Chemistry and Revised Structure of Suvanine

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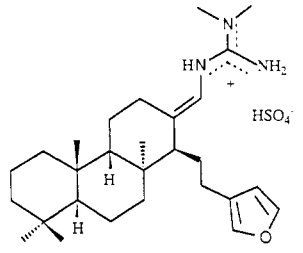
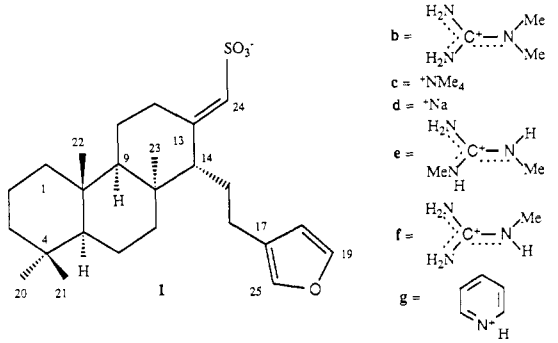
The structure **1a** that was previously proposed for suvanine, a novel tricyclic sesterterpene from the sponge *Ircinia* sp., has been revised to **1b**. Structure **1b** includes a dimethylguanidinium salt of an enol sulfate and an amended ring-junction stereochemistry. These changes were established by interpretation of two-dimensional NMR data, preparation of cation exchange reaction products **1c-g**, and an X-ray analysis of a key suvanine degradation product, diol **5**. Reexamination of the sponge suggests that it is in the genus *Coscinoderma*.

Suvanine is a tricyclic sesterterpene of unusual molecular formula, $C_{28}H_{47}N_3O_4S$, which contains an uncommon arrangement of functional groups.[1] The previous structure **1a** for suvanine was assigned primarily from interpretations of spectral data.[2] It became apparent that structure **1a** was incorrect when ^1H–^{13}C COSY (J = 140 Hz) NMR data were obtained[3] and when it was found that other cations could replace the dimethylguanidinium moiety. The subsequent reinvestigation suggested the revised structure **1b**, which included a dimethylguanidinium salt of an enol sulfate and an unusual cis BC ring junction.



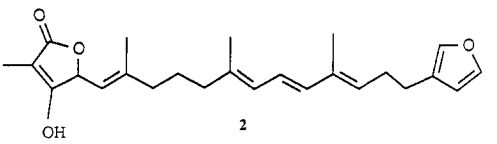
1a



1b

Results and Discussion

Suvanine (**1**) was isolated from two different sponge collections. One was harvested from Suva Harbor, Fiji Island, while the other was from Palau, and rexamination indicates they are in the genus *Coscinoderma*. Solvent partitioning (see the Experimental Section) of the crude oil from the Fiji collection gave a CCl_4 fraction containing only ircinic acid (**2**)[4] and a CH_2Cl_2 fraction containing only



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suvanine. After HPLC purification, suvanine could be crystallized from MeOH/Et_2O, but the fine needles that were formed were unsuitable for X-ray diffraction study. The Palau collection yielded a mixture of salts, which could be separated by chromatography on Sephadex LH-20 to obtain suvanine (**1b**) and the corresponding sodium salt (**1d**).

A ^1H–^{13}C COSY (J = 9 Hz) spectrum (shown in Figure 2S, supplementary material) of suvanine showed many strong correlations in the low field region of the spectrum including from H-19 to C-25 and C-18; from H-25 to C-19 and C-17; from H-18 to C-25 and C-19; and from H-24 to C-13, but none from H-24 to the N=C, which cast doubt on the proposed dimethylguanidinium enamine functionality. Attempts to acetylate suvanine using acetic anhydride in pyridine led to the fortuitous isolation of the pyridinium salt of suvanine (**1g**). This indicated that suvanine might be a dimethylguanidinium salt of an enol sulfate rather than the sulfate salt of a dimethylguanidinium enamine. Further proof for an enol functionality was obtained when suvanine was treated with tetramethylammonium chloride, yielding suvanine tetramethylammonium salt (**1c**). The ^{13}C NMR spectra of **1c** (Figure 1S, supplementary material) showed a large peak at 55.6 ppm corresponding to the four ammonium methyl groups, and a vestige of the N,N-dimethylguanidinium cation was observed by attenuated peaks at δ 157.4 and 38.4. Several other cation exchange products were also prepared, and these included **1d** (sodium salt), **1e** (N,N'-dimethylguanidinium salt), and **1f** (N-methylguanidinium salt). Treatment of salt **1d** with N,N-dimethylguanidinium hydrochloride gave suvanine, whereas treatment of **1d** with N,N'-dimethylguanidinium hydrobromide gave a new salt.

At this point, it was also possible to rationalize the original mass spectral data in favor of structure **1b**. No molecular ion could be observed by standard mass spec-

(1) (a) Crews, P.; Naylor, S. *Prog. Chem. Org. Nat. Prod.* **1985**, *48*, 203. (b) Hanson, J. R. *Nat. Prod. Rep.* **1986**, *3*, 87.

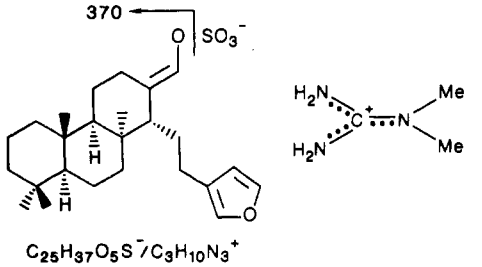
(2) Manes, L. V.; Naylor, S.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1985**, *50*, 284.

(3) Many original spectra are available in a recent Ph.D. dissertation: Manes, L. V. University of California, Santa Cruz, submitted June 1986.

(4) Manes, L. V.; Crews, P.; Ksebati, M. B.; Schmitz, F. J. *J. Nat. Prod.* **1986**, *49*, 787.

0022-3263/88/1953-0570$01.50/0

Chart I. Mass Spectral Data for Suvanine (1b)

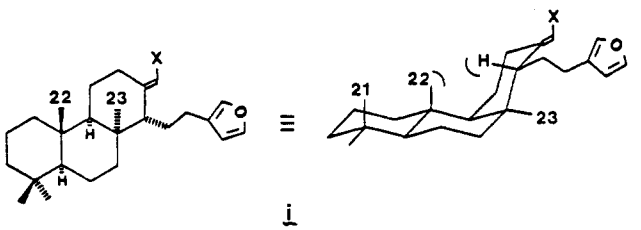


$C_{25}H_{37}O_5S^-/C_3H_{10}N_3^+$

method:	results:
CI [exact]	371.2920 ($^{12}C_{25}{}^{13}CH_{38}O_2$), 370.2843 ($C_{25}H_{38}O_2$), 352.2786 ($C_{25}H_{36}O$)
FAB [negative]	449 (base, $C_{25}H_{37}O_5S$), 921 ($(C_{25}H_{37}O_5S)_2Na$), 986 ($(C_{25}H_{37}O_5S)_2{\cdot}C_3H_{10}N_3$)$_2$
FAB [positive]	625.4110 ($C_{25}H_{37}O_5S{\cdot}(C_3H_{10}N_3)_2$)

trometry techniques including EI, CI, and CI field desorption. Instead, each of these methods displayed highest clusters at m/z 370, corresponding at high-resolution CI to $C_{25}H_{38}O_2$ (obsd 370.2843, calcd 370.2874), which were accompanied by a more intese cluster at m/z 352.2786 ($C_{25}H_{36}O$, calcd 352.2768). The higher m/z fragment could be ascribed to cleavage between O and S as shown in Chart I, while the other represents a loss of water. Additional fast atom bombardment (FAB) MS data were very revealing (see Chart I), and an important positive ion FAB peak was at m/z 625.4110, which corresponded to $[C_{25}H_{37}SO_5{\cdot}2(C_3H_{10}N_3)]^+$ (calcd 625.4114). Prominent peaks in the negative ion FAB mode were a large base peak at m/z 449, corresponding to the suvanine enol sulfate anion, and m/z peaks at 921 and 986, corresponding to $[2(C_{25}H_{37}SO_5)^-Na^+]$ and $[2(C_{25}H_{37}SO_5)^-C_3H_{10}N_3^+]$ aggregates, respectively.[5]

The stereochemistry of the tricyclic rings of suvanine was previously assigned from interpretations of ^1H NMR difference nuclear Overhauser enhancements. It now appears that the C-22 and C-23 methyl signals were incorrectly assigned. Additional two-dimensional NMR data revealed the true assignments for these methyl signals, and reinterpretation of the same NOE data led to the revised AB trans, BC cis ring stereochemistry as shown in structure i. A ^1H–^{13}C (J = 140 Hz) COSY NMR spectrum



i

revealed that the ^1H methyl signal at δ 0.92 correlated to the ^{13}C methyl signal at δ 17.7 whose chemical shift indicates that it must be assigned as an axial methyl group at a trans ring junction.[6] Also, the ^1H methyl signal at δ 0.75 correlated to the ^{13}C methyl signal at δ 26.0, and these data require that this methyl be located at a cis BC ring junction.[6] In addition, the ^1H–^{13}C COSY (J = 9 Hz) spectrum of **1b** (Figure 3S, supplementary material) clearly revealed long-range correlations from the ^1H δ 0.92 methyl singlet to C-9, C-1, and C-10; consequently, this methyl must be attached to C-10. Furthermore, the ^1H methyl singlet at δ 0.75 correlated, long range, to C-9, C-14, C-8, and C-7; hence, it must be attached to C-8. Finally,

(5) Howe, I.; Jarman, M. *Prog. Chem. Org. Nat. Prod.* **1985**, *47*, 107.
(6) Crews, P.; Bescansa, P. *J. Nat. Prod.* **1986**, *49*, 1041.

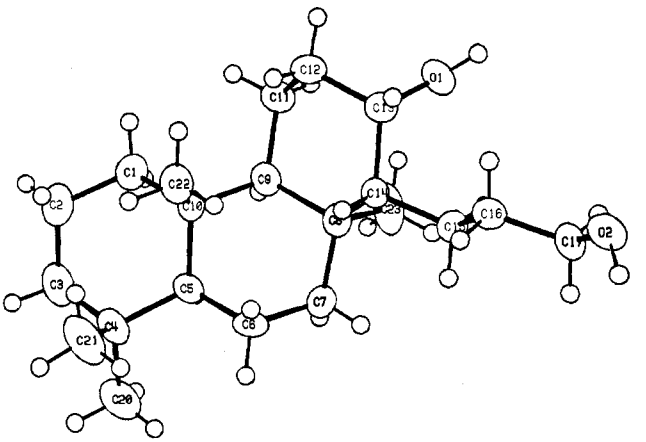
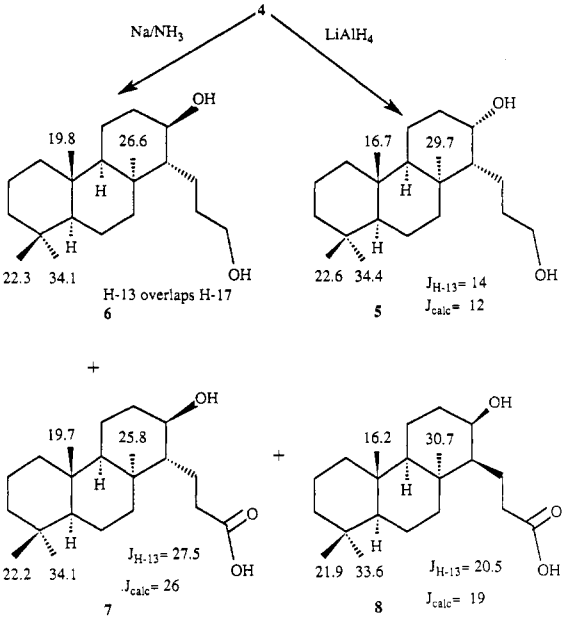


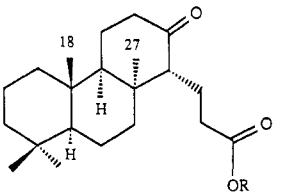
Figure 1. Computer-generated structure of **5** from a single-crystal X-ray diffraction study.

Scheme I. ^{13}C Methyl Shifts and Couplings to H-13 for Compounds 5–8



reinspection of the ^1H–^1H COSY spectrum of suvanine revealed a weak, long-range correlation between the ^1H methyl signal at δ 0.75 and H-14 (see Table II).

The above stereochemical assignments were confirmed by an X-ray analysis of a suvanine degradation product. Treatment of **1b** with ozone (–78 °C, methanol) yielded a mixture of a keto acid (**3**) and keto ester (**4**). The



3 R = H
4 R = CH_3

ozonolysis product **4** was reduced with lithium aluminum hydride (LAH) to yield the diol **5** (see Scheme I) having an axial secondary alcohol group at C-13. A crystalline sample of diol **5** was eventually obtained, and it was subjected to X-ray diffraction study. The X-ray structure of **5** confirms the stereochemical revisions shown in structure **1b** along with the stereochemical outcome of the reduction reaction. The computer-generated structure appears in

Table I. ^{13}C NMR Data

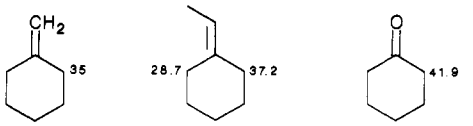
carbon no.	compound 1b	3	4	5	6	7	8
1	41.5*	41.8*	41.8*	42.4	42.1	41.9	42.4*
2	18.3	18.8+	18.5+	19.3+	19.8+	19.3+	19.7+
3	41.6*	42.0*	41.5*	42.4	42.1	41.9	41.4*
4	32.9	33.5	33.2	33.4	33.4	33.3	33.6
5	52.5	53.9	53.6	55.7	55.9	55.3	55.5
6	17.9	18.5+	18.3+	19.3+	19.0+	18.9+	18.8+
7	34.8	36.5	36.2	33.8	33.8	30.1	34.6
8	38.0*	41.4*	38.9*	36.9	39.7	39.1	40.2
9	56.5	56.6	56.3	56.9	57.0	56.6	55.9
10	38.4*	39.1*	41.0*	43.0	42.1	41.9	42.4
11	19.7	18.5+	18.3+	19.3+	19.0+	18.6+	18.8
12	23.9	39.9	39.6	39.2	39.7	38.9	40.2
13	118.4	214.2	213.5	67.7	73.3	79.9	82.0
14	41.7	53.9	53.6	38.9	44.7	41.9	40.8
15	24.9	20.9	20.6	22.0	24.5	22.2	24.1
16	23.0	33.5	33.0	33.7	33.8	29.9	29.8
17	124.9	179.3	173.9	63.6	62.2	180.5	179.7
18	111.0						
19	142.9						
20	33.2	33.5	33.2	34.4	34.1	34.1	33.6
21	21.6	21.8	21.5	22.6	22.3	22.2	21.9
22	17.7	17.8	17.5	16.7	19.8	19.7	16.2
23	26.0	27.0	26.7	29.7	26.6	25.8	30.7
24	133.3						
25	138.8						
26	156.7						
NMe_2	37.7						
OCH_3			51.1				

Table II. NMR Data for Suvanine (1b)

carbon no.	^{13}C NMR (300 MHz, DMSO-d_6)	^1H NMR δ (mult, J = Hz) (500 MHz, DMSO-d_6)	^1H–^{13}C COSY (J = 9) (300 MHz, DMSO-d_6)
1	41.5*	1.78, 0.78 (m)	H-22
2	18.3	1.35, 1.52 (m)	
3	41.6*	1.08, 1.35 (m)	
4	32.9		H-3e, H-20, H-21
5	52.5	0.97 (dd, 11.4)	H-20, H-21
6	17.9	1.20 (dddd, 12,11,8,4), 1.42 (dddd, 12,4,4,4)	
7	34.8	1.22 (ddd, 12,8,4), 1.79 (ddd, 12,4,4)	H-23
8	38.0*		H-23, H-14
9	56.5	0.83 (m)	H-22, H-23
10	38.4*		H-22
11	19.7	1.48 (ddd, 14,7,4), 1.60 (ddd, 14,4,2)	
12	23.9	2.03 (ddd, 14,7,2), 2.39 (ddd, 14,4,4)	
13	118.4		H-24
14	41.7	2.20 (dd, 8,1)	H-23
15	24.9	1.38 (dddd, 16,8,6,1), 1.72 (ddd, 16,8,8)	
16	23.0	2.29 (ddd, 16,8,8), 2.51 (m)	
17	124.9		H-25
18	111.0	6.36 (dd, 1.7,0.9)	H-19
19	142.9	7.55 (t, 1.7)	H-25, H-18
20	33.2	0.81 (s)	
21	21.6	0.82 (s)	
22	17.7	0.92 (s)	
23	26.0	0.75 (s)	H-14
24	133.3	6.22 (br s)	
25	138.8	7.40 (m)	H-18, H-19
26	156.7		
NMe_2	37.7	2.94 (s)	

Figure 1, and the structural data (Table 1S, supplementary material) reveals some atypical parameters for the B ring. Steric repulsions of the C-22 methyl with the C-12 methylene, C-14 methine, and C-21 methyl groups create large distances and angles as follows: C-9,C-10 = 1.571 (3) Å; C-8,C-9 = 1.569 (4) Å; C-8,C-9,C-10 = 119.6 (3)°; C-4,C-5,C-10 = 117.4 (2)°; C-4,C-5,C-6 = 116.1 (3)° (also, see Table 2S, supplementary material). In addition, the B ring is stretched at the top (compare C-10···C-8 = 2.714 (4) Å with C-5···C-7 = 2.470 (5) Å), and the dihedral angle C-7···C-10 = 36.9° is significantly reduced.

The stereochemistry of the 13(24)-olefinic bond was determined by noticing the difference in ^{13}C shifts of **1b** versus those of **3** and **4** at C-12 (16 ppm) and C-14 (12 ppm). This pattern was consistent with loss of a syn interaction at C-12 and could be confirmed by analysis of the ^{13}C shifts of the model compounds below.[7]



In contrast to the stereochemistry obtained on the $LiAlH_4$ reduction, treatment of **4** with Na/NH_3 yielded an equatorial alcohol at C-13 in compounds **6**–**8**. The proton coupling constants to H-13 could not be measured in compound **6** because this proton was isochronous with H-17,17′. However, compounds **7** and **8** gave excellent agreement between the calculated and observed values of the expected coupling constants to H-13 (see Table III). In compound **7**, the expected coupling constants to axial H-13 are as follows: two axial–axial couplings of 11 Hz each from H-12a and H-14a and one axial–equatorial coupling of 4 Hz from H-12e for a total calculated value of 26 Hz. The total observed coupling at H-13 in **7** is 27.5 Hz. An epimerization occurred at C-14 during the Na/NH_3 reduction to give compound **8**,[8] and this was evident from the combined couplings to the axial H-13, which are predicted to be 19 Hz and are observed as 20.5 Hz. The

(7) Model ^{13}C NMR data is from the Catalog of Carbon-13 NMR Spectra, Sadtler Research Laboratories, 1982, Philadelphia, PA.

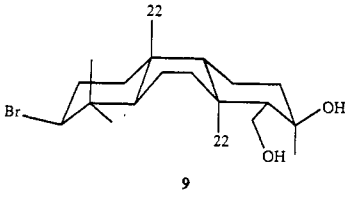
(8) This might be accounted for by the "2-alkyl ketone effect", as described in Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 240.

Table III. Suvanine Vicinal ^3J Values[a]

	sum of calcd ^3J's to H-13, Hz	sum of obsd ^3J's to H-13 (compd no.)[b]
H-13(eq), H-14(ax)	12	14 Hz (5)
H-13(eq), H-14(eq)	12	no example
H-13(ax), H-14(ax)	26	27.5 Hz (7)
H-13(ax), H-14(eq)	19	20.5 Hz (8)

[a] Calculated J's: J_{aa} = 11, J_{ae} = 4, and J_{ee} = 4 Hz. [b] OH proton coupling to H-13 not observed.

stereochemical features shown for 5–8 were also evident from the changes in ^{13}C methyl chemical shifts relative to those of **1b**. In **6** and **7**, the C-14 side chain is gauche to Me-23, and the OH group at C-13 is equatorial; consequently, the chemical shift position of Me-23 should be similar in these compounds. Such similarity is reflected in the observed Me-23 ^{13}C shifts in **1b** (δ 26.0), **6** (26.6), and **7** (25.8). In **5**, the C-13 OH group is axial, and a 4–5 ppm downfield shift at Me-23 is expected,[6] which is consistent with the observed shift of 29.7 ppm. Finally, in compound **8**, with the equatorial C-13 OH and the axial C-14 side chain, a 5–6 ppm downfield shift at Me-23 is expected due to loss of the γ-gauche interaction of the C-14 side chain,[6] which is consistent with the observed shift of δ 30.7. That the side chain at C-14 in **5** did not epimerize under the reaction conditions is supported by the similarity of the Me-23 ^{13}C methyl shift with that of suvanine (**1b**). In addition, the ^{13}C shifts of Me-22 and Me-23 were important in ruling out the possibility of a trans AB ring junction with the B ring in a boat conformation. Such a stereochemical situation exists in two natural products: isoaplysin-20 (**9**) in which the Me's attached to C-8 and



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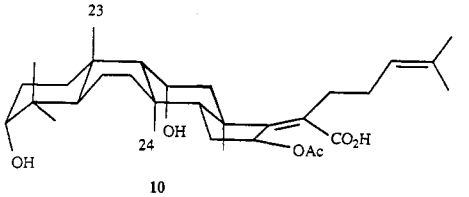

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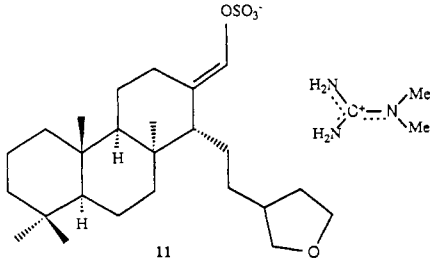
C-10 have chemical shifts of δ 21.9 and 22.0[9] and fusidic acid (**10**) in which the Me's attached to C-8 and C-10 have chemical shifts of δ 24 and 23.[10] A final straightforward chemical result involved hydrogenation of suvanine (**1b**) to tetrahydrofuran **11**.



11

The guanidinium salt of an enol sulfate is unique among marine natural products. The closest analogy in the literature is the choline salt of tyrindoxyl sulfate from marine molluscs.[11] Jacobs and co-workers have found that suvanine facilitates neuromuscular transmission in indirectly stimulated rat hemidiaphragm preparations. Suvanine is also an acetyl cholinesterase inhibitor, and similar properties are exhibited by the suvanine sodium salt (**1d**).[12]

Experimental Section

The NMR spectra were recorded on a JEOL FX-100 PFT spectrometer operating at 99.5 MHz for ^1H NMR analyses and 25.0 MHz for ^{13}C NMR analyses. High-field ^1H NMR spectra were recorded on a GN-300 spectrometer (at University of California, Santa Cruz) and on a Nicolet 360 spectrometer (at University of California, San Diego). Multiplicities of ^{13}C NMR peaks were determined from APT or DEPT data, and COSY NMR experiments were done on the GN-300 instrument. Electron-impact mass spectrometry data were obtained on a Finnigan 4000 instrument (6000 LS7 computer system, at USCS); field-desorption MS was performed by A. W. Szente, Mass Spectrometry Laboratory, Stanford University; high-resolution chemical-ionization MS was performed by H. Webb, University of California, Santa Barbara; and fast atom bombardment (negative) MS was performed by S. Naylor, Cambridge University, Cambridge, England, or (positive) at University of California, Riverside, and VG Analytical. High-performance liquid chromatography (HPLC) was done on a Waters ALC-201, using columns that include a Waters μ Porasil, Whatman Partisil, Rainin Microsorb C-18, or a Regis 10μ-ODS. All solvents were distilled and dried for HPLC use and were spectral grade for spectroscopy. Rotations were measured on a Perkin-Elmer 141 polarimeter (at UCSC) or on a Rudolph Research AutoPol III (at Stanford).

Two-Dimensional NMR Procedures. Standard pulse sequences[13] were used for the homo COSY (ref 13b, Figure 37) and the hetero COSY (ref 13b, Figure 35) experiments. For the hetero COSY experiments, a total of 128 evolution increments of 125 μs each were employed, beginning at an initial delay period of 10 μs with a relaxation pulse delay of 1 s. The initial 128 × 1024 data matrices were zero-filled in F_1, apodized by double exponential multiplication in each dimension, and then transformed to give 128 × 1024 data matrices. Detection of correlations was facilitated by utilizing the delay $\tau_1 = 0.5/J$ preceding the polarization transfer pulse and a refocussing delay, $\tau_2 = 0.3/J$, with τ's respectively for J = 140 Hz, 3.5 and 2.0 ms, and for J = 9 Hz, 55.6 and 33.3 ms. For the homonuclear ^1H COSY experiment, a total of 512 evolution increments of 416 μs each were employed beginning at an initial delay period of 416 μs with a relaxation pulse delay of 100 ms. Initial dimensions of the data matrices was 512 × 1024. Apodization by a $\pi/2$ shifted sinebell function and then transformation gave 512 × 512 data matrices, which were symmetrized.

For the hetero COSY experiments (300 MHz, UCSC) spectral acquisition parameters for suvanine (**1b**) were 3776 Hz in F_2 and 924 Hz in F_1. For the homonuclear ^1H COSY experiment, spectral acquistion parameters for suvanine were 944 Hz in the F_2 and F_1 dimensions. The one-dimensional long-range DEPT, hetero COSY (J = 140 Hz) and difference NOE experiments of suvanine were performed by Dr. Ralph Hurd at Nicolet Magnetics.

Collection and Isolation Procedures. The UCSC collections (accession numbers 83-21, 84-15, 85-1) were obtained from Suva Harbor, Fiji Island during the summers of 1983, 1984, and 1985. This sponge, initially designated as an *Ircinia* sp., has been reexamined and is very probably *Coscinoderma matthewsi* (family, Spongiidae). Freshly collected 1983 sponge (6.6 kg, wet weight), from Fiji was immediately extracted, in Nalgene bottles, with dichloromethane at ambient temperature. After the sponge was soaked for 2 days, the solvent was poured into a separatory funnel, and the water layer was removed and discarded. The extract was

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(11) Baker, J. T.; Duke, C. C. *Tetrahedron Lett.* **1976**, 1233.
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then concentrated by distillation of the methylene chloride, yielding a dark, viscous crude oil (24 g). The crude oil was transported back to UCSC where further isolation procedures began. A portion of the oil (8 g) was successively partitioned between aqueous methanol and the series: hexanes, CCl_4, and CH_2Cl_2. Each solvent fraction was examined by ^{13}C NMR and showed that the carbon tetrachloride partition fraction (1.6 g) contained ircinic acid (**2**) as the major component. The CH_2Cl_2 partition contained mostly suvanine (**1b**), which could be further purified by reverse-phase HPLC (10μ-ODS, MeOH).

The freeze-dried sponge (215.3 g) from Palau was soaked in methanol (1 L) at −20 °C for 1 week. The solvent was filtered and evaporated, and the residue was partitioned between water (200 mL) and CH_2CH_2 (2 × 200 mL). The combined organic extract was dried over sodium sulfate, and the solvent was evaporated to give a brown oil (2.26 g). This was chromatographed over LH-20 (MeOH, 100 × 2.5 cm) to give four fractions. Fraction 2 contained crude suvanine (**1b**) (1.3 g) and fraction 3 contained the crude suvanine sodium salt (**1d**) (0.3 g). Each of these crude compounds could be further purified by reverse-phase chromatography (85% aqueous MeOH, 85 × 2.5 cm).

Suvanine (1b). Isolation was as described above, and the following physical properties were observed: white powder; mp 218 °C (UCSC) or 224 °C (UCSD); $[\alpha]_D$ +9.5° (MeOH); IR (KBr) 3400, 3240, 1640 cm^{-1}; ^{13}C NMR (DMSO-d_6, 75 MHz) and ^1H NMR (DMSO-d_6, 500 MHz, by COSY) see Table II.

Suvanine Tetramethylammonium Salt (1c). Suvanine (**1b**) and tetramethylammonium chloride (2 equiv) were dissolved in MeOH, and the solvent was removed in vacuo. The product was then redissolved in chloroform, and the insolubles (suvanine and tetramethylammonium chloride) were removed by filtration. The filtrate was evaporated in vacuo to yield **1c**: white powder; mp 125 °C; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.4 (C-1 and C-3), 18.4, 18.9, 20.2 (C-2, C-6, and C-11), 33.4 (C-4), 52.9 (C-5), 35.2 (C-7), 38.6 and 40.0 (C-8 and C-10), 57.2 (C-9), 23.7, 24.6, 25.1 (C-12, C-15, and C-16), 123.6 (C-13), 42.8 (C-14), 125.5 (C-17), 111.2 (C-18), 142.7 (C-19), 33.5 (C-20), 21.9 (C-21), 26.3 (C-23), 18.1 (C-22), 132.5 (C-24), 138.9 (C-25), 55.6 (NMe_4); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.30 (br s, H-18), 7.32 (t, J = 1.0, H-19), 0.82 (H-20 and H-21), 0.79 (H-23), 0.97 (H-22), 6.25 (br s, H-24), 7.21 (br s, H-25), 3.30 ($N(CH_3)_4$); MS (20 eV), m/z 370 ($C_{25}H_{38}O_2$), 352 ($C_{25}H_{36}O$), 96, 82 (base).

Suvanine Sodium Salt (1d). This was isolated from the Palau sponge extract as described above, and the following physical properties were observed: white solid; mp 194 °C; UV (MeOH) 210 (ϵ 6300); IR 3500, 1640 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 142.6 (C-19), 139.0 (C-25), 131.6 (C-24), 126.7 (C-17), 125.2 (C-13), 111.0 (C-18), 57.0 (C-9), 53.0 (C-5), 42.6 (C-14), 42.0 t (2 C, C-1 and C-3), 39.9 and 38.6 (C-8 and C-10), 35.4 (C-7), 33.5 (C-4), 33.4 (C-20), 26.2 (t), 26.2 (C-23), 24.9 (t), 23.5 (t), 21.8 (C-21), 20.2 (t), 18.9 (t), 18.4 (t), 18.1 (C-22); ^1H NMR ($CDCl_3$) δ 7.34 (s, H-25), 7.23 (s, H-19), 6.32 (s, H-18), 6.29 (s, H-24), 2.53 (m, 2 H), 2.32 (ddd, 1 H), 2.29 (d, H-14), 2.12 (m, 1 H), 1.76 (m, 2 H), 1.56 (m, 2 H), 1.49 (m, 1 H), 1.38 (m, 1 H), 1.22 (m, 1 H), 1.13 (m, 1 H), 0.95 (m, 1 H), 0.92 (s, H-22), 0.85 (m, H-9a), 0.83 (s, H-20 and H-21), 0.77 (s, H-23); EIHRMS, m/z 370.2877 ($C_{25}H_{38}O_2$, calcd 370.2874).

Preparation of Suvanine Sodium Salt (1d). Suvanine (**1b**) (150 mg, 0.28 mmol) was dissolved in methanol (10 mL), 10 mL of 1 N aqueous NaOH was added, and the mixture was stirred for 30 min. This was taken up in CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed to give the crude sodium salt (77.5 mg). This was purified by HPLC on ODS-Partisil M9 10/50 (80% MeOH/H_2O) to give 65.2 mg of sodium salt (49%) as an oil, identical with **1d** by ^{13}C NMR, ^1H NMR, IR, and UV analyses. FAB-HRMS, m/z 495.2157 ($C_{25}H_{37}SO_5Na_2$, calcd 495.2159).

Preparation of Suvanine (1b) from Suvanine Sodium Salt (1d). A solution of the sodium salt (10.0 mg, 0.019 mmol) and *N,N*-dimethylguanidinium hydrochloride (2.5 mg, 0.020 mmol) was stirred in methanol (1 mL) for 30 min. This was taken up in CH_2Cl (5 mL) and washed (3 × 5 mL) with H_2O to give a white solid (8.0 mg, 80%), which was identical by TLC and NMR with the natural product.

Preparation of *N,N'*-Dimethylguanidinium Salt (1e) from Suvanine Sodium Salt (1d). A solution of the sodium salt (10.0 mg, 0.019 mmol) and *N,N'*-dimethylguanidinium hydrobromide (3.0 mg, 0.024 mmol) was stirred in methanol (1 mL) for 30 min. This was taken up in CH_2Cl_2 (5 mL) and washed (3 × 5 mL) with H_2O to give an oil (7.0 mg, 70%): ^{13}C NMR (DMSO-d_6) δ 157.1, 143.0, 139.0, 133.6, 125.2, 118.2, 111.2, 56.8, 57.6, 41.7, 40.9 (2 C), 40.0, 38.6, 35.0, 33.4, 33.1, 29.1, 27.9, 26.2, 25.1, 24.1, 24.1, 23.2, 21.8, 19.9, 18.5, 18.1, 17.9; ^1H NMR (DMSO-d_6) δ 7.57 (br s, 1 H), 7.42 (br s, 3 H, D_2O exchangeable), 7.32 (br s, 1 H, D_2O exchangeable), 7.32 (br s, 1 H), 6.38 (s, 1 H), 6.22 (s, 1 H), 2.72 (s, 6 H), 2.50–0.95 (many H's), 0.92 (s, 3 H), 0.82 (s, 6 H), 0.77 (s, 3 H).

Preparation of *N*-Methylguanidinium Salt (1f) from Suvanine Sodium Salt (1d). A solution of the sodium salt (10.0 mg, 0.019 mmol) and *N*-methylguanidinium hydrochloride (3.5 mg, 0.032 mmol) was stirred in methanol (1 mL) for 20 min. This was taken up in CH_2Cl_2 (5 mL) and washed (3 × 5 mL) with H_2O to give an oil (6.7 mg, 68%): ^{13}C NMR (DMSO-d_6) δ 142.8, 138.8, 125.0, 118.1, 111.0, 56.6, 52.4, 41.5, 40.7, 34.8, 33.2, 32.9, 28.9, 27.6, 26.0, 24.5, 23.8, 23.0, 21.6, 19.7, 18.3, 17.9, 17.7; ^1H NMR (DMSO-d_6) δ 7.55 (s, 1 H), 7.39 (s, 1 H), 7.30 (br s, 6 H), 6.36 (s, 1 H), 6.19 (s, 1 H), 2.68 (s, 3 H), 2.50–0.95 (many H's), 0.90 (s, 3 H), 0.80 (s, 6 H), 0.73 (s, 3 H).

Preparation of Pyridinium Salt (1g) from Suvanine (1b). In an attempted acetylation of suvanine, a solution of it (37.9 mg, 0.071 mmol) in pyridine (2 mL) and acetic anhydride (2 mL) was stirred under N_2 overnight at room temperature. The product was taken up in CH_2Cl_2 (10 mL) and washed with water (3 × 10 mL). The solvents were removed under vacuum, and the residue was purified by HPLC on ODS-Partisil M9 10/50 (80% MeOH/H_2O) to give the pyridinium salt as an oil (35.0 mg, 93%). This material decomposed during an instrument malfunction on the ^{13}C NMR. ^1H NMR ($CDCl_3$) δ 8.95 (br s, 2 H), 8.43 (br t, 1 H, J = 6, 9), 7.95 (br s, 2 H), 7.32 (s, 1 H), 7.19 (s, 1 H), 6.39 (s, 1 H), 6.26 (s, 1 H), 2.59 (dd, 1 H, J = 14.9), 2.56 (br t, 1 H, J = 7), 2.34 (dd, 1 H J = 7, 16), 2.28 (d, 1 H, J = 10), 2.18 (m, 1 H, J = 10, 3, 2), 1.78 (br d, J = 2, 13), 1.74 (dd, J = 9, 14), 1.60 (dd, J = 5, 12), 1.51 (m, J = 14, 3, 3), 1.36 (br d, J = 11), 1.26 (m, J = 14, 3), 1.12 (dd, J = 4, 13), 0.98 (dd, J = 3, 11), 0.94 (s, 3 H), 0.86 (m), 0.83 (s, 6 H), 0.79 (s, 3 H).

Ozonolysis of Suvanine (1b) to 3 and 4. A stirred solution of **1b** (200 mg) in dry CH_2Cl_2 (25 mL) at −78 °C was treated for 15 min with ozone (Welsbach Ozonator settings: 80 V, 0.2 L/min, 7.2 psi) until the solution turned a deep blue. Excess ozone was removed from the reaction mixture by bubbling with N_2. The solution was then quenched with dimethyl sulfide and allowed to warm to room temperature. The solvent was removed in vacuo, and the residue (272 mg) was chromatographed by reverse-phase HPLC (10μ-ODS, MeOH) to give, in order of elution, the keto acid **3** (47 mg) and the keto ester **4** (33 mg). **Keto acid 3**: ^{13}C NMR ($CDCl_3$, 75 MHz), see Table I; ^1H NMR ($CDCl_3$, 100 MHz) δ 0.85 (H-20, H-21), 0.74 (H-23), 1.10 (H-22). **Keto ester 4**: ^{13}C NMR ($CDCl_3$, 25 MHz), see Table I. ^1H NMR (100 MHz, $CDCl_3$) δ 3.59 (OMe), 0.86 (H-20, H-21), 0.74 (H-23), 1.12 (H-22).

LAH Reduction of 4 to Diol 5. To a stirred solution of lithium aluminum hydride (5 mg, 10 equiv) in dry THF (30 mL) was added, dropwise, a solution of **4** (50 mg) in dry THF (2 mL). The reaction mixture was refluxed overnight (15 h) under a nitrogen atmosphere, cooled in an ice bath, and quenched with ethyl acetate and then H_2O. The mixture was then extracted with CH_2Cl_2 and dried ($MgSO_4$), and the solvent was removed in vacuo to yield **5** (38 mg, 64% yield). Upon sitting in $CDCl_3$ in a capped NMR tube for several weeks, crystals of the diol formed: mp 156 °C; ^1H NMR ($CDCl_3$) δ 4.10 (br s, H-13), 3.68 (m, H-17), and Me's at 1.07, 1.04, and 0.84 (A = 2); ^{13}C NMR ($CDCl_3$, 75 MHz) see Table I; MS (20 eV) m/z 322 (M^+), 307 ($M^+ - CH_3$), 305 ($M^+ - OH$), 304 ($M^+ - H_2O$), 289 ($M^+ - CH_5O$), 123 (base).

Na/NH_3 Reduction of 4 to 6–8. A solution of **4** (45 mg, 0.13 mmol) in 5 mL of dry ether (distilled from LAH) was combined with 50 mL of liquid ammonia and 740 mg (10 mmol) of *tert*-butyl alcohol (as a proton source). To this solution was added 160 mg (7 mmol) of Na metal over a period of 30 min. The reaction was then quenched with ammonium chloride, the liquid ammonia was allowed to evaporate, and the residue was dissolved in H_2O (acidified with HCl). The water solution was extracted with CH_2Cl_2, and the solvent was removed in vacuo to give 42 mg of reaction product. This material was chromatographed on reverse-phase HPLC (10μ-ODS, MeOH) to give, in order of elution,

6 (12.5 mg), 7 (3.0 mg), and 8 (4.2 mg). Compound 6: oil; ^{1}H NMR ($CDCl_3$) δ 3.70 (m, H-13, H-17), and Me's at 0.87, 0.85 (A = 2), and 0.84; ^{13}C NMR ($CDCl_3$, 75 MHz) see Table I; MS (20 eV), m/z 304 ($M^+ - H_2O$), 289 ($M^+ - CH_5O$), 136 (base). Compound 7: oil; ^{1}H NMR ($CDCl_3$) δ 4.70 (m, H-13), 2.95 (H-17), and Me's at 0.91, 0.87, and 0.85 (A = 2); ^{13}C NMR ($CDCl_3$, 75 MHz), see Table I; MS (20 eV), m/z 319 ($M^+ - OH$), 318 ($M^+ - H_2O$), 303 ($M^+ - CH_5O$), 136 (base). Compound 8: oil; ^{1}H NMR ($CDCl_3$) δ 4.15 (m, H-13) and Me's at 0.87, 0.85 (A = 2), and 0.84; ^{13}C NMR ($CDCl_3$, 75 MHz), see Table I, MS (20 eV), m/z 319 ($M^+ - OH$), 318 ($M^+ - H_2O$), 304 ($M^+ - CH_4O$), 123 (base).

Hydrogenation of Suvanine (1b) to Tetrahydrofuran 11. A solution of suvanine (10.0 mg, 0.019 mmol) and Pd/C (1 mg) in EtOAc (5 mL) was stirred under H_2 (1 atm) for 48 h. The product was filtered through celite, and the solvent was removed to give 11 (10.1 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 6.97 (br s, 3 H, D_2O exchangeable), 6.66 (br s, 1 H, D_2O exchangeable), 6.18 (d, J = 5), 3.86 (m, 2 H, J = 7, 13), 3.70 (dd, 1 H, J = 8, 13), 3.34 (dt, 1 H, J = 7, 13), 2.50 (m, 1 H), 2.40 (m, 1 H), 2.28 (m, 1 H), 2.03 (m, 2 H), 1.80 (br d), 1.67 (dd), 1.54 (m), 1.36 (dd), 1.29 (dd), 1.17 (dd), 1.06 (m), 1.00 (s, 3 H), 0.89 (m, 1 H), 0.87 (s, 3 H), 0.85 (s, 3 H), 0.79 (s, 3 H).

X-ray Procedures. A colorless crystal of dimensions 0.20 × 0.24 × 0.52 mm was used for data collection on an Enraf-Nonius CAD4 diffractometer equipped with a Mo Kα radiation (wavelength = 0.71073 Å) and a graphite monochromator. Crystal data are as follows: $C_{21}H_{38}O_2$, monoclinic space group $P2_1$, a = 10.903 (2), b = 7.807 (4), and c = 11.491 (2) Å, β = 99.33 (2)°, V = 965.2 (9) Å^3, Z = 2, D_c = 1.110 g cm^{-3}, μ(Mo Kα) = 0.89 cm^{-1}, T = 21 °C. Intensity data were collected by Ω-2θ scans within one quadrant having 1° < θ < 27° by using varying scan speeds of 0.45–4.0°/min in order to measure all significant data with I = 50$\sigma(I)$. A maximum of 120 s was spent on any single scan. Data reduction included corrections for background, Lorentz, and polarization effects. Of 2257 unique data, 1416 had $I > 2\sigma(I)$ and were used in the refinement. The absolute configuration was not determined. The structure was solved by using MULTAN78[14] and refined by full-matrix least squares, treating non hydrogen atoms anisotropically. H atoms were located by difference maps. The hydroxyl hydrogen atoms were isotropically refined, while other H atoms were placed in calculated positions with C-H 0.95 Å, and B = 5.0 Å^2. Convergence was achieved with R = 0.048 and R_w = 0.043 for 216 variables, extinction coefficient = 7.7(15) × 10^{-7}, and maximum residual density 0.14 e Å^{-3}. Complete coordinates and anisotropic thermal parameters are in Tables 3S–5S, supplementary material.

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Supplementary Material Available: Figures of the ^{13}C NMR spectrum of 1c and ^{1}H–^{13}C COSY spectrum of 1b and tables containing bond distance and angles, torsion angles, and coordinates and anisotropic thermal parameters (8 pages). Ordering information is given on any current masthead page.

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Photorearrangements of Carbomethoxy-Substituted Cyclohexadienones in Neutral Media

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The photochemistry of several 2-carbomethoxy-3-keto-$\Delta^{1,4}$-hexahydronaphthalenes has been investigated. Unlike analogous bicyclic cyclohexadienones lacking a 2-carbomethoxy substituent, these systems do not undergo normal type-A photorearrangements upon irradiation in nonprotonating solvents. Instead, they afford exocyclic hydroazulenone olefins resulting from proton loss from their angular substituents as well as hydroxy ketones and decarbomethoxylated ethers which have been shown to arise from their derived Zimmerman–Schuster zwitterions by way of intramolecular processes involving attack of the carbomethoxy group upon the electrophilic C-9 center. The behavior of these systems is contrasted with that of a 4-carbomethoxy-substituted dienone and a monocyclic, 2-carbomethoxy-substituted dienone, both of which were found to undergo the expected type-A photorearrangements under neutral conditions.

In connection with efforts directed toward the synthesis of methyl homodaphniphyllate (1)[1,2] we have had occasion to examine the photochemistry of several carbomethoxy-substituted 2,5-cyclohexadienones in neutral media. A brief retrosynthetic analysis of this alkaloid is outlined in Scheme I.

Implementation of this approach requires a fairly general entry into hydroazulenone aldehydes of the type exemplified by 2. Since 2 might be obtainable through Claisen rearrangement of enol ether 3 we were motivated to explore routes to such compounds. Our attention was drawn to the work of Caine[3] who demonstrated that irradiation of the bicyclic 2-carboxycyclohexadienone 4 in anhydrous

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