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A SYNTHETIC APPROACH TO AROMATIC AMINOGLYCOSIDE AS A NEAMINE MIMIC†

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†Dedicated to Professor Dr. Albert Padwa on his 75th Birthday.

Abstract – This paper describes the synthetic approach to an aromatic α-glycoside as a mimic of neamine, which is a common core structure of some aminoglycoside antibiotics. We achieved the synthesis of the protected precursor of the neamine mimic, 4-(2,6-diamino-2,6-dideoxy-α-**D**-glucopyranosyloxy)-1,3-phenylenediamine, from *N*-acetyl-**D**-glucosamine and 2,4-diaminophenol as the starting materials using a glycosylation technique.

The aminoglycoside family is known as naturally occurring antibiotic drugs. They can bind to viral RNA structures, resulting in interference or blockage of protein biosynthesis in bacterial infections.[1] Some aminoglycosides, such as neomycin B and kanamycin B, have a common core structure, i.e., 4-*O*-(2,6-diamino-2,6-dideoxy-α-**D**-glucopyranosyl)-2-deoxystreptamine (Figure 1). The core structure is called neamine and is essential for their drug activities. The emergence of aminoglycoside-resistant pathogens has triggered the synthetic study of non-natural type aminoglycoside derivatives.[2] One of the recent focuses is directed to the synthetic exploration of potentially neamine-like small molecules.[3] Given that the RNA function is diverse, the discovery of small molecules that selectively bind to RNA may provide novel RNA-targeted drugs. Several groups have reported the syntheses of small molecules by mimicking neamine using carbohydrate[4] and heterocyclic compounds.[5] However, most of the small molecules reported so far have indicated only a modest affinity and selectivity for RNA.

We designed 4-(2,6-diamino-2,6-dideoxy-α-**D**-glucopyranosyloxy)-1,3-phenylenediamine (**1**) as a novel small neamine mimic as shown in Figure 1. Compound **1** has an aromatic aglycone structure which replaces the 2-deoxystreptamine unit of neamine with 2,4-diaminophenol, and is expected to have

aromatic π-π stacking abilities to increase the RNA-binding affinities. To the best of our knowledge, there has only been one report on the synthesis of an aromatic glycoside having more than one amino group in the monosaccharide moiety.[6] Scheme 1 shows the synthetic route for the preparation of **1**. One of the major concerns for synthesizing **1** was the formation of the α-glycosidic linkage. We decided to form the linkage by the glycosylation procedure using **2** and **7**, that is, **2** was the glycosyl acceptor and **7** was the glycosyl donor. Compound **2** was prepared in 94% yield from 2,4-diaminophenol dihydrochloride using *N*-(benzyloxycarbonyloxy)succinimide in pyridine.

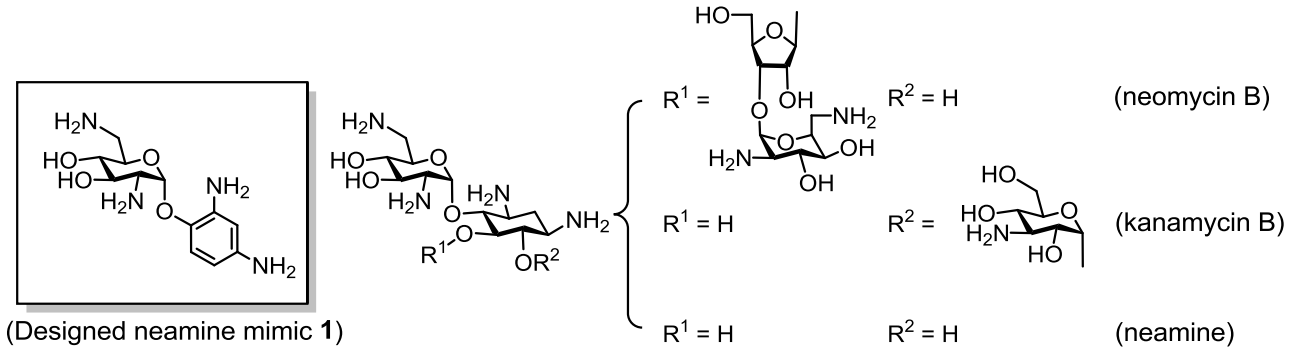
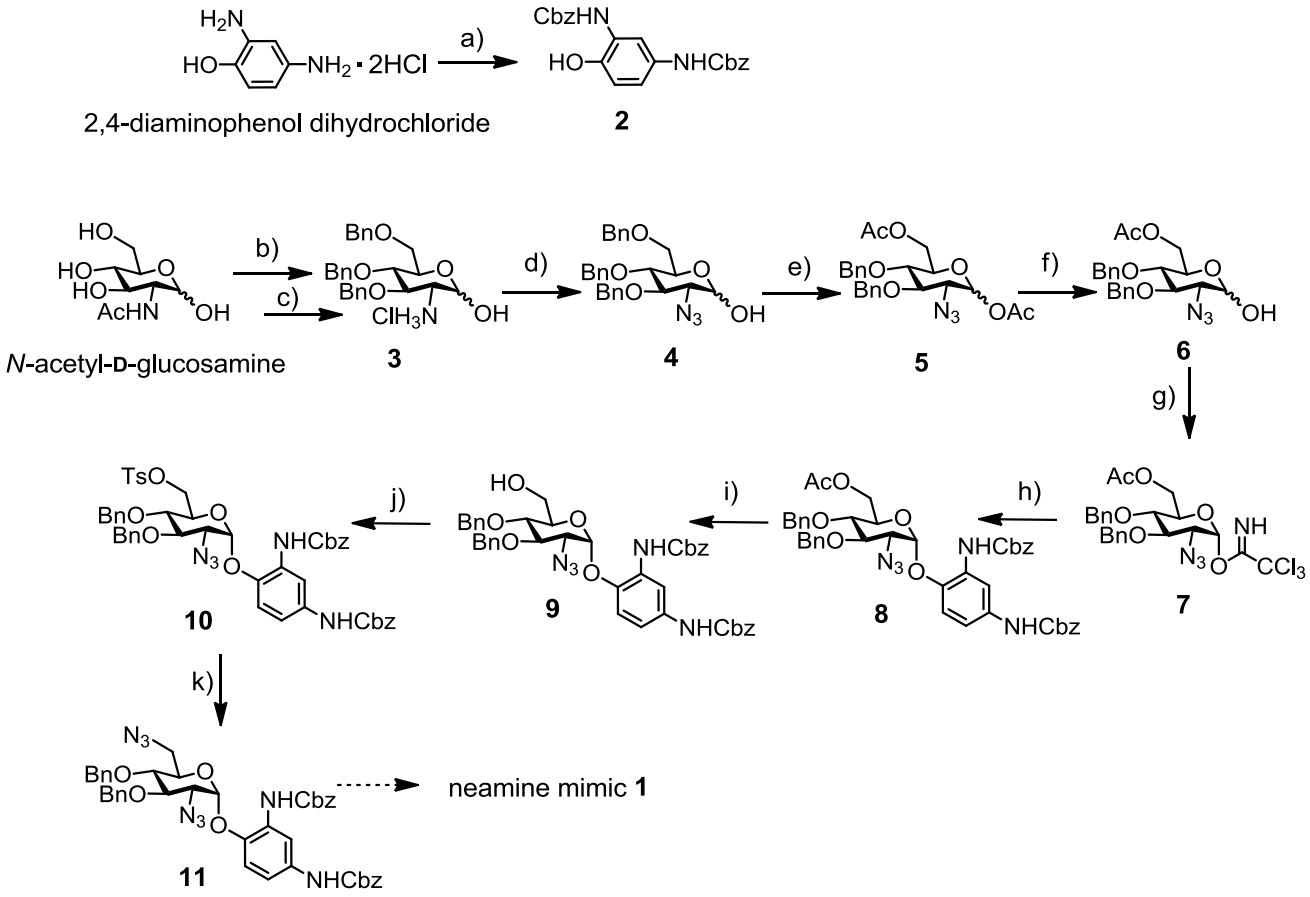


Figure 1

The convenient synthesis of **7** from *N*-acetyl-**D**-glucosamine was examined. The literature method using the benzylation of *N*-acetyl-**D**-glucosamine and the following acid hydrolysis afforded **3**.[7] Conversion of the amino group at C-2 of **3** into the azido group was achieved using Tf_2O and NaN_3[8] to produce **4** in 75% yield. The chemoselective conversion of the benzyloxy group at C-6 of **4** into the acetoxy group was then attempted using the acetolysis method. The optimized acetolysis conditions using TsOH in acetic anhydride[9] at 70 °C for 2 h successfully converted **4** into **5**[10] in 89% yield. Chemoselective deacetylation at C-1 of **5** was performed using $BnNH_2$ in THF to afford **6**[11] in 97% yield. The reaction of **6** with CCl_3CN using DBU in CH_2Cl_2 provided the glycosyl imidate **7**[12] in 98% yield.

When the glycosylation reaction of **2** with **7** was carried out using TMSOTf in CH_2Cl_2 at -20 °C for 6 h, the desired glycoside **8** was successfully obtained in 55% yield, and the glycosidic linkage of **8** was formed with an α-stereoselectivity. The α-stereoselectivity during the glycosidation would be explained by the effect of the acetoxy group at C-6 of **7**. Deprotection of the C-6 acetyl group of **8** was performed using NaOMe in MeOH-CH_2Cl_2 to afford **9** in 70% yield. The introduction of a tosyl group into the C-6 of **9** was carried out using TsCl in pyridine to provide **10** with quantitative yield. The following reaction of **10** with sodium azide in DMF at 60 °C quantitatively gave **11**. Compound **11** was corresponded to the protected precursor of **1**, which could be obtained by the hydrogenation of **11**. All compounds **2**-**11** were identified by their NMR and HRMS spectra.



Scheme 1. Synthetic route for the preparation of **1**

Reagents and conditions: a) Cbz-OSu, pyridine, 18 h, 94%; b) BnBr, BaO, $Ba(OH)_2$, DMF, 72 h, 68%[7]; c) 3M HCl, THF, reflux, 48 h, 83%[7]; d) Tf_2O, NaN_3, $CuSO_4$, K_2CO_3, MeOH-H_2O-CH_2Cl_2, 24 h, 75%; e) TsOH, Ac_2O, 70 °C, 24 h, 89%; f) $BnNH_2$, THF, 6 h, 97%; g) CCl_3CN, DBU, CH_2Cl_2, 0 °C, under Ar, 1 h, 98%; h) **2**, TMSOTf, $CaSO_4$, CH_2Cl_2, -20 °C, under Ar, 6 h, 55%; i) NaOMe, MeOH-CH_2Cl_2, 1.5 h, 70%; j) TsCl, pyridine, Et_3N, overnight, quant.; k) NaN_3, DMF, 60 °C, 8 h, quant.

In conclusion, the precursor **11** of the neamine mimic **1** was successfully synthesized from *N*-acetyl-**D**-glucosamine and 2,4-diaminophenol based on the glycosylation technique. We are now planning to evaluate the antibacterial activity of **1** and to design other aminoglycosides using **1** as a lead compound.

EXPERIMENTAL

^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a JEOL ECA-600 spectrometer in $CDCl_3$ or DMSO using TMS as an internal standard. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. Melting points were measured with a BÜCHI Melting Point B-545 and are uncorrected. HRMS were obtained on a Mariner spectrometer (PerSeptive Biosystems Inc.). Preparative TLC was performed using Merck silica gel 60GF254. Column chromatography was conducted using silica gel 60 N (40~50 μm, Kanto Chemical Co., INC.). All anhydrous solvents were purified according to standard methods.

Dibenzyl 4-hydroxy-1,3-phenylenedicarbamate (2): To a stirred solution of 2,4-diaminophenol dihydrochloride (107 mg, 0.54 mmol) in pyridine (5 mL) was added *N*-(benzyloxycarbonyloxy)-succinimide (402 mg, 1.6 mmol). After stirring for 18 h, a 30% aq. solution of citric acid (5 mL) was added to the reaction mixture. The resulting mixture was extracted with CH_2Cl_2 (5 mL), and the organic layer was washed with water and a sat. aq. NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was filtered and evaporated under reduced pressure. The crude product was purified using a preparative silica gel TLC (1:7 AcOEt-benzene) to give **2** (200 mg, 94% yield) as a white solid. mp 172-174 °C; ^{1}H NMR (DMSO): δ 6.51 (2H, s, CH_2), 6.55 (2H, s, CH_2), 8.14-9.25 (13H, m, Ph); ^{13}C NMR (DMSO): δ 66.9 (CH_2), 67.4 (CH_2), 112.6-143.7 (Ph), 154.9 (C=O), 155.6 (C=O).

2-Azido-3,4,6-tri-*O*-benzyl-2-deoxy-α,β-D-glucopyranose (4): A solution of NaN_3 (3.9 g, 60 mmol) in H_2O (12 mL)-CH_2Cl_2 (12 mL) was cooled in ice bath, and Tf_2O (2 mL, 12 mmol) was added to the mixture by a syringe during 5 min while vigorously stirring. After the reaction was maintained for 2 h in ice bath, the separated (TfN_3-containing) CH_2Cl_2 solution was added to a solution of **3** (3 g, 6.1 mmol), K_2CO_3 (1.3 g, 9.2 mmol) and $CuSO_4$•$5H_2O$ (15 mg, 0.061 mmol) in H_2O/ MeOH/ CH_2Cl_2 (20/ 40/ 20 mL). After the reaction mixture was stirred for 24 h, a sat. aq. NaCl solution (20 mL) was added to the reaction mixture. The resulting mixture was extracted with AcOEt (200 mL), and the organic layer was washed with water and a sat. aq. NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was filtered and evaporated under reduced pressure. The crude product was purified using a flash silica gel column chromatography (1:3 AcOEt-hexane) to give **4** (α/β ratio = 56/44, 2.2 g, 75% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.36 (t, *J* = 9.6 Hz, H-2β), 3.40 (dd, *J* = 2.7 Hz, *J* = 9.3 Hz, H-2α), 3.42 (t, *J* = 6.2 Hz, H-4β), 3.45-3.48 (m, H-5β), 3.54 (t, *J* = 9.6 Hz, H-3β), 3.57-3.68 (m, H-4α, H-6α, H-6β), 4.01 (t, *J* = 9.6 Hz, H-3α), 4.07-4.10 (m, H-5α), 4.47-4.58 (m, CH_2Ph), 4.50 (d, *J* = 7.6 Hz, H-1β), 4.77-4.81 (m, CH_2Ph), 4.85-4.88 (m, CH_2Ph), 5.30 (d, *J* = 2.7 Hz, H-1α), 7.12-7.37 (30H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 64.0 (C-2α), 67.4 (C-2β), 68.54 (C-6α or C-6β), 68.57 (C-6α or C-6β), 70.6 (C-5α), 73.45(CH_2Ph), 73.50 (CH_2Ph), 74.8 (C-5β), 74.98 (CH_2Ph), 75.00 (CH_2Ph), 75.50 (CH_2Ph), 75.54 (CH_2Ph), 77.7 (C-3β), 78.5 (C-4α), 80.1 (C-3α), 83.1 (C-4β), 92.0 (C-1α), 96.1 (C-1β), 127.8-137.8 (Ph); HRMS (ESI): m/z calcd for $C_{27}H_{29}N_3O_5$•Na^+: 498.1999, found: 498.1977.

1,6-Di-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α,β-D-glucopyranose (5): TsOH•H_2O (561 mg, 3 mmol) was added to a solution of **4** (701 mg, 1.5 mmol) in Ac_2O (10 mL). After stirring at 70 °C for 8 h, a sat. aq. $NaHCO_3$ solution (20 mL) was added to the reaction mixture. The resulting mixture was extracted with AcOEt (20 mL), and the organic layer was washed with water and a sat. aq. NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was filtered and evaporated under reduced

pressure. The crude product was purified using a flash silica gel column chromatography (1:3 AcOEt-hexane) to give **5** (α/β ratio = 63/37, 602 mg, 89% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.03 (s, CH_3), 2.15 (s, CH_3), 2.17 (s, CH_3), 3.55-3.61 (m, H-2β, H-3β, H-4β, H-5β), 3.60 (dd, *J* = 2.7 Hz, *J* = 10.3 Hz, H-2α), 3.64 (t, *J* = 9.6 Hz, H-4α), 3.91-3.93 (m, H-5α), 3.97 (t, *J* = 9.6 Hz, H-3α), 4.22 (dd, *J* = 4.1 Hz, *J* = 11.7 Hz, H-6aβ), 4.26-4.43 (m, H-6α, H-6bβ), 4.54-4.60 (m, CH_2Ph), 4.84-4.94 (m, CH_2Ph), 5.48 (d, *J* = 5.5 Hz, H-1β), 6.22 (d, *J* = 2.7 Hz, H-1α), 7.26-7.40 (20H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 20.7 (CH_3), 20.8 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 62.3 (C-6α), 62.4 (C-6β), 62.7 (C-2α), 65.1 (C-2β), 71.3 (C-5α), 73.9 (C-5β), 75.1 (CH_2Ph), 75.3 (CH_2Ph), 75.7 (CH_2Ph), 75.8 (CH_2Ph), 76.8 (C-3β or C-4β), 77.2 (C-4α), 80.5 (C-3α), 83.1 (C-3β or C-4β), 90.4 (C-1α), 92.7 (C-1β), 128.1-137.4 (Ph), 168.75 (C=O), 168.84 (C=O), 170.5 (C=O), 170.6 (C=O) [Lit. 10, ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.6 (CH_3), 20.7 (CH_3), 62.3 (C-6), 62.6 (C-2α), 65.0 (C-2β), 71.3, 77.2, 80.5 (C-3α, C-4α, C-5α), 73.7, 76.8, 83.0 (C-3β, C-4β, C-5β), 90.3 (C-1α), 92.5 (C-1β), 168.5, 170.3 (C=O)]; HRMS (ESI): m/z calcd for $C_{24}H_{27}N_3O_7$•Na^+: 492.1741, found: 492.1757.

6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α,β-D-glucopyranose (6): To a stirred solution of **5** (602 mg, 1.3 mmol) in THF (6 mL) was added benzylamine (0.56 mL, 5.1 mmol). After stirring for 6 h, a 30% aq. solution of citric acid (5 mL) was added to the reaction mixture. The resulting mixture was extracted with AcOEt (5 mL), and the organic layer was washed with water and a sat. aq. NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was filtered and evaporated under reduced pressure. The crude product was purified using a flash silica gel column chromatography (1:3 AcOEt-hexane) to give **6** (α/β ratio = 63/37, 529 mg, 97% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.03 (s, CH_3), 3.38 (t, *J* = 8.2 Hz, H-2β), 3.41 (dd, *J* = 2.7 Hz, *J* = 10.3 Hz, H-2α), 3.46-3.54 (m, H-3β, H-4β, H-5β), 3.56 (dd, *J* = 8.9 Hz, *J* = 9.6 Hz, H-4α), 4.06 (t, *J* = 10.3 Hz, H-3α), 4.10-4.12 (m, H-5α), 4.16 (dd, *J* = 4.1 Hz, *J* = 12.6 Hz, H-6aβ), 4.20 (dd, *J* = 4.1 Hz, *J* = 12.4 Hz, H-6aα), 4.32-4.36 (m, H-6bα, H-6bβ), 4.57 (d, *J* = 8.2 Hz, H-1β), 4.57-4.61 (m, CH_2Ph), 4.81-4.93 (m, CH_2Ph), 5.27 (t, *J* = 2.8 Hz, H-1α), 7.25-7.39 (20H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 20.8 (CH_3), 62.8 (C-6α), 62.8 (C-6β), 63.9 (C-2α), 67.4 (C-2β), 69.1 (C-5α), 73.2 (C-5β), 75.1 (CH_2Ph), 75.6 (CH_2Ph), 77.1 (C-3β or C-4β), 77.9 (C-4α), 80.1 (C-3α), 83.0 (C-3β or C-4β), 91.9 (C-1α), 96.1 (C-1β), 127.9-137.6 (Ph), 170.9 (C=O) [Lit. 11, ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4 (CH_3), 62.7 (C-6α, C-6β), 63.7 (C-2α), 66.0 (C-2β), 68.3, 77.7, 79.9 (C-3α, C-4α, C-5α), 74.6, 75.2 (CH_2Ph), 72.6, 76.9, 82.8 (C-3β, C-4β, C-5β), 91.3 (C-1α), 95.7 (C-1β), 171.0 (C=O)]; HRMS(ESI): m/z calcd for $C_{22}H_{25}N_3O_6$•Na^+: 450.1641, found: 450.1638.

6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-1-*O*-(2,2,2-trichloroacetimidoyl)-α-D-glucopyranose (7)[12a]: To a stirred solution of **6** (325 mg, 0.76 mmol) and in CH_2Cl_2 (2 mL) was added

2,2,2-trichloroacetonitrile (380 μL, 3.8 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (18 μL, 0.11 mmol) at 0 °C under Ar atmosphere. The above solution was stirred at 0 °C for 1 h, then concentrated and purified using a flash silica gel column chromatography (1:5 AcOEt-hexane) to give **7** (426 mg, 98% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.01 (3H, s, CH_3), 3.68 (1H, t, *J* = 9.6 Hz, H-4), 3.69 (1H, dd, *J* = 3.4 Hz, *J* = 9.6 Hz, H-2), 4.05-4.08 (1H, m, H-5), 4.06 (1H, t, *J* = 9.6 Hz, H-3), 4.24 (1H, dd, *J* = 4.1 Hz, *J* = 12.4 Hz, H-6a), 4.30 (1H, dd, *J* = 2.1 Hz, *J* = 12.4 Hz, H-6b), 4.60 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.88 (1H, d, *J* = 11.0 Hz, CH_2Ph), 4.94 (2H, s, CH_2Ph), 6.41 (1H, d, *J* = 3.4 Hz, H-1), 7.26-7.41 (10H, m, Ph), 8.74 (1H, s, NH) [Lit. 12a, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (3H, s, CH_3), 3.70 (2H, m, H-2, H-3 or H-4), 4.05 (2H, m, H-3 or H-4, H-5), 4.24-4.33 (2H, m, H-6), 4.61 (1H, m, CH_2Ph), 4.89 (1H, m, CH_2Ph), 4.96 (2H, s, CH_2Ph), 6.42 (1H, d, *J* = 3.8 Hz, H-1), 7.28-7.44 (10H, m, Ph), 8.76 (1H, s, NH)]; ^{13}C NMR ($CDCl_3$): δ 20.7 (CH_3), 62.2 (C-6), 63.1 (C-2), 71.7 (C-5), 75.3 (CH_2Ph), 75.6 (CH_2Ph), 77.3 (C-4), 80.2 (C-3), 90.8 (CCl_3), 94.5 (C-1), 128.1-137.4 (Ph), 160.7 (OC(NH)), 170.5 (C=O); HRMS (ESI): m/z calcd for $C_{24}H_{25}N_4O_6$•Na^+: 593.0732, found: 593.0721.

Dibenzyl 4-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyloxy)-1,3-phenylenedicarbamate (8): To a stirred solution of **2** (173 mg, 0.44 mmol) and **7** (167 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) was added TMSOTf (53 μL, 0.29 mmol) in the presence of anhydrous $CaSO_4$ (ca. 100 mg) at -20 °C under Ar atmosphere. After the reaction mixture was stirred for 6 h, the reaction was then quenched by addition of a sat. aq. $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (5 mL), and the organic layer was washed with water and a sat. aq. NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was filtered and evaporated under reduced pressure. The crude product was purified using a preparative silica gel TLC (1:2 AcOEt-hexane) to give **8** (130 mg, 55% yield) as a colorless oil. $[\alpha]_D^{25}$ +43° (*c* 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.16 (3H, s, CH_3), 3.61 (1H, dd, *J* = 8.9 Hz, *J* = 9.6 Hz, H-4), 3.69 (1H, dd, *J* = 4.1 Hz, *J* = 9.6 Hz, H-2), 4.11 (1H, dd, *J* = 8.9 Hz, *J* = 9.6 Hz, H-3), 4.20-4.23 (1H, m, H-5), 4.26 (1H, dd, *J* = 5.5 Hz, *J* = 11.7 Hz, H-6a), 4.36 (1H, dd, *J* = 2.1 Hz, *J* = 11.7 Hz, H-6b), 5.01 (1H, d, *J* = 4.1 Hz, H-1), 6.95-8.09 (22H, m, Ph, H-5' or H-6'), 7.03 (1H, d, *J* = 8.2 Hz, H-5' or H-6'); ^{13}C NMR ($CDCl_3$): δ 20.7 (CH_3), 62.6 (C-6), 64.1 (C-2), 66.9 (CH_2Ph), 70.3 (C-5), 75.1 (CH_2Ph), 75.8 (CH_2Ph), 77.8 (C-4), 81.0 (C-3), 99.6 (C-1), 120.1 (C-5' or C-6'), 127.9-137.2 (Ph, C-5' or C-6'), 153.2 (C=O), 163.6 (C=O), 170.6 (C=O); HRMS (ESI): m/z calcd for $C_{44}H_{43}N_5O_{10}$•Na^+: 824.2902, found: 824.2869.

Dibenzyl 4-(2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyloxy)-1,3-phenylenedicarbamate (9): To a solution of **8** (62 mg, 0.077 mmol) in MeOH (20 mL)-CH_2Cl_2 (0.5 mL) were added a 28% methanol solution of NaOMe (0.3 mL, 0.0016 mmol) at rt. After stirring 1.5 h, water (5 mL) was added to

the reaction mixture. The resulting mixture was extracted with AcOEt (5 mL), and the organic layer was washed with water and a sat. aq. NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the organic solvent was filtered and evaporated under reduced pressure. The crude product was purified using a preparative silica gel TLC (1:1 AcOEt-hexane) to give **9** (41 mg, 70% yield) as a colorless oil. $[\alpha]_D^{27}$ + 41° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.65 (1H, dd, *J* = 3.4 Hz, *J* = 9.6 Hz, H-2), 3.72 (1H, t, *J* = 9.6 Hz, H-4), 3.79 (1H, bd, *J* = 11.7 Hz, H-6a), 3.88 (1H, bd, *J* = 12.4 Hz, H-6b), 4.02-4.09 (1H, m, H-5), 4.11 (1H, t, *J* = 9.6 Hz, H-3), 4.99 (1H, d, *J* = 3.4 Hz, H-1), 6.95-8.09 (22H, m, Ph, H-5' or H-6'), 6.98 (1H, d, *J* = 8.2 Hz, H-5' or H-6'); ^{13}C NMR ($CDCl_3$): δ 61.2 (C-6), 64.2 (C-2), 66.9 (CH_2Ph), 72.6 (C-5), 75.1 (CH_2Ph), 75.8 (CH_2Ph), 77.5 (C-4), 80.8 (C-3), 99.8 (C-1), 120.3 (C-5' or C-6'), 127.8-137.6 (Ph, C-5' or C-6'), 153.1 (C=O), 153.2 (C=O); HRMS (ESI): m/z calcd for $C_{42}H_{41}N_5O_9$•Na^+: 782.2796, found: 782.2776.

Dibenzyl 4-(2-azido-3,4-di-*O*-benzyl-2-deoxy-6-*O*-tosyl-α-D-glucopyranosyloxy)-1,3-phenylenedicarbamate (10): To a solution of **9** (40 mg, 0.053 mmol) and TsCl (201 mg, 1.1 mmol) in pyridine (5 mL) was added Et_3N (147 μL, 1.1 mmol) at rt. After stirring for overnight, a 30% aq. solution of citric acid (5 mL) was added to the reaction mixture. The resulting mixture was extracted with CH_2Cl_2 (5 mL). After the organic layer was dried over anhydrous Na_2SO_4, the solvent was filtered and evaporated under reduced pressure. The crude product was purified using a preparative silica gel TLC (1:2 AcOEt-hexane) to give **10** (48 mg, quantitative yield) as a colorless oil. $[\alpha]_D^{25}$ +40° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.40 (3H, s, CH_3), 3.61 (1H, dd, *J* = 3.4 Hz, *J* = 9.6 Hz, H-2), 3.64 (1H, t, *J* = 9.6 Hz, H-4), 4.05 (1H, t, *J* = 9.6 Hz, H-3), 4.10-4.14 (1H, m, H-5), 4.24 (1H, bd, *J* = 10.3 Hz, H-6a), 4.29 (1H, dd, *J* = 4.1 Hz, *J* = 11.0 Hz, H-6b), 4.94 (1H, d, *J* = 3.4 Hz, H-1), 6.67-8.02 (24H, m, Ph, H-5' or H-6'), 6.86 (1H, d, *J* = 8.9 Hz, H-5' or H-6') 7.77 (2H, d, *J* = 7.6 Hz, $SO_2C_6H_4$); ^{13}C NMR ($CDCl_3$): δ 21.6 (CH_3), 63.9 (C-2), 66.9 (CH_2Ph), 67.7 (C-6 and CH_2Ph), 70.1 (C-5), 75.1 (CH_2Ph), 75.8 (CH_2Ph), 77.2 (C-4), 80.7 (C-3), 99.6 (C-1), 119.9 (C-5' or C-6'), 127.8-137.2 (Ph, C-5' or C-6'), 152.7 (C=O), 153.1 (C=O); HRMS (ESI): m/z calcd for $C_{49}H_{47}N_5O_{11}$•Na^+: 936.2885, found: 936.2877.

Dibenzyl 4-(2,6-diazido-3,4-di-*O*-benzyl-2,6-dideoxy-α-D-glucopyranosyloxy)-1,3-phenylenedicarbamate (11): To a solution of **10** (45 mg, 0.049 mmol) in DMF (5 mL) was added NaN_3 (16 mg, 0.24 mmol). After stirring at 60 °C for 8 h, water (5 mL) was added to the reaction mixture. The resulting mixture was extracted with AcOEt (5 mL). After the organic layer was dried over anhydrous Na_2SO_4, the solvent was filtered and evaporated under reduced pressure. The crude product was purified using a preparative silica gel TLC (1:3 AcOEt-hexane) to give **11** (39 mg, quantitative yield) as a colorless oil. $[\alpha]_D^{22}$ +52° (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.40 (1H, dd, *J* = 5.5 Hz, *J* = 13.1 Hz, H-6a), 3.57 (1H,

dd, J = 2.7 Hz, J = 13.1 Hz, H-6b), 3.64 (1H, dd, J = 8.9 Hz, J = 9.6 Hz, H-4), 3.70 (1H, dd, J = 3.4 Hz, J = 9.6 Hz, H-2), 4.09 (1H, t, J = 9.6 Hz, H-3), 4.13-4.15 (1H, m, H-5), 5.05 (1H, d, J = 3.4 Hz, H-1), 6.69-8.05 (22H, m, Ph, H-5' or H-6'), 7.04 (1H, d, J = 8.2 Hz, H-5' or H-6'); ^{13}C NMR ($CDCl_3$): δ 51.0 (C-6), 64.1 (C-2), 66.9 (CH_2Ph), 71.7 (C-5), 75.2 (CH_2Ph), 75.9 (CH_2Ph), 78.4 (C-4), 80.7 (C-3), 99.7 (C-1), 120.0 (C-5' or C-6'), 127.7-137.4 (Ph, C-5' or C-6'), 153.1 (C=O), 153.2 (C=O); HRMS (ESI): m/z calcd for $C_{42}H_{40}N_8O_8$•Na^+: 807.2861, found: 807.2892.

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