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REARRANGED ABIETANE DITERPENES FROM *SALVIA LIMBATA*

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Key Word Index—*Salvia limbata*; Lamiaceae; rearranged abietane diterpenes.

Abstract—Six new rearranged abietane diterpenes were isolated from the roots of *Salvia limbata*. Their structures were established by 1D and 2D NMR techniques including spin decoupling, COSY, APT, HETCOR and COLOC experiments

INTRODUCTION

Salvia species have been used in folk medicine all around the world. They have antibacterial and antifungal activities [1], and are used against psoriasis, seboreic eczema [2] and tuberculosis [3]. In China, *S. miltiorrhiza* is used in the treatment of coronary heart disease [4, 5]. In Turkey they have also many uses in folk medicine [6].

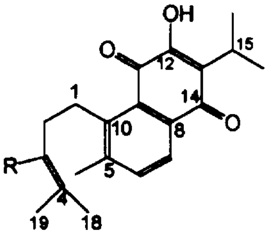
Salvia limbata C.A. Meyer (syn. *S. chrysadenia* Freyn) is found in Azerbaijan and eastern Turkey at elevations 1800–2000 m. This paper deals with the isolation and structure determination of six new rearranged abietane diterpenes (**1**–**6**), all of which were isolated from the roots of the plant together with the known diterpene manool [7, 8], and the flavonoids, pectolinarigenin and salvigenin, as well as the steroids, stigmasterol and sitosterol.

RESULTS AND DISCUSSION

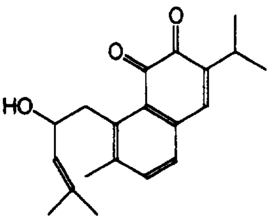
Dried and roughly powdered roots of *S. limbata* yielded six rearranged abietane diterpenes: 12-hydroxy-sapriparaquinone [4,5-seco-5,10-friedo-12-hydroxyabieta-3,5(10),6,8,12-pentaene-11,14-dione] (**1**), 3,12-dihydroxysapriparaquinone-1-ene [4,5-seco-5,10-friedo-3,12-dihydroxyabieta-1,3,5(10),6,8,12-hexaene-11,14-dione] (**2**), 2-hydroxysaprorthoquinone [4,5-seco-5,10-friedo-2-hydroxy-abieta-3,5(10),6,8,12-pentaene-11,12-dione] (**3**), limbinol [4,5-seco-5,10-friedo-2,12-dihydroxyabieta-3,5(10),6,8,11,13-hexaene-1-one] (**4**), salvilimbinol [4,5-seco-5,10(H)-friedo-4,9,11,12-tetrahydroxyabieta-5,7,11,13-tetraene-3-one] (**5**) and 4-dehydrosalvilimbinol [4,5-seco-5,10(H)-friedo-9,11,12-trihydroxyabieta-4(18),5,7,11,13-pentaene-3-one] (**6**).

The high resolution mass spectrum (HREIMS) of compound **1** indicated a molecular formula $C_{20}H_{24}O_3$ (*m/z* 312.1730; calc. 312.1725). The IR spectrum showed a sharp signal for a hydroxyl group at 3380 cm^{-1} and quinoid signals at 1700, 1650, 1580 cm^{-1}. The UV spectrum indicated an unsaturated quinoid structure with $\lambda_{max} = 390$ nm. The ^1H NMR spectrum of **1** exhibited lower field signals at δ7.96 (1H, *d*, $J = 8$ Hz, H-7), 7.50 (1H, *d*, $J = 8$ Hz, H-6) and 7.78 (1H, *br s*, C-12 OH) (D_2O exchangeable) indicating a *p*-quinoid structure while the *o*-quinoid isomer of compound **1**, saprorthoquinone, has lower field protons at δ7.36, 7.04 and 7.09 [9]. Other ^1H NMR signals of **1** were at δ5.29 (1H, *br t*, $J = 7.5$ Hz, H-3), 3.38 (1H, *septet*, $J = 7$ Hz, H-15), 3.19 (2H, *dd*, $J = 7.5$ and 11 Hz, H_2-1), 2.44 (3H, *s*, Me-20), 2.18 (2H, *ddd*, $J = 7.5$, 9 and 11 Hz, H_2-2), 1.72 (3H, *s*), 1.60 (3H, *s*) (Me-18 and Me-19) and 1.28 (6H, *d*, $J = 7$ Hz, Me-16 and Me-17). The sequence of the C-1 to C-3 protons was assigned from spin decoupling experiments. When the signal at δ5.29 (H-3) was irradiated only the signal at δ2.18 (H-2) collapsed to a triplet; when the latter signal was irradiated both signals at δ5.29 (H-3) and 3.19 (H_2-1) collapsed to singlets showing their respective places. The ^{13}C NMR (APT) displayed four methyl quartets corresponding to five methyl groups, two methylene triplets, four methine doublets and nine quaternary carbon singlets. The COSY and the HETCOR experiments allowed the assignment of protons and carbons (Table 1).

The HREIMS of compound **2** indicated a molecular formula $C_{20}H_{22}O_4$ (*m/z* 326.1522, calc. 326.1528). The IR spectrum showed hydroxyl absorption at 3400 cm^{-1}, and conjugated quinoid bands at 1700, 1685, 1650 cm^{-1}. The UV spectrum established the presence of conjugated *p*-quinone structure with $\lambda_{max} = 410$ nm. The ^1H NMR spectrum of **2** revealed its structure, showing signals at δ8.37 (1H, *d*, $J = 8$ Hz, H-1), 8.15 (1H, *d*, $J = 8.5$ Hz, H-7), 7.57 (1H, *d*, $J = 8$ Hz, H-2), 7.45 (1H, *d*, $J = 8.5$ Hz, H-6), 3.45 (1H, *septet*, $J = 7$ Hz, H-15), 2.81 (3H, *s*, Me-20), 1.79 (6H, *s*, Me-18 and Me-19) and 1.34 (6H, *d*, $J = 7$ Hz, Me-16 and Me-17). Spin decoupling experiments showed the relationship between H-1 and H-2 as well as between H-6 and H-7. Thus irradiation of H-1 and H-6 collapsed H-2 and H-7 to singlets, respectively. The ^{13}C NMR (APT) spectrum showed three quartets for five methyl groups, five methine doublets, four being



1 R=H
2 R=OH, $\Delta^{1,2}$



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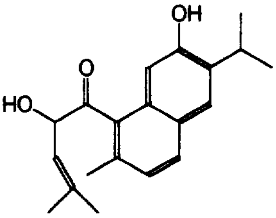

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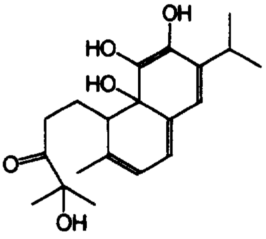

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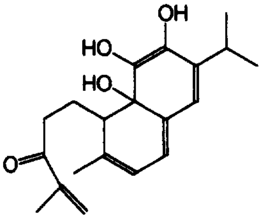

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Table 1. ^1H and ^{13}C NMR data of compounds 1–4

	1		2		3		4	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	3.19	30.2	8.37	129.6	1.18; 3.08	32.3	—	195.5
2	2.18	27.8	7.57	128.8	4.88	73.0	5.35	65.6
3	5.29	123.7	—	150.0	5.50	124.4	5.40	124.9
4	—	126.3	—	126.5	—	136.2	—	136.5
5	—	144.4	—	142.2	—	137.8	—	136.0
6	7.50	136.2	7.45	127.9	7.07	124.4	7.00	126.5
7	7.96	126.4	8.15	118.3	7.50	124.1	7.12	130.5
8	—	136.3	—	134.0	—	120.1	—	127.7
9	—	132.5	—	132.7	—	129.0	—	133.7
10	—	143.2	—	143.7	—	137.8	—	139.6
11	—	184.6	—	184.8	—	183.0	7.10	136.0
12	—	153.2	—	153.1	—	184.3	—	139.6
13	—	132.5	—	132.7	—	136.2	—	133.7
14	—	183.3	—	184.0	7.20	115.7	6.95	136.5
15	3.38	24.4	3.45	24.1	2.97	26.9	2.97	26.9
16	1.29	19.8	1.34	20.9	1.32	25.6	1.15	21.4
17	1.29	19.8	1.34	20.9	1.36	25.6	1.13	21.5
18	1.72	26.9	1.79	29.7	1.82	27.7	1.74	25.8
19	1.60	17.6	1.79	29.7	1.77	18.3	1.76	18.1
20	2.44	20.3	2.81	18.4	2.35	22.5	2.22	18.8

in the lower field, and 10 quaternary carbon signals. Methylene triplets were not present. The COSY and the HETCOR experiments showed the protons and carbons of the structure (Table 1).

The third compound (3) obtained from the extract had a molecular formula $C_{20}H_{24}O_3$ as derived from its HREIMS (*m/z* 312.1731; calc. 312.1725). The IR spectrum indicated hydroxyl groups at 3600 and 3400 cm^{-1}, and a conjugated quinoid structure at 1680 and 1650 cm^{-1}. The UV spectrum had a λ_{max} at 395 nm. The ^1H NMR spectrum of 3 indicated an orthoquinoid structure rather than a paraquinoid one: δ7.50 (1H, *d*, $J = 8$ Hz, H-7), 7.20 (1H, *br s*, H-14), 7.07 (1H, *d*, $J = 8$ Hz, H-6), 5.77 (1H, *br s*, C-2 OH) (D_2O exchange), 5.5 (1H, *dd*, $J = 8.5$ and 1.5 Hz, H-3), 4.88 (1H, *br t*, $J = 8.5$ Hz, H-2), 2.97 (1H, *septet*, $J = 7$ Hz, H-15), 3.08

Table 2. ^1H and ^{13}C NMR data and COLOC experimental data of compounds **5** and **6**

	5			**6**		
	^1H	^{13}C	COLOC correlations	^1H	^{13}C	COLOC correlations
1	1.86; 1.94	23.5	C-3, C-5, C-9	1.80; 2.30	24.4	C-3, C-9
2	2.57; 2.89	25.3	C-3, C-4, C-10	2.67; 2.90	25.1	C-1, C-4, C-10
3	—	210.7	—		201.7	
4	—	74.2	—		149.1	
5	—	138.7	—	—	137.3	
6	6.92	126.6	C-8, C-9, C-10, C-20	6.98	126.5	C-8, C-10, C-14, C-20
7	7.05	130.0	C-9, C-5	7.10	130.1	C-5, C-14
8	—	135.5	—	—	135.6	—
9	—	76.2	—	—	74.5	—
10	2.42	45.4	C-2, C-3, C-9, C-11	2.44	45.8	C-2, C-5, C-11
11	—	136.3	—	—	137.3	
12	—	141.0	—	—	141.9	—
13	—	128.1	—	—	126.6	
14	6.78	134.9	C-7, C-9, C-12	6.89	135.5	C-7, C-8, C-12
15	2.90	27.4	C-13, C-14	2.98	26.6	C-14
16	1.12	20.7	C-12, C-13, C-14	1.11	21.4	C-13, C-15
17	1.17	21.6	C-13, C-14	1.11	21.4	C-13, C-15
18	1.37	26.5	C-2, C-3, C-4	4.90; 4.91	111.7	C-3, C-4, C-19
19	1.42	32.6	C-2, C-3	2.01	24.5	C-3, C-18
20	2.24	19.8	C-6, C-7, C-10	2.25	19.8	C-6, C-7

(1H, *m*, H-1a), 2.35 (3H, *s*, Me-20), 1.82 (3H, *s*), 1.77 (3H, *s*) (Me-18 and Me-19), 1.36 (3H, *d*, $J = 7$ Hz), 1.32 (3H, *d*, $J = 7$ Hz) (Me-16 and Me-17), 1.18 (1H, *m*, H-1b). The protons of C-1, C-2 and C-3 were assigned from spin decoupling experiments. Irradiation of the vinylic proton at C-3 (δ5.50) collapsed the triplet at δ4.88 (H-2) to a doublet, irradiation of H-2 collapsed H-3 to a broadened singlet and the multiplet at δ3.08 (H-1a) and 1.18 (H-1b) simplified, irradiation of H-1a and H-1b signals affected only H-2 but not H-3. The ^{13}C NMR (APT) spectrum showed the presence of four quartets corresponding to five methyl groups, a methylene triplet, six methine doublets and eight quaternary carbon signals. Spin decoupling, the COSY and the HETCOR experiments allowed the assignment of the protons and carbons (Table 1).

The HREIMS of limbinol (**4**) indicated a molecular formula $C_{20}H_{24}O_3$ (*m/z* 312.1728; calc. 312.1725). The IR spectrum showed hydroxyl absorption at 3420 cm^{-1}, a conjugated carbonyl group at 1690 cm^{-1} and conjugated aromatic signals at 1610, 1580 and 1520 cm^{-1}. The UV spectrum confirmed the conjugated aromatic system by the presence of a $\lambda_{max} = 369$ nm. The ^1H NMR spectrum indicated an aromatic ring instead of a quinoid system, i.e. signals at δ7.12 (1H, *d*, $J = 8$ Hz, H-7), 7.0 (1H, *d*, $J = 8$ Hz, H-6), 7.1 (1H, *s*, H-11), 6.95 (1H, *s*, H-14). Other ^1H NMR signals were at δ5.40 (1H, *d*, $J = 4$ Hz, H-3), 5.35 (1H, *d*, $J = 4$ Hz, H-2), 2.97 (1H, *septet*, $J = 7$ Hz, H-15), 2.22 (3H, *s*, Me-20), 1.76 (3H, *s*), 1.74 (3H, *s*) (Me-18 and Me-19), 1.15 (3H, *d*, $J = 7$ Hz), 1.13 (3H, *d*, $J = 7$ Hz) (Me-16 and Me-17). The ^{13}C NMR (APT) indicated five methyl quartets, seven methine doublets five of them being in the lower field and eight quaternary carbon singlets one being at δ195.5 which indicated a conjugated carbonyl at C-1. This position for the oxo group was decided from the multiplicity of the C-2 and C-3 protons, if the oxo group was at C-2 instead of C-1 both signals for H-3 and H-1 would be observed as singlets. The assignments of the protons and carbons were made by the HETCOR and spin decoupling experiments (Table 1).

The HREIMS of **5**, salvilimbinol, indicated a molecular formula $C_{20}H_{28}O_5$ (*m/z* 348.1930; calc. 348.1936). Its IR spectrum showed the signals for an oxo group at 1700 cm^{-1}, unsaturation peaks at 1660 and 1600 cm^{-1}, and hydroxyl signal at 3500 cm^{-1}. The UV spectrum showed a λ_{max} at 329 nm. The ^1H NMR indicated the structure of **5** exhibiting signals at δ7.05 (1H, *d*, $J = 7.5$ Hz, H-7), 6.92 (1H, *d*, $J = 7.5$ Hz, H-6), 6.78 (1H, *d*, $J = 1$ Hz, H-14), 4.56 (1H, *br s*, OH) (D_2O exchange), 2.90 (1H, *septet*, $J = 7$ Hz, H-15), 2.89 (1H, *ddd*, $J = 11, 5.5, 2$ Hz, H-2a), 2.57 (1H, *ddd*, $J = 10, 10, 5.5$ Hz, H-2b), 2.42 (1H, *dd*, $J = 10, 5$ Hz, H-10), 2.24 (3H, *s*, Me-20), 1.94 (1H, *dd*, $J = 11, 5$ Hz, H-1a), 1.86 (1H, *m*, H-1b), 1.42 (3H, *s*), 1.37 (3H, *s*) (Me-18 and Me-19), 1.17 (3H, *d*, $J = 7$ Hz) and, 1.12 (3H, *d*, $J = 7$ Hz) (Me-16 and Me-17). Spin decoupling experiments showed the relationships between the protons of C-10, C-1 and C-2 as well as between those of C-6 and C-7. The ^{13}C NMR (APT) spectrum displayed five methyl quartets, two methylene triplets, five methine doublets and eight quaternary carbons. The HETCOR and COLOC experiment allowed the unambiguous assignment of protons and carbons (Table 2). Acetylation of compound **5** at room temp. for 24 hr gave a monoacetyl derivative exhibiting an acetyl signal at δ2.35 and thus placing this moiety at C-12, the other signals remained unchanged. However, acetylation of **5** under drastic conditions afforded compound **6** which can be explained by the loss of one molecule of water from C-4. The ^{1}H NMR data of this derivative was exactly the same as those of compound **6** verifying the structural relation between these two compounds.

The spectral data of compound **6**, 4-dehydrosalvilimbinol, were quite similar to those of **5**, but there was an isopropenyl instead of hydroxyisopropyl group at C-4. HREIMS indicated a molecular formula $C_{20}H_{26}O_4$ (*m/z* 330.1851; calc. 330.1830). The IR spectrum showed a hydroxyl signal at 3520 cm^{-1}, a conjugated oxo group signal at 1697 cm^{-1} and unsaturation signals at 1660 and 1600 cm^{-1}. The UV spectrum showed a λ_{max} at 336 nm. The ^{1}H NMR spectrum indicated the structure of **6**: δ7.10 (1H, *d*, $J = 7.5$ Hz, H-7), 6.98 (1H, *d*, $J = 7.5$ Hz, H-6), 6.89 (1H, *s*, H-14), 4.90 (1H, *s*) and 4.91 (1H, *s*) (CH_2-18), 2.98 (1H, *septet*, $J = 7$ Hz, H-15), 2.25 (3H, *s*, Me-20), 2.01 (3H, *s*, Me-19), 1.11 (6H, *d*, $J = 7$ Hz, Me-16 and Me-17). Spin decoupling experiments showed the relationship between H-10 (δ2.44, 1H, *dd*, $J = 4$, 12 Hz) and H-1a (δ1.80, *m*), H-1b (δ2.30, 1H, *ddd*, $J = 3$, 11, 12 Hz) and H-2a (δ2.67, 1H, *dd*, $J = 9$, 16 Hz) and H-2b (δ2.90, 1H, *m*), as well as the C-6 and C-7 protons. The ^{13}C NMR (APT) showed the presence of four methyl quartets, three methylene triplets, five methine doublets and eight quaternary carbon singlets. The HETCOR and the COLOC experiments allowed the unambiguous assignment of the protons and carbons (Table 2). The most favourable structures of compounds **5** and **6** were found in computer designed minimized energy formulae showing that H-10, C-9 hydroxyl as well as Me-20 were in β positions.

EXPERIMENTAL

General. All solvent evaporations were carried out at reduced pressure. Yields of the new compounds were as follows: **1**, 12 mg; **2**, 14 mg; **3**, 240 mg; **4**, 55 mg; **5**, 18 mg; **6**, 15 mg. CC: silica gel 40 (E. Merck), Sephadex LH-20 (Fluka), preparative plates (E. Merck).

Plant material, extraction and isolation. The roots of *S. limbata* C. A. Meyer were collected from eastern Turkey (Ilica-Erzurum) at elevations 1800–2000 m in July 1994. The plant was identified by Dr Kerim Alpinar (Istanbul), a voucher specimen is deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul, ISTE 66394. The dried and powdered plant material (650 g) was extracted with Me_2CO in a Soxhlet, after evaporation of the extract 9 g of residue was obtained. The residue was fractionated over a silica gel column (3.5 x 90 cm), the column was eluted with hexane, a gradient of CH_2Cl_2 up to 100% followed by EtOAc up to 30%.

12-Hydroxysapriparaquinone (**1**). Amorphous, yellow compound. UV λ_{max}^{MeOH} nm: 390 (log ε 3.0), 350 (log ε 3.4), 290 (log ε 3.95), 255 (log ε 4.2); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380, 3000, 2970, 2910, 1700, 1650, 1580, 1480, 1420, 1380, 1300, 1280, 1190, 1120, 1030, 1000, 920, 790; ^{1}H NMR ($CDCl_3$): see text; ^{13}C NMR ($CDCl_3$) and HETCOR: Table 1; HREIMS: 312.1730 $[C_{20}H_{24}O_3]^+$ (80), 294 $[M - H_2O]^+$ (80), 284 $[M - 28]^+$ (64), 245 $[M - C_5H_7]^+$ (100), 229 $[M - C_6H_{11}]^+$ (87), 201 (80), 141 (88), 128 (94), 115 (93), 70 (95).

3,12-Dihydroxysapriparaquinone-1-ene (**2**). Amorphous, deep yellow compound. UV λ_{max}^{MeOH} nm: 410 (log ε 3.6), 390 (log ε 3.6), 326 (log ε 3.9), 240 (log ε 4.4); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3000, 2980, 2940, 1700, 1685, 1650, 1600, 1580, 1520, 1450, 1380, 1210, 1180, 1100, 980, 780; ^{1}H NMR ($CDCl_3$): see text; ^{13}C NMR ($CDCl_3$) and HETCOR: Table 1; HREIMS: 326.1522 $[C_{20}H_{22}O_4]^+$ (15), 311 $[M - Me]^+$ (12), 308 $[M - H_2O]^+$ (10), 229 $[M - C_6H_9O]^+$ (80), 203 (95), 124 (87), 109 (75), 84 (97), 71 (100).

2,12-Dihydroxysaprorthoquinone (**3**). $[\alpha]_D - 3.0°$ ($CHCl_3$; c 1.3). Amorphous, yellow compound. UV λ_{max}^{MeOH}: 395 (log ε 2.7), 330 (log ε 3.1), 282 (log ε 3.4), 242 (log ε 4.5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3400, 3050, 2960, 2940, 1680, 1650, 1580, 1480, 1420, 1350, 1250, 1170, 1050, 970, 840, 750; ^{1}H NMR ($CDCl_3$): see text; ^{13}C NMR ($CDCl_3$) and HETCOR: Table 1; HREIMS: 312.1731 $[C_{20}H_{24}O_3]^+$ (23), 296 $[M - H_2O]^+$ (35), 213 $[M - C_6H_{11}O]^+$ (100), 185 (50), 165 (87), 141 (80), 115 (65), 83 (40), 69 (45).

Limbinol (**4**). $[\alpha]_D - 32.8°$ ($CHCl_3$; *c* 0.3). Amorphous, yellow compound. UV λ_{max}^{MeOH} nm: 369 (log ε 3.2), 310 (log ε 3.6), 240 (log ε 4.0); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 2950, 2880, 1690, 1610, 1580, 1520, 1485, 1360, 1150, 1060, 1000, 920, 780; ^{1}H NMR ($CDCl_3$): see text; ^{13}C NMR: Table 1; HREIMS: 312.1728 $[C_{20}H_{24}O_3]^+$ (18), 284 $[M - 28]^+$ (53), 227 $[M - C_5H_9O]^+$ (100), 199 $[M - C_6H_9O_2]^+$ (52), 185 (67), 141 (63), 115 (72), 83 (95), 69 (75).

Salvilimbinol (**5**). $[\alpha]_D - 17.6°$ ($CHCl_3$; *c* 0.2). Deep yellow compound. UV λ_{max}^{MeOH} nm: 329 (log ε 3.27), 242 (log ε 4.5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 2980, 1700, 1660, 1600, 1460, 1380, 1040, 750; ^{1}H NMR ($CDCl_3$): see text; ^{13}C NMR ($CDCl_3$) and HETCOR: Table 2; HREIMS: 348.1930 $[C_{20}H_{28}O_5]^+$ (2), 330 $[M - H_2O]^+$ (4), 312 $[M - 2 \times H_2O]^+$ (18), 296 (80), 268 (87), 225 (100), 213 (58), 185 (93), 165 (55), 115 (40), 69 (40).

4-Dehydrosalvilimbinol (**6**). $[\alpha]_D - 18.0°$ ($CHCl_3$; *c* 0.1). Deep yellow compound. UV λ_{max}^{MeOH} nm: 336 (log ε 3.40), 244 (log ε 4.5); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 2980, 2940, 1697, 1660, 1600, 1460, 1375, 1200, 1100, 1020, 900, 810; ^{1}H NMR ($CDCl_3$): see text; ^{13}C NMR ($CDCl_3$) and HETCOR: Table 2; HREIMS: 330.1851 $[C_{20}H_{26}O_4]^+$ (2), 312 $[M - H_2O]^+$ (14), 294 $[M - 2 \times H_2O]^+$ (18), 268 (65), 245 (27), 225 (100), 213 (33), 185 (27), 115 (12), 83 (52).

REFERENCES

1. Hitokoto, H., Morozumi, S., Wauke, T., Saiki, S. and Kurata, H. (1980) *App. Envin. Microbiol.* **39**, 818.
2. Janosik, J. (1980) *Ciheck Pat.* 185.262; *Chem. Abst.* (1981) **95**, 68027 f.
3. Dobrynin, V. N., Kolosov, M. N., Chernov, B. K. and Derbentseva, N. A. (1976) *Khim. Prir. Soedin.* **5**, 686.
4. Chen, W. Z. (1981) *Acta Pharm. Sinica* **19**, 876.

5. Chang, H. M. and But, P. P. (1986) in *Pharmacology and Applications of Chinese Materia Medica*. World Sci. Pub. Co. Singapore, Vol. **1**, p. 255.
6. Baytop, T. (1984) in *Therapy with Medicinal Plants of Turkey* Istanbul University, Pub. No. 3255, p. 156.
7. Thomas, B. K. (1952) *Nature* **170**, 1018.
8. Ulubelen, A., Topcu, G., Eriş, C., Sönmez, U., Kartal, M., Kurucu, S. and Bozok-Johansson, C. (1994) *Phytochemistry* **36**, 971.
9. Lin, L., Blasko, G. and Cordell, G. A. (1989) *Phytochemistry* **28**, 177.