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O-Glycosylation Enabled by *N*-(Glycosyloxy)acetamides

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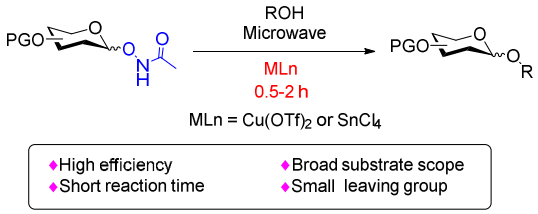


ABSTRACT: A novel glycosylation protocol has been established by using *N*-(glycosyloxy)acetamides as glycosyl donors. The *N*-oxyacetamide leaving group in donors could be rapidly activated in the presence of $Cu(OTf)_2$ or $SnCl_4$ under microwave irradiation. This glycosylation process afforded the coupled products in high yields, and the reaction enjoyed a broad substrate scope, even for disarmed donors and hindered acceptors. The easy availability of the donors, the high stability of *N*-(glycosyloxy)acetamides, as well as the small leaving group, make this method very practical.

■ INTRODUCTION

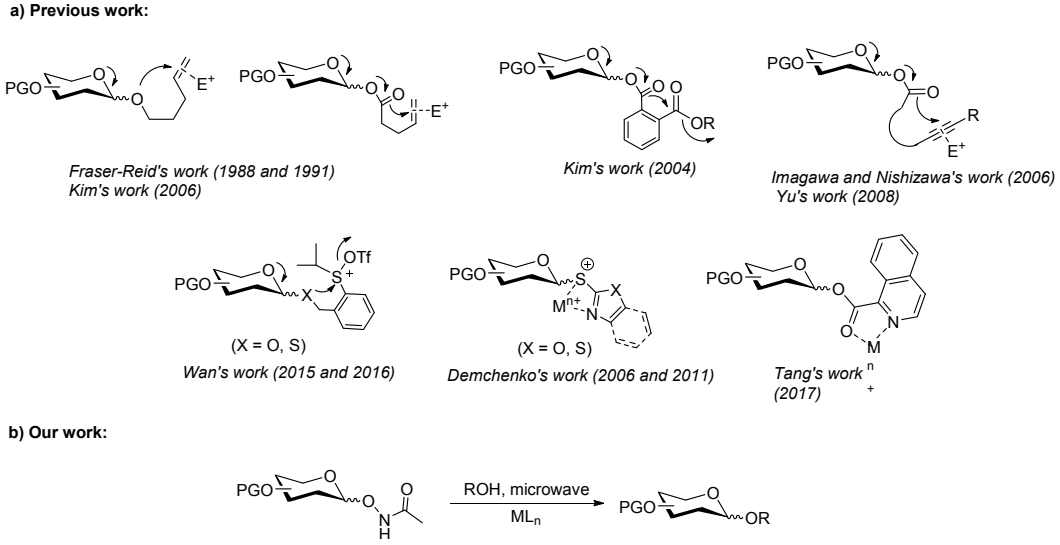
Oligosaccharides and glycoconjugates play significant roles in a large variety of biological processes.[1] However, due to the limited availability of homogeneous and structurally-defined oligosaccharides and glycoconjugates, the development in the area of glycobiology is hindered. The isolation of oligosaccharides from natural sources is a formidable task because they often exist in highly microheterogeneous forms.[2] In many cases, chemical synthesis is the major route to obtain this type of compounds. The key reaction in the chemical synthesis of oligosaccharides is the glycosylation reaction.[3] Tremendous efforts have been made to develop effective glycosylation methods. Especially, a large variety of glycosyl donors such as glycosyl halides,[4] thioglycosides,[5] glycosyl thioimidates,[6] glycosyl trichloroacetimidates,[7] glycals,[8] hemiacetals,[9] glycosyl phosphates,[10] and alkynyl glycosides[11] have been widely used for the assembly of oligosaccharides. Nevertheless, there is no general glycosylation method available and the synthesis of complex oligosaccharides is still difficult. Therefore, the development of new glycosyl donors is highly desirable.

Among various glycosyl donors, there is a class of glycosyl donors which could be activated with the assistance of vicinal exoanomeric-atom or remote functional-substituent on leaving group. Elegant studies on glycosyl donors such as *n*-pentenyl glycosides,[12] *n*-pentenyl esters,[13] glycosyl benzyl phthalates,[14] alkynoates,[15] glycosyl pentenoates,[16] glycosyl *ortho*-alkynylbenzoates,[11b] 2-(2-propylsulfinyl)benzyl glycosides,[17] propargyl 1,2-orthoesters,[18] *o*-(*p*-methoxyphenylethynyl)phenyl glycosides,[19] *S*-benzoxazolyl (SBox) glycosides,[20] *S*-thiazolinyl (STaz) glycosides,[21] and glycosyl isoquinoline-1-carboxylates,[22] were reported. These donors possess auxiliary activation functional groups such as alkenyl, alkynyl, SC=N and heterocyclic substituents, and they could be easily activated by either an electrophilic reaction or a chelating reaction under mild conditions (Scheme 1a). Some of them are compatible with orthogonal or latent-active oligo-

saccharide synthesis strategy. However, these donors still suffer from some drawbacks such as longer reaction time. Thus, we intend to develop new type of glycosyl donors for glycosylation reactions.

Hydroxamates usually have high affinity to Lewis acids or metal ions as bidentate ligands. Hydroxamate leaving groups have been used in BF_3•Et_2O-promoted coupling reaction of mixed acetals with organotrifluoroborates by Bode's group.[23] Inspired by these studies,[24] we envisaged that glycosylated hydroxamates might be good glycosyl donors for the construction of glycosidic bonds (Scheme 1b). Herein we describe our investigation on the glycosylation reaction using *N*-hydroxamate as the leaving group.

Scheme 1. Glycosyl donors activated by either an electrophilic reaction or a chelating reaction



■ RESULTS AND DISCUSSION

To assess the feasibility of our idea, a systematic survey of substitution patterns on hydroxamate was carried out. For this purpose, galactoside **3** with a phthalimidyl group,[25] galactoside **4** with a succinimidyl group,[18] galactoside **5** with a *N*-methylacetamidyl group,[4a] and galactoside **7** with an acetamidyl group,[26] were readily prepared from galactosyl bromide **1** (Scheme 2). With these glycosyl donors in hand, we evaluated the glycosylation reactions of glycosyl acceptor **8** with these donors under different conditions (Table 1, Tables S1 and S2 in the Supporting Information). The glycosyl donors **3** and **4** appeared inert to most of Lewis acids (Table 1, entries 1-4; Table S1**)**, probably due to the low reactivity of anomeric oxygen atom resulting from the introduction of two strong electron-withdrawing carbonyl groups. To our delight, the glycosyl donor **5** with an electron-donating *N*-methyl group could smoothly react with the acceptor **8** in the presence of 1.5 equiv. of $SnCl_4$ at room temperature (Table 1, entry 5, 80% yield). Increasing the reaction temperature to 40 °C not only shortened the reaction time to 40 min, but also improved the yield of coupled product **9** to 92% (Table 1, entry 6). Under the same reaction conditions, the glycosyl donor **7** with an acetyl substituent also worked well (Table 1, entry 7, 96% yield). This reaction could be accelerated by microwave irradiation (Table 1, entry 19). Moreover, the comparable outcome for the glycosylation of acceptor **8** with donor **7** could also be obtained in the presence of 2.0 equiv. $Cu(OTf)_2$ under microwave irradiation at 80 °C for one hour (Table 1, entry 15, 95% yield). Thus, both *N*-oxy-*N*-methylacetamide and *N*-oxyacetamide could be used as leaving groups.

Scheme 2. Synthesis of Glycosyl Donors 3-7

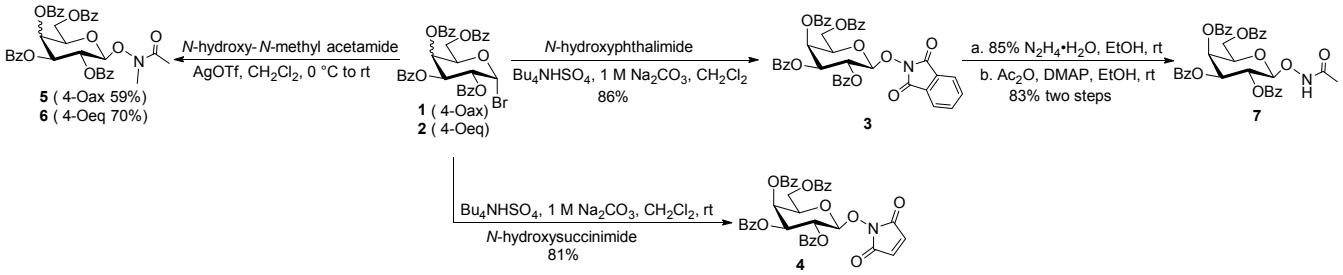
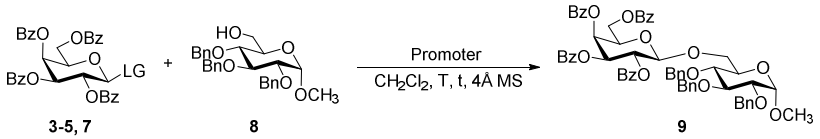


Table 1. Screening the Leaving Groups[a]



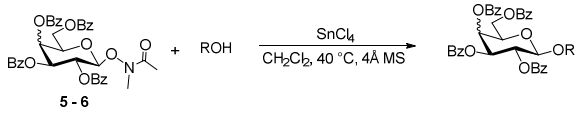
entry	donor	promoter (equiv.)	T (°C)	t (h)	yield (%)[b]
1	**3**	BF_3•Et_2O (1.5)	rt	8	N.R.[c]
2	**3**	TMSOTf (1.5)	rt	8	0
3	**4**	BCl_3 (1.5)	rt	8	0
4	**4**	$SnCl_4$ (1.5)	rt	8	0
5	**5**	$SnCl_4$ (1.5)	rt	8	80
6	**5**	$SnCl_4$ (1.5)	40	40 min	92
7	**7**	$SnCl_4$ (1.5)	40	40 min	96
8	**7**	$SnCl_4$ (0.8)	40	1	81
9	**7**	$SnCl_2$ (1.5)	40	8	0
10	**7**	$FeCl_3$ (1.5)	40	8	38
11	**7**	$B(C_6H_5)_3$ (0.1)	40	8	0
12	**7**	$Cu(OTf)_2$ (1.0)	rt	8	15
13	**7**	$Cu(OTf)_2$ (4.0)	rt	5	94
14[d]	**7**	$Cu(OTf)_2$ (2.0)	40	2	65
15[d, e]	**7**	$Cu(OTf)_2$ (2.0)	80	1	95
16[d, f]	**7**	$Cu(OTf)_2$ (2.0)	80	1	30
17[d, g]	**7**	$Cu(OTf)_2$ (2.0)	80	1	50
18[d, h]	**7**	$Cu(OTf)_2$ (2.0)	80	1	trace
19[d]	**7**	$SnCl_4$ (1.5)	40	0.5	96

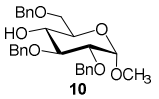
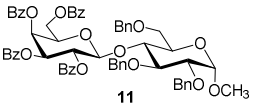
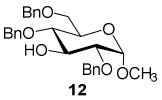
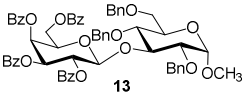
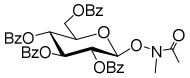
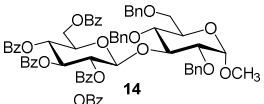
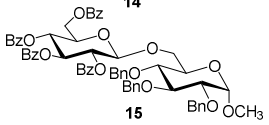
[a]Reaction conditions: donor (0.036 mmol), acceptor (0.026 mmol), CH_2Cl_2 (1.0 mL), under argon atmosphere. [b]Isolated yield. [c]N.R.: no reaction was detected. [d]Microwave irradiation (100 W). [e]$ClCH_2CH_2Cl$ (1.0 mL). [f]Et_2O (1.0 mL). [g]Toluene (1.0 mL). [h]CH_3CN (1.0 mL).

Since the suitable leaving groups were identified, we then turned our attentions to check the glycosylation substrate scope of the *N*-oxy-*N*-methylacetamide leaving group (Table 2). Considering that the glycosylation reaction of the acceptor **8** with the disarmed donor **5** proceeded smoothly in high yield, the coupling reaction of disarmed donor **5** with hindered acceptor **10** was examined firstly. Yet the desired disaccharide **11** was obtained in 33% yield (Table 2, entry 1), accompanying the galactosyl chloride as the main by-product. The reaction outcome of disarmed donors (**5**, **6**) and secondary alcohol **12** with a free hydroxyl at the C-3 position was still unsatisfactory (Ta-

ble 2, entries 2- 3), and the generated glycosyl chlorides did not continue to undergo the glycosylation at all. Besides, disaccharide **13** was also obtained in poor yield with the use of microwave irradiation (20%, Table 2, entry 2). Gratifyingly, the glucosyl donor **6** coupled with the acceptor **8** to afford the disaccharide **15** in 98% yield (Table 2, entry 4). Thus, the *N*-oxy-*N*-methylacetamide leaving group-containing donors might be suitable for the glycosylation of acceptors with high nucleophilicity.

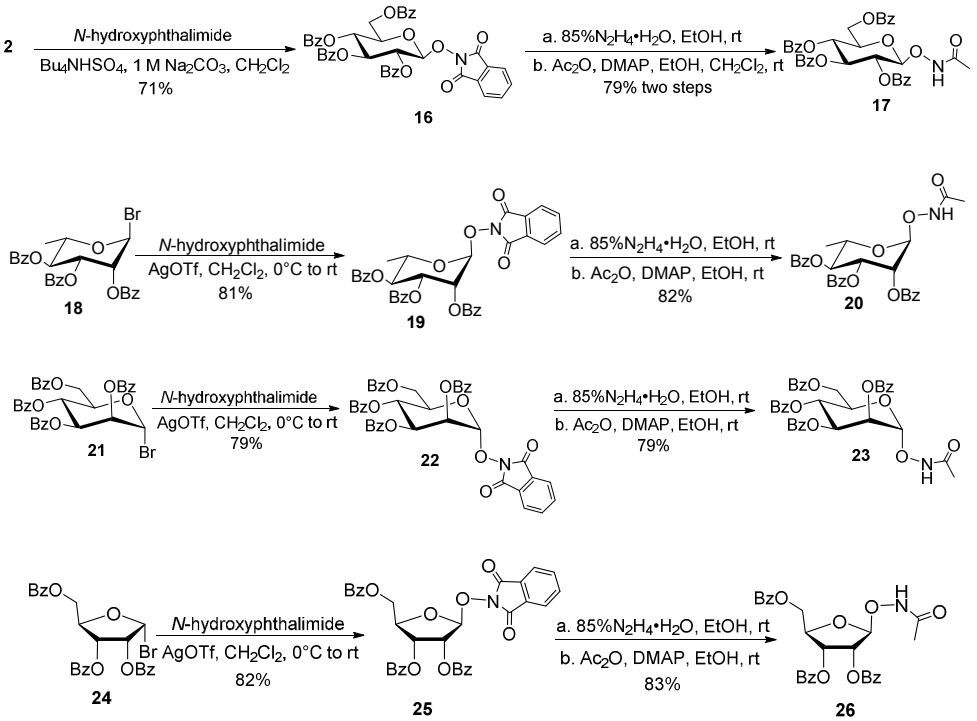
Table 2. The Coupling Reaction of *N*-Methylacetamidyl Glycosides[a]

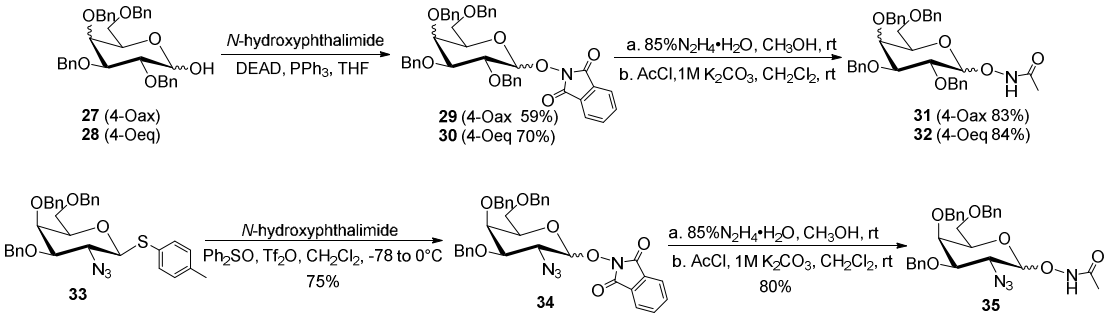


entry	glycosyl donor	glycosyl acceptor	product	yield[b]
1	**5**	 **10**	 **11**	33%
2	**5**	 **12**	 **13**	29% (20%[c])
3	 **6**	**12**	 **14**	32%
4	**6**	**8**	 **15**	98%

[a]Reaction conditions: donor (0.036 mmol), acceptor (0.026 mmol), $SnCl_4$ (0.039 mmol), CH_2Cl_2 (1.0 mL), under argon atmosphere. [b]Isolated yield. [c]Microwave (100 W, 40 °C)

Scheme 3. Synthesis of the donors of acetamidyl glycosides

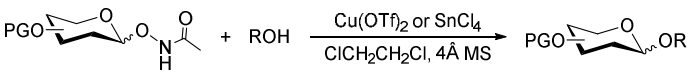


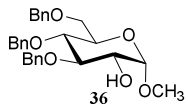
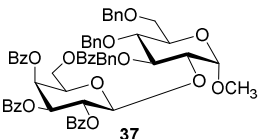
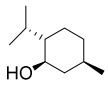
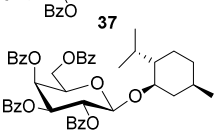
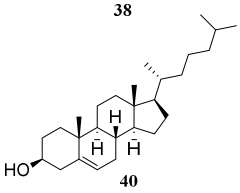
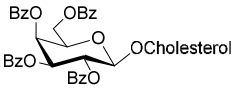
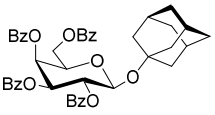
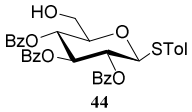
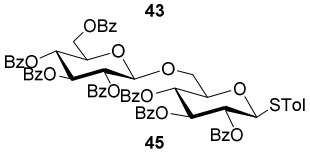
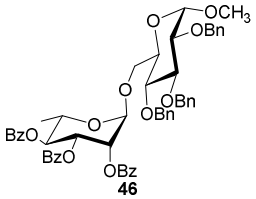


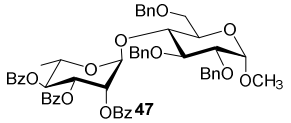
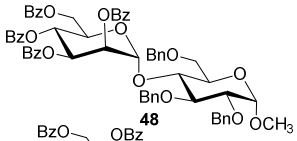
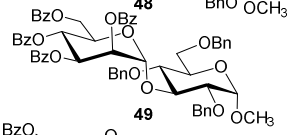
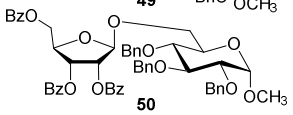
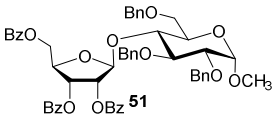
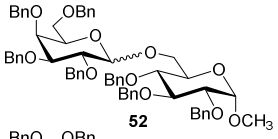
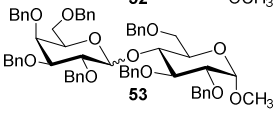
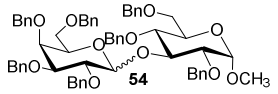
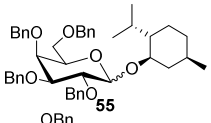
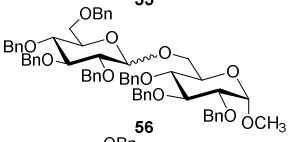
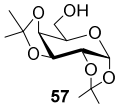
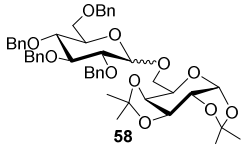
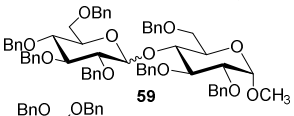
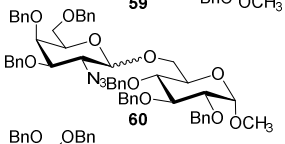
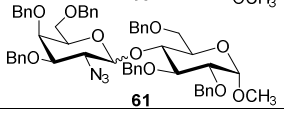
In view of the limited substrate scope, we next explored the glycosylation using glycosyl donors with *N*-oxyacetamide leaving group (Table 3). As shown in Scheme 3, various disarmed donors **17**, **20**, **23**, **26** were able to be readily prepared from the corresponding glycosyl bromides[27] via phthalimidyl glycosides. Compounds **29**-**30** were obtained from compounds **27**-**28** by Mitsunobu reaction,[28] which were transformed to armed donors **31**-**32** smoothly. The compound **34** was prepared from thiogalactoside **33**,[29] which was further converted to donor **35**. It is noteworthy that these donors were found to be very stable at room temperature for more than one year without noticeable decomposition. With all the glycosyl donors in hand, the glycosylation reaction was carried out. Under the promotion of 2.0 equiv. $Cu(OTf)_2$, the coupling reaction of the disarmed galactosyl donor **7** with acceptors **12**, **36** and **38** afforded the corresponding disaccharides **13**, **37** and **39** in 90%, 90% and 92% yields, respectively (Table 3, entries 2-4). Similarly, donor 7 could also react with acceptor **10** having a free hydroxyl group at the C-4 position, to produce disaccharide **11** in 75% yield (Table 3, entry 1). The coupling reaction of **7** with the hindered acceptors **40** and **42** also furnished the corresponding products **41** and **43** in 89% and 95% yields, respectively (Table 3, entries 5 and 6). Moreover, the glycosylation of the thioglycosyl acceptor **44** with the disarmed glycosyl donor **17** provided the desired disaccharide **45** (Table 3, entry 7), implying that the *N*-(glycosyloxy)acetamides could be probably applied to the orthogonal glycosylation strategy. The glycosyl coupling reaction of the benzoylated rhamnosyl, mannosyl, and ribosyl donors gave the desired disaccharides in high yields as well (Table 3, entries 10-15).

To further expand the substrate scope, this glycosylation method was applied to the armed donors. To our disappointment, only 50% yield of disaccharide **52** was obtained in the coupling reaction of donor **31** with **8** when using 1.5 equiv. of $SnCl_4$ as a promoter. In contrast, the use of $Cu(OTf)_2$ (2.0 equiv.) as a promoter produced compound **52** in 89% yield. To our surprise, decreasing the amount of $SnCl_4$ to 0.5 equiv. led to the formation of product **52** in excellent yield (97%, Table 3, entry 16). However, further decrease in the quantity of $SnCl_4$ gave the inferior result (Table S3 in Supporting Information). In the same conditions, the donor **31** reacted smoothly with acceptors **10** and **12** to give the corresponding glycosylation products **53** and **54** in 85% and 90% yields, respectively (Table 3, entries 17 and 18). Notably, the glycosylation of the acid-sensitive acceptor **57** with donor **32** produced disaccharide **58** in 78% yield (Table 3, entry 21). The aminosugar donor **35** also worked in the glycosylation reaction (Table 3, entries 23 and 24). The glycosylation yields obtained by using our donor are comparable/superior to the published data obtained by using trichloroacetimidate or thioglycoside donors, such as 88% *vs* 80% (using the trichloroacetimidate donor) yield of **56**,[30] and 85% *vs* 69% (using the thioglycoside donor **33**) yield of **60**.[31]

Table 3. The Substrate Scope of the Glycosylation Reaction[a]



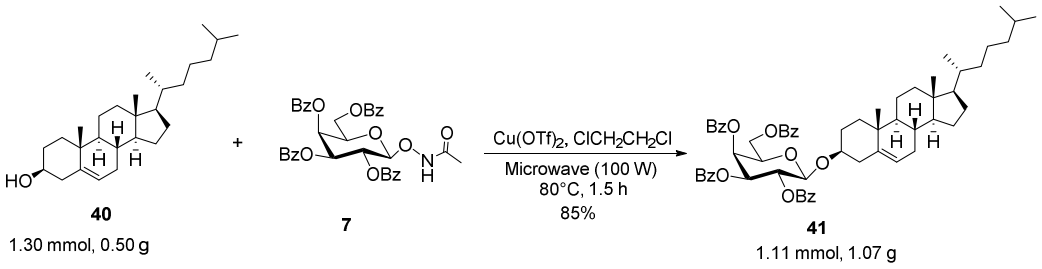
entry	glycosyl donor	glycosyl acceptor	promoter	product	yield[b]
1	**7**	**10**	$Cu(OTf)_2$	**11**	75%[c]
2	**7**	**12**	$Cu(OTf)_2$	**13**	90%[c]
			$SnCl_4$		95%[d]
3	**7**	 **36**	$Cu(OTf)_2$	 **37**	90%[c]
4	**7**	 **38**	$Cu(OTf)_2$	 **39**	92%[c]
			$SnCl_4$		90%[d]
5	**7**	 **40**	$Cu(OTf)_2$	 **41**	89%[c]
			$SnCl_4$		89%[d]
6	**7**	 **42**	$Cu(OTf)_2$	 **43**	95%[c]
			$SnCl_4$		93%[d]
7	**17**	 **44**	$SnCl_4$	 **45**	65%[d]
8	**17**	**8**	$Cu(OTf)_2$	**15**	90%[c]
			$SnCl_4$		91%[d]
9	**17**	**12**	$Cu(OTf)_2$	**14**	82%[c]
10	**20**	**8**	$Cu(OTf)_2$	 **46**	93%[c]
			$SnCl_4$		93%[d]

entry	glycosyl donor	glycosyl acceptor	promoter	product	yield[b]
11	**20**	**10**	$Cu(OTf)_2$	 **47**	85%[c]
12	**23**	**10**	$Cu(OTf)_2$	 **48**	80%[c]
13	**23**	**12**	$Cu(OTf)_2$	 **49**	90%[c]
14	**26**	**8**	$Cu(OTf)_2$ $SnCl_4$	 **50**	94%[c] 90%[d]
15	**26**	**10**	$Cu(OTf)_2$	 **51**	65%[c]
16	**31**	**8**	$Cu(OTf)_2$ $SnCl_4$	 **52**	89%[c] 97%[e], α/β = 2:1
17	**31**	**10**	$SnCl_4$ $Cu(OTf)_2$	 **53**	85%[e] 83%[f], α/β = 4:1
18	**31**	**12**	$SnCl_4$ $Cu(OTf)_2$	 **54**	90%[e] 85%[f], α/β = 4:1
19	**31**	**38**	$Cu(OTf)_2$	 **55**	87%[c], α/β = 1:1
20	**32**	**8**	$Cu(OTf)_2$	 **56**	88%[c], α/β = 2:1
21	**32**	 **57**	$SnCl_4$	 **58**	78%[e], α/β = 2:1
22	**32**	**10**	$Cu(OTf)_2$	 **59**	75%[f], α/β = 1:1
23	**35**	**8**	$SnCl_4$ $Cu(OTf)_2$	 **60**	80%[e] 85%[g], α/β = 1:1
24	**35**	**10**	$Cu(OTf)_2$	 **61**	61%[g], α/β = 4:1

[a]Reaction conditions: donor (0.036 mmol), acceptor (0.026 mmol), promoter, solvent (1.0 mL), under argon atmosphere. [b]Isolated yield. [c]$Cu(OTf)_2$ (0.052 mmol), microwave (100 W, 80 °C), 1-2 h. [d]$SnCl_4$ (0.039 mmol), microwave (100 W, 40 °C), 30 min. [e]$SnCl_4$ (0.013 mmol), microwave (100 W, 40 °C), 30 min. [f]$Cu(OTf)_2$ (0.104 mmol), dry CH_2Cl_2, rt, 5-8 h. [g]$Cu(OTf)_2$ (0.104 mmol), 50 °C, 5-8 h.

Interestingly, it was found that the leaving group could be detected in a very small amount after the simple filtration (see the Supporting Information), which would facilitate the separation. Finally, this protocol presents a great potential for the large-scale preparation. The reaction of the disarmed glycosyl donor **7** with glycosyl acceptor **40** was performed under the optimized conditions. A gram-scale glycoside **41** was obtained in 85% isolated yield, which is almost consistent with the yield of the small-scale reaction. This further proves the practicality of the glycosylation protocol (Scheme 4).

Scheme 4. Gram-Scale Synthesis of Compound 41



■ CONCLUSION

In conclusion, we have systematically examined the feasibility that hydroxamates are used as the leaving groups of glycosylation reactions. A survey of substitution patterns on hydroxamate showed that the *N*-oxy-*N*-methylacetamide and *N*-oxyacetamide could be used as the leaving groups. The *N*-oxy-*N*-methylacetamidyl-containing glycosides are suitable donors for the glycosylation of acceptors with high nucleophilicity. The glycosylation using the *N*-oxyacetamidyl-containing glycosides as donors can rapidly afford the coupled products in high yields in the presence of $Cu(OTf)_2$ or $SnCl_4$ under microwave irradiation. These new glycosyl donors are stable and can be conveniently prepared from the corresponding phthalimidyl glycosides via hydrazinolysis and subsequent acetylation. The leaving group in glycosyl donors could be precipitated from the reaction mixture, facilitating the subsequent separation. Moreover, this glycosylation process is able to be used in the gram-scale synthesis. Thus, *N*-(glycosyloxy)acetamides are novel and practical glycosyl donors which provides an alternative method for complex oligosaccharide synthesis.

■ EXPERIMENTAL SECTION

General Methods. All reagents and solvents were dried commonly before use according to standard methods. CH_2Cl_2 was distilled over CaH_2, THF and toluene were distilled over sodium. Commercial reagents were used without further purification unless otherwise noted. Reactions were monitored by analytical thin-layer chromatography (TLC) on silica gel-coated aluminium plates (60 F_{254}). Spots were detected under UV Light (254 nm) and charring with a solution of $(NH_4)_6Mo_7O_{24}•4H_2O$ (24.00 g, 19.4 mmol) and $Ce(NH_4)_2(NO_3)_6$ (0.50 g, 0.90 mmol) in sulfuric acid (5%, 500 mL). Column chromatography was performed on silica gel (200-300 mesh). The microwave reaction was carried out in a sealed microwave tube with Discover SP Microwave Synthesizer (CEM), and the reaction temperature was measured by an external infrared sensor. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ with TMS (δ = 0 ppm) as internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometer and were calibrated with $CDCl_3$ (δ = 77.00 ppm). The following standard abbreviations are used to indicate multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m =

multiplet, dd = doublet of doublets, dt = doublet of triplets, and br = broad. High resolution mass spectra were performed on a mass spectrometer (Q-TOF). Melting points were measured using a WRS-2A microcomputer melting point apparatus.

Preparation of Glycosyl Donors:

Phthalimidyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (3). In an oven-dried flask, compound **1** (1.22 mmol, 0.80 g), *N*-hydroxyphthalimide (8.54 mmol, 1.39 g), CH_2Cl_2 (9.6 mL) and 1M Na_2CO_3 solution (9.6 mL) were added. Then Bu_4NHSO_4 (1.22 mmol, 0.41 g) was added with vigorous stirring. The reaction mixture was stirred at room temperature and the reaction was monitored by TLC. After completion (~4 h), the mixture was extracted with CH_2Cl_2 for three times and the organic phases were combined, washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 4: 1, v/v) to afford **3** as a white solid (0.77 g, 86%). The ^{1}H NMR and ^{13}C NMR data for **3** are in accordance with those reported previously.[18]

Succinimidyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (4). In an oven-dried flask, compound **1** (1.22 mmol, 0.80 g), *N*-hydroxysuccinimide (8.54 mmol, 0.98 g), CH_2Cl_2 (9.6 mL) and 1M Na_2CO_3 solution (9.6 mL) were added. Then Bu_4NHSO_4 (1.22 mmol, 0.41 g) was added with vigorous stirring. The reaction mixture was stirred at room temperature and the reaction was monitored by TLC. After completion (~5 h), The mixture was extracted with CH_2Cl_2 for three times and the organic phases were combined, washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 3: 1, v/v) to afford **4** as a white solid (0.68 g, 81%). The ^{1}H NMR and ^{13}C NMR data for **4** are in accordance with those reported previously.[18]

***N*-Methylacetamidyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (5).** An oven-dried flask fitted with a magnetic stir-bar was charged with compound **1** (0.61 mmol, 0.40 g), *N*-hydroxy-*N*-methylacetamide (1.22 mmol, 0.11 g), activated 4Å molecular sieves (0.50 g), and CH_2Cl_2 (5 mL) under an argon atmosphere. After cooling to 0 °C, AgOTf (1.22 mmol, 0.32 g) dissolved in dry toluene (0.6 mL) was added. The reaction was warmed up, stirred at room temperature and monitored by TLC. After completion (~6 h), the reaction was quenched with triethylamine (0.3 mL), then filtered through Celite and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 3: 1, v/v) to afford **5** as a white solid (0.24 g, 59%). mp: 80.3 – 80.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.24 (m, 20H), 6.07 (d, *J* = 2.7 Hz, 1H), 5.92 (dd, *J* = 9.9, 8.8 Hz, 1H), 5.73 (dd, *J* = 10.3, 3.2 Hz, 1H), 5.27 (d, *J* = 8.4 Hz, 1H), 4.71 (dd, *J* = 11.3, 7.1 Hz, 1H), 4.54 (dd, *J* = 11.4, 5.5 Hz, 1H), 4.46 (t, *J* = 6.1 Hz, 1H), 3.30 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 166.0, 165.5, 165.4, 165.1, 133.8, 133.7, 133.5, 133.4, 130.0, 129.8, 129.7 (×2), 129.3, 128.9, 128.7 (×2), 128.6 (×2), 128.4, 105.4, 72.1, 71.6, 68.1, 68.0, 62.1, 36.7, 21.0; HRMS (ESI) calcd for $C_{37}H_{34}NO_{11}$ $[M+H]^+$ 668.2126, found 668.2128.

***N*-Methylacetamidyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (6).** The same procedure for the synthesis of **5** was applied, yielding **6** (0.28 g, 70%) as a white solid. mp: 77.9 – 78.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.78 (m, 8H), 7.60 – 7.23 (m, 12H), 5.96 (t, *J* = 9.7 Hz, 1H), 5.70 (t, *J* = 9.7 Hz, 1H), 5.62 (t, *J* = 9.1 Hz, 1H), 5.21 (d, *J* = 8.4 Hz, 1H), 4.72 (dd, *J* = 12.2, 2.8 Hz, 1H), 4.51 (dd, *J* = 12.2, 5.7 Hz, 1H), 4.26 – 4.17 (m, 1H), 3.22 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 165.7, 165.2, 164.9, 133.7, 133.6, 133.4, 133.3, 129.9, 129.8, 129.7 (×2), 129.4, 128.6 (×2), 128.5 (×3), 128.4, 104.8, 72.9, 72.6, 70.2, 69.2, 62.6, 36.6, 20.9; HRMS (ESI) calcd for $C_{37}H_{34}NO_{11}$ $[M+H]^+$ 668.2126, found 668.2133.

Acetamidyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (7). To a solution of **3** (1.21 mmol, 0.90 g) in ethanol (35 mL) was added slowly 85% hydrazine hydrate (1.44 mmol, 84 μL), and the reaction mixture was stirred at room temperature and the reaction was monitored by TLC. After completion (~4 h), DMAP (0.24 mmol, 0.03 g) and Ac_2O (6.06 mmol, 0.57 mL) were added at 0 °C, and the mixture was stirred for another 4 h. Then the reaction mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$ solution and sat. NaCl solution, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 1: 1, v/v) to afford **7** as a white solid (0.66 g, 83% yield over 2 steps). mp: 179.5 – 179.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.22 (m, 20H), 6.03 (s, 1H), 5.87 (t, *J* = 9.2 Hz, 1H), 5.73 (d, *J* = 10.1 Hz, 1H), 5.19 (br s, 1H), 4.70 (br s, 1H), 4.43 (s, 2H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 165.5, 165.4, 133.8, 133.6, 133.5, 133.4, 130.0, 129.9, 129.8, 129.3, 128.9, 128.8, 128.6, 128.5, 128.4, 103.9, 72.0, 71.4, 68.0, 67.9, 61.9, 20.0; HRMS (ESI) calcd for $C_{36}H_{32}NO_{11}$ $[M+H]^+$ 654.1970, found 654.1996.

Phthalimidyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (16). The same procedure for the synthesis of **3** was applied, yielding **16** (0.64 g, 71%) as a white solid. The ^{1}H NMR and ^{13}C NMR data for **16** are in accordance with those reported previously.[18]

Acetamidyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (17). Glycosyl donor **17** were prepared according to the procedure for the preparation of **7** (0.62 g, 79%) as a white solid. mp: 94.3 – 95.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 8.06– 7.28 (m, 20H), 6.00 (t, *J* = 9.5 Hz, 1H), 5.75 (t, *J* = 9.2 Hz, 1H), 5.64 (t, *J* = 8.7 Hz, 1H), 5.20 (br s, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.54 (dd, *J* = 12.2, 4.6 Hz, 1H), 4.30 – 4.21 (m, 1H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.7, 165.1, 133.6, 133.4, 133.3, 130.0, 129.9, 129.8, 129.4, 128.6, 128.5 (×2), 128.4, 103.4, 72.9, 72.5, 70.1, 69.1, 62.7, 20.0; HRMS (ESI) calcd for $C_{36}H_{32}NO_{11}$ $[M+H]^+$ 654.1970, found 654.1983.

Phthalimidyl 2,3,4,-tri-*O*-benzoyl-α-L-rhamnopyranoside (19). An oven-dried flask fitted with a magnetic stir-bar was charged with compound **18** (0.61 mmol, 0.33 g), *N*-hydroxyphthalimide (1.22 mmol, 0.20 g), activated 4 Å molecular sieves (0.50 g), and CH_2Cl_2 (5 mL) under an argon atmosphere, After cooling to 0 °C, AgOTf (1.22 mmol, 0.32 g) dissolved in dry toluene (0.6 mL) was added. The reaction was warmed up, stirred at room temperature and monitored by TLC. After completion (~4 h), the reaction was quenched with triethylamine (0.3 mL), then filtered through Celite and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 3: 1, v/v) to afford **19** as a white solid (0.31 g, 81%). mp: 102.3 – 103.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 7.23 (m, 19H), 6.17 (d, *J* = 1.6 Hz, 1H), 5.98 (dd, *J* = 10.0, 3.3 Hz, 1H), 5.80 (td, *J* = 10.0, 1.4 Hz, 1H), 5.67 (s, 1H), 5.22 – 5.08 (m, 1H), 1.43 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 165.3, 165.1, 163.1, 134.7, 133.6, 133.4, 133.2, 130.0, 129.9, 129.8, 129.2, 129.1 (×2), 128.9, 128.6, 128.5, 128.3, 123.8, 102.7, 71.0, 69.6, 69.3, 68.6, 17.4; HRMS (ESI) calcd for $C_{35}H_{31}N_2O_{10}$ $[M+NH_4]^+$ 639.1973, found 639.1984.

Acetamidyl 2,3,4,-tri-*O*-benzoyl-α-L-rhamnopyranoside (20). Glycosyl donor **20** was prepared according to the procedure for the preparation of **7** (0.53 g, 82% yield over 2 steps) as a white solid. mp: 83.4 – 84.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.06 – 7.24 (m, 15H), 5.87 – 5.75 (m, 2H), 5.70 (t, *J* = 9.8 Hz, 1H), 5.31 (s, 1H), 4.78 (br s, 1H), 2.04 (s, 3H), 1.39 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 165.5 (×2), 133.6, 133.4, 133.2, 130.0, 129.8, 129.7, 129.2, 129.1, 129.0, 128.6, 128.5, 128.3, 102.1, 71.2, 69.8, 69.0, 68.6, 20.0, 17.6; HRMS (ESI) calcd for $C_{29}H_{31}N_2O_9$ $[M+NH_4]^+$ 551.2024, found 551.2031.

Phthalimidyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (22). The same procedure for the synthesis of **19** was applied, yielding **22** (0.36 g, 79%) as a white solid. The ^{1}H NMR and ^{13}C NMR data for **22** are in accordance with those reported previously.[18]

Acetamidyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (23). Glycosyl donor **23** was prepared according to the procedure for the preparation of **7** (0.63 g, 79% yield over 2 steps) as a white solid. mp: 183.6 – 184.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.17 – 7.27 (m, 20H), 6.23 (t, *J* = 9.9 Hz, 1H), 5.90 (d, *J* = 10.5 Hz, 2H), 5.43 (s, 1H), 5.31 (s, 1H), 4.81 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 2.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 165.9, 165.4, 165.3, 133.5, 133.4, 133.1, 129.9, 129.8 (×2), 128.9 (×2), 128.8, 128.5 (×3), 128.4, 101.9, 77.3, 70.4, 68.5, 66.1, 62.5, 19.9; HRMS (ESI) calcd for $C_{36}H_{32}NO_{11}$ $[M+H]^+$ 654.1970, found 654.1974.

Phthalimidyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (25). The same procedure for the synthesis of **19** was applied, yielding **25** (0.30 g, 82%) as a white solid. The ^{1}H NMR and ^{13}C NMR data for **25** are in accordance with those reported previously.[18]

Acetamidyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (26). Glycosyl donor **26** was prepared according to the procedure for the preparation of **7** (0.43 g, 83% yield over 2 steps) as a white solid. mp: 70.5 – 71.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (br s, 1H), 8.11 – 7.23 (m, 15H), 5.95 (br s, 1H), 5.75 (t, *J* = 5.6 Hz, 1H), 5.61 (s, 1H), 5.05 (br s, 1H), 4.75 – 4.60 (m, 2H), 1.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 165.5, 164.9, 133.7, 133.6, 129.9 (×2), 129.8, 129.4, 128.9, 128.6 (×2), 128.4, 108.2, 81.8, 73.7, 72.2, 65.7, 20.0; HRMS (ESI) calcd for $C_{28}H_{26}NO_9$ $[M+H]^+$ 520.1602, found 520.1615.

Phthalimidyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (29). In an oven-dried flask, compound **27** (1.90 mmol, 1.03 g), *N*-hydroxyphthalimide (2.30 mmol, 0.37 g) and PPh_3 (2.30 mmol, 0.60 g) were added and dissolved in dry THF (10 mL) under an argon atmosphere. After the mixture was cooled to 0 °C, diethyl azodicarboxylate (2.30 mmol, 0.5 mL) was added dropwise. Afterwards, the reaction was warmed up and stirred at room temperature overnight. The reaction was quenched with sat. $NaHCO_3$ solution. The mixture was extracted with ethyl acetate, washed with sat. NaCl solution , dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 4: 1, v/v) to afford **29** as a white solid (0.77 g, 59%, α/β = 3: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 3H), 7.68 – 7.65 (m, 3H), 7.53 (t, *J* = 8.4 Hz, 3H), 7.43 – 7.15 (m, 30H), 5.67 (d, *J* = 3.8 Hz, 1H), 5.18 (d, *J* = 10.6 Hz, 0.38H), 5.06 (dd, *J* = 13.1, 9.6 Hz, 1.41H), 5.00 – 4.86 (m, 3.76H), 4.86 – 4.73 (m, 3.18H), 4.69 (d, *J* = 11.8 Hz, 0.55H), 4.61 (d, *J* = 11.3 Hz, 1.6H), 4.51 (dd, *J* = 27.5, 11.9 Hz, 2.32H), 4.43 – 4.36 (m, 1H), 4.29 (dd, *J* = 10.5, 3.9 Hz, 1H), 4.15-4.11 (m, 2.69H), 3.86 (d, *J* = 2.3 Hz, 0.4H), 3.69 – 3.51 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 162.9, 138.8, 138.7 (×2), 138.6, 138.5, 138.4, 138.1, 134.5, 129.1, 129.0, 128.6, 128.5 (×2), 128.4 (×3), 128.3 (×2), 128.0, 127.8 (×2), 127.7 (×2), 127.6 (×2), 123.7, 123.6, 108.5, 102.7, 82.0, 78.3, 78.0, 75.5, 75.4, 75.1 (×2), 74.7 (×2), 73.6 (×2), 73.5 (×2), 73.3, 72.9, 71.1, 68.9, 68.3; HRMS (ESI) calcd for $C_{42}H_{43}N_2O_8$ $[M+NH_4]^+$ 703.3014, found 703.3022.

Phthalimidyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (30). The same procedure for the synthesis of **29** was applied, yielding **30** (0.91 g, 70%, α/β = 2: 1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 3H), 7.75 – 7.68 (m, 3H), 7.51 (dd, *J* = 18.6, 7.2 Hz, 3H), 7.41 – 7.13 (m, 28H), 5.62 (d, *J* = 3.8 Hz, 1H), 5.18 (d, *J* = 10.6 Hz, 0.5H), 5.11 (t, *J* = 9.1 Hz, 1.5H), 5.03 (d, *J* = 10.9 Hz, 1H), 4.94 (d, *J* = 11.0 Hz, 0.5H), 4.90 – 4.69 (m, 5.5H), 4.65 – 4.50 (m, 3.5H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.13 (t, *J* = 9.5 Hz, 1H), 3.90 (dd, *J* = 10.9, 2.2 Hz, 1H), 3.85 – 3.60 (m, 5.5H), 3.59 – 3.48 (m, 0.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 163.0, 138.8, 138.5 (×2), 138.4, 138.1, 138.0 (×2), 137.7, 134.6, 129.0 (×2), 128.7, 128.6, 128.5, 128.4 (×2), 128.3, 128.1 (×2), 128.0 (×2), 127.9, 127.7 (×2), 127.6, 127.5, 123.7, 123.6, 107.7, 102.4, 84.4, 81.5, 80.6, 78.7, 76.0, 75.9, 75.7, 75.2, 75.1, 75.0, 73.6, 73.5, 72.8, 72.4, 68.9, 68.1; HRMS (ESI) calcd for $C_{42}H_{43}N_2O_8$ $[M+NH_4]^+$ 703.3014, found 703.3011.

Acetamidyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (31). To a solution of **29** (0.24 mmol, 0.17 g) in methanol (10 mL) was added slowly 85% hydrazine hydrate (0.72 mmol, 42 μL). The reaction was stirred at room temperature and monitored by TLC. After completion (~1 h), the mixture was concentrated. Then crude product was dissolved in CH_2Cl_2 (8 mL) and 1M K_2CO_3 solution (8 mL), AcCl (3.70 mmol, 266 μL) dissolved in dry CH_2Cl_2 (2 mL) was added slowly at 0 °C. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion (~2 h), the mixture was extracted with CH_2Cl_2 for three times and the organic phases were combined, washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 2: 1, v/v) to afford **31** as yellow oil (119 mg, 83% yield over 2 steps, α/β = 2: 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.54 – 7.16 (m, 20H), 5.23 (br s, 0.72H), 5.09 – 4.63 (m, 5.64H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.24 (s, 1H), 4.14 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.94 (s, 2.41H), 3.59 – 3.42 (m, 2H), 2.11 (s, 1H), 1.85 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 138.4, 138.2, 138.0, 137.4 (×2), 128.2 (×2), 128.1, 127.7 (×2), 127.5, 127.3 (×2), 101.4, 78.1, 75.3, 74.8, 74.6, 73.3, 73.0, 72.8, 70.6, 69.1, 19.6; HRMS (ESI) calcd for $C_{36}H_{43}N_2O_7$ $[M+NH_4]^+$ 615.3065, found 615.3082.

Acetamidyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (32). Glycosyl donor **32** was prepared according to the procedure for the preparation of **31** (0.12 g, 84% yield over 2 steps, α/β = 2: 1) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.42 – 7.23 (m, 17.45H), 7.14 – 7.12 (m, 1.88H), 5.21 (br s, 0.73H), 4.97 (d, *J* = 10.9 Hz, 1H), 4.92 – 4.74 (m, 3.61H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.49 (dd, *J* = 11.5, 4.4 Hz, 1.83H), 4.06 (br s, 0.65H), 3.96 (t, *J* = 9.2 Hz, 1H), 3.70 – 3.50 (m, 3.84H), 1.91 (s, 2H), 1.70 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 138.7, 138.2, 137.9, 137.7, 128.5 (×2), 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 101.0, 81.5, 78.9, 77.4, 75.7, 75.1, 73.6, 72.8, 71.9, 68.8, 19.9; HRMS (ESI) calcd for $C_{36}H_{43}N_2O_7$ $[M+NH_4]^+$ 615.3065, found 615.3070.

Phthalimidyl 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-galactopyranoside (34). An oven-dried flask fitted with a magnetic stir-bar was charged with **33** (1.27 mmol, 0.74 g), *N*-hydroxyphthalimide (6.13 mmol, 1.00 g), diphenyl sulfoxide (0.89 mmol, 0.18 g), activated 4Å molecular sieves (0.80 g), and CH_2Cl_2 (8 mL) under an argon atmosphere. After cooling to -78 °C, Tf_2O (0.76 mmol, 128 μL) was added dropwise. The reaction was warmed up slowly and monitored by TLC. After completion (~6 h), the reaction was quenched with triethylamine (200 μL), then filtered with Celite and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether: ethyl acetate = 3: 1, v/v) to afford **34** as a pale yellow oil (0.59 g, 75%). For the α-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 4H), 7.46 – 7.29 (m, 15H), 5.55 (d, *J* = 3.6 Hz, 1H), 4.94 – 4.90 (m, 2H), 4.83 – 4.74 (m, 2H), 4.60 (d, *J* = 11.6 Hz, 2H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.25 – 4.19 (m, 2H), 4.15 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.69 (t, *J* = 8.2 Hz, 1H), 3.58 (dd, *J* = 9.2, 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 138.3, 138.2, 137.5, 134.6, 128.9, 128.6, 128.4 (×2), 128.2, 128.1, 127.9, 127.8 (×2), 127.7, 123.7, 103.5, 77.0, 75.1, 73.4, 73.2, 72.4, 71.3, 68.0, 59.0; HRMS (ESI) calcd for $C_{35}H_{33}N_4O_7$ $[M+H]^+$ 621.2344, found 621.2345**.**

Acetamidyl 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-galactopyranoside (35). Glycosyl donor **35** was prepared according to the procedure for the preparation of **31** (0.10 g, 80% yield over 2 steps, α/β = 2: 1) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 7.40 – 7.23 (m, 15H), 5.13 (br s, 1H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.76 – 4.65 (m, 2H), 4.52 (d, *J* = 11.5 Hz, 2H), 4.46 – 4.25 (m, 2H), 4.07 (dd, *J* = 10.7, 3.5 Hz, 1H), 4.01 (s, 1H), 3.94 (br s, 1H), 3.56 (dt, *J* = 16.0, 9.2 Hz, 2H), 2.16 (s, 1H), 1.88 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 138.1, 137.7, 137.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0 (×2), 127.9 (×2), 102.3, 77.3, 74.9, 73.6, 73.4, 72.3, 71.1, 68.9, 59.1, 19.8; HRMS (ESI) calcd for $C_{29}H_{33}N_4O_6$ $[M+H]^+$ 533.2395, found 533.2399.

General Glycosylation Procedures:

General procedure A. An oven-dried flask fitted with a magnetic stir-bar was charged with donor (1.4 equiv., 0.036 mmol), acceptor (0.026 mmol), activated 4 Å molecular sieves (100 mg) and CH_2Cl_2 (1.0 mL) under an argon atmosphere. After cooling to 0 °C, $SnCl_4$ (1.5 equiv., 0.039 mmol) was added, then the mixture was stirred at 40 °C for 40 min. After completion, the reaction was quenched with triethylamine (5.0 μL), then filtered through Celite and concentrated in vacuo. The crude product was purified by flash column chromatography (eluting with petroleum ether/ethyl acetate) to give the desired product.

General procedure B. A dried microwave tube fitted with a magnetic stir-bar was charged with donor (1.4 equiv., 0.036 mmol), acceptor (0.026 mmol), activated 4Å molecular sieves (100 mg), and $ClCH_2CH_2Cl$ (1 mL) under an argon atmosphere. After stirring for 20 min, $Cu(OTf)_2$ (2.0 equiv., 0.052 mmol) was added at 0 °C, then put into themicrowave reactor at 80 °C for 1-2 h. After completion, the reaction mixture was quenched with triethylamine (0.1 mL) and the solids were filtered off through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to give the desired product.

General procedure C. A dried microwave tube fitted with a magnetic stir-bar was charged with donor (1.4 equiv., 0.036 mmol), acceptor (0.026 mmol), activated 4Å molecular sieves (100 mg), and $ClCH_2CH_2Cl$ (1 mL) under an argon atmosphere. After stirring for 20 min, $SnCl_4$ (1.5 equiv., 0.039 mmol) was added dropwise at 0 °C, then put into the microwave reactor at 40 °C for 30 min. After completion, the reaction was quenched with triethylamine (0.1 mL) and the solids were filtered off through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to give the desired product.

General procedure D. A dried microwave tube fitted with a magnetic stir-bar was charged with donor (1.4 equiv., 0.036 mmol), acceptor (0.026 mmol), activated 4Å molecular sieves (100 mg), and $ClCH_2CH_2Cl$ (1 mL) under an argon atmosphere. After stirring for 20 min, $SnCl_4$ (0.5 equiv., 0.013 mmol) was added dropwise at 0 °C, then put into the microwave reactor at 40 °C for 30 min. After completion, the reaction was quenched with triethylamine (0.1 mL) and the solids were filtered off through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to give the desired product.

General procedure E. An oven-dried flask fitted with a magnetic stir-bar was charged with donor (1.4 equiv., 0.036 mmol), acceptor (0.026 mmol), activated 4Å molecular sieves (100 mg), and CH_2Cl_2 (1 mL) under an argon atmosphere. After stirring for 20 min, $Cu(OTf)_2$ (4.0 equiv., 0.10 mmol) was added at 0 °C, then the mixture was stirred at room temperature for 5-8 h. After completion, the reaction was quenched with triethylamine (0.1 mL) and the solids were filtered off through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to give the desired product.

General procedure F. An oven-dried flask fitted with a magnetic stir-bar was charged with donor (1.4 equiv., 0.036 mmol), acceptor (0.026 mmol), activated 4Å molecular sieves (100 mg), and $ClCH_2CH_2Cl_2$ (1 mL) under an argon atmosphere. After stirring for 20 min, $Cu(OTf)_2$ (4.0 equiv., 0.10 mmol) was added at 0 °C, then the mixture was stirred at 50 °C for 8 h. After completion, the reaction was

quenched with triethylamine (0.1 mL) and the solids were filtered off through a pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate) to give the desired product.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-α-D-glucopyranoside (9). The reaction of donor **5** (25.0 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure A, affording **9** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 24.8 mg, 92% yield); The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **9** (25.7 mg, 95% yield); The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure C, affording **9** (25.9 mg, 96% yield). The ^{1}H NMR data for **9** are in accordance with those reported previously.[32]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-α-D-glucopyranoside (11). The reaction of donor **5** (25.0 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure A, affording **11** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 8.9 mg, 33% yield); The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **11** (20.2 mg, 75% yield). The ^{1}H NMR data for **11** are in accordance with those reported previously.[33]

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-α-D-glucopyranoside (13). The reaction of donor **5** (25.0 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure A, affording **13** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 7.8 mg, 29% yield); The reaction of donor **5** (25.0 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure **C**, affording **13** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 5.4 mg, 20% yield); The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **13** (24.3 mg, 90% yield); The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure C, affording **13** (25.7 mg, 95% yield). The ^{1}H NMR data for **13** are in accordance with those reported previously.[34]

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (14). The reaction of donor **6** (25.0 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure A, affording **14** (eluent: petroleum ether/ethyl acetate = 4: 1 (v/v); 8.7 mg, 32% yield); The reaction of donor **17** (24.1 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **14** (22.2 mg, 82% yield). The ^{1}H NMR data for **14** are in accordance with those reported previously.[35]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (15). The reaction of donor **6** (25.0 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure A, affording **15** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 26.5 mg, 98% yield)**;** The reaction of donor **17** (24.1 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **15** (24.4 mg, 90% yield); The reaction of donor **17** (24.1 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure C, affording **15** (24.6 mg, 91% yield). The ^{1}H NMR data for **15** are in accordance with those reported previously.[36]

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-α-D-glucopyranoside (37). The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **36** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording

37 (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 24.4 mg, 90% yield). The ^{1}H NMR data for **37** are in accordance with those reported previously.[34]

(1S,2R,5S)-(+)-1-Mentyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (39). The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **38** (4 mg, 0.026 mmol) was performed as described in the general procedure B, affording **39** (eluent: petroleum ether/ethyl acetate = 8: 1 (v/v); 17.6 mg, 92% yield)**;** The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **38** (4 mg, 0.026 mmol) was performed as described in the general procedure C, affording **39** (17.2 mg, 90% yield)**.** The ^{1}H NMR data for **39** are in accordance with those reported previously.[22]

Cholesteryl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (41). The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **40** (10 mg, 0.026 mmol) was performed as described in the general procedure B, affording **41** (eluent: petroleum ether/ethyl acetate = 7: 1 (v/v); 22.3 mg, 89% yield)**;** The reaction of donor **7** (1.21 g, 1.80 mmol) and acceptor **40** (500.0 mg, 1.30 mmol) was performed as described in the general procedure B, affording **41** (1.07 g, 85% yield); The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **40** (10 mg, 0.026 mmol) was performed as described in the general procedure C, affording **41** (22.3 mg, 89% yield)**;** The ^{1}H NMR data for **41** are in accordance with those reported previously.[37]

Adamantyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (43). The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **42** (4.0 mg, 0.026 mmol) was performed as described in the general procedure B, affording **43** (eluent: petroleum ether/ethyl acetate = 4: 1 (v/v); 18.0 mg, 95% yield); The reaction of donor **7** (24.1 mg, 0.036 mmol) and acceptor **42** (4.0 mg, 0.026 mmol) was performed as described in the general procedure C, affording **43** as a white solid (17.7 mg, 93% yield). mp: 240.6 – 241.9; ^{1}H NMR (400 MHz, $CDCl_3$). δ 8.15 – 7.19 (m, 20H), 5.96 (s, 1H), 5.77 (t, J = 9.1 Hz, 1H), 5.63 – 5.55 (m, 1H), 5.09 (d, J = 7.9 Hz, 1H), 4.66 – 4.55 (m, 1H), 4.46 (dd, J = 11.3, 5.2 Hz, 1H), 4.32 (t, J = 6.4 Hz, 1H), 2.04 (s, 3H), 1.85 (d, J = 11.5 Hz, 3H), 1.69 (d, J = 11.6 Hz, 3H), 1.61 – 1.46 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.8, 165.6, 165.1, 133.5, 133.2, 133.1, 130.2, 129.8, 129.7 (×2), 129.6 (×2), 129.1, 128.9, 128.6, 128.4 (×2), 128.3, 94.6, 75.8, 72.2, 71.2, 69.9, 68.3, 62.5, 42.4, 36.1, 30.6; HRMS (ESI) calcd for $C_{44}H_{46}NO_{10}$ $[M+H]^+$ 748.3116, found 748.3131.

4-Methylphenyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-1-thio-glucopyranoside (45). The reaction of donor **17** (24.1 mg, 0.036 mmol) and acceptor **44** (15.5 mg, 0.026 mmol) was performed as described in the general procedure C, affording **45** (eluent: petroleum ether/ethyl acetate = 3: 1 (v/v); 24.6 mg, 65% yield). The ^{1}H NMR data for **45** are in accordance with those reported previously.[38]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (46). The reaction of donor **20** (19.2 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **46** (eluent: petroleum ether/ethyl acetate = 4: 1 (v/v); 22.3 mg, 93% yield); The reaction of donor **20** (19.2 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure C, affording **46** (22.3 mg, 93% yield). The ^{1}H NMR data for **46** are in accordance with those reported previously.[19]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (47). The reaction of donor **20** (19.2 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording

47 (eluent: petroleum ether/ethyl acetate = 4: 1 (v/v); 20.4 mg, 85% yield). The ^{1}H NMR data for **47** are in accordance with those reported previously.[33]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-glucopyranoside (48). The reaction of donor **23** (24.1 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **48** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 21.7 mg, 80% yield). The ^{1}H NMR data for **48** are in accordance with those reported previously.[33]

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-α-D-glucopyranoside (49). The reaction of donor **23** (24.1 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **49** (eluent: petroleum ether/ethyl acetate = 4: 1 (v/v); 24.4 mg, 90% yield). The ^{1}H NMR data for **49** are in accordance with those reported previously.[39]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-α-D-glucopyranoside (50). The reaction of donor **26** (18.7 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **50** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 22.2 mg, 94% yield); The reaction of donor **26** (18.7 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure C, affording **50** (21.2 mg, 90% yield)**.** The ^{1}H NMR data for **50** are in accordance with those reported previously.[40]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-α-D-glucopyranoside (51). The reaction of donor **26** (18.7 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **51** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 15.3 mg, 65% yield). The ^{1}H NMR data for **51** are in accordance with those reported previously.[40]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (52). The reaction of donor **31** (21.5 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **52** (eluent: petroleum ether/ethyl acetate = 6: 1 (v/v); 22.8 mg, 89% yield, α/β = 2:1); The reaction of donor **31** (21.5 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure D, affording **52** (24.9 mg, 97% yield, α/β = 2:1). The ^{1}H NMR data for **52** are in accordance with those reported previously.[41]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (53). The reaction of donor **31** (21.5 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure D, affording **53** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 21.8 mg, 85% yield, α/β = 4:1); The reaction of donor **31** (21.5 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure E, affording **53** (21.3 mg, 83% yield, α/β = 4: 1). The ^{1}H NMR data for **53** are in accordance with those reported previously.[41]

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (54). The reaction of donor **31** (21.5 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure D, affording **54** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 23.0 mg, 90% yield, α/β = 4: 1); The reaction of donor **31** (21.5 mg, 0.036 mmol) and acceptor **12** (12.1 mg, 0.026 mmol) was performed as described in the general procedure E, affording **54** (21.8 mg, 85% yield, α/β = 4:1). The ^{1}H NMR data for **54** are in accordance with those reported previously.[42]

(1S,2R,5S)-(+)-1-Mentyl 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (55). The reaction of donor **31** (21.5 mg, 0.036 mmol) and acceptor **40** (4.0 mg, 0.026 mmol) was performed as described in the general procedure B, affording **55** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 15.3 mg, 87% yield, α/β = 1:1). The ^{1}H NMR data for **55** are in accordance with those reported previously.[43]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (56). The reaction of donor **32** (21.5 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure B, affording **56** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 22.6 mg, 88% yield, α/β = 2:1). The ^{1}H NMR data for **56** are in accordance with those reported previously.[41]

6-*O*-(2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (58). The reaction of donor **32** (21.5 mg, 0.036 mmol) and acceptor **57** (7.0 mg, 0.026 mmol) was performed as described in the general procedure D, affording **58** (eluent: petroleum ether/ethyl acetate = 4: 1 (v/v); 15.9 mg, 78% yield, α/β = 2:1). The ^{1}H NMR data for **58** are in accordance with those reported previously.[44]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside (59). The reaction of donor **32** (21.5 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure E, affording **59** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 19.2 mg, 75% yield, α/β = 1:1). The ^{1}H NMR data for **59** are in accordance with those reported previously.[44]

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-azide-2-deoxy-3,4,6-tri-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (60). The reaction of donor **35** (19.2 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure D, affording **60** (eluent: petroleum ether/ethyl acetate = 5: 1 (v/v); 19.2 mg, 80% yield, α/β = 1:1); The reaction of donor **35** (19.2 mg, 0.036 mmol) and acceptor **8** (12.1 mg, 0.026 mmol) was performed as described in the general procedure F, affording **60** (24.4 mg, 85% yield, α/β = 1:1). The ^{1}H NMR data for **60** are in accordance with those reported previously.[45]

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2-azide-2-deoxy-3,4,6-tri-*O*-benzyl-D-galactopyranosyl)-α-D-glucopyranoside (61). The reaction of donor **35** (19.2 mg, 0.036 mmol) and acceptor **10** (12.1 mg, 0.026 mmol) was performed as described in the general procedure F, affording **61** (eluent: petroleum ether/ethyl acetate = 4: 1 (v/v); 14.6 mg, 61% yield, α/β = 4:1). The ^{1}H NMR data for **61** are in accordance with those reported previously.[45]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Screening of reaction conditions and NMR spectra for compounds (PDF)

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Notes

The authors declare no competing financial interest.

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