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Note

Regioselective glycosylation of mono- and di-saccharides via organotin derivatives

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Organotin derivatives of alcohols are frequently used in regioselective acylation, alkylation, and oxidation reactions[1,2]. The glycosylation of simple stannylated alcohols in the presence of Lewis acids[3], the regioselective glycosylation of benzyl 2,6-di-*O*-benzyl-α-D-galactopyranoside via the corresponding 3,4-dibutylstannylene derivative[4], and the tributyltin ether-mediated glycosylation[5] of the unreactive HO-4 of 2-deoxy-α-L-fucopyranosides using the *N*-iodosuccinimide technique[6] have been reported. We now report on the tributyltin ether-mediated glycosylation of 1,6-anhydro-β-D-galactopyranose (**1**) and methyl β-lactoside (**9**) as a part of our continuing studies [7,8]. Tributyltin ether-mediated benzylation[7] proceeds best with vicinal *cis*-diols, and this arrangement is present in **9**.

Augé and Veyrières[4] showed that the glycosylation of the dibutylstannylene derivative of a galactose-derived 3,4-*cis*-diol takes place on the equatorial HO group with good regio- and stereo-selectivity when the glycosyl halide bears no participating group on position 2 and the reaction is carried out in a dipolar aprotic solvent in the presence of lithium halide. However, glycosylation of the diol under the conventional halide ion-catalysed conditions[9] gave similar results. Tributyltin ether-mediated alkylations are catalysed by quaternary ammonium halides[10] and the regioselectivity studies now reported were carried out under common-ion conditions with toluene or dichloromethane as the solvent.

Treatment of **1** with 1.5 mol of bis(tributyltin) oxide in toluene and then with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide (**2**) in the presence of tetraethylammonium bromide gave 1,6-anhydro-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranose (**3**, 14%) and a 4:1 mixture (79%) of 1,6-anhydro-4-*O*-(2,3,4,6-tetra-*O*-benzyl-β- and -α-D-galactopyranosyl)-β-D-galactopyranose (**5** and **6**). With dichloromethane as the solvent, **3** (30%) and a 2.5:1 mixture (50%) of **5** and **6** were obtained. For purposes of comparison, **1** was treated with polymeric dibutyltin oxide in toluene and then with **2** under the above conditions, to give **3** (18%) and a 3:1 mixture (65%) of **5** and **6**. Glycosylation of **1** with **2** in dichloromethane under conventional common-ion conditions[9] gave 35% of **6**. Acetylation of **3**, **5**, and **6** gave **4**, **7**, and **8**,

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respectively, the ^{1}H-n.m.r. spectra and microanalytical data of which accorded with the structures proposed.

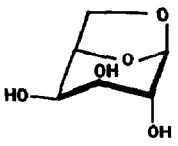
Reaction of **9** with 2 mol of bis(tributyltin) oxide in toluene and then with **2** in the presence of tetraethylammonium bromide gave a mixture of methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-*α*-D-galactopyransoyl)-*β*-lactoside (**11**, 16%) and methyl 6′-*O*-(2,3,4,6-tetra-*O*-benzyl-*α*-D-galactopyranosyl)-*β*-lactoside (**10**, 58%). Acetylation of **10** and **11** gave **12** and **13**, respectively, the ^{1}H-n.m.r. spectra of which were analysed completely using 2D-COSY spectroscopy.

The regioselectivity of the tributyltin ether-mediated glycosylation of **1** is lower than that of the conventional halide-ion-catalysed glycosylation because of some nucleophilic enhancement[8] of the unreactive HO-3. However, there is considerable activation, since the reaction yields 93% of isolated disaccharide derivatives versus 35% under conventional conditions. As expected, the stereoselectivity of glycosylation at HO-4 is lower than that on the less reactive HO-3. The glycosylation of methyl *β*-lactoside occurs regioselectively at the primary positions with complete *α*-stereoselectivity. The higher reactivity of HO-6 and HO-6′ under these conditions contrasts with the results on the tributyltin ether-mediated benzylation of **9**, which demonstrated that HO-3′ was the most reactive hydroxyl group[11].

EXPERIMENTAL

General. — T.l.c. was performed on Silica Gel GF_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Merck silica gel (70–230 mesh). ^{1}H-N.m.r. spectra (300 MHz) were recorded with a Varian XL-300 spectrometer, and ^{13}C-n.m.r. spectra (50 MHz) with a Bruker AM-200 spectrometer. Optical rotations were determined with a Perkin–Elmer 141 polarimeter.

Tributyltin ether-mediated glycosylation of 1,6-anhydro-β-D-galactopyranose (**1**). — (*a*) A stirred mixture of **1** (50 mg, 0.28 mmol), powdered molecular sieve type 4A (0.25 g), and bis(tributyltin) oxide (0.22 mL, 0.42 mmol) in toluene (8 mL) was heated for 15 h at 120° under argon. The mixture was cooled to 60°, a solution of tetraethylammonium bromide (0.35 g, 1.68 mmol) and 2,3,4,6-tetra-*O*-benzyl-*α*-D-galactopyranosyl bromide (**2**; 0.25 g, 0.42 mmol) in toluene (6 mL) was added, and the mixture was stirred in the dark for 4.5 days. The insoluble material was collected, and washed with chloroform and methanol, and the combined filtrate and washings were concentrated. Column chromatography (1:1 hexane–ethyl acetate) of the residue gave, first, 1,6-anhydro-3-*O*-(2,3,4,6-tetra-*O*-benzyl-*α*-D-galactopyranosyl)-*β*-D-galactopyranose (**3**; 27 mg, 14%), isolated as a syrup. Conventional acetylation of **3** gave the 2,4-diacetate **4**, isolated as a syrup, $[\alpha]_D$ +36° (*c* 0.2, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.34–7.27 (m, 20 H, 4 Ph), 5.30 (t, 1 H, $J_{1,2} = J_{1,3} = 1.4$ Hz, H-1), 5.09 (t, 1 H, $J_{1,2} = J_{2,3} = 1.4$ Hz, H-2), 4.99 (d, 1 H, H-4), 4.93 (d, 1 H, PhCH_2), 4.76 (d, 2 H, PhCH_2), 4.69 (d, 2 H, PhCH_2), 4.56 (d, 1 H, PhCH_2), 4.47 (d, 2 H, PhCH_2), 4.23 (t, 1 H, $J_{4,5} = J_{5,6exo} = 4.4$ Hz,



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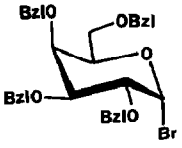

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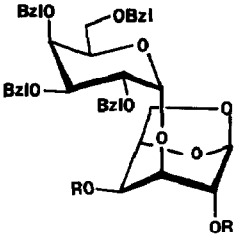

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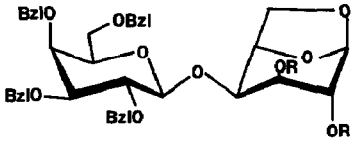
4 R = Ac



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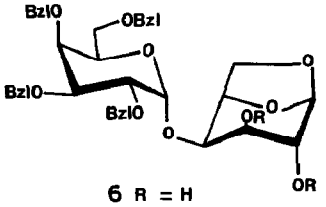
7 R = Ac



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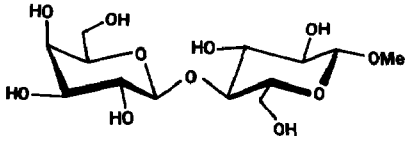
8 R = Ac



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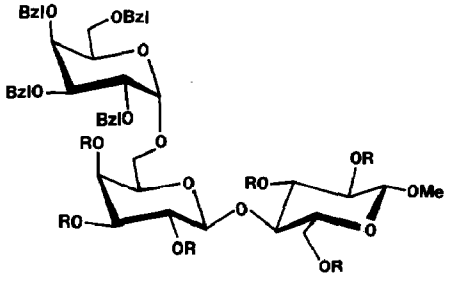

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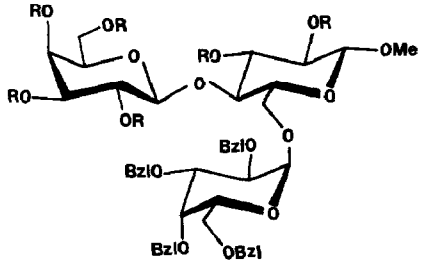
12 R = Ac



11 R = H

13 R = Ac

H-5), 4.18 (m, 1 H, H-3), 4.02 (m, 2 H, H-2′,4′), 3.90 (dd, 1 H, $J_{2',3'}$ 10.2, $J_{3',4'}$ 2.5 Hz, H-3′), 2.06 (s, 3 H, Ac), 1.79 (s, 3 H, Ac).

Anal. Calc. for $C_{44}H_{48}O_{12}$: C, 68.74; H, 6.29. Found: C, 68.89; H, 6.20.

Eluted second was a 4:1 mixture (150 mg, 79%) of **5** and **6**. ^{13}C-N.m.r. data ($CDCl_3$): **5**, δ 101.40 (C-1), 100.96 (C-1'), 82.87, 78.00, 75.39, 73.69, 73.49, 72.98, 72.64, 71.45, 69.10, 68.53, 64.26; **6**, δ 101.40 (C-1), 98.59 (C-1'), 78.74, 76.56, 74.59, 74.43, 73.99, 73.64, 73.49, 73.08, 72.34, 70.72, 70.63, 69.88, 64.45.

Acetylation of the above mixture gave **7** and **8**, which were isolated by column chromatography (7:3 hexane–ethyl acetate).

2,3-Di-*O*-acetyl-1,6-anhydro-4-*O*(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-β-D-galactopyranose (**7**) was isolated as a syrup, $[\alpha]_D$ +3° (*c* 0.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.41–7.29 (m, 20 H, 4 Ph), 5.38 (t, 1 H, $J_{1,2} = J_{1,3} = 1.4$ Hz, H-1), 5.28 (dq, 1 H, $J_{1,3} = J_{2,3} = J_{3,5} = 1.3$, $J_{3,4}$ 5.4 Hz, H-3), 4.91 (d, 1 H, PhCH_2), 4.80 (d, 1 H, PhCH_2), 4.72 (m, 2 H, H-2,5), 4.71 (s, 2 H, PhCH_2), 4.68 (d, 1 H, PhCH_2), 4.59 (d, 1 H, PhCH_2), 4.45 (d, 1 H, $J_{6endo,6exo}$ 7.5 Hz, H-6*endo*), 4.42 (s, 2 H, PhCH_2), 4.45 (d, 1 H, $J_{1',2'}$ 7.5 Hz, H-1'), 4.21 (t, 1 H, $J_{3,4} = J_{4,5} = 5.0$ Hz, H-4), 3.86 (d, 1 H, $J_{3',4'}$ 3.0 Hz, H-4'), 3.75 (dd, 1 H, $J_{2',3'}$ 9.7 Hz, H-2'), 3.69 (dd, 1 H, $J_{5,6exo}$ 5.1 Hz, H-6*exo*), 3.53 (m, 3 H, H-5',6,6'), 3.49 (dd, 1 H, H-3'), 2.10 (s, 3 H, Ac), 1.94 (s, 3 H, Ac).

Anal. Found: C, 68.70; H, 6.49.

2,3-Di-*O*-acetyl-1,6-anhydro-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranose (**8**) was isolated as a syrup, $[\alpha]_D$ +44° (*c* 0.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.39–7.20 (m, 20 H, 4 Ph), 5.30 (t, 1 H, $J_{1,2} = J_{1,3} = 1.3$ Hz, H-1), 5.15 (dq, 1 H, $J_{1,3} = J_{2,3} = J_{3,5} = 1.2$, $J_{3,4}$ 5.2 Hz, H-3), 4.85 (d, 1 H, PhCH_2), 4.84 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1'), 4.78 (d, 1 H, PhCH_2), 4.66 (s, 2 H, PhCH_2), 4.64 (t, 1 H, H-2), 4.49 (d, 1 H, PhCH_2), 4.48 (d, 1 H, PhCH_2), 4.39 (d, 2 H, PhCH_2), 4.27 (m, 2 H, H-5,6*endo*), 4.04 (t, 1 H, $J_{3,4} = J_{4,5} = 4.4$ Hz, H-4), 3.96 (dd, 1 H, $J_{2',3'}$ 9.8 Hz, H-2), 3.90 (d, 1 H, $J_{3',4'}$ 2.6 Hz, H-4'), 3.66 (dd, 1 H, H-3'), 3.50 (dd, 1 H, $J_{5,6exo}$ 4.2, $J_{6endo,6exo}$ 6.7 Hz, H-6*exo*), 3.43 (m, 3 H, H-5',6,6'), 1.93 (s, 3 H, Ac), 1.89 (s, 3 H, Ac).

Anal. Found: C, 68.35; H, 6.53.

(*b*) A stirred mixture of **1** (50 mg, 0.28 mmol), powdered molecular sieve type 4A (0.25 g), and bis(tributyltin) oxide (0.22 mL, 0.42 mmol) in toluene (8 mL) was heated at 120° under argon for 15 h, then concentrated. The residue was dissolved in dichloromethane (8 mL), and a solution of tetraethylammonium bromide (0.35 g, 1.68 mmol) and **2** (0.25 g, 0.42 mmol) in dichloromethane (6 mL) was added. The mixture was stirred in the dark at room temperature for 4 days, to give **3** (57 mg, 30%) and a 2.5:1 mixture (96 mg, 50%) of **5** and **6** isolated as in (*a*).

Dibutylstannylene-mediated glycosylation of **1**. — A stirred mixture of **1** (50 mg, 0.28 mmol), powdered molecular sieve 4A (0.25 g), and dibutyltin oxide (0.1 g, 0.42 mmol) in toluene (8 mL) was heated at 120° under argon for 15 h, then cooled. The mixture was treated with tetraethylammonium bromide and **2**, as above, to afford, after 4 days, **3** (35 mg, 18%) and a 3:1 mixture (124 mg, 65%) of **5** and **6**.

Glycosylation of **1** *under conventional common-ion conditions*. — A solution of **2** (0.25 g, 0.42 mmol) in dichloromethane (6 mL) was added to a stirred mixture of **1** (50 mg, 0.28 mmol), powdered molecular sieve type 4A (0.25 g), and tetraethylammonium bromide (0.35 g, 1.68 mmol) in dichloromethane (8 mL) under argon. The mixture was stirred in the dark at room temperature for 4 days, to give **6** (67 mg, 35%) and **1** (20 mg) isolated as in (*a*) above.

Tributyltin ether-mediated glycosylation of methyl β-lactoside (**9**). — A stirred mixture of **9** (0.20 g, 0.58 mmol), powdered molecular sieve type 4A (0.25 g), and bis-(tributyltin) oxide (0.6 mL, 1.16 mmol) in toluene (32 mL) was heated under argon at 120°. After 15 h, the mixture was cooled to 60°, a solution of tetraethylammonium bromide (0.73 g, 3.48 mmol) and **2** (0.52 g, 0.86 mmol) in toluene (10 mL) was added, and stirring was continued for 3 days. Insoluble material was collected, and washed with chloroform and methanol, and the combined filtrated and washings were concentrated. Column chromatography (7:1 chloroform–methanol) of the residue gave, first, methyl 6′-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-lactoside (**10**; 0.29 g, 58%) and then methyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-lactoside (**11**; 80 mg, 16%).

Treatment of **10** conventionally with acetic anhydride–pyridine gave the hexa-acetate **2** as a syrup, $[\alpha]_D$ +2° (*c* 0.8, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.36–7.27 (m, 20 H, 4 Ph), 5.42 (dd, 1 H, $J_{3',4'}$ 3.2, $J_{4',5'}$ 1.0 Hz, H-4′), 5.17 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.1 Hz, H-3), 5.02 (dd, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 10.5 Hz, H-2′), 4.97 (dd, 1 H, H-3′), 4.91 (d, 1 H, PhCH_2), 4.79 (d, 1 H, $J_{1'',2''}$ 3.5 Hz, H-1″), 4.76 (d, 1 H, PhCH_2), 4.74 (d, 1 H, PhCH_2), 4.66 (d, 1 H, PhCH_2), 4.55 (d, 1 H, PhCH_2), 4.21 (m, 1 H, H-6a), 4.21 (s, 2 H, PhCH_2), 4.38 (d, 1 H, H-1), 4.20 (d, 1 H, H-1′), 4.04 (dd, 1 H, $J_{5,6b}$ 5.2, $J_{6a,6b}$ 12.1 Hz, H-6b), 4.02 (dd, 1 H, $J_{2'',3''}$ 10.2 Hz, H-2″), 3.93 (dd, 1 H, $J_{3'',4''}$ 2.8, $J_{4'',5''}$ 1.0 Hz, H-4″), 3.88 (m, 1 H, H-5′), 3.87 (dd, 1 H, H-3″), 3.69 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 3.57 (m, 1 H, H-5), 3.55 (m, 1 H, H-6a′), 3.46 (s, 3 H, MeO), 3.40 (dd, 1 H, $J_{5',6b'}$ 4.7, $J_{6a',6b'}$ 9.7 Hz, H-6b′), 2.09 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.05 (s, 3 H, Ac), 2.03 (s, 3 H, Ac), 1.98 (s, 3 H, Ac), 1.96 (s, 3 H, Ac).

Anal. Calc for $C_{59}H_{62}O_{22}$: C, 63.10; H, 5.53. Found: C, 63.43; H, 5.71.

Likewise, **11** gave the hexa-acetate **13** as a syrup, $[\alpha]_D$ +17° (*c* 0.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.36–7.29 (m, 20 H, 4 Ph), 5.27 (dd, 1 H, $J_{3',4'}$ 3.4, $J_{4',5'}$ 1.0 Hz, H-4′), 5.17 (d, 1 H, $J_{1'',2''}$ 3.6 Hz, H-1″), 5.14 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.3 Hz, H-3), 5.05 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 10.3 Hz, H-2′), 4.96 (d, 1 H, PhCH_2), 4.90 (dd, 1 H, H-3′), 4.89 (dd, 1 H, $J_{1,2}$ 8.0 Hz, H-2), 4.83 (d, 1 H, PhCH_2), 4.81 (d, 1 H, PhCH_2), 4.76 (d, 1 H, PhCH_2), 4.74 (d, 1 H, PhCH_2), 4.67 (d, 1 H, H-1′), 4.58 (d, 1 H, PhCH_2), 4.50 (d, 1 H, PhCH_2), 4.42 (d, 1 H, PhCH_2), 4.32 (d, 1 H, H-1), 4.08 (dd, 1 H, $J_{2'',3''}$ 10.1 Hz, H-2″), 4.01 (m, 1 H, H-4″), 3.95 (m, 1 H, H-4), 3.90 (dd, 1 H, $J_{3'',4''}$ 2.7 Hz, H-3″), 3.40 (s, 3 H, MeO), 2.13 (s, 3 H, Ac), 2.05 (s, 6 H, 2 Ac), 1.99 (s, 3 H, Ac), 1.96 (s, 3 H, Ac), 1.94 (s, 3 H, Ac).

Anal. Found: C, 62.85; H, 5.82.

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