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Efficient macrocyclization by means of 2-nitrobenzenesulfonamide and total synthesis of lipogrammistin-A

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This paper is dedicated to Professor Yoshito Kishi of Harvard University on the occasion of his receiving the Tetrahedron Prize

Abstract—Synthesis of medium- and large-sized cyclic amines using alkylation with 2-nitrobenzenesulfonamides is described. Using either conventional alkylation procedures or Mitsunobu conditions, the cyclization reaction proceeded in a highly efficient manner. The usefulness of this methodology has been fully demonstrated in the total synthesis of lipogrammistin-A (**9**), an 18-membered cyclic polyamine. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Construction of medium- and large-sized cyclic amines is an important subject in organic synthesis, since these structural units are often found in the frameworks of a variety of medicinally interesting natural products. While many cyclization reactions have been reported, there seem to be few direct alkylations with nitrogen nucleophiles.[1,2] We have recently developed a novel transformation of primary amines to secondary amines using 2-nitrobenzenesulfonamides as an activating/protecting group (Ns-strategy).[3–8] We envisioned that an intramolecular alkylation with a Ns-amide would facilitate the construction of cyclic amines. Herein we report an efficient macrocyclization with 2-nitrobenzenesulfonamides and its application to the total synthesis of lipogrammistin-A (**9**).[9]

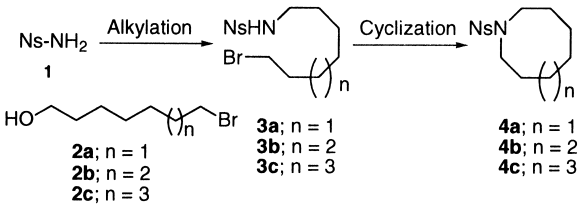
2. Results and discussion

Construction of medium-sized cyclic amines (8- to 10-membered rings) was investigated first using non-branched, simple substrates as shown in Table 1. Coupling between sulfonamide **1**[10] and ω-bromoalcohol **2a–c** was performed under Mitsunobu conditions to give the predominantly mono-alkylated products **3a–c**. Preliminary studies on the cyclization of **3a–c** revealed that high-dilution conditions (0.01 M) are preferred to achieve reasonable yields. Thus, when an acetonitrile solution of **3a–c** was slowly added (2 h) by means of a syringe pump to a mixture of tetrabutylammonium iodide and Cs_2CO_3 in acetonitrile at 60°C, the cyclization proceeded smoothly to give the desired products **4a–c** in good yields.

By contrast, the macrocyclization using *N-tert*-butoxycarbonyl-7-iodo-1-aminoheptane (**5**) did not give the desired 8-membered ring product (Scheme 1). While treatment of **5** with sodium hydride in DMF at room temperature resulted in almost complete recovery of the starting material, heating the mixture at 60°C caused dehydroiodination to give **6** as the major product.

In order to perform the cyclization under Mitsunobu conditions, the precursors **8a–c** were prepared from

Table 1. Synthesis of medium-sized ring via conventional alkylation



Ring size	Alcohol	Alkulation[a] (yield %)	Cyclization[b] (yield %)
8	**2a**	**3a** (70)	**4a** (62)
9	**2b**	**3b** (67)	**4b** (64)
10	**2c**	**3c** (74)	**4c** (66)

[a] Alkylation conditions: PPh_3, DEAD, toluene–THF (10:1).
[b] Cyclization conditions: Cs_2CO_3, CH_3CN, n-Bu_4NI, 60°C.

Keywords: lipogrammistin-A; cyclization; Mitsunobu conditions.

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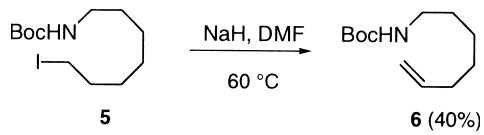


Scheme 1. Attempted cyclization of *N*-Boc-amide.

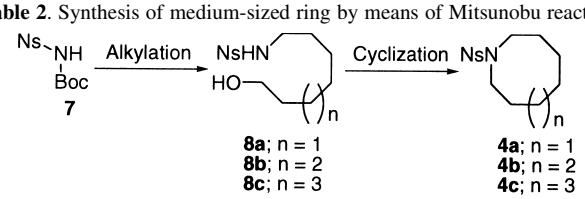
N-Boc-nitrobenzenesulfonamide **7** (Table 2). When the mixture of **7** and bromide **2a–c** was heated with K_2CO_3 in DMF, the alkylation proceeded smoothly to give the N-Boc protected precursors. Subsequent deprotection of the Boc group with trifluoroacetic acid and methanolysis of the trifluoroacetate formed during the deprotection provided the cyclization precursors **8a–c**. Upon treatment of **8a–c** with DEAD and PPh_3 in 0.01 M solution of toluene–THF at room temperature, the desired cyclization reaction proceeded smoothly to afford **4a–c** in moderate yields.

In both ring closures (Tables 1 and 2), the cyclization occurred successfully without the aid of the branching effect.[11] Thus, the Ns-strategy proved to be a powerful protocol for the construction of medium-sized rings, overriding the inherent entropic disadvantage of the ring closure. With these successful results in hand, we turned our attention to the construction of large-sized rings by means of the Ns-strategy. Many macrocyclic polyamine alkaloids (13- to 18-membered rings) have been isolated from plants and marine sources and shown to exhibit interesting biological activities.[12] Although many synthetic efforts have been made to date, only a few methodologies are available for the macrocyclization.[13] We anticipated that the Ns-strategy would also be suitable for the construction of large-sized rings. In order to demonstrate the utility of the Ns-strategy, we attempted to synthesize lipogrammistin-A (**9**) (Fig. 1).

Lipogrammistin-A (**9**) was isolated from the skin mucus of grammistid fish by Fusetani and Tachibana.[14] The structure of lipogrammistin-A was determined on the basis of extensive NMR studies, and the first total synthesis has recently been reported by Tachibana.[15] One of the key structural features of **9** is the acylated polyamine lactam ring. Firstly, construction of the 18-membered ring was examined in the model compounds **16** and **18** (Scheme 2).

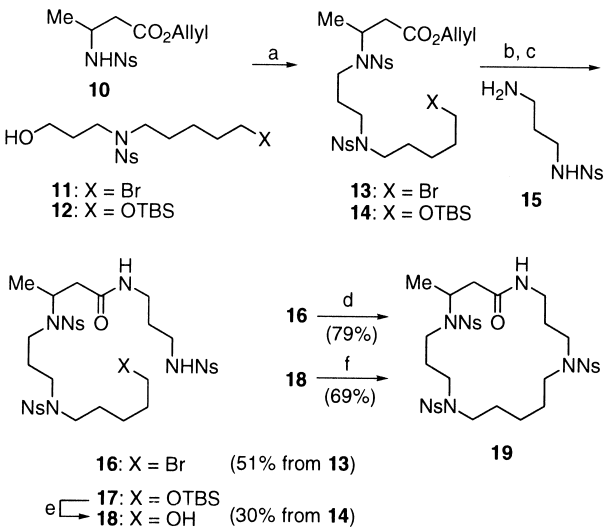
The cyclization precursors were synthesized from the sulfonamide **10**, which was readily available from

Table 2. Synthesis of medium-sized ring by means of Mitsunobu reaction



Ring size	Bromide	Alkylation[a] (yield %)	Cyclization[b] (yield %)
8	**2a**	**8a** (66)	**4a** (59)
9	**2b**	**8b** (85)	**4b** (57)
10	**2c**	**8c** (62)	**4c** (62)

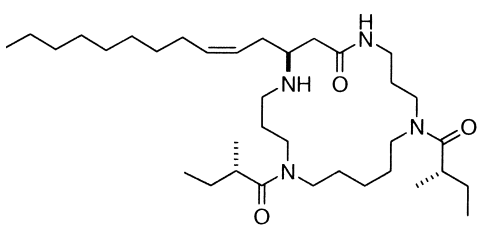
[a] Alkylation conditions: (1) K_2CO_3, *n*-Bu_4NI, DMF, 60°C. (2) TFA, CH_2Cl_2. (3) K_2CO_3, MeOH.
[b] Cyclization conditions: PPh_3, DEAD, toluene/THF (3:1).



Scheme 2. Construction of 18-membered ring. *Reagents and conditions*: (a) **11** or **12** (1.0 equiv.), DEAD (1.1 equiv.), PPh_3 (1.1 equiv.), benzene, room temperature, 10 min. (b) $Pd(PPh_3)_4$ (0.05 equiv.), pyrrolidine (1.2 equiv.), CH_2Cl_2, room temperature, 30 min. (c) **15** (1.2 equiv.), EDCI (1.2 equiv.), CH_2Cl_2, room temperature, 30 min. (d) Cs_2CO_3 (3.0 equiv.), *n*-Bu_4NI (2.0 equiv.), CH_3CN, 60°C, 2 h. (e) aq. HF (excess), CH_3CN, room temperature, 2 min. (f) DEAD (1.2 equiv.), PPh_3 (1.2 equiv.), benzene/CH_2Cl_2 (2:1), room temperature, 10 min.

3-amino-*n*-butyric acid. The coupling reaction between sulfonamide **10** and **11** was effected under Mitsunobu conditions to give the diamine derivative **13**. After the palladium-mediated deprotection of the allyl group, the resultant acid was condensed with diamine **15**[8] to give the cyclization precursor **16**. Upon treatment of **16** with Cs_2CO_3 at 60°C in acetonitrile, the desired cyclization proceeded smoothly to give **19** in 79% yield. In order to perform the similar macrocyclization under Mitsunobu conditions, the precursor **18** was prepared from **10** and **12** by the similar sequence described above. After removal of the TBS group, the resultant alcohol **18** was subjected to the Mitsunobu conditions to give the desired cyclization product **19** in 69% yield. Both ring closures were successfully performed even at 0.1 M concentration, obviating the need for high-dilution conditions. As we hoped, the nosyl (Ns) group-mediated cyclization proved to be an exceedingly effective method for the construction of 18-membered ring.

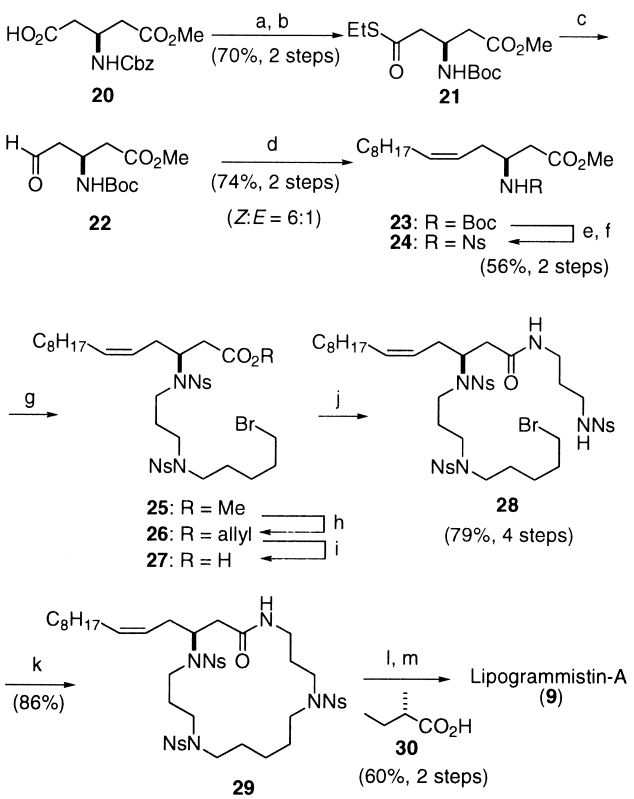
Our total synthesis of lipogrammistin-A (**9**) commenced with carboxylic acid **20**[16] (Scheme 2). After a one-pot exchange of the Cbz protecting group with a Boc group,[17] the carboxylic acid was converted to the corresponding thiol ester **21**.[18] Upon treatment with triethylsilane and 10% Pd on C at room temperature, the thiol ester **21** underwent



Lipogrammistin-A (**9**)

Figure 1. Structure of lipogrammistin-A (**9**).

smooth reduction to give aldehyde **22**,[19] which, without purification, was subjected to the Wittig reaction to afford the *cis*-alkene **23**. The direct conversion of the thiol ester into the aldehyde, which was developed in our laboratories, is particularly valuable in the case where the intermediate alcohol of the conventional acid-to-alcohol-to-aldehyde protocol would have a chance to be captured by an internal ester as a 5- or 6-membered lactone. At this stage, the Boc group in **23** was deprotected under acidic conditions and the resultant amine was converted to the 2-nitrobenzenesulfonamide **24** with NsCl and Et_3N. Coupling between the sulfonamide **24** and alcohol **11** was performed under the standard Mitsunobu conditions to give **25** in excellent yield. Since the undesired β-elimination of the alkylsulfonamide in **25** occurred under alkaline hydrolysis conditions, conversion of the methyl ester to the carboxylic acid **27** was performed in a two-step sequence via the corresponding allyl ester **26**. The carboxylic acid **27** thus obtained, was condensed with amine **15** in a conventional manner to give the amide **28**. Upon heating a mixture of the sulfonamide **28**, tetrabutylammonium iodide, and Cs_2CO_3 in acetonitrile at 60°C, the cyclization proceeded smoothly to give predominantly the desired product **29** in 86% yield. After removal of the three Ns groups in **29** with excess mercaptoethanol and DBU in acetonitrile, the resultant triamine was selectively diacylated with (*S*)-2-methylbutyric acid and BOPCl[20] to give **9**. All spectroscopic data (^1H and ^{13}C NMR, IR, and MS) of synthetic lipogrammistin-A (**9**) were identical with those of the natural product. The total synthesis of lipogrammistin-A (**9**) starting with carboxylic acid **20** has been achieved in a 13-step sequence in 12% overall yield (Scheme 3).



Scheme 3. Total synthesis of lipogrammistin-A. *Reagents and conditions*: (a) H_2 (1 atm), Pd/C (0.1 equiv.), Boc_2O (1.3 equiv.), MeOH, room temperature, 1 h; Et_3N (1.0 equiv.), room temperature, 30 min. (b) DCC (1.1 equiv.), EtSH (2.0 equiv.), DMAP (0.1 equiv.), CH_3CN, room temperature, 1 h. (c) Et_3SiH (2.2 equiv.), Pd/C (0.1 equiv.), acetone, room temperature, 30 min. (d) $C_8H_{17}CH{=}PPh_3$ (2.2 equiv.), THF, −78°C to room temperature, 30 min. (e) $SOCl_2$ (excess), MeOH, room temperature, 30 min. (f) NsCl (1.0 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2, 0°C, 10 min. (g) **11** (1.5 equiv.), DEAD (2.0 equiv.), PPh_3 (2.0 equiv.), benzene, room temperature, 10 min. (h) $Ti(OiPr)_4$ (1.5 equiv.), allyl alcohol, 95°C, 15 h. (i) $Pd(PPh_3)_4$ (0.05 equiv.), pyrrolidine (1.2 equiv.), CH_2Cl_2, room temperature, 30 min. (j) PivCl (1.2 equiv.), Et_3N (1.1 equiv.), CH_2Cl_2, room temperature, 30 min; **15** (1.2 equiv.), Et_3N (1.1 equiv.), room temperature, 30 min. (k) Cs_2CO_3 (3.0 equiv.), *n*-Bu_4NI (2.0 equiv.), CH_3CN, 60°C, 1 h. (l) $HS(CH_2)_2OH$ (5.0 equiv.), DBU (5.0 equiv.), CH_3CN, room temperature, 2 h. (m) **30** (3.0 equiv.), BOPCl (4.0 equiv.), Et_3N (5.0 equiv.), CH_2Cl_2, room temperature, 15 h.

3. Conclusion

In summary, the Ns-strategy proved to be a powerful protocol for the construction of medium- and large-sized rings. Considering the mildness of the alkylation and the deprotection conditions, the Ns-strategy would be compatible with a variety of functional groups. Furthermore, the fact that both alcohols and halides served as starting materials would allow preparation of a wide range of nitrogen heterocycles. Further applications of this methodology to the total syntheses of complex natural products are currently under investigation in our laboratories.

4. Experimental

4.1. General methods

Unless otherwise noted, solvents and reagents were reagent grade and used without purification. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal standard tetramethylsilane (TMS), which were taken on a JEOL JNM-LA400. Coupling constants are reported in Hertz (Hz). Spectra splitting patterns are designated as s, singlet; br, broad; d, doublet; t, triplet; m, multiplet. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured with a JEOL JMS-GCmate instrument.

4.1.1. *N*-(7-Bromoheptyl)-2-nitrobenzenesulfonamide (3a). To a stirred solution of 2-nitrobenzenesulfonamide (**1**) (3.20 g, 15.8 mmol), **2a** (1.00 g, 5.13 mmol), and Ph_3P (1.80 g, 8.91 mmol) in toluene (9.00 mL) and THF (1.20 mL) was added DEAD (40% in toluene, 4 mL, 8.80 mmol) dropwise at 0°C under argon atmosphere. The solution was stirred at 0°C for 5 min, and room temperature for 2.5 h. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (9:1 hexane/AcOEt) on a silica gel column, to give **3a** (1.36 g, 70%) as a white powder. Mp 69.5–71.0°C. IR (film, cm^{-1}): 3346, 3096, 2933, 2857, 1539, 1440, 1414, 1360, 1341, 1166, 1125, 1060, 853, 782. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.29 (4H, br), 1.33 (2H, br), 1.52 (2H, br), 1.81 (2H, m), 3.10 (2H, q, J=6.8 Hz), 3.37 (2H, t, J=6.8 Hz), 5.23 (1H, br), 7.76 (2H, m), 7.87 (1H, m), 8.14 (1H, m). ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 26.2, 27.8, 28.1, 29.4, 32.5, 33.8, 43.7, 125.3, 131.0, 132.8, 133.5, 133.7, 148.0. FAB-MS: 379 (MH^+). Anal. calcd for $C_{13}H_{20}BrN_2O_4S$: C, 41.17; H, 5.05; N, 7.39. Found: C, 41.24; H, 5.04; N, 7.30.

4.1.2. *N*-(8-Bromooctyl)-2-nitrobenzenesulfonamide (3b). In a manner similar to that used to prepare **3a**, treatment of **2b** (1.05 g, 5.04 mmol) gave **3b** (1.32 g, 67%) as a white powder. Mp 61.5–62.5°C. IR (film, cm^{-1}): 3346, 3099, 2930, 2856, 1592, 1539, 1440, 1414, 1360, 1342, 1165, 1125, 1061. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, m), 1.39 (2H, m), 1.53 (2H, m), 1.83 (2H, m), 3.10 (2H, q, J=6.8 Hz), 3.39 (2H, t, J=6.8 Hz), 5.23 (1H, m), 7.75 (2H, m), 7.87 (1H, m), 8.15 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4, 28.0, 28.6, 28.9, 29.6, 32.7, 34.0, 43.9, 125.4, 131.2, 132.8, 133.6, 133.8, 148.2. FAB-MS: 393 (MH^+); HRMS (FAB): 393.0411 ($C_{14}H_{22}BrN_2O_4S$, MH^+). Exact mass 393.0413 (MH^+).

4.1.3. *N*-(9-Bromononyl)-2-nitrobenzenesulfonamide (3c). In a manner similar to that used to prepare **3a**, treatment of **2c** (1.12 g, 5.02 mmol) gave **3c** (1.52 g, 74%) as a white powder. Mp 72.5–74.0°C. IR (film, cm^{-1}): 3346, 3099, 2930, 2856, 1592, 1539, 1440, 1414, 1360, 1342, 1165, 1125, 1061. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (8H, m), 1.40 (2H, m), 1.54 (2H, m), 1.83 (2H, t, J=4.0 Hz), 3.10 (2H, q, J=3.4 Hz), 3.40 (2H, t, J=3.4 Hz), 5.22 (1H, m), 7.75 (2H, m), 7.87 (1H, m), 8.15 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4, 28.0, 28.5, 28.8, 29.1, 29.5, 32.7, 34.0, 43.8, 125.3, 131.1, 132.7, 133.5, 133.8, 148.1. FAB-MS: 407 (MH^+). Anal. calcd for $C_{15}H_{24}BrN_2O_4S$: C, 44.23; H, 5.69; N, 6.88. Found: C, 44.46; H, 5.71; N, 6.64.

4.1.4. 1-(2-Nitrobenzenesulfonyl)-azocane (4a). To a stirred solution of Cs_2CO_3 (2.10 g, 6.45 mmol) and *n*-Bu_4NI (980 mg, 2.65 mmol) in CH_3CN (3.00 mL) was added **3a** (500 mg, 1.32 mmol) in CH_3CN (24.0 mL) via syringe pump over 2 h at 60°C. The reaction was stirred for 2 h at 60°C after the addition was complete. The reaction mixture was poured into water and extracted with AcOEt (3×50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash chromatography (Et_2O) on a silica gel column, to give **4a** (245 mg, 62%) as a white powder. Mp 94.0–95.0°C. IR (film, cm^{-1}): 2929, 2857, 1542, 1456, 1373, 1344, 1164, 993. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.59 (6H, m), 1.69 (4H, m), 3.25 (4H, t, J=6.0 Hz), 7.52 (1H, m), 7.61 (2H, m), 7.84 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.8, 26.5, 27.7, 49.3, 123.9, 130.4, 131.4, 132.5, 133.3, 148.4. FAB-MS: 299 (MH^+); HRMS (FAB): 299.0981 ($C_{13}H_{19}N_2O_4S$, MH^+). Exact mass 299.0995 (MH^+). Anal. calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39. Found: C, 52.29; H, 5.99; N, 9.35.

4.1.5. 1-(2-Nitrobenzenesulfonyl)-azonane (4b). In a manner similar to that used to prepare **4a**, treatment of **3b** (200 mg, 0.51 mmol) gave **4b** (102 mg, 64%) as a white powder. Mp 133.5–135.0°C. IR (film, cm^{-1}): 2931, 2859, 1725, 1546, 1463, 1373, 1347, 1290, 1161, 1125, 851, 777, 742. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (8H, m), 1.57 (4H, m), 3.25 (4H, t, J=8.0 Hz), 7.61 (1H, m), 7.68 (2H, m), 7.98 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.9, 27.9, 28.1, 47.8, 124.4, 129.0, 130.9, 131.8, 133.6, 148.4. FAB-MS: 313 (MH^+). Anal. calcd for $C_{14}H_{21}N_2O_4S$: C, 53.83; H, 6.45; N, 8.97. Found: C, 53.87; H, 6.29; N, 8.68.

4.1.6. 1-(2-Nitrobenzenesulfonyl)-azecane (4c). In a manner similar to that used to prepare **4a**, treatment of **3c** (200 mg, 0.49 mmol) gave **4c** (105 mg, 66 %) as a white powder. Mp 147.0–148.0°C. IR (film, cm^{-1}): 2928, 2855, 1542, 1463, 1373, 1346, 1160, 851. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (10H, m), 1.57 (4H, m), 3.29 (4H, t, J=8.0 Hz), 7.59 (1H, m), 7.67 (2H, m), 7.97 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.2, 27.9, 28.3, 28.5, 48.7, 124.0, 130.6, 131.4, 133.2, 133.3, 148.3. FAB-MS: 327 (MH^+); HRMS (FAB): 327.1311 ($C_{15}H_{23}N_2O_4S$, MH^+). Exact mass 327.1308 (MH^+). Anal. calcd for $C_{15}H_{22}N_2O_4S$: C, 54.96; H, 6.74; N, 8.30. Found: C, 55.19; H, 6.79; N, 8.58.

4.1.7. *N*-(7-Hydroxyheptyl)-2-nitrobenzenesulfonamide (8a). To a stirred solution of *N*-Boc-2-nitrobenzenesulfonamide (**7**) (1.25 g, 4.14 mmol), K_2CO_3 (2.50 g, 18.1 mmol) and *n*-Bu_4NI (40 mg, 0.11 mmol) in DMF (7.00 mL) was added **2a** (0.77 g, 3.98 mmol). The solution was stirred at 60°C for 10 h, and then poured into water. The reaction mixture was extracted with AcOEt (3×20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude residue was dissolved in CH_2Cl_2 (1.00 mL) and TFA (7.00 mL) stirred for 1 h at room temperature, and then it was concentrated. The residue was dissolved in MeOH (20 mL), and stirred for 10 min with K_2CO_3, then poured into water and extracted with CH_2Cl_2 (3×20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. Purification was performed by recrystallization with ether and hexane, to give **8a** (1.00 g, 60%) as a white powder. Mp 57.5–59.5°C. IR (film, cm^{-1}): 3343, 2933, 2859, 1543, 1413, 1364, 1339, 1165, 1126, 1059, 853, 783, 741. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (4H, m), 1.50 (2H, m), 1.53 (4H, m), 3.09 (2H), 3.63 (2H), 5.25 (1H, m), 7.75 (2H, m), 7.87 (1H, m), 8.14 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.4, 28.8, 29.5, 32.5, 43.8, 62.9, 125.4, 131.1, 132.8, 133.5, 133.8, 149.8. FAB-MS: 317 (MH^+); HRMS (FAB): 317.1180 ($C_{13}H_{21}O_2N_5S$, MH^+). Exact mass 317.1177 (MH^+).

4.1.8. *N*-(8-Hydroxyoctyl)-2-nitrobenzenesulfonamide (8b). In a manner similar to that used to prepare **8a**, treatment of **2b** (2.00 g, 9.60 mmol) gave **8b** (2.69 g, 85%) as a white powder. Mp 71.5–73.0°C. IR (film, cm^{-1}): 3289, 2931, 2856, 1540, 1418, 1362, 1338, 1163, 1126, 1058. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27 (6H, m), 1.52 (6H, m), 3.09 (2H, m), 3.62 (2H, m), 5.28 (1H, m), 7.71 (2H, m), 7.87 (1H, m), 8.14 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.3, 28.9, 29.1, 29.5, 32.6, 43.8, 62.9, 125.3, 131.1, 132.7, 133.5, 133.8, 148.1. FAB-MS: 331 (MH^+); HRMS (FAB): 331.1327 ($C_{14}H_{23}O_2N_5S$, MH^+). Exact mass 331.1329 (MH^+).

4.1.9. *N*-(9-Hydroxynonyl)-2-nitrobenzenesulfonamide (8c). In a manner similar to that used to prepare **8a**, treatment of **2c** (860 mg, 4.41 mmol) gave **8c** (812 mg, 54%) as a white powder. Mp 68.5–70.0°C. IR (film, cm^{-1}): 3287, 2926, 2853, 1541, 1360, 1333, 1163, 1126, 1062, 854,

780, 728. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (8H, m), 1.53 (6H, m), 3.09 (2H, q, J=6.8 Hz), 3.63 (2H, t, J=6.8 Hz), 5.27 (1H, m), 7.74 (2H, m), 7.87 (1H, m), 8.14 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 26.4, 28.9, 29.2, 29.3, 29.5, 32.7, 43.8, 63.0, 125.3, 131.1, 132.7, 133.5, 133.8, 148.0. FAB-MS: 345 (MH^+); HRMS (FAB): 345.1407 ($C_{15}H_{25}O_2N_5S$, MH^+). Exact mass 345.1414 (MH^+).

4.1.10. 1-(2-Nitrobenzenesulfonyl)-azocane (4a). *Mitsunobu conditions*. To a stirred solution of Ph_3P (463 mg, 2.29 mmol) and **8a** (200 mg, 0.63 mmol) in toluene (48.0 mL) and THF (16.0 mL) was added DEAD (40% in toluene, 1.05 mL, 2.31 mmol) dropwise, and the mixture was stirred for 3 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (1:4 AcOEt/hexane) on a silica gel column to give **4a** (112 mg, 59%) as white powder. All spectra data were identical with **4a** described above.

4.1.11. 1-(2-Nitrobenzenesulfonyl)-azonane (4b). *Mitsunobu conditions*. In a manner similar to that used to prepare **4a** using Mitsunobu conditions, treatment of **8b** (150 mg, 0.45 mmol) gave **4b** (80 mg, 57%) as a white powder. All spectra data were identical with **4b** described above.

4.1.12. 1-(2-Nitrobenzenesulfonyl)-azecane (4c). *Mitsunobu conditions*. In a manner similar to that used to prepare **4a** using Mitsunobu conditions, treatment of **8c** (300 mg, 0.87 mmol) gave **4c** (200 mg, 62%) as a white powder. All spectra data were identical with **4c** described above.

4.1.13. 3-(2-Nitrobenzenesulfonylamino)-butyric acid allyl ester (10). To a solution of 3-amino-butyric acid (4.12 g, 40.0 mmol) in allyl alcohol (15 mL) was slowly added thionyl chloride (8.26 mL, 120 mmol) at 0°C. After stirring at room temperature 15 h, the solvent was evaporated. The residue was diluted with dichloromethane, the organic layer was washed sequentially with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent gave the allyl ester (2.45 g, 43%). To a solution of the allyl ester (2.45 g, 17.1 mmol) in dichloromethane (50 mL) were added 2-nitrobenzenesulfonyl chloride (2.65 g, 12.0 mmol) and triethylamine (3.57 mL, 25.6 mmol) at 0°C. After stirring at room temperature for 30 min, 3N hydrochloric acid was added to the mixture. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (1:4 AcOEt/hexane) to give **10** (3.43 g, 87%) as a yellow solid. IR (film, cm^{-1}) 3334, 3096, 2982, 1735, 1593, 1541, 1442, 1420, 1363, 1295, 1169, 1125, 1088, 989, 854, 784, 742, 731. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (3H, d, J=5.6 Hz), 2.57 (2H, m), 3.56 (1H, m), 4.53 (2H, d, J=5.6 Hz), 5.27 (2H, m), 5.82–5.92 (2H, m), 7.72–7.78 (2H, m), 7.85 (1H, m), 8.17 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.0, 41.0, 47.6, 65.5, 118.9, 125.4, 130.7, 131.6, 132.9, 133.5, 134.7, 170.3.

4.1.14. *N*-(5-Bromopentyl)-*N*-(3-hydroxypropyl)-2-nitrobenzenesulfonamide (11). To a solution of 3-(2-nitrobenzenesulfonylamino)propan-1-ol[8] (2.72 g, 10.5 mmol) and dibromopentane (7.13 mL, 52.3 mmol) in acetonitrile (50 mL) were added cesium carbonate (10.3 g, 31.5 mmol) at room temperature. After stirring at 60°C for 2 h, 3N hydrochloric acid was added to the reaction mixture. The mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over $MgSO_4$. After the solvent was concentrated in vacuo, the residue was purified by column chromatography on silica gel (2:3 AcOEt/hexane) to give **11** (3.64 g, 85%) as a yellow oil. IR (film, cm^{-1}) 3560, 3417, 3094, 2941, 2880, 1543, 1465, 1438, 1374, 1344, 1159, 1125, 1059, 913, 852, 779, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39 (2H, tt, J=8.0, 8.0 Hz), 1.58 (2H, tt, J=8.0, 8.0 Hz), 1.76–1.88 (4H, m), 3.31 (2H, t, J=7.8 Hz), 3.35 (2H, t, J=6.4 Hz), 3.46 (2H, t, J=6.8 Hz), 3.71 (2H, tt, J=6.0, 6.0 Hz), 7.64 (1H, m), 7.67–7.73 (2H, m), 8.23 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 27.4, 30.8, 32.0, 33.4, 44.3, 47.4, 59.0, 124.2, 130.5, 131.7, 133.2, 133.6, 147.9.

4.1.15. 3-[{3-[(5-Bromopentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-butyric acid allyl ester (13). To a solution of **10** (533 mg, 1.62 mmol), **11** (664 mg, 1.62 mmol) and PPh_3 (468 mg, 1.79 mmol) in benzene (8.0 mL) was slowly added DEAD (40% in toluene, 0.81 mL, 1.79 mmol) at room temperature. After stirring for 10 min, the mixture was purified by flash column chromatography on silica gel (3:7 AcOEt/hexane) to give **13** (785 mg, 71%). IR (film, cm^{-1}) 3093, 2940, 1736, 1544, 1466, 1439, 1373, 1347, 1296, 1161, 1124, 1059, 968, 852, 778, 743. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, d, J=6.8 Hz), 1.40 (2H, tt, J=8.0, 8.0 Hz), 1.60 (2H, m), 1.85 (2H, tt, J=6.8, 6.8 Hz), 1.96 (2H, m), 2.46 (1H, dd, J=8.8, 15.6 Hz), 2.59 (1H, dd, J=6.0, 15.6 Hz), 3.25 (2H, t, J=8.4 Hz), 3.31–3.52 (6H, m), 4.52 (2H, d, J=6.0 Hz), 5.23–5.32 (2H, m), 5.83–5.92 (1H, m), 7.59–7.64 (2H, m), 7.69–7.71 (4H, m), 8.02–8.08 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.2, 25.1, 27.1, 30.0, 32.1, 33.5, 40.6, 41.6, 44.9, 47.2, 51.2, 65.6, 118.8, 124.1, 124.2, 130.8, 131.4, 131.8, 131.9, 132.9, 133.2, 133.6, 133.8, 147.9, 148.0, 169.9.

4.1.16. 3-[{3-[(5-Bromopentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-butyric acid. To a solution of **13** (1.19 g 1.62 mmol) in dichloromethane (15 mL) were added $Pd(PPh_3)_4$ (93.8 mg, 0.081 mmol) and pyrrolidine (0.135 mL, 1.94 mmol) at room temperature. After stirring for 30 min, 1N hydrochloric acid was added to the mixture. The phases were separated and the organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (3:2 AcOEt/hexane) to give the carboxylic acid (784 mg) as a yellow powder. IR (film, cm^{-1}) 3095, 2941, 1712, 1544, 1466, 1439, 1373, 1346, 1297, 1219, 1161, 1124, 1059, 969, 852, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (3H, d, J=6.8 Hz), 1.41 (2H, tt, J=7.5, 7.5 Hz), 1.57 (2H, tt, J=7.8, 7.8 Hz), 1.84 (2H, tt, J=7.8, 7.8 Hz), 1.94–1.99 (2H, m), 2.48 (1H, dd, J=8.1, 16.1 Hz), 2.62 (1H, dd, J=6.1, 15.4 Hz), 3.25 (2H, t, J=7.8 Hz), 3.32–3.38 (6H, m), 4.34 (1H, m), 7.62–7.64 (2H, m), 7.69–7.73 (4H, m), 8.02–8.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.3, 25.0, 27.1, 29.8, 32.0, 33.6, 40.3, 41.5, 44.8, 47.2, 51.0,

124.2, 130.5, 131.10, 131.9, 132.0, 132.1, 132.5, 132.9, 133.8, 134.0, 147.9, 147.9, 175.9.

4.1.17. 3-[{3-[(5-Bromopentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-*N*-[3-(2-nitrobenzenesulfonylamino)-propyl]-butyramide (16). To a solution of the carboxylic acid (784 mg, 1.15 mmol) in dichloromethane (12 mL) were added **15**[8] (314 mg, 1.21 mmol) and EDCI (265 mg, 1.38 mmol) at room temperature. After stirring for 30 min, 1N hydrochloric acid was added to the mixture. The phases were separated and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (4:1 AcOEt/hexane) to give **16** (760 mg, 51% from **13**) as a yellow powder. IR (film, cm^{-1}) 3403, 3095, 2941, 2874, 1661, 1591, 1543, 1440, 1372, 1343, 1266, 1163, 1124, 1060, 969, 852, 780, 740. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, d, $J=6.8$ Hz), 1.38 (2H, tt, $J=7.5$, 7.5 Hz), 1.68 (2H, tt, $J=6.0$, 6.0 Hz), 1.83 (2H, tt, $J=7.1$, 7.1 Hz), 1.90–2.01 (2H, m), 2.37 (1H, dd, $J=7.1$, 14.9 Hz), 2.54 (1H, dd, $J=7.1$, 14.9 Hz), 3.14 (2H, m), 3.25–3.39 (10H, m), 4.33 (1H, m), 6.02 (1H, t, $J=6.4$ Hz), 6.18 (1H, t, $J=6.2$ Hz), 7.60–7.65 (2H, m), 7.70–7.76 (6H, m), 7.83 (1H, dd, $J=1.7$, 8.6 Hz), 8.01 (1H, dd, $J=3.2$, 6.0 Hz), 8.09–8.15 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.1, 25.1, 27.1, 29.7, 32.0, 33.6, 36.1, 40.7, 41.7, 42.4, 45.3, 47.6, 51.7, 124.0, 124.1, 125.2, 128.4, 128.6, 130.4, 130.7, 131.2, 132.0, 132.7, 132.8, 132.8, 133.5, 133.8, 133.9, 147.9, 147.9, 147.9, 170.2. FAB-MS: 920 (MH^+); HRMS (FAB): 920.1249 ($C_{33}H_{43}BrN_7O_{13}S_3$, MH^+). Exact mass 920.1264 (MH^+).

4.1.18. 8-Methyl-1,9,13-tris-(2-nitrobenzenesulfonyl)-1,5,9,13-tetraazacyclooctadecan-6-one (19). *Alkylation conditions*. To a solution of **16** (27.9 mg, 0.03 mmol) in acetonitrile (0.76 mL) were added cesium carbonate (29.6 mg, 0.09 mmol) and *n*-Bu_4NI (22.4 mg, 0.06 mmol) at room temperature. After stirring at 60°C for 2 h, 1N hydrochloric acid was added to the mixture. The mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (AcOEt) to give **19** (20.1 mg, 79%) as a yellow powder. Mp 88.0–90.0°C. IR (film, cm^{-1}) 3409, 3092, 2940, 2874, 1670, 1590, 1543, 1466, 1439, 1374, 1345, 1267, 1162, 1125, 1060, 1032, 961, 852, 778, 737. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15 (3H, d, $J=6.6$ Hz), 1.37 (2H, tt, $J=7.3$, 7.3 Hz), 1.59–1.68 (4H, m), 1.82 (2H, m), 1.97–2.05 (2H, m), 2.44 (1H, dd, $J=4.3$, 16.1 Hz), 2.60 (1H, dd, $J=11.0$, 16.1 Hz), 3.20–3.43 (12H, m), 4.42 (1H, m), 6.30 (1H, t, $J=5.8$ Hz), 7.56–7.77 (9H, m), 7.90–7.96 (2H, m), 8.07–8.10 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7, 23.2, 27.5, 29.5, 28.4, 30.7, 37.3, 42.5, 42.8, 46.2, 46.4, 48.7, 49.1, 52.3, 123.9, 124.2, 130.1, 130.4, 131.0, 131.8, 131.9, 132.0, 132.4, 132.8, 133.1, 133.4, 133.8, 134.0, 148.1, 148.2, 148.3, 169.4. FAB-MS: 840 (MH^+); HRMS (FAB): 840.1970 ($C_{33}H_{42}N_7O_{13}S_3$, MH^+). Exact mass 840.2002 (MH^+).

4.1.19. *N*-[5-(*tert*-Butyl-dimethylsilanyloxy)-pentyl]-*N*-(3-hydroxypropyl)-2-nitrobenzenesulfonamide (12). To a solution of 3-(2-nitrobenzenesulfonylamino)propan-1-ol[8] (350 mg, 1.34 mmol) and 5-*tert*-butyldimethylsilyloxypent-1-yl-bromide (420 mg, 1.49 mmol) in acetonitrile (7 mL) was added cesium carbonate (1.46 g, 4.48 mmol) at room temperature. After stirring at 60°C for 15 h, 1N hydrochloric acid was added to the mixture. The combined mixture extracted with dichloromethane. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (3:7 AcOEt/hexane) to give **12** (521 mg, 95%) as a yellow oil. IR (film, cm^{-1}) 3557, 3430, 2932, 2858, 1546, 1471, 1373, 1347, 1256, 1161, 1098, 851, 836, 777, 748. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.29 (2H, m), 1.43–1.60 (4H, m), 1.79 (2H, tt, $J=6.1$, 6.1 Hz), 1.91 (1H, t, $J=6.0$ Hz), 3.29 (2H, t, $J=7.8$ Hz), 3.46 (2H, t, $J=6.8$ Hz), 3.55 (2H, t, $J=6.4$ Hz), 3.71 (2H, dt, $J=6.0$, 6.0 Hz), 7.61–7.69 (3H, m), 8.01 (1H, dd, $J=1.8$, 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.3, 22.9, 25.9, 28.0, 30.9, 32.3, 44.3, 47.8, 59.0, 62.8, 124.2, 130.6, 131.6, 133.4.

4.1.20. 3-[{3-[[5-(*tert*-Butyldimethylsilanyloxy)-pentyl]-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-butyric acid allyl ester (14). To a solution of **10** (262 mg, 0.799 mmol), **12** (327 mg, 0.799 mmol), and PPh_3 (252 mg, 0.959 mmol) in toluene (4.0 mL) were added DEAD in toluene (40%, 0.43 mL, 0.959 mmol) at room temperature. After stirring for 10 min, the mixture was concentrated and the residue was purified by flash column chromatography on silica gel (3:7 AcOEt/hexane) to give **14** (302 mg, 49%). IR (film, cm^{-1}) 3095, 2934, 2857, 1735, 1546, 1472, 1438, 1374, 1349, 1295, 1256, 1162, 1124, 1059, 966, 852, 836, 777, 743. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 1.20 (3H, d, $J=6.8$ Hz), 1.28 (2H, m), 1.44–1.52 (4H, m), 1.94 (2H, m), 2.45 (1H, dd, $J=8.3$, 15.5 Hz), 2.58 (1H, dd, $J=5.8$, 15.3 Hz), 3.22–3.36 (6H, m), 3.58 (2H, t, $J=6.4$ Hz), 4.33 (1H, m), 4.51 (2H, d, $J=5.6$ Hz), 5.23–5.32 (2H, m), 5.83–5.92 (1H, m), 7.59–7.62 (2H, m), 7.67–7.71 (4H, m), 8.01–8.07 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.3, 18.4, 19.3, 22.9, 25.9, 27.8, 30.0, 32.3, 40.6, 41.6, 44.8, 47.4, 51.2, 62.9, 65.6, 118.8, 124.1, 124.2, 130.8, 131.4, 131.8, 131.8, 133.0, 133.4, 133.5, 133.7, 148.1, 148.1, 169.9.

4.1.21. 3-[{3-[[5-(*tert*-Butyldimethylsilanyloxy)-pentyl]-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-butyric acid. To a solution of **14** (174 mg 0.226 mmol) in dichloromethane (2.0 mL) were added $Pd(PPh_3)_4$ (13.1 mg, 0.0113 mmol) and pyrrolidine (22.6 mL, 0.271 mmol) at room temperature. After stirring for 30 min, 1N hydrochloric acid was added to the mixture. The phases were separated and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue that was purified by column chromatography on silica gel (4:1 AcOEt/hexane) to give the carboxylic acid (143 mg, 86%) as a yellow powder.

4.1.22. 3-[{3-[[5-(*tert*-Butyldimethylsilanyloxy)-pentyl]-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-*N*-[3-(2-nitrobenzenesulfonylamino)-propyl]-butyramide (17). To a solution of the carboxylic acid (134 mg, 0.183 mmol) in acetonitrile (2.0 mL) were added DCC (45.3 mg, 0.220 mmol) and **15**[8]

(56.9 mg, 0.220 mmol) at room temperature. After stirring for 20 min, the mixture was filtered through a Celite pad and concentrated. The residue was purified by column chromatography on silica gel (4:1 AcOEt/hexane) to give **17** (132 mg, 74%) as a yellow powder. IR (film, cm^{-1}) 3402, 3096, 293, 2858, 1659, 1591, 1544, 1471, 1440, 1372, 1344, 1256, 1164, 1124, 1095, 1060, 966, 852, 836, 778, 741. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.87 (9H, s), 1.17 (3H, d, $J=6.8$ Hz), 1.24–1.29 (2H, m), 1.45–1.53 (4H, m), 1.65 (2H, tt, $J=6.2$, 6.2 Hz), 1.86–2.03 (2H, m), 2.38 (1H, dd, $J=7.6$, 14.0 Hz), 2.55 (1H, dd, $J=7.1$, 14.0 Hz), 3.14 (2H, dt, $J=6.8$, 6.8 Hz), 3.28–3.32 (8H, m), 3.55 (2H, t, $J=6.3$ Hz), 6.00 (1H, m), 4.33 (1H, m), 6.15 (1H, t, $J=6.0$ Hz, NH), 7.59–7.64 (2H, m), 7.70–7.76 (6H, m), 7.83 (1H, dd, $J=1.7$, 5.9 Hz), 7.98–8.01 (1H, m), 8.09–8.15 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.4, 18.3, 19.1, 22.8, 25.9, 27.8, 29.7, 30.1, 32.2, 36.0, 40.7, 41.6, 42.4, 45.2, 47.9, 51.7, 62.8, 124.0, 124.1, 125.1, 130.4, 130.7, 131.3, 131.9, 131.9, 132.8, 132.8, 132.9, 133.4, 133.7, 133.8, 133.9, 147.9, 147.9, 147.9, 176.2.

4.1.23. 3-[{3-[(5-Hydroxypentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-*N*-[3-(2-nitrobenzenesulfonylamino)-propyl]-butyramide (18). To a solution of **17** (56.1 mg, 0.058 mmol) in acetonitrile (0.5 mL) was added 48% hydrofluoric acid (100 μL) at 0°C. After stirring for 2 min, the reaction was quenched with saturated $NaHCO_3$ and the mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel (4:1 AcOEt/hexane) to give **18** (50 mg, 30% from **14**) as a yellow powder. IR (film, cm^{-1}) 3567, 3402, 3096, 2939, 2874, 1653, 1591, 1543, 1440, 1373, 1341, 1267, 1163, 1124, 1060, 959, 852, 780, 740. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.15 (3H, d, $J=6.8$ Hz), 1.35–1.39 (2H, m), 1.52–1.62 (4H, m), 1.68 (2H, tt, $J=6.1$, 6.1 Hz), 1.85–2.10 (2H, m), 2.37 (1H, dd, $J=7.0$, 14.3 Hz), 2.56 (1H, dd, $J=7.3$, 14.6 Hz), 3.14 (2H, dt, $J=6.3$, 6.3 Hz), 3.25–3.38 (8H, m), 3.62 (2H, t, $J=6.2$ Hz), 4.33 (1H, m), 6.00 (1H, d, $J=6.2$ Hz), 6.30 (1H, t, $J=6.2$ Hz), 7.60–7.64 (2H, m), 7.68–7.76 (6H, m), 7.83 (1H, dd, $J=2.4$, 7.4 Hz), 7.98–8.00 (1H, m), 8.08–8.15 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0, 22.8, 27.8, 29.7, 30.3, 31.9, 36.1, 40.8, 41.8, 42.6, 45.6, 48.2, 51.7, 62.3, 124.0, 124.1, 125.2, 130.5, 130.8, 131.3, 131.9, 132.0, 132.8, 132.8, 133.5, 133.7, 133.9, 133.9, 140.1, 147.9, 148.1, 170.3. FAB-MS: 858 (MH^+); HRMS (FAB): 858.2099 ($C_{33}H_{44}O_{14}N_7S_3$, MH^+). Exact mass 858.2108 (MH^+).

4.1.24. 8-Methyl-1,9,13-tris-(2-nitrobenzenesulfonyl)-1,5,9,13-tetraazacyclooctadecan-6-one (19). *Mitsunobu conditions*. To a solution of **18** (13.8 mg, 0.0161 mmol) and PPh_3 (5.1 mg, 0.0193 mmol) in dichloromethane (0.22 mL) and benzene (0.1 mL) was added DEAD (40% in toluene, 8.0 μL, 0.959 mmol) at room temperature. After stirring for 10 min, the mixture was purified by preparative TLC (AcOEt) to give **19** (9.4 mg, 69%). All spectra data were identical with **19** described above.

4.1.25. (3*R*)-3-*tert*-Butoxycarbonylamino-4-methoxycarbonyl-butyric acid. To a solution of **20**[16] (8.1 g, 27.4 mmol) and Boc_2O (7.7 g, 35.3 mmol) in methanol (100 mL) was added 10% Pd on C (2.9 g, 3.07 mmol). After stirring under hydrogen atmosphere at room temperature for 1 h, to the reaction mixture was added triethylamine (3.8 mL, 27.3 mmol). After stirred for 10 min, the catalyst was filtered through a Celite pad. The filtrate was evaporated to give residue, which was purified by column chromatography on silica gel (2:3 AcOEt/hexane) to give the carboxylic acid as a colorless oil (7.7 g). $[\alpha]_D^{24}=-1.36°$ ($c=0.746$, $CHCl_3$); IR (film, cm^{-1}) 3352, 2980, 1737, 1717, 1515, 1439, 1394, 1368, 1250, 1165, 1054, 1028, 850, 778. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.57–2.75 (4H, m), 3.69 (3H, s), 4.31 (1H, m), 5.40 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 37.9, 44.1, 51.8, 51.8, 79.8, 155.1, 171.6, 175.7.

4.1.26. (3*R*)-3-*tert*-Butoxycarbonylamino-4-ethylsulfanylcarbonyl-butyric acid methyl ester (21). To a solution of the carboxylic acid (7.7 g) in acetonitrile (100 mL) were added DCC (6.7 g, 2.95 mmol), ethanethiol (4.4 mL, 59 mmol), and DMAP (360 mg, 0.295 mmol) at 0°C. After stirring at room temperature for 1 h, the mixture was filtrated through a Celite pad. The filtrate was evaporated to give residue, which was purified by column chromatography on silica gel (1:9 AcOEt/hexane) to give **21** (5.9 g, 70%, 2 steps) as a colorless solid. $[\alpha]_D^{27}=+1.56°$ ($c=0.810$, $CHCl_3$); IR (film, cm^{-1}) 3371, 2976, 2932, 1737, 1717, 1697, 1502, 1367, 1250, 1168, 1049, 1024, 874, 851, 780, 752. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (3H, t, $J=7.8$ Hz), 1.43 (9H, s), 2.59–2.66 (2H, m), 2.81–2.96 (4H, m), 3.70 (3H, s), 4.30 (1H, m), 5.30 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 23.5, 28.4, 37.8, 45.0, 47.1, 79.6, 155.1, 171.6, 197.5.

4.1.27. (3*S*,5*Z*)-3-(*tert*-Butoxycarbonylamino)-tetradec-5-enoic acid methyl ester (23). To a solution of **21** (5.9 g, 19.3 mmol) and 10% Pd on C (2.05 g, 1.93 mmol) in acetone (120 mL) was added triethylsilane (6.8 mL, 42.4 mmol) at room temperature. After stirring at room temperature for 30 min, the catalyst was filtered off through a Celite pad. The filtrate was concentrated to give **22**, which was used in the next reaction without further purification. To a solution of (1-nonyl)triphenylphosphonium iodide (22.9 g, 44.4 mmol) in dry tetrahydrofuran (200 mL) was added 1 M LHMDS in tetrahydrofuran (42.5 mL, 42.5 mmol). After stirring at 0°C for 10 min and at room temperature for 15 min, to this solution was added **22** (19.3 mmol) in dry tetrahydrofuran (15 mL) at −78°C. This mixture was stirred at room temperature for 30 min and the reaction was quenched with aqueous ammonium chloride. The phases were separated and organic layer was washed sequentially with saturated $NaHCO_3$, saturated $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (1:4 Et_2O/hexane) to give **23** as a colorless solid (5.08 g, 74%, 2 steps). $[\alpha]_D^{27}=+11.1°$ ($c=0.43$, $CHCl_3$). IR (film, cm^{-1}) 3371, 2955, 2926, 2855, 1741, 1717, 1501, 1437, 1391, 1366, 1247, 1171, 1048, 1024, 856, 777, 721. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.9$ Hz), 1.26–1.30 (12H, m), 1.43 (9H, s), 1.99 (2H, dt, $J=7.1$, 7.1 Hz), 2.31 (2H, m), 2.52 (2H, d, $J=6.0$ Hz), 3.68 (3H, s), 3.95 (1H, m), 4.94 (1H, m), 5.32 (1H, m), 5.50 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 22.7, 27.5, 28.5, 29.4, 29.5, 29.5, 29.7, 32.0, 38.0,

51.7, 79.9, 128.5, 133.6, 155.2, 171.2. FAB-MS: 356 (MH^+); HRMS (FAB): 356.2770 ($C_{20}H_{38}NO_4$, MH^+). Exact mass 356.2801 (MH^+).

4.1.28. (3*S*,5*Z*)-3-(2-Nitrobenzenesulfonylamino)-tetradec-5-enoic acid methyl ester (24). To a stirred solution of **23** (5.08 g 14.3 mmol) in methanol (50 mL) was added thionyl chloride (20 mL, 278 mmol) in methanol (50 mL) at 0°C and stirred at room temperature for 30 min. After evaporating the solvent, the residue was sequentially diluted with dichloromethane. The organic layer washed sequentially with saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. Evaporation of the solvent gave the primary amine, which was used in the next reaction without purification. To a solution of the primary amine in dichloromethane (50 mL) were added 2-nitrobenzenesulfonyl chloride (3.17 g, 14.3 mmol) and triethylamine (3.98 mL, 28.6 mmol) at room temperature. After stirring for 10 min, 1N hydrochloric acid was added to the mixture. The phases were separated and organic layer was washed brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (3:2 AcOEt/hexane) to give **24** (3.5 g, 56%, 2 steps) as a yellow oil. $[\alpha]_D^{27}=+44.8°$ ($c=1.175$, $CHCl_3$); IR (film, cm^{-1}) 3341, 3097, 2954, 2926, 2855, 1738, 1594, 1543, 1440, 1418, 1361, 1302, 1168, 1125, 1062, 972, 854, 783, 742, 731. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=7.0$ Hz), 1.24–1.29 (12H, m), 1.90 (2H, dt, $J=7.1$, 7.0 Hz), 2.31 (2H, dt, $J=7.6$, 7.6 Hz), 2.53 (1H, dd, $J=5.9$, 8.1 Hz), 2.61 (1H, dd, $J=5.4$, 8.2 Hz), 3.61 (3H, s), 3.84 (1H, m), 5.13 (1H, dt, $J=7.6$, 10.8 Hz), 5.62 (1H, dt, $J=7.5$, 10.1 Hz), 5.86 (1H, d, $J=8.0$ Hz), 7.70–7.78 (2H, m), 7.88 (1H, m), 8.16 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 27.2, 29.0, 29.1, 29.3, 29.3, 31.7, 32.4, 38.4, 51.6, 51.7, 123.0, 125.2, 128.5, 130.5, 132.8, 133.4, 134.4, 134.7, 147.6, 171.2. FAB-MS: 441 (MH^+); HRMS (FAB): 441.2030 ($C_{21}H_{33}N_2O_6S_3$, MH^+). Exact mass 441.2059 (MH^+).

4.1.29. (3*S*,5*Z*)-3-[{3-[(5-Bromopentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-tetradec-5-enoic acid methyl ester (25). To a solution of **24** (169 mg, 0.385 mmol), **11** (238 mg, 0.578 mmol), and PPh_3 (202 mg, 0.770 mmol) in benzene (2.5 mL) was added DEAD (40% in toluene, 0.35 mL, 0.770 mmol) at room temperature. After stirring for 10 min, the mixture was concentrated and the residue was purified by flash column chromatography on silica gel (1:3 AcOEt/hexane) to give **25** (329 mg, including 10% of impurities from the reagent). Analytical sample was purified preparative TLC (1:1 AcOEt/hexane) to give **25**. $[\alpha]_D^{27}=+3.74°$ ($c=0.587$, $CHCl_3$); IR (film, cm^{-1}) 3092, 2927, 2855, 1738, 1545, 1466, 1438, 1373, 1350, 1263, 1216, 1162, 1125, 1059, 962, 852, 777, 743. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.9$ Hz), 1.26–1.32 (12H, m), 1.42 (2H, dt, $J=7.8$, 7.8 Hz), 1.59 (2H, tt, $J=8.0$, 8.0 Hz), 1.85 (2H, tt, $J=6.8$, 6.8 Hz), 1.95–2.05 (4H, m), 2.20 (1H, m), 2.37 (1H, m), 2.52 (2H, d, $J=7.3$ Hz), 3.25 (2H, t, $J=7.8$ Hz), 3.29–3.39 (6H, m), 3.60 (3H, s), 4.18 (1H, m), 5.13 (1H, m), 5.33 (1H, m), 7.58–7.63 (2H, m), 7.66–7.72 (4H, m), 8.03–8.08 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 25.1, 27.1, 27.4, 29.3, 29.3, 29.4, 29.5, 29.9, 31.4, 31.8, 32.1, 33.4, 38.6, 42.0, 44.9, 47.2, 51.9, 55.9, 123.7, 124.0, 124.2, 130.8, 131.6, 131.8, 132.9, 133.2, 133.5, 133.6, 133.7, 148.0, 170.9. FAB-MS: 831 (MH^+); HRMS (FAB): 831.2297 ($C_{35}H_{51}BrN_4O_{10}S_2$, MH^+). Exact mass 831.2308 (MH^+).

4.1.30. (3*S*,5*Z*)-3-[{3-[(5-Bromopentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-tetradec-5-enoic acid allyl ester (26). To a solution of **25** (329 mg, 0.395 mmol) in allyl alcohol (5.0 mL) was added $Ti(OiPr)_4$ (0.175 g, 0.593 mmol) at room temperature. After stirring at 95°C for 15 h, to the mixture was added 1N hydrochloric acid and extracted with dichloromathane. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (1:3 AcOEt/hexane) to give **26** (312 mg) as a colorless oil. $[\alpha]_D^{28}=+6.13°$ ($c=0.53$, $CHCl_3$); IR (film, cm^{-1}) 3092, 2926, 2855, 1736, 1546, 1466, 1439, 1372, 1350, 1264, 1161, 1125, 1059, 987, 852, 777, 743. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.8$ Hz), 1.25–1.32 (12H, m), 1.40 (2H, tt, $J=7.6$, 7.6 Hz), 1.57 (2H, tt, $J=8.0$, 8.0 Hz), 1.84 (2H, tt, $J=6.8$, 6.8 Hz), 1.93–2.00 (4H, m), 2.20 (1H, m), 2.37 (1H, m), 2.54 (2H, d, $J=6.8$ Hz), 3.23–3.80 (8H, m), 4.19 (1H, m), 4.50 (2H, d, $J=4.9$ Hz), 5.09 (1H, m), 5.23–5.35 (3H, m), 7.58–7.63 (2H, m), 7.67–7.71 (4H, m), 8.03–8.07 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 25.1, 27.4, 29.1, 29.2, 29.2, 29.3, 29.4, 29.5, 29.9, 31.8, 32.0, 33.4, 38.8, 42.0, 44.9, 47.1, 55.8, 65.5, 118.7, 123.7, 123.9, 123.9, 124.1, 130.7, 131.6, 131.6, 131.8, 132.9, 133.2, 133.6, 133.7, 147.9, 170.2. FAB-MS: 857 (MH^+); HRMS (FAB): 857.2460 ($C_{37}H_{54}BrN_4O_{10}S_2$, MH^+). Exact mass 857.2464 (MH^+).

4.1.31. (3*S*,5*Z*)-3-[{3-[(5-Bromopentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-tetradec-5-enoic acid (27). To a solution of **26** (312 mg, 0.364 mmol) in dichloromethane (4.0 mL) were added $Pd(PPh_3)_4$ (21.1 mg, 0.0182 mmol) and pyrrolidine (36.5 μL, 0.437 mmol) at room temperature. After stirring for 30 min, 1N hydrochloric acid was added to the mixture. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (3:2 AcOEt/hexane) to give **27** (0.277 g, 88%, 3 steps from **24**) as a yellow powder. $[\alpha]_D^{28}=+8.80°$ ($c=0.41$, $CHCl_3$); IR (film, cm^{-1}) 3095, 2927, 2855, 1711, 1591, 1545, 1466, 1438, 1373, 1349, 1161, 1125, 1059, 962, 852, 777, 742. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.8$ Hz), 1.24–1.28 (12H, m), 1.42 (2H, tt, $J=7.7$, 7.7 Hz), 1.84 (2H, tt, $J=7.6$, 7.6 Hz), 1.97–2.00 (4H, m), 2.27 (1H, m), 2.40 (1H, m), 2.58 (2H, d, $J=6.8$ Hz), 3.27–3.39 (8H, m), 4.13 (1H, m), 5.15 (1H, m), 5.35 (1H, m), 7.59–7.63 (2H, m), 7.68–7.72 (4H, m), 8.02–8.07 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 25.1, 27.1, 27.5, 29.1, 29.2, 29.2, 29.3, 29.4, 29.5, 31.8, 32.0, 33.5, 38.1, 42.0, 44.9, 47.1, 55.5, 123.6, 124.2, 130.7, 131.4, 131.7, 131.8, 132.6, 133.1, 133.7, 133.9, 134.0, 135.4, 147.9, 147.9, 176.4.

4.1.32. (3*S*,5*Z*)-3-[{3-[(5-Bromopentyl)-(2-nitrobenzenesulfonyl)-amino]-propyl}-(2-nitrobenzenesulfonyl)-amino]-tetradec-5-enoic acid [3-(2-nitrobenzenesulfonylamino)-propyl]-amide (28). To a solution of **27** (266 mg, 0.325 mmol) in dichloromethane (4.0 mL) were added

pivaloyl chloride (40 μL, 0.390 mmol) and triethylamine (45.3 μL, 0.358 mmol) at 0°C. After stirring for 30 min, **13** (101 mg, 0.390 mmol) and triethylamine (49.8 μL, 0.358 mmol) were added. After stirring for 30 min, 1N hydrochloric acid was added to the mixture. The phases were separated and organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (3:7 AcOEt/hexane) to give **28** as a yellow powder (309 mg, 90%). $[\alpha]_D^{25}=+6.93°$ ($c=0.407$, $CHCl_3$); IR (film, cm^{-1}) 3402, 3095, 2927, 2855, 1661, 1591, 1544, 1440, 1372, 1345, 1163, 1125, 1060, 963, 852, 779, 741. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.8$ Hz), 1.20–1.29 (12H, m), 1.38 (2H, tt, $J=7.9$ Hz), 1.55–1.59 (2H, m), 1.67 (2H, tt, $J=6.1$, 6.1), 1.82 (2H, tt, $J=6.8$, 6.8 Hz), 2.19 (1H, m), 1.90–2.01 (4H, m), 2.37 (1H, quintet, $J=7.6$ Hz), 2.50 (2H, dd, $J=7.8$, 7.8 Hz), 3.15 (2H, dt, $J=6.4$, 6.4 Hz), 3.26–3.44 (10H, m), 4.17 (1H, tt, $J=7.1$, 7.1 Hz), 5.07 (1H, m), 5.30 (1H, dt, $J=7.3$, 10.7 Hz), 6.03 (1H, t, $J=6.3$ Hz), 6.16 (1H, t, $J=6.2$ Hz, NH), 7.26–7.61 (1H, m), 7.63–7.65 (1H, m), 7.69–7.75 (6H, m), 7.81–7.84 (1H, m), 8.00–8.02 (1H, m), 8.09–8.14 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 22.9, 25.4, 27.5, 27.7, 29.5, 29.6, 29.6, 29.8, 30.1, 31.6, 32.1, 32.3, 32.8, 33.8, 36.4, 41.0, 42.5, 45.7, 48.0, 56.4, 124.2, 124.5, 125.5, 130.8, 132.0, 132.2, 132.2, 133.0, 133.1, 133.7, 133.8, 134.1, 134.4, 148.1, 148.3, 148.3, 170.8. FAB-MS: 1058 (MH^+); HRMS (FAB): 1058.2665 ($C_{43}H_{61}BrN_7O_{13}S_3$, MH^+). Exact mass 1058.2673 (MH^+).

4.1.33. (8*S*,2*Z*)-1,9,13-Tris-(2-nitrobenzenesulfonyl)-8-undec-2-enyl-1,5,9,13-tetraaza-cyclooctadecan-6-one (29). To a solution of **28** (94.1 mg, 0.0889 mmol) in acetonitrile (1.8 mL) were added cesium carbonate (86.8 mg, 0.267 mmol) and *n*-Bu_4NI (65.7 mg, 0.178 mmol) at room temperature. After stirring at 60°C for 1 h, 1N hydrochloric acid was added to the mixture. The mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave residue, which was purified by column chromatography on silica gel (4:1 AcOEt/hexane) to give **29** as a yellow powder (75.2 mg, 86%). Mp 78.0–79.0°C. $[\alpha]_D^{28}=-9.91°$ ($c=0.433$, $CHCl_3$); IR (film, cm^{-1}) 3403, 3093, 2927, 2855, 1670, 1590, 1544, 1466, 1439, 1373, 1346, 1264, 1162, 1125, 1060, 1028, 958, 852, 778, 742. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6.9$ Hz), 1.24–1.28 (12H, m), 1.59–1.67 (2H, tt, $J=7.2$, 7.2 Hz), 1.81 (2H, tt, $J=6.8$, 6.8 Hz), 1.94 (2H, m), 2.06 (2H, m), 2.17 (1H, m), 2.35–2.61 (3H, m), 3.19–3.41 (12H, m), 4.26 (1H, m), 5.23 (1H, m), 5.41 (1H, m), 6.26 (1H, t, $J=6.0$ Hz), 7.54–7.76 (9H, m), 7.90–7.96 (2H, m), 8.10–8.13 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 23.3, 27.3, 27.5, 28.4, 29.2, 29.2, 29.3, 29.4, 29.5, 31.3, 31.9, 37.4, 40.0, 46.1, 47.0, 48.7, 49.1, 123.7, 123.9, 124.1, 128.5, 128.6, 130.2, 130.4, 131.7, 131.8, 132.0, 133.1, 133.4, 133.8, 134.0, 134.1, 135.5, 148.0, 148.3, 148.4, 169.8. FAB-MS: 978 (MH^+); HRMS (FAB): 978.3414 ($C_{43}H_{60}N_7O_{13}S_3$, MH^+). Exact mass 978.3411 (MH^+).

4.1.34. Lipogrammistin-A (9). To a solution of **29** (30.0 mg, 0.0307 mmol) in acetonitrile (0.10 mL) were added mercaptoethanol (10.8 μL, 0.154 mmol) and DBU (22.9 μL, 0.154 mmol) at room temperature. After stirring for 2 h, the mixture was purified by column chromatography on silica gel (1:1:8 isopropylamine/MeOH/CH_2Cl_2) to give triamine. To a solution triamine and this acid **30** (9.4 mg, 0.092 mmol) in dichloromethane (0.10 mL) were added BOPCl (31.2 mg, 0.123 mmol) and triethylamine (21.4 μL, 0.154 mmol) at room temperature. After stirring at room temperature overnight, the mixture was purified by column chromatography on silica gel (methanol/dichloromethane 7:93) to give **7** (11.0 mg, 61%, 2 steps) as a oil. $[\alpha]_D^{25}=+11.9°$ ($c=0.60$, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD containing 1% TFA-*d*) δ: 0.89 (6H, m), 0.90 (3H, t, $J=7.0$ Hz), 1.09 (m, 6H), 1.23–1.50 (m, 16H), 1.60–2.07 (m, 10H), 2.09 (2H, m), 2.64–2.81 (4H, m), 2.41–2.56 (4H, m), 3.04–3.23 (3H, m), 3.25–3.55 (8H, m), 5.34 (1H, m), 5.69 (1H, m). ^{13}C NMR, IR and MS (FAB) data were identical to those of natural lipogrammistin-A.[14]

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