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Nagelamides K and L, Dimeric Bromopyrrole Alkaloids from Sponge *Agelas* Species

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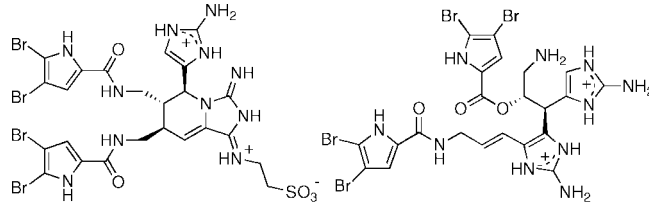
ABSTRACT



nagelamide K (1) nagelamide L (2)

Two new dimeric bromopyrrole alkaloids, nagelamides K (1) and L (2), have been isolated from Okinawan marine sponges *Agelas* species, and the structures and stereochemistry were elucidated from spectroscopic data. Nagelamide K (1) is a bromopyrrole alkaloid possessing a rare piperidinoiminoimidazolone ring with an aminoimidazole ring and a taurine unit, while nagelamide L (2) is a unique dimeric bromopyrrole alkaloid containing an ester linkage. Nagelamides K (1) and L (2) exhibited antimicrobial activity.

Bromopyrrole alkaloids are known to be common metabolites from marine sponges of several genera. During our search for bioactive substances from marine organisms,[1] we have isolated some bromopyrrole alkaloids with unique cyclic skeletons from sponges of the genus *Agelas* or *Hymeniacidon*.[2] Recently, we have investigated extracts of two collections of Okinawan marine sponges *Agelas* sp. (SS-1134 and SS-1077) and isolated two new dimeric bromopyrrole alkaloids, nagelamides K (**1**) and L (**2**), respectively.[3]

Nagelamide K (**1**, Figure 1) is a new dimeric bromopyrrole alkaloid possessing a piperidinoiminoimidazolone ring with an aminoimidazole ring and a taurine unit, while nagelamide L (**2**) is a unique dimeric bromopyrrole alkaloid containing an ester linkage. Here we describe the isolation and structure elucidation of **1** and **2**.

The sponge *Agelas* sp. (SS-1134) collected off Seragaki beach, Okinawa, was extracted with MeOH. BuOH-soluble materials of the extract were subjected to silica gel and C_{18} column chromatographies followed by C_{18} HPLC to yield nagelamide K (**1**, 0.0025% wet weight) as a colorless amorphous solid together with known related alkaloids,

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(3) Nagelamide K (**1**): colorless amorphous solid; $[\alpha]^{23}_{D}$ −4 (*c* 0.5, MeOH); UV (MeOH) λ_{max} 277 nm (ϵ 11 200); IR (KBr) ν_{max} 1685, 1220, 1150, and 1050 cm^{-1}; ESIMS (pos.) *m/z* 896, 898, 900, 902, and 904 [1:4:6:4:1, $(M + H)^+$]; HRESIMS (pos.) *m/z* 895.8573 [$(M + H)^+$, calcd for $C_{24}H_{26}N_{11}O_5{}^{79}Br_4S$, 895.8569]. Nagelamide L (**2**): colorless amorphous solid; $[\alpha]^{20}_{D}$ ν_{max} 3420, 1720, 1680, and 1640 cm^{-1}; ESIMS (pos.) *m/z* 791, 793, 795, 797, and 799 [1:4:6:4:1, $(M + H)^+$]; HRESIMS (pos.) *m/z* 790.8652 [$(M + H)^+$, calcd for $C_{22}H_{23}N_{10}O_3{}^{79}Br_4$, 790.8688].

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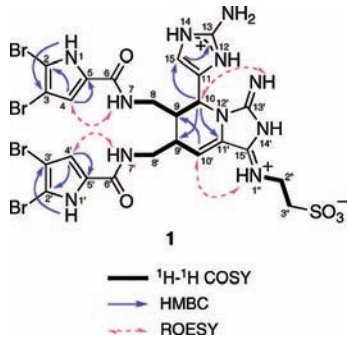

Figure 1. Selected 2D correlations for nagelamide K (**1**).

tauroacidin A,[4] taurodispacamide A,[5] and nagelamide C.[2a] The ESIMS spectrum of nagelamide K (**1**) showed the pseudomolecular ion peaks at *m*/*z* 896, 898, 900, 902, and 904 (1:4:6:4:1), indicating the presence of four bromine atoms, and the molecular formula of **1** was revealed to be $C_{24}H_{25}N_{11}O_5Br_4S$ by HRESIMS data [*m*/*z* 895.8573 (M + H)$^+$, Δ +0.4 mmu]. The UV absorption [λ_{max} = 277 nm (ϵ = 11 200)] was attributed to a substituted pyrrole chromophore,[6] while the IR absorption indicated the existence of amide carbonyl (1685 cm^{-1}) functionality.

The ^{13}C NMR (Table 1) spectrum disclosed 24 signals due to 13 sp^2 quaternary carbons, 4 sp^2 methines, 3 sp^3 methines, and 4 sp^3 methylenes. The ^{1}H NMR (Table 1) spectrum included 10 D_2O-exchangeable signals [δ_H 12.67, 12.62, 12.23, 12.19, 9.94, 9.60, 8.85, 8.31, 8.30, and 7.51] attributed to amino and/or amide protons. Comparison of the ^{1}H and ^{13}C NMR data for **1** with those of known bromopyrrole alkaloids such as nagelamide C[2a] indicated the presence of two 2,3-dibromopyrrole carbonyl moieties (N-1−C-6 and N-1′−C-6′) and a 4,5-disubstituted 2-aminoimidazole ring (C-11′−C-15′).

Detailed analyses of the ^{1}H−^{1}H COSY and HMQC spectra disclosed connectivities of NH-7 to C-10, NH-7′ to C-10′, and NH-1″ to C-3″. The ROESY spectrum showed correlations for NH-7 (δ_H 8.30)/H-4 (δ_H 6.88) and NH-7′ (δ_H 8.31)/H-4′ (δ_H 6.86), indicating that the two 2,3-dibromopyrrole moieties were attached to NH-7 and NH-7′, respectively, through an amide bond. The presence of a piperidinoiminoimidazolone ring (C-9−C-15 and C-9′−C-10′) was deduced from HMBC correlations for H-10′ (δ_H 6.52)/C-9 (δ_C 35.5), H-10 (δ_H 5.24)/C-9′ (δ_C 38.2), and C-11′ (δ_C 130.5). The HMBC cross peak for H-10/C-15 (δ_C 109.7) suggested that an aminoimidazole ring (C-11−C-15) was attached to C-10. The connection of a taurine unit and 13-NH to the piperidinoiminoimidazolone ring was deduced from ROESY correlations for H-10′/NH-1″ (δ_H 9.94) and H-10/13′-NH (δ_H 8.85), respectively. Thus, the gross structure of nagelamide K was assigned as **1**, possessing a piperidinoiminoimidazolone ring with an aminoimidazole ring and a taurine unit.

Table 1. ^{1}H and ^{13}C NMR Data of Nagelamide K (**1**) in DMSO-d_6

position	δ_H		δ_C
1	12.62	br s	–
2	–	–	105.0
3	–	–	98.1
4	6.88	s	113.3
5	–	–	128.1
6	–	–	159.5[a]
7	8.30	br t	–
8	3.20 (2H)	m	41.2
9	2.58	m	35.5
10	5.24	br s	46.9
11	–	–	124.0
12	12.19	br s	–
13	–	–	148.5
13-NH_2	7.51 (2H)	br s	–
14	12.23	br s	–
15	6.45	s	109.7
1′	12.67	br s	–
2′	–	–	104.9
3′	–	–	98.1
4′	6.86	s	113.2
5′	–	–	128.0
6′	–	–	159.4[a]
7′	8.31	br t	–
8′	3.05, 2.79	m	42.5
9′	2.81[a]	m	38.2
10′	6.52	br d	114.6
11′	–	–	130.5
12′	–	–	–
13′	–	–	164.0
13′-NH	8.85	br s	–
14′	9.60	br s	–
15′	–	–	165.2
1″	9.94	–	–
2″	3.69 (2H)	–	40.4
3″	2.82 (2H)	–	49.6

[a] Exchangeable.

The relative stereochemistry for C-9, C-10, and C-9′ in **1** was deduced from analysis of NOESY data. NOESY correlations for H_2-8′/H-9 and H-15 and H-10/H_2-8 indicated that both H-9/H-10 and H-9/H-9′ were *anti* as shown in Figure 2.

EtOAc-soluble materials of the MeOH extract of another sponge *Agelas* sp. (SS-1077) collected off Unten-Port, Okinawa, were subjected to silica gel and C_{18} column chromatographies followed by C_{18} HPLC to yield nagelamide L (**2**, 0.0047%, wet weight) as a colorless amorphous solid together with known related alkaloids, longamide A,[7] tauroacidin A,[4] taurodispacamide A,[5] mauritiamine,[8] and nagelamides B, C, H, and J.[2]

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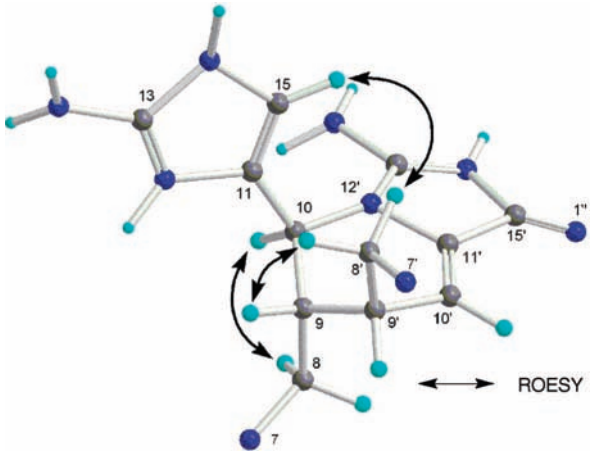

Figure 2. Selected ROESY correlations and relative stereochemistry for C-9, C-10, and C-9′ in nagelamide K (**1**).

The molecular formula of nagelamide L (**2**) was established to be $C_{22}H_{22}N_{10}O_3Br_4$ by HRESIMS data [*m*/*z* 790.8652 $(M + H)^+$, Δ −3.6 mmu]. ^{1}H and ^{13}C NMR data (Table 2) of **2** were close to those of nagelamide B,[2a] while a primary amino proton signal was observed at δ_H 8.23 (2H) in the ^{1}H NMR spectrum of **2**. The chemical shifts for C-8 (δ_C 41.1) and H-9 (δ_H 5.54) of **2** were different from those of nagelamide B (C-8: δ_C 48.6, H-9: δ_H 4.15). Comparison of NMR data of **2** and nagelamide B revealed the presence of two 2,3-dibromopyrrole carbonyl moieties (N-1−C-6 and N-1′−C-6′) and two 2-aminoimidazole moieties (C-11−C-15 and C-11′−C-15′) in **2**. The existence of two proton networks for NH_2-7−H-10 and NH-7′−H-10 was deduced from analyses of the ^{1}H−^{1}H COSY and HSQC spectra (Figure 3). The HMBC correlation for NH-7′ (δ_H 8.45)/C-6′ (δ_C 159.1) and the ROESY correlation for H-4′ (δ_H 6.94)/NH-7′ indicated that one of two bromopyrrole moieties was connected to N-7′ through an amide bond. HMBC correlations of H-10 (δ_H 4.57) to C-11 (δ_C 121.2), C-15 (δ_C 112.1), and C-15′ (δ_C 118.8) suggested that the two 2-aminoimidazole rings were attached to C-10. The connection of C-10′ to C-11′ in the 3,4-disubstituted 2-aminoimidazole ring was inferred from HMBC correlations for H-10′ (δ_H 6.44)/C-11′ (δ_C 123.4) and H-10′/C-15′ and the ROESY correlation for H-10/H-10′. The HMBC correlation for H-9 (δ_H 5.54)/C-6 (δ_C 157.6) indicated that one of 3,4-dibromopyrrole moieties was connected to C-9 through an ester linkage.

Table 2. ^{1}H and ^{13}C NMR Data of Nagelamide L (**2**) in DMSO-d_6

position	δ_H		δ_C
1	12.9	br s	–
2	–	–	108.3
3	–	–	99.3
4	6.91	s	118.8
5	–	–	123.2
6	–	–	157.6
7	8.23 (2H)	br t	–
8	3.21 (2H)	m	41.1
9	5.54	m	69.4
10	4.57	d 8.7	34.4
11	–	–	121.2
12	12.1	br s	–
13	–	–	147.9
13-NH_2	7.63 (2H)	br s	–
14	13.1	br s	–
15	7.04	–	112.1
1′	12.7	br s	–
2′	–	–	105.0
3′	–	–	98.2
4′	6.94	s	113.2
5′	–	–	128.4
6′	–	–	159.1
7′	8.45	t 5.3	–
8′	3.93 (2H)	m	40.9
9′	5.94	m	127.4
10′	6.44	d 15.9	116.3
11′	–	–	123.4
12′	12.5	br s	–
13′	–	–	148.5
13′-NH_2	7.74 (2H)	br s	–
14′	12.7	br s	
15′	–	–	118.8

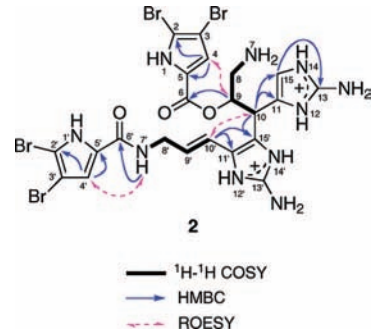

Figure 3. Selected 2D NMR correlations for nagelamide L (**2**).

The relative stereochemistry for the C-9−C-10 bond of nagelamide L (**2**) was elucidated by a relatively large *J*(H-9,H-10) value (8.7 Hz) and ROESY correlations for H_2-8 (δ_H 3.21)/H-15 (δ_H 7.04), H-9/H-15, and H-10/H-10′ (Figure 4).

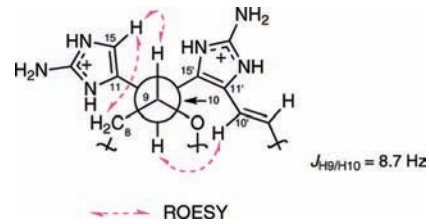

Figure 4. Rotation model for C-9/C-10 bond of nagelamide L (**2**).

Nagelamide K (**1**) is a new dimeric bromopyrrole alkaloid possessing a rare piperidinoiminoimidazolone ring[9] with an aminoimidazole ring and a taurine unit, while nagelamide L (**2**) is a new dimeric bromopyrrole alkaloid containing an ester linkage.[10] Nagelamides K (**1**) and L (**2**) exhibited antimicrobial activity against *Micrococcus luteus* (MIC, both 16.7 μg/mL).

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(10) It has been reported that treatment of oroidin with DMSO/TFA yielded a compound containing an ester linkage: Lindel, T.; Breckle, G.; Hochgürtel, M.; Volk, C.; Grube, A.; Köck, M. *Tetrahedron. Lett.* **2004**, *45*, 8149–8152, However, nagelamide C was not converted into nagelamide L (**2**) under the same condition as described above.

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Supporting Information Available: One- and two-dimensional NMR spectra for nagelamides K and L. This material is available free of charge via the Internet at http://pubs.acs.org.

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