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DITERPENES FROM *SIDERITIS INFERNALIS*

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Key Word Index—*Sideritis infernalis*; Labiatae; diterpenes; *ent*-kaurene; episinfernal; sinfernal; sinfernol; epoxysinfernol; canditriol.

Abstract—Five new *ent*-kaurene diterpenes, episinfernal, sinfernal, sinfernol, epoxysinfernol and canditriol, and the known one, candol B, candicandiol and candidiol, have been isolated from the aerial parts of *Sideritis infernalis*.

INTRODUCTION

The phytochemical study of the genus *Sideritis* (Labiatae), endemic to the Canary Islands, has been a subject of interest to us during the past 15 years [1, 2]. We have now investigated the aerial parts of *Sideritis infernalis*, a species endemic to the island of Tenerife, from which we have obtained five new diterpenes: episinfernal (*ent*-7α,18-dihydroxykaur-15-en-17-al, **1**), sinfernal (*ent*-7β,18-dihydroxykaur-15-en-17-al, **5**), sinfernol (*ent*-7β,17,18-trihydroxykaur-15-ene, **7**), epoxysinfernol (*ent*-15β,16β-epoxy-7β,17,18-trihydroxykaurane, **18**) and canditriol (*ent*-7β,15β,18-trihydroxykaur-16-ene, **21**).

RESULTS AND DISCUSSION

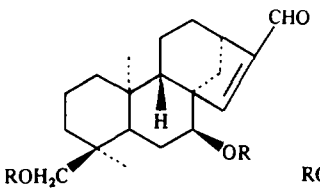
The structure **1** was assigned to episinfernal, the least polar new substance obtained from *S. infernalis*. This compound was isolated as its diacetate **2** by acetylation and chromatography of fractions obtained from the main chromatography. Its ^{1}H NMR spectrum showed the signals of two methyls, two acetates, the two hydrogens of an acetylated primary alcohol (δ3.68, *s*) the proton geminal to an acetylated secondary alcohol (δ4.81, *br s*), an aldehydic proton (δ9.71, *s*) and the hydrogen of a double bond conjugated with the carbonyl of the aldehyde (δ6.66, *s*). On the basis of these data and comparison with those of epicandicandiol diacetate (**3**) [3], we assigned this compound a kaurene skeleton with the two acetylated hydroxyls at C-7β and C-18. The rest of the molecule must be formed with the aldehyde at C-17 and the double bond at C-15, C-16. The ^{13}C NMR spectral data (Table 1) confirmed the structure of episinfernal diacetate (**2**).

The second new diterpene was named sinfernal (**5**). The ^{1}H NMR spectrum of its diacetate **6** was similar to that of **2**, but the resonance of the proton geminal to the acetylated secondary alcohol was different in both compounds, now being equatorial in **6** (4.96, *dd*, J = 11 and 4 Hz). Although the ^{13}C NMR spectrum confirmed the structure of **6**, the new compound sinfernal (**5**) was related to candicandiol (**9**) [4, 5] in the following way. The diacetate of candicandiol (**10**) was epoxidized with *m*-chloroperbenzoic acid giving the epoxide **11**. Treatment of this compound with boron trifluoride etherate in benzene afforded a mixture of the aldehydes **12** and **13** in the proportion 2:1 (^{1}H NMR: δ9.81 and 9.60). This mixture was easily oxidized by air forming the acids **14** and **15**, which were separated by chromatography and methylated with diazomethane to give the corresponding methyl esters **16** and **17**. These two compounds were identical with those obtained by hydrogenation of sinfernal diacetate (**6**), followed by air oxidation and methylation. The configurations at C-16 of the two acids, **14** and **15**, were assigned in accordance with the magnitude of the H-13,H-16 coupling patterns in the ^{1}H NMR spectra of their methyl esters **16** and **17**.

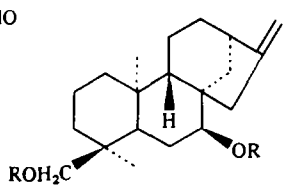
The third new compound, sinfernol (**7**), was a triol related to compound **5**. In its ^{1}H NMR spectrum the aldehydic proton had disappeared; being replaced now by the two doublets characteristic of a hydroxymethylene group, and the hydrogen of the double bond was now at a higher field than seen in **5**. In accordance with these data, the structure **7** was assigned to this new compound. Reduction of sinfernal (**5**) with sodium borohydride in the presence of cerium trichloride [6] afforded **7**, identical with the natural compound sinfernol.

Another new diterpene isolated from this species was epoxysinfernol (**18**). This compound was obtained in the form of the triacetate (**19**) by acetylation of some fractions of the extract that contained **18**. The ^{1}H NMR spectrum of **19** was also very similar to that of sinfernol triacetate (**8**), but it lacked the vinyl proton signal, a new one appearing that originated from the hydrogen geminal to an epoxidic function. Epoxidation of sinfernol triacetate (**8**) with *m*-chloroperbenzoic acid afforded the epoxide **19**, identical with the acetylated natural product. The α-configuration for the oxiranic ring was given because it is known that in this kind of compound oxidation occurs on this face.

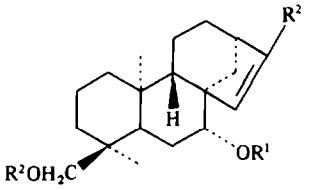
Finally, the most polar new compound was named canditriol and its structure determined as **21** on the basis of the following considerations. High resolution mass spectrometry was in accordance with the formula $C_{20}H_{32}O_3$. Its ^{1}H NMR spectrum displayed signals of a primary alcohol group, which must be equatorial as inferred from the chemical shift of the hydroxymethylene hydrogens in **21** and its acetate **22** [7]. Other signals observed in this spectrum were two methyl groups, an exocyclic double bond and two protons geminal to hydroxylic functions. One of these alcoholic groups must



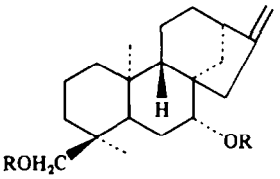
1 R = H
2 R = Ac



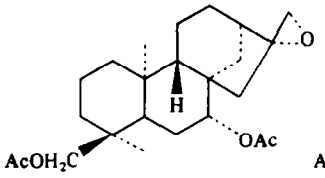
3 R = Ac
4 R = H



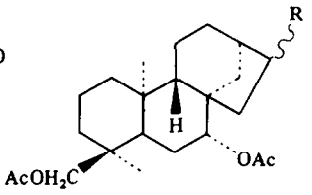
5 R^1 = H, R^2 = CHO
6 R^1 = Ac, R^2 = CHO
7 R^1 = H, R^2 = CH_2OH
8 R^1 = Ac, R^2 = CH_2OAc



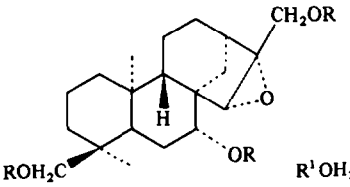
9 R = H
10 R = Ac



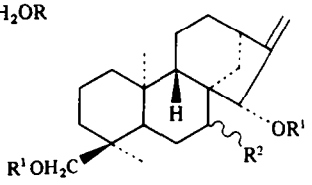
11



12 R = α-CHO
13 R = β-CHO
14 R = α-CO_2H
15 R = β-CO_2H
16 R = α-CO_2Me
17 R = β-CO_2Me



18 R = H
19 R = Ac



20 R^1 = R^2 = H
21 R^1 = H, R^2 = α-OH
22 R^1 = Ac, R^2 = α-OAc
23 R^1 = Ac, R^2 = β-OAc

be at C-7α, because in comparison with candicandiol its geminal proton has the same form of resonance. The other must be at C-15 because its geminal hydrogen appears in the spectrum as a singlet at δ4.06. The α-configuration was given to the C-15 alcohol on consideration that this plant also contains candidiol (**20**), a diterpene with a 15α-hydroxyl function. Oxidation of candicandiol (**9**) with selenium dioxide afforded a compound (**21**) identical with the natural substance. This reaction also confirmed the stereochemistry of the alcohol group at C-15, because it is known that in this reaction the hydroxyl formed has the α-stereochemistry [8].

Sideritriol, epoxysideritriol and eubotriol, the C-7 epimers of sinfernol (**7**), epoxysinfernol (**18**) and canditriol (**21**) respectively, have been isolated from other species of *Sideritis* genus [9–11]. We have now prepared eubotriol by selenium dioxide oxidation of epicandicandiol (**4**), and the ^{13}C NMR spectral data of its triacetate (**23**) is shown in Table 1.

We have also isolated from this species the known diterpenes candol B (18-hydroxy-*ent*-kaur-16-ene) [12], candidiol (**20**) [3] and candicandiol (**9**) [4, 5].

EXPERIMENTAL

Mps: uncorr.; NMR; $CDCl_3$, 200 MHz, unless indicated otherwise; MS: 70 eV (probe); column and dry column chromatography: silica gel 0.063–0.2 mm.

The air-dried aerial part of the plant, *Sideritis infernalis* (1.7 kg), collected at Barranco del Infierno (Adeje, Tenerife) in May, was used for this work. A voucher specimen has been deposited at the Herbarium of the Instituto Canario de Investigaciones Agrarias (ORT 28643).

A general description of the procedure to isolate the terpenoid substances of species of the genus *Sideritis* has been published previously [2]. In this way candol B (15 mg), candidiol (**20**, 3.5 g), candicandiol (**9**, 5.9 g), a mixture of episinfernal (**1**) and sinfernal (**5**) (60 mg), sinfernal (**5**, 120 mg), sinfernol (**7**, 80 mg), a mixture of sinfernol (**7**) and epoxysinfernol (**18**) (130 mg), and canditriol (**21**, 160 mg) were obtained. The mixture of the aldehydes **1** and **5** was acetylated and chromatographed to give pure compounds **2** (20 mg) and **6** (25 mg). In the same way the mixture of **7** and **18** was resolved as its acetates **8** (40 mg) and **19** (70 mg).

Episinfernal diacetate (**2**). Mp 125–127°, $[M]^+$ at *m/z* 402.2402. $C_{24}H_{34}O_5$ requires 402.2404; ^1H NMR: δ0.80 and 1.08 (each 3H,

Table 1. ^{13}C NMR spectral data ($CDCl_3$, 50.32 MHz)

Carbon	2	3*	6	8	10	19	22	23
1	39.68	39.5	39.73	39.09	39.68	39.77	39.53	39.56
2	17.76	17.6	17.75	17.85	17.72	17.70	17.73	17.78
3	35.66	35.5	35.70	35.92†	35.73	35.65	35.72	35.46
4	36.29	36.1	36.48	36.48	36.23	36.50	36.25	36.21
5	41.55	41.7	46.35†	46.73	46.55	46.79	45.59	41.57
6	23.89	24.8	25.29	25.60	25.56	26.63	26.35	24.20
7	76.00	79.3	76.53	75.99	76.40	74.59	73.11	74.68
8	53.65	46.8	55.61	53.84	48.19	47.49	50.76	49.79
9	43.10	51.2	46.69†	47.66	55.21	49.25	54.06	48.92
10	39.68	38.9	39.24	40.46	39.10	38.88	38.99	39.43
11	18.14	17.6	18.33	18.48	17.89	18.05	17.99	17.78
12	25.14	33.2	25.12	25.34	33.30	25.34	32.64	33.32
13	38.07	43.6	36.79	39.80	42.81	34.94	41.71	42.27
14	41.39	38.2	35.31	35.84†	31.84	24.64	30.94	35.38
15	155.63	45.1	158.47	135.32	43.00	63.50	82.14	80.49
16	149.38	154.1	149.25	142.04	154.38	61.20	154.85	154.95
17	189.44	103.7	189.15	62.33	103.32	62.04	109.68	110.60
18	72.53	72.4	72.31	72.42	72.21	72.35	72.20	72.52
19	17.39	17.3	17.56	17.60	17.53	17.63	17.43	17.60
20	18.03	17.8	18.29	18.28	18.06	17.92	17.86	18.02

*Taken from ref. [13].
†These values can be interchanged.

s), 2.04 and 2.11 (each 3H, *s*), 3.68 (2H, *s*, H-18), 4.81 (1H, *br s*, H-7), 6.66 (1H, *s*, H-15), 9.71 (1H, *s*, H-17); EIMS *m/z* (rel. int.): 402 $[M]^+$ (0.2), 360 (3), 342 (8), 300 (4), 298 (5), 285 (17), 282 (18), 269 (43), 267 (19), 254 (7), 253 (9), 251 (8), 239 (6), 225 (9).

Sinfernal (**5**). Obtained as a gum; ^1H NMR: δ0.72 and 1.07 (each 3H, *s*), 3.06 and 3.37 (each 1H, *d*, J = 10 Hz, H-18), 3.85 (1H, *br s*, H-7), 6.70 (1H, *s*, H-15), 9.71 (1H, *s*, H-17); EIMS *m/z* (rel. int.): 318 $[M]^+$ (0.5), 303 (0.7), 300 (1), 287 (29), 275 (4), 269 (6), 257 (3), 161 (4), 149 (17), 145 (4), 135 (6), 131 (4), 123 (13), 117 (5), 109 (16). Sinfernal diacetate (**6**), a gum $[M]^+$ at *m/z* 402.2355, $C_{24}H_{34}O_5$ requires 402.2406; ^1H NMR: δ0.77 and 1.06 (each 3H, *s*), 1.95 and 2.03 (each 3H, *s*), 1.95 and 2.03 (each 3H, *s*), 3.55 and 3.77 (each 1H, *d*, J = 10 Hz, H-18), 4.96 (1H, *dd*, J = 11 and 4 Hz, H-7), 6.62 (1H, *s*, H-15), 9.64 (1H, *s*, H-17); EIMS *m/z* (rel. int.): 402 $[M]^+$ (0.6), 360 (7), 342 (5), 300 (4), 282 (25), 270 (12), 269 (52), 267 (17), 254 (9), 225 (7).

Sinfernol (**7**). Mp 225–227°, $[M]^+$ at *m/z* 320.2312, $C_{20}H_{32}O_3$ requires 320.2351; ^1H NMR (C_5D_5N): δ0.84 and 1.11 (each 3H, *s*), 3.32 and 3.69 (each 1H, *d*, J = 10 Hz, H-18), 4.12 (1H, *br s*, H-7), 4.49 (2H, *s*, H-17), 5.81 (1H, *s*, H-15); EIMS *m/z* (rel. int.): 320 $[M]^+$ (1), 302 (12), 287 (22), 271 (18), 253 (7), 209 (7), 180 (6), 162 (13), 161 (10), 157 (6), 145 (11), 143 (6), 131 (12). Sinfernol triacetate (**8**), $[M-C_2H_2O]^+$ at *m/z* 404.2539, $C_{24}H_{36}O_5$ requires 404.2561; ^1H NMR: δ0.79 and 1.06 (each 3H, *s*), 1.99, 2.05 and 2.07 (each 3H, *s*), 3.58 and 3.80 (each 1H, *d*, J = 11 Hz, H-18), 4.53 and 4.63 (each 1H, *d*, J = 14 Hz, H-17), 4.89 (1H, *dd*, J = 11 and 5 Hz, H-7), 5.44 (1H, *s*, H-15); EIMS *m/z* (rel. int.): 404 $[M-C_2H_2O]^+$ (2), 386 (18), 345 (21), 344 (78), 327 (12), 326 (43), 311 (11), 284 (22), 266 (49), 253 (61), 251 (35), 237 (13), 225 (17), 223 (14), 197 (12).

Epoxysinfernol triacetate (**19**). $[M-C_2H_2O]^+$ at *m/z* 420.2878, $C_{24}H_{36}O_6$ requires 420.2512; ^1H NMR: δ0.78 and 1.02 (each 3H, *s*), 2.02 (3H, *s*), 2.04 (6H, *s*), 3.00 (1H, *s*, H-15), 3.59 and 3.76 (each 1H, *d*, J = 11 Hz, H-18), 3.98 and 4.62 (each 1H, *d*, J = 12 Hz, H-17), 5.01 (1H, *dd*, J = 11 and 5 Hz, H-7); EIMS *m/z* (rel. int.): 420 $[M-C_2H_2O]^+$ (1), 403 (51), 386 (3), 360 (2), 344 (6), 326 (5), 313 (4), 283 (11), 253 (9), 225 (5), 197 (4).

Canditriol (**21**). Mp 220–222°, $[M]^+$ at *m/z* 320.2393, $C_{20}H_{32}O_3$ requires 320.2352; ^1H NMR: δ0.72 and 1.05 (each 3H, *s*), 3.04 and 3.45 (each 1H, *d*, J = 11 Hz, H-18), 3.88 (1H, *dd*, J = 11 and 5 Hz, H-7), 4.06 (1H, *s*, H-15), 5.05 and 5.13 (each 1H, *s*, H-17); EIMS *m/z* (rel. int.): 320 $[M]^+$ (15), 302 (13), 287 (8), 271 (16), 262 (21), 261 (7), 253 (7), 201 (8), 180 (5), 162 (19), 147 (20). Canditriol triacetate (**22**), $[M-C_2H_2O]^+$ at *m/z* 404.2578, $C_{24}H_{36}O_5$ requires 404.2560; ^1H NMR: δ0.77 and 1.06 (each 3H, *s*), 1.96, 2.00 and 2.07 (each 3H, *s*), 3.60 and 3.77 (each 1H, *d*, J = 11 Hz, H-18), 4.81 (1H, *dd*, J = 11 and 5 Hz, H-7), 5.01 and 5.06 (each 1H, *s*, H-17), 5.41 (1H, *s*, H-15); EIMS *m/z* (rel. int.): 404 $[M-C_2H_2O]^+$ (23), 386 (10), 362 (6), 344 (71), 326 (26), 313 (15), 284 (31), 283 (22), 269 (28), 253 (36), 251 (24).

Epoxidation of compound **8**. Sinfernal triacetate (**8**, 17 mg) in $CHCl_3$ (2 ml) was added to a soln of *m*-chloroperbenzoic acid (10 mg) in $CHCl_3$ (2 ml). The mixture was left at room temp. for 90 min, washed with a satd soln of $NaHCO_3$ and then usual work-up and chromatography of the residue gave **19**, identical with the acetylated natural substance.

Epoxidation of compound **10**. Candicandiol diacetate (**10**, 300 mg) in $CHCl_3$ (8 ml) was treated as above for **8**. The reaction time in this case was 15 hr. Usual work-up afforded **11** (250 mg), ^1H NMR: δ0.77 and 1.06 (each 3H, *s*), 2.02 and 2.04 (each 3H, *s*), 2.76 and 2.84 (each 1H, *d*, J = 5 Hz, H-17), 3.54 and 3.78 (each 1H, *d*, J = 11 Hz, H-18), 4.64 (1H, *dd*, J = 11 and 5 Hz, H-7); EIMS *m/z* (rel. int.): 362 $[M-C_2H_2O]^+$ (1), 344 (5), 329 (2), 289 (37), 284 (87), 271 (94), 269 (53), 255 (24), 253 (22), 241 (16), 227 (40), 225 (11), 213 (16), 201 (11), 199 (13), 197 (13).

Preparation of compounds **16** *and* **17**. Compound **11** (230 mg) in dry C_6H_6 (9 ml) was treated with BF_3–Et_2O complex (3 drops) at 0° for 30 min. Usual work-up, evaporation of the solvent and chromatography of the residue gave a mixture of aldehydes **12** and **13** (200 mg). They were easily oxidized by air to a mixture of acids, which were separated by chromatography. Elution with C_6H_6–EtOAc (10%) afforded **14**, mp 207–209°; ^1H NMR: δ0.78 and 1.03 (each 3H, *s*), 2.01 and 2.05 (each 3H, *s*), 3.58 and 3.79 (each 1H, *d*, J = 11 Hz, H-18), 4.71 (1H, *dd*, J = 11 and 5 Hz, H-

7). Further elution gave **15**, mp 209–211°. ^{1}H NMR (200 MHz): δ0.77 and 1.03 (each 3H, *s*), 2.01 and 2.06 (each 3H, *s*), 3.55 and 3.80 (each 1H, *d*, J = 11 Hz, H-18), 4.65 (1H, *m*, H-7). Treatment of **14** and **15**, separately, with CH_2N_2 gave the corresponding methyl esters, **16** and **17**. *Methyl ester* **16**. ^{1}H NMR: δ0.79 and 1.04 (each 3H, *s*), 2.06 (6H, *s*), 2.45 (1H, *br s*, H-13), 2.60 (1H, *dd*, J_1 = 5, J_2 = 9 Hz, H-16), 3.58 and 3.79 (each 1H, *d*, J = 11 Hz, H-18), 3.62 (3H, *s*), 4.71 (1H, *dd*, J = 11 and 5 Hz, H-7); EIMS *m/z* (rel. int.): 403 $[M-MeO]^+$, 392 (2), 374 (3), 359 (2), 332 (4), 314 (79), 301 (81), 299 (30), 287 (18), 269 (14), 241 (21), 227 (27). *Methyl ester* **17**. $[M-C_2H_2O]^+$ at *m/z* 392.2542, $C_{23}H_{36}O_5$ requires 392.2562; ^{1}H NMR: δ0.77 and 1.03 (each 3H, *s*), 2.01 and 2.06 (each 3H, *s*), 2.54 (1H, *br s*, H-13), 2.83 (1H, *dt*, J_1 = 11, $J_2 = J_3$ = 7 Hz), 3.55 and 3.80 (each 1H, *d*, J = 11 Hz, H-18), 3.65 (3H, *s*), 4.66 (1H, *m*, H-7); EIMS *m/z* (rel. int.): 403 $[M-MeO]^+$ (0.5), 392 (2), 374 (3), 359 (2), 319 (22), 314 (89), 301 (100), 299 (26), 287 (14), 285 (8), 269 (10), 241 (17), 227 (22), 196 (150).

Hydrogenation of aldehyde **6**. Compound **6** (30 mg) was dissolved in EtOH and hydrogenated over C/Pd (5%), at room temp. for 12 hr. In this way a mixture of the aldehydes **12** and **13** was obtained. Oxidation with air of this mixture gave the corresponding acids. Methylation with CH_2N_2 and chromatography of the residue afforded the compound **16** and **17**, identical with the substances obtained above.

SeO_2 *oxidation of candicandiol* (**9**). Compound **9** (50 mg) was treated with SeO_2 (15 mg) in dioxan (5 ml) and H_2O (1.5 ml) at room temp. for 4 hr. Usual work-up and chromatography of the residue gave **21**, identical with the natural compound (canditriol).

Reduction of compound **5**. Compound **5** (50 mg) was added to a soln of $NaBH_4$ (50 mg) and cerium trichloride (280 mg) in MeOH (7 ml). The mixture was stirred at room temp. for 90 min, diluted with H_2O and extracted as usual. Evaporation of the solvent and chromatography of the residue afforded starting material (**5**) (17 mg) and the triol **7** (28 mg). Acetylation of **7** in the usual way afforded a compound identical with the acetylated natural product **8** (sinfernol triacetate).

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