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A highly efficient D-fructofuranosylation catalyzed by scandium(III) triflate

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Abstract—This Letter describes a highly efficient D-fructofuranosylation catalyzed by scandium(III) triflate. The benzylated and benzoylated D-fructofuranosyl acetate derivatives worked as good reactive donors in the presence of only 5 mol % scandium(III) triflate at 0 °C in toluene to afford the D-fructofuranosides in excellent yields. The fructofuranosylation also produced several non-reducing disaccharides of sucrose mimics using several aldopyranose derivatives as the acceptors.

1. Introduction

The 1-C-alkylated D-hexopyranoses are a novel class of artificial ketopyranoses, which have an alkyl group at the anomeric carbon centers.[1] We have studied the Lewis acid- or Brϕnsted acid-catalyzed O-ketosylation of several 1-C-alkylated D-hexopyranosyl donors,[2] and found that the 1-*C*-alkyl-D-glucopyranosyl acetates worked as good ketosyl donors to afford the 1-*C*-alkyl-α-*O*-glucopyranosides in good yields in the presence of only 5 mol % scandium(III) triflate ($Sc(OTf)_3$).[2a,e] This highly efficient O-ketosylation system was expected to be applicable to the ketosylation of the naturally occurring ketoses, which have functional groups very similar to the alkyl groups at the anomeric carbon centers. As one of such naturally occurring ketoses, D-fructofuranose has become the focus of our interest, because the D-fructofuranosyl compounds are abundantly found in nature and some of them are significant in food science.[3]

The classical standard glycosidations are ineffective for the D-fructofuranosylation.[4] The representative fructofuranosylation methods are the following combination of fructofuranosyl donors and activators; fructofuranose thio-orthoester-triphenylmethylperchlorate,[5] fructofuranosyl phosphate-trimethylsilyl triflate,[6] thio-fructofuranosides-dimethyl(methylthio)sulfonium triflate,[7] and thio-fructofuranosides-*N*-iodonium *di-sym*-collidine perchlorate.[8] In spite of the development of these D-fructofuranosylation reactions, it seems difficult to produce the D-fructofuranosides with a high efficiency, therefore, more efficient fructofuranosylation methods are needed.

The sucrose mimics are non-reducing disaccharides composed of D-fructofuranose and aldopyranoses and are expected to have biological functions useful for novel food ingredients. Therefore, the synthesis of these sucrose mimics is considered to be one of the significant subjects in the fructofuranosylation study. Only a few synthetic approaches to these sucrose mimics by the D-fructofuranosylation have been reported,[3b,9] and the detailed fructofuranosylation characteristics for the formation of the disaccharide linkages have not yet been clarified.

We have extended the scope of our O-ketosylation system to a highly efficient D-fructofuranosylation using the benzylated and benzoylated D-frucofuranosyl acetates as the ketosyl donors in the presence of metal triflates as the activators. The synthesis of several non-reducing disaccharides of the sucrose mimics, composed of D-fructofuranose and several aldopyranoses, was also attempted using the developed fructofuranosylation. The results are described in this Letter.

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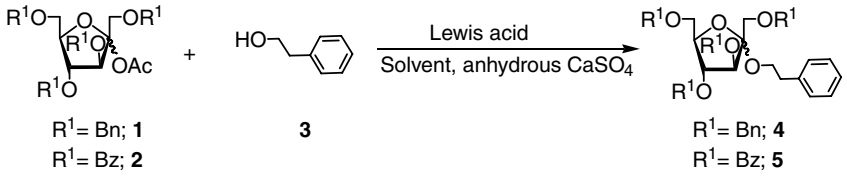
2. Results and discussion

We first investigated the fructofuranosylation using 1,3,4,6-tetra-*O*-benzyl-D-frucofuranosyl acetate ($\alpha/\beta = 1/2$) (**1**)[10] as the donor and phenethyl alcohol (**3**) as the acceptor under the various reaction conditions (Scheme 1). These results are summarized in Table 1.[11] When the reaction of **1** with **3** (1 equiv) in the presence of 5 mol % $Sc(OTf)_3$ in toluene at 0 °C for 1 h, which was the same reaction conditions as we previously reported, was investigated, the desired phenethyl fructofuranoside (**4**) was produced in high yield of 96% with an α/β ratio of 60/40. Our previously reported ketopyranosylation system was found to be applicable for the D-fructofuranosylation.[2a]

In order to elucidate the detailed fructofuranosylation specificities of **1**, the effects of various kinds of solvents, Lewis acids, and temperatures were examined. The similar reaction conditions in dichloromethane, benzene, and acetonitrile afforded **4** in good yields in the range of 77–89%. The difference in the stereoselectivities was only slightly observed. When copper(II) triflate ($Cu(OTf)_2$), tin(II) triflate ($Sn(OTf)_2$), zirconocene(II) triflate ($Cp_2Zr(OTf)_2$), bismuth(III) triflate ($Bi(OTf)_3$), and magnesium triflate ($Mg(OTf)_2$) were utilized as the metal triflates, 5 mol % of these triflates, except for $Mg(OTf)_2$, were effective for activating **1** to afford **4** in high yields of 86 to 96% with α/β ratios of 72/28 to 78/22. The species of the metal triflates slightly influenced the stereoselectivities of the fructofuranosylation. When several trityl salts such as triphenylmethyl perchlorate ($TrtClO_4$), triphenylmethyl tetrafluoroborate ($TrtBF_4$), triphenylmethyl hexachloroantimonate ($TrtSbCl_6$), and triphenylmethyl hexafluorophosphate ($TrtPF_6$) were also utilized as the activators, only $TrtClO_4$ worked as an effective activator. The reaction temperature at −78 °C made the fructofuranosylation smoothly proceed, and even the reaction using only 1 mol % $Sc(OTf)_3$ could afford **4** in 90% yield.

Next, we examined the fructofuranosylation using 1,3,4,6-tetra-*O*-benzoyl-D-fructofuranosyl acetate ($\alpha/\beta = 3/1$) (**2**)[4] as the glycosyl donor (Scheme 1). These results are also summarized in Table 1.[11] The reaction of **2** with **3** (1 equiv) using 5 mol % $Sc(OTf)_3$ in toluene at room temperature afforded **5** in the high yield of 94% with an α-stereoselectivity, though no **5** was produced at all under the reaction conditions at 0 °C. Only 5 mol % $Sc(OTf)_3$ could sufficiently activate **2**, and the effect of



Scheme 1.

Table 1. Reaction of **1** (or **2**) with phenethyl alcohol **3** under various reaction conditions

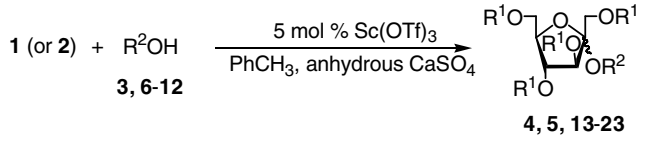
Entry[a]	Donor	Solvent	Temp (°C)	Activator	Yield (%)	α/β Ratio
1	**1**	$PhCH_3$	0	$Sc(OTf)_3$	96	60/40
2	**1**	CH_2Cl_2	0	$Sc(OTf)_3$	85	63/37
3	**1**	PhH	0	$Sc(OTf)_3$	89	65/35
4	**1**	CH_3CN	0	$Sc(OTf)_3$	77	63/37
5	**1**	$PhCH_3$	0	$Cu(OTf)_2$	95	75/25
6	**1**	$PhCH_3$	0	$Sn(OTf)_2$	90	72/28
7	**1**	$PhCH_3$	0	$Cp_2Zr(OTf)_2$	96	78/22
8	**1**	$PhCH_3$	0	$Bi(OTf)_3$	86	77/23
9	**1**	$PhCH_3$	0	$Mg(OTf)_2$	0	—
10	**1**	$PhCH_3$	0	$TrtClO_4$	88	66/34
11	**1**	$PhCH_3$	0	$TrtBF_4$	0	—
12	**1**	$PhCH_3$	0	$TrtSbCl_6$	0	—
13	**1**	$PhCH_3$	0	$TrtPF_6$	29	67/33
14	**1**	$PhCH_3$	−15	$Sc(OTf)_3$	93	65/35
15	**1**	$PhCH_3$	−40	$Sc(OTf)_3$	81	51/49
16	**1**	$PhCH_3$	−78	$Sc(OTf)_3$	85	58/42
17	**1**	$PhCH_3$	rt	$Sc(OTf)_3$	87	65/35
18[b]	**1**	$PhCH_3$	0	$Sc(OTf)_3$	90	67/33
19	**2**	$PhCH_3$	0	$Sc(OTf)_3$	Trace	—
20	**2**	$PhCH_3$	rt	$Cp_2Zr(OTf)_2$	71	α
21	**2**	$PhCH_3$	rt	$Sc(OTf)_3$	94	α
22	**2**	$PhCH_3$	rt	$Cu(OTf)_2$	89	α
23	**2**	$PhCH_3$	rt	$Bi(OTf)_3$	84	α

[a] Molar ratio: **1** (or **2**)–phenethyl alcohol–activator = 1:1:0.05; reaction time: 0.5–2 h.
[b] 1 mol % of $Sc(OTf)_3$ was used.

the neighboring participation by the benzoyl group at the C-3 of **2** seemed to make α-fructofuranosylation proceed. When $Sc(OTf)_3$, $Cu(OTf)_2$, $Bi(OTf)_3$, and $Cp_2Zr(OTf)_2$ were utilized as the metal triflates, 5 mol % of these triflates were effective for the activation of **2**, and in particular, the reaction using $Sc(OTf)_3$ afforded **5**α in the maximum yield of 94%.

The synthesis of several fructofuranosides was investigated using *n*-octyl alcohol (**6**) and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**7**) (Scheme 2, Fig. 1). These results are indicated in Table 2. A similar reaction of **1** with **6** or **7** (1 equiv) in toluene in the presence of 5 mol % $Sc(OTf)_3$ at 0 °C for 1 h afforded the corresponding fructofuranosides **13** and **15** in 92% and 83% yields with α/β ratios of 65/35 and 65/35, respectively. The reaction of **2** with **6** or **7** afforded the fructofuranosides **14**α and **16**α in 86% and 94% as single isomers, respectively.

Furthermore, the synthesis of the non-reducing disaccharides of the sucrose mimics was investigated by using several aldopyranose acceptors such as 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**8**), 3,4,6-tri-*O*-benzyl-2-benzyloxycarbonylamino-2-deoxy-D-glucopyranose (**9**), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**10**), 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (**11**), and 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**12**) (Scheme 2, Fig. 1). These results are also shown in Table 2. The reactions of **1** with **8**–**11** under the above reaction conditions afforded the corresponding non-reducing disaccharides **17**, **19**, **20**, and **22** in the good yields of 60–89% with two isomers. As the NMR spectra showed that all their aldopyranosidic linkages were α, interestingly, only the α-isomers of the aldopyranoses worked as the reactive acceptors in the fructofuranosylation system.[12] The α/β ratios of the formed fructofuranosidic linkages were from about 8/2 to 9/1. The reactions of **2** with **8**, **10**, and **12** also gave the non-reducing disaccharides **18**, **21**, and **23** in the satisfactory yields of 66–78%. The reaction using **8** produced the two isomers of **18**, while the reactions using **10** and **12** formed the four isomers of **21** and **23**. The formation of the β-aldopyranosidic linkages was observed in these reactions, and the isomer ratios of these disaccharides were remarkably influenced by the species of aldopyranoses. The formation of the β-fructofuranosidic linkages was slightly observed in the reactions using **10** and **12**. Thus, we could obtain several non-reducing disaccharides of the sucrose mimics and clarify some fructofuranosylation specificities for the formation of the non-reducing disaccharide linkages using **1** and **2**.



Scheme 2.

In summary, we developed a highly efficient D-fructofuranosylation using the benzylated and benzoylated D-fructofuranosyl acetate derivatives. Only 5 mol % $Sc(OTf)_3$ was an effective activator for them and could

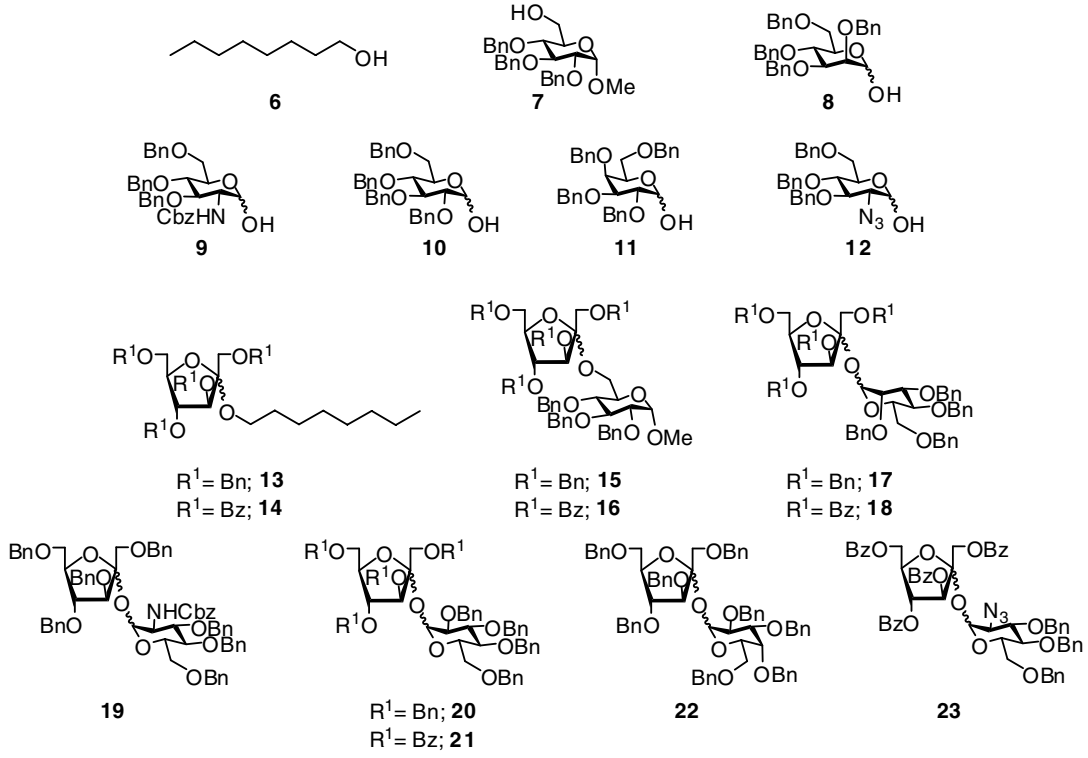


Figure 1.

Table 2. Synthesis of fructofuranosides and sucrose mimics by **1** (or **2**) with various alcohols **3**, **6**–**12** using 5 mol % $Sc(OTf)_3$ in toluene

Entry[a]	Donor	Acceptor	Product	Yield (%)	α/β Ratio or isomer ratio α·α/α·β/β·α/β·β of aldopyranosidic·fructofuranosidic linkages[b]
1	**1**	**3**	**4**	96	60/40
2	**1**	**6**	**13**	92	65/35
3	**1**	**7**	**15**	83	65/35
4[c]	**2**	**3**	**5**	94	α
5[c]	**2**	**6**	**14**	86	α
6[c]	**2**	**7**	**16**	94	α
7	**1**	**8**	**17**	89	80/20/—/—
8[d]	**1**	**9**	**19**	65	94/6/—/—
9	**1**	**10**	**20**	72	84/16/—/—
10	**1**	**11**	**22**	60	91/9/—/—
11[c]	**2**	**8**	**18**	78	79/—/21/—
12[c]	**2**	**10**	**21**	78	40/7/40/13
13[c,d]	**2**	**12**	**23**	66	14/5/67/14

[a] Molar ratio: **1** (or **2**)–alcohol–$Sc(OTf)_3$ = 1:1:0.05; temp: 0 °C; reaction time: 0.5 h-overnight.
[b] Determined by ^1H NMR; —: not detected.
[c] Temp: rt.
[d] CH_2Cl_2 was used as the solvent due to the poor solubility of aldopyranoses **9** and **12** in $PhCH_3$.

Table 3. ^1H and ^{13}C NMR data of fructofuranosides **4**, **5**, and **13**–**16** and sucrose mimics **17**–**23**

Entry[a]	Compound	Chemical shift (δ_C/ppm) of the C-2 in fructofuranosyl residue[b]	Chemical shift (δ_C; δ_H/ppm (*J* value/Hz)) of the C-1 and H-1 in aldopyranosyl residue
1	**4**	107.9[α], 104.2[β]	—
2	**5**	107.0[α]	—
3	**13**	107.9[α], 104.2[β]	—
4	**14**	107.2[α]	—
5	**15**	108.3[α], 104.1[β]	—
6	**16**	107.3[α]	—
7	**17**	108.9[α·α], 104.9[α·β]	90.3 (168);[c] 5.49 (2.1)[α·α], 93.5 (171);[c] 5.51 (2.1)[α·β]
8	**18**	108.0[α·α], 107.6[β·α]	91.4 (170);[c] 5.48 (1.4)[α·α], 94.7 (155);[c] 5.00 (2.8)[β·α]
9	**19**	109.6[α·α], 105.4[α·β]	91.1; 5.57 (2.8)[α·α], 92.3; 5.42 (3.4)[α·β]
10	**20**	108.5[α·α], 104.6[α·β]	90.0; 5.56 (3.4)[α·α], 89.9; 5.71 (3.4)[α·β]
11	**21**	107.5[α·α], 108.1[β·α], 103.8[α·β], 104.1[β·β]	90.6; 5.59 (3.4)[α·α], 96.4; 4.98 (7.6)[β·α], 91.4; 5.70 (3.4)[α·β], 95.3; 5.15 (7.3)[β·β]
12	**22**	108.2[α·α], 104.3[α·β]	90.8; 5.56 (3.4)[α·α], 90.7; 5.70 (3.4)[α·β]
13	**23**	107.8[α·α], 108.5[β·α], 103.9[α·β], 104.2[β·β]	90.6; 5.55 (4.8)[α·α], 94.8; 4.78 (7.6)[β·α], 91.9; 4.59 (4.8)[α·β], 94.2; 5.02 (8.3)[β·β]

[a] [·] Showed an isomer of aldopyranosidic·fructofuranosidic linkages.
[b] The empirical chemical shift value (δ_C/ppm) of the C-2 of fructofuranoside: α = 107–109 ppm; β = 103–105 ppm. See Ref. 7b.
[c] J_{C1-H1} value/Hz.

afford various D-fructofuranosides in good yields. As a part of this study, we successfully applied the fructofuranosylation to the synthesis of several non-reducing disaccharides as sucrose mimics.

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11. A typical glycosidation procedure is as follows: To a stirred solution of $Sc(OTf)_3$ (3.1 mg, 0.006 mmol) and **3** (15.9 μL, 0.13 mmol) in toluene (3.5 mL) was added **1** (77.4 mg, 0.13 mmol) at 0 °C in the presence of Drierite (ca. 100 mg). The resulting mixture was then stirred for 30 min. The reaction was next quenched by the addition of a satd. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a satd. 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 (ethyl acetate/hexane = 1/6) to give **4** as a colorless oil (81.8 mg, 96%). The ^1H and ^{13}C NMR data of the fructofuranosides **4**, **5**, and **13**–**16** and sucrose mimics **17**–**23** were shown in Table 3.
12. We also discussed the formation of the aldopyranosidic linkages with high α-stereoselectivities in the synthesis of the trehalose mimics by the ketopyranosylation of the 1-*C*-methyl-α-D-hexopyranose derivatives with **8** (or **10**) in Ref. 2c.