Stereospecific Synthesis of β-D-Fructofuranosides Using Thioglycoside Donors and Internal Aglycon Delivery†

Christian Krog-Jensen and Stefan Oscarson*

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

Received June 2, 1997

Stereospecific synthesis of β-D-fructofuranosides has been accomplished by the application of an internal acceptor delivery approach. The acceptor, ethanol or monosaccharides, is initially tethered to the fructofuranose 3-hydroxyl group, adjacent to the anomeric center and on the β-side of the furanose ring, as part of a mixed *p*-methoxybenzaldehyde acetal, which is formed by DDQ-oxidation of ethyl 1,4,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-2-thio-D-fructofuranoside in the presence of the acceptor or of the *p*-methoxybenzylated acceptor in the presence of the corresponding 3-OH fructofuranoside. Then, activation of the thioglycoside with a thiophilic promoter allows the delivery of the acceptor from the acetal to the activated anomeric center to yield the β-linked fructofuranoside in high yields (76−85%). If promoters with nonnucleophilic anions (triflate, perchlorate) are used, the intermediate acetal decomposes to produce the β-fructofuranoside products as 3-OH derivatives. However, if NIS is used as promoter, the *N*-succinimide anion interacts with the benzylidene carbon to give the β-fructofuranoside products as mixed fructofuranoside-3-*O*-yl *N*-succinimide *p*-methoxybenzaldehyde acetals.

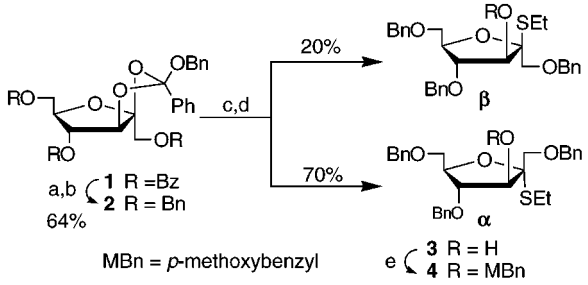
Introduction

Fructofuranosides are found in nature in both plants and bacteria, in sucrose, in fructofuranans, 1→6-linked inulins, and 1→2-linked levans, and as residues in bacterial capsular polysaccharides.[1] Apart from a few exceptions, fructofuranosides in natural saccharides are all β-linked. Hence, methods to stereoselectively construct β-fructofuranosidic linkages is a prerequisite for the synthesis of most fructose-containing structures from nature. Recently, we reported the successful application of the internal aglycon delivery approach[2−6] in the synthesis of β-fructofuranosides.[7] In this paper, we now give additional information of the scope of this reaction, including the effects of various promoters, solvents, acceptors, and donors.

Results and Discussion

A benzylated fructofuranose thioglycoside donor with a free 3-hydroxyl group was synthesized from the known ortho ester derivative **1**[8] by change of the benzoyl groups into benzyl groups and then rearrangement of the ortho ester **2** in the presence of an excess of ethanethiol to give ethyl 3-*O*-benzoyl-1,4,6-tri-*O*-benzyl-2-thio-D-fructofuranoside as an inseparable α/β-mixture. Treatment with sodium methoxide in methanol gave the two 3-hydroxyl compounds **3α** and **3*β***, which now could be separated by silica gel column chromatography. *p*-Methoxybenzylation then gave derivatives **4α** and **4*β*** (Scheme 1).

Scheme 1[a]



[a] Key: NaOMe, MeOH, −15 °C; (b) BnBr, NaH, DMF; (c) TMSOTf, EtSH, CH_2Cl_2; (d) NaOMe, MeOH; (e) MBnBr, NaH, DMF.

As discussed in our previous paper,[7] acceptors can now be linked to the β-side of the donor **4α** as part of a mixed *p*-methoxybenzaldehyde acetal by DDQ-oxidation of the 3-*O*-(*p*-methoxybenzyl) group in the presence of the acceptor, as described by Ito and Ogawa.[5,6] Activation of the thioglycoside with a thiophilic promoter then allows the delivery of the acceptor from the 3-*O*-acetal on the β-side to the anomeric center to give exclusively the β-linked fructofuranoside disaccharide as determined from the ^{13}C NMR chemical shift of the anomeric carbon of fructose (δ ∼103−105 ppm β-linked, ∼107−109 ppm α-linked).[9,10] In this paper, the effects of different solvents and different promoters in this reaction have been investigated. The use of **4*β*** as donor, instead of **4α**,

† Dedicated to Professor Hans Paulsen on the occasion of his 75th birthday.

(1) Lindberg, B. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 279−318.
(2) (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376−9377. (b) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759−761. (c) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447−1465.
(3) Stork, K.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088.
(4) (a) Bols, M. *J. Chem. Soc., Chem. Commun.* **1992**, 913−914. (b) Bols, M. *J. Chem. Soc., Chem. Commun.* **1993**, 791−792. (c) Bols, M. *Acta Chem. Scand.* **1993**, *47*, 829−834.
(5) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767.
(6) Dan, A., Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680−4681.
(7) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 4512−4513.
(8) Helferich, B.; Bottenbruch, L. *Chem. Ber.* **1953**, *86*, 651−657.
(9) Angyal, S. J.; Bethell, G. S. *Aust. J. Chem.* **1976**, *29*, 1249.
(10) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 1234−1238.

S0022-3263(97)00983-3 CCC: $15.00
Published on Web 02/20/1998

Scheme 2

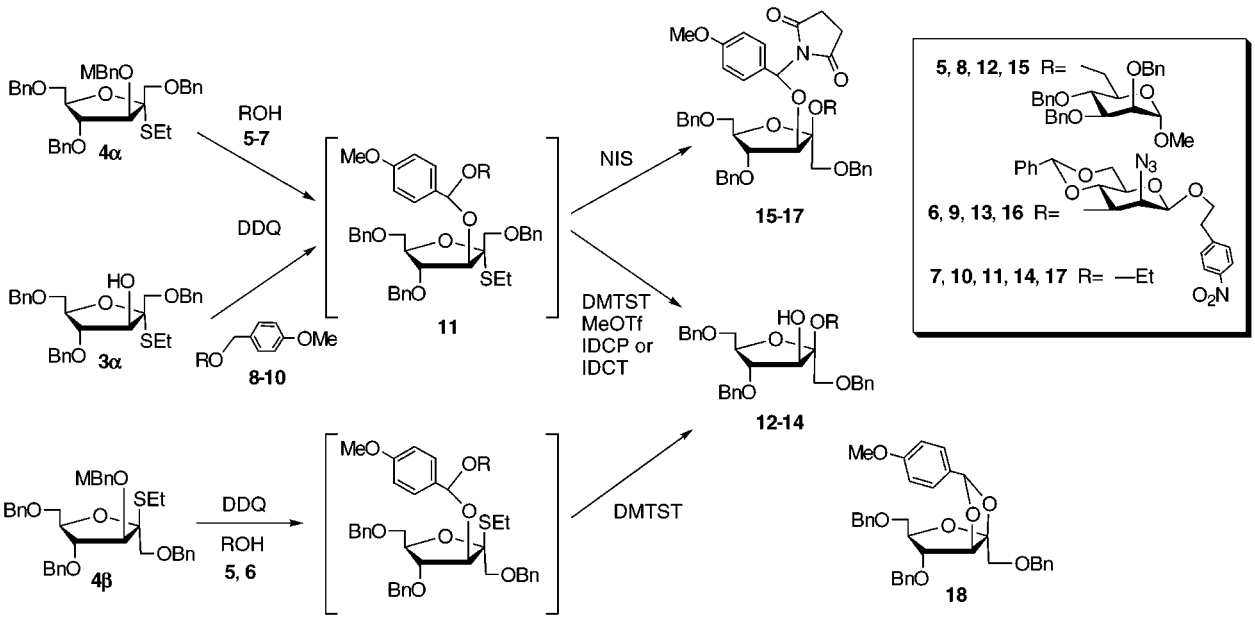


Table 1. Results from the Couplings

entry	donor	acceptor	promoter/solvent	product	yield (%)
1	**4α**	**5**	$MeOTf/CH_2Cl_2$	**12**	31
2	**4α**	**5**	$DMTST/CH_2Cl_2$	**12**	77
3	**4α**	**5**	$DMTST/CH_3CN$	**12**	66
4	**4α**	**5**	DMTST/toluene	**12**	15
5	**4α**	**5**	DMTST/DMF		0
6	**4α**	**5**	NIS/CH_2Cl_2	**15**	57
7	**4α**	**5**	$IDCT/CH_2Cl_2$	**12**	58
8	**4α**	**5**	$IDCP/CH_2Cl_2$	**12**	45
9	**4α**	**6**	$DMTST/CH_2Cl_2$	**13**	76
10	**4α**	**6**	$MeOTf/CH_2Cl_2$	**13**	59
11	**4α**	**6**	NIS/CH_2Cl_2	**16**	63
12	**4α**	**6**	$IDCT/CH_2Cl_2$	**13**	76
13	**4α**	**6**	$IDCP/CH_2Cl_2$	**13**	54
14	***4β***	**5**	$DMTST/CH_2Cl_2$	**12**	45
15	***4β***	**6**	$DMTST/CH_2Cl_2$	**13**	54
16	**3α**	**8**	$DMTST/CH_2Cl_2$	**12**	53
17	**3α**	**8**	NIS/CH_2Cl_2	**16**	53
18	**3α**	**9**	$DMTST/CH_2Cl_2$	**13**	57
19	**4α**	**7**	$DMTST/CH_2Cl_2$		0
20	**3α**	**10**	$DMTST/CH_2Cl_2$	**14** + **18**	25 + 60
21	**3α**	**10**	NIS/CH_2Cl_2	**17**	85
22	**3α**	**10**	$IDCP/CH_2Cl_2$	**14**	76

was also tried, as well as an "inverse" approach using **3α**, with a free 3-hydroxyl group, as donor and *p*-methoxybenzylated acceptors in the formation of the intermediate acetal. Furthermore, the result with an additional acceptor, ethanol, is included. With this acceptor, the intermediate acetal could be isolated and characterized by NMR. The results obtained are summarized in Scheme 2 and Table 1.

Methyl trifluoromethanesulfonate (MeOTf) was originally tried as promoter together with donor **4α**, using the conditions published by Ito and Ogawa.[5] This gave an acceptable yield of β-linked disaccharide with acceptor **6**[10] (→**13**, 59%, entry 10, Table 1) but a low yield with acceptor **5**[11] (→**12**, 31%, entry 1, Table 1). Dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST)[12] was then tested as promoter, which did not improve the yields. Slight alterations in the reaction conditions for the acetal formation (the reagents were added in a reversed order and triethylamine was added to the reaction mixture prior to workup) gave a cleaner reaction according to TLC, and now both acceptors gave good yields with DMTST as promoter (entries 2 and 9, Table 1). These new conditions were also tested with MeOTf as promoter, but no increase in yield was noticed. NIS was also tried as promoter, and a product was isolated in good yield with both **5** or **6** as acceptor and **4α** as donor (entries 6 and 11, Table 1), but both these products had a different mobility on TLC compared to the products obtained when using DMTST or methyl triflate as promoter. NMR on these new products showed them to be β-linked disaccharides but also showed the presence of both a *p*-methoxyphenyl group (^{13}C, δ ~55, 113, and 159 ppm) and a succinimide moiety (^{13}C, δ ~29 and 176 ppm). This suggested that the nucleophilic succinimide anion had reacted with the benzylidene carbon, during or after the leaving of the acceptor moiety, to form an *N*,*O*-acetal and give products **15** and **16**, whose structures were further confirmed by elemental analysis and FAB-MS. A singlet at around 6.5 ppm in the ^1H, and an additional signal in the ring carbon region (~60−85 ppm) in the ^{13}C NMR spectra, assigned as the acetal proton and the acetal carbon, respectively, provided additional proof to the suggested structures. According to NMR, one of the two possible stereoisomers is formed almost exclusively. Analogous *N*-succinimide isopropylidene acetals were found by Baressi and Hindsgaul, especially when using NBS as promoter in the activation.[2c] However, in their case, the acetals were found only rarely and as labile products, which could easily be hydrolyzed, in contrast to ours, which were the sole product and quite stable. Similar problems, with the nucleophilicity of the *N*-succinimide anion, have been encountered in NIS-promoted glycosylation with reactive donors and unreactive acceptors. In these reactions the corresponding anomeric succinimido *N*,*O*-acetal was formed.[10,13,14] Attempts to hydrolyze the *N*,*O*-acetals in **15** and **16** with

(11) Borén, R. K.; Eklind, K.; Garegg, P. J.; Lindberg, B.; Pilotti, Å. *Acta Chem. Scand.* **1972**, *26*, 4143.

(12) Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9.

(13) Öberg, L. Licentiate Thesis, Stockholm University, 1996.

acid were performed. However, these were surprisingly stable, inter alia, due to the two stabilizing electron-withdrawing carbonyl groups,[15] so it was easier to cleave the fructofuranosidic linkage than the *N*,*O*-acetal. This undesired formation of the *N*,*O*-acetal should be possible to avoid if iodonium promoters with less nucleophilic anions were used. Iodonium collidine perchlorate (IDCP)[16,17] and iodonium collidine triflate (IDCT)[18] were therefore tried as promoters and were found to give moderate to good yields of the 3′-OH disaccharides **12** and **13** (entries 7, 8, 12, and 13, Table 1).

The donor−acceptor pair **4α**−**5** and DMTST as promoter were chosen to evaluate the effect of the solvent in the reaction. CH_2Cl_2 was found to be the best solvent, but MeCN could also be used. DMF and toluene, however, were definitely inferior (entries 2−5, Table 1).

The effect of the anomeric configuration of the donor was also investigated. The α-linked donor **4α** was chosen primarily, since there are indications that the displacement of the activated thioglycoside with the internal acceptor is a concerted reaction (e.g., we found, as did Baressi and Hindsgaul,[2] that addition of external acceptor in the activation of the tethered acetal does not produce formation of any α-glycoside) and, thus, should proceed more smoothly with the trans-α-anomer of the donor. However, the *β*-linked donors were also found to give only the *β*-linked disaccharides but in lower yields (entries 14 and 15, Table 1).

In the formation of the intermediate acetal, so far only *p*-methoxybenzylated donors and acceptors with a free hydroxyl group had been used. However, it should be possible to instead use an "inverse" approach, in which the *p*-methoxybenzylated acceptor and a donor with a free 3-OH, e.g., **3**, are used. This approach has been used with silyl acetal tethering[3,4] but, as far as we know, not reported with isopropylidene or *p*-methoxybenzylidene acetal tethering. The method, if successful, can have definitive advantages, e.g., in the synthesis of the acceptor, in which then the *p*-methoxybenzyl group can be used as a temporary protecting group at the position that is going to be glycosylated. As can be seen from entries 16 and 18 in Table 1, this approach, with donor **3α** and the *p*-methoxybenzylated acceptors **8** or **9** activated by DMTST, also gave the desired *β*-linked disaccharides **12** and **13**, in these cases in slightly lower yields (compare entries 2 and 9, Table 1). The use of NIS as promoter gave the expected *N*,*O*-acetal product **16** (entry 17, Table 1).

A simpler acceptor alcohol was then tested, which might allow the isolation and characterization of the intermediate acetal, a task that had been proven difficult with the acceptors used earlier. This expected simplification, however, turned out to be a complication. With donor **4α** and ethanol (**7**), the acetal was not even formed according to TLC (entry 19, Table 1). However, when the reversed approach was tried, with **3α** and ethyl *p*-methoxybenzyl ether (**10**), the acetal **11** was smoothly formed and could, if desired, be purified by silica gel chromatography. Activation of the acetal **11** was then attempted using the crude, not purified acetal. With DMTST as promoter, the *β*-linked ethyl fructofuranoside **14** (^{13}C NMR: δ 103.7 ppm, C-2 fructose) was produced, but only in 25% yield (entry 20, Table 1). The major product (∼60% yield) in this reaction was a derivative, which was found to still contain a *p*-methoxybenzylidene group but no ethanol. Further characterization of this product proved it to be the 2,3-*O*-(*p*-methoxybenzylidene) acetal **18**. This product has also been found in reactions with some other acceptors, e.g., 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose in an attempt to synthesize sucrose.[19] Compound **18** is also formed if the reaction sequence, i.e., DDQ-oxidation and DMTST-activation, is performed in the absence of an acceptor. Activation of acetal **11** with NIS gave a high yield of ethyl *β*-fructofuranoside, but once more as the *N*,*O*-acetal (**17**, entry 21, Table 1). Finally, a good yield of ethyl *β*-D-fructofuranoside **14** could be obtained by the activation of acetal **11** with IDCP as promoter (entry 22, Table 1).

In conclusion, stereospecific formation of *β*-linked fructofuranosides can be performed in high yields by internal delivery of the acceptor from a 3-*O*-(*p*-methoxybenzylidene) acetal of a thioglycoside donor after activation with a thiophilic promoter. The acetal can be formed by oxidation with DDQ of either the 3-*O*-*p*-methoxybenzylated donor **4** and the acceptor or the 3-OH donor **3** and the *p*-methoxybenzylated acceptor. As promoters, DMTST, IDCP, and IDCT were found to function well, but both the formation of the tethered acetal and its activation are sensitive reactions and an optimization often has to be performed to find the best conditions and promoter. The use of NIS as promoter gave good yields of *β*-fructofuranosides, but as *N*-succinimidofructofuranoside-3-*O*-yl *p*-methoxybenzylidene acetals.

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 (δ = 0 ppm), unless otherwise stated. TLC was performed on silica gel F_{254} (E. Merck) with detection by UV light and/or charring with 8% sulfuric acid. Silica gel (0.040−0.063 mm, Amicon) was used for column chromatography. Reversed-phase TLC was performed on silanilized silica gel, 60 silanisiert (E. Merck). Silanilized silica gel (Kieselgel 60 silanisiert, 0.063−0.200 mm, E. Merck) was used for reversed-phase flash chromatography. The reversed-phase columns were eluted using a gradient of acetone−H_2O 1:1 → 14:1. HPLC was performed on a Gilson 305/306 using Dynamax-60A (Si-111-c) column and detected by UV light (260 nm).

1,4,6-Tri-*O*-benzyl-2,3-*O*-[1-(benzyloxy)benzylidene]-*β*-D-fructofuranose (2). A solution of 1,4,6-tri-*O*-benzoyl-2,3-*O*-[1-(benzyloxy)benzylidene]-*β*-D-fructofuranose[8] (**1**, 17.2 g, 25 mmol) in MeOH/$CHCl_3$ (200 mL, 1:1) was cooled to −15 °C, whereafter NaOMe (6 mL, 1 M in MeOH) was added. The mixture was left for 12 h at −15 °C and then concentrated and dried in vacuo. The debenzoylated product (9.3 g, 25 mmol) and benzyl bromide (24 mL, 34.5 g, 202 mmol) dissolved in DMF (50 mL) were added dropwise to a suspension of NaH (80% in oil, 7.3 g, 302 mmol) in DMF (50 mL) at 0 °C. After 2 h, the reaction mixture was allowed to attain room temperature and to react for another 10 h. The reaction was

(14) Oscarson, S.; Tedebark U.; Turek, D. *Carbohydr. Res.* **1997**, *299*, 159.

(15) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994, p 218.

(16) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.

(17) Konradsson, P.; Udodong, U. D.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313.

(18) van Boeckel, C. A. A.; Beetz, T. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 596.

(19) Krog-Jensen, C. Doctoral Thesis, Stockholm University, 1997.

quenched by the addition of MeOH (100 mL) at −5 °C, and the mixture was then diluted with toluene, filtered through Celite, washed with aq satd $NaHCO_3$ and water, dried, and concentrated. Crystallization of **2** was accomplished by the addition of light petroleum (bp 40−60 °C). The crystals were filtered off, and the mother liquor was concentrated and purified on a silica gel column (toluene−EtOAc 20:1) to give an additional amount of **2** (total yield: 10.3 g, 16 mmol, 64%): mp 62.5−63.5 °C; $[\alpha]_D$ +5.9°(*c* 1.04, $CHCl_3$); ^{13}C NMR δ 65.3, 70.1, 70.8, 71.5, 72.1, 73.1, 73.7, 83.0, 84.8, 85.2, 114.6, 122.9, 126.5−129.2, 137.3−138.3; ^1H NMR δ 3.18 (m), 3.8−4.05 (dd), 3.9 (d), 4.16−4.4 (m), 4.45−4.6 (m), 4.96 (s), 7.05−7.7 (m). Anal. Calcd for $C_{41}H_{40}O_7$: C, 76.38; H, 6.25. Found: C, 76.32; H, 6.30.

Ethyl 1,4,6-Tri-*O*-benzyl-2-thio-α-D-fructofuranoside (3α) and Ethyl 1,4,6-Tri-*O*-benzyl-2-thio-β-D-fructofuranoside (3β). Ethanethiol (116 mL, 1.58 mol) was added to a solution of **2** (10.2 g, 15.9 mmol) in freshly distilled CH_2Cl_2 (500 mL) containing Drierite (25 g). The mixture was stirred under an N_2 atmosphere at room temperature for 30 min, whereafter TMSOTf (287 μL, 1.58 mmol) was added. After 5 min, the reaction was quenched by the addition of triethylamine (6 mL), and the mixture was filtered through Celite and silica gel, concentrated, and purified by silica gel chromatography (toluene−EtOAc 9:1) to give a quantitative yield of ethyl 3-*O*-benzoyl-1,4,6-tri-*O*-benzyl-2-thio-D-fructofuranoside: ^{13}C NMR δ 14.6, 14.7, 21.7, 22.2, 69.0, 70.4, 72.2, 72.3, 73.0, 73.3, 73.6, 77.2, 79.2, 80.8, 80.9, 82.2, 82.5, 84.0, 93.8, 93.9, 127.4−138.1, 164.9, 165.2; ^1H NMR δ 1.07 (t), 1.23 (t), 2.63 (m), 3.6−3.8 (m), 4.1 (dd), 4.3−4.6 (m), 4.6−4.82 (dd), 5.6 (d), 6.05 (d), 7.1−8.0 (m). Anal. Calcd for $C_{36}H_{38}O_6S$: C, 72.22; H, 6.40. Found: C, 72.03; H, 6.32.

NaOMe (4.5 mL, 1M in MeOH) was added to this compound dissolved in MeOH (100 mL). After 10 h at room temperature, the mixture was neutralized with Dowex-50 H^+ ion-exchange resin, filtered, concentrated, and purified by silica gel chromatography (toluene−EtOAc 6:1) to give **3α** (5.8 g, 11 mmol, 70%) and **3β** (1.7 g, 3.2 mmol, 20%). **3α**: $[\alpha]_D$ +98° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 15.1, 22.3, 69.2, 71.9, 72.1, 73.3, 73.9, 79.1, 84.7, 85.9, 93.5, 127.6−138.0; ^1H NMR δ 1.2 (t), 2.58 (m), 3.55−3.90 (m), 4.2 (m), 4.55 (m), 4.73 (m), 7.3 (m). Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.21; H, 6.94. **3β**: $[\alpha]_D$ −14° (*c* 1.1, $CHCl_3$); ^{13}C NMR δ 14.7, 21.1, 71.2, 72.3, 73.1, 73.3, 73.7, 80.1, 80.9, 84.5, 94.9, 127.8−138.1; ^1H NMR δ 1.08 (t), 2.77 (q), 2.81 (d), 3.65 (m), 4.15 (m), 4.45−4.77 (m), 7.3 (m). Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93. Found: C, 70.24; H, 6.84.

Ethyl 1,4,6-Tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-2-thio-α-D-fructofuranoside (4α). A solution of **3α** (1.0 g, 2.02 mmol) and 4-methoxybenzyl bromide (2.03 g, 10.1 mmol) in DMF (5 mL) was added dropwise to a suspension of NaH (303 mg, 80% in oil, 10.1 mmol) in DMF (5 mL). The mixture was allowed to react for 10 h at room temperature and then cooled, and the reaction was quenched by careful addition of ice−water. The mixture was diluted with toluene, filtered through Celite, washed with aq satd $NaHCO_3$ and water, dried, and concentrated. Reversed-phase chromatography using a gradient of acetone−water 1:1−7:1, followed by silica gel chromatography (toluene−EtOAc 10:1 + 0.5% pyridine), gave **4α** (1.13 g, 1.84 mmol, 91%); $[\alpha]_D$ +35° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 14.8, 22.3, 55.3, 69.7, 70.5, 72.3, 72.7, 73.2, 73.5, 79.2, 84.0, 89.3, 93.8, 113.8, 127.5−130.0, 138.0, 138.2, 159.2; ^1H NMR δ 1.21 (t), 2.62 (m), 3.6−3.9 (m), 3.78 (s), 3.96 (dd), 4.03 (d), 4.2 (m), 4.4−4.7 (m), 6.8 (d), 7.3 (m). Anal. Calcd for $C_{37}H_{42}O_6S$: C, 72.29; H, 6.89. Found: C, 72.06; H, 6.76.

Ethyl 1,4,6-Tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-2-thio-β-D-fructofuranoside (4β). 4β was prepared from **3β** analogously to **4α**: yield 68%; $[\alpha]_D$ −29° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 14.7, 21.0, 55.2, 71.4, 72.4, 72.5, 73.1, 73.3, 73.5, 80.5, 84.5, 84.8, 94.0, 113.7, 127.6−130.1, 138.0, 138.2, 138.2, 159.2; ^1H NMR δ 1.18 (t), 2.59 (m), 3.6−3.8 (m), 3.77 (s), 4.2 (q), 4.27 (t), 4.43−4.68 (m), 6.8 (d), 7.3 (m). Anal. Calcd for $C_{37}H_{42}O_6S$: C, 72.29; H, 6.89. Found: C, 72.26; H, 6.88.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(4-methoxybenzyl)-α-D-mannopyranoside (8). Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[11] (**5**, 1 g, 2.2 mmol) was dissolved in DMF and the solution cooled to 0 °C, whereafter NaH (207 mg, 8.6 mmol) and, after 30 min, freshly distilled 4-methoxybenzyl bromide (1.73 g, 8.6 mmol) were added. The reaction mixture was allowed to attain room temperature and was, after 12 h, quenched by the addition of MeOH (1 mL), filtered through Celite, diluted with toluene (50 mL), and washed with aq satd $NaHCO_3$ and water, dried, concentrated, and purified by silica gel chromatography (toluene−EtOAc 9:1) to give **8** (954 mg, 1.63 mmol, 74%): $[\alpha]_D$ +29.5° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 54.7, 55.2, 68.8, 71.7, 72.1, 72.6, 73.0, 74.6, 74.9, 75.0, 80.2, 99.0, 113.7, 127.5−130.4, 138.4, 138.5, 159.1; ^1H NMR δ 3.5 (s), 3.7−4.0 (m), 3.73 (s), 4.4−4.9 (m), 6.8 (d), 7.1−7.4 (m). Anal. Calcd for $C_{36}H_{40}O_7$: C, 73.95; H, 6.90. Found: C, 73.73; H, 6.80.

2-(4-Nitrophenyl)ethyl 2-Azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(4-methoxybenzyl)-β-D-mannopyranoside (9). Barium oxide (38 mg, 249 μmol) and barium hydroxide octahydrate (10.1 mg, 34 μmol) were added to a stirred solution of 2-(4-nitrophenyl)ethyl 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranoside[10] (**6**, 50 mg, 113 μmol) in DMF (1.5 mL) containing molecular sieves (4 Å, 0.3 g). After 30 min, 4-methoxybenzyl bromide (135 mg, 670 μmol) was added. After an additional 12 h at ambient temperature, the reaction mixture was diluted with toluene and filtered through Celite. The filtrate was further diluted with toluene and washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (light petroleum (bp 40−60 °C)−EtOAc 3:1) to yield **9** (50 mg, 88.9 μmol, 79%); $[\alpha]_D$ −43° (*c* 0.30, $CHCl_3$); ^{13}C NMR δ 36.0, 55.2, 63.6, 67.4, 68.3, 69.8, 72.6, 75.6, 77.1, 78.4, 100.4, 101.6, 113.9, 123.6, 126.0−129.9, 137.2, 146.3, 146.3, 146.8, 149.0, 149.4, 149.8, 159.4; ^1H NMR δ 3.0 (m), 3.3 (m), 3.59 (s), 3.65−3.9 (m), 3.98 (t), 4.2 (m), 4.52 (d), 4.63−4.71 (dd), 6.8−8.2 (m).

Ethyl 4-Methoxybenzyl Ether (10). 4-Methoxybenzyl bromide (1 mL, 1 g/mL toluene solution) was added to a suspension of sodium hydride (750 mg, 25 mmol, 80% in oil) in distilled DMF (5 mL). The mixture was stirred under N_2 and cooled to 0 °C. Absolute ethanol (1.5 mL, 25 mmol) was added dropwise during 20 min. After an additional hour, the mixture was diluted with toluene, filtered through Celite and silica gel, washed with aq satd $NaHCO_3$ and brine, dried, filtered, and evaporated with care. The remaining yellow oil was further purified by silica gel chromatography (toluene−EtOAc 12:1 + 0.5% pyridine) to give **10** (650 mg, 78%, 3.9 mmol): ^{13}C NMR ($CDCl_3$/pyridine-d_6) δ 15.1, 55.1, 65.3, 72.3, 113.7, 128.1−130.6, 159.0; ^1H NMR ($CDCl_3$/pyridine-d_6) δ 1.25 (t), 3.55 (q), 3.8 (s), 4.45 (s), 6.85−7.23 (m).

General Procedure for the Formation of Mixed 4-Methoxybenzylidene Acetals. A solution of **4** (25 mg, 39 μmol) and the acceptor (50.5 μmol) (or **3α** and the 4-methoxybenzylated acceptor) in distilled CH_2Cl_2 (2 mL) containing molecular sieves (4 Å) was stirred at 0 °C for 30 min under an N_2 atmosphere. DDQ (21 mg, 93 μmol) in CH_2Cl_2 (4 mL) was added dropwise during 2 h. The reaction was allowed to continue at ambient temperature until the reaction was complete according to TLC (2−5 h) and then quenched by addition of triethylamine (1 mL). The mixture was filtered through a bilayer plug of Celite and silica gel, diluted with CH_2Cl_2 (20 mL), washed with a water solution of NaOH (0.9%), ascorbic acid (0.7%), citric acid (1.3%), and $NaHCO_3$ (3.5%) (25 mL) and twice with aq satd $NaHCO_3$ (25 + 50 mL), dried (Na_2SO_4), concentrated, filtered, and dried in vacuo for 1 h. The residue was used without further purification in the following step.

α-Ethoxy α-(ethyl 1,4,6-tri-*O*-benzyl-2-thio-α-D-fructofuranosid-3-*O*-yl)-4-methoxytoluene (11) was prepared, from **3α** and **10**, following the general procedure above. After the workup procedure the crude product was purified on a short silica gel column (toluene−EtOAc 9:1). This gave the *R*/*S*-acetal **11**, with only a trace of **3α** left: ^{13}C NMR ($CDCl_3$/pyridine-d_6) δ 15.1, 15.1, 22.1, 22.2, 55.2, 60.2, 60.5, 69.6, 69.8, 70.2, 71.2, 72.1, 73.2, 79.6, 80.4, 84.2, 85.0, 86.4, 93.9, 94.0, 100.9, 102.4, 113.4, 113.5, 127.3−138.3, 159.6, 159.66; ^1H NMR ($CDCl_3$/pyridine-d_6) δ 1.15−1.25 (m), 2.6 (m), 3.33−3.9 (m),

3.77 (s), 3.80 (s), 3.96 (dd), 4.1 (dd), 4.2−4.65 (m), 5.58 (s), 5.64 (s), 6.8 (d), 7.2−7.4 (m).

General Procedure for the Formation of Glycosides from the Tethered Acetals: With DMTST or MeOTf as Promoter. The promoter (4 equiv) was added under N_2 and at 0 °C to a stirred solution of the 4-methoxybenzaldehyde acetal (1 equiv) in CH_2Cl_2 (2 mL) containing molecular sieves (4 Å). The reaction mixture was allowed to attain room temperature and react for 16 h, whereafter the reaction was quenched by the addition of TEA (1 mL) and the mixture filtered through Celite, concentrated, and purified by silica gel chromatography (toluene−EtOAc 9:1).

With NIS, IDCP, or IDCT as Promoter. The promoter (NIS 3.4 equiv; IDCP or IDCT 1.5 equiv) was added under N_2 and at 0 °C to a stirred solution of the 4-methoxybenzylidene acetal (1 equiv) in CH_2Cl_2 (2 mL) containing molecular sieves (4 Å). The reaction mixture was allowed to attain room temperature and react for 16 h, whereafter the reaction was quenched by the addition of TEA (1 mL) and the mixture filtered through Celite, diluted with CH_2Cl_2, washed with aq satd $Na_2S_2O_3$, aq satd $NaHCO_3$, and water, dried, concentrated, and purified by silica gel chromatography (toluene−EtOAc 9:1).

Products. For yields see Table 1.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(1,4,6-tri-*O*-benzyl-*β*-D-fructofuranosyl)-α-D-mannopyranoside (12) was further purified by HPLC (hexane−EtOAc 3:1): $[\alpha]_D$ +23° (*c* 0.72, $CHCl_3$); ^{13}C NMR δ 54.5, 60.9, 69.4, 71.2, 71.8, 72.1, 72.7, 73.1, 73.6, 74.6, 74.7, 75.0, 79.1, 80.0, 84.2, 98.8, 103.9, 127.5−138.6; ^{1}H NMR δ 3.13 (s), 3.5−4.0 (m), 4.08−4.15 (m), 4.4 (d), 4.45 (d), 4.48−4.72 (m), 4.77 (d), 4.87 (d), 7.25−7.45 (m). Anal. Calcd for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.24; H, 6.39.

2-(4-Nitrophenyl)ethyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(1,4,6-tri-*O*-benzyl-*β*-D-fructofuranosyl)-*β*-D-mannopyranoside (13) was further purified by HPLC (hexane−EtOAc 3:1): $[\alpha]_D$ −16° (*c* 0.80, $CHCl_3$); ^{13}C NMR ($CDCl_3$/pyridine-d_6) δ 36.0, 66.2, 66.6, 68.2, 69.4, 71.6, 72.1, 73.7, 73.8, 76.8, 78.5, 78.7, 79.1, 99.4, 102.0, 105.0, 123.6−129.9, 136.5−138.1, 146.3; ^{1}H NMR ($CDCl_3$/pyridine-d_6) δ 2.5 (m), 2.95 (m), 3.3−3.95 (m), 4.03 (dd), 4.14 (t), 4.37−4.67 (m), 5.52 (s), 7.0−7.5 (m), 8.15 (d). Anal. Calcd for $C_{48}H_{50}O_{12}N_4$: C, 65.89; H, 5.76. Found: C, 65.93; H, 5.65.

Ethyl 1,4,6-tri-*O*-benzyl-*β*-D-fructofuranoside (14) was further purified by HPLC (hexane−EtOAc 3:1): $[\alpha]_D$ −11° (*c* 0.50, $CHCl_3$); ^{13}C NMR ($CDCl_3$/pyridine-d_6) δ 15.4, 57.1, 69.0, 71.6, 71.9, 73.3, 73.6, 79.5, 80.2, 85.0, 103.7, 127.6−138.2; ^{1}H NMR ($CDCl_3$/pyridine-d_6) δ 1.1 (t), 3.5−3.7 (m), 3.93 (t), 4.13 (1H, m), 4.35 (d), 4.5−4.65 (m), 4.8 (d), 7.3 (m). Anal. Calcd for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.52; H, 7.10.

α-*N*-Succinimido-α-[methyl 2,3,4-tri-*O*-benzyl-6-*O*-(1,4,6-tri-*O*-benzyl-*β*-D-fructofuranosyl-3-*O*-yl)-α-D-mannopyranoside]-4-methoxytoluene (15) was further purified by HPLC (hexane−EtOAc 7:3): $[\alpha]_D$ −62° (*c* 1.0,$CHCl_3$); ^{13}C NMR ($CDCl_3$/pyridine-d_6) δ 28.0, 54.5, 55.1, 60.8, 70.8, 71.3, 72.1, 72.3, 72.8, 73.3, 73.6, 74.8, 74.9, 75.2, 77.3, 79.4, 80.3, 81.6, 84.1, 84.5, 98.9, 103.3, 113.2, 122.3−129.1, 137.8, 138.4, 138.7, 138.9, 139.0, 159.3, 176.6; ^{1}H NMR ($CDCl_3$/pyridine-d_6) δ 2.23 (m), 3.13 (s), 3.57 (s), 3.55−3.93 (m), 3.98−4.1 (m), 4.18 (t), 4.30 (d), 4.35−4.7 (m), 4.8 (d), 6.57 (s), 6.65 (d), 7.1−7.4 (m), 8.1 (2H, d). Anal. Calcd for $C_{67}H_{71}O_{14}N$: C, 72.2; H, 6.42. Found: C, 71.99; H, 6.31.

α-*N*-Succinimido-α-[2-(4-nitrophenyl)ethyl 2-azido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(1,4,6-tri-*O*-benzyl-*β*-D-fructofuranosyl-3-*O*-yl)-*β*-D-mannopyranoside]-4-methoxytoluene (16): $[\alpha]_D$ −51° (*c* 1.0, $CHCl_3$); ^{13}C NMR ($CDCl_3$/pyridine-d_6) δ 27.9, 36.1, 55.2, 65.6, 67.4, 68.3, 69.56, 69.6, 71.6, 72.96, 73.0, 73.1, 73.6, 77.2, 79.7, 82.4, 83.1, 85.9, 100.0, 102.0, 102.9, 113.4, 123.6−129.9, 137.2, 137.3, 138.1, 138.2, 146.3, 146.8, 159.5, 176.5; ^{1}H NMR ($CDCl_3$/pyridine-d_6) δ 2.2 (m), 3.0 (m), 3.35 (dd), 3.45−3.8 (m), 3.75 (s), 3.95−4.15 (m), 4.2−4.5 (m), 5.5 (s), 6.55 (s), 6.7 (d), 7.1−7.5 (m), 8.1 (d); FAB-MS 1091.4 $[M - H]^+$. Anal. Calcd for $C_{60}H_{61}O_{15}N_5$: C, 65.98; H, 5.63. Found: C, 65.78; H, 5.52.

α-*N*-Succinimido-α-(ethyl 1,4,6-tri-*O*-benzyl-*β*-D-fructofuranosid-3-*O*-yl)-4-methoxytoluene (17): $[\alpha]_D$ −47° (*c* 1.0, $CHCl_3$); ^{13}C NMR δ 15.4, 28.0, 55.2, 57.4, 71.3, 71.5, 72.6, 73.4, 73.43, 78.7, 81.6, 83.4, 84.0, 103.4, 113.4, 127.4−128.8, 138.0, 138.5, 159.4, 176.2, 176.5; ^{1}H NMR δ 1.0 (t), 2.3 (s), 3.5−3.7 (m), 3.75 (s), 4.07 (m), 4.2 (t), 4.37 (d), 4.47−4.63 (m), 6.5 (s), 6.8 (d), 7.1−7.2 (m). Anal. Calcd for $C_{41}H_{43}O_9N$: C, 70.97; H, 6.24. Found: C, 69.53; H, 6.38.

1,4,6-Tri-*O*-benzyl-2,3-*O*-(4-methoxybenzylidene)-*β*-D-fructofuranose (18): mp 110−111.5 °C; $[\alpha]_D$ +28° (*c* 1.05, $CHCl_3$); FAB-MS 591.4 $[M + Na]^+$; ^{13}C NMR ($CDCl_3$/pyridine-d_6) δ 55.3, 69.6, 70.7, 72.0, 73.55, 73.63, 81.8, 82.6, 86.8, 103.9, 112.1, 113.7, 127.5−128.6, 137.4, 138.0, 138.1, 160.8; ^{1}H NMR ($CDCl_3$/pyridine-d_6) δ 3.6−3.9 (m), 3.8 (s), 4.2 (m), 4.5−4.8 (m), 4.9 (d), 6.0 (s), 6.8 (d), 7.2−7.4 (m). Anal. Calcd for $C_{35}H_{36}O_7$: C, 73.92; H, 6.38. Found: C, 74.00; H, 6.53.

Acknowledgment. We thank Professor Per J. Garegg for his interest in this work and the Swedish Natural Science Research Council for financial support.

Supporting Information Available: 270 MHz ^{1}H and 67.5 MHz ^{13}C NMR spectra of compounds **11** and **14**−**18** (12 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.

JO970983R