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# Direct thiophenylation accompanying orthoester-cleavage of 1,2,4-*O*-orthoacetyl-3,6-*O*-(*o*-xylylene)glucopyranose

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ABSTRACT

The 3,6-*O*-(*o*-xylylene) bridge locks the conformation of glucopyranose to an axial-rich form. Although the conformational lock induces complete β-selectivity in a glycosylation reaction, the leaving group of the glycosyl donor is limited to fluorine. On the other hand, the bridge confers the furanose-preferred property to glucose, which makes synthesis of corresponding pyranosyl derivatives that equip various leaving groups difficult. This problem was solved through direct phenylthio glucosidation of 3,6-*O*-(*o*-xylylene)-1,2,4-*O*-orthoacetylglucose accompanying cleavage of the orthoester moiety. This paper describes the process of establishing direct thiophenylation. This process reduced the synthetic steps for the known glucopyranosyl fluoride and will expand application of conformationally locked glycosyl donors.



Acquisition of varied leaving groups for glycosyl donors is important in the development of chemical glycosylation reactions. In the presence of several types of leaving groups, a chemoselective activation of a leaving group allows the other leaving groups to remain intact. The survivors behave as protecting groups of carbohydrates during the reaction, and can be activated afterward, through different methods, to enable elongation of sugar chains. This strategy is described as orthogonal,[1] and has streamlined oligosaccharide synthesis.[2–8] Among the variety of leaving groups used in the orthogonal synthesis, alkyl- and arylthio groups have been commonly used because these are stable under ubiquitous activating conditions for a halogen atom and trichloroacetimidate,[9,10] which are the frequently-used leaving groups of glycosyl donors. In addition, activation of the alkyl- and arylthio groups is possible chemoselectively when necessary.

Another important issue that must be considered in the development of glycosylation reactions is control of anomeric stereoselectivity. For a stereoselective preparation of a 1,2-*trans* glycosidic linkage, the neighboring group participation (NGP hereafter) of a 2-*O*-acyl protecting group has been proven.[11] Recently, it has been reported that conformational lock of a pyranose ring can be effective procedures to obtain the stereoselectivity.[12–19] In addition, control of reactivity in glycosylation due to the lock to a conformation that has more axial substituents has been reported with conformational armed–disarmed concept,[20] and thus, influence in glycosylation reactions contributed by the variation of conformation has attracted attention.[21–23] We reported a unique NGP-less 1,2-*trans*-selective glycosylation employing glycosyl fluoride **1** (Fig. 1a), the conformation of the pyranose ring of which was locked to an axial-rich form by a 3,6-*O*-(*o*-xylylene) bridge.[24] First, preparation of the glycosyl donor **1** required 13 steps (Fig. 1b, Route A); therefore, the route was inefficient, even in laboratory synthesis. Later, we improved the synthetic method of the glycosyl donor (Fig. 1b, Route B),[25] where the utilization of conformationally locked orthoester **2** contributed to the formation of the *o*-xylylene bridge. In the route, the orthoester group was removed by unusual thermal glycosylation[26,27] with *p*-methoxyphenol (step 1 in the transformation from **3** to **4**). The reason that we could not rely on the usual method for the removal of the orthoester group, hydrolysis, was the property of 3,6-*O*-(*o*-xylylene)glucose (**6**) that preferred the furanose form over the pyranose form (Fig. 1c).

Despite the complete β-selectivity in the glycosylation reaction using the *o*-xylylene bridged glycosyl donor, only glycosyl fluoride **1** has been investigated; none of the variants possessing the other leaving groups have been developed. Considering usability in orthogonal synthesis, a synthetic method for the corresponding thioglycosides must be established. A thioglycoside can be prepared from a glycosyl fluoride,[1,28] but application of the transformation of **1** to **7** would make the synthesis lengthy, and thus inefficient. Transformation from hemiacetal **5** is similarly lengthy.[29–32] The *p*-methoxyphenyl (*p*MP) group can also convert to an alkyl- or arylthio group,[33] but operation of the reported procedure to **4** was poor, as will be described later. In this study, we

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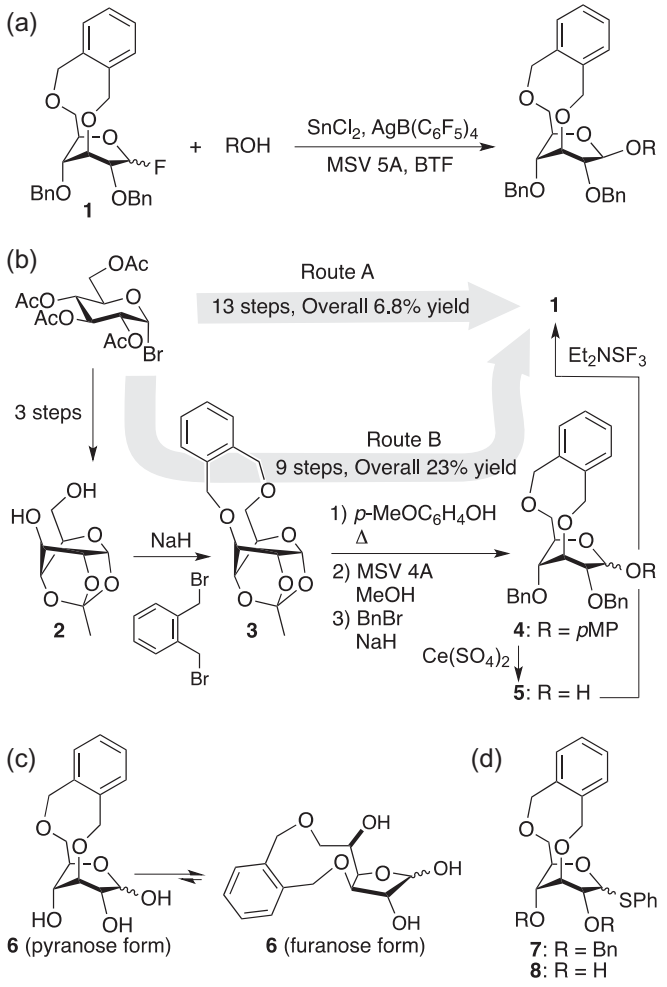
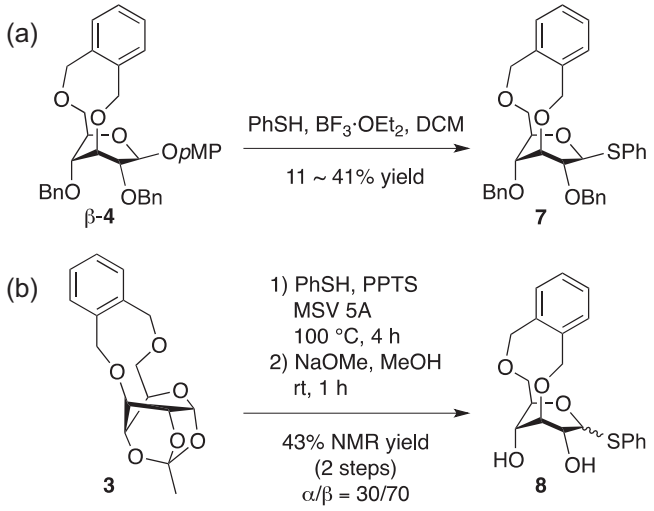



**Figure 1.** Reaction, preparation, and properties of *o*-xylylene bridged glucose: Ac = acetyl, Bn = benzyl, BTF = benzotrifluoride, Et = ethyl, MSV = molecular sieves, Ph = phenyl, *p*MP = *p*-methoxyphenyl.

describe investigations for direct conversion from 3,6-*O*-(*o*-xylylene)-1,2,4-*O*-orthoacetylglucose (**3**) to the corresponding alkyl- and arylthioglucosides, the optimized reaction conditions for phenylthioglucoside **8**, and the synthesis of glycosyl fluoride **1** from **8** via **7** which contributes to one-step shortening of the synthesis of **1**.

We first attempted the preparation of thioglycoside **7** from *p*MP glucoside β-**4**, (Scheme 1, a) applying the reported method.[33] Treatment of β-**4** with benzenethiol [3 equiv of β-**4**] and boron trifluoride diethyl etherate (1.5 equiv of β-**4**) in dichloromethane (DCM) under reflux provided **7** in 11% yield as a component of a complex mixture of products. Operation of the reaction at room temperature (rt) produced **7** at a 27% yield. During the investigations, we found that a decreased quantity of benzenethiol from 3 to 1 equiv resulted in a better yield, although it was still 41%. Therefore, we concluded that the transformation from β-**4** to **7** was inadequate, and strived for direct conversion from **3** to **8** (Scheme 1, b).

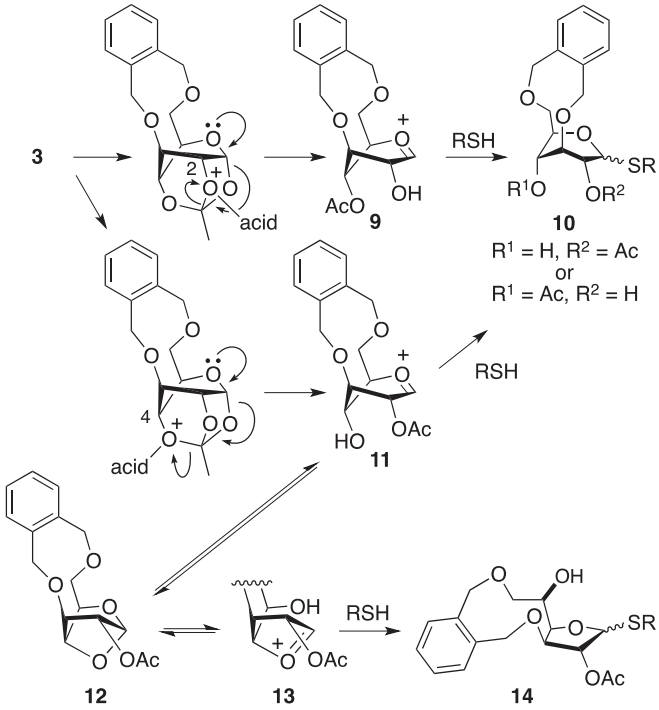
Our first choice for the direct conversion was thermal glycosylation similar to the first step in the transformation from **3** to *p*MP glucoside **4** in Scheme 1b. Thus, 6 equiv of benzenethiol as both nucleophile and solvent in the reaction was heated with **3** at 100 °C in the presence of pyridinium *p*-toluenesulfonate (PPTS) and molecular sieves (MSV) 5A. The reaction provided the desired phenylthioglucoside **8** accompanied with many by-products. The




**Scheme 1.** Attempts at synthesis of the 3,6-*O*-(*o*-xylylene) bridge-possessing thioglycosides through known methods.

yield of **8** was estimated to be 43% based on the $^1$H nuclear magnetic resonance (NMR) spectra of the crude product after removal of an acetyl group generated by cleavage of the orthoester. Because of the low yield and a poignant malodor at the workup operations due to the use of a large excess of benzenethiol, we decided not to apply the thermal glycosylation strategy for the transformation.

After the production of many by-products in the thermal thioglycosylation, we reconsidered the process of the orthoester cleavage (Scheme 2). The orthoester of **3** is cleaved by an acid. Coordination of the acid with the oxygen atom at the 2-position (O-2) and O-4 generates oxocarbenium ion intermediates **9** and **11**, respectively. The intermediate **9** would only induce **10**, which is the desired thiopyranoside, through the reaction with a thiol. Reaction of **11** with a thiol provides **10** but an intramolecular



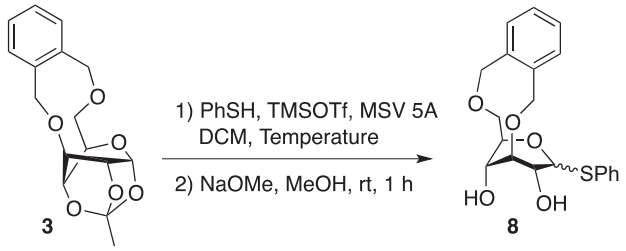

**Scheme 2.** A possible reaction mechanism for cleavage of orthoester **3**: R = an unspecified alkyl- or aryl group.

attack of the O-4 of **11** results in the formation of undesired furanoside **14** through **12** and **13**. Therefore, the process includes competition between the inter- and intramolecular reactions. Although an intramolecular reaction is generally faster, the strained structure of **12** that contains a 2,5,10,14-tetraoxatricyclo[9.3.0.0[3,25]] tetradecane skeleton, and stronger nucleophilicity of the sulfur atom of the thiol than nucleophilicity of O-4 are both favorable to the formation of **10** in this case. Thus, the transition state for **12** might be higher than that for **10**. Nevertheless, under the thermal reaction conditions, the pathway to **12** is allowed, and this might be the reason that the thermal introduction of the phenylthio group produced complex by-products in the reaction of Scheme 1b. When a thiol is treated with **3** at lower temperatures, the pathway to **10** might become conspicuous.

On the basis of the analysis described above, we examined the cleavage of orthoester at various temperatures (Table 1). In the examination, we used benzenethiol, trimethylsilyl (TMS) trifluoromethanesulfonate (triflate or OTf), and MSV 5A as the nucleophile, the activator, and the additive, respectively, in DCM. After the cleavage reaction, treatment of each crude product with sodium methoxide in methanol removed the remained acetyl group. The results clarified that the yield of **8** increased at a lower reaction temperature. The peak of the yield appeared when the temperature was −40 °C (Table 1, entry 2); at the temperature, the α/β-ratio was also most biased to β.

With the gratifying outcome at −40 °C (Table 1, entry 2), we then examined the employment of the other thiols to find that only benzenethiol was useful for the cleavage of orthoester (Table 2). In the examination, we fixed the solvent, the activator, and the additive at DCM, TMSOTf, and MSV 5A, respectively. The yields were obtained after removal of the acetyl group, the cleaved orthoester. The examination demonstrated that the reactions with ethanethiol and 1-dodecanethiol provided products as a complex mixture, hence the yields of the desired alkylthioglucosides **15** and **16** were low (Table 2, entries 1 and 2). The result listed in Table 2, entry 3 is a transcription of Table 1, entry 2, in which the chromatogram of thin layer chromatography (TLC) used for tracing the reaction was simple. On the other hand, the treatments with 2-methylbenzenethiol and 4-methylbenzenethiol produced a complex mixture containing desired thioglucosides **17** and **18** in 29% yields, respectively (Table 2, entries 4 and 5). In addition, the attempt at using 4-nitrobenzenthiol gave a complicated mixture that did not allow isolation of the desired product **19** (Table 2, entry 6). The NMR

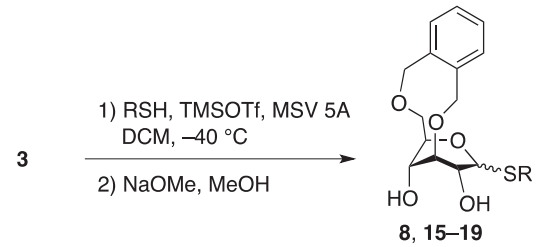
**Table 1**
Examination of reaction temperature for cleavage of orthoester in **3**




| Entry | Temperature (°C) | Time (h) | Yield[a] (%) | α/β ratio[b] |
|---|---|---|---|---|
| 1 | −50 | 48 | 84 | 5/95 |
| 2 | −40 | 10 | 88 (82)[c] | 3/97 |
| 3 | −30 | 4 | 79 | 5/95 |
| 4 | −20 | 1.5 | 76 | 7/93 |
| 5 | 0 | 0.75 | 44 | 12/88 |
| 6 | 23 | 0.5 | 14 | 22/78 |

[a] NMR yield.
[b] Determined by $^1$H NMR.
[c] Isolated yield.

**Table 2**
Search for appropriate thiols in direct thioglycosylation of **3**




**8**, **15**–**19**

| Entry | R | Product | Yield[a] (%) |
|---|---|---|---|
| 1 | $C_2H_5$ | **15** | 5 |
| 2 | *n*-$C_{12}H_{25}$ | **16** | 24 |
| 3 | $C_6H_5$ | **8** | 88 (82)[b] |
| 4 | $C_6H_4$-*o*-$CH_3$ | **17** | 29 |
| 5 | $C_6H_4$-*p*-$CH_3$ | **18** | 29 |
| 6 | $C_6H_4$-*p*-$NO_2$ | **19** | N.D. |

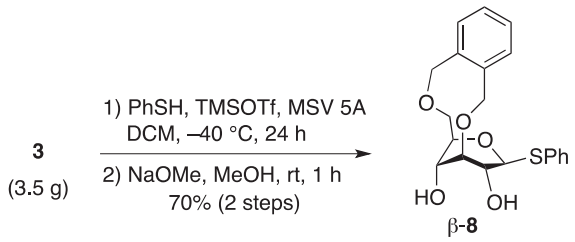
[a] NMR yield of each β-isomer.
[b] Isolated yield.

yields were calculated on the basis of the ratio of $^1$H NMR signal-areas between crude reaction-product and an internal standard that was non-deuterated acetone. The molar amount of acetone was identical to that of the starting material **3**. In order to obtain correct yields, signals definitely derived from the desired product of each entry should be recognized among the multiple signals of the crude products. For this purpose, we isolated compounds **8** and **15**–**18** in pure form after the $^1$H NMR observation of each crude product and confirmed the spectral data.

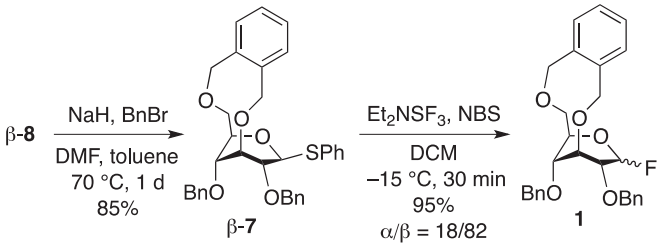
With benzenethiol, we explored the activator and reaction solvents to determine the reaction conditions listed in Table 2, entry 3, in which the use of TMSOTf and DCM as the activator and solvent, respectively, was optimal. As the activator, TMSOTf, *tert*-butyldimethylsilyl triflate, PPTS, boron trifluoride diethyl etherate, bismuth(III) bromide, and hafnium(IV) triflate[34] were attempted in DCM as the reaction solvent. However, they were all less effective than TMSOTf. Fixing TMSOTf as the activator, the use of acetonitrile, diethyl ether, *N*,*N*-dimethylformamide (DMF), pyridine, tetrahydrofuran (THF), and toluene were compared as reaction solvents. This examination showed that the yield and stereoselectivity of the cleaving reaction were highly dependent on the solvent, and the yield of **8** was highest in DCM. For details of these results, see Table S1 of the Supplementary data. The limitation of the method in the use of other thiols, activators, and solvents may involve the competition between intermediates **9** and **11** (Scheme 2). However, the formation of many by-products in the cases obtained lesser yield prevented accurate analysis for the limitation.

For each reaction in this paper so far, we handled 50 mg of **3** to find the optimal reaction conditions (Table 2, entry 3). We next applied the reaction conditions for a gram-scale synthesis of **8**. Thus, treatment of 3.5 g of **3** under the optimal conditions afforded β-**8** in a 70% yield (Scheme 3). From the experiment, we discovered that β-**8** could be purified by recrystallization from a mixture of $CHCl_3$ and *n*-hexane after removal of unreacted benzenethiol through short column chromatography. The obtained 70% yield after the recrystallization illustrated great practicality in laboratory synthesis.

As a bonus of the establishment of the direct production of phenylthioglucoside **8** from **3**, we were able to shorten the route for synthesizing glycosyl fluoride **1** (Fig. 1a). In our previous report,[25] we described the reduction in the number of preparation steps of **1** from 13 to 9 (Fig. 1b). The present work removed one more step (Scheme 4). Thus, after dibenzylation of **8** producing **7**, treatment of **7** with *N*,*N*-diethylaminosulfur trifluoride and *N*-bro-




**Scheme 3.** Gram-scale synthesis of **8**.




**Scheme 4.** Synthesis of glycosyl fluoride **1** from thioglucoside β-**8**.

mosuccinimide (NBS) in DCM at −15 °C for 30 min,[35] **1** was obtained in a 95% yield as a mixture of anomers (α/β = 18/82).

In conclusion, we have established an efficient synthetic method of 3,6-*O*-(*o*-xylylene) bridged thioglycoside **8** from ortho-acetylglucose **3**. The key point for this direct conversion was the choice of the low reaction temperature, which prevented side reactions including the formation of the corresponding furanoside **14**. For thiol, the reaction solvent, and activator, the adoption of benzenethiol, DCM, and TMSOTf, respectively, was optimal. Direct and efficient conversion of the phenylthioglucoside β-**7**, that was dibenzylated β-**8**, to the corresponding fluoride **1** was also possible, which reduced the previous number of synthetic steps for **1** by one. The successful preparation of the thioglucoside possessing the 3,6-*O*-(*o*-xylylene) bridge would expand the application of the conformationally locked carbohydrates to orthogonal synthesis providing oligosaccharides.

## 1. Experimental

### 1.1. General methods

Commercially available reagents were used without further purification except for NBS that was recrystallized from $H_2O$ and dried prior to use. Moisture and air sensitive reactions were performed in glassware equipped with rubber septa (or a septum) under the positive pressure of argon or nitrogen. When necessary, the glassware was dried under reduced pressure by heating with a heat-gun and solvents were distilled prior to use. MSV were dried under reduced pressure by heating with a heat-gun before use. The reaction mixture was magnetically stirred. Concentration was performed under reduced pressure.

The reactions were monitored by TLC and mass spectra (MS). Ethyl acetate (EtOAc) was used as the organic layer in extraction. Anhydrous $MgSO_4$ or $Na_2SO_4$ were used to dry organic layers after extraction, and it was removed by filtration through a cotton pad. The filtrate was concentrated and subjected to further purification protocols if necessary. This sequence was represented as 'the general drying procedure' in the following experimental methods.

TLC was performed on Merck precoated silica gel 60 F-254 plates. Spots were visualized by exposure to ultraviolet (UV) light, or by immersion into a solution of 2% anisaldehyde, 5% $H_2SO_4$ in ethanol or a solution of 10% phosphomolybdic acid in ethanol, followed by heating at ca. 200 °C. Column chromatography (CC) was performed on Merck silica gel 60 (63–200 or 40–63 μm) and Kanto Chemical silica gel 60 N (Spherical, neutral, 40–50 or 63–210 μm).

The melting points were uncorrected. Optical rotations were determined with a 100 mm cell at 589 nm. Infrared (IR) spectra were recorded with a spectrophotometer equipped with an attenuated total reflectance sampling unit, and the major absorbance bands are reported in wavenumbers ($cm^{-1}$). High-resolution (HR) MS were obtained for electrospray ionization (ESI). The data are reported in units of mass to charge.

NMR spectra were recorded at 400 and 100 MHz for $^1H$ and $^{13}C$ NMR, respectively, and with either tetramethylsilane or residual proton of deuterated solvent as internal reference in the indicated solvent in each parenthesis. The $^1H$ NMR data are indicated by a chemical shift ($\delta$), with the multiplicity, the coupling constants, and the integration in parentheses. The multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. The $^{13}C$ NMR data are reported as the chemical shift ($\delta$). When the number of the carbon was more than one, the number was added in the parentheses.

### 1.2. Experimental procedures

#### 1.2.1. Typical procedure for preparation of phenyl 2,4-di-*O*-benzyl-1-thio-3,6-*O*-(*o*-xylylene)-β-D-glucopyranoside (β-7) from *p*MP glucoside β-4 (Scheme 1a)

A mixture of 4-methoxyphenyl glucoside β-**4** (60.0 mg, 106 μmol) and PhSH (12.8 mg, 117 μmol) in DCM (2 mL) was stirred for 5 min at rt. To the mixture was added $BF_3{\cdot}Et_2O$ (7.5 mg 53 μmol). The mixture was stirred for 2 h at rt. Addition of saturated (satd) aqueous (aq) $NaHCO_3$ (2 mL) quenched the reaction. After extraction, the organic layer was successively washed with satd aq $NaHCO_3$, $H_2O$, and brine. After the general drying procedure, the crude product was purified by CC (2 g of $SiO_2$, *n*-hexane/EtOAc = 9:1) to afford β-**7** (24.1 mg, 41%) as a colorless amorphous solid $[\alpha]_D^{15}$ +15.9 (*c* 2.82, $CHCl_3$); IR 3059, 3028, 2869, 1108, 1027, 738, 694 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 20.1 °C) $\delta$ 7.46–7.26 (m, 13H), 7.24–7.10 (m, 6H), 5.58 (d, *J* = 9.9 Hz, 1H), 5.08 (d, *J* = 10.1 Hz, 1H), 4.95 (d, *J* = 9.2 Hz, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.44 (dd, *J* = 1.4, 1.4 Hz, 1H), 4.31 (d, *J* = 9.9 Hz, 1H), 4.24 (d, *J* = 10.1 Hz, 1H), 4.17 (dd, *J* = 3.4, 3.0 Hz, 1H), 3.93 (dd, *J* = 3.0, 1.4 Hz, 1H), 3.84 (d, *J* = 13.7 Hz, 1H), 3.75 (dd, *J* = 13.7, 3.4 Hz, 1H), 3.69 (dd, *J* = 9.2, 1.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 20.1 °C) $\delta$ 138.2, 137.8, 137.0, 136.4, 134.8, 130.8–126.7 (19C, eleven peaks were observed), 85.1, 84.5, 81.5, 74.7, 74.5, 73.2, 71.8, 70.6, 70.4, 70.2; ESIHRMS (*m*/*z*) calculated (calcd) for $C_{34}H_{34}O_5SNa$ $[M+Na]^+$ 577.2025, found 577.2032.

#### 1.2.2. Thermal thioglycosylation of 8 (Scheme 1b)

A mixture of MSV 5A (33 mg), PPTS (4.5 mg, 18 μmol), PhSH (108 mg, 978 μmol), and **3** (50.0 mg, 163 μmol) was stirred for 4 h at 100 °C. Addition of satd aq $NaHCO_3$ (2 mL) quenched the reaction. The mixture was filtered through a cotton-Celite pad to remove MSV 5A. After extraction of the aq filtrate, the organic layer was successively washed with satd aq $NaHCO_3$, $H_2O$, and brine. After the general drying procedure, a mixture of the crude product and NaOMe (26.4 mg, 490 μmol) in MeOH (3.26 mL) was stirred for 1 h at rt. After addition of 1 M hydrochloric acid (2 mL), the reaction mixture was extracted. The organic layer was successively washed with 1 M hydrochloric acid, $H_2O$, and brine. After the general drying procedure, a crude product (66.9 mg) was obtained as a yellow solid. $^1H$ NMR spectrum of the crude product showed that yields of phenyl 1-thio-3,6-*O*-(*o*-xylylene)-α-D-glucopyranoside (α-**8**) and β-**8** were 13% and 30%, respectively. A part of β-**8** was

separated by recrystallization from a mixture of $CHCl_3$ and *n*-hexane. Pure α-**8** was obtained by HPLC (column, RMC-Pack R&D SIL, D-SIL-5-A, 250 mm × 20 mm; eluent, *n*-hexane/EtOAc = 3:1; flow rate, 13.0 mL/min; detection, UV 254 nm; retention time, 50 min) followed by recrystallization from a mixture of $CHCl_3$ and *n*-hexane.

Data for α-**8** mp 164.1–165.7 °C; $[\alpha]_D^{22}$ −30.9 (*c* 0.27, $CHCl_3$); IR 3382, 3060, 3008, 2935, 2878, 1088, 1011, 755 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 22.5 °C) δ 7.47–7.45 (m, 2H), 7.35–7.20 (m, 7H), 5.39 (d, *J* = 1.4 Hz, 1H), 5.00 (d, *J* = 13.3 Hz, 1H), 4.88 (d, *J* = 10.3 Hz, 1H), 4.62 (d, *J* = 10.3 Hz, 1H), 4.56 (d, *J* = 13.3 Hz, 1H), 4.31 (br dd, *J* = 9.9, 7.1 Hz, 1H), 4.23 (br s, 1H), 4.15 (dd, *J* = 9.9, 9.6 Hz, 1H), 4.00 (ddd, *J* = 6.6, 6.6, 1.4 Hz, 1H), 3.97 (br d, *J* = 6.6 Hz, 1H), 3.92 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.61 (d, *J* = 6.6 Hz, 1H), 3.13 (d, *J* = 7.1 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 23.0 °C) δ 137.3, 135.7, 134.6, 131.4, 131.0 (2C), 130.2, 129.3, 129.1, 128.5, 127.3, 81.9, 78.5, 74.7, 74.2, 71.5, 70.6, 68.1, 63.6; ESIHRMS (*m*/*z*) calcd for $C_{20}H_{22}O_5SNa$ $[M+Na]^+$ 397.1086, found 397.1080.

Data for β-**8** mp 102.8–104.9 °C; $[\alpha]_D^{25}$ −73.2 (*c* 0.50, $CHCl_3$); IR 3384, 2870, 1109, 1078, 1052, 1024, 958, 740 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 25.1 °C) δ 7.50–7.47 (m, 2H), 7.29–7.14 (m, 7H), 5.56 (d, *J* = 9.9 Hz, 1H), 5.22 (d, *J* = 10.3 Hz, 1H), 4.84 (d, *J* = 8.7 Hz, 1H), 4.71 (br s, 1H), 4.40 (d, *J* = 10.3 Hz, 1H), 4.31 (d, *J* = 9.9 Hz, 1H), 4.03 (br d, *J* = 3.2 Hz, 1H), 3.87 (dd, *J* = 13.7, 3.2 Hz, 1H), 3.81 (br d, *J* = 13.7 Hz, 1H), 3.80 (br s, 1H), 3.69 (dd, *J* = 8.7, 0.7 Hz, 1H); $^{13}C$ NMR ($CD_3OD$, 25.4 °C) δ 138.5, 138.3, 136.3, 131.8 (2C), 130.3, 129.8 (2C), 129.5, 128.7, 128.6, 128.1, 88.0, 87.7, 81.4, 75.7, 75.1, 71.5, 71.4, 64.6; ESIHRMS (*m*/*z*) calcd for $C_{20}H_{22}O_5SNa$ $[M+Na]^+$ 397.1086, found 397.1102.

### 1.2.3. Examinations listed in Table 1

*Entry 1*: To a stirred mixture of MSV 5A (489 mg), **3** (50.0 mg, 163 μmol), and PhSH (25.2 mg, 229 μmol) in DCM (1.6 mL) was added TMSOTf (36.3 mg, 163 μmol) at −50 °C. The mixture was stirred for 48 h at −50 °C. After addition of satd aq $NaHCO_3$ (2 mL), the reaction mixture was filtered through a cotton-Celite pad to remove MSV 5A. After extraction of the aq filtrate, the organic layer was successively washed with satd aq $NaHCO_3$, $H_2O$, and brine. The general drying procedure gave a crude product. A mixture of the crude product and NaOMe (26.4 mg, 490 μmol) in MeOH (3.3 mL) was stirred for 1 h at rt. After addition of 1 M hydrochloric acid (2 mL), the aq mixture was extracted. The organic layer was successively washed with 1 M hydrochloric acid, $H_2O$, and brine. The general drying procedure gave a crude product. $^1H$ NMR spectrum of the crude product showed that the yields of α-**8** and β-**8** were 4% and 80%, respectively; the anomeric ratio was α/β = 5/95.

*Entry 2*: In a reaction similar to that described for Table 1, entry 1, the reaction temperature and time for the first step of this procedure were changed to −40 °C and 10 h, respectively, to provide a crude product containing **8**. The NMR yield of **8** was 88% (α/β = 3/97). Purification by CC (2 g of $SiO_2$, *n*-hexane/EtOAc = 5:1 to 2:1) afforded β-**8** (50.1 mg, 82%) as a white powder.

*Entry 3*: In a reaction similar to that described for Table 1, entry 1, the reaction temperature and time for the first step of this procedure were changed to −30 °C and 4 h, respectively, to provide a crude product containing **8**. The NMR yield of **8** was 79% (α/β = 5/95).

*Entry 4*: In a reaction similar to that described for Table 1, entry 1, the reaction temperature and time for the first step of this procedure were changed to −20 °C and 1.5 h, respectively, to provide a crude product containing **8**. The NMR yield of **8** was 76% (α/β = 7/93).

*Entry 5*: In a reaction similar to that described for Table 1, entry 1, the reaction temperature and time for the first step of this procedure were changed to 0 °C and 0.75 h, respectively, to provide a crude product containing **8**. The NMR yield of **8** was 44% (α/β = 12/88).

*Entry 6*: In a reaction similar to that described for Table 1, entry 1, the reaction temperature and time for the first step of this procedure were changed to 23 °C and 0.5 h, respectively, to provide a crude product containing **8**. The NMR yield of **8** was 14% (α/β = 22/78).

### 1.2.4. Examinations listed in Table 2

*Entry 1*: To a stirred mixture of MSV 5A (978 mg), **3** (100 mg, 326 μmol), and $C_2H_5SH$ (28.3 mg, 456 μmol) in DCM (3.3 mL) was added TMSOTf (72.5 mg, 326 μmol) at −40 °C. The mixture was stirred for 13 h at −40 °C. After addition of satd aq $NaHCO_3$ (2 mL), the mixture was filtered through a cotton-Celite pad to remove MSV 5A. After extraction of the aq filtrate, the organic layer was successively washed with satd aq $NaHCO_3$, $H_2O$, and brine. The general drying procedure gave a crude product. A mixture of the crude product and NaOMe (52.8 mg, 978 μmol) in MeOH (6.6 mL) was stirred for 1 h at rt. Amberlite IR 120 ($H^+$) ion exchange resin was added until the pH of the mixture was neutral. After filtration of the mixture through a cotton pad, the filtrate was concentrated to give a crude product containing ethyl 1-thio-3,6-*O*-(*o*-xylylene)-D-glucopyranoside (**15**). The NMR yield of β-**15** was 5%. CC (5 g of $SiO_2$, *n*-hexane/EtOAc = 5:1 to 2:1) separated a part of β-**15** in pure form $[\alpha]_D^{24}$ +16.4 (*c* 0.225, $CHCl_3$); IR 3380, 2928, 2870, 1114, 1023, 962 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 20 °C) δ 7.21–7.11 (m, 4H), 5.56 (d, *J* = 10.0 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.79 (br s, 1H), 4.49 (d, *J* = 8.4 Hz, 1H), 4.42 (d, *J* = 10.4 Hz, 1H), 4.33 (d, *J* = 10.0 Hz, 1H), 4.06 (br d, *J* = 2.4 Hz, 1H), 3.90 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.86–3.80 (m, 3H), 2.75–2.64 (m, 3H), 2.53 (br s, 1H), 1.29 (t, *J* = 7.6 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 20 °C) δ 137.0, 136.3, 129.5, 128.7, 127.9, 127.8, 86.9, 84.8, 78.5, 75.0, 74.5, 71.0, 70.5, 64.8, 25.0, 15.2; ESIHRMS (*m*/*z*) calcd for $C_{16}H_{22}O_5SNa$ $[M+Na]^+$ 349.1086, found 349.1086.

*Entry 2*: In a reaction similar to that described for Table 2, entry 1, the use of 1-dodecanethiol (92.4 mg, 456 μmol) provided a crude product containing dodecyl 1-thio-3,6-*O*-(*o*-xylylene)-D-glucopyranoside (**16**). The NMR yield of β-**16** was 24%. CC (5 g of $SiO_2$, *n*-hexane/EtOAc = 5:1 to 2:1) separated a part of β-**16** in pure form $[\alpha]_D^{23}$ +2.03 (*c* 1.0, $CHCl_3$); IR 3395, 2923, 2853, 1118, 964, 751 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 20 °C) δ 7.21–7.11 (m, 4H), 5.55 (d, *J* = 10.0 Hz, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 4.75 (br s, 1H), 4.45 (d, *J* = 8.0 Hz, 1H), 4.41 (d, *J* = 10.0 Hz, 1H), 4.32 (d, *J* = 10.0 Hz, 1H), 4.03 (br d, *J* = 2.4 Hz, 1H), 3.88 (dd, *J* = 13.4, 3.0 Hz, 1H), 3.84–3.78 (m, 3H), 2.83 (d, *J* = 7.6 Hz, 1H), 2.74 (d, *J* = 5.6 Hz, 1H), 2.68–2.64 (m, 2H), 1.66–1.58 (m, 2H), 1.36–1.20 (m, 18H), 0.88 (t, *J* = 7.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 20 °C) δ 140.0, 136.3, 129.4, 128.7, 127.9, 127.8, 86.9, 85.0, 78.5, 75.0, 74.6, 71.0, 70.5, 64.7, 32.0, 31.0, 30.1, 29.8, 29.7, 29.7, 29.6, 29.5, 29.3, 29.0, 22.8, 14.2; ESIHRMS (*m*/*z*) calcd for $C_{26}H_{42}O_5SNa$ $[M+Na]^+$ 489.2651, found 489.2644.

*Entry 4*: In a reaction similar to that described for Table 2, entry 1, the use of 2-methylbenzenethiol (56.6 mg, 456 μmol) provided a crude product containing *o*-tolyl 1-thio-3,6-*O*-(*o*-xylylene)-D-glucopyranoside (**17**). The NMR yield of β-**17** was 29%. CC (5 g of $SiO_2$, *n*-hexane/EtOAc = 5:1 to 2:1) separated a part of β-**17** in pure form $[\alpha]_D^{25}$ −20 (*c* 0.16, $CHCl_3$); IR 3395, 3017, 2924, 2857, 1112, 1051, 1025, 748 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 20 °C) δ 7.49–7.45 (m, 1H), 7.24–7.09 (m, 7H), 5.62 (d, *J* = 10.4 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 4.84 (br s, 1H), 4.78 (d, *J* = 8.4 Hz, 1H), 4.44 (d, *J* = 10.0 Hz, 1H), 4.35 (d, *J* = 10.4 Hz, 1H), 4.12 (d, *J* = 2.4 Hz, 1H), 3.96–3.85 (m, 3H), 3.88 (br s, 1H), 2.63 (d, *J* = 8.0 Hz, 1H), 2.40 (s, 3H), 2.38 (d, *J* = 5.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 20 °C) δ 138.6, 137.0, 136.2, 134.2, 130.2, 129.4, 129.1, 128.7, 127.9, 127.8, 127.1, 126.6, 86.7, 86.5, 78.5, 75.0, 74.4, 71.1, 70.4, 64.9, 20.8; ESIHRMS (*m*/*z*) calcd for $C_{21}H_{24}O_5SNa$ $[M+Na]^+$ 411.1242, found 411.1238.

*Entry 5*: In a reaction similar to that described for Table 2, entry 1, the use of 4-methylbenzenethiol (56.6 mg, 456 μmol) provided a crude product containing *p*-tolyl 1-thio-3,6-*O*-(*o*-xylylene)-D-glucopyranoside (**18**). The NMR yield of β-**18** was 29%. CC (5 g of $SiO_2$, *n*-hexane/EtOAc = 5:1 to 2:1) separated a part of β-**18** in pure form: $[\alpha]_D^{22}$ −33.5 (*c* 0.88, $CHCl_3$); IR 3396, 3018, 2923, 2870, 1118, 1026, 754 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 20 °C) $\delta$ 7.37 (d, *J* = 7.6 Hz, 2H), 7.23–7.17 (m, 2H), 7.15–7.09 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 5.57 (d, *J* = 10.0 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.73–4.67 (m, 2H), 4.36 (d, *J* = 10.4 Hz, 1H), 4.35 (d, *J* = 10.0 Hz, 1H), 4.01 (br s, 1H), 3.85 (br d, *J* = 0.8 Hz, 2H), 3.85–3.81 (br m, 1H), 3.76 (br d, *J* = 2.8 Hz, 1H), 3.01 (d, *J* = 8.0 Hz, 1H), 2.87 (d, *J* = 4.8 Hz, 1H), 2.27 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 20 °C) $\delta$ 137.6, 137.0, 136.3, 131.5 (2C), 130.7, 129.7 (2C), 129.4, 128.8, 127.9, 127.8, 87.6, 86.6, 78.6, 75.0, 74.2, 71.0, 70.4, 64.7, 21.2; ESIHRMS (*m*/*z*) calcd for $C_{21}H_{24}O_5SNa$ $[M+Na]^+$ 411.1242, found 411.1249.

*Entry 6*: In a reaction similar to that described for Table 2, entry 1, the use of 4-nitrobenzenthiol (71.0 mg, 456 μmol) provided a crude product. The reaction time was 24 h for the first step of this procedure. $^1H$ NMR spectra did not show the existence of the desired product *p*-nitrobenzyl 1-thio-3,6-*O*-(*o*-xylylene)-D-glucopyranoside (**19**).

### 1.2.5. Gram-scale synthesis of 8 (Scheme 3)

A mixture of **3** (3.50 g, 11.4 mmol), PhSH (1.76 g, 16.0 mmol), and MSV 5A (34.3 g) in DCM (114 mL) was stirred for 30 min at rt. After the mixture had cooled to −40 °C, to the mixture was added TMSOTf (2.54 g, 11.4 mmol). The mixture was stirred for 24 h at −40 °C. Addition of satd aq $NaHCO_3$ (150 mL) quenched the reaction. The reaction mixture was filtered through a cotton-Celite pad to remove MSV 5A. The aq mixture was extracted, and the organic layer was successively washed with satd aq $NaHCO_3$, $H_2O$, and brine. After the general drying procedure, the crude product was stirred with NaOMe (1.85 g, 34.3 mmol) in MeOH (229 mL) for 1 h at rt. Addition of 1 M hydrochloric acid (200 mL) quenched the reaction. After extraction of the reaction mixture, the organic layer was successively washed with 1 M hydrochloric acid, $H_2O$, and brine. After the general drying procedure, PhSH was removed from the crude product by short CC (70 g of $SiO_2$, *n*-hexane/EtOAc = 1:0 to 2:1). The fractions that contained **8** were concentrated. Pure β-**8** (3.00 g, 70%) was obtained through recrystallization from a mixture of $CHCl_3$ and *n*-hexane as a white powder.

### 1.2.6. 2,4-Di-*O*-benzyl-3,6-*O*-(*o*-xylylene)-D-glucopyranosyl fluoride (1)

To a solution of thioglycoside β-**7** (16.0 mg, 28.8 μmol) in DCM (500 μL) was added $Et_2NSF_3$ (7.3 mg, 45 μmol) at −15 °C, and the mixture was stirred for 2 min. To this mixture was added NBS (7.0 mg, 39 μmol) at −15 °C, and the mixture was stirred for 30 min at the same temperature. EtOAc (15 mL) was added to the mixture to dilute, and the mixture was poured into satd aq $NaHCO_3$ (10 mL) on ice. The organic layer was separated and successively washed with satd aq $NaHCO_3$, $H_2O$, and brine. After the general drying procedure, the resulting crude product was purified by CC (2 g of $SiO_2$, *n*-hexane/EtOAc = 9:1) to afford **1** (12.7 mg, 95%) as a mixture of anomers (α/β = 18/82). The $^1H$ and $^{13}C$ NMR spectral data were identical to those of the reported data.[24]

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2014.10.004.

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