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Partial Benzylation of Methyl *α*- and *β*-D-Galactopyranosides

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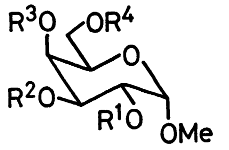
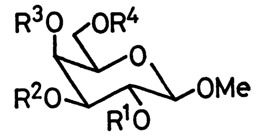
Synopsis. Partial benzylation of methyl *α*-D-galactopyranoside with benzyl chloride and LiOH selectively gave the 2,3,6-tribenzyl ether, while that using KOH or RbOH gave the 2,4,6-isomer as the main product. Methyl *β*-D-galactopyranoside afforded the 3,4,6-tribenzyl ether predominantly, irrespective of the alkali used.

Synthetic studies of oligosaccharides require the preparation of partially benzylated carbohydrates.1) Such compounds have often been prepared by kinetic benzylation2) of unprotected glycosides.3,4b) This paper will deal with a direct partial benzylation of methyl *α*- and *β*-D-galactopyranosides (**1** and **6**) and the dependence of the selectivity upon the alkali used and the anomeric configuration of the substrates.

The kinetic tribenzylation of **1** was carried out using benzyl chloride and a variety of alkalis (Table 1). The benzylation using excess LiOH (8 equiv.) for 9 h at 140 °C gave methyl 2,3,6-tri-*O*-benzyl-*α*-D-galactopyranoside (**3**) in a 52% yield, together with small amounts of the other tribenzyl ethers (**4** and **5**). This result contrasts with the observation that the reactivity of the axial OH-4 is higher than the equatorial OH-3 in the partial benzylation of methyl 2,6-di-*O*-benzyl-*α*-D-galactopyranoside (**11**) and methyl 6-deoxy-*α*-L-galactopyranoside with benzyl bromide and NaH in *N*,*N*-dimethylformamide.4) The use of NaOH, KOH, or RbOH, however, changed the selectivity of the reaction to produce the 2,4,6-tribenzyl ether **4** predominantly. Its maximized yield was 42% for the reaction using RbOH (4.5 equiv.) for 3 h at 70 °C. Controlled benzylation with a limited amount of alkali formed the 2,6-, the 3,6-, and the 4,6-dibenzyl ethers (**11**, **12**, and **13**), whose yields depended on the alkali used: 10, 9, and 1% for LiOH (4.0 equiv.) and 4, 6, and 8% for RbOH (2.5 equiv.) Furthermore, the selectivity in the monobenzylation of these dibenzyl ethers was also dependent upon the alkali used (Table 1). Thus, the equatorial OH-3 of **11** and the OH-2 of **12** were selectively benzylated with LiOH, while the axial OH-4 of **11** and **12** were selectively benzylated with RbOH.





	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
1	H	H	H	H	**6**	H	H	H	H
2	Bn	Bn	Bn	Bn	**7**	Bn	Bn	Bn	Bn
3	Bn	Bn	H	Bn	**8**	Bn	Bn	H	Bn
4	Bn	H	Bn	Bn	**9**	Bn	H	Bn	Bn
5	H	Bn	Bn	Bn	**10**	Bn	Bn	Bn	Bn
11	Bn	H	H	Bn	**14**	Bn	H	H	Bn
12	H	Bn	H	Bn	**15**	H	Bn	H	Bn
13	H	H	Bn	Bn	**16**	H	H	Bn	Bn
17	All	All	H	H	**19**	All	All	H	H
18	All	H	All	H					

Table 1. Partial benzylation of methyl *α*- and *β*-D-galactopyranosides (**1** and **6**) and their dibenzyl ethers with benzyl chloride^a)^ and alkali

Galactoside	Alkali (equiv.)	Temp/°C	Time/h	Yields of tetra- and tri-benzyl ether of **1** or **6**/%			
				2	**3**	**4**	**5**
1	LiOH (8.0)	140	9.0	8	52	10	3
	NaOH (4.0)	140	1.5	7	16	23	12
	KOH (4.5)	100	1.5	18	5	28	10
	RbOH (4.5)	70	3.0	13	6	42	14
	CsOH (4.5)	70	1.5	11	3	14	5
11b)	LiOH (2.0)	140	6.0	3	48	12	—
	RbOH (1.3)	70	3.0	6	29	41	—
12b)	LiOH (2.0)	140	6.0	5	41	—	5
	RbOH (1.3)	70	3.0	5	19	—	34
13b)	LiOH (2.0)	140	6.0	7	—	27	13
	RbOH (1.3)	70	3.0	0	—	25	13
				7	**8**	**9**	**10**
6	LiOH (8.0)	140	6.0	4	12	5	13
	NaOH (4.5)	100	4.5	6	11	13	26
	KOH (4.5)	100	1.5	9	10	19	34
	RbOH (4.5)	100	1.5	21	8	24	32
14b)	KOH (1.3)	100	3.0	5	27	41	—
15b)	KOH (1.3)	100	3.0	10	18	—	48
16b)	KOH (1.3)	100	3.0	7	—	25	45

a) Twenty parts of benzyl chloride was used. b) The reactions were conducted in 0.2—0.3 mmol scale.

Partial benzylation of **6** gave the 3,4,6-tribenzyl ether (**10**) as the main product, irrespective of the alkali used; the best of the alkalis was KOH (Table 1). The controlled benzylation of **6** using KOH (2.0 equiv.) afforded the 2,6- 3,6-, and 4,6-dibenzyl ethers (**14**, **15**, and **16**) in 5, 15, and 12% yields: the lower reactivity of OH-2 of **6** is similar to that of OH-3 of the *α*-gluco- and the *α*-xylopyranosides,3) both of which are located at the center of three contiguous equatorial hydroxyl groups. The OH-2 of **15** and **16** were also less susceptible to benzylation.

The structure of the tri- and the dibenzyl ethers were determined by examining ^{1}H NMR spectra of their acetates (Table 3). The new dibenzyl ethers were synthesized *via* alternative routes.

Experimental

General. See the previous papers.3) LiOH·H_2O and **1**·H_2O (Pfanstiehl) were dehydrated *in vacuo* at 105 and

Table 2. Physical and analytical data of tri- and dibenzyl ethers of methyl D-galactopyranosides

Compound	Mp θ_m/°C	$[\alpha]_D^{20}$/° (c, $CHCl_3$)	R_f (Toluene/2-Butanone)		Found(%) C	Found(%) H
Tribenzyl ether					72.39a)	6.94a)
3	—	+34(3.0)b)	0.43	(7/1)	72.07	6.89
4	—	+44(3.7)c)	0.34		72.20	6.93
5	85—88.5f)	+94(0.7)	0.26		72.07	6.90
8	—	+3.4(3.6)d)	0.40		72.30	6.88
9	—	+0.7(1.6)e)	0.49		72.41	6.87
10	99—99.5	−4.2(1.0)f)	0.20		72.61	6.91
Dibenzyl ether					67.36g)	7.00g)
11	—	+76(2.2)h)	0.37	(3/2)	66.93	7.01
12	—	+109(1.9)	0.33		66.90	6.92
13	—	+77(3.5)	0.22		67.65	6.99
14	—	+9.5(3.4)i)	0.45		67.55	7.11
15	—	+1.0(4.1)j)	0.37		66.92	7.05
16	116—117	−29(1.0)	0.20		67.59	7.09

a) Calcd for $C_{28}H_{32}O_6$. b) Lit,4b) $[\alpha]_D^{25}$ +39.5° (c 2.38, $CHCl_3$). c) Lit,4b) $[\alpha]_D^{20}$ +46.6° (c 1.04, $CHCl_3$). d) Lit,9) $[\alpha]_D$ +3° ($CHCl_3$). e) Lit,4b) $[\alpha]_D^{24}$ 3.1° (c 2.58, $CHCl_3$). f) Lit,10) mp 99—99.5 °C, $[\alpha]_D^{25}$ −5.4° (c 1, $CHCl_3$). g) Calcd for $C_{21}H_{26}O_6$. h) Lit,11) $[\alpha]_D^{22}$ +74.9° (c 1.68, $CHCl_3$). i) Lit,4a) mp 83—85 °C, $[\alpha]_D^{25}$ +8.6° (c 1.08, $CHCl_3$). j) Lit,12) $[\alpha]_D^{20}$ −1.9° (c 1.575, $CHCl_3$).

TABLE 3. ^{1}H NMR DATA FOR THE ACETATES OF THE TRI- AND DIBENZYL ETHERS AND DIALLYL ETHERS OF METHYL α- AND β-D-GALCTOPYRANOSIDES[a)]

Compound	δ H-1		H-2		H-3		H-4		MeO	Ac-2	Ac-3	Ac-4	Ac-6
	J/Hz	$J_{1,2}$		$J_{2,3}$		$J_{3,4}$		$J_{4,5}$					
Acetate of:													
3	4.58	3.5	3.58	9.7	3.83	3.2	5.48	1.2	3.33	—	—	1.99	—
4	4.60	3.6	3.87	10.7	5.13	3.2	3.90	1.4	3.30	—	1.89	—	—
5	4.86	3.5	5.15	10.5	3.81	3.9	n.d.	n.d.	3.30	1.99	—	—	—
11	4.61	3.6	3.65	10.5	5.17	3.3	5.33	1.2	3.34	—	1.87	1.94	—
12	4.81	3.6	4.85	9.8	3.75	3.6	5.49	1.0	3.31	1.99	—	1.99	—
13[b)]	4.90	2.9	5.21	11.2	4.36	2.3	4.10	n.d.	3.35	2.01 (1.99)	1.99 (1.98)	—	—
17[c)]	4.81	3.3	3.63	10.1	3.78	3.0	5.40	0.6	3.39	—	—	2.11	2.04
18[c)]	4.83	3.7	3.88	10.7	5.15	3.1	4.03	1.0	3.38	—	2.09	—	2.05
8	4.13	7.8	n.d.	n.d.	n.d.	2.1	5.43	1.3	3.44	—	—	1.99	—
9	4.19	8.1	3.57	10.2	4.71	3.3	3.84	1.1	3.45	—	1.81	—	—
10	4.19	7.9	5.22	10.0	3.40	3.0	3.86	0.9	3.34	1.93	—	—	—
14	4.24	7.8	3.36	10.2	4.82	3.4	5.27	1.1	3.48	—	1.84	1.94	—
15	4.17	8.0	4.91	10.1	3.38	3.3	5.47	0.7	3.36	1.93	—	2.02	—
16	4.27	7.8	5.16	10.4	4.79	3.2	3.88	0.6	3.37	1.98	1.90	—	—
19[c)]	4.12	8.4	3.63	7.3	3.75	1.2	5.33	0.8	3.52	—	—	2.10	2.04

a) Measured in CCl_4 with Me_4Si at 90 MHz. b) Measured in $(CD_3)_2CO$ with Me_4Si. The δ values for Ac group in CCl_4 are shown in parentheses. c) Measured in $CDCl_3$ with Me_4Si.

80 °C over P_2O_5.

*Procedure for the Partial Benzylation of Methyl α- and β-D-Galactopyranosides (**1** and **6**).* A mixture of **1** or **6** (1.0 g, 5.2 mmol) freshly crushed alkali, and $PhCH_2Cl$ (20 ml) was stirred under anhydrous conditions. After the usual work-up,[3)] chromatography (toluene: 2-butanone = 100: 1→1: 1, gradient) of the reaction mixture gave the totally and the partially benzylated derivatives of **1** or **6** (Table 1). Physical and analytical data of the tribenzyl ethers (**3**—**5** and **8**—**10**) and dibenzyl ethers (**11**—**16**) are listed in Table 2. The ^{1}H NMR data for the acetylated compounds derived from the tri- and dibenzyl ethers as well as the diallyl ethers desctibed below through the treatment with acetic anhydride in pyridine are given in Table 3.

*Methyl 2,6-Di-O-benzyl-α-D-galactopyranoside (**12**).* Methyl 3,6-di-*O*-trityl-α-D-galactopyranoside[5)] (0.75 g, 1.1 mmol) was refluxed in allyl bromide (7.5 ml) containing NaH (≈60% disp., 0.52 g) for 4 h. The filtrate of the reaction mixture was evaporated and heated in aq. AcOH (80%) at 100 °C for 1 h. After evaporation, chromatography (toluene: 2-butanone = 2: 1) and recrystallization from toluene containing diisopropyl ether gave methyl 2,4-di-*O*-allyl-α-D-galactopyranoside (**18**), (0.22 g, 73%): mp 129.5—130 °C; $[\alpha]_D^{20}$ +123° (*c* 0.7, $CHCl_3$). Found: C, 57.03; H, 8.16%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%. Benzylation of **18** (0.22 g, 0.80 mmol) with $PhCH_2Cl$ (4.4 ml) and KOH (0.90 g) at 100 °C for 4.5 h, followed by chromatography (toluene: 2-butanone = 30: 1), yielded the 2,3-diallyl-4,6-dibenzyl ether. This was then treated with chlorotris(triphenylphosphine)rhodium(I)[6)] (214 mg) in a mixed solvent (EtOH: benzene: H_2O = 7: 3: 1, 22 ml) for 26 h, followed by refluxing in a mixture of aq HCl (1 mol dm^{-3}, 0.8 ml) and acetone (20 ml) for 30 min. After evaporation, chromatography (diisopropyl ether: ethyl acetate = 7: 1) afforded **12** (0.24 g, 80%).

*Methyl 4,6-Di-O-benzyl-α-D-galactopyranoside (**13**).* Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside[7)] (1.4 g, 5 mmol) was refluxed in allyl bromide (35 ml) containing NaH (≈60% disp., 1.6 g) for 2 h. The filtrate of the reaction mixture was evaporated and heated in aq AcOH (80%) at 100 °C for 30 min. After evaporation, chromatography ($CHCl_3$: MeOH = 50: 1) gave methyl 2,3-di-*O*-allyl-α-D-galactopyranoside (**17**), (0.70 g, 51%): $[\alpha]_D^{20}$ +119° (*c* 4.4, $CHCl_3$). Found: C, 56.51; H, 8.14%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%. Compound **17** (0.45 g, 1.64 mmol) was benzylated with $PhCH_2Cl$ and KOH, and subsequently deallylated as described above to give **13** (0.36 g, 59%).

*Methyl 4,6-Di-O-benzyl-β-D-galactopyranoside (**16**).* Methyl 4,6-di-*O*-benzylidene-β-D-galactopyranoside[8)] (80 mg, 0.28 mmol) was similarly converted into methyl 2,3-di-*O*-allyl-β-D-galactopyranoside (**19**), (70 mg, 91%): $[\alpha]_D^{20}$ +1.7° (*c* 1.1, $CHCl_3$). Found: C, 56.50; H, 8.14%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%. Benzylation of **19** (70 mg, 0.26 mmol) and subsequent deallylation gave **16** (65 mg, 68%).

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