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ACETAL AND ESTER PROTECTING-GROUPS IN THE HYDROGEN FLUORIDE-CATALYSED SYNTHESIS OF D-FRUCTOSE AND L-SORBOSE DIFURANOSE DIANHYDRIDES*†‡

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ABSTRACT

Treatment of acetylated inulin with anhydrous hydrogen fluoride under mild conditions gave a good yield of tri-*O*-acetyl-α-D-fructofuranose tri-*O*-acetyl-β-D-fructofuranose 1,2′:2,1′-dianhydride together with smaller amounts of the corresponding β,β-anomer. When 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose was treated with hydrogen fluoride under similar conditions, with a short reaction time, α-L-sorbofuranose β-L-sorbofuranose 1,2′:2,1′-dianhydride was obtained. A longer reaction time led to a rearranged product, di-α-L-sorbofuranose 2,1′:3,2′-dianhydride.

INTRODUCTION

Treatment of D-fructose or inulin with anhydrous hydrogen fluoride (HF) yields a mixture of dianhydrides of D-fructose, of which six have been isolated and characterised[2]. By the same treatment, L-sorbose is also converted into a similar mixture of dianhydrides[3]. Variations in yields in each series, correlated with reaction temperatures within each series[2,3], led to the conclusion that these reactions were under thermodynamic control[4].

One of the dianhydrides obtained from D-fructose or inulin was α-D-fructofuranose β-D-fructofuranose 1,2′:2,1′-dianhydride (**7**), and L-sorbose gave α-L-sorbofuranose β-L-sorbofuranose 1,2′:2,1′-dianhydride (**13**). Each compound appeared to be a kinetic product and was isolated in low yield[2,3]. Since it was of interest to have these dihexulofuranose dianhydrides available in larger quantities, more convenient methods of preparation have been studied.

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RESULTS AND DISCUSSION

3,4,6-Tri-*O*-acetyl-α-D-fructofuranose 3′,4′,6′-tri-*O*-acetyl-β-D-fructofuranose 1,2′:2,1′-dianhydride (**6**) has been prepared by treatment of acetylated inulin (**1**) with fuming nitric acid[5–7]; although this reaction gave 50% of **6**, careful control of the conditions[5,6] was required and the reaction was not easy to reproduce. A low-yielding enzymic preparation of a "di-D-fructofuranose 1,2′:2,1′-dianhydride", presumably **7**, has also been described[8].

The hexa-acetate **6** can be obtained readily by treatment of acetylated inulin with HF. A series of experiments was carried out in order to determine the optimal conditions (Table I). Since heat is evolved when acetylated inulin is added to HF, it was advantageous to dilute the HF with sulfur dioxide in order to have a better

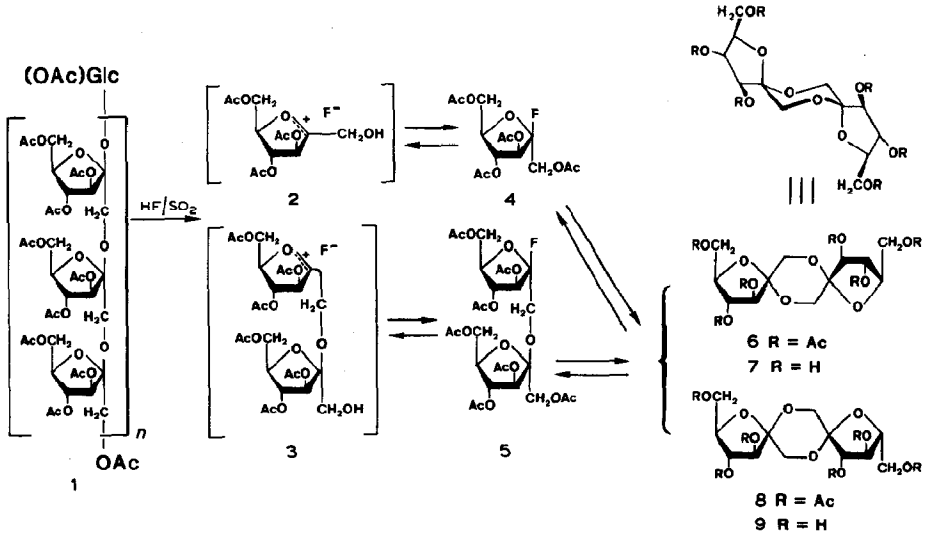


TABLE I

REACTION OF ACETYLATED INULIN (**1**) WITH HYDROGEN FLUORIDE–SULFUR DIOXIDE (OR 1,4-DIOXANE)

Substrate (g)	*HF (mL)/ SO_2 (mL)*	*Temp. (degrees)*	*Time*	*Products (%)*[a]			*Hexa-acetate* **8** *(%)*[b]
				8	**6**	*Fluorides*	
100	100/100	−25	2 h	29	47	24	25
120	120/120	−20	3 h	19	60	20	43
100	100/100	−20	17 h	11	71	18	62
100	100/100	−25	24 h	43	47	10	35
100	400/100[c]	20–25	1.5 h				
2	2/0	−10	10 min	25	45	30	20

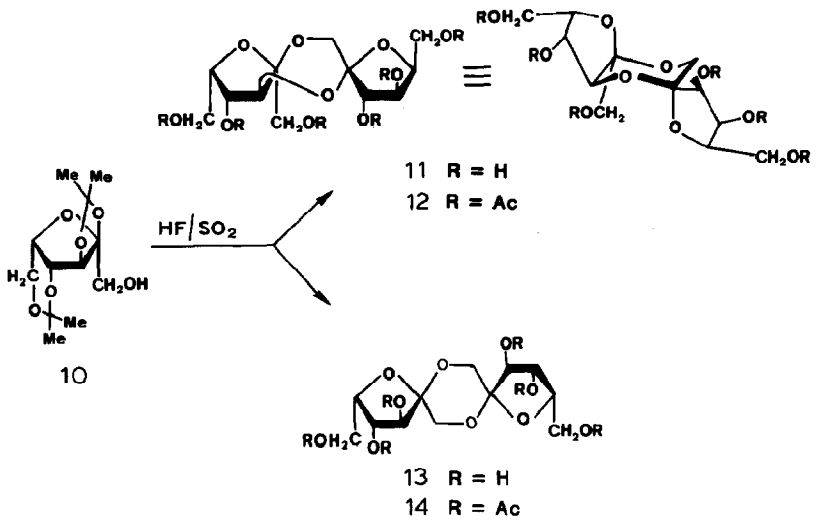
[a]Determined (see Experimental) from the ^{13}C-n.m.r. (25 MHz) spectra of solutions in $CDCl_3$. Signals in the range 108–124 p.p.m., arising from glycosyl fluorides, were summed and given as "fluorides". [b]Isolated by crystallisation from ether. [c]HF–1,4-dioxane.

control of the temperature. The HF may also be diluted with 1,4-dioxane, but liquid sulfur dioxide was the more convenient to give the best yield of **6** (Table I), which could be crystallised from the crude reaction mixtures and was obtained in 62% yield after a reaction time of 18 h at −20° (Table I). Deacetylation of **6** gave the known[2] dianhydride **7**.

A signal at 103.3 p.p.m., corresponding to a previously unknown dihexulofuranose dianhydride, was observed in the ^{13}C-n.m.r. spectra of each of the crude reaction mixtures of Table I. Chromatography of the material in the mother liquor from the crystallisation of **6** gave crystalline **8** and deacetylation gave syrupy **9**. The f.a.b.-mass spectrum of **9** contained a peak at *m/z* 325 for $[M + H]^+$ in agreement with the postulated structure. The ^{13}C-n.m.r. spectrum of **9** contained only six signals at rather high field, indicating it to be an α,α- or a β,β-difructofuranose dianhydride. This was confirmed by the ^{1}H-n.m.r. spectrum of the acetate **8** which showed small values for all the ^{1}H–^{1}H couplings. The symmetry of the n.m.r. spectrum suggests that the dioxane ring cannot adopt a rigid chair conformation, but must adopt a boat conformation, or change rapidly between two chairs. The anomeric configuration has not been proved unequivocally, but is assumed to be β,β since β-D-fructofuranosides are generally more stable than the α anomers[9]. In the α,β-dianhydride **7**, the dioxane ring probably adopts the chair conformation, in which the two oxygen substituents are axial, in agreement with the anomeric effect.

The reaction of acetylated inulin with HF probably leads initially to carbonium ions, such as **2** and **3**, which will be in equilibrium with the furanosyl fluorides **4** and **5** and with dihexulofuranose dianhydrides **6** and **8**. Each of the crude products obtained contained various amounts of glycosyl fluorides, as seen from the ^{13}C-n.m.r. spectra (Table I). Since inulin contains a terminal α-D-glucopyranosyl group, its reaction with HF should produce a small amount of acetylated α-D-glucopyranosyl fluoride, and signals corresponding to this product were observed.

2,3:4,6-Di-*O*-isopropylidene-α-L-sorbofuranose (**10**) is readily available[10], and, since it is in the furanose form, it might give the desired α-L-sorbofuranose β-L-sorbofuranose 1,2′:2,1′-dianhydride (**13**) on treatment with HF, provided that the 4,6-acetal group is stable under the reaction conditions. When **10** was treated with a mixture of HF and sulfur dioxide for 2 h at −20°, a dihexulofuranose dianhydride was obtained in at least 50% yield, as seen from a ^{13}C-n.m.r. spectrum of the crude product, but it was not **13**. Chromatography of the acetylated mixture of products yielded a syrupy hexa-acetate **12**, which on deacetylation gave **11**, also as a syrup. The ^{1}H-n.m.r. spectrum of **12** confirmed that the product contained two furanose rings because of the small ^{1}H–^{1}H coupling constants. The chemical shift of the signal for H-3 was at higher field (δ 4.23) than that of H-3′ (δ 4.98), indicating that O-3 was not acetylated and, therefore, probably involved in an ether linkage. Furthermore, the shifts of the resonances of H-1a and H-1b (δ 4.40 and 4.09) were at lower field than those of H-1′a and H-1′b, indicating that O-1 was acetylated. Thus, it is concluded that **12** is a di-L-sorbofuranose 2,1′:3,2′-dianhydride. The



3,2′-linked furanose ring must be α in order to have O-2 and O-3 *cis*. The anomeric configuration of the 1,2′-linked ring was not established firmly, but a molecular model showed that, if it was α, then the central dioxane ring would have two axial oxygen substituents, in agreement with the anomeric effect, and the three carbon substituents would be equatorial. Hence, **11** is assumed to be di-α-L-sorbofuranose 2,1′:3,2′-dianhydride.

(2→3)-Linked dianhydrides may be formed from D-fructose[2] and L-sorbose[3], especially when the reaction times with HF are extended, and, therefore, these derivatives are thermodynamic products. In order to avoid the formation of **11**, the di-*O*-isopropylidene derivative **10** was treated with HF–SO_2 for only 10 min at −20°. Under these conditions, **11** apparently was not formed, some **10** remained unreacted, and the desired 1,2′:2,1′-dianhydride **13** was formed and isolated as the crystalline hexa-acetate **14** (37%).

Hence, the two dihexulofuranose dianhydrides **7** and **13** can be prepared more readily than hitherto and from easily available starting materials. Furthermore, the isopropylidene groups as in **10**, although acid labile, may be used as temporary protecting groups in HF, provided that they are not linked to anomeric carbon atoms and the reaction is carried out under sufficiently mild conditions. Moreover, non-anomeric acyl esters may be considered as protecting groups in synthetic schemes when using HF, unless they are able to participate in rearrangement reactions involving acyloxonium ions[11].

EXPERIMENTAL

General methods. — ^{13}C-N.m.r. spectra were recorded with a Bruker WH-90, WP-100, or AM 500 instrument. Spectra of unacylated products were recorded for solutions in D_2O (internal 1,4-dioxane, 67.4 p.p.m.; or acetone, 31.07 p.p.m.). For

acetylated compounds, solutions in $CDCl_3$ (internal Me_4Si) were used with the central peak of the triplet (76.91 p.p.m.) as internal reference. F.a.b.-mass spectra were measured in the positive mode with an R 10-10 C/SIDAR 2072 A quadrupole instrument (NERMAG, Rueil-Malmaison), a glycerol matrix, and an accelerating potential of 8.5 kV. Melting points were recorded with a Zeiss microscope hot-stage and are corrected. Optical rotations were measured with a Perkin–Elmer 241 instrument.

The anhydrous hydrogen fluoride (HF) was a commercial product obtained in steel cylinders. Prior to use, it was kept in polyethylene bottles at 0°. Acetylations were effected conventionally with pyridine–acetic anhydride (1:1, 10 mL per 1 g of sample). Deacetylations were carried out, unless otherwise stated, using the Zemplén technique, followed by deionisation with Amberlite MB3 resin. T.l.c. of the hexa-acetates of dihexulose dianhydrides was performed on Silica Gel 60 F_{254} (Merck), using hexane–ethyl acetate (1:1) and detection by u.v. light and by charring with sulfuric acid. Column chromatography was performed on Silica Gel 60 (70–230 mesh, Merck) with *A*, ether; or *B*, ether–hexane (3:1).

Acetylated inulin (**1**). — A mixture of inulin (100 g), acetic anhydride (100 mL), and pyridine (100 mL) was boiled under reflux for 24 h and then concentrated *in vacuo*, leaving a dark, viscous residue from which methanol (100 mL) was evaporated, yielding **1** (178 g, 100%), m.p. 150° (from methanol), $[\alpha]_D^{20}$ −45° (*c* 1, chloroform); lit.[12] m.p. 150–160°, $[\alpha]_D^{20}$ −45.5° (acetic acid).

Reaction of acetylated inulin (**1**) *with HF.* — To **1** (100 g) at −20° was added a mixture of HF (100 mL) and liquid SO_2 (100 mL), with stirring, during a few min. The solution was kept at −20° for the appropriate time (Table I) and then cooled in liquid nitrogen; dichloromethane (500 mL) was added, followed by ice–water (300 mL), and the mixture was neutralised with sodium hydrogencarbonate (430 g). The organic phase was separated and the aqueous phase was washed with dichloromethane. The combined organic phases were dried (Na_2SO_4) and concentrated, leaving a syrup (100 g), the composition of which was determined by ^{13}C-n.m.r. spectroscopy ($CHCl_3$) at 25 MHz (Table I).

*3,4,6-Tri-*O*-acetyl-α-*D*-fructofuranose 3′,4′,6′-tri-*O*-acetyl-β-*D*-fructofuranose 1,2′:2,1′-dianhydride* (**6**). — The crude reaction mixtures, obtained as described above, were crystallised from ether (150 mL) to give **6** having m.p. 124–125° and 135–136° (dimorphs), $[\alpha]_D^{20}$ −0.9°. The ^{13}C-n.m.r. spectrum was identical with that previously described[2].

*3,4,6:3′,4′,6′-Hexa-*O*-acetyl-di-β-*D*-fructofuranose 1,2′:2,1′-dianhydride* (**8**). — The material in the mother liquor from the crystallisation of **6** in the experiment run for 17 h at −20° (Table I) contained **8** in admixture with fluorides. Flash chromatography of this mixture (14 g, solvent *A*) gave, first, a mixture (3 g) of fluorides and **6**. Eluted second was almost pure (n.m.r. spectra) **8** (1 g), m.p. 117–118° (from ether–pentane), $[\alpha]_D^{20}$ +119° (*c* 0.3, chloroform). N.m.r. data ($CDCl_3$): ^{13}C, δ 103.1 (C-2), 79.3, 79.1, 77.5 (C-3,4,5), 63.0, 60.7 (C-1,6); ^1H (500 MHz), δ 5.28 (H-3, $J_{3,4}$ 2.4 Hz), 4.95 (H-4, $J_{4,5}$ 5.8), 4.23 (H-5, $J_{5,6a}$ 3.8, $J_{5,6b}$ 5.8), 4.40 (H-6a, $J_{6a,6b}$ 11.7), 4.16 (H-6b), 3.90 (H-1a and H-1b), 2.14, 2.10, 2.09 (OAc).

Anal. Calc. for $C_{24}H_{32}O_{16}$: C, 50.00; 5.60. Found: C, 50.12; H, 5.68.

A third fraction (8 g) gave **6** (2 g) on recrystallisation from ether.

α-D-Fructofuranose β-D-fructofuranose 1,2':2,1'-dianhydride (**7**). — *O*-Deacetylation of **6** and recrystallisation of the product from ethanol yielded **7**, m.p. 161–162°, $[\alpha]_D^{22}$ +27° (*c* 1, water); lit.[2] m.p. 160–162°, $[\alpha]_D^{20}$ +27° (water). The ^{13}C-n.m.r. spectrum was identical with that described[2].

Di-β-D-fructofuranose 1,2':2,1'-dianhydride (**9**). — Deacetylation of **8** gave **9** as a syrup, $[\alpha]_D^{20}$ +93° (*c* 2.2, water). ^{13}C-N.m.r. data (D_2O): δ 104.6 (C-2), 83.7, 80.8, 77.6 (C-3,4,6), 61.8 (C-1,6). F.a.b.-mass spectrum: *m/z* 325 (100%, $[M + H]^+$).

Anal. Calc. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.22. Found: C, 44.16; H, 6.09.

1,4,6-Tri-O-acetyl-α-L-sorbofuranose 3,4,6-tri-O-acetyl-α-L-sorbofuranose 2,1':3,2'-dianhydride (**12**). — 2,3:4,6-Di-*O*-isopropylidene-α-L-sorbofuranose[10] (**10**, 5 g) was dissolved in a stirred mixture of HF/SO_2 (1:1, 10 mL) at −10°. The solution was kept for 2.25 h at −20°, then diluted with cold dichloromethane (100 mL), and neutralised with sodium hydrogencarbonate. Methanol (100 mL) was then added, and the suspension was filtered and concentrated. A ^{13}C-n.m.r. spectrum of the syrupy residue (3.5 g) indicated a mixture containing a large proportion of **11**. Acetylation gave a product (4.0 g), flash chromatography (solvent *B*) of which gave, first, a mixture (1 g) of dianhydrides of L-sorbose[3]. The second fraction (2 g), which contained almost exclusively **12**, was re-chromatographed to give pure **12** (500 mg) as a syrup, $[\alpha]_D^{20}$ +29° (*c* 1.4, chloroform). N.m.r. data ($CDCl_3$): ^{13}C, δ 102.2, 97.6 (C-1,1'), 77.8 , 76.6, 76.2, 74.8, 74.6, 71.7 (C-3,4,5,3',4',5'), 64.4, 62.8, 61.8, 60.9 (C-1,6,1',6'); ^{1}H (500 MHz), δ 5.51 (H-4'), 5.24 (H-4), 4.98 (H-3'), 4.63 (H-5), 4.57 (H-5'), 4.40 (H-1a), 4.25 (H-6'a), 4.23 (H-3), 4.2 (H-6a), 4.20 (H-6'b), 4.13 (H-6b), 4.12 (H-1'a), 4.09 (H-1b), 3.71 (H-1'b), $J_{1a,1b}$ 11.9, $J_{3,4}$ 0.7, $J_{4,5}$ 3.8, $J_{5,6a}$ 5, $J_{5,6b}$ 7, $J_{6a,6b}$ 11.6, $J_{1'a,1'b}$ 12.0, $J_{3',4'}$ 4.3, $J_{4',5'}$ 5.8, $J_{5',6'a} = J_{5',6'b} = 5.5$, $J_{6'a,6'b}$ 12 Hz.

Anal. Calc. for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.60. Found: C, 50.23; H, 5.73.

Di-α-L-sorbofuranose 2,1':3,2'-dianhydride (**11**). — Deacetylation of **12** gave **11** as a syrup, $[\alpha]_D^{20}$ −42° (*c* 1.2, methanol). F.a.b.-mass spectrum: *m/z* 325 (100%, $[M + H]^+$). ^{13}C-N.m.r. data (D_2O): δ 104.3, 98.2 (C-1,1'), 83.5 (C-3), 79.2, 78.8, 76.4, 76.0, 75.1 (C-4,5,3',4',5'), 65.2, 63.4, 61.5, 61.3 (C-1,6,1',6').

Anal. Calc. for $C_{12}H_{20}O_{10}$: C, 44.44; H, 6.22. Found: C, 44.10; H, 6.09.

3,4,6-Tri-O-acetyl-α-L-sorbofuranose 3',4',6'-tri-O-acetyl-β-L-sorbofuranose 1,2':2,1'-dianhydride (**14**). — 2,3:4,6-Di-*O*-isopropylidene-α-L-sorbofuranose (**10**, 5 g) was dissolved in 1:1 HF/SO_2 (10 mL) at −20°. The solution was kept at −20° for 10 min and then cooled, dichloromethane was added, and the solution was neutralised with sodium hydrogencarbonate. The mixture was then filtered and concentrated to leave **10** (2.0 g). The insoluble material was extracted with methanol (100 mL), the extract was concentrated, and the residue (2.1 g) was acetylated. The oily product (3.5 g) crystallised from ether to give **14** (2 g, 37%), m.p. 150–151°, $[\alpha]_D^{20}$ −23° (*c* 1, water); lit.[3] m.p. 155–156°, $[\alpha]_D^{20}$ −25.3°. A ^{13}C-n.m.r. spectrum of **14** was identical with that described[3].

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