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Carbohydrate-Derived Spiroketals: Stereoselective Synthesis of Di-D-fructose Dianhydrides via Intramolecular Aglycon Delivery

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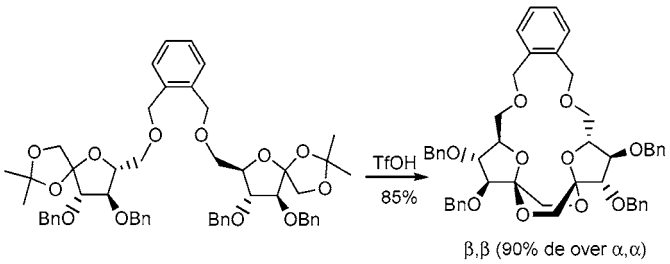
ABSTRACT



A one-pot synthesis of C_2-symmetric di-D-fructose dianhydrides having the 1,6,9,13-tetraoxadispiro [4.2.4.2]tetradecane skeleton has been accomplished via intramolecular aglycon delivery from (6 → 6) xylylene-tethered fructofuranose precursors. The stereochemical outcome of the glycosylation–spiroketalization process is governed by the geometrical constraints imposed by the rigid tetracyclic structure of the final compound.

The widespread occurrence of highly substituted and functionalized spiroketal subunits in many biologically significant natural products and the increasing pharmacological importance of some representatives have promoted considerable interest in the development of synthetic routes to these compounds.[1,2] Of special interest is the tricyclic dispiro arrangement, which appears in nature in a number of polyether ionophores such as narasin, salinomycin, noboritomycin, the antibiotics CP44 661 and X 14766A, and other substances isolated from marine organisms.[3,4] This structural element is also present in several diketose dianhydrides,[5,6] a unique class of cyclic disaccharides of which di-D-fructose

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dianhydrides (DFAs) are paradigmatic examples. DFAs have been isolated from microorganisms[7] and higher plants[8] and have also been identified in food materials such as caramel and chicory.[9]

Despite the variety of general methods existing for the construction of the spiroketal moiety, the control of the stereochemistry at the anomeric center is, almost exclusively, based on the relative thermodynamic stability of the different isomers in the acid-catalyzed spiroketalization. When all factors that control spirocyclization, i.e., a maximum anomeric effect and minimum steric interactions, are reinforcing, a major isomer is produced. The stereoselectivity is lower when these factors are in conflict. In tricyclic systems, however, such general statements must be applied carefully. A range of structures can usually accommodate the basic requirements with rather small differences in energy and low interconversion barriers. Actually, the dimerization reaction of D-fructose under acidic conditions leads to a complex mixture of up to 13 DFA isomers that differ in the ring size, linking position, and stereochemistry at the acetal stereocenters, seven of which possess a tetraoxadispiro core with either the [4.2.4.2]-, [5.2.4.2]-, or [5.2.5.2]tetradecane arrangement (Figure 1, types I−III, respectively).[5]

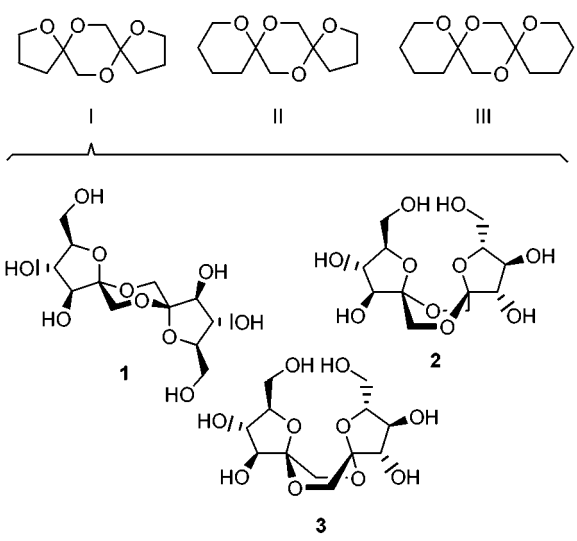

Figure 1. Tricyclic dispiroketal frameworks present in di-D-fructose dianhydrides: tetraoxadispiro [4.2.4.2]tetradecane (I), tetraoxadispiro [5.2.4.2]tetradecane (II), and tetraoxadispiro [5.2.5.2]-tetradecane core (III). The three possible type I DFA diastereomers **1**−**3** are also shown.

The stereoselective synthesis of DFAs of type I is particularly challenging due to the presence of two five-membered rings, for which the anomeric effect is considerably reduced as compared with six-membered rings. Of the three possible type-I diastereomers, the nonsymmetrical α-D-fructofuranose β-D-fructofuranose 1,2′:2,1′-dianhydride **1** is the thermodynamically favored diastereomer, since it can accommodate the oxygen substituents in an axial orientation and the carbon substituents in an equatorial disposition with the central 1,4-dioxane ring in a chair conformation. Such a situation does not prevail for the C_2-symmetric di-α- and di-β-D-fructofuranose 1,2′:2,1′-dianhydrides **2** and **3**, respectively, which must adopt a boat conformation at the central ring in order to accommodate the anomeric effect at both anomer centers, a less favorable arrangement (Figure 1).[5]

We have previously devised a stereoselective synthesis of **2**, having a trans relative disposition between the anomeric oxygen atoms and the vicinal hydroxyl groups, by taking advantage of the participating character of *O*-acyl groups during the Lewis acid-catalyzed glycosylation−spirocyclization reaction of 1,2-*O*-isopropylidene-β-D-fructofuranose precursors.[10] We now report the highly diastereoselective preparation of the di-β-isomer **3** by implementing the concept of intramolecular aglycon delivery (IAD),[11] originally introduced by Hindsgaul[12] and Stork[13] for the synthesis of β-mannosides, to the control of the stereochemical outcome in spiroketalization processes.

Our strategy relies on the significant differences in the through-space distance between the primary hydroxyl groups of the nonsymmetric **1** and the C_2-symmetric DFA isomers **2** and **3** in their most stable conformations. The restriction of this parameter by incorporation of an appropriate tether should favor the latter compounds by fixing the boat conformation. In a first approach, the *m*-xylylene spacer, previously used by Schmidt in oligosaccharide synthesis,[14] was considered. Thus, the dimeric 1,2-*O*-isopropylidene-β-D-fructofuranose derivative **8** was prepared by a reaction sequence involving selective protection of the primary

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(10) Benito, J. M.; Gómez-García, M.; Ortiz Mellet, C.; García Fernández, J. M.; Defaye, J. *Org. Lett.* **2001**, *3*, 549−552.

(11) Here we are using the notion of *intramolecular aglycon delivery* in a broad sense, to refer to transformations involving an intramolecular glycosylation reaction in which the acceptor and the donor moieties are linked through a tether that controls the stereochemical outcome, to produce product distributions different from those obtained in the intermolecular process, and that can be further removed. It should be noted, however, that classical IAD glycosylation reactions proceed to give, preferentially, the kinetic product, which is not necessary true in the present case.

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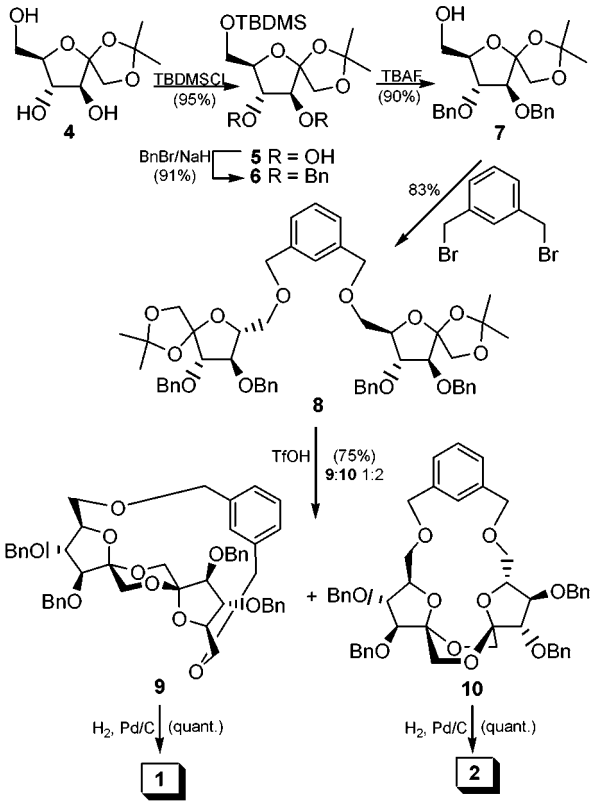
(13) (a) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248. (b) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088.

(14) (a) Müller, M.; Schmidt, R. R. *Eur. J. Org. Chem.* **2001**, 2055−2066. (b) Müller, M.; Huchel, U.; Geyer, A.; Schmidt, R. R. *J. Org. Chem.* **1999**, *64*, 6190−6201. (c) Huchel, U.; Schmidt, R. R. *Tetrahedron Lett.* **1998**, *39*, 7693−7694.

hydroxyl group in the known acetonide **4**[15] as the corresponding *tert*-butyl dimethyl silyl ether **5**, benzylation of the secondary hydroxyl groups (→ **6**), fluorolysis of the silyl ether group (→ **7**), and reaction of the resulting alcohol with α,α′-dibromo-*m*-xylene (Scheme 1).

Scheme 1. Stereoselective Synthesis of Type-I DFAs via IAD Using the *m*-Xylylene Tether

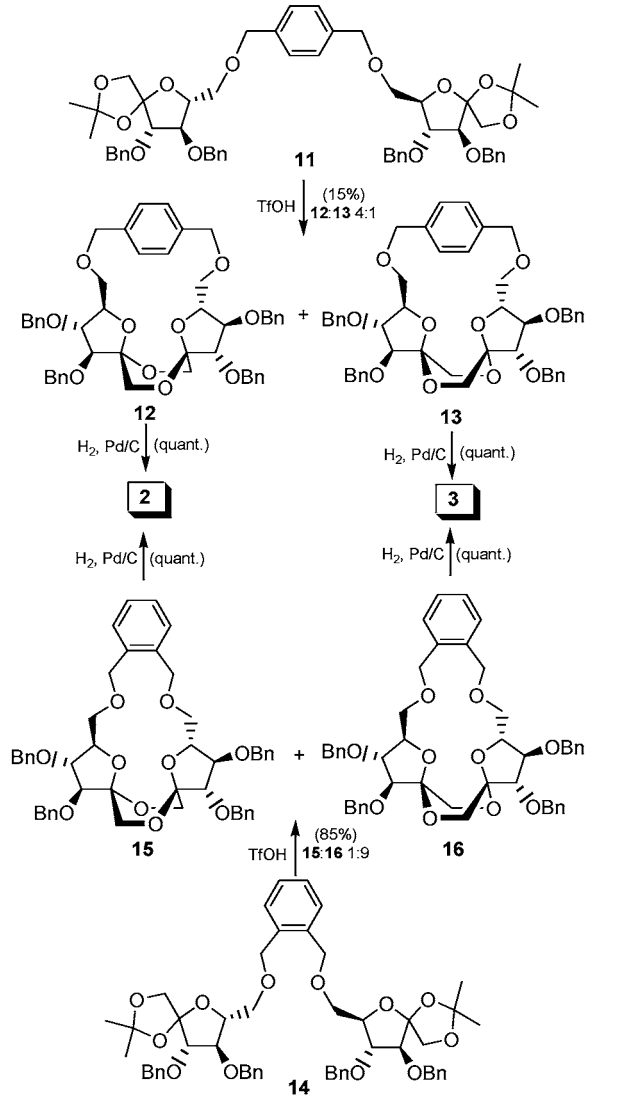


Cleavage of the acetal protecting groups in dimer **8**, intramolecular glycosylation, and subsequent spirocyclization were effected in a one-pot manner by using trifluoromethanesulfonic acid as the catalyst in dichloromethane solution. An inseparable mixture of the α,*β*- and α,α-isomers **9** and **10**, respectively, in a 1:2 relative proportion was thus obtained in 75% yield. Hydrogenolysis of the benzyl groups led to the fully unprotected DFAs **1** and **2** (Scheme 1).[16]

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

(16) **Typical IAD−Spirocyclization Procedure.** To a solution of the corresponding xylylene-tethered D-fructofuranose derivative **8**, **11**, or **14** (80 mg, 0.088 mmol) in dry CH_2Cl_2 (14 mL) at −78 °C was added trifluoromethanesulfonic acid (12 *μ*L, 1.5 equiv) under Ar. The reaction mixture was stirred for 1 h, allowed to reach room temperature, and then stirred for an additional 1 h. Et_3N (3 drops) was added, and the resulting solution was stirred for 10 min and then concentrated. Column chromatography (silica gel, 1:3 EtOAc−petroleum ether) afforded the corresponding two-component mixtures of DFAs (**9**, **10** and **12**, **13**, respectively) in the case **8** and **11** or the individual DFAs (**15** and **16**) in the case of **14**. Conventional hydrogenation of the benzyl xylylene derivatives with H_2 (1 atm) over 10% Pd/C in 2:1 EtOAc−MeOH for 24 h afforded the corresponding fully unprotected DFAs **1**−**3** whose relative proportions were stablished by GC following the procedure reported in ref 9d. In all cases, the physical and spectroscopic properties of the unprotected isomers were identical to those previously reported (cf. ref 5).

Scheme 2. Stereoselective Synthesis of Type-I DFAs via IAD Using the *p*- and *o*-Xylylene Tethers



The above result is in agreement with a destabilization of the chair conformation of the 1,4-dioxane ring in difuranose DFA isomers upon tethering of the primary hydroxyl groups. Actually, under identical reaction conditions, the monomeric 3,4,6-tri-*O*-benzyl-1,2-isopropylidene-*β*-D-fructofuranose[10] afforded the analogous hexa-*O*-bezyl α,*β*- and α,α-DFAs in a 3:1 relative proportion, as expected from the already discussed relative thermodynamic stabilities. It seems, however, that the *m*-xylylene linker is still too flexible to avoid formation of the thermodynamically favored nonsymmetrical diastereomer, and this situation prevents isolation of the elusive di-*β*-diastereomer.

To further limit the flexibility of the system, the dimeric *p*- and *o*-xylylene-tethered fructofuranose derivatives **11** and **14**, respectively, were prepared by reaction of the selectively protected acetonide **7** with α,α′-dibromo-*p*- and *o*-xylene, respectively. After treatment with trifluoromethanesulfonic acid, compound **11** afforded a mixture of the C_2-symmetric DFA diastereomers **12** and **13** in a 4:1 ratio, although in

disappointingly low yield (Scheme 2). In the case of **14**, having the shorter spacer, the IAD glycosylation−spirocyclization reaction led to the di-β-DFA **16** in 90% de over the di-α-isomer **15** and 85% total yield, which could be separated by silica gel column chromatography. Further hydrogenolysis afforded the fully unprotected di-α- and di-β-DFAs **2** and **3** (Scheme 2). To the best of our knowledge, this is the first synthesis of the latter compound, a minor component of the disaccharide fraction of sucrose and D-fructose caramels,[9] in good yield.

The remarkable differences in the stereoselectivity of the above spirocyclization reactions as a function of the substitution pattern of the xylylene spacer deserve a further comment. No traces of the α,β-diastereomer were detected in the last two cases, probably due to the interplay of stereoelectronic effects at the 1,4-dioxane ring and the geometrical constraints imposed by the rigid tether, in agreement with molecular mechanics calculations.[17] Stereoelectronic effects also influence the conformations of the five-membered rings in DFAs. Thus, α-D-fructofuranose rings in DFA derivatives have been shown to adopt a rather rigid ^3E conformation by X-ray, ^{1}H NMR, and molecular modeling data.[5] In spiroketalic β-linked D-fructofuranosyl moieties, O-2 and O-3 would be unfavorably eclipsed in certain conformations, which results in skewed conformations around E_o being favored over conformations in which C-2 and C-3 are in the same plane.[5] As a consequence, the hydroxymethyl groups in C_2-symmetric difuranose DFA derivatives are taken apart in the case of the di-α-isomer **2** and drawn nearer in the case of the di-β counterpart **3**. This is in agreement with the later isomer being favored for the shorter *o*-xylylene spacer.

In summary, we have demonstrated that the IAD approach represents a powerful tool for the control of the stereochemistry in spirocyclization reactions leading to complex dispiroketal derivatives. Extension of this strategy to the preparation of other systems is currently in progress in our laboratories.

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Supporting Information Available: Experimental procedures and data for compounds **8**, **11**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Molecular mechanics calculations for derivatives of DFAs **1**−**3** bearing xylylene tethers between the primary oxygen atoms were performed using MM2* as integrated in MACROMODEL 6.0 and the GBSA continuum solvent model for chloroform. The three-dimensional geometries obtained were in agreement with the discussed conformational and relative stability data.