ELSEVIER

Carbohydrate Research 265 (1994) 133–137

CARBOHYDRATE RESEARCH

Note

A convenient preparation of 5-benzyl ethers of D-gluco- and D-manno-furanose derivatives

Halszka Stępowska, Aleksander Zamojski *

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

Received 28 April 1994; accepted 6 June 1994

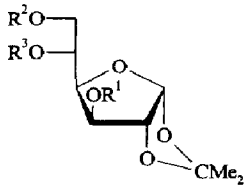
Keywords: Glucofuranose; Mannofuranose; Selective benzylation; Two-phase benzylation

Benzylation of sugar polyols with benzyl chloride (1.2 molar equiv per OH group) in a two-phase system (benzene/2-methyl-2-butanol–aq 50% sodium hydroxide, tetrabutylammonium hydrogen sulfate) leads in very good yields to perbenzylated derivatives [1]. We have found that benzylation of 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) under phase-transfer conditions (PTC) using benzyl bromide–aq 50% sodium hydroxide led, in 86% yield, to the 5-*O*-benzyl derivative (**2**). Under these conditions the 6-*O*-benzyl and 5,6-di-*O*-benzyl derivatives were formed only in trace amounts and were not isolated. Benzylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**3**) using the same method afforded the 3,5-di-*O*-benzyl derivative (**4**) in 78% yield. In this reaction the 3,5,6-tri-*O*-benzyl derivative (**5**) was formed in 12% yield.

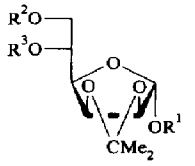
Application of the same procedure to benzylation of allyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**7**) led to the 5-benzyl ether (**8**) in 89% yield without the formation of the corresponding 5,6-di-*O*-benzyl derivative. In the case of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**9**), 63% of the 5-benzyl ether (**10**) and a substantial amount (35%) of the 6-*O*-benzylated compound (**11**) were obtained. These results are shown in Table 1.

* Corresponding author.

SSDI 0008-6215(94)00216-3



1: R^1 = All, R^2 = R^3 = H
2: R^1 = All, R^2 = H, R^3 = Bzl
3: R^1 = Bzl, R^2 = R^3 = H
4: R^1 = R^3 = Bzl, R^2 = H
5: R^1 = R^2 = R^3 = Bzl
6: R^1 = R^2 = Bzl, R^3 = H



7: R^1 = All, R^2 = R^3 = H
8: R^1 = All, R^2 = H, R^3 = Bzl
9: R^1 = CH_3, R^2 = R^3 = H
10: R^1 = CH_3, R^2 = H, R^3 = Bzl
11: R^1 = CH_3, R^2 = Bzl, R^3 = H
12: R^1 = CH_3, R^2 = Bzl, R^3 = p-$O_2NC_6H_4CO$

The location of the newly introduced *O*-benzyl group was evident from the ^{13}C NMR spectra (Table 2). To substantiate the spectral conclusions, **3** was benzylated conventionally (NaH/BzlBr in DMF, 0°C → room temperature) to yield 27% of the 6-*O*-benzyl derivative (**6**), 59% of **5**, and only 8% of **4** (Table 1, Entry 3). In the case of **4**, the ^{13}C NMR signal of C-5 was found at δ 76.10 whereas the signal of C-6 appeared at δ 62.17. For **6**, the

Table 1
Benzylation of D-glucofuranose (**1**, **3**) and D-mannofuranose (**7**, **9**) derivatives in two-phase benzyl bromide–aq 50% NaOH system (Bu_4NBr as catalyst)

Entry	Substrate	Product	Yield %	Other products
1	**1**	**2**	86.1	[a]
2	**3**	**4**	78.4	**5** (12.0%)
3 [b]	**3**	**4**	8.2	**5** (59.5%), **6** (27.4%)
4	**7**	**8**	89.5	
5	**9**	**10**	63.0	**11** (35.0%)

[a] Traces (TLC) of 5,6-di-*O*-benzyl and 6-*O*-benzyl derivatives of **1**. [b] Benzylation with NaH/BzlBr reagent system (cf. Experimental).

Table 2
^{13}C NMR (δ, DEPT mode) spectra of compounds **1**, **2**, and **4**–**12**

Compound no.	C-1	C-2	C-3	C-4	C-5	C-6	Other (inter alia)
1	104.96	81.74	82.09	79.77	69.02	64.24	71.07 [a], 26.09, 26.60 [b]
2	105.05	81.53	81.69	79.77	75.97	62.18	70.88 [a], 72.35 [c], 26.29, 26.76 [b]
4	105.10	81.73	81.83	79.84	76.11	62.17	71.92, 72.29 [c], 26.37, 26.85 [b]
5 [d]	105.11	81.76	81.80	79.01	75.53	71.30	71.95, 72.66, 73.36 [c], 26.32, 26.74 [b]
6	105.20	82.15	82.37	79.90	68.10	72.17	72.41, 73.54 [c], 26.36, 26.86 [b]
7	105.31	80.03	79.20	84.77	70.25	64.41	67.92 [a], 24.59, 25.89 [b]
8	105.53	79.86	79.31	84.92	76.58	62.60	68.01 [a], 72.87 [c], 24.99, 26.19 [b]
9	107.00	79.80	79.00	84.51	69.82	64.34	54.50 [e], 24.60, 25.80 [b]
10	107.15	79.78	79.10	84.76	76.55	62.53	54.52 [e], 72.79 [c], 24.95, 26.13 [b]
11	107.11	80.02	78.84	84.76	68.94	71.81	54.52 [e], 73.49 [c], 24.63, 25.97 [b]
12	107.15	79.56	77.25	84.73	72.15	68.97	54.57 [e], 73.32 [c], 24.84, 26.02 [b]

[a] Allyl OCH_2, the remaining signals at: δ 133.8 ± 0.1 (–CH=) and 117.6 ± 0.1 (CH_2=). [b] $C(CH_3)_2$. [c] $PhCH_2$. [d] Assignments corroborated by the ^1H–^{13}C COSY NMR spectrum. [e] OCH_3.

corresponding figures were δ 68.10 (C-5) and 72.17 (C-6). From **11**, the 5-*p*-nitrobenzoate (**12**) was obtained by conventional esterification (*p*-$O_2NC_6H_4COCl$, Et_3N, 4-dimethylaminopyridine). In the ^1H NMR spectrum of **12**, the octet of H-5 appeared at δ 5.54 which additionally confirmed the site of the *O*-benzyl group at C-6.

Preferential benzylation of the secondary hydroxyl group can be ascribed to its greater acidity in comparison with the primary OH group under the conditions employed. It is worth mentioning that the 5-benzyl ether **4** can be obtained in 48% yield when benzylation of **3** is conducted in the presence of Cu^{2+} ions [2]. However, 40% of **6** and 12% of **5** were also obtained [2]. Hexamethylenestannylene derivatives of carbohydrate 1,2-diols have been proposed recently as intermediates undergoing tosylation preferentially at the secondary oxygen atom [3].

1. Experimental

The ^1H and ^{13}C (DEPT mode) NMR spectra were recorded with a Varian Gemini 200 spectrometer for solutions in $CDCl_3$. Optical rotations were measured in chloroform solutions with a Perkin–Elmer 141 automatic polarimeter at 18 ± 2°C. TLC was performed on Silica Gel $60F_{254}$ (Alu Plates Merck) and column chromatography on Silica Gel 230–400 mesh (Merck). Substrates **1** [4], **3** [5], and **9** [6] were prepared according to literature methods.

*Allyl 2,3-*O*-isopropylidene-α-*D*-mannofuranoside* (**7**) (*with Z. Pakulski*).—To a solution of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (20.8 g, 80 mmol) in pyridine (50 mL) were added Ac_2O (14.2 mL, 150 mmol) and a few crystals of 4-dimethylaminopyridine. After 24 h, toluene (50 mL) was added and the solution was concentrated under reduced pressure to dryness. To the residue was added water (250 mL), and the product was extracted with $CHCl_3$ (4 × 100 mL). The combined $CHCl_3$ extracts were washed with water (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated to afford 24.4 g (100%) of crude 1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose. ^1H NMR: δ 6.12 (s, 1 H, H-1), 4.85 (dd, 1 H, $J_{3,2}$ 5.9, $J_{3,4}$ 3.6 Hz, H-3), 4.70 (d, 1 H, H-2), 4.40 (m, 1 H, H-5), 4.09 (dd, 1 H, $J_{6a,5}$ 6.1, $J_{6a,6b}$ 8.9 Hz, H-6a), 4.03 (m, 2 H, $J_{6b,5}$ 4.2 Hz, H-4,6b), 2.07 (s, 3 H, CH_3CO), 1.49, 1.46, 1.38, and 1.34 (4 s, 12 H, 2 × CMe_2).

This product was used in the next step. To a solution of the 1-*O*-acetyl derivative (10.0 g, 33.1 mmol) in CH_2Cl_2 (100 mL) were added allyl alcohol (11.3 g, 165.5 mmol) and $SnCl_4$ (4 mL). The mixture was stirred at room temperature for 24 h and a solution of satd aq $NaHCO_3$ (100 mL) was added. The mixture was filtered through a Celite pad and the products were extracted with $CHCl_3$ (3 × 100 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to dryness. Column chromatography of the residue with 1:1 pentane–EtOAc gave allyl 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranoside (2.9 g, 30%) and **7** (5.16 g, 60%). ^1H NMR data of **7**: inter alia, δ 5.08 (s, 1 H, H-1), 4.83 (dd, 1 H, $J_{3,4}$ 3.3 Hz, H-3) 4.62 (d, 1 H, $J_{2,3}$ 6.0 Hz, H-2), 3.92–4.19 (m, 4 H, H-4,5, allyl OCH_2), 3.87 (dd, 1 H, $J_{6a,5}$ 3.1, $J_{6a,6b}$ 11.4 Hz, H-6a), 3.72 (dd, 1 H, $J_{6b,5}$ 5.5 Hz, H-6b), 1.48, 1.35 (2 s, 6 H, CMe_2). Analytical and optical rotation data of **7**: Table 3.

*3-*O*-Allyl-5-*O*-benzyl-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**2**).—To 10 mL of aq 50% NaOH was added 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**) (1.25 g, 4.8

Table 3
Analytical and optical rotation data of compounds **1–12** [a]

Compound no.	Formula	Elemental analysis		$[\alpha]_D^{18}$ (c, $CHCl_3$) (deg)	Ref.
		Calcd C Found	Calcd H Found		
1	$C_{12}H_{20}O_6$	55.38 55.29	7.69 7.89	−38.4 (2.1)	[4]
2	$C_{19}H_{26}O_6$	65.14 64.85	7.42 7.62	−25.2 (2.1)	
3	$C_{16}H_{22}O_6$	61.93 61.77	7.09 7.27	−50.5 (1.7) [b]	[5]
4	$C_{23}H_{28}O_6$	69.00 69.18	7.00 7.21	−21.8 (1.2)	[2]
5	$C_{30}H_{34}O_6$	73.46 73.67	6.71 6.97	−55.1 (1.3) [c]	[1,7]
6	$C_{23}H_{28}O_6$	69.00 68.76	7.00 7.16	−17.2 (1.1) [d]	[7]
7	$C_{12}H_{20}O_6$	55.38 55.48	7.69 7.45	+66.2 (0.9)	
8	$C_{19}H_{26}O_6$	65.14 64.85	7.42 7.42	+38.1 (1.8)	
9	$C_{10}H_{18}O_6$	51.28 51.61	7.69 7.75	+82.6 (0.9) [e]	[6,8,9]
10	$C_{17}H_{24}O_6$	62.96 62.71	7.40 7.63	+62.4 (0.7)	
11	$C_{17}H_{24}O_6$	62.96 62.86	7.40 7.26	+59.5 (0.4)	
12 [f]	$C_{24}H_{27}NO_9$	60.88 61.08	5.70 5.75	+71.3 (2.4)	

[a] Compounds **1–11** are syrups. [b] Ref. [5]: $[\alpha]_D$ −49.9° (c 1.08, $CHCl_3$). [c] Ref. [7]: $[\alpha]_D$ −61.8° (c 0.3, $CHCl_3$). [d] Ref. [7]: $[\alpha]_D$ −14.5° (c 0.24, $CHCl_3$). [e] Ref. [8]: $[\alpha]_D$ +85.3° (c 1, $CHCl_3$); Ref. [9]: $[\alpha]_D$ +65.1° (c 0.99, $CHCl_3$). [f] Mp 93–94°C.

mmol) at room temperature and the mixture was stirred for a few minutes. Benzyl bromide (10 mL) and tetrabutylammonium bromide (150 mg) were added, and the mixture was vigorously stirred for 40 min. The layers were separated and the aqueous solution was extracted with $CHCl_3$ (30 mL). The combined organic layers were dried, filtered, and concentrated to dryness under reduced pressure. Column chromatography with 7:3 hexane–EtOAc gave **2** (1.45 g, 86.1%).

The two-phase benzylations of **3**, **7**, and **9** were performed according to this method. The results and the spectral and analytical data of the products are collected in Tables 1, 2, and 3.

*Benzylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-*D*-glucofuranose* (**3**) *in* N,N*-dimethylformamide with sodium hydride–benzyl bromide.*—To NaH (0.16 g, 50% suspension in mineral oil; washed with hexane and dried) was added dry DMF (15 mL), and the suspension was cooled to 0°C. A solution of **3** (0.93 g, 3 mmol) in DMF (10 mL) was added and the mixture was stirred. After a few minutes benzyl bromide (1.3 g, 7.6 mmol) was added and the mixture was allowed to attain room temperature. After 1 h, MeOH (1

mL) and water (25 mL) were added and the products were extracted with $CHCl_3$ (3×30 mL), dried, and concentrated under diminished pressure. The residue was separated by column chromatography with 4:1 then 1:1 hexane–EtOAc to yield **5** (0.873 g, 59.5%), **6** (0.327 g, 27.4%), and **4** (0.098 g, 8.2%).

Acknowledgements

The authors are grateful to Dr. Z. Pakulski for providing details of his preparation of **7**. This work was partially financed from grant no. P303 013 05 obtained from the State Committee for Scientific Research (KBN).

References

[1] W. Szeja, I. Fokt, and G. Grynkiewicz, *Recl. Trav. Chim. Pays-Bas*, 108 (1989) 224–226.
[2] R. Eby, K.T. Webster, and C. Schuerch, *Carbohydr. Res.*, 129 (1984) 111–120.
[3] T.B. Grindley and X. Kong, *Tetrahedron Lett.*, 34 (1993) 5231–5234.
[4] A.B. Smith III, R.A. Riviero, K.J. Hale, and H.V. Vaccaro, *J. Am. Chem. Soc.*, 113 (1991) 2092–2112.
[5] G.W.J. Fleet and D.R. Witty, *Tetrahedron: Asymm.*, 1 (1990) 119–136.
[6] T. Hanaya, H. Yamamoto, K. Ohmori, M.A. Armour, and A.M. Hogg, *Bull. Chem. Soc. Jpn.*, 63 (1990) 1174–1179.
[7] H. Hori, Y. Nishida, H. Ohrui, and H. Meguro, *J. Org. Chem.*, 54 (1989) 1346–1353.
[8] J.H. van Boom and G.H. Venneman, *Tetrahedron*, 45 (1989) 7433–7448.
[9] H. Yuasa, Y. Izukawa, and H. Hashimoto, *J. Carbohydr. Chem.*, 8 (1989) 753–763.