Supplemental Material (three pages) for:

STABLE SYNTHETIC CATIONIC BACTERIOCHLORINS AS SELECTIVE ANTIMICROBIAL PHOTOSENSITIZERS

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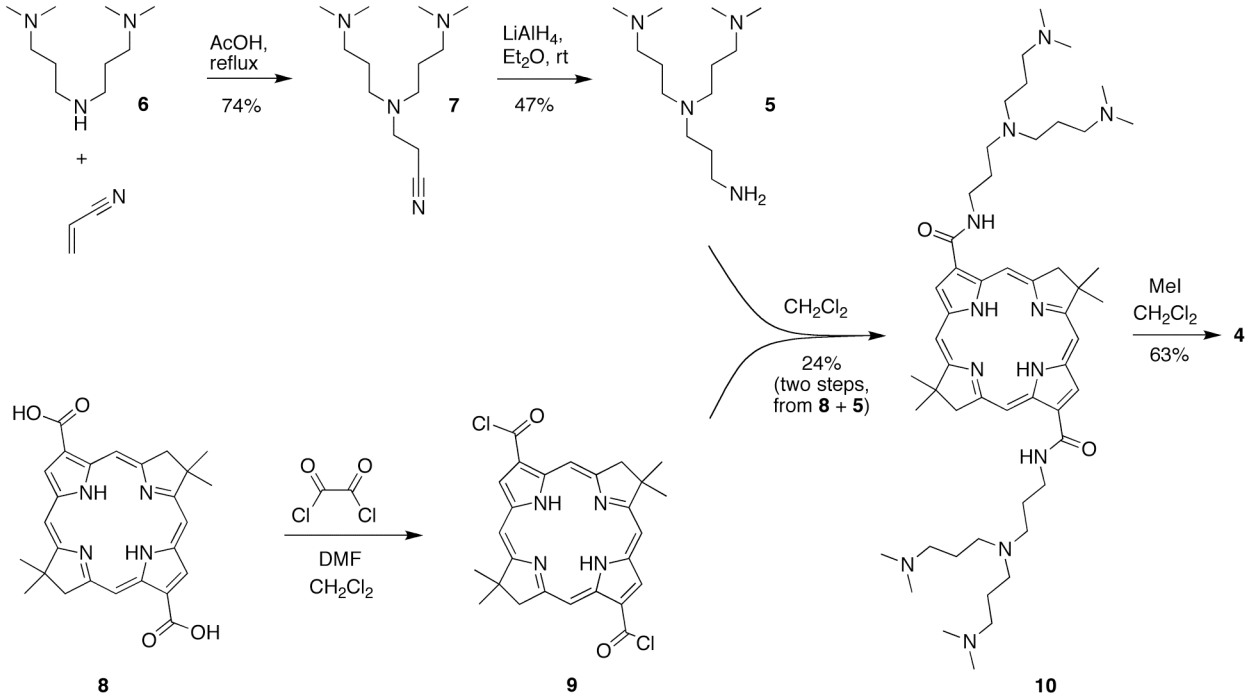
Bacteriochlorin synthesis

A general strategy has been to subject a 3,13-dibromobacteriochlorin building block to Pd-mediated carbonylation to give the corresponding diformyl or dicarboxy bacteriochlorin, which can then be further transformed via reductive amination or amidation (44). The synthesis of bacteriochlorin **4**, which is a diamide, relied on the latter approach (Scheme S1). The amine (**5**) to be used in the amidation procedure was not known. For the synthesis of **5**, a primary amine was prepared following the procedure for a similar compound (34) beginning with the commercially available bis(3-dimethylaminopropyl)amine (**6**). Acrylonitrile was added dropwise to a refluxing solution of amine **6** in glacial acetic acid. The resulting nitrile **7** was reduced with lithium aluminum hydride in anhydrous diethyl ether at room temperature to give the corresponding primary amine **5**.



Scheme S1

The 3,13-dicarboxybacteriochlorin **8** was converted to the corresponding diacid chloride **9** upon treatment with oxalyl chloride. Reaction of **9** with an excess of the primary amine **5** in anhydrous CH_2Cl_2 gave the desired bacteriochlorin-diamide **10** in crude form. Quaternization of

the latter with excess methyl iodide in anhydrous CH_2Cl_2 afforded bacteriochlorin **4** in 15% yield in two steps. The bacteriochlorin was characterized by absorption and fluorescence spectroscopy, and ^{1}H NMR spectroscopy. All attempts to obtain ESI-MS, fast-atom bombardment mass spectrometry, or LD-MS data were unsuccessful; however both ^{1}H NMR spectroscopy and logP data were consistent with the presence of six cationic charges.

Experimental Procedures

3,13-Bis[3-(bis(3-dimethylaminopropyl)amino)propylcarboxamido]-8,8,18,18-tetramethylbacteriochlorin (4). In this procedure, anhydrous MeOH, CH_2Cl_2 and DMF were reagent grade and were used as received. Following our earlier method (44), a suspension of 3,13-dicarboxybacteriochlorin **8** (20 mg, 0.044 mmol) in CH_2Cl_2 (8.0 mL) in a 50 mL round bottom flask under an inert atmosphere was treated with oxalyl chloride (40 μL) and DMF (20 μL). The resulting mixture was stirred at room temperature for 6 h. The reaction mixture became a clear pink solution and the absorption spectrum showed a shift of the Q_x and Q_y bands to 554 and 789 nm, respectively, signaling formation of the diacid chloride (**9**). The reaction mixture was concentrated under reduced pressure and dried under high vacuum. The resulting solid was dissolved in CH_2Cl_2 (6 mL) and then treated with amine **5** (100 mg in 1 mL of CH_2Cl_2) at room temperature. The mixture was stirred overnight. Dichloromethane (40 mL) and saturated aqueous $NaHCO_3$ (40 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL), and the combined organic extract was dried (Na_2SO_4) and filtered. The filtrate was concentrated to a green solid (9.5 mg, 24%). The resulting crude bacteriochlorin-diamide (**10**) was taken to the next step with no further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ –1.67 (br, 2H), 1.75 (m, 8H), 1.92 (s, 12H), 2.0 (m, 4H), 2.09 (s, 24H), 2.28 (t, J = 5.4 Hz, 8H), 2.63 (t, J = 5.4 Hz, 8H), 2.78 (t, J = 4.5 Hz, 8H), 3.90 (m, 4H), 4.42 (s, 4H), 8.56 (s, 2H), 8.63 (t, J = 3 Hz, 2H), 8.82 (s, 2H), 9.81 (s, 2H); λ_{abs} (CH_2Cl_2) 348, 372, 509, 740 nm; LD-MS (no matrix) obsd 910.8, calcd 910.7 ($C_{52}H_{86}N_{12}O_2$).

Following a standard procedure for amine quaternization (44), a solution of bacteriochlorin-diamide **10** (5.0 mg, 0.005 mmol) in CH_2Cl_2 (1 mL) was treated with MeI (200 μL) under argon. The mixture was stirred at room temperature for 24 h. The volatile components were removed under vacuum. The residue was treated with ether (10 mL), sonicated for 3 min, and centrifuged. The supernatant was decanted. The residue was dried under high vacuum to obtain the title compound as a red solid (6.0 mg, 63%): ^{1}H NMR (400 MHz, DMSO-d_6) δ –1.79 (br, 2H), 1.93 (s, 12H), 2.27 (br, 12H), 3.13 (s, 36H), 3.22 (s, 6H), 3.43 (br, 16H), 3.70 (br, 8H), 4.41 (s, 4H), 8.86 (s, 2H), 9.35 (m, 4H), 9.75 (s, 2H); λ_{abs} (H_2O) 346, 371, 512, 746 nm.

3-[Bis(3-dimethylaminopropyl)amino]propylamine (5). Following a reported procedure (34), a sample of lithium aluminum hydride (400 mg, 10.5 mmol) in a 100 mL round bottom flask under an inert atmosphere was treated with anhydrous diethyl ether (20 mL) with stirring for 1 h at room temperature. A solution of **7** (2.50 g, 10.4 mmol) in anhydrous THF/diethyl ether (10 mL, 1:1) was added dropwise. The resulting mixture was stirred for 1 h. The reaction was quenched by the addition of saturated aqueous solution of Na_2SO_4 (7-10 mL), and the mixture was stirred for 30 min. Ethyl acetate (50 mL) was added, and the mixture was filtered. The flask and the filter cake were rinsed with ethyl acetate. The filtrate was dried (Na_2SO_4) and filtered. The filtrate was concentrated and chromatographed [alumina, CH_2Cl_2/MeOH (1:0 → 9:1)] to obtain a colorless oil (1.2 g, 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (m, 6H), 2.08 (br, 2H), 2.20 (s, 12H), 2.25 (m, 4H), 2.42 (m, 6H), 2.70 (t, J = 7.2 Hz, 2H); GC-MS obsd *m/z* 244; ESI-MS obsd 245.2694, calcd 244.2627 [$(M + H)^+$, M = $C_{13}H_{32}N_4$].

3-[Bis(3-dimethylaminopropyl)amino]propionitrile (7). Following a reported procedure (34) with slight modification, a sample of **6** (9.7 g, 52 mmol) in a 100 mL round bottom flask under an inert atmosphere was treated with glacial acetic acid (15 mL). The mixture was heated to reflux, whereupon acrylonitrile (4.8 g, 90 mmol) was introduced dropwise. After the addition, the resulting mixture was refluxed for 7 h. The mixture was allowed to cool to room temperature and then was slowly added to a beaker containing CH_2Cl_2 (150 mL) and Na_2CO_3 (20 g). The flask was rinsed with CH_2Cl_2 (25 mL). The resulting mixture was stirred for 0.5 h and decanted. The decanted solution was dried over Na_2SO_4 and filtered. The filtrate was concentrated and chromatographed [alumina, CH_2Cl_2/MeOH (100:0 → 97:3)] to obtain a colorless oil (9.2 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (q, J = 7.6 Hz, 4H), 2.29 (s, 12H), 2.45 (m, 10H), 2.73 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.12, 25.37, 45.31, 49.53, 51.39, 57.20, 118.93; GC-MS obsd *m/z* 240; ESI-MS obsd 241.2381, calcd 240.2314 [$(M + H)^+$, M = $C_{13}H_{28}N_4$].