A Novel β-Directing Fructofuranosyl Donor Concept. Stereospecific Synthesis of Sucrose

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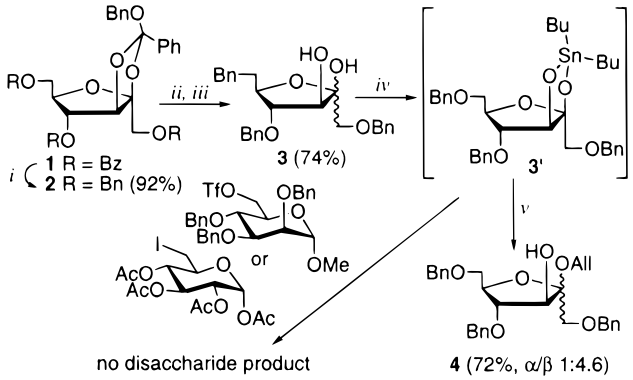
Abstract: A new concept for the construction of β-D-fructofuranosides based on the idea of locking the anomeric CH_2OH group to the α-side through an internal bridge to the 4-hydroxyl group is presented. Thioglycoside fructose donors containing an internal 1,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) (TIPS) acetal bridge have been constructed and used in glycosylations with dimethyl(thiomethyl)sulfonium triflate (DMTST) as promoter. The couplings were stereospecific to give β-D-fructofuranosyl disaccharides in high yields. Using this approach, sucrose has been synthesized stereospecifically in 80% yield.

1. Introduction

β-D-Fructofuranosides are found abundantly in nature, e.g., in plants as a constituent in levan, fructan, and, most well-known, sucrose, and in bacterial polysaccharides.[1] Their synthetic formation is, however, difficult. In glycosylations using fructose donors with participating protecting groups, α-linked products are obtained exclusively, because of neighboring group participation of the 3-*O*-substituent.[2] With nonparticipating groups α-fructofuranosides also predominate, due to their higher thermodynamic stabilities.[2] The synthesis of sucrose is especially problematic, since being a trehalose-type linkage, the stereochemistry at each anomeric center has to be controlled in the same glycosylation reaction. This intricate synthetic problem has been addressed in some classical publications.[3−5] The first chemical synthesis of sucrose was published almost 50 years ago by Lemieux and Huber,[3] who reported a yield of 5.5% in the coupling reaction. These earlier approaches were mainly concerned with optimizing the yield of the α-linked glucose moiety, the problem of α/β-mixture in the fructosyl acceptor residue being ignored. The first approach using fructofuranosyl donors, published in 1996,[2] was severely hampered by the predominant formation of the α-fructofuranoside, but nevertheless compared well with former syntheses using glucopyranosyl donors (about 20% yield).[5] Recently, we applied the internal aglycon delivery approach to fructofuranosides and found that with this method, β-fructofuranosides could be obtained in high yields and with excellent stereocontrol.[6,7] However, stability of the intermediate acetal was sometimes a problem, and this could be especially crucial in the case of sucrose, since the acetal is anomeric and, accordingly, quite labile.[8,9] To solve this problem a novel β-directing fructofuranosyl donor concept has been developed, and this has led to the first stereospecific synthesis of sucrose from glucose and fructose, which we report herein.

Scheme 1[a]



[a] Key: (i) BnBr, KOH, toluene; (ii) H_2SO_4 (0.5M, aqueous), dioxane; (iii) NaOMe, MeOH; (iv) Bu_2SnO, toluene; (v) AllBr, Bu_4NI.

2. Results and Discussion

Since the internal aglycon delivery approach failed both in the synthesis of more complex bacterial oligosaccharide structures containing β-fructofuranoside residues and in the synthesis of sucrose, the quest for a more reliable method to synthesize β-fructofuranosides was launched. Hodosi and Kovác have recently published a method for stereospecific synthesis of β-L-rhamno- and D-mannopyranosides using anomeric alkylation of 1,2-stannylidene acetals.[10] This methodology should be applicable also to β-D-fructofuranosides, in which the hydroxyl group adjacent to the anomeric center is β-oriented, and therefore capable of generating the appropriate 2,3-stannylidene acetal. Attempts to form the stannylidene directly from unprotected fructose failed, and, consequently, a derivative, **3**, was synthesized with only the 2- and 3-hydroxyl groups unprotected. This diol was easily obtained from the known 2,3-benzyl ortho ester **2**[7] (Scheme 1). Treatment of **3** with dibutyltin oxide followed by allyl bromide gave a regiospecific anomeric alkylation to form the allyl glycoside in good yield and with good β-selectivity (α/β 1:4.6). However, the use of glycosyl electrophiles, e.g. methyl 2,3,4-tri-*O*-benzyl-6-*O*-triflyl-α-D-

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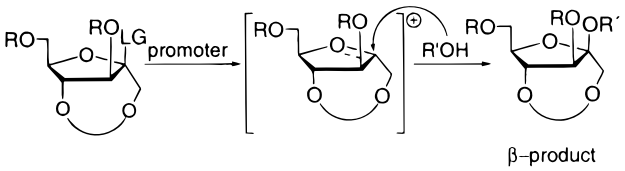
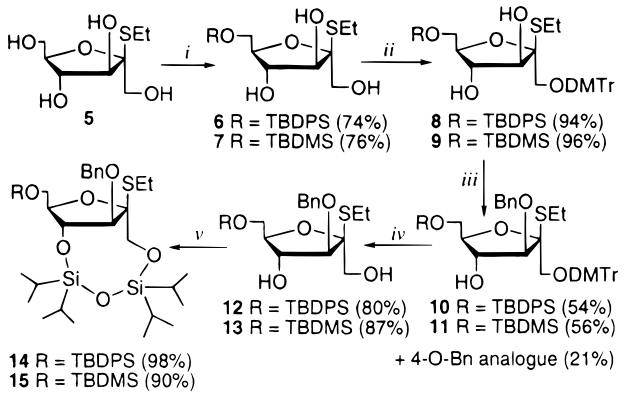
Scheme 2



Scheme 3[a]



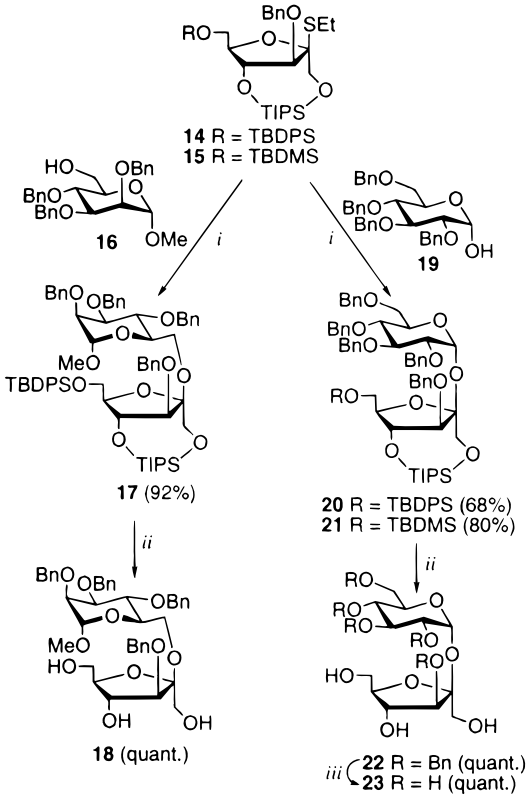
[a] Key: (i) TBDP(M)SCl, pyridine; (ii) DMTrCl, pyridine, DMAP; (iii) BnBr, Bu_4NHSO_4, NaOH (5%, aqueous), CH_2Cl_2; (iv) TFA (1%), Et_3SiH, CH_2Cl_2; (v) $TIPSCl_2$, imidazol, DMF.

mannopyranoside, did not give any alkylation products, i.e., disaccharides, at all.

A new concept was therefore invented, based on the unique feature of fructofuranosides that they contain a CH_2OH group attached to the anomeric position. Thus, instead of locking the anomeric oxygen in the β-position as in **3′**, we decided to lock the CH_2OH group to the α-side through the formation of an internal bridge to the 4-OH substituent. Since the acceptor can only approach from the β-face (Scheme 2), formation of the β-fructofuranoside in the glycosylation should be assured. Accordingly, glycosyl donors **14** and **15**, containing a 1,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) (TIPS) acetal bridge locking C-1 to the α-side, were designed and constructed. Thioglycoside donors were chosen since they are stable during most protecting group manipulations, but at the same time can easily be activated by specific thiophilic promoters.[11,12]

Silylation of ethyl 1-thio-β-D-fructofuranoside, **5**[2], using *tert*-butyldiphenylsilyl chloride (TBDPSCl) in pyridine, gave the 6-*O*-silylated derivative **6** with high regioselectivity (Scheme 3). An original attempt to form the 1,4-TIPS acetal directly from **6** gave exclusively the 1,3-TIPS acetal. Therefore, 3-OH was protected through tritylation of the other primary position (C-1), to give **8**, and consecutive regioselective monobenzylation using phase-transfer conditions,[13] to give the desired 3-*O*-benzyl derivatives **10** in good excess over the 4-*O*-benzyl isomer. Detritylation then yielded the 1,4-diol **12**, which was treated with $TIPSCl_2$ and imidazol to give the target donor **14**. The initial silylation could be performed with equal high regioselectivity by use of the less bulky *tert*-butyldimethylsilyl chloride (TBDMSCl) to yield **7**, which was then processed as discussed for compound **6** to produce the other donor **15**.

Scheme 4[a]



[a] Key: (i) DMTST, DTBMP, CH_2Cl_2; (ii) TAS-F, DMF; (iii) H_2, Pd/C, Amberlite IR-45 resin, MeOH, EtOAc.

With these donors containing the 1,4-TIPS acetal bridge in hand, the concept for the formation of β-fructofuranosides could then be investigated in various glycosylation reactions (Scheme 4). Coupling between model acceptor **16**[14] and donor **14** promoted by dimethyl(methylthio)sulfonium triflate (DMTST)[15] gave, as anticipated, only one product, **17**, in the excellent yield of 92%, as compared to the 77% yield obtained for a corresponding disaccharide using the internal aglycon delivery approach.[6,7] Since it was obvious from NMR that the TIPS acetal was still in place in the disaccharide product, the β-configuration of the fructofuranoside moiety was assumed. However, the assignment of the anomeric configuration in fructofuranosides is not obvious, due to the absence of an anomeric proton. Normally the ^{13}C chemical shift of the anomeric carbon is used as an empirical tool, shifts between 107 and 109 ppm being assigned as α-linkages, and between 103 and 105 ppm as β-linkages.[16] Surprisingly, the shift of the anomeric fructofuranosidic carbon in compound **17** was found to be 109.3 ppm. This anomaly was explained by the assumption that the TIPS-acetal bridge distorts the fructofuranose ring to give abnormal ^{13}C shifts. Indeed removal of the TIPS-acetal (as well as the TBDPS group) by fluoride treatment[17] gave the triol **18**, in which the ^{13}C shift of C-2′ was now at 103.6 ppm, as expected of a β-fructofuranoside.

Although the yield in the formation of disaccharide **17** was an improvement, the results from the attempted synthesis of sucrose were even more satisfying. Thus, coupling of donor **14** with the commercial acceptor **19** (which can be obtained as its

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pure α-anomer through recrystallization from EtOAc) using DMTST as promoter gave the sucrose derivative **20** in 68% yield in a stereospecific glycosylation reaction. The use of the TBDMS-protected donor **15** gave an even better yield, and derivative **21** was formed stereospecifically in 80% yield. To confirm the structure, the compounds were first desilylated to give **22** (C-2′-shift: 103.4 ppm) and then debenzylated to give a product, which was found to be identical in all aspects to sucrose.

In conclusion, by using a new concept involving the locking of C-1 to the α-side through an intramolecular bridge, most effective *β*-directing fructofuranosyl donors have been constructed, which has made it possible to efficiently and stereospecifically synthesize *β*-fructofuranosyl disaccharides. This has allowed the first stereospecific synthesis of sucrose in a high yield.

3. Experimental Section

General Remarks. Organic solutions were dried with $MgSO_4$ before concentration at 30 °C (bath temperature) under reduced pressure. CH_2Cl_2 and pyridine were distilled over CaH_2. NMR spectra were recorded on a Varian 300/400 MHz spectrometer at 25 °C in $CDCl_3$ with Me_4Si as internal standard ($\delta = 0$ ppm). A Gilson 305/306 chromatograph with a Dynamax 60A (Si 111-c) column and a UV detector was used for HPLC. TLC was performed on silica gel F_{254} (E. Merck) plates using UV light and/or charring with 8% aqueous sulfuric acid for detection. Silica gel Merck 60 (0.040−0.063 mm) was used for column chromatography. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

1,4,6-Tri-*O*-benzyl-2,3-*O*-[1-(benzyloxy)benzylidene]-*β*-D-fructofuranose (2). KOH (4 g, 71.2 mmol) was added to a solution of compound **1**[18] (3.2 g, 4.65 mmol) in toluene (30 mL). The solution was stirred for 3 min, whereafter benzyl bromide (15 mL) was added. The mixture was refluxed for 5 h, then cooled, diluted with CH_2Cl_2 (50 mL), washed with water (3 × 20 mL), dried, and concentrated. The product was purified on a column of silica gel (toluene−EtOAc 20:1) to yield **2** (2.7 g, 4.3 mmol, 92%). The melting point and NMR data correspond to the previously published data.[7]

1,4,6-Tri-*O*-benzyl-D-fructofuranose (3). Compound **2** (2.55 g, 3.9 mmol) was dissolved in dioxane (50 mL) and aqueous H_2SO_4 (5.2 mL, 0.5M) was added. The mixture was refluxed for 3 h and then concentrated to a volume of approximately 5−10 mL, diluted with CH_2Cl_2 (60 mL), washed with $NaHCO_3$ (aqueous saturated) and water, dried ($MgSO_4$), and concentrated. MeOH (20 mL) was added to the residual yellow syrup, and the solution was treated with methanolic MeONa (1 mL, 1 M). After 2 h the mixture was neutralized with Dowex 50 (H^+) ion-exchange resin, filtered, and concentrated. The residue was purified by column chromatography (toluene−EtOAc 5:1) to give **3** (2.9 g, 6.5 mmol, 74%, α:*β* 1:3.4). ^{13}C NMR ($CDCl_3$): **3**α, *δ* 69.78, 70.72, 72.13, 73.66, 77.53, 83.05, 85.34, 106.45; **3***β*, *δ* 70.24, 71.18, 71.81, 73.66, 77.64, 80.59, 83.86, 102.83, 127.66−137.82.

Allyl 1,4,6-Tri-*O*-benzyl-D-fructofuranoside (4). Bu_2SnO (119 mg, 0.48 mmol) was added to a solution of compound **3** (200 mg, 0.44 mmol) in toluene (70 mL, Na-dried). Toluene (50 mL) was distilled off and the remaining mixture was refluxed for 1 h, whereafter allyl bromide (76 *μ*L, 0.88 mmol) and Bu_4NI (162 mg, 0.44 mmol) were added. The reaction mixture was refluxed for 5 h more and then cooled, concentrated, and purified on a silica gel column (toluene−EtOAc 7:1) to yield **4** (150 mg, 0.32 mmol, 72%) as a mixture of anomers (α:*β* 1:4.6); $[\alpha]_D$ 15 (*c* 1.15, $CHCl_3$). ^{13}C NMR ($CDCl_3$): **4**α, *δ* 70.07, 70.85, 71.72, 71.79, 73.25, 73.74, 81.64, 82.72, 86.23, 105.54, 117.15, 137.93; **4***β*, *δ* 70.55, 71.72, 71.79, 72.15, 73.47, 73.58, 79.86, 83.24, 83.56, 102.37, 117.61, 134.09, 126.9−137.9. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.41; H, 7.05.

Ethyl 3-*O*-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-1,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-thio-*β*-D-fructofuranoside (14). *tert*-Butyldiphenylsilyl chloride (2.66 mL, 10.38 mmol) dissolved in pyridine (10 mL) was added under N_2 to a cooled (−20 °C) solution of **5**[2] (1.94 g, 8.65 mmol) in freshly distilled pyridine (20 mL). The reaction mixture was allowed to attain room temperature and stirred overnight, and the reaction was then quenched by adding MeOH (3 mL). Concentration and purification of the product by silica gel column chromatography ($CHCl_3$−MeOH 12:1) gave ethyl 6-*O*-*tert*-butyldiphenylsilyl-2-thio-*β*-D-fructofuranoside (**6**) (2.57 g, 5.55 mmol, 74%). $[\alpha]_D$ −48 (*c* 0.62, $CHCl_3$). ^{13}C NMR ($CDCl_3$): *δ* 14.84, 19.22, 20.78, 26.84, 65.05, 65.13, 77.53, 79.48, 82.94, 94.72, 127.77−135.58. Dimethoxytrityl chloride (0.88 g, 2.56 mmol) in pyridine (6 mL) was added under N_2 to a solution of **6** (0.90 g, 2.16 mmol) and 4-(dimethylamino)pyridine (27 mg, 0.2 mmol) in freshly distilled pyridine (15 mL). The mixture was stirred for 4 h, when MeOH (2 mL) was added. The mixture was concentrated and the residue applied to a silica gel column. Elution (toluene−EtOAc 6:1 + 1% Et_3N) gave ethyl 6-*O*-*tert*-butyldiphenylsilyl-1-*O*-(4,4′-dimethoxytriphenyl)methyl-2-thio-*β*-D-fructofuranoside (**8**) (2.8 g, 3.66 mmol, 94%). $[\alpha]_D$ −12 (*c* 1.63, $CHCl_3$). NMR ($CDCl_3$, filtered through basic Al_2O_3): ^{13}C, *δ* 14.50, 19.21, 21.28, 26.78, 55.08, 64.88, 67.00, 77.01, 80.10, 82.47, 94.15, 116.85−158.01; ^{1}H, *δ* 0.80 (s, t, 12H), 2.40 (m, 2H), 3.29 (d, 1H, $J = 9.9$ Hz), 3.41 (d, 1H, $J = 9.9$ Hz), 3.75 (s, 6H), 3.84 (m, 2H), 4.10 (m, 1H), 4.37 (t, 1H), 4.48 (d, 1H, $J = 6.9$ Hz), 6.78−7.8 (m). Compound **8** (1.99 g, 2.6 mmol), Bu_4NHSO_4 (0.23 g, 0.68 mmol, 0.26 equiv), and benzyl bromide (0.54 mL, 4.41 mmol) were dissolved in CH_2Cl_2 (50 mL). NaOH (5% aqueous, 3.7 mL) was added and the mixture was refluxed for 5 days and then cooled to room temperature. The organic phase was separated, washed with water (15 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (toluene−EtOAc, 43:1 + 1% Et_3N) to give ethyl 4-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-*O*-(4,4′-dimethoxytriphenyl)methyl-2-thio-*β*-D-fructofuranoside (0.47 g, 0.55 mmol, 21%) and ethyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-*O*-(4,4′-dimethoxytriphenyl)methyl-2-thio-*β*-D-fructofuranoside (**10**) (1.2 g, 1.4 mmol, 54%). **10**: $[\alpha]_D$ −15 (*c* 0.45, $CHCl_3$). NMR ($CDCl_3$, filtered through basic Al_2O_3): ^{13}C, *δ* 15.04, 19.52, 21.61, 27.22, 55.49, 65.34, 67.38, 72.96, 77.57, 82.13, 85.42, 93.58, 113.33−158.56; ^{1}H, *δ* 0.90 (st, 12H), 2.40 (m, 2H), 3.16 (d, 1H, $J = 10.2$ Hz), 3.58 (d, 1H, $J = 10.2$ Hz), 3.75 (s, 6H,), 3.89 (m, 2H), 4.10 (m, 1H), 4.38 (d, 1H, $J = 11.8$ Hz), 4.51 (m, 2H), 4.55 (d, 1H, $J = 12$ Hz), 6.75−7.79 (m, 28H). TFA in CH_2Cl_2 (1%, 5 mL, 0.65 mmol, 0.75 equiv) was added to a solution of **10** (0.75 g, 0.87 mmol) and Et_3SiH (0.24 mL, 1.47 mmol) in $CHCl_3$ (30 mL). The mixture was stirred for 2 h when water (15 mL) was added. The organic phase was separated, washed with $NaHCO_3$ (aqueous saturated, 15 mL) and water (15 mL), and dried ($MgSO_4$). After evaporation of the solvent, the resulting crude syrup was applied to a column of silica gel and eluted (toluene−EtOAc 6:1) to give ethyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2-thio-*β*-D-fructofuranoside (**12**) (0.38 g, 0.69 mmol, 80%). $[\alpha]_D$ −65 (*c* 1.92, $CHCl_3$). NMR ($CDCl_3$): ^{13}C, *δ* 14.77, 19.19, 20.63, 26.77, 64.96, 65.26, 72.81, 77.65, 82.32, 85.29, 93.87, 127.46−137.71; ^{1}H, *δ* 1.11 (st, 12H), 2.45 (q, 2H), 3.61 (m, 1H), 3.72 (m, 1H), 3.84 (m, 2H), 3.96 (q, 1H), 4.27 (d, 1H, $J = 7.3$ Hz), 4.52 (m, 1H), 4.67 (d, 1H, $J = 11.7$ Hz), 4.81 (d, 1H, $J = 11.7$ Hz,), 7.20−7.79 (m). Compound **12** (0.32 g, 0.58 mmol) and imidazol (0.18 g, 2.55 mmol) were dissolved in DMF (10 mL). The mixture was stirred under argon and cooled to −35 °C. TIPS-chloride (0.24 mL, 0.75 mmol) was added dropwise and the reaction mixture was allowed to attain room temperature while stirring for 3 h, when MeOH (4 mL) was added. The solvents were coevaporated with toluene and the crude residue was applied to a column of silica gel and eluted (light petroleum bp 60−70 °C−EtOAc 25:1) to afford **14** (0.46 g, 0.57 mmol, 98%). $[\alpha]_D$ −2.4 (*c* 0.71, $CHCl_3$). NMR ($CDCl_3$): ^{13}C, *δ* 12.55, 13.54, 13.64, 14.07, 14.75, 17.12−17.44, 19.26, 21.87, 26.74, 63.94, 64.09, 72.59, 78.94, 85.82, 89.03, 97.73, 127.16−135.31; ^{1}H, *δ* 0.90 (m, 9H), 2.59 (q, 2H), 3.80 (m, 3H), 4.17 (m, 2H), 4.28 (s, 1H), 4.58 (m, 3H), 7.20−7.70 (m). Anal. Calcd for $C_{43}H_{66}O_6SSi_3$: C, 64.94; H, 8.36. Found: C, 64.85; H, 8.49.

Ethyl 3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2-thio-*β*-D-fructofuranoside (15). Compound **5**[2] (1.94 g, 8.65 mmol) was silylated with *tert*-butyldimethylsilyl chloride (1.57 g, 10.38 mmol) as described above in the preparation of compound **6** to give, after silica gel chromatography ($CHCl_3$−MeOH 14:1), ethyl 6-*O*-*tert*-butyldimethylsilyl-2-thio-*β*-D-fructofuranoside (**7**)

(18) Helferich, B.; Bottenbruch, L. *Chem. Ber.* **1953**, *86*, 651−657.

(2.22 g, 6.57 mmol, 76%). $[\alpha]_D$ −65 (*c* 0.31, $CHCl_3$). ^{13}C NMR ($CDCl_3$): δ −5.31, −5.35, 14.95, 18.42, 20.75, 25.92, 64.56, 64.68, 77.10, 78.37, 82.90, 94.34. Derivative **7** (2.16 mmol) was tritylated as **6** above to yield (toluene−EtOAc 6:1 + 1% Et_3N) ethyl 6-*O*-*tert*-butyldimethylsilyl-1-*O*-(4,4′-dimethoxytriphenyl)methyl-2-thio-β-D-fructofuranoside (**9**) (2.8 g, 3.66 mmol, 96%). $[\alpha]_D$ −17 (*c* 0.39, $CHCl_3$). NMR ($CDCl_3$, filtered through basic Al_2O_3): ^{13}C, δ −5.40, −5.47, 14.57, 18.35, 21.45, 25.88, 55.09, 64.32, 67.30, 77.99, 80.68, 82.82, 94.67; ^1H, δ 0.094 (s, 6H), 0.91 (s, 9H), 1.14 (t, 3H), 2.49 (m, 2H), 3.31 (d, 1H, J = 9.9 Hz), 3.37 (d, 1H, J = 9.9), 3.77 (s, 6H), 3.84 (m, 2H), 3.99 (m, 1H), 4.27−4.28 (m, 2H), 6.83−7.49 (m). Compound **9** (1.98 g, 2.6 mmol) was benzylated as described for compound **8** above to give, after silica gel column chromatography (toluene−EtOAc 20:1 + 1% Et_3N), ethyl 4-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-1-*O*-(4,4′-dimethoxytriphenyl)-2-thio-β-D-fructofuranoside (0.42 g, 0.57 mmol, 22%) and ethyl 3-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-1-*O*-(4,4′-dimethoxytriphenyl)-2-thio-β-D-fructofuranoside (**11**) (1.06 g, 1.45 mmol, 56%). **11**: $[\alpha]_D$ 24 (*c* 0.53, $CHCl_3$). NMR ($CDCl_3$, filtered through basic Al_2O_3): ^{13}C, δ −5.39, −5.46, 14.57, 18.35, 21.44, 25.85, 55.07, 64.31, 67.29, 77.97, 80.66, 82.80, 86.63, 94.65, 127.39−137.75; ^1H, δ 0.09 (s, 6H), 0.92 (s, 9H), 1.10 (t, 3H), 2.44 (m, 2H), 3.19 (d, 1H, J = 10.3), 3.58 (d, 1H, J = 10.3 Hz), 3.75 (s, 6H), 3.80 (m, 2H), 4.02 (m, 1H), 4.41 (d, 1H, J = 12.1 Hz), 4.46 (m, 2H), 4.55 (d, 1H, J = 12.1 Hz), 6.77−7.46 (m). Compound **11** (0.64 g, 0.87 mmol) was detritylated as described for compound **10** above. After silica gel chromatography (toluene−EtOAc 4:1) ethyl 3-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-2-thio-β-D-fructofuranoside (**13**, 0.32 g, 0.75 mmol, 87%) was obtained. $[\alpha]_D$ −73.3 (*c* 0.6, $CHCl_3$). NMR ($CDCl_3$, filtered through basic Al_2O_3): ^{13}C, δ −4.72, 15.59, 18.97, 21.40, 26.52, 65.26, 65.96, 73.53, 78.70, 83.11, 85.93, 94.71, 128.22−138.46; ^1H, δ 0.08 (s, 6H), 0.90 (s, 9H), 1.20 (t, 3H), 2.57 (m, 2H), 3.61 (d, 1H, J = 12.1 Hz), 3.75−3.89 (m, 5H), 4.27 (d, 1H, J = 7.1 Hz), 4.46 (t, 1H), 4.67 (d, 1H, J = 11.8 Hz), 4.80 (d, 1H, J = 11.8 Hz), 7.26−7.41 (m). Compound **13** (0.25 g, 0.58 mmol) was acetalized as described for compound **12** above, to give **15** (0.35 g, 0.52 mmol, 90%) after silica gel chromatography (light petroleum bp 40−60 °C). $[\alpha]_D$ −32.5 (*c* 0.2, $CHCl_3$). NMR ($CDCl_3$): ^{13}C, δ 12.78, 13.67, 13.85, 14.22, 15.06, 17.64−17.36, 18.30, 22.13, 25.95, 63.94, 64.44, 73.02, 79.14, 86.11, 89.40, 97.89, 127.16−135.31; ^1H, δ 0.08 (s, 6H), 0.90 (m, 9H), 2.69 (q, 2H), 3.72 (m, 2H), 3.86 (d, 1H, J = 11.7 Hz) 4.17 (d, 1H, J = 11.7 Hz), 4.28 (s, 1H), 4.63 (m, 3H), 7.21−7.50 (m). Anal. Calcd for $C_{33}H_{62}O_6SSi_3$: C, 59.05; H, 9.31. Found: C, 58.91; H, 9.16.

General Glycosylation Procedure. The acceptor (63 μmol), the donor (1−2 equiv), and di-*tert*-butylmethylpyridine (DTBMP, 63 μmol) were dissolved in distilled CH_2Cl_2 (5−10 mL) containing crushed molecular sieves (4 Å, 0.2−0.4 g). The mixture was stirred under argon for 15 min (at room temperature) after which DMTST (4 equiv) was added and stirring continued for 2 h. The reaction was quenched by adding Et_3N (0.3 mL), diluted with CH_2Cl_2 (30 mL), filtered through Celite, and concentrated. The residue was purified by flash chromatography on a silica gel column.

General Desilylation Procedure. TAS-F[17] (1.3 M) in DMF (5 equiv) was added to a solution of the disaccharide (30−50 μmol) in DMF (5−8 mL) and the mixture stirred. When TLC indicated the reaction to be complete (approximately 1 h), the mixture was diluted with EtOAc (50 mL) and washed with a buffer solution from Reagecon (pH 7, 30 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried and concentrated, and the residue was purified first by silica gel flash chromatography and then by HPLC.

Methyl (3-*O*-Benzyl-β-D-fructofuranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (18). Donor **14** (50 mg, 63 μmol) and acceptor **16**[14] (32 mg, 63 μmol) were coupled according to the general procedure. Flash chromatography (light petroleum bp 40−65 °C−EtOAc 10:1) yielded methyl [3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-fructofuranosyl]-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**17**, 69 mg, 58 μmol, 92%). NMR ($CDCl_3$): ^{13}C, δ 12.55, 13.48, 13.55, 13.68, 16.96−17.41, 19.24, 26.79, 54.29, 61.76, 62.24, 63.98, 7134, 71.97, 72.30, 72.97, 74.61, 74.73, 79.35, 80.25, 82.38, 87.12, 90.92, 98.42, 109.32, 127.16−135.31; ^1H, δ 0.78 (m, 37H), 3.18 (s, 3H), 3.42 (m, 10H), 4.02 (m, 3H), 4.42 (m, 7H), 4.79 (d, 1H, J = 11.2 Hz), 5.57 (s, 1H), 7.01 (m, 30H). Desilylation of **17** according to the general procedure afforded, after column chromatography ($CHCl_3$−MeOH 10:1) and HPLC (*n*-hexanes−EtOAc 1:2), **18** in quantitative yield. $[\alpha]_D$ −6.9 (*c* 1.22, $CHCl_3$). NMR ($CDCl_3$): ^{13}C, δ 54.83, 61.02, 61.77, 63.43, 71.45, 72.06, 72.40, 72.55, 74.01, 74.50, 74.54, 75.06, 79.89, 81.60, 85.79, 98.82, 103.63, 127.46−136.35; ^1H, δ 3.27 (s, 3H), 3.61 (m, 11H), 4.02 (m, 2H), 4.39 (m, 1H), 4.62 (m, 8H), 7.10 (m, 20H). Anal. Calcd for $C_{41}H_{48}O_{11}$: C, 68.70; H, 6.75. Found: C, 68.52; H, 6.92.

2,3,3′,4,6-Penta-*O*-benzylsucrose (22). Donor **14** (100 mg, 0.12 mmol) and acceptor **19** (34 mg, 63 μmol) were coupled according to the general procedure. The product was purified by flash chromatography (toluene−EtOAc 25:1) to produce 2,3,3′,4,6-penta-*O*-benzyl-6′-*O*-*tert*-butyldiphenylsilyl-1′,4′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)sucrose (**20**, 54 mg, 43 μmol, 68%). NMR ($CDCl_3$): ^{13}C, δ 12.32, 12.78, 13.34, 13.67, 17.28−17.43, 19.25, 26.80, 60.22, 64.24, 68.08, 70.69, 71.46, 73.15, 73.22, 74.88, 75.28, 78.63, 79.32, 81.73, 81.95, 87.77, 91.01, 110.05, 127.28−139.15; ^1H, δ 0.72 (m, 37H), 3.39 (m, 22H), 5.14 (d, 1H, J = 12 Hz), 5.71 (d, 1H, J = 3.3 Hz), 6.83 (m, 35H). Donor **15** (43 mg, 63 μmol) and acceptor **19** (34 mg, 63 μmol) were coupled according to the general procedure and the product was purified by flash chromatography (toluene−EtOAc, 18:1) to produce 2,3,3′,4,6-penta-*O*-benzyl-6′-*O*-*tert*-butyldimethylsilyl-1′,4′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)sucrose (**21**, 57 mg, 50 μmol, 80%). NMR ($CDCl_3$): ^{13}C, δ −5.20, −5.27, 12.31, 13.67, 13.85, 14.56, 17.36−17.64, 18.09, 25.79, 60.03, 60.22, 63.56, 67.98, 70.64, 71.23, 73.09, 73.21, 74.81, 75.17, 77.31, 78.24, 81.63, 81.72, 87.84, 91.01, 109.92, 127.28−139.15; ^1H, δ −0.15 (s, 6H), 0.7 (m, 37H), 3.38 (m, 12H), 4.32 (m, 10H), 4.96 (d, 1H, J = 11.8 Hz), 5.27 (d, 1H, J = 3.5 Hz), 7.14 (m, 25 Hz). Compounds **20** and **21** were desilylated according to the general procedure. After column chromatography (toluene−EtOAc, 1:1) and HPLC ($CHCl_3$−MeOH 20:1) **22** was obtained in quantitative yield. $[\alpha]_D$ 2.5 (*c* 0.66, $CHCl_3$). NMR ($CDCl_3$): ^{13}C, δ 59.17, 63.70, 66.58, 70.69, 71.77, 72.39, 72.56, 73.66, 73.75, 74.47, 76.34, 77.42, 80.84, 80.90, 86.75, 89.71, 103.39, 127.28−138.50; ^1H, δ 3.58 (m, 14H), 4.35 (m, 10H), 4.96 (d, 1H, J = 11.6 Hz), 5.27 (d, 1H, J = 3.5 Hz). Anal. Calcd for $C_{47}H_{52}O_{11}$: C, 71.19; H, 6.61. Found: C, 71.03; H, 6.45.

***β*-D-Fructofuranosyl α-D-Glucopyranoside, Sucrose (23).** Compound **22** (82 mg, 0.1 mmol) was dissolved in MeOH−EtOAc (5:1, 8 mL). Amberlite IR-45(OH^-) resin (83 mg) and palladium on activated carbon were added. The mixture was hydrogenolysed at 110 psi overnight, filtered twice through Celite, and concentrated. Lyophilisation of the concentrate gave **23** (34 mg, 0.1 mmol, 100%). NMR data and optical rotation were identical with data from sucrose.

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