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1,2-*cis*-SELECTIVE FORMATION OF A UNIQUE AMINO-CONTAINING AMINO GLYCOSIDE BY ENDOCYCLIC CLEAVAGE STRATEGY

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Abstract – 2-Acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranoside (AAT), a unique aminated sugar unit, is often found in zwitterionic polysaccharides. Stereoselective formation of the 1,2-*cis* linkage of these unique sugar derivatives was achieved by an anomerization reaction based on an endocyclic cleavage process.

INTRODUCTION

The unusual amino sugar unit, 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranoside (AAT), is found in bacterial capsular polysaccharide glycans.[1] For example, AAT has been identified in zwitterionic polysaccharides (**1–3**), which are expressed on the capsules of the commensal bacteria *Bacteroides fragilis* and *Streptococcus pneumonia* (Figure 1).[2,3] It has also been found in type IV lipoteichoic acid (**4**).[4] The zwitterionic polysaccharides themselves, without conjugated proteins, stimulates CD-4$^+$ T-cell proliferation after being presented via the MHC-II processing pathway,[5] and also stimulates the innate immune system through interaction with the Toll-like receptor 2.[6] In connection with their biological activities, several attempts to synthesize zwitterionic polysaccharides have been reported.[7-10] One of the key features necessary for AAT-containing polysaccharide synthesis is construction of the 1,2-*cis* linkage. The 1,2-*cis*-selective glycosylation reaction of amino sugars is difficult; 2-azido-2-deoxy sugars have been used in the most cases.[11] Furthermore, because AAT contains two amino groups, differentiation between them is essential for efficient zwitterionic glycan synthesis. For these reasons, the design of AAT-related glycosyl donors has been complicated. To overcome these difficulties, several approaches have been reported, including *de novo* synthesis.[8,12-15]

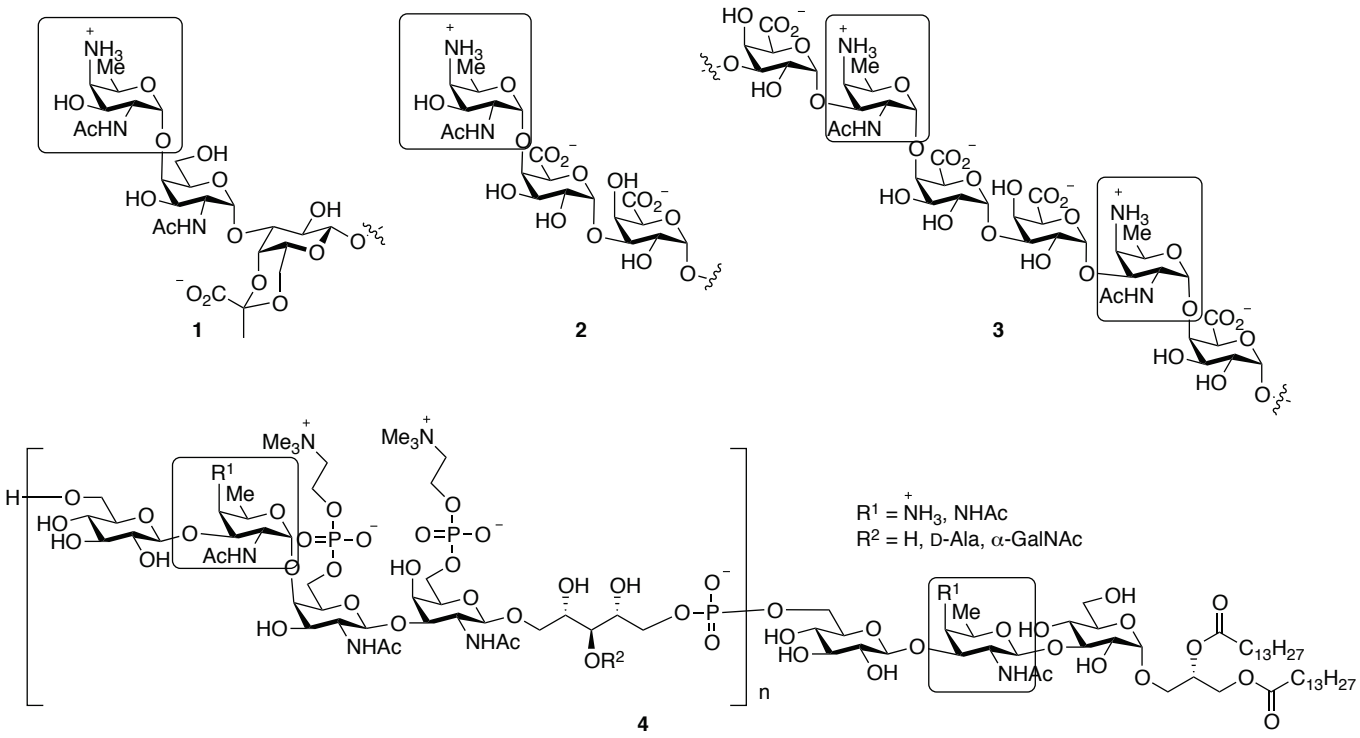
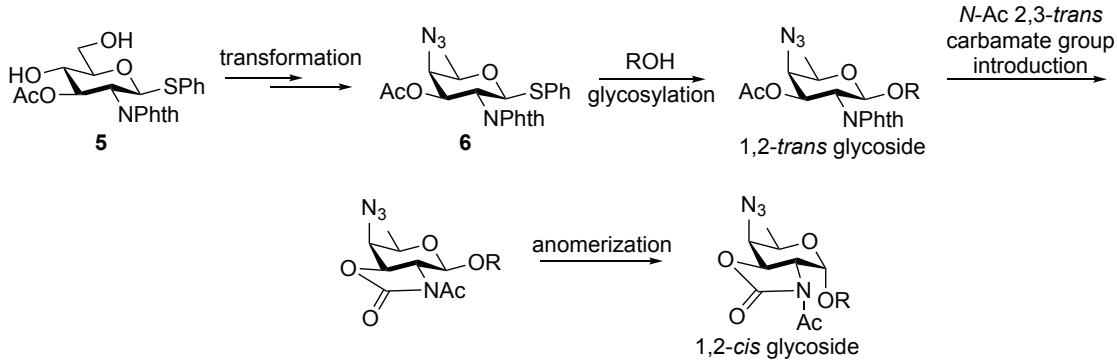


Figure 1. AAT-containing oligosaccharides

Previously, we reported that anomerization easily occurred under weak Lewis acidic conditions when an *N*-acetyl 2,3-*trans* carbamate group was installed in 2-amino-2-deoxy pyranosides.[16] The anomerization reaction gives the 1,2-*cis*-anomer from the 1,2-*trans*-anomer through an endocyclic cleavage reaction, in which the bond between the anomeric carbon and the ring oxygen (O5) is cleaved. After cleavage, recyclization of the linear cation gives the 1,2-*cis* glycoside with extremely high selectivity. Based on these results, we expected that the endocyclic cleavage reaction would be advantageous for 1,2-*cis* AAT formation in two ways. First, the 1,2-*cis* linkage would be created by endocyclic cleavage-mediated anomerization with extremely high selectivity. Second, the differential protecting groups from our previous examples could be used for the 2- and 4-amino groups.

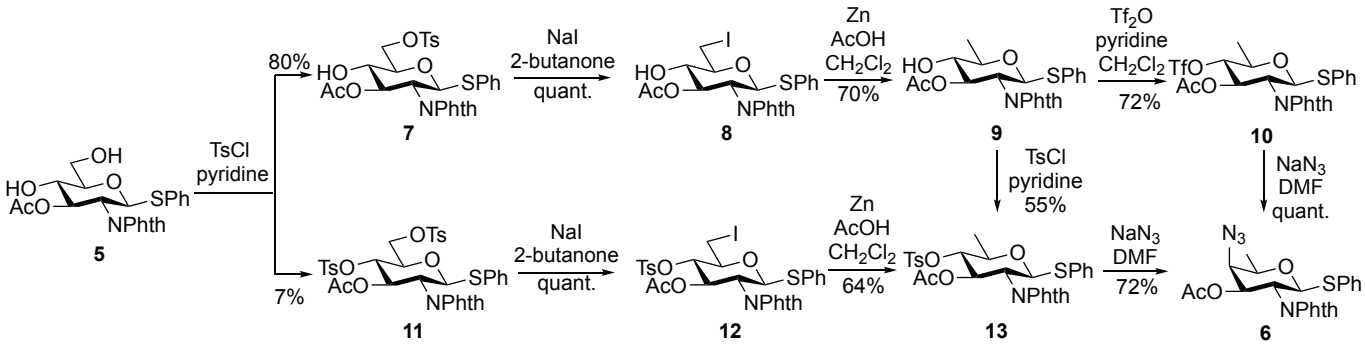
We applied our endocyclic cleavage reaction to the synthesis of AAT via the strategy shown in Scheme 1. First, from the glucosamine derivative **5**, the two amino groups are introduced/protected as the azide and phthalimide groups in **6**. Then, the 1,2-*trans* glycoside can be prepared using the phthalimide neighboring-participation effect. After the removal of phthalimide and acetyl group, the *N*-acetyl 2,3-*trans* carbamate group is introduced. Then, with treatment of the 1,2-*trans* glycoside under Lewis acidic conditions, the desired 1,2-*cis* glycoside is obtained.



Scheme 1. 1,2-*cis* AAT formation via anomerization through an endocyclic cleavage reaction

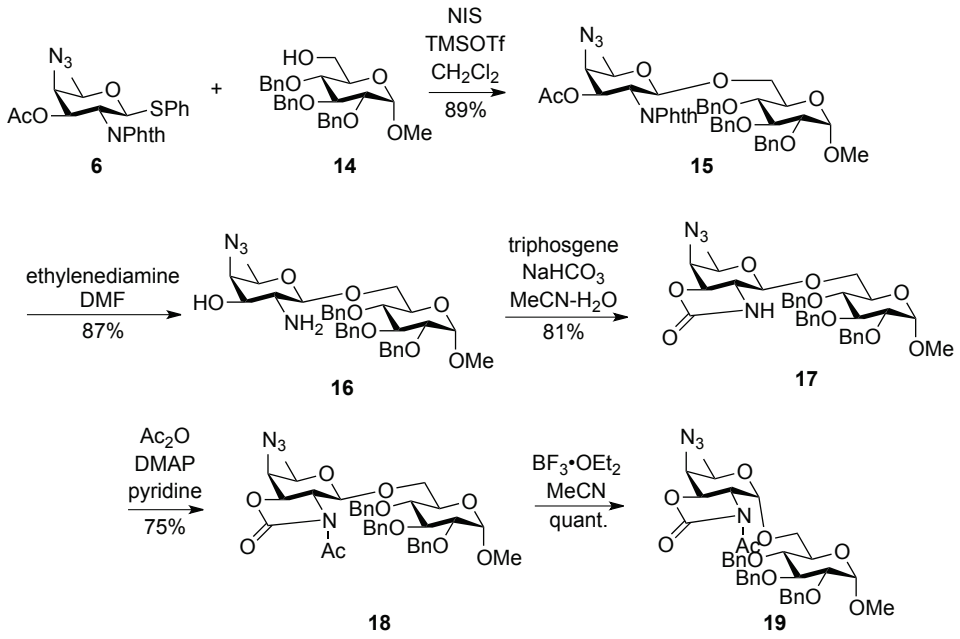
RESULTS AND DISCUSSION

The glycosyl donor was prepared as shown in Scheme 2. Tosylation of diol **5** gave mono-tosylate **7** and di-tosylate **11** in 80% and 7% yield, respectively. Treatment of tosylates **7** and **11** with NaI displaced the primary tosyl group to afford iodides **8** and **12** both in quantitative yields. Zn reduction of iodide **8** afforded 6-deoxy compound **9** in 70% yield. After triflation and azide substitution, donor **6** was obtained in 72% yield. Because of the low solubility and reactivities of **12** and **13**, yields of reduction and substitution reaction were low. From **12**, **6** was obtained in 46% yield over two steps.



Scheme 2. Glycosyl donor preparation from the diol **5**

The glycosylation reaction between donor **6** and acceptor **14** was carried out under typical glycosylation conditions for thioglycosides, using NIS-TMSOTf (Scheme 3). The 1,2-*trans* glycoside **15** was obtained in 89% yield, and the 1,2-*trans* linkage was confirmed from the ^{1}H NMR coupling constant (J = 8.8 Hz) of the anomeric position. After simultaneous removal of the phthalimide and acetyl groups by ethylenediamine, a 2,3-*trans* carbamate group was installed with triphosgene. *N*-Acetylation of the carbamate group was achieved with Ac_2O-pyridine in the presence of DMAP. The 1,2-*trans* glycoside **18** was quantitatively anomerized to give **19** in the presence of $BF_3{\cdot}OEt_2$ at –30 °C. The 1,2-*cis* configuration of anomeric position was confirmed by ^{1}H NMR coupling constant (J = 2.8 Hz).



Scheme 3. Glycosylation and anomerization through endocyclic cleavage reaction

In conclusion, we have demonstrated that our anomerization strategy is useful for the 1,2-*cis*-selective synthesis of amino sugar units. Although we have only reported a model study in this paper, our strategy could be generalized to the synthesis of zwitterionic polysaccharides in the future.

EXPERIMENTAL

^{1}H NMR spectra were recorded with AL 400 spectrometer (JEOL) at ambient temperatures (24–26 °C). Chemical shifts (δ) are reported in ppm relative to remaining solvent peak $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR spectra. ^{13}C NMR chemical shifts (δ) are reported in ppm relative to $\underline{C}DCl_3$ (δ = 77.00 ppm). Optical rotations were measured at room temperature (JASCO DIP-310). All commercial reagents were used without further purification. Analytical TLC was performed on silica gel 60 F254 plates (Merck) and visualized by UV fluorescence quenching and 12 Molybdo(VI) phosphoric acid acid/phosphoric acid/ sulfuric acid staining. Flash column chromatography was performed on silica gel 60N (spherical, neutral, 40–100 μm, Kanto Co.). Yields reported here are isolated yields.

Phenyl 3-*O*-acetyl-2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-1-thio-β-D-glucopyranoside

Phenyl 3-*O*-acetyl-4,6-*O*-isopropylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[17] (1.45 g, 3.29 mmol) was dissolved in pyridine (10 mL), and Ac_2O (5 mL) was added. After stirring the mixture overnight, the mixture was concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc 7:3-1:1) to give 1.56 g (98%) of acetate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.76-7.74 (m, 2H), 7.37-7.36 (m, 2H), 7.27-7.26 (m, 3H), 5.78 (d, *J* = 10.4 Hz, 1H), 5.70 (t, *J* = 9.2 Hz, 1H), 4.29 (t, *J* = 10.0 Hz, 1H), 4.03 (dd, *J* = 10.8 Hz, 5.2 Hz, 1H), 3.86-3.77 (m, 2H), 3.65-3.61 (m, 1H),

1.88 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 167.8, 167.3, 134.4, 134.2, 132.9, 131.7, 131.3, 131.2, 129.0, 128.2, 123.7, 99.8, 83.8, 71.8, 71.6, 71.0, 62.0, 54.3, 28.9, 20.6, 19.0. [α] +29.4 (*c* 1.2, $CHCl_3$). HRMS calcd for $[C_{25}H_{25}NO_7S+Na]^+$ 506.1244; found 506.1257.

Phenyl 3-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (5)

A mixture of acetal (1.56 g, 3.22 mmol) in trifluoroacetic acid (1 mL), H_2O (0.25 mL), and CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. After concentration, the mixture was washed with Et_2O-hexane to give diol **5** (1.28 g, 90%). The diol **5** was used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.76-7.75 (m, 2H), 7.39-7.37 (m, 2H), 7.27-7.17 (m, 3H), 5.76 (d, *J* = 10.8 Hz, 1H), 5.66 (t, *J* = 9.2 Hz, 1H), 4.30 (t, *J* = 10.8 Hz, 1H), 4.00 (dd, *J* = 15.2 Hz, 3.2 Hz, 1H), 3.87 (dd, *J* = 15.2 Hz, 4.4 Hz, 1H), 3.81 (t, *J* = 9.6 Hz, 1H), 3.68 (m, 1H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 134.5, 134.3, 122.7, 131.5, 131.4, 129.0, 128.2, 123.7, 83.1, 79.6, 74.5, 69.9, 62.4, 53.7, 20.7. [α] +41.4 (*c* 0.5, $CHCl_3$). HRMS calcd for $[C_{22}H_{21}NO_7S+Na]^+$ 466.0931; found 466.0926.

Phenyl 3-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-6-*O*-(4-toluenesulfonyl)-β-D-glucopyranoside (7)

To a solution of diol **5** (1.56 g, 3.52 mmol) in pyridine (20 mL), TsCl (1.34 g, 7.04 mmol) was added at room temperature in several portions. After overnight, pyridine was evaporated, and the residue was diluted with $CHCl_3$ and 1 M HCl. The aqueous layer was washed with $CHCl_3$ and the combined layers were washed with brine. After drying the mixture over Na_2SO_4 and evaporation, the residue was purified by silica gel column chromatography (hexane:EtOAc 4:1-1:1) to give compound **7** (1.68 g, 80%) and **11** (185 mg, 7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.76 (m, 6H), 7.36-7.33 (m, 4H), 7.26-7.20 (m, 3H), 5.70 (d, *J* = 10.8 Hz, 1H), 5.65 (t, *J* = 9.6 Hz, 1H), 4.41-4.36 (m, 2H), 4.23 (t, *J* = 10.8 Hz, 1H), 3.77 (m, 1H), 3.71 (m, 1H), 2.92 (bs, 1H), 2.44 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 145.1, 134.3, 132.9, 132.7, 131.2, 129.9, 128.9, 128.2, 128.1, 123.7, 83.0, 77.5, 74.1, 69.0, 68.4, 53.3, 21.7, 20.6. [α] +29.8 (*c* 0.98, $CHCl_3$). HRMS calcd for $[C_{29}H_{27}NO_9S_2+Na]^+$ 620.1019; found 620.1103.

Phenyl 3-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-4,6-di-*O*-(4-toluenesulfonyl)-β-D-glucopyranoside (11)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.72 (m, 10H), 7.35-7.24 (m, 7H), 5.78 (t, *J* = 8.8 Hz, 1H), 5.58 (d, *J* = 10.4 Hz, 1H), 4.68 (t, *J* = 9.2 Hz, 1H), 4.34 (d, *J* = 11.2 Hz, 1H), 4.24 (t, *J* = 10.0 Hz, 1H), 4.03 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.81 (m, 1H), 2.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 167.6, 166.8, 145.5, 145.1, 134.5, 133.3, 133.2, 132.7, 131.5, 130.4, 129.9, 129.0, 128.5, 128.2, 128.1, 127.7, 123.7, 100.5, 82.8, 75.4, 74.6, 70.7, 67.5, 21.7, 20.2. [α] +30.3 (*c* 0.61, $CHCl_3$). HRMS calcd for $[C_{35}H_{11}NO_{11}S_3+Na]^+$ 760.0951; found 760.0973.

Phenyl 3-*O*-acetyl-2,6-dideoxy-6-iodo-2-phthalimido-1-thio-β-D-glucopyranoside (8)

A suspension of tosylate **7** (955 mg, 1.60 mmol) and NaI (400 mg, 1.26 mmol) in 2-butanone (30 mL), was stirred at 80 °C overnight. After cooling the mixture to room temperature, sat. aq. $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc several times. The combined layers were washed with brine and dried over Na_2SO_4. After filtration and concentration, the mixture was purified by silica gel column chromatography (hexane:EtOAc 7:3-1:1) to give iodide **8** (850 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.78-7.76 (m, 2H), 7.51-7.49 (m, 2H), 7.29-7.26 (m, 3H), 5.74 (d, *J* = 10.4 Hz, 1H), 5.65 (t, *J* = 9.6 Hz, 1H), 4.28 (t, *J* = 10.8 Hz, 1H), 3.68-3.59 (m, 2H), 3.48-3.41 (m, 2H), 2.66 (d, *J* = 5.2 Hz, 1H), 1.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 134.5, 133.7, 130.7, 128.9, 128.4, 123.7, 82.7, 78.2, 74.4, 73.5, 53.4, 20.6, 5.8. [α] +19.2 (*c* 0.62, $CHCl_3$). HRMS calcd for $[C_{22}H_{20}NO_6IS+Na]^+$ 575.9948. found 575.9945.

Phenyl 3-*O*-acetyl-2,6-dideoxy-6-iodo-2-phthalimido-1-thio-4-*O*-(4-toluenesulfonyl)-β-D-glucopyranoside (12)

A suspension of tosylate **11** (0.23 g, 0.306 mmol) and NaI (56 mg, 0.380 mmol) in 2-butanone (5 mL), was stirred at 80 °C. After overnight, the mixture was diluted with EtOAc and sat. aq. $NaHCO_3$ was added. After extracted with EtOAc several times, the combined layers were washed with brine. After drying over Na_2SO_4 and concentration, the residue was washed with ether-hexane to give iodide **12** (66 mg, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.77-7.74 (m, 4H), 7.51-7.50 (m, 2H), 7.34-7.29 (m, 5H), 5.82 (t, *J* = 9.2 Hz, 1H), 5.72 (d, *J* = 10.4 Hz, 1H), 4.67 (t, *J* = 9.2 Hz, 1H), 4.28 (t, *J* = 10.8 Hz, 1H), 3.60 (m, 1H), 3.53 (dd, *J* = 12.8 Hz, 2.4 Hz, 1H), 3.19 (dd, *J* = 11.2 Hz, 7.2 Hz, 1H), 2.43 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.0, 145.3, 134.5, 134.0, 133.6, 130.1, 130.0, 128.9, 128.7, 127.7, 127.6, 123.7, 82.8, 78.8, 76.7, 70.4, 53.8, 21.6, 20.1, 3.6. [α] 25.7 (*c* 0.47, $CHCl_3$). HRMS calcd for $[C_{29}H_{26}NO_8S_2+Na]^+$ 730.0037. found 730.0045.

Phenyl 3-*O*-acetyl-2,6-dideoxy-2-phthalimido-1-thio-β-D-glucopyranoside (9)

To a solution of iodide **8** (0.85 g, 1.54 mmol) in AcOH (2 mL) and CH_2Cl_2 (20 mL), Zn (5 g) was added at room temperature. After stirring the mixture for 2 h, Zn was filtered through celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc 7:3-1:1) to give 0.46 g (70%) of iodide **9**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.78 (m, 2H), 7.76-7.74 (m, 2H), 7.40-7.38 (m, 2H), 7.26-7.25 (m, 3H), 5.71 (d, *J* = 10.8 Hz, 1H), 5.60 (t, *J* = 10.4 Hz, 1H), 4.30 (t, *J* = 10.8 Hz, 1H), 3.66 (m, 1H), 3.43 (m, 1H), 2.44 (bs, 1H), 1.90 (s, 3H), 1.43 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 134.4, 134.2, 132.7, 128.9, 128.0, 123.6, 82.9, 76.4, 74.9, 74.8, 53.9, 20.7, 17.9. [α] +45.7 (*c* 0.53, $CHCl_3$). HRMS calcd for $[C_{22}H_{21}NO_6S+Na]^+$ 450.0982. found 450.0976.

Phenyl 3-*O*-acetyl-2,6-dideoxy-2-phthalimido-1-thio-4-*O*-(4-toluenesulfonyl)-β-D-glucopyranoside (13)

From **9**) To a mixture of alcohol (0.46 g, 0.771 mmol) in pyridine (10 mL), TsCl (409 mg, 2.15 mmol) was added. The mixture was stirred at room temperature for 3 h, then, warmed at 70 °C. After overnight, the mixture was concentrated. The residue was dissolved in $CHCl_3$ and 1 M HCl. The aqueous layer was extracted with $CHCl_3$ and the combined layers were washed with brine. After drying over Na_2SO_4, the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc 7:3-1:1) to give 0.32 g (55%) of tosylate **13**.

From **12**) To a solution of iodide **12** (0.20 g, 0.266 mmol) in AcOH (1 mL) and CH_2Cl_2 (10 mL), Zn (1 g) was added at room temperature. After stirring the mixture for 2 h, Zn was filtered through celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc 7:3-1:1) to give 99 mg (64%) of tosylate **13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.86-7.74 (m, 4H), 7.39-7.37 (m, 2H), 7.32-7.23 (m, 5H), 5.78 (t, *J* = 10.4 Hz, 1H), 5.67 (d, *J* = 10.8 Hz, 1H), 4.55 (t, *J* = 9.2 Hz, 1H), 4.28 (t, *J* = 10.0 Hz, 1H), 3.77 (m, 1H), 2.42 (s, 3H), 1.83 (s, 3H), 1.35 (d, *J* = 6.4 Hz, 3H). [α] +22.1 (*c* 0.29, $CHCl_3$). HRMS calcd for $[C_{30}H_{29}NO_7S_2+Na]^+$ 602.1278; found 602.1285.

Phenyl 3-*O*-acetyl-2,6-dideoxy-2-phthalimido-1-thio-4-*O*-trifluoromethanesulfonyl-β-D-glucopyranoside (10)

To a mixture of alcohol (0.47 g, 0.787 mmol) in pyridine (1 mL) and CH_2Cl_2 (10 mL), Tf_2O (0.26 mL, 1.57 mmol) was added at -20 °C. The mixture was stirred at -20 °C for 30 min, then 1 M HCl and EtOAc were added. The aqueous layer was extracted with EtOAc and the combined layers were washed with brine. After drying over Na_2SO_4, the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (hexane:EtOAc 7:3) to give 0.41 g of triflate **10** (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.88 (m, 2H), 7.78-7.76 (m, 2H), 7.40-7.26 (m, 5H), 5.88 (t, *J* = 9.2 Hz, 1H), 5.74 (d, *J* = 10.8 Hz, 1H), 4.66 (t, *J* = 9.2 Hz, 1H), 4.31 (t, *J* = 10.0 Hz, 1H), 3.93 (m, 1H), 1.91 (s, 3H), 1.48 (d, *J* = 6.3 Hz, 3H). [α] +28.1 (*c* 0.41, $CHCl_3$).

Phenyl 3-*O*-acetyl-4-azido-2,4,6-trideoxy-2-phthalimido-1-thio-β-D-glucopyranoside (6)

Method A) To a mixture of tosylate (0.32 g, 0.550 mmol) in DMF (3 mL), NaN_3 (0.15 g, 2.31 mmol) was added. The mixture was stirred at 120 °C overnight. After cooling the mixture to room temperature, the mixture was diluted with EtOAc and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined layers were washed with brine, and dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography (hexane:EtOAc 7:3) to give 0.18 g (72%) of product **6**.

Method B) A mixture of triflate (0.41 g, 0.733 mmol) in DMF (3 mL), NaN_3 (0.15 g, 2.31 mmol) was added. The mixture was stirred at 40 °C overnight. After cooling the mixture to room temperature, the mixture was diluted with EtOAc and sat. aq. $NaHCO_3$. The aqueous layer was extracted with EtOAc. The

combined layers were washed with brine, and dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography (hexane:EtOAc 7:3) to give 0.33 g of product **6** (quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.75 (m, 4H), 7.40-7.37 (m, 2H), 7.26-7.24 (m, 3H), 5.84 (dd, *J* = 10.8 Hz, 4.0 Hz, 1H), 5.61 (d, *J* = 10.8 Hz, 1H), 4.65 (t, *J* = 10.4 Hz, 1H), 3.98-3.93 (m, 2H), 1.96 (s, 3H), 1.41 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 168.1, 167.1, 134.3, 132.6, 131.9, 131.6, 131.3, 128.9, 128.0, 123.8, 123.6, 83.6, 73.4, 71.4, 63.6, 50.0, 20.4, 17.8. HRMS calcd for $[C_{22}H_{20}N_4O_5S+Na]^+$ 475.1047; found 475.1057.

Methyl (3-*O*-acetyl-2-amino-4-azido-2,4,6-trideoxy-2-phthalimido-β-D-glucopyranosyl)-(1 → 4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (15)

To a suspension of acceptor **14** (145 mg, 0.313 mmol), donor **6** (184 mg, 0.407 mmol), and NIS (101 mg, 0.448 mmol) in CH_2Cl_2 (3 mL), TMSOTf (10 μL, 0.0448 mmol) was added at -40 °C under Ar atmosphere. After 30 min, the reaction was quenched with 10% $Na_2S_2O_3$, and the aqueous layer was extracted with EtOAc. The combined layers were washed with sat. aq. $NaHCO_3$ and brine. After during over Na_2SO_4, the solvent was removed under reduced pressure. The residue was purified by gel filtration (SX-4, toluene) and silica gel column chromatography (hexane:EtOAc 7:3-1:1) to give 224 mg (89%) of disaccharide **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.61-7.57 (m, 3H), 7.30-7.07 (m, 15 H), 7.08-7.07 (m, 2H), 5.80 (dd, *J* = 11.6 Hz, 4.0 Hz, 1H), 5.23 (d, *J* = 8.8 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.72-4.55 (m, 4H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.32 (d, *J* = 3.6 Hz, 1H), 4.20 (d, *J* = 10.8 Hz, 1H), 4.05 (d, *J* = 8.8 Hz, 1H), 3.95 (d, *J* = 2.8 Hz, 1H), 3.89-3.82 (m, 2H), 3.62 (m, 1H), 3.56 (dd, *J* = 10.0 Hz, 5.2 Hz, 1H), 3.35 (dd, *J* = 9.6 Hz, 3.2 Hz, 1H), 3.21 (t, *J* = 9.2 Hz, 1H), 3.12 (s, 3H), 1.97 (s, 3H), 1.38 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 170.1, 168.4, 167.2, 138.7, 138.1, 137.9, 134.1, 131.4, 131.3, 128.4, 128.3, 128.0, 127.9, 127.7, 127.5, 123.5, 123.3, 98.4, 97.6, 81.8, 79.7, 77.8, 75.6, 74.7, 73.3, 7.6, 69.3, 69.2, 68.3, 63.3, 54.8, 51.1, 20.4, 17.4. [α] -17.9 (*c* 0.43, $CHCl_3$). HRMS calcd for $[C_{22}H_{20}N_4O_5S+Na]^+$ 475.1047; found 475.1056.

Methyl (2-amino-4-azido-2,4,6-trideoxy-β-D-glucopyranosyl)-(1 → 4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside) (16)

A solution of compound **15** (278 mg, 0.345 mmol) and ethylenediamine (0.2 mL) in DMF (1 mL) was stirred at 100 °C under Ar atmosphere overnight. After concentration, the residue was purified by silica gel column chromatography ($CHCl_3$:MeOH 9:1) to 180 mg of amino alcohol **16** (87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 15H), 4.99 (d, *J* = 10. 8 Hz, 1H), 4.90 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 10.8 Hz, 1H), 4.79 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.66-4.58 (m, 2H), 4.07 (d, *J* = 9.6 Hz, 1H), 4.00 (t, *J* = 9.2 Hz, 1H), 3.94 (d, *J* = 7.6 Hz, 1H), 3.82 (m, 1H), 3.82 (m, 1H), 3.62-3.41 (m, 15H), 3.38 (s, 3H), 3.32 (t, *J* = 5.6 Hz, 1H), 2.84 (t, *J* = 7.6 Hz, 1H), 1.33 (d, *J* = 6.4 Hz, 3H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 138.6, 138.3, 138.1, 128.4, 128.1, 128.0, 127.9, 127.7, 104.8, 97.9, 82.0, 79.8, 78.0, 77.2, 75.8, 74.8, 74.2, 73.3, 69.8, 69.7, 68.2, 65.9, 55.2, 54.0, 17.6. [α] +4.2 (*c* 0.92, $CHCl_3$). HRMS calcd for $[C_{34}H_{42}N_4O_8+H]^+$ 635.3075. found 635.3066.

Methyl (2-amino-4-azido-2,3-*N*,*O*-carbonyl-2,4,6-trideoxy-β-D-glucopyranosyl)-(1 → 4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (17)

To a solution of amino alcohol **16** (159 mg, 0.251 mmol) in MeCN (2 mL) and sat. aq. $NaHCO_3$ (0.5 mL), triphosgene (222 mg, 0.75 mmol) was added at 4 °C. After stirring the mixture at room temperature overnight, the mixture was acidified with 1 M HCl, and the aqueous layer was extracted with $CHCl_3$. The combined layers were washed with brine, and dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc 7:3-1:1) to give 135 mg of carbamate **17** (81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 15H), 5.17 (bs, 1H), 5.00 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.58-4.52 (m, 2H), 4.29 (d, *J* = 7.6 Hz, 1H), 4.10 (dd, *J* = 11.6 Hz, 2.8 Hz, 1H), 4.02-3.97 (m, 2H), 3.89 (bs, 1H), 3.80-3.86 (m, 3H), 3.72-3.70 (m, 1H), 3.62 (dd, *J* = 11.2 Hz, 5.2 Hz, 1H), 3.51 (dd, *J* = 9.2 Hz, 3.6 Hz, 1H), 3.41 (t, *J* = 9.6 Hz, 1H), 3.37 (s, 3H), 1.34 (d, *J* = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 138.5, 138.2, 138.0, 128.5, 128.2, 128.0, 127.7, 102.1, 98.1, 81.9, 79.7, 77.7, 75.8, 74.9, 73.4, 71.9, 69.6, 68.0, 60.5, 55.5, 55.3, 17.2. [α] +8.1 (*c* 0.37, $CHCl_3$). HRMS calcd for $[C_{35}H_{40}N_4O_9+H]^+$ 683.2688. found 661.2865.

Methyl (*N*-acetyl-2-amino-4-azido-2,3-*N*,*O*-carbonyl-2,4,6-trideoxy-β-D-glucopyranosyl)-(1 → 4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (18)

To a solution of carbamate **17** (230.5 mg, 0.349 mmol) in pyridine (3 mL), Ac_2O (2 mL) and DMAP (10 mg) were added. After 2 h, the mixture was concentrated, and the residue was dissolved in $CHCl_3$, and the organic layer was washed with 1 M HCl and brine. After drying over Na_2SO_4 and concentration, the residue was purified by silica gel column chromatography ($CHCl_3$:EtOAc 4:1-7:3) to give 183.6 mg of *N*-acetyl carbamate **18** (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 15H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.81-4.78 (m, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 3.6 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 7.6 Hz, 1H), 4.21 (t, *J* = 11.6 Hz, 1H), 4.12 (bs, 1H), 4.08 (m, 1H), 4.05 (m, 1H), 3.99 (t, *J* = 10.0 Hz, 1H), 3.95 (m, 1H), 3.97-3.95 (m, 2H), 3.67 (dd, *J* = 10.8 Hz, 4.4 Hz, 1H), 3.59-3.53 (m, 2H), 3.38 (s, 3H), 2.46 (s, 3H), 1.32 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 153.5, 138.8, 138.7, 138.2, 128.4, 128.4, 128.1, 128.0, 127.6, 102.2, 98.0, 82.2, 80.0, 77.7, 77.5,

75.6, 74.5, 73.4, 71.6, 69.7, 66.8, 60.2, 56.6, 55.2, 25.0, 24.9, 17.2. [α] -31.2 (*c* 0.84, $CHCl_3$). HRMS calcd for $[C_{37}H_{42}N_4O_{10}+H]^+$ 703.2973. found 703.2974.

Methyl (*N*-acetyl-2-amino-4-azido-2,3-*N*,*O*-carbonyl-2,4,6-trideoxy-α-D-glucopyranosyl)-(1 → 4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (19)

To a solution of 1,2-*trans* glycoside **18** (123.0 mg, 0.175 mmol) in MeCN (2 mL), $BF_3{\cdot}OEt_2$ (11 μL, 0.088 mmol) was dropped at -30 °C. After 2 h, the reaction was quenched with Et_3N, then mixture was diluted with $CHCl_3$ and sat. aq. $NaHCO_3$. After extraction of the aqueous layer with $CHCl_3$ several times, the combined layers were washed with brine. After drying the extract over Na_2SO_4, the solvent was removed *in vacuo*. The residue was purified by preparative TLC (hexane:EtOAc 7:3) to give 1,2-*cis* glycoside **19** (122.8 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (m, 15H), 5.65 (d, *J* = 2.8 Hz, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.85-4.66 (m, 3H), 4.58 (d, *J* = 9.2 Hz, 1H), 4.56-4.54 (m, 3H), 4.12 (dd, *J* = 12.4 Hz, 2.8 Hz, 1H), 4.00-3.93 (m, 3H), 3.74-3.67 (m, 3H), 3.51 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 3.34 (s, 3H), 3.30-3.28 (m, 1H), 2.41 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 152.7, 138.7, 138.0, 128.4, 128.4, 128.4, 128.1, 127.9, 127.9, 127.8, 127.6, 97.8, 96.1, 81.9, 79.8, 77.2, 75.5, 74.6, 73.6, 73.2, 69.9, 67.0, 66.8, 61.8, 55.6, 55.1, 23.7, 17.1. [α] -73.2 (*c* 1.0, $CHCl_3$). HRMS calcd for $[C_{37}H_{42}N_4O_{10}+H]^+$ 703.2973. found 703.2974.

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