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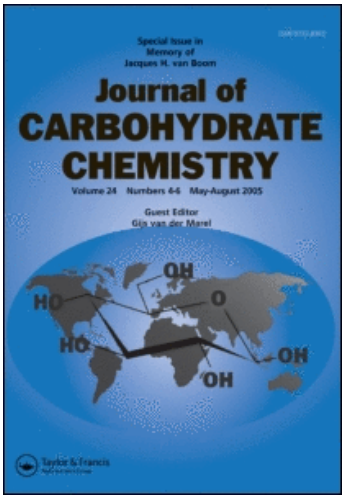

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Synthesis and Acidic Opening of Chlorinated Carbohydrate Orthoacetates

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COMMUNICATION

SYNTHESIS AND ACIDIC OPENING OF CHLORINATED CARBOHYDRATE ORTHOACETATES

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Acid-catalysed opening of five- and six-membered cyclic orthoesters of hexopyranosides is well explored and often used in synthetic pathways.[1-7] Opening of a five-membered ring orthoacetate or benzoate (formed from *cis-vic*-diols) gives the axial ester,[1,2] contrary to most other regioselective methods which give preferentially the equatorial ester, whereas opening of six-membered ring 4,6-orthoesters give a mixture of 4- and 6-esters, the ratio depending in part on the substituent at O-3 and on the amount of acyl migration during the reaction conditions.[3,4] Since chlorinated acetates (mono-, di- and tri-) are selectively removable in the presence of acetates and benzoates,[8] their introduction by means of the acidic opening of the corresponding orthoacetate could give a route to a flexible protecting group scheme with regioselective introduction of the selectively removable chloroacetate. This would open up a suitable way for synthesis of, *inter alia*, branched oligosaccharides. Therefore, mono-, di- and trichloroorthoacetates (both five- and six-membered) of different monosaccharide derivatives were synthesized and their acidic opening studied.

All orthoesters were synthesized by transesterification under acidic conditions of the corresponding trimethyl orthochloroacetates.[9,10] To form the di-and trichloroorthoacetates more reagent and stronger conditions, obtained by evaporating off the solvent during the reaction, were required. According to TLC, the yield was quantitative with mono-and dichloroorthoesters, but the formation of trichloroorthoacetates was more sluggish and gave, starting from the diol **8**, only around 50% of the desired cyclic trichloroorthoester **10**, together with starting material and 20% of a product which was

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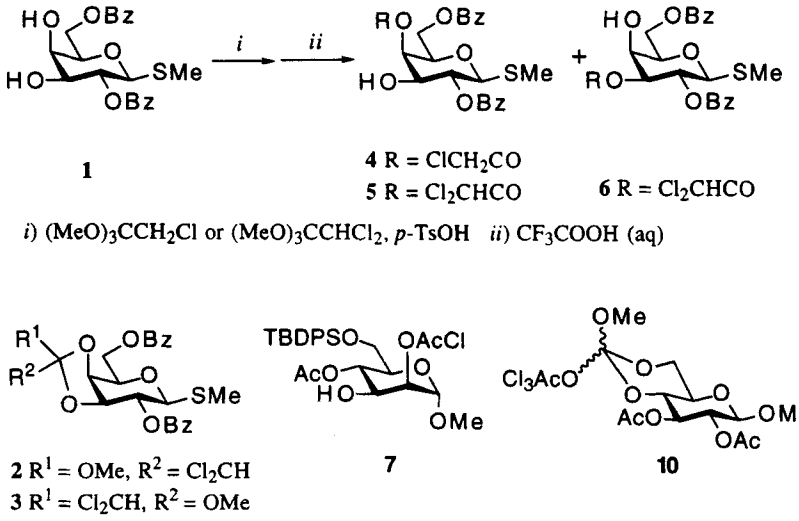

Scheme 1

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identified as a mixed open orthoester. Normally, the orthoesters were not isolated but directly opened up under acidic conditions to give the corresponding chloroacetates.

As expected the introduction of the electron withdrawing chlorine atoms meant that, as was also observed in the formation of the orthoesters, the opening of the chlorinated orthoesters required longer time and/or more acidic conditions compared to ordinary orthoacetates. Thus, monochloroorthoacetates could be opened using the same conditions as with orthoacetates but the reaction time was prolonged from almost instantaneous to around one hour. The dichloroacetates were opened using twice the amount of acid containing more water (30% instead of 10%) and also here evaporation of the solvent was used to speed up the reaction. The trichloroorthoacetate **10** under the stronger conditions necessary for reaction gave mainly hydrolysis of the orthoester back to the starting diol **8**. Due to this result, together with the low yield obtained in the formation of **10**, this line of approach to trichloroacetates was abandoned.

The opening of five-membered ring orthomonochloroacetates gave, as for non-chlorinated orthoacetates, exclusively the axial monochloroacetates in high yield (Scheme 1, Table). Methyl 2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside[5] (**1**) gave a 98% yield of the 4-*O*-chloroacetate **4**, and methyl 6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside gave, with acetylation prior to the orthoester opening, a 71% yield of the 2-*O*-chloroacetate **7**. Corresponding yields from the opening of normal orthoacetates, on the same or similar starting compounds, were 94%[5] and 94%,[6] respectively.

Table Yields and data of monoesters obtained from the opening of orthoesters

Compound	yield (%)	$[\alpha]_D$ ($CHCl_3$)	^{13}C NMR	^1H NMR
4 (4-*O*-AcCl)	98	-5.0°	11.9, 40.8, 61.9, 71.0, 71.9, 72.1, 74.6, 83.6, 125.3-133.6, 166.1, 166.7, 167.5	5.62 (d, $J_{3,4}$ 3 Hz, H-4).
5 and 6 (3 and 4-*O*-AcCl)	86		11.4, 11.5, 61.7, 62.7, 63.8, 64.3, 66.9, 67.2, 70.9, 72.3, 73.0, 74.3, 77.1, 83.2, 83.4, 128.5-133.7, 164.1, 165.3-166.6	5.31 (d, $J_{2,3}$ 10 Hz, H-3), 5.65 (d, $J_{3,4}$ 3 Hz, H-4).
7 (2-*O*-AcCl)	75	+18°	19.2, 20.8, 26.5, 26.7, 40.7, 55.2, 62.6, 68.8, 69.5, 70.8, 74.1, 97.7, 127.7-135.7, 167.0, 171.6	5.18 (t, J 10 Hz H-4), 5.13 (dd, $J_{1,2}$ 1.5 Hz, $J_{2,3}$ 3 Hz, H-2)
11 (4-*O*-AcCl)	11	-28°	20.6, 20.7, 40.3, 57.2, 61.2, 70.4, 71.3, 72.6, 73.7, 101.7, 166.6, 169.4, 170.4	
12 (6-*O*-AcCl)	68	-35°	20.7, 20.9, 40.7, 57.1, 64.4, 69.0, 71.1, 73.6, 75.7, 101.6, 167.7, 169.7, 171.6	
14 (6-*O*-$AcCl_2$)	72	-24°	20.7, 20.8, 56.9, 64.1, 65.7, 69.2, 71.2, 73.5, 75.9, 101.5, 164.6, 169.7, 171.7	
15 (4-*O*-AcCl)	42	+138°	40.3, 55.7, 61.1, 69.2, 70.2, 70.4, 71.9, 97.0, 128.4-133.4, 165.8, 166.9	
16 (6-*O*-AcCl)	29	+119°	40.8, 55.5, 64.6, 69.6, 71.3, 74.0, 97.1, 125.3-133.5 , 166.0, 167.4	
17 (4-*O*-$AcCl_2$)	37	+177°	55.7, 60.9, 63.7, 69.0, 69.8, 71.2, 71.9, 97.0, 128.5-133.5 , 163.8, 165.6, 165.8	
18 (6-*O*-$AcCl_2$)	52	+114°	55.6, 64.1, 65.7, 69.5, 69.8, 71.0, 74.4, 97.0, 128-133.6 , 164.5, 165.9, 167.7	
20 (4-*O*-AcCl)	11	-15°	40.4, 57.3, 61.6, 71.8, 73.7, 74.9, 75.2, 81.3, 82.0 , 104.7,127.8-138.2, 166.7	
21 (6-*O*-AcCl)	64	-18°	40.7, 57.3, 64.8, 69.6, 72.9, 74.6, 75.4, 81.7, 83.6, 104.9, 127.8-138.2, 167.4	
22 (4-*O*-$AcCl_2$)	32	+14°	57.4, 61.4, 64.0, 72.9, 73.4, 74.9, 75.3, 80.8, 82.0, 104.7, 125.3-138.1, 163.6	
23 (6-*O*-$AcCl_2$)	50	-11°	57.2, 64.1, 66.1, 69.7, 72.8, 74.6, 75.3, 81.7, 83.6, 104.8, 127.8-138.3, 164.5	

The opening of the five-membered ring orthodichloroacetates of **1** gave 86% of an inseparable mixture of the 4-*O* and the 3-*O*-dichloroacetates **5** and **6** (Scheme 1, Table). When the opening was followed on TLC it was observed that one of the isomers of the stereoisomeric mixture of dichloroacetetates was opened much faster than the other (almost instantaneous compared to days). Since the two isomers were clearly separated on

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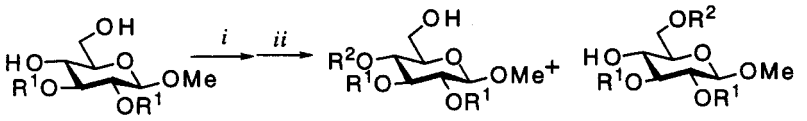
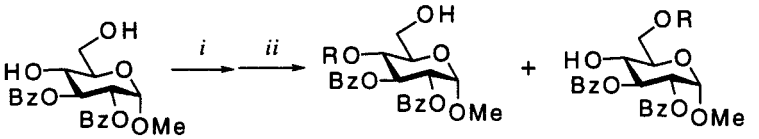


8 R^1 = Ac
9 R^1 = Bn

11 R^1 = Ac, R^2 = ClAc **12** R^1 = Ac, R^2 = ClAc
13 R^1 = Ac, R^2 = Cl_2Ac **14** R^1 = Ac, R^2 = Cl_2Ac
15 R^1 = Bn, R^2 = ClAc **16** R^1 = Bn, R^2 = ClAc
17 R^1 = Bn, R^2 = Cl_2Ac **18** R^1 = Bn, R^2 = Cl_2Ac

i) $(MeO)_3CCH_2Cl$, $(MeO)_3CCHCl_2$ or $(MeO)_3CCCl_3$, *p*-TsOH *ii*) CF_3COOH (aq)

Scheme 2



19

20 R = ClAc **21** R = ClAc
22 R = Cl_2Ac **23** R = Cl_2Ac

i) $(MeO)_3CCH_2Cl$ or $(MeO)_3CCHCl_2$, *p*-TsOH *ii*) CF_3COOH (aq)

Scheme 3

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TLC, the mixture was submitted to silica gel chromatography and the two stereoisomers **2** (*S*) and **3** (*R*) were separated and characterised. Isomer **3**, identified through a NOE between the proton of the *endo*-dichloromethyl group and H-2, was found to open up more rapidly but still gave a mixture of **5** and **6**, probably due to acyl migration under the more acidic conditions used compared to the monochloroacetates.

The results from the opening of six-membered ring mono- and dichloroortho-acetates are given in the Table (Scheme 2 and 3). All 4,6-diols gave a high yield (71-89%) of a mixture of the 4- and 6-monoesters (except compound **13**, which was not detected), easily identified by the C-6 shift in ^{13}C NMR (δ unacylated ~61 ppm, acylated ~64 ppm). The ratio between the monoesters is very dependent on reaction conditions, since after the initial opening of the orthoesters to esters, acid-catalysed acyl migration, usually from the 4- to the 6-position, can take place. However, with the monochloroacetate derivatives, the tendency observed earlier in the opening of 4,6-orthobenzoates that benzyl protecting groups at O-2 and 3 gave a higher ratio of the 4-acylated compounds as compared to compounds with benzoyl protecting groups at O-2 and 3, was once more found.[3]

In summary, formation and opening of mono-and dichloroorthoacetates of different carbohydrate diols give high yields of monoacylated derivatives. Especially, vicinal diols (*eq-ax*) with monochloroorthoacetates give the same regioselectivity as non-chlorinated orthoacetates, *i.e.*, exclusively the axial acetate, which produces in high yield regioselectively protected derivatives with selectively removable protecting groups that should be of interest in protecting group schemes.

EXPERIMENTAL

General methods. These were the same as earlier reported.[11]

General procedure for the formation of chloroacetates:

Method A (monochloroacetates): Trimethyl orthochloroacetate[9] (50 μL) was added to a stirred solution of the diol (or triol) (55 mg) and a catalytical amount of *p*-toluenesulfonic acid in acetonitrile (15 mL). After ten minutes the solvent was evaporated and the residue was dissolved in acetonitrile (15 mL) and aqueous trifluoroacetic acid (90%, 50 μL) was added. After 1 h the mixture was diluted with toluene, concentrated and put on top of a silica gel column and eluted (toluene-EtOAc) to give the monochloroacetate(s).

Method B (dichloroacetates): Trimethyl orthodichloroacetate[10] (100 μL) was added to a stirred solution of the diol (or triol) (55 mg) and a catalytical amount of *p*-toluenesulfonic acid in acetonitrile (15 mL). The mixture was concentrated and the residue was dissolved in acetonitrile (15 mL) and checked on TLC (toluene-EtOAc). When the reaction was complete, the reaction mixture was treated with aqueous trifluoroacetic acid (70%, 100 μL), concentrated to dryness, diluted with acetonitrile and again checked on TLC (toluene-EtOAc). When the reaction was complete, the reaction mixture was diluted with toluene, concentrated and purified by silica gel chromatography (toluene-EtOAc) to give the dichloroacetate(s).

Methyl 4-*O*-Acetyl-2-*O*-chloroacetyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-manno-pyranoside (**7**). Methyl 6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranoside (90 mg) was treated as in Method A above, except that the orthoester obtained was acetylated *in situ* with pyridine (5 mL) and acetic anhydride (0.3 mL) prior to the first concentration followed by two coevaporations with toluene and subsequent opening, to give **7** (82 mg, 71%) (Data see Table).

Methyl 2,6-Di-*O*-benzoyl-3,4-*O*-[(*S*)-1-methoxy-2-dichloroethylidene]-1-thio-β-D-galactopyranoside (2) and Methyl 2,6-Di-*O*-benzoyl-3,4-*O*-[(*R*)-1-methoxy-2-dichloroethylidene]-1-thio-β-D-galactopyranoside (**3**). Trimethyl orthodichloroacetate[10] (187 μL) was added to a solution of **1**[5] (100 mg) and a catalytical amount of *p*-toluenesulfonic acid in acetonitrile (15 mL), the mixture was concentrated and the residue

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was again dissolved in acetonitrile and checked on TLC (toluene-EtOAc 3:1). When the reaction was complete the reaction mixture was diluted with toluene, concentrated to dryness and put on top of a silica gel column and eluted (toluene-EtOAc 20:1) to give **2** (66 mg, 50%), $[\alpha]_D$ +38° (*c* 0.77 chloroform), ^{13}C NMR data: δ 12.1 (SMe), 51.5 (OMe), 63.3, 71.0, 72.2, 75.0, 77.2, 78.5 (C-2-6, $CHCl_2$), 83.1 (C-1), 121.3 (orthoester C), 128.5-133.6 (aromatic C), 165.2, 166.3 (PhCO), and **3** (63 mg, 48%), $[\alpha]_D$ +4.4° (*c* 0.69, chloroform), ^{13}C NMR data: δ 13.5 (SMe), 50.4 (OMe), 63.1, 70.2, 70.8, 73.9, 75.5, 77.7 (C-2-6, $CHCl_2$), 83.6 (C-1), 121.2 (orthoester C), 128.2-133.7 (aromatic C), 164.8, 166.2 (PhCO).

Anal. Calcd for $C_{24}H_{24}O_8SCl_2$: C, 53.05; H, 4.45. Found: C, 53.13; H, 4.57.

Methyl 2,3-Di-*O*-acetyl-4,6-*O*-(1-methoxy-2-trichloroethylidene)-β-D-glucopyranoside (10). Trimethyl orthotrichloroacetate[10] (130 mg) was added to a solution of methyl 2,3-di-*O*-acetyl-β-D-glucopyranoside (30 mg) and *p*-toluenesulfonic acid (20 mg) in acetonitrile (3 mL). The mixture was concentrated and the residue was again dissolved in acetonitrile and checked on TLC (toluene-ethyl acetate 3:1). The reaction mixture was diluted with toluene, concentrated to dryness and put on top of a silica gel column and eluted (toluene-EtOAc 20:1) to give **10** (22 mg, 48%), $[\alpha]_D$ -44° (*c* 0.88, chloroform), ^{13}C NMR data: δ 20.6, 20.7 (*Me*CO), 54.9 (orthoester OMe), 57.4 (OMe), 63.5, 65.2, 71.2, 72.0, 72.4 (C-2-6), 99.3 (CCl_3), 102.4 (C-1), 110.9 (orthoester C), 169.6, 169.9 (Me*C*O).

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