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Supporting Information

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Dimeric Aminoglycosides as Antibiotics

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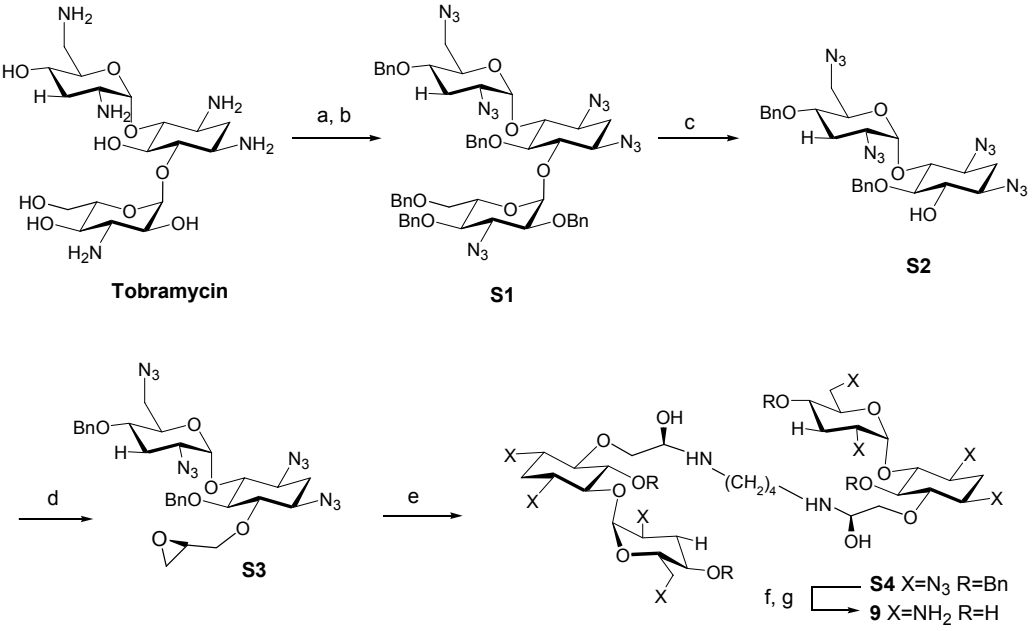
General Experimental. All reactions were performed in flame-dried glassware under an Ar atmosphere. THF and diethyl ether were distilled from benzophenone ketyl; acetonitrile, dichloromethane and toluene were distilled from calcium hydride. Reactions were monitored by analytical TLC on EM silicagel 60 F_{254} plates (film thickness 0.25 mm) and visualized by UV light and/or by staining with ceric ammonium molibdate or ninhydrin. NMR spectra were obtained on a Bruker AMX-400, DRX-500, DRX-600 or Varian Inova 400 spectrometers at room temperature. Perazido perbenzyl neamine was prepared as previously reported.[1]



Scheme S1. Reagents and conditions: (a)TfN_3, $ZnCl_2$, TEA, CH_2Cl_2/MeOH/H_2O, RT; (b) BnBr, NaH, Bu_4NI, DMF; (c) H_2SO_4, MeOH reflux; (d) (R)-(–)-glycidyl tosylate, NaH, DMF; (e) N,N'-dibenzyl-1,4-diaminobutane, EtOH, 70-85 °C ; (f) PMe_3, NH_4OH, H_2O/THF; (g) H_2, $Pd(OH)_2$/C, H_2O/AcOH.

Preparation of perazidotobramycin. Tobramycin pentasulfate (40 g, 56.1 mmol) was dissolved in 500 mL of water. A catalytic amount of $CuSO_4 \bullet 5H_2O$ (600 mg) was added followed by 80 mL of triethylamine (16 % the volume of H_2O). The mixture was diluted with 800 mL of MeOH (1.6 times the volume of water added) and cooled in an ice bath. Freshly prepared trifluormethane sulfonyl azide (561 mmol, 10 eq.) in dichloromethane was slowly added to this mixture. The reaction was allowed to warm to room temperature and stirred 16 h. The solution was concentrated to a volume consistent with that of the original amount of water added. The product was extracted four 300 mL-portions of ethyl acetate. The combined organics were washed 3 times with 1M NaOH and 3 times with saturated ammonium chloride and the organic layer dried (Na_2SO4), filtered, and concentrated to afford the product as a hygroscopic foam: 33.0 (99.5%);

silica gel TLC R_f 0.19 (1:2 hexanes-acetone); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.66-1.78 (m, 1 H), 2.02-2.09 (m, 2 H), 2.20 (dt, 1 H, *J* = 11.5, 4.5 Hz), 2.51 (dt, 1 H, *J* = 12.5, 4 Hz), 3.04 (1 H, br-s,), 3.25 (dt, 1 H, *J* = 12.3, 4.1 Hz), 3.38-3.90 (m, 10 H), 3.97-4.03 (m, 1 H), 4.09-4.15 (m, 1 H), 4.41 (d, 1 H, *J* = 8 Hz), 4.52 (br-s, 1 H), 4.78 (br-s, 1 H), 4.87 (d, 1 H, *J* = 4 Hz), 5.22 (d, 1 H, *J* = 3 Hz), 5.64 (d, 1 H, *J* = 3.5 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 32.2, 32.7, 52.2, 57.3, 60.4, 60.6, 62.0, 66.2, 68.5, 69.8, 72.0, 73.8, 73.9, 76.4, 79.9, 84.4, 98.0, 99.5; mass spectrum (ESI), *m*/*z* 620.1 $(M + Na)^+$ ($C_{18}H_{27}N_{15}NaO_9$ requires 620.2).

Preparation of perbenzyl-perazidotobramycin (S1). Perazidotobramycin (12.20 g, 20.4 mmol) was dissolved in 200 mL of dry DMF and cooled to 0 °C and purged with N_2. To the solution was added 12.25 g of 60 % sodium hydride (306 mmol) in paraffin over a 30-45 minute period. The resulting mixture was allowed to stir for 30 to 45 minutes at 0 °C. To the solution was added 26.71 mL of benzyl bromide (225 mmol) in a dropwise fashion over a 30-minutes. The reaction was allowed to warm to room temperature and stir for 2 hours. The completed reaction mixture was quenched with 400 mL of saturated ammonium chloride and extracted with three 300 mL-portions of diethyl ether. The combined organics were washed with water and brine. The organics were dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column chromatography on silica gel (110 g). Elution with (9:1 hexanes-ethyl acetate) afforded the product as a light yellow oil: 16.5 g (77% yield); TLC R_f 0.47 (4:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (q, 1 H, J = 12.5 Hz), 2.01 (q, 1 H, J = 11.5 Hz,), 2.35 (qt, 2 H, J = 13, 4.5 Hz), 3.00 (dt, 1 H, J = 12.5, 4 Hz), 3.10 (dd, 1 H, J = 11, 2.5 Hz), 3.26 (dd, 1 H, J = 11, 1.5 Hz), 3.32-3.82 (m, 11 H), 4.23 (t, 2 H, J =

11.5 Hz,), 4.46 (dd, 2 H, J = 12, 6 Hz), 4.58-4.83 (m, 6 H), 4.91 (m, 2 H), 5.5 (d, 1 H, J = 3.5 Hz), 5.64 (d, 1 H, J = 3.5 Hz), 6.94-7.44 (m, 25 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 32.0, 56.2, 59.4, 60.2, 64.0, 65.4, 67.7, 70.1, 70.8, 71.0, 71.8, 73.1, 73.5, 74.5, 74.9, 75.9, 77.1, 77.4, 77.8, 83.3, 95.8, 96.3,126.2, 127.2, 127.5, 127.8, 127.8, 127.9, 128.1, 128.1, 128.1, 128.2, 128.3, 128.5, 128.6, 137.3, 137.4, 137.5, 137.6, 137.9; mass spectrum (ESI), *m/z* 1070.4 $(M + Na)^+$ ($C_{53}H_{57}N_{15}NaO_9$ requires 1070.4).

Preparation of 5,4'-O-dibenzyl-perazidonebramine (S2). Perbenzyl-perazidotobramyicn (16.0 g, 15.3 mmol) was dissolved in 600 mL of methanol. To the solution was added 25 mL of concentrated sulfuric acid to make a 1.5 N methanolic solution. The reaction mixture was heated to gentle reflux for approximately 40 h, followed by careful TLC monitoring. After the starting material was consumed, the reaction mixture was cooled to room temperature and neutralized with 79 g of sodium bicarbonate (solid). The solution was concentrated to dryness and dissolved in 800 mL of ethyl acetate. The solid was extracted with three 400 mL-portions of ethyl acetate. The combined organics were dried (Na_2SO_4) filtered, concentrated, and purified by flash column chromatography on silica gel (110 g). Elution with a linear gradient of (2 % - 10 % acetone in hexane) afforded the product as a colorless oil: 4.82 g (65 %); TLC R_f 0.37 (4:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (m, 3 H), 2.1 (m, 1 H), 2.31 (m, 1 H), 2.40 (m, 1 H), 3.1 (m, 1 H), 3.48 (m, 6 H), 3.62 (m, 1 H), 4.22 (m, 1 H), 4.58 (m, 2 H), 4.90 (m, 1 H), 5.52 (d, 1 H, J = 3.5 Hz), 7.33 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.19, 32.29, 51.55, 56.58, 60.00, 60.44, 71.31, 71.36, 72.37, 75.69, 77.41, 77.63, 85.29, 97.18, 128.14, 128.29, 128.45, 128.96, 129.09, 137.9, 138.29 ; mass spectrum (ESI), m/z 613.2 $(M + Na)^+$ ($C_{26}H_{30}N_{12}NaO_5$ requires 613.2).

Preparation of 6-*O*-[(2*R*)-glycidyl]-perbenzyl-perazidonebramine (S3). 5,4'-*O*-Dibenzyl-perazidonebramine (2.78 g, 3.99 mmol) was dissolved in 30 mL dry DMF. The reaction mixture was purged with N_2 and cooled to 0 °C. To the solution was added 240 mg of 60 % NaH (5.99 mmol) in paraffin over a 30 minute period. The resulting solution was allowed to stir for 30 - 45 minutes at 0 °C. To the solution was added 1.37 g of (2*R*)-(-)-glycidyl tosylate (5.99 mmol) over a 30-minute period. The reaction was allowed to warm to room temperature and stirred 2 hours. The reaction was quenched with saturated ammonium chloride, extracted with diethyl ether, dried (Na_2SO_4) filtered and concentrated. The product was purified by flash column chromatography on silica gel (35 g). Elution with 8:1 hexanes-ethyl acetate afforded the product as a colorless oil: 2.28 g (76% yield); silica gel TLC R_f 0.55 (4:1 hexanes-ethyl actate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, 1 H, *J* = 13 Hz); 1.99-2.11 (m, 1 H); 2.26 (dt, 1 H, *J* = 13, 4.5 Hz); 2.37 (dt, 1 H, *J* = 11.5, 4.5 Hz); 2.50 (dd, 1 H, *J* = 5, 3 Hz); 2.78 (t, 1 H, *J* = 4.5 Hz); 3.07 (dt, 1 H, *J* = 13, 4 Hz); 3.17-3.22 (m, 1 H); 3.22 (m, 1 H); 3.25 (t, 1 H, *J* = 9 Hz); 3.33-3.70 (m, 5 H); 4.04 (dd, 1 H, *J* = 10.5, 3 Hz); 4.17-4.24 (m, 1 H); 4.47 (d, 1 H, *J* = 11.5 Hz);4.65 (d, 1 H, *J* = 11.5 Hz); 4.84 (d, 1 H, *J* = 10.5 Hz); 5.01 (d, 1 H, *J* = 10.5 Hz); 5.50 (d, 1 H, *J* = 3.5 Hz); 7.33 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.16, 32.52, 40.87, 50.83, 51.58, 56.49, 59.95, 60.32, 71.27, 71.35, 72.36, 75.63, 75.66, 77.60, 84.67, 86.18, 97.17, 128.19, 128.25, 128.31, 128.47, 128.87, 128.96, 137.90, 138.2; mass spectrum (ESI), *m*/*z* 669.3 $(M + Na)^+$ ($C_{29}H_{34}N_{12}NaO_6$ requires 669.3).

Preparation of perazidonebramine. Perazidotobramycin (17.00 g, 28.5 mmol) was taken up in 600 mL of methanol and concentrated H_2SO_4 (25 mL) was slowly added to the solution. The mixture was heated to reflux and stirred 22 h. The solution was

cooled to room temperature and neutralized with solid $NaHCO_3$. The solution was concentrated to dryness and the residue taken up in 100 mL of water. The solution was extracted with four 300 mL-portions of ethyl acetate, dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column chromatography on silica gel (120 g). Elution with 7:3 hexanes-ethyl acetate afforded the product as a colorless syrup: 7.59 g (65 %); silica gel TLC R_f 0.10 (6:1 hexanes- ethyl acetate); ^{1}H NMR (400 MHz, acetone-d_6): δ 1.46-1.56 (m, 1 H), 2.21 (dt, 1 H, J = 11, 4.5 Hz), 2.30-2.36 (m, 1 H), 2.91 (s, 1 H), 3.28 (dt, 1 H, J = 12.5, 4 Hz), 3.40-3.70 (m, 8 H), 4.09-4.14 (m, 1 H), 4.49 (d, 1 H, J = 5.5 Hz), 4.63 (s, 1 H), 4.90 (s, 1 H), 5.67 (d, 1 H, J = 3.5 Hz); ^{13}C NMR (100 MHz, acetone-d_6): δ 32.22, 32.96, 52.23, 57.31, 60.76, 61.38, 66.19, 73.80, 77.56, 77.88, 79.86, 97.70; mass spectrum (ESI), m/z 393.0 $(M - H_2O + H)^+$ ($C_{12}H_{17}N_{12}O_4$ requires 393.1).

Preparation of 4,5-*O*-cyclohexylidene perazidonebramine (10). Perazidonebramine (8.50 g, 20.70 mmol) was dissolved in 240 mL of a 1:1 toluene-acetonitrile solution. To the solution was added 5.97 g of 1,1-dimethoxycyclohexane (41.4 mmol) and a catalytic amount of *p*-toluenesulfonic acid (100 mg). The solution was placed on a rotary evaporator and allowed to stir at 50 °C under a reduced pressure of 400 mm Hg for 2 hours, followed by concentration to dryness. The crude mixture was taken up in diethyl ether and 20 mL of saturated sodium bicarbonate solution was added. The solution was extracted with three 50 mL-portions of diethyl ether. The organic were combined, dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column chromatography on silica (120 g). Elution with 6:1 hexanes-ethyl acetate afforded the product as a colorless oil: 8.84 g (87% yield); silica gel TLC R_f 0.40 (6:1

hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.72 (m, 12 H), 2.24 (dt, 1 H, *J* = 11.5, 4.5 Hz), 2.34 (dt, 1 H, *J* = 13.5, 5 Hz), 3.22 (dt, 1 H, *J* = 12, 4 Hz), 3.40-3.60 (m, 5 H), 3.63-3.73 (m, 2 H), 3.85-3.92 (m, 2 H), 5.50 (d, 1 H, *J* = 3.5 Hz,); ^{13}C NMR (100 MHz $CDCl_3$): δ 23.68, 23.72, 24.86, 31.39, 33.82, 35.99, 36.24, 51.30, 56.05, 57.22, 61.13, 65.94, 72.35, 77.01, 79.25, 79.45, 95.28, 113.74; mass spectrum (ESI), *m*/*z* 476.0, 415.1, 371.1, 327.0, 283.0, 238.9 $(M + H)^+$ ($C_{18}H_{27}N_{12}O_5$ requires 491.2).

Preparation of 4'-*O*-benzyl perazidonebramine (11). **Part a**: 4,5-*O*-cyclohexylidene perazidonebramine (1.2 g, 2.45 mmol) was taken up in 10 mL of dry DMF. The solution was cooled to 0 °C for 30 minutes followed by the addition of 60% NaH (117 mg, 2.94 mmol) in paraffin. The mixture was allowed to stir at 0 °C for 30 minutes. Benzyl bromide (502 mg, 2.94 mmol) was added dropwise at 0 °C. The mixture was allowed to warm up to room temperature after the addition of benzyl bromide was complete. The reaction was stirred 2 hours and quenched with 50 mL of aqueous ammonium chloride. The solution was extracted with three 50 mL-portions of diethyl ether, dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column chromatography on silica gel (35 g). Elution with 17:3 hexanes-ethyl acetate afforded the product as a colorless oil: 1.19 g (84% yield); silica gel TLC R_f 0.80 (4:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.72 (m, 11 H), 1.96-2.08 (m, 1 H), 2.22-2.37 (m, 2 H), 3.10 (dt, 1 H, *J* = 13, 3.5 Hz,), 3.33-3.62 (m, 7 H), 3.83 (t, 1 H, *J* = 9.5 Hz), 3.98-4.06 (m, 1 H), 4.43 (d, 1 H, *J* = 11.5 Hz,), 4.63 (d, 1 H, *J* = 11.5 Hz), 5.44 (d, 1 H, *J* = 3 Hz), 7.2-7.4 (m, 5 H); ^{13}C (100 MHz, $CDCl_3$) δ 23.76, 24.94, 28.36, 33.53, 36.02, 36.27, 51.24, 55.75, 56.61, 60.97, 61.03, 70.78, 72.14, 72.18, 79.22, 79.50, 95.53, 95.57, 113.61, 127.72, 128.12, 128.46, 137.70. **Part b**: 4'-*O*-

benzyl-4,5-*O*-cyclohexylidene perazidonebramine (1.19 g, 2.05 mmol) was dissolved in 100 mL of methanol. To the solution was added 1 mL of concentrated sulfuric acid. The solution was stirred at room temperature until complete. The solution was neutralized with saturated sodium bicarbonate, extracted with diethyl ether, dried (Na_2SO_4), filtered and concentrated. The product was purified by flash column chromatography on silica gel (35 g). Elution with a linear gradient of 10-40 % ethyl acetate in hexanes afforded the product as a colorless crystalline solid: 950 mg (92% yield); mp 80-81 ºC; silica gel TLC R_f 0.20 (6:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46-1.58 (m, 1 H), 1.99 (q, 1 H, J = 12 Hz), 2.32 (dt, 1 H, J = 13.5, 4 Hz), 2.41 (dt, 1 H, J = 11.5, 4.5 Hz), 3.30-3.60 (m, 10 H), 4.08-4.14 (m, 1 H), 4.50 (d, 1 H, J = 11.5 Hz), 4.67 (d, 1 H, J = 11.5 Hz), 5.20 (d, 1 H, J = 3.5 Hz), 7.29-7.41 (m, 5 H); ^{1}H NMR (100 MHz, $CDCl_3$) δ 28.18, 32.01, 51.15, 57.52, 58.97, 59.19, 71.13, 71.16, 71.81, 75.52, 76.23, 82.07, 97.81, 127.88, 128.13, 128.59, 137.42; mass spectrum (ESI), *m*/*z* 523.1 $(M + H)^+$ ($C_{19}H_{24}N_{12}NaO_5$ requires 523.2).

Preparation of 6-*O*-benzyloxymethoxy-4'-*O*-benzyl perazidonebramine (12). 4'-*O*-Benzyl perazidonebramine (2.62 g, 5.23 mmol) was dissolved in toluene (50 mL), added to a flask containing 3.43 g of dibutyl tin oxide (5.76 mmol) and equipped with a Dean-Stark trap. The solution was refluxed for 1 hour and cooled to room temperature. Benzyloxymethyl chloride (8.15g, 52.3 mmol) and 2.07 g of tetrabutylammonium iodide (5.23 mmol) were added to the solution and stirred at room temperature for 6 hours. The reaction was quenched with sodium bicarbonate, washed with diethyl ether and evaporated to dryness. The product was purified by flash column chromatography on silica gel (35 g). Elution with 8:1 hexanes-ethyl acetate afforded the product as a

colorless oil: 1.50 g (46 %); silica gel TLC R_f 0.55 (6:1 hexanes-ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (1H, ddd, *J* = 12.4, 13.0 Hz), 2.00 (1H, ddd, *J* = 11.9, 12.1 Hz), 2.22 (1H, ddd, *J* = 4.3, 13.0 Hz), 2.33 (1H, ddd, J = 4.4, 11.4 Hz), 3.16 (1H, ddd, *J* = 3.8, 12.6 Hz), 3.62-3.24 (13H, m), 4.13 (1H, m), 4.34 (1H, d, *J* = 2.0 Hz), 4.45 (2H, d, *J* = 11.5 Hz), 4.63 (2H, d, *J* = 11.4 Hz), 4.73 (1H, d, *J* = 11.2 Hz), 4.81 (1H, d, *J* = 7.0 Hz), 5.02 (1H, d, *J* = 7.0 Hz), 5.47 (1H, d, *J* = 3.4 Hz), 7.38-7.22 (10H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.30, 28.52, 32.46, 46.18, 51.62, 57.14, 59.39. 59.52, 60.02, 70.19, 71.00, 71.27, 71.34, 71.36, 72.48, 76.33, 80.61, 85.73, 96.72, 97.69, 127.42, 128.00, 128.26, 128.32, 128.49, 128.59, 128.32, 128.49, 128.63, 128.91, 128.95, 128.99, 129.06, 137.10, 137.98, 141.37; mass spectrum (ESI), *m*/*z* 643.2 $(M + Na)^+$ ($C_{27}H_{32}N_{12}NaO_6$ requires 643.3).

Preparation of 5-*O*-[(2*R*)-glycidyl]-6-*O*-benzyloxymethoxy-4'-*O*-benzyl perazidonebramine (13). Crude 4'-*O*-benzyl perazidonebramine (1.00 g, 1.61 mmol) was taken up in 10 mL of DMF and treated with 644 mg of 60 % sodium hydride in paraffin (16.1 mmol). To the solution was added 3.68 g of (2*R*)-(-)-glycidyl tosylate (16.1 mmol). The reaction was stirred 16 h and quenched with aqueous ammonium hydroxide. The solution was extracted with tree 100 mL-portions of diethyl ether. The organic layers were combined and dried ($MgSO_4$). The product was purified by flash column chromatography on silica gel (Biotage 40 M). Elution with 6:1 hexane-ethyl acetate afforded the product as a colorless glass: yield 200 mg; silica gel TLC R_f 0.57 (4:1 hexanes-ethyl acetate); ^{1}H NMR (400MHz, $CDCl_3$) δ 1.45 (ddd, 1 H, *J* = 13 Hz), 1.99 (ddd, 1 H, *J* = 13 Hz), 2.27 (m, 1 H), 2.32 (m, 1 H), 2.52 (dd, 1 H, *J* = 2.5, 5 Hz), 2.67 (t, 1 H, *J* = 4.5 Hz), 3.09 (m, 2 H), 3.27-3.51 (m, 9 H), 3.70 (dd, 1 H, *J* = 6, 10.5

Hz), 4.00 (dd, 1 H, *J* = 2.5, 10.5 Hz), 4.15 (m, 1 H), 4.41 (d, 1 H, *J* = 11.5 Hz), 4.60 (d, 1 H, *J* = 11.5 Hz), 4.75 (d, 1 H, *J* = 11.5 Hz), 4.88 (d, 1 H, *J* = 6.5 Hz), 4.96 (d, 1 H, *J* = 6.5 Hz), 5.44 (d, 1 H, *J* = 3.5 Hz), 7.20-7.31 (m, 10 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 28.23, 32.62, 44.50, 50.90, 51.54, 56.74, 59.81, 60.04, 60.20, 70.95, 71.34, 71.42, 72.44, 74.50, 77.52, 81.03, 85.421, 96.61, 97.19, 128.07, 128.16, 128.19, 128.27, 128.46, 128.86, 128.96, 137.94, 138.08; mass spectrum (ESI), *m*/*z* 700 $(M + Na)^+$ ($C_{30}H_{36}N_{12}NaO_7$ requires 699).

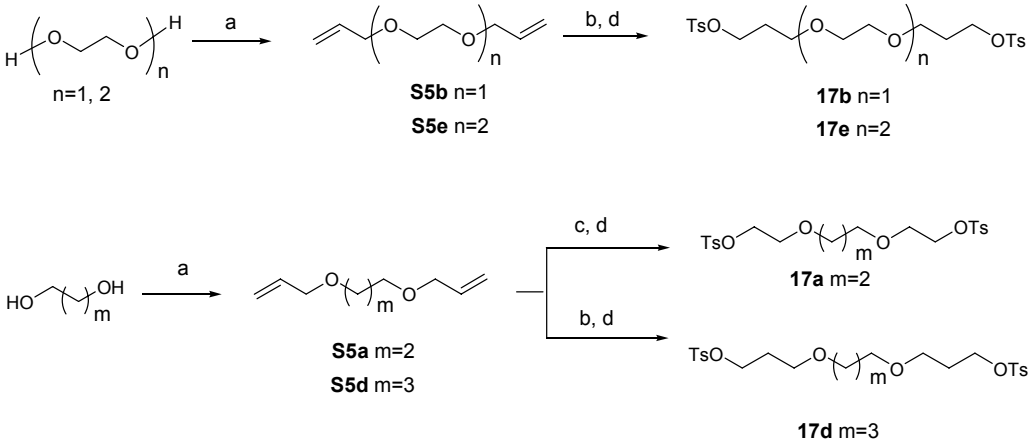
General Procedure for the Dimerization of Aminoglycoside Epoxides. In general 100 mg of epoxide and 0.5 equivalents of either 1,4-diaminobutane, *N*,*N*'-dibenzyl-1,4-diaminobutane or *N*,*N*' dimethyl-1,4-diaminobutane were dissolved in 1 mL of anhydrous ethanol in a 1 dram vial. The vial was capped and heated to 70-85 ºC for 24-48 h. The solution was concentrated and purified by flash column chromatography on silica gel (4 g). Elution with 95:5:1 dichloromethane-methanol-triethylamine to afford the products as foams: yields 50-80 %.

Deprotected Nebramine Dimer (9). Perazido-perbenzyl nebramine dimer **S4** (30 mg 0.022 mmol) was dissolved in 5 mL of tetrahydrofurane-water 10:1 with a catalytic amount of ammonium hydroxide. Trimethyl phosphine (1M in THF, 460 μL, 0.46 mmol) was added. The solution was stirred under N_2 for 24 hours followed by evaporation under diminished pressure. The resulting solid was dried under vacuum, dissolved in 2 mL of H_2O-AcOH (1:1) and 60 mg of 20% $Pd(OH)_2$/carbon (100 mg) was added to the solution. The mixture was stirred under H_2 (1 atm) for 24 hours, filtered through celite and dried under diminished pressure. The resulting solid was dissolved in water and purified by RP-HPLC (C18) to afford **9** as the pentafluoropropionate salt. The

salt was converted to the free base by cation exchange on Dowex® 50WX4-200 (H+ form) by elution with concentrated ammonium hydroxide. The product was lyophilized to provide a colorless microcrystalline solid: yield 8.3 mg (47 %); silica gel TLC R_f 0.68 (12:2:4:5 ammonium hydroxide-chloroform-ethanol-*n*-propanol); ^{1}H NMR (400MHz, D_2O) δ 1.77 (m, 4 H), 1.92 (ddd, 2 H, *J* = 13, 13, 13 Hz), 2.00 (ddd, 2 H, *J* = 9.5, 9.5, 9.5 Hz), 2.25 (ddd, 2 H, *J* = 4.5, 4.5, 13.5 Hz), 2.48 (ddd, 2 H, *J* = 12.5, 3.5, 3.5 Hz), 3.11 (m, 4 H), 3.20-3.24 (m, 6 H), 3.38-3.57 (m, 8 H), 3.66 (m, 4 H), 3.78-3.90 (m, 6 H), 4.02 (m, 4 H), 4.14 (m, 2 H), 5.72 (s, 2 H); ^{13}C NMR (100 MHz, D_2O); ^{13}C NMR (100 MHz, D_2O) δ 22.62, 28.01, 29.16, 39.80, 47.03, 47.77, 48.37, 49.02, 49.38, 64.43, 66.01, 70.12, 74.69, 75.38, 76.94, 81.61 and 94.02; mass spectrum (ESI+), *m/z* 813.5 $(M + H)^+$, ($C_{34}H_{73}N_{10}O_{12}$ requires 813.5).

Deprotected Nebramine Dimer (15). Perazido-perbenzyl nebramine dimer **14** (35 mg 0.022 mmol) was dissolved in 5 mL of tetrahydrofurane-water 10:1 with a catalytic amount of ammonium hydroxide. Trimethyl phosphine (1M in THF, 460 μL, 0.46 mmol) was added. The solution was stirred under N_2 for 24 hours followed by evaporation under diminished pressure. The resulting solid was dried under vacuum, dissolved in 2 mL of H_2O-AcOH (1:1) and 60 mg of 20% $Pd(OH)_2$/carbon (100 mg) was added to the solution. The mixture was stirred under H_2 (1 atm) for 24 hours, filtered through celite and dried under diminished pressure. The resulting solid was dissolved in water and purified by RP-HPLC (C18) to afford **15** as the pentafluoropropionate salt. The salt was converted to the free base by cation exchange on Dowex® 50WX4-200 (H+ form) by elution with concentrated ammonium hydroxide. The product was lyophilized to provide a colorless microcrystalline solid: yield 8.0 mg (45 %); silica gel TLC R_f 0.68

(12:2:4:5 ammonium hydroxide-chloroform-ethanol-*n*-propanol); ^{1}H NMR (400MHz, D_2O) δ 1.75 (m, 4H), 1.92 (ddd, 2H, *J* = 13, 13, 13 Hz), 2.02 (ddd, 2H, *J* = 9.5, 9.5, 9.5 Hz), 2.21 (ddd, 2H, *J* = 4.5, 4.5, 13.5 Hz), 2.48 (ddd, 2H, *J* = 12.5, 3.5, 3.5 Hz), 3.09 (m, 4H), 3.21-3.34 (m, 12H), 3.52 (m, 2H), 3.60 (dd, 2H, *J* = 9, 9 Hz), 3.67-3.79 (m, 6H), 3.83 (m, 2H), 3.95 (m, 2H), 4.06 (m, 2H), 4.12 (m, 4H), 5.57 (d, 2H, *J* = 3 Hz); ^{13}C NMR (100 MHz, D_2O) δ 22.7, 27. 9, 28.7, 39.3, 47.2, 47.4, 48.6, 49.7, 49.8, 50.3, 63.9, 65.9, 72.7, 73.9, 76.3, 82.8 and 93.5; mass spectrum (ESI+), *m/z* 814.4 $(M + D)^+$, ($C_{34}H_{72}DN_{10}O_{12}$ requires 814.6).



Scheme S2. Reagents and conditions: (a) Allyl Br, NaH, THF; (b) (i) BH_3, THF; (ii) H_2O_2, NaOH aq.; (c) (i) O_3, MeOH/CH_2Cl_2 -78 °C; (ii) $NaBH_4$ RT; d) TsCl, Py, 4 °C.

General Procedure for the Preparation of the Diallyl Ethers S5a, S5b, S5d and S5e. To a solution of the appropriate diol (20 mmol) in THF (40 mL) NaH (1.51 g, 3 eqs, 95% dry) was added and the resulting suspension was stirred at RT for 10 min. Bu_4NI (1.47 g, 0.2 eqs.) was then added, followed by allyl bromide (7.2 g, 3 eqs.) and stirring was continued for 3 hrs. The reaction was quenched with H_2O, diluted with

AcOEt (120 mL) and phases were separated. Organics were washed with HCl (1 N, 20 mL), H_2O (2 × 40 mL), brine (40 mL) and dried over $MgSO_4$. Excess solvent was removed *in vacuo* and the residue was distilled under reduced pressure to afford **S5a-e** as colorless oils.

Diallyl ether S5a. Obtained 1.72 g (56%, bp. 70 °C/10 mmHg). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 5.10 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1 H); 5.26 (ddd, *J* = 17.2, 3.3, 1.6 Hz, 1 H); 5.16 (ddd, *J* = 10.4, 2.9, 1.2 Hz, 1 H); 3.97 (dt, *J* = 5.6, 1.4 Hz, 2 H); 3.52 (t, *J* = 6.4 Hz, 2 H); 1.87 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 135.1, 116.3, 71.7, 67.3, 30.2.

Diallyl ether S5b. Obtained 2.15 g (76%, bp. 55 °C/10 mmHg). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 5.92 (ddt, *J* = 17.2, 10.4, 4.9 Hz, 1 H); 5.28 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1 H); 5.17 (dd, *J* = 10.4, 1.3 Hz, 1 H); 4.03 (dt, *J* = 5.6, 1.4 Hz, 2 H); 3.6 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 134.9, 116.6, 72.1, 69.5.

Dially ether S5d. Obtained 2.45 g (79%, bp. 90 °C/10 mmHg). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 5.91 (ddt, *J* = 17.3, 10.6, 5.6 Hz, 1 H); 5.26 (ddd, *J* = 17.3, 3.5, 1.5 Hz, 1 H); 5.15 (ddd, *J* = 10.6, 2.1, 1.2 Hz, 1 H); 3.96 (dt, *J* = 5.6, 1.5 Hz, 2 H); 3.45 (t, *J* = 6.2 Hz, 2 H); 1.67m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 135.1, 116.2, 71.6, 70.0, 26.4.

Diallyl ether S5e. Obtained 2.97 g (87%, bp. 108 °C/10 mmHg). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 5.91 (ddt, *J* = 17.3, 10.3, 5.9 Hz, 1 H); 5.27 (ddd, *J* = 17.1, 3.3, 1.8 Hz, 1 H); 5.15 (ddd, *J* = 10.6, 2.9, 1.5 Hz, 1 H); 4.02 (dt, *J* = 5.9, 1.5 Hz, 2 H); 3.66m, 2 H); 3.61m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 134.9, 116.5, 72.1, 70.6, 69.5.

Ditosylate 17a. A solution of **S5a** (500 mg, 3.2 mmol) in dichloromethane:methanol 5:1 (30 mL) was cooled to -78 °C and purged with O_2 for 5 min. Ozone was then bubbled in the solution for additional 10 min after persistent blue color formed and then purged with O_2 for additional 5 min. $NaBH_4$ (122 mg, 1 eq.) was then added and the solution allowed to warm RT over 1 hr. Excess $NaBH_4$ was quenched with acetone (2 mL) and the solvent removed *in vacuo*. The resulting residue was dissolved in dichloromethane, the white precipitate filtered and the filtrate was concentrated *in vacuo*. The resulting jellowish oil was dissolved in dry pyridine (1.8 mL), cooled to 4 °C and tosyl chloride (1.8 g, 3 eqs.) was added, stirring at this temperature overnight. The reaction mixture was partitioned between H_2O (40 mL) and EtOAc (70 mL) and phases were separated. Organics were washed with 1N HCl (2 × 40 mL), H_2O (40 mL), brine (20 mL) and dried over $MgSO_4$. Excess solvent was removed *in vacuo* and the resulting oil was column purified (silicagel, Hex:AcOEt 2:1) to obtain 550 mg (35%) of a colorless oil. ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.79 (d, J = 8.6 Hz, 2 H); 7.33 (d, J = 8.6 Hz, 2 H); 4.13 (t, J = 4.7 Hz, 2 H); 3.58 (t, J = 4.7 Hz, 2 H); 3.42 (t, J = 6.3 Hz, 2 H); 2.44 (s, 3 H); 1.70 (m, 1 H) ^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.7, 132.8, 129.7, 127.8, 69.2, 68.1, 67.8, 29.6, 21.5.

General Procedure for the Preparation of Ditosylates 17b, 17d and **17e.** To a solution of the appropriate diallyl ether **S5b-d** (2.9 mmol) in THF (20 mL) BH_3·THF complex (5.8 mL, 1M in THF, 2 eqs.) was added and stirred RT for 3 hrs. The reaction was quenched with H_2O (2 mL), followed by NaOH (2.9 mL, 15%) and H_2O_2 (2.9 mL, 30%) and stirring was continued for 3hrs. The reaction mixture was then diluted with AcOEt (40 mL), the acqueous phase was saturated with NaCl and the mixture stirred for

additional 30 min. Phases were separated and the acqueous layer was extracted with AcOEt (2 × 20 mL). The combined organics were dried over $MgSO_4$ and excess solvent was removed *in vacuo*. The resulting residue was dissolved in pyridine (2 mL), cooled to 4 °C and tosyl chloride (2.2 g, 2 eqs.) was added, stirring at this temperature overnight. The reaction mixture was partitioned between H_2O (40 mL) and EtOAc (70 mL) and phases were separated. Organics were washed with 1N HCl (2 × 40 mL), H_2O (40 mL), brine (20 mL) and dried over $MgSO_4$. Excess solvent was removed *in vacuo* and the resulting oil was column purified (silicagel, Hex:AcOEt 2:1) and/or recrystallized (hexanes:Et_2O), to obtain **17b-e** as white solids.

Ditosylate 17b. Obtained 621 mg (51%) ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.77 (d, *J* = 8.5 Hz, 2 H); 7.34 (d, *J* = 8.5 Hz, 2 H); 4.12 (t, *J* = 6.5 Hz, 2 H); 3.46 (t, *J* = 6.2 Hz, 2 H); 2.45 (s, 3 H); 1.90 (t, *J* = 6.2 Hz, 2 H); 1.25 (d, *J* = 6.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.6, 132.8, 129.7, 127.7, 69.9, 67.5, 66.4, 29.0, 21.4.

Ditosylate 17d. Obtained 733 mg (49%) ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.77 (d, *J* = 8.2 Hz, 2 H); 7.34 (d, *J* = 8.2 Hz, 2 H); 4.12 (t, *J* = 6.2 Hz, 2 H); 3.41 (t, *J* = 5.9 Hz, 2 H); 3.30 (s, 2 H); 2.44 (s, 3 H); 1.88 (m, 2 H); 1.48 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.6, 132.8, 129.7, 127.7, 70.6, 67.7, 65.8, 29.3, 26.1, 21.5.

Ditosylate 17e. Obtained 829 mg (54%) ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.78 (d, *J* = 7.9 Hz, 2 H); 7.34 (d, *J* = 7.9 Hz, 2 H); 4.13 (t, *J* = 6.1 Hz, 2 H); 3.53 (m, 2 H); 3.49 (m, 2 H); 2.44 (s, 3 H); 1.90 (q, *J* = 6.1 Hz, 2 H); 1.25 (d, *J* = 6.5 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 144.6, 133.0, 129.7, 127.8, 70.4, 70.2, 67.5, 66.4, 29.2, 21.5.

General Procedure for the Preparation of Protected Dimers 18a-h To a solution of perazido perbenzyl neamine (150 mg, 0.22 mmol) and the appropriate ditosylate **17a-h** (0.6 eqs) in DMF (2.2 mL) NaH (33 mg, 6 eqs., 95% dry) was added and the reaction was stirred at RT for 3 hrs. Excess NaH was quenched with 1 N HCl (1 mL), the resulting mixture diluted with AcOEt (100 mL) and organics were washed with H_2O (2 × 20 mL), brine and dried over $MgSO_4$. Excess solvent was removed *in vacuo* and the residue column purified (silicagel, gradient elution, Hex:AcOEt 8:1 to 4:1) to obtain the products as jellowish oils.

Dimer 18a. Obtained 85 mg (51 %). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.42 (d, *J* = 7.3 Hz, 2 H); 7.34 (m, 7 H); 7.28 (m, 6 H); 5.34 (d, *J* = 4.2 Hz, 1 H); 4.87 (m, 4 H); 4.78 (d, *J* = 11.0 H); 4.60 (d, *J* = 11.0 Hz, 1 H); 4.26 (m, 1 H); 4.05 (m, 1 H); 3.97 (m, 2 H); 3.52 (m, 7 H); 3.34 (m, 6 H); 2.23 (dt, *J* = 14.2, 4.6 Hz, 1 H); 1.84 (q, *J* = 6 Hz, 1 H); 1.40 (q, *J* = 13 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.7, 137.6, 137.4, 128.4, 128.0, 127.8, 127.6, 97.2, 84.6, 84.3, 80.0, 78.6, 75.7, 75.5, 75.0, 72.8, 70.9, 70.3, 68.4, 63.7, 59.9, 59.1, 50.9, 32.1, 30.1. MALDI-FTMS *(m / z)*: 1495.6767 $[(M-N_2+H_2)+H]^+$, $C_{73}H_{87}N_{22}O_{14}$ req. 1495.6767.

Dimer 18b. Obtained 88 mg (52%). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.32 (m, 15 H); 5.55 (d, *J* = 4.6 Hz, 1 H); 4.87 (s, 2 H); 4.87 (d, *J* = 11 Hz, 1 H); 4.79 (s, 2 H); 4.62 (d, *J* = 11 Hz, 1 H); 4.27 (m, 1 H); 4.00 (m, 2 H); 3.84 (dd, *J* = 8.3, 6.2 Hz, 1 H); 3.50 (m, 7 H); 3.32 (m, 6 H); 2.25 (dt, *J* = 13.4, 4.7 Hz, 1 H); 1.88 (m, 2 H); 1.42 (q, *J* = 13.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.6, 137.6, 137.3, 128.4, 128.2, 128.0, 127.9, 127.7, 97.5, 84.5, 79.9, 78.6, 77.4, 75.7, 75.4, 75.0, 70.9, 70.8, 70.0, 68.1, 63.2,

60.0, 59.1, 50.9, 32.1, 30.6. MALDI-FTMS *(m / z)*: 1509.7123 $[(M-N_2+H_2)+H]^+$, $C_{74}H_{89}N_{22}O_{14}$ req. 1509.6923.

Dimer 18c. Obtained 76 mg (46%). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.42 (d, *J* = 7.4 H); 7.31 (m, 13 H); 5.77 (d, *J* = 4.6 Hz, 1 H); 4.87 (m, 4 H); 4.78 (d, *J* = 10.3 Hz, 1 H); 4.61 (d, *J* = 11.2 Hz, 1 H); 4.25 (m, 1 H); 4.00 (m, 3 H); 3.57 (m, 8 H); 3.37 (m, 7 H); 2.23 (dt, *J* = 13.2, 4.6 Hz, 1 H); 1.41 (q, *J* = 12.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 138.0, 137.8, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 97.5, 84.8, 84.5, 80.1, 79.0, 77.5, 75.7, 75.4, 75.0, 72.8, 71.0, 70.7, 70.7, 70.6, 63.8, 60.4, 59.6, 51.3, 32.3. MALDI-FTMS *(m / z)*: 1525.7032 $[(M-N_2+H_2)+H]^+$, $C_{74}H_{89}N_{22}O_{15}$ req. 1525.6872.

Dimer 18d. Obtained 115 mg (67%). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.40 (d, *J* = 7.2 Hz, 2 H); 7.31 (m, 13 H); 5.56 (d, *J* = 4.2 Hz, 1 H); 4.88 (s, 2 H); 4.88 (d, *J* = 11.2 Hz, 1 H); 4.80 (s, 2 H); 4.62 (d, *J* = 11.2 Hz, 1 H); 4.28 (m, 1 H); 4.02 (m, 2 H); 3.87 (dd, *J* = 15.2, 6.4 Hz, 1 H); 3.52 (m, 7 H); 3.37 (m, 6 H); 2.25 (dt, *J* = 13.5, 4.2 Hz, 1 H); 1.88 (m, 2 H); 1.53 (s, 2 H); 1.42 (q, *J* = 13.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.7, 137.6, 137.4, 128.4, 128.2, 128.0, 127.9, 127.7, 97.5, 84.5, 79.9, 78.7, 77.5, 75.7, 75.4, 75.0, 71.0, 70.9, 70.7, 67.6, 63.3, 60.1, 59.2, 50.9, 32.2, 30.8, 26.3. MALDI-FTMS *(m / z)*: 1537.7273 $[(M-N_2+H_2)+H]^+$, $C_{76}H_{93}N_{22}O_{14}$ req. 1537.7236.

Dimer 18e. Obtained 76 mg (42%). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.34 (m, 15 H); 5.57 (d, *J* = 4.5 Hz, 1 H); 4.89 (s, 2 H); 4.89 (d, *J* = 7.3 Hz, 1 H); 4.80 (s, 2 H); 4.63 (d, *J* = 7.3 Hz, 1 H); 4.28 (m, 1 H); 4.01 (m, 2 H); 3.86 (dd, *J* = 14.3, 6.7 Hz, 1 H); 3.53 (m, 9 H); 3.36 (m, 6 H); 2.27 (dt, *J* = 13.2, 4.7 Hz, 1 H); 1.91 (m, 2 H); 1.44 (q, *J* = 12.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.6, 137.6, 137.3, 128.4, 128.2, 128.0,

127.9, 127.7, 97.5, 84.5, 79.9, 78.6, 77.4, 75.7, 75.4, 75.0, 70.9, 70.8, 70.4, 70.1, 68.1, 63.2, 60.0, 59.1, 50.9, 32.1, 30.7, 29.6. MALDI-FTMS *(m / z)*: 1553.7356 [(M-N_2+H_2)+H]$^+$, $C_{76}H_{93}N_{22}O_{15}$ req. 1553.7185.

Dimer 18f. Obtained 126 mg (72%). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.42 (d, *J* = 7.3 Hz, 2 H); 7.32 (m, 13 H); 5.77 (d, *J* = 4.2 Hz, 1 H); 4.87 (s, 2 H); 4.87 (d, *J* = 10.2 Hz, 1 H); 4.87 (d, *J* = 11.3 Hz, 1 H); 4.80 (d, *J* = 10.2 Hz, 1 H); 4.62 (d, *J* = 11.3 Hz, 1 H); 4.25 (m, 1 H); 4.02 (m, 2 H); 3.95 (dd, *J* = 9.8, 8.7 Hz, 1 H); 3.47 (m, 17 H); 2.25 (dt, *J* = 13.2, 4.1 Hz, 1 H); 1.40 (q, *J* = 12.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.6, 137.4, 128.4, 128.0, 128.0, 127.8, 127.8, 127.7, 97.2, 84.6, 84.3, 80.1, 78.6, 77.1, 75.7, 75.5, 74.9, 72.7, 70.8, 70.5, 70.4, 70.3, 63.5, 59.9, 59.0, 50.8, 32.1. MALDI-FTMS *(m / z)*: 1569.7126 [(M-N_2+H_2)+H]$^+$, $C_{76}H_{93}N_{22}O_{16}$ req. 1569.7134.

Dimer 18g. Obtained 115 mg (68%). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.36 (m, 15 H); 5.62 (d, *J* = 4.3 Hz, 1 H); 4.90 (s, 2 H); 4.90 (d, *J* = 11.3 Hz, 1 H); 4.86 (d, *J* = 10.1 Hz, 1 H); 4.81 (d, *J* = 10.1 Hz, 1 H); 4.64 (d, *J* = 11.3 Hz, 1 H); 4.29 (m, 1 H); 4.0 (dd, *J* = 10.5, 9.3 Hz, 1 H); 3.90 (q, *J* = 6.9 Hz, 1 H); 3.81 (q, *J* = 7.0 Hz, 1 H); 3.55 (m, 4 H); 3.37 (m, 5 H); 2.28 (dt, *J* = 13.2, 4.1 Hz, 1 H); 1.62 (m, 2 H); 1.44 (q, *J* = 13.2 Hz, 1 H); 1.27 (bs, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.6, 137.6, 137.4, 128.4, 128.1, 128.0, 127.9, 127.7, 97.5, 84.5, 84.3, 79.9, 78.6, 77.4, 75.7, 75.5, 75.0, 75.0, 74.1, 70.9, 63.3, 60.0, 59.1, 50.9, 32.2, 30.5, 29.6, 29.5, 26.1. MALDI-FTMS *(m / z)*: 15057389 [(M-N_2+H_2)+H]$^+$, $C_{76}H_{93}N_{22}O_{12}$ req. 1505.7338.

Dimer 18h. Obtained 85 mg (69%). ^{1}H NMNR (400 MHz, $CDCl_3$, δ): 7.33 (m, 15 H); 5.60 (d, *J* = 4.5 Hz, 1 H); 4.88 (s, 2 H); 4.88 (d, *J* = 10.8 Hz, 1 H); 4.88 (d, *J* =

10.0 Hz, 1 H); 4.82 (d, *J* = 10.0 Hz, 1 H); 4.62 (d, *J* = 10.8 Hz, 1 H); 4.28 (m, 1 H); 4.00 (dd, *J* = 10.2, 9.0 Hz, 1 H); 3.88 (dd, *J* = 13.7, 8.4 Hz, 1 H); 3.78 (q, *J* = 15.2, 7.4 Hz, 1 H); 3.54 (m, 4 H); 3.37 (m, 5 H); 2.26 (dt, *J* = 12.8, 4.1 Hz, 1 H); 1.60 (bs, 2 H); 1.42 (q, *J* = 13.4 Hz, 1 H); 1.24 (bs, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 137.6, 137.4, 128.4, 128.1, 128.0, 127.9, 127.7, 97.5, 84.6, 84.3, 79.9, 78.6, 77.4, 75.8, 75.5, 75.0, 74.1, 70.9, 63.3, 60.0, 59.1, 50.9, 32.2, 30.5, 29.6, 29.5, 26.1. MALDI-FTMS *(m / z)*: 1533.7652 $[(M-N_2+H_2)+H]^+$, $C_{78}H_{97}N_{22}O_{12}$ req. 1533.7651.

General Procedure for the Deprotection of Dimers 19a-h To a solution of protected dimers **18a-f** (0.05 mmol) in THF/MeOH 1:1 (10 mL) 20% $Pd(OH)_2/C$ (Degussa type) (1 weight equivalent) was added and the suspension was stirred under an H_2 atmosphere for 16 hrs. The catalyst was filtered and excess solvent removed in vacuo. The residue was dissolved in 0.1 N HCl (8 eq., 5 mL), diluted with MeOH (5 mL) and fresh palladium catalyst was added, stirring under an H_2 atmosphere for additional 16 hrs. The catalyst was filtered and the solvent was removed *in vacuo*. The glassy solid was dissolved in H_2O and directly applied onto a cation-exchange resin (Amberlite CG-50, 100-200 mesh, NH_4^+ form, pH 7.4) and eluted with aqueous NH_4OH (gradient elution 0 to 10%). The product-containing fractions were lyophilized to obtain **19a-f** as white solids.

Dimer 19a. Obtained 14 mg (36%). ^{1}H NMNR (400 MHz, D_2O, δ): 5.74 (d, *J* = 3.6 Hz, 1 H); 3.99 (m, 1 H); 3.87 (m, 2 H); 3.70 (m, 4 H); 3.62 (m, 3 H); 3.43 (m, 2 H); 3.25 (m, 4 H); 2.28 (dt, *J* = 12.2, 3.7 Hz, 1 H); 1.9 (p, *J* = 6.4 Hz, 1 H); 1.63 (q, *J* = 13 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O, δ): 94.9, 83.2, 77.4, 77.3, 73.1, 70.9, 70.4, 69.5,

69.0, 68.9, 67.9, 53.7, 50.1, 48.6, 40.2, 30.3, 28.1. MALDI-FTMS *(m / z)*: 773.4649 $[M+H]^+$, $C_{31}H_{66}N_8O_{14}$ req. 773.4615.

Dimer 19b. Obtained 15 mg (38%). ^{1}H NMNR (400 MHz, D_2O, δ): 5.24 (d, *J* = 1 H); 3.90 (m, 1 H); 3.82 (m, 2 H); 3.58 (m, 5 H); 3.35 (dd, *J* = 6.6, 2.7 Hz, 2 H); 3.28 (t, *J* = 9.3 Hz, 1 H); 3.21 (m, 1 H); 3.02 (dd, *J* = 13.6, 2.7 Hz, 1 H); 2.83 (m, 2 H); 2.69 (m, 3 H); 1.88 (m, 2 H); 1.14 (q, *J* = 12.5 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O, δ): 94.9, 80.3, 78.4, 73.7, 69.5, 68.7, 67.6, 65.4, 65.3, 64.0, 51.6, 46.4, 46.4, 37.7, 31.4, 25.4. MALDI-FTMS *(m / z)*: 1509.7123 $[(M-N_2+H_2)+H]^+$, $C_{74}H_{89}N_{22}O_{14}$ req. 1495.6767. MALDI-FTMS *(m / z)*: 784.4794 $[M+H]^+$, $C_{32}H_{67}N_8O_{14}$ req. 787.4771.

Dimer 19c. Obtained 15 mg (36%). ^{1}H NMNR (400 MHz, D_2O, δ): 5.79 (d, *J* = 3.9 Hz, 1 H); 4.21 (m, 1 H); 3.96 (m, 2 H); 3.85 (m, 2 H); 3.73 (bs, 6 H); 3.64 (t, *J* = 9.3 Hz, 1 H); 3.44 (m, 2 H); 3.33 (m, 4 H); 3.23 (m, 1 H); 2.35 (dt, *J* = 12.8, 4.2 Hz, 1 H); 1.72 (d, *J* = 12.2 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O, δ): 94.9, 83.0, 76.6, 73.0, 70.9, 70.5, 69.9, 69.5, 69.2, 68.5, 53.6, 50.0, 48.6, 40.2. MALDI-FTMS *(m / z)*: 803.4715 $[M+H]^+$, $C_{32}H_{67}N_8O_{15}$ req. 803.4720.

Dimer 19d. Obtained 13 mg (31%). ^{1}H NMNR (400 MHz, D_2O, δ): 5.79 (d, *J* = 3.9 Hz, 1 H); 4.21 (m, 1 H); 3.96 (m, 2 H); 3.85 (m, 2 H); 3.73 (bs, 6 H); 3.64 (t, *J* = 9.3 Hz, 1 H); 3.44 (m, 2 H); 3.33 (m, 4 H); 3.23 (m, 1 H); 2.35 (dt, *J* = 12.8, 4.2 Hz, 1 H); 1.72 (d, *J* = 12.2 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O, δ): 94.9, 83.0, 76.6, 73.0, 70.9, 70.5, 69.9, 69.5, 69.2, 68.5, 53.6, 50.0, 48.6, 40.2. MALDI-FTMS *(m / z)*: 815.5067 $[M+H]^+$, $C_{34}H_{71}N_8O_{14}$ req. 815.5084.

Dimer 19e. Obtained 17 mg (41%). ^{1}H NMNR (400 MHz, D_2O, δ): 5.26 (d, *J* = 3.5 Hz, 1 H); 3.89 (m, 1 H); 3.78 (m, 2 H); 3.64 (bs, 3 H); 3.59 (t, *J* = 6.6 Hz, 2 H); 3.37 (dd, *J* = 7.0,2.7 Hz, 1 H); 3.26 (m, 4 H); 3.07 (dd, *J* = 13.6, 2.7 Hz, 1 H); 2.86 (m, 2 H); 2.70 (dd, *J* = 10.1, 3.2 Hz, 3 H); 1.87 (m, 2 H); 1.16 (q, *J* = 12.5 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O, δ): 94.7, 80.3, 77.8, 69.3, 68.0, 67.5, 65.6, 65.4, 65.2, 63.9, 51.4, 46.4, 46.2, 37.4, 31.1, 25.4. MALDI-FTMS *(m / z)*: 831.5023 $[M+H]^+$, $C_{34}H_{71}N_8O_{15}$ req. 831.5033.

Dimer 19f. Obtained 17 mg (40%). ^{1}H NMNR (400 MHz, D_2O, δ): 5.90 (d, *J* = 4 Hz, 1 H); 4.29 (m, 1 H); 4.06 (m, 2 H); 3.96 (m, 1 H); 3.90 (m, 1 H); 3.80 (dd, *J* = 19.8, 9.5 Hz, 2 H); 3.71 (m, 9 H); 3.58 (m, 1 H); 3.47 (m, 1 H); 3.41 (dd, *J* = 11.0, 4.0 Hz, 1 H); 3.35 (dd, *J* = 12.5, 4.4 Hz, 1 H); 3.26 (dd, *J* = 13.9, 6.9 Hz, 1 H); 2.47 (dt, *J* = 12.5, 4.4 Hz, 1 H); 1.90 (q, *J* = 12.5 Hz, 1 H). ^{13}C NMR (100 MHz, D_2O, δ): 98.6, 84.6, 81.7, 81.7, 77.6, 73.1, 73.1, 72.0, 71.6, 70.9, 70.2, 69.7, 69.7, 69.6, 55.4, 50.2, 50.1, 35.2. MALDI-FTMS *(m / z)*: 847.4989 $[M+H]^+$, $C_{34}H_{71}N_8O_{16}$ req. 847.4982.

Dimer 19g. Obtained 15 mg (39%).^{1}H NMNR (400 MHz, D_2O, δ): 5.51 (d, *J* = 4 Hz, 1 H); 3.97 (m, 1 H); 3.91 (dd, *J* = 8.2, 7.6 Hz, 1 H); 3.74 (dd, *J* = 8.8, 7.0 Hz, 1 H); 3.70 (t, *J* = 9.9 Hz, 1 H); 3.56 (m, 1 H); 3.50 (d, *J* = 9.4 Hz, 2 H); 3.42 (dd, *J* = 13.5, 2.9 Hz, 1 H); 3.37 (t, *J* = 9.4 Hz, 1 H); 3.19 (m, 2 H); 3.07 (m, 1 H); 2.96 (dd, *J* = 10.6, 2.9 Hz, 1 H); 2.17 (dt, *J* = 12.9, 4.1 Hz, 1 H); 1.60 (m, 2 H); 1.50 (q, *J* = 12.3 Hz, 1 H); 1.27 (bs, 6 H). ^{13}C NMR (100 MHz, D_2O, δ): 94.5, 81.6, 76.5, 72.0, 70.9, 69.6, 69.4, 67.1, 52.7, 48.6, 47.4, 38.7, 29.5, 27.6, 26.9, 23.4. MALDI-FTMS *(m / z)*: 783.5183 $[M+H]^+$, $C_{34}H_{71}N_8O_{12}$ req. 783.5186.

Dimer 19h. Obtained 17 mg (42%).^{1}H NMNR (400 MHz, D_2O, δ): 5.80 (d, *J* = 4 Hz, 1 H); 3.97 (m, 4 H); 3.76 (dd, *J* = 16.1, 8.8 Hz, 1 H); 3.66 (p, *J* = 9.3 Hz, 2 H); 3.46 (m, 3 H); 3.40 (dd, *J* = 10.3, 4.0 Hz, 1 H); 3.31 (m, 1 H); 3.26 (dd, *J* = 13.5, 7.7 Hz, 1 H); 2.38 (dt, *J* = 12.5, 4.4 Hz, 1 H); 1.78 (q, *J* = 12.5 Hz, 1 H); 1.56 (bs, 2 H); 1.25 (bs, 8 H). ^{13}C NMR (100 MHz, D_2O, δ): 94.6, 84.1, 75.6, 75.6, 74.2, 73.8, 71.7, 71.1, 70.0, 54.8, 51.3, 50.3, 41.5, 30.3, 30.2, 26.6. MALDI-FTMS *(m / z)*: 811.5483 $[M+H]^+$, $C_{36}H_{75}N_8O_{12}$ req. 811.5499.

Antibiotic Testing. MIC values against three test organisms, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, and *Pseudomonas aeruginosa* ATCC 27853, were checked by broth microdilution in cation-adjusted Mueller-Hinton broth, according to NCCLS procedures.[2]

SPR Binding Studies. 5' biotinylated A site RNA (27-mer) was purchased protected as 2'-orthoester from Dharmacon Research, deprotected according to manufacturer's protocol and purified by electrophoresis in 20% polyacrylamide gel containing 8 M urea. The RNA band was then eluted from the gel in 3 M sodium acetate (pH 5.0) overnight and precipitated with ethanol. Immobilization and SPR binding assays were performed exactly as previously published.[3-6]

RNA sequences in Table 3:

1. 16S A site:
5' GGCGUCACACCUUCGGGUGAAGUCGCC 3'

2. Bcr-Abl translocation:
5' GGCUGACCAUCAAUAAGGAAGAAGCCCUUCAGCGGCCAGUA 3'

3. PAX3-FKHR translocation:
5' GGAUUUAAGCAGAGUUCAAAAGCCCUUCAGCGGCCAGUAG 3'

4. HIV Frameshift Signal (FSS)
5’ UUUUUUAGGGAAGAUCUGGCCUUCCUACAAGGGAAGGCCAGGGAAU 3’

5. HIV Protease Active Site mRNA (PAS)
5’ GAAGCUUUAUUAGAUACAGGAGCAGAUGAUACAGUAUUA 3’

6. HCV IRES IIb
5’ CUGUCUUCACGCAGAAAGCGUCUAGCCAUGGCGUUAGUAUGAGUGUCG 3’

7. HCV IRES IIId
5’ GGCCGAGUAGUGUUGGGUCGCGAAAGGCC 3’

8. *E. Coli* Transglycosylase mRNA
5’ GAAGACAGCCGCUUCUACGAGCAU 3’

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