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Solvent-Dependent Mechanism and Stereochemistry of Mitsunobu Glycosylation with Unprotected Pyranoses

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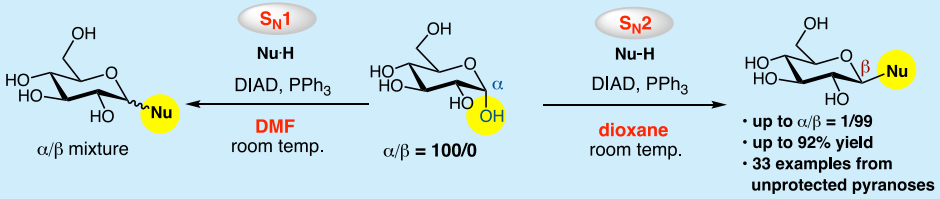

ABSTRACT: An S_N2 mechanism was proposed for highly stereoselective glycosylation of benzoic acid with unprotected α-D-glucose under Mitsunobu conditions in dioxane, while an S_N1 mechanism was indicated for nonstereoselective glycosylation in DMF. The S_N2-type stereoselective Mitsunobu glycosylation is generally applicable to various unprotected pyranoses as glycosyl donors in combination with a wide range of acidic glycosyl acceptors such as carboxylic acids, phenols, and imides, retaining its high stereoselectivity (33 examples). Glycosylation of a carboxylic acid with unprotected α-D-mannose proceeded also in an S_N2 manner to directly afford a usually less accessible 1,2-*cis*-mannoside. One- or two-step total syntheses of five simple natural glycosides were performed using the glycosylation strategy presented here using unprotected α-D-glucose.

Mitsunobu reactions have been extensively used to convert alcohols to the corresponding esters with inversion of the configuration of the carbon center substituted by the hydroxy group. Important applications of the Mitsunobu reaction include anomeric modification of carbohydrates (Mitsunobu glycosylation) and its application to total synthesis of natural glycosides.[1] A seminal work in this field was reported by Grynkiewicz in 1979, in which unprotected glucose was successfully used for glycosylation of phenol under Mitsunobu conditions using a more reactive phosphine, PBu_3.[2] The reaction of glucose with phenol was reported to take place in DMF regioselectively at the anomeric carbon to give the glycoside in a 1:8 α:β ratio (Scheme 1A). Since this surprising report, the related glycoside formation under Mitsunobu conditions between acidic glycosyl acceptors such as *p*-nitrophenol, butynoic acid, and hydrogen azide and unprotected glucose was reported to give the glycosides as 1:3, 41:59, and 2:5 α/β mixtures, respectively (Scheme 1B).[3] These reactions were usually performed in polar solvents such as DMF and dimethylethyleneurea. We applied Grynkiewicz's glycosylation to the preparation of glycoside **G**, a key intermediate for short-step total synthesis of natural glycosides, strictinin, tellimagrandin II, and pterocarinin C (Scheme 1C).[4] Highly stereoselective synthesis of the desired β-glycoside **G** was achieved when the reaction was performed in dioxane instead of a conventionally used solvent, DMF (the corresponding reaction in DMF gave **G** and its α-anomer in a 50:50 ratio).[4] Although glucose seemed not to be dissolving in dioxane, the use of finely powdered glucose effectively promoted the glycosylation reaction in a highly stereoselective manner.[4] While we noticed the critical importance of the solvent for the stereochemistry of the Mitsunobu glycosylation, the mechanism was totally unclear.

To clarify the origin of the high β-selectivity of the glycosylation performed in dioxane, we investigated the mechanism of the glycosylation using unprotected D-glucose. Here, we report that the β-selectivity of the glycosylation in dioxane results from an S_N2-type displacement of commercially available α-D-glucose (Scheme 1D).[5] On the other hand, glycosylation in DMF was found to proceed via an S_N1 mechanism, which is responsible for the nonstereoselective glycosylation. Therefore, the solvent was found to play a crucial role in the stereochemical course as well as the mechanism of Mitsunobu glycosylation using unprotected glucose. The low stereoselectivity observed for the reaction in DMF is somewhat consistent with the related pioneering examples of Mitsunobu glycosylation using unprotected monosaccharides (Scheme 1A,B).[1−3,6]

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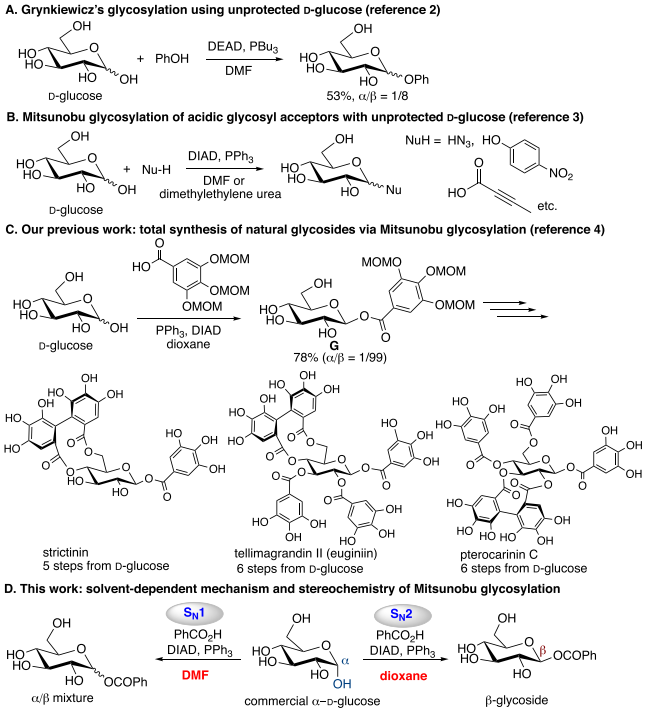
Scheme 1. Mitsunobu Glycosylation Using Unprotected Glucose



Initially, we were not aware of the configuration of the anomeric carbon of commercial glucose used for the preparation of **G** and imagined that it must be an α/β mixture. During the course of the mechanistic study of glycosylation with unprotected glucose, we noticed that commercial D-glucose is supplied as a pure or an almost pure α-anomer in most cases (Figure 1 and Table S1).[7] With pure α-D-glucose in

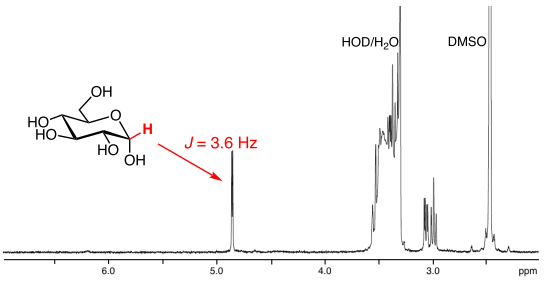
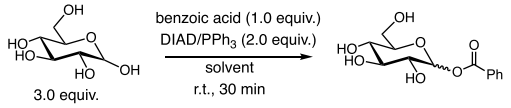


Figure 1. ^{1}H NMR spectra (400 MHz, 298 K, DMSO-d_6 and D_2O) of commercial D-glucose (Difco Dextrose purchased from Becton Dickinson) indicating its pure α-anomer structure.

hand, we reinvestigated the solvent effects of the glycosylation using benzoic acid as a simple glycosyl acceptor (Table 1; also see Table S2) and found that stereochemistry was highly dependent on the solvent polarity. The glycosylation with α-D-glucose (100:0 α:β) proceeded with high β-selectivity in dioxane [2:98 α:β (Table 1, entry 1)] and THF [2:98 α:β (Table 1, entry 2)], while it does so in a nonstereoselective manner in DMF [48:52 α:β (Table 1, entry 3)]. On the basis of these results, we hypothesized that the observed β-selectivity of the reaction in dioxane might be resulting from S_N2 displacement of an α-D-glucose, while S_N1 displacement of D-glucose could be responsible for the poorly stereoselective glycosylation in DMF. To investigate the S_N2 hypothesis, the

Table 1. Effects of Solvents and Anomeric Stereochemistry on the Stereochemical Course of Mitsunobu Glycosylation



entry	α:β ratio of D-glucose	solvent	yield[a] of glycoside (%)	α:β ratio of glycoside
1	100:0[b]	dioxane	66	2:98
2	100:0[b]	THF	11[c]	2:98
3	100:0[b]	DMF	54	48:52
4	78:22[d]	dioxane	79	18:82
5	51:49[d]	dioxane	76	38:62

[a]Yield based on benzoic acid. [b]Commercial D-glucose. [c]6-*O*-Benzoyl-β-glycoside was also obtained in 24% yield (see Table S2). [d]Partially anomerized D-glucose obtained by treatment of D-glucose (100:0 α:β) with a catalytic amount of TFA in MeOH (see Scheme S2).

glycosylation was further examined with partially epimerized anomeric mixtures (78:22 and 51:49 α:β) of D-glucose (Table 1, entries 4 and 5, respectively, and Scheme S2). While glycosylation of benzoic acid using pure α-glucose (100:0 α:β) in dioxane gave the β-glycoside in a 2:98 α:β ratio (Table 1, entry 1), a decrease in the α-anomer content in D-glucose resulted in a decrease in the β-isomer ratio of the glycoside (entries 4 and 5). These results suggest that the β-glycoside was generated selectively from α-D-glucose via formal inversion at the anomeric stereogenic center. The higher ratio of the β-isomer in the produced glycoside than the original ratio of the α-isomer of glucose was observed in entries 4 and 5. These phenomena could be ascribed to the higher reactivity of the α-isomer of D-glucose under the excess glucose (3 equiv) conditions. The observed α:β ratios were thought to result solely from the glycosylation step because no epimerization of glucose itself took place in DMF or dioxane under the reaction conditions.[8]

Possible reaction paths for β-selective glycosylation in dioxane and nonstereoselective glycosylation in DMF are shown in Scheme 2A. The regioisomeric mixture of oxyphosphonium ions **A** and **A′** is thought to be generated from α-D-glucose in a nonregioselective manner under equilibrium conditions (path I). Oxyphosphonium ion **A** generated at the anomeric position is expected to be the most reactive among the oxyphosphonium ions, and it would preferentially react with a benzoate anion under Curtin−Hammett situations. The β-selective glycosylation is thought to take place via an S_N2 displacement of oxyphosphonium ion **A** with an α-configuration by the benzoate anion (path II). Alternatively, the β-selectivity could be explained by an S_N1-type displacement via contact ion pair-like intermediate **B** (oxonium−zwitterion pair) preferentially formed in a less polar solvent, dioxane, where the α-face of the oxonium cation is shielded by the oxyphosphonium zwitter ion (path III). On the other hand, nonstereoselective glycosylation in DMF could be explained by the intervention of solvent-separated ion pair **C** (path IV). To elucidate the probability of the proposed mechanisms, the ^{13}C kinetic isotope effect (KIE)[9] of the present glycosylation reactions was measured (Scheme 2B). The ^{13}C KIE experiments were performed using α-D-glucose with natural ^{13}C abundance by the Singleton method[10] [200 MHz for ^{13}C measurement (800 MHz NMR instrument) with a cryogenic probe, S:N ratio of 1860−2660 (see Figure S3)]. Reproducible KIEs were obtained in the range between 1.026 and 1.033 for

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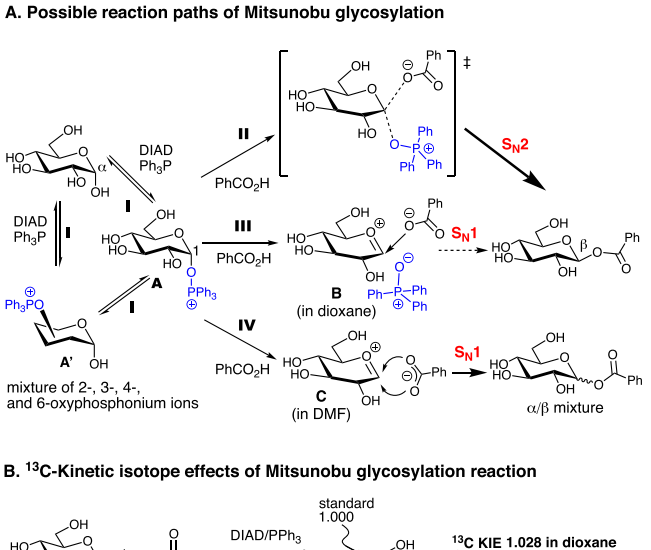
Scheme 2. Mechanistic Investigation of Mitsunobu Glycosylation of Benzoic Acid with α-D-Glucose

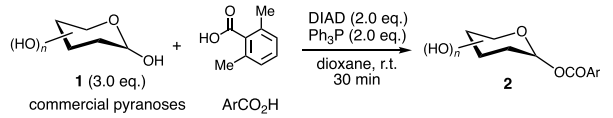


the reactions in dioxane (Scheme 2B and Table S3). On the basis of these data, the KIE at C(1) in dioxane was determined to be 1.028 (an average value of three experiments). The primary ^{13}C KIE at the anomeric carbon of glycosyl donors has been extensively studied in both chemical and enzymatic glycosylation reactions.[11] It has been suggested that smaller (≤1.01) and larger (1.02−1.06) KIEs are responsible for S_N1 and S_N2 displacement, respectively.[11b] Taking the observed KIE data (Scheme 2B) and the reported ones into consideration, we concluded that the present glycosylation reactions take place via an S_N2 mechanism in dioxane (Scheme 2A, path II), while it does so via an S_N1 mechanism in DMF (Scheme 2A, path IV). The observed solvent dependency seems to be consistent with the general aspects of Mitsunobu reactions that strongly favor S_N2 displacement and phenomena that S_N2 reactions proceed more smoothly in less polar solvents.

Our next question is whether the reaction proceeds in a solution phase or a suspension phase. To estimate the solubility of α-D-glucose in dioxane under the reaction conditions, we examined the following test. The reaction was performed typically with 54 mg (0.3 mmol) of finely ground α-D-glucose in 10 mL of dioxane (see S3 of the Supporting Information). The suspension of α-D-glucose (54 mg) in dioxane (10 mL) was treated with ultrasound irradiation at room temperature for 15 min. The resulting suspension was filtered through a membrane filter with a 0.45 μm pore size. The transparent filtrate was concentrated *in vacuo* to give 4.2 mg of α-D-glucose with negligible anomerization (<2%), as confirmed by ^1H NMR in DMSO-d_6 and D_2O. These results may indicate that the solute and/or a fine suspension of α-D-glucose at an effective concentration of 2.3 mM in dioxane could be responsible for the reaction.

While glycoside synthesis under Mitsunobu conditions has been known to be exceptionally useful because protective group-free carbohydrates can be employed, it is sometimes associated with poor stereocontrol for glycoside formation.[1−3,6] The synthetic utility of Mitsunobu glycosylation with unprotected carbohydrates is expected to be further increased if the stereochemistry of glycosylation is controlled well among the wide range of substrates. Then, we examined the scope of the S_N2-type glycosylation with various unprotected pyranoses (Table 2). The use of 2,6-dimethyl-

Table 2. Scope of Glycosyl Donors for S_N2-Type Mitsunobu Glycosylation[a]



entry	pyranose	product	yield[b] (α/β ratio)
1	α-D-Glc (**1a**) α/β = 100/0	**2a**	92% (α/β = 1/99)
2	β-D-Glc (**1b**) α/β = 4/96	**2b**	94% (α/β = 89/11)
3	D-Gal (**1c**) α/β = 96/4	**2c**	58% (α/β = 2/98)[c]
4	D-Xyl (**1d**) α/β = 100/0	**2d**	53% (α/β = 4/96)
5	D-Ara (**1e**) α/β = 4/96	**2e**	87% (α/β = 95/5)
6[d]	D-Man (**1f**) α/β = 100/0	**2f**	66% (α/β = 13/87)

X-ray of 2f

[a]The structure of the major stereoisomer is shown. [b]Yield based on $ArCO_2H$. [c]The observed β-selectivity was higher than the original α-content. This seems to be due to the faster reaction of the α-anomer of **1c**. [d]DIAD (3.0 equiv) and Ph_3P (3.0 equiv), rt.

benzoic acid as a glycosyl acceptor for glycosylation with glucose gave a yield [92% (Table 2, entry 1)] that was better than that of benzoic acid [66% (Table 1, entry 1)]. The outcome was thought to result from minimizing anhydride formation (major side reaction) from two molecules of the sterically demanding carboxylic acid. While α-D-glucose (**1a**, 100:0 α:β) gave β-glycoside **2a** (entry 1, 1:99 α:β, 92%), β-D-glucose (**1b**, 4:96 α:β) gave α-glycoside **2b** (entry 2, 89:11 α:β, 94% yield) by the same treatment. These results are quite compatible with the S_N2 process. Similarly, α-D-galactose (**1c**, 96:4 α:β) and α-D-xylose (**1d**, 100:0 α:β) gave β-glycosides **2c** (2:98 α:β, 58%) and **2d** (4:96 α:β, 52%), respectively, via treatment with 2,6-dimethylbenzoic acid (entries 3 and 4, respectively). The observed β-selectivity in **2c** was higher than the original α-content of **1c**. This could be ascribed to the higher reactivity of the α-anomer of **1c** than the β-anomer as observed in entries 4 and 5 in Table 1. Glycosylation with β-D-arabinose (**1e**, 4:96 α:β) also gave α-glycoside **2e** (95:5 α:β,

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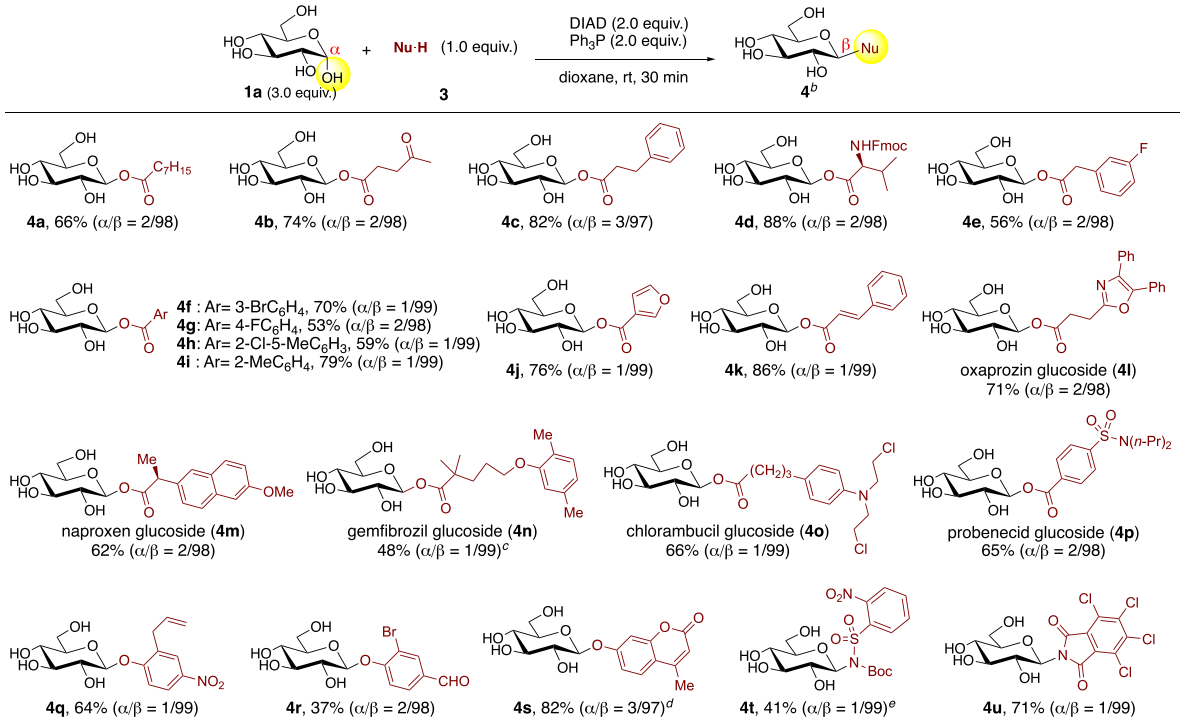
Scheme 3. Scope of Glycosyl Acceptors for S_N2-Type Mitsunobu Glycosylation[a]



[a]The structure of the major stereoisomer is shown. [b]Yield based on Nu-H. [c]DIAD (3.0 equiv) and Ph_3P (3.0 equiv), rt. [d]DIAD (4.0 equiv) and Ph_3P (4.0 equiv), 55 °C. [e]DIAD (4.0 equiv) and Ph_3P (4.0 equiv), rt.

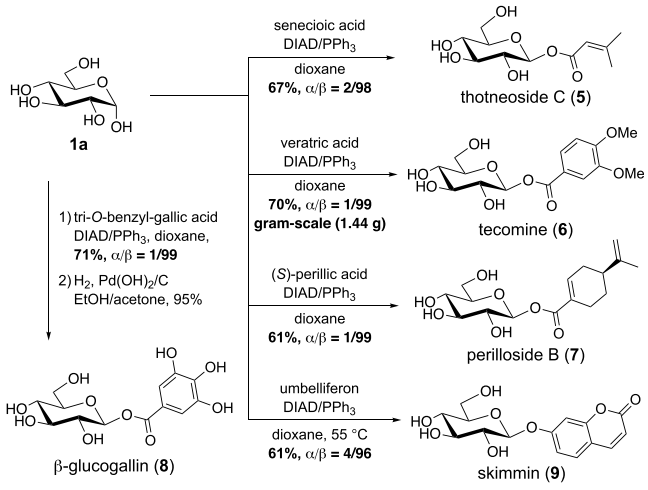
87%) (entry 5). Stereoinversion at the anomeric carbon was observed in each case. It is worth noting that glycosylation even with α-D-mannose (**1f**, 100:0 α:β) proceeded via inversion of the configuration at the anomeric carbon to give β-glycoside **2f** (13:87 α:β, 66%) (entry 6). The stereochemically pure **2f** was obtained by recrystallization from CH_3CN. The 1,2-*cis*-configuration of **2f** was determined by both single-crystal X-ray analysis and J_{C-H} (162 Hz for anomeric carbon at 94.9 ppm) of the pure isomer. Thus, glycosylation with unprotected D-mannose possessing β-axial C(2)−OH took place in a usually unfavorable β-selective manner to directly afford 1,2-*cis*-mannoside.[12] All of these observed phenomena are consistent with the proposed S_N2-type glycosylation.

In contrast to our result from the reaction of D-mannose to give 1,2-*cis*-mannoside **2f**, it is worth noting that Grynkiewicz's glycosylation of phenol with unprotected D-mannose (unknown anomeric stereochemistry) gave 1,2-*trans* glycoside, exclusively.[1,2,13]

The scope of glycosyl acceptors in the glycosylation with α-D-glucose presented here is shown in Scheme 3. Aliphatic and aromatic carboxylic acids with various functional groups were well tolerated in the glycosylation reactions to give the corresponding glycosides in a highly β-selective manner (glycosides **4a**−**4p**). Glycosylation of acids with an α-chiral center took place without any trace of epimerization of the chiral center (glycosides **4d** and **4m**). Because β-glycosylation is one of the metabolic pathways of medicines,[14] application to formation of the drug−glucose conjugate was also shown. Oxaprozin (nonsteroidal anti-inflammatory), naproxen (nonsteroidal anti-inflammatory), gemfibrozil (antihypertensive), chlorambucil (anticancer), and probenecid (treatment of hyperuricemia) gave the corresponding β-glycosides under the standard conditions (**4l**−**4p**). Phenol derivatives and imides also underwent glycosylation in moderate to good yields (**4q**−**4u**).

One-step syntheses of natural glycosides with a simple structure were performed (Scheme 4). Natural glycosides such

Scheme 4. One- or Two-Step Syntheses of Natural Glycosides



as thotneoside C (**5**),[15] tecomin (**6**)[16] (gram-scale synthesis), perilloside B (**7**),[17] and skimmin (**9**)[18] were obtained from α-D-glucose and commercially available reagents in one step under Mitsunobu conditions. β-Glucogallin (**8**)[19] was prepared in 67% yield in two steps from α-D-glucose.

In conclusion, we have elucidated the mechanism of Mitsunobu glycosylation of benzoic acid with α-D-glucose. The reaction proceeds stereoselectively via a direct S_N2

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mechanism in dioxane, while it proceeds in a nonstereoselective manner in DMF via an S_N1 mechanism. The S_N2-type stereoselective Mitsunobu glycosylation was widely applicable to glycoside formation between various commercial unprotected pyranoses as glycosyl donors and a variety of acidic glycosyl acceptors. This glycosylation method using unprotected carbohydrates could be applicable to glycodiversification of medicinally important molecules.[20,21]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01549.

Experimental details, spectral data, and characterization data for all new compounds (PDF)

Accession Codes

CCDC 1445049 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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