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Note

The Koenigs–Knorr reaction of benzyl 4,6-O-benzylidene-β-D-galactopyranoside with 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide

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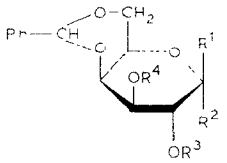
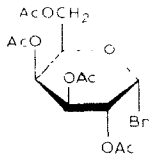
In continuation of our studies[1–4] on the relative reactivity of HO-2 and -3 in 4,6-*O*-benzylidene-D-glucopyranosides towards D-glucosylation in reactions of the Koenigs–Knorr type, we report here the determination of the ratio of 2- to 3-*O*-substitution in benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside[5] (**1**) towards 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**5**), in a silver carbonate-promoted, Koenigs–Knorr reaction, by careful isolation of the disaccharide derivatives formed. After this work had been completed, Gorin[6] reported that the ratio of 2- to 3-*O*-substitution in methyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**2**) towards **5** in a similar, silver carbonate-assisted reaction is ~2:3, as determined from the ^{13}C-n.m.r. spectrum of a mixture of the (1→2)- and (1→3)-β-D-linked disaccharide derivatives.



1 R^1 = OBzl, R^2 = R^3 = R^4 = H
2 R^1 = OMe, R^2 = R^3 = R^4 = H
3 R^1 = OBzl, R^2 = R^3 = H, R^4 = Bz
4 R^1 = R^3 = R^4 = H, R^2 = OMe



5

Because **1** is sparingly soluble in the solvents that are commonly used in the Koenigs–Knorr condensation[7], 1,1,2,2-tetrachloroethane[2] was used as the solvent. Treatment of **1** with 1.3 mol. equiv. of **5** in 1,1,2,2-tetrachloroethane at 30°, in the presence of silver carbonate and Drierite, gave a mixture that was shown by t.l.c. to contain two disaccharide derivatives and unreacted **1**, in addition to three mono-

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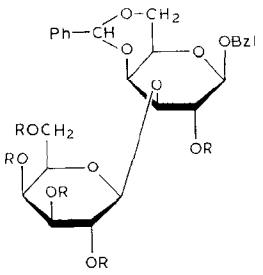
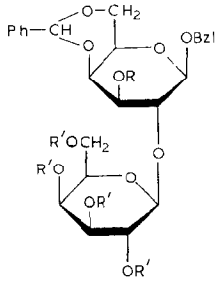
saccharide derivatives derived** from **5**. The mixture was fractionated on a prepacked column of silica gel. The *first* fraction eluted from the column afforded a mixture of two monosaccharide derivatives.

The *second* fraction eluted from the column gave a mixture of a mono- and a di-saccharide derivative. The mixture was acetylated, to facilitate isolation of the disaccharide derivative, and the resulting mixture of products was chromatographed on a column of silica gel to give, in 28% yield, benzyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (**6**) in crystalline form. The structure of **6** was established on the basis of the following observations. *O*-Deacetylation of **6** with methanolic sodium methoxide gave crystalline



6 R = Ac
7 R = H



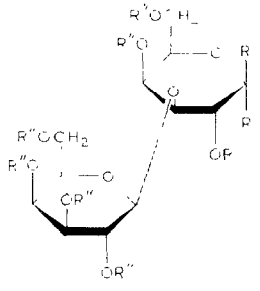
8 R = H, R′ = Ac
9 R = R′ = Ac
10 R = R′ = H

benzyl 4,6-*O*-benzylidene-3-*O*-β-D-galactopyranosyl-β-D-galactopyranoside (**7**). Removal of the benzylidene group of **7** with hot, aqueous acetic acid afforded crystalline benzyl 3-*O*-β-D-galactopyranosyl-β-D-galactopyranoside (**11**), which was hydrogenolyzed to provide the known[8-11] **12**. In view of the wide range of values of the m.p. and optical rotation reported[8-11] for **12**, compound **12** was successively methylated[12], the product hydrolyzed, the sugars reduced with sodium borohydride, and the alditols acetylated, to give a 1:1 mixture of the peracetates of 2,4,6-tri- and 2,3,4,6-tetra-*O*-methyl-D-galactitol (g.l.c.), thus confirming the structure of **12**.

The *third* fraction eluted from the column gave, in 20% yield, benzyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (**8**) as an amorphous powder, and its structure was determined as follows. Compound **8** was converted by acetylation with acetic anhydride–pyridine into the 3,2′,3′,4′,6′-penta-*O*-acetyl-4,6-*O*-benzylidene derivative **9**. Lipták and Nánási[13] described, without experimental details, the preparation of **9** by sequential saponification and

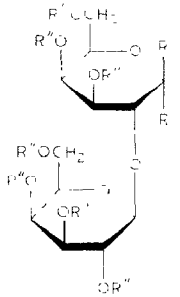
T.l.c. examination of the mixture obtained by treatment of **5 in 1,1,2,2-tetrachloroethane with silver carbonate and Drierite, under conditions identical (except for reaction time) with those for the reaction of **1** with **5**, showed the presence of these three derivatives. The compounds were neither isolated nor characterized.

acetylation of the disaccharide derivative obtained by coupling benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside[14] (**3**) with **5** in 1:1 benzene–nitromethane in the presence of mercuric cyanide, and reported m.p. 123–124° and $[\alpha]_D$ +8.7° for **9**. In our hands, however, **9** was obtained in two crystalline forms; one consisted of needles having a double m.p. between 120° and 194°, and the other, of prisms having a sharp m.p. at 193–194°. The optical rotation value ($[\alpha]_D$ +14.7°) of our sample was slightly different from that described[13]. *O*-Deacetylation of **8** gave crystalline benzyl 4,6-*O*-benzylidene-2-*O*-β-D-galactopyranosyl-β-D-galactopyranoside (**10**), which was debenzylidenated to afford crystalline benzyl 2-*O*-β-D-galactopyranosyl-β-D-galactopyranoside (**13**). Hydrogenolysis of **13** gave the known[15] **14**, whose m.p. agreed with that described[15], but it showed a mutarotation in water that differed somewhat from that reported[15].



11 R = OBzl, R′ = R″ = H

12 R, R′ = H, OH, R″ = H



13 R = OBzl, R′ = R = H

14 R, R′ = H, OH, R′ = H

In order to investigate the discrepancy observed for the physical constants of **9**, and to establish unambiguously the structure of **14**, the synthesis of **9**, according to the route described[13], as well as methylation studies of **14**, were undertaken. Condensation of **3** with 1.5 mol. equiv. of **5** in 1:1 benzene–nitromethane at 50° in the presence of mercuric cyanide, followed by *O*-deacylation, gave a mixture from which **10** was directly isolated in 70% yield in crystalline form, the physical constants being in good agreement with those of the compound prepared earlier from reaction of **1** with **5**, followed by *O*-deacetylation. Acetylation of **10** furnished crystalline **9** having the double m.p. and optical rotation values identical with those of the sample obtained earlier by reaction of **1** with **5**, and subsequent acetylation. Methylation[12] of **14**, followed by hydrolysis, reduction with sodium borohydride, and acetylation, produced a 1:1 mixture of the peracetates of 3,4,6-tri- and 2,3,4,6-tetra-*O*-methyl-D-galactitol (g.l.c.), which proved the structure of **14**.

The *fourth* fraction eluted from the column was unchanged **1**.

Thus, it was shown that (*a*) no product due to migration of the benzylidene acetal group, as encountered with the reaction between 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide and benzyl[16] or methyl 4,6-*O*-benzylidene-β-D-glucopyranoside[3], occurs in the reaction of **1** with **5**, and (*b*) on the basis of the yields

of the reaction products, the ratio of 2- to 3-*O*-substitution in **1** on silver carbonate-promoted reaction with **5** is 1:1.4. Recently, compound **14** was obtained[15] in low yield by condensation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**4**) with **5**, followed by acetolysis and *O*-deacetylation, but the isolation required a tedious, chromatographic separation. The reaction sequence **3** + **5**→**10**→**13**→**14**, giving **14** in an overall yield of 55% (based on **3**), appears to be practical for the preparation of **14**, as **3** is readily prepared[14,17] from **1** in high yield (89–95%), and no step needs purification of the products by column chromatography.

EXPERIMENTAL

General methods. — Unless stated otherwise, the general experimental conditions were the same as those described previously[18]. Retention times are given relative to that of 1,5-di-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-D-galactitol as unity. The following solvent systems (v/v) were used: (*1*) 2:1, (*2*) 1:1, and (*3*) 1:2 ethyl acetate–benzene.

*Condensation of benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside* (**1**) *with 1.3 mol. equiv. of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide* (**5**). — Compound **1** (3.01 g, 8.4 mmol) was dissolved, by heating, in anhydrous 1,1,2,2-tetrachloroethane (100 mL), and the solution was cooled to 30°. Dry silver carbonate (4 g) and ground Drierite (15 g) were added, and the mixture was stirred for 2 h in the dark with rigorous protection from moisture. Iodine (1 g) and **5** (4.49 g, 10.9 mmol) were added, and stirring was continued for 25 h at 30°, after which time, t.l.c. (solvent *1*) showed the disappearance of **5** and the presence of six components, having R_F values of 0.68, 0.63, 0.55, 0.51, 0.42 (**8**), and 0.25 (**1**), respectively. On the same t.l.c. plate, the mixture obtained by stirring **5** (0.25 g) in 1,1,2,2-tetrachloroethane (5.6 mL) in the presence of silver carbonate (0.22 g), Drierite (0.84 g), and iodine (56 mg) for 2 h at 30° indicated the disappearance of **5** and the presence of the components having R_F values of 0.68, 0.63, and 0.51. The reaction mixture was filtered through a pad of Celite, and the inorganic solids were washed with chloroform. The filtrate and washings were combined and evaporated, and the remaining solvent was co-evaporated with water *in vacuo* at 80°. A solution of the resulting syrup in chloroform was washed successively with water, 5% sodium thiosulfate, and water, dried (sodium sulfate), and evaporated to give a syrup which was fractionated on a pre-packed column (47 × 700 mm) of silica gel. The first fraction, eluted from the column with solvent *2*, gave a mixture of the two monosaccharide derivatives having R_F values of 0.68 and 0.63 in t.l.c. (solvent *1*).

The second fraction, eluted from the column with solvent *2*, gave a mixture of the disaccharide (R_F 0.55 in t.l.c.; solvent *1*) and monosaccharide (R_F 0.51 in t.l.c.; solvent *1*) derivatives. The mixture was acetylated with 1:1 (v/v) acetic anhydride–pyridine (20 mL) overnight at room temperature, and isolation in the usual way afforded a syrup which was chromatographed on a pre-packed column (38 × 520 mm) of silica gel. Elution with solvent *3* gave, first, a monosaccharide derivative

(not collected). Subsequent elution with solvent 2 gave benzyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (**6**) (1.72 g, 28%); m.p. 114–116° (ether–petroleum ether), $[\alpha]_D^{26}$ −13.4° (*c* 1.5, chloroform); n.m.r. data (chloroform-*d*): δ 7.62–7.29 (m, 10 H, arom. H), 5.56 (s, 1 H, benzylic-H), 2.13, 2.05, 2.02, 2.00, and 1.96 (s, each 3 H, 5 OAc).

Anal. Calc. for $C_{36}H_{42}O_{16}$: C, 59.17; H, 5.79. Found: C, 59.29; H, 5.85.

The third fraction, eluted from the column with solvent 1, gave benzyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (**8**) as an amorphous powder (1.16 g, 20%); $[\alpha]_D^{26}$ −17.0 (*c* 1.5, chloroform); n.m.r. data (chloroform-*d*): δ 7.57–7.10 (m, 10 H, arom. H), 5.53 (s, 1 H, benzylic-H), 2.58 (d, 1 H, *J* 6.0 Hz, disappeared on deuteration, HO-3), 2.11, 2.00, 1.92, and 1.90 (s, each 3 H, 4 OAc).

Anal. Calc. for $C_{34}H_{40}O_{15}$: C, 59.30; H, 5.85. Found: C, 59.39; H, 5.77.

The fourth fraction eluted from the column with methanol gave unchanged **1** (1.39 g).

Benzyl 4,6-O-benzylidene-3-O-β-D-galactopyranosyl-β-D-galactopyranoside (**7**). — A solution of **6** (3.67 g) in anhydrous methanol (80 mL) was treated with methanolic M sodium methoxide (1 mL). The solution was kept for 2 h at room temperature, made neutral with Amberlite IR-120 (H^+) ion-exchange resin, and the resin filtered off and washed with methanol. The filtrate and washings were combined, and evaporated to give a crystalline mass which was recrystallized from ethanol, to afford 7 (2.48 g, 95%); m.p. 263–264°, $[\alpha]_D^{25}$ +5.7° (*c* 1.4, *N*,*N*-dimethylformamide); n.m.r. data (dimethyl sulfoxide-d_6): δ 5.58 (s, 1 H, benzylic-H).

Anal. Calc. for $C_{26}H_{32}O_{11}$: C, 59.99; H, 6.20. Found: C, 60.10; H, 6.14.

Benzyl 3-O-β-D-galactopyranosyl-β-D-galactopyranoside (**11**). — A solution of **7** (2.0 g) in acetic acid (20 mL) was heated at 100°, and water (13 mL) was added in small portions during 15 min. After heating for 20 min at 100°, the solvents were removed by repeated codistillation with toluene, to give a solid which was recrystallized from ethanol, to afford **11** (1.54 g, 93%); m.p. 162–163°, $[\alpha]_D^{25}$ −4.2° (*c* 1.8, water).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.77; H, 6.53. Found: C, 52.69; H, 6.63.

3-O-β-D-Galactopyranosyl-D-galactose (**12**). — A solution of **11** (0.81 g) in acetic acid (10 mL) was hydrogenolyzed in the presence of 10% palladium-on-charcoal (0.3 g) at room temperature and pressure for 4 h. The catalyst was filtered off and washed with methanol, and the filtrate and washings were combined and evaporated. The residue was recrystallized from methanol, to give **12** (0.57 g, 86%); m.p. 198–200°, $[\alpha]_D^{21}$ +74.0° (2 min) → +62.7° (2 h, constant, *c* 1.6, water); lit.[8] m.p. 163–170° (aqueous methanol–1-butanol), $[\alpha]_D$ +75° (2 min) → +60° (2 h, constant; *c* 2.0, water); m.p.[9] 200° (aqueous methanol), $[\alpha]_D^{25}$ +54°; m.p.[10] 165°, $[\alpha]_D^{24}$ +84° (15 min) → +64° (4 h, constant; *c* 0.8, water); m.p.[11] 159–162° (aqueous ethanol), $[\alpha]_D^{22}$ +64° (*c* 1.0, water).

Methylation[12] of a portion of **12**, followed by hydrolysis with 0.5M sulfuric acid for 5 h at 100°, neutralization with barium carbonate, reduction with sodium

borohydride, acetylation, and g.l.c. of the resulting products, gave peaks corresponding to the peracetates of 2,3,4,6-tetra-*O*-methyl-D-galactitol (*T* 1.00, 50%) and 2,4,6-tri-*O*-methyl-D-galactitol (*T* 1.83, 50%).

Benzyl 3-O-acetyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (**9**). — A solution of **8** (0.66 g) in 1:1 (v/v) acetic anhydride–pyridine (7 mL) was kept overnight at room temperature. The solvents were removed by codistillation with toluene to give a white solid, which was recrystallized from ethanol to afford **9** as needles (0.65 g, 93%); m.p. 120–130° (broad), transformed into fine prisms, m.p. 193–194°, $[\alpha]_D^{25}$ +14.7° (*c* 1.9, chloroform); n.m.r. data: (chloroform-*d*): δ 7.55–7.25 (m, 10 H, arom. H), 5.50 (s, 1 H, benzylic-H), 2.13 (s, 6 H, 2 OAc), 1.97 (s 3 H, OAc), and 1.95 (s, 6 H, 2 OAc); lit.[13] m.p. 123–124°, $[\alpha]_D$ +8.7°. On some occasions, **9** crystallized from the same solvent as large prisms having m.p. 193–194°. Efforts to obtain each crystalline form by seeding failed, and **9** usually crystallized as needles.

Anal. Calc. for $C_{36}H_{42}O_{16}$: C, 59.17; H, 5.79. Found: C, 59.10; H, 5.74.

Benzyl 4,6-O-benzylidene-2-O-β-D-galactopyranosyl-β-D-galactopyranoside (**10**). — (*a*) *O*-Deacetylation of **8** (1.05 g), as described for the preparation of **7**, gave **10** (0.74 g, 94%); m.p. 262–263° (ethanol), $[\alpha]_D^{26}$ −5.9° (*c* 1.0, *N*,*N*-dimethylformamide); n.m.r. data (dimethyl sulfoxide-d_6): δ 5.60 (s, 1 H, benzylic-H).

Anal. Calc. for $C_{26}H_{32}O_{11}$: C, 59.99; H, 6.20. Found: C, 60.10; H, 6.26.

(*b*) A solution of **3** (1.88 g, 4.1 mmol) in 1:1 benzene–nitromethane (80 mL) was concentrated until 30 mL of the solvent mixture had distilled, and the mixture was then cooled to 50°. Mercuric cyanide (1.03 g, 4.1 mmol) and **5** (1.67 g, 4.1 mmol) were added, and the mixture was stirred for 8 h at 50°. Further additions of mercuric cyanide (0.51 g, 2 mmol) and **5** (0.83 g, 2 mmol) were made, and stirring was continued for another 10 h. The mixture was evaporated to dryness, and the residue was dissolved in chloroform. The solution was washed successively with water, aqueous potassium bromide, aqueous sodium hydrogencarbonate, and water, dried (magnesium sulfate), and evaporated. A solution of the residual syrup in dry methanol (50 mL) was treated with M sodium methoxide, and the mixture was processed as described for the preparation of **7**. The resulting residue was recrystallized twice from ethanol, to give **10** (1.48 g, 70%); m.p. and mixed m.p. 262–263°, $[\alpha]_D^{22}$ −5.8° (*c* 1.0, *N*,*N*-dimethylformamide); the n.m.r. spectrum was identical with that of the compound obtained in *a*.

Acetylation of **10** (0.44 g), as described earlier, afforded **9** as needles (0.57 g, 92%); double m.p. 120–130° and 193–194° (ethanol), $[\alpha]_D^{24}$ +14.8° (*c* 1.5, chloroform).

Benzyl 2-O-β-D-galactopyranosyl-β-D-galactopyranoside (**13**). — Treatment of **10** (1.18 g) in acetic acid (12 mL) with water (4 mL) at 100°, as described for **7**, gave **13** (0.90 g, 92%); m.p. 189–190° (ethanol), $[\alpha]_D^{25}$ −1.3° (*c* 1.5, water).

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.77; H, 6.53. Found: C, 52.71; H, 6.61.

2-O-β-D-Galactopyranosyl-D-galactose (**14**). — Compound **13** (0.50 g) was hydrogenolyzed, as described for **11**, to give **14** (0.34 g, 85%); m.p. 193–194° (metha-

nol), $[\alpha]_D^{22}$ +71.9° (2 min)→ +56.1° (2 h, constant; *c* 1.6, water); lit.[15] m.p. 195–196° (ethanol–water), $[\alpha]_D^{13}$ +86.4 (extrapolated)→ +63° (*c* 1.4, water).

Successive methylation[12] of a portion of **14**, hydrolysis, reduction with sodium borohydride, and acetylation, gave compounds that had the retention times of the peracetates of 2,3,4,6-tetra-*O*-methyl-D-galactitol (*T* 1.00, 50%) and 3,4,6-tri-*O*-methyl-D-galactitol (*T* 2.00, 50%).

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