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Apiananes: C_{23} Terpenoids with a New Type of Skeleton from *Salvia apiana*

Javier G. Luis[a]*, El Hassane Lahlou[a], Lucía S. Andrés[a], Geeta H. N. Sood[b] and Martín M. Ripoll[b]

[a]**Instituto Universitario de Bio-Orgánica "Antonio González".**
Universidad de La Laguna.
Carretera de la Esperanza 2, 38206 La Laguna, Tenerife. Canary Islands. Spain.

[b]**Instituto Rocasolano C.S.I.C. 28006 Madrid. Spain.**

Abstract: Two new C_{23} terpenoids 14-hydroxy-7-methoxy-11,16-diketo-apian-8-en-(22,6)-olide **2** and 7-methoxy-11,16-diketo-apian-8,14-dien-(22,6)-olide **3** were isolated from the aerial part of *Salvia apiana*. This two new C_{23} terpenoids have a new basic skeleton **1** for wich we propose the name of apianane. The structure of **2** was confirmed by X-ray analysis.

The huge *Salvia* genus (Lamiaceae) with over 500 species is formed throughout the world[1,2] and features in folk pharmacopoeias almost everywhere; as such, *Salvia* species are prime candidates for investigation.

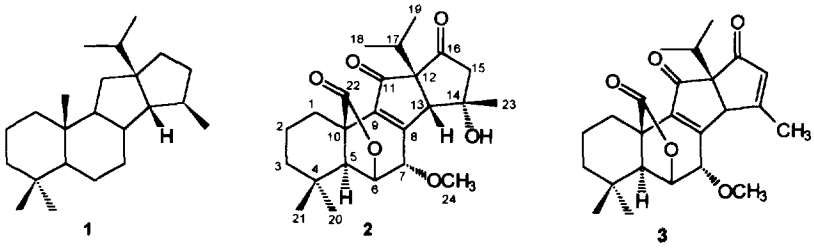
Salvia apiana Jeps, commonly known as white sage, is a large shrub with velvety greyish leaves formed in the coastal range and valleys of southern California, where infusion of the leaves is drunk as a diaphoretic or diuretic.

In a previous paper,[3] we described the isolation and characterization of several new abietane diterpenes and diterpenequinones from the roots of *S. apiana*.

The co-ocurrence of so many abietane diterpenes with different degrees of oxidation and modified skeletons was in accordance with our previously postulated[4] biosynthetic route for these highly oxidized abietatrienes in which enzymatic dehydrogenations and the participation of singlet oxygen are the key processes. Further studies[5,6] on the diterpenes from *Salvia* genus support that biosynthetic pathway. It would appear that compounds of this type have a powerful antioxidant effect on free radicals and singlet oxygen injuries to the plant cells of *Salvia* species and as many human ailments as well as aging are affected by the intervention of such reactive chemical species in biological processes, some of these substances may be interesting from the medicinal point of view.

Now, from the aerial part of *S. apiana*, the known diterpenes, 16-hydroxycarnosic acid, 16-hydroxycarnosol, 16-hydroxyrosmanol, 16-hydroxy-7-methoxyrosmanol, rosmanol, 7-epirosmanol and salvicanol were obtained and

identified by comparison with the spectral data of authentic samples. Two new C_{23} terpenoids with a new basic skeleton **1** for which we propose the name of apianane were also separated and their structures determined.



1 **2** **3**

The structure of **2** was established as follow. The low resolution mass spectrum showed $[M]^+$ at m/z 416 ($C_{24}H_{32}O_6$ by HRMS). The IR spectrum had bands for alcohol (3464 cm^{-1}), lactone (1779 cm^{-1}), pentacyclic ketone (1751 cm^{-1}), α,β-unsaturated ketone (1700 cm^{-1}) and ether (1089 cm^{-1}) groups. In the ^1H NMR spectrum,[8] signals for an isopropyl group on an aliphatic ring, three angular methyls, one of them (δ 1.62) on a carbon atom bearing an oxygen atom and an aliphatic methoxy group (three protons singlet at δ 3.75), were observed. No aromatic protons signals appear in this spectrum, but one proton singlet at δ 1.95 and two one-proton doublets at δ 4.71 and δ 4.11 assignable to the H-5, H-6 and H-7 protons respectively had multiplicities and chemical shifts similar with those found for the corresponding protons in the ^1H NMR spectrum of 7-methoxyrosmanol.[7]

	2	**3**
Proton	**Carbon**	**Carbon**
5	21,4,10,9,22	21,20,10,7,22
6	8,22	8,22
7	8,9	8,9,24
13	17,9,8,11	8,9,15,14
15	16,12,13,23	16,12,13,14
17	13,18,19	12,13,18,19
18	12,17,19	12,17,19
19	12,17,18	12,17,18
20	3,5,21	3,5,21
21	3,5,20	3,5,20
23	13,15	13,15,14

Table 1.- Three-Bond correlation for compounds **2** and **3** in the HMBC experiment.

The ^{13}C NMR spectrum[8] accounts for the presence of twenty four carbon atoms in the molecule of which those resonating at δ 175.87, 198.16 and 208.06 are assignable to a lactonic and two carbonyl groups respectively, and for the presence of a tetrasubstituted double bond (signals at δ 143.86 and δ 163.31). In the same spectrum, signals assignable to four carbon atoms bearing oxygen atom are also observable: 58.78 (q), 72.75 (d), 74.25 (s) and 76.83 (d).

The assignment of all the hydrogen and carbon atoms in the molecule was made by combined HMQC and HMBC (see Table 1) experiments. The above data are all in accordance with the structure **2** for this compound.

At the best of our knowledgement, the skeleton **1** present in **2** constitutes a new type of C_{23} terpenoid skeleton for which we propose the name of apianane.

A good crystal could be obtained and the structure of 14-hydroxy-7-methoxy-11,16-diketo-apian-8-en-(22,6)-olide for **2** and its absolute configuration were confirmed and established by X-ray difraction analysis. The final X-ray model[9] of **2** is shown in Fig 1. One molecule of acetone is included in the crystal but not shown in the figure. All the bond lengths and angles are within the expected range. Ring A is a distorted chair with q_2=0.149(3), q_3=0.502(2), θ=16.5(3), ϕ=106.7(9) whereas ring B shows a less distorted chair[10] conformation with q_2=0.539(2), q_3=0.393(2), θ=53.9(2), ϕ=4.4(2). Ring C is nearly a pure envelope with C-5 at the flap, deviating 0.652(2) Å from the plane defined by the other four atoms. Ring D and E are highly and slightly distorted envelops, respectively. C-12 is at the flap (0.139(2) Å out of the plane) of ring D and C-15 acts as a flap for ring E (0.382(3) Å out of the plane). The crystal packing is due to van der Waals contacts and an intramolecular hydrogen bond O5-H5...O6 (O5-O6=2.813(2), O5-H5=0.82 Å, H5...O6=2.07 Å angle at H5 atom=151°).

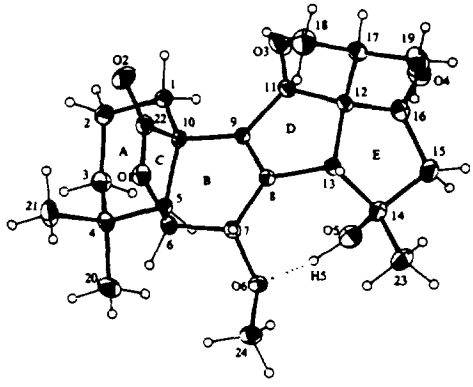


Figure 1.- Solid-state conformation of **2** showing the hydrogen bond (dotted lines) and the atomic numbering. Numbers only refer to carbon atoms.

The spectral data for **3** were similar to those of **2** where the only difference was a double bond between C-14 and C-15 and the abscense of the hydroxy group in C-14. The low resolution mass spectrum showed $[M]^+$ at m/z 398 ($C_{24}H_{30}O_5$ by HRMS). The IR spectrum had bands for lactone (1782 cm^{-1}), pentacyclic ketone (1728 cm^{-1}), α,β-unsaturated ketone (1686 cm^{-1}) and ether (1094 cm^{-1}) groups. In the ^1H NMR spectrum[12] signals for two angular methyls, an isopropyl group on an aliphatic ring, a vinylic methyl group (δ 2.34), aliphatic methoxy group (three protons singlet at δ 3.67) and a vinylic proton at δ 5.80 were observed. Again no aromatic proton signals appear in this spectrum which showed a proton singlet at δ 1.93 assignable to the H-5 proton and two one-proton doublets at δ 4.06 and δ 4.68 assignable to H-7 and H-6 protons respectively identical to those present in **2**.

The ^{13}C NMR spectrum[12] shows the presence of twenty four carbon atoms in the molecule of which those resonating at δ 175.83, 197.07 and 200.38 are assignable to a lactonic and two carbonyl groups respectively and signals at δ 144.30, 164.15, 131.13 and 175.93 assignable to a tetrasubstituted double bond (C8-C9) and a trisubstituted double bond (C14-C15) respectively.

The assignment of all the hydrogen and carbon atoms in the molecule was made by combined HMQC and HMBC (see Table 1) experiments. All these data are in accordance with the structure 7-methoxy-11,16-diketo-apian-8,14-dien-(22,6)-olide for **3** which is the dehydratation product of **2**.

Positive chemical proof for structure **3** was obtained when **2** was treated with *p*-toluenesulfonic acid in benzene to give a mixture of two products, one of which (the major one) having spectroscopic data identical to those of **3**.

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8. Compound **2**: ^{1}H NMR (400MHz, $CDCl_3$) δ: 0.59 (3H, d, *J*=6.6Hz, Me-19), 0.86 (3H, d, *J*=6.6Hz, Me-18), 0.88 (3H, s, Me-20), 0.98 (3H, s, Me-21), 1.62 (3H, s, Me-23), 1.95 (1H, s, H-5), 2.44 (1H, d, *J*=17.8Hz, H-15), 2.47 (1H, hept, *J*=6.6Hz, H-17), 2.67 (1H, d, *J*=17.8Hz, H-15), 2.85 (1H, d, *J*=14.2Hz, H-1β), 3.11 (1H, s, H-13), 3.75 (3H, s, O-CH_3), 4.11 (1H, d, *J*=2.1Hz, H-7), 4.71 (1H, d, *J*=2.1Hz, H-6). ^{13}C NMR (100MHz, $CDCl_3$) δ: 17.16 (q, C-18), 17.91 (q, C-2), 18.38 (q, C-19), 21.74 (q, C-20), 22.91 (t, C-1), 29.72 (q, C-23), 30.80 (s, C-4), 31.43 (q, C-21), 36.08 (d, C-17), 38.05 (t, C-3), 44.85 (s, C-10), 51.24 (d, C-5), 56.62 (d, C-13), 57.21 (t, C-15), 58.78 (q, O-CH_3), 72.75 (d, C-6), 73.92 (s, C-12), 74.25 (s, C-14), 76.83 (d, C-7), 143.86 (s, C-9), 163.31 (s, C-8), 175.87 (s, C-22), 198.16 (s, C-11), 208.06 (s, C-16).
9. Crystallographic data for **2**: $C_{24}H_{32}O_6.C_3H_6O$, Mr=474.6, orthorhombic $P2_12_12_1$, *a*=11.2424(7), *b*=12.0437(6), *c*=19.145(2) Å, *V*=2592.2(3) Å^3, *Z*=4, *Dc*=1.216 g.cm^{-3}. Intensity data were collected with graphite monochromated CuKα radiation (λ=1.5418 Å) on a Scifert XRD3000-S four-circle diffractometer, for both *hkl* and *-h-k-l* reflexions. A total of 4186 reflexions were measured in ω/2θ scan mode (2°<θ<65°), leading to 3835 observed reflexions with the $I<2\sigma(I)$ criterion. Absorption effects, corrected using azimuthal scan data gave a maximum and minimum transmision factors of 1.16 and 1.0, respectively. The structure was solved by direct methods allowing the location of all non-hydrogen atoms. All H-atoms were located on a difference map. A total of 308 variables (coordinates, thermal parameters and an isotropic extinction factor of 12.6(8).10^{-3}) were refined by least-squares procedures leading to R=0.041 (for the 3835 observed reflexions) and R=0.045 and Rw=0.122, using all 4186 reflexions. The absolute configuration was confirmed during the least-squares refinement allowing *f'* for O atoms to vary.[11] Atomic coordinates, thermal factors, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Centre.
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11. Rogers, D. *Acta Cryst.* **1981**, *A37*, 734-741.
12. Compound **3**: ^{1}H NMR (400Mz, $CDCl_3$) δ: 0.69 (3H, d, *J*=6.8Hz, Me-19), 0.78 (3H, d, *J*=6.8Hz, Me-18), 0.88 (3H, s, Me-21), 0.89 (3H, s, Me-20), 1.93 (1H, s, H-5), 2.34 (3H, s, Me-23), 2.68 (1H, hept, *J*=6.8Hz, H-17), 2.95 (1H, d, *J*=14.4Hz, H-1β), 3.46 (1H, s, H-13), 3.67 (3H, s, O-CH_3), 4.06 (1H, d, *J*=2.4Hz, H-7), 4.68 (1H, d, *J*=2.4Hz, H-6), 5.80 (1H, s, H-15). ^{13}C NMR (100MHz, $CDCl_3$) δ: 17.45 (q, C-19), 17.61 (q, C-18), 17.97 (t, C-2), 19.51 (q, C-23), 21.67 (q, C-20), 23.12 (t, C-1), 30.78 (q, C-21), 31.38 (s, C-4), 33.81 (d, C-17), 38.17 (t, C-3), 44.93 (s, C-10), 50.96 (d, C-5), 54.45 (d, C-13), 58.44 (q, O-CH_3), 73.07 (d, C-6), 73.96 (s, C-12), 77.15 (d, C-7), 131.13 (d, C-15), 144.30 (s, C-9), 164.15 (s, C-8), 175.83 (s, C-22), 175.93 (s, C-14), 197.07 (s, C-11), 200.38 (s, C-16).

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