Theopederins K and L. Highly Potent Cytotoxic Metabolites from a Marine Sponge *Discodermia* Species

Gopal K. Paul, Sarath P. Gunasekera,* Ross E. Longley, and Shirley A. Pomponi

Division of Biomedical Marine Research, Harbor Branch Oceanographic Institution, 5600 U.S. 1 North, Fort Pierce, Florida 34946

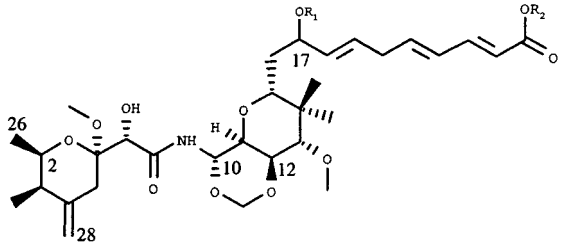
Received July 27, 2001

Theopederins K (**1**) and L (**2**) have been isolated from the marine sponge *Discodermia* sp. collected from Honduras. **1** and **2** showed in vitro cytotoxicity against P-388 and A-549 cell lines. The isolation, biological activities, and structure elucidation of theopederins K (**1**) and L (**2**) are described.

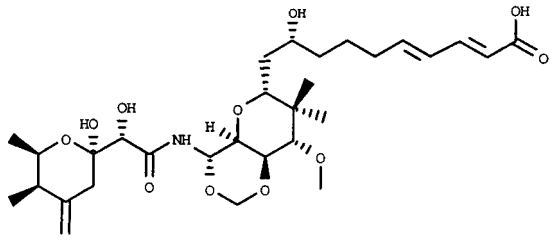
Marine sponges belonging to the genus *Discodermia* are a promising source of diverse chemical metabolites having a variety of bioactivities.[1] In a continuing search for new cytotoxic agents from the genus *Discodermia*,[2−4] we have isolated two new natural products that showed remarkable cytotoxicity against P-388 murine leukemia and A-549 human lung adenocarcinoma cell lines. These cytotoxic agents, trivially named theopederin K (**1**) and theopederin L (**2**), are 17-methoxy-6-hydroxy-18-en-theopederin G and 6-hydroxy-18-en-theopederin G, respectively, and have not been previously described in the literature. The structures were determined by a combination of NMR and mass spectral studies and by comparison with the NMR data of related compounds reported in the literature.

Pederin,[5] the first compound of this class of toxic alkaloids, was reported from the beetle *Paederus faucipes*. Subsequently, the New Zealand[6] and Harbor Branch groups[7] reported mycalamide A and onnamide A from the sponges of the genus *Theonella*, respectively, in two consecutive publications. Later, Fusetani's group in Japan reported eight related onnamides[8] and 10 related theopederins[9,10] from the sponges of the same genus *Theonella*. Recently, the same New Zealand group reported the mycalamides from the sponge genus *Stylinos*,[11] another New Zealand group in Wellington reported mycalamide D from the genus *Mycale*,[12] and an Australian group reported onnamide F from the genus *Trachycladus*.[13] Here, we report the isolation of theopederins K and L from the sponge genus *Discodermia*. It is remarkable to note that natural products incorporating the pederin skeleton with minor variations have now been isolated from five genera of the marine sponges, *Mycale* and *Stylinos* belonging to the order Poecilosclerida, *Trachycladus* belonging to the order Axinellida, *Theonella* and *Discodermia* belonging to the order Lithistida, as well as the blister beetle *Paederus fuscipes*. The presence of a rare class of alkaloids in such taxonomically distinct organisms may indicate a possible microbial biogenetic origin.

Four samples of the sponge *Discodermia* sp. were collected from Honduras in November 1997 and stored at −20 °C until extraction. The EtOH extract of the thawed sponge was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction was chromatographed over Si gel with CH_2Cl_2−MeOH step gradient, and the fractions were monitored for cytotoxicity against P388 and A549 cell lines. The cytotoxic fraction that eluted with 50% MeOH−CH_2Cl_2 was re-partitioned between heptane and 20% aqueous MeOH. The aqueous MeOH-soluble fraction on repeated reversed-phase chromatography gave theopederin K (**1**) and theopederin L (**2**) as white amorphous powders.



1 R_1 = Me R_2 = H
2 R_1 = H R_2 = H
3 R_1 = Me R_2 = Me



4

HRFABMS of theopederin K (**1**) supported the molecular formula $C_{32}H_{49}NO_{11}$ [$(M + Na)^+$ *m/z* 646.3188, Δ 1.5 mmu]. The UV spectrum displayed characteristic absorption for a conjugated carbonyl moiety at λ_{max} (MeOH) 254 nm (log ϵ 4.46) as reported for theopederin G (**4**).[10] IR spectral (KBr film) absorptions indicated the presence of hydroxyl (3387 cm^{-1}), an amide carbonyl (1535 cm^{-1}), and an acid carbonyl (1680 cm^{-1}) functionality. The ^1H NMR spectrum of theopederin K (Table 1) showed marked similarities to that of theopederin G[10] (Table 2) but contained two additional methoxy signals observed at δ 3.09 and 3.16 and two additional trans coupled olefinic protons observed at δ 5.10 (dd, 8.4, 15.4 Hz, H-18) and 5.67 (ddd, 6.5, 6.6, 15.4 Hz, H-19). Analysis of the COSY spectrum indicated that H-18 is coupled to both H-19 and H-17 methoxy methine protons at δ 3.50 (ddd, 3.2, 8.4, 10.1 Hz). The doubly allylic methylene protons at δ 2.86 (m) are coupled to H-19 on one side and to H-21 at δ 6.01 (dt, 6.6, 15.0 Hz) on the other side, which constitutes the conjugated trans-diene system. Analysis of the HMBC data (Table 1) confirmed that the three methoxy groups at δ 3.16, 3.44, and 3.09 are attached to C-6, -13, and -17, respectively, and the methylene group

* To whom correspondence should be addressed. Tel: 561-465-2400. Fax: 561-461-2221. E-mail: sgunaseker@hboi.edu.

10.1021/np0103766 CCC: $22.00
Published on Web 12/14/2001

Table 1. NMR Spectral Data for Theopederin K (**1**) in CD_3OD

position	δ_C	δ_H, mult, J (Hz)	HMBC
2	70.9 (d)	3.82 (overlapped)	C-4, C-6, C-27
3	43.0 (d)	2.13 (ddq, 7.0, 2.3, 7.0)	C-5, C-28
4	148.0 (s)		
5	34.6 (t)	2.27 (ABq, 14.0)	C-28, C-7
6	101.3 (s)		
7	73.5 (d)	4.18 (s)	C-5
8	174.0 (s)		
10	75.3 (d)	5.56 (d, 8.5)	C-(10-O-C), C-8
11	70.2 (d)	3.81 (overlapped)	C-13, C-15
12	74.9 (d)	4.06 (dd, 9.1, 6.1)	C-10, C-(10-O-C)
13	81.1 (d)	3.41 (d, 9.1)	
14	41.6 (s)		
15	77.1 (d)	3.22 (d, 9.8)	C-11, C-13, C-17
16	36.2 (t)	1.41 (10.6, 10.8) 1.61 (m)	C-18, C-17
17	81.6 (d)	3.50 (ddd, 3.2, 10.1, 8.4)	C-(17-O-C)
18	132.3 (d)	5.10 (dd, 8.4, 15.4)	C-16, C-20
19	134.5 (d)	5.67 (ddd, 6.5, 6.6, 15.4)	C-17, C-21
20	36.4 (t)	2.86 (m)	C-18, C-22
21	139.8 (d)	6.01 (dt, 15.0, 6.6)	C-19, C-23
22	131.1 (d)	6.19 (dd, 15.0, 14.4)	C-20, C-24
23	142.6 (d)	7.04 (t, 14.4)	C-21, C-25
24	127.1 (d)	5.79 (d, 14.4)	C-22
25	175.9 (s)		
26	18.2 (q)	1.14 (d, 6.5)	C-3
27	12.6 (q)	0.90 (d, 7.0)	C-2
28	110.3 (t)	4.56 (s) 4.73 (s)	C-3, C-5 C-3, C-5
14-Me_{eq}	24.1 (q)	0.88 (s)	C-13, C-15
14-Me_{ax}	15.0 (q)	0.75 (s)	C-13, C-15
10-OCH_2	87.2 (t)	4.70 (d, 7.0) 5.04 (d, 7.0)	C-12, C-10 C-12, C10
6-OCH_3	48.6 (q)	3.16 (s)	C-6
13-OCH_3	61.8 (q)	3.44 (s)	C-13
17-OCH_3	56.1 (q)	3.09 (s)	C-17

at δ 2.86 (H-20) is doubly allylic. Comparison of the NMR data (^{1}H, and ^{13}C) of the C-2 to C-16 subunit in **1** with the data reported for theopederin G (**4**) (Table 2) and the NMR data (^{1}H, ^{13}C and NOE) reported for mycalamide A[6] supported a common relative stereochemistry about the chiral centers within the subunit. The relative stereochemistry at C-17 was not determined. The presence of the terminal acid group in **1**, as in theopederin G, was established by methylation with diazomethane to give the methy ester (**3**), and its structure was confirmed by NMR and mass spectral studies. The combination of the above data established the structure for theopederin K (**1**).

HRFABMS of theopederin L (**2**) supported the molecular formula $C_{31}H_{47}NO_{11}$ [$(M + Na)^+$ m/z 632.3048, Δ 0.1 mmu]. Theopederin L (**2**) was isolated from a more polar fraction, and it indicated a difference in elements CH_2 (14 mmu) from theopederin K. The ^{1}H and ^{13}C NMR analysis revealed that theopederin L (**2**) is similar to theopederin K (**1**), and the only notable exception was the presence of only two OMe signals (Table 2, δ_H 3.23, 3.53; δ_C 48.3, 61.6) as compared to the presence of three OMe signals (δ_H 3.16, 3.44, 3.09; δ_C 48.6, 61.8, 56.1) in **1**. Similarly, the ^{1}H and ^{13}C spectra of **2** were almost identical to theopederin G (Table 2) with the significant difference being the presence of one more OMe group at δ 3.23 and an additional isolated double (δ_H 5.40, δ_C 133.2; δ_H 5.68, δ_C 128.3) in the side chain. The combination of these data assigned the two OMe groups to positions C-6 and C-13 and thus established the structure of theopederin L (**2**). The relative stereochemistry at C-17 was not determined.

Experimental Section

General Experiment Procedures. 1D and 2D NMR spectra were measured on a Bruker AMX-500 instrument. The ^{1}H NMR chemical shifts (referenced to CD_3OD observed at 3.30 ppm or $CDCl_3$ observed at 7.24 ppm) were assigned using a combination of data from COSY and HMQC experiments. Similarly, ^{13}C NMR chemical shifts (referenced to solvent) were assigned on the basis of DEPT and HMQC experiments. UV spectra were measured with a Hitachi U-3010 spectrophotometer. IR spectra were obtained on a Midac M-1200 with Galactic GRAMS/386 software. Optical rotations were recorded on a Jasco DIP-360 digital polarimeter. The HRMS were obtained on a Finnigan MAT95Q mass spectrometer at the Spectroscopic Services Group, University of Florida, Gainesville, FL.

Table 2. ^{1}H and ^{13}C NMR Data for Theopederin L (**2**) and Theopederin G (**4**)

	theopederin L		theopederin G	
position	δ_C[a]	δ_H, mult, J (Hz)[b]	δ_C[b]	δ_H, mult, J (Hz)[b]
2	70.4 (d)	4.12 (m)	71.1 (d)	4.16 (m)
3	41.4 (d)	2.18 (m)	43.1 (d)	2.19 (m)
4	146.0 (s)		148.5 (s)	
5	33.4 (t)	2.41 (d, 14.0) 2.32 (d, 14.0)	36.6 (t)	2.72 (d, 13.8) 2.10 (d, 13.8)
6	99.8 (s)		99.1 (s)	
7	73.2 (d)	4.23 (s)	71.1 (d)	3.94 (s)
8	172.4 (s)		175.2 (s)	
10	73.2 (d)	5.72 (m)	75.5 (d)	5.80 (d, 9.6)
11	69.5 (d)	3.98 (m)	71.1 (d)	3.97 (dd, 9.6, 7.2)
12	74.1 (d)	4.15 (m)	76.0 (d)	4.17 (dd, 10.2, 7.2)
13	79.3 (d)	3.60 (m)	80.7 (d)	3.67 (d, 10.2)
14	41.4 (s)		42.4 (s)	
15	79.1 (d)	3.55 (m)	78.9 (d)	3.43 (t, 6.6)
16	35.8 (t)	1.60 (m), 1.50 (m)	25.7 (t)	1.50 (m), 1.50 (m)
17	73.3 (d)	3.85 (m)	71.3 (d)	3.63 (m)
18	133.2 (d)	5.40 (dd, 15.4, 6.5)	36.7 (d)	1.28 (m), 1.48 (m)
19	128.3 (d)	5.68 (m)	37.1 (d)	1.58 (m), 1.44 (m)
20	35.1 (t)	2.93 (m)	34.0 (t)	2.33 (m), 2.18 (m)
21	138.4 (d)	6.25 (m)	146.7 (d)	6.20 (dt, 15.6, 8.4)
22	129.8 (d)	6.32 (m)	130.6 (d)	6.29 (dd, 15.6, 10.8)
23	141.7 (d)	7.27 (dd, 15.3, 10.2)	147.8 (d)	7.25 (dd, 15.0, 10.2)
24	128.3 (d)	5.82 (d, 15.3)	121.2 (d)	5.80 (d, 15.0)
25	168.8 (d)		170.6 (s)	
26	17.7 (q)	1.17 (d, 6.9)	18.2 (q)	1.07 (d, 6.6)
27	11.7 (q)	1.00 (d, 6.7)	12.0 (q)	1.00 (d, 7.2)
28	109.9 (t)	4.75, 4.64 (br, s)	110.6 (t)	4.68 (br s)
29	23.0 (q)	0.97 (s)	23.1 (q)	0.99 (s)
30	13.5 (q)	0.85 (s)	14.0 (q)	0.85 (s)
10-OCH_2	86.6 (t)	4.86 (d, 6.8) 5.18 (d, 6.8)	88.2 (t)	4.78 (d, 7.2) 5.22 (d, 7.2)
6-OMe	48.3 (q)	3.23 (s)		
13-OMe	61.6 (q)	3.53 (s)	62.1 (q)	3.56 (s)

[a] Measured in 10% $CD_3OD-CDCl_3$. [b] Measured in CD_3OD.

Animal Material. The sponge samples (HBOI #s 16-XI-97-1-005, 19-XI-97-3-002, 20-XI-97-1-002, 20-XI-97-1-003) were collected in November 1997 by manned submersible off the north coast of Honduras (latitude 16°24.847′ N; longitude 85°58.575′ W, depth 121 m; latitude 16°25.342′ N; longitude 85°58.477′ W, depth 122 m; latitude 16°25.394′ N; longitude 85°58.397′ W, depth 125 m; latitude 16°25.394′ N; longitude 85°58.397′ W, depth 125 m, respectively). The morphology of the sponge varies from club-shaped to lobate to knob-shaped. It is firm in consistency. The color is cream with tinges of pink or brown when alive, fading to white when preserved in EtOH. The spicule skeleton consists of desmas, discotriaenes, oxeotes, microxea, and acanthose microrhabds, as described in the literature.[14] Taxonomic reference samples have been deposited in the Harbor Branch Oceanographic Museum, catalog num-

bers 003:00977 (16-XI-97-1-005), 003:00978 (19-XI-97-3-002), 003:00979 (20-XI-97-1-002), and 003:00980 (20-XI-97-1-003).

Extraction and Isolation. The sponges were combined (5.6 kg), extracted in EtOH, and concentrated to give a pale brown EtOH extract. The EtOH extract was partitioned between EtOAc (1 L) and H_2O (3 × 2 L). The EtOAc-soluble fraction (~7.0 g) was column chromatographed over Si gel (350 g, 230−400 mesh) using a MeOH−CH_2Cl_2 step gradient, and the fractions were monitored for cytotoxicity against the P-388 murine leukemia cell line. The cytotoxic fraction that eluted with 50% MeOH−CH_2Cl_2 (1.44 g) was partitioned between heptane (3 × 200 mL) and 20% aqueous methanol (50 mL). The aqueous MeOH-soluble fraction (1.09 g) was column chromatographed over reversed-phase C_{18} using an H_2O−MeOH step gradient. The cytotoxic fractions that eluted with 40−60% MeOH−H_2O were combined and further purified by reversed-phase HPLC (VYDAC, C_{18}, 5 μm, 250 × 10 mm) with 40% MeCN−H_2O, which gave theopederin K (**1**) (21.9 mg, yield, 0.00039% wet wt) and theopederin L (**2**) (1.0 mg, yield, 0.000018% wet wt).

Theopederin K (1): $[\alpha]^{21}_D$ +90.3° (*c* 0.43, CH_3OH); UV (MeOH) λ_{max} (log ϵ) 254 (4.46), 202 (4.23) nm; IR (neat) ν_{max} 3387, 2971, 1680, 1535, 1109, 1023 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRFABMS (3-nitrobenzyl alcohol) *m/z* 646.3188, Δ 1.5 mmu for $C_{32}H_{49}NO_{11}Na$ $[M + Na]^+$.

Theopederin L (2): $[\alpha]^{21}_D$ +34.0° (*c* 0.05, CH_3OH); UV (MeOH) λ_{max} 260 (log ϵ) 260 (4.10), 202 (4.07) nm; IR (neat) ν_{max} 3429, 2977, 1701, 1528, 1109, 1028 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; ^1H NMR ($CDCl_3$) δ 3.98 (1H, *J* = 2.6, 6.4 Hz, H-2), 2.22 (1H, *J* = 2.6, 7.1 Hz, H-3), 2.36 (2H, ABq *J* = 15.3, H-5), 4.28 (1H, s, H-7), 7.47 (1H, d, *J* = 9.5 Hz, NH-9), 5.85 (1H, dd, *J* = 9.5, 9.6 Hz, H-10), 3.85 (1H, dd, *J* = 9.6, 6.6 Hz, H-11), 4.20 (1H, dd, *J* = 9.5, 6.6 Hz, H-12), 3.43 (1H, d, *J* = 9.5 Hz, H-13), 3.59 (1H, dd, *J* = 6.3, 5.8 Hz, H-15), 1.55 (2H, m, H-16), 4.11 (1H, dt, *J* = 5.8, 6.5 Hz, H-17), 5.43 (1H, dd, *J* = 15.4, 6.5 Hz, H-18), 5.66 (1H, dt, *J* = 15.4, 6.4 Hz, H-19), 2.89 (2H, t, *J* = 6.4, H-20), 6.15 (1H, dt, *J* = 15.4, 6.4 Hz, H-21), 6.20 (1H, dd, *J* = 15.3, 10.2 Hz, H-22), 7.30 (1H, dd, *J* = 15.3, 10.2 Hz, H-23), 5.79 (1H, d, *J* = 15.3 Hz, H-24), 1.18 (3H, d, *J* = 6.4 Hz, H-26), 1.01 (3H, d, *J* = 7.1 Hz, H-27), 4.72 (1H, s, H-28), 4.86 (1H, s, H-28), 0.97 (3H, s, Me_{eq}-14), 0.86 (3H, s, Me_{ax}-14), 4.83 (1H, d, *J* = 6.8 Hz, CH_2O-10), 5.12 (1H, d, *J* = 6.8 Hz, CH_2O-10), 3.29 (3H, s, MeO-6), 3.54 (3H, s, MeO-13); HRFABMS (3-nitrobenzyl alcohol) *m/z* 632.3048, Δ 0.1 mmu for $C_{31}H_{47}NO_{11}Na$ $[M + Na]^+$.

Preparation of Theopederin K Methyl Ester (3). Theopederin K (2 mg) in MeOH (0.5 mL) was treated with an excess of CH_2N_2 in ether in an ice bath for 2 h. The reaction mixture was dried under a stream of nitrogen, and the resulting residue on purification by HPLC (Lichrosorb 5μ, SiO_2, 250 × 10 mm column) using 3% MeOH−CH_2Cl_2 gave pure theopederin K methyl ester (**3**) (1.6 mg): $[\alpha]^{21}_D$ +69.6° (*c* 0.08, CH_3OH); UV (MeOH) λ_{max} (log ϵ) 262 (4.28), 203 (4.27) nm; IR (neat) ν_{max} 3350, 2980, 1688, 1528, 1380, 1131, 1084 cm^{-1}; ^1H NMR (CD_3OD) δ 3.92 (1H, overlapped, H-2), 2.21 (1H, m, H-3), 2.36 (2H, ABq, *J* = 14.1 Hz, H-5), 4.25 (1H, s, H-7), 5.63 (1H, d, *J* = 8.9 Hz, H-10), 3.89 (1H, overlapped, H-11), 4.14 (1H, dd, *J* = 6.3, 9.2 Hz, H-12), 3.48 (1H, d, *J* = 9.2 Hz, H-13), 3.26 (1H, overlapped, H-15), 1.47 (1H, m, H-16), 1.69 (1H, m, H-16), 3.55 (1H, m, H-17), 5.22 (1H, dd, *J* = 15.6, 8.4 Hz, H-18), 5.74 (1H, dt, *J* = 15.6, 6.6, H-19), 2.98 (2H, m, H-20), 6.28 (1H, overlapped, H-21), 6.34 (1H, overlapped, H-22), 7.32 (1H, dd, *J* = 10.2, 15.4 Hz, H-23), 5.88 (1H, d, *J* = 15.4 Hz, H-24), 1.18 (3H, d, *J* = 6.5 Hz, H-26), 0.98 (3H, d, *J* = 7.2 Hz, H-27), 4.64 (1H, br s, H-28), 4.85 (1H, br s, H-28), 0.96 (3H, s, Me_{eq}-14), 0.83 (3H, s, Me_{ax}-14), 4.78 (1H, d, *J* = 6.8 Hz, OCH-10), 5.12 (1H, d, *J* = 6.8 Hz, OCH-10), 3.16 (3H, s, MeO-17), 3.25 (3H, s, MeO-6), 3.51 (3H, s, MeO-13), 3.70 (3H, s, MeO-25); ^{13}C NMR (CD_3OD, 125.7 MHz) δ 70.9 (d, C-2), 43.0 (d, C-3), 148.0 (s, C-4), 34.7 (t, C-5), 101.3 (s, C-6), 73.7 (d, C-7), 174.2 (s, C-8), 75.2 (d, C-10), 70.2 (d, C-11), 75.0 (d, C-12), 81.0 (d, C-13), 41.7 (s, C-14), 77.0 (d, C-15), 36.5 (t, C-16), 81.6 (d, C-17), 132.7 (d, C-18), 134.1 (d, C-19), 36.1 (t, C-20), 143.7 (d, C-21), 130.3 (d, C-22), 146.6 (d, C-23), 120.4 (d, C-24), 169.3 (s, C-25), 18.1 (q, C-26), 12.5 (q, C-27), 110.3 (t, C-28), 24.0 (q, Me_{eq}-14), 14.9 (q, Me_{ax}-14), 87.2 (t, OCH_2-10), 48.5 (q, MeO-6), 61.8 (q, MeO-13), 56.1 (q, MeO-17) and 52.0 (q, MeO-25); HRFABMS (3-nitrobenzyl alcohol) *m/z* 660.3352, Δ 0.8 mmu for $C_{33}H_{51}NO_{11}$-Na $[M + Na]^+$.

Cytotoxicity Assay. Compounds **1**, **2**, and **3** exhibited in vitro cytotoxicity against the cultured murine P-388 tumor cell line, with IC_{50} values of 0.1, 7.3, and 0.3 nM and the human lung adenocarcinoma A-549 cell line, with IC_{50} values of 1.5, 3.2, and 0.8 nM, respectively.[15,16]

Acknowledgment. We thank Patricia Linley for her assistance with the cytotoxicity assays. We also thank Dr. David Powell of the University of Florida, Gainesville, for the HRFABMS measurements. This research was funded by a grant from the National Institute of Health/National Cancer Institute RO1-CA 74227. This is Harbor Branch Oceanographic Institution contribution no. 1454.

References and Notes

(1) Faulkner, D. J. *J. Nat. Prod. Rep*. **2001**, *18*, 1−49, and references therein.
(2) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912−4915. (correction: **1991**, *56*, 1346).
(3) Gunasekera, S. P.; Gunasekera, M.; McCarthy, P. *J. Org. Chem*. **1991**, *56*, 4830−4833.
(4) Gulavita, N. K.; Gunasekera, S. P.; Pomponi, S. A.; Robinson, E. V. *J. Org. Chem*. **1992**, *57*, 1767−1772.
(5) Matsumoto, T.; Yanagiya, M.; Maeno, S.; Yasuda, S. *Tetrahedron Lett*. **1968**, 6297−6300.
(6) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc*. **1988**, *110*, 4850−4851.
(7) Sakemi, S.; Ichiba, T.; Saucy, G.; Higa, T. *J. Am. Chem. Soc*. **1988**, *110*, 4851−4853.
(8) Matsunaga, S.; Fusetani, N.; Nakao, Y. *Tetrahedron* **1992**, *48*, 8369−8376.
(9) Fusetani, N.; Sugawara, T.; Matsunaga, S. *J. Org. Chem*. **1992**, *57*, 3828−3832.
(10) Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-e, A. *Tetrahedron* **1999**, *55*, 13697−13702.
(11) Simpson, J. S.; Garson, M. J.; Blunt, J. W.; Munro, M. H. G.; Hooper, N. A. *J. Nat. Prod*. **2000**, *63*, 704−706.
(12) West, L. M.; Northcote, P. T.; Hood, K. A.; Miller, J. H.; Page, M. J. *J. Nat. Prod*. **2000**, *63*, 707−709.
(13) Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *J. Nat. Prod*. **2001**, *64*, 640−642.
(14) van Soest, R. W. M.; Stentoft, N. *Barbados Deep-water Sponges: Studies on the Fauna Curacao and other Caribbean Islands*, 1988; Vol. 70, pp 50−52.
(15) Gunasekera, S. P.; Longley, R. E.; Paul, G.; Isbrucker, R. I.; Pomponi, S. A. serial number 09/835,692, U.S. Patent filed on April 20, 2001.
(16) Theopederins K and L were initially named as discalamides A and B, respectively, in the U.S. Patent application. Compounds were renamed to be consistent with the theopederin F−J series.

NP0103766