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STEREOSELECTIVE REDUCTION OF HIGHER SUGAR ENONES* WITH ZINC BOROHYDRIDE

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ABSTRACT

The higher sugar enones* 3-*O*-benzyl-5-deoxy-5-*C*-[(*E*)-7-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-heptopyranos-6-ulos-7-ylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (**2a**), 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-ylidene]-α-D-xylofuranose (**3a**), and 3-*O*-benzyl-6-*C*-[(*E*)-6-*O*-benzyl-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranos-7-ylidene]-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**4a**) on reduction with zinc borohydride afforded with high diastereoselectivities (~95:5) the higher sugar allylic alcohols 3-*O*-benzyl-5-deoxy-5-*C*-[(*E*)-7-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranos-7-yliden]-1,2-*O*-isopropylidene-α-D-xylofuranose (**2b**), 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 (**3b**), and 3-*O*-benzyl-6-*C*-[(*E*)-6-*O*-benzyl-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranos-7-ylidene]-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**4b**). The configurations at the new chiral centres in **2b–4b** were *R*. The diastereoisomeric *S*-alcohols (**2c–4c**) were obtained from the *R* isomers by a modified Mitsunobu reaction.

INTRODUCTION

Higher carbon sugars having ten or more carbon atoms, although not common in Nature, are important components of such antibiotics as tunicamycin[1] or hikizimycin[2]. Methods are available[3–6] which allow higher sugar enones of the general formula (*E*)-R^1CO–CH=CH–CHR^2 (**1** where R^1 and R^2 are sugar units) to be prepared in a simple manner.

One of the main problems of the conversion of **1** into the polyol system is the stereoselective reduction of the carbonyl group to give the *desired* allylic alcohol that would allow further stereoselective functionalization of the double bond[7,8].

*These compounds are C_{12} and C_{13} 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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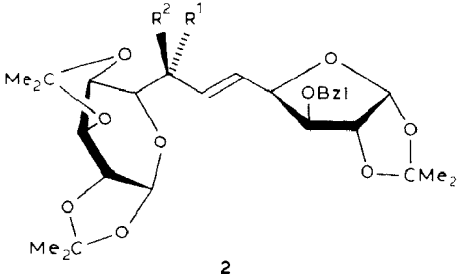

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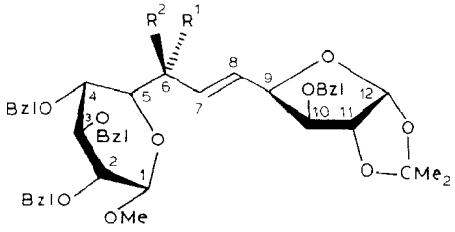

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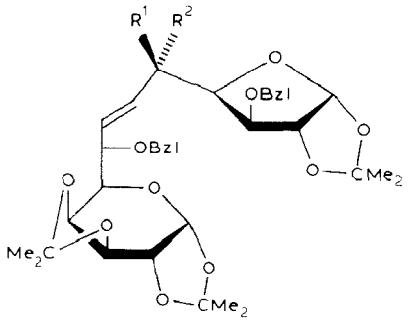

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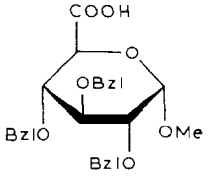
a series $R^1, R^2 = O$
b series $R^1 = OH, R^2 = H$
c series $R^1 = H, R^2 = OH$



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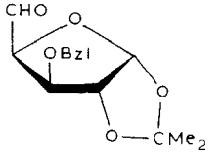

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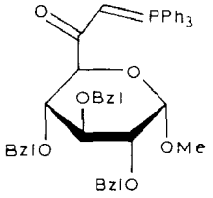

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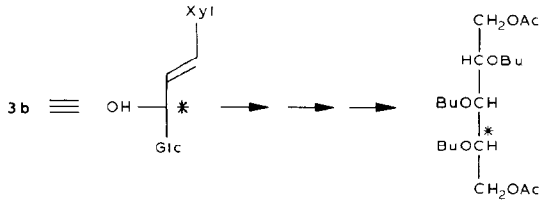
3-*O*-Benzyl-5-deoxy-5-*C*-[(*E*)-7-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-heptopyranos-6-ulos-7-ylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (**2a**) can be reduced stereoselectively to either 3-*O*-benzyl-5-deoxy-5-*C*-[(*E*)-7-deoxy-1,2:3,4-di-*O*-isopropylidene-D-*glycero*-α-D-*galacto*-heptopyranos-7-ylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (**2b**) or its L-*glycero* isomer (**2c**), using zinc borohydride or sodium borohydride/lanthanum chloride[6].

These results prompted a more detailed study of the stereoselective reduction of higher sugar enones having different sugar sub-units α to the carbonyl group.

RESULTS AND DISCUSSION

The higher sugar enones 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-ylidene]-α-D-xylofuranose (**3a**) and 3-*O*-benzyl-6-*C*-[(*E*)-6-*O*-benzyl-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranos-7-ylidene]-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose[5] (**4a**) having D-*gluco* and D-*xylo* derivatives α to the carbonyl group were selected for study.

Enone **3a** was prepared from methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosiduronic acid (**5**) and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[9] (**6**), using a modification of a published method[3]. Reduction of **3a** with di-isobutylaluminum hydride (DIBAL-H) afforded the diastereoisomeric allylic alcohols 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 (**3b**) and its L-*glycero* isomer (**3c**) in the ratio 71:29. The configuration of the main isomer **3b** was determined by its conversion[10] into known 1,5-di-*O*-acetyl-2,3,4-tri-*O*-butyl-L-arabinitol (**8**).



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Enones **2a, 3a,** and **4a** were treated with various reducing agents and the results are shown in Table I. The best stereoselectivities were obtained with L-selectride (lithium tri-*sec*-butylborohydride) which is known[11] to be sensitive to steric hindrance. These results indicated a marked differentiation between the *re* and *si* sides of the carbonyl group in the substrates. However, since the conformations of these complex systems are not known, no inference can be drawn about the stereochemistry of these processes. Higher sugar enones with fixed conformations

TABLE I

STEREOSELECTIVE REDUCTION OF **2a–4a**

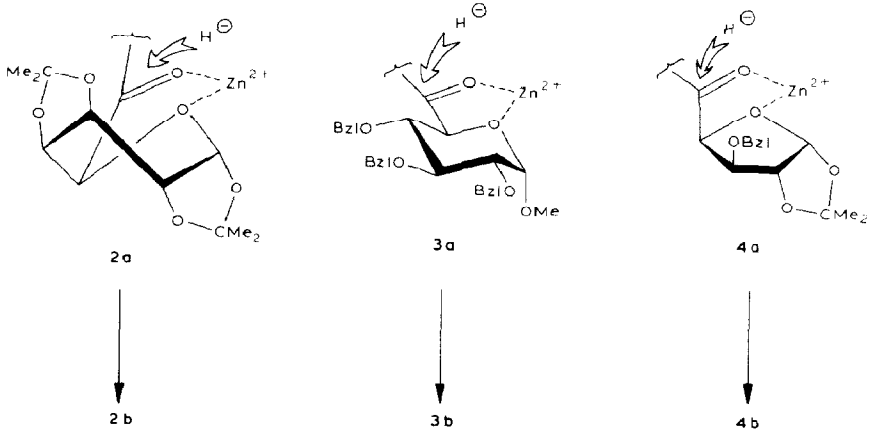
Substrate	*Products*	*Reducing agents*						
		$Zn(BH_4)_2$	*DIBAL-H*	*$NaBH_4$*	*$LiBH_4$*	*$NaBH_4/LaCl_3$*	*$LiAlH_4$*	*L-selectride*
2a	**2b:2c**	94:6[a]	15:85	48:52		10:90[a]	46:54[a]	5:95
3a	**3b:3c**	97:3	71:29	91:9	75:25	56:44	97:3	98:2
4a	**4b:4c**	98:2	28:72	78:22	30:70	56:44	77:23	98:2

[a]Ref. 6.

are required for analysis of the stereochemical outcome of these reactions. The conformations can be fixed by complexation with metal ions.

Reduction of **2a–4a** with zinc borohydride[12], which exhibits strong chelating properties, resulted in high diastereoselectivity (~95:5, see Table I) and gave the respective allylic alcohols **2b**[6], **3b**, and 3-*O*-benzyl-6-*C*-[(*E*)-6-*O*-benzyl-7-deoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-heptopyranos-7-ylidene-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[5] (**4b**), each having the *R* configuration at the new chiral centre.

Although there are many possibilities for the complexation of zinc ions to the various oxygen atoms present in both monosaccharide sub-units, it is assumed that complexation involves the carbonyl and ring oxygen atoms as in the Cram cyclic model for 1,2-asymmetric induction[13]. Only in this way can the configuration of the main products of the reduction of **2a–4a** be predicted easily by simple analysis of the steric factors.



Assuming that attack of the hydride anion occurs from the less-hindered side of the molecule, *si* attack (from "behind the ring") can be expected for **2a–4a**, to give allylic alcohols **2b–4b**. Indeed, reduction of **2a–4a** with zinc borohydride afforded (regardless of the substituent α to the carbonyl group), with high diastereo-

selectivity (~95:5), the allylic alcohols (**2b–4b**) having the *R* configuration at the new chiral centres. It is possible that this stereoselective reduction might be a general effect.

Generality in the reductions leading to the *S*-alcohols **2c**[6], **3c**, and **4c**[5] was not found. However, these compounds can be obtained in good yields from the *R* isomers using a modified[14] Mitsunobu reaction (*p*-nitrobenzoic acid, triphenylphosphine, and diethyl azodicarboxylate in boiling 1,4-dioxane).

The above method provides a route to allylic alcohols of the *desired* (*R* or *S*) configurations of the hydroxy group, which are substituted at both ends of the allylic system with *different* monosaccharide sub-units. Such allylic alcohols can be used in the synthesis of higher sugars.

EXPERIMENTAL

General. — Melting points were determined with a Kofler apparatus and were not corrected. 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 **3a, 3b-Ac,** and **3c-Ac** are shown in Table II) were recorded with a Bruker A-400 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Column chromatography was performed on silica gel (Merck 230–400 mesh). H.p.l.c. was performed on a Type 302 instrument (produced by the Institute of Physical Chemistry, Warsaw), using hexane–2-propanol (95.5). Organic solutions were dried over anhydrous magnesium sulfate.

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-ulose-7-ylidene]-α-D-xylofuranose (**3a**). — A solution of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[15] (20 g, 43 mmol) in acetone (200 mL) was titrated with Jones reagent[16] (~60 mL of a 1.6M solution) until the reaction was complete (t.l.c.; light petroleum–ethyl acetate, 1:1). Water (500 mL) was added and the product was extracted with ether (2 × 250 mL). The combined ether solutions were extracted with aqueous 2% NaOH, and the extract was acidified (to pH ~1) with aqueous 10% sulfuric acid and extracted with chloroform (2 × 200 mL). The combined extracts were washed with water (2 × 200 mL), dried, and concentrated to yield methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosiduronic acid (**5**; 15 g, 31 mmol, 73%) as an oil which was characterised as the methyl ester, $[\alpha]_D$ +49° (*c* 4.8).

Anal. Calc. for $C_{28}H_{30}O_7$: C, 70.3; H, 6.3. Found: C, 69.9; H, 6.5.

To a solution of this acid (14.1 g, 29.5 mmol, dried by evaporation of xylene thrice therefrom) in dry benzene (150 mL) under argon was added a solution of 1,1′-carbonyldi-imidazole (5.9 g, 36 mmol) in benzene (150 mL) dropwise at room temperature. After evolution of CO_2 had ceased (~30 min), a solution of methylenetriphenylphosphorane in benzene (generated from 30.3 g of methyltriphenylphosphonium iodide and 46 mL of 1.6M butyl-lithium in 300 mL of benzene for 1.5 h at room temperature) was added in ~5-mL portions during 3 h. The mixture was

then stirred for 3 h at room temperature, water (500 mL) was added, and the organic phase was dried and concentrated. To a solution of the resulting crude ylid **7** in dry benzene (300 mL) was added a solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[9] (**6**; 9.75 g, 35 mmol) in dry benzene (100 mL). After 3 h, t.l.c. (light petroleum–ethyl acetate, 1:1) showed that **1** had disappeared and the formation of a less polar product that was visible in u.v. light. Column chromatography (light petroleum–ethyl acetate, 4:1) of the product afforded **3a** (8.69 g, 40% overall), as an oil, $[\alpha]_D$ +3.5° (*c* 2).

Anal. Calc. for $C_{44}H_{48}O_{10}$: C, 71.7; H, 6.6. Found: C, 71.9; H, 6.2.

*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* (**3b**) *and its* L-glycero *isomer* (**3c**). — To a solution of **3a** (2.5 g, 3.39 mmol) in dry ether (20 mL) at −78° was added di-isobutylaluminum hydride (DIBAL-H, 4 mL of a 20% solution in toluene, ~4.7 mmol), and the mixture was stirred for 2 h at −78° and then allowed to attain room temperature. Water (10 mL) was added, and the organic layer was washed twice with water, dried, and concentrated. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue afforded, first, **3c** (667 mg, 26.5%) as an oil which was characterised as the acetate, m.p. 148–149° (from ether–hexane, 1:3), $[\alpha]_D$ +4° (*c* 2).

Anal. Calc. for $C_{46}H_{52}O_{11} \cdot 0.5\ H_2O$: C, 69.9; H, 6.8. Found: C, 69.7; H, 7.0.

Eluted second was **3b** (1.633 g, 65.2%) as an oil which was characterised as the acetate, $[\alpha]_D$ +27° (*c* 3).

Anal. Calc. for $C_{46}H_{52}O_{11}$: C, 70.8; H, 6.7. Found: C, 70.9; H, 7.1.

General procedures for the reduction of the enones **2a–4a**. — A solution of the enone (~0.25 mmol) in dry ether (20 mL) was treated with (*a*) zinc borohydride

TABLE II

^{1}H-N.M.R. DATA FOR **3a**, **3b-Ac**, AND **3c-Ac**[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*
3a	4.53	3.54	4.03	3.65	4.36		6.71[b]	6.98	4.75	3.95	4.61	5.93
3b-Ac	4.59	3.47	3.99	3.47	3.83	5.68	5.84	5.76	4.54	3.81	4.59	5.92
3c-Ac	4.60	3.54	4.00	3.45	3.74	5.78	5.93	5.93	4.60	3.83	4.58	5.90
	Coupling constants (Hz)											
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,10}$	$J_{10,11}$	$J_{11,12}$	
3a	3.5	9.7	9.0	9.9			15.8	4.5	3.0	0	3.7	
3b-Ac	2.6	9.2	9.2	10.2	1.7	7.6	15.6	5.8	3.2	0	3.8	
3c-Ac	3.6	9.4	9.0	10.3	1.7	n.d.[c]	n.d.	n.d.	3.4	0	3.7	

[a]See formula **3** for the numbering. [b]$J_{7,9}$ 1.7 Hz. [c]Not determined.

(0.5 mL of a ~1.5M solution in ether) for 30 min at 0°, (*b*) DIBAL-H (~1 mL of a 20% solution in toluene) for 30 min at −78°, (*c*) lithium aluminum hydride (~20 mg) for 1 h at −78°, (*d*) L-selectride (1 mL of a M solution in tetrahydrofuran) for 30 min at −78°. The reductions of enones **2a–4a** with sodium borohydride, lithium borohydride, and sodium borohydride/lanthanum chloride were performed on the same scale in methanol–tetrahydrofuran (1:1) for ~30 min at 0°. The yields were ~90%, the ratio of diastereoisomers was determined by h.p.l.c., and the results are collected in Table I.

General procedure for preparation of the L-glycero *isomers* **2c–4c**. — To a solution of each D-*glycero*-isomer (**2b–4b**, ~1 mmol) in dry 1,4-dioxane was added triphenylphosphine (534 mg, 2 mmol) followed by *p*-nitrobenzoic acid (302 mg, 2 mmol) and diethyl azodicarboxylate (0.4 mL, ~2.5 mmol). Each mixture was boiled under reflux for 3 h, then concentrated to dryness. Column chromatography (light petroleum–ethyl acetate, 3:1) of the residue gave the inverted allylic *p*-nitrobenzoates, each of which was stirred with a solution of sodium carbonate (1 g) in methanol (20 mL) for 1 h at room temperature to afford **2c**[6], **3c**, and **4c**[5], each of which was purified by column chromatography (3:2 light petroleum–ethyl acetate for **3c** and **4c**, and 4:1 toluene–ethyl acetate for **2c**). The L-*glycero* isomers **2c**[6], **3c**, and **4c**[5], the structures of which were proved by comparison (t.l.c., ^{1}H-n.m.r. spectroscopy) with standards, were obtained in ~70% overall yield.

ACKNOWLEDGMENTS

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