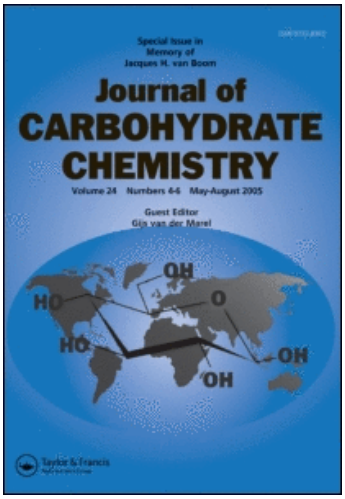

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A Facile Synthesis of 2. 4-DI*O*-Benzyl-L-Fucose from D-Glucose

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A FACILE SYNTHESIS OF 2,4-DI-O-BENZYL-L-FUCOSE FROM D-GLUCOSE

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ABSTRACT

2,4-Di-O-benzyl-L-fucose, a potential synthetic block of inner L-fucose residue having →3)-α-L-Fucp(1→ linkage, was derived from methyl 4,6-O-benzylidene-α-D-altropyranoside in 10 steps in 33% overall yield. The efficient formation of 5-enopyranoside by the modified dehydrobromination and the chemoselective deacylation in the presence of O-benzoyl groups are characteristics of this synthesis.

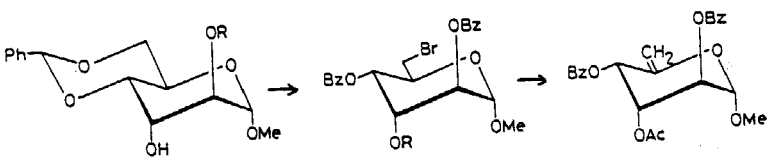
INTRODUCTION

Fucose,[3] especially the L-enantiomer, occurs biologically as a component of oligosaccharides of human milk, glycolipids, glyco-proteins which include several families of blood-group antigens, bacterial and plant polysaccharides. L-Fucose is generally located at the non-reducing end of complex carbohydrates, but there have been internally situated L-fucosyl residues in the O-antigenic side chains of lipopolysaccharides.[4] Among them, the →3)-α-L-Fucp(1→ type unit occurs quite often. The same unit was proposed[5] in an epitope moiety of antigenic lipooligosaccharides from Mycobacterium kansasii. Therefore, a fucose derivative having a non-participating protecting group at O-2 and suitably protected at O-3 and O-4 in such a way that 3-OH can be smoothly

regenerated for further glycosylation, is of significant importance. A practical synthesis of a derivative such as 2,4-di-O-benzyl-L-fucopyranose (12) is called for. The synthesis of 12 was first reported by Flowers[6] from L-fucose in rather low yield. On the other hand, L-fucose has been synthesized from L-arabinose,[7] D-galactose[8] and D-glucose.[9] Although the synthetic route from D-galactose may be the most convenient with respect to the number of steps and the overall yield, the intermediate 2,3:4,5-di-O-isopropylidene-L-fucitol is not appropriate for selective modification at O-2 and O-4. Thus, we adapted the route[8] from D-glucose using 2-O-benzoyl-4,6-O-benzylidene-α-D-altropyranoside (2) as the starting compound instead of the corresponding 2-acetate.[9] Recently demonstrated10 chemoselective deacetylation in the presence of benzoate ester was and the step of deoxygenative inversion of configuration at C-5 via 5-enopyranoside was considerably improved. We wish to report a practical synthesis of 12 from methyl 4,6-O-benzylidene-α-D-altropyranoside (1) in 38% overall yield (10 steps), i.e., from D-glucose in 12% overall yield (15 steps).

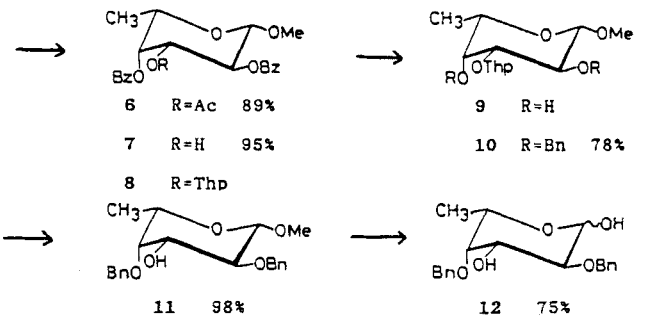
RESULTS and DISCUSSION

The 2-benzoate 2[11] was prepared in 84% yield by treatment of 1 with benzoic anhydride in dichloromethane containing triethylamine and a catalytic amount of 4-dimethylaminopyridine overnight at room temperature. The 4,6-O-benzylidene group was converted into bromobenzoate 3 with N-bromosuccinimide[12] in the presence of barium carbonate and then acetylation gave 4 in quantitative yield. The next step, i.e., the dehydrobromination, was successfully carried out with



1 R=H 3 R=H 5 95%

2 R=Bz 84% 4 R=Ac quant.



1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)[13] in dimethyl sulfoxide. The reaction proceeded smoothly at 80 ℃ to give 5-enopyranoside **5** in 95% yield. It is worth mentioning that this DBU-DMSO system worked equally good in a large scale preparation (10-15g). Applicability of this system to other hexo-pyranosides will be reported separately.[14] The L-sugar derivative, methyl 3-O-acetyl-2,4-di-O-benzoyl-β-L-galacto-pyranoside (**6**), was obtained in 89% yield by hydrogenation with H_2-Pd/C in methanol containing, a catalytic amount of acetic acid. Compound **6**, with its O-benzoyl group, was efficiently chemoselectively deacetylated by acid-catalyzed methanolysis without any benzoyl migration to give **7** in 95% yield. Methanolic hydrogen chloride prepared from concd hydrochloric acid and methanol was conveniently used instead of that prepared from acetyl chloride and methanol.[10] Furthermore, copper(I) chloride proved to be effective as a catalyst in chemoselective deacetylation.

Treatment of **7** with 2,3-dihydropyran and a catalytic amount of pyridinium p-toluenesulfonate, followed by conventional O-debenzoylation, gave the 3-O-tetrahydropyranyl glycoside **9**. The compound was converted into the 2,4-di-O-benzyl derivative **10** with sodium hydride-benzyl chloride in N,N-dimethylformamide in 78% yield (from **7**). The tetrahydropyranyl group of **10** was selectively hydrolyzed with 70% acetic acid at 50 ℃ for 2 h, giving **11**, which was further treated with a mixture of acetic acid and concd hydrochloric acid (6:1), to give 2,4-di-O-benzyl-L-fucopyranose **12** in 75% yield.

EXPERIMENTAL

General Methods. Melting points were determinined with Yanaco micro melting point appratus and are uncorrected. Optical rotations were determined with JASCO DIP-4 polarimeter in chloroform at 20±5℃. ^{1}H-NMR spectra were recorded with JEOL PS-100 spectrometer in chloroform-d using tetramethylsilane as the internal standard. For column chromatography Merck Kieselgel 60 and Wakogel G-300 were used.

Methyl 2-O-Benzoyl-4,6-O-benzylidene-α-D-altropyranoside (2). To a solution of **1** (5.0 g, 17.7 mmol) in dichloromethane (200 ml) containing triethylamine (3.7 ml, 26.6 mmol) and 4-dimethylaminopyridine (0.21 g, 1.7 mmol) was added benzoic anhydride (4.4 g, 19.4 mmol) and the mixture was stirred overnight at room temperature. TLC (benzene-acetone, 5:1) indicated complete disappearence of the strating material. The mixture was washed with water, dried over magnesium sulfate and concentreted to give a crystalline mass. Recrystallization from ethanol yielded **2** (5.74 g) in 84% yield. **2**: mp 137-138 ℃; $[\alpha]_D$ +8.5° (c 2.0, $CHCl_3$); lit.[9] mp 137-138.5℃, $[\alpha]_D^{24}$ -5.2° ($CHCl_3$); ^{1}H NMR δ 7.75 (s, 10H, Ph), 5.68 (s, 1H, Ph-CH), 5.25 (d, 1H, $J_{2,3}$=3.5 Hz, H-2), 4.80 (s, 1H, H-1), 4.6-3.6 (m, 4H, H-4, H-5, H-6a, H-6b), 3.40 (s, 3H, OMe), 3.28 (m, 1H, H-3).

Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.26; H, 5.71.

Methyl 3-O-Acetyl-2,4-di-O-benzoyl-6-bromo-6-deoxy-α-D-altropyranoside (4). A mixture of **2** (0.2 g, 0.52 mmol), N-bromosuccinimide (0.09 g, 0.51 mmol), and barium carbonate (0.12 g, 0.61 mmol) was refluxed in dry carbon tetrachloride (20 mL) for 1 h. After cooling to room temperature, the mixture was diluted with carbon tetrachloride and washed with aqueous sodium hydrogencarbonate and water. The organic layer was dried with magnesium sulfate and concentrated. The residual syrup of **2** was acetylated by a conventional procedure using pyridine-acetic anhydride (10 ml, 1:1). Solvents were removed by co-evaporation with toluene under reduced pressure and the product was purified on a short column of silica gel (benzene-acetone, 5:1) to afford **4** (0.26 g) as a syrup. **4**: $[\alpha]_D$ -24.2° (c 1.0, $CHCl_3$); ^{1}H NMR δ 8.04-7.50 (m, 10H, Ph), 5.54 (s, 1H, H-2), 5.49 (dd, 1H, $J_{3,4}$=3.0 Hz, $J_{4,5}$=8.0 Hz, H-4), 5.28 (m, 1H, H-3), 4.87 (s, 1H, H-1), 4.56 (m, 1H, H-5), 3.52 (s, 3H, OMe), 3.65-3.50 (m, 2H, H-6a,b), 2.11 (s, 3H, OAc).

Anal. Calcd for $C_{23}H_{23}O_8Br$: C, 54.44; H, 4.56. Found: C, 54.48; H, 4.65.

Methyl 3-O-Acetyl-2,4-di-O-benzoyl-6-deoxy-α-D-arabino-hex-5-enopyranoside (5). To a warmed (80 °C) and stirred solution of the bromo derivative **4** (0.78 g, 1.5 mmol) in dry dimethyl sulfoxide (10 mL) was added DBU (0.28 g, 1.8 mmol). After 30 min TLC (benzene-acetone 8:1) showed the complete disappearence of the starting material. The mixture was cooled to room temperature and poured into ice-water. The ether extract of the mixture was washed thoroughly with water, dried over magnesium sulfate, filtered and concentrated. Elution through a short column (benzene-acetone, 10:1) yielded **5** (0.62 g) in 78% yield, as syrup. **5**: $[\alpha]_D$ -36.6° (c 1.0, $CHCl_3$); ^1H NMR δ 8.10-7.50 (m, 10H, Ph), 6.08 (d, 1H, $J_{3,4}$=4.0 Hz, H-4), 5.70 (dd, 1H, $J_{1,2}$=5.5 Hz, $J_{2,3}$=8.5 Hz, H-2), 5.44 (dd, 1H, H-3), 4.98 (d, 1H, $J_{a,b}$=1 Hz, H-6a), 4.88 (d, 1H, H-6b), 4.82 (d, 1H, H-1), 3.58 (s, 3H, OMe), 1.96 (s, 3H, OAc).

Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.58; H, 5.32.

Methyl 3-O-Acetyl-2,4-di-O-benzoyl-6-deoxy-β-L-galactopyranoside (6). A solution of 5-enopyranoside **5** (2.0 g, 4.7 mmol) in methanol containing a few drops of acetic acid was stirred in the presence of hydrogen and palladium-charcoal (0.3 g) for 3 h. Filtation followed by evaporation of solvent afforded a solid which on recrystallization gave pure **6** (1.78 g, 89%), $[\alpha]_D$ -123° (c 1.0, $CHCl_3$); ^1H NMR δ 8.10-7.48 (m, 10H, Ph), 5.66-5.48 (m, 2H, H-2, H-4), 5.34 (dd, 1H, $J_{2,3}$=10.0 Hz, $J_{3,4}$=3.0 Hz, H-3), 4.62 (d, 1H, $J_{1,2}$=8.0 Hz, H-1), 4.02 (dq, 1H, $J_{4,5}$=1.0 Hz, $J_{5,6}$=6.5 Hz, H-5), 4.55 (s, 3H, OMe), 1.84 (s, 3H, OAc), 1.32 (d, 3H, H-6).

Anal. Calcd for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.43; H, 5.66.

Methyl 2,4-Di-O-benzoyl-6-deoxy-β-L-galactopyranoside (7).

a. Method A. A solution of **6** (2.0 g, 4.7 mmol) in conc. HCl-MeOH (1%, 50 ml) was heated under reflux until the starting material disappeared on TLC (benzene-acetone 5:1): 2 h. The mixture was cooled to room temperature and neutralized with basic lead carbonate. The undissolved materials were filtered off and the filtrate was concentrated to give a syrup, whose purification on a column of silica gel (benzene-acetone, 10:1) afforded **7** (1.7 g, 95%): $[\alpha]_D$ -79° (c 1.0, $CHCl_3$); ^1H NMR δ 8.10, 7.50 (m, 10H, Ph), 5.48 (dd, 1H, $J_{4,5}$=10 Hz, H-4), 5.32 (dd, 1H, $J_{1,2}$=8.0 Hz, $J_{2,3}$=10.0 Hz, H-2), 4.54 (d, 1H, H-1), 4.08 (dd, 1H,

$J_{3,4}$=3.8 Hz, H-3), 3.56 (s, 3H, OMe), 2.82 (bs, 1H, OH), 1.30 (d, 3H, H-6).

Anal. Calcd for $C_{21}H_{22}O_7$: C, 65.27; H, 5.74. Found: C, 65.17; H, 5.93.

b. Method B. A mixture of **6** (0.12 g, 0.28 mmol) and copper(I) chloride dihydrate (0.95, 0.56 mmol) in methanol-water (4 mL, 1:1) was heated under reflux for 18 h, cooled to room temperature, filtered and the filtrate was concentrated. The residue was triturated with chloroform. The chloroform layer was washed well with water and aq sodium hydrogencarbonate, dried over magnesium sulfate and concentrated. Purification of the residue as described in Method A yielded pure 7 as a syrup in 93% yield (0.10 g).

Methyl 2,4-Di-O-benzyl-6-deoxy-β-L-galactopyranoside (11). To a stirred solution of **7** (1.0 g, 2.6 mmol) in dichloromethane (20 mL) containing a catalytic amount (a few crystals) of pyridinium p-toluenesulfonate was added 2,3-dihydropyran (0.65 g, 7.8 mmol). After TLC (ethyl acetate-hexane, 1:2) indicated disappearance of the starting material (1 h), the mixture was washed with aq sodium hydrogencarbonate and water, dried over magnesium sulfate and concentrated to give **8** (1.2 g) as a syrup and a diastereomeric mixture, due to 3-O-tetrahydropyranyl group, in quantitative yield. A solution of compound **8** (1.2 g) dissolved in abs methanol containing sodium methoxide was stirred for 24 h at room temperature. The mixture was neutralized with acidic resin (IR 120 H^+), filtrated, and the filtrate was concentrated. The residue was purified on a column of silica gel (ethyl acetate-hexane, 1:2) to yield syrupy **9** quantitativelty (0.66 g). To a stirred suspension of sodium hydride (1.24 g, 55%, 25.9 mmol) in N,N-dimethylformamide (20 mL), was added a solution of **9** (0.85 g, 3.24 mmol) in dry N,N-dimethyl-formamide (10 mL) and benzyl chloride (1.5 mL, 13.0 mmol). After stirring overnight at room temperature, the excess reagent was decomposed by careful addition of small pieces of ice. An ether extract (50 mL x 2) was washed with aq sodium chloride and dried over magnesium sulfate. The residual syrup obtained after evaporation of solvent was chromatographed (ethyl acetate-hexane, 1:4) to afford the 2,4-di-O-benzyl derivative **10** in 78% yield (1.1 g). Treatment of **10** (0.5 g, 1.3 mmol) with acetic acid (70%, 5 mL) at 50°C for 2 h and removal of solvent under reduced pressure, followed by co-evaporation with toluene, yielded almost pure **11** (0.39 g). The

material was further purified on a column of silica gel (ethyl acetate-hexane, 1:4). 11: ^{1}H NMR δ 7.32 (s, 10H, Ph), 5.00-4.58 (m, 4H, $PhCH_2$), 4.23 (d, 1H, $J_{1,2}$=6.5 Hz, H-1), 3.72-3.31 (m, 4H, H-2,3,4,5), 3.33 (s, 3H, OMe), 2.34 (d, 1H, $J_{H,OH}$=4.0 Hz, OH), 1.24 (d, 3H, $J_{5,6}$=6.5 Hz, H-6).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.51; H, 7.17.

2,4-Di-O-benzyl-α-L-fucopyranose (12). A mixture of **11** (100 mg) and acetic acid-concd hydrochloric acid (1 mL, 10:1) was kept at 80°C for 30 min. After cooling, the mixture was extracted with chloroform and the chloroform layer washed successively with aq sodium chloride and aq sodium hydrogencarbonate. The organic layer was dried over magnesium carbonate and concentrated. A syrup (63 mg) was obtained, which on crystallization with hexane-ethyl acetate gave **12** as needles: mp 135 °C, $[\alpha]_D$ -72° (c 1.0 $CHCl_3$); lit. mp 133-135°C; $[\alpha]_D$ -75.5° (c 1.16 $CHCl_3$); ^{1}H NMR δ 7.33 (s, 10H, Ph), 5.24 (d, 1H, $J_{1,2}$=3 Hz, H-1), 1.16 (d, $J_{5,6}$=6.5 Hz, H-6).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.59; H, 6.86.

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