by recrystallization from cyclohexane/ethyl acetate, mp 168–169 °C. Anal. Calcd for $C_7H_5N_3O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.05; H, 3.27; N, 28.44.

Bis([1,2,4]triazolo[1,5-*a*]pyridin-5-yl)methanone (9). The procedure employed was the same as for compound 8. ^{1}H NMR: δ 7.75 (m, 4), 7.94 (s, 2), 8.05 (m, 2). ^{13}C NMR (CD_3SOCD_3): δ 117.52, 120.78, 129.99, 136.20, 149.99, 153.55, 179.65. IR (KBr): 1660, 1615, 1305, 1185 cm^{-1}. Chromatography solvent: 80% ethyl acetate in hexanes. An analytical sample was obtained by recrystallization from ethyl acetate, mp 234.5–236 °C. Anal. Calcd for $C_{13}H_8N_6O$: C, 59.09; H, 3.05; N, 31.80. Found: C, 58.85; H, 2.85; N, 31.45.

Pyrazolo[1,5-*a*]pyridines (10–13) were obtained by a procedure analogous to the general procedure.

7-(Ethylthio)pyrazolo[1,5-*a*]pyridine (10). ^{1}H NMR: δ 1.46 (t, 3, J = 7.4), 3.16 (q, 2, J = 7.4), 6.56 (d, 1, J = 2.2), 6.67 (d, 1, J = 7.0), 7.11 (dd, 1, J = 8.6, 7.0), 7.42 (d, 1, J = 8.6), 8.03 (d, 1, J = 2.2). IR (film): 1615, 1500, 1310, 1210, 775 cm^{-1}. Chromatography solvent: 5% ethyl acetate in hexanes. This compound was obtained as an oil. Anal. Calcd for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.71. Found: C, 60.36; H, 5.56; N, 15.70.

7-Methylpyrazolo[1,5-*a*]pyridine (11). ^{1}H NMR: δ 2.76 (s, 3), 6.56 (s, 1), 6.63 (d, 1, J = 6.6), 7.07 (dd, 1, J = 8.3, 6.6), 7.47 (d, 1, J = 8.3), 8.00 (s, 1). IR (film): 1550, 1310, 1185, 780 cm^{-1}. Chromatography solvent: 5% ethyl acetate in hexanes. This compound was obtained as an oil. Satisfactory analytical data could not be obtained for this compound. HRMS: calcd for $C_8H_8N_2$ 132.0687, found 132.0686.

α-[3-(Trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyridine-7-methanol (12). ^{1}H NMR: δ 6.00 (d, 1, J = 5.6), 6.34 (m, 2), 6.60 (d, 1, J = 2.3), 7.09 (dd, 1, J = 8.9, 7.0), 7.60 (m, 4), 7.84 (s, 1), 7.99 (d, 1, J = 2.3). IR (KBr): 3140, 1330, 1165, 1120, 790 cm^{-1}. Chromatography solvent: 5% ethyl acetate in hexanes. An analytical sample was obtained by recrystallization from hexanes, mp 74–75 °C. Anal. Calcd for $C_{15}H_{11}F_3N_2O$: C, 61.65; H, 3.79; N, 9.59. Found: C, 61.57; H, 3.70; N, 9.56.

7-(Trimethylsilyl)pyrazolo[1,5-*a*]pyridine (13). ^{1}H NMR: δ 0.46, (s, 9), 6.49 (d, 1, J = 2.4), 6.84 (dd, 1, J = 6.7, 1.6), 7.13 (dd, 1 J = 9.0, 6.7), 7.53 (dd, 1, J = 9.0, 1.6), 7.94 (d, 1, J = 2.4). IR (KBr): 1305, 845 cm^{-1}. Chromatography solvent: 1% ethyl acetate in hexanes. This compound was obtained as an oil. Anal. Calcd for $C_{10}H_{14}N_2Si$: C, 63.11; H, 7.41; N, 14.72. Found: C, 63.02; H, 7.25; N, 14.47.

Acknowledgment. The technical assistance of Melissa A. Martz and Christopher J. Strock is gratefully acknowledged. Helpful discussions with Drs. Stephen K. Gee, Matthew F. Schlecht, and Professor Victor Snieckus are also acknowledged.

Keramamide F, a New Thiazole-Containing Peptide from the Okinawan Marine Sponge *Theonella* sp.

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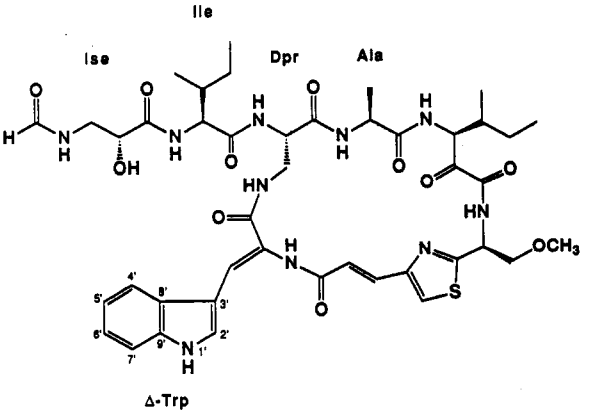
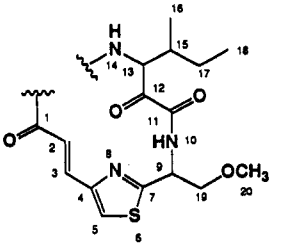
Recently, unique peptides have been isolated from marine sponges[2] and tunicates.[3] We have also reported new cyclic peptides, konbamide[4] and keramamides A–D,[5,6] from Okinawan marine sponges of the genus *Theonella*. Further investigation of extracts of the *Theonella* sponge, from which keramamides B–D have been obtained, resulted in isolation of a novel peptide, named keramamide F (1), containing unusual amino acids such as (*O*-methylseryl)thiazole, α,β-dehydrotryptophan, isoserine, 2,3-diaminopropionic acid, and 3-amino-4-methyl-2-oxohexanoic acid. Here we describe the isolation and structure elucidation of 1.

The MeOH/toluene (3:1) extract of the sponge *Theonella* sp. collected off Kerama Islands, Okinawa, was partitioned between toluene and water. The $CHCl_3$ extract of the aqueous phase was subjected to flash chromatography on a silica gel column followed by gel filtration on a Sephadex LH-20 column and reversed-phase HPLC on ODS to afford keramamide F (1, 0.0001% wet weight) as a colorless solid.



1



2

The molecular formula of keramamide F (1) was established to be $C_{43}H_{56}N_{10}O_{11}S$ by the HRFABMS data [m/z 921.3912 $(M + H)^+$ for $C_{43}H_{57}N_{10}O_{11}S$, Δ +1.7 mmu]. Its peptide nature was suggested by the ^{1}H NMR spectrum of 1, and the amino acid analysis of the hydrolysate of 1 showed the presence of 1 mol each of alanine (Ala), isoserine (Ise), isoleucine (Ile), and 2,3-diaminopropionic acid

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Table I. ^1H and ^{13}C NMR Data (DMSO-d_6) for Keramamide F (1)[a]

position		^1H	J (Hz)	^{13}C	HMBC(^1H)
CHO		8.03 (s)		161.4 (d)	
Ise	CO			171.3 (s)	Ise-OH, Ile-NH, Ise-α
	α	4.03 (m)		70.1 (d)	Ise-OH
	β	3.17 (m)		41.2 (t)	CHO, Ise-OH
		3.50 (m)			
	OH	5.92 (d)	5.9		
	β-NH	7.92 (m)			
Ile	CO			170.1 (s)	Ile-α, Dpr-α-NH
	NH	7.67 (m)			
	α	4.25 (dd)	8.8, 6.8	56.2 (d)	
	β	1.75 (m)		37.1 (d)	Ile-α
	γ-CH_3	0.83 (m)		15.3 (q)	Ile-α
	γ-CH_2	1.05 (m)		24.3 (t)	Ile-α
		1.42 (m)			
	δ-CH_3	0.82 (m)		11.0 (q)	
Dpr	CO			169.8 (s)	Ala-NH
	α-NH	8.17 (d)	7.3		
	α	4.44 (m)		51.1 (d)	
	β	3.00 (m)		41.3 (t)	
		3.94 (m)			
	β-NH	7.45 (m)			
Ala	CO			174.3 (s)	Ala-β, 2-14
	NH	8.11 (d)	5.4		
	α	4.37 (m)		48.8 (d)	Ala-β
	β	1.21 (d)	7.3	17.5 (q)	
2	1			163.8 (s)	Δ-Trp-α-NH, 2-2, 3
	2	7.17 (d)	14.7	124.4 (d)	
	3	7.43 (d)	14.7	132.2 (d)	2-5
	4			149.7 (s)	2-2, 3, 5
	5	7.92 (s)		123.1 (d)	
	7			167.3 (s)	2-5, 9, 19
	9	5.33 (m)		51.7 (d)	2-19
	10	9.06 (d)	8.3		
	11			162.6 (s)	2-10
	12			197.1 (s)	
	13	5.25 (dd)	8.5, 3.9	59.7 (d)	2-16
	14	8.36 (d)	8.5		
	15	2.32 (m)		36.2 (d)	2-16, 17
	16	0.95 (d)	6.8	16.0 (q)	2-17
	17	1.25 (m)		23.4 (t)	2-16
	18	0.82 (m)		11.6 (q)	2-17
	19	3.80 (m)		72.4 (t)	2-9, 20
	20	3.38 (s)		58.4 (q)	2-19
Δ-Trp	CO			165.0 (s)	Δ-Trp-β
	NH	9.03 (s)			
	α			121.7 (s)	
	β	7.83 (s)		123.7 (d)	Δ-Trp-α-NH
	1′-NH	11.52 (br s)			
	2′	7.31 (d)	2.0	127.1 (d)	Δ-Trp-β, 1′-NH
	3′			109.3 (s)	Δ-Trp-1′-NH, 2′
	4′	7.70 (d)	7.3	117.8 (d)	Δ-Trp-5′
	5′	7.18 (dd)	7.3, 6.8	121.9 (d)	Δ-Trp-4′
	6′	7.13 (dd)	7.8, 6.8	120.1 (d)	Δ-Trp-7′
	7′	7.40 (d)	7.8	111.4 (d)	Δ-Trp-6′
	8′			135.2 (s)	Δ-Trp-2′,4′,5′
	9′			127.2 (s)	Δ-Trp-1′-NH, 2′,6′,7′

[a] Recorded on a JEOL EX-400 spectrometer in DMSO-d_6.

(Dpr). Since 1 was negative to ninhydrin, the N-terminus was inferred to be substituted. Extensive analysis of the ^1H and ^{13}C NMR data of 1 (Table I) including ^1H–^1H COSY, HSQC,[7] HMBC,[8] and NOESY spectra in DMSO-d_6 suggested the presence of α,β-dehydrotryptophan (Δ-Trp) and segment 2. The UV spectrum (λ_{max} 339 nm in MeOH) of 1 corresponded well to that of janthinocin C (λ_{max} 339 nm in H_2O),[9] supporting the presence of a Δ-Trp residue. The ^1H and ^{13}C signals for the Δ-Trp residue were assigned by the ^1H–^{13}C long-range couplings observed in the HMBC spectrum (Table I). Moreover, hydrogenation (H_2/Pd–C) of 1 followed by mild acid hydrolysis gave tryptophan, which was detected by the amino acid analysis. The geometry of the α,β-double bond of the Δ-Trp was assigned as *Z* from comparison of the chemical shift of the β-proton (δ_H 7.83) with those of geometric isomers of methyl α-acetamido-6-methylindole-3-acrylate [δ_H 7.69 (*Z*) and 7.00 (*E*)].[10] This result was supported with the NOESY correlation between NH-α and H-2′ of Δ-Trp of 1. Segment 2 was deduced by the NMR data to consist of three modified amino acid residues. The presence of a thiazole ring in segment 2 was indicated by the ^1H and ^{13}C NMR spectral data of 1 [δ_H 7.92 (s, 1 H); δ_C 167.3 s, 123.1 d ($^1J_{C-H}$ = 189 Hz), and 149.7 s]. The thiazole ring was probably derived from an *O*-methylserine residue, and so we designated the C-4–N-10 moiety of segment 2 as (*O*-methylseryl)thiazole. The HMBC correlations for H-5/C-7, H-19/C-7, H-19/C-20, and NH-10/C-9 further verified the presence of the (*O*-methylseryl)thiazole moiety. The α,β-unsaturated amide group (C-1–C-3) attached to this thiazole ring was revealed by the HMBC correlations of H-2/C-4 and H-5/C-3. The (*O*-methylseryl)thiazole group was connected to a 3-amino-4-methyl-2-oxohexanoic acid, which was shown by the HMBC correlation observed between NH-10 and C-11.

Evidence for the amino acid sequence of 1 was provided by NOESY and HMBC correlations and established that segment 2, Δ-Trp, Dpr, and Ala residues were connected in this sequence to construct the cyclic portion of this peptide 1.[11] To the α-NH of the Dpr residue was attached Ile [NOESY cross-peak: Dpr-α-NH/Ile-α-H; HMBC cross-peak: Dpr-α-NH/Ile-CO] and the Ile in turn was connected to the Ise [HMBC cross-peak: Ile-NH/Ise-CO]. The presence of a formyl group (δ_H 8.03; δ_C 161.4 d) attached to the β-amino group of Ise was revealed by the HMBC correlation between the formyl proton and β-methylene carbon (δ_C 41.2) of Ise. Based on these NMR data the structure of keramamide F (1) was therefore as shown in 1, and further corroboration was obtained from the FAB MS/MS spectrum[12] of the molecular protonated ion of 1 (*m*/*z* 921).[13] Chiral GC analysis (Chirasil-Val, Alltech) of the *N*-trifluoroacetyl/methyl ester derivatives of the hydrolysate of 1 clarified that the Ala, Ile, and Dpr residues in 1 were L-form. Treatment of 1 with ozone[14] led to degradation of the (*O*-methylseryl)thiazole moiety to yield *O*-methylserine, while the C-11–N-14 moiety in segment 2 was transformed into isoleucine by treatment of 1 with H_2O_2/NaOH.[6] The *O*-methylserine and isoleucine residues thus obtained were also determined to be L by the chiral GC method, implying that the (*O*-methylseryl)thiazole and the β-amino acid in 2 were also

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(11) The following sequential cross peaks were observed: [NOESY] Dpr-α-CH/Ala-NH, 2-14-NH/Ala-α-CH, 2-2-H/Δ-Trp-α-NH, and Δ-Trp-α-NH/Dpr-β-NH; [HMBC] Δ-Trp-α-NH/2-1-CO and 2-14-NH/Ala-CO.
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(13) The following substantial daughter ions were observed: *m*/*z* 693 [*cyclo*-(Ala-2-Δ-Trp-Dpr) + 2H]$^+$, 607 [(Ala-2-Δ-Trp) + H]$^+$, 536 [(2-Δ-Trp) + H]$^+$, 315 [(HCO-Ise-Ile-Dpr) + H]$^+$, and 229 (HCO-Ise-Ile)$^+$. These MS/MS data, especially ions for the cleavage between ring and side chain (*m*/*z* 693 and 229), revealed the connectivity between ΔTrp and Dpr.
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L. The Ise unit was determined to be *R*-form by HPLC analysis of the *N*-benzoyl-derivatized hydrolysate of 1 on chiral columns (SUMIPAX). Therefore, the total structure of keramamide F was concluded to be 1.

Keramamide F (1) is a peptide having unique structural features containing some unusual amino acids such as isoserine, Δ-Trp, and (*O*-methylseryl)thiazole. (*R*)-Isoserine[15] and (*O*-methylseryl)thiazole have not been previously found in any naturally-occurring peptide. A few peptides containing Δ-Trp[16] have been reported as metabolites of terrestrial microorganisms. Keramamide F (1) showed cytotoxicity against human epidermoid carcinoma KB cells and murine lymphoma L1210 cells with IC_{50} values of 1.4 and 2.0 μg/mL, respectively.

Experimental Section

General Methods. FAB mass spectra were obtained using *m*-nitrobenzyl alcohol as a matrix [bombarding ions (Cs), acceleration (8 kV), and collison gas (He)].

Collection, Extraction, and Separation. The sponge *Theonella* sp. was collected off Kerama Island, Okinawa, and was kept frozen until used. The MeOH/toluene (3:1) extract (1 L × 2) of the sponge (4.0 kg, wet weight) was suspended in 1 M NaCl (1 L) and was extracted with toluene (600 mL × 2). The aqueous layer was subsequently extracted with $CHCl_3$ (800 mL × 2). The $CHCl_3$ soluble fraction (2.1 g) was subjected to flash silica gel column chromatography (4.5 × 36 cm) with gradient elution of MeOH (2–50%) in $CHCl_3$. The fraction eluted with 15% MeOH in $CHCl_3$ was then separated by gel filtration on Sephadex LH-20 (2 × 93 cm) with MeOH to give a crude peptide fraction in the 120–175-mL fraction, which was further purified by reversed-phase HPLC [YMC-Pack AM-324 ODS, Yamamura Chemical, 10 × 250 mm; flow rate 2.5 mL/min; eluent, CH_3CN/H_2O, 40:60] to yield keramamide F (1, 5.1 mg, t_R 23.4 min).

Keramamide F (1): colorless solid; mp 187 °C dec; $[\alpha]^{21}_D$ −25° (*c* 0.86, MeOH); IR (KBr) ν_{max} 3400, 1650, and 1520 cm^{-1}; UV (MeOH) 209 (ε 30 800), 220 (30 800), 275 (23 200), and 339 (9800) nm; ^1H and ^{13}C NMR (Table I); $^1J_{C-H}$ values (Hz) by INEPT experiments (DMSO-d_6) formamide 195 (CHO); Δ-Trp residue 151 (β), 187 (2′), 158 (4′), 160 (5′), and 164 (7′); 2 residue 158 (2), 155 (3), and 189 (5); FABMS (positive) *m/z* 921 $(M + H)^+$; exact mass found *m/z* 921.3912, calcd for $C_{43}H_{57}O_{11}N_{10}S$ 921.3895.

Hydrogenation and Mild Acid Hydrolysis of 1. A solution of compound 1 (100 μg) in MeOH (500 μL) was stirred in the presence of a catalytic amount of 10% Pd–C under H_2 for 1 h at room temperature. The reaction mixture was hydrolyzed with 4 N methanesulfonic acid (100 μL) at 115 °C for 24 h and subjected to amino acid analysis to detect tryptophan. Amino acid analysis indicated that Ala, Ise, Ile, Dpr, and Trp were present in the ratio of 1:1:1:1:0.2.

Amino Acid Analysis by Chiral GC. Compound 1 (100 μg) was hydrolyzed with 6 N HCl (1 mL) at 110 °C for 24 h. The reaction mixture was treated with 9% HCl/MeOH (1 mL) at 100 °C for 30 min and was then treated with trifluoroacetic anhydride (TFAA)/CH_2Cl_2 (1:1, 1 mL) at 100 °C for 5 min. Capillary GC analyses were carried out using a Chirasil-Val column (Alltech, 0.32 mm × 25 m; N_2 as a carrier gas; the program rate: 50–200 °C at 4 °C/min) to show peaks at t_R 3.9, 7.5, and 22.2 min. Standard amino acids were also converted to the TFA/Me derivatives by the same procedure. Retention times (minutes) were as follows: D-Ala (3.6), L-Ala (3.9), D-Ile (7.2), L-Ile (7.5), D-Dpr (21.6), and L-Dpr (22.2).

Determination of the Stereochemistry of the (*O*-Methylseryl)thiazole. A stream of O_3 was bubbled into a 1-mL MeOH solution of compound 1 (200 μg) at room temperature for 8 min. The reaction mixture was subjected to hydrolysis and TFA/Me derivatization. The chiral GC analysis of the TFA/Me derivatized hydrolysate was carried out as above and established the presence of L-*O*-methylserine [t_R: L-*O*-methylserine (6.8 min) and D-*O*-methylserine (6.6 min)].

Determination of the Stereochemistry of the C-11–C-14 Moiety in Segment 2. To a stirred solution of compound 1 (100 μg) in 5% NaOH (300 μL) was added dropwise 30% H_2O_2 (50 μL). After stirring at 65 °C for 20 min the reaction mixture was subjected to hydrolysis and TFA/Me derivatization. Only the L-form of Ile (t_R 7.5 min) was observed by the chiral GC analysis as above, and the peak area for Ile was nearly doubled compared to 1.

Determination of the Stereochemistry of the Isoserine. Compound 1 (100 μg) was hydrolyzed with 6 N HCl (500 μL) at 110 °C for 24 h. The reaction mixture was treated with 9% HCl/MeOH (1 mL) at 100 °C for 30 min and was then treated with benzoyl chloride/Et_3N/CH_2Cl_2 (1 μmol/1 μmol/0.5 mL) at room temperature for 2 h. Evaporation under reduced pressure afforded a residue, which was subjected to the chiral HPLC analysis using SUMIPAX OA-1000 (Sumitomo Chemical Industry, 4 × 150 mm) and two SUMIPAX OA-4100 (4 × 250 mm) columns connected in tandem [37 °C; flow rate: 0.7 mL/min; eluent: *n*-hexane/1,2-dichloroethane/ethanol (15:5:1); detection: UV at 240 nm]. Retention times of (*S*)- and (*R*)-*N*-benzoylisoserine were 35.5 and 36.6 min, respectively. The retention time of the *N*-benzoylisoserine derived from the hydrolysate of 1 was found to be 36.6 min.

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Supplementary Material Available: All spectra of keramamide F (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Stereoselective Synthesis of *N,N*-Divinylureas by Diiron Enneacarbonyl-Catalyzed Isomerization of N,N-Diallylic or N-Allylic *N*-Vinylureas

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In contrast to the well-developed chemistry of enamines and enamides,[1] the chemistry of amines with two vinyl groups attached to nitrogen has not been explored, in spite of its potential utility.[2] There are as yet no general methods available for the preparation of *N,N*-divinylamides. Although some *N,N*-divinylamides[3] have been

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