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SYNTHESIS OF 2-*O*-BENZYL- AND 2,3- AND 2,6-DI-*O*-BENZYL-D-GALACTOSE*

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ABSTRACT

The following ethers, of potential value for the synthesis of α-D-galactopyranosides, were prepared: 2-*O*-benzyl-D-galactose, 2,6-di-*O*-benzyl-D-galactose, and 2,3-di-*O*-benzyl-D-galactose. Isopropylidenation of methyl α-D-galactopyranoside in the presence of phosphorus pentaoxide gave its 3,4- and 4,6-*O*-isopropylidene derivatives. Treatment of the 3,4-acetal with trityl chloride in pyridine produced the 6-trityl ether, which was benzylated with benzyl chloride and sodium hydride in *N*,*N*-dimethylformamide to yield the 2-benzyl ether. Acid hydrolysis of this product gave 2-*O*-benzyl-D-galactose. Benzylation of methyl 3,4-*O*-isopropylidene-α-D-galactopyranoside, followed by hydrolysis, gave 2,6-di-*O*-benzyl-D-galactose. Similarly, 2,3-di-*O*-benzyl-D-galactose was obtained by acid hydrolysis of methyl 2,3-di-*O*-benzyl-4,6-*O*-isopropylidene-α-D-galactopyranoside and of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside.

INTRODUCTION

The Koenigs–Knorr reaction[1] for glycoside synthesis, in which an acylated glycosyl halide reacts with an aglycon derivative in the presence of a suitable catalyst to form a glycoside, generally results in the production of 1,2-*trans* glycosides, in which the substituents at C-1 and C-2 are *trans* to each other. One major factor involved in this stereospecificity may be neighboring-group participation by the acyl substituent at O-2. Recently, a number of workers have investigated the effects, on the ratio of anomeric products formed in the Koenigs–Knorr reaction, of employing glycosyl halides in which the acyl group at O-2, as well as at other oxygen atoms of the sugar, is replaced by the nonparticipating, benzyl ether group. Ishikawa and Fletcher[2]

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showed that methanolysis of *p*-nitrobenzoylated 2-*O*-benzyl-D-glucopyranosyl halides produces mainly the 1,2-*cis* (*i.e.*, α) anomer. Flowers[3] used this 2-*O*-benzyl-D-glucose derivative in the stereospecific synthesis of α-linked disaccharides. Dejter-Juszynski and Flowers[4] reported the stereospecific synthesis of α-linked L-fucosyl disaccharides in which the L-fucosyl group was substituted at O-2 with a benzyl ether group.

In addition, Ishikawa and Fletcher[2] examined the anomeric ratio of products formed in the methanolysis of partially benzylated D-glucopyranosyl bromides substituted at various oxygen atoms on the hexopyranosyl ring, and found that the ratio of *cis* to *trans* anomers formed is dependent on the number of benzyl groups present.

We have synthesized the 2-*O*-benzyl, 2,3-di-*O*-benzyl, and 2,6-di-*O*-benzyl derivatives of D-galactose as potential intermediates for Koenigs–Knorr reactions analogous to those just described, as part of a project for the stereospecific synthesis of α-linked galactosides.

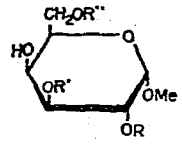
RESULTS AND DISCUSSION

Isopropylidenation of methyl α-D-galactopyranoside monohydrate (**1**) by the method of Wolfrom *et al.*[5] produced the 3,4- and 4,6-*O*-isopropylidene derivatives (**2** and **3**, respectively) in the ratio of ~4 to 1. Identification of **3** as the 4,6-isopropylidene acetal of **1** was achieved from the following evidence: (*a*) **3** was unchanged under the conditions of tritylation that convert **2** into **4**, and (*b*) benzylation of **3** followed by acid hydrolysis yielded the same dibenzyl ether (**10**) as that similarly derived from methyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**11**).

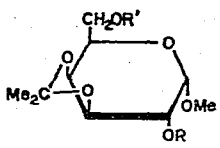
Although the isomers **2** and **3** could be conveniently separated by chromatography on silica gel, it was found that purification at this step was not necessary for synthesis of the ultimate benzyl ethers desired. Direct benzylation of the syrupy mixture of acetals was followed by chromatography on silica gel, which gave separation of the resultant 2,6- and 2,3-di-*O*-benzyl derivatives (**7** and **9**, respectively). Acid hydrolysis of purified **7** produced crystalline **8** in an overall yield of 41%. 2,3-Di-*O*-benzyl-D-galactose (**10**) was synthesized by acid hydrolysis of **9** (as well as by benzylation of **11**, followed by acid hydrolysis, as reported by Fréchet and Baer[6]).

In initial syntheses of 2-*O*-benzyl-D-galactose (**6**), the intermediates (**2**, **4**, and **5**) were isolated at each step in the reaction sequence; in later experiments, however, such purification was found unnecessary, and the reactions were conducted sequentially without the purifications. Upon acid hydrolysis of methyl 2-*O*-benzyl-3,4-*O*-isopropylidene-6-*O*-trityl-α-D-galactopyranoside (**5**), crystalline 2-*O*-benzyl-D-galactose (**6**) was obtained in 24% overall yield. Although the synthesis of **6** has been reported[7], the method described here employs fewer reaction steps and results in a higher overall yield.

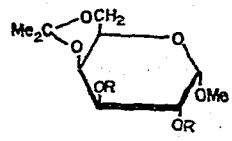
In separate, identical syntheses of 2-*O*-benzyl-D-galactose, crystals (designated *A* and *B*) of two different melting points were produced, one m.p. agreeing with the



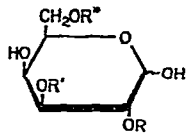
	1	7a	9a
R	H	$PhCH_2$	$PhCH_2$
R'	H	H	$PhCH_2$
R''	H	$PhCH_2$	H



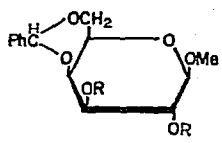
	2	4	5	7
R	H	H	$PhCH_2$	$PhCH_2$
R'	H	Ph_3C	Ph_3C	$PhCH_2$



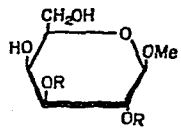
	3	9
R	H	$PhCH_2$



	6	8	10
R	$PhCH_2$	$PhCH_2$	$PhCH_2$
R'	H	H	$PhCH_2$
R''	H	$PhCH_2$	H



	11	12
R	H	$PhCH_2$



	12a
R	$PhCH_2$

literature value of Singh and Adams[7]. Elemental analyses of both materials showed good agreement with calculated values. P.m.r. spectra obtained for each of the two materials in several solvents showed them to be virtually identical. Borate chromatography and automated colorimetric analysis of both samples by the method of Lee[8] showed that they had identical elution times in this system. When the two products (*A* and *B*) were each reduced with sodium borohydride, and the corresponding peracetates and per(trimethylsilyl) ethers separately examined by gas–liquid chromatography, identical retention-times for the derivatives of *A* and *B* were measured.

EXPERIMENTAL

General methods. — Methyl α-D-galactopyranoside monohydrate (**1**) was obtained from Pfanstiehl Laboratories, Inc. (Waukegan, Illinois). Chlorotriphenylmethane was obtained from Raylo Chemicals Ltd. (Alberta, Canada). All solvents used were of reagent grade. Pyridine was dried by refluxing it over calcium hydride, followed by distillation, and was stored over Linde Molecular Sieves (type 4A) (Union Carbide). All other solvents used were dried by storage over Molecular Sieves. Sodium hydride (50% emulsion in oil) was obtained from Metal Hydrides (Beverly, Mass.) and was used without washing.

Melting points (uncorrected) were obtained with a Fisher–Johns melting-point apparatus. Optical rotations were measured with a Bendix ETL-NPL Automatic Polarimeter, Type 143A, or a Perkin–Elmer Model 141 polarimeter. P.m.r. spectra were recorded with a JEOL NMH-100 spectrometer, unless otherwise specified.

For thin-layer chromatography (t.l.c.), silica gel (0.25 mm thick) precoated on

aluminum sheets (E. Merck) was used. For column chromatography, silica-gel powder (70–235 mesh) (E. Merck) was used. Components on a t.l.c. plate were detected by spraying with 10% H_2SO_4 in ethanol, and then charring by heating at 130°, or by fluorescence quenching (when aromatic groups were present).

A Packard gas chromatograph (Model 7800) was used for gas–liquid chromatography with columns of 3% of SE-30 on Gas Chrom Q (100–120 mesh, 6 ft × 2 mm i.d.), and 3% of OV-17 on Gas Chrom Q (100–120 mesh, 6 ft × 4 mm i.d.). Flow rates of carrier gas (N_2) were 60 ml/min (SE-30) and 70 ml/min (OV-17), respectively. Anion-exchange chromatography of sugar–borate complexes was conducted on a column of Rexyn-201 (20–40 μm) (Fischer Scientific Co.) eluted (without a gradient) at 56° with 0.27M sodium borate buffer (pH 7.8), and analyzed by the automated, colorimetric method of Lee[8]. Elemental analyses (single analysis, unless otherwise indicated) were performed by Galbraith Laboratories, Inc. (Knoxville, Tenn.).

Methyl 3,4-O-isopropylidene-α-D-galactopyranoside (**2**) *and methyl 4,6-O-isopropylidene-α-D-galactopyranoside* (**3**). — The reaction was performed according to Wolfrom *et al.*[5]. Methyl α-D-galactopyranoside monohydrate (**1**, 21 g) was vigorously stirred in dry acetone (1,200 ml). To this suspension was added phosphorus pentaoxide (40 g) in 10-g portions at 5-min intervals. After 20 min, the insoluble material (mainly unreacted P_2O_5) was allowed to sediment, and the slightly yellowish, supernatant liquor was decanted, made neutral with anhydrous Na_2CO_3 powder, the suspension filtered, and the filtrate concentrated. Chromatography on silica gel with 4:1 (v/v) ethyl acetate–acetone gave 10.9 g (43%) of crystalline **2**, m.p. 101–102° (lit.[5] m.p. 97–98°) and 2.6 g (10%) of syrupy **3**. The p.m.r. spectra ($CDCl_3$) of **2** and **3** were consistent with the structures assigned. The two C–CH_3 (isopropylidene) signals of **2** were distinguishable, and appeared as singlets at δ 1.37 and 1.50. The corresponding methyl proton signals of **3** appeared as a singlet at δ 1.49.

Methyl 3,4-O-isopropylidene-6-O-trityl-α-D-galactopyranoside (**4**). — To a solution of **2** (2 g) in dry pyridine (28 ml) was added chlorotriphenylmethane (2.62 g, 10% molar excess). The mixture was stirred for 30 min at 100°, kept overnight at room temperature, diluted with dry toluene (20 ml), and evaporated to a yellow solid. The product was purified by gel filtration on a column (4 × 150 cm) of Sephadex LH-20, with 95% ethanol as eluant, to yield **4** almost quantitatively. The p.m.r. spectrum ($CDCl_3$, Varian A-60) of **4** agreed with the assigned structure: C–CH_3 (isopropylidene) signals appeared as singlets at δ 1.30 and 1.44, and aromatic protons as multiplets at δ 7.25–7.55.

Methyl 2-O-benzyl-3,4-O-isopropylidene-6-O-trityl-α-D-galactopyranoside (**5**). — To a solution of **4** (1.83 g) in dry *N*,*N*-dimethylformamide (22 ml) was added sodium hydride (1.47 g), and the mixture was stirred in a dry atmosphere for 2 h at room temperature. Dry benzyl chloride (2.2 ml) was then added, and the mixture was stirred overnight at room temperature. After careful addition of methanol to decompose the excess of sodium hydride, the mixture was evaporated *in vacuo* (vacuum pump) at 45° to a brownish syrup which was dissolved in benzene, and the solution

washed with water, and evaporated to a syrup. This material was purified on a column of Sephadex LH-20 (see preceding paragraph) and gave an almost quantitative yield of product, which was crystallized from ethyl ether–petroleum ether (b.p. 30–60°); m.p. 112–113.5°, $[\alpha]_D^{22}$ +29° (*c* 1.00, $CHCl_3$). The p.m.r. spectrum (CCl_4, Varian A-60) of **5** was in agreement with the structure assigned: *O*-methyl group, δ 3.35; isopropylidene-*C*-methyl groups, δ 1.33 and 1.26. The appropriate ratios of aromatic protons to *C*- and *O*-methyl protons were found.

Anal. Calc. for $C_{36}H_{38}O_6$: C, 76.30; H, 6.78. Found: C, 76.55; H, 6.91.

2-O-Benzyl-D-galactose (**6**). — Acid hydrolysis of **5** (2.4 g) was conducted with 0.5M H_2SO_4 in 1:4 water–1,4-dioxane (38 ml) for ~5 h at 100°. The mixture was then made neutral with ammonium hydroxide, and filtered, and the precipitate was extracted extensively with 1,4-dioxane. The extract was evaporated to a yellowish syrup, which was dissolved in water; the solution was washed with chloroform (to remove impurities), and concentrated, and compound **6** (260 mg) crystallized upon addition of a small volume of ethanol. An additional 280 mg of **6** was obtained after chromatography of the mother liquor on a column (2 × 150 cm) of Sephadex G-15; combined yield, 48%.

In most preparations of **6**, the intermediates (**2**, **4** and **5**) were not isolated; reactions were carried out consecutively, without purification, and gave the product in an overall yield of 24%, based on **1**.

Two forms of **6**. — Compound **6** was obtained in two forms having different melting points: form *A*, m.p. 63–65° (lit.[7] m.p. 70°), and form *B*, m.p. 143–144°. Elemental analyses of *A* and *B* (see later) were in agreement with the calculated values. P.m.r. spectra of both *A* and *B* in a number of solvent systems (D_2O, Me_2SO-d_6, or pyridine-d_5) supported the structure assigned, and showed close agreement in general characteristics. No significant differences in chemical shifts of signals were observable.

Mutarotation experiments were performed on *A* and *B*, with the following results: *A*: $[\alpha]_D^{22}$ +58.5 (5 min) → +61.5° (44 h) (*c* 0.20, H_2O); *B*: $[\alpha]_D^{22}$ +47.1 → +64.4° (44 h) (*c* 0.80, H_2O).

Attempts were also made to determine if the *A* and *B* forms differed in other respects. Forms *A* and *B* appeared at identical positions (elution volume, 15.5 ml) in borate-complex, anion-exchange chromatography (see *General methods*). Furthermore, when *A* and *B* were reduced with sodium borohydride, and the resulting alditols either peracetylated or per(trimethylsilyl)ated, the resulting products were indistinguishable by gas-chromatographic analysis. The retention times of the acetylated alditols from *A* and *B* were identical, either on a column of 3% of SE-30 at 200° (R_T 18 min) or on a column of 3% of OV-17 at 220° (R_T 14 min). Identical retention-times were also found for the per(trimethylsilyl)ated alditol derivatives from *A* and *B* on both columns (SE-30, R_T 23.4 min at 180°, and OV-17, R_T 9.7 min at 180°). Mixtures either of the acetylated alditols from *A* and *B*, or of the trimethylsilylated alditols from *A* and *B*, in widely different ratios always appeared as single, symmetrical peaks on both columns.

Anal. Calc. for $C_{13}H_{18}O_6$: C, 57.77, H, 6.71. Found: (*A*) C, 57.76; H, 6.80; (*B*) C, 57.56; H, 6.78.

Methyl 2,6-di-O-benzyl-3,4-O-isopropylidene-α-D-galactopyranoside (**7**). — *Method A.* To a stirred solution of **2** (9 g) in dry *N,N*-dimethylformamide (150 ml), was added sodium hydride (7 g) and, after 1.5 h at room temperature, dry benzyl chloride (70 ml), and stirring was continued for a further 4 h at room temperature. The product was then extracted into chloroform, the chloroform solution was washed with water, and concentrated, and residual benzyl chloride was removed by repeated co-evaporation with water, followed by co-evaporation with toluene. The residual syrup was dried *in vacuo* at 45–50°, dissolved in benzene, and purified by chromatography on silica gel. Benzene–ether (4:1, v/v) eluted 12 g (97%) of syrupy **7**; $[\alpha]^{22}$ +56.8° (*c* 1.70, $CHCl_3$); p.m.r. data ($CDCl_3$): δ 7.41 (m, 5, aryl protons), 1.36 and 1.39 (singlets, 3 each, *C*–CH_3).

Anal. Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.62; H, 7.39.

Method B. Compound **1** (15 g) was acetonated as already described, and the products were directly benzylated. Column chromatography of the benzylation product on silica gel gave 13.0 g (41%) of **7**, together with 2.0 g (6.3%) of **9**.

Hydrolysis of **7** with 60% acetic acid for 30 min at 100° gave methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside (**7a**) in quantitative yield; $[\alpha]_D^{22}$ +74.9° (*c* 1.68, $CHCl_3$). The p.m.r. ($CDCl_3$) spectrum of **7a** was consistent with the assigned structure: δ 3.38 (s, 3, *O*–CH_3), and 7.40 (m, 10, aryl protons).

Anal. Calc. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.16; H, 6.98.

2,6-Di-O-benzyl-β-D-galactose (**8**). — Hydrolysis of **7** (30 g) was achieved in 1M HCl in 83% aqueous 1,4-dioxane (300 ml) for 2 h at 95–100°. The hydrolyzate was diluted with chloroform, and the solution washed with sodium hydrogen carbonate and water, dried (sodium sulfate), and evaporated to a syrup. Crystals of **8** were formed on addition of a small volume of dichloromethane. Additional crystalline product was obtained after chromatography on silica gel with sequential elution with 4:1 (v/v) benzene–ether, 1:1 (v/v) benzene–ether, and 14:14:1 (v/v) benzene–ether–methanol. Recrystallization from dichloromethane–methanol gave 15.8 g (61%) of pure **8**, m.p. 142–144°, $[\alpha]_D^{22}$ +18.9 (5 min) → +22.9° (2 days) (*c* 2.89, methanol). The p.m.r. spectrum showed the presence of 2 benzyl groups in the compound.

Anal. Calc. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.51; H, 6.71.

Methyl 2,3-di-O-benzyl-4,6-O-isopropylidene-α-D-galactopyranoside (**9**). — A solution of **3** (2.3 g) in *N,N*-dimethylformamide (40 ml) was benzylated as already described. After the usual processing, the crude syrup obtained was dissolved in benzene, and chromatographed on silica gel. Benzene–ether (4:1, v/v) eluted the title compound as a syrup; yield 3.1 g (76%), $[\alpha]^{22}$ +49.1° (*c* 1.95, $CHCl_3$). The p.m.r. spectrum ($CDCl_3$) was consistent with the structure assigned: δ 3.36 (s, 3, *O*–CH_3), 1.43 and 1.40 (each s, 3, *C*–CH_3), and 7.42 (m, 10, aryl protons).

Anal. Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.74; H, 7.42.

Treatment of **9** with 60% acetic acid for 30 min at 100° gave compound **9a** as a

syrup. Its p.m.r. spectrum ($CDCl_3$) was in agreement with the structure assigned: δ 3.40 (s, 3, O–CH_3) and 7.42 (m, 10, aryl protons).

Acid hydrolysis of **9** with 1M HCl in 83% 1,4-dioxane for 5 h at 100° produced material identical, by thin-layer chromatography, to 2,3-di-*O*-benzyl-D-galactose (**10**) synthesized by the method described next.

2,3-Di-O-benzyl-D-galactose (**10**) *from methyl 4,6-O-benzylidene-β-D-galactopyranoside* (**11**). — Methyl 4,6-*O*-benzylidene-β-D-galactopyranoside (**11**) was prepared according to Overend and coworkers[9]. To a solution of **11** (12.3 g) in dry *N*,*N*-dimethylformamide (410 ml) was added sodium hydride (20.6 g), and the mixture was stirred for 2 h at room temperature, with exclusion of moisture. Benzyl chloride (32.8 ml) was then added, and the mixture was stirred overnight at room temperature. After addition of methanol to decompose the excess of sodium hydride, the mixture was concentrated *in vacuo* to a syrup, which was extracted with benzene. The benzene layer was washed with water, and concentrated. Crystallization of the residual syrup from benzene–petroleum ether (b.p. 30–60°) gave 16.5 g (80.3% yield) of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**12**). An additional 1.49 g (7.4%) was obtained from the mother liquor. After recrystallization from absolute ethanol, pure **12** had m.p. 132–133° (lit.[10] m.p. 135–136°). The p.m.r. spectrum ($CDCl_3$) was consistent with the structure assigned, and agreed with the data of Gros[10]: δ 5.53 (s, 1, PhCH), 3.58 (s, 3, O–CH_3); one set of benzylic methylene protons appeared as a singlet at δ 4.80, and the other as an AB quartet (δ 4.82 and 4.94, J 15 Hz).

Hydrolysis of **12** with 90% trifluoroacetic acid for 20 min at room temperature gave methyl 2,3-di-*O*-benzyl-β-D-galactopyranoside (**12a**) as a syrup. Its p.m.r. spectrum ($CDCl_3$) agreed with the structure assigned: δ 3.51 (s, 3, O–CH_3), 4.26 (d, 1, J 7 Hz, anomeric proton), and 7.25 (m, 10, aryl protons). The absence of the tertiary benzylidene proton signal from this spectrum indicated complete removal of the benzylidene group.

Hydrolysis of **12** (10 g) was performed in a mixture of 2.5M sulfuric acid (100 ml) and 1,4-dioxane (400 ml) for 5 h at 100°. The cooled reaction mixture was made neutral with concentrated ammonium hydroxide, and the precipitate of ammonium sulfate was filtered off, and washed with 1,4-dioxane. The filtrate was evaporated to an oily syrup, which was dissolved in chloroform (250 ml), and the solution washed with water (2 × 150 ml), dried (sodium sulfate), and evaporated to a syrup, which was dissolved in 1:1 (v/v) benzene–ethyl acetate and purified by chromatography on silica gel. After the column had been washed with the same mixture, 4:1 (v/v) ethyl acetate–acetone eluted pure **10**, isolated as a syrup (3.12 g, 40.2%). Fractions containing unhydrolyzed material were recovered, and subjected to a second hydrolysis followed by chromatography as just described, to yield an additional 0.8 g (10.2%) of syrupy product. The p.m.r. spectrum ($CDCl_3$) obtained was consistent with the structure assigned.

Anal. Calc. for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.81; H, 6.62.

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