PERGAMON

Phytochemistry 53 (2000) 911–915

PHYTOCHEMISTRY

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Icetexane and abietane diterpenoids from *Salvia gilliessi*

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Received 19 April 1999; received in revised form 29 July 1999

Abstract

One icetexane and two abietane diterpenes were isolated from the aerial parts of *Salvia gilliesii*, and characterized as 5-*epi*-icetexone; 12-hydroxy-11,14-diketo-6,8,12-abietatrien-19,20-olide and 6α,12,19-trihydroxy-11,14-diketo-8,12-abietadien-20,7β-olide, respectively. The structures were established by analysis of their ^{1}H and ^{13}C NMR spectra with the aid of 2D experiments. The triterpene oleanolic acid was isolated from the same source. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *Salvia gilliessi* Benth; Labiatae; Tomentellae; Diterpenoids; Abietane; Icetexane

1. Introduction

Several kinds of diterpenes containing abietane (Luis, 1991), cycloheptanenaphthoquinone (Luis, Quiñones & Echeverri, 1994), icetexane (González, San Andrés, Luis, Brito & Rodriguez, 1991; Esquivel, Flores, Hernández-Ortega, Toscano & Ramamoorthy, 1995; Esquivel, Calderón, Flores, Sánchez & Rosas Rivera, 1997), *neo*-clerodane, and *seco*-clerodane (Nieto, Gallardo, Rossomando & Tonn, 1996) skeletons, have been isolated from the large genus *Salvia* (Labiatae). Some of these diterpenoids have been reported as insect antifeedants (Sosa, Tonn & Giordano, 1994; Simmons, Blaney, Esquivel & Rodriguez Hahn, 1996), antivirals (Tada, Okuno, Chiba, Ohnishi & Yoshii, 1994), antibacterial agents (Moujir, Gutierrez-Navarro, San Andrés & Luis, 1993; Batista, Simoes, Duarte, Valdeira, de la Torre & Rodriguez, 1995), as well as having potential anti-oxidant activity (Luis, 1991; Luis, San Andrés & Fletcher, 1994). As a continuation of our search for diterpenoids from the Asteraceae (Favier, Nieto, Giordano & Tonn, 1997) and Labiatae (Nieto et al., 1996) families we have now studied the aerial parts of *Salvia gilliessi* Benth., collected in the central–western semi-arid area of Argentina. From the acetone extract, the icetexane diterpene **1** and the abietane diterpenes **3** and **5** were isolated, and their structures established from spectral data.

2. Results and discussion

The major component **1** was isolated as an orange solid which showed the formula $C_{20}H_{22}O_5$ by HR mass spectrometry. IR bands at 3350 (*br*), 1730, 1660 and 1630 cm^{-1} were indicative of hydroxyl, γ-lactone and quinone functions, respectively. The UV absorptions at 221 nm (log ε 4.30) and 313 nm (log ε 3.27) were in agreement with the presence of a *p*-benzoquinone ring. The ^{1}H NMR spectrum of **1** (Table 1) showed signals for an isopropyl group (δ 1.20, 6H, *d*, J = 6.8 Hz and δ 3.29, heptet J = 6.8 Hz) as well as one methyl group as a singlet at δ 1.25. The H-7, H-6 and H-5 protons appeared as an ABX system at δ 6.80 (*dd*, J = 12.3 and 3.8 Hz, H-7), 6.40 (*dd*, J = 12.3 and 4.5 Hz, H-6) and 2.60 (*dd*, J = 4.5 and 3.8 Hz, H-5), as detected by a COSY spectrum. One sharp singlet proton at δ 7.0 (exchangeable with D_2O) was in agreement with the C-12 chelated hydroxyl group. Finally, a clear AB system at δ 2.81 (*d*, J = 14.3 Hz)

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0031-9422/00/$ - see front matter
PII: S0031-9422(99)00480-X

Table 1
^{1}H NMR spectral data of diterpenoids (CDCl$_3$, TMS, δ values in ppm, J values in Hz)

H	**1**[a]	**3**[a]	**4**[b]	**5**[b]
5	2.60 (*dd*, J = 4.5, 3.8)	2.51 (*br s*, $W_{1/2}$ = 10.0 Hz)	2.60 (*br s*, $W_{1/2}$ = 8.0 Hz)	1.80 (*dd*, J = 8.0, 2.0)
6	6.40 (*dd*, J = 12.3, 4.5)	6.90 (*dd*, J = 9.0, 3.5)	6.81 (*dd*, J = 9.0, 3.0)	4.60 (*dd*, J = 8.0, 4.0)
7	6.80 (*dd*, J = 12.3, 3.8)	6.51 (*dd*, J = 9.0, 2.0)	6.48 (*dd*, J = 9.0, 2.3)	5.35 (*d*, J = 4.0)
15	3.29 (*h*, J = 6.8)	3.18 (*h*, J = 6.8)	3.12 (*h*, J = 7.0)	3.20 (*h*, J = 7.0)
16	1.20 (*d*, J = 6.8)	1.22 (*d*, J = 6.8)	1.20 (*d*, J = 7.0)	1.20 (*d*, J = 7.0)
17	1.20 (*d*, J = 6.8)	1.20 (*d*, J = 6.8)	1.20 (*d*, J = 7.0)	1.20 (*d*, J = 7.0)
18	1.25 (*s*)	1.40 (*s*)	1.40 (*s*)	1.30 (*s*)
19-pro *R*				3.05 (*dd*, J = 9.8, 2.0)
19-pro *S*				4.00 (*d*, J = 9.8)
20-pro *R*	3.10 (*d*, J = 14.3)	4.40 (*dd*, J = 10.0, 1.0)	4.45 (*dd*, J = 11.2, 1.5)	
20-pro *S*	2.81 (*d*, J = 14.3)	4.21 (*dd*, J = 10.0, 1.5)	4.20 (*dd*, J = 11.2, 2.0)	
–O$\underline{\text{H}}$	7.0 (*s*)	8.4 (*br s*)		7.0 (*s*)
Me-acetate			2.35 (*s*)	

[a] Run at 400 MHz.
[b] Run at 200 MHz.

and δ 3.10 (*d*, J = 14.3 Hz) suggested the C-20 methylene protons of an icetexane skeleton (Esquivel et al., 1997). ^{13}C NMR spectra (Table 2), analysed with the aid of DEPT, HMQC and HMBC experiments, showed the presence of three carbonyl groups, two of them corresponding to the *p*-benzoquinone moiety, the chemical shift of the third was indicative of a γ-lactone function. Two proton-bearing olefinic carbons, four methylene groups, three methyl groups, two sp^3 methines, two sp^3 quaternary carbon atoms and four quaternary sp^2 carbons were also displayed. Two and three bond HMBC correlations (Table 3) were observed using an instrument equipped with self-shielded gradients, and were conclusive in the assignment of the connectivities. The above data supported the icetexane skeleton proposed for compound **1**. Icetexone, **2**, had been isolated from *Salvia ballotaeflora* Benth (Section Tomentellae) and its structure and relative stereochemistry elucidated by single X-ray analysis (Watson, Taira, Dominguez, Gonzáles, Gutierrez & Aragón, 1976). This compound showed an $[\alpha]_D^{25}$ = +33.3° and a mp 226–227°C. Taking into account that compound **1** shows a negative optical rotation ($[\alpha]_D^{25}$ = −92.8°) and melts at 259–260°C, it is evident that the new diterpene possesses a different stereochemistry, probably at the C-5 asymmetric centre. The use of NOESY NMR allowed us to determinate the relative stereochemistry at this chiral carbon. Cross-peaks between H-5 and H-20β (pro-*S* diastereotopic proton) were observed, which is only possible if C-5 has an *R* configuration. Additional proof was obtained from a careful inspection of the ^{1}H NMR spectrum. The coupling constants (J = 4.5 Hz) for the system H-C(sp^3)$_5$–C(sp^2)$_6$-H were in agreement with a dihedral angle near 90°; this relationship only is possible in the

Table 2
^{13}C NMR spectral data of diterpenoids (CDCl$_3$)[a]

C	**1**[b]	**3**[c]	**4**[c]	**5**[c]
1	31.3 (*t*)	34.3 (*t*)	34.0 (*t*)	26.4 (*t*)
2	18.2 (*t*)	20.9 (*t*)	25.2 (*t*)	18.0 (*t*)
3	34.0 (*t*)	40.1 (*t*)	40.2 (*t*)	29.0 (*t*)
4	46.2 (*s*)	41.7 (*s*)	41.8 (*s*)	40.5 (*s*)
5	55.8 (*d*)	47.7 (*d*)	47.5 (*d*)	46.8 (*d*)
6	136.8 (*d*)	122.4 (*d*)	121.4 (*d*)	62.8 (*d*)
7	124.0 (*d*)	134.7 (*d*)	133.5 (*d*)	73.5 (*d*)
8	132.8 (*s*)	139.7 (*s*)	138.3 (*s*)[a]	143.0 (*s*)[a]
9	138.0 (*s*)	134.2 (*s*)	138.1 (*s*)[a]	146.0 (*s*)[a]
10	91.3 (*s*)	37.2 (*s*)	37.5 (*s*)	38.0 (*s*)
11	184.6 (*s*)	184.3 (*s*)	184.3 (*s*)	180.4 (*s*)
12	151.6 (*s*)	151.3 (*s*)	150.0 (*s*)	150.5 (*s*)
13	123.6 (*s*)	123.7 (*s*)	125.0 (*s*)	124.6 (*s*)
14	181.5 (*s*)	183.1 (*s*)	180.2 (*s*)	182.8 (*s*)
15	22.8 (*d*)	24.2 (*d*)	25.4 (*d*)	24.2 (*d*)
16	18.7 (*q*)[a]	19.9 (*q*)[a]	22.9 (*q*)[a]	19.9 (*q*)[a]
17	18.9 (*q*)[a]	19.7 (*q*)[a]	22.9 (*q*)[a]	19.9 (*q*)[a]
18	16.8 (*q*)	22.9 (*q*)	20.8 (*q*)[a]	28.0 (*q*)
19	175.0 (*s*)	174.2 (*s*)	174.5 (*s*)	63.2 (*t*)
20	28.2 (*t*)	72.4 (*t*)	72.5 (*t*)	179.1 (*s*)
$\underline{\text{C}}$H$_3$-COO–			20.3 (*q*)[a]	
CH$_3$-$\underline{\text{C}}$OO–			168.3 (*s*)	

[a] Values may be interchangeable in each column.
[b] Run at 100.60 MHz.
[c] Run at 50.23 MHz.

Table 3
Two and three bond HMBC correlations on compound **1**[a]

Proton	Correlated carbons
H-5	C-6, C-7, C-19
H-6	C-5, C-8, C-10
H-7	C-5, C-9, C-14
H-15	C-12, C-14
2H-20	C-5, C-8, C-9, C-10, C-11
O-$\underline{\text{H}}$	C-11, C-12, C-13

[a] Determined in CDCl$_3$ at 400 MHz.

aforementioned *R* configuration for the C-5 chiral centre (Jackman & Sternhell, 1972). On the other hand, the described stereochemistry could be responsible for the unexpectedly high value (3.8 Hz) for the allylic coupling between H-5 and H-7. Hence, on taking into account all the above data, compound **1** has the structure of 5-*epi*-icetexone.

High resolution mass spectrometry indicated the molecular formula $C_{20}H_{22}O_5$ for the minor compound **3**. The IR spectrum (ν_{max} 1665; 1630 cm^{-1}) as well as the UV absorptions at 221 (log ε 4.08) and 313 (log ε 3.60) agreed well with the presence of a *p*-benzoquinone grouping. Inspection of the ^1H NMR spectral data (Table 1) revealed the presence of an ABX system at δ 6.51 (*dd*, J = 9.0; 2.0 Hz) and 6.90 (*dd*, J = 9.0; 3.5 Hz) which were ascribed respectively to H-7 and H-6 protons, both clearly coupled with H-5 (δ 2.51 *br s*, $W_{1/2} = 10$ Hz) from the COSY spectrum. Two methyl groups at δ 1.20 (*d*, J = 6.8 Hz) and δ 1.22 (*d*, J = 6.8 Hz) both coupled with a heptet (J = 6.8 Hz) centered at δ 3.18 were indicative of an isopropyl group on the quinone ring. A three-proton singlet at δ 1.40 was ascribed to H-18, typically deshielded by the C-19 lactone carbonyl group.

An AB system assigned to the C-20 oxymethylene protons at δ 4.21 (pro-*S*, *dd*, J = 10.0, 1.5 Hz) and 4.40 (pro-*R*, *dd*, J = 10.0, 1.0 Hz) was observed in the ^1H NMR spectrum. From the COSY spectrum it was observed that the H-20 pro-*S* diastereotopic proton showed a *W* long-range coupling with H-1α, while the H-20 pro-*R* proton was clearly coupled with the H-5 methine proton. No cross peaks between H-18 and H-5 were displayed in the COSY spectrum. The above data were in agreement with a structure where C-18 and H-5 are on the same face of the molecule while the C-19–C-20 δ-lactone ring (ν_{max} 1730 cm^{-1} in the IR spectrum) is on the other face of the proposed framework (Ortega, Cárdenas, Gage & Maldonado, 1995). Finally, one singlet proton at δ 8.4, exchangeable with D_2O, was assigned to the C-12 chelated hydroxyl group.

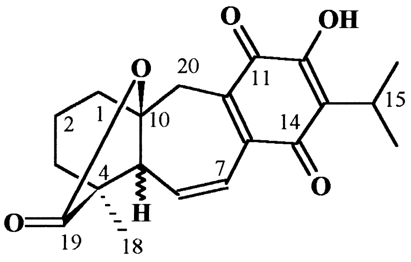
The ^{13}C NMR data (Table 2) showed that the molecule contained nine unsaturated carbons (three of them corresponding to carbonyl groups), three methyl groups attached to sp^3 carbon, one of them at δ 22.9, that was assigned to C-18. Four methylene carbons, one of these bearing an oxygen atom as part of the δ-lactone ring, and two olefinic methine carbons, were also observed. All unambiguous ^{13}C NMR assignments of **3** were resolved by a combination of 1D and 2D NMR spectroscopic techniques (DEPT, HETCOR and COLOC) and they were very similar to other closely related abietane diterpenes (Ortega et al., 1995). The long-range H–C connections from COLOC showed ^3J coupling between H-5/C-3, C-7, C-19, C-20 as well as H-20/C-5, C-9, as key correlations.

The acetyl derivative **4**, was prepared in the usual way and the NMR spectral data (Tables 1 and 2), showed similarity with **3** except for the three-proton singlet at δ 2.35 due to the acetoxy group on an unsaturated carbon. On the other hand, the COSY spectra showed the same coupling pattern observed for compound **3**. Accordingly, compound **2** was assigned as 12-hydroxy-11,14-diketo-6,8,12-abietatrien-19,20-olide.

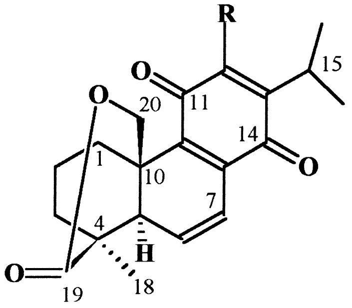
The molecular formula of compound **5** was established, by a combination of EI mass ^1H and ^{13}C NMR spectrometry, as $C_{20}H_{24}O_7$. No molecular ion peak was observed in its EIMS. The ^1H NMR spectrum was suggestive of a compound with an abietane skeleton; it showed the presence of two methyl groups as doublets (J = 7.0 Hz) at δ 1.20, clearly coupled with a one-proton heptet at δ 3.20 (J = 7.0 Hz) due to the isopropyl group on an unsaturated carbon. One three-proton singlet was observed at δ 1.30 corresponding to the methyl group on C-4. In the low-field region of the spectrum, one-proton (D_2O exchangeable) was detected and no olefinic proton-bearing carbons were observed.

An AB system centered at δ 3.05 (*dd*, J = 9.8, 2.0 Hz) and δ 4.00 (*d*, J = 9.8 Hz) was correlated with a carbon signal at 63.2 ppm in the ^{13}C NMR spectrum, corresponding to an hydroxymethyl group on C-4. From the COSY spectrum the signal at δ 3.05 was clearly coupled with a one-proton resonance at δ 1.80 (*dd*, J = 8.0, 2.0 Hz) assigned to H-5. Thus, the δ 3.05 signal was assigned to the H-19 pro-*R* diasterotopic proton, which showed long-range *W* coupling ($^4J =$ 2.0 Hz) with H-5. Furthermore, the ^{13}C NMR chemical shift of the hydroxymethylene carbon (C-19, δ 63.2, *t*) was consistent with a β-axial orientation for this function (Amaro-Luis, Herrera & Luis, 1998). Homonuclear correlations from COSY experiments also showed a three-proton system with signals at δ 5.35 (*d*, J = 4.0 Hz), δ 4.60 (*dd*, J = 8.0, 4.0 Hz), and δ 1.80 (*dd*, J = 8.0, 2.0 Hz). This information supports the deduction that the proton resonance at δ 4.60 must be vicinal with both H-5 (δ 1.80) and H-7 (δ 5.35). Location of the lactone ring closure on C-7 was deduced from the value of its chemical shift which agree with a proton bonded to an oxygen-bearing allylic carbon (Luis, Grillo, Quiñones & Kishi, 1994). The coupling constant obtained for H-6 allowed us to propose an α-configuration for the hydroxyl group at C-6, especially taking into account that the proposed connectivities suggest a boat-like conformation for B-ring. The ^{13}C NMR spectrum, with carbon multiplicities determined by DEPT, confirmed the presence of three carbonyl groups and four sp^2 carbons (quinone moiety) which accounted for all degrees of unsaturation requested by the proposed molecular formula. Hence, on taking into account all the above data, compound **5** structure was proposed as 6α,12,19-trihydroxy-11,14-diketo-8,12-abietadien-20,7β-olide.

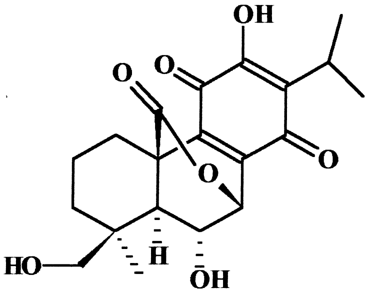
Compound **3** and **5** show an abietane skeleton with oxygenated functions at C-19. It has been reported that this oxidation pattern is relatively rare in diterpenoids isolated from *Salvia* species (Amaro-Luis et al., 1998). Moreover, both showed a positive optical rotation at 589 nm. These results have a great similarity with an important number of abietane diterpenes possessing a *trans*-A/B ring-junction with H-5α. On this basis, the relative stereochemistry of the decalin moiety is proposed, and it is assumed that **3** and **5** belong to the H-5α series, like other naturally-occurring abietanes. Finally, the triterpene oleanolic acid was isolated from the same source.



1 H-5β
2 H-5α



3 R= OH
4 R= OAc



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3. Experimental

3.1. General

The ^{1}H NMR spectra were recorded in $CDCl_3$ at 400.13 and 200.13 MHz, where the ^{13}C NMR spectra were obtained at 100.60 and 50.23 MHz. HMBC, HMQC, COSY, HETCOR, and COLOC experiments were collected using standard software. EIMS were obtained at 70 eV, direct inlet. CC were performed on Silica gel G 70–230 mesh and Kieselgel 60 H; TLC were carried out on Silica gel 60 F_{254} 0.2 mm thick plates using C_6H_6–dioxane–AcOH, 30 : 5 : 1 as solvent. HPLC chromatography was carried out using a UV–Vis detector at 235 nm and column was silica gel 25–40 µm (15 mm i.d. × 50 cm) with *n*-hexane–EtOAc (70 : 30) as solvent, flow 0.4 ml/min, fractions of 0.5 ml each.

3.2. Plant material

Specimens of *Salvia gilliessi* Benth. were collected at El Volcán, San Luis, Argentina, a herbarium sample is available from the Herbario of the Universidad Nacional de San Luis, L.A. Del Vitto (Voucher DPP 6087-UNSL).

3.3. Extraction and isolation

Dried aerial parts (400 g) were extracted with Me_2CO (twice) at room temperature, 1 week each. The extract was concentrated *in vacuo* and the resulting syrup (43.5 g) was dissolved in a mixture of MeOH : H_2O (9 : 1), filtered, and partitioned against *n*-hexane. To the hydro-alcoholic phase was added H_2O (7 : 3 ratio) and the whole was extracted with $CHCl_3$. After several CC and HPLC purification of the chloroform extract, the compounds **1** (536 mg) **3** (75 mg), and **5** (48 mg) were isolated. Oleanolic acid (1.29 g) was also isolated whose identity was determined by comparison with an authentic sample.

3.4. 5-epi-icetexone (*1*)

Mp 259–260°C. $[\alpha]_D^{25} - 92.8°$ ($CHCl_3$; *c* 1.04). UV λ_{max}^{MeOH} nm (log ε): 221 (4.30), 313 (3.27). IR ν_{max}^{KBr} cm^{-1}: 3350, 1730, 1660, 1630, 1450, 1370, 980, 750. ^{1}H and ^{13}C NMR spectral data: Tables 1 and 2. HR–MS 342.1463 (calcd for $C_{20}H_{22}O_5$, 342.1467). EIMS (direct inlet, 70 eV) *m/z* (rel int) 342 $[M]^+$ (100), 281 (21), 256 (38), 241 (22), 185 (15), 128 (21), 115 (31), 105 (18), HR–EIMS *m/z* 342.1463 ($C_{20}H_{22}O_5$ requires 342.1467).

3.5. 12-hydroxy-11,14-diketo-6,8,12-abietatrien-19,20-olide (*3*)

Amorphous solid. $[\alpha]_D^{25} + 42.8°$ ($CHCl_3$; *c* 0.03). λ_{max}^{MeOH} nm (log ε): 221 (4.08), 313 (3.60). IR ν_{max}^{KBr} cm^{-1}: 3400, 1730, 1665, 1630, 1450, 1365, 980, 750. ^{1}H and ^{13}C NMR spectral data: Tables 1 and 2. HR–MS 342.1464 (calcd for $C_{20}H_{22}O_5$, 342.1467). EIMS (direct inlet, 70 eV) m/z (rel int) 342 $[M]^+$ (98), 297 (21), 284 (34), 230 (100), 128 (15), 115 (32), 105 (10), 83 (33), HR–EIMS m/z 342.1464 ($C_{20}H_{22}O_5$ requires 342.1467).

*3.6. 12-acetoxyl-11,14-diketo-6,8,12-abietatrien-19,20-olide (**4**)*

Compound **3** (15 mg) was acetylated with Ac_2O-pyridine (two days) and after work-up and preparative TLC, 9 mg of compound **4** was recovered. ^1H and ^{13}C NMR spectral data: Tables 1 and 2.

*3.7. 6α,12,19-trihydroxy-11,14-diketo-8,12-abietadien-20,7β-olide (**5**)*

Amorphous solid. $[\alpha]_D^{25} + 56.5°$ ($CHCl_3$; c 0.20). ^1H and ^{13}C NMR spectral data: Tables 1 and 2. EIMS (direct inlet, 70 eV) m/z (rel int) 346 $[M-30]^+$ (100), 272 (20), 248 (35), 217 (37), 209 (16), 105 (12), 43 (60).

Acknowledgements

Financial support from CONICET and UNSL (Project 7301) is gratefully acknowledged. Thanks are also due to Prof. Dr. E. Manta and Prof. G. Hernández Dossi (Universidad de La República, Montevideo, Uruguay) for performing the 400 MHz NMR spectroscopy, Prof. L.A. Del Vitto for identification of the plant material and Prof. Dr. J.G. Luis (Universidad de La Laguna, Tenerife, Spain) for valuable advice.

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