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Flexible 1,2-cis α-Glycosylation Strategy Based on *in situ* Adduct Transformation

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Jhe-Cyuan Hu,[a] Ai-Fen Wendy Feng,[a] Bo-Yao Chang,[a] Chun-Hung Lin,*[,b] and Kwok-Kong Tony Mong*[a]

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A flexible 1,2-cis α-selective glycosylation strategy for a wide range of glycosyl donors and acceptors was developed, which features an *in situ* adduct transformation protocol. Based on this strategy, both NFM-derived and iodide covalent adducts can be accessed for glycosylation. With the low temperature NMR spectroscopy, the aforementioned glycosyl adducts were detected.

1 Introduction

Most efforts toward the chemical synthesis of oligosaccharides are devoted to protecting group manipulation, which is performed to control regio- and stereochemistry during glycosidic bond formation.[1,2] The typical strategy used for this type of stereochemical control relies on a specialized protecting group that acts to direct the attack of the acceptor along a specific route.[3,4] Unfortunately, the introduction and removal of the specialized protecting group often demand additional steps, leading to a lengthy synthetic process. Thus, a simple, more step-economical approach to synthesizing oligosaccharides would be greatly beneficial such as the one-pot regioselective protection of sugars[5,6] and one-pot oligosaccharide synthesis.[7-9]

The use a nucleophile additive as the stereo-directing agent during glycosylation is step-economical, whereby no additional protecting group manipulation is required and the additive can be easily removed after the reaction.[10] Lemieux explored the use of tetra-butylammonium bromide (TBAB)[11] to effect 1,2-*cis* α-glycosidic bond formation. This seminal work sparked the development of other additives for glycosylation, including tetrabutyl ammonium iodide (TBAI),[12,13] lithium iodide (LiI),[14] dimethylacetamide (DMA),[15] phosphine oxides ($R_3P=O$),[16] thioethers (RSR′),[17] dimethylformamide (DMF),[18] and *N*-formylmorpholine (NFM).[19] However, the nucleophile-modulated glycosylation generally suffers from a limited scope of application as the coupling efficiency depends heavily on the structure of the substrate. Because carbohydrates are structurally diverse compounds, a general 1,2-*cis* α-glycosylation strategy that is wholely based on the use of external agents is desirable and necessary.

In previous studies, we found that glycosyl oxacarbenium ions can be trapped by formamide nucleophiles such as DMF and diisopropylformamide to form a glycosyl imidinium adduct, which can be coupled with an acceptor to form a glycosylation product.[18,19] Among the formamide additives, NFM is the most reactive in glycosylation and it can be used for less reactive 2-azido-2-deoxyglycosyl donors. However, the α-selectivity of the NFM imidinium ion formed from the NFM additive is practical for less reactive acceptors, but is modest for more reactive primary acceptors.[19] In term of reactivity and selectivity, the NFM imidinium adduct is complementary to the glycosyl iodide. Base on such perception, we speculate that the reactive NFM imidinium adduct may be substituted with an iodide nucleophile to furnish a presumably more selective iodide donor. As such, the selectivity of the glycosyl adducts can be improved by simply *in situ* adduct transformation. The key to this strategy is finding suitable sets of conditions for substitution of NFM derived adduct with iodide nucleophile and subsequent glycosylation (Scheme 1). An advantage of the proposed method is that it can be modified according to the reactivity of the acceptor. For less reactive acceptors, the *in situ* substitution can be skipped and the more reactive NFM imidinium adduct is deployed for glycosylation.

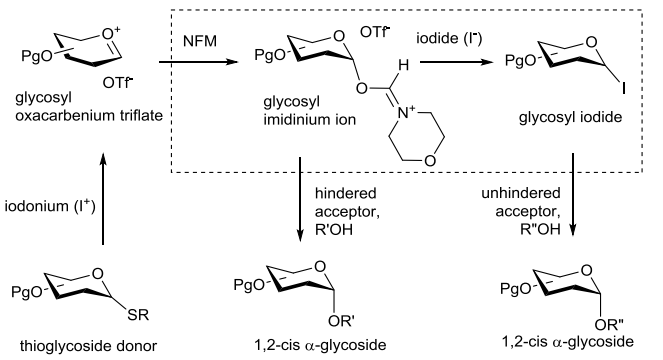

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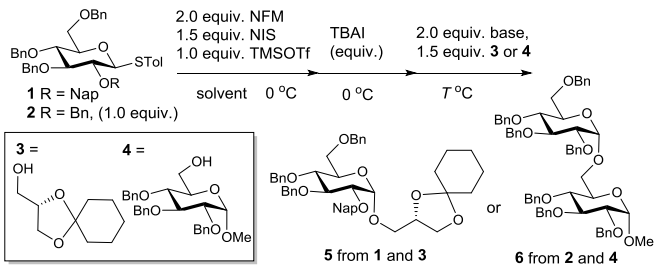
Figure 1 Working concept of *in situ* transformation of glycosyl adduct in glycosylation.

2 Results and discussion

2.1 Optimization of Conditions for *in situ* Adduct Transformation

To elucidate the optimal conditions for one-pot *in situ* adduct transformation and glycosylation, thioglucosides **1** and **2** were used as donors for the reaction along with acceptors **3** and **4** (Table 1). TBAI was used as the iodide additive because TBAI is used as the iodide additive because it is readily available and has widely been used in preparation of glycosyl iodide.[12a-d] First, 1.0 equiv. of thioglucoside **1** and 2.0 equiv. of NFM were treated with 1.5 equiv. of *N*-iodosuccinimide (NIS) and 1.0 equiv. of trimethylsilyltrifluoromethane sulfonate (TMSOTf) at 0 ºC.[20] After the formation of the NFM imidinium adduct (*ca* 1.0 h), TBAI was added to substitute the NFM leaving group of the NFM imidinium adduct (Entries 2–4). The substitution reaction was monitored by TLC. Then, 2.0 equiv. of di-*tert*-butylmethylpyridine (DTBP) and 1.5 equiv. of acceptor **3** were added, and the reaction temperature was raised to 30 ºC to initiate the coupling reaction. For comparison, the glycosylation was also performed in the absence of TBAI and DTBP.

Table 1. Elucidation conditions for the *in situ* adduct transformation.



Entry	Donor, acceptor	Formamide and TBAI (equiv)	Base [a]	*T* ℃	Product **5** or **6**	
					Yield (%)	α:β[b]
1	**1**, **3**	NFM (2), 0	-	0	**5**, 75	1.5:1
2	**1**, **3**	NFM (2), 2	A	30	**5**, 44	5:1
3	**1**, **3**	NFM (2), 5	A	30	**5**, 60	11:1
4	**1**, **3**	NFM (2), 10	A	30	**5**, 48	13:1
5	**1**, **3**	NFM (4), 5	A	30	**5**, 63	6:1
6	**1**, **3**	DMF (2), 5	A	30	**5**, 40	4:1
7	**2**, **4**	NFM (2), 5	A	15	**6**, 47	>19:1
8	**2**, **4**	NFM (2), 5	A	30	**6**, 55	>19:1
9	**2**, **4**	NFM (2), 5	A	50[c]	**6**, 23	3:1
10	**2**, **4**	NFM (2), 5	-	30	**6**, 66	5:1
11	**2**, **4**	NFM (2), 5	B	30	**6**, 76	>19:1
12	**2**, **4**	NFM (2), 5	C	30	**6**, 76	>19:1
13	**2**, **4**	NFM (2), 5	D	30	-	-
14	**2**, **4**	NFM (0), 5	B	30	-	-
15	**2**, **4**	NFM (2), 0	A	0	-[d]	-
16	**2**, **4**	NFM (0), 0	-	0	**6**, 75	1:1

[a] Base used in present study: A = DTBP, B = lutidine, C = DIEA, and D = DBU. [b] Ratio of α- and β-isomers was estimated from HPLC analysis or NMR spectroscopy. [c] 1,2-Dichloroethane ($C_2H_4Cl_2$) was used as solvent. [d] Only α-glucosyl formate, the hydrolysed product of the NFM imidinium adduct, was produced.

In the absence of TBAI and DTBP, the glycosylation of **3** with **1** produced a 1.5:1 α:β ratio of **5**, but in the presence of 2.0 equiv. of TBAI and DTBP, the α:β ratio was improved to 5:1 (Entries 1 vs. 2). Increased α-selectivity (*ca* 12:1 α:β ratio) was achieved by using 5.0 or 10.0 equiv. of TBAI (Entries 3 and 4). Interestingly, addition of 4.0 equiv. of NFM eroded the α-selectivity of the glycosylation, indicating the need of excessive amount of TBAI (Entry 5). In addition to NFM, DMF (2 equiv.) was also used for the glycosylation study, but the reaction was sluggish with a moderate α-selectivity (Entries 2 vs 6). In consideration of the α-selectivity and the yield of reaction, 2.0 equiv. of NFM and 5.0 equiv. of TBAI (with respect to the donor) would be used in subsequent glycosylations.

Next, we examined the effect of temperature (Entries 7–9). Since the *sn*-glycerol acceptor **3** was found to undergo racemization at a higher reaction temperature (≥ 50 °C), therefore glycosyl acceptor **4** and perbenzyl thioglucoside donor **2** were used. At either 15 ºC or 30 ºC, the α-selectivity of the glycosylation of **4** with **2** was excellent, but the yield of the reaction was lower at 15 ºC (Entry 7). Higher reaction temperature (50 ºC) was detrimental to present glycosylation protocol (Entry 9).[21]

Addition of the base is necessary in our method as indicated by the erosion of α-selectivity (α:β 5:1) without the base addition (Entry 10). Common organic bases such as diisopropylethyl amine (DIEA) and lutidine were effective in addition to DTBP (Entries 11 and 12). Amidine base such as diazabicyclo-[5.4.0]-undec-7-ene (DBU) spoiled the glycosylation, but the reason is unclear (Entry 13). For comparison, the glycosylation of **4** with **2** was repeated in the absence of (i) NFM (Entry 14), (ii) in the absence of TBAI and lutidine (Entry 15), or (iii) in the absence of NFM, TBAI and base (Entry 16). Under the conditions of entries 14 and 15, no glycosylation product was produced. In the absence of any additive and base (i.e. entry 16), the glycosylation product was found but with no α-selectivity.

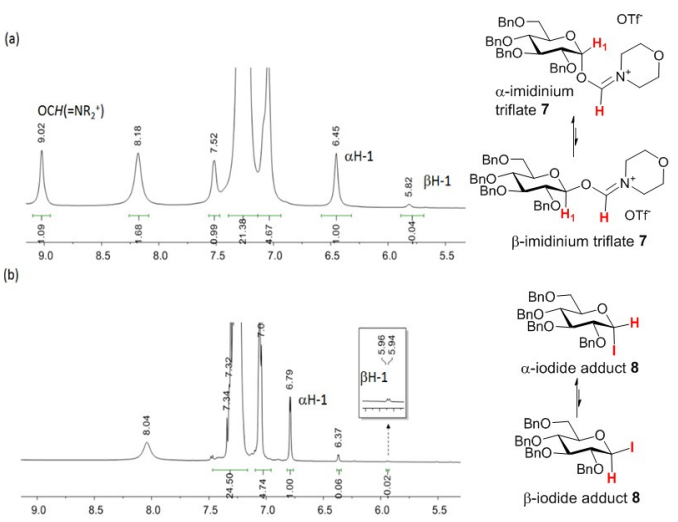


Figure 2. Representative ^{1}H NMR spectra (500 MHz) for samples taken after the activation of donor **2** in the presence of NFM (a) and after the substitution with TBAI (b).

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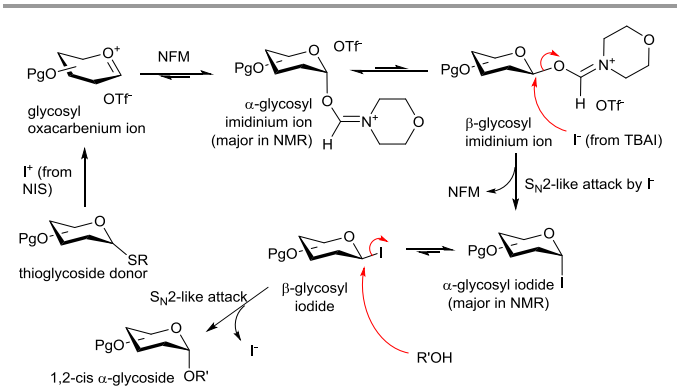
Having established the one-pot *in situ* adduct transformation and glycosylation, we applied the low temperature NMR spectroscopy to detect the glycosylation adducts. To this end, thioglucoside **2** in $CDCl_3$ solution was activated by NIS and TMSOTf in the presence of NFM, followed by the iodide substitution at 0 ºC. At different time points, an aliquot of the reaction mixture was taken for NMR analysis (Figure 2).

For the samples taken following the activation of donor **2**, α-glucosyl NFM imidinium **7** was observed as the major intermediate. The identity of this intermediate is supported by the observed chemical shifts (δ) of the proton signals at 6.45 and 9.02 ppm, respectively, which correspond to the anomeric and imidinum protons of **7** (Figure 2a).[18] In the samples taken after the substitution reaction, these anomeric and imidinum proton signals were diminished, and a new downfield signal appeared at 6.79 ppm with a corresponding ^{13}C signal at 80.6 ppm (see 1D ^{13}C, 2D-COSY, and 2D-HSQC NMR spectra). In the literature, similar signals have been identified as the anomeric ^{1}H and ^{13}C signals of α-glucosyl iodide **8** (Figure 2b).[22] Closer examination revealed a tiny proton signal at 5.95 ppm with a $^{3}J_{H\text{-}H}$ value of 8.0 Hz, which is likely to be the anomeric ^{1}H signal of the β-iodide.[23]

From above NMR studies, we propose the reaction mechanism to account for the α-selectivity obtained in glycosylation (Scheme 1). The thioglycoside donor is first activated by the NIS to give the glycosyl oxacarbenium ion, which is reacted with NFM additive to form a mixture α- and β-imidinium adducts. Thermodynamically, the α-imidinium adduct is more stable than its β-counterpart, but the β-imidinium is more reactive in glycosylation. When TBAI is added, the iodide nucleophile attacks the β-imidinium adduct via a S_N2-like mechanism forming the α-glycosyl iodide as the major pathway. Trace amount of the β-iodide anomer detected may be formed through a minor S_N1 reaction pathway and or through equilibrium with the α-iodide counterpart. Subsequent coupling of the β-iodide with an alcohol acceptor affords the α-glycosylation product.



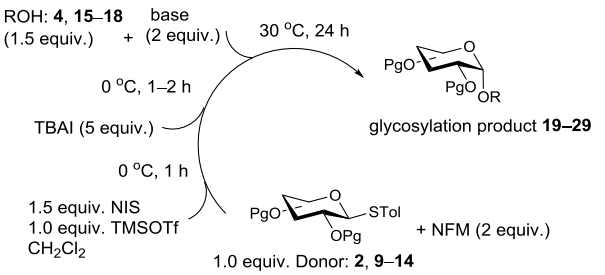
Scheme 1 Proposed mechanism for one-pot *in situ* adduct transformation and glycosylation.

2.2 Scope of Application to Thioglycosyl Donors

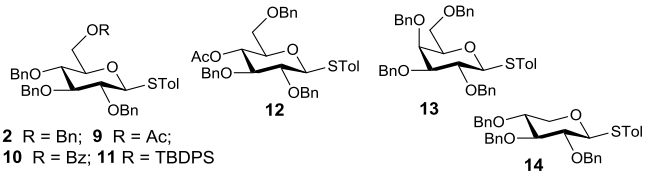
With the one-pot *in situ* adduct transformation and glycosylation protocol established, we next explored the substrate scope of this method (Table 2). In the beginning, per-*O*-benzyl protected thioglycoside donors **2**, **13**, **14** and orthogonally protected thioglucoside donors **9**, **10**, **11**, **12** were coupled with various acceptors **4**, **15-18**. The glycosylation of rhamnosyl acceptor **16**, diosgenin **17**, and thioglucosyl acceptor **18** with thioglucoside donor **2** produced the desired products **19**, **20**, and **21** at practical 60%–70% yields.

Table 2. Scope of application for non-amino thioglycoside donors **2**, **9**–**12**.

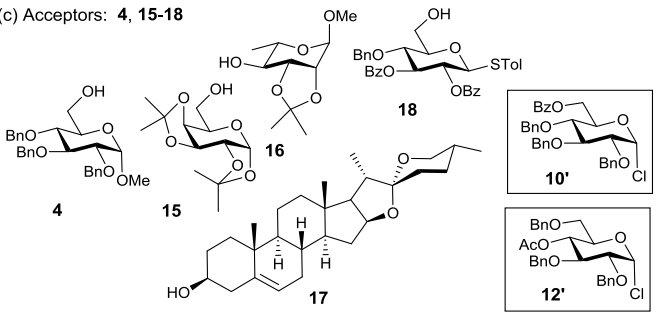
(a) One pot *in situ* adduct transformation and glycosylation



(b) Donors **2**, **9**–**14**



(c) Acceptors: **4**, **15-18**



Entry	Donor, acceptor	Base	Product no	Yield (%)	α:β
1	**2**, **16**	DIEA	**19**	70	19:1[a]
2	**2**, **17**	lutidine	**20**	60	14:1[a]
3	**2**, **18**	lutidine	**21**	68	9:1[a]
4	**9**, **15**	DIEA	**22**	34	>19:1[a]
5	**9**, **15**	lutidine	**22**	70	>19:1[a]
6	**9**, **4**	lutidine	**23**	70	>19:1[a]
7	**10**, **4**	lutidine	**24**	60	>19:1[b]
8	**11**, **4**	lutidine	**25**	65	>19:1[a]
9	**12**, **4**	lutidine	**26**	60	10:1[b]
10	**13**, **4**	DIEA	**27**	69	>19:1[a]
11	**13**, **15**	lutidine	**28**	65	13:1[a]
12	**14**, **15**	lutidine	**29**	77	5:1[b]

[a] α:β Anomer ratio was determined by HPLC analysis. [b] α:β Anomer ratio was determined by NMR analysis.

with good to excellent α:β ratios (Entries 1-3). For glycosylation of **15** with 6-*O*-acetyl (Ac)-protected thioglucosyl donor **9**, DIEA was initially used as the base, but the yield of the product

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15 was modest (34%) (Entry 4). Nonetheless, when lutidine was used, the yield of **15** was improved to 70% (Entry 5).

Next, we examined the glycosylation of **4** with orthogonally protected donors including 6-*O*-acetyl (Ac) thioglucoside **9**, 6-*O*-benzoyl (Bz) thioglucoside **10**, 6-*O*-*tert*-butyldiphenylsilyl (TBDP) thioglucoside **11**, and 4-*O*-Ac thioglucoside **12** (Entries 6–9). It should be noted that glycosyl donors containing either an electron-withdrawing (Ac or Bz) or sterically bulky (TBDP) protecting group have been shown be less reactive. For example, the glycosylation of acetonide protected *sn*-glycerol acceptor with 6-*O*-Ac glucosyl iodide required 6 days for completion.[24] A higher temperature[25] or microwave irradiation[26] was required to accelerate the reaction.

Our protocol was effective for the glycosylation of acceptor **4** with protected thioglycosides **9**, **10**, **11**, and **12**, and the desired disaccharides **23**, **24**, **25**, and **26** were obtained in satisfactory 60%–70% yields with high α-selectivity (Entries 6–9). It should be noted that during the glycosylation with donors **10** and **12**, small amounts (~5%–10%) of glycosyl chlorides **10′** and **12′** were detected (see inset) that were inseparable from their iodide counterparts. The identities of the chloride intermediates **10′** and **12′** were tentatively inferred from the mass spectrometry of the crude reaction mixtures. Such chloride byproducts have been reported in previous studies and was presumably derived from the solvent, i.e. CH_2Cl_2.[12a] For thiogalactoside donor **13**, the *in situ* prepared galactosyl iodide was not detectable during TLC examination due to the instability of the galactosyl iodide (Entries 10 and 11). For thioxylopyranosyl donor **14**, significant stereocontrol was obtained regardless of the lack of a substituent at C5 (Entry 12).[27]

2-Azido-2-deoxythioglycosides are common building blocks for construction of 2-acetamido-2-deoxy-α-glycosides and related oligosaccharide structures.[28,29] Therefore, it is practical to investigate the suitability of the present glycosylation protocol with 2-azido-2-deoxythioglycoside donors (Table 3). Thus, glucosyl acceptor **4** and cholesterol **33** were coupled with 2-azido-2-deoxythiogalactoside **30**. These reactions formed the desired products **35** and **36** at 65% and 60% yields, respectively, with high α:β ratios of >14:1 (Table 3, entries 1 and 2).

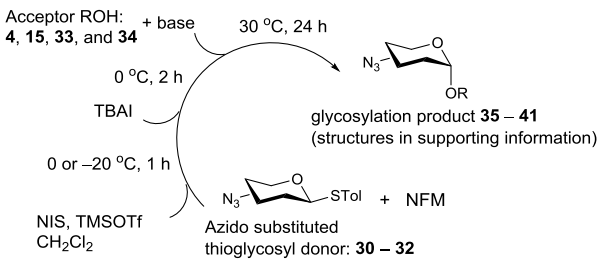
For the less reactive 2-azido-2-deoxythioglucoside donor **31**, 2.0 equiv. of the donor was used to couple with 1.0 equiv. of the acceptor. The stoichiometric amounts of NFM and TBAI used were 4 and 10 equiv., respectively. The glycosylation of acceptors **4**, **15**, and **33** with the azido donor **31** produced the expected products **37**, **38**, and **39**, respectively, in 58-84% yields with practical α-selectivity (Table 3, Entries 3-5).

In addition to 2-azido-2-deoxythioglycosides **30** and **31**, we applied the glycosylation protocol to 4-azido-4,6-dideoxy thiogalactoside **32**. Thioglycoside **32** can serve as a building block for the synthesis of 4-amino-4-deoxy-D-fucoside (Fuc4N), which is present in the cell wall of *Mycobacterium marinum* and various plants.[30] The galactosyl acceptor **15** and 2-deoxy glycosyl acceptor **34** were coupled with the 4-azido donor **32** using the one-pot *in situ* adduct transformation and glycosylation protocol (Entries 6 and 7).[31] As expected, the disaccharides **40** and **41** were produced as a single anomer at 76% and 70% yield, respectively.

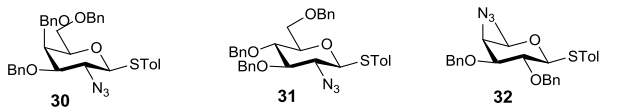
As mentioned earlier, the *in situ* adduct transformation and glycosylation protocol can be modified in accordance with the reactivity of the glycosyl acceptor. For illustration, the hindered secondary glucosyl and mannosyl acceptors **42** and **44** were employed for glycosylation with **2** (Scheme 2). When the unmodified in situ adduct transformation and glycosylation protocol was used to couple the hindered glucosyl acceptor **42** with **2**, the reaction was sluggish and the yield of the glycosylation was poor (Scheme 2a). To improve the conditions, , the iodide substitution step of the original protocol was skipped and the glucosyl NFM adduct could be used directly for coupling with the acceptor **42**. By optimizing the amount of NFM to 4

Table 3. Scope of application for azido thioglycoside donors **26**–**28**.

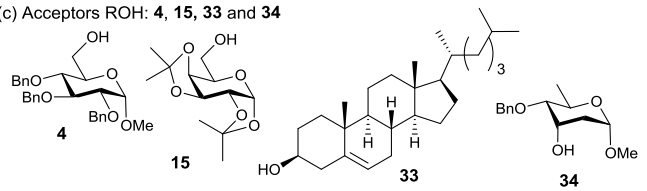
(a) One pot *in situ* adduct transformaton and glycosylation



(b) Azido substituted thioglycosyl donor: **30**–**32**



(c) Acceptors ROH: **4**, **15**, **33** and **34**



Entry	Donor, acceptor (equiv.)	Base (equiv.)	TBAI (equiv.)	Product no., %	Product α:β
1	**30**, **4** (1, 1.5)	DTBP (2.0)	5.0	**35**, 65	>19:1[a]
2	**30**, **33** (1, 1.5)	DTBP (2.0)	5.0	**36**, 60	>19:1[a]
3	**31**, **4** (2, 1)	lutidine (4.0)	10.0	**37**, 62	9:1[a,b]
4	**31**, **15** (2, 1)	lutidine (4.0)	10.0	**38**, 84	15:1[a,b]
5	**31**, **33** (2, 1)	lutidine (4.0)	10.0	**39**, 58	>19:1[a,b]
6	**32**, **15** (1, 1.5)	lutidine (2.0)	5.0	**40**, 76	α only[c]
7	**32**, **34** (1, 1.5)	lutidine (2.0)	5.0	**41**, 70	α only[c]

[a] α:β Anomer ratio was determined by HPLC analysis with α-anomer as standard. [b]10.0 equiv of TBAI, 3.0 equiv of NIS, and 2.6 equiv of TMSOTf, were used (see the procedure in SI). [c]α:β Anomer ratio was determined by NMR spectroscopy.

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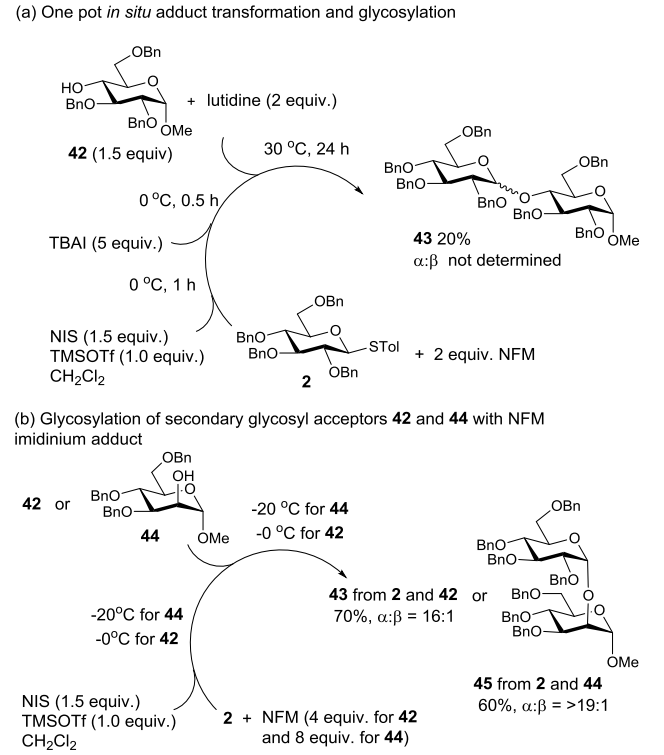
equiv., the glycosylation of **42** with **2** produced disaccharide **43** at a 70% yield and α:β ratio of 16:1 (Scheme 2b). Using the same modified protocol and 8.0 equiv. of NFM additive, the glycosylation of secondary mannosyl acceptor **44** with **2** formed disaccharide **45** at a practical 60% yield with excellent α-selectivity (Scheme 2b).



Scheme 2. a) Glycosylation of less reactive acceptor **42** with one-pot in situ adduct transformation and glycosylation protocol. b) Glycosylation of the less reactive acceptors **42** and **44** using the imidinium adduct

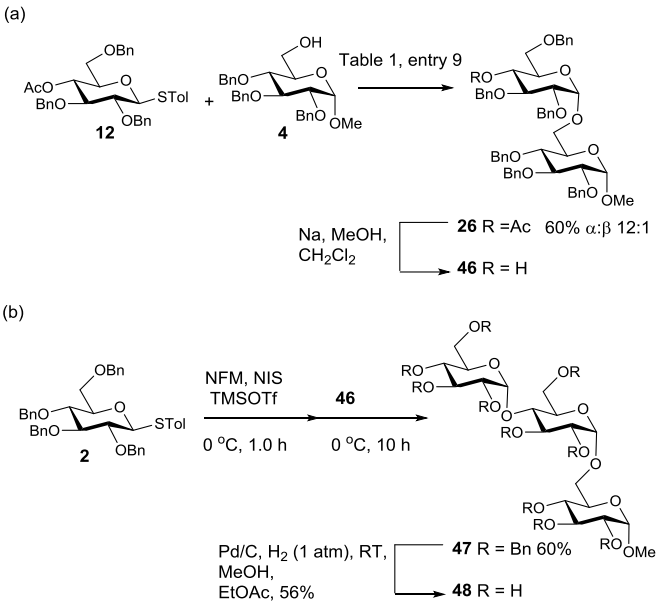
2.3 Application to Oligosaccharide Synthesis

The utility of the present *in situ* adduct transformation and glycosylation protocol was demonstrated by the synthesis of the trisaccharide compound **48**. As the target contains both a hindered α-(1→4) and an unhindered α-(1→6)-glycosidic bond, it should be constructed via the joined use of glycosyl NFM and iodide adducts (Scheme 3). Thus, the glycosylation of the methyl glucosyl acceptor **4** with the thioglucosyl donor **12** using the one-pot *in situ* adduct transformation and glycosylation protocol produced the α-(1→6)-linked disaccharide **26** at a 60% isolated yield and a high 12:1 α:β ratio (Scheme 3a).

Removal of the acetyl group of **26** produced a hindered disaccharide acceptor **46**. As **46** was a secondary acceptor, the iodide substitution step in the one-pot adduct transformation and glycosylation protocol was skipped and the glucosyl imidinium adduct derived from the donor **2** and NFM could directly react with the acceptor **46**. As such, a fully protected trisaccharide **47** was produced in 60% yield as the sole anomer (Scheme 3b). Global deprotection **47** to **48** was straightforward because only benzyl ether protecting groups are present in **47** and they could be removed cleanly by a single hydrogenolysis process.

3. Conclusion

In summary, a flexible glycosylation strategy was developed for the construction of 1,2-cis α-glycosidic bonds utilizing the theory underlying *in situ* transformation of glycosyl imidinium adduct to glycosyl iodide. The protocol is effective for reactive hydroxyl acceptors, and can also be modified for reactions with hindered acceptors. Further NMR studies were performed to confirm the presence of the glycosyl adducts.



Scheme 3. Synthesis of trisaccharide **48** from perbenzyl protected glucosyl building blocks **2**, **4**, and **12** with hindered and unhindered 1,2-*cis* α-glycosidic bonds.

4. Experimental

4.1 One-pot *in situ* adduct transformation and glycosylation protocol for thioglycoside donors (1, 2, 9-14, 30, and 32). Thioglycoside donor (1.0 equiv), *N*-formylmorpholine (2.0 equiv), and activated 4Å molecular sieve (MS) were added to dried CH_2Cl_2 such that final concentration of the donor was 50 mM. Resulting mixture was stirred at room temperature for 10 min and at 0 °C (for **1**, **2**, **9-13**, **30**) or at -20 °C (for **14**, **32**) for additional 20-30 min. Subsequently, NIS (1.5 equiv.) and TMSOTf (1.0 equiv.) were added, and the reaction progress was monitored by TLC. Upon the complete formation of the NFM imidinium ion (by TLC examination), TBAI (5.0 equiv.) was added. The mixture was stirred at 0 °C for 0.5 to 2 h. Glycosyl iodides from donors **1**, **2**, **9-12** were detectable by TLC, but glycosyl iodides from **13**, **14**, **30** and **32** were not detectable. After 0.5 - 2 h, an acceptor (1.5 equiv.) and a base (DTBP, DIEA, or lutidine) (2.0 equiv.) were added to the reaction mixture. The reaction temperature was then raised to 30 °C and the resulting mixture was continuously stirred for ~ 18 - 24 h (for **14**, a lower 15 ºC was applied), followed by the addition of satd. $NaHCO_3$ and $Na_2S_2O_3$(s). The mixture was vigorously stirred until the red color of the solution changed to the pale yellow. The mixture was diluted with CH_2Cl_2, followed by filtration, and concentrated for flash chromatography purification over silica gel to furnish the glycosylation product.

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4.2 One-pot *in situ* adduct transformation and glycosylation procedure for 2-azido-2-deoxythioglucoside donor (31). Mixture of 2-azido-2-deoxythioglucoside donor **31** (2.0 equiv.), *N*-formylmorpholine (4.0 equiv.), and activated 4Å molecular sieve (MS) was suspended in dried CH_2Cl_2 ([**31**] = 50 mM). Then, the resulting mixture was stirred at room temperature for 10 min and at 0 °C for an additional 20 min, followed by addition of NIS (3.0 equiv.) and TMSOTf (2.6 equiv.). The formation of the NFM imidinium ion intermediate was monitored by TLC. Upon complete formation of the imidinium ion, TBAI (10.0 equiv.) was added and the mixture was stirred ng mixture was stirred at room temperature for 10 min and at 0 °C until the formation of glycosyl iodide (detectable by TLC). At this stage, acceptor (1.0 equiv.) and lutidine (5.2 equiv.) were added and the reaction temperature was raised to 30 °C. After 24 h reaction, satd. $NaHCO_3$ and $Na_2S_2O_3$(s) were added to the mixture, followed by vigorous stirring until the color of the solution changed from the deep red to pale yellow. The resulting mixture was dried (over $MgSO_4$), filtered, and concentrated for flash chromatography purification over silica gel to furnish the glycosylation product.

4.3 3-*O*-[3,4,6-Tri-*O*-benzyl-2-*O*-(2-naphthylmethyl)-α-D-glucopyranosyl]-1,2-*O*-cyclohexylidene-*sn*-glycerol (5).[32] α-Glucopyranoside **5** was (126 mg, 60%) prepared from glycosylation of *sn*-glycerol acceptor **3** (72 mg, 0.42 mmol) with thioglucoside **1** (200 mg, 0.28 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (with DTBP as the base, Table 1, entry 3). For **5**, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.73 (m, 4H), 7.51 – 7.44 (m, 3H), 7.39 – 7.21 (m, 13H), 7.16 – 7.12 (m, 2H), 5.00 (d, *J* = 10.9 Hz, 1H, benzyl-H), 4.93 – 4.89 (m, 2H, including H-1′), 4.86 – 4.80 (m, 3H), 4.58 (d, *J* = 12.1 Hz, 1H, benzyl-H), 4.49 – 4.44 (m, 2H), 4.40 – 4.34 (m, 1H), 4.06 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.98 (t, *J* = 9.3 Hz, 1H), 3.81 – 3.76 (m, *J* = 8.9 Hz, 1H), 3.75 – 3.68 (m, 2H), 3.66 – 3.55 (m, 5H), 1.64 – 1.56 (m, 10H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.3, 137.9, 135.6, 133.2, 133.1, 128.4, 128.3, 128.2, 127.90, 127.86, 127.8, 127.7, 127.6, 127.5, 126.8, 126.1, 126.0, 125.9, 110.1, 97.3 (C-1′, $J_{CH'}$ = 167.8 Hz), 81.9, 79.9, 77.6, 75.7, 75.0, 74.3, 73.5, 73.1, 70.4, 69.0, 68.5, 66.6, 36.5, 35.0, 25.1, 24.0, 23.9.

4.4 Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (6).[33] α-Anomer of disaccharide **6** was synthesized from glycosylation of glucoside acceptor **4** (105 mg, 0.23 mmol) with thioglucoside donor **2** (100 mg, 0.15 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (55% yield from DTBP as the base, 76% yield from either DIEA or LTD as the base) (Table 1, entries 7, 10, and 11 in main text). For α-anomer of **6**, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.20 (m, 33H, Ar-H), 7.15 – 7.10 (m, 2H, Ar-H), 5.00 – 4.89 (m, 4H, including H-1′), 4.85 – 4.75 (m, 3H), 4.70 (d, *J* = 12.1 Hz, 1H, benzyl-H), 4.68 – 4.62 (m, 3H), 4.58 (d, *J* = 3.7 Hz, 1H), 4.55 (d, *J* = 3.7 Hz, 2H, including H-1), 4.45 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 12.1 Hz, 1H, benzyl-H), 4.02 – 3.93 (m, 2H), 3.82 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.80 – 3.76 (m, 2H), 3.71 (d, *J* = 11.1 Hz, 1H, benzyl-H), 3.68 – 3.59 (m, 3H), 3.57 – 3.52 (m, 2H, including H-2′), 3.44 (dd, *J* = 9.6, 3.5 Hz, 1H, H-2), 3.35 (s, 3H, OC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 138.7, 138.41, 138.37, 138.36, 138.1, 137.9, 128.38, 128.35, 128.30, 128.26, 128.24, 128.21, 128.0, 127.94, 127.91, 127.88, 127.81, 127.78, 127.66, 127.65, 127.57 127.56, 127.54, 127.52, 127.49, 127.47, 127.4, 97.9 (C-1, $^1J_{CH}$ = 166.3 Hz), 97.2 (C-1′, $^1J_{CH}$ = 167.8 Hz), 82.1, 81.6, 80.1, 79.9, 77.7, 77.6, 75.7, 75.4, 74.9, 74.8, 73.3, 73.3, 72.3, 70.3, 70.2, 68.4, 66.0, 55.1 (O*C*H$_3$).

4.5 Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (19).[17] α-Anomer of disaccharide **19** was (78 mg, 70%) synthesized from glycosylation of L-rhamnoside acceptor **16** (46 mg, 0.23 mmol) with thioglucoside donor **2** (100 mg, mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 1 in main text). For α-anomer of **19**, ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 18H, Ar-H), 7.19 – 7.15 (m, 2H, Ar-H), 4.97 (d, *J* = 3.5 Hz, 1H, H-1′), 4.95 (d, *J* = 10.1 Hz, 1H), 4.88 – 4.81 (m, 3H, including H-1), 4.79 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 4.12 – 4.08 (m, 1H), 4.08 – 4.04 (m, 2H), 3.98 (t, *J* = 9.4 Hz, 1H), 3.82 – 3.71 (m , 3H), 3.67 – 3.62 (m, 1H), 3.59 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.33 (m, 4H), 1.43 (s, 3H, isopropylidene-C*H*$_3$), 1.31 (d, *J* = 6.3 Hz, 3H, C*H*$_3$), 1.25 (s, 3H, isopropylidene-C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.8, 138.4, 138.0, 137.9, 128.4, 128.4, 128.3, 128.3, 128.2, 127.9, 127.9, 127.9, 127.8, 127.6, 127.6, 127.5, 108.9, 98.3 (C-1′, $J_{CH'}$ = 167.9 Hz,), 97.8 (C-1, J_{CH} = 167.4 Hz), 82.2, 80.9, 79.9, 77.9, 76.8, 75.9, 75.5, 75.1, 74.2, 73.5, 70.3, 68.0, 64.7, 54.6, 28.1, 26.3, 17.4; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{44}H_{52}NaO_{10}^+$, 763.3453; found 763.3450.

4.6 Diosgeninyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (20). Diogeninyl α-glucoside **20** was (75 mg, 60%) synthesized from glycosylation of diosgenine acceptor **17** (94 mg, 0.225 mmol) with thioglucoside donor **2** (100 mg, 0.15 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 2 in main text). For α-glucoside **20**, R_f 0.54 (hexanes/EtOAc 3/1); $[\alpha]_D^{35}$ +150 (*c* 0.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.25 (m, 18H, Ar-H), 7.13 (dd, *J* = 2.0, 7.5 Hz, 2H, Ar-H), 5.28 (d, *J* = 5.0 Hz, 1H), 5.00 (d, *J* = 11.0 Hz, 1H), 4.93 (d, *J* = 3.5 Hz, 1H, H-1), 4.82 (dd, *J* = 8.0, 10.5 Hz, 2H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 6.5 Hz, 1H), 4.44 (d, *J* = 8.0 Hz, 1H), 4.41 (q, *J* = 15.5 Hz, 1H), 3.99 (t, *J* = 9.5 Hz, 1H), 3.87 (d, *J* = 10.5 Hz, 1H), 3.73 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.64 – 3.61 (m, 2H), 3.55 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.48 – 3.43 (m, 2H), 3.37 (t, *J* = 10.5 Hz, 1H), 2.42 (t, *J* = 11.0 Hz, 1H) , 2.28 (dd, *J* = 3.0, 13.0 Hz, 1H), 2.00 – 1.95 (m, 2H), 1.88 – 1.84 (m, 3H), 1.79 – 1.72 (m, 2H), 1.68 – 1.60 (m, 5H), 1.54 – 1.50 (m, 3H), 1.48 – 1.42 (m, 2H), 1.31 – 1.27 (m, 2H), 1.20 – 1.07 (m, 3H), 1.04 – 1.01 (m, 4H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93 (dd, *J* = 5.0, 11.5 Hz, 1H), 0.78 (t, *J* = 3.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.95, 139.04, 138.35, 138.33, 138.05, 128.49, 128.46, 128.45, 128.41, 128.22, 128.05, 127.99, 127.93, 127.89, 127.84, 127.78, 127.71, 127.63, 127.61, 121.51, 109.36, 94.74, 82.20, 80.91, 80.03, 77.97, 76.57, 75.75, 75.21, 73.51, 73.17, 70.15, 68.69, 66.93, 62.20, 56.61, 50.12, 41.70, 40.36, 39.95, 39.87, 37.16, 37.02, 32.17, 31.94, 31.52, 31.48, 30.39, 29.78, 28.89, 27.57, 20.94, 19.50, 17.22, 16.37, 14.61; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{61}H_{76}NaO_8^+$, 959.5438; found, 959.5437.

4.5 *p*-Tolyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3-di-*O*-benzoyl-4-*O*-benzyl-thio-β-D-glucopyranoside (21). α-Anomer of disaccharide **21** was (101 mg, 68%) synthesized from glycosylation of thioglucoside acceptor **18** (132 mg, 0.23 mmol) with thioglucosyl donor **2** (100 mg, 0.15 mmol) and using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 3 in main article). For α-

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anomer of **21**, R_f 0.35 (hexanes/EtOAc 3/1); $[\alpha]_D^{35}$ +49.8 (*c* 0.610, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.77 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.52 – 7.46 (m, *J* = 7.4, 13.7 Hz, 2H, Ar-H), 7.40 – 7.24 (m, 25H, Ar-H), 7.15 – 7.12 (m, 2H, Ar-H), 7.11 – 7.08 (m, 2H, Ar-H), 7.06 – 7.03 (m, 4H, Ar-H), 5.65 (t, *J* = 9.4 Hz, 1H), 5.29 (t, *J* = 9.7 Hz, 1H), 5.11 (d, *J* = 3.5 Hz, 1H, H-1′), 5.01 (d, *J* = 10.9 Hz, 1H), 4.86 (d, *J* = 10.9 Hz, 1H), 4.83 (d, *J* = 10.9 Hz, 1H), 4.80 (d, *J* = 10.0 Hz, 1H), 4.73 – 4.68 (m, 2H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.54 – 4.49 (m, 4H), 4.02 (t, *J* = 9.3 Hz, 1H), 3.92 – 3.87 (m, 4H), 3.75 – 3.66 (m, 4H), 3.62 (dd, *J* = 9.6, 3.5 Hz, 1H, H-2′), 2.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6, 165.2, 138.8, 138.5, 138.4, 138.2, 138.0, 137.3, 134.0, 133.1, 133.0, 129.83, 129.77, 129.75, 129.5, 129.4, 128.5, 128.4, 128.29, 128.27, 128.19, 128.17, 127.91, 127.90, 127.84, 127.79, 127.71, 127.70, 127.63, 127.55, 97.1 (C-1′, J_{CH} = 168.8), 86.6, 81.9, 80.3, 79.6, 77.7, 76.3, 75.7, 75.6, 75.1, 74.6, 73.4, 72.9, 71.0, 70.3, 68.6, 65.2, 21.1 (*C*H_3); HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{68}H_{66}NaO_{12}S^+$, 1129.4167; found, 1129.4162.

4.6 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-*O*-diisopropylidene-α-D-galactopyranose (22).[34] α-Anomer of disaccharide **22** was (41 mg, 70%) synthesized from glycosylation of galactosyl acceptor **15** (31 mg, 0.12 mmol with thioglucosyl donor **9** (50 mg, 0.08 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 5 in main text). For α-anomer of **22**, ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 15H, Ar-H), 5.52 (d, *J* = 5.0 Hz, 1H, H-1), 5.00 (d, *J* = 10.8 Hz, 1H), 4.94 (d, *J* = 3.6 Hz, 1H, H-1′), 4.86 (d, *J* = 10.9 Hz, 1H), 4.81 (d, *J* = 10.8 Hz, 1H), 4.72 (q, *J* = 11.9 Hz, 2H), 4.60 (dd, *J* = 2.4, 7.9 Hz, 1H), 4.56 (d, *J* = 10.9 Hz, 1H), 4.35 – 4.29 (m, 3H), 4.23 (dd, *J* = 2.1, 12.0 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.94 (ddd, *J* = 2.1, 4.1, 10.1 Hz, 1H), 3.80-3.70 (m, 2H), 3.55 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.49 (dd, *J* = 9.1, 9.9 Hz, 1H), 2.02 (s, 3H, COC*H*$_3$), 1.54 (s, 3H, isopropylidene-C*H*$_3$), 1.45 (s, 3H, isopropylidene-C*H*$_3$), 1.33 (s, 3H, isopropylidene-C*H*$_3$), 1.31 (s, 3H, isopropylidene-C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8 (C=O), 138.7, 138.1, 137.9, 128.41, 128.37, 128.36, 128.1, 127.9, 127.83, 127.78, 127.75, 127.6, 109.2, 108.6, 97.0 (C-1′, $J_{CH'}$ = 168.0 Hz), 96.3 (C-1, J_{CH} = 178.4 Hz), 81.8, 79.8, 77.2, 75.6, 74.8, 72.4, 70.9, 70.6, 70.6, 68.6, 66.6, 65.9, 63.1, 26.1, 26.0, 24.9, 24.6, 20.8 (*C*H_3CO); HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{41}H_{50}NaO_{12}^+$, 757.3195; found, 757.3197.

4.7 Methyl 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (23).[33] α-Anomer of disaccharide **23** was (1.1 g, 70%) prepared from glycosylation of glucosyl acceptor **4** (1.2 g, 2.51 mmol) with thioglucoside donor **9** (1.0 g, 1.67 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 6 in main text). For α-anomer of **23**, ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.34 – 7.23 (m, 30H, Ar*H*), 4.98 (d, *J* = 1.4 Hz, 1H), 4.96 – 4.94 (m, 2H including H-1′), 4.93 (d, *J* = 11.4 Hz, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 10.8 Hz, 1H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.67 – 4.62 (m, 3H), 4.60 – 4.52 (m, 3H including H-1), 4.19 (d, *J* = 3.1 Hz, 2H), 3.98 (td, *J* = 9.2, 6.2 Hz, 2H), 3.85 (dt, *J* = 10.1, 3.0 Hz, 1H), 3.82 – 3.76 (m, 2H), 3.70 (d, *J* = 10.4 Hz, 1H), 3.64 (t, *J* = 9.4 Hz, 1H), 3.51 (dd, *J* = 9.6, 3.4 Hz, 1H, H-2′), 3.48 – 3.42 (m, 2H, including H-2), 3.36 (s, 3H, OC*H*$_3$), 1.96 (s, 3H, COC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6 (C=O), 138.7, 138.5, 138.3, 138.2, 138.1, 138.0, 128.4 128.3, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 97.9 (C-1, J_{CH} = 168.5 Hz), 97.0 (C-1′, $J_{CH'}$ = 167.1 Hz), 82.1, 81.5, 80.1, 79.9, 77.7, 77.1, 75.7, 75.5, 74.9, 74.8, 73.3, 72.3, 70.3, 68.7, 66.0, 63.0, 55.1 (O*C*H$_3$), 20.76 (*C*H$_3$CO). HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{57}H_{62}NaO_{12}^+$, 961.4134; found, 961.4135.

4.8 Methyl 6-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (24). α-Anomer of disaccharide **24** was (75 mg, 60%) synthesized from glycosylation of glucoside acceptor **4** (105 mg, 0.225 mmol) with 6-*O*-Bz protected thioglucosyl donor **10** (100 mg, 0.125 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 7 in main text). The resulting mixture was dried (over $MgSO_4$), filtered, and concentrated for flash chromatography purification over silica gel (Elution: hexanes/EtOAc 1/0 to 7/1) to furnish the glycosylation product. For α-disaccharide **24**, R_f 0.34 (hexanes/EtOAc 3/1); $[\alpha]_D^{35}$ +59.75 (*c* 0.569, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.88 (m, 2H, Ar-H), 7.45 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.32 – 7.22 (m, 13H, Ar-H), 7.20 – 7.15 (m, 19H, Ar-H), 4.90 (d, *J* = 3.2 Hz, 1H), 4.87 (t, *J* = 2.8 Hz, 2H), 4.84 (d, *J* = 5.6 Hz, 1H), 4.82 (d, *J* = 5.2 Hz, 1H), 4.72 (dd, *J* = 3.2, 10.8 Hz, 2H), 4.59 (t, *J* = 13.6 Hz, 4H), 4.53 (s, 1H), 4.50 (d, *J* = 2.0 Hz, 1H), 4.47 (d, *J* = 3.2 Hz, 1H), 4.42 (dd, *J* = 2.0, 12.0 Hz, 1H), 4.30 (dd, *J* = 4.4, 12.0 Hz, 1H), 3.96 – 3.88 (m, 3H), 3.75 – 3.69 (m, 2H), 3.62 (d, *J* = 10.0 Hz, 1H), 3.54 – 3.45 (m, 3H), 3.32 (dd, J = 3.6, 9.6 Hz, 1H), 3.27 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2 (C=O), 138.9, 138.6, 138.38, 138.37, 138.2, 138.0, 133.1, 130.0, 129.7, 128.47, 128.46, 128.41, 128.39, 128.2, 128.04, 128.03, 127.97, 127.90, 127.84, 127.78, 127.75, 127.72, 127.65, 127.63, 98.0 ($^1J_{CH}$ = 165.4 Hz), 97.0 ($^1J_{CH}$ = 168.4 Hz), 82.2, 81.8, 80.24, 80.20, 77.9, 77.6, 75.8, 75.1, 73.4, 72.5, 70.4, 68.9, 66.1, 63.5, 55.2; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{62}H_{64}NaO_{12}^+$, 1023.4290; found, 1023.4332.

4.9 Methyl 6-*O*-*tert*-Butyl-diphenylsilyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (25). α-Anomer of disaccharide **25** was (80 mg, 55%) synthesized from glycosylation of glucosyl acceptor **4** (87 mg, 0.188 mmol) with thioglucoside donor **11** (100 mg, 0.125 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 8 in main text). For α-disaccharide **25**, R_f 0.42 (hexanes/EtOAc 3/1); $[\alpha]_D^{28}$ +52.1 (*c* 2.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 – 7.63 (m, 4H, Ar-H), 7.38 – 7.23 (m, 34H, Ar-H), 7.15 – 7.12 (m, 2H, Ar-H), 5.01 (t, *J* = 3.6 Hz, 1H; H-1′), 4.95 – 4.87 (m, 4H), 4.83 – 4.77 (m, 2H), 4.71 – 4.53 (m, 7H including H-1), 4.02 – 3.95 (m, 2H), 3.82 – 3.64 (m, 9H), 3.57 – 3.52 (m, 1H), 3.44 – 3.40 (m, 1H), 3.35 (s, 3H; CH_3), 1.02 (s, 9H; *t*butyl-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.8, 138.64, 138.57, 138.4, 138.3, 135.9, 135.7, 133.7, 133.4, 129.62, 129.58, 128.5, 128.43, 128.41, 128.35, 128.2, 128.06, 128.03, 127.9, 127.8, 127.73, 127.69, 127.66, 127.60, 127.57, 98.02 ($^1J_{CH}$ = 168.5 Hz), 97.00 ($^1J_{CH}$ = 167.1 Hz), 82.2, 81.9, 80.5, 80.2, 77.84, 77.79, 75.75, 75.7, 75.1, 75.0, 73.4, 72.4, 71.7, 70.6, 65.7, 63.0, 55.2, 26.9, 19.4; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{71}H_{78}NaO_{11}Si^+$, 1157.5206; found, 1157.5227.

4.10 Methyl 4-*O*-Acetyl-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (26). α-Anomer of disaccharide **26** was (0.98 g, 60%) synthesized from glycosylation of glucoside acceptor **4** (1.17 g, 2.51 mmol) with 4-*O*-acetyl protected thioglucosyl donor **12** (1.0 g, 1.67 mmol) using one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 9 in main text). For α-disaccharide **26**, R_f 0.16 (hexanes/EtOAc 3/1); $[\alpha]_D^{30}$ +76.19 (*c*

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0.315, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.22 (m, 30H, Ar-H), 5.02 (d, *J* = 10.0 Hz, 1H) , 4.99 (d, *J* = 5.0 Hz, 1H) , 4.95 (d, *J* = 3.5 Hz, 2H, including H-1′), 4.92 (d, *J* = 10.5 Hz, 1H), 4.82 (t, *J* = 11.5 Hz, 2H) , 4.71 (d, *J* = 12.5 Hz, 1H) , 4.66 (d, *J* = 5.0 Hz, 2H) , 4.63 (d, *J* = 8.0 Hz, 1H) , 4.59 (d, *J* = 1.5 Hz, 1H) , 4.57 (d, *J* = 3.0 Hz, 1H; H-1) , 4.45 (q, *J* = 12.0 Hz, 2H) , 3.99 (t, *J* = 9.0 Hz, 1H) , 3.87 (t, *J* = 12.5 Hz, 1H) , 3.84 – 3.77 (m, 3H), 3.71 (d, *J* = 11.5 Hz, 1H) , 3.65 (t, *J* = 9.5 Hz, 1H) , 3.56 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.45 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.41 (dd, *J* = 3.0, 11.0 Hz, 1H), 3.37 (d, *J* = 5.0 Hz, 1H) , 3.35 (s, 3H, CH_3), 1.80 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7 (C=O), 138.9, 138.7, 138.5, 138.3, 138.2, 137.9, 128.51, 128.47, 128.46, 128.36, 128.34, 128.11, 128.07, 128.03, 127.94, 127.91, 127.77, 127.76, 127.73, 127.69, 127.65, 127.58, 98.1 ($^1J_{CH}$ = 165.0 Hz), 97.2 ($^1J_{CH}$ = 168.6 Hz), 82.22 80.3, 79.7, 78.6, 77.9, 75.8, 75.1, 74.9, 73.6, 73.5, 72.6, 70.5, 70.4, 68.94, 68.89, 66.3, 55.2, 20.9. HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{57}H_{62}NaO_{12}^+$, 961.4133; found, 961.4150.

4.11 Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (27).[34] α-Anomer of disaccharide **27** (54.4 mg, 69%) was obtained from glycosylation of thiogalactoside donor **13** (50 mg, 0.08 mmol) with glucoside acceptor **4** (56 mg, 0.12 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 10 in main text). For α-anomer of **27**, ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.17 (m, 35H, Ar-H), 4.99 (d, *J* = 3.5 Hz, 1H, H-1), 4.95 (d, *J* = 8.7 Hz, 1H), 4.93 (d, *J* = 9.2 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 4.8 Hz, 1H, H-1′), 4.78 (d, *J* = 5.9 Hz, 1H), 4.72 – 4.67 (m, 4H), 4.60 – 4.56 (m, 2H), 4.54 (d, *J* = 4.2 Hz, 1H), 4.53 (d, *J* = 3.5 Hz, 1H, H-1), 4.42 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 4.03 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.99 – 3.93 (m, 2H), 3.93 – 3.88 (m, 2H), 3.82 – 3.70 (m, 3H), 3.59 (t, *J* = 9.3 Hz, 1H), 3.54 – 3.46 (m,2H), 3.41 (dd, *J* = 3.6, 9.6 Hz, 1H, H-2′), 3.29 (s, 3H, O*CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 138.8, 138.71, 138.67, 138.4, 138.2, 138.1, 128.4, 128.32, 128.30, 128.25, 128.20, 128.15, 128.14, 128.09, 128.07, 128.01, 128.00, 127.93, 127.91, 127.8, 127.7, 127.60, 127.58, 127.5, 127.4, 127.3, 97.90 (C-1, $^1J_{CH}$ =168.3 Hz), 97.85 (C-1′, $^1J_{CH}$ =168.3 Hz), 82.0, 80.2, 78.2, 78.0, 76.51, 75.6, 75.1, 75.0, 74.7, 73.3, 73.3, 72.8, 72.5, 70.3, 69.4, 68.9, 66.4, 55.0 (O*CH*$_3$).

4.12 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (28).[12d] α-Anomer of disaccharide **28** was (135 mg, 63%, 13:1 α:β) synthesized from glycosylation of galactosyl acceptor **15** (117 mg, 0.45 mmol) with thiogalactoside donor **12** (200 mg, 0.30 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 11 in main text). For α-anomer of **28**, R_f 0.28 (hexanes/EtOAc 3/1); $[\alpha]_D^{35}$ +48.0 (*c* 0.248, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.78 (m, 3H, Ar-H), 7.75 – 7.72 (m, 1H, Ar-H), 7.50 – 7.44 (m, 3H, Ar-H), 7.39 – 7.38 (m, 2H, Ar-H), 7.35 – 7.22 (m, 11H, Ar-H), 5.52 (d, *J* = 4.8 Hz, 1H, H-1), 5.03 (d, *J* = 3.6 Hz, 1H, H-1'), 4.97 (dd, *J* = 4.8, 12.0 Hz, 2H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.78 (s, 2H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.57 (dd, *J* = 2.4, 8.0 Hz, 1H), 4.49 (d, *J* = 12.8 Hz, 1H), 4.43 (d, *J* = 12.8 Hz, 2H), 4.34 – 4.29 (m, 2H), 4.12 (dd, *J* = 1.6, 10.8 Hz, 1H), 4.07 – 4.01 (m, 3H), 3.83 – 3.73 (m, 2H), 3.62 – 3.52 (m, 2H), 1.50 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.79, 138.77, 138.1, 136.5, 133. 5, 132.9, 128.4, 128.30, 128.23, 128.17, 128.0, 127.94, 127.85, 127.8, 127.7, 127.54, 127.53, 126.03, 126.00, 125.8, 125.7, 109.2, 108.6, 97.6 (C-1, $^1J_{CH}$ = 168.5 Hz), 96.4 (C-1', $^1J_{CH}$ = 176.2 Hz), 79.0, 76.5, 75.1, 74.9, 73.4, 73.1, 72.7, 70.9, 70.71, 70.67, 69.2, 68.7, 66.4, 65.9, 26.2, 26.1, 24.5, 24.6.

4.13 2,3,4-Tri-*O*-benzyl-α-D-xylopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (29).[36] α-Anomer of disaccharide **29** was (47 mg, 75%) obtained from glycosylation of galactosyl acceptor **15** (36 mg, 0.14 mmol) with thioxyloside donor **14** (50 mg, 0.09 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 2, entry 12 in main article). For α-anomer of disaccharide **29**, ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 – 7.26 (m, 15H, Ar-H), 5.53 (d, *J* = 5.0 Hz, 1H, H-1), 4.92 (d, *J* = 10.9 Hz, 1H), 4.89 – 4.86 (m, 2H including H-1′), 4.75 – 4.70 (m, 3H), 4.64 – 4.59 (m, 2H), 4.36 (dd, *J* = 1.8, 7.9 Hz, 1H), 4.31 (dd, *J* = 2.3, 5.0 Hz, 1H), 4.07 – 4.03 (m, 1H), 3.93 – 3.87 (m, 1H), 3.77 (dd, *J* = 6.0, 10.2 Hz, 1H), 3.71 (dd, *J* = 7.7, 10.2 Hz, 1H), 3.62-3.55 (m, 3H), 3.46 (dd, *J* = 3.6, 9.5 Hz, 1H), 1.54 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.0, 138.4, 138.3, 128.39, 128.37, 128.30, 128.27, 128.25, 128.17, 127.94, 127.91, 127.80, 127.78, 127.75, 127.71, 127.6, 127.48, 127.46, 127.43, 109.1, 108.6, 97.2 (C-1′, $J_{CH'}$ = 167.6 Hz), 96.3 (C-1, J_{CH} = 178.6 Hz), 81.2, 79.6, 78.0, 75.6, 73.4, 72.5, 70.8, 70.7, 70.6, 66.3, 65. 8, 60.0, 26.1, 26.0, 24.9, 24.6.

4.14 Methyl 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galacto-pyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (35). α-Anomer of disaccharide **35** was (102 mg, 65%) obtained from glucosyl acceptor **4** (121 mg, 0.26 mmol) with 2-azido-2-deoxythiogalactoside donor **30** (100 mg, 0.17 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 3, entry 1 in main text). For α-anomer of disaccharide **35**, R_f 0.4 (hexanes/EtOAc 2.5/1); $[\alpha]_D^{25}$ +60.4 (*c* 0.345, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.20 (m, 30H, Ar-H), 5.01 – 4.96 (m, 2H including H-1′), 4.90 – 4.84 (m, 2H), 4.83 – 4.75 (m, 2H), 4.72 (d, *J* = 10.8 Hz, 1H), 4.65 (d, *J* = 10.7 Hz, 2H), 4.60 – 4.50 (m, 3H including H-1), 4.44 (d, *J* = 11.8 Hz, 1H, benzyl-H), 4.37 (d, *J* = 11.1 Hz, 1H, benzyl-H), 4.03 – 3.96 (m, 2H), 3.96 – 3.91 (m, 1H), 3.91 – 3.86 (m, 1H), 3.85 – 3.73 (m, 3H), 3.69 (d, *J* = 11.1 Hz, 1H, H-6), 3.59 – 3.48 (m, 4H), 3.33 (s, 3H, O*CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 138.2, 138.2, 138.1, 137. 8, 137.4, 128.5, 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 98.5 (C-1′, $J_{CH'}$ = 171.0 Hz), 97.8 (C-1, J_{CH} = 166.9 Hz), 81.9, 80.0, 77.8, 76.5, 75.7, 74.9, 74.7, 73.4, 73.3, 71.9, 69.9, 69.6, 68.5, 66.6, 59.8, 55.0; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{55}H_{59}N_3NaO_{10}^+$, 944.4093; found, 944.4097.

4.15 Cholesteryl 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-galactopyranoside (36). α-Anomer of cholesteryl galactoside **36** was (62 mg, 60%) obtained from glycosylation of cholesterol **33** (70 mg, 0.18 mmol) with 2-azido-2-deoxythiogalactoside donor **30** (70 mg, 0.12 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 3, entry 2 in main text) and was obtained as a white amorphous solid via column chromatography purification (Elution: hexanes/EtOAc/ CH_2Cl_2 30/1/1 to 26/1/1). For α-anomer of **36**, R_f 0.7

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(hexanes/EtOAc 5/1); $[\alpha]_D^{35}$ +51.0 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.22 (m, 15H), 5.28 (d, *J* = 5.0 Hz, 1H), 5.05 (d, *J* = 3.6 Hz, 1H, H-1), 4.88 (d, *J* = 11.3 Hz, 1H), 4.72 (q, *J* = 11.3 Hz, 2H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 2H), 4.10 – 4.03 (m, 2H), 3.98 (dd, *J* = 2.6, 10.7 Hz, 1H), 3.79 (dd, *J* = 3.6, 10.7 Hz, 1H, H-2), 3.63 – 3.53 (m, 2H), 3.51 – 3.43 (m, 1H), 2.41 – 2.28 (m, 2H), 2.06 – 1.89 (m, 3H), 1.90 – 1.78 (m, 2H), 1.63 – 0.84 (m, 33H), 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.6, 138.4, 137.9, 137.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6, 121.9, 96.8 (C-1, J_{CH} = 168.5 Hz), 78.2, 77.4, 74.8, 73.6, 73.5, 72.2, 69.6, 68.8, 59.7 (C-2), 56.8, 56.1, 50.1, 42.3, 40.0, 39.8, 39.5, 37.0, 36.7, 36.2, 35.8, 31.9, 31.9, 28.2, 28.0, 27.9, 24.3, 23.8, 22.8, 22.6, 21.0, 19.4, 18.7, 11.9. HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{54}H_{73}N_3NaO_5^+$, 866.5442; found, 866.5443.

4.16 Methyl 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (37). α-Anomer of disaccharide **37** was (30 mg, 55%) obtained from glycosylation of glucosyl acceptor **4** (28 mg, 0.06 mmol) with 2-azido-2-deoxythioglucoside donor **31** (70 mg, 0.12 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure with 2-azido-2-deoxythioglucoside donor (Table 3, entry 3 in main text). For α-anomer **37**, R_f 0.3 (hexanes/EtOAc 2.5/1); $[\alpha]_D^{25}$ +46.8 (*c* 0.513, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.24 (m, 28H, Ar-H), 7.15 – 7.17 (m, 2H, Ar-H), 5.00 (d, *J* = 3.5 Hz, 1H, H-1′), 4.98 (d, *J* = 10.8 Hz, 1H), 4.94 (d, *J* = 11.2 Hz, 1H, benzyl-H), 4.85 (d, *J* = 3.0 Hz, 2H), 4.81 – 4.78 (m, 2H), 4.77 (d, *J* = 2.7 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H, benzyl-H), 4.61 – 4.55 (m, 3H including H-1), 4.48 (d, *J* = 11.0 Hz, 1H, benzyl-H), 4.42 (d, *J* = 12.1 Hz, 1H, benzyl-H), 4.00 (t, *J* = 9.3 Hz, 1H, H-3), 3.92 (dd, *J* = 8.6, 10.2 Hz, 1H, H-3′), 3.82 (dd, *J* = 4.5, 11.3 Hz, 1H, H-6), 3.79 – 3.72 (m, 2H), 3.72 – 3.66 (m, 2H), 3.63 (dd, *J* = 3.3, 10.8 Hz, 1H, H-6′), 3.59 – 3.51 (m, 3H), 3.37 (s, 3H, OC*H*$_3$), 3.33 (dd, *J* = 3.5, 10.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 138.3, 138.1, 138.0, 137.9, 137.8, 128.43, 128.38, 128.37, 128.35, 128.14, 128.10, 128.05, 128.03, 127.96, 127.87, 127.85, 127.82, 127.76, 127.71, 127.69, 127.65, 127.63, 127.61, 127.60, 98.2 (C-1′, $J_{CH'}$ = 171.3 Hz), 97.9 (C-1, J_{CH} = 167.4 Hz), 82.0, 80.1, 79.8, 78.2, 77.7, 75.8, 75.2, 74.9, 735, 73.4, 70.7, 69.9, 68.1, 66.4, 63.5, 55.2 (O*C*H$_3$). HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{55}H_{59}N_3NaO_{10}^+$, 944.4093; found, 944.4094.

4.17 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (38). α-Anomer of disaccharide **38** was (27 mg, 84%) synthesized from galactosyl acceptor **15** (12 mg, 0.045 mmol) with 2-azido-2-deoxythioglucoside donor **31** (50 mg, 0.09 mmol) according to one-pot *in situ* adduct transformation and glycosylation procedure (Table 3, entry 4 in article). For α-anomer of **38**, R_f 0.2 (hexanes/EtOAc 3/1); $[\alpha]_D^{25}$ +37.4 (*c* 0.64, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.23 (m, 13H, Ar*H*), 7.18 – 7.13 (m, 2H, Ar-H), 5.51 (d, *J* = 5.0 Hz, 1H, H-1), 4.99 (d, *J* = 3.5 Hz, 1H, H-1′), 4.86 (s, 2H), 4.79 (d, *J* = 10.9 Hz, 1H, benzyl-H), 4.66 – 4.59 (m, 2H), 4.52 (d, *J* = 10.8 Hz, 1H, benzyl-H), 4.48 (d, *J* = 12.1 Hz, 1H, benzyl-H), 4.34 – 4.29 (m, 2H), 4.03 – 3.97 (m, 2H including H-3′), 3.90 – 3.86 (m, 1H), 3.82 (dd, *J* = 6.4, 10.3 Hz, 1H), 3.80 – 3.73 (m, 2H), 3.71 (dd, *J* = 5.0, 8.7 Hz, 1H), 3.66 (dd, *J* = 1.8, 10.8 Hz, 1H), 3.33 (dd, *J* = 3.5, 10.3 Hz, 1H, H-2′), 1.53 (s, 3H, C*H*$_3$), 1.43 (s, 3H, C*H*$_3$), 1.34 (s, 3H, C*H*$_3$), 1.33 (s, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 137.8, 128.40, 128.36, 128.35, 128.0, 127.9, 127.81, 127.77, 127.71, 127.68, 109.2, 108.6, 98.2 (C-1′, $J_{CH'}$ = 170.0 Hz), 96.2 (C-1, J_{CH} = 178.8 Hz), 79.9, 78.2, 75.2, 74.9, 73.5, 70.8, 70.7, 70.61, 70.55, 68.1, 66.8, 66.2, 63.4 (C-2′), 26.1, 25.94, 24.92, 24.4. HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{39}H_{47}N_3NaO_{10}^+$, 740.3154; found, 740.3155.

4.18 Cholesteryl 2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranoside (39). α-Anomer of cholesteryl 2-azido-2-deoxyglucoside **39** was (43 mg, 58%) synthesized as a white greasy solid from reaction of cholesterol **33** (33 mg, 0.085 mmol) with 2-azido-2-deoxythioglucoside donor **31** (100 mg, 0.17 mmol) according to one-pot *in situ* adduct transformation and glycosylation procedure (Table 3, entry 5 in main text). For α-anomer **39**, R_f 0.6 (hexanes/EtOAc 5/1); $[\alpha]_D^{35}$ +22 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.25 (m, 13H, Ar-H), 7.17 – 7.14 (m, 2H, Ar-H), 5.30 (d, *J* = 4.7 Hz, 1H), 5.08 (d, *J* = 3.5 Hz, 1H, H-1′), 4.88 (q, *J* = 10.7 Hz, 2H), 4.81 (d, *J* = 10.8 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.53 – 4.46 (m, 2H), 4.06 – 4.00 (m, 1H, H-3′), 3.97 – 3.91 (m, 1H), 3.80 – 3.75 (m, 1H), 3.73 – 3.68 (m, 1H), 3.68 – 3.63 (m, 1H), 3.55 – 3.46 (m, 1H), 3.30 (dd, *J* = 3.5, 10.3 Hz, 1H, H-2′), 2.40 – 2.30 (m, 2H), 2.04 – 1.91 (m, 3H), 1.90 – 1.78 (m, 2H), 1.62 – 1.31 (m, 13H), 1.20 – 1.02 (m, 9H), 0.95 – 0.84 (m, 11H)., 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.5, 138.04, 137.95, 137.8, 128.434, 128.425, 128.36, 128.0, 127.9, 127.82, 127.80, 127.7, 122.0, 96.3 (C-1′, $J_{CH'}$ = 168.0 Hz), 80.2, 78.4, 78.2, 75.3, 75.1, 73.5, 70.7, 68.4, 63.3, 56.8, 56.2, 50.1, 42.3, 40.0, 39.8, 39.5, 37.0, 36.7, 36.2, 35.8, 31.93, 31.87, 28.2, 28.0, 27.8, 24.3, 23.82, 22.81, 22.6, 21.0, 19.4, 18.7, 11.9; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{54}H_{73}N_3NaO_5^+$, 866.5442; found, 866.5433.

4.19 4-Azido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-fucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (40). α-Anomer of disaccharide **40** (53 mg, α only, 76%) was synthesized from reaction of galactosyl acceptor **15** (41 mg, 0.158 mmol) with Fuc4N$_3$ donor **32** (50 mg, 0.105 mmol) using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 3, entry 6 in main text). For α-anomer of **40**, R_f 0.48 (Hexanes/ EtOAc = 2/1); $[\alpha]_D^{35}$ +3.32 (*c* 2.85, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 – 7.27 (m, 10H, Ar-H), 5.52 (d, *J* = 5.0 Hz, 1H, H-1), 4.87 (d, *J* = 3.5 Hz, 1H, H-1′), 4.83 (d, *J* = 11.5 Hz, 1H, benzyl-H), 4.76 (d, *J* = 11.5, 1H, benzyl-H), 4.74 (d, *J* = 11.5, 1H, benzyl-H), 4.70 (d, *J* = 11.5, 1H, benzyl-H), 4.58 (dd, *J* = 2.5, 8.0 Hz, 1H), 4.31 (dd, *J* = 2.4 Hz, 1H), 4.28 (dd, *J* = 2.0, 8.0 Hz, 1H), 4.07 – 3.99 (m, 3H), 3.84 (dd, *J* = 3.5, 10.0 Hz, 1H), 3.73 (d, *J* = 3.5, 2H), 3.72 (d, *J* = 3.6, 1H), 1.51 (s, 3H, C*H*$_3$), 1.44 (s, 3H, C*H*$_3$), 1.33 (s, 3H, C*H*$_3$), 1.31 (s, 3H, C*H*$_3$), 1.22 (d, *J* = 6.4 Hz, 3H, C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 138.3, 128.4, 128.3, 127.7, 127.7, 127.6, 109.3, 109.3, 108.53, 108.5, 97.4 (C-1), 96.3 (C-1′), 78.0, 75.9, 73.1, 72.9, 71.0, 70.7, 70.6, 66.7, 66.2, 65.0, 64.5, 26.1, 26.0, 24.9, 24.6, 17.3; HRMS (ESI): calcd for $C_{32}H_{41}N_3O_9Na^+$ $[M + Na]^+$ requires 634.2735, found 634.2757 *m/z*. The α-anomer of disaccharide **40** was obtained as the only anomer and no HPLC analysis was performed for this reaction.

4.20 Methyl 4-Azido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-fucopyranosyl-(1→3)-4-*O*-benzyl-2,6-dideoxy-α-D-*ribo*-hexopyranoside (41). Disaccharide **41** (71 mg, 70%, α only) was synthesized from glycosylation of methyl α-digitoside acceptor **34** (40.6 mg, 0.161 mmol) with 4-azido-4-deoxy-1-thio-D-fucopyranosyl donor **32** (91.8 mg, 0.193 mmol) by using the one-pot *in situ* adduct transformation and glycosylation procedure (Table 3, entry 7 in main text). For **41**, R_f 0.30 (Hexanes/EtOAc = 5/1); $[\alpha]_D^{35}$ +75.1 (*c* 1.75, $CHCl_3$); ^1H NMR (500 MHz,

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$CDCl_3$): δ 7.38 (t, *J* = 8.5 Hz, 4H, Ar-H), 7.34 – 7.22 (m, 11H, Ar-H), 5.11 (d, *J* = 3.0 Hz, 1H, H-1′), 4.83 (d, *J* = 12.0 Hz, 1H), 4.80 (d, *J* =12.0 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 2.5 Hz, 1H, H-1), 4.59 (dd, *J* = 7.0, 12.0 Hz, 2H), 3.91 (dd, *J* = 6.5, 13.5 Hz, 1H), 3.87 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.55 (d, *J* = 2.5 Hz, 1H,), 3.21 (s, 3H, O*CH*$_3$), 3.18 (dd, *J* = 2.5, 8.5 Hz, 1H), 2.24 (dd, *J* = 2.0, 15.0 Hz, 1H, H-2$_{eq}$), 1.72 (dt, *J* = 4.0, 15.0 Hz, 1H, H-2$_{ax}$), 1.27 (d, *J* = 6.5 Hz, 1H, C*H*$_3$), 1.04 (d, *J* = 6.5 Hz, 1H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.4, 138.3, 128.3, 128.2, 128.1, 127.6, 127.6, 127.5, 127.3, 127.2, 127.2, 97.2 (C-1), 93.8 (C-1′), 79.9, 77.4, 76.1, 73.0, 71.8, 71.4, 67.34, 65.1, 64.4, 63.3, 54.9, 31.3, 17.97, 17.2; HRMS (ESI): calcd for $C_{34}H_{41}N_3O_7Na^+$ [M + Na]$^+$ requires 626.2837, found 626.2864 *m/z*. The α-anomer of disaccharide **41** was obtained as the only anomer and no HPLC analysis was performed for this reaction.

4.21 Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (43).[17] Mixture of thioglucoside donor **2** (100 mg, 0.15 mmol) and flame-dried molecular sieve (4Å, 300 mg) was suspended in dried CH_2Cl_2 (3 mL) such that the final concentration of **2** was 50 mM. Then, NFM (60 μL, 0.6 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for 10 min and at 0 °C for additional 20-30 min, followed by addition of NIS (50.6 mg, 0.225 mmol) and TMSOTf (27 μL, 0.15 mmol). The formation of NFM imidinium adduct was monitored by TLC. Upon complete formation of the imidinium adduct intermediate, methyl glucoside acceptor **42** (104.5 mg, 0.225 mmol) was added. The mixture was stirred at 0 °C. Upon completion of the glycosylation reaction (~24 h), the reaction was quenched by addition of Et_3N. Workup procedure: $NaHCO_3$ and $Na_2S_2O_3$(s) were added to the mixture, followed by stirring until the deep red color of the reacting solution changed to pale yellow. The resulting mixture was dried (over $MgSO_4$), filtered, and concentrated for flash chromatography purification over silica gel (Elution: hexanes/EtOAc 7:1) to furnish the glycosylation product. The disaccharide **43** (106 mg, 0.11 mmol, 70%, α:β 16:1 from NMR) was obtained as a glassy solid. For α-anomer of **43**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.18 (m, 33H, Ar-H), 7.11 – 7.08 (m, 2H, Ar-H), 5.69 (d, *J* = 3.6 Hz, 1H, H-1′), 5.02 (d, *J* = 11.6 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.81 – 4.75 (m, 4H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 3.6 Hz, 1H), 4.58 (d, *J* = 1.2 Hz, 1H, H-1), 4.54 (s, 1H), 4.52 (d, *J* = 3.6 Hz, 1H), 4.49 (d, *J* = 2.8 Hz, 2H), 4.42 (d, *J* = 10.8 Hz, 1H), 4.27 (d, *J* = 12.0 Hz, 1H), 4.12 – 4.01 (m, 2H), 3.93 – 3.81 (m, 3H), 3.73 – 3.64 (m, 3H), 3.59 (dd, *J* = 3.6, 8.8 Hz, 1H), 3.49 (dd, *J* = 3.6, 10.0 Hz, 2H), 3.40 (d, *J* = 1.6 Hz, 1H), 3.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 138.8, 138.6, 138.2, 138.1, 138.04, 138.00, 128.5, 128.37, 128.35, 128.30, 128.27, 128.25, 128.1, 128.0, 127.87, 127.86, 127.75, 127.67, 127.61, 127.5, 127.4, 127.3, 127.1, 126.8, 97.8 ($^1J_{CH}$ = 166.2 Hz), 96.70 ($^1J_{CH}$ = 168.4 Hz), 82.10, 82.08, 80.3, 79.5, 77.7, 75.6, 75.0, 74.5, 73.5, 73.4, 73.3, 73.2, 72.4, 71.0, 69.6, 69.1, 68.3, 55.2.

4.22 Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (45). Mixture of donor **2** (100 mg, 0.15 mmol) and flame-dried molecular sieve (4Å) (0.3 mg) was suspended in dried CH_2Cl_2 (3 mL). Then, NFM (120 μL, 1.2 mmol) was added to the mixture. The resulting mixture was stirred at room temperature for 10 min and at -20 °C for additional 20-30 min followed by addition of NIS (50.6 mg, 0.225 mmol) and TMSOTf (27 μL, 0.15 mmol). The reaction was monitored by TLC. Upon complete formation of imidinium ion adduct, methyl mannoside acceptor **44** (104.5 mg, 0.225 mmol) was added. The mixture was stirred at -20 °C for 24 h. The reaction was quenched by addition of $NaHCO_3$. Workup procedure: $NaHCO_3$ and $Na_2S_2O_3$(s) were added to the mixture, followed by stirring until the deep red color of the reacting solution changed to pale yellow. The resulting mixture was dried (over $MgSO_4$), filtered, and concentrated for flash chromatography purification (Elution: hexanes/EtOAc 1/0 to 5/1) to furnish disaccharide **43** (91 mg, 61%, α:β >19:1 from NMR) as a white amorphous solid. For α-anomer **45**, R_f 0.28 (hexanes/EtOAc 3/1); $[\alpha]_D^{17}$ +90.0 (*c* 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.20 (m, 25H, Ar-H), 7.17 – 7.10 (m, 10H, Ar-H), 5.48 (d, *J* = 3.6 Hz, 1H, anomeric-H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.83 (d, *J* = 10.8 Hz, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 2.4 Hz, 1H, anomeric-H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.66 (s, 1H), 4.63 (d, *J* = 2.8 Hz, 1H), 4.60 (s, 1H), 4.54 – 4.42 (m, 4H), 4.34 (d, *J* = 10.8 Hz, 1H), 4.20 (t, *J* = 2.0 Hz, 1H), 4.03 (q, *J* = 19.2 Hz, 2H), 3.94 – 3.87 (m, 2H), 3.83 – 3.79 (m, 1H), 3.75 – 3.65 (m, 4H), 3.60 (t, *J* = 9.2 Hz, 1H), 3.54 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 138.7, 138.6, 138.4, 138.2, 138.0, 128.5, 128.43, 128.37, 128.32, 128.31, 128.29, 128.1, 128.04, 127.96, 127.85, 127.81, 127.76, 127.70, 127.62, 127.50, 127.48, 127.4, 127.2, 100.1 ($^1J_{CH}$ = 168.9 Hz), 97.2 ($^1J_{CH}$ = 169.8 Hz), 81.5, 80.6, 79.7, 77.5, 75.6, 75.1, 75.0, 74.9, 73.5, 73.45, 73.1, 72.7, 72.3, 71.2, 70.7, 69.4, 68.6, 54.7; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{62}H_{66}NaO_{11}^+$, 1009.4503; found, 1009.4548.

4.23 Methyl 2,3,6-Tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (46): For α-disaccharide **46**, R_f 0.43 (hexanes/EtOAc/CH_2Cl_2 2/1/1); $[\alpha]_D^{30}$ +55.3 (*c* 1.012, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.20 (m, 30H, Ar-H), 4.98-4.94 (m, 3H, including anomeric-H), 4.92 (dd, *J* = 2.0, 11.0 Hz, 1H), 4.82 (dd, *J* = 2.5, 11.0 Hz, 1H), 4.73 – 4.63 (m, 5H), 4.55 – 4.52 (m, 3H, including anomeric-H), 4.48 (d, *J* = 12.0 Hz, 1H) , 3.99 (td, *J* = 2.5, 9.0 Hz, 1H), 3.84 – 3.73 (m, 5H), 3.70 (d, *J* = 11.5 Hz, 1H) , 3.66 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.62 – 3.57 (m, 3H), 3.51 (dt, *J* = 2.5, 9.5 Hz, 1H), 3.43 (dt, *J* = 2.5, 9.5 Hz, 1H), 3.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 138.7, 138.4, 138.3, 138.1, 138.0, 128.5, 128.38, 128.36, 128.33, 128.31, 128.30, 128.04, 127.95, 127.8, 127.7, 127.63, 127.56, 98.0 ($^1J_{CH}$ = 166.4 Hz), 97.2 ($^1J_{CH}$ = 168.1 Hz), 82.1, 80.6, 80.1, 79.6, 77.8, 75.8, 75.7, 75.6, 75.1, 75.01, 74.96, 73. 5, 73.43, 73.37, 73.33, 73.30, 72.14, 72.10, 72.07, 70.6, 70.3, 70.1, 69.5, 66.1, 55.1; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_{55}H_{60}NaO_{11}^+$, 919.4028; found, 919.4041.

4.24 Methyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (47): Trisaccharide **47** was (48 mg, 60%) synthesized from glycosylation of disaccharide **46** (100 mg, 0.12 mmol) with donor **2** (109 mg, 0.17 mmol) according to the glycosylation protocol for preparation of **43**. The trisaccharide **47** was obtained as a white glassy solid by flash chromatography purification (Elution: hexanes/EtOAc 7/1 to 5/1) and no other anomer was obtained. For trisaccharide **47**, R_f 0.19 (hexanes/EtOAc 3/1); $[\alpha]_D^{30}$ +71.6 (*c* 0.475, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.19 (m, 43H, Ar-H), 7.14 – 7.10 (m, 7H, Ar-H), 5.68 (d, *J* = 3.5 Hz, 1H, anomeric-H), 4.99 – 4.92 (m, 4H, including anomeric-H), 4.86 – 4.73 (m, 5H), 4.70 – 4.67 (m, 2H), 4.61 – 4.41 (m, 10H, including one anomeric-H), 4.27 (dd, *J* = 3.0, 12.0 Hz, 1H), 4.07 – 3.97 (m, 3H), 3.90-3.87 (m, 2H), 3.81 – 3.79 (m, 3H), 3.74 – 3.70 (m, 2H), 3.66 – 3.56 (m, 4H), 3.48 – 3.42 (m, 3H), 3.38 – 3.35 (m, 4H, including CH_3);

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^{13}C NMR (125 MHz, $CDCl_3$): δ 139.1, 138.9, 138.8, 138.6, 138.4, 138.3, 138.24, 138.19, 138.16, 138.0, 128.5, 128.44, 128.38, 128.34, 128.29, 128.25, 128.19, 128.03, 127.99, 127.93, 127.87, 127.85, 127.83, 127.74, 127.65, 127.60, 127.58, 127.52, 127.48, 127.38, 127.29, 127.0, 126.9, 98.0 ($^1J_{CH}$ = 165.5 Hz), 96.8 ($^1J_{CH}$ = 172.3 Hz), 96.8 ($^1J_{CH}$ = 168.6 Hz), 82.2, 82.1, 81.7, 80.2, 80.1, 79.5, 77.8, 77.7, 75.8, 75.5, 75.1, 75.0, 74.1, 73.5, 73.4, 73.2, 73.1, 72.9, 72.3, 71.0, 70.5, 69.9, 69.2, 68.3, 65.9, 55.3. HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{89}H_{94}NaO_{16}^+$, 1441.6434; found, 1441.6431.

4.25 Methyl D-Glucopyranosyl-(1→4)-α-D-glucopyranosyl-(1→6)-α-D-glucopyranoside (48): Protected trisaccharide **47** (147 mg, 0.10 mmol) dissolved in 4:1:0.5 MeOH/EtOAc/AcOH solvent mixture was treated with Pd/C (100 mg) under H_2 (1 atm). The reaction mixture was stirred at RT for 2 days and then filter (over celite) to remove Pd/C. The resulting filtrate was concentrated and purified by FPLC (Elution: 1:1 MeOH:H_2O, flow rate 0.5 mL/min) to obtain the trisaccharide **48** as a white glassy solid (30 mg, 56%). For **48**, R_f 0.09 (CH_2Cl_2/MeOH/H_2O 2/1/0.05); $[\alpha]_D^{35}$ +28.8 (*c* 0.35, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ 5.15 (d, *J* = 4.0 Hz, 1H, anomeric H), 4.85 (d, *J* = 4.0 Hz, 1H, anomeric H overlapped with residual H_2O signals), 4.67 (d, *J* = 4.0 Hz, 1H, H-1), 3.92 – 3.88 (m, 2H), 3.86 – 3.64 (m, 8H), 3.61 (td, *J* = 3.0, 9.5 Hz, 2H), 3.54 (t, *J* = 9.5 Hz, 1H), 3.47 – 3.43 (m, 2H), 3.42 (s, 3H, CH_3), 3.41 (m, 1H), 3.35 (dd, *J* = 10.0, 11.5 Hz, 1H), 3.27 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ 103.0 ($^1J_{CH}$ = 172.5 Hz), 101.5 ($^1J_{CH}$ = 171.3 Hz), 100.0 ($^1J_{CH}$ = 168.85 Hz), 81.8, 75.4, 75.2, 75.1, 74.9, 74.4, 73.5, 72.3, 72.1, 72.0, 71.6, 67.8, 62.9, 62.1, 56.0 (OCH_3); HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{19}H_{34}NaO_{16}^+$, 541.1739; found, 541.1745.

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Notes and references

[a] Applied Chemistry Department, National Chiao Tung University of Taiwan, 1001, University Road, Hsinchu, Taiwan, Republic of China. E-mail: tmong@mail.ncut.edu.tw; Fax: +886-3-5723764.

b Institute of Biological Chemistry, Academia Sinica, Room 802, 128, Academia Road Sec. 2, Nankang, Taipei 115, Taiwan, Republic of China.

Electronic Supplementary Information (ESI) of procedures, references, and spectroscopic data for preparation of building blocks **1**, **2a**, **2a′**, **2b**, **3**, **4-13**, oligomannans **14-21** are available. See DOI: 10.1039/b000000x/

1. R. Enugala, L. C. R. Carvalho, M. J. D. Pires, M. M. B. Marques, *Chem. Asian J.* 2012, **7**, 2482-2501.
2. L. K. Mydock, A. V. Demchenko, *Org. Biomol. Chem.* 2010, **8**, 497-510.
3. J. T. Walk, Z. Z. Buchan, J. Montgomery, *Chem. Sci.* 2015, **6**, 3448-3453.
4. K. L. M. Hoang, X. W. Liu, *Nature Commun.* 2014, **5**, 10.
5. C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang, S.-C. Hung, *Nature*, 2007, **446**, 896-899.
6. T.-Y. Huang, M.-M. Zulueta, S.-C. Hung, *Org. Biomol. Chem.* 2014, **12**, 376-382.
7. B. Yu, Z. Yang, H. Cao, *Curr. Org. Chem.* 2005, **9**, 179-194.
8. L. Yang, Q. Qin, X.-S. Ye, *Asian J. Org. Chem.* 2013, **2**, 30-49.
9. S. Manabe, Y. Ito, *Curr. Bioactive Compd.* 2008, **4**, 258-281.
10. S. K. Mulani, W.-C. Hung, A. B. Ingle, K.-S. Shiau, K.-K. T. Mong, *Org. Biomol. Chem.* 2014, **12**, 1184-1197.
11. a) R. U. Lemieux, K. B. Hendriks, R. V. Stick, K. James, *J. Am. Chem. Soc.* 1975, **97**, 4056-4062; b) R. U. Lemieux, H. Driguez, *J. Am. Chem. Soc.* 1975, **97**, 4063-4068.
12. a) M. J. Hadd, J. Gervay, *Carbohydr. Res.* 1999, **320**, 61-69; b) S. N. Lam, J. Gervay-Hague, *Org. Lett.* 2002, **4**, 2039-2042; c) S. N. Lam, J. Gervay-Hague, *Carbohydr. Res.* 2002, **337**, 1953-1965; d) A. H. Adam Chu, S. H. Nguyen, J. A. Sisel, A. Minciunescu, C. S. Bennett, *Org. Lett.* 2013, **15**, 2566-2569 (TBAI).
13. U. Schmid, H. Waldmann, *Eur. J. Org. Chem.* 1997, 2573-2577 (LiI).
14. S. Koto et al. *Bull. Chem. Soc. Jpn.* 1999, **72**, 765-777.
15. T. Mukaiyama, S. Suda, *Chem. Lett.* 1990, 143-146.
16. J. Park, S. Kawatkar, J. H. Kim, G. J. Boons, *Org. Lett.* 2007, **9**, 1959-1962.
17. S.-R. Lu, Y.-H. Lai, J.-H. Chen, C.-Y. Liu, K.-K. T. Mong, *Angew. Chem., Int. Ed.* 2011, **50**, 7315-7320
18. A. B. Ingle, C.-S. Chao, W.-C. Hung, K.-K. T. Mong, *Org. Lett.* 2013, **15**, 5290-5293.
19. For preparation of compounds 1-4 and related references, see ESI
20. G. H. Veeneman, S. H. van Leeuwen, J. H. van Boom, *Tetrahedron Lett.* 1990, **31**, 1331-1334.
21. The stereocenter of acceptor **3** was found undergoing racemization at higher reaction temperature and/or prolonged reaction time; therefore it was not suitable for glycosylation study at higher temperature and the reason for using the donor **2** is its simpler preparation procedure.
22. R. Caputo, H. Kunz, D. Mastroianni, G. Palumbo, S. Pedatella, F. Solla, *Eur. J. Org. Chem.* 1999, 3147-3150 (NMR iodide).
23. For NMR spectroscopic data of β-gluosyl iodide (observed at -100 ˚C), J. Gervay, T. N. Nguyen, M. J. Hadd, *Carbohydr. Res.* 1997, **300**, 119-125.
24. B. Cao, X.-Q. Chen, Y. Yamaryo-Botte, M. B. Richardson, K. L. Martin, G. N. Khairallah, T. W. T. Rupasinghe, R. M. O'Flaherty, R. A. J. O'Hair, J. E. Ralton, P. K. Crellin, R. L. Coppel, M. J. McConville, S. J. Williams, *J. Org. Chem.* 2013, **78**, 2175-2190 (long reaction time for iodide).
25. Y. F. Yen, R. C. Sawant, S. Y. Luo, *Synthesis*, **2013**, *45*, 511 (heat).
26. R. A. Davis, C. H. Lin, J. Gervay-Hague, *Chem. Commun.* **2012**, *48*, 9083 (Micorwave).
27. Preparation of **14** was given in supporting information.
28. H.-J. Lin, A. K. Adak, L. V. Reddy, S.-H. Wu, C.-C. Lin, *Chem. Eur. J.* 2013, **19**, 7989-7998.
29. A. Inglo, C.-S. Chao, W.-C. Hung, K.-K. Tony Mong, *Asian J. Org. Chem.* 2014, 2014, **3**, 870-876.
30. Y. Rombouts, E. Elass, C. Biot, E. Maes, B. Coddeville, A. Burguière, C. Tokarski, E. Buisine, X. Trivelli, L. Kremer, Y. Guérardel, *J. Am. Chem. Soc.* **2010**, *132*, 1607 (*Mycobacterium marinum*).
31. Preparation of **32** and **34** was given in supporting information.
32. B. Ghosh, Y. H. Lai, Y. Y. Shih, T. K. Pradhan, C. H. Lin, K. K. T. Mong, *Chem. Asian J.* 2013, **8**, 3191-3199 (**1**).
33. H. W. He, X. M. Zhu, *Org. Lett.* 2014, **16**, 3102-3105 (α-disaccharide **6**, **23**).
34. S. Valerio, A. Iadonisi, M. Adinolfi, A. Ravida, *J. Org. Chem.* 2007, **72**, 6097 (**22**).

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35. Nguyen, H. M.; Chen, Y. N.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* 2001, **123**, 8766 (**27**).
36. P. Wang, P. Haldar, Y. Wang, H. Hu, *J. Org. Chem.* 2007, **72**, 5870-5873 (**29**).

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