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Effects of frozen conditions on stereoselectivity and velocity of O-glycosylation reactions

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ABSTRACT

Rate acceleration of O-glycosylation had been observed in *p*-xylene under frozen conditions, when thioglycosides were activated by methyl trifluoromethane sulfonate. Curiously, significant perturbation of stereoselectivity was observed. Effects of various factors, such as solvent, concentration, anomeric configuration and protective groups of the donor, were systematically examined to clarify the mechanistic implications of stereoselectivity on glycosylation under frozen system. Our study revealed that the stereoselectivity was affected by concentration both in liquid as well as in frozen conditions, indicating that rate acceleration effect in frozen solvent was caused by highly concentrated environments.

1. Introduction

It is widely perceived that chemical reactions proceed most smoothly in homogeneous solutions, in which molecules diffuse without impediment. Therefore, it is almost a golden rule to keep the reaction temperature above melting point of the solvent. Most researchers probably believe that reactions in frozen solvents barely proceed, because diffusion of molecules must be severely restricted. However, several reports have shown that certain reactions, both chemical[1] and enzymatic,[2] proceed under frozen conditions. Contrary to the general belief, these reactions were shown to proceed with higher velocity compared to solution conditions. These observations may well be explained by the concentration effect.[3] Below freezing point, but above the eutectic temperature, frozen mixture contains liquid particles that are dispersed in a seemingly solidified mixture.[4] Freezing point-composition relationship predicts that solutes (reactants and reagents) are highly concentrated in liquid particles, which may be seen micropockets. If the effect of concentration overrides the rate reduction caused by reduced temperature associated with freezing, reactions would be accelerated.[5]

Our previous study provided the first example of the rate acceleration of O-glycosylation in frozen medium.[6] Namely, mannopyranosylation in the presence of methyl trifluoromethanesulfonate (MeOTf)[7] and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), enormous rate acceleration was observed, when the glycosylation was conducted in *p*-xylene (mp = 12–13 °C) below its freezing point. A similar effect was also observed in the synthesis of larger oligosaccharides, extending its practical utility to facile preparation of oligomannoside probes,[6] as well as block condensation of oligosaccharide fragments to provide a high-mannose type glycan analogue.[6,8] In addition, this technique was applied to the introduction of a fucose residue to highly hindered site of octasaccharide acceptor, completing the synthesis of complex-type glycans derived from parasitic helminthes.[9] As an additional example, arabinofuranosylation under frozen conditions was applied to the synthesis of mycobacterial arabinan fragment.[10]

In order to accelerate reactions, various types of conditions have proven useful, the most prominent being microwave irradiation,[11,12] ultrasound sonication,[13] high pressure compression,[14,15] and microfluidic conditions.[16,17] Compared to these techniques, which require special devices, freezing conditions are readily accessible to any researchers.

Incidentally, we came across to the phenomenon that stereoselectivity of glycosylation was significantly perturbed under frozen conditions. We anticipated that correlation of the rate enhancement with selectivity would provide a clue to understand the origin of the effects of frozen conditions.

2. Results and discussion

2.1. Effect of additive solvents in xylene under frozen conditions

As an exemplary reaction of our study, we revisited mannopyranosylation of **1**[18] through activation of **2**[19] with MeOTf and

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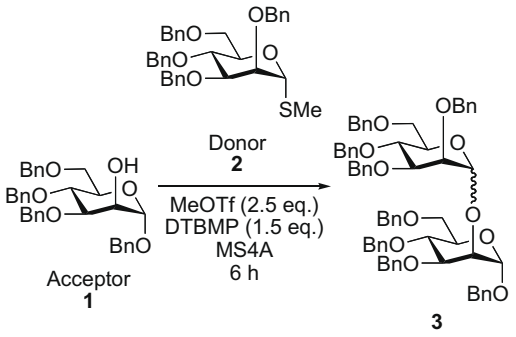


Scheme 1.

DTBMP (Scheme 1), because this reaction only proceeds slowly at room temperature in *p*-xylene or toluene. Selectivity was evaluated through ^{1}H NMR analysis of disaccharide fractions, which were separated from crude mixtures by size exclusion column chromatography. In some cases, deuterated benzyl protected substrates were used to evaluate selectivity with higher precision (Table 1). In accordance with our previous report, enormous rate acceleration was observed under frozen conditions at 4 °C and −20 °C (entries 1–6).[6] This reaction was thus further studied to explore factors that govern the outcome of glycosylation under frozen conditions. Glycosylations are generally conducted under anhydrous conditions. From pragmatic point of view, it would be of some merit, if such reactions are tolerant to the presence of water. Our initial anticipation was that water molecules are segregated from organic solvent when the latter was frozen. We thus attempted the glycosylation in *p*-xylene in the presence of deliberately added H_2O (1%) under frozen conditions (entry 7). It was observed that the disaccharide **3** was formed in a substantial yield (40%) indeed, indicating that the reactivity of the acceptor **1**, to some extent, competed successfully with that of H_2O under such circumstances, even though the amount of the water is more than ten times higher (0.56 mol/L) than **1**. However, further attempts to enhance the yield by lowering the temperature (entry 9) or using aq NaCl in order to attain better segregation of water (entries 8 and 10) did not give any improvement. The result suggested that, even under frozen condition, H_2O was not completely separated from organic solvent. Curiously, however, a significant reduction of stereoselectivity was seen when aq. NaCl was included.

We subsequently examined the effects of organic co-solvents such as toluene, Et_2O, CH_3CN, $CHCl_3$, and Et_2O–$CHCl_3$ (1:1),[20] anticipating that these co-solvents are concentrated in the liquid phase of frozen mixture and affect the selectivity (entries 11–15). However their effects on stereoselectivity were only marginal. Instead, the rate accelerating effect was deteriorated in these cases; even inclusion of 1% toluene was detrimental (entry 11), indicating that rigidly ordered frozen state of the mixture is crucial in order to optimally accelerate reactions.

2.2. Glycosylation in various solvents under frozen conditions

In order to clarify the generality of the frozen effect which was clearly observed in *p*-xylene,[21,22] we examined the glycosylation in other solvents which can be frozen at 4 °C and we compared them with non-freezing solvents possessing similar chemical property (Table 2). In the case of *p*-xylene, rate enhancement was observed compared to the reactions in toluene (Table 1) and *m*-xylene (entry 1). As an ethereal and a nitrile solvents, dioxane (mp = 10–12 °C) and *t*-BuCN (mp = 15–16 °C) were compared with tetrahydropyrane (mp = −45 °C) and MeCN (mp = −48 °C), respectively (entries 2–5). In these cases, rate acceleration was also seen, although the extents were smaller. Since proportion of the β-isomer was increased in frozen *p*-xylene (Table 1), we initially hoped that β-directing effect of nitrile solvent would be augmented. However the selectivity in frozen *t*-BuCN was nearly identical with that in MeCN. Interestingly, Mong et al reported that glycosylation with 2-O-benzylated galactopyranosyl or glucopyranosyl donor under diluted conditions in nitrile solvent gave higher 1,2-*trans* (β) selectivity under diluted conditions. These authors rationalized this intriguing results by enhanced formation of nitrilium ion intermediates with low concentration of substrates.[23]

Table 1
Glycosylation of **1** with **2** under frozen conditions:[a] effect of additive solvents and concentration

Entry	Solvent	Concn[b] (mol/L)	Temperature	Additive solvents (1%)	Yield (%)	Ratio (α:β)	Recovery	
							A	D (H)
1	*p*-Xylene	0.03	rt	None	33	51:1	49	85
2	*p*-Xylene[d,e]	0.03	rt	None	83	55:1	7	-
3	Toluene	0.03	4 °C	None	25	55:1	65	72
4[c]	*p*-Xylene[d]	0.03	4 °C	None	90	4.3:1	8	23
5	Toluene[f,6]	0.03	−20 °C	None	<1	-	89	87
6[c]	*p*-Xylene[f,6]	0.03	−20 °C	None	66	4.5:1	28	46
7[c]	*p*-Xylene	0.03	4 °C	H_2O	40	3.4:1	59	26 (32)
8[c]	*p*-Xylene	0.03	4 °C	Satd NaCl aq	24	1.5:1	76	43 (42)
9[c]	*p*-Xylene	0.03	−20 °C	H_2O	25	4.2:1	76	41 (41)
10[c]	*p*-Xylene	0.03	−20 °C	Satd NaCl aq	17	3.9:1	79	35 (49)
11[c]	*p*-Xylene	0.03	4 °C	Toluene	66	7.1:1	33	57
12[c]	*p*-Xylene	0.03	4 °C	CH_3CN	71	5.9:1	22	49
13[c]	*p*-Xylene	0.03	4 °C	Et_2O	50	5.8:1	48	68
14[c]	*p*-Xylene	0.03	4 °C	$CHCl_3$	54	6.6:1	43	73
15[c]	*p*-Xylene	0.03	4 °C	Et_2O–$CHCl_3$(1:1)	56	6.1:1	39	70
16	Toluene[d]	0.15	4 °C	None	78	13:1	10	39
17	Toluene[d]	0.3	4 °C	None	84	7.9:1	6	30
18	Toluene[d]	1.5	4 °C	None	90	4.5:1	10	14

[a] The yield and stereoselectivity were determined after gel filtration.
[b] Concentration of acceptor before freezing.
[c] Frozen conditions.
[d] The yield was determined by MALDI-TOF MASS quantitative analysis of crude sample. The stereoselectivity was determined by ^{1}H NMR of crude sample. Methyl 2,3,4,6-tetra-*O*-[D_7]benzyl-1-thio-α-D-mannopyranoside **[D_{28}]2** was used instead of **2**.
[e] For 14 days.
[f] The yield and stereoselectivity were determined based on isolated yield.

Table 2
Glycosylation of **1** with **2** at 4 °C: effect of solvents[a,b]

Entry	Solvent	Yield (%)	Ratio (α:β)	Recovery	
				A	D
1	*m*-Xylene	8	100:1	78	97
2[c]	Dioxane	87	3.7:1	11	34
3	THP	61	7.1:1	33	75
4[c]	*t*-BuCN	84	2.5:1	19	28
5	MeCN	54	2.1:1	39	61

[a] The reactions were carried out in 0.03 mol/L solution of acceptor before freezing.
[b] Compound **[D_{28}]2** was used. The yield was determined by MALDI-TOF MASS quantitative analysis of crude sample. The stereoselectivity was determined by ^{1}H NMR of crude sample.
[c] Solvent was freezing.

2.3. Effect of concentration on stereoselectivity of glycosylation

Rate-enhancing effect of the frozen system may be explained by its ability to generate highly concentrated micropockets. However, it is rather difficult to experimentally assess their substrate concentrations. On the other hand, our study has shown that rate acceleration in frozen systems was associated with alternation of stereoselectivity, leading us to explore the correlation between the selectivity and concentration. We expected that, by extrapolating the concentration-selectivity relationship of non-frozen reactions, reasonable estimate of the degree of concentration in frozen mixtures.

To this end, the effect of the concentration of the substrate in toluene (non-frozen) at 4 °C was evaluated (Table 1, entries 3 and 16–18). In toluene, the reaction was accelerated in a concentration dependent manner, while the α-selectivity of the glycoside **3** was reduced at higher concentrations. The result in concentrated toluene solution (1.5 mol/L, entry 18) was very similar to that in frozen *p*-xylene (0.03 mol/L, entry 4), in terms of both the product yield (90%) and selectivity (4.5:1 vs 4.3:1). These results support our hypothesis that the decrease of stereoselectivity in frozen systems was caused by increased concentration, and provided the estimate of substrate concentrations under frozen conditions, which seems to reached as high as ~1.5 mol/L.

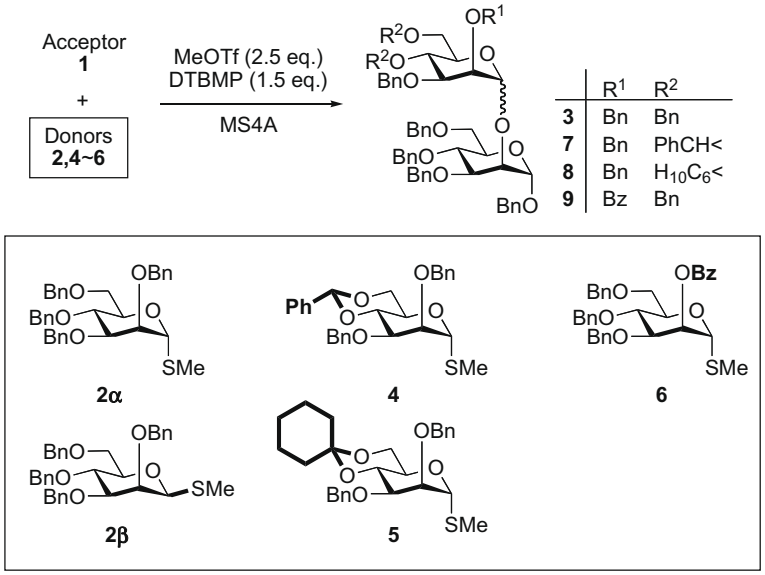
2.4. Effect of anomeric stereochemistry of donor on reactivity of donors and stereoselectivity of their glycosylation

Our study next addressed effect of the donor anomericity. That the glycosylation in frozen media proceeded with reduced α-selectivity may be explained by two different ways. As the first possibility, higher concentrations of substrates would perturb the nature (e.g., polarity) of the solvent, and affect the stereoselectivity. Alternatively, direct S_N2 type displacement of activated thioglycoside, which gives β-glycoside, might become functional as an alternative pathway that compete to oxocarbenium ion pathway, when concentrations of **1** and **2** are high. To gain a clue to distinguish these possibilities, we conducted reactions with β-thioglycoside **2β** as the donor, which was prepared from **10β**[24] (Scheme 3). As shown in Table 3 (entries 1–3), the reactivity of the β-isomer **2β** was much faster than that of the α-isomer (**2**), reactions proceeding to completion within 1 h both at rt and at 4 °C. In frozen *p*-xylene (entry 2), the α-selectivity was approximately two times higher than the same reaction using the α-thioglycoside **2** (Table 1, entry 4), while differences in the selectivity under non-frozen conditions are less marked and, instead, slightly shifted to less α-selective direction (entries 1 and 3). These results seem to suggest the occurrence of S_N2 type displacement of the activated intermediate in association with more dominant oxocarbenium ion like intermediate under highly concentrated conditions. However, it is certainly possible that the presence of substrates and reagents in high concentrations gave an impact and altered selectivity, although our current experimental setup is not able to address this possibility.

Table 3
Glycosylation of various donors under frozen conditions[a,b]

Entry	Donor	Solvent	Temp	Time	Yield (%)	Ratio (α:β)	Recovery	
							A	D (H)
1	**2β**	*p*-Xylene	rt	1 h	95	37:1	1	2
2[c]	**2β**	*p*-Xylene	4 °C	1 h	100	8.3:1	—	—
3	**2β**	Toluene	4 °C	1 h	73	26:1	20	37
4	**4**	*p*-Xylene	rt	6 h	1	1.8:1	87	130
5[c]	**4**	*p*-Xylene	4 °C	6 h	5	1:1.3	80	113
6	**4**	Toluene	4 °C	6 h	0	—	85	126
7	**4**	*p*-Xylene	rt	14 d	19	2.4:1	80	113
8[c]	**4**	*p*-Xylene	4 °C	14 d	51	1.2:1	32	49
9	**4**	Toluene	4 °C	14 d	14	1.4:1	82	97
10	**4**[d]	*p*-Xylene	rt	14 d	25	2.1:1	73	98
11[c]	**4**[d]	*p*-Xylene	4 °C	14 d	60	1:1.3	25	55
12	**4**[d]	Toluene	4 °C	14 d	18	1.1:1	83	100
13	**5**[e]	*p*-Xylene	rt	6 h	5	3.1:1	87	120
14[c]	**5**[e]	*p*-Xylene	4 °C	6 h	19	1:1.5	80	93
15	**5**[e]	Toluene	4 °C	6 h	0	—	89	128
16	**5**[e]	*p*-Xylene	rt	5 d	26	3.8:1	64	90
17[c]	**5**[e]	*p*-Xylene	4 °C	5 d	92	1.5:1	5	—
18	**5**[e]	Toluene	4 °C	5 d	17	2.1:1	74	112
19	**6**	*p*-Xylene	rt	6 h	2	α	90	110
20[c]	**6**	*p*-Xylene	4 °C	6 h	32	41:1	57	77
21	**6**	Toluene	4 °C	6 h	Trace	—	93	123
22	**6**	*p*-Xylene	rt	2 d	16	α	73	95
23[c]	**6**	*p*-Xylene	4 °C	2 d	82	46:1	10	33
24	**6**	Toluene	4 °C	2 d	5	α	90	110

[a] The reactions were carried out in 0.03 mol/L solution of acceptor before freezing.
[b] The yield and stereoselectivity were determined after gel filtration.
[c] Solvent was freezing.
[d] 2.5 equiv of MeOTf and 3.0 equiv of DTBMP were used.
[e] The yield was determined by MALDI-TOF MASS quantitative analysis of crude sample. The stereoselectivity was determined by ^{1}H NMR of crude sample.

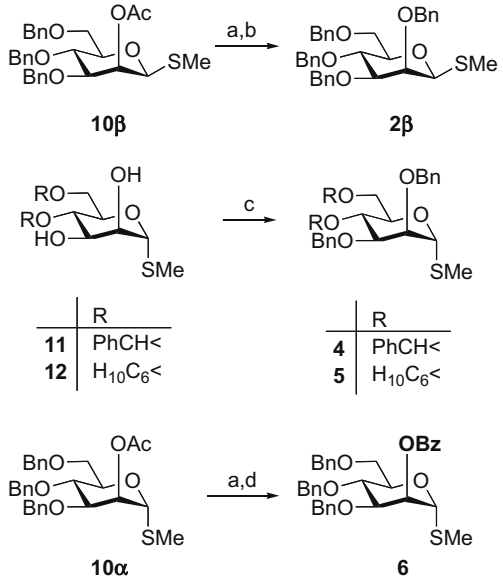


Scheme 2.

2.5. Effect of protective groups

In addition to the perbenzylated thioglycoside **2** (see Scheme 2), mannosyl donors with 4,6-*O*-cyclic (**4**, **5**) or 2-*O*-acyl (**6**) protection were studied, which in turn were prepared from **12**,[25] **13**,[26] and **11**,[24] respectively (Scheme 3). Results of reactions with **1** are tabulated in Table 3 (entries 4–24). In the case of 4,6-*O*-benzylidene protected donor **4**, which has been widely used for direct β-mannosylation,[27] the reaction was extremely slow under our standard conditions (entries 4–12). However, rate-enhancing effect of the frozen system is still evident. After 14 days under frozen conditions, 51% of the product was obtained with low selectivity ($\alpha:\beta$ = 1.2:1) (entry 8), although use of excess amount of DTBMP resulted in improvement of the yield slightly (60%) and the selectivity was slightly in favor of the β-glycoside (entry 11). On the other hand, the compound **5**, which carried a 4,6-*O*-cyclohexylidene group,[26,28] was revealed to be more reactive than **4** (entries 13–18). For instance, disaccharide was obtained in 92% ($\alpha:\beta$ = 1.5:1) under frozen conditions after 5 days (entry 17). Since we perceived that 4,6-*O*-cyclohexylidene group would be more deactivating than 4,6-*O*-benzylidene acetal, because the former would likely to confer higher degree of rigidity to the pyranose ring system, these results were somehow unexpected. In any event, we observed that the proportion of the β-isomer was uniformly increased when 4,6-*O*-cyclic protected donors **4** and **5** were used and that tendency was more prominent under frozen conditions.

The reactivity of 2-*O*-Bz protected donor **6** was revealed to be in between **2** and **4**/**5**, (entries 19–24), although much higher activity was initially expected due to the 'super arming' effect proposed by Demchenko.[29] Quite dramatic rate acceleration was observed in its reactions with **1** under frozen conditions. In these cases, the α-glycoside was obtained stereoselectively as expected, although formation of a small amount of the β-isomer was revealed, implicating the high precision of our setup in evaluating the selectivity (entries 20 and 23).



Scheme 3. Reagents and conditions: (a) NaOMe, MeOH, (b) NaH, BnBr, DMF, 0 °C to rt, 3 h, 71% in two steps from **10β**; (c) NaH, BnBr, DMF, 0 °C to rt, 3 h, 88%, (**4**) 78% (**5**); (d) BzCl, pyridine, DMAP, 0 °C to rt, 1.5 h, 92% in two steps from **10α**.

3. Conclusion

The aim of our study was to reveal the origin of rate-enhancing effect of frozen conditions on O-glycosylation. It first revealed that inclusion of small proportion of co-solvent was detrimental, indicating that rigidly frozen conditions are necessary to cause optimum rate enhancement. Secondly, the stereoselectivities under frozen and non-frozen conditions were compared. Concentration-selectivity relationship suggested that highly concentrated particles are generated in frozen solvents. Since selectivity and yield in frozen *p*-xylene (0.03 mol/L) were nearly identical with those in highly concentrated solution (1.5 mol/L) in toluene, frozen conditions seem to give rise to ~50 times increase of concentration.

Rate enhancements were also observed in other solvents such as dioxane and *t*-BuCN, although the extent of acceleration was less marked. In addition, reactions with donors having 4,6-*O*-cyclic as well as 2-*O*-acyl protection were accelerated also, indicating that rate enhancement effect of frozen *p*-xylene has some generality. However, our current study is not able to pin-down the dominant factor that attenuates stereoselectivity in a concentrated-dependent manner. Further study is underway to clarify this intriguing issue.

4. Experimental section

4.1. General procedures

All reactions sensitive to air or moisture were carried out under nitrogen or argon atmosphere with anhydrous solvent. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Thin-layer chromatography was performed using silica gel 60 F_{254} precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization on TLC was achieved by UV light (254 nm) and a typical TLC indication solution. Column chromatography was performed on silica gel 60 N, 100–210 mesh (Kanto Kagaku Co., Ltd.). ^{1}H NMR spectra were recorded at 400 MHz on a JEOL ECX 400 spectometer and chemical shifts were referred to internal tetramethylsilane (0 ppm) or $CDCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded at 100 MHz on the same instruments and chemical shifts were referred to internal $CDCl_3$ (77.0 ppm). Melting points were determined with Büchi 510 melting point apparatus. Optical rotations were measured with a JASCO DIP 370 polarimeter. MALDI-TOF mass spectra were recorded on a SHIMADZU Kompact MALDI AXIMA-CFR spectrometer with 2,5-dihydroxybenzoic acid as the matrix. ESI-TOF mass spectra were recorded on a JEOL AccuTOF JMS-T700LCK with CF_3CO_2Na as the internal standard.

4.2. Methyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-mannopyranoside (2β)

To a solution of methyl 2-*O*-acetyl-1-thio-3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (**10β**) (128.2 mg, 0.245 mmol) in dry methanol (2 mL) was added NaOMe to justify to alkaline, indicated by phenolphthalein, at room temperature, and the mixture was stirred for 1 h at the same temperature. Amberlist 15H$^+$ was added to the mixture to quench excess NaOMe. The resin was filtered off and concentrated. Crude mixture was then dissolved in dry DMF (2 mL) was added NaH (13.7 mg, 0.343 mmol) at 0 °C under Ar atmosphere and the mixture was stirred for 30 min at the same temperature. To the reaction mixture was added benzyl bromide (35.7 μL, 0.294 mmol), and the mixture was stirred for 3 h at room temperature under Ar atmosphere. After addition of triethylamine to the mixture followed by quenching by brine, the product was extracted with $CHCl_3$. Combined solutions were washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography using gradient solvent system (toluene/ethyl acetate = 50/1 to 20/1 to 10/1 to 5/1) to give the title compound (99.8 mg, 71%).

$[\alpha]_D^{28}$ −13.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, SMe, 3H), 3.42 (ddd, *J* = 11.4, 6.0, 1.4 Hz, 5-H, 1H), 3.53 (dd, *J* = 9.6, 2.8 Hz, 3-H, 1H), 3.65 (dd, *J* = 11.0, 6.0 Hz, 6a-H, 1H), 3.73 (dd, *J* = 11.4, 1.4 Hz, 6b-H, 1H), 3.84 (dd, *J* = 10.1, 9.6 Hz, 4-H, 1H), 3.91 (d, *J* = 2.8 Hz, 2-H, 1H), 4.38 (s, 1-H, 1H), 4.48–4.65 (m, –C*H*$_2$Ph, 5H), 4.76 (d, *J* = 11.9 Hz, –C*H*$_2$Ph, 1H), 4.80 (d, *J* = 11.0 Hz, –C*H*$_2$Ph, 1H), 4.89 (d, *J* = 11.9 Hz, –C*H*$_2$Ph, 1H), 7.11–7.13 (m, Ar, 2H), 7.18–7.28 (m, Ar, 16H), 7.37 (d, *J* = 6.9 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.4, 70.5, 73.1, 74.2, 75.5, 75.6, 75.9, 81.0, 85.0, 86.4, 128.1, 128.3, 128.4, 128.5, 128.8, 128.96, 129.03, 129.1, 138.77, 138.84; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{35}H_{38}O_5SNa$, 593.23, found 593.2; ESI-TOF MS: [M+Na]$^+$ calcd for $C_{35}H_{38}O_5S_1Na_1$, 593.23, found 593.21; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{35}H_{38}O_5S_1Na_1$, 593.2338, found 593.2339.

4.3. Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (4)

To a solution of methyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (**11**) (1.50 g, 5.03 mmol) in dry DMF (10 mL) was added NaH (0.563 g, 8.31 mmol) at 0 °C under Ar atmosphere and the mixture was stirred for 30 min at the same temperature. To the reaction mixture was added benzyl bromide (1.47 mL, 12.1 mmol), and the mixture was stirred for 3 h at room temperature under Ar atmosphere. After addition of triethylamine to the mixture followed by quenching by brine, the product was extracted with $CHCl_3$. Combined solutions were washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by flash column chromatography using gradient solvent system (toluene/ethyl acetate = 100/1 to 50/1 to 20/1 to 10/1 to 5/1) to give the title compound (2.11 g, 88%).

$[\alpha]_D^{28}$ 81.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.08 (s, SMe, 3H), 3.87 (dd, *J* = 3.2, 0.9 Hz, 2-H, 1H), 3.88 (dd, *J* = 10.1, 1.4 Hz, 6a-H, 1H), 3.91 (dd, *J* = 9.6, 3.2, 3-H, 1H), 4.15 (ddd, *J* = 9.6, 4.6, 1.4 Hz, 5-H, 1H), 4.22 (dd, *J* = 10.1, 4.6 Hz, 6b-H, 1H), 4.27 (t, *J* = 9.6 Hz, 4-H, 1H), 4.60 (d, *J* = 12.4, –C*H*$_2$Ph, 1H), 4.73–4.82 (m, –C*H*$_2$Ph, 3H), 5.19 (d, *J* = 0.9 Hz, 1-H, 1H), 5.63 (s, >C*H*Ph, 1H), 7.24–7.39 (m, Ar, 13H), 7.48–7.51 (m, Ar, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 64.6, 68.7, 72.99, 73.04, 76.4, 77.8, 79.2, 84.9, 101.5, 126.1, 127.55, 127.61, 127.8, 128.1, 128.2, 128.3, 128.4, 128.8, 137.6, 137.8, 138.4; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{28}H_{30}O_5S_1Na_1$, 501.17, found 501.20; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{28}H_{30}O_5S_1Na_1$, 501.1712, found 501.1706.

4.4. Methyl 4,6-*O*-cyclohexylidenel-2,3-di-*O*-benzyl-1-thio-α-D-mannopyranoside (5)

The title compound **5** was synthesized from methyl 4,6-*O*-cyclohexylidene-1-thio-α-D-mannopyranoside (**12**) according to the procedure for the synthesis of **4** from **11** (78%).

$[\alpha]_D^{28}$ 114.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.98 (s, SMe, 3H), 3.69 (dd, *J* = 9.6, 3.2 Hz, 3-H, 1H), 3.72 (dd, *J* = 10.1, 4.6 Hz, 6a-H, 1H), 3.77 (dd, *J* = 3.2, 1.4, 2-H, 1H), 3.85 (dd, *J* = 10.6, 10.1 Hz, 6b-H, 1H), 3.91 (ddd, *J* = 10.6, 9.6, 4.6 Hz, 5-H, 1H), 4.21 (t, *J* = 9.6 Hz, 4-H, 1H), 4.55 (d, *J* = 12.4, –C*H*$_2$Ph, 1H), 4.61–4.70 (m, –C*H*$_2$Ph, 2H), 4.79 (d, *J* = 12.4 Hz, –C*H*$_2$Ph, 1H), 5.06 (s, 1-H, 1H), 7.12–7.31 (m, Ar, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 22.6, 23.0, 25.6, 28.0, 38.2, 61.7, 65.6, 71.4, 73.0, 73.1, 76.8, 78.0, 85.0, 100.0, 127.4, 127.7, 128.0, 128.2, 128.3, 138.0, 138.9; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{27}H_{34}O_5S_1Na_1$, 493.20, found 492.50; ESI-TOF MS: [M+Na]$^+$ calcd for $C_{27}H_{34}O_5S_1Na_1$, 493.20, found 493.16; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{27}H_{34}O_5S_1Na_1$, 493.2025, found 493.2039.

4.5. Methyl 2-*O*-benzoyl-3,4,6-*O*-benzyl-1-thio-α-D-mannopyranoside (6)

To a solution of methyl 2-*O*-acetyl-3,4,6-*O*-benzyl-1-thio-α-D-mannopyranoside (**10β**) (300 mg, 0.57 mmol) in dry methanol (3 mL) was added NaOMe to justify to alkaline, indicated by phenolphthalein, at room temperature, and the mixture was stirred for 1 h at the same temperature. Amberlist 15H$^+$ was added to the mixture to quench excess NaOMe. Resin was filtered off and concentrated. Crude mixture was then dissolved in dry pyridine (3 mL), benzoyl chloride (66.2 mL, 0.57 mmol) and DMAP (7.0 mg, 0.057 mmol) were added to the mixture at 0 °C under Ar atmosphere. After being stirred at room temperature for 1.5 h, the reaction was quenched with methanol and co-evaporated with toluene. The residue was diluted with dichloromethane, washed with 1 N HCl, water, sat. $NaHCO_3$, water, and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography using gradient solvent system (toluene/ethyl acetate = 50/1 to 20/1 to 10/1 to 5/1) to give the title compound (325.1 mg, 94%).

$[\alpha]_D^{28}$ 31.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.19 (s, SMe, 3H), 3.81 (dd, *J* = 11.0, 1.4 Hz, 6a-H, 1H), 3.96 (dd, *J* = 11.0,

3.7 Hz, 6b-H, 1H), 4.08 (dd, J = 9.2, 3.2 Hz, 3-H, 1H), 4.17 (dd, J = 10.1, 9.2 Hz, 4-H, 1H), 4.23 (ddd, J = 10.1, 3.7, 1.4 Hz, 5-H, 1H), 4.55–4.62 (m, –CH_2Ph, 3H), 4.77 (d, J = 12.4 Hz, –CH_2Ph, 1H), 4.81 (d, J = 11.9 Hz, –CH_2Ph, 1H), 4.92 (d, J = 11.0 Hz, –CH_2Ph, 1H), 5.36 (d, J = 1.4 Hz, 1-H, 1H), 5.75 (dd, J = 3.2, 1.4 Hz, 2-H, 1H), 7.20–7.42 (m, Ar, 17H), 7.56–7.60 (m, Ar, 1H), 8.11–8.13 (m, Ar, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 69.0, 70.5, 71.6, 71.9, 73.2, 74.4, 75.2, 78.6, 83.9, 127.4, 127.6, 127.7, 127.9, 128.1, 128.27, 128.34, 129.9, 133.1, 137.6, 138.27, 138.31, 165.6; MALDI-TOF MS: $[M+Na]^+$ calcd for $C_{35}H_{36}O_6SNa_1$, 607.21, found 607.20; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{35}H_{36}O_6SNa_1$, 607.21, found 607.16; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{35}H_{36}O_6SNa_1$, 607.2130, found 607.2149.

4.6. General procedure for frozen conditions

After azeotropic removal of water with toluene, to the mixture of an acceptor **1** (8.1 mg, 15.0 μmol) and a donor **[D_{28}]2** (12.2 mg, 20.3 μmol, 1.35 equiv) in dry solvent (500 μL) were added MS 4A (ca. 0.3 g/0.1 mmol of acceptor) and DTBMP (5.7 mg, 22.5 μmol, 1.5 equiv) and mixture was stirred under Ar for at room temperature for 30 min. MeOTf (4.2 μL, 37.5 μmol, 2.5 equiv) was added to mixture, and the mixture was rapidly mixed and frozen by liquid nitrogen. The mixture was stored in refrigerator at 4 °C for 6 h and was defrosted at temperature. The reaction quenched with triethylamine followed by filtration through Celite pad and washing of pad with ethyl acetate. The combined solutions were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by gel filtration (Bio beads SX-3, toluene/ethyl acetate = 1:1) to give the mixture of the isomers (14.7 mg, 90%, $\alpha:\beta$ = 4.3:1).

The residue was purified by preparative TLC (toluene/ethyl acetate = 5/1) to afford 14.7 mg (90%) of compound. Detailed reaction conditions, yield and stereoselectivity of the products for each reaction were listed in Tables.

4.7. Benzyl 2,3,4,6-tetra-*O*-[D_7]benzyl-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside ([D_{28}]3)

Compound **[D_{28}]3α**: $[\alpha]_D^{26}$ 19.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51–3.88 (m, 3-H^{Man1}, 4-H^{Man1}, 5-H^{Man1}, 6a-H^{Man1}, 6b-H^{Man1}, 2-H^{Man2}, 3-H^{Man2}, 4-H^{Man2}, 5-H^{Man2}, 6a-H^{Man2}, 6b-H^{Man2}, 11H), 4.02 (dd, J = 2.4, 2.3 Hz, 2-H^{Man1}, 1H), 4.27 (d, J = 12.4 Hz, –CH_2Ph, 1H), 4.47 (d, J = 11.9 Hz, –CH_2Ph, 2H), 4.52–4.62 (m, –CH_2Ph, 4H), 4.76 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.89 (d, J = 1.4 Hz, 1-H^{Man1}, 1H), 5.10 (d, J = 1.4 Hz, 1-H^{Man2}, 1H), 7.08–7.26 (m, Ar, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.0, 69.1, 69.2, 72.1, 72.5, 73.3, 74.5, 74.7, 74.9, 75.1, 79.6, 79.9, 98.2, 99.5, 127.4, 127.5 127.7, 127.9, 128.0, 128.25, 128.32, 128.36, 128.40, 137.3, 138.0, 138.2, 138.3, 138.5; MALDI-TOF MS: $[M+Na]^+$ calcd for $C_{68}H_{42}D_{28}O_{11}Na_1$, 1113.66, found 1113.68; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{68}H_{42}D_{28}O_{11}Na_1$, 1113.66, found 1113.66; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{68}H_{42}D_{28}O_{11}Na_1$, 1113.6573, found 1113.6536.

Compound **[D_{28}]3β**: $[\alpha]_D^{27}$ −30.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32–3.37 (m, 5-H^{Man1}, 1H), 3.40 (dd, J = 9.6, 3.2 Hz, 3-H^{Man1}, 1H), 3.55–3.67 (m, 6a-H^{Man1}, 6b-H^{Man1}, 6a-H^{Man2}, 6b-H^{Man2}, 4H), 3.70–3.74 (m, 5-H^{Man2}, 1H), 3.79 (dd, J = 10.1, 9.6 Hz, 4-H^{Man1}, 1H), 3.82 (dd, J = 10.1, 9.2 Hz, 4-H^{Man2}, 1H), 3.92–3.95 (m, 3-H^{Man2}, 2-H^{Man1}, 2H), 4.29 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.36–4.43 (m, 2-H^{Man2}, 1-H^{Man1}, –CH_2Ph, 5H), 4.53 (d, J = 12.4 Hz, –CH_2Ph, 1H), 4.66 (d, J = 11.9 Hz, –CH_2Ph, 1H), 4.68 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.92 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.95 (d, J = 1.8 Hz, 1-H^{Man2}, 1H), 6.95–6.98 (m, Ar, 2H), 7.11–7.26 (m, Ar, 16H), 7.36–7.38 (m, Ar, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.9, 69.3, 69.9, 70.1, 71.5, 71.6, 73.3, 73.7, 74.1, 74.8, 74.0, 75.9, 77.2, 78.0, 81.5, 96.5 (C1^{Man1}, J_{C-H} = 169.8 Hz), 99.3 (C1^{Man2}, J_{C-H} = 157.4 Hz), 127.2, 127.5, 127.78, 127.84, 128.0, 128.1, 128.19, 128.21, 128.3, 128.4, 137.1, 137.87, 137.94, 138.2, 138.4, 138.6, 138.9; MALDI-TOF MS: $[M+Na]^+$ calcd for $C_{68}H_{42}D_{28}O_{11}Na_1$, 1113.66, found 1113.61; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{68}H_{42}D_{28}O_{11}Na_1$, 1113.66, found 1113.65; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{68}H_{42}D_{28}O_{11}Na_1$, 1113.6573, found 1113.6596.

4.8. Benzyl 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (3)

Compound **3α**: $[\alpha]_D^{27}$ 24.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52–3.88 (m, 3-H^{Man1}, 4-H^{Man1}, 5-H^{Man1}, 6a-H^{Man1}, 6b-H^{Man1}, 2-H^{Man2}, 3-H^{Man2}, 4-H^{Man2}, 5-H^{Man2}, 6a-H^{Man2}, 6b-H^{Man2}, 11H), 4.02 (dd, J = 2.4, 2.3 Hz, 2-H^{Man1}, 1H), 4.27 (d, J = 11.9 Hz, –CH_2Ph, 1H), 4.38–4.61 (m, –CH_2Ph, 13H), 4.74–4.78 (m, –CH_2Ph, 2H), 4.89 (d, J = 1.8 Hz, 1-H^{Man1}, 1H), 5.10 (d, J = 1.8 Hz, 1-H^{Man2}, 1H), 7.26–7.96 (m, Ar, 40H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.0, 69.2, 72.0, 72.1, 72.4, 73.3, 74.5, 74.9, 75.0, 79.6, 79.9, 98.2 (C1^{Man1}, J_{C-H} = 172.6 Hz), 99.5 (C1^{Man2}, J_{C-H} = 176.4 Hz), 127.4, 127.6, 127.7, 127.8, 128.2, 137.2, 138.2, 138.2, 138.4, 138.5; MALDI TOF MS: calcd for $C_{68}H_{70}NaO_{11}$ $[M+Na]^+$, 1085.48; found 1085.33; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{68}H_{70}O_{11}Na_1$, 1085.48, found 1085.43; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{68}H_{70}O_{11}Na_1$, 1085.4816, found 1085.4837.

Compound **3β**: $[\alpha]_D^{27}$ −57.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33–3.43 (m, 5-H^{Man1}, 3-H^{Man2}, 2H), 3.54–3.73 (m, 6a-H ^{Man1}, 6b-H^{Man1}, 5-H ^{Man2}, 6a-H ^{Man2}, 6b-H^{Man2}, 5H), 3.77–3.84 (m, 4-H^{Man1}, 4-H^{Man2}, 2H), 3.91–3.94 (m, 3-H^{Man1}, 2-H^{Man2}, 2H), 4.28 (d, J = 11.5 Hz, –CH_2Ph, 1H), 4.57–4.28 (m, 2-H^{Man1}, 1-H^{Man2}, –CH_2Ph, 10H), 4.64–4.70 (m, –CH_2Ph, 3H), 4.76 (d, J = 11.9 Hz, –CH_2Ph, 1H), 4.83 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.92 (d, J = 11.4 Hz, –CH_2Ph, 1H), 4.95 (d, J = 1.8 Hz, 1-H^{Man1}, 1H), 5.03 (d, J = 11.9 Hz, –CH_2Ph, 1H), 6.95–7.44 (m, Ar, 40H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.9, 69.2, 70.1, 70.8, 71.4, 71.5, 73.3, 73.4, 74.0, 74.2, 74.8, 74.9, 75.1, 75.8, 78.0, 81.6, 96.4 (C1^{Man1}, J_{C-H} = 172.6 Hz), 99.31 (C1^{Man2}, J_{C-H} = 158.3 Hz), 127.5, 127.5, 127.7, 127.7, 127.9, 128.0, 128.2, 128.4, 138.1, 138.4, 138.8; MALDI TOF MS: calcd for $C_{68}H_{70}NaO_{11}$ $[M+Na]^+$, 1085.48; found 1085.32; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{68}H_{70}O_{11}Na_1$, 1085.48, found 1085.44; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{68}H_{70}O_{11}Na_1$, 1085.4816, found 1085.4844.

4.9. Benzyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (7)

Compound **7α**: $[\alpha]_D^{24}$ 27.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.60–3.81 (m, 2-H^{Man1}, 5-H^{Man1}, 6-H^{Man1}, 4-H^{Man2}, 5-H^{Man2}, 6a-H^{Man2}, 6b-H^{Man2}, 7H), 3.86–3.91 (m, 3-H^{Man2}, 3-H^{Man1}, 2H), 3.98 (t, J = 2.3 Hz, 2-H^{Man2}, 1H), 4.02 (dd, J = 9.2, 3.2 Hz, 6a-H^{Man1}, 1H), 4.13 (t, J = 9.6 Hz, 4-H^{Man1}, 1H), 4.39–4.76 (m, –CH_2Ph, 12H), 4.85 (d, J = 1.8 Hz, 1-H^{Man2}, 1H), 5.08 (d, J = 1.4 Hz, H-1^{Man1}, 1H), 5.53 (s, >C*H*Ph, 1H), 7.14–7.45 (m, Ar, 35H); ^{13}C NMR (CDC_{l3}, 100 MHz): δ 64.6, 68.7, 69.1, 69.2, 72.2, 72.7, 73.0, 73.3, 73.4, 74.4, 74.9, 75.2, 76.2, 76.4, 77.2, 79.2, 80.1, 98.2 (C1^{Man2}, J_{C-H} = 171.7 Hz), 100.5 (C1^{Man1}, J_{C-H} = 179.3 Hz), 101.5 (J_{C-H} = 166.9 Hz), 126.1, 127.49, 127.52, 127.88, 127.93, 128.0, 128.1, 128.17, 128.21, 128.3, 128.4, 128.5, 137.1, 137.7, 138.09, 138.14, 138.3, 138.5, 138.8; MALDI-TOF MS: $[M+Na]^+$ calcd for $C_{61}H_{62}O_{11}Na$, 993.42, found 993.57; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{61}H_{62}O_{11}Na_1$, 993.42, found 993.39; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{61}H_{62}O_{11}Na_1$, 993.4190, found 993.4148.

Compound **7β**: $[\alpha]_D^{23}$ −44.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (dd, J = 10.1, 3.2 Hz, 3-H^{Man1}, 1H), 3.57 (dd, J = 11.0, 1.8 Hz, 6a-H^{Man2}, 1H), 3.63 (dd, J = 11.0, 4.6 Hz, 6b-H^{Man2}, 1H), 3.71–3.76 (m, 6a-H^{Man1}, 5-H^{Man2}, 2H), 3.84 (dd, J = 9.6,

9.2 Hz, 4-H^{Man2}, 1H), 3.90–3.93 (m, 2-H^{Man2}, 3-H^{Man1}, 2H), 4.12 (dd, J = 10.1, 9.2 Hz, 6b-H^{Man1}, 1H), 4.14 (dd, J = 10.5, 5.0 Hz, 6b-H^{Man1}, 1H), 4.21–4.24 (m, 2-H^{Man2}, –CH_2Ph, 2H), 4.37–4.78 (m, 1-H^{Man1}, –CH_2Ph, 11H), 4.93 (d, J = 1.8 Hz, 1-H^{Man2}, 1H), 5.00 (d, J = 11.9 Hz, –CH_2Ph, 1H), 5.51 (s, >C*H*Ph, 1H), 6.87–7.01 (m, Ar, 2H), 7.10–7.36 (m, Ar, 27H), 7.36–7.45 (m, Ar, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.6, 68.5, 68.9, 69.3, 70.7, 71.6, 71.8, 72.9, 73.3, 73.5, 74.3, 74.95, 75.04, 76.1, 77.2, 78.1, 78.3, 96.6 (C1^{Man2}, J_{C-H} = 170.7 Hz), 100.3 (C1^{Man1}, J_{C-H} = 154.5 Hz), 101.3 (J_{C-H} = 164.0 Hz), 126.0, 127.5, 127.8, 127.9, 128.1, 128.15, 128.24, 128.27, 128.30, 128.4, 128.7, 137.1, 137.6, 138.1, 138.3, 138.7; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{61}H_{62}O_{11}Na$, 993.42, found 993.42; ESI-TOF MS: [M+Na]$^+$ calcd for $C_{61}H_{62}O_{11}Na_1$, 993.42, found 993.36; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{61}H_{62}O_{11}Na_1$, 993.4190, found 993.4151.

4.10. Benzyl 4,6-*O*-cyclohexylidene-2,3-di-*O*-benzyl-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (8)

Compound **8α**: $[\alpha]_D^{25}$ 48.2° (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30–2,25 (m, 10H), 3.68–3.87 (m, 2-H^{Man1}, 3-H^{Man1}, 5-H^{Man1}, 6a-H^{Man1}, 6b-H^{Man1}, 4-H^{Man2}, 5-H^{Man2}, 6a-H^{Man2}, 6b-H^{Man2}, 9H), 3.94 (dd, J = 9.2, 3.2 Hz, 3-H^{Man2}, 1H), 4.04 (dd, J = 2.8, 1.8 Hz, 2-H^{Man2}, 1H), 4.22 (t, J = 9.6 Hz, 4-H^{Man1}, 1H), 4.46–4.65 (m, –CH_2Ph, 8H), 4.71 (d, J = 12.8 Hz, –CH_2Ph, 2H), 4.80 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.82 (d, J = 11.9 Hz, –CH_2Ph, 1H), 4.92 (d, J = 1.8 Hz, 1-H^{Man2}, 1H), 5.11 (d, J = 1.4 Hz, 1-H^{Man1}, 1H), 7.19–7.38 (m, Ar, 30H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 23.0, 25.6, 28.0, 38.2, 61.7, 65.5, 69.1, 71.3, 72.1, 72.6, 72.9, 73.3, 73.4, 74.0, 74.8, 75.2, 76.5, 77.2, 80.0, 98.4, 99.8 (C1^{Man2}, J_{C-H} = 171.7 Hz), 100.6 (C1^{Man1}, J_{C-H} = 179.3 Hz), 127.2, 127.4, 127.5, 127.7, 127.87, 127.92, 127.95, 128.10, 128.3, 128.36, 128.42, 128.5, 137.1, 138.1, 138.25, 138.31, 138.5, 139.3; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{60}H_{66}O_{11}Na_1$, 985.45. found 985.29; ESI-TOF MS: [M+Na]$^+$ calcd for $C_{60}H_{66}O_{11}Na_1$, 985.45, found 985.40; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{60}H_{66}O_{11}Na_1$, 985.4503, found 985.4527.

Compound **8β**: $[\alpha]_D^{26}$ −26.0° (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28–2.26 (m, 10H), 3.10 (ddd, 5-H^{Man1}, J = 9.6, 6.4, 3.2 Hz, 1H), 3.38 (dd, J = 9.6, 3.7 Hz, 3-H^{Man1}, 1H), 3.63 (dd, J = 10.6, 1.8 Hz, 6a-H^{Man2}, 1H), 3.68 (dd, J = 11.0, 4.6 Hz, 6b-H^{Man2}, 1H), 3.75–3.82 (m, 5-H^{Man2}, 6a-H^{Man1}, 6b-H^{Man1}, 3H), 3.88 (dd, J = 10.1, 8.7 Hz, 4-H^{Man2}, 1H), 3.93 (d, J = 3.2 Hz, 2-H^{Man1}, 1H), 3.97 (dd, J = 8.7, 3.2 Hz, 3-H^{Man2}, 1H), 4.19 (dd, J = 10.1, 9.6 Hz, 4-H^{Man1}, 1H), 4.26 (s, 2-H^{Man2}, 1H), 4.58 (d, J = 12.4 Hz, –CH_2Ph, 1H), 4.63 (d, J = 12.8 Hz, –CH_2Ph, 1H), 4.70–4.76 (m, –CH_2Ph, 3H), 4.81–4.87 (m, –CH_2Ph, 2H), 4.98 (d, J = 1.8 Hz, 1-H^{Man1}, 1H), 5.03 (d, J = 11.9 Hz, –CH_2Ph, 1H), 7.05–7.09 (m, Ar, 2H), 7.15–7.37 (m, Ar, 24H), 7.43–7.45 (m, Ar, 2H), 7.51–7.53 (m, Ar, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 23.0, 25.6, 28.0, 38.1, 61.5, 68.8, 68.9, 69.2, 70.5, 70.7, 71.6, 71.8, 72.9, 73.3, 74.3, 74.9, 77.7, 78.1, 96.7, 99.9 (C1^{Man2}, J_{C-H} = 169.8 Hz), 100.4 (C1^{Man1}, J_{C-H} = 157.4 Hz), 127.2, 127.3, 127.5, 127.8, 127.87, 127.92, 128.0, 128.06, 128.12, 128.2, 128.4, 128.6, 137.1, 138.1, 138.4, 138.78, 138.83, 138.9; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{60}H_{66}O_{11}Na_1$, 985.45. found 985.55; ESI-TOF MS: [M+Na]$^+$ calcd for $C_{60}H_{66}O_{11}Na_1$, 985.45, found 985.41; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{60}H_{66}O_{11}Na_1$, 985.4503, found 985.4537.

4.11. Benzyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (9)

Compound **9α**: $[\alpha]_D^{25}$ 11.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.55 (dd, J = 11.0, 1.8 Hz, 6a-H^{Man1}, 1H), 3.63 (dd, J = 10.5, 1.4 Hz, 6a-H^{Man2}, 1H), 3.68–3.75 (m, 6b-H^{Man1}, 5-H^{Man1}, 6b-H^{Man1}, 3H), 3.80 (dd, J = 9.6, 9.2 Hz, 4-H^{Man2}, 1H), 3.86–3.98 (m, 2-H^{Man2}, 4-H^{Man1}, 3-H^{Man2}, 5-H^{Man1}, 4H), 4.02 (dd, J = 99.2, 2.8 Hz, 3-H^{Man1}, 1H), 4.31 (d, J = 11.9, –CH_2Ph, 1H), 4.36–4.44 (m, –CH_2Ph, 3H), 4.48 (d, J = 11.9 Hz, –CH_2Ph, 2H), 4.57–4.64 (m, 5H), 4.68 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.68 (d, J = 11.0 Hz, –CH_2Ph, 2H), 4.75–4.80 (d, J = 11.0 Hz, –CH_2Ph, 2H), 4.91 (d, J = 1.8 Hz, 1-H^{Man2}, 1H), 5.11 (d, J = 1.8 Hz, 1-H^{Man1}, 1H), 5.70 (dd, J = 2.7, 2.3 Hz, 2-H^{Man1}, 1H), 7.10–7.30 (m, Ar, 37H), 7.48 (dd, J = 7.8, 1.4 Hz, Ar, 1H), 7.89–8.00 (dd, J = 9.6, 1.4 Hz, Ar, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 69.0, 69.2, 71.7, 72.96, 72.04, 72.2, 73.3, 73.4, 74.3, 74.7, 75.2, 77.2, 78.1, 80.0, 98.0 (C1^{Man2}, J_{C-H} = 172.6 Hz), 99.6 (C1^{Man1}, J_{C-H} = 178.4 Hz), 127.4, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.30, 128.32, 128.4, 129.9, 133.0, 137.2, 138.3, 138.4, 138.45, 138.50, 165.4; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{68}H_{68}O_{12}Na_1$, 1099.46, found 1099.48; ESI-TOF MS: [M+Na]$^+$ calcd for $C_{68}H_{68}O_{12}Na_1$, 1099.46, found 1099.47; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{68}H_{68}O_{12}Na_1$, 1099.4609, found 1099.4575.

Compound **9β**: $[\alpha]_D^{26}$ −55.7 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40–3.54 (m, 5-H^{Man1}, 4-H^{Man2}, 6a-H^{Man2}, 6b-H^{Man2}, 4H), 3.67–3.73 (m, 3-H^{Man1}, 5-H^{Man2}, 6a-H^{Man1}, 6b-H^{Man1}, 4H), 3.80–3.85 (m, –CH_2Ph, 3-H^{Man2}, 2H), 3.91 (dd, J = 10.1, 9.6 Hz, 4-H^{Man1}, 1H), 4.21 (d, J = 11.5 Hz, –CH_2Ph, 1H), 4.26 (d, J = 11.5, –CH_2Ph, 1H), 4.33 (t, J = 2.3 Hz, 2-H^{Man2}, 1H), 4.39–4.43 (m, –CH_2Ph, 3H), 4.47–4.53 (m, –CH_2Ph, 4H), 4.66 (d, J = 9.6 Hz, –CH_2Ph, 1H), 4.68 (s, 1-H^{Man1}, 1H), 4.75 (d, J = 11.4 Hz, –CH_2Ph, 1H), 4.82 (d, J = 11.9 Hz, –CH_2Ph, 1H), 4.83 (d, J = 11.0 Hz, –CH_2Ph, 1H), 4.93 (d, J = 1.8 Hz, 1-H^{Man2}, 1H), 5.81 (d, J = 3.2 Hz, 2-H^{Man1}, 1H), 6.81–6.83 (m, Ar, 2H), 7.02–7.34 (m, Ar, 36H), 8.04 (d, J = 8.2, Ar, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.7, 69.2, 69.3, 69.6, 70.6, 71.0, 71.4, 71.8, 73.1, 73.4, 74.3, 74.5, 75.3, 75.4, 77.2, 78.3, 80.0, 96.4 (x2, C1^{Man1}, C1^{Man2}, J_{C-H} = 166.0 Hz), 127.1, 127.4, 127.5, 127.7, 127.8, 128.0, 128.1, 128.19, 128.23, 128.3, 128.4, 130.3, 130.4, 132.6, 137.2, 137.6, 138.2, 138.3, 138.4, 138.9; MALDI-TOF MS: [M+Na]$^+$ calcd for $C_{68}H_{68}O_{12}Na_1$, 1099.46, found 1099.46; ESI-TOF MS: [M+Na]$^+$ calcd for $C_{68}H_{68}O_{12}Na_1$, 1099.46, found 1099.44; HRMS ESI-TOF: [M+Na]$^+$ calcd for $C_{68}H_{68}O_{12}Na_1$, 1099.4609, found 1099.4619.

4.12. General procedure for high through-put screening for O-glycosylation

Each 12.0 mL of solution of acceptor **1** (48.6 mg, 90.0 μmol), donor **[D$_7$]2** (72.8 mg, 122 μmol) and DTBMP (34.5 mg, 140 μmol) in 2.0 mL of CH_2Cl_2 were pipetted into multiplicate tubes, and the mixtures were evaporated by flashing with N_2 gas. In each tube, 15.0 μmol of acceptor, 20.3 μmol of donor and 22.5 μmol of DTBMP were prepared for the reaction. After MS4A (45 mg) and each solvent (500 μL) were added to the mixture, methyl trifluoromethanesulfonate (4.2 μL, 38.0 μmol) was added to each tube. the mixture was rapidly mixed and frozen by liquid nitrogen. The mixture was stored in refrigerator at 4 °C for 6 h and was defrosted at temperature. The reaction quenched with triethylamine followed by filtration through Celite pad and washing of pad with ethyl acetate. The combined solutions were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by gel filtration (Bio beads SX-3, toluene/ethyl acetate = 1:1) to give the mixture of the isomers (14.7 mg, 90%, α:β = 4.3:1). Results of glycosylations are listed in Table 1 (entries 15–17) and Table 2 which were obtained by following two analytical methods.

4.12.1. Determination of the stereoselectivities by ^{1}H-NMR analysis

The anomeric ratios of products were estimated from the relative intensities of H-1 signals (in C_6D_6) of α- and β-isomers by analyzing the crude mixture.

4.12.2. Determination of the yield by the quantitative MALDI-TOF MASS analysis

The crude mixtures were diluted with 15 mL of CH_3CN. A 50 μL measure of 1.0 mM standard solution of each of the three non-labeled compounds for the reaction was pre-mixed with 50 μL of the crude solutions for MS analysis. The resulting solutions were measured by MALDI-TOF MASS using the RASTER function. The molar ratio of labeled to non-labeled compound was obtained from the ratio of each value (mV) at the apex of the ion peak of $[M+Na]^+$. For Table 1 (entries 15–17) and Table 2, **[D_7]1**, **2** and **3** were used as standard for **1**, **[D_{28}]2** and **[D_{28}]3**. For Table 3 (entries 16–21), **[D_7]1**, **[D_{14}]5** and **[D_{14}]8** were used as standard for **1**, **5** and **8**. [D_7]Bn protected compounds **[D_{28}]2**, **[D_7]1** and **[D_{14}]5** were synthesized according to the synthesis of corresponding Bn protected compounds **2**, **1** and **5**, respectively; **[D_{28}]2**: HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{35}H_{10}D_{28}O_5S_1Na_1$, 621.4095, found 621.4068; **[D_7]1**: HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{34}H_{29}D_7O_6Na_1$, 570.2849, found 570.2831; **[D_{14}]5**: HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{27}H_{20}D_{14}O_5S_1Na_1$, 507.2903, found 507.2926.

4.12.3. Benzyl 4,6-*O*-cyclohexylidene-2,3-di-*O*-[D_7]benzyl-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**[D_{14}]8**) for Table 3 (entries 13–18) as the standard

Compound **[D_{14}]8α**: $[\alpha]_D^{26}$ 57.2° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.31–2,20 (m, 10H), 3.58–3.80 (m, 2-H^{Man1}, 3-H^{Man1}, 5-H^{Man1}, 6a-H^{Man1}, 6b-H^{Man1}, 4-H^{Man2}, 5-H^{Man2}, 6a-H^{Man2}, 6b-H^{Man2}, 9H), 3.86 (dd, *J* = 9.2, 2.7 Hz, 3-H^{Man2}, 1H), 3.96 (t, *J* = 2.3 Hz, 2-H^{Man2}, 1H), 4.15 (dd, *J* = 10.1, 9.6 Hz, 4-H^{Man1}, 1H), 4.38–4.58 (m, –C*H*$_2$Ph, 5H), 4.63 (d, *J* = 12.8 Hz, –C*H*$_2$Ph, 2H), 4.72 (d, *J* = 11.0 Hz, –C*H*$_2$Ph, 1H), 4.84 (d, *J* = 1.8 Hz, 1-H^{Man2}, 1H), 5.03 (d, *J* = 1.4 Hz, 1-H^{Man1}, 1H), 7.10–7.31 (m, Ar, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 23.0, 25.7 28.0, 38.2, 61.7, 65.5, 69.1, 71.3, 72.1, 72.6, 73.4, 74.0, 74.8, 75.2, 76.5, 80.1, 98.4, 99.8 (C1^{Man2}, J_{C-H} = 173.6 Hz), 100.7 (C1^{Man1}, J_{C-H} = 174.5 Hz), 127.4, 127.5, 127.7, 127.9, 128.0, 128.3, 128.37, 128.43, 128.5, 137.1, 138.0, 138.1, 138.3, 138.5; MALDI-TOF MS: $[M+Na]^+$ calcd for $C_{60}H_{52}D_{14}O_{11}Na_1$, 999.54, found 999.66; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{60}H_{52}D_{14}O_{11}Na_1$, 999.54, found 999.53; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{60}H_{52}D_{14}O_{11}Na_1$, 999.5382, found 999.5343.

Compound **[D_{14}]8β**: $[\alpha]_D^{26}$ −30.6° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.22–2.16 (m, 10H), 3.02 (td, *J* = 9.6, 6.0 Hz, 5-H^{Man1}, 1H), 3.29 (dd, *J* = 9.2, 2.8 Hz, 3-H^{Man1}, 1H), 3.55 (dd, *J* = 8.7, 1.8 Hz, 6a-H^{Man2}, 1H), 3.55 (dd, *J* = 8.1, 4.6 Hz, 6b-H^{Man2}, 1H), 3.67–3.74 (m, 5-H^{Man2}, 6a-H^{Man1}, 6b-H^{Man1}, 3H), 3.80 (dd, *J* = 10.1, 8.7 Hz, 4-H^{Man2}, 1H), 3.84 (d, *J* = 3.2 Hz, 2-H^{Man1}, 1H), 3.99 (dd, *J* = 9.2, 3.7 Hz, 3-H^{Man2}, 1H), 4.11 (dd, *J* = 10.1, 9.6 Hz, 4-H^{Man1}, 1H), 4.17 (s, 2-H^{Man2}, 1H), 4.18 (d, *J* = 11.0 Hz, –C*H*$_2$Ph, 1H), 4.36–4.44 (m, –C*H*$_2$Ph, 3H), 4.44 (s, 1-H^{Man1}, 1H), 4.50 (d, *J* = 12.4 Hz, –C*H*$_2$Ph, 1H), 4.64 (d, *J* = 11.9 Hz, –C*H*$_2$Ph, 1H), 4.67 (d, *J* = 11.5 Hz, –C*H*$_2$Ph, 1H), 4.74 (d, *J* = 11.4 Hz, –C*H*$_2$Ph, 1H), 4.90 (d, *J* = 2.3 Hz, 1-H^{Man2}, 1H), 6.97–7.01 (m, Ar, 2H), 7.10–7.27 (m, Ar, 16H), 7.35–7.37 (m, Ar, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 23.0, 25.6, 28.0, 38.1, 61.5, 68.8, 68.9, 69.2, 70.5, 70.7, 71.6, 72.9, 73.3, 74.9, 76.3, 77.6, 78.1, 96.7, 99.9 (C1^{Man2}, J_{C-H} = 169.8 Hz), 100.4 (C1^{Man1}, J_{C-H} = 157.4 Hz), 127.3, 127.5, 127.8, 127.9, 128.0, 128.07, 128.12, 128.2, 128.4, 137.1, 138.1, 138.4, 138.6, 138.8; MALDI-TOF MS: $[M+Na]^+$ calcd for $C_{60}H_{52}D_{14}O_{11}Na_1$, 999.54, found 999.51; ESI-TOF MS: $[M+Na]^+$ calcd for $C_{60}H_{52}D_{14}O_{11}Na_1$, 999.54, found 999.53; HRMS ESI-TOF: $[M+Na]^+$ calcd for $C_{60}H_{52}D_{14}O_{11}Na_1$, 999.5382, found 999.5343.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.04.013.

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