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THE MECHANISM OF, AND THE SOLVENT EFFECTS IN, THE GLYCOSIDATION OF D-GLUCOSYL CHLORIDES HAVING A NON-PARTICIPATING GROUP AT C-2, USING SILVER PERCHLORATE AS CATALYST

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ABSTRACT

The mechanism of, and the solvent effects in, the Koenigs–Knorr reaction of D-glucosyl chlorides having a non-participating group at C-2, using silver perchlorate as principal catalyst, were investigated. When a large excess of methanol was used, methyl D-glucopyranosides with inversion of the configuration at C-1 were predominantly obtained, except in one case. When 1 molar equivalent of nucleophile, such as methanol, methyl trityl ether, or 2-propanol, was used, the ratio of α- and β-D-glucopyranosides obtained varied with the solvent used. It is proposed that the reactions proceed *via* a common intermediate such as a D-glucosyl perchlorate. The following conclusions are made for the preparation of α-D-glucopyranosides: anhydrous ether is a preferable solvent, silver perchlorate and *sym*-collidine are superior to a mixture of silver perchlorate and silver carbonate in the presence of Drierite, β-D-glucosyl chloride is preferred to the α-D anomer, and the solvent and reagents should be as dry as possible.

INTRODUCTION

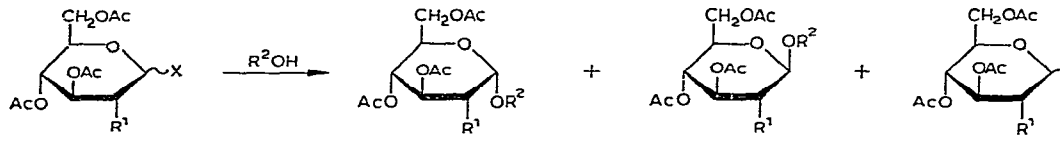
In carbohydrate chemistry, glycosidation reactions have been studied extensively. The synthesis of β-D-glucopyranosides is readily achieved by the Koenigs–Knorr reaction, in which a fully acylated D-glucosyl halide is reacted with an alcohol in the presence of a catalyst. For the preparation of α-D-glucopyranosides, it is preferable to use D-glucosyl halides having a non-participating group at C-2 such as a 2-*O*-nitro[1] or 2-*O*-benzyl group[2], but the yield is usually not high. Silver oxide, carbonate, and perchlorate, and mercuric oxide, bromide, and cyanide are often used as catalysts, together with a wide variety of solvents. Wolfrom and co-workers[1] found that the rate of the reaction increased very much when silver carbonate was supplemented with a little soluble silver perchlorate. It has often been proposed that an oxocarbonium ion is an intermediate in the Koenigs–Knorr reaction but the mechanism has not been investigated extensively. Lloyd and Roberts[3] investigated solvent effects in the reaction of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide with ethanol in the presence of various catalysts.

In previous papers[4,5], it was found that 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-D-glucopyranosyl perchlorate (**1c**) was obtained in the reactions of the corresponding α- and β-D-glucopyranosyl chlorides (**1a** and **1b**) with silver perchlorate. Methanolysis of **1c** gave a mixture of the methyl α- and β-D-glucopyranosides (**3a** and **3b**), and the proportion of **3a** and **3b** varied with the amount of methanol and solvent used. Furthermore, it was found that the β-D-glucosyl chlorides, which were considered to be difficult to prepare, were readily obtained in high yields from the α-D-glucosyl chlorides *via* the corresponding D-glucosyl perchlorates.

We now report on the mechanism of, and the solvent effects in, the glycosidation of D-glucosyl chlorides having a non-participating group at C-2, using silver perchlorate as a catalyst.

RESULTS AND DISCUSSION

Two pairs of D-glucosyl chlorides were chosen as starting compounds: **1a** and **1b**, which have an electron-withdrawing group at C-2; and 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α- (**2a**) and -β-D-glucopyranosyl chloride[5] (**2b**), which have a weakly electron-withdrawing group at this position. Glycosidation of the corresponding D-glucosyl perchlorates was also carried out for purposes of comparison. Methanol, methyl trityl ether, and 2-propanol were used as nucleophiles, and anhydrous ether, toluene, and nitromethane were used as solvents. The reactions were monitored by t.l.c. and the products were quantitatively analysed by g.l.c. The main products were the corresponding methyl and isopropyl α- and β-D-glucopyranosides, and the by-products were the hydrolysis products (**7** and **8**) of these chlorides, which were also analysed by g.l.c. after acetylation. The results are summarized in Tables I–III.



1a X = α-Cl, R¹ = Cl
1b X = β-Cl, R¹ = Cl
1c X = α-OClO₃, R¹ = Cl
2a X = α-Cl, R¹ = OCH₂Ph
2b X = β-Cl, R¹ = OCH₂Ph
2c X = α-OClO₃, R¹ = OCH₂Ph

3 R¹ = Cl, R² = Me
4 R¹ = OCH₂Ph, R² = Me
5 R¹ = Cl, R² = CHMe₂
6 R¹ = OCH₂Ph, R² = CHMe₂

7 R¹ = Cl
8 R¹ = OCH₂Ph

When a large excess of methanol was used, the methanolyses of the glucosyl chlorides and perchlorates proceeded mainly with inversion of configuration at C-1, except for **2c**, from which **4a**, with retention of configuration, was mainly obtained. When 1 molar equivalent of methanol, methyl trityl ether, or 2-propanol was used as nucleophile, the ratio of the products varied with the starting compounds, nucleophiles, solvents, and catalysts. As catalysts, silver perchlorate, silver carbonate–silver perchlorate, and silver perchlorate–*sym*-collidine were used. Lemieux and Morgan[6]

have reported that *sym*-collidine did not react with tetra-*O*-acetyl-α-D-glucopyranosyl bromide. It was established that the glucosyl chlorides and methyl and isopropyl glucopyranosides were not significantly affected under the conditions used in all solvents, unless otherwise stated.

TABLE I

THE KOENIGS–KNORR REACTIONS[a] OF 3,4,6-TRI-*O*-ACETYL-2-CHLORO-2-DEOXY-α- (**1a**) AND -β-D-GLUCOPYRANOSYL CHLORIDES (**1b**), AND THE PERCHLORATE (**1c**) WITH METHANOL AND METHYL TRITYL ETHER AT 30°

Expt. No.	*Starting compound*	*Solvent*	Ag_2CO_3	$AgClO_4$ (*moles/mole*)	sym-*Collidine*	*Ratio*[b] *of* 3a	3b	*Total yield* (%)	*Yield* (%)[c] *of* **7**
1	**1a**	Methanol				14.0	86.0	94.6	
2			7			5.5	94.5	91.4	
3			7	0.2		14.5	85.5	99.9	
4	**1b**					98.5	1.5	93.7	
5			7			95.8	4.2	95.9	
6			7	0.2		92.3	7.7	97.2	
7	**1c**[d]					10.4	89.6	88.6	
8	**1a**	Ether	1	0.2		67.5	32.5	72.7	22[e]
9				1		82.7	17.3	88.4	4
10				1	1	83.8	16.2	87.3	5
11				1		90.7	9.3	75.2	9[f]
12	**1b**		1	0.2		84.1	15.9	64.2	16[e]
13				1		91.3	8.7	88.2	4
14				1	1	93.1	7.9	85.7	7
15				1		89.2	10.8	74.1	10[f]
16	**1c**[d]					93.1	6.9	77.9	10
17					1	91.1	8.9	85.9	6
18						90.9	9.1	77.7	7[f]
19	**1a**	Toluene	1	0.2		52.9	47.1	76.7	6[e]
20				1		63.0	37.0	25	
21				1	1	56.0	44.0	75.3	7
22				1		51.0	49.0	77.6	9
23	**1b**		1	0.2		61.8	38.2	74.3	7[e]
24				1	1	59.3	40.7	84.2	7
25				1		53.5	46.5	86.4	9[f]
26	**1c**[d]				1	49.5	50.5	78.6	11
27						48.9	51.1	76.8	12[f]
28	**1a**	Nitro-methane	1	0.2		43.2	56.8	84.0	10
29				1		56.5	43.5	53.8	
30				1	1	43.9	56.1	85.1	7
31				1		42.9	57.1	90.8	6[f]
32	**1b**		1	0.2		41.6	58.4	71.6	8
33				1	1	44.4	55.6	86.6	9
34				1		45.0	55.0	86.3	8[f]

[a]Reactions were carried out with 1 molar equivalent of methanol or methyl trityl ether, except for Expts. 1–7 in which a large excess of methanol was used. [b]Analysed by g.l.c. [c]Analysed by g.l.c. after acetylation. [d]Prepared from **1a** with 1 molar equivalent of silver perchlorate, except for Expts. 26 and 27 in which 2.5 molar equivalents of silver perchlorate were used. [e]Reaction was carried out in the presence of Drierite. [f]Methyl trityl ether was used.

The reaction rates followed the solvent sequence nitromethane > ether ≫ toluene, and the 2-*O*-benzyl derivatives reacted faster than the 2-chloro-2-deoxy derivatives.

In anhydrous ether, α-D-glucopyranosides (**3a–6a**) were predominantly obtained, regardless of the starting compounds, catalysts, and nucleophiles.

β-D-Glucosyl chlorides (**1b** and **2b**) and α-D-glucosyl perchlorates (**1c** and **2c**) gave higher proportions of α-D-glucopyranosides (**3a–6a**) than α-D-glucosyl chlorides (**1a** and **2a**), except when methyl trityl ether was used as nucleophile. In the latter

TABLE II

THE KOENIGS–KNORR REACTIONS[a] OF 3,4,6-TRI-*O*-ACETYL-2-*O*-BENZYL-α- (**2a**) AND -β-D-GLUCOPYRANOSYL CHLORIDES (**2b**), AND THE PERCHLORATE (**2c**) WITH METHANOL AND METHYL TRITYL ETHER AT 0°

Expt. No.	*Starting compound*	*Solvent*	Ag_2CO_3	$AgClO_4$ (*moles/mole*)	sym-*Collidine*	*Ratio[b] of* 4a	4b	*Total yield* (%)	*Yield* (%)[c] *of* **8**
35	**2a**	Methanol	7	0.2		12.2	87.8	100	
36	**2b**		7	0.2		96.8	3.2	100	
37	**2c**[d]				1	55.8	44.2	74.0	
38	**2a**	Ether	1	0.2		78.5	21.5	81.0	9[e]
39				1		87.8	12.2	97.2	1
40				1	1	82.3	17.7	90.4	3
41				1		96.5	3.5	90.3	2
42	**2b**		1	0.2		92.6	7.4	75.6	17[e]
43				1		94.8	5.2	96.0	1
44				1	1	94.7	5.3	94.2	4
45				1		97.9	2.1	84.5	4[f]
46	**2c**[d]					96.5	3.5	86.9	3
47					1	96.6	3.4	87.5	3
48						98.1	1.9	81.9	6[f]
49	**2a**	Toluene	1	0.2		55.8	44.2	87.0	3[e]
50				1	1	62.6	37.4	88.1	1
51				1		69.8	30.2	84.0	1[f]
52	**2b**		1	0.2		77.2	22.8	82.8	2[e]
53				1	1	76.6	23.4	85.1	2
54				1		70.9	29.1	82.9	2[f]
55	**2c**[d]				1	79.9	20.1	68.4	2
56					1	67.5	32.5	77.7	3
57						71.4	28.6	67.3	2
58	**2a**	Nitro-methane	1	0.2		43.2	56.8	70.6	11[e]
59				1	1	46.8	53.2	83.7	2
60				1		46.5	53.5	74.5	4[e]
61	**2b**		1	0.2		46.1	53.9	76.8	10[d]
62				1	1	49.4	50.6	81.0	4
63				1		47.5	52.5	82.5	5[e]

[a]Reactions were carried out with 1 molar equivalent of methanol or methyl trityl ether, except for Expts. 35–37 in which a large excess of methanol was used. [b]Analysed by g.l.c. [c]Analysed by g.l.c. after acetylation. [d]**2c** was prepared from **2a** with 1 molar equivalent of silver perchlorate, except for Expt. 56 in which 2.5 molar equivalents of silver perchlorate were used. [e]Reaction was carried out in the presence of Drierite. [f]Methyl trityl ether was used.

TABLE III

THE KOENIGS–KNORR REACTIONS[a] OF 3,4,6-TRI-*O*-ACETYL-2-CHLORO-2-DEOXY-α- (**1a**) AND -β-D-GLUCOPYRANOSYL CHLORIDES (**1b**), 3,4,6-TRI-*O*-ACETYL-2-*O*-BENZYL-α- (**2a**) AND -β-D-GLUCOPYRANOSYL CHLORIDES (**2b**), AND THEIR PERCHLORATES (**1c** AND **2c**) WITH 2-PROPANOL

Expt. No.	*Starting compound*	*Solvent*	Ag_2CO_3	$AgClO_4$ (*moles/mole*)	sym-*Collidine*	*Ratio[b] of isopropyl glucoside*		*Total yield (%)*	*Yield (%)[c] of* **7** *or* **8**
						5a	**5b**		**7**
64	**1a**	Ether	1	0.2		72.3	27.7	59.2	35[d]
65				1		82.0	18.0	79.9	11
66				1	1	86.3	13.7	80.4	14
67	**1b**		1	0.2		87.8	12.2	61.7	36[d]
68				1		85.9	14.1	84.0	7
69				1	1	91.7	8.3	80.1	10
70	**1c**[e]					89.1	10.9	78.5	10
71					1	92.0	8.0	79.1	15
72	**1a**	Toluene	1	0.2		58.6	41.6	90.4	3[d]
73				1	1	63.5	36.5	86.5	4
74	**1b**		1	0.2		63.0	37.0	82.5	5[d]
75				1	1	66.3	33.7	88.0	3
76	**1c**[e]				1	57.3	42.7	71.8	14
77	**1a**	Nitro-methane	1	0.2		40.6	59.4	65.9	31[d]
78				1	1	44.1	55.9	84.5	10
79	**1b**		1	0.2		39.3	60.7	64.7	28[d]
80				1	1	43.8	56.2	81.0	13
						6a	**6b**		**8**
81	**2a**	Ether	1	0.2		86.4	13.6	71.3	23[d]
82				1		93.3	6.7	89.8	7
83				1	1	89.9	10.1	91.5	9
84	**2b**		1	0.2		96.5	3.5	66.7	29[d]
85				1		96.4	3.6	93.1	1
86				1	1	96.6	3.4	90.9	10
87	**2c**[e]					97.4	2.6	85.5	7
88					1	97.1	2.9	85.4	7
89	**2a**	Toluene	1	0.2		73.7	26.3	87.5	5[d]
90				1	1	79.5	20.5	87.9	4
91	**2b**		1	0.2		85.7	14.3	84.7	6[d]
92				1	1	86.0	14.0	86.5	6
93	**2c**[e]				1	90.7	9.3	71.2	3
94	**2a**	Nitro-methane	1	0.2		54.9	45.1	65.2	20[d]
95				1	1	57.6	42.4	75.3	8
96	**2b**		1	0.2		51.1	48.9	67.6	17[d]
97				1	1	57.6	42.4	79.2	9

[a]Reactions of **1a–c** and **2a–c** were carried out at 30 and 0°, respectively. [b]Analysed by g.l.c. [c]Analysed by g.l.c. after acetylation. [d]Reaction was carried out in the presence of Drierite. [e]The perchlorates were prepared from the corresponding chloride with 1 molar equivalent of silver perchlorate, except for Expt. 76 in which 2.5 molar equivalents of silver perchlorate were used.

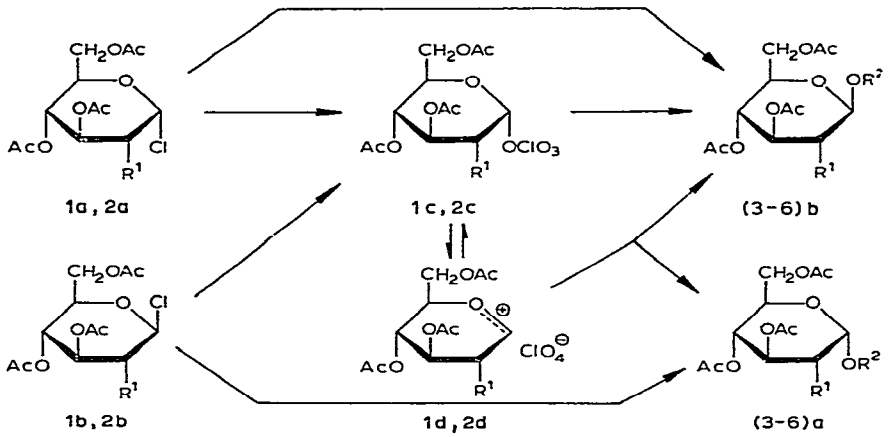
reaction, the ratio of α- and β-D-glucopyranosides was almost constant. When a mixture of silver perchlorate and silver carbonate in the presence of Drierite was used, the yields of glucopyranosides and the proportion of α-D anomers decreased and the amount of hydrolysis products (**7** and **8**) increased, as compared with other systems. Isolation of the products in Expts. 47 and 86 gave **4a** and **4b** in yields of 77.5 and 1.2%, respectively, in the former case, and isopropyl tetra-*O*-acetyl-α- (**9**) and -β-D-glucopyranosides (**10**) in yields of 79.5 and 0.8%, respectively, in the latter after debenzylation and reacetylation. Wolfrom and co-workers[7] obtained **9** and **10** in 35 and 4.7% yields, respectively, in the reaction of 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride with 2-propanol, using a mixture of silver perchlorate and silver carbonate as catalyst followed by hydrogenation and reacetylation. When the reactions were monitored by t.l.c., two new spots appeared as the starting compounds decreased, corresponding to an anomeric mixture of the glucosides (which increased) and to the hydrolysis products (which decreased). The latter compounds are probably formed by decomposition of the reaction intermediate during t.l.c., since the glucosides are not produced from the hydrolysis products under these conditions.

On changing the solvent to anhydrous toluene, the proportion of the α-D-glucopyranosides decreased as compared with that in ether. When silver perchlorate was used, decomposition and anomerisation of the products occurred, and the yields of glucosides were lower. In the glycosidation of **2c**, the proportion of the α-D-glucoside was lower when 2.5 molar equivalents of silver perchlorate were used (Expt. 56) than that when 1 molar equivalent was used (Expt. 55).

In anhydrous nitromethane, the proportion of the α-D-glucopyranosides was still lower, but almost constant regardless of the starting compounds, nucleophiles, and catalysts. When silver perchlorate alone was used, decomposition and anomerisation of the products occurred. The reactions of **1c** and **2c** could not be carried out in nitromethane, because rapid decomposition of **1c** and **2c** occurred before the starting glucosyl chlorides disappeared.

When a large excess of methanol was used (Expts. 1–7 and 35–37), the reactions mainly proceed *via* the S_N2 route, leading to the products with inversion of configuration at C-1, except in Expt. 37, in which **4a** was predominantly obtained. This result may be ascribed to the easier formation of an oxocarbonium ion (**2d**) than **1d**, owing to the difference of the inductive effect between the 2-*O*-benzyl and 2-chloro groups.

The course of the reaction was greatly changed when 1 molar equivalent of nucleophile was used. From the facts (*1*) that **1c** and **2c** were obtained in the reactions of **1a**, **1b**, **2a**, and **2b** with silver perchlorate in the absence of any other nucleophile[4]; (*2*) in the monitoring of reactions by t.l.c., spots corresponding to **7** and **8** were detected, which decreased with the reaction period; and (*3*) the ratio of α- and β-D-glucopyranosides obtained was not significantly different in comparable glycosidations of a glucosyl chloride and the corresponding glucosyl perchlorate, it is considered that the reactions proceed substantially *via* common intermediates, such as the glucosyl perchlorates **1c** and **2c**. It is reasonable to assume that **1c** and **2c** mainly react *via*



1 $R^1 = Cl$
2 $R^1 = OCH_2Ph$
3 $R^1 = Cl$, $R^2 = Me$
4 $R^1 = OCH_2Ph$, $R^2 = Me$
5 $R^1 = Cl$, $R^2 = CHMe_2$
6 $R^1 = OCH_2Ph$, $R^2 = CHMe_2$

the S_N1 route even in non-polar solvents, since it is well known that organic perchlorate esters are very reactive and the cations (**1d** and **2d**) formed are stabilized by participation of the lone-pair electrons on the ring oxygen. It is also reasonable that, in a non-polar solvent, α-D-glucopyranosides were predominantly obtained and that their proportion decreased in a polar solvent, since the group moments of the C-5–O–C-1 and C-1–O bonds in the formation of α-D-glucopyranoside are approximately opposed, consequently the net moment is expected to be smaller than that in the formation of β-D-glucopyranoside, where the group moments are approximately aligned. Moreover, the charge separation is unfavourable in non-polar solvents and favourable in polar solvents[8].

Comparing the reactivities of 2-*O*-benzyl and 2-chloro derivatives, the former reacts faster and, in methanolysis with a large excess of methanol, **2c** gave more α-D-glucoside than **1c**. This difference may be due to the fact that the electron-withdrawing power of the *O*-benzyl group is weaker than that of chlorine, and consequently the oxocarbonium ion **2d** is formed more easily than **1d**.

When methyl trityl ether was used as nucleophile under the same conditions, the ratio of α- and β-D-glucosides was almost constant regardless of the starting compounds. This behaviour is attributed to the steric hindrance of the methyl trityl ether, which prohibits the S_N2 type of reaction and causes the reactions to proceed *via* the perchlorates and the oxocarbonium ions.

In toluene, the reactions proceed in minor extent *via* the S_N2 route, leading to the products with inversion of configuration at C-1. In nitromethane, the reactions probably proceed *via* the S_N1 route, since, under the same conditions, the ratio of α- and β-D-glucosides is almost constant regardless of the starting compounds and nucleophiles. The formation of α-D-glucosides with higher stereoselectivity when ether was used as solvent cannot be explained only by its polarity. The dielectric

constants of ether and toluene are 4.22 and 2.38, respectively[9]. The results could be interpreted by invoking, to some extent, a double inversion at C-1 of glucosyl perchlorates involving the participation of an ether molecule. Kochetkov and his coworkers[10] have proposed a double-inversion mechanism in the formation of orthoesters from tetra-*O*-acetyl-α-D-glucopyranosyl bromide with alcohols in boiling ethyl acetate, in which an ethyl acetate molecule participates. In the methanolysis of **2c**, the proportion of **4a** became lower when 2.5 molar equivalents of silver perchlorate were used (Expt. 56) than when 1 molar equivalent of the catalyst was used (Expt. 55). This may be attributed to the common ion (ClO_4^-) effect, which increases the extent of the reaction route **2d** → **2c** → **4b**.

The yields of the hydrolysis products (**7** and **8**) in ether were higher than those in toluene or nitromethane when silver perchlorate–silver carbonate in the presence of Drierite was used as catalyst. This fact means that the rate of absorption by Drierite of water formed during the reactions, compared with the reaction rate of water with glucosyl perchlorates, is lower in ether than that in toluene or nitromethane.

EXPERIMENTAL

General. — Melting points were measured with a Monoscope (H. Boch, Frankfurt, Germany) and are uncorrected. N.m.r. spectra were obtained, unless otherwise stated, for solutions in chloroform-*d* with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard. Specific rotations were measured on solutions in chloroform with a Perkin–Elmer Model 141 polarimeter, unless otherwise stated. T.l.c. and preparative t.l.c. were performed with silica gel G or silica gel GF (E. Merck, AG, Darmstadt, Germany). Solvents were removed below 40°, using a rotatory evaporator, after drying over sodium sulphate.

Materials. — Silver perchlorate was purified according to the method of Pocker and Kevill[11]. 80mM Ethereal silver perchlorate was made by dissolving silver perchlorate (1.65 g) in anhydrous ether and diluting to 100 ml. Silver carbonate was dried over phosphorus pentaoxide in the dark at 20°/1 mmHg for 20 h. Drierite was dried over phosphorus pentaoxide at 230°/1 mmHg for 20 h.

Solvents and nucleophiles were purified as follows. Ether was refluxed over lithium aluminum hydride for 20 h, and distilled. To this was added an alloy of sodium and potassium, and the mixture was degassed by a freeze–thaw method and distilled. Toluene was washed with concentrated sulphuric acid and water, dried, and distilled over metallic sodium. Nitromethane was washed successively with 10% aqueous sodium carbonate, water, aqueous sodium bisulphite, water, conc. sulphuric acid, and water, dried over calcium chloride, and distilled over phosphorus pentaoxide. Methanol and 2-propanol were refluxed with magnesium and distilled (twice). *sym*-Collidine was refluxed with barium oxide for 20 h, and distilled (twice).

Compounds **1a**, m.p. 99–101°, $[\alpha]_D^{24}$ +227 ±2°; **1b**, m.p. 122.5–123°, $[\alpha]_D^{24}$ +42.7 ±0.7°; **3a**, $[\alpha]_D^{24}$ +171.2 ±2°; and **3b**, m.p. 154–155°, $[\alpha]_D^{23}$ +48.6 ±0.4°, were prepared as previously described[8]. Compounds **2a**, m.p. 88.5–89.5°, $[\alpha]_D^{22}$ +125.3

$\pm 1.7°$; and **2b**, m.p. 127.5–128.5°, $[\alpha]_D^{22}$ +51.4 $\pm 0.9°$, were also prepared as previously described[5]. Methyl trityl ether[12] had m.p. 85.5–86°; lit.[12] m.p. 82.6–82.9°. 1,3,4,6-Tetra-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranose, m.p. 75.5–76°, $[\alpha]_D^{23}$ +98.7 $\pm 1.4°$ (*c* 1.008); lit.[13] m.p. 75°, $[\alpha]_D^{22}$ +82°; and the β-D anomer, m.p. 97–98°, $[\alpha]_D^{25}$ +37.4 $\pm 0.4°$ (*c* 1.027); lit.[13] m.p. 88°, $[\alpha]_D^{22}$ +44°; were prepared as described in the literature[13].

*1,3,4,6-Tetra-*O*-acetyl-2-chloro-2-deoxy-α-D-glucopyranose.* — A mixture of **1b** (500 mg), mercuric acetate (500 mg), and glacial acetic acid (8 ml) was stirred at 70° for 2 h. The insoluble salts were filtered off and washed with dichloromethane. The combined filtrate and washings were successively washed with water, aqueous sodium hydrogencarbonate, and water, dried, and evaporated. The residue was recrystallized from ether–light petroleum to give the title compound (490 mg), m.p. 100–100.5°, $[\alpha]_D^{24}$ +154.7 $\pm 1.8°$ (*c* 1.170).

Anal. Calc. for $C_{14}H_{19}ClO_9$: C, 45.85; H, 5.22; Cl, 9.67. Found: C, 46.10; H, 5.35; Cl, 9.62.

*1,3,4,6-Tetra-*O*-acetyl-2-chloro-2-deoxy-β-D-glucopyranose.* — This compound was prepared from **1a** and mercuric acetate by the method described above, and had m.p. 114–115°, $[\alpha]_D^{23}$ +57.2 $\pm 2°$ (*c* 1.026).

Anal. Calc. for $C_{14}H_{19}ClO_9$: C, 45.85; H, 5.22; Cl, 9.67. Found: C, 45.97; H, 5.21; Cl, 9.87.

*Methyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-* (**4a**) *and -β-D-glucopyranosides* (**4b**). — To a solution of silver perchlorate (502 mg) in anhydrous ether (78 ml) was added **2a** (1.00 g) with stirring at 0°. After 2 min, methanol (78 mg) and *sym*-collidine (294 mg) in anhydrous ether (7 ml) were added, and the mixture was stirred at 0° for 10 min. The insoluble materials were filtered off and washed with ether. The combined filtrate and washings were washed with water, dried, and evaporated. The residue was fractionated by preparative t.l.c., using benzene–ethyl acetate (7:3). From the slower moving zone (R_F 0.59), syrupy **4a** (765 mg, 77.5%), $[\alpha]_D^{26}$ +76.1 $\pm 0.8°$ (*c* 1.007), was obtained. N.m.r. data: τ 2.72 (5-proton singlet, aromatic H), 5.32 (1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1), 6.63 (3-proton singlet, OCH_3). From the faster moving zone (R_F 0.66), **4b** (12 mg, 1.2%), m.p. 76.5–78° (from ether–light petroleum), $[\alpha]_D^{27}$ +43.4 $\pm 0.8°$ (*c* 0.998) was obtained; lit.[12] m.p. 70°, $[\alpha]_D$ +38°. N.m.r. data: τ 2.72 (5-proton singlet, aromatic H), 5.62 (1-proton doublet, $J_{1,2}$ 8.0 Hz, H-1), 6.44 (3-proton singlet, OCH_3).

*Isopropyl 3,4,6-tri-*O*-acetyl-2-chloro-2-deoxy-α-* (**5a**) *and -β-D-glucopyranosides* (**5b**). — A mixture of silver perchlorate (120 mg), silver carbonate (500 mg), Drierite (2.5 g), 2-propanol (12 ml), and **1a** (1.0 g) was stirred at room temperature for 1 h. The inorganic salts were filtered off and washed with dichloromethane. The combined filtrate and washings were washed with water, dried, and evaporated. The residue was crystallized from ether–hexane to give crude **5b** (474 mg). The mother liquor was fractionated by preparative t.l.c., using dichloromethane–ether (15:1). From the slower moving zone (R_F 0.47), **5b** (100 mg) was obtained. The combined **5b** (574 mg) was recrystallized from ether–hexane to give the analytical sample, m.p. 105–107°,

$[\alpha]_D^{22.5}$ +33.1 ±0.8° (*c* 1.010). N.m.r. data: τ 5.46 (1-proton doublet, $J_{1,2}$ 8.3 Hz, H-1), 8.74 and 8.77 (3-proton doublets, *J* 6.0 Hz, isopropyl CH_3).

Anal. Calc. for $C_{15}H_{23}ClO_8$: C, 49.12; H, 6.32; Cl, 9.66. Found: C, 49.12; H, 6.31; Cl, 9.86.

From the faster moving zone (R_F 0.52), **5a** (249 mg), m.p. 98–99° (from ether–hexane), $[\alpha]_D^{23.5}$ +171.9 ±2.2° (*c* 1.008), was obtained. N.m.r. data: τ 4.98 (1-proton doublet, $J_{1,2}$ 3.4 Hz, H-1), 8.73 and 8.78 (3-proton doublets, *J* 6.0 Hz, isopropyl CH_3).

Anal. Calc. for $C_{15}H_{23}ClO_8$: C, 49.12; H, 6.32; Cl, 9.66. Found: C, 49.34; H, 6.34; Cl, 9.83.

*Isopropyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-*D*-glucopyranoside* (**6a**). — Crude **6a** was obtained from silver perchlorate (502 mg), **2a** (1.0 g), *sym*-collidine (292 mg), and 2-propanol (145 mg) in anhydrous ether, as described in the preparation of **4a**. Acetate **6a** was hydrolyzed with sodium methoxide in anhydrous methanol, and the product was recrystallized from ether (3 times) to give isopropyl 2-*O*-benzyl-α-D-glucopyranoside (383 mg), m.p. 121–122°, $[\alpha]_D^{23.5}$ +117.5 ±1.7° (*c* 0.974).

Anal. Calc. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 61.38; H, 7.75.

The foregoing product was acetylated with acetic anhydride and pyridine to give **6a** as a colourless syrup, $[\alpha]_D^{23.5}$ +89.3 ±1.4° (*c* 0.971). N.m.r. data: τ 2.72 (5-proton singlet, aromatic H), 5.11 (1-proton doublet, $J_{1,2}$ 3.5 Hz, H-1).

*Isopropyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-β-*D*-glucopyranoside* (**6b**). — A mixture of silver carbonate (80 mg), Drierite (700 mg), 2-propanol (14 ml), and **2a** (207 mg) was stirred at room temperature for 7.5 h. The inorganic salts were filtered off and washed with dichloromethane. The solvents were evaporated and the residue was purified by preparative t.l.c., using dichloromethane–ether (15:1). From a zone (R_F 0.37), **6b** (195 mg), m.p. 86–87° (from hexane), $[\alpha]_D^{24}$ +38.0 ±0.8° (*c* 1.017), was obtained. N.m.r. data: τ 2.73 (5-proton singlet, aromatic H), 5.46 (1-proton doublet, $J_{1,2}$ 7.9 Hz, H-1).

Anal. Calc. for $C_{22}H_{30}O_9$: C, 60.26; H, 6.90. Found: C, 60.53; H, 6.99.

*Isopropyl 2,3,4,6-tetra-*O*-acetyl-α- and -β-*D*-glucopyranosides (isolation of the products in Expt. 86).* — To a mixture of silver perchlorate (101 mg), *sym*-collidine (58 mg), 2-propanol (30 mg), and anhydrous ether (17 ml) was added **2b** (200 mg) with stirring at 0°, and the mixture was stirred for a further 1 h. The insoluble materials were filtered off and washed with dichloromethane. The combined filtrate and washings were washed with water, dried, and evaporated. The residue was dissolved in methanol (10 ml) and hydrogenated over palladium obtained from palladium chloride (200 mg). After the hydrogenation was finished (30 min), the catalyst was removed by filtration and washed with methanol. The solvent was evaporated and the residue was acetylated with acetic anhydride (4 ml) and sodium acetate (0.3 g) by refluxing for 1 h. The crude product was recrystallized from ether–light petroleum to give isopropyl tetra-*O*-acetyl-α-D-glucopyranoside (129 mg, 68.3%), m.p. 88–89°, $[\alpha]_D^{22.5}$ +143.2 ±1.8° (*c* 1.023); lit.[7] m.p. 85–88°, $[\alpha]_D^{24}$ +143° (*c* 2). The mother liquor was fractionated by preparative t.l.c., using dichloromethane–ether (15:1). From the faster moving zone (R_F0.45), the α-D anomer (21 mg; total 150 mg, 79.3%),

m.p. 88–89°, was obtained. From the slower moving zone (R_F 0.34), the β-D anomer (1.5 mg, 0.8%), m.p. 140–141°; lit.[7] m.p. 137–138°, was obtained after recrystallization from alcohol.

G.l.c. — G.l.c. analyses were carried out with a Yanagimoto Gas Chromatograph GCG-550F with a flame-ionization detector. Areas were determined by the product of the peak height and the half-height width. Calibration curves for all compounds were linear and the lines crossed their origins. To establish identity by g.l.c., comparisons were made both by retention times and by simultaneous injection of a standard to observe peak enhancement. The results are summarized in Tables I–III. Each experiment was repeated twice, and in each run areas were taken as the mean values of duplicate chromatograms. The values shown in Tables I–III are the mean values of the above data.

Analyses of **3a** and **3b** were carried out by using methyl tetra-*O*-acetyl-α-D-glucopyranoside[14], m.p. 104–105.5°, $[\alpha]_D^{24}$ +130.4 ±1.6° (*c* 1.004) {lit.[14] m.p. 101–103°, $[\alpha]_D^{25}$ +130° (*c* 2)}, as an internal standard with a stainless-steel column (1.5 m × 3 mm i.d.) packed with 1.5% of diethyleneglycol succinate on Gaschrom Q (100–120 mesh) under the following conditions: column temperature, 190°; injection temperature, 270°; nitrogen as a carrier gas, 1.08 kg/cm^2; hydrogen, 30 ml/min. Retention times (min) were: **3a**, 7.1; **3b**, 8.0; the internal standard, 10.6. Analyses of the acetates of **7** were similarily carried out, except that the nitrogen pressure was 2.0 kg/cm^2. Retention times (min) were: acetate of **7** (α-anomer), 5.38; the β-anomer, 5.77; internal standard, 3.95.

Analyses of **4a**, **4b**, and the acetates of **8** were carried out using benzyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[15], m.p. 104–105°, $[\alpha]_D^{26}$ −89.4 ±1.2° (*c* 1.119, tetrachloroethane) {lit.[15] m.p. 98°, $[\alpha]_D^{24}$ −93.1° (*c* 5, tetrachloroethane)}, as an internal standard with a stainless-steel column (75 cm × 3 mm i.d.) packed with 1.5% of diethyleneglycol succinate on Gaschrom Q (100–120 mesh) under the following conditions: column temperature, 200°; injection temperature, 300°; nitrogen as a carrier gas, 1.10 kg/cm^2; hydrogen, 30 ml/min. Retention times (min) were: **4a**, 7.30; **4b**, 5.50; acetate of **8** (α-anomer), 10.17; the β-anomer, 12.73; internal standard, 17.89.

Analyses of **5a** and **5b** were carried out using methyl tetra-*O*-acetyl-α-D-glucopyranoside as an internal standard with a stainless-steel column (2.25 m × 3 mm id.) packed with 1.5% of diethyleneglycol succinate on Gaschrom Q (100–120 mesh) under the following conditions: column temperature, 192°; injection temperature, 300°; nitrogen as a carrier gas, 1.75 kg/cm^2; hydrogen, 30 ml/min. Retention times (min) were: **5a**, 5.56; **5b**, 6.90; internal standard, 11.53.

Analyses of **6a** and **6b** were carried out using benzyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside as an internal standard with a stainless-steel column (75 cm × 3 mm i.d.) packed with 1.5% of XE-60 on Gaschrom Q (100–120 mesh) under the following conditions: column temperature, 186°; injection temperature, 300°; nitrogen as a carrier gas, 0.83 kg/cm^2; hydrogen, 30 ml/min. Retention times (min) were: **6a**, 11.56; **6b**, 9.58; internal standard 17.89.

Glycosidation of **1a–c** *and* **2a–c**. — (*a*) *With a large excess of methanol.* Glucosyl

chloride (**1a**, **1b**, **2a**, and **2b**) (100 mg) was dissolved in methanol (4 ml), an appropriate amount of catalyst was added, and the mixture was stirred at 30° using a thermostated bath until the reaction was complete (t.l.c.). To the mixture was added the internal standard (100 mg). The insoluble materials were filtered off and washed with dichloromethane. The combined filtrate and washings were washed with water, aqueous sodium hydrogen carbonate, and water, dried, and evaporated. The residue was dissolved in carbon disulphide containing a small amount of dichloromethane, and the solution was analysed by g.l.c.

For the glucosyl perchlorates (**1c** and **2c**), the experiments were carried out as follows. A sealed ampoule, which contained methanol (4 ml), was placed in a flask, which was predried at 50°/1 mmHg and then filled with dry argon. Glucosyl chloride (**1a** and **2a**) and 80mM ethereal silver perchlorate (3.64 ml) were added to the flask and the mixture was stirred at 0°. After the starting chloride disappeared, the temperature was raised to 30°, *sym*-collidine (1 mole) was added if needed, the ampoule was crushed, and the mixture was stirred at 30°. The reaction mixture was treated as above and analysed by g.l.c.

(*b*) *With 1 molar equivalent of nucleophiles.* The reactions of 2-chloro and 2-*O*-benzyl derivatives were carried out at 30 and 0°, respectively, using a thermostated bath.

A sealed ampoule, which contained a solution of glucosyl chloride (**1a**, **1b**, **2a**, and **2b**) (100 mg) in anhydrous solvent, was placed in a flask, which was predried at 50°/1 mmHg and then filled with dry argon. Appropriate amounts of catalysts and nucleophile, and the solvent (5.5 ml) were added to the flask. When a mixture of silver perchlorate and silver carbonate was used, Drierite (350 mg) was added. The ampoule was crushed and the mixture was stirred. After the reaction was complete, the mixture was treated as described above and analysed by g.l.c. For the analysis of the hydrolysis products (**7** and **8**), the reaction product was acetylated and anlyzed by g.l.c.

For the glucosyl perchlorates (**1c** and **2c**), the experiments were carried out as follows. A sealed ampoule, which contained nucleophile (1 mole) in an anhydrous solvent (3 ml) with or without *sym*-collidine (1 mole), was placed in a flask. Glucosyl chloride (**1a** or **2a**) (100 mg) was dissolved in the solvent (5.5 ml), and silver perchlorate (1 mole) was added at 0° with stirring. After the starting chloride had disappeared, the ampoule was crushed and the mixture was stirred. After the reaction was complete, the mixture was treated as above and analysed by g.l.c.

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