Triterpenoids from the Leaves of *Ilex hainanensis*

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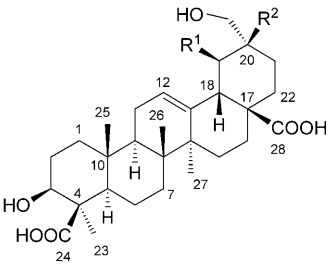
Phytochemical investigation on the leaves of *Ilex hainanensis* MERR. led to the isolation of four new ursane- and oleanane-based triterpenoids, ilexhainanins A–D (**1**–**4**), as well as two known compounds, 2α,3β,19α-trihydroxyurs-12-ene-23,28-dioic acid and 2α,3β,19α-trihydroxyolean-12-ene-23,28-dioic acid. Their structures were elucidated on the basis of chemical and spectroscopic evidence, and by comparison with literature data.

Introduction. – *Ilex hainanensis* MERR. (Aquifoliaceae) is distributed mainly in the southern region of the People's Republic of China. The leaves of this plant is a traditional tea product, known as '*shan-lv-cha*'. It is also used in traditional Chinese medicine (TCM) as a diuretic, antihypertensive, antilipemic, and anti-inflammatory agent. There are numerous clinical research reports on the use of '*shan-lv-cha*' for treatment of hypertension [1]. However, only a few phytochemical investigations have been performed, and as few as five compounds have been isolated from *I. hainanensis* [2][3]. Therefore, a more systematic chemical investigation was carried out.

Herein, we report four new triterpenoids, ilexhainanins A–D (**1**–**4**), from the leaves of *I. hainanensis*. They were isolated together with the two known constituents 2α,3β,19α-trihydroxyurs-12-ene-23,28-dioic acid [4] and 2α,3β,19α-trihydroxyolean-12-ene-23,28-dioic acid [5].



1 R^1 = Me, R^2 = H
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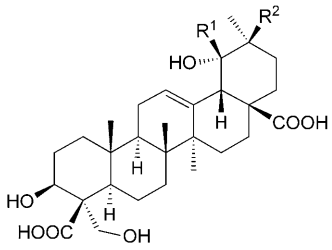

3 R^1 = Me, R^2 = H
4 R^1 = H, R^2 = Me

Results and Discussion. – Compound **1** was obtained as an optically active powder ($[\alpha]_D^{26} = +42.3$ ($c = 1.3$, MeOH)). It gave rise to a positive *Liebermann–Burchard* coloration test, indicating a triterpenoid structure. The molecular formula $C_{30}H_{46}O_6$ was deduced by negative-ion HR-ESI-MS (*m/z* 501.3217 ($[M-H]^-$)), in accord with eight degrees of unsaturation. The IR spectrum of **1** showed characteristic bands for OH (3401) and C=O (1692 cm^{-1}) groups. The ^{1}H- and ^{13}C-NMR data of **1** (*Table 1*) indicated a pentacyclic triterpenoid, assignments being confirmed with the help of 2D-NMR (HMBC, HSQC, NOESY) experiments.

The ^{1}H-NMR spectrum of **1** (*Table 1*) revealed the presence of four Me groups at δ(H) 1.08 (2*s*), 1.25 (*s*), and 1.70 (*s*), a Me *doublet* at δ(H) 1.15 ($J = 6.5$ Hz), one olefinic signal at δ(H) 5.52 (br. *s*, H–C(12)), and a characteristic signal for H–C(18) at δ(H) 2.73 (*d*, $J = 12$ Hz). The ^{13}C-NMR spectrum indicated a C=C bond (δ(C) 125.8, 139.1), two COOH groups (δ(C) 180.9, 179.9), and two oxygenated C-atoms (δ(C) 78.2 (OCH), 65.1 (OCH_2)). The above data pointed to a triterpenoid with an urs-12-ene skeleton.

A typical signal of an axial H–C(3) atom at δ(H) 3.34 (*dd*, $J = 12.0$, 4.0 Hz) was observed, indicating a β-equatorial orientation of the 3-OH group in **1** [6]. In the HMBC spectrum (*Fig. 1,a*), correlation peaks were observed from δ(H) 3.34 (H–C(3)) to δ(C) 180.9 (COOH) and 24.7 (Me), and from δ(H) 1.70 (Me) to δ(C) 180.9, 78.2 (C(3)), and 49.2 (C(4)), which indicated that a COOH and a Me group were both attached to C(4), the Me(23) group being in α-equatorial position, on the basis of its ^{13}C-NMR chemical shift (*Table 1*) [7]. The HMBC correlation between δ(H) 2.73 (H–C(18)) and δ(C) 179.9 indicated that the second COOH group (C(28)) was linked at C(17). The second OH group was placed at C(30), on the basis of NMR resonances at δ(H) 3.91, 3.97 (2*dd*, $J = 5.5$, 2.5 Hz each) in combination with HMBC analysis (*Fig. 1,a*).

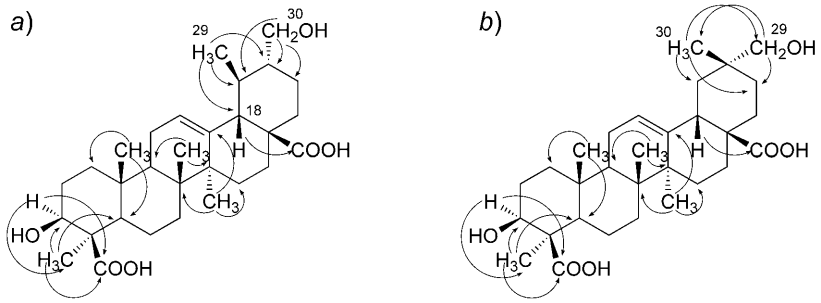

Fig. 1. *Key HMBC correlations of* a) **1** *and* b) **2**

The relative configuration of **1** was confirmed by a NOESY experiment. The 3β-OH, 4α-Me, and 4β-COOH groups were in accord with the following NOESY correlations: H–C(3)/H–C(5) [δ(H) 1.03–1.07 (*m*)], H–C(3)/Me(23) (δ(H) 1.70 (*s*, 3 H)), and Me(23)/H–C(5). The correlations between H–C(18) and Me(29) (δ(H) 1.15 (*d*, $J = 6.5$ Hz)), and between H–C(18) and H–C(20) (δ(H) 1.26–1.30 (*m*)) indicated an α-configured CH_2OH group at C(20). From the above evidence, the structure of com-

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** *and* **2**. At 500 (^{1}H) and 125 MHz (^{13}C), in C_5D_5N; δ in ppm, J in Hz.

Position	**1**		**2**	
	δ(C)	δ(H)	δ(C)	δ(H)
1	39.7	1.02–1.06 (*m*)	39.6	1.04–1.10 (*m*)
		1.64–1.70 (*m*)		1.58–1.62 (*m*)
2	29.5	1.24–1.26 (*m*)	29.5	1.26–1.30 (*m*)
		1.30–1.32 (*m*)		
3	78.2	3.34 (*dd*, *J* = 14.0, 4.0)	78.2	3.34 (*dd*, *J* = 14.0, 4.0)
4	49.2		49.2	
5	56.8	1.03–1.07 (*m*)	56.8	1.06–1.10 (*m*)
6	20.7	2.02–2.08 (*m*)	20.8	2.02–2.08 (*m*)
		2.10–2.16 (*m*)		2.10–2.16 (*m*)
7	33.9	1.40–1.46 (*m*)	33.5	1.46–1.56 (*m*)
		1.48–1.56 (*m*)		
8	39.8		39.5	
9	47.3	1.60–1.64 (*m*)	47.4	1.60–1.64 (*m*)
10	37.8		37.8	
11	23.8	1.92–2.00 (*m*)	24.0	1.94–2.02 (*m*)
12	125.8	5.52 (br. *s*)	122.6	5.59 (br. *s*)
13	139.1		144.8	
14	42.6		42.2	
15	29.0	1.88–1.96 (*m*)	28.3	1.08–1.12 (*m*)
		2.38–2.44 (*m*)		2.10–2.16 (*m*)
16	25.0	1.98–2.04 (*m*)	23.8	1.90–1.94 (*m*)
		2.20–2.26 (*m*)		2.12–2.16 (*m*)
17	48.3		47.2	
18	53.6	2.73 (*d*, *J* = 12.0)	41.5	3.41 (*dd*, *J* = 14.0, 4.0)
19	33.9	1.98–2.06 (*m*)	41.2	1.46–1.50 (*m*)
				2.06–2.10 (*m*)
20	47.4	1.26–1.30 (*m*)	36.6	
21	25.7	1.56– 1.62 (*m*)	29.0	1.35–1.39 (*m*)
		1.94–1.98 (*m*)		1.76–1.80 (*m*)
22	37.4	1.98–2.04 (*m*)	32.6	1.86–1.90 (*m*)
		2.08–2.10 (*m*)		2.10–2.14 (*m*)
23	24.7	1.70 (*s*)	24.7	1.69 (*s*)
24	180.9		180.9	
25	14.0	1.08 (*s*)	13.8	1.06 (*s*)
26	17.4	1.08 (*s*)	17.3	1.08 (*s*)
27	23.8	1.25 (*s*)	26.0	1.29 (*s*)
28	179.9		180.2	
29	17.2	1.15 (*d*, *J* = 6.5)	73.8	3.60 (*s*)
30	65.1	3.91 (*dd*, *J* = 5.5, 2.5)	19.8	1.20 (*s*)
		3.97 (*dd*, *J* = 5.5, 2.5)		

pound **1** was unequivocally established as (3β)-3,30-dihydroxyurs-12-ene-24,28-dioic acid, and named *ilexhainanin A*.

Compound **2**, isolated as a colorless, amorphous powder, gave a positive *Liebermann–Burchard* coloration test. Its molecular formula was $C_{30}H_{46}O_6$ according to HR-ESI-MS (m/z 501.3218 ($[M-H]^-$)), corresponding to eight degrees of unsatura-

tion. The compound was optically active, with $[\alpha]_D^{26} = +53.5$ ($c = 2.3$, MeOH). The IR spectrum revealed the presence of OH (3430) and C=O (1692 cm^{-1}) groups. The ^{1}H-NMR spectrum of **2** showed signals of five Me *singlet*s at δ(H) 1.06, 1.08, 1.20, 1.29, 1.69, one olefinic H-atom at δ(H) 5.59 (br. *s*), and a characteristic signal for H–C(18) at δ(H) 3.41 (*dd*, $J = 14.0$, 4.0 Hz). The ^{13}C-NMR spectrum indicated one C=C bond (δ(C) 122.6, 144.8), two COOH functions (δ(C) 180.2, 180.9), and two oxygenated C-atoms (δ(C) 73.8 ($HOCH_2$), 78.2 (OCH)). The above evidence suggested that compound **2** was a triterpenoid with an olean-12-ene C skeleton, and an isomer of compound **1**.

Careful comparison of the ^{13}C-NMR spectroscopic data of **2** with those of **1** showed that the signals for C(1) to C(11) and C(23) to C(26) were basically identical in both compounds, which indicated identical rings *A*, *B*, and *C*. To confirm the substitution pattern of **2** in ring *E*, the known triterpenoid (3β)-3,29-dihydroxyolean-12-ene-23,28-dioic acid [8] was used as a reference compound. The signals of C(12) to C(22) and of C(27) to C(30) of **2** matched well with those of the known triterpenoid, which suggested that their *C*-, *D*-, and *E*-rings were similar. The NMR data assignments were further corroborated by HSQC and HMBC correlations (*Fig. 1,b*). Thus, based on the above evidence, the structure of compound **2** was elucidated as (3β)-3,29-dihydroxyolean-12-ene-24,28-dioic acid, and named *ilexhainanin B*.

Compound **3**, isolated as an amorphous powder and showing a positive *Liebermann–Burchard* test, was found to have the molecular formula $C_{30}H_{46}O_7$ by HR-ESI-MS (*m*/*z* 517.3168 ($[M-H]^-$), indicating eight degrees of unsaturation. It was optically active, with $[\alpha]_D^{26} = +28.8$ ($c = 0.9$, MeOH). The IR spectrum indicated the presence of OH (3427) and C=O (1690 cm^{-1}) groups. These data, together with a comparison of the ^{1}H- and ^{13}C-NMR data of **3** (*Table 2*) with those of **1**, indicated that **3** was a triterpenoid with an urs-12-ene C skeleton.

The ^{13}C-NMR spectrum of **3** indicated two COOH groups (δ(C) 179.2, 180.6), three oxygenated C-atoms (δ(C) 64.4 ($HOCH_2$), 73.2 (OCH), and 72.6 (C_q)). Oxygenation at C(19) was inferred from the low-field-shifted signal at δ(C) 72.6 (C(19)) showing long-range HMBC correlations with H–C(18) (δ(H) 3.03 (br. *s*)), Me(29) (δ(H) 1.43 (*s*)), and Me(30) (δ(H) 1.10 (*d*, $J = 6.5$ Hz)). The second OH group was considered to be at C(3). Its β-configuration was derived from the coupling pattern of axial H–C(3) (δ(H) 4.21 (*dd*, $J = 13.0$, 4.0 Hz)). Careful comparison of the ^{1}H- and ^{13}C-NMR data of **3** with those of ilexagenin A (=3β,19α-dihydroxyurs-12-ene-24,28-dioic-acid) [9] exhibited differences only in ring *A*. Thus, the signal for Me(23), which was observed at δ(H) 1.70 and δ(C) 24.7 in ilexagenin A, was not present in **3**; instead, the signals of a CH_2OH group were detected in **3** (δ(H) 4.39, 4.73 (*AB*-type *q*, $J = 10.5$ Hz); δ(C) 64.4). Both a COOH and a CH_2OH group were attached to C(4), as confirmed by the key HMBC correlations (*Fig. 2,a*) from δ(H) 4.21 (H–C(3)) to δ(C) 179.2 (COOH) and δ(C) 64.4 (CH_2OH), and from δ(H) 4.39, 4.73 (CH_2(23)) to δ(C) 179.2 (C(24)), δ(C) 55.1 (C(4)), and δ(C) 73.2 (C(3)). The HMBC correlations between δ(H) 3.03 (H–C(18)) and δ(C) 180.6 confirmed that the second COOH group was linked at C(17).

The relative configuration of **3** was deduced by a NOESY experiment. The 3β-OH, 4β-COOH, and 4α-CH_2OH groups were in accord with the following NOESY correlations: H–C(3)/H–C(5) and H–C(3)/CH_2(23). Further, H–C(18) correlated with

Table 2. *^{1}H- and ^{13}C-NMR Data of* **3** *and* **4**. At 500 (^{1}H) and 125 MHz (^{13}C) in C_5D_5N; δ in ppm, J in Hz.

Position	**3**		**4**	
	δ(C)	δ(H)	δ(C)	δ(H)
1	39.6	1.08–1.16 (*m*)	39.3	1.08–1.16 (*m*)
		1.68–1.72 (*m*)		1.68–1.72 (*m*)
2	29.3	1.20–1.30 (*m*)	29.2	1.10–1.20 (*m*)
3	73.2	4.21(*dd*, *J*=13.0, 4.0)	73.0	4.21 (*dd*, *J*=13.0, 4.0)
4	55.1		55.1	
5	49.3	1.82–1.86 (*m*)	49.3	1.82–1.86 (*m*)
6	20.7	2.20–2.28 (*m*)	20.7	2.16–2.24 (*m*)
7	33.6	1.44–1.48 (*m*)	33.6	1.70–1.76 (*m*)
		1.98–2.02 (*m*)		2.12–2.16 (*m*)
8	40.2		39.8	
9	47.3	1.90–1.94 (*m*)	47.9	1.86–1.90 (*m*)
10	37.6		37.8	
11	24.3	2.00–2.10 (*m*)	24.3	2.00–2.10 (*m*)
12	128.0	5.95 (br. *s*)	123.0	5.56 (br. *s*)
13	139.9		144.8	
14	42.3		42.2	
15	29.3	2.06–2.14 (*m*)	29.1	2.06–2.14 (*m*)
		2.26–2.32 (*m*)		2.26–2.32 (*m*)
16	26.4	1.98–2.06 (*m*)	27.0	2.00–2.10 (*m*)
17	48.2		46.0	
18	54.6	3.03 (br. *s*)	44.8	3.60 (br. *s*)
19	72.6		81.0	3.60 (br. *s*)
20	42.3	1.46–1.50 (*m*)	35.5	
21	27.0	1.30–1.34 (*m*)	28.4	2.06–2.12 (*m*)
		1.40–1.44 (*m*)		2.76–2.80 (*m*)
22	38.4	1.98–2.06 (*m*)	33.3	1.38–1.42 (*m*)
		2.08–2.16 (*m*)		1.60–1.66 (*m*)
23	64.4	4.39, 4.73 (*AB q*, *J*=10.5)	64.3	4.40, 4.74 (*AB q*, *J*=10.5)
24	179.2		179.2	
25	14.3	1.20 (*s*)	14.1	1.20 (*s*)
26	17.1	1.16 (*s*)	17.3	1.16 (*s*)
27	24.5	1.68 (*s*)	24.6	1.60 (*s*)
28	180.6		180.8	
29	26.9	1.43 (*s*)	28.8	1.18 (*s*)
30	16.7	1.10 (*d*, *J*=6.5)	24.8	1.09 (*s*)

Me(29) (δ(H) 1.43 (*s*)), which indicated an α-OH group at C(19). On the basis of the above evidence, the structure of compound **3** was, thus, determined as (3β,19*R*)-3,19,23-trihydroxyurs-12-ene-24,28-dioic acid, and named *ilexhainanin C*.

Compound **4**, obtained as an amorphous powder, also gave a positive *Liebermann–Burchard* test. The molecular formula of **4** was determined as $C_{30}H_{46}O_7$ by HR-ESI-MS (*m*/*z* 517.3169 ($[M-H]^-$)), suggesting eight degrees of unsaturation. The compound was optically active, with $[\alpha]_D^{26}=+36.6$ ($c=1.0$, MeOH). The IR spectrum showed signals for OH (3428) and C=O (1690 cm^{-1}) groups. The above data, together with a detailed comparison of its ^{1}H- and ^{13}C-NMR data (*Table 2*) with those of **2**, manifested

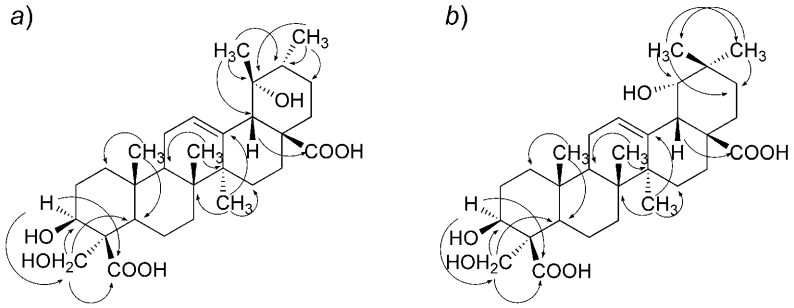

Fig. 2. *Key HMBC correlations of* a) **3** *and* b) **4**

that **4** was an isomer of **3**. By comparing their ^{13}C-NMR spectroscopic data, in combination with those of the known triterpenoid ilexolic acid B (=3β,19α-dihydroxyolean-12-ene-23,28-dioic acid) [10], rings *A*–*C* of **4** were similar to those of **3**, and rings *C*–*E* of **4** were similar to those of ilexolic acid B, respectively. NMR Assignments were confirmed with the help of HSQC and HMBC experiments (*Fig. 2*, *b*). Accordingly, the structure of **4** was unambiguously established as (3β,19α)-3,19,23-trihydroxyolean-12-ene-24,28-dioic acid, and named *ilexhainanin D.*

The two known compounds, 2α,3β,19α-trihydroxyurs-12-ene-23,28-dioic acid [4] and 2α,3β,19α-trihydroxyolean-12-ene-23,28-dioic acid [5], were identified by comparison of their spectroscopic data with those reported in the literature.

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Experimental Part

General. Column chromatography (CC): silica gel *H* (200–300 mesh; *Qingdao Marine Chemical Industry*), *Sephadex LH-20* gel (*Pharmacia*), *ODS* gel (25–40 μm; *Merck*), and *D101* porous polymer resin (*Tianjin Chemical Industry*). Semi-prep. HPLC: *ODS* column (250×10 mm, 5 μm; *Alltech*), with *ELSD* detector (*Alltech)*; flow rate, 2.5 ml/min. Optical rotations: *Perkin-Elmer-243B* digital polarimeter. NMR Spectra: *Varian Inova-500* apparatus; at 500 (^{1}H) or 125 MHz (^{13}C) in C_5D_5N at r.t.; δ in ppm rel. to Me_4Si, *J* in Hz. HR-ESI-MS (neg.): *Bruker APEX-II FT-ICR-MS* mass spectrometer; in *m*/*z*.

Plant Material. The leaves of *Ilex hainanensis* were purchased in Guangxi Province, South China, in March 2005, and identified by Prof. *P.-F. Tu*. A voucher specimen (SLC 200503) was deposited at the Herbarium of Peking University, Modern Research Center for Traditional Chinese Medicine.

Extraction and Isolation. The air-dried leaves (20 kg) of *I. hainanensis* were extracted with 70% aq. EtOH at 60° (3×). The combined extract was concentrated under vacuum, and the residue (1.7 kg) was suspended in H_2O, and extracted first with $CHCl_3$ and then with BuOH. The BuOH-soluble extract (300 g) was dissolved in H_2O, and the water-dissolved fraction (190 g) was subjected to CC (*D101* porous polymer resin; 1. H_2O, 2. 10, 30, 50, 70, and 95% aq. EtOH). The fraction eluted with 70% aq. EtOH (20 g) was subjected to CC (SiO_2; $CHCl_3$/MeOH/H_2O 20:1:0 → 7:3:0.5) to afford 10 subfractions (*Fr. 1–10*). *Fr. 2* was purified by CC (1. *Sephadex LH-20*, MeOH; 2. *ODS*, 70% aq. MeOH) followed by semi-prep. HPLC (MeOH/H_2O 2:1) to furnish **1** (13 mg) and **2** (23 mg). *Fr. 5* was subjected to CC (1. *Sephadex LH-20*, MeOH; 2. *ODS*, 65% aq. MeOH) followed by semi-prep. HPLC (MeOH/H_2O 2:1)

to afford **3** (9 mg) and **4** (10 mg). Purification of *Fr. 8* by CC (ODS; 60% aq. MeOH) and then by semi-prep. HPLC (MeCN/H_2O 35 : 65) afforded the two known compounds 2α,3β,19α-trihydroxyurs-12-ene-23,28-dioic acid (12 mg) [4] and 2α,3β,19α-trihydroxyolean-12-ene-23,28-dioic acid (13 mg) [5].

Ilexhainanin A (*=(3β)-3,30-Dihydroxyurs-12-ene-24,28-dioic Acid*; **1**). Colorless, amorphous powder. $[\alpha]_D^{26} = +42.3$ ($c = 1.3$, MeOH). IR (KBr): 3401, 1692. ^{1}H- and ^{13}C-NMR: see *Table 1*. HR-ESI-MS: 501.3217 ($[M-H]^-$), $C_{30}H_{45}O_6^-$; calc. 501.3216).

Ilexhainanin B (*=(3β)-3,29-Dihydroxyolean-12-ene-24,28-dioic Acid*; **2**). Colorless, amorphous powder. $[\alpha]_D^{26} = +53.5$ ($c = 2.3$, MeOH). IR (KBr): 3430, 1692. ^{1}H- and ^{13}C-NMR: see *Table 1*. HR-ESI-MS: 501.3218 ($[M-H]^-$), $C_{30}H_{45}O_6^-$; calc. 501.3216).

Ilexhainanin C (*=(3β,19*R*)-3,19,23-Trihydroxyurs-12-ene-24,28-dioic Acid*; **3**). Colorless, amorphous powder. $[\alpha]_D^{26} = +28.8$ ($c = 0.9$, MeOH). IR (KBr): 3427, 1690. ^{1}H- and ^{13}C-NMR: see *Table 2*. HR-ESI-MS: 517.3168 ($[M-H]^-$) $C_{30}H_{45}O_7^-$; calc. 517.3165).

Ilexhainanin D (*=(3β,19α)-3,19,23-Trihydroxyolean-12-ene-24,28-dioic Acid*; **4**). Colorless, amorphous powder. $[\alpha]_D^{26} = +36.6$ ($c = 1.0$, MeOH). IR (KBr): 3428, 1690. ^{1}H- and ^{13}C-NMR: see *Table 2*. HR-ESI-MS: 517.3169 ($[M-H]^-$)), $C_{30}H_{45}O_7^-$; calc. 517.3165).

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