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Rigid Spacer-Mediated Synthesis of Bis-Spiroketal Ring Systems: Stereoselective Synthesis of Nonsymmetrical Spiro Disaccharides

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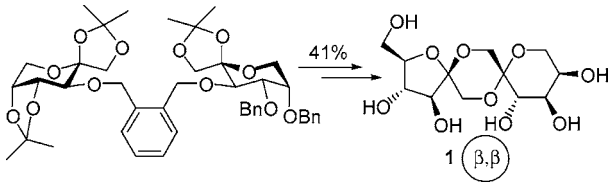
ABSTRACT



The application of the "rigid spacer-mediated linkage between nonreacting centers" concept to the preparation of nonsymmetrical bis-spiroketal structures is demonstrated by the stereoselective synthesis of the bis-spiro fructodisaccharide 1, a minor component of industrial caramels. An *o*-xylylene bridge has been used to limit the conformational space during the intramolecular glycosylation-spirocyclization reaction of a difructopyranose precursor, thus controlling both the ring size and the stereochemistry at the spiro centers.

Di-D-fructose dianhydrides (DFAs)[1] represent a unique class of cyclodisaccharides isolated from microorganisms and higher plants having a mono- or bis-spiroketal basic framework, a structural feature that is shared by many biologically relevant natural products, including steroidal saponins, polyether ionophores, macrolide antibiotics, insect pheromones, and toxic metabolites from algae and fungi,[2] being the target of much synthetic effort.[3] These spiro disaccharides have also been identified as the major components of the thermolysis product of sucrose- and D-fructose-containing food materials, such as caramel or chicory.[4,5] Three different bis-spiroketal ring systems, namely 1,6,9,13-tetraoxadispiro[4.2.4.2]tetradecane, 1,6,9,14-tetraoxadispiro[4.2.5.2]pentadecane, and 1,7,10,15-tetraoxadispiro[5.2.5.2]hexadecane core structures (type I, II, and III DFAs, respectively), are formed during such transformations (Scheme 1).

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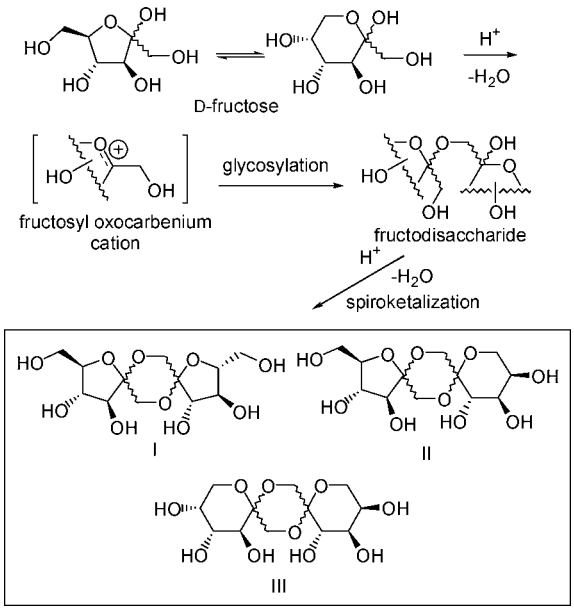
Scheme 1. Bis-spiro Fructodisaccharides (Type I−III DFAs) Formed by Acid (or Thermal) Activation of D-Fructose



We have recently reported the preparation of type I and type III DFAs from anomeric isopropylidene fructofuranose or fructopyranose precursors, respectively, by selective activation with boron trifluoride−diethyl ether complex or trifluoromethanesulfonic acid in organic solvents.[6] Highly stereoselective syntheses of the nonsymmetrical (α,*β*) or the C_2-symmetrical (α,α or *β*,*β*) diastereomers were achieved through protecting group participation and intramolecular aglycon delivery strategies. However, fixing the cyclic form of the D-fructose precursor does not allow accessing the mixed furanose−pyranose type II spiro disaccharides, which represent a serious limitation. We have now implemented the "spacer-mediated linkage via nonreacting centers" concept, previously exploited in anomeric configuration control during glycosidic bond-forming reactions,[7] for the synthesis of nonsymmetrical bis-spiroketal compounds. This has been translated into the first stereoselective synthesis of the type II DFA diastereomer having the *β*-configuration at both anomeric carbons, namely *β*-D-fructofuranose *β*-D-fructopyranose 1,2′:2,1′-dianhydride (**1**), a minor component of sucrose caramel.[5]

Our strategy for the stereoselective synthesis of bis-spiro fructodisaccharide derivatives stems from the consideration of the particular conformational properties of these compounds as dictated by stereoelectronic factors. Thus, DFA diastereomers having different configuration (α,*β*) at both anomeric carbons keep the central 1,4-dioxane ring in a chair conformation, whereas the C_2-symmetrical di-α and di-*β* isomers must adopt a boat (or skew-boat) conformation at the central ring in order to accommodate the anomeric effect at both anomeric centers.[8] On the other hand, the fructopyranose ring adopts a $^5C_2$ or $^2C_5$ chair conformation depending on the α or *β* anomeric configuration of the respective subunit to fit the anomeric effect. The analysis of the three-dimensional structure of the four possible furanose−pyranose diastereomers **1**−**4** (Figure 1) revealed that the O-3−O-3′

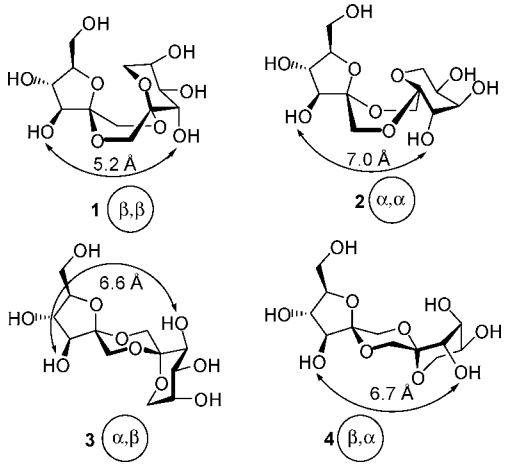


Figure 1. Conformations of the different type II DFA diastereomers with indication of the O-3−O-3′ interatomic distance.

interatomic distance is significantly shorter in the first one, suggesting that incorporation of a rigid spacer between these positions, thereby transforming the intermolecular dimerization reaction into an intramolecular process, would favor its formation upon acid-promoted intramolecular glycosylation−spiroketalization.

From preliminary molecular modeling calculations, the incorporation of an *o*-xylylene bridge was considered, keeping in mind that this tether can be quantitatively removed in a last step by catalytic hydrogenation. While regioselective differentiation of OH-3 in frutopyranose derivatives can be readily achieved through the corresponding 1,2:4,5-diacetonide **5**,[9] a similar functionalization in the cyclic furanose form is much less evident. Taking into consideration that the formation of five-membered ringed spiroketals is kinetically favored, we envisioned that a dipyranose derivative could be a convenient precursor for furanose−pyranose spiro disaccharides provided that tautomeric equilibration is permitted at one of the two pyranoid rings.

The tethering reaction sequence is depicted in Scheme 2. Reaction of **5** with excess α,α′-dibromo-*o*-xylene (**6**) led to the corresponding monoether derivative **7**, keeping a reactive bromobenzyl group, which was subjected to selective nona-

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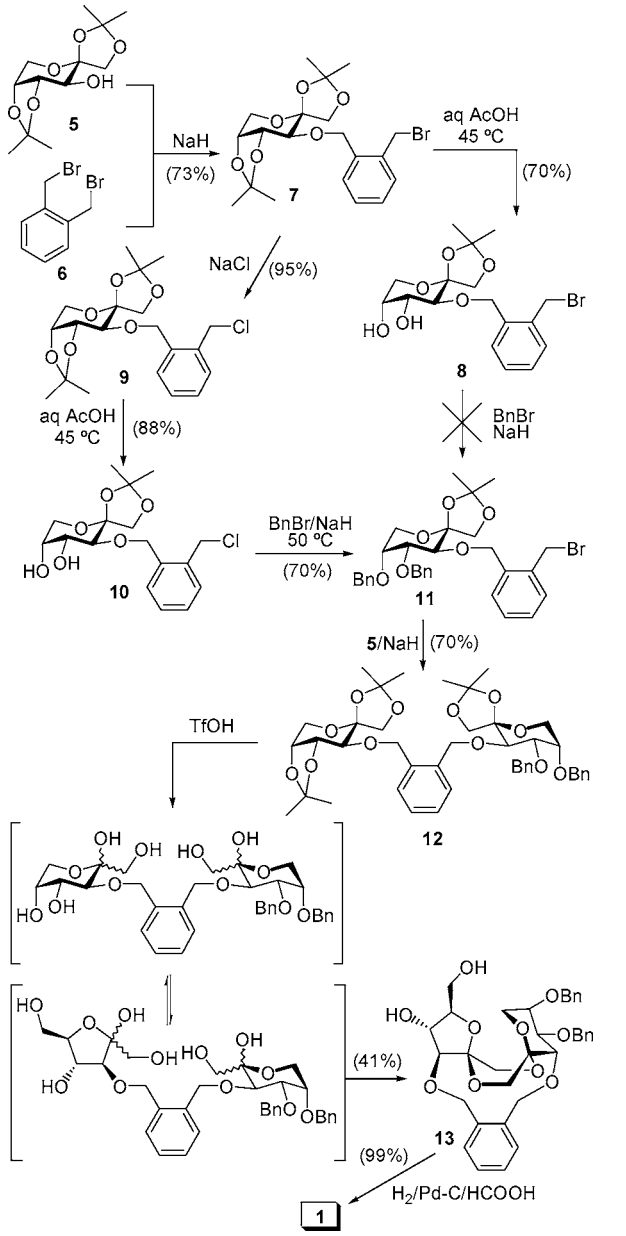
Scheme 2



nomeric isopropylidene cleavage to afford diol **8**. Attempts to protect the free hydroxyls in **8** as the corresponding benzyl ethers by reaction with benzyl bromide failed, the intramolecular reaction leading to a cyclic 3,4-*O*-(*o*-xylylene) derivative competing with intermolecular etherification even after using a large excess of reagent. To circumvent this problem, the bromide substituent was exchange into chloride (→ **9**), thus decreasing its reactivity, prior to hydrolysis of the 4,5-*O*-isopropylidene group (→ **10**) and the subsequent hydroxyl protection step. Since bromide anion is generated during benzylation, we chose to provoke the in situ regeneration of the bromobenzyl functionality at this stage (→ **11**), thus recovering the reactivity at this position. Nucleophilic displacement of bromine in **11** by the alcoholate of **5** afforded the key nonsymmetrical *o*-xylylene−difructopyranose adduct **12**.

Activation of **12** with trifluoromethanesulfonic acid (TfOH) in dichloromethane resulted in the cleavage of all isopropylidene groups, allowing the existence of an equilibrium between the furanose and pyranose forms in one of the fructose moieties while the other one remains fixed in the pyranose form. The higher reactivity of the fructofuranosyl oxocarbenium cation as compared with the homologous six-membered isomer resulted in the formation of the furanose−pyranose DFA **13**, isolated in 41% yield, as the only detectable bis-spiro disaccharide product. It is noteworthy that this critical step set not only the ring size of the tricyclic core but also the stereochemistry at the stereogenic spiro centers, leading to a single compound from up to six different diastereomeric possibilities (the four furano−pyrano DFAs derived from **1**-**4** and the α,*β* and *β*,*β* dipyranose bis-spiro DFA derivatives).[10] Simultaneous catalytic hydrogenolysis of the benzyl and xylylene groups gave the target fully unprotected cyclic fructodisaccharide **1**, with physicochemical, spectroscopic, and chromatographical properties identical in all respects to those reported in the literature,[1,5,11] in quantitative yield (Scheme 2).

The results here reported demonstrate that the rigid spacer concept can be successfully applied to the control of the stereochemistry in the preparation of bis-spiroketal compounds. The present example is particularly notworthy because both the ring size and the stereochemistry at the new stereogenic centers are controlled by judicious choice of the spacer and of the linking positions on the reactive subunits. A thermodynamically unfavored diastereomer is thus obtained with total stereoselectivity in 25% overall yield from the readily available D-fructose derivative **5**. A powerful methodology for spiro oligosaccharide synthesis in general can be based on this new conceptual approach.

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Supporting Information Available: Experimental details and characterization data for compounds **7**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Higher oligomers, resulting from competition between the intramolecular transformation and intermolecular glycosylation−spiroketalization processes, were also present in the reaction mixture, as seen from a mass spectrum of the crude product.

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