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Comparing the use of 2-methylenenapthyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl and 2,4,6-trimethoxybenzyl as N–H protecting groups for *p*-tolyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucosides

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ABSTRACT

A hurdle in glycosylation reactions of 2-acetamido glycosyl donors is the formation of a stable and unreactive oxazoline that decreases the yield of these reactions significantly. As an effort to prevent oxazoline formation during glycosylation reactions, we protected the N–H of the acetamido group within a 2-acetamido-2-deoxy-1-thio-β-D-glucoside with one of four different protecting groups. These groups were either 2-methylenenapthyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl or 2,4,6-trimethoxybenzyl. The resulting *N*-alkylacetamides were then used in glycosylation reactions with ethanol as a model acceptor. We observed that the ethyl glycosides obtained in each case were obtained with exclusive β-selectivity without the formation of oxazoline sideproducts. The resulting products were then used to screen conditions for protecting group removal.

1. Introduction

Oligosaccharides play diverse biological functions in living organisms.[1] They are responsible for important biological roles such as providing conformation and stability to protein structures, mediating host–microbe interactions and many more.[1,2] A very important class of oligosaccharides are the glycosides of *N*-acylglucosamines that serve as building blocks for peptidoglycans, mucopolysaccharides, and bacterial lipopolysaccharides, which make them excellent targets for organic synthesis.[2,3] An obstacle to the synthesis of this class of oligosaccharide is the formation of stable and unreactive oxazolines when unprotected 2-*N*-acylglycosides are used.[4,5] During glycoside formation the activated anomeric leaving group generates a oxacarbenium ion, which is attacked by the neighboring *N*-acyl group to form an *N*-acyloxonium intermediate that deprotonates to the oxazoline.[4–6] In order to overcome this difficulty the 2-amino group in a glycosyl donor is usually protected with a bivalent or monovalent protecting group, for example, phthaloyl, tetrachlorophcoloyl, dithiasuccinoyl, trichloroacetyl, allyloxycarbonyl, etc. In some cases double protection with dibenzyl, diacetyl or acetyl/trichloroethoxycarbonyl is used, and the desired acyl group is installed.[7–19] After the glycosylation reaction the protecting groups are removed. Another important aspect is to use a protecting group capable of generating diastereoselectivity in these glycosylation reactions. A study by the Jensen group reported the use of the 2,4-dimethoxybenzyl (Dmob) group for protection of 2-acetamido glycosyl donors and obtained exclusively the β-glycoside product.[6] Another observation inspiring our study was that previous strategies to generate differentially acylated *N*-2 amide-containing oligosaccharides have been linear involving the protection of the C-2 NH in the two monosaccharide units with orthogonal protecting groups before the glycosylation step. The orthogonal protecting groups in the glycosides were then sequentially removed and differentially acylated to produce the required C-2 amide-containing glycosides. A fundamentally different and more convergent strategy would be to install the acyl groups on each glycoside first and then perform the glycosylation step. This strategy requires the protection of the C-2 amide NH to avoid the formation of oxazoline side products (Fig. 1). The protecting group would then be removed under mild oxidative conditions. We were interested in exploring this avenue, and we hypothesized that protection of the 2-acetamido glycosyl donors with protecting groups like 2-methylenenaphthyl (2-NAP), 4-methoxybenzyl, 3,4-dimethoxybenzyl, and 2,4,6-trimethoxybenzyl will not only nullify the issues of oxazoline formation but it will also pave the way for the convergent synthesis of oligosaccharides of 2-deoxy-*N*-acylglucosamines.

2. Results and discussion

In order to validate our hypothesis, four different C-2 N–H protected glucosamide donors were synthesized. We first synthesized 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose

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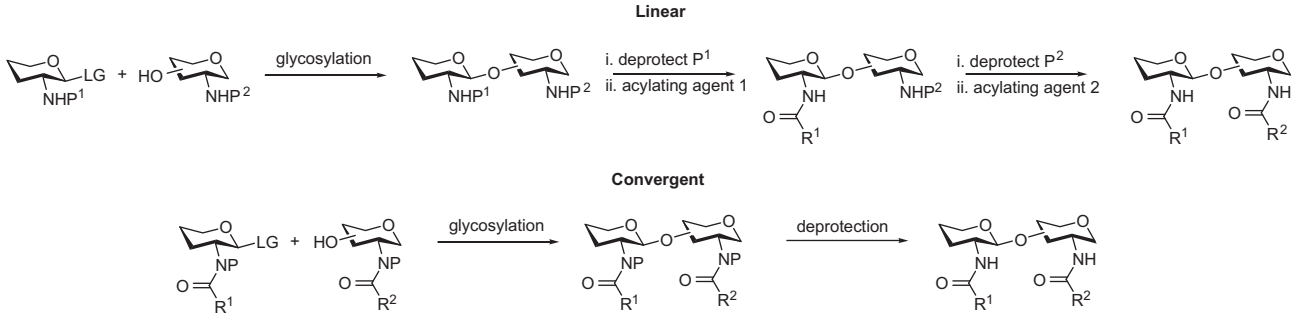
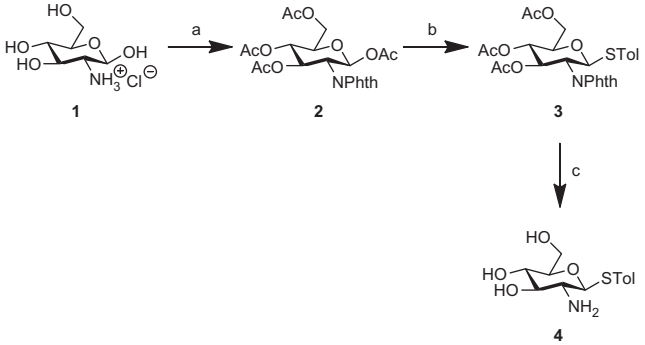


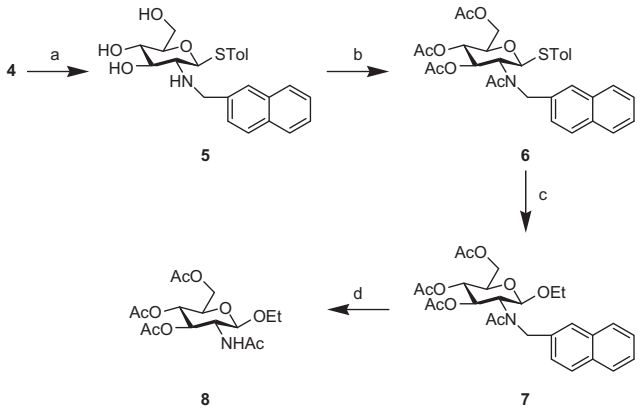
Figure 1. Comparision of convergent versus linear synthesis of 2-acylamino glycosides (LG = leaving group, P = protecting group, R^1 and R^2 = alkyl or aromatic groups).

(**2**, Scheme 1) in a series of three steps starting from glucosamine hydrochloride (44% overall).[20] Compound **2** was glycosylated with *p*-thiocresol (4-methylthiophenol) in the presence of boron trifluoride diethyl etherate in dichloromethane to generate *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**3**) with a yield of 82.4%.[21] The phthalimido as well as the acetyl groups in **3** were deprotected by refluxing with hydrazine monohydrate in dry MeOH to quantitatively yield *p*-methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (**4**).[22] Compound **4** served as the common intermediate for conjugation with four different aldehydes in order to synthesize the C-2 N–H protected glucosamide donor analogs.

The 2-methylenenapthyl (2-NAP) group was chosen to be our first protecting group for the C-2 amide, as we predicted it to be more sensitive to hydrogenolysis than the benzyl group, and hence, it could be removed efficiently after the glycosylation step.[31] In an effort to synthesize the C-2 amide donor containing the 2-NAP protecting group, the amine **4** was condensed with 2-naphthaldehyde in THF under refluxing conditions (Scheme 2), and finally the resulting imine was subjected to sodium triacetoxyborohydride-mediated reductive amination to generate *p*-methylphenyl 2-deoxy-2-[(naphthalen-2ylmethyl)amino]-1-thio-β-D-glucopyranoside (**5**) in 71% yield over two steps.[23,24] The reductive amination step was first attempted with sodium cyanoborohydride, but we observed that the aldehyde was reduced as well, leading to the low yield of this step. Therefore, we switched to sodium triacetoxyborohydride which is reported to be more selective and would preferentially reduce the resulting imine to the amine.[24,25] Compound **5** was then peracetylated with Ac_2O in anhydrous pyridine to produce the fully protected thioglycoside donor *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(naphthalen-2ylmethyl)amino]-1-thio-β-D-glucopyranoside (**6**) in quantitative yield.[6] A careful investigation of the ^1H and ^{13}C NMR spectrum of **6** revealed that the



Scheme 1. Reagents and conditions: (a) (i) NaOMe, MeOH; (ii) $Phth_2O$, Et_3N; (iii) Ac_2O, pyridine (44%); (b) TolSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (82.4%); (c) $NH_2NH_2{\cdot}H_2O$, MeOH, reflux (quant).



Scheme 2. Reagents and conditions: (a) (i) 2-naphthaldehyde, THF, reflux; (ii) $NaB(OAc)_3H$ (71%); (b) Ac_2O, pyridine (quantitative); (c) EtOH, 2,4,6-tri-*tert*-butylpyridine, NIS, TMSOTf, mol. sieves (3 Å), CH_2Cl_2 (48%); (d) (i) Na/NH_3 (l); (ii) Ac_2O, pyridine (87%).

isolated compound was actually a mixture of rotational isomers at ambient temperatures. The ^1H NMR spectrum of **6** recorded at 600 MHz ($CDCl_3$) showed the acetyl groups as two different sets each of four sharp singlet peaks at δ 2.37, 2.28, 2.22, 2.19 and δ 2.07, 2.04, 2.02, 1.99. This was attributed to the slow rotation of the *N*–Ac bond at room temperatures. For carrying out the crucial glycosylation step, non-acidic conditions were necessary; therefore, we used the acid scavenger 2,4,6-tri-*tert*-butylpyridine (TTBP) which has been used in acid-sensitive glycosylation reactions.[26,27] For all the glycosylation reactions ethanol was chosen as a model acceptor for its availability and to simplify the study (Table 1). Compound **6** was glycosylated with ethanol in presence of TTBP and *N*-iodosuccinimide (NIS) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as activators to generate ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(naphthalen-2ylmethyl)amino]-β-D-glucopyranoside (**7**) in 48% yield.[27] The yield for the ethyl glycoside **7** was calculated based on the donor **6** as the limiting reagent. For compound **7** the ^1H and ^{13}C NMR spectra revealed that the compound was a mixture of non-separable rotational isomers that occurred

Table 1
Reactions of glycosyl donors with ethanol as a model acceptor

Donor	Equiv of donor	Equiv of acceptor	Solvent	% Yield[a]
6	1.00	2.16	CH_2Cl_2	48
10	1.00	2.00	CH_2Cl_2	31
13	1.00	2.25	CH_2Cl_2	72
16	1.00	2.06	CH_2Cl_2	22

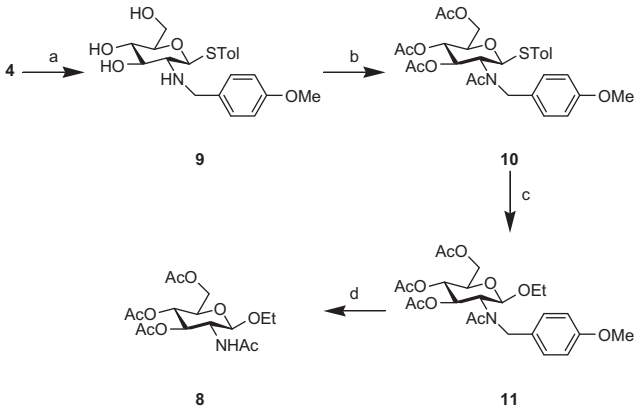
[a] All yields were calculated based on the respective glycosyl donors as limiting reagents.

due to the slow rotation of the N–Ac groups. Nevertheless, partial analysis of the ^{1}H NMR spectrum revealed that the generated ethyl glycoside possessed exclusively the β conformation where one of the assignable H-1 protons appeared as a doublet at δ 5.61 with a $J_{1,2}$ value of 7.8 Hz. It is important to note that there was no oxazoline formation, which was confirmed from analysis of the mass spectrum of the crude reaction mixture.

Our next step was the deprotection of the 2-NAP group. Our effort to deprotect this group under oxidative conditions using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), ceric ammonium nitrate (CAN) or hydrogenolysis using palladium chloride, palladium–charcoal in MeOH–HOAc acid medium, or in the presence of Et_3N and HCO_2H failed.[28–33] Ultimately we resorted to cleaving the NAP group in **7** under Birch reduction conditions. The product was reacetylated with Ac_2O in pyridine to afford ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**8**) in an excellent yield of 87% (Table 2).[6,34] The ^{1}H and ^{13}C NMR spectra confirmed that the β glycoside was the exclusive product, where the H-1 proton appeared as a doublet centered at δ 4.73 with a $J_{1,2}$ value of 8.4 Hz. It was also concluded from the NMR spectrum that compound **8** was a pure isomer. Thus, it was evident that the bulky 2-*N*-NAP group was responsible for the origin of the rotational isomers. Another important observation was that deprotection of the 2-*N*-NAP group under Birch reduction conditions requires a much longer duration (6 h) than that reported for the deprotection of *N*- or *O*-benzyl amides. Therefore, we speculate that the 2-NAP group can be used as an orthogonal protecting group in presence of the above mentioned groups.

We explored this avenue further by using the *p*-methoxybenzyl group (PMB) to protect the C-2 amide (Scheme 3). The free amine **4** was condensed with *p*-methoxybenzaldehyde in THF, and the imine was reduced by sodium triacetoxyborohydride to afford *p*-methylphenyl 2-deoxy-2-(4-methoxybenzylamino)-1-thio-β-D-glucopyranoside (**9**) with an yield of 76% over two steps.[23,24] Compound **9** was peracetylated with Ac_2O in anhydrous pyridine to generate the C-2 amide-protected thioglycoside donor *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(4-methoxybenzyl)amino]-1-thio-β-D-glucopyranoside (**10**) in 94% yield.[6] Compound **10** was isolated as a mixture of two rotational isomers because of the slow rotation of the *N*–Ac bond at room temperature. Next, the donor **10** was glycosylated with ethanol in presence of TTBP, NIS, and TMSOTf to afford ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(4-methoxybenzyl)amino]-β-D-glucopyranoside (**11**) in 31% yield.[27] Further, the ethyl glycoside **11** was isolated as a mixture of rotational isomers. Nevertheless, the *N*-PMB-protected ethyl glycoside **11** was exclusively β as determined by ^{1}H NMR spectroscopy, with the assignable H-1 proton appearing as a doublet centered at δ 4.01 with $J_{1,2}$ values of 8.4 Hz. Deprotection of the *N*-PMB group was attempted using the same oxidative and hydrogenolysis conditions as discussed earlier, but herein our efforts also failed. The PMB group in compound **11** was finally deprotected using sodium metal and liquid ammonia in a span of six hours, and the product was reacetylated to generate **8** (79.5%) as the exclusive β anomer and as a single isomer.[6,34]

We were also interested in observing the effect of an increase in the number of electron-donating substituents on the phenyl ring in the possibility of deprotection of these protecting groups under milder conditions. Therefore, we chose the 3,4-dimethoxybenzyl and the 2,4,6-trimethoxybenzyl as protecting groups for the C-2 amide. The glycosyl donors *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(3,4-dimethoxybenzyl)amino]-1-thio-β-D-glucopyranoside (**13**, Scheme 4) and *p*-methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(2,4,6-trimethoxybenzyl)amino]-1-thio-β-D-glucopyranoside (**16**, Scheme 5) were synthesized following procedures as described above using 3,4-dimethoxybenzaldehyde and 2,4,6-trimethoxybenzaldehyde for condensation with the free amine **4**, followed by peracetylating the respective products. Glycosylation of **13** and **16** with ethanol afforded ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(3,4-dimethoxybenzyl)amino]-β-D-glucopyranoside (**14**) in 72% yield and ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(2,4,6-trimethoxybenzyl)amino]-β-D-glucopyranoside (**17**) in 22% yield. The ethyl glycoside **14** was isolated as a pure isomer with the H-1 proton appearing as a doublet at δ 5.49 with a $J_{1,2}$ value of 9 Hz, whereas the ethyl glycoside **17** was isolated as a mixture of rotational isomers with the assignable H-1 and H-1′ protons appearing as doublets at δ 5.98 and 4.94 with $J_{1,2}$ values of 9.2 and 9.6 Hz, confirming exclusive β selectivity. Next, we tried to remove the 2,4-dimethoxybenzyl and the 3,4,6-trimethoxybenzyl groups under oxidative and hydrogenolysis conditions, but unfortunately we were not successful in our efforts. Thereafter compounds **14** and **17** were both subjected to Birch reduction conditions followed by reacetylation that furnished **8** in excellent yields of 81% and 84%, respectively (Table 2).



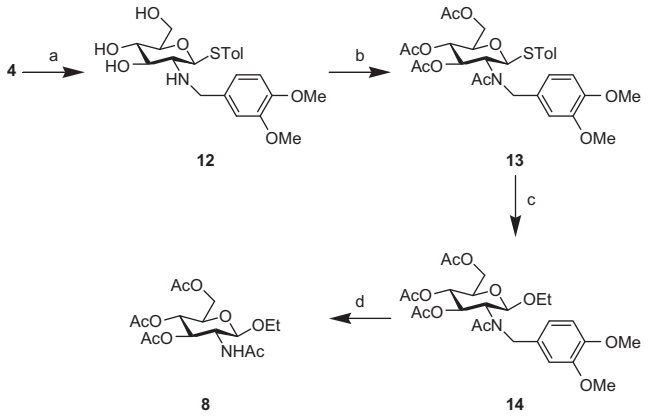
Scheme 3. Reagents and conditions: (a) (i) 4-methoxybenzaldehyde, THF, reflux; (ii) $NaB(OAc)_3H$ (76%); (b) Ac_2O, pyridine (94%); (c) EtOH, 2,4,6-tri-*tert*-butylpyridine, NIS, TMSOTf, mol. sieves (3 Å), CH_2Cl_2 (31%); (d) (i) Na/NH_3 (l); (ii) Ac_2O, pyridine (80%).

In conclusion, we have successfully synthesized 2-*N*-NAP, PMB, 3,4-dimethoxybenzyl, and 2,4,6-trimethoxybenzyl C-2 protected glucosamide thioglycoside donors, which were glycosylated with ethanol as a model acceptor. The ethyl glycosides in each case showed exclusive β selectivity with no formation of oxazoline. These protecting groups showed resistance to cleavage under oxidative and hydrogenolysis conditions, but either functional group can be deprotected efficiently in excellent yields under Birch reduction conditions.

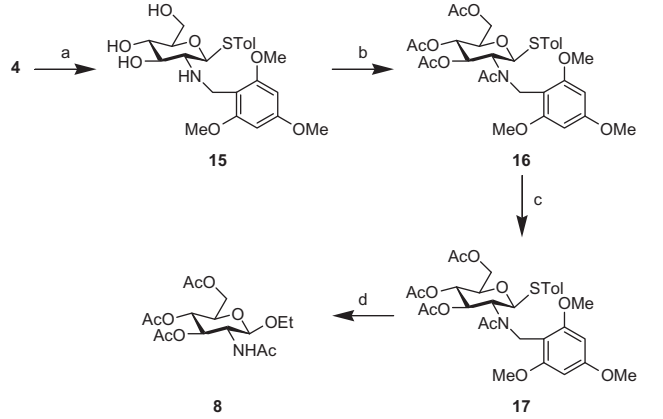
Table 2
Deprotection of protected ethyl glycosides and subsequent reacetylation

Compound	Equivalents of compound	Time subjected to Birch reduction conditions (h)	Equivalents of Ac_2O/pyridine used[a]	% Yield of **8**
7	1.00	6	9.14/16.89	87
11	1.00	6	9.14/16.89	79
14	1.00	6	9.14/16.89	81
17	1.00	6	9.14/16.89	84

[a] The acetylation step was carried out for 12 h for each compound.



Scheme 4. Reagents and conditions: (a) (i) 3,4-dimethoxybenzaldehyde, THF, reflux; (ii) $NaB(OAc)_3H$ (55%); (b) Ac_2O, pyridine (38%); (c) EtOH, 2,4,6-tri-*tert*-butylpyridine, NIS, TMSOTf, mol. sieves (3 Å), CH_2Cl_2 (72%); (d) (i) Na/NH_3 (l); (ii) Ac_2O, pyridine (81%).



Scheme 5. Reagents and conditions: (a) (i) 2,4,6-trimethoxybenzaldehyde, THF, reflux; (ii) $NaB(OAc)_3H$ (91%); (b) Ac_2O, pyridine (78%); (c) EtOH, 2,4,6-tri-*tert*-butylpyridine, NIS, TMSOTf, mol. sieves (3 Å), CH_2Cl_2 (22%); (d) (i) Na/NH_3 (l); (ii) Ac_2O, pyridine (84%).

3. Experimental

3.1. General methods

All fine chemicals such as glucosamine hydrochloride, phthalic anhydride, *p*-thiocresol, sodium triacetoxyborohydride, 2-napthaldehyde, and anhyd solvents such as anhyd MeOH were purchased from Acros Organics. Boron trifluoride diethyl etherate was from Sigma–Aldrich. The chemicals were used without further purification. All solvents were obtained from Fisher Scientific Co. and were used as received except dichloromethane, which was dried and distilled following the standard procedures.[35] Silica gel (230–400 mesh) for flash column chromatography was obtained from Sorbent Technologies; precoated plates for thin-layer chromatography (TLC) were from E. Merck. TLCs (Silica Gel 60, F_{254}) were visualized under UV light or by charring (5% H_2SO_4–MeOH). Flash column chromatography was performed on silica gel (230–400 mesh) using solvents as received. ^1H NMR spectra were recorded either on a Varian VXRS 400 MHz or an INOVA 600 MHz spectrometer in $CDCl_3$ or CD_3OD using residual $CHCl_3$ and CHD_2OH as internal references, respectively. ^{13}C NMR spectra were recorded on a Varian VXRS 100.56 MHz in $CDCl_3$ using the triplet centered at δ 77.273 or in CD_3OD using the septet centered at δ 49.0 as internal reference. High-resolution mass spectrometry (HRMS) was performed on a TOF mass spectrometer.

3.2. General procedures

3.2.1. Condensation of 2-amino-2-deoxythioglycosides with aldehydes, and subsequent reductive amination

p-Methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (**4**) (1.0 equiv) was suspended in dry THF (8 mL) and refluxed until it dissolved. The aldehyde (1.2 equiv) was added, and the reflux was continued for 2 h. The solution was cooled and followed by the addition of sodium triacetoxyborohydride (1.2 equiv) and stirred for another 12 h under an N_2 atmosphere at room temperature. The reaction mixture was filtered through Celite and concentrated under reduced pressure. Silica gel flash column chromatography (1:19 MeOH–CH_2Cl_2) afforded the product.

3.2.2. Acetylation employing C-2 N–H protected thioglycosides

The C-2 N–H protected thioglycosides (1.0 equiv) were dissolved in anhyd pyridine (16.0 equiv) followed by the addition of Ac_2O (8.0 equiv). The reaction mixture was stirred for 12 h under an N_2 atmosphere at room temperature. Excess Ac_2O was quenched by addition of EtOH (0.1 mL). Excess pyridine was co-distilled with toluene (3 × 2 mL). Purification by silica gel flash column chromatography (2:3 EtOAc–toluene) afforded the product.

3.2.3. Glycosylation employing protected C-2 *N*-acetylamino thioglycosides

To a mixture of the glycosyl donor (1.0 equiv), EtOH (2.2 equiv), 2,4,6-tri-*tert*-butylpyridine (0.35 equiv) and molecular sieves (3 Å, 138 mg) in CH_2Cl_2 (2 mL) was added NIS (2.2 equiv) followed by TMSOTf (0.08 equiv) at 10 °C. The reaction mixture was stirred at room temperature for 12 h and quenched by the addition of Et_3N (10 μL). It was diluted with CH_2Cl_2 (3 mL) and filtered through Celite, dried over anhyd Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (2:3 EtOAc–toluene) generated the product.

3.2.4. Deprotection of ethyl glycosides and reacetylation

Ammonia gas was condensed in a cold finger at −78 °C. Sodium metal was added to the solution until a blue color persisted. The ethyl glycoside (1.0 equiv) was dissolved in dry THF (0.5 mL) and added to the ammonia solution. The resulting solution was stirred for 6 h. The reaction was quenched by NH_4Cl (s). Excess NH_3 was evaporated off using a stream of dry N_2 gas. The product was extracted by MeOH containing 10% EtOAc (10 mL) and concentrated under reduced pressure. The product was redissolved in pyridine (16.9 equiv) followed by the addition of Ac_2O (9.13 equiv) and stirred at room temperature for 12 h. The reaction was quenched by addition of EtOH (0.1 mL). Excess pyridine was co-distilled with toluene (3 × 2 mL) and purified by silica gel flash column chromatography (2:1 EtOAc–toluene) to yield the product.

3.3. Synthesis of *p*-methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (4)

3.3.1. 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (2)

A 1 M NaOMe solution was prepared by dissolving small pieces of Na metal (5.33 g, 0.232 mol) in anhyd MeOH (232 mL) at −5 °C in a 500-mL round-bottomed flask equipped with a $CaCl_2$ drying tube. This solution was slowly added to a 1-L round-bottomed flask containing glucosamine hydrochloride (50.0 g, 0.232 mol) at 0 °C, and the solution was stirred at ambient temperature for 2 h. Finely ground phthalic anhydride (19 g, 0.128 mol) was added to the solution, and the mixture was stirred for another 45 min, followed by the

addition of a second batch of phthalic anhydride (19.0 g, 0.128 mol), Et_3N (35.5 mL, 0.255 mol), and MeOH (230 mL). The reaction mixture was vigorously stirred at room temperature for 24 h. During this period the milky white solution changed to a thick yellow paste. The product was precipitated as a white solid by cooling the solution to −20 °C for a period of 4 h. The product was filtered and washed thoroughly with cold MeOH and dried overnight under reduced pressure. The solid was redispersed in pyridine (500 mL) followed by the addition of Ac_2O (330 mL, 15 equiv), and the mixture was stirred at room temperature for 48 h during which time it changed from a transient white to a opaque yellow solution. Cold EtOH (100 mL) was added to quench the excess Ac_2O. Excess pyridine was co-distilled with toluene (3 × 100 mL) under reduced pressure. The remaining slurry was dissolved in $CHCl_3$ (1 L), and the solution was washed with distilled H_2O (4 × 100 mL) and brine (250 mL), and dried over anhyd Na_2SO_4, filtered, and evaporated to dryness. The crude product was dissolved in a minimum volume of hot EtOAc (100 mL) and diluted with hexanes (400 mL) and left to cool at −5 °C. The recrystallized product was filtered, washed with cold hexanes, and dried to yield the desired tetraacetate as an 8:1 mixture of anomers (48.5 g, 44%).[20]

3.3.2. *p*-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (3)

To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**2**) (48.5 g, 0.102 mol) and *p*-thiocresol (16.4 g, 0.132 mol) in CH_2Cl_2 (400 mL) boron trifluoride diethyl etherate (17.5 mL, 0.138 mol) was slowly added at 0 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 22 h. The reaction mixture was diluted with CH_2Cl_2 (400 mL) and washed sequentially with cold NaOH (2 × 200 mL) and distilled water (2 × 500 mL). The organic layer was dried over anhyd Na_2SO_4. Crystallization from hot EtOAc afforded **3** as an off-white solid (45.3 g, 82.4%).[21]

3.3.3. *p*-Methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (4)

p-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (**3**) (10 g, 18.46 mmol) was suspended in dry MeOH (250 mL), and hydrazine monohydrate (60 mL, 1.24 mol) was added to it. The mixture was refluxed under a dry N_2 atmosphere for 12 h. The reaction mixture was concentrated and co-evaporated with EtOH (2 × 10 mL). The residue was purified by silica gel flash column chromatography (2:15:83 NH_4OH–MeOH–$CHCl_3$) to yield **4** as a pale-yellow solid (5.3 g, quant). ^1H NMR (600 MHz, CD_3OD): δ 7.48 (dd, 2H, *J* = 1.8, 6.6 Hz, ArH), 7.15 (d, 2H, *J* = 8.4 Hz, ArH), 4.48 (d, 1H, *J* = 9.6, H-1), 3.87 (dd, 1H, *J* = 2.4, 13.8 Hz, H-5), 3.67 (q, 1H, *J* = 6 Hz, H-4), 3.29 (d, 1H, *J* = 4.5 Hz, H-6a), 3.25 (t, 1H, *J* = 9.7 Hz, H-3), 3.24 (s, 1H, H-6e), 2.59 (t, 1H, *J* = 9.6 Hz, H-2), 2.32 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, CD_3OD): δ 139.37, 133.94, 130.81, 130.40 (4C, Ar-C), 89.79 (1C, C-1), 82.44, 78.98, 71.63, 63.02, 57.03 (5C, C-2, C-3, C-4, C-6, C-5), 21.28 (1C, Ar-CH_3); HRMS: calcd for $C_{13}H_{19}NO_4SNa$, *m/z* $[M+Na]^+$ 308.0932, found *m/z* 308.0920.

3.4. Synthesis of ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(naphthalen-2ylmethyl)amino]-β-D-glucopyranoside (7)

3.4.1. *p*-Methylphenyl 2-deoxy-2-[acetyl(naphthalen-2ylmethyl)amino]-1-thio-β-D-glucopyranoside (5)

p-Methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (**4**) (266 mg, 0.93 mmol) was condensed with 2-naphthaldehyde (174 mg, 1.12 mmol), and the product was subjected to reductive amination with sodium triacetoxyborohydride (236 mg, 1.12 mmol) according to procedures described in Section 3.2.1 to afford **5** as a white foam (281 mg, 71%). ^1H NMR (600 MHz, CD_3OD): δ 7.82 (m, 4H, ArH), 7.54 (dd, 1H, *J* = 1.8, 8.4 Hz, ArH), 7.46 (m, 4H, ArH), 7.09 (d, 2H, *J* = 7.8 Hz, ArH), 4.67 (d, 1H, *J* = 9.6 Hz, H-1), 4.21 (d, 1H, *J* = 12.6 Hz, N–CH_a), 4.13 (d, 1H, *J* = 12.6, N–CH_b), 3.86 (dd, 1H, *J* = 2.4, 12.3 Hz, H-6a), 3.70 (dd, 1H, *J* = 5.4, 12.3 Hz, H-5), 3.50 (t, 1H, *J* = 9 Hz, H-3), 3.34 (d, 1H, *J* = 7.8 Hz, H-4), 3.29 (m, 1H, H-6e), 2.63 (t, 1H, *J* = 9.6 Hz, H-2), 2.30 (s, 3H, Ar-CH_3). ^{13}C NMR (100 MHz, CD_3OD): δ 139. 01, 135.07, 134.45, 133.25 (2), 131.18, 130.81 (2), 129.36, 128.96, 128.80, 128.17, 127.26, 126.98 (16C, C-aromatic), 89.35 (1C, C-1), 82.34, 78.46, 71.97, 63.13, 62.97 (5C, C-2, C-3, C-3, C-4, C-5, C-6), 53.76 (1C, N–CH_2), 21.27 (1C, Ar-CH_3); HRMS: calcd for $C_{24}H_{28}NO_4S$ *m/z* $[M+H]^+$ 426.1739; found, *m/z* 426.1731.

3.4.2. *p*-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(naphthalen-2ylmethyl)amino]-1-thio-β-D-glucopyranoside (6)

p-Methylphenyl2-deoxy-2-[(naphthalen-2ylmethyl)amino]-1-thio-β-D-glucopyranoside (**5**) (500 mg, 1.03 mmol) was acetylated according to procedures described in Section 3.2.2 to afford **6** as a white foam that was a mixture of two rotational isomers (613 mg, quantitative). ^1H NMR (600 MHz, $CDCl_3$): δ 7.77 (m, 7H, ArH), 7.49 (m, 7H, ArH), 7.32 (d, 1H, *J* = 8.4 Hz, ArH), 7.13 (d, 2H, *J* = 7.8 Hz, ArH), 6.79 (d, 1H, *J* = 8.4 Hz, ArH), 6.74 (d, 1H, *J* = 8.4 Hz, ArH), 6.21 (t, 1H, *J* = 9.3 Hz, H-3), 5.95 (d, 1H, *J* = 9.6 Hz, H-1), 5.46 (t, 1H, *J* = 9.6 Hz, H-3′), 5.10 (t, 1H, *J* = 9.6 Hz, H-4′), 4.90 (t, 1H, *J* = 9.6 Hz, H-4), 4.63 (d, 1H, *J* = 10.2 Hz, H-1′), 4.27 (t, 1H, *J* = 6 Hz, H-6a′), 4.23 (m, 1H, H-6e′), 4.12 (d, 1H, *J* = 2.4 Hz, H-6e), 4.10 (m, 1H, H-6a), 4.07 (t, 1H, *J* = 11.2 Hz, H-2′), 3.80 (m, 1H, H-5), 3.67 (m, 1H, H-5′), 3.28 (t, 1H, *J* = 9.9 Hz, H-2), 2.37, 2.28, 2.22, 2.19 (4s, 12H, CH_3–CO), 2.07, 2.04, 2.02, 1.99 (4s, 12H, CH_3–CO′), 1.95 (s, 3H, Ar-CH_3), 1.46 (s, 3H, Ar-CH_3'). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172. 51, 172.44, 170.78, 170.71 (4C, CH_3–*C*O), 170.17, 169.97, 169.85, 169.62 (4C, CH_3–*C*O′), 138.28, 138.15, 135.62, 133.48, 133.34, 133.29, 133.00, 132.87, 132.50 (4), 132.17 (16C, C-aromatic), 129.97, 129.50, 128.83, 128.30, 128.04, 127.97, 127.81, 127.73, 127.45, 126.99, 126.90, 126.77, 126.57, 126.05, 125.93, 125.82 (16C, C′-aromatic), 85.64 (1C, C-1), 84.75, 77.55, 77.23, 76.91, 75.42 (5C, C-2, C-4, C-3, C-6, C-5), 71.73 (1C, C-1′), 71.22, 69.92, 69.42, 64.44, 62.55 (5C, C-2′, C-4′, C-3′, C-6′, C-5′), 57.02 (1C, *N*–CH_2), 45.57 (1C, *N*–CH_2'), 23.91 (1C, Ar-CH_3), 22.65 (1C, Ar-CH_3'), 21.33, 21.21, 20.92 (2), (4C, *C*H_3–CO), 20.81 (3), 20.70 (4C, *C*H_3–CO′); HRMS: calcd for $C_{32}H_{35}NO_8S$-Na, *m/z* $[M+Na]^+$ 616.1981; found, *m/z* 616.1964.

3.4.3. Ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(naphthalen-2ylmethyl)amino]-β-D-glucopyranoside (7)

p-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(*N*-2-methylene-naphthylacetamido)-1-thio-β-D-glucopyranoside (**6**) (100 mg, 0.168 mmol) was glycosylated with EtOH (22 μL, 0.363 mmol) according to procedures described in Section 3.2.3 to generate **7** as colorless oil that was a mixture of rotational isomers (41.3 mg, 48%). ^1H NMR (600 MHz, $CDCl_3$): δ 7.77 (m, 6H, ArH), 7.46 (m, 5H, ArH), 7.18 (m, 3H, ArH), 6.14 (t, 1H, *J* = 9.3 Hz, H-3), 5.61 (d, 1H, *J* = 7.8 Hz, H-1), 4.93 (t, 1H, *J* = 9.3 Hz, H-4), 4.27 (m, 2H, H-6), 3.81 (m, 1H, H-5), 3.42 (m, 1H, O–CH_a–CH_3), 3.15 (t, 1H, *J* = 8.7 Hz, H-2), 2.33 (m, 1H, O–CH_b–CH_3), 2.21, 2.18, 2.12, 2.05 (4s, 12H, CH_3–CO), 2.04, 2.03, 2.00, 1.98 (4s, 12H, CH_3–CO′), 0.90 (t, 3H, *J* = 6.9 Hz, CH_2–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.88 (2), 173.18, 172.69, (4C, CH_3–CO), 171.03, 170.91, 170.25, 169.88 (4C, CH_3–*C*O′), 135.99, 133,38, 132.75, 129.20, 128.64, 128.39, 128.31, 127.94, 127.84, 127.81 (10C, C-aromatic), 126.81, 126.65, 126.36 (3), 126.18, 126.16, 126.02, 125.65, 125.45 (10C, C′-aromatic), 99.99 (2C, C-1, C-1′), 71.44, 71.33 (2C, C-4, C-4′), 71.25, 69.90 (2C, C-2, C-2′), 69.82, 69.57 (2C, C-3, C-3′), 66.07, 65.96 (2C, C-6, C-6′), 62.45, 62.38 (2C, O–CH_2, O–CH_2'), 62.09, 61.89 (2C, C-5, C-5′), 56.95, 44.75 (2C, N–CH_2, N–CH_2'), 29.90, 29.77, 23.71,

22.68, (4C, CH_3–CO), 21.07, 20.99, 20.95, 20.87 (4C, CH_3–CO′), 15.48, 14.93 (2C, O–CH_2–CH_3, O–CH_2–CH_3'); HRMS: calcd for $C_{27}H_{33}NO_9Na$, *m/z* $[M+Na]^+$ 538.2053; found, *m/z* 538.2039.

3.5. Synthesis of ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(*N*-(4-methoxybenzyl)acetamido)-β-D-glucopyranoside (11)

3.5.1. *p*-Methylphenyl 2-deoxy-2-(4-methoxybenzylamino)-1-thio-β-D-glucopyranoside (9)

p-Methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (**4**) (500 mg, 1.75 mmol) was condensed with 4-methoxybenzaldehyde (0.24 mL, 1.97 mmol), and the product was subjected to reductive amination with sodium triacetoxyborohydride (447 mg, 1.97 mmol) according to procedures described in Section 3.2.1 to afford **9** as a white foam (538 mg, 76%). ^{1}H NMR (600 MHz, CD_3OD): δ 7.45 (d, 2H, *J* = 7.8 Hz, ArH), 7.29 (d, 2H, *J* = 9 Hz, ArH), 7.14 (d, 2H, *J* = 7.8 Hz, ArH), 6.89 (d, 2H, *J* = 9 Hz, ArH), 4.64 (d, 1H, *J* = 10.2 Hz, H-1), 3.97 (d, 2H, *J* = 12 Hz, *N*–CH_2), 3.92 (d, 1H, *J* = 12 Hz, H-5), 3.85 (dd, 1H, *J* = 2.4, 12 Hz, H-6a), 3.78 (s, 3H, *O*–CH_3), 3.67 (q, 1H, *J* = 5.8 Hz, H-6e), 3.46 (t, 1H, *J* = 9 Hz, H-3), 3.28 (m, 1H, H-4), 2.58 (t, 1H, *J* = 10.2 Hz, H-2), 2.32 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 160.73, 139.09, 133.27 (2), 132.49, 131.25 (2), 131.13, 130.84 (2), 115.06 (2) (12C, C-aromatic), 89.19 (1C, C-1), 82.32, 78.24, 71.97, 63.20, 62.94 (5C, C-2, C-3, C-4, C-6, C-5), 55.81 (1C, *O*–CH_3), 53.21 (1C, *N*–CH_2), 21.27 (1C, Ar-CH_3); HRMS: calcd for $C_{21}H_{28}NO_5S$ *m/z* $[M+H]^+$ 406.1688; found *m/z* 406.1684.

3.5.2. *p*-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(4-methoxybenzyl)amino]-1-thio-β-D-glucopyranoside (10)

p-Methylphenyl 2-deoxy-2-(4-methoxybenzylamino)-1-thio-β-D-glucopyranoside (**9**) (538 mg, 1.33 mmol) was acetylated according to procedures described in Section 3.2.2 to afford **10** as a white foam that was a mixture of two rotational isomers (0.132 mg, 94%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (d, 3H, *J* = 7.8 Hz, ArH), 7.25 (m, 2H, ArH), 6.86 (d, 2H, *J* = 7.8 Hz, ArH), 6.71 (m, 1H, ArH), 6.15 (t, 1H, *J* = 9 Hz, H-3), 5.89 (d, 1H, *J* = 9.6 Hz, H-1), 5.36 (t, 1H, *J* = 9.6 Hz, H-3′), 5.05 (t, 1H, *J* = 9.3 Hz, H-4′), 4.98 (m, 1H, H-6′), 4.90 (t, 1H, *J* = 8.4 Hz, H-4), 4.57 (d, 1H, *J* = 10.2 Hz, H-1′), 4.20 (dd, 1H, *J* = 5.4, 12.3 Hz, H-6a), 4.10 (m, 1H, H-6′), 4.05 (t, 1H, *J* = 10.8 Hz, H-2′), 4.01 (m, 1H, H-5), 3.79 (s, 3H, *O*–CH_3), 3.71 (s, 3H, *O*–CH_3'), 3.63 (m, 1H, H-6e), 3.52 (m, 1H, H-5′), 3.18 (t, 1H, *J* = 9.9 Hz, H-2), 2.96 (s, 2H, *N*–CH_2), 2.82 (s, 2H, *N*–CH_2'), 2.33, 2.30, 2.21, 2.13 (4s, 12H, CH_3–CO), 2.07, 2.03, 2.00, 1.96 (4s, 12H, CH_3–CO′), 1.68 (s, 3H, Ar-CH_3), 1.24 (s, 3H, Ar-CH_3'); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.32, 172.21, 170.56, 170.68 (4C, CH_3–*C*O), 170.04, 169.97, 169.85, 169.56 (4C, CH_3–*C*O′), 159.49, 158.91 (2C, *O*–C-aromatic, O–C′-aromatic), 132.46, 129.96, 129.91, 129.87, 129.81, 129.69, 129.47, 128.60, 128.34, 128.02 (10C, C-aromatic), 86.45, 84.91 (2C, C-1, C-1′), 77.44, 77.23, 77.02, 75.37, 71.52, 71.18, 69.85, 69.44, 63.82, 62.54 (10C, C-3, C-3′, C-2, C-2′, C-4, C-4′, C-6, C-6′, C-5, C-5′), 61.43, 56.07 (2C, *O*–*C*H_3, *O*–*C*H_3'), 55.41, 55.21 (2C, *N*–*C*H_2, *N*–*C*H_2'), 23.78, 22.55 (2C, Ar-*C*H_3, Ar-*C*H_3'), 21.24 (2), 20.97, 20.86 (2), 20.78, 20.75, 20.64 (8C, CH_3–CO, CH_3–CO′); HRMS: calcd for $C_{29}H_{35}NO_9SNa$ *m/z* $[M+Na]^+$ 596.1930; found *m/z* 596.1903.

3.5.3. Ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(4-methoxybenzyl)amino]-β-D-glucopyranoside (11)

p-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(4-methoxy benzyl)amino]-1-thio-β-D-glucopyranoside (**10**) (220 mg, 0.384 mmol) was glycosylated with EtOH (43 μL, 0.770 mmol) according to procedures described in Section 3.2.3 to generate **11** as colorless oil that was a mixture of two rotational isomers (59 mg, 31%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37–6.86 (m, 8H, ArH), 5.46 (t, 1H, *J* = 9.9 Hz, H-3), 5.08 (t, 1H, *J* = 9.6 Hz, H-4), 4.29 (dd, 1H, *J* = 4.8, 12.0 Hz, H-6a), 4.13 (dd, 1H, *J* = 1.8, 12.3 Hz, H-6e), 4.01 (d, 1H, J = 8.4 Hz, H-1), 3.93 (t, 1H, *J* = 10.8 Hz, H-3), 3.85 (m, 1H, *O*–CH_a–CH_3'), 3.80, 3.78 (2s, 6H, *O*–CH_3), 3.59 (m, 1H, *O*–CH_a–CH_3), 2.76 (s, 2H, *N*–CH_2), 2.54 (m, 1H, O–CH_b–CH_3), 2.35 (m, 1H, O–CH_b–CH_3'), 2.13, 2.10, 2.07, 2.06, 2.04, 2.03, 2.02, 1.99 (8s, 24H, CH_3–CO, CH_3–CO′), 1.22 (t, 3H, *J* = 7.2 Hz, *O*–CH_2–CH_3'′), 1.04 (t, 3H, *J* = 7.2 Hz, *O*–CH_2–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.99 (2), 170.99 (2), 170.90, 170.16 (2), 169.88 (8C, C-aromatic, C′-aromatic), 158.99 (1C, *O*–C-aromatic), 147.69 (1C, O–C′-aromatic), 133.76, 132.87, 130.58, 130.13, 130.06, 129.21, 128.76, 128.41, 114.18, 113.96 (10C, C-aromatic, C′-aromatic), 100.17, 99.57 (2C, C-1, C-1′), 71.66, 71.44, 71.38, 70.90, 69.79, 69.61, 68.13, 65.91, 65.73, 65.52 (10C, C-4, C-4′, C-3, C-3′, C-2, C-2′, C-6, C-6′, C-5, C-5′), 61.41, 62.12 (2C, *O*–*C*H_2–CH_3, *O*–CH_2–*C*H_3'), 59.07, 56.13 (2C, N–CH_2, N–CH_2'), 55.52, 43.92 (2C, *O*–CH_3, *O*–CH_3'), 22.63, 21.56, 21.34, 21.06, 20.97, 20.94, 20.89, 20.83 (8C, CH_3–CO, CH_3–CO′), 15.38, 15.03 (2C, *O*–CH_2–*C*H_3, *O*–CH_2–*C*H_3); HRMS: calcd for $C_{24}H_{33}NO_{10}Na$ *m/z* $[M+Na]^+$ 518.2002; found *m/z* 518.1993.

3.6. Synthesis of ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(3,4-dimethoxybenzyl)amino]-β-D-glucopyranoside (14)

3.6.1. *p*-Methylphenyl 2-deoxy-2-(3,4-dimethoxybenzylamino)-1-thio-β-D-glucopyranoside (12)

p-Methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (**4**) (500 mg, 1.75 mmol) was condensed with 3,4-dimethoxybenzaldehyde (326 mg, 1.96 mmol) and subjected to reductive amination with sodium triacetoxyborohydride (443 mg, 1.96 mmol) according to procedures described in Section 3.2.1 to afford **12** as a white foam (419 mg, 55%). ^{1}H NMR (600 MHz, CD_3OD): δ 7.44 (d, 2H, *J* = 8.4 Hz, ArH), 7.13 (d, 2H, *J* = 8.4 Hz, ArH), 7.02 (s, 1H, ArH), 6.90 (s, 1H, ArH), 4.65 (d, 1H, *J* = 10.2 Hz, H-1), 4.00, 3.92 (2d, 2H, *J* = 12.3 Hz, *N*–CH_2), 3.85 (m, 1H, H-5), 3.83, 3.81 (2s, 6H, *O*–CH_3), 3.67 (dd, 2H, *J* = 5.4, 12 Hz, H-6), 3.48 (t, 1H, *J* = 9 Hz, H-3), 3.29 (m, 1H, H-4), 2.59 (t, 1H, *J* = 10.2 Hz, H-2), 2.31 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ 150.56, 150.01, 139.04, 133.16 (2), 131.11, 130.83 (3), 122.57, 113.85, 112.87 (12C, C-aromatic), 89.13 (1C, C-1), 82.28, 78.23, 71.91, 62.91 (4C, C-2, C-3, C-4, C-6), 52.57, 56.51 (2C, *O*–CH_3), 53.38 (1C, C-5), 21.27 (1C, Ar-CH_3); HRMS: calcd for $C_{22}H_{29}NO_6SNa$ *m/z* $[M+Na]^+$ 458.1613; found *m/z* 458.1605.

3.6.2. *p*-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(3,4-dimethoxybenzyl)amino]-1-thio-β-D-glucopyranoside (13)

p-Methylphenyl 2-deoxy-2-(3,4-dimethoxybenzylamino)-1-thio-β-D-glucopyranoside (**12**) (250 mg, 0.574 mmol) was acetylated according to procedures described in Section 3.2.2 to afford **13** as a white foam that was a mixture of two rotational isomers (260 mg, 38%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37–6.53 (14H, ArH), 6.11 (t, 1H, *J* = 9.3 Hz, H-3), 5.90 (d, 1H, *J* = 10.2 Hz, H-1), 4.89 (t, 1H, *J* = 9.6 Hz, H-4), 4.60, 4.48 (2d, 4H, *J* = 10.8 Hz, N–CH_2, N–CH_2'), 4.19 (dd, 1H, *J* = 5.4, 12.3 Hz, H-6a), 4.09 (dd, 1H, *J* = 1.8, 5.6 Hz, H-6e), 3.85, 3.84 (2s, 6H, *O*–CH_3), 3.81, 3.76 (2s, 6H, O–CH_3'), 3.63 (m, 1H, H-5), 3.17 (t, 1H, *J* = 9.6 Hz, H-2), 2.31, 2.28, 2.19, 2.13 (4s, 12H, CH_3–CO), 2.05, 2.02, 2.00, 1.95 (4s, 12H, CH_3–CO′), 1.68 (s, 3H, Ar-CH_3), 1.23 (s, 3H, Ar-CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.23, 172.15, 170.66, 170.03, 169.90, 169.76, 169.53 (8C, CH_3–*C*O, CH_3–*C*O′), 149.95, 149.91, 149.18, 148.39, 138.26, 138.06, 132.48, 132.12, 131.91, 130.50, 129.84, 129.64, 129.58, 129.33, 129.09, 128.44, 128.29, 120.89, 120.56, 111.34, 111.42, 111.19, 110.47, 110.26 (24C, C-aromatic, C′-aromatic), 86.36, 84.84 (2C, C-1, C-1′), 77.55, 77.23, 76.91, 75.36, 71.66, 71.04, 69.48, 64.11, 62.48 (10C, C-3, C-3′, C-2, C-2′, C-4, C-4′, C-6, C-6′, C-5, C-5′), 56.45, 56.00 (4C, *O*–CH_3, *O*–CH_3'), 55.60, 48.30 (2C, *N*–CH_2, *N*–CH_2'), 29.75 (2C, Ar-CH_3, Ar-CH_3'), 23.72, 22.64, 22.52, 21.53, 21.19, 20.80, 20.75, 20.57 (8C, *C*H_3–CO,

CH_3–CO′); HRMS: calcd for $C_{30}H_{37}NO_{10}SNa$ *m/z* $[M+Na]^+$ 626.2026; found *m/z* 626.2012.

3.6.3. Ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(3,4-dimethoxybenzyl)amino]-β-D-glucopyranoside (14)

p-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(3,4-dimethoxybenzyl)amino]-1-thio-β-D-glucopyranoside (**13**) (50 mg, 0.08 mmol) was glycosylated with EtOH (10 μL, 0.18 mmol) according to procedures described in Section 3.2.3 to generate **14** as colorless oil (31 mg, 72%). ^{1}H NMR (600 MHz, CDCl3): δ 7.38–6.75 (3H, ArH), 5.49 (d, 1H, *J* = 9 Hz, H-1), 5.07, 4.92 (2d, 2H, *J* = 7.8 Hz, *N*–CH_2), 5.00 (dd, 1H, *J* = 3, 6 Hz, H-6e), 4.27 (m, 1H, H-5), 4.04 (t, 1H, *J* = 9.6 Hz, H-3), 4.02 (q, 2H, *J* = 7.2 Hz, *O*–CH_2–CH_3), 3.87, 3.85 (2*s*, 6H, *O*–CH_3), 3.72 (dd, 1H, *J* = 8.4, 14.2 Hz, H-6a), 3.52 (d, 1H, *J* = 8.4 Hz, H-4), 2.28, 2.14, 2.04, 1.98 (4s, 12H, CH_3CO), 1.01 (t, 3H, *J* = 6.9 Hz, *O*–CH_2–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.99, 170.93, 170.16, 169.83 (4C, CH_3CO), 149.29, 148.50 (2C, *O*–C-aromatic), 131.30, 120.20, 111.63, 110.91 (4C, C-aromatic), 100.14 (1C, C-1), 79.30, 71.31, 69.66, 65.49, 62.36 (5C, C-3, C-2, C-4, C-6, C-5), 56.48 (1C, *O*–CH_2–CH_3), 56.15, 56.13 (2C, O–CH_3), 44.26 (1C, *N*–CH_2), 22.70, 21.03, 20.93, 20.89 (4C, CH_3–CO), 15.10 (1C, *O*–CH_2–CH_3); HRMS: calcd for $C_{25}H_{35}NO_{11}Na$ *m/z* $[M+Na]^+$ 548.2108; found *m/z* 548.2109.

3.7. Synthesis of ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(2,4,6-trimethoxybenzyl)amino]-β-D-glucopyranoside (17)

3.7.1. *p*-Methylphenyl 2-deoxy-2-(2,4,6-trimethoxybenzylamino)-1-thio-β-D-glucopyranoside (15)

p-Methylphenyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (**4**) (500 mg, 1.75 mmol) was condensed with 2,4,6-trimethoxybenzaldehyde (385 mg, 1.96 mmol) and subjected to reductive amination with sodium triacetoxyborohydride (444 mg, 1.96 mmol) according to procedures described in Section 3.2.1 to afford **15** as a white foam (744 mg, 91%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, 3H, *J* = 7.8 Hz, ArH), 7.12 (d, 3H, *J* = 7.8 Hz, ArH), 6.12 (s, 1H, N–H), 4.87 (br s, 3H, OH), 4.65 (d, 1H, *J* = 10.2 Hz, H-1), 4.26, 4.16 (2d, 2H, *J* = 12.6 Hz, *N*–CH_2), 3.88 (t, 1H, *J* = 9 Hz, H-3), 3.85 (s, 6H, *O*–CH_3), 3.82 (s, 3H, *O*–CH_3), 3.78 (dd, 2H, *J* = 4.8, 11.7 Hz, H-6), 3.47 (t, 1H, *J* = 9.6 Hz, H-4), 3.36 (m, 1H, H-5), 2.66 (t, 1H, *J* = 10.2 Hz, H-2), 1.95 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.07, 159.64 (2) (3C, *O*–C-aromatic), 138.98, 133.35 (2), 130.09 (2), 128.03, 103.82, 90.62 (2) (9C, C-aromatic), 86.36 (1C, C-1), 80.06, 74.69, 71.05, 63.04, 60.93 (5C, C-2, C-3, C-4, C-6, C-5), 55.94 (2), 55.60 (3H, *O*–CH_3), 40.53 (1C, *N*–CH_2), 21.39 (1C, Ar-CH_3); HRMS: calcd for $C_{23}H_{31}NO_7SNa$ *m/z* $[M+Na]^+$ 488.1719; found *m/z* 488.1728.

3.7.2. *p*-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(2,4,6-trimethoxybenzyl)amino]-1-thio-β-D-glucopyranoside (16)

p-Methylphenyl 2-deoxy-2-(2,4,6-trimethoxybenzylamino)-1-thio-β-D-glucopyranoside (**15**) (700 mg, 1.50 mmol) was acetylated according to procedures described in Section 3.2.2 to afford **16** as a white foam (741 mg, 78%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33, 7.06 (2d, 6H, *J* = 7.8 Hz, ArH), 6.15 (s, 1H, *N*–H), 6.11 (t, 1H, *J* = 9.6 Hz, H-3), 5.91 (d, 1H, *J* = 10.2 Hz, H-1), 4.85 (t, 1H, *J* = 9.6 Hz, H-4), 4.55, 4.43 (2d, 2H, *J* = 14.4 Hz, N–CH_2), 4.17 (q, 1H, *J* = 6 Hz, H-6e), 4.03 (dd, 1H, *J* = 1.8, 12 Hz, H-6a), 3.85, 3.83 (2s, 9H, *O*–CH_3), 3.76 (m, 1H, H-5), 3.37 (t, 1H, *J* = 10.2 Hz, H-2), 2.32, 2.31, 2.03, 1.97 (4s, 12H, CH_3–CO), 1.74 (s, 3H, Ar-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.57 (2), 169.96 (2) (4C, CH_3–*C*O), 161.74, 160.13 (2) (3C, *O*–C-aromatic), 137.50, 131.86 (3), 129.73 (3), 105.05 (2) (9C, C-aromatic), 90.78 (1C, C-1), 86.05, 75.29, 71.52, 70.51, 63.17 (5C, C-2, C-4, C-3, C-6, C-5), 61.37, 55.73, 55.57 (3C, *O*–CH_3), 44.11 (1C, *N*–CH_2), 23.39 (1C, Ar-CH_3), 21.31, 20.96 (2), 20.73 (4C, *C*H_3–CO); HRMS: calcd for $C_{31}H_{39}NO_{11}SNa$ *m/z* $[M+Na]^+$ 656.2142; found *m/z* 656.2112.

3.7.3. Ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(2,4,6-trimethoxybenzyl)amino]-β-D-glucopyranoside (17)

p-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-[acetyl(2,4,6-trimethoxybenzyl)amino]-1-thio-β-D-glucopyranoside (**16**) (100 mg, 0.16 mmol) was glycosylated with EtOH (18.5 μL, 0.33 mmol) according to procedures described in Section 3.2.3 to generate **17** as colorless oil that was a mixture of rotational isomers (19 mg, 22%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–6.95 (4H, ArH), 6.12 (m, 1H, H-5), 5.98 (d, 1H, *J* = 9.2 Hz, H-1), 5.45 (t, 1H, *J* = 7.8 Hz, H-3), 4.94 (d, 1H, *J* = 9.6 Hz, H-1′), 4.85 (m, 1H, H-6), 4.54 (m, 1H, H-6′), 4.48, 4.38 (2d, 4H, *J* = 12 Hz, *N*–CH_2, *N*–CH'_2), 4.25 (m, 1H, H-5′), 4.23 (t, 1H, *J* = 9.2 Hz, H-3′), 4.19 (t, 1H, *J* = 9.6 Hz, H-2), 4.04 (t, 1H, *J* = 9.6 Hz, H-4′), 3.91 (m, 1H, H-6′), 3.78 (m, 1H, H-6), 3.61 (t, 1H, *J* = 9.3 Hz, H-2′), 3.24 (t, 1H, *J* = 8.4 Hz, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.07 (4), 167.53 (4) (8C, CH_3CO, CH_3CO'), 161.82, 160.02 (2) (3C, *O*–C-aromatic), 129.83, 129.67, 129.24, 128.88, 125.93, 125.57 (6C, C-aromatic, C′-aromatic), 99.65, 90.72 (2C, C-1, C-1′), 71.30, 71.09, 70.55, 68.59, 67.76, 65.80, 65.17, 63.60, 62.98, 62.78 (10C, C-4, C-4′, C-3, C-3′, C-2, C-2′, C-6, C-6′, C-5, C-5′), 62.38, 62.27 (2C, *N*–CH_2, *N*–CH'_2), 56.65, 56.07, 55.73 (4) (6C, *O*–CH_3, *O*–CH'_3), 55.59, 44.29 (2C, *O*–CH_2–CH_3, *O*–CH_2–CH'_3), 23.36, 21.22, 21.15 (2), 21.05 (2), 20.82 (2) (8C, CH_3–CO, CH_3–CO′), 15.36, 14.41 (2C, *O*–CH_2–CH_3, *O*–CH_2–CH'_3); HRMS: calcd for $C_{26}H_{37}NO_{12}Na$ *m/z* $[M+Na]^+$ 578.2213; found *m/z* 578.2194.

3.8. Ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (8)

Each of the ethyl glycosides **7** (30 mg, 0.058 mmol), **11** (31.6 mg, 0.064 mmol), **14** (15.3 mg, 0.029 mmol), and **17** (12 mg, 0.022 mmol) was subjected to Birch reduction conditions and subsequent reacetylation according to procedures described in Section 3.2.4 to yield **8** as a colorless oil (19 mg, 87% from **7**; 18.6 mg, 79.5% from **11**; 8.9 mg, 81% from **14**; 6.8 mg, 84% from **17**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.51 (d, 1H, *J* = 9 Hz, N–H), 5.33 (t, 1H, *J* = 14.1 Hz, H-3), 5.08 (t, 1H, *J* = 9.6 Hz, H-4), 4.73 (d, 1H, *J* = 8.4 Hz, H-1), 4.27 (dd, 1H, *J* = 4.8, 12.6 Hz, H-6a), 4.14 (dd, 1H, *J* = 2.4, 12.3 Hz, H-6e), 3.90 (m, 1H, O–CH_a–CH_3), 3.79 (q, 1H, *J* = 9.2 Hz, H-2), 3.72 (m, 1H, H-5), 3.59 (m, 1H, O–CH_b–CH_3), 2.14, 2.09, 2.08, 2.04 (4s, 12H, CH_3–CO), 1.21 (t, 3H, *J* = 7.2 Hz, O–CH_2–CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.09 (2), 170.42, 169.67 (4C, CH_3–*C*O), 100.59 (1C, C-1), 72.54, 72.01, 68.91, 65.53, 62.40 (5C, C-4, C-2, C-3, C-6, C-5), 55.24 (1C, O–CH_2–CH_3), 32.15, 31.15, 29.92, 29.58 (4C, *C*H_3–CO), 17.82 (1C, O–CH_2–CH_3); HRMS: calcd for $C_{16}H_{25}NO_9Na$ *m/z* $[M+Na]^+$ 398.1247; found *m/z* 398.1409.

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Supplementary data

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