Carbohydrate Research, 106 (1982) 170–173
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

Syntheses of 3(4)-*O*-allyl-, 3(4)-*O*-benzyl- and 1,2,3 (4),5,6-penta-*O*-benzoyl-D-mannitol

JOHN W. VAN CLEVE

Northern Regional Research Center, Agricultural Research Service, U.S. Department of Agriculture, Peoria, Illinois 61604 (U.S.A.)*

(Received October 9th, 1981; accepted for publication in revised form, December 25th, 1981)

As part of a recent program at this laboratory concerning sweetening agents, n.m.r. reference-spectra were required for one of the reduction products of maltulose, namely, 3(4)-*O*-(α-D-glucopyranosyl)-D-mannitol (**1**). For the definitive synthesis of **1**, certain known and unknown derivatives of D-mannitol were of interest, among them the known 3(4)-*O*-allyl-D-mannitol[1] (**2**) and the unknown 3(4)-*O*-benzyl- (**3**) and 1,2,3(4),5,6-penta-*O*-benzoyl-D-mannitol (**4**). Compound **2** has been prepared previously by mono-allylation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**5**), and it has also been obtained as a by-product in the di-allylation of compound[1] **5**. In the present investigation, compound **2** was prepared alternatively by definitive synthesis. Both **2** and **3** were prepared by etherification of the known 3(4)-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol[2] (**6**), followed by removal of the protecting groups. An improved method for preparing **6** is offered that gives a purer product in better yield. The unknown compound **4** was readily prepared by partial benzoylation of the known 1,2,5,6-tetra-*O*-benzoyl-D-mannitol[3] (**7**), a simplified preparation of which is also offered. As a route to the synthesis of **1**, attempts were made to condense phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside[4] with **4** and with **6** to give 3(4)-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-mannitol 1,2,(3)4,5,6-pentabenzoate (**8**) and 3(4)-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-3(4)-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (**9**), respectively. Both attempts were unsuccessful.

EXPERIMENTAL

General methods. — Evaporations were performed at diminished pressure (water aspirator). Melting points are uncorrected. The pyridine was anhydrous. The silver

---

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

oxide was freshly prepared. The activated charcoal was Darco G-60 (ICI United States Inc., Specialty Chemicals Division, Wilmington, DE 19897). The silica-gel column and its preconditioning before use are described elsewhere[5].

*1,2,5,6-Tetra-O-benzoyl-*D*-mannitol* (**7**). — A solution of 1,2,5,6-tetra-*O*-benzoyl-3,4-*O*-isopropylidene-D-mannitol[3] (5.0 g) in a 1:1 mixture of 90% formic acid–90% acetic acid (100 mL) was heated (steam bath) for 1 h, whereupon deacetalation was complete. Evaporation to dryness gave a syrup that was freed of residual acid by distilling benzene or ethyl acetate from it. Two crystallizations from benzene and one from chloroform–heptane gave **7**, m.p. 123–124°; mixed m.p. with product prepared by E. Fischer's method[3], 123–124°; yield (two crops), 3.5 g (75%) (lit.: E. Fischer[3] reported m.p. 122–123°, yield 80% and N.-J. Chü and C. E. Ballou[3] reported m.p. 116–119°, yield 75–80% for **7**).

*1,2,3(4),5,6-Penta-O-benzoyl-*D*-mannitol* (**4**). — To a solution of **7** (1.0 g) in pyridine (10 mL) was added benzoyl chloride (0.29 mL, 1.5 equivs), and the mixture was heated for 1.5 h at 90° (bath). The mixture was processed by the method described elsewhere[5]. The crude product was passed through a silica-gel column with 4:1 (v/v) benzene–ethyl acetate as irrigating solvent. Combination of the appropriate fractions, evaporation to dryness, and crystallization of the residue from ethyl acetate–heptane gave **4**, m.p. 150° (0.72 g, 61%).

Anal. Calc. for $C_{41}H_{34}O_{11}$: C, 70.1; H, 4.9. Found: C, 70.1; H, 5.0.

*3(4)-O-Benzoyl-1,2:5,6-di-O-isopropylidene-*D*-mannitol* (**6**). — To a solution of **5** (10.0 g) in pyridine (100 mL) was added benzoyl chloride (4.5 mL), and the mixture was heated for 1.5 h at 80–90° (bath). The mixture, processed conventionally[5], gave a syrup which, when dissolved in a little warm heptane and seeded, gave **6** admixed with some **5**. Removal of **5** was effected by washing the mixture with water. Recrystallization from heptane then gave pure **6**, m.p. 108–109°, yield 7.71 g (55%), $[\alpha]_D^{20}$ +1.8° (*c* 5, ethyl acetate) (lit.: J. M. Sugihara and G. U. Yuen[2] reported m.p. 104–107°, $[\alpha]_D^{20}$ −8.5° [*c* 2.6, chloroform], yield 46% for **6**.)

Anal. Calc. for $C_{19}H_{26}O_7$: C, 62.3; H, 7.2. Found: C, 62.3; H, 7.2.

*3(4)-O-Allyl-*D*-mannitol* (**2**). — To a solution of **6** (5 g) in *N,N*-dimethylformamide (50 mL) was added allyl bromide (15 mL). While the mixture was stirred, silver oxide (15 g) was added portionwise. After 4 h of vigorous stirring, t.l.c. with 1:4 (v/v) ethyl acetate–benzene as irrigant revealed the reaction to be complete. The mixture was diluted with benzene, filtered, and water was distilled from the filtrate until all organic solvent had been removed. The remaining, syrupy suspension was extracted with heptane, and the extract was filtered and evaporated to a syrup.

The syrup was dissolved in a saturated solution (100 mL) of barium hydroxide octahydrate in methanol. After 1.5 h at ambient temperature, t.l.c. with the foregoing ethyl acetate–benzene solvent revealed that saponification was complete. The mixture was carbonated with Dry Ice and evaporated to dryness. The residue was extracted with chloroform and the extracts were filtered and evaporated to a syrup.

The syrup was dissolved in 7:3 acetic acid–water and kept for 66 h at room temperature, whereupon deacetalation was complete. Solvent was removed by evaporation, and ethyl acetate was distilled from the residue to remove residual acetic acid. The syrupy residue was extracted with water and the extract was filtered. Evaporation to dryness with the aid of abs ethanol gave a crystalline residue that was extracted with boiling ethyl acetate. The hot extract was filtered rapidly and then was evaporated to low volume from which crystallized **2**, m.p. 120–121°, $[\alpha]_D^{20}$ +16.7° (*c* 2.5, water) (lit.[1]: m.p. 119–120°, $[\alpha]_D^{20}$ +15.8° [*c* 4, water] and m.p. 117°, $[\alpha]_D^{20}$ +15.3° [*c* 1, water]).

Anal. Calc. for $C_9H_{18}O_6$: C, 48.7; H, 8.2. Found: C, 48.5; H, 8.2.

To a solution of **2** (0.11 g) in pyridine (5 mL) was added chlorotriphenylmethane (0.32 g, 2.2 equivs). After 3–4 days, the mixture was poured into saturated sodium hydrogencarbonate (250 mL) and then was processed as for isolation of esters[5]. The crude, syrupy product was purified by passage through a silica-gel column with 6:1 (v/v) benzene–ethyl acetate to give the chromatographically pure, syrupy tritylated derivative (0.26 g). The syrup was dissolved in pyridine (10 mL), and *p*-nitrobenzoyl chloride (0.58 g) was added. The mixture was heated for 1.5 h at 90° (bath) and then processed conventionally[5]. The crude ester was dissolved in ethyl acetate (250 mL) and the solution was decolorized with activated charcoal (2 g) and evaporated. The residue, crystallized from heptane, gave 3(4)-*O*-allyl-1,6-di-*O*-trityl-2,4(3),5-tri-*O*-*p*-nitrobenzoyl-D-mannitol, m.p. 109–112°.

Anal. Calc. for $C_{68}H_{55}N_3O_{15}$: C, 70.9; H, 4.6; N, 3.7. Found: C, 71.2; H, 4.9; N, 3.5.

3(4)-O-Benzyl-D-mannitol (**3**). — To a solution of **6** (8.81 g) in *N,N*-dimethylformamide (100 mL) was added benzyl bromide (40 mL). To the stirred solution was added silver oxide (30 g) portionwise during 1 h. The mixture was stirred vigorously for 29 h and then diluted with chloroform and filtered. The filtrate was evaporated (bath 80–90°) until distillation ceased, after which time pyridine (80 mL) was added. The mixture was warmed (steam bath) for 15 min, and then it was diluted with chloroform and extracted with water. Water was evaporated from the remaining chloroform solution until all organic solvents had been removed. The syrupy suspension was re-extracted with chloroform, and the extract evaporated to a syrup. The syrup was dissolved in methanol (20 mL) that had been saturated with barium hydroxide octahydrate. After 3 days, the mixture was evaporated to a residue that was extracted with acetone, and the extracts were evaporated to a syrup that was dissolved in 7:3 (v/v) acetic acid–water, and the solution was kept for 4 h at 40° (bath), whereupon deacetalation was complete. The mixture was evaporated and the resulting syrup freed of residual acid and water by distilling ethyl acetate from it. The remaining syrup was extracted with heptane–water and the aqueous phase evaporated to give crude, syrupy **3**, which was purified by passage through a silica-gel column with 4:1 ethyl acetate–methanol, thus giving chromatographically pure **3** (4.49 g, 68.7%).

To a solution of **3** (0.12 g) in pyridine (5 mL) was added chlorotriphenylmethane (0.26 g, 2.2 equivs). After 5 days at room temperature, the mixture was poured into saturated sodium hydrogencarbonate and processed as for the isolation of esters[5].

The crude, tritylated product was purified by passage through a silica-gel column, with 1:6 (v/v) ethyl acetate–heptane, to give a chromatographically pure syrup (0.16 g), which was dissolved in pyridine (10 mL), and *p*-nitrobenzoyl chloride (0.4 g) was added. The mixture was heated for 2 h at 80–90° (bath), and then it was poured into saturated sodium hydrogencarbonate (250 mL) and processed in the usual way[5]. A solution of the crude ester in ethyl acetate (250 mL) was decolorized with activated charcoal (2 g), evaporated, and the residue crystallized from heptane to give 3(4)-*O*-benzyl-1,6-di-*O*-trityl-2,4(3),5-tri-*O*-*p*-nitrobenzoyl-D-mannitol, m.p. 114–116° (51 mg).

Anal. Calc. for $C_{72}H_{57}N_3O_{15}$: C, 71.8; H, 4.8; N, 3.5. Found: C, 71.7; H, 4.9; N, 3.4.

REFERENCES

1 A. N. WRIGLEY AND E. YANOVSKY, *J. Am. Chem. Soc.*, 70 (1948) 2194–2196; P. BLADON AND L. N. OWEN, *J. Chem. Soc.*, (1950) 591–597.

2 J. M. SUGIHARA AND G. U. YUEN, *J. Am. Chem. Soc.*, 79 (1957) 5780–5782.

3 E. FISCHER, *Ber.*, 48 (1915) 266–275; N.-J. CHÜ AND C. E. BALLOU, *J. Am. Chem. Soc.*, 83 (1961) 1711–1715.

4 R. J. FERRIER, G. W. HAY, AND N. VETHAVIYASAR, *Carbohydr. Res.*, 27 (1973) 55–61; J. W. VAN CLEVE, *Carbohydr. Res.*, 70 (1979) 161–164.

5 J. W. VAN CLEVE, *Carbohydr. Res.*, 106 (1982) 239–245.