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SCANDIUM TRIFLATE-CATALYZED D-FRUCTOFURANOSYLATION REACTIONS USING DISACCHARIDE UNITS†

Takashi Yamanoi[1],* Noriko Misawa,[1,2] Sho Matsuda,[1] Mikio Watanabe,[2] and Yoshiki Oda[1]

[1]The Noguchi Institute, 1-8-1 Kaga, Itabashi-ku, Tokyo 173-0003, Japan: tyama@noguchi.or.jp; [2]Department of Chemistry, School of Science, Tokai University, 4-1-1 Kitakaname, Hiratsuka, Kanagawa, 259-1292, Japan

†Dedicated to Professor Dr. Ei-ichi Negishi on his 77th birthday.

Abstract – This paper describes efficient D-fructofuranosylation reactions catalyzed by scandium triflate. The reactions used several benzoylated or benzylated glycosyl acylate derivatives from disaccharides containing the D-fructofuranose moiety at the reducing ends. Only 5 - 10 mol% scandium triflate effectively promoted the D-fructofuranosylation reactions using the disaccharide derivatives as the glycosyl donors. The structures and protecting groups of the disaccharide donors and alcohol acceptor species influenced the stereoselectivity and reactivity of the fructofuranosylation reactions. The fructofuranosylation reactions could be applied to synthesize several non-reducing trisaccharides containing a sucrose-like disaccharide unit.

D-Fructose is abundant in nature, and mostly occurs in the furanose form. It plays an important role in several biological processes,[1] and considerable attention is paid to fructosylated compounds and their biological functions. For example, the non-reducing oligosaccharides, which contain the disaccharide unit of D-glucopyranosyl-(1→2)-D-fructofuranoside, are classified as sucrose derivatives and mimics, and are expected to have biological functions useful in food ingredients. They are also useful compounds to be employed as synthetic targets.[2] Consequently, several chemical glycosidations using D-fructofuranose derivatives have been studied, i.e., D-fructofuranosylation reactions.[3]

We have recently reported a highly efficient D-fructofuranosylation method catalyzed by scandium triflate ($Sc(OTf)_3$).[4] This method utilized the 1,3,4,6-tetra-*O*-benzoyl-D-fructofuranosyl acetates (**1**) or 1,3,4,6-tetra-*O*-benzyl-D-fructofuranosyl acetates (**2**) as the glycosyl donor, as shown in Figure 1, and $Sc(OTf)_3$ as the activator. Only 5 mol% $Sc(OTf)_3$ facilitated the smooth completion of the fructofuranosylation reactions using **1** or **2**. Compound **1** was slightly less reactive than **2** due to the effect of the electron-withdrawing benzoyl groups. However, the reactions using **1** provided α-fructofuranosides with higher stereoselectivities than those using **2**. The high α-stereoselectivity could be explained by the effect of the neighboring-group participation of the benzoyloxy group at C-3 of **1**.

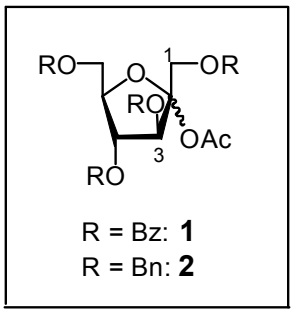


Figure 1

Lacturose, malturose, and palatinose are disaccharides containing the D-fructofuranose moiety at the reducing ends. They are commercially available reagents. Heijden et al. reported the glycosidation reaction using these unprotected disaccharides and aliphatic alcohol solvents in the presence of the MCM-41 catalyst.[5] Although this method could only afford simple alkyl glycosides directly from the unprotected disaccharides, it indicated the possibility that various novel fructosylated compounds could be designed and synthesized by the fructofuranosylation technique using the glycosyl donors prepared from these disaccharides.

We applied our $Sc(OTf)_3$-catalyzed D-fructofuranosylation method to the glycosidation reaction, using the glycosyl donors prepared from the disaccharides containing the D-fructofuranose moiety at the reducing ends, in order to expand the versatility of our method and to demonstrate the synthesis of novel fructofuranoside compounds from these disaccharides. We also studied the synthesis of the non-reducing trisaccharides containing a sucrose-like disaccharide unit based on the fructofuranosylation strategy.

Figure 2 shows the disaccharide derivatives used as glycosyl donors, alcohols utilized as glycosyl acceptors, and products. We first investigated the D-fructofuranosylation reactions using the fully benzoylated disaccharides **3**-**5**. Compounds **3**-**5** were readily prepared in 77%, 91%, and 84% yields with α/β ratios of 72/28, 70/30, and 90/10 from lacturose, malturose, and palationose according to the general benzoylation procedure by using benzoyl chloride and pyridine in dichloromethane.[6] When the reaction of **3** with **10** was examined using 5, 10, and 20 mol% $Sc(OTf)_3$ in toluene at room temperature (Scheme 1), the corresponding fructofuranoside **15** was successfully obtained in the range 84% - 92% yield (Table 1, Entries 1-3). Only 10 mol% $Sc(OTf)_3$ could sufficiently activate **3**, and the C-2 benzoyloxy group of **3** acted as the good leaving group.

The α/β anomer ratios of **15** obtained from these reactions were 84/16, 83/17, and 84/16, respectively

(Entries 1-3). In addition, the reaction of **3** with several types of acceptor alcohols **11**-**13** under similar reaction conditions also afforded the corresponding fructofuranosides **16**-**18** in excellent yields of 88%, 80%, and 86%, and their α/β anomer ratios were 84/16, 84/16, and 88/12, respectively (Entries 4-6). Although these reactions mainly produced α-anomers, β-anomers were also produced in small amounts. The predominance of the α-stereoselectivity was attributed to the effect of the neighboring-group participation of the benzoyloxy group at C-3. This indicated that the α-stereoselectivity of fructofuranosylation using **3** was slightly poorer than that using **1**. We assumed that the steric hindrance of the benzoylated β-D-galactopyranosyl moiety at C-4 of **3** would slightly reduce the α-stereoselectivity of the fructofuranosylation reactions.

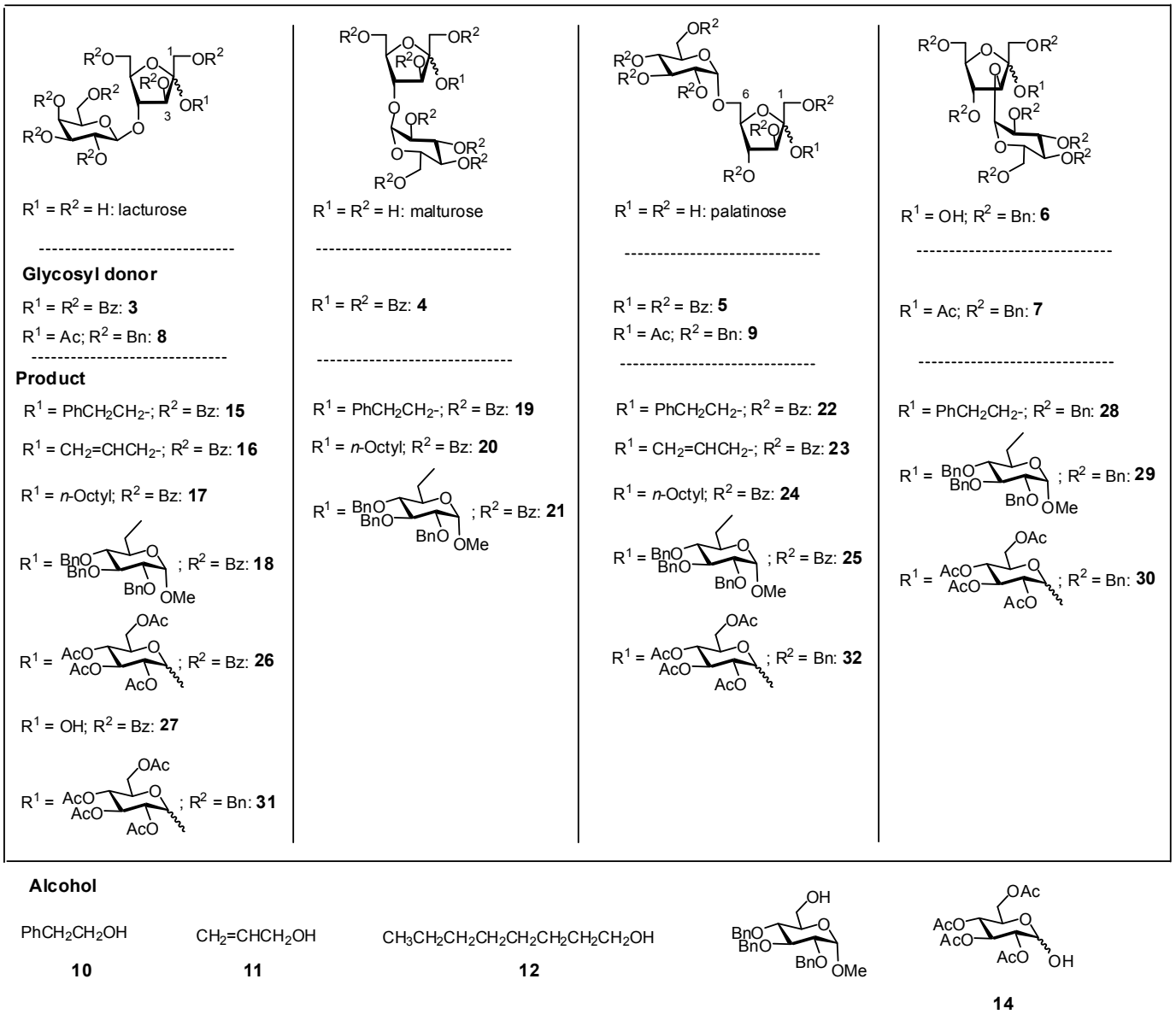
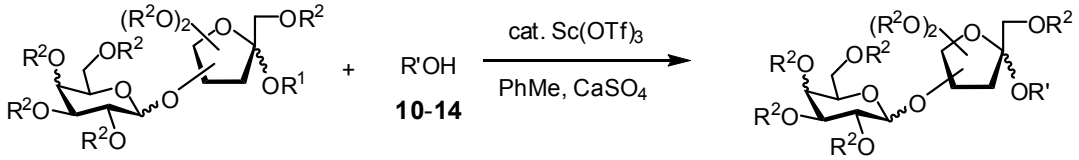


Figure 2. Disaccharide derivatives and alcohols utilized in this study, and products



3-5, 7-9 **15-26, 28 -32**

Scheme 1

Table 1. D-Fructofuranosylation reactions using the disaccharide derivatives

Entry[a)]	Donor	Acceptor	$Sc(OTf)_3$ (mol%)	Product	Yield (%)	α/β Anomer ratio[b)]
1	**3**	**10**	5	**15**	84	84/16
2	**3**	**10**	10	**15**	91	83/17
3	**3**	**10**	20	**15**	92	84/16
4	**3**	**11**	10	**16**	88	84/16
5	**3**	**12**	10	**17**	80	84/16
6	**3**	**13**	10	**18**	86	88/12
7	**4**	**10**	10	**19**	81	83/17
8	**4**	**12**	10	**20**	71	80/20
9	**4**	**13**	10	**21**	55	77/23
10	**5**	**10**	10	**22**	83	α
11	**5**	**11**	10	**23**	90	α
12	**5**	**12**	10	**24**	86	α
13	**5**	**13**	10	**25**	84	α
14	**3**	**14**	10	**26**	trace	N.D.[c)]
15[d,e)]	**7**	**10**	5	**28**	87	61/39
16[d,e)]	**7**	**13**	5	**29**	82	73/27
17[d,f)]	**7**	**14**	5	**30**	53	α (65/35)[g)]
18[d,f)]	**8**	**14**	5	**31**	48	α (68/32)[g)]
19[d,f)]	**9**	**14**	5	**32**	47	α (65/35)[g)]

a) Molar ratio: donor/acceptor = 1/1; Reaction time = 1 h - over night; Temp. = rt b) Determined by ^{1}H NMR. c) N.D. = Not determined. d) Temp. = 0 ºC e) Reaction time = 20 min. f) Reaction time = 30 – 90 min. g) α/β Anomer ratio of the glucopyranosyl moiety at C-1". The fructofuranosidic linkage = α only.

Next, we investigated the fructofuranosylation reactions using **4** and **5** with the benzoylated α-D-glucopyranose moiety at C-4 or C-6 in order to clarify their influence on the fructofuranosylation stereoselectivities. When the reactions between **4** and alcohols **10**, **12**, and **13** were conducted under similar reaction conditions, the corresponding fructofuranosides **19-21** were obtained in 81%, 71%, and

55% yields with α/β anomer ratios of 83/17, 80/20, and 77/23, respectively (Entries 7-9). The stereoselectivities of these reactions using **4** almost corresponded with those using **3**. The reactions of **5** with **10**-**13** under similar reaction conditions produced the corresponding fructofuranosides **22**-**25** in high yields of 83%-90% (Entries 10-13). All these reactions only produced α-anomers. The stereoselectivities of the reactions using **5** were slightly different from those using **3** and **4**, and the high α-stereospecificity corresponded with our past results for the reactions using **1**. These observations exhibited a high possibility that the steric hindrance of the benzoylated carbohydrate moieties at C-4 in the disaccharide donors **3** and **4** may partially prevent the acceptor alcohols from α-attacking.

Furthermore, we attempted to synthesize the non-reducing trisaccharides containing the D-glucopyranosyl-(1→2)-D-fructofuranoside unit by the fructofuranosylation reactions using the disaccharide donors. When the fructofuranosylation of **14** using **3** was examined under similar reaction conditions, the desired non-reducing trisaccharide **26** was obtained in trace amounts, and compound **27** having an anomeric hydroxyl group was the main product (Entry 14). It appeared that compound **14** was much less reactive than alcohols **10**-**13**.

We additionally investigated the fructofuranosylation reactions using the benzyl group-protected disaccharide **7** containing the C-2 acetoxy group as the leaving group. The disaccharide derivative **7** was expected to act as a highly reactive glycosyl donor because of the effect of the electron-donating benzyl groups. Compound **7** was obtained in 75% yield with an α/β ratio of 73/27 by the acetylation of **6**[7] using *n*-butyllithium and acetic anhydride in THF at -30 ºC. Subsequently, we examined the reactions of **7** with the alcohols **10**, **13**, and **14** under similar reaction conditions using 5 mol% $Sc(OTf)_3$ in toluene at 0 ºC. The corresponding fructofuranosides **28** and **29** were obtained in excellent yields of 87% and 82% with α/β anomer ratios of 61/39 and 73/27 (Entries 15 and 16). It was noteworthy that the reaction between **7** and **14** smoothly proceeded to give the desired non-reducing trisaccharide **30** in a satisfactory yield of 53% with both isomers (Entry 17).

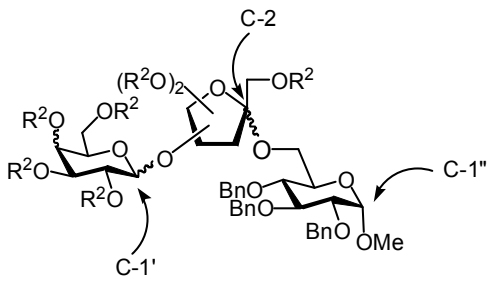
The results using **7** urged us to prepare two new disaccharide donors **8** and **9** from lacturose and palatinose, and to use them in the synthesis of the non-reducing trisaccharides. The benzyl group-protected **8** and **9** containing the C-2 acetoxy group were prepared from **16** and **23** by the following synthetic steps: deprotection of the benzoyl groups of **16** and **23** using NaOMe in MeOH-$CHCl_3$ and subsequent benzylation using BnBr-NaH in DMF (87%, 45%); deprotection of the allyl group using 75% aqueous H_2SO_4-1,4-dioxane[7] (88%, 95%); and subsequent acetylation using *n*-BuLi and Ac_2O in THF (82%, 83%). The fructofuranosylation of **14** using the disaccharide donors **8** and **9** under similar reaction conditions succeeded in providing the desired trisaccharides **31** and **32** in 48% and 47% yields with both isomers, respectively (Entries 18 and 19). Thus, we successfully synthesized the non-reducing trisaccharides **31** and **32** by the fructofuranosylation method.

The NMR spectra showed that all fructofuranosidic linkages of **30**, **31**, and **32** were α,[8] and the α/β ratios of the formed glucopyranosidic linkages were 65/35, 68/32, and 65/35, respectively (Entries 17-19). The ^{13}C NMR data of each anomeric carbons in the fructofuranosides **15**-**25**, and **28**-**32** are shown in Table 2.

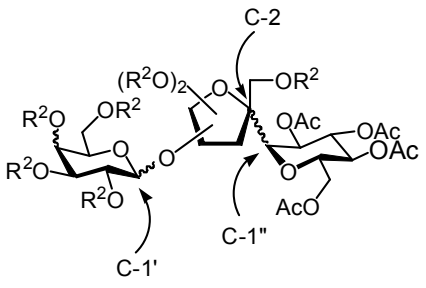
Table 2. Chemical shift (δ/ppm) of each anomeric carbons in the fructofuranoside product[a)]

Entry	Product	C-2 of fructose	C-1' of galactose (Gal) or glucose (Glc)	C-1" of Glc
1	**15**	106.8 [α], 102.2 [β]	102.1 and 101.7 [βGal]	-
2	**16**	107.1 [α], 103.1 [β]	102.1 and 101.7[βGal]	-
3	**17**	106.8 [α], 103.0 [β]	102.1 and 101.7 [βGal]	-
4	**18**	106.9 [α], 102.2 [β]	102.7 and 101.1[βGal]	97.3, 96.4 [α]
5	**19**	107.0 [α], 102.7 [β]	95.8 and 96.9 [αGlc]	-
6	**20**	107.1 [α], 102.8 [β]	95.8 and 96.8 [αGlc]	-
7	**21**	106.8 [α], 103.2 [β]	96.4 and 97.0 [αGlc]	97.4, 96.4 [α]
8	**22**	106.7 [α]	95.8 [αGlc]	
9	**23**	107.2 [α]	95.9 [αGlc]	
10	**24**	107.9 [α]	95.9 [αGlc]	-
11	**25**	107.1 [α]	95.8 [αGlc]	97.5 [α]
12	**28**	108.3 [α], 104.1 [β]	94.2 and 99.1 [αGlc]	-
13	**29**	108.7 [α], 103.6 [β]	94.2 and 99.9 [αGlc]	97.7, 96.7 [α]
14	**30**	109.4 and 108.8 [α]	94.4 and 95.2 [αGlc]	88.8 [α], 93.9 [β]
15	**31**	108.8 and 108.9 [α]	104.7 and 103.8 [βGal]	89.6 [α], 94.3 [β]
16	**32**	109.3 and 108.6 [α]	97.1 and 97.2 [αGlc]	89.0 [α], 94.0 [β]

a) The empirical chemical shift value (δ_C/ppm) of the C-2 of fructofuranoside; α = 107-109 ppm: β = 103-105 ppm. See Ref. 8.



18, **21**, **25**, **29**



30 - **32**

In summary, we developed efficient $Sc(OTf)_3$-catalyzed D-fructofuranosylation reactions using several benzoylated or benzylated disaccharide derivatives as the glycosyl donors. Only 5 – 10 mol% $Sc(OTf)_3$

successfully activated these disaccharide donors to effectively promote fructofuranosylations.[9] The structures and protecting groups of the disaccharide donors and alcohol acceptor species influenced the stereoselectivity and reactivity of the fructofuranosylation reactions. We succeeded in establishing the synthetic protocol to produce several non-reducing trisaccharides containing a sucrose-like disaccharide unit based on the fructofuranosylation strategy.

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9. A typical glycosidation procedure is as follows: To a stirred suspension of $Sc(OTf)_3$ (4.3 mg, 0.009 mmol) and **10** (10.3 μL, 0.09 mmol) in toluene (5 mL), **3** (101.5 mg, 0.09 mmol) was added at rt in the presence of drierite (ca. 100 mg). The resulting mixture was then stirred for 4.5 h. The reaction was then quenched by the addition of a sat. aq. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a sat. aq. NaCl solution. After the organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative silica gel TLC (EtOAc/hexane = 1/2) to give **15** as a colorless oil (92.1 mg, 91%, Entry 2 of Table 1).