **7** and **8** differ only in the position of the acetoxyl group at



C-1. Deacetylation of **7** and conversion of the product into the 6′,6″-di-*O*-trityl derivative, followed by reacetylation, resulted in an oil (not isolated); this was detritylated to give the crystalline nonaacetate **9** having free hydroxyl groups at C-6′ and C-6″. This compound is most probably the β anomer, as hot acetic anhydride–pyridine favors the formation of the β anomer. The elemental analysis obtained for this compound is consistent only with coupling at the 6-hydroxyl group for both compound **4** and **6**; hence, acetyl migration from O-6 to O-4 occurs under alkaline conditions. Apparently, under our conditions, either an equilibrium develops that favors subsequent reaction at the more reactive 6-hydroxyl group, or the acetyl group on O-1 is involved. The latter possibility arises from the fact that the migration apparently does not occur when O-1 is protected by a methyl group in the methyl D-glucosides[2].

EXPERIMENTAL

General. — Solutions were evaporated under diminished pressure unless otherwise indicated. Melting points were determined on either a Kofler hot-stage or a Nalge–Axelrod micro melting-point apparatus, and are corrected unless otherwise



indicated. Elemental analyses were performed by Schwartzkopf Microanalytical Laboratory. The yields reported are those obtained after at least one recrystallization of the crude products. 4,6-*O*-Ethylidene-D-glucopyranose (**1**) was prepared by the procedure of Hall and Stamm[5].

4-O-(1-Acetoxyethyl)-1,2,3,6-tetra-O-acetyl-α-D-glucopyranose (**2**). — With stirring, **1** (6.5 g) was slowly added to a mixture of acetic anhydride (50 ml) and sulfuric acid (0.5 ml). After 1 h, the solution was poured onto cracked ice (500 g). The solution was made neutral with solid sodium carbonate, and the viscous gum that was precipitated was dissolved in chloroform. The chloroform layer was washed successively with sodium hydrogen carbonate solution (1%) and water, and dried (anhydrous calcium sulfate). The product need not be isolated if further reactions are to be performed.

The product can be purified by evaporating the chloroform and precipitating the product 3 times from ether by addition of petroleum ether, to give about 7 g (90%) of a stiff gum that hardens to a glass after several weeks over phosphorus pentaoxide. It had $[\alpha]_D^{20}$ −78.1° (*c* 1.6, chloroform).

Anal. Calc. for $C_{18}H_{26}O_{12}$: C, 50.0; H, 6.0. Found: C, 50.0; H, 6.0.

1,2,3,6-Tetra-O-acetyl-4-O-nitro-α-D-glucopyranose (**3**). — The dried chloroform extract containing **2** was concentrated to ~20 ml and cooled to −5° in an ice–salt bath. A solution consisting of 90% fuming nitric acid (20 ml), chloroform (20 ml), and

phosphorus pentaoxide (1 g), at −5°, was added and the mixture was kept for 15 min at −5° and then poured onto cracked ice. The chloroform layer was separated, washed with sodium hydrogen carbonate solution (1%) and water, dried, and evaporated to a syrup. An equally good, alternative method utilized acetic anhydride (25 ml) containing fuming nitric acid (10 ml); this reagent at −5° was added to **2** (5 g) in acetic anhydride (10 ml) at −5°. After 20 min at −5°, the mixture was poured onto cracked ice, and neutralized to pH 5 with solid potassium carbonate. Chloroform was added, and the mixture treated as previously described.

1,2,3,6-Tetra-O-*acetyl*-α-D-*glucopyranose* (**4**). — The syrupy product **3** from three such nitrations was dissolved in glacial acetic (40 ml) and treated with a mixture of zinc dust (6 g) and iron filings (2.5 g) on a steam bath until the solution gave no color with diphenylamine–sulfuric acid reagent. The solution was diluted with water (40 ml) and filtered. The residue was extracted with chloroform, and the extracts were used to extract the filtrate. The chloroform layer was successively washed with sodium hydrogen carbonate (1%) and water, dried (anhydrous calcium sulfate), and evaporated. The syrupy product was three times precipitated from ethyl ether with petroleum ether, to give 10.5 g (40%) of a light-amber gum that hardened to a glass, $[\alpha]_D^{20}$ −78.3° (*c* 1.66, chloroform).

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.7. Found C, 48.3; H, 5.7.

A sample of compound **4** was converted into 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose (m.p., and mixed m.p. with authentic pentaacetate, 112–113°).

1,2,3,6-Tetra-O-*acetyl-4*-O-*nitro*-β-D-*glucopyranose* (**5**). — The syrupy product **3** (8 g) was deacetylated with 1M sodium methoxide for 24 h. Glacial acetic acid (5 ml) was added, and the mixture was concentrated. Acetic anhydride (50 ml) and sodium acetate (5 g) were added, and the mixture was heated on a steam bath for 3 h, poured onto cracked ice (500 g), and extracted with chloroform. The extract was successively washed with sodium hydrogen carbonate solution and water, evaporated, and the resulting solid recrystallized twice from anhydrous ethyl ether plus petroleum ether, to give 4 g of product having m.p. 125–127° (corr.), $[\alpha]_D^{20}$ −24.0° (*c* 2.5, chloroform).

1,2,3,6-Tetra-O-*acetyl*-β-D-*glucopyranose* (**6**). — Compound **5** (1.75 g) was denitrated by the procedure used for preparing **4**, and the solid product was recrystallized thrice from ethyl ether plus petroleum ether, to give 1.25 g (84%) of needles having m.p. 131–132°, $[\alpha]_D^{20}$ −32° (*c* 2.5, chloroform); lit.[3] m.p. 131°, $[\alpha]_D^{25}$ −33° (in chloroform).

O-β-*Cellobiosyl*-(*1*→*6*)-α-D-*glucopyranose hendecaacetate* (**7**). — To **4** (18 g, dry) were added dry chloroform (25 ml), anhydrous calcium sulfate (25 g), iodine (2 g), and silver oxide (10 g); the mixture was stirred for 1 h, and then a solution of hepta-*O*-acetyl-α-cellobiosyl bromide (15 g) in absolute chloroform (25 ml) was added dropwise during 2 h. The mixture was boiled under reflux for 2 h, chloroform (50 ml) was added, and the suspension was cooled and filtered. The solids were washed with chloroform, and the filtrate and washings were combined and evaporated to a syrup. The product was crystallized and recrystallized from 95% ethanol, to give needles (10 g) having m.p. 190–191°, $[\alpha]_D^{20}$ −17.5° (*c* 2.5, chloroform).

O-β-Cellobiosyl-(1→6)-β-D-glucopyranose hendecaacetate (**8**). — *Method A*. A mixture of **6** (0.5 g), anhydrous calcium sulfate (3.0 g), absolute chloroform (20 ml), and silver oxide (4.0 g) was stirred for 1 h; a solution of hepta-*O*-acetyl-α-cellobiosyl bromide (1 g), in absolute chloroform (10 ml), was added slowly, the mixture was boiled under reflux for 2 h, and the product was purified as for **7** to give 0.41 g of needles, m.p. 192°. Two recrystallizations from 95% ethanol afforded 0.22 g of microneedles having m.p. 195–195.5° (mixed m.p., with **8** obtained by method *B*, undepressed), $[\alpha]_D^{20}$ −30.9° (*c* 1.62, chloroform).

Anal. Calc. for $C_{40}H_{24}O_{27}$: C, 49.7; H, 5.6. Found: C, 49.7; H, 5.9.

Method B. To a solution of **7** (0.5 g) in absolute methanol (25 ml) was added 1M sodium methoxide (1 ml). The resulting solution was kept for 24 h at room temperature, glacial acetic acid (1 ml) was added, and the mixture was evaporated to a syrup. A suspension of sodium acetate trihydrate (1 g) in acetic anhydride (25 ml) was added, and the solution was heated on a steam-bath for 2 h, cooled, and poured onto cracked ice (500 g). The mixture was extracted with chloroform, and the extract washed successively with sodium hydrogen carbonate solution (1%) and water, and evaporated. The product was crystallized and recrystallized from 95% ethanol, to give 88 mg of needles (m.p. and mixed m.p. with **8** prepared by method *A*, 194–195°).

1,2,3,4,2',3',2'',3'',4''-Nona-O-acetyl-O-β-cellobiosyl-(1→6)-β-D-glucopyranose (**9**). — To compound **7** (0.5 g) was added 1M sodium methoxide in methanol (25 ml). The solution was kept for 24 h, glacial acetic acid (1 ml) was added, and the mixture was evaporated to a syrup and dried over phosphorus pentaoxide *in vacuo*. Pyridine (20 ml, dried over potassium hydroxide) and chlorotriphenylmethane (1 g) were added, and the mixture was heated on a steam-bath for 2 h. Acetic anhydride (50 ml) was added to the hot mixture, and this was heated for 0.5 h on the steam-bath, and then kept for 12 h at 25°. The ditrityl ether was isolated by pouring into water, and extracting with chloroform. The chloroform layer was dried (anhydrous calcium sulfate), and evaporated to a syrup; 4:1 (v/v) acetic acid–water (20 ml) was added, and the mixture was heated on a steam-bath for 1 h. cooled, and filtered to remove triphenylmethanol. The filtrate was poured onto cracked ice, giving crystals which were twice recrystallized from 95% ethanol, to give 110 mg (24%) of needles m.p. 166–167°.

Anal. Calc. for $C_{36}H_{50}O_{25}$: C, 49.0; H, 5.7. Found: C, 49.0; H, 5.7.

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