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One-pot protection Strategy of glucosamine for the Assembling of building block of chitosan and Lipid A

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Dedication ((optional))

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Abstract: This investigation describes a one-pot reaction to prepare a series of building blocks for glycosylation reactions, such as 3-alcohol glucosamines, fully protected glucosamines, *O*-4 and *O*-6 alcohol glucosamines. These reactions readily produce not only glycosyl donors and acceptors, but also different glycosyl units that can be changed based on the needs of the experiment. The synthesis of some molecules containing glucosamines, including saccharide chains of glycopeptide (GP) and precursors of lipid A disaccharide backbone, are also described. GP has good selectivity for tumor angiogenesis and this phenomenon makes the GP a potential target drug. Lipid A has recently been adopted as an adjuvant for human vaccines.

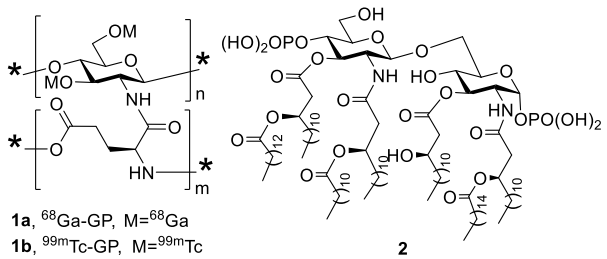
Introduction

Carbohydrates play an essential role in biomolecules, because they are involved in many important biological activities,[1] including viral and bacterial infections, cell growth, cell proliferation, cell-cell communication, and immune responses.[2] Therefore, carbohydrates are considered to be vital participants in physiological and pathology, making them a target for drug development.[3] Among many saccharides, D-glucosamine and its *N*-acetylation derivatives exist in many biomolecules, such as cell surface proteins, proteoglycans, glycosphingolipids, blood group antigens, bacterial cell walls, chitin and chitosan.[4]

Chitosan is a marine biopolymer that has attracted considerable attention due to its non-toxic and anti-microbial properties and biodegradability and biocompatibility.[5] Chitosan comprises glucosamine units GlcNAc, which connected with β-(1,4) glycosidic linkages.[6] Yang and co-workers found that chitosan combines with glutamic acid and ^{68}Ga or ^{99m}Tc, forming molecules (figure 1) such as ^{68}Ga-glycopeptide **1a** (^{68}Ga-GP)[7a] and ^{99m}Tc-glycopeptide **1b** (^{99m}Tc-GP).[7b] In the literature, ^{68}Ga-GP was found to have good selectivity for tumor angiogenesis, enabling the molecule to concentrate on the blood vessel walls of tumor cells in the body. Researchers have also found that tumor cells take up GP products, making these to be potential target drugs.

Lipid A **2** (figure 1) is a lipopolysaccharide (LPS), which is present in Gram-negative bacteria and is an important constituent in the cell membrane. It consists of a D-glucosamine disaccharide unit linked by β-(1→6) glycosidic bonds. The hydroxyl groups and amine groups on the disaccharide are connected with long-chain fatty acids and phosphates that are present in the *C*-1 and *C*-4′ positions.[8] Lipid A, which was isolated from the cell surface of Gram-negative bacteria by Westphal and Lüderitz in 1954[9a] and was first synthesized by Shiba's team in 1985 using chemical methods,[9b] has recently been used as an adjuvant for human vaccines.[9c-e]

The glucosamine molecule has an amine group and a plurality of hydroxyl groups having similar reactivity. In the synthesis process, the protecting groups are typically applied to mask the hydroxyl groups and the amino group to control the regioselectivity and stereoselectivity of glycosylation step,[10,11] while the induced effect of the protecting groups also affects the reactivity and solubility in the organic solvent. Due to the wide application of protecting groups in sugar chemistry, chemists are working to develop new strategies of protection and deprotection strategies.[12,13]



1a, ^{68}Ga-GP, M=^{68}Ga
1b, ^{99m}Tc-GP, M=^{99m}Tc
2

Figure 1. The structures of glycopeptide **1** and *Salmonella minnesota* lipid A **2**.

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Chemists have long sought an effective assembly method for synthesis of oligosaccharides and their analogs. Many factors must be considered in the synthesis of oligosaccharides. A system of donors and promoters are necessary. The selectivity of the protecting group is used to distinguish among hydroxyl groups, especially when the sugar acceptor usually has only one hydroxyl group exposed. Additionally, the choice of protecting group also affects the reactivity and stereoselectivity of the glycosyl structural unit.[14] Thus, stepwise assembly of the oligosaccharides are still the most commonly adopted method. Despite much progress in the field, new efficient and convenient methods for the synthesis of oligosaccharides are still required.[13,15]

The proposed synthesis methods include developing one-pot protection for glycosyl donors and acceptors. Such technologies have raised concern in the synthesis community,[16] principally because the target oligosaccharide can use the fewest protecting groups and save time for intermediate separation. Hung *et al.* employed TMSOTf as an acidic catalytic reagent for one-pot protection[4,18] and one-pot protection-glycosylation reactions[19] of glucose, galactose, mannose and glucosamine. Beau and co-workers applied TfOH[20], $Cu(OTf)_2$[21] and $FeCl_3{\cdot}6H_2O$[22] instead of TMSOTf for a one-pot reaction.

Considering the importance of glucosamine, this article explores a one-pot glucosamine reaction. Because GP and lipid A **2** are crucial biomolecules, the multi-step reaction and several purifications take a long to carry out using a conventional synthesis method.[23] This study performs a one-pot protection of glucosamine units (figure 2) for glycosylation to prepare the glucosamine chain of the glycopeptide and the precursor of lipid A.

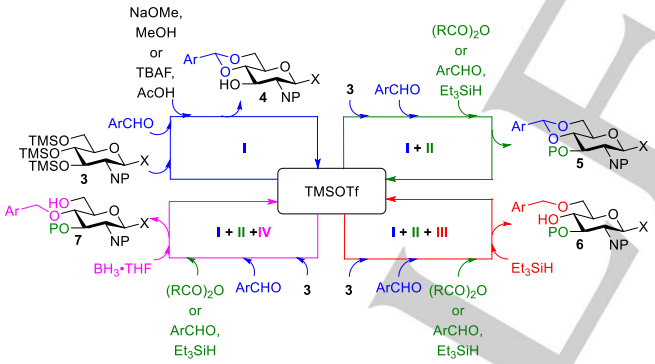
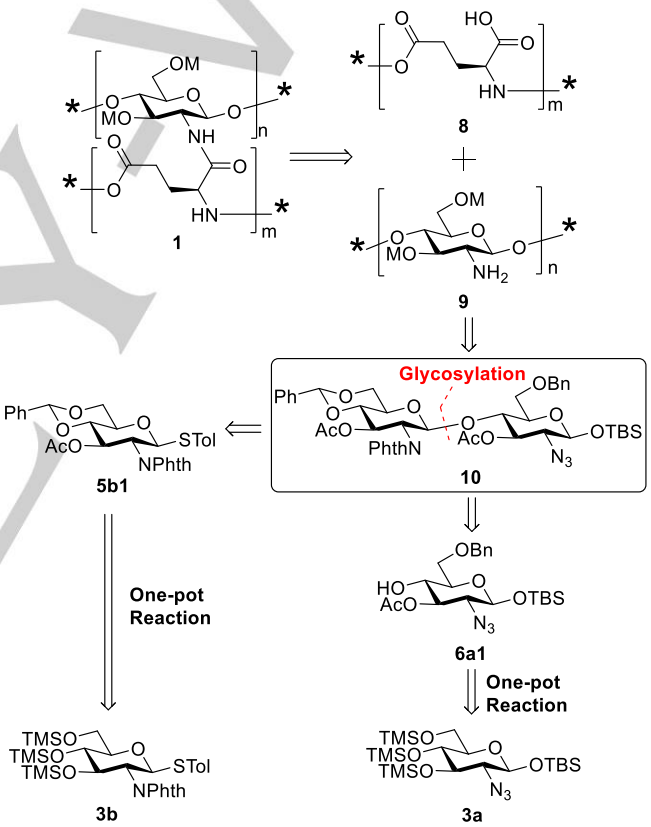


Figure 2. One-pot reactions of glycosyl units with TMSOTf

Our method improves upon the study of Hung and co-workers that they have to purify α- and β-mixtures in acidic one-pot reactions.[4] In Hung's report, the *O*-1 and/or *O*-3 acetate protecting groups have to use different catalysts and acetic anhydride after protection of arylidene. The side product, acetic acid, prevents subsequent one-pot ether protection in their method. Therefore, our design is using azide groups to protect the amine of glucosamine and tert-butyldimethylsilyl (TBS) groups that is high steric hindrance to afford only β-glycosyl acceptors.[24] Our glycosyl donors from the amino group of glucosamine is protected by phthalimide are β-thioglycosides because of the neighboring group effect. Based on our design, the structures of β-t-butyldimethylsilyl acceptors and β-thioglycosides are identified easily and one-pot reactions are tracked simply. Furthermore, acidic benzylation can be handled in an one-pot manner of glucosamines.

Results and Discussion

Scheme 1 depicts the retrosynthetic analysis of GP **1**. Compounds **3a** and **3b** are the starting materials of the glycosyl donor **5b1** and glycosyl acceptor **6a1**. The literature procedure was followed to prepare the required synthons and assemble them in desired manner. Glycosylation of acceptor **6a1** and donor **5b1** yielded disaccharide **10** with 4,6-benzylidiene protection, which then underwent regio-selective *O*-4 ring opening to obtain the second *O*-4 acceptor. The glycosylation steps were performed using the same method for di- and trisaccharide units successively to obtain the glucosamine chain of the polysaccharide



Scheme 1. Retrosynthetic Analysis of GP **1.**

Scheme 2 displays the retrosynthetic analysis of *Neisseria meningitidis* lipid A.[25] Lipid A **13** could be derived from the phosphorylating agent **14** and tetra-acylated disaccharide **15** in presence of a base. Compound **15** was obtained from the fully protected disaccharide **18**, myristic acid derivative **16** and commercially available lauric acid **17**. The β-selective 1→6-linked glucosamine disaccharide backbone **18**, which was generated from the donor **5b1** and acceptor **7a6** in the presence of an acid catalyst and neighboring group participation, had the highest β-selectivity. The one-pot reaction with compounds **3a**

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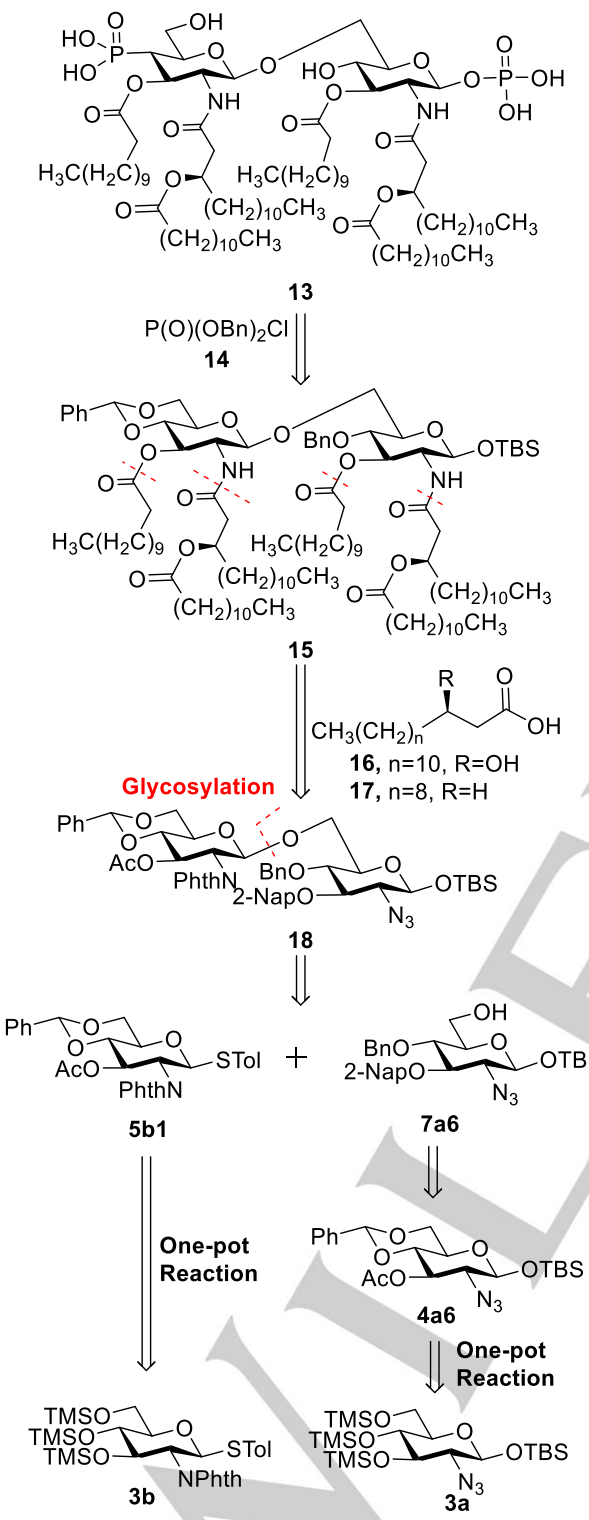
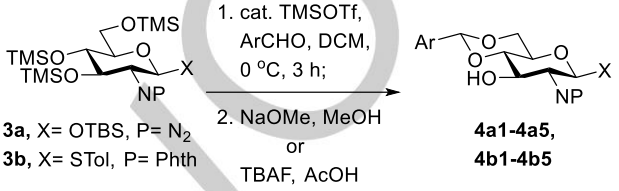
and **3b** were then adopted to obtain the glycosylation unit comprising acceptor **4a1** and donor **5b1**.



Scheme 2. Retrosynthetic Analysis of *Neisseria meningitidis* Lipid A **13.**

Using the method of Hung and co-workers,[18b] the use of chlorotrimethylsilane and triethylamine would give the corresponding starting materials **3a** and **3b**. According to the Marques and his team developing a one-pot method for glucosamine,[26] we used to separate the position of *C*-1 for tert-butyldimethylsilyl (TBS) protection and p-methylphenylthiol (STol) formation to distinguish between the donor and acceptor of glucosamine. Our general approach involves selective protection at the *O*-4 and *O*-6 as arylidene acetals, followed by etherification or acylation at *O*-3 to form fully protected mono-saccharides. The method modulates the reaction conditions to generate a single regio-isomer at each stage by the sequential addition of reagents in the same reaction flask.

Table 1. Synthesis of the 3-alcohol (**4a** and **4b**).



Entry	SM	Ar	TMSOTf (equiv.)	Prod. (Yield %)
1	**3a**	Ph	0.1	**4a1** (77%)
2	**3a**	Ph	0.15	**4a1** (86%)
3	**3a**	Ph	0.2	**4a1** (95%)
4	**3a**	2-Naph	0.2	**4a2** (91%)
5	**3a**	4-OMePh	0.2	**4a3** (85%)
6	**3a**	4-ClPh	0.2	**4a4** (82%)
7	**3a**	4-BrPh	0.2	**4a5** (92%)
8	**3b**	Ph	0.1	**4b1** (4%)
9	**3b**	Ph	0.15	**4b1** (80%)
10	**3b**	Ph	0.18	**4b1** (41%)
11	**3b**	2-Naph	0.15	**4b2** (81%)
12	**3b**	4-OMePh	0.15	**4b3** (73%)
13	**3b**	4-ClPh	0.15	**4b4** (88%)
14	**3b**	4-BrPh	0.15	**4b5** (87%)

The *C*-3 position maintained the trimethylsilyl (TMS) protecting group after arylidene acetalization was performed. In order to obtain the glycosyl acceptor **4a**, the TMS group had to remove optimizing conditions are sought. To produce **4a**, *C*-3 TMS protection was achieved in sodium methoxide (NaOMe) in methanol (MeOH) to measure the selectivity of *C*-3 TMS and *C*-4 TBS. However, this optimization was not useful in production of **4b**. Applying *tetra-n*-butyl-ammonium fluoride (TBAF) to produce **4a**, the effect was not good and producing many side-products. Therefore, in order to reduce the basicity, the reaction was executed in a mixture of TBAF and acetic acid (AcOH), obtaining good yields as expected.[27]

Table 1 lists the results of the *O*-4,6 arylidenation. Acceptor **3a** and donor **3b** were applied as the initial substrate for benzylidene acetalization. To test benzylidene acetalization, the

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reaction was performed with acceptor **3a**, 4 Å molecular sieves, trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.1 equiv.) and benzaldehyde (PhCHO, 1.05 equiv.) in dichloromethane (DCM) under a nitrogen atmosphere at 0 °C. The starting material had not been consumed after 3 hours. The desired product **4a1** was obtained in 77% isolated yield (entry 1). In an effort to raise the yield of the product of 4,6-*O*-benzylidene acetalization, the quanitity of TMSOTf was increased to 0.15 equivalent. This change significantly increased the yield of **4a1** to 86% without changing other reaction conditions (entry 2). Using 0.2 equivalent of TMSOTf achieved a good yield of the desired product **4a1** (95%, entry 3). Benzaldehyde was similarly used to form the benzylidene for the donor **3b**. The reaction was started under the conditions with donor **3b**, 4Å molecular sieves, TMSOTf (0.1 equiv.) and PhCHO (1.05 equiv.) in DCM under an atmosphere of nitrogen at 0 °C. As before, the starting material had not been consumed after 3 hours. The desired product **4b1** was obtained in trace quantity (entry 8). To increase the yield of **4b1**, the amount of TMSOTf was raised to 0.15 equivalent, significantly changing the yield of **4b1** to 80%. (entry 9). Further raising the quantity of TMSOTf to 0.18 equivalent reduced the yield of **4b1** to 41% (entry 10).

Therefore different substrates were screened, under the improved reaction conditions of acetalization by TMSOTf. Different aldehydes, such as 2-naphthaldehyde (2-NaphCHO), 4-anisaldehyde (4-OMePhCHO), 4-chlorobenzaldehyde (4-ClPhCHO), and 4-bromobenzaldehyde (4-BrPhCHO) also participated in the reaction. The reaction to produce acceptor **3a** proceeded under the same reaction conditions with 0.2 equivalent of TMSOTf, producing **4a2** in 91%, **4a3** in 85%, **4a4** in 81% and **4a5** in 92% yields (entries 4-7) and donor **3b** under the same reaction conditions with 0.15 equivalent of TMSOTf, producing **4b2** in 81%, **4b3** in 73%, **4b4** in 88% and **4b5** in 87% yields (entries 11-14).

In the first step shown in Table 1, the acid anhydride and TMSOTf reacted with free hydroxyl group of the compounds **4a1-4a5** and **4b1-4b5**, which protect *C*-3 to form a protecting group of ester in the second step. The acetic anhydrate was initially used to find the best condition for catalysis by TMSOTf. Based on the literature by Hatakeyama & Nishizawa,[27] the aldehyde was reduced by triethylsilane to form the protecting group of ether.

The fully protection reactions were shown in Table 2. After acceptor **3a** formed a ring formation of arylidene acetal at *O*-4 and *O*-6 in first step as in Table 1, acetic anhydride (1.2 equiv.) and TMSOTf (0.3 equiv.) were added to the mixture at 0 °C. After 2 hours, the desired product **5a1** was obtained in 85% yield (entry 1). In an effort to increase the yield of fully protected product, the amount of TMSOTf was increased to 0.3 equivalent in second step, significantly raising the yield of **5a1** to 90% (entry 2). However, further increasing the amount of TMSOTf to 0.4 equivalent lowered the yield of **5a1** to 57% (entry 3). After protecting the *O*-4 and *O*-6 positions of **3b** with an arylidene acetal, acetic anhydride (1.2 equiv.) and TMSOTf (0.2 equiv.) were added to the reaction mixture at 0 °C for acetylation. After 2 hours, the product **5b1** was obtained with a yield of 77% (entry 13). Initial attempts were made to find the appropriate amount to increase the yield of the desired product **5b1**. Interestingly, raising the amount of TMSOTf to 0.4 equivalent increased the yield of **5b1** to 83% (entry 14). In another set of experiments, the first step was performed as such; benzaldehyde (1.05 equiv.) and triethylsilane (1.1 equiv.) were added, then TMSOTf (0.17 equiv.) was catalyzed for benzylation. After 6 hours, the product **5a4** was obtained (57%, entry 6). In order to increase the yield of product **5a4**, the quantity of TMSOTf was increased to 0.18 equivalents, and the yield of product **5a4** was 65% (entry 8). However, raising the TMSOTf level to 0.2 equivalent decreased the yield of the desired product **5a4** to 46% (entry 10). Under 0.18 equivalents of TMSOTf, the yield of **5a4** was 59% when the temperature was lowered to -40 °C (entry 7), but fell to 54% when the temperature was raised to 40 °C (entry 9). Experimental results revealed that using 0.18 equivalents of TMSOTf gave the best result in the second step of benzylation at 0 °C.

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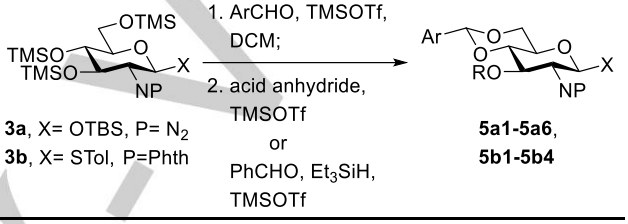
Table 2. Synthesis of the fully protected glucosamines (**5a** and **5b**).



3a, X= OTBS, P= N_2
3b, X= STol, P=Phth

5a1-5a6, **5b1-5b4**

Entry	S.	Ar	R	TMSOTf (equiv.)	Prod. (Yield, %)
1	**3a**	Ph	Ac	0.2	**5a1** (85%)
2	**3a**	Ph	Ac	0.3	**5a1** (90%)
3	**3a**	Ph	Ac	0.4	**5a1** (57%)
4[a]	**3a**	Ph	Bz	0.3	**5a2** (70%)
5[b]	**3a**	Ph	Piv	0.3	**5a3** (89%)
6[b]	**3a**	Ph	Bn	0.17	**5a4** (57%)
7[c]	**3a**	Ph	Bn	0.18	**5a4** (59%)
8[b]	**3a**	Ph	Bn	0.18	**5a4** (65%)
9[d]	**3a**	Ph	Bn	0.18	**5a4** (54%)
10[b]	**3a**	Ph	Bn	0.2	**5a4** (46%)
11	**3a**	2-Naph	Ac	0.3	**5a5** (82%)
12	**3a**	4-BrPh	Ac	0.3	**5a6** (91%)
13	**3b**	Ph	Ac	0.3	**5b1** (77%)
14	**3b**	Ph	Ac	0.4	**5b1** (83%)
15[e]	**3b**	Ph	Piv	0.4	**5b2** (74%)
16	**3b**	2-Naph	Ac	0.4	**5b3** (82%)
17	**3b**	4-BrPh	Ac	0.4	**5b4** (88%)

[a] Reactions were performed at 40 °C for 4 h. [b] Reactions were performed at 0 °C for 6 h. [c] Reactions were performed at -40 °C for 6 h. [d] Reactions were performed at 40 °C for 6 h. [e] Reactions were performed at 0 to r.t. °C for 2 h.

Experiments were performed on various substrates for *O*-3 protection were studied, with different equivalents of the same

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acid anhydride or another acid anhydride was added to the mixture at 0 °C. The reaction produced fully protecting compounds. Table 2 shows the yields of the corresponding *O*3-protection **5a2**-**5a3**, **5a5**-**5a6** and **5b2**-**5b4** (entries 4-5, 11-12 & 15-17) measured by column chromate-graphy. Various combinations of acid anhydrides, including acetic anhydride (Ac2O), benzoic anhydride (Bz2O) and pivalic anhydride (Piv2O), worked well under the conditions, forming the corresponding fully protected derivatives

Using the reaction conditions listed in Table 1 and Table 2, the 4-alcohol (Table 3) and 6-alcohol (Table 4) were obtained via *O*-4 and *O*-6 ring-opening of arylidene, and the results depended on whether the third step used triethylsilane (Et_3SiH) or boron trifluoride tetrahydrofuran complex (BH_3·THF) as reductant.

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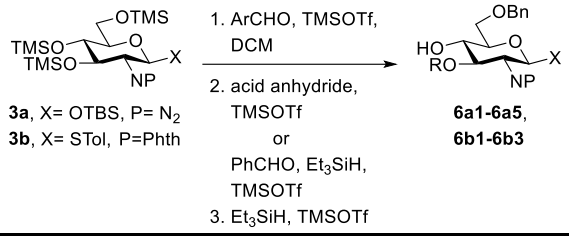
Table 3. Synthesis of 4-alcohols (**6a** and **6b**).



3a, X= OTBS, P= N_2
3b, X= STol, P=Phth

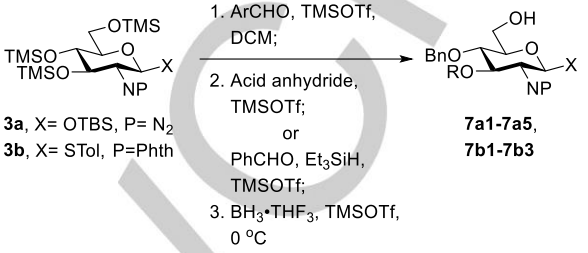
6a1-6a5, **6b1-6b3**

Entry	SM	Ar	R	Prod. (Yield, %)
1[a]	**3a**	Ph	Ac	**6a1** (4%)
2	**3a**	Ph	Ac	**6a1** (78%)
3[b]	**3a**	Ph	Ac	**6a1** (52%)
4[c]	**3a**	Ph	Ac	**6a1** (61%)
5	**3a**	Ph	Piv	**6a2** (69%)
6	**3a**	Ph	Bn	**6a3** (43%)
7	**3a**	2-Naph	Ac	**6a4** (43%)
8	**3a**	4-BrPh	Ac	**6a5** (45%)
9	**3b**	Ph	Ac	**6b1** (58%)
10	**3b**	2-Naph	Ac	**6b2** (41%)
11	**3b**	4-BrPh	Ac	**6b3** (45%)

[a] The TMSOTf was used 0.9 equiv. [b] The triethylsilane was used 1.5 equiv. [c] The reaction temperature is 0 °C.

The results of regio-selective *O*-4 ring opening of arylidene are summarized in Table 3. The acceptor **3a** was the starting material to determine the best catalysis condition required in the third step. The reaction was carried out at 0 °C with Et_3SiH (2.0 equiv.) and TMSOTf (0.9 equiv.), then moving to room temperature for 2 hours, obtaining only a small amount of product **6a1** (entry 1). To increase the yield of product **6a1**, the amount of TMSOTf was raised to 1.0 equivalent, and the yield was raised to 78% (Table 3, entry 2). Reducing Et_3SiH to 1.5 equivalent decreased the yield of product **6a1** to 52% (entry 3).Setting the temperature to 0 °C yielded only 61% of the product **6a1** (entry 4). The yield of **6b1** from starting material **3b** was 58% (entry 9). Under this condition, the reactions of Piv and Bn at the *O*-3 position formed **6a2** and **6a3** at 69% and 43% yield (entries 5-6). Similarly, 2-Naph arylidene and 4-BrPh arylidene at *O*-4 and *O*-6 obtained the corresponding products **6a4-6a5** and **6b2-6b3** of *O*-4 ring opening reactions (entries 7-8 & 10-11).

Table 4. Synthesis of 6-alcohols (**7a** and **7b**).



3a, X= OTBS, P= N_2
3b, X= STol, P=Phth

7a1-7a5, **7b1-7b3**

Entry	SM	Ar	R	TMSOTf (Equiv.)	Prod. (Yield, %)
1	**3a**	Ph	Ac	0.4	**7a1** (NR)
2	**3a**	Ph	Ac	0.5	**7a1** (87%)
3	**3a**	Ph	Ac	0.6	**7a1** (58%)
4	**3a**	Ph	Piv	0.5	**7a2** (15%)
5	**3a**	Ph	Piv	0.4	**7a2** (75%)
6	**3a**	Ph	Piv	0.3	**7a2** (37%)
7	**3a**	Ph	Bn	0.5	**7a3** (61%)
8	**3a**	2-Naph	Ac	0.5	**7a4** (62%)
9	**3a**	4-BrPh	Ac	0.5	**7a5** (41%)
10	**3b**	Ph	Ac	0.5	**7b1** (37%)
11	**3b**	Ph	Ac	0.6	**7b1** (45%)
12	**3b**	2-Naph	Ac	0.6	**7b2** (41%)
13	**3b**	4-BrPh	Ac	0.6	**7b3** (30%)

Table 4 lists the results of the arylidene regio-selective *O*-6 ring opening reactions. The minimum amount of TMSOTf required for these catalytic steps was initially employed, with acceptor **3a** as a starting material to find the optimal conditions. The reaction was added BH_3·THF (5.0 equiv.) and TMSOTf (0.4 equiv.) at 0 °C in this steps. The mixture was reacted for 16 hours, but the desired product **7a1** was not obtained (entry 1). For the purpose of finding the reaction condition for product **7a1**, the quantity of TMSOTf in the third step was increased to 0.5 equivalent, and product **7a1** was obtained with a yield of 87% (entry 2). The yield of product **7a1** is reduced to 58% when TMSOTf was increased to 0.6 equivalent (entry 3). It can be seen that the acceptor in the third step of *O*-6 ring opening at 0 °C and 0.5 equivalent of TMSOTf is the best reaction condition for this reaction. When using the donor **3b** as the starting material under the same condition in the third step, the reaction did not complete and the yield of the obtained product **7b1** was only 37% (entry 10). Increasing the amount of TMSOTf to 0.6

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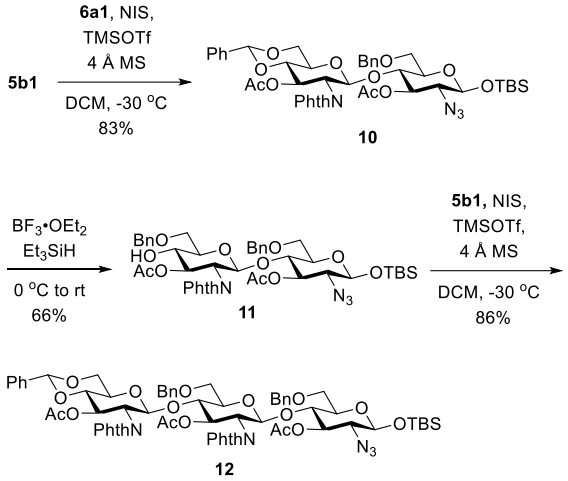
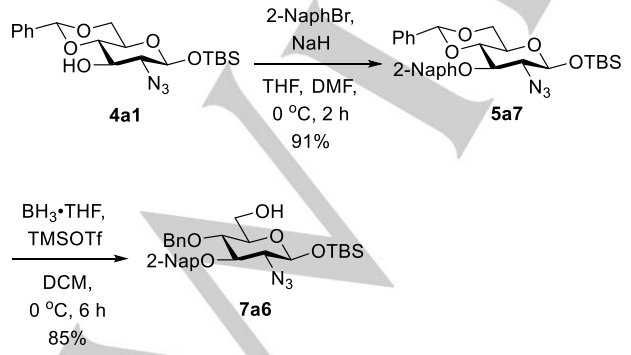
equivalent led to a complete reaction yielding 45% of the product **7b1** (entry 11).

Regio-selective *O*-6 ring opening reactions of other derivatives were performed under the same conditions. The reaction yield of product **7a2** could be obtained by a slight decrease in the catalyst equivalent. (0.4 equiv., entry 5). In entry 7, the Bn group in *O*-3 position is readily provided the corresponding product **7a3** almost quantitatively, whereas arylidene on 2-Naph afforded the product **7a4** in very good yield (entry 8). As indicated in entry 9, the corresponding product **7a5** was obtained in yield when *O-4,6* was 4-bromobenzylidene. Similar results were observed in the case of the donor (entries 12-13), and the products **7b2-7b3** were isolated at 41% and 30% yields with 0.6 equivalent of catalyst.



Scheme 3. Synthesis of the glycan part of glycopeptide

The glycopeptides present on the surfaces of the cell, play vital roles in biology.[29] However, glyco-peptides of defined length are difficult to isolate. Synthetic glucosamine chains of GP with precise numbers of saccharides could be formed with donors **5b1** and acceptors **6a1**. Scheme 3 depicts the preparation of disaccharides and trisaccharides. Glycosylation of **5b1** and **6a1** by *N*-iodo-succinimide (NIS) and TMSOTf supplied the disaccharide **10** in 83% yield. Here, the phthaloyl (Phth) group situated at the *O*-2 position of the donor assisted in generating the exclusive β-linkage.

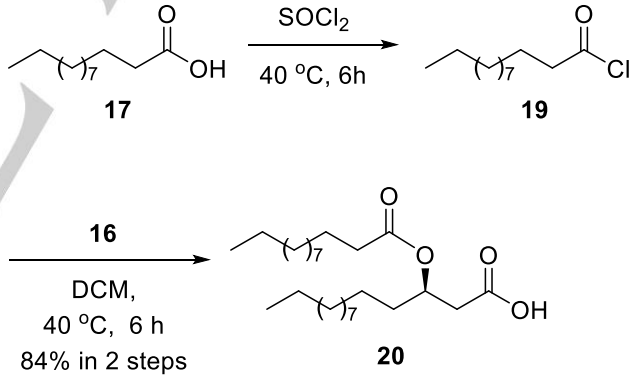


Scheme 4. Preparation of the acceptor of lipid A.

After glycosylation, the regioselective *O*-4 ring opening of the benzylidene acetal to form 4-alcohol **11** was attempted with sodium cyanoborohydride ($NaBH_3CN$) and methanesulfonic acid (MsOH).[30] The reaction took more than 24 hours, and was unable to achieve a high yield. Therefore, reagent Et_3SiH and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) were utilized to supply 4-alcohol **11**,[31] as used by some chemists for this purpose. Nonetheless, the reaction of *O*-4 ring opening employing Et_3SiH and trifluoroacetic acid (TFA) obtained the de-benzylidene product (4,6-diol) with very little desired product,[24] possibly because TFA was highly acidic for this reaction. Conversely, the target compound **12** was isolated in 66% yield when using $BF_3{\cdot}OEt_2$ in place of TFA.

Lipid A, being more readily available than glycopeptides, is often the main assembly and venomous factor on the Gram-negative bacterial cell surface.[32] The major structure of lipid A comprises a disaccharide with β-1,6-linked contented phosphoryl at *O*-1,4′ position, and 2,2′-*N*- and 3,3′-*O*-acylation.[33] Hence, chemists have developed several processes for forming these chemicals.

An alcohol at the *C*-6 position of acceptor **7a6** could also be accessed from the per-TMS glucosamine **3a** (Scheme 4). The 3-alcohol **4a1** was first prepared from the tri-TMS **3a**. The 3-*O*-2-Naphthylmethyl (2-Nap) **5a7**, generated upon treatment with 2-(bromomethyl)-naphthalene (2-NapBr), was convert-ed to the 3-alcohol in the presence of NaH. The ensuing *C*-6-alcohol was generated with $BH_3{\cdot}THF$ and TMSOTf to obtain acceptor **7a6**. In Scheme 5, myristic acid derivative **20** could be easily received from two fatty acids **16** and **17.**



Scheme 5. Synthesis of the derivative of myristic acid.

Our synthesis of Lipid A **13** is outlined in Scheme 6. Building blocks **5b1** and **7a6** were synthesized following a series of one-pot reactions. The glycosylation of **5b1** and **7a6** was achieved with NIS and TfOH as promoters, and the β-conformation of the glycosidic linkage was acquired. Next, the Phth and Ac in **18** were simultaneously removed by treatment with hydrazine in refluxing ethanol to give the intermediate of an amino group. The ensuing selective acylation of the free amino groups by myristic acid derivative **20**,[34] using 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide (EDC) as activation reagent, smoothly gave compound **21** in 71% yield over two steps. The free hydroxyl group underwent acylation smoothly with lauric acid **17** in the presence of EDC activator in DCM, producing the compound **22** in 92% yield.

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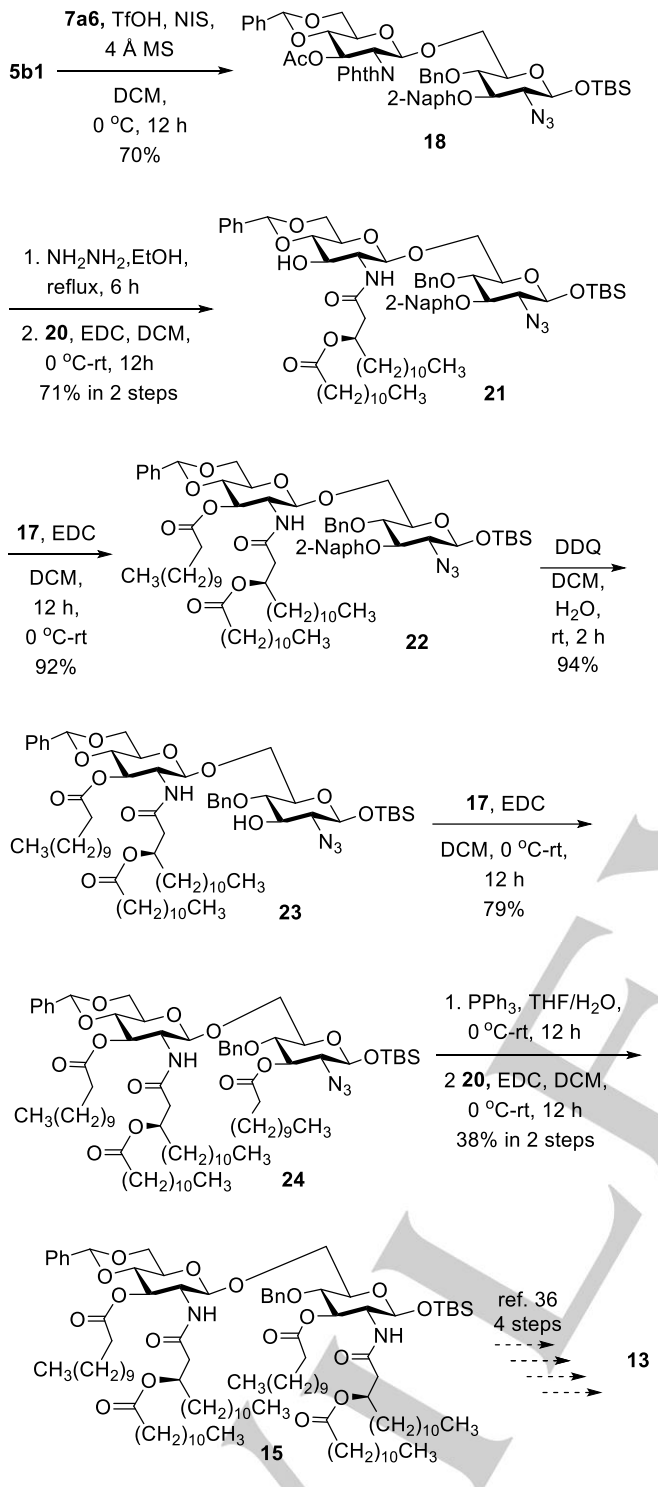

Scheme 6. Formal Synthesis of lipid A **13**

To synthesize lipid A, the 2-Nap protecting group of **22** was removed by reaction with 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (DDQ) in the presence of DCM/H_2O as the solvent system to give *C*3′-alcohol **23** with an excellent yield of 94%. Acylation of the *C*-3′ hydroxyl group of **23** using lauric acid **17** produced **24** in 79% yield. The azido moiety of **24** was then reduced by treatment with Staudinger's reaction condition[35] and the amine of the resulting compound acylated with **20** in the presence of EDC to obtain **15**. The conversion of fully protecting compound **15** to lipid A **13** was thus realized in four steps.[36] The interception of this late-stage intermediate thus completed the formal synthesis of lipid A **13**.

While the preparation of this manuscript was in progress, Mong and co-workers reported a reductive etherification in this glucosamines protection using polymethylhydrosiloxane as the reducing source.[37] The selectivity of reduction is important in a one-pot reaction, which needs to distinguish acetal protection and reductive etherification.

Conclusion

In summary, this study has successfully developed a one-pot reaction method for the formation of building blocks. Because the donors have a neighbouring group effect, the glycosylation reaction exclusively generated β-isomers. This simple and rapid method can be used instead of time-consuming multistep synthetic strategies. The one-pot reaction is a convergent and efficient strategy that was developed for the glucosamine chain of glycopeptide (GP) and formal synthesis of lipid A. The saccharide chain was extended from the regio-selective *O*-4 ring opening by Et_3SiH and $BF_3{\cdot}OEt_2$ as the key step before glycosylation. The strategy of lipid A should also be generally applicable in preparing other derivatives and lipid A carbohydrate conjugates. This method also showed in this study that the two amine groups exhibit selectivity while reacting with the different lipids. A central step in the synthesis is connecting fatty acids with disaccharides using EDC as activating reagent, which delivers acylation containing the free amino and free hydroxyl of the disaccharide. The shorter pathways of synthesis about di-, tri-, oligosaccharides and Lipid A are currently under active investigation in our laboratories.

Experimental Section

General Information

The reactions were conducted in flame-dried glassware, under the nitrogen atmosphere. Acetonitrile and dichloromethane were purified and dried from a safe purification system containing activated Al_2O_3. All reagents obtained from commercial sources were used without purification unless otherwise mentioned. Flash column chromatography was carried out on Silica Gel 60. TLC was performed on pre-coated glass plates of Silica Gel 60 F254 detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$ (0.5 g), $(NH_4)_6Mo_7O_{24}$ (24.0 g) and H_2SO_4 (28.0 mL) in water (500.0 mL) and subsequent heating on a hot plate. Optical rotations were measured at 589 nm (Na), ^1H, and ^{13}C NMR spectra were recorded with 400 MHz instruments. Chemical shifts are in ppm from Me_4Si generated from the $CDCl_3$ lock signal at δ 7.26. IR spectra were taken with a FT-IR spectrometer using NaCl plates. Mass spectra were analyzed on Orbitrap instrument with an ESI source.

General procedure for one-pot synthesis of the 3-alcohol glucose-amine. (Table 1)

Method A: To the solution of **3a** (200 mg, 1.0 equiv.) in dichloromethane (2.0 mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve (200 mg) was added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. The mixture was added trimethylsilyl trifluoromethanesulfonate (0.2 equiv.) and stirred for 2 hours at 0 ˚C. Followed by the addition of sodium methoxide (2.0 equiv.) and methanol (1.0 mL) and stirred for 2 hours at 0 °C. After completion of reaction, the mixture was diluted with ethyl acetate (20 mL), filtered through celite pad

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and extracted with water (20 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **4a1-4a5.**

Method B: To the solution of **3b** (200 mg, 1.0 equiv.) in dichloromethane (2.0 mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve (200 mg) were added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. The mixture was added trimethylsilyl trifluoromethanesulfonate (0.15 equiv.) and stirred for 2 hours at 0 ˚C. Followed by the addition of a mixture of TBAF (1.5 equiv.) and acetic acid (1.5 equiv.), then stirred for 30 min at 0 ºC. After completion of reaction, the mixture was diluted with ethyl acetate (20 mL), filtered through celite pad and extracted with water (20 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **4b1-4b5.**

2-Azido-4,6-*O*-benylidene-*O*-*tert*-butyldimethylsilyl-2-deoxy-D-glucopyranoside (4a1)

Prepared according to the general procedure discussed above: Colorless oil. (145 mg, 95%); R_f 0.59 (EtOAc/Hex = 1/1); $[\alpha]^{28}_D$ -51.10 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3443, 2958, 2931, 2860, 2112, 1644, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 3.6, 7.2 Hz, 2H), 7.37-7.36 (m, 3H), 5.53 (s, 1H), 4.66 (d, *J* = 7.6 Hz, 1H), 4.29 (dd, *J* = 4.8, 10.4 Hz, 1H), 3.79 (t, *J* =10.4 Hz, 1H), 3.64 (t, *J* =7.6 Hz, 1H), 3.57 (t, *J* =8.8 Hz, 1H), 3.42 (td, *J* = 4.4, 9.6 Hz, 1H), 3.34 (dd, *J* =7.6, 9.2 Hz, 1H), 2.62 (s, 1H), 0.94 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 129.2, 128.3, 126.2, 101.8, 97.4, 80.6, 71.5, 68.8, 68.4, 66.1, 25.4, 17.8, -4.4, -5.2; HRMS (ESI, M+H^+) calcd for $C_{19}H_{30}N_3O_5Si$ 408.1954, found 408.1949.

2-Azido-1-*O*-*tert*-Butyldimethylsilyl-2-deoxy-4,6-*O*-(2-naphthalidene)-D-gluco-pyranoside (4a2)

Prepared according to the general procedure discussed above: white solid. (155 mg, 91%); R_f 0.60 (EtOAc/Hex = 1/1); mp 78-79 ºC; $[\alpha]^{28}_D$ -64.30 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3439, 2957,2931, 2885, 2859, 2112, 1471, 1393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.87-7.82 (m, 3H), 7.58 (d, *J* =8.8 Hz,1H), 7.50-7.48 (m, 2H), 5.71 (s, 1H), 4.68 (d, *J* = 7.6, 1H), 4.35 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.85 (t, *J* = 10 Hz, 1H), 3.70-3.61 (m, 2H), 3.47 (td, *J* = 5.2, 9.2 Hz, 1H), 3.37 (t, *J* = 8 Hz, 1H), 2.64 (s, 1H), 0.95 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 134.1, 133.7, 132.8, 128.3, 128.2, 127.6, 126.5, 126.2, 125.8, 123.5, 102.0, 97.5, 80.7, 71.7, 68.9, 68.6, 66.3, 25.5, 17.9, -4.3, -5.1; HRMS (ESI, M+Na^+) calcd for $C_{23}H_{31}N_3O_5SiNa$ 480.1936 found 480.1931.

2-Azido-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-4,6-*O*-(4-methoxy-benzylidene)-D-glucopyranoside (4a3)

Prepared according to the general procedure discussed above: White solid. (139 mg, 85%); R_f 0.50 (EtOAc/Hex = 1/9) ; mp 58-60 ºC; $[\alpha]^{25}_D$ -56.70 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3455, 2958, 2932, 2885, 2860, 2112, 1616, 1589, 1519, 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 6.90-6.88 (m, 2H), 5.48 (s, 1H), 4.63 (d, *J* = 7.6 Hz, 1H), 4.26 (dd, *J* = 4.8, 10.4 Hz, 1H), 3.80 (s, 3H), 3.75 (t, *J* = 10.4 Hz, 1H), 3.60 (t, *J* = 9.2 Hz, 1H), 3.53 (t, *J* =8.8 Hz, 1H), 3.38 (td, *J* = 5.2, 9.6 Hz, 1H), 3.31 (dd, *J* = 7.6, 9.2 Hz, 1H), 2.79 (s, 1H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 129.2, 127.5, 113.7, 101.8, 97.5, 80.6, 71.7, 68.9, 68.4, 66.2, 55.2, 25.5, 17.8, -4.3, -5.2; HRMS (ESI, M+Na^+) calcd for $C_{20}H_{31}N_3O_6SiNa$ 460.1874, found 460.1880.

2-Azido-1-*O*-*tert*-butyldimethylsilyl-4,6-*O*-4-chlorobenzylid-ene-2-deoxy-D-gluco-pyranoside (4a4)

Prepared according to the general procedure discussed above: White solid. (135 mg, 82%); R_f 0.61 (EtOAc/Hex = 1/1); mp 62-63 ºC; $[\alpha]^{29}_D$ -46.50 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3437, 2957, 2931, 2885, 2860, 2113, 1649, 1604, 1494, 1469, 1257, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.34-7.32 (m, 2H), 5.49 (s, 1H), 4.63 (d, *J* = 7.6 Hz, 1H), 4.27 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.76 (t, *J* = 10 Hz, 1H), 3.61-3.51 (m, 2H), 3.37 (m, 1H), 3.31 (dd, *J* = 8, 8.8 Hz, 1H), 2.87 (s, 1H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 135.1, 128.5, 127.7, 101.0, 97.5, 80.6, 71.6, 68.9, 68.4, 66.1, 25.5, 17.8, -4.4, -5.2; HRMS (ESI, M+Na^+) calcd for $C_{19}H_{28}ClN_3O_5SiNa$ 464.1384, found 464.1376.

2-Azido-4,6-*O*-4-bromobenzylidene-1-*O*-*tert*-butyldimethy-lsiyl-2-deoxy-D-gluco-pyranoside (4a5)

Prepared according to the general procedure discussed above: White solid. (167 mg, 92%); R_f 0.62 (EtOAc/Hex = 1/1); mp 79-80 ºC; $[\alpha]^{28}_D$ -57.70 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3439, 2956, 2931, 2884, 2860, 2112, 1599, 1491, 1469 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* =8.8 Hz, 2H), 7.35 (d, *J* =8.4 Hz, 2H), 5.47 (s, 1H), 4.63 (d, *J* = 7.6 Hz, 1H), 4.27 (dd, *J* = 4.8, 10.4 Hz, 1H), 3.75 (t, *J* =10.4 Hz, 1H), 3.55 (m, 2H), 3.37 (m, 1H), 3.31 (dd, *J* = 7.6, 9.6 Hz, 1H), 2.91 (s, 1H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 131.4, 128.0, 123.3, 101.0, 97.4, 80.6, 71.5, 68.9, 68.4, 66.1, 25.5, 17.8, -4.4, -5.2 HRMS (ESI, M+H^+) calcd for $C_{19}H_{29}BrN_3O_5Si$ 486.1059, found 486.1782.

4,6-*O*-Benzylidene-2-deoxy-2-phthalimido-1-thio-D-glucopy-ranoside (4b1)

Prepared according to the general procedure discussed above: White solid. (125 mg, 80%); R_f 0.44 (EtOAc/Hex = 1/1); mp 121-122 ºC; $[\alpha]^{25}_D$ +39.70 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3444, 2925, 2870, 2088, 1775, 1711, 1644, 1493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90-7.85 (m, 2H), 7.75 (dd, *J* = 2.8, 5.6 Hz, 2H), 7.48 (dd, *J* = 4.4, 7.6 Hz, 2H), 7.37 (dd, *J* = 2, 5.2 Hz, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 5.63 (d, *J* = 10.4 Hz, 1H), 5.56 (s, 1H), 4.63 (t, *J* = 10 Hz, 1H), 4.40 (dd, *J* = 4.8, 10.4 Hz, 1H), 4.31 (t, *J* = 10.4 Hz, 1H), 3.82 (t, *J* = 10 Hz, 1H), 3.70 (td, *J* = 4.8, 9.6 Hz, 1H), 3.59 (t, *J* = 9.2 Hz, 1H), 2.46 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.5, 138.4, 136.8, 134.2, 133.3, 131.6, 129.6, 129.3, 128.3, 127.7, 126.2, 123.8, 123.3, 101.9, 84.4, 81.8, 70.2, 69.7, 68.5, 55.5, 21.1; HRMS (ESI, M+Na^+) calcd for $C_{28}H_{25}NO_6SNa$ 526.1300, found 526.1294.

2-Deoxy-4,6-*O*-(2-naphthalidene)-2-phthalimido-1-thio-D-gluco-pyranoside (4b2).

Prepared according to the general procedure discussed above: White solid. (142 mg, 81%); R_f 0.46 (EtOAc/Hex = 1/1); mp 99-100 ºC; $[\alpha]^{22}_D$ +32.30 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3446, 2922, 2857, 1775, 1715, 1646, 1388 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.92-7.91 (m, 1H), 7.87-7.81 (m, 4H), 7.76-7.74 (m, 2H), 7.58 (dd, *J* =1.2, 8.4 Hz, 1H), 7.50-7.47 (m, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 5.73 (s, 1H), 5.66 (d, *J* = 10.4 Hz, 1H), 4.66 (t, *J* = 10 Hz, 1H), 4.45 (dd, *J* = 4.8, 10.4 Hz, 1H), 4.31 (t, *J* = 10.4 Hz, 1H), 3.88 (t, *J* = 10.4 Hz, 1H), 3.78-3.72 (m, 1H), 3.66 (t, *J* =9.2 Hz, 1H), 2.54 (s, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.5, 138.3, 134.1, 133.6, 133.2, 132.7, 131.5, 131.4, 129.6, 128.3, 128.2, 127.7, 127.6, 126.4, 126.2, 125.8, 123.7, 123.6, 123.2, 101.9, 84.4, 81.8, 70.2, 69.6, 68.5, 55.5, 21.1; HRMS (ESI, M+Na^+) calcd for $C_{32}H_{27}NO_6SNa$ 576.1451, found 576.1472.

2-Deoxy-4,6-*O*-(4-methoxybenzylidene)-2-phthalimido-1-thio-D-glucopyranoside (4b3)

Prepared according to the general procedure discussed above: White solid. (123 mg, 73%); R_f 0.37 (EtOAc/Hex = 1/1); mp 130-131 ˚C; $[\alpha]^{29}_D$ +38.50 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3472, 2961, 2934, 2871, 1775, 1713, 1386 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90-7.84 (m, 2H), 7.75 (dd, *J* = 2.4, 5.2 Hz, 2H) 7.40 (dd, *J* = 2, 6.8 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H), 6.89 (dd, *J* = 2 Hz, 2H), 5.63 (d, *J* = 10.8 Hz, 1H), 5.52 (s, 1H), 4.61 (t, *J* = 9.2 Hz, 1H), 4.38 (dd, *J* = 4.8, 10.4 Hz, 1H), 4.31 (t, *J* = 10.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 1H), 3.68 (td, *J* = 4.8, 9.2 Hz, 1H), 3.57 (t, *J* = 9.2 Hz, 1H), 2.44 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.5, 160.2, 138.4, 134.1, 133.2, 131.5, 129.6, 129.3, 127.6, 127.6, 123.8, 123.3, 113.7, 101.8, 84.4, 81.7, 70.2, 69.6, 68.5, 55.5, 55.2, 21.1; HRMS (ESI, M+Na^+) calcd for $C_{29}H_{27}NO_7SNa$ 556.1400 , found 556.1397.

4,6-*O*-(4-Chlorobenzylidene)-2-deoxy-2-phthalimido-1-thio-D-gluco-pyranoside (4b4)

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Prepared according to the general procedure discussed above: White solid. (149 mg, 88%); R_f 0.45 (EtOAc/Hex = 1/3); mp 118-120 °C; $[\alpha]^{25}_D$ +38.40 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3477, 3059, 2978, 2925, 2870, 1775, 1713, 1493, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90-7.85 (m, 2H), 7.76 (dd, *J* = 2.8, 5.6 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4, 2H), 7.27 (d, *J* = 9.6 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 5.62 (d, *J* = 10.8 Hz, 1H), 5.53 (s, 1H), 4.61 (t, *J* = 9.6 Hz, 1H), 4.39 (dd, *J* = 5.2, 10.4 Hz, 1H), 4.30 (t, *J* = 10.4 Hz, 1H), 3.81 (t, *J* = 10.4 Hz, 1H), 3.67 (td, *J* = 4.8, 9.6 Hz, 1H), 3.58 (t, *J* = 8.8 Hz, 1H), 2.43 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.5, 138.4, 135.3, 135.0, 134.1, 133.2, 131.5, 131.4, 129.6, 128.4, 127.7, 123.8, 123.3, 100.9, 84.4, 81.7, 70.1, 69.6, 68.4, 55.6, 21.1; HRMS (ESI, M+Na^+) calcd for $C_{28}H_{24}ClNO_6SNa$ 560.0916, found 560.0913.

4,6-*O*-(4-Bromobenzylidene)-2-deoxy-2-phthalimido-1-thio-D-glucopyranoside (4b5)

Prepared according to the general procedure discussed above: White solid. (159 mg, 87%); R_f 0.43 (EtOAc/Hex = 1/3); mp 112-113 °C; $[\alpha]^{29}_D$ 34.60 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3477, 2924, 2870, 1775, 1713, 1468, 1468, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (s, 2H), 7.76 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 7.07 (d, *J* = 8 Hz, 2H), 5.62 (d, *J* = 10.4 Hz, 1H), 5.52 (s, 1H), 4.61 (t, *J* = 9.2 Hz, 1H), 4.39 (dd, *J* = 4.4, 10 Hz, 1H), 4.30 (t, *J* = 10 Hz, 1H), 3.80 (t, *J* = 10 Hz, 1H), 3.70-3.64 (m, 1H), 3.58 (t, *J* = 8.8 Hz, 1H), 2.38 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.5, 138.4, 135.8, 134.2, 133.3, 131.4, 129.7, 128.0, 127.6, 123.8, 123.4, 123.3, 101.0, 84.4, 81.8, 70.1, 69.6, 68.4, 55.5, 21.1; HRMS (ESI, M+Na^+) calcd for $C_{28}H_{24}BrNO_6SNa$ 604.0410 found 604.0408.

General procedure for one-pot synthesis of the fully protected glucosamine (Table 2)

Method A: To the solution of **3** (200 mg, 1.0 equiv.) in dichloromethane (2.0 mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve (200 mg) were added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. The mixture was added TMSOTf (0.2 equiv. **5a1-5a3, 5a5- 5a6** and 0.15 equiv. **5b1-5b4**) and stirred for 2 hours at 0 ˚C. To a solution of the residue were added anhydrides (1.2 equiv. for **5a1-5a3, 5a5-5b4**), TMSOTf (0.3 equiv. for **5a1**- **5a3, 5a5-5a6** and 0.4 equiv. for **5b1-5b4**). After completion of reaction, the mixture was diluted with ethyl acetate (20 mL), filtered through celite pad and extracted with water (20 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **5a1-5a3** and **5a5-5b4.**

Method B: To the solution of **3a** (200 mg, 1.0 equiv.) in dichloromethane (2.0 mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve (200 mg) were added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. The mixture was added TMSOTf (0.2 equiv.) and stirred for 2 hours at 0 ˚C. Followed by the addition of triethylsilane (1.1 equiv.) and benzaldehyde (1.2 equiv.) and TMSOTf (0.18 equiv.). After completion of reaction, the mixture was diluted with ethyl acetate (20 mL), filtered through celite pad and extracted with water (20 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **5a4.**

3-*O*-Acetyl-2-Azido-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-4,6-*O*-benzylidene-β-D-glucopyranoside (5a1)

Prepared according to the general procedure discussed above: White solid. (151 mg, 90%); R_f 0.42 (EtOAc/Hex = 1/4); mp 97-98 °C; $[\alpha]^{29}_D$ -76.20 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2956, 2932, 2885, 2860, 2112, 1754, 1469, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 4, 8 Hz, 2H), 7.35 (dd, *J* = 2.4, 6.4 Hz, 3H), 5.48 (s, 1H), 5.12 (t, *J* = 9.6 Hz, 1H), 4.71 (d, *J* = 7.6 Hz, 1H), 4.30 (dd, *J* = 4.8,10.4 Hz, 1H), 3.79 (t, *J* = 10 Hz, 1H), 3.63 (t, *J* = 9.6 Hz, 1H), 3.48 (td, *J* = 5.2, 9.6 Hz, 1H), 3.41 (dd, *J* = 7.6, 10 Hz, 1H), 2.13 (s, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 136.7, 129.0, 128.1, 126.1, 101.4, 97.5, 78.6, 70.9, 68.4, 67.1, 66.5, 25.4, 20.8, 17.8, -4.4, -5.24; HRMS (ESI, M+Na^+) calcd for $C_{21}H_{31}N_3O_6SiNa$ 472.1874, found 472.1879.

2-Azido-3-*O*-benzoyl-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-4,6-*O*-benzylidene-β-D- glucopyranoside (5a2)

Prepared according to the general procedure discussed above: White solid. (139 mg, 70%); R_f 0.30 (EtOAc/Hex = 1/9); mp 102-104 °C; $[\alpha]^{25}_D$ -73.80 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2956, 2932, 2885, 2860, 2113, 1773, 1469, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09-8.06 (m, 2H), 7.59-7.55 (m, 1H), 7.47-7.43 (m, 2H), 7.39-7.36 (m, 2H), 7.30-7.28 (m, 3H), 5.50 (s, 1H), 5.39 (t, *J* = 9.6 Hz, 1H), 4.80 (d, *J* = 7.6 Hz, 1H), 4.33 (dd, *J* = 4.8, 10.4, 1H), 3.85-3.77 (m, 2H), 3.59-3.53 (m, 2H), 0.95 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 136.7, 133.2, 129.8, 129.5, 129.0, 128.3, 128.1, 126.0, 101.5, 97.7, 78.8, 71.5, 68.5, 67.4, 66.6, 25.5, 17.9, -4.4, -5.1; HRMS (ESI, M+H^+) calcd for $C_{26}H_{34}N_3O_6Si$ 512.2216, found 512.2177.

2-Azido-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-4,6-*O*-benzylid-ene-3-*O*-trimethyl-acetyl-β-D-glucopyranoside (5a3)

Prepared according to the general procedure discussed above**:** White solid. (163 mg, 89%); R_f 0.41 (EtOAc/Hex = 1/9); mp 112-113 °C; $[\alpha]^{25}_D$ -79.10 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2959, 2932, 2861, 2112, 1743, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 4, 7.6 Hz, 2H), 7.34 (dd, *J* = 0.8, 4.4 Hz, 3H), 5.49 (s, 1H), 5.13 (t, *J* = 9.6 Hz, 1H), 4.71 (d, *J* = 7.6 Hz, 1H), 4.31 (dd, *J* = 4.8, 10.4 Hz, 1H), 3.79 (t, *J* = 10.4 Hz, 1H), 3.65 (t, *J* = 9.2 Hz, 1H), 3.50-3.45 (m, 1H), 3.43 (dd, *J* = 7.6, 10.4 Hz, 1H), 1.24 (s, 9H), 0.95 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 136.8, 128.8, 128.1, 125.8, 101.1, 97.4, 78.8, 70.8, 68.4, 67.4, 66.4, 38.8, 27.0, 25.4, 17.8, -4.4, -5.2; HRMS (ESI, M+Na^+) calcd for $C_{24}H_{37}N_3O_6SiNa$ 514.2349, found 514.2334.

2-Azido-3-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-2-deoxy-4,6-*O*-benzylidene-β-D-glucopyranoside (5a4)

Prepared according to the general procedure discussed above: White solid. (121 mg, 65%); R_f 0.49 (EtOAc/Hex = 1/9); mp 90-91 °C; $[\alpha]^{29}_D$ -109.20 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 3066, 3035, 2956, 2931, 2884, 2859, 2111, 1497, 1455, 1389, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 3.2, 8 Hz, 2H), 7.39-7.37 (m, 5H), 7.35-7.28 (m, 3H), 5.57 (s, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 7.6 Hz, 1H), 4.29 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.80 (t, *J* = 10 Hz, 1H), 3.72 (t, *J* = 9.2 Hz, 1H), 3.52 (t, *J* = 9.2 Hz, 1H), 3.41-3.34 (m, 2H), 0.94 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.1, 129.0, 128.3, 128.2, 128.0, 127.7, 125.9, 101.2, 97.45, 81.5, 78.7, 74.7, 68.6, 68.5, 66.2, 25.5, 17.9, -4.3, -5.2; HRMS (ESI, M+Na^+) calcd for $C_{26}H_{35}N_3O_5SiNa$ 520.2249, found 520.2241.

3-*O*-Acetyl-2-azido-1-*O*-*tert*-butyldimethylsiyl-2-deoxy-4,6-*O*-(2-naphthalidene)- β-D-glucopyranoside (5a5)

Prepared according to the general procedure discussed above**:** white solid. (151 mg, 82%); R_f 0.45 (EtOAc/Hex = 1/4); mp 132-133 °C; $[\alpha]^{25}_D$ -94.70 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2957, 2932, 2886, 2859, 2111, 1753, 1643, 1470, 1393 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.86-7.82 (m, 3H), 7.52 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.49-7.46 (m, 2H), 5.64 (s, 1H), 5.16 (t, *J* = 10 Hz, 1H), 4.74 (d, *J* = 7.6 Hz, 1H), 4.35 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.85 (t, *J* = 10 Hz, 1H), 3.70 (t, *J* = 9.6 Hz, 1H), 3.54 (td, *J* = 4.8, 9.6 Hz, 1H), 3.43 (dd, *J* = 7.6, 10 Hz, 1H), 2.13 (s, 3H), 0.95 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 134.1, 133.6, 132.7, 128.3, 128.0, 127.6, 126.4, 126.1, 125.7, 123.6, 101.7, 97.6, 78.7, 70.9, 68.5, 67.2, 66.5, 25.5, 20.8, 17.9, -4.4, -5.2; HRMS (ESI, M+Na^+) calcd for $C_{25}H_{33}N_3O_6SiNa$ 522.2030, found 522.2032.

3-*O*-Acetyl-2-Azido-4,6-*O*-(4-bromobenzylidene)-1-*O*-*tert*-butyl-dimethylsiyl-2-deoxy-β-D-glucopyranoside (5a6)

Prepared according to the general procedure discussed above: White solid. (180 mg, 91%); R_f 0.42 (EtOAc/Hex = 1/4); mp 96-97 °C; $[\alpha]^{25}_D$ -92.9 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2957, 2932, 2885, 2860, 2113, 1752, 1645, 1491, 1469, 1370 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 2, 6.8 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.43 (s, 1H), 5.10 (t, *J* = 9.6 Hz,

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1H), 4.70 (d, *J* = 7.6 Hz, 1H), 4.28 (dd, *J* = 4.8, 10.4 Hz, 1H), 3.77 (t, *J* = 10.4 Hz, 1H), 3.61 (t, *J* = 9.6 Hz, 1H), 3.48-3.44 (m, 1H), 3.40 (dd, *J* = 7.6, 10 Hz, 1H), 2.13 (s, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.7, 131.3, 127.8, 123.2, 100.7, 97.6, 78.6, 70.9, 68.4, 67.1, 66.4, 25.5, 20.8, 17.8, -4.4, -5.2; HRMS (ESI, M+Na$^+$) calcd for $C_{21}H_{30}BrN_3O_6SiNa$ 550.0984, found 550.0981.

3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranosi-de (5b1)

Prepared according to the general procedure discussed above: White solid. (143 mg, 83%); R_f 0.54 (EtOAc/Hex = 1/2); mp 120-121 °C; $[\alpha]^{28}_D$ +21.00 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 3066, 2979, 2927, 2870, 1776, 1748, 1718, 1384 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 3.6, 8.4 Hz, 2H), 7.76-7.74 (m, 2H), 7.44 (dd, *J* = 4, 7.6 Hz, 2H), 7.35 (dd, *J* = 1.6, 4.4 Hz, 3H), 7.28 (d, *J* = 8 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 5.88 (t, *J* = 9.2 Hz, 1H), 5.76 (d, *J* = 10.4 Hz, 1H), 5.53 (s, 1H), 4.42 (dd, *J* = 2.8, 8.8 Hz, 1H), 4.33 (t, *J* = 10 Hz, 1H), 3.85-3.71 (m, 3H), 2.32 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.1, 167.50, 138.9, 137.1, 134.6, 134.4, 133.9, 131.9, 131.4, 130.0, 129.4, 128.5, 127.4, 126.5, 123.9, 123.8, 101.8, 84.2, 79.2, 70.8, 70.7, 68.8, 54.5, 21.4, 20.8; HRMS (ESI, M+Na$^+$) calcd for $C_{30}H_{27}NO_7SNa$ 568.1404, found 568.1392.

4,6-*O*-Benzylidene-2-deoxy-2-phthalimido-1-thio-3-*O*-trimethylacetyl-β-D-gluco-pyranoside (5b2)

Prepared according to the general procedure discussed above: White solid. (137 mg, 74 %); R_f 0.58 (EtOAc/Hex = 1/1.5); mp 192-193 °C; $[\alpha]^{29}_D$ +1.10 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2975, 2934, 2873, 1777, 1736, 1718, 1645, 1383 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.83 (m, 2H), 7.76-7.71 (m, 2H), 7.41 (dd, *J* = 4, 9.6 Hz, 2H), 7.35-7.32 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8 Hz, 2H), 5.89-5.85 (m, 1H), 5.78 (d, *J* = 10.4 Hz, 1H), 5.55 (s, 1H), 4.44 (dd, *J* = 3.2, 9.6 Hz, 1H), 4.36 (t, *J* = 10.4 Hz, 1H), 3.86-3.76 (m, 3H), 2.32 (s, 3H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 167.7, 167.1, 138.5, 136.8, 134.3, 134.1, 133.5, 131.6, 131.2, 129.7, 128.9, 128.1, 127.3, 125.8, 123.7, 123.3, 101.1, 84.2, 79.2, 70.5, 70.2, 68.5, 54.2, 38.6, 26.8, 21.1; HRMS (ESI, M+Na$^+$) calcd for $C_{33}H_{33}NO_7SNa$ 610.1869, found 610.1878.

3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranosi-de (5b3)

Prepared according to the general procedure discussed above: White solid. (154 mg, 82%); R_f 0.60 (EtOAc/Hex = 1/1.5); mp 179-180 °C; $[\alpha]^{25}_D$ +19.8 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2930, 3036, 2871, 1776, 1745, 1716, 1644, 1493, 1469 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.88 (dd, *J* = 4, 8.8 Hz, 2H), 7.83 (dd, *J* = 4, 8.8 Hz, 3H), 7.76-7.74 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.48-7.46 (m, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 5.91 (t, *J* = 9.6 Hz, 1H), 5.79 (d, *J* = 10.4 Hz, 1H), 5.69 (s, 1H), 4.47 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.35 (t, *J* = 10.8 Hz, 1H), 3.91-3.77 (m, 3H), 2.33 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.15, 167.8, 167.2, 136.6, 134.4, 134.1, 133.6, 132.7, 131.6, 131.1, 129.7, 128.3, 128.0, 127.6, 127.1, 126.4, 126.1, 125.8, 123.7, 123.6, 123.5, 101.8, 84.0, 79.0, 70.6, 70.5, 68.6, 54.3, 21.1, 20.5; HRMS (ESI, M+Na$^+$) calcd for $C_{34}H_{29}NO_7SNa$ 618.1562, found 618.1545.

3-*O*-Acetyl-4,6-*O*-(4-bromobenzylidene)-2-deoxy-2-phthal-imido-1-thio-β-D-glu-copyranoside (5b4)

Prepared according to the general procedure discussed above: White solid. (175 mg, 88%); R_f 0.56 (EtOAc/Hex = 1/1.5); mp 121-122 °C; $[\alpha]^{25}_D$ +12.6 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 2931, 2970, 1776, 1748, 1717, 1492, 1383, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 3.6 Hz, 2H), 7.76-7.74 (m, 2H), 7.48 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.31 (d, *J* = 0.8 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 2H), 7.25 (s, 1H), 7.07 (d, *J* = 8 Hz, 2H), 5.86 (t, *J* = 8.8 Hz, 1H), 5.74 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.48 (s, 1H), 4.41 (dd, *J* = 2.8, 9.6 Hz, 1H), 4.34-4.39 (m, 1H), 3.82-3.68 (m, 3H), 2.32 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 167.8, 167.2, 138.7, 135.8, 134.4, 134.2, 133.6, 131.6, 131.3, 131.1, 129.7, 128.0, 127.1, 123.7, 123.6, 123.2, 100.8, 84.0, 79.9, 70.5, 70.3, 68.5, 54.2, 21.1, 20.5; HRMS (ESI, M+Na$^+$) calcd for $C_{30}H_{26}BrNO_7SNa$ 646.0511, found 646.0501.

General procedure for one-pot region-selective *O*-4 ring opening reactions. (Table 3)

Method A: To the solution of **3** (200 mg, 1.0 equiv.) in dichloromethane (2.0mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve (200 mg) was added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. The mixture was added trimethylsilyl trifluoro-methanesulfonate (0.2 equiv. for **6a1-6a2, 6a4-6a5** and 0.15 equiv. for **6b1-6b3**) and stirred for 2 hours at 0 ˚C. Followed by the addition of acetic anhydride (1.2 equiv. for **6a1-6a2**, **6a4-6a5** and **6b1-6b3**) and trimethylsilyl trifluoromethanesulfonate (0.3 equiv. for **6a1-6a2**, **6a4-6a5** and 0.4 equiv. for **6a1-6b3**). The reaction was stirred for the reaction time (2 hours for **6a1**, **6a4-6a5**, **6b1-6a3** and 6 hours for **6a2**) at 0 °C, Followed by the addition of triethylsilane (2.0 equiv) and trimethylsilyl trifluoro-methanesulfonate (1.0 equiv) at 0 °C. After stirring for 2 hours at room temperature, the mixture was filtered through celite pad and diluted with ethyl acetate (20 mL) and extracted with water (20 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **6a1-6a2** and **6a4-6b3.**

Method B: To the solution of **3a** (200 mg, 1.0 equiv.) in dichloromethane (2.0 mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve (200 mg) were added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. The mixture was added trimethylsilyl trifluoromethane-sulfonate (0.2 equiv.) and stirred for 2 hours at 0 ˚C. Followed by the addition of triethylsilane (1.1 equiv.), benzaldehyde (1.2 equiv.) and trimethylsilyl trifluoro-methanesulfonate (0.18 equiv.). Then the reaction was stirred for 6 hours at 0 °C, triethylsilane (2.0 equiv.) and trimethylsilyl trifluoromethanesulfonate (1.0 equiv.) was added at 0 °C. After stirring for 2 hours at room temperature, the mixture was filtered through celite pad and diluted with ethyl acetate (20 mL) and extracted with water (20 mL×3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **6a3.**

3-*O*-Acetyl-2-azido-6-*O*-benzyl-2-deoxyl-1-*O*-*tert*-butyldime-hylsilyl-β-D-gluco-pyranoside (6a1)

Prepared according to the general procedure discussed above: colorless oil. (131 mg, 78% in 3 steps); R_f 0.51 (EtOAc/Hex = 1/2); $[\alpha]^{25}_D$ -22.33 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 4H), 4.79 (dd, *J* = 10.4 9.6 Hz, 1H), 4.62-4.54 (m, 2H), 3.74 (m, 2H), 3.67 (t, *J* = 9.2 Hz, 1H), 3.47 (m, 1H), 3.34 (dd, *J* = 10.4, 7.6 Hz, 1H), 2.98 (s, 1H), 2.16 (s, 3H), 0.93 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 137.6, 128.5, 127.8, 127.6, 97.1, 75.3, 74.3, 73.7, 70.9, 70.1, 66.0, 25.6, 21.0, 17.9, -4.4, -5.2.; HRMS (ESI, M+Na$^+$) calcd for $C_{21}H_{33}N_3O_6SiNa$ 474.2036 found 474.2020.

2-Azido-4-*O*-benzyl-2-deoxyl-3-*O*-pivaloyl-1-*O*-*tert*-butyldime-thylsilyl-β-D-glu-copyranoside (6a2)

Prepared according to the general procedure discussed above: colorless oil. (128 mg, 69% in 3 steps); R_f 0.09 (EtOAc /Hex=1/8); $[\alpha]^{24}_D$ -12.7 (*c* 1.0, CH_2Cl_2); IR (NaCl) v 3485, 3065, 2959, 2932, 2860, 2111, 1733, 1478, 1396, 1257, 1103, 1005, 960, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 5H), 4.73 (dd, J = 9.2, 0.8 Hz, 2H), 4.59 (d, J = 7.2 Hz, 3H), 3.74 (d, J = 4.4 Hz, 2H), 3.67 (td, J = 9.6, 3.6 Hz, 1H), 3.45-3.50 (m, 1H), 3.36 (dd, J = 7.6, 2.4 Hz, 1H), 2.97 (d, J = 3.6 Hz, 1H), 1.25 (s, 9H), 0.93 (s, 9H), 0.16 (d, J = 1.6 Hz, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.17, 137.72, 128.37, 127.71, 127.56, 96.94, 75.37, 74.65, 73.60, 70.55, 69.74, 66.35, 38.93, 27.13, 27.00, 25.51, 17.89, -4.37, -5.31.; HRMS (ESI+, M+Na$^+$) calcd for $C_{24}H_{39}N_3O_6SiNa$ 516.2506, found 516.2516.

2-Azido-2-deoxyl-3,4-*O*-dibenzyl-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosi-de (6a3)

Prepared according to the general procedure discussed above: as colorless oil. (80 mg, 43% in 3 steps); R_f 0.17 (EtOAc /Hex=1/9); $[\alpha]^{23}_D$ -22.1 (*c* 1.0, CH_2Cl_2); IR (NaCl) v 3448,3065, 2954, 2859, 2110, 1497, 1362, 1258, 1078, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 10H), 4.92 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 4

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Hz, 2H), 4.53 (d, *J* = 6.4 Hz, 1H), 3.72 (d, *J* = 4.4 Hz, 2H), 3.64 (t, *J* = 8.8 Hz, 1H), 3.41 (dt, *J* = 9.6 Hz, 4.8 Hz, 1H), 3.32 (dd, *J* = 10 Hz, 7.6 Hz, 1H), 3.22 (dd, *J* = 10 Hz, 8.8 Hz, 1H), 2.65 (s, 1H), 0.94 (s, 9H) , 0.17 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.14, 137.71, 128.55, 128.39, 128.03, 127.95, 127.73, 127.59, 97.18, 82.26, 74.94, 73.97, 73.63, 71.84, 70.26, 68.04, 25.56, 17.95, -4.30, -5.26. HRMS (ESI+, M+Na$^+$) calcd for $C_{26}H_{37}N_3O_5SiNa$ 522.2400, found 522.2401.

2-Azido-2-deoxyl-6-*O*-(2-naphthylmethyl)-3-*O*-pivaloyl-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (6a4)

Prepared according to the general procedure discussed above: colorless oil. (80 mg, 43% in 3 steps); R_f 0.42 (EtOAc /Hex=1/2); $[\alpha]^{25}_D$ +32.6 (*c* 1.0, CH_2Cl_2); IR (NaCl) v 3448, 3058, 2954, 2859, 2111, 1748, 1639, 1510, 1468, 1367, 1253, 1073, 910, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.81 (m, 3H), 7.77 (s, 1H), 7.52-7.43 (m, 3H), 4.81 (dd, *J* = 10.4, 9.6 Hz, 1H), 4.74 (d, *J* = 2.0 Hz, 2H), 4.62 (d, *J* = 7.6 Hz, 1H), 3.78 (d, *J* = 4.8 Hz, 2H), 3.69 (t, *J* = 9.6 Hz, 1H), 3.53-3.46 (m, 1H), 3.35 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.10 (brs, 1H), 2.16 (s, 3H), 0.95 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.42, 171.28, 135.04, 133.13, 132.95, 128.25, 127.80, 127.65, 126.43, 126.14, 125.94, 125.48, 97.05, 75.20, 74.38, 73.77, 70.64, 69.92, 65.88, 25.52, 20.96, 17.91, -4.33, -5.29.; HRMS (ESI+, M+Na$^+$) calcd for $C_{25}H_{35}N_3O_6SiNa$ 524.2193, found 524.2198.

3-*O*-Acetyl-2-azido-6-*O*-(4-boromobenzyl)-2-deoxyl-1-*O*-*tert*-butyl-dimethylsilyl-β-D-glucopyranoside (6a5)

Prepared according to the general procedure discussed above: colorless oil. (90 mg, 45% in 3 steps); R_f 0.22 (EtOAc /Hex=1/2); $[\alpha]^{25}_D$ +1.2 (*c* 1.0, CH_2Cl_2); IR (NaCl) v 3459, 2928, 2861, 2111, 1715, 1646, 1385, 1228, 1087, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.76 (dd, *J* = 10.4, 9.2 Hz, 1H), 4.59 (d, *J* = 7.6 Hz, 1H), 4.53 (s, 2H), 3.73 (d, *J* = 4.4 Hz, 2H), 3.69-3.63 (m, 1H), 3.50-3.44 (m, 1H), 3.35 (dd, *J* = 10.4, 7.6 Hz, 1H), 2.89 (brs, 1H), 2.17 (s, 3H), 0.93 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.7, 131.5, 129.1, 121.5, 97.0, 92.9, 75.4, 74.6, 72.8, 70.3, 69.8, 65.9, 61.4, 25.5, 20.9, 17.9, -0.3, -4.4, -5.3; HRMS (ESI+, M+Na$^+$) calcd for $C_{21}H_{32}N_3O_6SiBrNa$ 552.141, found 552.1139.

3-*O*-Acetyl-6-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-gluco-pyranoside (6b1)

Prepared according to the general procedure discussed above: white solid. (100 mg, 58% in 3 steps); R_f 0.38 (EtOAc /Hex=1/1); mp 54-56 °C; $[\alpha]^{23}_D$ +17.0 (*c* 1.0, CH_2Cl_2); IR (NaCl) v 3478, 3030, 2922, 2855, 1750, 1494, 1430, 1369 cm^{-1}.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.84 (m, 2H), 7.77-7.72 (m, 2H), 7.40-7.31 (m, 5H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 5.68-5.61 (m, 2H), 4.60 (q, *J* = 11.8 Hz, 2H), 4.26 (t, *J* = 10.4 Hz, 1H), 3.88-3.72 (m, 4H), 2.91 (s, 1H), 2.29 (s, 3H), 1.91 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 167.8, 167.3, 138.4, 137.7, 134.3, 134.1, 133.5, 131.6, 131.2, 129.6, 128.4, 127.8, 127.7, 127.5, 123.6, 123.5, 83.2, 78.3, 74.3, 73.7, 71.0, 70.2, 53.6, 52.6, 21.1, 20.7, 20.5, 13.9.; HRMS(ESI, M+Na$^+$) calcd for $C_{30}H_{29}NO_7SNa$ 570.1562, found 570.1561.

3-*O*-Acetyl-2-deoxyl-6-*O*-(2-naphthylmethyl)-2-phthalimido-1-thio-β-D-glucopy-ranoside (6b2)

Prepared according to the general procedure discussed above: white solid. (77 mg, 41% in 3 steps); R_f 0.39 (EtOAc /Hex=1/1); mp 71-72 °C; $[\alpha]^{24}_D$ +12.6 (*c* 0.5, CH_2Cl_2); IR (NaCl) v 3473, 3056, 2920, 1716, 1358, 1231, 1076 cm^{-1}.; ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.88-7.72 (m, 8H), 7.52-7.44 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.70-5.62 (m, 2H), 4.77 (q, *J* = 12.0 Hz, 2H), 4.28 (t, *J* = 10.4 Hz, 1H), 3.94-3.74 (m, 4H), 2.93 (brs, 1H), 2.25 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 167.8, 167.3, 138.4, 135.1, 134.4, 134.2, 133.5, 133.2, 133.0, 131.6, 131.2, 129.6, 128.3, 127.9, 127.7, 127.5, 126.6, 126.2, 126.0, 125.6, 123.7, 123.6, 83.3, 78.3, 74.4, 73.8, 71.1, 70.2, 53.6, 21.1, 20.7; HRMS (ESI+, M+Na$^+$) calcd for $C_{34}H_{31}N_3O_7SNa$ 620.1719, found 620.1726.

3-*O*-Acetyl-6-*O*-(4-boromobenzyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (6b3)

Prepared according to the general procedure discussed above: whait solid. (86 mg, 46% in 3 steps); R_f 0.18 (EtOAc /Hex=1/2); mp 105-106 °C; $[\alpha]^{23}_D$ +13.3 (*c* 1.0, CH_2Cl_2); IR (NaCl) v 3444, 2927, 1715, 1645, 1385, 1231, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.84 (m, 2H), 7.77-7.70 (m, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 5.71-5.58 (m, 2H), 4.55 (d, *J* = 4.8 Hz, 1H), 4.27 (t, *J* = 10.4 Hz, 1H), 3.86 -3.82 (m, 2H), 3.81-3.71 (m, 2H), 2.82 (brs, 1H), 2.29 (s, 3H), 1.91 (s, 3H).; ^{13}C NMR (101 MHz, cd$_3$od) δ 171.24, 167.86, 167.21, 138.32, 136.90, 134.35, 134.19, 133.30, 131.46, 131.13, 129.60, 129.25, 127.54, 123.58, 121.52, 83.12, 78.71, 74.40, 72.81, 70.58, 69.96, 53.60, 21.11, 20.64.; HRMS (ESI+, M+Na$^+$) calcd for $C_{30}H_{28}N_3O_7SNa$ 648.0668, found 648.0675.

General procedure for one-pot region-selective *O*-6 ring opening reactions. (Table 4)

Method A: To the solution of **3** (200 mg, 1.0 equiv.) in dichloromethane (2.0mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve were added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. After the mixture was add trimethylsilyl trifluoromethane-sulfonate (0.2 equiv. for **7a1-7a2, 7a4-7a5** and 0.15 equiv. for **7b1-7b3**) and stirred for 2 hours at 0 ˚C. To a solution of the residue was added acetic anhydride (1.2 equiv. for **7a1-7a2**, **7a4-7a5** and **7b1-7b3**) and TMSOTf (0.3 equiv. for **7a1-7a2**, **7a4-7a5** and 0.4 equiv. for **7a1-7b3**). Then the reaction stirred for reaction times (2 hours for **7a1**, **7a4-7a5**, **7b1-7b3** and 6 hours for **7a2**) at 0 °C, the residue was added borane tetrahydrofuran complex solution 1.0 M in THF (5.0 equiv.) and trimethylsilyl trifluoromethane-sulfonate (0.4 equiv. for **7a2**, 0.5 equiv. for **7a1, 7a3-7a5** and 0.6 equiv. for **7b1-7b3**) under 0 ˚C and stirred for 12 hours. The reaction quenched by methanol and concentrated. After completion, the mixture was diluted with ethyl acetate (20 mL) and filtered through celite pad , then extracted with water (20 mL×3). The combined organic layer was dried over with anhydrous $MgSO_4$, filtered and concentrated. The crude is purified with column chromatography to afford the product **7a1-7a2** and **7a4-7b3.**

Method B: To the solution of **3a** (200 mg, 1.0 equiv.) in dichloromethane (2.0mL), aromatic aldehydes (1.05 equiv.) and 4 Å molecular sieve were added under nitrogen atmosphere. The reaction was stirred under 0 ˚C for 1 hour. After the mixture was add trimethylsilyl trifluoromethane-sulfonate (0.2 equiv.) and stirred for 2 hours at 0 ˚C. To a solution of the residue was added triethylsilane (1.1 equiv.), benzaldehyde (1.2 equiv.) and trimethylsilyl trifluoro-methanesulfonate (0.18 equiv.). Then the reaction stirred for 6 hours at 0 °C, the residue was added borane tetrahydrofuran complex solution 1.0 M in THF (5.0 equiv) and trimethylsilyl trifluoromethanesulfonate (0.5 equiv.) under 0 ˚C and stirred for 12 hours. The reaction quenched by methanol and concentrated. After completion, the mixture was diluted with ethyl acetate (20 mL) and filtered through celite pad , then extracted with water (20 mL×3). The combined organic layer was dried over with anhydrous $MgSO_4$, filtered and concentrated. The crude is purified with column chromatography to afford the product **7a3.**

3-*O*-Acetyl-2-azido-4-*O*-benzyl-2-deoxyl-1-*O*-*tert*-butyldime-thylsilyl-β-D-glucopyranoside (7a1)

Prepared according to the general procedure discussed above: white solid. (148 mg, 87%); R_f 0.32 (EtOAc /Hexane = 1/9); mp 132-134 °C; $[\alpha]^{25}_D$ -87.80 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3793, 2960, 2930, 2860, 2115, 1725, 1400, 1362, 1322, 1254, 1163, 1101, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 3H), 7.26 (d, *J* = 1.6 Hz, 1H, Ar-H), 7.24 (brs, 1H, Ar-H), 5.03 (dd, *J* = 9.2, 10.4 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 4.60 (d, *J* = 3.6 Hz, 2H), 3.88-3.83 (m, 1H), 3.75-3.61 (m, 1H), 3.63 (t, *J* = 9.6 Hz, 1H), 3.42-3.38 (m, 1H), 3.29 (dd, *J* = 7.6, 10.4 Hz, 1H), 3.29 (dd, *J* = 7.6, 10.4 Hz, 1H) 2.02 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 137.4, 128.5, 128.0, 97.0, 75.4, 75.3, 74.6, 73.7, 66.6, 61.6, 25.5, 20.9, 17.9, -4.4, -5.2; HRMS (ESI, M+Na$^+$) calcd for $C_{21}H_{33}N_3O_6SiNa$ 474.2036, found 474.2027.

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2-Azido-4-*O*-benzyl-2-deoxyl-3-*O*-pivaloyl-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (7a2)

Prepared according to the general procedure discussed above: colorless oil. (139 mg,75%); R_f 0.38 (EtOAc /Hex=1/8); $[\alpha]^{25}_D$ -28.2 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3455, 2959, 2932, 2860, 2112, 1739, 1643, 1461, 1396, 1154, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 3H), 7.26-7.22 (m, 2H), 5.13-5.04 (m, 1H), 4.67-4.54 (m, 3H), 3.84 (ddd, *J* = 12.0, 5.2, 2.8 Hz, 1H), 3.74-3.64 (m, 2H), 3.45-3.40 (m, 1H), 3.31 (dd, *J* = 10.4, 7.6 Hz, 1H), 1.24 (s, 9H), 0.93 (s, 3H), 0.16 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 137.4, 128.4, 127.9, 127.5, 96.9, 75.5, 75.2, 74.5, 73.7, 67.2, 61.6, 38.9, 27.1, 25.5, 17.9, -4.4, -5.2; HRMS (ESI+, M+Na^+) calcd for $C_{24}H_{35}N_3O_6SiNa$ 516.2506, found 216.2513.

2-Azido-2-deoxyl-3,4-*O*-dibenzyl-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (7a3)

Prepared according to the general procedure discussed above: colorless oil. (115 mg, 61%) R_f 0.45 (EtOAc/Hex = 1/5); $[\alpha]^{23}_D$ -22.7 (*c* 0.01, CH_2Cl_2); IR (NaCl) *v* 3445, 2957, 2930, 2859, 2110, 1645, 1456, 1256, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.37 (m, 10H), 4.79-4.91 (m, 3H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 7.6 Hz, 1H), 3.83 (dd, *J* = 12.0, 2.8 Hz, 1H), 3.69 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.56 (t, *J* = 9.2 Hz, 1H), 3.42 (t, *J* = 10.0 Hz, 1H), 3.29-3.36 (m, 2H), 0.94 – 0.92 (m, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 137.8, 128.5, 128.5, 128.0, 128.0, 127.9, 97.1, 82.8, 75.5, 75.3, 75.0, 68.7, 62.0, 52.4, 25.6, 18.0, 8.6, -4.2, -5.1.

2-Azido-2-deoxyl-4-*O*-(2-naphthylmethyl)-3-*O*-pivaloyl-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (7a4)

Prepared according to the general procedure discussed above: white solid. (113 mg, 62%); R_f 0.26 (EtOAc /Hex=1/8); mp 155-156 °C; $[\alpha]^{25}_D$ -39.4 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3476, 2961, 2857, 2113, 1725, 1644, 1463, 1253, 1043, 842 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.78 (m, 2H), 7.72 (brs, 1H), 7.52-7.45 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 5.07 (t, *J* = 10.0 Hz, 1H), 4.77 (q, *J* = 11.6 Hz, 2H), 4.66 (d, *J* = 7.6 Hz, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.80-3.67 (m, 2H), 3.46-3.40 (m, 1H), 3.30 (dd, *J* = 10.4, 7.6 Hz, 1H), 1.97 (s, 3H), 0.94 (s, 9H), 0.170 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.88, 134.83, 133.11, 132.96, 128.30, 127.89, 127.63, 126.76, 126.22, 126.09, 125.76, 125.38, 96.97, 75.39, 75.28, 74.65, 73.68, 66.58, 61.58, 25.49, 20.91, 17.88, -4.30, -4.39, -5.22.; HRMS (ESI+, M+Na^+) calcd for $C_{25}H_{35}N_3O_6SiNa$ 524.2193 found 524.2190.

3-*O*-Acetyl-2-azido-4-*O*-(4-boromobenzyl)-2-deoxyl-1-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (7a5)

Prepared according to the general procedure discussed above: white solid. (82 mg, 44%) R_f 0.63 (EtOAc/Hex = 1/3); mp 120-121 °C; $[\alpha]^{23}_D$ -39.7 (*c* 0.01, CH_2Cl_2); IR (NaCl) *v* 3477, 2930, 2859, 2116, 1724, 1644, 1487, 1259, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.37 (m, 10H), 4.99 (t, *J* = 9.6 Hz, 1H), 4.49-4.63 (m, 3H), 3.84 (d, *J* = 12.0 Hz, 1H), 3.76-3.68 (m, 1H), 3.61 (t, *J* = 9.6 Hz, 1H), 3.35 (dt, *J* = 9.6, 2.8 Hz, 1H), 3.23 (dd, *J* = 7.6 Hz, 1H), 2.01 (s, 1H), 0.91 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 136.5, 131.6, 129.4, 128.5, 121.9, 96.9, 75.5, 75.2, 73.7, 73.6, 66.5, 61.5, 25.5, 20.9, 17.9, -4.4, -5.2. HRMS (ESI+, M+Na^+) calcd for $C_{21}H_{32}N_3O_6SiBrNa$ 552.141, found 552.1143.

3-*O*-Acetyl-4-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (7b1)

Prepared according to the general procedure discussed above: white solid. (80 mg, 45% in 3 steps); R_f 0.35 (EtOAc /Hexane = 1/2); mp 140-141 °C; $[\alpha]^{25}_D$ +44.1 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3474, 3063, 2925, 2874, 1716, 1648, 1384, 1227, 1087, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.82 (m, 2H), 7.72 (dd, *J* = 5.2, 2.4 Hz, 2H), 7.33-7.21 (m, 6H), 7.06 (d, *J* = 8.0 Hz, 1H), 5.77 (dd, *J* = 10.0, 9.2 Hz, 1H), 5.69 (d, *J* = 10.4 Hz, 1H), 4.62 (q, *J* = 11.6 Hz, 2H), 4.19 (t, *J* = 10.4 Hz, 1H), 3.93 (d, *J* = 12.0 Hz, 1H), 3.71 (d, *J* = 9.6 Hz, 2H), 3.64-3.59 (m, 1H), 2.30 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.1, 167.8, 167.3, 138.6, 137.6, 134.4, 134.1, 133.6, 131.7, 131.2 129.7, 128.5, 127.9, 127.7, 127.2, 123.7, 123.5, 83.0, 79.3, 76.0, 74.7, 73.9, 61.7, 54.2, 21.1, 20.5; HRMS (ESI+, M+Na^+) calcd for $C_{30}H_{29}NO_7SNa$ 570.1562, found 570.1567.

2-Deoxyl-4-*O*-(2-naphthylmethyl)-2-phthalimido-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside (7a2)

Prepared according to the general procedure discussed above: white solid. (77 mg, 41% in 3 steps); R_f 0.25 (EtOAc /Hexane = 1/2); mp 80-81 °C; $[\alpha]^{24}_D$ +42.7 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3477, 3056,2923, 2873, 1716, 1384, 1227, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.69 (m, 8H), 7.49-7.42 (m, 2H), 7.35 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.84 (dd, *J* = 10.4, 9.2 Hz, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 4.81 (q, *J* = 12.0 Hz, 2H), 4.23 (t, *J* = 10.4 Hz, 1H), 3.98 (d, *J* = 11.6 Hz, 1H), 3.81 (m, 2H), 3.72-3.64 (m, 1H), 2.31 (s, 3H), 1.98 (bs, 1H) 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 138.7, 135.1, 134.4, 134.1, 133.6, 133.1, 132.9, 131.7, 131.2, 129.8, 128.2, 127.9, 127.6, 127.2, 126.4, 126.2, 126.0, 125.5, 123.7, 123.5, 83.0, 79.3, 76.1, 74.8, 73.9, 61.8, 54.2, 21.2, 20.5.; HRMS (ESI+, M+Na^+) calcd for $C34H_{31}N_1O_7SNa$ 620.1719, found 620.1749.

3-*O*-Acetyl-6-*O*-(4-boromobenzyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (7b3)

Prepared according to the general procedure discussed above: white solid. (60 mg, 30% in 3 steps); R_f 0.34 (EtOAc/Hexane = 1/2); mp 51-53 °C; $[\alpha]^{21}_D$ +21.75 (*c* 0.8, CH_2Cl_2); IR (NaCl) *v* 3476, 2926, 2870, 1717, 1491, 1385, 1228, 1089, 964 cm^{-1}; ^1H NMR (400 MHz, $cdcl_3$) δ 7.86 (dd, *J* = 4.4, 2.4 Hz, 2H), 7.74 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H) 5.78 (dd, *J* = 10.0, 9.2 Hz, 1H), 5.71 (d, *J* = 10.8 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H) 4.21 (t, *J* = 10.4 Hz, 1H), 3.96 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.74 (t, *J* = 9.6 Hz, 1H), 3.66-3.60 (m, 1H), 2.31 (s, 2H), 1.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.7, 136.7, 134.4, 134.1, 133.6, 131.6, 129.8, 129.2, 127.1, 123.7, 123.6, 123.5, 83.0, 82.8, 79.6, 79.1, 76.1, 73.9, 73.8, 73.4, 61.7, 61.6, 54.2, 22.7, 22.5, 21.2, 20.6, 20.5; HRMS (ESI, M+Na^+) calcd for $C_{30}H_{28}BrNO_7SNa$ 648.0668, found 648.0667.

3-*O*-Acetyl-4,6-*O*-benzylidene-2-phthalimido-2-deoxy-β-D-glucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-acetyl-6-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-glucopyranoside (10)

To the solution of acceptor **6a1** (105 mg, 0.23 mmol) and donor **5b1** (152 mg, 0.28 mmol) in dichloro-methane (1.0 mL), 4 Å molecular sieve (200 mg) was added under nitrogen atmosphere. The resulting solution was stirred for 30 min and cooled to -30 °C. *N*-iodo-succinimide (73 mg, 0.33 mmol) was added under nitrogen atmosphere followed by addition of trimethylsilyl tri-fluoromethanesulfonate (4 µL, 0.023 mmol) and stirred for 1 hour at -30 °C. After completion, reaction mixture was neutralized by triethylamine and filtered through celite pad, then removed solvent under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford product **10** (168 mg, 83%) as white solid. R_f 0.42 (EtOAc/Hex = 4/7); mp 81-83 °C; IR (NaCl); $[\alpha]^{25}_D$ -8.99 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 3417. 2111, 1748, 1718, 1644, 1384, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.8, 2.6 Hz, 2H), 7.70 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.45-7.41 (m, 2H), 7.37-7.33 (m, 3H), 7.32-7.25 (m, 3H), 7.21-7.17 (m, 2H), 5.84 (dd, *J* = 10.0, 9.2 Hz, 1H), 5.51-5.47 (m, 2H), 4.90 (dd, *J* = 10.4, 9.2 Hz, 1H), 4.47 (d, *J* = 7.6 Hz, 1H), 4.40-4.35 (m, 2H), 4.27 (d, *J* = 12 Hz, 1H), 4.21 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.93 (t, *J* = 9.6 Hz, 1H), 3.79-3.69 (m, 2H), 3.64-3.56 (m, 1H), 3.35-3.30 (m, 1H), 3.31-3.23 (m, 3H), 2.15 (s, 3H), 1.86 (s, 3H), 0.88 (s, 9H), 0.060 (s, 3H), 0.057 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.3, 137.9, 136.7, 134.3, 131.3, 129.2, 128.2, 128.2, 127.5, 127.3, 126.2, 123.5, 101.6, 98.3, 96.9, 79.0, 74.7, 74.4, 72.8, 72.6, 69.7, 68.7, 67.4, 66.4, 65.9, 55.6, 25.5, 21.3, 20.5, 17.9, -4.5, -5.3; HRMS (ESI, M+Na^+) calcd for $C_{44}H_{52}N_4O_{13}SiNa$ 895.3198, found 895.3188.

3-*O*-Acetyl-4-hydroxyl,6-*O*-benzyl-2-phthalimido-2-deoxy-β-D-glucopyranosyl-(1→4')-2'-azido-2'-deoxy-3'-*O*-acetyl-6'-*O*-benzyl-1'-*O*-*tert*-butyldimethylsilyl-D-glucopyranoside (11)

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To the solution of compound **10** (870 mg, 0.997 mmol) in dry dichloromethane (20.0 mL), triethylsilane (250 µL, 10.97 mmol) and boron trifluoride etherate (250 µL, 1.99 mmol) was added at 0 °C under nitrogen. The reaction was allowed to warm and further stirred at 20 °C for 3 hours. After completion, the reaction was quenched by $NaHCO_3$ solution and water work up was carried out. The solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel to afford product **11** (575 mg, 66%) as white solid. R_f 0.35 (EtOAc/Hex = 2/3); mp 72-73 °C; $[\alpha]^{25}_D$ -34.5 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v* 3425, 2958, 2862, 2111, 1714, 1640, 1496, 1469, 1386 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.81 (m, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.39-7.27 (m, 10H), 5.59 (dd, *J* = 10.6, 8.9 Hz, 1H), 5.39 (d, *J* = 8.3 Hz, 1H), 4.89 – 4.83 (m, 1H), 4.62-4.56 (m, 2H), 4.52 (d, *J* = 13.3 Hz, 1H), 4.48-4.43 (m, 2H), 4.37 (d, *J* = 12.3 Hz, 1H), 4.10 (dd, *J* = 10.7, 8.4 Hz, 1H), 3.96 (t, *J* = 9.6 Hz, 1H), 3.85-3.81 (m, 1H), 3.81-3.77 (m, 1H), 3.73 (dd, *J* = 10.1, 4.7 Hz, 1H), 3.40 (d, *J* = 9.9 Hz, 1H), 3.36-3.31 (m, 1H), 3.27 (dd, *J* = 10.4, 7.7 Hz, 2H), 2.90 (d, *J* = 3.3 Hz, 1H), 2.06 (s, 3H), 1.90 (s, 3H), 0.88 (s, 9H), 0.07 (3H), 0.06 (3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 170.1, 138.3, 137.7, 134.7, 134.3, 131.7, 128.3, 128.2, 128.1, 127.9, 127.8, 127.5, 123.9, 123.6, 97.5, 97.3, 76.1, 73.8, 73.3, 72.9, 72.5, 71.5, 71.3, 70.4, 70.1, 69.9, 67.8, 66.7, 55.3, 55.0, 26.7, 26.2, 21.0, 18.1, -4.1, -4.6; HRMS (ESI, M+Na^+) calcd for $C_{44}H_{54}N_4O_{13}SiNa$ 897.3354, found 897.3353.

3-*O*-Acetyl-4,6-*O*-benzylidene-2-phthalimido-(1→4')-β-D-gluco-pyranosyl-3'-*O*-acetyl,6'-*O*-benzyl-2'-phthal-imido-2'-deoxy-β-D-glucopyranosyl-(1→4'')-2''-azido-deoxy-3''-*O*-acetyl-6-*O''*-benzyl-1-*O''-tert*-butyldimeth-ylsilyl-D-glucopy-ranoside (12)

A suspension of the acceptor **11** (40 mg, 0.045 mmol), donor **5b1** (29 mg, 0.054 mmol) and 4 Å molecular sieves (100 mg) in dichloromethane (2.5 mL) was stirred at room temperature under a nitrogen atmosphere for 60 min. Reaction mixture was cooled to -30 °C and *N*-iodosuccinimide (14 mg, 0.064 mmol) was added slowly followed by trimethylsilyl trifluoromethane-sulfonate (1.0 µL, 0.004 mmol). Reaction mixture was stirred for 2 h at the same temperature. After completion, reaction mixture was filtered through celite pad, filtrate was treated with $Na_2S_2O_3$ and $NaHCO_3$. Organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **12** (51 mg, 86%) as white solid. R_f 0.44 (EtOAc/Hex = 2/3); mp 119-120 °C; $[\alpha]^{25}_D$ -42.6 (*c* 0.1, CH_2Cl_2); IR (NaCl) *v 3425,* 2111, 1716, 1641, 1386, 1226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.3, 3.2 Hz, 4H), 7.70 (dd, *J* = 5.6, 3.0 Hz, 4H), 7.44-7.40 (m, 2H), 7.34 (dd, *J* = 2.6 Hz, 5H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.24 (d, *J* = 4.0 Hz, 3H), 7.20 (d, *J* = 7.8 Hz, 3H), 7.09 (t, *J* = 7.3 Hz, 1H), 5.79 (d, *J* = 9.6 Hz, 1H), 5.62 (dd, *J* = 10.5, 8.7 Hz, 1H), 5.52 (d, *J* = 8.4 Hz, 1H), 5.46 (s, 1H), 5.27 (d, *J* = 8.4 Hz, 1H), 4.82 (t, *J* = 8.0 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.43-4.39 (m, 1H), 4.30-4.26 (m, 3H), 4.18 (dd, *J* = 10.3, 8.3 Hz, 1H), 4.13 (t, *J* = 8.0 Hz, 1H), 4.01 (dd, *J* = 10.6, 8.4 Hz, 1H), 3.92 (t, *J* = 9.6 Hz, 1H), 3.70 – 3.64 (m, 2H), 3.42 (d, *J* = 10.0 Hz, 3H), 3.35-3.30 (m, 2H), 3.26-3.19 (m, 3H), 1.93 (s, 3H), 1.90 (s, 3H), 1.85 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 170.1, 170.0, 138.3, 138.1, 137.0, 134.8, 134.3, 131.7, 128.7, 128.5, 128.3, 127.9, 127.5, 126.7, 126.2, 124.0, 123.6, 115.0, 102.7, 101.8, 98.6, 97.9, 97.3, 97.1, 96.5, 79.4, 79.8, 74.9, 74.6, 74.2, 72.9, 72.8, 72.3, 71.9, 70.0, 69.8, 68.8, 68.0, 67.8, 66.5, 66.3, 66.0, 56.0, 55.8, 55.6, 55.4, 26.1, 25.9, 25.6, 25.4, 21.2, 21.0, 20.7, 18.1, -4.2, -5.1; HRMS (ESI, M+Na^+) calcd for $C_{67}H_{73}N_5O_{20}SiNa$ 1318.4516, found 1318.4507.

2-Azido-4,6-*O*-benzylidene-1-*O-tert*-butyldimethylsiyl-2-de-oxy-3-*O*-(2-naphtha-lenylmethyl)-D-glucopyranoside (5a7)

To a solution of **4a1** (1.0 g, 0.73 mmol) in dry tetra-hydrofuran/DMF 7/3 (10 mL) were added 2-(bromomethyl)-naphthalene (2.17 g, 9.79 mmol) and portion-wise addition (65 mg × 3) of the sodium hydride (195 mg, 4.90 mmol) over 1 hour at 0 °C under nitrogen atmosphere. After stirring for 2 hours, the mixture was diluted with water and extracted with dichloromethane (25 mL × 3). The organic layer was dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford product **5a7** (1.23 g, 91%) as white solid. R_f 0.71 (EtOAc/Hexane = 1/9); mp 90-92 °C; $[\alpha]^{25}_D$ -116.90 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3058, 2930, 2869, 2110, 1485, 1374, 1275, 1257, 1177, 1097, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.80 (m, 3H, Ar-H), 7.77-7.71 (m, 1H, Ar-H), 7.55-7.44 (m, 5H, Ar-H), 7.41-7.39 (m, 3H, Ar-H), 5.59 (s, 1H), 5.01 (q, *J* = 11.6 Hz, 2H), 4.59 (d, *J* = 7.6 Hz, 1H), 4.30 (dd, *J* = 5.2, 10.8 Hz, 1H), 3.81 (t, *J* = 10 Hz, 1H), 3.75 (t, *J* = 9.2 Hz, 1H), 3.57 (t, *J* = 9.6 Hz, 1H), 3.44-3.337 (m, 2H), 0.93 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 135.0, 132.8, 132.6, 128.8, 127.9 (2), 127.7, 127.5, 127.2, 126.5, 125.7 (2), 125.6, 125.4, 101.0, 97.0, 81.2, 78.2, 14.3, 68.4, 68.2, 65.9, 25.1 (4), 17.5, -4.7, -5.5; HRMS (ESI, M+Na^+) calcd for $C_{30}H_{37}N_3O_5SiNa$ 570.2400 found 570.2400.

2-Azido-4-*O*-benzyl-1-*O-tert*-butyldimethylsiyl-2-deoxy-3-*O*-(2-naphthalenylme-thyl)-D-glucopyranoside (7a6)

To a solution of **5a7** (2.0 g, 3.65 mmol) in dichloro-methane (20 mL), boron trifluoride tetra-hydrofuran complex 1 M solution (18.27 mL, 18.27 mmol) and TMSOTf (0.27 mL, 1.46 mmol) was added slowly over 5 minutes at 0 °C under nitrogen atmosphere. After stirring for 6 hours at 0 °C, the reaction was quenched by methanol and concentrated. After completion, the mixture was diluted with dichloromethane (20 x3) and extracted with water. The combined organic layer was dried over with anhydrous $MgSO_4$, filtered and concentrated. The crude is purified with column chromatography to afford the product **7a6** (1.70 g, 85%) as a white solid. R_f0.71 (EA/Hexane = 3/7); mp 64-66 °C; $[\alpha]^{25}_D$ -34.20 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3591, 3504, 3060, 3032, 2955, 2930, 2884, 2858, 1209, 1510, 1462, 1257 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 4H, Ar-H), 7.52-7.41 (m, 3H, Ar-H), 7.34-7.26 (m, 5H, Ar-H), 5.02 (q, *J* = 10.8 Hz, 2H), 6.88 (d, *J* = 11.2 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.58 (d, *J* = 7.6 Hz, 1H), 3.88-3.83 (m, 1H), 3.74-3.71 (m, 1H), 3.61 (t, *J* = 9.2 Hz, 1H), 3.48 (t, *J* = 10 Hz, 1H), 3.37 (t, *J* = 8 Hz, 2H), 0.96 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.3, 133.2, 132.9, 128.4 (2), 128.1, 127.9 (2) 127.8 (2), 127.6, 126.7, 126.0, 125.9 (2), 96.9, 82.4, 77.4, 75.4, 75.2, 75.0, 68.5, 61.9, 25.5 (3), 17.8, -4.1, -5.2; HRMS (ESI, M+Na^+) calcd for $C_{30}H_{39}N_3O_5SiNa$ 572.2556 found 572.2549.

(*R*)-3-(Dodecanoyloxy)tetradecanoic acid (20)

To the round bottom flask (20 mL) charged with lauric acid **17** (2.7 g, 13.48 mmol) under nitrogen atmosphere, thionyl chloride ($SOCl_2$) (2.0 mL, 26.96 mmol) was added. The reaction mixture was placed into preheated oil bath at 60 °C. After 5 minutes the nitrogen balloon was changed, due to hydrogen chloride gas released in the reaction, this process was continued until there is no more hydrogen chloride gas evolved from the reaction. Excess thionyl chloride was removed under reduced pressure and dried over high vacuum for overnight. The residue is used in next step without further purification. To a solution of **19** (2.68 g, 12.28 mmol) in dichloromethane, (*R*)-3-hydroxy myristic acid **16** (2.0 g, 8.18 mmol) was added at room temperature under nitrogen atmosphere. The reaction mixture was placed into preheated oil bath at 40 °C. After 5 minutes the nitrogen balloon was changed, due to hydrogen chloride gas released in the reaction, this process was continued until there is no more hydrogen chloride gas evolved from the reaction. After completion of the reaction, the solution was extracted with dichloromethane (30 x 4). The organic portion was treated with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The resulting residue was chromatographed on silica gel to afford product **20** (3.43 g, 94%) as colourless oil. R_f0.40 (EA/Hexane = 3/7); $[\alpha]^{25}_D$ -34.20 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 2925, 2856, 1740, 1715, 1465, 1377, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (quintet, *J* = 5.6 Hz, 1H), 2.65-2.54 (m, 2H), 2.27 (t, *J* = 7.2 Hz, 2H), 1.61-1.58 (m, 4H), 1.25 (s, 34H), 0.87 (t, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 173.2, 69.9, 38.8, 34.4, 33.9, 31.8, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 25.0, 24.9, 22.6, 14.0; HRMS (ESI, M+Na^+) calcd for $C_{26}H_{50}O_4Na$ 449.6718, found 449.6711.

3-*O*-acetyl-4,6-*O*-benzylidene-1-*O-tert*-butyldimethyl-silyl-2-deoxy-2-phthalimi-do-β-D-glucopyranosyl-(1→6)-4-*O*-benzyl-2-deoxy-2-azido-3-*O*-(2-naphthalenyl-methyl)-β-D-glucopyra-noside (18)

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To a solution of donor **5b1** (1.09 g, 0.20 mmol), activated 4 Å molecular sieves (700 mg) in dry dichloromethane (10 mL), were added a solution of acceptor **7a6** (1.0 g, 1.82 mmol) and *N*-iodosuccinimide (470 mg, 2.09 mmol) in dry dichloromethane (15 mL) stirred for 1 hour at room temperature. TfOH (0.47 mL, 0.55 mmol) was added slowly dropwise over 5 minutes to the reaction mixture and stirred for 16 hours at 0 ºC. The reaction was quenched by trimethylamine, filtered through celite pad and extracted with dichloromethane (30 mL x 3) and saturated sodium thiosulfate solution. The organic layer was treated with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chroma-tography on silica gel to afford product **18** (1.22 g, 70%) as a white solid. *Rf* 0.59 (EtOAc/Hexane = 1/4); mp 92-94 ºC; $[\alpha]^{25}_D$ -92.47 (*c* 1.0 , CH_2Cl_2); IR (NaCl) *v* 3414, 2106, 1748, 1718, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86-7.76 (m, 3H, Ar-H), 7.75-7.72 (m, 3H, Ar-H), 7.60-7.58 (m, 2H, Ar-H), 7.51-7.45 (m, 5H, Ar-H), 7.39-7.38 (m, 3H, Ar-H), 7.28-7.20 (m, 3H, Ar-H), 7.03 (d, J = 6.0 Hz, 2H, Ar-H), 5.87 (t, *J* = 10.0 Hz, 1H), 5.57 (s, 1H, PhCH), 5.53 (d, *J* = 8.4, 1H), 5.00 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.60 (d, J = 10.8 Hz, 1H), 4.48 (d, *J* = 7.2 Hz, 1H), 4.41-4.36 (m, 2H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.05 (d, *J* = 10.0 Hz, 1H), 3.88-3.79 (m, 2H), 3.77-3.69 (m, 2H), 3.46-3.42 (m, 1H), 3.39-3.36 (m, 2H), 3.34-3.25 (m, 2H), 1.90 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 137.4, 136.8, 135.3, 134.0, 133.1, 132.8, 131.1, 130.7, 129.9, 129.01, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.5, 126.5, 126.1, 125.9, 125.9, 125.8, 123.3, 101.5, 98.0, 96.9, 82.4, 79.0, 77.5, 75.2, 74.7, 74.1, 69.8, 68.5, 68.3, 67.9, 66.1, 55.0, 30.7, 25.4, 20.4, 17.7, -4.4, -5.6; HRMS (ESI, M+Na+) calcd for $C_{53}H_{58}N_4O_{12}SiNa$ 993.3718, found 993.3707.

1-*O*-*tert*-butyldimethylsiyl-4,6-*O*-benzylidene-2-deoxy-2-[(*R*)-3-(dodecanoyloxy)-tetradecanamido]-β-D-gluco-pyranosyl-(1→6)-3-*O*-(2-naphthalenylmethyl)-4-*O*-benzyl-2-deoxy-2-azido-β-D-gluco-pyranoside (21)

To a solution of disaccharide **18** (620 mg, 0.64 mmol) in ethanol (10.0 mL), hydrazine (5.0 mL) was added at room temperature under nitrogen atmosphere, the reaction was allowed to stir at 80 ºC overnight. After completion of the reaction, it was extracted with ethyl acetate (30 mL x 3) and water. The organic layer was treated with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was dried over high vacuum for one day and used in next step without further purification. To the amine intermediate (390 mg, 0.48 mmol) in dry dichloromethane were added myristic acid derivative **20** (860 g, 1.94 mmol) and dropwise addition of *N*-(3-Dimethyl-aminopropyl)-*N*-ethylcarbodiimide (282 µL, 1.60 mmol) at 0 ºC under nitrogen atmosphere. After 20 minutes the reaction was warmed up to room temperature. After stirring for 16 hours, the mixture was diluted with dichloromethane (20 x 3) and extracted with water. The organic layer was treated with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford product **21** (415 mg, 71%) as colourless viscous liquid. *Rf* 0.57 (EtOAc/Hexane = 1/3); $[\alpha]^{25}_D$-80.50 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3289, 2926, 2855, 2109, 1731, 1714, 1650, 1554, 1465, 1378, 1258, 1174, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.76 (m, 4H, Ar-H), 7.750-7.44 (m, 5H, Ar-H), 7.37-7.29 (m, 6H, Ar-H), 7.25-7.23 (m, 2H, Ar-H), 6.26 (d, *J* = 6.0 Hz, 1H), 6.16 (d, *J* = 6.4 Hz, 1H), 5.53 (s, 1H, PhCH), 5.12-5.07 (m, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 4.86-4.82 (m, 2H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.53 (t, *J* = 5.6 Hz, 1H), 4.30-4.25 (m, 1H), 4.18 (t, *J* = 11.2 Hz, 1H), 4.02 (t, *J* = 7.2 Hz, 1H), 3.74 (t, *J* = 11.2 Hz, 1H), 3.73 (t, *J* = 10.8 Hz, 1H), 3.55-3.42 (m, 5H), 5.40-3.32 (m, 2H), 2.33-2.25 (m, 4H), 1.64-1.55 (m, 4H), 1.23 (2, 34H), 0.95 (s, 9H), 0.87 (t, *J* = 5.6 Hz, 6H), 0.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 171.2, 137.8, 137.1, 135.4, 133.2, 133.0, 129.1, 128.5, 128.19, 128.15, 127.9, 127.73, 127.70, 127.6, 126.7, 126.3, 126.1, 126.0, 125.9, 101.8, 99.8, 97.0, 82.7, 81.3, 78.0, 75.5, 74.9, 74.4, 71.4, 70.4, 68.7, 68.6, 67.6, 66.3, 59.1, 42.5, 34.5, 34.4, 33.9, 31.9, 29.6, 29.51, 29.48, 29.4, 29.31, 29.28, 29.13, 29.07, 25.6, 22.7, 17.9, 14.1, -4.1, -5.3; HRMS (ESI, M+) calcd for $C_{69}H_{102}N_4O_{12}Si$ 1206.7264, found 1207.7350.

1-*O*-*tert*-butyldimethylsiyl-4,6-*O*-benzylidene-2-deoxy-2-[(*R*)-3-(dodecanoyloxy)-tetradecanamido]-3-*O*-dodec-anoyl-β-D-gluco-pyranosyl-(1→6)-3-*O*-(2-naphtha-lenylmethyl)-4-*O*-benzyl-2-deoxy-2-azido-β-D-glucopyranoside (22)

To a solution of **19** (650 g, 0.55 mmol) in dry dichloromethane (6.0 mL), lauric acid **17** (440 mg, 2.19 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (240 µL, 1.40 mmol) and 4-dimethylaminopyridine (66 mg, 0.60 mmol) were added at 0 ºC under nitrogen atmosphere. After 10 minutes the reaction slowly warmed up to room temperature. After stirring for 16 hours, the mixture was extracted with water and dichloromethane (40 mL x 4). The organic layer was treated with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford product **22** (701 mg, 92%) as a white solid. *Rf* 0.38 (EtOAc /Hexane = 1/4); mp 96-98 ºC; $[\alpha]^{25}_D$ -107.20 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3308, 2925, 2854, 2112, 1736, 1664, 1541, 1464, 1374, 1254, 1100, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.80 (m, 2H, Ar-H), 7.79-7.76 (m, 2H, Ar-H), 7.48-7.44 (m, 3H, Ar-H), 7.43-7.39 (m, 2H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.30-7.28 (m, 2H, Ar-H), 7.25-7.23 (m, 2H, Ar-H), 6.02 (d, *J* = 9.2 Hz, 1H), 5.96 (d, *J* = 9.2 Hz, 1H), 5.48 (s, 1H, PhCH), 5.27 (q, *J* = 9.6 Hz , 1H), 5.03 (d, *J* = 11.2 Hz, 1H), 5.00-4.97 (m, 1H), 4.91 (d, *J* = 11.2 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.61 (d, *J* = 10.8 Hz, 1H), 4.53-4.50 (m, 1H), 4.30-4.23 (m, 1H), 4.05 (q, *J* =10 Hz, 1H), 3.98-3.93 (m, 2H), 3.81-3.68 (m, 3H), 3.66-3.63 (m, 1H), 3.55-3.47 (m, 2H), 3.44-3.40 (m, 2H), 3.36-3.31 (m, 1H), 2.40-2.19 (m, 6H), 1.58-1.50 (m, 6H), 1.24 (s, 50H), 0.95 (s, 9H), 0.87 (t, *J* = 6.4 Hz, 9H), 0.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 173.1, 169.2, 138.0, 136.9, 135.4, 133.1, 132.9, 128.8, 128.3, 128.02, 127.97, 127.8, 127.61, 127.56, 127.51, 126.6, 126.5, 125.9 125.7, 100.9, 97.0, 82.6, 78.8, 77.4, 75.2, 74.6, 74.4, 71.8, 71.7, 70.7, 70.5, 68.5, 66.9, 66.4, 65.8, 53.7, 53.4, 41.4, 34.4, 34.3, 34.1, 34.0, 31.8, 29.6, 29.4, 29.3, 29.3, 29.12, 29.09, 28.96, 25.5, 25.2, 25.1, 25.0, 24.9, 22.6, 17.8, 14.0, -4.1, -5.4; HRMS (ESI, M+Na^+) calcd for $C_{81}H_{124}N_4O_{13}SiNa$ 1411.8831, found 1411.8835.

1-*O*-*tert*-butyldimethylsiyl-4,6-*O*-benzylidene-2-deoxy-2-[(*R*)-3-(dodecanoyloxy)-tetradecanamido]-3-*O*-dodec-anoyl-β-D-gluco-pyranosyl-(1→6)-4-*O*-benzyl-2-deoxy-2-azido-β-D-glucopyranoside (23)

To a solution of **22** (340 mg, 0.24 mmol) in a mixture of CH_2Cl_2/H_2O (9:1) (5.0 mL) solvent, 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone (76 mg, 0.34 mmol) was added at room temperature under nitrogen atmosphere and stirred for 4 hours, the mixture was diluted by dichloromethane and extracted with aqueous 10% sodium hydroxide solution, then the organic layer was washed with brine solution and treated with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford product **23** (284 mg, 94%) as a white solid. *Rf* 0.27 (EtOAc /Hexane = 1.5/3.5); mp = 108-110 ºC; $[\alpha]^{25}_D$-32.70 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3308, 3365, 2925, 2855, 2114, 1737, 1665, 1542, 1464, 1375, 1257, 1181, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.74 (m, 2H, Ar-H), 7.37-7.27 (m, 8H, Ar-H), 6.11 (d, *J* = 9.2 Hz, 1H), 5.98 (d, *J* = 9.2 Hz, 1H), 5.48 (s, 1H, PhCH), 5.31-5.23 (m, 1H), 5.04-4.97 (m, 1H), 4.81 (d, *J* = 4.4 Hz, 1H), 4.79 (d, *J* = 4.8 Hz, 1H), 4.65 (dd, *J* =11.2, 7.6 Hz, 1H), 4.58 (t, *J* = 8.0 Hz, 1H), 4.52-4.49 (m, 1H), 4.30-4.25 (m, 1H), 4.06-4.02 (m, 2H), 3.96-3.92 (m, 1H), 3.76-3.71 (m, 2H), 3.66 (t, *J* = 10.0 Hz, 1H), 3.53-3.48 (m, 1H), 3.45-3.43 (m, 2H), 3.39-3.37 (m, 1H), 3.23-3.18 (m, 1H), 2.73 (d, *J* = 12.0 Hz, 1H), 2.42-2.24 (m, 6H), 1.58-1.51 (m, 6H), 1.25 (s, 50H), 0.94 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.74, ,173.68 169.44, 169.39 138.2, 136.9, 129.0, 128.5, 128.1, 128.0, 127.9, 127.8, 126.0, 101.2, 97.0, 78.7, 77.5, 75.0, 74.5, 74.3, 71.6, 71.4, 71.0, 68.5, 67.5, 67.2, 66.3, 54.3, 54.2, 41.6, 34.5, 34.2, 34.1, 31.9, 29.61, 29.59, 29.5, 29.44, 29.39, 29.32, 29.17, 29.0, 25.6, 25.3, 25.2, 24.99, 24.96 22.6, 17.9, 14.1, -4.0 -5.27, -5.30; HRMS (ESI, M+Na^+) calcd for $C_{70}H_{117}N_4O_{13}Si$ 1249.8386, found 1249.8380.

1-*O*-*tert*-butyldimethylsiyl-4,6-*O*-benzylidene-2-deoxy-2-[(*R*)-3-(dodecanoyloxy)-tetradecanamido]-3-*O*-dodec-anoyl-β-D-gluco-pyranosyl-(1→6)-3-*O*-dodecanoyl-4-*O*-benzyl-2-deoxy-2-azido-β-D-glucopyranoside (24)

To a solution of **23** (360 mg, 0.28 mmol) in dichloromethane (4.0 mL), lauric acid **17** (0.28 g, 1.14 mmol), *N*-(3-dimethyl-aminopropyl)-*N*-

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ethylcarbodiimide (125 µL, 0.71 mmol) and 4-dimethyl-aminopyridine (34 mg, 0.34 mmol) were added at 0 °C under nitrogen atmosphere. After 10 minutes, the reaction was slowly warmed up to room temperature and stirred for 18 hours, the mixture was then extracted with water and dichloromethane (30 mL x 2). The organic layer was treated with $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford product **24** (320 mg, 79%) as a white solid. R_f 0.48 (EtOAc /Hexane = 1/4); mp = 124-126 °C $[\alpha]^{25}_D$-79.70 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3357, 2924, 2853, 2113, 1740, 1663, 1538, 1466, 1379, 1161, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.40 (m, 2H, Ar-H), 7.35-7.31 (m, 4H, Ar-H), 7.30-7.28 (m, 2H, Ar-H), 7.23-7.21 (m, 2H, Ar-H), 6.02 (d, *J* = 8.0 Hz, 1H), 5.49 (s, 1H, Ph-CH), 5.26 (t, *J* = 9.6 Hz, 1H), 5.03-4.95 (m, 2H), 4.69-4.58 (m, 2H), 4.53 (s, 2H), 4.31-4.26 (m, 1H), 4.09-3.93 (m, 1H), 3.85-3.82 (m, 1H), 3.74-3.68 (m, 2H), 3.58 (t, *J* = 9.2 Hz, 1H), 3.49-3.45 (m, 2H), 3.30-3.25 (m, 1H), 2.41-2.17 (m, 8H), 1.66-1.54 (m, 9H), 1.25 (s, 66H), 0.93 (s, 9H), 0.87 (t, *J* = 6.0 Hz, 12H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 173.5, 172.7, 169.5, 137.7, 136.9, 128.3, 128.1, 127.6, 125.9, 101.3, 101.1, 97.0, 78.6, 75.8, 74.3, 74.1, 73.4, 71.8, 71.0, 68.4, 66.5, 66.1, 53.8, 41.6, 34.4, 34.2, 33.9, 31.8, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 29.2, 29.03, 28.99, 25.5, 25.1, 25.0, 24.9, 24.8, 24.7, 22.6, 17.8, 14.0, -4.2, -5.4.; HRMS (ESI, M+Na^+) calcd for $C_{82}H_{138}N_4O_{14}SiNa$ 1453.9876, found 1453.9861.

1-*O*-*tert*-butyldimethylsiyl-4,6-*O*-benzylidene-2-deoxy-2-[(*R*)-3-(dodecanoyloxy)-tetradecanamido]-3-*O*-dode-canoyl-β-D-gluco-pyranosyl-(1→6)-3-*O*-dodeca-noyl-4-*O*-benzyl-2-deoxy-2-[(*R*)-3-(dodecanoyloxy)-tetradeca-namido]-β-D-gluco-pyranoside (15)

To a solution of **24** (680 mg, 0.47 mmol) in THF/H_2O (6:0.5) (6.5 mL), triphenylphosphane (250 mg, 0.95 mmol) was added at 0 °C. After 5 minutes, the solution is warmed up to room temperature and stirred for 16 hours. The solvent removed and dried over high vacuum for one day. The residue was used in next step without further purification. The mixture of amine intermediate (670 mg, 0.47 mmol) in dry dichloromethane (7.0 mL), myristic acid derivative **20** (810 mg, 1.90 mmol) and *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (276 µL, 1.60 mmol) were added at 0 °C under nitrogen atmosphere. After 5 minutes, the reaction is slowly warmed up to room temperature. After stirring for 18 hours, the mixture was extracted with water and dichloromethane (30 mL x 3). The organic layer was treated with over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford product **15** (0.33 g, 38%) as a white solid. R_f 0.25 (EtOAc/Hexane = 1/4); mp = 108-110 °C $[\alpha]^{25}_D$-71.00 (*c* 1.0, CH_2Cl_2); IR (NaCl) *v* 3372, 2925, 2855, 1743, 1718, 1671, 1542, 1462, 1276, 1260, 1179, 1105, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.41 (m, 2H, Ar-H), 7.33-7.28 (m, 5H, Ar-H), 7.25-7.22 (m, 3H, Ar-H), 6.00-5.92 (m, 1H), 5.65 (d, *J* = 15.2 Hz, 1H), 5.62-5.50 (m, 2H), 5.48 (s, 1H, Ph-CH), 5.37-5.33 (m, 1H), 5.29 (t, *J* =10 Hz, 1H), 5.10-5.02 (m, 1H), 4.76-4.71 (m, 1H), 4.65-4.61 (m, 1H), 4.58 (s, 2H), 4.34-4.30 (m, 1H), 4.12-4.05 (m, 2H), 4.01-3.90 (m, 2H), 2.38-2.07 (m, 12H), 1.61-1.52 (m, 12H), 1.25 (s, 98H), 0.91-0.84 (m, 27H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 173.7, 173.6, 172.5, 169.4, 165.6, 137.8, 137.0, 128.9, 128.4, 128.1, 127.8, 127.6, 126.0, 101.2, 96.6, 78.8, 75.9, 74.8, 74.4, 71.4, 70.9, 68.5, 67.9, 66.3, 64.6, 55.5, 54.6, 41.7, 41.5, 36.9, 34.5, 34.5, 34.2, 34.1, 32.0, 31.9, 29.6, 29.5, 29.4, 29.4, 29.3, 29.2, 29.13, 29.10, 29.0, 28.6, 28.3, 25.9, 25.6, 25.5, 25.2, 25.00, 24.9, 22.6, 17.8, 14.1, -3.9, -5.2; HRMS (ESI, M+Na^+) calcd for $C_{108}H_{188}N_2O_{17}SiNa$ 1814.3711, found 1837.3711.

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Keywords: one-pot reaction •beta-selectivity •glucosamine •carbohydrate •glycan

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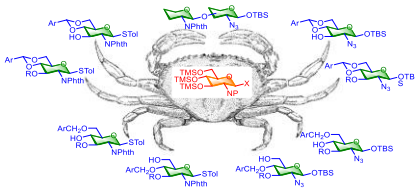

This investigation describes preparing a series of building blocks of glucosamines for glycosylation reactions, such as 3-alcohol glucosamines, fully protected glucosamines, *O*-4 and *O*-6 alcohol glucosamines by a one-pot reaction. These reactions readily produce not only beta-form only glycosyl donors and acceptors, but also different glycosyl units that can be changed based on the needs of the experiment. Since glycopeptide (GP) has good selectivity for tumor angiogenesis and this phenomenon makes the GP a potential target drug and Lipid A has recently been adopted as vaccines for human. The synthesis of glycan of GP and precursors of lipid A disaccharide backbone is also described in this work.

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