Phytochemistry, Vol. 27, No. 10, pp. 3155 3159, 1988.
Printed in Great Britain.

0031-9422/88 $3.00+0.00

FLAVONOIDS AND OTHER PHENOLICS FROM *ARTEMISIA HISPANICA*

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(*Received* 10 *February* 1988)

Key Word Index—*Artemisia hispanica*; Compositae; Anthemideae; phenolics; flavonoids; glycosides; 5,3',4'-trihydroxy-6,7,5'-trimethoxyflavone; isoetin 5'-glucoside; ^{1}H NMR; ^{13}C NMR.

Abstract—Extraction of aerial parts of *Artemisia hispanica* and chromatographic separation yielded chrysosplenetin, chrysosplenol D, 5,7,3',4'-tetrahydroxy-6,5'-dimethoxyflavone, 5,7,3'-trihydroxy-6,4',5'-trimethoxyflavone, arteanoflavone, cirsilineol, penduletin, axillarin, jaceosidin, apigenin, luteolin, *p*-hydroxyacetophenone, 4-(*p*-hydroxyphenyl) butan-2-one, methyl caffeate, esculetin, apigenin 7-glucoside, luteolin 7-glucoside and the new flavonoids 5,3',4'-trihydroxy-6,7,5'-trimethoxyflavone and isoetin 5'-glucoside.

INTRODUCTION

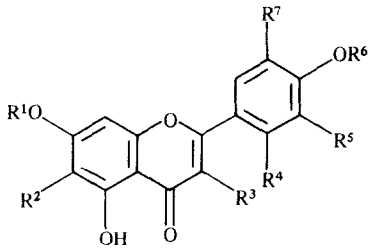
Artemisia hispanica Lam. non Weber ex Stechm. is a small shrub with grey-greenish leaves and a markedly aromatic, slightly acrid odour. It can be found as disperse populations in arid zones of south-east Spain and is considered to be synonymous with *A. reptans* C. Sm. ex Link in Buch [1]. Very recently, however, it has been claimed that the species growing in South Spain is actually different from *A. reptans* and the new name *A. lucentica* O. Bolòs, Vallès et Vigo has been proposed [2]. Because of our current interest in the chemotaxonomy of the genus *Artemisia* [3], we have investigated the flavonoids and other phenolic constituents of *A. hispanica* with the aim of clarifying the taxonomic position of this species. We now present the results of our investigation in which 17 known products and two new ones: isoetin 5'-glucoside **1** and 5,3',4'-trihydroxy-6,7,5'-trimethoxyflavone **2** have been identified.

RESULTS AND DISCUSSION

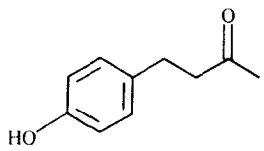
Compound **1** appeared as a yellow amorphous powder, which darkened above 260° without melting and which showed the chromatographic behaviour of a flavonoid monoglycoside. UV data (see Experimental) clearly showed the presence of hydroxyl groups at C-5, C-7 and C-4' in a flavone nucleus. Complete hydrolysis and separation of the sugar and aglycone fractions enabled the identification of glucose as the glycosidic part of **1**. The ^{1}H NMR (DMSO-d_6) showed a pair of doublets at δ 6.15 and 6.49 from C-6 and C-8, respectively (*meta* coupling $J=2$ Hz), and three singlets at δ 6.51, 7.03 and 7.67 (1H each). A doublet at δ 4.66 ($J=7.2$ Hz) was assigned to the anomeric proton of the sugar residue, the other glycosidic protons appearing as a broad multiplet in the range 3–4 ppm. In order to account for these data, one could suggest a 5,7,4'-trihydroxylated flavone with further OH-/OGlc residues at C-2'/C-5' [4]. The ^{1}H NMR spectrum of the aglycone **12**, obtained by hydrolysis of **1**, showed three singlets at δ 7.26, 7.02 and 6.50, and two doublets ($J=2$ Hz) at δ 6.15 and 6.38. The pronounced downfield shift experienced by the singlet at δ 7.26 in **12** after glycosylation (*ca* 0.4 ppm) suggested this signal may be coming from a proton *ortho* to the glycosylated hydroxyl. Since chemical shift considerations also suggested this proton to be H-6', this pointed to the presence of the glucose residue at C-5'. Comparison of the ^{13}C NMR spectra of **1** and **12** with those of closely related compounds [5–7] further supported the placement of the sugar residue at C-5'. The negative ion FAB mass spectrum showed a peak at m/z 463.0885 $[M-H]^-$, as expected for a product with a molecular formula $C_{21}H_{20}O_{12}$. Compound **1** would thus be the 5'-glucoside of the rare aglycone isoetin **12** (5,7,2',4',5'-pentahydroxyflavone) [8], which has been found up to now only in glycosidic form. An isoetin glucoside was reported 13 years ago in the quillwort *Isoetes delilei* (Lycopsida) [9] but the authors did not determine the position of the sugar residue. They also did not give NMR data of the glucoside in their paper but the reported R_f values are comparable with those found by us (see Experimental).

Compound **11** was obtained only in minute amount. The UV data indicated free hydroxyl groups at C-5, C-3' and C-4'. In the ^{1}H NMR spectrum, only singlets were visible at δ 7.19 (2H), 6.90, 6.86 (aromatic hydrogens), 3.93, 3.87 and 3.72 (MeO signals). This suggested a 5,3',4'-trihydroxyflavone with additional methoxyl groups at C-6, C-7 and C-5'. The mass spectrum showed a molecular peak (base peak) at m/z 360, consistent with a molecular formula $C_{18}H_{16}O_8$, and further peaks at m/z 359 (25%), 345 (90%) and 342 (5%), a fact which supported the proposed substitution pattern [10]. The ^{13}C NMR spectrum was also in accord with this structure the C-8 peak at δ 91.41 pointing to the presence of a methoxy group (not hydroxyl) at C-7 [3, 5].

The remaining compounds described in the present communication were identified by their spectral properties and, in several cases, by direct comparison with authentic samples (see Experimental). Some of them are very rare in nature. For instance, arteanoflavone **3** (5,7-dihydroxy-6,3',4',5'-tetramethoxyflavone) has been reported before in *A. anomala* [11], our paper being only the



1	$R^1 = R^2 = R^3 = R^5 = R^6 = H$; $R^4 = OH$; $R^7 = O\beta Glc$	Isoetin 5′-glucoside
2	$R^1 = R^3 = R^4 = R^6 = H$; $R^2 = R^7 = OMe$; $R^5 = OH$	
3	$R^1 = R^3 = R^4 = H$; $R^2 = R^5 = R^7 = OMe$; $R^6 = Me$	Arteanoflavone
4	$R^1 = R^4 = R^6 = R^7 = H$; $R^2 = R^3 = OMe$; $R^5 = OH$	Axillarin
5	$R^1 = Me$; $R^2 = R^5 = OMe$; $R^3 = R^4 = R^6 = R^7 = H$	Cirsilineol
6	$R^1 = Me$; $R^2 = R^3 = OMe$; $R^4 = R^6 = R^7 = H$; $R^5 = OH$	Chrysosplenol D
7	$R^1 = Me$; $R^2 = R^3 = R^5 = OMe$; $R^4 = R^6 = R^7 = H$	Chrysosplenetin
8	$R^1 = Me$; $R^2 = R^3 = OMe$; $R^4 = R^5 = R^6 = R^7 = H$	Penduletin
9	$R^1 = R^3 = R^4 = R^6 = R^7 = H$; $R^2 = R^5 = OMe$	Jaceosidin
10	$R^1 = R^3 = R^4 = H$; $R^2 = R^7 = OMe$; $R^5 = OH$; $R^6 = Me$	
11	$R^1 = Me$; $R^3 = R^4 = R^6 = H$; $R^2 = R^7 = OMe$; $R^5 = OH$	
12	$R^1 = R^2 = R^3 = R^5 = R^6 = H$; $R^4 = R^7 = OH$	Isoetin



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second record of this compound. This is also true of the flavones **2** and **10**, which have been described only in *A. frigida* [12, 13], and compound **13**, 4-(*p*-hydroxyphenyl)butan-2-one, which was first isolated from *Scutellaria rivularis* (Scrophulariaceae) [14]. The *ortho* isomer was reported seven years ago in *Artemisia campestris* subsp. *glutinosa* [15].

The observed flavonoid pattern and the abundance of polymethylated flavonols supports the inclusion of *A. hispanica* in the subgenus *Artemisia* (sect. *Abrotanum*) [16–18]. This would exclude the possibility of *A. hispanica* being identical with, or a subspecies of, *A. herba alba* [2], as it has been suggested [1]. We are presently trying to confirm this conclusion by an analysis of the sesquiterpene lactones and other terpenoid constituents of *A. hispanica*.

EXPERIMENTAL

The NMR spectra were measured in $CDCl_3$ or DMSO-d_6 solution at 27°, taking the solvent signals as ref. PC was performed on paper sheets Macherey Nagel MN 216. Polyamide for CC was Macherey Nagel SC6.

Plant material. Aerial parts of *A. hispanica* (= *A. lucentica*) were collected in the vicinity of Callosa de Segura (Alicante, Spain) in November 1986 and identified by Dr A. Aguilella, from the Department of Botany at the Faculty of Biology (University of Valencia, Spain). A voucher specimen (VAB-861962) has been deposited in the herbarium of this Department.

Extraction and chromatography. The plant material (1 kg) was air-dried, finely ground and extracted successively at room temp. with 80% MeOH (10 l, 5 days) and 50% MeOH (10 l, 5 days). The combined extracts were concentrated *in vacuo* to 2 l and extracted successively with hexane (3 × 2 l), Et_2O (4 × 2 l) and EtOAc (4 × 2 l). The hexane extract contained mainly waxes and essential oils and was not studied.

The Et_2O extract (6.7 g) was chromatographed on a polyamide column (50 × 6 cm) with toluene–MeOH mixtures of increasing MeOH percentage. Three main fractions were made, after TLC inspection, corresponding to percentages of up to 15% MeOH (E-1), 15 to 25% MeOH (E-2) and 25% MeOH (E-3). Fraction E-1 was rechromatographed on silica gel with $CHCl_3$–Et_2O mixtures of increasing Et_2O percentage. After chromatographic inspection by TLC, three main fractions (E-11 to E-13) were collected. Repeated prep. TLC of fraction E-11 with several solvent mixtures allowed separation of *p*-hydroxyacetophenone (5 mg) and 4-(*p*-hydroxyphenyl) butan-2-one **13** (3 mg). Fraction E-12 was rechromatographed on silica gel (elution with hexane–Et_2O mixtures) giving a flavonoid, which was further purified by CC on Sephadex LH-20 (elution with MeOH), affording chrysosplenetin **7** (25 mg). Fraction E-13 was rechromatographed on silica gel (elution with hexane–Et_2O mixtures) and the flavonoid fractions submitted to CC on polyamide (toluene–MeOH mixtures) and then Sephadex LH-20 (MeOH or 80% MeOH) giving arteanoflavone **3** (6 mg), penduletin **8** (7 mg), cirsilineol **5** (46 mg) and further chrysosplenetin (12 mg).

Fraction E-2 was rechromatographed on polyamide with

toluene–MeOH 10:1. Two main fractions, E-21 and E-22, were recovered after TLC inspection, Fraction E-21 was chromatographed on Sephadex LH-20 (elution with MeOH) to give two fractions, one of which contained chrysosplenol D **6** (20 mg). The other one was purified by prep. TLC on polyamide and percolation through Sephadex LH-20 (MeOH), affording 5,7,3′-trihydroxy-6,4′,5′-trimethoxyflavone **10** (7 mg). Fraction E-22 was chromatographed on Sephadex LH-20 (MeOH) to give methyl caffeate (160 mg) and a second fraction, which was submitted to PPC (35% HOAc). The main bands were eluted with MeOH, and percolated through Sephadex LH-20 (MeOH) to give more chrysosplenol D (5 mg) and 5,3′,4′-trihydroxy-6,7,5′-trimethoxyflavone **11** (3 mg).

Fraction E-3 was rechromatographed on a polyamide column as for fraction E-2. This gave two fractions, E-31 and E-32, which were further chromatographed on Sephadex LH-20 (MeOH). E-31 gave successively esculetin (15 mg), axillarin **4** (3 mg), jaceosidin **9** (15 mg) and 5,7,3′,4′-tetrahydroxy-6,5′-dimethoxyflavone **2** (65 mg). E-32 yielded luteolin (16 mg) and apigenin (30 mg).

The EtOAc extract (7 g) was chromatographed on polyamide (60 × 4 cm) and elution with toluene–MeOH mixtures gave two fractions, A-1 and A-2. Fraction A-1 was rechromatographed on a Sephadex LH-20 column (100 × 2 cm, elution with 80% aq MeOH), affording luteolin 7-glucoside (20 mg) and a crude mixture from which apigenin 7-glucoside (10 mg) was separated by PC (15% HOAc). Fraction A-2 was also chromatographed on Sephadex LH-20 as for fraction A-1, affording pure isoetin 5′-glucoside **1** (20 mg).

Chrysosplenetin, chrysosplenol D, penduletin, jaceosidin, cirsilineol, axillarin, apigenin, luteolin, esculetin, luteolin 7-glucoside, apigenin 7-glucoside and *p*-hydroxyacetophenone were compared with authentic samples of natural origin. Methyl caffeate and 4-(*p*-hydroxyphenyl)butan-2-one were compared with synthetic samples obtained, respectively, by Fischer esterification of caffeic acid and by catalytic hydrogenation of *p*-hydroxybenzylideneacetone [20, 21].

Isoetin 5′-glucoside (**1**). Yellow powder with no defined mp (darkening above *ca* 260°). R_f values: PC TBA, 0.50 (0.86 relative to rutin); 15% HOAc, 0.06 (0.12 rel. to rutin); TLC on silica gel, $CHCl_3$–MeOH–H_2O 14:6:1, 0.27 (1.50 rel. to rutin); elution with EtOAc–MeCOEt–HCOOH–H_2O 5:3:3:1, 0.63 (2.03 rel. to rutin); TLC on polyamide, $CHCl_3$–MeOH–MeCOEt–acetylacetone 20:10:1:1, 0.05 (0.38 rel. to rutin); TLC on cellulose, water, *ca* O. UV λ_{max}^{MeOH} nm: 256, 288, 362; (+NaOMe): 265, 311, 422; (+$AlCl_3$); 269, 295, 401; (+$AlCl_3$+HCl): 265, 293, 397; (+NaOAc): 267, 309, 402; (+NaOAc+H_3BO_3): 266, 287sh, 369. FAB MS, *m/z*: 463.0885 $[M-H]^-$, calc. for $C_{21}H_{19}O_{12}$, M_r 463.0877. For ^1H and ^{13}C NMR spectra see Tables 1 and 2.

5,7,3′,4′-*Tetrahydroxy*-6,5′-*dimethoxyflavone* (**2**). Yellow plates, mp 267–269° (from MeOH). UV λ_{max}^{MeOH} nm: 273, 351; (+NaOMe): 260, 415; (+$AlCl_3$): 271, 432; (+$AlCl_3$+HCl): 282, 375; (+NaOAc): 320 sh, 409; (+NaOAc+H_3BO_3): 380, 430 sh.

Table 1. ^1H NMR spectra of compounds **1–3, 6, 7** and **10–12***

Compound	H-3	H-6	H-8	H-2′	H-3′	H-5′	H-6′	H-1″	OMe
1	7.03 *s*	6.15 *d* (2.0)	6.49 *d* (2.0)		6.51 *s*		7.67 *s*	4.66 *d* (7.3)	
2	6.81 *s*		6.55 *s*	7.13[a] *d* (2.0)			7.15[a] *d* (2.0)		3.74 *s* 3.86 *s*
3	6.99 *s*		6.55 *s*	7.31 *s*			7.31 *s*		3.73 *s* (×2) 3.89 *s* (×2)
3†	6.61[a] *s*		6.58[a] *s*	7.07 *s*			7.07 *s*		3.92 *s* 3.95 *s* (×2) 4.04 *s*
6			6.86 *s*	7.58 *d* (2.2)		6.89 *d* (8.4)	7.48 *dd* (8.4; 2.2)		3.71 *s* 3.78 *s* 3.90 *s*
7			6.88 *s*	7.66 *d* (2.0)		6.96 *d* (8.4)	7.61 *dd* (8.4; 2.0)		3.72 *s* 3.80 *s* 3.86 *s* 3.91 *s*
7†			6.48 *s*	7.69 *d* (2.0)		7.03 *d* (8.4)	7.65 *dd* (8.4; 2.0)		3.85 *s* 3.91 *s* 3.95 *s* 3.97 *s*
10	6.90 *s*		6.57 *s*	7.15 *br s*			7.15 *br s*		3.74 *s* (×2) 3.87 *s*
11	6.91[a] *s*		6.86[a] *s*	7.19 *br s*			7.19 *br s*		3.72 *s* 3.87 *s* 3.93 *s*
12	7.02 *s*	6.15 *d* (2.0)	6.38 *d* (2.0)		6.50 *s*		7.26 *s*		

*At 200.13 MHz in DMSO-d_5 (30°) unless otherwise stated; δ values are followed by multiplicity and below, in parentheses, coupling constants in Hz. Only aromatic, anomeric and methoxyl signals are given. The 5-OH originates a broad singlet at δ 12.5–13.0 in all compounds.

†In $CDCl_3$.

[a] Signals may be interchanged within the same spectrum.

Table 2. ^{13}C NMR spectra of compounds **1–3, 6, 7** and **10–12***

C	1†	2	3‡	6	7	7‡	10	11	12
2	161.64[a]	163.89	163.97	155.95	155.72	155.96	163.11	164.42	161.70[a]
3	107.44	102.83	105.05	137.64	137.70	138.68	104.15	102.83	106.77
4	182.08	182.07	182.91	178.18	178.18	178.86	182.09	181.89	181.74
5	161.19[a]	152.77[a]	153.19[a]	151.66	151.68[a]	152.74[a]	152.47[a]	152.04[a]	161.41[a]
6	98.81	131.34	130.46	131.55	131.58	132.32	131.48	131.77	98.49
7	164.11	157.31	155.17	158.59	158.59	158.77	157.87	158.41	163.88
8	94.39	94.17	93.46	91.24	91.38	90.35	94.30	91.41	93.48
9	157.65	152.38[a]	152.13[a]	151.66	151.61[a]	152.28[a]	152.68[a]	152.52[a]	157.19
10	103.77	104.06	105.85	105.52	105.52	106.56	104.00	104.97	103.46
1′	107.85	120.49	126.51	120.72	120.69	122.41	125.85	—§	106.97
2′	151.87	107.52	103.92	115.69[a]	112.10	110.96	107.62	107.18	150.50
3′	104.45	145.94	153.68	145.26	147.47	146.42	150.86	102.83	104.20
4′	154.17	138.61	141.64	148.82	149.90	148.42	139.61	—§	151.60
5′	139.50	148.61	153.68	115.53[a]	115.62	114.62	153.53	148.52	138.73
6′	116.55	102.38	103.92	120.61	122.29	122.60	102.10	102.46	113.44
OMe		59.92	61.07	60.02	59.99	60.84	60.03	59.95	
		56.25	60.91	59.61	59.62	60.13	59.88	56.38	
			56.44 (×2)	56.43	56.43	56.31	56.14	56.23	
					55.78	56.13			

*At 50.32 MHz in DMSO-d_6 (30°) unless otherwise stated.
† Sugar signals: 103.44 (1″), 77.42 (5″), 75.96 (3″), 73.45 (2″), 70.02 (4″), 61.08 (6″).
‡ In $CDCl_3$.
§ Not emerged from the background.
[a] The signals may be interchanged within the corresponding spectrum.

EIMS (probe) *m/z* (% rel. int.): 346 (100, $[M]^+$), 345 (7, $[M-H]^+$), 331 (65, $[M-Me]^+$), 328 (65, $[M-H_2O]^+$), 317 (8), 303 (51), 300 (19), 167 (17), 165 (18), 164 (16), 139 (17). For ^1H and ^{13}C NMR spectra see Tables 1 and 2.

5,7-*Dihydroxy*-6,3′,4′,5′-*tetramethoxyflavone* (*arteanoflavone*) (**3**). Yellow needles, mp 173–175° (from MeOH, lit. [11] mp 173–175°). UV λ_{max}^{MeOH} nm 277, 333; (+NaOMe): 277, 370; (+$AlCl_3$): 285, 361; (+$AlCl_3$+HCl): 292, 356, (+NaOAc): 277, 370; (+NaOAc+H_3BO_3): 278, 333. EIMS (probe) *m/z* (% rel. int.): 374 (100, $[M]^+$), 373 (6, $[M-H]^+$), 359 (60, $[M-Me]^+$), 356 (63, $[M-H_2O]^+$), 344 (14, $[M-CH_2O]^+$), 331 (42), 193 (7). For ^1H and ^{13}C NMR spectra see Tables 1 and 2.

5,7,3′-*Trihydroxy*-6,4′,5′-*trimethoxyflavone* (**10**). Yellow needles, mp 239–241° (from MeOH, lit. [12] mp 243–245°). UV λ_{max}^{MeOH} nm: 277, 337; (+NaOMe): 273, 313sh, 380; (+$AlCl_3$): 286, 364; (+$AlCl_3$+HCl): 293, 360; (NaOAc): 278, 305sh, 382; (+NaOAc+H_3BO_3): 280, 342. EIMS (probe), *m/z* (% rel. int.): 360 (100, $[M]^+$), 359 (5, $[M-H]^+$), 345 (57, $[M-Me]^+$), 343 (17, $[M-OH]^+$), 342 (60, $[M-H_2O]^+$), 330 (58, $[M-CH_2O]^+$), 317 (37), 315 (36), 312 (27), 287 (25), 179 (13), 167 (16), 139 (18). For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

5,3′,4′-*Trihydroxy*-6,7,5′-*trimethoxyflavone* (**11**). Yellow product, which darkened above 240° (could not be crystallized because of the small amount). R_f relative to luteolin, TLC on silica gel: 0.61 (elution with Et_2O), 0.94 (elution with MeOH). UV λ_{max}^{MeOH} nm: 277, 351; (+NaOMe): 265, 416; (+$AlCl_3$): 275, 434; (+$AlCl_3$+HCl): 286, 376; (+NaOAc): 270, 411; (+NaOAc+H_3BO_3): 270, 380. EIMS (probe), *m/z* (% rel. int.): 360 (100, $[M]^+$), 359 (25, $[M-H]^+$), 345 (90, $[M-Me]^+$), 343 (15, $[M-OH]^+$), 342 (5, $[M-H_2O]^+$), 331 (36, $[M-CHO]^+$), 330 (63, $[M-CH_2O]^+$), 317 (24), 315 (42), 312 (36), 287 (27), 181 (21), 165 (21), 153 (43). For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

5,7,2′,4′,5′-*Pentahydroxyflavone* (*isoetin*) (**12**). Obtained by acid hydrolysis (1 M HCl, 100°, 30 min) of **1**. Yellow needles which do not melt up to 340°. UV λ_{max}^{MeOH} nm: 265, 374; (+NaOMe): 266, 329 (dec.); (+$AlCl_3$): 270, 335, 444; (+$AlCl_3$+HCl): 272, 408; (+NaOAc): 261, 313, 425 (dec.); (+NaOAc+H_3BO_3): 267, 399, 445sh. EIMS (probe), *m/z* (% rel. int.): 302 (100, $[M]^+$), 301 (5), 285 (14, $[M-OH]^+$), 153 (47), 152 (15), 151 (15), 150 (16). For ^1H and ^{13}C NMR spectra, see Tables 1 and 2.

4-(*p-Hydroxyphenyl*)*butan-2-one* (**13**). Obtained as a gum (lit. [21] solid mp. 83.5–84.5°). UV λ_{max}^{MeOH} nm: 279; (+NaOMe): 296. ^1H NMR, δ ppm ($CDCl_3$): 7.04 (2H, *d*, $J=8.4$ Hz, arom. H *meta* to OH), 6.74 (2H, *d*, $J=8.4$ Hz, arom. H *ortho* to OH), 2.76 (4H, A_2B_2 system, CH_2CH_2), 2.13 (3H, s, Me). ^{13}C NMR, δ ppm ($CDCl_3$): 210.55 (CO), 154.39 (C–OH), 132.24 (arom. C *para* to OH), 129.29 (2 arom. C *meta* to OH), 115.46 (2 arom. C *ortho* to OH), 45.43 ($\underline{C}H_2$–CO), 30.09 (Me), 28.91 (CH_2–Ar). EIMS (probe) *m/z* (% rel. int.): 164 (38, $[M]^+$), 149 (6, $[M-Me]^+$), 121 (15, $[M-Ac]^+$), 107 (100, $[M-CH_2Ac]^+$), 43 (60).

Acknowledgements—O. B. thanks the Conselleria de Cultura, Educación y Ciencia de la Generalitat Valenciana for a grant. The authors also wish to thank Dr J. Vallès (Univ. Barcelona) and Dr A. Aguilella (Univ. Valencia) for their invaluable help in the localization and botanical classification of the plant. The kind help of Prof. Dr D. Strack and Dr V. Wray (respectively from the Technical University and the Institute of Biotechnological Research Braunschweig, F.R.G.), and of Professor Dr J. Primo (Universidad Politècnica de Valencia) for the measurement of some mass spectra is also gratefully acknowledged.

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