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Slagenins A ~ C, Novel Bromopyrrole Alkaloids from Marine Sponge *Agelas nakamurai*

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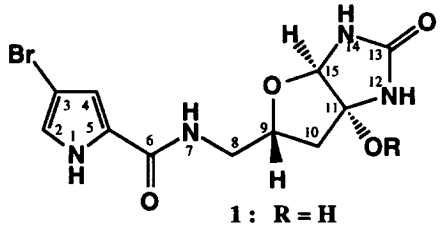
Abstract; Three novel bromopyrrole alkaloids with a unique tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety, slagenins A ~ C (**1** ~ **3**), have been isolated from the Okinawan marine sponge *Agelas nakamurai*, and the structures were elucidated from spectroscopic data.

keywords: sponges; alkaloids; imidazolidines/imidazolidinones

Bromopyrrole alkaloids are known to be one of the most popular metabolites contained in marine sponges.[1] During our search for bioactive substances from marine organisms,[2] we previously isolated several bromopyrrole alkaloids with unique cyclic skeletons such as ageliferins,[3] manzacidins A ~ C,[4] konbu'acidin A,[5] and tauroacidins A and B[6] from *Agelas* or *Hymeniacidon* sponges. Recently we have investigated extracts of the Okinawan marine sponge *Agelas nakamurai*, and isolated three new bromopyrrole alkaloids, slagenins A ~ C (**1** ~ **3**), with a unique tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety. Here we describe the isolation and structure elucidation of **1** ~ **3**.

The sponge *Agelas nakamurai*, collected off Ie Island, Okinawa, was extracted with MeOH. The EtOAc-soluble materials of the extract were subjected to Sephadex LH-20 ($CHCl_3$/MeOH) column chromatography and then repeatedly separated by C_{18} HPLC to yield slagenins A (**1**, 0.0021 %, wet weight), B (**2**, 0.0003 %), and C (**3**, 0.0003 %) as colorless amorphous solids.

Slagenin A[7] {**1**, $[\alpha]_D^{27}$ +11° (*c* 1.2, MeOH)} was revealed to possess the molecular formula, $C_{11}H_{13}N_4O_4Br$, by HRFABMS [*m/z* 345.0206 $(M+H)^+$, Δ +0.8 mmu]. IR absorptions indicated the presence of OH and/or NH (3430 cm^{-1}) and amide carbonyl (1685 cm^{-1}) groups. The UV absorption [λ_{max}270nm (ε 10500)] was attributable to a substituted pyrrole chromophore.[8] The ^1H and ^{13}C NMR (Table 1) spectra showed signals due to a 3-bromopyrrole carbonyl moiety (N-1 ~ C-6).[9] Detailed analyses



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2: R = CH_3
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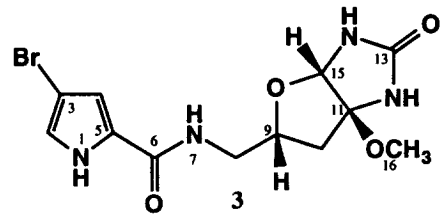

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Table 1. ^{1}H and ^{13}C NMR Data of Slagenin A (**1**) in DMSO-d_6.

position	δ_H[a]			δ_C[b]		NOESY (H)	HMBC (H)
1	11.81	brs				2	
2	6.97	brs		126.7	d		4
3				94.9	s		1, 2
4	6.87	brs		111.7	d	7	1, 2
5				126.7	s		2, 4
6				159.7	s		
7	8.21	t	5.6			8, 9, 10β	
8	3.38	m		41.5	t	10α, 10β	10β
	3.34	m					
9	4.00	m		76.1	d	10α	10β, 15
10 α	2.06	dd	3.6, 11.6	43.0	t	10β, 12	
β	1.73	t	11.6			11-OH, 12	
11				93.3	s		10β, 14, 15
OH	6.25	s				12, 15	
12	7.28	s					
13				159.7	s		12, 14, 15
14	7.30	s				15	
15	4.94	s		91.9	d		10α, 12

[a]600 MHz. [b]125 MHz

of 2D NMR data (^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY) disclosed the presence of a tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety in **1** (Fig. 1). ^{1}H-^{1}H COSY data revealed the connectivities from NH-7 to H_2-10 and from NH-14 to H-15. The NOESY spectrum showed a cross peak for H-4 to NH-7, indicating that the 3-bromopyrrole carbonyl moiety (N-1 ~ C-6) was connected to NH-7 through an amide bond. Long-range correlations from two NH protons (NH-12, δ_H 7.28; NH-14, δ_H 7.30) to an amide carbonyl (C-13, δ_C 159.7) were observed in the HMBC spectrum, suggesting the presence of an ureido moiety. These ureido NH protons, NH-12 and NH-14, showed the three-bond correlations for C-15 [δ_C 93.3 (d)] and C-11 [δ_C 91.9 (s)], respectively. The relatively low-field resonances of C-11 and C-15 implied that these carbons were adjacent to both nitrogen and oxygen atoms. NOESY correlations were observed for NH-12 to 11-OH (δ_H 6.25), indicating that a hydroxyl group was attached to C-11.[10] The methine proton (δ_H 4.94) at C-15 showed the NOESY correlation for NH-14, suggesting the presence of an imidazolidin-2- one moiety. The imidazolidin-2-one ring was shown to be connected to C-10 through C-11 from the HMBC correlations for H-10 (δ_H 2.06) to C-15 and for H-10 (δ_H 1.73) to C-11. The HMBC cross-peak from H-15 to C-9 [δ_C 76.1 (d)] indicated the presence of an ether linkage between C-9 and C-15. Thus slagenin A (**1**) was revealed to have a tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety. Relative stereochemistry of the bicyclic system in **1** was deduced mainly from NOESY data (Fig. 2). The NOESY spectrum of **1** showed the correlations for H-9 to H-10β and H-8 to H-10α, indicating that H-9 was β-oriented. The *cis* ring junction of the bicyclic moiety was suggested by the NOESY correlation for 11-OH to H-15. The NOESY correlation for H-10β to NH-12 indicated that both 11-OH and H-15 possessed α-orientations. Thus the structure of slagenin A was concluded to be **1**.

The molecular formula of slagenin B[11] {**2**, $[\alpha]_D^{26}$ +33° (*c* 0.2, MeOH)} was established to be $C_{12}H_{15}N_4O_4Br$ by HRFABMS [*m/z* 359.0352 $(M+H)^+$, Δ -0.3 mmu]. The ^{1}H and ^{13}C NMR data of **2**

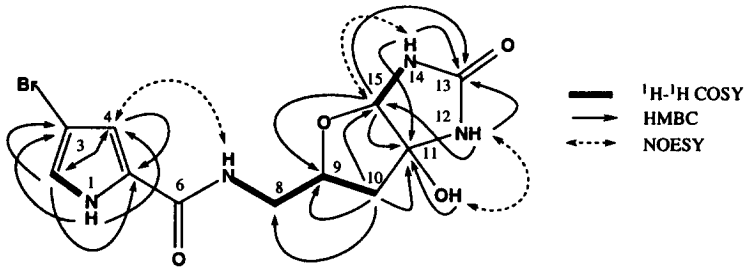

Fig. 1. 2D NMR Correlations for Slagenin A (**1**).

differed from those of **1** only in the presence of a methoxy signal [H_3-16: δ_H 3.13 (s), C-16: δ_C 50.3 (q)]. The HMBC spectrum revealed the long-range correlation from the methoxy proton to C-11 (δ_C 97.8), suggesting that the methoxy group was attached to C-11. The NOESY correlations for H-10α to H_3-16, H-9 to H-10β, and H-15 to H_3-16 implied that H-9, H-15, and the methoxy group at C-11 were β-, α-, and α-oriented, respectively. Thus slagenin B (**2**) was elucidated to be the 11-*O*-methoxy form of slagenin A (**1**).

HRFABMS data [*m/z* 359.0340 $(M+H)^+$, Δ -1.5 mmu] of slagenin C^{12} {**3**, $[\alpha]_D^{25}$ -35° (*c* 0.2, MeOH)} indicated the same molecular formula, $C_{12}H_{15}N_4O_4Br$, as that of slagenin B (**2**), and ^{1}H and ^{13}C NMR data of **3** were close to those of **2**. Although detailed analyses of ^{1}H-^{1}H COSY, HMQC, and HMBC data suggested that slagenin C (**3**) possessed the same gross structure as slagenin B (**2**), the NOESY spectrum implied **3** to be a stereoisomer of **2** in the tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety. The NOESY correlations for H-9 to H-15 and H-15 to H_3-16 indicated that H-9, H-15, and the methoxy group at C-11 were all β-oriented (Fig. 2). Therefore the structure of slagenin C was elucidated to be **3**.

Slagenins A ~ C (**1** ~ **3**) are the first natural products with a tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety.[13] Slagenins B (**2**) and C (**3**) exhibited cytotocity against murine leukemia L1210 cells in vitro with IC_{50} values of 7.5 and 7.0 μg/mL, respectively, whereas slagenin A (**1**) did not show such activity (IC_{50} >10 μg/mL).

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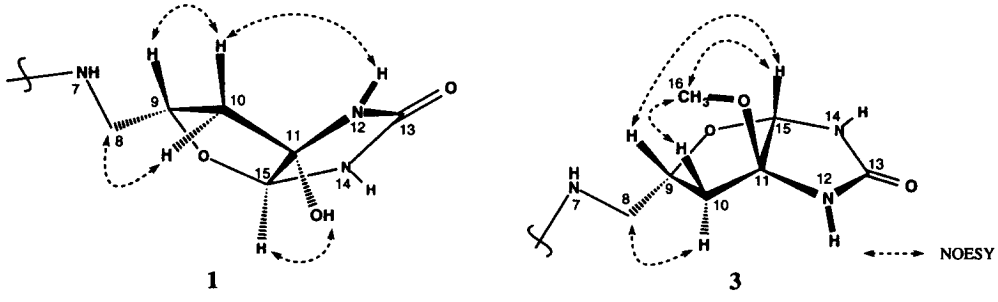

1 **3**

Fig. 2. Relative Stereochemistry of Tetrahydrofuro [2,3-*d*]imidazolidin-2-one Moieties in Slagenins A (**1**) and C (**3**).

References and Notes

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7. **1:** Colorless amorphous solid; $[\alpha]_D^{27}$ +11° (*c* 1.2, MeOH); UV (MeOH) λ_{max} 270 nm (ε 10500); IR (KBr) ν_{max} 3430, 1685, 1635, and 1070 cm^{-1}; FABMS *m/z* 345 and 347 [$(M+H)^+$, 1:1]; HRFABMS *m/z* 345.0206 $(M+H)^+$, calcd for $C_{11}H_{14}N_4O_4{}^{79}Br$, 345.0198.
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11. **2:** Colorless amorphous solid; $[\alpha]_D^{26}$ +33° (*c* 0.2, MeOH); UV (MeOH) λ_{max} 269 nm (ε 9000); IR (KBr) ν_{max} 3435, 1695, 1635, and 1205 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.75 (1H, t, *J* = 11.5 Hz, H-10α), 1.90 (1H, dd, *J* = 3.9 and 11.8 Hz, H-10β), 3.13 (3H, s, H_3-16), 3.40 (2H, m, H_2-8), 4.04 (1H, m, H-9), 5.17 (1H, s, H-15), 6.86 (1H, s, H-4), 6.96 (1H, brs, H-2), 7.45 (1H, s, NH-12), 7.50 (1H, s, NH-14), 8.22 (1H, t, *J* = 5.7 Hz, NH-7), and 11.80 (1H, brs, NH-1); ^{13}C NMR (DMSO-d_6) δ 41.3 (t, C-10), 42.7 (t, C-8), 50.3 (q, C-16), 76.0 (d, C-9), 88.4 (d, C-15), 94.9 (s, C-3), 97.8 (s, C-11), 111.6 (d, C-4), 121.2 (d, C-2), 126.8 (s, C-5), 159.3 (s, C-13), and 160.0 (s, C-6); FABMS *m/z* 359 and 361 [$(M+H)^+$, 1:1]; HRFABMS *m/z* 359.0352 $(M+H)^+$, calcd for $C_{12}H_{16}N_4O_4{}^{79}Br$, 359.0355.
12. **3:** Colorless amorphous solid; $[\alpha]_D^{25}$ -35° (*c* 0.2, MeOH); UV (MeOH) λ_{max} 269 nm (ε 9000); IR (KBr) ν_{max} 3435, 1695, 1635, and 1205 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.89 (1H, dd, *J* = 6.5 and 12.9 Hz, H-10α), 2.27 (1H, dd, *J* = 6.7 and 12.9 Hz, H-10β), 3.11 (3H, s, H_3-16), 3.40 (2H, m, H_2-8), 4.13 (1H, m, H-9), 5.00 (1H, brs, H-15), 6.86 (1H, s, H-4), 6.96 (1H, brs, H-2), 7.65 (1H, s, NH-14), 7.69 (1H, s, NH-12), 8.15 (1H, t, *J* = 5.5 Hz, NH-7), and 11.80 (1H, brs, NH-1); ^{13}C NMR (DMSO-d_6) δ 40.8 (t, C-10), 41.2 (t, C-8), 49.7 (q, C-16), 76.0 (d, C-9), 89.3 (d, C-15), 94.9 (s, C-3), 97.2 (s, C-11), 111.6 (d, C-4), 121.2 (d, C-2), 126.9 (s, C-5), 159.3 (s, C-13), and 159.6 (s, C-6); FABMS *m/z* 359 and 361 [$(M+H)^+$, 1:1]; HRFABMS *m/z* 359.0340 $(M+H)^+$, calcd for $C_{12}H_{16}N_4O_4{}^{79}Br$, 359.0355.
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