NMR ($CDCl_3$) δ 0.70 (3 H, s, 18-H), 1.04 (3 H, s, 19-H), 5.03 (1 H, m, 7-H); MS, *m/e* (relative intensity) 402 (M^+, 0.7), 111 (100), 84 (73); high-resolution mass calcd for $C_{27}H_{46}O_2$ 402.3498, found 402.3545.

To the lactol **51** (60 mg) in dry benzene (8 mL) containing pyridine (0.1 mL) was added mercury(II) oxide (65 mg) and iodine (76 mg). The solution was irradiated for 1.5 h to give a crude oily product (85 mg). This was subjected to preparative TLC with benzene to yield three fractions. The most TLC mobile fraction (11 mg) was an oily formate (**52**): IR (neat) 1738 (OCHO), 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (3 H, s, 18-H), 1.46 (3 H, s, 19-H), 3.34 and 3.57 (each 1 H, d, J = 9.76 Hz, 7-H), 8.16 (1 H, s, OCHO); MS, *m/e* (relative intensity) 528 (M^+, 2), 482 ($M^+ - OCH_2O$, 3), 459 (16), 401 ($M^+ - I$, 2), 111 (100) 95 (79); high-resolution mass calcd for $C_{27}H_{45}IO_2$ 528.2463, found 528.2478. The second (15 mg) and the third fractions were lactone **50** and a mixture of unidentified products. A solution of the formate **52** (30 mg) in THF (10 mL) was treated with methyllithium in diethyl ether (1 M, solution) (0.12 mL) as in the case of 4-oxa-5α-cholestane (**30**) to yield a crystalline 3α,5-cyclo-6-oxa-5α-cholestane (**54**) (25 mg). This was recrystallized from methanol to yield pure needles (18 mg): mp 95.5–97.5 °C; IR 1250, 1091, 1007 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55–0.69 (1 H, m, 3-H), 0.72 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 3.09 (1 H, t, J = 10.75 and 10.75 Hz, 7α-H), 3.6. (1 H, dd, J = 10.75 and 4.2 Hz, 7β-H); MS, *m/e* (relative intensity) 372 (M^+, 100), 111 (89); high-resolution mass calcd for $C_{26}H_{44}O$ 372.3392, found 372.3412.

Reduction of 1-Oxa-*A*-homo-5α-cholestan-2-one (55). To a solution of the lactone **55** (340 mg) in dry toluene (40 mL) cooled at −78 °C was added dropwise DIBAL in hexane (1.25 mL). The solution was stirred for 1.5 h at −78 °C and poured into iced water. After the solution had been filtered, the filtrate was worked by the usual method to yield lactol **56**; this was in the form of a ring-opened aldehyde (340 mg) (**57**): IR (neat) 3410 (OH) and 1722 cm^{-1} (CHO); ^1H NMR δ 0.66 (3 H, s, 18-H), 0.98 (3 H, s, 19-H), 2.33–2.55 (2 H, m, 2-H), 9.75 (1 H, t, J = 2, CHO); MS, *m/e* (relative intensity) 404 (M^+, 0.2), 386 ($M^+ - H_2O$, 0.2), 55 (26), 43 (100); high-resolution mass calcd for $C_{27}H_{48}O_2$ 404.3652, found 404.3647.

Registry No. **11**, 570-46-7; **12**, 31239-55-1; **13**, 93789-70-9; **15**, 93789-71-0; **16**, 93920-67-3; **17**, 566-88-1; **18**, 71766-31-9; **19**, 1982-71-4; **20**, 93789-73-2; **21**, 93789-74-3; **22**, 93789-81-2; **23**, 96616-58-9; **24**, 91796-74-6; **25**, 566-51-8; **26**, 58323-66-3; **27**, 93789-75-4; **28**, 96616-59-0; **29**, 93789-83-4; **30**, 2672-41-5; **31**, 567-71-5; **32**, 96616-60-3; **33**, 96616-61-4; **34**, 96616-62-5; **35**, 96647-92-6; **36**, 963-74-6; **37**, 2466-25-3; **38**, 96616-63-6; **39**, 83625-92-7; **40**, 83679-49-6; **41**, 1032-16-2; **42**, 60243-87-0; **43**, 93789-72-1; **44**, 93789-77-6; **45**, 93789-78-7; **46**, 93789-88-9; **47**, 93789-84-5; **48**, 93861-55-3; **49**, 3839-09-6; **50**, 31239-51-7; **51**, 96616-64-7; **52**, 96632-86-9; **54**, 96616-65-8; **55**, 96616-66-9; **57**, 96616-67-0.

Agelasidines. Novel Hypotaurocyamine Derivatives from the Okinawan Sea Sponge *Agelas nakamurai* Hoshino†

Hideshi Nakamura,*‡ Houming Wu,[1,‡] Jun'ichi Kobayashi,‡ Masaki Kobayashi,‡ Yasushi Ohizumi,‡ and Yoshimasa Hirata§

Mitsubishi-Kasei Institute of Life Sciences, 11 Minamiooya, Machida-shi, Tokyo 194, Japan, and Faculty of Pharmacy, Meijo University, Nagoya 468, Japan

Received December 7, 1984

Two new diterpene derivatives of hypotaurocyamine, agelasidine B (**2a**) and agelasidine C (**3a**), have been isolated from the Okinawan sea sponge *Agelas nakamurai* Hoshino. The structures of agelasidine B and agelasidine C were elucidated by interpretation of spectral data and chemical degradation experiments. The agelasidines show inhibitory effects on growth of microorganisms, contractile responses of smooth muscle, and enzymic reactions of Na,K-ATPase.

Recent studies on bioactive metabolites of sea sponges of the genus *Agelas* revealed the presence of sesqui- and diterpenes with polar functionalities possessing inhibitory effects on growth of microorganisms,[4] contractile responses of smooth muscles,[6] and enzymic reactions of Na,K-ATPase.[3,5] A quarternary 9-methyladenine derivative of an unidentified bicyclic dideterpene has been reported as a constituent of the sea sponge *Agelas dispar* by Cullen and Devlin.[2] Recently, quaternary 9-methyladenine derivatives of bicyclic diterpenes, agelasine A (**4**), agelasine B (**5**), agelasine C (**6**), agelasine D (**7**), and ageline B (**8**), and monocyclic diterpenes, agelasine E (**9**) and ageline A (agelasine F, **10**),[7] have been isolated from the Okinawan sea sponge *A. nakamurai* by us[3,5] and from a Pacific sea sponge *A.* sp. by Capon and Faulkner.[4] In contrast to the structural variety of the diterpene derivatives of 9-methyladenine, only one sesquiterpene derivative of hypotaurocyamine, agelasidine A (**1a**), has been reported as a constituent of the two sponges.[4,6] Our further study on physiologically active metabolites of the sponge resulted in the isolation of two novel diterpene derivatives of hypotaurocyamine, named agelasidine B and C. In this paper, we report the structural elucidation of agelasidine B (**2a**) and C (**3a**) (Figures 1 and 2).

Specimens of *A. nakamurai* were collected at Zampa Cape, Okinawa, using SCUBA (-10 to -20 m) and stored at -20 °C until needed. The chloroform-soluble material from the methanolic extracts of the sponge was chromatographed on a silica gel column with 3:12:2:2 chloroform-

† Physiologically active marine natural products from Porifera VIII.

‡ Mitsubishi-Kasei Institute of Life Sciences.

§ Faculty of Pharmacy, Meijo University.

(1) Permanent address: Shanhai Institute of Organic Chemistry, academia Sinica, 345 Linglin Lu, Shanghai, China.

(2) Cullen, E.; Devlin, J. P. *Can. J. Chem.* **1975**, *53*, 1690–1691.

(3) Nakamura, H.; Wu, H.; Ohizumi, Y.; Hirata, Y. *Tetrahedron Lett.* **1984**, *25*, 2989–2992.

(4) Capon, R. J.; Faulkner, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 1819–1822.

(5) Wu, H.; Nakamura, H.; Kobayashi, J.; Ohizumi, Y; Hirata, Y. *Tetrahedron Lett.* **1984**, *25*, 3719–3722.

(6) Nakamua, H.; Wu, H.; Kobayashi, J.; Ohizumi, Y.; Hirata, Y.; Higashijima, T.; Miyazawa, T. *Tetrahedron Lett.* **1983**, *24*, 4105–4108.

(7) While the manuscript concerning agelasine F was in preparation, the structure of ageline A was reported. Ageline A was identical with agelasine F.

0022-3263/85/1950-2494$01.50/0

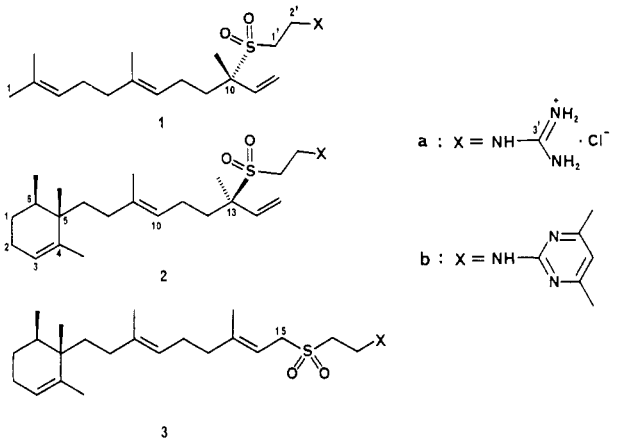

Figure 1.

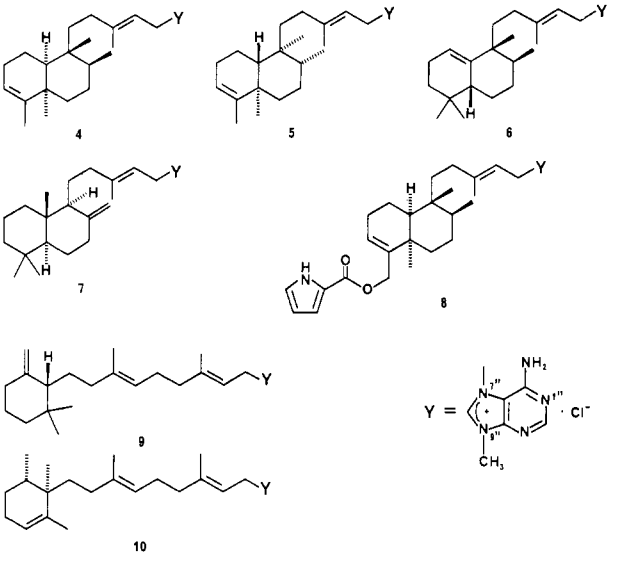

Figure 2.

/1-butanol/acetic acid/water as eluant to give two fractions. The polar fraction was repeatedly chromatographed by HPLC using C_{18} and C_8 columns with a methanol/water solvent system containing 0.2 M sodium chloride as a mobile phase to yield agelasine A, B, C, D, and E and ageline A. The less polar fraction was separated into two fractions by HPLC on a C_{18} column with 8:2 methanol/water containing 0.2 M sodium chloride as a mobile phase. Agelasidine A (**1a**) was eluted faster than a 1:6 mixture of agelasidine B and C. Complete separation of agelasidine B and C was achieved by HPLC on a C_{18} column. The isolation yields of agelasidine A, B, and C (**1a–3a**) were 0.034%, 0.0043%, and 0.026%, respectively, from the wet weight of the sponge.

Agelasidine B and C were established as guanidine derivatives by positive coloration with Sakaguchi reagent and ^{13}C NMR signals (δ 158.6 (s) for **2a** and 158.5 (s) for **3a**) and confirmed chemically by their conversion with 2,4-pentanedione to the corresponding pyrimidine derivatives **2b** and **3b**, which could be easily separated by flash chromatography on a silica gel column with 9:1 benzene/acetone as eluant. The molecular formulas of **2b** and **3b** were determined as $C_{28}H_{45}N_3SO_2$ by high-resolution electron impact mass spectrometry (HREIMS). Field desorption mass spectra (FDMS) of **2a** and **3a** showed M + H molecular ions at m/z 424, which was consistent with a molecular formula $C_{23}H_{41}N_3SO_2$. Comparison of ^1H and ^{13}C NMR spectra of **2a** and **3a** with those of **1a** indicated that both **2a** and **3a** contained a common unit $-S(O_2)-CH_2CH_2-NHC(=NH)NH_2$ as did **1a**. The remaining portions of **2a** and **3a** were composed of diterpenoid units, $C_{20}H_{33}$.

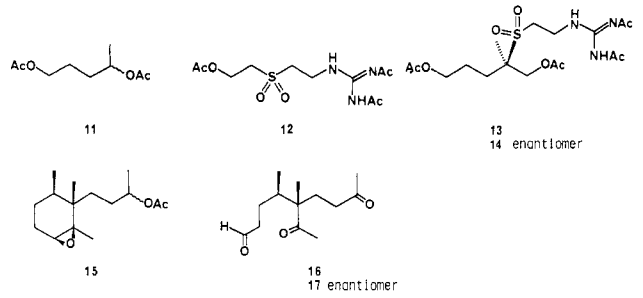

Figure 3.

The ^1H NMR spectrum of agelasidine B (**2a**) contained three proton signals due to a terminal olefin at δ 5.47 (d, 1 H, J = 17 Hz), 5.55 (d, 1 H, J = 11 Hz), and 6.02 (dd, 1 H, J = 17, 11 Hz) like **1a**. On the other hand, the ^1H NMR spectrum of **3a** did not show signals for the terminal olefin but showed an isolated spin system, δ 3.91 (d, 2 H, J = 8 Hz) and 5.30 (t, 1 H, J = 8 Hz), due to the allyl grouping which must be connected to sulfur. Reductive ozonolysis of the mixture of **2a** and **3a** (ozone at −78 °C, followed by sodium borohydride), followed by acetylation with acetic anhydride and pyridine furnished a diacetyl compound (**11**), a triacetyl compound (**12**), and a tetraacetyl compound (**13**) with product **15** from a terminal cyclic part. The compounds **11** and **13** were identical with 1,4-diacetoxypentane and an authentic tetraacetyl compound prepared from nerolidol and agelasidine A, respectively. High-field olefinic methyl signals of **2a** (δ 16.3) and **3a** (δ 16.2 and 17.0) indicated that **2a** and **3a** contained one and two *trans*-$(CH_3)C{=}CH$ units, respectively, leading to the structures in the C-9 to C-15 of agelasidine B and C as illustrated (Figure 3).

The electron impact mass spectra (EIMS) of **2b** and **3b** showed a common fragment ion at m/z 123 (C_9H_{15}), indicating the presence of a common unit composed of C_9H_{15} as their terminal parts.[8] The ^1H NMR spectra of **2a** and **3a** due to the common unit were superimposable: δ 0.86 (s, 3 H), 0.87 (d, 3 H, J = 7 Hz), 1.61 (br s, 3 H), 5.40 (br s, 1 H). These data and the ozonolysis product **15** were consistent with a common structure having the 1-alkyl-1,2,6-trimethyl-2-cyclohexene ring system which was also found in ageline A (**10**). Comparison of ^1H and ^{13}C NMR spectra of **2a** and **3a** with those of **10** (Table I) indicated that the ring systems of the three compounds were identical in the relative stereochemistry.

Agelasidine B (**2a**) contained a quaternary carbon atom attached to a sulfur atom as did agelasidine A (**1a**). However, the tetraacetyl compound **13** from **2a** was not identical with that (**14**) obtained from agelasidine A (**1a**) in optical properties. The $[\alpha]^{25}_D$ value of **13** (+7.0°) was opposite to that of **14** (−7.6°), suggesting that the absolute configurations at the quaternary carbons attached to the sulfur atoms of **1a** (C-10) and **2a** (C-13) were reversed.[9]

(8) Takeda, R.; Naoki, H.; Iwashita, T.; Mizukawa, K.; Hirose, Y.; Isida, T.; Inoue, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1125–1132.

(9) We tentatively assigned the absolute configurations of **1a** and **2a** as *S* and *R*, respectively, on the basis of empirical rules. According to empirical rules used by Brewster[10] for open chain compounds, the magnitude of rotation is related to the refractions of the atoms attched to a center of optical activity and the sign and magnitude of rotation could be predicted. In the case of **1a**, it could be estimated that the order of polarizabilities of substituents in $H_2NC(=NH)NHCH_2CH_2S(O_2)$ > $(CH_3)_2C{=}CHCH_2CH_2(CH_3)C{=}CHCH_2CH_2$ > $H_2C{=}CH$ > CH_3 in comparison with those of nerolidol.[11]

(10) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475–5483.

(11) Grimm, R. A.; Bonner, W. A. *J. Org. Chem.* **1967**, *32*, 3470–3474.

Table I. ^{13}C NMR Spectral Data for Agelasidine A (1a), Agelasidine B (2a), Agelasidine C (3a), and Ageline A (10)[a]

carbon	1a	2a	3a	10
1	25.6 (q)	26.5 (t)	26.4 (t)	25.2 (t)
2	131.3 (s)	28.2 (t)	28.0 (t)	26.8 (t)
3	122.6 (d)	123.6 (d)	124.0 (d)	122.4 (d)
4	26.6 (t)	140.6 (s)	140.5 (s)	139.3 (s)
5	39.6 (t)	41.6 (s)	41.4 (s)	40.1 (s)
6	136.4 (s)	34.5 (d)	34.4 (d)	33.0 (d)
7	124.1 (d)	35.4 (t)	35.3 (t)	34.0 (t)
8	31.6 (t)	36.4 (t)	36.4 (t)	35.0 (t)
9	22.8 (t)	138.5 (s)	137.6 (s)	136.5 (s)
10	68.3 (s)	123.6 (d)	124.0 (d)	123.7 (d)
11	134.7 (d)	23.1 (t)	27.2 (t)	26.1 (t)
12	121.7 (d)	33.2 (t)	40.8 (t)	39.4 (t)
13		69.3 (s)	148.0 (s)	146.8 (s)
14		136.3 (d)	110.6 (d)	115.2 (d)
15		121.9 (t)	54.5 (t)	48.4 (t)
4-CH_3		19.5 (q)	19.4 (q)	18.9 (q)
5-CH_3		16.2 (q)	16.2 (q)	15.6 (q)
6-CH_3		21.5 (q)	21.4 (q)	20.8 (q)
9-CH_3		16.3 (q)	16.3 (q)	16.0 (q)
13-CH_3		16.2 (q)	17.0 (q)	17.2 (q)
1′	46.0 (t)	46.5 (t)	51.4 (t)	
2′	35.0 (t)	35.8 (t)	36.0 (t)	
3′	157.5 (s)	158.6 (s)	158.5 (s)	
2″				155.7 (d)
4″				149.2 (s)
5″				109.5 (s)
6″				152.2 (s)
8″				141.2 (d)
9″-CH_3				31.7 (q)
2-CH_3	17.6 (q)			
6-CH_3	16.0 (q)			
10-CH_3	16.0 (q)			

[a] **1a**, **2a**, and **3a** in CD_3OD and **10** in $CDCl_3$.

On the other hand, comparison of the $[\alpha]_D$ values of **3a** (+8.5°) and **10** (-5.5°) suggested that the absolute configuration of **3a** was opposite to that of **10**. Reductive ozonolysis (ozone at -78 °C, followed by dimethyl sulfide) of **2b** and **3b** gave the identical aldehyde **16** [δ 0.85 (d, 3 H, J = 7 Hz), 1.03 (s, 3 H), 2.11 (s, 6 H), 9.75 (t, 1 H, J = 2 Hz)]. The CD spectra of the aldehydes, $[\Theta]_{295}$ -156° (from **2b**) and $[\Theta]_{295}$ -141° (from **3b**) were opposite to that of the aldehyde **17**, $[\Theta]_{295}$ +131°, obtained from **10** by the same procedure. The absolute configurations of the cyclohexene ring structure in agelasidine B and C were defined as 1*R*,4*R* since that of **10** has been confirmed to be 1*S*,4*S* by its successive conversion to a known octalone.[5] The absolute configuration of the cyclohexene ring in agelasidine B and C is the same as that of a diterpene alcohol isolated from the liverwort.[8]

From the biogenetic point of view, agelasidines may be produced from the corresponding terpene alcohols through direct replacement by hypotaurocyamine or sigmatropic rearrangement of their hypotaurocyamine sulfenic acid esters. It is of some biosynthetic interest that the cyclohexene parts of agelasidine B and C and ageline A are enantiomeric and that the absolute configurations at the quaternary carbons attached to hypotaurocyamine of agelasidine A and B are opposite.

Agelasidines inhibited growth of microorganisms such as *Staphylococcus aureus* (minimum inhibitory concentration, 3.3 μg/mL) and showed inhibitory effects on contractile responses of smooth muscles, such as isolated guinea pig ileum (concentration of 50% inhibition, $\sim 1 \times 10^{-6}$M), and enzymic reactions of Na,K-ATPase isolated from pig brain (concentration for 50% inhibition, (1–5) $\times 10^{-5}$ M). The conversion of agelasidines to the corresponding pyrimidine derivatives decreased the activities. Pharmacological activities of agelasidines and agelasines will be reported elsewhere in detail.

Experimental Section

General Methods. All melting points were measured on a Yanagimoto micro melting point apparatus and uncorrected.

Collection, Extraction, and Separation. *Agelas nakamurai* Hoshino, an orange sea sponge, was collected at Zampa Cape, Okinawa, in 1981 using SCUBA (-10 to -20 m), frozen, and shipped via air to Tokyo. The sponge (5 kg, weight), stored at -20 °C, was cut into small pieces and extracted with methanol (10 L × 3). The solvent evaporated under reduced pressure to give a crude extract (195 g), which was dissolved in methanol. The methanol-soluble material (125 g) was partitioned into chloroform-soluble and water-soluble fractions. Each 12 g of the chloroform-soluble fraction (60 g) was separated into two fractions by flash chromatography on a silica gel column (Wako gel C-300, Wako Chemical, 50 × 600 mm) with 3:12:2:2 chloroform/1-butanol/acetic acid/water as eluant, monitored by TLC.

The less polar fraction (1080–1500 mL, 12 g) containing agelasidines (positive coloration with Sakaguchi reagent) was chromatographed on a C_{18} column (Develosil ODS 15/30, Nomura Chemical, packed in a column 21 × 250 mm, × 3) with 8:2 methanol/water containing 0.2 M sodium chloride (flow rate 28 mL/min) to obtain two fractions (t_R 20 and 65 min). Methanol was removed in vacuo and the resulted water layer was extracted with ethyl acetate. This procedure was used to recover compounds from the eluants containing salts at all separation steps by HPLC. After crystalization from ethyl acetate, agelasidine A (**1a**, 1.7 g) was obtained from the first fraction (t_R 20 min). The second fraction (t_R 65 min) gave a 1:6 mixture of agelasidine B and C (**2a** and **3a**, 2.7 g). HPLC of the mixture (250 mg) on a C_{18} column (YMC-Pack AM-324(ODS), Yamamura Chemical, 10 × 300 mm) with a 75:25 methanol/water containing 0.2 M sodium chloride (flow rate 3 mL/min) yielded pure samples of agelasidine B (**2a**, t_R 87 min, 120 mg) and C (**3a**, t_R 81 min, 20 mg).

The polar fraction (1760–3000 mL, 28.3 g) of the silica gel column chromatography contained agelasines (slightly positive coloration with Sakaguchi reagent and strong UV absorption). The material was purified by chromatography on a C_{18} column (Develosil ODS 15/30, 21 × 250 mm, × 3) with 8:2 methanol/water containing 0.2 M sodium chloride (flow rate 28 mL/min) to give a mixture of agelasines (22 g). A part of the mixture (2 g) was chromatographed on a C_{18} column (Develosil ODS-5, 10 × 250 mm) with 8:2 methanol/water containing 0.2 M sodium chloride (flow rate 4 mL/min) to give agelasine A (**4**, t_R 17.3 min, 170 mg), a mixture of agelasine B–D (**5–7**, t_R 18 min, 822 mg), agelasine E (**9**, t_R 19.8 min, 255 mg), and ageline A (**10**, t_R 21 min, 368 mg).

Agelasidine A (1a): Colorless crystals (EtOAc); $[\alpha]^{25}_D$ +19.1° (c 1.0, MeOH); UV (MeOH) λ_{max} <210 nm; IR (KBr) ν_{max} 3350, 3160, 2940, 1678, 1648, 1620, 1460, 1380, 1295, 1135, 1005, 945, 830 cm^{-1}; ^1H NMR (CD_3OD, 270 MHz) δ 1.44 (s, 3 H), 1.50 (br s, 6 H), 1.58 (br s, 3 H), 1.68–2.06 (m, 8 H), 3.25, 3.28 (ABX center, 2 H, J = 14, 7 Hz), 3.68 (t, 2 H, J = 7 Hz), 5.05 (br t, 1 H, J = 7 Hz), 5.11 (br t, 1 H, J = 6 Hz), 5.49 (d, 1 H, J = 18 Hz), 5.56 (d, 1 H, J = 11 Hz), 5.98 (dd, J = 11, 18 Hz); FDMS, m/z 356 (M + H); Anal. Calcd $C_{18}H_{33}N_3O_2S \cdot HCl \cdot {}^1/_3H_2O$): S, 8.06; Cl, 8.91. Found: S., 7.50; Cl, 9.72.

Agelasidine B (2a): a colorless syrup; $[\alpha]^{25}_D$ -2.5° (c 0.43, CH_3OH); UV (CH_3OH) λ_{max} <210 nm; IR ($CHCl_3$) ν_{max} 3350, 3170, 2980, 2945, 1675, 1650, 1625, 1455, 1415, 1380, 1290, 1240, 1135, 1080, 1010, 940, 800, 735 cm^{-1}; ^1H NMR (CD_3OD, 90 MHz) δ 0.86 (s, 3 H), 0.87 (d, 3 H, J = 7 Hz), 1.52 (s, 3 H), 1.59 (br s, 3 H), 1.61 (br s, 3 H), 1.1–2.2 (m, 13 H), 3.28 (t, 2 H, J = 6 Hz), 3.72 (t, 2 H, J = 6 Hz), 5.12 (br t, 1 H, J = 6 Hz), 5.40 (br s, 1 H), 5.47 (d, 1 H, J = 17 Hz), 5.55 (d, 1 H, J = 11 Hz), 6.02 (dd, 1 H, J = 17, 11 Hz); FDMS, m/z 424 (M + H).

Agelasidine C (3a): a colorless syrup; $[\alpha]^{25}_D$ +8.5° (c 2.0, CH_3OH) λ_{max} <210 nm; IR ($CHCl_3$) ν_{max} 3350, 3170, 2980, 2940, 1675, 1655, 1620, 1455, 1380, 1300, 1240, 1120, 845, 800, 735 cm^{-1}; ^1H NMR (CD_3OD, 90 MHz) δ 0.86 (s, 3 H), 0.87 (d, 3 H, J = 7 Hz), 1.61 (br s, 6 H), 1.78 (br s, 3 H), 1.2–2.4 (m, 13 H), 3.34 (t, 2 H, J = 6 Hz), 3.75 (t, 2 H, J = 6 Hz), 3.91 (d, 2 H, J 8 Hz), 5.10 (br s, 1 H), 5.30 (t, 1 H, J = 8 Hz), 5.40 (br s, 1 H); FDMS, m/z 424 (M + H).

Ageline A (10): colorless crystals; mp 178–180 °C; $[\alpha]^{25}_D$ -5.5° (c 2.45, CH_3OH); UV (CH_3OH) λ_{max} 272 nm (ϵ 7700); IR ($CHCl_3$) ν_{max} 3300, 3150, 2970, 1640, 1610, 1595, 1455, 1380, 1300, 1235,

1090 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 3 H), 0.85 (d, 3 H, J = 7 Hz), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.86 (s, 3 H), 1.0–2.2 (m, 13 H), 4.10 (s, 3 H), 5.02 (br s, 1 H), 5.42 (br s, 1 H), 5.47 (br t, 1 H, J = 7 Hz), 5.72 (br d, 2 H, J = 7 Hz), 6.87 (br s, 2 H, exchangable), 8.50 (s, 1 H), 10.83 (br s, 1 H); FDMS, m/z 422 (M - Cl); EIMS, m/z 421 (M - HCl), 298, 217, 216, 150, 149, 123, 121; HREIMS, m/z obsd 421.3202, $C_{26}H_{39}N_5$ required 421.3202, obsd 149.0722, $C_8H_7N_5$ required 149.0701.

Conversion of Agelasidine A (1a) to Pyrimidine Derivative 1b. A solution of agelasidine A (**1a**, 10 mg, 0.025 mmol) in pyridine (0.2 mL) and 2,4-pentanedione (0.2 mL) was heated at 125 °C for 2.5 h in a sealed tube. The solution was evaporated in vacuo and the residue was separated on a silica gel column by using 9:1 chloroform/methanol to give **1b** (10 mg, 93% theoretical) as colorless needles: mp 52–53 °C; $[\alpha]^{25}_D$ + 11.3° (c 1.0, MeOH); UV (MeOH) λ_{max} 235 (ϵ 17 500), 294 nm (4000); IR (KBr) ν_{max} 3250, 3085, 1600, 1570, 1360, 1340, 1295, 1135, 1095, 935, 795 cm^{-1}; ^1H NMR (C_6D_6, 270 MHz) δ 1.19 (s, 3 H), 1.50 (br s, 3 H), 1.57 (br s, 3 H), 1.69 (br s, 3 H), 1.88 (m, 2 H), 2.00 (m, 2 H), 2.02 (m, 2 H), 2.09 (s, 6 H), 2.13 (m, 2 H), 2.92 (t, 2 H, J = 7 Hz), 3.91 (q, 2 H, J = 7 Hz), 4.90 (d, 1 H, J = 17 Hz), 4.98 (d, 1 H, J = 11 Hz), 5.57 (t, 1 H, J = 7 Hz), 5.87 (dd, 1 H, J = 11, 17 Hz), 5.90 (s, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 16.0 (q), 17.7 (q), 22.2 (t), 23.9 (q, 2 C), 25.6 (q), 26.7 (t), 32.0 (t), 35.0 (t), 39.7 (t), 46.7 (t), 67.9 (s), 110.1 (d), 120.1 (t), 123.0 (d), 124.3 (d), 131.3 (s), 136.0 (d), 136.2 (s), 161.9 (s, 2 C), 167.4 (s); EIMS, m/z 419 (M^+), 269, 216, 151, 136; HREIMS, m/z obsd 419.2601, $C_{23}H_{37}N_3SO_2$ required 419.2604.

Conversion of Agelasidine B (2a) and C (3a) to Pyrimidine Derivatives 2b and 3b. A mixture of agelasidine B and C (**2a** and **3a**, 400 mg, 0.87 mmol) was dissolved in pyridine (2.5 mL) and 2,4-pentanedione (2.5 mL) and heated in a sealed tube at 125–128 °C for 3 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with 9:1 benzene/acetone to give pyrimidine derivatives **2b** (25 mg) and **3b** (184 mg). **2b**: colorless crystals; mp 86–87 °C; $[\alpha]^{25}_D$ +1.3° (c 1.5, CH_3OH); UV (CH_3OH) λ_{max} 235 (ϵ 16 200), 294 nm (ϵ 3800); IR ($CHCl_3$) ν_{max} 3450, 3030, 2980, 2940, 1595, 1570, 1525, 1460, 1380, 1340, 1290, 1235, 1140, 1080, 1005, 940 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.87 (d, 3 H, J = 7 Hz), 0.90 (s, 3 H), 1.22 (s , 3 H), 1.55 (br s, 3 H), 1.67 (s, 3 H), 2.11 (s, 6 H), 2.94 (t, 2 H, J = 6 Hz), 3.93 (m, 3 H), 4.96 (d, 1 H, J = 17 Hz), 5.04 (d, 1 H, J = 11 Hz), 5.13 (br t, J = 6 Hz), 5.53 (br s, 2 H), 5.94 (dd, 1 H, J = 17, 11 Hz), 5.96 (s, 1 H): ^{13}C NMR (C_6D_6, 22.5 MHz) δ 16.0 (q, 2 C), 16.3 (q), 19.4 (q), 21.3 (q), 22.6 (t), 23.8 (q, 2C), 25.9 (t), 27.4 (t), 32.5 (t), 33.6 (d), 34.5 (t), 35.2 (t), 35.5 (t), 40.7 (s), 47.0 (t), 67.6 (s), 110.0 (d), 119.4 (t), 123.0 (d), 124.5 (d), 136.6 (d), 137.0 (s), 139.6 (s), 162.4 (s, 2 C), 167.4 (s); EIMS, m/z 487, 364, 269, 216, 151, 136, 123; HREIMS, m/z obsd 487.3236, $C_{28}H_{45}N_3SO_2$ required 487.3230. **3b**: a colorless syrup; $[\alpha]^{25}_D$ +9.1° (c 1.8, CH_3OH); UV (CH_3OH) λ_{max} 235 (ϵ 16 200), 294 nm (ϵ 3900); IR ($CHCl_3$) ν_{max} 3450, 3030, 2980, 2940, 1595, 1570, 1525, 1440, 1385, 1343, 1305, 1230, 1120, 1020 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.87 (d, 3 H, J = 7 Hz), 0.90 (s, 3 H), 1.42 (br s, 3 H), 1.57 (br s , 3 H), 1.67 (br s, 3 H), 2.11 (s, 6 H), 2.92 (t, 2 H, J = 6 Hz), 3.36 (d, 2 H, J = 8 Hz), 3.76 (q, 2 H, J = 6 Hz), 5.19 (br t, 1 H, J = 6 Hz), 5.27 (t, 1 H, J = 8 Hz), 5.44 (br t, J = 6 Hz), 5.51 (br s, 1 H), 5.96 (s, 1 H); ^{13}C NMR (C_6D_6, 22.5 MHz) δ 16.0 (q), 16.3 (q), 16.7 (q), 19.4 (q), 21.2 (q), 23.8 (q, 2 C), 25.8 (t), 26.6 (t), 27.4 (t), 33.6 (d), 34.7 (t), 35.7 (t), 35.8 (t), 39.9 (t), 40.7 (s), 51.5 (t), 54.0 (t), 110.1 (d), 111.2 (d), 123.3 (d), 124.4 (d), 136.5 (s), 139.6 (s), 145.4 (s), 162.4 (s, 2 C), 167.4 (s, 2C); MS, m/z 487 (M^+), 364, 282, 269, 216, 151, 136, 123; HREIMS, m/z obsd 487.3212, $C_{28}H_{45}N_3SO_2$ required 487.3230.

Ozonolysis of Agelasidine A (1a). A solution of agelasidine A (**1a**, 20 mg, 0.05 mmol) in methanol (1 mL) was saturated with ozone for 1.5 h at -78 °C. Excess ozone was removed by nitrogen and then sodium borohydride (47.5 mg) was added to the solution. The solution was stirred at 0 °C for 30 min and warmed up to room temperature. Acetic acid (0.09 mL) was added to the solution and the solvent was removed under reduced pressure. The residue was dissolved in pyridine (1.6 mL) and acetic anhydride (0.4 mL) and stirred at room temperature overnight. After the solvent was removed, the residue was put on a silica gel column and eluted with 4:1 benzene/acetone to give 1,4-diacetoxypentane (11, 5 mg, 64% theoretical), which was identical in all respects with an authentic sample, and the tetraacetyl compound **14** (7 mg, 33% theoretical): $[\alpha]^{25}_D$ -7.6° (c 1.90, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3300, 3040, 1740, 1705, 1620, 1560, 1380, 1325, 1300, 1115, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.39 (s, 3 H), 1.86 (m, 4 H), 2.05 (s, 3 H), 2.10 (s, 3 H), 2.12 (s, 3 H), 2.17 (s, 3 H), 3.37 (t, 2 H, J = 6 Hz), 4.03 (q, 2 H, J = 6 Hz), 4.06 (t, 2 H, J = 6 Hz), 4.34 (s, 2 H), 9.42 (br t, 1 H, J = 6 Hz), 12.99 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 15.6 (q), 20.7 (q), 20.8 (q), 23.0 (t), 24.9 (q), 27.7 (t), 28.6 (q), 33.8 (t), 49.2 (t), 63.9 (t), 64.8 (t), 64.9 (s), 155.4 (s), 169.6 (s), 170.8 (s), 172.2 (s), 185.9 (s); MS, m/z 436 (M + H), 435 (M^+), 378, 276, 178, 170, 128; HREIMS, m/z obsd 436.1724, $C_{17}H_{29}N_3SO_8$ + H required 436.1697, obsd 435.1687, $C_{17}H_{29}N_3SO_8$ required 435.1701.

Ozonolysis of a Mixture of Agelasidine B (2a) and C (3a). Ozone was bubbled in a methanol solution (17 mL) of agelasidine B (**2a**) and C (**3a**) (220 mg, 0.48 mmol) for 45 min at -78 °C. Excess ozone was removed by a nitrogen stream. Sodium borohydride (270 mg) was added to the solution in six portions. The solution was stirred for 30 min at 0 °C and for 30 min at room temperature. To the solution acetic acid (0.45 mL) was added, the solvent removed, and the residue extracted with 9:1 chloroform and methanol. The resulted products were dissolved in a mixture of ethyl acetate (5 mL), pyridine (5 mL), and acetic anhydride (2.5 mL) and stirred at room temperature overnight. The solution was evaporated under reduced pressure and the residue was chromatographed on a silica gel column by using benzene/acetone (from 97.5:2.5 to 70:30) as eluants to give an epoxide (**15**, 22.5 mg) and a mixture of tri- and tetraacetyl compounds, which was separated by a silica gel column chromatography with 87.5:12.5 chloroform/acetone to furnish **12** (8.5 mg) and **13** (65 mg). **12**: a colorless syrup; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.10 (s, 3 H), 2.13 (s, 3 H), 2.17 (s, 3 H), 3.34 (t, 2 H, J = 8 Hz), 3.37 (t, 2 H, J = 8 Hz), 3.92 (q, 2 H, J = 8 Hz), 4.49 (t, 2 H, J = 8 Hz), 9.35 (br t, 1 H, J = 8 Hz), 13.0 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 20.7 (q) 24.9 (q), 28.5 (q), 34.4 (t), 52.9 (t), 53.1 (t), 57.5 (t), 155.4 (s), 170.1 (s), 172.4 (s), 185.9 (s); MS m/z 322 (M + H), 321 (M^+), 306, 264, 222, 204, 179, 170, 128. **13**: $[\alpha]^{25}_D$ +7.0° (c 0.4, $CHCl_3$); ^1H and ^{13}C NMR spectra were identical with those of **14**. **15**: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.77 (d, 3 H, J = 6 Hz), 0.87 (s, 3 H), 1.22 (d, 3 H, J = 3 Hz), 1.26 (s, 3 H), 2.02 (s, 3 H), 2.98 (br s, 1 H), 4.82 (m, 1 H); EIMS, m/z 254 (M^+).

Ozonolysis of Pyrimidine Derivatives 2b and 3b and Ageline A (10) with Dimethyl Sulfide Reduction. A solution of the pyrimidine derivative **2b** (30 mg, 0.062 mmol) in methanol (1.5 mL) was saturated with ozone at -78 °C for 15 min. After excess ozone was removed by a nitrogen stream, dimethyl sulfide (0.05 mL) was added to the solution and the mixture was allowed to stand at 0 °C for 30 min and at room temperature overnight. The solvent was removed under reduced pressure and the residue was separated by HPLC on a silica gel column (Develosil 60-3, 10×250 mm) with 8:2 benzene/acetone to give the aldehyde **16** (8 mg, 57% theoretical yield). By the same procedure, the aldehydes **16** and **17** were obtained from **3b** (46% theoretical yield) and **10** (17% theoretical yield), respectively. The $[\alpha]^{20}_{296}$ values of the aldehydes in hexane from **2b**, **3b**, and **10** were -156°, -141° (**16**), and +130° (**17**), respectively. **16**: ^1H NMR ($CDCl_3$, 90 MHz) δ 0.85 (d, 3 H, J = 7 Hz), 1.03 (s, 3 H), 2.11 (s, 6 H), 9.75 (t, 1 H, J = 2 Hz).

Acknowledgment. We acknowledge Dr. T. Hoshino (Mukaishima Marine Biological Station, Hiroshima University) for his kind identification of the sea sponge and Prof. T. Miyazawa, Dr. Higashijima (Department of Biophysics and Biochemistry, University of Tokyo), Dr. H. Ohtani, and T. Hayase (Central Research Laboratories, Mitsubishi Chemical Industries Ltd.) for NMR measurements. We also thank Z. Nagahama for his assistance of collecting the sea sponge and R. Abe for her technical assistance.

Registry No. **1a**, 87853-53-0; **1b**, 87853-54-1; **2a**, 96617-50-4; **2b**, 96617-51-5; **3a**, 96617-52-6; **3b**, 96617-53-7; **10**, 88929-28-6; **12**, 96617-54-8; **13**, 96648-00-9; **14**, 87891-78-9; **15**, 96617-55-9; **16**, 96617-56-0; **17**, 96617-57-1; ATPase, 9000-83-3; 2,4-pentanedione, 123-54-6.