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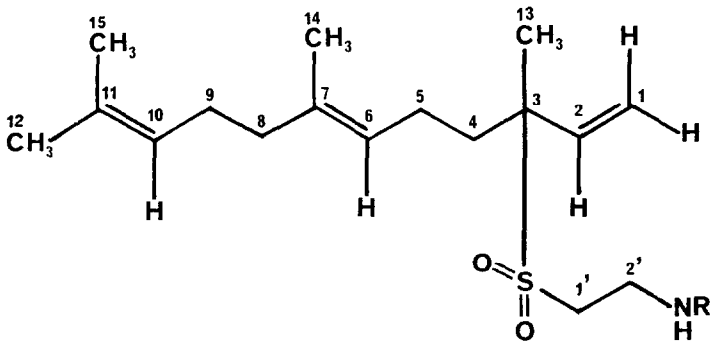
AGELASIDINE-A, A NOVEL SESQUITERPENE POSSESSING ANTISPASMODIC ACTIVITY FROM THE OKINAWA SEA SPONGE AGELAS SP.[1)]

Hideshi Nakamura*, Houming Wu[2)], Jun'ichi Kobayashi and Yasushi Ohizumi
Mitsubishi-Kasei Institute of Life Sciences,
11 Minamiooya, Machida-shi, Tokyo 194, Japan
Yoshimasa Hirata
Faculty of Pharmacy, Meijo University, Tempaku, Nagoya 468, Japan
Tsutomu Higashijima and Tatsuo Miyazawa
Department of Biophysic and Biochemistry, Faculty of Science,
University of Tokyo, Hongo, Tokyo, Japan

Summary: A novel sesquiterpene, agelasidine-A possessing antispasmodic activity has been isolated from the sea sponge Agelas sp. and the structure has been determined on the basis of the spectral data and chemical degradation experiments.

In the course of our survey on physiologically active substances in marine organisms[3)], much attention was given to the occurrence of substances possessing antispasmodic activity in the Okinawa sea sponge Agelas sp. We now report here the structure of a main active component, named agelasidine-A isolated from the sea sponge. Agelasidine-A has a uniquely substituted acyclic sesquiterpene structure with sulfone and guanidine functions.

The sea sponge Agelas sp. was collected at Okinawa island in July, 1981. The methanolic extract of the sea sponge (5 Kg, wet weight) was fractionated by monitoring the antispasmodic activity using isolated guinea-pig ileum[4)]. The methanol soluble material (125 g) of the extracts was partitioned between chloroform and water. The chloroform layer was evaporated under reduced pressure to obtaine a brownish residue (60 g), which was separated by flash chromatography on a silica gel column using chloroform-n-butanol-acetic acid-water (1.5:6:1:1) as eluant to give a crude material (12 g). The crude material was further chromatographed twice on a ODS column using first methanol-water (8:2) containing 0.2 M NaCl and then methanol-water (3:1) containing 0.2M NaCl as mobile phase to yield a colorless oil (2.8 g). The material was crystalized from ethyl acetate to afford colorless crystals (1.7 g, 0.034% yield from wet weight of the sea sponge) of agelasidine-A hydrochloride 1, mp. 108-108.5°C, $[\alpha]_D^{25}$ +19.1° (c 1, MeOH).[5)] The elemental analysis of 1 indicated the presence of sulfur (Found: C, 54.39%; H, 8.52%; N, 10.43%; S, 7.50%; Cl, 9.72%, Calcd for $C_{18}H_{33}N_3O_2S \cdot HCl \cdot 1/3H_2O$: C, 54.32%; H, 8.78%; N, 10.56%; S,



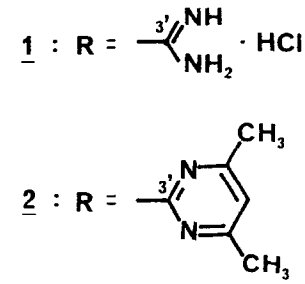


Table 1. ^{1}H-NMR data[a)] for agelasidine-A 1 and the pyrimidine derivative 2 in CD_3OD and C_6D_6, respectively.

	1	2
1-H	5.49 (d, J=17.5 Hz)	4.90 (d, J=17 Hz)
	5.56 (d, J=11 Hz)	4.98 (d, J=11 Hz)
2-H	5.98 (dd, J=11,17.5 Hz)	5.87 (dd, J=11,17 Hz)
3-CH_3	1.44 (s)	1.19 (s)
4-H	1.68-2.06 (m)	2.00 (m)
5-H		1.88 (m)
6-H	5.11 (brt, J=6.0 Hz)	5.06 (brt, J=6.3 Hz)
7-CH_3	1.50 (brs)	1.50 (s)
8-H	1.68-2.06 (m)	2.02 (m)
9-H		2.13 (m)
10-H	5.05 (brt, 7.0 Hz)	5.21 (brt, J=6.5 Hz)
11-CH_3	1.50 (brs)	1.57 (brs)
12-H	1.58 (brs)	1.69 (brs)
1'-H	3.25, 3.28 (ABX_2, J=14,6.5 Hz)	2.92 (t, J=6.5 Hz)
2'-H	3.68 (t, J=6.5 Hz)	3.91 (q, J=6.5 Hz)
NH	——	5.57 (brt, J=6.5 Hz)
Pyrimidine	——	2.09 (s), 5.90 (s)

a) δ in ppm.

8.06%; Cl, 8.91%). The field desorption mass spectrometry of 1 showed the most intense M+H ion at m/z 356.

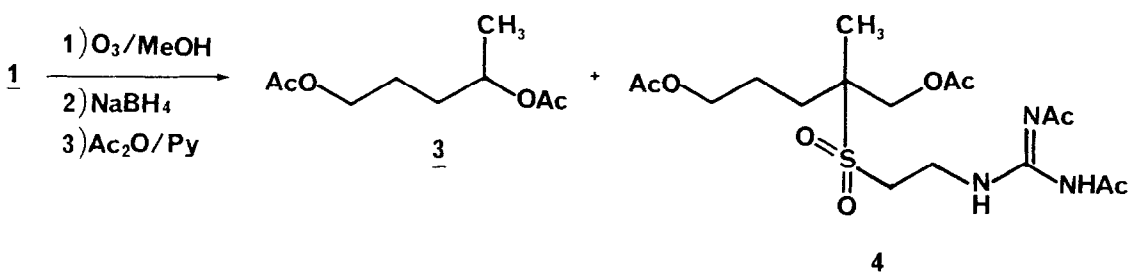
The guanidine function was suggested by a positive Sakaguchi test and a ^{13}C-NMR absorption at δ 157.5 ppm and was confirmed by the formation of the pyrimidine derivative 2[6)] on treatment with 2,4-pentanedione in pyridine (125°C, 2.5 hr)[7)]. The product 2 gave a high resolution electron impact molecular ion at m/z 419.2601 ($C_{23}H_{37}N_3O_2S$, calcd mass; 419.2604), indicating the molecular formula $C_{18}H_{33}N_3O_2S$ for 1. The 270 MHz ^{1}H-NMR spectrum of 2 showed well resolved signals (Table 1). The double resonance decoupling

Table 2. ^{13}C-NMR data[a] for agelasidine-A 1 and the pyrimidine derivative 2 in CD_3OD and C_6D_6, respectively.

	1	2		1	2
1-C	121.7 (t)	120.1 (t)	10-C	122.6 (d)[b]	123.0 (d)[b]
2-C	134.7 (d)	136.0 (d)	11-C	131.3 (s)	131.3 (s)
3-C	68.3 (s)	67.9 (s)	11-CH_3	17.6 (q)	17.7 (q)
3-CH_3	16.0 (q)	16.0 (q)	12-C	25.6 (q)	25.6 (q)
4-C	22.8 (t)	22.2 (t)	1'-C	46.0 (t)	46.7 (t)
5-C	31.6 (t)	32.0 (t)	2'-C	35.0 (t)	35.0 (t)
6-C	124.1 (d)[b]	124.3 (d)[b]	3'-C	157.5 (s)	161.9 (s)
7-C	136.4 (s)	136.2 (s)	pyrimidine	——	167.4 (s)
7-CH_3	16.0 (q)	16.0 (q)		——	23.9 (q)
8-C	39.6 (t)	39.7 (t)		——	110.1 (d)
9-C	26.6 (t)	26.7 (t)			

a) δ in ppm. ( ); Multiplicity in off-resonance decoupled spectra.

b) Each assignment may be exchanged.



experiments indicated the partial structures, $(CH_3)_2C=CH-CH_2-CH_2-$, $CH_3-\overset{|}{C}=CH-CH_2-CH_2-$, $CH_2=CH-$, $CH_3-\overset{|}{C}-$ and $-CH_2-CH_2-NH-X$. The X part is a pyrimidine group in 2, i.e., aminoiminomethyl in 1. The remained elements are one sulfur and two oxygen atoms.

As shown in Table 2, the ^{13}C-NMR spectrum of 2 showed 21 signals, which were assigned to each carbons by the off-resonance and proton selective decoupling experiments. In the molecule, there is no carbon attach to an oxygen atom. Furthermore, the signals corresponding to 3 and 1' carbons were observed at δ 68.3 and 46.0 ppm, respectively, suggesting that the two carbons attach to a sulfur atom of a sulfone group.

The location of double bonds of 1 was established by ozonolysis. Compound 1 was treated with ozone in methanol at -78°C for 1.5 hr. The product of ozonolysis was reduced with sodium borohydride, followed by acetylation with acetic anhydride in pyridine, to afford a diacetyl compound 3[8] and a tetra-acetyl compound 4[9]. The high field resonance (δ 16.0 ppm) for the vinyl methyl carbon at 7 position of 1 indicated steric shielding by the cis-allylic methylene group, namely, an E-configuration for the trisubstituted double bond at 6 position.

Agelasidine-A is the first marine natural product containing guanidine and sulfone units. From a biogenetic point of view, agelasidine-A may be originated from farnesol and cysteine.

The chemical and pharmacological study in detail on agelasidine-A and its related substances are in progress.

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4. J. Kobayashi, H. Nakamura, Y. Hirata and Y. Ohizumi, Toxicon, 20, 823 (1982).
5. 1: UV(MeOH) λ_{max} < 200 nm. IR(KBr) ν_{max} 3350, 3160, 1678, 1648, 1620, 1460, 1380, 1295, 1135, 1005, 945 and 830 cm^{-1}.
6. 2: colorless needles, mp 52-53°. UV(MeOH) λ_{max} 235 nm (ε 17500) and 294 nm (ε 4000). $[\alpha]_D^{25}$ +11.3° (c 1, MeOH). IR(KBr) ν_{max} 3250, 3085, 1600, 1570, 1360, 1340, 1295, 1135, 1095, 935 and 795 cm^{-1}.
7. M.T. Cheng and K.L. Rinehart, Jr., J. Amer. Chem. Soc., 100, 7409 (1978).
8. 3 was identical with an authentic sample prepared from nerolidol by the same procedure.
9. 4: IR($CHCl_3$) ν_{max} 3300, 3040, 1740, 1705, 1620, 1560, 1380, 1325, 1300, 1115 and 1045 cm^{-1}. High resolution mass; 436.1724 (M+1, calcd for $C_{17}H_{30}N_3O_8S$, 436.1697) and 435.1687 (M^+, calcd for $C_{17}H_{29}N_3O_8S$, 435.1701) ^{1}H-NMR ($CDCl_3$) 1.39 (3H, s), 1.86 (4H, m), 2.05 (3H, s), 2.10 (3H, s), 2.12 (3H, s), 2.17 (3H, s), 3.37 (2H, t, J=6.1 Hz), 4.03 (2H, q, J=6.1 Hz), 4.06 (2H, t, J=6.1 Hz), 4.34 (2H, s), 9.42 (1H, brt, J=6.1 Hz) and 12.99 (1H, brs).

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