Synthesis of D-Fructofuranosides Using Thioglycosides as Glycosyl Donors

Christian Krog-Jensen and Stefan Oscarson*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden

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Benzylated and benzoylated ethyl thioglycosides of D-fructofuranose have been synthesized and tested as glycosyl donors in couplings to various primary and secondary carbohydrate acceptors. Treatment of 2-*O*-acetyl-1,3,4,6-tetra-*O*-benzoyl-D-fructofuranose with ethyl mercaptan in a BF_3·-etherate-promoted reaction gave the benzoylated ethyl 2-thio-α,*β*-D-fructofuranosides, which after deacylation and benzylation afforded the benzylated derivatives. These thiofructofuranosides, using dimethyl(methylthio)sulfonium triflate (DMTST) or *N*-iodosuccinimide as promoter, were found to be excellent donors, which gave disaccharide coupling products in quantitative or almost quantitative yields with all tested acceptors, yields rarely found in oligosaccharide synthesis. The benzoylated donors gave only α-linked fructofuranosides, due to participation of the 3-*O*-benzoyl group, whereas the benzylated donors gave α/*β*-mixtures.

Introduction

Apart from in sucrose, D-fructofuranosides are also found in nature in bacterial polysaccharides and in plant polysaccharides.[1] Generally, D-fructose occurs as *β*-furanosyl residues; the only known exceptions are D-fructans from *Zymomonas mobilis* and *Yersinia intermedia*, which contain both α- and *β*-furanosidic residues.[2,3] Our interest in synthesizing structures from some of the bacterial polysaccharides, which contain *β*-linked fructofuranosides, made us look for adequate glycosylation methods. Syntheses of D-fructofuranosides using fructofuranosyl donors are not very frequent; *e.g.*, most syntheses of sucrose have been performed with glucosyl donors and fructosyl acceptors. Kotchetkov *et al.* have used fructofuranosyl thioorthoesters and thioglycosides as donors in combination with tritylated acceptors,[4,5] and recently, Schmidt *et al.* investigated the use of anomeric phosphites as donors in the synthesis of fructofuranosides.[6] Considering our earlier successful use of thioglycosides as glycosyl donors, we decided to further evaluate the use of these donors in the synthesis of fructofuranosides. Both benzoylated and benzylated ethyl α- and *β*-2-thio-D-fructofuranosides were synthesized and tested as donors in couplings with different carbohydrate acceptors and promoters.

Results and Discussion

In their publication, the Russian workers synthesized benzoylated ethyl 2-thio-D-fructofuranosides through rearrangement of the corresponding thioorthoesters.[5] We found it more convenient and high-yielding to prepare the thioglycoside directly from 2-*O*-acetyl-1,3,4,6-tetra-*O*-benzoyl-D-fructofuranose[7] (**1**) and ethyl mercaptan in a BF_3·etherate-promoted reaction. The yield was 95% of an inseparable α/*β*-mixture (**2**). As observed by the Russian workers, this mixture could be separated after deacylation to give in quantitative yield 57% of the α-anomer **3**α and 43% of the *β*-anomer **3***β*, which were benzylated to give the other donors **4**α and **4***β*, in 80 and 76% yield, respectively (Scheme 1).

As acceptor compounds **5**,[8] **6**,[9] and **7** were chosen, one primary alcohol acceptor and two secondary, the latter of interest for the synthesis of the *β*-fructofuranosidic-containing repeating unit of the capsular polysaccharide from *Haemophilus influenzae* type e.[10]

Dimethyl(methylthio)sulfonium triflate (DMTST)[11] and *N*-iodosuccinimide (NIS)[12,13] were used as promoters. *N*-Bromo and -chlorosuccinimide as well as methyl triflate and a heterogenous catalyst, silver aluminum silicate,[14] were also tried together with the benzylated donors **4**α and *β* and aglycon **7** in attempts to optimize the yield of *β*-fructofuranosidic product, but all the latter promoters were markedly inferior to the other two used (Table 3).

The results of the couplings are summarized in Schemes 2−4 and Tables 1−3. As criteria for the anomeric configuration of the fructofuranosidic linkage in the disaccharide products, the characteristic shifts of the C-2 signals in the ^{13}C NMR spectra were used. C-2 signals at higher fields around 103−4 ppm were assigned as *β*-fructofuranosides, and C-2 signals at lower field around 107−8 ppm were assigned as α-linkages.[15] These values were originally assigned for unprotected fructofuranoses

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(1) Lindberg, B. *Adv. Carbohydr. Chem. Biochem.* **1990**, 48, 279.
(2) Barrow, K. D.; Collins, J. G.; Rogers, P. L.; Smith, G. M. *Eur. J. Biochem.* **1984**, 145, 173.
(3) Gorshovska, R. P.; Kovalchuk, S. V.; Isakov, V. V.; Frolova, G. M.; Ovodov, Yu. S. *Bioorg. Khim.* **1987**, 13, 818.
(4) Backinowsky, L. V.; Balan, N. F.; Betaneli, V. I.; Kotchetkov, N. K. *Carbohydr. Res.* **1982**, 99, 189.
(5) Balan, N. F.; Backinowsky, L. V.; Betaneli, V. I.; Kotchetkov, N. K. *Bioorg. Khim.* **1981**, 7, 1566.
(6) Müller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, 27, 4763.
(7) Bouali, A.; Descotes, G.; Ewing, D. F.; Grouiller, A.; Lefkidou, J.; Lespinasse, A.-D.; Mackenzie, G. *J. Carbohydr. Chem.* **1992**, 11, 159.
(8) Borén, R. K.; Eklind, K.; Garegg, P. J.; Lindberg, B.; Pilotti, Å. *Acta Chem. Scand.* **1972**, 26, 4143.
(9) Gibbs, C. F.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1965**, 1, 290.
(10) Branefors-Helander, P.; Kenne, L.; Lindberg, B.; Petersson, K.; Unger, P. *Carbohydr. Res.* **1981**, 88, 77.
(11) Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, 149, C9.
(12) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, 31, 1331.
(13) Konradsson, P.; Udodong, U. D.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, 31, 4313.
(14) van Boeckel, C. A. A.; Beetz, T. *Recl. Trav. Chim. Pays-Bas* **1987**, 106, 596
(15) Angyal, S. J.; Bethell, G. S. *Aust. J. Chem.* **1976**, 29, 1249.

0022-3263/96/1961-1234$12.00/0

Scheme 1. Synthesis of Thiofructofuranoside Donors

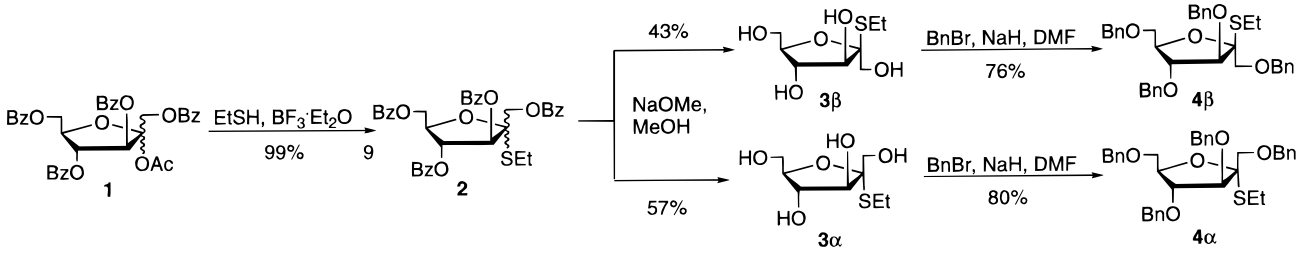


Table 1. Results and Conditions for Couplings between Acceptor 5 and Different Thiofructofuranoside Donors

donor	promoter	solvent	initial temp (°C)	yield of disaccharide (%)	α:β[a]
2	DMTST	CH_2Cl_2	−20	95 (**8**)	α
2	DMTST	CH_3CN	−35	100 (**8**)	α
4α	DMTST	CH_2Cl_2	−78	100 (**9**)	3.6:1
4*β*	DMTST	CH_2Cl_2	−78	100 (**9**)	3.2:1
4α	DMTST	CH_2Cl_2	−20	99 (**9**)	2.3:1
4*β*	DMTST	CH_2Cl_2	−20	99 (**9**)	2.2:1
4α	DMTST	CH_2Cl_2	rt	100 (**9**)	1.6:1
4α	DMTST	CH_3CN	−35	91 (**9**)	2.5:1
4*β*	DMTST	CH_3CN	−35	89 (**9**)	2.1:1
4α	NIS	CH_2Cl_2	rt	87 (**9**)	1.7:1
4α	NIS	CH_2Cl_2	−40	97 (**9**)	1:1.6
4α	NIS	CH_3CN	−35	97 (**9**)	2.1:1

[a] The α/*β* ratio is determined from ^{1}H NMR spectra by comparing the intensity of the OMe signals (see Experimental Section).

Table 2. Results and Conditions for Couplings between Acceptor 6 and Different Thiofructofuranoside Donors

donor	promoter	solvent	initial temp (°C)	yield of disaccharide (%)	α:β[a]
2	DMTST	CH_2Cl_2	−20	95 (**10**)	α
4α	DMTST	CH_2Cl_2	−20	99 (**11**)	7:1
4*β*	DMTST	CH_2Cl_2	−20	96 (**11**)	5:1
4α	NIS	CH_2Cl_2	−40	94 (**11**)	7:1
4α	NIS	CH_3CN	−35	64 (**11**)	4:1

[a] The α/*β* ratio is determined from ^{1}H NMR spectra by comparing the intensity of the OMe signals and also the axial proton signals of the 4,6-benzylidene group (see the Experimental Section).

and furanosides but have also been used *inter alia* by Kotchetkov *et al.*[4,5] for protected derivatives. Our results (Table 4) were also consistent with this assignment. All couplings with participating protecting groups gave products with typical anomeric α-values, whereas nonparticipating protecting groups gave product mixtures with both typical α- and *β*-values. It can also be seen from Table 4 that the anomeric shift is hardly influenced by the type of protecting groups on the fructofuranosidic moiety and that the anomeric assignment of the thioglycosides from their ^{13}C spectra seems not to be possible. One of the pure α-linked products, **8** (Scheme 2), obtained from coupling with a benzoylated donor, was transformed by debenzoylation and benzylation into **9**α and was found to have ^{13}C NMR spectra identical with the α-assigned part of the mixture obtained from the coupling with a benzylated donor. The α/*β*-ratio in mixtures were determined by comparing integrals of separable signals in the ^{1}H NMR spectra (see Tables 1−3 and the Experimental Section). Generally, it was not possible to separate the α/*β*-mixtures by chromatography.

When the benzoylated donor **2** and DMTST as promoter were used, an almost quantitative yield of exclu-

Table 3. Results and Conditions for Couplings between Acceptor 7 and Different Thiofructofuranoside Donors

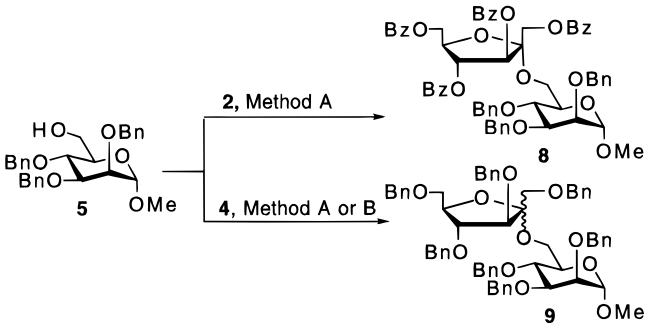
donor	promoter	solvent	initial temp (°C)	yield of disaccharide (%)	α:β[a]
2	DMTST	CH_2Cl_2	−20	92 (**12**)	α
4α	DMTST	CH_2Cl_2	−78	76 (**13**)	4.2:1
4*β*	DMTST	CH_2Cl_2	−78	80 (**13**)	4.2:1
4α	DMTST	CH_2Cl_2	−20	97 (**13**)	3.4:1
4*β*	DMTST	CH_2Cl_2	−20	99 (**13**)	3.5:1
4α	NIS	CH_2Cl_2	rt	60 (**13**)	2:1
4α	NIS	CH_2Cl_2	−40	72 (**13**)	1.4:1
4*β*	NIS	CH_2Cl_2	−40	79 (**13**)	1.4:1
4α	NIS	CH_2Cl_2	−78	79 (**13**)	1.3:1
4α	NIS	Et_2O	−35	62 (**13**)	2.2:1
4α	NIS	CH_3CN	−35	98 (**13**)	1:1.3
4*β*	NIS	CH_3CN	−35	98 (**13**)	1:1.3
4α	NIS	CH_3CN	rt	69 (**13**)	1.4:1
4α	NBS	CH_2Cl_2	−40	26 (**13**)	1:1
4α	NCS	CH_2Cl_2	−40	no reaction	
4α	Ag−Al−Si	CH_2Cl_2	rt	no reaction	
4*β*	MeOTf	CH_2Cl_2	−40	∼20 (TLC, **13**)	

[a] The α/*β* ratio is determined from ^{1}H NMR spectra by comparison of the intensity of the axial proton signals of the 4,6-benzylidene group and also the CH_2CH_2Ph signals of the spacer (see the Experimental Section).

Table 4. ^{13}C NMR Value for Anomeric Fructofuranoside Carbons

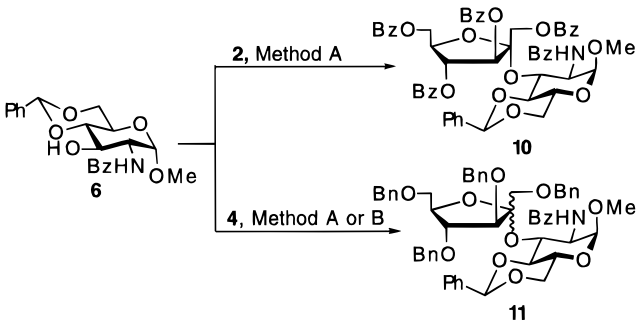
substance	C-2$_{Fru}$	substance	C-2$_{Fru}$
2α	93.5	**11α**	107.1
2*β*	92.6	**11*β***	104.2
3α	93.1	**12α**	108.9
3*β*	94.4	**13α**	108.9
4α	93.8	**13*β***	104.8
4*β*	94.0	14	99.8
8α	107.0	**15***β*,α	104.6
9α	107.9	**15**α,α	108.5
9*β*	104.4	**15**α,*β*	108.3
10α	107.3		

Scheme 2. Synthesis of Fructofuranosides Using 5 as Acceptor

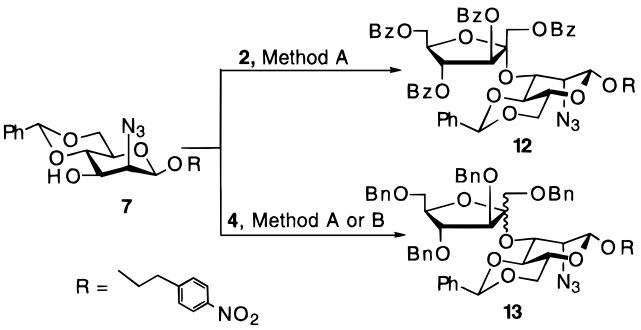


sively the α-linked products **8**, **10**, and **12** was obtained with all three aglycons. Thus, synthesis of α-linked fructofuranosides seems to offer few problems. Kotchetkov *et al.* also obtained high yields (71−82%, only α-product) using the perbenzoylated thioorthoester as donor.[4] With donor **2**, using tritylium perchlorate as

Scheme 3. Synthesis of Fructofuranosides Using 6 as Acceptor



Scheme 4. Synthesis of Fructofuranosides Using 7 as Acceptor



promotor, no product was obtained, but with donor **4** a high yield (94%) of disaccharide product (α/β-mixture $\approx$ 1:1) was obtained in a coupling with 1,2,3,4-tetra-*O*-acetyl-6-*O*-trityl-β-D-glucopyranosyl as acceptor.[5] Schmidt *et al*. reported high yields of exclusively α-fructofuranosidic product with the perbenzoylated phosphite donor with 6-OH or 1-OH in glucose as acceptor, but with secondary hydroxyl groups as aglycons, β-products were also obtained. Thus, coupling at 3′-OH in lactose and 4-OH in glucose was claimed to give exclusively the β-fructofuranosidic product in 88 and 93% yields, respectively.[6] Unfortunately, only selected ^{1}H-NMR data, no ^{13}C NMR data, and no criteria for the determination of the anomeric configuration are given in the paper. In our hands, the benzoylated phospite donor with **7** as acceptor using the conditions of Schmidt *et al*. gave only the α-linked product as determined by the criteria discussed above.

Since most naturally occuring fructofuranosides are β-linked, the synthesis of this linkage is perhaps more interesting, but also much more complicated. Since our ethyl thioglycosides with participating benzoate protecting groups could not, as shown, be used, nonparticipating benzyl groups were introduced. Couplings with the benzylated donors **4**α and **4**β with the different aglycons gave once more very high yields of disaccharide products **9**, **11**, and **13**, this time as α/β-mixtures, most often with the α-form dominating (Tables 1−3). The influence on the α/β-ratio by different conditions such as temperature, promoter, solvent, etc. was small and seemed to vary between the different couplings. General rules were difficult to find, and an optimization of β-linked product has to be made for each separate combination of acceptor and donor. One observation was consistent throughout all experiments: the anomeric configuration of the donor did not affect the yield or the stereochemical outcome of the glycosylations to any greater extent. With acceptor **6**, DMTST and NIS in CH_2Cl_2 gave the same α/β-ratio, acetonitrile as solvent together with NIS gave more of the β-product but also lower yield (Table 2, Scheme 3). For the other two aglycons **5** and **7**, a more thorough study on the dependence of the α/β-ratio of the products on different conditions was made (Tables 1 and 3, Schemes 2 and 4). The variation of the ratio was not dramatic in any case; variations from 3.6/1 up to 1/1.6 were observed. These small variations also make it difficult to discuss trends. When CH_2Cl_2 was used as solvent, DMTST and NIS at room temperature gave about the same ratio, but when the temperature was lowered, DMTST gave more of the α-product whereas NIS gave more of the β-product. The effect of acetonitrile as solvent, often used as β-directing in D-hexopyranosyl glycosylation without participating protecting groups,[16] especially efficient with primary carbohydrate aglycons, was diverse. With NIS as promoter and the primary aglycon **5** the α/β-ratio actually increased compared to CH_2Cl_2, whereas for the secondary acceptor **7** the ratio decreased. The yields in these reactions also varied, but when DMTST was used almost quantitative yields were always obtained independent of solvent and with NIS the yields were lowered with acetonitrile as solvent for acceptor **6**, improved for acceptor **7**, and the same for acceptor **5**. Other solvents and promoters tried gave inferior results (Table 3).

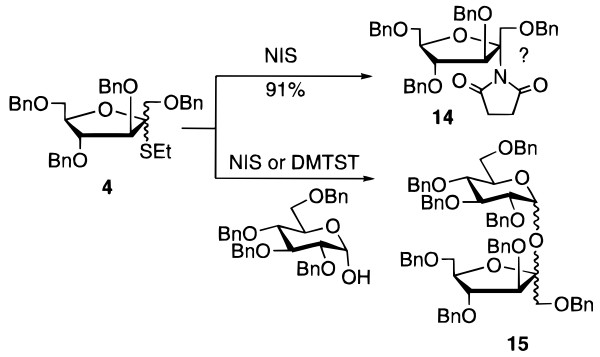
When the reactions using **4** as donor and NIS as promoter were followed by TLC, the formation of an intermediate was observed prior to the formation of the product. This intermediate was found to form also in the absence of aglycon and was then stable. Isolation and analysis of this intermediate proved it to be a *N*-succinimide glycoside **14** (Scheme 5). Only one anomer was isolated both from **4**α and **4**β, but the configuration is not proven. The observation that only one anomer is formed and that the optical rotation of this product is +29° indicates that it is an α-anomer, but further proof is needed. Attempted synthesis of the perbenzoylated corresponding derivative failed. *N*-Succinimide pyranosides have been previously synthesized by the reaction between NIS and glycals[17] or thioglycopyranosides.[18] **14** is probably not an actual intermediate in the glycosylation reaction, but only formed on the TLC-plate, since addition of an acceptor to isolated **14** did not produce any disaccharide. Furthermore, reversed addition of reagents, first mixing of donor and NIS and then addition of aglycon, also resulted only in the formation of **14** and no disaccharide product.

The synthesis of sucrose using a fructofuranosidic donor was also attempted (Scheme 5). The crystalline and commercially available derivative 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose was used as acceptor. The temperature was kept low to avoid anomerization of the glucopyranosyl moiety to the undesired β-form. DMTST once more gave a quantitative yield of disaccharide product but gave at this low temperature (−78 °C) mainly the α-furanosidic linkage. NIS gave a lower yield (67%), but also more of the desired β-furanosidic linkage. According to ^{1}H-NMR, 32% of the product mixture consisted of sucrose, *i.e.*, a total yield of about 20%, a yield that compares well with syntheses performed with glucopyranosyl donors.[19]

In conclusion, ethyl 2-thio-D-fructofuranosides are excellent glycosyl donors, which in most cases give

(16) Braccini, I.; Derouet, C.; Esnault, J.; Hervé du Penhoat, C.; Mallet, J.-M.; Michon, V.; Sinaÿ, P. *Carbohydr. Res.* **1993**, 246, 23.
(17) Laupichler, L. Ph.D. Thesis, Hamburg University, 1992.
(18) Konradsson, P.; Oscarson, S.; Öberg, L. Unpublished results.
(19) Khan, R. *Adv. Carbohydr. Chem. Biochem.* **1976**, 33, 235.

Scheme 5. Synthesis of *N*-D-Fructofuranosylsuccinimide and D-Fructofuranosyl D-Glucopyranosides



oligosaccharide products in quantitative or near-quantitative yields using only a small excess of donor. Such yields, in contrast to peptide and oligonucleotide synthesis, are very rarely found in oligosaccharide couplings. Benzoylated donors using DMTST as promoter give almost quantitative yields of α-fructofuranosidic oligosaccharides. Benzylated derivatives using DMTST as promoter also give quantitative yields of fructofuranosides but as an α/β-mixture. The use of NIS as promoter, especially at lower temperatures, can improve the amount of β-furanosidic product.

Experimental Section

General Remarks. Melting points are corrected. Organic solutions were dried over $MgSO_4$ before concentration, which was performed under reduced pressure at <40 °C (bath temperature). NMR spectra were recorded at 25 °C at 270 MHz (^{1}H) or 67.5 MHz (^{13}C) in $CDCl_3$ with Me_4Si as internal standard ($\delta = 0$), unless otherwise stated. The FAB mass spectrum was recorded in the negative mode (matrix NBA). TLC was performed on silica gel F_{254} (E. Merck) with detection by UV light and/or by charring with 8% sulfuric acid. Silica gel (0.040−0.063 mm, Amicon) was used for column chromatography. Eluants used for column chromatography and TLC: A, toluene−EtOAc 10:1; B, toluene−EtOAc 9:1; C, toluene−EtOAc 6:1.

Ethyl 1,3,4,6-Tetra-*O*-benzoyl-2-thio-D-fructofuranoside (2). BF_3·etherate (384 μL, 3.13 mmol) was added at 0 °C to a solution of ethyl mercaptan (348 μL, 4.70 mmol) and 2-*O*-acetyl-1,3,4,6-tetra-*O*-benzoyl-D-fructofuranoside[7] (**1**, 2.0 g, 3.13 mmol) in dry chloroform (35 mL). The reaction mixture was stirred at 0 °C for 2.5 h and then diluted with chloroform, washed with saturated $NaHCO_3$ solution and water, dried, and concentrated. Purification of the residue on a silica gel column (petroleum ether bp 60−70 °C−EtOAc 3:1) gave **2** (99%, 1.99 g, 3.10 mmol): ^{13}C NMR δ 14.5, 14.8, 21.6 22.3, 62.7, 63.2, 64.6, 65.6, 77.6, 78.1, 78.9, 79.7, 79.8, 82.4, 92.6, 93.5, 128.3−149.7, 164.9, 165.6, 165.68, 165.74, 166.0. Anal. Calcd for $C_{36}H_{32}O_9S$: C, 67.49; H, 5.03. Found: C, 67.40 ; H, 5.18.

Ethyl 2-Thio-α-D-fructofuranoside (3α) and Ethyl 2-Thio-β-D-fructofuranoside (3β). Sodium methoxide in methanol (1.5 mL, 1 M) was added to a suspension of **2** (11.1 g, 17.3 mmol) in methanol (200 mL). After 3 h, TLC (chloroform−methanol 5:1) showed two slower spots. Careful neutralization with methanol-washed Dowex 50 (H^+) ion exchange resin, followed by filtration, concentration, and purification on a silica gel column (chloroform−methanol 9:1), gave a quantitative yield of **3**α (57%, 2.2 g, 9.89 mmol) [mp 93−94 °C; $[\alpha]_D$ +135° (*c* 1.1, H_2O) (lit.[5] mp 89−91 °C; $[\alpha]_D$ +140°)] and **3**β (43%, 1.66 g, 7.40 mmol): $[\alpha]_D$ −94° (*c* 1.3, H_2O) (lit.[5] $[\alpha]_D$ −93°);^{13}C NMR (CD_3OD−$CDCl_3$ 3:1, acetone as internal standard $\delta = 31.0$): **3**α, δ 15.1, 22.4, 60.0, 64.6, 80.7, 85.0, 85.1, 93.1; **3**β, δ 15.0, 20.8, 63.4, 63.9, 76.5, 77.4, 83.0, 94.4.

Ethyl 1,3,4,6-Tetra-*O*-benzyl-2-thio-α-D-fructofuranoside (4α). Benzyl bromide (5.8 mL, 48.6 mmol) was added dropwise to a mixture of **3**α (2.22 g, 9.89 mmol) and NaH (1.6 g, 65.1 mmol) in DMF (20 mL). The mixture was stirred for 4 h at rt, quenched by adding 1 mL of methanol, diluted with toluene (100 mL), and washed with saturated $NaHCO_3$ solution (2 × 200 mL) and water (2 × 200 mL). Drying and concentration followed by purification repeated twice on a silica gel column (system A) yielded **4**α (80%, 4.60 g, 7.87 mmol): $[\alpha]_D$ +38° (*c* 1.06, chloroform) (lit.[5] $[\alpha]_D$ +38.6°); ^{13}C NMR δ 14.8, 22.3, 69.6, 70.4, 72.3, 73.0, 73.2, 73.5, 79.2, 84.0, 89.7, 93.8, 127.5−138.2.

Ethyl 1,3,4,6-Tetra-*O*-benzyl-2-thio-β-D-fructofuranoside (4β). Compound **3**β (1.67 g, 7.40 mmol) was benzylated as described for **3**α above to give **4**β (76% , 3.33 g, 5.69 mmol): $[\alpha]_D$ −36° (*c* 0.73, chloroform) (lit.[5] $[\alpha]_D$ −37.3°); ^{13}C NMR δ 14.8, 21.0, 71.4, 72.5, 72.8, 73.1, 73.3, 73.5, 80.5, 84.8, 85.0, 94.0, 127.6−138.1.

2-(*p*-Nitrophenyl)ethyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranoside (7). Synthesis of this acceptor will be presented elsewhere: mp 151 °C (from MeOH); $[\alpha]_D$ −82° (*c* 1.02, chloroform); ^{13}C NMR δ 36.0, 64.6, 67.1, 68.3, 69.8, 69.9, 78.4, 100.6, 102.1, 123.6, 126.2, 128.3, 129.3, 129.9, 136.9, 146.3, 146.8. Anal. Calcd for $C_{21}H_{22}O_7N_4$: C, 57.01; H, 5.01. Found: C, 57.12 ; H, 5.03.

Glycosylation Procedures. Method A (DMTST). The donor (50−100 mg, 85−170 μmol) and the acceptor (40−80 mg, 1 equiv) were dissolved in 5−10 mL of distilled solvent together with crushed molecular sieves (4 Å, 0.3−0.5 g). The mixture was stirred under nitrogen and allowed to attain the desired initial reaction temperature (−78 °C −25 °C). After 30 min, DMTST (4 equiv) was added. The temperature program for the cold (below −20 °C) reactions was 3−4 h at the initial temperature, 12 h at −20 °C, and finally 30 min at rt. When TLC (system C) indicated the reaction to be complete triethylamine was added, whereafter the mixture was concentrated and purified on a silica gel column (system B).

Method B (NIS, NBS, or NCS). The donor (50−65 mg, 85−110 μmol) and the acceptor (26−39 mg, 1 equiv) were dissolved in 4−8 mL of distilled solvent together with crushed molecular sieves (4 Å, 0.2−0.4 g). The mixture was stirred under a nitrogen atmosphere and allowed to attain the desired reaction temperature. After 30 min, NIS (1.5 equiv) was added. Reaction temperature intervals were as for method A. When TLC (system C) indicated the reaction to be complete, the mixture was diluted with CH_2Cl_2 and filtered through Celite into a separatory funnel, washed twice with saturated $Na_2S_2O_3$ solution and water, dried, concentrated, and purified on a silica gel column (system B).

Products. Details on the conditions and yields for the different couplings as well as the α/β-ratios of the products are presented in Tables 1−3. The ratios were determined by integration of peaks in ^{1}H NMR, since none of the α/β-product mixtures could be separated by chromatography. The peaks used are given below for each α/β-mixture. The distinction between the anomers is made from mixtures with a large excess of α-compound as determined from the ^{13}C NMR spectrum. ^{13}C NMR data is presented for the anomeric fructofuranosidic carbons in Table 4.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-α-D-mannopyranoside (8). Coupling of donor **2** and acceptor **5** according to method A: $[\alpha]_D$ +29° (*c* 0.74, chloroform); ^{13}C NMR δ 54.4, 59.6, 61.6, 63.4, 71.0, 72.1, 72.5, 74.3, 75.0, 79.3, 80.3, 81.0, 81.7, 98.6, 107.0, 126.1−138.8, 165.3, 165.4, 165.7, 166.8. Anal. Calcd for $C_{62}H_{58}O_{15}$: C, 71.39; H, 5.60. Found: C, 71.15 ; H, 5.59.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl)-α-D-mannopyranoside (9). Coupling of donor **4** and acceptor **5**: ^{13}C NMR δ 54.4, 61.2, 61.4, 67.3, 70.0, 71.2, 71.3, 71.4, 71.6, 72.0, 72.1, 72.2, 72.3, 72.4, 72.6, 72.6, 73.2, 73.5, 74.7, 74.7, 74.8, 74.9, 75.1, 75.4, 77.2, 79.0, 80.1, 80.2, 80.5, 84.0, 84.5, 84.7, 87.5, 98.6, 98.7, 104.4, 107.9, 127.2−139.0; ^{1}H NMR δ 3.13 (s, OMe, α-Fru*f*), 3.19 (s, OMe, β-Fru*f*). Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 74.70 ; H, 6.80.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(1,3,4,6-tetra-*O*-benzyl-α-D-fructofuranosyl)-α-D-mannopyranoside (9α). Sodium methoxide in methanol (0.1 mL, 1 M) was added to a solution

of **8** (143 mg, 147 μmol) in methanol (20 mL). When TLC showed the reaction to be complete, the mixture was neutralized by methanol-washed Dowex 50(H^+) ion exchange resin, filtered, concentrated, and purified on a silica gel column (chloroform−methanol 9:1) to yield methyl 2,3,4-tri-*O*-benzyl-6-*O*-α-D-fructofuranosyl-α-D-mannopyranoside (86%, 79 mg, 126 μmol): ^{13}C NMR δ 55.1, 59.3, 60.2, 61.9, 70.7, 72.2, 72.8, 74.1, 75.1, 75.2, 78.5, 79.8, 86.9, 99.2, 109.5, 127.6−138.4. Benzylation of this intermediate (79 mg, 126 μmol) as described for compound **3**α above gave **9**α (95%, 119 mg, 120 μmol): $[\alpha]_D$ +39° (*c* 0.84, chloroform); ^{13}C NMR δ 54.4, 61.2, 67.3, 70.0, 71.3, 72.0, 72.1, 72.4, 72.6, 73.2, 73.6, 74.8, 75.4, 80.2, 80.5, 84.6, 87.5, 98.6, 107.9, 127.4−138.8. Anal. Calcd for $C_{62}H_{66}O_{11}$: C, 75.43; H, 6.74. Found: C, 74.85 ; H, 6.86.

Methyl 2-Benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-α-D-glucopyranoside (10). Coupling of donor **2** and acceptor **6** using method A: $[\alpha]_D$ +30° (*c* 1.22, chloroform); ^{13}C NMR δ 53.7, 55.5, 62.8, 63.1, 63.2, 69.0, 71.3, 76.9, 78.6, 80.6, 82.5, 99.2, 102.1, 107.3, 126.1−136.7, 164.8, 165.3, 165.4, 165.7. Anal. Calcd for $C_{55}H_{49}O_{15}N$: C, 68.53; H, 5.12. Found: C, 67.61; H, 5.10.

Methyl 2-Benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl)-α-D-glucopyranoside (11). Coupling of donor **4** and acceptor **6**: NMR ^{13}C δ 54.7, 54.9, 55.5, 63.1, 63.2, 69.1, 69.6, 70.7, 70.8, 71.5, 71.6, 72.2, 72.3, 72.8, 73.2, 73.5, 73.9, 78.8, 79.6, 80.7, 81.0, 81.5, 83.1, 85.4, 90.6, 98.9, 99.2, 101.6, 101.9, 104.2, 107.1, 126.1−138.3, 167.0, 167.4; ^{1}H δ 4.97 (d, *J* 3.3 Hz, H-1, β-Fru*f*), 5.14 (d, *J* 3.3 Hz, H-1, α-Fru*f*), 5.53 (s, PhCH, β-Fru*f*), 5.55 (s, PhCH, α-Fru*f*). Anal. Calcd for $C_{55}H_{57}O_{11}N$: C, 72.75; H, 6.33. Found: C, 72.37 ; H, 6.52.

2-(*p* -Nitrophenyl)ethyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(1,3,4,6-tetra-*O*-benzoyl-α-D-fructofuranosyl)-β-D-mannopyranoside (12). Coupling of donor **2** and acceptor **7** by method A: $[\alpha]_D$ −28° (*c* 1.1, chloroform); ^{13}C NMR δ 36.0, 61.7, 63.4, 65.0, 67.8, 68.3, 69.8, 70.5, 76.3, 78.5, 82.1, 82.5, 100.6, 102.4, 108.9, 123.7−146.8, 164.6, 165.4, 165.9, 166.1. Anal. Calcd for $C_{55}H_{48}O_{16}N_4$: C, 64.70; H, 4.74. Found: C, 64.57 ; H, 4.85.

2-(*p*-Nitrophenyl)ethyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl)-β-D-mannopyranoside (13). Coupling of donor **4** and acceptor **7**: ^{13}C NMR δ 35.9, 36.0, 65.7, 67.3, 67.8, 68.4, 69.2, 69.4, 69.6, 69.7, 70.0, 70.4, 71.3, 72.0, 72.5, 72.6, 72.8, 73.1, 73.2, 73.4, 73.6, 78.3, 81.8, 84.0, 88.5, 99.6, 100.3, 102.0, 102.2, 104.8, 108.9, 123.5−146.7; ^{1}H NMR δ 2.96 (t, CH_2CH_2Ar, β-Fru*f*), 3.04 (t, CH_2CH_2Ar, α-Fru*f*), 5.51 (s, PhCH, β-Fru*f*), 5.53 (s, PhCH, α-Fru*f*). Anal. Calcd for $C_{55}H_{56}O_{12}N_4$: C, 68.45; H, 5.85. Found: C, 68.18 ; H, 5.84.

(1,3,4,6-Tetra-*O*-benzyl-D-fructofuranosyl)-*N*-succinimide (14). A solution of **4**α or **4**β (65 mg, 111 μmol) in CH_2Cl_2 (5 mL) containing 4 Å crushed molecular sieves (0.3 g) under a nitrogen atmosphere was cooled to −78 °C and stirred for 30 min. Then NIS (30 mg, 132 μmol) was added, and the temperature was allowed to rise. After 30 min (temperature −20 °C), TLC indicated that all starting material was consumed. The mixture was diluted with CH_2Cl_2, filtered through Celite into a separatory funnel containing saturated $Na_2S_2O_3$ solution, washed, dried, and concentrated. The residue was purified on a silica gel column (system C) to yield **14** (91%, 63 mg, 101 μmol): $[\alpha]_D$ +29° (*c* 1.0, chloroform); ^{13}C NMR δ 28.4, 68.9, 69.9, 71.6, 72.6, 73.2, 73.4, 83.3, 83.5, 83.7, 99.8, 127.4−138.3, 177.0; MS (FAB) *m*/*e* 620.2 ($M^+ - 1$). Anal. Calcd for $C_{38}H_{39}O_7N$: C, 73.41; H, 6.32. Found: C, 73.16 ; H, 6.28.

Synthesis of Sucrose. Attempts to optimize the yield of sucrose was made in four different couplings, using **4**α as donor and 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose as acceptor.

1. Method A: CH_2Cl_2, −78 °C. Yield quantitative of mainly the α,α-isomer.
2. Method B: CH_2Cl_2, −60 °C. See below.
3. Method B: CH_3CN, −35 °C. Yielded no disaccharide product.
4. Method B: CH_2Cl_2, −78 °C, 3 equiv of acceptor. Yield as for 2.

1,3,4,6-Tetra-*O*-D-fructofuranosyl 2,3,4,6-Tetra-*O*-D-glucopyranoside (15). Using method B, **4**α (65 mg, 111 μmol) was reacted with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (46 mg, 85 μmol) in CH_2Cl_2 at −60 °C. The total yield of disaccharides was 67% (60.1 mg, 57 μmol): NMR ^{13}C δ 68.2, 68.4, 69.1, 70.0, 70.5, 71.0, 71.2, 71.4, 71.5, 72.1, 72.2, 72.5, 72.6, 72.7, 73.0, 73.2, 73.4, 74.7, 74.8, 75.0, 75.5, 77.6, 79.6, 79.8, 80.4, 81.9, 82.4, 83.9, 84.3, 84.9, 87.8, 89.0, 89.9, 96.8, 104.6, 108.3, 108.5, 127.1−138.4; ^{1}H δ 5.55 (d, $J = 3$ Hz, H-1, α-Glc*p*-α-Fru*f*), 5.72, (d, $J = 3$ Hz, H-1, α-Glc*p*-β-Fru*f*). The amount of **15**β,α (octabenzyl sucrose) of the disaccharide mixture was 32% as estimated from ^{1}H NMR. The main side product was the α,α-isomer (56%), and also the α,β-isomer (isosucrose) (12%) could be detected. To be able to quantify the amount of **15**β,α, the NMR data was compared to octabenzyl sucrose synthesized from sucrose.[20]

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Supporting Information Available: 270 MHz ^{1}H NMR spectra for all fructose-containing derivatives and acceptor **7** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(20) Tate, M. E.; Bishop, C. T. *Can. J. Chem.* **1963**, 41, 1801.