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Note

Glycosidation of 2,5-anhydro-3,4-di-*O*-benzyl-D-mannitol with different glucopyranosyl donors. A comparative study

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Abstract—2,5-Anhydro-3,4-di-*O*-benzyl-D-mannitol was glycosylated using different donors such as tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of $Hg(CN)_2$, the corresponding β-thiophenylglycoside in the presence of NIS and TfOH as well as the α- and β-trichloroimidate with TMSOTf as promoter. The resulting mixtures were analyzed by HPLC and the following main components were isolated and characterized: 2,5-anhydro-3,4-di-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-D-mannitol; 6-*O*-acetyl-2,5-anhydro-3,4-di-*O*-benzyl-1-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-D-mannitol; 2,5-anhydro-3,4-di-*O*-benzyl-1,6-bis-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-D-mannitol; 2,5-anhydro-3,4-di-*O*-benzyl-1-*O*-[-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl]-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-D-mannitol and 2,5-anhydro-3,4-di-*O*-benzyl-1,6-bis-*O*-(3,4,6-tri-*O*-acetyl-1,2-*O*-ethylidene-2′-yl-α-D-glucopyranosyl)-D-mannitol. The latter compound representing a bis-orthoester might be a common intermediate in all the investigated reactions, as its rearrangement and/or decomposition can yield all of the isolated compounds.

Keywords: 2,5-Anhydro-D-mannitol derivatives; Mono-, di- and triglycosylated derivatives; Orthoesters and their decomposition products

Recently, we reported[1] the synthesis of several 1,6-di-O-glycosylated 2,5-anhydro-D-mannitol derivatives using 2,5-anhydro-3,4-di-*O*-benzoyl-D-mannitol **3** as acceptor and the following donors: acetobromo derivatives in the presence of $Hg(CN)_2$ or thioglycosides in the presence of NIS and TfOH, respectively. In every case complex mixtures were formed from which the 1,5-di-O-glycosylated trisaccharides could be obtained after column chromatography in disappointingly low yields only. This is more inconceivable as the primary OH groups of **3** should react more readily than the secondary OH groups of 2,5-anhydro-1,6-di-*O*-benzoyl-D-mannitol, which afforded the corresponding 3-O-glycosides in high yields.[2] For getting a better insight into the reaction mentioned above, a systematic investigation was started. To avoid a possible interference of the *O*-benzoyl groups of **3**, the corresponding 3,4-di-*O*-benzyl analogue **2** was used as acceptor and acetobromo α-D-glucopyranose **5** in the presence of $Hg(CN)_2$, the corresponding β-thiophenylglycoside **6** in the presence of NIS and TfOH as donors as well as the α- and β-trichloroimidate **7** and **8** with TMSOTf as promoter. The molar ratio of the acceptor and donor was 1:2.2 and the reactions were quenched after the donor had been consumed (TLC). The crude mixtures obtained after the usual processing were analyzed by HPLC and submitted thereafter to preparative column chromatography. In most cases the multi-component mixtures could only be separated partially in one run and the main components of the so obtained fractions were isolated usually by repeated column chromatography. The structures of the purified components were established by NMR spectroscopy and the corresponding data, including the conditions of the reactions are listed in Tables 1–5.

As can be seen from Table 1, the 1,6-di-O-glycosylated compound **11** was formed in highest yield (44%), when bromide **5** was used as donor, but a substantial amount (9%) of the O-monoglycosylated compound **9**

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Table 1. Glycosidation of **4** with different donors applied in a molar ratio of 1:2.2

Run	Donor	Temp	Time	Promoter	% Of products according to HPLC				
					9	**10**	**11**	**12**	**13**
1	**5**	rt	20 h	$Hg(CN)_2$	9	15	44	—	—
2	**6**	−40 °C	2 h	NIS; TfOH	—	26	21	15	—
3	**7**	−40 °C	25 min	TMSOTf[a]	—	2	18	—	21
4	**7**	−40 °C	10 min	TMSOTf[b]	—	9	24	24	1
5	**8**	−40 °C	10 min	TMSOTf[b]	—	10	25	23	1

[a] 10 mol %.
[b] 20 mol %.

Table 2. Data of the isolated compounds

	9	**10**	**11**	**12**	**13**
$[\alpha]_D$ ($CHCl_3$)	0	+2	+5	+15	+40
R_f (TLC)[a]	0.4	0.7	0.5	0.4	0.6
t_R (HPLC) min	3.6	6.6	8.0	8.8	9.6
Anal. Calcd for	$C_{34}H_{42}O_{14}$	$C_{36}H_{44}O_{15}$	$C_{48}H_{60}O_{23}$	$C_{60}H_{76}O_{31}$	$C_{48}H_{60}O_{23}$
C	60.53	60.33	57.37	55.73	57.37
H	6.27	6.19	6.02	5.92	6.02
Found: C	60.37	60.21	57.13	55.40	57.24
Found: H	6.42	6.30	6.14	6.09	6.26

[a] Solvent: EtOAc–hexane 2:1.

Table 3. Characteristic ^1H NMR chemical shifts

	2,5-Anhydro-D-mannitol unit									Glucopyranosyl unit(s)						
	H-1a	H-1b	H-2	H-3	H-4	H-5	H-6a	H-6b		H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
9	3.63	3.92	4.18	4.01	4.03	4.08	3.64	3.70		4.54	5.00	5.19	5.08	3.66	4.10	4.24
10	3.63	3.94	4.19	4.03	3.96	4.21	4.15–4.18			4.54	5.02	5.20	5.08	3.67	4.11	4.25
11	3.61	3.91	4.12	3.99	3.99	4.12	3.61	3.91		4.52	5.00	5.20	5.07	3.66	4.10	4.24
12	3.65	3.93	4.12	4.11[a]	4.04[a]	4.12	3.56	3.92	′	4.79	3.71	5.16	4.96	3.63	4.07	6.03
									″	4.44	4.96	5.13	5.02	3.70	4.11	6.03
									‴	4.47	5.00	5.18	5.08	3.67	4.11	6.04
13	3.55	3.58	4.12	3.96	3.96	4.12	3.55	3.58		5.57	4.34	5.17	4.89	3.94	4.19	

[a] Interchangeable assignation.

Table 4. Characteristic $J_{H,H}$ couplings

	2,5-Anhydro-D-mannitol unit									Glucopyranosyl unit(s)						
	$^2J_{1a,1b}$	$^3J_{1a,2}$	$^3J_{1b,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6a}$	$^3J_{5,6b}$	$^2J_{6a,6b}$	$^3J_{1,2}$	$^3J_{2,3}$	$^3J_{3,4}$	$^3J_{4,5}$	$^3J_{5,6a}$	$^3J_{5,6b}$	$^2J_{6a,6b}$
9	10.6	6.3	5.5	3.7	3.0	4.2	~6.0	3.7	11.9	8.0	9.5	9.7	9.7	2.8	4.7	12.3
10	10.5	5.8	6.1	3.6	3.6	3.2				8.0	9.6	9.6	9.7	2.4	4.6	12.3
11	10.6	5.9	5.7	7.0		7.0	5.9	5.7	10.6	8.0	9.6	9.6	9.7	2.3	4.7	12.3
12	10.6						5.5		10.4	′ 7.5	9.3	9.6	9.7			
										″ 8.0	9.6	9.6	9.7			
										‴ 7.9	9.6	9.6	9.7			
13	10.1	6.1	6.2	4.1		4.1	6.1	6.2	10.1	5.2	2.0	2.0	9.5			

and its 6-*O*-acetylated derivative **10** (15%) could also be detected in the reaction mixture. Formation of the latter can be explained by the formation of an orthoacetate **14**, the decomposition of which can lead according to the mechanism suggested by Garegg et al.[3] either to the O-acetylated derivative **10**, to the O-glycoside **11** or to an intermediate, in which a free OH group is present at C-2 of the glycosyl moiety (**15**).[4–7] Although this latter could not be detected in the aforementioned reaction, when the thioglycoside **6** was used as donor and NIS as promoter (Table 1, Run 2) the 1,6-bis-glycosylated anhydro derivative **12** could be isolated from the resulting mixture carrying a 2-*O*-glycosido-glycosyl unit at one of the terminal positions of the anhydro-mannitol