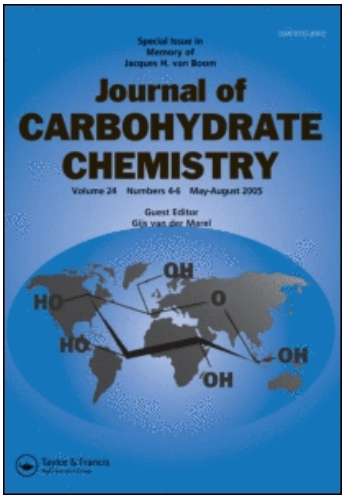

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SELECTIVE α-D-GALACTOSYLATION OF BENZYL 4,6-O-BENZYLIDENE-β-D-GALACTOPYRANOSIDE WITH 2,3,4,6-TETRA-O-BENZYL-α-D-GALACTOPYRANOSYL BROMIDE UNDER CATALYSIS BY HALIDE ION

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ABSTRACT

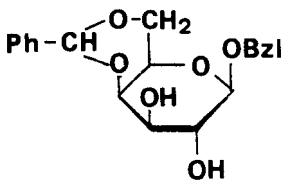
Selective glycosylation of benzyl 4,6-O-benzylidene-β-D-galactopyranoside (1) with 1.5 mole equivalent of 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl bromide (2) catalyzed by halide ion gave the (1→2)-α- (5) and (1→3)-α-D-linked disaccharide (7) derivatives in 22 and 40% yields, respectively. The D-galactose unit at the reducing end of 2-O-α-D-galactopyranosyl-D-galactose (11) at equilibrium in D_2O was shown by ^{13}C NMR spectroscopy to exist in the pyranose and furanose forms in the ratio of ∿2:1.

INTRODUCTION

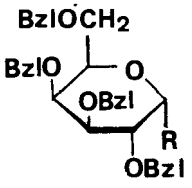
The present paper is concerned with an extension of our studies[1] of the relative reactivity of C-2 and C-3 hydroxyl groups in 4,6-O-benzylidene-D-hexopyranosides toward D-glycosylation in reactions of the Koenigs-Knorr type and reports preferential α-D-galactosylation of benzyl 4,6-O-benzylidene-β-D-galactopyranoside (1) with 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl bromide[2] (2) catalyzed[2] by halide ion.

RESULTS AND DISCUSSION

Condensation of 1 with 1.5 mole equivalent of 2 in 1,2-dichloroethane and N,N-dimethylformamide in the presence of tetraethylammonium bromide[2] and molecular sieve gave a mixture, which was chromatographed

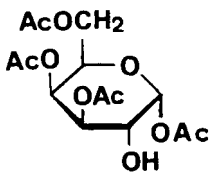


1



2 R = Br

3 R = Cl



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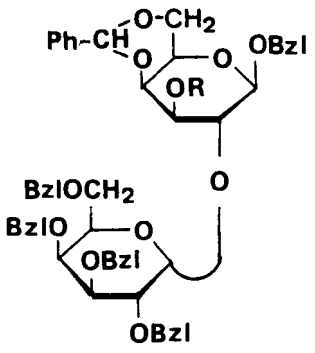
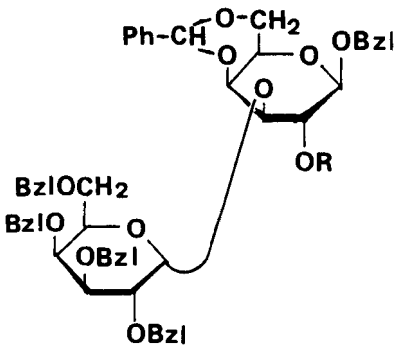


5 R = H

6 R = Bz

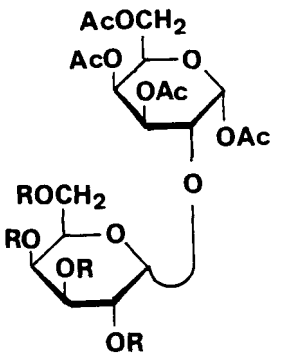


7 R = H

8 R = Bz

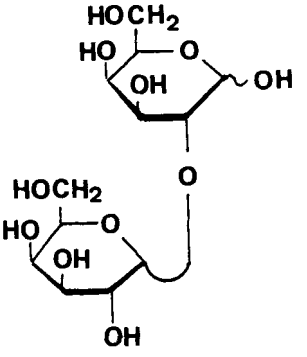
to afford, as the major products, crystalline benzyl 4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (5) and benzyl 4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (7) in 22 and 40% yields, respectively. The position of the interglycosidic linkages in 5 and 7 was assigned from the ^{1}H NMR spectra of the 3-O- and 2-O-benzoyl derivatives 6 and 8, derived from 5 and 7, respectively. The H-3 resonance of 6 appeared at δ 5.38 as a doublet of doublets ($J_{2,3}$ 10.1 and $J_{3,4}$ 3.7 Hz), whereas the H-2 resonance of 8 occurred at δ 5.77 as a doublet of doublets ($J_{1,2}$ 8.3 and $J_{2,3}$ 10.2 Hz). The coupling constants indicated[3] that the benzoyl groups in 6 and 8 were located at O-3 and O-2, respectively, proving the (1→2) and (1→3)-D-interglycosidic linkages in 5 and 7, respectively. The α configuration of the interglycosidic bonds in 5 and 7 was inferred[4] from the ^{13}C NMR signals for C-1' at 96.65 and 94.5 ppm , respectively.

Catalytic hydrogenolysis of 5 and 7 in acetic acid in the presence of Pd/C gave 2-O-α-D-galactopyranosyl-D-galactose[5] (11) and 3-O-α-D-galactopyranosyl-D-galactose[2,6,7] (13), respectively. Reduction of 11 with sodium borohydride gave the crystalline disaccharide alditol 12,

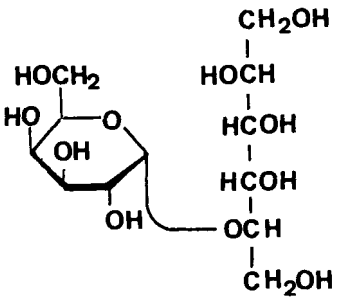


9 R = Bzl

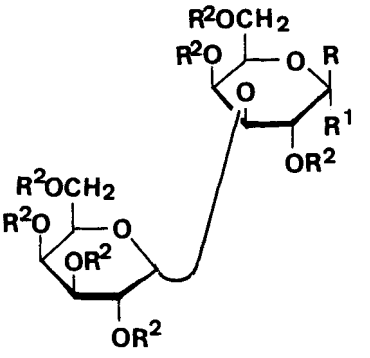
10 R = H



11



12



13 R, R^1 = H, OH; R^2 = H

14 R = OAc, R^1 = H, R^2 = Ac

the ^{13}C NMR of which showed a signal for C-1' at 100.7 ppm , in accord[4] with the α configuration at C-1'. Compound 13 was characterized further as the β-octaacetate[6,7] 14. However, the physical constants (mp 201-203 °C, $[\alpha]_D$ +159.5° → +167.1°) of 11 were very different from those (mp 173-175 °C, $[\alpha]_D$ +105°) reported by Doboszewski and Zamojski[5] for this compound. The ^{13}C NMR spectrum of 11 in D_2O contained, within the region of the signals for anomeric carbon atoms,[4] significant signals at 102.4 and 100.95 ppm, in addition to the signals for C-1' at 100.7 and 99.2 ppm and the signals for C-1β and C-1α at 99.0 and 92.3 ppm, respectively, which suggested that the pyranose anomers at the reducing end of 11 exist in equilibrium with the furanose anomers. The ratio of the pyranose and furanose forms was ∿2:1, as estimated by the relative peak intensities of the signals for the anomeric carbon atoms. The observation that the D-galactose derivative glycosylated or alkylated at O-2 tends to exist as

furanose forms to a greater extent at equilibrium in D_2O than does the parent sugar was also supported by comparison of the ^{13}C NMR spectrum of 2-O-methyl-D-galactose[8] with that of D-galactose. The ^{13}C NMR spectrum of 2-O-methyl-D-galactose at equilibrium in D_2O showed the signals for C-1 of the pyranose and furanose anomers at 98.9 and 92.2 ppm and 102.2 and 96.3 ppm with a pyranose to furanose ratio of ~6.4:1. D-Galactose at equilibrium in D_2O showed the pyranose and furanose forms in the ratio of ~12.1:1. A similar finding, that 2,3-di-O-methyl-D-galactose also tends to exist as the furanose forms to a greater extent than does D-galactose itself in D_2O and dimethyl sulfoxide, has been reported.[9]

In investigating the above discrepancies of the physical properties of 11, an alternative preparation of 11 was explored in which 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose (4) was coupled with 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl chloride[10] (3) in ether and 1,2-dimethoxyethane[11,12] in the presence of silver perchlorate[11-13] and molecular sieve[11,12] to give the known[5] 9 in 66% yield after column chromatography. Hydrogenolysis of 9 afforded 10, which was O-deacetylated to provide 11, identical (mp, $[\alpha]_D$, and ^{13}C NMR[14]) with the compound obtained earlier by reaction of 1 with 2.

In the reaction of 1 with 2, the possibility of the formation of (1→2)-β- and (1→3)-β-D-linked disaccharide derivatives and/or trisaccharide derivatives substituted both at O-2 and -3 in 1 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 towards selective α-D-galactosylation with 2 in the halide-ion catalyzed reaction is 1:1.8.

EXPERIMENTAL

General Methods. These were the same as those reported previously.[12] The solvent systems (v/v), (A) 1:1, (B) 2:1, and (C) 4:1 hexane-ethyl acetate, were used for chromatography.

Condensation of Benzyl 4,6-O-Benzylidene-β-D-galactopyranoside (1) With 2,3,4,6-Tetra-O-benzyl-α-D-galactopyranosyl Bromide (2). A solution of 1 (2.0 g, 5.6 mmol) in dry 1,2-dichloroethane (40 mL) and N,N-dimethylformamide (15 mL) was stirred for 2 h at room temperature with exclusion of moisture in the presence of tetraethylammonium bromide (1.76 g, 8.4 mmol) and molecular sieves 4A (10 g). A solution of 2 [freshly prepared[15] from the 1-(p-nitrobenzoate)[2], (5.77 g, 8.4 mmol)] in 1,2-dichloroethane (20 mL) was added, and the mixture was stirred for 3 days at room tempera-

ture. Methanol (5 mL) was added to decompose traces of remaining 2, and the mixture was stirred for 6 h. TLC (solvent A) showed the presence of 5 and 7 (R_F 0.33 and 0.60, respectively), together with minor side products (R_F 0.86, 0.79, 0.70, 0.53, 0.23, and 0.17) and unchanged 1 (R_F 0.07). Insoluble material was collected on a bed of Celite and washed with dichloromethane. The combined filtrate and washings were washed successively with water, aqueous sodium hydrogencarbonate, and water, dried, and concentrated, and the residue was subjected to column chromatography. Elution with solvent B gave benzyl 4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (7) (1.97 g, 40%), mp 171-172 °C (from ethanol-chloroform), $[\alpha]_D^{20}$ +35.4° (c 1.48, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 101.9 (C-1), 101.0 (PhCH), 94.5 (C-1'), 66.5 (C-6'), 78.6, 76.8, 76.2, 75.1, 74.6, 73.1 (2C), 72.5, 72.3, 70.3, 69.8, and 69.2 (3C) ($PhCH_2$ and remaining carbon atoms).

Anal. Calcd for $C_{54}H_{56}O_{11}$: C, 73.62, H, 6.41. Found: C, 73.79; H, 6.34.

Further elution of the column with solvent A afforded benzyl 4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (5) (1.08 g, 22%), mp 158-159 °C (from ethanol), $[\alpha]_D^{20}$ +34.2° (0.98, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 102.3 (C-1), 101.25 (PhCH), 96.65 (C-1'), 66.5 (C-6'), 79.2, 76.2, 75.95, 75.2, 75.0, 74.2, 73.2 (2C), 72.0, 71.65, 70.5, 69.9, 69.4, and 69.05 ($PhCH_2$ and remaining carbon atoms).

Anal. Calcd for $C_{54}H_{56}O_{11}$: C, 73.62; H, 6.41. Found: C, 73.70, H, 6.51.

Benzyl 3-O-Benzoyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (6). Conventional benzoylation of 5 (95 mg) with benzoyl chloride-pyridine, followed by column chromatography (solvent C) of the product, afforded amorphous 6 (96 mg, 94%), $[\alpha]_D^{20}$ +74.0° (c 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.13-6.91 (m, 35H, 7 Ph), 5.72 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1'), 5.48 (s, 1H, PhCH), 5.38 (dd, 1H, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 3.7 Hz, H-3).

Anal. Calcd for $C_{61}H_{60}O_{12}$: C, 74.37; H, 6.14. Found: C, 74.50; H, 6.02.

Benzyl 2-O-Benzoyl-4,6-O-benzylidene-3-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (8). Conventional benzoylation of 7 (90 mg), followed by column chromatography (solvent C) of the product, gave amorphous 8 (94 mg, 93%), $[\alpha]_D^{20}$ +50.5° (c 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.17-6.99 (m, 35H, 7 Ph), 5.77 (dd, 1H, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.43 (s, 1H, PhCH), and 5.13 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1').

Anal. Calcd for $C_{61}H_{60}O_{12}$: C, 74.37; H, 6.14. Found: C, 74.47; H, 6.25.

2-O-α-D-Galactopyranosyl-D-galactose (11). (a) A solution of 5 (0.75 g) in acetic acid (15 mL) was hydrogenated in the presence of 10% Pd/C (0.8 g) at atmospheric pressure for 2 days at room temperature. The catalyst was filtered off on a Celite pad and washed with methanol, and the combined filtrate and washings were concentrated. The residue was crystallized from aqueous ethanol to give 11 (0.24 g, 82%), mp 201-203 °C, $[\alpha]_D^{20}$ +159.5° (2 min) → +167.1° (final; c 1.82, H_2O); lit.[5] mp 173-175 °C, $[\alpha]_D$ +105° (c 2, H_2O); ^{13}C NMR (D_2O): δ 102.4 (C-1βf*), 100.95 (C-1αf), 100.7 and 99.2 (C-1'p*), 99.0 (C-1βp), 96.65 (C-2βf), 92.3 (C-1αp), 90.0 (C-2αf), 84.15 (C-4βf), 83.3 (C-4αf), 79.7 (C-2βp), 77.65 (C-2αp, C-5βp), 75.9 (C-3βp), 65.5 and 65.1 (C-6α,βf), 63.75 and 63.7 (C-6, 6'p), and 84.5, 77.2, 75.6, 74.5, 74.2, 74.0, 73.7, 73.3, 73.1, 71.9, 71.65, 71.1, 71.0, 70.8, and 70.4 (remaining carbon atoms).

Anal. Calcd for $C_{12}H_{22}O_{11}$: C, 42.11; H, 6.48. Found: C, 42.01; H, 6.00.

(b) A mixture of 4 (2.11 g, 6.1 mmol), silver perchlorate (2.07 g, 10 mmol), and powdered molecular sieves 4A (10 g) in ether (100 mL) and 1,2-dimethoxyethane (10 mL) was stirred for 2 h at room temperature in the dark with exclusion of moisture, and then cooled to -10 °C. A solution of 3 (5.08 g, 9.1 mmol) in ether (30 mL) was added dropwise during 30 min, and the mixture was allowed to attain 0 °C gradually, and then stirred for 2 h at 0 °C. The solid was collected on a Celite pad and washed with ether, and the combined filtrate and washings were washed successively with water, aqueous sodium hydrogencarbonate, and water, dried, and concentrated. Column chromatography (solvent B) of the product gave 1,3,4,6-tetra-O-acetyl-2-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-α-D-galactopyranose (9) as a syrup (3.48 g, 66%), which failed to crystallize; $[\alpha]_D^{20}$ +78.9° (c 2.01, $CHCl_3$); lit.[5] mp 109-110 °C, $[\alpha]_D$ +69° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 6.45 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.97 (d, 1H, $J_{1',2'}$ = 3.3 Hz, H-1'), and 1.98 (s, 12H, 4 OAc); ^{13}C NMR ($CDCl_3$): δ 170.1-169.0 (C=O), 96.5 (C-1'), 89.0 (C-1), 61.2 (C-6), 20.6-20.4 ($CO\underline{C}H_3$), 78.6, 75.5, 74.9, 74.7, 73.45, 72.8, 69.9, 69.1, 68.75, 68.6, 68.3, and 67.6 ($Ph\underline{C}H_2$ and remaining carbon atoms).

Hydrogenolysis of 9 (3.02 g), as described for 5, afforded 1,3,4,6-tetra-O-acetyl-2-O-α-D-galactopyranosyl-α-D-galactopyranose (10) as a

* f : furanose, p : pyranose.

syrup (1.65 g, 93%), $[\alpha]_D^{21}$ +154.4° (c 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 170.3 -169.9 (C=O), 98.2 (C-1'), 89.8 (C-1), 61.8 and 61.2 (C-6, 6'), 21.0, 20.7, 20.6, and 20.45 ($COCH_3$), 70.7, 70.5, 70.1, 69.8, 68.8, 68.6 (2C), and 67.5 (remaining carbon atoms).

A solution of 10 (1.30 g) in methanol (20 mL) was treated with methanolic 1M sodium methoxide (0.5 mL) for 2 h at room temperature, neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated to give 11 (0.70 g, 80%), mp (from aqueous ethanol) and mixture mp 201-203 °C, $[\alpha]_D^{21}$ +160.0° (2 min) → +167.4° (final; c 1.05, H_2O); the ^{13}C NMR spectrum was identical to that of the compound prepared in a.

2-O-α-D-Galactopyranosyl-D-galactitol (12). Compound 11 (110 mg) was reduced with sodium borohydride (20 mg) in water (3 mL) overnight at room temperature. The solution was treated with Amberlite IR-120 (H^+) resin to decompose the excess of hydride. The resin was filtered off and washed with methanol, and the combined filtrate and washings were concentrated. Several additions and evaporations of methanol gave a solid, which was recrystallized from methanol to give 12 (103 mg, 91%), mp 160-160.5 °C, $[\alpha]_D^{25}$ +115.8° (c 1.51, H_2O); ^{13}C NMR (D_2O): δ 100.7 (C-1'), 79.3 (C-2), 65.9 (C-1), 63.9 (2C, C-6, 6'), 74.2, 72.7, 72.1 (2C), 71.9, 71.8, and 71.3 (remaining carbon atoms).

Anal. Calcd for $C_{12}H_{24}O_{11}$: C, 41.86; H, 7.03. Found: C, 41.62; H, 7.20.

3-O-α-D-Galactopyranosyl-D-galactose (13). Hydrogenolysis of 7 (1.07 g), as described for 5, gave 13 (0.37 g, 90%), $[\alpha]_D^{20}$ +156.3° (c 1.20, H_2O); lit. $[\alpha]_D$ +184° (c 1.25, H_2O),[2] $[\alpha]_D^{25}$ +155° (c 0.3, H_2O),[6] $[\alpha]_D^{26}$ +149° (c 1.6, H_2O).[7]

1,2,4,6-Tetra-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl)-β-D-galactopyranose (14). Conventional acetylation of 13 (108 mg) with acetic anhydride-pyridine gave 14 (156 mg, 73%), mp 155-156 °C (from ethanol), $[\alpha]_D^{25}$ +110.8° (c 0.71, $CHCl_3$); lit. mp 157.5-158.5 °C, $[\alpha]_D^{25}$ +110.2° (c 0.5, $CHCl_3$)[6]; mp 156-157 °C, $[\alpha]_D^{26}$ +114° (c 0.95, $CHCl_3$).

ACKNOWLEGMENT

We thank Prof. A. Zamojski of Polish Academy of Sciences for the ^{13}C NMR spectrum of 11.

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14. The ^{13}C NMR spectrum of 11 was essentially identical with that kindly given by Dr. Zamojski after this work had been completed. Their spectrum of 11 also contained the signals that may be attributable to the furanose forms. We do not have any doubts about the identity of our and their[5] compounds 11, but we were unable to explain the striking differences between the physical constants reported here and given in the literature.[5]

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