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Stereoselective synthesis of nonsymmetrical difructose dianhydrides from xylylene-tethered D-fructose precursors

Farida Louis [a,†], M. Isabel García-Moreno [a], Patricia Balbuena [a], Carmen Ortiz Mellet [a,*], José M. García Fernández [b,*]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Profesor García González 1, E-41012 Sevilla, Spain
[b] Instituto de Investigaciones Químicas, CSIC—Universidad de Sevilla, Américo Vespucio 49, Isla de la Cartuja, E-41092 Sevilla, Spain

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Abstract

Nonsymmetrical furanose–pyranose difructose dianhydrides (DFAs), a class of cyclic disaccharides present in foodstuffs, have been prepared in high yield by connecting the reacting monosaccharide moieties through a xylylene bridge prior to triflic acid-promoted bis-spiroketalization. The reaction can then proceed either intra- or intermolecularly, both the regio- and the stereoselectivity being strongly dependent on the spacer length. Noteworthy, the longer *m*- and *p*-xylylene positional isomers led to the thermodynamic α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dyanhydride **1**, the major DFA in commercial caramel, in a stereoselective manner. The shorter *o*-xylylene tether afforded preferentially the elusive contra-thermodynamic β-D-fructofuranose α-D-fructopyranose diastereomer **2**, a trace constituent of caramel. The results have been rationalized in terms of stereoelectronic and conformational properties and offer new perspectives for the preparation of pure DFA standards for analytical and nutritional studies.

Keywords: Spiroketals; Difructose dianhydrides; Fructose; Prebiotics; Xylylene; Spiro-sugars

1. Introduction

The stereocontrolled construction of polyfunctional tricyclic bis-spiroketals, especially the control of the stereochemistry at the two spiroketal centers, continues to present a stimulating challenge in target and diversity oriented synthesis.[1] This substructure is present in a wide range of interesting natural products, including several marine toxins and ionophore antibiotics, and is also the underlying structural element of a unique class of spirodisaccharides isolated from microorganisms and higher plants recently identified as prebiotic food products, namely di-D-fructose dianhydrides (DFAs).[2] Up to 13 different DFA diastereoisomers are formed during the acid or thermal-promoted dimerization–spiroketalization of fructose-containing materials (sucrose, glycosyl fructoses, inulin), being present in dietary foods such as caramel, chicory, fructose syrups, or torrefacted coffee.[3] The implications of this discovery in human nutrition have strongly stimulated research in these and related spiro-sugars.[4]

The structural and stereochemical diversity of DFAs makes these compounds ideal targets for evaluating new spiroketal synthetic methodologies. Almost quantitative conversions of D-fructose and oligosaccharides thereof into DFAs have been achieved by using anhydrous hydrogen fluoride (HF) or pyridinium poly(hydrogen fluoride) complexes as solvents and catalysts.[5] Separation of pure compounds from these multicomponent mixtures becomes, however, extremely difficult, making this approach unsuitable for the preparation of single isomers in most cases.

Fueled by the need of pure DFA standards for the investigation of their impact in the human diet,[6] we recently developed

* Corresponding authors. Tel.: +34 954551519; fax: +34 954624960 (C.O.M.); tel.: +34 954489559; fax: +34 954460565 (J.M.G.F.).
E-mail addresses: mellet@us.es (C.O. Mellet), jogarcia@iiq.csic.es (J.M. García Fernández).
† Present address: Department of Chemistry, Faculty of Sciences, University of Alexandria, PO Box 426, Ibrahimia, 21321 Alexandria, Egypt.

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a new strategy for the stereoselective synthesis of DFAs based on the insertion of an appropriate spacer between the reacting fructose moieties.[7] The methodology takes advantage of the conformational differences at the central 1,4-dioxane ring (chair or boat) in DFA diastereomers as a function of the relative stereochemistry at the spiroketal centers and proved very successful for accessing difuranose (type I) and dipyranose (type III) DFAs (Fig. 1, n=m=1 or 2, respectively).

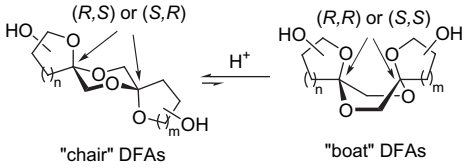


Figure 1. Preferred conformations of bis-spiroketal difructose dianhydrides as a function of the relative configuration at the spiroketal centers.

The situation is much more complicated in the case of furanose–pyranose (n=1, m=2 in Fig. 1; type II) DFAs. The four diastereomeric possibilities are encountered in food products in this case, namely the α,β-, β,α-, di-α-, and di-β-1,2′:2,1′-dianhydrides (**1**–**4**; Fig. 2).[8] Examination of the interatomic distances in 3D molecular models suggested that the chair compounds **1** (thermodynamic) and **2** (contra-thermodynamic[9]) could be obtained selectively by restraining the distance between positions O-6 and O-3′ in appropriately tethered furanose–pyranose precursors.

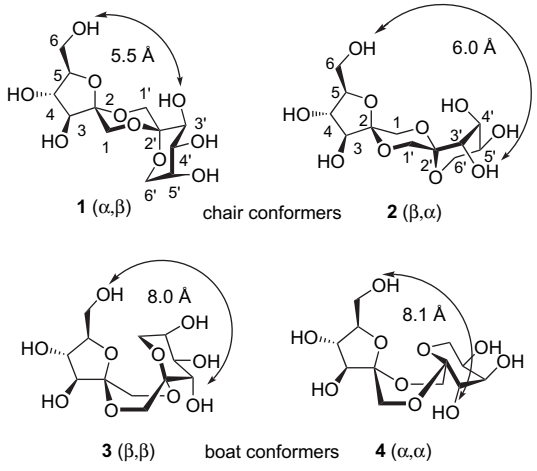


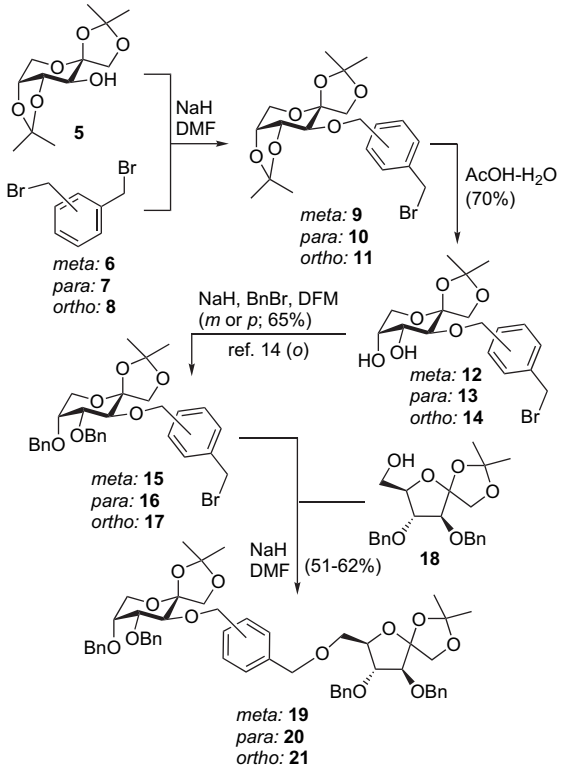
Figure 2. Conformations of the different type II DFA diastereomers with indication of the O-6–O-3′ interatomic distance.

Preliminary results supported the above hypothesis and indicated the possibility of further discriminating between both chair isomers by using xylylene positional isomers as distance restriction elements.[10] We now report the synthesis of the whole series of *m*-, *p*-, and *o*-xylylene-tethered fructose precursors and a complete comparative study of their reactivity. The structure and relative proportions of the products resulting from intra- and intermolecular spiroketalization, as well as the influence of the tether in the stereochemistry at the new spiroketal centers is discussed and rationalized in terms of stereoelectronic and conformational properties.

2. Results and discussion

2.1. Synthesis of xylylene-tethered D-fructose precursors

In order to install the xylylene tether between ring-size anchored D-fructopyranose and D-fructofuranose scaffolds, the reaction sequence depicted in Scheme 1 was implemented.[11]

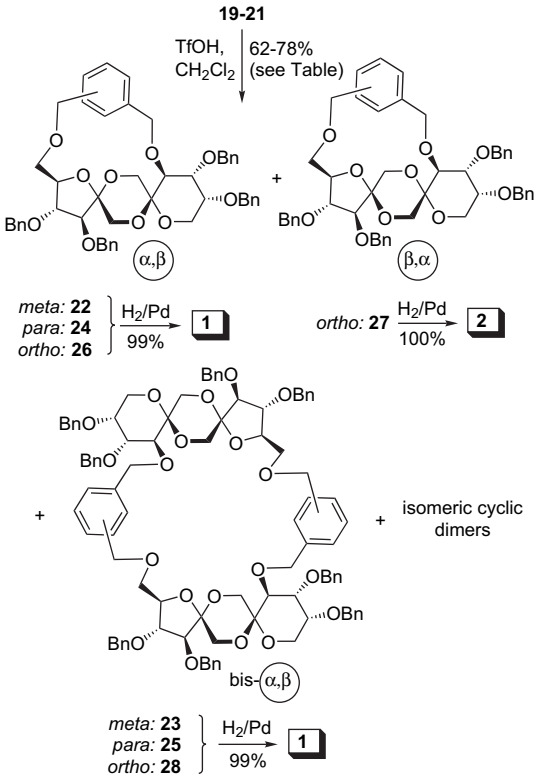


Scheme 1. Tethering reaction sequence for fructofuranose–fructopyranose derivatives.

Etherification of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose[12] (**5**) by reaction with excess of commercial α,α′-dibromoxylene (**6**–**8**) afforded the corresponding monobromobenzyl derivatives **9**–**11**. The *meta* and *para* positional isomers **9** and **10** were transformed into the 4,5-di-*O*-benzyl derivatives **15** and **16**, respectively, through a two-step reaction sequence that involved selective hydrolysis of the nonanomeric isopropylidene group with aq acetic acid (→**12** and **13**) and conventional benzylation with excess of benzyl bromide. The *ortho* isomer **14** affords a cyclic 3,4-*O*-(*o*-xylylene) derivative, resulting from intramolecular etherification reaction, under these conditions.[13] Preparation of the requested bromobenzyl-armed derivative **17** was achieved after transient replacement of the bromo group by chloro following a previously reported procedure.[7a] Nucleophilic displacement of the halogen atom by 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructofuranose[14] (**18**) provided the target xylylene-bridged precursors **19**–**21**.

2.2. Synthesis of fructofuranose–fructopyranose bis-spiroacetals (type II DFAs)

Activation of the xylylene-tethered fructofuranose–fructopyranose derivatives **19** and **20** with trifluoromethanesulfonic acid (TfOH) in dichloromethane promoted the tandem isopropylidene cleavage–glycosylation–spiroketalization transformation. In both cases the intramolecular process led to a single bis-spiroacetal, namely the thermodynamic α,β type II DFA derivative **22** or **24**, respectively. Intermolecular spirocyclization, leading to oligomeric material, was an expected competing reaction. Double bis-spirocyclization leading to macrocyclic dimers was strongly favored as compared to the formation of linear or higher order cyclic oligomers, as seen from mass spectrometry data. The corresponding C_2-symmetric bis-α,β diastereomer **23** or **25** was by far the major compound in this fraction, which is in agreement with the high thermodynamic stability of the α-D-fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydride basic structure. In fact, the first bis-spiroacetal formed in the intermolecular reaction acts as a tether-like template to control the stereochemical issues of the next intramolecular bis-spirocyclization process during macrocyclic ring formation,[15] which further favors the formation of the C_2-symmetric derivative. Not surprisingly, the more rigid *p*-xylylene bridge resulted in higher macrocyclization rates. Nevertheless, simultaneous removal of the xylylene spacer and the benzyl protecting groups could be accomplished in quantitative yield by catalytic hydrogenolysis in both the intramolecular (**22** and **24**) and the intermolecular derivatives (**23** or **25**), leading exclusively to the fully unprotected thermodynamic DFA **1**. Combining these fractions together, the methodology allows accessing **1** (18% in the DFA fraction of commercial caramels) in 71 and 58% yields, respectively, with 100% de (Scheme 2).



Starting material	Products (%)			
	α,β	β,α	bis-α,β	isomeric cyclic dimers
19	**22** (59)	n.d.	**23** (12)	(10)
20	**24** (25)	n.d.	**25** (33)	(14)
21	**26** (30)	**27** (42)	**28** (7)	(6)

Scheme 2. Stereoselective synthesis of type II DFAs.

We hypothesized that shortening the O-6–O-3′ distance in **1** and **2** (5.5–6.0 Å; Fig. 2), by inserting an *o*-xylylene tether (~3 Å), would provoke a substantial steric constrain in their chair ground state conformation upon intramolecular spirocyclization. This situation should be better accommodated by the less rigid contra-thermodynamic β,α isomer **2**. Actually, the thermodynamic (α,β) and contra-thermodynamic (β,α) DFA diastereomers **26** and **27** were now formed in 1:1.5 relative proportion, which represents a 90-fold increase in the selectivity toward the contra-thermodynamic structure as compared with the thermodynamic equilibrium for the unprotected bis-spiroacetals **1** and **2** (the **1/2** relative proportion reaches 60:1 after thermodynamic equilibration). Compound **2** (less than 1% in commercial caramel) was obtained in quantitative yield by hydrogenolysis of **27**. No significant differences were observed, however, in the composition of the dimer fraction as a function of the xylylene positional isomer, the bis-α,β macrocycle **28** being the privileged structure (Scheme 2).

The switch in the stereochemical outcome of the spirocyclization process by acting on the spacer length, in spite of the almost identical interatomic distances between the concerned oxygens in the ground state of both diastereomeric DFAs **1** and **2**, is remarkable. Examination of the ^{1}H NMR data revealed that the *o*-xylylene-tethered α,β-derivative **26** keeps the same conformation at the six-membered rings as compared with the *m*- or *p*-positional isomers **22** and **24** or the unprotected derivative **1**, that is, the central 1,4-dioxane ring in chair conformation and the fructopyranose ring in the $^2C_5$ conformation. Partial steric release can only be achieved at the expenses of conformational distortion of the furanose ring. In contrast, the vicinal proton–proton coupling constants around the α-fructopyranose ring in **27** evidenced a profound conformational change as compared with reported data for DFAs incorporating this structural subunit, including **2**. Thus, the presence of the *o*-xylylene bridge provokes the flip of the $^5C_2$ conformation ($J_{3',4'}$=3.2 Hz for **2**) to the reverse $^2C_5$ disposition ($J_{3',4'}$=7.9 Hz for **27**). Simultaneously, the central 1,4-dioxane ring shifts to a skew–boat arrangement, as seen by NOE contacts, thereby bringing closer the bridged positions ($d_{O\text{-}6\text{–}O\text{-}3'}$=3.2 Å). The energetic cost of loosing an anomeric effect stabilization is then overcome by the release in the steric constrain imposed by the spacer (Fig. 3).

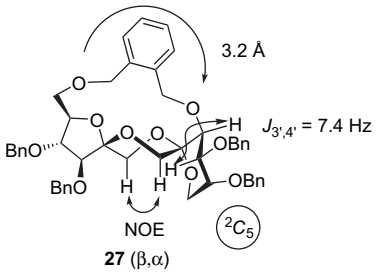


Figure 3. Conformation of **27** as determined by NMR in chloroform-*d* solution with indication of diagnostic data.

3. Summary and conclusions

In summary, the above results broaden the concept of rigid spacer-mediated spirocyclization by taking advantage not only of distance restrictions but also of subtle molecular flexibility differences. Limiting the conformational space during the intramolecular reaction leading to the bis-spiroketal framework, by judicious choice of the spacer and of the linking positions on the reactive subunits, allows discrimination between DFA diastereomers depending on their chair or boat ground state conformation. By additionally introducing steric constrains, the more flexible contra-thermodynamic structures are privileged. The combination of both aspects provides alternative opportunities for the preparation of complex bis-spiroketal frameworks, as illustrated by the rational design of stereoselective syntheses for the nonsymmetrical difructose dianhydrides **1** and **2**.

4. Experimental

4.1. General methods

All solvents and reagents were purchased from commercial sources and used without further purification, except for dichloromethane, which was distilled under Ar stream over CaH_2 and DMF, which was dried over BaO, distilled and kept over 4 Å molecular sieves. Optical rotations were measured at 20 °C in 1-cm or 1-dm tubes. IR spectra were recorded on an FTIR. ^{1}H (and ^{13}C NMR) spectra were recorded at 500 (125.7) or 300 (75.5) MHz. 2D COSY, 2D NOESY, 1D TOCSY, HMQC, and HSQC experiments were used to assist on NMR assignments. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with Kieselgel 60 F254 (E. Merck), with visualization by UV light and by charring with 10% H_2SO_4. The operating conditions for FAB mass spectra were the following: the primary beam consisted of Xe atoms with a maximum energy of 8 keV; the samples were dissolved in thioglycerol, and the positive ions were separated and accelerated over a potential of 7 keV; NaI was added as cationizing agent. For ESI mass spectra, 0.1 pM sample concentrations were used, the mobile phase consisting of 50% aq acetonitrile at 0.1 L min^{-1}. Elemental analyses were performed at the Instituto de Investigaciones Químicas (Sevilla, Spain). Calculations were performed with the MACROMODEL 6.0 package using the MM2* force field and the GB/SA continuous solvent model for water (**1**–**4**) or chloroform (**27**). 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (**5**), 3,4-di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructofuranose[7a] (**18**), and 4,5-di-*O*-benzyl-3-*O*-(2-bromomethylbenzyl)-1,2-*O*-isopropylidene-β-D-fructopyranose[14] (**17**) were prepared according to described procedures.

*4.2. 3-O-(3-Bromomethylbenzyl)-1,2:4,5-di-O-isopropylidene-β-D-fructopyranose (**9**)*

To a solution of 1,3-bis(bromomethyl)benzene (**6**, 1.99 g, 7.56 mmol, 2 equiv) in dry DMF (50 mL), NaH (60% in mineral oil, 378 mg, 9.45 mmol) was added and the suspension was stirred at room temperature for 15 min. 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (**5**, 1.0 g, 3.78 mmol) was then added and the reaction mixture was further stirred for 24 h. Et_2O (15 mL) and water (15 mL) were added, the organic layer was separated, washed with water (5×10 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography (1:10 EtOAc–petroleum ether) to yield **9** (955 mg, 57%); R_f=0.56 (1:3 EtOAc–petroleum ether); $[\alpha]_D$ −88.1 (*c* 1.0, CH_2Cl_2); IR: ν_{max}=3030, 2986, 1512, 1454, 1375, 1217, 1080, 885, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.40–7.26 (m, 4H, Ph), 4.97, 4.65 (2d, 2H, $^2J_{H,H}$=12.1 Hz, C*H*Ph), 4.48 (s, 2H, CH_2Br), 4.38 (dd, 1H, $J_{3,4}$=7.3 Hz, $J_{4,5}$=6.0 Hz, H-4), 4.22 (dd, 1H, $J_{5,6a}$=2.6 Hz, H-5), 4.15 (dd, 1H, $J_{6a,6b}$=13.4 Hz, H-6a), 4.10 (d, 1H, $J_{1a,1b}$=8.5 Hz, H-1a), 4.00 (d, 1H, H-6b), 3.91 (d, 1H, H-1b), 3.49 (d, 1H, H-3), 1.54, 1.50, 1.43, 1.38 (4s, 12H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=139.0–127.5 (Ph), 112.2, 109.0 (*C*Me$_2$), 104.3 (C-2), 77.7 (C-4), 76.2 (*C*H$_2$Ph), 73.8 (C-5), 72.5 (C-1), 71.9 (C-3), 60.1 (C-6), 33.3 (CH_2Br), 28.2, 26.8, 26.2, 26.0 (C*Me*$_2$); FABMS: *m*/*z* 445, 443 (20%, $[M+H]^+$). Anal. Calcd for $C_{20}H_{27}BrO_6$: C, 54.18; H, 6.14. Found: C, 54.26; H, 6.03.

*4.3. 3-O-(4-Bromomethylbenzyl)-1,2:4,5-di-O-isopropylidene-β-D-fructopyranose (**10**)*

Compound **10** (402 mg, 48%) was obtained from **5** (0.5 g, 1.89 mmol) and 1,4-bis(bromomethyl)benzene (**7**, 1.06 g, 7.56 mmol) following the procedure above described for **9**; R_f=0.42 (1:3 EtOAc–petroleum ether); $[\alpha]_D$ −68.0 (*c* 1.0, CH_2Cl_2); IR: ν_{max}=3035, 2986, 1651, 1514, 1454, 1379, 1219, 1090, 874 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.37–7.26 (m, 4H, Ph), 4.96, 4.65 (2d, 2H, $^2J_{H,H}$=12.1 Hz, C*H*Ph), 4.49 (s, 2H, CH_2Br), 4.37 (dd, 1H, $J_{3,4}$=7.5 Hz, $J_{4,5}$=6.0 Hz, H-4), 4.22 (dd, 1H, $J_{5,6a}$=2.5 Hz, H-5), 4.14 (dd, 1H, $J_{6a,6b}$=13.5 Hz, H-6a), 4.08 (d, 1H, $J_{1a,1b}$=8.5 Hz, H-1a), 4.00 (d, 1H, H-6b), 3.90 (d, 1H, H-1b), 3.49 (d, 1H, H-3), 1.53, 1.49, 1.41, 1.38 (4s, 12H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.9–127.8 (Ph), 112.2, 109.0 (*C*Me$_2$), 104.3 (C-2), 77.6 (C-4), 76.3 (*C*H$_2$Ph), 73.7 (C-5), 72.5 (C-1), 71.9 (C-3), 60.1 (C-6), 33.2 (CH_2Br), 28.1, 26.8, 26.1, 26.0 (C*Me*$_2$); FABMS: *m*/*z* 467, 465 (20%, $[M+Na]^+$). Anal. Calcd for $C_{20}H_{27}BrO_6$: C, 54.18; H, 6.14. Found: C, 54.14; H, 6.16.

4.4. 3-O-(3-Bromomethylbenzyl)-1,2-O-isopropylidene-β-D-fructopyranose (12)

Compound **9** (400 mg, 0.9 mmol) was dissolved in 60% aq acetic acid (2.4 mL) and stirred at 45 °C for 2 h. The reaction mixture was then diluted with water (5 mL) and extracted with EtOAc (4×4 mL). The combined organic phase was washed with saturated aq $NaHCO_3$ (6 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by column chromatography (2:1 EtOAc–petroleum ether) to give **12** (254 mg, 70%); R_f=0.44 (2:1 EtOAc–petroleum ether); $[\alpha]_D$ −81.4 (*c* 0.98, CH_2Cl_2); IR: ν_{max}=3428, 2936, 1458, 1379, 1220, 1077, 887, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.42–7.26 (m, 4H, Ph), 4.83, 4.73 (2d, 2H, $^2J_{H,H}$=11.6 Hz, C*H*Ph), 4.48 (s, 2H, CH_2Br), 4.06 (d, 1H, $J_{1a,1b}$=8.7 Hz, H-1a), 4.03 (dd, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=5.0 Hz, H-4), 3.99 (d, 1H, H-1b), 3.98 (m, 1H, H-5), 3.96 (d, 1H, $J_{6a,6b}$=12.4 Hz, H-6a), 3.77 (dd, 1H, $J_{5,6b}$=1.5 Hz, H-6b), 3.67 (d, 1H, H-3), 2.58, 2.52 (2br s, 2H, 2OH), 1.49, 1.44 (2s, 6H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.7–127.7 (Ph), 111.9 (*C*Me_2), 105.5 (C-2), 76.6 (C-3), 74.8 (*C*H_2Ph), 71.8 (C-1), 71.3 (C-4), 69.7 (C-5), 63.6 (C-6), 33.2 (CH_2Br), 26.7, 26.2 (C*Me*$_2$); FABMS: *m/z* 427, 425 (90%, $[M+Na]^+$), 347 (95%, $[M+Na-Br]^+$). Anal. Calcd for $C_{17}H_{23}BrO_6$: C, 50.63; H, 5.75. Found: C, 50.69; H, 5.67.

4.5. 3-O-(4-Bromomethylbenzyl)-1,2-O-isopropylidene-β-D-fructopyranose (13)

Compound **13** (253.9 mg, 70%) was obtained from **10** (400 mg, 0.9 mmol) following the procedure above described for **12**; R_f=0.44 (2:1 EtOAc–petroleum ether); $[\alpha]_D$ −9.9 (*c* 1.0, CH_2Cl_2); IR: ν_{max}=3422, 2988, 1651, 1514, 1454, 1377, 1225, 1090, 876 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.45–7.26 (m, 4H, Ph), 4.82, 4.72 (2d, 2H, $^2J_{H,H}$=11.7 Hz, C*H*Ph), 4.48 (s, 2H, CH_2Br), 4.04 (d, 1H, $J_{1a,1b}$=8.7 Hz, H-1a), 4.01 (m, 1H, H-4), 3.98 (d, 1H, H-1b), 3.96 (dd, 1H, H-5), 3.95 (dd, 1H, $J_{6a,6b}$=12.9 Hz, $J_{5,6a}$=1.5 Hz, H-6a), 3.76 (dd, 1H, $J_{5,6b}$=1.8 Hz, H-6b), 3.66 (d, 1H, $J_{3,4}$=9.3 Hz, H-3), 2.61, 1.72 (2br s, 2H, 2OH), 1.49, 1.42 (2s, 6H, CMe_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=138.1–128.0 (Ph), 111.8 (*C*Me_2), 105.4 (C-2), 76.4 (C-3), 74.6 (*C*HPh), 71.7 (C-1), 71.2 (C-4), 69.6 (C-5), 63.5 (C-6), 33.0 (CH_2Br), 26.6, 26.0 (C*Me*$_2$); FABMS: *m/z* 427, 425 (40%, $[M+Na]^+$). Anal. Calcd for $C_{17}H_{23}BrO_6$: C, 50.63; H, 5.75. Found: C, 50.40; H, 5.67.

4.6. 4,5-Di-O-benzyl-3-O-(3-bromomethylbenzyl)-1,2-O-isopropylidene-β-D-fructopyranose (15)

To a suspension of NaH (60% in mineral oil, 154 mg, 4.0 mmol) and benzyl bromide (1.9 mL, 16 mmol) in dry DMF (5 mL), a solution of **12** (323 mg, 0.80 mmol) in dry DMF (3 mL) was added. The reaction mixture was stirred for 1 h at room temperature, then quenched with H_2O (5 mL), extracted with Et_2O (5×10 mL), the combined organic layer was washed with water (3×15 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified by column chromatography (1:6 EtOAc–petroleum ether) to give **15** (303 mg, 65%); R_f=0.57 (1:3 EtOAc–petroleum ether); $[\alpha]_D$ −9.9 (*c* 1.0, CH_2Cl_2); IR: ν_{max}=3030, 2986, 1645, 1516, 1366, 1244, 1072, 748, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.31–7.23 (m, 14H, Ph), 5.01, 4.63 (2d, 2H, $^2J_{H,H}$=11.7 Hz, C*H*Ph), 4.74, 4.68 (2d, 2H, $^2J_{H,H}$=12.5 Hz, C*H*Ph), 4.59 (s, 2H, CH_2Ph), 4.43 (s, 2H, CH_2Br), 4.01 (d, 1H, $J_{1a,1b}$=8.5 Hz, H-1a), 3.97 (d, 1H, H-1b), 3.92 (dd, 1H, $J_{3,4}$=9.8 Hz, $J_{4,5}$=2.1 Hz, H-4), 3.90 (d, 1H, H-3), 3.81 (m, 1H, H-5), 3.80 (dd, 1H, $J_{6a,6b}$=13.0 Hz, $J_{5,6a}$=1.9 Hz, H-6a), 3.75 (dd, 1H, $J_{5,6b}$=1.4 Hz, H-6b), 1.47, 1.42 (2s, 6H, CMe_2); ^{13}C NMR (127.5 MHz, $CDCl_3$): δ=139.3–127.6 (Ph), 111.9 (*C*Me_2), 105.9 (C-2), 80.1 (C-4), 75.5 (C-3), 74.9 (*C*H_2Ph), 73.3 (C-5), 72.0 (C-1), 71.9, 71.5 (*C*H_2Ph), 61.3 (C-6), 33.5 (CH_2Br), 27.1, 26.3 (C*Me*$_2$); FABMS: *m/z* 607, 605 (35%, $[M+Na]^+$), 527 (25%, $[M+Na-Br]^+$). Anal. Calcd for $C_{31}H_{35}BrO_6$: C, 63.81; H, 6.05. Found: C, 63.80; H, 5.84.

4.7. 4,5-Di-O-benzyl-3-O-(4-bromomethylbenzyl)-1,2-O-isopropylidene-β-D-fructopyranose (16)

Compound **16** (204 mg, 65%) was obtained from **13** (203 mg, 0.50 mmol) following the procedure above described for **15**; R_f=0.26 (1:3 EtOAc–petroleum ether); $[\alpha]_D$ −106.5 (*c* 1.0, CH_2Cl_2); IR: ν_{max}=3030, 2988, 1645, 1516, 1454, 1370, 1223, 1072, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.40–7.26 (m, 14H, Ph), 5.04, 4.66 (2d, 2H, $^2J_{H,H}$=11.8 Hz, C*H*Ph), 4.77, 4.70 (2d, 2H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.61 (s, 2H, CH_2Ph), 4.50 (s, 2H, CH_2Br), 4.02 (d, 1H, $J_{1a,1b}$=8.5 Hz, H-1a), 3.98 (d, 1H, H-1b), 3.94 (m, 1H, H-4), 3.90 (d, 1H, $J_{3,4}$=9.5 Hz, H-3), 3.82 (dd, 1H, $J_{6a,6b}$=13.0 Hz, $J_{5,6a}$=2.0 Hz, H-6a), 3.78 (m, 1H, H-5), 3.76 (dd, 1H, $J_{5,6b}$=1.7 Hz, H-6b), 1.49, 1.43 (2s, 6H, CMe_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=138.9–127.4 (Ph), 111.7 (*C*Me_2), 105.7 (C-2), 79.9 (C-4), 75.2 (C-3), 74.7 (*C*H_2Ph), 73.1 (C-5), 71.8 (*C*H_2Ph), 71.7 (C-1), 71.3 (*C*H_2Ph), 61.2 (C-6), 33.3 (CH_2Br), 26.9, 26.1 (C*Me*$_2$); FABMS: *m/z* 606, 604 (30%, $[M+Na]^+$). Anal. Calcd for $C_{31}H_{35}BrO_6$: C, 63.81; H, 6.05. Found: C, 64.10; H, 6.03.

4.8. General procedure for the preparation of (O-6→O-3′)-xylylene-tethered fructofuranose–fructopyranose derivatives (19–21)

To a solution of 2,3-di-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructofuranose **18** (188 mg, 0.47 mmol) in dry DMF (3 mL), NaH (60% in mineral oil, 46 mg, 0.98 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. A solution of **15**, **16**, or **17** (225 mg, 0.39 mmol) in dry DMF (4 mL) was then added, the reaction mixture was further stirred at room temperature for 3 h, quenched by addition of H_2O (2 mL), concentrated, and the resulting residue was purified by column chromatography using the eluent indicated in each case.

4.8.1. 3,4-Di-O-benzyl-1,2-O-isopropylidene-β-D-fructofuranose 4′,5′-di-O-benzyl-1′,2′-O-isopropylidene-β-D-fructopyranose 6,3′-O-(m-xylylene) (19)

Eluent: 1:6 EtOAc–toluene; yield: 190 mg (54%); R_f=0.47 (1:6 EtOAc–toluene); $[\alpha]_D$ −62.0 (*c* 1.0, $CHCl_3$); ^1H NMR

(500 MHz, $CDCl_3$): δ=7.31–7.22 (m, 24H, Ph), 5.02, 4.62 (2d, 1H, $^2J_{H,H}$=11.5 Hz, C*H*Ph), 4.74, 4.67 (2d, 1H, $^2J_{H,H}$=12.5 Hz, C*H*Ph), 4.68 (s, 2H, CH_2Ph), 4.60, 4.57 (2d, 1H, $^2J_{H,H}$=13.3 Hz, C*H*Ph), 4.60, 4.54 (2d, 1H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.52 (s, 2H, CH_2Ph), 4.10 (m, 2H, H-4, H-5), 4.01 (d, 1H, $J_{1a,1b}$=9.0 Hz, H-1a), 3.99 (d, 1H, $J_{1a',1b'}$=8.5 Hz, H-1′a), 3.98 (d, 1H, $J_{3,4}$= 5.0 Hz, H-3), 3.95 (d, 1H, H-1′b), 3.92 (d, 1H, H-1b), 3.91 (d, 1H, $J_{3',4'}$=9.5 Hz, H-3′), 3.88 (dd, 1H, $J_{4',5'}$=2.8 Hz, H-4′), 3.79 (dd, 1H, $J_{6a',6b'}$=12.8 Hz, $J_{5',6a'}$=2.3 Hz, H-6′a), 3.78 (m, 1H, H-5′), 3.74 (dd, 1H, $J_{5',6b'}$=1.8 Hz, H-6′b), 3.61 (m, 1H, H-6a), 3.55 (m, 1H, H-6b), 1.45, 1.42, 1.40 (3s, 12H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.8–126.9 (Ph), 111.8, 111.5 (*C*Me_2), 109.0 (C-2), 105.9 (C-2′), 84.5 (C-4), 83.1 (C-3), 80.2 (C-5), 80.1 (C-4′), 75.4 (C-3′), 75.3 (*C*H_2Ph), 73.5 (*C*H_2Ph), 73.4 (C-5′), 72.4 (C-6), 72.3, 72.2, 72.0 (*C*H_2Ph), 72.0 (C-1′), 71.5 (*C*H_2Ph), 71.3 (C-1), 61.4 (C-6′), 27.1, 26.4, 26.2 (C*Me*$_2$); FABMS: *m*/*z* 926 (20%, $[M+Na]^+$). Anal. Calcd for $C_{54}H_{62}O_{12}$: C, 71.82; H, 6.92. Found: C, 71.92; H, 7.04.

*4.8.2. 3,4-Di-O-benzyl-1,2-O-isopropylidene-β-D-fructofuranose 4′,5′-di-O-benzyl-1′,2′-O-isopropylidene-β-D-fructopyranose 6,3′-O-(p-xylylene) (**20**)*

Eluent: 1:8 EtOAc–toluene; yield: 216 mg (51%); R_f=0.41 (1:4 EtOAc–toluene); $[\alpha]_D$ −80.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.31–7.24 (m, 24H, Ph), 5.01, 4.63 (2d, 2H, $^2J_{H,H}$=11.5 Hz, C*H*Ph), 4.74, 4.67 (2d, 2H, $^2J_{H,H}$=12.5 Hz, CH_2Ph), 4.68 (s, 2H, CH_2Ph), 4.60 (m, 4H, CH_2Ph), 4.55 (s, 2H, CH_2Ph), 4.10 (m, 2H, H-4, H-5), 4.02 (d, 1H, $J_{1a,1b}$=9.3 Hz, H-1a), 4.00 (d, 1H, $J_{1a',1b'}$=8.6 Hz, H-1′a), 3.99 (d, 1H, $J_{3,4}$=6.2 Hz, H-3), 3.95 (d, 1H, H-1′b), 3.92 (m, 2H, H-1b, H-3′), 3.89 (dd, 1H, $J_{3',4'}$=9.9 Hz, $J_{4',5'}$=2.7 Hz, H-4′), 3.79 (m, 2H, H-5′, H-6′a), 3.74 (dd, 1H, $J_{6'a,6'b}$=12.9 Hz, $J_{5',6'b}$=1.0 Hz, H-6′b), 3.61 (dd, 1H, $J_{6a,6b}$=9.9 Hz, $J_{5,6a}$=6.2 Hz, H-6a), 3.56 (dd, 1H, $J_{5,6b}$=6.1 Hz, H-6b), 1.53–1.39 (m, 12H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.5–127.6 (Ph), 111.8, 111.5 (*C*Me_2), 109.0 (C-2), 105.9 (C-2′), 84.5 (C-4), 83.1 (C-3), 80.2 (C-5, C-4′), 75.3 (C-3′), 75.2 (*C*H_2Ph), 73.4 (C-5′), 73.3 (*C*H_2Ph), 72.3–71.9 (3*C*H_2Ph, C-6, C-1′), 71.5 (*C*H_2Ph), 71.3 (C-1), 61.4 (C-6′), 27.1–26.2 (C*Me*$_2$); ESIMS: *m*/*z* 925.5 ($[M+Na]^+$). Anal. Calcd for $C_{54}H_{62}O_{12}$: C, 71.82; H, 6.92. Found: C, 71.86; H, 7.11.

*4.8.3. 3,4-Di-O-benzyl-1,2-O-isopropylidene-β-D-fructofuranose 4′,5′-di-O-benzyl-1′,2′-O-isopropylidene-β-D-fructopyranose 6,3′-O-(o-xylylene) (**21**)*

Eluent: 1:8→1:6 EtOAc–toluene; yield: 220 mg (62%); R_f=0.47 (1:6 EtOAc–toluene); $[\alpha]_D$ −74.3 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.31–7.22 (m, 24H, Ph), 5.08, 4.69 (2d, 2H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.73, 4.68 (2d, 2H, $^2J_{H,H}$=12.5 Hz, C*H*Ph), 4.67 (s, 2H, CH_2Ph), 4.59, 4.55 (2d, 2H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.58, 4.53 (2d, 2H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.58 (s, 2H, CH_2Ph), 4.09 (m, 2H, H-4, H-5), 4.01 (d, 1H, $J_{1a,1b}$=9.0 Hz, H-1a), 3.97 (d, 1H, $J_{3,4}$=6.5 Hz, H-3), 3.90 (dd, 1H, $J_{3',4'}$=9.5 Hz, $J_{4',5'}$=3.0 Hz, H-4′), 3.90 (d, 1H, H-1b), 3.89 (d, 1H, H-3′), 3.88 (d, 1H, $J_{1a',1b'}$=9.0 Hz, H-1′a), 3.83 (d, 1H, H-1′b), 3.75 (m, 3H, H-5′, H-6′a, H-6′b), 3.57 (dd, 1H, $J_{6a,6b}$=10.0 Hz, $J_{5,6a}$=6.0 Hz, H-6a), 3.54 (dd, 1H, $J_{5,6b}$=6.5 Hz, H-6b), 1.48–1.38 (m, 12H, CMe_2); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.5–127.6 (Ph), 111.7, 111.5 (*C*Me_2), 109.0 (C-2), 105.9 (C-2′), 84.6 (C-4), 83.1 (C-3), 80.2 (C-5), 80.0 (C-4′), 75.0 (C-3′), 73.3 (C-5′), 72.4 (C-6, *C*H_2Ph), 72.3, 72.2, 72.1 (*C*H_2Ph), 71.9 (C-1′), 71.5 (C-1), 71.3, 70.6 (*C*H_2Ph), 61.4 (C-6′), 26.9–26.4 (C*Me*$_2$); FABMS: *m*/*z* 926 (20%, $[M+Na]^+$). Anal. Calcd for $C_{54}H_{62}O_{12}$: C, 71.82; H, 6.92. Found: C, 71.55; H, 6.84.

*4.9. General procedure for the xylylene-mediated stereoselective synthesis of type II DFA derivatives (**22–28**)*

To a solution of the corresponding *m*-, *p*-, or *o*-xylylene-tethered precursor **19**, **20**, or **21** (280 mg, 0.31 mmol) in CH_2Cl_2 (20 mL) at −78 °C under Ar, trifluoromethanesulfonic acid (41 μL) was added. The reaction mixture was allowed to reach room temperature and stirred for 1 h, then quenched by addition of Et_3N (0.1 mL), and concentrated. Column chromatography of the resulting residue (1:3→1:1 EtOAc–petroleum ether for **19** and **20**; 1:5→1:2 EtOAc–petroleum ether for **21**) afforded first the intramolecular reaction products **22**, **24** or **26** and **27**, respectively. A second fraction contained the pure bis(α,β) macrocyclic dimer **23**, **25**, or **28**. A third fraction consisted in an inseparable mixture of isomeric macrocyclic dimers, as seen from mass spectrometry data (see Scheme 2 for relative proportions and isolated yields).

*4.9.1. 3,4-Di-O-benzyl-α-D-fructofuranose 4,5-di-O-benzyl-β-D-fructopyranose 6,3′-O-(m-xylylene) 1,2′:2,1′-dianhydride (**22**)*

Yield: 142 mg (59%); R_f=0.51 (1:2 EtOAc–petroleum ether); $[\alpha]_D$ +10.1 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.32–6.96 (m, 24H, Ph), 5.18, 4.52 (2d, 2H, $^2J_{H,H}$=13.0 Hz, C*H*Ph), 4.75, 4.64 (2d, 2H, $^2J_{H,H}$=12.7 Hz, C*H*Ph), 4.68, 4.60 (2d, 2H, $^2J_{H,H}$=11.5 Hz, C*H*Ph), 4.67 (s, 2H, CH_2Ph), 4.47 (s, 2H, CH_2Ph), 4.51, 4.41 (2d, 2H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.16 (d, 1H, $J_{1a',1b'}$=11.6 Hz, H-1′a), 4.14 (m, 1H, H-5), 4.00 (d, 1H, $J_{3,4}$=2.5 Hz, H-3), 3.99 (m, 1H, H-6a), 3.96 (d, 1H, $J_{1a,1b}$=11.8 Hz, H-1a), 3.94 (dd, 1H, $J_{3',4'}$=9.5 Hz, $J_{4',5'}$=3.2 Hz, H-4′), 3.83 (d, 2H, $J_{6a',6b'}$=12.0 Hz, H-6′a, H-1b), 3.74 (m, 1H, H-6b), 3.72 (m, 1H, H-5′), 3.61 (d, 1H, H-3′), 3.60 (d, 1H, H-6′b), 3.54 (dd, 1H, $J_{4,5}$=7.5 Hz, H-4), 3.39 (d, 1H, H-1′b); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=140.5–124.9 (Ph), 102.3 (C-2), 95.9 (C-2′), 89.0 (C-3), 85.1 (C-4), 80.1 (C-5), 78.9 (C-3′), 78.6 (C-4′), 73.5 (C-5′), 75.8 (*C*H_2Ph), 74.8 (C-6), 74.3, 72.5, 72.3, 71.2 (*C*H_2Ph), 62.5 (C-1′), 62.0 (C-1), 60.3 (C-6′); FABMS: *m*/*z* 809 (60%, $[M+Na]^+$). Anal. Calcd for $C_{48}H_{50}O_{10}$: C, 73.26; H, 6.40. Found: C, 73.07; H, 6.07.

*4.9.2. Macrocyclic dimer (**23**)*

Yield: 28.4 mg (12%); R_f=0.24 (1:2 EtOAc–petroleum ether); $[\alpha]_D$ −27.5 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.16–7.09 (m, 48H, Ph), 4.98, 4.56 (2d, 4H, $^2J_{H,H}$=11.4 Hz, CH_2Ph), 4.74, 4.67 (2d, 4H, $^2J_{H,H}$=12.7 Hz, C*H*Ph), 4.63 (s, 2H, CH_2Ph), 4.64, 4.59 (2d, 4H, $^2J_{H,H}$=11.7 Hz, C*H*Ph), 4.52, 4.48 (2d, 4H, $^2J_{H,H}$=12.4 Hz, C*H*Ph), 4.41, 4.36

(2d, 4H, $^2J_{H,H}$=11.8 Hz, CH_2Ph), 4.33 (d, 2H, $J_{1a,1b}$=11.4 Hz, H-1a), 4.27 (m, 2H, H-5), 4.00 (d, 2H, $J_{3,4}$=1.9 Hz, H-3), 3.99 (dd, 2H, $J_{3',4'}$=9.4 Hz, $J_{4',5'}$=3.2 Hz, H-4′), 3.96 (dd, 2H, $J_{4,5}$=5.4 Hz, H-4), 3.92 (d, 2H, $J_{1a',1b'}$=11.9 Hz, H-1′a), 3.83 (dd, 2H, $J_{6a',6b'}$=12.6 Hz, $J_{5',6a'}$=1.7 Hz, H-6′a), 3.79 (dd, 2H, $J_{6a,6b}$=10.0 Hz, $J_{5,6a}$=3.4 Hz, H-6a), 3.78 (d, 2H, H-1′b), 3.74 (m, 2H, H-5′), 3.71 (d, 2H, H-3′), 3.67 (dd, 2H, $J_{5,6b}$=6.1 Hz, H-6b), 3.56 (d, 2H, H-6′b), 3.39 (d, 2H, H-1b); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.6–127.1 (Ph), 102.4 (C-2), 96.1 (C-2′), 88.9 (C-3), 84.3 (C-4), 81.4 (C-5), 78.3 (C-4′), 77.0 (C-3′), 75.4 (*C*H_2Ph), 73.8 (C-5′, *C*H_2Ph), 72.5, 72.0, 71.7, 71.3 (*C*H_2Ph), 70.6 (C-6), 62.1 (C-1′), 62.0 (C-1), 60.5 (C-6′); ESIMS: *m/z* 1596.5 ([M+Na]$^+$). Anal. Calcd for $C_{96}H_{100}O_{20}$: C, 73.26; H, 6.40. Found: C, 73.13; H, 6.42.

*4.9.3. 3,4-Di-O-benzyl-α-D-fructofuranose 4,5-di-O-benzyl-β-D-fructopyranose 6,3′-O-(p-xylylene) 1,2′:2,1′-dianhydride (**24**)*

Yield: 60.2 mg (25%); R_f=0.5 (2:3 EtOAc–petroleum ether); $[\alpha]_D$ +29.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.72–7.03 (m, 24H, Ph), 4.84, 3.97 (2d, 2H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.74, 4.69 (2d, 2H, $^2J_{H,H}$=12.7 Hz, C*H*Ph), 4.64, 4.56 (2d, 2H, $^2J_{H,H}$=12.1 Hz, C*H*Ph), 4.56 (s, 2H, CH_2Ph), 4.55, 3.67 (2d, 2H, $^2J_{H,H}$=12.2 Hz, C*H*Ph), 4.53 (s, 2H, CH_2Ph), 3.96 (m, 1H, $J_{5',6b'}$=9.8 Hz, $J_{4',5'}$=6.8 Hz, H-5′), 3.90 (t, 1H, $J_{3',4'}$=7.2 Hz, H-4′), 3.78 (m, 2H, H-5, H-6a), 3.73 (m, 1H, $J_{3,4}$=2.6 Hz, H-4), 3.62 (d, 1H, $J_{1a,1b}$=11.0 Hz, H-1a), 3.59 (d, 1H, H-3′), 3.55 (m, 1H, H-6b), 3.44 (d, 1H, $J_{6a',6b'}$=10.0 Hz, H-6′a), 3.31 (d, 1H, H-3), 3.12 (d, 1H, H-1b), 3.09 (d, 1H, H-6′b), 2.79 (d, 1H, $J_{1a',1b'}$=12.5 Hz, H-1′a), 1.14 (d, 1H, H-1′b); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.6–127.4 (Ph), 99.6 (C-2), 92.9 (C-2′), 83.5 (C-3), 83.2 (C-4), 80.6 (C-5), 76.8 (C-4′), 73.4 (C-3′), 72.8, 72.7, 72.6, 72.3 (*C*H_2Ph), 71.9 (C-5′), 71.2 (*C*H_2Ph), 70.9 (C-6), 63.3 (C-1′), 61.7 (C-1), 57.3 (C-6′); ESIMS: *m/z* 809.37 ([M+Na]$^+$). Anal. Calcd for $C_{48}H_{50}O_{10}$: C, 73.26; H, 6.40. Found: C, 73.24; H, 6.62.

*4.9.4. Macrocyclic dimer (**25**)*

Yield: 79.5 mg (33%); R_f=0.44 (1:1 EtOAc–petroleum ether); $[\alpha]_D$ −7.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.50–7.07 (m, 48H, Ph), 5.01, 4.55 (2d, 4H, $^2J_{H,H}$=12.2 Hz, C*H*Ph), 4.73, 4.66 (2d, 4H, $^2J_{H,H}$=12.3 Hz, C*H*Ph), 4.66, 4.60 (2d, 4H, $^2J_{H,H}$=12.4 Hz, C*H*Ph), 4.60, 4.56 (2d, 4H, $^2J_{H,H}$=12.6 Hz, C*H*Ph), 4.56, 4.51 (2d, 4H, $^2J_{H,H}$=12.2 Hz, C*H*Ph), 4.42, 4.37 (2d, 4H, $^2J_{H,H}$=11.7 Hz, C*H*Ph), 4.23 (d, 2H, $J_{1a,1b}$=11.7 Hz, H-1a), 4.20 (m, 1H, H-5), 3.99 (dd, 2H, $J_{3',4'}$=9.6 Hz, $J_{4',5'}$=3.1 Hz, H-4′), 3.96 (d, 2H, $J_{3,4}$=2.1 Hz, H-3), 3.89 (d, 2H, $J_{1a',1b'}$=11.7 Hz, H-1′a), 3.83 (dd, 2H, $J_{6a,6b}$=12.4 Hz, H-6a), 3.76 (d, 2H, H-1b), 3.74 (dd, 2H, $J_{4,5}$=7.8 Hz, H-4), 3.73 (m, 4H, H-5′, H-6′a), 3.67 (d, 2H, H-3′), 3.59 (d, 2H, $J_{6a',6b'}$=10.7 Hz, $J_{5',6b'}$=5.1 Hz, H-6′b), 3.55 (d, 1H, H-6b), 3.26 (d, 1H, H-1′b); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.6–127.5 (Ph), 102.4 (C-2), 96.0 (C-2′), 88.7 (C-3), 84.8 (C-4), 81.3 (C-5), 78.4 (C-4′), 76.8 (C-3′), 75.2 (*C*H_2Ph), 73.7 (C-5′), 73.3, 72.4, 71.9, 71.8, 71.3 (*C*H_2Ph), 71.3 (C-6), 62.1 (C-1, C-1′), 60.5 (C-6′); ESIMS: *m/z* 1595.76 ([M+Na]$^+$). Anal. Calcd for $C_{48}H_{50}O_{10}$: C, 73.26; H, 6.40. Found: C, 72.99; H, 6.28.

*4.9.5. 3,4-Di-O-benzyl-α-D-fructofuranose 4′,5′-di-O-benzyl-β-D-fructopyranose 6,3′-O-(o-xylylene) 1,2′:2,1′-dianhydride (**26**)*

Yield: 70.3 mg (30%); R_f=0.66 (1:1 EtOAc–petroleum ether); $[\alpha]_D$ +4.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.32–7.16 (m, 24H, Ph), 5.53, 4.91 (2d, 2H, $^2J_{H,H}$=14.6 Hz, C*H*Ph), 4.97, 4.63 (2d, 2H, $^2J_{H,H}$=12.0 Hz, C*H*Ph), 4.74, 4.68 (2d, 2H, $^2J_{H,H}$=12.7 Hz, C*H*Ph), 4.68, 4.61 (2d, 2H, $^2J_{H,H}$=10.0 Hz, C*H*Ph), 4.48, 4.40 (2d, 2H, $^2J_{H,H}$=11.7 Hz, C*H*Ph), 4.47, 4.41 (2d, 2H, $^2J_{H,H}$=11.8 Hz, C*H*Ph), 4.06 (d, 1H, $J_{6a,6b}$=12.6 Hz, H-6a), 4.01 (br d, 1H, $J_{4,5}$=8.7 Hz, H-5), 3.98 (dd, 1H, $J_{3',4'}$=9.7 Hz, $J_{4',5'}$=3.1 Hz, H-4′), 3.88 (d, 1H, $J_{3,4}$=3.7 Hz, H-3), 3.86 (d, 1H, $J_{1a,1b}$=13.7 Hz, H-1a), 3.84 (m, 1H, H-6b), 3.72 (dd, H, $J_{6a',6b'}$=11.5 Hz, $J_{5',6a'}$=3.0 Hz, H-6′a), 3.71 (m, 1H, H-5′), 3.70 (d, 1H, H-1b), 3.65 (d, 1H, H-6′b), 3.61 (dd, 1H, H-4), 3.55 (d, 1H, H-3′), 3.39 (d, 1H, $J_{1a',1b'}$=12.0 Hz, H-1′a), 3.05 (d, 1H, H-1′b); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=140.6–126.7 (Ph), 102.0 (C-2), 95.2 (C-2′), 88.8 (C-3), 86.2 (C-4), 79.6 (C-5), 78.9 (C-4′), 74.5 (C-3′), 73.4 (C-5′), 72.9, 72.5, 72.4, 72.0, 71.4 (*C*H_2Ph), 71.2 (C-6), 68.5 (*C*H_2Ph), 62.6 (C-1′), 62.4 (C-1), 60.6 (C-6′); ESIMS: *m/z* 809 [M+Na]$^+$, 825 [M+K]$^+$. Anal. Calcd for $C_{48}H_{50}O_{10}$: C, 73.26; H, 6.40. Found: C, 73.13; H, 6.48.

*4.9.6. 3,4-Di-O-benzyl-β-D-fructofuranose 4′,5′-di-O-benzyl-α-D-fructopyranose 6,3′-O-(o-xylylene) 1,2′:2,1′-dianhydride (**27**)*

Yield: 98 mg (42%); R_f=0.65 (1:1 EtOAc–petroleum ether); $[\alpha]_D$ +18.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.31–7.13 (m, 24H, Ph), 5.34, 4.53 (2d, 2H, $^2J_{H,H}$=10.9 Hz, C*H*Ph), 4.69, 4.64 (2d, 2H, $^2J_{H,H}$=11.1 Hz, C*H*Ph), 4.68, 4.51 (2d, 2H, $^2J_{H,H}$=10.0 Hz, C*H*Ph), 4.68 (s, 4H, CH_2Ph), 4.60, 4.32 (2d, 2H, $^2J_{H,H}$=12.2 Hz, C*H*Ph), 4.59 (d, 1H, $J_{1a,1b}$= 12.5 Hz, H-1a), 4.24 (dt, 1H, $J_{5,6b}$=10.5 Hz, $J_{5,6a}$=$J_{4,5}$=4.5 Hz, H-5), 4.19 (d, 1H, $J_{1a',1b'}$=11.4 Hz, H-1′a), 4.15 (d, 1H, $J_{3',4'}$=7.9 Hz, H-3′), 4.13 (dd, 1H, $J_{3,4}$=6.3 Hz, H-4), 4.05 (dd, 1H, $J_{6a',6b'}$=12.2 Hz, $J_{5',6a'}$=5.8 Hz, H-6′a), 3.87 (d, 1H, H-3), 3.74 (dt, 1H, $J_{4',5'}$=$J_{5',6b'}$=3.0 Hz, H-5′), 3.70 (d, 1H, H-1b), 3.65 (dd, 1H, $J_{6a,6b}$=10.5 Hz, H-6a), 3.60 (t, 1H, H-6b), 3.52 (d, 1H, H-1′b), 3.45 (dd, 1H, H-6′b), 3.41 (dd, 1H, H-4′); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.6–127.2 (Ph), 101.4 (C-2), 97.7 (C-2′), 85.1 (C-4), 84.7 (C-3), 79.0 (C-5), 78.0 (C-3′), 76.3 (C-4′), 72.9, 72.7, 72.0 (*C*H_2Ph), 71.9 (C-6), 71.6 (C-5′), 71.2, 70.9, 70.2 (*C*H_2Ph), 63.8 (C-1′), 61.0 (C-6′), 59.8 (C-1); ESIMS: *m/z* 809 [M+Na]$^+$, 825 [M+K]$^+$. Anal. Calcd for $C_{48}H_{50}O_{10}$: C, 73.26; H, 6.40. Found: C, 73.13; H, 6.06.

*4.9.7. Macrocyclic dimer (**28**)*

Yield: 31.8 mg (7%); R_f=0.47 (1:1 EtOAc–petroleum ether); $[\alpha]_D$ −2.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.30–7.11 (m, 48H, Ph), 4.98, 4.89 (2d, 4H, $^2J_{H,H}$=12.9 Hz, C*H*Ph), 4.97, 4.70 (2d, 4H, $^2J_{H,H}$=11.7 Hz, C*H*Ph), 4.75, 4.68 (2d, 4H, $^2J_{H,H}$=12.5 Hz, C*H*Ph), 4.71, 4.63 (2d, 4H, $^2J_{H,H}$=11.7 Hz, C*H*Ph), 4.52 (s, 4H, CH_2Ph), 4.34, 4.23 (2d, 4H, $^2J_{H,H}$=11.9 Hz,

C*H*Ph), 4.27 (m, 2H, $J_{5,6b}$=6.3 Hz, $J_{5,6a}$=4.2 Hz, H-5), 4.01 (dd, 2H, $J_{3',4'}$=9.8 Hz, $J_{4',5'}$=3.1 Hz, H-4′), 3.95 (dd, 2H, $J_{6a,6b}$= 9.8 Hz, H-6a), 3.92 (m, 4H, H-3, H-4), 3.87 (d, 2H, $J_{1a,1b}$= 12.0 Hz, H-1a), 3.79 (d, 4H, $J_{6a',6b'}$=12.3 Hz, H-6′a, H-1b), 3.76 (d, 2H, H-1′a), 3.73 (m, 2H, H-5′), 3.70 (dd, 2H, H-6b), 3.68 (d, 2H, H-3′), 3.51 (d, 2H, H-6′b), 2.94 (d, 1H, H-1′b); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=138.9–126.8 (Ph), 102.6 (C-2), 95.6 (C-2′), 88.5 (C-3), 84.8 (C-4), 82.3 (C-5), 79.0 (C-4′), 74.1 (C-3′), 73.7 (C-5′), 73.1, 72.7, 72.0 (*C*H_2Ph), 71.3 (*C*H_2Ph), 71.1 (C-6), 70.1 (*C*H_2Ph), 61.9 (C-1′), 61.5 (C-1), 60.6 (C-6′); ESIMS: *m*/*z* 1596 $[M+Na]^+$, 1612 $[M+K]^+$. Anal. Calcd for $C_{48}H_{50}O_{10}$: C, 73.26; H, 6.40. Found: C, 73.22; H, 6.29.

*4.10. α-D-Fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydride (**1**)*

Conventional catalytic hydrogenation of any of the DFA derivatives **22**, **24**, or **26**, or the corresponding dimers **23**, **25**, or **28** (0.038 mmol) with 10% Pd–C in 1:1 EtOAc–MeOH containing 10% HCOOH (0.4 mL) at 1 atm overnight, afforded the fully unprotected bis-spiro fructodisaccharide **1** (12.2 mg, 99%) having physicochemical and spectroscopic properties identical to those reported; $[\alpha]_D$ −39.5 (*c* 1.0, H_2O); lit.[2] $[\alpha]_D$ −39 (*c* 4.0, H_2O). The identity of **1** was additionally confirmed by GC after transformation into the corresponding hexa-*O*-trimethylsilyl derivative, following the protocol previously reported.[3d]

*4.11. β-D-Fructofuranose α-D-fructopyranose 1,2′:2,1′-dianhydride (**2**)*

Conventional catalytic hydrogenation of **27** (30 mg, 0.038 mmol) as above described for the preparation of **1** afforded **2** (12.4 mg, 100%) having physicochemical and spectroscopic properties identical to those reported; $[\alpha]_D$ +5.1 (*c* 1.0 in H_2O); lit.[3c] $[\alpha]_D$ +4.8 (*c* 2.1, H_2O). The identity of **2** was additionally confirmed by GC after transformation into the corresponding hexa-*O*-trimethylsilyl derivative, following the protocol previously reported.[3d]

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