New Labdane-Type Diterpenoids from *Leonurus heterophyllus* Sw.

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Five new natural labdane-type diterpenoids (5—9), designated leoheteronins A—E, together with four known diterpenoids (1—4), two phytosterols as a mixture of β-sitosterol and stigmasterol, and the flavone genkwanin (10) were isolated from the aerial parts of *Leonurus heterophyllus* Sw. (Lamiaceae) collected in northern Vietnam. Compound 1 was isolated for the first time from a *Leonurus* species, and 10 is considered to be a chemotaxonomic marker of the *Leonurus* genus. Their structures were determined using spectroscopic analyses.

Key words *Leonurus heterophyllus*; Lamiaceae; labdane

In Vietnamese traditional medicine, the plant *Leonurus heterophyllus* Sw. is known as Ich mau thao, Sung uy, or Choi den. The dried aerial parts of *L. heterophyllus* (*Herba Leonuri*) are applicable in the treatment of menstrual pain and child birth, as well as high blood pressure, blood stasis, heart disorders, and dysentery. The dried ripe fruits (*Fructus Leonuri*) are used to treat edema and as a diuretic.[1)] Several prefuranic and furanic labdane-type diterpenoids were isolated in previous studies on *L. heterophyllus* collected in Guangdong province, China.[2,3)] It is well known that the chemical composition of plants is geographically varied, and the reason for that may be related to the ability of each species to cope with its habitat environment. Therefore we carried out systematic extraction and isolation of the *L. heterophyllus* species grown in Vietnam, which led to the structure determination of nine labdane-type diterpenoids, including five new compounds, designated leoheteronins A—E (**5**—**9**), two phytosterols as a mixture of β-sitosterol and stigmasterol, and the flavone genkwanin (**10**). The structures of the known diterpenoids hispanone (**1**), leoheterin (**2**), hispanolone (**3**), and galeopsin (**4**), and **10** were determined by comparing their physical ($[\alpha]_D$) and spectroscopic data with the literature values.[3—6)] Compounds **2**—**4** were among the previous isolates from *L. heterophyllus*, **1** was isolated from *Ballota* species (Lamiaceae)[4)] but for the first time from a *Leonurus* species, and **10** is considered to be a chemotaxonomic marker of the genus *Leonurus*.[7)] This paper deals with the structure elucidation of the five new labdane-type diterpenoids **5**—**9**.

Results and Discussion

The extraction of the dried aerial parts of *L. heterophyllus* with MeOH and sequential fractionation using solvents of increasing polarity gave *n*-hexane-, ethyl acetate-, and 1-BuOH-soluble fractions. Separation of the *n*-hexane-soluble fraction with silica (Si) gel open-column chromatography, octadecyl Si (ODS) gel open-column chromatography, and repeated preparative ODS HPLC led to the isolation of compounds **1**—**10** together with a mixture of β-sitosterol and stigmasterol.

Leoheteronin A (**5**) was isolated as an amorphous powder, $[\alpha]_D^{25}$ +8.4° (c=1.19, $CHCl_3$). Its molecular formula was determined to be $C_{20}H_{28}O_3$ by positive-ion high-resolution (HR)-FAB-MS (m/z 315.1923, $[M+Na]^+$). The IR spectrum indicated the presence of γ-lactone (1747 cm^{-1}) and conjugated ketone (1664 cm^{-1}) functional groups. The ^{1}H- (Table 1) and ^{13}C-NMR (Table 2) spectroscopic data and heteronuclear single quantum correlation (HSQC) spectrum of **5** showed the presence of 20 carbons that were assignable to three tertiary methyl groups [δ_H 0.90 (s), 0.93 (s), 1.12 (s); δ_C 33.1 (q), 21.3 (q), 18.1 (q)], an α,β-unsaturated ketone [δ_C 199.7 (s), 164.6 (s), 131.0 (s)] and its olefinic methyl [δ_H 1.77 (s), δ_C 11.5 (q)], and a β-substituted butenolide ring [δ_C 145.2 (s) (C-13); δ_H 5.93 (s), δ_C 115.8 (C-14); δ_C 168.7 (s) (C-15); δ_H 4.78 (d, J=1.5 Hz, 2H), δ_C 72.7 (t) (C-16)], six methylene and one methine groups, and two quaternary carbons. Analysis of the data suggested the structure of **5** to be 15,16-epoxylabda-8,13-diene-7,15-dione, which was confirmed on comparison of the NMR data with those of the related compound leopersin G.[8)]

Leoheteronin B (**6**), an amorphous powder, $[\alpha]_D^{25}$ −10.7° (c=1.77, $CHCl_3$), had the molecular formula $C_{20}H_{28}O_3$ based on the results of positive-ion HR-FAB-MS (m/z 339.1923, $[M+Na]^+$). The IR spectrum indicated the presence of γ-lactone (1747 cm^{-1}) and conjugated ketone (1665 cm^{-1}) functional groups. The ^{1}H- (Table 1) and ^{13}C-NMR (Table 2) spectroscopic data and HSQC spectrum of **6** showed the presence of 20 carbons that were arranged similarly to those in **5**, except for the replacement of the β-substituted butenolide ring with an α-substituted butenolide ring [δ_C 133.8 (s) (C-13); δ_H 7.19 (s), δ_C 144.3 (d) (C-14); δ_H 4.80 (s, 2H), δ_C 70.1 (t) (C-15); 173.8 (s) (C-16)]. Therefore **6** was determined to be 15,16-epoxylabda-8,13-diene-7,16-dione.

Leoheteronin C (**7**) was isolated as an amorphous powder, $[\alpha]_D^{25}$ +57.8° (c=1.35, $CHCl_3$). Its molecular formula was determined to be $C_{20}H_{28}O_4$ in negative-ion HR-FAB-MS (m/z 331.1903 $[M-H]^-$). The IR spectrum indicated the presence of hydroxyl (3400 cm^{-1}), γ-lactone (1735 cm^{-1}), and conjugated ketone (1665 cm^{-1}) functional groups. The ^{1}H- (Table 1) and ^{13}C-NMR (Table 2) spectroscopic data showed that **7** was closely related to **5**, and the presence of an additional hydroxyl group was deduced from the mass unit of **7**. The magnitude of the NMR chemical shifts [δ_H 6.02 (s), δ_C 102.8] was in good agreement with the placement of the hydroxyl group at C-16 in the β-substituted butenolide ring. The heteronuclear multiple bond correlation (HMBC) cross-peaks were detected between H-14 (δ_H 5.86, δ_C 117.8, correlated from the HSQC spectrum) and C-15 (δ_C 170.9) and C-16 (δ_C 102.8); between Me-17 (δ_H 1.69, δ_C 11.4) and C-7 (δ_C

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Table 1. ^{1}H-NMR Spectroscopic Data of **5**—**9** (δ in ppm, 400 MHz, $CDCl_3$)

H	5	6	7	8	9
1a	1.91 br d (14.9)[a)]	1.99 br d (12.2)	1.85 br d (12.2)	1.57 m	1.45 m
b	1.35 ddd (14.9, 12.7, 3.2)	1.40 ddd (12.2, 12.0, 3.9)	1.30 ddd (13.0, 12.2, 3.6)	1.11 m	1.45 m
2a	1.62 m	1.62 m	1.55 m	1.61 m	1.55 m
b	1.62 m	1.62 m	1.55 m	1.46 m	1.55 m
3a	1.51 br d (14.9)	1.49 br d (13.4)	1.43 br d (13.2)	1.35 m	1.20 m
b	1.26 m	1.23 ddd (13.4, 13.4, 4.2)	1.15 ddd (13.2, 13.1, 3.6)	1.14 m	1.20 m
5	1.71 dd (14.4, 3.7)	1.72 dd (14.4, 3.7)	1.64 dd (14.2, 3.6)	1.02 dd (14.6, 2.4)	2.03 dd (13.9, 3.2)
6a	2.52 m	2.51 dd (17.3, 3.7)	2.45 dd (17.6, 3.6)	1.65 m	2.40 dd (13.9, 3.2)
b	2.40 br d (14.4)	2.36 dd (17.3, 14.4)	2.30 dd (17.6, 14.2)	1.30 m	2.29 t (13.9)
7a				1.60 m	
b				1.10 m	
8					2.72 q (6.6)
9				0.99 br s	
11a	2.50 m	2.46 m	2.47 m	1.80 m	1.90 m
11b	2.50 m	2.46 m	2.47 m	1.80 m	1.90 m
12a	2.50 m	2.46 m	2.44 m	1.99 t (8.1)	2.40 m
12b	2.50 m	2.46 m	2.47 m	1.99 t (8.1)	2.40 m
14	5.93 s	7.19 s	5.86 s	5.44 t (6.8)	7.14 br s
15		4.80 s		4.15 dd (6.8, 2.2)	4.78 br s
16	4.78 d (1.5)		6.02 s	1.70 s	
17	1.77 s	1.80 s	1.69 s	1.45 s	1.11 d (6.0)
18	0.90 s	0.90 s	0.83 s	0.79 s	0.88 s
19	0.93 s	0.93 s	0.86 s	0.86 s	0.90 s
20	1.12 s	1.11 s	1.05 s	1.08 s	1.17 s

a) Coupling constants (*J* in Hz) are given in parentheses.

200.5), C-8 (δ_C 130.9), and C-9 (δ_C 165.8); between H-5 (δ_H 1.64) and C-7; and between both Me-18 (δ_H 0.83) and Me-19 (δ_H 0.86) and C-5 (δ_C 50.4); as well as between Me-20 (δ_H 1.05) and C-5 and C-9 confirmed the structure of **7** to be 15,16-epoxy-16ζ-hydroxylabda-8,13-diene-7,15-dione. The absolute configuration at C-16 could not be determined using direct methods.

Leoheteronin D (**8**), isolated as colorless needles, $[\alpha]_D^{25}$ $-0.0°$ (c=0.20, $CHCl_3$), was analyzed for $C_{20}H_{36}O_2$ using negative-ion HR-FAB-MS (*m/z* 307.2625, $[M-H]^-$). The IR spectrum indicated the presence of hydroxyl (3418 cm^{-1}) and olefinic (1669 cm^{-1}) functional groups. The ^{1}H- (Table 1) and ^{13}C-NMR (Table 2) spectroscopic data of **8** showed the presence of three tertiary methyl groups [δ_H 0.79 (s), 0.86 (s), 1.08 (s); δ_C 33.2 (q), 21.3 (q), 24.8 (q), respectively, correlated from the HSQC spectrum], and a methyl group that was geminal to a tertiary hydroxyl group [δ_H 1.45 (s); δ_C 32.1 (q)], an olefinic methyl [δ_H 1.70 (s), δ_C 16.9 (s)], and a primary allyl alcohol [δ_H 5.44 (t, J=6.8 Hz), δ_C 123.0 (d); δ_H 4.15 (dd, J=6.8, 2.2 Hz), δ_C 59.4 (t)]. Significant HMBC correlations were detected between Me-17 (δ_H 1.45) and C-7 (δ_C 37.7) and C-9 (δ_C 60.9); between Me-16 (δ_H 1.70) and C-12 (δ_C 43.1) and C-13 (δ_C 140.9); between H-15 (δ_H 4.15) and C-13 and C-14 (δ_C 123.0); between Me-20 (δ_H 1.08) and C-5 (δ_C 46.5) and C-9; and between both Me-18 (δ_H 0.79) and Me-19 (δ_H 0.86) and C-3 (δ_C 42.3), C-4 (δ_C 32.9), and C-5. Thus **8** was suggested to be labd-13-ene-8,15-diol based on the spectroscopic data. The configuration of the double bond was determined to be *E* by observing the signal for both allylic protons (2H-15) at δ_H 4.15,[9] since the *Z*-isomer would show two distinct dd signals. Labd-13(*E*)-ene-8α,15-diol was isolated with the same optical rotation as **8** from *Cipadessa fruticosa*,[10] *Citrus symphytifolius*,[11] and *Citrus incanus*,[12] or as vulgarol from *Otostegia fruticosa*,[13] but it showed an upfield chemical shift of the Me-17 signal (δ_H 1.12, $\Delta\delta$ -0.33 ppm; δ_C 16.4, $\Delta\delta$ -15.7 ppm), suggesting that **8** is its C-8 epimer. This is in good agreement with the α-orientation of the deshielded equatorial methyl group at C-17 in methylcyclohexane.[14] The ^{13}C-NMR chemical shifts of **8** are essentially identical to those of vulgarol, and therefore the structure of the title compound should be revised to **8**. The relative stereochemistry of **8** was determined as follows. The nuclear Overhauser enhancement and exchange spectroscopy (NOESY) correlations between H-14 (δ_H 5.44) and H-12 (δ_H 1.99), and between H-15 (δ_H 4.15) and H-16 (δ_H 1.70) provided confirmation of the *E*-configuration of the double bond. The NOESY cross-peak detected between the axial Me-20 and H-11 (δ_H 1.80), but not between Me-20 and

Table 2. ^{13}C-NMR Spectroscopic Data of **5**—**9** (δ in ppm, 100 MHz, $CDCl_3$)

C	5	6	7	8	9
1	36.1	36.0	35.9	36.5	31.9
2	18.5	18.6	18.5	18.6	18.5
3	41.2	41.3	41.2	42.3	41.3
4	33.1	33.1	33.1	32.9	33.6
5	50.4	50.3	50.4	46.5	46.5
6	35.1	35.1	35.2	20.7	39.2
7	199.7	200.1	200.5	37.7	211.6
8	131.0	130.8	130.9	73.5	51.0
9	164.6	165.8	165.8	60.9	81.4
10	41.0	41.0	41.0	38.8	43.5
11	27.8	27.4	26.9	25.5	22.1
12	26.7	24.9	26.4	43.1	32.0
13	145.2	133.8	168.1	140.9	134.5
14	115.8	144.3	117.8	123.0	144.3
15	168.7	70.1	170.9	59.4	70.2
16	72.7	173.8	102.8	16.6	174.4
17	11.5	11.5	11.4	32.1	8.3
18	33.1	32.6	32.5	33.2	33.1
19	21.3	21.4	21.3	21.3	21.4
20	18.1	18.1	18.1	24.8	16.3

Me-17 (δ_H 1.45) suggested the same β-orientation of the C-9 side chain as Me-20, which was opposite to the α-orientation of Me-17. Therefore the new natural compound **8** was formulated as labd-13(*E*)-ene-8β,15-diol.

Leoheteronin E (**9**) was isolated as an amorphous powder, $[\alpha]_D^{25}$ −9.3° (c=2.91, $CHCl_3$), and found to have the molecular formula $C_{20}H_{29}O_4$ using negative-ion HR-FAB-MS (*m/z* 333.2077, $[M-H]^-$). The IR spectrum indicated the presence of hydroxyl (3504 cm^{-1}), γ-lactone (1752 cm^{-1}), and isolated ketone (1703 cm^{-1}) functional group. The ^{1}H- (Table 1) and ^{13}C-NMR (Table 2) spectroscopic data of **9** were reminiscent of those of hispanolone (**3**),[2] which was also isolated from the same extract, in the Decalin ring and of **6** in the C-9 side chain. An α-subsituted butenolide ring [δ_C 134.5 (s) (C-13); δ_H 7.14 (br s), δ_C 144.3 (d) (C-14); δ_H 4.78 (br s, 2H), δ_C 70.2 (t) (C-15); 174.4 (s) (C-16)], and two methylene signals [δ_C 22.1 (t), 32.0 (t)] made up the C-9 side chain. HMBC cross-peaks were detected in this part from H-14 to C-15 and C-16, and from H-15 to C-13 and C-14. The substitution patterns of the Decalin ring was deduced from the comparison of the ^{1}H- and ^{13}C-NMR spectroscopic data with those of hispanolone.[2] In this part, HMBC correlations were observed between H-17 (δ_H 1.11) and C-7 (δ_C 211.6), C-8 (δ_C 51.0), and C-9 (δ_C 81.4); between both H-18 (δ_H 0.88) and H-19 (δ_H 0.90) and C-3 (δ_C 41.3) and C-5 (δ_C 46.5); between H-20 (δ_H 1.17) and C-1 (δ_C 31.9), C-9, and C-10 (δ_C 43.5); between H-5 (δ_H 2.03) and C-7; and between both H-6 (δ_H 2.29/2.40) and C-7. The relative stereochemistry of Me-17 was determined to be α-orientated based on NOESY cross-peaks from H-8 [δ_H 2.72 (q, J=6.6 Hz)] to Me-20, and to H-6β [δ_H 2.29 (t, J=13.9 Hz)]. The relative stereochemistry of the side chain at C-9 was β-orientated due to the NOE between H-8 and H_2-11 (δ_H 1.90). Thus **9** was determined to be 15,16-epoxy-9α-hydroxylabd-13-ene-7,16-dione, as shown in Fig. 1.

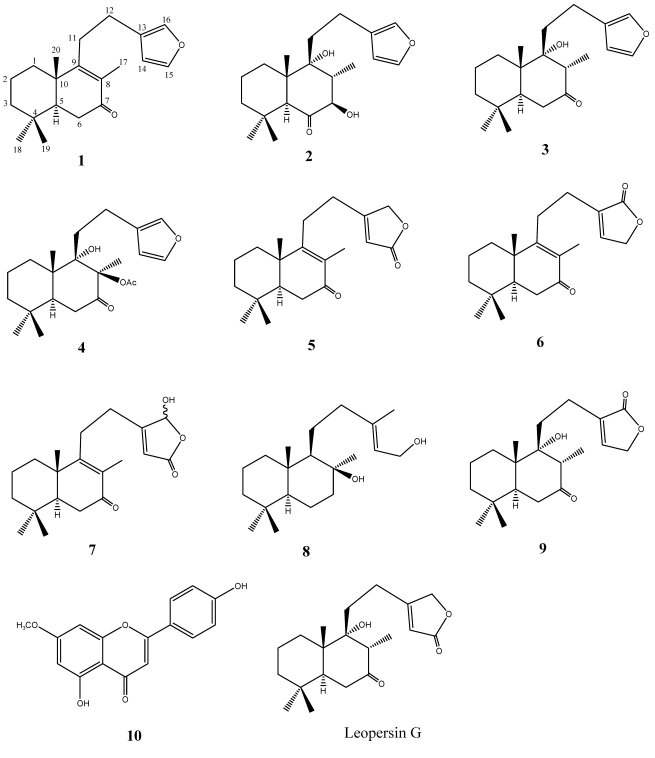

Fig. 1. Structures of Compounds **1**—**10** and Leopersin G

The absolute configurations of the new labdane-type diterpenoids **5**—**9** were reasonably assumed to be of *normal* nature on the basis of the co-occurrence of the known labdanes **1**—**4**. Labdane-type diterpenoids occur abundantly in *Leonurus sibiricus*,[6] *L. persicus*,[7] and *L. cardiaca*.[15]

Experimental

General Procedure A melting point was determined on a Yanagimoto micromelting point apparatus and is reported without correction. Optical rotations were measured on a Union Giken PM-101 digital polarimeter. FT-IR spectra were recorded on a Horiba FT-710 spectrophotometer. ^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded using a JEOL JNM-α 400 NMR spectrometer. Positive-ion and negative-ion HR-FAB-MS were measured on a JEOL SX-102 mass spectrometer with PEG-600 or PEG-400 as a calibration matrix. HPLC was carried out with a JASCO PU-1580 pump and an UV-2075 Plus detector (set at 210 nm) on YMC ODS columns (150×4.6 mm i.d. in analytical and 150×20 mm i.d. in preparative scales) at the corresponding flow rates of 0.5 and 5 ml/min. Silica gel 60 (0.063—0.200 mm, Merck, Germany) and reversed-phase octadecyl Si (ODS) gel (YMC, Japan) were used for open-column chromatography. TLC was carried out on Merck precoated TLC sheets (Si gel 60 F_{254}), and detected by spraying with 10% H_2SO_4 in 50% EtOH, followed by heating on a hot plate at 200 °C.

Plant Material The aerial parts of *L. heterophyllus* were collected from Dai Yen village, in Hanoi, Vietnam, and identified by Professor Vu Van Chuyen of the Hanoi College of Pharmacy (Hanoi, Vietnam), in May 2004. A voucher specimen (no. HCTN 2004-5) is deposited in the Herbarium of the Hanoi College of Pharmacy.

Extraction and Isolation of 1—10 The powdered air-dried aerial parts of *L. heterophyllus* (2.0 kg) were extracted with MeOH by percolation at room temperature (3 times, for 3 d each). After filteration and evaporation, the obtained brownish syrup was suspended in H_2O and subjected to sequential fractionation with *n*-hexane, ethyl acetate, and 1-BuOH. The *n*-hexane-soluble fraction (64.9 g) was chromatographed on a Si gel open column using stepwise gradients of *n*-hexane with increasing amounts of EtOAc to afford four pooled fractions: fraction 1 (18.1 g, *n*-hexane–EtOAc, 10 : 1), fraction 2 (37.5 g, *n*-hexane–EtOAc, 4 : 1), fraction 3 (4.1 g, *n*-hexane–EtOAc, 2 : 1), and fraction 4 (0.5 g, *n*-hexane–EtOAc, 1 : 1). Separation of fraction 1 on a Si gel open column (*n*-hexane–EtOAc, 10 : 1) followed by precipitation with MeOH afforded **1** (10 mg, white amorphous powder). Separation of fraction 2 on a Si gel open column (*n*-hexane–EtOAc, 4 : 1), on an ODS gel open column (MeOH–H_2O, 7 : 3, 4 : 1), and finally by repeated ODS preparative HPLC (MeOH–H_2O, 4 : 1) afforded **2**—**4** as white amorphous powders (70.2 mg, 36.7 mg, 408.4 mg, respectively). β-Sitosterol and stigmasterol were also precipitated as a mixture (168.4 mg) from fraction 2 after treatment with MeOH. After precipitation of **10** (55.1 mg, yellowish amorphous powder) from fraction 3 by treatment with MeOH, this fraction was subjected to ODS gel open-column chromatography (MeOH–H_2O, 4 : 1) and repeated ODS preparative HPLC (MeOH–H_2O, 4 : 1) to yield compounds **5** (11.9 mg), **6** (19.8 mg), **7** (15.3 mg), **8** (220 mg), and **9** (29.1 mg).

Leoheteronin A (**5**): White amorphous powder, $[\alpha]_D^{25}$ +8.4° (c=1.19, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2929, 2870, 1747, 1664, 1605, 1456, 1373, 1279. ^{1}H- and ^{13}C-NMR: see Tables 1 and 2. Positive-ion HR-FAB-MS: *m/z* 339.1923 $[M+Na]^+$ (Calcd for $C_{20}H_{28}O_3Na$: 339.1936).

Leoheteronin B (**6**): White amorphous powder, $[\alpha]_D^{25}$ −10.7° (c=1.77, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 2930, 2869, 1747, 1665, 1606, 1451, 1374, 1252. ^{1}H- and ^{13}C-NMR: see Tables 1 and 2. Positive-ion HR-FAB-MS: *m/z* 339.1923 $[M+Na]^+$ (Calcd for $C_{20}H_{28}O_3Na$: 339.1936).

Leoheteronin C (**7**): White amorphous powder, $[\alpha]_D^{25}$ +57.8° (c=1.35, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3400, 2930, 2869, 1735, 1665, 1603, 1469, 1375, 1257. ^{1}H- and ^{13}C-NMR: see Tables 1 and 2. Negative-ion HR-FAB-MS: *m/z* 331.1903 $[M-H]^-$ (Calcd for $C_{20}H_{27}O_4$: 331.1909).

Leoheteronin D (**8**): Colorlees needles, mp 134—135 °C, $[\alpha]_D^{25}$ −0.0° (c=0.20, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3418, 2926, 2860, 1669, 1460, 1383, 1251. ^{1}H- and ^{13}C-NMR: see Tables 1 and 2. Negative-ion HR-FAB-MS: *m/z* 307.2625 $[M-H]^-$ (Calcd for $C_{20}H_{35}O_2$: 307.2637).

Leoheteronin E (**9**): White amorphous powder, $[\alpha]_D^{25}$ −9.3° (c=2.91, $CHCl_3$). IR ν_{max} (film) cm^{-1}: 3504, 2935, 2870, 1752, 1703, 1652, 1458, 1252. ^{1}H- and ^{13}C-NMR: see Tables 1 and 2. Negative-ion HR-FAB-MS: *m/z* 333.2077 $[M-H]^-$ (Calcd for $C_{20}H_{29}O_4$: 333.2066).

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