A Chemical Study of Cyclic Depsipeptides Produced by a Sponge-Derived Fungus

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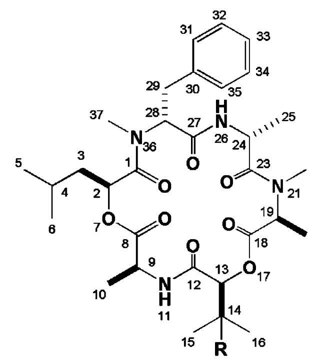
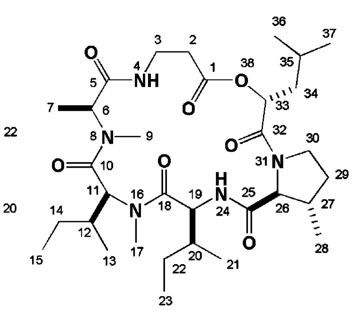
Two novel cyclic depsipeptides, guangomides A (**1**) and B (**2**), together with a new destruxin derivative (**3**) were isolated from the cytotoxic extract obtained from the saltwater culture of an unidentifiable sponge-derived fungus. The new structures were elucidated on the basis of analysis of extensive 1D and 2D NMR data sets, and the absolute configurations of 2*S*, 9*S*, 13*S*, 19*S*, 24*R*, 28*R* of **1** were determined on the basis of the combined X-ray and Marfey's method structure analysis. Identical absolute configurations were assumed for **2**. The cytotoxicity of the extract was found to be due to brefeldin A, while **1** and **2** showed weak antibacterial activity against *Staphylococcus epidermidis* and *Enterococcus durans*.

Marine invertebrates are known to be a source of structurally fascinating and biologically active peptides and depsipeptides. Some most noteworthy examples include the peptide anticancer drug candidates dolastatin 10,[1] from the sea hare *Dolabella auricularia* (but also the cyanophyte *Symploca* sp. VP642[2]), and kahalalide F[3] from the herbivorous marine mollusk *Elysia rufescens* (and also its dietary alga *Bryopsis* sp.). Significantly, both of these chemotypes are continuing subjects of clinical evaluation.[4] Two closely related PKS/NRPS cyclidepspeptides—jasplakinolide from sponges[5] and chondramide C from myxobacteria[6]—are of much interest because they are both potent in causing the hyperassembly of G-actin into F-actin.[4,7] Our attempts to date to discover marine-derived fungi as a source of unusual peptides have been somewhat successful. These include the isolation of the cytotoxic bicyclic peptide malformin C from *Aspergillus niger*[8] and highly *N*-methylated linear peptides of the RHM family from an atypical sponge-derived *Acremonium* sp.[9] Recently we began a project stimulated by the observation that extracts of an unidentifiable fungal strain (see Experimental Section) separated from an *Ianthella* sponge possessed potent cytotoxicity and selectivity in our disk diffusion assay system.[10] Most importantly its ^{13}C NMR spectra displayed clusters of peaks centered at δ 175. The initial bioassay-guided dereplication efforts showed that brefeldin A[11] was a nonpeptide major component responsible for the cytotoxicity. Subsequently, deeper evaluation of crude extract fractions to obtain minor cytotoxic metabolites employing bioassay and LCMS data led to the discovery of three novel cyclic depsipeptides, named guangomides A (**1**) and B (**2**) and homodestcardin (**3**). We now describe the structure elucidation and the biological activity of these depsipeptides.



1: R = OH
2: R = H



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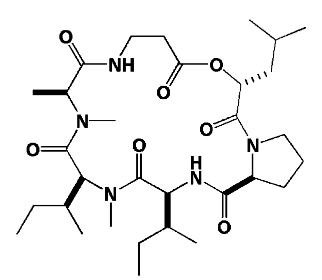

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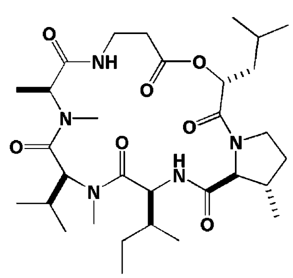

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Results and Discussion

The molecular formula of $C_{31}H_{46}N_4O_9$ (m/z = 641.3152 [M + Na]$^+$) was established for guangomide A (**1**) by the HRESIMS data. The low-field ^{13}C NMR resonances noted above were confirmed to be associated with a peptidic functionality, which was further validated by ^{1}H NMR data showing the presence of two amide protons, six α-protons, and two *N*-methyl groups. There were a total of six carbonyl carbons in the ^{13}C NMR spectrum (Table 1). Four of those carbonyl carbons were assigned as amide carbons and consistent with the four nitrogen atoms in the molecular formula. Therefore, the assumption that two ester carbons were present was verified by the HMBC correlations from two α-oxy methines (δ_H 5.00, δ_C 70.5 and δ_H 5.22, δ_C 76.5) to these carbonyl carbons (δ_C 172.6, 169.0).

There were six carbonyl-containing substructures envisioned on the basis of the 2D NMR data, and they are shown in Figure 1. Further, as expected, the gCOSY spectrum of **1** revealed six distinct spin systems. The first included the subset associated with the 2-hydroxyisocaproic acid (**A**). Another cluster included the three sets of overlapping resonances for the alanine residues (**B**, **D**, and **E**). The protons associated with the phenylalanine residue (**F**) were identified by HMBC correlations (H28/C30 and H29/C31, C35) shown in Figure 1. Finally, the remaining subunit, 2,3-dihydroxy-isovaleric acid (**C**), was established by the HMBC correlations

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Table 1. ^{1}H and ^{13}C NMR Data for Guangomides A (**1**) and B (**2**) in $CDCl_3$[a]

		1					**2**		
structural	unit	δ_C (mult.)	δ_H (J in Hz)	gCOSY	gHMBC	NOESY	δ_C (mult.)	δ_H (J in Hz)	gHMBC
S-Hic	1	172.4 (qC)					172.4 (qC)		
	2	70.5 (CH)	5.00 dd, (8.7, 6.2)	3a, 3b	1, 3, 4, 8	3a, 3b, 4, 5, 6, 37	70.3 (CH)	5.00 dd (8.9, 6.4)	1, 3, 4, 8
	3a	38.8 (CH_3)	0.98 ddd, (14.2, 6.2, 5.3)	2, 3b	1, 4, 5, 6	2, 3b, 4, 5, 6, 37	38.8 (CH_3)	0.96 ddd (14.2, 6.4, 5.3)	2, 4, 5, 6
	3b		1.55 ddd (14.2, 8.7, 6.7)	2, 3a, 4	1, 2, 4, 5, 6	2, 3a, 4, 5, 6		1.54 m	4, 5, 6
	4	23.8 (CH)	1.15 m	3a, 5, 6	3, 5, 6	2, 3a, 3b, 5, 6, 31, 32, 34, 35, 37	23.8 (CH)	1.19 hept (6.7)	
	5	22.8 (CH_3)	0.78 d (6.6)	4	3, 4, 6	2, 3a, 3b, 4, 31, 32, 34, 35, 37	22.9 (CH_3)	0.78 d (6.6)	3, 4, 6
	6	22.3 (CH_3)	0.72 d (6.6)	4	4, 5, 6	2, 3a, 3b, 4, 31, 32, 34, 35, 37	22.2 (CH_3)	0.72 d (6.6)	4, 5, 6
L-Ala	8	172.6 (qC)					172.9 (qC)		
	9	47.1 (CH)	4.97 dq (8.7, 7.1)	11	8, 10, 12	10, 11	47.0 (CH)	4.98 dq (8.9, 7.4)	8, 10
	10	19.3 (CH_3)	1.53 d (7.1)		8, 9	9, 11	19.3 (CH_3)	1.52 d (7.4)	8, 9
	11		8.22 d (8.7)	9	12	9, 10, 13, 15		7.89 d (8.5)	
S-Dhiv	12	169.8 (qC)					168.5 (qC)		
(*S*-Hiv)	13	76.5 (CH)	5.22 s		12, 14, 15, 16, 18	11, 15, 16	78.0 (CH)	5.23 d (2.5)	12, 14, 15, 16
	14	71.8 (qC)					30.0 (CH)	2.61 hept d (6.7, 2.5)	
	15	26.7 (CH_3)	1.17 s		12, 13, 14, 16	11, 13, 16, OH	19.2 (CH_3)	0.93 d (6.7)	13, 14, 16
	16	24.1 (CH_3)	1.26 s		13, 14, 15	13, 15, OH	15.8 (CH_3)	0.92 d (6.7)	13, 14, 15
	OH		5.27 br s			15, 16			
L-N-MeAla	18	169.0 (qC)					169.7 (qC)		
	19	60.5 (CH)	3.69 q (6.8)	20	18, 20, 22, 23	20, 22	60.7 (CH)	3.69 q (6.8)	18, 20, 22, 23
	20	13.5 (CH_3)	1.52 d (6.8)	19	18, 19	19, 22	13.6 (CH_3)	1.54 d (6.9)	18, 19
	22	36.9 (CH_3)	3.20 s		19, 23	19, 20, 24, 25	36.9 (CH_3)	3.19 s	19, 23
D-Ala	23	171.3 (qC)					171.1 (qC)		
	24	46.2 (CH)	4.85 quint (7.1)	25, 26	23, 25, 27	22, 25, 26	46.3 (CH)	4.84 quint (7.1)	23
	25	18.1 (CH_3)	1.41 d (6.8)	24	23, 24	22, 26, 37	18.1 (CH_3)	1.42 d (6.7)	23, 24
	26		7.09 d (7.3)	24	27	24, 25, 28, 29a		7.12 d (7.4)	
D-N-Me-Phe	27	168.5 (qC)					168.5 (qC)		
	28	56.6 (CH)	5.76 dd (11.9, 5.3)	29a, 29b	1, 27, 29, 37	26, 29a, 29b, 31, 35	56.5 (CH)	5.76 dd (11.8, 5.3)	1, 27, 29, 37
	29a	33.2 (CH_2)	2.92 dd (15.3, 11.8)	28, 29b	27, 28, 30, 31, 35	26, 29b, 28, 31, 35	33.2 (CH_2)	2.92 dd (15.1, 11.8)	27, 30, 31, 35
	29b		3.49 dd (15.3, 5.3)	28, 29a	28, 30, 31, 35	28, 29a, 31, 35		3.47 dd (15.1, 5.3)	27, 30, 31
	30	137.1 (qC)					137.1 (qC)		
	31, 35	128.6 (CH)	7.16 m	32, 34	29, 30, 32, 33, 34	5, 6, 28, 29a, 29b	128.6 (CH)	7.16 m	29, 30, 32, 33, 34
	32, 34	128.4 (CH)	7.24 m	31, 33, 35	30, 31, 33, 35	5, 6	128.4 (CH)	7.24 m	30, 31, 33, 35
	33	126.6 (CH)	7.19 m	32, 34	31, 32, 34, 35		126.6 (CH)	7.19 m	31, 32, 34, 35
	37	30.2 (qC)	2.92 s		1, 28	2, 3a, 4, 5, 6, 25	30.1 (qC)	2.92 s	1, 28

[a] Measured at 500 MHz (^{1}H) and 125 MHz (^{13}C).

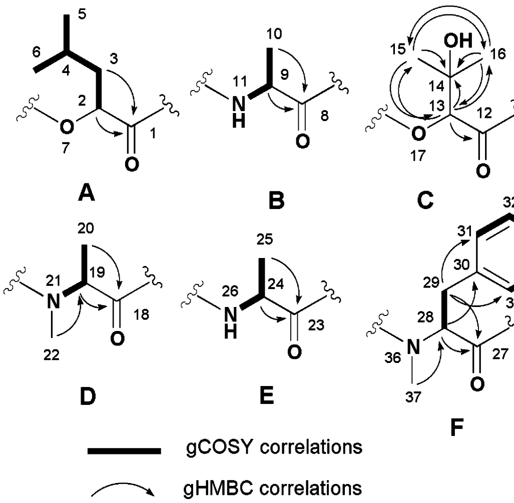

Figure 1. Structural units for **1**.

(H13/C14, C15, C16, H15, H16/C13) also shown in Figure 1. Next, the locations of the *N*-methyl groups (δ_H 3.20, δ_C 36.9 and δ_H 2.92, δ_C 30.2) were affirmed as connected to the alanine (**D**) and the phenylalanine (**F**) on the basis of the HMBC correlations (H22/C19, H37/C28). The final task of sequencing the six subunits was accomplished on the basis of the HMBC correlations from the α-protons, the amide protons, and the *N*-methyl groups to the carbonyl carbons (H2/C8, H9, NH11/C12, H13/C18, H19, H22/C23, H24, NH26/C27, H28, H37/C1), as detailed in Figure 2.

Assignment of the absolute configuration for the amino acid residues was accomplished using complementary approaches. A D-*N*-methyl-phenylalanine was assigned on the basis of results derived from HPLC analysis of the products obtained from the Marfey's acid hydrolyzate.[12] Though our attempts to determine the relative configurations of chiral centers using NOESY data were unsuccessful, positive results were obtained through the X-ray analysis structure of **1** shown in Figure 3.[13] Combining the relative configurations deduced from the X-ray data and using the D-*N*-methyl-phenylalanine as an anchor point supported the final absolute stereostructure as 2*S*, 9*S*, 13*S*, 19*S*, 24*R*, 28*R*.

The next compound to be analyzed was guangomide B (**2**), whose molecular formula of $C_{31}H_{46}N_4O_8$ differed from that of **1** by just a single oxygen atom. Not surprisingly, its ^{13}C and ^1H NMR spectra (Table 1) were almost identical with those of **1**. The differences included shifted ^{13}C resonances for the C13/C14/C15/C16 of **2** versus **1**, consistent with the proposal that an H group replaced the OH group at C14 of substructure **C** (Figure 1). Likewise the ^1H NMR spectrum of **1** showed diastereotopic $H_3$15 and $H_3$16 as doublets. Thus, these data were in firm support of substructure **C** as 2-hydroxyisovaleric acid, which was further confirmed by the COSY and the HMBC measurements. The stereochemistry assignments shown for **2** are based on a biogenetic analogy to **1** plus the observations that both compounds have the same sign of the optical rotation and both have parallel NMR shifts at each of the chiral centers.

The last new compound, homodestcardin (**3**), had the molecular formula $C_{32}H_{55}N_5O_7$, established by the HRESIMS data. This compound was concluded to be a member of the destruxin family on the basis of the similar profile of ^1H and ^{13}C NMR (Table 2) to that of homodestruxin B (**4**)[14] and roseocardin (**5**).[15] Detailed analysis of the 2D NMR data of **3** pinpointed the β-methyl proline and *N*-methyl leucine residues versus the proline residue on **4** and *N*-methyl valine residue on **5**, respectively. Our proposed planar structure derived by analogy to **4** and **5** was confirmed from the 2D NMR data (Figure 4). Extending the comparisons of the NMR data between this trio further revealed that **3** and **4** possessed identical shifts at the western chiral centers (C6, C11, C12, C19, and C20). Alternatively **3** and **5** possessed parallel shifts at the eastern chiral centers (C26, C27, and C33) that were almost identical with those of **5**. The significant NOE observed between H26 and H28 was also consistent with these stereochemical conjectures. The final relative stereoassignments proposed for **3** are shown in Figure 4.

The literature, aside from that noted above for cyclic depsipetides, including those with significant bioactivity properties isolated from marine-derived fungi, is rather sparse. One set of compounds includes 15G256γ, 156G256δ, and 15G256ϵ, which are lipodepsipeptides isolated from a *Hypoxylon oceanium* separated from mangrove wood.[16] Exumolides A and B isolated from a marine plant-derived *Scytaladium* sp. are cytostatic cyclic hexadepsipetides.[17] Sansalvamide[18] and *N*-methylsansalvamide[19] isolated from two different marine alga-derived *Fusarium* spp. are cytotoxic cyclic pentadepsipeptides. Those previous examples contain one ester group in the molecule. By contrast, the guangomides (**1** and **2**) isolated in this study are different from known cyclic depsipetides from marine-derived fungi because of the presence of two ester groups in the molecule. In addition, homodestcardin (**3**) is the first example of a destruxin analogue from marine-derived fungi. The biological properties of **1** and **2** were investigated and deserve brief comment. Guangomide A (**1**) was inactive against murine and human tumor cell lines in a disk diffusion assay. Cytotoxicity evaluation of the other two new compounds was not carried out due to their low yield. However, **1** and **2** showed weak antibacterial activity against *Staphylococcus epidermidis* (MIC = 100 μg/mL, each) and *Enterococcus durans* (MIC = 100 μg/mL, each).

Experimental Section

General Experimental Procedures. Optical rotations were obtained on a JASCO DIP-370 digital polarimeter. UV/vis measurements were recorded on a HP 8453 diode array spectrometer. The NMR spectra were recorded on a Varian UNITY INOVA-500 spectrometer, operating at 500 and 125.7 MHz for ^1H and ^{13}C, respectively. Tetramethylsilane (TMS) was used as an internal standard for ^1H and ^{13}C NMR spectra. High-resolution mass measurements were obtained on a benchtop Mariner ESI-TOF mass spectrometer. HPLC was performed with a column of 4 μm ODS.

Biological Materials. The fungus (strain no. 001314c) was isolated from a yellow fan-shaped sponge (coll. no. 00314) collected by the UCSC group using scuba off the coast of Guango, Papua New Guinea, in December 2000 by the same techniques described previously.[20] Attempts to identify this fungal strain by the alignment of the D2 region of the 25S ribosomal DNA sequence and its fruiting body were unsuccessful (the closest fungus: *Fusarium graminearum*, with a genetic distance of 9.75%). Therefore, the isolate was concluded to be an unidentifiable fungus. This fungus is maintained in a cryopreserved state at UCSC. The sponge was identified as an *Ianthella* sp. (order Verongidae, family Ianthellidae).

Culture Conditions. The fungal strain was grown in a liquid medium (20 L) containing 1.5% malt extract broth in filtered Monterey Bay seawater adjusted to pH 7.4 at 180 rpm for 28 days at room temperature (25 °C).

Biological Assays. The disk diffusion soft agar colony formation assay was employed to identify solid tumor selectivity for original extracts, extract partition fractions, and pure compounds. The differential cytotoxicity is expressed by observing a zone differential between any solid tumor cell (colon 38, colon H116, lung H125) and either leukemia cells (L1210 or CEM) or normal cells (CFU-GM). The sample is designated as "solid tumor selective" if the zone units of solid tumor − normal cell or leukemia cells is greater than 250 units. The antimicrobial assay was carried out as previously reported.[21]

Extraction and Isolation. The culture was filtered under suction, and the broth was extracted with equal volumes of EtOAc three times. The EtOAc extract was partitioned by Kupchan type extraction reported previously.[22] The CH_2Cl_2 extract (EFD; 2.6 g) contained crystals, which were purified by washing with MeOH and were identified as brefeldin A (560 mg) by comparison of its spectral data to the published data.[8] The CH_2Cl_2-soluble portion was separated with flash Si gel chromatography using a CH_2Cl_2−MeOH stepwise gradient as the eluent. B3 (170 mg) obtained from MeOH−CH_2Cl_2 (1:99) was purified by

Table 2. ^{1}H and ^{13}C NMR Data for Homodestcardin (**3**) in $CDCl_3$[a]

structural unit		δ_C (mult.)	δ_H (*J* in Hz)	gCOSY	gHMBC	NOESY
β-Ala	1	173.8 (qC)				
	2a	34.5 (CH_2)	2.56 ddd (18.5, 5.0, 1.8)	2b, 3b	1, 3	2b, 3a
	2b		2.68 ddd (18.5, 11.5, 2.1)	2a, 3a		2a, 3a, 4
	3a	33.2 (CH_2)	3.08 m	2b, 3b, 4		2a, 2b, 3b, 4
	3b		4.05 m	2a, 3a,4		3a
	4		8.27 d (8.5)	3a, 3b		2b, 3a, 6, 20, 22b, 24
N-Me-Ala	5	169.7 (qC)				
	6	55.5 (CH)	5.16 q (6.8)	7	5, 8	4, 7, 11
	7	15.3 (CH)	1.30 d (6.9)	6	5, 6	6, 9
	9	28.1 (CH_3)	2.73 s		6, 10	7
N-Me-Ile	10	171.1 (qC)[b]				
	11	56.8 (CH)	5.03 d (10.9)	12	9, 10, 12, 14, 18	6, 12, 14a, 14b, 15
	12	33.5 (CH)	2.06 m	11, 13		11, 13, 14b, 15, 17
	13	16.2 (CH_3)	0.85 m[c]	11	11, 12, 14	12
	14a	25.8 (CH_2)	0.98 m	14b, 15		11
	14b		1.43 m	14a, 15		11, 12, 14b, 17
	15	11.1 (CH_3)	0.91 t (7.2)	14a, 14b	12, 14	11, 12, 14a
	17	31.0 (CH_3)	3.20 s		11, 18	12, 14b, 19, 20
Ile	18	173.6 (qC)				
	19	53.5 (CH)	4.83 dd (9.2, 6.8)	20, 24	18, 20	17, 20, 21, 22a, 22b, 24
	20	37.5 (CH)	1.92 m	19, 21		4, 17, 19, 21, 22b, 24
	21	15.3 (CH_3)	0.84 m[c]	20	19, 20	19, 20
	22a	24.6 (CH_2)	1.29 m	22b, 23		19, 23, 24
	22b		1.44 m	22a, 23		4, 19, 20, 22b, 23, 24
	23	11.4 (CH_3)	0.85 m[c]	22a, 22b	19, 20	22a, 22b
	24		7.07 d (8.8)	19		4, 19, 20, 22a, 22b, 26, 30b
3-Me-Pro	25	171.0 (qC)[b]				
	26	67.1 (CH)	4.27 d (0.3)	27	25, 27, 28, 29	24, 27, 28
	27	36.2 (CH)	2.78 m	26, 28, 29b		26, 28, 29a, 29b
	28	19.0 (CH_3)	1.11 m	27	26, 27, 29	26, 27, 29a, 30a
	29a	30.9 (CH_2)	1.70 m	29b, 30a, 30b		28, 29b, 30a, 27
	29b		2.09 m	27, 29a, 30a, 30b		27, 29a, 30b
	30a	44.9 (CH_2)	3.56 dt (9.5, 7.4)	29a, 29b, 30b		28, 29a, 30b, 33, 34a
	30b		3.86 td (9.5, 3.0)	29a, 29b, 30a		24, 29b, 30a, 33
Hica	32	169.9 (qC)				
	33	71.9 (CH)	4.90 dd (10.4, 3.3)	34a, 34b		30a, 30b, 34a, 34b, 37
	34a	39.3 (CH_2)	1.37 ddd (14.5, 9.0, 3.4)	34b, 35	32, 35, 36	30a, 33, 34b, 35
	34b		1.97 m	34a	32, 35, 36	33, 34a, 35, 36
	35	24.4 (CH)	1.85 m	34a, 36, 37		34a, 34b, 36, 37
	36	23.4 (CH_3)	1.00 d (6.6)	35	35, 37	34b, 35
	37	21.7 (CH_3)	0.96 d (6.6)	35	35, 36	33, 35

[a] Measured at 500 MHz (^{1}H) and 125 MHz (^{13}C). [b] Assignment may be interchanged. [c] Coupling constant could not be measured due to signal overlap.

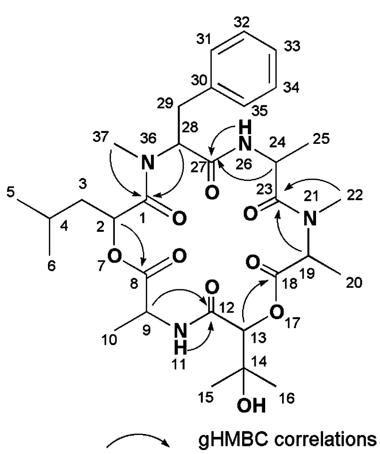

Figure 2. Selected gHMBC correlations for **1**.

reversed-phase HPLC with $MeOH-H_2O$ (7:3 up to 1:0) to give a semipure fraction (H9; 3.2 mg), which was purified again by reversed-phase HPLC with CH_3CN-H_2O (3:2 isocratic) to furnish **2** (1.5 mg). The flash column chromatography fraction B4 (190 mg) obtained from $MeOH-CH_2Cl_2$ (1:49) was purified by reversed-phase HPLC with $MeOH-H_2O$ (7:3 up to 1:0) to furnish **1** (11.0 mg) and a semipure fraction (H7; 3.7 mg), which was purified again by reversed-phase HPLC with $MeOH-H_2O$ (3:1 isocratic) to furnish **3** (1.2 mg).

Guangomide A (1): colorless crystals from hexane−EtOAc−MeOH (1:1:1); mp 255−257 °C; $[\alpha]^{28}_D$ −44.6 (*c* 0.8, $CHCl_3$); λ_{max} (MeOH) 203 nm (log ϵ 4.38); ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 641.3152 [M + Na]$^+$ (calcd for $C_{31}H_{46}N_4O_9Na$, 641.3157).

Guangomide B (2): white amorphous powder; $[\alpha]^{28}_D$ −18.1 (*c* 0.9, $CHCl_3$); λ_{max} (MeOH) 204 nm (log ϵ 4.38); ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 625.3208 [M + Na]$^+$ (calcd for $C_{31}H_{46}N_4O_8Na$, 625.3208).

X-ray Crystallography of 1. The single-crystal X-ray analysis was conducted as follows. Suitable crystals were obtained from hexane−EtOAc−MeOH (1:1:1) by the vapor diffusion method. This crystal (0.60 × 0.40 × 0.30 mm^3) was mounted on a Bruker SMART diffractometer (Mo Kα; −100 °C). A hemisphere of data was taken using a narrow-scan routine (1406 frames, 0.3° steps ω-scan, exposure time was 30 s/frame, $2\theta_{max}$ = 63.62°). Raw data were integrated with the Bruker SAINT+ program[23] to yield a total of 33 908 reflections, of which 10 117 were independent (R_{int} = 2.58%, completeness 94.9%) and 8852 with $I > 2\sigma(I)$. Data were collected for absorption using the SADABS program (min. and max. transmissions are 0.9479 and 0.9735, respectively).[24] The structure was solved by direct methods and refined by full matrix least-squares on F^2 techniques using anisotropic displacement parameters for all non-hydrogen atoms.[25] All hydrogen atoms were found in the difference Fourier map and refined isotropically. At final convergence, R_1 = 3.88% and GOF = 1.022 for 581 parameters.

Amino Acid Analysis of 1 Using Marfey's Method. Guangomide A (**1**) (1.4 mg) and 6 N HCl (2 mL) were added to MeOH (0.2 mL) and heated at 110 °C for 14 h in a sealed vial. The cooled reaction mixture was evaporated to dryness. To the residue was added 1 M $NaHCO_3$ (0.1 mL) and 1% Marfey's reagent (FDAA) in acetone (0.1 mL), incubated at 37 °C for 0.5 h. The reaction mixture was quenched with 2 N HCl (50 μL) and analyzed by reversed-phase HPLC. The

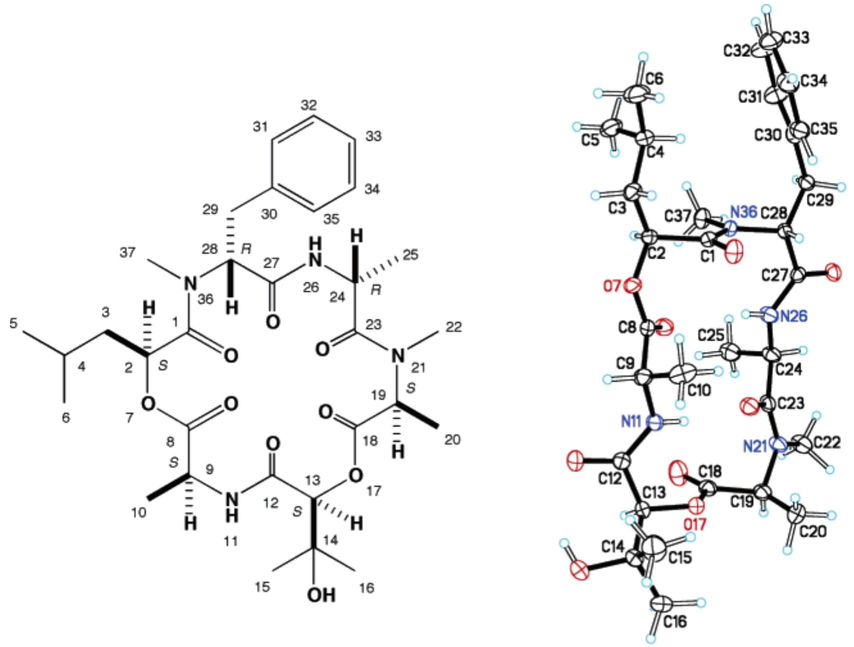

Figure 3. Absolute structure of **1** including X-ray crystal structure.

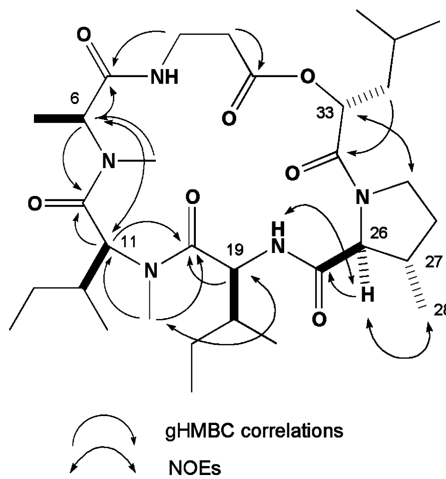

Figure 4. Selected 2D NMR correlations and the relative structure of **3**.

analysis was performed with the following conditions: Alltech Altima C18 column (5 μm, 250 mm × 10 mm i.d.), solvent system CH_3CN−H_2O (4:1 up to 1:1) over 60 min with 1 mL/min flow rate, UV detection at 340 nm. Separately *N*-methyl-D- and L-phenylalanine were derivatized with FDAA in the same manner as that of **1**. The HPLC conditions gave distinguishable retention times for the D and L forms (51.0 and 50.3 min, respectively). The configuration of the *N*-methylphenylalanine was determined to be D-form on the basis of co-injection of each form of the standard amino acids and the derivatized hydrolyzate of **1**.

Homodestcardin (3): white, amorphous powder; $[\alpha]^{27}_{D}$ −143.8 (*c* 0.9, $CHCl_3$); λ_{max} (MeOH) 204 nm (log ϵ 3.75); ^1H and ^{13}C NMR data, see Table 2; HRESIMS *m/z* 622.4170 $[M + H]^+$ (calcd for $C_{32}H_{56}N_5O_7$, 622.4174).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **1**−**3**, bioassay data, and X-ray data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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