postulated intermediate **3** can be deprotonated to the corresponding ortho ester, whose formation provides positive proof of its existence along the reaction pathway.[12] Conditions were chosen such as to maximize its stability toward fragmentation and to maximize its deprotonation rate by the base over the nucleophilic attack of the latter at the precursor ion **2**. Table II illustrates the mixed success encountered in the experiments directed to isolate ortho esters. Successful results have been obtained when one or more of the following conditions were fulfilled: (i) the presence of a strong base of moderate nucleophilicity, such as NEt_3, (ii) the presence of a phenyl substituent at the carbon center, which stabilizes **3** relative to **2**,[13] (iii) the presence of fluorine atoms in R or R',[2c] which inductively destabilize **2** with respect to **3**.

In conclusion, the evidence from this study supports an addition-elimination mechanism as the major pathway for the gas-phase cation-induced ester alcoholysis, showing that the latter occurs via a tetrahedral intermediate, the discrepancy with the mechanism invoked in low-pressure ICR spectrometry probably arising from the different reaction environment. Fast collisional quenching of excited intermediates and stabilization of charged species by multiple interactions with dipolar molecules make the fundamental difference between low-pressure mass spectrometric studies and the radiolytic approach, undoubtedly a better way to derive reactivity models for liquid-phase reactions.

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Registry No. $MeCO_2Et$, 141-78-6; $MeCO_2Me$, 79-20-9; $PhCO_2Me$, 93-58-3; $MeCO_2H$, 64-19-7; $MeCO_2Ph$, 122-79-2; $PhCO_2Et$, 93-89-0; $C_6F_5CO_2Et$, 4522-93-4; Me_2F, 64710-12-9.

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Papuamine, an Antifungal Pentacyclic Alkaloid from a Marine Sponge, *Haliclona sp.*[1]

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Haliclona sp., a thin red encrusting sponge from Papua New Guinea, which overgrows and kills coral, contains as its major metabolite (1.3% of dry weight) a pentacyclic alkaloid, papuamine (**1**), which is formally derivable from a C_{22} unbranched hydrocarbon and 1,3-diaminopropane. Pure papuamine inhibits the growth of the fungus *Trichophyton mentagrophytes*.[2]

Haliclona sp. (120 g wet) was collected in November, 1985, at South Lion island, Papua New Guinea; the frozen sponge was thawed and extracted three times with MeOH and then chloroform. The aqueous methanolic concentrate was subjected to successive partition with hexane, carbon tetrachloride, and chloroform.[3] The antifungal activity resided in the two chloroform extracts and remained at the origin in normal (silica, EtOAc) and reversed phase TLC (RP-18, MeOH). It moved in either mode when triethylamine (5%) was added. Final purification was achieved either by flash chromatography[4] (BioSil A, EtOAc/MeOH, Et_3N, 55:40:5) which produced the natural ammonium salt (**2**)[5] or by HPLC (Waters Porasil, EtOAc/Et_3N, 95:5), which freed the amine **1** (180 mg).[6]

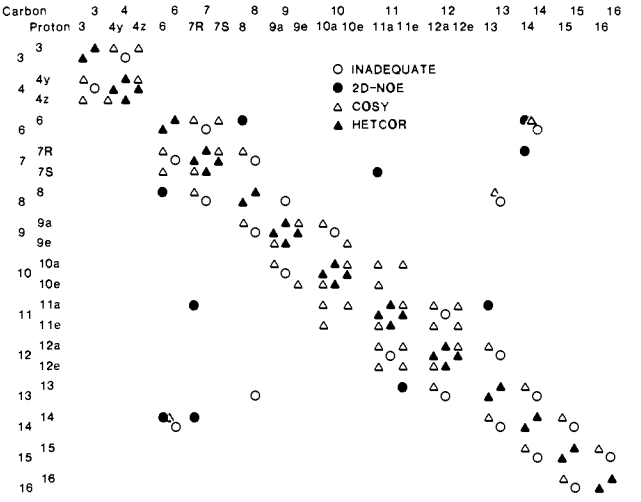

Figure 1. Selected correlations of papuamine (**1**) from INADEQUATE, 2D-NOE, COSY, and HETCOR experiments.

Papuamine (**1**) is an optically active solid of composition $C_{25}H_{40}N_2$. A diacetamide **3**,[7] $C_{29}H_{44}N_2O_2$, produced an EIMS fragment at m/z 294 ($C_{22}H_{30}$). This corresponds to the molecular ion $C_{29}H_{44}N_2O_2$ (m/z 452) minus two acetyls ($C_4H_6O_2$) minus $C_3H_8N_2$. The structure of this fragment $\rangle N^A CH_2{}^B CH_2{}^{A'} CH_2 N\langle$ rests on ^{1}HNMR data of the salt **2**. Two proton multiplets at δ 3.19 and 2.98 are assigned to pseudoaxial and pseudoequatorial protons A and A', while an apparent one-proton multiplet at δ 2.0 represents the B protons based on heteronuclear correlation data (Table V, Supplementary Material). Additionally, two complex olefinic ^{1}H NMR signals at δ 6.50 and 5.89 representing four protons are assigned to an s-trans-diene (λ_{max} 241 nm), after comparison with computer-generated spectra of conjugated dienes of different geometry. Mutually coupled signals at δ 3.55 and 2.63 arise from methines vicinal to nitrogen and olefin, respectively.

[†] University of Hawaii at Manoa.
[‡] Varian.
(1) From the Ph.D. Dissertation of B.J.B., University of Hawaii, 1986.
(2) A 6-mm disk containing 10 μg of papuamine produced a 12-mm zone of growth inhibition.
(3) Kupchan, S. M.; Britton, R. W.; Zeigler, M. F.; Sigel, C. W. *J. Org. Chem.* **1973**, *38*, 178-179.
(4) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
(5) Papuamine dihydrochloride (**2**): white solid, mp 230 °C dec; $[\alpha]_D$ -140° (c 1.3, MeOH); UV λ_{max}^{MeOH} 241 (3000) nm; IR ($CHCl_3$) ν_{max} 3700 br, 2930, 2850, 1560, 1450, 1230, 1050, 1010, 730 cm^{-1}; HREIMS m/z 368.3173 ($C_{25}H_{40}N_2$ requires 368.3192); FABMS (positive ion) m/z 369 (100%); HRFABMS m/z 369.3258 ($C_{25}H_{41}N_2$ requires 369.3270); ^{1}H NMR (300 MHz, CD_3OD) δ 6.50 (2 H, H-16, 17, complex dd, J = 10.5, 15.8 Hz), 5.89 (2 H, H-15, 18, complex dd, J = 8.3, 15.8), 3.55 (2 H, H-6, 27, br ddd, J = 8.2, 8.2, 8.8 Hz), 3.19 (2 H, H-2y, 4y, br ddd, $J_{2y\text{-}3}$ = 13.5), 2.98 (2 H, H-2z, 4z, br dt, J = 3, 10.6 Hz), 2.63 (2 H, H-14, 19, br ddd, J = 9.3, 9.3, 10.6 Hz), 2.41 (2 H, H-7R, 26S, ddd, $J_{7R\text{-}8}$ = 4.8 Hz, $J_{7R\text{-}6}$ = 8.8 Hz, $J_{7R\text{-}7S}$ = 12.0 Hz), 2.0 (2 H, H_2-3, multiplet), 1.9-1.6 (8 H, multiplet of equatorial protons), 1.4 (2 H, H-13, H-20, dddd J = 10.6), 1.3-1.1 (10 H, multiplet of axial protons), 1.0 (2 H, H-10a, 23a, ddd, J = 3, 10.2, 12.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 136.02 (d), 130.46 (d), 62.09 (d), 50.49 (d), 49.28 (d), 46.97 (t), 44.65 (d), 39.14 (t), 32.07 (t), 30.79 (t), 27.04 (t), 24.60 (t).
(6) Papuamine (**1**): white solid, mp 167.5-169 °C; $[\alpha]_D$ -150° (c 1.5, MeOH); IR (film): ν_{max} 3000, 2920, 2850, 1400, 1100 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 6.22 (2 H, H-16, 17, dd, J = 10.5, 15.8 Hz), 5.71 (2 H, H-15, 18, dd, J = 8.3, 15.8 Hz), 3.05 (2 H, H-6, 27, br dd, J = 8.2, 8.2, 8.8 Hz), 2.64 (2 H, H-2y, 4y, m), 2.22 (2 H, H-2z, 4z, m), 2.21 (2 H, H-14, 19, m), 2.17 (2 H, H-7R, 26S, m), 1.82 (2 H, H-9e, 24e, m), 1.78 (2 H, H-12e, 21e, m), 1.70 (2 H, H-10e, 23e, m), 1.68 (2 H, H-11e, 22e, m), 1.6 (2 H, H_2-3, m), 1.23 (2 H, H-8, 25, m), 1.2 (4 H, H-7S, 26R, 11a, 22a, m), 1.19 (4 H, H-13, 20, 10a, 23a, m), 0.9 (4 H, H-9a, 24a, 12a, 21a, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.85 (d), 129.37 (d), 60.91 (d), 50.02 (d), 48.88 (d), 45.99 (t), 43.58 (d), 40.40 (t), 31.26 (t), 30.09 (t), 26.08 (t), 26.03 (t).
(7) Papuamine diacetamide (**3**): prepared from 6.6 mg of **1**, 0.5 mL of Ac_2O, 2 mL of pyridine, <5 min; purified by Bond Elut (EtOAc/Et_3N, 95:5), HPLC (Waters Micro BondaPak, EtOAc/petroleum ether, 70:30); white semisolid; EIMS (70 eV) m/z (%) 452 (9.5), 409 (17.5), 294 (47.0); HREIMS 452.34071, $C_{29}H_{44}N_2O_2$ requires 452.340287; 409.32259, $C_{27}H_{41}N_2O$ requires 409.321896; 294.23466, $C_{22}H_{30}$ requires 294.234756; 158.10605, $C_7H_{14}N_2O_2$ requires 158.105531; 115.08792, $C_5H_{11}N_2O$ requires 115.087140; 43.018124, C_2H_3O requires 43.018391; FABMS (positive ion) m/z 453 (100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.1 (2 H, H-16, 17, br s), 5.6 (2 H, H-15, 18, br s), 4.5 (2 H, br s) 4.3 (2 H, br s), 3.7 (2 H, br s), 3.5 (2 H, br s), 3.2 (2 H, br s), 2.8 (2 H, br s), 2.6 (2 H, br s), 2.1 (3 H, OAc), 2.1 (3 H, OAc), 1.8 (10 H, br m), 1.2 (12 H, br m).

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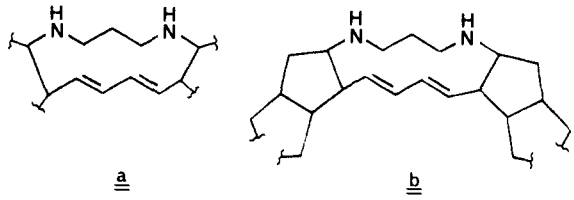
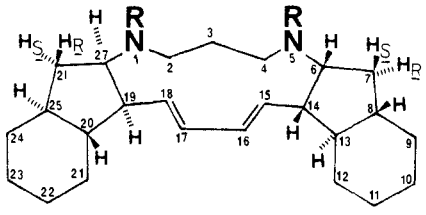
These data delineate part structure **a**.



a b



1 R = H

2 R = H_2^+ Cl^-

3 R = Ac

Only 12 ^{13}C NMR signals are observed: ten (δ 136.02-30.79) represent two carbons each; a triplet at δ 27.04 integrates for one, a triplet at δ 24.60 for four carbons.[5] Papuamine (**1**) therefore is a pentacyclic diamine symmetrical about a line through the central methylene (δ 27.04) and bisecting the C-16,17 bond (C_2 symmetry axis). COSY, RCT[8] (Tables I and II, Supplementary Material), and 2D INADEQUATE (Table III, Supplementary Material) experiments allowed expansion to part structure **b**, which is compatible with **1** or a cage structure, where C-10 is bonded to C-23 or C-22 and C-11 to C-22 or C-23. Observed coupling between C-10,11 (or C-22,23) methylenes eliminates the cage structure. A 2D NOE experiment (Table IV, Supplementary Material) allowed stereochemical assignments, and heteronuclear correlation data (Table V, Supplementary Material) confirmed the structure. Figure 1 summarizes the essential data from Tables I-V (Supplementary Material).

Evidence that the natural compound is a dihydrochloride derives from treatment of **2** with triethylamine in methanol, yielding crystalline triethylammonium chloride, and by quantitative high performance ion chromatography.[9]

A Dreiding model of papuamine (**2**) reveals a flexible 13-membered ring, which allows many spatial arrangements of the two trans hydrindanes. This unique alkaloid bears no biogenetic resemblance to other known *Haliclona* metabolites, polymeric alkylpyridines,[10] irregular sesquiterpenes,[11] or a complex polycyclic alkaloid.[12]

Acknowledgment. We thank Dr. Don Gerhart for help with the field collection; Professor P. Bergquist for identification of the sponge; Helen Karuso for antifungal assays; the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln for mass measurements; Dr. Robin Kinnel for helpful discussions; the Department of Environment and Conservation, Government of Papua New Guinea for permission to collect the sponge; the staff of the Motopore Island Research Station of the University of Papua New Guinea for assistance with field work; the Dionex Corporation for the loan of an HPIC instrument; the National Science Foundation; and the University of Hawaii Sea Grant College Program under Institutional Grant NA81AA-D-0070 from NOAA, Office of Sea Grant, U.S. Department of Commerce for financial support.

Supplementary Material Available: Tables I-V of ^1H-^1H correlation of **1** and **2**, ^{13}C-^{13}C connectivity of **1**, NOE of **2**, and ^1H-^{13}C correlation of **1** (4 pages). Ordering information is given on any current masthead page.

(8) RCT = relay coherence transfer: Bax, A; Drobny, G. *J. Magn. Reson.* **1985**, *61*, 306-320.

(9) Carried out with a Dionex AS4A column, eluted with 2.0 mM Na_2CO_3/0.75 mM $NaHCO_3$, 12.5 mM H_2SO_4 suppressor, conductivity detection. Papuamine dihydrochloride (**2**) prepared from **1** (440 ppm) was compared with NaCl (993 ppm). In three runs the retention times of **2** varied from 3.25 to 3.45 min, the area from 54.6 to 57.6 mm^2, while those of NaCl varied from 3.45 to 3.55 min, and the areas from 135.0 to 140.7 mm^2.

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Stereospecific Replacement of Sulfur from Chiral γ-Arylsulfanylbutyrolactones. Synthesis of Optically Pure Ring-Fused γ-Butyrolactones

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The transfer of chirality from sulfur to carbon has become a useful tool in asymmetric synthesis. Particularly notable in this area is the use of a chiral sulfinyl group to induce asymmetry in adjacent carbon centers.[1] Within this context, we have reported that γ-arylsulfanyl-γ-butyrolactones can be prepared in optically pure form and in useful yields by an enantiospecific [3,3] sigmatropic rearrangement of chiral vinyl sulfoxides with ketenes.[2,3] A distinctive feature of this new lactonization reaction is the transfer of chirality from sulfur to as many as three contiguous carbon centers.[2b]

In order to extend the synthetic utility of the sulfoxide-directed lactonization, we investigated the stereospecific replacement of the sulfur auxiliary from the newly created chiral γ-arylsulfanylbutyrolactones. Our first expectation was that an intramolecular substitution of the arylsulfanyl moiety by a carbon-based group would result in the formation of a ring-fused butyrolactone in optically active form. Such a strategy would be very valuable in the synthesis of naturally occurring sesquiterpene lactones. In this paper, we report that a variety of chiral ring-fused butyrolactones **4** can be prepared in a stereocontrolled fashion as outlined in Scheme I. Method A proceeds by homolytic cleavage of the γ-carbon–sulfur bond and subsequent intramolecular trapping of the resulting α-acyloxy radical.[4,5] Method B, on the other hand, formally involves an oxygen-assisted ionization of the arylsulfanyl group and a nucleophilic attack at the newly generated α-acyloxy carbocation. Method A is best suited for the synthesis of cis fused cyclopentabutyrolactones, whereas method B is the preferred route

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