Pergamon

Tetrahedron, Vol. 52, No. 37, pp. 12309-12312, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00717-X

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

Javier G. Luis*, El Hassane Lahlou and Lucía S. Andrés

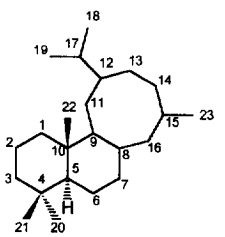
Instituto Universitario de Bio-Orgánica "Antonio González". Universidad de La Laguna
Carretera de la Esperanza, 2. 38206 La Laguna, Tenerife, Canary Islands, SPAIN

Abstract: A new C_{23} terpenoid, 13,14-dioxo-11-hydroxy-7-methoxy-hassane-8,11,15-trien-(22,6)-olide **2** was isolated from the aerial part of *Salvia apiana* Jeps. This new C_{23} terpenoid has a new basic skeleton **1** for wich we propose the name of hassanane. The structure of **2** was established from its spectroscopic data. A possible common biosynthetic origin of **2** and the previously reported apiananes is also discussed.

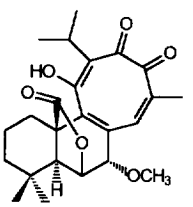
Salvia species (Labiatae) figure prominently in the pharmacopoeias of many countries throughout the world[1,2] and , as such, are prime candidates for investigation.

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

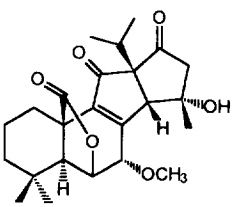
We have already[3] reported the isolation of the new C_{23} terpenoids with a new skeleton 14-hydroxy-7-methoxy-11,16-diketo-apian-8-en-(22,6)-olide **3** and 7-methoxy-11,16-diketo-apian-8,14-dien-(22,6)-olide together with the known diterpenes 16-hydroxycarnosic acid, 16-hydroxycarnosol, 16-hydroxyrosmanol, 16-hydroxy-7-methoxyrosmanol, rosmanol, 7-epirosmanol and salvicanol from the aerial part of *S. apiana*. Further examination of the same extract has led to the isolation of a new C_{23} terpenoid with a new basic skeleton **1** for which we propose the name of hassanane.



1



2



3

The structure of **2** was established as follows. The low resolution mass spectrum showed $[M]^+$ at m/z 414 ($C_{24}H_{30}O_6$ by HRMS). The IR spectrum had bands for hydroxyl group (3400 cm^{-1}), 1,2-diketone (1654 and 1586 cm^{-1}) and γ-lactone (1788 cm^{-1}) groups. In the ^1H NMR spectrum signals for three angular methyls, one of these vinylic (δ 2.46), an isopropyl group on an aromatic ring (two methyl doublets at δ 1.09 and δ 1.24,

J=6.8Hz, a proton heptuplet at δ 3.29, *J*=6.8Hz) and an aliphatic methoxy group (δ 3.65) were observed. A signal for a vinylic proton as a singlet at δ 6.56 was also observed in this spectrum and signals assignable to the H-5, H-6 and H-7 protons with multiplicities and chemical shifts similar with those found for the corresponding protons in the ^{1}H NMR spectrum of 7-methoxyrosmanol[4].

The ^{13}C NMR spectrum accounts for the presence of twenty four carbon atoms in the molecule of which those resonating at δ 175.71, 189.11 and 203.12 are assignable to a lactonic and two ketone groups respectively, and for the presence of two tetrasubstituted double bond (signals at δ 132.07, δ 146.62, δ 119.82 and δ 149.08). In the same spectrum signals assignable to four carbon atoms bearing oxygen atom are also observed: δ 59.19 (q), 73.02 (d), 79.45 (d) and 149.08 (s). This last one corresponding to vinylic alcohol group.

The assignment of all the hydrogen and carbon atoms in the molecule was made by combined HMQC and HMBC (see Table **1**) experiments, in this late the more important datum was the three-bond correlation between the hydroxyl group and the carbonyl group from the lactone. This correlation confirmed the presence of hydrogen bridge between C-22 and the proton from the hydroxyl group, which could explain the unusual low chemical shift (δ 17.03) observed for this proton in the ^{1}H NMR spectrum.

Proton	Three-bond correlation	Two-bond correlation
H-5	C-9, C-20, C-21, C-22	C-4, C-10
H-6	C-8, C-22	--------
H-7	C-9, C-16, C-24	C-8
H-16	C-7, C-9, C-23	C-15
H-17	C-11	C-18, C-19
OH	C-12, C-9, C-22	C-11
H-23	C-14	--------

Table 1.- Three and two-bond correlations for compound **2** in the HMBC experiment.

Because the product **2** did not crystallize, it was impossible to do a X-ray difraction study.

Molecular mechanics studies using the PCMODEL Program confirmed the existence of the hydrogen bridge between the carbon C-22 and the proton from the hydroxyl group on C-11 (Fig. **1**). The above data are all in accordance with the structure **2** for this compound.

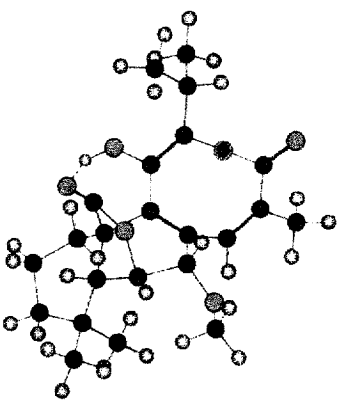


FIGURE 1 - Structure for compound **2** by PCMODEL Program.

The isolation of **2** is in accordance and also supports the biogenetic origin of the previously reported 14-hydroxy-7-methoxy-11,16-diketo-apian-8-en-(22,6)-olide[3] **3**. The formation of **3** could be explained through a pathway (Fig. **2**) in which the condensation of 7-methoxyrosmanol **4** with acetoacetyl-Scoenzyme A or its equivalent followed by benzilic acid-type rearrangement and intramolecular aldol condensation could give (through the intermediate **5**) the acid **5a**, oxidative decarboxylation of which could account for the formation of **3**.

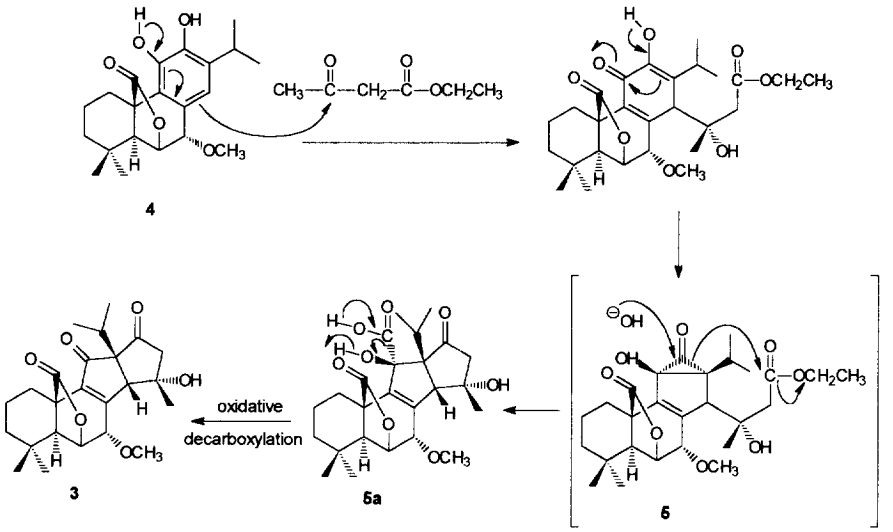


FIGURE 2

This biosynthetic route is also supported and account for the isolation of **2** whose formation could be explained like shown in Figure **3** via the same intermediate **5a** through autooxidation followed by eliminative decarboxylation.

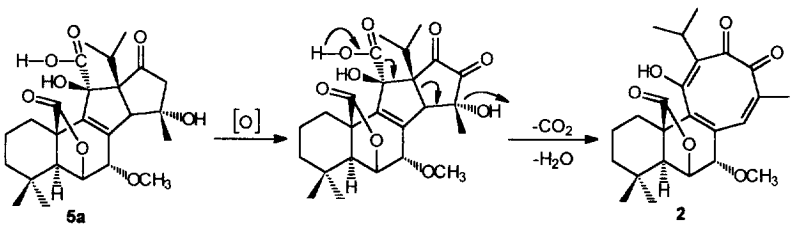


FIGURE 3

The skeleton **1** present in **2** constitutes a new type of C_{23} terpenoid skeleton for which we propose the name of hassanane.

EXPERIMENTAL

General.- ^{1}H, ^{13}C and bidimensional spectra were recorded on Bruker AMX400 and WP200SY spectrometers, IR spectra were taken on a Bruker IFS 28/55 (FTIR) spectrometer, UV spectra were taken on a JASCO V-560

instrument and $[\alpha]_D$ on a PERKIN Elmer Mod 141 polarimeter. High resolution mass spectra were run on a VG-MICROMASS ZAB-2F at 70eV.

Isolation of Products.- *S. apiana* Jeps was collected on Sierra de Juárez (Baja California, Mexico) in January 1991 and a voucher speciment is on file in the Musseum of Systematic Biology, University of California and in the Department of Botany, University of Baja California (Ensenada, Mexico). The dried, ground stems and leaves (6.0Kg) were extracted with distilled Me_2CO at room temperature and the solvent eliminated under reduced pressure at 40°C giving an extract (300.0g) which was subjected to SEPHADEX LH-20 column using a mixture of n-Hexane/$CHCl_3$/MeOH (2:1:1) as eluent. The fractions which contained **2** were purified by chromatography column on silica gel and then by preparative TLC.

13,14-Dioxo-11-hydroxy-7-methoxy-hassane-8,11,15-trien-(22,6)-olide (2).- (7.0mg) was isolated as an amorphous solid; $[M]^+$ at m/z 414.20492 (calc. for $C_{24}H_{30}O_6$, 414.20424); $[\alpha]_D^{25}$= +78° ($CHCl_3$; c 0.14); UV λ_{max} (EtOH) nm: 320, 271; IR ν_{max} ($CHCl_3$) cm^{-1}: 3400, 2932, 1788, 1654, 1586, 1420, 1345, 1090; ^1H NMR (200MHz, $CDCl_3$) δ: 0.93 (3H, s, Me-21), 1.01 (3H, s, Me-20), 1.09 (3H, d, *J*=6.8Hz, Me-18), 1.24 (3H, d, *J*=6.8Hz, Me-19), 2.03 (1H, s, H-5), 2.46 (3H, s, Me-23), 2.75 (1H, d, *J*=13.3Hz, H-1α), 3.29 (1H, hept, *J*=6.8Hz, H-17), 3.65 (3H, s, -OC<u>H</u>$_3$), 4.01 (1H, d, *J*=1.8Hz, H-7), 4.63 (1H, d, *J*=1.8Hz, H-6), 6.56 (1H, s, H-16), 17.03 (1H, s, -O<u>H</u>); ^{13}C NMR (400MHz, $CDCl_3$) δ: 18.60 (t, C-2), 21.88 (q, C-18), 22.34 (s, C-4), 22.76 (q, C-19), 26.40 (t, C-1), 28.08 (q, C-23), 30.20 (d, C-17), 31.34 (q, C-20 and C-21), 38.14 (t, C-3), 45.83 (s, C-10), 50.18 (d, C-5), 59.19 (q, -OCH_3), 73.02 (d, C-6), 79.45 (d, C-7), 119.82 (s, C-12), 132.00 (d, C-16), 132.07 (s, C-8), 146.62 (s, C-9), 149.08 (s, C-11), 175.41 (s, C-15), 175.71 (s, C-22), 189.11 (s, C-13), 203.12 (s, C-14); EIMS (rel. int) m/z: 414 $[M]^+$ (8), 399 (1), 383 (2), 371 (1), 369 (2), 321 (2), 255 (2), 217 (2), 203 (3), 177 (5), 150 (25), 125 (10), 111 (15), 97 (34).

Acknowledgements: This research has been partly subsidized by Grant AMB95-0428-C02-02 from Spanish Government. We are grateful to J. Delgadillo from Universidad de Baja California (Mexico) for the collection of the plant.

REFERENCES

1.- (a) Morton, J.F. *Atlas of Medicinal Plants of Middle America;* Charles C. Thomas; Springfield, **1981**; pp 780-784; (b) Duke, J.A. *Handbook of Medicinal Herbs;* CRC Press Inc.; Boca Ratón, **1985**; pp 118, 419-422; (c) Bergwein, K. *Am. Perfum. Cosmet.* **1968**, *83*, 41.

2.- Scott, G. *Chem. Brit.* **1985**, 648.

3.- Luis, J. G.; Lahlou, E.H.; San Andrés, L.; Sood, G. H. N.; Ripoll, M. M. *Tetrahedron Letters,* **1996**, in press.

4.- González, A. G.; San Andrés L.; Herrera, J. R.; Luis, J. G.; Ravelo, A. G.; *Canadian J. Chem.* **1989**, *67*, 208-212.

(*Received in UK* 2 *July* 1996; *revised* 30 *July* 1996; *accepted* 1 *August* 1996)