Hz, 1 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.26 (d of t, J = 8.6, 7.9 Hz, 1 H), 1.82–1.25 (m, 4 H), 1.19 (br, s, 1 H); ^{13}C NMR δ 144.293, 142.216, 128.487, 127.642, 126.252, 114.120, 62.887, 49.704, 31.664, 30.878. Anal. Found: C, 81.97%; H, 9.14%. Calcd for $C_{12}H_{16}O$: C, 81.77%; H, 9.15%.

Reaction of 2-methyloxetane with allyltrimethylsilane as above gave 3-methyl-5-hexen-1-ol in 20% yield.[33]

Preparative Reaction of (2-Methylallyl)trimethylsilane with Oxetane. A stirred solution of (2-methylallyl)trimethylsilane, 9.3 g (0.073 mol), and 9.5 mL of oxetane in 25 mL of CH_2Cl_2 which was cooled to −100 °C under an atmosphere of nitrogen was prepared. To this was added over about 15 min 8.5 mL of titanium tetrachloride (0.073 mol) dissolved in 15 mL of CH_2Cl_2. The reaction was then stirred overnight while it gradually warmed to room temperature. The resulting mixture was then slowly poured into cold 0.1 N potassium hydroxide. The resulting suspension was extracted 3 times with about 60 mL of CH_2Cl_2. The organic solution was dried over anhydrous magnesium sulfate and filtered and the solvent removed by evaporation under reduced pressure. The product mixture was filtered through a short column of alumina. A 1:1 mixture of ether/petroleum ether was used as the eluent. This process serves to remove any titanium residues. Failure to follow this procedure may result in isomerization of the carbon–carbon double bond of the product. The volatile material was distilled through a 66-cm vacuum-jacketed column which was packed with a spiral glass band. 3-Chloropropanol distilled at 60–62 °C (25 mm). The desired product 5-methyl-5-hexen-1-ol distilled at 53–54 °C (9 mm), lit. bp 74–76 °C (15 mm).[34] Its spectra were in complete agreement with those previously reported. A yield of 5.4 g (0.048 mol), 69% , was obtained.

Acknowledgment. We thank the Air Force Office of Scientific Research for their generous support (Grant 82-0333).

Registry No. Allyltrichlorosilane, 107-37-9; methylmagnesium bromide, 75-16-1; allyltrimethylsilane, 762-72-1; (2-methylallyl)trimethylsilane, 18292-38-1; 2-methylallyl chloride, 563-47-3; trichlorosilane, 10025-78-2; (*Z*)-1-bromo-2-butene, 39616-19-8; (*E*)-1-bromo-2-butene, 29576-14-5; 3-bromo-1-butene, 22037-73-6; (*Z*)-crotyltrimethylsilane, 17486-13-4; (*E*)-crotyltrimethylsilane, 17486-12-3; cinnamyltrimethylsilane, 19752-23-9; cinnamyl bromide, 4392-24-9; 2-methyloxetane, 2167-39-7; oxetane, 503-30-0; titanium tetrachloride, 7550-45-0; (γ,γ-dimethylallyl)trimethylsilane, 18293-99-7; 4,4-dimethyl-5-hexen-1-ol, 86549-26-0; 2-(trimethylsilyl)ethylidenecyclohexane, 63922-76-9; 1-vinyl-1-(3′-hydroxypropyl)cyclohexane, 96746-39-3; 3-cyclopentenyltrimethylsilane, 14579-08-9; 3-(3′-cyclopentenyl)propanol, 2910-50-1; 5-hexen-1-ol, 821-41-0; 4-methyl-5-hexen-1-ol, 25906-56-3; 4-phenyl-5-hexen-1-ol, 96746-40-6; 3-methyl-5-hexen-1-ol, 25913-87-5; 5-methyl-5-hexen-1-ol, 5212-80-6.

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5-*epi*-Ilimiquinone, a Metabolite of the Sponge *Fenestraspongia* Sp.

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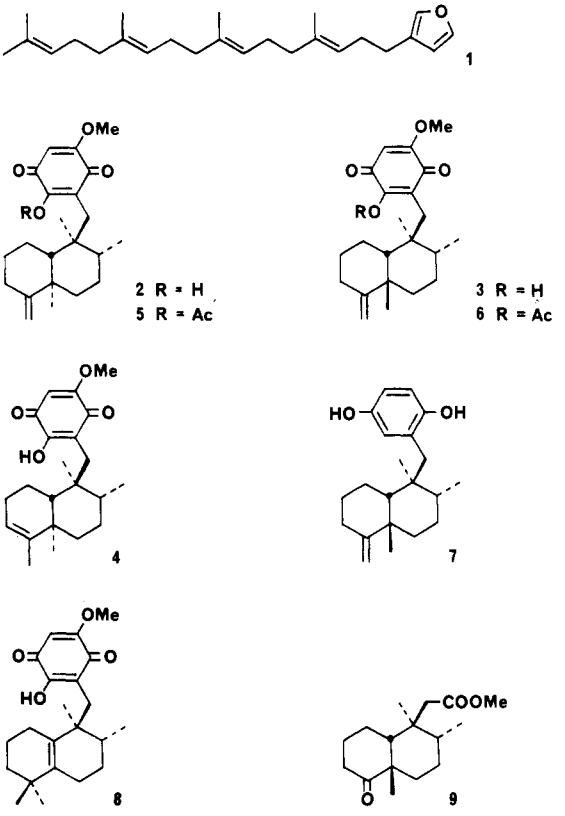
Our research on the chemical constituents of sponges from Palau has been directed primarily toward the structural elucidation of novel antimicrobial agents. Crude extracts of a sponge tentatively identified as a species of *Fenestraspongia*[1] exhibited in vitro antimicrobial activity and inhibited cell division in the fertilized sea urchin egg assay. Extracts of the sponge material contained the inactive metabolite furospinulosin-1 (**1**)[2] and the active metabolites ilimaquinone (**2**)[3] and 5-*epi*-ilimaquinone (**3**). In this note we report the structural elucidation of 5-*epi*-ilimaquinone (**3**) (Chart I).

Chart I



Specimens of *Fenestraspongia* sp. were collected near Urukthapel Island, Palau, and were stored frozen until required. Chromatography of a methanolic extract on Sephadex LH-20 using 1:1 dichloromethane–methanol as eluant separated the major inactive metabolite furospinulosin-1 (**1**, 0.4% dry weight) from a 6:4 mixture of ilimaquinone (**2**) and 5-*epi*-ilimaquinone (**3**) (2.1% dry weight). We had previously encountered a number of sponge samples from Palau that contained ilimaquinone (**2**) mixed with 10–20% isospongiaquinone (**4**),[4,5] but the active mixture from this sponge contained two compounds both having an exocyclic methylene group. The ^{1}H NMR spectrum contained the signals expected for ilimaquinone (**2**) at δ 5.86 (s, 1 H), 4.45 (br s, 1 H), 4.43 (br s, 1 H), and 3.87 (s, 3 H) together with an additional set of signals at δ 5.87 (s, 1 H), 4.70 (br s, 1 H), 4.67 (br s, 1 H), and 3.88 (s, 3 H) in the low-field region. These data suggested that

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(1) The sponge was in an unusually poor condition for identification but has the basic characteristics of the genus *Fenestraspongia* Bergquist.
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(5) The arguments presented in ref 4 for the relative stereochemistry of isospongiaquinone (**4**) appear to be correct and have not been challenged. We have adopted the proposed relative stereochemistry although the authors were more cautious.

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the second compound was a stereoisomer of ilimaquinone (2). Attempts to separate ilimaquinone (2) from its isomer (3) were unsuccessful.

Acetylation of the mixture of quinones with acetic anhydride in pyridine gave a mixture of acetates that were separated by LC on μ-Porasil by using 40% ether in hexane as eluant. Ilimaquinone acetate (5), $[\alpha]_D$ −8.3° (c 1.05, $CHCl_3$) was identical in all respects with an authentic sample. 5-*epi*-Ilimaquinone acetate (6), $[\alpha]_D$ +22.6° (c 0.95, $CHCl_3$), had the molecular formula $C_{24}H_{32}O_5$ and is isomeric with ilimaquinone acetate (5). Comparison of the ^1H and ^{13}C NMR spectra of 5 and 6 indicated that both compounds had the same substitution pattern about the quinone ring. The remaining ^{13}C NMR signals were consistent in chemical shift and multiplicity with corresponding signals of arenarol (7).[6] The 360-MHz ^1H NMR spectrum supported the proposed structure since it contained three methyl signals at δ 0.88 (s, 3 H), 0.90 (d, 3 H, J = 6.5 Hz), and 1.06 (s, 3 H) and exocyclic methylene proton signals at δ 4.67 (br s, 1 H) and 4.71 (br s, 1 H). The corresponding signals for arenarol (7) are at δ 0.92 (s, 3 H), 0.96 (d, 3 H, J = 7 Hz), 1.06 (s, 3 H), 4.71 (br s, 1 H), and 4.72 (br s, 1 H). Irradiation of the methyl doublet at δ 0.96 caused the C-8 axial proton signal at δ 1.30 to appear as a doublet of doublets (J = ~13, 3 Hz). Irradiation of the C-10 proton signal at δ 1.18 (br d, 1 H, J = 6 Hz) caused the C-14 methyl signal at δ 0.88 (s, 3 H) to sharpen, indicating that the proton at C-10 and the C-14 methyl group were w-coupled and hence both axial to ring B. Unfortunately the C-10 proton signal is too close to the C-12 methyl signal to allow a meaningful NOE experiment.

Evidence for the isomeric relationship between acetates 5 and 6 was provided by the boron trifluoride catalyzed isomerization of the 6:4 mixture of 5 and 6 to a single product in 67% yield after chromatography. The reaction product was tentatively assigned the structure 8 by analogy with the similar rearrangement of avarol dimethyl ether.[7] The ^1H NMR spectrum contained four methyl signals at δ 0.78 (d, 3 H, J = 7 Hz), 0.83 (s, 3 H), 0.96 (s, 3 H), and 1.00 (s, 3 H), signals for an isolated methylene group at δ 2.57 (d, 1 H, J = 13 Hz) and 2.71 (d, 1 H, J = 13 Hz), a methoxyl signal at δ 3.87 (s, 3 H), a signal for the quinone proton at δ 5.85 (s, 1 H), an exchangeable OH signal at δ 7.34 (br s, 1 H), and no acetate or vinyl proton signals.

Ozonolysis of the 3:2 mixture of ilimaquinone (2) and 5-*epi*-ilimaquinone (3) followed by Jones oxidation of the ozonolysis product and methylation of the resulting acids with diazomethane gave a mixture of keto esters. The major keto ester is the expected product from ilimaquinone (2)[8] while the minor keto ester 9 is identical in all respects with the material produced by oxidation of arenarol (7) to the corresponding quinone, which was then subjected to the same ozonolysis, oxidation, and methylation sequence. 5-*epi*-Ilimaquinone (5) must therefore have the same stereochemistry about the AB ring system as arenarol (7).

The mixture of ilimaquinone (2) and 5-*epi*-ilimaquinone (3) was tested in a number of bioassays that screen for ecological activity. When applied to food pellets at 5 μg/mg, the quinone mixture caused significant inhibition of feeding by goldfish.

Experimental Section[9]

Isolation of Quinones. *Fenestraspongia* sp. (specimen no. 81-124) was hand-collected by using SCUBA (−3 m) at Urukthapel Island, Palau, and was frozen within 1 h of collection. The frozen sample was homogenized in methanol (1 L), and, after 4 h at 25 °C, the solid material (21 g dry weight) was removed by filtration. The extract was evaporated to obtain an aqueous suspension (300 mL) which was extracted with ethyl acetate (4 × 200 mL). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent was evaporated to obtain a brown gum (2.15 g).

The crude extract was chromatographed on Sephadex LH-20 by using methanol/dichloromethane (1:1) as eluant to obtain furospinulosin-1 (1, 90 mg, 0.04% dry weight) and a 3:2 mixture of ilimaquinone (2) and 5-*epi*-ilimaquinone (3, 460 mg, 2.1% dry weight). Furospinulosin-1 (1) was identical in all respects with an authentic sample.[2]

Acetylation of Quinones and Separation of Acetates 5 and 6. The 3:2 mixture of ilimaquinone (2) and 5-*epi*-ilimaquinone (3) (100 mg) was dissolved in pyridine (2 mL) and acetic anhydride (1 mL), and the solution was stirred at 25 °C for 16 h. The solvents were removed under reduced pressure and the product was chromatographed by LC on μ-Porasil by using 40% ether in hexane as eluant to obtain ilimaquinone acetate (5, 58 mg, 52% theoretical), identical in all respects with an authentic sample, and 5-*epi*-ilimaquinone (6, 39 mg, 35% theoretical).

5-*epi*-Ilimaquinone acetate (6): $[\alpha]^D$ +22.6° (c 0.95, $CHCl_3$); UV (MeOH) 367 nm (ε 700), 274 nm (12 200); IR ($CHCl_3$) 1760, 1650, 1600 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 0.90 (d, 3 H, J = 6.5 Hz), 1.06 (s, 3 H), 1.18 (br d, 1 H, J = 6 Hz), 2.36 (s, 3 H), 2.48 (d, 1 H, J = 13 Hz), 2.58, (d, 1 H, J = 13 Hz), 3.86 (s, 3 H), 4.67 (br s, 1 H), 4.71 (br s, 1 H), 5.91 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 181.6 (s), 179.1 (s), 167.8 (s), 159.7 (s), 152.9 (s), 152.0 (s), 134.4 (s), 106.4 (t), 105.4 (d), 55.5 (q), 48.6 (d), 45.6 (s), 39.9 (d), 39.7 (s), 38.1 (t), 33.5 (t), 33.1 (q), 32.3 (t), 28.1 (t), 25.3 (t), 23.0 (t), 20.3 (q) 18.9 (q), 18.7 (q); mass spectrum, m/z 400.2257, $C_{24}H_{32}O_5$ requires 400.2251.

Treatment of Acetates 5 and 6 with Boron Trifluoride Etherate. A 3:2 mixture of ilimaquinone acetate (5) and 5-*epi*-ilimaquinone acetate (6) (25 mg) was dissolved in benzene (10 mL) containing boron trifluoride etherate (2 drops) and the solution was stirred at 10 °C for 30 min. The benzene solution was washed with water (3 × 3 mL) and dried over anhydrous sodium sulfate, and the solvent was evaporated to obtain a single major product. The product was purified by flash chromatography on silica gel (15% ether in hexane) to obtain hydroxyquinone 8, (15 mg, 67% theoretical): ^1H NMR (360 MHz, $CDCl_3$) δ 0.78 (d, 3 H, J = 7 Hz), 0.83 (s, 3 H), 0.96 (s, 3 H), 1.00 (s, 3 H), 2.57 (d, 1 H, J = 13 Hz), 2.71 (d, 1 H, J = 13 Hz), 3.87 (s, 3 H), 5.85 (s, 1 H); 7.34 (br s, 1 H, OH); mass spectrum, m/z 358, 191.

Ozonolysis of a 3:2 Mixture of Ilimaquinone (2) and 5-*epi*-Ilimaquinone (3). A stream of ozone in oxygen was bubbled into a solution of the mixture of quinones 2 and 3 (3:2, 57 mg) in dry acetone (10 mL) at −70 °C until the color of the solution changed from yellow to blue (2 min). After allowing the solution to stand at −70 °C for 10 min, excess ozone was removed in a stream of dry nitrogen, and the solution was warmed to 0 °C. Jones reagent (2.5 mL of 6 N solution) was added and the reaction mixture was stirred for 1 h at 0 °C. The product was diluted with water and extracted with ether (4 × 15 mL). The combined ether extracts were washed with water and then with 5% sodium bicarbonate solution (10 mL). The acidified bicarbonate extract was extracted with ether (4 × 12 mL), the combined ether extracts

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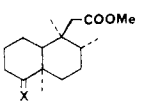

i, X = O
ii, X = CH_2

(9) For general procedures, see: Carté, B.; Faulkner, D. J. *J. Org. Chem.* **1983**, *48*, 2314.

were washed with water and dried over sodium sulfate, and the solvent was evaporated. A solution of diazomethane in ether was added to an ethereal solution of the residue to obtain a pale yellow solution that was allowed to stand for 10 min at 25 °C. Evaporation of the solvent gave a mixture (25 mg) of two keto esters which was purified by LC on Partisil using 20% ether in hexane as eluant. Keto ester **9** (minor): oil; IR ($CHCl_3$) 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.87 (d, 3 H, J = 6.8 Hz), 1.27 (s, 3 H), 2.38 (d, 1 H, J = 14 Hz), 2.46 (d, 1 H, J = 14 Hz), 2.68 (m, 1 H, J = 14, 10, 8 Hz); mass spectrum, m/z 266, 251, 235, 193, 192.

Ozonolysis of Arenarol (7). Silver oxide (400 mg) was added to a solution of arenarol (225 mg) in dry ether (25 mL) and the suspension was stirred for 1 h at 25 °C. The reaction mixture was filtered through Celite and the solvent was evaporated to obtain arenarone (166 mg). The arenarone (166 mg) was subjected to the ozonolysis procedure above to obtain a crude mixture of methyl esters (86 mg). A portion of the mixture was chromatographed by LC using 20% ether in hexane as eluant to obtain the keto ester **9** as the major product.

Acknowledgment. The sponge sample was identified by Dr. Klaus Rützler (Smithsonian Institution). The research was funded by the National Institutes of Health (AI-11969) and the California Sea Grant College Program (R/MP-23, NA80AA-D-00120).

Registry No. **2**, 71678-03-0; **3**, 96806-31-4; **5**, 71678-04-1; **6**, 96806-32-5; **7**, 87764-13-4; **8**, 96806-33-6; **9**, 96893-68-4; arenarone, 87764-16-7.

A Convenient Method for the Preparation of 2-(1-Aminoalkyl)thiazole-4-carboxylic Acids, Key Intermediates in the Total Synthesis of Naturally Occurring Antitumor Cyclopeptides

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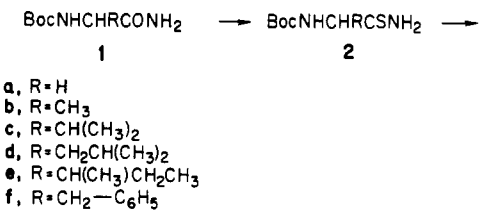
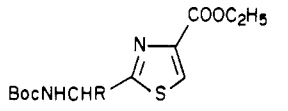
The structure of some naturally occurring peptides of significant biological and pharmaceutical interest have been found to possess the thiazole ring. Such is the case of thiostrepton,[1,2] bottromycin,[3] dysidenin,[4] or isodysidenin[5] and of the well-known antitumor drug bleomycin, which binds to DNA by intercalation of its bithiazole part.

In a continuing search for pharmacologically active natural products, it has been found that a series of cytotoxic cyclic peptides isolated from marine animals contain a 2-(1-aminoalkyl)thiazole-4-carboxylic acid moiety which appears to have been formed by biosynthetic condensation of an amino acid with cysteine. Structures of these compounds such as dolastatin (isolated from a mollusk[6]), ulicyclamide, ulithiacyclamide,[7] and patellamides[8-11] isolated from tunicates have been proposed, and a great deal of research has gone into establishing the mode of antitumor action of these drugs. For this purpose, it seems necessary to undertake the total synthesis of the peptides extracted from marine animals in very small amounts. Thiazole amino acids that may play a key role in the biological activity of the peptides are also important intermediates for their total synthesis. The preparations of (gly)Thz and (gln)Thz[12] recently described[13] involve a multiple step method. We propose here a simpler alternative method starting from commercially available α-amino carboxamides. Initial N-protection afforded *t*-Boc-*N*-α-amino carboxamides **1** (Scheme I) as shown by an IR carbamate band at 1665–1670 cm^{-1}. Thionation of amides by a modification of the initial procedure of Lawesson[14] using

Scheme I





3

3a, Boc-gly(Thz)OEt
b, Boc-ala(Thz)OEt
c, Boc-val(Thz)OEt
d, Boc-leu(Thz)OEt
e, Boc-ile(Thz)OEt
f, Boc-phe(Thz)OEt

Table I

compd[a]	isolated yield, %	mp, °C	R_f
1a	62	94	0.02
b	74	123.5	0.07
c	90	157	0.03
d	92	144	0.23
e	90	166	0.11
f	96	148	0.08
2a	88	124.5	0.06
b	60	103	0.15
c	66	108	0.16
d	73	157.5	0.29
e	86	132	0.24
f	70	101	0.26
3a	75	133	0.42
b	35	89.5	0.34
c	42	125.5	0.64
d	33	92	0.38
e	63	103	0.66
f	39	111	0.75

[a] Satisfactory analyses were obtained for all compounds.

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‡ INSERM U-16.

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