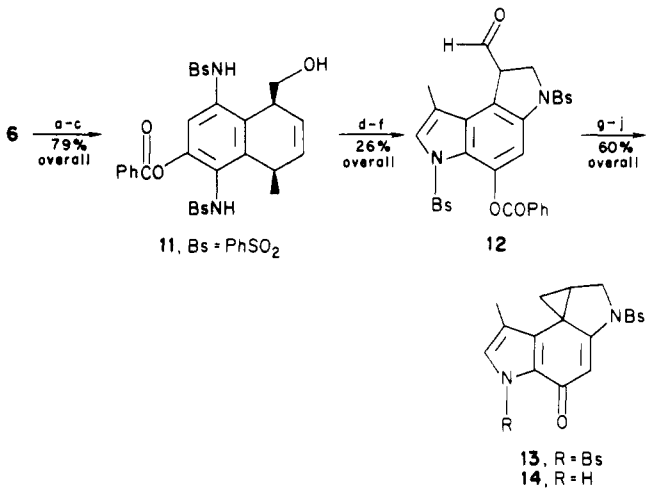
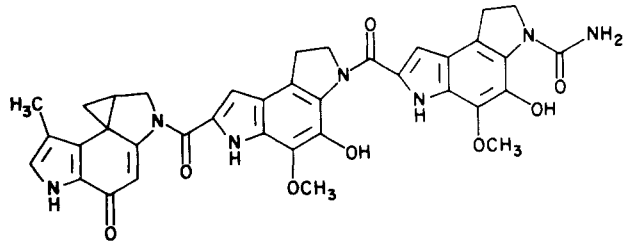
Scheme I[a]



[a] Reaction conditions: (a) BBr_3 in hexane/CH_2Cl_2, -78 °C → 30 °C, 20 min. (b) $(PhCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 24 h. (c) Dioxane, 4 M H_2SO_4, MeOH (4:1:1). (d) $PhSO_2Cl$, 2 equiv of Et_3N, 0 °C, CH_2Cl_2. (e) O_3, 1:1 CH_2Cl_2:MeOH, -78 °C; excess Me_2S, catalytic H_2SO_4, 0 °C. (f) HCl, dioxane. (g) Dibal, THF, 0 °C. (h) CH_3SO_2Cl, Et_3N, CH_2Cl_2; room temperature. (i) $LiAlH_4$, THF, 0 °C. (j) DBU, $PhCH_3$, 50 °C.

Whatever governs the selectivity, the results will be useful in synthetic design. We have found that the selective production of **6** forms the basis for an expedient synthesis of **14**, the left-hand portion of CC-1065, a natural



CC-1065

product which exhibits inhibitory activity against L1210 and P388 leukemias in mice.[13] This portion was initially synthesized by Wierenga in 15 steps.[14] Recently, Magnus has reported an elegant synthesis of this portion by way of a dipolar cycloaddition strategy.[15] Our approach begins with the cleavage of the arylmethyl ether of **6** with BBr_3 in methylene chloride.[16] Benzoylation of the resulting phenol ($(PhCO)_2O$, Et_3N) and selective hydrolysis of the acetate provided alcohol **11** (Scheme I). Aldehyde was synthesized by phenylsulfonylation of the alcohol followed in situ by ring formation. Ozonolysis with reductive workup under acidic conditions[17] furnished a 2-methoxy-2,3-dihydroindole unit which was readily aromatized (HCl, dioxane) to indole **12**. Dibal reduction of aldehyde **12** followed by mesylation of the resulting alcohol and debenzoylation afforded a hydroxymesylate which was converted into **13**[18] with DBU in toluene at 50 °C. Removal of the phenylsulfonyl group attached to the indole nitrogen atom could be selectively achieved by using $NaOCH_3$.[15] Overall the synthesis proceeds in 11 steps from **6** with an overall yield of 10%.

Acknowledgment. We thank the National Institutes of Health and the A. P. Sloan Foundation for support of this work. We thank Dr. Ray Firestone for helpful suggestions.

Registry No. (*E,E*)-**2a**, 93923-35-4; (*E,E*)-**2b**, 57006-69-6; (*E,E*)-**2c**, 93923-36-5; (*E,E*)-**2d**, 93923-37-6; (*E,E*)-**2e**, 93923-38-7; (*E,E*)-**3**, 93923-39-8; **4**, 93923-40-1; **5**, 93923-43-4; **6**, 93923-44-5; **7**, 93923-45-6; **8**, 93923-46-7; **9** (isomer 1), 93923-47-8; **9** (isomer 2), 93923-48-9; **10** (isomer 1), 93923-49-0; **10** (isomer 2), 93923-50-3; **22**, 93942-85-9; **12**, 93923-51-4; **13**, 93923-52-5; **14**, 93923-53-6; CC-1065, 69866-21-3; ethyl propiolate, 623-47-2; ethyl acrylate, 140-88-5; *p*-toluic acid, 99-94-5; methyl (1α,4α,4aβ,8aβ)-1-(methoxymethyl)-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4-carboxylate, 93923-41-2; methyl (1α,4α,4aα,8aα)-1-(methoxymethyl)-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate, 93984-17-9; methyl (1α,4α,4aβ,8aβ)-1-[(1-oxo-2,2-dimethylpropoxy)methyl]-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate, 93923-42-3; methyl (1α,4α,4aα,8aα)-1-[(1-oxo-2,2-dimethylpropoxy)methyl]-4-methyl-5,8-dioxo-1,4,4a,5,8,8a-hexahydronaphthalene-4a-carboxylate, 93984-18-0; carbomethoxybenzoquinone, 3958-79-0; (*E,E*)-sorbyl chloride, 17100-75-3; methoxybenzoquinone bis(benzenesulfonimide), 83202-21-5.

(13) Martin, D. G.; Hanka, L. J.; Neil, G. L. *Proc. Am. Assoc. Cancer Res.* **1978**, *19*, 99.
(14) Wierenga, W. *J. Am. Chem. Soc.* **1981**, *103*, 5621.
(15) Magnus, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 389. Magnus, P.; Or, Y.-S. *J. Chem. Soc., Chem. Commun.* **1983**, 26. Halazy, S.; Magnus, P. *Tetrahedron Lett.* **1984**, *25*, 421.
(16) McOmie, J. F. W.; West, D. E. *Org. Synth.* **1969**, 50.
(17) After Me_2S is added, catalytic H_2SO_4 is necessary to ensure a clean reaction. Presumably, it increases the rate of methoxydihydroindole formation.
(18) Cyclopropane **13**: 300-MHz NMR ($CDCl_3$) δ 0.91 (t, J = 5 Hz, 1 H), 1.76 (dd, 1 H), 1.93 (s, 3 H), 2.84–2.89 (m, 1 H), 3.94 (dd, 1 H), 4.10 (d, J = 10 Hz, 1 H), 6.38 (s, 1 H), 7.47–8.07 (m, 10 H); 75-MHz ^{13}C NMR δ 9.81, 21.29 (2 C), 32.31, 54.76, 108.44, 115.50, 126.99, 127.16, 128.48, 128.60, 129.50, 133.68, 134.04, 134.39, 136.82, 138.66, 157.05, 174.87.

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Received September 24, 1984

Suvanine, a Novel Sesterterpene from an *Ircinia* Marine Sponge

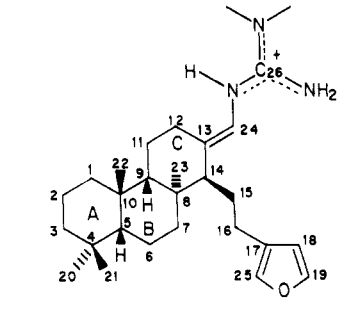
Summary: Reported is a novel sesterterpene, suvanine (**1**), which contains both guanidinium bisulfate and furan functionality and the same tricarbocyclic skeleton as cheilanthatriol (**3**) but with different stereochemical features.

Sir: A growing list of sponges in the order Dictyoceratida are sources of sesterterpenes, and the family Thorectidae has the largest representation.[1] Within this latter group is the genus *Ircinia* which stands out because nine described species and two undescribed species are sources of a variety of acyclic sesterterpenes, acyclic sesterterpenes with mixed biogenesis, or novel polyoxygenated carbocyclic lactones.[2] During recent field work we collected an un-

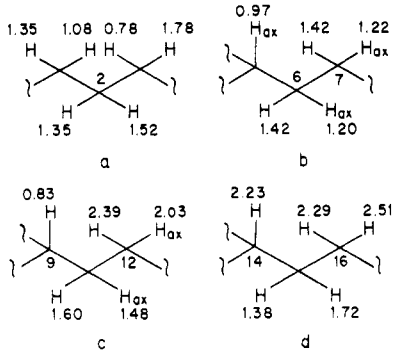
(1) Crews, P.; Naylor, S. *Prog. Chem. Org. Nat. Prod.*, submitted for publication.
(2) (a) Cimino, G.; De Stefano, S.; Minale, L.; Fattorusso, E. *Tetrahedron* **1972**, *28*, 333. (b) Cimino, G.; De Stefano, S.; Minale, L. *Tetrahedron* **1972**, *28*, 1315. (c) Cafieri, F.; Fattorusso, E.; Santacroce, C.; Minale, L. *Tetrahedron* **1972**, *28*, 1579. (d) Faulkner, D. J. *Tetrahedron Lett.* **1973**, 3821. (e) Rothberg, I.; Shubiak, P. *Tetrahedron Lett.* **1975**, 769. (f) Baker, J. T. *Pure Appl. Chem.* **1976**, *48*, 35. (g) Hofheinz, W.; Schonholzer, P. *Helv. Chim. Acta* **1977**, *60*, 1367. (h) Alfano, G.; Cimino, G.; De Stefano, S. *Experimentia* **1979**, *35*, 1136. (i) Gregson, R. P.; Ouvrier, D. *J. Nat. Prod.* **1982**, *45*, 412. (j) Gonzalez, A. G.; Rodriguez, M. L.; Barrientos, S. M. *J. Nat. Prod.* **1983**, *46*, 256.

0022-3263/85/1950-0284$01.50/0

described *Ircinia* sp. and now extend the above list by reporting a polar ichthyotoxic metabolite (1) which has an uncommon tricarbocyclic sesterterpene skeleton with both novel functionality and stereochemistry.



1



a b c d

The *Ircinia* sponge[3] was collected from Suva Harbor, Fiji Is. in 1983 and immediately extracted with dichloromethane. The resulting crude oil was partitioned between hexane–methanol (10% aqueous), CCl_4–methanol (30% aqueous), and CH_2Cl_2–methanol (35% aqueous). Monitoring the progress of the partition by ^{13}C NMR showed that the methanol fraction contained only 1 and when dried and evaporated deposited 1[4] as an amorphous solid: mp 218 °C; $[\alpha]_D$ +9.5°; IR (KBr) 3400, 3240, 1640 cm^{-1}. Analysis of ^{13}C NMR spectra of 1 revealed a partial molecular formula of $C_{28}H_{43}$, and the lowest field peak at δ 156.7 (s) along with a UV λ_{max} 210 nm (ϵ 10 500, 0.01 N NaOH in absolute EtOH) and 200 nm (ϵ 13 000 in MeOH)[5] suggested a guanidine group. A molecular formula of $C_{28}H_{45}N_3O \cdot H_2SO_4$ was established by elemental analysis (Found: C, 62.70; H, 8.78; N, 7.74; O + S, 20.78. Calcd: C, 62.57; H, 8.75; N, 7.82; O, 14.90; S, 5.96).[6] Corroborating evidence from mass spectrometry was at first obscure because the highest m/z cluster was at 371 and 370 (by chemical ionization field desorption) and 371.2920 and 370.2843 (by high resolution) corresponding to formulae of $C_{25}H_{39}O_2$ (calcd = 371.2952) and $C_{25}H_{38}O_2$ (calcd = 370.2873).[7] These were accompanied by a m/z base peak at 352.2786 ($C_{25}H_{36}O$, calcd = 352.2706). A straightaway interpretation of such data was impossible as only one oxygen could be located by ^{13}C NMR, and it was associated with a furan ring (δ 142.9 d, 138.8 d, 124.9 s, 111.0 d). A possible rationalization could be OH^- displacement of the guanidinium ion subunit under thermal or electron impact conditions.[7]

With the molecular formula securely established we were able to properly define the carbon skeleton and sites of substituent attachment. The ^{13}C data above along with ^1H resonances δ 7.55 t (J = 1.7, 1.7 Hz, H-19), 7.40 br m (H-25), and 6.36 dd (J = 0.9, 1.7, H-18) indicated a β-substituted furan. A trisubstituted $R_2C{=}C(H)N$ was indicated by ^{13}C and ^1H data (δ 118.4 s and 133.3 d with J_{CH} = 184.1 Hz; δ 6.22 br s, H-24).[8] This N was also presumed to be a part of the guanidinium constellation which could be written as $=CNC(NH_2)NMe_2$ on the basis of the following NMR data: a ^1H six-proton sharp singlet at δ 2.94 (NMe_2), two NMe_2 carbons as a single peak (δ 37.7), and a two-proton broad singlet at δ 7.18 (exchangeable with D_2O). An NMR heteronuclear polarization transfer experiment using a one-dimensional DEPT pulse sequence with selective proton irradiation at the NMe_2, set to observe only $^3J_{CH}$ effects,[9] showed just two signals in the ^{13}C NMR at δ 157 and 38 (as shown in the supplementary material), confirming the $CNMe_2$ group. The remaining ^{13}C NMR resonances and unsaturation indicated the gross structure of a tricarbocycle shown in **1**. Three natural products are known which have a related skeleton, including degraded sesterpenes luteone **2a**[10a] from a nudibranch, **2b** from Athabasca oil sand bitumen,[10b] and

(3) Voucher specimen (nos. 83-21, 84-16) represent an undescribed species of *Ircinia*. Specimens were generally collected from −2 to −25 m (underwater photo available from P.C.). They were grey in color and massive, measuring up to 30 cm in diameter. The surface is slightly rough, the consistency spongy, and the body tough. The dermal membrane contains numerious spicules and sand grains. They have a mesh work of main and secondary fibers. Openings in the mesh work are generally subspherical and measure from 50 to 200 μm in greatest diameter. The main fibers measure 30–50 μm in diameter and are cored with sand and a variety of sponge spicules. The collagenous filaments measure 15–20 μm in diameter and lack terminal knobs; their ends attenuate rapidly to a dull point.

(4) 1: ^{13}C NMR (Me_2SO-d_6, 75 MHz, shift assignments in ppm from Me_4Si by assessing number of attached protons) 41.5 and 41.6 (C-1 and C-3), 18.3 (C-2), 32.9 (C-4), 52.5 (C-5), 17.9 (C-6), 34.8 (C-7), 38.0 and 38.4 (C-8 and C-10), 56.6 (C-9), 19.7 (C-11), 23.9 (C-12), 118.4 (C-13), 41.7 (C-14), 24.9 (C-15), 23.0 (C-16), 124.9 (C-17), 111.0 (C-18), 142.9 (C-19), 33.2 (C-20), 21.6 (C-21), 26.0 (C-22), 17.7 (C-23), 133.3 (C-24), 138.8 (C-25), 156.7 (C-26), 37.7 ($N(CH_3)_2$); ^1H NMR (Me_2SO-d_6, 500 MHz, shift assignments in ppm from Me_4Si by COSY) 0.78 and 1.78 (H-1 and H-1′ or H-3 and H-3′), 1.35 and 1.52 (H-2 and H-2′), 1.08 and 1.35 (H-3 and H-3′), 0.97 (dd, J = 11.4, H-5a), 1.20 (dddd, J = 12, 11, 8, 4, H-6a), 1.42 (dddd, J = 12, 4, 4, 4, H-6e), 1.22 (ddd, J = 12, 8, 4, H-7a), 1.79 (ddd, J = 12, 4, 4, H-7e), 0.83 (H-9), 1.48 (ddd, J = 14, 7, 4, H-11a), 1.60 (ddd, J = 14, 4, 2, H-11e), 2.03 (ddd, J = 14, 7, 2, H-12a), 2.39 (ddd, J = 14, 4, 4, H-12e), 2.20 (dd, J = 8, 1, H-14), 1.38 (dddd, J = 16, 8, 6, 1, H-15), 1.72 (dddd, J = 16, 8, 8, 6, H-15′), 2.29 (ddd, J = 16, 8, 8, H-16′), 2.51 (m, H-16), 6.36 (dd, J 1.7, 0.9, H-18), 7.55 (t, J = 1.7, H-19), 0.81 and 0.82 (H-20 and H-21), 0.75 (H-22), 0.92 (H-23), 6.22 (bs, H-24), 7.40 (m, H-25), 2.94 ($N(CH_3)_2$).

(5) The UV λ_{max} of guanidine·HCl is 212 nm (ϵ 790, aqueous EtOH) or 265 nm (ϵ 15, water), and when conjugated to C=O or C=C the ϵ increases to >10 000 as seen by data in the following sources: (a) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. In "Tables of Spectral Data for Structure Determinations of Organic Compounds"; Springer-Verlag: New York, 1983. (b) Harbour, G. C.; Tymiak, A. A.; Rinehart, K. L., Jr.; Shaw, P. D.; Hughs, R. G., Jr.; Mizsak, S. A.; Coats, J. H.; Zurenko, G. E.; Li L. H.; Kuentzel, S. L. *J. Am. Chem. Soc.* **1981**, *103*, 5604. (c) Matsumoto, K.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 552. (d) Szilagyi, I.; Valyi-Nagy, T.; Keresztes, T. *Nature (London)* **1962**, *196*, 376. Furans (β-substituted) have UV λ_{max} 218 (ϵ 4500) as seen by data in ref 2b.

(6) That crystalline 1 contained sulfur was determined by Energy Dispersive Spectroscopy with a 50 kV beam as described in Goldstein, J. I.; Newbury, D. E.; Echlin, P.; Joy, D. C.; Hill, M.; Fiori, C.; Lifshin, E. In: "Scanning Electron Microscopy and X-ray Microanalysis"; Plenum Press: New York, 1981; pp 205-304.

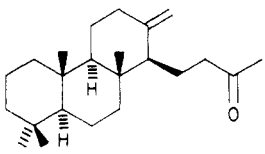
(7) Simple guanidinium salts exhiibit MS M^+ peaks accompanied by a complex fragmentation pattern [Benyon, J. H.; Hopkinson, J. A.; Williams, A. E. *Org. Magn. Reson.* **1968**, *1*, 169], whereas guandinium sulfates sometimes do not display a M^+ peak under conditions where it is visible for the corresponding halide or carbonate salts [Bell, N. A.; Hutley, B. G.; Shelton, J.; Turner, J. B. *Thermochim. Acta*, **1977**, *21*, 255].

(8) Comparison to the following J_{CH} data (Hz) is informative: C=C(H)Y, Y = R, 157; Y = NR, 176; Y = OR, 195; Y = Cl, 195.

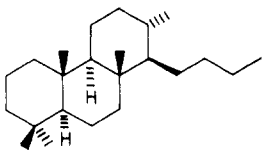
(9) This is a one-dimension version of the more common "long range" heteronuclear 2D COSY NMR experiment. For some recent reviews of 2D NMR, see: (a) Shoolery, J. N. *J. Nat. Prod.* **1984**, *47*, 226. (b) Gunther, H.; Benn, R. *Angew Chem., Int. Ed. Engl.* **1983**, *22*, 350.

(10) (a) Hellou, J.; Andersen, R. J.; Rafii, S.; Arnold, E.; Clardy, J. *Tetrahedron Lett.* **1981**, *22*, 4173. (b) Sierra, M. G.; Cravero, R. M.; Laborde, M. de los Angeles; Ruveda, E. A. *J. Chem. Soc., Chem. Commun.* **1984**, 417. (c) Kahn, H.; Zaman, A.; Chetty, G. L.; Gupta, A. S.; Dev. S. *Tetrahedron Lett.* **1971**, 4443.

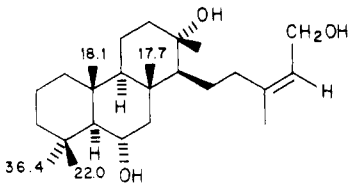
cheilanthatriol 3[10c] from a fern.



2a

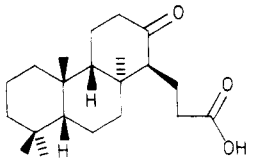


2b

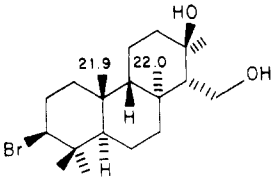


3

Additional confirmation for the proposed carbon skeleton 1 came from homonuclear correlation spectroscopy (COSY) as shown in the supplementary material. Specifically, carbon subunits a–d were identified, and these data also required the side-chain furan be attached at C-14 and the imine N at C-24. The stereochemistry shown across the C-13 to C-24 C=C bond was determined by treatment of 1 with ozone (−78 °C, methanol) to yield 4.[11]



4



5

This was accompanied by a downfield shift of C-12 in 1 (δ 23.7) vs. that in 4 (δ 39.9), consistent with the loss of a syn interaction at C-12. Additional NMR data facilitated stereochemical assignment of the ring junctions and C-14 side chain. First, ^{1}H difference NOE spectra (300 MHz, Me_2SO-d_6) provided the following enhancement percentages: between Me-23, by irradiation at δ 0.92, and protons H-14 (4%), H-11a (2%), and H-7e (1%),[12] between Me-21, by irradiation at δ 0.82, and Me-22 (1%); between Me-22, by irradiation at δ 0.75, and Me-21 (1%). Next, from a hetero COSY NMR spectrum (shown in the supplementary material) Me-23 could be correlated to ^{13}C resonance at δ 17.7, and this same spectrum provided ^{1}H and ^{13}C NMR shifts assigned for Me-22 (δ 0.75, 26.0). Finally, an expanded ^{1}H NMR trace showed ^3Js of 11 and 4 Hz to H-5. Interpretation of the above supports the following conclusions for 1. (a) The *J*s to H-5 and comparison of the ^{13}C Me-22 shift (δ 26.0) in 1 to those of 3 (C-22 = δ 17.7, C-23 = δ 18.1)[13] and to those of a cis A/B ring steroid (lithocholic acid Me = δ 23)[14] clearly show cis A/B ring stereochemistry for 1 with Me-22 and H-5 respectively equatorial and axial relative to ring B.[15] (b) The ^{13}C Me-23 (δ 17.9) shift shows that the B/C ring junction must be trans; (c) the NOE between Me-23 and H-14 shows a trans relationship between that methyl and side chain attached at C-14.

Suvanine 1 represents the first C_{25} tricarbocycle isolated from a marine organism. By contrast, nine such frameworks are known from terrestrial organisms.[1] A possible chemical defensive role for 1 is also suggested by its ichthyotoxicity to goldfish at 10 μg/mL. Finally, this compound exhibits >90% inhibition of sea urchin egg cell division at 16 μg/mL.[18]

Acknowledgment. Partial research support to P.C. was from NOAA, National Sea Grant College Program, Department of Commerce, and University of California project number R/MP-33, and L.V.M. was a Sea Grant Trainee. A grant to P.C. from the University Research Expeditions Program supported our field work in Fiji. We thank Dr. Mike Maddox, Syntex; Dr. Chin Yu, UCD; and Dr. Ralph Hurd, Nicolet Magnetics for assistance with certain NMR experiments, Mr. Rob Franks (UCSC, CMS Analytical Lab) for the elemental analysis; and Ms. Patsy Bolt (UCSC, EM lab) for the EDS results.

Registry No. 1, 94203-53-9.

Supplementary Material Available: Figures of ^{1}H NMR COSY of 1, ^{1}H–^{13}C hetero COSY NMR of 1, and ^{13}C NMR of 1 including DEPT and selective INEPT (3 pages). Ordering information is given on any current masthead page.

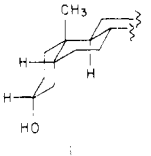
(11) 4: ^{13}C NMR ($CDCl_3$, 25 MHz, 25 MHz, shift assignments in ppm from Me_4Si by assessing number of attached protons) 41.8 and 42.0 (C-1 and C-3), 18.8 (C-2), 33.5 (C-4), 53.9 (C-5), 18.5 (C-6), 36.5 (C-7), 39.1 and 41.4 (C-8 and C-10), 56.6 (C-9), 18.5 (C-11), 39.9 (C-12), 214.2 (C-13), 53.9 (C-14), 20.9 (C-15), 33.5 (C-16), 179.3 (C-17), 33.5 (C-20), 21.8 (C-21), 27.0 (C-22), 17.8 (C-23); ^{1}H NMR ($CDCl_3$, 100 MHz, shift assignments in ppm from Me_4Si) 0.85 (H-20), 0.85 (H-21), 0.74 (H-22), 1.10 (H-23).

(12) Switching the assignments of subunits b and c derived from the proton NMR COSY spectrum can be ruled out owing to the NOE observed between Me-23 and H-7e (vs. the alternative of assuming this is between Me-23 and H-12e). Also, the resonance for C-12 (correlated to H-12 by hetero COSY) is greatly shifted when 1 is converted to 4 whereas the chemical shift for C-7 remains approximately constant.

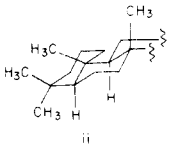
(13) Gupta, A. S.; Dev, S.; Sangare, M.; Septe, B.; Lukacs, G. *Bull. Soc. Chim. Fr.* **1976**, 1879.

(14) Leibfritz, D.; Roberts, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 4996.

(15) Note that the cis A/B ring stereochemistry in 1 is "non-steroid like" (compare the chair structuresof lithocohlic acid i vs. 1). The alternative cis A/B ring stereochemistry with the Me-22 and H-5 respectively equatorial and axial relative to ring A and ring B in a boat conformation having dihedral angles of approximately 60° and 180° between H-5 and H-6 and H-6′ can be ruled out owing to the NOE observed between Me-22 and Me-21. Also, proton *J*s to H-5 and ^{13}C shifts of Me-22 and Me-23 were important in ruling out a trans AB ring junction with a B ring in a boat conformation. Such a stereochemical situation exists in two natural products: isoaplysin-20 (5) in which Me's attached to C-8 and C-10 have chemical shifts of δ 21.9 and 22.0 (ref 16) and fusidic acid in which Me's attached to C-8 and C-10 have parallel chemical shifts of δ 24 and 23 (ref 17).



i



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