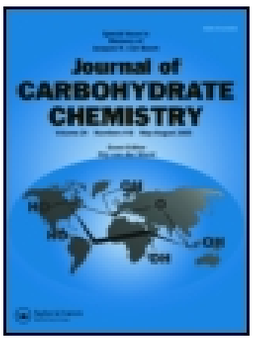

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Evaluating the reactivity and stereoselectivity of salicyl-type thioglycosides as non-malodorous thioglycoside alternatives for oligosaccharide synthesis

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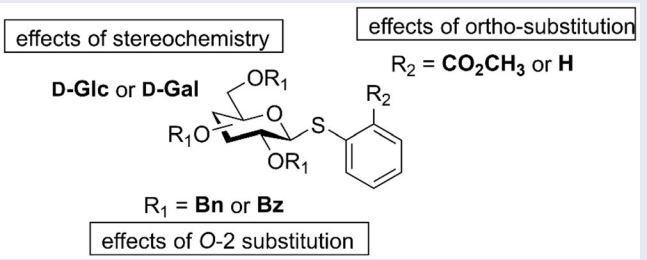
ABSTRACT

Herein, *o*-(methoxycarbonyl)phenyl thioglycosides [or (methyl)-salicyl 1-thioglycosides] were evaluated as non-malodorous thioglycoside alternatives. The *o*-methoxycarbonyl group was expected to assist in the departure of leaving group. Salicyl-type thioglycosides exhibited high reactivity and glycosylation yields when *N*-iodosuccinimide and trifluoromethanesulfonic acid were used as promoters. Glycosylation with these thioglycosides in dichloromethane showed similar reactivity and stereoselectivity as those of phenyl thioglycosides. Glycosylation with *per-O*-benzyl salicyl-type thioglycosides in dichloromethane showed 1,2-*cis*-selectivity, while the same reaction in nitriles afforded predominantly 1,2-*trans* glycosides. In contrast, glycosylation with *per-O*-benzoyl thioglycosides afforded exclusively 1,2-*trans* glycosides. These results strongly suggest that salicyl-type thioglycosides can serve as non-malodorous alternatives for phenyl thioglycosides.

GRAPHICAL ABSTRACT



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Introduction

Since the importance of glycoconjugates has been recognized in diverse biological processes,[1] the development of practical methods for their

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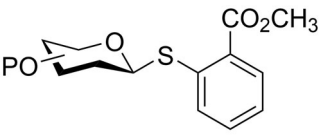
synthesis is strongly desired to evaluate their biological functions based on precise and exact molecular information. Among the chemical methodologies for carbohydrate synthesis, glycosylation procedures have attracted considerable attention because the anomeric configuration along with the location of the glycosidic bond are crucial for the structure-activity relationships of glycoconjugates. The current glycosylation methodologies involve the activation of a sugar unit with a leaving group at the anomeric position (glycosyl donor) in the presence of an appropriately protected sugar unit with a free hydroxyl group (glycosyl acceptor). The stereoselectivity of glycosylation is controlled by several factors, such as the type of solvent and the reaction temperature. The structure of glycosyl donor and the chemical properties of leaving and protecting groups, in particular, are also crucial factors for determining the configuration. Therefore, carbohydrate chemists have devoted significant efforts to the development of various glycosyl donors for controlling the stereoselective formation of glycosidic bonds. Thioglycosides such as aryl and alkyl thioglycosides, along with glycosyl halides and imidates, have been extensively employed as glycosyl donors for the construction of both 1,2-*trans* and 1,2-*cis* glycosides[2] owing to their high chemical stability during regioselective protection of the parent sugar unit. Furthermore, thioglycosides can be readily synthesized by treatment of a thiol with a *per*-*O*-acetylated sugar in the presence of an appropriate acid or with a glycosyl bromide under basic conditions. One of the most remarkable features of thioglycosides is that their thioglycosidic bonds can be orthogonally activated by multiple thiophiles, such as halogen and alkyl cations, in the presence of glycosyl acceptors bearing a heterogeneous aglycon. This feature allows for sequential glycosylation reactions.

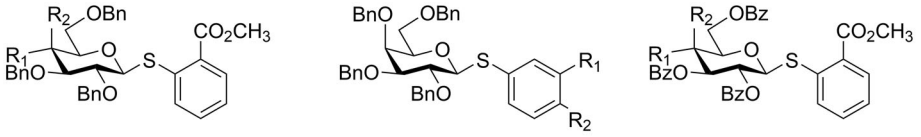
However, from a practical viewpoint, the unpleasant smell arising from the mercaptans during the preparation of the thioglycosides is a major impediment in the use of these glycosyl donors for oligosaccharide synthesis. To overcome this problem, several studies have been conducted on the odorless formation of thioglycosyl donors[3] such as using tolyl,[4–8] lauryl,[9,10] (2-methyl-5-*tert*-butyl)phenyl[11–13] and alkylphenyl[14,15] thioglycosides. In our efforts to develop a novel class of non-malodorous thioglycosides, we focused on methyl thiosalicylate. Most alkyl and aryl thiols possess an unpleasant odor, even those with high boiling points. In contrast, methyl thiosalicylate has an inoffensive odor, which somewhat resembles the odor of methyl salicylate.

Using methyl thiosalicylate, we have previously reported non-malodorous thioglycosides **1** (Fig. 1), which can be prepared without the emission of an unpleasant odor and has been shown to serve as a glycosyl donor in a manner similar to conventional thioglycosides.[16] These thioglycosides



1

Figure 1. Non-malodorous salicyl-type phenylthioglycosides **1**.



2: R_1=H, R_2=OBn
3: R_1=OBn, R_2=H

4: R_1=CO_2CH_3, R_2=H
5: R_1=H, R_2=CO_2CH_3

6: R_1=H, R_2=OBz
7: R_1=OBz, R_2=H

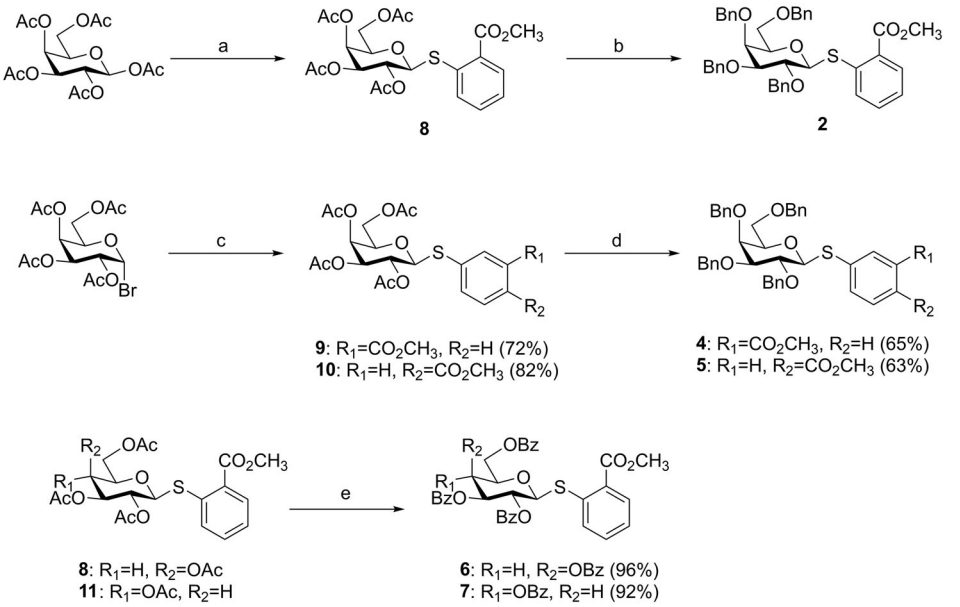
Figure 2. Designed (methoxycarbonyl)phenyl thioglycosides **2**–**7**.

allowed us to synthesize bioactive oligosaccharides, e.g., globo-series[17] and LewisX[18] oligosaccharides, and glycoglycerolipids.[19] To confirm the wide applicability of our non-malodorous thioglycosides for oligosaccharide synthesis, extensive investigation of their behavior in glycosylation reactions under various conditions is important.

In this study, we prepared a series of salicyl-type thioglycosides with either benzyl or benzoyl protecting groups and subjected them to glycosylation with glycosyl acceptors having primary or secondary alcohols under various conditions. Their reactivity and stereoselectivity were compared with those of the corresponding phenyl thioglycosides and regioisomeric *m*- and *p*-(methoxycarbonyl)phenyl thioglycosides.

Results and discussion

Previously, we demonstrated that *per*-*O*-benzyl salicyl-type thioglycosides can serve as glycosyl donors to promote 1,2-*trans* glycosylation of a primary alcohol at a low temperature; however, the use of sterically hindered secondary alcohols afforded 1,2-*cis* glycosylation.[16–19] The details of these reactions, particularly the promoter sensitivity, temperature dependence of stereoselectivity and reactivity, remain unclear. Therefore, *o*-(methoxycarbonyl)phenyl thioglycosides **2**[16,17] and **3**[19] (Fig. 2), as well as *m*- and *p*-(methoxycarbonyl)phenyl thioglycosides **4** and **5**, were prepared to investigate the effect of the methoxycarbonyl group on the reactivity and stereoselectivity in glycosylation. Moreover, the 2-*O*-acyl group-assisted 1,2-*trans* glycosylation of our non-malodorous phenyl thioglycosides has not yet been investigated. Hence, *per*-*O*-benzoyl salicyl-type thioglycosides **6** and **7** were prepared to demonstrate the wide applicability of

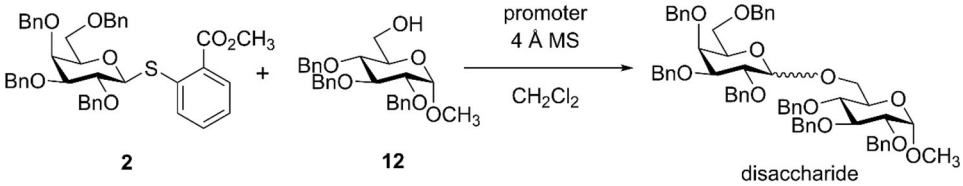


Scheme 1. *Reagents and conditions*: (a) methyl thiosalicylate, $BF_3{\cdot}OEt_2$, CH_2Cl_2, r.t, 2 h, 79%; (b) (i) NaOMe, MeOH, r.t., 3 h (ii) BnBr, NaH, DMF, 0 °C→r.t., 24 h, 79% (2 steps); (c) 3- or 4-mercaptobenzoate, K_2CO_3, DMF, r.t., 2–4 h, 72–82%; (d) (i) NaOMe, MeOH, r.t., 4 h (ii) BnBr, NaH, DMF, 0 °C→r.t., 14–19 h, 63–65% (2 steps); (e) (i) NaOMe, MeOH, r.t., 2 h (ii) BzCl, Py, 0 °C→r.t., 12 h, 92–96% (2 steps).

o-(methoxycarbonyl)phenyl thioglycosides for oligosaccharide synthesis including 1,2-*trans* glycosylation.

Per-O-benzylated galactosyl thioglycoside **2** was prepared from *per-O*-acetyl-β-galactopyranose (Scheme 1). The *prr-O*-acetate was treated with methyl thiosalicylate in the presence of $BF_3{\cdot}OEt_2$ to afford the corresponding thiogalactoside **8**, and the acetyl groups in each thioglycoside were then converted to benzyl groups via deacylation and benzylation to afford **2**. During benzylation, an undesired, transesterified byproduct was generated, possibly because of the poor stability of the methyl ester group under strongly basic conditions (NaH/BnBr), resulting in a poor yield of **2**. This could be avoided by the prolonged stirring of reaction mixture after quenching of the reaction upon addition of excess methanol, which promotes transesterification to produce the desired methyl ester **2**. $BF_3{\cdot}OEt_2$ catalyzed thioglycosydation using methyl 3- and 4-mercaptobenzoates was unsuccessful because of dimerization of the mercaptobenzoates; therefore, *m*- and *p*-(methoxycarbonyl)phenyl isomers **4** and **5** were prepared via galactosyl bromide. Galactosyl bromide was reacted with methyl mercaptobenzoate in the presence of K_2CO_3 to afford the corresponding *m*- and *p*-(methoxycarbonyl)phenyl thiogalactosides **9** and **10**, respectively, which were subsequently converted to furnish *m*- and *p*-(methoxycarbonyl) phenyl thiogalactosides **4** and **5** on deacylation and then benzylation.

Table 1. Promoter sensitivity of salicyl thiogalactoside **2**.



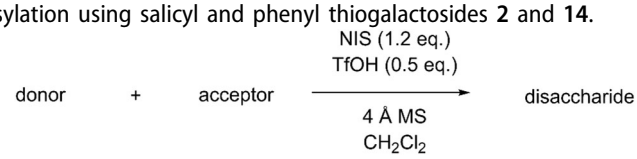
Entry	Promoter (eq)	Temp. °C	Time	Yield %	α/β[b]
1	NIS (1.2) / TfOH (0.1)	−78	48 h	83	1/3.9
2	NIS (1.2) / TfOH (0.5)	−78	30 min	>99	1/6.7
3	NBS (1.5)	0	24 h	19	4/1
4	AgOTf (1.0)	0	48 h	n.r.[a]	-[c]
5	$Cu(OTf)_2$ (1.0)	0	48 h	5	2.8/1
6	TMSOTf (1.0)	0	48 h	n.r.[a]	-[c]
7	MeOTf (3.0)	r.t,	5 h	88	1.9/1

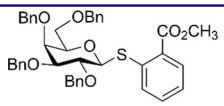
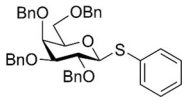
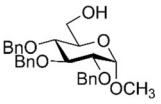
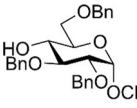
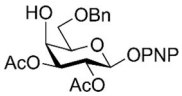
[a]Not reacted.
[b]Determined by ^{1}H NMR. [c]Not determined.

Per-O-benzoylated thioglycosides **6** and **7** were obtained from *per-O*-acetates **8** and **11**,[19] respectively, via successive deacetylation and benzoylation reactions.

With the designed non-malodorous thioglycosides in hand, the glycosylation of alcohols with (*o*-methoxycarbonyl)phenyl thioglycosides **2** and **4**–**7** was investigated and their reactivity and stereoselectivity were compared to the glycosylation reactions using corresponding phenyl thioglycosides. Initially, *per-O*-benzylated *o*-(methoxycarbonyl)phenyl thioglycoside **2** was subjected to glycosylation of glucoside **12** with a primary alcohol[20] in dichloromethane using a series of Lewis acids, which have been reported to serve as promoters for several glycosyl donors (Table 1). A combination of *N*-iodosuccinimide (NIS, 1.2 eq.) and trifluoromethanesulfonic acid (TfOH, 0.1 eq.), a typical promoter for phenyl thioglycosides, activated **2** at −78 °C to afford the desired disaccharide (entry 1). The disaccharide could be easily separated from methyl thiosalicylate residue by silica gel column chromatography. However, some amount of donor **2** remained unreacted even after 48 h, resulting in an insufficient yield of glycosylation product. Using a greater amount of TfOH (0.5 eq.) solved this problem, leading to the formation of the disaccharide in a good yield, even at a low temperature (entry 2). Note that large amount of TfOH obviously increased the β-selectivity. This phenomenon might be attributed to increase of an α-triflate, which assists S_N2-like substitution by the reactive primary alcohol. *N*-Bromosuccinimide (NBS) promoted glycosylation resulted in poor yield because of the presence of inseparable side products such as *N*-succinimidyl glycoside (entry 3). Metal triflates such as AgOTf and $Cu(OTf)_2$, which have been reported as excellent promoters for *S*-benzoxazolyl (SBox) glycosides,[21] were inactive for **2** (entries 4 and 5). Similarly, trimethylsilyl

Table 2. Glycosylation using salicyl and phenyl thiogalactosides **2** and **14**.



Entry	Donor	Acceptor	Temp. °C	Time	Yield %	α/β[a]
1			0	15 min	>99	1/1.4
	2					
2			0	5 min	>99	1/1.3
	14	**12**				
3	**2**		−78	30 min	>99	1/6.7
4	**14**		−78	30 min	72	1/12
5	**2**		0	15 min	61	2.1/1
6	**14**		0	5 min	69	3.3/1
7	**2**		−78	1.5 h	73	1/1.1
8	**14**		−78	30 min	85	1.1/1
		13				
9[b]	**2**		0	1 h	89	4.9/1
		15				

[a]Determined by ^{1}H NMR.
[b][16].

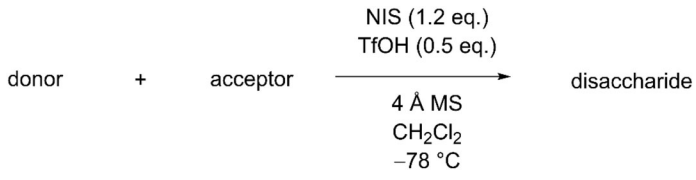
trifluoromethanesulfonate (TMSOTf), a typical promoter of glycosyl imidates, was unable to activate *o*-(methoxycarbonyl)phenyl thioglycosides either (entry 6). For the phenyl thioglycosides, methyl triflate acted as a promoter to afford the disaccharide in excellent yield (entry 7). These results indicated that the non-malodorous thioglycoside **2**, despite having a methoxycarbonyl group at the ortho position of the thioether, was able to undergo an activation mechanism similar to that of conventional phenyl thioglycosides, i.e., via activation of the thioether by halogen cations.

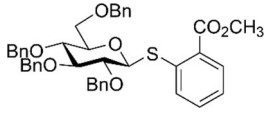
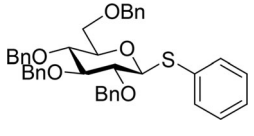
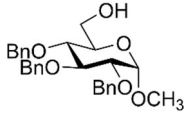
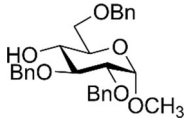
Considering the promoter sensitivity of our non-malodorous thioglycosides, glucosides with primary and secondary hydroxyl groups **12** and **13**[20] were subsequently coupled with thioglycosides **2**, as well as phenyl thioglycosides **14**, [22] using the NIS/TfOH system. The yields and α/β ratios of the resulting disaccharides are listed in Table 2. The glycosylation reaction was conducted using 1.2 eq. of glycosyl donor (with respect to glycosyl acceptor) along with a combination of NIS and TfOH (1.2 and 0.5 eq., respectively). Glycosylation with *per*-*O*-benzylated galactosyl donor **2**

slightly favored the formation of β-anomer at 0 °C (α/β = 1/1.4, entry 1). This tendency became more evident at lower temperatures, and higher β-selectivity (α/β = 1/6.7) was observed at −78 °C (entries 1 and 2). Glycosylation with **14** at −78 °C showed slightly higher β-selectivity than that with **2** (α/β = 1/12, entry 4). Although 4-*O*-benzyl group of galactosyl donors **2** and **14** blocks the β-face to promote α-glycosylation, glycosylations at low temperatures showed excellent β-selectivity. These result were presumably originated from the predominance of S_N2-like substitution with glycosyl α-triflate, whose chemical stability is much higher at low temperatures. In contrast to glycosylation of primary alcohol **12**, glycosylation of secondary alcohol **13** with **2** showed α-selectivity. These glycosylation reactions were expected to show α-selectivity because the steric effect of 4-*O*-benzyl group affects strongly against secondary alcohols. However, when the reaction was conducted at a lower temperature, the reaction showed β-selectivity (entries 5 and 7). As in the case of glycosylation with a primary alcohol, the observed β-selectivity can also be rationalized by the enhancement of the stability of the α-glycosyl triflate to promote S_N2-like nucleophilic substitution. These results are contrary to our previous observation that the glycosylation of a sterically hindered secondary alcohol favors the formation of α-glycoside. For example, glycosylation of galactosyl acceptor **15** with galactosyl donor **2** at 0 °C showed α-selectivity (α/β = 4.9/1, entry 9).[16] This contradiction can be attributed to the different reactivities of the acceptor alcohols. In galactosyl acceptor **15** with a 4-OH, which showed high α-selectivity, the hydroxyl group was in the axial position, and an electron-withdrawing acetyl group was at the neighboring 3-*O* position. These factors remarkably decreased the reactivity of the alcohol. Compared to glycosyl acceptor **13**, which had an equatorial hydroxyl group with an electron-donating benzyl group at the neighboring 3-*O* position, **15** was endowed with sufficient reactivity to induce S_N2-like substitution with the unstable β-triflate during *in situ* anomerization, although the reactivity was insufficient to react with the more stable α-triflate. In contrast, phenyl thiogalactoside **14** showed slightly higher reactivity than salicyl-type thioglycoside **2** in glycosylation with secondary alcohol **13** (entries 7 and 8). This difference in reactivity could be explained by the fact that the electron-withdrawing *o*-methoxycarbonyl group of **2** decreased the electron density on the sulfur atom.

Next, glycosylation reactions of gluco-type thioglycoside **3** were examined at −78 °C and the results are presented in Table 3. Overall, glycosylation with glucose donor **3** led to similar results as in the case of donor **2** except for the observation of higher β-selectivity at −78 °C (entry 1). This phenomenon is likely attributed to the higher chemical stability of glucosyl triflate than that of the galactosyl triflate. The reactivities of gluco-type

Table 3. Glycosylation using salicyl- and phenyl-type thioglucosides **3** and **16**.



Entry	Donor	Acceptor	Time h	Yield %	α/β[a]
1	 **3**		6	>99	1/13
2	 **16**	 **12**	2	95	1/8.4
3	**3**		10	85	1/2.3
4	**16**	 **13**	1	95	1/1.3

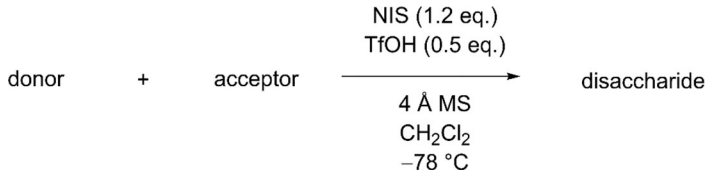
[a]Determined by ^{1}H NMR.

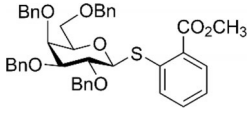
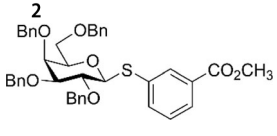
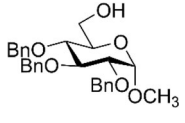
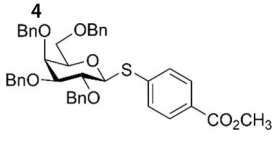
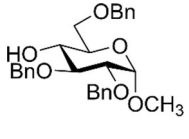
donors were obviously lower than those of galacto-type donors, probably due to the difference in the activation energy over the oxocarbenium intermediate. Unlike *o*-(methoxycarbonyl)phenyl thioglucoside **3**, phenyl thioglucoside **16**[22] was found to glycosylate **12** quickly even at −78 °C (entries 1 and 2). As in the case of primary alcohol, phenyl thioglucoside **16** also demonstrated higher reactivity than the salicyl-type thioglycoside **3** in glycosylation with the secondary alcohol **13** (entry 3 and 4). As shown in Tables 2 and 3, salicyl-type thioglycosides may show similar stereoselectivity and yields as phenyl thioglycosides, whereas salicyl-type thioglycosides displayed slightly lower reactivities than phenyl thioglycosides at low temperature. This result indicated the role of the *o*-methoxycarbonyl group in determining the reactivity in glycosylation.

To gain insights into the role of the *o*-methoxycarbonyl group in glycosylation, we investigated glycosylation using *m*- and *p*-(methoxycarbonyl)phenyl thioglycosides **4** and **5** at −78 °C and compared their reactivity and stereoselectivity with those of the *o*-isomer **2** (Table 4). Regardless of the type of glycosyl acceptor, *m*-isomer **4** showed the highest reactivity, which is comparable to those of phenyl thioglycoside (entries 2 and 5). This result can be rationalized by the fact that the electron-withdrawing methoxycarbonyl group in **4** is located at the *meta* position of the thioether group. In contrast, the reactivities of *o*- and *p*-isomers **2** and **5** were apparently different, possibly because the thioether group in these instances experienced a different magnitude of the electron withdrawal effect due to the methoxycarbonyl group. This phenomenon was probably due to the fact that the *o*-carbonylgroup in **2** formed an orthoester-like intermediate by the attack of carbonyl oxygen at the anomeric center, which assisted in the departure of the thioether group from the anomeric center of **2**, as is the case with a superarmed donor.[23]

We subsequently turned our attention to the applicability of the stereochemical regulation by solvent effects and 2-*O*-acyl participation in glycosylation using our non-malodorous phenyl thioglycosides (Table 5). The glycosylation of primary alcohol **12** with (*o*-methoxycarbonyl)phenyl thiogalactoside **2** was initially conducted in solvents such as nitriles and ethers that promote stereoselectivity. Compared to dichloromethane, acetonitrile enhanced β-selectivity when glycosylation was conducted at −35 °C (α/β = 1/9, entry 1), and the glycosylation in propionitrile at −60 °C further increased this tendency (α/β = 1/16, entry 2). The combination of cyclopentyl methyl ether and chloroform (3/1), which has been reported to induce 1,2-*cis*-selective glycosylation,[24] possibly promoted α-selective glycosylation (entry 3). For glycosylation of the secondary alcohol **13**, the use of nitriles as solvents drastically shifted the stereoselectivity toward the β-glycoside product (entry 4). Each glycosylation using glucosyl donor in acetonitrile or cyclopentyl methyl ether and chloroform (3/1) showed

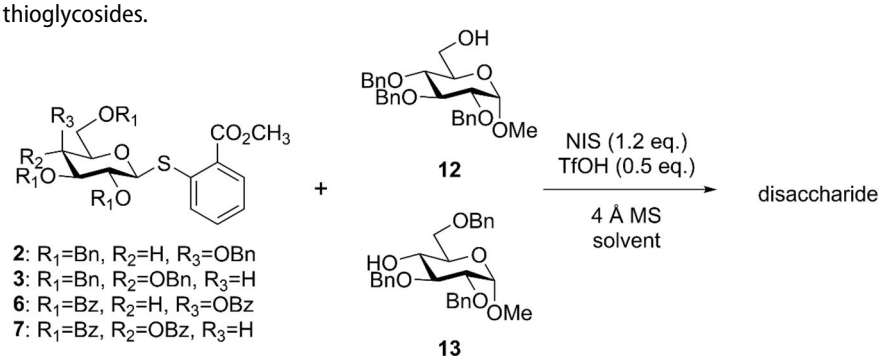
Table 4. Glycosylation using (methoxycarbonyl)phenyl thiogalactosides **2**, **4** and **5**.



Entry	Donor	Acceptor	Time	Yield %	α/β[a]
1	 **2**		30 min	>99	1/6.7
2	 **4**	 **12**	30 min	86	1/8
3	 **5**		3 h	86	1/8.1
4	**2**	 **13**	1.5 h	73	1/1.1
5	**4**		30 min	83	2.6/1
6	**5**		4 h	86	1.9/1

[a]Determined by ^{1}H NMR.

Table 5. Solvent effects and 2-*O*-acyl participation in glycosylation using nonmalodorous phenyl thioglycosides.



Entry	Donor	Acceptor	Solvent	Temp. °C	Time h	Yield %	α/β[a]
1	**2**	**12**	MeCN	−35	6	96	1/9
2	**2**	**12**	EtCN	−60	4.5	78	1/16
3	**2**	**13**	MeCN	−35	1.5	80	1/2.7
4	**2**	**12**	$CPME/CHCl_3$ (3/1)	r.t.	24	89	1.6/1
5	**3**	**13**	MeCN	−35	4	94	1/4.5
6	**3**	**12**	$CPME/CHCl_3$ (3/1)	r.t.	24	82	3.7/1
7	**6**	**12**	CH_2Cl_2	0	2.5	93	>1/19
8	**7**	**12**	CH_2Cl_2	0	1.5	88	>1/19
9	**6**	**13**	CH_2Cl_2	0	2.5	98	>1/19
10	**7**	**13**	CH_2Cl_2	0	1.5	97	>1/19

[a]Determined by ^{1}H NMR.

solvent effect to give β- or α-selectivity, respectively (entries 5 and 6). Then, neighboring group participation-assisted stereoselective glycosylation was confirmed using *per*-*O*-benzoylated non-malodorous phenyl thioglycosides. The *per*-*O*-benzoylated glycosyl donor **6** could be activated smoothly under the same conditions as for the *per*-*O*-benzylated analogues to glycosylate the primary alcohol **12**, giving exclusively the β-glycosylated disaccharide. A similar result was obtained using the glycose-type donor **7** ($\alpha/\beta > 1/19$, entries 7 and 8). Moreover, the glycosylation of secondary alcohol **13** with the *per*-*O*-benzoylated thioglycosides **6** and **7** proceeded stereoselectively to afford exclusively β-glycosides ($\alpha/\beta > 1/19$, entries 9 and 10). These results support the theory that salicyl-type thioglycosides undergo solvent effects and 2-*O*-acyl participation similar to conventional glycosyl donors. Although the reactivity was slightly lower, salicyl thioglycosides exhibited reaction behaviors similar to phenyl thioglycosides, indicating that our non-malodorous thioglycosides can be used for oligosaccharide synthesis. These results indicated that salicyl-type thioglycosides have great potential as non-malodorous phenyl thioglycoside alternatives for oligosaccharide synthesis.

Conclusion

In summary, a series of *o*-(methoxycarbonyl)phenyl thioglycosides were synthesized via an alternative pathway to access the previously reported *o*-(methoxycarbonyl)phenyl thiogalactoside using *per*-*O*-acetylated β-D-galactose and methyl thiosalicylate in the presence of $BF_3{\cdot}OEt_2$. A comprehensive investigation of their reactivity and stereoselectivity in glycosylation reactions has shown that all the salicyl-type thioglycosides can function as glycosyl donors when a combination of NIS and TfOH was used as the promoter. Although their reactivities were slightly lower than those of conventional phenyl thioglycosides, the resulting reaction yields and stereochemical outcomes were comparable to those of authentic thioglycosides. The *o*-methoxycarbonyl group of salicyl-type thioglycosides was expected to not only decrease the reactivity by the electron withdrawal effect but also assist in the departure of the thioether group by the formation of an orthoester-like intermediate. The stereoselectivities of the designed salicyl-type thioglycosides could be controlled by solvent effects and neighboring group participation of the 2-*O*-acyl group as well as the reaction temperature, promoting 1,2-*trans*- or 1,2-*cis*-selective glycosylation. Hence, the promising efficacy of our non-malodorous thioglycosides for oligosaccharide synthesis is expected to solve the problem of unpleasant odors arising during the preparation of thioglycosides. The investigation of modified salicyl-type thioglycosides and their use in the synthesis of oligosaccharides is in progress and these results will be reported elsewhere.

Experimental section

General methods

All reactions were carried out under a dry argon atmosphere. Yields refer to chromatographically and spectroscopically homogeneous material. Anhydrous solvents were purchased from Wako Pure Chemical Industries Co., Ltd. All other chemicals for the syntheses were purchased from Wako Pure Chemical Industries Co., Ltd. (Osaka, Japan), Sigma-Aldrich Co., or Tokyo Kasei Kogyo (Tokyo, Japan). Reagents were purchased at the highest commercial quality and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel 60-F_{254} precoated plates (Merck) using UV light and cerium sulfate/molybdic acid solution as visualizing agent. Silica gel BW-80S (average particle size 100 mesh, Fuji Silicia Chemical Co., Ltd.) or BW-300 (average particle size 60 mesh, Fuji Silicia Chemical Co., Ltd.) was employed for flash column chromatography.

NMR spectra were recorded with a JEOL ECA 500 spectrometer equipped with Delta 5.02. Unless otherwise stated, ^{1}H NMR (500 MHz) spectra were recorded at 25 °C using internal tetramethylsilane (TMS) at 0 ppm, and ^{13}C NMR (125 MHz) spectra were recorded at 125 MHz using internal $CDCl_3$ at 77.16 ppm. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Optical rotations were measured with a JASCO DIP 370 polarimeter. HRESIMS spectra were recorded on a ThermoFisher Exactive.

2-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside (8)

To a solution of penta-*O*-acetyl-β-D-galactopyranose (12.5 g, 31.9 mmol) and methyl thiosalicylate (17.6 mL, 128 mmol) in CH_2Cl_2 (319 mL) was added $BF_3{\cdot}OEt_2$ (4.0 mL, 31.9 mmol), and the reaction mixture was stirred at rt for 27 h. The reaction was quenched by addition of Et_3N and extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, hexane:EtOAc = 1:1) to give compound **8** (12.5 g, 79%) as a white crystal; $[\alpha]_D$ −22.5 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (dd, 1H, J = 1.4 and 7.6 Hz, Ar*H*), 7.65 (dd, 1H, J = 0.9 and 8.0 Hz, Ar*H*), 7.46 (dt, 1H, J = 1.6 and 7.4 Hz, Ar*H*), 7.30 (dt, 1H, J = 1.1 and 7.6 Hz, Ar*H*), 5.47 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 0.9 Hz, H-4), 5.37 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, H-2), 5.11 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.88 (d, 1H, $J_{1,2}$ = 10.1 Hz, H-1), 4.20 (dd, 1H, $J_{5,6a}$ = 7.2 Hz, J_{gem} = 11.4 Hz, H-6_a), 4.13 (dd, 1H, $J_{5,6b}$ = 5.8 Hz, J_{gem} = 11.2 Hz, H-6_b), 4.03 (br-dt, 1H, $J_{4,5}$ = 0.9 Hz, $J_{5,6a}$ = 7 Hz, H-5), 3.90 (s, 3H, C*H*$_3$OCOAr), 1.99, 2.05, 2.06 and 2.17 (s × 4, 12H, C*H*$_3$CO$_2$-); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.49, 170.34, 170.21, 169.43, 166.92, 136.92, 132.28, 130.88, 130.75, 129.41, 126.36, 84.89, 74.53, 72.16, 67.34, 66.96, 61.91, 52.33, 20.88, 20.81 × 2, 20.73; HRESIMS: Calcd for $C_{22}H_{26}O_{11}S$ $[M + NH_4]^+$ 516.1534; found 516.1523.

2-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-galactopyranoside (2)

To a solution of compound **8** (5.00 g, 10 mmol) in MeOH (80 mL) was added NaOMe (27 mg, 0.5 mmol), and the reaction mixture was stirred at rt for 3 h. The reaction was quenched by addition of Amberlite ion-exchange resin and the mixture was filtered. The filtrate was concentrated and the residue was coeveporated with toluene. To a solution of the residue in DMF (100 mL) was added NaH (2.4 g, 60 mmol) and BnBr (7.13 mL,

59.2 mmol) slowly at 0 °C, and the reaction mixture was stirred at rt for 24 h. The reaction was quenched by addition of MeOH, and EtOAc was added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, toluene:EtOAc = 50:1) to give compound **2** (5.43 g, 79% over 2 steps) as a white powder; $[\alpha]_D$ −30.5 (c 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, 1H, J = 1.8 and 7.5 Hz, Ar*H*), 7.78 (dd, 1H, J = 1.2 and 7.7 Hz, Ar*H*), 7.24–7.37 (m, 20H, Ar*H*), 7.17 (dt, 1H, J = 1.7 and 7.5 Hz, Ar*H*), 7.14 (dt, 1H, J = 1.4 and 7.7 Hz, Ar*H*), 4.99 (d, 1H, J_{gem} = 11.5 Hz, ArCH_2-), 4.72–4.80 (m, 4H, ArCH_2-), 4.77 (d, 1H, $J_{1,2}$ = 8.9 Hz, H-1), 4.61 (d, 1H, J_{gem} = 11.5 Hz, ArCH_2-), 4.49 (d, 1H, J_{gem} = 11.5 Hz, ArCH_2-), 4.41 (d, J_{gem} = 11.7 Hz, 1H, ArCH_2-), 4.04 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.5 Hz, H-2), 4.00 (br-d, 1H, J = 2.6 Hz, H-4), 3.86 (s, 3H, CH_3OCOAr), 3.62–3.68 (m, 4H, H-3, H-5, H-6a and H-6b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.02, 139.30, 138.78, 138.34, 138.23, 137.97, 132.45, 130.78, 129.23, 128.90, 128.57, 128.56, 128.38, 128.08, 128.05, 127.95, 127.85, 127.72, 125.10, 86.04, 84.25, 77.48, 77.37, 76.01, 74.60, 73.76, 73.69, 72.90, 69.10, 52.24; HRESIMS: Calcd for $C_{42}H_{46}O_7NS$ $[M + NH_4]^+$ 708.2989; found 708.2979.

3-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside (9)

To a solution of tetra-*O*-acetyl-α-D-galactopyranosyl bromide (6.66 g, 16.2 mmol) and methyl 3-mercaptobenzoate (3.34 g, 19.4 mmol) in DMF (84 mL) was added K_2CO_3 (3.45 g, 24.3 mmol), and the reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with EtOAc and the organic layer was washed with brine three times, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, toluene:EtOAc = 10:1) to give compound **9** (5.84 g, 72%) as a white solid; $[\alpha]_D$ −6.1 (c 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (t, 1H, J = 1.7 Hz, Ar*H*), 7.98 (dt, 1H, J = 1.4 and 7.8 Hz, Ar*H*), 7.71 (dq, 1H, J = 1.1, 2.0 and 8.0 Hz, Ar*H*), 7.41 (t, 1H, J = 7.7 Hz, Ar*H*), 5.43 (dd, 1H, $J_{3,4}$= 3.4 Hz, $J_{4,5}$= 0.86 Hz, H-4), 5.23 (t, 1H, $J_{1,2}$= $J_{2,3}$= 10.0 Hz, H-2), 5.06 (dd, 1H, $J_{2,3}$= 10.0 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.75 (d, 1H, $J_{1,2}$= 9.7 Hz, H-1), 4.20 (dd, 1H, $J_{5,6a}$= 7.2 Hz, J_{gem} = 11.5 Hz, H-6a), 4.14 (dd, 1H, $J_{5,6b}$= 6.3 Hz, J_{gem} = 11.5 Hz, H-6b), 3.97 (br-t, 1H, H-5), 3.93 (s, 3H, CH_3OCOAr), 1.98–2.12 (s × 4, 12H, CH_3CO$_2$-); ^{13}C NMR (125 MHz, $CDCl_3$): δ170.76, 170.52, 170.38, 169.77, 166.64, 137.10, 133.74, 133.42, 131.29, 129.57, 129.24, 86.53, 74.83, 67.50, 67.46, 61.09, 52.71, 21.18, 21.00, 20.95 × 2; HRESIMS: Calcd for $C_{22}H_{30}O_{11}NS$ $[M + NH_4]^+$ 516.1534; found 516.1533.

4-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside (10)

To a solution of tetra-*O*-acetyl-α-D-galactopyranosyl bromide (6.09 g, 14.8 mmol) and methyl 4-mercaptobenzoate (3.00 g, 17.8 mmol) in DMF (75 mL) was added K_2CO_3 (3.08 g, 22.3 mmol), and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with EtOAc and the organic layer was washed with brine three times, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, toluene:EtOAc = 10:1) to give compound **10** (6.06 g, 82%) as a white solid; $[\alpha]_D$ 5.7 (c 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (dt, 1H, J = 2.0 and 8.9 Hz, Ar*H*), 7.53 (dt, 1H, J = 1.7 and 7.8 Hz, Ar*H*), 5.46 (dd, 1H, $J_{3,4}$= 3.4 Hz, $J_{4,5}$= 0.9 Hz, H-4), 5.29 (t, 1H, $J_{1,2}$= $J_{2,3}$= 10.0 Hz, H-2), 5.09 (dd, 1H, $J_{2,3}$= 10.0 Hz, $J_{3,4}$= 3.44 Hz, H-3), 4.84 (d, 1H, $J_{1,2}$= 10.0 Hz, H-1), 4.20 (dd, 1H, $J_{5,6a}$= 7.2 Hz, J_{gem} = 11.5 Hz, H-6a), 4.14 (dd, 1H, $J_{5,6b}$= 5.7 Hz, J_{gem} = 11.5 Hz, H-6b), 4.01 (br-t, 1H, H-5), 3.92 (s, 3H, C*H*$_3$OCOAr), 1.99–2.15 (s × 4, 12H, C*H*$_3$CO$_2$-); ^{13}C NMR (125 MHz, $CDCl_3$): δ170.73, 170.50, 170.37, 169.76, 166.86, 139.67, 130.67, 130.31, 129.51, 85.87, 75.02, 72.22, 67.53, 67.33, 62.08, 52.61, 21.15, 21.07, 21.03, 20.93; HRESIMS: Calcd for $C_{22}H_{30}O_{11}NS$ $[M + NH_4]^+$ 516.1534; found 516.1536.

3-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-galactopyranoside (4)

To a solution of compound **9** (3.56 g, 7.14 mmol) in MeOH (50 mL) was added NaOMe (19 mg, 0.36 mmol), and the reaction mixture was stirred at rt for 4 h. The reaction was quenched by addition of Amberlite ion-exchange resin and the mixture was filtered. The filtrate was concentrated and the residue was coevaporated with toluene under diminished pressure. To a solution of the residue in DMF (60 mL) were added NaH (1.71 g, 42.8 mmol) and BnBr (5.12 mL, 42.8 mmol) slowly at 0 °C, and the reaction mixture was stirred at rt for 14 h. The reaction was quenched by addition of MeOH, and EtOAc was added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, toluene:EtOAc = 50:1) to give compound **4** (3.21 g, 65% over 2 steps) as a white powder; $[\alpha]_D$ − 5.3 (c 1.19, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (br-ddd, 1H, J = 1.7 Hz, Ar*H*), 7.86 (br-dt, 1H, J = 1.4 and 8.0 Hz, Ar*H*), 7.78 (br-dt, 1H, J = 1.2. 2.0 and 8.0 Hz, Ar*H*), 7.24–7.38 (m, 20H, Ar*H*), 7.17 (dt, 1H, J = 1.7 and 7.5 Hz, Ar*H*), 7.20 (t, 1H, J = 8.0 Hz, Ar*H*), 4.94 (d, 1H, J_{gem} = 11.5 Hz, ArC*H*$_2$-), 4.69–4.81 (m, 4H, ArC*H*$_2$-), 4.67 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 4.60 (d, 1H, J_{gem} = 11.5 Hz, ArC*H*$_2$-), 4.46 (d, 1H,

J_{gem} = 11.5 Hz, ArCH_2-), 4.41 (d, J_{gem} = 11.7 Hz, 1H, ArCH_2-), 3.98 (br-d, 1H, $J_{3,4}$ = $J_{4,5}$ = 2.6 Hz, H-4), 3.91 (t, 1H, J = 9.5 Hz, H-2), 3.83 (s, 3H, CH_3OCOAr), 3.59–3.66 (m, 4H, H-3, H-5, H-6a and H-6b); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.59, 138.78, 138.30, 138.27, 137.96, 135.99, 134.96, 132.44, 130.78, 128.98, 128.58, 128.56, 128.49, 128.34, 128.05, 127.94, 127.92, 127.84, 127.70, 127.67, 87.55, 84.24, 77.48, 76.90, 75.87, 74.61, 73.73, 73.56, 72.83, 68.82, 52.28; HRESIMS: Calcd for $C_{42}H_{46}O_7NS$ $[M + NH_4]^+$ 708.2989; found 708.2985.

4-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-galactopyranoside (5)

To a solution of compound **10** (2.34 g, 4.69 mmol) in MeOH (40 mL) was added NaOMe (13 mg, 0.22 mmol), and the reaction mixture was stirred at rt for 4 h. The reaction was quenched by addition of Amberlite ion-exchange resin and the mixture was filtered. The filtrate was concentrated and the residue was coevaporated with toluene under diminished pressure. To a solution of the residue in DMF (50 mL) were added NaH (1.13 g, 28.1 mmol) and BnBr (3.36 mL, 28.1 mmol) slowly at 0 °C, and the reaction mixture was stirred at rt for 19 h. The reaction was quenched by addition of MeOH, and EtOAc was added to the mixture. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, toluene:EtOAc = 50:1) to give compound **5** (5.43 g, 63% over 2 steps) as a white powder; $[\alpha]_D$ −16.8 (c 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (br-dt, 2H, J = 2.0 and 8.9 Hz, ArH), 7.56 (br-dt, 2H, J = 1.7 and 8.6 Hz, ArH), 7.25–7.36 (m, 20H, ArH), 4.97 (d, 1H, J_{gem} = 11.2 Hz, ArCH_2-), 4.70–4.76 (m, 5H, H-1 and ArCH_2-), 4.60 (d, 1H, J_{gem} = 11.5 Hz, ArCH_2-), 4.49 (d, 1H, J_{gem} = 11.5 Hz, ArCH_2-), 4.43 (d, 1H, J_{gem} = 11.7 Hz, ArCH_2-), 3.97–4.01 (m, 2H, H-2 and H-4), 3.90 (s, 3H, CH_3OCOAr), 3.60–3.66 (m, 4H, H-3, H-5, H-6a and H-6b); ^{13}C NMR (125 MHz, $CDCl_3$): δ166.86, 141.27, 138.68, 138.25, 138.16, 137.88, 130.00, 129.48, 128.58, 128.48, 128.42, 128.40, 128.07, 127.98, 127.94, 127.86, 127.74, 127.67, 86.50, 84.18, 77.59, 77.42, 75.86, 74.68, 73.75, 73.55, 72.83, 68.84, 52.15; HRESIMS: Calcd for $C_{42}H_{46}O_7NS$ $[M + NH_4]^+$ 708.2989; found 708.2990.

2-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-galactopyranoside (6)

To a solution of compound **8** (1.00 g, 2.01 mmol) in MeOH (10 mL) was added NaOMe (11 mg, 0.2 mmol), and the reaction mixture was stirred at

rt for 2 h. The reaction was quenched by addition of Amberlite ion-exchange resin and filtered, and toluene was added to the filtrate. The solution was concentrated under reduced pressure and the residue was dissolved in pyridine (20 mL). Benzoyl chloride (1.11 mL, 9.65 mmol) was gradually added to the solution at 0 °C and the reaction mixture was stirred at rt for 12 h. The reaction was quenched by addition of an excess amount of MeOH, and the mixture was repeatedly azeotroped with toluene. The residue was dissolved in $CHCl_3$ and the organic layer was successively washed with 1N HCl aq, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, toluene:EtOAc = 100:1) to give compound **6** (1.44 g, 96% over 2 steps) as a white solid; $[\alpha]_D$ +130.7 (c 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21–8.08 (m, 24H, ArH), 6.06 (br-d, 1H, J = 2.7 Hz, H-4), 5.91 (t, 1H, $J_{1,2} = J_{2,3}$ = 9.9 Hz, H-2), 5.66 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 5.22 (d, 1H, $J_{1,2}$ = 10.1 Hz, H-1), 4.63 (dd, 1H, $J_{5,6a}$ = 7.4 Hz, J_{gem} = 11.4 Hz, H-6a), 4.52 (dd, 1H, $J_{5,6b}$ = 5.2 Hz, J_{gem} = 11.4 Hz, H-6b), 4.47 (br-t, 1H, H-5), 3.64 (s, 3H, C*H*$_3$OCOAr); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.95, 166.18, 165.63 × 2, 165.17, 136.10, 133.83, 133.50, 133.46, 133.41, 132.25, 131.61, 130.74, 130.39, 130.16, 129.98, 129.95, 129.91, 129.52, 129.26, 129.01, 128.79, 128.61, 128.46, 128.43, 126.58, 85.16, 77.36, 75.37, 73.07, 68.51, 67.72, 62.85, 52.16; HRESIMS: Calcd for $C_{42}H_{38}O_{11}NS$ $[M + NH_4]^+$ 764.2160; found 764.2146.

2-(Methoxycarbonyl)phenyl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranoside (7)

To a solution of compound **11** (0.69 g, 1.39 mmol) in MeOH (7 mL) was added NaOMe (7.6 mg, 0.14 mmol), and the reaction mixture was stirred at rt for 3 h. The reaction mixture was added Amberlite ion-exchange resin and filtered, and to the filtrate was added toluene. The solution was concentrated under reduced pressure and the residue was dissolved in pyridine (14 mL). Benzoyl chloride (0.77 mL, 6.67 mmol) was gradually added to the solution at 0 °C and the reaction mixture was stirred at rt for 12 h. The reaction was quenched by addition of an excess amount of MeOH, and the mixture was repeatedly azeotroped with toluene under reduced pressure. The residue was dissolved in $CHCl_3$ and the organic layer was successively washed with 1N HCl aq, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, toluene:EtOAc = 100:1) to give compound **4** (954 mg, 92% over 2 steps) as a white solid: $[\alpha]_D$ +17.8 (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11–8.05 (m, 24H, ArH), 5.98 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.4 Hz, H-3), 5.62 – 5.69 (m, 2H, H-2 and H-4), 5.21 (d, 1H, $J_{1,2}$ =

10.1 Hz, H-1), 4.69 (dd, 1H, $J_{5,6a}$ = 2.7 Hz, J_{gem} = 12.1 Hz, H-6a), 4.50 (dd, 1H, $J_{5,6b}$ = 6.5 Hz, J_{gem} = 12.1 Hz, H-6b), 4.29 (ddd, 1H, $J_{4,5}$ = 9.7 Hz, $J_{5,6a}$ = 2.7 Hz, $J_{5,6b}$ = 6.5 Hz, H-5), 3.63 (s, 3H, C*H*$_3$OCOAr); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.90, 166.15, 165.86, 165.35, 165.05, 136.22, 133.66, 133.38, 132.24, 131.46, 130.63, 130.10, 130.01, 129.98, 129.90, 129.85, 129.63, 129.15, 128.78, 128.71, 128.57, 128.53, 128.40, 126.56, 85.18, 76.44, 74.20, 70.35, 69.57, 63.51, 52.12; HRESIMS: Calcd for $C_{42}H_{38}O_{11}NS$ $[M + NH_4]^+$ 764.2160; found 764.2129.

General procedures for glycosylation

Powder-type molecular sieves 4Å (ca. 10% of the solvent) was activated in preliminary dried eggplant-type flasks under reduced pressure at 170 °C for 2 h. After cooling to rt, an adequately dried mixture of glycosyl donor and acceptor, in a solvent (100 mM) under an argon atmosphere, was added to the flask through a cannula. After stirring at ambient temperature for 30 min, the mixture was cooled to a target temperature. A promotor was added to the mixture, and the reaction mixture was stirred until the glycosyl acceptor or donor was consumed. Reactions was quenched after consumption of glycosyl acceptor or donor. When both glycosyl acceptor and donor remained, the reaction was continued up to 48 h and quenched. After quenching by addition of triethylamine, and the mixture was filtered through a pad of Celite. The filtrate was diluted with ethyl acetate, and the organic layer was washed with satd. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to gel partition chromatography (Bio-Beads S-X3, Bio-Rad Laboratories, Inc., toluene:ethyl acetate = 3:1), and the fractions containing glycosylated compounds were collected. After concentration of the combined fractions under reduced pressure, the residue was dried under vacuum to allow calculation of the yield. The α/β ratio for the glycosylation was estimated from the integration value originating from each anomer in the ^{1}H NMR spectrum of the residue. The NMR spectra of all obtained disaccharides, including methyl (galactopyranosyl)glucopyranosides[25,26] and (glucopyranosyl)glucopyranosides[27], were consistent with those in the literatures.

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Author contributions

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