Madangamines B−E, Pentacyclic Alkaloids from the Marine Sponge *Xestospongia ingens*

Fangming Kong, Edmund I. Graziani, and Raymond J. Andersen*

Departments of Chemistry and Oceanography−Earth and Ocean Sciences, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z1

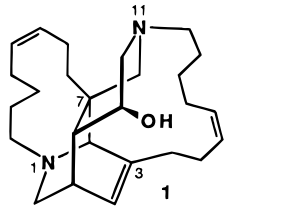
Received September 15, 1997

Four new pentacyclic alkaloids, madangamines B−E (**3**−**6**), have been isolated from the marine sponge *Xestospongia ingens* collected in Papua New Guinea.

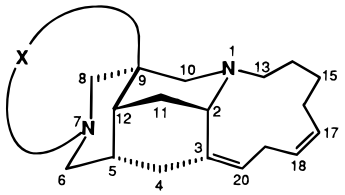
Marine sponges belonging to the order Haplosclerida have been a rich source of 3-alkylpiperidine alkaloids.[1] Recently we reported that specimens of *Xestospongia ingens* Van Soest (order Haplosclerida, family Petrosiidae) collected in Papua New Guinea contained the 3-alkylpiperidine alkaloids ingenamine (**1**),[2] ingenamines B−F,[3] ingamines A and B,[4] and madangamine A (**2**).[5] This group of metabolites represented the first examples of the unprecedented ingenamine and madangamine pentacyclic alkaloid skeletons.[6] As part of ongoing chemical investigations of *X. ingens* extracts, we have isolated four new alkaloids, madangamines B−E (**3**−**6**), whose structures are described in this report.

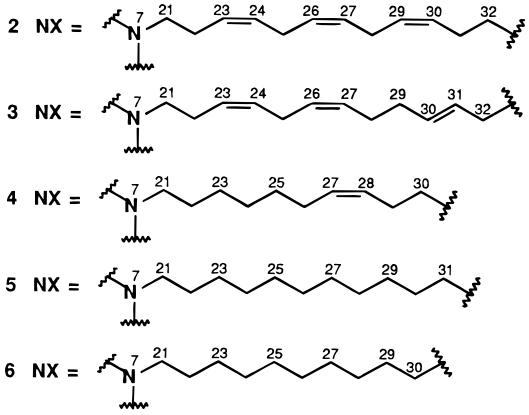
Specimens of *X. ingens* were collected by hand using scuba on reefs off Madang, Papua New Guinea. The sponge samples were deep frozen on site and transported to Vancouver over dry ice. Thawed specimens of *X. ingens* were extracted multiple times with MeOH and the combined MeOH extracts were reduced *in vacuo* to an aqueous suspension. The aqueous suspension was diluted with distilled H_2O and then partitioned sequentially against hexanes and EtOAc. Repeated fractionation of the hexane-soluble materials using Si gel flash chromatography and normal-phase HPLC led to the isolation of madangamines A−E (**2**−**6**).

Madangamine B (**3**) was isolated as an optically active colorless glass that gave an intense parent ion in the HREIMS at *m*/*z* 432.3498 appropriate for a molecular formula of $C_{30}H_{44}N_2$ (ΔM −0.6 mmu), identical to the molecular formula of madangamine A (**2**). Table 1 lists the NMR data for madangamine B (**3**) acquired in C_6D_6. The ^{1}H-NMR spectrum of **3** showed a close correspondence with the ^{1}H-NMR spectrum of madangamine A (**2**), particularly the proton resonances assigned to the central core and the linear alkyl bridge connecting N-1 and C-3. The significant differences in the two spectra were the absence in the spectrum of **3** of two well-resolved signals at chemical shifts of δ 1.00 (H-32′) and 5.55 (H-30) that were present in the spectrum of **2**, and the appearance of a broad doublet of doublet resonance at δ 1.62 (H-32′) and an overlapped olefinic proton resonance at δ 5.20 (H-27) in the spectrum of **3** that were not present in the spectrum of **2**. Similarly, the ^{13}C- and APT NMR spectra of madangamine B (**3**) were



1





nearly identical with those of madangamine A (**2**) except for the resonances assigned to the C-28 to C-32 fragment (Table 1). Thus, a superficial examination of the MS and NMR data suggested that madangamine B (**3**) differed from madangamine A (**2**) only in the C-29 to C-32 region of the N-7 to C-9 alkyl bridge. This was confirmed by detailed analysis of the COSY, COSYLR, NOE, HMQC, and HMBC data obtained for madangamine B, which showed that the tricyclic core (N-1 to C-12) and the N-1 to C-3 bridge in **3** were identical to the corresponding fragments in madangamine A (**2**) (Table 1).

Subtraction of the atoms present in the already-identified tricyclic core and N-1 to C-3 bridge ($C_{18}H_{26}N_2$) from the molecular formula of madangamine B (**3**)

* To whom correspondence should be addressed. Phone: (604)822-4511. Fax: (604)822-6091. E-mail: randersn@unixg.ubc.ca.

S0163-3864(97)00377-7 CCC: $15.00
Published on Web 02/10/1998

Table 1. NMR Data of Madangamines A−E (**2**−**6**) Recorded in C_6D_6 at 500 MHz (^1H)

	madangamine A (**2**)		madangamine B (**3**)		madangamine C (**4**)[a]		madangamine D (**5**)		madangamine E (**6**)	
C#	δ ^{13}C	δ ^1H	δ ^{13}C	δ ^1H	δ ^{13}C	δ ^1H	δ ^{13}C	δ ^1H	δ ^{13}C	δ ^1H
2	51.8	3.69 br s	51.8	3.71, t (3.1)	51.6	3.70, t (3.2)	51.8	3.69, br s	51.8	3.69, br s
3	139.3		139.2		139.2		139.5		139.5	
4ax	38.3	3.07 t (16.5)	38.3	3.11, m	38.6	3.11, ddt (16.4, 11.7, 3.2)	39.0	3.0	39.0	3.00
4eq		2.21 dd (16.5, 7.7)		2.24, dd (16.9, 8.4)		2.23		2.21		2.21
5	37.1	1.70 m	37.1	1.72, m	37.4	1.71 m	36.5	1.8, m	36.5	1.8, m
6eq	61.6	2.31 bd (10.8)	61.1	2.32, bd (10.8)	62.6	2.32, br d (10.7)	60.0	2.29	60.0	2.29
6ax		2.11 dd (10.8, 3.1)		2.11, dd (10.8, 3.1)		2.15, dd (10.7, 3.4)		2.19		2.19
8eq	59.4	2.72 d (11.2)	59.3	2.48, dd (11.4, 1.6)	63.3	2.73, dd (11.8, 1.8)	62.0	2.55	62.0	2.55
8ax		1.38 d (11.2)		1.38, d (11.4)		1.52, d (11.8)		1.77		1.77
9	37.0		37.1		38.2		37.0		37.0	
10ax	52.4	3.10 d (12.0)	53.0	3.14, d (12.2)	53.8	3.40, dd (11.9, 1.6)	58.2	3.25	58.2	3.25
10eq		2.45 d (12.0)		2.47, d (12.2)		2.67, d (11.9)		2.45		2.45
11ax	32.4	2.40 dt (12.4, 3.4)	32.4	2.37, dt (12.4, 3.5)	32.1	2.34, dt (12.5, 3.4)	32.2	2.30	32.2	2.30
11eq		1.27 dt (12.4, 2.6)		1.28, dt (12.4, 2.8)		1.26, dt (12.5, 2.9)		1.30		1.30
12	39.1	1.14 m	38.4	1.22, m	39.9	1.20, m	40.1	1.18	40.1	1.18
13	55.6	2.81 ddd (13.5, 11.9, 5.8)	56.2	2.89, ddd (13.8, 11.8, 5.6)	56.2	2.82, ddd (13.8, 11.7, 5.4)	56.0	2.81	56.0	2.81
13′		2.63 br t (13.5)		2.69, td (12.5, 2.1)		2.59, tr d (13.8, 4.5)		2.61		2.61
14	23.2	1.81	23.8	1.88, m	24.5	1.82	23.2	1.85	23.2	1.85
14′		1.42 m		1.46, m		1.43		1.42		1.42
15	25.4	1.19	25.4	1.20	25.5	1.22	25.2	1.19	25.2	1.19
15′		1.19		1.20		1.12, m		1.19		1.19
16	25.8	2.24	26.0	2.27	26.4	2.24	25.8	2.24	25.8	2.24
16′		1.80		1.82, m		1.84		1.80		1.80
17	129	5.38	128.9	5.40	129.1	5.39	129.0	5.38	129.0	5.38
18	129	5.43 td (10.7, 4.1)	129.1	5.45	129.0	5.43	129.2	5.48	129.2	5.48
19	26.8	3.34 dt (13.3, 11.3)	26.8	3.34, dt (13.3, 11.3)	26.8	3.33, dt (13.4, 11.1)	27.1	3.34	27.1	3.34
19′		2.32 dd (13.3, 3.0)		2.33		2.31		2.34		2.34
20	121.8	5.16 dt (11.5, 2.8)	122.0	5.20, m	122.0	5.19, dt (11.7, 3.3)	122.0	5.20, br t	122.0	5.20, br t
21	57.7	2.47 td (11, 5.9)	57.7	2.53, ddd (12.0, 10.4, 6.8)	55.6	2.31	57.2	2.30	57.2	2.30
21′		2.14 ddd (11, 5.5, 3.3)		2.17, ddd (9.7, 6.4, 3.2)		2.18		2.15		2.15
22	25.5	2.40	24.7	2.37, m	30.1	1.68, m				
22′		1.94		1.96, m		1.43, m				
23	129.2	5.36	129.5	5.41	24.9	1.22				
23′						1.15, m				
24	128.0	5.36	128.0	5.44	26.0	1.62, m				
24′						1.27, m				
25	26.6	3.07	26.3	3.00	28.0	1.49, m				
25′		2.60 br d (16.9)		2.54, br d (17.0)		1.39, m				
26	127.5	5.35	129.6	5.38	25.0	2.20				
26′						2.06, m				
27	128.3	5.35	129.2	5.20, m	129.1	5.16, m				
27′										
28	26.7	3.12	28.9	2.14	133.7	5.44				
28′		2.56 br d (16.5)		1.96						
29	125.9	5.31	31.7	2.11	23.3	2.25				
29′				1.95		2.09, m				
30	132.8	5.55 m	133.1	5.43	36.2	2.70 ddd (12, 3.7, 2.0)				
30′						0.89 ddt (12, 9.2, 1.9)				
31	22.7	2.25	128.5	5.48						
31′		1.93								
32	36.1	2.50 ddd (13, 10.5, 3.0)	40.0	3.01 dd (12.3, 6.8)						
32′		1.00 bdd (13, 7.2)		1.62, br dd (12.3, 7.4)						

[a] NMR data of madangamine C (**3**) was recorded at 65 °C; ax = axial, eq = equatorial, LR = long-range COSY.

indicated that the N-7 to C-9 bridge contained 12 carbons with three alkene functionalities ($C_{12}H_{18}$). The ^{13}C/APT NMR spectra obtained for **3** showed that all of the bridge carbons were either aliphatic methylenes or olefinic methines. Further analysis of the NMR data for **3** identified three independent fragments that together composed the 12-carbon chain spanning N-7 and C-9. An HMBC correlation between H-6_{eq} (δ 2.32) and a carbon resonance at δ 57.7 (C-21) identified this carbon as the attachment point of the 12-carbon bridge to N-7. HMQC correlations to δ 57.7 identified the H-21/H-21′ proton resonances at δ 2.53 and 2.17. COSY correlations were observed between the H-21/H-21′ and the H-22/H-22′ (δ 2.37/1.96) resonances that were, in turn, further coupled into a vinyl proton at δ 5.41 (H-23), demonstrating that the functionality at C-21, C-22, C-23, and C-24 in madangamine B (**3**) was identical to the functionality at the corresponding carbons in madangamine A (**2**). Resonances at δ 3.00 and 2.54 ppm (H-25/H-25′), assigned to a pair of geminal methylene protons by virtue of their HMQC correlations to a common carbon resonance (δ 26.3, C-25), had chemical shifts typical of doubly allylic methylene protons. Both the H-25 and H-25′ proton resonances showed COSY correlations to resonances in the severely overlapped olefinic proton region at δ 5.44 (H-24) and δ 5.38 (H-26). The H-26 resonance (δ 5.38) showed a further COSY correlation to a relatively shielded olefinic proton resonance at δ 5.20 (H-27), and the latter was correlated to a pair of geminal singly allylic proton resonances at δ 2.14 and 1.96 (H-28/H-28′). A COSYLR correlation observed between δ 5.20 (H-27) and the doubly allylic

proton resonance at δ 3.00 (H-25) confirmed the assigned connectivity. This set of COSY correlations identified a disubstituted olefinic subfragment linked to a doubly allylic methylene carbon on one end and a singly allylic methylene carbon on the other end. Further analysis of the COSY spectrum revealed additional vinyl to allylic correlations between resonances at δ 3.01/1.62 (H-32/H-32′) and δ 5.48 (H-31) and between δ 5.43 (H-30) and δ 2.11/1.95 (H-29/H-29′). Three-bond HMBC correlations observed between both diagnostic H-32 protons and the most deshielded olefinic methine carbon at δ 133.1 (C-30), and two-bond HMBC correlations observed between δ 133.1 (C-30) and H-29/H-29′ were in complete agreement with a further disubsituted olefinic subfragment attached at each end to singly allylic methylene carbons. An HMBC correlation between H-10_{ax} (δ 3.14) and one of these allylic methylene carbons at δ 40.0 (C-32) anchored this fragment to the C-9 attachment point of the central tricyclic core. Inserting the remaining disubstituted olefinic subfragment (C-25 to C-28) between C-24 and C-29 completed the structure of the N-7 to C-9 bridge in madangamine B (**3**). The chemical shifts of the allylic carbons at C-22 (δ 24.7), C-25 (δ 26.3), and C-28 (δ 28.9) were consistent with the *Z* configurations for the alkenes at $\Delta^{23,24}$ and $\Delta^{26,27}$.[7] The chemical shift of the C-29 resonance (δ 31.7) indicated that the $\Delta^{30,31}$ double bond had the *E* geometry (**2**).

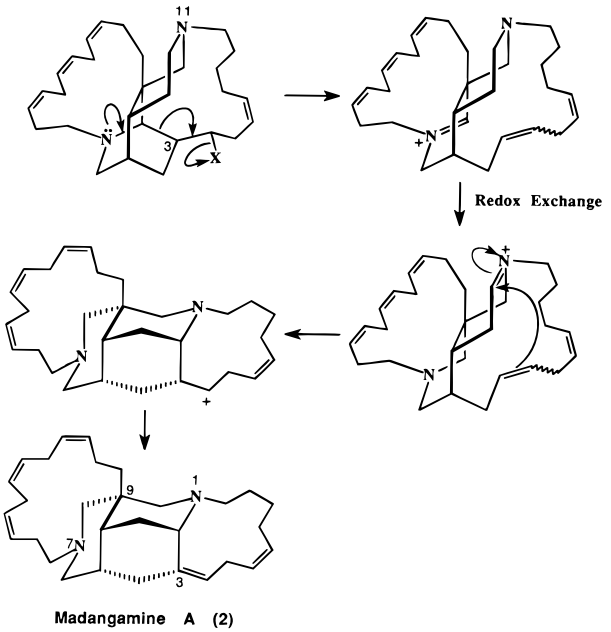
Madangamine C (**4**) was obtained as an optically active colorless glass. The HREIMS of **4** gave an intense parent ion at *m*/*z* 408.3507 corresponding to a molecular formula of $C_{28}H_{44}N_2$ (ΔM 0.3 mmu), which required eight degrees of unsaturation. Initially, the 1D and 2D NMR data for **4** were acquired at room temperature; however, it was found that the ^{13}C/APT NMR spectra recorded at room temperature showed only 16 strong resonances and not the 28 resonances expected from the molecular formula. Recording the ^{13}C-NMR spectrum at 65 °C sharpened the resonances, which facilitated the observation of all the expected 28 resonances, and it also improved the heteronuclear 2D NMR spectra. The ^{1}H-NMR spectrum of **4** was similar in most respects to that of madangamine A (**2**). The most notable differences were the smaller number of olefinic proton resonances and the greater complexity in the upfield region in the ^{1}H-spectrum of compound **4**. Six deshielded resonances in the ^{13}C-NMR spectrum of **4** could be assigned to three olefins. The absence of NMR evidence for additional unsaturated functionality indicated that madangamine C (**4**) was also pentacyclic, as required by its unsaturation number. Comparison of the ^{13}C NMR data obtained for madangamine C (**4**) with that of madangamine A (**2**) suggested that both molecules contained identical tricyclic cores and linear eight carbon bridges connecting N-1 and C-3 (see Table 1). This was confirmed by detailed analysis of the COSY, COSYLR, and HMBC data obtained for madangamine C (**4**).

Subtraction of the atoms present in the readily identified tricyclic core and N-1 to C-3 bridge ($C_{18}H_{26}N_2$) from the molecular formula of madangamine C (**4**) indicated that the N-7 to C-9 bridge contained 10 carbons and one alkene functionality ($C_{10}H_{18}$). The ^{13}C-NMR and APT data obtained for **4** showed that all of the 10 carbons in the bridge were aliphatic methylenes and olefinic methines, which required a linear chain. Thus, the remaining structural problem was to determine the position and configuration of the lone olefin in the linear bridge. HMBC correlations between the H-10_{ax} (δ 3.40), H−10_{eq} (δ 2.67), and H-8_{ax} (δ 1.52) proton resonances, and a carbon resonance at δ 36.2 (C-30) identified this methylene carbon as the C-9 attachment point of the 10-carbon bridge. HMQC correlations were observed between the C-30 methylene carbon resonance at δ 36.2 and a pair of proton resonances at δ 0.89 (H-30′) and 2.70 (H-30). The most upfield resonance at 0.89 ppm (H-30′) showed a COSY correlation to a vicinal methylene proton resonance at δ 2.25 (H-29), which was further coupled to an olefinic proton resonance at δ 5.44 (H-28). A COSY correlation was observed between the olefinic proton resonance at δ 5.44 (H-28) and another olefinic proton resonance at δ 5.16 (H-27), which was in turn correlated to a pair of geminal allylic methylene proton resonances at δ 2.20 and 2.06 (H-26/H-26′). The very diagnostic H30′ proton resonance (δ 0.89) showed a two-bond HMBC correlation to the shielded methylene carbon assigned to C-29 (δ 23.3) and a three-bond correlation to the deshielded olefinic methine carbon assigned to C-28 (δ 133.7) in agreement with the location of the vinyl group at $\Delta^{27,28}$. COSYLR correlations observed between H-26 (δ 2.20) and H-28 (δ 5.44) and between H-27 (δ 5.16) and H-29′ (δ 2.09) were also consistent with the proposed structure. The chemical shifts of the resonances assigned to the allylic carbons C-26 (δ 25.0) and C-29 (δ 23.3) indicated that the alkene at $\Delta^{27,28}$ had the *Z* geometry. Several of the resonances assigned to carbon atoms in this bridge were very broad when the ^{13}C-NMR spectrum of **3** was acquired at room temperature, presumably due to a slow conformational exchange of the atoms in this bridge.

Madangamines D (**5**) and E (**6**) were isolated as an inseparable mixture. The HREIMS of the mixture of **5** and **6** showed intense ions at *m*/*z* 424.381 95 and 410.365 58 appropriate for elemental compositions of $C_{29}H_{48}N_2$ (ΔM −0.2 mmu) and $C_{28}H_{46}N_2$ (ΔM 0.5 mmu), respectively. Detailed analysis of the 1D and 2D NMR data obtained for the mixture of **5** and **6** (Table 1) confirmed the presence of the same central tricyclic core and N-1 to C-3 bridge found in madangamines A (**2**), B (**3**), and C (**4**). Subtraction of the atoms in the central core and N-1 to C-3 bridge from the molecular compositions of the putative molecular ions in the HREIMS of the mixture gave residues of $C_{10}H_{20}$ and $C_{11}H_{22}$, respectively. Thus, these residues, which had to compose the N-7 to C-9 bridges in **5** and **6**, contained no sites of unsaturation. This was consistent with the absence of any olefinic resonances in either the ^{1}H- or ^{13}C-NMR spectra of the mixture that could not be accounted for by functionality in the already identified N-1 to C-3 bridge. Furthermore, since the ^{1}H-NMR spectrum of the mixture contained no methyl residues, the bridges had to be linear chains of eleven and 10 methylene carbons, respectively. It was not possible to assign ^{1}H- or ^{13}C-NMR resonances to the individual atoms in the N-7 to C-9 bridges of madangamines D (**5**) and E (**6**) other than the initial C-21 resonance.

Madangamines B (**3**), C (**4**), D (**5**), and E (**6**) are new members of the madangamine family of pentacyclic alkaloids.[1] The basic madangamine skeleton consists

Scheme 1. Proposed Biosynthesis for Madangamine A.



of a tricyclic core and two linear bridges. Structural variations in this group of alkaloids occur only in the N-7 to C-9 bridge that varies both in carbon length and in the position and degree of unsaturation. This is in contrast to the co-occurring ingenamine alkaloids that show variations in carbon length and unsaturation pattern in both the N-1 to C-7 and the C-3 to N-11 bridges. We have proposed that the madangamine skeleton arises via rearrangement of an ingenamine precursor (Scheme 1). It may be that the enzyme(s) catalyzing this rearrangement has a specific requirement for a particular chain length and functionality in the C-3 to N-11 bridge in the putative ingenamine precursor. Thus, all the resulting magangamines have identical N-1 to C-3 bridges but show variations in the N-7 to C-9 bridge.

The tricyclic core of the madangamines possesses a diamond-lattice structure in which all three of the six-membered rings are in chair conformations. An sp^2 hybridized carbon situated at C-3 forces one carbocyclic ring into a slightly flattened chair conformation. Models indicate that strong steric repulsion should exist between the two protons H-4_{ax} and H-10_{ax} in the madangamines. Observation of strong NOEs between H-4_{ax} and H-10_{ax} and the anomolously large (δ >3) proton chemical shifts assigned to H-4_{ax} and H-10_{ax} are consistent with a strong steric interaction between these two protons.

The madangamine alkaloids are extremely nonpolar compounds relative to the closely related ingenamine alkaloids. For example, the madangamines dissolved in the hexanes layer, while the ingenamines remained in the aqueous layer when the crude extract of *X. ingens* was partitioned between H_2O and hexanes. The significant difference in polarity between these two types of compounds can perhaps be attributed to their different core structures. In the madangamines, one of the two nitrogen atoms, namely N-7, cannot readily invert because the cavity of the central core is too small to easily accommodate the C-21 alkyl group. As a consequence, the lone pair on the N-7 nitrogen atom is locked in the center of the tricyclic core where it is relatively inaccessible for protonation and hydrogen bonding. The anticipated result would be a decreased basicity for the N-7 amine and consequently a reduced polarity for the madangamines. In contrast, both the N-1 and N-11 nitrogen atoms in the ingenamine alkaloids can invert, making the lone pairs on both N-1 and N-11 readily accessible for protonation and hydrogen bonding and, therefore, increasing the polarity of the molecules.

Experimental Section

Biological Material. Specimens of *Xestospongia ingens* Van Soest were collected by hand using scuba on reefs at depths of −15 to −20 m near Sek Point off Madang, Papua New Guinea, in 1992. Freshly collected sponge samples were frozen on site and transported to Vancouver over dry ice. The sponge was identified by Dr. R. van Soest. A voucher sample (ZMA 10701) has been deposited at the Zoologisch Museum, University of Amsterdam.

Isolation of Madangamines. Specimens (200 g, wet wt) of *X. ingens* were thawed and extracted with MeOH (500 mL × 3; 24 h between extractions). The MeOH extract was filtered and concentrated *in vacuo* to give a dark brown aqueous suspension that was diluted with H_2O to a final volume of 300 mL and partitioned sequentially against hexanes (400 mL × 3) and EtOAc (400 mL × 3). The hexane-soluble fraction (770 mg) was subjected to Si gel flash chromatography using a gradient elution of hexanes−EtOAc (1:9 to 1:1) to give three fractions A (120 mg), B (290 mg), and C (200 mg) in sequence. Normal-phase HPLC chromatography of fraction A using an eluent of hexane−EtOAc−diisopropylamine (98.4:1.5:0.1) gave crude madangamines B, C, and D/E (20 mg) and pure madangamine A (**2**) (60 mg). Further recycling of the madangamine B, C, and D/E mixture using the same HPLC conditions yielded pure madangamine B (**3**) (5.5 mg), pure madangamine C (**4**) (11 mg), and an inseparable mixture of madangamines D (**5**) and E (**6**) (5 mg).

Madangamine B (3): colorless glass; $[\alpha]_D$ +150.7° (*c* 0.067, EtOAc); ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 1; LREIMS *m/z* (% rel int) 432 (M^+, 100), 378 (17), 337 (16), 283 (33), 269 (19), 254 (16), 242 (22), 91 (27), 79 (25), 67 (20); HREIMS $(M)^+$ *m/z* 432.3498 ($C_{30}H_{44}N_2$, ΔM −0.6 mmu).

Madangamine C (4): colorless glass; $[\alpha]_D$ +140.8° (*c* 0.09, EtOAc); ^{1}H NMR, see Table 1; ^{13}C NMR; LREIMS *m/z* (% rel int) 408 (M^+, 100), 296 (18), 282 (13), 230 (33), 216 (24); HREIMS $(M)^+$ *m/z* 408.3507 ($C_{28}H_{44}N_2$, ΔM 0.3 mmu).

Madangamine D (5) and madangamine E (6) mixture: colorless glass; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 1; HREIMS $(M)^+$ *m/z* 424.3819 ($C_{29}H_{48}N_2$, ΔM −0.2 mmu) and $(M)^+$ *m/z* 410.3655 ($C_{28}H_{46}N_2$, ΔM 0.5 mmu).

Acknowledgment. Financial support was provided by the Natural Sciences and Engineering Research Council of Canada and the National Cancer Institute of Canada. The authors wish to thank M. Le Blanc (UBC), Larry Orsac (CRI), and the staff of the Christensen Research Institute, Madang, PNG, for assisting with the collection of *X. ingens*, and Prof. Rob van Soest for identifying the sponge.

References and Notes

(1) Andersen, R. J.; van Soest, R. W. M.; Kong, F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1996; Vol. 10, pp 301−355.
(2) Kong, F.; Andersen, R. J.; Allen, T. M. *Tetrahedron Lett.* **1994**, *35*, 1643−1646.
(3) Kong, F.; Andersen, R. J. *Tetrahedron* **1995**, *51*, 2895−2906.
(4) Kong, F.; Andersen, R. J.; Allen, T. M. *Tetrahedron* **1994**, *50*, 6137−6144.
(5) Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007−6008.
(6) For other examples see (a) Kobayashi, J.; Tsuda, M.; Kawasaki, N.; Matsumoto, K.; Adachi, T. *Tetrahedron Lett*. **1994**, *35*, 4383−4386, and (b) Rodriguez, J.; Crews, P. *Tetrahedron Lett*. **1994**, *35*, 4719−4722.
(7) *Z* alkenes have allylic carbons at $\delta < 27$, *E* alkenes have allylic carbons at $\delta > 30$; see (a) Fusetani, N.; Yasumoto, Y.; Matsunaga, S.; Hirota, H. *Tetrahedron Lett*. **1989**, *30*, 6891−6894, (b) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem*. **1992**, *57*, 2480−2483.

NP970377R