Stereospecific Synthesis of β-D-Fructofuranosides Using the Internal Aglycon Delivery Approach

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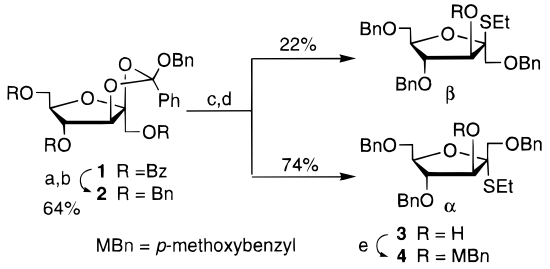
Syntheses of fructofuranosides using fructofuranosyl donors are not very frequent. Only a small number of papers have been published on this subject.[1−4] Although the methods used generally give high yields of fructofuranosides, a definitive drawback is that exclusively the α-fructofuranoside (when a participating group at the 3-position is used) or a mixture of α- and β-anomers (if a nonparticipating group is used) are obtained. A further complication is that these anomeric mixtures often are impossible or difficult to separate by chromatography. Since most fructofuranosides found in nature are β-linked,[5] the need for a stereospecific β-glycosylation method for fructofuranosides is obvious.

In a program directed toward synthesis of capsular polysaccharides (CPS:s) from *Haemophilus influenzae*, we became interested in the synthesis of β-fructofuranosides, since this is a motif in the type e CPS.[6] Our earlier successful experience with thioglycosides as glycoside donors led us to synthesize and try this type of donors in the fructofuranosidic field as a continuation of the work of Kochetkov and co-workers.[1,2] Although exceptionally high yields of fructofuranosides were obtained, the best ratio of β- to α-linked product obtained was 1.6/1 in inseparable mixtures.[4]

Since 1,2-*cis*-pyranosides, especially the difficult β-D-*manno*-configuration and also the α-D-*gluco*-configuration, have successfully been synthesized using the internal aglycon delivery approach,[7−11] we decided to try this method with furanosides. Of the existing variation of silicon and carbon acetals used earlier, the *p*-methoxybenzaldehyde acetal, introduced by Ito and Ogawa,[10] seems to be the most promising, especially in oligosaccharide synthesis.[11] Thus, the key thioglycoside ethyl 1,4,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-2-thio-α-D-fructofuranoside (**4**α) was synthesized together with its β-anomer (Scheme 1). The known,[12] crystalline orthoester **1**

Scheme 1[a]



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

was deacylated using sodium methoxide and then benzylated to give **2** in an overall yield of 64%. Rearrangement of the anomeric orthoester using trimethylsilyl trifluoromethylsulfonate in the presence of a large excess of ethyl mercaptan (∼100 equiv) gave ethyl 1,4,6-tri-*O*-benzyl-3-*O*-benzoyl-2-thio-D-fructofuranoside as an inseparable α/β-mixture. Debenzoylation of this mixture afforded the 3-OH compounds, which could easily be separated by silica gel chromatography to give pure **3**α and **3**β in overall yields of 74 and 22%, respectively, from **2**. Then *p*-methoxybenzylation gave the key intermediates **4**α (91%) and **4**β (68%), ready for acetal tethering with different aglycons.

Two different acceptors, both used in the earlier work,[4] were chosen as model compounds, one primary alcohol, methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**5**), and one secondary, 2-(4-nitrophenyl)ethyl 2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranoside (**8**), the latter of interest for the synthesis of the *Haemophilus influenzae* type e CPS. When a slight modification of the published procedure was used,[11] the two intermediate acetals **6** and **9** were formed in high yields, according to TLC, when **4**α was reacted with DDQ in the presence of **5** or **8**, respectively (Schemes 2 and 3). No characterization of the tethered acceptor−donor acetals **6** and **9** were performed, but immediately after workup they were activated by a promoter. The addition of dimethyl(methylthio)sulfonium trifluoromethanesulfonate[13] (DMTST) to a solution of either of the two acetals in CH_2Cl_2 gave a main product, which was found to be the pure β-fructofuranosyl disaccharide, no α-product was isolated. **6** gave **7** in 77% yield and **9** gave **10** in 76% overall yield from **4**α (Schemes 2 and 3). Methyl trifluoromethanesulfonate[11] gave lower yields, especially with the primary acceptor **5** (31% yield of **7**, 59% yield of **10**).

The β-furanosyl configuration in disaccharide products **7** and **10** was assigned using the ^{13}C chemical shift of the anomeric carbon. *O*-β-linked fructofuranosides give resonance at a higher field (∼103−105 ppm) than the corresponding α-anomer (∼107−109 ppm).[14] The C-2′ shift in derivative **7** was 104.0 ppm, whereas that in disaccharide **10** was found to be 105.0 ppm. These values can also be compared to the values of the corresponding 3′-*O*-benzyl derivatives, obtained earlier as α/β-mixtures, which were 107.9/104.2 ppm and 108.9/104.8

(1) Balan, N. F.; Backinowsky, L. V.; Betaneli, V. I.; Kochetkov, N. K. *Bioorg. Khim.* **1981**, *7*, 1566−1577.
(2) Backinowsky, L. V.; Balan, N. F.; Betaneli, V. I.; Kochetkov, N. K. *Carbohydr. Res.* **1982**, *99*, 189−193.
(3) Müller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *27*, 4763-4766.
(4) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 1234−1238.
(5) Lindberg, B. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 279−318.
(6) Branefors-Helander, P.; Kenne, L.; Lindberg, B.; Petersson, K.; Unger, P. *Carbohydr. Res.* **1981**, *88*, 77−84.
(7) (a) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.***1991**, *113*, 9376−9377; (b) *Synlett* **1992**, 759−761; (c) *Can. J. Chem.* **1994**, *72*, 1447−1465.
(8) Stork, K.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088.
(9) (a) Bols, M. *J. Chem. Soc., Chem. Commun.***1992**, 913−914; (b) *J. Chem. Soc., Chem. Commun.* **1993**, 791−792; (c) *Acta Chem. Scand.* **1993**, *47*, 829−834.
(10) Ito, Y.; Ogawa, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767.
(11) Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680−4681.
(12) Helferich, B.; Bottenbruch, L. *Chem. Ber.* **1953**, *86*, 651−657.
(13) Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9-C12.
(14) Angyal, S. J.; Bethell, G. S. *Aust. J. Chem.* **1976**, *29*, 1249−1265.

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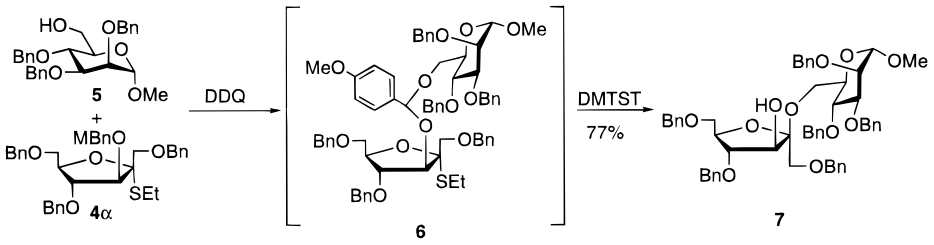
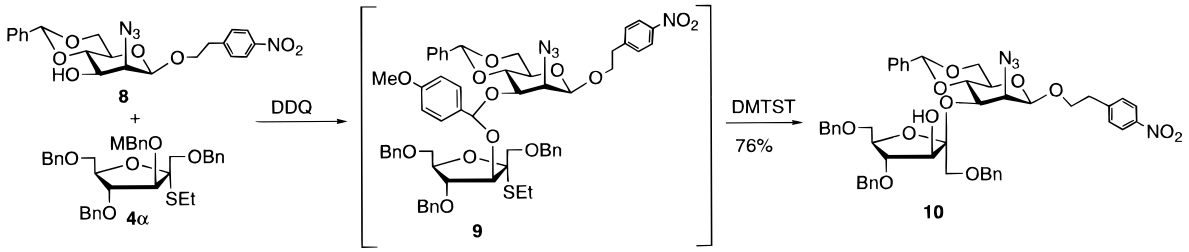
Scheme 2



Scheme 3



ppm, respectively.[4] Furthermore, benzylation of compound **7** gave a derivative with NMR identical to the assigned β-part of the previously synthesized 3′-*O*-benzyl derivative.

In conclusion, the intricate problem of synthesizing β-D-fructofuranosides (and probably other 1,2-*cis*-furanosides) can be solved by using an internal glycosidation procedure.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **4**, **7**, and **10** (3 pages).

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