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DITERPENES FROM THE ROOTS OF *SALVIA CANARIENSIS*

BRAULIO M. FRAGA, ANTONIO G. GONZÁLEZ*, JUAN R. HERRERA*, JAVIER G. LUIS* and ANGEL G. RAVELO*

Instituto de Productos Naturales Orgánicos, CSIC, La Laguna, Tenerife, Canary Islands, Spain; *Instituto de Química Orgánica, Universidad de La Laguna, La Laguna, Tenerife, Canary Islands, Spain

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Key Word Index—*Salvia canariensis*; Labiatae; diterpenes; deoxocarnosol 12-methyl ether; salvicanol; 6α-hydroxydemethylcryptojaponol.

Abstract—The new diterpenes, deoxocarnosol 12-methyl ether, salvicanol and 6α-hydroxydemethylcryptojaponol, and the known ones, sugiol and demethylcryptojaponol, have been isolated from the bark of the roots of *Salvia canariensis*.

INTRODUCTION

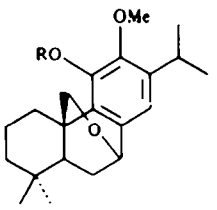
Earlier we reported the isolation and structural determination of the diterpenes galdosol [1] and arucatriol [2] from the aerial part, and rosmanol [3] from the flowers of *Salvia canariensis*, a species endemic of the Canary Islands. Continuing with this work we describe here the structural study of three other new diterpenes obtained from the roots of the same plant.

RESULTS AND DISCUSSION

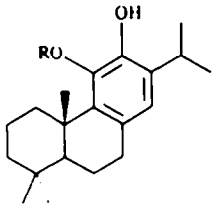
The structure of the less polar new compound isolated from *S. canariensis* was assigned as deoxocarnosol 12-methyl ether (**1**) in accordance with the following data. The empirical formula, $C_{21}H_{30}O_3$, was established by combustion analysis. The IR spectrum showed absorptions by hydroxyl groups, while in the ^{1}H NMR spectrum there appeared signals typical of a methoxyl, an isopropyl, two methyls, an oxymethylene group and a hydrogen geminal to an oxygen function. The chemical shift and the form of resonance of this last signal indicated that this hydrogen is at C-7. Acetylation of **1** gave a monoacetate **2** and methylation with dimethyl sulphate afforded the corresponding ether **3**. The structure **1** was chosen and not the alternative **4** because the difference in the chemical shift between the methyls of the isopropyl group in the ^{1}H NMR spectrum measured in $CDCl_3$ and pyridine-d_5 was only 0.03 ppm. Wenkert's studies [4] have shown that a hydroxyl group at C-13 produces a solvent shift of 0.4 ppm.

Chemical proof of structure **1** for this new compound was obtained because oxidation of its methyl ether **3** with *t*-butyl chromate [5] afforded carnosol dimethyl ether (**8**) [6, 7]. Although compound **1** is new in nature its 12-demethyl derivative, 20-deoxocarnosol, has been isolated from *Coleus barbatus* [8].

To the second new compound, named salvicanol, the structure **6** was assigned on the basis of the following considerations. Its IR spectrum showed bands characteristic of an aromatic ring and hydroxyl groups. In the ^{1}H NMR spectrum signals of a methoxyl, two angular methyls and an isopropyl group could be observed. Notable features were the absence in the spectrum of the C-20 methyl signals and the presence in the spectrum of a pair of doublets (J = 14 Hz) centred at δ2.50 and 3.25 which were assigned to the two hydrogens on C-20. Acetylation of **6** gave a monoacetate **7** with hydroxyl absorptions in the IR spectrum. In the ^{13}C NMR spec-



1 R = H
2 R = Ac
3 R = Me



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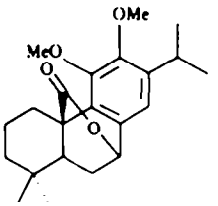

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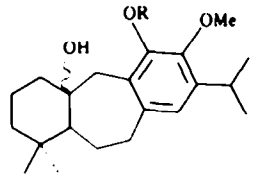
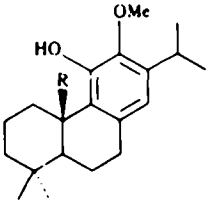
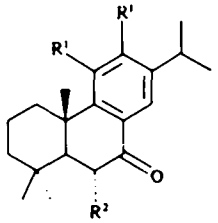


6 R = H
7 R = Ac



8 R = Me
9 R = CH_2OH



10 R^1 = OAc, R^2 = H
11 R^1 = R^2 = OAc
12 R^1 = R^2 = OH

trum of this monoacetate, in addition to the aromatic carbons and those of the acetate there appear resonances of four methyls, six methylenes, two methines and two fully substituted carbon atoms; one of these last atoms (C-10, δ70.69) is attached to an oxygen function.

The seven-membered ring of salvicanol can be formed by enzymic abstraction of a hydrogen from the C-20 methyl or by solvolysis of a hydroxyl group from the C-20 hydroxymethylene in compounds such as **8** or **9**, respectively. Then bond migration can take place from C-9, C-10 to C-9, C-20, and attack of OH^- can occur at C-10. Thus the stereochemistry at C-5 must be that of the precursor, H-5α, in diterpenes derived from a dehydroabietane skeleton. The stereochemistry at C-10 remained undetermined, but studies with Dreiding models indicated that an attack of the OH^- on the α-face is favoured.

Other diterpenes with a seven-membered ring B are icetexone and romulogarzone, isolated from *Salvia ballotaeflora* [9], nilgherrons A and B from *Plectranthus nilgherrieus* [10], barbatusol from *Coleus barbatus* [11], and pisiferin and isopisiferin from *Chamaecyparis pisifera* [12].

Acetylation and rechromatography of several fractions obtained from the main chromatography of the extract afforded the third new diterpene in the form of a triacetate. With a molecular formula of $C_{26}H_{34}O_7$, this substance showed in the IR spectrum characteristic absorptions of an aromatic function and of carbonyl groups. One of these carbonyls must be conjugated (1685 cm^{-1}). Its ^1H NMR spectrum had signals of three acetates, three angular methyls and an isopropyl group. This must be attached to an aromatic ring because a multiplet at δ2.87 can be assigned to the hydrogen of the isopropyl function. Other signals of this spectrum are a proton geminal to an equatorial acetate at δ5.78 (*d*, J = 14 Hz) and an aromatic hydrogen at δ7.95 (*s*). All these data are in accordance with the structure **11** given for this compound. When compound **11** was treated with zinc in acetic acid, the diacetate of demethylcryptojaponol (**10**) was obtained, identical with that obtained by acetylation of demethylcryptojaponol. Therefore, the natural compound was 6α-hydroxydemethylcryptojaponol (**12**), because in the ^1H NMR spectrum of the fraction prior to acetylation there were no signals of acetates.

A further two compounds isolated from *Salvia canariensis* were identified with sugiol (12-hydroxy-8,11,13-abietatrien-7-one) [13] and demethylcryptojaponol (11,12-dihydroxy-8,11,13-abietatrien-7-one) [14].

EXPERIMENTAL

Mps are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained using $CDCl_3$ as solvent, unless otherwise stated. IR spectra were obtained in $CHCl_3$. Dry CC was performed on silica gel 0.05–0.2 mm. Voucher specimens have been deposited at the Herbarium of the Department of Botany, Faculty of Biology, University of La Laguna.

The finely cut bark of the roots of *Salvia canariensis* (1 kg) was extracted with Me_2CO (5 l.) at room temp. for 4 weeks. Filtration and evaporation of the solvent gave an extract (26 g). Dry CC of this extract eluting with petrol–EtOAc mixtures afforded in order of elution: deoxocarnosol 12-methyl ether (**1**, 550 mg), salvicanol (**6**, 210 mg), sugiol (480 mg) and a complex mixture. Acetylation of this mixture and chromatography afforded demethylcryptojaponol acetate (**10**, 240 mg) and 6α-hydroxydemethylcryptojaponol triacetate (**11**, 345 mg).

Deoxocarnosol 12-methyl ether (**1**). Mp 188–190°. (Found: C, 76.30; H, 9.30. $C_{21}H_{30}O_3$ requires C, 76.36; H, 9.09%.) ^1H NMR (200 MHz): δ0.85 and 1.16 (each 3H, *s*), 1.23 and 1.25 (each 3H, *d*, J = 6 Hz), 2.63 (1H, *m*, H-1β), 3.10 (1H, *dd*, J = 2 and 8 Hz, H-20), 3.23 (1H, *m*, H-15), 3.77 (3H, *s*, OMe), 4.36 (1H, *d*, J = 8 Hz, H-20), 4.73 (1H, *dd*, J = 1 and 2 Hz, H-7), 6.67 (1H, *s*, H-14); ^1H NMR (90 MHz, pyridine-d_5): δ0.79 and 1.18 (each 3H, *s*), 1.27 and 1.30 (each 3H, *d*, J = 6 Hz), 3.29 (1H, *br d*, J = 8 Hz, H-20), 3.33 (1H, *m*, H-15), 3.79 (3H, *s*, OMe), 4.46 (1H, *d*, J = 8 Hz), 4.98 (1H, *br s*, H-7), 6.86 (1H, *s*, H-14). ^{13}C NMR (50 MHz): δ19.23 (C-2), 21.44 (C-19), 23.93 and 24.00 (C-16 and C-17), 26.73 (C-15), 30.05 and 30.76 (C-1 and C-6), 33.13 (C-18), 34.07 (C-4), 40.11 (C-10), 41.48 (C-3), 43.27 (C-5), 62.03 (OMe), 68.81 (C-20), 71.13 (C-7), 112.43 (C-14), 127.77 and 129.23 (C-8 and C-9), 137.64, 138.65 and 143.55 (C-11, C-12 and C-13). EIMS *m/z* (rel. int.): 330 $[M]^+$ (3), 300 (27), 285 (4), 233 (3), 231 (3), 229 (2), 218 (3), 215 (4), 115 (2), 81 (3), 69 (48). *Acetate* (**2**). $[M]^+$ at 372.2299 (Calc. for $C_{23}H_{32}O_4$ 372.2301). ^1H NMR (60 MHz): δ0.86 and 1.16 (each 3H, *s*), 1.23 (6H, *t*), 2.30 (3H, *s*, OAc), 3.07 (1H, *br d*, J = 9 Hz, H-20), 3.20 (1H, *m*, H-15), 3.75 (3H, *s*, OMe), 4.32 (1H, *d*, J = 9 Hz, H-20), 4.80 (1H, *dd*, J = 2 Hz, H-7). EIMS *m/z* (rel. int.): 372 $[M]^+$ (8), 342 (31), 300 (100), 285 (15). *Methyl ether* (**3**). Mp 121–123°; ^1H NMR (200 MHz): δ0.82 and 1.12 (each 3H, *s*), 1.17 (6H, *d*, J = 7 Hz), 2.99 (1H, *dd*, J = 1.7 and 8 Hz, H-20), 2.28 (1H, *m*, H-15), 3.74 and 3.80 (each 3H, *s*, OMe), 4.28 (1H, *d*, J = 8 Hz, H-20), 4.70 (1H, *dd*, J = 1 and 2 Hz, H-7), 6.79 (1H, *s*, H-14). EIMS *m/z* (rel. int.): 344 $[M]^+$ (21), 329 (3), 314 (100), 299 (24), 247 (17), 232 (23).

Salvicanol (**6**). Obtained as a gum. $[M]^+$ at *m/z* 332.2367 (Calc. for $C_{21}H_{32}O_3$ 332.2351); IR ν_{max} cm^{-1}: 3520, 1620, 1575, 1450, 1420, 1360, 1330, 1300, 1095, 1080, 1050, 1030, 1020, 995, 970, 940, 860; ^1H NMR (200 MHz): δ0.89 and 0.92 (each 3H, *s*), 1.19 and 1.23 (each 3H, *d*, J = 7 Hz), 2.50 and 3.25 (each 1H, *d*, J = 14 Hz, H-20), 3.22 (1H, *m*, H-15), 3.75 (3H, *s*, OMe), 6.55 (1H, *s*, H-14). EIMS *m/z* (rel. int.): 332 $[M]^+$ (14), 314 (17), 300 (11), 285 (8), 245 (14), 206 (100), 194 (24), 193 (27), 191 (17), 177 (14). *Acetate* (**7**). $[M-H_2O]^+$ at *m/z* 374.2504 (Calc. for $C_{23}H_{34}O_4$ 374.2456). ^1H NMR (200 MHz): δ0.86 and 0.89 (each 3H, *s*), 1.17 and 1.20 (each 3H, *d*, J = 7 Hz), 2.34 (3H, *s*, OAc), 2.63 (2H, *d*, J = 3 Hz, H-20), 2.75 (2H, *m*, H-7), 3.23 (1H, *m*, H-15), 3.68 (3H, *s*, OMe), 6.84 (1H, *s*, H-14); ^{13}C NMR (50 MHz): δ18.84 (C-2), 20.85 (Ac), 21.80 and 32.39 (C-18 and C-19), 23.60 and 23.96 (C-16 and C-17), 23.60 (C-6), 34.56 (C-4), 36.65 (C-5). EIMS *m/z* (rel. int.): 374 $[M-H_2O]^+$ (13), 332 (20), 314 (6), 300 (11), 285 (7), 248 (7), 236 (16), 206 (100), 194 (65), 193 (35), 191 (15), 177 (11), 151 (8).

Sugiol, mp 294–296° (lit. 291–293°) [15]. ^1H NMR (200 MHz): δ0.89 and 0.95 (each 3H, *s*), 1.82 and 1.85 (each 3H, *d*, J = 7 Hz), 3.11 (1H, *m*, H-15), 5.67 (1H, *s*, H-11), 7.88 (1H, *s*, H-14). MS identical with that reported [16].

Demethylcryptojaponol diacetate (**10**). Mp 182–184°. $[M]^+$ at *m/z* 400.2245 (Calc. for $C_{24}H_{32}O_5$ 400.2248); ^1H NMR (200 MHz): δ0.90 and 0.93 (each 3H, *s*), 1.16 and 1.19 (each 3H, *d*, J = 7 Hz), 1.29 (3H, *s*), 2.27 and 2.28 (3H, *s*), 2.80 (1H, *m*, H-15), 7.98 (1H, *s*, H-14). EIMS *m/z* (rel. int.): 400 $[M]^+$ (7), 358 (6), 316 (100), 301 (30), 231 (13), 219 (14), 205 (6), 179 (4). Identical with a sample obtained by acetylation of demethylcryptojaponol [14].

6α-Hydroxydemethylcryptojaponol triacetate (**11**). Mp 179–181°; $[M]^+$ at *m/z* 458.2317 ($C_{26}H_{34}O_7$ requires 458.2304). IR ν_{max} cm^{-1}: 3020, 2460, 1770, 1735, 1700, 1600, 1365, 1200, 1140, 1050, 1010, 880. ^1H NMR (200 MHz): δ1.02 and 1.11 (each 3H, *s*), 1.15 and 1.18 (each 3H, *d*, J = 7 Hz), 1.48 (3H, *s*), 2.21 (1H, *d*, J = 14 Hz, H-5), 2.22, 2.28 and 2.29 (each 3H, *s*, Ac), 2.87 (1H, *m*, H-15), 5.78 (1H, *d*, J = 14 Hz, H-6), 7.95 (1H, *s*, H-14). ^{13}C NMR (50 MHz): δ18.88 (C-2), 20.48, 21.34 and 22.13 (3 OAc), 22.55 (C-19), 22.71 and 22.89 (C-16 and C-17), 27.83 (C-15), 33.84 (C-4), 35.53 (C-18), 37.11 (C-1), 41.87 (C-3), 42.20 (C-

10), 52.26 (C-5), 74.72 (C-6), 124.85 (C-14), 128.85 (C-8), 141.25, 142.41, 143.65 and 145.66 (C-9, C-10, C-11 and C-12), 192.66 (C-7). EIMS *m/z* (rel. int.): 458 [M]$^+$ (8), 416 (5), 374 (100), 332 (12), 314 (43), 299 (34), 271 (10), 247 (13), 231 (8), 219 (15).

Oxidation of **3** *with t-butyl chromate.* The dimethyl ether (**3**) (43 mg) in CCl_4 (4 ml) was treated with *t*-butyl chromate–CCl_4 (0.8 M) (2.1 ml), glacial HOAc (0.6 ml) and Ac_2O (0.3 ml). The reaction mixture was refluxed under an inert atmosphere for 10 hr. An aq. soln of oxalic acid was added to eliminate the *t*-butyl chromate excess and the mixture was then poured into H_2O and extracted with $CHCl_3$ as usual. Chromatography of the residue afforded carnosol dimethyl ether (**5**), mp 154–156° (lit. 156° [17]), spectroscopic data identical with those reported [6, 7].

Reduction of **11** *with* Zn HOAc. 6α-Hydroxydemethylcryptojaponol triacetate (**11**) (60 mg) in HOAc (30 ml) was treated with powdered zinc with stirring and under argon for 3 hr. The filtrate was evaporated off and the residue treated with an aq. soln of NaOH (5%) and extracted with Et_2O as usual. Evaporation of the solvent and chromatography of the residue afforded demethylcryptojaponol diacetate (**10**), identical with the data reported above.

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