PRACTICAL SYNTHESIS OF METHYL 4-*O*-METHYL- AND METHYL 4-*O*-BENZYL-α-D-GLUCOPYRANOSIDE

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ABSTRACT

Gram amounts of pure, crystalline methyl 4-*O*-methyl- and methyl 4-*O*-benzyl-α-D-glucopyranoside have been prepared from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in 40% overall yields by a method that appears to constitute a practical synthesis of methyl 4-*O*-alkyl-α-D-glucopyranosides.

INTRODUCTION

Investigations of the structure and chemical reactivity of starch have often benefited from insights provided by parallel studies of model compounds. Thus our interest in the reactivity of starch towards grafting reagents under various conditions could be served, it appeared, by studies of the chemical behavior of methyl 4-*O*-alkyl-α-D-glucopyranosides under the same conditions.

The simplest model compound analogous to the α-D-(1→4)-linked D-glucose residues of starch is methyl 4-*O*-methyl-α-D-glucopyranoside (**1**). This compound, from which 4-*O*-methyl-D-glucose has been derived[1,2], has been prepared by four methods: (*a*) reduction of methyl (methyl 4-*O*-methyl-α,β-D-glucopyranosid)uronate derived from mesquite gum or wood hemicellulose[1], (*b*) methylation of methyl 2,3-di-*O*-acetyl-[3a]** or (*c*) methyl 2,3-di-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside [3e] followed, in each case, by removal of blocking groups, and (*d*) benzylation of amylose with subsequent methanolysis, methylation, and debenzylation[4]. As practical methods for the preparation of **1**, these earlier procedures are of limited value for various reasons: (*a*) the product is impure[2], (*b*) the yield is low and purification is laborious[3e,4], or

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Two attempts have been made to prepare **1 by methylation of this intermediate. Purdie methylation was accompanied by acetyl migration and, after removal of blocking groups, the product, at first thought to be **1** (ref. 3b), was later proved to be methyl 2-*O*-methyl-α-D-glucopyranoside[3c]. Subsequently Deferrari and his associates[3d] introduced diazomethane–boron trifluoride etherate as a reagent for methylating partially acetylated sugars without acyl migration. With this reagent Trimnell *et al.*[3a] succeeded in preparing **1** in good yield from the above intermediate.

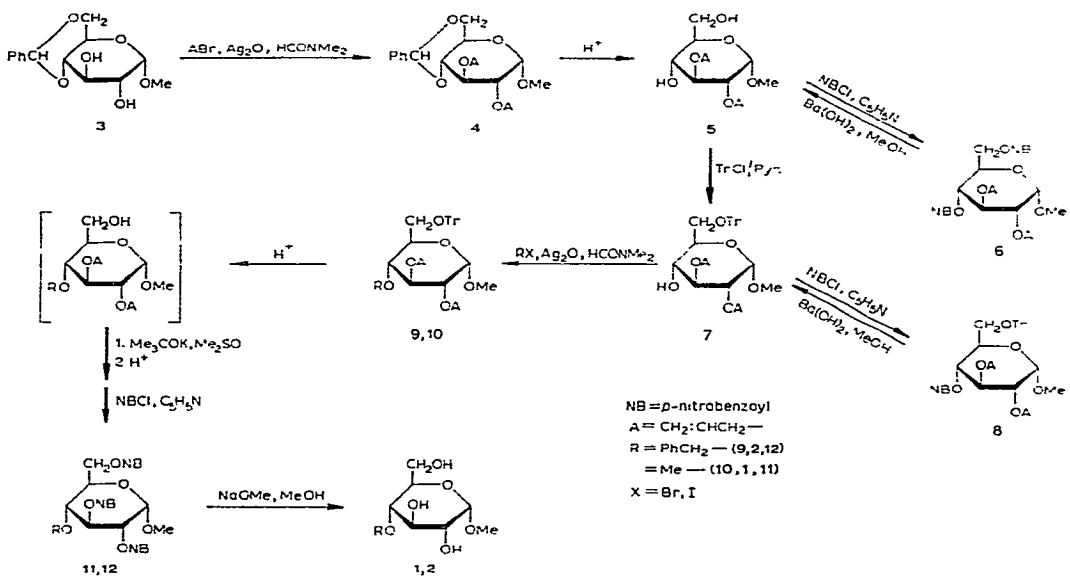
(*c*) the product is a mixture of the α,β-glycosides from which the α-form must be separated[1,4], and finally, (*d*) the syrupy or amorphous nature of most of the intermediates[3a,3e,4] and final products[1,2,4], coupled with the absence of crystalline, characterizing derivatives tend to make the purity and identity of these substances uncertain. Indeed, the identity of the product, **1**, in each instance, was assumed from its method of synthesis; only the derived reducing sugar was characterized (as the crystalline 4-*O*-methyl-D-*arabino*-hexulose phenylosazone).

In addition to **1**, our immediate interest in model compounds included methyl 4-*O*-benzyl-α-D-glucopyranoside (**2**), a compound that has been prepared in admixture with its 6-*O*-benzyl isomer[5] but not isolated. Possible extension of our interest to include additional analogous model-compounds prompted an attempt to devise a general, preparative method for the synthesis of methyl 4-*O*-alkyl-α-D-glucopyranosides.

RESULTS AND DISCUSSION

We present herein a practical synthesis of methyl 4-*O*-alkyl-α-D-glucopyranosides. The intermediates are easily prepared by conventional procedures in excellent yield. No chromatographic separations are involved. The effectiveness of the method is demonstrated by the preparation in gram amounts of pure, crystalline **1** and **2** in 40% overall yields.

As shown in Scheme 1, the general plan of our synthesis is similar to that of an earlier method[3e], also definitive. However, yield and preparative value have been greatly increased by incorporating two recent developments in an analogous synthesis. The starting compound, **3**, formerly somewhat tedious to prepare and



Scheme 1

purify, can now be rapidly prepared in adequate amounts analytically pure[6]. Secondly, the use of allyl[7] rather than benzyl or acyl groups for blocking purposes has contributed most significantly to the success and reliability of our synthesis; the low yields and uncertain results of earlier methods[3b,3e], due to incomplete debenzylation or acyl migration, have been avoided.

Initially, we had been alerted to possible difficulties in the deallylation procedure from an unfavorable report of Brimacombe *et al.*[8], who had been unable to achieve complete isomerization of the allyl group in the first step of this procedure. Gigg[7], who subsequently repeated Brimacombe's work with satisfactory results, inferred the importance of the temperature and of the duration of the reaction in the alkaline isomerization step. Our results support Gigg's inference and suggest that the quality of the catalyst (potassium *tert*-butoxide) is also important. Old preparations of catalyst, which may have partially decomposed, invariably gave poor results regardless of the reaction conditions, but fresh preparations used under suitable conditions always gave excellent results, permitting complete removal of the allyl groups.

The steps of the synthesis and the characterization of intermediates are indicated in Scheme 1.

EXPERIMENTAL

General. — Evaporations were performed under diminished pressure (water aspirator). Melting points were determined with a Fisher–Johns apparatus* and are uncorrected. Esterification and tritylation reaction mixtures were worked up by pouring them, with stirring, into saturated, aqueous sodium hydrogen carbonate (1–1.5 l). After 0.5–1 h the aqueous suspension was extracted with chloroform (2 × 200 ml). To the extract was added water (250 ml) and the whole was evaporated. When all chloroform had thus been removed, the remaining pyridine–water mixture, containing the insoluble product in suspension, was further evaporated until all pyridine had been removed (odor). The remaining water was carefully decanted from the suspended product, which was then dissolved in abs. ethanol. The (moist) ethanol was evaporated off. Again the product was dissolved in abs. ethanol and the solvent was evaporated. The process was repeated, if necessary, to afford an anhydrous, pyridine-free product. A final, brief evacuation of the flask (bath, 50–60°) removed traces of ethanol.

Reagents. — The methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (3) was analytically pure[6]. Methyl sulfoxide used for the alkaline-isomerization reactions had been dried by keeping the solvent (reagent-grade, 250 ml) over freshly regenerated Drierite[9] (nonindicating, 8 mesh, 1 lb) for 24 h. The dried solvent, containing some finely divided Drierite in suspension, was decanted directly into the reaction flask. The activated charcoal was Darco G-60**. The silver oxide was moist, finely divided,

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and recently prepared. The potassium *tert*-butoxide was a commercial preparation, recently procured, that had been kept in an efficient desiccator.

A. Preparation and characterization of intermediates. (*a*) *Methyl 2,3-di-*O*-allyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside* (**4**). — To a solution of **3** (22.6 g, 0.08 mole) in a mixture of *N,N*-dimethylformamide (200 ml) and allyl bromide (70 ml, 0.8 mole) was added, with rapid stirring, silver oxide (100 g), portionwise, during 1 h. Stirring (vigorous) was continued for 17 h. The mixture was diluted with chloroform until no further precipitation occurred and was then filtered through sintered glass (M). The silver compounds were washed thoroughly with chloroform. The combined filtrate and washings were evaporated (bath initially 50°, and then gradually raised to 95°) to give an essentially solvent-free syrup that was shaken with a mixture of heptane (800 ml) and water (300 ml). The separated heptane layer was evaporated to a syrup that was crystallized from hot 65% ethanol (400 ml). The product (**4**) was washed with ice-cold 65% ethanol and dried on a porous tile. A second crop was obtained from the evaporated mother liquor by dissolving the residue in heptane (500 ml), treating the solution with activated charcoal (5 g), evaporating the solvent, and crystallizing the purified residue as before; yield (two crops), 24.5 g (84%), m.p. 68° and $[\alpha]_D^{20}$ +54° (*c* 2, benzene). (Lit.[8] m.p. 62–63°, $[\alpha]_D^{18}$ +54° in chloroform).

Anal. Calc. for $C_{20}H_{26}O_6$: C, 66.3; H, 7.2. Found: C, 66.4; H, 7.3.

(*b*) *Methyl 2,3-di-*O*-allyl-α-*D*-glucopyranoside* (**5**). — To a suspension of **4** (5.0 g) in methanol–water (2:1 v/v) (225 ml) in a flask fitted with a reflux condenser was added Dowex-50 (H^+) cation-exchange resin (12 g). The mixture was vigorously stirred for 2.5 h at 60–65° (bath), cooled, and filtered. The resin was washed with methanol. The combined filtrate and washings, after concentration, were evaporated with water (600 ml) to dryness. The resulting benzaldehyde-free syrup was dried by successively evaporating solutions of it in abs. ethanol and in benzene.

To a solution of the syrup in anhydrous pyridine (50 ml) was added *p*-nitrobenzoyl chloride (7.5 g). After 2.5 days at room temperature, the reaction mixture was worked up as already described. The dark, crude product was exhaustively extracted with hot heptane (1.5 l, total) and the combined extracts were evaporated. The resulting crystalline residue was dissolved in warm ethanol (125 ml) and the solution was cooled and seeded. The crystalline product was washed with a little ice-cold ethanol and dried on the funnel by aspiration. A second crop resulted from evaporating the mother liquor to dryness, dissolving the residue in warm ethanol (25 ml), cooling, and seeding. The two crops were recrystallized from hot ethanol (125 ml) to give methyl 2,3-di-*O*-allyl-α-D-glucopyranoside 4,6-di-*p*-nitrobenzoate (**6**) (4.8 g, 61%); m.p. 99–100° and $[\alpha]_D^{20}$ +115° (*c* 2, chloroform).

Anal. Calc. for $C_{27}H_{28}N_2O_{12}$: C, 56.7; H, 4.9; N, 4.9. Found: C, 56.8; H, 4.9; N, 5.0.

To a solution of the ester (2.0 g) in methanol (50 ml) was added a solution of barium hydroxide octahydrate (4 g) in methanol (50 ml). The mixture was kept for 48 h at room temperature, and then diluted with water (100 ml), and neutralized with excess Dry Ice. Filtration and evaporation gave a residue that was extracted

thoroughly with hot heptane (300 ml). The hot extract was treated with activated charcoal (2 g) and filtered hot through sintered glass (M). Evaporating the filtrate, dissolving the residue in petroleum ether (b.p. 30–50°), and refrigerating the solution, gave crystalline **5**; m.p. 35–36° and $[\alpha]_D^{20}$ +95° (*c* 2.1, chloroform).

(*c*) *Methyl 2,3-di-*O*-allyl-6-*O*-trityl-α-*D*-glucopyranoside* (**7**). — To a solution of **5** (0.50 g) in anhydrous pyridine (5 ml) was added chlorotriphenylmethane (0.51 g). The mixture was kept for 3 days at room temperature and then worked up as described above.

The dry syrup was dissolved in anhydrous pyridine (5 ml) and *p*-nitrobenzoyl chloride (0.55 g) was added. After 24 h at room temperature, the reaction mixture was worked up as before. The dry syrup was purified by extracting it with hot heptane and evaporating the filtered solution. The resulting syrup was then dissolved in warm 85% ethanol (23 ml). Crystallization in the cooling, seeded solution was complete after several h at room temperature followed by refrigeration (4°) overnight. Filtered, washed with a little ice-cold 85% ethanol, and dried on the funnel by aspiration, the product, methyl 2,3-di-*O*-allyl-4-*O*-*p*-nitrobenzoyl-6-*O*-trityl-α-D-glucopyranoside (**8**) (0.94 g), had m.p. 127–128° and $[\alpha]_D^{20}$ +39° (*c* 2, chloroform).

Anal. Calc. for $C_{39}H_{39}NO_9$: C, 70.4; H, 5.9; N, 2.1. Found: C, 70.4; H, 5.9; N, 2.0.

To a solution of **8** (1.94 g) in methanol (50 ml) was added a solution of barium hydroxide octahydrate (4 g) in methanol (50 ml) and the mixture was kept for 7 days at room temperature. It was then poured into chloroform (250 ml) and the resulting solution was washed with water until it was neutral. Evaporation gave a syrup that was extracted with heptane (20–25°). The syrup obtained by evaporation of the extract was dissolved in abs. ethanol (20 ml) and water (8 ml) was added. The turbid mixture, on seeding and refrigerating (18 h, 4°), gave crystalline **7** which, after two more recrystallizations in the same manner had m.p. 91° and $[\alpha]_D^{20}$ +65° (*c* 1.1, abs. ethanol).

Anal. Calc. for $C_{32}H_{36}O_6 \cdot C_2H_5OH$: C, 72.6; H, 7.5. Found: C, 72.8; H, 7.1.

(*d*) *Methyl 2,3-di-*O*-allyl-4-*O*-benzyl-6-*O*-trityl-α-*D*-glucopyranoside* (**9**). — The crude, syrupy product (**7**, 2.89 g) of the saponification (as above) of **8** (3.52 g) was dissolved in a mixture of *N*,*N*-dimethylformamide (25 ml) and benzyl bromide (10 ml). Silver oxide (10 g) was added, portionwise during 1 h, with vigorous stirring that was continued for 23 h. The reaction mixture was then diluted with chloroform until precipitation had ceased, and the silver compounds were filtered off and washed well with chloroform. To the filtrate and washings (~300 ml, total) was added pyridine (20 ml), and the mixture was kept for 4 days at room temperature. It was then washed with water (2 × 350 ml), filtered, and evaporated with water (200 ml; bath, 50° initially, and then gradually raised to 90°) until all distillation had ceased. The syrup remaining was digested (steam bath) with hot 50% ethanol (400 ml) and the hot extract was decanted. The insoluble syrupy residue remaining was dissolved in hot 80% ethanol (100 ml) and the solution was cooled and seeded. The crystalline product that resulted was recrystallized the same way. A second crop was obtained by evapor-

ating the mother liquors to dryness, digesting the residue as before with hot 50% ethanol (100 ml), decanting off the hot extract, and crystallizing the remaining syrup from hot 80% ethanol (75 ml). The second crop was recrystallized the same way. Total yield (recrystallized crops), 2.59 g (81%) of **9**; m.p. (each crop) 100.5–101.5° and $[\alpha]_D^{20}$ +77° (*c* 2, benzene).

Anal. Calc. for $C_{39}H_{42}O_6$: C, 77.2; H, 6.9. Found: C, 77.3; H, 7.1.

(*e*) *Methyl 2,3-di-*O*-allyl-4-*O*-methyl-6-*O*-trityl-α-*D*-glucopyranoside* (**10**). — To a solution of **7** (11.5 g) in a mixture of *N,N*-dimethylformamide (50 ml) and methyl iodide (20 ml) in a flask fitted with a reflux condenser was added silver oxide (25 g), portionwise during 1 h, with vigorous stirring. The stirring was continued for 21 h. The silver salts were filtered off and washed well with chloroform; the combined filtrate and washings were then shaken with water and evaporated to dryness. The syrup remaining was remethylated in the same manner. The twice-methylated syrup was dissolved in heptane; the solution was shaken with water, treated with activated charcoal (5 g), and evaporated to a syrup that was dissolved in 2-methoxyethanol (~50 ml). Addition of water, seeding the just-turbid mixture, and several h of refrigeration (4°) gave the crystalline product, which upon recrystallization in the same way became pure **10**; m.p. 74–75° and $[\alpha]_D^{20}$ +74° (*c* 2, chloroform).

Anal. Calc. for $C_{33}H_{38}O_6$: C, 74.7; H, 7.2. Found: C. 74.6; H, 7.3.

*B. Synthesis of methyl 4-*O*-alkyl-α-*D*-glucopyranosides. I. Methyl 4-*O*-methyl-α-*D*-glucopyranoside* (**1**). — Debenzylidenation of **4** (10 g), as described under (*b*), with the same proportions of solvents and resin, gave syrupy **5** (7.45 g), which was dissolved in anhydrous pyridine (35 ml). To the mixture was added chlorotriphenylmethane (7.65 g). After 6 days at room temperature, the reaction mixture was worked up as described earlier. The resulting, crude, syrupy **7**, was purified by extracting it with hot heptane, cooling to room temperature, and filtering and evaporating the extract. The purified syrup (14 g) was dissolved in a mixture of *N,N*-dimethylformamide (30 ml) and methyl iodide (35 ml) in a flask fitted with a reflux condenser. Addition of silver oxide (65 g), portionwise, was performed with vigorous stirring that was continued 18 h. The reaction mixture was worked up as in (*e*). The crude, crystalline product (two crops), recrystallized as before, gave **10**; m.p. 74–75° (10.85 g or 74% based on **4**).

To a suspension of **10** (9.86 g) in 80% methanol (200 ml) was added Dowex-50 (H^+) cation-exchange resin (25 g), and while being stirred vigorously, the mixture was refluxed (bath, 85–90°) for 5.5 h. It was then cooled and filtered and the resin was washed well with methanol. The combined filtrate and washings were made alkaline with saturated aqueous barium hydroxide; after the mixture had been neutralized by the addition of excess Dry Ice, it was evaporated to dryness. The residue was extracted with chloroform and the extract was filtered and evaporated with water (500 ml) until all chloroform had been removed. The aqueous portion was then separated by filtration, the syrup remaining was redissolved in chloroform, and water (500 ml) was again distilled from the solution until all chloroform had been removed. Separated as before, the aqueous portion was combined with the first aqueous portion, and the

whole was evaporated to dryness. The syrup remaining was freed of moisture by adding abs. ethanol and evaporating it. It was then extracted with heptane and the extract was filtered and evaporated to give crude, syrupy methyl 2,3-di-*O*-allyl-4-*O*-methyl-α-D-glucopyranoside (5.22 g or 97% based on **10**).

This syrup was dissolved in dry methyl sulfoxide (140 ml) and potassium *tert*-butoxide (5.0 g) was added. While dry nitrogen was slowly bubbled through it, the mixture, protected from atmospheric moisture (Drierite tube), was heated (bath, 100–105°) for 1 h. It was then cooled and poured with stirring into water (500 ml). The resulting alkaline solution was neutralized with excess Dry Ice and the mixture was evaporated (bath gradually raised to 100°) until no further distillation occurred. The remaining (dark) syrup was thoroughly extracted with chloroform. The extracts were filtered and evaporated to a syrup that was repeatedly extracted with hot heptane. Upon cooling, the combined extracts were filtered and evaporated to a syrup that was dissolved in acetone (180 ml). To the solution was added M hydrochloric acid (20 ml) and the mixture was refluxed for 45 min. After cooling, it was neutralized with barium carbonate, filtered, and evaporated to a syrup from which abs. ethanol was distilled to remove moisture. The syrupy residue was extracted thoroughly with chloroform, and the extracts were filtered and evaporated to give crude, syrupy **1**.

The syrup was dissolved in anhydrous pyridine (75 ml) and *p*-nitrobenzoyl chloride (11.8 g) was added. The mixture was heated for 1 h at 85–90° (bath) and cooled. It was then worked up as already described. The crude product was digested with hot water (steam bath), filtered, and then redissolved in chloroform (500 ml); the (colored) solution was treated with activated charcoal (5 g) and evaporated to give a glassy residue that was dissolved in hot 2-methoxyethanol (15 ml). Upon cooling and seeding, the solution yielded the crystalline ester. A second crop was obtained by evaporating the mother liquor to dryness, dissolving the residue in 2-methoxyethanol (5 ml), cooling, and seeding. The two crops were combined and recrystallized from the same solvent (10 ml) by keeping the flask first for several h at room temperature and then for 2 days at 4°. The product, methyl 4-*O*-methyl-α-D-glucopyranoside 2,3,6-tri-*p*-nitrobenzoate (**11**), had m.p. 199–200°, $[\alpha]_D^{20}$ +177° (*c* 2, chloroform), and weighed 9.2 g (75% based on **10**).

Anal. Calc. for $C_{29}H_{25}N_3O_{15}$: C, 53.1; H, 3.8; N, 6.4. Found: C, 53.4; H, 3.9; N, 6.4.

A pea-sized piece of sodium was dissolved in anhydrous methanol (100 ml) and to the solution, protected from atmospheric moisture (Drierite tube) ,was added **11** (2.5 g, finely ground). The mixture was stirred for 4 h and was then kept for 13 h at room temperature. The clear solution was slightly acidified with dilute hydrochloric acid, and then was neutralized with sodium hydrogen carbonate, and poured with stirring into water (500 ml). The insoluble methyl *p*-nitrobenzoate immediately crystallized. Filtration, evaporation of the filtrate, and distillation of the resulting residue with abs. ethanol gave an anhydrous mixture of crude product and salts. Extracting with chloroform, filtering the extract, and evaporating to dryness gave a

syrup that was dissolved in ethyl acetate (5 ml). Heptane was added until turbidity occurred. Upon seeding, the mixture yielded the crystalline product. The flask was refrigerated (4°) for a few h, and then the product was filtered, washed with a little heptane, and dried by aspiration. Recrystallization in the same manner gave **1** (0.69 g, or 86% based on **11**, 41% based on **3**) having m.p. 97–98° and $[\alpha]_D^{20}$ +165° (*c* 1.2, water), +183° (*c* 1.2, methanol). Lit.[3e] m.p. 94–95°, $[\alpha]_D^{52}$ +167° (in water).

Anal. Calc. for $C_8H_{16}O_6$: C, 46.2; H, 7.8. Found: C, 46.5; H, 7.5.

II. Methyl 4-O-benzyl-α-D-glucopyranoside (**2**). — Debenzylidenation of **4** (10 g) and tritylation of the crude product (**5**) were performed as described already for synthesis of **1**. The resulting crude, syrupy product (**7**) was benzylated as described under (*d*) but with five times the amounts of reagents specified. The product (**9**), worked up as under (*d*), weighed 12.7 g (two crops, 76% based on **4**) and had m.p. 101–102°.

To a solution of **9** (5.00 g) in acetone (180 ml) was added M hydrochloric acid (20 ml). The mixture was refluxed for 1 h, cooled, neutralized with excess barium carbonate, and filtered. Evaporation gave a residue from which abs. ethanol was distilled. The dry residue was extracted thoroughly with chloroform and the extracts were evaporated to a partially crystalline syrup* that was deallylated as in the synthesis of **1** (under *B-I*). The crude, syrupy product, a mixture of **2** with triphenylcarbinol, was thoroughly extracted with hot water (~1.5 l, total). The cooled, turbid extracts were filtered and evaporated to a syrup from which abs. ethanol was distilled. The dry syrup was dissolved in anhydrous pyridine (40 ml) and *p*-nitrobenzoyl chloride (6.9 g) was added. The mixture was heated for 1 h at 85–90° (bath) and cooled. The dry, syrupy product, isolated as already described, was dissolved in warm ethyl acetate (20 ml). By gradually adding abs. ethanol to the solution, seeding, and refrigerating it (4°) for several h, a crystalline product was obtained. A second crop resulted from evaporating the mother liquor to dryness and crystallizing the residue in the same way. The two crops were combined and dissolved in chloroform (250 ml); the solution was treated with activated charcoal (5 g) and evaporated to dryness. The residue was crystallized as before, a second crop being obtained from the mother liquor. The two crops were combined and recrystallized the same way, a second crop from this second recrystallization being, itself, recrystallized. The combined, recrystallized crops of methyl 4-*O*-benzyl-α-D-glucopyranoside 2,3,6-tri-*p*-nitrobenzoate (**12**) (4.30 g, 70% based on **9**) had m.p. 167–168° and $[\alpha]_D^{20}$ +164° (*c* 2, chloroform).

Anal. Calc. for $C_{35}H_{29}N_3O_{15}$: C, 57.5; H, 3.9; N, 5.7. Found: C, 57.4; H, 4.0; N, 5.9.

Catalytic deacylation by the Zemplén method of **12** (2.61 g)[10] and subsequent work-up of the reaction mixture were performed as in the synthesis of **1** (under *B-I*). The crude product was crystallized from ethyl acetate (5 ml) by adding heptane (5 ml). Crystallization started immediately and was completed after 16 h at room temperature.

*Separation of the triphenylcarbinol at this point was exceedingly difficult, but it was easy after deallylation.

The crystalline product was filtered off, washed with a little heptane, and dried by aspiration. A small second crop, obtained from the mother liquor, was combined with the first to give **2** (0.94 g, 93% based on **12**, 43% based on **3**) having m.p. 127.5–128.5° and $[\alpha]_D^{20}$ +131° (*c* 2, water), +146° (*c* 2.2, methanol).

Anal. Calc. for $C_{14}H_{20}O_6$: C, 59.1; H, 7.1. Found: C, 59.2; H, 7.2.

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