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Preliminary communication

Intermediates for the stepwise synthesis of (1→3)-β-D-galacto-oligosaccharides or their methyl β-glycosides

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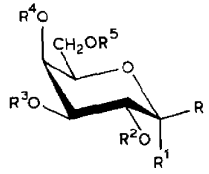
(1→3)-Galacto-oligosaccharides have been isolated from partial acid hydrolyzates of various plant galactans[1], and both α- and β-linked disaccharides in this series have been synthesized[1–3]. The methyl β-glycoside of β-(1→3)-galactobiose was prepared by Gorin[4] in admixture with the α- and 2-*O*-α- and -β-linked isomers, as the synthesis[4] was based on the condensation of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide.

In connection with specificity studies on monoclonal antibodies, a need arose for methyl-β-glycosides of (1→3)-β-D-galacto-oligosaccharides. A prerequisite for an efficient, stepwise synthesis of this class of oligosaccharides is ready access to a 2,4,6-tri-*O*-substituted methyl β-D-galactopyranoside, to be used as the initial nucleophile. Whereas the D-galactopyranosyl end-group of the di- and higher oligo-saccharides may be constructed by using simple D-galactosyl halides, the addition of the internal D-galactopyranosyl residues requires a D-galactopyranosyl halide bearing a temporary blocking group at O-3. Hitherto, a suitable compound of this class has not been available. We here report the facile synthesis of *all* intermediates needed to synthesize (1→3)-β-D-galacto-oligosaccharides.

Following the methodology of regioselective enhancement of the nucleophilicity of hydroxyl groups through alkyl stannylation[5,6], an equimolar mixture of methyl β-D-galactopyranoside (**1**) and dibutyltin oxide was stirred in boiling benzene for 16 h, followed by treatment of the putative 3,4-*O*-stannylene derivative with benzyl bromide and tetrabutylammonium iodide (1 molar proportion of each), to give* methyl 3-*O*-benzyl-β-D-galactopyranoside (**2**), 64%, m.p. 138–139°, lit.[7] m.p. 135–137°. Benzoylation of **2** (benzoyl chloride in pyridine) afforded **3** (95%), m.p. 142–143°, $[\alpha]_D$ +94° (*c* 1.6), from which the benzyl group was removed by catalytic hydrogenolysis to give **4** in theoretical yield, $[\alpha]_D$ +8.3° (*c* 1.5).

Treatment of **3** with 1,1-dichloromethyl methyl ether in purified chloroform (3 mL/g) and a catalytic amount of freshly fused zinc chloride for 1 h at 55–60° gave the corresponding glycosyl chloride **5**, $[\alpha]_D$ +174° (*c* 1.5) in 75–80% yield. When treated

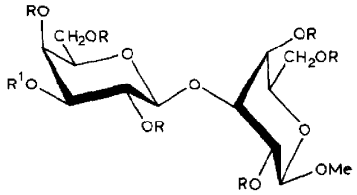
*All compounds gave ^{1}H- and/or ^{13}C-n.m.r. spectral data consistent with their structures; all new compounds gave correct elemental analyses; unless otherwise states $[\alpha]_D$ values were determined at 25° for solutions in $CHCl_3$.



	R	R^1	R^2	R^3	R^4	R^5
1	OMe	H	H	H	H	H
2	OMe	H	H	Bn	H	H
3	OMe	H	Bz	Bn	Bz	Bz
4	OMe	H	Bz	H	Bz	Bz
5	H	Cl	Bz	Bn	Bz	Bz
6	OAc	H	Bz	Bn	Bz	Bz
7	OAc	H	Bz	H	Bz	Bz
8	H	Br	Bz	Bz	Bz	Bz

with silver acetate (100% molar excess) in acetonitrile, compound **5** afforded the corresponding β-acetate **6**, $[\alpha]_D$ +108° (*c* 1.18); $J_{1,2}$ 8.0 Hz. Compound **7**, m.p. 166–166.5° (from ethanol), $[\alpha]_D$ +27.7° (*c* 0.72), a useful glycosyl acceptor in the synthesis of any reducing (oligo) glycosyl-(1→3)-galactose, was obtained in theoretical yield from **6** by removal of the benzyl group by catalytic hydrogenolysis.

The suitability of **4** and **5** in the synthesis of methyl β-glycosides of (1→3)-β-D-galacto-oligosaccharides was verified by the reaction† of **4** with **8** or **5**, which gave respectively, **9**, $[\alpha]_D$ +91° (*c* 1.26), and **11**, $[\alpha]_D$ +71.7° (*c* 0.82). Conventional debenzoylation of **9** gave **10**, m.p. 200–201° ($[\alpha]_D$ +24.5°, water), and cleavage of the benzyl group from **11** by catalytic hydrogenation gave **12**, $[\alpha]_D$ +31.2° (*c* 1.44).



	R	R^1
9	Bz	Bz
10	H	H
11	Bz	Bn
12	Bz	H

†Condensation reactions were conducted under base-deficient conditions[8] at −25° in 1:1 nitromethane–toluene, in the presence of silver triflate and *sym*-collidine. The mixtures were processed conventionally and the desired products isolated by preparative column chromatography in 60–85% yields (not optimized).

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