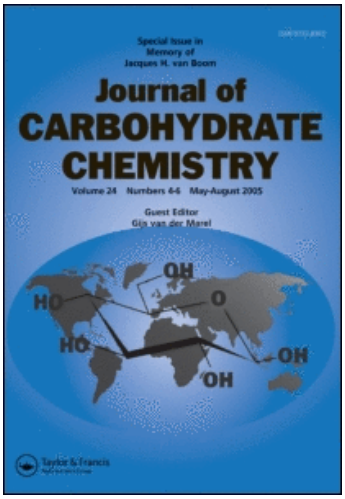

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2-DICHLOROMETHYL-1,3-DIOXOLAN-2-YL ORTHOESTERS. A POTENTIAL PROTECTING GROUP FOR SUGAR DERIVATIVES

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ABSTRACT

Reactions of 2-dichloromethylene-1,3-dioxolane (**2**) with acetal protected sugar derivatives in neutral media gave 2-dichloromethyl-1,3-dioxolan-2-yl orthoesters. These orthoesters are readily hydrolysed under mild acidic conditions offering a new method for the preparation of readily removable protecting groups. This strategy was realised in the preparation of 6-*O*-acetyl-3,5-di-*O*-methyl-1,2-*O*-isopropylidene-α-D-glucofuranose.

Key Words: Sugar derivatives; Protecting groups; Orthoesters; Ketene acetals

INTRODUCTION

The importance of protecting groups in carbohydrate chemistry is well known and many such groups are widely used.[1] However, a wider choice of protecting groups would be useful and might help to solve some specific problems. Protection of a single hydroxyl group without using an acidic or basic medium, and its removal under very mild acidic conditions may be beneficial in some cases. Or-

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thoester[2] groups are base stable and can be removed like cyclic acetals under acidic conditions. 2-Dichloromethyl-1,3-dioxolan-2-yl orthoesters reported here are comparable to the isopropylidene acetals in terms of acid stability, but unlike cyclic acetals, they can be prepared without any acid catalyst and used for the protection of a single hydroxyl group. Related to this work, reactions of sugars with the ketene acetal 1,1-dimethoxyethene under kinetic control to give cyclic orthoesters have been described.[3,4]

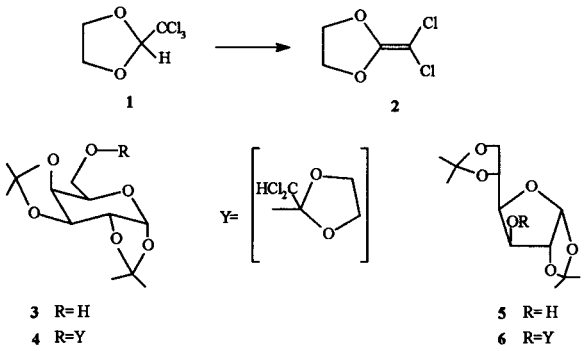
RESULTS AND DISCUSSION

The ketene acetal 2-dichloromethylene-1,3-dioxolane[5] (**2**) was prepared by dehydrochlorination of 2-trichloromethyl-1,3-dioxolane[5] (**1**) with potassium *t*-butoxide in *t*-butyl alcohol at room temperature and was purified by crystallization from petroleum ether. The ketene acetal **2** was prepared freshly prior to the orthoester reaction since it was sensitive to atmospheric moisture. In most cases, the solvent was evaporated under reduced pressure, the product was extracted with petroleum ether, and **2** was obtained as a solid after removal of the solvent and used as such. The IR spectrum of pure **2** contained a sharp peak at 1702 cm^{-1} due to the ketene acetal double bond.[6] When the product was partially hydrolyzed, a carbonyl (1753 cm^{-1}) and a hydroxyl peak (3380 cm^{-1}) appeared. This method was used as a test to monitor the purity of **2**. Alternatively **2** can be purified by distillation under reduced pressure according to the method of McElvaine and Curry.[5]

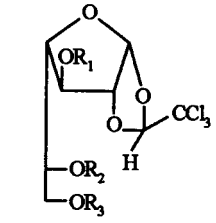
Nitromethane was the most suitable solvent for reactions of **2** with sugar derivatives. When the solubility of the substrate in this solvent was satisfactory, the reaction was completed at a relatively low temperature. In one case, an *N*,*N*-dimethylformamide-nitromethane mixture was used. However *N*,*N*-dimethylformamide was not preferred due to the difficulties in drying of this solvent completely. Excess of **2** was usually necessary to complete the reaction.

2-Dichloromethyl-1,3-dioxolan-2-yl orthoesters reported here were difficult to crystallise but they could be purified by chromatography on silica gel. These orthoesters were sensitive to acidic conditions, hence the solvents must be free of traces of acid. Although the total yields of the orthoester derivatives were reasonable, the yields of the individual compounds were low due to the low regioselectivity which is somewhat less than that of the tosyl esters. This low regioselectivity reduces the efficiency of this method as a protecting group for polyhydroxy compounds. Nevertheless, we think that the method may be useful in some applications especially where acidic and basic media are not preferred.

The reactivity of ketene acetal **2** towards a primary hydroxyl group was demonstrated by its reaction with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[7] (**3**) which yielded 6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**) (63%). Furthermore 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[7] (**5**) gave 3-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**) in 31% yield, indicating that appreciable reaction on a secondary hydroxyl group is also possible.



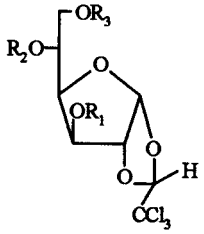
Further reactions of **2** were carried out with 1,2-*O*-alkylidene protected furanose derivatives **7, 10** and **13**. The absolute configuration of the acetal carbon of 1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose[8] (**7**) was determined by us recently,[9] relative to the diastereoisomer of **10** (β-chloralose).[10] Reaction of **2** with **7** gave crystalline 6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose (**8**) in 50% yield and was characterised as its diacetate **9**. The reaction mixture contained three other products as judged from TLC, but these were not isolated.



7 $R_1 = R_2 = R_3 = H$

8 $R_1 = R_2 = H$; $R_3 = Y$

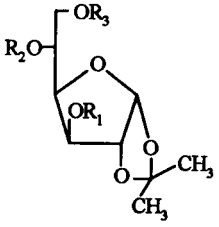
9 $R_1 = R_2 = Ac$; $R_3 = Y$



10 $R_1 = R_2 = R_3 = H$

11 $R_1 = R_3 = Y$; $R_2 = Ac$

12 $R_1 = R_2 = Ac$; $R_3 = Y$



13 $R_1 = R_2 = R_3 = H$

14 $R_1 = H$; $R_2 = R_3 = Y$

15 $R_1 = Ac$; $R_2 = R_3 = Y$

16 $R_1 = R_2 = Me$; $R_3 = Y$

17 $R_1 = R_2 = Me$; $R_3 = Ac$

1,2-*O*-(*R*)-Trichloroethylidene-α-D-glucofuranose[10] (**10**) is a commercially available compound also known as α-chloralose, which is used as an anesthetic for animals.[11] The acetal carbon configuration of **10** was first assigned, on the basis of the relative chemical shift values of this compound and its diastereoisomer.[10] The structure of **10** is also supported by published x-ray crystallographic data.[12] Reaction of **2** with **10** was completed (TLC) in 20 minutes at 40°C, but the yields of the isolated pure compounds were low, due to separation problems. Chromatography on silica gel, eluting with dichloromethane–ethyl acetate (4:1), afforded as the first product 3,6-di-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose in low yield, which was characterised as its monoacetate **11**. The second fraction gave a mixture which could not be purified, even after acetylation. The final product eluted

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from the column contained 6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose which was acetylated to give the diacetate **12**.

The reaction of **2** with 1,2-*O*-isopropylidene-α-D-glucofuranose[7] (**13**) also gave a mixture of products. Column chromatography on silica gel yielded a mixture of two minor products as a first fraction. Crystallization of this mixture from toluene afforded 5,6-di-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**14**) in a low yield and was characterised as its monoacetate **15**. Further fractions gave a syrupy product which mainly contained 6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-isopropylidene-α-D-glucofuranose. This product was also obtained by removing the minor components from the main mixture, with boiling petroleum ether extraction. Methylation of the crude 6-*O*-orthoester fraction was carried out without further purification to give 3,5-di-*O*-methyl-6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**16**). Hydrolysis of **16** in aqueous methanol using Amberlite IR-120 (H^+) as acid catalyst and subsequent acetylation and purification gave 6-*O*-acetyl-3,5-di-*O*-methyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**17**).

EXPERIMENTAL

General methods. ^1H (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded with a Bruker DPX-400 High Performance FT NMR spectrometer in $CDCl_3$. IR spectra (KBr) were obtained on a Mattson 1000 FTIR spectrophotometer. Mass spectra were recorded with a Micromass UK Platform-II spectrometer. Optical rotations were measured with a Schmidt–Haensch Polartronic-E polarimeter. Column chromatography and TLC were performed on Merck G-60 silica gel (7734) and on precoated silica gel plates (Merck 5553), respectively. Chlorinated solvents were shaken with a sodium carbonate solution (5%) and dried with anhydrous sodium sulfate before use. Petroleum ether refers to the fraction having bp 40–60°C.

2-Trichloromethyl-1,3-dioxolane (1). A mixture of chloral (108 g, 0.73 mol), ethylene glycol (46 g, 0.74 mol) and concentrated sulfuric acid (25 mL) was heated at 90°C for 2 h. The mixture was poured over crushed ice and extracted with chloroform (5×50 mL) after adjusting to pH = 5.5 with sodium hydroxide solution (10%). The combined chloroform extracts were washed with water and dried with anhydrous sodium sulfate. The solvent was removed and the residue was dissolved in petroleum ether (250 mL) and decolorised with activated carbon. The compound **1** (80 g, 56%) was crystallised by concentrating the petroleum ether solution; mp 41–42°C, lit. mp 41–42°C.[5]

2-Dichloromethylene-1,3-dioxolane (2). A solution of compound **1** (3.0 g, 15.67 mmol) in *t*-butyl alcohol (50 mL) was stirred under dry nitrogen with potassium *t*-butoxide (2.0 g, 17.84 mmol) at 20–25°C for 16 h. The solvent was removed completely under vacuum at 60°C, and the residue was extracted with petroleum ether (3×25 mL), filtered and concentrated under reduced pressure to give a product which solidified. The concentrated solution of this product in petroleum ether gave crystals of **2** (2.0 g, 82%); mp 54–55°C, lit mp 55–57°C.[5]

6-*O*-(2-Dichloromethyl-1,3-dioxolan-2-yl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (4). A solution of the ketene acetal **2** (1.2 g, 7.74 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**3**) (1.9 g, 7.30 mmol) in nitromethane (25 mL) was stirred for 16 h under dry nitrogen at room temperature. The solvent was removed, and the residue was purified on a silica gel column, eluting with dichloromethane-petroleum ether (19:1). Compound **4** was obtained as a syrup (1.9 g, 63%), $[\alpha]_D^{24} - 51°$ (*c* 0.07, dichloromethane). IR: 3004, 2927, 1395, 1242, 1089, 1012, 910, 808, 782 cm^{-1}. ^1H NMR: δ 5.78 (s, 1H, $HCCl_2$), 5.50 (d, $J_{1,2} = 5.0$ Hz, H-1), 4.60 (dd, 1H, $J_{2,3} = 7.8$, $J_{3,4} = 2.0$ Hz, H-3), 4.35–4.29 (m, 6H, H-2, H-4 and dioxolane ring H), 4.00 (td, 1H, $J_{4,5} = \sim 1.5$ Hz, H-5), 3.82 (dd, 1H, $J_{5,6a} = \sim 6.5$, $J_{6a,6b} = 9.8$ Hz, H-6_a), 3.73 (dd, 1H, $J_{5,6b} = \sim 6.5$ Hz, H-6_b), 1.53 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.34 and 1.32 ($2 \times$ s, 6H, $2 \times CH_3$). ^{13}C NMR: δ 121.27 (orthoester C), 109.63 and 109.06 ($2 \times$ ketal C), 96.70 (C-1), 73.12, 71.23, 71.15, 70.97, 67.86, 67.72, 67.04, 62.05 (C-2 to C-6, $HCCl_2$ and dioxolane ring C), 26.43, 26.36, 25, 37, 24.77 ($4 \times$ isopropylidene CH_3). MS (EI): *m/z* 415, 417 (9/6; $2 \times$ Cl; $M^+ + 1$), 413 ($M^+ - 1$), 399, 401, 403 (9/6/1; $2 \times$ Cl; $M^+ - CH_3$), 243 [M^+-(*O*-dichloromethyl-dioxolane)], 155, 157, 159 (9/6/1; $2 \times$ Cl; dichloromethyldioxolanyl).

Anal. Calcd for $C_{16}H_{24}Cl_2O_8$: C, 46.27; H, 5.82. Found: C, 46.35; H, 5.92%.

3-*O*-(2-Dichloromethyl-1,3-dioxolan-2-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (6). A solution of the ketene acetal **2** (1.3 g, 8.39 mmol) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) (1.6 g, 6.15 mmol) in nitromethane (15 L) was stirred for 72 h under dry nitrogen at room temperature. The solvent was removed under reduced pressure and the residue was purified on a silica gel column, eluting with chloroform-ethyl acetate (1:4) to give **6** as a syrup (0.8 g, 31%), $[\alpha]_D^{28} - 1.5°$ (*c* 0.06, dichloromethane). ^1H NMR: δ 5.87 (d, 1H, $J_{1,2} = 3.7$ Hz, H-1), 5.69 (s, 1H, $HCCl_2$), 4.66 (d, 1H, $J_{2,3} = 0$ Hz, H-2), 4.40–4.28 (m, 6H, H-3, H-5 and dioxolane ring H), 4.21 (dd, 1H, $J_{3,4} = 3.1$, $J_{4,5} = 6.3$ Hz, H-4), 4.06 (dd, 1H, $J_{5,6a} = 6.4$, $J_{6a,6b} = 8.4$ Hz, H-6_a), 3.98 (dd, 1H, $J_{5,6b} = 6.0$ Hz, H-6_b), 1.48 (s, 3H, CH_3), 1.41 (s, 3H, CH_3) 1.32, 1.30 ($2 \times$ s, 6H, $2 \times CH_3$). ^{13}C NMR: δ 121.51 (orthoester C), 112.26, 109.24 and 105.45 (C-1 and $2 \times$ ketal C), 84.32, 80.74, 76.32, 73.00 ($2 \times$ C), 72.90, 68.09, 67.68, 67.02 (C-2 to C-6, $CHCl_2$ and dioxolane ring C), 27.17, 27.08, 26.71, 25.69 ($4 \times CH_3$). MS (EI): *m/z* 415, 417 (9/6; $2 \times$ Cl; $M^+ + 1$), 399, 401, 403 (9/6/1; $2 \times$ Cl; $M^+ - CH_3$), 243 [M^+-(*O*-dichloromethyl-dioxolane)], 155, 157, 159 (9/6/1; $2 \times$ Cl; dichloromethyldioxolanyl), 185 (243-acetone), 101 (2,2-dimethyl-1,3-dioxolane, from C-5, C-6 bond fission).

Anal. Calcd for $C_{16}H_{24}Cl_2O_8$: C, 46.27; H, 5.82. Found: C, 46.38; H, 5.92%.

6-*O*-(2-Dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose (8). Reagent **2** (1.6 g, 10.32 mmol) and 1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose (**7**) (1.6 g, 5.17 mmol) were dissolved in a mixture of *N*,*N*-dimethylformamide (25 mL) and nitromethane (25 mL). The solution was stirred for 8 h at 75–80°C. TLC (dichloromethane-methanol, 9:1) indicated four spots. The solvent was removed under reduced pressure, and the residue was extracted with dichloromethane, which contained a main product and a trace of **7** (TLC). The solvent was removed, and the residue was extracted with boiling water to remove unreacted **7**. The

remaining part was crystallized from ethyl acetate to give **8** (1.2 g, 50%); mp 176–177°C, $[\alpha]_D^{24} - 30°$ (*c* 0.01, methanol). IR: 3565, 3489, 3004, 2927, 1319, 1217, 1165, 1114, 1112, 1089, 961, 808, 627 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}O_8Cl_5$: C, 31.03; H, 3.25. Found C, 30.90; H, 3.48%.

3,5-Di-*O*-acetyl-6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose (9). A solution of **8** (0.16 g, 0.34 mmol) in pyridine (5 mL) was acetylated with acetic anhydride (0.5 mL, 5.3 mmol) for 16 h at room temperature. The solvent was removed under reduced pressure, and the residue was extracted with dichloromethane. Removal of the solvent and crystallization of the residue from petroleum ether-ethanol gave **9** (0.16 g, 85%); mp 101–102°C, $[\alpha]_D^{24} - 22°$ (*c* 0.01, dichloromethane). IR: 3037, 2987, 2975, 2925, 2900, 1753, 1228, 1160, 1114, 1040, 1012, 978, 808, 649 cm^{-1}. ^1H NMR: δ 6.26 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1) 5.80 (s, 1H, $CHCl_2$), 5.75 (s, 1H, $HC-CCl_3$), 5.29 (dt, 1H, $J_{4,5} = \sim 12$ Hz, H-5), 5.24 (d, 1H, $J_{2,3} = 0$, $J_{3,4} = 1.3$ Hz, H-3), 4.96 (d, 1H, H-2), 4.38–4.29 (m, 5H, dioxolane ring H and H-4), 3.87 (dd, 1H, $J_{5,6a} = 5.5$, $J_{6a,6b} = 10.7$ Hz, H-6_a), 3.81 (dd, 1H, $J_{5,6b} = 5.5$ Hz, H-6_b), 2.16 (s, 3H, OAc), 2.11 (s, 3H, OAc). ^{13}C NMR: δ 170.47 and 169.95 ($2 \times OCOCH_3$), 121.26 (orthoester C), 109.97 and 107.75 (C-1 and acetal C), 99.59 (CCl_3), 86.94, 85.21, 77.02, 73.03, 70.88, 67.98 ($2 \times$ C), 61.53 (C-2 to C-6, $HCCl_2$ and dioxolane ring C), 21.15, 21.02 ($2 \times OCOCH_3$).

Anal. Calcd for $C_{16}H_{19}Cl_5O_{10}$: C, 35.03; H, 3.49. Found: C, 35.12; H, 3.78%.

5-*O*-Acetyl-3,6-di-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (11). A solution of the reagent **2** (1.0 g, 6.45 mmol) and 1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (**10**) (1.8 g, 5.81 mmol) in nitromethane (25 mL) was stirred at 40°C for 20 min. TLC indicated three spots (dichloromethane-ethyl acetate, 4:1) and no remaining **10**. The mixture was poured into ice–water containing Na_2CO_3. The resultant solution was slightly alkaline (pH 8). The mixture was extracted with dichloromethane (4×25 mL), dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to give a syrupy mixture (2.7 g). This mixture was applied to a silica gel column which was eluted with dichloromethane-ethyl acetate (4:1). The first fraction collected (0.39 g) gave a single spot on TLC (the fastest moving). The IR spectrum of this product showed a carbonyl peak, indicating contamination due to the decomposition products of the ketene acetal **2**. A solution of this syrupy mixture in dichloromethane was extracted with alkaline water (pH 8) several times. The purified syrup was crystallized from carbon tetrachloride-petroleum ether at 0°C to give a crude product (0.39 g, 11%; mp 140–143°C, $[\alpha]_D^{22} - 11°$ (*c* 0.02, methanol). IR: 3489, 3004, 2928, 1217, 1114, 1063, 961, 808 cm^{-1}) an aliquot of which (0.09 g, 0.145 mmol) was acetylated in pyridine (5 mL) with acetic anhydride (0.5 mL, 5.3 mmol) as described for **9**, and **11** was obtained (0.08 g, 83%); mp 188–190°C (from ethyl acetate), $[\alpha]_D^{20} - 7°$ (*c* 0.01, dichloromethane). IR: 3004, 2927, 1753, 1268, 1414, 1040, 1012, 961, 808 cm^{-1}. ^1H NMR: δ 6.10 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 5.70, 5.69 ($2 \times$ s, 2H, $2 \times HCCl_2$), 5.33 (s, 1H, $HC-CCl_3$), 5.08 (ddd ~ dt, 1H, $J_{4,5} = 9.9$ Hz, H-5), 4.95 (dd, 1H, H-4), 4.94 (d, 1H, $J_{2,3} = 0$ Hz, H-2), 4.48 (d, 1H, $J_{3,4} = 3.5$ Hz, H-3), 4.44–4.25 (m, 8H, dioxolane ring H),

4.00 (dd, 1H, $J_{5,6a}=2.3$, $J_{6a,6b}=11.1$ Hz, H-6_a), 3.81 (dd, 1H, $J_{5,6b}=3.4$ Hz, H-6_b), 2.07 (s, 3H, OAc).

Anal. Calcd for $C_{18}H_{21}Cl_7O_{11}$: C, 32.68; H, 3.20. Found: C, 32.90; H, 3.38%.

3,5-Di-*O*-acetyl-6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (12). A part (0.13 g, 0.280 mmol) of the third fraction from the previous column separation (0.6 g, 22.2%, $[\alpha]_D^{22}-21°$ (*c* 0.03, methanol). IR: 3490, 3004, 2953, 2927, 1319, 1217, 1114, 1063, 961, 808 cm^{-1}) was acetylated in pyridine (5 mL) with acetic anhydride (0.5 mL, 5.3 mmol) as described for **9** to give syrupy **12** (0.10 g, 65%). $[\alpha]_D^{20}-14.5°$ (*c* 0.01, dichloromethane), IR: 2928, 2876, 1753, 1302, 1248, 1174, 1100, 1010, 965, 817 cm^{-1}. ^{1}H NMR: δ 6.10 (d, 1H, $J_{1,2}=3.7$ Hz, H-1), 5.70 (s, 1H, $HCCl_2$), 5.57 (d, 1H, $J_{3,4}=2.9$ Hz, H-3), 5.35 (s, 1H, $HC-CCl_3$), 5.14 (dt, 1H, H-5), 4.94 (dd, 1H, $J_{4,5}=9.6$ Hz, H-4), 4.67 (d, 1H, $J_{2,3}=0$ Hz, H-2), 4.30–4.28 (m, 4H, dioxolane ring H), 3.94 (dd, 1H, $J_{5,6a}=2.0$ Hz, H-6_a), 3.80 (dd, 1H, $J_{5,6b}=4.6$, $J_{6a,6b}=10.9$ Hz, H-6_b), 2.08 (s, 3H, OAc), 2.03 (s, 3H, OAc).

Anal. Calcd for $C_{16}H_{19}Cl_5O_{10}$: C, 35.15; H, 3.50. Found: C, 35.32; H, 3.72%.

5,6-Di-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-isopropylidene-α-D-glucofuranose (14). A solution of the reagent **2** (2.2 g, 14.2 mmol) and 1,2-*O*-isopropylidene-α-D-glucofuranose (**13**) (3.0 g, 13.6 mmol) in nitromethane (25 mL) was stirred at 75°C for 16 h. The solvent was removed under reduced pressure, and the syrupy residue was dissolved in dichloromethane. The unreacted starting material crystallized on standing and was filtered off. The TLC of the remaining solution indicated a major and two minor faster moving spots (chloroform-ethyl acetate; 1:4). Evaporation of the solvent gave a syrup (2.9 g), which was applied to a silica gel column eluting with (chloroform-ethyl acetate; 4:1) to give two fractions. The first fraction eluted as a mixture and was obtained as a syrup (0.4 g) after removal of the solvent. The toluene solution of this mixture gave crystalline **14** at 0°C (0.2 g, 2.7%); mp 149–150°C, $[\alpha]_D^{26}-39°$ (*c* 0.01, dichloromethane). IR: 3489, 3004, 2935, 2927, 1390, 1370, 1252, 1212, 1123, 1093, 1014, 954, 806, 766 cm^{-1}. ^{1}H NMR: δ 5.92 (d, $J_{1,2}=3.3$ Hz, H-1), 5.79 (s, 1H, $HCCl_2$), 5.77 (s, 1H, $HCCl_2$), 4.53 (d, 1H, $J_{2,3}=0$ Hz, H-2), 4.44–4.25 (m, 9H, H-4 and dioxolane ring H), 4.15 (bm, 1H, H-5), 4.00 (dd, 1H, $J_{5,6a}=2.2$, $J_{6a,6b}=10.6$ Hz, H-6_a), 3.82 (dd, 1H, $J_{5,6b}=4.2$ Hz, H-6_b), 3.39 (bs, 1H, H-3), 1.49 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR: δ 121.68 and 121.15 (2 × orthoester C), 112.25 and 105.51 (C-1 and acetal C), 85.12, 79.14, 74.92, 73.20, 73.02, 71.01, 68.09, 67.80, 67.64 (2 × C), 64.06 (C-2 to C-6, $HCCl_2$ and dioxolane ring C), 27.22, 26.69 (2 × CH_3).

Anal. Calcd for $C_{17}H_{24}Cl_4O_{10}$: C, 38.51; H, 4.56. Found: C, 38.61; H, 4.72%.

3-*O*-Acetyl-5,6-di-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-isopropylidene-α-D-glucofuranose (15). Acetylation of **14** (0.13 g, 0.245 mmol) in pyridine (5 mL) with acetic anhydride (0.5 mL, 5.3 mmol) as described for **9** gave crystalline **15** (0.13 g, 92%), from ethanol–petroleum ether; mp 167–168°C, $[\alpha]_D^{24}-23°$ (*c* 0.013, dichloromethane). IR: 2992, 2930, 1751, 1741, 1377, 1243, 1221, 1200, 1108, 1073, 1044, 1023, 959, 796 cm^{-1}. ^{1}H NMR: δ 5.88 (d, $J_{1,2}=3.7$ Hz, H-1), 5.79 (s, 1H, $HCCl_2$),

5.73 (s, 1H, $HCCl_2$), 5.27 (d, 1H, $J_{3,4}=2.7$ Hz, H-3), 4.49 (d, 1H, $J_{2,3}=0$ Hz, H-2), 4.41–4.25 (m, 10H, H-4, H-5 and dioxolane ring H), 4.03 (dd, 1H, $J_{5,6a}=2.7$ Hz, H-6_a), 3.84 (dd, 1H, $J_{5,6b}=4.2$, $J_{6a,6b}=10.6$ Hz, H-6_b), 2.12 (s, 3H, OAc), 1.52 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR: δ 170.22 (O*C*OCH_3), 121.48 and 121.08 (2 × orthoester C), 112.79 and 105.09 (C-1 and acetal C), 83.54, 75.88, 73.37, 72.97, 69.97 (2 × C), 67.94, 67.78, 67.35, 64.19 (C-2 to C-6, $HCCl_2$ and dioxolane ring C), 27.04, 26.69, 21.34 (3 × CH_3).

Anal. Calcd for $C_{19}H_{26}Cl_4O_{11}$: C, 39.89; H, 4.58. Found: C, 39.87; H, 4.22%.

3,5-Di-*O*-methyl-6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-isopropylidene-α-D-glucofuranose (16). The crude syrupy orthoester mixture (3.0 g) from the reaction of **2** with **13** as described for **14** was boiled with petroleum ether several times, and the solvent layer was decanted until TLC of the residue indicated no diorthoester spots. The remaining syrup (1.6 g) contained impure 6-*O*-(2-dichloromethyl-1,3-dioxolan-2-yl)-1,2-*O*-isopropylidene-α-D-glucofuranose. An aliquot (0.9 g, max 2.2 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred with methyl iodide (2.5 mL, 40 mmol) and BaO (2.5 g) at room temperature for 16 h. The solid material was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane which was washed with 5% sodium thiosulfate and then with water several times and dried with anydrous sodium sulfate. Removal of dichloromethane afforded a crude product, which was purified on a silica gel column, eluting with dichloromethane-ethyl acetate (4:1) to give **16** as a syrup (0.5 g, 16%), $[\alpha]_D^{27}$ − 24° (*c* 0.02, dichloromethane). ^1H NMR: δ 5.65 (d, $J_{1,2}=3.8$ Hz, H-1), 3.58 (d, 1H, $J_{3,4}=3.0$ Hz, H-3), 5.57 (s, 1H, $HCCl_2$), 4.34 (d, 1H, $J_{2,3}=0$ Hz, H-2), 4.13–4.03 (m, ∼4H, dioxolane ring H), 3.85 (dd, 1H, $J_{4,5}=\sim 9.0$ Hz, H-4), 3.82–3.76 (m, 1H, H-5), 3.52–3.48 (m, 2H, H-6_a and H-6_b), 3.29 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 1.13 (s, 3H, CH_3), 1.10 (s, 3H, CH_3).

Anal. Calcd for $C_{15}H_{24}Cl_2O_8$: C, 44.68; H, 6.00. Found: C, 44.34; H, 5.84%.

6-*O*-Acetyl-3,5-di-*O*-methyl-1,2-*O*-isopropylidene-α-D-glucofuranose (17). The solution of the dimethyl ether **16** (0.25 g, 0.62 mmol) in methanol (15 mL) was stirred at room temperature for 8 h with 2 mL of ion exchange resin Amberlite IR-120 (H^+) and water (1 mL). TLC indicated the completion of hydrolysis. The solvent mixture was concentrated under reduced pressure to give a syrup (0.13 g) which was acetylated to give **17** (0.12 g, ∼67%), $[\alpha]_D^{28}$ − 20° (*c* 0.01, dichloromethane). The product contained a trace impurity, most probably due to the trace hydrolysis of the 1,2-*O*-isopropylidene group, as implied by the very small extra methyl (OAc and OMe) signals in the ^1H NMR spectrum. ^1H NMR: δ 5.97 (d, 1H, $J_{1,2}=3.7$ Hz, H-1), 4.70 (dd, 1H, $J_{5,6a}=2.3$, $J_{6a,6b}=12.0$ Hz, H-6_a), 4.68 (d, 1H, H-2), 4.27 (dd, 1H, $J_{3,4}=3.1$, $J_{4,5}=9.2$ Hz, H-4), 4.19 (dd, 1H, $J_{5,6b}=4.7$ Hz, H-6_b), 3.91(d, 1H, $J_{2,3}=0$ Hz, H-3), 3.79 (ddd, 1H, H-5), 3.56, 3.55 (2 × s, 6H, 2 × OMe), 2.19 (s, 3H, OAc), 1.59 (s, 3H, CH_3), 1.43 (s, 3H, CH_3).

Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.64. Found: C, 54.04; H, 7.34%.

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