

A Simple Synthesis of Methyl 2,3,6- and 2,4,6-Tri-*O*-benzyl- α -D-mannosidesShinkiti KOTO,* Kazuhiro TAKENAKA, Naohiko MORISHIMA, Akiko SUGIMOTO, and Shonosuke ZEN
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Synopsis. Controlled benzylation of methyl α -D-mannopyranoside with benzyl chloride and LiOH selectively gave the 2,3,6-tribenzyl ether in a 53% yield. Such a reaction using benzyl chloride and KOH afforded mainly the 2,4,6-tribenzyl ether in a 41% yield. The products were allylated and then hydrolyzed to give the corresponding 1-OH derivatives.

Various methods for the synthesis of partially benzylation carbohydrates have been proposed.¹⁾ This kind of compound, however, has often been prepared through direct benzylation²⁾ of readily available methyl glycosides.^{3–5)}

Benzylation of methyl α -D-mannopyranoside (**1**) in benzyl chloride (BnCl) and LiOH (8equiv) at 140°C for 9 h selectively gave the 2,3,6-tribenzyl ether **2** in a 53% yield. Benzylation of **1** in BnCl and KOH (4.5 equiv) at 140°C for 3 h mainly furnished the 2,4,6-tribenzyl ether **3**⁶⁾ in a 41% yield.

A trace (<1%) of the 3,4,6-tribenzyl ether **4**⁷⁾ and an appreciable quantity (3–8%) of the 2,3,4-tribenzyl ether **5**⁸⁾ were always isolated from the reaction mixture. Controlled benzylation of the 3,4-dibenzyl ether **7**⁹⁾ also gave **5** as the main product. These show that

the 2-OH group, rather than the 6-OH group, of **1** has an unusual susceptibility to benzylation.

Other mannosides, benzyl,¹⁰⁾ allyl,¹¹⁾ and phenyl α -D-mannopyranosides¹²⁾ (**8**, **12**, and **16**) afforded preferentially the corresponding 2,3,6-tribenzyl ethers *via* the benzylation with LiOH.

The tribenzyl ethers, **2** and **3**, were allylated and hydrolyzed to the respective 1-OH derivatives, **20** and **21**.^{6c)}

Experimental^{3–5)}

4-O-Allyl-2,3,6-tri-*O*-benzyl-D-mannopyranose (20). Compound **2** (157.7 mg, 0.34 mmol) was allylated in allyl bromide (Wako, 3 ml) in the presence of NaH (Wako, 60%, 95 mg) at 70°C for 2 h. The allyl ether was hydrolyzed in a mixture of AcOH (5.4 ml) containing aq H₂SO₄ (3M, 0.75 ml (1 M=1 mol dm⁻³)) at 100°C for 1.3 h to give **20** (70.0 mg, 42%).

3-O-Allyl-2,4,6-tri-*O*-benzyl-D-mannopyranose (21). Compound **3** (145.9 mg) was converted into **21** (50.8 mg, 33%).

Methyl 2-O-Acetyl-3,4,6-tri-*O*-benzyl- α -D-mannopyranoside. 1,2,3,4,6-Penta-*O*-acetyl- α -D-mannopyranose (Kyowa, 250 mg, 0.64 mmol) was stirred in CH₂Cl₂ (0.65 ml) containing

TABLE 1. THE RESULTS OF BENZYLATION OF MANNOPYRANOSIDES

Run	Starting Material	Alkali(equiv)	Temp °C	Time h	Yield %							
					2,3,4,6-Bn ₄				2,3,6-Bn ₃			
1	1	LiOH (8.0)	140	9	6	14	2	53	3	10	5	6
2	1	LiOH (8.0)	140	24	6	24	2	38	3	3	5	4
3	1	LiOH (13.5)	140	6	6	14	2	50	3	6	5	3
4	1	KOH (4.5)	100	9	6	12	2	17	3	30	5	3
5	1	KOH (4.5)	140	3	6	20	2	18	3	41	5	8
6	1	RbOH (4.5)	70	5.5	6	9	2	19	3	33	5	5
7	8	LiOH (8.0)	140	9	11	8	9	31	10	5	— ^a	— ^a
8	8	KOH (4.5)	140	3	11	14	9	13	10	17	— ^a	— ^a
9	12	LiOH (8.0)	140	9	15	20	13	35	14	3	— ^a	— ^a
10	12	KOH (4.5)	100	3	15	21	13	21	14	19	— ^a	— ^a
11	16	LiOH (8.0)	140	9	19	4	17	35	18	4	— ^a	— ^a
12	16	KOH (4.5)	100	3	19	10	17	23	18	19	— ^a	— ^a

a: Not isolated.

TABLE 2. PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS

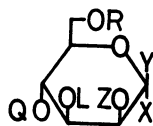
Compd	$[\alpha]_D^{20}(c, \text{CHCl}_3)$ deg	<i>R</i> _f	Toluene Butanone	Mol. Form.	Calcd C	Anal/%		
						H	Found C	H
2	+2(2.0)	0.54	(5/1)	C ₂₈ H ₃₂ O ₆	72.39	6.94	71.73	6.91
3	+17(0.2)	0.60					72.04	6.94 a
4	+56(3.0)	0.23					72.53	6.95 b
5	+29(0.2)	0.27					72.39	6.92 c
9	+30(0.3)	0.47	(10/1)	C ₃₄ H ₃₈ O ₆	75.53	6.71	75.23	6.71
10	+33(0.2)	0.56					75.50	6.93
13	+3(1.6)	0.51	(6/1)	C ₃₀ H ₃₄ O ₆	73.45	6.99	73.43	6.97
14	+46(0.2)	0.62					72.92	6.83
20	+21(1.0)	0.42					73.18	7.00
21	+21(1.7)	0.38					73.73	6.81
17	+35(0.4)	0.60	(7/1)	C ₃₃ H ₃₄ O ₆	75.26	6.51	75.36	6.43
18	+66(0.2)	0.70					75.35	6.49
11	+51(0.3)	0.65	(10/1)	C ₄₁ H ₄₂ O ₆	78.07	6.71	77.81	6.63
15	+51(0.3)	0.70	(6/1)	C ₃₇ H ₄₀ O ₆	76.53	6.94	76.18	6.94
19	+71(0.3)	0.84	(7/1)	C ₄₀ H ₄₀ O ₆	77.90	6.55	77.71	6.53

a Ref. 7a: $[\alpha]_D^{21}+59.7^\circ(c\ 1.85, \text{CH}_2\text{Cl}_2)$, Ref. 7b: $[\alpha]_D^{20}+57.7^\circ(c\ 0.485, \text{CHCl}_3)$. b Ref. 6a: $[\alpha]_D^{25}+14.4^\circ(c\ 1, \text{CHCl}_3)$, Ref. 6b: $[\alpha]_D^{25}+16.9^\circ(c\ 1.5, \text{CHCl}_3)$, Ref. 6c: $[\alpha]_D^{25}+17.2^\circ(c\ 1.0, \text{CHCl}_3)$. c Ref. 8: $[\alpha]_D^{20}+30^\circ(c\ 0.49, \text{CHCl}_3)$.

TABLE 3. ^1H NMR DATA FOR THE ACETATES OF THE TRIBENZYL ETHERS OF MANNOPYRANOSIDES^a

Compd	(ppm) H-1 (Hz)	H-2 J_{12}	H-3 J_{23}	H-4 J_{34}	H-4 J_{45}	Ac-3	Ac-4
Acetates ^b of.							
2	4.61	2.1	—	—	5.20	—	1.82
3	4.61	1.8	3.77	5.03	3.80	1.84	—
9	4.76	2.0	—	—	5.22	—	1.80
10	4.75	2.0	3.80	5.12	3.92	1.87	—
13	4.60	1.6	—	—	5.17	—	1.80
14	4.73	2.0	—	5.08	—	1.89	—
17	5.37	1.6	3.81	3.87	5.31	—	1.80
18	5.37	2.3	3.97	5.22	4.00	1.85	—
			3.0	8.4	9.6		

a: At 90 Mz in CCl_4 with Me_4Si . b: Acetylation of a sample with excess Ac_2O in pyridine at room temperature overnight, followed by chromatography on silica gel using benzene-2-butanone system gave a homogeneous acetate.



All=allyl
Bn=benzyl

Compd	X	Y	Z	L	Q	R
1	OMe	H	H	H	H	H
2	OMe	H	Bn	Bn	H	Bn
3	OMe	H	Bn	H	Bn	Bn
4	OMe	H	H	Bn	Bn	Bn
5	OMe	H	Bn	Bn	Bn	H
6	OMe	H	Bn	Bn	Bn	Bn
7	OMe	H	H	Bn	Bn	H
8	OBn	H	H	H	H	H
9	OBn	H	Bn	Bn	H	Bn
10	OBn	H	Bn	H	Bn	Bn
11	OBn	H	Bn	Bn	Bn	Bn
12	OAll	H	H	H	H	H
13	OAll	H	Bn	Bn	H	Bn
14	OAll	H	Bn	H	Bn	Bn
15	OAll	H	Bn	Bn	Bn	Bn
16	OPh	H	H	H	H	H
17	OPh	H	Bn	Bn	H	Bn
18	OPh	H	Bn	H	Bn	Bn
19	OPh	H	Bn	Bn	Bn	Bn
20	OH, $\overbrace{\quad\quad}$	H	Bn	Bn	All	Bn
21	OH, $\overbrace{\quad\quad}$	H	Bn	All	Bn	Bn

AcBr (Wako, 0.55 ml) and H_2O (0.11 ml).¹⁴ After stirring for 3 h at room temperature, evaporation and co-evaporation with toluene gave a syrup, which was treated in MeNO_2 (0.64 ml) with 2,6-dimethylpyridine (0.24 ml) and MeOH (0.20 ml) at room temperature overnight. The mixture was diluted with CHCl_3 , washed with aq NaHCO_3 (5%) and the organic layer evaporated to give a syrup, which was stirred in BnCl (4 ml) containing crushed KOH (1.0 g) at 110–120°C for 2 h. After filtration and evaporation, the mixture was chromatographed on alumina (Woelm, 02084) just with hexane-toluene and subsequently with diisopropyl ether-2-butanone systems to give a syrup (294.2 mg). This was treated in CH_2Cl_2 (4 ml) with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (5 μl) at room temperature for 5 min, followed by chromatography, to give the titled compound (232.3 mg, 72%, $[\alpha]_D^{20} +26^\circ$ (c 6, CHCl_3), lit.^{7a}) $[\alpha]_D^{27} +27.9^\circ$ (c 2.24, CH_2Cl_2). Found: C, 71.42; H, 6.80%. Calcd for $\text{C}_{30}\text{H}_{34}\text{O}_7$: C, 71.13; H, 6.77%.

This was quantitatively deacetylated with dil methanolic

NaOMe to give 4.

Benzylation of Methyl 3,4-Di-O-benzyl- α -D-mannopyranoside (7). The dibenzyl ether **7**⁹ (63.5 mg, 0.17 mmol) was stirred in BnCl (1.2 ml) containing LiOH (12.2 mg at 140°C for 9 h. Chromatography gave a trace of **6**,¹³ **5** (21.7 mg, 28%), **4** (4.1 mg, 5%), and unchanged **7**.

When **7** (63.2 mg), KOH (14.3 mg) and BnCl (1.2 ml) was stirred at 140°C for 3 h, **5** (15.6 mg, 20%) and **4** (12%) were obtained after chromatography.

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