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Stereoselective Synthesis of Di-β-D-fructopyranose 1,2':2,1'-Dianhydride, a Spirodioxanyl Pseudodisaccharide with Metal Cation Complexing Properties[1]

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Key Words: Carbohydrate reactivity in anhydrous hydrogen fluoride; D-fructose; di-D-fructose dianhydrides; glycosyl fluorides; glycosylation.

Abstract: A stereoselective synthesis of di-β-D-fructopyranose 1,2':2,1'-dianhydride by protonic activation of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose with anhydrous hydrogen fluoride is reported. The reaction involves the formation of 1,3:4,5-di-*O*-isopropylidene-β-D-fructopyranosyl fluoride as isolable intermediate.

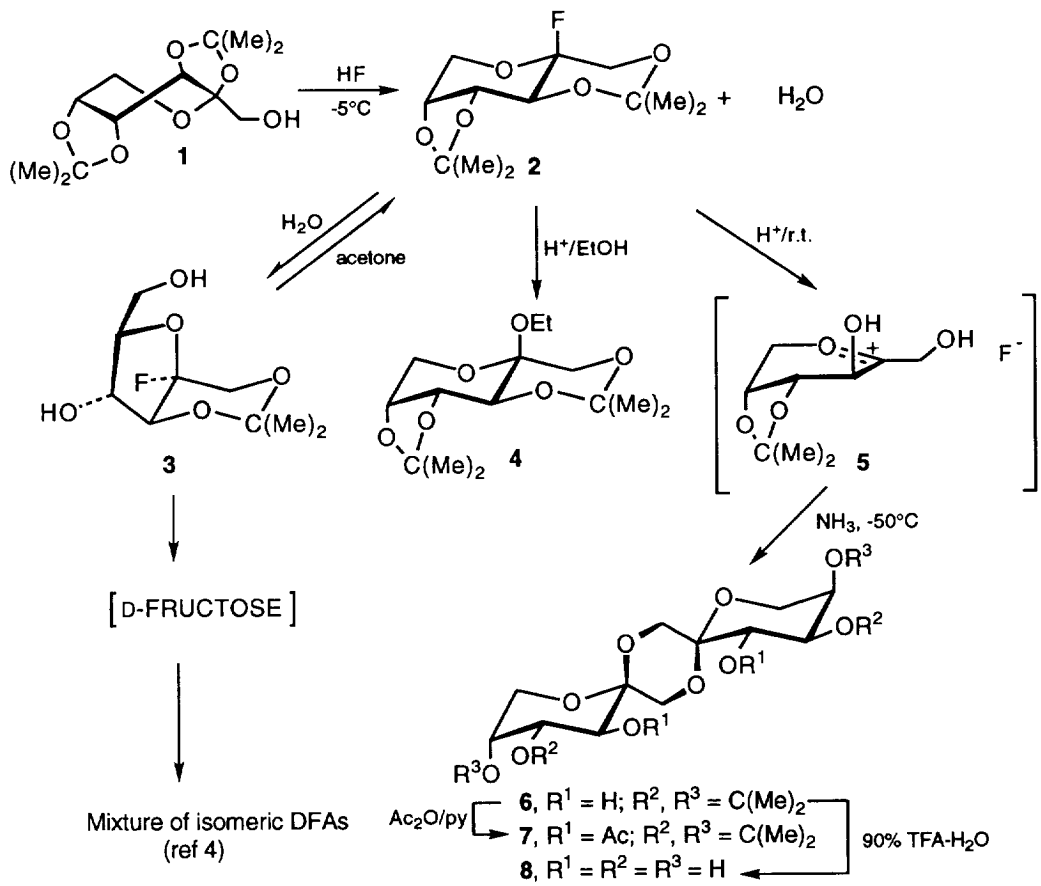
INTRODUCTION

Di-D-fructose dianhydrides (DFAs) are formed during thermal or acidic treatment of D-fructose-containing materials[3-6] and have been recently found as major constituents of caramel[7]. They are generally obtained as complex mixtures of isomers having a tricyclic spiroketal structure with a central 1,4-dioxane ring. The composition of the mixture is initially dependent on the tautomeric form of the D-fructose or D-fructose-containing precursor[8,9]. Further thermodynamic equilibration is governed by stereoelectronic factors, mainly the anomeric and exoanomeric effects[4,6,10]. On the basis of such mechanistic considerations, stereoselective syntheses of some D-fructofuranose-containing DFAs have been devised using pyridinium poly(hydrogen fluoride) as mild protonic catalyst and sucrose or fructooligosaccharides as D-fructofuranose precursors[9], and these compounds have been further used as building blocks for the preparation of liquid crystals, polymers, and surfactants[9] as well as chiral pool compounds[11]. Stereoelectronic considerations[10] however preclude the possibility of an efficient preparation of symmetrical dipyranose derivatives using a similar strategy. In the later case, the dispirodixane ring system must adopt a boat conformation in order to comply with the anomeric and exoanomeric effects. Preservation of the fructopyranose cyclic form becomes then a prerequisite for this purpose. We now disclose a stereoselective synthesis of di-β-D-fructopyranose 1,2':2,1'-dianhydride (**8**), a dispirodioxane derivative having a C_2 symmetry and strong metal cation complexing properties[12], by use of cyclic acetals as temporary hydroxyl protecting groups. Di-β-D-

fructopyranose 1,2':2,1'-dianhydride (**8**) was previously obtained in only 16% yield, as a minor component of the reaction product of D-fructose[4] or D-fructose-containing materials[6] in anhydrous hydrogen fluoride (HF).

RESULTS AND DISCUSSION

Treatment of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[13] (**1**) with HF at -5°C resulted in the obtention of a major product having higher mobility (TLC, 1:1 EtOAc-hexane). However, attempts to isolate this compound by neutralisation of the reaction mixture with $NaHCO_3$ or CaO resulted in complete hydrolysis of the acetal groups with formation of a complex mixture of unprotected DFAs, the thermodynamic α-D-fructofuranose β-D-fructopyranose 1,2':2,1'-dianhydride[4] being the major component (^{13}C NMR). When the neutralisation process was performed at -50°C with dry ammonia, thus avoiding in situ formation of water, 1,3:4,5-di-*O*-isopropylidene-β-D-fructopyranosyl fluoride (**2**) was isolated in 65% yield (Scheme 1).



Scheme 1.

Compound **2** is very sensitive to moisture and traces of acid. In the presence of water, it undergoes conversion into 1,3-*O*-isopropylidene-α-D-fructofuranosyl fluoride (**3**) and then into D-fructose which, in the presence of HF, generates a mixture of DFAs (Scheme 1). Compound **3** was also formed as by-product during the formation and isolation of **2**, probably due to the stoichiometric release of 1 equiv of water in the first step of the reaction, resulting in decrease in yield. This side reaction was minimized by carrying out the reaction in the presence of an excess of acetone, thus shifting the acetalation/hydrolysis equilibrium towards the diisopropylidene derivative **2**. In the absence of moisture, the fructopyranosyl fluoride **2** is a crystalline, stable compound which may be used as glycosyl donor in the regioselective preparation of β-pyranosides. As a matter of fact, addition of EtOH to a partially neutralised reaction mixture at -50°C led to the exclusive formation of ethyl 1,3:4,5-di-*O*-isopropylidene-β-D-fructopyranoside (**4**).

When the reaction mixture arising from the treatment of **1** with HF at -5°C was allowed to reach room temperature (20°C) for 10 min before quenching and neutralisation with ammonia, formation of a slower moving product was observed (TLC, 1:1 EtOAc-hexane). Some decomposition also occurred which could be avoided by effecting a partial neutralisation of the reaction mixture at -50°C, then increasing the temperature to 20°C. Crystalline 4,5:4',5'-di-*O*-isopropylidene-di-β-D-fructopyranose 1,2':2,1'-dianhydride (**6**) was thus obtained in 67% yield. It is noteworthy that no isomer incorporating an α-D-fructopyranose moiety could be detected, i.e., the 4,5-*O*-isopropylidene group not only preserves the pyranose cyclic form but also acts as a stereodirecting group in the selective formation of the β-anomeric linkage. This effect is probably related to steric hindrance at the α-side in the oxocarbenium ion intermediate **5** as well as to destabilisation of the known $^5C_2$ (D) conformation of the α-D-fructopyranose subunit in the isomeric α-D-fructopyranose β-D-fructopyranose 1,2':2,1'-dianhydride[4,6]. The diol **6** was transformed into the corresponding diacetate **7** by treatment with Ac_2O-pyridine, whereas deacetalation with TFA-H_2O afforded the target unprotected dianhydride **8** in 60% overall yield from **1** (Scheme 1).

The analytical, MS, and NMR data for the new compounds **2-4**, **6** and **7** confirmed the proposed structures. Furthermore, the values of $^3J_{H,H}$ and $^3J_{F,H}$ were consistent with the β-configuration in the $^2C_5$ (D) conformation for the pyranose rings of **2**, **4**, **6**, and **7**, in agreement with the anomeric effect. In the case of **3**, the coupling constants values were in agreement with the α-anomeric configuration for the furanose ring in a conformation close to ^3E (D), with the fluorine substituent in a quasi-axial disposition.

EXPERIMENTAL SECTION

General. Anhydrous hydrogen fluoride (HF) was a commercial product obtained in steel cylinders. Prior to use, it was distilled and kept in polyethylene bottles at -25°C. All reactions using HF were carried out in polyethylene bottles.

^1H (200 and 500 MHz) and ^{13}C NMR spectra (50.3 MHz) where recorded with Bruker AC 200 and Bruker AMX 500 instruments using $MeSi_4$ as internal standard. FAB-mass spectra (Cs gun, acceleration potential 8 kV) were measured in the positive mode with a VG ZAB-SEQ spectrometer. The samples were dissolved in *m*-nitrobenzyl alcohol and NaI was added as 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.

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 conducted on Silica Gel 60 (230-400 mesh, E. Merck).

Microanalyses were obtained from the Service Central de Microanalyse du CNRS in Solaize.

***1,3:4,5-Di-O-isopropylidene-β-D-fructopyranosyl fluoride* (2).** To a stirred solution of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose[13] (**1**, 0.5 g, 1.92 mmol) in Me_2CO (2 mL) under N_2 at -5°C was added freshly distilled HF (1 mL). After 10 min, the reaction mixture was cooled to -50°C and adjusted to pH 8-9 by dropwise addition of a saturated solution of dry (KOH) ammonia in purified CH_2Cl_2. Stirring was continued for 10 min at room temperature keeping an alkaline pH, afterwards the salts were filtered off and washed with additional CH_2Cl_2. Evaporation of the solvent and flash chromatography (2:3 EtOAc-hexane) of the residue yielded **2** (0.33 g, 65%) as a syrup which crystallised on standing at 5°C, mp 80-81°C, $[\alpha]_D$ -103.1 (*c* 0.6, $CHCl_3$); FABMS: *m/z* 285 (10%, $[M + Na]^+$), 263 (100, $[M + H]^+$). NMR data ($CDCl_3$): ^1H (200 MHz), δ 4.30 (m, H-4,5), 4.16 (dd, H-6, $J_{5,6}$ 3.5, $J_{6,6'}$ 13.0), 4.02 (dt, H-6', $J_{F,6'}$ 2.4, $J_{5,6'}$ 2.4), 3.89 (dd, H-3, $J_{3,4}$ 7.5, $J_{F,3}$ 25.4), 3.82 (dd, H-1, $J_{1,1'}$ 15.1, $J_{F,1}$ 23.0), 3.76 (dd, H-1', $J_{F,1'}$ 2.3), 1.49, 1.47, 1.46, 1.33 (4 s, each 3 H, 4 Me); ^{13}C (50.3 MHz): δ 109.5 (*C*Me_2, dioxolane), 104.7 (d, C-2, $J_{2,F}$ 228), 99.9 (*C*Me_2, 1,3-dioxane), 72.8 (C-4), 72.4 (C-5), 71.6 (d, C-3, $J_{3,F}$ 26.5), 64.1 (d, C-1, $J_{1,F}$ 26.1), 62.4 (d, C-6, $J_{6,F}$ 3.5), 28.4, 27.9, 25.7, 18.2 (4 Me). Anal. Calcd for $C_{12}H_{19}FO_5$: C, 54.95; H, 7.30; F, 7.24. Found: C, 55.29; H, 7.12; F, 7.09.

***1,3-O-Isopropylidene-α-D-fructofuranosyl fluoride* (3).** A similar reaction to that above described for the preparation of **2** but carried out in the absence of acetone gave a product (0.2 g) which showed two main spots on TLC (1:1 EtOAc-hexane). Column chromatography (1:3 → 3:1 EtOAc-hexane) first afforded the fructopyranosyl fluoride **2** (0.1 g, 20%) and then syrupy **3** (0.08 g, 18%), having $[\alpha]_D$ +25.2 (*c* 2.5, $CHCl_3$); FABMS: *m/z* 245 (25%, $[M + Na]^+$), 223 (100, $[M + H]^+$). NMR data ($CDCl_3$): ^1H (200 MHz), δ 4.35 (m, H-5), 4.25 (d, H-3, $J_{3,4}$ 0, $J_{F,3}$ 4.7), 4.12 (m, H-4), 3.98 (dd, H-1, $J_{F,1}$ 6.3, $J_{1,1'}$ 15.2), 3.87 (dd, H-1, $J_{F,1'}$ 5.2), 3.80 (m, H-6,6'), 2.65 (d, OH-4, $J_{4,OH}$ 7.4), 2.42 (s, OH-6), 1.48, 1.36 (2 s, each 3 H, 2 Me); ^{13}C (50.3 MHz): δ 113.2 (d, C-2, $J_{2,F}$ 226), 99.4 (*C*Me_2, 1,3-dioxane), 88.6 (C-5), 80.0 (d, C-3, $J_{3,F}$ 33.5), 62.3 (C-5), 62.3 (C-6), 62.2 (d, C-1, $J_{1,F}$ 37.9), 27.1, 19.6 (2 Me). Anal. Calcd for $C_9H_{15}FO_5$: C, 48.64; H, 6.80; F, 8.55. Found: C, 48.40; H, 6.67; F, 8.39.

***Ethyl 1,3:4,5-Di-O-isopropylidene-β-D-fructopyranoside* (4).** The reaction mixture arising from the treatment of **1** with HF (see above) was cooled to −50°C and a saturated solution of dry ammonia in CH_2Cl_2 (75 mL) at the same temperature was dropwise added under vigorous stirring. Ethanol (5 mL) was then added and, after 15 min, the reaction mixture was adjusted to alkaline pH and worked-up as described above. Column chromatography (2:3 EtOAc-hexane) afforded syrupy **4** (0.32 g, 58%) having $[\alpha]_D$ -147.6 (*c* 0.5, $CHCl_3$); FABMS: *m/z* 311 (100%, $[M + Na]^+$), 279 (60, $[M + H]^+$). NMR data ($CDCl_3$): ^1H (200 MHz), δ 4.29 (m, H-4,5), 4.00 (dd, H-6, $J_{5,6}$ 1.0, $J_{6,6'}$ 13.1), 3.90 (dd, H-1, $J_{1,1'}$ 12.7), 3.89 (dd, H-6', $J_{5,6'}$ 2.4), 3.84 (d, H-3, $J_{3,4}$ 7.9), 3.62, 3.48 (2 dq, CH_2CH_3), 3.59 (dd, H-1'), 1.53, 1.48, 1.46, 1.33 (3 s, each 3 H, 3 Me), 1.21 (t, CH_2CH_3); ^{13}C (50.3 MHz): δ 108.8 (*C*Me_2, dioxolane), 99.9 (C-2), 92.6 (*C*Me_2, 1,3-dioxane), 73.6 (2 C), 72.8 (C-3,4,5), 61.2, 60.8 (C-1,6), 56.3 (CH_2CH_3), 28.9, 28.3, 26.1 (3 Me), 18.4 (CH_2CH_3). Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.31; H, 8.39. Found: C, 58.12; H, 8.18.

4,5:4',5'-Di-O-isopropylidene-di-β-D-fructopyranose 1,2':2,1'-dianhydride (6). The reaction mixture arising from the treatment of **1** with HF (see above) was cooled to −50°C and a saturated solution of ammonia in CH_2Cl_2 (75 mL) at the same temperature was dropwise added under vigorous stirring. The still acidic reaction mixture was allowed to reach room temperature and, after 10 min, cooled down and adjusted to pH 8-9. Work-up as described above and crystallisation of the residue from boiling hexane yielded **6** (0.26g, 67%) having mp 182-184°C, $[\alpha]_D$ -297.7 (*c* 0.8, MeOH); FABMS: *m/z* 427 (100%, $[M + Na]^+$). NMR data ($CDCl_3$): ^1H (500 MHz), δ 4.25 (t, H-4, $J_{3,4}$ 6.2, $J_{4,5}$ 6.2), 4.14 (ddd, H-5, $J_{5,6}$ 2.5, $J_{5,6'}$ 1.0), 3.98 (dd, H-6, $J_{6,6'}$ 13.1), 3.84 (dd, H-6'), 3.81 (d, H-1, $J_{1,1'}$ 12.5), 3.70 (d, H-3), 3.67 (d, H-1'), 1.42, 1.29 (2 s, each 3 H, 2 Me); ^{13}C (50.3 MHz): δ 109.3 (*C*Me_2, dioxolane), 95.5 (C-2), 76.0, 72.8 (2C) (C-3,4,5), 63.7, 61.4 (C-1,6), 27.4, 25.5 (2 Me). Anal. Calcd for $C_{14}H_{24}O_6$: C, 53.45; H, 6.98. Found: C, 53.38; H, 6.82.

3,3'-Di-O-acetyl-4,5:4',5'-di-O-isopropylidene-di-β-D-fructopyranose 1,2':2,1'-dianhydride (7). Diol **6** (0.1 g, 0.25 mmol) was treated with Ac_2O-pyridine (1:1, 2 mL) overnight. The reaction mixture was poured into ice-water (10 mL) to give a white solid which was collected, dried (P_2O_5) and crystallised from EtOH to give the corresponding diacetate **7** (0.116 g, 96%) having mp 238-239°C, $[\alpha]_D$ -310.9 (*c* 1, $CHCl_3$); FABMS: *m/z* 511 (100%, $[M + Na]^+$). NMR data ($CDCl_3$): ^1H (200 MHz), δ 5.05 (d, H-3, $J_{3,4}$ 7.6), 4.21 (m, H-4,5), 4.00 (m, H-6,6'), 3.85 (d, H-1, $J_{1,1'}$ 12.6), 3.47 (d, H-1') 2.18 (s, 3 H, Ac), 1.51, 1.32 (2 s, each 3 H, 2 Me); ^{13}C (50.3 MHz): δ 170.8 (CO), 109.4 (*C*Me_2, dioxolane), 95.9 (C-2), 73.9 (2C), 73.5 (C-3,4,5), 62.9, 60.5 (C-1,6), 27.7, 26.1 (2 Me), 20.7 (CO*C*H_3). Anal. Calcd for $C_{14}H_{24}O_6$: C, 54.09; H, 6.60. Found: C, 53.80; H, 6.58.

Di-β-D-fructopyranose 1,2':2,1'-dianhydride (8). A solution of **6** (0.2 g, 0.49 mmol) in TFA-H_2O (9:1, 2 mL) was kept at room temperature for 10 min under reduced pressure (water pump).The solvents were then evaporated at T < 40°C and the residue was crystallised from 1:1 EtOH-water to give the unprotected derivative **8** (0.141 g, 91%) having the physical and spectroscopic data previously reported.

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REFERENCES AND NOTES

1. Carbohydrate reactivity in hydrogen fluoride, Part 19. For part 18, see ref 9.
2. Present adress: Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 553, E-41071 Sevilla, Spain.
3. McDonald, E.J. *Adv. Carbohydr. Chem.*, **1946**, *2*, 253-277; Verstraeten, L.M.J. *Adv. Carbohydr. Chem. Biochem.*, **1967**, *22*, 229-305.
4 Defaye, J., Gadelle, A.; Pedersen, C. *Carbohydr. Res.*, **1985**, *136*, 53-65.
5. Chu, J.D.; Shian, L.D.; Berglund, K.A. *J. Cryst. Growth*, **1989**, *97*, 689-696.
6. Defaye, J.; García Fernández, J.M. *Carbohydr. Res.*, **1992**, *237*, 223-247; *Ibid.* **1994**, *251*, 1-15; *Ibid.* **1994**, *251*, 17-31.

7. Defaye, J.; García Fernández, J.M. *Carbohydr. Res.*, **1994**, *256*, C-1–C-4.
8. García Fernández, J.M.; Defaye, J. *Tetrahedron Lett.*, **1992**, *33*, 7861-7864.
9. García Fernández, J.M.; Gadelle, A.; Defaye, J. *Carbohydr. Res.*, **1994**, in press.
10. Bock, K.; Pedersen, C.; Defaye, J.; Gadelle, A. *Carbohydr. Res.*, **1991**, *216*, 141-148.
11. Defaye, J.; García Fernández, J.M. *Tetrahedron: Asymmetry*, **1994**, *5*, 2241-2250.
12. Angyal, S.J.; Craig, D.C.; Defaye, J.; Gadelle, A. *Can. J. Chem.*, **1990**, *68*, 1140-1144.
13. Brady, R.F., Jr. *Carbohydr. Res.*, **1970**, *15*, 35-40.

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