Absolute Structure and Total Synthesis of Lipogrammistin-A, a Lipophilic Ichthyotoxin of the Soapfish

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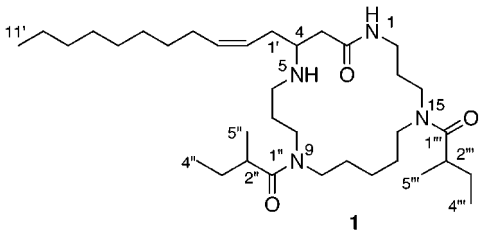
Lipogrammistin-A (**1b**) was isolated as an ichthyotoxic and hemolytic constituent of the skin mucus of the grammistid fish *Aulacocephalus temmincki*. Its absolute stereochemistry was established by chemical degradation and total synthesis. The stereochemistry of the 2-methylbutyryl moieties attached to N9 and N15 was determined to be *S* by HPLC analysis of a diastereomeric derivative. The stereochemistry of the remaining C4 position was elucidated to be *S* by a total synthesis of the two diastereomers (4*S*)- and (4*R*)-**1**.

Introduction

More than 10 species of marine fishes possess ichthyotoxic components in their skin secretions.[1−3] These toxic secretions clearly function as a chemical defense against predators and other enemies. However, the chemical components of these ichthyotoxins have been elucidated in only a very few cases; e.g., pahutoxin, a choline ester of 3-acetoxypalmitic acid from the Hawaiian boxfish *Ostracion lentiginosus*,[4,5] and pardaxins (peptides) and pavoninins (steroid glycosides) from the two soles *Pardachirus pavoninus* and *P. marmoratus*.[6−10]

Soapfish, another well-known ichthyocrinotoxic family, are known to secrete copious amounts of mucus, which produces a soaplike foam in water. Hashimoto et al. have reported the peptidic ichthyotoxin named grammistins in the four typical grammistid fishes *Pogonoperca punctata*,[11] *Grammistes sexlineatus*, *Diploprion bifasciatum*, and *Aulacocephalus temmincki*.[12,13] Recently, two grammistins isolated from *G. sexlineatus* were shown to be simple peptides containing 24 and 25 amino acids, respectively.[14]

In addition to grammistins, the skin secretion of *D. bifasciatum* also contains lipophilic ichthyotoxins that are positive to Dragendorff's test.[13] We previously reported the isolation and gross structure of the lipophilic ichthyotoxin lipogrammistin-A (**1**) from the skin secretion of *D. bifasciatum*.[15] Lipogrammistin-A was considered



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to be an 18-membered polyamine lactam on the basis of spectral data. However, the three asymmetric centers at C4, C2″, and C2‴ in **1** were not determined since they were separated by more than seven bonds, which prevented the application of spectroscopic methods such as the nuclear Overhauser effect (NOE). NMR data suggested that **1** exists in solution as a mixture of four conformers probably due to conformational changes around tertiary amide linkages, which further hampered the configurational analysis of **1** by NMR.

Therefore, we decided to determine the absolute stereochemistry of lipogrammistin-A by chemical degradation

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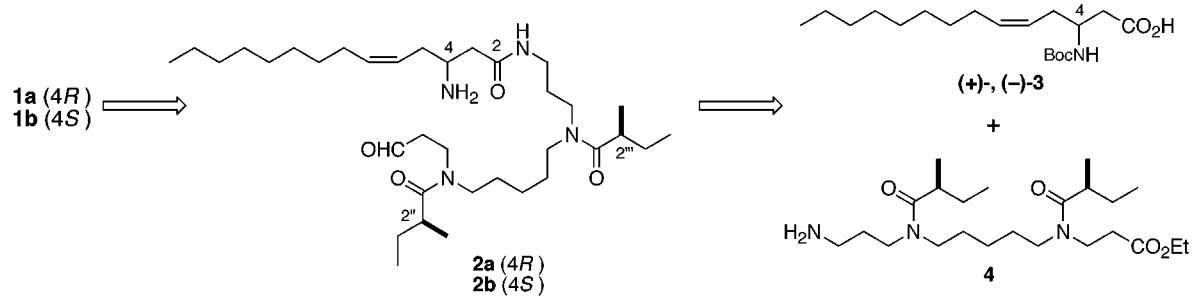
Scheme 1



as well as by the total synthesis of possible diastereomers. This paper describes the complete structural elucidation of lipogrammistin-A based on a total synthesis, as well as the isolation of **1** from another soapfish *A. temmincki*.

Results

Isolation of Lipogrammistin-A (1) from *A. temmincki*. Building upon our previous report, which described the isolation and structure of lipogrammistin-A from *D. bifasciatum*, in this study we investigated another soapfish, *A. temmincki*.[15] Isolation of lipophilic ichthyotoxins was carried out as reported for *D. bifasciatum*. Mucus (0.75 g) was scratched from the skin of one specimen of *A. temmincki* that had been collected off Izu Peninsula and extracted with acetone. The extract was partitioned between water and ethyl acetate. The organic layer was fractionated on a silica gel column ($CHCl_3$−MeOH 98:2) with guidance of the ichthyotoxicity of the killifish *Oryzias latipes*. Further purification was carried out by reversed-phase HPLC to furnish 3.0 mg of lipogrammistin-A (yield, 0.4% of wet mucus). This ichthyotoxin was indistinguishable from lipogrammistin-A isolated from *D. bifasciatum* on silica gel TLC, reversed-phase HPLC, and ^1H and ^{13}C NMR spectra. Therefore, the following degradation experiments were carried out for **1** from *D. bifasciatum*.

Stereochemistry of the 2-Methylbutyryl Moiety. To determine the configuration of 2-methylbutyric acid, **1** was hydrolyzed under acidic conditions (3 N HCl, 5 h, 110 °C), and the hydrolysate was derivatized with the chiral reagent (*S*)-1-(1-naphthyl)ethylamine to give the corresponding amide, which possessed dual chiral carbons.[16] Comparison of the amide with authentic diastereomeric amides by HPLC led to the identification of (*S*)-2-methylbutyric acid as the dominant enantiomer from natural **1** (78% diastereomeric excess). A small amount of the *R* enantiomer is considered to arise during acid hydrolysis. We also observed the same degree of racemization when a model compound (**17**) was hydrolyzed under similar conditions. Therefore, the stereochemistry of the 2-methylbutyric acid as components of lipogrammistin-A was originally *S*, assuming that an exceeding discrimination between the two amide moieties is improbable in the hydrolysis. It was accordingly concluded that the absolute stereochemistry of the two 2-methylbutyric acyl moieties in **1** was *S*.

Total Synthesis of Two C4-Diastereomers for Lipogrammistin-A (1). Since the stereochemistry of the two 2-methylbutyryl moieties was determined, one chiral center (C4) remained to be elucidated. The only possible solution to this problem seemed to involve the total synthesis of (4*R*)- and (4*S*)-lipogrammistin-A. Therefore, we planned the total synthesis of both the 4*R* and 4*S* diastereomers (**1a** and **1b**) as depicted in Scheme 1. The crucial step is the construction of an 18-membered lactam ring, which should be achieved by the intramolecular reductive amination of amino aldehydes **2a** and **2b**. These aldehydes can be built by the condensation of optically active β-amino carboxylic acid (+)- or (−)-**3** with polyamine **4** bearing two (*S*)-2-methylbutyryl side chains.

The β-amino acid moiety was synthesized as illustrated in Scheme 2. The regioselective reduction of diyne **5**[17] by $LiAlH_4$ gave (*E*)-allyl alcohol **6**. Sharpless asymmetric epoxidation using (+)-DET afforded the chiral epoxide (+)-**7**,[18] while (−)-**7** was obtained from **6** with (−)-DET. Reduction of the triple bond by Lindlar hydrogenation gave (+)-**8**, which was subjected to regioselective hydrogenation with Red-Al to give 1,3-diol (−)-**9** in good yield. Selective protection of a primary hydroxyl group with TBDPS, followed by mesylation and inversion with NaN_3, furnished the corresponding azide (+)-**10**. Selective reduction of the azide in the presence of the double bond was successfully carried out using Ph_3P in aqueous THF.[19] Protection of the amino group with a *tert*-butoxycarbonyl group (Boc) provided (+)-**11**. Removal of a silyl group with *n*-Bu_4NF afforded the primary alcohol (+)-**12**, which was subjected to sequential oxidation (Swern oxidation, $NaClO_2$) to yield the carboxylic acid (+)-**3**. The enantiomer (−)-**3** was similarly synthesized from the enantiomeric epoxide (−)-**8**. Although the absolute stereochemistry of each enantiomer ((+)- and (−)-**3**) could be predicted from the enantioselectivity of Sharpless asymmetric epoxidation, the optical purity of **3** was determined to be 95% ee by a modification of Mosher's method.[20,21]

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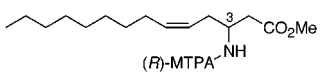
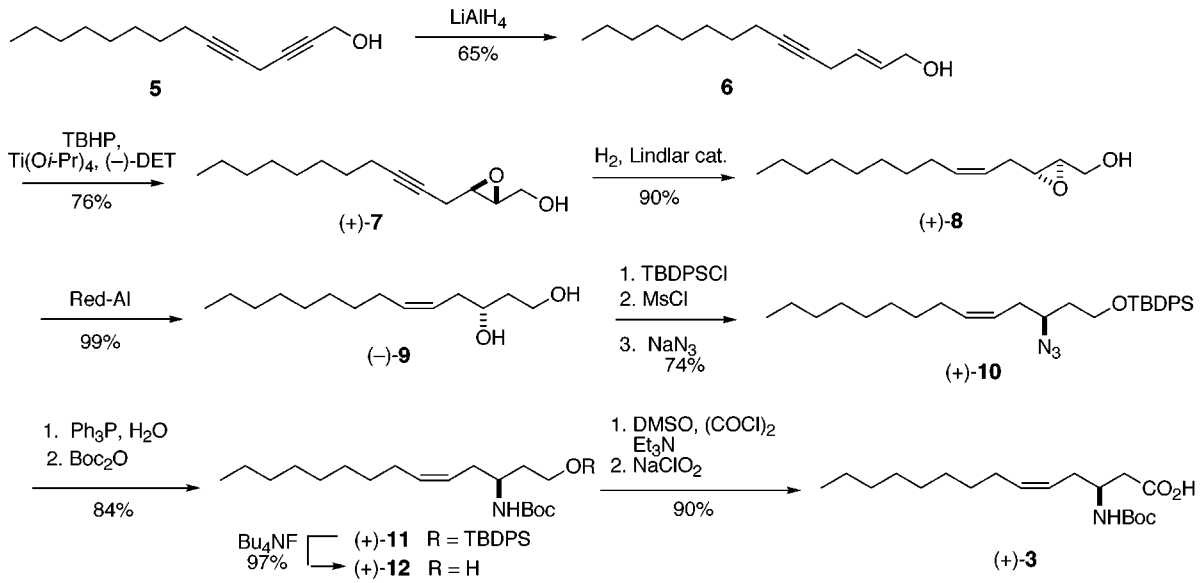
(21) To determine the absolute configuation of carboxylic acid **3**, we converted it to MTPA derivative **11** by a three-step sequence ((1) $TMSCHN_2$, (2) TFA, (3) (+)-(*R*)-MTPAOH, DCC). Assignment of all proton signals of each MTPA derivative was established by the HH−COSY spectra. The result indicated that the absolute configuration of the original carboxylic acid (−)-**3** was *R* and its optical purity was 95% ee, judging from a ratio of the integration for methoxy protons of **13a** and **13b**.

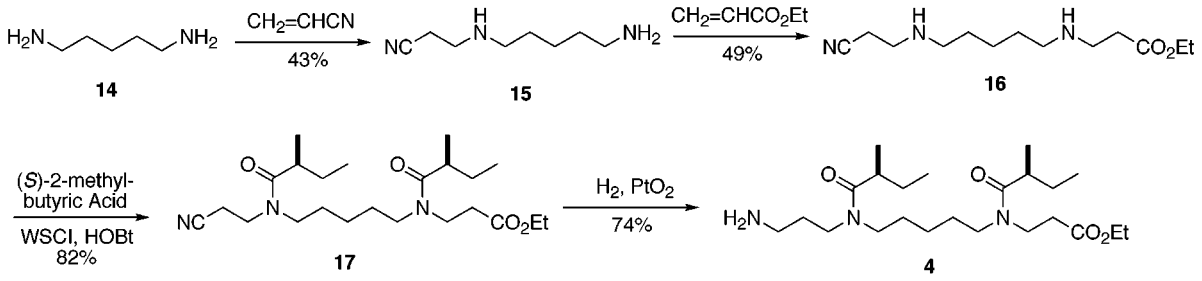


(3*R*) **13a**
(3*S*) **13b**

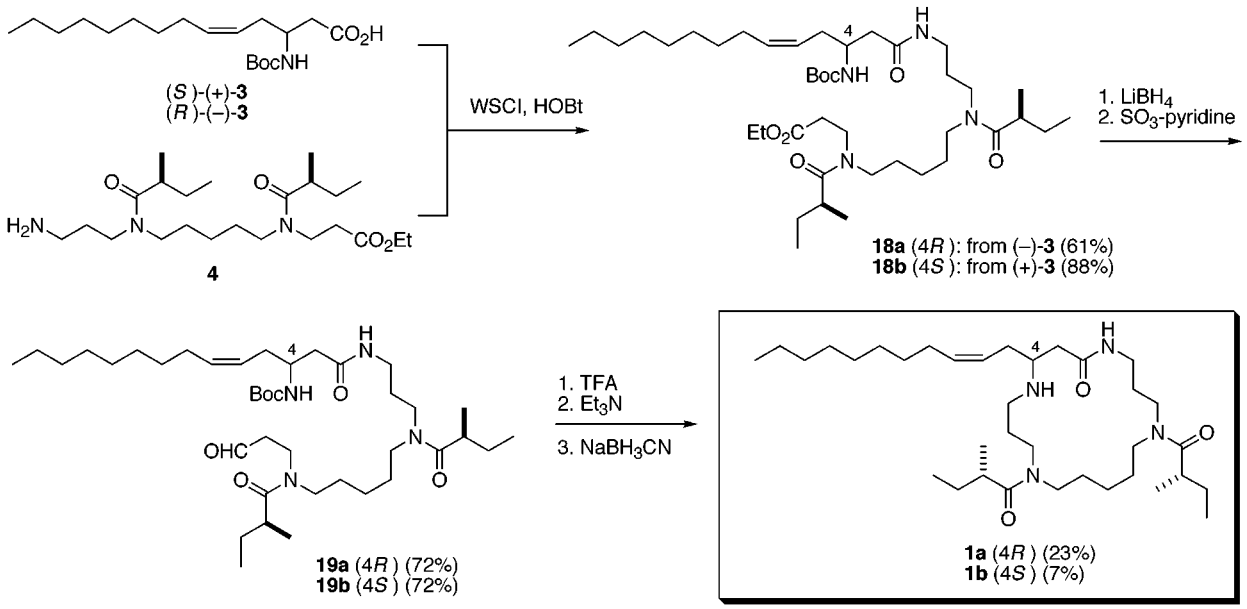
Scheme 2



Scheme 3



Scheme 4



Synthesis of the polyamine moiety was carried out as depicted in Scheme 3. Cyanoethylation of cadaverine (**14**) provided monoalkylated diamine **15**, which was then converted to asymmetric diamine **16** by Michael addition with ethyl acrylate.[22] Acylation of **16** with (*S*)-2-methylbutyric acid gave diamide **17**, which yielded primary amine **4** upon subsequent hydrogenation over PtO_2.

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The 4*R* diastereomer **1a** was synthesized by condensation of carboxylic acid (−)-**3** with amine **4** (Scheme 4). The resulting amide **18a** was converted to aldehyde **19a** by successive reduction with $LiBH_4$ followed by oxidation with SO_3−pyridine in DMSO. After deprotection of the Boc group with TFA, cyclization was carried out by reduction of the resultant Shiff base to furnish **1a** in a modest yield. After successive purification by alumina column chromatography and reversed-phase HPLC, syn-

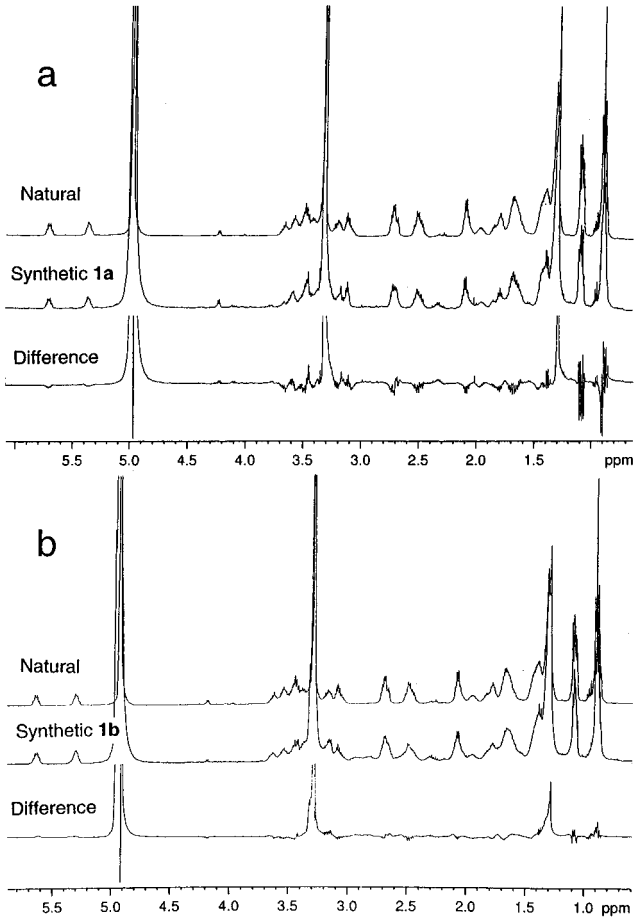

Figure 1. ^{1}H NMR of natural and synthetic lipogrammistin-A and the difference spectra: (a) natural lipogrammistin-A and synthetic **1a**; (b) natural lipogrammistin-A and synthetic **1b**.

thesis of the 4*R* diastereomer of **1** was complete. Likewise, the 4*S* diastereomer **1b** was synthesized via amide **18b**.

Comparison of the Synthetic Diastereomers 1a and 1b with Natural Lipogrammistin-A. The two diastereoisomers **1a** and **1b** were indistinguishable by chromatography; the R_f value on silica gel TLC and the retention time in reversed-phase HPLC for both diastereomers were identical to those of the natural product. Comparison of the specific optical rotations was not successful because these two isomers showed quite similar values and the amounts of synthetic samples available were too small to detect their minute difference. Thus, the diastereomers were compared with natural **1** using NMR spectroscopy.

To make the secondary amine in **1** completely ionized, 1% TFA-*d* was added to CD_3OD. Under these conditions, the spectrum of the 4*S* isomer **1b** again agreed completely with that of the natural lipogrammistin-A, while minute but distinct differences were observed between the 4*R* isomer **1a** and the natural product, as depicted in the difference spectra (Figure 1). Thus, the absolute configuration at the C4 position was determined to be *S*, and elucidation of the entire structure and the total synthesis of lipogrammistin-A (**1**) were accomplished simultaneously.

Discussion

It is noteworthy that lipogrammistin-A exists in solution as a conformational mixture of four different states, as shown by the dependence of its NMR-signal on temperature.[15] In general, tertiary amides undergo conformational alteration in solution due to the restricted rotation of their amide bonds. The presence of these four conformers for lipogrammistin-A could be attributed not only to amide bond rotation but also to conformational exchanges in the 18-membered ring, which was inferred from the following observations: (a) Several signals observed as multiplets at 300 K were sharpened at 333 K, and some became singlets. In particular, the carbon on the 2-methylbutyryl moieties showed this feature. (b) Some split signals at 300 K became much broader at 333 K (their coalescence points were around 333 K), which was typically observed for carbons residing on the polyamine ring but was also seen even for those in the fatty acyl chain, such as C1′, C2′, and C3′. These phenomena appeared to imply that there were two rate constants for the conformational change; the faster one is due to alteration of the tertiary amide and the slower one is due to ring conformation. However, on the basis of our intensive analysis of the ^{13}C spectra of **1** taken at various lower temperatures (−30 to +5 °C) in CD_3OD−1% TFA or pyridine-d_5, we concluded that the two rate constants were almost identical. In other words, the ring motion is controlled by alteration of the amide bonds. The spectra showed that the differences in the ^{13}C-chemical shifts among the conformers were smaller for carbons in the methylbutyryl moieties (∼0.2 ppm) than for those in the ring portions (0.5−2.1 ppm).

Lipogrammistin-A is the first polyamine lactam to be isolated from an animal, although similar compounds with a pithecolobine-type skeleton have been isolated from terrestrial plants.[23] In contrast to spermine (1,5,-10,14-tetraazatetradecane) alkaloids from terrestrial plants, lipogrammistin-A has a 1,5,11,15-tetraazapentadecane moiety as a polyamine component, which is presumably biosynthesized from cadaverine. Although cadaverine and its derivatives are found throughout the animal kingdom, no natural alkaloids have hitherto been reported to have this uncommon polyamine unit.

Experimental Section

General Methods. NMR spectra were recorded at 500 MHz for ^{1}H, 125 MHz for ^{13}C or 400 MHz for ^{1}H, 100 MHz for ^{13}C at 300 K unless otherwise noted. ^{1}H chemical shifts were referenced on the basis of residual solvent peaks: C*H*Cl$_3$ (δ 7.24) in $CDCl_3$, CD_2HOD (δ 3.30) in CD_3OD, or Cα-H of pyridine-d_4 (δ 8.50) in pyridine-d_5. ^{13}C chemical shifts were referenced with respect to the ^{13}C signal of $CDCl_3$ (δ 77.0), CD_3OD (δ 49.0), or Cα of pyridine-d_5 (δ 149.8). Reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen or argon with dry, freshly distilled solvents.

Extraction and Isolation of Lipogrammistin-A from *A. temmincki*. From the skin of one specimen of thawed fish *A. temmincki* (17 cm length, 77.5 g weight), which was collected off Izu Penninsula, Japan, the mucus was scraped off with spatula (0.75 g wet weight) and suspended in acetone (300 mL). The surface of the fish was washed well with acetone (100 mL). The combined acetone extracts were filtered and concentrated, and the resultant residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (200 mL × 3), the combined organic layer was concentrated, and the crude residue (45.4 mg) was fractionated by silica gel flash column chromatogra-

(23) For example: Mar, W.; Tan, G. T.; Cordell, G. A.; Pezzuto, J. M.; Jurcic, K.; Offermann, F.; Redl, K.; Steinke, B.; Wagner, H. *J. Nat. Prod.* **1991**, 54, 1531−1542.

phy (3 g, $CHCl_3$ to 16% MeOH−$CHCl_3$ stepwise elution). Dragendorff-positive fractions were combined (13.8 mg) and subjected to reversed-phase HPLC (ODS, YMC AM-323, 10 × 250 mm, CH_3CN-H_2O−TFA, 60:40:0.05, UV at 220 nm and RI detections). The major peak was collected and further purified by silica gel column chromatography (0.5 g, $CHCl_3$ to 8% MeOH−$CHCl_3$ stepwise elution) to afford 3.0 mg of lipogrammistin-A (0.4% yield based on wet mucus): $[\alpha]^{25}_D$ +13.8 (*c* 0.2, MeOH); other spectroscopic data were identical to that of lipogrammistin-A isolated from *D. bifasciatum*.[15]

Acid Hydrolysis of Lipogrammistin-A and Determination of the Stereochemistry of 2-Methylbutyric Acid. A mixture of lipogrammistin-A (1.5 mg) and 3 N aqueous HCl (1 mL) in a capped vial tube was heated at 110 °C for 5 h. After cooling, the reaction mixture was extracted with Et_2O and CH_2Cl_2, and the combined organic layer was dried over MS4A. To this, HOBt, DCC, and (*S*)-1-(1-naphthyl)ethylamine were added (each 10 mg). After the mixture was stirred overnight, filtration and concentration gave a residue, which was purified by preparative TLC, followed by HPLC (SiO_2, YMC A-012, 6 × 150 mm, hexane−EtOAc, 5:1, UV detection at 280 nm). Determination of the diastereomeric ratio was performed by reversed-phase HPLC (ODS, Develosil HG-5, 4.6 × 150 mm, CH_3CN-H_2O, 40:60, 1 mL/min, UV detection at 280 nm): retention time, (*S*)-2-methyl-*N*-[(*S*)-1-(1-naphthyl)-ethyl]butyramide in 27.4 min; (*R*)-2-methyl-*N*-[(*S*)-1-(1-naphthyl)ethyl]butyramide in 28.6 min. The ratio of *S*:*R* was 85:15 as the peak area.

(*E*)-Tetradec-2-en-5-yn-1-ol (6). To a solution of diyne **5**[17] (65.0 mg, 0.315 mmol) in Et_2O (10 mL) was added $LiAlH_4$ in Et_2O (1 M solution, 0.35 mL, 0.35 mmol) at room temperature. After the mixture was stirred for 2 h, 1 N HCl was added. The organic layer was washed with 1 N HCl, water, and brine and dried over Na_2SO_4. Filtration and concentration gave a residue, which was chromatographed on silica gel (hexane−AcOEt) to afford 42.7 mg (65%) of **6** as a colorless oil: IR (film) 3342, 2215 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (dtt, 1H, J = 15, 6, 2 Hz), 5.67 (dtt, 1H, J = 15, 5, 1 Hz), 4.10 (dd, 2H, J = 6, 1 Hz), 2.91 (m, 2H), 2.14 (m, 2H), 1.46 (tt, 2H, J = 8, 8 Hz), 1.35−1.19 (m, 10H), 0.85 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ130.2, 127.4, 82.8, 76.5, 63.2, 31.8, 29.2, 29.1, 29.0, 28.9, 22.6, 21.7, 16.7, 14.1; MS (EI) *m*/*z* (rel intensity) 208 (48), 192 (100), 190 (59); HRMS (EI) *m*/*z* calcd for $C_{14}H_{22}O$ (M^+) 208.1827, found 208.1837.

(2*S*,3*R*)- and (2*R*,3*S*)-2,3-Epoxytetradec-5-yn-1-ol ((+)- and (−)-7). A mixture of alcohol **6** (1.49 g, 7.15 mmol) and MS4A in dry CH_2Cl_2 (50 mL) was cooled to −23 °C. To this mixture were added (+)-DET (1.50 mL, 8.58 mmol) and Ti(O-*i*-Pr)$_4$ (2.2 mL, 7.15 mmol) successively. After the mixture was stirred for 1 h, *tert*-butyl hydroperoxide (5.5 M in 2,2,4-trimethylpentane solution, 2.60 mL, 14.3 mmol) was added. The mixture was kept at −25 °C overnight. The reaction was quenched by addition of EtOAc and saturated aqueous Na_2SO_4. After being stirred for 30 min, the mixture was filtered through a Celite pad. Evaporation of the solvent gave a crude residue, which was chromatographed on silica gel (hexane−EtOAc) to afford 1.37 g (85%) of (+)-**7** as a colorless solid: mp 55−56 °C; $[\alpha]^{28}_D$ +8.3 (*c* 1.24, $CHCl_3$); IR (film) 3401, 2230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (dd, 1H, J = 13, 2 Hz), 3.63 (dd, 1H, J = 13, 4 Hz), 3.09 (m, 2H), 2.58 (ddt, 1H, J = 18, 4, 2 Hz), 2.46 (ddt, 1H, J = 18, 5, 2 Hz), 2.10 (tt, 2H, J = 7, 2 Hz), 1.44 (tt, 2H, 7, 7 Hz), 1.35−1.19 (m, 10H), 0.85 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.9, 73.8, 61.2, 57.8, 53.6, 31.8, 29.1, 29.0, 28.8, 28.8, 22.6, 21.6, 18.7, 14.0; MS (EI) *m*/*z* (rel intensity) 244 (5), 182 (10), 134 (19), 92 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{24}O_2$ (M^+) 224.1776, found 224.1751. By the same procedure using (−)-DET instead of (+)-DET, 1.22 g of (−)-**7** was obtained from 1.36 g of **6** in 83% yield: $[\alpha]^{25}_D$ −8.5 (*c* 0.83, $CHCl_3$).

(−)-(2*S*,3*R*,5*Z*)- and (+)-(2*R*,3*S*,5*Z*)-2,3-Epoxy-5-tetradecen-1-ol ((+)- and (−)-8). Lindlar catalyst (1 g) in MeOH (30 mL) and quinoline (0.3 g) was hydrogenated until absorption of hydrogen ceased. To this mixture was added epoxide (+)-**7** (1.36 g, 6.06 mmol) in MeOH (10 mL), and the mixture was then hydrogenated under hydrogen atmosphere overnight. The catalyst was filtered off through Celite, and the filtrate was concentrated. The residue was dissolved in EtOAc, washed with 1 N aqueous HCl and then H_2O, and dried over $MgSO_4$. Filtration and concentration gave a crude residue that was chromatographed on silica gel (hexane−EtOAc) to afford 1.24 g (90%) of (+)-**8** as a colorless oil: $[\alpha]^{25}_D$ +15.8 (*c* 1.01, $CHCl_3$); IR (film) 3376 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49 (m 1H), 5.34 (m, 1H), 3.87 (dd, 1H, J = 13, 2 Hz), 3.56 (dd, 1H, J = 13, 6 Hz), 2.95 (m, 1H), 2.37 (m, 1H), 1.99 (m, 2H), 1.35−1.19 (m, 10H), 0.84 (m, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 122.7, 61.6, 58.1, 55.2, 31.6, 29.5, 29.4, 29.3, 29.3, 29.2, 27.3, 22.6, 14.0; MS (EI) *m*/*z* (rel intensity) 226 (30), 196 (39), 161 (62), 135 (68), 83 (100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{26}O$ (M^+) 226.1933, found 226.1960. By the same procedure, 809 mg of (−)-**8** was obtained from 1.12 g of (−)-**7** in 71% yield: $[\alpha]^{25}_D$ −16.9 (*c* 1.14, $CHCl_3$).

(3*R*,5*Z*)- and (3*S*,5*Z*)-5-Tetradecene-1,3-diol ((−)- and (+)-9). To a solution of (+)-**8** (1.34 g, 5.92 mmol) and dry THF (50 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (70% in toluene solution; 3.7 mL, 11.8 mmol) at 0 °C. The mixture was stirred at 0 °C overnight. Saturated aqueous NH_4Cl was added, and the mixture was diluted with EtOAc. The resulting insoluble material was filtered off, and the filtrate was washed with brine and dried over $MgSO_4$. Filtration and concentration gave a residue, which was chromatographed on silica gel (hexane−EtOAc) to give 1.34 g (99%) of diol (−)-**9** as a colorless oil: $[\alpha]^{29}_D$ −4.5 (*c* 1.15, $CHCl_3$); IR (film) 3381 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (m, 1H), 5.35 (m, 1H), 3.83 (m, 1H), 3.82 (m, 1H), 3.77 (m, 1H), 2.22 (m, 2H), 2.01 (brtd, 2H, J = 7, 7 Hz), 1.67 (m, 2H), 1.35−1.17 (m, 12H), 0.84 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 124.5, 71.8, 61.7, 37.7, 35.6, 31.6, 29.5, 29.4, 29.3, 29.2, 27.4, 22.6, 14.1; MS (EI) *m*/*z* (rel intensity) 228 (0.8), 210 (16), 154 (40), 75(100); HRMS (EI) *m*/*z* calcd for $C_{14}H_{26}O$ ($M - H_2O$)$^+$ 210.1984, found 210.2002. By the same procedure 342.1 mg of (+)-**9** was obtained from 369.9 mg of (−)-**8** in 92% yield: $[\alpha]^{29}_D$ +5.7 (*c* 0.93, $CHCl_3$)

(3*S*,5*Z*)- and (3*R*,5*Z*)-3-Azido-1-[(*tert*-butyldiphenylsilyl)oxy]-5-tetradecene ((+)- and (−)-10). To a solution of diol (−)-**9** (1.18 g, 5.20 mmol) and imidazole (0.96 g, 14.1 mmol) in DMF (30 mL) was added TBDPSCl (1.3 mL, 5.72 mmol) at 0 °C. The mixture was stirred for 30 min at this temperature, diluted with Et_2O, washed with H_2O and then saturated aqueous NH_4Cl, and dried over $MgSO_4$. Filtration and concentration gave a crude silyl ether, which was dissolved in dry CH_2Cl_2 (40 mL). To this solution were added Et_3N (3.6 mL, 26 mmol) and MsCl (0.8 mL, 10.3 mmol) at 0 °C. After the mixture was stirred at 0 °C for 1 h, saturated aqueous NH_4Cl was added. The organic layer was washed with saturated aqueous NH_4Cl, aqueous $NaHCO_3$, and brine and dried over $MgSO_4$. Filtration and concentration gave the crude mesylate, which was dissolved in DMF (40 mL). To this solution was added NaN_3 (90% purity, 1.7 g, 26 mmol). After being stirred at 50 °C overnight, the reaction mixture was poured into Et_2O, washed with H_2O, and dried over $MgSO_4$. Filtration and concentration gave a residue, which was chromatographed on silica gel (hexane−Et_2O) to yield 2.27 g (89%) of azide (+)-**10** as a colorless oil: $[\alpha]^{26}_D$ +13.7 (*c* 1.39, $CHCl_3$); IR (film) 2099 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.44−7.36 (m, 6H), 5.54 (m, 1H), 5.38 (m, 1H), 3.82−3.71 (m, 2H), 3.64 (m, 1H), 2.32 (m, 2H), 2.06 (brtd, 2H, J = 7, 7 Hz), 1.77 (m, 1H), 1.62 (m, 1H), 1.39−1.20 (m, 12H), 1.03 (s, 9H), 0.86 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 135.5, 133.7, 133.5, 133.4, 129.7, 127.7, 124.3, 60.4, 59.5, 36.7, 32.4, 31.8, 29.5, 29.5, 29.3, 29.3, 27.5, 26.8, 22.7, 19.2 (3C), 14.1; MS (EI) *m*/*z* (rel intensity) 434 (25), 406 (100), 391 (17); HRMS (EI) *m*/*z* calcd for $C_{30}H_{45}ONSi$ ($M - N_2$)$^+$ 463.3271, found 463.3228. By the same procedure, 963.0 mg of (−)-**10** was obtained in three steps from 574.6 mg of (+)-**9** in 78% yield: $[\alpha]^{25}_D$ −17.3 (*c* 1.16, $CHCl_3$).

(3*S*,5*Z*)- and (3*R*,5*Z*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-3-[(*tert*-butoxycarbonyl)amino]-5-tetradecene ((+)- and (−)-11). A solution of azide (+)-**10** (2.27 g, 4.63 mmol) and Ph_3P (2.5 g, 9.2 mmol) in THF (40 mL) and H_2O (0.9 mL) was stirred at 45 °C overnight. Evaporation of the solvent gave a

crude residue, which was dissolved in EtOAc and dried over Na_2SO_4. Filtration and concentration gave a crude amine, which was dissolved in dry CH_2Cl_2 (50 mL). To this solution were added Et_3N (0.8 mL, 5.6 mmol) and Boc_2O (1.5 mL, 6.9 mmol), and the mixture was stirred at room temperature overnight. Evaporation of the solvent gave a residue, which was chromatographed on silica gel (hexane−Et_2O) to afford 2.50 g (96%) of (+)-**11** as a colorless oil: $[\alpha]^{25}_D$ +12.8 (*c* 1.17, $CHCl_3$); IR (film) 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.43−7.34 (m, 6H), 5.45 (m, 1H), 5.30 (m, 1H), 5.05 (br, 1H), 3.75 (br, 2H), 3.68 (brm, 1H), 2.26 (br, 2H), 1.97 (brtd, 2H, J = 7, 7 Hz), 1.78 (br, 1H), 1.56 (br, 1H), 1.40 (s, 9H), 1.34−1.17 (m, 12H), 1.04 (s, 9H), 0.86 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 135.6, 133.4, 132.6, 129.9, 127.7, 125.0, 78.8, 61.5, 49.1, 35.7, 32.4, 31.9, 29.7, 29.5, 29.3, 29.3, 28.4 (3C), 27.4, 26.8, 22.7, 19.1 (3C), 14.1; MS (EI) *m*/*z* (rel intensity) 565 (0.1), 492 (7.3), 452 (100), 412 (16), 356 (38), 330 (49), 254 (16), 234 (20), 224 (19), 199 (19), 176 (10), 57 (22); HRMS (EI) *m*/*z* calcd for $C_{35}H_{55}NO_3Si$ (M^+) 565.3951, found 565.3996. By the same procedure, 811.7 mg of (−)-**11** was obtained from 963.0 mg of (−)-**10** in 73% yield: $[\alpha]^{23}_D$ −13.4 (*c* 0.90, $CHCl_3$)

(+)-(3*S*,5*Z*)- and (−)-(3*R*,5*Z*)-3-[(*tert*-Butoxycarbonyl)amino]-5-tetradecen-1-ol ((+)- and (−)-12). A mixture of (+)-**11** (96.1 mg, 0.170 mmol), dry THF (3 mL), and tetrabutylammonium fluoride (1 M in THF solution; 0.28 mL, 0.28 mmol) was stirred at room temperature for 3 h. Concentration and chromatography of the crude residue on silica gel (hexane−Et_2O) gave 53.9 mg (97%) of (+)-**12** as a colorless oil: $[\alpha]^{26}_D$ +17.1 (*c* 1.37, $CHCl_3$); IR (film) 3300, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (brm, 1H), 5.32 (brm, 1H), 4.46 (brd, 1H), 3.81 (br, 1H), 3.61 (brm, 2H), 3.50−3.30 (br, 1H), 2.28 (m, 1H), 2.15 (m, 1H), 1.99 (brtd, 2H, J = 7, 7 Hz), 1.80 (m, 1H), 1.41 (s, 9H), 1.36−1.18 (m, 12H), 0.85 (3H, t, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 133.4, 124.4, 79.7, 58.9, 47.1, 38.2, 32.8, 31.9, 29.6, 29.5, 29.3, 29.2, 28.3, 27.4, 22.6, 14.1; MS (EI) *m*/*z* (rel intensity) 327 (0.1), 272 (2.7), 254 (12), 174 (28), 118 (52), 74 (34), 57 (100), 41(36); HRMS (EI) *m*/*z* calcd for $C_{19}H_{37}NO_3$ (M^+) 327.2774, found 327.2790. By the same procedure, 135.1 mg of (−)-**12** was obtained from 237.9 mg of (−)-**11** in 98% yield: $[\alpha]^{27}_D$ −15.7 (*c* 0.99, $CHCl_3$).

(3*S*,5*Z*)- and (3*R*,5*Z*)-3-[(*tert*-Butoxycarbonyl)amino]-5-tetradecenoic Acid ((+)- and (−)-3). To a solution of oxalyl chloride (1.35 mL, 17.3 mmol) and dry DMSO (2.12 mL) in dry CH_2Cl_2 (60 mL) at −78 °C was added (+)-**12** (1.41 g, 4.32 mmol) in CH_2Cl_2 (5 mL) and the mixture stirred for 20 min. After addition of Et_3N (12.5 mL), the mixture was stirred for 1 h at 0 °C, and then satuated aqueous NH_4Cl was added. The organic layer was washed with satuated aqueous NH_4Cl and satuated aqueous $NaHCO_3$ and then dried over Na_2SO_4. Filtration and concentration gave a residue, which was dissolved in 2-methyl-2-propanol (40 mL) and H_2O (16 mL). To this solution were added 2-methyl-2-butene (1.12 mL, 19.4 mmol), $NaH_2PO_4 \cdot 2H_2O$ (382 mg, 4.75 mmol), and $NaClO_2$ (86% purity, 1.22 g, 14.3 mmol). After the mixture was stirred for 30 min, 5% aqueous $KHSO_4$ (3 mL) was added. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$, filtered, and concentrated. Chromatography of the residue on silica gel ($CHCl_3$) gave 1.32 g (90%) of (+)-**3** as a colorless oil, which solidified upon standing: mp 53−55 °C; $[\alpha]^{27}_D$ +10.2 (*c* 0.76, MeOH); IR (film) 3500−3000 (br), 1714, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (m, 1H), 5.32 (m, 1H), 3.96 (br, 1H), 2.53 (br, 2H), 2.30 (brm, 2H), 2.01 (brtd, 2H, J = 7, 7 Hz), 1.41 (s, 9H), 1.37−1.17 (m, 12H), 0.86 (3H, t, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 155.5, 133.6, 124.3, 79.5, 47.6, 38.7, 32.1, 31.9, 29.6, 29.5, 29.3, 29.3, 28.4 (3C), 27.4, 22.6, 14.1; MS (EI) *m*/*z* (rel intensity) 341 (0.7), 285 (2), 268 (8), 224 (12), 188 (35), 132 (53), 88 (75), 57 (100); HRMS (EI) *m*/*z* calcd for $C_{19}H_{35}NO_4$ (M^+) 341.2566, found 341.2574. By the same procedure 93.1 mg of (−)-**3** was obtained from 116.2 mg of (−)-**12** in 77% yield: $[\alpha]^{27}_D$ −13.8 (*c* 0.91, MeOH).

Determination of the Optical Purity and Absolute Stereochemistry of (+)- and (−)-3. To a solution of carboxylic acid (−)-**3** (3 mg) in PhH−MeOH (3:1, 3 mL) was added (trimethylsilyl)diazomethane (10% in hexane solution, 1 mL). The mixture was stirred at room temperature for 10 min and concentrated. A resulting crude methyl ester was dissolved in CH_2Cl_2 (2 mL), and to this solution was added TFA (1 mL). Stirring for 20 min and concentration gave a crude residue, which was dissolved in EtOAc (5 mL) and neutralized with saturated aqueous $NaHCO_3$ (2 mL). The organic layer was dried by passing through a Na_2SO_4 column (0.5 × 3 cm), and the eluent was concentrated. A crude residue was dissolved in CH_2Cl_2 (1 mL), and to this solution were added (*R*)-MTPAOH (8 mg) and DCC (15 mg). The mixture was stirred at room temperature for 30 min and purified directly by preparative TLC (hexane−EtOAc 2:1) to give **13a** as an (*R*)-MTPA amide. In the same way, **13b** was prepared from (+)-**3**. Judging from the ^1H NMR spectra of **13a** and **13b**, the optical purity of (−)-**3** was 95% ee, and that of (+)-**3** was 95% ee: ^1H NMR (500 MHz, $CDCl_3$) **13a** δ 5.46 (m, 1H), 5.23 (m, 1H), 4.31 (m, 1H), 3.66 (s, 3H), 3.39 (d, 3H, $^5J_{HF}$ = 1 Hz), 2.58 (d, 2H, J = 5.5 Hz), 2.31 (brt, 2H, J = 7 Hz), 1.91 (m, 2H), 1.35−1.20 (m, 12H), 0.86 (t, 3H, J = 7 Hz); **13b** δ 5.53 (m, 1H), 5.30 (m, 1H), 4.28 (m, 1H), 3.58 (s, 3H), 3.38 (d, 3H, $^5J_{HF}$ = 1 Hz), 2.54 (d, 2H, J = 5.5 Hz), 2.37 (brt, 2H, J = 7 Hz), 1.98 (m, 2H), 1.35−1.20 (m, 12H), 0.86 (t, 3H, J = 7 Hz).

***N*-(Cyanoethyl)-1,5-diaminopentane (15).** Acrylonitrile (0.377 mL, 5.13 mmol) was added dropwise to a solution of 1,5-diaminopentane (**14**) (0.500 mL, 4.27 mmol) in MeOH (10 mL) at room temperature. The resulting mixture was allowed to stand at room temperature for 2 h. Concentration and flash chromatography on silica gel ($CHCl_3$−MeOH−*i*-$PrNH_2$) gave 287 mg (43%) of **15** as a colorless oil: IR (film) 3354, 2247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.61 (t, 2H, J = 7 Hz), 2.40 (brt, 2H, J = 7 Hz), 2.34 (t, 2H, J = 7 Hz), 2.24 (t, 2H, J = 7 Hz), 1.21 (tt, 2H, J = 7, 7 Hz), 1.19 (t, 2H, J = 7 Hz), 1.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) 118.3, 48.2, 44.3, 32.2, 28.9, 24.0, 23.6, 17.8; MS (EI) *m*/*z* (rel intensity) 155 (51), 138 (34), 128 (25), 115 (40), 109 (86), 86 (64), 56 (95), 42 (100), 30 (97); HRMS (EI) *m*/*z* calcd for $C_8H_{17}N_3$ (M^+) 155.1423, found 155.1439.

Ethyl 12-Cyano-4,10-diazadodecanoate (16). To a solution of **15** (2.76 g, 17.8 mmol) in EtOH (50 mL) was added ethyl acrylate (2.32 mL, 21.3 mmol) dropwise at room temperature. Stirring was continued at room temperature for 24 h. Evaporation of the solvent left an oil, which was subjected to flash column chromatography on silica gel ($CHCl_3$−*i*-$PrNH_2$) to give 2.22 g (49%) of **16** as an oil: IR (film) 3319, 2247, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.84 (q, 2H, J = 7 Hz), 2.63 (t, 2H, J = 7 Hz), 2.58 (t, 2H, J = 7 Hz), 2.37−2.31 (m, 4H), 2.25 (t, 2H, J = 7 Hz), 2.22 (t, 2H, J = 7 Hz), 1.21 (t, 2H, J = 7 Hz), 1.22 (m, 4H), 1.09 (m, 2H), 0.97 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) 172.4, 116.7, 60.0, 49.0, 48.8, 44.9, 44.8, 34.5, 29.6, 29.6, 24.6, 18.4, 14.0; HRMS (EI) *m*/*z* calcd for $C_{13}H_{25}N_3O_2$ (M^+) 255.1947, found 255.1935.

Ethyl 12-Cyano-4,10-bis((2*S*)-2-methylbutyryl)-4,10-diazadodecanoate (17). To a stirred solution of **16** (2.22 g, 8.71 mmol), DMF (50 mL), (*S*)-2-methylbutyric acid (2.09 mL, 19.2 mmol), and HOBt (3.33 g, 21.8 mmol) was added WSCI (4.17 mg, 21.8 mmol). The mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo, and the residue was dissolved in EtOAc and washed successively with 5% aqueous $KHSO_4$, aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Filtration and concentration gave a residue, which was purified by flash column chromatography on silica gel ($CHCl_3$−MeOH) to give 3.02 g (82%) of diamide **17** as a colorless oil: $[\alpha]^{25}_D$ +27.7 (*c* 1.23, $CHCl_3$); IR (film) 2249, 1730, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.09 and 3.99 (q each, 2H, J = 7 Hz), 3.45 (m, 2H), 3.40 (m, 2H), 3.35−3.13 (m, 4H), 2.58 (m, 2H), 2.54−2.36 (m, 2H), 1.63−1.40 (m, 6H), 1.30 (m, 2H), 1.20 (m, 2H), 1.15 and 1.12 (t each, 3H, J = 7 Hz), 0.97 (m, 6H), 0.74 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 177.1, 177.0, 176.5, 176.5, 172.1, 170.9, 118.4, 118.3, 118.3, 60.8, 60.4, 49.1, 49.1, 49.1, 48.4, 45.4, 43.2, 43.2, 43.1, 43.0, 42.7, 37.3, 37.2, 37.1, 34.5, 32.9, 29.6, 29.5, 29.5, 29.3, 27.3, 27.3, 27.3, 27.2, 23.9, 23.9, 17.7, 17.7, 17.6, 17.6, 16.2, 16.2, 16.1, 14.1, 14.1, 11.9, 11.9; MS (EI) *m*/*z* (rel intensity) 423 (M^+, 23), 378 (14), 366 (17), 338 (100), 292

(19), 184 (12), 168 (17), 137 (18), 130 (44), 85 (19), 57 (69); HRMS (EI) *m*/*z* calcd for $C_{23}H_{41}N_3O_4$ (M^+) 423.3097, found 423.3079.

Ethyl 4,10-Bis((2*S*)-2-methylbutyryl)-4,10,14-triazatetradecanoate (4). To a solution of **17** (3.02 g, 7.14 mmol) in EtOH (80 mL) and $CHCl_3$ (1.6 mL) was added platinum(IV) oxide (200 mg). The mixture was stirred under hydrogen atmosphere overnight at room temperature. The catalyst was filtered off through a Celite pad. The filtrate was neutralized with *i*-$PrNH_2$ and evaporated to give a crude residue that was chromatographed on silica gel ($CHCl_3$−MeOH−*i*-$PrNH_2$) to afford 2.25 g (74%) of **4** as a colorless oil: $[\alpha]^{25}_D$ +23.3 (*c* 1.29, $CHCl_3$); IR (film) 3461, 3288, 1734, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.14−4.05 (m, 2H), 3.62−3.41 (m, 2H), 3.45−3.12 (m, 6H), 2.74−2.59 (m, 2H), 2.58−2.43 (m, 4H), 1.65 (m, 4H), 1.54 (m, 4H), 1.36 (m, 2H), 1.30−1.18 (m, 5H), 1.15 (m, 6H), 0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) 176.8, 176.7, 176.5, 176.5, 176.4, 172.2, 172.2, 170.9, 60.9, 60.8, 60.5, 60.4, 48.6, 48.5, 47.4, 47.3, 45.8, 45.6, 45.5, 45.4, 43.2, 43.1, 42.8, 42.6, 39.4, 39.3, 38.9, 37.3, 37.2, 37.2, 37.1, 37.1, 34.5, 34.5, 33.3, 32.9, 29.6, 29.5, 29.4, 29.3, 27.5, 27.4, 27.4, 27.3, 24.2, 24.1, 17.9, 17.9, 17.8, 17.8, 17.7, 17.7, 14.1, 14.1, 12.0, 12.0, 12.0, 11.9, 11.9; MS (EI) *m*/*z* (rel intensity) 427 (33), 382 (12), 370 (32), 342 (67), 325 (33), 313 (100), 299 (81), 270 (16), 213 (17), 186 (23), 184 (37), 130 (26), 112 (17), 98 (42), 57 (83); HRMS (EI) *m*/*z* calcd for $C_{23}H_{45}N_3O_4$ (M^+) 427.3410, found 427.3386.

Ethyl 14-[(3*R*,5*Z*)-3-[(*tert*-Butoxycarbonyl)amino]-5-tetradecenyl]-4,10-bis((2*S*)-2-methylbutyryl)-4,10,14-triazatetradecanoate (18a). To a solution of carboxylic acid (−)-**3** (38.6 mg, 0.113 mmol) in dry CH_2Cl_2 (2 mL) were added successively HOBt (35.0 mg, 0.226 mmol), amine **4** (72.5 mg, 0.170 mmol) in dry CH_2Cl_2 (2 mL) and WSCI (43.4 mg, 0.226 mmol). After being stirred at room temperature overnight, the mixture was diluted with EtOAc and washed with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Filtration and concentration gave a residue, which was chromatographed on silica gel ($CHCl_3$−MeOH) to afford (51.9 mg, 61%) of **18a** as a colorless oil: $[\alpha]^{27}_D$ +10.9 (*c* 2.77, $CHCl_3$); IR (film) 3309, 1733, 1708, 1645, 1637, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.07 (brt), 7.00 (brt), 6.88 (m), and 6.79 (m) (1H for four signals), 5.45 (m, 1H), 5.27 (m, 1H), 4.13 and 4.09 (each q, 2H, J = 7 Hz), 3.89 (brm, 1H), 3.60 and 3.51 (m, 2H), 3.45−3.15 (m, 6H), 3.10 (m, 2H), 2.60−2.45 (m, 4H), 2.38 (br, 2H), 2.28 (brt, 1H), 1.97 (m, 2H), 1.70−1.50 (m, 8H), 1.39 (s, 9H), 1.39 (m, 2H), 1.33−1.26 (m, 17H), 1.07 (m, 6H), 0.85 (m, 9H); MS (FAB, *m*-nitrobenzyl alcohol) *m*/*z* 751 $(M + H)^+$, 651 $(M - Boc + H)^+$.

14-[(3*R*,5*Z*)-3-[(*tert*-Butoxycarbonyl)amino]-5-tetradecenyl]-4,10-bis((2*S*)-2-methylbutyryl)-4,10,14-triazatetradecanal (19a). To a solution of **18a** (49.5 mg, 0.070 mmol) in dry THF (3 mL) and MeOH (10 μL) was added $LiBH_4$ (8 mg, 0.37 mmol). After the mixture was stirred at 0 °C for 20 min and at room temperature overnight, 1 M aqueous potassium sodium tartarate was added. The mixture was stirred at 0 °C for 1 h and extracted with $CHCl_3$. The combined organic layer was washed with brine and dried over Na_2SO_4. Filtration and concentration gave a residue, which was subjected to flash chromatography on silica gel ($CHCl_3$−MeOH) to afford 39.4 mg (84%) of the alcohol as a colorless oil. To a solution of this alcohol (39.4 mg, 0.056 mmol) in dry CH_2Cl_2 (2 mL) and DMSO (1 mL) were added Et_3N (55 μL, 0.39 mmol) and SO_3-pyridine complex (35.4 mg, 0.22 mmol) at 0 °C. After the mixture was stirred at 0 °C for 2 h and at room temperature for 1 h, EtOAc (20 mL) was added. Washing with H_2O, 5% aqueous $KHSO_4$, and brine, drying over Na_2SO_4, and concentration gave a crude residue, which was chromatographed on silica gel ($CHCl_3$−MeOH) to afford 33.8 mg (86%) of aldehyde **19a** as an oil: $[\alpha]^{22}_D$ +11.7 (*c* 0.35, MeOH); IR (film) 3313, 3302, 1708, 1699, 1633, 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.82 and 9.75 (m, 1H), 7.1−6.9 (brm, 1H), 5.46 (m, 1H), 5.33 (m, 1H), 3.87 (m, 1H), 3.65−3.53 (brm, 2H), 3.40−3.11 (m, 8H), 2.76 and 2.72 (m, 2H), 2.56−2.27 (m, 6H), 1.98 (m, 2H), 1.70−1.50 (m, 8H), 1.40 (m, 2H), 1.39 (brs, 9H), 1.33−1.20 (m, 12H), 1.08 (m, 6H), 0.85 (m, 9H); MS (FAB, *m*-nitrobenzyl alcohol) *m*/*z* 707 $(M + H)^+$, 607 $(M - Boc + H)^+$.

(4*R*)-Lipogrammistin-A (1a). A solution of aldehyde **19a** (29.2 mg, 0.0413 mmol) in dry CH_2Cl_2 (3 mL) and TFA (1 mL) was stirred at room temperature for 20 min. Concentration gave a residue that was dissolved in dry MeOH (120 mL). To this solution were added MS3A (10 g) and Et_3N to adjust the pH of the solution to 7. After the solution was stirred at room temperature overnight, $NaBH_3CN$ (26 mg, 0.41 mmol) was added. The mixture was stirred at room temperature for 72 h and filtered through a Celite pad, followed by addition of water. The mixture was extracted with EtOAc, and the extract was dried over Na_2SO_4. Concentration and chromatography on alumina (neutral, activity II, 2 g, $CHCl_3$) gave a crude residue, which was further purified by HPLC (ODS, YMC AM-323, 10 × 250 mm, CH_3CN-H_2O−TFA 60:40:0.05) to afford 5.7 mg (23%) of **1a**: $[\alpha]^{30}_D$ +18 (*c* 0.06, MeOH); ^1H NMR (500 MHz, CD_3OD containing 1% TFA-*d*) δ 5.69 (m, 1H), 5.34 (m, 1H), 3.66−3.25 (m, 8H), 3.20−3.08 (m, 3H), 2.81−2.64 and 2.56−2.41 (m, each 4H), 2.09 (brdd, 2H, J = 7, 7 Hz), 2.07−1.60 (m, 10H), 1.50−1.23 (m, 16H), 1.09 (m, 6H), 0.90 (t, 3H, J = 7 Hz), 0.89 (m, 6H); MS (EI) data were identical to those of lipogrammistin-A.

Ethyl 14-[(3*S*,5*Z*)-3-[(*tert*-Butoxycarbonyl)amino]-5-tetradecenyl]-4,10-bis((2*S*)-2-methylbutyryl)-4,10,14-triazatetradecanoate (18b). To a mixture of carboxylic acid (+)-**3** (132.2 mg, 0.388 mmol) and HOBt (90.0 mg, 0.589 mmol) in dry CH_2Cl_2 (5 mL) were added successively amine **4** (211.5 mg, 0.495 mmol) in dry CH_2Cl_2 (8 mL) and WSCI (111.5 mg, 0.582 mmol). After being stirred at room temperature overnight, the mixture was diluted with EtOAc and washed with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Filtration and concentration gave a residue, which was chromatographed on silica gel ($CHCl_3$−MeOH) to afford (256.4 mg, 88%) of **18b** as a colorless oil: $[\alpha]^{25}_D$ +17.7 (*c* 0.59, $CHCl_3$); IR (film) 3307, 1734, 1711, 1643, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.07 (brt), 7.00 (brt), 6.88 (m), and 6.79 (m) (1H for four signals), 5.45 (m, 1H), 5.27 (m, 1H), 4.13 and 4.09 (each q, 2H, J = 7 Hz), 3.89 (brm, 1H), 3.60 and 3.51 (m, 2H), 3.45−3.15 (m, 6H), 3.10 (m, 2H), 2.60−2.45 (m, 4H), 2.38 (br, 2H), 2.28 (brt, 2H), 1.97 (m, 2H), 1.70−1.50 (m, 8H), 1.39 (s, 9H), 1.39 (m, 2H), 1.33−1.26 (m, 17H), 1.07 (m, 6H), 0.85 (m, 9H); MS (FAB, *m*-nitrobenzyl alcohol) *m*/*z* 751 $(M + H)^+$, 651 $(M - Boc + H)^+$.

14-[(3*S*,5*Z*)-3-[(*tert*-Butoxycarbonyl)amino]-5-tetradecenyl]-4,10-bis((2*S*)-2-methylbutyryl)-4,10,14-triazatetradecanal (19b). To a solution of **18b** (131.8 mg, 0.176 mmol) in THF (5 mL) and MeOH (14 μL) was added $LiBH_4$ (8 mg, 0.38 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then at room temperature overnight. Additional $LiBH_4$ (8 mg, 0.38 mmol) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with 1 M aqueous potassium sodium tartarate (2 mL). The mixture was stirred for 1 h at 0 °C and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a crude residue, which was subjected to flash chromatography on silica gel ($CHCl_3$−MeOH) to afford 120.8 mg (97%) of the alcohol. A part of this alcohol (99.9 mg, 0.141 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and DMSO (1 mL). To this solution were added Et_3N (138 μL, 0.99 mmol) and SO_3-pyridine complex (89.8 mg, 0.56 mmol) at 0 °C. After the mixture was stirred for 2 h at 0 °C and then at room temperature for 1 h, EtOAc (30 mL) was added. Washing with H_2O, 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, drying over Na_2SO_4, and concentration gave a crude residue, which was subjected to flash chromatography on silica gel ($CHCl_3$−MeOH) to afford 74.0 mg (74%) of **19b** as an oil: $[\alpha]^{22}_D$ +24.3 (*c* 1.48, MeOH); IR (film) 3313, 1705, 1701, 1697, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.82 and 9.75 (m, 1H), 7.1−6.9 (brm, 1H), 5.46 (m, 1H), 5.33 (m, 1H), 3.87 (m, 1H), 3.65−3.53 (brm, 2H), 3.40−3.11 (m, 8H), 2.76 and 2.72 (m, 2H), 2.56−2.27 (m, 6H), 1.98 (m, 2H), 1.70−1.50 (m, 8H), 1.40 (m, 2H), 1.39 (brs, 9H), 1.33−

1.20 (m, 12H), 1.08 (m, 6H), 0.85 (m, 9H); MS (FAB, *m*-nitrobenzyl alcohol) *m*/*z* 707 $(M + H)^+$, 607 $(M - Boc + H)^+$.

(4*S*)-Lipogrammistin-A (1b). A solution of aldehyde **19b** (56.8 mg, 0.083 mmol) in dry CH_2Cl_2 (3 mL) and TFA (1 mL) was stirred at room temperature for 20 min. Concentration gave a residue that was dissolved in dry MeOH (100 mL). To this solution were added MS3A (5 g) and Et_3N to adjust the pH of the solution to 7. After the solution was stirred at room temperature overnight, $NaBH_3CN$ (50 mg, 0.80 mmol) was added. The mixture was stirred at room temperature for 72 h and filtered through a Celite pad, followed by addition of water. The mixture was extracted with EtOAc and the extract was dried over Na_2SO_4. Concentration and chromatography on alumina (neutral, activity II, 2 g, $CHCl_3$) gave a crude residue, which was further purified by HPLC (ODS, YMC AM-323, 10 × 250 mm, CH_3CN-H_2O−TFA, 60:40:0.05) to afford 3.4 mg (7%) of **1b**: $[\alpha]^{30}_D$ +11 (*c* 0.03, MeOH); ^{1}H NMR (500 MHz, CD_3OD containing 1% TFA-*d*) δ 5.69 (m, 1H), 5.34 (m, 1H), 3.55−3.25 (m, 8H), 3.23−3.04 (m, 3H), 2.81−2.64 and 2.56−2.41 (m, each 4H), 2.09 (brdd, 2H, J = 7, 7 Hz), 2.07−1.60 (m, 10H), 1.50−1.23 (m, 16H), 1.09 (m, 6H), 0.90 (t, 3H, J = 7 Hz), 0.89 (m, 6H); MS (EI) data were identical to those of lipogrammistin-A.

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Supporting Information Available: ^{1}H spectra of natural lipogrammistin-A, **1a**,**b**, **3**, **4**, **6**−**12**, **15**−**17**, **18a**,**b**, and **19a**,**b**; ^{13}C NMR spectra of **3**, **4**, **6**−**12**, **15**−**17**, and natural lipogrammistin-A at 300 and 333 K; mass spectra of natural lipogrammistin-A and **1a**,**b** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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