Carbohydrate Research, 52 (1976) 17–22

HYDROGENOLYSIS OF BENZYLIDENE ACETALS: SYNTHESIS OF BENZYL 2,3,6,2′,3′,4′-HEXA-*O*-BENZYL-β-CELLOBIOSIDE, -MALTOSIDE, AND -LACTOSIDE, BENZYL 2,3,4,2′,3′,4′-HEXA-*O*-BENZYL-β-ALLOLACTOSIDE, AND BENZYL 2,3,6,2′,3′,6′-HEXA-*O*-BENZYL-β-LACTOSIDE

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(Received February 16th, 1976; accepted for publication, May 25th, 1976)

ABSTRACT

Hydrogenolysis of benzyl penta-*O*-benzyl-4′,6′-*O*-benzylidene-β-cellobioside (**4**), -maltoside (**5**), and -allolactoside (**16**) with $LiAlH_4$–$AlCl_3$ gave only the corresponding derivatives having HO-6′ free, in yields of 55, 78, and 90%, respectively. The main product of the hydrogenolysis of benzyl penta-*O*-benzyl-4′,6′-*O*-benzylidene-β-lactoside (**6**) also had HO-6′ free, but the isomer having HO-4′ free was also isolated. The role of the C-1 substituent in the galactose moiety in the direction of benzylidene ring-cleavage is discussed.

INTRODUCTION

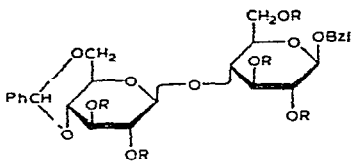
For the synthesis of 6-deoxyhexosyl-hexoses or (glycosyluronic acid)-hexoses, protected disaccharides (stable under the conditions of hydride reduction and oxidation) having HO-6′ free were required. Such compounds were obtained by using the method for stereoselective benzylidene ring-cleavage, observed for some 2,3-di-*O*-benzyl- and 3-*O*-benzyl-4,6-*O*-benzylidenehexopyranosides[1,2].

RESULTS AND DISCUSSION

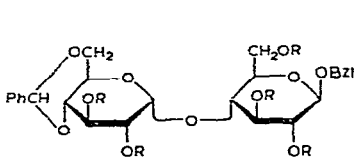
Benzyl 4′,6′-*O*-benzylidene-β-cellobioside[3] (**1**), -maltoside[3] (**2**), and -lactoside (**3**), when treated with benzyl chloride in the presence of powdered potassium hydroxide, gave the benzylated derivatives **4**, **5**, and **6**, respectively.

With an equimolar amount of the $LiAlH_4$–$AlCl_3$ reagent[1,2], benzyl 2,3,6,2′,3′-penta-*O*-benzyl-4′,6′-*O*-benzylidene-β-cellobioside (**4**) and the maltoside analogue (**5**) each gave only one product, namely, a hexa-*O*-benzyl derivative (**7** and **8**).

However, under similar conditions, the lactoside derivative **6** gave two isomeric hexa-*O*-benzyl compounds **9** and **10** in the ratio 83:17. This ratio corresponds to the proportion of 4- (84%) and 6-*O*-benzyl- (16%) derivatives obtained[2] on hydrogenolysis of phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside, but differs



1 R = H
4 R = Bzl



2 R = H
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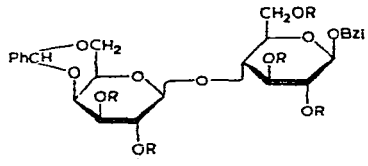
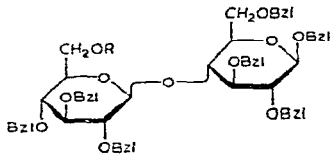
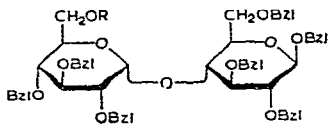


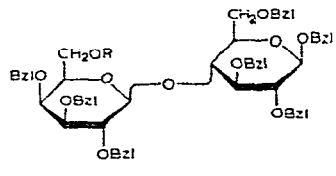
3 R = H
6 R = Bzl



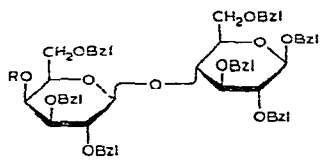
7 R = H
17 R = Me



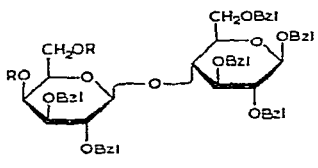
8 R = H
18 R = Me



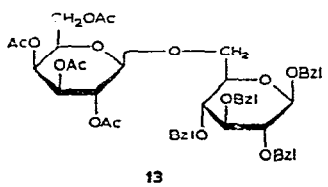
9 R = H
19 R = Me



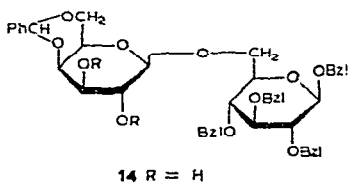
10 R = H
20 R = Me



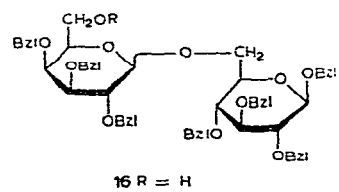
22 R = H
23 R = Me



13



14 R = H
15 R = Bzl



16 R = H
21 R = Me

from the ratio (95:5) observed on ring-cleavage of benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside. The higher proportion of the 6-*O*-benzyl compound (**10**) in the hydrogenolysis of **6** indicates that the direction of benzylidene ring-cleavage of galactoside derivatives is determined by both the steric bulk of the O-3 substituent and the character of the aglycon group. For benzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside, the aglycon moiety, because of free rotation around the $-CH_2$ group, hinders the attack of the reagent at HO-4. There is no such steric hindrance in **6** and phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside. This view is supported by the fact that hydrogenolysis of benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (**15**) (allolactoside derivative) gave only one product (**16**), as indicated by t.l.c. Compound **15** was synthesized as follows. Reaction of benzyl 2,3,4-tri-*O*-

benzyl-β-D-glucopyranoside[2] (**11**) with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**12**) in the presence of $Hg(CN)_2$ gave **13**. Deacetylation (Zemplén) of **13** gave **14**, which was benzylidenated and then benzylated to afford **15**.

The structures of the benzyl hexa-*O*-benzyldisaccharides **7**–**10** and **16** were confirmed by conversion into the corresponding methyl derivatives (**17**–**21**). The chemical shifts of the OMe groups in the n.m.r. spectra of **17**–**19** and **21** (δ 3.19, 3.23, 3.29, and 3.26, respectively) are similar to the values for the OMe groups in the spectra of benzyl 2,3,4-tri-*O*-benzyl-6-*O*-methyl-β-D-gluco- (δ 3.39) and -galactopyranoside (δ 3.33). According to the n.m.r. data, the structure of compound **21** was questionable, because the signal of MeO-4′ (δ 3.14) was 0.4–0.5 p.p.m. higher than for other methylated galactopyranoside derivatives[2,4,5]. Thus, the structures of **9** and **10** were also undecided. Therefore, **20** and **21** were catalytically hydrogenated and then acid-hydrolysed to give 6- and 4-*O*-methyl-D-galactose, respectively, which were identified by g.l.c. (10% OV-1 column) of their alditol acetates.

The apparent irregularity observed in the n.m.r. spectrum of **21** was also found for benzyl 2,3,6,2′,3′-penta-*O*-benzyl-4′,6′-di-*O*-methyl-β-lactoside (**23**) (δ 3.23 and 3.58). Compound **23** was prepared from **6** by acid hydrolysis (→ **22**) followed by methylation.

EXPERIMENTAL

Melting points were obtained with a Kofler apparatus and are uncorrected. Optical rotations were measured on solutions in $CHCl_3$ with a Polamat A (Zeiss) automatic photoelectric polarimeter at room temperature. I.r. spectra were recorded for KBr pellets with a Perkin–Elmer 700 instrument. N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Jeol MH-100 instrument. Reactions were monitored, and the purity of products was assessed, by t.l.c. on Kieselgel G (Merck). Kieselgel G was also used for short-column chromatography[6] with benzene–methanol mixtures, the proportions of which are given in brackets where R_F values are stated. Compounds were detected by charring with sulphuric acid. G.l.c. was performed with a Hewlett–Packard 5830 A chromatograph using helical stainless-steel columns.

*Benzyl 2,3,6,2′,3′-penta-*O*-benzyl-4′,6′-*O*-benzylidene-β-cellobioside* (**4**). — Benzyl 4′,6′-*O*-benzylidene-β-cellobioside[3] (**1**, 6.2 g) was treated with benzyl chloride (14 ml) and powdered KOH (2.1 g) for 6 h at 105–110°. Crystallization of the product from acetone (50 ml) gave **4** (7.40 g, 64.3%), m.p. 170–174°, $[\alpha]_D$ −13.5° (*c* 1.72), R_F 0.85 (97:3). N.m.r. data: δ 7.60–7.10 (m, 35 H, aromatic protons), 5.48 (s, 1 H, PhC*H*), and 5.15–3.00 (m, 26 H, benzyl, anomeric, and skeleton protons).

Anal. Calc. for $C_{61}H_{62}O_{11}$: C, 75.44; H, 6.43. Found: C, 74.98; H, 6.52.

*Benzyl 2,3,6,2′,3′,4′-hexa-*O*-benzyl-β-cellobioside* (**7**). — To a solution of **4** (6.5 g) in 1:1 ether–dichloromethane (200 ml), 2.21 g of $LiAlH_4$ was added in three portions with stirring and the mixture was slowly heated to the boiling point. To the hot solution, 6.5 g of $AlCl_3$ dissolved in ether (60 ml) was added during 30 min and

boiling was continued for 1.5–2 h. T.l.c. then indicated the absence of starting material. To the cooled mixture, ethyl acetate was added, and $Al(OH)_3$ was precipitated by the addition of water (10 ml). After dilution with ether (40 ml), the organic layer was separated and the residue was washed with a little ether. The organic phase was washed with water (3 × 20 ml), dried, and concentrated to give **7** (3.56 g, 54.6%), m.p. 96–98°, $[\alpha]_D$ +7.5° (*c* 1.06), R_F 0.82 (95:5). N.m.r. data: δ 7.40–7.15 (m, 35 H, aromatic protons), 5.15–4.30 (m, 15 H, benzyl and anomeric protons), 4.15–3.10 (m, 13 H, skeleton protons), and 1.70 (broad, 1 H, OH).

Anal. Calc. for $C_{61}H_{64}O_{11}$: C, 75.28; H, 6.63. Found: C, 75.53; H, 6.41.

*Benzyl 2,3,6,2',3',4'-hexa-*O*-benzyl-6'-*O*-methyl-β-cellobioside* (**17**). — To a solution of **7** (197 mg) in *N*,*N*-dimethylformamide (3 ml), methyl iodide (0.2 ml) and Ag_2O (200 mg) were added. After shaking for 24 h, the mixture was diluted with chloroform and filtered. The filtrate was washed successively with 1% aqueous KCN (3 × 20 ml) and water (3 × 20 ml), dried, and concentrated to give syrupy **17** (170 mg, 85.4%), $[\alpha]_D$ +5° (*c* 1.64), R_F 0.8 (97:3). N.m.r. data: δ 7.50–7.06 (m, 35 H, aromatic protons) and 5.15–3.05 [m, 31 H, benzyl, anomeric, and skeleton protons, and OMe (δ 3.20)].

Anal. Calc. for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.21; H, 6.58.

*Benzyl 2,3,6,2',3'-penta-*O*-benzyl-4',6'-*O*-benzylidene-β-maltoside* (**5**). — Compound **2**[3] (2 g) was benzylated, as described above for **4**, to give **5** (1.41 g, 43.6%), m.p. 96–98°, $[\alpha]_D$ −8° (*c* 0.79), R_F 0.82 (98:2). N.m.r. data: δ 7.65–7.05 (m, 35 H, aromatic protons), 5.71 (d, 1 H, *J* 4.5 Hz, H-1'), 5.54 (s, 1 H, PhC*H*), 5.15–4.35 (m, 13 H, benzyl and anomeric protons), and 4.35–3.35 (m, 12 H, skeleton protons).

Anal. Calc. for $C_{61}H_{62}O_{11}$: C, 75.44; H, 6.43. Found: C, 75.98; H, 6.55.

*Benzyl 2,3,6,2',3',4'-hexa-*O*-benzyl-β-maltoside* (**8**). — Hydrogenolysis of **5** (1 g), as described above for **7**, gave syrupy **8** (0.78 g, 78%), $[\alpha]_D$ +19° (*c* 0.84), R_F 0.61 (97:3).

Anal. Calc. for $C_{61}H_{64}O_{11}$: C, 75.28; H, 6.63. Found: C, 75.45; H, 6.35.

*Benzyl 2,3,6,2',3',4'-hexa-*O*-benzyl-6'-*O*-methyl-β-maltoside* (**18**). — Methylation of **8**, as described for **17**, gave syrupy **18** (150 mg, 79%), $[\alpha]_D$ +16.5° (*c* 0.97), R_F 0.81 (97:3). N.m.r. data: δ 7.65–7.00 (m, 35 H, aromatic protons), 5.66 (d, 1 H, *J* 3 Hz, H-1'), 5.10–4.35 (m, 15 H, benzyl and anomeric protons), and 4.30–3.10 [m, 15 H, skeleton protons and OMe (δ 3.23)].

Anal. Calc. for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.21; H, 6.58.

*Benzyl 4',6'-*O*-benzylidene-β-lactoside* (**3**). — Benzyl β-lactoside[7] (7.5 g) was treated with benzaldehyde (25 ml) and freshly fused $ZnCl_2$ (5 g) at room temperature. Crystallization of the product from 1-butanol gave **3** (4.8 g, 45.2%), m.p. 167°, $[\alpha]_D$ −51° (*c* 1.64, pyridine), R_F 0.3 (8:2).

Anal. Calc. for $C_{26}H_{32}O_{11}$: C, 59.99; H, 6.19. Found: C, 58.52; H, 5.80.

*Benzyl 2,3,6,2',3'-penta-*O*-benzyl-4',6'-*O*-benzylidene-β-lactoside* (**6**). — Benzylation of **3** (11.3 g), as described above for **4**, and crystallization of the product from 1:3 acetone–ethanol gave **6** (14.1 g, 70.5%), m.p. 122–123°, $[\alpha]_D$ −19° (*c* 1.35), R_F 0.72

(97:3). N.m.r. data: δ 7.65–7.05 (m, 35 H, aromatic protons), 5.48 (s, 1 H, PhC*H*), and 5.35–2.88 (m, 26 H, benzyl, anomeric, and skeleton protons).

Anal. Calc. for $C_{61}H_{62}O_{11}$: C, 75.44; H, 6.43. Found: C, 75.08; H, 6.31.

Benzyl 2,3,6,2',3',4'-hexa-O-benzyl-β-lactoside (**9**) *and benzyl 2,3,6,2',3',6'-hexa-O-benzyl-β-lactoside* (**10**). — Hydrogenolysis of **6**, as described for **7**, gave two compounds (R_F 0.21 and 0.35, benzene–methanol, 98.5:1.5). Crystallization of the former from ethanol yielded **9** (3.55 g, 71%), m.p. 109–111°, $[\alpha]_D$ −14° (*c* 1.29). N.m.r. data: δ 7.55–7.15 (m, 35 H, aromatic protons), 5.15–4.05 (m, 15 H, benzyl and anomeric protons), 4.05–3.50 (m, 13 H, skeleton protons), and 2.10 (t, 1 H, *J* 7.5 Hz, OH).

Anal. Calc. for $C_{61}H_{64}O_{11}$: C, 75.28; H, 6.63. Found: C, 75.53; H, 6.48.

The residue obtained after crystallisation was purified by short-column chromatography (benzene–methanol, 97:3) to give syrupy **10** (0.71 g, 14.4%), $[\alpha]_D$ +4° (*c* 0.55).

Anal. Calc. for $C_{61}H_{64}O_{11}$: C, 75.28; H, 6.63. Found: C, 74.93; H, 6.53.

Benzyl 2,3,6,2',3',4'-hexa-O-benzyl-6'-O-methyl-β-lactoside (**19**). — Compound **9** (550 mg) was methylated, as described above for **17**, to yield syrupy **19** (500 mg, 90%) which crystallized on storage at room temperature, m.p. 75–76°, $[\alpha]_D$ −9° (*c* 0.43), R_F 0.78 (97:3). N.m.r. data: δ 7.40–6.90 (m, 35 H, aromatic protons), and 5.00–3.10 [m, 31 H, benzyl, anomeric, and skeleton protons, and OMe (δ 3.29)].

Benzyl 2,3,6,2',3',6'-hexa-O-benzyl-4'-O-methyl-β-lactoside (**20**). — Methylation of **10** (186 mg) in the usual manner gave syrupy **20** (150 mg, 79.5%), $[\alpha]_D$ −5° (*c* 0.4), R_F 0.78 (97:3). N.m.r. data: δ 7.70–6.90 (m, 35 H, aromatic protons) and 5.10–3.00 [m, 31 H, benzyl, anomeric, and skeleton protons, and OMe (δ 3.14)].

Anal. Calc. for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 75.59; H, 6.61.

Benzyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**13**). — A solution of $Hg(CN)_2$ (1.32 g) and 2.7 g of benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**11**) in 150 ml of dry benzene–nitromethane (1:1) was concentrated at atmospheric pressure to 40 ml, and 2.16 g of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**12**) were added. After stirring for 2 h at 45°, the mixture was cooled, filtered, and concentrated. A solution of the residue in chloroform was filtered, washed successively with 5% aqueous KI (3 × 50 ml) and water (3 × 50 ml), dried, and concentrated. Crystallization of the residue from ethanol (85 ml) gave **13** (4.2 g, 96.5%), m.p. 172–174°, $[\alpha]_D$ −20.5° (*c* 0.97), R_F 0.70 (97:3).

Anal. Calc. for $C_{48}H_{54}O_{15}$: C, 66.18; H, 6.22. Found: C, 66.25; H, 6.44.

Benzyl 2,3,4-tri-O-benzyl-6-O-(4,6-O-benzylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (**14**). — To a solution of **13** (2.4 g) in methanol (100 ml), 0.5 ml of 0.1M methanolic NaOMe was added. After 24 h, the solution was neutralized with acetic acid and concentrated, and benzene (3 × 20 ml) was distilled from the residue. The residue was shaken benzaldehyde (20 ml) and $ZnCl_2$ (2 g) for 12 h and then poured onto ice–water (50 ml). The precipitate was washed with hexane (3 × 30 ml), dried, and crystallized from ethyl acetate to give **14** (1.65 g, 76%), m.p. 200–202°, $[\alpha]_D$ −23° (*c* 0.61), R_F 0.64 (9:1).

Anal. Calc. for $C_{47}H_{50}O_{11}$: C, 71.38; H, 6.37. Found: C, 70.62; H, 6.39.

Benzyl 2,3,4-tri-O-benzyl-6-O-(2,3-di-O-benzyl-4,6-O-benzylidene-β-D-galactopyranosyl)-β-D-glucopyranoside (**15**). — Treatment of **14** (1.1 g) with benzyl chloride (10 ml) and powdered KOH (1 g) at 100–105° for 6 h, followed by crystallization of the product from 2:1 acetone–ethanol (60 ml), gave **15** (1.15 g, 94.2%), m.p. 190–192°, $[\alpha]_D$ +4° (*c* 1.11), R_F 0.8 (97:3).

Anal. Calc. for $C_{61}H_{62}O_{11}$: C, 75.44; H, 6.43. Found: C, 75.62; H, 6.47.

Benzyl 2,3,4-tri-O-benzyl-6-O-(2,3,4-tri-O-benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**16**). — Compound **15** (0.8 g) was hydrogenolyzed as described above for **7**. Crystallization of the product from cyclohexane (15 ml) gave **16** (0.72 g, 90%), m.p. 148–150°, $[\alpha]_D$ −25° (*c* 0.71), R_F 0.75 (97:3).

Anal. Calc. for $C_{61}H_{64}O_{11}$: C, 75.28; H, 6.63. Found: C, 75.40; H, 6.86.

Benzyl 2,3,4-tri-O-benzyl-6-O-(2,3,4-tri-O-benzyl-6-O-methyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**21**). — Methylation of **16** (150 mg) was carried out as described above for **17**. Crystallization of the product from cyclohexane (7 ml) yielded **21** (130 mg, 85.5%), m.p. 141–142°, $[\alpha]_D$ −5° (*c* 0.4), R_F 0.65 (97:3). N.m.r. data: δ 7.44–6.95 (m, 35 H, aromatic protons) and 5.05–3.10 [m, 31 H, benzyl, anomeric, and skeleton protons, and OMe (δ 3.26)].

Anal. Calc. for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.73. Found: C, 75.11; H, 6.51.

Benzyl 2,3,6,2',3'-penta-O-benzyl-β-lactoside (**22**). — A mixture of **6** (3 g) in acetic acid (70 ml) and ethanol (40 ml) was heated at 80°. After 5 h, t.l.c. indicated the absence of starting material. The reaction mixture was diluted with chloroform, washed till neutral, and concentrated, and the residue was recrystallized from ethanol to give **22** (2.35 g, 86.4%), m.p. 146–147°, $[\alpha]_D$ +13° (*c* 0.67, acetone), R_F 0.46 (97:3).

Anal. Calc. for $C_{54}H_{58}O_{11}$: C, 73.44; H, 6.62. Found: C, 72.98; H, 6.53.

Benzyl 2,3,6,2',3'-penta-O-benzyl-4',6'-di-O-methyl-β-lactoside (**23**). — Compound **22** (1.5 g) was methylated in the usual manner and the product was crystallized from ethanol to give **23** (1.25 g, 81.2%), m.p. 100–101°, $[\alpha]_D$ +7° (*c* 1.09, acetone), R_F 0.78 (97:3). N.m.r. data: δ 7.50–6.85 (m, 30 H, aromatic protons) and 5.05–3.05 [m, 32 H, benzyl, anomeric, and skeleton protons, and OMe (δ 3.58 and 3.23)].

Anal. Calc. for $C_{56}H_{62}O_{11}$: C, 73.82; H, 6.85. Found: C, 74.08; H, 6.58.

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