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A Novel Aspect in Chlorination of D-Glucal Derivatives. Important Roles of the 4,6-*O*-Benzylidene Group and Substituent at *C*-3 in the Selective Formation of β-D-*Manno* and β-D-*Arabino* Isomers#

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In contrast with the precedent reports described in peracetyl- and perbenzyl-D-glucal, chlorination of 3-*O*-acetyl- and 3-deoxy-4,6-*O*-benzylidene-D-glucal in carbon tetrachloride predominantly occurred from the β-side to give the β-D-*manno* and β-D-*arabino* adducts, respectively.

Detailed studies upon chlorination to tri-*O*-acetyl-(**1a**)[1,2] and tri-*O*-benzyl-D-glucal (**1b**)[3] revealed that in nonpolar solvents *cis* addition from the α-side occurred almost exclusively to give the α-D-*gluco* isomers **2a** and **2b**, respectively, in high yields, together with a small amount of β-D-*manno* isomers **3a** and **3b**, respectively. Moreover, chlorination of 4,6-*O*-benzylidene-3-deoxy-3-nitro-D-glucal (**4c**) in carbon tetrachloride expectedly afforded the α-D-glucopyranosyl chloride **5c** in 80% yield, however, that in tetrahydrofuran (THF) gave the 4-chlorobutyl β-D-glucopyranoside **6c** in 93% yield.[4]

Expecting that such a participation of THF should occur to other glucal derivatives, we firstly performed chlorination of **1a** and indeed obtained a mixture of 4-chlorobutyl β-D-glucopyranoside **7** (64% yield, syrup, $[\alpha]_D^{14}$ +21.8° (*c* 1.2, acetone), $J_{1,2}$=8.3 and $J_{2,3}$=9.8 Hz) and α-D-mannopyranoside **8** (28% yield, syrup, $[\alpha]_D^{14}$ +40.5° (*c* 1.1, acetone), $J_{1,2}$=1.5 and $J_{2,3}$=3.2 Hz). Stereoselectivity of

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†Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

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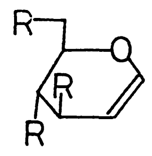

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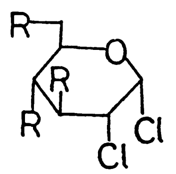

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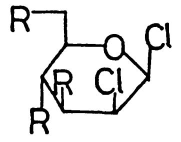

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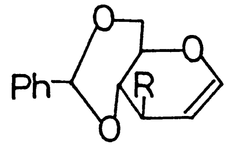

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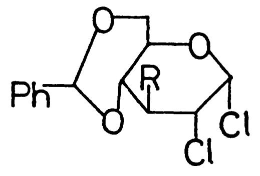

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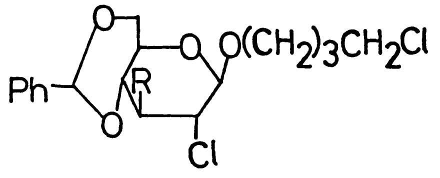

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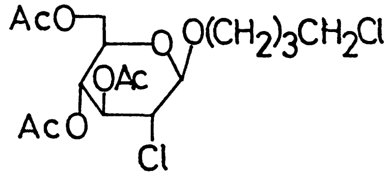

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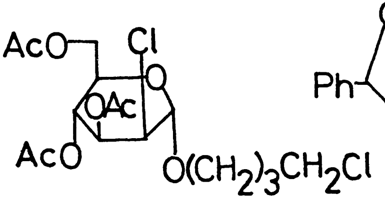

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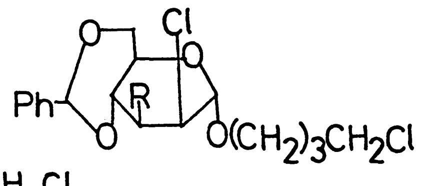

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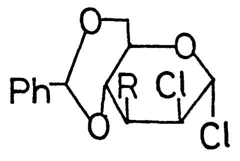

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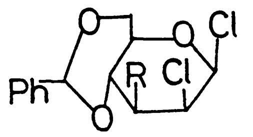

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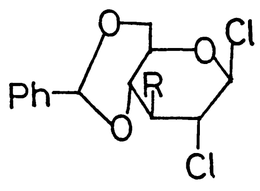

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R ; a=OAc, b=$OCH_2C_6H_5$, c=NO_2, d=H

the present reaction was lower than that observed in the reaction of 3-nitro-*D*-glucal **4c**; this may be attributable to conformational flexibility of **1a** due to the lack of 4,6-*O*-benzylidene group. Then we carried out chlorination of 3-*O*-acetyl-4,6-*O*-benzylidene-*D*-glucal (**4a**) and unexpectedly isolated 4-chlorobutyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-chloro-2-deoxy-α-*D*-mannopyranoside (**9a**) (58% yield, syrup, $[\alpha]_D^{20}$ +21.0° (*c* 0.73, acetone), $J_{1,2}$=1.2 and $J_{2,3}$=3.8 Hz) as the major product besides β-*D*-glucopyranoside **6a** (30% yield, mp 91-93 °C, $[\alpha]_D^{20}$ -44.1° (*c* 0.24, acetone), $J_{1,2}$=8.7 and $J_{2,3}$=11 Hz) and 2-chloro-α-*D*-mannopyranosyl chloride **10a**

(12% yield, mp 126-127 °C, $[\alpha]_D^{20}$ +156° (*c* 0.82, acetone) $J_{1,2} \leq 1.0$ Hz). These results indicated that, in contrast with the precedent examples,[1-3] chlorine preponderantly approached from the β-side of **4a** to give the α-D-*manno* isomers **9a** and **10a**. Predominant attack from the β-side was again observed in similar chlorination of 4,6-*O*-benzylidene-3-deoxy-D-glucal **4d**, in which 4-chlorobutyl 2-chloro-2,3-dideoxy-α-D-*arabino*-hexopyranoside **9d** (34% yield, syrup, $[\alpha]_D^{25}$ +48.8° (*c* 1.92, acetone), $J_{1,2}$ ca. 0 Hz), 2-chloro-2,3-dideoxy-α-D-*arabino*-hexopyranosyl chloride **10d** (31% yield, mp 88-89 °C, $[\alpha]_D^{14}$ +119.5° (*c* 0.82, acetone), $J_{1,2} \leq 1.0$ Hz), and 4-chlorobutyl 2-chloro-2,3-dideoxy-β-D-*ribo*-hexopyranoside **6d** (25% yield, mp 90-92 °C, $[\alpha]_D^{25}$ -31.6° (*c* 0.45, acetone), $J_{1,2}=8.3$ Hz) were obtained.

In view of the above results, 2-chloro-β-D-mannopyranosyl cloride, hitherto obtained as only a minor product, should be selectively formed in a nonpolar, low-nucleophilic solvent such as carbon tetrachloride. This expectation was indeed realized. Chlorination of **4a** in carbon tetrachloride[5] afforded the β-D-mannopyranosyl chloride **11a** (52% yield, mp 71-73 °C, $[\alpha]_D^{20}$ -67.7° (*c* 2.5, acetone), $J_{1,2} \leq 1.0$ Hz) and α-D-mannopyranosyl chloride **10a** (23% yield), together with the α-D-glucopyranosyl chloride **5a** (24% yield, mp 130-131.5 °C, $[\alpha]_D^{20}$ +133° (*c* 1.7, acetone), $J_{1,2}=3.7$ Hz) and β-D-glucopyranosyl chloride **12a** (trace, mp 118-120 °C, $[\alpha]_D^{20}$ -15.9° (*c* 0.44, acetone), $J_{1,2}=8.8$ Hz). Similar chlorination of 4,6-*O*-benzylidene-3-*O*-benzyl-D-glucal (**4b**), however, gave the α-D-*gluco* isomer **5b** (56% yield, mp 110-112 °C, $[\alpha]_D^{20}$ +119° (*c* 1.0, acetone), $J_{1,2}=3.2$ Hz) predominantly over the α-D-*manno* isomer **10b** (30% yield, mp 125-126.5 °C, $[\alpha]_D^{20}$ +23.7° (*c* 0.27, acetone), $J_{1,2} \leq 1.0$ Hz). As judged from ^{1}H-NMR spectrum of a crude product, the latter compound **10b** should be formed *via* anomerization of β-D-*manno* isomer **11b** during the chromatographic separation. Highest stereoselectivity was observed in the case of 4,6-*O*-benzylidene-3-deoxy-D-glucal (**4d**); the β-D-*arabino* isomer **11d** (mp 150-152 °C, $[\alpha]_D^{14}$ +3.3° (*c* 0.6, acetone), $J_{1,2} \leq 1.0$ Hz) was formed in 89% yield. The structure of all of these adducts was determined by ^{1}H-NMR data (chemical shift of H-1 and $J_{1,2}$ values) and specific rotation. Since partial or complete anomerization occurred during the chromatographic separation, the ratios of the anomers were not shown but those of D-*manno* and D-*gluco* isomers were shown in Table 1 including those reported in the literature. The following trends may be pointed out; i) if the *C*-3 substituent is the same, the reactions of 4,6-*O*-benzylidene derivatives **4a** and **4b** gave D-*manno* isomer preferably to those of the corresponding, conformationally flexible derivatives **1a** and **1b**, respectively, ii) in a series of 4,6-O-benzylidene derivatives the approaching direction of chlorine varied depending on the substituents at C-3. Obviously, the precedent argument[1-3] is not feasible herein, at least, in the predominant formation of β-D-manno and β-D-arabino isomers.

Table 1. The ratios of D-manno to D-Gluco Isomers in Chlorination of D-Glucal Derivatives

Compound	The ratios of adducts	
	D-Manno isomers (Arabino for **4d**)	D-Gluco isomers (Ribo for **4d**)
1a[2]	0.15	1
1b[3]	0.03	1
4a	3	1
4b	0.5	1
4c[4]	not detected	1
4d	10	1

References

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2) K. Igarashi, T. Honma, and T. Imagawa, J. Org. Chem., 35, 610 (1970).
3) P. Boullanger and G. Descotes, Carbohydr. Res., 55, 55 (1976).
4) T. Sakakibara, Y. Nomura, K. Yoshino, and R. Sudoh, J. Chem. Soc., Chem. Commun., 1983, 449.
5) Typical procedure: To a solution of **4a** in carbon tetrachloride was added a 1.5 equivalent amount of chlorine (1 mol dm^{-3} carbon tetrachloride solution) at 0 °C and stirred for 1 h at ca. 0 °C and for 1 h at room temperature. After evaporation below 20 °C (bath temperature), the residual syrup was chromatographed on silica gel with a 1 : 1 mixture of carbon tetrachloride and benzene as eluant.

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