The *o*-xylylene protecting group as an element of conformational control of remote stereochemistry in the synthesis of spiroketals†

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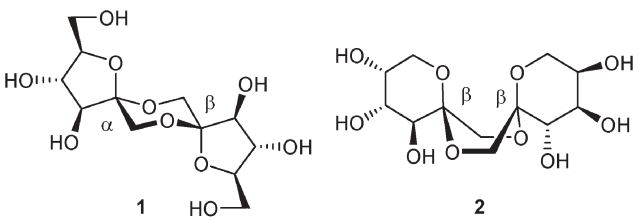
Protection of *trans*-1,2-diol segments as cyclic *o*-xylylene ethers strongly favours diequatorial over diaxial dispositions; the possibility of using this grouping for remote control of the stereochemistry in the synthesis of spiroketals is here demonstrated by the stereoselective synthesis of tricyclic spirodisaccharides (di-D-fructose dianhydrides).

The stereocontrolled construction of spiroketals continues to present a stimulating challenge in target- and diversity oriented synthesis.[1] A major unresolved issue is the control of the stereochemistry at the two spiroketal centres in polyfunctional tricyclic bis-spiroketal systems.[1a,2] This basic framework is the underlying structural element of a unique class of spirodisaccharides[3] isolated from microorganisms and higher plants recently identified as prebiotic food products, namely di-D-fructose dianhydrides (DFAs).[4] Up to thirteen different DFA diastereoisomers are formed during the acid or thermal-promoted dimerization-spiroketalization of fructose-containing materials.[5] This structural and stereochemical diversity makes DFAs ideal targets for evaluating new spiroketal synthetic methodologies.[6]

The conformational properties of DFAs are dictated by stereoelectronic effects. Thus, the central dioxane ring adopts a chair (*e.g.* **1**) or a boat conformation (*e.g.* **2**) depending on the relative configuration at the spiro-centres (different or identical, respectively), in order to achieve double anomeric stabilisation.[4a]



With a view toward exploiting conformational restrictions for remote stereochemical control in the synthesis of the tricyclic spiroketal framework, we recently implemented a new approach in which the insertion of a transient tether forces the relative orientation of the reacting D-fructose moieties.[7] While meeting significant success, relatively long reaction sequences, involving ring-size blocking of the ketose precursor, selective hydroxyl group protection, tethering and final acid-catalysed dimerization, are needed. Interestingly, the configuration at the spiroketal centres in DFAs also governs the conformation of the external five- or six-membered rings. Designing monomeric species with predictable conformational biases for stereochemical control during spiroketalization then becomes an attractive alternative.

We have recently introduced the use of the cyclic *o*-xylylene group for benzyl-type protection of *vic*-diols in carbohydrate chemistry.[8] Preliminary calculations indicated that the diequatorial disposition of the oxygens at the eight-membered dioxacyclooctene-type ring would be strongly favoured as compared to the diaxial orientation (Fig. 1), therefore offering a possibility for conformational selection at the initial protection step and subsequent remote configurational control during spiroketalization reactions. Here we demonstrate this concept by the high yielding preparations of the tricyclic spirodisaccharides **1** and **2**. The difuranose compound **1** has been isolated from natural sources and is the major prebiotic spirodisaccharide present in sucrose caramels.[9] The dipyranose isomer **2**, also present in caramel, has been shown to be an excellent complexing agent for divalent cations such as Ca^{2+} and Sr^{2+}.[10]

Preliminary results indicated that trifluoromethanesulfonic acid-promoted anomeric activation of tri-*O*-benzylated 1,2-*O*-isopropylidene-β-D-fructofuranose and fructopyranose derivatives (**3** and **4**), for which neither anchimeric assistance nor distance constrains apply, results in the formation of two-component mixtures containing the thermodynamically favoured α,β-isomer (**5** or **6**) and a contra-thermodynamic[11] C_2-symmetric α,α-(difuranose, **5**) or β,β-DFA (dipyranose, **7**) in 2 : 1 and 25 : 1 relative proportions, respectively (Scheme 1).[12]

The α-D-fructofuranose rings in these bis-spirodisaccharides adopt a rather rigid ^3E conformation, while skewed conformations around E_O are privileged for β-linked D-fructofuranosyl moieties. Fructopyranose rings adopt the $^5C_2$ or $^2C_5$ chair conformation for the α or β configuration, respectively, in order to place the anomeric oxygen in axial disposition and the bulky hydroxymethyl group in equatorial orientation (Fig. 2). Such a scenario results in

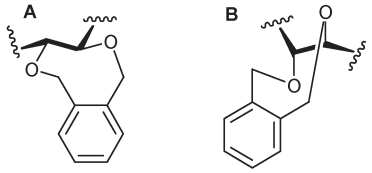


Fig. 1 Schematic representation of *o*-xylylene-protected *trans*-diequatorial (A) and *trans*-diaxial diol segments (B).

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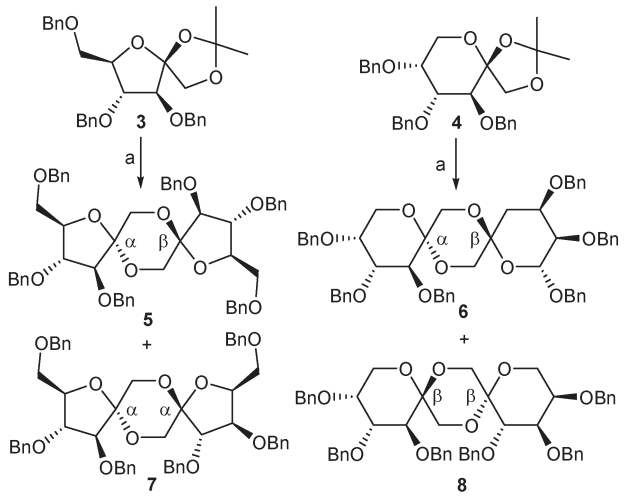


Scheme 1 Synthesis of difuranose and dipyranose DFAs from unconstrained precursors TfOH, CH_2Cl_2, −78 → 20 °C, 1–5 h, 65–75% (relative proportion 2 : 1 for **5** : **7** and 25 : 1 for **6** : **8**).

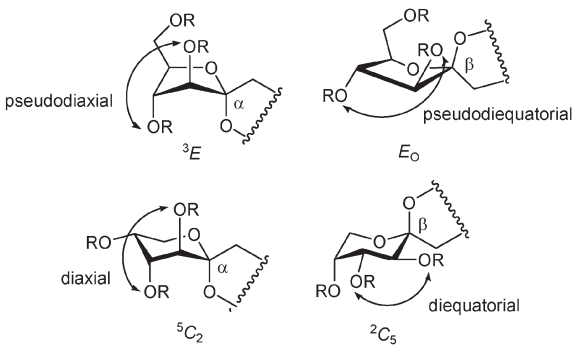
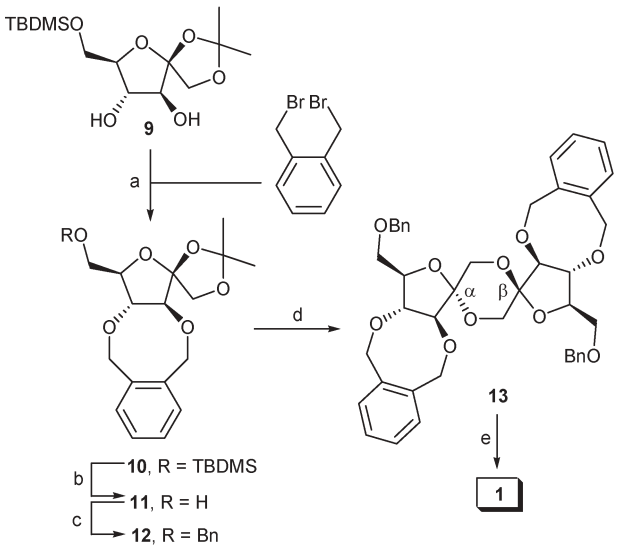


Fig. 2 Conformations of the fructofuranose and fructopyranose rings in the bis-spirodisaccharides **5–8**; the relative disposition of the *trans*-oriented substituents at C-3 and C-4 is indicated.

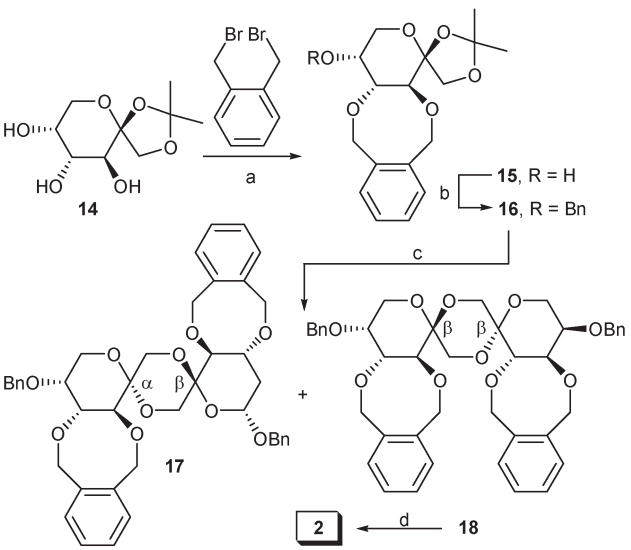
1,2-*trans* diequatorial (or pseudodiequatorial) relative orientations for the hydroxy groups at C-3 and C-4 in β-D-fructofuranose and β-D-fructopyranose rings, while the respective α-anomers exhibit 1,2-*trans* diaxial (or pseudodiaxial) dispositions at the same diol group. We speculated that by introducing an element of conformational restriction at this segment on the ketose precursor, a remote control on the configuration of the forming spiroketal stereogenic centres, favouring the formation of β-configured-containing subunits could be achieved.[13]

Reaction of the known 1,2-*O*-isopropylidene-β-D-fructofuranose derivative **9**,[7c] available in two steps from commercial D-fructose, with α,α′-dibromo-*o*-xylene under conventional benzylation conditions afforded the corresponding cyclic diether **10**, which was further transformed into the 6-*O*-benzyl derivative **12** by fluorolysis of the silyl ether group (→**11**) and reaction with benzyl bromide. Further trifluoromethanesulfonic acid-promoted spiroketalization afforded exclusively the α,β-thermodynamic derivative **13** in 70% yield. No traces of the di-α-diastereomer, holding two 3,4-*trans*-diaxial diol segments, were detected. Simultaneous removal of the xylylene and benzyl groups in **13** was quantitatively achieved by catalytic hydrogenation to give the target DFA **1** (Scheme 2).



Scheme 2 Stereoselective synthesis of DFA **1** from an *o*-xylylene precursor: (a) NaH, DMF, RT, 1 h, 78%; (b) TBAF, THF, RT, 4 h, 93%; (c) NaH, DMF, RT, 3 h, 80%; (d) TfOH, CH_2Cl_2, −78 °C → RT, 1 h, 70%; (e) Pd/C, H_2 (1 atm), 1 : 1 EtOAc–MeOH, RT, 16 h, 100%.

Extending the above tactic to the preparation of DFA **2** was particularly challenging. This is actually a contra-thermodynamic isomer that cannot accommodate dual anomeric effect stabilisation at both spiroketal centres in the chair conformation, being present in very minor proportion in equilibrium mixtures. Direct *o*-xylylenation of β-D-fructopyranose 1,2-*O*-acetonide[14] (**14**) afforded preferentially the *trans*-diequatorial cyclic diether **15** (37%; 50% of unreacted starting material **14** was recovered), which is remarkable considering that benzyl protection of polyols is seldom a regioselective reaction.‡ Benzylation of the remaining hydroxy group afforded the fully protected derivative **16**. Upon dimerization under the above irreversible reaction conditions, a



Scheme 3 Stereoselective synthesis of DFA **2** from an *o*-xylylene precursor: (a) NaH, DMF, RT, 16 h, 37%; (b) BnBr, NaH, DMF, RT, 30 min, 75%; (c) TfOH, CH_2Cl_2, −78 °C → RT, 1 h, 81% (3 : 1 **18** : **19**); (d) Pd/C, H_2 (1 atm), 1 : 1 EtOAc–MeOH, RT, 16 h, 100%.

mixture of the α,β (**17**) and β,β (**18**) bis-spiroketal disaccharides in 1 : 3 relative proportion and 81% yield was obtained (Scheme 3).

Comparison of the results collected in Scheme 1 with those in Schemes 2 and 3 clearly demonstrate the stereodirecting effect of the *o*-xylylene group in bis-spiroketal-forming reactions. In the furanose series, the isomer presenting a *trans*-diequatorial diol segment (α,β) is also thermodynamically favoured, resulting in total stereoselectivity in the creation of the two spiroketal centres (to be compared with only 33% de in the absence of the cyclic diether group). For the pyranose counterparts, the maximum number of *trans*-diequatorial diol segments and thermodynamic stability are mismatching. Nevertheless, an over 100-fold increase in the selectivity of the reaction towards the *o*-xylylene-controlled β,β-diastereomer was attained (the α,α : β,β ratio changes from 25 : 1 to 1 : 3). Further applications of this protecting group in selective protection of *trans*-diequatorial 1,2-diols and remote control of the stereochemistry in spiroketalizations are ongoing.

Notes and references

‡ Compound **15** has been previously prepared from 1,2:3,4-di-*O*-isopropylydene-β-D-fructopyranose through a three-step reaction sequence involving monoetherification of α,α′-dibromoxylene, selective removal of the nonanomeric acetal protecting group and regioselective intramolecular etherification (see ref. 8). The new synthesis here presented represents the first example of selective diol protection using the *o*-xylylene group. Further applications of this strategy in carbohydrate chemistry are currently under development in our laboratories.

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