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(+)-CORALLOIDIN-A AND (−)-CORALLOIDIN-B, TWO NEW SESQUITERPENOIDS FROM THE MEDITERRANEAN ALCYONACEAN *ALCYONIUM CORALLOIDES*

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ABSTRACT.—The Mediterranean alcyonacean *Alcyonium coralloides* is shown here to contain two novel sesquiterpenoids, (+)-coralloidin-A and (−)-coralloidin-B, for which we propose the structures (+)-eudesma-5,7(11)-dien-8β-yl acetate [(+)-**1a**] and (−)-bicyclogermacra-1,4-dien-12-yl acetate [(−)-**2a**]. Compound (+)-**1a** is the first naturally occuring 5,6-dehydroeudesmane to be described.

The distribution of alcyonaceans is primarily in tropical seas, except the Caribbean, and typically such tropical animals contain diterpenoids or sesquiterpenoids. Many of the diterpenoids are of the cembrane type (1) though xenicanes (2) and seco-xenicanes (3) are also encountered. The sesquiterpenoids often encountered with tropical alcyonaceans are capnellanes (4), eremophilanes and neolemnanes (5), copaanes and ylanganes (6), africanes (7), aristolanes (8), nardosinanes (9), germacranes and guaianes (10), and cyclic furanosesquiterpenoids (11). Finally, tropical alcyonaceans also contain degraded sesquiterpenoids, such as the trinor sesquiterpene 1,4-dimethyl-2,3,3a,4,5,6-hexahydroazulene (12) and a nor nardosinane (13).

The Mediterranean is populated by only a few species of alcyonaceans, and organic chemical work has only been reported for the abundant *Alcyonium palmatum*, which has been shown to contain a simple linear furanosesquiterpenoid (14).

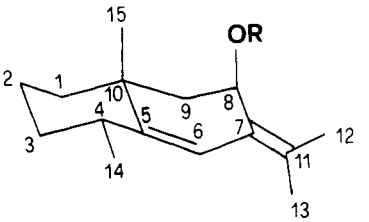
We report here on two new sesquiterpenoids isolated from a Mediterranean collection of the less abundant alcyonacean *Alcyonium* (=*Parerythropodium*) *coralloides* Pallas (Cnidaria, Anthozoa, Alcyonacea, Alcyoniidae). In the most common form, *A. coralloides* is a beautiful cardinal-red alcyonacean with white polyps, living either on rock or Phaeophyceae, usually of the genera *Sargassum* and *Cystoseira*, or gorgonians of the genera *Eunicella, Paramuricea,* and *Lophogorgia* (15). It is from the latter habitat that *A. coralloides* is relatively easy to collect by scuba diving. In our case, gorgonians of the genus *Eunicella* were always the substrate.

RESULTS AND DISCUSSION

The first compound isolated in pure form was (+)-coralloidin-A [(+)-**1a**], for which mass spectral and nmr data indicated the composition $C_{17}H_{26}O_2$, i.e., five unsaturations. Uv spectra suggested a *trans*-diene system, which, in order to rationalize the ^{1}H-nmr spectrum, must be 1,1′-dimethyl-2,4,4′-trialkyl substituted. Also, in agreement with ir spectral data, an acetoxyl group was revealed, and, consequently, the compound must be bicyclic. The ^{1}H-nmr data, which revealed two methyl groups, one at a tertiary carbon and the other one at a quaternary carbon, also suggested that the methine carbon of a H_2C-CH-OAc unit, showing up as the X part of an ABX system,[1] is bound to C-2 of the diene system. Joining the 4-carbon substituent with the H_2C-CH-OAc methylene leads to a cyclohexene ring bearing a conjugated *exo*-dimethylmethylene and fused, via the cyclohexene carbon and the adjacent quaternary carbon, to the other ring, which must be a cyclohexane.

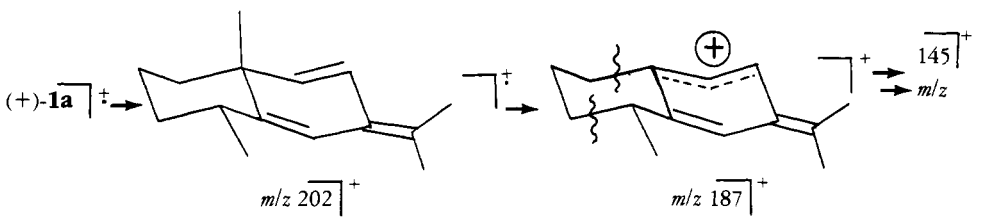
[1]The ABX system is supported by double irradiation at δ 6.15 (H-8) whereby the dd's; at δ 2.12 (H_b-9) and 1.50 (H_α-9) became an AB system, J=14.6. Correspondingly, on double irradiation at either δ 2.12 or 1.50, the δ 6.15 dd became a d with J=2.5.

At this point, a literature search for model compounds brought to our attention the enone (4aα,8β)-4a,8-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone, isolated from the terrestrial plant *Vetiveria zizanoides* (16) and also obtained by synthesis (17). In fact, ^{13}C-nmr data for (+)-coralloidin-A proved similar, as concerns the bicyclic system, to those for the model compound (17). This suggested an eudesmane structure, uncommonly dehydrogenated at C-5-C-6, for (+)-coralloidin-A, and, in fact, we show below that all our data fit the structure (+)-**1a**.[2]



(+)-**1a** R=Ac
(+)-**1b** R=H

The mass spectrum is in agreement with structure (+)-**1a** substantially because of allylic-assisted breaking of both the C-3-C-4 and the C-10-C-1 bond in the *m/z* 187 fragment ion to give the *m/z* 145 ion (Scheme 1). This, in accordance with the ^{13}C-nmr data, suggests that a methyl substituent is at C-4. The tertiary nature of C-4 is supported by experiments of double irradiation at δ 2.18 (H-4), whereby the doublet for the methyl at C-4 changed into a singlet.



SCHEME 1. Proposed mass spectral fragmentation of coralloidin-A [(+)-**1a**].

^{1}H-nmr data in C_6D_6, in the presence of the shift reagent Eu(fod)$_3$, for the product, (+)-**1b**, of hydrolysis of (+)-**1a** proved the relative configurations. Thus, we observed a downfield shift, in decreasing order of magnitude, of the signals assigned to H-8>H_β-9>H_3-15>H-6≃H_α-9≃H_3-12>H-4>H_3-13>H_3-14. This is clearly only consistent with the β and α positions for C-15 and C-14, respectively.

A few dehydroeudesmanes have been isolated from terrestrial plants, such as (+)-selina-4(14),7(11)-dien-8-one, from *Atractylodes japonica* (Compositae) (18). Also, a few marine eudesmanes (selinanes) are known. They have been isolated from Rhodophyta of the genus *Laurencia*, as well as from Opisthobranchia of the genus *Aplysia* (19). Moreover, during the preparation of this manuscript, it was reported that an Australian alcyonacean, *Nephthea* sp., contains both eudesma-4,7(11)-diene-8β-ol and the corresponding 8-keto derivative (20). In conclusion, (+)-**1a** is the first described, naturally occurring 5,6-dehydroeudesmane. It is curious that (+)-**1a** has been isolated from a member of a phylum where the eudesmanes are most rarely encountered.[3] Previously, 5,6-dehydroeudesmanes were only known as products of the chemical transformation of "terrestrial" eremophilanolides (21,22).

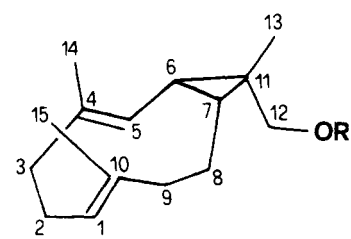
[2]No absolute configuration significance is to be attached to any of the structural formulae given here.

[3]Implicitly, this rules out the origin of (+)-**1a** from the close living gorgonian, which belongs to the same phylum as the soft coral. We will see that a similar conclusion applies as to the origin of (−)-**2a**.

Next, (−)-coralloidin-B was examined. Mass spectra indicated the composition $C_{17}H_{26}O_2$, i.e., five unsaturations. As ^{1}H-nmr spectra revealed an acetoxymethyl group, two trisubstituted double bonds bearing a methyl group each, and a methyl group at a quaternary carbon, the compound must be bicyclic. It is suggested that one ring is a cyclopropane (and consequently the other ring a cyclodecadiene) because of a signal at δ 0.58 in the ^{1}H-nmr spectrum. The presence of the small ring is further supported by two doublets at δ 30.6 and 27.9 and a singlet at δ 23.4 in the ^{13}C-nmr spectrum. This also implies that the cyclopropane ring is tetrasubstituted, bearing geminal methyl and acetoxymethyl groups.

The relatively low field resonance (δ 1.39 dd) for the other cyclopropane proton suggests conjugation with a carbon-carbon double bond in the larger ring. Moreover, a H-5/H-6 coupling of 11.5 Hz, implying a *trans*-periplanar relationship of these protons (23), indicates that the methyl group at such a double bond is in the β-position with respect to the cyclopropane ring.

The complete structural assignment of (−)-coralloidin-B as the bicyclogermacrene (−)-**2a** is derived from double resonance experiments, COSY 2D, differential nOe's, and ^{1}H-nmr spectra of the hydrolysis product (−)-deacetylcoralloidin-B [(−)-**2b**] in the presence of a shift reagent. Thus, on irradiation at δ 4.37 d (H-5), the resonance for the C-14 methyl changed from a doublet to a singlet, while the δ 1.39 doublet of doublets became a doublet with loss of a coupling constant of 11.5 Hz. Moreover, on irradiation at δ 0.58 (H-7), the δ 1.39 doublet of doublets became a doublet, with a loss of a coupling constant of 8.5 Hz, while the δ 1.19 dddd (H_α-8) became a ddd with loss of a coupling constant of 12.0 Hz and a ddd system was seen to emerge at δ 1.85 (H_β-8), J= 14.0, 3.5, 3.5. This served to establish the connectivity C-14-C-4-C-5-C-6-C-7-C-8. Moreover, the 90/45 COSY experiments reveal that δ 1.19 (H_α-8) is connected to the signals at the following δ: 0.58 (H-7), 1.59 (H_β-9), 1.85 (H_β-8), and 2.36 (H_α-9). This extends the connectivity of C-8 to C-9 as in structure (−)-**2a**.



(−)-**2a** R=Ac
(−)-**2b** R=H

The 90/45 COSY experiments also show that δ 4.68 (H-1) is correlated with δ 1.40 (H_3-15), δ 2.07 (H_β-2), and δ 1.9 (H_α-2), while the latter two signals are correlated with both δ 1.7 and δ 1.9 (H_α-3 and H_β-3, or vice-versa). This establishes the C-15-C-10-C-1-C-2-C-3 connectivity.

The connectivities C-9-C-10 and C-3-C-4 were established by differential nOe's. On irradiation at δ 4.68 (H-1) a ca. 4%, positive nOe showed up at δ 2.36 (H_α-9), 1.89 (H_α-2), and 1.19 (H_α-8) whereas on irradiation at δ 4.37 (H-5) a ca. 3%, positive nOe showed up at δ 1.76 (H_α-3) and 1.19 (H_α-8).

This establishes the gross structure of (−)-coralloidin-B whereas the configurations at C-11 and the double bonds were established as follows. On irradiation of (−)-coralloidin-B at δ 4.27 (H_2-12) a 8% differential, positive nOe was revealed at δ 1.19 (H_α-8) whereas on irradiation at δ 1.10 (H_3-13) a 10% differential, positive nOe showed up at δ 0.58 (H-7). This clearly establishes the configuration at C-11 as in (−)-**2a**, which

is also in accordance with ^{1}H-nmr spectra of the hydrolysis product (−)-deacetylcoralloidin-B [(−)-**2b**] in the presence of Eu(fod)$_3$. In fact, in this case we observed a downfield shift, in the order of decreasing magnitude, of the signals assigned to H_2-12>H_3-13>H-5>H-6>H_3-14>H_3-15 ≃H-1. This trend also suggests the *E*-configuration at both double bonds in the conformation shown in (−)-**2b**. That both double bonds have the *E*-configuration is also in accordance with the relatively high-field resonances of the two methyl groups (see Experimental section).

The above conclusions are in accordance with ^{1}H- and ^{13}C-nmr assignments for other bicyclogermacrenes. These include the $(OAc)_\alpha$-3 isomer of (−)-**2a**, isolated from the Australian *Parerythropodium fulvum* (24), the parent hydrocarbon, bicyclogermacrene, isolated from both the terrestrial fruit *Citrus junos* (25) and the marine sponge *Axinella cannabina* (26).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Uv and ir spectra were taken on a Beckmann DB-4 and a Perkin-Elmer 337 spectrophotometer, respectively. Nmr spectra were taken with either a Varian CFT-20 (^{13}C at 20 MHz, with a microinsert, multiplicities from off-resonance decoupling; ^{1}H at 80 MHz) or a Varian XL-300 (^{1}H at 300 MHz) spectrometer. Chemical shifts are given in parts per million (δ) from internal TMS (^{1}H) or C_6D_6, taken as 128.0 (^{13}C), while coupling constants, *J*, are given in Hz. Mass spectra were taken with either a home-made spectrometer, based on the ELFS 4-162-8 Extranuclear quadrupole, or [for high resolution and linked scans (B/E)] a VG ZAB2F spectrometer in the DEI mode (27). Hplc was carried out on either a 25×1 cm Merck LiChrosorb Si60 column, 7 μm, or a 25×1 cm Merck LiChrosorb RP-18 column, 7 μm, 5 ml/min solvent flow in both cases, monitoring by uv absorption at 254 nm.

ISOLATION OF (+)-**1a** AND (−)-**2a**.—Specimens of *A. coralloides* were collected in the French East Pyrenean Mediterranean area, by scuba diving, at depths of 20-35 m, in July 1983, and August 1984. Vouchers of this animal are in the possession of Dr. S. Winberg, Ecole Europeenne, Bd. K. Adenauer, L-115 Luxenbourg. When found in contact with *Eunicella* colonies, *A. coralloides* was immediately separated. Then, the alcyonacean, still on the skeleton of the dead gorgonian, was immersed in 95% EtOH. Five 1.5-liter vessels of closely packed specimens were thus obtained and stored at low temperature in the dark. After a few days, the extraction solvent was decanted and filtered, the whole procedure being repeated four times. The solvent was evaporated at 20 torr, and the aqueous residue was throughly extracted with petroleum ether (bp 40-70°). Evaporation lead to a viscous, dark oil (18 g) that was column chromatographed on 0.5 kg of Merck Kieselgel 60, 70-230 mesh, petroleum ether/Et_2O gradient elution, starting from neat petroleum ether. With petroleum ether-Et_2O (9:1), (+)-**1a** and (−)-**2a** were collected together. This mixture was subjected to hplc with *n*-hexane-THF (99:1), collecting (+)-**1a** (0.036 g, 0.20%) at 6 min and (−)-**2a** (0.028 g, 0.016%) at 7 min.

(+)-CORALLOIDIN-A [(+)-EUDESMA-5,7(11)-DIEN-8β-YL ACETATE] [(+)-**1a**].—Semisolid oil; $[\alpha]^{20}D$ +225° (0.08, cyclohexane); ir (liquid film) 2917s, 1734vs, 1457m, 1244m, 1030m, 760m cm^{-1}; uv λ max (ε) (cyclohexane) 249 (22,500); ^{1}H nmr (80 MHz, C_6D_6) δ 6.19 (1H, s, H-6), 6.15 (1H, X part of ABX, as dd, *J*=2.6, 2.5, H-8), 2.18 (1H, m, H-4), 2.12 (1H, A part of ABX, as dd, *J*=14.6, 2.5, H_β-9), 1.75, 1.67 (each 3H, s, H_3-12 and H_3-13), 1.73 (3H, s, acetyl methyl), 1.50 (this signal emerges from the signals that follow; 1H, B part of ABX, as dd, *J*=14.6, 2.5, H_α-9), 1.25 (3H, s, H_3-15), 1.05 (3H, d, $J_{14,4}$=6.4, H_3-14), 1.7-1.1 (6H, series of m, H_2-1, H_2-2, and H_2-3); ^{13}C nmr (C_6D_6) δ 169.5 (s, C=O), 147.3 (s, C-5), 131.4 (s, C-7), 127.4 (s, C-11), 115.4 (d, C-6), 67.9 (d, C-8), 44.2 (t, C-9), 43.0 (t, C-1), 37.5 (t, C-3), 34.3 (s, C-10), 33.6 (d, C-4), 25.2 (q, C-12), 22.1 (t, C-2), 21.0 (q, acetyl methyl), 20.6 (q, C-15), 19.9 (q, C-14), 18.9 (q, C-13); ms *m/z* (rel. int.) 262 ($M^{+\cdot}$, 4), 202 (it was the only signal observed on B/E linked scans, $M^{+\cdot}$-AcOH, 79), 187 (100), 173 (8), 159 (25), 145 (41), 131 (67), 119 (13), 105 (23), 91 (23), 77 (8), 55 (8), 43 (33); hrms 262.1939±0.005 (calcd. for $C_{17}H_{26}O_2$, $M^{+\cdot}$, 262.19327).

HYDROLYSIS OF (+)-CORALLOIDIN-A TO (+)-**1b**.—A solution of (+)-**1a**, 0.015 g, in 2 ml of 2% methanolic KOH was heated at reflux for 2.5 h. The mixture was neutralized with concentrated HCl, decanted from the precipitated salt, evaporated, and subjected to hplc, eluent 85:15 *n*-hexane-diisopropyl ether (85:15), to give (+)-**1b**, 0.0058 g (47%).

(+)-DEACETYLCORALLOIDIN-A [(+)-**1b**)].—Semisolid oil; $[\alpha]^{20}D$ +262.0 (0.07, cyclohexane); uv λ max (ε) (cyclohexane) 248 (15,900); ^{1}H nmr (80 MHz, C_6D_6) δ 6.16 (1H, br. s, H-6), 4.72 (1H, X part of ABX, as a br. dd, *J*=3.0, 3.0, H-8), 2.20 (1H, m, H-4), 1.96 (1H, A part of ABX, as a dd,

J_{gem}=14.4, J_{AX}=3.0, H_β-9), 1.69 (6H, s, H_3-12 and H_3-13), 1.43 (3H, s, H_3-15), 1.08 (3H, d, J=6.4, H_3-14), 1.9-1.0 (8H, series of m, H_2-1, H_2-2, H_2-3, H_α-9 and OH); ^{13}C nmr (C_6D_6) δ 147.7 (s, C-5), 131.8 (s, C-7), 128.8 (s, C-11), 114.6 (d, C-6), 65.5 (d, C-8), 46.7 (t, C-9), 43.6 (t, C-1), 37.7 (t, C-3), 34.5 (s, C-10), 33.6 (d, C-4), 25.8 (q, C-12), 22.1 (t, C-2), 20.2 (q, C-15), 19.8 (q, C-14), 19.0 (q, C-13); ms *m/z* (rel. int.) 220 (M^+, 7), 202 (56), 187 (100), 173 (10), 159 (22), 147 (18), 145 (49), 131 (87), 105 (23), 91 (21).

(−)-CORALLOIDIN-B [(−)-BICYCLOGERMA-1,4-DIEN-12-YL ACETATE] [(−)-**2a**].—Semisolid oil; $[\alpha]^{20}D$ −33.2° (0.30, cyclohexane); ir (liquid film) 2917s, 1739vs, 1447m, 1364m, 1240m, 1030m, 853m; uv λ max (ε) (cyclohexane) 227 (3,900); ^{1}H nmr (300 MHz, C_6D_6) δ 4.68 (1H, br. ddq, J=10.5, 5.0, 1.4, H-1), 4.37 (1H, br. d, $J_{5,6}$=11.5, H-5), 4.29, 4.26 (2H, AB, J=11.7, H_2-12), 2.36 (1H, br. d, J_{gem}=12.5, H_α-9), 1.70 (3H, s, acetyl methyl), 1.59 (1H, ddd, J_{gem}=12.5, $J_{9\beta,8\alpha}$=12.0, $J_{9\beta,8\beta}$=4.0, H_β-9), 1.56 (3H, d, $J_{14,5}$=1.4, H_3-14), 1.40 (3H, br. d, $J_{15,1}$=1.4, H_3-15), 1.39 (1H, dd, $J_{6,5}$=11.5, $J_{6,7}$=8.5, H-6), 1.19 (1H, dddd, J_{gem}=14.0, J=12.0, 12.0, 4.5, H_α-8), 1.10 (3H, s, H_3-13), 0.58 (1H, ddd, $J_{7,8\alpha}$=12.0, $J_{7,6}$=8.5, $J_{7,8\beta}$=2.5, H-7); the following signals, though superimposed to other signals, were assigned by differential nOe: 2.07 (1H, H_β-2), 1.9 (1H, H_β-3), 1.89 (1H, H_α-2), 1.85 (1H, H_β-8), 1.76 (1H, H_α-3); ^{13}C nmr (C_6D_6) (the assignments of C-2, C-3, C-8, and C-9 are tentative) δ 170.1 (s, C=O), 139.9 (s, C-4), 128.8 (s, C-10), 125.6, 125.0 (two d, C-1, C-5, or vice versa), 65.8 (t, C-12), 41.3 (t, C-8), 37.4 (t, C-2), 30.6 (d, C-6), 27.9 (d, C-7), 26.8, 26.3 (two t, C-9, C-3, or vice versa), 24.8 (q, C-13), 23.4 (s, C-11), 21.0 (q, C-15), 20.5 (q, acetyl methyl), 16.6 (q, C-14); ms *m/z* (relative intensity) 262 (M^+, 2), 202 (34), 187 (33), 173 (7), 159 (21), 145 (27), 134 (41), 121 (100), 119 (82), 105 (62), 93 (89), 91 (58), 79 (58), 67 (33), 55 (48), 43 (72), 41 (79); hrms 262.2043±0.01 (calcd. for $C_{17}H_{26}O_2$, M^+, 262.19327).

HYDROLYSIS OF (−)-CORALLOIDIN-B TO (−)-**2b**.—Following the above procedure for (−)-**1a**, (−)-**2b** was obtained in 66% yield after purification by RP-18 reverse-phase hplc, eluent acetonitrile-H_2O (75:25), retention time 9 min.

(−)-DEACETYLCORALLOIDIN-B [(−)-**2b**].—Semisolid oil; $[\alpha]^{20}D$ −82.6 (0.14, cyclohexane); uv λ max (ε) (cyclohexane) 226 (3,800); ^{1}H nmr (80 MHz, C_6D_6) δ 4.77 (1H, m, H-1), 4.36 (1H, br. d, $J_{5,6}$=11.0, H-5), 3.58 (2H, s, H_2-12), 1.57 (3H, d, $J_{14,5}$=1.3, H_3-14), 1.42 (3H, d, $J_{15,1}$=1.5, H_3-15), 1.13 (3H, s, H_3-13), 0.53 (1H, m, H-7), 2.4-1.0 (10H, series of m, H_2-2, H_2-3, H-6, H_2-8, H_2-9, and OH); ^{13}C nmr (C_6D_6) (the assignments of C-2, C-3, C-8, and C-9 are tentative) 140.3 (s, C-4), 128.4 (s, C-10), 125.7, 125.4 (two d, C-1, C-5, or vice versa), 63.4 (t, C-12), 41.5 (t, C-8), 37.6 (t, C-2), 31.0 (d, C-6), 27.7 (d, C-7), 26.7 (s, C-11), 26.4 (t, C-3 and C-9), 24.8 (q, C-13), 21.0 (q, C-15), 16.6 (q, C-14); ms *m/z* (rel. int.) 220 (M^+, 2). 205 (0.5), 202 (3), 189 (9), 187 (11), 159 (8), 147 (12), 145 (12), 133 (12), 121 (60), 119 (56), 107 (38), 105 (65), 93 (100), 79 (77), 77 (36).

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