

Synthesis and Biological Evaluation of Aminopolyamines

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SUPPORTING INFORMATION

Experimental procedures and analytical and spectral data for 6ADESPM.

Experimental Procedures

Reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI), and Fisher Optima-grade solvents were routinely used. Reactions were run under a nitrogen atmosphere. Sodium hydride reactions were run in distilled DMF. Organic extracts were dried with sodium sulfate. Silica gel 32–63 from Selecto Scientific, Inc. (Suwanee, GA) was used for flash column chromatography. NMR spectra were obtained at 300 MHz (^1H) or 75 MHz (^{13}C) on a Varian Unity 300. Chemical shifts (δ) for ^1H spectra are given in parts per million downfield from tetramethylsilane for CDCl_3 (not indicated) or sodium 3-(trimethylsilyl)propionate-2,2,3,3- d_4 for D_2O . Coupling constants (J) are in hertz. Chemical shifts (δ) for ^{13}C spectra are given in parts per million referenced to 1,4-dioxane (δ 67.19) in D_2O or to the residual solvent resonance in CDCl_3 (δ 77.16). HRMS analyses were performed by Spectroscopy Services in the Department of Chemistry (University of Florida). Elemental analyses were run by Atlantic Microlabs (Norcross, GA).

***N,N'*-Bis(mesitylenesulfonyl)-*N*-(3,4-epoxybutyl)-*N'*-ethyl-1,3-diaminopropane (4).** Sodium hydride (60%, 0.110 g, 2.75 mmol) was introduced into a solution of **2**^{19,28} (1.16 g, 2.50 mmol) in DMF (20 mL) with ice bath cooling. The mixture was stirred at room temperature for 30 min, and a solution of **3**^{29,30} (0.378 g, 2.50 mmol) in DMF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 18 h, and solvent was removed in vacuo. Water (50 mL) was added, and the mixture was extracted with CHCl_3 (2 \times 50 mL). Organic extracts were washed with H_2O (100 mL) and saturated NaCl (100 mL) and were concentrated in vacuo. Flash chromatography with 2:1 hexanes:EtOAc gave 0.89 g (66%) of **4** as a colorless viscous oil: ^1H NMR δ 0.98 (t, 3 H, J = 7.2), 1.67 (m, 4 H), 2.30 (s, 6 H), 2.40 (dd, 1 H, J = 4.8, 2.7), 2.55 (s, 6 H), 2.57 (s, 6 H), 2.69 (dd, 1 H, J = 4.8, 4.2), 2.75 (m, 1 H), 3.08 (m, 6 H), 3.27 (m, 2 H), 6.93 (s, 2 H), 6.94 (s, 2 H); ^{13}C NMR δ 12.66, 20.91, 22.71, 22.77, 25.44, 30.75, 40.12,

42.58, 42.84, 43.63, 46.86, 49.84, 131.90, 131.97, 132.94, 133.12, 140.06, 140.11, 142.37, 142.59; HRMS m/z calcd for $C_{27}H_{40}N_2O_5S_2$ 536.2378 (M), found 536.2382.

N^1, N^{12} -Diethyl-6-hydroxy- N^1, N^4, N^9, N^{12} -tetrakis(mesitylenesulfonyl)spermine (5). Sodium hydride (60%, 2.34 g, 58.4 mmol), **2** (24.79 g, 53.12 mmol), and **3** (4.01 g, 26.6 mmol) in DMF (220 mL) were reacted as for **4**, followed by heating at 70 °C for 18 h. Solvent was removed in vacuo, and H_2O (200 mL) was added. The mixture was extracted with $CHCl_3$ (3 × 300 mL), and organic extracts were washed with saturated NaCl (500 mL). Purification as for **4** afforded 21.43 g (80%) of **5**: 1H NMR δ 0.93 (m, 6 H), 1.40–1.66 (m, 6 H), 2.27 (s, 6 H), 2.28 (s, 6 H), 2.53 (s, 12 H), 2.55 (s, 12 H), 2.98–3.09 (m, 15 H), 3.22 (m, 1 H), 3.34 (m, 1 H), 3.70 (m, 1 H), 6.91 (s, 4 H), 6.93 (s, 4 H); ^{13}C NMR δ 12.17, 20.48, 22.27, 22.40, 24.90, 32.00, 39.49, 39.59, 42.13, 43.03, 44.67, 51.75, 66.43, 131.54, 131.63, 131.69, 132.33, 132.73, 139.51, 139.64, 141.97, 142.00, 142.16, 142.27; HRMS m/z calcd for $C_{50}H_{75}N_4O_9S_4$ 1003.4417 (M + H), found 1003.442.

N^1, N^{12} -Diethyl- N^1, N^4, N^9, N^{12} -tetrakis(mesitylenesulfonyl)-6-(*p*-toluenesulfonato)spermine (6). *p*-Toluenesulfonyl chloride (2.44 g, 12.8 mmol) in CH_2Cl_2 (20 mL) was added dropwise to **5** (6.44 g, 6.42 mmol) in pyridine (20 mL) with ice bath cooling, and the solution was stirred at room temperature for 1 day. After dilution with $CHCl_3$ (300 mL), the mixture was poured into 1 N HCl (600 mL) and ice (300 g). The organic layer was washed with H_2O (300 mL), saturated $NaHCO_3$ (300 mL), and saturated NaCl (300 mL). After solvent removal under vacuum, flash chromatography, eluting with 2:1 hexanes/EtOAc, gave 4.56 g (61%) of **6**: 1H NMR δ 0.92 (t, 3 H, $J = 7.2$), 0.93 (t, 3 H, $J = 7.2$), 1.62 (m, 6 H), 2.28 (s, 12 H), 2.44 (s, 3 H), 2.50 (s, 12 H), 2.54 (s, 12 H), 2.98 (m, 14 H), 3.32 (dd, 1 H, $J = 15.6, 5.7$), 3.38 (dd, 1 H, $J = 15.6, 4.2$), 4.35 (m, 1 H), 6.92 (m, 8 H), 7.36 (d, 2 H, $J = 8.4$), 7.75 (d, 2 H, $J = 8.4$); ^{13}C NMR δ 12.19, 12.36, 20.68, 21.43, 22.47, 22.63, 24.11, 24.95, 29.24, 39.49, 39.73, 41.10, 42.01, 42.22, 42.90, 44.43, 48.10, 77.98, 127.60, 129.87, 131.70, 131.79, 131.99, 132.24, 132.67, 132.89, 132.92, 139.71, 139.79,

139.83, 142.12, 142.14, 142.29, 142.67, 145.08; HRMS m/z calcd for $C_{57}H_{81}N_4O_{11}S_5$ 1157.4505 (M + H), found 1157.4528.

N^1, N^{12} -Diethyl-6-phthalimido- N^1, N^4, N^9, N^{12} -tetrakis(mesitylenesulfonyl)spermine (7). Potassium phthalimide (3.41 g, 18.4 mmol) was added to **6** (14.17 g, 12.2 mmol) in DMF (60 mL), and the reaction mixture was heated at 85 °C for 18 h. Solvent was removed in vacuo. The residue was treated with H_2O (300 mL) and was extracted with $CHCl_3$ (500 mL). The organic phase was washed with saturated NaCl and was concentrated under reduced pressure. Flash chromatography with 8:1 then 4:1 $CHCl_3$:EtOAc generated 8.59 g (62%) of **7**: 1H NMR δ 0.81 (t, 3 H, $J = 7.2$), 0.96 (t, 3 H, $J = 7.5$), 1.51 (m, 2 H), 1.75 (m, 4 H), 2.01 (s, 3 H), 2.16 (s, 3 H), 2.20 (s, 3 H), 2.24 (s, 3 H), 2.26 (s, 6 H), 2.36 (s, 6 H), 2.41 (s, 6 H), 2.52 (s, 6 H), 2.87–3.18 (m, 15 H), 3.75 (dd, 1 H, $J = 14.7, 10.8$), 4.14 (m, 1 H), 6.43 (s, 2 H), 6.73 (s, 2 H), 6.81 (s, 2 H), 6.88 (s, 2 H), 7.56–7.63 (m, 4 H); ^{13}C NMR δ 12.51, 12.68, 20.88, 22.49, 22.59, 22.72, 24.82, 25.29, 27.41, 39.90, 40.12, 42.40, 42.53, 42.88, 43.14, 43.44, 45.98, 46.65, 122.91, 131.33, 131.72, 131.81, 131.86, 131.90, 132.51, 132.85, 133.01, 133.66, 139.69, 139.88, 140.01, 141.97, 142.24, 142.28, 142.46, 167.39; HRMS m/z calcd for $C_{58}H_{78}N_5O_{10}S_4$ 1132.4631 (M + H), found 1132.4667.

6-Amino- N^1, N^{12} -diethyl- N^1, N^4, N^9, N^{12} -tetrakis(mesitylenesulfonyl)spermine (8). Sodium borohydride (1.04 g, 27.4 mmol) was introduced into an efficiently stirred mixture of **7** (6.20 g, 5.47 mmol) in CH_2Cl_2 (12 mL), 2-propanol (100 mL), and H_2O (16.8 mL), and the reaction was stirred at room temperature for 18 h. Acetic acid (6.5 mL) was carefully added, and the mixture was heated to 80 °C for 18 h. After solvents were removed in vacuo, the residue was treated with H_2O (100 mL) and was extracted with $CHCl_3$ (6 \times 100 mL). The organic extracts were washed with saturated $NaHCO_3$ (400 mL), H_2O (400 mL), and saturated NaCl (400 mL) and were concentrated under reduced pressure. Flash chromatography with 1:1 $CHCl_3$:EtOAc furnished

4.07 g (74%) of **8**: ^1H NMR (DMSO- d_6 -2.49) δ 0.86 (t, 6 H, $J = 7.2$), 1.34–1.51 (m, 6 H), 2.25 (s, 12 H), 2.42 (s, 2 H), 2.45 (s, 24 H), 2.91–3.14 (m, 17 H), 7.02 (s, 8 H); ^{13}C NMR δ 12.49, 12.53, 20.87, 22.66, 22.76, 22.84, 25.06, 25.27, 32.64, 39.85, 39.97, 42.41, 42.51, 42.97, 43.19, 44.02, 46.63, 53.56, 131.86, 131.94, 132.05, 132.98, 133.04, 133.08, 139.89, 139.97, 142.30, 142.48, 142.60; HRMS m/z calcd for $\text{C}_{50}\text{H}_{75}\text{N}_5\text{O}_8\text{S}_4$ 1001.4498 (M), found 1001.4525.

6-Amino- N^1,N^{12} -diethylspermine Pentahydrochloride (6ADESPM, **1).** Hydrogen bromide in HOAc (30%, 55 mL) was added to a solution of **8** (2.77 g, 2.76 mmol) and phenol (10.39 g, 0.110 mol) in CH_2Cl_2 (50 mL) with ice bath cooling. The reaction mixture was stirred at room temperature for 18 h and was cooled in an ice bath; H_2O (80 mL) was slowly added. The layers were separated, and the aqueous portion was extracted with CH_2Cl_2 (3×80 mL). The aqueous portion was concentrated under high vacuum, mixed with $\text{CH}_3\text{CH}_2\text{OH}$ (40 mL), heated on a steam bath, cooled, and filtered. The solid was dissolved in H_2O (4 mL) followed by basification with 2 N NaOH (4 mL) and 50% (w/w) NaOH (10 mL) with ice bath cooling. The aqueous phase was extracted with CHCl_3 (6×20 mL), and these extracts were concentrated in vacuo. The residue was dissolved in $\text{CH}_3\text{CH}_2\text{OH}$ (30 mL) and was acidified to $\text{pH} < 1$ with concd HCl. Filtration and recrystallization from aqueous $\text{CH}_3\text{CH}_2\text{OH}$ gave 0.66 g (52%) of **1** as a white solid: ^1H NMR (D_2O) δ 1.28 (t, 6 H, $J = 7.5$), 2.15 (m, 6 H), 3.13–3.40 (m, 16 H), 3.75 (m, 1 H); ^{13}C NMR (D_2O) δ 11.10, 23.35, 23.42, 28.11, 43.71, 44.26, 44.40, 45.40, 46.27, 47.18, 49.67; HRMS m/z calcd for $\text{C}_{14}\text{H}_{36}\text{N}_5$ 274.2971 (M + H, free amine), found 274.2979. Anal. ($\text{C}_{14}\text{H}_{40}\text{Cl}_5\text{N}_5$): C, H, N.

Elemental Analyses

Cmpd no.	C calcd	C found	H calcd	H found	N calcd	N found
1	36.89	36.80	8.85	8.88	15.37	15.24