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EFFICIENT D-FRUCTOPYRANOSYLATION METHOD CATALYZED BY SCANDIUM TRIFLATE AND PREPARATION OF NEW SUCROSE ANALOGS†

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†Dedicated to Professor Dr. Masakatsu Shibasaki's 70th birthday

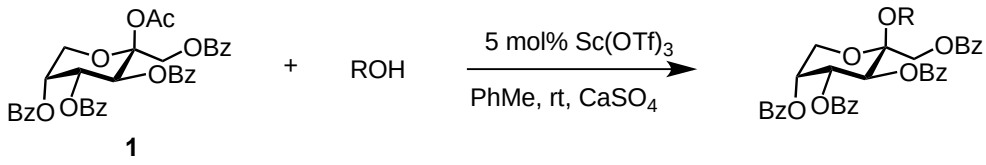
Abstract – We successfully established a highly efficient β-fructopyranosylation method that used a fully benzoylated β-D-fructopyranosyl acetate as the glycosyl donor and $Sc(OTf)_3$ as the catalytic activator. The syntheses of non-reducing disaccharide units as new sucrose analogs were achieved based on the β-fructopyranosylation reaction of 1-hydroxy group of glucose derivatives.

D-Fructose is abundant in nature, and fructose-containing sugars are expected to have several outstanding properties such as sweetness, non-cariogenicity, and low digestivity.[1] The development of novel fructosides possessing such unique properties can significantly contribute to food science. Considerable attention has been paid to the sucrose analogs comprising a D-fructose moiety, which are categorized as non-reducing disaccharides. Some sucrose analogs having a D-fructofuranose moiety, i.e., D-aldopyranosyl-(1→2)-D-fructofuranosides, have been prepared using chemical synthetic or enzymatic approaches.[2] However, to the best of our knowledge, there has been only one report on the synthesis of the sucrose analog having a D-fructopyranose moiety, though a few D-fructopyranosylation reactions have been recently reported.[3]

We have recently reported a highly efficient D-fructofuranosylation method that used a fully benzoylated or benzylated D-fructofuranosyl acetate as the glycosyl donor and scandium triflate [$Sc(OTf)_3$] as the catalytic activator.[4] The fructofuranosylation method successfully achieved the syntheses of several non-reducing disaccharides of the sucrose analogs, i.e., D-aldopyranosyl-(1→2)-D-fructofuranosides. Our attention was then directed toward developing the D-fructopyranosylation reaction which enabled us to prepare the non-reducing disaccharides containing a D-fructopyranose moiety as new sucrose analogs.

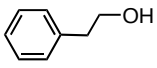
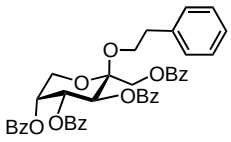
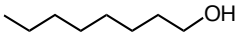
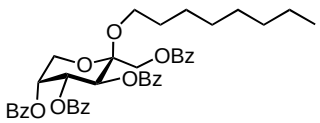
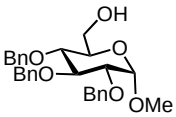
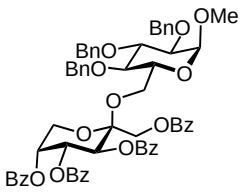
In this study, we describe the application of our fructofuranosylation method to the D-fructopyranosylation strategy and the syntheses of non-reducing disaccharides containing a D-fructopyranose moiety as new sucrose analogs based on the D-fructopyranosylation reaction of 1-hydroxy group of glucose derivatives.

First, the preparation of the glycosyl donor 1,3,4,5-tetra-*O*-benzoyl-D-fructopyranosyl acetate (**1**) was attempted according to our reported method for acetylating the anomeric hydroxyl function of ketoses.[5] Compound **1** was obtained in 88% yield with a β-stereoselectivity via the acetylation of 1,3,4,5-tetra-*O*-benzoyl-D-fructopyranose[6] using *n*-butyllithium and acetic anhydride in tetrahydrofuran at −78 ºC.



Scheme 1

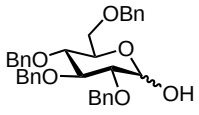
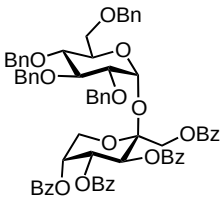
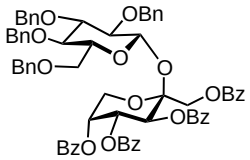
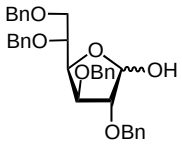
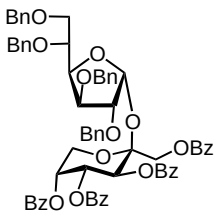
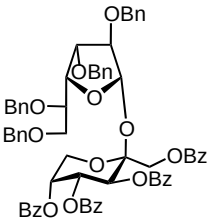
Table 1. D-Fructopyranosylation reactions with **1** of **2–4**

Entry[a)]	Alcohol acceptor	Product[b)]	Yield/%	Chemical shift of C-2/ppm[c)]
1	 **2**	 **5**	85	99.2
2	 **3**	 **6**	76	99.3
3	 **4**	 **7**	55	99.4

a) Reaction conditions: Molar ratio: donor/acceptor/$Sc(OTf)_3$ = 1/1/0.05, reaction time = 2 h (Entry 1); 3 h (Entry 2); 1 h (Entry 3), and temperature = rt. b) Only β-anomer was formed. c) The ^{13}C NMR chemical shifts of C-2 of the fructopyranose moieties were reported in the range of 99 - 102 ppm. See. Ref. 3b.

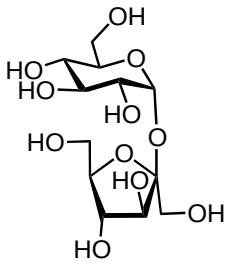
Next, the D-fructopyranosylation reactions between **1** and several alcohols were investigated using $Sc(OTf)_3$ as the activator, as shown in Scheme 1. The alcohols utilized as the glycosyl acceptors were phenethyl alcohol (**2**), *n*-octanol (**3**), and sugar alcohol (**4**). The reactions of **1** with **2 – 4** were examined under the same reaction conditions as we previously reported.[4] The fructopyranosylation reactions smoothly proceeded under the reaction conditions using 5 mol% $Sc(OTf)_3$ in toluene at room temperature, and the corresponding β-fructopyanosides **5 – 7** were stereoselectively produced in the range of 55% – 85% yield. These results are summarized in Table 1.[7] The β-stereochemistry of the fructopyranosidic linkages was determined by the nuclear Overhauser effect interaction between H-1 and H-3 on the fructopyranosyl moiety. The high β-stereoselectivity of the reaction could be explained by the anomeric effect and the equatorial orientation of the benzoyloxymethyl group at C-2. Table 1 also shows the ^{13}C NMR chemical shifts of C-2 of the fructopyranose moieties of compounds **5** - **7**. We confirmed that these ^{13}C NMR data agreed with the reported data of similar β-D-fructopyranosyl compounds.[3b] Thus, we demonstrated that our D-fructofuranosylation method could be applied to the syntheses of D-fructopyranosides.

Table 2. Syntheses of non-reducing disaccharides by D-fructopyranosylation reaction with **1** of **8** (or **9**)

Entry[a]	Acceptor	Product[c] (Yield/%) [isomer ratio]		Chemical shift/ppm	
				C-2 of fructose	H-1 of glucose (*J*/Hz)
1	 **8**	 **10** (15)	 **11** (26) [37:63]	**10**: 101.2[d] **11**: 101.1	5.50 (d, 3.4)[d] 4.90 (d, 8.3)
2	 **9**	 **12** (18)	 **13** (14) [55:45]	**12**: 100.3 **13**: 100.6	5.73 (d, 3.6) 5.56 (s)
3[b]	**9**	**12** (27)	**13** (26) [52:48]	-	-

a) Reaction conditions: Molar ratio: donor/acceptor/$Sc(OTf)_3$ = 1/1/0.05, reaction time = 1 h (Entry 1); 4 h (Entry 2); overnight (Entry 3), and temperature = rt. b) Molar ratio: donor/acceptor/$Sc(OTf)_3$ = 1/2/0.05. c) Isolated yield. Only β-fructopyranosyl linkage was formed. d) The reported values were 101.3 and 5.51 (d, 3.3). See. Ref. 3b.

Next, to prepare two kinds of non-reducing disaccharide units as sucrose analogs, we investigated the D-fructopyranosylation reaction with **1** of the glucose derivatives 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**8**) and 2,3,5,6-tetra-*O*-benzyl-D-glucofuranose (**9**).[8] The reaction of **1** with **8** under similar reaction conditions using 5 mol% $Sc(OTf)_3$ yielded the non-reducing disaccharide with the two isomers **10** and **11** in 15% and 26% yields, respectively. The total yield was 41%. Similarly, the reaction of **1** with **9** afforded the non-reducing disaccharide with the two isomers (**12** and **13**) in 18% and 14% yields, respectively (total yield: 32%), whereas the reaction with two equivalents of **9** afforded **12** and **13** in 27% and 26% yields, respectively (total yield: 53%). These results are summarized in Table 2. In these isomers, both α- and β-glucosidic linkages were formed although all of their fructopyranosidic linkages were only the β-form. The stereospecific formation of these glucosidic linkages seemed to depend on the anomer ratios of the glucose derivatives **8** and **9**.[9] The structures of the sucrose analogs (**10** and **12**) are very interesting compared with the structure of the natural sucrose molecule. While the natural sucrose molecule has a fructose moiety of the five-membered furanose ring, compound **10**[3b] has a fructose moiety of the six-membered pyranose ring. Compound **12** has a six-membered fructopyanose ring and a five-membered glucofuranose ring, indicating that the ring sizes are reversed between the fructose and glucose of the natural sucrose. Compounds **12** and **13** were novel. Thus, we succeeded in synthesizing the two kinds of non-reducing disaccharide as sucrose analogs using the β-fructopyranosylation reaction with **8** and **9**.



sucrose

In summary, we established a β-fructopyranosylation protocol that used a fully benzoylated D-fructopyranosyl acetate as the glycosyl donor and $Sc(OTf)_3$ as the activator and successfully demonstrated the syntheses of two kinds of non-reducing disaccharide units as sucrose analogs based on the β-fructopyranosylation strategy.

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7. A typical fructopyranosylation procedure: To a stirred suspension of $Sc(OTf)_3$ (2.4 mg, 0.005 mmol) and **2** (12 μL, 0.1 mmol) in toluene (3 mL), **1** (62 mg, 0.1 mmol) was added in the presence of anhydrous $CaSO_4$ (approximately 100 mg) under an Ar atmosphere and stirred for 1.5 h. The reaction was subsequently quenched by adding a saturated aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a saturated aqueous NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified using a preparative silica gel TLC (PTLC; EtOAc/hexane = 1/2) to yield **5** (58 mg, 85%) as amorphous. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.01-3.06 (2H, m, C*H*$_2$Ph), 3.40 (1H, d, *J* = 13.1 Hz, H$_a$-6), 3.81 (1H, d, *J* = 13.1 Hz, H$_b$-6), 3.90-3.93 (2H, m, C*H*$_2$CH$_2$Ph), 4.24 (1H, d, *J* = 11.7 Hz, H$_a$-1), 4.77 (1H, d, *J* = 11.7 Hz, H$_b$-1), 5.55 (1H, d, m, H-5), 5.86 (1H, dd, *J* = 3.4 Hz, 10.3 Hz, H-4), 6.27 (1H, d, *J* = 10.3 Hz, H-3), 7.09-7.90 (25H, m, Ph). ^{13}C NMR (150 MHz, $CDCl_3$): δ 36.3 (*C*H$_2$Ph), 61.6 (C-1), 62.7 (*C*H$_2$CH$_2$Ph), 62.9 (C-6), 68.4 (C-3), 69.2 (C-4), 70.0 (C-5), 99.2 (C-2), 126.2-138.7 (Ph), 165.3-165.4 (C=O). HRMS (ESI): *m/z* calcd for $C_{42}H_{36}O_{10}\cdot Na^+$: 723.2201; found: 723.2170. $[\alpha]_D^{25}$ -163 (*c* 2.9, $CHCl_3$).
8. Compound **9** was readily obtained in 83% yield from the corresponding methyl 2,3,5,6-tetra-*O*-benzyl-D-glucofuranoside via acidic hydrolysis using 3 M HCl-THF. The preparation of methyl 2,3,5,6-tetra-*O*-benzyl-D-glucofuranoside is explained in the following study: S. Ghorai, R. Mukhopadhyay, A. P. Kundu, and A. Bhattacharjya, *Tetrahedron*, 2005, **61**, 2999.
9. The ^{1}H NMR spectrum showed that the α/β anomer ratio of compound **9** in $CDCl_3$ was 42/58. We have reported the α/β anomer ratio of compound **8** in solution and already discussed the influence to the non-reducing disaccharide synthesis based on the glycosylation reaction. See: T. Yamanoi, R. Inoue, S. Matsuda, K. Katsuraya, and K. Hamasaki, *Tetrahedron: Asymmetry*, 2006, **17**, 2914.