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Tricyclic furanoid dichloroacetyl orthoesters of D-mannose from 1,2-*O*-trichloroethylidene-β-D-mannofuranose

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Abstract—1,2-*O*-(*R*)-Trichloroethylidene-β-D-mannofuranose (**1**) was obtained from the reaction of D-mannose with chloral. Reaction of **1** with potassium *tert*-butoxide (3 M equiv) gave the thermodynamically stable 1,2,5-*O*-orthodichloroacetyl-β-D-mannofuranose as the sole product whereas 1.5 M equiv of reagent gave the kinetically controlled 1,2,3-*O*-orthodichloroacetyl-β-D-mannofuranose (**10**) as the main product. Orthoester **10** gave the 5,6-isopropylidene derivative, which was also obtained from the reaction of 5,6-*O*-isopropylidene-1,2-*O*-(*R*)-trichloroethylidene-β-D-mannofuranose with potassium *tert*-butoxide (1.5 M equiv). These novel orthoesters are expected to prove useful as protecting groups and as building blocks in the formations of new mannofuranisidic units.

Keywords: Sugar acetals; Sugar orthoesters; Trichloroethylidene acetals; Glycosylation

1. Introduction

Mannose would be expected to form furanoid 1,2-, 2,3-, 3,5- and 5,6-acetals.[1] However, known furanoid derivatives of D-mannose usually involve 2,3- and 5,6-ketal rings. As far as we are aware, no furanoid 1,2-*O*-alkylidene acetal of D-mannose has been reported. Isopropylidenation of D-mannose with acetone using sulfuric or hydrochloric acids (1%) as catalyst or with 2,2-dimethoxypropane (2,2-DMP) in DMF using *p*-toluenesulfonic acid both afforded 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose as the major product, partial hydrolysis of which gave 2,3-*O*-isopropylidene-D-mannofuranose.[1,2] These ketals have been used for the preparation of 1-*O*-isobutyryl and pivaloyl esters of 2,3-isopropylidene-α-D- and β-D-mannofuranose, which exhibited biological activities.[3] The condensation of D-mannose with cyclohexanone in the presence of sulfuric acid catalyst also gave the furanoid 2,3:5,6-di-*O*-ketal.[1] Isopropylidenation of D-mannose with 2 M equiv of isopropenyl methyl ether afforded 4,6-*O*-isopropylidene-α-D-mannopyranose as kinetically controlled product where as a large excess of the reagent gave 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranose.[4] Sugars preferably react in their furanose forms with chloral to give trichloroethylidene acetals. Thus 1,2-*O*-trichloroethylidene acetals of D-glucofuranose[5], D-galactofuranose[6] and D-arabinofuranose[7] are known. 1,2-*O*-(*R*)-Trichloroethylidene-α-D-glucofuranose is a commercially available compound, also known as α-chloralose, which is used as an anaesthetic for animals.[8] Tricyclic dichloroacetyl orthoester formations using 1,2-*O*-trichloroethylidene acetals of D-galactose and D-arabinose were reported by us previously.[7] The reactions most probably proceed via formation of dichloroethylidene ketene acetal by dehydrochlorination of the trichloroethylidene acetal group, followed by the nucleophilic attack of the stereochemically suitable hydroxyl group, on the ketene acetal carbon. The use of 1,2-*O*-alkyl orthoesters in the glycosylation reactions are well known, but recently tricyclic orthoesters have also been an area of interest since these are suitable compounds for the

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stereoselective formation of interglycosidic linkages.[9] For example, 1,2,5-orthobenzoate and 1,2,5-orthodichloroacetate esters of D-arabinose have been used as building blocks for the formation of the arabinofuranosidic units and thereby the synthesis of the tetrasaccharidic cap of the lipoarabinomannan of *Mycobacterium tuberculosis* was realised.[10,11] Some tricyclic orthoesters of D-mannopyranose derivatives are known. Thus, 4-*O*-benzyl-1,2,3-*O*-orthoacetyl-6-*O*-(triphenylmethyl)-β-D-mannopyranose has been prepared and used as a building block for the synthesis of the disaccharidic unit of the bleomycin group antibiotics.[12] Formation of 3-*O*-acetyl-1,2,4-*O*-orthoacetyl-6-*O*-(triphenylmethyl)-β-D-mannopyranose, in low yield was also reported in the same work. Formation of the 1,2,6-*O*-orthoacetyl derivative of D-mannopyranose and its glycosylation reactions have also been described.[9]

2. Results and discussion

Reaction of D-mannose with chloral using sulfuric acid as catalyst formed a complicated mixture of products. However the dominating product, which was 1,2-*O*-(*R*)-trichloroethylidene-β-D-mannofuranose (**1**) (β-mannochloralose) was easily isolated. The relatively low yield is attributed to the possibility of some degradation of the sugar by the sulfuric acid catalyst. In the reaction of D-mannose, the amount of the acid catalyst was critical as excess use of sulfuric acid caused the formation of an infusible and insoluble black powder, whereas insufficient acid catalyst or lower reaction temperatures were found to decrease the yields. The reaction product of D-mannose could be separated into dichloromethane insoluble and soluble parts, the former of which contained the crude 1,2-*O*-trichloroethylidene acetal (**1**). The dichloromethane soluble part probably contained mainly self-condensation products of chloral, some mono acetals and diastereoisomers of diacetals and anhydro mannose derivatives. A single diastereoisomer of 1,2-*O*-trichloroethylidene-β-D-mannofuranose (**1**) was the only monoacetal, which could be obtained in pure form in 25% yield. Although the yield of this compound is low, the reactants are inexpensive and readily available and the compound could easily be prepared repeatedly if required in larger amounts. All other products observed in TLC, seem to be present in much lower yields under the reaction conditions. The first evidence for the structure of **1** was provided by the ^{1}H NMR spectrum of its triacetate **2** in which the proton signals on C-3, as well as C-5 and C-6 appeared at relatively low fields, as expected from *O*-acetyl substitution, whereas the value for the H-1 signal (δ 6.03) is not at sufficiently low field when compared with the H-1 signal (δ 6.24) of 1,5,6-tri-*O*-acetyl-2,3-*O*-isopropylidene-α-D-mannofuranose in $CDCl_3$.[4] However, complete structural information of the free acetal **1** was provided by its ^{1}H NMR and NOESY spectra (400 MHz) in Me_2SO-d_6 in which all proton signals are well resolved including the free hydroxyl ones. Thus free hydroxyl protons at C-3 and C-5 appeared as doublets ($J = 5.5$ Hz for each) at δ 5.51 and δ 4.58 and the free hydroxyl proton on C-6 appeared at δ 4.37 as a dd ($J_{OH,H6a} = J_{OH,H6b} = 5.5$ Hz). Free hydroxyl protons underwent exchange upon addition of a drop of D_2O and the related signals disappeared. The only signal patterns, which did not change after the addition of D_2O, belonged to H-1, H-2 and H-4. The signals arising from H-3, H-5 and H-6 were complicated due to the couplings to the free hydroxyl protons but produced simplified patterns after D_2O exchange (Tables 1 and 2). The analysis was also supported by the NOESY spec-

Table 1. ^{1}H NMR (400 MHz) chemical shifts (δ ppm) of 1,2-*O*-trichloroethylidene-β-D-mannofuranose (**1**) and 1,2,5-tri-*O*-dichloroacetyl-β-D-mannofuranose (**8**) in Me_2SO-d_6

Compound	H Acetal	CCl_2H	OH-3	OH-5	OH-6	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
1	5.68 s		5.46 d	4.58 d	4.37 dd	5.83 d	5.00 dd	4.87 m	3.74 dd	3.81 m	3.57 ddd	3.36 m
1[a]	5.68 s		—	—	—	5.83 d	5.00 dd	4.22 dd	3.74 dd	3.80 ddd	3.56 dd	3.35 dd
8	—	6.44 s	5.33 d	—	5.01 dd	5.95 d	4.62 dd	4.11 dd	4.34 d	4.00 dd	3.61 m	3.50 m
8[a]	—	6.40 s	—	—	—	5.93 d	4.61 dd	3.99 dd	4.31 d	4.01 dd	3.58 dd	3.48 dd

[a] After D_2O exchange.

Table 2. ^{1}H NMR (400 MHz) $J_{H,H}$ values (Hz) of 1,2-*O*-trichloroethylidene-β-D-mannofuranose (**1**) and 1,2,5-tri-*O*-dichloroacetyl-β-D-mannofuranose (**8**) in Me_2SO-d_6

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{3,OH-3}$	$J_{5,OH-5}$	$J_{6a,OH-6}$ and $J_{6b,OH-6}$
1	4.3	5.5	4.7	8.8	3.0	5.5	11.3	5.5	5.5	5.5
1[a]	4.7	5.1	4.7	8.8	2.8	5.8	11.3	—	—	—
8	3.5	5.0	6.6	0.0	7.8	5.5	—	5.5	—	5.5
8[a]	3.9	5.0	6.6	0.0	5.0	5.0	11.0	—	—	—

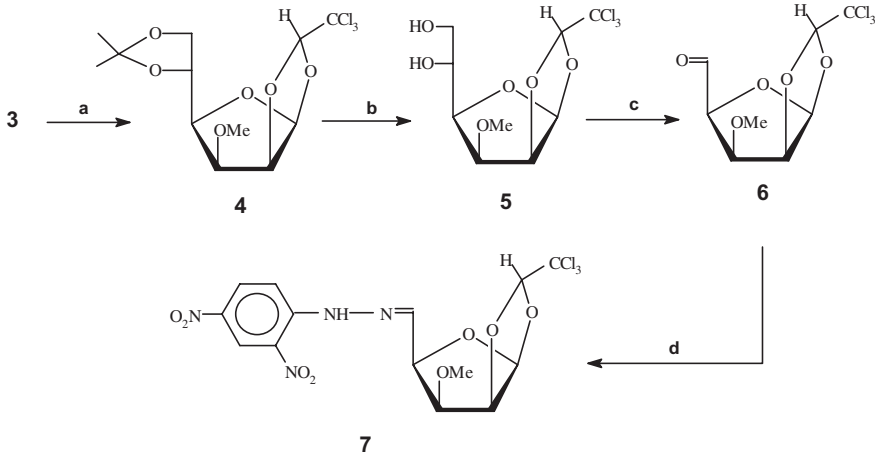
[a] After D_2O exchange.

trum and simulation. These results indicate that the trichloroethylidene group must occupy the positions C-1 and C-2 on a furanose structure.

Evidence for the acetal carbon configuration was also provided by the NOESY spectrum in which an interaction is apparent between the acetal proton and H-5. This indicates that the acetal proton occupies the *endo* position and therefore the acetal carbon configuration must be (*R*). Furthermore there are no cross peaks between the acetal proton signal and the signals of H-1 and H-2 showing that they have a *trans* stereochemical relation. Cross peaks between the hydroxyl protons are also observed indicating their proximity. Isopropylidenation of **1** gave 5,6-*O*-isopropylidene-1,2-*O*-trichloroethylidene-β-D-mannofuranose (**3**), methylation of which gave the 3-*O*-methyl derivative **4**. The removal of the isopropylidene group of **4** with acidic hydrolysis using Amberlite-120 (H^+) gave 3-*O*-methyl-1,2-*O*-trichloroethylidene-β-D-mannofuranose (**5**). A solution of the compound **5** in equal volumes of methanol–water, containing 1% hydrochloric acid, was refluxed for several hours and compound **5** was recovered unchanged. The compound **5** was smoothly oxidised with sodium metaperiodate in methanol–water to give 3-*O*-methyl-1,2-*O*-trichloro-ethylidene-β-D-*lyxo*-1,4-furanodialdose (**6**) in a crystalline form. The dialdose **6** was also characterised as its 2,4-dinitrophenylhydrazone **7** (Scheme 1). The ^{1}H NMR chemical shift values of the hydrazone **7** are in close agreement with the known L-*arabino* and D-*xylo* analogues.[6,13] The above results and the orthoester formation reactions described below clearly indicate that the compound **1** has the proposed 1,2-*O*-(*R*)-trichloroethylidene-β-D-mannofuranose structure. The acetal carbon configuration is expected to be *R* for a more stable diastereoisomer since the trichloromethyl group should prefer to occupy an *exo* position for steric reasons. Indeed, the acetal proton signals of **1** and its derivatives (**2**–**7**) resonate at relatively lower fields (δ 5.50–6.00), which are consistent with the values of (*S*)-1,2-*O*-trichloroethylidene-α-D-glucofuranose[5] and (*S*)-1,2-*O*-trichloroethylidene-α-D-galactofuranose derivatives[6,14] when compared with the values of (*R*)-1,2-*O*-trichloroethylidene-α-D-glucofuranose and its derivatives, which are in the range of δ 5.3–5.5.[5,13,15] Based on these results we believe we can safely assume that the acetal carbon configuration of **1** is (*R*).

A 3 h reflux of **1** with excess potassium *tert*-butoxide (appr. 3 M equiv) in *tert*-butanol gave essentially a single product (TLC). Intermediate products were observable by TLC at the early stages of the reaction. The pure compound isolated in 65% yield was shown to be 1,2,5-*O*-orthodichloroacetyl-β-D-mannofuranose (**8**) by spectroscopy. (The reaction completed in only 10 min when 6.0 M equiv *tert*-butoxide was used.) In the ^{1}H NMR spectrum of **8** in Me_2SO-d_6, the free hydroxyl protons appeared as a doublet ($J_{OH,H-3} = 5.5$ Hz) and as a dd ($J_{OH,H-6a} = J_{OH,H-6b} = 5.5$ Hz). These signals disappeared after D_2O exchange and only the splitting patterns of the H-3 and H-6 signals changed to the simplified patterns at the same time, indicating that the free hydroxyl groups are bound to C-3 and C-6 (Tables 1 and 2). It is also worth mentioning that the coupling constant $J_{4,5}$ is zero in the spectra of **8** and its acetate derivative **9**, (Tables 2 and 3). Molecular models indicate that the dihedral angle between H-4 and H-5 is almost 90°, which is consistent with the observed $J_{4,5}$ values. These results clearly show the assigned structure. The additional data for **8** is provided by its ^{13}C spectrum (see Section 3) (Scheme 2).

The structure of 1,2,3-*O*-orthodichloroacetyl-β-D-mannofuranose (**10**) was studied with spectroscopy as well as chemical reactions. This compound was obtained as a syrup, however it reacted with 2,2-DMP to form the 5,6-*O*-isopropylidene derivative **11**, which is crystalline. Compound **11** was also directly and more easily obtained from 5,6-*O*-isopropylidene-1,2-*O*-trichloroethylidene-β-D-mannofuranose (**3**) with a much better yield (85%) by dehydrochlorination, using appr. 1.5 M equiv

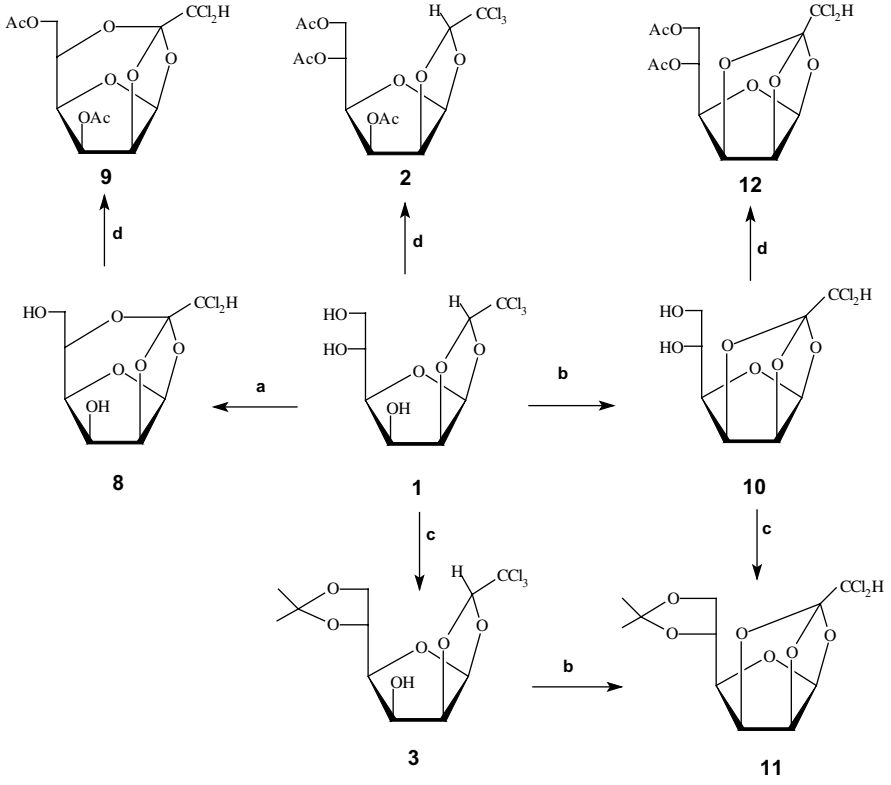


Scheme 1. Reagents and conditions: (a) MeI, BaO; (b) IR-120 (H^+), H_2O; (c) $NaIO_4$; (d) 2,4-DNPH, H^+.

Table 3. ^{1}H NMR (400 MHz) chemical shifts (δ ppm) and $J_{H,H}$ values (Hz) in $CDCl_3$, for the ring protons

Compound	H-1	$J_{1,2}$	H-2	$J_{2,3}$	H-3	$J_{3,4}$	H-4	$J_{4,5}$	H-5	$J_{5,6a}$	H-6a	$J_{6a,6b}$	H-6b	$J_{5,6b}$
2	6.06 d	4.4	5.15 dd	6.0	5.32 dd	6.0	4.31 dd	9.5	5.43 ddd	2.4	4.64 dd	12.4	4.14 dd	5.2
3	6.02 d	4.3	5.02 dd	5.8	4.39 dd	5.8	3.99 dd	8.5	4.40	6.2	4.16 dd	9.0	4.02 dd	5.1
4	5.92 d	4.3	5.05 dd	5.5	3.86 dd	5.5	4.08 dd	9.0	3.97 m	6.6	4.38 dd	13.5	3.97	—
5	6.07 d	4.3	5.04 dd	4.7	4.07 dd	7.0	4.14 dd	9.4	3.98 ddd	3.5	3.85 dd	11.5	3.67 dd	5.0
6	6.14 d	3.9	5.01 dd	3.9	4.24 dd	7.8	4.58 dd	0.8	9.70 d					
7[a]	6.22 d	3.9	5.15 dd	5.0	4.15 dd	7.4	4.96 dd	6.6	7.53 d					
8	5.97 d	3.9	4.70 dd	6.0	4.28 dd	6.0	4.36 d	0.0	4.41 dd	5.5	3.89 dd	12.0	3.83 dd	5.0
9	5.87 d	3.7	4.89 dd	4.5	4.81 dd	5.7	4.39 d	0.0	4.34 dd	7.0	4.21 dd	11.2	4.09	7.5
10	5.64 d	2.3	5.35 dd	2.3	4.72 dd	3.0	4.25 dd	8.6	3.96 ddd	3.0	3.88 dd	11.5	3.74 dd	5.0
11	5.66 d	2.4	5.35 dd	2.8	4.62 dd	2.8	4.20 dd	7.4	4.30 ddd	6.0	4.11 dd	9.0	4.03 dd	4.6
12	5.65 d	2.7	4.35 dd	2.7	4.58 dd	2.7	4.43 dd	8.8	5.14 ddd	3.0	4.62 dd	12.5	4.20 dd	3.9

[a]Data for the nonsugar part is given in Section 3.



Scheme 2. Reagents and conditions: (a) K *tert*-butoxide (3.0 M equiv); (b) K *tert*-butoxide (1.5 M equiv); (c) 2,2-DMP, *p*-TsOH; (d) Py, Ac_2O.

potassium *tert*-butoxide. Both products were identical (mp, mmp and their ^{1}H NMR spectra were all identical). The mass spectrum of compound **11** showed a main peak (100%) at m/z 101, which indicates that the 5,6-*O*-isopropylidene group is intact overall, therefore, the results indicate that the assigned structure for **10** is correct. Previous studies have indicated that in accordance with electronic factors, the Lewis acid catalysed opening of the tricyclic orthodichloroacetyl derivative of D-arabinose is more difficult than for the corresponding orthobenzoate derivatives and more Lewis acid catalyst is necessary to bring the reaction to completion.[10,11] The opening of 5,6-*O*-isopropylidene-1,2,3-*O*-orthodichloroacetyl-β-D-mannofuranose (**11**) is expected to be easier due to the strained ring structure of this compound. ^{1}H NMR data in $CDCl_3$ for the compounds **2**–**12** are given in Tables 3 and 4.

3. Experimental

3.1. General methods

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) and NOESY spectra were recorded on a Varian AS 400 instrument. Optical rotation measurements were carried out on a Schmidt–Haensch Polartronic E polarimeter. TLC and column chromatography were performed on precoated

Table 4. ^{1}H NMR (400 MHz) chemical shifts (δ ppm) for nonring protons, in $CDCl_3$ (all singlets)

Compound	H Acetal	CCl_2H	OCH_3	OAc	CH_3 Isopropylidene
2	5.69			2.12; 2.09; 2.00	
3	5.73				1.44; 1.38
4	5.64		3.58		1.40; 1.36
5	5.69		3.60		
6	5.57		3.57		
7[a]	5.74		3.56		
8		6.40			
9		5.77		2.15; 2.08	
10		6.03			
11		6.05			1.44; 1.37
12		5.99		2.07; 2.06	

[a]Data for the nonsugar part is given in Section 3.

aluminium plates (Merck 5554) and silicagel G-60 (Merck 7734), respectively. All solvent removals were carried out under reduced pressure. Mass spectra were recorded on HP 6890 GC/MS. Dichloromethane–methanol (9:1) was used for TLC.

3.2. 1,2-*O*-(*R*)-Trichloroethylidene-β-D-mannofuranose (β-mannochloralose) (1)

Dry D-mannose (35 g, 194 mmol) and concentrated sulfuric acid (0.3 g) were added to freshly distilled chloral (92 mL, 944 mmol) gradually, under continuous stirring and the mixture was refluxed for 3 h. Excess chloral was removed under reduced pressure and the black coloured syrupy mixture obtained was added to dichloromethane (50 mL) while slightly warm (the syrupy mixture solidifies on cooling and dissolution in dichloromethane becomes difficult). An additional 300 mL dichloromethane was added in order to break up and dissolve all solidified material. Subsequently, the ice-cooled dichloromethane solution deposited the crude β-mannochloralose (**1**) as a brown solid, which was air dried and dissolved in methanol and decolourised with activated charcoal. The product was obtained as colourless crystals (15 g, 25%) from methanol solution, mp 205–206 °C, $[\alpha]_D^{27}$ −13.0 (*c* 0.4, MeOH); ^{13}C NMR (Me_2SO-d_6): δ 109.59 (H*C*CCl_3), 105.30 (C_1), 99.71 (CCl_3), 83.39, 81.77 (C_2 and C_3), 70.05, 69.99 (C_4 and C_5), 63.83 (C_6).

Anal. Calcd for $C_8H_{11}Cl_3O_6$: C, 31.04; H, 3.58. Found: C, 31.04; H, 3.54.

3.3. 3,5,6-Tri-*O*-acetyl-1,2-*O*-(*R*)-trichloroethylidene-β-D-mannofuranose (2)

Acetylation of **1** (0.5 g, 1.6 mmol) in pyridine (5 mL) with Ac_2O (1.5 mL, 16 mmol) at room temperature afforded the triacetate **2** (0.8 g, 71%), mp 162–164 °C, $[\alpha]_D^{29}$ −22.5 (*c* 0.5, CH_3OH).

Anal. Calcd for $C_{14}H_{17}Cl_3O_9$: C, 38.60; H, 3.93. Found: C, 38.14; H, 3.89.

3.4. 5,6-*O*-Isopropylidene-1,2-*O*-(*R*)-trichloroethylidene-β-D-mannofuranose (3)

A solution of compound **1** (5 g, 16.2 mmol) in DMF (25 mL) was stirred with 2,2-DMP (5 mL, 40.8 mmol) and *p*-toluenesulfonic acid (10 mg) for 7 h at room temperature and then neutralised with sodium bicarbonate solution. The solvent was removed and the residue was crystallised from methanol at 0 °C to give pure **3** (4.6 g, 81%) mp 168–169 °C, $[\alpha]_D^{26}$ −34.0 (*c* 0.25, $CHCl_3$); ^{13}C NMR ($CDCl_3$): δ 110.55, 110.41 (2× acetal carbons), 106.03 C_1, 99.35 (CCl_3), 82.35, 81.67, 74.04, 71.57, 67.72 (C_2 to C_6), 27.10, 25.53 (2× CH_3).

Anal. Calcd for $C_{11}H_{15}Cl_3O_6$: C, 37.79; H, 4.32. Found: C, 37.74; H, 3.99.

3.5. 5,6-*O*-Isopropylidene-3-*O*-methyl-1,2-*O*-(*R*)-trichloroethylidene-β-D-mannofuranose (4)

A solution of compound **3** (1 g, 2.86 mmol) in DMF (20 mL) was stirred with BaO (1 g, 6.52 mmol) and MeI (1 mL, 16.06 mmol) at room temperature until TLC indicated the completion of the reaction (6 h). The solvent was removed and the residue was extracted with dichloromethane (2 × 30 mL), which was decolourised with dilute sodium thiosulfate solution and washed with water (3 × 25 mL). The dried dichloromethane solution was rotary evaporated to give the title compound **4** as pure white crystals (0.88 g, 85%), mp 108–109 °C, $[\alpha]_D^{21}$ −30.2 (*c* 0.1, CH_2Cl_2).

Anal. Calcd for $C_{12}H_{17}Cl_3O_6$: C, 39.64; H, 4.71. Found: C, 39.90; H, 4.50.

3.6. 3-*O*-Methyl-1,2-*O*-(*R*)-trichloroethylidene-β-D-mannofuranose (5)

A solution of compound **4** (0.73 g, 2.0 mmol) in methanol (50 mL) was stirred with Amberlite IR-120 (H^+) resin (15 mL) and water (5 mL) for 3 h, by which time TLC indicated the complete hydrolysis of **4**. The solvent was removed after the filtration of resin to give the title compound **5** as a syrup (0.51 g, 78%), $[\alpha]_D^{21}$ −48.1 (*c* 0.16, CH_2Cl_2).

Anal. Calcd for $C_9H_{13}Cl_3O_6$: C, 33.41; H, 4.05. Found: C, 33.64; H, 4.12.

3.7. 3-*O*-Methyl-1,2-*O*-(*R*)-trichloroethylidene-β-D-*lyxo*-1,4-furanodialdose (6)

A solution of the 3-*O*-methyl ether **5** (0.41 g, 1.26 mmol) in methanol (15 mL) was mixed with a solution of sodium metaperiodate (0.33 g, 1.5 mmol) in water and

kept at room temperature for 3 h by which time TLC indicated a single product. The solution was concentrated approximately to half volume and extracted with dichloromethane (2 × 40 mL). The organic phase was separated and washed with water and dried to give the pure dialdose **6** (0.32 g, 87%), mp 96–97 °C, $[\alpha]_D^{20}$ 49.4 (*c* 0.28, CH_2Cl_2).

Anal. Calcd for $C_{11}H_{15}Cl_3O_6$: C, 32.96; H, 3.11. Found: C, 33.14; H, 3.27.

3.8. 3-*O*-Methyl-1,2-*O*-(*R*)-trichloroethylidene-β-D-*lyxo*-1,4-furanodialdose-2,4-dinitrophenylhydrazone (7)

A solution of the dialdose **6** (0.16 g, 0.55 mmol) in ethanol (20 mL) was mixed with an acidified solution (with 1.4 mL concentrated hydrochloric acid) of 2,4-dinitrophenylhydrazine (0.113 g, 0.57 mmol). The reaction was complete in 20 min (TLC). The solvent was removed and the residue was extracted with dichloromethane (5 × 20 mL), which was then washed with dilute sodium carbonate solution and water (5 × 10 mL), and then dried with sodium sulfate. The solvent was removed and the residual syrup was crystallised from ethanol saturated with petroleum ether (40–60 °C) to give the title compound **7** (0.18 g, 69%), mp 150–152 °C, $[\alpha]_D^{20}$ 99.5 (*c* 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.16 (s, 1H, NH), 9.12 (d, 1H, J_{meta} 2.7 Hz, Ph), 8.33 (dd, 1H, $J_{ortho} = 9.5$ Hz, Ph), 7.98 (d, 1H, Ph), 7.53 (d, 1H, $J_{4,5} = 6.6$ Hz, H_5), 6.22 (d, 1H, $J_{1,2} = 3.9$ Hz, H_1), 5.74 (s, 1H, $HCCCl_3$), 5.15 (dd, 1H, $J_{2,3} = 3.9$ Hz, H_2), 4.96 (dd, 1H, H_4), 4.15 (dd, 1H, $J_{3,4} = 7.4$ Hz, H_3), 3.56 (s, 3H, OCH_3).

Anal. Calcd for $C_{14}H_{13}Cl_3N_4O_8$: C, 35.65; H, 2.78; N, 11.87. Found: C, 35.80; H, 3.05; N, 11.5.

3.9. 1,2,5-*O*-Orthodichloroacetyl-β-D-mannofuranose (8)

A solution of the acetal **1** (0.97 g, 3.0 mmol) in *tert*-butanol (50 mL) was mixed with potassium *tert*-butoxide (1.03 g, 9.0 mmol) and the mixture was refluxed for 40 min by which time TLC indicated a single product. (The reaction completed in only 10 min when 6.0 M equiv *tert*-butoxide was used.) The mixture was filtered and the filtrate was evaporated. The syrupy residue was dissolved in dichloromethane, which on cooling afforded the crystals of the orthoester **8** (0.56 g, 65%), mp 110–111 °C, $[\alpha]_D^{24}$ −35.6 (*c* 0.08, CH_2Cl_2).

Anal. Calcd for $C_8H_{10}Cl_2O_6$: C, 35.19; H, 3.69. Found: C, 35.52; H, 3.57.

3.10. 3,6-Di-*O*-acetyl-1,2,5-*O*-orthodichloroacetyl-β-D-mannofuranose (9)

Acetylation of **8** (0.2 g, 0.7 mmol) in pyridine (2 mL) with Ac_2O (0.7 mL, 7.4 mmol) gave the diacetate **9** (0.22 g, 84%), mp 139–140 °C, $[\alpha]_D^{15}$ −93.8 (*c* 0.08, EtOAc). ^{13}C NMR (Me_2SO-d_6): δ 170.54, 170.00 (2× $OCOCH_3$), 120.23 (orthoester C), 104.00 (C_1), 79,57, 75.76, 75.23, 73.81, 69.28, 62.75 (C_2 to C_6 and CCl_2H), 20.99, 20.75 (2× $OCOCH_3$). EI-MS: *m*/*z* 357 (M^+), 283 (M^+-CH_2OAc), 225 (283−OAc), 43 (Ac, 100%).

Anal. Calcd for $C_{12}H_{14}Cl_2O_8$: C, 40.36; H, 3.95. Found: C, 40.39; H, 3.99.

3.11. 1,2,3-*O*-Orthodichloroacetyl-β-D-mannofuranose (10)

A solution of the acetal **1** (0.70 g, 2.26 mmol) in *tert*-butanol (50 mL) was mixed with potassium *tert*-butoxide (0.39 g, 3.47 mmol; 1.46 M equiv) and the mixture was refluxed for 6 h. TLC showed that some 1,2,5-*O*-orthodichloroacetyl-β-D-mannofuranose (**8**) had formed but a slower moving compound was present as the main product as well as some unreacted acetal **1**. The reaction mixture was filtered and the solvent was removed to give a residue (0.61 g), which was applied to a silicagel column (1.8 × 60 cm), eluting with dichloromethane (500 mL) first and then with dichloromethane–methanol (99:1). 1,2,5-*O*-Orthodichloro-acetyl-β-D-mannofuranose (**8**) (0.12 g, 19%) was eluted first. The title compound 1,2,3-*O*-orthodichloroacetyl-β-D-mannofuranose (**10**) was eluted as a second product (0.30 g, 48%), which was obtained as a pure syrup after removal of the solvent, (the unreacted starting compound (**1**) (0.12 g) was eluted finally).

Anal. Calcd for $C_8H_{10}Cl_2O_6$: C, 35.19; H, 3.69. Found: C, 35.53; H, 3.97.

3.12. 5,6-*O*-Isopropylidene-1,2,3-*O*-orthodichloroacetyl-β-D-mannofuranose (11)

A—A solution of the orthoester **10** (0.38 g, 1.39 mmol) in DMF (50 mL) was stirred with the addition of 2,2-dimethoxypropane (2 mL, 16.3 mmol) and *p*-toluen-sulfonic acid (10 mg). TLC revealed that the reaction had practically ended after 2 h. The mixture was neutralised with sodium bicarbonate solution and the solvent was removed. The residue (0.29 g) obtained was purified on a silicagel column, eluting with dichloromethane (100 mL) first and then with dichloromethane–methanol (99:1) to give the pure title compound **11** (0.28 g, 64%), which was crystallised from hot carbon tetrachloride, mp 130–132 °C, $[\alpha]_D^{21}$ −27.8 (*c* 0.66, CH_2Cl_2).

B—A solution of 5,6-*O*-isopropylidene-1,2-*O*-(*S*)-trichloroethylidene-β-D-mannofuranose (**3**) (2.0 g, 5.7 mmol) in *tert*-butanol (95 mL) was stirred and refluxed with potassium *tert*-butoxide (0.97 g, 8.6 mmol) for 2 h, by which time TLC showed the completion of the reaction. The mixture was filtered and the filtrate was rotary evaporated to give a syrup, which was crystallised from hot carbontetrachloride to give the pure title compound **11** (1.51 g, 84%), mp and mmp 130–132 °C, $[\alpha]_D^{26}$ −27.5 (*c* 0.35 CH_2Cl_2). ^{13}C NMR ($CDCl_3$):

117.77 (orthoester C), 109.60 (acetal C), 102.55 (C_1), 81.59, 80.62, 76.71, 74.35, 66.64, 64.50 (C_2 to C_6 and CCl_2H), 27.11, 25.36 ($2\times CH_3$); EI-MS: m/z 297 (M^+-Me, 25%), 101 (2,2-dimethyl-1,3-dioxolane, 100%).

Anal. Calcd for $C_{11}H_{14}Cl_2O_6$: C, 42.19; H, 4.51. Found: C, 42.29; H, 4.27.

3.13. 5,6-Di-*O*-acetyl-1,2,3-*O*-orthodichloroacetyl-β-D-mannofuranose (12)

Acetylation of **10** (0.2 g, 0.73 mmol) in pyridine (2 mL) with Ac_2O (0.7 mL, 7.4 mmol) gave the diacetate **12** (0.24 g, 91%) as a syrup, $[\alpha]_D^{15}$ −16.6 (*c* 2.3, EtOAc). ^{13}C NMR ($CDCl_3$): δ 170.75, 169.48 ($2\times OCOCH_3$), 117.94 (orthoester C), 102.55 (C_1), 80.56, 78.65, 76.28, 70.27, 64.27, 62.32 (C_2 to C_6 and CCl_2H), 21.09, 20.98 ($2\times OCOCH_3$).

Anal. Calcd for $C_{12}H_{14}Cl_2O_8$: C, 40.36; H, 3.95. Found: C, 40.51; H, 4.22.

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