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Preliminary communication

Systematic chemical synthesis of (1→6)-β-D-galacto-oligosaccharides and related compounds

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Studies of the interaction of (1→6)-β-D-galactan-specific, monoclonal antibodies with saccharides required a series of methyl-β-glycosides of (1→6)-β-D-galacto-oligosaccharides. Synthesis of lower oligosaccharides of this type had previously been achieved in this laboratory and by others[1,2]. In the past, we used as glycosyl donors 2,3,4-tri-*O*-acetyl-6-*O*-(chloroacetyl)-α-D-galactopyranosyl bromide[3,4] (**1**), the corresponding 6-*O*-(bromoacetyl) derivative[5,6] (**2**), or 2,3,4-tri-*O*-benzoyl-6-*O*-(bromoacetyl)-α-D-galactopyranosyl bromide[7] (**3**). The advantage of the last reagent lies in the stability of the benzoyl groups both under the conditions of *O*-de(haloacetyl)ation with thiourea and during glycosylation reactions promoted with silver trifluoromethanesulfonate (triflate).

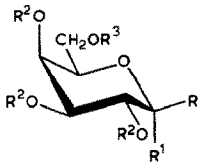
Compound **3** proved to be an excellent glycosyl donor, but its preparation[7] in larger amounts, required for the stepwise construction of oligosaccharides, is somewhat tedious. In the search for a more efficient source of a glycosylating reagent suitable for the synthesis of the target compounds, we have now developed a facile route to 2,3,4-tri-*O*-benzoyl-6-*O*-(bromoacetyl)-α-D-galactopyranosyl chloride (**4**), and used it as the key intermediate in the synthesis of methyl β-glycosides of the title oligosaccharides (up to a hexasaccharide) by a stepwise and by a blockwise approach*.

Compound **4** {84% yield; $[\alpha]_D$ +218° (*c* 1.6)} was obtained by conventional[7] bromoacetylation of methyl 2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside[8] (**5**), followed by cleavage of the resulting **6** with 1,1-dichloromethyl methyl ether** (DCMME) in the presence of $ZnCl_2$. To test the suitability of **4** as a glycosyl donor, its reaction with **5** and with 1,2,3,4-tetra-*O*-benzoyl-α- (**7**) and -β-D-galactopyranose[7] (**8**) was investigated. Condensation*** of **4** with **5** gave **10** {91%; m.p. 258–259°, $[\alpha]_D$ +158° (*c* 0.7)}. Likewise, reaction of **4** with **7** and **8** gave, respectively, **11** {73%; m.p. 216–216.5°, $[\alpha]_D$ +190.3° (*c* 0.65)} and **12** {86%; m.p. 128–129°, $[\alpha]_D$ +138° (*c* 0.7)}.

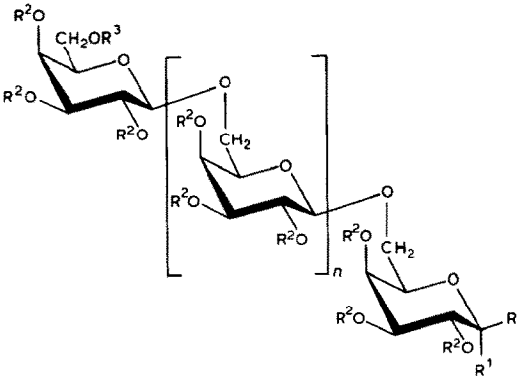
*New compounds gave correct microanalyses and ^{1}H- or ^{13}C-n.m.r. spectra, or both, consistent with the expected structures; $[\alpha]_D$ values for solutions in chloroform were determined at 25°.

**DCMME is a suspected carcinogen[9], and all operations employing it should be conducted in a well-ventilated hood.

***Reactions involving glycosyl chlorides (1.2 molar proportions with respect to the nucleophiles used) were conducted under base-deficient conditions[7] at room temperature in dichloromethane, in the presence of silver triflate and 2,4,6-trimethylpyridine. Direct crystallization from crude products, or column chromatography on Silica Gel 60, or both, gave the desired products.



	R	R^1	R^2	R^3
1	H	Br	Ac	$COCH_2Cl$
2	H	Br	Ac	$COCH_2Br$
3	H	Br	Bz	$COCH_2Br$
4	H	Cl	Bz	$COCH_2Br$
5	OMe	H	Bz	H
6	OMe	H	Bz	$COCH_2Br$
7	H	OBz	Bz	H
8	OBz	H	Bz	H
9	OBz	H	Bz	$COCH_2Br$



	n	R	R^1	R^2	R^3
10	0	OMe	H	Bz	$COCH_2Br$
11	0	H	OBz	Bz	$COCH_2Br$
12	0	OBz	H	Bz	$COCH_2Br$
13	0	OMe	H	Bz	H
14	1	OMe	H	Bz	$COCH_2Br$
15	1	OMe	H	Bz	H
16	2	OMe	H	Bz	$COCH_2Br$
17	0	H	Cl	Bz	$COCH_2Br$
18	2	OMe	H	Bz	H
19	3	OMe	H	Bz	$COCH_2Br$
20	4	OMe	H	Bz	$COCH_2Br$

To prepare methyl β-glycosides of higher (1→6)-β-D-galacto-oligosaccharides by stepwise synthesis, compound **10** was *O*-de(bromoacetyl)ated[7], and the resulting nuclophile **13** was condensed with **4**, to give **14** {89%; m.p. 233–234°, $[\alpha]_D$ +162° (*c* 0.8)}. Compound **14** was deprotected at O-6 of the (terminal) D-galactopyranosyl group, to give **15**, whose reaction with **4** gave **16** {78%; m.p. 273–275°, $[\alpha]_D$ +104° (*c* 0.7)}.

The blockwise synthesis of oligosaccharides of the present series required, as a glycosyl donor, a disaccharide conventionally blocked but having, at O-2, a substituent capable of neighboring-group participation, and, at O-6′, a protecting group that could be selectively removed; compound **12** satisfied these requirements. Trimethylsilyl triflate was recently introduced as a powerful promoter of glycosylations, and β-1-*O*-acetyl[10–12] and 1-hydroxy[13] derivatives of otherwise fully protected carbohydrates have been used as glycosylating reagents. We have now found that β-1-benzoates react similarly. Thus, reaction of **5** and the previously prepared[7] **9** in dichloromethane in the presence of trimethylsilyl triflate gave **10** (77%). When **13** was similarly treated with **12**, the tetrasaccharide **16** was obtained in 72% yield.

The highest oligosaccharides synthesized in this series were most conveniently obtained by using, as the glycosyl donor, the disaccharide glycosyl chloride **17** {m.p. 225–227°, $[\alpha]_D$ +236° (*c* 0.4)}, which was readily obtained from either **11** (76%) or **12** (85%) by cleavage with DCMME. Accordingly, the halide **17** was treated separately with

15 and **18** [obtained by *O*-de(bromoacetyl)ation of **16**], to give, respectively, **19** {67.7%; m.p. 263–264°, $[\alpha]_D$ +85.6° (*c* 0.55)} and **20** {66%; m.p. 303.5–304.5°, $[\alpha]_D$ +77° (*c* 1.24)}. Deacylations of **10**, **14**, **16**, **19**, and **20** gave the corresponding methyl β-glycosides of (1→6)-β-D-galacto-oligosaccharides, whose ^{13}C-n.m.r. spectra were consistent with the structures expected.

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