A Simple Synthesis of Methyl 2,3,6- and 2,4,6-Tri-*O*-benzyl-α-D-mannosides

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(Received June 12, 1984)

Synopsis. Cotrolled 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 benzylated carbohydrates have been proposed.[1] This kind of compound, however, has often been prepared through direct benzylation[2] of readily available methyl glycosides.[3-5]

Benzylation of methyl α-D-mannopyranoside (**1**) in benzyl chloride (BnCl) and LiOH (8 equiv) 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-mannopyranosides[12] (**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 H_2SO_4 (3M, 0.75 ml (1 M=1 mol dm^{-3})) at 100 °C for 1.3 h to gave **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 CH_2Cl_2 (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$_3$		2,4,6-Bn$_3$		2,3,4-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]
8	**8**	KOH	(4.5)	140	3	**11**	14	**9**	13	**10**	17		—[a]
9	**12**	LiOH	(8.0)	140	9	**15**	20	**13**	35	**14**	3		—[a]
10	**12**	KOH	(4.5)	100	3	**15**	21	**13**	21	**14**	19		—[a]
11	**16**	LiOH	(8.0)	140	9	**19**	4	**17**	35	**18**	4		—[a]
12	**16**	KOH	(4.5)	100	3	**19**	10	**17**	23	**18**	19		—[a]

a: Not isolated.

Table 2. Physical and analytical data of compounds

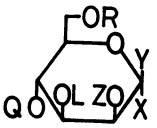
Compd	$[\alpha]_D^{20}$(*c*, $CHCl_3$) deg	R_f	Toluene/Butanone	Mol. Form.	Anal/% Calcd C	Calcd H	Found C	Found H
2	+2(2.0)	0.54	(5/1)	$C_{28}H_{32}O_6$	72.39	6.94	71.73	6.91
3	+17(0.2)	0.60					72.04	6.94 a
4	+56(3.0)	0.23					72.53	6.95 b
5	+29(0.2)	0.27					72.39	6.92 c
9	+30(0.3)	0.47	(10/1)	$C_{34}H_{36}O_6$	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°(*c* 1.85, CH_2Cl_2), Ref. 7b: $[\alpha]_D^{25}$+57.7°(*c* 0.485, $CHCl_3$). b Ref. 6a: $[\alpha]_D^{25}$+14.4°(*c* 1, $CHCl_3$), Ref. 6b: $[\alpha]_D^{23}$+16.9°(*c* 1.5, $CHCl_3$), Ref. 6c: $[\alpha]_D^{25}$+17.2°(*c* 1.0, $CHCl_3$). c Ref. 8: $[\alpha]_D$+30°(*c* 0.49, $CHCl_3$).

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

Compd	(ppm) H-1 (Hz)	J_{12}	H-2	J_{23}	H-3	J_{34}	H-4	J_{45}	Ac-3	Ac-4
Acetates[b] of.										
2	4.61	2.1	—	—	—	9.0	5.20	9.0	—	1.82
3	4.61	1.8	3.77	3.2	5.03	8.7	3.80	9.6	1.84	—
9	4.76	2.0	—	—	—	9.0	5.22	9.0	—	1.80
10	4.75	2.0	3.80	3.0	5.12	8.1	3.92	8.1	1.87	—
13	4.60	1.6	—	—	—	9.0	5.17	9.0	—	1.80
14	4.73	2.0	—	3.5	5.08	8.5	—	—	1.89	—
17	5.37	1.6	3.81	3.0	3.87	8.7	5.31	9.8	—	1.80
18	5.37	2.3	3.97	3.0	5.22	8.4	4.00	9.6	1.85	—

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	O‾H,		H	Bn	All	Bn
21	O‾H,		H	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 $BF_3 \cdot Et_2O$ (5 μl) at room temperature for 5 min, followed by chromatography, to give the titled compound (232.3 mg, 72%, $[\alpha]_D^{20}$ +26° (*c* 6, $CHCl_3$), lit,[7a] $[\alpha]_D^{27}$ +27.9° (*c* 2.24, CH_2Cl_2). Found: C, 71.42; H, 6.80%. Calcd for $C_{30}H_{34}O_7$: 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.

References

1) T. Ogawa and M. Matsui, *Carbohydr. Res.*, **62**, C 1 (1978); R. Taman, J. Rosik, and M. Zikmund, *ibid.*, **103**, 165 (1982); P. J. Garegg, T. Iversen, and S. Oscarson, *ibid.*, **50**, C12 (1976); R. Eby and C. Schuerch, *ibid.*, **100**, C41 (1982); A. Lipták, *Tetrahedron Lett.*, **1976**, 3551.

2) G. Zemplén, Z. Csüros, and S. Angyal, *Chem. Ber.*, **70**, 1848 (1937).

3) S. Koto, Y. Takebe, and S. Zen, *Bull. Chem. Soc. Jpn.*, **45**, 291 (1972).

4) N. Morishima, S. Koto, M. Oshima, A. Sugimoto, and S. Zen, *Bull. Chem. Soc. Jpn.*, **56**, 2849 (1983).

5) N. Morishima, S. Koto, C. Kusuhara, and S. Zen, *Bull. Chem. Soc. Jpn.*, **55**, 631 (1982).

6) a) V. K. Handa, J. J. Barlow, and K. L. Matta, *Carbohydr. Res.*, **76**, Cl (1979); b) A. J. Verma and C. Schuerch, *J. Org. Chem.*, **46**, 799 (1981); c) F. Kong and C. Schuerch, *Carbohydr. Res.*, **112**, 141 (1983).

7) a) N. E. Franks and R. Montgomery, *Carbohydr. Res.*, **6**, 286 (1968); b) T. Ogawa, K. Katano, K. Sasajima, and M. Matsui, *Tetrahedron*, **37**, 2779 (1981).

8) H. B. Borén, K. Eklind, P. J. Garegg, B. Lindberg, Å. Pilotti, *Acta Chem. Scand.*, **26**, 4143 (1972).

9) S. Koto, N. Morishima, T. Yoshida, M. Uchino, and S. Zen, *Bull. Chem. Soc. Jpn.*, **56**, 1171 (1983).

10) P. A. J. Gorin and A. S. Perlin, *Can. J. Chem.*, **39**, 2476 (1961).

11) F. M. Winnik, J. P. Carver, and J. J. Krepinsky, *J. Org. Chem.*, **47**, 2701 (1982).

12) B. Helferich and S. Winkler, *Chem. Ber.*, **66**, 1556 (1933).

13) S. Koto, N. Morishima, Y. Miyata, and S. Zen, *Bull. Chem. Soc. Jpn.*, **49**, 2639 (1976).

14) S. Koto, N. Morishima, T. Irisawa, Y. Hashimoto, M. Yamazaki, and S. Zen, *Nippon Kagaku Kaishi*, **1982**, 1651.