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NEW ROUTES TO THE SYNTHESIS OF 2,3,6-TRI-*O*-SUBSTITUTED METHYL β-D-GLUCOPYRANOSIDES. AN IMPROVED SYNTHESIS OF α-CELLOTRIOSE HENDECAACETATE

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ABSTRACT

Various preparative routes to 2,3,6-tri-*O*-substituted methyl β-D-glucopyranosides have been investigated, and an improved procedure for synthesizing methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside is recorded. Some of the compounds have been used in the synthesis of higher oligomers related to cellulose, and the synthesis of α-cellotriose hendecaacetate is reported.

INTRODUCTION

For synthesis of cellulose oligosaccharides, we have attempted to use D-glucopyranosides substituted at all hydroxyl groups except that on C-4. The preparation of a number of such substituted D-glucopyranosides had been reported, but most of the syntheses had as their primary objective the preparation of the 4-methyl ether[1–5]. We first studied use of methyl 2,3-di-*O*-benzyl-6-*O*-trityl-β-D-glucopyranoside[1] for the synthesis of methyl β-cellotrioside, but found that it does not react with hepta-*O*-acetyl-α-cellobiosyl bromide, possibly because of steric hindrance caused by the bulky trityl group.

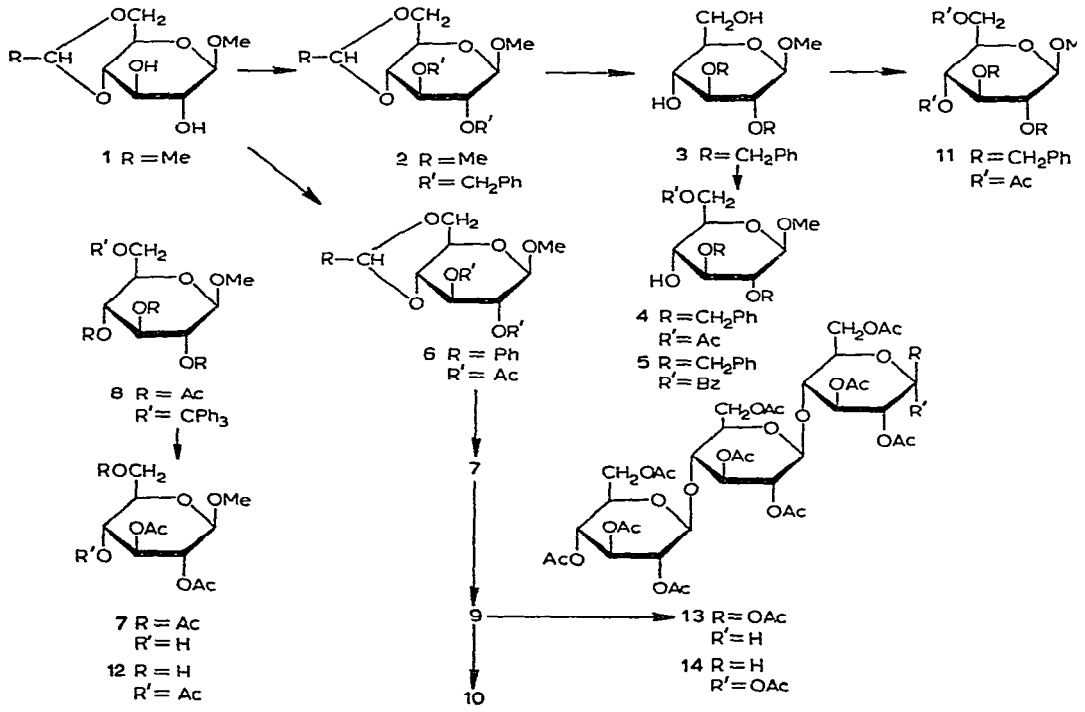
DISCUSSION

It appeared possible that a smaller group at O-6 would not hinder condensation at O-4 of the substituted D-glucopyranoside. Accordingly, we synthesized the 6-acetate (**4**) and 6-benzoate (**5**) of methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (**3**), which was prepared from methyl 2,3-di-*O*-benzyl-4,6-*O*-ethylidene-β-D-glucopyranoside (**2**) in higher overall yields than those previously reported[6]. [A by-product, namely, methyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-β-D-glucopyranoside (**11**), is formed in the reaction of **3** with acetyl chloride.] Unlike the 6-trityl ether of **3**, both **4** and **5** are crystalline compounds that are readily characterized.

Another derivative useful for the synthesis of cellulose oligosaccharides is methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (**7**). The synthesis of this compound has been reported by several workers[3–5] by routes that are quite complicated and that afford very low yields. We have found that the preparation of **7** reported by Bell and

Synge[4] suffers from the fact that, during nitration with fuming nitric acid, no more than one gram of compound at a time can be nitrated safely without greatly lessening the yield. An acceptable, unequivocal synthesis of **7** was reported by Levene and Raymond[5]; however, methyl 4,6-*O*-benzylidene-β-D-glucopyranoside[7], the principal intermediate, was obtained in low yield (30%) from methyl β-D-glucopyranoside. The 4,6 ethylidene acetal (**1**) is obtained in considerably higher yield[1,6], and we have obtained methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranoside (**6**) directly from **1** in excellent yield. Although the benzylidene group can be readily removed from **6** by mild hydrolysis with acid[5,8], we found, as have other workers[4,9], that the ethylidene group is removed from **1** with greater difficulty; also, the more vigorous treatment with acid that is required for cleaving the ethylidene group could remove the acetyl groups on O-2 and O-3. Conversion of **1** into the benzylidene acetal **6** allows the subsequent use of milder conditions for hydrolysis of the acetal group while lessening the possibility of removal of the acetyl groups.

Compound **7** was first synthesized by Helferich *et al.*[3] from methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside (**8**), which is readily prepared. Detritylation with acid gave methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside (**12**), isolated in 46% yield. Treatment of this compound with dilute alkali then gave **7**, which was characterized as its 4-*p*-toluenesulfonate. We have found that, if the acidic detritylation of **8** is performed in the presence of pyridine, acetyl migration from O-4 to O-6 occurs concomitantly; and crystalline **7** can be isolated directly. This method eliminates intermediate steps and gives an improved over-all yield of **7**.



Helferich and Bredereck[2] prepared methyl β-cellobioside by condensation of **7** with tetra-*O*-acetyl-α-D-glucopyranosyl bromide followed by deacetylation; acetyl migration did not occur during the condensation. By a similar procedure, we have condensed **7** with hepta-*O*-acetyl-α-cellobiosyl bromide, to give a methyl deca-*O*-acetylcellotrioside. Although the possibility of occurrence of acetyl migration must be borne in mind, this compound is probably methyl β-cellotrioside decaacetate (**9**); Bills and Green[10] obtained mainly β-D-linked disaccharide glycosides on condensation of methyl β-D-glucopyranoside with tetra-*O*-acetyl-α-D-glucopyranosyl bromide. Deacetylation of **9** gave a methyl cellotrioside (**10**) as a viscous gum that defied attempts at crystallization. Acetolysis of **9** by means of sulfuric acid–acetic anhydride gave α-cellotriose hendecaacetate (**13**) in excellent yield. This preparation of **13** from compound **9** gave strong supporting (but not conclusive) evidence of a β-D-(1→4)-linkage in **9**. Compound **13** could be converted into the β anomer (**14**), the identity of which was verified by a mixed melting point with authentic* **14**.

The synthesis of **9** has been described[11]; however, the physical constants for the compound had not been reported. Our first preparation of **9** gave an oil, possibly because of some deacetylation caused by the silver carbonate employed. Better results were obtained by refluxing the reaction mixture and shortening the reaction time; the properties of crystalline **9** are given.

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. Elementary analyses were performed by Schwartzkopf Microanalytical Laboratory. The yields reported are those obtained after at least one recrystallization of the crude products.

Methyl 2,3-di-O-benzyl-4,6-O-ethylidene-β-D-glucopyranoside (**2**). — With stirring, benzyl chloride (125 ml) was added to air-dried methyl 4,6-*O*-ethylidene-β-D-glucopyranoside (**1**, 43 g) (prepared by O'Meara and Shepherd's procedure[9]) in a 250-ml, 3-necked, round-bottomed flask. The temperature was raised to 90° (oil bath), and 3 pellets of potassium hydroxide were added. Potassium hydroxide (30 g) was then added portionwise during 2 h at 100–105°. After a total of 5 h at this temperature, the mixture was cooled, and xylene (100 ml) was added; the mixture was filtered, and the precipitate was washed with xylene. The filtrate and washing were combined, and evaporated to a syrup; benzyl chloride was removed at 1 torr (liquid-air trap). The residual, viscous product was crystallized from heptane, to give 63 g (82%) of needles, m.p. 90–92°. One recrystallization gave pure **2**, m.p. 92–92.5°, $[\alpha]_D^{25}$ 0.0° (*c* 1.5, chloroform).

Anal. Calc. for $C_{23}H_{28}O_6$: C, 69.0; H, 7.0. Found: C, 69.0; H, 7.0.

*The authors thank Professor Derek Horton of The Ohio State University for a sample of compound **14**.

Methyl 2,3-di-O-benzyl-β-D-glucopyranoside (**3**). — Removal of the ethylidene group from **2** was accomplished by a modification of the procedure of O'Meara and Shepherd[9]. To 12.5 g of **2** were added 96 ml of acetone, 48 ml of water, and 2.4 ml of concentrated sulfuric acid. The solution was boiled for 8 h under reflux, cooled, and poured into 500 ml of ice–water. The acid was neutralized with sodium hydrogen carbonate, the suspension was filtered, and the precipitate was air-dried (10 g). Recrystallization from benzene–petroleum ether gave 5.2 g of **3**; evaporation of the mother liquor gave 4 g of **2**. The aqueous filtrate was evaporated to give a further 1.5 g of **3**. Total yield of **3**, 6.7 g (57%); m.p. 124–124.5°; $[\alpha]_D^{25}$ −13.3° (*c* 1.5, chloroform); lit.[6] m.p. 122–123°, $[\alpha]_D^{30}$ −13.3° (chloroform).

Methyl 6-O-acetyl-2,3-di-O-benzyl-β-D-glucopyranoside (**4**). — *A. With acetic anhydride.* Compound **4** was prepared by a modification of the procedure of Levene and Raymond[5]. Purified **3** (11 g) was dissolved in dry pyridine (50 ml), with rapid, mechanical stirring, and a solution of 3.3 g of acetic anhydride (1.1 moles/mole) in 20 ml of chloroform was added dropwise during 1 h. The solution was kept overnight; water (5 ml) and chloroform (50 ml) were then added, and, after 30 min, the solution was washed successively with cold, dilute sulfuric acid (2%), sodium hydrogen carbonate solution (2%), and distilled water, dried (anhydrous calcium sulfate), and evaporated to dryness under diminished pressure. Crystallization and recrystallization from ether–petroleum ether gave 7.8 g (64%) of needles having m.p. 120–121° (depressed on admixture with **3**), $[\alpha]_D^{25}$ −25.7° (*c* 1.6, chloroform).

Anal. Calc. for $C_{23}H_{28}O_7$: C, 66.3; H, 6.8. Found: C, 66.4; H, 6.9.

When the reaction was repeated with 10 g of **3**, 6 g of a product having m.p. 125–126° was obtained; however, the optical rotation was identical with that of the compound of m.p. 120–121°; evidently, the compound is polymorphic. Also, 2.7 g of an oil was obtained; this was reprecipitated three times from ether–petroleum ether; $[\alpha]_D^{25}$ −19.2° (*c* 1.62, chloroform). It appeared to be methyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-β-D-glucopyranoside (**11**).

Anal. Calc. for $C_{25}H_{30}O_8$: C, 65.5; H, 6.6. Found: C, 65.9; H, 6.7.

B. With acetyl chloride. To a solution of compound **3** (3 g) in dry pyridine (15 ml) was added dropwise, with rapid stirring, a solution of acetyl chloride (0.9 g) in absolute chloroform (20 ml) during 2 h. After 4 h, water (5 ml) was added, and the product was purified as in *A*. Recrystallization from ether–petroleum ether gave needles (2.3 g, 69%) having m.p. 120–121°; mixture m.p. with **4** prepared by method *A*, undepressed.

Methyl 6-O-benzoyl-2,3-di-O-benzyl-β-D-glucopyranoside (**5**). — To a solution of **3** (5 g) in dry pyridine (15 ml) was added dropwise, with stirring, a solution of 2.4 g of benzoyl chloride (1.25 moles/mole) in 20 ml of absolute chloroform during 2 h. After 4 h, the product was isolated and purified as for **4**; it was crystallized and recrystallized from ether–petroleum ether, to give 5.3 g (83%) of needles having m.p. 95.0–95.5°, $[\alpha]_D^{25}$ −5.16° (*c* 1.5, chloroform).

Anal. Calc. for $C_{28}H_{30}O_7$: C, 70.3; H, 6.3. Found: C, 70.5; H, 6.6.

Methyl 2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranoside (**6**). — Methyl

2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucoside was prepared from methyl 4,6-*O*-ethylidene-β-D-glucoside by the usual methods[4,16], and the crude diacetate was recrystallized once. This compound (3 g) was added to 20 ml of redistilled benzaldehyde; anhydrous zinc chloride (3 g) was added, and the mixture was shaken for 48 h, and then poured into 20% sodium hydrogen sulfite solution. After the benzaldehyde had dissolved, the solution was extracted with choroform, and the extract was sucessively washed with sodium hydrogen sulfite solution, dilute sodium hydroxide solution, and water, dried (calcium sulfate), and evaporated to dryness. The residue was crystallized from ether, and the product was recrystallized from ethanol, to give 2.9 g (80%) of micro-needles; m.p. 168–170°, $[\alpha]_D^{25}$ −90.8° (*c* 1.6, chloroform); lit.[12] m.p. 169–170°, $[\alpha]_D$ −95.2°; lit.[13] m.p. 171–172°, $[\alpha]_D$ −90.1°.

*Methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside* (7). — Methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-glucopyranoside (**8**) was prepared by a method similar to that reported for 1,2,3,4-tetra-*O*-acetyl-D-glucose[14], except that 1.10 moles of trityl chloride were used per mole of methyl β-D-glucopyranoside, and the reaction was allowed to proceed for 1 h before acetic anhydride was added; the mixture was kept overnight before it was poured into water. Anhydrous methyl β-D-glucopyranoside (75 g) gave 435 g of crude, air-dried product (**8**).

Crude compound **8** (135 g) was detritylated by the procedure of McGilvray[1]. The aqueous layer from the detritylation was extracted with chloroform, and the extract was washed successively with dilute sulfuric acid (2%), sodium hydrogen carbonate solution (2%), and water, dried (calcium sulfate), and evaporated to dryness. The residue was crystallized, and recrystallized, from ether, to give 33.4 g of **7** as needles, m.p. 113–115°, $[\alpha]_D^{25}$ −63.1° (*c* 2.12, chloroform); lit.[3] m.p. 114–115°, $[\alpha]_D$ −64.9°.

Alternatively, compound **8** was recrystallized (to remove pyridine), and a solution of the pure compound (20 g) in 100 ml of 4:1 (v/v) acetic acid–water containing 5 ml of pyridine was heated for 3 h at 95°, and cooled. The triphenylmethanol was removed by filtration, the filtrate was extracted with chloroform, and the extract was processed as for compound **7**, giving an oil that was dissolved in hot ether–petroleum ether; on cooling, the solution gave 5.7 g of needles having m.p. 109–111°. An additional 1.9 g was obtained by evaporating the mother liquor to an oil, and treating this oil in the same way. [An oil (5 g), probably partially deacetylated **7**, was also obtained which did not give further crystals]. Recrystallization of the crude solid from ether–petroleum ether gave 6.7 g of compound **7**, having the same m.p., mixed m.p., and specific optical rotation as were observed for compound **7** prepared by the method of Bell & Synge[4].

If the reaction is conducted with compound **8** in the absence of pyridine, methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside (**12**) is obtained, m.p. 133–134°, $[\alpha]_D^{25}$ −20.1° (*c* 0.78, chloroform); lit.[3] m.p. 134°, $[\alpha]_D^{18}$ −18.8°. Compound **12** could not be isomerized to compound **7** by means of the mixture described.

Methyl β(?)-cellotrioside decaacetate (**9**). — *Method A.* To a solution of compound **7** (1.5 g) in 5 ml of chloroform were added 2.5 g of silver oxide and 15 g of

anhydrous calcium sulfate. After the suspension had been shaken for a few minutes, a solution of 6 g of hepta-*O*-acetyl-α-cellobiosyl bromide in 20 ml of absolute chloroform was added. The mixture was shaken for 1 h, and then refluxed for 3 h. Chloroform (50 ml) was added, and the suspension was cooled and filtered. The solids were washed with chloroform, and the filtrates and washings were combined, and evaporated to a syrup that was dissolved in hot benzene; on being cooled overnight, the solution gave 2 g of needles having m.p. 185–189°. Three recrystallizations from benzene afforded 1.2 g of micro-needles, $[\alpha]_D^{25}$ +34.2° (*c* 1.6, chloroform), having m.p. 210–211°, unchanged on admixture with the compound prepared by method *B*.

Method B. A solution of crude compound **7** (3.5 g.; m.p. 112–115°, prepared by the method of Bell and Synge[4]) in 25 ml of absolute chloroform was dried for 24 h with anhydrous calcium sulfate (10 g). A solution of hepta-*O*-acetyl-α-cellobiosyl bromide (15.5 g) in anhydrous chloroform (15 ml) was added, and the mixture was shaken for 15 min. Freshly prepared, anhydrous silver carbonate (16 g) and iodine (0.15 g) were added, and the mixture was shaken for 48 h. Chloroform (25 ml) was added, the suspension was filtered, and the solid was washed with chloroform. The filtrate and washings were combined, and evaporated to a syrup which was crystallized from benzene–petroleum ether, to give 4 g of crude material. One recrystallization from benzene and one from ether gave 2.5 g of micro-needles having m.p. 210–211°; $[\alpha]_D^{25}$ +34.5° (*c* 1.62, chloroform).

Anal. Calc. for $C_{39}H_{54}O_{26}$: C, 49.9; H, 5.8. Found: C, 49.6; H, 5.8.

α-Cellotriose hendecaacetate (**13**). — Compound **9** (0.35 g) was added to a cold solution of sulfuric acid (1 ml) in acetic anhydride (25 ml). The resulting solution was kept for 20 h at room temperature, and then poured into 500 ml of ice–water containing 5 g of sodium hydrogen carbonate. The suspension was filtered, and the crystals were well washed with water, and air-dried; yield 250 mg. The compound was recrystallized from 95% ethanol to give micro-needles (230 mg) having m.p. 221–225°; after a further recrystallization, it had m.p. 223.5–224°; lit.[15] m.p. 223–224°.

β-Cellotriose hendecaacetate (**14**). — To a solution of **13** (70 mg) in 25 ml of absolute methanol was added 1 ml of M sodium methoxide. The resulting solution was kept for 24 h at 5° and then concentrated to ~5 ml; 14:11 (v/v) acetic acid–water (10 ml) was added, and the mixture was evaporated to a syrup. A suspension of sodium acetate trihydrate (2 g) in acetic anhydride (35 ml) was heated to 95° and quickly added, giving a homogeneous solution, which was kept for 2 h at 95–100°. The solution was then poured onto cracked ice, adjusted to pH 5 by addition of solid sodium hydrogen carbonate, and extracted with chloroform. The extract was successively washed with sodium hydrogen carbonate solution and water, and evaporated, giving crystals which were recrystallized from 95% ethanol to give 33 mg of product. After two recrystallizations, the melting point and mixed melting point were 205–208° (uncorr.).

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