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SESQUITERPENOIDS AND NORSESQUITERPENOIDS FROM THE SOFT CORAL *LEMNALIA AFRICANA*

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ABSTRACT.—Sixteen sesquiterpenoids and norsesquiterpenoids, six of them new, were isolated from the octocoral *Lemnalia africana*. Antileukemia activity (P-388) was found only in the known eremophilane derivative **15**.

Beginning with the isolation of the sesquiterpene alcohol africanol [**1**] from an Indonesian octocoral *Lemnalia africana* (May) (1), this Pacific soft coral and other members of the family Nephteidae have been a source of diverse sesquiterpenoids. The EtOAc extract of *L. africana* from Pohnpei, Micronesia, displayed P-388 antileukemia activity. Fractionation and purification furnished sixteen sesquiterpenoids and norsesquiterpenoids, six of which are new and will be described in this paper. The P-388 activity appeared to be confined to the known 11,12-dihydroxy-6,10-eremophiladiene [**15**] (2).

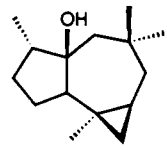
RESULTS AND DISCUSSION

An EtOAc extract of the soft coral *L. africana*, collected by scuba on the east shore of Pohnpei, Micronesia, at −7 m, displayed antileukemia activity in the P-388 assay. Repeated cc, tlc, and hplc of the extract afforded 16 compounds, six of them (**2–7**) new.

^{1}H-nmr and ^{13}C-nmr spectra of the neolemnane **2** displayed signals similar to those of the known compounds **12** and **16** (2). Hreims and ^{13}C-nmr measurements of **2** suggested a formula of $C_{17}H_{24}O_3$ with six degrees of unsaturation. Ir signals at 1737 and 1717 cm^{-1}, coupled with ^{13}C-nmr signals at 76.3, 170.2, and 202.7 ppm, indicated acetoxy and carbonyl functions for **2**. These data together with four signals of olefinic carbons required that **2** was bicyclic. HMQC and HMBC correlation studies allowed unambiguous assignment of all ^{13}C-nmr signals and their connectivities. The value of the diaxial coupling constant (J = 10.0 Hz) of H-12 (from a spin-decoupling experiment) and nOe correlations (Me-15 to H-2; H-12 to H-4; H-6 to H-4) allowed assignment of relative stereochemistry of **2**. The difference of **2** compared to previously reported **12** and **16** (2) was the lack of oxygenation at C-10.

The ir spectrum of aristolane derivative **3** displayed strong absorption at 1730 cm^{-1}. The ^{13}C-nmr spectrum indicated the presence of an ester (171.4 ppm) and a trisubstituted double bond (143.3 and 121.0 ppm). These data and the molecular formula of $C_{17}H_{26}O_2$ derived from hreims required **3** to be tricyclic. The ^{1}H-nmr spectrum revealed three methyl groups (two singlets at 1.10, 1.09 and a doublet at 0.97 ppm), and a methylene group adjacent to an oxygen (3.81 and 3.63 ppm, doublets, J = 10.8 Hz). Detailed analysis of ^{1}H- and ^{13}C-nmr spectra plus HH COSY and HMQC experiments allowed unambiguous assignment of all ^{1}H and ^{13}C signals, leading to a tricyclic skeleton including cyclopropane. This conclusion was further supported by an HMBC spectrum. Placement of the C-C double bond was possible by long-range correlation of H-9 to C-10, C-1, C-5, C-7, and C-8. ^{1}H-nmr spin-decoupling revealed an equatorial Me-14 on the basis of a diaxial H-4–H-3β coupling constant (J = 13.5 Hz). This result together with nOe correlations between H-15 and H-6; H-13 and H-8α, and H-4; H-14 and H-9β, H-3β, H-6 disclosed the relative stereochemistry and established the exo position of the C-12 acetate.

Tricyclic diketone **4** had a molecular formula of $C_{15}H_{22}O_3$ (hreims and ^{13}C-nmr data), requiring five sites of unsaturation. From ir and ^{13}C-nmr data, which suggested



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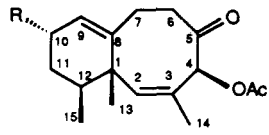
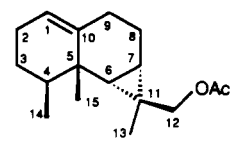


2 R=H
12 R=OH
16 R=OAc



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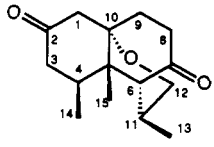

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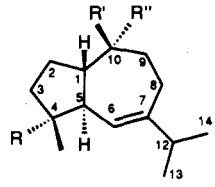
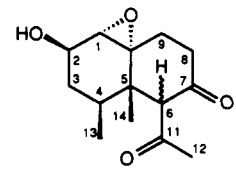
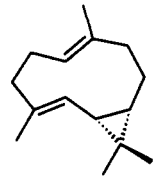


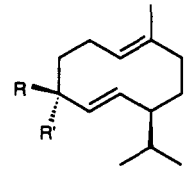
5 R=OAc; R′, R″=CH_2=
18 R=OH; R′, R″=CH_2=
19 R=R′=OH, R″=Me



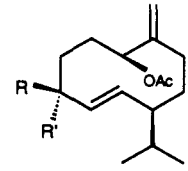
6 H=6β
7 H=6α



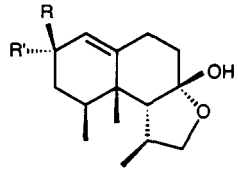
8



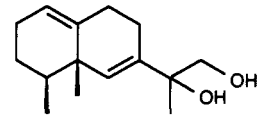
9 R, R′=CH_2
10 R=Me, R′=OH



11 R, R′=CH_2
17 R=Me, R′=OH



13 R=H, R′=OH
14 R, R′=O



15

^{1}H- and ^{13}C-nmr spectra of guaiane derivative **5** displayed strong similarity to those of the known 6,10-guaiadien-4-ol [**18**] (4). The hreims suggested a molecular formula of $C_{17}H_{26}O_2$ with five degrees of unsaturation. On the basis of ^{13}C-nmr signals of two C-C double bonds (153.4, 149.1, 121.3, 106.9 ppm) and an ester carbonyl (170.6 ppm, ν max 1725 cm^{-1}), **5** was bicyclic. A ^{13}C-nmr triplet at 106.9 ppm and, correspondingly, two broad singlets at 4.77 and 4.70 ppm in the ^{1}H-nmr spectrum were indicative of an exocyclic methylene. A methyl group (s, 1.46 ppm) presumably was attached to the carbon bearing the acetoxy group. The nature of the bicyclic system with all carbon connectivities was established by analysis of HMQC and HMBC spectra. Because of full analogy of the spectral data and optical rotation ([α]D 0°) of **5** with the known racemic alcohol **19** (4), these two compounds should have the same relative stereochemistry. The racemic nature of **18** as reported by Bowden *et al.* (4) is based on an X-ray crystallographic analysis carried out on the related diol **19**. While a detailed X-ray structural analysis of diol **19** was not carried out, diol **19** crystallizes in a space group that requires a racemic mixture (J. Clardy, personal communication).

The hreims of nornardosinane derivative **6** indicated a molecular formula of $C_{14}H_{20}O_4$ with five degrees of unsaturation. The ir spectrum showed strong absorptions at 3568 and 1706 cm^{-1} which, coupled with ^{13}C-nmr signals at 205.7, 202.1, and 63.1 ppm, indicated an hydroxyl and two oxo carbonyls. The remaining oxygen atom was part of a trisubstituted epoxide bsed upon ^{1}H- and ^{13}C-nmr signals (δ 3.23 d; 65.1, 59.4 ppm); hence **6** was bicarbocyclic. HMQC and HMBC experiments furnished unambiguous assignment of all ^{13}C-nmr signals. The ^{1}H-nmr spectrum of **6** (in Me_2CO-d_6) and appropriate spin-decoupling experiments proved the regiochemistry. H-2 was equatorial on the basis of two small (J = 6.7 and 1.2 Hz) coupling constants with H_2-3. The coupling constant of H-1 with H-2 (J = 4.4 Hz) and W-coupling with H-3eq (J = 1.2 Hz) indicated an α-epoxide fused to ring A in boat conformation. Furthermore, the diaxial coupling of H-4 with H-3ax (J = 12.8 Hz) established the equatorial conformation of Me-13. The ^{1}H-nmr spectrum of **6** showed W coupling (J = 1.6 Hz) between H-6eq and H-8eq implying a C-6 alpha substituent. These assignments were supported by an nOe experiment, which showed correlations of Me-13 to H-6, and Me-14 to H-9ax. [After this paper was submitted D. Green and Y. Kashman (*J. Nat. Prod.*, **55**, 1186, 1992) reported the isolation of what appears to be the C-2 epimer of **6**.]

A slightly more polar isomeric nornardosinane **7** had analogous spectral features. However, lack of W coupling between H-6 and H-8eq and absence of an nOe between Me-13 and H-6 pointed to H-6ax. Although compounds **6** and **7** are 1,3-diketones, ^{1}H-nmr spectra (in $CDCl_3$) did not show the presence of an enol. However, adsorption of **6** on Si gel for 5 h resulted in epimerization at C-6 and afforded a mixture of both compounds in approximate ratio 8:2 (**6**:**7**). Therefore, generation of **7** from **6** during isolation cannot be excluded.

In addition to the six new compounds **2–7**, several known sesquiterpenoids were isolated from this specimen of *L. africana*. They were: bicyclogermacrene [**8**] (5), germacrene D [**9**] (6), 1,6-germacradien-5-ol [**10**] (7), 1(11),5(12),6-germacratrien-2-ol acetate [**11**] (8), 4-acetoxy-10-hydroxy-5-oxo-2,8-neolemnadiene [**12**] (2), lemnacarnol [**13**] (9), 2-oxolemnacarnol [**14**] (5,9), 11,12-dihydroxy-6,10-eremophiladiene [**15**] (2), 4,10-diacetoxy-5-oxo-2,8-neolemnadiene [**16**] (2), and 2-acetoxy-1(11),6-germacradien-5-ol [**17**] (7).

The biologically active component of the extract of *L. africana* was eremophilane-derived diol **15** (2). This compound displayed activity against leukemia in the P-388 assay at 1 μg/ml. Its cytotoxicity in the CV-1 assay was 10 μg/ml.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were measured in $CHCl_3$ solution on Perkin-Elmer 1420 or Nicolet 5-MX Ft-ir spectrometers. Uv spectra were taken in MeOH on a Hewlett Packard 8452A spectrophotometer. ^{1}H-nmr spectra were recorded at 500 MHz and ^{13}C-nmr spectra at 125 MHz on a General Electric GE Ω-500 in $CDCl_3$, unless otherwise stated. Mass spectra were obtained with a VG 70/SE mass spectrometer by electron impact. Optical rotations were determined on a Japan Spectroscopic DIP-370 polarimeter at 25°. All solvents were distilled prior to use. The yield of each compound is based on the weight of the initial extract.

ISOLATION.—*L. africana* was collected by SCUBA on the east shore of Pohnpei, Federated States of Micronesia, in June 1990, at −7 m. The soft coral was frozen on collection, identified by Dr. Y. Benayahu of Tel-Aviv University, and lyophilized to yield 103.0 g of dry mass, which was extracted thrice with EtOAc, followed by removal of the solvent in vacuo. The extract (13.3 g) was subjected to Si gel flash chromatography and rapidly eluted with a step gradient of EtOAc in hexane.

The fraction eluted with hexane-EtOAc (95:5) (3.46 g) was subjected to RP-18 flash chromatography. The fraction eluted with MeCN was purified by hplc on RP-18 in MeCN.

4-Acetoxy-2,8-neolemnadien-5-one [**2**].—Oil (32 mg, 0.24%): $[\alpha]_D$ +441° (c = 0.2, $CHCl_3$); uv λ max 286 nm (ε 205); hrms $[M]^+$ 276.1726 (5%) (calcd for $C_{17}H_{24}O_3$, 276.1726); ir ν max 1737, 1717 cm^{-1}; ^{1}H nmr δ 6.42 (1H, s, H-4), 5.69 (1H, m, H-9), 5.48 (1H, bs, H-2), 2.63 (1H, dd, J = 5.0, 2.4 Hz, H-6), 2.61 (1H, dd, J = 8.5, 5.0 Hz, H-6), 2.38 (1H, m, H-7), 2.17 (2H, m, H-10), 2.10 (3H, s, Ac), 2.09 (1H, m, H-7), 1.91 (1H, ddq, J_q = 7.0, J_d = 10.0, 5.0 Hz, H-12), 1.68 (3H, d, J = 1.5 Hz, H-14), 1.53 (2H, m, H-11), 1.01 (3H, s, H-13), 0.94 (3H, d, J = 7.0 Hz, H-15); ^{13}C-nmr δ 202.7 (C-5), 170.2 (Ac), 144.6 (C-8), 139.4 (C-2), 126.3 (C-3), 124.4 (C-9), 76.3 (C-4), 44.4 (C-6), 43.6 (C-1), 39.0 (C-12), 28.3 (C-7), 27.0 (C-11), 25.3 (C-10), 22.5 (C-13), 20.6 (Ac), 18.3 (C-14), 17.0 (C-15).

12-Acetoxy-1(10)-aristolene [**3**].—Colorless oil (65 mg, 0.48%): $[\alpha]_D$ −62° (c = 1.0, $CHCl_3$); hrms $[M]^+$ 262.1934 (10%) (calcd for $C_{17}H_{26}O_2$, 262.1932); ir ν max 1730 cm^{-1}; ^{1}H nmr δ 5.27 (1H, dd, J = 2.2, 4.5 Hz, H-1), 3.81 (1H, d, J = 10.8 Hz, H-12), 3.63 (1H, d, J = 10.8 Hz, H-12), 2.25 (1H, m, H-9β), 2.05 (3H, s, Ac), 2.02 (1H, m, H-8β), 1.96 (2H, m, H-2), 1.77 (1H, ddd, J = 13.0, 5.7, 1.2 Hz, H-9α), 1.72 (1H, ddq, J_q = 7.0, J_d = 13.5, 7.5 Hz, H-4), 1.44 (2H, m, H-3), 1.43 (1H, m, H-8α), 1.10 (3H, s, H-13), 1.09 (3H, s, H-15), 0.97 (3H, d, J = 7.0 Hz, H-14), 0.95 (1H, ddd, J = 9.5, 8.9, 2.9 Hz, H-7), 0.76 (1H, d, J = 9.5 Hz, H-6); ^{13}C nmr δ 171.4 (AcO), 143.3 (C-10), 121.0 (C-1), 75.5 (C-12), 36.5 (C-4), 36.3 (C-5), 30.9 (C-6), 29.5 (C-9), 27.1 (C-3), 25.6 (C-2), 22.7 (C-14), 22.4 (C-11), 21.0 (Ac), 19.9 (C-8), 16.8 (C-7), 15.7 (C-15), 12.3 (C-13).

4-Acetoxy-6,10-guaiadiene [**5**].—Oil (3 mg, 0.02%): $[\alpha]_D$ 0° (c = 0.1, $CHCl_3$); hrms $[M]^+$ 262.1936 (10%) (calcd for $C_{17}H_{26}O_2$, 262.1932); ir ν max 1725 cm^{-1}; ^{1}H nmr δ 5.58 (1H, d, J = 3.1 Hz, H-6), 4.77 (1H, bs, H-11), 4.70 (1H, bs, H-11), 2.55 (1H, m, J = 12.9, H-5), 2.50 (1H, m, H-9α), 2.27 (1H, m, H-1), 2.26 (1H, m, H-3), 2.22 (1H, m, H-8β), 2.12–1.97 (4H, m, H-3, H-8α, H-9β, H-12), 1.98 (3H, s, AcO), 1.88 (1H, m, H-2), 1.78 (1H, m, H-2), 1.46 (3H, s, H-15), 1.01 (3H, d, J = 6.5 Hz, H-13), 1.00 (3H, d, J = 6.5 Hz, H-14); ^{13}C nmr δ 170.6 (AcO), 153.4 (C-10), 149.1 (C-7), 121.3 (C-6), 106.9 (C-11), 89.8 (C-4), 53.4 (C-5), 45.9 (C-1), 37.5 (C-12), 37.2 (C-3), 36.9 (C-9), 29.7 (C-8), 25.7 (C-2), 22.3 (AcO), 21.5, 21.3 (C-13, C-14), 21.1 (C-15).

1,6-Germacradien-5-ol [**10**].—Compound **10** (43 mg, 0.32%): spectral data identical with literature (7).

1(11),5(12),6-Germacratrien-2-ol acetate [**11**].—Compound **11** (27 mg, 0.20%): spectral data identical with reported data (8).

The fraction eluted with EtOAc/hexane (6:4) was evaporated (3.8 g) and subjected to cc on Si gel and eluted with a step gradient of EtOAc in CH_2Cl_2. The fraction eluted with EtOAc-CH_2Cl_2 (2:8) was purified using Sephadex LH-20 [MeOH-CH_2Cl_2 (1:1)] followed by RP-18 (elution with MeCN) to yield 900 mg oily residue after evaporation. Part of this product (180 mg) was subjected twice to preparative tlc on silica using toluene-EtOAc (1:1) and hexane-EtOAc (1:1) as developers, which yielded three compounds, **4**, **12** and **15**.

2,7-Nardosinoxanedione [**4**].—White, semicrystalline (9 mg, 0.33%): $[\alpha]_D$ +87° (c = 0.3, $CHCl_3$); uv λ max 286 nm (ε 107); ir ν max 1710 cm^{-1}; hrms $[M]^+$ 250.1518 (100%) (calcd 250.1569); ^{1}H nmr δ 3.91 (1H, dd, J = 6.8, 12.7 Hz, H-12eq), 3.60 (1H, dd, J = 12.7, 12.3 Hz, H-12ax), 2.93 (1H, ddq, J_q = 7.1, J_d = 5.2, 12.3 Hz, H-4), 2.66 (1H, dddd, J = 19.2, 8.4, 3.1, 1.2 Hz, H-8eq), 2.50 (1H, d, J = 5.1, H-6), 2.42 (2H, m, H-11 and H-8ax), 2.39 (2H, s, H-1), 2.28 (1H, dd, J = 14.8, 5.2 Hz, H-3eq), 2.23 (1H, dd, J = 14.8, 12.3 Hz, H-3ax), 2.10 (2H, m, H-9), 1.00 (3H, s, H-15), 0.88 (3H, d, J = 7.1 Hz, H-14), 0.73 (3H, d, J = 6.7 Hz, H-13); ^{13}C nmr δ 211.5 (C-7), 207.7 (C-2), 78.0 (C-10),

67.6 (C-12), 56.8 (C-6), 50.2 (C-1), 44.8 (C-3), 40.0 (C-5), 39.0 (C-8), 31.8 (C-4), 31.5 (C-9), 25.9 (C-11), 16.0 (C-15), 14.8 (C-13), 14.2 (C-14).

4-Acetoxy-10-hydroxy-5-oxo-2,8-neolemnadiene [**12**] (67 mg, 2.5%), was identified by comparing its spectral data with reported values (2). For *11,12-Dihydroxy-6,10-eremophiladiene* [**15**] (12 mg, 0.45%), spectral data were identical with those reported (2).

Lemnacarnol [**13**] (80 mg, 0.60%) was obtained from a fraction eluted with EtOAc by crystallization from $CHCl_3$. Spectral data were identical with those reported (9). 2-Oxolemnacarnol [**14**] (200 mg, 3.0%) crystallized in the refrigerator from a fraction eluted with EtOAc-CH_2Cl_2 (4:6) after solvent evaporation. Spectral data were identical with reported values (5).

1(10)-Epoxy-2-hydroxy-12-nornardosin-7,11-dione [**6**,**7**].—The fraction eluted with EtOAc (1.75 g) was evaporated and subjected to crystallization in C_6H_6. Crude lemnacarnol [**13**] was removed and the mother liquor (1.07 g) was subjected to silica flash chromatography. Elution with hexane–*t*-BuOH (4:6) followed by hplc on RP-18 in MeCN afforded 12 mg (0.09%) of **6** as a yellow oil: $[\alpha]_D$ −307° (*c* = 1.0, $CHCl_3$); uv λ max 298 nm (ε 193); ir ν max 3568, 1706 cm^{-1}; hrms $[M]^+$ 252.1368 (10%) (calcd for $C_{14}H_{20}O_4$, 252.1361); ^1H nmr ($CDCl_3$) δ 4.04 (1H, bs, H-2), 3.78 (1H, d, *J* = 1.6 Hz, H-6), 3.23 (1H, dd, *J* = 4.4, 0.9 Hz, H-1), 3.15 (1H, ddd, *J* = 14.4, 13.4, 8.0, H-8ax), 2.46 (1H, ddd, *J* = 14.4, 13.4, 5.5 Hz, H-9ax), 2.39 (1H, ddt, J_d = 14.4, 5.5, J_t = 1.6 Hz, H-8eq), 2.27 (3H, s, H-12), 2.17 (1H, ddq, J_q = 6.8, J_d = 6.1, 10.3 Hz, H-4), 1.59 (1H, ddd, *J* = 14.4, 8.0, 1.6 Hz, H-9eq), 1.48 (1H, m, H-3), 1.45 (1H, m, H-3), 0.91 (3H, s, H-14), 0.82 (3H, d, *J* = 6.8 Hz, H-13); ^1H nmr (Me_2CO-d_6) δ 4.02 (1H, bdd, *J* = 6.7, 4.4 Hz, H-2), 3.65 (1H, d, *J* = 1.6 Hz, H-6), 3.11 (1H, dd, *J* = 4.4, 1.2, H-1), 3.07 (1H, ddd, *J* = 14.7, 13.3, 7.7 Hz, H-8ax), 2.83 (1H, bs, OH), 2.53 (1H, ddd, *J* = 14.5, 13.3, 5.9 Hz, H-9ax), 2.30 (1H, ddt, *J* = 14.7, 5.9, 1.6 Hz, H-8eq), 2.25 (3H, s, H-12), 2.22 (1H, m, H-4), 1.57 (1H, ddd, *J* = 15.1, 12.8, 6.7 Hz, H-3ax), 1.47 (1H, ddd, *J* = 14.5, 7.7, 1.6 Hz), 1.34 (1H, ddt, J_d = 15.1, 3.8, J_t = 1.2 Hz, H-3eq), 0.90 (3H, s, H-14), 0.82 (3H, d, *J* = 6.7 Hz, H-13); ^{13}C nmr ($CDCl_3$) δ 205.7 (C-7), 202.1 (C-11), 72.7 (C-6), 65.1 (C-10), 63.1 (C-2), 59.4 (C-1), 43.2 (C-5), 36.4 (C-8), 35.7 (C-3), 32.8 (C-12), 30.1 (C-9), 25.0 (C-4), 17.7 (C-14), 15.4 (C-13).

Elution with hexane–*t*-BuOH (2:8) followed by hplc on RP-18 in MeCN afforded 5 mg of **7** (0.04%) as a yellow oil: $[\alpha]_D$ −78° (*c* = 0.3, $CHCl_3$); hrms $[M]^+$ 252.1358 (20%) (calcd for $C_{14}H_{20}O_4$, 252.1361); ^1H nmr δ 4.09 (1H, m, H-2), 3.73 (1H, s, H-6), 3.41 (1H, dd, *J* = 4.7, 1.3 Hz, H-1), 2.73 (1H, ddd, *J* = 13.7, 13.3, 5.5 Hz, H-8ax), 2.51 (1H, m, H-8eq), 2.50 (1H, m, H-9ax), 2.24 (3H, s, H-12), 2.06 (1H, ddq, J_q = 6.7, J_d = 13.0, 2.7 Hz, H-4), 1.51 (1H, ddd, *J* = 15.0, 13.0, 5.8 Hz, H-3ax), 1.48 (1H, m, H-9eq), 1.35 (1H, dddd, *J* = 15.0, 2.7, 1.3, 1.1 Hz, H-3eq), 1.21 (3H, s, H-14), 0.72 (3H, d, *J* = 6.7, H-13); ^{13}C nmr δ 206.4 (C-7), 205.4 (C-11), 69.5 (C-6), 68.1 (C-10), 63.8 (C-1), 63.0 (C-2), 44.9 (C-5), 38.5 (C-8), 36.5 (C-3), 34.1 (C-12), 30.6 (C-4), 29.7 (C-9), 17.8 (C-13), 14.2 (C-14).

Bicyclogermacrene [**8**] *and germacrene D* [**9**].—The fraction eluted with hexane (90 mg) was subjected to Si gel flash cc and afforded 85 mg of an oil (eluted with hexane). This mixture was then purified twice by hplc on silica in hexane, yielding 6 mg (0.04%) of **8**. Spectral data were identical with reported values (5).

Purification of the oil by hplc on silica in hexane, followed by hplc on RP-18 in MeCN afforded 23 mg (0.17%) of **9**, with spectral data as previously reported (6).

4,10-Diacetoxy-5-oxo-2,8-neolemnadiene [**16**] *and 2-acetoxy-1(11),6-germacradien-5-ol* [**17**].—The fraction eluted with hexane-EtOAc (7:3) (1.15 g) was subjected to RP-18 cc. The fraction eluted with MeCN was purified twice by hplc on RP-18 using MeCN and MeCN-H_2O (4:1), which afforded 36 mg (0.27%) of **16** (2) and 19 mg (0.14%) of **17** (7).

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