Total Synthesis of Polyamine Toxin HO-416b and Agel-489 Using a 2-Nitrobenzenesulfonamide Strategy

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Total synthesis of spider toxins HO-416b (1) and Agel-489 (2) was accomplished using the 2-nitrobenzenesulfonamide (Ns) group as both a protecting and activating group. In this strategy, the C–N bonds were constructed by alkylation of sulfonamides with alkyl halides or Mitsunobu reaction with the corresponding alcohol. Beginning with monoprotection of the symmetrical diamine, the construction of the backbone from diamine 3 was efficiently accomplished in 7 steps for 14 and 9 steps for 29. Removal of the Ns group while the substrate was attached to a novel solid support enabled the efficient isolation of this highly polar compound.

Key words 2-nitrobenzenesulfonamide (Ns) group; protecting and activating group; alkylation; monoprotection; solid support

Polyamine toxins derived from spider venom have been shown to be specific glutamate receptor blockers.[1] They are expected to be useful as tools for studying neurophysiology and as lead structures for pharmacological and agrochemical agents. Although many synthetic studies of these compounds have been reported,[2] there are still few versatile syntheses of sequential secondary amines.[3] Recently, we reported an efficient method for the construction of secondary amines using the Ns group as a protecting and activating group.[4] We envisioned that this protocol would provide an efficient synthetic route to polyamine toxins. Described herein is our practical total synthesis of the polyamine spider toxin HO-416b (**1**)[5] and Agel-489 (**2**).[6]

Monoprotected diamines seemed to be ideal starting materials for incorporation into a polyamine chain. Selective protection and purification of diamines is reported to be difficult[7]; however, the Ns group provided good results. Thus, treatment of 1,3-diaminopropane with 2-nitrobenzenesulfonyl chloride, followed by neutralization with NaOEt afforded the monosulfonyl adduct **3** in high yield. This procedure was applied to other diamines to provide **4** and **5**. We used these compounds as the key building blocks in our total synthesis of **1** and **2**.

The synthesis of **1** began from monoprotected diamine **3**. Treatment of **3** with Boc_2O and selective alkylation with 1,3-dibromopropane afforded bromide **7**. Sulfonamide **9**, readily obtained from 3-aminopropanol (**8**), was converted to the right-hand triamine **10** by treatment with **7** and Cs_2CO_3. The left-hand fragment **13** was obtained by condensation of 3-indoleacetic acid (**12**) and **4** under mixed-anhydride conditions. Although the two sides can be coupled under Mitsunobu conditions, we chose the conventional alkylation methods to simplify the purification of alkyl adduct **14**. Conversion of alcohol **10** to the iodide **11** was performed by mesylation and iodide displacement. Upon treatment with **11** and Cs_2CO_3, the sulfonamide **13** underwent smooth alkylation to provide **14**. Subsequent removal of the Boc group under acidic conditions gave the primary amine **15**.

Solid phase supports have proven effective as tools for the isolation of highly polar compounds, making their use in our final deprotection attractive. Initial attempts to load **15** onto a commercially available 2-chlorotrityl chloride resin were inefficient. We thus planned to prepare the novel resin **16**. This resin would be more reactive since a phenol unit separated the bulky polystyrene support from the reactive site and an alkoxy group stabilized the trityl cation. Treatment of Merrifield resin with *p*-hydroxytrityl alcohol[8] and K_2CO_3, followed by reaction with $SOCl_2$, afforded the desired resin **16** (Chart 3). This resin could be recycled by treatment with $SOCl_2 : CH_2Cl_2$ (1 : 9) after cleavage of the substrates.

Linkage of Ns-protected HO-416b **15** to the resin **16** was induced by *i*-Pr_2NEt (Chart 4). Upon treatment of the resin with 2-mercaptoethanol and DBU, the Ns groups were removed.[9] Cleavage from the resin under acidic conditions (1% TFA/CH_2Cl_2) and evaporation of the solvent provided **1** without the need for any chromatographic purification (Chart 4). ^{1}H- and ^{13}C-NMR spectral data of **1** indicated the presence of highly pure material, and tandem FAB MS-MS spectroscopy also proved **1** was identical with naturally occurring HO-416b.

Next, we turned our attention to the synthesis of Agel-489

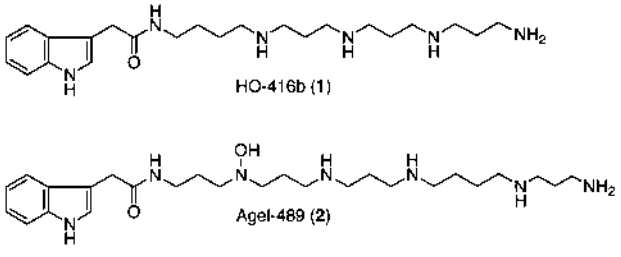

Fig. 1

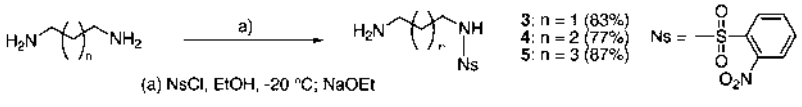

Chart 1

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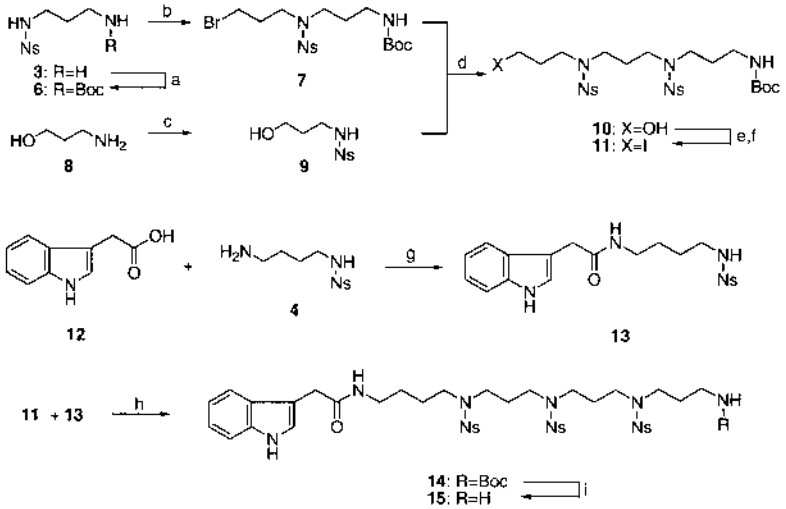
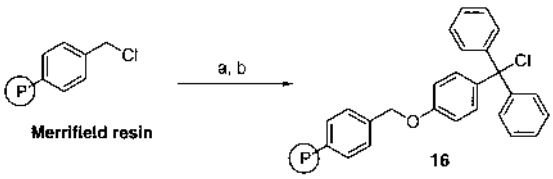


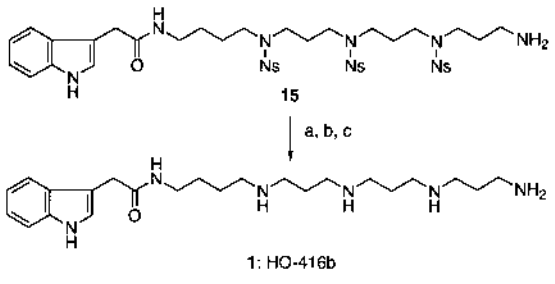
(a) Boc_2O, Et_3N, CH_2Cl_2, rt (99%) (b) 1,3-dibromopropane, K_2CO_3, DMF, 60°C (97%) (c) NsCl, Py, CH_2Cl_2, 0°C (99%) (d) Cs_2CO_3, *n*-Bu_4NI, CH_3CN, 60°C (86%) (e) MsCl, Et_3N, CH_2Cl_2, rt (99%) (f) NaI, 2-butanone, 60°C (99%) (g) PivCl, Et_3N, CH_2Cl_2, rt; **4**, Et_3N, DMAP (97%) (h) Cs_2CO_3, *n*-Bu_4NI, CH_3CN, 60°C (94%) (i) $SOCl_2$, MeOH, rt (96%)

Chart 2



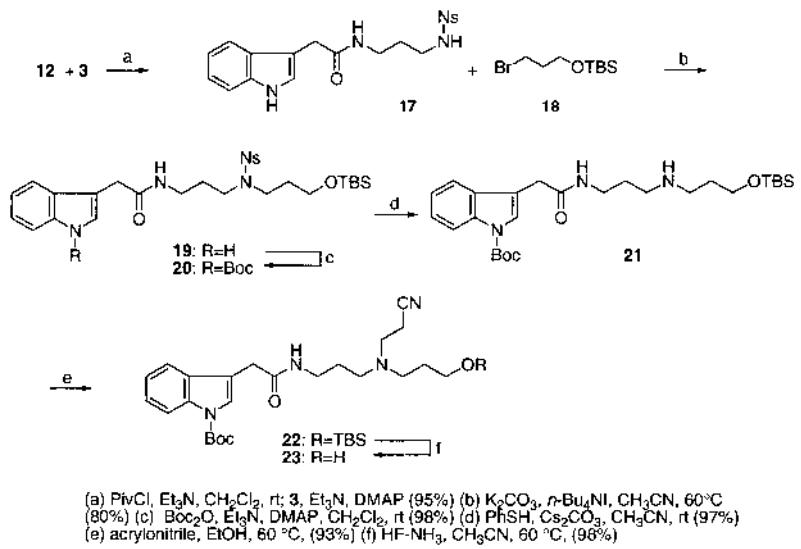
(a) *p*-hydroxytrityl alcohol, K_2CO_3, DMF, 60 °C (b) $SOCl_2$, CH_2Cl_2, rt

Chart 3



(a) resin **16**, *i*-Pr_2NEt, CH_2Cl_2, rt (b) 2-mercaptoethanol, DBU, DMF, rt (c) TFA, CH_2Cl_2 (68% from **15**)

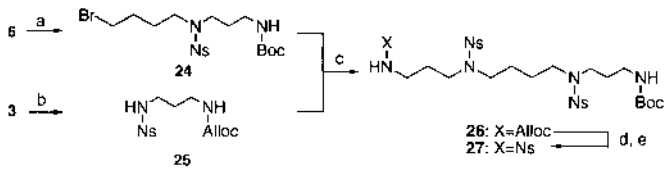
Chart 4



(a) PivCl, Et_3N, CH_2Cl_2, rt; **3**, Et_3N, DMAP (95%) (b) K_2CO_3, *n*-Bu_4NI, CH_3CN, 60°C (80%) (c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt (98%) (d) PhSH, Cs_2CO_3, CH_3CN, rt (97%) (e) acrylonitrile, EtOH, 60 °C, (93%) (f) HF-NH_3, CH_3CN, 60 °C, (98%)

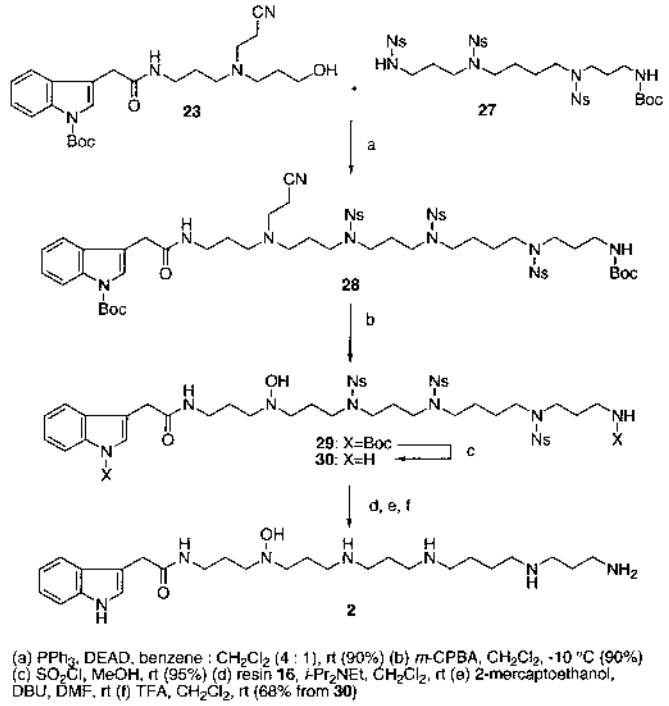
Chart 5

(**2**), isolated from the venomous spider *Agelenopsis apearta*. The key structural feature of **2** is a hydroxylamine-containing polyamine chain. Because of the inherent instability of secondary hydroxylamines, we planned to generate this functionality late in our synthesis. Although several methods have been reported for the transformation,[10] we planned to construct this group by oxidation of a 2-cyanoethylamine and subsequent elimination of acrylonitrile by *retro*-Michael re-



(a) dibromobutane, K_2CO_3, DMF, 60°C (81%) (b) AllocCl, Et_3N, CH_2Cl_2, 0°C (89%) (c) Cs_2CO_3, n-Bu_4NI, CH_3CN, 60°C (97%) (d) $Pd(PPh_3)_4$, PPh_3, pyrrolidine, CH_2Cl_2, rt (99%) (e) NsCl, Et_3N, CH_2Cl_2, rt (94%)

Chart 6



(a) PPh_3, DEAD, benzene : CH_2Cl_2 (4 : 1), rt (90%) (b) m-CPBA, CH_2Cl_2, -10 °C (90%) (c) SO_2Cl, MeOH, rt (95%) (d) resin **16**, i-Pr_2NEt, CH_2Cl_2, rt (e) 2-mercaptoethanol, DBU, DMF, rt (f) TFA, CH_2Cl_2, rt (68% from **30**)

Chart 7

action.[11] We would assemble the backbone **2** by coupling the cyanoethylamine **23** with the spermine derivative **27**.

The left-hand fragment **23** was obtained by an efficient 6-step synthesis (Chart 5). Condensation of 3-indoleacetic acid (**12**) and diamine **3** under mixed-anhydride conditions provided the sulfonamide **17**. Bromide **18**, readily obtained from 3-bromopropanol, was converted to a precursor of **19** by treatment with **17** and Cs_2CO_3. Protection of the indole **19** with Boc_2O and selective removal of the Ns group with thiophenol[3a] yielded amine **21**. Upon treatment with acrylonitrile, the amine **21** underwent smooth cyanoethylation. Removal of the TBS group gave the primary alcohol **23**.

The protected spermine derivative **27** was also synthesized from the monoprotected diamine **3** (Chart 6). Selective alkylation of **6** with 1,3-dibromopropane afforded bromide **24**. Sulfonamide **25**, readily prepared from diamine **3**, was converted to the tetraamine **26** by treatment with **24** in the presence of Cs_2CO_3. A change of protecting groups from *N*-Alloc to Ns provided sulfonamide **27**.

Condensation of primary alcohol **23** and sulfonamide **27** was accomplished under Mitsunobu conditions. Treatment of **23** and **27** with DEAD and triphenylphosphine provided hexamine **28**. Upon treatment of cyanoethylamine **28** with *m*-CPBA, smooth oxidation and *retro*-Michael reaction gave hydroxy amine **29**. Subsequent removal of the Boc group with TFA afforded the primary amine **30**. A similar treatment to that used for the Ns deprotection of HO-416 provided the natural product **2** (Chart 7). $^1H/^{13}C$ NMR spectra and tandem FAB MS-MS spectroscopy data of synthetic **2** were identical with those of naturally occurring Agel-489.

In conclusion, utilizing the 2-nitrobenzenesulfonamide (Ns) group as both a protecting and activating group (Ns-strategy), the total synthesis of **1** was accomplished in 11 steps and 41% total yield, while the total synthesis of **2** was achieved in 12 steps and 31% yield. In both cases, efficient monoprotection of symmetrical diamines allowed very short syntheses. All C–N bond formations were accomplished in high yield by alkylation of 2-nitrobenzenesulfonamides. Finally, removal of the Ns group while the substrate was attached to a novel solid support enabled the efficient isolation of these highly polar compounds.

Experimental

General Comments IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer. Nuclear magnetic resonance. ^1H- and ^{13}C-NMR spectra were taken on a JEOL JNM-LA400 spectrometer with tetramethylsilane (TMS) as the internal standard. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured with a JEOL JMS-GCmate instrument.

***N*-(3-Aminopropan-1-yl)-2-nitrobenzenesulfonamide (3) (Large-Scale Preparation)** To a stirred solution of 55.6 g (75.0 mmol) of 1,3-diaminopropane in 1 l of ethanol was slowly added 55.4 g (25.0 mmol) of 2-nitrobenzenesulfonyl chloride at −20 °C under an argon atmosphere. After 30 min, the reaction mixture was quenched with 1 N sodium ethoxide, filtered with celite, concentrated *in vacuo* and excess 1,3-diaminopropane was removed under reduced pressure (40—50 °C/0.02 mmHg). Purification of the crude product by recrystallization with ethyl acetate in ether yielded sulfonamide **3** (38.0 g, 59%) as a yellow powder. IR ($CHCl_3$) cm^{-1}: 3368, 3310, 3099, 2939, 2877, 1540, 1440, 1368, 1334, 1162, 1127, 1092, 853, 782, 741; ^1H-NMR (DMSO) δ: 1.46 (2H, tt, J=6.7, 6.7 Hz), 2.52 (2H, t, J=6.7 Hz), 2.93 (2H, t, J=6.7 Hz), 3.94 (1H, bs), 7.81—7.87 (2H, m), 7.92—7.99 (2H, m); ^{13}C-NMR (DMSO) δ: 32.3, 41.0, 124.3, 129.4, 132.5, 132.9, 133.8, 147.8; MS: m/z=260 (MH^+); HRMS ($C_9H_{14}N_3O_3S$, MH^+): Calcd for 260.0705. Found: 260.0701.

***N*-(3-Aminopropan-1-yl)-2-nitrobenzenesulfonamide (3)** (Small-Scale Preparation) To a stirred solution of 2.64 g (30 mmol) of 1,3-diaminopropane in 50 ml of ethanol was slowly added 2.2 g (10 mmol) of 2-nitrobenzenesulfonyl chloride at 0 °C under an argon atmosphere. After 30 min, the reaction mixture was quenched with a solution of 1 N sodium ethoxide, filtered with celite, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of isopropylamine : methanol : dichloromethane (0 : 2 : 98 to 2.5 : 2.5 : 95), furnished sulfonamide **3** (2.15 g, 83%) as a yellow powder.

***N*-(4-Aminobutan-1-yl)-2-nitrobenzenesulfonamide (4)** Similar treatment of 2.64 g (30 mmol) of 1,4-diaminobutane and 2.2 g (10 mmol) of 2-nitrobenzenesulfonyl chloride to the reaction of 1,3-diaminopropane provided sulfonamide **4** (2.10 g, 77%) as a yellow powder. IR ($CHCl_3$): 3365, 3308, 3094, 2936, 2867, 1734, 1592, 1540, 1466, 1440, 1417, 1369, 1335, 1242, 1163, 1127, 1092, 853, 782, 742 cm^{-1}; ^1H-NMR (DMSO) δ: 1.31 (2H, tt, J=6.8, 6.8 Hz), 1.43 (2H, tt, J=6.8, 6.8 Hz), 2.47 (2H, t, J=6.8 Hz), 2.85 (2H, t, J=6.8 Hz), 4.25 (1H, bs), 7.80—7.87 (2H, m), 7.92—7.98 (2H, m); ^{13}C-NMR (DMSO) δ: 27.0, 29.8, 40.8, 42.8, 124.2, 129.4, 132.4, 133.2, 133.7, 147.8; MS: m/z=274 (47, MH^+); HRMS ($C_{10}H_{16}N_3O_4S$, MH^+): Calcd for 274.0862. Found: 274.0868.

***N*-(5-Aminopentan-1-yl)-2-nitrobenzenesulfonamide (5)** Similar treatment of 3.06 g (30 mmol) of 1,5-diaminopentane and 2.2 g (10 mmol) of 2-nitrobenzenesulfonyl chloride to the reaction of 1,3-diaminopropane provided sulfonamide **5** (2.50 g, 87%) as a yellow powder. IR ($CHCl_3$): 3365, 3308, 3094, 2936, 2867, 1734, 1592, 1540, 1466, 1440, 1417, 1369, 1335, 1242, 1163, 1127, 1092, 853, 782, 742 cm^{-1}; ^1H-NMR (DMSO) δ: 1.31 (2H, tt, J=6.8, 6.8 Hz), 1.43 (2H, tt, J=6.8, 6.8 Hz), 2.47 (2H, t, J=6.8 Hz), 2.85 (2H, t, J=6.8 Hz), 4.25 (1H, bs), 7.80—7.87 (2H, m), 7.92—7.98 (2H, m); ^{13}C-NMR (DMSO) δ: 27.0, 29.8, 40.8, 42.8, 124.2, 129.4, 132.4, 133.2, 133.7, 147.8; MS: m/z=274 (47, MH^+); HRMS ($C_{10}H_{16}N_3O_4S$, MH^+): Calcd for 274.0862. Found: 274.0868.

***N*-(3-*tert*-Butoxycarbonylaminopropan-1-yl)-2-nitrobenzenesulfonamide (6)** To a stirred solution of 2.23 g (8.61 mmol) of diamine **3** in 30 ml of dichloromethane were added 1.43 ml (10.3 mmol) of triethylamine and 2.37 ml (10.3 mmol) of di-*tert*-butyl dicarbonate at room temperature under an argon atmosphere. After 1 h, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (60% ethyl acetate in hexane) yielded diamine **6** (2.43 g, 99%) as a yellow solid. IR ($CHCl_3$): 3344, 2977, 1690, 1593, 1542, 1442, 1414, 1366, 1342, 1301, 1274, 1254, 1166, 1127, 1088, 854, 783, 741; ^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s), 1.69 (2H, tt, J=6.3, 6.3 Hz), 3.16 (2H, dt, J=6.3, 6.3 Hz), 3.21 (2H, dt, J=6.3, 6.3 Hz), 4.67 (1H, bs), 5.87 (1H, bs), 7.72—7.74 (2H, m), 7.84—7.86 (1H, m), 8.12—8.14 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 28.3, 30.6, 37.1, 40.8, 79.6, 125.2, 130.9, 132.7, 133.4, 148.0, 156.4; MS: 360 (MH^+), 359 (M^+); HRMS: Calcd for ($C_{10}H_{12}N_3O_5S$, $M^+-C_4H_9O$): 287.0576. Found: 287.0576.

7-*tert*-Butoxycarbonylamino-4-(2-nitrobenzenesulfonyl)-4-azaheptan-1-yl Bromide (7) To a stirred solution of 3.57 g (25.8 mmol) of potassium carbonate in 4.3 ml (43 mmol) of 1,3-dibromopropane was added slowly the crude diamine **6** in 10 ml of DMF at 60 °C under an argon atmosphere. After 1 h, the reaction mixture was poured into water, and the aqueous layer was extracted thoroughly with ether (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (20% ethyl acetate in hexane) yielded bromide **7** (3.27 g, 97%) as a yellow oil. IR ($CHCl_3$): 3423, 2976, 1707, 1545, 1458, 1367, 1348, 1251, 1163, 1125, 1060, 1040, 852, 779, 748 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.77 (2H, tt, J=6.7, 6.7 Hz), 2.11 (2H, tt, J=6.7, 6.7 Hz), 3.17 (2H, m), 3.37 (2H, t, J=6.7 Hz), 3.38 (2H, t, J=6.7 Hz), 3.44 (2H, t, J=6.7 Hz), 4.81 (1H, bs), 7.64—7.66 (1H, m), 7.69—7.74 (2H, m), 8.03—8.05 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 28.5, 28.6, 30.1, 31.4, 37.5, 45.8, 46.3, 80.0, 124.5, 131.2, 131.9, 133.9, 148.2, 156.2; MS: m/z=408 ($MH^+-C_4H_9O$); HR MS ($C_{13}H_{17}BrN_3O_5S$, $M^+-C_4H_9O$): Calcd for 407.0151. Found: 407.0150.

3-(2-Nitrobenzenesulfonylamino)propan-1-ol (9) To a stirred solution of 1.54 g (20.5 mmol) of 3-aminopropanol in 50 ml of dichloromethane were added 3.48 g (15.7 mmol) of 2-nitrobenzenesulfonyl chloride and 1.48 ml (17.3 mmol) of pyridine at 0 °C under an argon atmosphere. After 10 min, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give amino alcohol **9** (4.04 g, 99%) as a white solid. IR ($CHCl_3$): 3546, 3336, 3100, 2948, 2886, 1593, 1541, 1441, 1413, 1364, 1338, 1164, 1126, 1068, 1005, 960, 854, 784, 741, 731 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.79 (2H, tt, J=6.1, 6.1 Hz), 3.26 (2H, dt, J=6.1, 6.1 Hz), 3.77 (2H, t, J=6.1 Hz), 5.83 (1H, bs), 7.72—7.78 (2H, m), 7.84—7.90 (1H, m), 8.12—8.17 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 31.5, 41.5, 60.3, 125.4, 131.1, 132.8, 133.5, 148.0. MS: m/z=264 (MH^+), 260 (M^+); HRMS ($C_9H_{12}N_2O_5S$, MH^+): Calcd for 260.0467. Found: 260.0475.

11-*tert*-Butoxycarbonylamino-4,8-bis(2-nitrobenzenesulfonyl)-4,8-diazaundecan-1-ol (10) To a stirred solution of 310 mg (1.19 mmol) of amino alcohol **9**, 800 mg (1.67 mmol) of bromide **7**, and 1.16 g (3.58 mmol) of cesium carbonate in 4 ml of acetonitrile was added a catalytic amount of *n*-tetrabutylammonium iodide (88 mg, 0.24 mmol) at 60 °C under an argon atmosphere. After 90 min, the reaction mixture was poured into brine, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (80% ethyl acetate in hexanes) yielded alcohol **10** (675 mg, 86%) as a yellow oil. IR ($CHCl_3$): 3423, 3094, 2937, 1695, 1544, 1459, 1440, 1370, 1346, 1252, 1161, 1126, 1059, 979, 914, 852, 779, 734 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.74 (2H, tt, J=7.4, 7.4 Hz), 1.78 (2H, tt, J=7.0, 7.0 Hz), 1.89 (2H, tt, J=7.6, 7.6 Hz), 3.12 (2H, m), 3.29 (2H, t, J=7.6 Hz), 3.30 (2H, t, J=7.6 Hz), 3.32 (2H, t, J=7.4 Hz), 3.42 (2H, t, J=7.0 Hz), 3.66 (2H, bs), 4.85 (1H, bs), 7.61—7.65 (2H, m), 7.69—7.74 (4H, m), 7.98—8.00 (2H, m); ^{13}C-NMR ($CDCl_3$) δ: 27.5, 28.4, 28.8, 31.1, 37.6, 45.0, 45.5, 45.6, 45.7, 59.1, 79.4, 124.2, 130.7, 131.8, 132.8, 133.7, 148.1, 156.1; MS: m/z=660 (MH^+); *Anal.* ($C_{26}H_{37}N_5O_{11}S_2$): Calcd for C, 47.33; H, 5.65; N, 10.62. Found: C, 47.54; H, 5.58; N, 10.33.

11-*tert*-Butoxycarbonylamino-4,8-bis(2-nitrobenzenesulfonyl)-4,8-diazaundecan-1-yl Iodide (11) To a stirred solution of 1.98 g (3.00 mmol) of alcohol **10** in 10 ml of dichloromethane were added 0.50 ml (3.61 mmol) of triethylamine, and 0.28 ml (3.61 mmol) of methanesulfonyl chloride at 0 °C under an argon atmosphere. After 10 min at room temperature, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give crude mesylate which was used in the subsequent step without purification.

To a stirred solution of 2.20 g (2.98 mmol) of mesylate in 20 ml of 2-butanone was added 1.34 g (8.94 mmol) of sodium iodide at 60 °C under an argon atmosphere. After 1 h, the reaction mixture was poured into water, and the aqueous layer was extracted thoroughly with ether (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give the iodide **11** (2.28 g, 99%) as a yellow oil. IR ($CHCl_3$): 3423, 3093, 2931, 1706, 1544, 1458, 1439, 1369, 1347, 1251, 1162, 1125, 1059, 914, 852, 778, 734 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.74 (2H, tt, J=6.9, 6.9 Hz), 1.87 (2H, tt, J=7.4, 7.4 Hz), 2.04 (2H, tt, J=6.8, 6.8 Hz), 3.11 (2H, t, J=6.8 Hz), 3.14 (2H, m), 3.29 (2H, t, J=7.4 Hz), 3.31 (2H, t, J=7.4 Hz), 3.34 (2H, t, J=6.9 Hz), 3.36 (2H, t, J=6.8 Hz), 4.80 (1H, bs), 7.62—7.66 (2H, m), 7.70—7.75 (4H, m), 7.99—8.03 (1H, m), 8.04—8.06, (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 1.65, 27.4, 28.4, 28.6, 31.8, 37.4, 45.2, 45.4, 45.6, 48.2, 124.3, 124.3, 130.1, 131.1, 131.9, 132.0, 132.8, 133.7, 133.9, 148.0; MS: m/z=770 (MH^+), 769 (M^+); HRMS ($C_{26}H_{37}IN_5O_{10}S_2$, MH^+): Calcd for 770.1071. Found: 770.1046.

***N*-[4-(2-Nitrobenzenesulfonyl)aminobutan-1-yl]-1*H*-indole-3-acetamide (13)** To a solution of 1.08 g (6.16 mmol) of indole-3-acetic acid in 15 ml of dichloromethane were added 0.94 ml (6.78 mmol) of triethylamine and 0.83 ml (6.78 mmol) of pivaloyl chloride at 0 °C under an argon atmosphere. After 3 min at room temperature, the reaction mixture was cooled at 0 °C. To the above stirred solution was added 2.07 g (8.01 mmol) of diamine **4**, 0.94 ml (6.78 mmol) of triethylamine and 76 mg (0.62 mmol) of 4-dimethylaminopyridine (DMAP). After 10 min at room temperature, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexane (50 to 70%), furnished sulfonamide **13** (2.43 g, 97%) as a yellow solid. IR ($CHCl_3$): 3402, 2931, 1647, 1540, 1457, 1339, 1164, 1125, 853, 782, 741 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.40 (4H, m), 3.00 (2H, bs), 3.14 (2H, m), 3.72 (2H, s), 5.30 (1H, bs), 5.73 (1H, bs), 7.14 (1H, dd, J=7.4, 1.0 Hz), 7.16 (1H, d, J=7.4 Hz), 7.24 (1H, dd, J=7.4, 1.0 Hz), 7.42 (1H, d, J=8.0 Hz), 7.53 (1H, d, J=7.4 Hz), 7.69—7.74 (2H, m), 7.80—7.84 (1H, m), 8.06—8.10 (1H, m), 8.38 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: 26.1, 26.4, 33.1, 38.3, 42.9, 108.7, 111.2, 118.3, 119.8, 122.4, 123.5, 125.0, 126.6, 130.7, 132.5, 133.2, 133.2, 136.1, 171.4; MS: m/z=431 (MH^+), 430 (M^+); HRMS ($C_{20}H_{22}N_4O_5S$, M^+): Calcd for 430.1311. Found: 430.1333.

***N*-[16-*tert*-Butoxycarbonylamino-5,9,13-tris(2-nitrobenzenesulfonyl)-5,9,13-triazahexadecan-1-yl]-1*H*-indole-3-acetamide (14)** To a stirred solution of 1.20 g (1.55 mmol) of iodide **11**, and 977 mg (3.00 mmol) of cesium carbonate in 6 ml of acetonitrile was added 430 mg (1.00 mmol) of sulfonamide **13** at 60 °C under an argon atmosphere. After 1 h, the reaction mixture was poured into brine, and the aqueous layer was extracted thoroughly with ethyl acetate (3×). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (80% ethyl acetate in hexanes) yielded polyamine **14** (1.01 g, 94%) as a yellow powder. IR ($CHCl_3$): 3412, 2936, 1702, 1655, 1544, 1458, 1439, 1370, 1344, 1162, 1125, 1060, 942, 852, 779, 742 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.35 (2H, bs), 1.44 (9H, s), 1.61 (2H, bs), 1.72 (4H, m), 1.82 (2H, m), 3.09—3.28 (14H, m), 3.31 (2H, t, J=7.20 Hz), 3.72 (2H, s), 4.88 (1H, bs), 5.85 (1H, m), 7.11 (2H, dt, J=7.6, 1.0 Hz), 7.19 (2H, dt, J=7.6, 1.0 Hz), 7.20 (1H, bs), 7.41 (1H, d, J=8.1 Hz), 7.54 (1H, d, J=7.6 Hz), 7.57—7.63 (3H, m), 7.66—7.72 (6H, m), 7.88—7.99 (3H, m), 8.62 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: 25.1, 26.1, 27.3, 27.3, 28.1, 28.4, 33.1, 37.1, 37.2, 38.3, 47.4, 108.6, 111.3, 118.4, 119.5, 122.1, 123.8, 123.9, 123.9, 124.0, 126.8, 130.2, 130.6, 131.6, 131.7, 131.8, 132.2, 132.5, 133.4, 133.5, 133.6, 136.1, 147.6, 147.7, 155.8, 171.5; HRMS ($C_{46}H_{57}N_9O_{15}S_3Na$, $MH^+ + Na^+$): Calcd for 1094.3034. Found: 1094.3057.

***N*-[16-Amino-5,9,13-tris(2-nitrobenzenesulfonyl)-5,9,13-triazahexadecan-1-yl]-1*H*-indole-3-acetamide (15)** To a stirred solution of 1.61 g (1.50 mmol) of polyamine **14** in 3 ml of dichloromethane and 6.0 ml of methanol was added excess thionyl chloride (1.0 ml, 13.7 mmol) at 0 °C under an argon atmosphere. After 1 h, the reaction mixture was evaporated.

Purification of the crude product by column chromatography on silica gel (10% methanol in chloroform) yielded polyamine **15** (1.40 g, 96%) as a yellow powder. IR ($CHCl_3$): 2961, 1638, 1543, 1458, 1439, 1373, 1344, 1262, 1216, 1160, 1124, 1059, 941, 852, 750 cm^{-1}; ^{1}H-NMR (DMSO) δ: 1.28 (2H, m), 1.37 (2H, m), 1.59 (2H, m), 1.68 (2H, m), 1.78 (2H, m), 2.73 (2H, m), 2.98 (2H, m), 3.09—3.23 (6H, m), 3.47 (2H, s), 6.94 (1H, dt, J=7.7, 1.0 Hz), 7.03 (1H, dt, J=7.7, 1.0 Hz), 7.16 (1H, bs), 7.31 (1H, d, J=8.1 Hz), 7.51 (1H, d, J=7.7 Hz), 7.80—7.98 (12H, m), 8.31 (1H, s); ^{13}C-NMR (DMSO) δ: 26.1, 26.2, 26.6, 32.7, 36.4, 38.0, 44.8, 44.8, 47.1, 108.9, 111.3, 118.2, 118.6, 120.9, 123.7, 124.3, 124.4, 124.5, 127.2, 129.6, 129.6, 131.4, 131.6, 132.4, 132.5, 132.6, 134.5, 134.7, 136.1, 147.4, 170.6; HRMS ($C_{41}H_{50}N_9O_{13}S_3$, M^+): Calcd for 972.2690. Found: 972.2682.

4-(Chlorodiphenylmethyl)phenoxymethylated Polystyrene Polymer (16) Merrifield resin 2.14 g (1% cross-linked polystyrene beads with 1.20 mmol of benzyl groups per gram of resin), excess *p*-hydroxytrityl alcohol (6.66 g, 24.1 mmol) and excess potassium carbonate (16.6 g, 120.5 mmol) were suspended in 30 ml of DMF under an argon atmosphere. After 24 h at 60 °C, the resin was washed five times with THF–H_2O (1 : 1), five times with THF, and five times with dichloromethane, and dried under vacuum for 24 h to give 2.72 g of trityl alcohol resin. To a suspension of 305 mg (0.27 mmol) of trityl alcohol resin in 2.3 ml of dichloromethane was added excess thionyl chloride (0.25 ml, 3.4 mmol) at room temperature under an argon atmosphere. After 1 h, the resin was washed five times with dichloromethane and dried under vacuum for 8 h to give trityl chloride resin **16**.

HO 416b (1) To a suspension of the freshly prepared resin **16** and 65.0 mg (0.068 mmol) of amine **15** in 2.5 ml of CH_2Cl_2 was added 0.141 ml (0.828 mmol) of iso-Pr_2NEt at room temperature. After shaking for 48 h, 0.1 ml of MeOH was added to the reaction mixture. The resin was filtered, washed with MeOH : CH_2Cl_2 (1 : 9), H_2O : MeOH : CH_2Cl_2 (1 : 1 : 8), and CH_2Cl_2, and then dried *in vacuo* for 8 h to give the resin. To a suspension of the above resin in 1.5 ml of DMF was added 0.140 ml (2.00 mmol) of 2-mercaptoethanol and 0.30 ml (2.00 mmol) of DBU at room temperature under an argon atmosphere. After shaking for 26 h, the resin was filtered, washed with H_2O : THF (1 : 9), MeOH : CH_2Cl_2 (1 : 9), and CH_2Cl_2 and dried *in vacuo* for 8 h to give the resin. To a mixture of the resulting resin in 2.5 ml of CH_2Cl_2 was added 25 μl (0.324 mmol) of TFA at room temperature. After shaking for 5 min, the resin was filtered and washed with MeOH : CH_2Cl_2 (1 : 9). The combined washings were evaporated and dried *in vacuo* to provide **1** (25.5 mg, 68%) as the TFA salt. ^{1}H-NMR (D_2O) δ: 1.36—1.40 (4H, m), 1.87—1.98 (6H, m), 2.80—3.05 (16H, m), 3.59 (2H, s), 7.02 (1H, dt, J=7.6, 1.0 Hz), 7.12 (1H, dt, J=7.6, 1.0 Hz,), 7.18 (1H, s), 7.38 (1H, d, J=8.0 Hz), 7.46 (1H, d, J=7.6 Hz); ^{13}C-NMR (D_2O) δ: 23.4, 24.5, 26.3, 33.3, 37.2, 39.2, 44.8, 45.3, 45.5, 47.9, 57.2, 108.4, 112.8, 119.1, 120.3, 122.9, 125.9, 127.4, 137.1, 176.2; MS: 417 (MH^+), 416 (M^+); HRMS ($C_{23}H_{41}N_6O$, MH^+): Calcd for 417.3342. Found: 417.3355; MS/MS (FAB); 422 ($M^+-H^++Na^+-NH_2$), 408 ($M^+-H^++Na^+-CH_4N$), 394 ($M^+-H^++Na^+-C_2H_6N$), 380 ($M^+-H^++Na^+-C_3H_8N$), 365 ($M^+-H^++Na^+-C_3H_9N_2$), 351 ($M^+-H^++Na^+-C_4H_{11}N_2$), 337 ($M^+-H+Na-C_5H_{13}N_2$), 323 ($M^+-H+Na-C_6H_{15}N_2$), 308 ($M^+-H+Na-C_6H_{16}N_3$), 294 ($M^+-H^++Na^+-C_7H_{18}N_3$), 280 ($M^+-H^++Na^+-C_8H_{20}N_3$), 266 ($M^+-H^++Na^+-C_9H_{22}N_3$), 252 ($M^+-H^++Na^+-C_9H_{22}N_4$), 238 ($M^+-H^++Na^+-C_{10}H_{24}N_4$), 223 ($M^+-H^++Na^+-C_{11}H_{27}N_4$), 210 ($M^+-H^++Na^+-C_{12}H_{28}N_4H_5$), 130 ($C_9H_8N^+$).

***N*-[3-(2-Nitrobenzenesulfonyl)amino-propan-1-yl]-1*H*-indole-3-acetamide (17)** To a stirred solution of 1.08 g (6.16 mmol) of 3-indoleacetic acid in 15 ml of dichloromethane were added 0.94 ml (6.78 mmol) of triethylamine and 0.83 ml (6.78 mmol) of pivaloyl chloride at 0 °C under an argon atmosphere. After 3 min at room temperature, the reaction mixture was cooled at 0 °C. To the above stirred solution was added 0.94 ml (6.78 mmol) of triethylamine, 2.07 g (8.01 mmol) of diamine **3** and 76 mg (0.62 mmol) of 4-dimethylaminopyridine. After 10 min at room temperature, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ether in hexane (50 to 70%), furnished sulfonamide **17** (2.43 g, 95%) as a yellow solid. IR ($CHCl_3$): 3401, 1645, 1539, 1457, 1339, 1164, 1125, 1094, 911, 853, 740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.58 (2H, tt, J=6.3, 6.3 Hz), 2.98 (2H, dt, J=6.3, 6.3 Hz), 3.27 (2H, dt, J=6.3, 6.3 Hz), 3.74 (2H, s), 5.87 (1H, m), 6.00 (1H, m), 7.13 (1H, dt, J=7.7, 1.0 Hz), 7.19 (1H, d, J=2.4 Hz), 7.25 (1H, dt, J=7.7, 1.0 Hz), 7.43 (1H, d, J=8.3 Hz), 7.52 (1H, d, J=7.7 Hz), 7.64—7.72 (2H, m), 7.78—7.82 (2H, m), 8.35 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: 30.0, 33.3, 36.0, 40.7, 108.8, 111.5, 118.6, 120.1, 122.6, 124.1, 125.2, 127.1, 130.7, 132.7, 133.4, 133.9, 136.5, 148.0, 172.4; MS: m/z=417 (MH^+), 416 (M^+); HRMS ($C_{19}H_{21}N_4O_5S$, MH^+): Calcd for 417.1233. Found: 417.1233.

3-*tert*-Butyldimethylsilyloxypropan-1-yl-bromide (18) To a stirred solution of 2.95 g (21.2 mmol) of 3-bromopropan-1-ol in 3 ml of dichloromethane were added 4.16 g (27.6 mmol) of *t*-butyldimethylsilyl chloride and 4.82 ml (27.6 mmol) of *N*,*N*-diisopropylethylamine at 0 °C under an argon atmosphere. After 20 min at room temperature, the reaction mixture was poured into water, and the aqueous layer was extracted thoroughly with hexane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (hexane) yielded silyl ether **18** (4.40 g, 83%) as a colorless oil. IR ($CHCl_3$): 2955, 2929, 2858, 1472, 1387, 1361, 1257, 1211, 1147, 1103, 1062, 1006, 952, 836, 777 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.01 (6H, s), 0.83 (9H, s), 1.97 (2H, tt, J=6.1, 6.1 Hz), 3.50 (2H, t, J=6.1 Hz), 3.67 (2H, t, J=6.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: −5.40, 18.3, 25.9, 30.7, 35.5, 60.4; MS: m/z=254 (MH^+); HRMS (C_9H_{22}BrOSi, M^+): Calcd for 253.0623. Found: 253.0620.

***N*-(7-*tert*-Butyldimethylsilyloxy-4-(2-nitrobenzenesulfonyl)-4-azaheptan-1-yl)-1*H*-indole-3-acetamide (19)** To a stirred solution of 3.10 g (7.45 mmol) of sulfonamide **17**, 7.28 g (22.3 mmol) of cesium carbonate and 1.37 g of (3.73 mmol) *n*-tetrabutylammonium iodide in 10 ml of acetonitrile was added slowly 1.89 ml (8.20 mmol) of bromide **18** at 60 °C under an argon atmosphere. After 90 min, the reaction mixture was poured into water, and the aqueous layer was extracted thoroughly with ethyl acetate (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (70% ethyl acetate in hexane) yielded indole **19** (3.47 g, 80%) as a yellow oil. IR ($CHCl_3$): 3403, 2929, 2856, 1653, 1545, 1458, 1437, 1373, 1342, 1256, 1163, 1099, 1009, 957, 836, 777, 744 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.01 (6H, s), 0.85 (9H, s), 3.24—3.31 (4H, m), 3.12 (2H, t, J=6.5 Hz), 3.24 (2H, t, J=5.6 Hz), 3.29 (2H, t, J=6.5 Hz), 3.51 (2H, t, J=5.6 Hz), 3.75 (2H, s), 6.24 (1H, bs), 7.13 (1H, t, J=7.7 Hz), 7.20 (1H, d, J=7.7 Hz), 7.23 (1H, bs), 7.37 (1H, d, J=7.6 Hz), 7.58 (1H, d, J=7.7 Hz), 7.59—7.68 (4H, m), 8.29 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: −5.45, 18.2, 25.8, 27.6, 31.4, 33.4, 35.6, 44.8, 45.1, 60.0, 109.0, 111.4, 118.6, 119.8, 122.3, 124.0, 124.2, 127.2, 130.4, 131.6, 133.3, 136.9, 171.9; MS: m/z=588 (M^+); HRMS ($C_{28}H_{40}N_4O_6SSi$, M^+): Calcd for 588.2438. Found: 588.2423.

***N*-[7-*tert*-Butyldimethylsilyloxy-4-(2-nitrobenzenesulfonyl)-4-azaheptan-1-yl]-1-*tert*-butoxycarbonyl-indole-3-acetamide (20)** To a stirred solution of 3.14 g (5.33 mmol) of indole **19** in 25 ml of dichloromethane were added 0.8 ml (5.86 mmol) of triethylamine, 1.3 ml (5.86 mmol) of di-*tert*-butyl dicarbonate, and 65 mg (0.53 mmol) of 4-dimethylaminopyridine (DMAP) at room temperature under an argon atmosphere. After 1 h, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give indole **20** (3.60 g, 98%) as a yellow oil. IR ($CHCl_3$): 3298, 2930, 1734, 1654, 1546, 1453, 1370, 1308, 1257, 1227, 1159, 1087, 1016, 957, 836, 774, 747 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.01 (6H, s), 0.85 (9H, s), 1.64 (9H, s), 1.68—1.71 (4H, m), 3.16 (2H, t, J=6.3 Hz), 3.28 (2H, t, J=5.9 Hz), 3.30 (2H, t, J=6.3 Hz), 3.52 (2H, t, J=5.9 Hz), 3.68 (2H, s), 6.20 (1H, bs), 7.25 (1H, d, J=7.7 Hz), 7.27 (1H, bs), 7.34 (1H, t, J=7.7 Hz), 7.54 (1H, d, J=7.7 Hz), 7.57—7.70 (4H, m), 8.17 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: −5.36, 3.90, 18.3, 25.9, 27.7, 28.2, 31.4, 33.5, 36.0, 44.9, 45.2, 60.1, 83.8, 113.9, 115.4, 119.0, 122.9, 124.1, 124.8, 125.2, 130.5, 131.7, 133.2, 133.5, 170.6; MS: m/z=588 (MH^+−Boc); HRMS ($C_{33}H_{49}N_4O_8SSi$, MH^+): Calcd 689.3040. Found: 689.3070.

***N*-(7-*tert*-Butyldimethylsilyloxy-4-azaheptan-1-yl)-1-*tert*-butoxycarbonyl-indole-3-acetamide (21)** To a stirred solution of 1.11 g (1.61 mmol) of indole **21** and 2.62 g (8.06 mmol) of cesium carbonate in 5 ml of acetonitrile was added 0.33 ml (3.22 mmol) of thiophenol at room temperature under an argon atmosphere. After 10 h, the reaction mixture was poured into brine, and the aqueous layer was extracted thoroughly with ethyl acetate (3×). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (10% methanol in chloroform) yielded secondary amine **21** (787 mg, 97%) as a yellow oil. IR ($CHCl_3$): 2958, 2928, 2853, 1734, 1654, 1560, 1455, 1369, 1256, 1159, 1086, 835, 776, 747 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.01 (6H, s), 0.84 (9H, s), 1.61 (4H, m), 1.63 (9H, s), 2.59—2.63 (4H, m), 3.28 (2H, m), 3.59 (2H, t, J=7.3 Hz),

3.62 (2H, s), 6.67 (1H, bs), 7.21 (1H, t, J=7.5 Hz), 7.30 (1H, t, J=7.5 Hz), 7.47 (1H, d, J=7.5 Hz), 7.51 (1H, s), 8.10 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: −5.4, 0.0, 18.3, 25.9, 28.0, 28.2, 29.7, 31.1, 33.2, 37.9, 47.0, 61.5, 83.9, 113.8, 115.4, 119.0, 122.9, 124.9, 129.8, 149.5; MS: m/z=504 (MH^+), 503 (M^+); HRMS ($C_{27}H_{46}N_3O_4SSi$, MH^+): Calcd for 504.3258. Found: 504.3254.

***N*-(7-*tert*-Butyldimethylsilyloxy-4-(2-cyanoethyl)-4-azaheptan-1-yl)-1-*tert*-butoxycarbonyl-indole-3-acetamide (22)** To a stirred solution of 2.27 g (4.50 mmol) of secondary amine **21** in 9 ml of ethanol was added excess acrylonitrile (9.0 ml, 37.4 mmol) at 60 °C under an argon atmosphere. After 24 h, the reaction mixture was evaporated. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of ethyl acetate in hexane (30 to 70%), furnished indole **22** (2.22 g, 93%) as a yellow oil. IR ($CHCl_3$): 3297, 2930, 2857, 1732, 1649, 1547, 1453, 1369, 1308, 1256, 1227, 1158, 1086, 1016, 836, 774, 747 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.01 (6H, s), 0.85 (9H, s), 1.43 (2H, tt, J=6.6, 6.6 Hz), 1.55 (2H, tt, J=6.3, 6.3 Hz), 1.67 (9H, s), 2.14 (2H, t, J=6.3 Hz), 2.30 (2H, t, J=6.5 Hz), 2.35 (2H, t, J=6.6 Hz), 2.49 (2H, t, J=6.5 Hz), 3.27 (2H, dt, J=6.3, 6.3 Hz), 3.51 (2H, t, J=6.6 Hz), 3.64 (2H, s), 6.13 (1H, bs), 7.25 (1H, t, J=7.0 Hz), 7.34 (1H, t, J=7.0 Hz), 7.51 (1H, d, J=7.0 Hz), 7.54 (1H, s), 8.15 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: −5.85, 15.4, 17.7, 25.4, 26.1, 27.7, 29.1, 37.7, 49.0, 50.9, 60.1, 83.5, 113.5, 114.9, 118.6, 122.4, 124.4, 124.5, 129.4, 149.0, 169.8; MS: m/z=556 (M^+); HRMS ($C_{30}H_{49}N_4O_4Si$, MH^+): Calcd for 557.3523. Found: 557.3505.

***N*-[4-(2-Cyanoethyl)-7-hydroxy-4-azaheptan-1-yl]-1-*tert*-butoxycarbonyl-indole-3-acetamide (23)** To a stirred solution of 1.90 g (3.41 mmol) of indole **22** in 20 ml of acetonitrile was added 973 mg (17.1 mmol) of ammonium fluoride at 60 °C under an argon atmosphere. After 10 h, the reaction mixture was poured into a solution of saturated sodium bicarbonate, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of methanol in chloroform (10 to 30%), furnished alcohol **23** (1.47 g, 98%) as a yellow oil. IR ($CHCl_3$): 3298, 2934, 1731, 1654, 1540, 1453, 1369, 1308, 1257, 1227, 1158, 1086, 1017, 942, 856, 768, 748 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.44 (2H, tt, J=6.2, 6.2 Hz), 1.60 (2H, tt, J=6.8, 6.8 Hz), 1.68 (9H, s), 2.29 (2H, t, J=6.8 Hz), 2.32 (2H, t, J=7.1 Hz), 2.46 (2H, t, J=6.2 Hz), 2.61 (2H, t, J=7.1 Hz), 3.26 (2H, dt, J=6.8, 6.8 Hz), 3.62 (2H, t, J=6.2 Hz), 3.66 (2H, s), 6.19 (1H, bs), 7.27 (1H, t, J=7.6 Hz), 7.36 (1H, t, J=7.6 Hz), 7.53 (1H, d, J=7.6 Hz), 7.57 (1H, s), 8.16 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: 15.7, 26.6, 28.3, 28.5, 33.4, 37.7, 49.3, 50.8, 52.3, 62.3, 84.1, 114.0, 115.5, 118.7, 119.1, 123.0, 125.0, 125.1, 130.0, 135.7, 149.6, 170.5; MS: m/z=442 (M^+); HRMS ($C_{24}H_{35}N_4O_4$, MH^+): Calcd for 443.2658. Found: 443.2669.

8-*tert*-Butoxycarbonylamino-5-(2-nitrobenzenesulfonyl)-5-azaoctan-1-yl Bromide (24) To a stirred solution of 8.50 g (61.8 mmol) of potassium carbonate in 3.7 ml (30.9 mmol) of 1,4-dibromobutane was added the 1.60 g (6.18 mmol) of diamine **6** in 10 ml of DMF at 60 °C under an argon atmosphere. After 30 min, the reaction mixture was poured into water, and the aqueous layer was extracted thoroughly with ether (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (30% ethyl acetate in hexane) yielded bromide **24** (2.47 g, 81%) as a yellow oil. IR ($CHCl_3$): 2975, 1700, 1545, 1457, 1367, 1252, 1162, 852, 778 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.70 (2H, tt, J=7.4, 7.4 Hz), 1.76 (2H, tt, J=6.9, 6.9 Hz), 1.83 (2H, tt, J=6.9, 6.9 Hz), 3.15 (2H, m), 3.33 (2H, t, J=7.4 Hz), 3.35 (2H, t, J=6.9 Hz), 3.38 (2H, t, J=6.9 Hz), 4.78 (1H, bs), 7.62—7.66 (1H, m), 7.67—7.74 (2H, m), 8.00—8.02 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 26.6, 26.6, 28.4, 29.4, 32.9, 37.4, 45.0, 46.6, 124.3, 130.7, 131.7, 133.3, 133.6, 148.1; MS: m/z=438 (MH^+−*tert*-Bu), 394 (MH^+−Boc); *Anal.* ($C_{18}H_{28}BrN_3O_6S$): Calcd for C, 43.73; H, 5.71; N, 8.50. Found: C, 44.03; H, 5.52; N, 8.35.

***N*-(3-Allyloxycarbonylaminopropan-1-yl)-2-nitrobenzenesulfonamide (25)** To a stirred solution of 1.99 g (7.68 mmol) of diamine **3** in 30 ml of dichloromethane were added 1.28 ml (9.22 mmol) of triethylamine and 0.97 ml (9.22 mmol) of allyl chloroformate at room temperature under an argon atmosphere. After 30 min, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (40% ethyl acetate in hexane) yielded diamine **25** (2.33 g, 89%) as a yellow powder. IR ($CHCl_3$): 3340, 3096, 2946, 2883, 1699, 1647, 1593, 1539, 1442, 1418, 1363, 1340, 1302, 1259, 1165, 1126, 1089, 1037, 996, 933, 854, 782, 741, 730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.73 (2H, tt, J=6.3, 6.3 Hz), 3.17 (2H, dt, J=6.3, 6.3 Hz), 3.30 (2H, dt, J=6.3, 6.3 Hz), 4.55 (2H, d, J=6.0 Hz), 4.96 (1H, bs), 5.21 (1H, d, J=10.8 Hz), 5.30 (1H, d, J=15.6 Hz), 5.78 (1H, bs), 5.91 (1H, ddt, J=15.6, 10.8, 6.0 Hz), 7.72—7.76 (2H, m), 7.85—7.88 (1H, m), 8.12—8.15 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 30.4, 37.5, 40.7, 65.7, 117.8, 125.4, 130.9, 132.8, 133.5, 133.9, 148.1, 156.7, 167.6, 173.1; MS: m/z=344 (MH^+), 343 (M^+); HRMS ($C_{13}H_{18}N_3O_6S$, MH^+): Calcd for 344.0916. Found: 344.0910.

***N*-(12-Allyloxycarbonylamino-4,9-bis(2-nitrobenzenesulfonyl)-4,9-diazadodecan-1-yl)-*tert*-butoxycarbamide (26)** To a stirred solution of 1.95 g (3.95 mmol) of bromide **24**, 3.49 g (10.7 mmol) of cesium carbonate, and 133 mg (0.36 mmol) of *n*-tetrabutylammonium iodide in 5 ml of acetonitrile was added 1.12 g (3.29 mmol) of diamine **25** at 60 °C under an argon atmosphere. After 1 h, the reaction mixture was poured into brine, and the aqueous layer was extracted thoroughly with ethyl acetate (3×). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (60% ethyl acetate in hexane) yielded tetramine **26** (2.39 g, 97%) as a yellow solid. IR ($CHCl_3$): 3414, 3092, 2934, 1709, 1544, 1460, 1440, 1372, 1346, 1251, 1162, 1125, 1060, 1032, 914, 852, 779, 733 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.51 (4H, bs), 1.73 (4H, m), 3.12 (2H, m), 3.20 (2H, m), 3.25—3.36 (8H, m), 4.55 (2H, d, J=4.8 Hz), 4.81 (1H, bs), 5.13 (1H, bs), 5.21 (1H, d, J=8.8 Hz), 5.30 (1H, d, J=18.8 Hz), 5.92 (1H, ddt, J=18.8, 8.8, 4.8 Hz), 7.61—7.64 (2H, m), 7.70—7.72 (4H, m), 7.98—7.99 (2H, m); ^{13}C-NMR ($CDCl_3$) δ: 25.1, 28.4, 28.7, 37.7, 45.1, 45.2, 47.0, 65.5, 68.2, 117.6, 124.3, 130.6, 130.6, 131.8, 132.9, 133.7, 148.0; MS: m/z=757 (MH^+); *Anal.* ($C_{31}H_{44}N_6O_{12}S_2$): Calcd for C, 49.20; H, 5.86; N, 11.10. Found: C, 48.82; H, 5.74; N, 10.60.

***N*-(12-*tert*-Butoxycarbonylamino-4,9-bis(2-nitrobenzenesulfonyl)-4,9-diazadodecan-1-yl)-2-nitrobenzenesulfonamide (27)** To a stirred solution of 2.29 g (3.03 mmol) of tetramine **26** in 20 ml of dichloromethane were added 159 mg (0.61 mmol) of triphenylphosphine, 175 mg (0.15 mmol) of $Pd(PPh_3)_4$ and 0.8 ml (9.09 mmol) of pyrrolidine consecutively at 0 °C under an argon atmosphere. After 90 min at room temperature, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel, eluted with a gradient of methanol in chloroform (0 to 10%) furnished tetramine (2.13 g, 99%) as a yellow solid. IR ($CHCl_3$): 2962, 1685, 1542, 1461, 1370, 1260, 1160, 1028, 852, 798 cm^{-1}; ^{1}H-NMR (DMSO) δ: 1.29 (9H, s), 1.36 (2H, bs), 1.50 (2H, m), 1.73 (2H, m), 2.67 (2H, m), 2.80 (2H, m), 3.11—3.20 (4H, m), 4.29 (2H, bs), 6.75 (1H, bs), 7.75—7.85 (4H, m), 7.89—7.96 (4H, m); ^{13}C-NMR (DMSO) δ: 18.5, 24.8, 25.0, 26.4, 28.2, 28.5, 36.5, 37.3, 44.7, 45.3, 47.0, 56.0, 77.6, 124.3, 124.3, 129.6, 131.6, 131.7, 132.4, 132.5, 134.5, 134.6, 147.5, 155.6; MS: m/z=672 (M^+); HRMS ($C_{27}H_{41}N_6O_{10}S_2$, MH^+): Calcd for 673.2325. Found: 673.2324.

To a stirred solution of 2.02 g (3.00 mmol) of the above tetramine and 798 mg (3.60 mmol) of 2-nitrobenzenesulfonyl chloride in 20 ml of dichloromethane was added 0.50 ml (3.60 mmol) of triethylamine at 0 °C under an argon atmosphere. After 30 min at room temperature, the reaction mixture was poured into a solution of 1 N hydrochloric acid, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by column chromatography on silica gel (50% ethyl acetate in hexane) yielded sulfonamide **27** (2.42 g, 94%) as a yellow solid. IR ($CHCl_3$): 3414, 2937, 1706, 1544, 1465, 1373, 1345, 1252, 1160, 1125, 1060, 998, 852, 778, 744 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.51 (4H, bs), 1.72 (2H, m), 1.85 (2H, m), 3.13 (2H, m), 3.23—3.38 (10H, m), 4.83 (1H, bs), 7.60—7.63 (3H, m), 7.69—7.72 (6H, m), 7.97—8.01 (3H, m); ^{13}C-NMR ($CDCl_3$) δ: 25.0, 25.0, 27.4, 28.4, 42.4, 44.4, 44.9, 45.1, 46.9, 47.1, 124.2, 130.5, 130.6, 130.8, 130.8, 130.9, 131.8, 131.9, 131.9, 133.0, 133.6, 133.7, 148.0; MS: m/z=758 (MH^+−Boc); *Anal.* ($C_{33}H_{43}N_7O_{14}S_3$): Calcd for C, 46.20; H, 5.05; N, 11.43. Found: C, 46.08; H, 5.04; N, 10.77.

***N*-[20-*tert*-Butoxycarbonylamino-4-(2-cyanoethyl)-8,12,17-tris(2-nitrobenzenesulfonyl)-4,8,12,17-tetraazaicosan-1-yl]-1-*tert*-butoxycarbonyl-indole-3-acetamide (28)** To a stirred solution of 225 mg (0.51 mmol) of alcohol **23**, 520 mg (0.61 mmol) of sulfonamide **27** and 200 mg (0.76 mmol) of triphenylphosphine in 2 ml of dichloromethane and 8 ml of benzene was slowly added 345 μl (0.76 mmol) of diethyl azodicarboxylate (40% in toluene) at room temperature under an argon atmosphere. After 10 min, the reaction mixture was evaporated. Purification of the crude

product by column chromatography on silica gel, eluted with a gradient of ethyl acetate in hexane (80 to 100%), furnished polyamine **28** (587 mg, 90%) as a yellow powder. IR ($CHCl_3$): 2931, 1715, 1669, 1545, 1455, 1369, 1256, 1160, 1086, 852, 736 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.32 (2H, m), 1.43 (9H, s), 1.49 (2H, m), 1.58 (4H, m), 1.66 (9H, s), 1.68 (2H, m), 1.83 (2H, m), 2.26 (2H, t, J=6.4 Hz), 2.32 (4H, t, J=6.4 Hz), 2.55 (2H, t, J=6.4 Hz), 3.11 (2H, m), 3.20—3.31 (14H, m), 3.64 (2H, s), 4.84 (1H, bs), 6.16 (1H, bs), 7.23 (1H, t, J=7.5 Hz), 7.32 (1H, t, J=7.5 Hz), 7.47—7.65 (5H, m), 7.67—7.71 (6H, m), 7.95—7.98 (3H, m), 8.14 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: 16.5, 23.9, 25.1, 25.2, 27.9, 28.3, 28.5, 28.8, 30.4, 33.4, 37.9, 38.9, 45.2, 45.5, 46.5, 47.2, 47.4, 49.4, 50.6, 51.1, 114.2, 115.5, 119.2, 123.0, 124.2, 124.3, 124.4, 124.9, 125.1, 128.6, 128.7, 128.9, 128.9, 130.1, 130.6, 130.8, 131.0, 132.0, 132.1, 132.1, 132.2, 132.3, 132.9, 132.9, 133.0, 133.2, 133.8, 148.1, 170.6; HRMS ($C_{57}H_{76}N_{11}O_{17}S_3$, MH^+): Calcd for 1282.4583. Found: 1282.4578.

***N*-[20-*tert*-Butoxycarbonylamino-4-hydroxy-8,12,17-tris(2-nitrobenzenesulfonyl)-4,8,12,17-tetraazaicosan-1-yl]-1-*tert*-butoxycarbonyl-indole-3-acetamide (29)** To a stirred solution of 220 mg (0.172 mmol) of polyamine **28** in 5 ml of dichloromethane was slowly added 30 mg (0.173 mmol) of 3-chloroperoxybenzoic acid (*m*-CPBA) in 3 ml of dichloromethane at −10 °C. After 1 h, excess dimethyl sulfide (0.25 ml, 3.42 mmol) was added to the reaction mixture, and the vessel was allowed to warm to room temperature. The mixture was poured into a solution of saturated sodium bicarbonate, and the aqueous layer was extracted thoroughly with dichloromethane (3×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification of the crude product by preparative thin layer chromatography (10% methanol in chloroform) afforded hydroxylamine **29** (192 mg, 90%) as a yellow powder. IR ($CHCl_3$): 3413, 3093, 2934, 1729, 1654, 1591, 1544, 1453, 1370, 1309, 1256, 1227, 1160, 1125, 1086, 1060, 1017, 912, 852, 773, 733 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.23 (2H, m), 1.42 (9H, s), 1.49 (2H, bs), 1.66 (9H, s), 1.70 (4H, m), 1.84 (2H, m), 2.47 (2H, t, J=6.4 Hz), 2.51 (2H, t, J=6.4 Hz), 3.10 (2H, m), 3.20—3.34 (14H, m), 3.64 (2H, s), 4.86 (1H, bs), 6.21 (1H, bs), 7.24 (1H, t, J=7.5 Hz), 7.33 (1H, t, J=7.5 Hz), 7.51 (1H, d, J=7.5 Hz), 7.56 (1H, bs), 7.59—7.62 (3H, m), 7.67—7.71 (6H, m), 7.95—7.98 (3H, m), 8.14 (1H, bs); ^{13}C-NMR ($CDCl_3$) δ: 13.7, 22.2, 24.5, 24.7, 25.3, 26.2, 27.1, 27.8, 28.0, 28.2, 31.1, 32.8, 37.6, 44.7, 44.8, 45.4, 46.6, 56.7, 57.8, 111.9, 113.7, 115.0, 118.6, 122.5, 123.7, 123.8, 124.4, 129.4, 130.1, 130.3, 131.4, 131.5, 132.4, 132.5, 132.6, 133.2, 133.3, 147.5, 147.5, 155.6, 169.8; HRMS ($C_{54}H_{73}N_{10}O_{18}S_3$, MH^+): Calcd for 1245.4266. Found: 1245.4265.

***N*-(20-Amino-4-hydroxy-8,12,17-tris(2-nitrobenzenesulfonyl)-4,8,12,17-tetraazaicosan-1-yl)-1*H*-indole-3-acetamide (30)** To a stirred solution of 108 mg (0.0867 mmol) of hydroxylamine **29** in 0.4 ml of dichloromethane and 1.2 ml of methanol was added excess thionyl chloride (0.4 ml, 5.48 mmol) at 0 °C under an argon atmosphere. After 2.5 h at room temperature, the reaction mixture was evaporated. Purification of the crude product by column chromatography on silica gel (10% methanol in chloroform) yielded polyamine **30** (89 mg, 95%) as a yellow powder. IR ($CHCl_3$): 3020, 1653, 1541, 1457, 1373, 1340, 1215, 1160, 1125, 1060, 852, 757 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.39 (4H, m), 1.69 (2H, m), 1.79 (4H, m), 1.90 (2H, m), 2.73 (2H, m), 3.09—3.32 (18H, m), 3.49 (2H, s), 6.95 (1H, t, J=7.4 Hz), 7.04 (1H, t, J=7.4 Hz), 7.18 (1H, s), 7.32 (1H, d, J=8.0 Hz), 7.53 (1H, d, J=7.4 Hz), 7.81—7.90 (9H, m), 7.93—8.00 (3H, m), 10.9 (1H, s); ^{13}C-NMR ($CDCl_3$) δ: 24.7, 24.8, 26.2, 32.7, 36.4, 44.9, 47.1, 111.3, 118.3, 118.6, 120.9, 123.8, 124.3, 124.4, 127.2, 129.6, 131.5, 131.6, 132.5, 134.6, 136.1, 147.4, 147.9; HRMS ($C_{44}H_{57}N_{10}O_{14}S_3$, MH^+): Calcd for 1045.3218. Found: 1045.3214.

Agel 489 (2) To a suspension of the freshly prepared resin **16** (0.13 mmol) and 27.0 mg of amine **30** (0.025 mmol) in 1.5 ml of dichloromethane was added excess *N*,*N*-diisopropylethylamine (55 μl, 0.32 mmol) at room temperature. After shaking for 24 h, excess methanol (0.3 ml, 7.5 mmol) was added to the reaction mixture. The resin was filtered, washed with MeOH : CH_2Cl_2 (1 : 9), H_2O : MeOH : CH_2Cl_2 (1 : 1 : 8), and CH_2Cl_2, and then dried *in vacuo* for 8 h to give the resin. To a suspension of the resulting resin in 1.5 ml of DMF was added excess 2-mercaptoethanol (0.053 ml, 0.75 mmol) and excess DBU (0.11 ml, 0.75 mmol) at room temperature under an argon atmosphere. After shaking for 26 h, the resin was filtered, washed with H_2O : THF (1 : 9), MeOH : CH_2Cl_2 (1 : 9), and CH_2Cl_2 and dried *in vacuo* for 8 h to give the resin. To a mixture of the resulting resin in 2.5 ml of CH_2Cl_2 was added trifluoroacetic acid (30 μl, 0.36 mmol) at room temperature. After shaking for 5 min, the resin was filtered and washed with MeOH : CH_2Cl_2 (1 : 1). The combined washings were evaporated and dried *in vacuo* to provide **2** (27.0 mg, 92%) as the TFA salt. ^{1}H-NMR (D_2O) δ: 1.72 (4H, m), 1.92—2.06 (8H, m), 3.02—3.17 (20H, m), 3.71 (2H, s), 7.13 (1H, dt, J=7.3, 1.0 Hz), 7.22 (1H, dt, J=7.3, 1.0 Hz), 7.29 (1H, s), 7.48 (1H, d, J=8.0 Hz), 7.56 (1H, d, J=7.3 Hz); ^{13}C-NMR (D_2O) δ: 23.5, 24.5, 33.2, 36.8, 37.3, 45.2, 45.3, 47.8, 56.4, 57.4, 108.4, 112.8, 119.1, 120.3, 122.9, 126.0, 127.3, 137.1, 176.8; HRMS ($C_{26}H_{48}N_7O_2$, MH^+): Calcd for 490.3869. Found: 490.3878; MS/MS (FAB) 474 (MH^+-NH_2), 460 (MH^+-CH_4N), 446 ($MH^+-C_2H_6N$), 432 ($MH^+-C_3H_8N$), 416 ($M^+-C_3H_9N_2$), 402 ($M^+-C_4H_{11}N_2$), 374 ($M^+-C_6H_{13}N_2$), 360 ($M^+-C_7H_{17}N_2$), 345 ($M^+-C_7H_{18}N_3$), 317 ($M^+-C_9H_{22}N_3$), 275 ($MH^+-C_{11}H_{27}N_4$), 258 ($M^+-C_{11}H_{28}N_4O$), 244 ($M^+-C_{12}H_{30}N_4O$), 215 ($M^+-C_{13}H_{32}N_5O$), 130 ($C_9H_8N^+$).

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References and Notes

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