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Difructose Dianhydrides as Synthetic Intermediates. A Synthesis of 3,6-Anhydro-keto-D-fructose

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Abstract: A preparation of 3,6-anhydro-*keto*-D-fructose from α-D-fructofuranose ß-D-fructofuranose 1,2':2,1'-dianhydride is reported. The synthetic scheme involves selective halogenation of the primary hydroxyl groups and intramolecular nucleophilic displacement of the later by OH-3,3'. A significant difference towards formation of the 3,6-anhydro bridge between the α- and ß-D-fructofuranosyl subunits has been observed and adscribed to conformational features. The corresponding 3,6-anhydro derivative of α-D-fructofuranose ß-D-fructopyranose 1,2':2,1'-dianhydride has also been prepared for comparative purposes. Mild acid hydrolysis of the dispiroketal structure in 3,6-anhydro-α-D-fructofuranose 3,6-anhydro-ß-D-fructofuranose 1,2':2,1'-dianhydride yielded the target α-hydroxyketone in quantitative yield.

INTRODUCTION

α-Hydroxycarbonyl compounds (acyloins) are important synthetic intermediates which have been utilized in the total synthesis of a variety of bioactive molecules including antitumor agents, antibiotics, and pheromones[2]. This structural feature is also found in a number of biologically relevant molecules among which carbohydrates are, by far, the widerspread and less expensive representatives. The use of sugar derivatives as readily available acyloin templates is therefore worth of consideration.

Sugar derived α-hydroxyketones can be prepared by oxidation of hydroxyl groups in aldose derivatives[3]. A straighter approach would involve the *keto* form of ketoses. However, the complexity of the tautomeric equilibria of ketose solutions[4] requires in this case the preparation of derivatives having the *keto* form anchored. A valuable approach would then consist in the use of anhydroketose derivatives. Thus, 1,5-anhydro-*keto*-D-fructose[5] has been applied to the synthesis of naturally occurring hexahydrodipyranopyrazines[6]

and is also a key intermediate in the biosynthesis of cortalcerone and michrotecin, two ß-pyrone antibiotics found in basidiomycete species[7]. Analogously, its 3,6-anhydro isomer has been proposed as chiral template for the synthesis of oxaprostaglandines[8]. Hitherto, although some protected derivatives have been obtained by oxidation of 3,6-anhydro-D-mannitol[9] or Lowry-de-Bruyn — Alberda-van-Ekenstein transposition of 3,6-anhydromannose derivatives[8], the fully unprotected 3,6-anhydro-*keto*-D-fructose remained unknown.

We now report a high yielding preparation of the title α-hydroxyketone from α-D-fructofuranose ß-D-fructofuranose 1,2':2,1'-dianhydride (**1**) in three steps via dihalogenated derivatives. The starting pseudo-disaccharide is readily available from inuline, sucrose, or fructo-oligosaccharides upon protonic activation with anhydrous hydrogen fluoride or pyridinium poly(hydrogen fluoride)[10,11]. Compound **1** can be considered as a synthetic equivalent of a fructofuranose unit having the anomeric hydroxyl group and the primary OH-1 selectively protected by spiroacetalation.

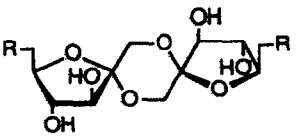
RESULTS AND DISCUSSION

Dihalo derivatives of **1** having the primary OH-6,6' groups replaced by chlorine (**2**) and iodine (**3**) have been previously obtained by selective protonic activation of the corresponding 6,6'-dideoxy-6,6'-dihalosucroses with pyridinium poly(hydrogen fluoride)[11]. Since the parent difructose dianhydride **1** can be obtained in higher scale and yield from readily available biotechnological sources such as fructo-oligosaccharides[11], it was of interest to consider its direct halogenation.

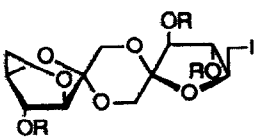
Replacement of the primary hydroxyl groups in **1** by chlorine using triphenylphosphine-carbon tetrachloride[12] afforded the desired dichloro derivative **2** as the sole reaction product. In contrast, treatment of **1** with the Garegg's iodination reagent[13] (triphenylphosphine-imidazole-iodine) in *N,N*-dimethylformamide, following the procedure already successfully used in the preparation of 6,6'-dideoxy-6,6'-diiodosucrose[11], did not result in the formation of the target diiodo compound **3**. Instead, the product of partial anhydrisation at the ß-D-fructofuranosyl moiety **4** and the pentacyclic tetra-anhydride **6** were obtained. Conversion of **1** into **3** could be achieved by in situ generation of a Vilsmeier iodide from the reaction of iodine and triphenylphosphine in *N,N*-dimethylformamide[14]. Simultaneous formation of a small proportion of the tri-anhydride **4** was also observed under these reaction conditions.

The different behaviour of the difructose dianhydride **1** towards the above iodination systems was not due to further anhydrisation of the diiodo derivative **3** in the reaction medium. Thus, compound **3** was recovered unchanged after treatment with both reagents under identical reaction conditions. Therefore, the outcome of the iodination reaction must be the result of a competition between intermolecular nucleophilic displacement by iodide anion and intramolecular attack by the δ-located OH-3(3') in the respective reaction intermediates. Although the corresponding reaction mecanisms have not been fully established, it has been found that (alkoxymethylene)dimethyliminium halides (Vilsmeier-Haak complexes) are formed in the reaction

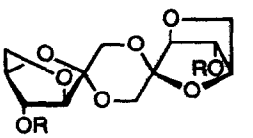
of halogenotriphenylphosphonium halides with alcohols in *N,N*-dimethylformamide[15], while a phosphonium salt, a better living group, has been postulated in the case of the Garegg's iodination system[16]. The higher reactivity of the second intermediate may explain the present result. Anhydrization in this case may be also favoured by the slightly alcaline medium due to the presence of imidazole.



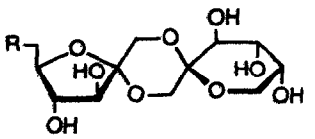
1 R = OH
2 R = Cl
3 R = I



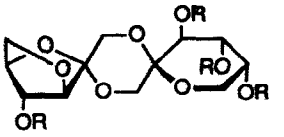
4 R = H
5 R = Ac



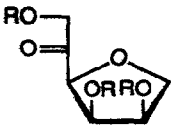
6 R = H
7 R = Ac



8 R = Cl
9 R = I



10 R = H
11 R = Ac



12 R = H
13 R = Ac

The above result also evidenced a disparity in the reactivities of the α- and ß-D-fructofuranose subunits in compound **1** towards formation of the oxolane ring. The product of partial anhydrization at the α-D-fructofuranose site (**4**) was exclusively detected. It has been shown that α-D-fructofuranose ß-D-fructofuranose 1,2':2,1'-dianhydride (**1**) and derivatives exist in a rather rigid conformation[17] with the central 1,4-dioxane system in a chair conformation and both oxygen substituents in axial disposition, in agreement with the anomeric effect. The α- and ß-D-fructofuranose rings adopt envelop conformations with respectively C-3 and C-4 out of the main plan. In the first case, OH-3 is held much closer to C-6, which probably explains its higher tendency to participate in the formation of an intramolecular anhydride.

Both the dichloro (**2**) and the diiodo derivative (**3**) underwent quantitative transformation into 3,6-anhydro-α-D-fructofuranose 3,6-anhydro-ß-D-fructofuranose 1,2':2,1'-dianhydride (**6**) on treatment with methanolic sodium methoxide under reflux[18]. In the case of **3**, the difference in anhydrization rates at the α- and ß-D-fructofuranose moieties allowed control of the reaction. Thus, after 2 h at room temperature the product of partial anhydrization **4** was the main reaction product (59% isolated yield), whereas the tetra-anhydride **6** was the sole reaction product after a 24 h reaction time. For comparative purposes, 3,6-anhydro-α-D-fructofuranose ß-D-fructopyranose 1,2':2,1'-dianhydride (**10**) has been analogously prepared from either

the corresponding 6-chloro-6-deoxy[11] (**8**) or the 6-deoxy-6-iodo derivative[11] (**9**). The anhydrization rate observed in this case fully agreed with that for the α-D-fructofuranose moiety of **3**, supporting a similar conformational arrangement.

The structures of the 3,6-anhydro-D-fructofuranose derivatives **4**, **6**, and **10** were established on the basis of their ^1H (Table 1) and ^{13}C NMR spectral data (Table 2) as well as data for the corresponding peracetates **5**, **7**, and **11**. A ^{13}C resonance at δ 8.5-9.4 (C-6') confirmed the presence of the iodine substituent in **4** and **5**, while comparison of the corresponding ^1H and ^{13}C NMR spectra with data[11] for the diiodo difructofuranose dianhydride precursor (**3**) unequivocally proved its location at the ß-D-fructofuranosyl part of the molecule. The ^{13}C resonances for C-6 in **4** and **10** and for C-6,6' in **6** (71.2-71.5 ppm) were shifted downfield by 9 ppm as compared to the parent difructose dianhydrides[17a], supporting their involvement in the corresponding ether linkages. The values of the vicinal coupling constants in 3,6-anhydro-D-fructofuranose structures agreed with reported data for the fructofuranose ring in 3',6'-anhydrosucrose derivatives[19]. Noteworthy, some long-range proton-proton coupling constants could be measured for this compounds, in agreement with the rigidity of the structures. Specially interesting was $^5J_{1a,5}$ (0.5-0.7 Hz), which allowed unequivocal assigment of the methylene protons in the 1,4-dioxane central system.

Despite the fact that the stability of difructose dianhydrides towards acidic hydrolysis is known to be much higher as compared to normal fructosides[20], the pentacyclic derivative **6** was very sensitive to acid, presumably as a consequence of its molecular strain. Treatment of **6** with dilute aqueous hydrogen chloride or acid ion exchange resin resulted in fast opening of the spiroketalic linkages to give the target 3,6-anhydro-*keto*-D-fructose (**12**) in quantitative yield. A one-pot preparation of **12** from 6-chloro-6-deoxy-α-D-fructofuranose 6-chloro-6-deoxy-ß-D-fructofuranose 1,2':2,1'-dianhydride (**2**) has also been devised.

The ^{13}C NMR data of **12** (Table 2) agreed with data reported for its 4,5-di-*O*-isopropylidene derivative[8] and confirmed the α-hydroxyketone structure. On treatment with acetic anhydride in pyridine, the corresponding 1,4,5-tri-*O*-acetate was obtained as the sole reaction product, as seen from the ^1H (Table 1) and ^{13}C (Table 2) NMR spectra.

In conclusion, this work shows the potential utility of the readily available α-D-fructofuranose ß-D-fructofuranose 1,2':2,1'-dianhydride as a chiral template in organic synthesis. The development of regioselective syntheses with other isomeric difructose dianhydrides and their use as organic synthons is currently under investigation in our laboratory.

Table 1. ^{1}H NMR Data (δ, ppm; J, Hz) for compounds **4-7** and **10-13**.

Compound	*H-1a*	*H-1b*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	*H-1'a*	*H-1'b*	*H-3'*	*H-4'*	*H-5'*	*H-6'a*	*H-6'b*
4[a,d]	4.49d	3.82d	4.30d	4.54dd	4.69ddd	4.06dd	3.83d	4.24d	3.70d	3.99d	4.22dd	4.03ddd	3.59dd	3.52dd
5[b,e]	4.32d	3.70d	4.38d	4.84d	4.58bs	3.89dd	3.69d	4.10d	3.49d	5.10d	5.34dd	4.18m	3.46dd	3.35dd
6[a,d]	4.46d	3.91d	4.35d	4.55dd	4.68q	4.05dd	3.81d	4.17d	4.06d	4.28d	4.60dd	4.59ddd	4.13dd	3.99d
7[b,e]	4.27dd	3.74d	4.37dd	4.81dd	4.54bs	3.84dd	3.59d	4.00d	3.69d	4.12d	4.98dd	4.18m	<-----3.96s----->	
10[a,d]	4.21dd	3.80dd	4.28dd	4.56dd	4.72bs	4.08ddd	3.86d	4.42d	3.63dd	3.69dd	4.02d	4.13md	3.97dd	3.83dd
11[c,e]	4.10dd	3.84d	4.58d	4.71dd	4.29bs	3.42dd	3.49d	4.49d	3.80d	5.76d	5.97dd	5.63ddd	3.68dd	3.58dd
12[a,e]	<-----4.30s----->		4.58d	5.40t	4.23m	3.87dd	3.56dd	---	---	---	---	---	---	---
13[c,e]	5.06d	4.87d	4.56d	5.62t	5.36q	4.12dd	3.96dd	---	---	---	---	---	---	---

	$J_{1a,1b}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{1'a,1'b}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$	Long Range Coupling Constants $J_{3,5}$	$J_{1a,5}$	$J_{1b,1'b}$
4	12.4	2.4	0.6	1.3	0	8.9	12.3	8.0	6.7	5.1	6.7	10.8	0.4	0.6	---
5	11.8	2.2	0	1.0	0	8.6	12.1	6.4	4.5	6.4	8.0	10.4	---	0.5	---
6	12.3	2.8	0.7	1.3	0	9.0	12.3	2.8	0.9	1.5	0	9.0	---	0.7	---
7	12.1	2.4	0.5	1.1	0	8.6	11.8	2.6	3.4	---	---	---	0.4	0.5	0.4
10	12.3	2.5	0.7	1.2	0	8.6	12.2	9.9	3.4	1.3	2.0	12.7	0.4	0.7	---
11	11.7	2.2	0.5	1.0	0	8.5	11.7	10.6	3.4	1.8	1.6	13.1	---	0.5	---
12	---	4.8	4.8	7.5	6.0	8.6	---	---	---	---	---	---	---	---	---
13	18.0	6.0	6.0	6.0	7.5	9.6	---	---	---	---	---	---	---	---	---

[a]In D_2O. [b]In $CDCl_3$. [c]In C_6D_6. [d]At 400 MHz. [e]At 200 MHz.

Table 2. ^{13}C NMR Chemical Shifts for Compounds **4-7** and **10-13**.

Comp.	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
4[a]	64.7	102.0	77.7	75.4	81.4	71.4	63.6	99.8	78.1	79.0	81.0	8.5
4[b]	64.7	102.2	77.4	77.0	81.8	71.3	64.0	100.2	80.2	80.2	82.1	9.4
5[c]	64.9	100.7	76.3	75.5	77.9	70.1	62.6	100.0	76.6	78.7	81.1	6.0
6[a]	65.9	104.6	77.2	75.4	81.8	71.5	64.2	103.6	78.8	76.3	81.4	72.1
6[b]	65.6	105.0	77.3	77.0	81.6	71.2	64.0	103.9	78.9	76.4	81.6	71.8
7[c]	66.0	103.0	76.6	75.8	77.5	70.3	63.6	101.2	78.0	77.0	78.9	71.3
10[a]	63.9	101.8	77.8	75.4	81.5	71.5	64.5	96.6	69.3	69.7	69.8	62.7
11[c]	63.6	100.3	75.9	75.3	77.7	69.7	61.2	94.8	67.1	68.8	67.2	61.4
12[a]	69.1	212.7	86.8	74.9	73.6	73.6	---	---	---	---	---	---
13[c]	67.2	200.6	82.1	72.2	71.0	70.0	---	---	---	---	---	---

[a]In D_2O. [b]In acetone-d_6. [c]In $CDCl_3$.

EXPERIMENTAL SECTION

General. ^{13}C NMR spectra (50.3 MHz) were recorded with a Bruker AC-200 instrument. Spectra of unacetylated products were recorded for solutions in D_2O (internal acetone, 31.1 ppm) or acetone-d_6 (central peak at 29.8 ppm). For acetylated compounds, solutions in $CDCl_3$ were used with the central peak of the triplet (76.9 ppm) as internal reference. ^1H NMR spectra (200 and 400 MHz) were recorded with Bruker AC-200 and Bruker AMX-400 instruments for solutions in D_2O (unacetylated products, external tetramethylsilane), $CDCl_3$ or C_6D_6 (acetylated products, internal tetramethylsilane). Assignments were confirmed by 2D COSY and HETCOR experiments.

FAB-mass spectra (Cs gun, acceleration potential 8 kV) were measured in the positive mode with a VG ZAB-SEQ instrument. The samples were dissolved in thioglycerol (unacetylated products) or *m*-nitrobenzyl alcohol (peracetylated derivatives). NaI was usually added as a cationizing agent. Melting points were determined with a Büchi 535 capillary equipement and are uncorrected. Optical rotations were measured with a Jobin Yvon digital micropolarimeter using 0.5 cm cells.

Acetylations were effected conventionally with Ac_2O-pyridine (1:1, 10 mL for 1 g of sample). TLC was performed on Silica Gel 60 F_{254} plates (E. Merck) and detection by UV light and by charring with H_2SO_4. Column chromatography was performed on Silica Gel 60 (230-400 mesh, E. Merck). Microanalyses were obtained from the Service Central de Microanalyse du CNRS in Solaize.

***6-Chloro-6-deoxy-α-D-fructofuranose 6-chloro-6-deoxy-ß-D-fructofuranose 1,2':2,1'-dianhydride* (2).** To a solution of α-D-fructofuranose ß-D-fructofuranose 1,2':2,1'-dianhydride (**1**) (0.5 g, 1.5 mmol) in pyridine (30 mL) were successively added Ph_3P (2.3 g, 8.8 mmol) and CCl_4 (2.3 mL). The reaction mixture

was heated at 65-70°C for 0.5 h, MeOH (2.3 mL) was then added, and after 1 h at 50°C the mixture was concentrated. Traces of pyridine were eliminated by co-evaporation with toluene. The residue was triturated with water (3 x 50 mL), filtered, the combined aqueous filtrates were evaporated, and the product was subjected to flash chromatography (45:5:3 EtOAc-EtOH-H_2O) to give **2** (0.47 g, 87%) having the physical data already reported[11].

***6-Deoxy-6-iodo-α-D-fructofuranose 6-deoxy-6-iodo-β-D-fructofuranose 1,2':2,1'-dianhydride* (3).** To a solution of **1** (1.17 g, 3.6 mmol) in DMF (42 mL) were added Ph_3P (4.14 g, 15.7 mmol) and I_2 (3.73 g, 14.7 mmol), and the reaction mixture was heated at 80°C for 1.5 h. The solvent was evaporated under reduced pressure to ~1/3 of the initial volume, MeOH (10 mL) was added, and the resulting solution was adjusted to pH 9 by addition of 3 M sodium methoxide. After 15 min, the reaction mixture was neutralised with Amberlite IRN-77 (H^+) ion exchange resin. The resin was filtered off, washed with MeOH (2 x 25 mL), boiling MeOH (1 x 25 mL), and the combined filtrates were evaporated. The residue, which showed a main spot on TLC (45:5:3 EtOAc-EtOH-H_2O), was subjected to flash chromatography with the above eluent to give the diiodo derivative **3** (1.37 g, 70%, R_f 0.64) having the physical data already reported[11]. A minor proportion of the tri-anhydride **4** (0.18 g, 11%) was additionally obtained under these reaction conditions.

***3,6-Anhydro-α-D-fructofuranose 6-deoxy-6-iodo-β-D-fructofuranose 1,2':2,1'-dianhydride* (4).** A solution of the diiodo derivative **3** (0.38 g, 0.7 mmol) in methanolic sodium methoxide (1 M, 10 mL) was stored at room temperature with monitoring by TLC (EtOAc-EtOH-H_2O 45:5:3). After 2 h, the tri-anhydride **4** was the major component of the reaction mixture (R_f 0.43), along with some starting material and the tetra-anhydride **6** (R_f 0.30). The reaction was then cooled at 0°C and neutralized by addition of Amberlite IRN-77 (H^+) and Amberlite IRC 50 (H^+) ion exchange resins. The resins were filtered off, washed with MeOH, and the combined filtrates were evaporated. Column chromatography of the resulting syrupy residue with the above eluent afforded, successively, residual **3** (34 mg, 9%), tri-anhydride **4** (0.172 g, 59%), and tetra-anhydride **6** (24 mg, 12%). Compound **4**, isolated as a syrup, had $[\alpha]_D^{20}$ +29 (*c* 1.2, acetone). FABMS: *m/z* 439 (98%, $[M+Na]^+$), 417 (100, $[M+H]^+$). ^1H NMR (400 MHz, D_2O) in Table 1. ^{13}C NMR (50.3 MHz, D_2O and acetone-d_6) in Table 2. Anal. Calcd for $C_{12}H_{17}IO_8$: C, 34.62; H, 4.12; I, 30.51. Found: C, 34.93; H, 3.91; I, 29.97.

***4-O-Acetyl-3,6-anhydro-α-D-fructofuranose 3,4-di-O-acetyl-6-deoxy-6-iodo-β-D-fructofuranose 1,2':2,1'-dianhydride* (5).** Conventional acetylation of **4** (0.1 g, 0.24 mmol) yielded the corresponding tri-acetate **5** (0.116 g, 90%) as a syrup having $[\alpha]_D^{20}$ +24 (*c* 1, $CHCl_3$). FABMS: *m/z* 735 (100%, $[M+Na]^+$), 713 (66, $[M+H]^+$). ^1H NMR (200 MHz, $CDCl_3$) in Table 1 and δ 2.13, 2.05, and 1.99 (Ac);

^{13}C NMR (50.3 MHz, $CDCl_3$)in Table 2. Anal. Calcd for $C_{18}H_{23}IO_{11}$: C, 39.86; H, 4.27; I, 23.42. Found: C, 40.23; H, 4.32; I, 23.10.

***3,6-Anhydro-α-D-fructofuranose 3,6-anhydro-β-D-fructofuranose 1,2':2,1'-dianhydride* (6).** Treatment of the dihalo derivatives **2** or **3** (0.33 mmol) with methanolic sodium methoxide (1 M, 10 mL) under reflux for 2 h resulted in total conversion into a single product (TLC, 45:5:3 EtOAc-EtOH-H_2O). The reaction mixture was then cooled at 0°C and the pH was carefully adjusted to 7-8 with Amberlite IRN-77 (H^+) and Amberlite IRC 50 (H^+) ion exchange resins[18]. The resins were immediately filtered off and washed with MeOH. Evaporation of the combined filtrates and crystallization of the residue from EtOH yielded **6** (69 mg, 72%) having mp 204-205°C; $[\alpha]_D^{20}$ +77 (*c* 1, H_2O). FABMS: *m/z* 289 (100%, $[M+H]^+$). ^1H NMR (400 MHz, D_2O) in Table 1; ^{13}C (50.3 MHz, D_2O and acetone-d_6) in Table 2. Anal. Calcd for $C_{12}H_{16}O_8$: C, 50.00; H, 5.59. Found: C, 50.01; H, 5.66.

***4-O-Acetyl-3,6-anhydro-α-D-fructofuranose 4-O-acetyl-3,6-anhydro-β-D-fructofuranose 1,2':2,1'-dianhydride* (7).** Conventional acetylation of **6** (0.1 g, 0.34 mmol) yielded the corresponding di-acetate **7** (0.119 g, 92%) having mp 152-153°C (from EtOH); $[\alpha]_D^{20}$ +40 (*c* 1, $CHCl_3$). FABMS: *m/z* 395 (100%, $[M+Na]^+$), 373 (70, $[M+H]^+$). ^1H (200 MHz, $CDCl_3$) in Table 1 and δ 2.03 and 1.97 (Ac); ^{13}C (50.3 MHz, $CDCl_3$) in Table 2. Anal. Calcd for $C_{16}H_{20}O_{10}$: C, 51.61; H, 5.41. Found: C, 51.37; H, 5.56.

***3,6-Anhydro-α-D-fructofuranose β-D-fructopyranose 1,2':2,1'-dianhydride* (10).** A solution of 6-chloro-6-deoxy- (**8**) or 6-deoxy-6-iodo-α-D-fructofuranose ß-D-fructopyranose 1,2':2,1'-dianhydride (**9**) (0.73 mmol) in methanolic sodium methoxide (1 M, 10 mL) was heated under reflux with monitoring by TLC (2:1 $CHCl_3$-MeOH). After 2 h, the reaction mixture was cooled at 0°C and neutralized as above described for the preparation of **6**. Evaporation of the solvent and column chromatography of the resulting residue afforded **50** (0.192 g, 86%) as a syrup having $[\alpha]_D^{20}$ -50 (*c* 1.1, H_2O). FABMS: *m/z* 329 (100%, $[M+Na]^+$), 307 (23, $[M+H]^+$). ^1H NMR (400 MHz, D_2O) in Table 1; ^{13}C NMR (50.3 MHz, D_2O) in Table 2. Anal. Calcd for $C_{12}H_{18}O_9$: C, 47.06; H, 5.92. Found: C, 47.00; H, 5.82.

***4-O-Acetyl-3,6-anhydro-α-D-fructofuranose 3,4,5-tri-O-acetyl-β-D-fructopyranose 1,2':2,1'-dianhydride* (11).** Conventional acetylation of **10** (0.1 g, 0.33 mmol) yielded the corresponding tetra-acetate **51** (0.15 g, 97%) having mp 164-165°C (from $CHCl_3$-hexane); $[\alpha]_D^{20}$ -18 (*c* 1.3, $CHCl_3$). FABMS: *m/z* 497 (60%, $[M+Na]^+$), 475 (100, $[M+H]^+$). ^1H (200 MHz, C_6D_6) in Table 1 and δ 1.93, 1.89, 1.88, and 1.85 (Ac); ^{13}C (50.3 MHz, $CDCl_3$) in Table 2. Anal. Calcd for $C_{20}H_{26}O_{13}$: C, 50.63; H, 5.52. Found: C, 50.60; H, 5.47.

***3,6-Anhydro*-keto-D-*fructose* (12).** Treatment of the tetra-anhydride **6** (0.2 g, 0.75 mmol) with 0.1 M HCl (10 mL) at room temperature resulted in almost instantaneous conversion into a single lower R_f product (45:5:3 EtOAc-EtOH-H_2O). After 5 min, the reaction mixture was neutralized with Amberlite IRA 93 (OH^-) ion exchange resin, filtered and freeze dried to give **12** (0.218 g, 97%) as an amorphous solid having $[\alpha]_D^{20}$ -49 (*c* 1.1, H_2O). FABMS: *m/z* 185 (100%, $[M+Na]^+$), 163 (33, $[M+H]^+$). ^1H NMR (200 MHz, D_2O) in Table 1; ^{13}C NMR (50.3 MHz, D_2O), Table 2. Anal. Calcd for $C_6H_{10}O_5$: C, 44.45; H, 6.22. Found: C, 44.65; H, 6.11.

Compound **12** was also obtained in a one-pot reaction from 6-chloro-6-deoxy-α-D-fructofuranose 6-chloro-6-deoxy-ß-D-fructofuranose 1,2':2,1'-dianhydride (**2**) by in situ hydrolysis of the tetra-anhydride **6**. The reaction mixture arising from the action of 1 M sodium methoxide on **2** (0.24 g, 0.66 mmol), was treated with H_2O (10 mL) and adjusted to pH 2-3 by addition of Amberlite IRN-77 (H^+) resin. The mixture was stirred for 1 h at room temperature, filtered, and deionized by passing through a column (3 x 12 cm) of Duolite MB-6113 (H^+, OH^-) ion exchange resin. Evaporation of the solvent yielded **12** (0.18 g, 89%).

***1,2,5-Tri-O-acetyl-3,6-anhydro*-keto-D-*fructose* (13).** Conventional acetylation of **34** (90 mg, 0.56 mmol) and column chromatography (2:3 EtOAc-hexane) of the peracetylated product yielded the corresponding tri-acetate **35** (0.139 g, 87%), as a syrup having $[\alpha]_D^{20}$ +2 (*c* 1, $CHCl_3$). FABMS: *m/z* 311 (65%, $[M+Na]^+$), 289 (100, $[M+H]^+$). ^1H NMR (200 MHz, C_6D_6) in Table 1 and δ 2.10, 2.02, and 2.01 (Ac); ^{13}C (50.3 MHz, $CDCl_3$) in Table 2. Anal. Calcd for $C_{12}H_{16}O_8$: C, 50.00; H, 5.59. Found: C, 49.80; H, 5.57.

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