Table I. Patellazole C: ^1H and ^{13}C NMR Data

C no.	$^{13}C^a$ ppm (mult)^b		$^1H^c$ ppm (mult, J (Hz))
1	171.36 (s)		
2	81.25 (s)		
3	32.65 (t)	A	1.90 (bdd, 13.6, 4.4)
		B	2.62 (dd, 13.6, 4.4)
4	32.14 (t)	A	1.06 (m)
		B	1.44 (m)
5	28.17 (d)		1.85 (bm)
6	44.32 (t)	A	1.30 (ddd, 11.3, 11.3, 2.3)
		B	1.56 (dd, 11.3, 5.7)
7	72.56 (d)		3.87 (bm)
8	50.05 (d)		3.13 (dq, 9.5, 6.8)
9	216.43 (s)		
10	56.28 (d)		4.28 (ddd, 10.8, 7.6, 4.0)
11	124.85 (d)		5.22 (dd, 10.8, 10.8)
12	134.39 (d)		5.93 (dt, 10.8, 5.7)
13	32.37 (t)	A	1.53 (m)
		B	3.48 (dd, 12.1, 12.1)
14	38.86 (d)		1.95 (m)
15	74.32 (d)		3.68 (bd, 9.7)
16	69.44 (d)		3.90 (bd, 8.6)
17	87.01 (d)		4.09 (d, 8.6)
18	132.15 (s)		
19	133.36 (d)		6.38 (d, 10.8)
20	125.31 (d)		6.62 (dd, 15.3, 10.8)
21	136.14 (d)		6.30 (dd, 15.3, 5.6)
22	35.69 (d)		3.25 (m)
23	85.62 (d)		4.87 (d, 2.3)
24	75.38 (s)		
25	130.40 (d)		5.47 (s)
26	133.96 (s)		
27	34.68 (t)	A	3.52 (d, 13.4)
		B	3.83 (d, 13.4)
28	154.05 (s)		
29	114.21 (d)		6.26 (s)
30	174.76 (s)		
31	59.98 (s)		
32	65.00 (d)		2.73 (q, 5.4)
33	14.03 (q)		0.92 (d, 5.4)
34	175.39 (s)		
35	49.49 (d)		2.51 (dq, 9.0, 7.1)
36	69.29 (d)		3.85 (m)
37	20.36 (q)		1.11 (d, 6.5)
38	24.20 (q)		1.49 (s)
39	18.13 (q)		0.93 (d, 6.8)
40	13.52 (q)		0.82 (d, 6.8)
41	62.52 (t)	A	3.77 (dd, 10.8, 4.0)
		B	4.05 (bdd, 10.8, 7.6)
42	16.03 (q)		1.12 (d, 7.1)
43	56.01 (q)		3.26 (s)
44	10.99 (q)		2.00 (s)
45	19.08 (q)		1.60 (d, 7.1)
46	27.49 (q)		1.47 (s)
47	24.79 (q)		1.62 (fd, 1.1)
48	15.58 (q)		1.67 (s)
49	14.85 (q)		1.12 (d, 7.1)

[a] Measured at 125 MHz; referenced to C_6D_6 (128.0 ppm). [b] Multiplicity determined with DEPT experiment. [c] Measured at 500 MHz; referenced to C_6D_5H (7.15 ppm).

NMR experiments (Table I). INAPT connections from H3 and H38 to C1 and C2 plus INADEQUATE connection C38–C2–C3 confirmed placement of the ester carbonyl at 171.36 ppm as C1. Irradiation of H8 and H10 gave a signal at 216.43 ppm in the INAPT which indicated that C9 is a ketone and extended the carbon chain to C15. Although H15 failed to show vicinal coupling to H16, H17 showed connections to C15 in the INAPT and to C16 in the COLOC. The O-methyl exhibited an INAPT connection to C17, and both H15 and H16 sharpened in the D_2O exchange ^1H NMR spectrum, indicating that C15 and C16 bear secondary hydroxyls and C17 a methoxyl. Furthermore, the INADEQUATE data showed clear evidence for the sequence C15–C16–C17–C18, which effectively extends the carbon chain to C23. Both the COLOC and INAPT data showed strong correlation of H23 to the ester carbonyl at 171.36 ppm which was previously shown to be C1. This connection establishes a 24-membered macrolide. The proton on C23 showed further INAPT correlations to C24, C25 and C46, and H25 and H46 correlated to C24 in the COLOC. The remainder of the side chain was also established from long-range correlation data and was confirmed by isolation of **4**. Protons 35 and 49 correlated to the remaining carbonyl at 175.39 ppm confirming the presence of an α-methyl-β-hydroxy butyrate. The ester was attached at C2 based on deuterium exchanged ^{13}C NMR studies in which C7, C15, C16, C24, and C36 all exhibited upfield isotope induced shifts from 0.10 to 0.17 ppm, whereas C2, C17, and C23 showed negligible changes. This assignment was also substantiated by ^1H NMR data.

The patellazoles represent a new class of macrolides which incorporate an unusual thiazole moiety. A full paper discussing the chemistry and biological activity of all three members of this family is in preparation.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra, double quantum COSY, selected INAPT, and 2D INADEQUATE connections (23 pages). Ordering information is given on any current masthead page.

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Patellazole B: A Novel Cytotoxic Thiazole-Containing Macrolide from the Marine Tunicate *Lissoclinum patella*[1]

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Didemnid tunicates, marine chordates that are well-known for symbiotic associations with microscopic algae, produce a fascinating array of unusual natural products.[2] *Lissoclinum patella*, for example, produces several novel cyclic peptides characterized

(1) A preliminary account of this work was made at the 16th International Symposium on the Chemistry of Natural Products, IUPAC '88, Kyoto, Japan, May 29–June 4, 1988.

(2) The most important compounds discovered to date are the didemnins, potent cytotoxic and antiviral cyclic depsipeptides from Caribbean *Tridemnum solidum* [Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857]. Didemnin B is currently in Phase II clinical trials at the National Cancer Institute for the treatment of human cancer. For a current review, see: Rinehart, K. L., Jr.; Kishore, V.; Bible, K. C.; Sakai, R.; Sullins, D. W.; Li, K.-M. *J. Nat. Prod.* **1988**, *51*, 1.

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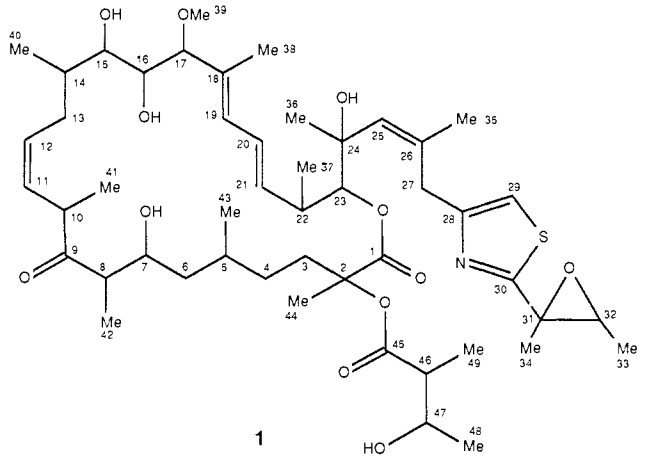
Table I. ^{13}C (125 MHz) and ^{1}H (500 MHz) NMR Spectral Data for Patellazole B in Benzene-d_6 (0.018 M)

atom	^{13}C (mult)	^{1}H (mult, J (Hz), intgrtn)	atom	^{13}C (mult)	^{1}H (mult, J (Hz), intgrtn)
1	172.04 (s)		27a	34.68 (t)	4.001 (d, −13.0, 1 H)
2	81.20 (s)		27b		3.250 (d, −13.0, 1 H)
3a	32.34 (t)	2.605 (td, −13.4, 13.4, 5.0, 1 H)	28	154.22 (s)	
3b		1.770 (td, −13.4, 13.4, 3.4, 1 H)	29	114.66 (d)	6.194 (s, 1 H)
4a	32.20 (t)	1.41 (m, 1 H)	30	174.93 (s)	
4b		0.975 (m, 1 H)	31	60.34 (s)	
5	28.43 (d)	1.675 (m, 1 H)	32	65.70 (d)	2.683 (q, 5.4, 1 H)
6a	44.43 (t)	1.531 (td, −14.0, 14.0, 2.0, 1 H)	33	14.07 (q)	0.896 (d, 5.4, 3 H)
6b		1.278 (ddd, −14.0, 12.0, 2.6, 1 H)	34	15.99 (q)	1.754 (s, 3 H)
7	73.01 (d)	3.86 (m, 1 H)	35	24.66 (q)	1.552 (d, 1.2, 3 H)
8	48.66 (d)	3.25 (m, 1 H)	36	27.16 (q)	1.424 (s, 3 H)
9	214.46 (s)		37	18.89 (q)	1.600 (d, 7.2, 3 H)
10	48.45 (d)	4.085 (dq, 10.7, 6.6, 1 H)	38	11.05 (q)	2.005 (d, 0.7, 3 H)
11	130.63 (d)	5.288 (t, 10.7, 1 H)	39	56.14 (q)	3.197 (s, 3 H)
12	131.65 (d)	5.860 (td, 10.7, 5.6, 1 H)	40	15.94 (q)	1.110 (d, 6.9, 3 H)
13a	32.77 (t)	3.575 (t, 11.4, 1 H)	41	15.31 (q)	1.326 (d, 6.6, 3 H)
13b		1.51 (m, 1 H)	42	13.77 (q)	0.832 (d, 6.8, 3 H)
14	38.91 (d)	2.00 (m, 1 H)	43	18.20 (q)	0.706 (d, 6.4, 3 H)
15	74.71 (d)	3.680 (d,[a] 9.8, 1 H)	44	24.27 (q)	1.450 (s, 3 H)
16	69.61 (d)	3.924 (d, 8.8, 1 H)	45	175.79 (s)	
17	87.44 (d)	4.086 (d, 8.8, 1 H)	46	49.58 (d)	2.497 (dq, 9.0, 7.1, 1 H)
18	132.47 (s)		47	69.55 (d)	3.85 (m, 1 H)
19	133.64 (d)	6.336 (dq, 10.7, 0.7, 1 H)	48	20.43 (q)	1.097 (d, 6.4, 3 H)
20	125.54 (d)	6.630 (ddd, 15.5, 10.7, 1.5, 1 H)	49	14.85 (q)	1.090 (d, 7.1, 3 H)
21	136.70 (d)	6.389 (dd, 15.5, 5.0, 1 H)			
22	35.70 (d)	3.282 (m, 1 H)	7 OH		not obsd
23	86.34 (d)	4.787 (d, 1.9, 1 H)	15 OH		3.382 (br s, 1 H)
24	75.67 (s)		16 OH		2.546 (s, 1 H)
25	131.33 (d)	5.318 (q, 1.2, 1 H)	24 OH		6.112 (s, 1 H)
26	133.56 (s)		47 OH		4.302 (d, 5.2, 1 H)

[a] This signal was a triplet (showing coupling to the OH on C-15) in another less concentrated sample.

by the presence of thiazole amino acids.[3] In screening tunicates that contain algal symbionts[4] for pharmacological activity, the crude lipophilic extract (1:1 CH_2Cl_2/EtOH) of young colonies of *L. patella*[5] from Piti Bomb Holes, Guam was found to exhibit potent cytotoxicity against the KB cell line (IC_{50} 15 ng/mL). We report here the isolation and structure determination of the major cytotoxin, patellazole B (**1**) (IC_{50} 300 pg/mL), a unique thiazole-containing macrolide.



1

The crude extract (1.6 g) was purified by silica gel chromatography (9:1 CH_2Cl_2/acetone) followed by reverse-phase C-18 HPLC (8:2 MeOH/H_2O) to yield patellazole B (12 mg, 0.75% yield from crude extract).[6] A molecular weight of 903 was indicated from FABMS (MH^+, m/z 904; MK^+, m/z 942) and high resolution EIMS revealed the formula $C_{49}H_{77}NSO_{12}$ (m/z 903.5167, 0 mmu error). The ^{13}C NMR spectrum of **1** (Table I) confirmed the presence of 49 carbons[7] and suggested at first that the molecule had one ketone carbonyl (δ 214.5), three ester carbonyls (δ 172–176), and five carbon–carbon double bonds (δ 114–156), with the remaining three degrees of unsaturation assigned to rings. Eventually the spectrum was interpreted to have only two ester carbonyl signals, with the carbon signal at 174.93 ppm along with the carbon–carbon double bond signals at 154.22 and 114.66 ppm reassigned to a thiazole system.[8] Seventy-two

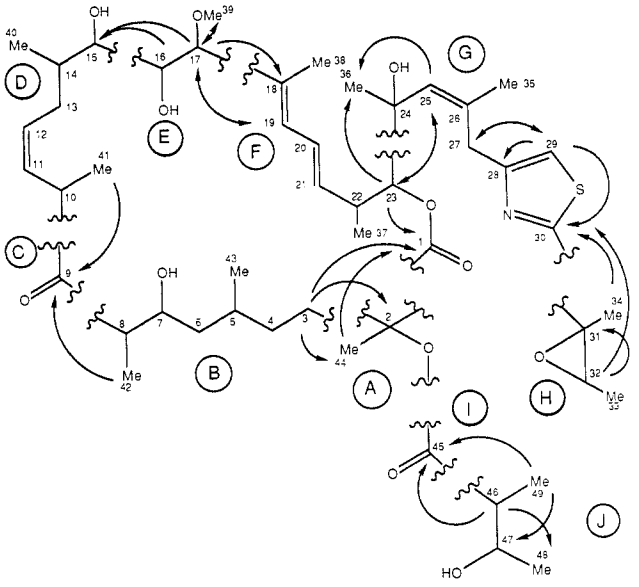


Figure 1. Units A–J with arrows showing two- and three-bond ^{1}H to ^{13}C correlations that are important in sequencing units or confirming partial structures inferred from COSY data.

(3) Sesin, D. F.; Gaskell, S. J.; Ireland, C. M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 853 and references therein.

(4) Prochloron is reported [Parry, D.; Kott, P. *Bull. Mar. Sci.* **1988**, *42*, 149] to be the only algal symbiont in *L. patella* colonies; however, populations from Guam were not examined.

(5) The tunicate was identified by Patricia Kott, Queensland Museum.

(6) IR (CH_2Cl_2) ν_{max} 3550, 1740, 1730, 1705 cm^{-1}; UV (MeCN) λ_{max} 194 nm (ϵ 20000), 241 (16000).

(7) The multiplicities of the carbon atoms were revealed by the DEPT experiment [Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323].

protons were accounted for from the ^{13}C data. The remaining five protons were concluded to be exchangeable protons, but only four could be detected in the ^1H NMR spectrum in benzene-d_6.

Ten partial structures, units A–J (Figure 1), were generated mainly from 2D ^1H NMR, viz. COSY,[9] Relay (RCT1),[10] Double Relay (RCT2),[10] TOCSY,[11] phase-sensitive NOESY,[12] and ROESY[13a,b] experiments, and ^{13}C chemical shift data (Table I). Sequencing units A–J into a gross structure for **1** was then readily accomplished from proton-detected one-bond and long-range ^1H–^{13}C NMR experiments, viz. HMQC[14] and HMBC.[15]

The homonuclear connectivities in the various units were deduced from the 2D data as illustrated in the following two examples. For unit F the H-20 signal showed COSY cross peaks to H-19 and H-21, relay cross peaks to H-22 and H_3-38, and double relay cross peaks to H-23 (weak) and H_3-37; no additional cross peaks were seen in the TOCSY spectrum. In unit B the H_3-43 signal showed a COSY cross peak to H-5, a relay cross peak to H-6b (failure to see cross peaks to H-4a, H-4b, and H-6a indicated small couplings from H-5 to these protons), a double relay cross peak to H-6a and H-7 (weak), and TOCSY cross peaks to H-3a, H-3b, H-4a, H-4b, H-8, and H_3-42. The only proton signal for unit B that was not observed as a cross peak in the TOCSY spectrum was the one for the exchangeable OH proton on C-7.

Four-bond ^1H–^1H coupling was important in determining the structure of unit G, including the placement of a hydroxyl group on C-24 (COSY shows cross peaks from the OH on C-24 to H-25 and H_3-36), and in connecting a methyl group to C-18 in unit F. Vicinal coupling constants indicated that (1) the geometries of the Δ^{11} and Δ^{20} double bonds were cis and trans, respectively, (2) hydroxyl groups were attached to C-15, C-16, and C-47, and (3) a methyl group was attached to the C-32 methine in an epoxide ring. NOEs established that (1) the geometries of the Δ^{18} and Δ^{25} double bonds were *E* and *Z*, respectively, (2) a second methyl group was attached to the epoxide ring at C-31 and oriented cis to the methyl group on C-32, and (3) the methoxyl group was on C-17.

The chemical shift of H-23 indicated that an ester oxygen was attached to C-23 as shown in unit F. The chemical shift of H-32 further supported its attachment to an epoxide ring as shown in unit H.

After assigning all the protonated carbons by the HMQC experiment, units A–J were easily connected from the HMBC[16] data (see Table II in Supplementary Material). The key two- and three-bond heteronuclear connectivities (^1H to ^{13}C) that established the gross structure of **1** were as follows: H_3-44 to C-1; H-3a to C-1, C-2, and C-44; H_3-42 to C-9; H_3-41 to C-9; H-16 to C-15; H-17 to C-15, C-18, C-19, and C-39; H_3-39 to C-17; H-23 to C-1, C-25, and C-36; H-25 to C-23 and C-36; H-27a to C-29; H-29 to C-27, C-28 and C-30; H-32 to C-30 and C-31; H_3-34 to C-30; H-46 to C-45 and C-48; H_3-49 to C-45 and C-47 (indicated by arrows in Figure 1). No direct NMR evidence was obtained to link A to I to J. The only alternative would be to link J to the oxygen on C-7. The chemical shift of H-7 (δ 3.86), however, strongly supported the placement of a hydroxyl on C-7. Unit J, therefore, had to be connected to I, and I in turn to the oxygen on C-2 by process of elimination. Even though vicinal coupling was not observed between H-15 and H-16, an NOE between these two protons as well as two- and three-bond heteronuclear correlations from H-16 and H-17 to C-15 firmly established the attachment of D and E as shown.

Patellazole B appears to be predominantly polyketide-derived, but the thiazole probably originates from an amino acid. Studies on the biosynthesis of patellazole B and the role of the algal symbiont in its production have been initiated.

Acknowledgment. This research was supported by the University of Hawaii Sea Grant College Program under Institutional Grant NA 81AA-D-0070 from NOAA, Office of Sea Grant, U.S. Department of Commerce, and NIH Grants CA12623 (R.E.M.) and GM28624 (V.J.P.). We thank Faith Caplan and Kay Larsen for performing the cytotoxicity tests.

Supplementary Material Available: Table II listing the homonuclear and heteronuclear connectivities for patellazole B and ^1H NMR, PSCOSY, RCT1, RCT2, TOCSY, PSNOESY, ROESY, HMQC, and HMBC spectra of patellazole B in benzene-d_6 (0.018 M for all spectra except RCT1 and RCT2) (14 pages). Ordering information is given on any current masthead page.

(8) Mycothiazole shows carbon signals at 154.9, 111.8, and 179.4 ppm for the thiazole carbons corresponding to C-28, C-29, and C-30 in patellazole B [Crews, P.; Kakou, Y.; Quinoa, E. *J. Am. Chem. Soc.* **1988**, *110*, 4365]. We thank P. Crews for sending us a preprint.

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(16) A mixing time of 70 ms was used to detect 7 Hz coupling. The total acquistion time was 1.5 h.

Unprecedented Stereochemical Control in the Claisen Rearrangement of Allyl Vinyl Ethers Using Organoaluminum Reagents

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The Claisen rearrangement and its variants (Carroll, the ortho ester, Eschenmoser, and Ireland rearrangements)[1] offer many attractive synthetic advantages in view of the simplicity and versatility as exemplified by the broad applications to the stereo- and regiochemically defined synthesis of a wide variety of natural products.[2] Among these, the basic Claisen rearrangement of vinyl ethers **1** of secondary allylic alcohols affords γ,δ-unsaturated aldehydes in which the *E*-isomer, (*E*)-**2**, invariably predominates with the extent of $E/Z = \sim 9{:}1$.[3] Apparently, such *E*-selectivity is a general attribute of the Claisen family.[4] The opposite *Z*-

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