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Note

Synthesis of benzyl α- and β-sophorosides, and of benzyl α-laminarabioside

KEN'ICHI TAKEO
Department of Agricultural Chemistry, Kyoto Prefectural University, Shimogamo, Kyoto 606 (Japan)
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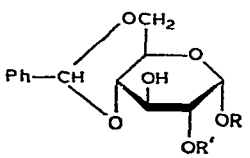
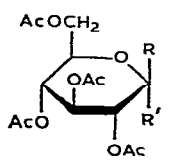
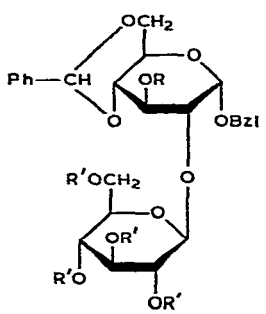
Benzyl glycosides of disaccharides are useful starting materials for the chemical modification of disaccharides and in the synthesis of higher oligosaccharides. Of the eight benzyl D-glucobiosides, benzyl β-cellobioside[1], benzyl α-[2] and β-maltosides[3–5], and benzyl β-laminarabioside[6,7] (benzyl 3-*O*-β-D-glucopyranosyl-β-D-glucopyranoside) (**19**) have been synthesized. The preparation of benzyl β-gentiobioside heptaacetate has also been reported[8]. This paper describes the synthesis of benzyl α- and β-sophorosides (benzyl 2-*O*-β-D-glucopyranosyl-α- and -β-D-gluco-



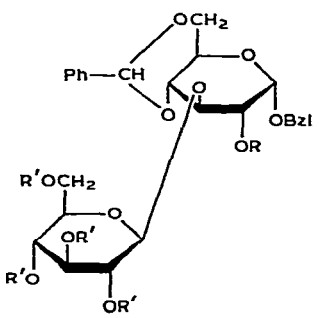
1 R = Me, R′ = H
2 R = Bzl, R′ = H
3 R = Bzl, R′ = Bz



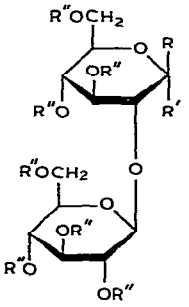
4 R = H, R′ = Br
5 R, R′ = H, OH



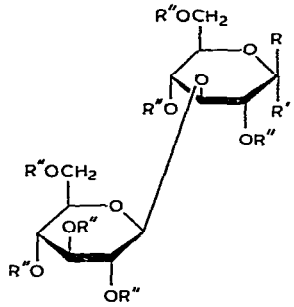
6 R = H, R′ = Ac
7 R = R′ = H
8 R = R′ = Ac



9 R = R′ = Ac
10 R = R′ = H
11 R = Bz, R′ = Ac



12 R = R″ = H,R′ = OBzl
13 R = R″ = H,R′ = OH
14 R = H,R′ = OBzl,R″ = Ac
15 R = R′ = H,OH,R″ = Ac
16 R = H,R′ = Br,R″ = Ac
17 R = OBzl,R′ = H,R″ = Ac
18 R = OBzl,R′ = R″ = H



19 R = OBzl,R′ = R″ = H
20 R = R″ = H,R′ = OBzl
21 R = R′ = H,OH,R″ = H
22 R = H,R′ = OBzl,R″ = Ac
23 R = R′ = H,OH,R″ = Ac

pyranosides) (**12** and **18**) and of benzyl α-laminarabioside (benzyl 3-*O*-β-D-glucopyranosyl-α-D-glucopyranoside) (**20**).

Previous studies[9,10] showed that, as a route to **12**, condensation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**4**) in the presence of silver carbonate results in the preferential formation of a β-(1→2)-linked disaccharide derivative. This observation suggested that, for the preparation of **12**, benzyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**6**) might be obtained, under comparable conditions, by reaction of benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside[11] (**2**) with **4**. Condensation of **2** with 1.3 mol. equiv. of **4** in dichloromethane in the presence of silver carbonate gave a mixture that was shown by t.l.c. to contain two disaccharide derivatives having a similar rate of migration, in addition to unchanged **2** and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**5**), which arose from the hydrolysis of **4**. From the mixture, **6** crystallized in 36% yield, and its structure was established on the basis of the following observations: the compound gave microanalytical values and an n.m.r. spectrum that were appropriate for the expected disaccharide derivative **6**. *O*-Deacetylation of **6** with methanolic sodium methoxide gave crystalline benzyl 4,6-*O*-benzylidene-2-*O*-β-D-glucopyranosyl-α-D-glucopyranoside (**7**). Removal of the benzylidene group of **7** with hot, aqueous acetic acid gave crystalline **12**, which was hydrogenolyzed to give known[12] **13** as a monohydrate. The overall yield of **12** was 32% based on **2**. Acetylation of **6** gave **8** in crystalline form, whereas acetylation of the mother liquor of **6** gave, in 11% yield, crystalline benzyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**9**). The structure of **9** was assigned on the basis of its *O*-deacetylation, which gave crystalline benzyl 4,6-*O*-benzylidene-3-*O*-β-D-glucopyranosyl-α-D-glucopyranoside

(**10**). Removal of the benzylidene group afforded **20** as an amorphous powder. Hydrogenolysis of **20** provided known[13] **21**. Simultaneous formation of the derivatives of **13** and **21** as the major and minor products, respectively, in the reaction of **2** with **4** has also been observed for the analogous reaction[10] between **1** and **4**.

In a practical approach to **20**, treatment of benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside[14] (**3**) with 1.5 mol. equiv. of **4** in the presence of silver trifluoromethanesulfonate (triflate) and 1,1,3,3-tetramethylurea[15] in dichloromethane gave, in 78% yield, benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**11**) as an amorphous solid, after column chromatography on silica gel. *O*-Deacylation of **11** gave **10**, which was debenzylidenated to provide **20**. The overall yield of **20** was 67% based on **3**. Compound **3** was obtained in 76% yield by the partial benzoylation of **2** with 1.1 mol. equiv. of benzoyl chloride in the presence of triethylamine[16] in chloroform. Similar selective benzoylation of **2** with *N*-benzoylimidazole was reported to give **3** in 40% yield[14].

Acetylation of **12** and **20** gave benzyl α-sophoroside heptaacetate (**14**) and benzyl α-laminarabioside heptaacetate (**22**), respectively, which were hydrogenolyzed to afford the reducing heptaacetates **15** and **23**, respectively, both compounds being obtained in crystalline form. The anomeric configuration of **15** and **23** was not clearly determined. Both **15** and **23** showed a slight downward mutarotation in pyridine. This suggested the α-D configuration, but did not exclude the possibility of an anomeric mixture richer in the α-D anomer than is the equilibrium mixture of anomers in pyridine. The starting materials **15** and **23** could be recovered in crystalline form in high yield from the products of mutarotation, which confirmed that the change in optical rotation was a true mutarotation and not an acyl migration.

Condensation of hepta-*O*-acetyl-α-sophorosyl bromide[12] (**16**) with benzyl alcohol in the presence of mercuric cyanide in benzene gave, despite the presence of a nonparticipating β-D-glucopyranosyl group at O-2, a high yield (76%) of crystalline benzyl β-sophoroside heptaacetate (**17**), which was *O*-deacetylated to furnish **18** in crystalline form.

EXPERIMENTAL

General methods. — Unless otherwise stated, the general experimental conditions were the same as those described previously[17]. The following solvent systems (v/v) were used: (*A*) 1:1 and (*B*) 4:1 benzene–ethyl acetate.

Condensation of benzyl 4,6-O-benzylidene-α-D-glucopyranoside (**2**) *with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide* (**4**). — A solution of **2** (10 g) in dichloromethane (120 mL) was stirred with silver carbonate (10 g) and Drierite (30 g) for 2 h at room temperature, in the dark with exclusion of moisture. Iodine (3 g) and **4** (15 g, 1.3 mol. equiv.) were added, and the mixture was stirred for 30 h at room temperature, when t.l.c. (solvent *A*) showed the disappearance of **4**. The suspension was filtered through a bed of Celite, and the inorganic solids were washed with

chloroform. The combined filtrate and washings were evaporated to a syrup which was extracted with boiling water (3 × 150 mL) to remove[17] **5**. The resulting residue was crystallized from ethanol and recrystallized from the same solvent to give benzyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**6**; 6.91 g, 36%), m.p. 193–194°, $[\alpha]_D^{26}$ +52.3° (*c* 2.0, chloroform); n.m.r. (dimethyl sulfoxide-d_6): δ 7.53–7.25 (m, 10 H, arom. H), 5.60 (s, 1 H, PhC*H*), 5.37 (d, 1 H, $J_{3,OH-3}$ 5.0 Hz, exchangeable with D_2O, OH-3), 4.49, 4.77 (AB q, 2 H, *J* 12.0 Hz, PhCH_2O), 1.99 (s, 6 H, 2 OAc), 1.95 (s, 3 H, OAc), and 1.93 (s, 3 H, OAc).

Anal. Calc. for $C_{34}H_{40}O_{15}$: C, 59.30; H, 5.85. Found: C, 59.41; H, 5.79.

The mother liquors were evaporated to a syrup that was acetylated with acetic anhydride (30 mL) and pyridine (30 mL) overnight at room temperature. The mixture was poured into ice–water, and the precipitate formed was filtered off, washed with water, and dried. Crystallization from ethanol and recrystallization from ethanol–chloroform gave benzyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**9**; 2.31 g, 11%), m.p. 196–197°, $[\alpha]_D^{25}$ +49.7° (*c* 1.6, chloroform); n.m.r. (chloroform-*d*): δ 7.58–7.25 (m, 10 H, arom. H), 5.56 (s, 1 H, PhC*H*), 4.77, 4.89 (AB q, 2 H, *J* 12.0 Hz, PhCH_2O), 2.09 (s, 3 H, OAc), 1.98 (s, 6 H, 2 OAc), and 1.97 (s, 6 H, 2 OAc).

Anal. Calc. for $C_{36}H_{42}O_{16}$: C, 59.17; H, 5.79. Found: C, 59.11; H, 5.72.

Benzyl 4,6-O-benzylidene-2-O-β-D-glucopyranosyl-α-D-glucopyranoside (**7**). — A solution of **6** (3 g) in anhydrous methanol (50 mL) was treated with methanolic 0.5M sodium methoxide (2 mL). The solution was kept for 1 h at room temperature, neutralized with Amberlite IR-120 (H^+) ion-exchange resin, filtered, and evaporated to give a crystalline solid, which on recrystallization from methanol afforded **7** (2.11 g, 93%), m.p. 202–203°, $[\alpha]_D^{26}$ +72.7° (*c* 1.4, *N*,*N*-dimethylformamide); n.m.r. (dimethyl sulfoxide-d_6): δ 5.59 (s, 1 H, Ph-C*H*).

Anal. Calc. for $C_{26}H_{32}O_{11}$: C, 59.99; H, 6.20. Found: C, 60.12; H, 6.17.

Benzyl 2-O-β-D-glucopyranosyl-α-D-glucopyranoside (**12**). — A solution of **7** (2 g) in acetic acid (20 mL) was heated to 100°, water (12.5 mL) was added in small portions within a few min, and the mixture was kept for 15 min at 100°. The solvents were evaporated and the last traces of volatile compounds were removed by repeated co-distillation with toluene to give a crystalline mass, which was recrystallized from ethanol to afford **12** (1.53 g, 92%), m.p. 214–215°, $[\alpha]_D^{25}$ +90.6° (*c* 1.6, water); n.m.r. (deuterium oxide): δ 5.26 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.77; H, 6.53. Found: C, 52.70; H, 6.58.

A solution of **12** (0.4 g) in 95% ethanol (50 mL) was shaken with hydrogen at atmospheric pressure in the presence of palladium black (150 mg) for 24 h. The catalyst was removed by filtration, and the filtrate was evaporated to a solid which was recrystallized from aqueous ethanol–ether to give **13** as a monohydrate (277 mg, 83%), m.p. 190–192°, $[\alpha]_D^{23}$ +33.0 (10 min)→+20.3° (24 h, *c* 1.5, water); lit.[12] m.p. 180°, $[\alpha]_D^{20}$ +34.5→19.9° (20 h, *c* 4.0, water).

Benzyl 3-O-acetyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**8**). — Conventional acetylation of **6** (0.5 g) with 1:1

(v/v) acetic anhydride–pyridine (6 mL) overnight at room temperature and isolation in the usual way gave **8** (472 mg, 89%), m.p. 151–152° (ethanol), $[\alpha]_D^{26}$ +41.8° (*c* 2.0, chloroform).

Anal. Calc. for $C_{36}H_{42}O_{16}$: C, 59.17; H, 5.79. Found: C, 59.26; H, 5.71.

Benzyl 4,6-O-benzylidene-3-O-β-D-glucopyranosyl-α-D-glucopyranoside (**10**). — *O*-Deacetylation of **9** (1.6 g), as described for **6**, gave **10** (1.07 g, 94%), m.p. 234–235° methanol), $[\alpha]_D^{25}$ +70.8° (*c* 0.8, *N,N*-dimethylformamide); n.m.r. (dimethyl sulfoxide-d_6): δ 5.63 (s, 1 H, Ph-C*H*).

Anal. Calc. for $C_{26}H_{32}O_{11}$: C, 59.99; H, 6.20. Found: C, 60.09; H, 6.26.

Benzyl 3-O-β-D-glucopyranosyl-α-D-glucopyranoside (**20**). — Treatment of **10** (0.9 g) in acetic acid (10 mL) with water (6.7 mL) at 100°, as described for **7**, afforded **20** (703 mg, 94%) as an amorphous powder, $[\alpha]_D^{25}$ +77.2° (*c* 1.8, water); n.m.r. (deuterium oxide): δ 5.05 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.77; H, 6.53. Found: C, 52.65; H, 6.63.

Hydrogenolysis of **20** (0.3 g), as described for **12**, gave **21** (215 mg, 86%), m.p. 202–204° (aqueous methanol), $[\alpha]_D^{23}$ +15.8 (10 min)→+18.5° (24 h, *c* 0.8, water); lit.[13] m.p. 196–198° (aqueous methanol), $[\alpha]_D$ +15 (10 min)→+18.5° (24 h, *c* 3.0, water).

Benzyl 3,4,6-tri-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**14**). — Acetylation of **12** (0.9 g) with acetic anhydride–pyridine gave **14** (1.39 g, 92%) as an amorphous powder, $[\alpha]_D^{26}$ +51.6° (*c* 3.0, chloroform).

Anal. Calc. for $C_{33}H_{42}O_{18}$: C, 54.54; H, 5.83. Found: C, 54.67; H, 5.71.

Benzyl 2,4,6-tri-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**22**). — Acetylation of **20** with acetic anhydride–pyridine afforded **22** (780 mg, 93%), m.p. 185–186° (ethanol), $[\alpha]_D^{26}$ +57.0° (*c* 2.7, chloroform).

Anal. Calc. for $C_{33}H_{42}O_{18}$: C, 54.54; H, 5.83. Found: C, 54.47; H, 5.87.

Benzyl 2-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranoside (**3**). — A solution of benzoyl chloride (1.79 ml, 1.1 mol. equiv.) in dry chloroform (30 mL) was added at room temperature to a stirred solution of **2** (5 g) in anhydrous chloroform (40 mL) containing triethylamine (2.14 mL, 1.1 mol. equiv.). The solution was stirred for 24 h at room temperature, washed successively with cold, 3% hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried (Na_2SO_4), and evaporated. T.l.c. (solvent *B*) showed the presence of **3** (R_F 0.45) as the major product, together with two faster-moving, minor components (R_F 0.84 and 0.69), and some unchanged **2** (R_F 0.07). Elution of the mixture from a column of silica gel (300 g) with solvent *B* afforded **3** (4.91 g, 76%), double m.p. 61–62° and 105–106° (ethanol), $[\alpha]_D^{22}$ +113.0° (*c* 2.0, chloroform); lit.[14] m.p. 63–64° (ethanol), $[\alpha]_D$ +109.5° (*c* 0.82, chloroform).

Benzyl 2-O-benzoyl-4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**11**). — A solution of **4** (5.33 g, 1.5 mol. equiv.) in dry dichloromethane (20 mL) was added dropwise over a period of 20 min, with rigorous exclusion of moisture and light, to a stirred solution of **3** (4 g), silver triflate (3.66 g), and 1,1,3,3-tetramethylurea (3.89 mL) in dry dichloromethane (60 mL). The mixture was stirred overnight at room temperature, and then filtered through a Celite pad.

Following extraction of the solution with aqueous sodium hydrogencarbonate and water, the product obtained after concentration of the organic phase to a syrup was purified by elution from a column of silica gel (220 g) with solvent *B* to give **11** (5.35 g, 78%) as an amorphous solid, $[\alpha]_D^{18}$ +52.0° (*c* 1.5, chloroform); n.m.r. (chloroform-*d*): δ 8.18–7.15 (m, 15 H, arom. H), 5.59 (s, 1 H, Ph-C*H*), 4.48, 4.77 (AB q, 2 H, *J* 12.0 Hz, PhCH_2O), 1.97, 1.95, 1.88, and 1.58 (4 s, each 3 H, 4 OAc).

Anal. Calc. for $C_{41}H_{44}O_{16}$: C, 62.12; H, 5.59. Found: C, 62.05; H, 5.53.

O-Deacylation of **11** (5 g), as described for **6**, gave **10** (3.05 g, 93%), m.p. and mixed m.p. 234–235°, $[\alpha]_D^{22}$ +71.2° (*c* 1.0, *N*,*N*-dimethylformamide).

3,4,6-Tri-O-*acetyl-2*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-D-*glucopyranose* (**15**). — Compound **14** (0.6 g) was hydrogenolyzed, as described for **12**, to give **15** (469 mg, 89%), m.p. 150–152° (ethanol), $[\alpha]_D^{16}$ +27.7 (10 min)→+23.0° (48 h, *c* 1.8, pyridine).

Anal. Calc. for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 48.92; H, 5.76.

2,4,6-Tri-O-*acetyl-3*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-D-*glucopyranose* (**23**). — Hydrogenolysis of **22** (0.35 g), as described for **12**, afforded **23** (282 mg, 92%), m.p. 232–234° (ethanol), $[\alpha]_D^{16}$ +11.5 (10 min)→+4.6° (48 h, *c* 1.3, pyridine).

Anal. Calc. for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 48.94; H, 5.61.

Benzyl 3,4,6-tri-O-*acetyl-2*-O-(*2,3,4,6-tetra*-O-*acetyl-β*-D-*glucopyranosyl*)-*β*-D-*glucopyranoside* (**17**). — To a solution of **16** (3 g) in dry benzene (20 mL) containing mercuric cyanide (1.1 g) was added dry benzyl alcohol (5 mL), and the mixture was stirred for 5 h at room temperature. The solution was evaporated, and most of the benzyl alcohol was removed *in vacuo* at 90° by repeated co-distillation with water. The residue was dissolved in chloroform, and the solution was washed successively with aqueous potassium bromide and water, dried (Na_2SO_4), and evaporated to a crystalline mass, which was recrystallized from ethanol to give **17** (2.37 g, 76%), m.p. 113–114°, $[\alpha]_D^{18}$ −16.7° (*c* 1.9, chloroform).

Anal. Calc. for $C_{33}H_{42}O_{18}$: C, 54.54; H, 5.83. Found: C, 54.46; H, 5.75.

Benzyl 2-O-*β*-D-*glucopyranosyl*-*β*-D-*glucopyranoside* (**18**). — *O*-Deacetylation of **17** (2 g), as described for **6**, gave **18** (1.09 g, 92%), m.p. 192–194° (methanol), $[\alpha]_D^{18}$ −33.8° (*c* 1.7, water).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.77; H, 6.53. Found: C, 52.88; H, 6.59.

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