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PAPER

O,*O*-Dimethylthiophosphonosulfenyl bromide-silver triflate: a new powerful promoter system for the preactivation of thioglycosides†‡

Peng Peng and Xin-Shan Ye*

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O,*O*-Dimethylthiophosphonosulfenyl bromide (DMTPSB) in combination with silver triflate provides a powerful thiophilic promoter system. Both "armed" and "disarmed" thioglycoside glycosyl donors can be activated to form glycosidic linkages efficiently by the pre-activation protocol. The usefulness of this new promoter is illustrated by a successful iterative one-pot oligosaccharide assembly.

Introduction

Oligosaccharides and glycoconjugates play an important role in many biological processes.[1] However, understanding the functions of carbohydrates is hampered by the lack of general methods for the preparation of this class of compounds. In the past decades, many advances on oligosaccharide synthesis have been achieved, including solid-phase strategy,[2] solution-phase protocol,[3] and chemo-enzymatic method.[4] Among these strategies, the one-pot multi-step glycosylation approach[5] is very attractive. The reactivity-based one-pot sequential glycosylation relies on the relative reactivities of glycosyl donors. To obtain glycosyl donors with suitable anomeric reactivities, extensive protective group manipulations must be carried out, making the synthetic process complicated and the overall efficiency decreased. Our recently developed preactivation-based iterative one-pot glycosylation[6] conceptually overcomes the shortages of reactivity-based glycosylation. Furthermore, since the acceptor is absent in the process of donor activation and reacts with the "activated donor" (the intermediate resulting from the reaction of donor and promoter), the stereochemistry[7–11] and reaction capacity[6,12,13] of pre-activation glycosylation could be different from the traditional glycosylation protocol. Because of these advantages, pre-activation strategy holds the potential for the assembly of oligosaccharide library and automated synthesis.

In pre-activation one-pot glycosylation, the widely-used glycosyl donors are thioglycosides, which are convenient in preparation and stable in many functional group transformations. The thioacetal functionality combines the role of an anomeric protective group and an efficient leaving group.[14] So far there are many promoter systems available for the activation of thioglycosides towards glycosylations.[15] However, only limited promoters have been used in pre-activation approach. The widely-used promoters for thioglycoside activation (*e.g.* NIS/TfOH; NIS/AgOTf; NIS/TESOTf) cannot be used in pre-activation one-pot oligosaccharide synthesis, due to the formation of succinimide by-products which may result in the complication of coupling products and decrease the efficacy of glycosylations.[5b,16] The promoters currently used in pre-activation protocol mainly include benzenesulfinyl piperidine/triflic anhydride (BSP/Tf_2O),[15h] diphenyl sulfoxide/triflic anhydride (DPSO/Tf_2O),[15i] *p*-toluenesulfinyl chloride/silver triflate (*p*-TolSCl/AgOTf),[6] and benzenesulfinyl morpholine/triflic anhydride (BSM/Tf_2O).[15l] Recently, methyl triflate (MeOTf) and Me_3OBF_4 have also been used for pre-activation of thioglycosides.[17] In spite of the promoters available, they still have some disadvantages. For instance, *p*-TolSCl is unstable and it needs to be distilled under an inert atmosphere before use; BSP and BSM are not efficient for the activation of some low-reactive "disarmed" donors, and they as well as DPSO would produce an unfavorable *S*-thioalkyl sulfonium by-product[18] which would decompose the coupling product in one-pot oligosaccharide synthesis. Therefore, new and powerful promoters for the pre-activation of thioglycosides, especially for the "disarmed" donors, are in great demand.

O,*O*-Dimethylthiophosphonosulfenyl bromide (DMTPSB, **1**, Fig. 1), prepared from tetramethyl thioperoxydiphosphate (**2**) and bromine, is a "soft" electrophilic reagent and easily binds to the "soft" sulfur atom. Since it was first synthesized by Michalski and co-workers,[19] DMTPSB has attested considerable interest in the field of organic chemistry, due to its easy preparation and low cost. However, DMTPSB has never been applied to the glycosylation reaction. Herein, we report DMTPSB as a new promoter for the pre-activation of thioglycoside donors.

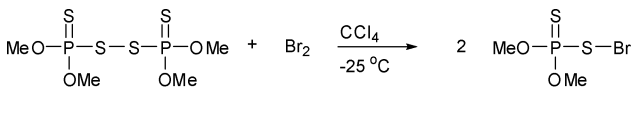

Fig. 1 *O*,*O*-Dimethylthiophosphonosulfenyl bromide (DMTPSB, **1**).

State Key Laboratory of Natural and Biomimetic Drugs, Peking University, and School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd No. 38, Beijing, 100191, China. E-mail: xinshan@bjmu.edu.cn; Fax: +86-10-82802724; Tel: +86-10-62014949

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‡ Dedicated to Professor Henry N. C. Wong on the occasion of his 60th birthday.

Results and discussion

Firstly, to test the activating capability of DMTPSB, the glycosylation reaction of benzoylated thioglycoside donor **3** with glucoside acceptor **10** was investigated by the use of pre-activation protocol. Through a preliminary screening of conditions, we found that DMTPSB alone was unable to activate donor **3**. However, when the combination of DMTPSB and AgOTf was used, donor **3** was activated promptly at low temperature. We proposed that DMTPSB may react with silver triflate to produce a more electrophilic reagent $(MeO)_2P(S)SOTf$, which can activate the thioglycosides easily. Thus, donor **3** was quickly activated (monitored by TLC) after the addition of the mixture of DMTPSB and AgOTf at –72 °C. Subsequently, acceptor **10** was added to the reaction mixture, and the coupling reaction was completed smoothly, providing the disaccharide **17** in 90% isolated yield as a pure β-isomer (Table 1, entry 1). Under the DMTPSB/AgOTf pre-activation conditions, a variety of glycosyl donors and acceptors were employed to evaluate the efficacy and scope of this new promoter (Table 1). As shown, the "disarmed" thioglycoside **3**, activated by DMTPSB-AgOTf, reacted readily with the glucoside acceptors **11**, **12**, and **13** having a free hydroxyl group exposed at the *C*-3, *C*-4, and *C*-2 positions, respectively, affording the corresponding disaccharides **18**, **19**, and **20** in high yields (entries 2–4). The low-reactive benzoyl-protected acceptor **14** also coupled smoothly with **3** to obtain disaccharide **27** in 95% isolated yield (entry 11). Other "disarmed" donors, such as thioglucoside **5** (entries 6, 7), thiomannoside **7** (entry 9), and glucosamine derivative **8** (entry 10), were also activated quickly and efficiently at –72 °C and the coupling products were obtained in high yields.

The "disarmed" donor **9** underwent the glycosylation reaction with the "armed" thioglycoside acceptor **15** to provide the coupling product **28** in an acceptable yield (entry 12), whereas this reaction was unable to be realized by the reactivity-based chemoselective method.[5b] The donor **9** also reacted with the low-reactive benzoyl-protected thioglycoside acceptor **16** giving disaccharide **29** in a good yield (entry 13).

All the disaccharides formed above were completely single anomers. Most glycosylations (entries 1–4, 6, 7, 9, 11, 12, 13) afforded 1,2-*trans* stereoselectivity because of the neighboring group participation at *C*-2, whereas the glucosamine donor **8** (entry 10) showed 1,2-*cis* stereoselectivity owing to the special protective group and an excess of AgOTf.[10,20]

As expected, the "armed" donors were able to be activated more easily. The glycosylations of benzylated thioglycosides **4** and **6** with acceptor **11** having a secondary hydroxyl group exposed proceeded smoothly. The coupling reaction of thiogalactoside donor **4** and glucoside acceptor **11** (entry 5) displayed good α-selectivity, whereas the reaction of thioglucoside donor **6** and acceptor **11** resulted in a poor anomeric selectivity (entry 8).

To check the efficiency of this new promoter, the glycosylation reactions promoted by DMTPSB/AgOTf and *p*-TolSCl/AgOTf, respectively, were investigated, and the similar yields of glycosylations were obtained.[21] Although it seemed that the yields of the former are a little lower, DMTPSB is more readily prepared and can be stored.

The next issue was to determine if DMTPSB/AgOTf could be applied to a preactivation-based iterative one-pot oligosaccharide synthesis. Indeed, this promoter system worked well, by using nearly equimolar promoter to minimize the formation of by-products. As exemplified in Scheme 1, the thiogalactoside donor **9** was pre-activated by DMTPSB/AgOTf at –72 °C, followed by the addition of building block **16**. After the coupling reaction was completed, the newly formed disaccharide without isolation was activated again with DMTPSB/AgOTf, then followed by the addition of acceptor **10**, providing the final trisaccharide **30** in 60% isolated yield and with good stereoselectivity. This demonstrated that this new promoter system can be used in the preactivation-based one-pot assembly of oligosaccharides.

Conclusion

In summary, DMTPSB as a new and highly powerful promoter for the glycosylation reactions has been identified. The combination of DMTPSB and AgOTf works as an efficient promoter system for the pre-activation of thioglycosides. Both "disarmed" and "armed" glycosyl donors can be activated smoothly at low temperature, and the coupling reactions proceed very well with a range of acceptors in high yields. This reagent overcomes some limitations of the current promoters for the pre-activation protocol and can be employed in iterative one-pot oligosaccharide assembly.

Experimental

General

All chemicals were purchased as reagent grade and used without further purification, unless otherwise noted. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride (CaH_2), carbon tetrachloride was distilled over calcium chloride ($CaCl_2$). All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper or rubber septa under a positive pressure of argon or nitrogen. Analytical TLC was performed on silica gel 60-F_{254} precoated on aluminium plates (E. Merck), with detection by UV (254 nm) and/or by staining with acidic ceric ammonium molybdate. Solvents were evaporated under reduced pressure and below 35 °C (bath). Organic solutions of crude products were dried over anhydrous Na_2SO_4. Optical rotations were measured with a AA-10R automatic polarimeter. Column chromatography was performed employing Silica Gel 200–300 mesh. ^{1}H NMR spectra were recorded on a JEOL AL-300, Varian INOVA-500 or Advance DRX Bruker-400 spectrometers at 25 °C. Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$ ppm) in deuterated chloroform. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ ($\delta = 77.00$ ppm). High-resolution mass spectra were recorded on a Bruker APEX IV. Low-resolution mass spectra were recorded on Finnigan TRACE 2000 MS. IR was measured with a Thermo Nicolet Nexus 470.

Compound **2** was prepared as described in the literature[22] as white crystals: m.p. 53 °C (from methanol) (lit[22a] 51 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 6H), 3.83 (s, 6H); ^{31}P NMR (121.5 MHz, $CDCl_3$, 85% H_3PO_3 as external standard) δ 96.1 (lit[22b] 89.5); *m*/*z* (EI) 314 (M^+), 125 ($(MeO)_2P^+S$); The spectroscopic data coincide with the previous report.[22]

O,*O*-Dimethylthiophosphonosulfenyl bromide (**1**) was prepared as described in the literature.[19] A solution of Br_2 (0.51 g,

Table 1 Glycosylations promoted by DMTPSB-AgOTf under pre-activation conditions

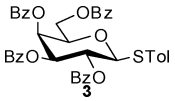
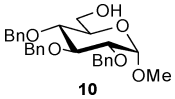
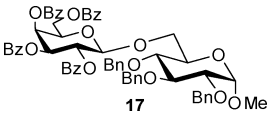
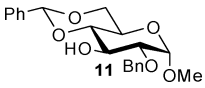
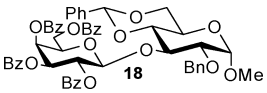
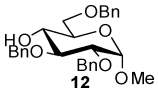
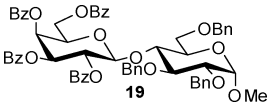
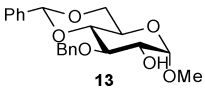
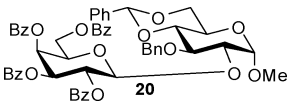
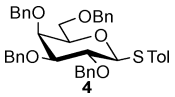
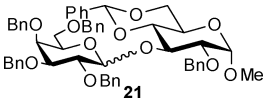
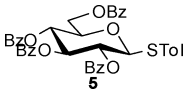
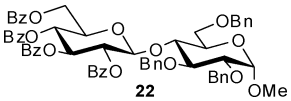
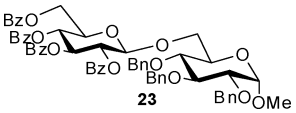
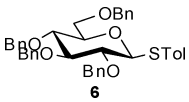
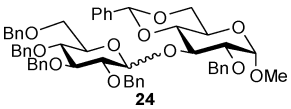
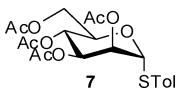
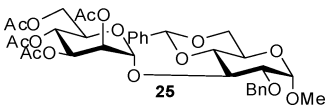
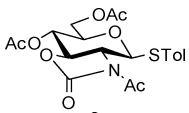
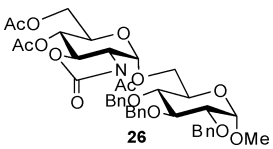
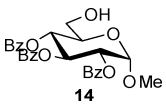
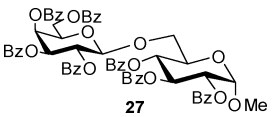
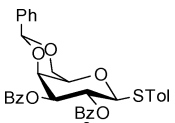
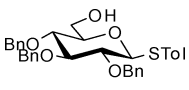
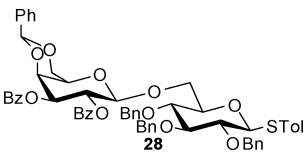
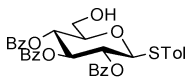
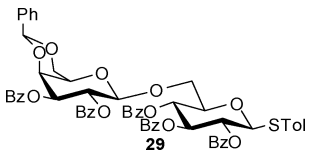
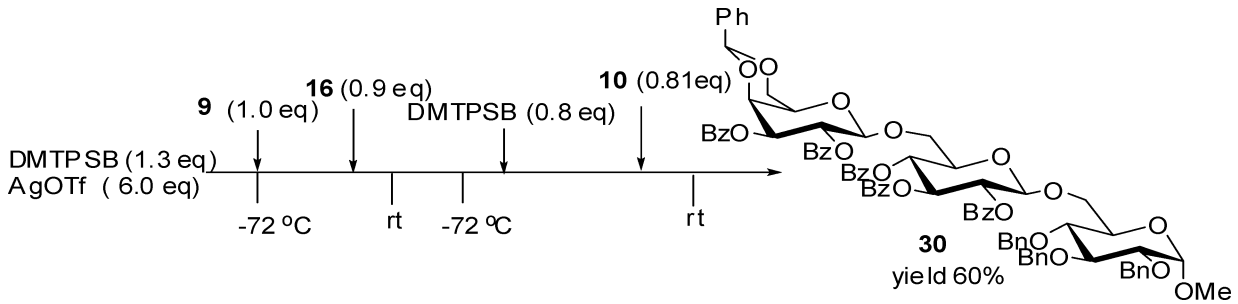
Entry	Donor	Acceptor	Product	Yield	α : β
1	 **3**	 **10**	 **17**	90%	β only
2	**3**	 **11**	 **18**	89%	β only
3	**3**	 **12**	 **19**	91%	β only
4	**3**	 **13**	 **20**	84%	β only
5	 **4**	**11**	 **21**	85%	5.5 : 1[a]
6	 **5**	**12**	 **22**	89%	β only
7	**5**	**10**	 **23**	92%	β only
8	 **6**	**11**	 **24**	83%	1.4 : 1
9	 **7**	**11**	 **25**	93%	α only
10	 **8**	**10**	 **26**	75%	α only
11	**3**	 **14**	 **27**	95%	β only
12	 **9**	 **15**	 **28**	63%	β only

Table 1 *(Contd.)*

Entry	Donor	Acceptor	Product	Yield	α : β
13	**9**	 **16**	 **29**	73%	β only

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



Scheme 1 Preactivation-based iterative one-pot assembly of **30**.

3.2 mmol) in CCl_4 (1.0 mL) was added to a stirred solution of **2** (1.0 g, 3.2 mmol) in CCl_4 (4.0 mL) at −25 °C, the mixture was stirred for 10 min. The solution was used as the promoter directly without purification. The solution can be stored for several weeks avoided from moisture in fridge.

General procedure for pre-activation glycosylation

A mixture of AgOTf (18.5 mg, 72 μmol) and activated molecular sieves (4 Å powder, 300 mg) in dry CH_2Cl_2 (3 mL) was cooled to −72 °C under argon atmosphere. After stirring for 5 min, DMTPSB (23 μL, 1.23 M in CCl_4 solution, 28 μmol) and donor **3** (15.5 mg, 22 μmol) were added *via* a micro-syringe. After TLC detection indicated that donor **3** was completely consumed, acceptor **10** (10.5 mg, 19 μmol) was added. The reaction was further stirred for 15 min and warmed gradually to room temperature. The reaction was quenched by triethylamine (0.2 mL) and the precipitate was filtered off through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether/ether acetate = 5 : 1), affording **17** (17.7 mg, 90%) as a semisolid.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside (17). Compound **17**[23] (17.7 mg, 90% yield as a semisolid) was prepared according to the general procedure for pre-activation glycosylation from donor **3** (15.5 mg, 22 μmol) and acceptor **10** (10.5 mg, 19 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 5 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–8.09 (m, 4H), 7.88 (d, 2H, J = 6.9 Hz), 7.76 (d, 2H, J = 6.9 Hz), 7.37–7.63 (m, 9H), 7.19–7.33 (m, 18H, aromatic), 7.11–7.13 (m, 2H), 5.97 (d, 1H, J = 3.3 Hz, 4′-H), 5.85 (dd, 1H, J = 10.2, 7.8 Hz, 2′-H), 5.59 (dd, 1H, J = 10.2, 3.3 Hz, 3′-H), 4.90 (d, 1H, J = 11.1 Hz, PhCH_2), 4.64–4.77 (m, 4H, 1′-H, 6′-H, PhCH_2×2), 4.49–4.60 (m, 3H, 1-H, PhCH_2×2), 4.35–4.43 (m, 2H), 4.18–4.27 (m, 2H), 3.90 (t, 1H, J = 9.3 Hz), 3.75 (d, 2H, J = 9.0 Hz), 3.37–3.42 (m, 2H), 3.20 (s, 3H, OMe). The spectroscopic data coincide with the previous report.[23]

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-2-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (18). Compound **18**[15e] (16.5 mg, 89% yield as a semisolid) was prepared according to the general procedure for pre-activation glycosylation from donor **3** (15.0 mg, 21 μmol) and acceptor **11** (7.1 mg, 19 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 5 : 1). $[\alpha]_D^{27}$: +4° (c = 1 in $CDCl_3$), (lit[15e] $[\alpha]_D^{25}$: +3.5° (c = 1.5 in $CDCl_3$)); ν_{max}(KBr)/cm^{-1}: 3065, 3033, 1731, 1602, 1585, 1493, 1452, 1267, 1093, 1071, 1027, 710; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04–8.06 (m, 2H), 7.93–7.97 (m, 5H), 7.75–7.78 (m, 2H), 7.51–7.58 (m, 5H), 7.37–7.48 (m, 8H), 7.20–7.32 (m, 15H), 7.08–7.11 (m, 2H), 5.95 (d, 1H, J = 3.3 Hz, 4′-H), 5.88 (dd, 1H, J = 10.5, 7.8 Hz, 2′-H), 5.58–5.63 (m, 2H, 3′-H, PhCH), 5.22 (d, 1H, J = 8.1 Hz, 1′-H), 4.61 (d, 1H, J = 12.3 Hz, PhCH_2), 4.22–4.43 (m, 6H), 4.13 (t, 1H, J = 7.5 Hz), 3.61–3.80 (m, 3H, OMe), 3.46 (dd, 1H, J = 9.6, 3.9 Hz), 3.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.78, 165.60, 165.47, 165.39, 138.13, 137.36, 133.41, 133.18, 129.95, 129.76, 129.39, 129.15, 128.91, 128.81, 128.57, 128.35, 128.24, 128.17, 127.84, 127.71, 125.95, 101.35, 101.09, 99.01, 79.79, 79.24, 77.40, 73.99, 71.95, 70.91, 70.37, 68.97, 67.99, 62.29, 61.42, 55.24. HRMS (ESI) calcd for $C_{55}H_{50}NaO_{15}$ [M + Na]$^+$: 973.3042, found 973.3031.

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (19). Compound **19**[24] (18.1 mg, 91% yield as a semisolid) was prepared according to the general procedure for pre-activation glycosylation from donor **3** (15.0 mg, 21 μmol) and acceptor **12** (10.5 mg, 19 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 4 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, 2H, J = 7.2 Hz), 7.93 (d, 2H, J = 7.2 Hz), 7.85 (d, 2H, J = 7.2 Hz), 7.74

(d, 2H, J = 7.2 Hz), 7.18–7.56 (m, 31H), 5.84 (d, 1H, J = 3.6 Hz), 5.69 (dd, 1H, J = 10.2, 8.1 Hz), 5.29 (dd, 1H, J = 10.5, 3.3 Hz), 5.17 (d, 1H, J = 11.1 Hz), 4.90 (d, 1H, J = 11.4 Hz), 4.73–4.81 (m, 3H), 4.64 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 3.3 Hz), 4.39 (dd, 1H, J = 11.4, 6.3 Hz), 4.31 (d, 1H, J = 12.3 Hz), 4.18 (dd, 1H, J = 11.1, 7.5 Hz), 4.02 (t, 1H, J = 9.6 Hz), 3.88–3.94 (m, 2H), 3.69–3.70 (m, 1H), 3.41–3.55 (m, 3H), 3.30 (s, 3H). The spectroscopic data coincide with the previous report.[24]

Methyl 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (20). Compound **20**[25] (15.5 mg, 84% yield as a semisolid) was prepared according to the general procedure for pre-activation glycosylation from donor **3** (15.0 mg, 21 μmol) and acceptor **13** (7.1 mg, 19 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 5 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 2H, J = 7.2 Hz), 8.02 (d, 2H, J = 7.2 Hz), 7.88 (d, 2H, J = 6.9 Hz), 7.77 (d, 2H, J = 7.2 Hz), 7.38–7.66 (m, 11H), 7.32–7.34 (m, 3H), 7.20–7.26 (m, 8H), 7.10–7.16 (m, 3H), 6.99–7.03 (m, 2H), 5.93–6.00 (m, 2H), 5.59 (dd, 1H, J = 10.5, 3.6 Hz), 5.50 (s, 1H), 5.18 (d, 1H, J = 8.1 Hz), 5.02 (d, 1H J = 3.6 Hz), 4.42–4.66 (m, 4H), 4.25–4.36 (m, 2H), 3.97 (t, 1H, J = 9.0 Hz), 3.80–3.88 (m, 2H), 3.70 (t, 1H, J = 10.2 Hz), 3.55 (t, 1H, J = 9.0 Hz), 3.45 (s, 3H). The spectroscopic data coincide with the previous report.[25]

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-*α*-D-glucopyranoside (21). Compound **21**[15o] (16.0 mg, 85% yield, α/β inseparable mixture as an oil) was prepared according to the general procedure for pre-activation glycosylation from donor **4** (15.0 mg, 23 μmol) and acceptor **11** (7.8 mg, 21 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 6 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01–7.40 (m, 45H), 5.61 (d, 1.0H, J = 3.3 Hz), 5.50 (s, 0.17H), 5.43 (s, 1H), 4.69–5.03 (m, 6.6 H), 4.19–4.60 (m, 13.6 H), 3.53–3.98 (m, 12.7H), 3.33–3.43(m, 4.6H). The spectroscopic data coincide with the previous report.[15o]

Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-*α*-D-glucopyranoside (22). Compound **22**[24] (20.9 mg, 89% yield as a foam) was prepared according to the general procedure for pre-activation glycosylation from donor **5** (20.0 mg, 29 μmol) and acceptor **12** (11.0 mg, 23 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 5 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 1H, J = 7.2 Hz), 7.87 (d, 4H, J = 7.8 Hz), 7.79 (d, 2H, J = 7.2 Hz), 7.17–7.52 (m, 34H), 5.43–5.64 (m, 3H), 5.07 (d, 1H, J = 11.1 Hz, 1′-H), 4.72–4.81 (m, 4H), 4.58 (d, 1H, J = 12.0 Hz), 4.54 (d, 1H, J = 3.6 Hz), 4.39 (dd, 1H, J = 12.3, 3.6 Hz), 4.34 (d, 1H, J = 12.3 Hz), 4.25 (dd, 1H, J = 12.3, 5.1 Hz), 3.84–3.99 (m, 2H), 3.67–3.74 (m, 2H), 3.40–3.51 (m, 3H), 3.27 (s, 3H). The spectroscopic data coincide with the previous report.[24]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside (23). Compound **23**[26] (22.0 mg, 92% yield as a semisolid) was prepared according to the general procedure for pre-activation glycosylation from donor **5** (20.0 mg, 29 μmol) and acceptor **10** (11.0 mg, 23 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 5 : 1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, 2H, J = 7.2 Hz), 7.81–7.90 (m, 6H), 7.03–7.52 (m, 31H), 5.89 (t, 1H, J = 9.6 Hz), 5.67 (t, 1H, J = 9.6 Hz), 5.59 (dd, 1H, J = 9.6, 8.1 Hz), 4.89 (d, 1H, J = 11.1 Hz), 4.82 (d, 1H, J = 7.8 Hz, 1′-H), 4.73 (d, 1H, J = 12.0 Hz), 4.68 (d, 1H, J = 10.8 Hz), 4.57–4.61 (m, 2H), 4.47–4.54 (m, 3H), 4.27 (d, 1H, J = 11.4 Hz), 4.06–4.16 (m, 2H), 3.88 (t, 1 H, J = 9.0 Hz), 3.70–3.76 (m, 2H), 3.34–3.45 (m, 2H), 3.20 (s, 3H). The spectroscopic data coincide with the previous report.[26]

Methyl 3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-4,6-*O*-benzylidene-2-*O*-benzyl-*α*-D-glucopyranoside (24). Compound **24**[15o] was prepared according to the general procedure for pre-activation glycosylation from donor **6** (15.0 mg, 23 μmol) and acceptor **11** (7.1 mg, 19 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 6 : 1).

For **24-α** (8.0 mg, 47% yield as a semisolid): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06–7.41 (m, 36H), 6.91 (d, 2H, J = 6.9 Hz), 5.59 (d, 1H, J = 3.6 Hz, 1′-H), 5.47 (s, 1H), 5.00 (d, 1H, J = 10.8 Hz), 4.80 (dd, 2H, J = 11.1, 2.4 Hz), 4.71 (d, 1H, J = 3.6 Hz), 4.65 (d, 1H, J = 11.4 Hz), 4.54–4.61 (m, 3H), 4.18–4.41 (m, 6H), 3.97 (t,, 1H, J = 9.6 Hz), 3.63–3.88 (m, 5H), 3.45–3.53 (m, 3H), 3.41 (s, 3H). For **24-β** (6.2 mg, 36% yield as a semisolid): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14–7.42 (m, 30H, aromatic), 5.47 (s, 1H), 5.07 (d, 1H, J = 11.4 Hz), 4.87–4.93 (m, 2H), 4.70–4.80 (m, 4H), 4.45–4.51 (m, 5H), 4.36 (t, 1H, J = 9.0 Hz), 4.21 (dd, 1H, J = 9.6, 4.2 Hz), 3.80 (dd, 1H, J = 9.9, 4.5 Hz), 3.46–3.71 (m, 8H), 3.35 (s,3H), 3.23–3.25 (m, 1H). The spectroscopic data coincide with the previous report.[15o]

Methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranosyl)-2-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside (25). Compound **25** (24.2 mg, 93% yield as a white amorphous solid) was prepared according to the general procedure for pre-activation glycosylation from donor **7** (20.0 mg, 44 μmol) and acceptor **11** (13.7 mg, 37 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 4 : 1). $[\alpha]_D^{27}$: +26° (c = 1 in $CDCl_3$); ν_{max}(KBr)/cm^{-1}: 3067, 3036, 2993, 2918, 2876, 1750, 1604, 1454, 1371, 1231, 1141, 1088, 1047, 980, 753, 701; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31–7.39 (m, 11H), 5.52 (s, 1H, PhC*H*), 5.33–5.38 (m, 3H, 1′-H, 2′-H, 3′-H), 5.26 (t, 1H, J = 9.9 Hz, 4′-H), 4.62–4.71 (m, 3H, 1-H, PhCH_2), 4.20–4.36 (m, 3H, 5′-H, 6a-H, 3-H), 3.97–4.01 (m, 2H, 6′-H), 3.61–3.84 (m, 3H, 5-H, 6b-H, 4-H), 3.54 (dd, 1H, J = 9.6, 3.6 Hz, 2-H), 3.39 (s, 3H, OMe), 2.09 (s, 6H, OAcX2), 1.99 (s, 6H, OAcX2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.79, 170.04, 169.79, 169.63, 137.49, 136.91, 128.83, 128.54, 128.26, 128.13, 128.04, 125.96, 101.12, 98.40, 97.55, 82.31, 77.60, 73.18, 72.91, 69.29, 69.23, 68.84, 68.31, 65.68, 61.84 × 2, 55.28, 20.78, 20.71. HRMS (ESI) calcd for $C_{35}H_{42}NaO_{15}$ [M + Na]$^+$: 725.2416, found 725.2400; $C_{35}H_{43}O_{15}$ [M + H]$^+$: 703.2596, found 703.2591.

Methyl 6-*O*-(*N*-acetyl-2-amino-2,3-*N*,*O*-carbonyl-4,6-di-*O*-acetyl-2-deoxy-*α*-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside (26). Compound **26**[10a] (18.1 mg, 75% yield as an oil) was prepared according to the general procedure for pre-activation glycosylation from donor **8** (15.0 mg, 34 μmol) and acceptor **10** (14.3 mg, 31 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.38 (m, 18H), 5.78 (d, 1H, J = 2.8 Hz, 1′-H), 5.26 (t, 1H, J = 10.0 Hz), 5.01 (d, 1H, J = 10.8 Hz), 4.87 (d, 1H, J = 11.6 Hz), 4.76–4.81 (m, 2H), 4.68 (d, 1H, J = 12.0 Hz), 4.47–4.58 (m, 3H), 4.11–4.14 (m, 2H), 3.99 (t, 1H, J = 9.2 Hz), 3.70–3.88 (m, 5H), 3.52 (dd, 1H, J = 9.6, 3.2 Hz), 3.36 (s, 3H),

3.31 (t, 1H, J = 9.2 Hz), 2.40 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H). The spectroscopic data coincide with the previous report.[10a]

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-*β*-D-galactopyranosyl)-2,3,4-tri-*O*-benzoyl-*α*-D-glucopyranoside (27). Compound **27**[27] (18.0 mg, 95% yield as a foam) was prepared according to the general procedure for pre-activation glycosylation from donor **3** (15.0 mg, 21 μmol) and acceptor **14** (8.5 mg, 17 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 4 : 1). $[\alpha]_D^{27}$: +72° (c = 1 in $CDCl_3$), (lit[27] $[\alpha]_D^{20}$: +78.1° (c = 1 in $CDCl_3$)); ν_{max}(KBr)/cm^{-1}: 3067, 2936, 1731, 1602, 1452, 1270, 1105, 1069, 1028, 710; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–8.07 (m, 14H), 7.21–7.60 (m, 25H), 6.08 (t, 1H, J = 9.9 Hz, 3-H), 5.99 (d, 1H, J = 3.3 Hz, 4′-H), 5.84 (dd, 1H, J = 10.5, 7.8 Hz, 2′-H), 5.63 (dd, 1H, J = 10.5, 3.6 Hz, 3′-H), 5.33 (t, 1H, J = 10.5 Hz, 4-H), 5.06 (dd, 1H, J = 10.5, 3.9 Hz, 2-H), 4.95 (d, 1H, J = 7.8 Hz, 1′-H), 4.91 (d, 1H, J = 3.6, 1-H), 4.61 (dd, 1H, J = 10.8, 6.3 Hz, 6a′-H), 4.16–4.43 (m, 4H, 6b′-H, 5′-H, 5-H, 6a-H), 3.79 (dd, 1H, J = 11.4, 7.8 Hz, 6b-H), 3.10 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.98, 165.65, 165.54, 165.49, 165.45, 165.34, 133.54, 133.46, 133.26, 133.04, 129.99, 129.85, 129.78, 129.61, 129.38, 129.19, 129.01, 128.73, 128.58, 128.49, 128.35, 128.26, 102.24, 96.39, 71.96, 71.55, 71.35, 70.28, 69.72, 69.57, 69.17, 68.68, 68.01, 61.79, 55.00. HRMS (ESI) calcd for $C_{62}H_{52}NaO_{18}$ $[M + Na]^+$: 1107.3046, found: 1107.3027.

***p*-Tolyl 6-*O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-*β*-D-galacto-pyranosyl)-2,3,4-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside (28).** Compound **28** (13.5 mg, 63% yield as a semisolid) was prepared according to the general procedure for pre-activation glycosylation from donor **9** (15.0 mg, 26 μmol) and acceptor **15** (11.6 mg, 21 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 3 : 1). $[\alpha]_D^{25}$: +44° (c = 1 in $CDCl_3$); ν_{max}(KBr)/cm^{-1}: 3063, 3031, 2924, 2858, 1729, 1601, 1494, 1453, 1402, 1365, 1316, 1275, 1179, 1093, 1069, 1026, 1000, 738, 709, 699; ^{1}H NMR (400 MHz, $CDCl_3$): 8.00 (m, 2H), 7.84 (m, 2H), 7.48–7.53 (m, 5H), 7.22–7.43 (m, 28H), 7.12–7.15 (m, 4H), 5.89 (dd, J = 8.4, 10.4 Hz, 1H, 2′-H), 5.55 (s, 1H, PhC*H*), 5.29 (dd, J = 3.6, 10.4 Hz, 1H, 3′-H), 4.91 (d, J = 8.0 Hz, 1H, 1′-H), 4.83 (t, J = 10.0 Hz, 2H), 4.75 (d, J = 10.8 Hz, 1H, PhCH_2), 4.66 (d, J = 10.4 Hz, 1H, PhCH_2), 4.65 (d, J = 10.8 Hz, 1H, PhCH_2), 4.59 (d, J = 3.6 Hz, 1H, 4′-H), 4.51 (d, J = 9.2 Hz, 1H, 1-H), 4.50 (d, J = 10.4 Hz, 1H, PhCH_2) 4.40 (d, J = 10.8 Hz, 1H, PhCH_2), 4.14(t, J = 12.4 Hz, 2H), 3.94 (m, 1H), 3.57–3.61(m, 2H), 3.42–3.44 (m, 2H), 3.35 (t, J = 9.2 Hz, 1H, 2-H), 2.25 (s, 3H, SPhMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.20, 165.14, 138.37, 138.09, 137.97, 137.84, 137.55, 133.31, 132.90, 129.93, 129.87, 129.64, 129.33, 129.16, 128.87, 128.37, 128.23, 128.18, 128.08, 127.86, 127.79, 127.73, 127.68, 127.60, 126.29, 100.88 × 2, 87.55, 86.55, 80.40, 79.26, 77.48, 75.61, 75.28, 74.90, 73.60, 72.98, 69.05, 68.92, 67.28, 66.58, 21.02. HRMS (ESI) calcd for $C_{61}H_{58}KO_{12}S$ $[M + K]^+$: 1053.3275, found 1053.3311; $C_{61}H_{62}NO_{12}S$ $[M + NH_4]^+$: 1032.3987, found 1032.3987.

***p*-Tolyl 6-*O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-*β*-D-galacto-pyranosyl)-2,3,4-tri-*O*-benzoyl-1-thio-*β*-D-glucopyranoside (29).** Compound **29** (17.0 mg, 73% yield as a semisolid) was prepared according to the general procedure for pre-activation glycosylation from donor **9** (15.0 mg, 26 μmol) and acceptor **16** (13.0 mg, 22 μmol) and purified by column chromatography (petroleum ether/ethyl acetate = 2 : 1). $[\alpha]_D^{27}$: +50° (c = 1 in $CDCl_3$); ν_{max}(KBr)/cm^{-1}: 3065, 3034, 2925, 2868, 1732, 1601, 1584, 1493, 1452, 1402, 1368, 1316, 1277, 1179, 1094, 1069, 1026, 999, 806, 755, 709; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98–8.04 (m, 2H), 7.91–7.95 (m, 4H), 7.83–7.86 (m, 2H), 7.72–7.75 (m, 2H), 7.21–7.60 (m, 28H), 7.10 (d, 2H, J = 7.8 Hz), 5.88 (dd, 1H, J = 10.5, 8.1 Hz, 2′-H), 5.75 (t, 1H, J = 9.3 Hz, 3-H), 5.53 (s, 1H, PhC*H*), 5.25–5.35 (m, 3H, 3′-H, 2-H, 4-H), 4.94 (d, 1H, J = 8.1 Hz, 1′-H), 4.79 (d, 1H, J = 10.2 Hz, 1-H), 4.60 (d, 1H, J = 3.0 Hz, 4′-H), 4.30 (d, 1H, J = 11.4 Hz, 6′-H), 3.89–4.11 (m, 4H, 5-H, 6a-H, 6b-H, 6b′-H), 3.63 (s, 1H, 5′-H), 2.30 (s, 3H, SPhMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.19, 165.63, 165.40, 165.36, 164.94, 138.65, 137.39, 133.71, 133.45, 133.35, 133.22, 133.11, 132.98, 129.78, 129.24, 129.09, 128.87, 128.77, 128.60, 128.38, 128.26, 128.19, 128.07, 127.60, 126.19, 101.10, 100.76, 85.97, 78.54, 74.12, 73.48, 72.91, 70.35, 69.29, 68.92, 68.83, 67.73, 66.55, 21.16. HRMS (ESI) calcd for $C_{61}H_{52}KO_{15}S$ $[M + K]^+$: 1095.2653, found 1095.2655; $C_{61}H_{52}NaO_{15}S$ $[M + Na]^+$: 1079.2919, found 1079.2927.

Methyl 6-*O*-(6-*O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-*β*-D-galactopyranosyl)-2,3,4-tri-*O*-benzoyl-*β*-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside (30). A mixture of AgOTf (53 mg, 204 μmol) and activated molecular sieves (500 mg, 4 Å powder) in dry CH_2Cl_2 (5 mL) was cooled to −72 °C under argon atmosphere. After stirring for 5 min, DMTPSB (36 μL, 1.23 M in CCl_4 solution, 44 μmol) and donor **9** (20.0 mg, 34 μmol) were added *via* a micro-syringe. After TLC detection indicated that donor **9** was completely consumed, acceptor **16** (18.3 mg, 31 μmol) was added. The reaction mixture was warmed to room temperature and further stirred for 15 min before cooling down back to −72 °C. Subsequently, DMTPSB (29 μL, 1.23 M in CCl_4 solution, 35 μmol) was added to the reaction mixture. After the newly formed disaccharide was consumed by TLC detection, acceptor **10** (13.0 mg, 28 μmol) was added. The reaction mixture was stirred and gradually warmed to room temperature. The reaction was quenched by triethylamine (0.2 mL) and the precipitate was filtered off through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (petroleum ether/ether acetate = 1.5 : 1), affording trisaccharide **30** (24.0 mg, 60%) as a semisolid. $[\alpha]_D^{27}$: +26° (c = 1 in $CDCl_3$); ν_{max}(KBr)/cm^{-1}: 3064, 3033, 2933, 1733, 1602, 1585, 1495, 1368, 1315, 1277, 1178, 1095, 1069, 1027, 741, 710; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.96 (m, 4H), 7.87 (dd, 2H, J = 8.0, 1.0 Hz), 7.83 (dd, 2H, J = 8.0, 1.0 Hz), 7.76 (dd, 2H, J = 8.0, 1.0 Hz), 7.21–7.51 (m, 32H), 7.15 (t, 2H, J = 8.0 Hz), 6.98–7.00 (m, 2H), 5.84 (dd, 1H, J = 10.5, 8.0 Hz, 2″-H), 5.74 (t, 1H, J = 9.5 Hz, 3′-H), 5.50 (s, 1H, PhC*H*), 5.42 (dd, 1H, J = 9.5, 8.0 Hz, 2′-H), 5.27–5.34 (m, 2H, 3″-H, 4′-H), 4.86 (d, 1H, J = 12.0 Hz, PhCH_2), 4.84 (d, 1H, J = 8.5 Hz, 1″-H), 4.72 (d, 1H, J = 12.0 Hz, PhCH_2), 4.65 (d, 1H, J = 11.0 Hz, PhCH_2), 4.56 (d, 1H, J = 12.0 Hz, PhCH_2), 4.51 (m, 2H, 4″-H, 1-H), 4.47 (d, 1H, J = 8.0 Hz, 1′-H), 4.37 (d, 1H, J = 11.0 Hz, PhCH_2), 4.31 (m, 1H, 6a″-H), 4.17 (d, 1H, J = 11.5 Hz, PhCH_2), 4.02–4.06 (m, 2H, 6b″-H), 3.76–3.90 (m, 4H, 5′-H, 6a′-H, 6b′-H), 3.57 (s, 1H, 5″-H), 3.27–3.93 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.08, 165.69, 165.47, 165.14, 164.82, 138.88, 138.37, 138.18, 137.35, 133.49, 133.37, 133.13, 129.83, 129.66, 129.54, 129.10, 129.02, 128.87, 128.75, 128.40, 128.20, 128,11, 127.79, 127.37, 127.28, 126.13,

101.46, 100.66 × 2, 98.08, 81.80, 79.65, 76.84, 75.37, 74.33, 74.18, 73.52, 73.39, 72.75, 72.45, 71.78, 69.57, 69.39, 69.29, 68.78, 68.20, 67.28, 66.45, 55.28. HRMS (ESI) calcd for $C_{82}H_{76}NaO_{21}$ [M + Na]$^+$: 1419.4771, found 1419.4727.

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