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PHENYLPROPANOIDS FROM *BUPLEURUM FRUTICOSUM*

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Key Word Index—*Bupleurum fruticosum*; Umbelliferae; Apiaceae; phenylpropanoids.

Abstract—The aerial parts of *Bupleurum fruticosum* yielded, in addition to spinasterol and erythrodiol, nine phenylpropanoids, of which eight are new natural products. Their structures were established by spectroscopic means. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The genus *Bupleurum* L. which comprises about 200 species is primarily located in the northern hemisphere, Eurasia and North Africa. The more investigated taxa come from China and Japan (*B. falcatum*, *B. chinense* and *B. radix*) and have been used for stimulant, diuretic, antithermic and expectorant purposes in Oriental medicine. *Bupleurum falcatum*, for instance, is an important original plant of the crude drug '*saiko*', which possesses similar activity to 'ginseng' (*Panax ginseng*).

A relatively small number of plants of this genus have been subjected to phytochemical investigations. They revealed the presence of saponins [1, 2], terpenoids [3], coumarins [4, 5], flavonoids [1, 6], polyacetylenes [7–9] and lignanes [10–13].

Bupleurum fruticosum L. is a shrub often localized in shaded holm-oak forests on calcareous grounds. Essential oils of this plant have been investigated by Italian chemists at the beginning of this century [14, 15]. Essential oil composition was subsequently re-examined [16, 17]. Further reports showed the presence of triterpene saikosaponins [18, 19], coumarins [20] and phenylpropanoids [20].

As a part of our chemical investigation on plants of the Apiaceae family, we report the isolation and structural elucidation, in addition to spinasterol and erythrodiol, of nine phenylpropanoids, of which eight are new compounds from this species.

RESULTS AND DISCUSSION

Compound **1**, $C_{22}H_{28}O_7$, $[M]^+$ at *m/z* 404, showed IR bands for α,β-unsaturated esters (1714 cm^{-1}) and double bonds (1651, 1584 cm^{-1}). Its ^1H NMR spectrum (Table 1) indicated the presence of a 3-aryl-*trans*-allyloxy moiety [δ 4.81 (2H, *dd*, $J = 6.4$, 1.1 Hz, H-1), 6.21 (1H, *dt*, $J = 15.8$, 6.4 Hz, H-2), 6.59 (1H, *dt*, 15.8, 1.0 Hz, H-3)]. The presence of three methoxyl groups [δ 3.87 (6H, *s*), 3.84 (3H, *s*)] and two aromatic protons [δ 6.60 (2H, *s*, H-2′, H-6′] accounted for a *O*-sinapyl alcohol derivative structure. The ^{13}C NMR data (Table 2) confirmed the placement of the three methoxyl resonances at C-3′, C-4′ and C-5′. Thus C-4′ appears at δ 138.9, shielded by two adjacent oxygen substituents, and 4′-OCH_3 at δ 60.9, typical of an *o*-disubstituted position. The alternative C-2′, C-4′ and C-6′ pattern would also have led to two equivalent aromatic protons. The remaining signals were attributed to a diester side chain constituted by a sarracinate unity [δ 6.47 (1H, *qt*, $J = 7.3$, 0.9 Hz, H-3″, 4.84 (2H, *br s*, 2H-5″), 2.13 (3H, *dt*, $J = 7.2$, 0.8 Hz, C-4″ Me)] esterified with an angelate group [δ 6.03 (1H, *qq*, $J = 7.3$, 1.4 Hz, H-3″), 1.94 (3H, *dq*, $J = 7.3$, 1.4 Hz, C-4‴ Me), 1.85 (3H, *dq*, $J = 1.4$, 1.4 Hz, C-5‴ Me)]. ^1H–^1H, ^1H–^{13}C correlations and DEPT experiments confirmed these assignations. The presence of this diester moiety also followed from its EI-mass spectrum showing fragments at *m/z* 304, 223, 207, 176 and 83 (base peak) (Fig. 1). From the above data, structure **1** is proposed for this new natural compound.

The second metabolite **2**, an oily substance, had a molecular formula $C_{21}H_{26}O_6$. The EI-mass spectrum showed the molecular ion at *m/z* 374 and fragments at 274, 193, 177 and 83 (base peak). The ^1H NMR of **2** (Table 1) was very similar to that of **1** except for the signals corresponding to the aromatic ring, for which the 1′,3′,4′ substitution pattern was easily established [δ 6.90 (1H, *dd*, $J = 8.1$, 2.0 Hz), 6.92 (1H, *d*, $J =$ 2.0 Hz), 6.81 (1H, *d*, $J = 8.1$ Hz)]. This compound has been recently isolated by Pistelli *et al.* [20] from the same plant.

Compound **3** had the molecular formula $C_{21}H_{26}O_6$ on the basis of an ion peak at *m/z* 374 in its EI-mass spectrum. Its ^1H NMR spectrum (Table 1) exhibited close similarities to those of **1** and **2**. Signals of the

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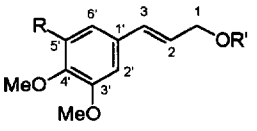

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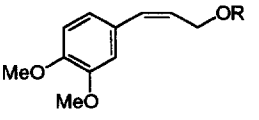
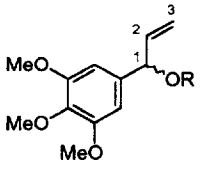
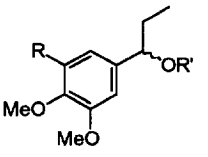
2 R= H, R'= **A**
7 R= OMe, R'= Et
8 R= H, R'= Et



3 R= **A**

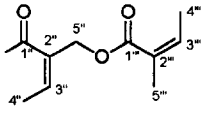


4 R= **A**
9 R= Et



5 R= OMe, R'= **A**
6 R= H, R'= **A**

A =



same ester side chain present in **1** and **2** were detected, while the substitution pattern of the aromatic ring proved to be similar to that of **2**. The only significant differences were the value of the coupling constant between H-2 and H-3 ($J = 11.5$ Hz) and the chemical shift of H-2 (δ 5.76). These differences can be explained if we assume a *cis*-disposition for the double bond between C-2 and C-3.

Compound **4**, $C_{22}H_{28}O_7$ ($[M]^+$ at *m/z* 404), was optically active ($[\alpha]_D$ −25°). Its ^{1}H NMR spectrum (Table 1) resembled that of **1** except for the signals attributed to the protons of the C-1, C-2, C-3 moiety: three doublets of triplets at δ 5.33 ($J = 17.2$, 1.3 Hz), 5.24 ($J = 10.4$, 1.3 Hz) and 6.30 ($J = 5.7$, 1.3 Hz) and a three-fold doublet at δ 6.00 ($J = 17.0$, 10.5, 5.7 Hz). These chemical shifts and multiplicity values are in accord with the partial structure: ϕ-CH(OCOR)–CH=CH_2. Therefore, structure **4** has been assigned to this compound. The spontaneous transformation of **4** into **1** at room temperature is in accordance with the proposed structure.

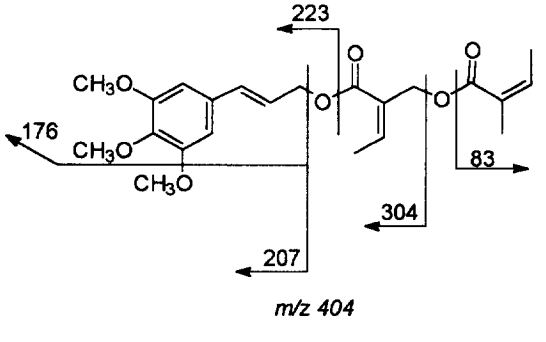


Fig. 1. Fragmentation pattern for compound **1**.

Compound **5**, $C_{22}H_{30}O_7$ ($[M]^+$ at *m/z* 406) exhibited bands for an α,β-unsaturated ester (1713 cm^{-1}) in its IR spectrum. The ^{1}H NMR spectral data (Table 1) resembled those of **4**, except for the presence of an ethyl group [δ 1.80 (1H, *ddq*, $J = 15.0$, 7.4, 7.4 Hz), 1.90 (1H, *ddq*, $J = 15.0$, 7.4, 7.4 Hz), 0.89 (1H, *t*, $J = 7.5$)] in place of the vinylic group attached to C-1. In accordance with this assumption, the proton geminal to the ester group appeared at δ 5.69 as a triplet ($J = 7.4$ Hz). Thus, compound **5** is the C-2, C-3 dihydro derivative of **4**.

The IR spectrum of **6** ($[M]^+$ at *m/z* 376, base peak 179) showed the presence of an α,β-unsaturated ester (ν_{max} cm^{-1}: 1714). The ^{1}H NMR data (Table 1) indicated that it differed from **5** in that the aromatic ring presents a 1′,3′,4′ substitution pattern [δ 6.88 (1H, *dd*, $J = 8.3$, 1.8 Hz), 6.84 (1H, *d*, $J = 1.8$ Hz), 6.79 (1H, *d*, $J = 8.3$ Hz)].

Compound **7** lacked the band due to the α,β-unsaturated ester in its IR spectrum (ν_{max} cm^{-1}: 1678, 1587 and 1126). The ^{1}H NMR spectrum (Table 1) clearly showed the presence of the *trans*-1-ethoxy-2-propenyl side chain with two protons quartet at δ 3.56 ($J =$ 7.0 Hz), a three protons triplet at δ 1.26 ($J = 7.0$ Hz), two vinylic protons at δ 6.22 (*dt*, $J = 15.8$, 6.0 Hz), 6.54 (*dt*, $J = 15.8$, 1.1 Hz) and allylic CH_2 at δ 4.14 (*dd*, $J = 6.0$, 1.1 Hz). The 1′,3′,4′,5′ substitution pattern followed from the ^{1}H NMR (Table 1) and ^{13}C NMR data (Table 2).

The structure of **8** was deduced by comparison of its ^{1}H NMR and ^{13}C NMR spectra with those of com-

Table 1. ^{1}H NMR spectral data for compounds **1–9**

H	1	2	3	4	5	6	7	8	9
1	4.81 *dd* (6.4, 1.1)	4.80 *dd* (6.4, 1.0)	4.94 *dd* (6.7, 1.5)	6.30 *dt* (5.7, 1.3)	5.69 *t* (7.4)	5.71 *t* (7.4)	4.14 *dd* (6.0, 1.1)	4.13 *dd* (6.1, 1.1)	4.65 *dt* (6.8, 1.1)
2	6.21 *dt* (15.8, 6.4)	6.17 *dt* (15.8, 6.4)	5.76 *dt* (11.5, 6.7)	6.00 *ddd* (17.1, 10.5, 5.7)	1.80 *ddq* (15.0, 7.4, 7.4) 1.90 *ddq* (15.0, 7.4, 7.4)	1.80 *ddq* (15.0, 7.4, 7.4) 1.94 *ddq* (15.0, 7.4,7.4)	6.22 *dt* (15.8, 6.0)	6.18 *dt* (15.8, 6.1)	5.93 *ddd* (17.0, 10.2, 6.8)
3	6.59 *dt* (15.8, 1.0)	6.60 *dt* (15.8, 1.1)	6.59 *dt* (11.5, 1.5)	5.33 *dt* (17.2, 1.3) 5.24 *dt* (10.4, 1.3)	0.89 *t* (7.5)	0.87 *t* (7.4)	6.54 *dt* (15.8, 1.1)	6.55 *dt* (15.8, 1.1)	5.26 *dt* (17.0, 1.1) 5.19 *dt* (10.2, 1.1)
2′	6.60 *s*	6.92 *d* (2.0)	6.78 *d* (1.7)	6.59 *s*	6.54 *s*	6.84 *d* (1.8)	6.62 *s*	6.96 *d* (1.9)	6.56 *s*
5′	—	6.81 *d* (8.1)	6.85 *d* (8.1)	—	—	6.79 *d* (8.3)	—	6.81 *d* (8.1)	—
6′	6.60 *s*	6.90 *dd* (8.1, 2.0)	6.79 *dd* (8.1, 1.7)	6.59 *s*	6.54 *s*	6.88 *dd* (8.3, 1.8)	6.62 *s*	6.93 *dd* (8.1, 1.9)	6.56 *s*
3″	6.47 *qt* (7.3, 0.9)	6.44 *qt* (7.2, 0.8)	6.45 *qt* (7.3, 0.9)	6.49 *qt* (7.3, 0.9)	6.45 *qt* (7.2, 0.9)	6.42 *qt* (7.3, 0.9)	—	—	—
4″	2.13 *dt* (7.2, 0.8)	2.10 *dt* (7.2, 0.9)	2.10 *dt* (7.3, 0.9)	2.13 *dt* (7.3, 0.8)	2.10 *dt* (7.2, 0.9)	2.08 *dt* (7.3, 0.9)	—	—	—
5″	4.84 *br s*	4.82 *br s*	4.82 *dq* (0.9, 0.9)	4.87 *br s*	4.87 *ddq* (12.4, 0.9, 0.9) 4.81 *ddq* (12.4, 0.9, 0.9)	4.85 *ddq* (12.4, 0.9, 0.9) 4.81 *ddq* (12.4, 0.9, 0.9)	—	—	—
3‴	6.03 *qq* (7.3, 1.4)	6.01 *qq* (7.3, 1.5)	6.04 *qq* (7.3, 1.5)	6.04 *qq* (7.3, 1.5)	6.03 *qq* (7.3, 1.5)	6.03 *qq* (7.3, 1.5)	—	—	—
4‴	1.94 *dq* (7.3, 1.4)	1.91 *dq* (7.3, 1.5)	1.93 *dq* (7.3, 1.5)	1.90 *dq* (7.2, 1.6)	1.90 *dq* (7.3, 1.5)	1.90 *dq* (7.3, 1.5)	—	—	—
5‴	1.85 *dq* (1.4, 1.4)	1.84 *dq* (1.5, 1.5)	1.85 *dq* (1.5, 1.5)	1.79 *dq* (1.5, 1.5)	1.79 *dq* (1.5, 1.5)	1.79 *dq* (1.5, 1.5)	—	—	—
OCH_3	3.87 *s* 3.87 *s* 3.84 *s*	3.90 *s* 3.88 *s*	3.88 *s* 3.87 *s*	3.85 *s* 3.85 *s* 3.84 *s*	3.84 *s* 3.84 *s* 3.82 *s*	3.86 *s* 3.85 *s*	3.87 *s* 3.87 *s* 3.85 *s*	3.90 *s* 3.88 *s*	3.86 *s* 3.86 *s* 3.82 *s*
$OC\underline{H}_2CH_3$	—	—	—	—	—	—	3.56 *q* (7.0)	3.55 *q* (7.0)	3.51 *dq* (17.0, 9.2) 3.45 *dq* (17.0, 9.2)
$OCH_2C\underline{H}_3$	—	—	—	—	—	—	1.26 *t* (7.0)	1.25 *t* (7.0)	1.24 *t* (7.0)

Table 2. ^{13}C NMR spectral data for compounds **1–9**

C	1	2	3	4	6	7	8	9
1	64.9	65.1	61.5	76.5	77.5	71.1	71.3	82.9
2	122.6	121.0	124.2	136.2	29.3	125.9	124.4	138.9
3	134.3	134.2	133.0	117.1	10.0	132.0	132.1	116.0
1′	132.0	129.2	131.1	134.5	132.9	132.5	129.9	137.0
2′	103.9	108.8	110.9	104.6	109.9	103.6	108.9	103.6
3′	153.4	149.0	?	153.5	148.7	153.3	?	153.2
4′	138.9	149.2	?	138.1	148.7	132.5	?	137.0
5′	153.4	111.0	111.8	153.5	110.9	153.4	111.1	153.2
6′	103.9	120.0	121.4	104.6	119.2	103.6	119.7	103.6
1″	165.8	165.8	?	164.9	165.3	—	—	—
2″[a]	127.8	127.8	128.9	127.7	127.6	—	—	—
3″	143.6	143.5	143.6	144.4	143.3	—	—	—
4″	15.9	15.8	15.8	16.0	15.7	—	—	—
5″	66.0	65.1	65.1	65.3	65.2	—	—	—
1‴	167.6	167.6	?	167.8	167.5	—	—	—
2‴[a]	127.8	127.7	127.7	128.0	128.1	—	—	—
3‴	138.1	138.1	138.1	138.5	138.3	—	—	—
4‴	15.8	15.7	15.8	15.9	15.7	—	—	—
5‴	20.6	20.5	20.6	20.6	20.4	—	—	—
OMe	56.2	55.8	55.8	56.3	55.8	56.1	55.8	56.0
OMe	56.2	55.9	55.9	56.3	56.1	56.1	55.9	56.0
OMe	60.9	—	—	60.9	—	60.9	—	60.7
$OCH_2\underline{C}H_3$	—	—	—	—	—	15.2	15.2	15.2
$O\underline{C}H_2CH_3$	—	—	—	—	—	65.7	65.6	63.9

[a]Interchangeable signals.

pound **7**. These data clearly indicated that both compounds differed only in the substitution pattern of their aromatic rings. The similarities of the aromatic resonances of **8** with those of **2**, **3** and **6** indicated that the former also have a 1′,3′,4′ substitution pattern.

The remaining compound **9** was a 1-ethoxy derivative of 3′,4′,5′-trimethoxyphenyl-prop-2-ene. The location of the three methoxy groups was assigned taking into account that the aromatic signals (Tables 1 and 2) were essentially identical to those of **1**, **4**, **5** and **7**. The partial structure -CH(OR)–CH=CH_2 for **9** followed from the ^1H NMR and ^{13}C NMR data.

The identities of spinasterol and erythrodiol were determined by comparison with the literature data of both compounds and their acetate derivatives.

EXPERIMENTAL

General. Mps: uncorr., HPLC: LiChrosorb Si 60 (Merck) column (10 × 250 mm), flow rate 3 ml min^{-1}, differential refractometer detector. EI-MS: directed inlet 70 eV. ^1H NMR at 399.95 MHz, $CDCl_3$, signal of residual $CHCl_3$ centred at δ 7.25. ^{13}C NMR at 100.577 MHz, $CDCl_3$, central signal of $CDCl_3$ at δ 77.0. CC and TLC: silica gel.

Plant material. Bupleurum fruticosum was collected in Serranía de Grazalema (Zahara de la Sierra, Cádiz, Spain) in June 1986. Voucher specimens are deposited in the Department of Botany, University of Sevilla, Spain, and in the Department of Organic Chemistry, University of Cádiz, Spain.

Extraction and isolation. The dried aerial parts of *B. fruticosum* (1.1 kg) were extracted with CH_2Cl_2 in a soxhlet apparatus, affording 17 g of syrup. Further extraction with EtOH gave 89.4 g of extract.

3-(3,4,5-*Trimethoxyphenyl*)-2E-*propenyl* 2-(2-*methyl*-2Z-*butenoyloxymethyl*)-2Z-*butenoate* (**1**). Oil. IR ν_{max}^{film} cm^{-1}: 2943, 1714, 1584, 1238, 1135; UV λ_{max}^{EtOH} nm: 224.7, 269.7; MS *m/z* (rel. int.): 404 $[M]^+$ (33), 304 $[M-HOAng]^+$ (4), 223 $[M-C_{10}H_{13}O_3]^+$, 207 $[M-C_{10}H_{13}O_4]^+$ (57), 176 $[M-C_{10}H_{13}O_4-OCH_3]^+$ (57), 83 $[C_5H_7O]^+$ (100).

3-(3,4-*Dimethoxyphenyl*)-2E-*propenyl* 2-(2-*methyl*-2Z-*butenoyloxymethyl*)-2Z-*butenoate* (**2**). Oil. IR ν_{max}^{film} cm^{-1}: 2949, 1714, 1594, 1511, 1454, 1239, 1147; UV λ_{max}^{EtOH} nm: 213.1, 265.9; MS *m/z* (rel. int.): 374 $[M]^+$ (15), 274 $[M-HOAng]^+$ (8), 193 $[M-C_{10}H_{13}O_3]^+$ (50), 177 $[M-C_{10}H_{13}O_4]^+$ (53), 83 $[C_5H_7O]^+$ (100).

3-(3,4-*Dimethoxyphenyl*)-2Z-*propenyl* 2-(2-*methyl*-2Z-*butenoyloxymethyl*)-2Z-*butenoate* (**3**). Oil. IR ν_{max}^{film} cm^{-1}: 2949, 1714, 1593, 1512, 1455, 1244, 1148, 1039; UV λ_{max}^{EtOH} nm: 300.0; MS *m/z* (rel. int.): 374 $[M]^+$ (31), 275 $[M-HOAng]^+$ (4), 274 $[M-HOAng]^+$ (24), 193 $[M-C_{10}H_{13}O_3]^+$ (87), 177 $[M-C_{10}H_{13}O_4]^+$ (73), 83 $[C_5H_7O]^+$ (100).

1-(3,4,5-*Trimethoxyphenyl*)-2-*propenyl* 2-(2-*methyl*-2Z-*butenoyloxymethyl*)-2Z-*butenoate* (**4**). Oil. $[\alpha]_D^{25}$ −25° ($CHCl_3$; *c* 0.09), UV λ_{max}^{EtOH} nm: 210.7, 268.3; MS *m/z* (rel. int.): 404 $[M]^+$ (36), 304 $[M-HOAng]^+$ (3), 223 $[M-C_{10}H_{13}O_3]^+$ (26), 176 $[M-C_{10}H_{13}O_4]^+$ (27), 83 $[C_5H_7O]^+$ (48), 57 $[C_3H_5O]^+$ (100).

1-(3,4,5-*Trimethoxyphenyl*)-*propyl* 2-(2-*methyl*-2Z-*butenoyloxymethyl*)-2Z-*butenoate* (**5**). Oil. $[\alpha]_D^{25}$ −30° ($CHCl_3$; *c* 0.04), IR ν_{max}^{film} cm^{-1}: 1713, 1593, 1504, 1457, 1234, 1133; UV λ_{max}^{EtOH} nm: 284.8; MS *m/z*

(rel. int.): 406 $[M]^+$ (19), 225 $[M - C_{10}H_{13}O_3]^+$ (40), 209 $[M - C_{10}H_{13}O_4]^+$ (63), 83 $[C_5H_7O]^+$ (100).

1-(3,4-*Dimethoxyphenyl*)-*propyl* 2-(2-*methyl*-2Z-*butenoyloxymethyl*)-2Z-*butenoate* (**6**). Oil. $[\alpha]_D^{25}$ −46° ($CHCl_3$; *c* 0.2), IR ν_{max}^{film} cm^{-1}: 1714, 1652, 1594, 1512, 1457, 1381, 1240, 1139, 1036; UV λ_{max}^{EtOH} nm: 289.6; MS *m/z* (rel. int.): 376 $[M]^+$ (29), 306 $[M - C_4H_6O]^+$ (5), 247 (10), 179 $[M - C_{10}H_{13}O_4]^+$ (100), 165 $[M - C_{10}H_{13}O_3]^+$ (13).

1,2,3-*Trimethoxy*-5-(3-*ethoxy*-1E-*propenyl*)-*benzene* (**7**). Oil. IR ν_{max}^{film} cm^{-1}: 2937, 1678, 1587, 1503, 1460, 1335, 1241, 1126, 1009; UV λ_{max}^{EtOH} nm: 292.0; MS *m/z* (rel. int.): 252 $[M]^+$ (100), 237 $[M - CH_3]^+$ (6), 223 $[M - C_2H_5]^+$ (37), 207 $[M - OC_2H_5]^+$ (22), 176 $[M - C_2H_5 - CH_3]^+$ (28).

1,2-*Dimethoxy*-4-(3-*ethoxy*-1E-*propenyl*)-*benzene* (**8**). Oil. IR ν_{max}^{film} cm^{-1}: 2989, 2855, 1600, 1513, 1463, 1421, 1378, 1338, 1268, 1135, 1028, 970. UV λ_{max}^{EtOH} nm: 295.2; MS *m/z* (rel. int.): 222 $[M]^+$ (4), 193 $[M - C_2H_5]^+$ (5), 191 $[M - OCH_3]^+$ (9), 167 $[M - C_4H_7]^+$ (75), 85 (100).

1,2,3-*Trimethoxy*-5-(1-*ethoxy*-2-*propenyl*)-*benzene* (**9**). Oil. $[\alpha]_D^{25}$ 0°, IR ν_{max}^{film} cm^{-1}: 2938, 2839, 1594, 1502, 1462, 1421, 1334, 1234, 1128, 1012; UV λ_{max}^{EtOH} nm: 301.6; MS *m/z* (rel. int.): 252 $[M]^+$ (90), 237 $[M - CH_3]^+$ (4), 225 $[M - C_2H_3]^+$ (19), 223 $[M - C_2H_5]^+$ (19), 207 $[M - OC_2H_5]^+$ (54), 195 (20), 193 $[M - C_3H_7O]^+$ (39), 176 $[M - OCH_3 - OC_2H_5]^+$ (92), 55 (100).

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