Curcumaromins A, B, and C, Three Novel Curcuminoids from *Curcuma aromatica*

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Three novel curcuminoids, curcumaromins A – C (**1** – **3**, resp.), along with a known compound, longiferone B (**4**) were isolated from *Curcuma aromatica* SALISB. The structures of the new compounds were elucidated as (1*E*,4*Z*,6*E*)-5-hydroxy-7-{4-hydroxy-3-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl)phenyl}-1-(4-hydroxyphenyl)hepta-1,4,6-trien-3-one (**1**), 2,3-dihydro-2-(4-hydroxyphenyl)-6-[(*E*)-2-(4-hydroxyphenyl)ethenyl]-5-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl]-4*H*-pyran-4-one (**2**), and (1*E*,6*E*)-1,7-bis(4-hydroxyphenyl)-4-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl]hepta-1,6-diene-3,5-dione (**3**) on the basis of spectroscopic analysis. Curcumaromins A – C (**1** – **3**) represented the first examples of menthane monoterpene-coupled curcuminoids. The known compound, longiferone B (**4**), was the first daucane sesquiterpene isolated from the genus *Curcuma*.

Introduction. – *Curcuma aromatica*, a traditional Chinese herb, is a member of the *Curcuma* genus belonging to the family Zingiberaceae. Among the phytochemical constituents reported from the genus *Curcuma* [1 – 7], sesquiterpenes and curcuminoids were the two fundamental groups of compounds [6]. Curcuminoids, with a 1,7-diphenylheptanoid skeleton, are considered to be the main bioactive constituents of *Curcuma* sp. with inhibitory activity on nitric oxide (NO) production [8], inhibitory effects on melanogenesis [9], antiproliferative and immunomodulatory activities [10], antitumor activity [11], and anti-oxidant activity [12] reported.

In our phytochemical research on *C. aromatica*, three novel curcuminoids, curcumaromins A – C (**1** – **3**, resp.), were isolated along with a known compound, longiferone B (**4**) [13] (*Fig. 1*). Curcumaromins A – C (**1** – **3**) are firstly obtained from nature with an unusual skeleton combined by a menthane-type monoterpene and a 1,7-diphenylheptanoid, representing the first examples of menthane monoterpene-coupled curcuminoids. The known compound, longiferone B (**4**), is the first daucane sesquiterpene isolated from the genus *Curcuma*. Herein, we report the isolation and structure elucidation of the three novel curcuminoids **1** – **3**.

Results and Discussion. – Curcumaromin A (**1**) was isolated as orange powder. The molecular formula was determined as $C_{29}H_{32}O_4$ by HR-ESI-MS (*m*/*z* 445.2375 ($[M+H]^+$)), as well as the ^{1}H- and ^{13}C-NMR data. The IR spectrum indicated the presence of OH (3423 cm^{-1}), conjugated C=O (1623 cm^{-1}), and phenyl (1599, 1512, and 1438 cm^{-1}) moieties. The UV spectrum showed a maximum absorption at 423 nm. The ^{1}H-NMR

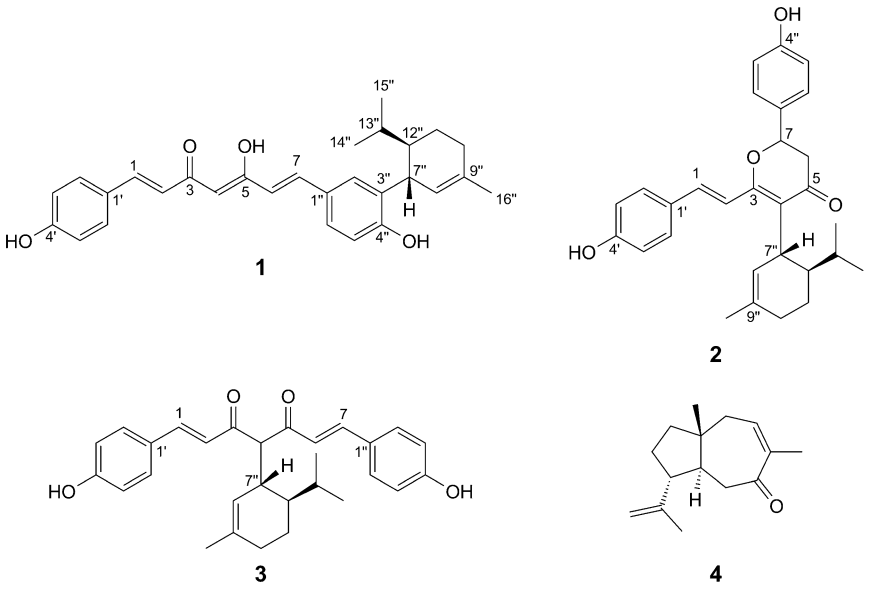

Fig. 1. *Structures of curcumaromins A – C* (**1** – **3**, resp.) *and* **4**

spectrum (*Table*) showed signals for two OH groups (δ(H) 10.03 and 9.96 (*s*, each 1 H)), a 1,4-disubstituted aromatic ring (δ(H) 7.49 and 6.76 (*d*, $J = 8.4$, each 2 H)), and a 1,3,4-trisubstituted aromatic ring (δ(H) 7.24 (*d*, $J = 2.4$, 1 H), 6.78 (*d*, $J = 8.4$, 1 H), 7.35 (*dd*, $J = 8.4$, 2.4, 1 H)). The ^{13}C-NMR spectrum (*Table*), together with HSQC spectrum, revealed the presence of one conjugated C=O group (δ(C) 183.1), five aromatic quaternary C-atoms (δ(C) 126.0, 159.9, 125.9, 132.9, 157.9), seven aromatic CH groups (δ(C) 130.4, 116.1, 130.4, 116.1, 129.7, 115.7, 127.4), two olefinic quaternary C-atoms (δ(C) 183.5, 133.8), six olefinic CH groups (δ(C) 140.4, 120.9, 100.9, 120.7, 141.0, 125.1), three aliphatic CH groups (δ(C) 37.2, 45.1, 27.5), two aliphatic CH_2 groups (δ(C) 29.6, 21.6), and three Me groups (δ(C) 21.6, 17.4, 23.5). The unambiguous sequence and linkage sites were determined by HMBC spectrum (*Fig. 2*). In the HMBC spectrum, the correlations of H–C(1) (δ(H) 7.47) with C(3) (δ(C) 183.1), H–C(2) (δ(H) 6.59) with C(4) (δ(C) 100.9), H–C(6) (δ(H) 6.57) with C(4), and H–C(7) (δ(H) 7.46) with C(5) (δ(C) 183.5) suggested the existence of a heptanoid moiety. The correlation of H–C(1) with C(2′) (δ(C) 130.4) and the correlation of H–C(6) with C(1″) (δ(C) 125.9) indicated that the 1,4-disubstituted aromatic ring was attached to C(1) and the 1,3,4-trisubstituted aromatic ring was attached to C(7). The correlations of Me(14″) (δ(H) 0.79) and Me(15″) (δ(H) 0.73) with C(12″) (δ(C) 45.1), CH_2(11″) (δ(H) 1.24 – 1.32, 1.56 – 1.61) with C(7″) (δ(C) 37.2), H–C(8″) (δ(H) 5.06) with C(10″) (δ(C) 29.6) and C(12″) (δ(C) 45.1), and Me(16″) (δ(H) 1.62) with C(8″) (δ(C) 125.1) indicated the presence of a menthane-type monoterpene moiety, which was assigned to be linked to C(3″) through C(3″)–C(7″) bond by the HMB correlation of H–C(2″) (δ(H) 7.24) with C(7″).

Table. *^{1}H- and ^{13}C-NMR Data* (600 and 150 MHz, resp.) *of* **1** ((D$_6$)DMSO), **2** ((D$_6$)acetone) *and* **3** (CD$_3$OD). δ in ppm, J in Hz.

Position	**1**		**2**		**3**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	7.47 (*d*, *J* = 15.6)	140.4	7.20 (overlapped)	136.1	7.65 (*d*, *J* = 15.6)	146.5
2	6.59 (*d*, *J* = 15.6)	120.9	7.20 (overlapped)	118.4	6.83 (*d*, *J* = 15.6)	122.8
3		183.1		165.5		197.0
4	6.04 (*s*)	100.9		119.0	4.48 (*d*, *J* = 10.2)	70.6
5		183.5		192.2		197.1
6	6.57 (*d*, *J* = 15.6)	120.7	2.90 (*dd*, *J* = 13.8, 16.8, 1 H), 2.60 (*dd*, *J* = 16.8, 3.0, 1 H)	43.9	6.85 (*d*, *J* = 15.6)	122.8
7	7.46 (*d*, *J* = 15.6)	141.0	5.37 (*dd*, *J* = 13.8, 3.0)	79.7	7.67 (*d*, *J* = 15.6)	146.4
1′		126.0		128.5		127.1
2′	7.49 (*d*, *J* = 8.4)	130.4	7.35 (*d*, *J* = 8.4)	129.8	7.52 (*d*, *J* = 8.4)	132.0
3′	6.76 (*d*, *J* = 8.4)	116.1	6.86 (*d*, *J* = 8.4)	116.7	6.81 (*d*, *J* = 8.4)	117.0
4′		159.9		159.8		162.0
5′	6.76 (*d*, *J* = 8.4)	116.1	6.86 (*d*, *J* = 8.4)	116.7	6.81 (*d*, *J* = 8.4)	117.0
6′	7.49 (*d*, *J* = 8.4)	130.4	7.35 (*d*, *J* = 8.4)	129.8	7.52 (*d*, *J* = 8.4)	132.0
1″		125.9		131.1		127.1
2″	7.24 (*d*, *J* = 2.4)	129.7	7.42 (*d*, *J* = 8.4)	128.8	7.52 (*d*, *J* = 8.4)	132.0
3″		132.9	6.90 (*d*, *J* = 8.4)	116.1	6.81 (*d*, *J* = 8.4)	117.0
4″		157.9		158.5		162.0
5″	6.78 (*d*, *J* = 8.4)	115.7	6.90 (*d*, *J* = 8.4)	116.1	6.81 (*d*, *J* = 8.4)	117.0
6″	7.35 (*dd*, *J* = 8.4, 2.4)	127.4	7.42 (*d*, *J* = 8.4)	128.8	7.52 (*d*, *J* = 8.4)	132.0
7″	3.61 (*dd*, *J* = 5.4, 2.4)	37.2	3.93 (*d*, *J* = 7.8)	34.4	3.26 (*dd*, *J* = 10.2, 4.2)	39.2
8″	5.06 (br. *s*)	125.1	5.24 (*s*)	128.3	5.23 (*d*, *J* = 4.2)	121.9
9″		133.8		133.5		137.6
10″	1.91 (*d*, *J* = 20.4, 1 H), 1.98–2.04 (*m*, 1 H)	29.6	2.09–2.13 (*m*, 1 H), 2.18–2.24 (*m*, 1 H)	31.5	1.78–1.84 (*m*, 1 H), 1.91–1.96 (*m*, 1 H)	27.3
11″	1.24–1.32 (*m*, 1 H), 1.56–1.61 (*m*, 1 H)	21.6	1.36–1.42 (*m*, 1 H), 1.78–1.82 (*m*, 1 H)	23.3	1.72–1.81 (*m*, 2 H)	21.5
12″	1.40–1.47 (*m*)	45.1	1.58–1.63 (*m*)	46.4	0.97–1.02 (*m*)	42.4
13″	1.39–1.46 (*m*)	27.5	1.75 (overlapped)	28.4	1.54–1.60 (*m*)	28.4
14″	0.79 (*d*, *J* = 6.6, 3 H)	21.6	0.84 (*d*, *J* = 7.2, 3 H)	22.0	0.95 (*d*, *J* = 9.6, 3 H)	22.2
15″	0.73 (*d*, *J* = 6.6, 3 H)	17.4	0.81 (*d*, *J* = 7.2, 3 H)	16.4	0.88 (*d*, *J* = 9.6, 3 H)	21.1
16″	1.62 (*s*, 3 H)	23.5	1.75 (*s*, 3 H)	23.6	1.59 (*s*, 3 H)	24.0
*H*O–C(4′)	10.03 (*s*)		9.02 (*s*)			
*H*O–C(4″)	9.96 (*s*)		8.72 (*s*)			

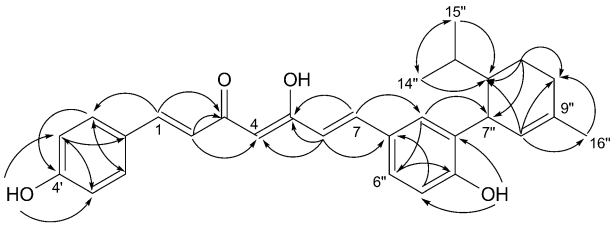

Fig. 2. *Selected HMBCs* (H → C) *of* **1**

The J(H,H) was 15.6 Hz between H–C(1) and H–C(2), and between H–C(6) and H–C(7), indicating the (*E*)-configuration of those C=C bonds. The ROESY correlations between H–C(2) and H–C(4) (δ(H) 6.04), H–C(4) and H–C(6) suggested a (*Z*)-configuration of the C=C bond at C(4). The relative configuration of **1** was determined on the basis of ROESY correlations. The ROESY correlation between H–C(7″) (δ(H) 3.61) and Me(14″), indicated that H–C(7″) was β-oriented, and H–C(12″) was α-oriented. Thus, **1** was elucidated as (1*E*,4*Z*,6*E*)-5-hydroxy-7-{4-hydroxy-3-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl]phenyl}-1-(4-hydroxyphenyl)hepta-1,4,6-trien-3-one.

Curcumaromin B (**2**) was isolated as yellow powder. The molecular formula was established as $C_{29}H_{32}O_4$ by HR-ESI-MS (*m*/*z* 445.2371 ([$M+H$]$^+$)). The IR spectrum indicated the presence of OH (3417 cm^{-1}) and phenyl (1600, 1516, and 1443 cm^{-1}) moieties. The UV spectrum showed a maximum absorption at 370 nm. The ^{1}H-NMR spectrum (*Table*) exhibited signals for two OH groups (δ(H) 9.02 and 8.72 (*s*, each 1 H)), two 1,4-disubstituted aromatic rings (δ(H) 7.35, 6.86, 7.42, 6.90 (*d*, J = 8.4, each 2 H)). The ^{13}C-NMR spectrum (*Table*) and HSQC spectrum revealed the presence of one C=O group (δ(C) 192.2), four aromatic quaternary C-atoms (δ(C) 128.5, 159.8, 131.1, 158.5), eight aromatic CH groups (δ(C) 129.8, 116.7, 128.8, 116.1, each 2 C), three olefinic quaternary C-atoms (δ(C) 165.5, 119.0, 133.5), three olefinic CH groups (δ(C) 136.1, 118.4, 128.3), four aliphatic CH groups (δ(C) 79.7, 34.4, 46.4, 28.4), three aliphatic CH_2 groups (δ(C) 43.9, 31.5, 23.3), and three Me groups (δ(C) 22.0, 16.4, 23.6). These data suggested that compound **2** was also a menthane monoterpene-coupled diphenylheptanoid similar to **1**. Considering the same degrees of unsaturation of **1** and **2**, the replacement of two olefinic CH signals (δ(C) 120.7, 141.0) in **1** by one aliphatic CH_2 signal (δ(C) 43.9) and one aliphatic CH signal (δ(C) 79.7) in **2** suggested an extra ring *A* in **2**, which was confirmed by the key HMBCs of H–C(7) (δ(H) 5.37) with C(3) (δ(C) 165.5; *Fig. 3*). In the HMBC spectrum, the observable correlations of H–C(7″) (δ(H) 3.93) with C(3), C(4) (δ(C) 119.0), and C(5) (δ(C) 192.2) indicated that the monoterpene moiety was linked to C(4) through a C(4)–C(7″) bond. The position of two aromatic rings was determined to be at C(1) and C(7) by the correlations of H–C(2′) (δ(H) 7.35) with C(1) (δ(C) 136.1) and H–C(2″) (δ(H) 7.42) with C(7) (δ(C) 79.7). Thus, **2** was elucidated as 2,3-dihydro-2-(4-hydroxyphenyl)-6-[(*E*)-2-(4-hydroxyphenyl)ethenyl]-5-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl]-4*H*-pyran-4-one.

Curcumaromin C (**3**) was isolated as yellow powder. The molecular formula was established as $C_{29}H_{32}O_4$ by HR-ESI-MS (*m*/*z* 467.2193 ([$M+Na$]$^+$)). The IR spectrum

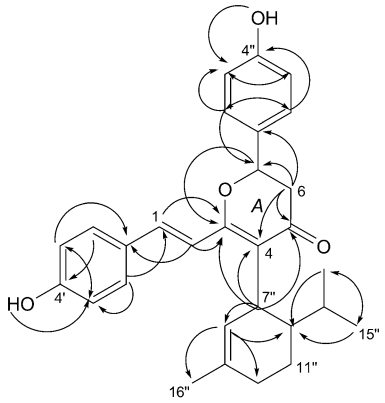

Fig. 3. *Selected HMBCs* (H → C) *of* **2**

indicated the presence of OH (3406 cm^{-1}), and phenyl (1598, 1579, 1512 and 1440 cm^{-1}) moieties. The UV spectrum showed a maximum absorption at 346 nm. The ^{1}H-NMR spectrum (*Table*) exhibited signals for two 1,4-disubstituted aromatic rings (δ(H) 7.52, 6.81 (*d*, J = 8.4, each 4 H)). The ^{13}C-NMR spectrum (*Table*) and HSQC spectrum revealed the presence of two C=O groups (δ(C) 197.0, 197.1), four aromatic quaternary C-atoms (δ(C) 127.1, 162.0, each 2 C), eight aromatic CH groups (δ(C) 132.0, 117.0, each 4 C), one olefinic quaternary C-atom (δ(C) 137.6), five olefinic CH groups (δ(C) 146.5, 122.8, 146.4, 122.8, 121.9), four aliphatic CH groups (δ(C) 70.6, 39.2, 42.4, 28.4), two aliphatic CH_2 groups (δ(C) 27.3, 21.5), and three Me groups (δ(C) 22.2, 21.1, 24.0). Analysis of the spectroscopic data revealed that compound **3** was composed of a symmetrical diphenylheptanoid unit and a menthane unit. Taking the symmetry of the diphenylheptanoid into consideration, the location of the menthane moiety was assigned at C(4). The linkage sites were further determined by the HMBC spectrum (*Fig. 4*), in which the key correlations of H–C(7″) (δ(H) 3.26) with C(3) (δ(C) 197.0), C(4) (δ(C) 70.6), and C(5) (δ(C) 197.1) were observed. Thus, **3** was established to be (1*E*,6*E*)-1,7-bis(4-hydroxyphenyl)-4-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl]hepta-1,6-diene-3,5-dione.

The known compound was identified as longiferone B (**4**) by comparing its spectroscopic data with those reported [13].

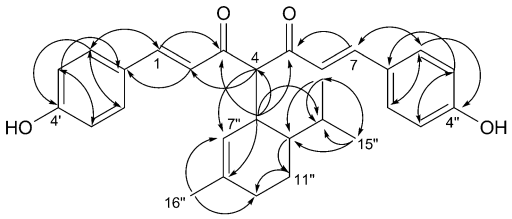

Fig. 4. *Selected HMBCs* (H → C) *of* **3**

Experimental Part

General. TLC: Silica gel GF_{254} (SiO_2; *Qingdao Marine Chemical Factory*, Qingdao, P. R. China). Column chromatography (CC): SiO_2 (100–200 and 200–300 mesh; *Qingdao Marine Chemical Factory*), *Sephadex LH-20* (*Amersham Biosciences*, Uppsala, Sweden), *MCI* gel *CHP 20P* (75–150 μm, *Mitsubishi Chemical Corp.*, Tokyo, Japan), and *Chromatorex C-18* (40–75 μm, *Fuji Silysia Chemical Ltd.*, Japan). Optical rotations: *Jasco P-1020* digital polarimeter. UV Spectra: *Agilent 1200* HPLC; λ_{max} in nm. IR Spectra: *Bruker Tensor 27 FT-IR* spectrometer; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker Avance III 600* spectrometer; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI-MS and HR-ESI-MS: *Agilent 6230 TOF* mass spectrometer; in m/z (rel. %).

Plant Material. C. aromatica was collected from Yunnan Province, P. R. China, in July, 2011, and identified by Mr. *Yu Chen* of Kunming Institute of Botany, CAS. A voucher specimen (No. BBP0372) was deposited at *BioBioPha*.

Extraction and Isolation. Dried and powdered *C. aromatica* (4.0 kg) were extracted with 95% aq. EtOH (3 × 15 l) at r.t. for 7 d. The EtOH extract was evaporated to yield a thick, dark extract (*ca.* 300 g), which was subjected to CC (SiO_2; petroleum ether (PE)/acetone 10:1 → 0:1) to yield eight fractions. *Fr. 1* (15 g) was further separated by CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1; SiO_2; PE/Acetone 200:1) to afford **4** (1.61 g). *Fr. 6* (25 g) was subjected to CC (SiO_2; $CHCl_3$/MeOH 100:1 → 50:1) to give four fractions. *Fr. 6.1* (3 g) was further separated by CC (*MCI* gel *CHP 20P*; MeOH/H_2O 70% → 85%; *Sephadex LH-20*; MeOH) to afford **1** (14 mg). *Fr. 6.3* (5 g) was separated by CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1; *MCI* gel *CHP 20P*; MeOH/H_2O 80% → 85%; *Sephadex LH-20*; MeOH) to afford **2** (11 mg). *Fr. 6.4* (3 g) was separated by CC (*Sephadex LH-20*; $CHCl_3$/MeOH 1:1; *Sephadex LH-20*; MeOH; *Chromatorex C-18*; MeOH/H_2O 8:2; SiO_2; $CHCl_3$/MeOH 40:1) to afford **3** (71 mg).

Curcumaromin A (= *(1*E*,4*Z*,6*E*)-5-Hydroxy-7-{4-hydroxy-3-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)-cyclohex-2-en-1-yl]phenyl}-1-(4-hydroxyphenyl)hepta-1,4,6-trien-3-one*; **1**). Orange powder. $[\alpha]_D^{17.5} = -237.0$ ($c = 0.1$, MeOH). UV (MeOH): 423. IR (KBr): 3423, 1623, 1599, 1512, 1438. ^{1}H- and ^{13}C-NMR ((D_6)DMSO): see *Table*. HR-ESI-MS: 445.2375 ($[M+H]^+$, $C_{29}H_{33}O_4^+$; calc. 445.2379).

Curcumaromin B (= *2,3-Dihydro-2-(4-hydroxyphenyl)-6-[(*E*)-2-(4-hydroxyphenyl)ethenyl]-5-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl]-4*H*-pyran-4-one*; **2**). Yellow powder. $[\alpha]_D^{17.6} = +17.0$ ($c = 0.1$, MeOH). UV (MeOH): 370. IR (KBr): 3417, 1600, 1516, 1443. ^{1}H- and ^{13}C-NMR ((D_6)acetone): see *Table*. HR-ESI-MS: 445.2371 ($[M+H]^+$, $C_{29}H_{33}O_4^+$; calc. 445.2379).

Curcumaromin C (= *(1*E*,6*E*)-1,7-Bis(4-hydroxyphenyl)-4-[(1*R**,6*R**)-3-methyl-6-(propan-2-yl)cyclohex-2-en-1-yl]hepta-1,6-diene-3,5-dione*; **3**). Yellow powder. $[\alpha]_D^{17.5} = -149.7$ ($c = 0.1$, MeOH). UV (MeOH): 346. IR (KBr): 3406, 1598, 1579, 1512, 1440. ^{1}H- and ^{13}C-NMR (CD_3OD): see *Table*. HR-ESI-MS: 467.2193 ($[M+Na]^+$, $C_{29}H_{32}NaO_4^+$; calc. 467.2198).

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