Three New Sesquiterpenes from *Croton arboreous*

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Three new sesquiterpenes, 5α,7α,10β*H*-3-patchoulen-2-one (**1**), 5α,7α10β*H*-4(14)-patchoulen-2α-ol (**2**), and 9α,10β-dihydroxy-2β,4β-peroxy-1α,5β,7α*H*-guaiane (**3**), were isolated from the aerial parts of *Croton arboreous* along with 14 known compounds. The structures of these compounds were determined on the bases of their spectroscopic data (IR, UV, OR, 1D and 2D NMR, and MS). The anti-inflammatory activity against ear edema in mice produced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) was evaluated for all the pure compounds and showed that compounds **4**−**7** are active.

The aerial parts of *Croton arboreous* (Euphorbiaceae), common name "cascarillo", are the source of a popular beverage used in Tabasco and Chiapas, Mexico, as an auxiliary anti-inflammatory agent in the treatment of respiratory ailments. The *n*-hexane, acetone, and methanol extracts of this plant were analyzed in the anti-inflammatory assay against ear edema in mice produced by TPA (0.5 mg/ear),[1,2] and the *n*-hexane and acetone extracts were active. The *n*-hexane and acetone extracts were analyzed on TLC, and on the basis of their similar chemical composition and anti-inflammatory activity these extracts were combined. Purification of the nonactive fractions yielded 10 known natural products and three new sesquiterpenes, 5α,7α,10β*H*-3-patchoulen-2-one (**1**), 5α,7α,10β*H*-4(14)-patchoulen-2α-ol (**2**), and 9α,10β-dihydroxy-2β,4β-peroxy-1α,5β,7α*H*-guaiane (**3**), whose structure elucidation is described herein. Fractionation of the active residue on CC afforded three active groups of fractions, whose further purification yielded four anti-inflammatory compounds, 5α,10β-4(15)-eudesmen-1β,6β-diol (**4**),[3] spathulenol (**5**),[4] 5α,10β-3-eudesmen-1β,6α-diol (**6**),[5] and junceic acid (**7**).[6]

Compound **1** was isolated as a yellowish oil. The HREIMS data indicated a molecular formula $C_{15}H_{22}O$ on the basis of the *m*/*z* 218.3383 and five unsaturation degrees, two of them due to the presence of a α,β-unsaturated ketone in accord with the absorptions at 1669 and 1457 cm^{-1} in the IR spectrum. The ^{13}C NMR and DEPT spectra of **1** showed 15 carbon resonances, corresponding to four CH_3, three CH_2, four CH, and four C, establishing a patchoulene skeleton for this natural product. This deduction was supported by the ^1H NMR and HMQC spectra, where **1** showed signals of four methyl groups, two singlets at δ 1.14 (δ_C 27.1, C-13) and 1.01 (δ_C 28.0, C-12) and two doublets at δ 1.29 (d, J = 7.1 Hz, δ_C 15.3, C-15) and δ 1.98 (d, J = 1.2 Hz, δ_C 25.5, C-14), one vinyl hydrogen at δ 5.65 (q, J = 1.2 Hz, δ_C 125.6, C-3), and the bridged hydrogen H-7 at δ 1.99−1.91 (m, δ_C 58.3). Long-range $^1H-^{13}C$ couplings observed in the HMBC spectrum supported the structure shown for **1**: the coupling between δ 2.33 (H-5) and the signals at δ_C 65.6 (C-1), 165.3 (C-4), 125.6 (C-3), 25.5 (C-14), and 58.3 (C-7) revealed that the α,β-unsaturated ketone is located in the A ring; that between δ 1.14 (H-13) and 1.01 (H-12) and the signals at δ_C 42.5 (C-11) and 58.3 (C-7) confirmed the connectivity of the five-membered B ring, and that between δ 1.29 (H-15) and the signals at δ_C 65.6 (C-1), 44.0 (C-10), and 39.7 (C-9) revealed the connectivity of the six-membered C ring. The configuration of **1** was assigned by the observation of three important correlations in the NOESY spectrum (Figure 1). The signal at δ 2.33 (H-5) showed correlation to H-6a (δ1.75), while the signal at δ 1.94 (H-6b) showed correlation to H-12 (δ1.01). Additionally the methyl group C-13 showed strong correlations to protons H-10 (δ1.69) and H-8b (δ1.49). Thus, the structure of **1** was established as 5α,7α,10β*H*-3-patchoulen-2-one.

Compound **2** was an alcohol in accord with its absorption at 3408 cm^{-1} in the IR spectrum and the signal at δ 3.84 in ^1H NMR. The spectroscopic data in the ^1H, ^{13}C NMR and ^{13}C DEPT spectra were very similar with those of compound **1**. However, **2** showed only three signals for methyl groups [singlets at δ 1.01 (H-13) and 0.96 (H-12) and a doublet at δ 1.14 (H-15)] and one AB system at δ 4.59 and 4.55, which was assigned to an exocyclic methylene (H-14). In the COSY spectrum, both signals for H-14 showed correlation with the signal at δ 2.14−2.05 (m, H-3a) and also with the signal for H-3b at δ 2.69 and between the latter two with the signal at δ 3.84, establishing that the alcohol was located at C-2. The set of correlations shown in the NOESY spectrum for **1** were also observed for **2**, in addition to the correlation between H-10 (δ1.61) and H-2 (δ 3.84), establishing an α orientation of the hydroxyl group on C-2 and the structure 5α,7α,10β*H*-4(14)-patchoulen-2α-ol for compound **2**.

Compound **3** was a yellowish oil with molecular formula $C_{15}H_{26}O_4$ ($M^+ - O_2$, *m*/*z* 238.1933), indicating three unsaturation degrees. The ^{13}C NMR spectrum of **3** showed 15 carbon resonances, corresponding to four CH_3, three CH_2, six CH, and two C in accord with the DEPT spectrum. The two quaternary carbons of **3** showed binding to oxygen, in accord with their chemical shifts at δ_C 87.4 (s) and 77.4 (s). This characteristic and the multiplicity of the 13 other carbons established a totally saturated guaiane skeleton for this natural product, which justified two unsaturation degrees. The two quaternary carbons corresponded to C-4 and C-10 in accord with the chemical shift for the methyl groups C-14 and C-15 at δ 1.49 (s, δ_C 21.5) and 1.17 (s, δ_C 32.1), respectively, in the ^1H, ^{13}C NMR and HMQC spectra. The presence of two additional tertiary carbons joined to oxygen was established by the signals at δ 3.91 and 3.80. The first one corresponds to H-9 in accord with a correlation of this signal with the signal at δ 1.68 (H-8a) in the COSY spectrum and with the long-range $^1H-^{13}C$ coupling of the

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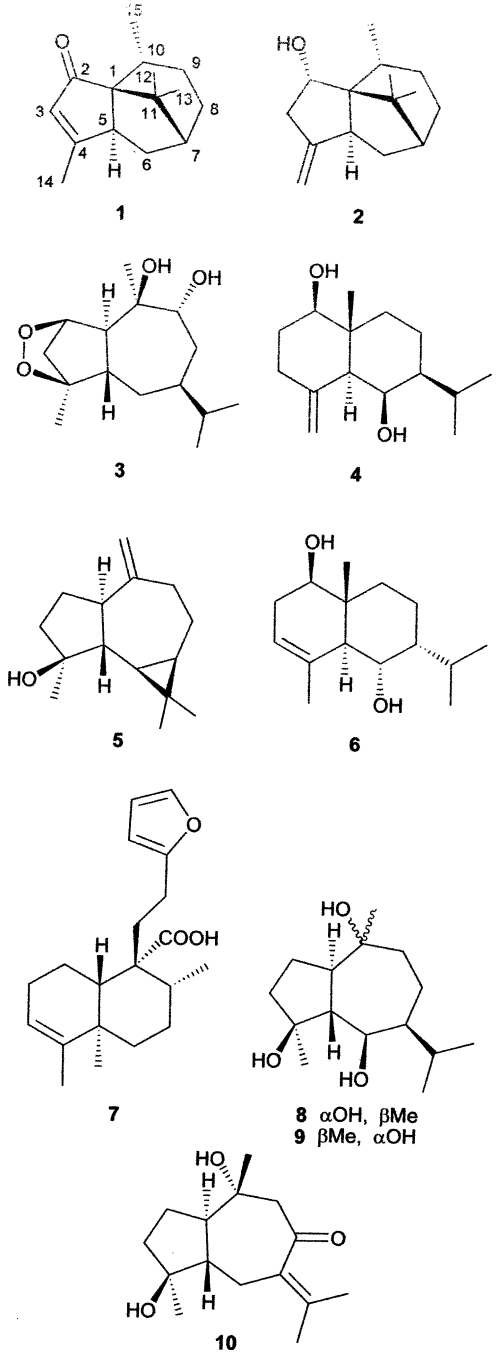

signal at δ 1.17 (H-15) with the signal at δ_C 86.8 (C-9) in the HMBC spectrum. The second one corresponded to H-2 in accord with the correlation of the signal with the signals at δ 0.98 (H-3a) and 1.41 (H-3b) in the COSY spectrum. The downfield shift observed in the ^{1}H and ^{13}C NMR spectra for H-14 ($\Delta\delta$ 1.49−1.20 = 0.29) and C-4 ($\Delta\delta$ 87.4−81.2 = 7.2) with respect to teuclatriol (**8**)[7] and $\Delta\delta$ 1.49−1.26 = 0.23 and $\Delta\delta$ 87.4−81.1 = 7.3 with respect to 10-epiteuclatriol (**9**)[7] established a peroxide function on C_4−C_2, justifying the third unsaturation in this natural product. The other two oxygenated functions correspond to hydroxyl groups, in accord with the absorption at 3398 cm^{-1} in the IR spectrum. The junction of the guaiane rings was *trans*, in accord with a J_{H1-H5} = 12.8 Hz.[7,8] The relative configuration at C-10 was established by comparison of the chemical shift due to C-15 in **3** with those of zedoarondiol (**10**, δ_{C15} 20.6), a guaiane whose 10α-hydroxy configuration has been determined by X-ray analysis,[9] and the epimeric compounds at C-10 teuclatriol (**8**, 10α-hydroxy, δ_{C15} 22.2)

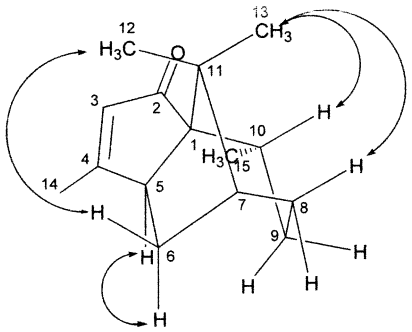

Figure 1. Spatial correlations observed from NOESY spectra of **1** and **2**.

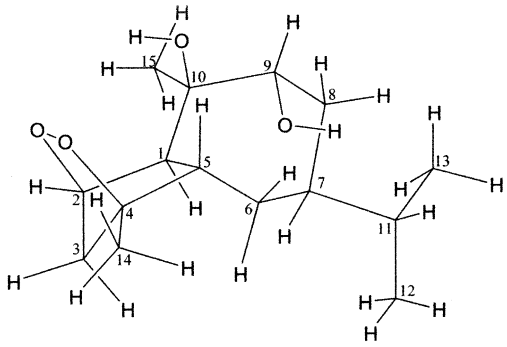

Figure 2. Energy-minimized molecular model of **3**.

and epiteuclatriol (**9**, 10β-hydroxy, δ_{C15} 29.9).[7] Compound **3** showed a chemical shift for C-15 similar to **9** at δ 32.1, establishing a β orientation for the hydroxyl group and an α orientation for C-15. A *trans* and *syn* relationship between H-1 and H-2 should have a $J_{H1\alpha-H2\beta}$ = 9.0 Hz and $J_{H1\alpha-H2\alpha}$ = 5.0 Hz, respectively.[8] Compound **3** showed a $J_{H1\alpha-H2\alpha}$ = 4.8 Hz, corresponding to a *syn* relationship, establishing that the C_4−C_2 peroxide was β. Additionally observed coupling constants were $J_{H5\beta-H6\alpha}$ = 9.2 Hz and $J_{H5\beta-H6\beta}$ = 4.0 Hz, $J_{H6\alpha-H7\alpha}$ = 5.2 Hz, and $J_{H8\alpha-H9\beta}$ = 5.2 Hz, which could be explained in accord with the H−H dihedral angles of 147°, 27°, 47°, and 48°, respectively, obtained from the energy-minimized molecular model calculation (Figure 2). Thus, the structure of **3** was established as 9α,10β-dihydroxy-2β,4β-peroxy-1α,5β,7α*H*-guaiane and was confirmed by the HMBC spectrum, where **3** showed long-range ^{1}H−^{13}C couplings between δ 0.99 (H-13) and 0.98 (H-12) and the signals at δ_C 47.5 (C-7) and 28.5 (C-11); between δ 1.49 (H-14) and the signals at δ_C 87.4 (C-4), 30.2 (C-3), and 61.8 (C-5); between δ 1.17 (H-15) and the signals at δ_C 41.6 (C-1) and 86.8 (C-9); between δ 1.30 (H-6) and 61.8 (C-5); and between δ 1.24 (H-8) and 86.8 (C-9).

Experimental Section

General Experimental Procedures. The *n*-hexane−acetone extract from *C. arboreous* was fractionated using open CC (Merck Kiesel-gel 60 and Supelclean SPE LC-SI 6 mL tubes) and TLC (ALUGRAM SIL G/UV$_{254}$ silica gel plates), using mixtures of *n*-hexane−acetone as eluent. In the TLC analysis, the compounds were visualized by UV light and spraying with a 1% solution of $(NH_4)_4Ce(SO_4)$ in 2 N H_2SO_4; UV spectra were recorded on a Hewlett-Packard 8453 spectrophotometer in $CHCl_3$. IR spectra were recorded with Bruker Vector 22 IR instrument in $CHCl_3$ solution; ^{1}H and ^{13}C NMR spectra as well as 2D NMR experiments were recorded in $CDCl_3$ on Varian Unity 400 and Varian-Gemini 300 spectrometers, and the chemical shifts were expressed in parts per

million (δ) relative to TMS as internal standard. Mass spectra were measured on a JEOL JMS-AX 505 HA mass spectrometer. Electron impact mass spectra were obtained at 70 eV ionization energy.

Plant Material. The aerial parts of *C. arboreous* (6 m tree with red resin) were collected and identified by Biol. Esteban Manuel Martínez on March 13, 2002, at 4 km SE of La Nueva Vida, Camino a Xpujil (18°46′30 N, 89°22′23 W) at 270 m above sea level in Calakmul, Campeche, México. A voucher specimen was deposited at the National Herbarium (MEXU, voucher 27171) at the Instituto de Biología, UNAM, México.

Extraction and Isolation. The air-dried parts of *C. arboreous* (3.48 kg) were powdered and exhaustively extracted with *n*-hexane, acetone, and MeOH (12 L × 3 each) to yield 45.8, 38.6, and 148.1 g of residue, respectively. These extracts were evaluated in the anti-inflammatory assay,[1,2] the *n*-hexane and acetone extracts being active. On the basis of their similar anti-inflammatory activity and chemical composition on TLC, the *n*-hexane and acetone extracts were joined and absorbed on silica gel (85 g) and chromatographed on CC over silica gel 60 (850 g), using a gradient of *n*-hexane−acetone as eluent. The composition of the obtained fractions (500 mL each) was monitored by TLC, and the chromatographically identical fractions were combined, yielding eight groups, G-1 [3.9 g, *n*-hexane 100%], G-2 [9.8 g, *n*-hexane−acetone, 95:5], G-3 [8.3 g, *n*-hexane−acetone, 95:5], G-4 [7.3 g, *n*-hexane−acetone, 9:1], G-5 [2.3 g, *n*-hexane−acetone, 85:15], G-6 [1.7 g, *n*-hexane−acetone, 8:2], G-7 [2.6 g, *n*-hexane−acetone, 7:3], and G-8 [3.1 g, *n*-hexane−acetone, 6:4], which were evaluated in the anti-inflammatory assay.[1,2] G-2, G-3, and G-5 displayed anti-inflammatory activity. Each group was further separated using CC over silica gel 60, with a gradient of *n*-hexane−acetone as eluent. Fraction G-2 yielded junceic acid[6] (**7**, 236 mg, 0.52%) and β-sitosterol. Fraction G-3 yielded 1β,10α-4β,5α-diepoxy-7α*H*-germacran-6β-ol[10] ([α]$^{25}_D$ −28.6° (*c* 0.2, $CHCl_3$), 96 mg, 0.21%), 1α,10β-4β,5α-diepoxy-7α*H*-germacran-6β-ol[11] ([α]$^{25}_D$ +152.2° (*c* 0.5, $CHCl_3$), 52 mg, 0.11%), 5α,10β-4(15)-eudesmen-1β,6α-diol[3] ([α]$^{25}_D$ −51.6° (*c* 0.1, $CHCl_3$), 193 mg, 0.42%), and 5α,10β-4(15)-eudesmen-1β,6β-diol[3] ([α]$^{25}_D$ +15.7° (*c* 0.1, $CHCl_3$), **4**, 177 mg, 0.39%). Fraction G-5 yielded spathulenol[4] ([α]$^{25}_D$ +3.7° (*c* 0.01, $CHCl_3$), **5**, 259 mg, 0.57%), 5α,10β-3-eudesmen-1β,6α-diol[5] ([α]$^{25}_D$ +44.0° (*c* 0.52, $CHCl_3$), **6**, 48 mg, 0.11%), and 9α,10β-dihydroxy-2β,4β-peroxy-1α,5β,7α*H*-guaiane ([α]$^{25}_D$ +8.3° (*c* 0.05, $CHCl_3$), **3**, 39 mg, 0.08%). Additional constituents of the inactive fractions were 5α,7α,10β*H*-3-patchoulen-2-one (**1**, 47 mg, 0.10%), 5α,7α,10β*H*-4(14)-patchoulen-2α-ol (**2**, 56 mg, 0.12%), lupenone[12] (286 mg, 0.62%), 4β,6β-dihydroxy-1α*H*,5β*H*-9-guaiene[13] ([α]$^{25}_D$ +10.5° (*c* 0.60, $CHCl_3$), 88 mg, 0.19%), teucladiol[7] ([α]$^{25}_D$ +2.1° (*c* 0.43, $CHCl_3$), 79 mg, 0.17%), quercetin-3,4′-dimethyl ether[14] (266 mg, 0.58%), 2′-*O*-β-D-glucopyranosyl-5,7,5′-trihydroxy-3,4′-dimethoxyflavone[15] (141 mg, 0.31%), and β-sitosteryl-β-D-glucopyranoside.[16]

5α,7α,10β*H*-3-Patchoulen-2-one (1): yellowish oil; [α]$^{25}_D$ −53.9° (*c* 3.6, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 239 (3.68), 205 (3.40) nm; IR ($CHCl_3$) ν_{max} 2946, 2870, 1669 (CO), 1457 (C=C), 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65 (1H, q, J = 1.2 Hz, H-3), 2.33 (1H, d, J = 3.6 Hz, H-5), 1.99−1.91 (1H, m, H-7), 1.98 (3H, d, J = 1.2 Hz, H-14), 1.94 (1H, d, J = 11.2 Hz, H-6b), 1.94 (1H, m, H-9a), 1.75 (1H, ddd, J = 11.2, 3.6, 3.6 Hz, H-6a), 1.70 (1H, dd, J = 11.2, 5.2 Hz, H-8a), 1.69 (1H, ddd, J = 8.4, 7.1, 4.8 Hz, H-10), 1.62 (1H, dd, J = 10.4, 5.2 Hz, H-9b), 1.49 (1H, dd, J = 11.2, 4.4 Hz, H-8b), 1.29 (3H, d, J = 7.1 Hz, H-15), 1.14 (3H, s, H-13), 1.01 (3H, s, H-12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.8 (C, C-2), 165.3 (C, C-4), 125.6 (CH, C-3), 65.6 (C, C-1), 59.1 (CH, C-5), 58.3 (CH, C-7), 44.8 (CH_2, C-6), 44.0 (CH, C-10), 42.5 (C, C-11), 39.7 (CH_2, C-9), 28.0 (CH_3, C-12), 27.1 (CH_3, C-13), 26.7 (CH_2, C-8), 25.5 (CH_3, C-14), 15.3 (CH_3, C-15); EIMS *m*/*z* 218 [M^+, $C_{15}H_{22}O$] (100), 203 [$M^+ - CH_3$] (27), 176 [$M^+ - C_3H_6$] (43), 175 [$M^+ - C_3H_6 - H$] (42), 161 [$M^+ - C_3H_6 - CH_3$] (51), 147 [$M^+ - C_3H_6 - CH_3 - CH_2$] (20), 136 (29), 135 (28), 121 (28), 95 (15), 91 (13), 81 (9), 55 (9), 41 (12); HREIMS *m*/*z* 218.3383 (calcd for $C_{15}H_{22}O$, 218.3390).

5α,7α,10β*H*-4(14)-Patchoulen-2α-ol (2): colorless oil; [α]$^{25}_D$ −16.4° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3408 (OH), 2927, 2862, 1463 (C=C), 1387 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.59 (1H, td, J = 3.0, 0.9 Hz, H-14a), 4.55 (1H, dd, J = 3.0, 3.0 Hz, H-14b), 3.84 (1H, dd, J = 9.3, 6.9 Hz, H-2), 2.69 (1H, dd, J = 15.3, 6.9 Hz, H-3b), 2.18 (1H, d, J = 4.2 Hz, H-5), 2.14−2.05 (1H, m, H-3a), 1.90 (1H, m, H-9a), 1.72 (1H, dd, J = 12.3, 3.2 Hz, H-6b), 1.61(2H, m, H-7, H-10), 1.59 (1H, m, H-8a), 1.58 (1H, m, H-6a), 1.42 (1H, m, H-9b), 1.40 (1H, m, H-8b), 1.14 (3H, d, J = 7.5 Hz, H-15), 1.01 (3H, s, H-13), 0.96 (3H, s, H-12); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.8 (C, C-4), 108.2 (CH_2, C-14), 73.4 (CH, C-2), 60.6 (CH, C-7), 58.3 (C, C-1), 52.5 (CH, C-5), 45.3 (CH, C-10), 42.8 (CH_2, C-6), 41.5 (C, C-11), 40.3 (CH_2, C-9), 40.2 (CH_2, C-3), 27.0 (CH_3, C-13), 26.6 (CH_2, C-8), 25.6 (CH_3, C-12), 14.7 (CH_3, C-15); EIMS *m*/*z* 220 [M^+, $C_{15}H_{24}O$] (26), 202 [$M^+ - H_2O$] (100), 160 [$M^+ - H_2O - C_3H_6$] (41), 159 [$M^+ - H_2O - C_3H_6 - H$] (29), 137 (14), 97 (8); HREIMS *m*/*z* 220.3553 (calcd for $C_{15}H_{24}O$, 220.3549).

9α,10β-Dihydroxy-2β,4β-peroxy-1α,5β,7α*H*-guaiane (3): yellowish oil; [α]$_D^{25}$ −8.4° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3398 (OH), 2928, 1377, 1266, 1005, and 978 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.91 (1H, d, J = 5.2 Hz, H-9), 3.80 (1H, ddd, J = 4.8, 4.4, 3.2 Hz, H-2), 2.15 (1H, dd, J = 12.8, 4.8 Hz, H-1), 1.98 (1H, ddd, J = 12.8, 9.2, 4.0 Hz, H-5), 1.68 (1H, m, H-8a), 1.66 (1H, dh, J = 6.8, 2.4 Hz, H-11), 1.63 (1H, m, H-7), 1.53 (1H, dd, J = 9.2, 5.2 Hz, H-6b), 1.49 (3H, s, H-14), 1.41 (1H, m, H-3b), 1.30 (1H, m, H-6a), 1.24 (1H, m, H-8b), 1.17 (3H, s, H-15), 0.99 (3H, d, J = 6.8 Hz, H-13), 0.98 (3H, d, J = 6.8 Hz, H-12), 0.98 (1H, m, H-3a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 87.4 (C, C-4), 86.8 (CH, C-9), 77.4 (C, C-10), 68.7 (CH, C-2), 61.8 (CH, C-5), 47.5 (CH, C-7), 41.6 (CH, C-1), 32.1 (CH_3, C-15), 31.5 (CH_2, C-6), 30.2 (CH_2, C-3), 28.5 (CH, C-11), 26.6 (CH_2, C-8), 21.5 (CH_3, C-14), 21.4 (CH_3, C-12), 21.3 (CH_3, C-13); EIMS *m*/*z* 238 [$M^+ - O_2$, $C_{15}H_{26}O_2$] (9), 220 [$M^+ - O_2 - H_2O$] (23), 205 [$M^+ - O_2 - H_2O - CH_3$] (9), 195 [$M^+ - O_2 - C_3H_7$] (50), 181 [$M^+ - O_2 - C_3H_6 - CH_3$] (39), 177 (38), 162 (45), 152 (55), 140 (37), 123 (81), 109 (83), 94 (100), 81 (53), 43 (67); HREIMS *m*/*z* 238.1933 (calcd for $C_{15}H_{26}O_2$, $M^+ - O_2$, 238.3702).

Anti-inflammatory Assay. The anti-inflammatory activity of extracts, fractions, and pure compounds at a dose of 0.5 mg/ear was evaluated against the ear edema in mice produced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), according to the previously described procedure,[1,2] using indomethacin (61.2% inhibition, 0.5 mg/ear) as positive control. The *n*-hexane and acetone extracts showed activity (48.6 and 54.1% of inhibition, respectively) and were combined for fractionation. Fractions G-2, G-3, and G-5 were active (32.9, 22.7, and 29.3% inhibition), which after purification afforded the active natural products 5α,10β-4(15)-eudesmen-1β,6β-diol (**4**),[3] spathulenol (**5**),[4] 5α,10β-3-eudesmen-1β,6α-diol (**6**),[5] and junceic acid (**7**),[6] which showed 29.9, 31.5, 28.0, and 38.4% inhibition, respectively.

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