s^{-1} (R = hexenyl), which is ca. 4 times slower than the corresponding reaction with tributyltinhydride.[12]

In conclusion, tris(trimethylsilyl)silane functions as a free radical reducing agent that rivals tributyltin hydride in its efficiency and is probably more acceptable from an ecological and toxicological perspective.[13] Further work on the kinetics and synthetic scope of these reactions is in progress.

Acknowledgment. D.G. and C.C. thank NATO for a grant which made this collaboration possible.

Registry No. $(Me_3Si)_3SiH$, 1873-77-4; $C_{18}H_{37}Cl$, 3386-33-2; $PhCH_2Br$, 100-39-0; $C_{16}H_{33}Br$, 112-82-3; $C_{18}H_{37}I$, 629-93-6; $C_{18}H_{38}$, 593-45-3; C_7H_8, 108-88-3; $C_{16}H_{34}$, 544-76-3; 2-norbornyl chloride, 29342-53-8; 3-chloro-2-norbornanone, 61914-03-2; norbornane, 279-23-2; 2-norbornanone, 497-38-1.

---

(11) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317-323.

(12) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7799-7742.

(13) Tacke, R.; Wannegat, U.; Vorontow, N. G. In *Topics in Current Chemistry, 84, Bioactive Organosilicon Compounds*; Springer Verlag: New York, 1979.

C. Chatgilialoglu,*[2] D. Griller,[1] M. Lesage[1]

Division of Chemistry
National Research Council of Canada
Ottawa, Ontario, Canada K1A 0R6
and Istituto dei Composti del Carbonio Contenenti
Eteroatomi e loro Applicazioni
CNR, Ozzano Emilia, Italy 40064

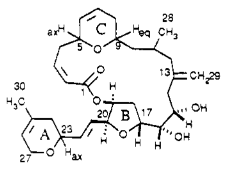
Received November 5, 1987

Fijianolides, Polyketide Heterocycles from a Marine Sponge

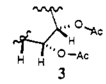
Summary: Two cytotoxic macrocyclic lactones, fijianolides A and B, were isolated from *Spongia mycofijiensis* collected from Vanuatu. These are the first 20-membered ring lactones to be observed from a marine sponge.

Sir: A chocolate sponge, *Spongia mycofijiensis*, became the object of an intense study because the liquid squeezed from freshly collected material rapidly killed (≈10 min) common tropical fish being held in an aquarium. Furthermore, its organic extracts showed anthelminthic activity. The first of the active principles, isolated from Fijiian material, included dendrolassin, a bioinactive furanosesquiterpene, and latrunculin A,[1] an ichthyotoxic ketide–amino acid previously reported by Kashman[2] which also exhibits in vitro anthelminthic activity.[1] Specimens from Vanuatu were chemically different, dendrolassin was absent and latrunculin A was accompanied by mycothiazole, an anthelminthic ketide–amino acid.[3] We now describe new cytotoxic polyketide constituents of the Vanuatu collection which are fijianolides A (1) and B (2).

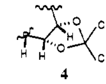
The previously described general workup of 1.7 kg (wet) of *S. mycofijiensis* from Vanuatu[3] involved successive extractions with methanol (twice) and CH_2Cl_2 which afforded three separate dark viscous oils (respectively 1.96 g, 2.06 g, 2.50 g). Fijianolide B (2) was isolated from the first oil and was accompanied by only traces of fijianolide A (1), but additional amounts of 1 were obtained from the other two oils. Structural work focused first on A whose molecular formula of $C_{30}H_{42}O_7$ was deduced by mass spectrometry [FAB (513 M^+ − H), LRCIMS (515 M^+ + H), LREIMS (514 M^+)] and a ^{13}C APT NMR spectrum (a difference of H_2 by APT versus the MF indicated a diol). The collective NMR data revealed five double bonds and an ester carbonyl which meant that four rings were also present.[4]



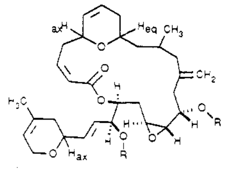
1 (fijianolide A)



3



4



2 R = H (fijianolide B)

5 R = Ac

The unsaturated substructures were established as follows. A but-2(*Z*)-enoyl array (as a lactone) was recognized by the IR 1720 cm^{-1}, and NMR ($CDCl_3$) resonances at ^{13}C δ = 165.6, ^1H δ = 5.84 (d = 11.7 Hz) and 6.20 (ddd = 11.4, 10.8, 6.9 Hz). A dihydropyran (the A ring) with a vinylic methyl and an equatorial (*E*)-ethenyl respectively γ and α to the ring oxygen was identified by NMR resonances ($CDCl_3$) at δ = 23.0/1.66 (s) [C/H-30] and δ = 125.8/5.69 ddd = 15.6, 6.0, 0.9 Hz [C/H-21], 134.0/5.90 dd = 15.6, 6.0 Hz [C/H-22], 73.4/3.97 ddd = 9.6, 5.1, 4.5 Hz [C/H-23] and the large *J* at H-23 was due to diaxial coupling with H-24. A second dihydropyran (the C ring) with a disubstituted double bond was deduced from $^3J_{6-7}$ = 10.5 Hz. The 1,3-C-ring substituents were assigned as trans. The $^3J_{9-8}$ = $^3J_{9-8'}$ = 3.6 Hz indicated an equatorial H-9 as this would have equivalent dihedral angles to both adjacent H-8 protons, and the $^3J_{5-6}$ = 2.1 suggested a pseudo-axial H-5 by analogy to our analysis of this same stereochemical situation in the xestins.[5] Analysis of ^1H–^1H COSY NMR data (regular and long range) and the regular and long range ^1H–^{13}C COSY NMR correlations that were observed allowed a 2-methyl-4-methylenepentanyl group

---

(1) Kakou, Y.; Crews, P.; Bakus, G. J. *J. Nat. Prod.* **1987**, *50*, 482.

(2) (a) Groweiss, A.; Shmueli, U.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3512. (b) Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, *21*, 3629.

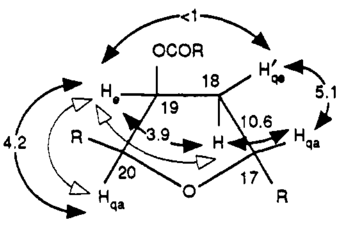
(3) Crews, P., Kakou, Y.; Quiñoâ, E. *J. Am. Chem. Soc.*, in press.

(4) 1: $[\alpha]^{20}{}_D$ −8.0° (*c* 0.04, $CHCl_3$). NMR: in C_6D_6 with shifts in ppm from TMS and assignments based on results of ^1H–^1H and ^{13}C–^1H COSY [atom number], ^{13}C δ's at 75 MHz, ^1H δ's and *J*'s at 300 MHz (*J*'s from C_6D_6) or additional {*J*'s from $CDCl_3$} [1], 165.2; [2] 123.2, 5.80 (m) {d = 11.7}; [3] 142.2, 5.80 (m) {ddd = 11.4, 10.8, 6.9}; [4] 35.6, 3.09 (m) {ddd = 14.4, 11.4, 5.4}, 2.20 (m) {ddd = 14.4, 9.9, 7.2}; [5] 72.9, 4.34 (m) {ddd = 11.4, 4.5, 2.1}; [6] 128.5, 5.58 (bd = 10.8) {dd = 10.5, 2.7}; [7] 125.3, 5.69 (bd = 12.3); [8] 31.8, 1.80 (m) 1.65 (m); [9] 66.5, 3.50 (m) {dq = 8.7, 3.6}; [10] 42.9, 1.50 (m) {ddd = 14.4, 8.7, 2.7}, 0.95 (m) {ddd = 14.4, 9.9, 3.0}; [11] 27.0, 1.90 (m); [12] 45.4, 2.25 (m), 2.00 (m); [13] 145.6; [14] 35.6, 2.25 (m, 2 H); [15] 71.3, 4.18 (m) {ddd = 9.3, 3.6, 2.7}; [16] 75.7, 4.18 (m) {dd = 4.5, 2.7}; [17] 78.3, 4.46 (m) {ddd = 10.5, 5.1, 4.8}; [18] 34.9, 2.30 (m) {ddd = 15.0, 10.8, 4.2}, 2.20 (m); [19] 76.8, 5.57 (m) {ddd = 3.9, 3.6, <1}; [20] 81.5, 4.56 (dd = 4.2, 4.0); [21] 125.9, 5.85 (dd = 15.3, 5.4) {ddd = 15.6, 6.0, 0.9}; [22] 133.5, 6.04 (dd = 15.3, 5.1); [23] 73.4, 3.91 (m) {ddd = 9.6, 5.1, 4.5}; [24] 35.9, 1.90 (m) {dd = 13.8, 8.1}, 1.80 (m) {dd = 13.8, 3.5}; [25] 131.1; [26] 120.0, 5.19 (bs); [27] 65.4, 4.11 (bs), 4.04 (bs); [28] 19.7, 0.87 (d = 5.7, 3 H); [29] 113.4, 5.00 (s), 4.92 (s); [30] 22.7, 1.55 (s, 3 H). $CDCl_3$ NMR data in Table 1S, supplementary material. MS: FAB (thioglycerol/glycerol) scanned up to *m/z* 1300; 621 [M^+ + thioglycerol], 513 [M^+ − H]. IR: (neat) cm^{-1} 3600–3200, 2900, 1720, 1050. UV: (MeOH) 208 (10 500).

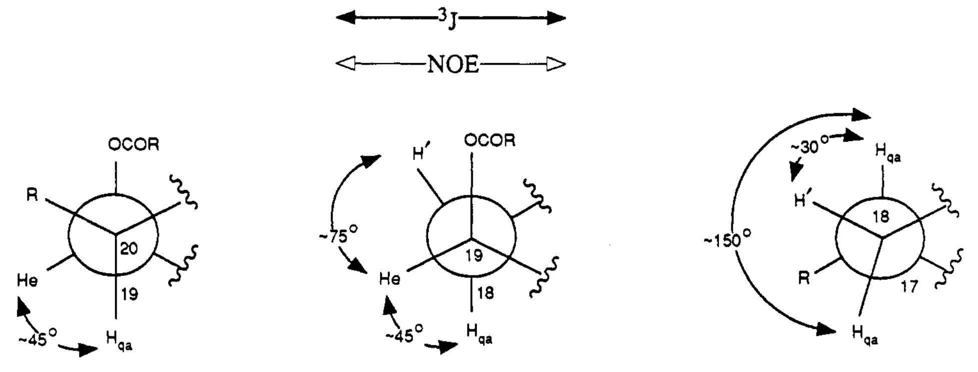
(5) Quiñoâ, E.; Kho, E.; Manes, L. V.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4260. However, an MM2 calculation by W. Inman (UCSC) on *trans*-1,5-dimethyl-2,3-dihydropyran predicts that the two chair forms differ in energy by only 1 kcal/mol.

0022-3263/88/1953-3642$01.50/0

Chart I. Stereochemistry of the B Ring



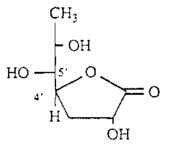
B-ring



a b c

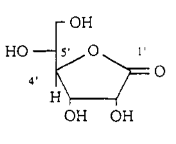
to be proposed. Finally, the COSY NMR data also verified the connections shown in 1 between all the other contiguous carbons.

The moieties encompassing the remaining oxygenated carbons were established as follows. A vicinal diol was recognized ($CDCl_3$: $\delta = 70.5/4.06, 74.6/4.11$) when the hydroxyls were converted to respectively fijianolide A diacetate (**3**) and fijianolide A dioxolane (**4**) whose NMR data are in the supplementary material. The carbinol H's, at positions 15 and 16, were shifted to lower field (>1 ppm) in **3** and the *J*'s between H-15/16 changed once they were tied together in the dioxolane ring of **4**. A cis stereochemistry was evident between H-15/16 in **4** by the $^3J_{15-16} = 5.7$ Hz ($CDCl_3$, or 6.0-Hz CD_3OD) in view of our analysis of analogous five-membered rings in connection with stereochemical assignments in the bengazoles[6] and the bengamides.[7] The remaining segment of C_4H_5O displayed a ^{1}H NMR spectra consistent with a furan (the B ring) and the δ 5.55 ($CDCl_3$) of H-19 indicated that this was the attachment point of the lactone functionality. The ^{1}H–^{1}H COSY NMR spectrum ($CDCl_3$) revealed that the furan oxygenated carbons at positions 20 (δ 81.5/4.60) and 17 (δ 78.1/4.34) were joined to the C's at positions 21 and 16, respectively. Comparisons to furanose rings supported the relative stereochemistry proposed within the B ring. More specifically, furanose ring ^3J's have been extensively used to predict the conformational and substitution patterns by comparing observed and calculated values and the most definitive work is that of Serianni.[8] There is good agreement between estimated dihedral angles and calculated ^3J values for furanose ring models versus the experimental *J*'s of fijianolide A[9] and this was used to suggest the geometry depicted in Chart I for the B ring, where a, e, qa, and qe denote respectively axial, equatorial, quasi-axial, and quasi-equatorial arrangements (the Jardetzky nomenclature).[10] The approximate angles that correspond to each of the three segments are shown in the Newman projections a, b, c. The angles shown in a and b are the *only* possibilities that are consistent with the experimental *J*'s between H-19/20 and H-18/19. Furthermore a 2D-NOE measurement showed a very strong cross peak from H-20 to H-19 and a weaker cross peak from H-19 to H-18, confirming the cis relationship among these respective proton sets. The relative stereochemistry at C-17 was decided by the $J = 10.6$ Hz between H-18 and H-17 because this value requires that they assume an anti-like orientation with a dihedral angle of >150°. This, in turn, implies a dihedral angle of ≈30° between H-17/18′ that fits very well with the experimental $^3J_{17-18'} = 5.1$ Hz, indicating that their relative stereochemistry is cis. Similar *J* values were recorded for the analogous protons in derivatives **3** and **4** in support of the relative trans stereochemistry between substituents at C-17/20 and also at C-17/19.[11] The relative H-16/17 erythro stereochemistry was proposed, by a strategy we have previously utilized,[6] because $J_{16-17} = 4.5$ Hz (**1**) was analogous to those of close models including **6** ($J_{4'-5'} = 4.8$ Hz [erythro H's]) and **7** ($J_{4'-5'} = 5.2$ Hz [erythro H's]) while different versus **8** ($J_{4'-5'} = 2.4$ Hz [threo H's]).[6] At this point the complete structure



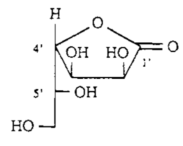
6

$J_{4'-5'} = 4.8$



7

$J_{4'-5'} = 5.2$



8

$J_{4'-5'} = 2.4$

---

[6] Adamczeski, M.; Quiñoâ, E.; Crews, P. *J. Am. Chem. Soc.* **1988**, *110*, 1598.

[7] Adamczeski, M.; Quiñoâ, E.; Crews, P., submitted for publication.

[8] Serianni, A. S.; Barker, R. *J. Org. Chem.* **1984**, *49*, 3292.

[9] Match-up of estimated angles and *J*'s for the furan B ring (via strategies of ref 8) versus experimental *J*'s for **1**: [H–H], (dihedral angle in deg), ⟨$^3J_{calc}$⟩, {$^3J_{exp}$($CDCl_3$)}: [19–20], (38°/40°), ⟨4.1 Hz/3.8 Hz⟩, {4.2 Hz}; [18–19], (40°), ⟨4.9 Hz⟩, {3.9 Hz}; [18′–19], (80°), ⟨0.7 Hz⟩, {≈1 Hz}; [17–18], (152°/160°), ⟨9.9 Hz/10.2 Hz⟩, {10.6 Hz}; [17–18′], (32°/40°), ⟨6.5 Hz/5.6 Hz⟩, {5.1 Hz}.

[10] Jardetzky, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 62.

[11] The orientation of the *trans*-1,3-dialkyl substituents in a quasi-equatorial orientation is consistent with the conformational preferences of substituted furanoses: see ref 8 and 10.

with the relative 15*S**,16*S**,17*R**,19*S**,20*S** was proposed, but this relative stereochemistry could not be related to the axial geometry at H-5 and H-23 or equatorial geometry at H-9.

Fijianolide B (**2**),[12] $C_{30}H_{42}O_7$, was recognized as a structural isomer of A by the many $^{13}C-^{1}H$ and $^{1}H-^{1}H$ correlations that were visible in the COSY NMR spectra. The COSY NMR data along with the $^{13}C/^{1}H$ chemical shift comparisons between **2** and **1** showed that the structure and stereochemistry of fijianolide B was the same as A except within the region of C-15 to C-20. The ^{1}H shift of δ 5.25 (C_6D_6) at H-19 in **2** was nearly identical with that in **1**, indicating that the ester linkage was still at C-19. Acetylation of **2** yielded **5** in which downfield shifts of $\approx$1 ppm were observed for the protons at H-20 and H-15. The most important of the long range $^{13}C-^{1}H$ COSY NMR correlations for fijianolide B acetate (**5**) were those from C-9 to H-5, from C-23 to H-27, and from C-1 to H-3. The trans epoxide ring at C-16/17 was identified by the characteristic $^{13}C/^{1}H$ NMR (C_6D_6) shifts of δ 61.1/2.84 dd = 2.1, 2.1 Hz [C/H-16] and 52.5/3.10 ddd = 11.1, 1.9, 1.9 Hz [C/H-17] and the $J_{16-17} \approx 2$ Hz.[13] If fijianolides A and B are biogenetically related by an obvious S_n2 transposition which involves an inversion of stereochemistry at C-17 in going from **1** to **2** or vice versa, then it can be assumed that the relative stereochemistry at C-15/16/19/20 in **2** is the same as in **1**, thus the five chiral centers in **2** are proposed as 15*S**,16*S**,17*S**,19*S**,20*S**.

The separate crude extract of the nudibranch *Chromodoris lochi*, often found attached to *S. mycofijiensis*, contained fijianolide B and mycothiazole. These metabolites may be products of symbionts which pass them along to the sponge where they are stored in such a manner as to be transmitted to the nudibranch. Moderate in vitro cytotoxicity was shown by the fijianolides, IC_{50}'s (μg/mL) for **1** and **5** were respectively 11 and 0.5 against HT-29 (human colon tumor cells) and respectively 9 and 6 against P388 (murine lymphoma cells).[14] The fijianolides can now be added to a short list of fascinating bioactive macrocyclic polyketides from marine organisms, and some of these have either been implied or have been shown as being produced by symbiotic microbiota.[15] We are now attempting to identify the symbiont(s) that may be responsible for the production of the fijianolides in order to understand their biosynthetic origin.

Acknowledgment. Partial research support was from NOAA, National Sea Grant College Program, Department of Commerce, University of California project number R/MP-41. The U.S. Government is authorized to produce and distribute reprints for governmental purposes. Other grant support was from Syntex Inc. We thank Mr. Jim Loo (UCSC) for assistance with NMR measurements, Dr. Julie Leary (UCB MS lab) for the FABMS data, and Dr. Tom Matthews (Syntex) for bioactivity data.

Registry No. **1**, 114995-72-1; **2**, 114995-73-2.

Supplementary Material Available: NMR data for **1**–**5** (2 pages). Ordering information is given on any current masthead page.

Emilio Quiñoá, Yao Kakou, Phillip Crews*
Department of Chemistry and
Institute for Marine Sciences
University of California
Santa Cruz, California 95064

Received March 15, 1988

---

(12) **2**: NMR (C_6D_6) shifts in ppm from TMS, assignments based on results of $^{1}H-^{1}H$ and $^{13}C-^{1}H$ COSY NMR data; [atom number], ^{13}C δ's at 75 MHz, ^{1}H δ's and *J*'s at 300 MHz [1], 166.3; [2] 120.9, 5.80 (d = 12.3); [3] 150.4, 6.12 (ddd = 12.0, 10.8, 4.5); [4] 34.0, 3.90 (m), 2.08 (m); [5] 73.3, 4.12 (m); [6] 129.3, 5.48 (bd = 10.2); [7] 125.3, 5.67 (bd = 10.2); [8] 32.1, 1.75 (m); [9] 68.1, 3.71 (m); [10] 43.9, 1.50 (m), 1.20 (bd = 12.0); [11] 29.9, 1.75 (m); [12] 46.2, 2.55 (dd = 10.8, 2.4), 1.85 (dd = 10.8, 5.4); [13] 145.9; [14] 37.7, 2.14 (bs), 2.13 (bs); [15] 67.3, 4.04 (m); [16] 61.1, 2.84 (dd = 2.1, 2.1); [17] 52.5, 3.10 (ddd = 11.1, 1.9, 1.9); [18] 33.4, 2.36 (ddd = 10.8, 1.5, <1), 1.55 (m); [19] 72.7, 5.25 (ddd = 10.5, 3.9, 1.8); [20] 72.9, 4.18 (dd = 9.3, 4.5); [21] 129.2, 5.81 (dd = 16.2, 5.4); [22] 133.4, 5.94 (dd = 16.2, 5.4); [23] 73.6, 3.90 (m); [24] 36.0, 2.03 (m), 1.60 (m); [25] 131.3; [26] 120.2, 5.16 (bs); [27] 65.8, 4.09 (bs), 3.95 (bs); [28] 21.1, 0.86 (d = 6.0, 3 H); [29] 112.4, 4.94 (bs), 4.89 (bs); [30] 23.0, 1.50 (s, 3 H). $CDCl_3$ ^{13}C NMR data in Table 1S, supplementary material. MS: LREI *m/z* (relative intensity) 514 [M^+ (13)], 496 [$M^+ - H_2O$ (5)], 478 [$M^+ - 2H_2O$ (3)], 361 [$M^+ - C_9H_{13}O_2$ (10)], 53 [(100)]. IR: (neat) cm^{-1} 3600–3200, 2900, 1720, 1270. UV: (MeOH) 208 (10 500). **5** $[\alpha]^{20}{}_D$ −8.0° (*c* 0.04, $CHCl_3$). MS: FAB (thioglycerol/glycerol) 705 [M^+ + thioglycerol], 597 [$M^+ - H$].

(13) Lyle, G. G.; Keefer, L. K. *J. Org. Chem.* **1966**, *31*, 3921.

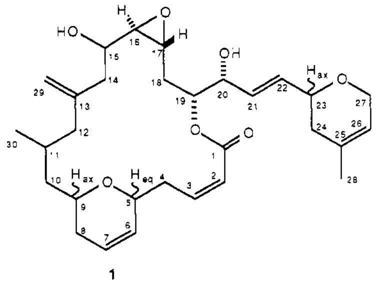
(14) Additional cytotoxicity IC_{50}'s (μg/mL) for **1** and **5** were respectively 12 and 2 against A549 (human lung tumor cells) and respectively 14 and 5 against HL-60 (human promyelocytic leukemia). We warmly thank Dr. N. Burres of the Harbor Branch SeaPharm Project for these results.

(15) For examples of parallel chemistry comparable to **1** or **2** being ascribed to microorganisms, see: (a) Schmitz, F., J.; Gunasekara, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251. (b) Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *51*, 5300. (c) Kobayashi, J.; Ishibashi, M.; Wälchili, M. R.; Nakamura; H.; Hirata, Y.; Sasaki, S.; Ohizumi; Y.; *J. Am. Chem. Soc.* **1988**, *110*, 490.

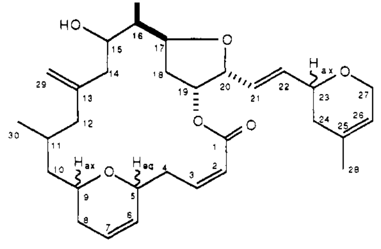
Laulimalides: New Potent Cytotoxic Macrolides from a Marine Sponge and a Nudibranch Predator[†]

Summary: Two new macrolides, laulimalide and isolaulimalide, were isolated from an Indonesian sponge, *Hyattella* sp., and a nudibranch predator, *Chromodoris lochi*. Laulimalide displays potent cytotoxicity, IC_{50} = 15 ng/mL, against the KB cell line.

Sir: While screening marine invertebrates suspected of having symbiotic microalgae for cytotoxicity, we found that the lipophilic extract of an Indonesian sponge, *Hyattella* sp.,[1] had an IC_{50} of 50 ng/mL against the KB cell line. Chromatography of 50-mg batches, first on silica Bond Elut (dichloromethane/acetone), then C-18 Bond Elut (methanol/water, 7:3), and finally reversed phase HPLC



1



2

[†] A preliminary account of this work was made at the Gordon Research Conference on Marine Natural Products, Oxnard, CA, Feb 29–Mar 4, 1988.

0022-3263/88/1953-3644$01.50/0 © 1988 American Chemical Society