Sesquiterpenes from *Lippia integrifolia* Essential Oil

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Four sesquiterpenes (**1**−**4**) with the africanane skeleton [of which only 5-africanene (**1**) has been previously reported] and the new asteriscane derivative asterisca-3(15),6-diene (**5**) were isolated from the essential oil of *Lippia integrifolia*. A further new compound, african-2(6)-ene (**7**), was obtained as a semisynthetic product by derivatization of isoafricanol (**6**). The structures of the new compounds were assigned on the basis of spectroscopic data, enantioselective gas chromatography, and by chemical correlations.

The genus *Lippia* is a member of the family Verbenaceae and consists of approximately 200 species, which are mostly native to South and Central America. In the traditional medicine of north and central Argentina, the species *Lippia integrifolia* (Griseb.) Hieron is used as a remedy for stomach disorders and as a sedative. In previous reports, the essential oil of *L. integrifolia* was found to be rich in constituents based on the rare africanane skeleton.[1−7] A reinvestigation of the steam distillation products resulted in the identification of three africanane-type sesquiterpene hydrocarbons: the known compound **1**, previously extracted from the liverwort *Pellia epiphylla* (L.) Corda;[8] two new hydrocarbons (**2** and **3**); a new africanane alcohol (**4**); and a new asteriscadiene (**5**). The isolation and characterization of these compounds are the subject of the present communication.

Results and Discussion

The plant material was collected in February 1996, and submitted to steam distillation. The essential oil was fractionated by preparative gas chromatography (GC) using a nonpolar column (SE-30). The known sesquiterpenes 5-africanene (**1**), (*E*)-*β*-caryophyllene, α-humulene, lippifoli-1(6)-en-5-one,[2] davanone;[10] the compounds **2**−**4** based on the rare africanane skeleton; and compound **5**, with an asteriscane skeleton, were obtained. The fractions were analyzed by capillary GC on columns with heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-*β*-cyclodextrin (6-TBDMS-2,3-Me-*β*-CD) and heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-*β*-cyclodextrin (2,6-Me-3-Pe-*β*-CD).[9] However, the main peak of the sesquiterpene hydrocarbon fraction was a mixture (60:40%) of the two components **2** and **3**, both having identical retention times on columns with a nonpolar dimethylpolysiloxane phase (CpSil 5). Nonetheless, both components could then be isolated by preparative GC using 6-TBDMS-2,3-Me-*β*-CD as the stationary phase. The structures and relative configurations of **2**−**5** were derived from extensive 1D and 2D NMR studies, chemical correlations, and enantioselective GC. African-5-ene (**1**) has recently been detected as a constituent of the liverwort *P. epiphylla*.[8] The compound isolated from *L. integrifolia* was identified by comparison of the MS, GC retention times, and NMR data of the africanene (**1**) isolated from *P. epiphylla*. Both have the same absolute configuration, which is concluded from identical GC retention times on several modified cyclodextrin stationary phases, and the same optical rotation values.

The ^{1}H NMR spectra of african-1-ene (**2**) displayed a highfield signal (δ 0.27 and 0.48) associated with the cyclopropyl methylene group and a methine proton signal at δ 0.63, indicating a triple-substituted cyclopropane moiety. Furthermore, the three tertiary methyl groups were observed as single resonances at δ 0.93, 0.94, and 1.05; a secondary methyl doublet at δ 0.98 and an olefinic proton at δ 4.89 were also identified. The nonequivalent methylene proton signals were observed at δ 1.05/1.82, 1.60/1.72, and 1.55/1.69. Finally, two methine proton signals were found at δ 2.30 and 2.44. The assignments of the ^{1}H NMR signals were confirmed from the corresponding ^{13}C NMR signals and the HMQC and HMBC NMR spectra of **2**. The relative configuration of **2** was assigned on the basis of NOESY data and was supported by its formation from isoafricanol (**6**) (which, again, was isolated from *P. epiphylla*, see below) whose configuration has been elucidated.[11] The NOESY signal enhancements of **2** proved the spatial relationship of H-6 with H-8α and H-10α, which indicated an α-orientation of H-6.

The ^{1}H NMR spectra of africa-1,5-diene (**3**) also exhibited highfield methylene and methine signals (δ 0.42/0.75 and 0.83) of a cyclopropane ring system. The signals of three tertiary methyl groups were observed at δ 0.99, 1.15, and 1.20. The resonance signal of a secondary methyl group was observed at δ 1.04. Furthermore, two olefinic protons (δ 5.05 and 5.96), two methylene protons (δ 1.21/1.95 and 1.91/2.49), and a methine proton (δ 2.72) were also observed. The relative configuration of **3** was derived by its correlation with **2** by partial hydrogenation.

To confirm the structural assignments of **2** and **3**, isoafricanol (**6**) (a compound previously identified as a constituent of the ascomycete fungus *Leptographium lundbergii*),[11] isolated from *P. epiphylla*,[12] was treated with thionyl chloride and pyridine to effect dehydration. This resulted in the formation of the new african-2(6)-ene (**7**) (90%), which has not yet been identified as a natural product, and a minor product (10%) whose spectroscopic characteristics are identical to that of african-1-ene (**2**). The structure of **7** was supported by its ^{1}H and ^{1}H−^{1}H COSY NMR spectra and by correlation with **6**. Partial catalytic hydrogenation of africa-1,5-diene (**3**) also afforded **2** and **7** (identified by GC−MS). The relative configurations of **2**, **3**, and **7** were thus confirmed by correlation with isoafricanol (**6**). Unfortunately, the absolute configuration is still unknown.

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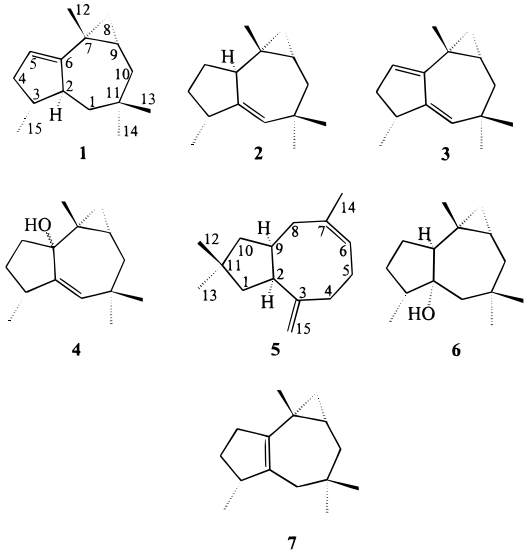

Another africanane derivative isolated from the essential oil of *L. integrifolia* was african-1-en-6-ol (**4**). Its MS featured a molecular ion signal at *m/z* 220. Its NMR spectra indicated the presence of a tricyclic sesquiterpene alcohol with an endocyclic olefinic double bond. In the ^{1}H NMR spectrum, the methylene protons (δ 0.40/1.02) and a methine proton (δ 0.72) of a cyclopropyl ring system were observed. In addition, three tertiary methyl resonances (δ 0.95, 1.00, and 1.08), a doublet due to a secondary methyl group (δ 1.09), and the signal of an olefinic proton of a trisubstituted double bond (δ 5.10) were also apparent. Three additional methylene resonances, together with the H-3 methine signal, were found in the range 1.4−2.4 ppm. In the ^{13}C NMR spectrum of **4** a quaternary carbon signal was observed at δ 80.75, typical of a carbon atom bearing a hydroxyl group. The limited quantity of **4** that accumulated was insufficient for NOESY investigations, and the orientation of the hydroxyl group at C-6 could not be established.

Dehydration of african-1-en-6-ol (**4**) yielded *ent*-africa-1,5-diene (*ent*-**3**) with NMR and MS identical to the compound isolated from *L. integrifolia*. The dehydration product *ent*-**3** and natural product **3** gave different retention times in GC with cyclodextrin stationary phases, indicating that the compounds have opposite configuration. Because of the small amount of *ent*-**3** isolated, its optical rotation could not be determined.

Finally, a novel sesquiterpene hydrocarbon with the rare asteriscane skeleton, asterisca-3(15),6-diene (**5**), was isolated from *L. integrifolia*. The ^{1}H NMR spectrum exhibited singlet signals for two geminal methyl groups (δ 1.02 and 1.08) and a methyl group located on an olefinic double bond (δ 1.68). The other characteristic signals in the ^{1}H NMR spectrum of **5** were assigned to five methylene groups (δ 1.17/1.68, 1.59, 1.83/2.06−2.22, 1.96/2.43, 2.06−2.22/2.28), two methine protons (δ 1.52, 2.06−2.22), two olefinic protons of an exocyclic double bond (δ 4.66 and 4.81), and one proton located at an endocyclic double bond (δ 5.20). The structure of **5** was verified by 2D NMR techniques (^{1}H−^{1}H COSY, HMQC, HMBC, and NOESY). Catalàn et al. reported the isolation of 3α-hydroxy-6-asteriscene from *L. integrifolia*[6] with a cis configuration of H-2 and H-9 (based on the large coupling constant of 11.0 Hz), as is the case in asteriscanolide, which has been studied by X-ray diffraction.[13] The coupling constant of 10.7 Hz between H-2 and H-9 observed in **5** (see the ^{1}H NMR spectrum in C_6D_6) indicates the same configuration, but this needs to be confirmed by synthesis.

Experimental Section

General Experimental Procedures. NMR measurements were carried out with WM 400 (400 MHz) and WM 500 (500 MHz) instruments (Bruker) using $CDCl_3$ and C_6D_6 as solvent and TMS as internal standard. GC−MS analyses were performed on a Hewlett−Packard HP 5890 gas chromatograph equipped with a 25-m fused silica capillary with CpSil 5 (Chrompack) coupled to a VG Analytical 70−250S mass spectrometer operating in the EI mode (70 eV). Exact mass measurements were performed on the same instrument at a resolution of 5000 with perfluorokerosene as reference. A capillary column with a dimethylpolysiloxane (CpSil 5, Chrompack) phase was used for analytical GC and enantioselective GC measurements performed with capillary columns with cyclodextrin derivatives, prepared as described earlier.[15] Optical rotations were measured on a Perkin−Elmer 241 MC polarimeter.

Plant Material. *L. integrifolia* (Griseb.) Hieron[5] was collected in February 1996, near Cordoba, Argentina, and voucher specimens were deposited in the herbarium of the Catedra de Botanica, Universidad Nacional de Cordoba. The liverwort *P. epiphylla* L. Corda was collected near Hamburg, Germany, and a voucher specimen was deposited in the herbarium of the Institut für Allgemeine Botanik, University of Hamburg.

Extraction and Isolation. The essential oil of *L. integrifolia* was obtained by steam distillation of the fresh plant and dried over Na_2SO_4. The essential oil of *P. epiphylla* was obtained by steam distillation of the fresh plant. For the isolation of the pure compounds **1**, **5**, (*E*)-*β*-caryophyllene, α-humulene, **4**, davanone, and lippifoli-1(6)-en-5-one from the essential oil of *L. integrifolia* (in this elution order) a 1.85-m (4.3 mm i.d.) stainless steel column (Silcosteel, Amchro), with 10% SE 30 on Chromosorb W−HP (Merck) and He as carrier gas at a flow rate of 120 mL min^{-1}, was used in a modified Varian 1400 instrument. The time program started at an initial temperature of 80 °C and a heating rate of 1 °C/min and ended with a temperature of 200 °C. Compounds **1** and **6** were isolated by the same polysiloxane column (SE-30) and the same conditions (see above) from the essential oil of *P. epiphylla*. With the use of the nonpolar column SE-30, it was impossible to isolate **2** and **3** as pure compounds (just as a mixture) from the essential oil of *L. integrifolia*. In addition an equivalent column with heptakis(6-*O*-*tert*-hexyldimethylsilyl-2,3-di-*O*-methyl)-*β*-cyclodextrin was used,[14] with He as carrier gas and a flow rate of 120 mL min^{-1}. The temperature was constant at 110 °C.

African-1-ene (2): colorless oil; about 3 mg; $[\alpha]^{25}_D$ +95°; (*c* 0.2, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.27 (1H, dd, J = 4.1, 5.1 Hz, H-8α), 0.48 (1H, dd, J = 4.1, 8.1 Hz, H-8*β*), 0.63 (1H, m, H-9*β*), 0.93 (3H, s, Me-13), 0.94 (3H, s, Me-12), 0.98 (3H, d, J = 6.6 Hz, Me-15), 1.05 (3H, s, Me-14), 1.05 (1H, m, H-4α), 1.55 (1H, m, H-10α), 1.60 (1H, m, H-5*β*), 1.69 (1H, m, H-10*β*), 1.72 (1H, m, H-5α), 1.82 (1H, m, H-4*β*), 2.30 (1H, m, H-3*β*), 2.44 (1H, m, H-6α), 4.89 (1H, dd, J = 4.5 Hz; allylic coupling with H-3, J = 2.0 Hz; allylic coupling with H-6, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8 (q, C-15), 20.6 (d, C-9), 21.1 (q, C-14), 21.8 (t, C-8), 22.6 (s, C-7), 26.4 (t, C-5), 28.0 (q, C-12), 33.0 (q, C-13), 37.3 (s, C-11), 37.3 (t, C-4), 40.6 (t, C-10), 40.9 (d, C-3), 46.4 (d, C-6), 129.0 (d, C-1), 145.9 (s, C-2); EIMS *m/z* 204 [M]$^+$ (22), 189 (30), 147 (35), 135 (100), 121 (53), 105 (76), 91 (50), 81 (32), 79 (30), 77 (28), 69 (24), 67 (23), 65 (16), 55 (42), 41 (68); HREIMS *m/z* 204.1885 (calcd for $C_{15}H_{24}$, 204.1878).

Africa-1,5-diene (3): colorless oil; about 3 mg; $[\alpha]^{25}_D$ +44°, (*c* 0.05, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.42 (1H, dd, J = 4.1, 5.1 Hz, H-8α), 0.75 (1H, dd, J = 4.1, 8.1 Hz, H-8*β*), 0.83 (1H, m, H-9*β*), 0.99 (3H, s, Me-13), 1.04 (3H, d, Me-15, J = 7.1 Hz), 1.15 (3H, s, Me-14), 1.21 (1H, dd, J = 4.1, 10.2 Hz, H-10α), 1.20 (3H, s, Me-12), 1.91 (1H, m, H-4α), 1.95 (1H, m, H-10*β*), 2.49 (1H, ddd, J = 3.0, 8.1, 16.8 Hz, H-4*β*), 2.72 (1H, dq, J =

3.0, 7.1 Hz, H-3β), 5.05 (1H, s, H-1), 5.96 (1H, dd, J = 1.5, 4.5 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (s, C-7), 20.6 (d, C-9), 22.8 (t, C-8), 27.6 (q, C-14), 28.0 (q, C-15), 28.4 (q, C-12), 35.0 (q, C-13), 35.6 (s, C-11), 39.4 (t, C-4), 39.8 (d, C-3), 44.1 (t, C-10), 129.5 (d, C-1), 134.7 (d, C-5), 145.6 (s, C-2), 149.2 (s, C-6); EIMS m/z 202 $[M]^+$ (66), 187 (66), 173 (10), 159 (85), 145 (95), 131 (100), 119 (32), 105 (44), 91 (46), 77 (30), 55 (26), 41 (50). HREIMS m/z 202.1735 (calcd for $C_{15}H_{22}$, 202.1722).

1-Africanen-6-ol (4): colorless oil; about 0.8 mg; $[\alpha]^{25}_D$ +95°, (c 0.1, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (1H, dd, J = 4.1, 8.6 Hz, H-8β), 0.72 (1H, m, H-9), 1.02 (1H, dd, J = 4.1, 5.1 Hz, H-8α), 0.95 (3H, s, Me-12), 1.00 (3H, s, Me-14), 1.08 (3H, s, Me-13), 1.09 (3H, d, J = 6.6 Hz, Me-15), 1.41 (1H, dd, J = 6.1, 11.7 Hz, H-4), 1.54 (1H, dd, J = 6.1, 11.7 Hz, H-4), 1.73 (1H, ddd, J = 2.0, 5.6 Hz, H-10β), 1.81 (1H, ddt, J = 1.5, 6.1, 12.7 Hz, H-5), 1.89 (1H, dd, J = 2.0, 14.2 Hz, H-10α), 1.97 (1H, dt, J = 6.1, 12.7 Hz, H-5), 2.36 (1H, m, H-3), 5.10 (1H, t, J = 2.0 Hz, H-1), (the hydroxy proton could not be identified); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (t, C-8), 19.7 (d, C-9), 21.2 (q, C-12), 24.8 (q, C-13), 24.9 (s, C-7), 27.9 (q, C-15), 32.6 (t, C-5), 32.9 (q, C-14), 37.0 (s, C-11), 38.4 (t, C-4), 39.9 (t, C-10), 40.5 (d, C-3), 80.8 (s, C-6), 134.6 (d, C-1), the C-2 absorption could not be detected, because the sample amount was too small; EIMS m/z 220 $[M^+]$ (6), 202 (54), 187 (55), 179 (100), 159 (72), 145 (84), 131 (86), 121 (56), 105 (52), 91 (58), 77 (40), 76 (25), 55 (44), 41 (84). HREIMS m/z 220.1801 (calcd for $C_{15}H_{24}O$, 220.1827).

Asterisca-3(15),6-diene (5): colorless oil; about 3 mg; $[\alpha]^{22}_D$ −150°, (c 0.3, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, s, Me-12), 1.08 (3H, s, Me-13), 1.17 (1H, dd, J = 12.7, 11.4 Hz, H-10β), 1.52 (1H, m, H-9), 1.59 (2H, dd, J = 9.7, 0.8 Hz, H-1α and H-1β), 1.68 (1H, dd, J = 12.7, 7.1 Hz, H-10α), 1.68 (3H, s, Me-14), 1.83 (1H, dd, J = 13.2, 2.5 Hz, H-8β), 1.96 (1H, m, H-5), 2.06−2.22 (3H, m, H-4, H-8α and H-2), 2.28 (1H, m, H-4), 2.43 (1H, m, H-5), 4.66 (1H, s, H-15), 4.81 (1H, s, H-15), 5.20 (1H, m, H-6);^{1}H NMR (400 MHz, C_6D_6) δ 1.01 (3H, s, Me-12), 1.07 (3H, s, Me-13), 1.08 (1H, t, J = 7.1 Hz, H-10β), 1.58 (1H, t, J = 7.1 Hz, H-10α), 1.63 (1H, m, H-9), 1.66 (2H, t, J = 8.14 Hz, H-1), 1.72 (3H, s, Me-14), 1.89 (1H, dd, J = 13.2, 2.0 Hz, H-8β), 1.90 (1H, m, H-5α), 2.04 (1H, dt, J = 10.7, 8.14 Hz, H-2), 2.16 (2H, m, H-4β and H-8α), 2.24 (1H, m, H-4α), 2.37 (1H, m, H-5β), 4.82 (1H, s, H-15), 4.96 (1H, s, H-15), 5.29 (1H, m, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (t, C-5), 25.1 (q, C-14), 31.7 (q, C-12), 31.8 (q, C-13), 35.0 (s, C-11), 37.4 (t, C-8), 39.4 (t, C-4), 47.8 (d, C-9), 49.4 (d, C-2), 49.6 (t, C-1), 50.1 (t, C-10), 109.4 (t, C-15), 123.5 (d, C-6), 137.1 (s, C-7), 152.0 (s, C-3); EIMS m/z 204 $[M]^+$ (35), 189 (38), 176 (22), 161 (40), 136 (50), 121 (100), 107 (45), 93 (54), 79 (46), 67 (26), 55 (32), 41 (64); HREIMS m/z 204.1875 (calcd for $C_{15}H_{24}$, 204.1878).

Dehydration of Isoafricanol (6). A solution 2 mg of **6** in 0.5 mL pyridine was cooled to 0 °C, one drop of thionyl chloride was added, and the mixture was stirred for 3 min in an ice bath. To the mixture, H_2O and *n*-hexane were added, and the organic phase was washed three times with H_2O. The main dehydration products were identified by ^{1}H and ^{1}H−^{1}H COSY NMR as african-2(6)-ene (**7**) and african-1-ene (**2**) (ratio 9:1), the latter being identical with **2** isolated from *L. integrifolia* in all spectroscopic data and also by co-injection on GC using cyclodextrin stationary phases.

African-2(6)-ene (7): colorless oil; 0.1 mg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.27 (1H, dd), 0.66 (1H, dd), 0.79 (1H, m), 0.84 (3H, s), 0.98 (3H, s), 1.02 (3H, d), 1.03 (3H, s), 1.15−1.57 (7H, m), 1.67 (1H, m), 1.98 (1H, m); EIMS m/z 204 $[M]^+$ (40), 189 (92), 175 (8), 161 (26), 147 (100), 133 (64), 119 (84), 105 (81), 91 (75), 77 (28), 69 (16), 55 (32), 41 (58).

Dehydration of African-1-en-6-ol (4). A solution of 0.5 mg african-1-en-6-ol (**4**) in 0.5 mL pyridine was cooled to 0 °C, one drop of thionyl chloride was added, and the mixture was stirred for 3 min at 0 °C. To the mixture, H_2O and *n*-hexane were added, and the organic phase was washed three times with H_2O. The main dehydration product was *ent*-africa-1,5-diene (*ent*-**3**), which was identical with africa-1,5-diene (**3**) isolated from *L. integrifolia* in all physical data, except for different GC retention times on the cyclodextrin stationary phases used.

Partial Hydrogenation of Africa-1,5-diene (3). To a solution of 0.5 mg of **3** in 1 mL of *n*-hexane was added a trace of palladium−charcoal catalyst, and H_2 was bubbled through this suspension for 1 min. After 15 min of additional stirring at room temperature, the suspension was filtered over Celite. African-2(6)-ene (**7**) (60%) was formed as the main product, together with a smaller amount of african-1-ene (**2**) (40%). The main partial hydrogenation products were identified by comparison of their GC−MS spectra with those of the isolated compounds.

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