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Keramamides M and N, Two New Cyclic Peptides with a Sulfate Ester from *Theonella* Sponge

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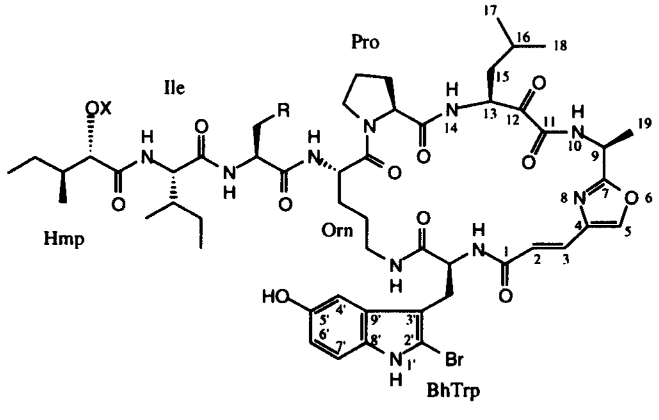
Abstract: Two new cyclic peptides with a sulfate ester, keramamides M (**1**) and N (**2**), have been isolated from an Okinawan marine sponge *Theonella* sp., and the structures were elucidated on the basis of 2D NMR and FABMS/MS data.

Marine sponges are a rich source of bioactive cyclic peptides and depsipeptides with unique structures.[1] Particularly, many cyclic peptides and depsipeptides have been isolated from sponges of the genus *Theonella*.[2,3] In our continuing search for bioactive substances from marine organisms,[4,5] we previously isolated a series of novel cyclic peptides, keramamides A ~ H and J ~ L, from Okinawan marine sponges *Theonella* sp.[6~10] Further investigation on extracts of another *Theonella* sponge resulted in the isolation of two new cyclic peptides with a sulfate ester, keramamides M (**1**) and N (**2**). Here we describe the isolation and structure elucidation of **1** and **2**.

The MeOH extract of the sponge *Theonella* sp. (SS-952) collected off Nakijin, Okinawa, was partitioned between EtOAc and water. The n-BuOH soluble materials of the aqueous layer were subjected



1 $R = CH_3, X = SO_3H$ **3** $R = CH_3, X = H$
2 $R = CH_2CH_3, X = SO_3H$ **4** $R = CH_2CH_3, X = H$

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Table 1. ^1H and ^{13}C NMR Data of Keramamide M (1) in DMSO-d_6.

position		δ_H[a]		δ_C[b]		position		δ_H[a]		δ_C[b]	
Hmp	CO			170.6	s	1				163.9	s
	α	4.35 (m)		79.2	d	2		6.56 (d, 15.8)		123.6	d
	β	1.66 (m)		38.9	d	3		7.15 (d, 15.8)		127.2	d
	γ-CH_2	1.40 (m)	1.03 (m)	23.0	t	4				136.9	s
	γ-CH_3	0.84 (m)		15.9	q	5		8.21 (s)		139.4	d
	δ-CH_3	0.83 (m)		11.8	q	7				165.3	s
Ile	CO			170.3	s	9		4.82 (m)		44.0	d
	NH	8.42 (m)				10		9.17 (d, 5.1)			
	α	4.22 (m)		56.2	d	11				159.3	s
	β	1.61 (m)		37.5	d	12				195.7	s
	γ-CH_2	1.40 (m)	0.98 (m)	24.1	t	13		4.89 (m)		52.7	d
	γ-CH_3	0.84 (m)		15.4	q	14		8.16 (m)			
	δ-CH_3	0.82 (m)		11.4	q	15		1.36 (m)		29.5	t
Aba	CO			170.5	s	16		1.46 (m)		25.3	d
	NH	8.26 (m)				17		0.89 (m)		20.7	q
	α	4.14 (m)		54.8	d	18		0.91 (m)		23.1	q
	β	1.53 (m)		28.5	t	19		1.51 (d, 6.8)		18.1	q
	γ	0.84 (m)		10.5	q	BhTrp	CO			170.2	s
Orn	CO			169.2	s		NH	8.09 (m)			
	NH	7.93 (m)					α	4.57 (m)		53.4	d
	α	4.46 (m)		49.8	d		β	3.05 (m)	2.83 (m)	28.0	t
	β	1.60 (m)	1.36 (m)	37.6	t		1'	11.23 (brs)			
	γ	1.37 (m)		25.1	t		2'			109.6	s
	δ	3.48 (m)	2.70 (m)	38.9	t		3'			109.6	s
	δ-NH	7.47 (m)					4'	6.87 (s)		102.3	d
Pro	CO			171.0	s		5'			150.8	d
	α	4.34 (m)		58.8	d		6'	6.59 (d, 8.6)		111.5	s
	β	2.17 (m)	1.86 (m)	29.0	t		7'	7.01 (d, 8.6)		110.9	d
	γ	1.96 (m)	1.92 (m)	24.4	t		8'			128.3	s
	δ	3.71 (m)	3.51 (m)	46.8	t		9'			130.5	s
							5'-OH	8.16 (brs)			

[a]in 600 MHz. [b]in 125 MHz

to a silica gel ($CHCl_3$/n-BuOH/AcOH/H_2O, 1.5:6:1:1) and an LH-20 ($CHCl_3$/MeOH, 1:1) columns followed by reversed-phase HPLC on ODS ($CH_3CN/H_2O/CF_3CO_2H$, 38:62:0.1) to afford keramamides M (**1**, 2.2 x 10^{-4} %, wet weight) and N (**2**, 1.8 x 10^{-4} %) together with a known peptide, orbiculamide A (1.2 x 10^{-4} %).[11]

Keramamide M (**1**) showed the pseudomolecular ion peak at *m/z* 1187 and 1189 $[(M-H)^-]$ in the ratio of 1:1 in the negative ion ESIMS spectrum, and the molecular formula was established as $C_{52}H_{73}N_{10}O_{15}SBr$ by the positive ion HRESIMS data [*m/z* 1189.4227 $(M+H)^+$, Δ -1.0 mmu]. The intense ion peaks at 80 and 97 observed in the negative ion FABMS spectrum as well as the IR absorption at 1230 cm^{-1} indicated the presence of sulfate ester(s), which was confirmed by ion chromatography of sulfate ions liberated by solvolysis of **1**.[11] Amino acid analyses of the hydrolysate of **1** revealed 1 mol each of alanine (Ala), α-aminobutylic acid (Aba), isoleucine (Ile), proline (Pro), and ornithine (Orn). ^1H and ^{13}C NMR data (Table 1) of **1** were close to those of keramamides B ~ E.[7,9] Extensive analyses of 2D NMR data containing ^1H-^1H COSY, TOCSY, HMQC, HMBC, and ROESY spectra revealed that **1** possessed a 2-hydroxy-3-methylpentanoic acid (Hmp), a 2-bromo-5-hydroxytryptophan (BhTrp), an (alanyl)oxazole (C-1–N-10, and C-19), and a 3-amino-5-methyl-2-oxohexanoic acid (C-11–C-18) moieties. The sequence of amino acid

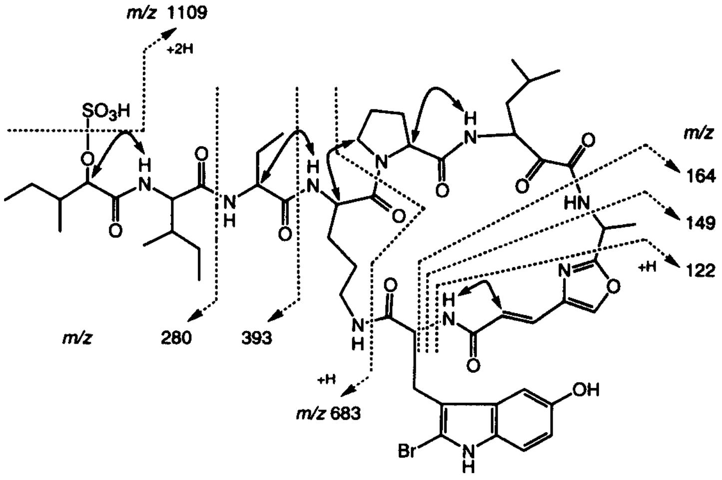

Figure 1. Fragmentation Patterns Observed in Positive Ion FABMS/MS Spectra (Precursor Ion: *m/z* 1191.5) and ROESY Correlations (Arrows) of Keramamide M (**1**).

residues in **1** was elucidated on the basis of FABMS/MS data as well as ROESY data (Figure 1). Signals for α-H (δ_H 4.35) and α-C (δ_C 79.2) of the Hmp residue in **1** were located at lower-field than those (δ_H 3.70 and δ_C 75.0, respectively) of keramamide D[7] (**3**), suggesting that the sulfate group was attached at the α-hydroxy group of the Hmp residue in **1**. Chiral HPLC analyses (SUMICHIRAL OA-5000) of the hydrolysate of **1** revealed that Ala, Aba, Ile, Pro, and Orn were L-form. The BhTrp was converted into Asp by treatment of **1** with ozone followed by CH_3CO_3H, while the 3-amino-5-methyl-2-oxohexanoic acid was transformed into Leu by treatment of **1** with H_2O_2/NaOH.[13] Both Asp and Leu in the degradation products were clarified to be L-form by chiral HPLC analyses. The absolute stereochemistry of Hmp generated by alkaline hydrolysis of **1** was determined to be 2*S* and 3*S* by comparison of retention times in chiral HPLC with those of (2*S*,3*S*)-, (2*S*,3*R*)-, (2*R*,3*R*)-, and (2*R*,3*S*)-Hmp.[14] Thus the structure of keramamide M was concluded to be **1**, corresponding to be the sulfate ester of the Hmp residue of keramamide D (**3**).

The molecular formula of keramamide N (**2**) was elucidated as $C_{53}H_{75}N_{10}O_{15}SBr$ by the positive ion HRESIMS data [*m/z* 1203.4381 $(M+H)^+$, Δ -1.3 mmu]. Amino acid analysis of the hydrolysate of **2** revealed 1 mol each of Ala, Ile, Pro, Orn, and *nor*-valine (*n*-Val). ^{1}H NMR data of **2** were close to those of keramamide E[9] (**4**), except for the chemical shift of α-H (δ_H 4.35) of the Hmp residue, which was almost the same as that of the Hmp residue in **1**, and its molecular formula corresponded to be that of the sulfate ester of **4**. The sequence of amino acid residues in **2** was elucidated by FABMS/MS data. Absolute stereochemistry of each amino acid in **2** was determined to be the same as that of keramamide E (**4**) by chiral HPLC analyses as described above. Thus the structure of keramamide N was assigned to be **2**.

Keramamides M (**1**) and N (**2**) are new keramamide congeners possessing a sulfate ester. Cyclic peptides with a sulfate ester from marine sponges are very rare,[15] although peptides possessing a sulfonate group have been reported.[16] Compounds **1** and **2** exhibited cytotoxicity against L1210 murine leukemia cells (IC$_{50}$ 2.4 and 2.8 μg/mL, respectively) and KB epidermoid carcinoma cells (IC$_{50}$ 6.0 and 7.5 μg/mL, respectively) in vitro.

Experimental Section

General Methods. ^{1}H and 2D NMR spectra were recorded on a 600 MHz spectrometer, and ^{13}C NMR spectra were measured on a 500 MHz spectrometer. ESIMS spectra were recorded on a JEOL JMX-SX-102A spectrometer at 50 V (positive) and -40 V (negative) as a focus voltage using samples dissolved in MeOH with flow rate of 2 μL/min. The MS/MS spectra were obtained on a JEOL HX-110/HX-110 tandem mass spectrometer using dithiothreitol/dithioerythritol as a matrix.

Isolation. The sponge *Theonella* sp. (SS-952) was collected off Nakijin, Okinawa, and kept frozen until used. The sponge (5.8 kg, wet weight) was extracted with methanol (2 L x 2). The methanolic extract (360 g) was patitioned between 1 M NaCl aq. (300 mL) and ethyl acetate (400 mL x 3), and the aqueous layer was subsequently extracted with *n*-BuOH (400 mL x 3). The *n*-BuOH soluble material (6.6 g) was subjected to a silica gel (CHCl$_3$/*n*-BuOH/AcOH/H$_2$O, 1.5:6:1:1), and Sephadex LH-20 columns (CHCl$_3$/MeOH, 1:1), and then C$_{18}$ HPLC [Develosil ODS-HG-5, Nomura Chemical, 10 x 250 mm; eluent, CH$_3$CN/H$_2$O/CF$_3$CO$_2$H (38:62:0.1); flow rate, 2.5 mL/min; UV detection at 270 nm] to afford keramamides M (**1**, 2.2 x 10^{-4} %, wet weight, t_R 20 min), N (**2**, 1.8 x 10^{-4} %, t_R 24 min) and orbiculamide A (1.2 x 10^{-4} %, t_R 38 min). Spectral data of orbiculamide A were in good agreement with reported data.[11]

Keramamide M (1): colorless amorphous solid; IR (film) ν_{max} 3430, 1680, 1650, and 1230 cm^{-1}; UV (MeOH) λ_{max} 269 nm (ε 20000); ^{1}H and ^{13}C NMR (Table 1); ESIMS (negative) 1187 and 1189 (1:1) (M-H)$^-$; FABMS (negative) *m/z* 1187, 1189 (1:1) (M-H)$^-$, 97 (OSO$_3$H$^-$) and 80 (SO$_3^-$); HRESIMS *m/z* 1189.4227 (M+H)$^+$, calcd for C$_{52}$H$_{74}$N$_{10}$O$_{15}$S^{79}Br, 1189.4237.

Keramamide N (2): colorless amorphous solid; IR (film) ν_{max} 3430, 1680, 1650, and 1230 cm^{-1}; UV (MeOH) λ_{max} 270 nm (ε 18000); ^{1}H NMR (DMSO-*d*$_6$) δ [Hmp] 4.35 (1H, m, αH), 1.66 (1H, m, βH), 1.35 (1H, m, γH), 1.12 (1H, m, γH), 0.85 (3H, m, γCH$_3$), 0.84 (3H, m, δCH$_3$), [L-Ile] 8.43 (1H, m, NH), 4.20 (1H, m, αH), 1.60 (1H, m, βH), 1.40 (1H, m, γH), 0.98 (1H, m, γH), 0.84 (3H, m, γCH$_3$), 0.84 (3H, m, δCH$_3$), [L-*n*-Val] 8.12 (1H, m, NH), 4.20 (1H, m, αH), 1.52 (1H, m, βH), 1.43 (1H, m, βH), 1.25 (2H, m, γH$_2$), 0.84 (3H, m, CH$_3$), [L-Orn] 7.90 (1H, m, αNH), 4.45 (1H, m, αH), 1.62 (1H, m, βH), 1.36 (1H, m, βH), 1.35 (2H, m, γH$_2$), 3.70 (1H, m, δH), 3.48 (1H, m, δH), 6.58 (1H, t, *J* = 5.5 Hz, δNH), [L-Pro] 4.32 (1H, m, αH), 2.18 (1H, m, βH), 1.85 (1H, m, βH), 1.95 (1H, m, γH), 1.90 (1H, m, γH), 3.70 (1H, m, δH), 3.48 (1H, m, δH), 6.58 (1H, m, H-2), 7.14 (1H, d, *J* = 16.0 Hz, H-3), 8.20 (1H, s, H-5), 4.80 (1H, m, H-9), 9.15 (1H, d, *J* = 5.3 Hz, H-10), 4.89 (1H, m, H-13), 8.18 (1H, d, *J* = 5.5 Hz, H-14), 1.36 (2H, m, H$_2$-15), 1.46 (1H, m, H-16), 0.94 (6H, m, H$_3$-17 and H$_3$-18), 1.49 (3H, d, *J* = 7.1 Hz, H$_3$-19), [L-BhTrp] 8.05 (1H, d, *J* = 10.5 Hz, NH), 4.57 (1H, m, αH), 3.05 (1H, m, βH), 2.86 (1H, m, βH), 11.18 (1H, brs, H-1'), 6.87 (1H, brs, H-4'), 6.60 (1H, m, H-6'), 7.00 (1H, d, *J* = 8.7 Hz, H-7'), and 8.70 (1H, brs, 5'-OH); ^{13}C NMR (DMSO-*d*$_6$) δ [Hmp] 170.6 (s, CO), 79.3 (d, αC), 39.0 (d, βC), 23.0 (t, γCH$_2$), 15.6 (q, γCH$_3$), 11.8 (q, δCH$_3$), [L-Ile] 170.1 (s, CO), 56.0 (d, αC), 37.2 (d, βC), 24.0 (t, γCH$_2$), 15.4 (q, γCH$_3$), 11.4 (q, δCH$_3$), [L-*n*-Val] 171.5 (s, CO), 51.5 (d, αC), 34.3 (t, βC), 19.0 (t, γC), 13.5 (q, δC), [L-Orn] 169.4 (s, CO), 49.7 (d, αC), 38.0 (t, βC), 25.0 (t, γC), 38.6 (t, δC), [L-Pro] 171.3 (s, CO), 58.3 (d, αC), 29.3 (t, βC), 24.4 (t, γC), 46.6 (t, δC), 163.8 (s, C-1), 123.5 (d, C-2), 127.4 (d, C-3), 137.0 (s, C-4), 139.4 (d, C-5), 165.2 (s, C-7), 43.9 (d, C-9), 159.5 (s, C-11), 195.7 (s, C-12), 52.3 (d, C-13), 29.0 (t, C-15), 24.8 (d, C-16), 20.8 (q, C-17), 23.0 (q, C-18), 17.8 (q, C-19), [L-BhTrp] 170.6 (s, CO), 53.5 (d, αC), 28.0 (t, βC), 109.3 (s, C-2'), 109.2 (s, C-3'), 102.3 (d, C-4'), 150.7 (s, C-5'), 111.3 (d, C-6'), 111.0 (d, C-7'), 128.0 (s, C-8'), and 130.5 (s, C-9'); ESIMS (negative) 1201 and 1203 (1:1) (M-H)$^-$; HRESIMS *m/z* 1203.4381 (M+H)$^+$, calcd for $C_{53}H_{76}N_{10}O_{15}S^{79}Br$, 1203.4394; FABMS/MS (precursor ion: 1203.4) *m/z* 122, 149, 164, 280 (Hmp+SO_3H+Ile)$^+$, 407 (Hmp+SO_3H+Ile+*n*-Val)$^+$, 697 (Hmp+SO_3H+Ile+*n*-Val+Orn)$^+$, and 1123 (M-SO_3H+2H)$^+$.

Solvolysis of Keramamides M (1) and N (2) and Ion Chromatography of Sulfate Ion. Keramamides M or N (**1** or **2**, each 50 µg) were treated with pyridine (20 µL) and dioxane (20 µL) at 120 °C for 1 h. After evaporation, the residue was dissolved in H_2O (100 µL), and passed through a Sep-Pak C_{18} cartridge. The fraction eluting with H_2O was subjected to HPLC analyses (YMC Pack AM-303, YMC Co., Ltd., 4.6 x 250 mm; eluent, H_2O containing 1 mM tetra-*n*-butylammonium hydroxide and 0.8 mM 1,3,5-benzenetricarboxylic acid; flow rate, 0.2 mL/min; UV detection at 280 nm). Retention time of sulfate ion using Na_2SO_4 was found to be 8.4 min. Retention time of solvolysis products of **1** and **2** were found to be both 8.4 min.

Amino Acid Analysis by Chiral HPLC. Keramamides M or N (**1** or **2**, each 100 µg) was dissolved in 6N HCl (100 µL) and heated in a sealed tube at 110 °C for 24 h. Chiral HPLC analyses were carried out using a SUMICHIRAL OA-5000 column [Sumitomo Chemical Ind.; 4 x 150 mm; 40 °C, detection at 254 nm]. Retention times (min) of authentic amino acids were as follows: L-Aba (13.4), D-Aba (16.8), L-Orn (13.9), and D-Orn (17.8) [eluent: 0.8 mM $CuSO_4$ aq., flow rate 0.2 mL/min]; L-Ala (6.6), D-Ala (9.6), L-Pro (12.0), D-Pro (25.2), L-*n*-Val (21.5), and D-*n*-Val (38.7) [eluent: 1.0 mM $CuSO_4$ aq., flow rate 1.0 mL/min]; L-Ile (11.0) and D-Ile (18.4), [eluent: MeOH/H_2O (15:85) containing 2.0 mM $CuSO_4$, flow rate 1.0 mL/min]. Retention times (min) of the hydrolysate of **1** were as follows: L-Aba (13.4), L-Orn (13.9), L-Ala (6.6), L-Pro (12.0), and L-Ile (11.0). Retention times (min) of the hydrolysate of **2** were as follows: L-Orn (13.9), L-Ala (6.6), L-Pro (12.0), L-*n*-Val (21.5), and L-Ile (11.0).

Determination of the Stereochemistry of BhTrp. Keramamides M or N (**1** or **2**, each 100 µg) in AcOH (100 µL) was treated with ozone at -78 °C for 1 min. After remove of excess ozone by a stream of nitrogen, the mixture was treated with 30% H_2O_2 (100 µL) at room temperature for 3 h. The reaction mixture was hydrolyzed with 6N HCl (100 µL) at 110 °C for 5 h. The hydrolysate was subjected to chiral HPLC analyses [SUMICHIRAL OA-5000, 4 x 150 mm; 40 °C, flow rate, 1.0 mL/min; eluent: 1.0 mM $CuSO_4$ aq.]. Retention times of authentic L- and D-Asp were found to be 6.5 and 9.8 min, respectively. The retention times of Asp in the degradation product of **1** and **2** were found to be both 6.5 min (L-Asp].

Determination of the Stereochemistry at C-13. Keramamides M or N (**1** or **2**, each 100 µg) was treated with 5 % NaOH (0.5 mL) and 30 % H_2O_2 aqueous solutions at 65 °C for 45 min. The reaction mixture was hydrolyzed with 6N HCl at 110 °C for 24 h. The hydrolysate was subjected to chiral HPLC analyses using a SUMICHIRAL OA-5000 column [eluent: H_2O containing 1.0 mM $CuSO_4$, flow rate 1.0 mL/min]. Retention times of authentic L-Leu and D-Leu were 4.8 and 6.4 min, respectively, and the retention time of Leu in the hydrolysate of **1** and **2** were both 4.8 min (L-Leu).

Determination of the Stereochemistry of Hmp. Keramamides M or N (**1** or **2**, each 100 µg) was treated with 1N NaOH/MeOH (1:4, 100 µL) at 50 °C for 4 h. After addition of 1N HCl (50 µL) the reaction mixture was extracted with EtOAc (100 µL x 2), and then the organic phase was subjected to chiral HPLC analyses [SUMICHIRAL OA-5000, 4 x 150 mm; eluent: CH_3CN/H_2O (20:80) containing 2.0 mM $CuSO_4$, flow rate 1.0 mL/min]. Retention times (min) of authentic four Hmp isomers were as follows: (2*S*,3*R*)- (24.0), (2*S*,3*S*)- (27.8), (2*R*,3*S*)- (37.5), and (2*R*,3*R*)-Hmp (40.8). The retention times of Hmp in the hydrolysates of **1** and **2** were found to be both 27.8 min [(2*S*, 3*S*)-Hmp].

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