PERKIN 1

Synthesis of sphingosine relatives. Part 22.[1] Synthesis of sulfobacin A, B and flavocristamide A, new sulfonolipids isolated from *Chryseobacterium* sp.

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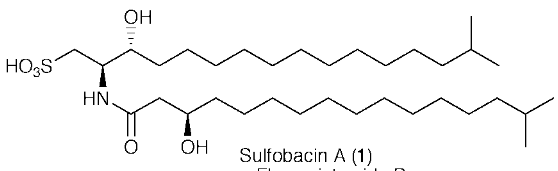
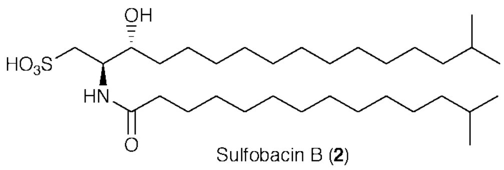
Sulfobacin A (**1**), B (**2**), and flavocristamide A (**3**), new sulfonolipids isolated from *Chryseobacterium* sp. were synthesized stereoselectively by starting from L-cysteine.

Introduction

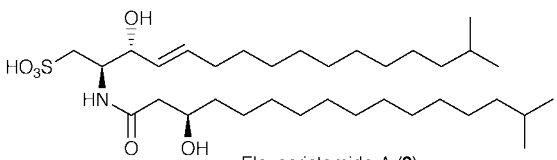
In 1995 sulfobacin A (**1**) and B (**2**), von Willebrand factor



Sulfobacin A (**1**)
= Flavocristamide B



Sulfobacin B (**2**)



Flavocristamide A (**3**)

receptor antagonists, were isolated by Kamiyama *et al.* from the culture broth of *Chryseobacterium* sp.[2] Almost simultaneously, the isolation of flavocristamide A (**3**) and B (= sulfobacin A, **1**), DNA polymerase α inhibitors, from the cultured mycelium of *Flavobacterium* sp. (= *Chryseobacterium* sp.) was reported by Kobayashi *et al.*[3] These compounds are novel sulfonolipids and are unusual sphingosine derivatives. Similar sulfonolipids, *N*-acyl-2-amino-3-hydroxy-15-methylhexadecane-1-sulfonic acids, were previously found in the cell envelope of gliding bacteria of the genera *Cytophaga*, *Capnocytophaga*, *Sporacytophaga* and *Flexibacter*.[4,5] Although a structurally similar sulfonolipid was previously synthesized by Kamikawa *et al.*,[6] the synthesis of these sulfonolipids (**1**, **2** and **3**) had not been reported. We therefore became interested in synthesizing these three compounds as a part of our work in preparing unusual sphingosine derivatives.[7] Recently, two syntheses of sulfobacins were reported as preliminary communications. The first one was carried out by Irako and Shioiri,[8] and the second was accomplished by us.[9] Herein we describe our improved synthesis of sulfobacins and the details of the first synthesis of flavocristamide A (**3**).

Results and discussion

Synthetic plan

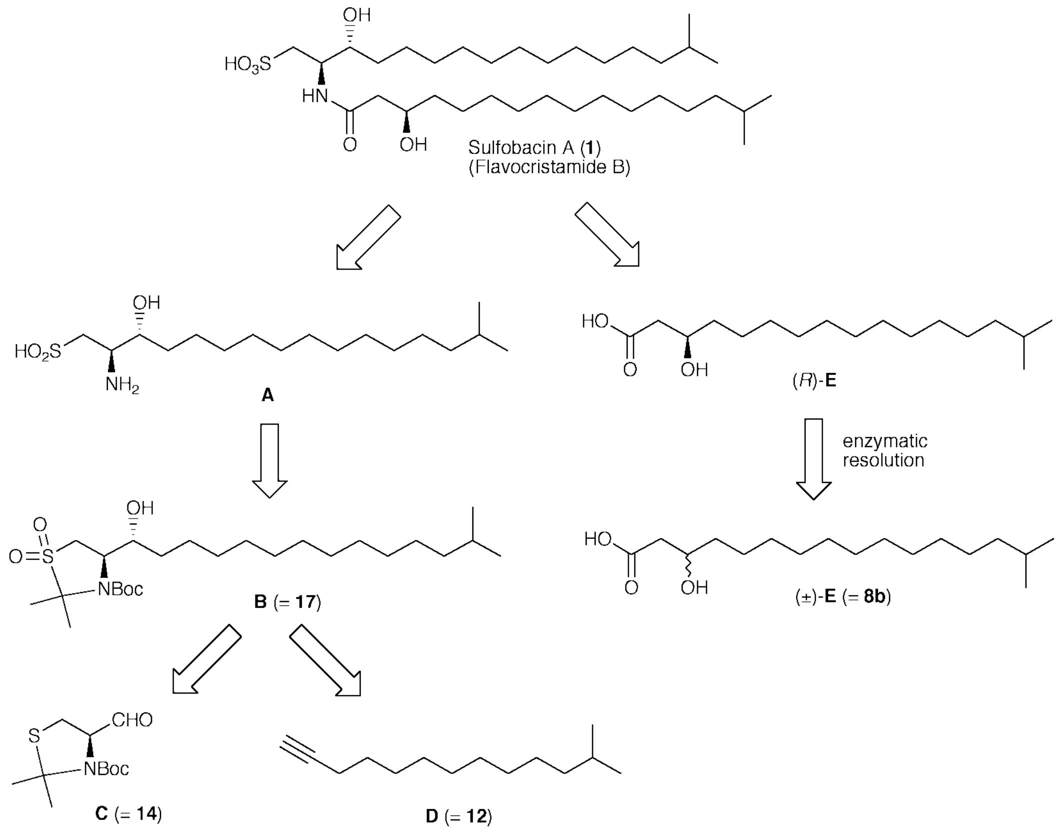
Scheme 1 shows our synthetic plan for **1**. The target compound **1** can be prepared from an aminosulfinic acid **A**, which is obtainable from the key intermediate **B**. Since the sulfone portion of **B** is a part of the acetonide group, this is considered a sulfinic acid equivalent. The key intermediate **B** may be synthesized by diastereoselective coupling of **C** with **D**. For the preparation of optically active **E**, we adopt enzymatic resolution. This synthetic plan could also be applicable for the synthesis of the other two target compounds (**2** and **3**).

Synthesis of the key intermediates B and E

First we synthesized the intermediate **E** (= **8b**) as follows. 10-Bromodecan-1-ol **4** was treated with isoamylmagnesium bromide in the presence of dilithium tetrachlorocuprate (Li_2CuCl_4) to give alcohol **5** (Scheme 2). This was then oxidized to give either the corresponding aldehyde **6** or the carboxylic acid **7**. The aldehyde **6** was treated with the lithium enolate of ethyl acetate followed by hydrolysis to give (±)-**8b** (= **E**). This racemate was resolved with lipase PS in the presence of vinyl acetate[10] to afford the desired (*R*)-**8b** in 28% yield, $[\alpha]_D^{23} = -12.7$ (*c* 1.02 in $CHCl_3$) {lit.[11] $[\alpha]_D^{20} = -12.0$ (*c* 1.0 in $CHCl_3$)}. The enantiomeric purity of (*R*)-**8** was estimated by GLC analysis on a chiral stationary phase to be ~100% ee. The hydroxy acid (*R*)-**8b** was then converted into the corresponding TBDMS ether **9**.

We then prepared the intermediate **D** (= **12**) as follows. Commercially available dec-9-en-1-ol **10a** was treated with toluene-*p*-sulfonyl chloride (TsCl), which was employed in a Grignard coupling with isobutylmagnesium bromide in the presence of Li_2CuCl_4 to afford **11**. Dibromination of **11** was followed by dehydrobromination[12] to give **12**.[13]

The known aldehyde **14**[14] (= **C**) was prepared from L-cysteine hydrochloride **13**. At that time we found that the enantiomeric purity of the obtained **14** (after chromatographic purification) was 93% ee, and that of the crude **14** was ~100% ee by HPLC analysis. The decrease of enantiomeric purity could be due to the partial racemization of aldehyde **14** in the course of the purification. We therefore decided to employ **14** in the next step without purification. Diastereoselective addition of lithium alkynide derived from 12-methyltridec-1-yne (**12**) to **14** was performed by Fujisawa's procedure[14] to give the desired *anti*-adduct **15** in 65% yield (2 steps) after chromatographic separation (*anti*:*syn* = *ca.* 6:1). The enantiomeric purity of **15** was determined by HPLC analysis to be 95% ee. After reduction of the triple bond, the sulfur atom at the thiazolidine ring was oxidized with MCPBA to afford the key intermediate **17** (= **B**). At this stage an alternative route to **17** was also examined. The known ester **18**[15] was oxidized with MCPBA to give **19**. First we attempted to prepare aldehyde **21** by the reduction of **19** with DIBAL-H. Although the reaction proceeded cleanly, the enantiomeric purity of the resulting **21** (after chromatographic



Scheme 1 Synthetic plan for **1**.

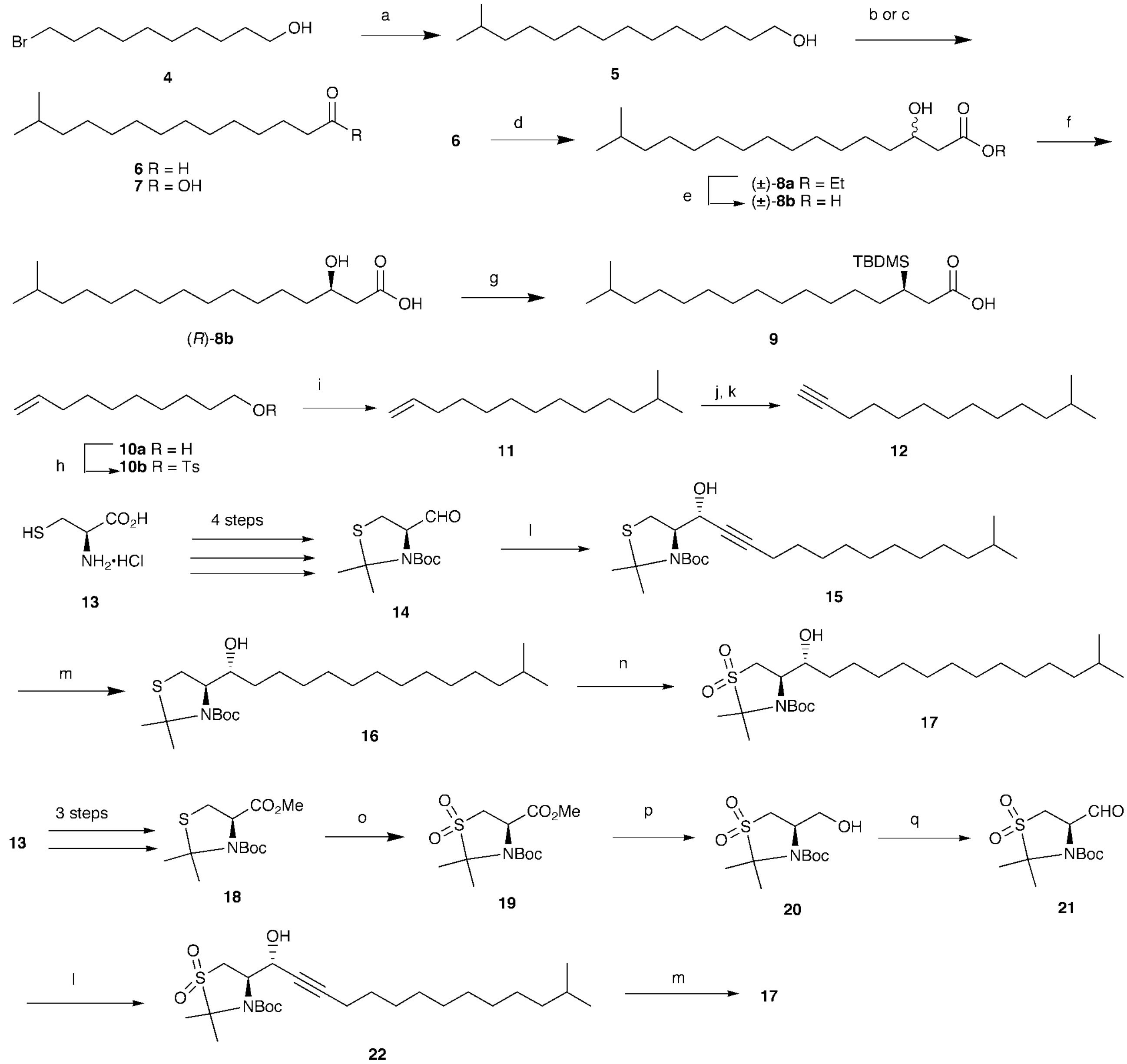
purification) was <20% ee and that of the crude **21** was *ca.* 60% ee. The following reduction–oxidation sequence was therefore chosen. The ester **19** was reduced with LAH, which was followed by oxidation with Dess–Martin periodinane[16] to give aldehyde **21**. The enantiomeric purity of the resulting **21** (without purification) was estimated to be ~100% ee by HPLC analysis. This aldehyde **21** was immediately employed in diastereoselective addition of lithiated **12** to give **22** in 65% yield under the same conditions as for the preparation of **15**. Although the chemical yield was moderate, the diastereoselectivity was excellent (*anti* : *syn* = 99 : 1). Several attempts were made in vain to improve the yield of **22** by using differently metallated **12**. The triple bond of **22** was then reduced to give **17**. The enantiomeric purity of **17** was estimated to be 97.8% ee by HPLC analysis. Judging from the overall efficiency, it was concluded that the latter procedure was more efficient and practical for the preparation of **17**.

Synthesis of sulfobacin A and B

The next step is one of the key steps in our synthesis. As mentioned in the synthetic plan, the sulfone portion of **17** (= **B**) is a part of the acetonide group and is thought of as a sulfinic acid equivalent. Therefore deprotection of the acetonide group should give the corresponding sulfinic acid. This idea was realized as follows. The cleavage of Boc and acetonide protecting groups of **17** was achieved by treatment with hydrochloric acid to give crystalline sultine **23**,[17] not sulfinic acid (**A**) (Scheme 3). The formation of the cyclic sulfinate was not expected but welcome to us nevertheless, because it also served as the protection for the hydroxy group. Moreover, the enantiomeric purity of **23** could be enriched to ~100% ee by recrystallization at this stage. The orientation of the oxygen atom on the sulfur atom of **23** was determined to be β on the basis of the similarity of its ^{1}H-NMR spectrum to that of **29a** (*vide infra*). The amino group of **23** was acylated with **7** in the presence of DCC to give the amide **24**. Hydrolysis of the sulfinate portion with aqueous ammonia was followed by oxidation with hydrogen peroxide to furnish sulfobacin B (**2**), $[\alpha]_D^{20} = -10.7$ (c 0.14 in MeOH) {lit.[2] $[\alpha]_D^{23} = -19$ (c 0.14 in MeOH)}. The overall yield of **2** was 28% prepared in 9 steps starting from **18**. Although the reason for the disagreement in the optical rotation value is not clear, the ^{1}H-NMR, ^{13}C-NMR, IR and mass spectra of synthetic **2** were in good accord with those reported. Indeed the direct comparison of our spectra with the copies of the spectra of the natural product fully supported the identity of our synthetic **2** as sulfobacin B.

By the same procedure as described above, sulfobacin A (**1**) was also synthesized. The aminosultine **23** was acylated with **9** to give **26a**. The deprotection of the TBS group of **26a** afforded **26b**. The resulting **26b** was converted to sulfobacin A (**1**) in 2 steps, $[\alpha]_D^{25} = -15$ (c 0.14 in MeOH), {lit.[2] $[\alpha]_D^{24} = -35$ (c 0.14 in MeOH), lit.[3] $[\alpha]_D^{20} = -7.9$ (c 0.18 in MeOH)}. The overall yield of **1** was 22% prepared in 10 steps starting from **18**. The optical rotation value of synthetic **1** was not in good accord with those of Kamiyama's[2] and Kobayashi's.[3] To clarify the reason for the disagreement, we remeasured the optical rotation value of natural **1** kindly supplied by Kamiyama. It was not identical with that reported, $[\alpha]_D^{18} = -8.1$ (c 0.10 in MeOH). The optical rotation value of this type of compounds seems to be sensitive to temperature, pH and/or concentration. In addition, we prepared the sodium salt of **1** according to Kobayashi's advice and measured its optical rotation value. This was in good accord with that of Kobayashi's, $[\alpha]_D^{24} = -9.0$ (c 0.10 in MeOH). The ^{1}H-NMR data of synthetic **1** was also slightly different from those reported.[2,3] We therefore remeasured ^{1}H-NMR spectra of Kamiyama's natural **1** and our synthetic **1** under almost the same conditions. These two spectra were superimposable supporting the conclusion that our synthetic **1** was identical with Kamiyama's natural **1**. The ^{13}C-NMR, IR and mass spectra of synthetic **1** were also in good accord with those of Kamiyama's. We then measured ^{1}H-NMR spectrum of the sodium salt of synthetic **1**, and it was in good accord with that of Kobayashi's.

It was therefore concluded that Kamiyama's group isolated



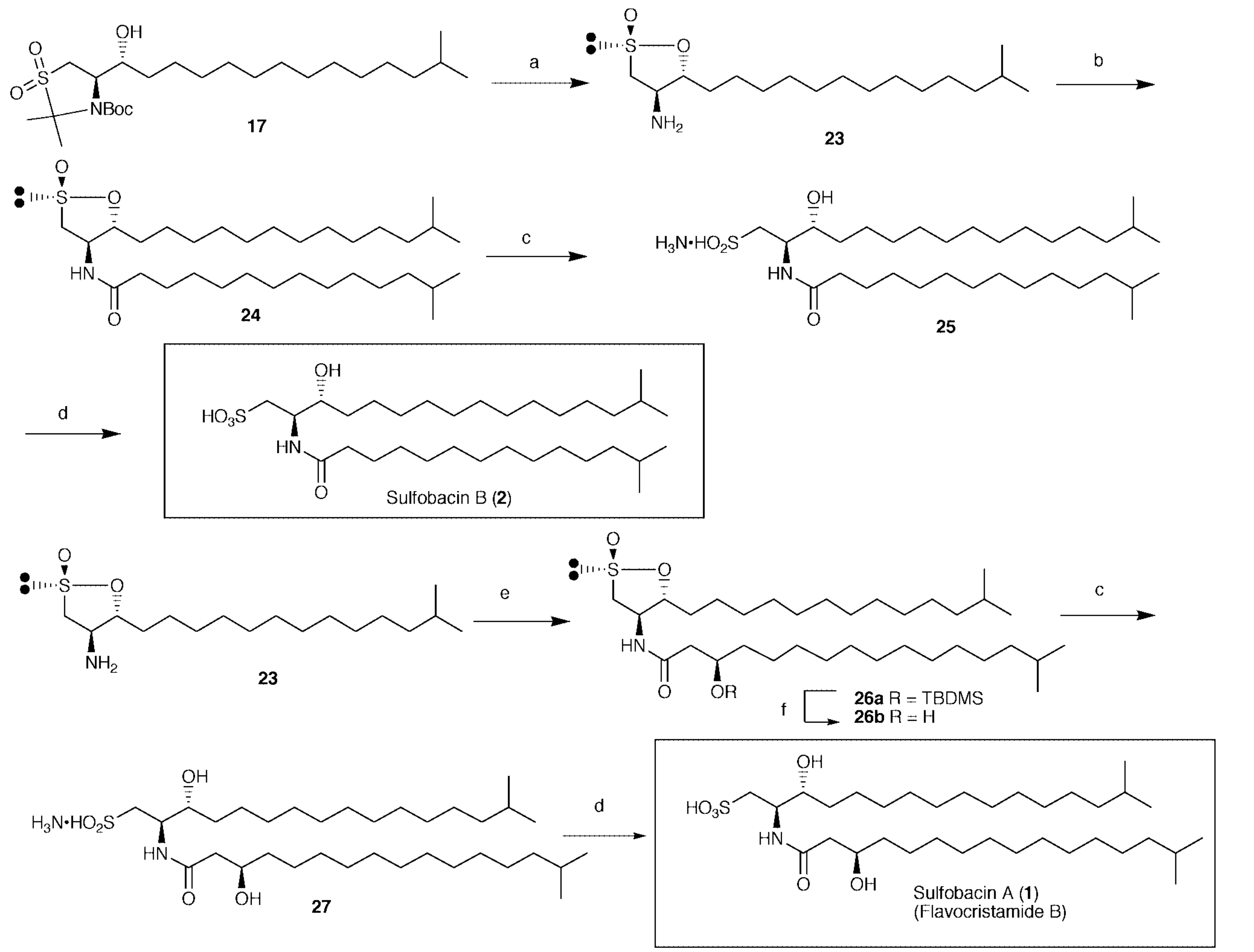
Scheme 2 Synthesis of **1** and **2**—(1). *Reagents*, *conditions and yields*: (a) $Me_2CH(CH_2)_2MgBr$, Li_2CuCl_4, THF (96%); (b) PCC, MS 4 Å, CH_2Cl_2 (78%); (c) Jones' CrO_3, acetone (70%); (d) EtOAc, LDA, THF (79%); (e) LiOH, aq MeOH–THF (86%); (f) lipase PS, vinyl acetate, BHT, 60 °C (28%, ~100% ee); (g) TBDMSCl, imidazole, DMF, then dilute HCl (82%); (h) TsCl, pyridine (quantitative); (i) Bu^iMgBr, Li_2CuCl_4, THF (94%, 2 steps); (j) Br_2, CH_2Cl_2; (k) Bu^tOK, 18-crown-6, petroleum ether (72%, 2 steps); (l) Bu^nLi, 12-methyltridec-1-yne (**12**), HMPA, THF (65% for **15** and 65% for **22**); (m) PtO_2, H_2, EtOAc (97% for **16** and 97% for **17**); (n) MCPBA, $CHCl_3$ (95%); (o) MCPBA, CH_2Cl_2 (99%); (p) LAH, THF (81%); (q) Dess–Martin periodinane (quantitative).

sulfobacin A as the free sulfonic acid and Kobayashi's group isolated flavocristamide B (= sulfobacin A) as its sodium salt.

Synthesis of flavocristamide A

The next subject we addressed was the synthesis of flavocristamide A (**3**). Attempts were initially made to prepare the intermediate **28** by reduction of **22**. Although a variety of reduction conditions were examined, we could not find any appropriate conditions. We therefore turned our attention to using nucleophilic addition of alkenylmetal to **21** and carried out a series of experiments as shown in Table 1. The same conditions employed for the synthesis of **17** and **22** gave the desired diastereomer **28**, although the chemical yield was less than 30% (Scheme 4). We therefore tried to use different alkenylmetals under various conditions (Table 1). As a result, the conditions listed in entry 5 were selected as those optimal to obtain **28**.

Diastereoselective addition of 12-methyltridec-1-enylmagnesium bromide to **21** gave **28** in 67% yield. The diastereoselectivity was estimated by HPLC analysis to be *anti*:*syn* = 96:4. Cleavage of the Boc and the acetonide protecting groups of **28** gave aminosultines **29a** and **29b** as a mixture (*ca.* 4:1) in 96% yield. Based on the careful comparison of their ^{1}H-NMR spectra, the less polar and major product was thought to be **29a**, while the other was **29b**. MM3 calculations also supported our hypothesis. This mixture was acylated with **9** and then the products were separated by silica gel column chromatography to give amides **30a** and **30b** in 49% and 14% yield respectively. In the same manner as mentioned before, the two isomers **30a** and **30b** were finally converted to flavocristamide A (**3**), $[\alpha]_D^{22} = -21$ (*c* 0.27, MeOH) {lit.[2] $[\alpha]_D^{20} = -17$ (*c* 0.27, MeOH)}. The overall yield of **3** was 19% prepared in 9 steps starting from **18**. The sodium salt of **3** was then prepared, $[\alpha]_D^{18} = -16$ (*c* 0.10 in MeOH). Although the ^{1}H-NMR spectrum of synthetic **3** (sulfonic acid) was slightly different from that reported, that of the sodium salt was in good accord with the reported data. The ^{13}C-NMR, IR and mass spectra of synthetic **3** were also in good accord with those reported.



Scheme 3 Synthesis of **1** and **2**—(2). *Reagents, conditions and yields*: (a) 6 M HCl, MeOH (80%); (b) **7**, DCC, $CHCl_3$ (71%); (c) aq NH_3, $CHCl_3$–MeOH; (d) aq H_2O_2 (99% for **2** and 98% for **1**, 2 steps); (e) **9**, DCC, $CHCl_3$ (64%); (f) TBAF, THF (85%).

Table 1 Diastereoselective addition of (*E*)-12-methyltridec-1-enylmetal to **21**

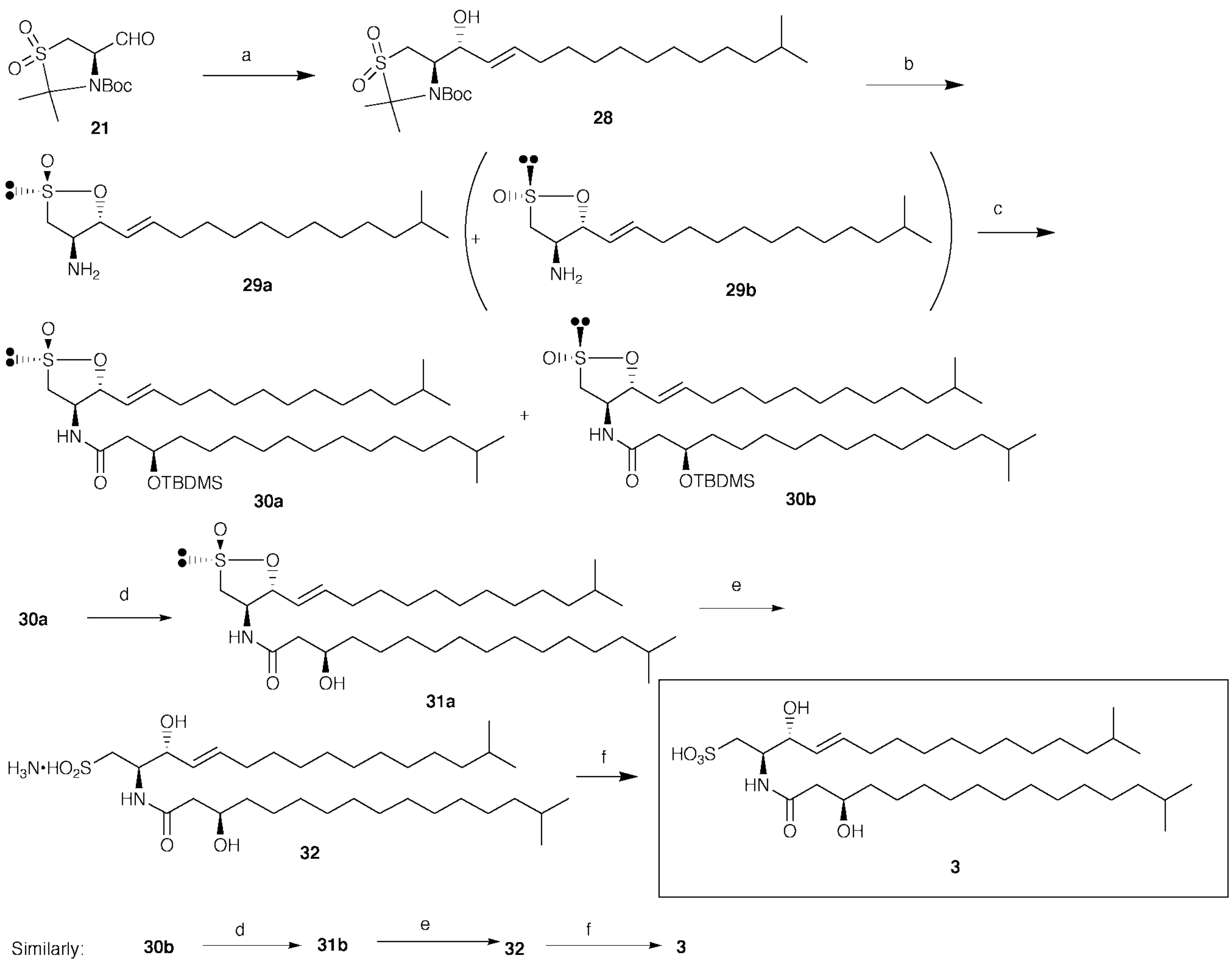
Entry	Metal[a]	Solvent	Additive	Temp./°C	Time	Yield[b] (%)	Ratio[c] (*anti*:*syn*)
1	Li	Et_2O	HMPA	−78	15 min	29[d]	>99:<1
2	$Al(^iBu)_2$[e]	Et_2O	none	−78–25	12 h	36[f]	25:75
3	$Al(^iBu)_2$[e]	Et_2O	HMPA	−78–25	12 h	5[g]	92:8
4	MgBr[h]	Et_2O–THF	none	−78	15 min	75	86:14
5	MgBr[h]	Et_2O–THF	HMPA	−78	15 min	75	96:4
6	$CeCl_2$[i]	Et_2O–THF	none	−78	1 h	0[j]	—

[a] (*E*)-12-Methyltridec-1-enylmetal was used as the nucleophile. [b] Isolated yield as a mixtute of *syn* and *anti* isomers. [c] The ratio of *anti*:*syn* was estimated by HPLC analysis of compound **17** after reduction of the double bond. [d] **21** was not recovered. [e] Prepared by the treatment of **12** with DIBAL-H. [f] The amount of recovered **21** was ~60%. [g] The amount of recovered **21** was >80%. [h] See Experimental section. [i] Prepared by the same metal exchange method as entries 4 and 5. [j] The amount of recovered **21** was ~20%.

In summary, the syntheses of new sulfonolipids sulfobacin A (**1**), B (**2**) and flavocristamide A (**3**) were achieved by starting from L-cysteine. We have clarified that sulfobacin A (**1**) and B (**2**) isolated by Kamiyama and his co-workers were sulfonic acids and that flavocristamide A (**3**) and B (= sulfobacin A, **2**) isolated by Kobayashi and his co-workers were sodium salts.

Experimental

All mps and bps are uncorrected. All mps were measured on a Yanaco micro melting point apparatus. IR spectra were measured on a JASCO A-102 spectrometer as films for oils or as Nujol mulls and KBr disks for solids. ^{1}H-NMR spectra were recorded at 90 MHz on a JEOL JNM-EX 90A spectrometer, at 400 MHz on a JEOL JNM-LA400 spectrometer and at 500 MHz on a JEOL JNM-LA500. The peak for TMS, $CDCl_3$ (at δ 7.26), DMSO-d_6 (at δ 2.49) or CD_3OD (at δ 3.30) was used for the internal standard. Chemical shifts are reported in ppm on the δ scale, and J values are given in Hz. ^{13}C-NMR spectra were recorded at 100 MHz on a JEOL JNM-LA400 spectrometer and at 126 MHz on a JEOL JNM-LA500. The peak for $CDCl_3$ (at δ 77.0), DMSO-d_6 (at δ 39.5) or CD_3OD (at δ 49.0) was used as internal standard. Optical rotations were taken with a JASCO DIP-1000 polarimeter $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were measured with a JEOL JMS-SX102A spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734. TLC analyses were performed on Merck silica gel plates 60F-254.



Scheme 4 Synthesis of **3**. *Reagents, conditions and yields*: (a) (*E*)-12-methyltridec-1-enylmagnesium bromide, HMPA, THF (67%, 2 steps); (b) 3 M HCl, MeOH (96%); (c) **9**, DCC, DMAP, $CHCl_3$ (49% for **30a** and 14% for **30b**); (d) TBAF, THF (59% for **31a** and 62% for **31b**); (e) aq NH_3, $CHCl_3$–MeOH; (f) aq H_2O_2 (95% based on **31a** or **31b**, 2 steps).

13-Methyltetradecan-1-ol 5

To a stirred and cooled solution of **4** (20.0 g, 84.3 mmol) in dry THF (200 cm^3) was added a solution of $(Me)_2CH(CH_2)_2MgBr$ in dry THF (1.32 mol dm^{-3}; 239 cm^3, 316 mmol) followed by a solution of Li_2CuCl_4 in dry THF (0.2 mol dm^{-3}; 5 cm^3, 1 mmol) at −78 °C under Ar. The resulting mixture was allowed to warm to room temperature with stirring overnight. After the reaction mixture was quenched with saturated aq. NH_4Cl, it was extracted with ethyl acetate. The extract was washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **5** (18.5 g, 96%) as a colorless oil, n_D^{25} 1.4462 (Found: C, 78.47; H, 14.19. $C_{15}H_{32}O$ requires C, 78.87; H, 14.12%); ν_{max}(film)/cm^{-1} 3370s (OH), 1055m (C–O), 760s; δ_H(400 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.8, $CH(CH_3)_2$), 1.15–1.65 (24H, m, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11- and 12-H_2, 13-H and OH), 3.64 (2H, q, *J* 6.1, 1-H_2).

13-Methyltetradecanal 6

A solution of **5** (21.8 g, 95.5 mmol) in dry CH_2Cl_2 (150 cm^3) was added dropwise to a stirred suspension of PCC (29.0 g, 134 mmol) and powdered MS 4 Å (20 g) in dry CH_2Cl_2 (150 cm^3). After having been stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. The residue in Et_2O was filtered through SiO_2, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *aldehyde* **6** (16.9 g, 78%) as a colorless oil, n_D^{25} 1.4408; ν_{max}(film)/cm^{-1} 2720w (CHO), 1725s (C=O), 755s; δ_H(90 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.2, $CH(CH_3)_2$), 1.10–1.65 (21H, m, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11- and 12-H_2 and 13-H), 2.41 (2H, t, *J* 6.6, 2-H_2), 9.76 (1H, t, *J* 1.8, CHO). This was employed in the next step without further purification.

13-Methyltetradecanoic acid 7

To a stirred and cooled solution of **6** (1.00 g, 4.38 mmol) in acetone (10 cm^3) was added Jones' CrO_3 reagent (2.69 mol dm^{-3}; 3.1 cm^3, 8.3 mmol) dropwise at 0 °C and the reaction mixture was stirred at room temperature for 1 h. After the reaction mixture was quenched with propan-2-ol, it was extracted with ethyl acetate. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *acid* **7** (744 mg, 70%) as a colorless solid, mp 43–46 °C (lit.,[11] 52 °C); ν_{max}(Nujol)/cm^{-1} 1700s (C=O), 930m; δ_H(90 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.2, $CH(CH_3)_2$), 1.00–1.70 (21H, m, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11- and 12-H_2 and 13-H), 2.35 (2H, t, *J* 6.8, 2-H_2).

Ethyl (±)-3-hydroxy-15-methylhexadecanoate (±)-8a

LDA was prepared from diisopropylamine (11.6 cm^3, 81.8 mmol) and Bu^nLi (1.59 mol dm^{-3} in hexane; 51.5 cm^3, 81.9 mmol) in dry THF (80 cm^3) under Ar. Ethyl acetate (8.0 cm^3, 82 mmol) was added dropwise to the LDA solution at −78 °C. After the mixture was stirred for 30 min at this temperature, a solution of **6** (16.5 g, 72.9 mmol) in dry THF (100 cm^3) was added dropwise at −78 °C. After having been stirred for 10 min, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with ethyl acetate. The extract was washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *hydroxy ester* (±)-**8a** (18.2 g, 79%) as a colorless oil, n_D^{25} 1.4448 (Found: C, 72.69; H, 12.32. $C_{19}H_{38}O_3$ requires C, 72.56; H, 12.18%); ν_{max}(film)/cm^{-1} 3470m (OH), 1720s (C=O), 1180s, 1025m, 755m; δ_H(400 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.10–1.60 (26H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13- and 14-H$_2$, 15-H and OCH$_2$C*H*$_3$), 2.39 (1H, dd, *J* 16.6 and 9.0, 2-H$_a$), 2.50 (1H, dd, *J* 16.6 and 3.0, 2-H$_b$), 2.92 (1H, d, *J* 3.9, OH), 3.99 (1H, m, 3-H), 4.17 (2H, q, *J* 7.2, OC*H*$_2$CH$_3$).

(±)-3-Hydroxy-15-methylhexadecanoic acid (±)-8b

To a stirred solution of (±)-**8a** (16.4 g, 52.2 mmol) in THF (100 cm^3) and MeOH (50 cm^3) was added aq. LiOH (1 mol dm^{-3}; 60 cm^3, 60 mmol) at room temperature. After having been stirred overnight, the reaction mixture was concentrated under reduced pressure. The residue was poured into ethyl acetate, acidified with dilute aq. HCl to pH 3, and extracted with ethyl acetate. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was recrystallized from hexane to give the *hydroxy acid* (±)-**8b** (12.8 g, 86%) as colorless plates, mp 59–61 °C; ν_{max}(KBr)/cm^{-1} 3470m (OH), 2900s (CH), 2690m, 2580m, 1720s (C=O), 910m; δ_H(400 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.10–1.60 (23H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13- and 14-H$_2$ and 15-H), 2.47 (1H, dd, *J* 16.6 and 9.0, 2-H$_a$), 2.58 (1H, dd, *J* 16.6 and 3.2, 2-H$_b$), 4.02 (1H, m, 3-H); these spectral data were identical with those reported for (*R*)-**8b**.[11]

(*R*)-3-Hydroxy-15-methylhexadecanoic acid (*R*)-8b

To a stirred solution of (±)-**8b** (2.00 g, 6.98 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (20 mg) in vinyl acetate (30 cm^3) was added lipase PS (1.00 g), and the mixture was stirred at 60 °C for 48 h. After cooling, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on SiO_2, and the resulting solid was recrystallized from hexane to give the *hydroxy acid* (*R*)-**8b** (562 mg, 28%) as colorless plates, mp 55–57 °C; $[a]_D^{23}$ −12.7 (*c* 1.02 in $CHCl_3$) {lit.[11] $[a]_D^{20}$ = −12.0 (*c* 1.0 in $CHCl_3$)} (Found: C, 70.82; H, 11.86. $C_{17}H_{34}O_3$ requires C, 71.28; H, 11.96%); IR and ^{1}H NMR spectra were identical with those of (±)-**8b**.

Determination of the enantiomeric purity of (*R*)-8b

A small amount of (*R*)-**8b** was converted to the methyl ester by treatment with diazomethane. The resulting methyl ester was analyzed by GLC to determine its enantiomeric purity. GLC analysis [column: Chirasil-DEX® CB (0.25 mm × 25 m, 180 °C; carrier gas: He, pressure 110 kPa)]. t_R/min 50.0 [no peak, methyl ester of (*S*)-**8b**], 51.0 [100%, methyl ester of (*R*)-**8b**]. The enantiomeric purity of (*R*)-**8b** was estimated to be ~100% ee.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)-15-methylhexadecanoic acid 9

To a stirred solution of (*R*)-**8b** (210 mg, 0.733 mmol) and imidazole (200 mg, 2.94 mmol) in DMF (5 cm^3) was added TBDMSCl (400 mg, 2.65 mmol) at room temperature. After having been stirred at room temperature for 3 h, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, and concentrated under reduced pressure. The residue was diluted with THF (5 cm^3). Then to the solution was added aq. HCl (0.2 mol dm^{-3}; 1 cm^3) and the mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *acid* **9** (246 mg, 82%) as a colorless oil, $[a]_D^{23}$ +1.35 (*c* 1.07 in $CHCl_3$); n_D^{26} 1.4479; ν_{max}(film)/cm^{-1} 1715s (C=O), 1255s (TBDMS), 1100m, 940m, 840s, 780s; δ_H(400 MHz; $CDCl_3$) 0.10 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.86 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 0.90 (9H, s, SiBu^t), 1.10–1.60 (23H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13- and 14-H$_2$ and 15-H), 2.49 (1H, dd, *J* 15.3 and 5.5, 2-H$_a$), 2.56 (1H, dd, *J* 15.3 and 5.1, 2-H$_b$), 4.08 (1H, quintet, *J* 5.7, 3-H). This was employed in the next step without further purification.

Dec-9-enyl toluene-*p*-sulfonate 10b

To a solution of dec-9-en-1-ol **10a** (21.7 g, 139 mmol) in pyridine (43 cm^3) and CH_2Cl_2 (60 cm^3), toluene-*p*-sulfonyl chloride (53.0 g, 208 mmol) was added at 0 °C. The mixture was stirred for 12 h at 4 °C. This mixture was poured into water and extracted with *n*-hexane. The extract was washed with water, dilute aq. HCl and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the *crude tosylate* **10b** (44.2 g, quantitative), ν_{max}(film)/cm^{-1} 3080m (C=CH$_2$), 1645m (C=C), 1600m (Ar), 1500m (Ar), 1360s (SO$_2$), 1190s (SO$_2$), 1180s (SO$_2$); δ_H(90 MHz; $CDCl_3$) 1.10–1.70 (12H, m, 2-, 3-, 4-, 5-, 6-, 7-H$_2$), 1.90–2.20 (2H, m, 8-H$_2$), 2.45 (3H, s, ArMe), 4.02 (2H, t, *J* 6.1, 1-H$_2$), 4.93 (1H, br d, *J* 1.2 and 17.3, 10-H), 4.96 (1H, br d, *J* 1.2 and 10.1, 10-H), 5.87 (1H, ddt, *J* 6.7, 10.1 and 17.3, 9-H), 7.34 (2H, d, *J* 8.4, Ar-H), 7.79 (2H, d, *J* 8.4, Ar-H). This was employed in the next step without further purification.

12-Methyltridec-1-ene 11

A dry THF solution of isobutylmagnesium bromide was prepared from isobutyl bromide (20.0 cm^3, 184 mmol) and magnesium (5.39 g, 222 mmol) in dry THF (165 cm^3). The resulting Grignard reagent and Li_2CuCl_4 (0.10 mol dm^{-3} in THF; 18 cm^3, 1.8 mmol) were added successively to a solution of tosylate **10b** (44.2 g, 142 mmol) in dry THF (200 cm^3) at −78 °C under Ar. This mixture was allowed to warm to room temperature with stirring overnight. After quenching with saturated aq. NH_4Cl, it was extracted with *n*-hexane. The extract was washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 and distilled to give the *alkene* **11** (25.5 g, 94% from **10a**) as a colorless oil, bp 84 °C/3.6 mmHg; n_D^{25} 1.4341 (Found: C, 85.80; H, 14.33. $C_{14}H_{28}$ requires C, 85.63; H, 14.37%); ν_{max}(film)/cm^{-1} 3080m (C=CH$_2$), 2975s (C=CH), 2940s (CH), 2850s (CH), 1645m (C=C), 995m (CH=CH$_2$), 910s (CH=CH$_2$); δ_H(90 MHz; $CDCl_3$) 0.89 (6H, d, *J* 6.1, CH(C*H*$_3$)$_2$), 1.26 (17H, br s, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-H$_2$ and 12-H), 1.90–2.20 (2H, m, 3-H$_2$), 4.93 (1H, br d, *J* 10.2, 1-H), 4.97 (1H, br d, *J* 17.2, 1-H), 5.83 (1H, ddt, *J* 6.7, 10.2 and 17.2, 2-H).

12-Methyltridec-1-yne 12

To a solution of **11** (2.71 g, 13.8 mmol) in dry CH_2Cl_2 (30 cm^3), bromine (0.78 cm^3, 15.2 mmol) was added and the mixture was stirred for 10 min at 0 °C. After quenching with saturated aq. $Na_2S_2O_3$, it was extracted with *n*-hexane. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 1,2-dibromo-12-methyltridecane (5.00 g, quantitative) as a colorless oil. This was employed in the next step without further purification. A small amount of this was chromatographed on SiO_2 to give an analytical sample as a colorless oil, n_D^{25} 1.4496 (Found: C, 47.40; H, 7.75. $C_{14}H_{28}Br_2$ requires C, 47.21; H, 7.92%); ν_{max}(film)/cm^{-1} 2940s (CH), 2860s (CH), 1460m (CH), 1430m, 1380m (CH), 1365m (CH); δ_H(400 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.15–1.60 (17H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-H$_2$ and 12-H), 1.73–1.83 (1H, m, 3-H), 2.10–2.21 (1H, m, 3-H), 3.63 (1H, t, *J* 10.1, 1-H), 3.85 (1H, dd, *J* 4.4 and 10.1, 1-H), 4.17 (1H, m, 2-H). To a solution of the dibromide (5.00 g, 14.0 mmol) in petroleum ether (70 cm^3), Bu^{t}OK (4.65 g, 41.4 mmol) and 18-crown-6 (11 mg, 0.041 mmol) were added and the mixture was stirred for 2 h under reflux. This mixture was poured into water and extracted with *n*-hexane. The extract was washed with dilute aq. HCl, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 and distilled to give the *alkyne* **12** (1.93 g, 72%) as a colorless oil, bp 75 °C/1.6 mmHg; n_D^{25} 1.4381 (Found: C, 86.56; H, 13.61. $C_{14}H_{26}$ requires C, 86.52; H, 13.48%); ν_{max}(film)/cm^{-1} 3340m (C≡CH), 2140w (C≡C); δ_H(90 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.2, $CH(CH_3)_2$), 1.00–1.65 (17H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-H_2 and 12-H), 1.93 (1H, t, *J* 2.7, 1-H), 2.05–2.30 (2H, m, 3-H_2).

tert-Butyl (4*R*,1′*R*)-4-(1′-hydroxy-13′-methyltetradec-2′-ynyl)-2,2-dimethyl-1,3-thiazolidine-3-carboxylate 15

To a stirred solution of **12** (1.39 g, 7.17 mmol) in dry THF (10 cm^3), Bu^{n}Li (1.54 mol dm^{-3} in *n*-hexane; 4.89 cm^3, 7.53 mmol) was added dropwise at −10 °C under Ar. After stirring for 30 min at 0 °C, a solution of **14** (0.88 g, 3.59 mmol) in dry THF (10 cm^3) and HMPA (3.74 cm^3) was added dropwise to this mixture at −78 °C. It was stirred for 15 min at −78 °C, quenched with saturated aq. NH_4Cl, and extracted with ethyl acetate. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **15** (1.03 g, 65%) as a colorless oil, $[\alpha]_D^{20}$ −26.2 (*c* 1.41 in $CHCl_3$); n_D^{24} 1.4849; ν_{max}(film)/cm^{-1} 3450m (OH), 2230w (C≡C), 1690s (C=O), 1460m, 1365s, 1170s; δ_H(90 MHz; $CDCl_3$) 0.85 (6H, d, *J* 6.1, $CH(CH_3)_2$), 1.05–1.40 (18H, m, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-H_2 and 13′-H and OH), 1.49 (9H, s, $OCMe_3$), 1.78 (3H, s, acetonide), 1.80 (3H, s, acetonide), 2.21 (2H, m, 4′-H), 3.21 (2H, m, SCH_2), 4.44 (1H, m, 4-H), 4.76 (1H, m, 1′-H) [Found: (HRFAB-MS) $(M - H)^+$ 440.3185. $C_{25}H_{46}NO_3S$ requires *m*/*z* 440.3198].

Determination of the enantiomeric and diastereomeric purity of 15

The enantiomeric purity of the resulting **15** was estimated by HPLC analysis. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, *n*-hexane–EtOH (100 : 1); flow, 0.3 cm^3 min^{-1}; detector at 210 nm]: t_R/min 17.67 [2.46%, (4*S*,1′*S*)-**15**], 19.16 [97.54%, (4*R*,1′*R*)-**15**]. The enantiomeric purity of **15** was estimated to be 95.1% ee. The diastereomeric purity of the resulting **15** was estimated by weighing the isolated isomers. The diastereomeric purity of **15** was estimated to be *ca*. 65% de.

tert-Butyl (4*R*,1′*R*)-4-(1′-hydroxy-13′-methyltetradecyl)-2,2-dimethyl-1,3-thiazolidine-3-carboxylate 16

A mixture of **15** (3.23 g, 7.35 mmol) and PtO_2 (300 mg) in ethyl acetate (25 cm^3) was stirred for 36 h at room temperature under H_2. This mixture was filtered through Celite and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **16** (3.17 g, 97%) as a colorless oil, $[\alpha]_D^{20}$ −17.4 (*c* 1.88 in $CHCl_3$); n_D^{24} 1.4761; ν_{max}(film)/cm^{-1} 3460s (OH), 1695s (C=O), 1670s, 1355s, 1175s; δ_H(90 MHz; $CDCl_3$) 0.85 (6H, d, *J* 6.4, $CH(CH_3)_2$), 1.00–1.35 (23H, m, 2′-, 3′-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-H_2 and 13′-H), 1.48 (9H, s, $OCMe_3$), 1.78 (6H, s, acetonide), 2.15 (1H, m, OH), 2.85–3.25 (2H, m, SCH_2), 3.93 (1H, m, 4-H), 4.31 (1H, m, 1′-H) [Found: (HRFAB-MS) $(M - H)^+$ 444.3516. $C_{25}H_{50}NO_3S$ requires *m*/*z* 444.3511].

tert-Butyl (4*R*,1′*R*)-4-(1′-hydroxy-13′-methyltetradecyl)-2,2-dimethyl-1,1-dioxo-1λ^6,3-thiazolidine-3-carboxylate 17 (from 16)

To a stirred solution of **16** (178 mg, 0.401 mmol) in $CHCl_3$ (3 cm^3) was added MCPBA (70% purity; 311 mg, 1.26 mmol) at 0 °C. After having been stirred at room temperature for 4 h, the reaction mixture was poured into 10% aq. Na_2SO_3 and extracted with $CHCl_3$. The extract was washed with saturated aq. $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **17** (182 mg, 95%) as a colorless oil, $[\alpha]_D^{20}$ −21.2 (*c* 1.03 in $CHCl_3$); n_D^{24} 1.4720; ν_{max}(film)/cm^{-1} 3530s (OH), 1710s (C=O), 1370s, 1320s (SO_2), 1170s, 1140s, 1100s (C–O), 1070s; δ_H(400 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.6, $CH(CH_3)_2$), 1.12–1.38 (23H, m, 2′-, 3′-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-H_2 and 13′-H), 1.50 (9H, s, $OCMe_3$), 1.66 (3H, s, acetonide), 1.69 (3H, s, acetonide), 2.04 (1H, m, OH), 3.15 (1H, dd, *J* 8.3 and 13.4, SO_2CHH), 3.51 (1H, dd, *J* 6.8 and 13.4, SO_2CHH), 4.17 (1H, m, 4-H), 4.25 (1H, m, 1′-H).

tert-Butyl (*R*)-4-methoxycarbonyl-2,2-dimethyl-1,1-dioxo-1λ^6,3-thiazolidine-3-carboxylate 19

To a stirred solution of **18** (10.1 g, 36.7 mmol) in $CHCl_3$ (150 cm^3) was added MCPBA (70% purity; 19.0 g, 110 mmol) at 0 °C. After having been stirred at room temperature for 12 h, the reaction mixture was poured into 10% aq. Na_2SO_3 and extracted with $CHCl_3$. The extract was washed with saturated aq. $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *ester* **19** (11.1 g, 99%) as a white solid. A small portion of **19** was further purified by recrystallization from *n*-hexane to give an analytical sample as colorless plates, mp 61–62 °C; $[\alpha]_D^{23}$ −43.1 (*c* 1.43 in $CHCl_3$) (Found: C, 46.82; H, 6.69; N, 4.56. $C_{12}H_{21}O_6NS$ requires C, 46.89; H, 6.89; N, 4.56%); ν_{max}(KBr)/cm^{-1} 1765s (C=O), 1715s (C=O); δ_H(90 MHz; $CDCl_3$) 1.47 (9H, s, $OCMe_3$), 1.73 (6H, s, acetonide), 3.42 (2H, d like, *J* 7.4, SO_2CH_2), 3.79 (3H, s, OMe), 4.81 (1H, br, NCH).

Determination of the enantiomeric purity of 19

The enantiomeric purity of the resulting **19** was estimated by HPLC analysis. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, *n*-hexane–Pr^{i}OH (9 : 1); flow, 0.4 cm^3 min^{-1}; detector at 210 nm]: t_R/min 39.80 [100%, (*R*)-**19**], 33.41 [no peak, (*S*)-**19**]. The enantiomeric purity of **19** was estimated to be ~100% ee.

tert-Butyl (*R*)-4-hydroxymethyl-2,2-dimethyl-1,1-dioxo-1λ^6,3-thiazolidine-3-carboxylate 20

A solution of **19** (4.00 g, 13.0 mmol) in THF (100 cm^3) was added dropwise to a stirred and cooled suspension of LAH (990 mg, 26.0 mmol) in THF (50 cm^3) at −20 °C, and the reaction mixture was stirred for 10 min. The excess LAH was destroyed by the addition of water (1 cm^3), 15% aq. NaOH (1 cm^3), and water (3 cm^3) at 0 °C. After having been stirred for 1 h, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was recrystallized from hexane to give the *alcohol* **20** (2.95 g 81%) as colorless plates, mp 112–114 °C; $[\alpha]_D^{24}$ −18.1 (*c* 1.15 in $CHCl_3$) (Found: C, 47.33; H, 7.44; N, 4.99. $C_{11}H_{21}O_5NS$ requires C, 47.30; H, 7.58; N, 5.01%); ν_{max}(Nujol)/cm^{-1} 3540m (OH), 3370w, 1690s (C=O); δ_H(400 MHz; $CDCl_3$) 1.51 (9H, s, $OCMe_3$), 1.67 (3H, s, acetonide), 1.68 (3H, s, acetonide), 2.34 (1H, br, OH), 3.27 (1H, dd, *J* 13.7 and 8.5, SO_2CHH), 3.47 (1H, dd, *J* 13.7 and 2.4, SO_2CHH), 3.75–3.90 (2H, m, CH_2OH), 4.40 (1H, m, NCH).

Determination of the enantiomeric purity of 20

The enantiomeric purity of the resulting **20** was estimated by HPLC analysis. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, *n*-hexane–Pr^{i}OH (9 : 1); flow, 0.5 cm^3 min^{-1}; detector at 210 nm]: t_R/min 24.7 [100%, (*R*)-**20**], 26.9 [no peak, (*S*)-**20**]. The enantiomeric purity of **20** was estimated to be ~100% ee.

tert-Butyl (*R*)-4-formyl-2,2-dimethyl-1,1-dioxo-1λ^6,3-thiazolidine-3-carboxylate 21

To a stirred solution of **20** (2.90 g, 10.5 mmol) in dry CH_2Cl_2

($50\ cm^3$) was added a suspension of Dess–Martin periodinane (6.69 g, 15.1 mmol) in dry CH_2Cl_2 ($50\ cm^3$) at room temperature. After having been stirred for 10 min, the reaction mixture was poured into Et_2O ($400\ cm^3$). A solution of saturated aq. $NaHCO_3$ ($100\ cm^3$) and 10% aq. $Na_2S_2O_3$ ($100\ cm^3$) was added to this mixture. After having been stirred for 10 min, it was extracted with ether. The extract was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the *crude aldehyde* **21** (2.93 g, quantitative), ν_{max}(film)/cm^{-1} 2850w (CHO), 1740s (C=O), 1690s (C=O); δ_H(90 MHz; $CDCl_3$) 1.51 (9H, s, $OCMe_3$), 1.72 (3H, s, acetonide), 1.76 (3H, s, acetonide), 3.30–3.60 (2H, m, SO_2CH_2), 4.45–4.70 (1H, m, NCH), 9.50 (1H, s, CHO). This was employed in the next step without further purification.

Determination of the enantiomeric purity of 21

A small amount of **21** was reduced with $NaBH_4$ to **20** and the resulting **20** was analyzed by HPLC. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, *n*-hexane–Pr^{i}OH (9:1); flow, 0.5 cm^3 min^{-1}; detector at 210 nm]: t_R/min 23.4 [100%, (*R*)-**20**], 26.3 [no peak, (*S*)-**20**]. The enantiomeric purity of **21** was estimated to be ~100% ee.

tert-Butyl (4*R*,1′*R*)-4-(1′-hydroxy-13′-methyltetradec-2′-ynyl)-2,2-dimethyl-1,1-dioxo-1λ^6,3-thiazolidine-3-carboxylate 22

To a stirred solution of **12** (273 mg, 1.41 mmol) in dry THF ($3\ cm^3$), Bu^{n}Li (1.54 mol dm^{-3} in *n*-hexane; 1.01 cm^3, 1.55 mmol) was added dropwise at 0 °C under Ar. After having been stirred for 30 min at 0 °C, a solution of **21** (260 mg, 0.937 mmol) in dry THF ($2\ cm^3$) and HMPA ($0.426\ cm^3$) was added dropwise to this solution at −78 °C. It was stirred for 15 min at −78 °C, quenched with saturated aq. NH_4Cl and extracted with ethyl acetate. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **22** (289 mg, 65% based on **20**) as a colorless oil, $[\alpha]_D^{25}$ −30.7 (*c* 1.33 in $CHCl_3$); n_D^{25} 1.4849 (Found: C, 63.47; H, 9.99; N, 2.82. $C_{25}H_{45}NO_5S$ requires C, 63.66; H, 9.62; N, 2.97%); ν_{max}(film)/cm^{-1} 3510m (OH), 2240w (C≡C), 1700s (C=O); δ_H(400 MHz; $CDCl_3$) 0.85 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.12–1.30 (17H, m, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-H$_2$ and 13′-H), 1.50 (9H, s, $OCMe_3$), 1.66 (3H, s, acetonide), 1.70 (3H, s, acetonide), 2.18 (2H, dt, *J* 2.0 and 7.2, 4′-H), 3.06 (1H, m, OH), 3.35 (1H, dd, *J* 8.5 and 13.8, SO_2C*H*H), 3.63 (1H, dd, *J* 6.9 and 13.8, SO_2CH*H*), 4.40 (1H, ddd, *J* 2.9, 6.9 and 8.5, 4-H), 4.93 (1H, dt, *J* 2.0 and 6.9, 1′-H).

Determination of the diastereomeric purity of 22

The diastereomeric purity of the resulting **22** was estimated by HPLC analysis. HPLC analysis [column, Pegasil Silica 60-5 (4.6 mm × 25 cm); solvent, *n*-hexane–THF (10:1); flow, 1.0 cm^3 min^{-1}; detector at 210 nm]: t_R/min 18.31 [99.30%, (4*R*,1′*R*)], 30.27 [0.70%, (4*R*,1′*S*)]. The diastereomeric purity of **22** was estimated to be 98.6% de.

tert-Butyl (4*R*,1′*R*)-4-(1′-hydroxy-13′-methyltetradecyl)-2,2-dimethyl-1,1-dioxo-1λ^6,3-thiazolidine-3-carboxylate 17 (from 22)

A mixture of **22** (285 mg, 0.604 mmol) and PtO_2 (6 mg) in ethyl acetate ($3\ cm^3$) was stirred for 12 h at room temperature under H_2. This solution was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **17** (278 mg, 97%) as a colorless oil, $[\alpha]_D^{23}$ −21.9 (*c* 1.05 in $CHCl_3$); n_D^{25} 1.4772 (Found: C, 63.05; H, 10.60; N, 3.02. $C_{25}H_{49}NO_5S$ requires C, 63.12; H, 10.38; N, 2.94%). Its IR and ^{1}H NMR spectra were identical with those of **17** from **16**.

Determination of the enantiomeric purity of 17

The enantiomeric purity of the resulting **17** was estimated by HPLC analysis. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, *n*-hexane–EtOH (20:1); flow, 0.5 cm^3 min^{-1}; detector at 210 nm]: t_R/min 15.36 [1.12%, (4*S*,1′*S*)-**17**], 20.41 [98.88%, (4*R*,1′*R*)]. The enantiomeric purity of **17** was estimated to be 97.8% ee.

(2*S*,4*R*,5*R*)-4-Amino-5-(12′-methyltridecyl)-1,2-oxathiolane 2-oxide 23

To a solution of **17** (1.01 g, 2.12 mmol) in MeOH ($10\ cm^3$) was added aq. HCl (6.0 mol dm^{-3}; 1 cm^3), and the reaction mixture was stirred for 12 h at 60 °C. After the reaction mixture was concentrated under reduced pressure, the residue was diluted with $CHCl_3$, and washed with saturated aq. $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 and recrystallized from *n*-hexane–$CHCl_3$ to give the *amine* **23** (0.541 g, 80%) as colorless plates, mp 75–77 °C; $[\alpha]_D^{21}$ +94.6 (*c* 1.05 in $CHCl_3$) (Found: C, 64.14; H, 10.88; N, 4.36. $C_{17}H_{35}NO_2S$ requires C, 64.30; H, 11.11; N, 4.41%); ν_{max}(KBr)/cm^{-1} 3395m (NH), 3300w (NH), 1605w, 1115s (S=O); δ_H(400 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.6, CH(C*H*$_3$)$_2$) 1.12–1.56 (23H, m, 1′-, 2′-, 3′-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-H$_2$ and 12′-H), 1.66 (2H, br s, NH_2), 2.97 (1H, dd, *J* 2.9 and 13.2, 3-H$_\beta$), 3.28 (1H, dd, *J* 7.9 and 13.2, 3-H$_\alpha$), 3.47 (1H, m, 4-H), 4.84 (1H, dt, *J* 4.6 and 7.8, 5-H).

Determination of the enantiomeric purity of 23

The enantiomeric purity of the resulting **23** was estimated by HPLC. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, *n*-hexane–EtOH–diethylamine (10:1:0.01); flow, 0.4 cm^3 min^{-1}; detector at 210 nm]: t_R/min 29.4 [100%, (4*R*,5*R*)], 26.4 [no peak, (4*S*,5*S*)-**23**]. The enantiomeric purity of **23** was estimated to be ~100% ee.

(2*S*,4*R*,5*R*)-4-(13′-Methyltetradecanoylamino)-5-(12″-methyltridecyl)-1,2-oxathiolane 2-oxide 24

To a solution of **23** (108 mg, 0.340 mmol) and **7** (87 mg, 0.36 mmol) in dry CH_2Cl_2 ($8\ cm^3$) was added DCC (74 mg, 0.36 mmol), and the reaction mixture was stirred for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *amide* **24** (131 mg, 71%) as a white solid, mp 83–85 °C; $[\alpha]_D^{21}$ +60.3 (*c* 1.03 in $CHCl_3$) (Found: C, 71.04; H, 11.54; N, 2.75. $C_{32}H_{63}NO_3S$ requires C, 70.92; H, 11.72; N, 2.59%); ν_{max}(KBr)/cm^{-1} 3320m (NHCO), 1645s (NHCO), 1535m (NHCO), 1120m (S=O), 1110m; δ_H(500 MHz; $CDCl_3$) 0.86 (12H, d, *J* 6.7, CH(C*H*$_3$)$_2$), 1.14 (4H, m, 12′- and 11″-H$_2$), 1.25 (34H, m, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 1″-, 2″-, 3″-, 4″-, 5″-, 6″-, 7″-, 8″-, 9″- and 10″-H$_2$), 1.40–1.71 (6H, m, 3′-, 4′-H$_2$ and 13′- and 12″-H), 2.16 (2H, t, *J* 7.6, 2′-H$_2$), 3.03–3.10 (2H, m, 3-H$_2$), 4.85–4.90 (2H, m, 4- and 5-H), 6.95 (1H, d, *J* 9.2, NH).

Ammonium (2*R*,3*R*)-3-hydroxy-2-(13′-methyltetradecanoylamino)-15-methylhexadecanesulfinate 25

To a solution of **24** (19 mg, 0.035 mmol) in $CHCl_3$ ($0.8\ cm^3$) and MeOH ($0.8\ cm^3$) was added 29% aq. NH_3 ($0.4\ cm^3$), and the reaction mixture was stirred at room temperature for 12 h. Then the reaction mixture was concentrated under reduced pressure to give the *crude sulfinate* **25** (20 mg, quantitative), δ_H(400 MHz; CD_3OD) 0.87 (12H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 1.15–1.60 (44H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 3′-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-H$_2$ and 15-, 13′-H), 2.17–2.20 (2H, m, 2′-H$_2$), 2.42–2.46 (1H, m, 1-H), 2.63–2.69 (1H, m, 1-H), 3.60–3.68 (1H, m, 3-H), 4.12 (1H, m, 2-H). This was employed in the next step without further purification.

(2*R*,3*R*)-3-Hydroxy-2-(13′-methyltetradecanoylamino)-15-methylhexadecanesulfonic acid (sulfobacin B) 2

To a suspension of **25** (20 mg) in water (2.0 cm^3) was added 30% aq. H_2O_2 (0.4 cm^3), and the reaction mixture was stirred for 12 h at room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was chromatographed on SiO_2 to give the *sulfonic acid* **2** (20 mg, 99% based on **24**) as a white solid, mp 201–203 °C; $[\alpha]_D^{22}$ −10.7 (*c* 0.14 in CH_3OH); ν_{max}(KBr)/cm^{-1} 3300m (OH and NH), 2940s (CH), 2860s (CH), 1650m (NHCO), 1550m (NHCO), 1470m (CH), 1385w (CH), 1365w (CH), 1200m (SO_2), 1065m (SO_2), 800w, 720w (CH); δ_H(400 MHz; DMSO) 0.83 (12H, d, *J* 6.8, $CH(CH_3)_2$), 1.12 (4H, m, 14- and 12′-H_2), 1.22 (34H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′- and 11′-H_2), 1.38–1.51 (6H, m, 3′-, 4′-H_2 and 15- and 13′-H), 2.01 (2H, t, *J* 7.1, 2′-H_2), 2.64 (1H, dd, *J* 14.2 and 4.4, 1-H_a), 2.76 (1H, dd, *J* 14.2 and 6.1, 1-H_b), 3.50 (1H, m, 3-H), 3.85 (1H, m, 2-H), 4.83 (1H, d, *J* 5.6, OH), 7.62 (1H, d, *J* 8.5, NH); δ_C(100 MHz; DMSO) 22.5, 25.3, 25.4, 26.8, 27.4, 28.6, 28.9, 29.1, 29.2, 29.3, 33.3, 35.8, 51.1, 51.8, 71.7, 171.6 [Found: (HRFAB-MS) $(M - H)^-$, 574.4517. $C_{32}H_{64}NO_5S$ requires *m*/*z* 574.4505].

(2*S*,4*R*,5*R*,3′*R*)-4-(3′-*tert*-Butyldimethylsilyloxy-15′-methylhexadecanoylamino)-5-(12″-methyltridecyl)-1,2-oxathiolane 2-oxide 26a

To a solution of **23** (150 mg, 0.472 mmol) and **9** (218 mg, 0.543 mmol) in dry CH_2Cl_2 (15 cm^3) was added DCC (107 mg, 0.519 mmol), and the reaction mixture was stirred for 30 min. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *amide* **26a** (210 mg, 64%) as a colorless oil, $[\alpha]_D^{22}$ +40.5 (*c* 0.97 in $CHCl_3$); n_D^{26} 1.4730 (Found: C, 68.54; H, 11.85; N, 1.66. $C_{40}H_{81}NO_4SSi$ requires C, 68.61; H, 11.66; N, 2.00%); ν_{max}(film)/cm^{-1} 3305m (NHCO), 1650m (NHCO), 1530m (NHCO); δ_H(500 MHz; $CDCl_3$) 0.04 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.85–0.89 (21H, m, $CH(CH_3)_2$ and Bu^t), 1.14 (4H, m, 14′- and 11″-H_2), 1.25 (38H, m, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′-, 1″-, 2″-, 3″-, 4″-, 5″-, 6″-, 7″-, 8″-, 9″- and 10″-H_2), 1.45–1.74 (4H, m, 4′-H_2 and 15′- and 12″-H), 2.26 (1H, dd, *J* 14.4 and 6.4, 2′-H_a), 2.34 (1H, dd, *J* 14.4 and 4.3, 2′-H_b), 2.98 (1H, d, *J* 13.1, 3-H_β), 3.14 (1H, dd, *J* 13.1 and 7.7, 3-H_α), 4.08 (1H, m, 3′-H), 4.79–4.87 (2H, m, 4- and 5-H), 7.17 (1H, d, *J* 9.2, NH).

(2*S*,4*R*,5*R*,3′*R*)-4-(3′-Hydroxy-15′-methylhexadecanoylamino)-5-(12″-methyltridecyl)-1,2-oxathiolane 2-oxide 26b

To a solution of **26a** (106 mg, 0.151 mmol) in THF (6 cm^3) was added TBAF (1.00 mol dm^{-3} in THF; 0.167 cm^3, 0.167 mmol) at 0 °C, and the reaction mixture was stirred for 45 min at room temperature. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **26b** (75 mg, 85%) as a white solid, mp 85–88 °C; $[\alpha]_D^{20}$ +49.6 (*c* 0.68 in $CHCl_3$) (Found: C, 69.79; H, 11.72; N, 2.39. $C_{34}H_{67}NO_4S$ requires C, 69.69; H, 11.53; N, 2.39%); ν_{max}(KBr)/cm^{-1} 3350m (OH), 1630m (NHCO), 1550m (NHCO), 1105 (S=O); δ_H(500 MHz; $CDCl_3$) 0.86 (12H, d, *J* 6.5, $CH(CH_3)_2$), 1.14 (4H, m, 14′- and 11″-H_2), 1.25 (38H, m, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′-, 1″-, 2″-, 3″-, 4″-, 5″-, 6″-, 7″-, 8″-, 9″- and 10″-H_2), 1.17–1.72 (4H, m, 15′-, 12″-H and 4′-H), 2.25 (1H, dd, *J* 15.6 and 9.2, 2′-H), 2.34 (1H, dd, *J* 15.6 and 2.4, 2′-H), 3.09 (2H, m, 3-H_2), 3.39 (1H, m, 4-OH), 3.97 (1H, m, 3′-H), 4.85 (1H, m, 4-H), 4.91 (1H, m, 5-H), 7.27 (1H, m, NH).

Ammonium (2*R*,3*R*,3′*R*)-3-hydroxy-2-(3′-hydroxy-15′-methylhexadecanoylamino)-15-methylhexadecanesulfinate 27

To a solution of **26b** (27 mg, 0.046 mmol) in $CHCl_3$ (1 cm^3) and MeOH (1 cm^3) was added 29% aq. NH_3 (0.5 cm^3), and the reaction mixture was stirred at room temperature for 12 h. Then the reaction mixture was concentrated under reduced pressure to give the *crude sulfinate* **27** (30 mg, quantitative), δ_H(400 MHz; CD_3OD) 0.87 (12H, d, *J* 6.6, $CH(CH_3)_2$), 1.02–1.57 (46H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′-, 14′-H_2 and 15-, 15′-H), 2.32 (2H, d, *J* 6.6, 2′-H), 2.46 (1H, dd, *J* 13.4 and 3.7, 1-H), 2.62 (1H, dd, *J* 13.4 and 9.0, 1-H), 3.60 (1H, m, 3-H), 3.95 (1H, m, 3′-H), 4.16 (1H, m, 2-H). This was employed in the next step without further purification.

(2*R*,3*R*,3′*R*)-3-Hydroxy-2-(3′-hydroxy-15′-methylhexadecanoylamino)-15-methylhexadecanesulfonic acid (sulfobacin A) 1

To a suspension of **27** (30 mg) in water (1.5 cm^3) was added 30% aq. H_2O_2 (0.4 cm^3), and the reaction mixture was stirred for 12 h at room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was chromatographed on SiO_2 to give the *sulfonic acid* **1** (28 mg, 98% based on **26b**) as a white solid, mp 233–235 °C; $[\alpha]_D^{22}$ −15 (*c* 0.14 in CH_3OH); ν_{max}(KBr)/cm^{-1} 3310m (OH and NH), 2940s (CH), 2860s (CH), 1645m (NHCO), 1550m (NHCO), 1470m (CH), 1410w, 1385w (CH), 1370w (CH), 1290w, 1195m (SO_2), 1065m (SO_2), 800w, 725w (CH); δ_H(400 MHz; DMSO) 0.83 (12H, d, *J* 6.6 $CH(CH_3)_2$), 1.12 (4H, m, 14- and 14′-H_2), 1.22 (38H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′- and 13′-H_2), 1.30–1.53 (4H, m, 4′-H_2 and 15-, 15′-H), 2.05–2.15 (2H, m, 2′-H_2), 2.69–2.72 (2H, m, 1-H_2), 3.43 (1H, m, 3-H), 3.73 (1H, m, 3′-H), 3.89 (1H, m, 2-H), 4.66 (1H, d, *J* 4.4, 3′-OH), 4.78 (1H, d, *J* 5.6, 3-OH), 7.65 (1H, d, *J* 8.5, NH); δ_C(100 MHz; DMSO) 22.5, 25.1, 25.4, 26.8, 27.4, 29.1, 29.21, 29.26, 29.32, 33.3, 36.6, 44.7, 51.0, 51.7, 63.9, 67.5, 71.8, 170.2 [Found: (HRFAB-MS) $(M - H)^-$, 618.4778. $C_{34}H_{68}NO_6S$ requires *m*/*z* 618.4768].

Sodium salt of 1

To **1** (7.0 mg, 0.011 mmol) was added aq. Na_2CO_3 (8.1 mmol dm^{-3}; 0.70 cm^3), and the mixture was concentrated under reduced pressure. The residue in $CHCl_3$ was filtered through Celite, and the filtrate was concentrated under reduced pressure to give the *sodium salt of* **1**, $[\alpha]_D^{18}$ −9.0 (*c* 0.10 in CH_3OH); δ_H(400 MHz; CD_3OD) 0.92 (12H, d, *J* 6.1, $CH(CH_3)_2$), 1.18–1.43 (44H, m, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′- and 14′-H_2), 1.57 (2H, m, 15- and 15′-H), 2.37 (2H, m, 2′-H_2), 3.08 (1H, dd, *J* 14.6 and 8.8, 1-H_a), 3.17 (1H, dd, *J* 14.4 and 3.4, 1-H_b), 3.69 (1H, m, 3′-H), 4.01 (1H, m, 3-H), 4.29 (1H, m, 2-H).

***tert*-Butyl (4*R*,1′*R*,2′*E*)-4-(1′-hydroxy-13′-methyltetradec-2′-enyl)-2,2-dimethyl-1,1-dioxo-1λ^6,3-thiazolidine-3-carboxylate 28**

To a suspension of magnesium (1.62 g, 66.7 mmol) in dry Et_2O (60 cm^3), a solution of 1,2-dibromoethane (11.0 g, 58.6 mmol) in dry benzene (20 cm^3) was added dropwise over 30 min and the resulting solution was stirred for 30 min. To a solution of (*E*)-1-iodo-12-methyltridec-1-ene (9.50 g, 29.4 mmol), which was prepared by hydroalumination of **12** followed by cleavage of the aluminium–carbon bond by iodine, in dry Et_2O was added dropwise Bu^tLi (1.56 mol dm^{-3} in pentane; 41.5 cm^3, 64.7 mmol) at −80 °C, and the solution was stirred for 1 h. The above described freshly prepared solution of magnesium bromide was added. The resulting heterogeneous mixture was stirred for 1 h and transferred *via* cannula into a solution of **21** (2.93 g, 10.5 mmol) in THF (100 cm^3) and HMPA (3.6 cm^3) at −80 °C. After having been stirred for 10 min, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with ethyl acetate. The extract was washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *alcohol* **28** (3.34 g, 67% based on **21**) as a colorless oil, $[a]_D^{25}$ −18.2 (*c* 0.95 in $CHCl_3$); n_D^{25} 1.4778 (Found: C, 63.26; H, 9.63; N, 2.95. $C_{25}H_{47}O_5NS$ requires C, 63.39; H, 10.00; N, 2.96%); ν_{max}(film)/cm^{-1} 3510m (OH), 1705s (C=O); δ_H(500 MHz; $CDCl_3$) 0.86 (6H, d, *J* 6.4, CH(CH_3)$_2$), 1.10–1.40 (17H, m, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′- and 12′-H_2 and 13′-H), 1.50 (9H, s, $OCMe_3$), 1.66 (3H, s, acetonide), 1.70 (3H, s, acetonide), 2.02 (2H, q, *J* 7.2, 4′-H_2), 2.20 (1H, m, OH), 3.17 (1H, dd, *J* 13.5 and 8.3, SO_2C*H*H), 3.50 (1H, dd, *J* 13.5 and 5.9, SO_2CH*H*), 4.33 (1H, m, 4-H), 4.66 (1H, m, 1′-H), 5.38 (1H, dd, *J* 15.4 and 6.6, 2′-H), 5.76 (1H, dt, *J* 15.4 and 7.2, 3′-H).

Determination of the enantiomeric and diastereomeric purity of 28

The enantiomeric purity of the resulting **28** was estimated by HPLC analysis. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, *n*-hexane–EtOH (20:1); flow, 0.4 cm^3 min^{-1}; detector at 210 nm]: t_R/min 21.4 [0.98%, (4*S*,1′*S*)-**28**], 23.2 [99.02%, (4*R*,1′*R*)-**28**]. The enantiomeric purity of **28** was estimated to be 98.0% ee. The diastereomeric purity of the resulting **28** was estimated by HPLC analysis. HPLC analysis [column, Pegasil Silica 60-5 (4.6 mm × 25 cm); solvent, *n*-hexane–THF (10:1); flow, 1.0 cm^3 min^{-1}; detector at 210 nm]: t_R/min 29.0 [96.56%, (4*R*,1′*R*)], 34.8 [3.44%, (4*R*,1′*S*)]. The diastereomeric purity of **28** was estimated to be 93.1% de.

(2*S*,4*R*,5*R*,1′*E*)-4-Amino-5-(12′-methyltridec-1′-enyl)-1,2-oxathiolane 2-oxide 29a and its (2*R*,4*R*,5*R*,1′*E*) isomer 29b

To a solution of **28** (55 mg, 0.12 mmol) in MeOH (5 cm^3) was added aq. HCl (1.0 mol dm^{-3}; 2 cm^3), and the reaction mixture was stirred at 60 °C overnight. After the reaction mixture was concentrated under reduced pressure, the residue was chromatographed on SiO_2 to give the mixture of **29a** and **29b** (total 35 mg, 96%). The ratio of **29a** and **29b** was determined to be 4:1 based on ^{1}H NMR analysis. This was employed in the next step without further purification. A small amount of this mixture was carefully chromatographed on SiO_2 to give the analytical samples of **29a** and **29b**. Isomer **29a** (colorless oil), $[a]_D^{25}$ +85.3 (*c* 1.03 in $CHCl_3$); n_D^{24} 1.4879; ν_{max}(film)/cm^{-1} 3390m (NH), 3310m (NH), 1670m (C=C), 1600m, 1120s (S=O); δ_H(400 MHz; $CDCl_3$) 0.85 (6H, d, *J* 6.8, CH(CH_3)$_2$), 1.10–1.60 (17H, m, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′- and 11′-H_2 and 12′-H), 1.80 (2H, br s, NH_2), 2.07 (2H, q, *J* 6.7, 3′-H_2), 2.93 (1H, dd, *J* 12.9 and 3.8, 3-H_β), 3.41 (1H, dd, *J* 12.9 and 7.6, 3-H_α), 3.48 (1H, m, 4-H), 5.19 (1H, dd, *J* 7.6 and 4.6, 5-H), 5.39 (1H, dd, *J* 15.1 and 7.6, 1′-H), 5.89 (1H, dt, *J* 15.1 and 6.8, 2′-H). Isomer **29b** (wax), $[a]_D^{25}$ +79.1 (*c* 0.36 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3380m (NH), 1620w, 1550w, 1520w, 1090m (S=O); δ_H(400 MHz; $CDCl_3$) 0.85 (6H, d, *J* 6.6, CH(CH_3)$_2$), 1.10–1.70 (19H, m, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′- and 11′-H_2, 12′-H and NH_2), 2.00–2.20 (2H, m, 3′-H_2), 2.93 (1H, dd, *J* 12.2 and 10.7, 3-H_β), 3.25 (1H, dd, *J* 12.2 and 5.6, 3-H_α), 4.07 (1H, m, 4-H), 4.43 (1H, t, *J* 8.3, 5-H), 5.57 (1H, dd, *J* 15.3 and 8.6, 1′-H), 5.86 (1H, dt, *J* 15.3 and 6.7, 2′-H).

(2*S*,4*R*,5*R*,3′*R*,1″*E*)-4-(3′-*tert*-Butyldimethylsilyloxy-15′-methylhexadecanoylamino)-5-(12″-methyltridec-1″-enyl)-1,2-oxathiolane 2-oxide 30a and its (2*R*,4*R*,5*R*,3′*R*,1″*E*) isomer 30b

To a solution of **29** (35 mg, 0.11 mmol), **9** (49 mg, 0.12 mmol) and DMAP (14 mg, 0.11 mmol) in dry CH_2Cl_2 (1 cm^3) was added DCC (27 mg, 0.13 mmol), and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the *amide* **30a** (38 mg, 49%) as a colorless oil and **30b** (11 mg, 14%) as a wax. Isomer **30a**, $[a]_D^{20}$ +60.1 (*c* 0.70 in $CHCl_3$); n_D^{25} 1.4511 (Found: C, 68.66; H, 11.31; N, 2.08. $C_{40}H_{79}O_4NSSi$ requires C, 68.81; H, 11.41; N, 2.01%); ν_{max}(film)/cm^{-1} 3360m (NH), 1670s (NHCO), 1540m (NHCO), 1265m (TBDMS), 1130s (S=O), 850s, 790s; δ_H(500 MHz; $CDCl_3$) 0.05 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.86 (12H, d, *J* 6.4, CH(CH_3)$_2$), 0.88 (9H, s, SiBu^t), 1.10–1.60 (40H, m, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′-, 14′-, 4″-, 5″-, 6″-, 7″-, 8″-, 9″-, 10″- and 11″-H_2, 12″-H and 15′-H), 2.05 (2H, q, *J* 7.2, 3″-H_2), 2.27 (1H, dd, *J* 14.4 and 6.4, 2′-H_a), 2.37 (1H, dd, *J* 14.4 and 4.4, 2′-H_b), 2.97 (1H, dd, *J* 13.4 and 1.8, 3-H_β), 3.20 (1H, dd, *J* 13.4 and 7.5, 3-H_α), 4.08 (1H, m, 3′-H), 4.86 (1H, m, 4-H), 5.31 (1H, m, 5-H), 5.44 (1H, dd, *J* 15.3 and 6.7, 1″-H), 5.83 (1H, dt, *J* 15.3 and 7.2, 2″-H), 7.24 (1H, d, *J* 9.2, NH). Isomer **30b**, $[a]_D^{20}$ +74.4 (*c* 0.63 in $CHCl_3$) (Found: C, 68.90; H, 11.36; N, 2.08. $C_{40}H_{79}O_4NSSi$ requires C, 68.81; H, 11.41; N, 2.01%); ν_{max}(film)/cm^{-1} 3300w (NH), 1640m (NHCO), 1540m (NHCO), 1250m (TBDMS), 1120m (S=O), 835s, 775s, 720s; δ_H(500 MHz; $CDCl_3$) 0.08 (3H, s, SiMe), 0.09 (3H, s, SiMe), 0.84 (12H, d, *J* 6.4, CH(CH_3)$_2$), 0.89 (9H, s, SiBu^t), 1.10–1.55 (40H, m, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′-, 14′-, 4″-, 5″-, 6″-, 7″-, 8″-, 9″-, 10″- and 11″-H_2, 12″-H and 15′-H), 2.04 (2H, q, *J* 7.2, 3″-H_2), 2.30 (1H, dd, *J* 15.5 and 4.4, 2′-H_a), 2.46 (1H, dd, *J* 15.5 and 4.3, 2′-H_b), 3.19 (1H, dd, *J* 12.7 and 9.2, 3-H_β), 3.32 (1H, dd, *J* 12.7 and 6.1, 3-H_α), 3.96 (1H, m, 3′-H), 4.75 (1H, t, *J* 7.6, 5-H), 4.97 (1H, m, 4-H), 5.63 (1H, dd, *J* 15.4 and 8.4, 1″-H), 5.82 (1H, dt, *J* 15.4 and 7.2, 2″-H), 6.92 (1H, d, *J* 7.6, NH).

(2*S*,4*R*,5*R*,3′*R*,1″*E*)-4-(3′-Hydroxy-15′-methylhexadecanoylamino)-5-(12″-methyltridec-1″-enyl)-1,2-oxathiolane 2-oxide 31a

To a solution of **30a** (362 mg, 0.518 mmol) in THF (10 cm^3) was added TBAF-2.5H_2O (300 mg), and the reaction mixture was stirred at room temperature for 10 min. The mixture was poured into water and extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed on SiO_2, and the solid was recrystallized from hexane to give the *pure alcohol* **31a** (178 mg, 59%) as colorless needles, mp 87–89 °C; $[a]_D^{20}$ +61.9 (*c* 0.89 in $CHCl_3$) (Found: C, 69.79; H, 11.09; N, 2.73. $C_{34}H_{65}O_4NS$ requires C, 69.93; H, 11.22; N, 2.40%); ν_{max}(KBr)/cm^{-1} 3350s (OH and NH), 1630s (NHCO), 1550s (NHCO), 1110s (SO_2), 970s, 900s, 760s; δ_H(500 MHz; $CDCl_3$) 0.89 (12H, d, *J* 6.5, CH(CH_3)$_2$), 1.10–1.60 (40H, m, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′- 14′-, 4″-, 5″-, 6″-, 7″-, 8″-, 9″-, 10″- and 11″-H_2, 12″-H and 15′-H), 2.05 (2H, q, *J* 7.2, 3″-H_2), 2.27 (1H, dd, *J* 15.7 and 9.5, 2′-H_a), 2.36 (1H, dd, *J* 15.7 and 2.8, 2′-H_b), 3.08 (1H, dd, *J* 13.5 and 2.0, 3-H_β), 3.12 (1H, dd, *J* 13.5 and 6.3, 3-H_α), 3.36 (1H, d, *J* 4.0, OH), 3.98 (1H, m, 3′-H), 4.91 (1H, m, 4-H), 5.35–5.45 (2H, m, 1″-H and 5-H), 5.84 (1H, dt, *J* 15.0 and 7.0, 2″-H), 7.32 (1H, d, *J* 9.5, NH).

(2*R*,4*R*,5*R*,3′*R*,1″*E*)-4-(3′-Hydroxy-15′-methylhexadecanoylamino)-5-(12″-methyltridec-1″-enyl)-1,2-oxathiolane 2-oxide 31b

In the same manner as described above, **30b** (112 mg, 0.160 mmol) was converted into the *pure alcohol* **31b** (58 mg, 62%) as colorless plates, mp 84–86 °C; $[a]_D^{20}$ +51.9 (*c* 0.30 in $CHCl_3$) (Found: C, 69.65; H, 11.17; N, 2.63. $C_{34}H_{65}O_4NS$ requires C, 69.93; H, 11.22; N, 2.40%); ν_{max}(KBr)/cm^{-1} 3300s (OH and NH), 1645s (NHCO), 1550s (NHCO), 1515m, 1130s (SO_2), 1110s (SO_2), 970m; δ_H(500 MHz; $CDCl_3$) 0.86 (12H, d, *J* 6.5, CH(CH_3)$_2$), 1.10–1.60 (40H, m, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′-, 14′-, 4″-, 5″-, 6″-, 7″-, 8″-, 9″-, 10″- and 11″-H_2, 12″-H and 15′-H), 2.07 (2H, q, *J* 7.2, 3″-H_2), 2.28 (1H, dd, *J* 15.4 and 8.8, 2′-H_a), 2.40 (1H, dd, *J* 15.4 and 2.5, 2′-H_b), 2.73

(1H, d, *J* 4.0, OH), 3.33 (1H, dd, *J* 12.7 and 8.3, 3-H$_\beta$), 3.37 (1H, dd, *J* 12.7 and 6.0, 3-H$_\alpha$), 3.97 (1H, m, 3′-H), 4.85 (1H, t, *J* 7.3, 5-H), 4.90 (1H, quintet, *J* 7.0, 4-H), 5.65 (1H, dd, *J* 15.4 and 8.0, 1″-H), 5.84 (1H, dt, *J* 15.4 and 7.3, 2″-H), 6.23 (1H, d, *J* 7.5, NH).

Ammonium (2*R*,3*R*,3′*R*)-3-hydroxy-2-(3′-hydroxy-15′-methylhexadecanoylamino)-15-methylhexadec-4-enesulfinate 32

To a solution of **31a** (77 mg, 0.13 mmol) in $CHCl_3$ (3 cm^3) and MeOH (4 cm^3) was added 29% aq. NH_3 (2 cm^3), and the reaction mixture was stirred at room temperature overnight. Then the reaction mixture was concentrated under reduced pressure to give the *crude sulfinate* **32** (78 mg, 95%), δ_H(500 MHz; CD_3OD) 0.87 (12H, d, *J* 6.7, $CH(CH_3)_2$), 1.15–1.45 (38H, m, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′- and 14′-H_2), 1.52 (2H, m, 15- and 15′-H), 2.04 (2H, q, *J* 7.0, 6-H_2), 2.27 (1H, dd, *J* 14.3 and 7.5, 1-H_a), 2.31 (1H, dd, *J* 14.3 and 5.2, 1-H_b), 2.48 (1H, dd, *J* 13.4 and 4.1, 2′-H_a), 2.57 (1H, dd, *J* 13.4 and 9.2, 2′-H_b), 3.94 (1H, m, 3′-H), 4.07 (1H, t, *J* 6.1, 3-H), 4.23 (1H, m, 2-H), 5.46 (1H, dd, *J* 15.4 and 6.9, 4-H), 5.70 (1H, dt, *J* 15.4 and 6.7, 5-H). In the same manner as described above, compound **31b** (10 mg, 0.017 mmol) was also converted into the *crude sulfinate* **32** (12 mg, quantitative). This was employed for the next step without further purification.

(2*R*,3*R*,3′*R*)-3-Hydroxy-2-(3′-hydroxy-15′-methylhexadecanoylamino)-15-methylhexadec-4-enesulfonic acid (flavocristamide A) 3

To a suspension of **32** (78 mg) in water (10 cm^3) was added 30% H_2O_2 (0.1 cm^3), and the reaction mixture was stirred at room temperature overnight. After the reaction mixture was concentrated under reduced pressure, the residue was chromatographed on SiO_2 to give the *sulfonic acid* **3** (78 mg, 95% based on **31a**) as a white solid, mp 210–213 °C; $[\alpha]_D^{22}$ −21 (*c* 0.27 in CH_3OH); ν_{max}(film)/cm^{-1} 3300m (OH and NH), 2940m (CH), 2870m (CH), 1640s (NHCO), 1550s (NHCO), 1470s, 1390m, 1370m, 1200s, 1060s (SO_3), 970m, 805m, 725m; δ_H(500 MHz; CD_3OD) 0.87 (12H, d, *J* 6.7, $CH(CH_3)_2$), 1.13–1.48 (38H, m, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′- and 14′-H_2), 1.52 (2H, m, 15- and 15′-H), 2.05 (2H, m, 6-H_2), 2.33 (1H, dd, *J* 14.6 and 8.4, 2′-H_a), 2.38 (1H, dd, *J* 14.6 and 3.7, 2′-H_b), 2.89 (1H, dd, *J* 14.3 and 9.9, 1-H_a), 3.19 (1H, dd, *J* 14.3 and 2.2, 1-H_b), 3.97 (1H, m, 3′-H), 4.07 (1H, t, *J* 6.3, 3-H), 4.39 (1H, m, 2-H), 5.46 (1H, dd, *J* 15.4 and 6.9, 4-H), 5.74 (1H, dt, *J* 15.4 and 6.8, 5-H). δ_C(126 MHz; CD_3OD) 23.0, 26.8, 28.55, 28.58, 29.2, 30.4, 30.5, 30.7, 30.81, 30.83, 30.9, 31.07, 31.1, 33.5, 38.1, 38.4, 40.26, 40.28, 44.7, 52.3, 52.4, 69.8, 74.9, 130.4, 135.4 [Found: (HRFAB-MS) $(M - H)^-$ 616.4612. $C_{34}H_{66}NO_6S$ requires *m*/*z* 616.4611].

Sodium salt of 3

To **3** (5.5 mg, 0.0089 mmol) was added aq. Na_2CO_3 (8.1 mmol dm^{-3}; 0.55 cm^3), and the mixture was concentrated under reduced pressure. The residue in $CHCl_3$ was filtered through Celite, and the filtrate was concentrated under reduced pressure to give the *sodium salt of* **3**, $[\alpha]_D^{18}$ −16 (*c* 0.10 in CH_3OH); δ_H(400 MHz; CD_3OD) 0.87 (12H, d, *J* 6.6, $CH(CH_3)_2$), 1.13–1.48 (38H, m, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 4′-, 5′-, 6′-, 7′-, 8′-, 9′-, 10′-, 11′-, 12′-, 13′- and 14′-H_2), 1.52 (2H, m, 15- and 15′-H), 2.04 (2H, m, 6-H_2), 2.29 (1H, m, 2′-H_a), 3.00 (1H, dd, *J* 14.4 and 8.8, 1-H_a), 3.11 (1H, dd, *J* 14.4 and 3.4, 1-H_b), 3.95 (1H, m, 3′-H), 4.17 (1H, t, *J* 6.2, 3-H), 4.31 (1H, m, 2-H), 5.47 (1H, dd, *J* 15.4 and 6.8, 4-H), 5.74 (1H, dt, *J* 15.4 and 7.2, 5-H).

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References

1 Part 21. K. Otaka and K. Mori, *Eur. J. Org. Chem.*, 1999, in the press.
2 T. Kamiyama, T. Umino, T. Satoh, S. Sawairi, M. Shirane, S. Ohshima and K. Yokose, *J. Antibiot.*, 1995, **48**, 924.
3 J. Kobayashi, S. Mikami, H. Shigemori, T. Takao, Y. Shimonishi, S. Izuta and S. Yoshida, *Tetrahedron*, 1995, **51**, 10487.
4 W. Godchaux III and E. R. Leadbetter, *J. Bacteriol.*, 1980, **144**, 592.
5 W. Godchaux III and E. R. Leadbetter, *J. Biol. Chem.*, 1984, **259**, 2982.
6 K. Ohashi, S. Kosai, M. Arizuka, T. Watanabe, Y. Yamagiwa, T. Kamikawa and M. Kates, *Tetrahedron*, 1989, **45**, 2557.
7 (*a*) H. Takikawa, T. Maeda, M. Seki, H. Koshino and K. Mori, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 97; (*b*) A. Yajima, H. Takikawa and K. Mori, *Liebigs Ann. Chem.*, 1996, 1083.
8 (*a*) N. Irako and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 5793; (*b*) N. Irako and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 5797.
9 H. Takikawa, S. Muto, D. Nozawa, A. Kayo and K. Mori, *Tetrahedron Lett.*, 1998, **39**, 6931.
10 T. Sugai, H. Ritzén and C. H. Wong, *Tetrahedron: Asymmetry*, 1993, **4**, 1051.
11 I. Uchida, K. Yoshida, Y. Kawai, S. Takase, Y. Itoh, H. Tanaka, M. Kohsaka and H. Imanaka, *J. Antibiot.*, 1985, **38**, 1476.
12 E. V. Dehmlow and M. Lissel, *Liebigs Ann. Chem.*, 1980, 1.
13 M. Honda, Y. Ueda, S. Sugiyama and T. Komori, *Chem. Pharm. Bull.*, 1991, **39**, 1385.
14 T. Fujisawa, M. Nagai, Y. Koike and M. Shimizu, *J. Org. Chem.*, 1994, **59**, 5865.
15 (*a*) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan and H. Vorbrüggen, *J. Am. Chem. Soc.*, 1966, **88**, 852; (*b*) D. S. Kemp and R. I. Carey, *J. Org. Chem.*, 1989, **54**, 3640.
16 D. B. Dess and I. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.
17 For recent works on the synthesis of sultines, see: (*a*) S. Yolka, R. Fellous, L. Lizzani-Cuvelier and M. Loiseau, *Tetrahedron Lett.*, 1998, **39**, 991; (*b*) T. J. Connolly and T. Durst, *Tetrahedron Lett.*, 1997, **38**, 1337; (*c*) C. M. Marson and P. R. Giles, *J. Org. Chem.*, 1995, **60**, 8067.

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