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Stereoselective Synthesis of Difructose Dianhydrides by Use of the Xylylene Group as Stereodirecting Element in Spiroketalisation Reactions

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The use of the *o*-xylylene protecting group as an element of remote stereochemical control in bis(spiroketalisation) reactions of D-fructose has been investigated. The presence of the cyclic diether functionality favours the *trans*-diequatorial disposition of oxygen substituents, a conformational arrangement that is encountered in the 3-O/4-O segment in β-D-fructopyranoside and β-D-fructofuranoside moieties in di-D-fructose dianhydrides (DFAs). Moreover, the presence of the *o*-xylylene group in *cis*-oriented *vic*-diol segments slows down the interconversion rate between the two chair conformers in fructopyranose rings, which has a strong influence on the stereochemical outcome of the dimerisation reaction. Those features have been exploited to develop stereoselective syntheses of dipyranose and difuranose DFAs with the aid of triflic acid activation of 1,2-*O*-isopropylidene-D-fructose precursors. For difuranose DFAs, the combination of this strategy with the concept of rigid spacer-mediated intramolecular spiroketalisation, with use of xylylene-tethered D-fructose precursors, further allows double stereocontrol. The conclusions of this study open new perspectives in the stereoselective synthesis of complex spiroketal derivatives in general and in the preparation of pure DFA standards with application in food chemistry in particular.

Introduction

Di-D-fructose dianhydrides (DFAs; Figure 1) comprise a unique class of stereoisomeric mono- or bis(spiroketal) disaccharides first identified in mixtures resulting from the treatment of D-fructose with mineral acids and further isolated from microorganisms and higher plants.[1,2] Their identification as the major components of the thermolysis products of sucrose- and D-fructose-containing food materials, such as caramel or chicory,[3–6] together with their promising prebiotic properties, have strongly stimulated research into their preparation and nutritional properties.[7–11] Recently, a methodology for the preparation of DFA-enriched caramels based on the use of acid ion-exchange resins as caramelisation promoters has been reported.[12] The resulting products, containing up to 70% of DFA derivatives, exhibited a protective effect against inflammatory bowel disease (Crohn's disease) in an animal model.[13] Those results highlighted the need to obtain pure DFA standards for their analytical identification and quantification in food and biological samples.[14,15]

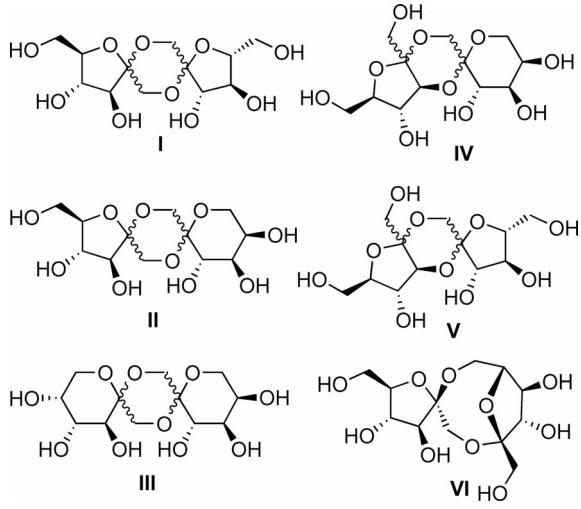

Figure 1. Spiroketal disaccharide cores (types **I**–**VI**) of DFAs.

The underlying spiroketal framework of DFAs is shared by many biologically relevant natural products such as steroidal saponins, polyether ionophores, macrolide antibiotics, insect pheromones and toxic metabolites from algae and fungi.[16–19] Many of these compounds exhibit important biological activities, and consequently there is sustained interest in the controlled construction of this structural motif.[20–29] Up to six different tricyclic cores and 14 DFA isomers (types **I**–**VI**, Figure 1) differing in the ring sizes, linking positions and stereochemistry of the spiroketal centres

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have been identified in caramel or in chemically obtained mixtures.[7] This structural and stereochemical diversity makes DFAs ideal targets for evaluating new synthetic methodologies.

Except for structure **VI**, each DFA possesses a central 1,4-dioxane ring that can adopt a chair (Figure 2, **A**) or boat (or skew-boat; Figure 2, **B**) conformation in order to optimise all factors governing spiroketal stability: that is, maximum anomeric effect (i.e., oxygen substituents in axial relative orientations) and minimum steric interactions (i.e., carbon substituents in equatorial disposition). Thermodynamic DFAs have different configurations (α,β) at the spiroketal centres and can fulfil those requirements in the *chair* arrangement. DFA diastereomers with identical configurations at both spirocentres (α,α or β,β) tend to adopt the less favourable *boat* arrangement. Some representatives can be obtained preferentially under kinetic conditions, but in most cases they are neither thermodynamically nor kinetically favoured: that is, they are contra-thermodynamic[30] and cannot be accessed in significant yields under reversible reaction conditions.

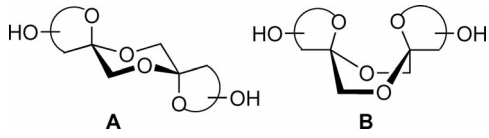
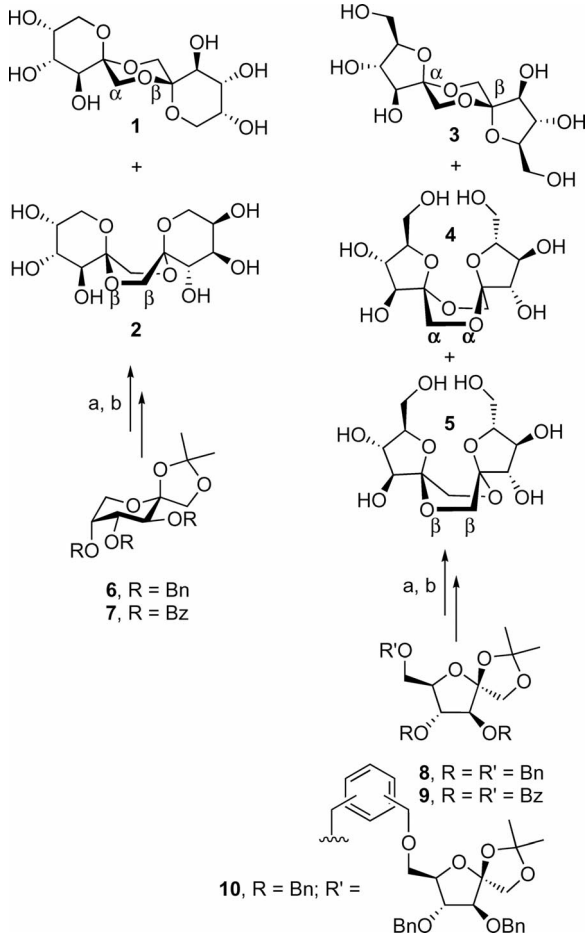


Figure 2. Schematic representation of the *chair* and *boat* conformations of dispiro-DFAs for derivatives with different (**A**), or identical (**B**) configurations at the anomeric centres.

Most of the reported approaches for the synthesis of DFAs are based on the use of protecting group strategies to block the cyclic form of fructose during the dimerisation/spiroketalisation of monomeric precursors.[31–34] Non-participating groups (e.g., benzyl groups; see precursors **6** and **8**) then favour the unsymmetrically configured (α,β) thermodynamic diastereomers (Scheme 1, compounds **1** and **3**), whereas in the case of participating groups (e.g., benzoyl; see precursors **7** and **9**) kinetically favoured symmetric DFAs can be accessed through formation of cyclic oxacarbenium intermediates (Scheme 1, compounds **2** and **4**). The incorporation of distance-restriction elements, by tethering the fructose units under reaction through xylylene segments (rigid spacer-mediated glycosylation[35,36]/spirocyclisation; e.g. precursor **10**), has been exploited to access contra-thermodynamic DFA derivatives (e.g., **5**).[37–41]

The "external" D-fructose rings in DFAs have also been shown to adopt distinct conformations depending on the stereochemistry of the corresponding spiroketal centres, which makes DFAs rather rigid molecules. Thus, α- and β-D-fructopyranose fragments[1,42–44] are found in the two limit chairs ($^5C_2$ and $^2C_5$), whereas α- and β-D-fructofuranose moieties[1,45] take on conformational arrangements close to ^3E and E_O, respectively (Figure 3). The close relationship between configuration aspects and conformation aspects suggests that it might be possible to influence the stereochemical courses of DFA-forming reactions by imposing conformational restrictions on the reacting D-fructose subunits. With this idea in mind, we conceived that cyclic protecting groups favouring precise orientations of the diol segments might be exploitable as remote stereocontrol elements, alone or in combination with tethering strate-



Scheme 1. Synthesis of dipyranose (**1** and **2**) and difuranose (**3**–**5**) DFAs from monomeric or dimeric D-fructose precursors. Reagents and conditions: (a) Lewis acid, CH_2Cl_2 or toluene; (b) conventional catalytic hydrogenolysis (Pd/C) or conventional catalytic transesterification (MeOH/NaOMe).

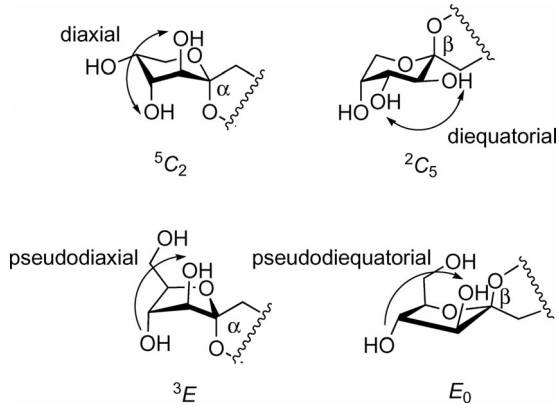


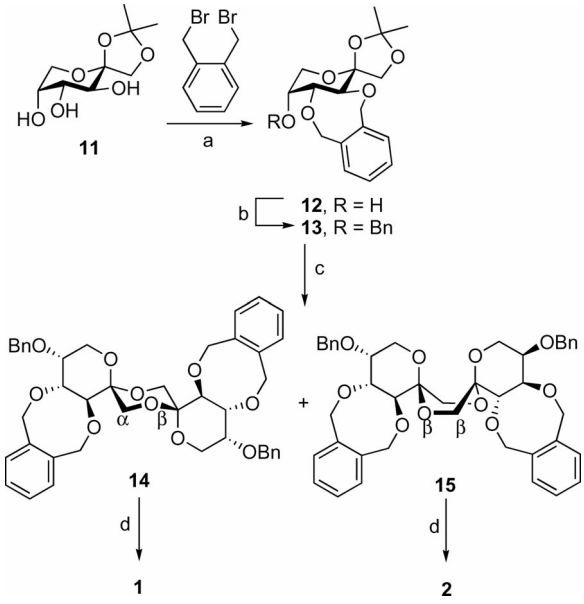
Figure 3. Preferred conformations of fructopyranose (top) and fructofuranose (bottom) rings in DFA bis(spirodisaccharides). The relative dispositions of the *trans*-oriented substituents at C-3 and C-4 are indicated.

gies. The cyclic di-*O*-(*o*-xylylene) protecting group, recently proposed for the selective protection of *trans*-diequatorial hydroxy groups in pyranoses[46–48] and furanoses,[49] seemed particularly well suited for such a purpose, because it is stable under the acidic conditions used to promote DFA formation.[50] The potential of this approach for the preparation of difructofuranose and difructopyranose DFAs has now been examined. The potential to apply double conformational control by cyclic protection/tethering of the D-fructose precursors and the scope and limitations of the methods are discussed.

Results and Discussion

Synthesis of Di-D-fructopyranose Dianhydrides

The α- and β-D-fructopyranose subunits in difructopyranose DFAs adopt the $^5C_2$ and $^2C_5$ chair conformations, respectively, in order to comply with the anomeric effect at both spiroketal centres (Figure 3, top).[1] This scenario results in *trans*-diaxial or *trans*-diequatorial relative orientations for the vicinal hydroxy groups 3-OH and 4-OH. The latter arrangement was expected to be better accommodated in the dioxacyclooctane-type ring after *o*-xylylene protection. Actually, cyclic diether protection of these two hydroxy groups can be effected directly in the triol derivative **11**[51,52] (Scheme 2) by treatment with α,α′-dibromo-*o*-xylene in the presence of sodium hydride (→ **12**; 37% yield, 74% based on reacted **11**), which is notable in view of the general lack of selectivity of benzylation reactions under these conditions. Compound **12** had previously been obtained by a three-step reaction sequence from 1,2:4,5-di-*O*-isopropylidene-D-fructopyranose[50,51] through the reaction between 3-OH and α,α′-dibromo-*o*-xylene, regioselective hydrolysis of the non-anomeric isopropylidene group and intramolecular etherification involving 4-OH, which allowed a direct confirmation of the structure.[46] Benzylation of the remaining hydroxy group (5-OH) in **12** (→ **13**) and subsequent TfOH-promoted dimerisation/spirocyclisation afforded a mixture of the two dipyranose α,β- and β,β-DFAs **14** and **15** in a 1:3 relative proportion, which represents a 75-fold increase in selectivity towards the di-β-diastereomer relative to the result previously observed for the tribenzylated derivative **6** (α,β/β,β = 25:1; Table 1). Simultaneous hydrogenolysis of the benzyl and cyclic *o*-xylylene groups with Pd/C in the presence of formic acid proceeded smoothly to give the fully unprotected DFAs **1** and **2** in quantitative yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) NaH, DMF, 16 h (37%); (b) BnBr, NaH, DMF, 30 min (75%); (c) TfOH, CH_2Cl_2, –78 °C to room temp., 1 h (**14**, 20% and **15**, 61%); (d) Pd/C, H_2 (1 atm), HCOOH (10%), EtOAc/MeOH (1:1), 16 h (100%).

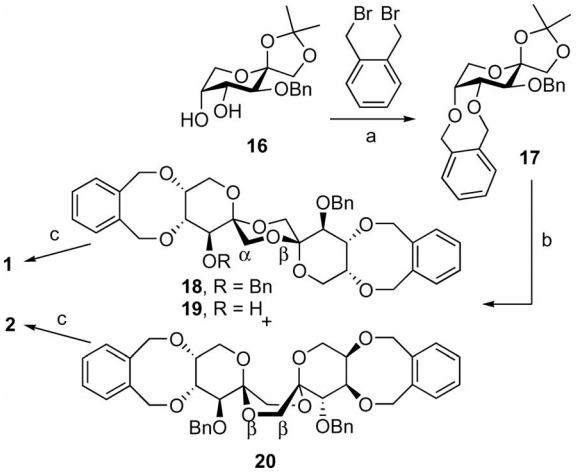
Table 1. Relative proportions (%) of α,β- and β,β-dipyranose DFA diastereomers obtained by TfOH activation of D-fructopyranose precursors incorporating cyclic *o*-xylylene groups (**13**, **17** and **24**–**26**) in comparison with classical acyclic protection (**6** and **7**).[33]

Starting material	α,β diastereomer	β,β diastereomer
6	96	4
7	50	50
13	25	75
17	78[a]	22
24	83[b]	17[b]
25	80[b]	20[b]
26	84[b]	16[b]

[a] Calculated by considering the combined proportions of compounds **18** and **19**. [b] Calculated from the relative proportion of the corresponding unprotected DFAs **1** and **2** after hydrogenolysis of the oligomeric adducts.

The 4-OH/5-OH *vic*-diol segment adopts analogous *cis*-(axial-equatorial) dispositions in either of the two possible chair conformations of the D-fructopyranose moieties in dipyranose DFAs. Nevertheless, installation of a cyclic *o*-xylylene protection linking those positions was expected to slow down the conformational interconversion rate. If the precursor has the β-configuration in the $^2C_5$ conformation, the di-β-DFA diastereomer should be then kinetically favoured relative to the use of acyclic benzyl protection. To verify this hypothesis, the known 3-*O*-benzyl derivative **16**[51] (Scheme 3) was transformed into the corresponding cyclic diether **17**. After TfOH activation, the α,β- and β,β-DFA derivatives **18** and **20** were formed in 3.3:1 relative proportions (to be compared with 25:1 in the case of **6**; Table 1). A small amount of the α,β-DFA **19**, in which the benzyl group at 2-O had been cleaved, was also isolated. In all cases, hydrogenolysis afforded the corresponding unprotected DFA **1** or **2** in quantitative yield (Scheme 3).

The $^5C_2$ and $^2C_5$ conformations for the α- and β-fructopyranosyl rings, respectively, in the protected DFA products **14**, **15** and **18**–**20** were confirmed by the corresponding $^3J_{H,H}$ values. The $J_{3,4}$ and $J_{4,5}$ coupling constants are diagnostic in this respect, ranging from 2.9–3.0 or 9.6–10.0 Hz for *gauche* or *trans* dispositions of the corresponding protons. The α,β diastereomers **14**, **18** and **19** each displayed two spin systems in their ^1H and ^{13}C NMR spectra,

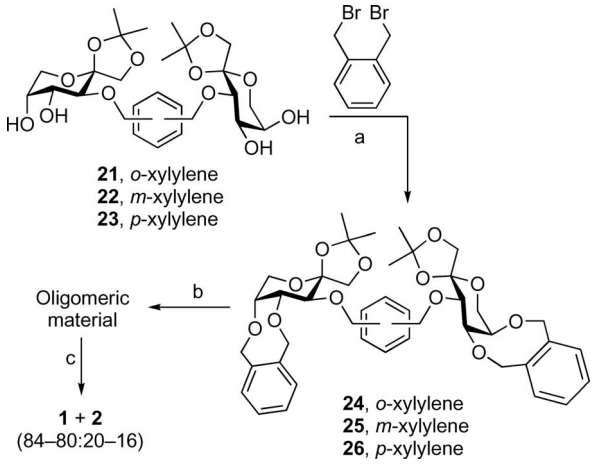


Scheme 3. Reagents and conditions: (a) NaH, DMF, 16 h (42%); (b) TfOH, CH_2Cl_2, –78 °C to room temp., 1 h (**18**, 50%, **19**, 6% and **20**, 15%); (c) Pd/C, H_2 (1 atm), HCOOH (10%), EtOAc/MeOH (1:1), 16 h (100%).

whereas the di-β derivatives **15** and **20** each showed a single one, consistent with a C_2 symmetric structure. The C-2 chemical shifts, which have been shown to be fingerprints for given DFA structures,[1,53] agreed with the expected stereochemistry. The assignment was further unequivocally confirmed by comparison of the deprotected products **1** and **2** with authentic samples.

Our next goal was to examine whether or not the selectivity could be further influenced by bridging the fructose units undergoing reaction, thereby transforming DFA formation into an intramolecular process. Linking of the 3-O positions by insertion of *o*-, *m*- or *p*-xylylene segments has previously been found to privilege the thermodynamically less favoured di-β-DFA by inducing the boat conformation at the central 1,4-dioxane ring.[37]

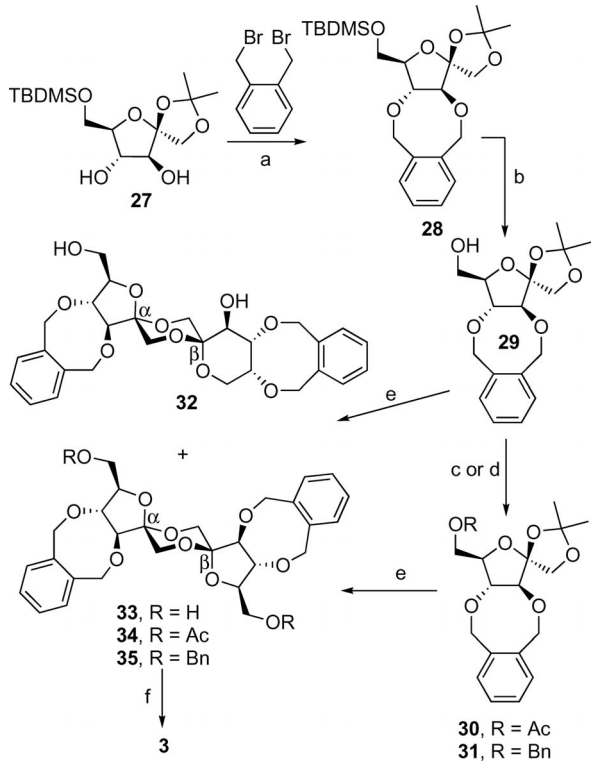
The corresponding precursors **24**–**26** (Scheme 4) were thus prepared by *o*-xylylenation of the known tethered derivatives **21**–**23**.[39] In these cases, however, TfOH activation led to mixtures of oligomers from which no pure compounds could be isolated. Hydrogenation of the mixtures and gas chromatography (GC) analysis of the spirodisaccharide products after trimethylsilylation, by a reported protocol,[12,14] indicated relative proportions of the α,β and β,β diastereomers **1** and **2** very close to those obtained from the monomeric precursor **17** (Table 1). Probably the intramolecular reaction is strongly disfavoured in these systems, due to the rigidity of the resulting polycyclic structure, preventing a double stereocontrol mechanism (Scheme 4).



Scheme 4. Reagents and conditions: (a) NaH, DMF, 3 h (**24**, 45%, **25**, 30% and **26**, 35%); (b) TfOH, CH_2Cl_2, –78 °C to room temp., 1 h; (c) Pd/C, H_2 (1 atm), HCOOH (10%), EtOAc/MeOH 1:1, 16 h (100%).

Synthesis of Di-D-fructofuranose Dianhydrides

Although in principle more flexible, the furanose rings in difructofuranose DFAs also adopt distinct conformations depending on the anomeric α or β configuration, which imply pseudoaxial or pseudoequatorial relative dispositions for the secondary hydroxy groups 3-OH and 4-OH (Figure 3, bottom).[1] Imposition of a conformational restriction in this region by cyclic *o*-xylylenation in a β-D-fructofuranose precursor was thus considered. The known 6-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-β-D-fructofuranose (**27**,[21] Scheme 5) was transformed into the cyclic diether **28** and, after removal of the silyl ether group at 6-O (→ **29**), acetylation (→ **30**) and benzylation (→ **31**) reactions were carried out (Scheme 5).



Scheme 5. Reagents and conditions: (a) NaH, DMF, 1 h (78%); (b) TBAF, THF, 4 h (93%); (c) Ac_2O, pyridine (85%); (d) BnBr, NaH, DMF, 3 h (80%); (e) TfOH, CH_2Cl_2, –78 °C to room temp., 40 min (**32**, 12%, **33**, 41%, **34**, 75% and **35**, 70%); (f) Pd/C, H_2 (1 atm), HCOOH (10%), EtOAc/MeOH 1:1, 16 h (100%).

Dimerisation/spirocyclisation of the 6-*O*-protected derivatives **30** and **31** led exclusively to the corresponding α-D-fructofuranose β-D-fructofuranose dianhydride derivatives **34** and **35** in excellent yields. No traces of the symmetric α,α or β,β diastereomers were detected. The latter anomeric combination is very unfavourable both under thermodynamic and under kinetic reaction conditions, and its absence in the reaction mixtures was expected.[33] Nevertheless, the total preference for the unsymmetrical α,β compound over the α,α diastereomer is remarkable. Although the unsymmetrical derivative is thermodynamically favoured, precursors bearing acyclic protecting groups systematically gave mixtures with α,β/α,α relative proportions ranging from 1:1 to 7:1 (for derivatives bearing a nonparticipating group at 3-O; e.g., **8**) or 1:24 to 1:25 (for derivatives bearing a participating group at 3-O; e.g., **9**).[33] To the best of our knowledge, the present results represent the first stereospecific synthesis of the α,β-difructofuranose DFA diastereomer.

Compound **29**, in which the 6-OH hydroxy group is free, can undergo furanose/pyranose interconversion through the open-chain *aldehydo* form after removal of the anomeric isopropylidene group by TfOH activation. In this case the spirocyclisation reaction afforded the corresponding α,β-difuranose DFA derivative **33** as the major reaction product, accompanied by the α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydride derivative **32** (**33**/**32** = 3.4:1). The latter structure is actually the thermodynamically most stable DFA.[1,2,7] The fact that the difuranose compound is preferentially obtained even in this case underlines the importance of kinetic considerations when designing stereoselective syntheses of spiroketal derivatives (Table 2). Catalytic hydrogenolysis of **33**–**35** (with prior deacetylation in the case of **34**) afforded the fully unprotected DFA **3** (Scheme 5).

Table 2. Relative proportions (%) of α,β-, α,α- and β,β-difuranose DFA diastereomers obtained by TfOH activation of D-fructofuranose precursors incorporating cyclic *o*-xylylene groups (**29**–**31** and **36**–**38**) in comparison with classical acyclic protection (**8**, **9** and **10**-*ortho*, -*meta* or -*para*).[33,39]

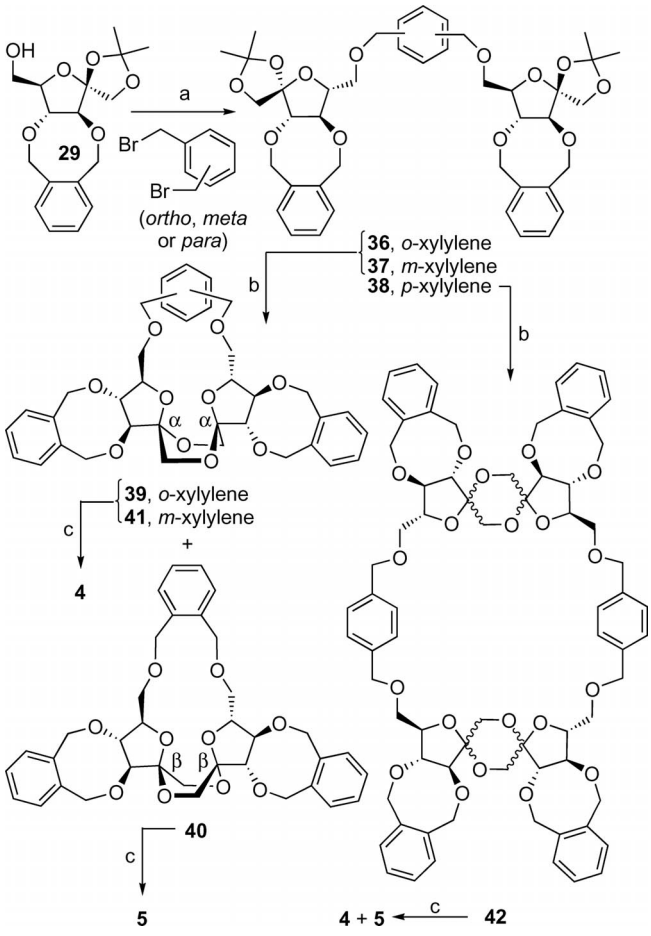
Starting material	α,β diastereomer	α,α diastereomer	β,β diastereomer
8	75	25	0
9	4	96	0
10-*ortho*	0	11	89
10-*meta*	34	66	0
10-*para*	0	80	20
29	81[a]	0	0
30	100	0	0
31	100	0	0
36	0	43	57
37	0	100	0
38	0	80[b]	20[b]

[a] The α-D-fructofuranose β-D-fructopyranose 1,2:2,1′-dianhydride diastereomer **32** was also formed in 19% proportion. [b] Calculated from the relative proportion of the corresponding unprotected DFAs **4** and **5** after hydrogenolysis of the macrocyclic adduct **41** by GC.[14]

The ^{1}H and ^{13}C NMR spectra of the protected DFAs **33**–**35** each displayed two spin systems and agreed with the presence of two fructofuranose rings with α and β configurations. In the β-fructofuranose ring the $J_{3,4}$ and $J_{4,5}$ values (4.5–6.1 Hz) are consistent with a conformation close to E_O, meaning that the incorporation of the cyclic protecting group does not cause a significant distortion of the scenario encountered in other derivatives of DFA **3**.[1,27] In the α-fructofuranose ring, however, the large $J_{4,5}$ values (8.9–9.0 Hz) imply a *trans*-diaxial disposition of the corresponding protons and point to the $^4T_5$ conformation. This places the 3-O and 4-O substituents in a pseudoequatorial orientation, in contrast to the pseudoaxial disposition in the absence of cyclic protection.[1,27] This conformational distortion probably implies an energy penalty and might be responsible for the absence of the α,α diastereomer in the reaction mixtures. In compound **32** the situation in the α-fructofuranose ring is analogous. The β-fructopyranose moiety adopts the expected $^2C_5$ chair conformation, as already discussed for compounds **18**–**20**.

The relative proportions of thermodynamic (α,β) versus kinetic or contra-thermodynamic diastereomers (α,α and β,β) in the difructofuranose DFA series have been shown to be influenced by tethering of the primary 6-O positions of the reacting D-fructose precursors.[21] To investigate the effects of simultaneous conformational and distance constraints on the stereochemical outcome of the reaction, the *o*-, *m*- and *p*-xylylene-bridged precursors **36**–**38** (Scheme 6) were synthesised. Use of the two first linkers led preferentially to products of intramolecular glycosylation/spirocyclisation. No traces of the α,β-unsymmetric DFA diastereomers were detected in this fraction, probably because the presence of the bridge induces the boat conformation at the central 1,4-dioxane ring in this series. The α,α-DFA derivative **40** was the only product in the case of the *m*-xylylene-bridged precursor **37**, whereas a 1:1.3 mixture of the α,α and β,β isomers **39** and **40**, respectively, was obtained in the case of the shorter *o*-xylylene spacer. No intramolecular reaction took place with the *p*-xylylene derivative **38**, which led preferentially to the formation of a mixture of the macrocyclic intermolecular dimers **42**, as seen by mass spectrometry. After hydrogenolysis, a mixture of the DFAs **4** and **5** (4:1) was obtained. Their identities were unequivocally determined by GC after trimethylsilylation and comparison with authentic standards (Scheme 6 and Table 2).[14]

The above results indicate that shortening of the through-space distance between the primary 6-O positions by the rigid spacer strategy completely reversed the stereochemical outcome of the spirocyclisation reaction from the unsymmetrical (α,β) to the symmetrical (α,α and β,β) diastereomers. The presence of the cyclic *o*-xylylene protecting group results in analogous conformations for the α- and β-fructofuranose rings that are analogous to those discussed above for the non-tethered DFAs **33**–**35**, as seen from the coupling constant values around the five-membered rings. The cyclic protection also contributes to the observed stereoselection, because in the case of acyclic benzyl protecting groups the α,β-DFA was present in the reaction mixture in a significant proportion, even when the *m*-xylylene tether



Scheme 6. Reagents and conditions: (a) NaH, DMF, 1 h (**36**, 70%, **37**, 73% and **38**, 42%); (b) TfOH, CH_2Cl_2, –78 °C to room temp., 55–70 min (**39**, 29%, **40**, 37%, **41**, 52% and **42**, 22%); (c) Pd/C, H_2 (1 atm), HCOOH (10%), EtOAc/MeOH 1:1, 16 h, 100%.

was installed[39] (the α,α/α,β ratio shifts from 50:50 to 100:0). The presence of the *o*-xylylene spacer between the primary positions is able to induce formation of the elusive contra-thermodynamic β,β diastereomer **40**, although its combination with cyclic diether protection seems to be detrimental in this case relative to the use of classical benzyl protection at 3-O and 4-O. The α,α/β,β ratio thus shifts from 1:8 for **10**-*ortho* to 1:1.3 for **36** (Table 2). The conformational constraints in the very rigid macrocyclic products **39** and **40** probably play a more important role in determining the stereochemical course of the reaction than the preferred conformation of the relatively flexible furanose rings. In any case, the results clearly demonstrate that cyclic diol protection and rigid spacer tethering are very potent strategies for control of the stereochemistry of bis(spiroketal) formation reactions.

Conclusions

Spiroketal compounds exhibit an intimate relationship between configurational pattern and conformational preferences as a result of combined stereoelectronic effects, a fact that is exacerbated in bis(spiroketal) compounds such as difructose dianhydrides. It was therefore conceivable that protecting group tactics that favour particular conformational arrangements in the synthetic intermediates might be implemented to achieve stereoselective syntheses of DFA diastereomers. The results collected in Tables 1 and 2 clearly illustrate the potential of cyclic *o*-xylylene groups in achieving this goal. Through stabilisation of the *trans*-diequatorial dispositions of the 3-O/4-O substituents, the spiroketalisation reactions of D-fructopyranose and D-fructofuranose precursors can be directed towards the β,β-dipyranose and α,β-difuranose diastereomers, respectively. In the difuranose series, further tethering of two fructofuranose units through their primary 6-O positions by xylylene segments allows the selectivity to be shifted towards the C_2-symmetric α,α- or β,β-DFAs. It is worth mentioning that by this strategy the first stereospecific syntheses of α-D-fructofuranose β-D-fructofuranose 1,2′-2,1′-dianhydride (**3**) and di-α-D-fructofuranose 1,2′-2,1′-dianhydride (**4**), two of the most abundant DFAs in commercial caramel,[7] have been achieved. Moreover, the use of cyclic *o*-xylylene groups allows selective protection of *trans*-diol segments and has added value in terms of atom economy in relation to classical benzyl protection.

Experimental Section

General: 1,2-*O*-Isopropylidene-β-D-fructopyranose (**11**)[51,52] and 6-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-β-D-fructofuranose (**27**)[39] were obtained according to literature procedures. Reagents and solvents were purchased from commercial sources and were used without further purification, with the exception that dichloromethane was distilled under an Ar stream from CaH_2. Optical rotations were measured at 20 °C in 1 cm or 1 dm tubes with a Perkin–Elmer 141 MC polarimeter. IR spectra were recorded with a Bomem Michelson MB-120 FTIR spectrometer. ^1H (and ^{13}C NMR) spectra were recorded at 500 (125.7) and 300 (75.5) MHz with Bruker 500 DRX spectrometers and 300 AMX spectrometers, respectively. 2D COSY and HMQC experiments were used to assist in NMR assignments. For NMR notation purposes, *f* and *p* indicate proton or carbon atoms located at a furanose or pyranose unit, respectively. Thin-layer chromatography (TLC) was carried out on aluminium sheets coated with Kieselgel 30 F245 (E. Merck), with visualisation with UV light and by charring with H_2SO_4 (10%). Column chromatography was carried out on silica gel 60 (E. Merck, 230–400 mesh). FAB mass spectra were obtained with a Kratos MS-80 RFA instrument. The operating conditions were as follows: the primary beam consisted of Xe atoms with a maximum energy of 8 keV, the samples were dissolved in thioglycerol, the positive ions were separated and accelerated over a potential of 7 keV, and NaI was added as cationising agent. Elemental analyses were performed at the Instituto de Investigaciones Químicas (Sevilla, Spain). For GC analysis, samples were transformed into their corresponding per-*O*-trimethylsilyl or per-*O*-trimethylsilyl oxime derivatives according to literature procedures.[12,14] GC experiments were carried out with an Agilent 6890 Series Plus chromatograph with an EPC injector fitted with a cross-linked 5% phenyldimethylsiloxane column (HP-5; 30 m × 320 μm × 0.25 μm). Operating conditions were: injection port temperature 310 °C, splitting ratio 25:1, injection volume 1 μL of derivatised samples,

column oven temperature programmed from 180 to 310 °C at 5 °C min^{-1}, with 25 min hold at 310 °C, carrier gas helium (constant flow at 1.2 mL min^{-1}), detector port temperature 310 °C. Total acquisition time was 56 min.

1,2-*O*-Isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructopyranose (12): NaH (60% in mineral oil, 55 mg, 2.9 mmol) was added to a solution of **11** (250 mg, 1.46 mmol) in DMF (18 mL), and the suspension was stirred at room temperature for 16 h. A solution of 1,2-bis(bromomethylbenzene) (302 mg, 1.46 mmol) in DMF (3 mL) was then added dropwise; the reaction mixture was further stirred for 3 h, quenched by addition of H_2O (0.5 mL) and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether, 1:2 → 1:1) to give **12** (132 mg, 37%), with physicochemical and spectroscopic properties identical to those previously reported,[46] together with unreacted **11** (125 mg, 50%).

5-*O*-Benzyl-1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructopyranose (13): NaH (60% in mineral oil, 52 mg, 1.3 mmol) was added to a solution of **12** (168 mg, 0.522 mmol) in dry DMF (7 mL), and the suspension was stirred at room temperature for 15 min. Benzyl bromide (130 μL, 10.4 mmol) was added, and the mixture was stirred at room temperature for 30 min. MeOH (4 mL), Et_2O (16 mL) and H_2O (8 mL) were added, and the organic phase was decanted, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether, 1:8) to give **13** (161 mg, 75%). $[\alpha]_D$ = –158.9 (c = 0.8, $CHCl_3$). R_f = 0.33 (EtOAc/petroleum ether, 1:6). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.08 (m, 9 H, Ph), 5.11, 4.75 (2 d, $^2J_{H,H}$ = 13.5 Hz, 2 H, CH_2), 4.96, 4.67 (2 d, $^2J_{H,H}$ = 12.3 Hz, 2 H, CH_2), 4.18 (d, $J_{1a,1b}$ = 8.5 Hz, 1 H, 1a-H), 4.04 (d, 1 H, 1b-H), 3.96 (m, 2 H, 3-H, 4-H), 3.84 (m, 1 H, 5-H), 3.82 (dd, $J_{6a,6b}$ = 11.7, $J_{5,6a}$ = 1.1 Hz, 1 H, 6a-H), 3.74 (dd, $J_{5,6b}$ = 2.0 Hz, 1 H, 6b-H), 1.47, 1.41 (2 s, 6 H, CMe_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 137.2–127.4 (Ph), 111.8 (*C*Me$_2$), 105.9 (C-2), 79.6 (C-4), 77.2 (C-3), 76.1 (C-5), 72.5, 72.0 (CH_2), 71.8 (C-1), 62.8 (C-6), 27.1, 26.1 (C*Me*$_2$) ppm. FABMS: *m*/*z* (%) = 435 (30) [M + Na]$^+$. $C_{24}H_{28}O_6$ (412): calcd. C 69.88, H 6.84; found C 69.77, H 6.78.

5-*O*-Benzyl-3,4-*O*-(*o*-xylylene)-α-D-fructopyranose 5′-*O*-Benzyl-3′,4′-*O*-(*o*-xylylene)-β-D-fructopyranose 1,2′:2,1′-Dianhydride (14) and 5,5′-Di-*O*-benzyl-3,4:3′,4′-di-*O*-(*o*-xylylene)-di-β-D-fructopyranose 1,2′:2,1′-Dianhydride (15): Trifluoromethanesulfonic acid (TfOH, 50 μL, 0.580 mmol) was added at –78 °C to a solution of **13** (160 mg, 0.387 mmol) in freshly distilled CH_2Cl_2 (8 mL). The reaction mixture was allowed to reach room temperature and further stirred for 1 h. Et_3N (5 drops) was then added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:3 → 1:2) to give **14** (27 mg, 20%) and **15** (84 mg, 61%).

Data for 14: R_f = 0.54 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = –72.4 (c = 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22–7.02 (m, 18 H, Ph), 5.22–4.62 (12 d, 12 H, CH_2), 4.43 (d, $J_{1a,1b}$ = 11.1 Hz, 1 H, 1a-H), 4.16 (d, $J_{1a,1b}$ = 12.2 Hz, 1 H, 1′a-H), 3.98 (dd, $J_{3,4}$ = 9.6, $J_{4,5}$ = 3.0 Hz, 1 H, 4α-H), 3.95 (br. d, $J_{6a,6b}$ = 13.1 Hz, 1 H, 6aβ-H), 3.94 (d, $J_{3,4}$ = 10.3 Hz, 1 H, 3β-H), 3.83 (m, $J_{6a,6b}$ = 12.2, $J_{5,6a}$ = 1.8 Hz, 1 H, 6aα-H), 3.81–3.82 (m, 2 H, 5α-H, 5β-H), 3.68 (d, $J_{3,4}$ = 9.6 Hz, 1 H, 3α-H), 3.64 (dd, 1 H, 6bβ-H), 3.64 (dd, 1 H, 6bα-H), 3.64 (d, 1 H, 1′b-H), 3.55 (d, 1 H, 1b-H), 3.51 (dd, $J_{4,5}$ = 3.3 Hz, 1 H, 4β-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 138.7–127.35 (Ph), 96.8 (C-2α), 95.9 (C-2β), 81.7 (C-3β), 79.5 (C-4β), 78.9 (C-3α), 77.6 (C-4α), 76.0 (C-5β), 75.1 (CH_2), 74.6 (CH_2), 74.3 (C-5α), 73.0, 72.6, 72.3 (CH_2), 64.1 (C-6β), 62.5 (C-1), 61.7 (C-6α), 56.1 (C-1′) ppm. FABMS: *m*/*z* (%) = 731 (10) [M + Na]$^+$. $C_{42}H_{44}O_{10}$ (708): calcd. C 71.17, H 6.26; found C 71.33, H 6.46.

Data for 15: $[\alpha]_D$ = –173.5 (c = 0.29, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.05 (m, 18 H, Ph), 5.10, 4.96 (2 d, $^2J_{H,H}$ = 14.3 Hz, 4 H, CH_2), 5.05 (br. s, 4 H, CH_2), 4.74, 4.69 (2 d, $^2J_{H,H}$ = 12.4 Hz, 4 H, CH_2), 4.12 (dd, $J_{3,4}$ = 10, $J_{4,5}$ = 3.21 Hz, 2 H, 4-H), 4.06 (d, $J_{1a,1b}$ = 11.8 Hz, 1 H, 1a-H), 3.92 (d, 1 H, 3-H), 3.83 (m, 2 H, 5-H), 3.74 (s, 4 H, 6a-H, 6b-H), 3.65 (d, 2 H, 1b-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 138.7–127.4 (Ph), 96.6 (C-2), 80.5 (C-3), 78.8 (C-4), 75.9 (C-5), 73.9 (CH_2), 73.0 (CH_2), 72.4 (CH_2), 62.7 (C-6), 64.6 (C-1) ppm. FABMS: *m*/*z* (%) = 731 (15) [M + Na]$^+$. $C_{42}H_{44}O_{10}$ (708): calcd. C 71.17, H 6.26; found C 71.35, H 6.61.

3-*O*-Benzyl-1,2-*O*-isopropylidene-4,5-*O*-(*o*-xylylene)-β-D-fructopyranose (17): NaH (60% in mineral oil, 135 mg, 3.37 mmol, 5 equiv.) was added at 0 °C to a solution of **16**[52] (209 mg, 0.67 mmol) in dry DMF (4 mL), and the reaction mixture was stirred at room temperature for 15 min. 1,2-Bis(bromomethyl)benzene (356 mg, 1.35 mmol, 2 equiv.) was added, and the solution was further stirred for 1 h. Et_2O (10 mL) and water (10 mL) were added, and the organic layer was decanted, dried and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether, 1:8 → 2:1) to give **17** (117 mg, 42%). R_f = 0.60 (EtOAc/petroleum ether, 1:4). $[\alpha]_D$ = +35.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.09 (m, 9 H, Ph), 5.95, 4.59 (2 d, $^2J_{H,H}$ = 11.5 Hz, 2 H, CH_2), 5.42, 4.71 (2 d, $^2J_{H,H}$ = 16.0 Hz, 2 H, CH_2), 5.30, 4.71 (2 d, $^2J_{H,H}$ = 11.6 Hz, 2 H, C*H*Ph), 4.05 (dd, $J_{3,4}$ = 9.8, $J_{4,5}$ = 2.9 Hz, 1 H, 4-H), 4.02 (d, $J_{1a,1b}$ = 8.5 Hz, 1 H, 1a-H), 3.97 (d, 1 H, 3-H), 3.93 (d, 1 H, 1b-H), 3.84 (dd, $J_{6a,6b}$ = 12.6, $J_{5,6a}$ = 1.4 Hz, 1 H, 6a-H), 3.79 (m, 1 H, 5-H), 3.59 (dd, $J_{5,6b}$ = 1.7 Hz, 1 H, 6b-H), 1.44, 1.41 (2 s, 6 H, CMe_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 140.6–125.5 (Ph), 111.9 (*C*Me$_2$), 105.8 (C-2), 83.3 (C-4), 75.3 (CH_2), 74.2 (C-3), 72.0 (C-1), 71.6, 71.3 (*C*H$_2$Ph), 69.8 (C-5), 63.3 (C-6), 27.0, 26.2 (C*Me*$_2$) ppm. FABMS: *m*/*z* (%) = 435 (20) [M + Na]$^+$. $C_{24}H_{28}O_6$ (412): calcd. C 69.88, H 6.84; found C 69.72, H 6.46.

3-*O*-Benzyl-4,5-*O*-(*o*-xylylene)-α-D-fructopyranose 3′-*O*-Benzyl-4′,5′-*O*-(*o*-xylylene)-β-D-fructopyranose 1,2′:2,1′-Dianhydride (18), 4,5-*O*-(*o*-Xylylene)-α-D-fructopyranose 3′-*O*-Benzyl-4′,5′-*O*-β-D-fructopyranose 1,2′:2,1′-Dianhydride (19) and 3,3′-Di-*O*-benzyl-4:5,4′,5′-di-*O*-(*o*-xylylene)-di-β-D-fructopyranose 1,2′:2,1′-Dianhydride (20): TfOH (115 μL, 1.32 mmol, 1.5 equiv.) was added at –78 °C to a solution of **17** (263 mg, 0.878 mmol) in freshly distilled CH_2Cl_2 (24 mL). The reaction mixture was allowed to reach room temperature and was further stirred for 30 min. Et_3N (12 drops) was then added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:3 → 1:1) to give **18** (158 mg, 51%), **19** (19 mg, 6%) and **20** (45 mg, 15%).

Data for 18: R_f = 0.53 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +22.4 (c = 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.09 (m, 18 H, Ph), 5.90, 4.60 (2 d, $^2J_{H,H}$ = 11.6 Hz, 2 H, CH_2), 5.46, 4.55 (2 d, $^2J_{H,H}$ = 13.5 Hz, 2 H, CH_2), 5.44, 5.42 (2 d, $^2J_{H,H}$ = 14.4 Hz, 2 H, CH_2), 4.98, 4.66 (2 d, $^2J_{H,H}$ = 11.8 Hz, 2 H, CH_2), 4.67, 4.50 (2 d, $^2J_{H,H}$ = 14.2 Hz, 2 H, CH_2), 4.62, 4.51 (2 d, $^2J_{H,H}$ = 11.5 Hz, 2 H, C*H*Ph), 4.34 (d, $J_{1a,1b}$ = 11.5 Hz, 1 H, 1a-H), 4.13 (dd, $J_{3,4}$ = 9.8, $J_{4,5}$ = 3.0 Hz, 1 H, 4α-H), 3.94 (dd, $J_{6a,6b}$ = 11.7, $J_{5,6a}$ = 7.0 Hz, 1 H, 6aβ-H), 3.87 (m, 1 H, 5β-H), 3.82 (d, $J_{1a,1b}$ = 12.0 Hz, 1 H, 1a′-H), 3.79 (m, 1 H, 5α-H), 3.76 (d, 1 H, 3α-H), 3.70 (d, 1 H, 1b′-H), 3.68 (s, 2 H, 3β-H, 4β-H), 3.62 (dd, $J_{5,6b}$ = 3.3 Hz, 1 H, 6bβ-H), 3.61 (br. s, 2 H, 6aα-H, 6aβ-H), 3.41 (d, 1 H, 1b-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 140.7–125.7 (Ph), 95.9 (C-2α), 95.3 (C-2β), 81.3 (C-4α), 78.8 (C-4β), 75.1 (C-3β), 74.8 (C-3α), 74.7, 74.1 (CH_2), 72.3 (C-5β), 71.5, 71.4, 71.3, 71.0 (CH_2), 70.1 (C-5α),

62.5 (C-6α), 61.7 (C-1), 60.9 (C-6β), 59.3 (C-1′) ppm. FABMS: *m*/*z* (%) = 731 (98) $[M + Na]^+$. $C_{42}H_{44}O_{10}$ (708): calcd. C 71.17, H 6.26; found C 70.95, H 6.15.

Data for 19: R_f = 0.37 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = –11.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.09 (m, 18 H, Ph), 5.99, 4.54 (2 d, $^2J_{H,H}$ = 11.3 Hz, 2 H, CH_2), 5.95, 4.57 (2 d, $^2J_{H,H}$ = 11.8 Hz, 2 H, CH_2), 5.52, 4.70 (2 d, $^2J_{H,H}$ = 15.9 Hz, 2 H, CH_2), 5.41, 4.70 (2 d, $^2J_{H,H}$ = 16.0 Hz, 2 H, CH_2), 5.00, 4.85 (2 d, $^2J_{H,H}$ = 11.9 Hz, 2 H, CH_2), 4.14 (dd, $J_{3,4}$ = 9.7, $J_{4,5}$ = 2.9 Hz, 1 H, 4β-H), 4.06 (br. t, $J_{3,4}$ = $J_{4,5}$ = 8.8 Hz, 1 H, 4α-H), 3.93 (d, 1 H, 3β-H), 3.92 (d, $J_{1a,1b}$ = 12.4 Hz, 1 H, 1a-H), 3.83 (dd, $J_{6a,6b}$ = 12.1, $J_{5,6a}$ = 1.0 Hz, 1 H, 6aα-H), 3.80 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 2.0 Hz, 1 H, 6aβ-H), 3.77 (m, 2 H, 5α-H, 3α-H), 3.75 (m, 1 H, 5β-H), 3.65 (d, 1 H, 1b-H), 3.62 (m, 1 H, OH), 3.60 (dd, $J_{5,6b}$ = 1.5 Hz, 1 H, 6bα-H), 3.53 (d, $J_{1a,1b}$ = 12.4 Hz, 1 H, 1a′-H), 3.52 (dd, $J_{5,6b}$ = 1.7 Hz, 1 H, 6bβ-H), 3.41 (d, 1 H, 1b′-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 140.7–125.5 (Ph), 97.1 (C-2α), 96.9 (C-2β), 82.6 (C-4β), 81.7 (C-3α*), 77.6 (C-3β), 74.9 (CH_2), 72.7 (C-4α), 71.5, 71.3, 71.2, 71.1 (CH_2), 69.9 (C-5α*), 69.3 (C-5β), 64.3 (C-1), 64.2 (C-1′), 63.7 (C-6α), 63.3 (C-6β) ppm. FABMS: *m*/*z* (%) = 641 (90) $[M + Na]^+$. $C_{35}H_{38}O_{10}$ (614): calcd. C 67.95, H 6.19; found C 67.92, H 6.00.

Data for 20: R_f = 0.66 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = –11.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.11 (m, 18 H, Ph), 5.85, 5.45 (2 d, $^2J_{H,H}$ = 12.0 Hz, 4 H, CH_2), 4.97, 4.73 (2 d, $^2J_{H,H}$ = 12.0 Hz, 4 H, CH_2), 4.67, 4.56 (2 d, $^2J_{H,H}$ = 11.5 Hz, 4 H, CH_2), 4.22 (dd, $J_{3,4}$ = 10, $J_{4,5}$ = 3.0 Hz, 2 H, 4-H), 3.94 (d, 2 H, 3-H), 3.84 (d, $J_{1a,1b}$ = 12.0 Hz, 2 H, 1a-H), 3.79 (m, 2 H, 5-H), 3.76 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.5 Hz, 2 H, 6a-H), 3.57 (dd, $J_{5,6b}$ = 2.0 Hz, 2 H, 6b-H), 3.54 (d, 2 H, 1b-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 140.4–126.1 (Ph), 97.5 (C-2), 80.5 (C-4), 77.5 (C-3), 73.4, 71.4, 71.2 (CH_2), 70.6 (C-5), 63.9 (C-1), 63.4 (C-6) ppm. FABMS: *m*/*z* (%) = 731 (98) $[M + Na]^+$. $C_{42}H_{44}O_{10}$ (708): calcd. C 71.17, H 6.26; found C 70.97, H 6.23.

General Procedure for the Preparation of the Cyclic (4-O,5-O)-*o*-Xylylene-Protected (3-O→3′-O)-Xylylene-Tethered Fructopyranose Derivatives 24–26: NaH (60% in mineral oil, 204 mg, 5.085 mmol, 10 equiv.) was added to a solution of the corresponding 1,2-, 1,3- or 1,4-bis[(1,2-*O*-isopropylidene-β-D-fructopyranos-3-*O*-yl)-methyl]benzene **21**–**23**[21] (275 mg, 0.51 mmol) in dry DMF (3.1 mL), and the suspension was stirred under Ar at room temperature for 1 h. A solution of 1,2-bis(bromomethylbenzene) (603 mg, 2.54 mmol, 5 equiv.) in dry DMF (3.1 mL) was then added, the reaction mixture was further stirred under Ar for 3 h and quenched by addition of water (0.63 mL), and the solvents were evaporated. The resulting residue was extracted with Et_2O (2 × 20 mL), washed with water (20 mL), dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/petroleum ether, 1:2, containing 0.5% Et_3N).

1,2-Bis[(1,2-*O*-isopropylidene-4,5-*O*-(*o*-xylylene)-β-D-fructopyranos-3-*O*-yl)methyl]benzene (24): Yield: 144 mg (38%). R_f = 0.70 (EtOAc/petroleum ether, 1:1). $[\alpha]_d$ = +4.7 (*c* = 1.0, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.01 (m, 12 H, Ph), 5.92 (d, $^2J_{H,H}$ = 11.5 Hz, 2 H, CH_2), 5.41 (d, $^2J_{H,H}$ = 16.0 Hz, 2 H, CH_2), 5.21 (d, $^2J_{H,H}$ = 12.0 Hz, 2 H, CH_2), 4.80, 4.70, 4.50 (3 d, 6 H, CH_2), 4.01 (dd, $J_{3,4}$ = 9.5, $J_{4,5}$ = 2.5 Hz, 2 H, 4-H), 3.94 (d, 2 H, 3-H), 3.86 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 1a-H), 3.83 (d, 2 H, 1b-H), 3.81 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.0 Hz, 2 H, 6a-H), 3.76 (br. s, 1 H, 5-H), 3.53 (dd, $J_{5,6b}$ = 1.5 Hz, 1 H, 6b-H), 1.41 (s, 12 H, CMe_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 140.6–125.2 (Ph), 111.7 (CMe_2), 105.7 (C-2), 83.6 (C-4), 74.0 (C-3), 72.3 (CH_2), 72.1 (C-1), 71.7, 71.1 (CH_2), 69.4 (C-5), 63.2 (C-6), 26.7, 26.3 (CMe_2) ppm. IR: $\tilde{\nu}_{max}$ = 2986, 2926, 2889, 1455, 1370, 1216, 1186, 1128, 1104, 1022, 881, 735 cm^{-1}. FABMS: *m*/*z* (%) = 769 (5) $[M + Na]^+$. $C_{42}H_{50}O_{12}$ (747): calcd. C 67.54, H 6.75; found C 67.56, H 6.70.

1,3-Bis[(1,2-*O*-isopropylidene-4,5-*O*-(*o*-xylylene)-β-D-fructopyranos-3-*O*-yl)methylbenzene (25): Yield: 114 mg (30%). R_f = 0.34 (EtOAc/petroleum ether, 1:2). $[\alpha]_D$ = –0.9 (*c* = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.1 (m, 12 H, Ph), 5.96 (d, $^2J_{H,H}$ = 11.4 Hz, 2 H, CH_2), 5.45 (d, $^2J_{H,H}$ = 16.0 Hz, 2 H, CH_2), 5.09 (d, $^2J_{H,H}$ = 12.6 Hz, 2 H, CH_2), 4.77, 4.72 (2 d, 4 H, CH_2), 4.62 (d, $^2J_{H,H}$ = 11.5 Hz, 2 H, CH_2), 4.09 (dd, 4 H, 4-H, 1a-H), 3.99 (d, 4 H, 3-H, 1b-H), 3.88 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.6 Hz, 2 H, 6a-H), 3.82 (s, 1 H, 5-H), 3.64 (d, $J_{5,6b}$ = 1.4 Hz, 1 H, 6b-H), 1.46, 1.44 (s, 12 H, CMe_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 140.5–125.5 (Ph), 111.8 (CMe_2), 105.7 (C-2), 83.1 (C-4), 75.1 (CH_2), 74.3 (C-3), 72.1 (C-1), 71.5, 71.2 (CH_2), 69.7 (C-5), 63.1 (C-6), 27.0, 26.0 (CMe_2) ppm. IR: $\tilde{\nu}_{max}$ = 2985, 2930, 2880, 1444, 1370, 1105, 1022, 969, 881, 735 cm^{-1}. FABMS: *m*/*z* (%) = 769 (3) $[M + Na]^+$. $C_{42}H_{50}O_{12}$ (747): calcd. C 67.54, H 6.75; found C 67.54, H 6.44.

1,4-Bis[(1,2-*O*-isopropylidene-4,5-*O*-(*o*-xylylene)-β-D-fructopyranos-3-*O*-yl)methylbenzene (26): Yield: 133 mg (35%). R_f = 0.5 (EtOAc/petroleum ether, 1:2). $[\alpha]_D$ = +0.9 (*c* = 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.1 (m, 12 H, Ph), 5.99 (d, $^2J_{H,H}$ = 11.4 Hz, 2 H, CH_2), 5.48 (d, $^2J_{H,H}$ = 16.0 Hz, 2 H, CH_2), 5.08 (d, $^2J_{H,H}$ = 12.6 Hz, 2 H, CH_2), 4.77, 4.74 (2 d, 4 H, CH_2), 4.64 (d, $^2J_{H,H}$ = 11.5 Hz, 2 H, CH_2), 4.07 (dd, 4 H, 4-H, 1a-H), 3.98 (d, 4 H, 3-H, 1b-H), 3.88 (dd, $J_{6a,6b}$ = 12.5, $J_{5,6a}$ = 1.6 Hz, 2 H, 6a-H), 3.84 (s, 1 H, 5-H), 3.63 (d, $J_{5,6b}$ = 1.4 Hz, 1 H, 6b-H), 1.46, 1.44 (s, 12 H, CMe_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 140.7–125.5 (Ph), 112.0 (CMe_2), 106 (C-2), 83.3 (C-4), 75.1 (CH_2), 74.3 (C-3), 72.2 (C-1), 71.6, 71.3 (CH_2), 69.8 (C-5), 63.4 (C-6), 27.1, 26.3 (CMe_2) ppm. IR: $\tilde{\nu}_{max}$ = 2986, 2930, 2891, 2360, 1455, 1370, 1254, 1216, 1184, 1128, 1105, 1021, 981, 882, 772, 735 cm^{-1}. FABMS: *m*/*z* (%) = 769 (6) $[M + Na]^+$. $C_{42}H_{50}O_{12}$ (747): calcd. C 67.54, H 6.75; found C 67.61, H 6.64.

6-*O*-(*tert*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranose (28): A suspension of NaH (60% in mineral oil, 80 mg, 2 mmol) was added to a solution of **27**[39] (135 mg, 0.4 mmol) in dry DMF (2.5 mL), and the suspension was stirred at room temperature for 20 min. 1,2-Bis(bromomethylbenzene) (264 mg, 1 mmol) was then added, and the reaction mixture was further stirred for 1 h, quenched by addition of H_2O (0.5 mL) and concentrated. The residue was purified by column chromatography (EtOAc/petroleum ether, 1:10, containing 0.5% Et_3N) to give **28** (136 mg, 78%). R_f = 0.31 (EtOAc/petroleum ether, 1:6). $[\alpha]_D$ = –5.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.32 (m, 4 H, Ph), 5.07 (d, $^2J_{H,H}$ = 12.6 Hz, 1 H, C*H*Ph), 4.80 (m, 3 H, CH_2), 4.18 (dd, $J_{3,4}$ = 6.3, $J_{4,5}$ = 4.6 Hz, 1 H, 4-H), 3.96 (d, $J_{1a,1b}$ = 8.9 Hz, 1 H, 1a-H), 3.89 (ddd, $J_{5,6b}$ = 6.9 Hz, 1 H, 5-H), 3.86 (d, 1 H, 1b-H), 3.84 (d, 1 H, 3-H), 3.72 (dd, $J_{6a,6b}$ = 10.3 Hz, 1 H, 6a-H), 3.67 (dd, 1 H, 6b-H), 1.45, 1.40 (2 s, each 3 H, CMe_2), 0.88 (s, 9 H, $SiCMe_3$), 0.02 (s, 6 H, $SiMe_2$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 137.1–129.4 (Ph), 111.7 (CMe_2), 110.5 (C-2), 83.1 (C-4), 82.9 (C-5), 81.2 (C-3), 71.0 (C-1), 69.6, 69.4 (CH_2), 64.9 (C-6), 27.1, 26.0 (CMe_2), 25.9 ($SiCMe_3$), 18.3 ($SiCMe_3$) ppm. FABMS: *m*/*z* (%) = 459 (100) $[M + Na]^+$. $C_{23}H_{36}O_6Si$ (436): calcd. C 63.30, H 8.30; found C 63.36, H 8.30.

1,2-*O*-Isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranose (29): TBAF (1 M in THF, 1.21 mL) was added under Ar at 0 °C to a stirred solution of **28** (478 mg, 1.09 mmol) in THF (25 mL). The reaction mixture was stirred for 4 h until disappearance of the starting material (TLC) and was then diluted with Et_2O (15 mL), washed with water (2 × 8 mL), dried ($MgSO_4$), filtered and concen-

trated. Purification of the residue by column chromatography (EtOAc/petroleum ether, 1:1) gave **29** (326 mg, 93%). R_f = 0.58 (EtOAc/petroleum ether, 2:1). $[\alpha]_D$ = +11.6 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 4 H, Ph), 5.10, 4.76 (2 d, $^2J_{H,H}$ = 13.0 Hz, 2 H, CH_2), 4.81, 4.78 (2 d, $^2J_{H,H}$ = 8.7 Hz, 2 H, CH_2), 4.50 (dd, $J_{3,4}$ = 6.6, $J_{4,5}$ = 5.5 Hz, 1 H, 4-H), 4.01 (ddd, $J_{5,6b}$ = 3.4, $J_{5,6a}$ = 2.6 Hz, 1 H, 5-H), 3.98 (d, $J_{1a,1b}$ = 9.2 Hz, 1 H, 1a-H), 3.91 (d, 1 H, 1b-H), 3.84 (d, 1 H, 3-H), 3.74 (dt, $J_{6a,6b}$ = 12.1, $J_{OH,6a}$ = 2.3 Hz, 1 H, 6a-H), 3.63 (ddd, $J_{OH,6b}$ = 9.7 Hz, 1 H, 6b-H), 2.72 (br. s, 1 H, OH), 1.50, 1.41 (2 s, each 3 H, CMe_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 137.2–129.5 (Ph), 112.1 (CMe_2), 110.2 (C-2), 83.8 (C-5), 81.0 (C-3), 80.7 (C-4), 70.9 (C-1), 69.9, 69.0 (CH_2), 63.0 (C-6), 27.1, 25.5 (CMe_2) ppm. FABMS: m/z (%) = 345 (98) $[M + Na]^+$. $C_{17}H_{22}O_6$ (322): calcd. C 63.34, H 6.88; found C 63.00, H 6.92.

6-*O*-Acetyl-1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranose (30): Acetic anhydride (0.4 mL) was added at 0 °C to a solution of **29** (120 mg, 0.37 mmol) in pyridine (0.4 mL). The solution was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (15 mL) and washed with H_2SO_4 (2 N, 3 × 5 mL) and $NaHCO_3$ (3 × 5 mL), dried, filtered and concentrated. The resulting residue was purified by column chromatography (EtOAc/petroleum ether, 1:5 → 1:3). Yield: 115 mg (85%). R_f = 0.31 (EtOAc/petroleum ether, 1:2). $[\alpha]_D$ = +7.9 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 4 H, Ph), 5.08, 4.80 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.79 (s, 2 H, CH_2), 4.23 (dd, $J_{6a,6b}$ = 11.0, $J_{5,6a}$ = 4.5 Hz, 1 H, 6a-H), 4.18 (dd, $J_{3,4}$ = 6.8, $J_{4,5}$ = 5.0 Hz, 1 H, 4-H), 4.17 (dd, $J_{5,6b}$ = 7.5 Hz, 1 H, 6b-H), 4.04 (dt, 1 H, 5-H), 3.96 (d, $J_{1a,1b}$ = 8.8 Hz, 1 H, 1a-H), 3.86 (d, 1 H, 1b-H), 3.84 (d, 1 H, 3-H), 2.04 (s, 3 H, OAc), 1.44, 1.39 (2 s, 6 H, CMe_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 170.8 (CO), 136.9–129.6 (Ph), 112.0 (CMe_2), 110.6 (C-2), 82.7 (C-4), 80.5 (C-3), 80.0 (C-5), 70.8 (C-1), 69.6, 69.4 (CH_2Ph), 65.7 (C-6), 27.0, 25.9 (CMe_2), 20.9 ($MeCO$) ppm. FABMS: m/z (%) = 387 (20) $[M + Na]^+$. $C_{19}H_{24}O_7$ (364): calcd. C 62.63, H 6.64; found C 62.51, H 6.57.

6-*O*-Benzyl-1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranose (31): A suspension of NaH (60% in mineral oil, 17 mg, 0.43 mmol) and benzyl bromide (21 μL, 0.17 mmol) were added to a solution of **29** (55 mg, 0.17 mmol) in dry DMF (2 mL). The reaction mixture was stirred at room temperature for 3 h, saturated aqueous NH_4Cl (2 mL) was then added, and the solvents were evaporated. The resulting residue was extracted with Et_2O (5 mL), washed with water (3 mL), dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/petroleum ether, 1:4) to yield **30** (57 mg, 80%). R_f = 0.59 (EtOAc/petroleum ether, 1:2). $[\alpha]_D$ = +4.6 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 9 H, Ph), 5.08, 4.81 (2 d, $^2J_{H,H}$ = 12.6 Hz, 2 H, CH_2), 4.82, 4.78 (2 d, $^2J_{H,H}$ = 12.9 Hz, 2 H, CH_2), 4.56 (s, 2 H, CH_2), 4.18 (dd, $J_{3,4}$ = 6.5, $J_{4,5}$ = 4.8 Hz, 1 H, 4-H), 4.09 (ddd, $J_{5,6a}$ = 7.5, $J_{5,6b}$ = 5.4 Hz, 1 H, 5-H), 3.99 (d, $J_{1a,1b}$ = 8.9 Hz, 1 H, 1a-H), 3.88 (d, 1 H, 1b-H), 3.87 (d, 1 H, 3-H), 3.65 (dd, $J_{6a,6b}$ = 9.9 Hz, 1 H, 6a-H), 3.56 (dd, 1 H, 6b-H), 1.45, 1.40 (2 s, each 3 H, CMe_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.2–127.6 (Ph), 111.8 (CMe_2), 110.6 (C-2), 83.2 (C-4), 81.4 (C-5), 80.9 (C-3), 72.2 (C-6), 71.0 (C-1), 69.6, 69.4 (CH_2), 27.1, 26.0 (CMe_2) ppm. FABMS: m/z (%) = 435 (35) $[M + Na]^+$. $C_{24}H_{28}O_6$ (413): calcd. C 69.88, H 6.84; found C 69.85, H 6.70.

3,4-*O*-(*o*-Xylylene)-α-D-fructofuranose 3′,4′-*O*-(*o*-Xylylene)-β-D-fructopyranose 1,2′:2,1′-Dianhydride (32) and 3,4-*O*-(*o*-Xylylene)-α-D-fructofuranose 3′,4′-*O*-(*o*-Xylylene)-β-D-fructofuranose 1,2′:2,1′-Dianhydride (33): TfOH (37 μL, 0.43 mmol) was added at –78 °C to a solution of **29** (92 mg, 0.29 mmol) in freshly distilled CH_2Cl_2 (8 mL). The reaction mixture was allowed to reach room temperature and was stirred for 10 min. Et_3N (2 mL) was then added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:1 → 6:1) to give **32** (9 mg, 12%) and **33** (31 mg, 41%).

Data for 32: R_f = 0.26 (EtOAc/petroleum ether, 3:1). $[\alpha]_D$ = –24.0 (c = 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29–6.99 (m, 8 H, Ph), 5.35, 4.63 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 5.28, 4.68 (2 d, $^2J_{H,H}$ = 15.3 Hz, 2 H, CH_2), 4.94, 4.65 (2 d, $^2J_{H,H}$ = 12.3 Hz, 2 H, CH_2), 4.77 (s, 2 H, CH_2), 4.27 (d, $J_{1a,1b}$ = 11.2 Hz, 1 H, 1′a-H), 4.12 (dd, $J_{4,5}$ = 8.5, $J_{3,4}$ = 4.7 Hz, 1 H, 4*f*-H), 4.01 (m, 1 H, 5*p*-H), 3.97 (dd, $J_{3,4}$ = 9.1, $J_{4,5}$ = 3.5 Hz, 1 H, 4*p*-H), 3.96 (d, $J_{1a,1b}$ = 12.2 Hz, 1 H, 1a-H), 3.95 (m, 1 H, 5*f*-H), 3.93 (d, $J_{6a,6b}$ = 12.5 Hz, 1 H, 6a*f*-H), 3.92 (d, 1 H, 3*f*-H), 3.81 (dd, $J_{6a,6b}$ = 12.6, $J_{5,6a}$ = 1.5 Hz, 1 H, 6a*p*-H), 3.73 (d, 1 H, 6b*p*-H), 3.72 (d, 1 H, 6b*f*-H), 3.68 (br. s, 1 H, OH), 3.63 (d, 1 H, 1b-H), 3.50 (d, 1 H, 3*p*-H), 3.39 (d, 1 H, 1′b-H), 2.44 (s, 1 H, OH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 136.5–127.7 (Ph), 102.1 (C-2*f*), 96.1 (C-2*p*), 87.4 (C-3*f*), 81.4 (C-4*f*), 79.1 (C-6*f*), 77.1 (C-3*p*), 75.1 (C-5*f*), 74.4, 71.5, 70.8 (CH_2), 68.8 (C-5*p*), 67.6 (CH_2), 62.6 (C-6*p*), 62.3 (C-1), 61.7 (C-1′), 60.8 (C-4*p*) ppm. FABMS: m/z (%) = 551 (100) $[M + Na]^+$. $C_{28}H_{32}O_{10}$ (528): calcd. C 63.63, H 6.10; found C 63.25, H 5.76.

Data for 33: R_f = 0.17 (EtOAc/petroleum ether, 7:1). $[\alpha]_D$ = +28.7 (c = 1.0, MeOH). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 8 H, Ph), 5.07, 4.79 (2 d, $^2J_{H,H}$ = 12.8 Hz, 2 H, CH_2), 4.92, 4.63 (2 d, $^2J_{H,H}$ = 12.3 Hz, 2 H, CH_2), 4.77 (s, 2 H, CH_2), 4.75 (s, 2 H, CH_2), 4.38 (dd, $J_{3,4}$ = 6.1, $J_{4,5}$ = 5.6 Hz, 1 H, 4β-H), 4.12 (d, $J_{1a,1b}$ = 12.3 Hz, 1 H, 1aα-H), 4.08 (m, 1 H, 5β-H), 4.07 (d, $J_{1a,1b}$ = 11.8 Hz, 1 H, 1aβ-H), 4.05 (dd, $J_{4,5}$ = 9.3, $J_{3,4}$ = 4.5 Hz, 1 H, 4α-H), 3.94 (dd, $J_{6a,6b}$ = 12.4, $J_{5,6a}$ = 2.6 Hz, 1 H, 6aα-H), 3.90 (m, 1 H, 5α-H), 3.86 (d, 1 H, 3α-H), 3.76 (dd, $J_{6a,6b}$ = 11.9, $J_{5,6a}$ = 4.1 Hz, 1 H, 6aβ-H), 3.70 (dd, $J_{5,6b}$ = 6.1 Hz, 1 H, 6bβ-H), 3.67 (dd, $J_{5,6b}$ = 2.6 Hz, 1 H, 6bα-H), 3.64 (d, 1 H, 1bα-H), 3.59 (d, 1 H, 3β-H), 3.28 (d, 1 H, 1bβ-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 136.9–129.6 (Ph), 102.1 (70.7, C-2α, 101.3 (C-2β), 87.3 (C-3α), 84.2 (C-5β), 82.8 (C-3β), 81.6 (C-4β), 81.5 (C-4α), 79.0 (C-5α), 69.7, 69.2, 67.6 (CH_2), 64.0 (C-6β), 63.3 (C-1β), 63.0 (C-1α), 61.0 (C-6α) ppm. FABMS: m/z (%) = 551 (80) $[M + Na]^+$. $C_{28}H_{32}O_{10}$ (528): calcd. C 63.63, H 6.10; found C 63.34, H 5.88.

6-*O*-Acetyl-3,4-*O*-(*o*-xylylene)-α-D-fructofuranose 6′-*O*-Acetyl-3′,4′-*O*-(*o*-xylylene)-β-D-fructofuranose 1,2′:2,1′-Dianhydride (34): TfOH (39 μL, 0.45 mmol) was added at –78 °C to a solution of **30** (110 mg, 0.30 mmol) in freshly distilled CH_2Cl_2 (8 mL). The reaction mixture was allowed to reach room temperature and stirred for 40 min. Et_3N (2 mL) was then added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:3 → 1:1) to give **34** (70 mg, 75%). R_f = 0.32 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +69.1 (c = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 8 H, Ph), 5.04, 4.78 (2 d, $^2J_{H,H}$ = 12.8 Hz, 2 H, CH_2), 4.86, 4.64 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.78, 4.70 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.76 (s, 2 H, CH_2Ph), 4.34 (dd, $J_{6a,6b}$ = 12.0, $J_{5,6a}$ = 2.7 Hz, 1 H, 6aα-H), 4.23 (t, $J_{3,4}$ = $J_{4,5}$ = 6.0 Hz, 1 H, 4β-H), 4.22 (dd, $J_{6a,6b}$ = 11.3, $J_{5,6a}$ = 5.1 Hz, 1 H, 6aβ-H), 4.17 (dd, $J_{5,6b}$ = 6.8 Hz, 1 H, 6bβ-H), 4.15 (m, 1 H, 5β-H), 4.12 (dd, $J_{5,6b}$ = 5.6 Hz, 1 H, 6bβ-H), 4.07 (dd, $J_{1a,1b}$ = 12.4 Hz, 1 H, 1aα-H), 4.06 (d, $J_{1a,1b}$ = 11.6 Hz, 1 H, 1aβ-H), 4.00 (ddd, $J_{4,5}$ = 8.9 Hz, 1 H, 5α-H), 3.88 (d, $J_{3,4}$ = 4.6 Hz, 1 H, 3α-H), 3.79 (dd, 1 H, 4α-H), 3.59 (d, 1 H, 3β-H), 3.57 (d, 1 H, 1bα-H), 3.25 (d, 1 H, 1bβ-H), 2.09, 2.04 (2 s,

6 H, MeCO) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 170.9 (CO), 136.7–129.6 (Ph), 102.0 (C-2α), 101.7 (C-2β), 87.3 (C-3α), 83.1 (C-4β), 82.8 (C-4α), 82.5 (C-3β), 80.7 (C-5β), 76.2 (C-5α), 70.4, 69.6, 69.4, 68.0, (CH_2), 65.6 (C-6β), 63.5 (C-6α), 63.2 (C-1β), 62.7 (C-1α), 20.9 (*Me*CO) ppm. FABMS: *m*/*z* (%) = 635 (98) $[M + Na]^+$. $C_{32}H_{36}O_{12}$ (612): calcd. C 62.74, H 5.92; found C 62.71, H 5.81.

6-*O*-Benzyl-3,4-*O*-(*o*-xylylene)-α-D-fructofuranose 6′-*O*-Benzyl-3′,4′-*O*-(*o*-xylylene)-β-D-fructofuranose 1,2′:2,1′-Dianhydride (35): TfOH (28 μL, 0.33 mmol, 1–5 equiv.) was added at –78 °C to a solution of **31** (90 mg, 0.22 mmol) in freshly distilled CH_2Cl_2 (6 mL). The reaction mixture was allowed to reach room temperature and was stirred for 10 min. Et_3N (1.6 mL) was then added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:4 → 1:3) to give **35** (54 mg, 70%). R_f = 0.48 (EtOAc/petroleum ether, 1:2). $[\alpha]_D$ = +47.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.23 (m, 18 H, Ph), 5.02, 4.76 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.86, 4.63 (2 d, $^2J_{H,H}$ = 12.7 Hz, 2 H, CH_2), 4.79, 4.75 (2 d, $^2J_{H,H}$ = 13.0 Hz, 2 H, CH_2), 4.78, 4.70 (2 d, $^2J_{H,H}$ = 13.0 Hz, 2 H, C*H*Ph), 4.62, 4.59 (2 d, $^2J_{H,H}$ = 12.0 Hz, 2 H, CH_2), 4.58, 4.55 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.22 (dd, $J_{3,4}$ = 5.9, $J_{4,5}$ = 4.7 Hz, 1 H, 4β-H), 4.14 (td, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, 1 H, 5β-H), 4.06 (d, $J_{1a,1b}$ = 11.7 Hz, 2 H, 1aα-H, 1aβ-H), 4.02 (ddd, $J_{4,5}$ = 9.0, $J_{5,6b}$ = 6.0, $J_{5,6a}$ = 2.5 Hz, 1 H, 5α-H), 3.89 (d, $J_{3,4}$ = 4.5 Hz, 1 H, 3α-H), 3.83 (dd, 1 H, 4α-H), 3.72 (dd, $J_{6a,6b}$ = 11.4 Hz, 1 H, 6aα-H), 3.64 (dd, $J_{6a,6b}$ = 9.5 Hz, 1 H, 6aβ-H), 3.61 (dd, 1 H, 6bα-H), 3.58 (d, 1 H, 3β-H), 3.54 (dd, 1 H, 6bβ-H), 3.53 (d, 1 H, 1bα-H), 3.24 (d, 1 H, 1bβ-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 136.9–127.5 (Ph), 102.0 (C-2α), 101.6 (C-2β), 87.4 (C-3α), 83.9 (C-4β), 82.9 (C-3β), 82.8 (C-4α), 81.6 (C-5β), 78.5 (C-5α), 73.4, 73.1, 70.4, 69.5, 69.3, 68.1 (CH_2), 71.9 (C-6β), 69.7 (C-6α), 63.3 (C-1β), 62.8 (C-1α) ppm. FABMS: *m*/*z* (%) = 731 (98) $[M + Na]^+$. $C_{42}H_{44}O_{10}$ (708): calcd. C 71.17, H 6.26; found C 70.99, H 6.16.

General Procedure for the Preparation of the Cyclic (4-O,5-O)-*o*-Xylylene-Protected (6-O→6′-O)-Xylylene-Tethered Fructofuranose Derivatives 36–38: NaH (60% in mineral oil, 78 mg, 1.9 mmol, 2.5 equiv.) was added to a solution of **29** (250 mg, 0.76 mmol) in dry DMF (7 mL), and the suspension was stirred under Ar at room temperature for 5 min; 1,2-, 1,3- or 1,4-bis(bromomethyl)benzene (100 mg, 0.38 mmol, 0.5 equiv.) was then added, the reaction mixture was further stirred under argon for 1 h and quenched by addition of saturated aqueous NH_4Cl (9 mL), and the solvents were evaporated. The resulting residue was partitioned between Et_2O (30 mL) and water (30 mL), extracted with Et_2O (2 × 20 mL), washed with water (30 mL), dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/petroleum ether, 1:1).

1,2-Bis[(1,2-*O*-isopropylidene-3,4-*O*-(*o*-xylylene)-β-D-fructofuranos-6-*O*-yl)methyl]benzene (36): Yield: 195 mg, 69%. R_f = 0.48 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +15 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.14 (m, 12 H, Ph), 5.06 (d, $^2J_{H,H}$ = 13.0 Hz, 1 H, CH_2), 4.78 (m, 3 H, CH_2), 4.62, 4.57 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.16 (dd, $J_{3,4}$ = 6.5, $J_{4,5}$ = 5.0 Hz, 1 H, 4-H), 4.06 (ddd, $J_{5,6a}$ = 7.5, $J_{5,6b}$ = 5.5 Hz, 1 H, 5-H), 3.97 (d, $^2J_{H,H}$ = 9.0 Hz, 1 H, 1a-H), 3.86 (d, 1 H, 1b-H), 3.85 (d, 1 H, 3-H), 3.62 (dd, $J_{6a,6b}$ = 10.0 Hz, 1 H, 6a-H), 3.55 (dd, 1 H, 6b-H), 1.44, 1.39 (2 s, 12 H, CMe_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 137.9–127.5 (Ph), 111.7 (*C*Me_2), 110.5 (C-2), 83.2 (C-4), 81.1 (C-5), 80.8 (C-3), 72.4 (C-6), 70.9 (C-1), 70.7, 69.5, 69.3 (CH_2), 26.9, 25.9 (C*Me*$_2$) ppm. IR: $\tilde{\nu}_{max}$ = 2985, 2932, 2879, 1457, 1370, 1216, 1187, 1126, 1074, 893, 741 cm^{-1}. FABMS: *m*/*z* (%) = 769 (2) $[M + Na]^+$. $C_{42}H_{50}O_{12}$ (746): calcd. C 67.54, H 6.75; found C 67.28, H 6.57.

1,3-Bis[(1,2-*O*-isopropylidene-3,4-*O*-(*m*-xylylene)-β-D-fructofuranos-6-*O*-yl)methyl]benzene (37): Yield: 207 mg, 73%. R_f = 0.68 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +8.4 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.16 (m, 12 H, Ph), 5.11 (d, $^2J_{H,H}$ = 13.0 Hz, 2 H, CH_2), 4.83 (m, 3 H, CH_2), 4.58 (2 d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.21 (dd, $J_{3,4}$ = 6.5, $J_{4,5}$ = 5.0 Hz, 1 H, 4-H), 4.11 (ddd, $J_{5,6a}$ = 7.5, $J_{5,6b}$ = 5.5 Hz, 1 H, 5-H), 4.02 (d, $^2J_{H,H}$ = 9.0 Hz, 1 H, 1a-H), 3.91 (d, 1 H, 1b-H), 3.88 (d, 1 H, 3-H), 3.67 (dd, $J_{6a,6b}$ = 10.0 Hz, 1 H, 6a-H), 3.60 (dd, 1 H, 6b-H), 1.48, 1.43 (2 s, 12 H, CMe_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.0–126.9 (Ph), 111.7 (*C*Me_2), 110.5 (C-2), 83.2 (C-4), 81.1 (C-5), 80.8 (C-3), 73.2 (CH_2), 72.1 (C-6), 70.9 (C-1), 69.6, 69.4 (CH_2), 27.0, 26.0 (C*Me*$_2$) ppm. IR: $\tilde{\nu}_{max}$ = 3065, 2989, 2928, 2878, 1456, 1370, 1217, 1187, 1125, 1073, 893, 792, 741 cm^{-1}. FABMS: *m*/*z* (%) = 769 (6) $[M + Na]^+$. $C_{42}H_{50}O_{12}$ (746): calcd. C 67.54, H 6.75; found C 67.51, H 6.68.

1,4-Bis[(1,2-*O*-isopropylidene-3,4-*O*-(*p*-xylylene)-β-D-fructofuranos-6-*O*-yl)methyl]benzene (38): Yield: 106 mg, 42%. R_f = 0.62 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +9.9 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.29 (m, 12 H, Ph), 5.11 (d, $^2J_{H,H}$ = 13.0 Hz, 2 H, CH_2), 4.83 (m, 3 H, C*H*Ph, CH_2), 4.58 (2 d, $^2J_{H,H}$ = 12.0 Hz, 2 H, CH_2), 4.22 (dd, $J_{3,4}$ = 6.5, $J_{4,5}$ = 5.0 Hz, 1 H, 4-H), 4.11 (ddd, $J_{5,6a}$ = 7.2, $J_{5,6b}$ = 5.5 Hz, 1 H, 5-H), 4.02 (d, $^2J_{H,H}$ = 9.0 Hz, 1 H, 1a-H), 3.92 (d, 1 H, 1b-H), 3.89 (d, 1 H, 3-H), 3.67 (dd, $J_{6a,6b}$ = 16.0 Hz, 1 H, 6a-H), 3.58 (dd, 1 H, 6b-H), 1.49, 1.44 (2 s, 12 H, CMe_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.5–127.6 (Ph), 111.7 (*C*Me_2), 110.5 (C-2), 83.1 (C-4), 81.1 (C-5), 80.8 (C-3), 73.1 (CH_2), 72.2 (C-6), 70.9 (C-1), 69.3, 69.2 (CH_2), 27.0, 26.0 (C*Me*$_2$) ppm. IR: $\tilde{\nu}_{max}$ = 2983, 2929, 2878, 1455, 1370, 1309, 1262, 1216, 1187, 1126, 1074, 1020, 984, 950, 892, 824, 792, 741 cm^{-1}. FABMS: *m*/*z* (%) = 769 (2) $[M + Na]^+$. $C_{42}H_{50}O_{12}$ (746): calcd. C 67.54, H 6.75; found C 67.21, H 6.54.

3,4:3′,4′:6,6′-Tri-*O*-(*o*-xylylene)di-α-D-fructofuranose 1,2′:2,1′-Dianhydride (39) and 3,4:3′,4′:6,6′-Tri-*O*-(*o*-xylylene)di-β-D-fructofuranose 1,2′:2,1′-Dianhydride (40): TfOH (21 μL, 0.24 mmol, 1.5 equiv.) was added at –78 °C under Ar to a solution of **36** (120 mg, 0.16 mmol) in freshly distilled CH_2Cl_2 (21 mL). The mixture was stirred for an additional 10 min, allowed to reach room temperature and then stirred for 1 h. Et_3N (5 drops) was then added, the solvent was eliminated under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:4 → 1:2) to give **39** (5 mg, 5%) and **40** (23 mg, 23%).

Data for 39: R_f = 0.73 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +117 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 12 H, Ph), 4.89 (d, $^2J_{H,H}$ = 13.0 Hz, 2 H, CH_2), 4.87 (d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.81 (d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.74 (d, 2 H, CH_2), 4.71 (d, 2 H, CH_2), 4.68 (d, 2 H, CH_2), 4.10 (d, $^2J_{H,H}$ = 12.0 Hz, 2 H, 1a-H), 3.99 (ddd, $J_{4,5}$ = 9.0, $J_{5,6b}$ = 7.5, $J_{5,6a}$ = 2.0 Hz, 2 H, 5-H), 3.81 (dd, $J_{6a,6b}$ = 12.0 Hz, 2 H, 6a-H), 3.58 (d, $J_{4,5}$ = 5.0 Hz, 2 H, 3-H), 3.59 (d, 2 H, 1b-H), 3.58 (dd, 2 H, 4-H), 3.43 (dd, *J* = Hz, 2 H, 6b-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 136.7–127.1 (Ph), 103.0 (C-2), 87.2 (C-3), 83.3 (C-4), 78.3 (C-5), 71.2, 70.4 (CH_2), 70.3 (C-6), 68.4 (CH_2), 63.6 (C-1) ppm. IR: $\tilde{\nu}_{max}$ = 2915, 1454, 1359, 1264, 1105, 1013, 951, 739 cm^{-1}. FABMS: *m*/*z* (%) = 653 (35) $[M + Na]^+$. $C_{36}H_{38}O_{10}$ (630): calcd. C 68.56, H 6.07; found C 68.39, H 5.96.

Data for 40: R_f = 0.53 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +49 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 12 H, Ph), 5.03 (d, $^2J_{H,H}$ = 13.0 Hz, 2 H, CH_2), 4.98 (d, $^2J_{H,H}$ = 11.5 Hz, 2 H, CH_2), 4.77 (m, 4 H, CH_2), 4.73 (d, 2 H, CH_2), 4.51 (d, 2 H, CH_2), 4.06 (m, 4 H, 4-H, 5-H), 3.94 (d, $^2J_{H,H}$ = 12.0 Hz, 2 H, 1a-H), 3.84 (dd, $J_{6a,6b}$ = 11.5, $J_{5,6a}$ = 2.0 Hz, 2 H, 6a-H), 3.73

(dd, $J_{5,6b}$ = 9.5 Hz, 2 H, 6b-H), 3.68 (d, 2 H, 1b-H), 3.58 (d, $J_{3,4}$ = 5.9 Hz, 2 H, 3-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 137.3–127.3 (Ph), 105.0 (C-2), 83.0 (C-4), 82.8 (C-3), 82.1 (C-5), 73.8 (C-6), 71.7, 64.8 (C-1), 69.6, 69.2 (CH_2) ppm. IR: $\tilde{\nu}_{max}$ = 2980, 2880, 1454, 1365, 1216, 1180, 1127, 1016, 950, 741 cm^{-1}. FABMS: *m*/*z* (%) = 653 (100) $[M + Na]^+$: calcd. $C_{36}H_{38}O_{10}$ (630): calcd. C 68.56, H 6.07; found C 68.37, H 5.81.

6,6′-*O*-(*m*-Xylylene)-3,4:3′,4′-di-*O*-(*o*-xylylene)di-α-D-fructofuranose 1,2′:2,1′-Dianhydride (41): TfOH (16 μL, 0.20 mmol, 1.5 equiv.) was added at –78 °C under argon to a solution of **37** (97 mg, 0.129 mmol) in freshly distilled CH_2Cl_2 (17 mL). The mixture was stirred for 10 min, allowed to reach room temperature and then stirred for an additional 45 min. Et_3N (5 drops) was then added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:4 → 1:2) to give **41** (42 mg, 52%). R_f = 0.71 (EtOAc/petroleum ether, 1:1). $[\alpha]_D$ = +160 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.23 (m, 12 H, Ph), 4.97 (d, $^2J_{H,H}$ = 13.0 Hz, 2 H, CH_2), 4.87 (d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.78 (d, $^2J_{H,H}$ = 12.5 Hz, 2 H, CH_2), 4.76 (d, 2 H, CH_2), 4.66 (d, 2 H, CH_2), 4.61 (d, 2 H, CH_2), 4.14 (d, $^2J_{H,H}$ = 12.0 Hz, 2 H, 1a-H), 4.04 (ddd, $J_{4,5}$ = 9.0, $J_{5,6b}$ = 7.5, $J_{5,6a}$ = 2.0 Hz, 2 H, 5-H), 3.98 (d, $J_{4,5}$ = 5.0 Hz, 2 H, 3-H), 3.83 (dd, $J_{6a,6b}$ = 10.0, $J_{5,6a}$ = 2.0 Hz, 2 H, 6a-H), 3.79 (dd, 2 H, 4-H), 3.68 (d, 2 H, 1b-H), 3.54 (dd, $J_{5,6b}$ = 7.5 Hz, 2 H, 6b-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 139–126 (Ph), 103.5 (C-2), 86.7 (C-3), 82.4 (C-4), 77.4 (C-5), 72.0, 70.3 (CH_2), 69.7 (C-6), 68.3 (CH_2), 61.7 (C-1) ppm. IR: $\tilde{\nu}_{max}$ = 2921, 1714, 1628, 1454, 1363, 1261, 1187, 1107, 1011, 949, 790, 740 cm^{-1}. ESIMS: *m*/*z* (%) = 653 [M + Na]. $C_{36}H_{38}O_{10}$ (630): calcd. C 68.56, H 6.07; found C 68.39, H 6.00.

Macrocyclic DFA Derivatives 42: TfOH (28 μL, 0.33 mmol, 1.5 equiv.) was added at –78 °C under Ar to a solution of **38** (167 mg, 0.223 mmol) in freshly distilled CH_2Cl_2 (29 mL). The mixture was stirred for 10 min and was then allowed to reach room temperature and further stirred for 45 min. Et_3N (8 drops) was then added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/petroleum ether, 1:1 → 4:1, → EtOAc) to give **42** (63 mg, 22%) as an inseparable mixture of diastereomers. R_f = 0.28 (EtOAc/petroleum ether, 2:1). FABMS: *m*/*z* (%) = 1284 [M + Na].

General Procedure for the Preparation of Fully Unprotected DFAs 1–5: Simultaneous removal of xylylene and benzyl groups on DFA derivatives or their mixtures was effected by catalytic hydrogenolysis with Pd/C (10%) at 1 atm in EtOAc/MeOH (1:1) containing formic acid (10%). The identities and relative proportions of diastereomers in the reaction mixtures were determined by GC, by comparison with authentic standards,[1,2,7] after transformation into the corresponding mixtures of fully unprotected DFAs and further derivatisation as the corresponding hexa-*O*-trimethylsilyl derivatives, according to the previously reported protocol.[12,14]

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all new compounds.

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