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OSMYLATION OF HIGHER SUGAR ALLYLIC ALCOHOLS*

SŁAWOMIR JAROSZ
Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 01-224 Warszawa (Poland)
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ABSTRACT

Catalytic osmylation of 3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-[methyl (*E*)-2,3,4-tri-*O*-benzyl-7-deoxy-α-D-*gluco*-heptopyranosid-6-ulos-7-yl-idene]-α-D-xylofuranose (**1**) afforded 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*C*-(methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-heptopyranosid-6-ulos-6-yl)-L-*glycero*-α-D-*gluco*- (**2**) and -D-*glycero*-β-L-*ido*-hexo-1,4-furanose (**3**) in the ratio 68:32. Osmylation of 3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-[methyl (*E*)-2,3,4-tri-*O*-benzyl-7-deoxy-D-*glycero*-α-D-*gluco*-heptopyranosid-7-ylidene]-α-D-xylofuranose (**4**) afforded 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*C*-(methyl 2,3,4-tri-*O*-benzyl-D-*glycero*-α-D-*gluco*-hexopyranosid-6-yl)-L-*glycero*-α-D-*gluco*- (**5**) and -D-*glycero*-β-L-*ido*-hexo-1,4-furanoses (**6**) in the ratio 86:14. Osmylation of the L-*glycero* isomer (**7**) of **4** yielded 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*C*-(methyl 2,3,4-tri-*O*-benzyl-L-*glycero*-α-D-*gluco*-hexopyranosid-6-yl)-D-*glycero*-β-L-*ido*- (**8**) and -L-*glycero*-α-D-*gluco*-hexo-1,4-furanoses (**9**) in the ratio 33:67. The configurations of **2** and **3**, **5** and **6**, and **8** and **9** were determined by chemical correlations. Triol **5** was converted into known 1,5-di-*O*-acetyl-2,3,4-tri-*O*-butyl-L-arabinitol (**10**). Reduction of **2** afforded **5** and **9** in the ratio 98:2 and, likewise, **3** yielded **8** and **6** in the ratio 98:2. The osmylation of the unsaturated higher sugars **1**, **4**, and **7** followed Kishi's empirical rule.

INTRODUCTION

Higher carbon sugars having ten or more carbon atoms can be obtained by coupling of a sugar derivative with either an achiral molecule[1–3], which can be further converted into a polyhydroxylated system, or by coupling of two sugar subunits[4–11]. The latter method is more convenient, since most of the chiral centres of the target molecule are present in the precursors. Allylic alcohols of desired stereochemistry, substituted at both ends of the allylic system with two appropriately chosen monosaccharide moieties, are suitable starting materials for the preparation of higher sugars.

*These compounds are C_{12} sugar derivatives but, because of their resemblance to disaccharides and for easier comprehension, they are named as *x*-deoxy-*x*-(*C*-glycosyl)glycose derivatives.

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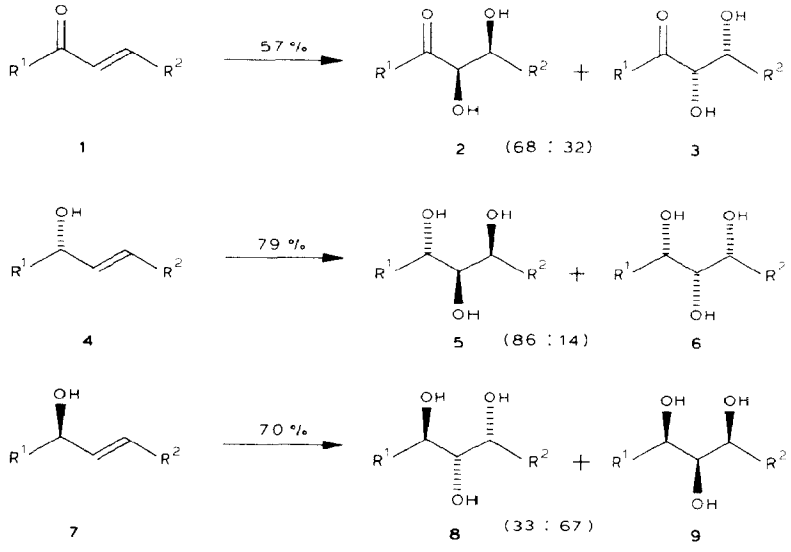
The problem of the preparation of higher sugar allylic alcohols of the *desired* configuration has been solved by either stereoselective reduction of higher sugar enones[5,6] or direct coupling of vinyl anions with sugar aldehydes[11]. The results of osmylation of the double bond of these valuable synthons is now reported.

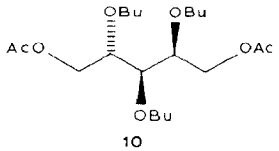
Oxidation of allylic alcohols and allylic ethers with osmium tetraoxide is claimed to be efficient and stereoselective. The configuration of the resulting polyols can be predicted by Kishi's empirical rule[12], from which there are few exceptions[13].

RESULTS AND DISCUSSION

Catalytic osmylation of 3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-[methyl (*E*)-2,3,4-tri-*O*-benzyl-7-deoxy-α-D-*gluco*-heptopyranosid-6-ulos-7-yl-idene]-α-D-xylofuranose[6] (**1**) afforded 57% of 3-*O*-benzyl-1,2-*O*-isopropylidene-6-



1 **2** **3** **4** **5** **6** **7** **8** **9**



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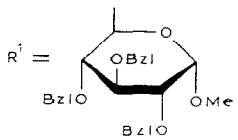
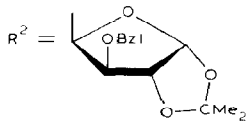


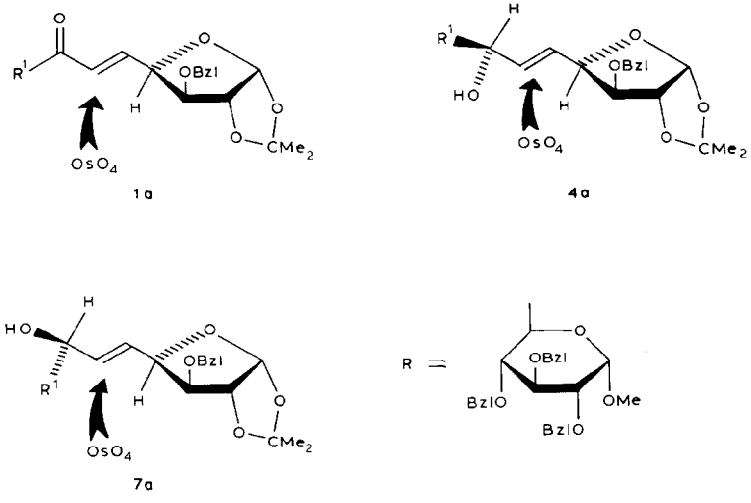


C-(methyl 2,3,4-tri-*O*-benzyl-α-D-*gluco*-heptopyranosid-6-ulos-6-yl)-L-*glycero*-α-D-*gluco*- (**2**) and -D-*glycero*-β-L-*ido*-hexo-1,4-furanoses (**3**) in the ratio 68:32. Application of this reaction to 3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-[methyl (*E*)-2,3,4-tri-*O*-benzyl-7-deoxy-D-*glycero*-α-D-*gluco*-heptopyranosid-7-yl-idene]-α-D-xylofuranose[6] (**4**) afforded 79% of 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*C*-(methyl 2,3,4-tri-*O*-benzyl-D-*glycero*-α-D-*gluco*-hexopyranosid-6-yl)-L-*glycero*-α-D-*gluco*- (**5**) and -D-*glycero*-β-L-*ido*-hexo-1,4-furanoses (**6**) in the ratio 86:14. Oxidation of the L-*glycero* isomer[6] (**7**) of **4** afforded 70% of 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*C*-(methyl 2,3,4-tri-*O*-benzyl-L-*glycero*-α-D-*gluco*-hexopyranosid-6-yl)-D-*glycero*-β-L-*ido*- (**8**) and -L-*glycero*-α-D-*gluco*-hexo-1,4-furanoses (**9**) in the ratio 33:67.

The configurations of **2, 3, 5, 6, 8**, and **9** were established by chemical correlations. The triol **5** was converted into the known[14] 1,5-di-*O*-acetyl-2,3,4-tri-*O*-butyl-L-arabinitol (**10**) by *O*-butylation, removal of the benzyl, isopropylidene, and methoxyl groups, periodate oxidation of the resulting polyol, followed by borohydride reduction and acetylation. This result confirmed the L-*arabino* configuration of **5** and the D-*glycero* configuration of **4**. Reduction of **2** with sodium borohydride afforded the triol **5** contaminated with small amounts of **9**, thus proving the respective L-*threo* and D-*xylo* configurations. Consequently, **3** must have the D-*threo* configuration. Reduction of **3** with sodium borohydride afforded the triol **8** contaminated with small amounts of **6** to which the D-*arabino* and L-*xylo* configurations, respectively, were assigned.

The explanation of the stereochemical outcome of these reactions is based on Kishi's empirical rule[12] for *cis*-hydroxylation of allylic alcohols and their derivatives.

The conformations (**1a, 4a**, and **7a**) of **1, 4**, and **7** involved in the osmylation



Scheme 1. Direction of attack of OsO_4 on **1a**, **4a**, and **7a**.

reaction (the same as in Kishi's model[12]) are shown in Scheme 1. Attack of osmium tetraoxide is postulated[12] to occur from the side opposite to the hydroxyl (alkoxyl) groups. Thus, **1** should afford **2** as the main product. Osmylation of alcohol **4** should be more stereoselective, since attack of the oxidant leading to **5** occurs from the side opposite to both the hydroxyl and alkoxyl groups. The stereoselectivity should be decreased in the oxidation of **7**, because the hydroxyl and alkoxyl groups are on the opposite sides of the molecule which makes the configuration of the main product of osmylation difficult to predict.

The results of the oxidation of **1**, **4**, and **7** accord with these predictions. Osmylation of **1** proceeded with low selectivity (the ratio of **2:3** was 68:32), whereas higher stereoselectivity was observed in the oxidation of **4** (the ratio of 5:6 was 86:14) and the configuration of the main stereoisomer was that predicted by Kishi's rule. Osmylation of **7** afforded **8** and **9** in the ratio 33:67, showing that the stereoelectronic effect exhibited by the ring oxygen atom of the "*xylose*" part of **1** was more important than that of the hydroxyl group.

Thus, osmylation of allylic alcohols and enones substituted with two *different* monosaccharide moieties provides a simple and efficient route to higher carbon sugars. The osmylation reactions obey Kishi's empirical rule and the approach should be of general applicability in the stereoselective syntheses of other higher sugars.

EXPERIMENTAL

General. — Optical rotations were measured with a Perkin–Elmer 141 polarimeter on solutions in ethyl acetate at 20°. ^{1}H-N.m.r. spectra (the data for **5a**, **6a**, **8a**, and **9a** are shown in Table I) were recorded with Bruker A-400 and GCX 200 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). The ^{13}C-n.m.r. spectrum was recorded with a JEOL X 90Q spectrometer on a solution in $CDCl_3$. Column chromatography was performed on silica gel (Merck, 230–400 mesh). Organic solutions were dried over anhydrous magnesium sulfate.

*3-O-Benzyl-1,2-O-isopropylidene-6-C-(methyl 2,3,4-tri-O-benzyl-α-*D-gluco-*heptopyranosid-6-ulos-6-yl)-*L-glycero-*α-*D-gluco- (**2**) *and* -D-glycero-*β*-L-ido-*hexo-1,4-furanose* (**3**). — To a solution of **1**[6] (660 mg, 0.9 mmol) in tetrahydrofuran (7 mL), *tert*-butyl alcohol (0.7 mL), and water (0.1 mL) was added *N*-methylmorpholine *N*-oxide (140 mg) followed by osmium tetraoxide (0.5 mL of a ~2% solution in *tert*-butyl alcohol). The mixture was stirred in the dark for 24 h, then diluted with ether (50 mL), and washed twice with aqueous 5% mannitol. The organic phase was separated, dried, and concentrated. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue afforded amorphous **2** (270 mg, 39%), $[\alpha]_D$ −27° (*c* 3). ^{1}H-N.m.r. data: *inter alia* δ 5.85 (d, 1 H, $J_{11,12}$ 3.5 Hz, H-12), 4.0 (d, 1 H, $J_{9,10}$ 4.0 Hz, H-10), 3.95 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 3.65 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.40 (dd, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 3.22 (s, 3 H, OMe), 1.50 and 1.30 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{44}H_{50}O_{12}$: C, 68.5; H, 6.5. Found: C, 68.1; H, 6.6.

Eluted second was amorphous **3** (125 mg, 18%), $[\alpha]_D$ +33° (*c* 3). ^{1}H-N.m.r. data: *inter alia* δ 5.95 (d, 1 H, $J_{11,12}$ 3.5 Hz, H-12), 3.95 (bs, 1 H, H-10), 3.88 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 3.70 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 3.50 (dd, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 3.28 (s, 3 H, OMe), 1.50 and 1.30 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{44}H_{50}O_{12}\cdot H_2O$: C, 67.0; H, 6.6. Found: C, 67.3; H, 6.8.

3-O-Benzyl-1,2-O-isopropylidene-6-C-(methyl 2,3,4-tri-O-benzyl-D-glycero-α-D-gluco-*heptopyranosid-6-yl)*-L-glycero-α-D-gluco- (**5**) *and* -D-glycero-β-L-ido-*hexo-1,4-furanose* (**6**). — To a solution of **4**[6] (928 mg, 1.26 mmol) in tetrahydrofuran (10 mL), *tert*-butyl alcohol (1 mL), and water (0.15 mL) was added *N*-methylmorpholine *N*-oxide (150 mg) followed by osmium tetraoxide (0.8 mL of ~2% solution in *tert*-butyl alcohol. The mixture was stirred in the dark for 48 h, then diluted with methanol (20 mL), and aqueous 40% sodium hydrogensulfite was added. The mixture was stirred for 30 min, filtered through Celite, poured into water (50 mL), and extracted with ether (2 × 50 mL). The combined extracts were washed with water, dried, and concentrated. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue afforded amorphous **5** (660 mg, 68%), which was characterised as the amorphous triacetate **5a**, $[\alpha]_D$ +1° (*c* 3).

Anal. Calc. for $C_{50}H_{58}O_{15}$: C, 66.8; H, 6.5. Found: C, 66.9; H, 6.6.

Eluted second was amorphous **6** (112 mg, 11%), which was characterised as the amorphous triacetate **6a**, $[\alpha]_D$ +36° (*c* 3).

Anal. Found: C, 66.9; H, 6.6.

3-O-Benzyl-1,2-O-isopropylidene-6-C-(methyl 2,3,4-tri-O-benzyl-L-glycero-α-D-gluco-*heptopyranosid-6-yl)*-D-glycero-β-L-ido- (**8**) *and* -L-glycero-α-D-gluco-*hexo-1,4-furanose* (**9**). — The alcohol **7**[6] (760 mg, 1.03 mmol) was treated with osmium tetraoxide as described above, to afford amorphous **8** (185 mg, 23%), which was characterised as the amorphous triacetate **8a**, $[\alpha]_D$ +9° (*c* 2.5).

Anal. Calc. for $C_{50}H_{58}O_{15}$: C, 66.8; H, 6.5. Found: C, 66.8; H, 6.9.

Eluted second was amorphous **9** (370 mg, 46.6%), which was characterised as the amorphous triacetate, $[\alpha]_D$ +2° (*c* 2).

Anal. Found: C, 66.5; H, 6.8.

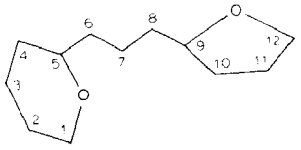
Determination of the configuration of **5**. — To a solution of **5** (115 mg, 0.15 mmol) in *N,N*-dimethylformamide (5 mL) was added sodium hydride (50 mg) followed by butyl bromide (1 mL), and the mixture was stirred overnight at room temperature. Excess of hydride was decomposed with water and the product was extracted with ether. The extract was washed twice with water, dried, and concentrated (finally at 50°/0.2 Torr). The crude product was hydrogenated (in ethyl acetate over 10% Pd/C, overnight) and the isopropylidene group was hydrolysed in tetrahydrofuran–AcOH–H_2O (1:1:1, 5 mL) at reflux for 5 h. Ether (50 mL) was added to the cooled mixture, and the acetic acid was neutralised with aqueous 5% sodium hydrogencarbonate. Excess of sodium periodate (1 g) was added and the mixture was stirred for 2 h. The organic phase was separated, dried, and concentrated, and the residue was reduced with sodium borohydride (50 mg) in tetra-

TABLE I

^{1}H-N.M.R. DATA OF ACETATES **5a, 6a, 8a**, AND **9a**[a]

Compound	*Chemical shifts (δ)*											
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-7*	*H-8*	*H-9*	*H-10*	*H-11*	*H-12*	*Ac-O*
5a	4.60	3.38	3.91	3.38	3.88	5.46	5.69	5.65	4.09	3.79	4.51	5.79	2.03, 1.91, 1.82
6a	4.46	3.38	3.85	3.59	3.96	5.32	5.61	5.58	4.00	3.73	4.37	5.81	2.04, 2.02, 1.92
8a	4.49	3.47	3.96	3.60	3.86	5.52	5.63	5.62	4.38	3.83	4.45	5.80	1.97, 1.88, 1.73
9a	4.60	3.47	4.00	3.26	3.89	5.53	5.66	5.54	4.08	3.72	4.52	5.77	2.04, 2.03, 1.72
	Coupling constants (Hz)											
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$	$J_{10,11}$	$J_{11,12}$		
5a	3.8	9.2	9.2	9.6	3.4	7.4	1.7	8.3	3.0	0	3.8		
6a	3.5	9.0	9.0	9.8	1.6	8.4	2.2	5.7	3.7	0	3.9		
8a	3.8	9.2	9.2	10.0	3.9	9.4	3.0	9.7	3.6	0	3.6		
9a	3.3	9.4	8.8	9.5	0.9	9.8	2.0	8.9	2.8	0	3.7		

[a]The numbering is as follows:



hydrofuran–methanol (1:1) for 2 h. The crude product, isolated in the usual manner, was boiled under reflux in tetrahydrofuran–M HCl (1:1, 10 mL) for 6 h in order to remove the methoxyl group. Ether (30 mL) was added to the cooled mixture, and the acid was neutralised with aqueous 5% sodium hydrogencarbonate. Sodium periodate (300 mg) was added and the mixture was stirred for 2 h at room temperature. The organic phase was separated, dried, and concentrated. A solution of the residue in tetrahydrofuran–methanol (1:1) was treated with sodium borohydride (30 mg). The crude product, isolated in the usual manner, was acetylated (Ac_2O, pyridine, 4-dimethylaminopyridine) and the acetate was subjected to h.p.l.c. (Siemens chromatograph; gel SI 60; hexane–ethyl acetate, 3:1) to give 1,5-di-*O*-acetyl-2,3,4-tri-*O*-butyl-L-arabinitol (**10**; 11.5 mg, 20%), isolated as an oil, $[\alpha]_D$ −11.5° (*c* 1); lit.[14] +14° (*c* 6) for the D isomer. ^{13}C-N.m.r. data: *inter alia* δ 170.81 and 170.40 (2 $COCH_3$), 63.61 and 62.80 (2 CH_2OAc). Compound **10** and the D isomer gave identical i.r. spectra.

Reduction of **2** *and* **3**. — A solution of **2** (150 mg, 0.195 mmol) in tetrahydrofuran–methanol (1:1, 5 mL) was treated with sodium borohydride (30 mg) as described above. H.p.l.c. of the crude product (138 mg, 91%) revealed **5** and **9** in the ratio 98:2. The same reaction performed for **3** afforded 90% of **8** and **6** in the ratio 98:2.

ACKNOWLEDGMENTS

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