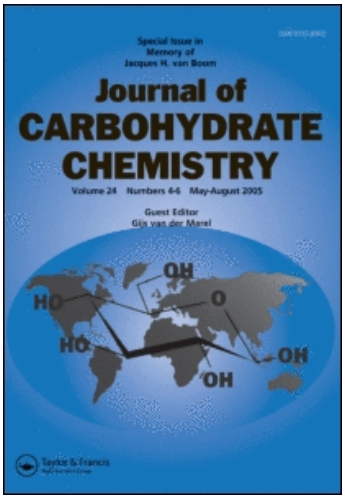

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Efficient Synthesis of Some Dichloroalditols: Direct Regioselective Chlorination of Some Unprotected Alditols by 1-Chlorocarbonyl-1-methylethyl Acetate

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EFFICIENT SYNTHESIS OF SOME DICHLOROALDITOLS: DIRECT REGIOSELECTIVE CHLORINATION OF SOME UNPROTECTED ALDITOLS BY 1-CHLOROCARBONYL-1-METHYLETHYL ACETATE

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ABSTRACT

Treatment of unprotected hexitols (D-glucitol, D-mannitol) and pentitols (D-arabinitol, xylitol and ribitol) with 1-chlorocarbonyl-1-methylethyl acetate ($Me_2C(OAc)COCl$), in 1,4-dioxane, leads to α,ω-dichloro derivatives in good yields. A route to some α,ω-dichloroacetoxy regioisomers has been elucidated.

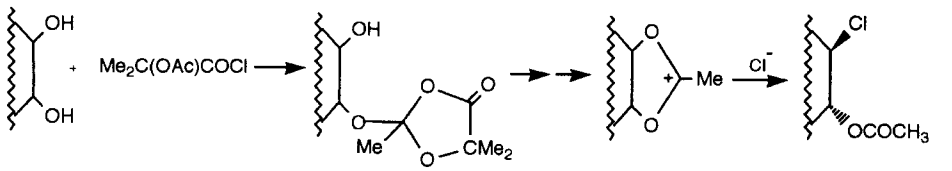
INTRODUCTION

We have often considered that the cyclodehydration taking place during the direct chlorination of unprotected alditols was essentially caused by either the acidic[1] or basic[2] reaction conditions used. Thus, we have shown that this chlorination was largely accompanied by cyclodehydration, even when the medium contained a mild base such as methanesulfonate ion ($CH_3SO_3^-$) formed during chlorination[3] by methanesulfonyl chloride (CH_3SO_2Cl) in DMF.[4] Absence in DMF of such a base when Vilsmeier's salt

($[Me_2N{=}CHCl]^+$, Cl^-)[3] was used, favours to a greater degree the formation of dichloroalditols.

Our work with the related Viehe's salt[5] ($[Me_2N{=}CCl_2]^+$, Cl^-) as a chlorinating reagent has enabled us to increase considerably the yield (70-79%) of dichloropentitols.[6] The intramolecular cyclisation was limited to D-glucitol. This interesting result may be due to the change in the conformation of the alditol and simultaneous protection of the hydroxyl groups eliminated during dehydration.

In order to complete our study on the direct chlorination of unprotected alditols, we now report our recent results in which chlorination is carried out by 1-chlorocarbonyl-1-methylethyl acetate ($Me_2C(OAc)COCl$ = RCOCl).[7] This reagent like Viehe's salt, reacts with two hydroxyl groups and the chlorination occurs via an acetoxonium ion.[8]



oxolanone acetoxonium ion chloroacetate

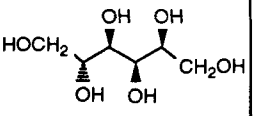
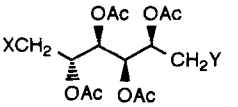
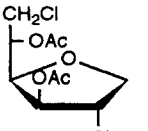
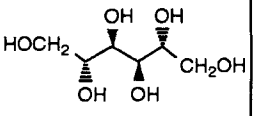
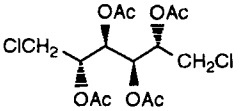
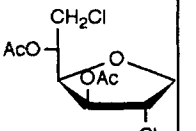
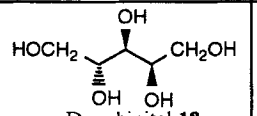
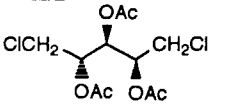
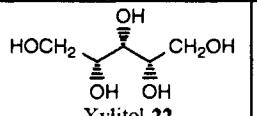
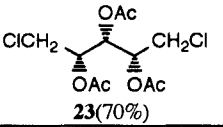
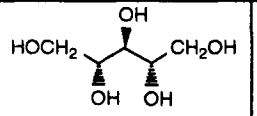
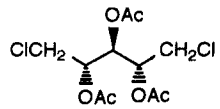
RESULTS AND DISCUSSION

D-Glucitol **1** was treated with acid chloride RCOCl (3 equiv., R.T., 4 h) in 1,4-dioxane to afford, after acetylation with acetic anhydride, 2,3,4,5-tetra-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-glucitol **2**[3] as the major product (52% yield). A mixture of by-products was also formed: 2,3,4,5,6-penta-*O*-acetyl-1-chloro-1-deoxy-D-glucitol **3** and 1,2,3,4,5-penta-*O*-acetyl-6-chloro-6-deoxy-D-glucitol **4** in total yield of 24%; traces of 3,5-di-*O*-acetyl-1,4-anhydro-2,6-dichloro-2,6-dideoxy-L-iditol **5** were also isolated (Table).

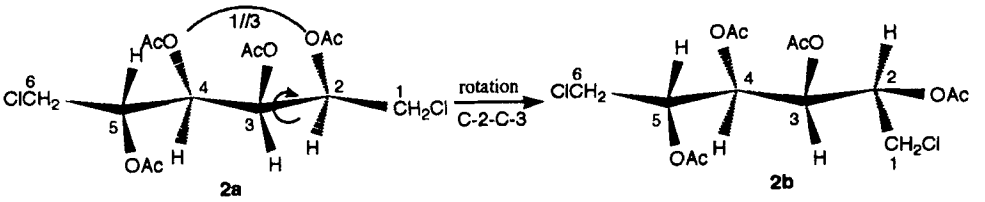
In the mixture of by-products, **3** and **4** were identified as hexitols with one primary CH_2Cl-group. 1,2,3,4,5-Penta-*O*-acetyl-6-chloro-6-deoxy-D-glucitol was prepared according to literature methods starting from methyl α-D-glucopyranoside,[9,10] this compound was identical with **4**. Hence **3** must be the 1-chloro derivative.

The ^1H NMR spectrum of **2** shows a sequence *anti*, *syn* and *anti* methine coupling constants (7 Hz, 3.5 Hz and 6.6 Hz, respectively). These values are consistent with the *anti* methine conformation **2b** resulting from C(2)-C(3) rotation due to 1,3-parallel interaction between AcO-2 and AcO-4 in a planar conformation **2a** (Scheme 1). The same

Table: Chlorination of unprotected alditols by 1-chlorocarbonyl-1-methylethyl acetate

Substrats [b]	RCOCl	Time/h	Isolated yield [a]	
 D-glucitol **1**	3	4	 **2** : X = Cl, Y = Cl (52%) **3** : X = OAc, Y = Cl **4** : X = Cl, Y = OAc	 **5**
 D-mannitol **6**	2,5	76	 **7**(64%)	 **8**(8%)
 D-arabinitol **18**	4	17	 **19**(80%)	
 Xylitol **22**	4	17	 **23**(70%)	
 Ribitol **24**	4	17	 **25**(72%)	

R = $Me_2C(OAc)$-, [a] after acetylation with Ac_2O in pyridine, [b] 5 10^{-2} g/mL, solvent: 1,4-dioxane, R.T.



Scheme 1

coupling constant sequence was observed in **3** ($J_{2,3}$ = 6.6 Hz, $J_{3,4}$ = 3.8 Hz and $J_{4,5}$ = 7.2 Hz) and **4** ($J_{2,3}$ = 5.9 Hz, $J_{3,4} \approx 3$ Hz and $J_{4,5}$ = 6 Hz).

To identify unambiguously the H-1 and H-6 in **2**, we established a correlation between the chemical shifts of **2**, **3** and **4** (Figure). For **3** and **4**, the chemical shifts of both H-2 and H-5 are unmodified by the vicinal RCH_2-group (R = Cl or AcO). If H-4 shows the same behaviour in **3** and **4**, the H-3 is shielded in **4**. This effect can be attributed to the anisotropy of the acetoxy group of C-1 in the non planar conformation of **4**. This correlation leads us to the assignment of H-2, H-3, H-4 and H-5 in **2** derivative and consequently H-1a, H-1b and H-6a, H-6b.

The *trans* configuration of the vicinal protons H-2, H-3 in 2,6-dichloro-1,4-anhydro derivative **5** was indicated from the coupling constant $J_{2,3} \approx 0$ Hz. The 3,6-anhydro formation[6,13] probably took place by attack of the 3-OH on an 5,6-acetoxonium ion. This left an acetoxy group at C-5, which could form a 4,5-acetoxonium ion. Subsequent opening at C-5 by Cl^- would cause inversion at this carbon.

Chlorination (2.5 equiv. RCOCl, R.T., 76 h) followed by acetylation of D-mannitol **6**, gives mainly 2,3,4,5-tetra-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol **7**[3] in 64% yield. Under these conditions only a small quantity of 3,5-di-*O*-acetyl-1,4-anhydro-2,6-dichloro-2,6-dideoxy-D-glucitol **8** was formed (8%). As with the anhydro derivative **5**, compound **8** shows a *trans* configuration of methine protons H-2, H-3 with a value of $J_{2,3}$ = 0 Hz; S_N2 chlorination at C-2 proceeds similarly. Due to the *C2* symmetry axis of the D-mannitol, **8** obtained from 1,4-anhydro-D-mannitol was identical to that of 6,3-anhydro derivative.

To elucidate the route leading to 1,6-dichloro derivatives, the crude product obtained before acetylation was chromatographed on GLC. The D-glucitol **1** gave two major fractions: **A** (the less polar and minor fraction) and **B** (the more polar and major fraction) (Scheme 2).

Fraction **A** was a mixture of 2,5-di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-3,4-*O*-isopropylidene-D-glucitol **9** and another derivative which was identified as either 4,5-di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-2,3-*O*-isopropylidene-D-glucitol **10a** or 2,3-di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-4,5-*O*-isopropylidene-D-glucitol **10b**. The acetonisation[11] of fraction **B** leads to the same derivatives **9** and **10a** or **10b**. The structure of **10a** or **10b** could not be distinguished using NMR spectroscopy. Investigation of the products formed, showed that they could be mono-isopropylidene derivatives (**9**, **10**) or partly acetylated products having two free hydroxyl groups (**11**, **12**). While formation of the latter is not surprising (see ref. 8), formation of the former was unexpected.

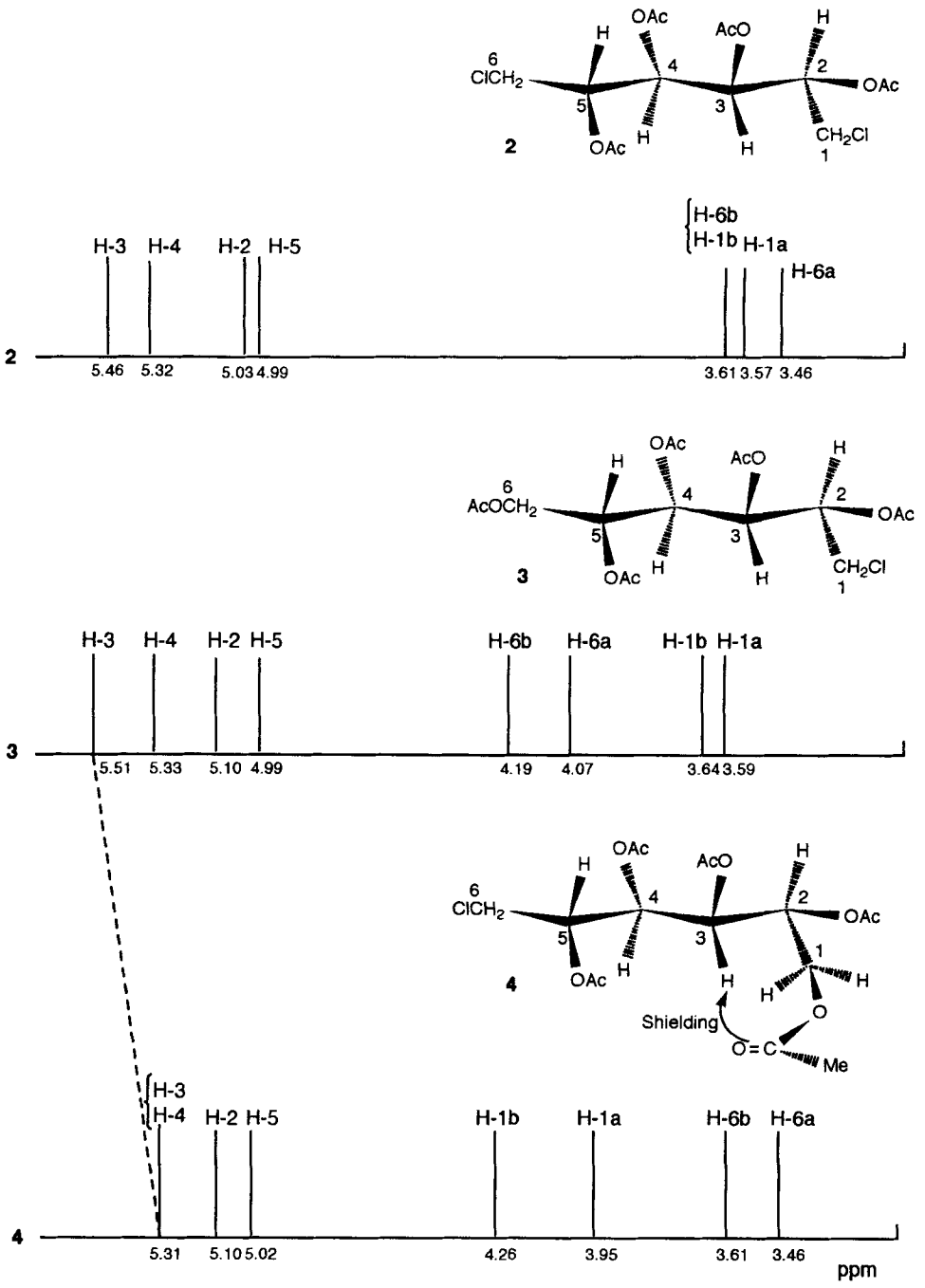
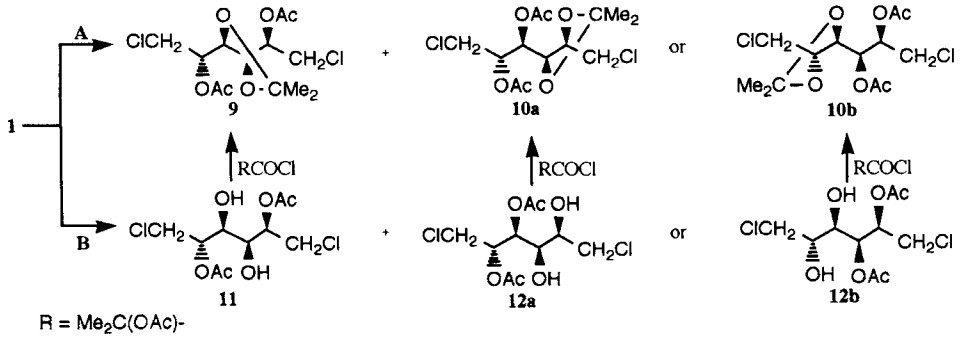


Figure: ^{1}H NMR shift correlations for **2**, **3** and **4** derivatives



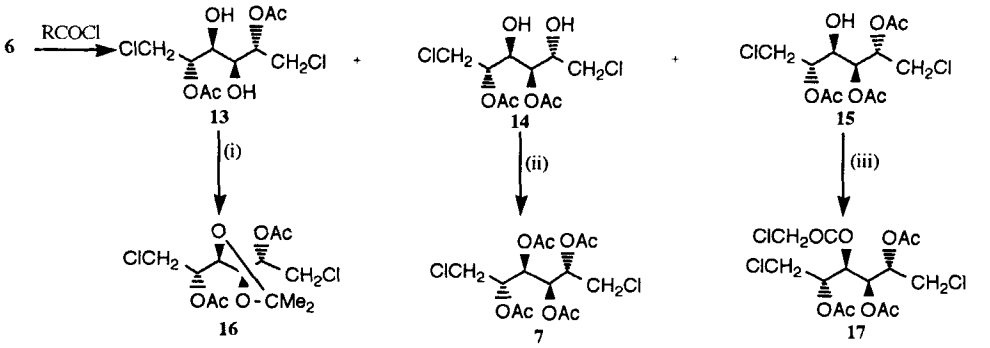
Scheme 2

By a similar route, chlorination of D-mannitol **6** gave 2,5-di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol **13** as the main product, the structure of which was confirmed by conversion to its 3,4-*O*-isopropylidene derivative **16** (Scheme 3). D-mannitol **6** also gave 3,5-di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol **14** as a by-product which was peracetylated to give **7**, and 2,3,5-tri-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol **15** which was also identified by conversion to its 4-*O*-chloroacetyl derivative **17** after chloroacetylation.[12]

In contrast with Viehe's salt,[6] 1-chlorocarbonyl-1-methylethyl acetate does not react exclusively with vicinal hydroxyl groups at the end of a chain of unprotected hexitols; instead it gives mixtures of acetoxy regioisomers. However, chlorination is effected mainly at primary carbon atoms.

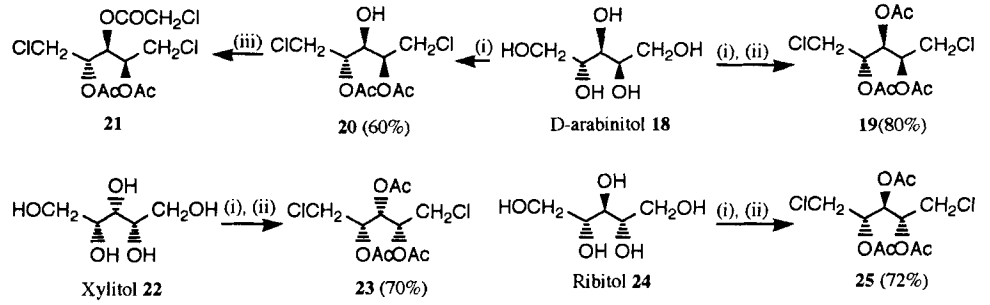
Chlorination of pentitols gave excellent results. D-Arabinitol (**18**), xylitol (**22**) and ribitol (**24**) (4 equiv. RCOCl, R.T., 17 h) gave, after acetylation, the corresponding 2,3,4-tri-*O*-acetyl-1,5-dichloro-1,5-dideoxy derivatives **19** , **23** and **25** (Scheme 4) in yields of 80%, 70% and 72%, respectively. When chlorination was not followed by acetic anhydride treatment, only D-arabinitol **18** gave 2,4-di-*O*-acetyl-1,5-dichloro-1,5-dideoxy-D-arabinitol **20** (60%) as the major product; its structure was confirmed by conversion[12] to its 3-*O*-chloroacetyl derivative **21**. The ^{1}H NMR signal corresponding to H-3 in compound **20** (4.18 ppm) is shifted to 5.56 ppm in compound **21**. Xylitol (**22**) and ribitol (**24**) led, under the same conditions, to mixtures of inseparable 1,5-dichloro acetoxy regioisomers.

In conclusion, the utilisation of 1-chlorocarbonyl-1-methylethyl acetate as chlorinating reagent leads to α,ω-dichloroalditols in high yields. As with the Viehe's salt, the competitive dehydration reaction usually observed was minimized. This interesting



(i) Acetone 5% H_2SO_4 (ii) Ac_2O/pyridine (iii) $ClCH_2COCl$, pyridine/CH_2Cl_2 R = $Me_2C(OAC)$-

Scheme 3



(i) 4 equiv. $Me_2C(OAc)COCl$, 1,4-dioxane, R.T., 17h (ii) Ac_2O/pyridine (iii) $ClCH_2COCl$, pyridine/CH_2Cl_2

Scheme 4

result is attributed to the simultaneous protection of the hydroxyl groups involved in the dehydration reaction.

EXPERIMENTAL

General Methods. Melting points were determined with an Electrothermal 1A 9200 digital melting point apparatus and are uncorrected. Optical rotations were measured with DIP-370 digital polarimeter. ^1H and ^{13}C NMR spectra were recorded with Bruker 300 WB spectrometer Aspect 3000 and chemical shifts are reported in δ units (ppm) relative to Me_4Si. All ^{13}C spectra are assigned through 2D XH-correlated spectra in accord with the

XHCORRD.AUR program. TLC was performed on silica gel 60F-254 (Merck, 230 mesh) with hexane-ethyl acetate as eluent, and zones were detected by vanillin-H_2SO_4 reagents. The silica gel used in column chromatography was 35-70 μ (Amicon).

General Procedure. To a suspension of alditol (D-glucitol **1**, D-mannitol **6**, D-arabinitol **18**, xylitol **22** and ribitol **24**) in dry 1,4-dioxane, was added 1-chlorocarbonyl-1-methylethyl acetate (Aldrich) under conditions reported in the Table. The mixture was stirred during the time indicated in the Table. Evaporation of the solvent gave a syrup which was treated overnight with an excess of acetic anhydride in anhydrous pyridine. The solvent was removed and the residue was passed through a column of silica gel with hexane-ethyl acetate as eluent.

The following hexitol and pentitol derivatives were prepared according to this general procedure.

2,3,4,5-Tetra-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-glucitol (**2**). mp 53-55 °C, $[\alpha]_D^{22}$ + 40.6° (*c* 1.22, chloroform), R_f 0.47 (5:2, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (dd, H-1a, $J_{1a,1b}$ =12.3 Hz, $J_{1a,2}$ = 4.5Hz), 3.61 (dd, H-1b, $J_{1b,2}$ = 3.8 Hz), 5.03 (m, H-2, $J_{2,3}$ = 6.6 Hz), 5.46 (dd, H-3, $J_{3,4}$ = 3.5 Hz), 5.32 (dd, H-4, $J_{4,5}$ = 7 Hz), 4.99 (m, H-5, $J_{5,6a}$ = 5.6 Hz, $J_{5,6b}$ = 4.8 Hz), 3.46 (dd, H-6a, $J_{6a,6b}$ = 12.4 Hz), 3.62 (dd, H-6b), 2.07 (3H), 2.01 (3H), 2 (3H), 1.99 (3H) (CH_3CO); ^{13}C NMR δ 42.06 (C-1), 70.45 (C-2), 68.39 (C-3), 68.87 (C-4), 69.60 (C-5), 42.20 (C-6), 20.25, 20.08 ($\underline{C}H_3CO$), 169.41, 169.21, 168.85 ($CH_3\underline{C}O$)

Anal. Calcd for $C_{14}H_{20}Cl_2O_8$: C, 43.41; H, 5.17; Cl, 18.35. Found: C, 43.50; H, 5.31; Cl, 18.05.

Derivatives **3** and **4** were obtained in a total yield of 24%. Compound **3** was extracted in pure form by recrystallization of the mixture in absolute ethanol. Compound **4** was identified in the mixture using NMR spectroscopy.

2,3,4,5,6-Penta-*O*-acetyl-1-chloro-1-deoxy-D-glucitol (**3**). mp 105-106 °C, $[\alpha]_D^{22}$ +22.8° (*c* 0.26, acetone); ^1H NMR (300 MHz, $CDCl_3$) δ 3.59 (dd, H-1a, $J_{1a,1b}$ =12.3 Hz, $J_{1a,2}$ = 4.8Hz), 3.64 (dd, H-1b, $J_{1b,2}$ = 5 Hz), 5.1 (m, H-2, $J_{2,3}$ = 6.6 Hz), 5.51 (dd, H-3, $J_{3,4}$ = 3.8 Hz), 5.33 (dd, H-4, $J_{4,5}$ = 7.2 Hz), 4.99 (m, H-5, $J_{5,6a}$ = 5.2 Hz, $J_{5,6b}$ = 3.6 Hz), 4.07 (dd, H-6a, $J_{6a,6b}$ = 12.4 Hz), 4.19 (dd, H-6b), 2.06 (3H), 2.04 (3H), 2.01 (3H), 2 (3H), 1.99 (3H) (CH_3CO; ^{13}C NMR δ 41.87 (C-1), 70.52 (C-2), 68.47 (C-3, C-4), 68.37 (C-5), 61.25 (C-6), 20.53, 20.32 ($\underline{C}H_3CO$), 170.30, 169.78, 169.63, 169.41 ($CH_3\underline{C}O$).

Anal. Calcd for $C_{16}H_{23}ClO_{10}$: C, 46.77; H, 5.60; Cl, 8.65. Found: C, 46.18; H, 5.52; Cl, 8.73.

The pure product **4** was prepared in five steps starting from methyl α-D-glucopyranoside according to the procedure described by waites and coworkers[10] (mp 69 °C).

1,2,3,4,5-Penta-*O*-acetyl-6-chloro-6-deoxy-D-glucitol (4). mp 68.8-69.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (dd, H-1a, $J_{1a,1b}$ =12.2 Hz, $J_{1a,2}$ = 6 Hz), 4.26 (dd, H-1b, $J_{1b,2}$ = 3.8 Hz), 5.1 (m, H-2, $J_{2,3}$ = 5.9 Hz), 5.31 (dd, H-3), 5.31 (dd, H-4, $J_{4,5}$ = 6 Hz), 5.02 (m, H-5, $J_{5,6a}$ = 5.7 Hz, $J_{5,6b}$ = 3.8 Hz), 3.46 (dd, H-6a, $J_{6a,6b}$ = 12.2 Hz), 3.61 (dd, H-6b), 2.04 (3H), 1.98 (3H), 1.97 (3H), 1.96 (3H), 1.95 (3H) (CH_3CO),; ^{13}C NMR δ 61.66 (C-1), 69.23 (C-2), 69.08 (C-3), 68.13 (C-4), 69.87 (C-5), 42.13 (C-6),20.47, 20.30 ($\underline{C}H_3CO$), 169.47, 169.65, 170.12 ($CH_3\underline{C}O$).

Anal. Calcd for $C_{16}H_{23}ClO_{10}$: C, 46.77; H, 5.60; Cl, 8.65. Found: C, 46.89; H, 5.69; Cl, 8.59.

2,5-Di-*O*-acetyl-1,4-anhydro-2,6-dichloro-2,6-dideoxy-L-iditol (5). R_f 0.54 (4:1, hexane-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (dd, H-1a, $J_{1a,1b}$ =10.4 Hz, $J_{1a,2}$ = 1.1 Hz), 4.27 (dd, H-1b, $J_{1b,2}$ = 4.5 Hz), 4.17 (d, H-2, $J_{2,3}$ = 0 Hz), 5.33 (d, H-3, $J_{3,4}$ = 3.4 Hz), 4.43 (dd, H-4, $J_{4,5}$ = 9.3 Hz), 5.13 (m, H-5, $J_{5,6a}$ = 4.9 Hz, $J_{5,6b}$ = 2.9 Hz), 3.67 (dd, H-6a, $J_{6a,6b}$ = 12.2 Hz), 2.80 (dd, H-6b), 1.99 (3H), 1.98 (3H) (CH_3CO); ^{13}C NMR δ 74.74 (C-1), 59.32 (C-2), 77.33 (C-3), 76.94 (C-4), 68.55 (C-5), 44.67 (C-6), 20.54 ($\underline{C}H_3CO$),169.47, 169.06 ($CH_3\underline{C}O$).

2,3,4,5-Tetra-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol (7). mp 131-132 °C, $[\alpha]_D^{22}$ + 36.1° (*c* 1.41, chloroform), R_f 0.42 (5:2, hexane-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (dd, H-1a, H-6a, $J_{1a,1b} = J_{6a,6b}$ = 12.3 Hz, $J_{1a,2} = J_{5,6a}$ = 5.5 Hz), 3.62 (dd, H-1b, H-6b, $J_{1b,2} = J_{5,6b}$ = 3.6 Hz), 5.04 (m, H-2 = H-5, $J_{2,3} = J_{4,5}$ = 8.4 Hz), 5.36 (d, H-3 = H-4, $J_{3,4}$ = 0 Hz), 2.03 (6H), 2.04 (6H) (CH_3CO); ^{13}C NMR δ 42.77 (C-1, C-6), 69.10 (C-2, C-5), 68.28 (C-3, C-4), 20.60, 20.49 ($\underline{C}H_3CO$), 169.64, 169.46 ($CH_3\underline{C}O$).

Anal. Calcd for $C_{14}H_{20}Cl_2O_8$: C, 43.41; H, 5.17; Cl, 18.35. Found: C, 43.19; H, 5.22; Cl, 18.18.

3,5-Di-*O*-acetyl-1,4-anhydro-2,6-dichloro-2,6-dideoxy-D-glucitol (8). mp 44-48 °C, R_f 0.48 (3:2, hexane-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (dd, H-1a, $J_{1a,1b}$ =10.4 Hz, $J_{1a,2}$ = 0 Hz), 4.28 (dd, H-1b, $J_{1b,2}$ = 4.5 Hz), 4.18 (m, H-2, $J_{2,3}$ = 0 Hz), 5.96 (dd, H-3, $J_{3,4}$ = 3.3 Hz), 4.45 (dd, H-4, $J_{4,5}$ = 9.4 Hz), 5.14 (m, H-5, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.7 Hz), 3.70 (dd, H-6a, $J_{6a,6b}$ = 12.2 Hz), 3.82 (dd, H-6b), 1.97 (3H), 1.98 (3H) (CH_3CO); ^{13}C NMR δ 74.77 (C-1), 59.32 (C-2), 77.29 (C-3), 76.90 (C-4), 68.52 (C-5), 44.72 (C-6), 20.62 ($\underline{C}H_3CO$), 169.56, 169.15 ($CH_3\underline{C}O$).

Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.11; H, 4.91; Cl, 24.91. Found: C, 42.16; H, 4.74; Cl, 24.56.

2,3,4-Tri-*O*-acetyl-1,5-dichloro-1,5-dideoxy-D-arabinitol (19).[4] mp 75-76 °C, $[\alpha]_D^{22}$ +42° (*c* 2.4, ethyl acetate), R_f 0.46 (4:1, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.41 (dd, H-1a, $J_{1a,1b}$ =11.5 Hz, $J_{1a,2}$ = 7.3 Hz), 3.49 (dd, H-1b, $J_{1b,2}$ = 6 Hz), 5.28 (m, H-2, $J_{2,3}$ = 2.2 Hz), 5.41 (dd, H-3, $J_{3,4}$ = 8.7 Hz), 5.12 (m, H-4, $J_{4,5a}$ = 5.2 Hz, $J_{4,5b}$ = 3.3), 3.53 (dd, H-5a, $J_{5a,5b}$ = 12.4 Hz), 3.64 (dd, H-5b), 2.03 (6H), 2.08 (3H) (CH_3CO); ^{13}C NMR δ 41.79 (C-1), 69.86 (C-2), 69.32 (C-3), 69.06 (C-4), 42.96 (C-5), 20.49, 20.60 ($\underline{C}H_3CO$), 169.41, 169.42, 169.77 ($CH_3\underline{C}O$).

Anal. Calcd 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.

2,3,4-Tri-*O*-acetyl-1,5-dichloro-1,5-dideoxy-xylitol (22).[4] mp 65-66 °C, R_f 0.28 (4:1, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 (dd, H-1a, H-5a, $J_{1a,1b} = J_{5a,5b}$ = 12.2 Hz, $J_{1a,2} = J_{4,5a}$ = 5.6 Hz), 3.51 (dd, H-1b, H-5b, $J_{1b,2} = J_{4,5b}$ = 4.9 Hz), 5.06 (m, H-2, H-4, $J_{2,3} = J_{3,4}$ = 5 Hz), 5.39 (t, H-3), 2.08 (3H), 2.07 (6H) (CH_3CO); ^{13}C NMR δ 42.15 (C-1, C-5), 70.44 (C-2, C-4), 69.56 (C-3), 20.56, 20.36 ($\underline{C}H_3CO$), 169.44, 169.81 ($CH_3\underline{C}O$).

2,3,4-Tri-*O*-acetyl-1,5-dichloro-1,5-dideoxy-ribitol (23).[4] R_f 0.35 (4:1, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 (dd, H-1a, H-5a, $J_{1a,1b} = J_{5a,5b}$ = 12.1 Hz, $J_{1a,2} = J_{4,5a}$ = 6.9 Hz), 3.62 (dd, H-1b, H-5b, $J_{1b,2} = J_{4,5b}$ = 3 Hz), 5.1 (m, H-2 = H-4, $J_{2,3} = J_{3,4}$ = 5.2 Hz), 5.18 (t, H-3), 2.06 (6H), 2.02 (3H) (CH_3CO); ^{13}C NMR δ 42.25 (C-1, C-5), 70.90 (C-2, C-4), 70.11 (C-3), 20.51, 20.41 ($\underline{C}H_3CO$), 168.97, 169.52 ($CH_3\underline{C}O$).

When chlorination of D-glucitol **1** (3 equiv. RCOCl, 4 h) is not followed by acetylation, the crude product gave two main fractions **A** ($R_f > 0.77$) and **B** ($R_f < 0.54$)by separation on silica gel using 3:2, hexane-ethyl acetate as eluent. A second separation of fraction **A** on silica gel with 5:1, hexane-ethyl acetate as eluent gives the following products:

2,5-Di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-3,4-*O*-isopropylidene-D-glucitol (9). R_f 0.64 (4:1, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (dd, H-1a, $J_{1a,1b}$ =11.1 Hz, $J_{1a,2}$ = 6.3 Hz), 3.62 (dd, H-1b, $J_{1b,2}$ = 6.7 Hz), 4.96 (m, H-2, $J_{2,3}$ = 2.9 Hz), 5.33 (dd, H-3, $J_{3,4}$ = 7 Hz), 3.85 (t, H-4, $J_{4,5}$ = 7.8 Hz), 5.01 (m, H-5, $J_{5,6a}$ = 5.4 Hz, $J_{5,6b}$ = 3.2 Hz), 3.65 (dd, H-6a, $J_{6a,6b}$ = 12.1 Hz), 3.8 (dd, H-6b), 2 (6H) (CH_3CO), 1.36 (3H), 1.34 (3H) (($\underline{C}H_3)_2C<$); ^{13}C NMR δ 41.05 (C-1), 70.45 (C-2), 76.55 (C-3), 73.57 (C-4), 72.18 (C-5), 42.50 (C-6), 19.74 ($\underline{C}H_3CO$), 169.03, 169.91 ($CH_3\underline{C}O$), 26.28, 25.70 (($\underline{C}H_3)_2C<$), 109.87 (($CH_3)_2\underline{C}<$).

2,3-Di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-4,5-*O*-isopropylidene-D-glucitol (10a) or **4,5-Di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-2,3-*O*-isopropylidene-D-glucitol (10b)**. R_f 0.58 (4:1, hexane-ethyl acetate). ^1H NMR (300 MHz, C_5D_5N) δ 3.94 (dd, H-1a, $J_{1a,1b}$ =12.3 Hz, $J_{1a,2}$ = 6.8 Hz), 4.24 (dd, H-1b, $J_{1b,2}$ = 2.7 Hz), 5.68 (m, H-2), 5.68 (m, H-3, $J_{3,4}$ = 1.5 Hz), 4.49 (t, H-4, $J_{4,5}$ = 7.5 Hz), 4.27 (m, H-5, $J_{5,6a}$ = 5.2 Hz, $J_{5,6b}$ = 4.9 Hz), 3.83 (dd, H-6a, $J_{6a,6b}$ = 12.2 Hz), 3.89 (dd, H-6b), 2.1 (3H), 2 (3H) ($\underline{C}H_3CO$), 1.33 (3H), 1.35 (3H) (($\underline{C}H_3)_2C<$); ^{13}C NMR δ 43.79 (C-1), 72.89 (C-2), 69.87 (C-3), 77.92 (C-4), 76.75 (C-5), 44.49 (C-6),20.55 ($\underline{C}H_3CO$),169.94, 170.33 ($CH_3\underline{C}O$), 26.84 (($\underline{C}H_3)_2C<$), 110.66 (($CH_3)_2\underline{C}<$).

The most polar fraction **B** gave after acetonisation,[11] the same dichloromonoisopropylidene derivatives **9** and **10** as those obtained from fraction **A**.

Chlorination of D-mannitol **6** with 2.5 equivalents of RCOCl for 76 h, gave after separation by silica gel chromatography, 1,6-dichloro derivatives **13** and **14** using 2:1, hexane-ethyl acetate and **15** with 1:1, hexane-ethyl acetate as the eluent.

2,5-Di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol (13). R_f 0.6 (1:1, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (dd, H-1a, H-6a, $J_{1a,1b} = J_{6a,6b}$ = 12.1 Hz, $J_{1a,2} = J_{5,6a}$ = 4.9 Hz), 3.89 (dd, H-1b, H-6b, $J_{1b,2} = J_{5,6b}$ = 2.7 Hz), 5 (m,H-2, H-5, $J_{2,3} = J_{4,5}$ = 9 Hz), 5.67 (d, H-3, H-4, $J_{3,4}$ = 0 Hz), 2.09 (6H) (CH_3CO), 4.67 (2H, OH); ^{13}C NMR δ 43.88 (C-1, C-6), 71.43 (C-2, C-5), 67.33 (C-3, C-4), 20.56 ($\underline{C}H_3CO$), 170.98 ($CH_3\underline{C}O$).

3,5-Di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol (14). R_f 0,52 (1:1, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (dd, H-1a, $J_{1a,1b}$ = 11.5 Hz, $J_{1a,2}$ = 6.8 Hz), 3.63 (dd, H-1b, $J_{1b,2}$ = 3.4 Hz), 4.11 (m, H-2, $J_{2,3}$ = 7.8 Hz), 5.08 (dd, H-3, $J_{3,4}$ = 1 Hz), 4.34 (dd, H-4, $J_{4,5}$ = 8 Hz), 4.91 (m, H-5, $J_{5,6a}$ = 3.2 Hz, $J_{5,6b}$ = 3.2 Hz), 3.82 (m, H-6a), 3.82 (m, H-6b), 2.05 (3H), 2.04 (3H) (CH_3CO); ^{13}C NMR δ 45.90 (C-1), 69.30 (C-2), 70.71 (C-3), 66.81 (C-4), 69.20 (C-5), 43.20 (C-6), 19.76, 19.84 ($\underline{C}H_3CO$), 169.53, 169.42 ($CH_3\underline{C}O$).

2,3,5-Tri-*O*-acetyl-1,6-dichloro-1,6-dideoxy-D-mannitol (15). R_f 0.7 (1:1, hexane-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (dd, H-1a, $J_{1a,1b}$ =12.2 Hz, $J_{1a,2}$ = 7.4 Hz), 3.67 (dd, H-1b, $J_{1b,2}$ = 3 Hz), 5.23 (m, H-2, $J_{2,3}$ = 7.4 Hz), 5.11 (dd, H-3, $J_{3,4}$ = 1 Hz), 3.94 (dd, H-4, $J_{4,5}$ = 9.1 Hz), 4.84 (m, H-5, $J_{5,6a}$ = 3.1 Hz, $J_{5,6b}$ = 3.6 Hz), 3.78 (dd, H-6a, $J_{6a,6b}$ = 12.3 Hz), 3.74 (dd, H-6b), 2.02 (3H), 2.04 (3H), 2.13 (3H) (CH_3CO); ^{13}C NMR δ 43.13 (C-1), 71.37 (C-2), 69.50 (C-3), 67.19 (C-4), 69.65 (C-5), 44.10 (C-6), 20.73, 20.55 ($\underline{C}H_3CO$), 169.75, 169.98, 171.30 ($CH_3\underline{C}O$).

2,5-Di-*O*-acetyl-1,6-dichloro-1,6-dideoxy-3,4-*O*-isopropylidene-D-mannitol (16). Compound **16** was obtained in 70% yield by acetonisation[11] of **13**,

$[\alpha]_D^{22}$ + 27.1° (*c* 1.53, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (dd, H-1a, H-6a, $J_{1a,1b} = J_{6a,6b} = 12.1$ Hz, $J_{1a,2} = J_{5,6a} = 5.8$ Hz), 3.74 (dd, H-1b, H-6b, $J_{1b,2} = J_{5,6b} =$ 3.6 Hz), 5.05 (m,H-2, H-5, $J_{2,3} = J_{4,5} = 1.1$ Hz), 4.10 (dd, H-3, H-4, $J_{3,4} = 4.9$ Hz), 2.09 (6H) (CH_3CO), 1.34 (6H) ($(\underline{C}H_3)_2C<$); ^{13}C NMR δ 42.71 (C-1, C-6), 72.96 (C-2, C-5), 77.11 (C-3, C-4), 20.61 ($\underline{C}H_3CO$), 169.78 ($CH_3\underline{C}O$), 26.95 ($(\underline{C}H_3)_2C<$), 111.24 ($(CH_3)_2\underline{C}<$).

2,3,5-Tri-*O*-acetyl-4-*O*-chloroacetyl-1,6-dichloro-1,6-dideoxy-D-mannitol (17). Compound **17** was obtained in 63% yield by chloroacetylation[12] of **15**, mp. 115-117, $[\alpha]_D^{22}$ + 30.9° (*c* 1.18, chloroform). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46 (dd, H-1a, $J_{1a,1b}$ =12.3 Hz, $J_{1a,2} = 5.6$ Hz), 3.63 (dd, H-1b, $J_{1b,2} = 3.5$ Hz), 5.05 (m, H-2, $J_{2,3} = 8.6$ Hz), 5.41 (dd, H-3, $J_{3,4} = 2.3$ Hz), 5.44 (dd, H-4, $J_{4,5} = 8.4$ Hz), 5.06 (m, H-5, $J_{5,6a} = 5.2$ Hz, $J_{5,6b} = 3.7$ Hz), 3.49 (dd, H-6a, $J_{6a,6b} = 12.4$ Hz), 3.65 (dd, H-6b), 2.06, 2.05 (9H, CH_3CO), 4.04 (2H) ($ClCH_2CO$); ^{13}C NMR δ 42.71 (C-1), 69.05 (C-2), 68.05 (C-3), 70.04 (C-4), 68.89 (C-5), 42.49 (C-6), 20.62, 20.51 ($\underline{C}H_3CO$), 169.78, 169.60, 169.40 ($CH_3\underline{C}O$), 40.30 ($Cl\underline{C}H_2CO$), 166.27 ($ClCH_2\underline{C}O$).

Chlorination of D-arabinitol **18** (4 equiv. RCOCl, R.T., 18 h) followed by separation on silica gel with 2:1, hexane-ethyl acetate as eluent gave derivative **20** in 60% yield.

2,4-Di-*O*-acetyl-1,5-dichloro-1,5-dideoxy-D-arabinitol (20). R_f 0.36 (5:1, hexane-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (dd, H-1a, $J_{1a,1b}$ =11 Hz, $J_{1a,2} = 6.7$ Hz), 3.67 (dd, H-1b, $J_{1b,2} = 7.4$ Hz), 5.1 (m, H-2, $J_{2,3} = 1.7$ Hz), 4.18 (dd, H-3, $J_{3,4} = 9.3$ Hz), 4.93 (m, H-4, $J_{4,5a} = J_{4,5a} = 3.6$ Hz), 3.80 (dd, H-5a, $J_{5a,5b}$ = 16.3 Hz), 3.86 (dd, H-5b), 4.44 (1H, OH), 2.4 (3H), 2.03 (3H) (CH_3CO); ^{13}C NMR δ 41.01 (C-1), 71.04 (C-2), 67.83 (C-3), 70.39 (C-4), 44.03 (C-5), 20.67, 20.55 ($\underline{C}H_3CO$), 169.96, 170.12 ($CH_3\underline{C}O$).

2,4-Di-*O*-acetyl-3-*O*-chloroacetyl-1,5-dichloro-1,5-dideoxy-D-arabinitol (21). Compound **21** was obtained by chloroacetylation[12] of **20**. R_f 0.39 (5:1, hexane-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (dd, H-1a, $J_{1a,1b}$ =11.6 Hz, $J_{1a,2} = 7$ Hz), 3.53 (dd, H-1b, $J_{1b,2} = 6.2$ Hz), 5.37 (m, H-2, $J_{2,3} = 2.4$ Hz), 5.56 (dd, H-3, $J_{3,4} = 8$ Hz), 5.23 (dd, H-4, $J_{4,5a} = 5.2$ Hz, $J_{4,5b} = 3.4$ Hz), 5.06 (m, H-5a, $J_{5a,5b} = 12.42$ Hz), 2.12 (3H), 2.11 (3H), 4.14 (2H) ($ClCH_2CO$); ^{13}C NMR δ 41.25 (C-1), 69.36 (C-2), 70.91 (C-3), 68.74 (C-4), 42.38 (C-5), 20.27, 20.17 ($\underline{C}H_3CO$), 169.36, 169.24 ($CH_3\underline{C}O$), 39.96 ($Cl\underline{C}H_2CO$), 165.86 ($ClCH_2\underline{C}O$).

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