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FULL PAPER

A 1,2-*trans*-selective glycosyl donor bearing cyclic protection at the C2 and C3 hydroxyl groups

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Abstract: A new 1,2-*trans*-selective glycosidation reaction is described. Glucosyl donors protected cyclically at the C2 and C3 hydroxyl groups as six- (butanediacetal), seven- (tetraisopropyldisiloxanylidene) or eight (2,3-*o*-xylylene) membered fused ring were synthesized in a straightforward manner. The glycosidation reactions of the glucosyl donors with various acceptors mainly generated β-glycosides under conventional reaction conditions. The results showed that the *o*-xylylene-group is suitable as a 1,2-*trans*-directing functionality from the perspective of stereoselectivity and chemical stability. The conformation study on oxocarbenium ion of an *o*-xylylene-protected glucose by NMR and computational simulation implied that the oxocarbenium ion mainly adopt the $^4H_3$ conformation owing to the rigid *trans*-fused ring at C2 and C3 while non-cyclically protected one might fluctuate among possible conformations. The results suggested that an eclipsing interaction between the C2-pseudo-equatorial xyloxy group and the incoming nucleophile hampered the 1,2-*cis*-attack.

Keywords: carbohydrates; glycosylation; cyclic protecting group; stereoselectivity;1,2-*trans*-glycoside

Introduction

Precise syntheses of glycans are essential for a thorough understanding of the molecular basis underlying the biological functions of glycans and for developing glycan-based therapeutics. There are various methods for assembling diverse glycan sequences, mainly for stereoselective glycosidation reactions.[1] β (1,2-*trans*)-Glycosides of D-*gluco*-type sugars are abundant in natural glycans; thus, their synthesis has long been a focus of carbohydrate chemistry. In their stereoselective β-glycosidation, the neighboring effect of acyl functionalities, the nitrile solvent effect,[2] and the α-coordination of triflate[3] have been widely exploited in independent or synergic ways in the construction of diverse glycan sequences. However, various synthetic studies have also uncovered the limited scope of these approaches. The most widely used neighboring effect-assisted β-glycosidation is unpredictably accompanied by various side reactions, such as the formation of the glycosyl orthoester and migration of the acyl functionality to both the anomeric center and the glycosyl acceptor, and the reaction requires orthogonality with other acyl groups used for tentative protection of other hydroxyl groups. In addition, the method is not always suitable for synthesizing molecules that contain ester moieties in their accessories of hydroxyl groups of sugar residues and aglycones. Syntheses using the nitrile solvent effect or the α-coordination of triflate often encounter a decline of stereoselectivity and glycosidation yield depending on the reactant structures and reaction conditions. Therefore, it is still necessary to develop stereoselective β-glycosidation methods based on different principles of β-selectivity for glycan synthesis.[4] Recently, Demchenko *et al*. developed a β-selective glycosidation effected by a 2-*O*-picolinyl group,[5] and furthermore they showcased β-selective glycosidation via remote picolinyl group mediated aglycon delivery.[6] Meanwhile, several studies have described conformationally modified glucosyl donors that impart β-selectivity.[7] For furanosyl donor, Lowary et al first demonstrated that 2,3-*o*-xylylene-protected arabinosyl donor provided high β-selectivity, the efficay of which was evidenced by the synthesis of heptasaccharide.[8] Our interest was drawn by the Lowary's pioneering work and Crich and Jayalath,[9] which described a

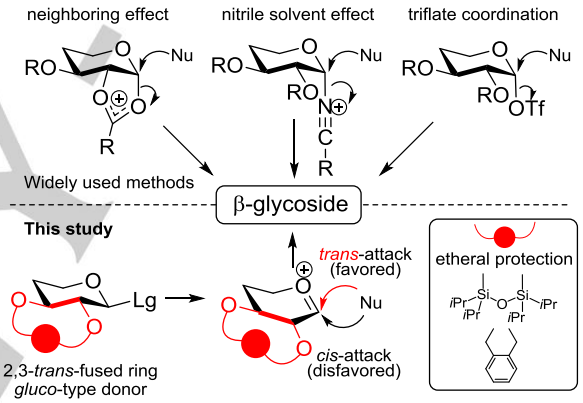

Fig. 1. 1,2-*trans*-Glycosidation developed in this study.

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simple β-selective glycosidation using a 2,3-*O*-carbonylated bicyclic glucosyl thioglycoside donor in combination with their glycosidation promoters to generate an α-triflate intermediate. In the present study, we explored the potential of bicyclic glucosyl sugar analogs containing non-acyl cyclic protecting groups at the C2 and C3 positions as β-selective glycosyl donors, and found that 2,3-*o*-xylylene (Xyln)-protected glycosyl donors are useful for acyl-free β-selective glycosidation (Fig 1).

Results and Discussion

First, we synthesized variations of a 2,3-*trans*-fused ring at a thioglucoside donor by using the available non-acyl cyclic protecting groups, di-*tert*-butylsilylene (DTBS)[10], butanediacetal (BDA)[11], tetraisopropyldisiloxanylidene (TIPDS)[12], and Xyln[13] (Fig. 2).The BDA-, TIPDS-, and Xyln-protected thioglucoside derivatives (**1**–**3**) were obtained with six-, seven-, and eight-membered fused rings, respectively, through straightforward protection-deprotection of the hydroxy groups. The synthetic procedures for **1**–**3** are described in Supporting Information Schemes 1–2. In contrast, the DTBS-protected analog was not isolable due to its lability.

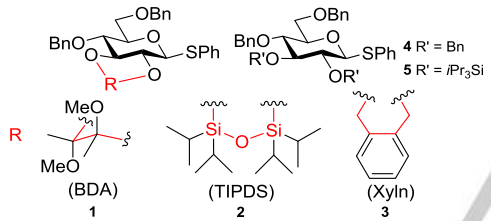
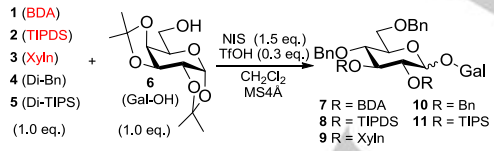


Fig. 2. Glucosyl donors used in this study.

Table 1. Glycosidation of cyclically protected glucosyl donor



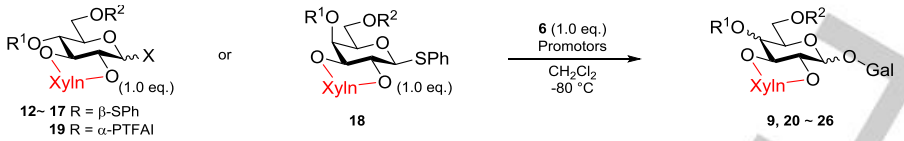
Entry	Donor	Temp. (°C)	Time	Product	Yield (%)	α/β
1	**1**	-40	1.0 h	**7**	80	1/4.6
2	**2**	-80	9.0 h	**8**	97	1/10.1
3	**2**	-40	1.0 h	**8**	99	1/3.8
4	**2**	0	15 min	**8**	97	1/1.4
5	**3**	-80	7.5 h	**9**	93	1/11.5
6	**3**	-40	1.5 h	**9**	92	1/3.8
7	**3**	0	30 min	**9**	87	1/1.7
8	**4**	-80	24 h	**10**	81	1/6.1
9	**5**	-80	3.0 h	**11**	68	1/0.72

Next, the β-selectivity of bicyclic glucosyl donors **1**–**3** were examined by glycosidation with a galactosyl acceptor **6** in the presence of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH)[14] in CH_2Cl_2 (Table 1). In all cases, the bicyclic donors provided β-glycosides as the major stereoisomer, with a ratio greater than the α-isomers by a factor of 1.4 to 11.5. BDA donor **1** needed a higher temperature than bicyclic donors **2** and **3** to complete the glycosidation reaction. However, at -40 °C, BDA donor **1** gave good β-selectivity (Entry 1), which was comparable to those of donors **2** and **3** at the same temperature (Entries 3 and 6). Glycosidation with the TIPDS (**2**) and Xyln (**3**) donors, the β-selectivity was considerably higher at -80 °C, affording β-glycosides almost exclusively (**2**: α/β = 1/10.1; **3**: α/β = 1/11.5) with high yields (Entries 2 and 5) slightly higher than that obtained with the corresponding 2,3-*O*-carbonyl analog (84%,α/β= 1/9).[8] We confirmed by thin layer chromatography that **8** and **9** did not anomerize under the reaction conditions. At higher temperatures, β-selectivity decreased, which suggested that β-glycosides were formed under kinetic control. Furthermore, the results obtained by glycosidations of acyclic donors **4** and **5** at -80 °C indicated that the β-selectivity of the glucosyl donors (**1**–**3**) was conferred by the 2,3-cyclic protection (Entries 8 and 9) (Supporting Information Table 1).

Next, we examined the effect of the reaction solvent on the β-selectivity using glycosyl donor **3** (Supporting Information Table 2). To dissolve the reaction substrates completely in all reaction media, the glycosidation reactions were performed at 0 °C for Entries 1 to 4. The selectivity was reproducible in less polar solvents, such as toluene and CCl_4, producing similar results to CH_2Cl_2 (Entries 1–3). However, the more polar solvent propionitrile increased the β-anomer ratio (α/β = 1/5.3) (Entry 4), although at -80 °C, propionitrile exhibited the opposite effect on the selectivity, decreasing the β-selectivity (α/β = 1/3.5) compared with CH_2Cl_2 (α/β = 1/11.5; Table 1, Entry 5). Furthermore, in cyclopentyl methyl ether, which is more likely to coordinate at the β-face of the oxocarbenium ion,[15] the ratio of the α-isomer was increased considerably at -80 °C to give the reversed α/β ratio of 1.2/1. These results implied that the α-coordination of the nitrile solvent molecule to the oxocarbenium ion generated from donor **3** would be highly restricted at very low temperatures, enhancing the β-coordination of the nucleophilic solvent molecule and increasing the generation of the α-glycoside via an S_N2-like pathway.

Next, we examined the effect on the stereoselectivity of the donor's protecting groups, configuration at C4 and the leaving group. The TIPDS group was labile under various reaction conditions while modifying **3**. Hence, the Xyln group was used as the 2,3-cyclic protecting group for further experiments.[16] The β-selectivity of the Xyln-protected donor was affected by the chemical properties of the protecting groups of C4 and C6 hydroxyl groups (Table 2, Entries 1 to 6). Electron-donating protecting groups at both hydroxyl groups increased the β-selectivity, whereas electron-withdrawing acetyl groups at either or both positions decreased the selectivity to a greater or lesser extent. For C4-epimer **18**, the glycosidation product was also dominated by the β-anomer with an acceptable anomer ratio (α/β = 1/5.3), which suggested that this method could be used for β-galactoside formation. *N*-Phenyltrifluoroacetimidate[17] donor **19** was also β-selectively glycosidated in the presence of a catalytic amount of Lewis acid (Entries 8 and 9).

Table 2. Examination of glycosidation of Xyln-protected glycosyl donors **12**-**17** and **19**.



Entry	Donor	X	R^1	R^2	Time (h)	Product	Yield (%)	α/β
1[a]	**12** (Glc)	SPh (β)	MPM	MPM	4.5	**20**	76	1/15.7
2[a]	**13** (Glc)	SPh (β)	Bn	TBDPS	17.0	**21**	91	1/24
3[a]	**14** (Glc)	SPh (β)	Bn	Ac	5.0	**22**	99	1/7.3
4[a]	**15** (Glc)	SPh (β)	TBDPS	Bn	4.0	**23**	87	1/7.3
5[a]	**16** (Glc)	SPh (β)	Ac	Bn	3.0	**24**	99	1/5.3
6[a]	**17** (Glc)	SPh (β)	Ac	Ac	21.0	**25**	91	1/2.6
7[a]	**18** (Gal)	SPh (β)	Bn	Bn	3.0	**26**	94	1/5.3
8[b]	**19** (Glc)	PTFAI (α)	Bn	Bn	1.0	**9**	90	1/8.1
9[c]	**19** (Glc)	PTFAI (α)	Bn	Bn	4.0	**9**	81	1/32.3

[a] performed in the presence of NIS (1.5 eq.), TfOH (0.3 – 0.9 eq.) and molecular sieves 4Å.

[b] performed in the presence of TMSOTf (0.05 eq.) and molecular sieves AW 300.

[c] performed in the presence of $BF_3{\cdot}OEt_2$ (0.1 eq.) and molecular sieves 4Å. PTFAI : *N*-phenyltrifluoroacetimidate

The best β-selectivity (α/β = 1/32.3) was provided by activation with $BF_3{\cdot}OEt_2$. In contrast, the 2,3- dibenzylated analog of **19** decreased the anomeric ratio to 1/5.3 (Supporting Information Scheme 6).

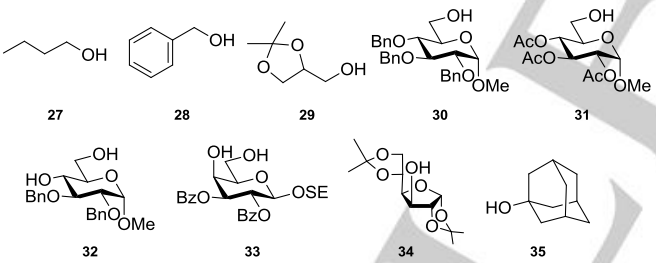
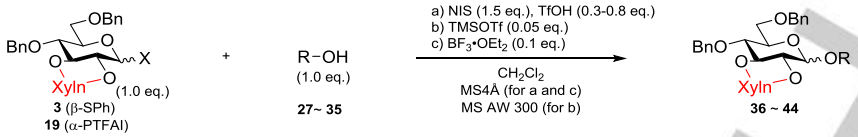


Fig 3. Acceptors used in the glycosidation of **3** and **19**.

The glycosidation of the thioglycoside donor **3** with simple alcohols (**27**-**29**), glycosyl acceptors (**30**-**34**) and tertiary hydroxyl group of 1-adamantanol **35** provided β-glycosides as the major product in all cases (Fig 3 and Table 3, Entries 1-9). The results of the thioglycoside **3** indicated the match-mismatch between the donor and acceptor, as has been widely observed in stereoselective glycosidation reactions that are independent of neighboring participation effect. Likewise, *N*-phenyltrifluoroacetimidate donor **19** preferentially produced β-glycosides with moderate to excellent stereoselectivity (Entries 10-17). It was also revealed by **19** that glycosylation promotor strongly affected the stereoselectivity of products. Taken together with the results of the thioglylcoside donor **3**, excellent selectivity was gained with acceptors (**27**, **30**, **34** and **35**) with a suitable donor-promotor combination (Entries 1, 12, 15 and 16).

To determine the reaction mechanism by which the β-glycoside was dominant in the glycosidation of the 2,3-Xyln donors, we investigated the conformation of the oxocarbenium ions formed from **3** and **4**. First, we attempted to determine the conformation of the oxocarbenium ion of **45**[16] by following Woerpel's method,[18] but it was unsuccessful because the ions were unstable. Instead, the conformations of lactone derivatives **45** and **46** were analyzed by NMR in CD_2Cl_2 at -80 °C. Fig 4 shows the difference in coupling constants for H2 and H5 between **45** and **46** (Supporting Information Fig 1 and Supporting Information Table 3). Based on the coupling constants, we assumed that Xyln-protected derivative **45** mainly adopted the $^4H_3$ conformation, whereas the conformation of 2,3-dibenzylated derivative **46** may fluctuate among possible conformations. Likewise, it is plausible that the oxocarbenium ion generated from Xyln-protected donor **3** may mainly adopt the $^4H_3$ conformation owing to the rigid *trans*-fused ring at C2 and C3. The computational study of the oxocarbenium ion of **45** also supported $^4H_3$ conformation (**A**) as the minimum energy conformation (Data are dedcribed in Supporting Information Table 2). Therefore, there might be an eclipsing interaction between the C2-pseudo-equatorial xyloxy group and the incoming nucleophile, thereby disfavoring the 1,2-*cis*-attack. This mechanism would also account for the impaired β-selectivity in EtCN-CH_2Cl_2 and the reversed stereoselectivity in CPME-CH_2Cl_2 at -80 °C (Table 2, Entries 5 and 6).

Table 3. Glycosidation of **3** and **19**.



Entry	Donor	Acceptor	Promotor	Time	Product	Yield (%)	α/β
1	**3**	**27**	a	4.0 h	**36**	83	1/19
2	**3**	**28**	a	30 min	**37**	98	1/7.3
3	**3**	**29**	a	20 min	**38**	97	1/6.7
4	**3**	**30**	a	1.0 h	**39**	88	1/4.6
5	**3**	**31**	a	2.0 h	**40**	83	1/4.3
6	**3**	**32**	a	5.5 h	**41**	71	1/13.3
7	**3**	**33**	a	20 min	**42**	60	1/9.0
8	**3**	**34**	a	5.5 h	**43**	70	1/2.3
9	**3**	**35**	a	1.0 h	**44**	76	1/15.7
10	**19**	**27**	b	5.0 h	**36**	98	1/9.0
11	**19**	**27**	c	7.0 h	**36**	95	1/24
12	**19**	**30**	b	30 min	**39**	91	1/24
13	**19**	**30**	c	30 min	**39**	55	1/3.5
14	**19**	**34**	b	5.0 min	**43**	72	1/2.7
15	**19**	**34**	c	3.0 h	**43**	59	1/5.3
16	**19**	**35**	b	10 min	**44**	85	1/9.0
17	**19**	**35**	c	2.5 h	**44**	89	1/3.2

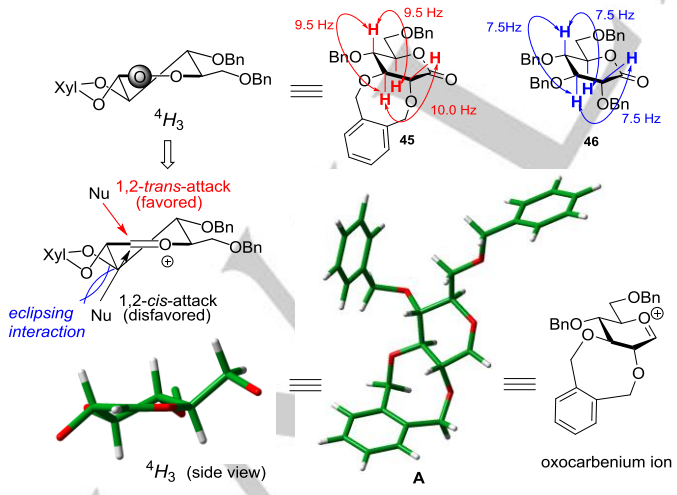


Fig 4. Conformational study of oxocarbenium ion generated from 2,3-Xyln glucosyl donor. Structure A drawn in stick model indicates the optimized structure obtained by DFT calculations (B3LYP/ 6-311G(d)).

Conclusions

We have demonstrated that a 2,3-*trans*-fused ring in a glucosyl donor served as a stereo-directing factor for imparting β-selectivity. A detailed examination of the glycosidation reaction of Xyln-bearing donors revealed the importance of the structural factors of reactants, including stereoelectronic factors, in exerting the β-selectivity. Our method can be used as an alternative for β -glycosidation with the most widely used leaving group-promotor systems. Moreover, our method would streamline the syntheses of glycans or glycoconjugate-bearing acyl moieties, such as partially acetylated glycans and glycoglycerolipids.

Experimental Section

General procedures: All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise noted. Molecular sieves were purchased from Wako Chemicals Inc. and pre-dried

at 300 °C for 2 h in a muffle furnace, and dried in a flask at 300 °C for 12 h in vacuo prior to use. Dry solvents for reaction media (CH_2Cl_2, toluene, THF, CH_3CN, DMF, pyridine) were purchased from Kanto Chemical Co. Inc. (Tokyo, Japan) and used without purification. Other solvents as reaction media were dried over molecular sieves and used without further purification. TLC analysis was performed on Merck TLC plates (silica gel 60F254 on glass). Compounds were visualized either by exposure to UV light (254 nm) or by soak in 10 % H_2SO_4 solution in EtOH or 20 % phosphomolybdic acid solution in EtOH, followed by heating. Silica gel (80 mesh and 300 mesh; Fuji Silysia Co.,(Aichi, Japan) was used for flash column chromatography. The quantity of silica gel was usually 100 to 200 times the weight of the crude sample to be charged. Sephadex (Pharmacia LH-20) was used for size exclusion chromatography. Solvent systems for chromatography were specified as *v*/*v* ratios. Evaporation and concentration were conducted in vacuo. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance III 500 spectrometers. Chemical shifts in ^{1}H NMR spectra are expressed in ppm (*δ*) relative to the Me_4Si signal, adjusted to *δ* 0.00 ppm. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, td = triple doublet, m = multiplet and/or multiple resonances), integration, coupling constant in hertz (*Hz*), and position of the corresponding proton. COSY methods were used to confirm the NMR peak assignments. High-resolution mass spectrometry (HRMS) was performed with a Bruker Daltonics micrOTOF (ESI-TOF) mass spectrometer. Specific rotations were determined with a Horiba SEPA-300 high-sensitivity polarimeter.

Phenyl 4,6-di-*O*-benzyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-β-D-glucopyranoside (1): Butane-2,3-dione (79.0 µL, 890 µmol), $BF_3{\cdot}OEt_2$ added under argon atmosphere to a solution of phenyl 4,6-di-*O*-benzyl-β-D-glucopyranoside (53.7 mg, 119 µmol) in MeOH (600 µL). The mixture was stirred for 42 h at room temperature as the progress of the reaction was monitored by TLC (EtOAc/Toluene = 1/10). Next, the reaction mixture was concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane = 1/10 → 1/3) to give **1** (64.4 mg, 84%); $[\alpha]_D$ -92.2 ° (c 0.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.19 (m, 15 H, 3 Ph), 4.92 (d, 1 H, J_{gem} = 11.0 Hz, PhCH_2), 4.74 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.58 (d, 1 H, J_{gem} = 12.0 Hz, PhCH_2), 4.57 (d, 1 H, PhCH_2), 4.51 (d, 1 H, PhCH_2), 3.92 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.78-3.68 (m, 4 H, H-2, H-4, H-6a, H-6b), 3.53 (m, 1 H, H-5), 3.29 (s, 3 H, OCH_3), 3.20 (s, 3 H, OCH_3), 1.35-1.34 (2s, 6 H, 2 CH_3); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.4, 138.3, 133.5, 131.6, 128.7, 128.3, 128.3, 128.0, 127.7, 127.6, 127.5, 127.2, 100.1, 99.5, 84.8, 79.5, 77.6, 75.5, 75.0, 74.6, 73.4, 69.1, 68.0, 48.1, 47.9, 17.8, 17.6; HRMS (ESI) *m/z*: found $[M+Na]^+$ 589.2230, $C_{31}H_{38}O_7S$ calcd for $[M+Na]^+$ 589.2230.

Phenyl 4,6-*O*-benzylidene-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-1-thio-β-D-glucopyranoside: 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (7.70 mL, 25.0 mmol) and imidazole (3.40 g, 50.0 mmol) were added to a solution of phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside (3.00 g, 8.30 mmol) in DMF (83.0 mL) under argon atmosphere. The mixture was stirred for 30 min at 50 °C as the progress of the reaction was monitored by TLC (EtOAc/*n*-Hexane = 1/3). The reaction mixture was neutralized with sat. $NaHCO_3$ aq. in the ice bath and extracted with EtOAc. The organic phase was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane = 1/15) to give phenyl 4,6-*O*-benzylidene-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-1-thio-β-D-glucopyranoside (5.00 g, quant.); $[\alpha]_D$ -16.0 ° (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.18 (m, 10 H, 2 Ph), 5.57 (s, 1 H, >C*H*Ph), 4.71 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.36 (dd, 1 H, $J_{5,6a}$ = 5.0 Hz, J_{gem} = 10.5 Hz, H-6a), 3.89 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.79 (t, 1 H, $J_{5,6b}$ = 10.5 Hz, H-6b), 3.72 (t, 1 H, H-2), 3.59 (t, 1 H, $J_{4,5}$ = 9.5 Hz, H-4), 3.44 (td, 1 H, H-5), 1.18-0.86 (m, 28 H, 4 ^{i}Pr); ^{13}C NMR (125 Hz, $CDCl_3$) δ 137.5, 134.2, 131.7, 128.9, 128.7, 128.1, 128.1, 127.5, 125.9, 101.0, 89.8, 80.3, 77.8, 76.5, 70.6, 68.7, 17.5, 17.4, 17.2, 17.2, 17.2, 17.1, 17.0, 12.9, 12.8, 12.3; HRMS (ESI) *m/z*: found $[M+Na]^+$ 625.2244, $C_{31}H_{46}O_6SSi_2$ calcd for $[M+Na]^+$ 625.2246.

Phenyl 4-*O*-benzyl-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-1-thio-β-D-glucopyranoside: Dichlorophenylborane (650 µL, 4.40 mmol) and triethylsilane (680 µL, 4.40 mmol) were added to a suspension of phenyl 4,6-*O*-benzylidene-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-1-thio-β-D-glucopyranoside (1.00 g, 1.70 mmol) and molecular sieves 4Å (1.00 g) in CH_2Cl_2 (16.0 mL) under argon atmosphere. The mixture was stirred for 5.5 h at -80 °C as the progress of the reaction was monitored by TLC (EtOAc/*n*-Hexane = 1/3). The reaction mixture was quenched with Et_3N and MeOH, filtered through a pad of Celite and the filtered residue was washed with $CHCl_3$. The combined filtrate and washings were washed with sat. $NaHCO_3$ aq., H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane = 1/7) to give phenyl 4-*O*-benzyl-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-1-thio-β-D-glucopyranoside (1.00 g, quant.); $[\alpha]_D$ -11.5° (c 0.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.23 (m, 10 H, 2 Ph), 4.95, (d, 1 H, J_{gem} = 11.5 Hz, PhCH_2), 4.65 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.64 (d, 1 H, PhCH_2), 3.87 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3), 3.80 (ddd, 1H, $J_{5,6a}$ = 3.0 Hz, J_{gem} = 10.0 Hz, $J_{6a,OH}$ = 7.0 Hz, H-6a), 3.66 (dd, 1 H, H-2), 3.61 (m, 1 H, H-6b), 3.49 (t, 1 H, $J_{4,5}$ = 8.5 Hz, H-4), 3.37-3.33 (m, 1 H, H-5), 1.78 (t, 1 H, $J_{6b,OH}$ = 7.0 Hz, OH), 1.17-0.97 (m, 28 H, 4^{i}Pr); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.0, 134.3, 131.4, 128.9, 128.5, 128.3, 127.9, 127.3, 88.4, 82.2, 78.9, 77.7, 75.8, 75.4, 62.4, 17.6, 17.5, 17.5, 17.5 17.3, 17.2, 17.2, 12.9, 12.8, 12.3; HRMS (ESI) *m/z*: found $[M+Na]^+$ 672.2602, $C_{32}H_{48}O_7SSi_2$ calcd for $[M+Na]^+$ 672.2602.

Phenyl 4,6-di-*O*-benzyl-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-1-thio-β-D-glucopyranoside (2): Benzyl bromide (344 µL, 2.90 mmol) and sodium hydride (60.4 mg, 868 µmol) were added to a solution of phenyl 4-*O*-benzyl-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-1-thio-β-D-glucopyranoside (350 mg, 579 µmol) in DMF (2.90 mL) at -20 °C under argon atmosphere. The mixture was stirred for 4.0 h at -20 °C as the progress of the reaction was monitored by TLC (EtOAc/*n*-Hexane = 1/3). The reaction mixture was quenched with MeOH, co-evaporated with toluene and diluted with EtOAc. The solution was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane = 1/30) to give **2** (320 mg, 79%); $[\alpha]_D$ -16.5 ° (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.18 (m, 15 H, 3 Ph), 4.93 (d, 1 H, J_{gem} = 11.0 Hz, PhCH_2), 4.61 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.57 (d, 1 H, PhCH_2,), 4.59 (d, 1 H, J_{gem} = 12.5 Hz, PhCH_2), 4.50 (d, 1 H, PhCH_2), 3.84 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.74-3.69 (m, 2 H, H-2, H-5), 3.64 (dd, $J_{5,6a}$ = 4.5 Hz, J_{gem} = 10.5 Hz, H-6a), 3.54 (t, 1 H, $J_{4,5}$ = 9.0 Hz, H-4), 3.47 (dd, 1 H, $J_{5,6b}$ = 5.0 Hz, H-6b), 1.15-0.98 (m, 28 H, 4 ^{i}Pr); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.3, 138.2, 134.9, 131.3, 128.8, 128.3, 128.1, 127.7, 127.7, 127.5, 127.0, 88.5, 82.3, 80.0, 78.8, 77.6, 75.7, 75.4,

73.4, 69.2, 30.9, 17.6, 17.5, 17.5, 17.3, 17.3, 17.3, 17.2, 12.9, 12.8, 12.3, 12.3; HRMS (ESI) *m/z*: found $[M+Na]^+$ 717.3075, $C_{32}H_{48}O_7SSi_2$ calcd for $[M+Na]^+$ 717.3072.

Phenyl 4,6-*O*-benzylidene-2,3-*O*-(*o*-xylylene)-1-thio-β-D-glucopyranoside: Sodium hydride (2.60 g, 64.0 mmol) was added to a solution of phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside (5.00 g, 12.8 mmol) in DMF (256 mL) in the ice bath under argon atmosphere. The mixture was stirred for 30 min. To the mixture was added α-α'-dibromo-*o*-xylene (3.80 g, 14.1 mmol), and the stirring was continued for 11.5 h at room temperature as the progress of the reaction was monitored by TLC (EtOAc/*n*-Hexane = 1/3). Next, the reaction mixture was quenched with MeOH, co-evaporated with toluene and diluted with EtOAc. The solution was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (Chloroform/Toluene = 1/1) to give phenyl 4,6-*O*-benzylidene-2,3-*O*-(*o*-xylylene)-1-thio-β-D-glucopyranoside (5.00 g, 84%); $[\alpha]_D$ +6.5 ° (c 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.55-7.12 (m, 14 H, 3 Ar), 5.51 (s, 1 H, >C*H*Ph), 5.18 (d, 1 H, J_{gem} = 13.5 Hz, ArCH_2), 5.15 (d, 1 H, J_{gem} = 9.5 Hz, ArCH_2), 5.12 (d, 1 H, ArCH_2), 4.89 (d, 1 H, ArCH_2), 4.71 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.34 (dd, 1 H, $J_{5,6a}$ = 4.5 Hz, J_{gem} = 10.5 Hz, H-6a), 3.82 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.73 (t, 1 H, $J_{5,6b}$ = 10.5 Hz, H-6b), 3.53 (t, 1 H, $J_{4,5}$ = 9.0 Hz, H-4), 3.50-3.46 (m, 2 H, H-2, H-5); ^{13}C NMR (125 Hz, $CDCl_3$) δ 139.0, 137.1, 136.6, 136.4, 132.9, 132.3, 131.3, 129.1, 129.1, 129.0, 128.3, 128.1, 127.9, 127.2, 126.4, 120.9, 101.8, 87.7, 81.4, 79.4, 79.3, 79.3, 73.5, 73.0, 72.4, 70.3, 68.6; HRMS (ESI) *m/z*: found $[M+Na]^+$ 485.1391, $C_{27}H_{26}O_5S$ calcd for $[M+Na]^+$ 485.1393.

Phenyl 4-*O*-benzyl-2,3-*O*-(*o*-xylylene)-1-thio-β-D-glucopyranoside: Dichlorophenylborane (334 µL, 2.58 mmol) and triethylsilane (265 µL, 2.58 mmol) were added to a suspension of phenyl 4,6-*O*-benzylidene-2,3-*O*-(*o*-xylylene)-1-thio-β-D-glucopyranoside (350 mg, 760 µmol) and molecular sieves 4Å (350 mg) in CH_2Cl_2 (7.20 mL) under argon atmosphere. The mixture was stirred for 1.0 h at -80 °C as the progress of the reaction was monitored by TLC (EtOAc/*n*-Hexane = 1/3). The reaction mixture was quenched with Et_3N and MeOH, filtered through a pad of Celite and the filtered residue was washed with $CHCl_3$. The combined filtrate and washings were washed with sat. $NaHCO_3$ aq., H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane = 1/7) to give phenyl 4-*O*-benzyl-2,3-*O*-(*o*-xylylene)-1-thio-β-D-glucopyranoside (323 mg, 92%); $[\alpha]_D$ +50.3 ° (c 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.12 (m, 14 H, 3 Ar), 5.18 (d, 1 H, J_{gem} = 13.0 Hz, ArCH_2), 5.11 (s, 1 H, ArCH_2), 5.10 (s, 1 H, ArCH_2), 4.94 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.85 (d, 1 H, ArCH_2), 4.66 (d, 1 H, ArCH_2), 4.63 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 3.83 (m, 1 H, H-6a), 3.72 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3), 3.62 (m, 1 H, H-6b), 3.45 (t, 1 H, $J_{4,5}$ = 8.5 Hz, H-4), 3.37-3.36 (m, 2 H, H-2, H-5), 1.84 (t, 1 H, $J_{6a,OH}$ = $J_{6b,OH}$ = 5.0 Hz, OH); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.3, 136.8, 136.6, 133.1, 131.9, 130.7, 129.3, 129.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 86.6, 86.0, 79.6, 79.0, 76.7, 75.0, 73.1, 73.0, 62.4; HRMS (ESI) *m/z*: found $[M+Na]^+$ 487.1554, $C_{34}H_{34}O_5S$ calcd for $[M+Na]^+$ 487.1550.

Phenyl 4,6-di-*O*-benzyl-2,3-*O*-(*o*-xylylene)-1-thio-β-D-glucopyranoside (3): Sodium hydride (42.8 mg, 1.07 mmol) was added to a solution of phenyl 4-*O*-benzyl-2,3-*O*-(*o*-xylylene)-1-thio-β-D-glucopyranoside (331 mg, 713 µmol) in DMF (3.60 mL) at -20 °C under argon atmosphere. The mixture was stirred for 30 min at -20 °C, and benzyl bromide (423 µL 3.56 mmol) was added. The stirring was continued for 2.0 h at -20 °C as the progress of the reaction was monitored by TLC (EtOAc/*n*-Hexane = 1/3). The reaction mixture was quenched with MeOH, co-evaporated with toluene and diluted with EtOAc. The solution was washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/Toluene = 1/10) to give **3** (395 mg, quant.); $[\alpha]_D$ +22.1 ° (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.73-7.11 (m, 19 H, 3 Ar), 5.17 (d, 1 H, J_{gem} = 13.5 Hz, ArCH_2), 5.09 (s, 2 H, 2 ArCH_2), 4.92 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.90 (d, 1 H, ArCH_2), 4.59 (d, 1 H, $J_{1,2}$ = 10.0 Hz, H-1), 4.56 (d, 2 H, J_{gem} = 15.5 Hz, 2 ArCH_2), 4.50 (d, 1 H, ArCH_2), 3.76 (d, 1 H, J_{gem} = 10.5 Hz, H-6a), 3.70 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3), 3.66 (dd, 1 H, $J_{5,6b}$ = 4.5 Hz, H-6b), 3.51 (t, 1 H, $J_{4,5}$ = 8.5 Hz, H-4), 3.47 (m, 1 H, H-5), 3.40 (t, 1 H, H-2); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.3, 138.2, 134.9, 131.3, 128.8, 128.3, 128.1, 127.7, 127.7, 127.5, 127.0, 88.5, 82.3, 78.8, 77.9, 75.6, 75.4, 73.4, 69.2, 30.9, 17.6, 17.5, 17.5, 17.3, 17.3, 17.2, 17.2, 12.9, 12.8, 12.3, 12.3; HRMS (ESI) *m/z*: found $[M+Na]^+$ 577.2016, $C_{34}H_{34}O_5S$ calcd for $[M+Na]^+$ 577.2019.

[4,6-Di-*O*-benzyl-2,3-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-D-glucopyranosyl]-(1 → 6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (7): Molecular sieves 4 Å (20.0 mg) were added to a solution of **1** (25.0 mg, 44.2 µmol) and **6** (14.8 mg, 66.2 µmol) in CH_2Cl_2 (0.40 µL) under argon atmosphere. The suspension was stirred at ambient temperature for 30 min and cooled to -40 °C. To the suspension were added NIS (14.8 mg, 66.2 µmol) and TfOH (1.20 µL, 13.2 µmol), and then the reaction mixture was stirred for 1 h at -40 °C as the progress of the reaction was monitored by TLC (EtOAc/Toluene = 1/5). Then, the reaction mixture was neutralized with Et_3N, filtered through a pad of Celite, and the filtered residue was washed with $CHCl_3$. The combined filtrate and washings were washed with sat. $Na_2S_2O_3$ aq., H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/Toluene = 1/10) to give **7** as β-glycoside (18.2 mg, 66%) and α-glycoside (2.6 mg, 14%); **β-form** $[\alpha]_D$ +13.3 ° (c 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.21 (m, 10 H, 2 Ph), 5.50 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1^{Gal}), 4.90 (d, J_{gem} = 11.0 Hz, 1 H, PhCH_2) 4.60 (d, J_{gem} = 12.0 Hz, 1 H, PhCH_2), 4.55 (dd, 1 H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 8.0 Hz, H-3^{Gal}), 4.53 (d, 1 H, PhCH_2), 4.52 (d, 1 H, PhCH_2), 4.51 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1^{Glc}), 4.32 (dd, 1 H, $J_{4,5}$ = 1.5 Hz, H-4^{Gal}), 4.27 (dd, 1 H, H-2^{Gal}), 4.05-4.01 (m, 2 H, H-6a^{Gal}, H-6b^{Gal}), 3.87 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, H-3^{Glc}), 3.71 (dd, 1 H, $J_{5,6a}$ = 5.0 Hz, $J_{5,6b}$ = 9.5 Hz, H-5^{Gal}), 3.71-3.68 (m, 2 H, H-6a^{Glc}, H-6b^{Glc}), 3.67 (t, 1 H, $J_{4,5}$ = 10.0 Hz, H-4^{Glc}), 3.57 (dd, 1 H, H-2^{Glc}), 3.48 (m, 1 H, H-5^{Glc}), 3.29 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_3), 1.41-1.26 (m, 24 H, 6 CH_3); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.4, 138.3, 128.3, 128.0, 127.8, 127.7, 127.5, 109.1, 108.5, 100.8, 99.4, 96.3, 75.6, 74.8, 74.8, 73.7, 73.4, 71.1, 70.7, 70.6, 69.4, 69.0, 68.9, 68.6, 67.2, 47.8, 26.0, 26.0, 25.0, 24.4, 17.8, 17.6; HRMS (ESI) *m/z*: found $[M+Na]^+$ 739.3302, $C_{38}H_{52}O_{13}$ calcd for $[M+Na]^+$ 739.3300; **α-form** $[\alpha]_D$ -47.7 ° (c 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.05 (m, 10 H, 2 Ph), 5.48 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1^{Gal}), 4.93 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1^{Glc}), 4.90 (d, 1 H, J_{gem} = 11.0 Hz, PhCH_2), 4.64 (d, 1 H, J_{gem} = 12.0 Hz, 1 H, PhCH_2), 4.57 (dd, 1 H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 8.0 Hz, H-3^{Gal}), 4.49 (d, 1 H, PhCH_2), 4.45 (d, 1 H, PhCH_2), 4.31 (dd, 1 H, $J_{4,5}$ = 1.5 Hz, H-4^{Gal}), 4.26 (dd, 1 H, H-2^{Gal}), 4.18 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, H-3^{Glc}), 4.05 (m, 1 H, H-5^{Gal}), 4.64 (m, 1 H, H-6a^{Gal}), 3.84-3.74 (m, 5 H, H-2^{Glc}, H-4^{Glc}, H-5^{Glc}, H-6a^{Glc}, H-6b^{Gal}), 3.63 (dd, 1 H, $J_{5,6b}$ = 2.0 Hz, J_{gem} = 10.5 Hz, H-6b^{Glc}), 3.27 (s, 3 H, OCH_3), 3.25 (s, 3 H, OCH_3), 1.46-1.21 (m, 24 H, 6 CH_3); ^{13}C NMR (125 Hz, $CDCl_3$) δ 128.3,

128.2, 127.9, 127.8, 127.6, 127.5, 109.1, 108.6, 99.3, 97.9, 96.2, 75.0, 74.7, 70.8, 70.6, 70.4, 68.4, 68.3, 47.8, 29.7, 26.0, 25.0, 24.3, 22.7, 18.0, 17.6; HRMS (ESI) *m/z*: found $[M+Na]^+$ 739.3303, $C_{38}H_{52}O_{13}$ calcd for $[M+Na]^+$ 739.3300.

[4,6-Di-*O*-benzyl-2,3-*O*-(1,1,3,3-tetraisopropyldisiloxanylidene)-D-glucopyranosyl]-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (8): Molecular sieves 4 Å (70.0 mg) were added to a solution of **2** (100 mg, 144 µmol) and **6** (37.4 mg, 144 µmol) in CH_2Cl_2 (1.40 mL) under argon atmosphere. The suspension was stirred at ambient temperature for 30 min and cooled to -80 °C. To the suspension were added NIS (48.6 mg, 240 µmol) and TfOH (3.80 µL, 43.2 µmol), and then the reaction mixture was stirred for 9 h at -80 °C as the progress of the reaction was monitored by TLC (EtOAc/Toluene = 1/5). Then, the reaction mixture was neutralized with Et_3N, filtered through a pad of Celite, and the filtered residue was washed with $CHCl_3$. The combined filtrate and washings were washed with sat. $Na_2S_2O_3$ aq., H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/Toluene = 1/30) to give **8** as β-glycoside (106 mg, 88%) and α-glycoside (11.0 mg, 9%).; **β-form** $[\alpha]_D$ -20.8 ° (c 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.18 (m, 10 H, 2 Ph), 5.49 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1^{Gal}), 4.91 (d, 1 H, J_{gem} = 11.0 Hz, PhCH_2), 4.58 (d, 1 H, J_{gem} = 12.0 Hz, PhCH_2), 4.56 (d, 1 H, PhCH_2), 4.55 (s, 1 H, PhCH_2), 4.54 (m, 1 H, H-3^{Gal}), 4.32 (dd, 1 H, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 1.5 Hz, H-4^{Gal}), 4.29 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1^{Glc}), 4.27 (dd, 1 H, $J_{2,3}$ = 2.5 Hz, H-2^{Gal}), 4.09 (dd, $J_{5,6a}$ = 6.5 Hz, J_{gem} = 10.5 Hz, H-6a^{Gal}), 3.98 (td, 1 H, $J_{5,6b}$ = 6.5 Hz, H-5^{Gal}), 3.82 (t, $J_{2,3}$ = $J_{3,4}$ = 8.5 Hz, H-3^{Glc}), 3.72-3.67 (m, 2 H, H-6a^{Glc}, H-6b^{Gal}), 3.65 (dd, 1 H, $J_{5,6b}$ = 4.5 Hz, J_{gem} = 11.0 Hz, H-6b^{Glc}), 3.53 (dd, 1 H, H-2^{Glc}), 3.51 (t, 1 H, $J_{4,5}$ = 8.5 Hz, H-4^{Glc}), 3.42 (m, 1 H, H-5^{Glc}), 1.54-1.26 (4 s, 12 H, 4 CH_3), 1.10-0.94 (m, 28 H, 4 ^{i}Pr); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.3, 138.3, 128.3, 128.3, 128.1, 127.9, 127.7, 127.6, 109.0, 108.4, 103.3, 96.4, 81.2, 78.1, 76.5, 75.3, 74.5, 73.5, 70.9, 70.7, 70.6, 68.9, 68.6, 66.4, 26.1, 26.0, 25.0, 24.3, 17.5, 17.4, 17.4, 17.4, 17.3, 17.3, 17.3, 17.3, 13.0, 12.8, 12.6, 12.2; HRMS (ESI) *m/z*: found $[M+Na]^+$ 867.4141, $C_{44}H_{68}O_{12}Si_2$ calcd for $[M+Na]^+$ 867.4142; **α-form** $[\alpha]_D$ +73.3 ° (c 0.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.15 (m, 10 H, 2 Ph), 5.48 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1^{Gal}), 4.91 (d, 1 H, J_{gem} = 11.0 Hz, PhCH_2), 4.90 (d, 1 H, $J_{1,2}$ = 4.5 Hz, H-1^{Glc}), 4.61 (d, 1 H, J_{gem} = 12.0 Hz, PhCH_2), 4.56 (dd, 1 H, $J_{2,3}$ = 2.5 Hz, $J_{3,4}$ = 8.0 Hz, H-3^{Gal}), 4.49 (d, 1 H, PhCH_2), 4.48 (d, 1 H, PhCH_2), 4.34 (dd, 1 H, $J_{4,5}$ = 2.0 Hz, H-4^{Gal}), 4.28 (dd,1 H, H-2^{Gal}), 4.12 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3^{Glc}), 3.94 (td, 1 H, $J_{5,6a}$ = 6.0 Hz, $J_{5,6b}$ = 8.5 Hz, H-5^{Gal}), 3.80 (m, 1 H, H-5^{Glc}), 3.76-3.68 (m, 4 H, H-2^{Glc}, H-6a^{Glc}, H-6a^{Gal}, H-6b^{Gal}), 3.63 (dd, 1 H, $J_{5,6b}$ = 2.0 Hz, J_{gem} = 10.5 Hz, H-6b^{Glc}), 3.58 (t, 1 H, $J_{4,5}$ = 9.0 Hz, H-4^{Glc}) 151-1.29 (4 s, 12 H, 4 CH_3), 1.43-0.91 (m, 28 H, 4 ^{i}Pr); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.3, 128.3, 128.3, 128.1, 127.9, 127.6, 127.5, 109.0, 108.4, 103.3, 96.3, 81.2, 78.1, 77.6, 76.5, 75.2, 74.5, 73.5, 70.9, 70.7, 70.6, 68.9, 68.6, 66.4, 26.1, 26.0, 25.0, 24.3, 17.5, 17.4, 17.4, 17.3, 17.3, 17.3, 17.3, 17.2, 13.0, 12.8, 12.2; HRMS (ESI) *m/z*: found $[M+Na]^+$ 867.4147, $C_{44}H_{68}O_{12}Si_2$ calcd for $[M+Na]^+$ 867.4142.

[4,6-Di-*O*-benzyl-2,3-*O*-(*o*-xylylene)-D-glucopyranosyl]-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (9)

Glycosidation of **3:** Molecular sieves 4 Å (90.0 mg) were added to a solution of **3** (100 mg, 182 µmol) and **6** (46.8 mg, 182 µmol) in CH_2Cl_2 (1.80 mL) under argon atmosphere. The suspension was stirred at ambient temperature for 30 min and cooled to -80 °C. To the suspension were added NIS (60.7 mg, 274 µmol) and TfOH (4.40 µL, 55.0 µmol), and then the reaction mixture was stirred for 7.5 h at -80 °C as the progress of the reaction was monitored by TLC (EtOAc/Toluene = 1/5). Then, the reaction mixture was neutralized with Et_3N, filtered through a pad of Celite, and the filtered residue was washed with $CHCl_3$. The combined filtrate and washings were washed with sat. $Na_2S_2O_3$ aq., H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane = 1/5) to give **9** as β-glycoside (106 mg, 86%) and α-glycoside (9.3 mg, 7%).

Glycosidation of **19 :** Molecular sieves AW 300 (35.0 mg) were added to a solution of **19** (45.3 mg, 71.5 µmol) and **6** (18.6 mg, 71.5 µmol) in CH_2Cl_2 (0.70 mL) under argon atmosphere. The suspension was stirred at ambient temperature for 5 min and cooled to -80 °C. To the suspension were added TMSOTf (0.60 µL, 3.60 µmol), and then the reaction mixture was stirred for 1.0 h at -80 °C as the progress of the reaction was monitored by TLC (EtOAc/Toluene = 1/5). Then, the reaction mixture was neutralized with Et_3N, filtered through a pad of Celite, and the filtered residue was washed with $CHCl_3$. The combined filtrate and washings were washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography (EtOAc/*n*-Hexane = 1/5) to give **9** as β-glycoside (39.5 mg, 80%) and α-glycoside (4.88 mg, 10%); **β-form** $[\alpha]_D$ +5.26 ° (c 0.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.07 (m, 14 H, 3 Ar), 5.56 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1^{Gal}), 5.23 (d, 1 H, J_{gem} = 13.0 Hz, ArCH_2), 5.10 (d, 1 H, J_{gem} = 15.0 Hz, ArCH_2), 5.05 (d, 1 H, ArCH_2), 4.91 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.81 (d, 1 H, ArCH_2), 4.60 (dd, 1 H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 8.0 Hz, H-3^{Gal}), 4.57 (d, 1 H, J_{gem} = 12.0 Hz, ArCH_2), 4.54 (d, 1 H, ArCH_2), 4.50 (d, 1 H, ArCH_2), 4.42 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1^{Glc}), 4.31 (dd, 1 H, H-2^{Gal}), 4.29 (dd, 1 H, $J_{4,5}$ = 1.5 Hz, H-4^{Gal}), 4.08-4.04 (m, 2 H, H-5^{Gal}, H-6a^{Gal}), 3.78 (dd, 1 H, $J_{5,6b}$ = 8.0 Hz, J_{gem} = 12.5 Hz, H-6b^{Gal}), 3.72-3.67 (m, 2 H, H-3^{Glc}, H-6a^{Glc}), 3.64 (dd, 1 H, $J_{5,6b}$ = 4.5 Hz, J_{gem} = 11.0 Hz, H-6b^{Glc}), 3.49 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 8.0 Hz, H-4^{Glc}), 3.41 (m, 1 H, H-5^{Glc}), 3.36 (t, 1 H, $J_{2,3}$ = 8.0 Hz, H-2^{Glc}), 1.55-1.32 (4 s, 12 H, 4 CH_3)**;** ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.6, 138.3, 137.5, 136.8, 131.6, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 109.3, 108.6, 102.9, 96.4, 84.2, 80.8, 77.8, 76.9, 74.8, 74.5, 73.5, 73.0, 72.5, 71.4, 70.8, 70.6, 69.3, 69.0, 67.7, 26.2, 26.0, 25.1, 24.5; HRMS (ESI) *m/z*: found $[M+Na]^+$ 727.3089, $C_{40}H_{48}O_{11}$ calcd for $[M+Na]^+$ 727.3089; **α-form;** $[\alpha]_D$ +47.1 ° (c 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.10 (m, 14 H, 3 Ar), 5.47 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1^{Gal}), 5.15 (d, 1 H, J_{gem} = 13.5 Hz, ArCH_2), 5.03 (d, 1 H, J_{gem} = 14.5 Hz, ArCH_2), 5.00 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1^{Glc}), 4.98 (d, 1 H, ArCH_2), 4.96 (d, 1 H, ArCH_2), 4.90 (d, 1 H, J_{gem} = 11.0 Hz, ArCH_2), 4.61 (d, 1 H, J_{gem} = 12.5 Hz, ArCH_2), 4.56 (dd, 1 H, $J_{2,3}$ = 2.0 Hz, $J_{3,4}$ = 8.0 Hz, H-3^{Gal}), 4.53 (d, 1 H, ArCH_2), 4.45 (d, 1 H, ArCH_2), 4.27-4.20 (m, 2 H, H-2^{Gal}, H-4^{Gal}), 4.01-3.98 (m, 2 H, H-5^{Gal}, H-6a^{Gal}), 3.88 (dt, 1 H, $J_{5,6a}$ = 2.0 Hz, J_{gem} = 7.5 Hz, H-6a^{Glc}), 3.81-3.73 (m, 3 H, H-3^{Glc}, H-4^{Glc}, H-6b^{Gal}), 3.66-3.73 (m, 2 H, H-5^{Glc}, H-6b^{Glc}), 3.56 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, H-2^{Glc}), 1.45-1.35 (4 s, 12 H, 4 CH_3); ^{13}C NMR (125 Hz, $CDCl_3$) δ 138.7, 138.1, 137.2, 136.9, 129.7, 129.2, 128.2, 128.2, 127.8, 127.8, 127.6, 127.5, 127.5, 109.1, 108.5, 98.1, 96.2, 82.3, 80.4, 74.7, 73.6, 73.4, 73.3, 71.0, 70.7, 70.6, 70.0, 68.5, 67.1, 66.5, 29.7, 26.1, 26.0, 25.0, 24.4; HRMS (ESI) *m/z*: found $[M+Na]^+$ 727.3093, $C_{40}H_{48}O_{11}$ calcd for $[M+Na]^+$ 727.3089.

Computational detail: All DFT calculations were carried out with GAUSSIAN 09 program package[19]. We use B3LYP hybrid exchange-correlation functional[20] and 6-311G(d) electronic basis set for calculations. Solvent effects (Solvent = CH_2Cl_2) were included using the polarizable

continuum model (PCM),[21] The initial structure of oxocarbenium ion intermediate was built with the aid of GaussView 5 visualization software [22]. The geometry optimization was performed without any geometrical restrictions. We also performed the normal mode analysis to characterize the optimized structure, and confirmed that the optimized structure has no imaginary frequencies.

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Notes and references

1. (a) R. E. J. N. Litjens, L. J. van den Bos, J. D. C. Codée, H. S. Overkleeft and G. A. van der Marel, *Carbohydr. Res*., **2007**, *342*, 419; (b) T. J. Boltje, T. Buskas and G. -J. Boons, *Nat. Chem.*, **2009**, *1*, 611; (c) J. Guo and X. -S. Ye, *Molecules*, **2010**, *15*, 7235; (d) S. S. Nigudkar and A. V. Demchenko, *Chem. Sci.*, **2015**, *6*, 2687.

2. (a) R. R. Schmidt and E. Rücker, *Tetrahedron Lett.*, **1980**, *21*, 1421; (b) S. Hashimoto, M. Hayashi, and R. Noyori, *Tetrahedron Lett.*, **1984**, *25*, 1379. (c) H. Satoh, H. S. Hansen, S. Manabe, W. F. van Gunsteren and P. H. Hü nenberger, *J. Chem. Theory Comput.* **2010**, *6*, 1783.

3. (a) D. Kahne, S. Walker, Y. Cheng and D. van Engen, *J. Am. Chem. Soc.*, **1989**, *111*, 6881; (b) D. Crich and S. Sun, *J. Org. Chem.*, **1996**, *61*, 4506.

4. J. -H. Kim, H. Yang and G. -J Boons, *Angew. Chem. Int. Ed.* **2005**, *44*, 947.

5. (a) J. T. Smoot, P. Pornsuriyasak and A. V. Demchenko, *Angew. Chem. Int. Ed.* **2005**, *44*, 7123. (b) J. T. Smoot, and A. V. Demchenko, *J. Org. Chem.* **2008**, *73*, 8838.

6. J. P. Yasomanee and A. V. Demchenko, *J. Am. Chem. Soc.*, **2012**, *134*, 20097.

7. (a) Y. Okada, T. Mukae, K. Okajima, M. Taira, M. Fujita and H. Yamada, *Org. Lett.*, **2007**, *9*, 1573; (b) Y. Okada, O. Nagata, M. Taira and H. Yamada, *Org. Lett.*, **2007**, *9*, 2755; (c) C. M. Pedersen, L. U. Nordstrøm and M. Bols, *J. Am. Chem. Soc.*, **2007**, *129*, 9222; (d) T. Furukawa, H. Hinou and S.-I. Nishimura, *Org. Lett.*, **2012**, *14*, 2102; (e) Y. Okada, N. Asakura, M. Bando, Y. Ashikaga and H. Yamada, *J. Am. Chem. Soc.*, **2012**, *134*, 6940.

8. A. Imamura and T. L. Lowary, *Org. Lett.*, **2010**, *12*, 3686.

9. D. Crich and P. Jayalath, *J. Org. Chem.*, **2005**, *70*, 7252.

10. B. M. Trost and C. G. Caldwell, *Tetrahedron Lett.*, **1981**, *22*, 4999.

11. U. Berens, D. Leckel and S. C. Oepen, *J. Org. Chem.*, **1995**, *60*, 8204.

12. W. T. Markiewicz, *J. Chem. Res. (S)*, **1979**, 24.

13. J. Poss and M. S. Smyth, *Synth. Commun.*, **1989**, *19*, 3363.

14. (a) G. H. Veeneman, S. H. van Leeuwen and J. H. van Boom, *Tetrahedron Lett.*, **1990**, *31*, 1331; (b) P. Konradsson, U. E. Udodong and B. Fraser-Reid, *Tetrahedron Lett.*, **1990**, *31*, 4313.

15. R. Eby and C. Schuerch, *Carbohydr. Res.*, **1974**, *34*, 79.

16. For detailed synthetic procedures, see the Supporting Information.

17. B. Yu and H. Tao, *Tetrahedron Lett.*, **2001**, *42*, 2405.

18. (a) S. Chamberland, J. W. Ziller and K. A. Woerpel, *J. Am. Chem. Soc.*, **2005**, *127*, 5322; (b) M. T. Yang and K. A. Woerpel, *J. Org. Chem.*, **2009**, *74*, 545.

19. M. J. Frisch, G. W. Trucks, H. B Schlegel, G. E Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P.Hratchain, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov. T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, *Gaussian 09*, Revision B.01; Gaussian, Inc.: Wallingford CT, 2010

20. A. D. Becke, *J. Chem. Phys.*, **1993**, *98*, 5648.

21. G. Scalmani and M. J. Frisch, *J. Chem. Phys.*, **2010**, *132*, 114110.

22. R. Dennington, T. Keith and J. Millam, *GaussView*, Version 5; Semichem Inc.: Shawnee Mission, KS, 2009

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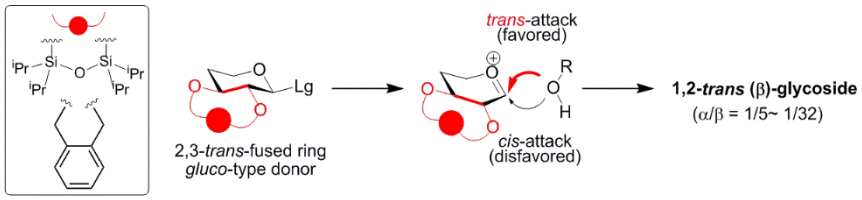

A new 1,2-*trans*-selective glycosidation reaction is described. Glucosyl donors protected cyclically at the C2 and C3 hydroxyl groups mainly generated β-glycosides under conventional glycosidation conditions. The results showed that the *o*-xylylene-group is suitable as a 1,2-*trans*-directing functionality.

Glycosylation

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A 1,2-*trans*-selective glycosyl donor bearing cyclic protection at the C2 and C3 hydroxyl groups