Labdane Diterpenoids from *Marrubium globosum* ssp. *libanoticum*

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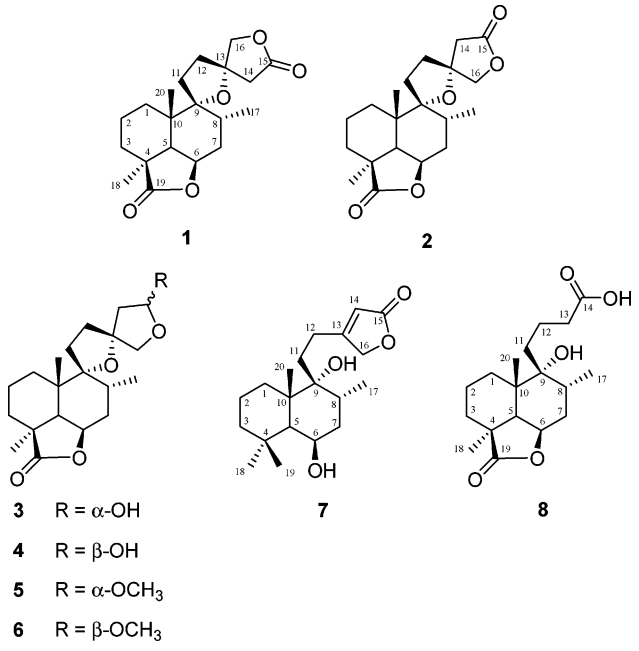
From the aerial parts of *Marrubium globosum* ssp. *libanoticum*, seven labdane diterpenoids were isolated. Three of them are new natural products [(13*R*)-9α,13α-epoxylabda-6*β*(19),16(15)-diol dilactone (**2**), deacetylvitexilactone (**7**), marrulanic acid (**8**)], whereas the other four, namely, (13*S*)-9α,13α-epoxylabda-6*β*(19),16(15)-diol dilactone (**1**), cyllenin A (**3**), 15-*epi*-cyllenin A (**4**), and marrulibanoside, are previously known compounds. The structures of **2**, **7**, and **8** were determined by spectroscopic and chemical methods.

The genus *Marrubium* (Lamiaceae) is widespread in the temperate regions of the Eurasian zone. About 50 species grow in the countries along the Mediterranean Sea.[1] Most of the species are annual or rhizomatous herbs. Aqueous or hydro alcoholic extracts of the flowered aerial parts of this species, called "hashiashat el kelb" in Northern Lebanon, are used in folk medicine. Decoctions or infusions of the flowers and leaves are used in internal medicine as hypoglycemics (diabetes), febrifuges (malaria), and antispasmodics (colics) and have external applications against snake bites and as cicatrizants of wounds.[2] The genus is known to produce many diterpenoids; the best known and the first one to be isolated and characterized is marrubiin, based on a labdane skeleton. Several species of *Marrubium* have been studied and a number of diterpenoids described.[3−5]

Recently, we undertook a phytochemical study of *Marrubium globosum* Montbr. et Auch. ex Benth. ssp. *libanoticum* Boiss., harvested in Lebanon and not investigated previously. Labdane diterpenoids have been isolated from the similar taxon *Marrubium globosum* Montbr. et Auch. ex Benth. ssp. *globosum*, growing in Turkey.[6] After an initial investigation on the acetone extract of *M. globosum* ssp. *libanoticum*, we reported the identification of a new natural compound, marrulibanoside, a labdane diterpenoid.[7] This product was known, as it had been prepared semisynthetically[8] some years ago by chemical transformation of marrubiin. A reinvestigation of a larger quantity of plant material harvested two years later led to the isolation of several additional components: the present note reports on their structures.

The acetone-soluble extract of the aerial parts of the title plant was fractionated by column chromatography. Repeated column chromatography and HPLC led to the isolation of three new labdane diterpenoids (**2**, **7**, **8**) and four previously known compounds, marrulibanoside,[7] (13*S*)-9α,13α-epoxylabda-6*β*(19),16(15)-diol dilactone (**1**),[9] cyllenin A (**3**),[10] and 15-*epi*-cyllenin A (**4**).[10]

The fraction eluting with *n*-hexane−EtOAc (1:1) was subjected to HPLC (*n*-hexane−EtOAc, 1:1), yielding a subfraction that was apparently homogeneous, but its ^{1}H and ^{13}C NMR spectra showed several split signals, indicating the presence of an unresolvable mixture (3:2) of two compounds. Elemental analysis and ESIMS proved that the products were isomers with the elemental formula $C_{20}H_{28}O_5$. The ^{1}H NMR spectrum showed the presence in both compounds of two tertiary methyl groups (*δ* 1.29, s and 1.05, s for both compounds), a secondary methyl group (*δ* 0.88, d and 0.86, d, respectively), and a methine bearing an oxygen (*δ* 4.70, m). Also, there were two pairs of AB systems at *δ* 2.92, d and 2.59, d (J = 17.2 Hz) and at *δ* 4.27, d and 4.14, d (J = 9.2 Hz) for the major compound, and at *δ* 2.83, d and 2.56, d (J = 17.2 Hz) and at *δ* 4.40, d and 4.22, d (J = 9.2 Hz) for the minor one. The ^{13}C NMR spectrum of the mixture indicated the presence of two lactone carbonyl groups (*δ* 183.4 × 2, 174.6/174.5), four other quaternary carbons, two of which are bonded to an oxygen (*δ* 92.2/92.0 and 86.0 × 2), three methines, eight methylenes, and three methyl groups. It is important to note that the splitting of almost all the carbons of the two compounds was very small, with the only exception being the methylene at *δ* 41.9 and 43.0. All these data allowed us to assign to the two compounds the C-13 epimeric structures **1** and **2**, respectively. Although at this point the configuration at C-13 was not rigorously proved, this was done at a later stage in the present investigation.



From the fraction eluting with *n*-hexane−EtOAc (1:1) we obtained another subfraction that once again was apparently homogeneous, but whose ^{1}H and ^{13}C NMR spectroscopic data showed several split signals, indicating the presence of an unresolvable mixture (11:9) of two compounds. Elemental analysis and ESIMS demonstrated that the products were isomers with the elemental formula $C_{20}H_{30}O_5$. The ^{13}C NMR spectrum was similar

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to that recently reported for the two (13*R*)-C-15 epimeric equilibrium hemiacetals, cyllenin A (**3**) and 15-*epi*-cyllenin A (**4**).[10]

Treatment of the mixture of **3** and **4** with MeOH in AcOH yielded the corresponding C-15 epimeric acetals **5** and **6**, in which the C-15 stereochemistry was assigned by comparison with literature data for compounds having an identical C-11/C-16 moiety.[11] These products were separated by column chromatography, allowing us to confirm the identity of the hemiacetal compounds **3** and **4** as cyllenin A and 15-*epi*-cyllenin A, respectively. A ROESY NMR experiment was carried out on compound **5**, and diagnostic NOEs between the H-16 protons at δ 4.02 and 3.85 and Me-17 at δ 0.83 clearly proved the 13*R* stereochemistry.

Finally, oxidation of the mixture of **3** and **4** with PDC in CH_2Cl_2 yielded a 15-oxo derivative, identical to compound **2**, proving its 13*R* configuration. This reaction also allowed us to assign the 13*S* stereochemistry to compound **1**. The structures of compounds **1** and **2** were therefore assigned as (13*S*)-9α,13α-epoxylabda-6β-(19),16(15)-diol dilactone and (13*R*)-9α,13α-epoxylabda-6β(19),-16(15)-diol dilactone, respectively.

The structure of compound **7** was determined by analysis of its UV, positive ESIMS, and homo- and heteronuclear 1D and 2D NMR data. Its elemental analysis and ESIMS were in agreement with an elemental formula of $C_{20}H_{32}O_4$. The ^{1}H and ^{13}C NMR spectra showed signals for three tertiary methyl groups, a secondary methyl group, an α,β-unsaturated γ-lactone (δ_H 4.76 d, 2H, H-16; δ_C 73.2 t, C-16; δ_H 5.84 dddd, 1H, H-14; δ_C 114.9 d, C-14; δ_C 174.1 s, C-15), and a methine (δ_C 67.3 d, C-6; δ_H 4.36 ddd, 1H, H-6) carrying a free hydroxyl group. To confirm the relative stereochemistry of all stereogenic centers, a NOESY experiment was carried out: clear correlations were observed for Me-20 with Me-19, H-8, and H-11b, but not with H-6, whose α-equatorial orientation was proved by its correlation with H-5. A search of the literature indicated that this compound is the deacetyl derivative of vitexilactone, a labdane diterpenoid isolated from *Vitex rotundifolia*.[12]

Compound **8** was assigned the molecular formula $C_{18}H_{28}O_5$, and its ^{1}H and ^{13}C NMR spectra showed the same functionalization as cyllenin A (**3**) and 15-*epi*-cyllenin A (**4**) for the decalin moiety. Signals were evident for two tertiary methyl groups at δ 1.29, s and 1.04, s, a secondary methyl group at δ 0.92, d (J = 6 Hz), and a saturated γ-lactone involving C-19 (δ_C 184.0, s) and C-6 (δ_C = 76.28, d, C-6; δ_H 4.74, dd, 1H, H-6). Furthermore, the presence of both a carboxylic acid and its α-methylene group was indicated clearly by the signals at δ_C 177.4, s and at δ_C 34.1, t, C-13; δ_H 2.39, t, 2H, H-13, respectively. Diagnostic NOE cross-peaks were observed between Me-20 and H-8 as well as H-11b; the α-orientation of H-6 was proved by correlations with H-5 and Me-18. This information allowed us to assign the dinorlabdane structure depicted in formula **8** to this compound, for which the trivial name marrulanic acid has been given.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO P-1010 digital polarimeter. UV spectra were obtained on a JASCO 7800 UV−vis spectrophotometer. IR spectra were obtained on a Shimadzu FTIR-8300 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz NMR spectrometer (^{1}H at 400.4 MHz, ^{13}C at 100.7 MHz), δ (ppm), J in Hz, using the residual solvent signal (δ 7.27 in ^{1}H and δ 77.0) as reference. ^{13}C NMR assignments were determined by DEPT and HSQC experiments. ESIMS was obtained on an Applied Biosystem API-2000 mass spectrometer. Elemental analysis was carried out with a Perkin-Elmer 240 apparatus. Merck silica gel (70−230 mesh), deactivated with 15% H_2O, was used for column chromatography. Normal-phase HPLC was performed with a TSP SpectraSeries P100 instrument equipped with rheodyne injector and a refractive index detector, using a Hypersil silica column (Thermo, 250 × 4.6 mm, flow rate 1.5 mL/min). Thin-layer chromatography (TLC) was performed on plates coated with silica gel 60 F_{254} Merck, 0.25 mm. All solvents (analytical, deuterated, and HPLC grade) were purchased from Carlo Erba Reagenti, Milan, Italy.

Plant Material. *M. globosum* ssp. *libanoticum* aerial parts were collected from flowering plants in July 2004 on Col de Cèdres, Lebanon, at 2340 m above sea level. The identification was done by one of us (N.A.A.) and confirmed by Prof. T. Raus, Botanische Garten, Berlin. A voucher specimen (NAP #23) is deposited at the Herbarium Neapolitanum (NAP), Dipartimento di Biologia Vegetale, Università degli Studi di Napoli "Federico II", Italy.

Extraction and Isolation. Dried and finely powdered aerial parts of *Marrubium globosum* Montbr. et Auch. ex Benth. ssp. *libanoticum* Boiss. (1 kg) were extracted with Me_2CO (3 × 5 L) at room temperature for 1 week. After filtration, the solvent was evaporated at low temperature (35 °C) to give a gum (60 g), which was dissolved in $CHCl_3$ and then submitted to column chromatography on silica gel 60 Merck (70−230 mesh, deactivated with 15% H_2O) eluting with *n*-hexane−EtOAc (from 100:0 to 0:100 gradient) to afford 28 fractions of 250 mL each. The fractions were examined by TLC, using as eluent *n*-hexane−EtOAc (1:1) and as spray reagent $Ce(SO_4)_2$ in H_2SO_4. Fraction 14 (0.296 g), eluted with *n*-hexane−EtOAc (4:1), was subjected to HPLC (*n*-hexane−EtOAc, 1:1) to give 8.7 mg of a mixture of compounds **1** and **2**; t_R 3.0 min. Fractions 15 and 16 (0.375 g), eluted with *n*-hexane−EtOAc (3:2), were subjected to HPLC (*n*-hexane−EtOAc, 3:2) to give 7.5 mg of compound **7** and 65 mg of a mixture of compounds **3** and **4**; t_R 6.5 and 9.0 min, respectively. Fractions 21 and 22 (1.195 g), eluted with *n*-hexane−EtOAc (3:7), were subjected to HPLC (*n*-hexane−EtOAc, 7:13) to afford 100 mg of marrulibanoside; t_R 5 min. Fractions 24−26 (0.284 g), eluted with *n*-hexane−EtOAc (1:4), were subjected to HPLC (*n*-hexane−EtOAc, 2:3) to give 5.8 mg of compound **8**; t_R 4.5 min.

(13*R*)-9α,13α-epoxylabda-6β(19),16(15)-diol dilactone (2): amorphous solid; $[\alpha]^{25}_D$ +0.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max} 2985, 1772, 1759, 1470, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 100.7 MHz), see Table 1; ESIMS (positive-mode) *m*/*z* 371 $[M + Na]^+$ (100); *anal.* C 68.97%, H 8.08%, calcd for $C_{20}H_{28}O_5$, C 68.94%, H 8.10%.

Cyllenin A (3) and 15-*epi*-cyllenin A (4): amorphous solid; ^{1}H NMR ($CDCl_3$, 400 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 100.7 MHz), see Table 1; ESIMS (positive-mode) *m*/*z* 389 $[M + K]^+$ (61), 373 $[M + Na]^+$ (100), 351 $[M + H]^+$ (37); *anal.* C 68.52%, H 8.67%, calcd for $C_{20}H_{30}O_5$, C 68.54%, H 8.63%.

Compounds 5 and 6. A solution of 30 mg of the mixture of cyllenin A (**3**) and 15-*epi*-cyllenin A (**4**) in 2 mL of a 1:1 mixture of AcOH and MeOH was allowed to stand overnight to give a mixture of two compounds, which were separated by column chromatography [silica gel, *n*-hexane−EtOAc (7:3) as eluent], yielding 13 mg of 15-methoxycyllenin A (**5**) and 10 mg of 15-methoxy-15-*epi*-cyllenin A (**6**).

15-Methoxycyllenin A (5): amorphous solid; $[\alpha]^{25}_D$ +14.2 (*c* 0.6, $CHCl_3$); IR (film) ν_{max} 2960, 2928, 1750, 1599, 1464, 1376, 1099, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.10 (1H, d, J = 5.6 Hz, H-15β), 4.70 (1H, dd, J = 4.4, 3.6 Hz, H-6), 4.02 (1H, d, J = 9.2 Hz, H-16a), 3.85 (1H, d, J = 9.2 Hz, H-16b), 3.32 (3H, s, OMe), 2.28 (1H, dd, J = 13.2, 5.6 Hz, H-14a), 1.96 (1H, d, J = 13.2 Hz, H-14b), 1.27 (3H, s, Me-18), 1.03 (3H, s, Me-20), 0.83 (3H, d, J = 6.0 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 100.7 MHz), δ 183.7 (C, C-19), 105.7 (CH, C-15), 90.7 (C, C-9), 90.2 (C, C-13), 77.5 (CH_2, C-16), 76.8 (CH, C-6), 54.7 (CH_3, OCH_3), 48.4 (CH_2, C-14), 46.0 (CH, C-5), 44.1 (C, C-4), 39.0 (C, C-10), 37.8 (CH_2, C-12), 32.0 (CH, C-8), 31.9 (CH_2, C-7), 29.7 (CH_2, C-11), 29.0 (CH_2, C-1), 28.3 (CH_2, C-3), 23.8 (CH_3, C-20), 23.0 (CH_3, C-18), 18.1 (CH_2, C-2), 17.3 (CH_3, C-17); ESIMS (positive-mode) *m*/*z* 387 $[M + Na]^+$ (20), 332 $[M - MeOH]^+$ (100); *anal.* C 69.23%, H 8.86%, calcd for $C_{21}H_{32}O_5$, C 69.20%, H 8.85%.

15-Methoxy-15-*epi*-cyllenin A (6): amorphous solid; $[\alpha]^{25}_D$ −20.3 (*c* 0.6, $CHCl_3$); IR (film) ν_{max} 2955, 2928, 1740, 1603, 1464, 1380, 1098, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.97 (1H, dd, J = 6.0, 3.6 Hz, H-15α), 4.69 (1H, dd, J = 4.4, 3.6 Hz, H-6), 3.92 (1H, d, J = 8.4 Hz, H-16a), 3.60 (1H, d, J = 8.4 Hz, H-16b), 3.39 (3H, s, OMe), 2.22 (1H, dd, J = 13.6, 6.0 Hz, H-14a), 1.26 (3H, s, Me-18), 1.02 (3H, s, Me-20), 0.81 (3H, d, J = 6.0 Hz, Me-17); ^{13}C NMR ($CDCl_3$, 100.7 MHz), δ 183.8 (C, C-19), 105.0 (CH, C-15), 90.0 (C, C-9), 89.3 (C, C-13), 76.4 (CH, C-6), 75.2 (CH_2, C-16), 55.2 (CH_3, OCH_3), 47.4 (CH_2, C-14), 45.7 (CH, C-5), 44.0 (C, C-4), 39.6 (CH_2, C-12), 39.0 (C, C-10), 31.9 (CH, C-8), 31.4 (CH_2, C-7), 29.0 (CH_2,

Table 1. NMR Data of Compounds **2**−**4**, **7**, and **8** in $CDCl_3$ Solution[a,b]

	2		**3**		**4**		**7**		**8**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1a	1.24 m	29.3 t	1.52 m	28.9 t	1.52 m	28.8 t	2.28 m	34.3 t	1.74 m	28.5 t
1b	1.24 m		1.28 m		1.28 m		150 m		1.28 m	
2a	1.78 m	17.9 t	1.70 m	17.8 t	1.70 m	18.0 t	1.48 m	18.6 t	1.71 m	18.1 t
2b	1.50 m		1.48 m		1.48 m		0.90 m		1.48 m	
3a	2.11 m	28.1 t	2.10 m	28.0 t	2.10 m	28.1 t	1.35 m	43.7 t	2.11 m	28.3 t
3b	1.42 m		1.42 m		1.42 m		1.15 m		1.44 m	
4		44.0 s		44.0 s		44.0 s		34.8 s		43.8 s
5	2.08 m	45.9 d	1.91 d (3.6)	46.4 d	1.91 d (3.6)	46.4 d	1.36	48.8 d	2.24 d (4.4)	44.7 d
6α	4.70 m	75.9 d	4.68 dd (4.4, 3.6)	75.9 d	4.68 dd (4.4, 3.6)	76.4 d	4.36 ddd (2.0, 2.0, 2.0)	67.3 d	4.74 dd (4.4, 5.6)	76.3 d
7a	2.08 m	31.6 t	2.08 m	31.7 t	2.08 m	31.7 t	1.60 m	40.2 t	2.14 m	31.5 t
7b	1.61 m		1.62 m		1.62 m		1.48 m		1.65 m	
8β	2.18 m	31.9 d	2.08 m	31.8 d	2.08 m	31.8 s	2.28 m	31.3 d	2.05 m	32.2 d
9		92.0 s		92.1 s		90.5 s		75.9 s		75.5 s
10		39.0 s		39.1 s		38.9 s		43.6 s		39.7 s
11a	2.08 m	29.0 t	2.08 m	29.4 t	2.08 m	29.6 t	1.98 m	31.7 t	1.48	34.2 t
11b	1.83 m		1.78 m		1.78 m		1.72 m		1.33	
12a	2.10 m	36.9 t	2.09 m	34.6 t	2.18 m	37.7 t	2.50 m	25.4 t	1.77 m	20.2 t
12b	2.10 m		1.92 m		2.09 m		1.35 m		1.72 m	
13		86.0 s		90.1 s		90.0 s		171.3 s	2.39 t (6.4) (2H)	34.1 t
14a	2.83 d (17.2)	43.0 t	2.26 brd (12.0)	45.8 t	2.29 dd (12.0, 4.4)	48.6 t	5.84 dddd (1.2, 1.2, 1.2, 1.2)	114.9 d		177.4 s
14b	2.56 d (17.2)		2.09 m		1.95 m					
15α		174.5 s		99.3 d	5.61 d (4.4)	99.1 d		174.1 s		
15β			5.42 m							
16a	4.40 d (9.2)	78.3 t	4.21 d (7.2)	77.2 t	3.99 d (7.2)	77.6 t	4.76 d (1.2)	73.2 t		
16b	4.22 d (9.2)		3.71 d (7.2)		3.97 d (7.2)					
17	0.86 d (6.4)	17.3 q	0.87 d (5.2)	17.4 q	0.81 d (5.2)	17.2 q	0.93 d (6.8)	16.2 q	0.92 d (6.0)	16.5 q
18	1.29 s	23.0 q	1.26 s	23.1 q	1.26 s	22.9 q	1.24 s	24.6 q	1.29 s	22.9 q
19	-	183.4 s		183.4 s		183.8 s	0.99 s	33.8 q		184.0 s
20	1.05 s	23.4 q	1.04 s	23.4 q	1.02 s	23.6 q	1.28 s	19.4 q	1.04 s	22.3 q

[a] *J* values (in Hz) are presented in parentheses. [b] The assignments are based on HSQC, HMBC, and $^1H-^1H$ COSY experiments.

C-11), 28.6 (CH_2, C-1), 28.2 (CH_2, C-3), 23.2 (CH_3, C-20), 23.0 (CH_3, C-18), 17.8 (CH_2, C-2), 16.9 (CH_3, C-17); ESIMS (positive-mode) *m*/*z* 403 $[M + K]^+$ (35), 387 $[M + Na]^+$ (100), 332 $[M - MeOH]^+$ (86); *anal*. C 69.18%, H 8.89%, calcd for $C_{21}H_{32}O_5$, C 69.20%, H 8.85%.

Preparation of Compound 2 from a Mixture of 3 and 4. Treatment of 30 mg of the mixture of cyllenin A (**3**) and 15-*epi*-cyllenin A (**4**) with 1.2 equiv of PDC (38 mg) in CH_2Cl_2 under stirring for 24 h, after purification by column chromatography [silica gel, *n*-hexane−EtOAc (7:3) as eluent], gave 20 mg of compound **2**.

Deacetylvitexilactone (7): amorphous solid; $[\alpha]^{25}_D$ +4.3 (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 210 (4.15), 269 (3.27) nm; IR (film) ν_{max} 3520, 2954, 2855, 1748, 1635, 1464, 1127 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 100.7 MHz), see Table 1; ESIMS (positive-mode) *m*/*z* 375 $[M + K]^+$ (100), 359 $[M + Na]^+$ (64), 337 $[M + H]^+$ (32); *anal*. C 71.35%, H 9.60%, calcd for $C_{20}H_{32}O_4$, C 71.39%, H 9.59%.

Marrulanic acid (8): amorphous solid; $[\alpha]^{25}_D$ −10.8 (*c* 1.2, $CHCl_3$); IR (film) ν_{max} 3580, 2960, 2930, 1755, 1710, 1602, 1460, 1378, 1110, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 100.7 MHz), see Table 1; ESIMS (positive-mode) *m*/*z* 363 $[M + K]^+$ (81), 347 $[M + Na]^+$ (100); *anal*. C 66.60%, H 8.68%, calcd for $C_{18}H_{28}O_5$, C 66.64%, H 8.70%.

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