New Diarylheptanoids and Kavalactone from *Alpinia katsumadai* HAYATA

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Two new diarylheptanoids, katsumains A (**1**) and B (**2**), and one new kavalactone, katsumadain (**3**), together with the three known compounds (4*E*,6*E*)-1,7-diphenylhepta-4,6-dien-3-one (**4**), (5*R*,6*E*)-1,7-diphenyl-5-hydroxyhept-6-en-3-one (**5**), and cardamonin (**6**), were isolated from the seeds of *Alpinia katsumadai* HAYATA. Their structures were elucidated mainly by spectroscopic methods (1D- and 2D-NMR) and by mass spectrometry (HR-ESI-MS). Besides, the erroneous nomenclatures for (+)-linderatin and (+)-neolinderatin as given in [10][11] were corrected to be 2′,4′,6′-trihydroxy-3′-[(3*R*,4*R*)-4-isopropyl-1-methylcyclohex-1-en-3-yl]dihydrochalcone for (+)-linderatin and 2′,4′,6′-trihydroxy-3′,5′-bis[(3*R*,4*R*)-4-isopropyl-1-methylcyclohex-1-en-3-yl]dihydrochalcone for (+)-neolinderatin, respectively.

Introduction. – *Alpinia katsumadai* HAYATA (Zingiberaceae) occurs mainly in the Hainan, Guangxi, and Guangdong provinces in southern China, and the seeds of this plant are recorded in the Chinese Pharmacopoeia as Semen Alpinae Katsumadai (Cao Dou Kou in Chinese) for treatments of gastric disorders such as epigastric distension, nausea, vomiting, and anorexia [1]. Previous investigations of *A. katsumadai* have reported a variety of diarylheptanoids, flavonoids, monoterpenes, stilbenes, and diphenylpropanoids [2–4], among which the diarylheptanoids and flavonoids indicated potential bioactivities on antibiosis and vasorelaxation, and as anti-emetic compounds [5–7]. In our continuous investigation into the screening of bioactive lead compounds from *Alpinia* plants [4–6], we describe in this article the isolation and structure determination of two new diarylheptanoids bearing a chalcone moiety, namely katsumains A[1]) (**1**) and B[1]) (**2**), one new kavalactone, katsumadain[1]) (**3**), along with the three known compounds (4*E*,6*E*)-1,7-diphenylhepta-4,6-dien-3-one (**4**), (5*R*,6*E*)-1,7-diphenyl-5-hydroxyhept-6-en-3-one (**5**), and cardamonin (**6**) from the seeds of *A. katsumadai* (*Fig. 1*).

Results and Discussion. – The powdered seeds were extracted with 70% EtOH to give the crude extract (4 kg). The total extract was suspended in H_2O and partitioned

[1]) Trivial atom numbering; for systematic names, see *Exper. Part.*

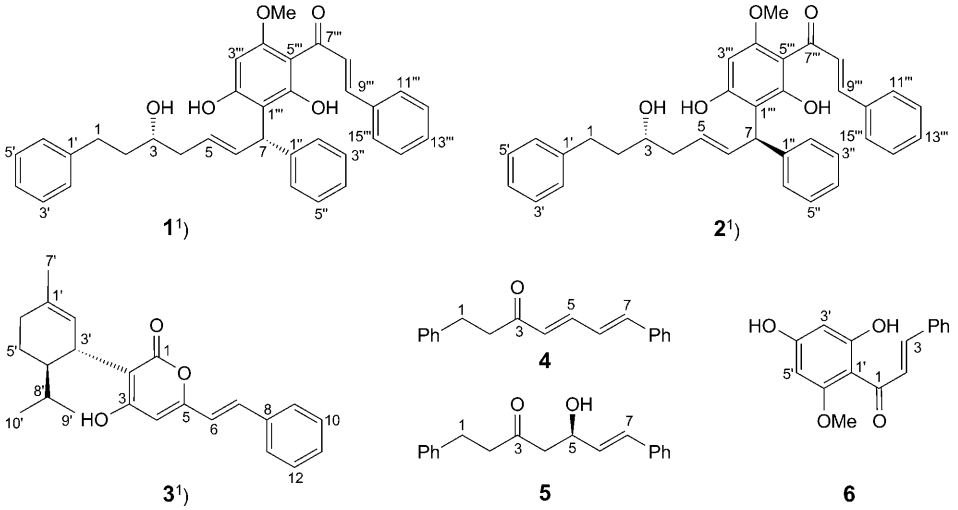

Fig. 1. *Compounds* **1**–**6** *isolated from the seeds of* Alpinia katsumadai HAYATA

successively with AcOEt and BuOH. The AcOEt fraction was separated by column chromatography on silica gel and *ODS* C_{18} repeatedly, followed by *Sephadex LH-20* column chromatography and prep. reversed-phase HPLC, affording the three new compounds **1**–**3** and the three known ones **4**–**6**. The structures of the known compounds were confirmed by comparison of their physical and spectral data with the reported data, as (4*E*,6*E*)-1,7-diphenylhepta-4,6-dien-3-one [2] (**4**), (5*R*,6*E*)-1,7-diphenyl-5-hydroxyhept-6-en-3-one [2] (**5**), and cardamonin [2] (**6**).

Compound **1** was an optically active pale yellow amorphous solid, whose molecular formula was determined as $C_{35}H_{34}O_5$ by positive-ion HR-ESI-MS (*m*/*z* 557.2314, $[M+Na]^+$, $C_{35}H_{34}NaO_5^+$). The IR spectrum indicated the presence of OH (3448 cm^{-1}) and ketone (1604 cm^{-1}) functional groups and aromatic rings (1567, 1514, and 1449 cm^{-1}). The ^{1}H- and ^{13}C-NMR data of **1** (*Table 1*) showed the presence of three CH_2 (δ(C) 33.1 (C(1)), 39.7 (C(2)), and 41.7 (C(4))), one OH-bearing CH (δ(C) 72.1 (C(3)); δ(H) 3.52–3.57 (H–C(3))), and one CH group (δ(C) 44.3 (C(7)); δ(H) 5.14 (H–C(7)), assigned by the HSQC spectrum. Two sets of *trans* C=C bonds (δ(C) 128.6 (C(5)) and 135.3 (C(6)); δ(H) 5.50–5.56 (H–C(5)) and 6.29 (H–C(6)); δ(C) 129.5 (C(8‴)) and 142.7 (C(9‴)); δ(H) 7.83 (H–C(8‴)) and 7.57 (H–C(9‴))) were indicated by their coupling constants (J = 15.4 and J = 15.6 Hz, resp.). One C=O at δ(C) 194.1 (C(7‴)), one MeO at δ(C) 56.5 and δ(H) 3.80, and 24 sp^2 aromatic C-atoms were also evident. These observations indicated that **1** has a diarylheptanoid structure containing a chalcone (=1,3-diphenylprop-2-en-1-one) moiety. In the HMBC spectrum of **1** (*Fig. 2*), the cross-peaks δ(H) 5.14 (H–C(7))/δ(C) 145.9 (C(1″)), 128.8 (C(2″,6″)), 128.6 (C(5)), and 135.3 (C(6)), δ(H) 2.59–2.65 and 2.48–2.54 (CH_2(1))/δ(C) 144.0 (C(1′)), 129.7 (C(2′,6′)), 39.7 (C(2)), and 72.1 (C(3)), δ(H) 5.50–5.56 (H–C(5))/δ(C) 72.1 (C(3)) and 41.7 (C(4)) confirmed the presence of the diarylheptanoid part. The correlations δ(H) 7.57 (H–C(9‴))/δ(C) 129.5 (C(8‴)), 137.3 (C(10‴)), and 129.5 (C(11‴,15‴)), δ(H) 7.83 (H–C(8‴))/δ(C) 194.1 (C(7‴)), 142.7 (C(9‴)), and 137.3

Table 1. *^{1}H- and ^{13}C-NMR Data* of **1**[1]) *and* **2**[1]). δ in ppm, J in Hz.

	1		**2**	
	δ(H)[a])	δ(C)[b])	δ(H)[a])	δ(C)[b])
CH_2(1)	2.59–2.65 (*m*), 2.48–2.54 (*m*)	33.1	2.59–2.65 (*m*), 2.48–2.54 (*m*)	33.0
CH_2(2)	1.69–1.72 (*m*), 1.55–1.57 (*m*)	39.7	1.67–1.74 (*m*), 1.58–1.60 (*m*)	39.7
H–C(3)	3.52–3.57 (*m*)	72.1	3.49–3.54 (*m*)	72.0
CH_2(4)	2.20 (*t*, *J* = 6.2)	41.7	2.20 (*q-like*, *J* = 7.2)	41.9
H–C(5)	5.50–5.56 (*m*)	128.6	5.48–5.54 (*m*)	128.6
H–C(6)	6.29 (*dd*, *J* = 15.4, 8.7)	135.3	6.28 (*dd*, *J* = 15.4, 8.7)	135.4
H–C(7)	5.14 (*d*, *J* = 8.7)	44.3	5.14 (*d*, *J* = 8.7)	44.3
H–C(1′)		144.0		144.0
H–C(2′,6′)	7.01–7.02 (*m*)	129.7	7.04–7.06 (*m*)	129.6
H–C(3′,5′)	7.09–7.11(*m*)	128.9	7.08–7.10 (*m*)	128.9
H–C(4′)	6.98–7.00 (*m*)	126.9	6.97–6.98 (*m*)	126.8
H–C(1″)		145.9		145.9
H–C(2″,6″)	7.12–7.14 (*m*)	128.8	7.13–7.15 (*m*)	128.8
H–C(3″,5″)	7.07–7.08 (*m*)	129.5	7.07–7.09 (*m*)	129.5
H–C(4″)	6.95–6.97 (*m*)	126.5	6.95–6.97 (*m*)	126.5
C(1‴)		112.3		112.3
C(2‴)		165.0		165.3
H–C(3‴)	5.94 (*s*)	92.6	5.94 (*s*)	92.7
C(4‴)		163.3		163.3
C(5‴)		106.8		106.8
C(6‴)		166.5		166.6
C(7‴)		194.1		194.0
H–C(8‴)	7.83 (*d*, *J* = 15.6)	129.5	7.83 (*d*, *J* = 15.6)	129.5
H–C(9‴)	7.57 (*d*, *J* = 15.6)	142.7	7.57 (*d*, *J* = 15.6)	142.7
C(10‴)		137.3		137.3
H–C(11‴,15‴)	7.50–7.53 (*m*)	129.5	7.51–7.53 (*m*)	129.5
H–C(12‴,14‴)	7.30–7.31 (*m*)	130.3	7.31–7.32 (*m*)	130.3
H–C(13‴)	7.27–7.29 (*m*)	131.3	7.28–7.30 (*m*)	131.3
MeO	3.80 (*s*)	56.5	3.80 (*s*)	56.5

[a]) Measured at 500 MHz. [b]) Measured at 125 MHz.

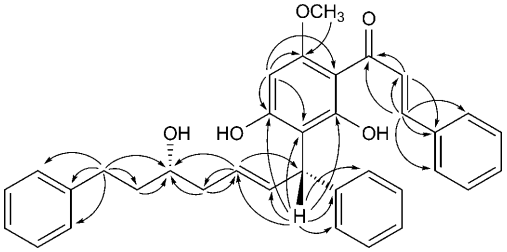

Fig. 2. *Selected HMBCs* (H → C) *of* **1**

(C(10‴)), and δ(H) 3.80 (MeO)/δ(C) 163.3 (C(4‴)) confirmed the presence of the chalcone part. The link position of the chalcone and the diarylheptanoid parts was determined by the correlations δ(H) 5.14 (H–C(7))/δ(C) 112.3 (C(1‴)), 165.0

(C(2‴)), and 166.5 (C(6‴)). Thus, the constitutional formula of **1** was established as shown in *Fig. 1*. The ^{1}H- and ^{13}C-NMR spectra of **1** were similar to the known compounds calyxin B (=(2*E*)-1-{2,4-dihydroxy-3-[(1*S*,2*E*,5*S*)-5-hydroxy-1,7-bis(4-hydroxyphenylhept-2-en-1-yl]-6-methoxyphenyl}-3-(4-hydroxyphenyl)prop-2-en-1-one) and epicalyxin B (=(2*E*)-1-{2,4-dihydroxy-3-[(1*R*,2*E*,5*S*)-5-hydroxy-1,7-bis(4-hydroxyphenylhept-2-en-1-yl]-6-methoxyphenyl}-3-(4-hydroxyphenyl)prop-2-en-1-one) [8].

The relative configuration at C(3) and C(7) was determined by comparison of the splitting patterns of CH_2(4) in the ^{1}H-NMR spectrum, and the absolute configuration by comparison of the optical activity with those of calyxin B and epicalyxin B [8]. Compound **1** was levorotatory and showed a *t* for CH_2(4) (δ(H) 2.20 (*t*, J = 6.2 Hz)) in the ^{1}H-NMR spectrum, identical to those of calyxins B and H [8][9]. The absolute configuration at C(3) and C(7) of **1** was determined to be (3*S*,7*S*). Thus, the structure of **1** was elucidated as (2*E*)-1-{2,4-dihydroxy-3-[(1*S*,2*E*,5*S*)-5-hydroxy-1,7-diphenylhept-2-en-1-yl]-6-methoxyphenyl}-3-phenylprop-2-en-1-one and named katsumain A.

Compound **2**, a pale yellow amorphous solid, was also optically active. The IR spectrum indicated the presence of OH (3434 cm^{-1}) and ketone (1600 cm^{-1}) functional groups and aromatic rings (1565, 1514, and 1450 cm^{-1}). The molecular formula was determined as $C_{35}H_{34}O_5$ by positive-ion HR-ESI-MS (*m*/*z* 557.2327 ($[M+Na]^+$, $C_{35}H_{34}NaO_5^+$)) and thus was the same as that of **1**, indicating that **2** was an isomer of **1**. The ^{1}H- and ^{13}C-NMR (*Table 1*) data of **2** were almost the same as those of **1**, except for the ^{1}H-NMR splitting pattern of CH_2(4), which was *q*-like in **2** but a *t* in **1**. The *q*-like splitting pattern of CH_2(4) (δ(H) 2.20 (*q*-like, J = 7.2 Hz)) and the optical-rotation sign of compound **2** were the same as those of epicalyxins B and H [8][9]. Therefore, the absolute configuration of **2** was determined to be (3*S*,7*R*) as shown in *Fig. 1*, and the structure of **2** was elucidated as (2*E*)-1-{2,4-dihydroxy-3-[(1*R*,2*E*,5*S*)-5-hydroxy-1,7-diphenylhept-2-en-1-yl]-6-methoxyphenyl}-3-phenylprop-2-en-1-one and named katsumain B.

Compound **3** was an optically active pale white powder. The molecular formula was determined as $C_{23}H_{26}O_3$ by negative-ion HR-ESI-MS (*m*/*z* 349.1790 ($[M-H]^-$, $C_{23}H_{25}O_3^-$)). The IR spectrum showed absorption bands for OH (3432 cm^{-1}) and conjugated C=O (1649 cm^{-1}) groups. The ^{1}H-NMR spectrum of **3** (*Table 2*) indicated the presence of one Ph group (δ(H) 7.57–7.32 (5 H)), a pair of *trans*-positioned olefinic H-atoms (δ(H) 7.38 (H–C(7)) and 6.77 (H–C(6), J = 16 Hz each)), and three Me groups (δ(H) 0.77 (Me(9′)), 0.84 (Me(10′)), and 1.64 (Me(7′))). The ^{13}C-NMR spectrum of **3** (*Table 2*) showed the presence of two CH_2 groups (δ(C) 24.3 (C(5′)) and 32.1 (C(6′))), three CH groups (δ(C) 30.3 (C(8′)), 37.5 (C(3′)), and 42.4 (C(4′))).

In the HMBC experiments with **3** (*Fig. 3*), the Me signals at δ(H) 0.77 (Me(9′)) and 0.84 (Me(10′))) showed correlations with the signals at δ(C) 30.3 (C(8′)) and 42.4 (C(4′)), and the Me signal at δ(H) 1.64 (Me(7′)) showed correlations with the signals at δ(C) 32.1 (C(6′)), 125.6 (C(2′)), and 135.1 (C(1′)). These observations together with the CH_2 and CH ^{1}H,^{1}H-correlation shown in *Fig. 3* suggested that **3** is a 3-substituted menthene derivative with a freely rotating side-chain [10][11]. The olefinic H-atoms at δ(H) 7.38 (H–C(7)) and 6.77 (H–C(6)) correlated with a quaternary C-atom at δ(C) 158.8 (C(5)) and the aromatic C-atom at δ(C) 137.2 (C(8)). The olefinic H–C(4) (δ(H) 6.16 (*s*)) showed correlations with the quaternary C-atoms at δ(C) 158.8 (C(5)),

Table 2. *^{1}H- and ^{13}C-NMR Data of* **3**[1]). δ in ppm, J in Hz.

	δ(H)[a])	δ(C)[b])
C(1)		166.7
C(2)		108.4
C(3)		168.5
H–C(4)	6.16 (*s*)	102.9
C(5)		158.8
H–C(6)	6.77 (*d*, *J* = 16.0)	120.4
H–C(7)	7.38 (*d*, *J* = 16.0)	136.0
C(8)		137.2
H–C(9,13)	7.55–7.57 (*m*)	128.7
H–C(10,12)	7.35–7.37 (*m*)	130.2
H–C(11)	7.29–7.32 (*m*)	130.5
C(1′)		135.1
H–C(2′)	5.08 (*s*)	125.6
H–C(3′)	3.59 (*d*, *J* = 9.1)	37.5
H–C(4′)	2.07–2.09 (*m*)	42.4
CH_2(5′)	1.27–1.36 (*m*), 1.74–1.76 (*m*)	24.3
CH_2(6′)	1.94–1.97 (*m*), 2.11–2.14 (*m*)	32.1
Me(7′)	1.64 (*s*)	23.9
H–C(8′)	1.56–1.58 (*m*)	30.3
Me(9′)	0.77 (*d*, *J* = 7.0)	17.2
Me(10′)	0.84 (*d*, *J* = 7.0)	22.1

[a]) Measured at 500 MHz. [b]) Measured at 125 MHz.

168.5 (C(3)), and 108.4 (C(2)). These observations indicated the presence of a yangonin-like moiety [7] (yangonin = 4-methoxy-6-[(1*E*)-2-(4-methoxyphenyl)ethenyl]-2*H*-pyran-2-one). The attachment of the 3-substituted menthene moiety at C(2) was established by HMBCs from H–C(3′) (δ(H) 3.59 (*d*, *J* = 9.1 Hz)) to δ(C) 108.4 (C(2)). The ^{1}H,^{1}H-COSY data (*Fig. 3*) confirmed the structure of **3**.

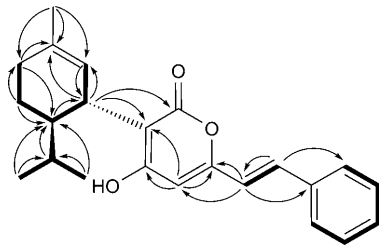

Fig. 3. *Selected HMBCs* (H → C) *and ^{1}H,^{1}H-COSY* (—) *of* **3**

The configuration at C(3′) and C(4′) of **3** was deduced from the ^{1}H-NMR and NOESY data. The position of H–C(3′) and H–C(4′) was established by the relevant ^{1}H,^{1}H-COSY. The large coupling constant (J = 9.1 Hz) for H–C(3′) showed that the menthene moiety had a 3′,4′ *trans*-configuration. The absolute configuration at C(3′) and C(4′) was determined by comparison of the sign of the optical activity of **3** with that of the known compounds (+)-linderatin (= 3-phenyl-1-{2,4,6-trihydroxy-3-[(1*R*,3*R*)-3-

methyl-6-(1-methylethyl)cyclohex-2-en-1-yl]phenyl}propan-1-one) and (+)-neolinderatin (= 3-phenyl-1-{2,4,6-trihydroxy-3,5-bis[(1*R*,3*R*)-3-methyl-6-(1-methylethyl)cyclohex-2-en-1-yl]phenyl}propan-1-one). Compound **3** was dextrorotatory, as (+)-linderatin [10][11]. Thus, the absolute configuration at C(3′) and C(4′) was determined to be (3′*R*,4′*R*). The correlation from H–C(3′) to H–C(8′) and Me(9′) in the NOESY (*Fig. 4*) confirmed the stereostructure of **3**. Thus, the structure of **3** was determined as 4-hydroxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)cyclohex-2-en-1-yl]-6-[(1*E*)-2-phenylethenyl]-2*H*-pyran-2-one and named katsumadain (*Fig. 1*).

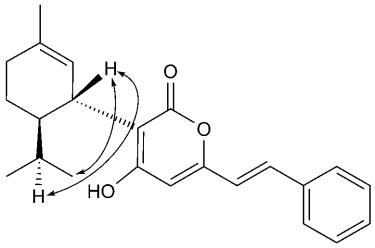

Fig. 4. *Key NOESY* (↔) *correlations of* **3**

We found that the absolute configuration at C(3) of the cyclohex-1-en-3-yl moieties of (+)-linderatin and (+)-neolinderatin in [10][11] is (3*R*), and not (3*S*) as expressed in those articles. Thus, the name of (+)-linderatin and (+)-neolinderatin should be 2′,4′,6′-trihydroxy-3′-[(3*R*,4*R*)-4-isopropyl-1-methylcyclohex-1-en-3-yl]dihydrochalcone and 2′,4′,6′-trihydroxy-3′,5′-bis[(3*R*,4*R*)-4-isopropyl-1-methylcyclohex-1-en-3-yl]dihydrochalcone (for the systematic name of (+)-linderatin and (+)-neolinderatin, see above).

Experimental Part

General. TLC: silica gel GF_{254} plates (SiO_2; *Qingdao Ocean Chemical Co., Ltd.*, Qingdao, P. R. China). Column chromatography (CC): SiO_2 (100–200 or 200–300 mesh; *Qingdao Ocean Chemical Co., Ltd.*, Qingdao, P. R. China), *ODS* (*SepaxGP-*C_{18}, 40–60 μm, HPLC packing material), *Sephadex LH-20* (*GE-Healthcare Bio-Sciences AB*), *Ultimate XB-*C_{18} column (250 × 4.6 mm, 5 μm, *Welch Materials Inc.*). HPLC: *Agilent* HPLC series *1100* (*Agilent*, Waldbronn, Germany), equipped with ChemStation software, a *G1322A* degasser, a *G1312A* binary gradient pump, a *G1313A* autosampler, a *G1316A* column oven, and a *G1315A* diode array detector. Optical rotations: *Krüss-P800-T* polarimeter. UV Spectra: *TU-1901* spectrometer (*Beijing Purkinje General Instrument Co., Ltd.*). IR Spectra: *Nicolet*™-*380* spectrometer from *Thermo Electron*; $\tilde{\nu}$ in cm^{-1}. 1D- and 2D-NMR Spectra: *Bruker-AV-500* or *Bruker-AV-400* instruments; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS: *Premior-Q-TOF* spectrometer; in *m*/*z* (rel. %).

Plant Material. The seeds of *Alpinia katsumadai* were collected in Hainan Province, P. R. China, in April 2007, and identified by *Li-Hong Wu* (Shanghai R&D Center for Standardization of Chinese Medicines). A voucher specimen (No. 07-04-29) was deposited with the Herbarium of Shanghai R&D Center for Standardization of Chinese Medicines.

Extraction and Column Chromatography. The air-dried, powdered seeds of *Alpinia katsumadai* (18 kg) were extracted with 70% EtOH (3 × 120 l) under reflux for 2.0 h. After removal of EtOH by evaporation, the resulting residue (4 kg) was suspended in H_2O (8 l) and extracted successively with AcOEt (1 × 4 l, 2 × 3 l) and BuOH (1 × 4 l, 2 × 3 l). The AcOEt fraction (1 kg) was subjected to CC (SiO_2, gradient petroleum ether/AcOEt 50:1 → AcOEt): *Fractions 1–6* (by TLC). *Fr. 2* (150 g) was

subjected to CC (SiO_2, gradient petroleum ether/AcOEt 30:1 → 10:1): *Frs. 2a–2c. Fr. 2b* (30 g) was recrystallized from MeOH: **4** (20 g). *Fr. 4* (200 g) was subjected to CC (SiO_2, gradient petroleum ether/CH_2Cl_2 10:1 → CH_2Cl_2): *Frs. 4a–4f. Fr. 4c* (15 g) was submitted successively to CC (SiO_2, petroleum ether/CH_2Cl_2 1:1) and CC (*Sephadex LH-20*, MeOH): **5** (300 mg). *Fr. 4d* (20 g) was subjected to CC (*ODS*, MeOH/H_2O 3:7), and the crude isolate was recrystallized from MeOH: **3** (76 mg). *Fr. 4e* (7 g) was submitted to repeated CC (SiO_2, CH_2Cl_2) and reversed-phase HPLC (*Ultimate XB-C_{18}* (4.6 × 250 mm), MeOH/H_2O 79:21, flow rate 1 ml/min): **1** (12.9 mg) and **2** (7.5 mg). *Fr. 5* (100 g) was subjected to CC (SiO_2, gradient petroleum ether/AcOEt 10:1 → 1:1): *Frs. 5a–5c. Fr. 5b* (35 g) was recrystallized from AcOEt: **6** (25 g).

*(2*E*)-1-{2,4-Dihydroxy-3-[(1*S*,2*E*,5*S*)-5-hydroxy-1,7-diphenylhept-2-en-1-yl]-6-methoxyphenyl}-3-phenylprop-2-en-1-one* (= *Katsumain A*; **1**): Pale yellow amorphous solid. $[\alpha]_D^{22} = -68.2$ ($c = 0.45$, MeOH). IR (KBr): 3448, 1604, 1567, 1514, 1449. ^{1}H- and ^{13}C-NMR: *Table 1*. HR-ESI-MS (pos.): 557.2314 ($[M+Na]^+$; calc. 557.2304).

*(2*E*)-1-{2,4-Dihydroxy-3-[(1*R*,2*E*,5*S*)-5-hydroxy-1,7-diphenylhept-2-en-1-yl]-6-methoxyphenyl}-3-phenylprop-2-en-1-one* (= *Katsumain B*; **2**): Pale yellow amorphous solid. $[\alpha]_D^{22} = +102$ ($c = 0.5$, MeOH). IR (KBr): 3434, 1600, 1565, 1514, 1450. ^{1}H- and ^{13}C-NMR: *Table 1*. HR-ESI-MS (pos.): 557.2327 ($[M+Na]^+$; calc. 557.2304).

*4-Hydroxy-3-[(1*R*,6*R*)-3-methyl-6-(1-methylethyl)-cyclohex-2-en-1-yl]-6-[(1*E*)-2-phenylethyl]-2*H*-pyran-2-one* (= *Katsumadain*; **3**): Pale white powder. $[\alpha]_D^{22} = +170$ ($c = 0.4$, MeOH). IR (KBr): 3432, 1649. ^{1}H- and ^{13}C-NMR: *Table 2*. HR-ESI-MS (neg.): 349.179 ($[M-H]^-$; calc. 349.1804).

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