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DITERPENOIDS FROM *SIDERITIS FOETENS**

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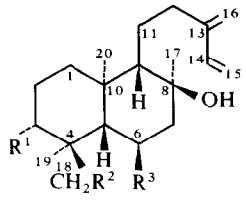
Abstract—From the aerial parts of *Sideritis foetens*, the previously known *ent*-13(16),14-labdadiene-6α,8α,18-triol (andalusol) has been isolated. In addition, two new natural andalusol monoacetates and the novel *ent*-6α-acetoxy-13(16),14-labdadiene-3β,8α-diol have also been obtained from the same source. The structures of these new diterpenoids have been established by chemical and spectroscopic means.

INTRODUCTION

In our search for new natural diterpenoids in plants endemic in the Iberian Peninsula [1–5], we have examined the aerial parts of *Sideritis foetens* Clemen. (Labiatae), a species which grows only in reduced areas of south-east Spain. From this source four diterpenic compounds have been isolated. One of these diterpenoids is the previously known *ent*-13(16),14-labdadiene-6α,8α,18-triol (**1**, andalusol) [6], whereas the others are new natural products.

RESULTS AND DISCUSSION

Two of the new diterpenoids isolated are isomeric compounds, $C_{22}H_{36}O_4$. On alkaline hydrolysis, both substances yielded the known diterpenoid andalusol (**1**), the structure of which is firmly established by X-ray analysis [6]. The first one of these andalusol monoacetate (**2**) had the C-6 hydroxyl group esterified (^1H NMR spectrum: H-6 at δ 5.10, 2H-18 as an AB system centred at 3.24, C<u>H</u>$_3$COO– at 2.08). The other one is the 18-acetyl derivative **3** (H-6 at δ 3.80, 2H-18 as an AB system centred at 4.18, C<u>H</u>$_3$COO– at 2.08). Andalusol 6,18-diacetate (**4**) had resonances at δ 5.10 (H-6) and 3.83 (2H-18) [6]. The new compounds are thus 6-acetyl andalusol (**2**, *ent*-6α-acetoxy-13(16),14-labdadiene-8α,18-diol) and 18-acetyl andalusol (**3**, *ent*-18-acetoxy-13(16),14-labdadiene-6α,8α-diol).



	R¹	R²	R³
1	H	OH	OH
2	H	OH	OAc
3	H	OAc	OH
4	H	OAc	OAc
5	OH	H	OAc
6	OH	H	OH

The last diterpenoid isolated from *S. foetens* has been named 6-acetyl *iso*-andalusol (**5**) and its molecular formula was also $C_{22}H_{36}O_4$. The IR spectrum of this substance showed hydroxyl (3440 cm^{-1}) and acetoxyl (1710, 1270, 1260 cm^{-1}) absorptions. Alkaline hydrolysis of **5** yielded the triol **6** ($C_{20}H_{34}O_3$). The ^1H NMR spectrum of compound **5** (see Experimental) suggested a structure closely related to diterpenoid **2** with an identical side chain, a tertiary hydroxyl function on C-8 and an equatorial acetoxyl group attached to the C-6 carbon atom, but lacking the C-18 hydroxymethylene grouping of compound **2**, which was substituted in **5** by an additional C-Me singlet. The ^1H NMR spectrum of compound **5** showed also a one proton quartet (δ 3.22) which was attributed to the axial proton geminal to a secondary hydroxyl group. This alcohol must be placed between a tetrasubstituted sp^3 carbon atom and a methylene grouping ($J_{aa'} = 10$ Hz, $J_{ae'} = 6$ Hz). Thus, the new diterpenoid must be a 6-acetyl-18-desoxyandalusol with an equatorial alcohol on the C-3 or C-1 position. However, this last alternative location for the secondary hydroxyl group in compound **5** must be discarded on the basis of its ^{13}C NMR spectrum (Table 1), which also provided conclusive proof of the structure of this new diterpenoid.

Effectively, C-6 to C-17 and C-20 carbon resonances of compound **5** were identical with the same carbon resonances of 6,18-diacetyl andalusol (**4**) (Table 1), whereas the observed differences between compounds **5** and **4** in the C-1, C-2, C-3, C-4, C-5, C-18 and C-19 carbon resonances were clearly explained taking into account the change of the C-18 acetoxyl function in compound **4** by the C-3 equatorial alcohol in **5** [7–10]. In particular, the absence of a γ-gauche effect on the C-20 carbon atom, firmly discarded the C-1 position for the secondary free alcohol of compound **5** [11–13].

Finally, the absolute configuration of this new diterpenoid (**5**) was established as follows. Application of

* Part 43 in the series "Diterpenoids from *Sideritis*". For Part 42 see Escamilla, E. M. and Rodríguez, B. (1980) *An. Quím.* **76**, (in press).

Table 1. ^{13}C NMR chemical shifts* of compounds **5** and **4**

Carbon No.	5	4
1	37.8	39.1
2	26.7	17.3
3	78.1	37.0
4	38.8	36.3
5	57.8	51.8
6	70.2	70.5
7	50.1	50.1
8	73.3	73.1
9	60.6	60.8
10	39.4	39.3
11	24.3	24.5
12	34.5	34.7
13	146.8	146.9
14	138.5	138.5
15	115.6	115.6
16	113.4	113.5
17	25.4	25.2
18	30.0	74.1
19	15.7	17.9
20	16.4	16.7
MeCOO-	169.8	170.8
	—	170.0
CH$_3$COO-	21.8	21.7
	—	21.0

* All ^{13}C chemical shifts are given in ppm relative to TMS.

Horeau's method [14] to compound **5** defined the absolute stereochemistry of this equatorial alcohol as 3*R* and, as in these experimental conditions the tertiary C-8 OH group is unreactive [6], the new diterpenoid is thus *ent*-6α-acetoxy-13(16),14-labdadiene-3β,8α-diol (**5**, 6-acetyl *iso*-andalusol).

EXPERIMENTAL

Mps were determined in a Kofler apparatus and are uncorr. ^1H and ^{13}C NMR spectra were measured at 90 and 25.2 MHz, respectively, in $CDCl_3$ soln with TMS as internal standard. Assignments of ^{13}C chemical shifts were made with the aid of off-resonance and noise-decoupled ^{13}C NMR spectra. Elemental analyses were carried out in this laboratory with the help of an automatic analyser. Plant materials were collected in June 1979, near Almería, and voucher specimens were deposited in the Herbarium of the Faculty of Pharmacy (Madrid, 'Complutense' University).

Extraction and isolation of the diterpenoids. Dried and finely powdered *S. foetens* plants (3 kg) were extracted for 72 hr with petrol (20 l.) in a Soxhlet. The extract was concd under vacuum to leave a residue (42 g) which was repeatedly chromatographed on Si gel columns with petrol and petrol–EtOAc mixtures as eluents, yielding the following compounds in order of elution: 6-acetyl *iso*-andalusol (**5**, 460 mg), 18-acetyl andalusol (**3**, 690 mg), 6-acetyl andalusol (**2**, 980 mg) and andalusol (**1**, 1.3 g) [6]. The previously known diterpenoid (**1**) was identified by its physical (mp, $[\alpha]_D$) and spectroscopic (IR, ^1H NMR, MS) data and by comparison with an authentic sample. Compound **4** was previously described in ref. [6].

6-Acetyl andalusol (**2**). Mp 111.5–112° (Me$_2$CO–*n*-hexane), $[\alpha]_D^{20}$ − 64.4° (*c* 0.59, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3460, 3100, 3050, 2995, 2940, 2880, 1705, 1635, 1600, 1465, 1400, 1380, 1370, 1270, 1250, 1140, 1080, 1060, 1035, 997, 970, 955, 890, 805. UV λ_{max}^{EtOH} nm (ε): 225 (11 000). ^1H NMR (δ): vinyl group (ABX system, δ_A = 5.08, δ_B = 5.30, δ_X = 6.38; J_{AB} = 1.5, J_{AX} = 10.5, J_{BX} = 17.5 Hz, H-14 and 2H-15 protons), 5.10 (1H, *sextet*, $J_{aa'} = J_{aa''}$ = 9.5 Hz, $J_{ae'}$ = 4.5 Hz, H-6), 5.02 (2H, *s*, 2H-16), 3.53 and 2.95 (2H, AB system, *J* = 12 Hz, 2H-18), 2.08 (3H, *s*, –OAc), C–Me singlets at 1.27, 0.92 and 0.76. MS (12 eV, direct inlet) *m/e* (rel. int.): M$^+$ absent, 333 (M$^+$ − CH$_2$OH, 2.3), 304 (5), 289 (5), 286 (10), 273 (18), 255 (67), 206 (45), 187 (100), 175 (55), 173 (65), 151 (32), 135 (62), 121 (45), 109 (30), 95 (28), 93 (32). (Found: C, 72.67; H, 10.02. $C_{22}H_{36}O_4$ requires: C, 72.49; H, 9.96%.)

18-Acetyl andalusol (**3**). A syrup, n_D^{10} 1.5269, $[\alpha]_D^{20}$ − 27.4 (*c* 1.46, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3390, 3095, 3010, 2940, 2880, 1715, 1635, 1598, 1465, 1390, 1260, 1140, 1050, 998, 945, 896. ^1H NMR (δ): vinyl group (ABX system, δ_A = 5.07, δ_B = 5.29, δ_X = 6.37; J_{AB} = 1.5, J_{AX} = 10.5, J_{BX} = 17.5 Hz, H-14 and 2H-15 protons), 5.01 (2H, *s*, 2H-16), 4.48 and 3.88 (2H, AB system, *J* = 10.5 Hz, 2H-18), 3.80 (1H, *sextet*, $J_{aa'} = J_{aa''}$ = 10, $J_{ae'}$ = 4 Hz, H-6), 2.08 (3H, *s*, OAc), C–Me singlets at 1.20, 0.99 and 0.86. MS (12 eV, direct inlet) *m/e* (rel. int.): M$^+$ absent, 346 (M$^+$ − H$_2$O, 5), 331 (5), 328 (6), 313 (5), 289 (8), 286 (10), 271 (20), 255 (40), 253 (15), 249 (20), 187 (95), 175 (70), 173 (60), 151 (60), 135 (60), 123 (100), 109 (65), 95 (45), 93 (60). (Found: C, 72.68; H, 10.12. $C_{22}H_{36}O_4$ requires: C, 72.49; H, 9.96%.)

6-Acetyl iso-andalusol (**5**). Mp 117–117.5° (Me$_2$CO–*n*-hexane), $[\alpha]_D^{20}$ − 47.8° (*c* 0.71, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3440, 3085, 3005, 2990, 2940, 2870, 1710, 1630, 1595, 1465, 1400, 1385, 1370, 1270, 1260, 1145, 1035, 985, 965, 925, 905, 890. UV λ_{max}^{EtOH} nm (ε): 225.5 (11 300). ^1H NMR (δ): vinyl group (ABX system, δ_A = 5.07, δ_B = 5.28, δ_X = 6.38; J_{AB} = 1.5, J_{AX} = 10.5, J_{BX} = 17.3, H-14 and 2H-15 protons), 5.15 (1H, *sextet*, $J_{aa'} = J_{aa''}$ = 9, $J_{ae'}$ = 4 Hz, H-6), 5.01 (2H, *s*, 2H-16), 3.22 (1H, *q*, $J_{aa'}$ = 10, $J_{ae'}$ = 6 Hz, H-3), 2.04 (3H, *s*, –OAc), C–Me singlets at 1.28, 1.14, 0.88 and 0.82. ^{13}C NMR: see Table 1. MS (75 eV, direct inlet) *m/s* (rel. int.): M$^+$ absent, 304 (M$^+$ − HOAc, 3), 289 (5), 286 (7), 271 (6), 268 (5), 253 (8), 206 (35), 187 (90), 173 (30), 133 (50), 119 (70), 107 (55), 95 (50), 93 (70), 87 (100), 81 (95). (Found: C, 72.57; H, 10.03. $C_{22}H_{36}O_4$ requires: C, 72.49; H, 9.96%.)

Alkaline hydrolysis of **2** *and* **3** *to yield andalusol* (**1**). A soln of compound **2** (100 mg) in 1N ethanolic KOH (20 ml) was left at room temp. for 2 days. The soln was then diluted with H$_2$O, extracted with $CHCl_3$, and the $CHCl_3$ extract was dried, filtered and concd *in vacuo* to leave a residue (82 mg) of pure **1**, identical in all respects (mp, mmp, $[\alpha]_D$, IR, MS) to an authentic sample. Treatment of compound **3** (80 mg) under the same conditions also yielded andalusol (**1**).

Alkaline hydrolysis of **5** *to yield* ent-13(16),14-*labdadiene*-3β,6α,8α-*triol* (**6**). Treatment of compound **5** (150 mg) as described above yielded triol **6** (128 mg), mp 102–105° (aq. EtOH), $[\alpha]_D^{20}$ − 33.9° (*c* 1.49, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3520, 3440, 3310, 3090, 3000, 2940, 2870, 1630, 1595, 1390, 1285, 1130, 1040, 995, 930, 900, 800. ^1H NMR (δ): vinyl group (ABX system, δ_A = 5.07, δ_B = 5.28, δ_X = 6.38; J_{AB} = 1.5, J_{AX} = 10.5, J_{BX} = 17.5 Hz, H-14 and 2H-15 protons), 5.01 (2H, *s*, 2H-16), 3.93 (1H, *sextet*, $J_{aa'} = J_{aa''}$ = 10 Hz, $J_{ae'}$ = 4 Hz, H-6), 3.25 (1H, *q*, $J_{aa'}$ = 9 Hz, $J_{ae'}$ = 6 Hz, H-3), C–Me singlets at 1.28, 1.22, 0.94 and 0.83. MS (12 eV, direct inlet) *m/e* (rel. int.): 322 (M$^+$, 0.5), 304 (2), 289 (4), 286 (12), 271 (8), 269 (5), 253 (20), 133 (55), 121 (85), 119 (80), 107 (65), 95 (50), 93 (85), 91 (75), 81 (100). (Found: C, 74.71; H, 10.47. $C_{20}H_{34}O_3$ requires: C, 74.49; H, 10.63%.)

Application of Horeau's method [14] *to compound* **5**. A mixture of (±)-α-phenylbutyric anhydride (0.353 mmol) and **5** (0.114 mmol) in pyridine soln (2 ml) was kept at room temp. for 20 hr. α_1 = −1.108, α_2 = −1.348; $\alpha_1 - 1.1\alpha_2$ = +0.375. Configuration: 3*R*

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