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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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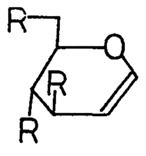

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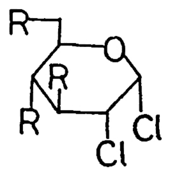

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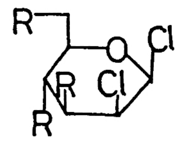

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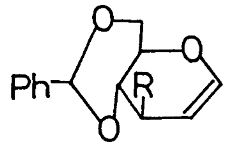

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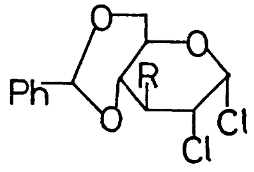

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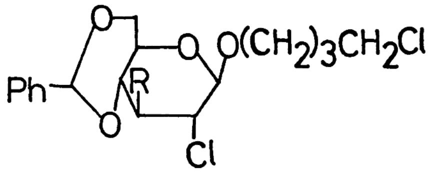

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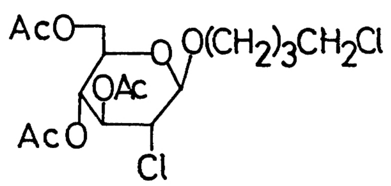

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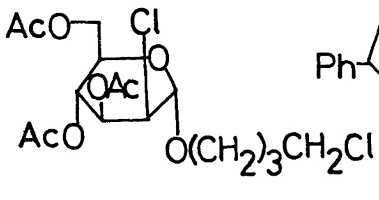

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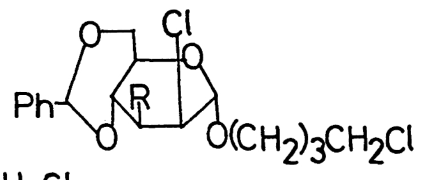

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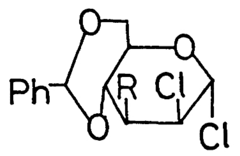

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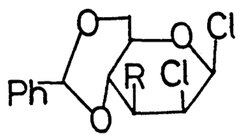

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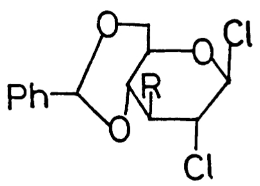

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R ; a=OAc, b=$OCH_2C_6H_5$, c=NO_2, d=H

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 argument1-3) 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**)
1a2)	0.15	1
1b3)	0.03	1
4a	3	1
4b	0.5	1
4c4)	not detected	1
4d	10	1

References

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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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