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Note

1,2-*O*-Trichloroethylidene acetal group protected 3,5-dieno-1,4-furanose derivatives

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Abstract

The preparation of 3,5-(*E*)-dieno-3,5,6,8-tetradeoxy-(*S*)-1,2-*O*-trichloroethylidene-α-D-*glycero*-octo-1,4-furano-7-ulose starting from either 1,2-*O*-(*S*)-trichloroethylidene-α-D-glucofuranose (β-chloralose) or 1,2-*O*-(*S*)-trichloroethylidene-α-D-galactofuranose (galactochloralose) and the preparation of methyl 3,5-(*E*)-dieno-3,5,6-trideoxy-(*S*)-1,2-*O*-trichloroethylidene-α-D-*glycero*-hepta-1,4-furano-uronate starting from β-chloralose are described. Endocyclic double bond formations were realised by the elimination of 3-acetoxy groups using DMF–sodium bicarbonate. This elimination was not successful when the starting compound was 1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (α-chloralose), where the trichloromethyl group occupies the endo position.

Keywords: Cyclic acetals; Trichloroethylidene acetals; Chloralose; Unsaturated sugar derivatives

Reactions of aldohexoses with chloral using concentrated sulphuric acid as catalyst normally produce 1,2-*O*-trichloroethylidene acetals in which the sugar ring adopts the furanose form. Thus, 1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (**1**), 1,2-*O*-(*S*)-trichloroethylidene-α-D-glucofuranose (**2**), 1,2-*O*-(*R*)-trichloroethylidene-α-D-galactofuranose (**3**) and 1,2-*O*-trichloroethylidene-α-D-arabinofuranose are known[1,2] compounds. The compound **1** is also known as α-chloralose, which is a commercial compound used as an animal anaesthetic.[3] Trichloroethylidene acetal rings are stable under acidic and mildly basic conditions and they are useful protecting groups for further modifications of sugars. Under strongly basic conditions e.g. potassium *tert*-butoxide, these acetals can form dichloroethylidene ketene acetals and when the sugar stereochemistry permits, tricyclic ortho esters can also be formed.[2] Both of these structural types are useful intermediates for glycosidic bond formations.[4,5] Unsaturated sugar derivatives are additionally important as they can be used for the synthesis of many important substances.[6] The acetal carbon configuration of the compound **1** has been assigned by X-ray crystallography.[7] All other configurational assignments of the acetal carbons are based on the chemical shift comparison of the acetal proton singlets in their ^{1}H NMR spectra.[1,2] Acetals **1**, **2** and **3** were reacted with sodium periodate to give the crude dialdofuranoses in solid form. TLC indicated the presence of at least two components. It was shown by Inch[8] that the periodate oxidation of 1,2-*O*-iso-propylidene-α-D-glucofuranose provided the expected dialdofuranose mainly as a dimer, as expected from a β-hydroxy aldehyde. This reaction mixture also contained 3,5-methylene acetal as a byproduct. The dimer formation is favoured in non-polar solvents and Inch isolated the periodate oxidation products by extracting the crude product with chloroform. In our case the reaction solvent was a mixture of methanol and water since the acetals **1**, **2** and **3** are insoluble in water at room temperature. We have not studied the periodate oxidation products in detail but we assume that the crude mixture contained mainly the hydrate forms and some methyl acetals of the expected dialdofuranoses and possibly some 3,5-methylene acetal. In one case, 1,2-*O*-(*R*)-trichloro-ethylidene-α-D-glucofuranose (**1**), we obtained the dialdofuranose in good yield, in its pure hydrated form, by crystallization from hot water. The reactions of the crude periodate oxidation products

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from **1**, **2**, and **3** with appropriate phosphorane derivatives ($PPh_3=CHCOR$, R = CH_3 and OCH_3) and subsequent acetylations gave the compounds **4** to **9**. *Trans* isomers were the main products as expected. Small amounts of *cis* isomers were also present but these were not isolated in the pure state. The compounds **6**, **7**, and **8** were heated at 100 °C in *N*,*N*-dimethylformamide with solid sodium bicarbonate to obtain the dienes **10** and **11**. The compounds **6** and **8** gave the same diene **10** and thus, the assumed (*S*) acetal cofiguration of the previously known 1,2-*O*-(*S*)-trichloro-ethylidene-α-D-galactofuranose (**3**) was confirmed to be correct. Diene formation from **4** and **5** could not be effected even at higher temperatures with longer reaction times. Only a trace of product could be observed by TLC. The possible reason for this, is that the *endo*-trichloromethyl group is too close to H-4 (as indicated previously by the excessive down field shift of H-4 signal in the NMR spectrum)[1] which results in the repulsion of the base by this polar group (Scheme 1).

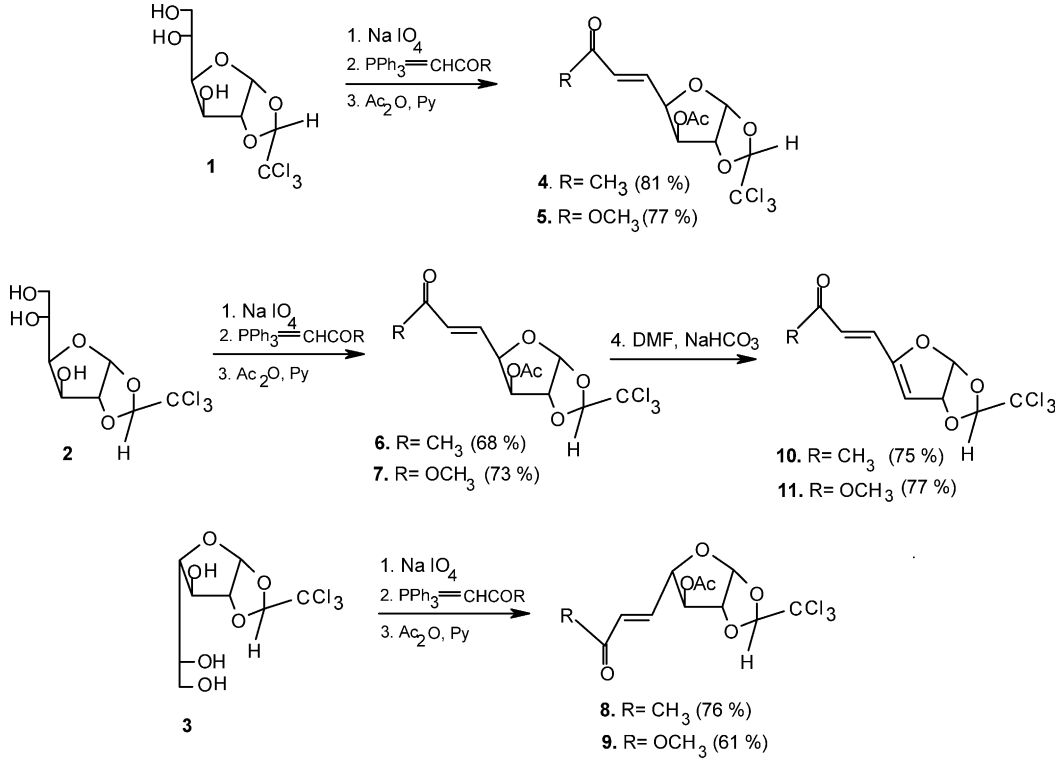
1. Experimental

1.1. General methods

^{1}H NMR spectra (Brucker GMBH DPX-400, and DPX-250) and MS spectra (Micromass UK Platform-II) were obtained at the Research Council (TUBITAK), Laboratories, Ankara, Turkey. Optical rotation measurements were carried out on a Schmidt-Haensch Polartronic E polarimeter. TLC and column chromatography were performed on precoated aluminium plates (Merck 5554) and silicagel G-60 (Merck 7734) respectively. Yield calculations for the compounds **4** to **9** are based on the hydrate forms of the dialdose derivatives.

1.2. Periodate oxidation of (*R*)-1,2-*O*-trichloroethylidene-α-D-glucofuranose (α-chloralose)

A hot solution of α-chloralose (10 g, 0.33 mol) in CH_3OH (150 mL) was mixed with a solution of $NaIO_4$ (8 g, 0.038 mol) in H_2O (200 mL) and stirred to give a clear solution. The solution was allowed to stand at room temperature (rt) for 2 h. The mass of crystals which formed was filtered and washed with CH_3OH. The filtrate and the washings were combined and concentrated under vacuum to give a solid product (9.4 g). Part of this crude product (4.7 g) was crystallised from hot water, filtered and air dried to give the expected dialdofuranose as the hydrate form (3.7 g, 78%): mp 138–142 °C (decomp.); $[\alpha]_D^{24}$ 4.4 (*c* 1.4, H_2O); ^{1}H NMR (CD_3OD, 100 MHz): δ 6.06 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.34 (s, 1 H, $HCCCl_3$), 4.63 (d, 1 H, $J_{2,3}$ 0 Hz, H-2); EIMS. *m*/*z* 277 (M^+-H_2O), 247 [$M^+-CH(OH_2)$], 101 (247−CCl_3CHO). Anal. Calcd for $C_7H_9Cl_3O_6$: C, 28.64; H, 2.73; Cl, 35.33. Found: C, 28.45; H, 2.39; Cl, 35.99.



Scheme 1.

1.3. 3-*O*-Acetyl-(*R*)-1,2-*O*-trichloroethylidene-5,6,8-trideoxy-α-D-*xylo*-oct-5(*E*)-eno-1,4-furano-7-ulose (4)

A solution of the above crude α-chloralose oxidation product (1 g) in DMF (30 mL) was stirred and heated at 100 °C with $PPh_3=CHCOCH_3$ (1.4 g, 0.0044 mol) for 2 h. The solvent was removed under vacuum and the resulting syrupy mixture was acetylated with Ac_2O (1 mL) in pyridine (30 mL) overnight at rt. Pyridine was removed under vacuum and the syrupy residue was applied to a silicagel column eluting with CH_2Cl_2–EtOAc (19/1). After combining the appropriate fractions, the solvent was evaporated to give a product which was crystallized from EtOAc (0.99 g, 81%), mp 134–135 °C, $[\alpha]_D^{19}$ 31.9 (*c* 0.56, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz): δ 6.57 (dd, 1 H, $J_{4,5}=4.3$ Hz, $J_{5,6}=16.2$ Hz, H_5), 6.36 (dd, 1 H, $J_{4,6}=1.2$ Hz, H_6), 6.15 (d, 1 H, $J_{1,2}=4.0$ Hz, H_1), 5.45 (d, 1 H, $J_{3,4}=3.4$ Hz, H_3), 5.35 (bm, 1 H, H_4), 5.32 (s, 1 H, $HCCCl_3$), 4.75 (d, 1 H, H_2), 2.22 (s, 3 H, CH_3CO), 2.00 (s, 3 H, $OCOCH_3$). Anal. Calcd for $C_{12}H_{13}Cl_3O_6$: C, 40.08; H, 3.64. Found: C, 40.10; H, 3.70.

1.4. Methyl 3-*O*-acetyl-5,6-dideoxy-(*R*)-1,2-*O*-trichloroethylidene-α-D-*xylo*-hept-5 (*E*)-eno-1,4-furano-uronate (5)

A solution of the above crude α-chloralose oxidation product (1 g) in DMF (30 mL) was stirred and heated at 100 °C with $PPh_3=CHCOOCH_3$ (1.4 g, 0.0042 mol) for 2 h. The solvent was removed under reduced pressure and the syrupy residue was acetylated in pyridine. Solvent was removed and the residue was purified on a silicagel column to give a syrupy product (0.98 g, 77%), $[\alpha]_D^{21}$ 26 (*c*, 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.78 (dd, 1 H, $J_{4,5}=4.6$ Hz, $J_{5,6}=15.7$ Hz, H_5), 6.19 (dd, 1 H, $J_{4,6}=1.7$ Hz, H_6), 6.19 (d, 1 H, $J_{1,2}=4.0$ Hz, H_1), 5.49 (d, 1 H, $J_{3,4}=3.4$ Hz, H_3), 5.34 (s, 1 H, $HCCCl_3$), 5.33 (m, 1 H, H_4), 4.78 (d, 1 H, $J_{2,3}=0$ Hz, H_2), 3.75 (s, 3 H, OCH_3), 2.05 (s, 3 H, $OCOCH_3$). Anal. Calcd for $C_{12}H_{13}Cl_3O_7$: C, 38.37; H, 3.49. Found: C, 38.38; H, 3.65.

1.5. Periodate oxidation of (*S*)-1,2-*O*-trichloroethylidene-α-D-glucofuranose (β-chloralose)

The title compound (10 g) was dissolved in hot CH_3OH (260 mL) and the procedure for the periodate oxidation of α-chloralose was followed to give 8.5 g of a crude solid product which was used for the following preparations without further purification.

1.6. 3-*O*-Acetyl-(*S*)-1,2-*O*-trichloroethylidene-5,6,8-trideoxy-α-D-*xylo*-oct-5(*E*)-eno-1,4-furano-7-ulose (6)

A DMF solution (30 mL) of the above β-chloralose oxidation product (1 g) was stirred with $PPh_3=CHCOCH_3$ (1.1 g, 0.0035 mol) at 100 °C for 2 h. The solvent was removed under reduced pressure and the residue was acetylated with Ac_2O (2 mL) in pyridine (20 mL), overnight at rt. The solution was concentrated to half volume and poured into crushed ice (100 g). The separated solid was filtered, dried and extracted with boiling petroleum ether to remove the *cis*-isomer. The remaining solid was decolourised with charcoal in CH_3OH. The title compound was crystallized from CH_3OH at ~5 °C, (0.83 g, 68%), mp 139–140 °C, $[\alpha]_D^{19}$ −19.9 (*c*, 0.6, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.61 (dd, 1 H, $J_{5,6}=16.1$ Hz, $J_{4,5}=4.6$ Hz, H_5), 6.41 (dd, 1 H, $J_{4,6}=1.6$ Hz, H_6), 6.33 (d, 1 H, $J_{1,2}=3.8$ Hz, H_1), 5.69 (s, 1 H, $HCCCl_3$), 5.41 (d, 1 H, $J_{3,4}=3.0$ Hz, H_3), 5.00 (d, 1 H, $J_{2,3}=0$ Hz, H_2), 4.91 (m, 1 H, H_4), 2.27 (s, 3 H, CH_3CO), 2.04 (s, 3 H, $OCOCH_3$). Anal. Calcd for $C_{12}H_{13}Cl_3O_6$: C, 40.08; H, 3.64. Found: C, 40.36; H, 3.71.

1.7. Methyl 3-*O*-acetyl-5,6-dideoxy-(*S*)-1,2-*O*-trichloroethylidene-α-D-*xylo*-hept-5 (*E*)-eno-1,4-furano-uronate (7)

The procedure of the previous experiment was followed using the above β-chloralose oxidation product (1 g) and $PPh_3=CHCOOCH_3$ (1.4 g, 0.0042 mol). Acetylated crude solid product was extracted with methanol, decolourised and crystallised at ~5 °C, after addition of some petroleum ether (0.93 g, 73%), mp 119–120 °C, $[\alpha]_D^{24}$ −34.8 (*c*, 0.7, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.80 (dd, 1 H, $J_{4,5}=4.7$ Hz, $J_{5,6}=15.7$ Hz, H_5), 6.33 (d, 1 H, $J_{1,2}=3.8$ Hz, H_1), 6.21 (dd, 1 H, $J_{4,6}=1.6$ Hz, H_6), 5.69 (s, 1 H, $HCCCl_3$), 5.41 (d, 1 H, $J_{3,4}=3.0$ Hz, H_3), 4.99 (d, 1 H, $J_{2,3}=0$ Hz, H_2), 4.90 (m, 1 H, H_4), 3.77 (s, 3 H, OCH_3), 2.06 (s, 3 H, $OCOCH_3$). Anal. Calcd for $C_{12}H_{13}Cl_3O_7$: C, 38.37; H, 3.48. Found: C, 38.28; H, 3.70.

1.8. Periodate oxidation of (*S*)-1,2-*O*-trichloroethylidene-α-D-galactofuranose (β-galactochloralose)

The procedure for the periodate oxidation of α-chloralose (10 g) was followed to give 8.3 g of a crude solid product, which was used for the following preparations without further purification. (This product dissolves in hot water and forms a gel on cooling.)

1.9. 3-*O*-Acetyl-(*S*)-1,2-*O*-trichloroethylidene-5,6,8-trideoxy-α-D-*arabino*-oct-5(*E*)-eno-1,4-furano-7-ulose (8)

The above β-galactochloralose oxidation product (1 g) was reacted first with $PPh_3=CHCOCH_3$ and then acetylated as for **4** to give the title compound as a syrup (0.84 g, 76%), $[\alpha]_D^{18}$ −45.1 (*c*, 0.58, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.83 (dd, 1 H, $J_{4,5}=3.7$ Hz, $J_{5,6}=16.0$ Hz, H_5), 6.36 (d, 1 H, $J_{1,2}=3.9$ Hz, H_1), 6.52 (dd, 1 H, $J_{4,6}=2.1$ Hz, H_6), 5.35 (s, 1 H, $HCCCl_3$), 5.22 (bs, 1 H, H_3), 5.02 (d, 1 H, $J_{2,3}=0$ Hz, H_2), 4.86 (bt, 1 H, H_4), 2.31 (s, 3 H, CH_3CO), 2.13 (s, 3 H, $OCOCH_3$). Anal. Calcd for $C_{12}H_{13}Cl_3O_6$: C, 40.08; H, 3.64. Found: C, 39.86; H, 3.57.

1.10. Methyl 3-*O*-acetyl-5,6-dideoxy-(*S*)-1,2-*O*-trichloroethylidene-α-D-*arabino*-hept-5 (*E*)-eno-1,4-furanouronate (9)

The above β-galactochloralose oxidation product (1 g) was reacted with $PPh_3=CHCOOCH_3$ (1.4 g, 0.0042 mol) as for **5**, to give the title compound as a syrup (0.78 g, 61%), $[\alpha]_D^{20}$ −52.45 (*c*, 0.6, CH_2Cl_2). ^1H NMR ($CDCl_3$, 250 MHz): δ 6.94 (dd, 1 H, $J_{4,5}=3.7$ Hz, $J_{5,6}=15.8$ Hz, H_5), 6.28 (d, 1 H, $J_{1,2}=3.9$ Hz, H_1), 6.22 (dd, 1 H, $J_{4,6}=2.2$ Hz, H_6), 5.31 (s, 1 H, $HCCCl_3$), 5.14 (bs, 1 H, H_3), 4.94 (d, 1 H, $J_{2,3}=0$ Hz, H_2), 4.77 (bt, 1 H, H_4), 3.71 (s, 3 H, OCH_3), 2.05 (s, 3 H, $OCOCH_3$). Anal. Calcd for $C_{12}H_{13}Cl_3O_7$: C, 38.37; H, 3.48. Found: C, 38.58; H, 3.26.

1.11. 3,5-(*E*)-Dieno-3,5,6,8-tetradeoxy-(*S*)-1,2-*O*-trichloroethylidene-α-D-*glycero*-octofurano-7-ulose (10)

A solution of the compound **6** (3 g, 0.0083 mol) in DMF (70 mL) was refluxed after the addition of sodium bicarbonate (1 g) for 90 min. TLC (toluene–methanol; 9/1) indicated one product. The solution was concentrated under vacuum and poured into crushed ice (200 g). The solid was filtered and washed with water and dried to give 1.94 g product. Crystallization from CCl_4 gave the pure **10** (1.87 g, 75%): mp 112–114 °C, $[\alpha]_D^{21}$ −97.6 (*c* 0.78, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.92 (d, 1 H, $J_{5,6}$ 15.8 Hz, H_5), 6.63 (d, 1 H, H_6), 6.32 (d, 1 H, $J_{1,2}$ 4.8 Hz, H_1), 5.74 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H_2), 5.54 (d, 1 H, H_3), 5.49 (s, 1 H, $HCCl_3$), 2.32 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ 197.2, 157.3, 131.3, 128.1, 106.9, 105.6, 105.3, 98.2, 85.5, 28.5. EI-MS: *m*/*z* 299.4 (M^+ + 1, 2.5%), 181.3 (M^+-CCl_3, 18%), 153.2 (M^+-CCl_3CHO, 14%), 117 ($^+CCl_3$, 37%), 82 (100%), 283.3 (M^+-CH_3, vs). Anal. Calcd for $C_{10}H_9Cl_3O_4$: C, 40.10; H, 3.03. Found: C, 40.32; H, 3.02.

This reaction was repeated by using the compound **8**, in place of **6**, to give the product, identical with compound **10** (74%), (IR and ^1H NMR, were identical and mp and mixed mp was 112–113 °C).

1.12. Methyl 3,5-(*E*)-dieno-3,5,6-trideoxy-(*S*)-1,2-*O*-trichloroethylidene-α-D-*glycero*-heptafuranouronate (11)

A solution of the compound **7** (0.5 g, 0.0013 mol) in DMF (15 mL) was refluxed after the addition of sodium bicarbonate (0.15 g) for 90 min. TLC (toluene–methanol, 9:1) indicated one product. The solution was concentrated under vacuum and poured onto crushed ice (50 g). A syrupy product separated which was taken into dichloromethane, washed with water and dried. Removal of the solvent gave the crude product (0.39 g) which was crystallized from petroleum ether (0.3 g, 77%), mp 128–129 °C, $[\alpha]_D^{24}$ −84.08 (*c* 0.66, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.06 (d, 1 H, $J_{5,6}$ 15.7 Hz, H_5), 6.32 (d, 1 H, H_6), 6.29 (d, 1 H, $J_{1,2}$ 4.8 Hz, H_1), 5.70 (b, 1 H, H_2), 5.47 (d, 1 H, $J_{2,3}$ 2.2 Hz, H_3), 5.45 (s, 1 H, $HCCl_3$), 3.75 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$): δ 166.5, 157.3, 130.8, 124.3, 107.2, 105.7, 105.3, 98.6, 85.8, 52.3; MS: *m*/*z* 314 (M^+, 17%), 283 (M^+-OCH_3, 30%), 197 (M^+-CCl_3, 100%), 169 (M^+-CCl_3CHO, 60%). Anal. Calcd for $C_{10}H_9Cl_3O_5$: C, 38.05; H, 2.87. Found: C, 38.35; H, 3.16.

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