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Synthesis of β-D-fructopyranosides with *N*-phenyl trifluoroacetimidate donor

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ABSTRACT

Fructopyranosyl *N*-phenyl trifluoroacetimidate was demonstrated to be effective glycosyl donor for β-D-fructopyranosides preparation that exhibited good β-selectivity and good yields. X-ray data of two β-D-fructopyranosides were obtained and help to determine the anomeric configuration of these ketoses.

1. Introduction

D-Fructose is the second most abundant simple sugar in nature, and fructosides are involved in a wide range of biological processes.[1–5] D-Fructose crystallizes in β-pyranoid form[6] and appears mainly as mixtures of two pyranose and two furanose tautomers in solution.[7,8] In nature, D-fructosides generally appear as furanose, so chemical approaches to fructosides are mostly relevant to the synthesis of fructofuranosides,[9–13] and the reports of D-frutopyranoside synthesis are limited.[14,15] However, fructopyranosides demonstrate excellent bioactivity and pharmaceutical value.[16] For example, Topamax® (**1**) was the Top-10 anticonvulsant drug with $ 2.7 billion annual sale in 2008.[17] It might also be used to treat obesity.[18] In 2010, *n*-butyl β-D-frutopyranoside (**2**) isolated from traditional Chinese medicine was reported to exhibit gastric cancer inhibition activity[19] (Fig. 1).

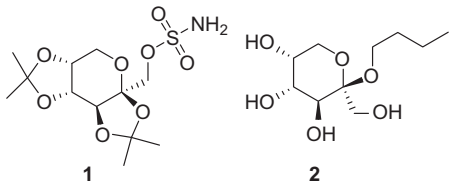

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Fig. 1. Some fructopyranosides with pharmaceutical value.

Increasing works on fructopyranosides synthesis were reported in recent years.[20,21] Unfortunately, a general and effective glycosylation method for fructopyranosides synthesis is not available till now. Several fructopyranosyl donors, such as fluoride, 1-propenyl, 1,2-sulfite, and 1,2-carbonate were investigated.[22] Among them, fructopyranosyl fluoride provided the highest yield with good β-selectivity, but only 57% yield for disaccharide, and for trisaccharide the yield was dropped to 22%. Unprotected D-fructose could be directly converted into alkyl D-fructopyranosides by $FeCl_3$, but the yield was low (~30%).[21,23] The known fructopyranosyl glycosylation all suffered from the low yield; and some general donors, such as Schmidt's imidate and bromide, could not be applied in this glycosylation, because of their instability in ketose.[22] Lichtenthaler and co-workers' study indicated that, under forced acetylation condition, fructopyranosyl ring could be opened,[24] which implied that fructopyranoside was more sensitive. But the known fructopyranosyl glycosylations all required 1 equiv of Lewis acid and the preparation of donor often required somewhat strong condition. Under these conditions, some side reactions of fructopyranoid likely occurred, which maybe the reason for the low yield of some donors' preparation and glycosylation.[22] In order to develop an effective and general method for fructopyranosides synthesis, we aimed at developing a mild fructopyranosyl glycosylation method, with mild condition for the corresponding donors' preparation.

Yu and co-workers recently developed *N*-phenyl trifluoroacetimidate donor,[25,26] which was successfully applied in direct sialylation, glycosylation of primary amides, hydroxamic

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acid, deoxysugars, and several total synthesis.[27] In 2008, we reported an efficient fructofuranosylation employing *N*-phenyl trifluoroacetimidate donor.[28] We further investigate its application in fructopyranosides synthesis.

1,3,4,5-Tetra-*O*-benzoyl-β-D-fructose **3**[24] reacted with *N*-phenyl trifluoroacetimidoyl chloride in the presence of K_2CO_3 in acetone to afford β-trifluoroacetimidate **4** ($J_{3,4}$=10.4 Hz) in 98% yield. The solvent with a little moisture benefited the reaction (Table 1). The fructopyranosyl imidate **4** was stable in storage at 4 °C for weeks, showing it a stable glycosyl donor (Scheme 1).

Table 1
Optimization of *N*-phenyl trifluoroacetimidate **4** preparation

Entry	Equiv of *N*-phenyl trifluoroacetimidoyl chloride	Solvent	Reaction time	Yield
1	7	Anhydrous CH_2Cl_2	20 h	10%
2	7	Hydrous CH_2Cl_2	8 h	70%
3	7	Anhydrous acetone	16 h	40%
4	3	AR grade acetone	2 h	98%

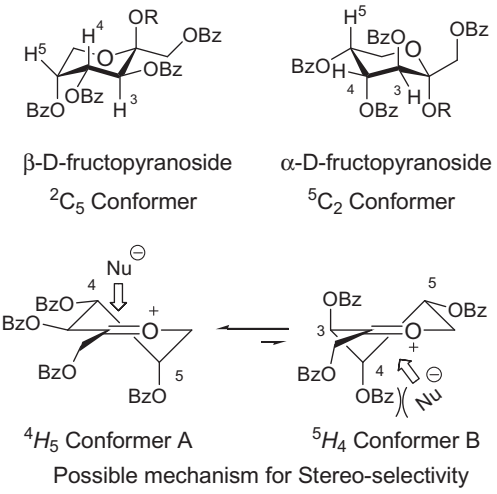
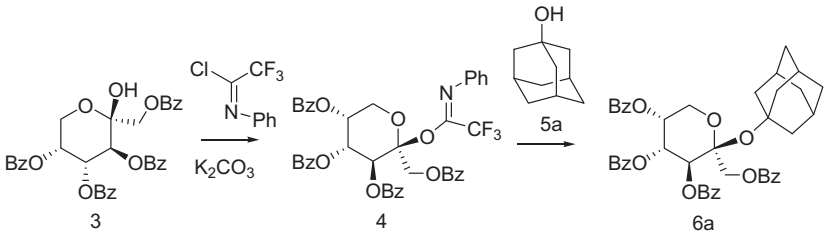


Fig. 2. Conformers of β or α-D-fructopyranoside and the possible mechanism for β-selective fructopyranosylation.



Scheme 1.

Donor **4** and adamantanol **5a** (1.5 equiv to donor **4**) in CH_2Cl_2 at −20 °C with TMSOTf (0.06 equiv) provided adamantanyl β-fructopyranoside **6a** stereoselectively in 91% yield (Table 2, entry 1). Replacement of CH_2Cl_2 with CH_3CN or a mixed solvent of CH_3CN/CH_2Cl_2 (1:2) or THF/CH_2Cl_2 (1:2) resulted in the similar yield and the same stereoselectivity (entry 2,3). When $BF_3{\cdot}Et_2O$ (0.2 equiv) was used as promoter, the result was the same as TMSOTf's case (entry 4). Acetonitrile was used to affect the stereo outcome through 'solvent effect' in aldose glycosylation;[29] but in cases here, solvent did not affect the stereo outcome. Addition of TMSOTf at higher temperature (0 °C) caused decomposition of donor **4** and lowered the yield (entry 5); when 1 equiv of $BF_3{\cdot}Et_2O$ was used, **3** was the major product with 67% yields (entry 6). Because perbenzoyl protected donor **4** should be the most inert donor of this type, these above results indicated that strong conditions were unfavorable for this type of donor. The anomeric configuration of **6a** was assigned as β-D-fructopyranoside according to the X-ray analysis (Fig. 3).

Table 2
Optimization of glycosylation conditions with donor **4** and adamantanol

Entry	Lewis acid	Solvent	T/°C	Product	Yield	β:α
1	0.06 equiv TMSOTf	CH_2Cl_2	−20	**6a**	91	β only
2	0.06 equiv TMSOTf	CH_3CN	−20	**6a**	90	β only
3	0.06 equiv TMSOTf	THF/CH_2Cl_2 (1:2)	−20	**6a**	87	β only
4	0.2 equiv $BF_3{\cdot}Et_2O$	CH_2Cl_2	−20	**6a**	88	β only
5	0.06 equiv TMSOTf	CH_2Cl_2	0	**6a**	76	β only
6	1 equiv $BF_3{\cdot}Et_2O$	CH_2Cl_2	−20	**3**	67	—

Other acceptors (**5b**–**h**) were investigated with the optimized condition. This glycosylation method worked well with several kinds of acceptors (Table 3). For acceptors **5a**, **5c**–**f**, the β-fructopyranosides were obtained in high yields and high selectivity as

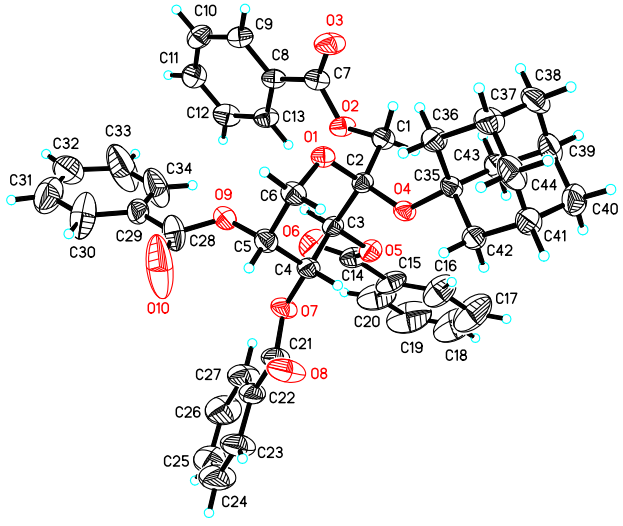


Fig. 3. ORTEP drawing of compound **6a**.

determined by ^1H NMR (entries 1, 3–6). For **5b** and **5g**, the yields were good, the β:α selectivity was about 3.2:1 (entries 2 and 7). For 2, 3, 4, 6-tetra-*O*-benzyl-D-glucopyranose (**5h**), 39% α-glucosyl β-fructoside (indicated as α; β) **6h** ($J_{3,4}$=10.5 Hz, $J_{1',2'}$=3.3 Hz) was isolated with 9:1 α/β-glucosyl selectivity (entry 8). In this reaction, only the major product α; β stereomer could be isolated in pure form, from four possible stereomers: α; β,β; β,α; α and β; α. The α/β-glucosyl selectivity was mainly affected by anomeric effect of **5h**. The disaccharide **6h** is a derivative of sucrose. The anomeric carbon signal for β-D-fructosyl group is 101.3 ppm; for α-D-glucopyranosyl group is 91.7 ppm (Scheme 2).

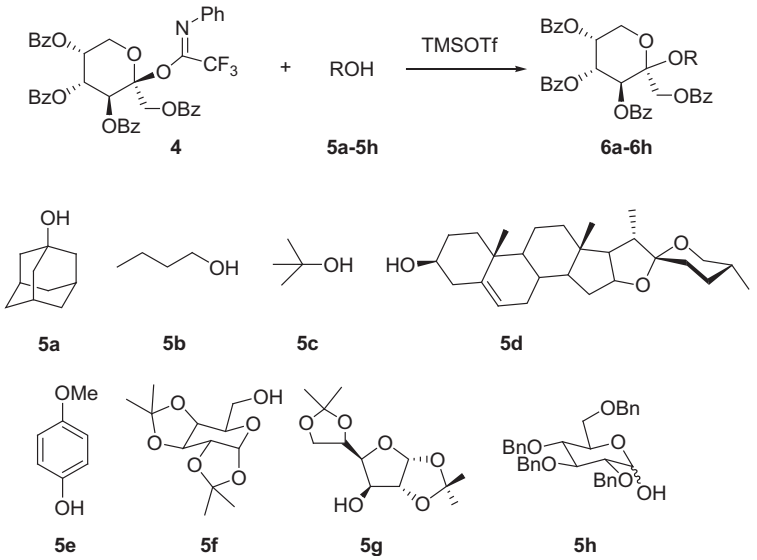
Table 3
Glycosylation with donor **4**[a]

Entry	Acceptor	Product	Yield[b]	β:α[d]
1	**5a**	**6a**	91	β only
2	**5b**	**6b**	59 (β)	β:α=3.2:1
3	**5c**	**6c**	63 (β)	β:α=10:1
4	**5d**	**6d**	73[c]	β only
5	**5e**	**6e**	81	β only
6	**5f**	**6f**	96	β only
7	**5g**	**6g**	85(β)	β:α=3.2: 1
8	**5h**	**6h**	39 (α; β)	β mainly[e]

[a] Condition: −20 °C, 0.06 equiv TMSOTf, CH_2Cl_2, 30 min then rt 1 h.
[b] Isolated yield.
[c] Recovered 20% of **5d**.
[d] Determined by crude product ^{1}H NMR.
[e] With 9:1 α/β-glucosyl selectivity.

Optical activity, ^{13}C NMR,[23] HMQC, NOE,[22] and ^3J coupling between C-1 and H-3 (so called JBCA method) were also used to determine the anomeric configuration.[31] It was reported that β-D-fructopyranoside usually adopts a $^2C_5$ conformation in crystal and solutions,[24] therefore, $J_{3,4}$ value are large (commonly 9–11 Hz) while $J_{4,5}$ and the two $J_{5,6}$ values are small (commonly 3–5 Hz). On the contrary, for α-D-fructopyranoside, $J_{3,4}$ and $J_{4,5}$ values (3–5 Hz) are small and one of the $J_{5,6}$ values is large, indicating a $^5C_2$ conformation.[24] Could this provide a simplified anomeric α,β-determination method for fructopyranoside?

Because the 3, 4, and 5-CH of tetra-*O*-benzoyl fructopyranosides provide distinct chemical shift (usually>5.8 ppm, far from other glycosyl CH) and coupling patterns, the key $J_{3,4}$ and $J_{4,5}$ values could be obtained unambiguously from 1D ^{1}H NMR. This advantage in our



Scheme 2. Pyrano-type fructosylation with donor **4**.

For most of known glycosylation of ketopyranosyl donors, 1 equiv of catalyst was needed, such as Cp_2ZrCl_2–AgOTf for fluoride,[22] DICP for thioketoside.[30] So this mild glycosylation, which required catalytic amount of TMSOTf, is more environment-friendly and effective.

Since the anomeric proton is lacking, the anomeric configuration determination of fructopyranoside is relatively complicated. Optical activity, ^{13}C NMR,[23] HMQC, NOE,[22] and ^3J coupling between C-1 and H-3 (so called JBCA method) were also used to determine the anomeric configuration.[31] It was reported that β-D-fructopyranoside usually adopts a $^2C_5$ conformation in crystal and solutions,[24] therefore, $J_{3,4}$ value are large (commonly 9–11 Hz) while $J_{4,5}$ and the two $J_{5,6}$ values are small (commonly 3–5 Hz). On the contrary, for α-D-fructopyranoside, $J_{3,4}$ and $J_{4,5}$ values (3–5 Hz) are small and one of the $J_{5,6}$ values is large, indicating a $^5C_2$ conformation.[24] Could this provide a simplified anomeric α,β-determination method for fructopyranoside?

Because the 3, 4, and 5-CH of tetra-*O*-benzoyl fructopyranosides provide distinct chemical shift (usually>5.8 ppm, far from other glycosyl CH) and coupling patterns, the key $J_{3,4}$ and $J_{4,5}$ values could be obtained unambiguously from 1D ^{1}H NMR. This advantage in our cases prompted us to evaluate the configuration determine methods mentioned above.

We obtained two crystals: **6a** and **6d**. Their X-ray structural analysis clearly indicated β-pyranosides with $^2C_5$ conformation[32] (Figs. 3 and 4), in accordance well with the ^{1}H NMR data ($J_{3,4}$=9.9 and 10.5 Hz, respectively). The major glycosyl products of **6b**–**g** were assigned as β-D-fructopyranosides, according to their optical

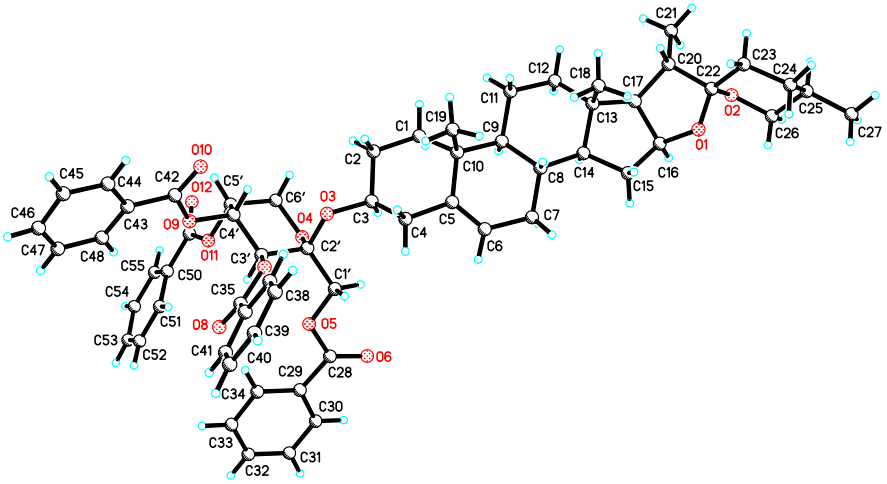


Fig. 4. ORTEP drawing of compound **6d**.

rotation (between −70° and −111°)[23] and C-2 anomeric ^{13}C NMR data (in the range of 99–102 ppm), and their $J_{3,4}$ value was also in the range of 9–11 Hz. But **6g-α**, whose α configuration was confirmed by NOE signals between H-1 and H-6_{ax}, provided big $J_{3,4}$ value ($J_{3,4}$=10.2 Hz) indicating a $^2C_5$ conformation. We suggested that because of the bulky secondary alcohol, the pyranoside most likely adopted $^2C_5$ conformation. To these cases, NOE must be done to confirm the anomeric configuration. So the *J* value pattern of H-3,4,5 provided the conformation information, but it was insufficient to judge the anomeric configuration.

There are three interesting aspects of the stereoselectivity of this ketose glycosylation. First, there are two neighboring benzoyl groups: on 1 and 3 position. The neighboring group participation (NGP) of 3-OBz will result in 2,3-*trans* structure, that is, α-glycoside, while NGP of 1-OBz will result in α- or β-glycosylation. The excellent β-selectivity shown in Table 3 indicated that the selectivity was less likely affected by NGP of 3-OBz. Second, if NGP occurred in this glycosylation, some kind of *ortho*-ester will be formed and could be captured. Experiments were designed to capture the *ortho*-ester intermediate,[33] but only normal glycosylation product or hydrolyzed product **3** was obtained. We noticed that Crich and the coworkers used O-BOC protected glycosides to trap the participation groups.[34] Further works should be done to investigate the possible NGP of 1, 4 or 5-OBz, to provide us more information on this interesting β-glycosylation. Third, the conformation analysis of the keto-oxonium ion (Fig. 2) indicated that $^4H_5$ conformer A was preferred over $^5H_4$ conformer B (OBz group at C-3 favors equatorial position, while C-4,5 favor axial position).[35] The stereoelectronic preference for nucleophilic addition of conformer B, which provides α-glycoside, is unfavorable because of the big hindrance. Nucleophilic addition from the stereoelectronic preferred face of conformer A, which is also less hindered, resulted in β-anomer product. So the stereoelectronic factors may be the major reason for excellent β-selectivity of this glycosylation.

In conclusion, fructopyranosyl trifluoroacetimidate **4** exhibited good glycosyl donor properties. With mild condition and good yield, this new glycosylation method will be a general method for fructopyranoside synthesis. The β-selectivity of glycosylation may be mainly determined by the stereoelectronic factors, following the Curtin–Hammet principle, while NGP effect of 2-OBz did not work. Further work should be done to evaluate the possible NGP effect of 1,4 or 5-OBz. Two crystals of β-D-fructopyranosides **6a** and **6d** with $^2C_5$ conformation were obtained. Several empirical anomeric determination methods were checked and discussed, but none of them alone could clearly judge the anomeric configuration.

2. Experimental section

2.1. 1,3,4,5-Tetra-*O*-benzoyl-β-D-fructopyranosyl-2-(*N*-phenyl)-trifluoroacetimidate (4)

To 1,3,4,5-tetra-*O*-benzoylfructose **3** (594 mg, 1 mmol) and *N*-phenyl trifluoroacetimidoyl chloride (0.45 mL, 3 mmol) in acetone (AR grade, 8 mL) was added K_2CO_3 (410 mg, 3 mmol), and the mixture was stirred at rt for 2 h. The mixture was filtered, concentrated, and the residue was purified by column chromatography (hexane/EtOAc 7:1) to obtain **4** as white foam (756 mg, 98%).

$[\alpha]_D^{25}$ −120 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.05–7.82 (m, 8H, Ar), 7.60–7.24 (m, 14H, Ar), 7.09 (t, 1H, *J*=7.6 Hz, Ar), 6.77 (d, 1H, *J*=7.6 Hz, Ar), 6.41 (d, 1H, $J_{3,4}$=10.4 Hz, H3), 5.95 (dd, 1H, *J*=10.4, 2.8 Hz, H4), 5.92 (m, 1H, H5), 5.33 and 4.97 (AB, 2H, *J*=11.6 Hz, H-6),4.33 (s, 2H, H1). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 165.5, 165.3, 165.2, 143.0, 141.0 (q, *J*=36 Hz, *C*=NPh), 133.5, 133.4, 133.3, 133.1, 129.8–128.3 (CH_{arom}), 124.5, 118.9, 115.9 (q, *J*=287 Hz, CF_3) *104.9*, 69.1, 68.1, 63.6, 62.9 ESIMS (*m*/*z*) calcd for $C_{42}H_{32}NF_3O_{10}Na$ 790.19, found 790.65. Anal. Calcd for $C_{42}H_{32}NF_3O_{10}$: C, 65.71; H, 4.20, N, 1.82. Found: C, 65.94; H, 4.35; N, 1.75.

2.2. Adamantan-1-yl 1,3,4,5-tetra-*O*-benzoyl-β-D-fructopyranoside (6a)

Yield: 91%. $[\alpha]_D^{25}$ −102 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.21–7.23 (m, 20H, Bz), 6.35 (d, 1H, *J*=9.9 Hz, H-3), 5.82 (m, 2H, H-4 and H-5), 5.16 and 4.27 (AB, 2H, *J*=11.1 Hz, H-1), 4.40 and 4.06 (AB, 2H, *J*=13.2 Hz, H-6), 2.22–2.03 (m, 9H, OAda), 1.71 (br s, 6H, OAda). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 165.7, 165.6, 165.5, 133.1–128.2, *101.5*, 77.2, 70.1, 69.8, 68.0, 63.5, 61.9, 44.2, 36.0, 30.9. HRMS (ESI) calcd for $C_{44}H_{42}O_{10}Na$ 753.2670, found 753.2672. Anal. Calcd for $C_{44}H_{42}O_{10}$: C, 72.31; H, 5.79. Found: C, 72.44; H, 5.62. IR (cm^{-1}) ν_{max}=2919, 1721, 1270, 1107, 711.

2.3. *n*-Butyl 1,3,4,5-tetra-*O*-benzoyl-D-fructopyranoside (6b)

Yield: 59%. β:α=3.2:1; for β-anomer: $[\alpha]_D^{25}$ −69.2 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 8.11–7.18 (m, 20H, Bz), 6.26 (d, 1H, *J*=10.5 Hz, H-3), 5.82 (dd, 1H, *J*=10.5, 3.6 Hz, H-4), 5.75–5.73 (m, 1H, H-5), 4.76 and 4.24 (AB, 2H, *J*=11.7 Hz, H-1), 4.05 (AB, 2H, *J*=13.2, 1.5 Hz, H-6), 3.79–3.51 (m, 2H), 1.75–1.60 (m, 2H), 1.58–1.40 (m, 2H), 0.94 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C, 2C), 165.7 (C), 165.6(C), 133.2–128.3 (CH_{arom}), 99.41 (C), 70.10, 69.63, 68.43, 62.98 (CH_2), 61.95 (CH_2), 61.60 (CH_2), 32.04 (CH2), 19.57 (CH_2), 13.93; HRMS (ESI) calcd for $C_{38}H_{36}O_{10}Na$ 675.2207, found 675.2190. Anal. Calcd for $C_{38}H_{36}O_{10}$: C, 69.93; H, 5.56. Found: C, 69.79; H, 5.33.

2.4. *t*-Butyl 1,3,4,5-tetra-*O*-benzoyl-D-fructopyranoside (6c)

Yield: 63%. β:α=10:1; for β-anomer: $[\alpha]_D^{25}$ −107.8 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, 2H, *J*=8.1 Hz), 7.96 (t, 4H, *J*=2.7 Hz), 7.84 (d, 2H, *J*=3.3 Hz), 7.62–7.22 (m, 12H), 6.35 (d, 1H, *J*=12.0 Hz, H-3), 5.85–5.80 (m, 2H, H-4 and H-5), 5.12 and 4.28 (AB, 2H, *J*=11.1 Hz, H-1), 4.33 and 4.07 (AB, 2H, *J*=11.4, 1.8 Hz, H-6), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C), 165.8 (C), 165.7 (C), 165.6 (C), 133.2–128.2 (CH_{arom}), 101.4 (C), 70.2, 70.0, 68.2, 63.2(CH_2), 61.8(CH_2), 30.7; HRMS (ESI) calcd for $C_{38}H_{36}O_{10}Na$ 675.2207, found 675.2190.

2.5. Diosgenin-3-yl-1,3,4,5-tetra-*O*-benzoyl-β-D-fructopyranoside (6d)

Yield: 73%. β only; $[\alpha]_D^{25}$ −94.1 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–7.25 (m, 20H), 6.34 (d, 1H, *J*=10.5 Hz), 5.88 (dd, 1H, *J*=10.8, 3.3 Hz), 5.79 (m, 1H), 5.29 (m, 1H), 4.86 and 4.30 (AB, 2H, *J*=12 Hz), 4.48–4.36 (m, 2H), 4.11–3.94 (m, 1H), 3.82 (m, 1H), 3.52–3.34 (m, 2H), 2.54 (t, 1H, *J*=14.4 Hz), 2.35–2.20 (m, 1H), 2.04–0.80 (m, 22H), 1.12 (s, 3H), 0.98 (d, 3H, *J*=6.9 Hz), 0.81–0.78 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (2C), 165.7, 165.6, 140.2 (C, C-5), 133.2–128.3 (CH_{arom}), 122.2 (C-6),109.3 (C, C-22), 100.4 (C, C-2′), 80.8 (C-16), 72.6, 70.2, 69.6, 68.2, 66.8 (CH_2, C-26), 63.2 (CH_2), 62.3 (CH_2), 62.1, 56.4, 50.0,41.6, 41.3 (CH_2), 40.3 (C), 39.7 (CH_2), 37.4 (CH_2), 36.7 (C), 32.1 (CH_2), 31.9, 31.5, 31.4 (CH_2), 30.3, 30.3 (CH_2), 28.8 (CH_2), 20.9 (CH_2), 19.5, 17.1, 16.3, 14.5; HRMS (ESI) calcd for $C_{61}H_{68}O_{12}Na$ 1015.4603, found 1015.4603. Anal. Calcd for $C_{61}H_{68}O_{12}$: C, 73.77; H, 6.90. Found: C, 73.49; H, 7.06. IR (cm^{-1}) ν 2951, 1731, 1449, 1278, 1065, 711.

2.6. 4′-Methoxyphenyl-1,3,4,5-tetra-*O*-benzoyl-β-D-fructopyranoside (6e)

Yield: 81%. β only; $[\alpha]_D^{25}$ −107.8 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 8.52–6.78 (m, 24H), 6.38 (d, 1H, *J*=10.5 Hz, H-3), 5.99 (dd, 1H, *J*=10.5, 3.6 Hz, H-4), 5.82 (m, 1H, H-5), 4.60 and 4.15 (AB, 2H, *J*=11.7 Hz,

H-1), 4.50 and 4.20 (AB, 2H, J=12.9, 2.4 Hz, H-6), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C), 165.6 (C), 165.5 (C, 2C), 156.4 (C), 146.7 (C), 133.9–114.8 (CH_{arom}), *102.0* (C), 70.0, 69.5, 67.9, 62.7 (CH_2), 62.5 (CH_2), 55.6; HRMS (ESI) calcd for $C_{41}H_{34}O_{11}Na$ 725.1985, found 725.1982. IR (cm^{-1}) ν_{max}=1731, 1508, 1270, 1238, 1021, 716.

2.7. 1,3,4,5-Tetra-*O*-benzoyl-β-D-fructopyranosyl-(2→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (6f)

Yield: 96%. β only; $[\alpha]_D^{25}$ −139.3 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–7.26 (m, 20H), 6.35 (d, 1H, J=10.5 Hz, H-3′), 5.87 (dd, 1H, J=10.5, 3.6 Hz, H-4′), 5.60–5.78 (m, 1H, H-5′), 5.55 (d, 1H, J=4.8 Hz, H-1), 4.98 (d, 1H, J=11.7 Hz), 4.71 (dd, 1H, J=7.8, 2.1 Hz), 4.40–3.90 (m, 8H), 1.57, 1.50, 1.43, 1.36 (4s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C), 165.71 (C), 165.70 (C), 165.6 (C), 133.2–128.3 (CH_{arom}), 109.5 (C), 108.7 (C), *99.7* (C), 96.3 (CH, C-1), 71.0, 70.73, 70.69, 70.1, 69.6, 68.1, 66.7, 62.9 (CH_2), 62.4 (CH_2), 61.0 (CH_2), 26.1 (CH_3), 26.0 (CH_3), 25.0 (CH_3), 24.6 (CH_3), ESIMS m/z calcd for $C_{46}H_{46}O_{15}Na$ 861.27, found 861.20. Anal. Calcd for $C_{46}H_{46}O_{15}$: C, 65.86; H, 5.53. Found: C, 65.90; H, 5.73. IR (cm^{-1}) ν 2988, 1725, 1271, 1070, 705.

2.8. 1,3,4,5-Tetra-*O*-benzoyl-β-D-fructopyranosyl-(2→3)-1,2:5,6-di-*O*-isopropylidene-D-glucofuranoside (6g)

Yield: 85%, β:α=3.2:1. β anomer: $[\alpha]_D^{25}$ −90.4 (*c* 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–7.13 (m, 20H), 6.29 (d, 1H, J=10.5 Hz, H-3′), 5.85 (dd, 1H, J=10.5, 3.0 Hz, H-4′), 5.82 (m, 1H, H-5′), 5.65 (d, 1H, J=3.3 Hz, H-1), 4.81 and 3.99 (AB, 2H, J=13.2, 1.2 Hz, H-6′), 4.75 and 4.32 (AB, 2H, J=12.0 Hz, H-1′), 4.60 and 4.48 (AB, 2H, J=3.3 Hz, H-6), 4.58–4.55 (m, 1H), 4.28 (dd, 1H, J=8.7, 6.3 Hz), 4.17 (dd, 1H, J=8.7, 3.3 Hz), 4.05–4.01 (m, 1H),1.45 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8 (C), 165.7 (C), 165.52 (C), 165.48 (C), 133.4–128.3 (CH_{arom}), 112.2 (C), 110.0 (C), 104.8 (CH, C-1), 100.7 (C, C-2′), 84.7, 81.8, 74.7, 71.7, 70.3, 70.0, 68.4 (CH_2), 68.3, 64.1 (CH_2), 62.5 (CH_2), 26.9 (CH_3), 26.3 (CH_3, 2C), 25.5 (CH_3); ESIMS m/z calcd for $C_{46}H_{46}O_{15}Na$ 861.27, found 861.21. Anal. Calcd for $C_{46}H_{46}O_{15}$: C, 65.86; H, 5.53. Found: C, 65.71; H, 5.68. IR (cm^{-1}) ν 2986, 1728, 1274, 1069, 708.

α anomer; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10–7.23 (m, 20H), 6.34 (d, 1H, J=10.2 Hz, H-3′), 6.05 (d, 1H, J=3.6 Hz, H-1), 5.88 (dd, 1H, J=10.2, 3.6 Hz, H-4′), 5.78 (m, 1H, H-5′), 4.81 (d, 1H, J=12 Hz), 4.63 (m, 2H), 4.38–4.26 (m, 3H), 4.09–3.84 (m, 4H), 1.52 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.74 (2C), 165.50, 165.3, 133.0–128.1, 112.1, 106.3 (CH, C-1), 100.8, 99.3, 84.1, 79.0, 75.1, 71.2, 70.1, 69.5, 68.2, 62.9, 62.4, 62.2, 29.4, 27.3, 26.7, 22.7; ESIMS m/z calcd for $C_{46}H_{46}O_{15}Na$ 861.27, found 861.23. Anal. Calcd for $C_{46}H_{46}O_{15}$: C, 65.86; H, 5.53. Found: C, 65.64; H, 5.51.

2.9. 1,3,4,5-Tetra-*O*-benzoyl-β-D-fructopyranosyl-(2→1)-2, 3, 4, 6-tetra-*O*-benzyl-α-D-glucopyranoside (6h)

Yield: 39%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20–7.15 (m, 40H), 6.47 (d, 1H, J=10.5 Hz, H-3′), 5.80–5.76 (m, 2H, H-4′ and H-5′), 5.51 (d, 1H, J=3.3 Hz, H-1), 4.96–4.51 (m, 10H), 4.28–4.01 (m, 4H), 3.79–3.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6 (C), 165.5 (C), 138.0–127.6 (CH_{arom}), 101.3 (C, C-2′), 91.7 (CH, C-1), 82.8, 78.8, 77.9, 76.0 (CH_2), 75.3 (CH_2), 74.3 (CH_2), 73.5 (CH_2), 72.0, 69.9, 68.9 (CH_2), 67.3, 63.5 (CH_2). ESIMS (m/z) calcd for $C_{68}H_{62}O_{15}Na$ 1141.40, found 1141.40. Anal. Calcd for $C_{68}H_{62}O_{15}$: C, 72.97; H, 5.58. Found: C, 72.67, H, 5.53. IR (cm^{-1}) ν_{max}=2923, 1731, 1267, 1101, 711.

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Supplementary data

^{1}H and ^{13}C NMR spectra and CIF files for compound **6a** and **6d**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.11.058.

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33. Compound **4** and **5b** in CH_2Cl_2, THF or Et_2O at −60 °C with TMSOTf (0.06 equiv) for 30 min, TLC showed 50% conversion, quench at −60 °C by NEt_3, after column chromatography, no *ortho*-ester was obtained, but only normal glycosylation product or hydrolyzed product.
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