Synthesis A. Motoyama et al. Paper

α-Selective Glycosylation of 3,6-*O*-*o*-Xylylene-Bridged Glucosyl Fluoride

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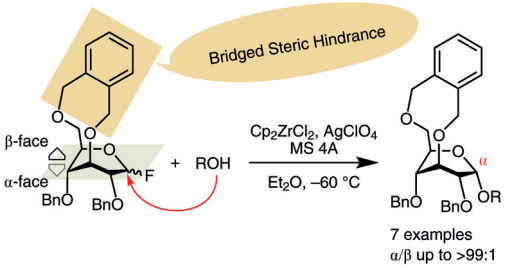

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Abstract A 1,2-*cis*-(α)-selective glycosylation has been developed. An *ortho*-xylylene group bridged between 3-O and 6-O of D-glucosyl fluoride, which straddles the β-face of the pyranose ring, hinders the approach of glycosyl acceptors from that face. The determination of the three-dimensional structure of the bridged glucosyl fluoride, the optimization process of the reaction conditions oriented toward kinetic control to realize the high α-selectivity, and the scope of the reaction are described.

Key words glycosylation, 1,2-*cis*-selectivity, kinetic control, conformation, *o*-xylylene bridge

The structures of aldopyranosides can be divided into four types on the basis of the orientation of O-2 (axial or equatorial) and the relative configuration between C-1 and C-2 (*trans* or *cis*) (Figure 1).[1] Thus, the classes correspond to (i) axially oriented O-2 and 1,2-*trans* type (ax-O2/*trans*) as α-D-mannosides, (ii) equatorially oriented O-2 and 1,2-*trans* type (eq-O2/*trans*) as β-D-glucosides, (iii) ax-O2/*cis* as β-D-mannosides, and (iv) eq-O2/*cis* as α-D-glucosides (Figure 1). Among the four, the synthesis of 1,2-*trans*-glycosides (types i and ii) is reliable because of the inherent preference for ax-O2/*trans*-glycosides[2] and the existence of the neighboring group participation (NGP) method for eq-O2/*trans*-glycosides.[3] In contrast, the synthesis of 1,2-*cis*-glycosides (types iii and iv) is difficult. Although classic methods achieve 1,2-*cis*-selectivity, the origin of the selectivity is often unclear.[4] Therefore, chemists have tested a variety of working hypotheses.[5]

Among the hypotheses, successful methods for the induction of eq-O2/*cis* stereoselectivity can be roughly classified into four categories (Figure 1, a–d). The first method (a) utilizes facial selective intramolecular participation of a protecting group,[6–8] similar to NGP. Recently, Boons and co-workers reported more aggressive methods for controlling the direction of the participation exploiting protecting groups bearing an asymmetric carbon (a-2).[9] The second method (b) is intramolecular aglycon delivery.[10] In this method, an aglycon is first installed to a hanger (Q in the structure) on an oxygen of the glycosyl donor, where the oxygen orients to a desired face of the pyranose ring, and then migrates with retention of the face to the anomeric position. For the hanger, atoms such as Si,[11] C,[10b,12] and B,[13] and molecular clamps[14] are applied. The third method (c) involves the dragging of a glycosyl acceptor by hydrogen bonding. Demchenko and co-workers have reported a remarkable dragging effect of the nitrogen atom of pyridine, as illustrated in Figure 1, c.[15] The fourth method (d) relies simply on steric hindrance of the approach of the glycosyl acceptor,[16] on which we report herein.

Previously, we reported a complete 1,2-*trans*-(β)-selective glycosylation reaction without NGP by adopting 3,6-*O*-*o*-xylylene-bridged glycosyl fluoride **1** (Figure 1, e).[17] This reaction consists of glycosylation and isomerization cycles, catalyzed respectively by $SnB(C_6F_5)_4Cl$ and $HB(C_6F_5)_4$, both generated *in situ*. The 1,2-*trans*-selectivity arises thermodynamically in the isomerization cycle because of the steric repulsion between α-O-1 and O-2. Here, both the oxygens orient axially to the α-face of the pyranose due to the restricted conformation resulting from the *o*-xylylene bridge. On the other hand, the drawn scheme for **1**, in which the bridge covers the β-face of the pyranose ring, is expected to induce 1,2-*cis*-(α)-selectivity if its actual structure is as drawn. Here, we report the development of a 1,2-*cis*-(α)-selective glycosylation using **1**.

We first determined the three-dimensional structure of **1** on the basis of NMR studies and chemical calculation. In the NMR studies, the correlation between H-1 and H-5 in the NOESY spectrum indicated the axial orientation of

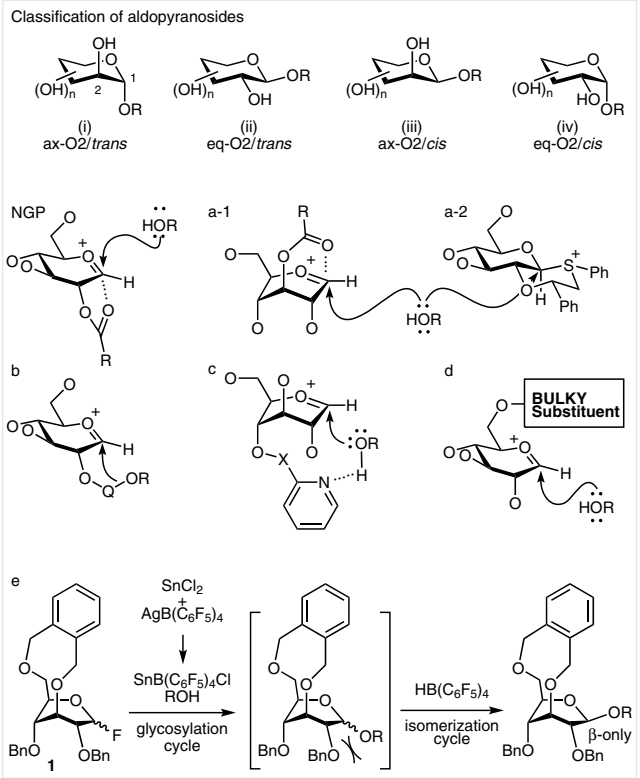


Figure 1 Classification of aldopyranosides, neighboring group participation (NGP), (a–d) methods for induction of eq-O2/stereoselectivity [(a) facial selective intramolecular participation, (b) intramolecular aglycon delivery, (c) dragging of glycosyl acceptors, (d) use of steric hindrance], and (e) completely β-selective glycosylation by adopting 3,6-*O*-*o*-xylylene-bridged glucosyl fluoride **1**

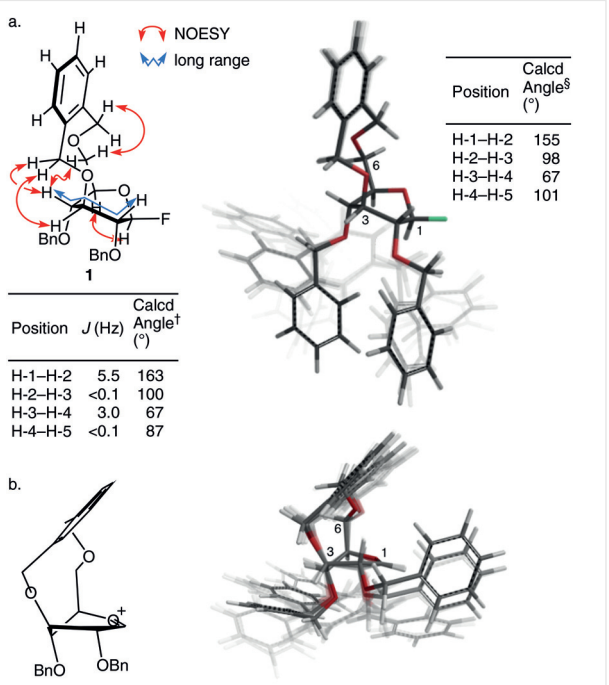


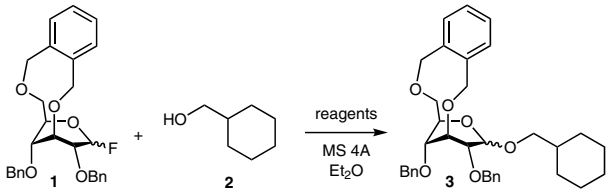
Figure 2 Conformational representation of **1** (a) and the oxocarbenium ion intermediate derived from **1** (b). (a) Left: Observed long-range coupling (blue arrow) and selected NOESY correlations (red arrows). † The most reasonable value is listed between solutions given by the modified Karplus equation. Right: Composite view of calculated conformers: the color strength reflects the Boltzmann distributions of each conformer. § Weighted average based on the Boltzmann distribution of conformers. (b) Composite view of calculated conformers: the color strength reflects the Boltzmann distributions of each conformer

these protons (Figure 2, a, left). $^3J_{H-H}$ values provided dihedral angles of the adjacent C–H bonds on the pyranose ring.[18] A molecular model assembled on the basis of the angles had a $^1S_3$ pyranose ring. A $^4J_{H-H}$ coupling between H-2 and H-4 (0.7 Hz) supported the ring conformation.

The model illustrated in Figure 2, a, right was rendered computationally using Spartan 14 software. In the calculation, a molecular force field calculation was used to obtain the distribution of conformers, and then each conformer within 16.75 kJ/mol from the most stable one was optimized applying the DFT calculation at the B3LYP/6-31G* level *in vacuo*.[19] Figure 2 displays the top eight stable conformers after the DFT calculations. The potential energy range of the eight is within 7.75 kJ/mol, which suggests the existence of a rigid 3,6-*O*-*o*-xylylene-bridged pyranose and flexible benzyl groups. The calculated dihedral angles were reasonably consistent with those derived from the NMR studies. Hence, the *o*-xylylene moiety stands upright to the β-face of the pyranose ring and might become a steric hindrance for the approach of an alcohol. Similar calculation of the corresponding oxocarbenium ion intermediate indicated that the bridge could be steric hindrance over the β-face (Figure 2, b). In Figure 2, the top 10 stable conformers are displayed. The potential energy range of the conformers is within 8.56 kJ/mol.

To obtain high α-selectivity exploiting the steric hindrance over the β-face, kinetic reaction conditions are required because the corresponding glucosides converge to the β-isomer under thermodynamic conditions (Figure 1, e and Table 1, entry 1).[17] Thus, we surveyed the α/β ratio of the glycosylation reaction of **1** with cyclohexylmethanol (**2**) under several reported conditions for the activation of glycosyl fluorides (Table 1, entries 2–7).[20] Among them, the use of $AgClO_4$ and AgOTf provided more of the α-isomer than the β-isomer (entries 4–7). For the second survey of the reagents, the adoption of various Lewis acids with $AgClO_4$ was tested (Table 1, entries 8–15).[20a,f,g] In these tests, the reactions were started at –25 °C. When the reaction was quite slow at –25 °C, the temperature was raised. The results indicated that various Lewis acids activated **1** with α-selectivity. Among the Lewis acids tested, Cp_2ZrCl_2 (entry 10) gave the best α-selectivity; therefore, on the basis of this condition, the optimization of the reaction was continued.

Table 1 Reagent Survey

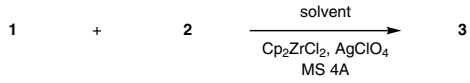


Entry	Reagents	Temp	Yield (%)	α/β Ratio
1[a,b]	$SnCl_2$, $AgB(C_6F_5)_4$	rt	96	1:>99
2	TMSOTf	–25 °C	70	1:>99
3	$BF_3{\cdot}OEt_2$	–25 °C	88	31:69
4[b]	$SnCl_2$, $AgClO_4$	rt	83	58:42
5	$SnCl_2$, $AgClO_4$	rt	85	62:38
6	$SnCl_2$, AgOTf	rt	82	60:40
7	**Cp_2ZrCl_2, $AgClO_4$**	**rt**	**94**	**73:27**
8	$Sc(OTf)_3$, $AgClO_4$	–25 °C	50	74:26
9	Cp_2TiCl_2, $AgClO_4$	–25 °C to rt	25	77:23
10	**Cp_2ZrCl_2, $AgClO_4$**	**–25 °C**	**89**	**89:11**
11	$Cp_2Zr(OTf)_2$, $AgClO_4$	–25 °C	91	61:39
12	Cp_2HfCl_2, $AgClO_4$	–25 °C to rt	78	70:30
13	$Tb(OTf)_3$, $AgClO_4$	–25 °C to rt	63	88:12
14	$Er(OTf)_3$, $AgClO_4$	–25 °C to rt	79	69:31
15	$Yb(OTf)_3$, $AgClO_4$	–25 °C	47	80:20

[a] Molecular sieves 5A were used.
[b] Benzotrifluoride (BTF) was used as the solvent.

The optimization using Cp_2ZrCl_2 and $AgClO_4$ as the activator of **1** began with an investigation of the reaction solvent (Table 2). Among them, entries 1–6 are the results when the type of solvent was varied; in entries 7–11, various (thio)ethers were used. Thus, in pyridine or DMF, the reaction was quite slow (Table 2, entries 1 and 2). The use of toluene induced complete β-selectivity (entry 3). In contrast, the reaction in benzene was slightly β-selective (entry 4). Similar moderate β-selectivity was observed when DCM or acetonitrile was the solvent (entries 5 and 6). Therefore, none of the tested solvents provided better α-selectivity than Et_2O at room temperature (α/β = 73:27; Table 1, entry 7). The use of other ethers was also investigated. DME did not induce remarkable α-selectivity (Table 2, entry 7). Reactions in *i*-Pr_2O, *t*-BuOMe, and cyclopentyl methyl ether (CPME) provided α-selectivity better than α/β = 9:1 (Table 2, entries 8–10), which in turn were better than Et_2O at –25 °C (Table 1, entry 10). However, the melting point of *i*-Pr_2O is –60 °C, which would limit further investigations at varied reaction temperature. The use of *t*-BuOMe resulted in poor yield (37% yield with 38% recovery of the starting material **1**) because of poor solubility of **1** in the solvent. When CPME was used, the stereoselectivity was similar to

Table 2 Solvent Selection

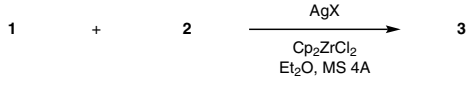


Entry	Solvent	Temp	Yield (%)	α/β Ratio
1	pyridine	–25 °C	trace	–
2	DMF	0	0	–
3	toluene	rt	83	1:>99
4	benzene	rt	96	40:60
5	DCM	rt	69	46:54
6	MeCN	rt	52	41:59
7	DME	–25 °C	87	56:44
8	*i*-Pr_2O	–25 °C	58	94:6
9	*t*-BuOMe	–25 °C	37	90:10
10	CPME	–25 °C	81	90:10
11	Me_2S	–25 °C to rt	20	36:64

when Et_2O was used, but the yield was decreased. The reaction in Me_2S gave **3** in poor yield and the selectivity moved to slightly β (Table 2, entry 11). Hence, Et_2O was adopted for the subsequent investigations.

We then obtained information regarding a change of the silver salt counteranion (Table 3). The reaction with $AgBF_4$ (entry 1) produced **3** in a highly β-selective manner, indicating that this combination of the reagents induced anomeric isomerization. Adoption of $AgB(C_6H_5)_4$ gave a 1:1 mixture of the anomers (entry 2). This result is in contrast to that obtained by the use of $AgBF_4$, although both are silver borates. Similarly, $AgSbF_6$ provided a 1:1 mixture (entry 3). Only a trace of the ion signal for **3** was detected in mass spectra in the reactions with Ag_2CO_3 and Ag_2SO_4 (entries 4

Table 3 Variation of the Silver Salt Anion

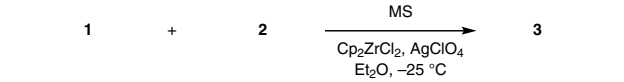


Entry	AgX	Temp	Yield (%)	α/β Ratio
1	$AgBF_4$	–25 °C	87	2:98
2	$AgB(C_6F_5)_4$	rt	70	49:51
3	$AgSbF_6$	–25 to 0 °C	73	50:50
4	Ag_2CO_3	–25 °C to rt	trace	–
5	Ag_2SO_4	–25 °C to rt	trace	–
6	AgOTf	rt	90	65:35
7	$AgOCOCF_3$	–25 to 0 °C	58	78:22
8	$AgNO_3$	–25 °C to rt	70	79:21

and 5). AgOTf, $AgOCOCF_3$, and $AgNO_3$ induced α-selectivity (entries 6–8), but the selectivities were lower than that with $AgClO_4$ (Table 1, entry 10). Collectively, the use of $AgClO_4$ had advantages.

To investigate the effect of molecular sieves (MS) (Table 4), the use of MS 3A, 5A, or 13X was tested (entries 1–4), but all results were less selective than when MS 4A was employed. Additionally, the reaction was carried out without molecular sieves for comparison, and complete β-selectivity was obtained (entry 5), which demonstrates the occurrence of anomeric isomerization. Thus, molecular sieves might act as an acid scavenger.

Table 4 Effect of Molecular Sieves

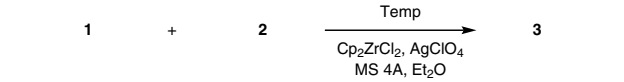


Entry	MS	Yield (%)	α/β Ratio
1	3A	58	86:14
2[a]	4A	89	89:11
3	5A	28	78:22
4	13X	64	87:13
5	none	80	1:>99

[a] Copy of Table 1, entry 10.

Finally, the effect of the reaction temperature was investigated (Table 5). The peak of the α-selectivity (α/β = 97:3) was obtained when the temperature was –60 °C (entry 5). At –78 °C, both the reaction rate and the α-selectivity decreased (entry 6). Therefore, the optimized reaction conditions were concluded to be as follows: **1** (1.0 equiv), **2** (1.2 equiv), Cp_2ZrCl_2 (2.5 equiv), $AgClO_4$ (5.0 equiv), and MS 4A (3.0 g/mmol) in Et_2O at –60 °C.

Table 5 Effect of Temperature



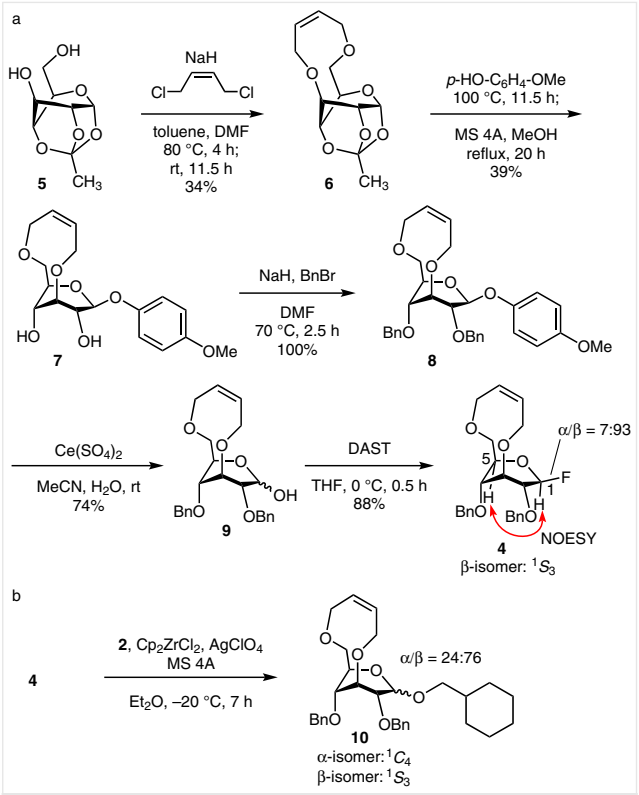
Entry	Temp	Yield (%)	α/β Ratio
1[a]	rt	94	73:27
2	0 °C	82	73:27
3[b]	–25 °C	89	89:11
4	–50 °C	91	94:6
5	**–60 °C**	**93**	**97:3**
6	–78 °C	25	84:16

[a] Copy of Table 1, entry 7.
[b] Copy of Table 1, entry 10.

Changing the amounts of the reagents was ineffective. Thus, doubling (5.0 and 10.0 equiv for Cp_2ZrCl_2 and $AgClO_4$, respectively) provided **3** quantitatively with a 96:4 α/β ratio, a result which was close enough to the optimized one (Table 5, entry 5) where 2.5 and 5.0 equivalents of Cp_2ZrCl_2 and $AgClO_4$, respectively, were used. When both the reagents were decreased to 1.5 equivalents, the reaction decelerated drastically.

The effect of the *o*-xylylene group in obtaining the α-selectivity was confirmed by using the glucosyl fluoride **4** with a (*Z*)-2-butenylene group[21] bridged between the 3-O and 6-O (Scheme 1). Compound **4** was synthesized from 1,2,4-*O*-orthoacetyl-D-glucose (**5**). Thus, double etherification of **5** with (*Z*)-1,4-dichloro-2-butene furnished **6** in 34% yield. Thermal cleavage of the orthoester in **6** associated with the introduction of a 4-methoxyphenyloxy group to the anomeric position followed by MS 4A mediated methanolysis of the acetyl group,[22] which arises from the orthoester, yielded diol **7** as the β-isomer. Benzylation of **7** gave **8**. Oxidative removal of the 4-methoxyphenyl group from **8** with $Ce(SO_4)_2$ followed by fluorination of the anomeric position of **9** with (diethylamino)sulfur trifluoride (DAST) afforded **4** as a mixture of diastereomers (α/β = 7:93). The predominance of the β-isomer was determined on the basis of the NOE correlation between H-1 and H-5 of the major isomer in C_6D_6. The pyranose ring of β-**4** was $^1S_3$ form, the conformation of which was determined on the basis of the $^3J_{H-H}$ values observed for hydrogens on the pyranose ring. The glycosylation reaction of **4** with cyclohexylmethanol (**2**) produced the corresponding glucoside **10** with 24:76 α/β-selectivity at –20 °C. Although the optimal temperature was –60 °C with **1**, no reaction occurred with **4** even when the temperature was –40 °C. The moderate β-selectivity clearly demonstrates that the *o*-xylylene group has a key role in hindering the β-face of the pyranose. The pyranose rings of α- and β-**10** were $^1C_4$ and $^1S_3$ form, respectively, the conformation of which were determined on the basis of the $^3J_{H-H}$ values with information derived by chemical calculations. As additional information, β-**10** is unstable on silica gel, the details of which are described in the Supporting Information, Section 4.4.

Table 6 summarizes the scope of the glycosyl acceptor. The optimized reaction conditions (Table 5, entry 5) were applied to each glycosyl acceptor listed. The reaction at 6-OH of a glucose derivative (Table 6, entry 1) provided the corresponding disaccharide **11** in 76% yield with a >97:3 α/β ratio. The α-selectivity was similar to that observed in the reaction with **2**. Entries 2 to 5 show the results of the reactions with secondary alcohols. In the reactions with each enantiomer of menthol (entries 2 and 3), a difference in stereoselectivity was observed. Thus, the reaction with (+)-menthol proceeded with higher α-selectivity (entry 2, α/β = 89:11) than the reaction with the (–)-isomer (entry 3, α/β = 72:28). The matching and mismatching effect of the

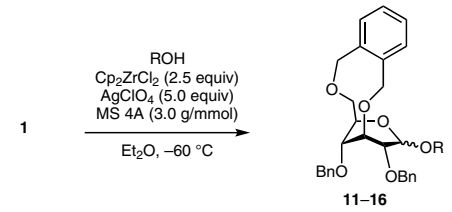


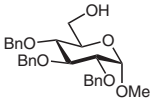
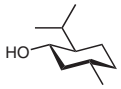
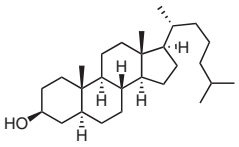
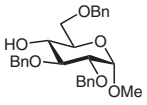
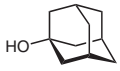
Scheme 1 (a) Synthesis of **4** equipped with a (*Z*)-2-butenylene group. (b) Glycosylation reaction of **4**

enantiomers could explain the difference.[23] The α/β ratio (79:21) of **14** provided by the reaction with β-cholestanol (entry 4) was between the results of entries 2 and 3. The hydroxy group at the 4-position of a glucose derivative (entry 5) reacted with a low isolated yield (12%) of **15**, while the α-selectivity was perfect. The reaction with a tertiary alcohol, 1-adamantanol, proceeded in a moderately α-selective manner to give **16** (entry 6, α/β = 86:14).

In summary, we have developed a highly α-selective reaction using the *o*-xylylene group as the steric hindrance for the approach of glycosyl acceptors. The *o*-xylylene group bridging the 3-O and 6-O of the glucopyranosyl ring stands upright to the β-face of the pyranose ring, as the computer calculations and the NMR studies suggest, and generates the steric hindrance. The optimization process could be understood as the search for discovering the kinetic reaction conditions that inhibit isomerization of the resulting α-glycosides to the β-isomers. The 3,6-*O*-*o*-xylylene bridge generates steric hindrance over the β-face, while the bridge locks the conformation of the pyranose ring to orient the 2-O of the glucose axially, which causes steric hindrance at the α-face. Because of the steric hindrance at both faces, selectivity was achieved by control that diminishes reactivity as a whole, which presumably is the reason for the stagnant chemical yields in the reactions with sterically hindered alcohols.

Table 6 Scope of the α-Selective Glycosylation



Entry	ROH	Time (h)	Yield[a] (%), α/β ratio[b]	Glucoside
1		24	76,[c] >97:3	**11**
2		2	86, 89:11	**12**
3		2	86, 72:28	**13**
4		2	77,[d] 79:21	**14**
5		24	12, >99:1	**15**
6		24	66,[e] 86:14	**16**

[a] Isolated yield of the anomeric mixture.
[b] Determined by ^{1}H NMR spectroscopy, after isolation of the glucoside as the anomeric mixture.
[c] 2% of **1** was unreacted.
[d] 12% of **1** was unreacted.
[e] 32% of **1** was unreacted.

All commercially available reagents were used without further purification. Reactions were performed under a positive pressure of N_2, unless otherwise noted. When necessary, glassware was dried under reduced pressure by heating with a heat gun. Reaction mixtures were magnetically stirred. Concentration was performed under reduced pressure. The reactions were monitored by TLC and mass spectrometry. Anhydrous $MgSO_4$ was used to dry organic layers after extraction and was removed by filtration through a cotton pad. The filtrate was concentrated and subjected to further purification protocols if necessary. This sequence is represented as 'the general drying procedure' in the experimental section. TLC was performed on Merck precoated silica gel 60 F-254 plates. Spots were visualized by exposure to UV light,

or by immersion into a solution of 2% anisaldehyde, 5% H_2SO_4 in EtOH, followed by heating at ca. 200 °C. Column chromatography (CC) was performed on Merck silica gel 60 (0.063–0.200 or 0.040–0.063 mm) or Kanto Chemical silica gel 60 N (spherical, neutral, 40–50 or 63–210 μm). Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined using a JASCO DIP-370 polarimeter with a 100-mm cell at 589 nm. For IR spectra, the major absorbance bands are reported in wavenumbers (cm^{-1}). HRMS data were obtained on a JEOL JMS-T100LC spectrometer. NMR spectra were recorded on JEOL JNM-ECX-400 or JNM-ECX-500 spectrometers at 400 or 500 MHz for ^1H NMR and 100 or 126 MHz for ^{13}C NMR, respectively, with either TMS or residual proton of the deuterated solvent as internal reference in the indicated solvent. The ^1H NMR data are indicated by chemical shifts (δ), with the multiplicity (standard abbreviations), the coupling constants, and the number of protons in parentheses. The ^{13}C NMR data are reported as the chemical shifts (δ) with the hydrogen multiplicity in parentheses (s, C; d, CH; t, CH_2; q, CH_3) obtained from the DEPT spectra. When the number of carbons was more than one, the number has been added in parentheses.

Cyclohexylmethyl 2,4-Di-*O*-benzyl-3,6-*O*-*o*-xylylene-D-glucopyranoside (3)

Table 1, Entry 1

Prepared according to a literature procedure.[17]

Table 1, Entry 2

A mixture of glucosyl fluoride **1** (24.5 mg, 52.7 μmol), cyclohexylmethanol (**2**; 6.9 mg, 60 μmol), TMSOTf (24 mg, 130 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred at –25 °C for 18 h. After addition of saturated aq $NaHCO_3$ (5 mL), the mixture was filtered through a cotton–Celite pad. The pad was washed with Et_2O. The Et_2O layer of the filtrate was separated, and the aqueous layer was extracted with Et_2O. The combined Et_2O layer was washed with brine. After the general drying procedure, ^1H NMR spectroscopy of the crude product detected only β-**3** as the glycosylated product. Purification by CC (2 g of silica gel; hexane/Et_2O, 10:1 to 8:1) provided β-**3** (20.6 mg, 70% yield).

Table 1, Entry 3

In a reaction similar to that of Table 1, entry 2, use of **1** (23.8 mg, 51.2 μmol) and $BF_3{\cdot}OEt_2$ (10 mg, 65 μmol), instead of TMSOTf, provided a crude product. The reaction time was 2 h. In the crude product, the ratio of α-**3**/β-**3**/unreacted **1** was 31:69:<1 on the basis of the integral of the anomeric signals in the ^1H NMR spectrum. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product gave a mixture of α- and β-**3** (25.2 mg, 88% yield).

Table 1, Entry 4

A mixture of **1** (30.0 mg, 64.6 μmol), **2** (8.8 mg, 78 μmol), $SnCl_2$ (14.7 mg, 77.5 μmol), $AgClO_4$ (16.1 mg, 77.5 μmol), and MS 4A (97 mg) in BTF (1.3 mL) was stirred for 12 h at rt. After addition of saturated aq $NaHCO_3$ (5 mL), the mixture was filtered through a cotton–Celite pad. The pad was washed with EtOAc. The EtOAc layer of the filtrate was separated, and the aqueous layer was extracted with EtOAc. The combined EtOAc layer was successively washed with H_2O and brine. After the general drying procedure, purification by CC (hexane/EtOAc, 10:1 to 4:1) provided a mixture of α- and β-**3** (30.1 mg, 83% yield, α/β = 58:42).

Table 1, Entry 5

In a reaction similar to that of Table 1, entry 4, use of Et_2O (1.3 mL), instead of BTF, gave a crude product. The reaction time was 1.5 h. CC (hexane/EtOAc, 10:1 to 6:1) of the crude product provided **3** (30.8 mg, 85% yield, α/β = 62:38).

Table 1, Entry 6

In a reaction similar to that of Table 1, entry 4, use of AgOTf (19.9 mg, 77.5 μmol) and Et_2O (1.3 mL), instead of $AgClO_4$ and BTF, respectively, provided a crude product. The reaction time was 1.5 h. CC (hexane/EtOAc, 10:1 to 6:1) of the crude product provided **3** (29.7 mg, 82% yield, α/β = 60:40).

Table 1, Entry 7

In a reaction similar to that of Table 1, entry 4, use of Cp_2ZrCl_2 (47.4 mg, 162 μmol), instead of $SnCl_2$, $AgClO_4$ (67.0 mg, 323 μmol), and Et_2O (1.3 mL), instead of BTF, gave a crude product. The reaction time was 1.5 h. CC (hexane/EtOAc, 10:1 to 5:1) of the crude product provided **3** (34 mg, 94% yield, α/β = 73:27).

Table 1, Entry 8

A mixture of **1** (23.8 mg, 51 μmol), **2** (9.0 mg, 79 μmol), $Sc(OTf)_3$ (66.2 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred at –25 °C for 6 h. After addition of saturated aq $NaHCO_3$ (5 mL), the mixture was filtered through a cotton–Celite pad. The pad was washed with Et_2O. The Et_2O layer of the filtrate was separated, and the aqueous layer was extracted with Et_2O. The combined Et_2O layer was washed with brine. After the general drying procedure, the ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 40:14:46 on the basis of the integral of the anomeric signals in the ^1H NMR spectrum. Purification by CC (2 g of silica gel; hexane/Et_2O, 9:1 to 17:2) provided a mixture of α- and β-**3** (14.4 mg, 50% yield) as a colorless syrup. On the basis of the isolated amount of **3**, the amount of unreacted **1** was calculated to be 10.2 mg (43%).

Table 1, Entry 9

In a reaction similar to that described in the previous procedure, use of **1** (29.5 mg, 64 μmol), Cp_2TiCl_2 (40 mg, 160 μmol), and $AgClO_4$ (67 mg, 320 μmol) gave a crude product. The reaction temperature was –25 °C for the first 3 h, and then rt for the subsequent 15 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 20:6:74. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (29.6 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 8.8 mg (25% yield) and 20.8 mg (71% unreacted).

Table 1, Entry 10

In a reaction similar to that of Table 1, entry 8, use of **1** (30.0 mg, 65 μmol), Cp_2ZrCl_2 (47 mg, 160 μmol), $AgClO_4$ (67 mg, 320 μmol), and MS 4A (194 mg) gave a crude product. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 89:11:<1. CC (hexane/Et_2O, 10:1 to 9:1) of the crude product provided a mixture of α- and β-**3** (32.1 mg, 89% yield).

Table 1, Entry 11

In a reaction similar to that of Table 1, entry 8, use of **1** (30.0 mg, 65 μmol), $Cp_2Zr(OTf)_2$ (99 mg, 160 μmol), $AgClO_4$ (67 mg, 320 μmol), and MS 4A (194 mg) gave a crude product. The reaction time was 30 min. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 61:39:<1. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α- and β-**3** (32.8 mg, 91% yield).

Table 1, Entry 12

In a reaction similar to that of Table 1, entry 8, use of **1** (28.5 mg, 61 μmol), Cp_2HfCl_2 (63 mg, 170 μmol), $AgClO_4$ (67 mg, 320 μmol), and MS 4A (194 mg) gave a crude product. The reaction time was 18 h. The reaction temperature was –25 °C for the first 3 h, and then rt for the subsequent 15 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 70:30:<1. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α- and β-**3** (26.6 mg, 78% yield).

Table 1, Entry 13

In a reaction similar to that of Table 1, entry 8, use of **1** (24.8 mg, 53 μmol), $Tb(OTf)_3$ (81.5 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) gave a crude product. The reaction temperature was –25 °C for the first 3 h, and then rt for the subsequent 21 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 66:9:25. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (24.0 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 18.8 mg (63% yield) and 5.2 mg (21% unreacted).

Table 1, Entry 14

In a reaction similar to that of Table 1, entry 8, use of **1** (22.0 mg, 47 μmol), $Er(OTf)_3$ (83 mg, 130 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) gave a crude product. The reaction temperature was –25 °C for the first 3 h, and then rt for the subsequent 21 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 69:31:<1. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α- and β-**3** (20.8 mg, 79% yield).

Table 1, Entry 15

In a reaction similar to that of Table 1, entry 8, use of **1** (24.6 mg, 53 μmol), $Yb(OTf)_3$ (83.4 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) gave a crude product. The reaction time was 3 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 39:10:51. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (26.0 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 13.9 mg (47% yield) and 12.1 mg (49% unreacted).

Table 2, Entry 1

A mixture of **1** (30.9 mg, 66.5 μmol), **2** (8.8 mg, 77.5 μmol), Cp_2ZrCl_2 (47.4 mg, 162 μmol), $AgClO_4$ (67.0 mg, 323 μmol), and MS 4A (194 mg) in pyridine (1.0 mL) was stirred for 21 h at –25 °C. After addition of saturated aq $NaHCO_3$ (5 mL), the mixture was filtered through a cotton–Celite pad. The pad was washed with EtOAc. The EtOAc layer of the filtrate was separated, and the aqueous layer was extracted with EtOAc. The combined EtOAc layer was successively washed with H_2O and brine. Most of the crude product was unreacted **1**; only a trace amount of α-**3** was in the crude product.

Table 2, Entry 2

A mixture of **1** (31.9 mg, 68.7 μmol), **2** (8.8 mg, 78 μmol), Cp_2ZrCl_2 (47.4 mg, 162 μmol), $AgClO_4$ (67.0 mg, 323 μmol), and MS 4A (194 mg) in DMF (1.0 mL) was stirred for 24 h at 0 °C. No reaction occurred.

Table 2, Entry 3

In a reaction similar to that of Table 2, entry 1, use of **1** (30.0 mg, 64.6 μmol), **2** (8.8 mg, 77.5 μmol), Cp_2ZrCl_2 (94.4 mg, 323 μmol), $AgClO_4$ (67.0 mg, 323 μmol), and MS 4A (97 mg) in toluene (1.2 mL) gave a crude product. The reaction temperature and time were rt and 2 h, respectively. CC (hexane/EtOAc, 10:1 to 6:1) of the crude product provided **3** (30.0 mg, 83% yield, α/β = 1:>99).

Table 2, Entry 4

In a reaction similar to that of Table 2, entry 3, use of benzene, instead of toluene, provided a crude product. The reaction temperature and time were rt and 1.5 h, respectively. CC (hexane/EtOAc, 10:1 to 5:1) of the crude product provided **3** (34.8 mg, 96% yield, α/β = 40:60).

Table 2, Entry 5

In a reaction similar to that of Table 2, entry 1, use of **1** (29.5 mg, 63.5 μmol), **2** (8.7 mg, 76 μmol), Cp_2ZrCl_2 (93.0 mg, 318 μmol), $AgClO_4$ (65.9 mg, 318 μmol), and MS 4A (95 mg) in DCM (1.2 mL) gave a crude product. The reaction temperature and time were rt and 1.5 h, respectively. CC (hexane/EtOAc, 10:1 to 8:1) of the crude product provided **3** (24.6 mg, 69% yield, α/β = 46:54).

Table 2, Entry 6

In a reaction similar to that of Table 2, entry 3, use of MeCN, instead of benzene, provided a crude product. The reaction temperature and time was rt and 1.5 h, respectively. CC (hexane/EtOAc, 10:1 to 6:1) of the crude product provided **3** (18.6 mg, 52% yield, α/β = 41:59).

Table 2, Entry 7

A mixture of **1** (22.4 mg, 48.2 μmol), **2** (6.9 mg, 65 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) in DME (1.0 mL) was stirred for 30 min at –25 °C. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 56:44:<1. CC (hexane/Et_2O, 10:1 to 9:1) of the crude product provided a mixture of α- and β-**3** (23.4 mg, 87% yield).

Table 2, Entry 8

In a reaction similar to that of Table 2, entry 7, use of **1** (24.9 mg, 54.0 μmol) and *i*-Pr_2O, instead of DME, gave a crude product. The reaction time was 40 min. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 76:5:19. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (20.8 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 17.4 mg (58% yield) and 3.4 mg (14% unreacted).

Table 2, Entry 9

In a reaction similar to that of Table 2, entry 7, use of **1** (25.1 mg, 55.0 μmol), **2** (9.1 mg, 80 μmol), Cp_2ZrCl_2 (48.5 mg, 166 μmol), $AgClO_4$ (68.7 mg, 332 μmol), and MS 4A (199 mg) in *t*-BuOMe (1.2 mL), instead of DME, gave a crude product (20.3 mg). The reaction time and temperature were 18 h and –25 °C, respectively. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 44:5:51. On the basis of the ratio, the respective amounts of **3** and **1** were calculated to be 10.9 mg (37% yield) and 9.4 mg (38% unreacted).

Table 2, Entry 10

In a reaction similar to that of Table 2, entry 7, use of **1** (23.4 mg, 50.4 μmol) and CPME, instead of DME, gave a crude product. The reaction time was 1.5 h. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α- and β-**3** (22.7 mg, 81% yield, α/β = 90:10).

Table 2, Entry 11

In a reaction similar to that of Table 2, entry 7, use of **1** (23.6 mg, 50.8 μmol) and Me_2S, instead of DME, gave a crude product. The reaction time and temperature were 3 h and –25 °C to rt, respectively. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 8:14:78. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (26.9 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 6.8 mg (20% yield) and 20.1 mg (85% unreacted).

Table 3, Entry 1

A mixture of **1** (24.9 mg, 53.6 μmol), **2** (6.9 mg, 65 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgBF_4$ (52.4 mg, 269 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred for 24 h at –25 °C. After addition of saturated aq $NaHCO_3$, the mixture was filtered through a cotton–Celite pad. The pad was washed with Et_2O. The Et_2O layer of the filtrate was separated, and the aqueous layer was extracted with Et_2O. The combined Et_2O layer was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, CC (2 g of silica gel; hexane/Et_2O, 9:1 to 4:1) of the crude product provided a mixture of α- and β-**3** (26.0 mg, 87% yield, α/β = 2:98).

Table 3, Entry 2

In a reaction similar to that of Table 3, entry 1, use of **1** (25.0 mg, 53.8 μmol) and $AgB(C_6F_5)_4$ (50.8 mg, 64.6 μmol), instead of $AgBF_4$, gave a crude product. The reaction temperature and time were rt and 1.5 h, respectively. CC (hexane/Et_2O, 10:1 to 9:1) of the crude product provided a mixture of α- and β-**3** (21.0 mg, 70% yield, α/β = 49:51).

Table 3, Entry 3

In a reaction similar to that of Table 3, entry 1, use of **1** (22.9 mg, 49.3 μmol) and $AgSbF_6$ (92.4 mg, 269 μmol), instead of $AgBF_4$, gave a crude product. The reaction temperature was –25 °C for the first 4 h, and then 0 °C for the subsequent 1.5 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 50:50:<1. CC (hexane/Et_2O, 9:1 to 17:2) of the crude product provided a mixture of α- and β-**3** (20.1 mg, 73% yield).

Table 3, Entry 4

In a reaction similar to that of Table 3, entry 1, **1** (22.0 mg, 47.4 μmol) and Ag_2CO_3 (74.2 mg, 269 μmol), instead of $AgBF_4$, were used. The reaction temperature was –25 °C for the first 4 h, 0 °C for the subsequent 9 h, and then rt for the final 24 h. Most of the crude product was unreacted **1**; only a trace amount of **3** was in the crude product.

Table 3, Entry 5

In a reaction similar to that of Table 3, entry 1, **1** (25.6 mg, 53.8 μmol) and Ag_2SO_4 (83.9 mg, 269 μmol), instead of $AgBF_4$, were used. The reaction temperature was –25 °C for the first 4 h, 0 °C for the subsequent 9 h, and then rt for the final 24 h. Most of the crude product was unreacted **1**; only a trace amount of **3** was in the crude product.

Table 3, Entry 6

In a reaction similar to that of Table 3, entry 1, use of **1** (24.3 mg, 52.3 μmol), MS 4A (81 mg), and AgOTf (69.1 mg, 269 μmol), instead of $AgBF_4$, gave a crude product. The reaction temperature and time were rt and 1.5 h, respectively. CC (hexane/Et_2O, 10:1 to 9:1) of the crude product provided a mixture of α- and β-**3** (26.3 mg, 90% yield, α/β = 65:35).

Table 3, Entry 7

In a reaction similar to that of Table 3, entry 1, use of **1** (22.4 mg, 48.2 μmol) and $AgOCOCF_3$ (59.4 mg, 269 μmol), instead of $AgBF_4$, gave a crude product. The reaction temperature was –25 °C for the first 4 h, and then 0 °C for the subsequent 9 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 61:17:22. CC (hexane/Et_2O, 8:1 to 15:2) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (19.4 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 15.7 mg (58% yield) and 3.7 mg (17% unreacted).

Table 3, Entry 8

In a reaction similar to that of Table 3, entry 1, use of **1** (23.7 mg, 51.0 μmol) and $AgNO_3$ (45.7 mg, 269 μmol), instead of $AgBF_4$, gave a crude product. The reaction temperature was –25 °C for the first 4 h, 0 °C for the subsequent 9 h, and then rt for the final 12 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 77:21:2. CC (hexane/Et_2O, 8:1 to 15:2) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (20.2 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 19.9 mg (70% yield) and 0.3 mg (1% unreacted).

Table 4, Entry 1

A mixture of **1** (23.2 mg, 49.9 μmol), **2** (6.9 mg, 65 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 3A (161 mg) in Et_2O (1.0 mL) was stirred for 15 min at –25 °C. After addition of saturated aq $NaHCO_3$, the mixture was filtered through a cotton–Celite pad. The pad was washed with Et_2O. The Et_2O layer of the filtrate was separated, and the aqueous layer was extracted with Et_2O. The combined Et_2O layer was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 67:11:22. CC (2 g of silica gel; hexane/Et_2O, 9:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (20.0 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 16.2 mg (58% yield) and 3.8 mg (16% unreacted).

Table 4, Entry 2

See Table 1, entry 10.

Table 4, Entry 3

In a reaction similar to that of Table 4, entry 1, use of **1** (25.5 mg, 54.9 μmol) and MS 5A, instead of MS 3A, gave a crude product. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 25:7:68. CC (hexane/Et_2O, 9:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (24.0 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 8.7 mg (28% yield) and 15.3 mg (60% unreacted).

Table 4, Entry 4

In a reaction similar to that of Table 4, entry 1, use of **1** (24.9 mg, 53.6 μmol) and MS 13X, instead of MS 3A, gave a crude product. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 67:10:23. CC (hexane/Et_2O, 9:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (24.0 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 19.2 mg (64% yield) and 4.8 mg (19% unreacted).

Table 4, Entry 5

In a reaction similar to that of Table 4, entry 1, but without the molecular sieves, use of **1** (25.3 mg, 54.5 μmol) provided a crude product

(24.4 mg), in which the ratio of α-**3**/β-**3**/unreacted **1** was <1:99:<1; thus, the yield of β-**3** was 80%.

Table 5, Entry 1

See Table 1, entry 7.

Table 5, Entry 2

A mixture of **1** (29.8 mg, 64.2 μmol), **2** (8.8 mg, 78 μmol), Cp_2ZrCl_2 (47.4 mg, 162 μmol), $AgClO_4$ (67.0 mg, 323 μmol), and MS 4A (194 mg) in Et_2O (1.0 mL) was stirred for 30 min at 0 °C. After addition of saturated aq $NaHCO_3$ (5 mL), the mixture was filtered through a cotton–Celite pad. The pad was washed with Et_2O. The Et_2O layer of the filtrate was separated, and the aqueous layer was extracted with Et_2O. The combined Et_2O layer was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, CC (2 g of silica gel; hexane/Et_2O, 9:1 to 4:1) of the crude product provided a mixture of α- and β-**3** (29.5 mg, 82% yield, α/β = 73:27).

Table 5, Entry 3

See Table 1, entry 10.

Table 5, Entry 4

In a reaction similar to that of Table 5, entry 1, use of **1** (29.0 mg, 62.4 μmol) at –50 °C gave a crude product. The reaction time was 14 h. CC (hexane/Et_2O, 9:1 to 4:1) of the crude product provided a mixture of α- and β-**3** (31.6 mg, 91% yield, α/β = 94:6).

Table 5, Entry 5

In a reaction similar to that of Table 5, entry 1, use of **1** (31.5 mg, 67.8 μmol) at –60 °C gave a crude product. The reaction time was 20 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 92:3:5. CC (hexane/Et_2O, 10:1 to 4:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (36.7 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 35.2 mg (93% yield) and 1.5 mg (5% unreacted).

Table 5, Entry 6

In a reaction similar to that of Table 5, entry 1, use of **1** (25.0 mg, 53.8 μmol) at –78 °C gave a crude product. The reaction time was 54 h. The ratio of α-**3**/β-**3**/unreacted **1** in the crude product was 26:5:69. CC (hexane/Et_2O, 10:1 to 8:1) of the crude product provided a mixture of α-**3**, β-**3**, and **1** (21.5 mg). On the basis of the isolated amount, the respective amounts of **3** and **1** were calculated to be 7.5 mg (25% yield) and 14 mg (56% unreacted).

3,6-*O*-[(*Z*)-2-Butenylene]-1,2,4-*O*-orthoacetyl-D-glucopyranose (6)

To a stirred mixture of NaH (60% in mineral oil, 607 mg; 364 mg as NaH, 15.2 mmol) in toluene (253 mL) at 80 °C were added a solution of diol **5** (516 mg, 2.53 mmol) in DMF (50.6 mL) and a solution of (*Z*)-1,4-dichloro-2-butene (348 mg, 2.78 mmol) in toluene (50.6 mL), respectively, using syringe pumps (rate of addition: each 0.25 mL/min). After the end of the additions, the mixture was stirred for 11.5 h at rt. The mixture was cooled to 0 °C and H_2O was added to quench the reaction. The aqueous mixture was extracted with EtOAc. The organic layer was successively washed with H_2O and brine. After the general drying procedure, the concentrated extract was purified by CC (26 g of silica gel; hexane/EtOAc, 1:0 to 7:1) to give (*Z*)-butenylene-bridged **6** (220 mg, 34% yield) as a colorless powder; mp 76.8–78.0 °C; $[\alpha]_D^{25}$ –36 (*c* 0.65, $CHCl_3$).

IR (ATR): 2897, 2860, 1740, 1404, 1321, 1121, 1078, 1055, 1015, 974, 887 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ = 5.84–5.75 (m, 2 H), 5.77 (d, *J* = 5.0 Hz, 1 H), 4.66 (dd, *J* = 4.4, 2.1 Hz, 1 H), 4.60 (dd, *J* = 4.1, 2.1 Hz, 1 H), 4.53 (m, 1 H), 4.44 (m, 1 H), 4.42 (d, *J* = 5.0 Hz, 1 H), 4.08 (dd, *J* = 12.4, 4.6 Hz, 1 H), 3.97 (dd, *J* = 11.1, 5.5 Hz, 1 H), 3.91 (dd, *J* = 4.4, 2.1 Hz, 1 H), 3.74 (dd, *J* = 13.5, 4.1 Hz, 1 H), 3.74 (dd, *J* = 13.5, 2.1 Hz, 1 H), 1.65 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 130.7 (d), 128.1 (d), 119.4 (s), 97.8 (d), 78.6 (d), 73.9 (d), 81.7 (d), 70.0 (d), 69.3 (t), 69.0 (t), 66.3 (t), 20.5 (q).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{16}NaO_6$: 279.08446; found: 279.08492.

4-Methoxyphenyl 3,6-*O*-[(*Z*)-2-Butenylene]-β-D-glucopyranoside (7)

A mixture of orthoester **6** (275 mg, 1.07 mmol) and 4-methoxyphenol (1.33 g, 10.7 mmol) was stirred at 100 °C for 11.5 h, then cooled to rt. MeOH (10.7 mL) and MS 4A (1.6 g) were added, and the mixture was stirred for 20 h at reflux. After cooling to rt, the mixture was filtered through a cotton–Celite pad. The concentrated filtrate was purified by CC (10 g of silica gel; hexane/EtOAc, 5:1 to 1:2). The separated, desired product was crystallized ($CHCl_3$ and hexane) to give 4-methoxyphenyl glucoside **7** (134 mg, 39% yield, dr 98:2) as a colorless solid; mp 143–145 °C; $[\alpha]_D^{24}$ +79.1 (*c* 1.03, $CHCl_3$).

IR (ATR): 3600–3160, 2866, 1510, 1215, 1109, 1059, 1036, 970, 826, 748 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, 24 °C): δ = 6.97 (d, *J* = 9.2 Hz, 2 H), 6.81 (d, *J* = 9.2 Hz, 2 H), 5.85 (m, 1 H), 5.64 (m, 1 H), 5.31 (d, *J* = 3.4 Hz, 1 H), 4.75 (br s, 1 H), 4.50 (dd, *J* = 10.3, 6.3 Hz, 1 H), 4.31–4.17 (m, 4 H), 4.03 (br d, *J* = 3.4 Hz, 1 H), 3.98 (dd, *J* = 10.3, 6.3 Hz, 1 H), 3.81 (br s, 1 H), 3.77 (s, 3 H), 3.68 (dd, *J* = 10.3, 5.7 Hz, 1 H), 3.61 (br s, 1 H), 3.15 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$, 24 °C): δ = 154.9 (s), 151.1 (s), 131.4 (d), 127.2 (d), 117.8 (d, 2 C), 114.7 (d, 2 C), 101.1 (d), 79.1 (d), 75.6 (d), 72.4 (d), 69.3 (t), 69.2 (t), 64.0 (t), 63.2 (d), 55.8 (q).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_7$: 361.1263; found: 361.1265.

4-Methoxyphenyl 2,4-Di-*O*-benzyl-3,6-*O*-[(*Z*)-2-butenylene]-β-D-glucopyranoside (8)

A mixture of diol **7** (127 mg, 374 μmol) and NaH (60% in mineral oil, 60 mg; 36 mg as NaH, 1.5 mmol) in DMF (3.7 mL) was added BnBr (259 mg, 1.50 mmol) at 0 °C. The mixture was stirred for 2.5 h at 70 °C, then cooled to rt. H_2O was added to quench the reaction. The aqueous mixture was extracted with EtOAc. The organic layer was successively washed with 1 M HCl and brine. After the general drying procedure, the concentrated extract was purified by CC (3 g of silica gel; hexane/EtOAc, 9:1 to 5:1) to give dibenzylated **8** (194 mg, 100% yield) as a colorless syrup; $[\alpha]_D^{23}$ +28.5 (*c* 0.2, $CHCl_3$).

IR (ATR): 2880, 2859, 1520, 1456, 1217, 1109, 1040, 739, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 7.39–7.37 (m, 2 H), 7.34–7.27 (m, 8 H), 7.38 (dd, *J* = 7.7, 1.7 Hz, 2 H), 6.93 (d, *J* = 9.2 Hz, 2 H), 6.81 (d, *J* = 9.2 Hz, 2 H), 5.79–5.71 (m, 2 H), 5.25 (d, *J* = 6.6 Hz, 1 H), 4.80 (d, *J* = 12.0 Hz, 1 H), 4.72 (d, *J* = 12.0 Hz, 1 H), 4.70 (br d, *J* = 10.3 Hz, 1 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.35 (m, 1 H), 4.30 (dd, 12.3, 2.9 Hz, 1 H), 4.17 (br d, *J* = 4.0 Hz, 1 H), 3.98 (dd, *J* = 12.3, 4.8 Hz, 1 H), 3.91–3.87 (m, 2 H), 3.83 (d, *J* = 3.4 Hz, 1 H), 3.77 (s, 3 H), 3.76 (dd, *J* = 13.2, 4.0 Hz, 1 H), 3.69 (dd, *J* = 13.2, 1.2 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$, 24 °C): δ = 155.1 (s), 151.4 (s), 138.6 (s), 138.0 (s), 129.7 (d), 129.7 (d), 128.5 (d, 2 C), 128.3 (d, 2 C), 127.9 (d), 127.8 (d, 6 C), 127.8 (d, 2 C), 127.6 (d), 117.9 (d), 114.6 (d), 101.1 (d), 82.6 (d), 82.1 (d), 75.5 (d), 72.8 (t), 71.8 (t), 70.3 (d), 70.0 (t), 68.2 (t), 65.4 (t), 55.8 (q).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{34}NaO_7$: 541.2202; found: 541.2205.

2,4-Di-*O*-benzyl-3,6-*O*-[(*Z*)-2-butenylene]-D-glucopyranose (9)

A mixture of 4-methoxyphenyl glucoside **8** (194 mg, 374 μmol) and $Ce(SO_4)_2$ (621 mg, 1.87 mmol) in a mixture of MeCN (4.7 mL) and H_2O (0.7 mL) was stirred for 3 h at rt. Then, the mixture was filtered through a cotton–Celite pad. After addition of 10% aq $Na_2S_2O_3$ to the filtrate, the aqueous mixture was extracted with EtOAc. The organic layer was successively washed with 10% aq $Na_2S_2O_3$, H_2O, and brine. After concentration, the mixture was diluted to a solution of MeCN (3.1 mL) and H_2O (1.5 mL). To this was added $Ce(SO_4)_2$ (370 mg, 1.11 mmol). The mixture was stirred for 6 h at rt. To the mixture, further $Ce(SO_4)_2$ (290 mg, 873 μmol) was added. The mixture was stirred for 2.5 h at rt. Again, to the mixture was added $Ce(SO_4)_2$ (370 mg, 1.11 mmol). The mixture was stirred at 40 °C for 2 h. Then, the mixture was filtered through a cotton–Celite pad. To the filtrate, 10% aq $Na_2S_2O_3$ was added. The aqueous mixture was extracted with EtOAc. The organic layer was successively washed with 10% aq $Na_2S_2O_3$, H_2O, and brine. After the general drying procedure, the crude product was purified by CC (5 g of silica gel; hexane/EtOAc, 5:1 to 2:1) to give **9** (115 mg, 74% yield) as a mixture of anomers.

2,4-Di-*O*-benzyl-3,6-*O*-[(*Z*)-2-butenylene]-D-glucopyranosyl Fluoride (4)

A mixture of pyranose **9** (115 mg, 278 μmol) and DAST (134 mg, 833 μmol) in THF (2.8 mL) was stirred for 30 min at 0 °C. MeOH (1 mL) was added to quench the reaction; to this was further added saturated aq $NaHCO_3$. The aqueous mixture was extracted with EtOAc. The organic layer was successively washed with saturated aq $NaHCO_3$, H_2O, and brine. After the general drying procedure, the crude product was purified by CC (5 g of silica gel; hexane/EtOAc, 7:1 to 5:1) to give **4** (102 mg, 88% yield, α/β = 7:93) as a colorless syrup; $[\alpha]_D^{23}$ +106 (*c* 0.9, $CHCl_3$).

IR (ATR): 3030, 2664, 1456, 1107, 1090, 1028, 737, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 24 °C): δ = 7.38–7.28 (m, 10 H), 5.75 (m, 1 H), 5.68 (m, 1 H), 5.60 (dd, *J* = 53.3, 4.0 Hz, 1 H), 4.74 (d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 4.61 (d, *J* = 12.0 Hz, 1 H), 4.55 (d, *J* = 12.0 Hz, 1 H), 4.41 (ddd, *J* = 13.2, 4.0, 2.3 Hz, 1 H), 4.34 (m, 1 H), 4.32–4.26 (m, 2 H), 4.10 (dd, *J* = 13.2, 5.2 Hz, 1 H), 3.91 (dd, *J* = 12.0, 4.6 Hz, 1 H), 3.90 (dd, *J* = 11.7, 6.3 Hz, 1 H), 3.81 (br s, 1 H), 3.76 (dd, *J* = 12.0, 5.2 Hz, 1 H), 3.72 (dd, *J* = 18.0, 4.0 Hz, 1 H).

^{1}H NMR (500 MHz, C_6D_6, 23.6 °C): δ = 7.25 (d, *J* = 7.5 Hz, 4 H), 7.19–7.06 (m, 6 H), 5.81 (dd, *J* = 53.8, 4.6 Hz, 1 H), 5.55 (m, 1 H), 5.43 (m, 1 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 4.42 (d, *J* = 11.5 Hz, 1 H), 4.39 (m, 1 H), 4.28 (d, *J* = 11.5 Hz, 1 H), 4.25–4.19 (m, 2 H), 4.17 (d, *J* = 11.5 Hz, 1 H), 4.11 (dd, *J* = 4.6, 4.6 Hz, 1 H), 3.93 (dd, *J* = 18.9, 4.6 Hz, 1 H), 3.86 (dd, *J* = 13.2, 5.2 Hz, 1 H), 3.83 (dd, *J* = 11.7, 4.6 Hz, 1 H), 3.79 (br s, 1 H), 3.63 (dd, *J* = 11.2, 6.3 Hz, 1 H), 3.57 (dd, *J* = 11.7, 4.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$, 24 °C): δ = 138.0 (s), 137.9 (s), 130.7 (d), 128.6 (d, 2 C), 128.5 (d, 2 C), 128.2 (d), 128.0 (d), 127.9 (d, 4 C), 127.9 (d), 109.2 (d, *J* = 216 Hz), 80.2 (d, *J* = 29 Hz), 79.9 (d), 74.0 (d, *J* = 6 Hz), 72.7 (t), 72.0 (t), 69.8 (t), 69.0 (d), 68.8 (t), 64.6 (t).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{27}FNaO_5$: 437.1740; found: 437.1735.

Cyclohexylmethyl 2,4-Di-*O*-benzyl-3,6-*O*-[(*Z*)-2-butenylene]-D-glucopyranoside (10)

To a mixture of $AgClO_4$ (29.4 mg, 142 μmol), Cp_2ZrCl_2 (45.2 mg, 155 μmol), and MS 4A (56.0 mg) in Et_2O (0.5 mL) was added cyclohexylmethanol (**2**; 8.2 mg, 72 μmol) at rt. After the reaction mixture was stirred for 0.5 h at rt, to the mixture was added dropwise a solution of glucosyl fluoride **4** (20.3 mg, 49.0 μmol) in Et_2O (1.0 mL) at –20 °C. The mixture was stirred for 7 h at –20 °C. Saturated aq $NaHCO_3$ was added at –20 °C to quench the reaction. After warming to rt, the mixture was filtered through a cotton–Celite pad. The filtrate was extracted with EtOAc. The organic layer was successively washed with saturated aq $NaHCO_3$ and brine. After the general drying procedure, the crude product of this reaction was obtained (28 mg), the ^{1}H NMR spectrum of which indicated that the anomeric ratio of the obtained glucoside **10** was α/β = 24:76. The crude product was purified by preparative TLC (hexane/EtOAc, 8:1) to give β-**10** (2.4 mg, 10% yield) as a colorless syrup and an unpurified mixture which included α-**10**. The mixture was further purified by preparative TLC (toluene/EtOAc, 8:1) to give α-**10** (7.0 mg, 28% yield) as a colorless syrup. The ratio of α-**10** and β-**10** at this stage was α/β = 74:26 on the basis of each isolated amount. For the reason for this inversion of the α/β ratio, see the Supporting Information, Section 4.4.

Data for α-**10**:

$[\alpha]_D^{25}$ +40.3 (*c* 0.35, $CHCl_3$).

IR (ATR): 2922, 2852, 1454, 1111, 1045, 735, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 24 °C): δ = 7.40 (d, *J* = 7.5 Hz, 2 H), 7.37 (d, *J* = 7.5 Hz, 2 H), 7.32–7.23 (m, 6 H), 5.73 (ddd, *J* = 11.5, 6.9, 6.3 Hz, 1 H), 5.58 (ddd, *J* = 11.5, 4.6, 1.2 Hz, 1 H), 4.95 (d, *J* = 3.4 Hz, 1 H), 4.84 (d, *J* = 12.6 Hz, 1 H), 4.66 (d, *J* = 12.6 Hz, 1 H), 4.64 (d, *J* = 12.6 Hz, 1 H), 4.60 (d, *J* = 12.6 Hz, 1 H), 4.32 (dd, *J* = 6.9, 6.3 Hz, 1 H), 4.25–4.18 (m, 4 H), 3.95 (dd, *J* = 9.7, 6.9 Hz, 1 H), 3.89 (m, 1 H), 3.85 (dd, *J* = 10.9, 6.9 Hz, 1 H), 3.68–3.61 (m, 3 H), 3.17 (dd, *J* = 9.2, 6.9 Hz, 1 H), 1.80–1.60 (m, 6 H), 1.30–1.10 (m, 3 H), 1.00–0.89 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$, 24 °C): δ = 139.2 (s), 138.8 (s), 131.2 (d), 128.3 (d, 2 C), 128.3 (d, 2 C), 128.1 (d), 127.9 (d, 2 C), 127.9 (d, 2 C), 127.5 (d), 127.4 (d), 95.6 (d), 75.6 (d), 75.2 (t), 74.9 (d), 74.5 (d), 73.2 (t), 71.8 (t), 69.1 (d), 68.8 (t), 68.7 (t), 62.9 (t), 38.2 (d), 30.3 (t), 30.2 (t), 26.7 (t), 26.0 (t), 26.0 (t).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{40}NaO_6$: 531.2723; found: 531.2704.

Data for β-**10**:

$[\alpha]_D^{24}$ +42.5 (*c* 0.12, $CHCl_3$).

IR (ATR): 2920, 2852, 1454, 1112, 1037, 735, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 24 °C): δ = 7.39–7.26 (m, 10 H), 5.78–5.68 (m, 2 H), 4.77 (d, *J* = 12.0 Hz, 1 H), 4.71 (m, 1 H), 4.66 (d, *J* = 12.0 Hz, 1 H), 4.65 (d, *J* = 6.3 Hz, 1 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.28–4.24 (m, 2 H), 4.02 (br d, *J* = 3.4 Hz, 1 H), 3.94 (dd, *J* = 12.3, 5.2 Hz, 1 H), 3.87 (dd, *J* = 10.9, 6.3 Hz, 1 H), 3.74 (br d, *J* = 2.9 Hz, 1 H), 3.71 (dd, *J* = 12.6, 3.4 Hz, 1 H), 3.69 (dd, *J* = 9.5, 3.4 Hz, 1 H), 3.66 (d, *J* = 12.6 Hz, 1 H), 3.61 (d, *J* = 6.3 Hz, 1 H), 3.23 (dd, *J* = 9.5, 6.9 Hz, 1 H), 1.82–1.56 (m, 6 H), 1.25–1.10 (m, 3 H), 0.98–0.83 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$, 24 °C): δ = 139.0 (s), 138.2 (s), 129.9 (d), 129.7 (d), 128.5 (d, 2 C), 128.4 (d, 2 C), 127.9 (d, 2 C), 127.9 (d), 127.8 (d, 2 C), 127.5 (d), 102.8 (d), 82.8 (d), 82.5 (d), 75.7 (d), 75.3 (t), 72.7 (t), 71.9 (t), 70.5 (d), 70.3 (t), 68.1 (t), 65.4 (t), 38.2 (d), 30.3 (t), 30.0 (t), 26.8 (t), 26.0 (t), 26.0 (t).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{40}NaO_6$: 531.2723; found: 531.2722.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,4-di-*O*-benzyl-3,6-*O*-*o*-xylylene-α-D-glucopyranosyl)-α-D-glucopyranoside (α-11; Table 6, Entry 1)

A mixture of **1** (25.3 mg, 54.5 μmol), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (30.0 mg, 64.6 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred for 24 h at –60 °C. After addition of saturated aq $NaHCO_3$ (5 mL), the mixture was filtered through a cotton–Celite pad. The pad was washed with Et_2O. The Et_2O layer of the filtrate was separated, and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine. After the general drying procedure, the ratio of α-**11**/β-**11**/unreacted **1** in the crude product was 95:<3:2. Purification by CC (2 g of silica gel; hexane/Et_2O, 10:1 to 4:1) provided almost pure α-**11** (37.5 mg, 76% yield), a part of which (15.0 mg) was isolated in pure form as a colorless syrup to obtain the following spectroscopic data.

$[\alpha]_D^{23}$ +207 (*c* 0.75, $CHCl_3$).

IR (ATR): 3030, 2924, 1455, 1110, 1029, 749, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.41–7.39 (m, 2 H), 7.34–7.28 (m, 8 H), 7.24–7.07 (m, 19 H), 5.26 (d, *J* = 10.5 Hz, 1 H), 5.15 (d, *J* = 5.5 Hz, 1 H), 4.98 (d, *J* = 10.5 Hz, 1 H), 4.90 (d, *J* = 11.0 Hz, 1 H), 4.87 (d, *J* = 11.7 Hz, 1 H), 4.75 (d, *J* = 11.0 Hz, 1 H), 4.67 (d, *J* = 11.4 Hz, 1 H), 4.66 (d, *J* = 12.1 Hz, 1 H), 4.60 (d, *J* = 11.4 Hz, 1 H), 4.57 (d, *J* = 11.7 Hz, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.51 (d, *J* = 12.1 Hz, 1 H), 4.47 (d, *J* = 3.4 Hz, 1 H), 4.41 (d, *J* = 10.5 Hz, 1 H), 4.38 (d, *J* = 11.7 Hz, 1 H), 4.36 (d, *J* = 10.5 Hz, 1 H), 4.19 (br s, 1 H), 4.09 (br s, 1 H), 4.08 (m, 1 H), 4.02 (br s, 1 H), 3.92–3.87 (m, 2 H), 3.73 (dd, *J* = 12.8, 2.1 Hz, 1 H), 3.70–3.65 (m, 2 H), 3.63 (br d, *J* = 11.4 Hz, 1 H), 3.58 (dd, *J* = 12.8, 3.9 Hz, 1 H), 3.28 (s, 3 H), 3.25 (dd, *J* = 11.4, 3.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 139.2 (s), 139.1 (s), 139.0 (s), 138.4 (s), 138.3 (s), 137.0 (s), 136.8 (s), 130.0 (d), 129.4 (d), 128.5–127.4 (overlapped 27 doublets), 98.2 (d), 96.4 (d), 82.1 (d), 80.2 (d), 77.7 (d), 76.0 (d), 76.0 (d), 75.5 (t), 74.8 (t), 74.2 (t), 73.9 (d), 73.5 (t), 72.1 (t), 71.7 (t), 70.6 (t), 70.2 (d), 69.9 (d), 69.6 (t), 67.5 (t), 55.2 (q).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{56}H_{60}NaO_{11}$: 931.4033; found: 931.4030.

(+)-Menthyl 2,4-Di-*O*-benzyl-3,6-*O*-*o*-xylylene-α-D-glucopyranoside (α-12; Table 6, Entry 2)

A mixture of **1** (26.6 mg, 57.2 μmol), (+)-menthol (10.1 mg, 64.6 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred for 2 h at –60 °C. The workup procedure was similar to that for the synthesis of **11**. The ratio of α-**12**/β-**12**/unreacted **1** in the crude product was 89:11:<1. Purification by CC (2 g of silica gel; hexane/Et_2O, 10:1 to 19:2) provided a mixture of α- and β-**12** (29.6 mg, 86% yield), of which a part of α-**12** (16.5 mg) was isolated in pure form as a white amorphous solid to obtain the following spectroscopic data.

$[\alpha]_D^{21}$ +122 (*c* 0.83, $CHCl_3$).

IR (ATR): 2952, 2926, 2869, 1455, 1114, 1035, 750, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.35–7.33 (m, 2 H), 7.26–7.21 (m, 6 H), 7.18–7.10 (m, 5 H), 7.04 (m, 1 H), 5.21 (d, *J* = 10.5 Hz, 1 H), 5.17 (d, *J* = 6.0 Hz, 1 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.68 (d, *J* = 12.1 Hz, 1 H), 4.56 (d, *J* = 12.4 Hz, 1 H), 4.54 (d, *J* = 12.4 Hz, 1 H), 4.36 (d, *J* = 10.8 Hz, 1 H), 4.35 (d, *J* = 12.1 Hz, 1 H), 4.23 (d, *J* = 10.5 Hz, 1 H), 4.10 (br s, 1 H), 4.07 (br s, 1 H), 3.89 (dd, *J* = 2.3, 2.3 Hz, 1 H), 3.79 (br d, *J* = 6.0 Hz, 1 H), 3.66 (dd, *J* = 12.7, 2.0 Hz, 1 H), 3.47–3.40 (m, 2 H), 2.52 (qqd, *J* = 7.1, 7.1, 2.5 Hz, 1 H), 2.00 (br d, *J* = 11.7 Hz, 1 H), 1.58–1.55 (m, 2 H), 1.32–1.26 (m, 2 H), 0.92–0.85 (m, 6 H), 0.72 (d, *J* = 7.1 Hz, 3 H), 0.63 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 138.9 (s), 138.6 (s), 137.2 (s), 136.9 (s), 130.0 (d), 129.4 (d), 128.3 (d, 2 C), 128.2 (d, 2 C), 128.1 (d), 128.0 (d, 2 C), 127.9 (d), 127.8 (d, 2 C), 127.5 (d), 127.5 (d), 91.7 (d), 75.9 (d), 75.7 (d), 75.5 (d), 75.2 (d), 74.0 (t), 72.1 (t), 71.8 (t), 71.0 (t), 70.2 (d), 69.0 (t), 48.0 (d), 40.0 (t), 34.6 (t), 31.6 (d), 24.3 (d), 22.9 (t), 22.5 (q), 21.2 (q), 15.4 (q).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{48}NaO_6$: 623.3349; found: 623.3345.

(–)-Menthyl 2,4-Di-*O*-benzyl-3,6-*O*-*o*-xylylene-α-D-glucopyranoside (α-13; Table 6, Entry 3)

A mixture of **1** (27.4 mg, 59.0 μmol), (–)-menthol (10.1 mg, 64.6 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred for 2 h at –60 °C. The workup procedure was similar to that for the synthesis of **11**. The ratio of α-**13**/β-**13**/unreacted **1** in the crude product was 72:28:<1. Purification by CC (2 g of silica gel; hexane/Et_2O, 10:1 to 8:1) provided a mixture of α- and β-**13** (30.5 mg, 86% yield), of which a part of α-**13** (19.2 mg) was isolated in pure form as a colorless syrup to obtain the following spectroscopic data.

$[\alpha]_D^{21}$ +29.3 (*c* 1.26, $CHCl_3$).

IR (ATR): 2952, 2923, 2868, 1454, 1112, 1029, 750, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.32–7.30 (m, 2 H), 7.26–7.12 (m, 11 H), 7.06 (m, 1 H), 5.03 (d, *J* = 5.0 Hz, 1 H), 5.01 (d, *J* = 12.6 Hz, 1 H), 4.71 (d, *J* = 11.2 Hz, 1 H), 4.67 (d, *J* = 12.4 Hz, 1 H), 4.61 (d, *J* = 12.4 Hz, 1 H), 4.48 (d, *J* = 12.4 Hz, 1 H), 4.42 (d, *J* = 11.2 Hz, 1 H), 4.34 (d, *J* = 12.6 Hz, 1 H), 4.33 (d, *J* = 12.4 Hz, 1 H), 4.15 (dd, *J* = 3.8, 3.8 Hz, 1 H), 3.93 (dd, *J* = 2.5, 2.5 Hz, 1 H), 3.88 (br s, 1 H), 3.78–3.74 (m, 2 H), 3.54 (dd, *J* = 12.1, 4.4 Hz, 1 H), 3.23 (td, *J* = 10.7, 4.3 Hz, 1 H), 2.29 (qqd, *J* = 6.9, 6.9, 2.5 Hz, 1 H), 2.06 (d, *J* = 12.2 Hz, 1 H), 1.56–1.50 (m, 2 H), 1.36–1.18 (m, 2 H), 1.06 (ddd, *J* = 6.1, 6.1, 6.1 Hz, 1 H), 0.92–0.73 (m, 8 H), 0.60 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 138.8 (s), 138.7 (s), 137.5 (s), 136.9 (s), 130.2 (d), 129.9 (d), 128.3 (d), 128.3 (d, 2 C), 128.2 (d, 2 C), 128.1 (d), 127.9 (d, 2 C), 127.7 (d, 2 C), 127.4 (d, 2 C), 96.9 (d), 81.0 (d), 76.0 (d), 75.7 (d), 75.4 (d), 73.9 (t), 72.3 (t), 71.5 (t), 71.0 (d), 70.9 (t), 68.7 (t), 48.7 (d), 42.9 (t), 34.4 (t), 31.9 (d), 24.9 (d), 23.0 (t), 22.5 (q), 21.4 (q), 16.0 (q).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{48}NaO_6$: 623.3349; found: 623.3332.

Dihydrocholesteryl 2,4-Di-*O*-benzyl-3,6-*O*-*o*-xylylene-α-D-glucopyranoside (α-14; Table 6, Entry 4)

A mixture of **1** (25.1 mg, 53.8 μmol), dihydrocholesterol (25.1 mg, 64.6 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred for 2 h at –60 °C. The workup procedure was similar to that for the synthesis of **11**. After the general drying procedure, the ratio of α-**14**/β-**14**/unreacted **1** in the crude product was 70:18:12, as determined from the ^1H NMR spectrum. Purification by CC (2 g of silica gel; hexane/Et_2O, 10:1 to 17:2) provided a mixture of α- and β-**14** (34.7 mg, 77% yield), of which a part of α-**14** (11.0 mg) was isolated in pure form as a white powder to obtain the following spectroscopic data.

$[\alpha]_D^{24}$ +62.5 (*c* 0.55, $CHCl_3$).

IR (ATR): 2930, 2906, 2866, 1455, 1113, 1028, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.42–7.40 (m, 2 H), 7.37–7.27 (m, 7 H), 7.24–7.16 (m, 4 H), 7.12 (m, 1 H), 5.19 (d, *J* = 10.8 Hz, 1 H), 5.16 (d, *J* = 5.5 Hz, 1 H), 4.88 (d, *J* = 10.8 Hz, 1 H), 4.79 (d, *J* = 12.6 Hz, 1 H), 4.63 (d, *J* = 12.6 Hz, 2 H), 4.48 (d, *J* = 12.6 Hz, 1 H), 4.40 (d, *J* = 10.8

Hz, 1 H), 4.35 (d, *J* = 10.8 Hz, 1 H), 4.18 (br s, 1 H), 4.13 (br s, 1 H), 3.92 (br s, 1 H), 3.79–3.75 (m, 2 H), 3.62–3.54 (m, 2 H), 1.99–0.94 (m, 30 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.82 (s, 3 H), 0.65 (s, 3 H), 0.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 139.0 (s), 138.8 (s), 137.1 (s), 137.0 (s), 130.1 (d), 129.5 (d), 128.4 (d, 2 C), 128.3 (d, 2 C), 128.2 (d), 128.0 (d), 128.0 (d), 128.0 (d), 128.0 (d), 128.0 (d), 127.6 (d), 127.5 (d), 93.3 (d), 76.8 (d), 75.9 (d), 75.6 (d), 75.4 (d), 74.1 (t), 72.2 (t), 71.8 (t), 70.8 (t), 69.8 (d), 69.3 (t), 56.6 (d), 56.4 (d), 54.5 (d), 45.3 (d), 42.7 (s), 40.2 (t), 39.7 (t), 37.1 (t), 36.3 (t), 35.9 (d), 35.9 (s), 35.9 (t), 35.6 (d), 32.3 (t), 28.9 (t), 28.4 (t), 28.2 (d), 27.6 (t), 24.4 (t), 24.0 (t), 23.0 (q), 22.7 (q), 21.4 (t), 18.8 (q), 12.5 (q), 12.2 (q).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{55}H_{76}NaO_6$: 855.5540; found: 855.5552.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-*o*-xylylene-α-D-glucopyranosyl)-α-D-glucopyranoside (α-15; Table 6, Entry 5)

A mixture of **1** (31.5 mg, 67.8 μmol), methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (25.2 mg, 54.2 μmol), Cp_2ZrCl_2 (49.5 mg, 170 μmol), $AgClO_4$ (70.3 mg, 339 μmol), and MS 4A (203 mg) in Et_2O (1.0 mL) was stirred for 24 h at –60 °C. The workup procedure was similar to that for the synthesis of **11**. In the crude product, β-**15** was not detected. Purification by CC (2 g of silica gel; hexane/Et_2O, 9:1 to 31:4) provided α-**15** (5.8 mg, 12% yield) as a colorless syrup.

$[\alpha]_D^{21}$ +53.3 (*c* 0.29, $CHCl_3$).

IR (ATR): 3029, 2903, 1454, 1097, 1044, 750, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.41–7.38 (m, 4 H), 7.34–7.28 (m, 11 H), 7.21–7.17 (m, 10 H), 7.14–7.10 (m, 3 H), 6.98 (m, 1 H), 5.32 (d, *J* = 9.9 Hz, 1 H), 5.17 (d, *J* = 11.7 Hz, 1 H), 5.07 (d, *J* = 10.1 Hz, 1 H), 4.87 (d, *J* = 6.9 Hz, 1 H), 4.78 (d, *J* = 12.2 Hz, 1 H), 4.75 (d, *J* = 11.7 Hz, 2 H), 4.69 (d, *J* = 11.7 Hz, 1 H), 4.64 (d, *J* = 12.2 Hz, 1 H), 4.58 (d, *J* = 3.7 Hz, 1 H), 4.51 (d, *J* = 11.7 Hz, 1 H), 4.43 (d, *J* = 11.9 Hz, 1 H), 4.39 (d, *J* = 11.7 Hz, 1 H), 4.33 (br s, 1 H), 4.29 (d, *J* = 10.1 Hz, 1 H), 4.25 (d, *J* = 11.9 Hz, 1 H), 4.05 (br s, 1 H), 3.99 (dd, *J* = 9.5, 9.5 Hz, 1 H), 3.93 (d, *J* = 2.5 Hz, 1 H), 3.88 (d, *J* = 12.2 Hz, 1 H), 3.86 (dd, *J* = 9.3, 9.3 Hz, 1 H), 3.77 (d, *J* = 9.9 Hz, 1 H), 3.69–3.58 (m, 5 H), 3.53 (dd, *J* = 9.6, 3.7 Hz, 1 H), 3.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 140.1 (s), 138.7 (s), 138.6 (s), 138.3 (s), 137.9 (s), 137.2 (s), 136.5 (s), 129.6 (d), 128.4–127.7 (overlapped 24 doublets), 127.3 (d), 127.1 (d, 2 C), 126.9 (d), 101.8 (d), 98.5 (d), 83.8 (d), 83.5 (d), 80.7 (d), 78.7 (d), 77.4 (d), 75.1 (t), 75.1 (d), 74.4 (t), 73.8 (t), 72.8 (t), 72.6 (t), 71.8 (t), 70.5 (d), 70.5 (t), 70.4 (t), 70.0 (d), 67.7 (t), 55.4 (q).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{56}H_{60}NaO_{11}$: 931.4033; found: 931.4015.

1-Adamantanyl 2,4-Di-*O*-benzyl-3,6-*O*-*o*-xylylene-α-D-glucopyranoside (α-16; Table 6, Entry 6)

A mixture of **1** (25.3 mg, 54.5 μmol), 1-adamantanol (9.8 mg, 65 μmol), Cp_2ZrCl_2 (39.3 mg, 135 μmol), $AgClO_4$ (55.8 mg, 269 μmol), and MS 4A (161 mg) in Et_2O (1.0 mL) was stirred for 24 h at –60 °C. The workup procedure was similar to that for the synthesis of **11**. The ratio of α-**16**/β-**16**/unreacted **1** in the crude product was 58:10:32. Purification by CC (2 g of silica gel; hexane/Et_2O, 10:1 to 17:2) provided a mixture of α- and β-**16** (21.4 mg, 66% yield), of which a part of α-**16** (11.2 mg) was isolated in pure form as a colorless syrup to obtain the following spectroscopic data.

$[\alpha]_D^{22}$ +43.2 (*c* 0.56, $CHCl_3$).

IR (ATR): 2917, 2906, 2850, 1110, 1028, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.43–7.41 (m, 2 H), 7.34–7.15 (m, 12 H), 5.41 (d, *J* = 4.6 Hz, 1 H), 5.05 (d, *J* = 11.0 Hz, 1 H), 4.83 (d, *J* = 12.6 Hz, 1 H), 4.80 (d, *J* = 11.0 Hz, 1 H), 4.66 (d, *J* = 12.6 Hz, 1 H), 4.54 (d, *J* = 12.6 Hz, 1 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 4.47 (d, *J* = 11.0 Hz, 1 H), 4.44 (d, *J* = 12.6 Hz, 1 H), 4.27 (dd, *J* = 4.5, 4.5 Hz, 1 H), 3.97 (br s, 2 H), 3.86 (dd, *J* = 12.1, 4.3 Hz, 1 H), 3.73–3.65 (m, 2 H), 2.14 (br s, 3 H), 1.90 (br d, *J* = 11.4 Hz, 3 H), 1.87 (br d, *J* = 11.4 Hz, 3 H), 1.63 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 139.2 (s), 138.9 (s), 137.2 (s), 137.2 (s), 130.4 (d), 129.7 (d), 128.2 (d), 128.2 (d), 128.2 (d), 128.2 (d), 127.8 (d), 127.8 (d), 127.8 (d), 127.8 (d), 127.8 (d), 127.8 (d), 127.4 (d), 127.3 (d), 88.0 (d), 76.5 (d), 75.7 (d), 75.4 (d), 74.3 (s), 74.2 (t), 72.4 (t), 71.5 (t), 71.0 (t), 70.0 (d), 69.7 (t), 42.6 (t, 3 C), 36.5 (t, 3 C), 30.8 (d, 3 C).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{38}H_{44}NaO_6$: 619.3036; found: 619.3048.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590927.

References

(1) (a) Boons, G.-J.; Hale, K. J. *Organic Synthesis with Carbohydrates*; Sheffield Academic Press: Sheffield, **2000**. (b) Demchenko, A. V. *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Wiley-VCH: Weinheim, **2008**.
(2) Gridley, J. J.; Osborn, H. M. I. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1471.
(3) (a) Banoub, J.; Bundle, D. R. *Can. J. Chem.* **1979**, *57*, 2091. (b) Flitsh, S. L. *Nature* **2005**, *437*, 201. (c) Guo, J.; Ye, X.-S. *Molecules* **2010**, *15*, 7235.
(4) Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35.
(5) (a) Demchenko, A. V. *Synlett* **2003**, 1225. (b) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687. (c) Komarova, B. S.; Tsvetkov, Y. E.; Nifantiev, N. E. *Chem. Rec.* **2016**, *16*, 488.
(6) For NGP based on acyl groups at O-3, see: (a) Parameswar, A. R.; Pornsuriyasak, P.; Lubanowski, N. A.; Demchenko, A. V. *Tetrahedron* **2007**, *63*, 10083. (b) Alpe, M.; Oscarson, S. *Carbohydr. Res.* **2002**, *337*, 1715. (c) Ennis, S. C.; Cumpstey, I.; Fairbanks, A. J.; Butters, T. D.; Mackeen, M.; Wormald, M. R. *Tetrahedron* **2002**, *58*, 9403.
(7) For NGP based on acyl groups at O-4, see: (a) Nunomura, S.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 5681. (b) Budhadev, D.; Mukhopadhyay, B. *Carbohydr. Res.* **2014**, *394*, 26.
(8) For NGP based on acyl groups at O-6, see: (a) Lourenço, E. C.; Maycock, C. D.; Ventura, M. R. *Carbohydr. Res.* **2009**, *344*, 2073. (b) Mandal, P. K.; Chheda, P. R. *Tetrahedron Lett.* **2015**, *56*, 900.
(9) (a) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090. (b) Boltje, T. J.; Kim, J.-H.; Park, J.; Boons, G.-J. *Nat. Chem.* **2010**, *2*, 552. (c) Boltje, T. J.; Kim, J.-H.; Park, J.; Boons, G.-J. *Org. Lett.* **2011**, *13*, 284. (d) Fang, T.; Mo, K.-F.; Boons, G.-J. *J. Am. Chem. Soc.* **2012**, *134*, 7545. (e) Fang, T.; Gu, Y.; Huang, W.; Boons, G.-J. *J. Am. Chem. Soc.* **2016**, *138*, 3002.

(10) (a) Fairbanks, A. J. *Synlett* **2003**, 1945. (b) Ishiwata, A.; Lee, Y. J.; Ito, Y. *Org. Biomol. Chem.* **2010**, *8*, 3596.
(11) (a) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. (c) Partridge, K. M.; Bader, S. J.; Buchan, Z. A.; Taylor, C. E.; Montgomery, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 13647.
(12) (a) Attolino, E.; Cumpstey, I.; Fairbanks, A. J. *Carbohydr. Res.* **2006**, *341*, 1609. (b) Leigh, C. D.; Bertozzi, C. R. *J. Org. Chem.* **2008**, *73*, 1008.
(13) (a) Nakagawa, A.; Tanaka, M.; Hanamura, S.; Takahashi, D.; Toshima, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 10935. (b) Tanaka, M.; Nashida, J.; Takahashi, D.; Toshima, K. *Org. Lett.* **2016**, *18*, 2288. (c) Tanaka, M.; Takahashi, D.; Toshima, K. *Org. Lett.* **2016**, *18*, 5030.
(14) Pornsuriyasak, P.; Jia, X. G.; Kaeothip, S.; Demchenko, A. V. *Org. Lett.* **2016**, *18*, 2316.
(15) (a) Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem. Int. Ed.* **2005**, *44*, 7123. (b) Yasomanee, J. P.; Demchenko, A. V. *J. Am. Chem. Soc.* **2012**, *134*, 20097.
(16) (a) Houdier, S.; Vottero, P. J. A. *Carbohydr. Res.* **1992**, *232*, 349. (b) Fukase, K.; Nakai, Y.; Kanoh, T.; Kusumoto, S. *Synlett* **1998**, 84. (c) Fukase, K.; Nakai, Y.; Egusa, K.; Porco, J. A. Jr.; Kusumoto, S. *Synlett* **1999**, 1074. (d) Tokimoto, H.; Fujimoto, Y.; Fukase, K.; Kusumoto, S. *Tetrahedron: Asymmetry* **2005**, *16*, 441.
(17) Okada, Y.; Asakura, N.; Bando, M.; Ashikaga, Y.; Yamada, H. *J. Am. Chem. Soc.* **2012**, *134*, 6940.
(18) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
(19) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.
(20) (a) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431. (b) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379. (c) Nicolaou, K. C.; Chucholowski, A.; Dolle, R. E.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1155. (d) Kunz, H.; Sager, W. *Helv. Chim. Acta* **1985**, *68*, 283. (e) Ogawa, T.; Takahashi, Y. *Carbohydr. Res.* **1985**, *138*, C5. (f) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567. (g) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3571. (h) Mukaiyama, T.; Maeshima, H.; Jona, H. *Chem. Lett.* **2001**, 388.
(21) Cao, Y.; Kasai, Y.; Bando, M.; Kawagoe, M.; Yamada, H. *Tetrahedron* **2009**, *65*, 2574.
(22) Mizuno, M.; Kobayashi, K.; Nakajima, H.; Koya, M.; Inazu, T. *Synth. Commun.* **2002**, *32*, 1665.
(23) Spijker, N. M.; van Boekel, C. A. A. *Angew. Chem. Int. Ed.* **1991**, *30*, 180.