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Carbohydrate-Derived Spiroketals. Stereoselective Synthesis of Di-D-fructose Dianhydrides by Boron Trifluoride Promoted Glycosylation–Spiroketalization of Acetal Precursors†

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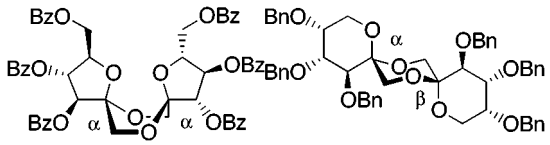
ABSTRACT



Di-D-fructose 1,2′:2,1′-dianhydrides, *dispiro*-tricyclic disaccharides widely found in food materials, have been stereoselectively prepared in one-pot reaction from *O*-protected D-fructose 1,2-acetonide precursors by treatment with boron trifluoride diethyl etherate. The dimerization sequence involves (i) cleavage of the anomeric acetal linkage, (ii) autoglycosylation, and (iii) final spiroketalization, the stereochemical outcome being strongly dependent on the nature of the hydroxyl protecting groups.

The spiroketal unit is a widespread substructure in many biologically active natural products, including steroidal saponins, polyether ionophores, macrolide antibiotics, insect pheromones, and toxic metabolites from algae and fungi.[1,2] A main strategy for its elaboration relies on the acid-catalyzed intramolecular cyclization of the corresponding dihydroxy-keto precursors or their equivalents. Since such a basic skeleton is present in ketoses, it was anticipated that

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(1) For general and specialized reviews on the synthesis of spiroketals see: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661. (b) Imanishi, T.; Iwata, C. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994; Vol. 14, pp 517−550. (c) Ichihara, A.; Oikawa, H.; Toshima, H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1996; Vol. 18, pp 269−313. (d) Pietruszka, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2629−2636. (e) Brimble, M. A.; Farès, F. A. *Tetrahedron* **1999**, *55*, 7661−7706.

(2) For selected recent examples of spiroketal syntheses, see: (a) Crimmins, M. T.; Katz, J. D. *Org. Lett.* **2000**, *2*, 957−960. (b) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863−866. (c) Zuev, D,; Paquette, L. A. *Org. Lett.* **2000**, *2*, 679−682. (d) Drouet, K. E.; Ling, T.; Tran, H. V.; Theodorakis, E. A. *Org. Lett.* **2000**, *2*, 207−210. (e) Barret, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375−380. (f) Brimble, M. A.; Caprio, V. E.; Johnston, A. D.; Sidford, M. H. *Tetrahedron Lett.* **2000**, *41*, 3955−3958. (g) Arterburn, J. B.; Perry, M. C. *Org. Lett.* **1999**, *1*, 769−771. (h) Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **1999**, *1*, 451−453. (i) Trost, B. M.; Corte, J. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3664−3666. (j) Carretero, J. C.; de Diego, J. E.; Hamdouchi, C. *Tetrahedron* **1999**, *55*, 15159−15166. (k) Bueno, A. B.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 684−690.

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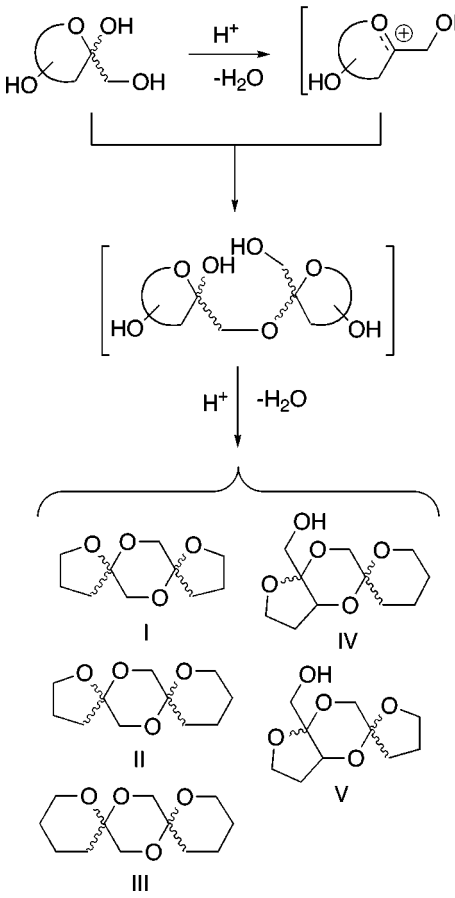
spiroketalization might occur more universally in carbohydrate transformation schemes. In fact, spirodioxanyl disaccharides have long been known as the dimerization products arising from the acid treatment of ketoses.[3] Some members of this family derived from D-fructose, termed generically di-D-fructose dianhydrides (DFAs), have also been isolated from microorganisms[4] and higher plants.[5] Their potential use as sweetners,[6] bifidogenic agents,[7] or polyhydroxylated spiroketal chiral templates[8] has triggered intense interest in the synthesis of these and related *spiro* sugars.[9] The identification of DFAs as the major components of the thermolysis product of sucrose- and D-fructose-containing food materials, such as caramel or chicory,[10] and the need for pure standards for their analytical evaluation[11] has provided a further impetus.

High yielding preparations of DFAs have been previously achieved by protonic activation of D-fructose, sucrose, or inulin with anhydrous hydrogen fluoride (HF) or its complex with pyridine.[12] Under such conditions, a fructosyl oxocarbenium cation is generated, which undergoes in situ glycosylation into the corresponding *keto*-disaccharide. Further spiroketalization is a reversible process governed mainly by stereoelectronic factors, i.e., maximum anomeric effect and minimum steric interactions (Scheme 1).[13]

In tricyclic systems such general principles must be applied carefully. A range of structures can usually accommodate the basic requirements—oxygen substituents at anomeric centers in axial disposition, carbon substituents in equatorial disposition—with rather small differences in energy and low

Scheme 1. Protic Acic Catalyzed Dimerization of Ketoses



interconversion barriers. Consequently, a complex distribution of isomers that differ on the ring size, linking position, and stereochemistry at the acetal stereocenters is generally obtained. Up to five different tricyclic cores (Types I to V) and 12 DFA isomers may be present in the reaction mixtures. Although their relative proportions can be varied to some extent by modulation of the acid strength, isolation of pure samples from these isomeric mixtures remains a difficult task.[3]

We have previously reported the stereospecific synthesis of a Type III DFA, namely, di-β-D-fructopyranose 1,2′:2,1′-dianhydride, by use of an acetal-protected D-fructopyranose precursor and HF as promotor.[14] The rather severe reaction conditions prevent, however, extension of this approach to other selectively protected derivatives. On the other hand, boron trifluoride diethyl etherate has been widely used for the cleavage of acetal protecting groups,[15] as promoter in glycosylation reaction,s[16] and as catalyst in spiroketalization processes.[1a] We assumed that these three transformations might proceed in a tandem manner for ketoses bearing acetonide groups at the anomeric position, taking advantage

(3) For a recent review, see: Manley-Harris, M.; Richards, G. N. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 207−266.

(4) (a) Tanaka, K.; Uchiyama, T.; Ito, A. *Biochim. Biophys. Acta* **1972**, *284*, 248−256. (b) Tanaka, K.; Sonobe, K.; Uchiyama, T.; Matsuyama, T. *Carbohydr. Res.* **1979**, *75*, 340−344. (c) Matsuyama, T.; Tanaka, K.; Mashiko, M.; Kanamoto, M. *J. Biochem.* **1982**, *92*, 1325−1328. (d) Haraguchi, K.; Kishimoto, M.; Seki, K.; Hayashi, K.; Kobayashi, S.; Kainuma, K. *Agric. Biol. Chem.* **1988**, *52*, 291−292. (e) Kawamura, M.; Takahashi,, Uchiyama, T. *Agric. Biol. Chem.* **1988**, *52*, 3209−3210. (f) Matsuyama, T.; Tanaka, K.; Uchiyama, T. *Agric. Biol. Chem.* **1991**, *55*, 1413−1414.

(5) Li, H.; Zhu, W.; Yokoyama, C.; Harada, N. *Carbohydr. Res.* **1997**, *299*, 301−305.

(6) Uchiyama, T. In *Science and Technology of Fructans*; Suzuki, M., Chatterton, N. J., Eds.; CRC: Boca Raton, FL, 1993; pp 170−190.

(7) (a) Manley-Harris, M.; Richards, G. N. *Zuckerindustrie* **1994**, *119*, 924−928. (b) Tanaka, M.; Nakajima, Y.; Nisio, K. *J. Carbohydr. Chem.* **1993**, *12*, 49−61.

(8) (a) García Fernández, J. M.; Gadelle, A.; Defaye, J. *Carbohydr. Res.* **1994**, *265*, 249−269. (b) Defaye, J.; García Fernández, J. M. *Tetrahedron: Asymmetry* **1994**, *5*, 2241−2250.

(9) (a) García Fernández, J. M.; Ortiz Mellet, C.; Defaye, J. *J. Org. Chem.* **1998**, *63*, 3572−3580. (b) Bextermöller, R.; Redlich, H.; Schnieders, K.; Thrmählen, S.; Frölich, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2496−2500. (c) Regelin, H.; Sunghwa, F.; Zwanenburg, B.; Gelder, R.; Chittenden, G. J. F. *Carbohydr. Polymers* **1998**, *37*, 323−333. (d) Martín, A.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1996**, *61*, 3999−4006. (e) García Fernández, J. M.; Schnelle, R.-R.; Defaye, J. *Aust. J. Chem.* **1996**, *49*, 319−325.

(10) (a) Defaye, J.; García Fernández, J. M. *Carbohydr. Res.* **1994**, *256*, C1. (b) Defaye, J.; García Fernández, J. M. *Zuckerindustrie* **1995**, *120*, 700. (c) Manley-Harris, M.; Richards, G. N. *Carbohydr. Res.* **1996**, *287*, 183−202.

(11) Ratsimba, V.; García Fernández, J. M.; Defaye, J.; Nigay, H., Voilley, A, *J. Chromatogr. A* **1999**, *844*, 283−293.

(12) (a) Defaye, J.; García Fernández, J. M. *Carbohydr. Res.* **1994**, *251*, 17−31. (b) Defaye, J.; García Fernández, J. M. *Carbohydr. Res.* **1994**, *251*, 1−15. (a) Defaye, J.; García Fernández, J. M. *Carbohydr. Res.* **1992**, *237*, 223−247 and references therein.

(13) Bock, K.; Pedersen, C.; Defaye, J.; Gadelle, A. *Carbohydr. Res.* **1991**, *216*, 141−148.

(14) García Fernández, J. M.; Schnelle, R.-R.; Defaye, J. *Tetrahedron: Asymmetry* **1995**, *6*, 307−312.

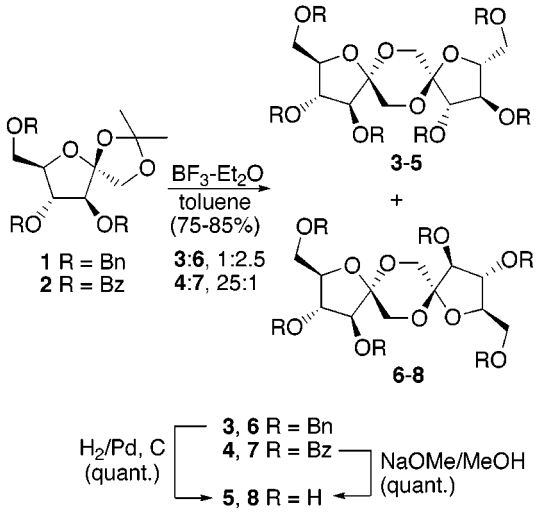
(15) Ishihara, K. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol.1, pp 89−133.

(16) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503−1531.

of their propensity to develop tertiary glycosyl oxocabenium cations. We now report on the application of this strategy to the stereoselective preparation of DFAs having the 1,6,9,13-tetraoxadispiro[4.2.4.2]tetradecane (Type I) and 1,7,10,15-tetraoxadispiro[5.2.5.2]hexadecane (Type III) dispiroketal frameworks.

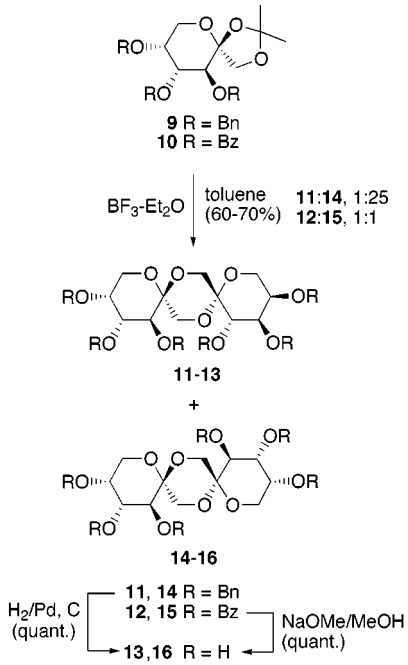
Treatment of 3,4,6-tri-*O*-benzyl-1,2-*O*-isopropylidene-*β*-D-fructofuranose **1**, readily accessible from D-fructose in two steps via the corresponding fructofuranose 1,2-*O*-acetonide,[17] with 1 equiv of boron trifluoride diethyl etherate in toluene afforded a 1:2.5 mixture of the hexa-*O*-benzylated di-α-D-fructofuranose (**3**) and α-D-fructofuranose *β*-D-fructofuranose (**6**) 1,2′:2,1′-dianhydrides,[18] which were separated and deprotected to the known cyclic disaccharides **5** and **8**, respectively.[3] Replacement of the benzyl groups by benzoyl groups likewise preserved the furanose form of fructose while reversing the stereochemical outcome of the spiroketalization reaction. Thus, upon treatment of **2** with the Lewis acid promoter the C_2 symmetric dianhydride **4** was obtained in 96% de over the asymmetric diastereomer **7** (Scheme 2).[18]

Scheme 2. Stereoselective Synthesis of Type I DFAs



To implement this approach for the stereoselective preparation of *dispiro*-difructopyranose dianhydrides, 3,4,5-tri-*O*-benzyl- and 3,4,5-tri-*O*-benzoyl-1,2-*O*-isopropylidene-*β*-D-fructopyranose (**9** and **10**, respectively), available in three steps from D-fructose,[19] were used as pyranose-anchored D-fructose templates. The dimerization process proceeded more slowly in these cases as compared with the furanose counterparts, in agreement with the expected lower stability of the six-membered cyclic oxocarbenium ion intermediate. Nevertheless, satisfactory yields in the corresponding hexa-*O*-benzyl (**11** and **14**) and hexa-*O*-benzoyl (**12** and **15**) difructopyranose dianhydrides were obtained within 16 h by using 2.5 equiv of $BF_3{\cdot}Et_2O$.[18] The relative proportion between the C_2 symmetric (di-*β*-D) and the asymmetric diastereomer (α,*β*-D) was, as in the furanose series, strongly dependent upon the nature of the hydroxyl protecting groups. Whereas the benzyl-protected acetonide **9** resulted almost exclusively in the α-D-fructopyranose *β*-D-fructopyranose 1,2′:2,1′-dianhydride derivative **14** (**11**:**14**, 1:25), the tribenzoate **10** gave a 1:1 mixture of **12** and **15**. The structural assignment was confirmed by transformation into the known fully unprotected DFAs **16** and **17** (Scheme 3).[3]

Scheme 3. Stereoselective Synthesis of Type III DFAs



The possibility to control not only the ring size but also the stereochemistry at the spiroketal centers is noteworthy. In contrast to the protic acid catalyzed reaction, spiroketalization occurs now under irreversible conditions. The preference for asymmetric dispiroketal structures in the case of nonparticipating benzyl substituents (i.e., **6** and **14**) agrees with a preferred chair conformation at the incipient 1,4-dioxane ring, analogous to that encountered in the final

(17) Chittenden, G. J. F. *J. Chem. Soc., Chem. Commun.* **1980**, 882−883.

(18) **Typical Dimerization Procedure.** To a solution of the corresponding D-fructose 1,2-*O*-acetonide derivative **1**, **2**, **9**, or **10** (0.3 mmol) in dry toluene (2 mL) at −20 °C was added $BF_3{\cdot}Et_2O$ (1 equiv for **1** and **9**; 2.5 equiv for **2** and **10**) under Ar. The reaction mixture was allowed to reach room temperature and stirred for 4 h (**1** and **9**) or overnight (**2** and **10**). MeOH (1.5 mL) and CH_2Cl_2 (10 mL) were then added, and the resulting solution was washed with 5% aqueous $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), and concentrated. Column chromatography (silica gel, 1:5 EtOAc−hexanes) afforded the corresponding two-component mixtures of DFAs in 60−85% yield. Conventional hydrogenation of the benzylated derivatives (**3**, **6** or **11**, **13**) with H_2 (1 atm) over 10% Pd/C in 2:1 EtOAc−MeOH for 24 h or debenzoylation (**4**, **7** or **14**, **16**) with 0.1 M NaOMe in MeOH afforded the corresponding mixtures of fully unprotected DFAs **5**, **8** or **17**, **19** whose relative proportions were stablished by GC following the procedure reported in ref 10. The hexabenzyl derivatives **3**, **6** and **11**, **13** could also be separated by column chormatography using the above eluent. Alternatively, the mixtures of unprotected DFAs were separated as their corresponding hexaacetates using 1:3 EtOAc−hexanes as the eluent. In all cases, the physical and spectroscopic properties of the separated unprotected isomers were identical to those previously reported (cf. ref 3).

(19) Brady, R. F., Jr. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 197−278.

compounds, with the oxygen substituents in axial disposition and the carbon substituents in equatorial disposition (Figure 1, B).[3] Such situation does not prevail for the symmetric

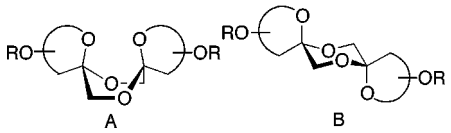


Figure 1. Conformations at the central dioxane ring for C_2 symmetric (A) and asymmetric (B) dispiroketals.

isomers, which must adopt a boat conformation at the central ring in order to accommodate the anomeric effect at both anomeric centers, a less favorable arrangement (Figure 1, A).[3]

For derivatives bearing participating acyl substituents, the reaction probably proceeds through 2,3-acyloxonium entities (**18** and **19**). In the furanose series, this situation leads with high stereoselectivity to the expected di-α dianhydride **4**, having the oxygen substituents at C-2 and C-3 in trans relative disposition. In the pyranose series, however, pyramidalization of the anomeric carbon likely increases the crowding of the already hindered α-face. Glycosylation at this stage may then compete with the attack by the axially disposed benzoate group at C-5 to give a 2,5-acyloxonium intermediate (**20**) that, at its turn, will undergo glycosylation−spiroketalization through the *β*-face to give **12** (Figure 2).

In summary, we have demonstrated that boron trifluoride is a suitable reagent to promote dimerization of ketoses to

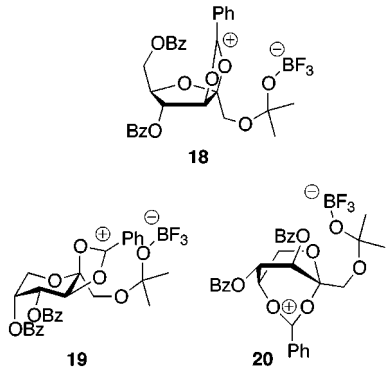


Figure 2. Probable structure of the acyloxocarbenium cations involved in the BF_3-catalyzed glycosylation−spiroketalization of benzoylated D-fructose precursors.

dispiro-cyclic disaccharides. Both the ring size and the stereochemistry at the spiroketal centers can be controlled by judicious choice of the protecting groups in the monosaccharide template. Extension of this procedure to the preparation of other spiroketal frameworks is currently in progress in our laboratories.

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