Carbohydrate Research, 218 (1991) 75–81
Elsevier Science Publishers B.V., Amsterdam

Selective chlorination of pentitols

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(Received February 4th, 1990; accepted for publication, in revised form, September 19th, 1990)

ABSTRACT

Methanesulfonyl chloride in *N,N*-dimethylformamide transformed unprotected D-arabinitol into its 1,5-dichloro derivative in 50% yield. Other pentitols also reacted to give the corresponding 1,5-dichloropentitols, but with lower yields. The structures of the products were determined by n.m.r. spectroscopy.

INTRODUCTION

As part of our study on the preparation of chlorinated carbohydrate derivatives, we were interested in the synthesis of 1,5-dichloropentitols, and more specifically 1,5-dichloroarabinitol, starting from the unprotected alditols. The most widely used method of chlorination of polyols involves fuming hydrochloric acid as reagent[1]. Thus, galactitol and mannitol were converted into their 1,6-dichloro derivatives in 10 and 40% yield, respectively[2,3]. Under these drastic conditions, the pentitols are converted mainly into anhydro derivatives, with chloropentitols being formed in small proportions[4]. When milder acidic conditions are employed, arabinitol was resistant to anhydride formation[5], whereas ribitol and xylitol gave anhydro derivatives in small or negligible proportions. Recently, it was shown that in pyridine, equimolar concentrations of pentitols and *p*-toluenesulfonyl chloride, or under conditions where the latter compound is in excess, reacted to give mono- and di-anhydro derivatives or anhydrodichloropentitols[6]. Similar results were obtained when methanesulfonyl chloride was utilized[7]. Another route to dichloroalditols is based on successive protection, chlorination, and deprotection steps. Thus, 1,6-dichloro-1,6-dideoxy-D-glucitol was prepared in six steps in $< 10\%$ yield[8]. In a preceding paper, we have shown that in *N,N*-dimethylformamide, methanesulfonyl chloride reacted with 2,3-*O*-isopropylidene-α-L-sorbofuranose at the primary hydroxymethyl group to give 1,6-dichloro-1,6-dideoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose in 90% yield[9], and no anhydro compound was formed. The high selectivity observed in this reaction led us to study how unprotected alditols react with methanesulfonyl chloride in *N,N*-dimethylformamide.

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RESULTS AND DISCUSSION

In the presence of a large molar excess of methanesulfonyl chloride (6 equivs., 65°), D-arabinitol (**1**) is transformed into 1,5-dichloro-1,5-dideoxy-D-arabinitol (**2**) in 50% yield, 1,4-anhydro-5-chloro-5-deoxy-D-arabinitol (**3**) in 23% yield, 1-chloro-1-deoxy-D-arabinitol (**4**) in 10% yield, and 1,4-anhydro-D-arabinitol (**5**) in a small proportion. Structures of these derivatives were determined by ^{1}H-, ^{13}C-, and COSY-heteronu-

TABLE I

^{1}H-Chemical shifts (δ)[a] and coupling constants (in Hz) for D-arabinitol (**2–5**), ribitol (**7–10**), and xylitol derivatives[b] (**12–15**)

Compd.	*Chemical shifts*						
	H-1a	*H-1b*	*H-2*	*H-3*	*H-4*	*H-5a*	*H-5b*
2	3.41 (dd)	3.49 (dd)	5.28 (dq)	5.41 (dd)	5.12 (dq)	3.53 (dd)	3.64 (dd)
3	3.94 (m)	3.99 (dd)	5.08 (ddd)	5.02 (m)	3.96 (m)	3.61 (dd)	3.67 (dd)
4	3.41 (dd)	3.47 (dd)	5.27 (m)	5.38 (ddd)	5.05 (ddd)	4.05 (dd)	4.16 (dd)
5	3.74 (dd)	3.82 (dd)	4.93 (ddd)	4.81 (m)	3.78 (m)	3.96 (dd)	4.08 (dd)
7	3.45 (dd)	3.62 (dd)	5.10 (m)	5.18 (t)	5.10 (m)	3.45 (dd)	3.62 (dd)
8	3.59 (dd)	3.95 (dd)	5.09 (m)	4.92 (dd)	3.92 (m)	3.40 (dd)	3.49 (d)
9	3.78 (dd)	3.88 (dd)	4.07 (m)	4.83 (m)	3.74 (dq)	3.45 (dd)	3.52 (dd)
10	3.62 (dd)	3.66 (dd)	4.23 (dt)	5.62 (dd)	5.26 (dq)	3.56 (dd)	3.82 (dd)
12	3.45 (dd)	3.51 (dd)	5.06 (q)	5.39 (t)	5.06 (dq)	3.45 (dd)	3.51 (d)
13	3.45 (dd)	3.97 (m)	4.83 (m)	5.04 (dd)	4.0 (m)	3.84 (dd)	3.93 (m)
14	3.50 (dd)	3.98 (dd)	4.85 (m)	5.07 (d)	4.03 (dd)	3.35 (d)	3.35 (dd)
15	3.64 (dd)	3.72 (dd)	5.41 (m)	5.33 (dd)	4.12 (m)	3.43 (dd)	3.49 (dd)

Compd.	*Coupling constants*							
	$J_{1a,1b}$	$J_{1a,2}$	$J_{1b,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$
2	11.5	7.3	6	2.2	8.7	5.2	3.3	12.4
3	10.9	1.6	4.1	1.5	4.1	6.3	5.3	11.5
4	11.5	7.2	6.1	2.3	8.8	4.8	2.5	12.5
5	10.8	1.6	4.3	2.3	3.4	6.5	4.7	12.1
7	12.1	6.9	3.0	5.2	5.2	6.9	3.0	12.1
8	10.3	3.6	4.9	5.4	6.4	4.5	3.8	11.4
9	10.7	2	4.1	2	3.1	6.7	5.4	12.4
10	11.7	7	7.4	2	8.4	4.3	3.3	12.2
12	12.2	5.6	4.9	5.0	5.0	5.6	4.9	12.2
13	10.6	2.3	4.6	1.1	3.6	6.8		11.2
14	10.6	1.8	4.6	0	4.0	6.8	6.8	12.2
15	11.4	6.7	6.4	2.4	8.8	5.8	4.2	11.6

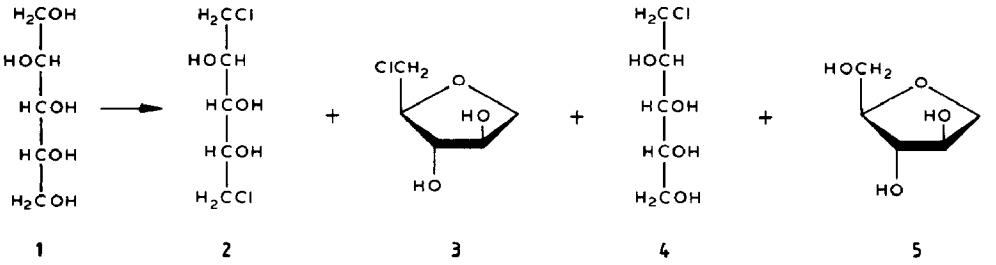
[a] Relative to the signal of internal tetramethylsilane for solutions in (^{2}H)chloroform. [b] Peracetylated derivatives.

TABLE II

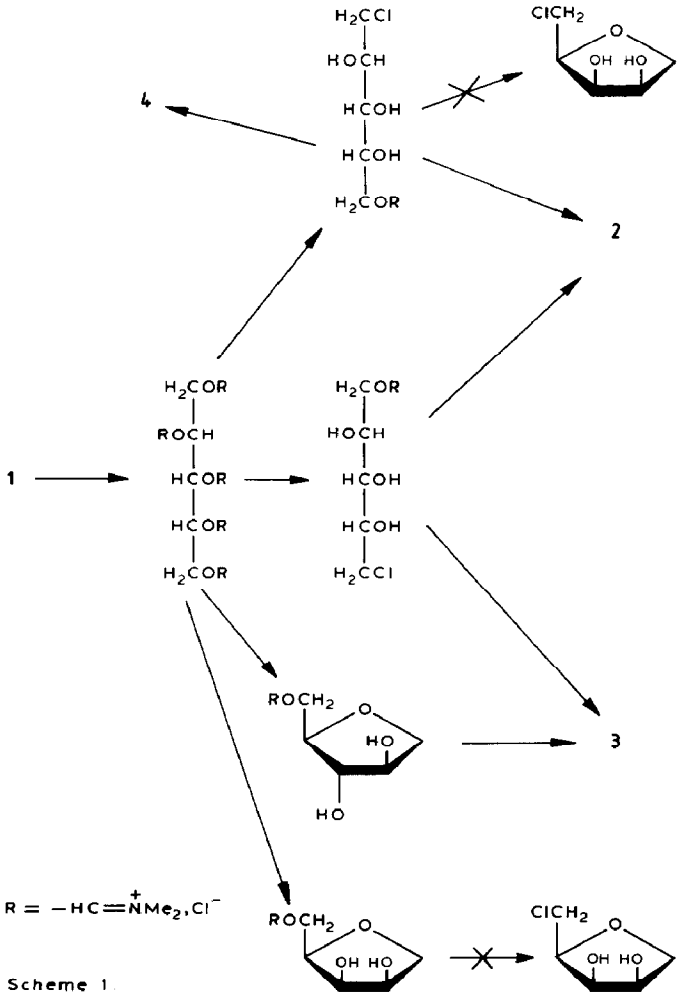
^{13}C-Chemical shifts (δ)[a] for D-arabinitol (**2**–**5**), ribitol (**7**–**10**), and xylitol derivatives[b] (**12**–**15**)

Compd.	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	CH_3		$C=O$		
2	41.79	69.86	69.32	69.06	42.96	20.60	20.49	169.41	169.42	169.77
3	72.08	77.07	78.73	83.58	43.64	20.65	20.73	169.75	169.92	
4	41.67	69.83	68.37	68.01	61.60	20.49	20.69	169.51	169.70	170.46
5	71.63	77.22	78.03	81.43	63.11	20.32	20.39	169.55	169.39	
7	42.25	70.90	70.11	70.90	42.25	20.41	20.51	168.97	169.52	
8	70.53	71.15	72.34	79.24	44.29	20.09	20.19	169.43	169.52	
9	74.03	59.58	81.25	83.66	44.15	20.22		169.32		
10	44.41	59.42	68.92	70.72	42.60	20.48	20.72	169.33		
12	42.15	70.44	69.56	70.44	42.15	20.56	20.36	169.44	169.81	
13	71.49	77.05	75.68	77.05	61.54	20.30	20.44	169.21	169.43	170.20
14	71.58	76.79	75.17	79.31	40.19	20.00	20.17	168.88	169.17	
15	41.46	57.52	71.15	70.53	45.63	20.44	20.34	169.41	169.25	

[a] Relative to the signal of internal tetramethylsilane for solutions in (^{2}H)chloroform. [b] Peracetylated derivatives.



clear-n.m.r. spectroscopy (Tables I and II) after peracetylation. Compound **2** showed a large coupling constant of 8.7 Hz for anti-3,4-methine protons; this value is consistent with planar and zig-zag conformation previously proposed for D-arabinitol pentaacetate[10].

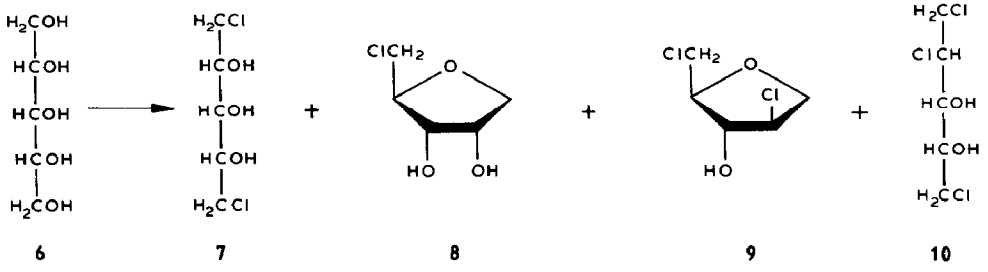


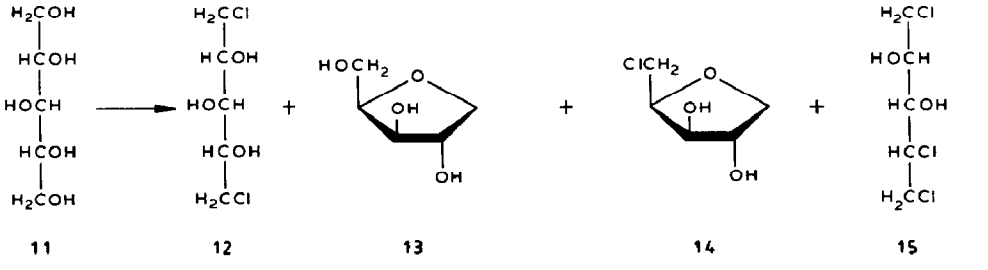
Scheme 1

Based on the structures of the main derivatives, a mechanism for the formation of these products is proposed (Scheme 1). It is well known that in *N,N*-dimethylformamide methanesulfonyl chloride reacts with the solvent to give an iminium chloride[10,11], $Me_2N^+ = CH–OSO_2Me\ Cl^-$. Steric hindrance of this salt leads, in the first step, to a highly selective replacement of the primary hydroxyl groups in D-arabinitol. This intermediate can react further in two manners: (a) The chloride ion may attack the methylene carbon atom of the alkoxyl group to convert this intermediate into 1-chloro-1-deoxy-D-arabinitol (**4**), or (b) OH-4 may attack C-1 to give 1,4-anhydro-D-arabinitol (**5**). Although 5-chloro-5-deoxy-D-arabinitol was not observed, its formation cannot be excluded, owing to the fact that it may be rapidly transformed into 1,4-anhydro-5-chloro-5-deoxy-D-arabinitol (**3**) and the 1,5-dichloro derivative **2**. 1,5-Anhydro-D-arabinitol and its chloro derivative were not detected.

Under similar reaction conditions, ribitol (**6**) gave 1,4-anhydro-2,5-dichloro-2,5-dideoxy-DL-arabinitol (**9**) as the major product (52% yield). This derivative was obtained from 1,4-anhydro-5-chloro-5-deoxy-DL-ribitol (**8**) in which replacement at C-2 occurs but at a lower rate than at the primary carbon. The 1,5-dichloro acyclic derivative **7** was formed in a small proportion (11% yield). Modification of the experimental conditions (8 equivs. of methanesulfonyl chloride at room temperature for three days) afforded **7** in 27% yield. This yield is lower than that obtained with D-arabinitol, but is still useful for direct chlorination. Thus, an increased concentration of methanesulfonyl chloride and a lower temperature favor the formation of the 1,5-dichloro derivative. The 1,2,5-trichloro derivative **10** was obtained in 6% yield.

When xylitol (**11**) was treated with methanesulfonyl chloride (6 equivs., 65°; 16 h) 1,5-dichloro-1,5-dideoxyxylitol (**12**) was produced in 5% yield, and the anhydro derivatives **13** and **14** in 18 and 24% yields, respectively. Under mild conditions (25°; 10





days), the yield of acyclic dichloroderivative **12** increased to 19%, and that of the anhydro products **13** and **14** remained unchanged. The 1,4,5-trichloro derivative **15** was obtained in 8% yield.

In conclusion, the methanesulfonyl chloride–*N,N*-dimethylformamide reagent transformed D-arabinitol into the 1,5-dichloro derivative in good yield. With pentitols showing a greater tendency towards anhydro sugar formation (*e.g.*, xylitol, ribitol), a large excess of methanesulfonyl chloride, or a lower temperature, or both, favored the formation of the 1,5-dichloropentitols with yields equal or greater than those obtained by the Bouchardat[1] reaction applied to hexitols.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Jobin–Yvon polarimeter at 20°. ^{1}H- and ^{13}C-n.m.r. spectra were recorded with a Bruker WB 300 instrument. T.l.c. was performed on Silica gel 60F-254 (E. Merck, 230 mesh) with 4:1 hexane–ethyl acetate as eluent. The silica gel used in column chromatography was 35–70 μm Amicon.

General procedure. — To a solution of pentitol (D-arabitinol, ribitol, or xylitol) (10 g, 65.8 mmol) in dry *N,N*-dimethylformamide (100 mL) was added methanesulfonyl chloride (400 mmol, 6 equivs.). The mixture was stirred at 65° overnight (16 h). Evaporation of the solvent gave a syrup which was treated with 1.3M methanolic sodium ethoxide (100 mL) at 0°. After evaporation, the brown residue was dissolved in dry pyridine (100 mL) and a two-fold excess of acetic anhydride was added. The mixture was stirred overnight at room temperature, the solvent was removed under reduced pressure, and the acetylated derivatives were extracted with dichloromethane. The organic layer was washed successively with aqueous HCl, aqueous saturated $NaHCO_3$ solution, and water. The solvent was removed and the dried residue was passed through a column of silica gel (360 g) with 3:1 hexane–ethyl-acetate as an eluent. Compounds **2**, **4**, **10**, **12**, and **15** crystallized from ethanol.

The following pentitols derivatives were prepared according to this general procedure.

2,3,4-Tri-O-*acetyl-1,5-dichloro-1,5-dideoxy*-D-*arabinitol* (**2**). Yield 10.36 g (50%), m.p. 75–76°, $[\alpha]_D$ + 42° (*c*, 1.34, chloroform), R_F 0.46.

Anal. Calc. for $C_{11}H_{16}Cl_2O_6$: C, 41.90; H, 5.08; Cl, 22.54. Found: C, 41.95; H, 5.15; Cl, 22.27.

2,3-Di-O-*acetyl-1,4-anhydro-5-chloro-5-deoxy*-D-*arabinitol* (**3**). Yield 3.58 g (23%); syrup, $[\alpha]_D$ −22° (*c* 2.4, ethyl acetate), R_F 0.37.

Anal. Calc. for $C_9H_{13}ClO_5$: C, 45.66; H, 5.50; Cl, 15.01. Found: C, 45.12; H, 5.54; Cl, 15.91.

2,3,4,5-Tetra-O-*acetyl-1-chloro-1-deoxy*-D-*arabinitol* (**4**). Yield 2.23 g (10%); m.p. 117–118°, $[\alpha]_D$ + 37° (*c* 0.82, chloroform), R_F 0.20.

Anal. Calc. for $C_{13}H_{19}ClO_8$: C, 46.08; H, 5.60; Cl, 10.49. Found: C, 46.35; H, 5.54; Cl, 10.44.

2,3,4-Tri-O-*acetyl-1,5-dichloro-1,5-dideoxyribitol* (**7**). Yield 2.28 g (11%); syrup, R_F 0.35

Anal. Calc. for $C_{11}H_{16}Cl_2O_6$: C, 41.90; H, 5.08; Cl, 22.54. Found: C, 41.96; H, 5.22; Cl, 22.44.

2,3-Di-O-*acetyl-1,4-anhydro-5-chloro-5-deoxy*-DL-*ribitol* (**8**). Yield 1.86 g (12%); syrup, R_F 0.29; m.s.: *m/z* 254,256 ($M + NH_4^+$).

Anal. Calc. for $C_9H_{13}ClO_5$; C, 45.66; H, 5.50; Cl, 15.01. Found: C, 45.38; H, 5.51; Cl, 15.21.

3-O-*Acetyl-1,4-Anhydro-2,5-dichloro-2,5-dideoxy*-DL-*arabinitol* (**9**). Yield 7.29 g (52%); syrup, R_F 0.46; m.s.: *m/z* 230,232,234 ($M + NH_4^+$).

Anal. Calc. for $C_7H_{10}Cl_2O_3$: C, 39.44; H, 4.70; Cl, 33.33. Found: C, 39.85; H, 4.70; Cl, 33.48.

3,4-Di-O-*acetyl-1,2,5-trichloro-1,2,5-trideoxy*-D-*arabinitol* (**10**). Yield 1,15 g (6%); m.p. 125–127°, R_F 0.52.

Anal. Calc. for $C_9H_{14}Cl_3O_4$: C, 37.05; H, 4.46; Cl, 36.54. Found: C, 37.51; H, 4.50; Cl, 36.54.

2,3,4-Tri-O-*acetyl-1,5-dichloro-1,5-dideoxyxylitol* (**12**). Yield 1.03 g, (5%); m.p. 65–66°, R_F 0.28.

Anal. Calc. for $C_{11}H_{16}Cl_2O_6$: C, 41.90; H, 5.08; Cl, 22.54. Found: C, 41.96; H, 5.12; Cl, 22.43.

2,3,5-Tri-O-*acetyl-1,4-anhydro*-DL-*xylitol* (**13**). Yield 3.08 g, (18%); syrup, R_F 0.18.

Anal. Calc. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.15. Found: C, 50.06; H, 6.00.

2,3-Di-O-*acetyl-1,4-anhydro-5-chloro-5-deoxy*-DL-*xylitol* (**14**). Yield 3.72 g (24%); syrup, R_F 0.37.

Anal. Calc. for $C_9H_{13}ClO_5$: C, 45.66; H, 5.50; Cl, 15.01. Found: C, 45.37; H, 5.75; Cl, 14.41.

2,3-Di-O-*acetyl-1,4,5-trichloro-1,4,5-trideoxy*-D-*arabinitol* (**15**). Yield 1.6 g (8%); m.p. 74–75, R_F 0.51.

Anal. Calc. for $C_9H_{13}Cl_3O_4$: C, 37.05; H, 4.46; Cl, 36.54. Found: C, 37.59; H, 4.59; Cl, 36.41.

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