Carbohydrate Research, 145 (1986) 307–311
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

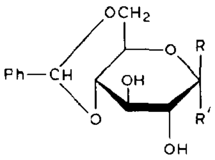
Selective α-D-glucosylation of methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranosides with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide under catalysis by halide ion

KEN'ICHI TAKEO* AND SAIMEI TEI

Department of Agricultural Chemistry, Kyoto Prefectural University, Shimogamo, Kyoto 606 (Japan)

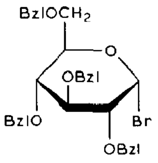
(Received March 15th, 1985; accepted for publication, May 22nd, 1985)

Our previous publications[1] reported the relative reactivity of HO-2 and -3 in 4,6-*O*-benzylidene-D-hexopyranosides towards D-glucosylation in reactions of the Koenigs–Knorr type. This paper describes the ratio of 2- to 3-*O*-substitution in methyl 4,6-*O*-benzylidene-α- (**1**) and β-D-glucopyranoside (**2**) by α-D-glucosylation with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide[2] (**3**) catalyzed[3] by halide ion.



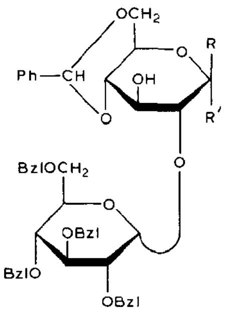
1 R = H, R′ = OMe

2 R = OMe, R′ = H



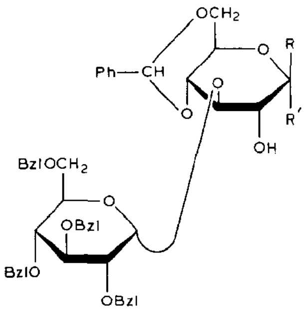
3

Bzl = $PhCH_2$



4 R = H, R′ = OMe

5 R = OMe, R′ = H



6 R = H, R′ = OMe

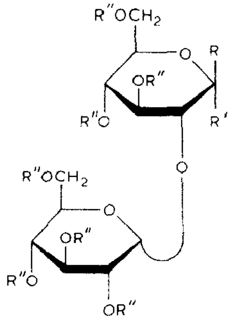
7 R = OMe, R′ = H

---

*To whom enquiries should be addressed.

0008-6215/86/$ 03.50

Condensation of **1** with 1.5 mol. equiv. of **3** in 1,2-dichloroethane and *N,N*-dimethylformamide in the presence of tetraethylammonium bromide[3] and molecular sieves gave a mixture containing two disaccharide derivatives as the major products, as well as some minor products and unreacted **1**. The major products were isolated by chromatography on a column of silica gel. The faster-moving disaccharide derivative (23%) was crystalline methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**4**). The structure of **4** was established by conversion into the known[4] α-kojibiose octaacetate (**10**). Catalytic hydrogenation of **4** in acetic acid in the presence of palladium-on-charcoal gave amorphous methyl α-kojibioside (**8**). Acetylation of **8** produced crystalline methyl α-kojibioside heptaacetate (**9**), which was acetolyzed[5] to furnish **10**. The slower-moving disaccharide (37%) was crystalline methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**6**). The structure of **6** was confirmed by hydrogenolysis, which produced the known[6] methyl α-nigeroside (**13**).



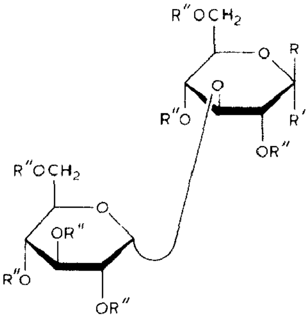
8 $R = R'' = H, R' = OMe$

9 $R = H, R' = OMe, R'' = Ac$

10 $R = H, R' = OAc, R'' = Ac$

11 $R = OMe, R' = R'' = H$

12 $R = OMe, R' = H, R'' = Ac$



13 $R = R'' = H, R' = OMe$

14 $R = OMe, R' = R'' = H$

Similar reaction of **2** with 1.5 mol. equiv. of **3**, followed by column chromatography, afforded crystalline methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**5**) and methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**7**) in 30 and 34% yields, respectively. Compound **5** was hydrogenolyzed to give amorphous methyl β-kojibioside[7] (**11**), characterized further as the crystalline heptaacetate[7] **12**, and hydrogenolysis of **7** yielded methyl β-nigeroside[8] (**14**), thus proving the structures of **5** and **7**.

The possibility of the formation of (1→2)-β- or (1→3)-β-D-linked disaccharide derivatives and/or trisaccharide derivatives substituted both at O-2 and -3 in **1** and **2** can not be precluded, as none of the minor products were isolated. However, on the basis of the yields of the major products, the approximate ratio of 2- to

3-*O*-substitution in **1** and **2** towards selective α-D-glucosylation with **3** in the halide-ion catalyzed reaction is 1:1.6 and 1:1.1, respectively.

EXPERIMENTAL

General methods. — Unless stated otherwise, the general experimental conditions were the same as those described previously[9]. ^{13}C-N.m.r. spectra (22.6 MHz) were recorded with a Hitachi R-90H spectrometer; tetramethylsilane (in chloroform-*d*) and sodium 4,4-dimethyl-4-silapentanoate-d_4 (in deuterium oxide) were the internal standards. For t.l.c. and column chromatography, the solvent system, 2:1 (v/v) hexane–ethyl acetate, was used.

*Condensation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside* (**1**) *with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide* (**3**). — A solution of **1** (2.0 g, 7.1 mmol) in dry 1,2-dichloroethane (25 mL) and *N,N*-dimethylformamide (7.5 mL) was stirred for 2 h at room temperature in the presence of tetraethylammonium bromide (2.23 g, 10.6 mmol) and 4A molecular sieves (10 g). A solution of **3** [freshly prepared[2] from the 1-(*p*-nitrobenzoate)[10] (7.33 g, 10.6 mmol)] in 1,2-dichloroethane (20 mL) was added, and the mixture was stirred for 2 days at room temperature. Methanol (5 mL) was added to decompose traces of remaining **3** (R_F 0.85), and the mixture was stirred for 5 h. T.l.c. showed the presence of **4** and **6** (major, R_F 0.46 and 0.24, respectively), together with minor by-products (R_F 0.75, 0.65, 0.56, and 0.15) and unchanged **1** (R_F 0.03). The solids were removed by filtration, and washed with dichloromethane. The combined filtrate was washed successively with aqueous sodium hydrogencarbonate and water, dried, and evaporated to a syrup, which was fractionated on a column of silica gel. The fractions containing the faster-moving product (R_F 0.46) were evaporated and the residue was recrystallized from ethanol to give methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**4**) (1.31 g, 23%), m.p. 159–160°, $[\alpha]_D^{26}$ +75.6° (*c* 2.0, chloroform); n.m.r. data (chloroform-*d*): δ_c 101.9 (benzylic C), 98.3 (C-1), 96.3 (C-1′), and 55.3 (OMe).

Anal. calc. for $C_{48}H_{52}O_{11}$: C, 71.62; H, 6.51. Found: C, 71.55; H, 6.70.

The fractions containing the slower-moving product (R_F 0.24) afforded methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**6**) (2.11 g, 37%), m.p. 126–127° (ether–petroleum ether), $[\alpha]_D^{26}$ +92.0° (*c* 1.2, chloroform); n.m.r. data (chloroform-*d*): δ_c 102.0 (benzylic C), 100.2 (C-1), 96.3 (C-1′), and 55.3 (OMe).

Anal. Calc. for $C_{48}H_{52}O_{11}$: C, 71.62; H, 6.51. Found: C, 71.81; H, 6.64.

*Methyl 2-*O*-α-D-glucopyranosyl-α-D-glucopyranoside* (**8**). — A solution of **4** (0.72 g) in acetic acid (10 mL) was hydrogenated in the presence of 10% palladium-on-charcoal (0.5 g) at atmospheric pressure for 1 day at room temperature. The mixture was processed conventionally and the product was purified by precipitation from ethanol–ether giving **8** as a white, hygroscopic powder (0.27 g, 84%), $[\alpha]_D^{25}$ +160.7° (*c* 1.6, water); n.m.r. data (deuterium oxide): δ_c 99.1, 99.0 (C-1,C-1′) and 57.5 (OMe).

*Methyl 3,4,6-tri-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl-α-*D*-glucopyranosyl)-α-*D*-glucopyranoside* (**9**). — Conventional acetylation of **8** (0.21 g) with acetic anhydride–pyridine gave **9** (0.34 g, 89%), m.p. 116–117° (ethanol), $[\alpha]_D^{24}$ +184.9° (*c* 1.6, chloroform); n.m.r. data (chloroform-*d*): δ_c 96.6 (C-1), 95.4 (C-1′), and 55.3 (OMe).

Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.85; H, 5.89. Found: C, 49.71; H, 5.96.

To a cooled solution of **9** (0.15 g) in acetic anhydride (0.5 mL) was added 4% (v/v) sulfuric acid in acetic anhydride (0.5 mL). The mixture was kept for 4 h at room temperature and processed, as described earlier[5], to give 1,3,4,6-tetra-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-glucopyranose (**10**) (0.12 g, 75%), m.p. 165–166° (ethanol), $[\alpha]_D^{24}$ +151.1° (*c* 1.6, chloroform); lit.[4] m.p. 166° (ethanol), $[\alpha]_D$ +150° (*c* 2.1, chloroform).

*Methyl 3-O-α-*D*-glucopyranosyl-α-*D*-glucopyranoside* (**13**). — Hydrogenolysis of **6** (1.05 g) as described for **4** gave **13** (0.41 g, 89%), m.p. 193–195° (2-propanol), $[\alpha]_D^{24}$ +208.5° (*c* 1.0, water); lit.[6] m.p. 193.5–195.5° (2-propanol), $[\alpha]_D^{20}$ +211° (*c* 0.41, water).

*Condensation of methyl 4,6-O-benzylidene-β-*D*-glucopyranoside* (**2**) *with* **3**. — Treatment of **2** (2.0 g, 7.1 mmol) with **3** [prepared from the 1-(*p*-nitrobenzoate), (7.33 g, 10.6 mmol)] as described for reaction of **1** with **3** gave a mixture containing **5** (R_F 0.53) and **7** (R_F 0.31) as the major products. Some by-products (R_F 0.82, 0.72, 0.61, and 0.16) and unreacted **2** were also present. The mixture was processed as already described to afford methyl 4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**5**) and methyl 4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranoside (**7**).

Compound **5** (1.73 g, 30%) had m.p. 169–170° (ethanol), $[\alpha]_D^{24}$ +36.9° (*c* 1.7, chloroform); n.m.r. data (chloroform-*d*): δ_c 104.2 (C-1), 101.6 (benzylic C), 96.9 (C-1′), and 57.2 (OMe).

Anal. Calc. for $C_{48}H_{52}O_{11}$: C, 71.62; H, 6.51. Found: C, 71.71; H, 6.60.

Compound **7** (1.93 g, 34%) had m.p. 179–180° (ethanol), $[\alpha]_D^{24}$ +21.8° (*c* 1.6, chloroform); n.m.r. data (chloroform-*d*): δ_c 104.1 (C-1), 101.9 (benzylic C), 96.3 (C-1′), and 57.4 (OMe).

Anal. Calc. for $C_{48}H_{52}O_{11}$: C, 71.62; H, 6.51. Found: C, 71.70; H, 6.45.

*Methyl 2-O-α-*D*-glucopyranosyl-β-*D*-glucopyranoside* (**11**). — Hydrogenolysis of **5** (1.05 g) afforded **11** as an amorphous powder (0.38 g, 83%), $[\alpha]_D^{24}$ +82.1° (*c* 1.1, water); lit.[7] $[\alpha]_D^{20}$ +83° (*c* 0.8, water).

*Methyl 3,4,6-tri-O-acetyl-2-O-(2,3,4,6-tetra-O-acetyl-α-*D*-glucopyranosyl)-β-*D*-glucopyranoside* (**12**). — Acetylation of **11** (0.16 g) gave **12** (0.25 g, 86%), m.p. 144–145° (ethanol), $[\alpha]_D^{24}$ +127.4° (*c* 2.0, chloroform); lit.[7] m.p. 142–143° (methanol).

*Methyl 3-O-α-*D*-glucopyranosyl-β-*D*-glucopyranoside* (**14**). — Hydrogenolysis of **7** (0.97 g) gave **14** (0.39 g, 91%); m.p. 210–211° (ethanol), $[\alpha]_D^{24}$ +228.5° (*c* 0.9, water); lit.[8] m.p. 208–209° (ethanol), $[\alpha]_D^{24}$ +229.4° (*c* 1.0, water).

REFERENCES

1 K. TAKEO, *Carbohydr Res.*, 59 (1977) 258–260; 77 (1979) 131–140; 86 (1980) 151–157; 87 (1980) 147–152; K. TAKEO, M. KITAJIMA, AND T. FUKATSU, *ibid* , 112 (1983) 158–164.

2 T ISHIKAWA AND H. G. FLETCHER, JR., *J. Org. Chem.*, 34 (1969) 563–571.

3 R. U. LEMIEUX, K. B. HENDRIKS, R. V. STICK, AND K. JAMES, *J. Am Chem. Soc.*, 97 (1975) 4056–4062; O. HINDSGAUL, T. NORBERG, J. LE PENDU, AND R. U. LEMIEUX, *Carbohydr. Res.*, 109 (1982) 109–142.

4 K. MATSUDA, *Nature,* 180 (1957) 985.

5 K. TAKEO, *Carbohydr. Res.*, 77 (1979) 245–251.

6 J.-R. POUGNY, M. A. M. NASSR, N. NAULET, AND P. SINAY, *Nouv. J. Chem.*, 2 (1978) 389–395.

7 T. USUI, M YOKOYAMA, N. YAMAOKA, K. MATSUDA, AND K. TSUJIMURA, *Carbohydr. Res.*, 33 (1974) 105–116.

8 K. TAKEO AND S. MATSUZAKI, *Carbohydr. Res.*, 113 (1983) 281–289.

9 K. TAKEO AND K. SHINMITSU, *Carbohydr. Res.*, 133 (1984) 135–145.

10 C. P. J. GLAUDEMANS AND H. G. FLETCHER, JR., *Methods Carbohydr. Chem.*, 6 (1972) 373–376.