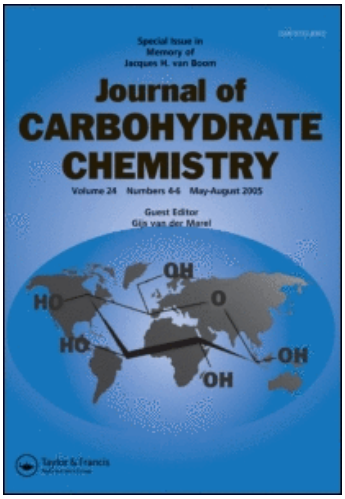


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# Selective Halogenation of L-Sorbose Derivatives

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*COMMUNICATION*

# SELECTIVE HALOGENATION OF L-SORBOSE DERIVATIVES

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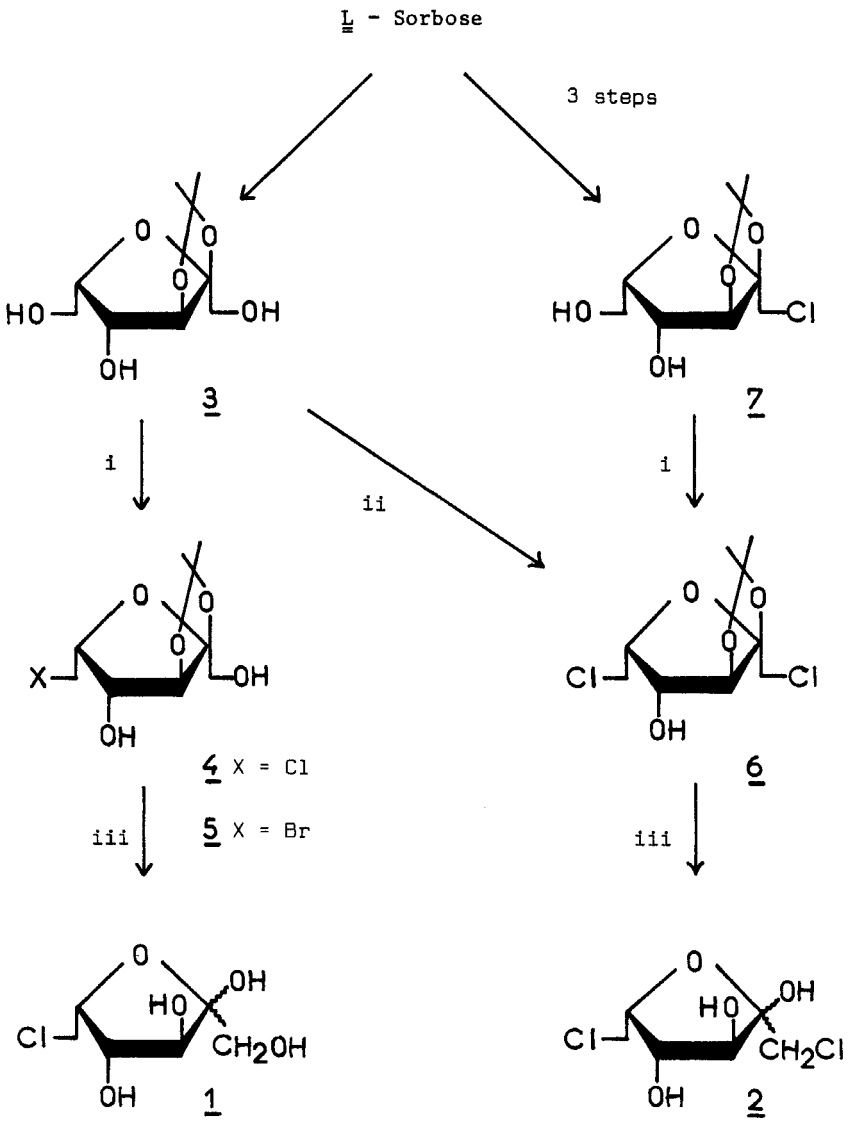
Deoxyhalogenosugars constitute an important class of compounds for the synthesis of other carbohydrate derivatives.[1-3] Several members of this class are of interest in their own right, being intensely sweet[4,5] or possessing anti-cariogenic [6,7] or male anti-fertility properties.[8-11]

As part of an ongoing programme on the synthesis of chlorinated carbohydrates, we became interested in the preparation of deoxyhalosorbose derivatives. A recent publication[12] about selective sulphonylation of sorbose derivatives prompted us to disclose at this time our results on selective halogenation, which has lead to the preparation of 6-chloro-6-deoxy-L-sorbose (1) and 1,6-dichloro-1,6-dideoxy-L-sorbose (2).

Preliminary experiments aimed at the selective halogenation of sorbose itself failed to give encouraging results and therefore the use of a blocked cyclic form was envisioned. Readily available sorbofuranose acetal 3[13] was used as a common starting material. The order of reactivity of the various hydroxyl groups was expected to be OH-6 > OH-1 > OH-4. Thus when treated with triphenylphosphine/carbon tetrachloride in pyridine,[14,15] 3 smoothly led to the monochlorinated derivative 4 in 81 % yield after purification. That the chlorine was introduced at position -6 was revealed by the high-field resonance of C-6 in the $^{13}C$ NMR spectrum ($\delta$=40.1 ppm),




i = P $(C_6 H_5)_3$, C $X_4$, pyr.

ii = MsCl, DMF

iii= DOWEX

the C-1 resonance remaining unchanged ($\delta$=63.6 ppm). Substitution of carbon tetrachloride by carbon tetrabromide gave the corresponding bromo derivative 5. These halogenation reactions are reminiscent of similar results that have been obtained with sucrose derivatives.[16-18]

A different approach was necessary to obtain a dichloro derivative, namely double displacement of a dimesylate by chloride.[19,20] This one pot reaction when applied to 3 (MsCl/DMF-65°C-18 h) gave 6 in 79 % isolated yield. For comparison purposes, 6 was also obtained indirectly. Compound 7, available in three steps from sorbose,[21] was submitted to the above triphenylphosphine/carbon tetrachloride reaction which yielded the same dichlorinated compound. Once again, no halogenation of the secondary alcohol was observed.

Hydrolysis of the acetal group was non-trivial as a number of acidic reagents (tosic acid, formic acid, hydrochloric acid, trifluoracetic acid and resins such as Amberlite 200 or IRC 50) were tried unsucessfully. However, excellent results were subsequently achieved with Dowex 50W X8, which allowed the preparation of pure 1 and 2 in quantitative yield. It is of interest from a conformational stability point of view to note that 2 in aqueous solution gave the expected $\alpha$ and $\beta$ anomeric forms ($^{13}C$ NMR spectrum) but only one of these ($\alpha$) could be detected for the monochlorinated derivative 1.



## EXPERIMENTAL

General Methods. Solvents and reagents were obtained from Aldrich. TLC : Precoated silica gel 60 F - 254 plates (Merck). Column chromatography : silica gel (35-70µm AMICON). $^1H$ NMR and $^{13}C$ NMR : Spectrometer Brucker WB 300 ; chemical shifts are expressed in ppm relative to tetramethylisane as an internal standard (solvent : $CDCl_3$). For spectra recorded in $D_2O$, chemical shifts, expressed in ppm, are relative to a reference located at -2000 Hz from Deuterium resonance. Coupling constants are given in Hz.

Melting points are incorrected and optical rotations were determined on a Jobin Yvon polarimeter.

1,6-Dichloro-1,6-dideoxy-2,3-O-isopropylidene-α-L-sorbofuranose (6).

a) To a solution of carbon tetrachloride (20 mL, 206 mmol) in pyridine (145 mL) dried over KOH, were added 7 (5 g, 21 mmol) and triphenylphosphine (10.5 g, 40 mmol) at 0°C. The mixture was then stirred at 50 °C for 25 min.

and 20 mL of methanol were added to quench excess reagents. After evaporation of the volatiles under reduced pressure, column chromatography was performed. Elution with 3:2 acetone-cyclohexane afforded 6 (4.6 g, 85 %) : mp 69-71 °C; $[\alpha]_D^{20}$ = -3.0 (C = 1, EtOH); $^1$H NMR ($CDCl_3$) δ 1.37 ($CH_3$), 1.49 ($CH_3$), 3.65 (d, H-6 and H-6'), 3.71 (d, 1H, $J_{1,1'}$ = 11.9 Hz, H-1), 3.76 (d, 1H, H-1'), 4.29 (d, 1H, $J_{4,5}$ = 2.5 Hz, H-4), 4.44 (m, 1H, $J_{5,6}$ = 7.8 Hz, H-5), 4.51 (s, 1H, H-3); $^{13}$C NMR ($CDCl_3$) δ 39.53 (C-6), 44.47 (C-1), 73.90 (C-5), 81.80 (C-4), 85.16 (C-3), 113.0, 113.51 (C-2 and C iPr), 26.30 ($CH_3$), 27.40 ($CH_3$).

Anal. Calcd for $C_9H_{14}O_4Cl_2$: C, 42.02; H, 5.45; Cl, 27.62. Found : C, 41.90; H, 5,46; Cl, 27.58.

b) A solution of 3 (1.0 g, 4.54 mmol) and mesyl chloride (2.1 g, 18.33 mmol) in dimethylformamide (25 mL) was stirred at 65 °C for 16 h. After treatment with a solution of sodium methoxide in methanol and evaporation of the volatiles under reduced pressure, column chromatography (hexane - ethyl acetate 8:2) gave pure 6 (1.05 g, 90 %).

6-Chloro-6-deoxy-2,3-O-isopropylidene-α-L-sorbofuranose (4).

When submitted to the same conditions as described for 6 (procedure a) compound 3 gave 4 in 82 % isolated yield on a 20 mmol scale. Chromatographic purification was achieved eluting with 6:4 hexane - acetone : mp 107-108 °C; $[\alpha]_D^{20}$ = +4.0 (C = 1, MeOH); $^1$H NMR ($CDCl_3$) δ 1.30 ($CH_3$), 1.48 ($CH_3$), 3.65 (d, 1H, $J_{1,1'}$ = 11.6 Hz, H-1), 3.66 (d, 2H, H-6 and H-6'), 3.86 (d, 1H, H-1'); 4.18 (d, 1H, $J_{4,5}$ = 2.5 Hz, H-4), 4.41 (m, 1H, $J_{5,6}$ = 7.4 Hz, H-5), 4.42 (s, 1H, H-3); $^{13}$C NMR ($CDCl_3$) δ 40.10 (C-6), 63.63 (C-1), 73.85 (C-5), 82.02 (C-4), 86.10 (C-3), 112.60, 113.63 (C-2 and C iPr), 27.11 ($CH_3$), 26.14 ($CH_3$).

Anal. Calcd for $C_9H_{15}O_5Cl$ : C, 45.28; H, 6.29; Cl, 14.88. Found : C, 45.15; H, 6.40; Cl, 14.79.

6-Bromo-6-deoxy-2,3-O-isopropylidene-α-L-sorbofuranose (5).

Substituting carbon tetrachloride with carbon tetrabromide, the procedure a) described for the preparation of 6, gave 5 in 82 % yield from 3 : mp 109-110 °C, $[\alpha]_D^{20}$ = +13.6 (C = 1, MeOH); $^1$H NMR ($CDCl_3$) δ 1.31 ($CH_3$), 1.50 ($CH_3$), 3.45 (m, 1H, $J_{6,6'}$ = 10.6 Hz, $J_{5,6}$ = $J_{5,6'}$ = 6.4 Hz, H-6), 3.50 (m, 1H, H-6'), 3.66 (d, 1H, $J_{1,1'}$ = 11.5 Hz, H-1), 3.87 (d, 1H, H-1'), 4.22 (d, 1H, $J_{4,5}$ = 2.5 Hz, H-4), 4.45 (s, 1H, H-3), 4.48 (m, 1H, H-5); $^{13}$C NMR ($CDCl_3$) δ 27.19 (C-6), 66.63 (C-1), 74.0 (C-5), 81.91 (C-4), 86.12 (C-3), 112.60, 113.77 (C-2 and C iPr), 26.15 ($CH_3$), 27.13 ($CH_3$).
Anal. Calcd for $C_9H_{15}O_5Br$ : C, 38.16; H, 5.30; Br, 28.30. Found : C, 38.04; H, 5.34; Br, 28.16.

1,6-Dichloro-1,6-dideoxy-L-sorbose (2).

Dowex resin (50 WX8 - 14 mL - 70 eq.$H^+$) was added to 6 (4 g, 15.6 mmol) in water (35 mL). The mixture was stirred for 3 h at 60 °C. After filtration, the resin was washed with water. The aqueous phase was then concentrated under reduce pressure and 2 was obtained as a syrup (3.3 g) which crystallized upon standing as a waxy solid : mp 75 °C (softens), 88-89 °C (fully melts) ; $^{13}C$ NMR ($D_2O$) δ 44.17 (C-6 α and β), 46.79 (C-1 β), 48.0 (C-1 α) 76.54, 78.18, 79.49 (C-3, C-4, C-5 α), 83.86, 81.13, 77.19 (C-3, C-4, C-5 β) 102.67 (C-2α), 107.15 (C-2 β).

Anal. Calcd for $C_6H_{10}O_4Cl_2$ : C, 33.18; H, 4.61; Cl, 32.72. Found : C, 33.10; H, 4.69; Cl, 32.68.

6-Chloro-6-deoxy-L-sorbose (1).

Using the procedure described for 2, 1 was obtained quantitatively from 4 as a colorless syrup : $^{13}C$ NMR ($D_2O$) δ 44.21 (C-6), 64.0 (C-1), 75.70, 76.39, 78.17 (C-3, C-4, C-5), 102.50 (C-2).

Anal. Calcd for $C_6H_{11}O_5Cl$ : C, 36.27; H, 5.54; Cl, 17.88. Found : C, 36.41; H, 5.57; Cl, 17.78.



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