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Note

2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl phenyl sulfoxide as a glycosyl donor. Synthesis of some oligosaccharides containing an α-D-galactopyranosyl group *

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Oligosaccharides containing an α-D-Gal*p*-(1 → 4)-D-Gal and α-D-Gal*p*-(1 → 3)-D-Gal sequence constitute[2,3] an important part of glycoprotein and glycolipid structures, and they play an important role in biological processes. Thus, as a part of our continuing efforts towards the chemical synthesis of biologically important carbohydrates, we describe herein the synthesis of two isomeric disaccharides, methyl *O*-α-D-galactopyranosyl-(1 → 3)- (**8**) and -(1 → 4)-β-D-galactopyranoside (**10**), and two isomeric trisaccharides, *O*-α-D-galactopyranosyl-(1 → 3)- (**14**) and -(1 → 4)-*O*-β-D-galactopyranosyl-(1 → 4)-D-glucopyranose (**16**). Our interest in the synthesis of these compounds was also enhanced by recent developments[3] concerning the study of an endo-D-galactosidase that acts upon the carbohydrate components of glycoproteins and glycolipids.

Disaccharide **10** and trisaccharide **16** have been synthesized previously[4–6], mainly by use of perbenzylated galactosyl bromide or chloride as a glycosyl donor or by activation of perbenzylated thioglycoside in the crucial glycosylation step. Recently, Kahne et al.[7] reported the usefulness of peracylated or peralkylated D-glucosylsulfoxide as a glycosyl donor for the high yield glycosylation of unreactive substrates. For the synthesis of our target compounds we chose 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl phenyl sulfoxide as the glycosyl donor and suitably protected galactose or lactose derivatives as acceptors in the crucial glycosylation step.

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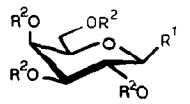
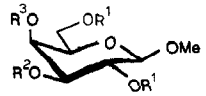


1 R^1 = SPH, R^2 = Ac
2 R^1 = SPh, R^2 = H
3 R^1 = SPh, R^2 = Bn
4 R^1 = OSPh, R^2 = Bn



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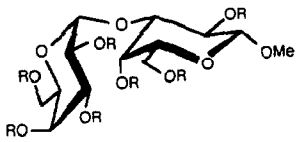

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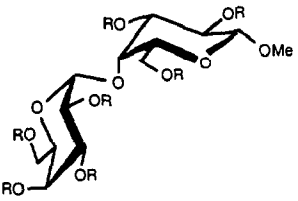

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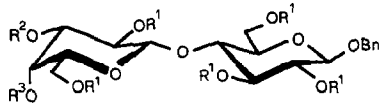
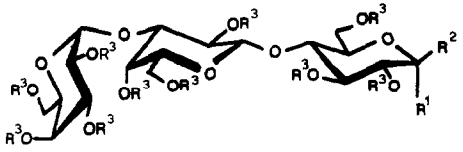


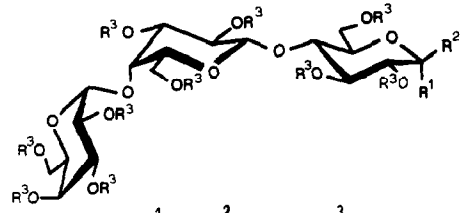
11 R^1 = R^3 = Bn, R^2 = H
12 R^1 = R^2 = Bn, R^3 = H

Treatment of 1,2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranose with phenylthiotrimethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate afforded compound **1** as a mixture of α and β anomers which was not isolated but *O*-deacetylated to give phenyl 1-thio-β-D-galactopyranoside[8] (**2**), after purification. Benzylation of **2** in the usual way afforded the known[9] tetra-*O*-benzyl derivative **3**. Oxidation of compound **3** with 0.01 M solution of 3-chloroperoxybenzoic acid gave the key glycosyl donor, 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl phenyl sulfoxide (**4**) in 90% yield. Condensation of compound **4** with methyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside[10] (**5**) in the presence of trifluoromethanesulfonic anhydride in toluene afforded the fully protected disaccharide **7** in almost quantitative yield. A similar condensation of compounds **4** and **6**[11] afforded methyl *O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (**9**). The configuration of C-1′ (δ 100.54) was confirmed by ^{13}C NMR spectroscopy.

Reaction of sulfoxide **4** with the protected lactose derivative[12] **11** gave the protected trisaccharide derivative **13** in 90% yield. The α-D configuration of C-1″



13 R^1 = H, R^2 = OBn, R^3 = Bn
14 R^1, R^2 = H, OH, R^3 = H



15 R^1 = H, R^2 = OBn, R^3 = Bn
16 R^1, R^2 = H, OH, R^3 = H

was confirmed by the appearance of a peak at δ 97.10 in the ^{13}C NMR spectrum of **13**. Condensation of **4** with the protected lactose derivative[6] **12** afforded the perbenzylated trisaccharide derivative **15**. The ^{13}C NMR spectrum of compound **15** was in agreement with the structure assigned. Hydrogenolysis of compounds **7** and **9**, and **13** and **15** afforded the disaccharides methyl *O*-α-D-galactopyranosyl-(1 → 3)-β-D-galactopyranoside (**8**) and methyl *O*-α-D-galactopyranosyl-(1 → 4)-β-D-galactopyranoside (**10**), and the trisaccharides *O*-α-D-galactopyranosyl-(1 → 3)-*O*-β-D-galactopyranosyl-(1 → 4)-D-glucopyranose (**14**) and *O*-α-D-galactopyranosyl-(1 → 4)-*O*-β-D-galactopyranosyl-(1 → 4)-D-glucopyranose (**16**), respectively.

EXPERIMENTAL

General methods.—These methods were described earlier[12].

Phenyl 1-thio-β-D-galactopyranoside (**2**).—To a cold (0°) solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (10 g, 25.62 mmol) in 1,2-dichloroethane (100 mL) was added trimethylsilyl trifluoromethanesulfonate (12.6 g, 54 mmol), and phenylthiotrimethylsilane (14 g, 77 mmol). The mixture was allowed to stir under N_2 for 16 h at room temperature. It was then washed successively with water, satd aq $NaHCO_3$, and water, dried, and concentrated to dryness. The crude syrupy residue was *O*-deacetylated with 0.25 M NaOMe in MeOH. Purification of the resultant crude mixture by column chromatography (solvent 5–15% MeOH in

$CHCl_3$) gave compound **2** (5.1 g, 74% overall yield); mp 98–100° (EtOH), $[\alpha]_D$ −55° (*c* 1.1, MeOH); lit.[8] mp 94–95°, $[\alpha]_D$ −53.4°.

*Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-*D*-galactopyranoside* (**3**).—Compound **2** (5 g, 18.4 mmol) was benzylated in exactly the same way as described earlier[9] to give **3** (9.5 g, 82%); mp 86–88° (ether–hexane), $[\alpha]_D$ +5° (*c* 1, $CHCl_3$); lit.[9] mp 88–89°, $[\alpha]_D$ + 1°; ^{1}H NMR ($CDCl_3$): δ 7.5–7.1 (m, 25 H, arom), 4.66 (d, 1 H, H-1).

*2,3,4,6-Tetra-*O*-benzyl-β-*D*-galactopyranosyl phenyl sulfoxide* (**4**).—To a cooled (−65°) solution of compound **3** (8 g, 12.6 mmol) in CH_2Cl_2 (200 mL) was added, dropwise during 45 min a solution of 3-chloroperoxybenzoic acid (3.67 g, 60%, 12.6 mmol) in CH_2Cl_2 (800 mL) with stirring. Stirring was continued until the temperature gradually increased to 10°. The mixture was then added to a stirred satd aq solution of $NaHCO_3$ (400 mL). The organic layer was washed with water, dried, and evaporated to a solid mass, which was purified by column chromatography (2:1 hexane–EtOAc). Crystallization from toluene–hexane gave **4** (7 g, 86%); mp 93–95°, $[\alpha]_D$ −79° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.8–7.1 (m, 25 H, arom), 4.80 (d, 1 H, *J* 8.4 Hz, H-1).

Anal. Calcd for $C_{40}H_{40}SO_6$: C, 74.05; H, 6.21. Found: C, 74.40; H, 6.45.

General procedure for glycosidation.—A solution of sulfoxide **4** (0.65 g, 1 mmol) in dry toluene (10 mL) was added with stirring to a solution of trifluoromethanesulfonic anhydride (0.17 mL, 1 mmol) in toluene (8 mL) at −78° under Ar. 2,6-Di-*tert*-butyl-5-methylpyridine (0.15 g, 0.75 mmol) was added and a solution of the acceptor (0.4 mmol) in toluene (10 mL) was added. Stirring was continued under Ar until the temperature increased to −55° (within 2 h), and then the mixture was diluted with CH_2Cl_2, and poured into a stirred, satd solution of aq $NaHCO_3$ (50 mL). The organic layer was washed with water, dried, and concentrated to dryness.

Methyl O-*(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-(1 → 3)-2,4,6-tri-*O*-benzyl-β-*D*-galactopyranoside* (**7**).—Glycosidation of methyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranoside[10] (**5**; 0.19 g, 0.4 mmol) gave **7** (0.36 g, 90%), after column chromatography (6:1 hexane–EtOAc); $[\alpha]_D$ +68° (*c* 0.7, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 105.25 (C-1), 95.92 (C-1′), 79.13 (C-3), and 56.90 (OMe).

Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.44; H, 6.74. Found: C, 75.19; H, 6.92.

Methyl O-*(2,3,4-6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-galactopyranoside* (**9**).—Glycosidation of methyl 2,3,6-tri-*O*-benzyl-β-D-galactopyranoside[11] (**6**, 0.19 g, 0.4 mmol) gave **9** (0.34 g, 84%) after column chromatography (6:1 hexane–EtOAc); $[\alpha]_D$ +90° (*c* 0.8, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 105.07 (C-1), 100.54 (C-1′), 80.95 (C-4), and 57.05 (OMe).

Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.44; H, 6.74. Found: C, 75.41; H, 7.01.

Benzyl O-*(2,3,4-6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-(1 → 3)-*O*-(2,4,6-tri-*O*-benzyl-β-*D*-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**13**).—Glycosidation of benzyl *O*-(2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[12] (**11**, 0.39 g, 0.4 mmol) gave **13** (0.52 g, 87%) after column chromatography (7:1 hexane-EtOAc); $[\alpha]_D$ +16° (*c* 1, $CHCl_3$);

^{13}C NMR ($CDCl_3$): δ 102.66 (C-1, C-1′), 97.10 (C-1″), 81.63 (C-4), and 81.46 (C′-3).

Anal. Calcd for $C_{95}H_{98}O_{16}$: C, 76.28; H, 6.60. Found: C, 76.01; H, 6.61.

Benzyl O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-(1 → 4)-O-(2,3,6-tri-O-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**15**).—Glycosidation of benzyl *O*-(2,3,6-tri-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside[6] (**12**, 0.39 g, 0.4 mmol) gave **15** (0.53 g, 89%) after column chromatography (7:1 hexane-EtOAc); $[\alpha]_D$ +20° (*c* 0.8, $CHCl_3$); lit.[6] $[\alpha]_D$ +24°; ^{13}C NMR ($CDCl_3$): δ 102.91 (C-1′), 102.59 (C-1), 100.76 (C-1″), 82.72 (C-4′), and 81.77 (C-4).

Anal. Calcd for $C_{95}H_{98}O_{16}$: C, 76.28; H, 6.60. Found: C, 76.16; H, 6.82.

Methyl O-α-D-galactopyranosyl-(1 → 3)-β-D-galactopyranoside (**8**).—A mixture of **7** (0.2 g) and 10% Pd–C (0.2 g) in glacial acetic acid (5 mL) was stirred under H_2 at 345 kPa for 24 h at room temperature, filtered and the filtrate concentrated to dryness. Column chromatography (5:4:1 $CHCl_3$–MeOH–H_2O) of the syrupy residue gave **8** (0.05 g, 70%); $[\alpha]_D$ +105° (*c* 0.6, H_2O): ^{13}C NMR (D_2O): δ 106.43 (C-1), 98.09 (C-1′), 80.15 (C-3), 59.93 (OMe).

Anal. Calcd for $C_{13}H_{24}O_{11} \cdot 0.5\ H_2O$: C, 42.74; H, 6.90. Found: C, 42.80; H, 7.00.

Methyl O-α-D-galactopyranosyl-(1 → 4)-β-D-galactopyranoside (**10**).—Compound **9** (0.2 g) was hydrogenolyzed under the conditions described above to give **10** (0.05 g, 78%); $[\alpha]_D$ +95° (*c* 1, H_2O); lit.[4] $[\alpha]_D$ +88°; ^{13}C NMR (D_2O): δ 106.71 (C-1), 103.23 (C-1′), and 60.01 (OMe).

Anal. Calcd for $C_{13}H_{24}O_{11} \cdot H_2O$: C, 41.71; H, 7.00. Found: C, 41.52; H, 6.88.

O-α-D-Galactopyranosyl-(1 → 3)-O-β-D-galactopyranosyl-(1 → 4)-D-glucopyranose (**14**).—Hydrogenolysis of **13** (0.3 g) gave **14** (0.08 g, 80%); $[\alpha]_D$ +79° (*c* 0.7, H_2O): ^{13}C NMR (D_2O): δ 105.48 (C-1′), 98.58 (C-1β), 98.28 (C-1″), 94.63 (C-1α), 81.20 (C-4), and 80.06 (C′-3).

Anal. Calcd for $C_{18}H_{32}O_{16}$: C, 42.86; H, 6.40. Found: C, 42.68; H, 6.86.

O-α-D-Galactopyranosyl-(1 → 4)-O-β-D-galactopyranosyl-(1 → 4)-D-glucopyranose (**16**).—Hydrogenolysis of **15** (0.3 g) gave **16** (0.08 g, 79%); $[\alpha]_D$ +101° (*c* 1, H_2O); ^{13}C NMR (D_2O): δ 106.5 (C-1′), 103.12 (C-1″), 98.6 (C-1β), 95.1 (C-1α), 81.14 (C-4), and 81.02 (C-4′).

Anal. Calcd for $C_{18}H_{32}O_{16} \cdot 0.5\ H_2O$: C, 42.10; H, 6.48. Found: C, 42.02; H, 6.80.

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