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Note

Silver trifluoromethanesulfonate-promoted Koenigs–Knorr reaction of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide

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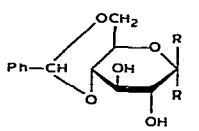
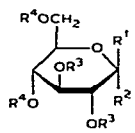
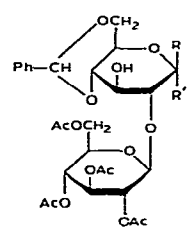
Recently, we reported[1] that the Koenigs–Knorr reaction of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**1**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**) in 1,1,2,2-tetrachloroethane in the presence of silver carbonate gives methyl 4,6-*O*-benzylidene-2-*O*- (**7**) and -3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**9**), and a trisaccharide derivative, methyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→3)-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)]-β-D-glucopyranoside (**16**). Condensation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**2**) with **3** in the presence of silver trifluoromethanesulfonate (triflate) and 1,1,3,3-tetramethylurea has been reported[2] to give methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**8**) in a yield (41%) comparable to that obtained by the reaction of **2** with **3** in the presence of silver carbonate[3,4]. This led us to investigate the reaction of **1** with **3** using this combination of catalyst and acid acceptor.



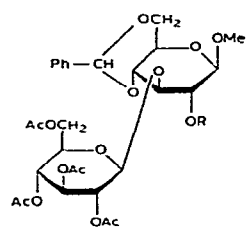
1 R = OMe R' = H
2 R = H, R' = OMe



3 R^1 = H R^2 = Br R^3 = R^4 = Ac
4 R^1 R^2 = H OH R^3 = R^4 = Ac
5 R^1 = OAc R^2 = H R^3 = R^4 = Ac
6 R^1 = OBzl R^2 = R^3 = H R^4 = Bzl



7 R = OMe R' = H
8 R = H R' = OMe



9 R = H
10 R = Ac

From the reaction mixture obtained by treating **1** with 1.1 mol. equiv. of **3** in 1,1,2,2-tetrachloroethane for 1.5 h at 25° in the presence of silver triflate and 1,1,3,3-tetramethylurea, the known[1] **7** was isolated in 19% yield by fractional crystallization, and the mother liquor was fractionated on silica gel by dry-packed column chromatography[5]. The first fraction was another 9% of **7**.

The second fraction eluted from the column initially appeared to be homogene-

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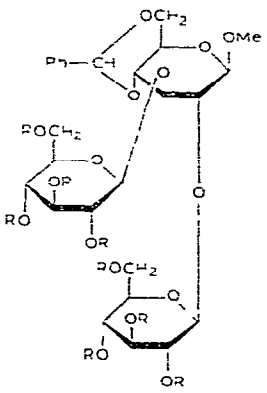
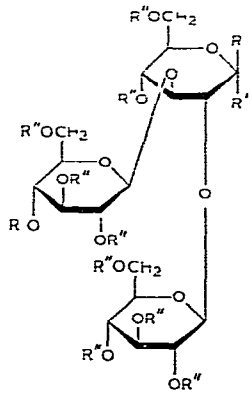
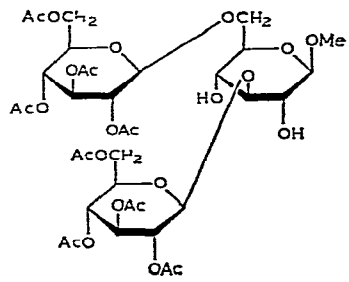


11 R = Ac
12 R = H



13 R = OMe, R' = R'' = H
14 R = OMe, R' = H, R'' = Me
15 R, R' = H, OH; R'' = H



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ous. but careful t.l.c. examination showed it to be a mixture of a minor and a major component having R_F values similar to that of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**4**), which arose from the hydrolysis of **3**. Efforts to separate the components by preparative t.l.c. were unsuccessful. When the components were acetylated with acetic anhydride and sodium acetate, t.l.c. indicated that the minor component was converted into a faster-moving product, while the major component remained intact. Fractionation of the mixture by column chromatography on silica gel gave, in the first fraction, 1,2,3.4,6-penta-*O*-acetyl-β-D-glucopyranose[6] (**5**), which was identified by comparison with an authentic specimen. To the component of lower mobility, obtained in 26% yield as an amorphous powder, was assigned the structure methyl *O*-(2.3,4.6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→2)-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)]-4,6-*O*-benzylidene-β-D-glucopyranoside (**11**) on the basis of the following observations: The n.m.r spectrum of **11** in chloroform-*d* showed a 5-proton multiplet at δ 7.50–7.33 for a phenyl group, 1-proton singlet at δ 5.57 for a benzylidene methine group, a 3-proton singlet at δ 3.53 for a methoxyl group, and 24-proton overlapping singlets at δ 2.10–1 98 for acetyl groups. which, combined with the results of the elemental analysis, suggested an octa-*O*-acetyl-mono-*O*-benzylidene derivative. *O*-Deacetylation of **11** gave the crystalline 4,6-*O*-benzylidene derivative **12**. which was debenzylidenated to give the crystalline free sugar **13**. Compound **13** was methylated with methyl iodide and sodium hydride in *N*,*N*-dimethylformamide[7] to afford the deca-*O*-methyl derivative **14** which, on successive hydrolysis, reduction with sodium borohydride, and acetylation produced a 1:2 mixture of the peracetates of 4,6-di-*O*- and 2,3,4,6-tetra-*O*-methyl-D-glucitol (g.l.c.). This indicated that **11** is a branched trisaccharide derivative containing (1→2)- and (1→3)-interglycosidic linkages. The n.m.r. spectrum of **13** in deuterium oxide at 40° showed three 1-proton doublets at δ 4.54 (*J* 7.5 Hz), 4.76 (*J* 7.0 Hz), and 4.82 (*J* 7.5 Hz), which were assigned to one anomeric and two inter-sugar anomeric protons, but they could not be differentiated. The magnitude of the coupling constants was

indicative of the β-D anomeric configuration of the inter-sugar glycosidic linkages in **11**. Partial acid hydrolysis of **13** gave a mixture, in which sophorose and laminarabiose were identified by p.c., confirming the interglycosidic linkages in **11**.

The third fraction eluted from the column proved to be the known[1] **9** (obtained in 14% yield as an amorphous solid), which was characterized as the crystalline 2,2',3',4',6'-penta-*O*-acetyl-4,6-*O*-benzylidene derivative[1] **10**. The final fraction was shown to be unreacted **1**.

Condensation of **1** with 2.2 mol. equiv. of **3** under the aforementioned conditions, followed by fractionation of the resulting product by the same procedure described above, gave **11** as the major product (87%), together with traces of **7** (3%) and **9** (2%).

It is noteworthy that the silver triflate-promoted reaction between **1** and **3** led to **11** besides **7** and **9**, whereas a similar silver carbonate-assisted reaction[1] between **1** and **3** led to **16**, as well as **7** and **9**. The formation of **16** has been explained[1] by assuming a synchronous mechanism[8,9] involving a migration of the benzylidene acetal group from O-4,6 to O-2,4 in **9**. At present, we cannot give any pertinent explanation as to the mechanism leading to **11** which resulted in the silver triflate-promoted reaction. However, the yields of **7**, **9**, and **11** (obtained by treatment of **1** with 1.1 or 2.2 mol. equiv. of **3**) indicate that HO-2 in **9** and HO-3 in **7**, both which are sterically hindered hydroxyl groups having a neighboring bulky tetra-*O*-acetyl-β-D-glucopyranosyl residue, could be further glucosylated to give **11**, suggesting that the intermediate formed from **3** in the silver triflate-promoted reaction is more activated than that produced from **3** in the silver carbonate-assisted reaction. 2,3-Di-*O*-β-D-glucopyranosyl-D-glucopyranose (**15**) has previously been obtained in 1.5% yield by condensation of benzyl 4,6-di-*O*-benzyl-β-D-glucopyranoside (**6**) with 3 mol. equiv. of **3** in the presence of silver oxide, followed by deblocking reactions[10].

EXPERIMENTAL

General methods. — Unless otherwise stated, the general experimental conditions were the same as those described previously[1]. Dry column chromatography was performed on Silica Gel No. 7734 (Merck) according to the procedure described by Hough *et al.*[5]. Descending paper chromatography was performed on Whatman No 1 paper in 3:1:1 (v/v) 1-butanol–pyridine–water[10], and detection with aniline hydrogenphthalate. The following solvent systems (v/v) were used: (*A*) 3:2 and (*B*) 1:1 ethyl acetate–benzene, and (*C*) 9:1 benzene–methanol.

Condensation of methyl 4,6-O-benzylidene-β-D-glucopyranoside (**1**) *with 1.1 mol. equiv. of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide* (**3**). — Compound **1** (3 g, 10.6 mmol) was dissolved by heating in anhydrous 1,1,2,2-tetrachloroethane (150 mL), the solution was cooled to 25°, and silver triflate (3.3 g, 12.8 mmol) and 1,1,3,3-tetramethylurea (3.85 mL, 32.4 mmol) were added. To the stirred mixture was added dropwise, over a period of 20 min, a solution of **3** (4.81 g, 11.7 mmol) in 1,1,2,2-tetrachloroethane (10 mL) with rigorous exclusion of moisture and light; the

temperature was controlled to 25° by external cooling. The mixture was stirred for 70 min at 25°, after which time t.l.c. (solvent *A*) indicated the absence of **3**. The reaction mixture was filtered through a bed of Celite, and the inorganic solids were washed with chloroform. The combined filtrate and washings were evaporated, and the remaining solvent was coevaporated with water *in vacuo* at 80° to give a syrup, which was crystallized from ethanol and recrystallized from the same solvent to give methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**7**) (1.21 g, 18.6%), m.p. 194–195°, $[\alpha]_D^{22}$ −29.6° (*c* 1.2, chloroform); lit.[1] m.p. 194–195°, $[\alpha]_D^{24}$ −29.7° (*c* 1.5, chloroform).

The mother liquors were evaporated to a syrup which was fractionated on a dry column of silica gel (400 g) with solvent *B*. The first fraction gave additional **7** (0.58 g, 8.9%).

The second fraction afforded a mixture of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**4**) and methyl *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→2)-*O*-[2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)]-4,6-*O*-benzylidene-β-D-glucopyranoside (**11**). Heating of the mixture in acetic anhydride (30 mL) with sodium acetate (3 g) at reflux for 10 min, and isolation in the usual way, gave a yellow solid which was fractionated by column chromatography on silica gel (150 g) with solvent *B*. The first-eluted component crystallized from ethanol to give 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**5**) (0.49 g), m.p. 132–133°, $[\alpha]_D^{23}$ +3.8° (*c* 1.1, chloroform); lit.[6] m.p. 132°, $[\alpha]_D^{20}$ +4° (chloroform)

The next-eluted component was unchanged **11** (2.61 g, 26.0%), $[\alpha]_D^{20}$ −29.1° (*c* 1.8, chloroform).

Anal. Calc. for $C_{42}H_{54}O_{24}$: C, 53.50; H, 5.77. Found: C, 53.67; H, 5.70.

The third fraction gave methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**9**) (0.91 g, 14.0%), $[\alpha]_D^{22}$ −30.4° (*c* 1.3, chloroform); lit.[1] $[\alpha]_D^{24}$ −30.7° (*c* 2.5, chloroform).

Conventional acetylation of **9** (0.53 g) with 1:1 (v/v) acetic anhydride–pyridine (5 mL) afforded methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**10**) (0.53 g, 92%), m.p. 227–228° (ethanol), $[\alpha]_D^{22}$ −67.0° (*c* 1.1, chloroform); lit.[1] m.p. 228–229°, $[\alpha]_D^{24}$ −67.9° (*c* 1.3, chloroform).

The fourth fraction contained **1** and was discarded.

Methyl O-β-D-*glucopyranosyl*-(1→2)-O-[β-D-*glucopyranosyl*-(1→3)]-*4,6*-O-*benzylidene*-β-D-*glucopyranoside* (**12**). — A solution of **11** (2 g) in anhydrous methanol (30 ml) was treated with methanolic 0.5M sodium methoxide (1 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 mass, which on recrystallization from ethanol gave **12** (1.2 g, 93%), m.p. 280–282°, $[\alpha]_D^{20}$ −44.5° (*c* 1.2, *N*,*N*-dimethylformamide); n.m.r. (dimethyl sulfoxide-d_6): δ 5.61 (s, 1 H, C_6H_5CH).

Anal. Calc. for $C_{26}H_{38}O_{16}$: C, 51.48; H, 6.31. Found: C, 51.65; H, 6.23.

Methyl O-β-D-*glucopyranosyl*-(1→2)-O-[β-D-*glucopyranosyl*-(1→3)]-β-D-*gluco*-

pyranoside (**13**). — A solution of **12** (1 g) in acetic acid (10 mL) was heated to 100°, water (6.5 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 codistillation with toluene to give a solid, which was crystallized from ethanol to afford **13** (0.78 g, 91%), m.p. 249–251°, $[\alpha]_D^{20}$ −32.0° (*c* 1.0, water).

Anal. Calc. for $C_{19}H_{34}O_{16}$: C, 44.02; H, 6.61. Found: C, 44.21; H, 6.51.

A solution of **13** (20 mg) in 25mM sulfuric acid (2 mL) was heated for 8 h at 100°, neutralized with barium carbonate, and evaporated to a syrup, in which sophorose (R_{Glc} 0.44) and laminarabiose (R_{Glc} 0.56) were identified by p.c.

Methyl O-(*2,3,4,6-tetra*-O-*methyl*-β-D-*glucopyranosyl*)-(*1*→*2*)-O-[*2,3,4,6-tetra*-O-*methyl*-β-D-*glucopyranosyl*-(*1*→*3*)]-*4,6-di*-O-*methyl*-β-D-*glucopyranoside* (**14**). — Sodium hydride (1.5 g) was added to a solution of **13** (0.5 g) in *N,N*-dimethylformamide (30 mL) at 0°. The mixture was stirred for 1 h, methyl iodide (8 mL) was added during 15 min, and the mixture was stirred with cooling for 2 h and for 30 h at room temperature. Methanol was added to destroy the excess of the hydride, the mixture was filtered, and the filtrate was evaporated. The resulting residue was purified by elution from a column of silica gel (35 g) with solvent *C* to give **14** (0.53 g, 83%), $[\alpha]_D^{20}$ −25.1° (*c* 0.8, chloroform); n.m.r. (chloroform-*d*): δ 6.68–6.19 (overlapping singlets, 33 H, 11 OMe).

Anal. Calc. for $C_{29}H_{54}O_{16}$: C, 52.88; H, 8.26. Found: C, 52.95; H, 8.41.

Hydrolysis of a portion of **14**, followed by reduction with sodium borohydride and acetylation gave compounds that had the retention times[1] of the peracetates of 2,3,4,6-tetra-*O*-methyl-D-glucitol (*T* 1.00, 66%) and 4,6-di-*O*-methyl-D-glucitol (*T* 4.01, 33%) on column *B*.

Condensation of **1** *with 2.2 mol. equiv. of* **3**. — Treatment of **1** (0.5 g) with **3** (1.6 g, 2.2 mol. equiv.) in 1,1,2,2-tetrachloroethane (25 mL) for 1.5 h at 25° in the presence of silver triflate (1.1 g) and 1,1,3,3-tetramethylurea (1.3 mL), followed by processing as described above, gave a syrupy product which was eluted on a dry column of silica gel (80 g) with solvent *B*, as described previously, to afford **7** (35 mg, 3.2%), **9** (19 mg, 1.8%), and a mixture of **4** and **11** (1.76 g). The mixture was acetylated as described previously, and the resulting product was fractionated on a column of silica gel (50 g) with solvent *B* to give **5** (0.22 g) and **11** (1.45 g, 86.8%).

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