

Venturamides A and B: Antimalarial Constituents of the Panamanian Marine Cyanobacterium *Oscillatoria* sp.¹

Roger G. Linington,^{†,‡} José González,^{‡,§} Luis-David Ureña,[‡] Luz I. Romero,[‡] Eduardo Ortega-Barría,[‡] and William H. Gerwick^{*,†}

Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography and Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, California 92093, and Instituto de Investigaciones Científicas Avanzadas y Servicios de Alta Tecnología, INDICASAT, Clayton, Edificio 175, PO Box 7250, Panamá 5, Panamá

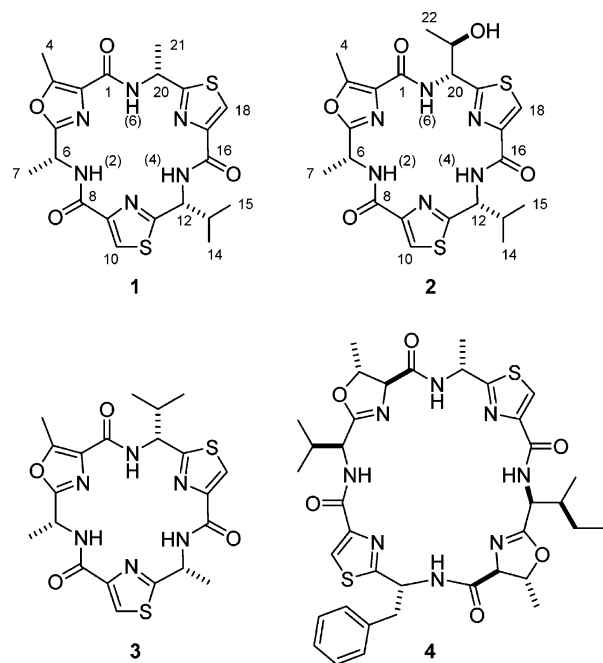
Received November 16, 2006

Two new modified cyclic hexapeptides, venturamides A (**1**) and B (**2**), were isolated from the marine cyanobacterium *Oscillatoria* sp. by antimalarial bioassay-guided fractionation. The isolation of **1** and **2** represents the first example of the identification of cyanobacterial peptides with selective antimalarial activity. The planar structures of **1** and **2** were determined by 1D and 2D NMR analyses and, in the case of venturamide A (**1**), comparison with the literature data for a previously reported synthetic compound. The absolute configuration of the amino acid residues was determined by selective hydrolysis in conjunction with Marfey's analysis. Compounds **1** and **2** were tested for biological activity against a range of tropical parasites.

Malaria is a significant health risk on a planetary scale with an estimated 500 million people affected by this debilitating and often fatal disease.¹ In recent years, the societal impact of malaria has increased, mainly due to the emergence of resistant strains of *Plasmodium falciparum* and *P. vivax* to chloroquine, mefloquine, and pyrimethamine.^{1b} In an effort to contribute to the development of effective and more affordable treatments for this disease, the Panamanian International Cooperative Biodiversity Group (ICBG) program is engaged in the search for antimalarial agents from both terrestrial and marine sources. Our recent attention has focused upon the evaluation of marine cyanobacteria as a source of lead compounds for antimalarial drug development. A systematic collection and evaluation program led us to investigate a field-collected strain of *Oscillatoria* sp., which showed strong initial activity in our *in vitro* antimalarial assay.² Subsequently, we isolated from the extract of this strain two new cyclic peptides, venturamides A (**1**) and B (**2**), both of which showed low micromolar activity in the antimalarial assay.

Results and Discussion

The crude organic extract of a Panamanian collection of *Oscillatoria* sp. from Buenaventura Bay was subjected to normal-phase VLC chromatography to give nine prefractions, which were evaluated for their biological activities. Two contiguous fractions showed strong antimalarial activity and were separately profiled by HPLC-MS and then fractionated by C₁₈ reversed-phase HPLC to give venturamides A (**1**) and B (**2**) as optically active white solids.³



HREIMS for **1** gave an M⁺ at *m/z* 488.1283, which was consistent with the molecular formula C₂₁H₂₄N₆O₄S₂ (13 degrees of unsaturation). Consideration of the ¹H and ¹³C NMR spectra, in conjunction with the phase-sensitive multiplicity-edited HSQC spectrum, revealed the presence of five methyl, six methine, and 10 quaternary carbon atoms, and by their chemical shifts (see Table 1), **1** was deduced to possess four rings. Additionally, the ¹H NMR spectrum showed the presence of three broad exchangeable doublets (δ 8.44, 8.60, 8.63) that were attributed to amide NH signals. Interpretation of the gCOSY and gHMBC data afforded three subunits (**a–c**) that accounted for all the atoms predicted by the molecular formula (Figure 1).

Partial structure **a** was largely determined by ¹H–¹H COSY and HMBC, which identified a contiguous spin system comprising an amide NH proton (δ 8.44; N-4) and two sequential methine protons (δ 5.47; H-12 and δ 2.28; H-13), the second of which also showed

¹ Dedicated to the late Dr. Kenneth L. Rinehart of the University of Illinois at Urbana–Champaign for his pioneering work on bioactive natural products.

* Corresponding author. Tel: (858) 534-0578. Fax: (858) 534-0529. E-mail: wgerwick@ucsd.edu.

[†] University of California San Diego.

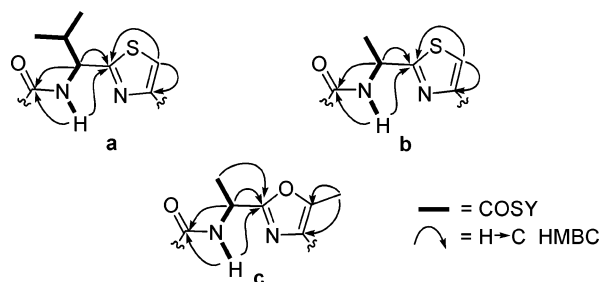
[‡] INDICASAT, Panamá.

[§] Present address: Instituto de Investigaciones Biomédicas “Alberto Sols”, CSIC, Universidad Autónoma de Madrid, Arturo Duperier 4, 28029 Madrid, Spain.

Table 1. NMR Data for Venturamides A (**1**) and B (**2**) (CDCl₃)

position	venturamide A (1)			venturamide B (2)		
	δ_{H}^a	δ_{C}^b	HMBC	δ_{H}^a	δ_{C}^b	HMBC
1		159.9 (qC)			162.5 (qC)	
2		153.9 (qC)			154.8 (qC)	
3		128.4 (qC)			127.9 (qC)	
4	2.68	11.6 (CH ₃)	C2, C3	2.68	11.7 (CH ₃)	C2, C3
5		161.7 (qC)			161.9 (qC)	
6	5.27	44.0 (CH)	C5, C7	5.27	44.0 (CH)	C5, C7
7	1.68	20.8 (CH ₃)	C5, C6	1.69	20.7 (CH ₃)	C5, C6
NH (2)	8.60		C5, C8	8.60		C5, C8
8		160.5 (qC)			159.9 (qC)	
9		149.2 (qC)			149.1 (qC)	
10	8.10	123.2 (CH)	C9, C11	8.11	123.3 (CH)	C8, C9, C11
11		168.4 (qC)			168.4 (qC)	
12	5.47	55.7 (CH)	C11, C13, C14, C15	5.47	55.7 (CH)	C11, C13, C14, C15, C16
13	2.28	35.5 (CH)	C12, C14, C15	2.27	35.5 (CH)	C11, C12, C14, C15
14	1.01	18.8 (CH ₃)	C12, C13, C15	1.01	18.9 (CH ₃)	C12, C13, C15
15	1.08	18.5 (CH ₃)	C12, C13, C14	1.07	18.4 (CH ₃)	C12, C13, C14
NH (4)	8.44		C11, C16	8.38		C16
16		159.7 (qC)			159.5 (qC)	
17		148.7 (qC)			148.9 (qC)	
18	8.14	124.2 (CH)	C17, C19	8.21	125.1 (CH)	C16, C17, C19
19		171.3 (qC)			166.3 (qC)	
20	5.43	47.5 (CH)	C19, C21	5.49	58.1 (CH)	C1, C19, C21
21	1.72	24.9 (CH ₃)	C19, C20	4.25	73.0 (CH)	
22				1.23	18.1 (CH ₃)	C20, C21
OH				4.12		
NH (6)	8.63		C1, C19	8.65		C1, C19

^a Recorded at 400 MHz. ^b Recorded at 100 MHz.

**Figure 1.** Subunits **a–c** of venturamide A (**1**) showing ¹H–¹H COSY- and HMBC-derived partial structures.

¹H–¹H COSY correlations to two doublet methyl groups at δ 1.01 (H₃-14) and 1.08 (H₃-15). These assignments could only be the result of the presence of a valine residue in **1**; however, HMBC correlations of the amide NH (δ 8.44) and α -proton (δ 5.47) as well as an additional methine singlet at δ 8.10 (H-10) to a quaternary carbon at δ 168.4 (C-11) suggested that the valine residue was modified by the inclusion of an aromatic heterocycle in place of the more usual carbonyl moiety. This was further confirmed by HSQC and HMBC correlations from δ 8.10 to carbons at δ 123.2 (C-10) and 149.2 (C-9), respectively. Taken together, these three carbon signals (δ 123.2, 149.2, and 168.4) were indicative of a thiazole ring, a moiety with ample precedent in cyanobacterial peptides.^{4,5} Finally, both the α - and NH-protons showed HMBC correlations to a conjugated amide carbonyl at δ 159.7 (C-16), completing partial structure **a** (Figure 1).

Partial structure **b** was composed of a methine multiplet at δ 5.43 (H-20) that showed ¹H–¹H COSY correlations to both an amide NH at δ 8.63 (N-6) and a doublet methyl group at δ 1.72 (H₃-21), indicating that subunit **b** contained an alanine residue. In an analogous fashion to subunit **a**, HMBC correlations from the NH (δ 8.63), α -proton (δ 5.43), and singlet methine (δ 8.14; H-18) signals to a quaternary carbon at δ 171.3 (C-19) showed that the carbonyl of this amino acid residue had also been replaced by a thiazole ring. The α - and NH-protons in partial structure **b** also showed HMBC correlations to a second conjugated amide carbonyl at δ 159.9 (C-1), completing this partial structure (Figure 1).

Partial structure **c** was composed of an amide NH proton (δ 8.60; N-2) that showed a ¹H–¹H COSY correlation to a complex multiplet (δ 5.27; H-6) integrating for one proton, which in turn showed a ¹H–¹H COSY correlation to a doublet methyl group at δ 1.68 (H₃-7). All three signals exhibited HMBC correlations to a quaternary carbon at δ 161.7 (C-5), indicating that subunit **c** was also comprised of an alanine residue adjacent to an aromatic heterocycle. However, unlike partial structures **a** and **b**, partial structure **c** did not show evidence of a thiazole ring. Consideration of the molecular formula for **1** in conjunction with the structures of subunits **a** and **b** indicated that the remaining heterocycle had the formula C₄H₃NO. This could only be explained by a disubstituted methyl oxazole residue, an assignment that was further confirmed by a methyl singlet at δ 2.68 (H₃-4), which showed an HSQC correlation to a carbon at δ 11.6 (C-4) and HMBC correlations to quaternary carbons at δ 128.4 (C-3) and 153.9 (C-2). The α - and NH-protons of partial structure **c** showed HMBC correlations to a third conjugated amide carbonyl at δ 160.5 (C-8), completing the final partial structure (Figure 1). This completed the assignment of partial structures **a–c** and accounted for all of the atoms predicted by the molecular formula.

Despite acquiring HMBC data optimized for several different long-range heteronuclear coupling constants (4, 6, and 8 Hz), we were unable to detect any correlations connecting these three subunits. However, examination of the literature revealed one natural product, dendroamide A (**3**),⁴ which was composed solely of these same three subunits. Careful comparison of the carbon chemical shifts for **1** and **3** revealed chemical shift disparities between these two compounds (Figure 2a), suggesting that **1** differed from **3** either (a) configurationally at one or two of the three chiral centers in the molecule, (b) constitutionally in the connectivity of the three subunits, or (c) in a combination of these characteristics. As a first step in deconvoluting these possibilities, the absolute configuration of each amino acid was determined by Marfey's analysis. It has been shown that for peptides containing both oxazole and thiazole heterocycles direct hydrolysis under acidic conditions results in the exclusive cleavage of the oxazole rings.⁵ In order to liberate amino acids adjacent to thiazole rings, it is necessary to cleave these rings by ozonolysis prior to hydrolysis.

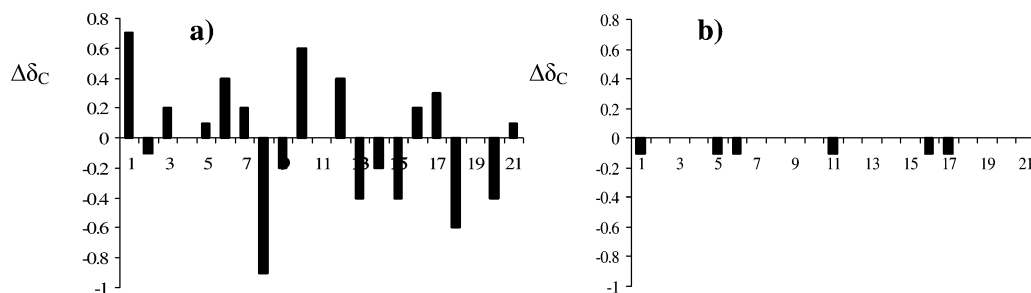


Figure 2. (a) Comparison of $\Delta\delta_C$ values for venturamide A (**1**) versus **3**. (b) Comparison of $\Delta\delta_C$ values for venturamide A (**1**) versus synthetic **1**.^{6a}

We elected to take advantage of this difference in reactivity to determine the configuration of each amino acid by performing two separate Marfey's analyses, one before and one after ozonolysis. In the first instance, direct hydrolysis of **1** combined with Marfey's derivatization and comparison with derivatized commercially available standards showed that the alanine adjacent to the oxazole ring was of D configuration. In the second instance, ozonolysis of **1** followed by hydrolysis and Marfey's analysis gave exclusively D-alanine and D-valine, thus identifying all stereogenic centers in **1** as having the D configuration. This mirrored the situation for **3**, which also contained D amino acids exclusively. Given that all three stereogenic subunits in **1** and **3** had the same absolute configurations, we concluded that the two compounds must therefore differ constitutionally. Fortunately, there have been a number of recent total syntheses of dendroamide A (**3**),⁶ including one^{6a} that constructed the target molecule by generating three independent subunits and allowing these to self-assemble as the final step. As a result of this self-assembly, both dendroamide A (**3**) and its previously unknown positional isomer **1** were generated. Comparison of the carbon chemical shifts for this synthetic compound with those of venturamide A showed excellent correlation (Figure 2b), thus completing the structural assignment for venturamide A (**1**) as depicted.

HREIMS for venturamide B (**2**) gave an M^+ at m/z 518.1393 that was consistent with the molecular formula $C_{22}H_{26}N_6O_5S_2$. Consideration of the proton spectrum indicated that **2** differed from **1** in the presence of two new signals at δ 4.25 and 4.12, each of which integrated for one proton. Further interpretation of the gCOSY, gHSQC, and gHMBC data indicated that these represented a methine (δ 4.25) and a broad exchangeable proton (δ 4.12) and suggested that **2** contained a threonine in place of the alanine adjacent to the thiazole ring in **1**. This positional assignment was substantiated by observation of HMBC correlations between thiazole proton H-10 and carbonyl C-8 as well as between thiazole proton H-18 and carbonyl C-16. These correlations, along with those between α -amino protons H-6 and carbonyl C-8, H-12 and C-16, and H-20 and C-1, indicated that the alanine adjacent to the thiazole ring in **1** was exchanged with a threonine residue in **2**. This was additionally confirmed by differential hydrolysis as described previously. Direct hydrolysis followed by Marfey's analysis gave exclusively D-alanine (i.e., adjacent to the oxazole ring in **2**). Subsequently, ozonolysis of **2** followed by hydrolysis and Marfey's analysis indicated the presence of D-alanine, D-valine, and D-allo-threonine, thus confirming that the remaining alanine residue was adjacent to the oxazole ring and that the threonine residue was adjacent to the remaining thiazole in **2**. Therefore, venturamide B (**2**) was identified as cyclo-D-allo-Thr-Tzl-D-Val-Tzl-D-Ala-mOzl as depicted.

The related cyanobacterial peptide patellamide C (**4**) has been the subject of a number of recent investigations regarding its biosynthetic origin.⁷ Shotgun cloning and subsequent heterologous expression of random-sized fragments of genomic DNA from the patellamide-producing *Prochloron* sp. has shown that the cyanobacterium possesses the biosynthetic capacity to generate both

patellamide D and ascidiacyclamide.⁸ Careful analysis of the biosynthetic pathways for this family of natural products has indicated that members of the patellamide family are produced by the expression of precursor peptides that contain conserved sequences for patellamide natural products.⁹ These pro-peptide sections consist of distinctive sequences of alternating aliphatic and ser, thr, or cys amino acids. The heteroatom-containing amino acids in these sequences are proposed to undergo enzyme-catalyzed heterocyclization reactions to form thiazoline or oxazoline rings prior to cleavage of the modified peptide precursor and macrocyclization. In some instances these heterocycles are further oxidized to thiazoles or oxazoles. Additionally, amino acids adjacent to these heterocycles are often epimerized to their D-configurations. There is still some uncertainty as to both the mechanism and order of these epimerization and oxidation events in the biosynthetic scheme. Current opinion is divided between (a) discrete epimerization and aromatization events¹⁰ and (b) epimerization and aromatization as a single concerted step.^{7a} It is reasonable to suggest on the basis of structural homology between the patellamides and venturamides that the latter natural products are assembled by similar biosynthetic machinery. Indeed, a similar biosynthetic pathway has recently been discovered in *Trichodesmium*,¹¹ which is a closely related genus to *Oscillatoria*. The presence of D-alanine residues α to the oxazole ring in the venturamides, in contrast to L-isoleucine residues adjacent to the nonaromatic methyl-oxazoline rings in patellamide C (**4**), provides support to the hypothesis that the epimerization of these centers occurs as a direct consequence of the oxidative aromatization of the thiazoline and oxazoline rings to their corresponding thiazole and oxazole forms.

Venturamides A (**1**) and B (**2**) were tested for their antimalarial activity against the W2 chloroquine-resistant strain of the malaria parasite. Compound **1** showed strong *in vitro* activity against *Plasmodium falciparum* (8.2 μ M), with only mild cytotoxicity to mammalian Vero cells (86 μ M), giving an order of magnitude differential in activity to the parasite over host cells. Compound **2** also showed strong antimalarial activity against *Plasmodium falciparum* (5.6 μ M) and mild cytotoxicity to mammalian Vero cells (56 μ M). Compounds **1** and **2** exhibited only mild activity when tested against *Trypanosoma cruzi*, *Leishmania donovani*, and MCF-7 cancer cells (Table 2).

The isolation of venturamides A (**1**) and B (**2**) represents an important addition to the knowledge of dendroamide-type natural products for several reasons. The selective antimalarial activity of both **1** and **2** makes these compounds exciting lead structures for further possible development. The unusual regioisomerism of **1** in comparison to the dendroamides presents an interesting chemical feature and indicates biosynthetic flexibility in the order of amino acids in the precursor pro-peptide. Venturamide B is only the second natural product in this structure class to possess an uncyclized hydroxy amino acid,⁹ and this offers insights into SAR features in this structure class as well as a potential site for derivatization with fluorescent labels or biotin complexes to aid efforts aimed at describing the target of these drugs. Finally, this is the first isolation of this structure class from a field-collected free-living marine

Table 2. *In Vitro* Activity of Venturamides A (1) and B (2) against Tropical Parasites and Mammalian Cell Lines

compound	IC ₅₀ (μM) ^a				
	<i>P. falciparum</i>	<i>T. cruzi</i>	<i>L. donovani</i>	Vero cells	MCF-7 cells
1	8.2	14.6	>20	86	13.1
2	5.2	15.8	>19	56	>54

^a Mean values of the IC₅₀ were determined by testing the concentration of each sample in triplicate.

cyanobacterium, giving further evidence of the natural source of these unique cyclic peptides in nature and extending the taxonomic range of cyanobacteria to be found with this biosynthetic capacity.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Rudolf Research Analytical Autopol II polarimeter. UV spectra were acquired on a Shimadzu UV2401-PC spectrophotometer. NMR spectra were acquired on a JEOL Eclipse 400 MHz spectrometer and referenced to residual solvent proton and carbon signals (δ_{H} 7.26, δ_{C} 77.0 for CDCl₃). Low-resolution APCI mass spectra were acquired on a JEOL LC-mate mass spectrometer (INDICASAT). Accurate mass EI mass spectra were acquired on a ThermoFinnigan MAT900XL mass spectrometer (UCSD Chemistry Department). HPLC purifications were performed on an Agilent 1100 series HPLC system employing a G1312A binary gradient pump, a G1322A degasser, a G1314A variable-wavelength detector tuned to 210 nm, and either Phenomenex Jupiter C₁₈ (4.6 × 250 mm) or Protosil-120 C₁₈ (4.6 × 150 mm) RP-HPLC columns. All solvents were HPLC grade and were used without further purification.

Collection. The cyanobacterium *Oscillatoria* sp. (1.09 kg dry wt) was collected by hand from a depth of 0.1–0.3 m in a shallow sandy inlet in Buenaventura Bay in the Portobelo National Marine Park, Colon Province, on the north coast of Panama. The cyanobacterium was strained through a mesh bag to remove excess seawater, frozen on site, and stored at –4 °C until workup. The taxonomy was identified by comparison with characteristics described by Geitler.¹² A voucher was deposited at the Smithsonian Tropical Research Institute, Panama (voucher number PAP-01-APR-05-8).

Extraction and Isolation. Freshly thawed material was extracted exhaustively with CH₂Cl₂/MeOH (2:1, 5 × 1500 mL), and the combined organic extracts were partitioned against H₂O (500 mL) and concentrated to dryness *in vacuo* to give 8.52 g of a dark brown gum. This material was subjected to flash Si gel CC (Aldrich, Si gel 60, 230–400 mesh, 40 × 180 mm) eluting with 100% hexanes (300 mL); 9:1 hexanes/EtOAc (300 mL); 8:2 hexanes/EtOAc (300 mL); 6:4 hexanes/EtOAc (300 mL); 4:6 hexanes/EtOAc (300 mL); 2:8 hexanes/EtOAc (300 mL); 100% EtOAc (300 mL); 3:1 EtOAc/MeOH (300 mL); 100% MeOH (300 mL). Two contiguous fractions (2:8 hexanes/EtOAc; 100% EtOAc) showed strong antimalarial activity (1 and 3 μg/mL, respectively) and possessed similar LC-MS and NMR features. These were separately subjected to C₁₈ RP-HPLC to give from the less polar active fraction (Phenomenex Jupiter C₁₈ 4.6 × 250 mm RP-HPLC column, 5 μm, 62% MeOH/38% H₂O, 210 nm, 1 mL/min, *t*_R 24.5 min) venturamide A (**1**) as a colorless glass (1.8 mg, 0.02% of crude extract). HPLC of the more polar active fraction (Protosil-120 C₁₈ 4.6 × 150 mm RP-HPLC column, 10 μm, 60% MeOH/40% H₂O, 210 nm, 1 mL/min, *t*_R 26.1 min) gave venturamide B (**2**) as a colorless glass (0.8 mg, 0.009% of crude extract).

Venturamide A (1): colorless glass; [α]_D²⁵ +53.4 (*c* 0.001, MeOH); UV (MeOH) λ_{max} (log ϵ) 224 (4.17) nm; ¹H and ¹³C NMR data, see Table 1; HREIMS *m/z* M⁺ 488.1283 (calcd for C₂₁H₂₄N₆O₄S₂, 488.1300)

Venturamide B (2): colorless glass; [α]_D²⁵ +53.6 (*c* 0.0004, MeOH); UV (MeOH) λ_{max} (log ϵ) 224 (4.08) nm; ¹H and ¹³C NMR data, see Table 1; HREIMS *m/z* M⁺ 518.1393 (calcd for C₂₂H₂₆N₆O₅S₂, 518.1406)

Marfey's Analysis of 1 and 2. Authentic samples of **1** (0.1 mg, 0.2 μmol) and **2** (0.1 mg, 0.2 μmol) were independently treated with 6 N HCl in sealed vials at 120 °C for 18 h. The solutions were concentrated to dryness *in vacuo* and treated with a solution of 1-fluoro-2,4-dinitrophenyl-5-L-valine-amide (FDVA) (0.25 mg, 0.8 μmol) in acetone (50 μL) and a solution of 0.1 M NaHCO₃ (100 μL) in a sealed vial at 90 °C for 5 min. The reaction mixture was neutralized with 2 N HCl (50 μL) and diluted with CH₃CN (100 μL). The resulting solution was

analyzed by RP-HPLC employing a Phenomenex Jupiter C₁₈ column (4.6 × 250 mm) and a gradient elution profile of 15% CH₃CN/85% H₂O (acidified with 0.02% AcOH) to 50% CH₃CN/50% H₂O (acidified with 0.02% AcOH) over 70 min at a flow of 0.5 mL/min, monitoring at 340 nm.

Ozonolysis of 1 and 2. A stream of ozone gas (4% in O₂, 1/16 L/min) was bubbled through a solution of each compound (0.1 mg in 200 μL of CH₂Cl₂) independently at RT for 5 min. The solvent was removed under N₂ and dried *in vacuo* for 1 h. Subsequent hydrolysis and Marfey's analysis of the corresponding ozonates were performed as described above. Comparison with commercially available amino acid standards derivatized using identical Marfey's methodology established **1** as containing exclusively D-alanine and D-valine, while **2** contained D-alanine, D-valine, and D-*allo*-threonine. Retention times in minutes for the derivatized amino acid standards were as follows: L-threonine 14.69; L-*allo*-threonine 15.15; D-*allo*-threonine 17.53; L-alanine 17.78; D-threonine 20.54; D-alanine 23.10; L-valine 23.51; D-valine 31.52 (see Supporting Information).

Bioassays. All bioassays were performed in duplicate, testing at 10, 2, 0.4, 0.08, and 0.016 μg/mL. Malaria bioassays were performed as previously reported by our program, using chloroquine as a positive control (IC₅₀ = 80–100 nM).² Chagas bioassays were performed following the protocol of Buckner et al. and using nifurtimox as a positive control (IC₅₀ 3–5 μg/mL).¹³ Leishmaniasis bioassays were performed using a method previously employed in our laboratory, based on parasite DNA fluorescence.¹⁴ In this latter assay, amphotericin-B was used as the positive control and had an IC₅₀ value of 80 ng/mL. Cancer bioassays were performed following the standard protocol of the National Cancer Institute.¹⁵ Cytotoxicity bioassays were performed following an MTT cell proliferation assay protocol with green monkey Vero kidney cells.¹⁶ Additional details on bioassays may be found in the Supporting Information.

Acknowledgment. We thank the Government of Panama for support of the ICBG program, G. Pattenden for providing original ¹H and ¹³C NMR spectra of synthetic **1**, T. L. Simmons for assistance with the collection of the cyanobacterium, and R. Coates and N. Engene for microscopic images and identification of the cyanobacterium. Financial support was provided by the Fogarty International Center's International Cooperative Biodiversity Groups (ICBG) program in Panama (ICBG TW006634). Accurate mass measurements were provided by Y. Su at the Department of Chemistry and Biochemistry Mass Spectrometry Facility, UCSD.

Supporting Information Available: ¹H and ¹³C NMR spectra of **1** and **2**, HPLC analysis of the FDVA derivatized hydrolysate of **1** and **2**, HPLC analysis of the FDVA derivatized hydrolysate of the ozonolysis product of **1** and **2**, experimental details of bioassays, and color photomicrographs of the field-collected *Oscillatoria* sp. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

- (a) <http://www.who.int>. (b) Cunha-Rodrigues, M.; Prudencio, M.; Mota, M. M.; Haas, W. *Biotech. J.* **2006**, *1*, 321–332. (c) Snow, R. W.; Guerra, C. A.; Noor, A. M.; Myint, H. Y.; Hay, S. I. *Nature* **2005**, *434*, 214–217.
- Corbett, Y.; Herrera, L.; Gonzalez, J.; Cubilla, L.; Capson, T. L.; Coley, P. D.; Kursar, T. A.; Romero, L. I.; Ortega-Barria, E. *Am. J. Trop. Med. Hyg.* **2004**, *70*, 119–124.
- The venturamides were named after Buenaventura Bay, where the source organism was collected.
- Ogino, J.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Nat. Prod.* **1996**, *59*, 581–586.
- Ireland, C. M.; Durso, A. R.; Newman, R. A.; Hacker, M. P. *J. Org. Chem.* **1982**, *47*, 1807–1811.
- (a) Bertram, A.; Pattenden, G. *Synlett* **2000**, *10*, 1519–1521. (b) Xia, Z.; Smith, C. D. *J. Org. Chem.* **2001**, *66*, 3459–3466. (c) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506–9509.

- (7) (a) Schmidt, E. W.; Nelson, J. T.; Rasko, D. A.; Sudek, S.; Eisen, J. A.; Haygood, M. G.; Ravel, J. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 7315–7320. (b) Milne, B. F.; Long, P. F.; Starcevic, A.; Hranueli, D.; Jaspers, M. *Org. Biomol. Chem.* **2006**, *4*, 631–638.
- (8) Long, P. F.; Dunlap, W. C.; Battershill, C. N.; Jaspers, M. *ChemBioChem* **2005**, *6*, 1760–1765.
- (9) Donia, M. S.; Hathaway, B. J.; Sudek, S.; Haygood, M. G.; Rosovitz, M. J.; Ravel, J.; Schmidt, E. W. *Nat. Chem. Biol.* **2006**, *2*, 729–35.
- (10) Milne, B. F.; Long, P. F.; Starcevic, A.; Hranueli, D.; Jaspers, M. *Org. Biomol. Chem.* **2006**, *4*, 631–638.
- (11) Sudek, S.; Haygood, M. G.; Youssef, D. T. A.; Schmidt, E. W. *Appl. Environ. Microbiol.* **2006**, *72*, 4382–4387.
- (12) Geitler, L. *Cyanophyceae*; Koeltz Scientific Books: Koenigstein, Germany, 1932 (Reprint 1985).
- (13) Buckner, F. S.; Verlinde, C. L. M. J.; La Flamme, A. C.; Van Voorhis, W. C. *Antimicrob. Agents Chemother.* **1996**, *40*, 2592–2597.
- (14) Calderon, A.; Romero, L. I.; Ortega-Barría, E.; Brun, R.; Correa, M. A.; Gupta, M. P. *Panama Pharm. Biol.* **2006**, *44*, 1–16.
- (15) Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.
- (16) Van de Loosdrecht, A. A.; Beelen, R. H. J.; Ossenkoppele, G. J.; Broekhoven, M. G.; Langenhuijsen, M. M. A. C. *J. Immunol. Methods* **1994**, *174*, 311–320.

NP0605790