# FOUR NEW DITERPENES FROM SIDERITIS SERRATA\*

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Abstract—Four new diterpenes have been isolated from Sideritis serrata: lagascol (4, ent-8,5-friedopimar-5-ene-15S,16-diol), tobarrol (8, ent-15-beyerene-12 $\alpha$ ,17-diol), benuol (12, ent-15-beyerene-7 $\alpha$ ,17-diol) and serradiol (18, ent-16R-atis-13-ene-16,17-diol). The previously known diterpenes lagascatriol (1, ent-8,5-friedopimar-5-ene-11 $\beta$ ,15S,16-triol), jativatriol (2, ent-15-beyerene-1 $\beta$ ,12 $\alpha$ ,17-triol), conchitriol (3, ent-15-beyerene-7 $\alpha$ ,12 $\alpha$ ,17-triol) and sideritol (17, ent-16R-atis-13-ene-1 $\beta$ ,16,17-triol) have also been obtained from the same source.

### INTRODUCTION

Continuing our studies on the diterpene fraction of plants of the genus *Sideritis* [1–3], we have looked at the composition of *S. serrata* Lag. a mountain shrub growing in the Southeast of Spain in Sierra de Benú, near Tobarra (Albacete province). Eight diterpenes have been isolated from this plant, four of which were already known: lagascatriol (1, *ent*-8,5-*friedo*pimar-5-ene-11 $\beta$ ,15*S*,16-triol) [4], jativa-triol (2, *ent*-15-beyerene-1 $\beta$ ,12 $\alpha$ ,17-triol) [2], conchitriol (3, *ent*-15-beyerene-7 $\alpha$ ,12 $\alpha$ ,17-triol) [2] and sideritol (17, *ent*-16*R*-atis-13-ene-1 $\beta$ ,16,17-triol) [5]; the remaining four diterpenes, minor components, appear to be desoxy-derivatives of the others.

# **RESULTS AND DISCUSSION**

The first new diterpene, lagascol (4),  $C_{20}H_{34}O_2$ , by acetylation yields a diacetate (5). Comparison of the NMR spectrum of 5 with the triacetate of lagascatriol (6) reveals the absence of the signal assigned to the proton geminal to the C-11 acetoxyl group (see Experimental). Treatment of 4 with acetone in the presence of anhydrous CuSO<sub>4</sub> affords the acetonide 7 identical (physical and spectroscopic data) with the acetonide of 11-desoxylagascatriol [4] and with the synthetic product previously obtained by McCrindle *et al.* [6] the structure of which has been established by X-ray crystallography [7]. Therefore lagascol (4) is *ent*-8,5-*friedo*pimar-5-ene-15*S*,16-diol.

Acetylation of the second minor component, tobarrol (8),  $C_{20}H_{32}O_2$ , gives a diacetate (9) probably related to jativatriol triacetate (10) since comparison of the NMR spectra of both shows a striking similarity except for the signal due to the C-1 proton of 10 which is lacking in the NMR spectrum of 9. Again treatment of 8 with anhydrous CuSO<sub>4</sub>/acetone affords the acetonide 11 identical in all respects with the 12,17-acetonide of 1-desoxyjativatriol [2]. Tobarrol (8) is thus *ent*-15-beyerene-12 $\alpha$ ,17-diol.

Benuol (12), the third component, is an isomer of tobarrol. Acctylation of 12 gives the corresponding diacetate (13) the NMR spectrum of which shows low field signals due to a *cis*-olefin attached to fully substituted carbon atoms plus two other signals assigned to protons geminal to acetoxyl groups, a secondary group in axial configuration and a primary one (see Experimental). These signals are also encountered in the NMR spectrum of triacetyl conchitriol [2] (14) which in addition shows another multiplet at 4.93  $\delta$ . Benuol (12) could that be *ent*-15-beyerene-7x,17-diol.

In order to confirm this structure we proceeded to synthesize benuol from conchitriol (3). Hydrolysis of conchitriol triacetate (14) under mild conditions allows the isolation of the 7-monoacetyl derivative [2] which when treated with  $\Lambda c_2 O/Py$  during 1 hour affords a 1:3 mixture of the 7,12- and

<sup>\*</sup> Part XVII in the series Studies on diterpenes from *Sideritis* genus. For Part XVI see Rabanal, R. M., Rodriguez, B. and Valverde, S. (1974) *Anal. Quím.*, **70**, in press.



7,17-diacetates respectively and small quantities of 14. This mixture could not be resolved chromatographically and it was treated directly with Jones reagent yielding a readily separable ketone (15) and acid (16). Huang-Minlon reduction of 15 affords a diol identical with benuol (12).

The last of the new diterpenes, serradiol (18,  $C_{20}H_{32}O_2$ ), on acetylation gives a monoacetate (19) and a diacetate (20). The only difference between the NMR spectra of 19 and 20 (see Experimental) appears to be in the number of acetyl groups; thus the –OH group acetylated with more difficulty must be a tertiary one. Since acetylation of the more hindered –OH causes a paramagnetic shift for the position of the –CH<sub>2</sub>OAc group in compound 20 relative to compound 19 ( $\Delta\delta = +$  0.46) it is likely that the tertiary OH is vicinal to the primary one forming a 1,2-glycol system.



In fact, the NMR spectrum of the diacetate 20 is very similar to the NMR spectrum of sideritol triacetate (21) [5] except for the following differences: the signal due to the C-1 proton of 21 is lacking in 20 which at the same time shows the two vinylic protons as two singlets (see Experimental) while compound 21 exhibits a complex signal ( $-C\underline{H}=C\underline{H}-C\underline{H}<$ system) for the same two protons. The aspect of the signals due to the vinyl protons

in compounds of these series varies greatly from one to other [8]: derivatives of sideritol (17) such as 17-nor-16-keto-sideritol show two singlets [5] while in the NMR spectrum of compound 19 the vinyl protons appear with the same complexity as observed in the NMR spectrum of sideritol triacetate (21).

Thus serradiol (18) could be the 1-desoxyderivative of sideritol (17). In order to confirm this, we proceeded to reduce (Huang Minlon procedure) the 1-keto-acetonide of sideritol (22) obtaining compound 23 which without further characterization was converted by treatment with acetic acid to a product identical to serradiol (18).

## EXPERIMENTAL

For most details, see Part 13 [2] of this series. For physical and spectroscopic data relative to compounds 1. 6 and 7 see reference [4], for compounds 2. 3. 10, 11 and 14 see ref. [2] and ref. [5] for compounds 17, 21 and 22. All identities were confirmed by comparison of IR and NMR spectra, m.p., m.m.p. and  $[\alpha]_D$  values.

Isolation of the diterpenes from Sideritis servata. The air-dried aerial part of the plant (310 g), collected on the Sierra de Benú of Tobarra (Albacete), was chopped and Soxhlet extracted with light petroleum (b.p. 50–70), 164.) during 72 hr. The petrol, extract, concentrated to 600 ml, was extracted (4 × 500 ml) with 90% aq. McOH. The methanolic extract was concen (400 ml), diluted with H<sub>2</sub>O (1-51.) and extracted with CHCl<sub>3</sub> (8 × 200 ml). The CHCl<sub>3</sub> soln, once evaporated, left a residue (5-8 g) which was chromatographed on an Al<sub>2</sub>O<sub>3</sub> column. C<sub>6</sub>H<sub>6</sub>.- EtOAc (19:1) eluted mixtures which were rechromatographed on SiO<sub>2</sub> and SiO<sub>2</sub> + 40% AgNO<sub>3</sub> dry columns [9] with C<sub>6</sub>H<sub>6</sub>.- EtOAc (95:5) yielding the following compounds in order of elution: tobarrol (8, 180 mg), servatiol (18, 138 mg), lagascol (4, 210 mg), benuol (12, 175 mg), lagascatriol (1, 950 mg), conchitriol (3, 870 mg), jativatriol (2, 1-1 g) and sideritol (17, 650 mg).

*Lagascol* (4). It was purified as its *diacetate* 5. m.p.  $129 \cdot 132^{-1}$  (aq. EtOH),  $[\alpha]_D^{28} = -57^{-1}$  (c. 0·2, CHCl<sub>3</sub>). IR:  $v_{max}$ (KBr) 3050, 1740, 1250, 1220, 860 cm<sup>-1</sup>, NMR ( $\delta$ ); 5·53 (1H, m, W) 8 Hz, C-6 vinylic proton), 4·96 (1H, q, X part,  $J_{XY}$  10 Hz,  $J_{XB}$  2·6 Hz, C-15 proton), 4·26 (2H, 8 lines, AB part,  $J_{XB}$  12 Hz, C-16 protons),

2·11 and 2·04 (s, 3H each, 2 –OAc), C–Me singlets at 1·07, 1·00 (6H) and 0·65. (Found: C, 73·50; H, 9·53.  $C_{24}H_{38}O_4$  requires C, 73·80; H, 9·81%).

Acetonide 7. Compound 5 was treated with a 4% soln of ethanolic KOH at room temp overnight and the resulting diol (4), in dry acetone soln and anhydrous CuSO<sub>4</sub>, was heated under reflux for 16 hr. yielding 7. Compound 7 is identical with the acetonide of 11-desoxylagascatriol [4] and the derivative obtained previously by McCrindle *et al.* [6].

Toharrol (8). M.p. 137° (*n*-hexane),  $[\alpha]_{D}^{24} + 18.7°$  (*c*, 0.24, CHCl<sub>3</sub>). IR:  $\nu_{max}$  (KBr) 3350, 3060, 1040, 1030, 760 cm<sup>-1</sup>. (Found: C, 79.09; H, 10.27.  $C_{20}H_{32}O_2$  requires C, 78.89; H, 10.59%). Diacetate 9. thick oil. NMR ( $\delta$ ): 5.83 (2H, AB quartet, J 6 Hz, 15.16-vinylic protons). 5.04 (1H, *m*,  $W_{\pm}$  7 Hz, C-12 proton), 3.95 (2H, AB quartet, J 12 Hz, C-17 methylene), 2.03 (s, 6H, two –OAc), C–Me singlets at 0.87, 0.83 and 0.70.

Acetonide 11. From 8 at the usual manner. Compound 11 is identical with the acetonide of 1-desoxylativatriol [2].

Benuol (12). M.p. 114-6° (*n*-hexane).  $[\alpha]_{2}^{24^{-}} + 73 \cdot 1^{\circ}$  (*c*, 0.59, CHCl<sub>3</sub>). IR:  $v_{max}$ (KBr) 3450, 3040, 1035, 760 cm<sup>-1</sup>. (Found: C, 78.92; H. 10<sup>1</sup>9. C<sub>20</sub>H<sub>32</sub>O<sub>2</sub> requires C. 78.89; H. 10<sup>5</sup>9%). Diacetate 13, m.p. 115-7° (aq. EtOH),  $[\alpha]_{2}^{24^{-}} + 68.3°$  (*c*, 0.60, CHCl<sub>3</sub>). IR:  $v_{max}$ (KBr) 3060, 3050, 1745, 1255, 1035, 763 cm<sup>-1</sup>. NMR ( $\delta$ ): 5<sup>6</sup>8 (2H, *s*, 15,16-vinylic protons), 493 (1H, *m*, *W*<sub>3</sub> 7 Hz, C-7 proton), 3-98 (2H, AB quartet, *J* 12 Hz, C-17 methylene), 2-05 (6H, two -OAc, *s*), C-Me singlets at 0.80 (6H) and 0.76. (Found: C, 74-23; H, 9.51. C<sub>24</sub>H<sub>36</sub>O<sub>4</sub> requires C, 74-19; H, 9-34%).

Transformation from 3 to 12. Conchitriol triacetate (14) was treated with 5% ethanolic KOH for 2 hr at 0°. The solution was poured on ice-water and extracted with CHCl<sub>3</sub>. Evaporation of the CHCl<sub>3</sub> soln and subsequent chromatography of the residue on preparative plates yields  $7\beta$ -conchitriol monoacetate [2]. The monoacetate was dissolved in Py/Ac<sub>2</sub>O at 0° during 1 hr. affording a 1:3 mixture of 7,12- and 7,17-diacetyl derivatives (NMR) which could not be separated by TLC. The mixture was oxidized with Jones reagent yielding 15 after purification on preparative plates. Compound 15, a syrup, was subjected to the Huang. Minlon reduction (N<sub>2</sub> atmosphere) to yield a product identical in all respects with 12.

Serradiol (18). M.p.  $141-3^{\circ}$  (*n*-hexane).  $[\alpha]_{23}^{23} + 6\cdot 2^{\circ}$  (*c*, 0.16, CHCl<sub>3</sub>). IR:  $v_{max}$ (KBr) 3360, 3040, 1055, 735 cm<sup>-1</sup>. (Found: C, 78·81; H, 10·43,  $C_{20}H_{32}O_2$  requires C, 78·89; H, 10·89%).

Acetylation of 18: Compounds 19 and 20. Serradiol (18, 70 mg) in  $Py/Ac_2O$  soln was left overnight at room temp. Evaporation of the solvent *in vacuo* left a residue formed by two products (TLC) which could be separated by PLC on silica gel plates (eluted with CHCl<sub>3</sub>-MeOH 97:3).

Serradiol monoacetate (19). Most polar component (20 mg). m.p. 105-8° (aq. EtOH),  $[\alpha]_{2}^{2+6} + 9 \cdot 5^{\circ}$  (c, 0·21, CHCl<sub>3</sub>). IR:  $v_{max}$ (KBr) 3560, 3520, 3060, 3040, 1750, 1720, 1270, 740 cm<sup>-1</sup>. NMR ( $\delta$ ): 5·93 (2H, m, vinylic C-13 and C-14 protons), 3·82 (2H, s, C-17 methylene), 2·50 (1H, m, C-12 allylic proton), 2·08 (3H, s, -OAc), C-Me singlets at 0·86, 0·79 and 0·59. (Found: C, 73·30; H, 9·79. C<sub>22</sub>H<sub>34</sub>O<sub>3</sub> requires C, 73·26; H, 9·89%). Serradiol diacetate (20). Less polar component (45 mg), m.p. 120-6° (aq. EtOH),  $[\alpha]_{2}^{2+6} + 23^{\circ}$  (c, 0·34, CHCl<sub>3</sub>). IR:  $v_{max}$ (KBr) 3060, 1730, 1255, 725, 710 cm<sup>-1</sup>. NMR ( $\delta$ ): 6·01 and 5·95 (1H each. s, vinylic protons), 4·28 (2H, AB quartet. J 12 Hz, C-17 methylene). 3·0 (1H, m, allylic C-12 proton). 2·05 and 2·03 (3H each, s, two – OAc), C-Me singlets at 0·87, 0·80 and 0·59. (Found: C, 74·21; H, 9·22, C<sub>2</sub>A<sub>14</sub>, O<sub>4</sub> requires C, 74·19; H, 9·34%).

Transformation from 22 to 18. Compound 22 [5] (115 mg) was subjected to the Huang-Minlon reduction (N<sub>2</sub> atmosphere) to yield 23 (90 mg), which without characterization was treated with 60% aq. soln of AcOH to give a substance (65 mg) identical in all respects to 18.

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