Structures of New Sesquiterpenes from *Curcuma comosa*

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Received September 1, 2008; accepted October 7, 2008; published online October 10, 2008

From the methanolic extract of the rhizomes of *Curcuma comosa* cultivated in Thailand, six new sesquiterpenes, (+)- and (−)-comosols (1, 2), comosones I (3), II (4), and III (5), and dimethoxycurcumenone (6), were isolated. Their structures were elucidated on the basis of chemical and physicochemical evidence.

Key words *Curcuma comosa*; Zingiberaceae; sesquiterpene; comosol; comosone; dimethoxycurcumenone

Curcuma (*C.*) *comosa*, a member of the Zingiberaceae, is widely distributed in tropical and subtropical regions of Asia, especially Thailand, Indonesia, and Malaysia. The rhizome of *C. comosa* has been used extensively in indigenous medicine in Thailand as an antiinflammatory agent for the treatment of postpartum uterine bleeding. It has also been widely used as an aromatic stomachic.[1,2] Previous phytochemical investigations of this plant yielded diarylheptanoids.[3] In the course of our characterization studies of traditional Thai medicines,[4—17] six new sesquiterpenes named (+)- and (−)-comosols (**1**, **2**), comosones I (**3**), II (**4**), and III (**5**), and dimethoxycurcumenone (**6**) were isolated from the rhizomes of *C. comosa*.[18,19] Here we describe the isolation and structural elucidation of six new constituents (**1**—**6**).

Extraction and Isolation The methanolic extract from the dried rhizomes of *C. comosa* (cultivated in Thailand) was partitioned into the ethyl acetate (EtOAc)-soluble fraction and an aqueous layer. The aqueous layer was extracted with *n*-butanol (*n*-BuOH) to give *n*-BuOH- and H_2O-soluble fractions. The EtOAc-soluble fraction was subjected to silica gel and octa decyl silica (ODS) column chromatography and finally HPLC to furnish six new sesquiterpenes, (+)- and (−)-comosols as a mixture (**1** and **2**, 0.0030%, from natural medicine), comosones I (**3**, 0.00036%), II (**4**, 0.00082%), and III (**5**, 0.00021%), and dimethoxycurcumenone (**6**, 0.0038%) (Chart 1).

Structures of (+)- and (−)-Comosols (1, 2), Comosones I (3), II (4), and III (5), and Dimethoxycurcumenone (6) An enantiomeric mixture of (+)- and (−)-comosols (**1**, **2**) was isolated as a colorless oil with an optical rotation ($[\alpha]_D^{25}$ +1.2°). Its molecular formula was established to be $C_{15}H_{24}O_2$ by high-resolution (HR) electron impact (EI) MS analysis. Its structure including the relative configuration was determined by detailed analysis of the 1D and 2D NMR spectra (Fig. 1). However, in the process of determining its absolute structure using a modified Mosher's method, both (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester derivatives were found to be a mixture on the basis of their ^{1}H- and ^{13}C-NMR spectra, which indicated that the original compound was a mix**t**ure. Based upon its low optical rotation value and clear NOE spectrum, we assumed that it was an enantiomeric mixture. However, these (*R*)- or (*S*)-(MTPA) esters could not be separated using HPLC analysis with various types of chromatography including chiral. After many trials, successful resolution of the enantiomers was achieved based on its acetal formation using a highly efficient chiral resolving reagent, an alkenyl ether, (*S*)-5-allyl-2-oxabicyclo[3,3,0]oct-8-ene (ALBO) developed by Nemoto *et al.*[20,21]

Acetalization of an enantiomeric mixture (**1**, **2**) using ALBO in the presence of *p*-toluenesulfonic acid (*p*-TsOH) followed by silica gel column separation gave the acetals **1a** and **2a** in a *ca.* 1 : 1 ratio. Treatment of **1a** and **2a** with aqueous MeOH in the presence of *p*-TsOH furnished **1** and **2**, respectively, which were obtained as colorless oils with positive and negative optical rotations (**1**: $[\alpha]_D^{23}$ +34.7°; **2**: $[\alpha]_D^{22}$ −32.2°) (Chart 2). The EI-MS data of **1** and **2** showed a common molecular ion peak at *m/z* 236 $[M]^+$ together with a

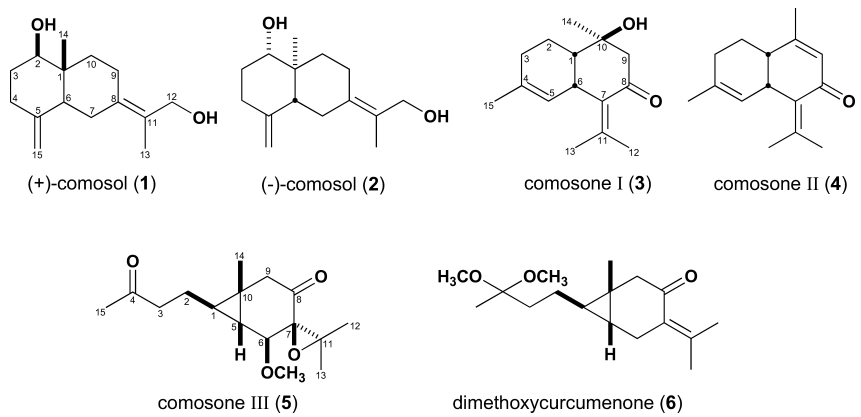

Chart 1. Structures of New Constituents Isolated from the Rhizomes of *C. comosa*

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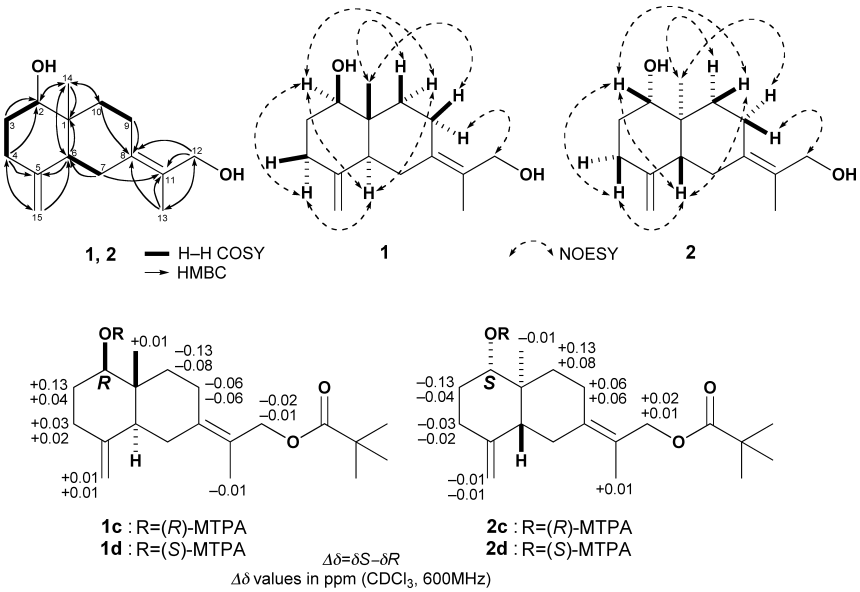
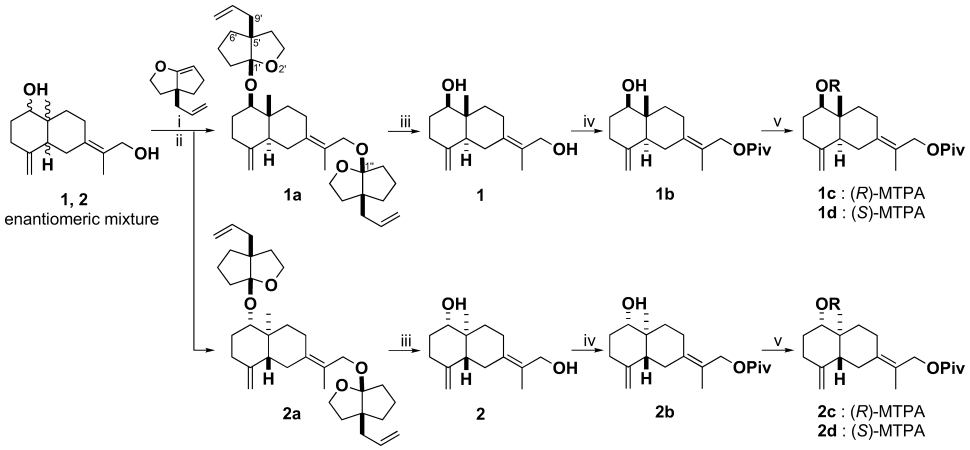


Fig. 1. Significant H–H COSY, HMBC, and NOE Correlations for **1** and **2** as Well as Application of Modified Mosher's Method to **1c**, **1d**, **2c**, and **2d**



Reagents and conditions: (i) (*S*)-5-allyl-2-oxabicyclo[3,3,0]oct-8-ene, *p*-TsOH, CH_2Cl_2, 0 °C; (ii) separation with SiO_2 column; (iii) *p*-TsOH, aqueous MeOH, r.t.; (iv) pivaloyl chloride, dry pyridine, r.t.; (v) (+)- or (−)-MTPA-Cl, dry pyridine, r.t.

Chart 2. Reactions Performed to Resolve an Enantiomeric Mixture and Determine Absolute Structures

fragment ion at *m/z* 218 $[M-H_2O]^+$ (base peak), and HR-EI-MS analysis revealed the molecular formula of **1** and **2** to be $C_{15}H_{24}O_2$. The IR spectra of **1** and **2** showed the same absorption band at 3420, 1655, 1541, and 754 cm^{-1} due to hydroxyl and olefin functions. The ^1H- and ^{13}C-NMR ($CDCl_3$, Table 1) spectra of **1** and **2**, which were assigned in various NMR experiments, also showed identical signals assignable to one tertiary methyl [δ 0.80 (3H, s, H_3-14)], one vinyl methyl [δ 1.79 (3H, s, H_3-13)], two methines, one of which bears an oxygen function [δ 1.73 (1H, br d, J=*ca.* 12 Hz, H-6), 3.39 (1H, dd, J=11.6, 4.1 Hz, H-2)], five methylenes {δ 1.16, 1.99 (1H each, both m, H_2-10), 1.59, 1.82 (1H each, both m, H_2-3), [1.88 (1H, dd, J=13.0, 11.7 Hz), 2.53 (1H, br d, J=*ca.* 13 Hz), H_2-7], [1.94 (1H, dd like, J=13.7 Hz), 2.67 (1H, br d, J=*ca.* 14 Hz), H_2-9], 2.10, 2.32 (1H each, both m, H_2-4)}, one methylene bearing an oxygen founction [δ 4.16 (2H, s, H_2-12)], one exomethylene [δ 4.57, 4.82 (1H each, both br s, H_2-15)]. ^1H–^1H correlation spectroscopy (^1H–^1H COSY) experiments on **1** and **2** indicated the presence of three partial structures (bold lines in Fig. 1). In the

Table 1. ^{13}C-NMR Data for **1**—**6**

	1	**2**	**3**	**4**	**5**	**6**
C-1	40.5	40.5	43.9	38.3	25.9	24.7
C-2	79.1	79.1	23.5	25.3	23.0	23.9
C-3	31.4	31.4	29.6	26.0	43.3	36.7
C-4	34.1	34.1	134.8	135.1	208.0	101.3
C-5	148.8	148.8	121.6	122.0	30.4	24.1
C-6	48.1	48.1	36.0	39.8	79.3	28.0
C-7	28.1	28.1	134.3	133.5	69.9	128.2
C-8	136.5	136.5	203.4	191.8	204.9	201.7
C-9	25.0	25.0	51.5	130.8	47.2	49.0
C-10	38.3	38.3	72.9	158.6	18.8	20.0
C-11	125.4	125.4	141.6	141.8	62.6	147.0
C-12	63.4	63.4	22.4	23.0	19.4	23.4
C-13	16.4	16.4	22.5	21.9	20.8	23.4
C-14	9.8	9.8	27.6	20.8	19.3	19.1
C-15	107.0	107.0	23.7	23.5	30.0	20.9
OCH_3					57.7	48.0
						48.0

Measured in $CDCl_3$ at 150 MHz.

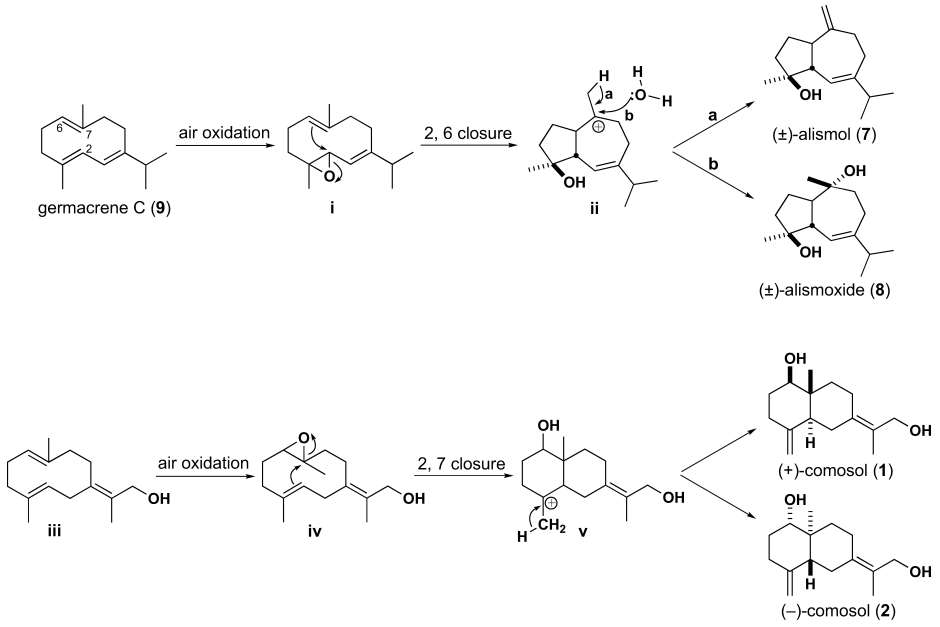


Chart 3. Assumed Biogenesis of **1**, **2**, **7**, and **8**

heteronuclear multiple-bond correlation (HMBC) experiment, long-range correlations were observed between the following protons and carbons: H-2 and C-14; H_2-3 and C-2; H_2-4 and C-2, 5, 15; H-6 and C-1, 5, 14; H_2-7 and C-6, 11; H_2-9 and C-8; H_2-10 and C-8, 14; H_2-12 and C-8, 11, 13; H_3-13 and C-8, 11, 12; H_3-14 and C-1, 2, 6, 10; and H_2-15 and C-4, 6. Furthermore, the relative stereostructures of **1** and **2** were characterized on the basis of the nuclear Overhauser effect spectroscopy (NOESY) experiment, in which correlations were observed between the following proton pairs: **1**: H-2α and H-4α, H-6, H-10α; H-4α and H-6; H-6 and H-10α; H-9α and H_2-12; and H-9β, H-10β and H_3-14; and **2**: H-2β and H-4β, H-6, H-10β; H-4β and H-6; H-6 and H-10β; H-9β and H_2-12; and H-9α, H-10α and H_3-14. Finally, the absolute configurations of **1** and **2** were determined using a modified Mosher's method.[22] Thus, **1** and **2** were treated with pivaloyl chloride to give **1b** and **2b**. Treatment of **1b** and **2b** with (+)- or (−)-α-methoxy-α-(trifluoromethyl) phenylacetyl chloride [(+)- or (−)-MTPA-Cl] afforded the (*R*)- or (*S*)-MTPA esters (**1c**, **1d**) and (**2c**, **2d**), respectively (Chart 2). As shown in Fig. 1, the protons attached to the C-3, -4, and -15 in the (*S*)-MTPA ester (**1d**) resonated at lower fields than those of the (*R*)-MTPA ester (**1c**) ($\Delta\delta$: positive), while the protons at C-9, -10, -12, and -13 of **1d** were observed at higher fields compared with those of **1c** ($\Delta\delta$: negative). On the other hand, the protons at the 9-, 10-, 12-, and 13-carbons of the (*S*)-MTPA ester (**2d**) appeared at lower fields than those of the (*R*)-MTPA ester (**2c**) ($\Delta\delta$: positive), while the protons at the 3-, 4-, and 15-carbons in **2d** were observed at higher fields compared to those of **2c** ($\Delta\delta$: negative). Consequently, the absolute configurations at the 2-position of **1** and **2** are *R* and *S*, respectively, and the total structures of enantiomers **1** and **2** were determined to be as shown.

Previously, alismol (**7**) and alismoxide (**8**) from *Alisma orientale* were reported to be secondary racemic products from germacrene C (**9**), as shown in Chart 3,[23] during the isolation procedure. In a similar manner, (+)- and (−)-comosols (**1**, **2**) were considered to be secondarily formed from a germacrane-type sesquiterpene (iii) as shown in Chart 3, starting with the epoxidation of iii, followed by epoxy-ring opening, 2,7-cyclization, and finally deprotonation.

Comosone I (**3**) was obtained as a colorless oil with positive optical rotation ($[\alpha]_D^{25}$ +15.4°). The EI-MS of **3** showed a molecular ion peak at *m/z* 234 $[M]^+$ and the molecular formula $C_{15}H_{22}O_2$ of **3** was determined from the molecular ion peaks and by HR-EI-MS measurement. Its IR spectrum showed absorption bands at 3430 and 1671 cm^{-1} due to hydroxyl and carbonyl functions, while its UV spectrum showed absorption maxima at 221 nm ($\log\varepsilon$ 3.78), which suggested the presence of an α,β-unsaturated ketone. The ^1H- and ^{13}C-NMR ($CDCl_3$, Table 1) spectra of **3** showed signals assignable to one tertiary methyl [δ 1.34 (3H, s, H_3-14)], three vinyl methyls [δ 1.65, 1.92, 1.92 (3H each, all s, H_3-15, 12, and 13)], three methylenes {δ 1.22, 1.74 (1H each, both m, H_2-2), 1.92 (2H, m, H_2-3), [2.35 (1H, dd, J=18.3, 1.6 Hz, H-9β), 2.50 (1H, d, J=18.3 Hz, H-9α)]}, two methines [δ 1.96 (1H, m, H-1), 3.74 (1H, br s, H-6)], and a trisubstituted olefin group [δ 5.33 (1H, br s, H-5)]. The planar structure of **3** was constructed on the basis of ^1H–^1H COSY and HMBC experiments. Thus, the ^1H–^1H COSY experiment on **3** indicated the presence of a partial structure as shown in the bold line in Fig. 2. In the HMBC experiment, long-range correlations were observed between the following protons and carbons: H-1 and C-10; H_2-2 and C-1, 3, 4, 6; H_2-3 and C-5; H-5 and C-1, 3, 6, 15; H_2-9 and C-1, 7, 8, 10, 14; H_3-12 and C-7, 11, 13; H_3-13 and C-7, 11, 12; H_3-14 and C-1, 9, 10; and H_3-15 and C-3, 4, 5. The relative stereostructure of **3** was determined by consideration of the ^1H–^1H couplings as well as difference NOE and NOESY experiments on **3** (Fig. 2). A small coupling constant between H-1 and H-6 suggested that the rings were *cis*-fused, and this was supported by the observation of an NOE at H-1 upon irradiation of H-6. On the basis of this evidence, the structure of **3** was determined to be as shown.

Comosone II (**4**) was isolated as a colorless oil with posi-

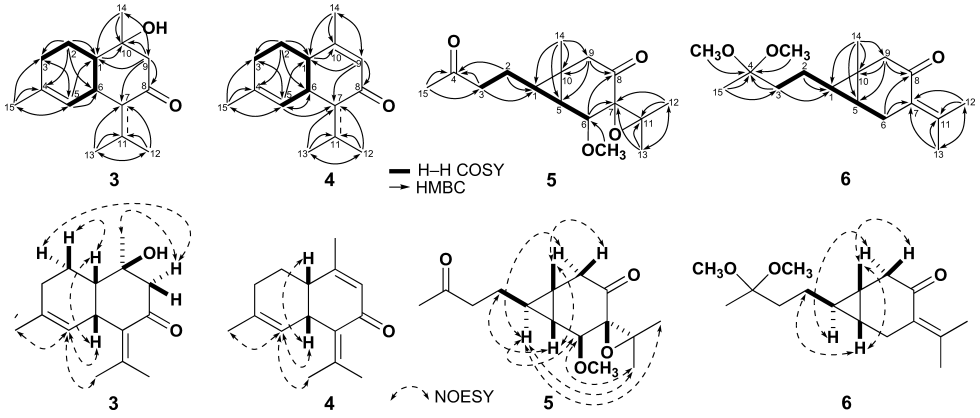


Fig. 2. Significant H–H COSY, HMBC, and NOE Correlations for **3**—**6**

tive optical rotation ($[\alpha]_D^{27}$ +10.1°). The molecular formula was established to be $C_{15}H_{20}O$ on the basis of HR-EI-MS measurement. The IR spectrum of **4** showed absorption bands at 1665, 1651 and 1615 cm^{-1} due to carbonyl and olefin functions, while its UV spectrum showed absorption maxima at 237 nm (log ε 3.77) which suggested the presence of an α,β-unsaturated ketone. The ^{1}H- and ^{13}C-NMR ($CDCl_3$, Table 1) spectra of **4** showed signals assignable to four vinyl methyls [δ 1.58, 1.87, 1.93, 2.06 (3H each, all s, H_3-15, 13, 14, 12], two methylenes [δ 1.82 (2H, m, H_2-3), 1.83, 2.20 (1H each, both m, H_2-2)], two methines [δ 2.75 (1H, m, H-1), 3.76 (1H, br s, H-6)], and two trisubstituted olefin groups [δ 4.92 (1H, br s, H-5), 5.90 (1H, s, H-9)]. By comparing the spectral characteristics of **4** with those of **3**, it was found that the signals due to a quaternary carbon bearing an oxygen at C-10 and a methylene disappeared, while the signals due to a trisubstituted olefin group were observed [(δ_C 130.8, δ_H 5.90); (δ_C 158.6)]. This evidence suggests that **4** possesses a dehydrated structure of **3**. This was confirmed in ^{1}H–^{1}H COSY and HMBC experiments. Thus, the former indicated the presence of a partial structure shown in the bold line in Fig. 2. In the HMBC experiment, long-range correlations were observed between the following proton and carbon pairs: H-1 and C-10; H_2-2 and C-1, 3, 4, 6; H_2-3 and C-5; H-5 and C-1, 3, 6, 7, 15; H_2-6 and C-5; H_2-9 and C-1, 7, 8, 14; H_3-12 and C-7, 11, 13; H_3-13 and C-7, 11, 12; H_3-14 and C-1, 9, 10; and H_3-15 and C-3, 4, 5. Its relative stereostructure was determined using a difference NOE experiment (Fig. 2). As in the case of **3**, irradiation of H-1 resulted in an enhancement at H-6, which indicated that the molecule of **4** also has a *cis* ring junction. On the basis of these findings, the structure of **4** was determined to be as shown.

Comosone III (**5**) was isolated as a colorless oil with positive optical rotation ($[\alpha]_D^{24}$ +23.9°). The molecular formula of **5** was established to be $C_{16}H_{24}O_4$ by HR-EI-MS measurement. Its IR spectrum suggested the presence of a carbonyl function (1713 cm^{-1}). The ^{1}H- and ^{13}C-NMR ($CDCl_3$, Table 1) spectra of **5** showed signals assignable to three methines, one of which bears an oxygen function [δ 0.79 (1H, ddd, J=8.1, 5.4, 5.4 Hz, H-1), 1.13 (1H, t like, J=*ca.* 5 Hz, H-5), 3.88 (1H, d, J=4.1 Hz, H-6)], four tertiary methyls [δ 1.18, 1.21, 1.39, 2.17 (3H each, all s, H_3-12, 14, 13, 15)], three methylenes [δ 1.64, 1.76 (1H each, both m, H_2-2), 2.56 (2H, t, J=7.6 Hz, H_2-3), 2.68, 2.77 (1H each, both d, J=19.9 Hz, H_2-9)], a methoxyl group [δ 3.43 (3H, s, OCH_3-6)]. By comparing the spectral characteristics of **5** with those of curcumenone,[24] it was found that the signals due to a tetrasubstituted double bond and a methylene at the 6-position disappeared, while the signals due to an epoxy group as well as a methine and a methoxy group were observed [δ_C (62.6, 69.9); (δ_C 79.3, δ_H 3.88); (δ_C 57.7, δ_H 3.43)], which indicates that **5** is an analogue of curcumenone. Its planar structure was confirmed by 2D NMR experiments. The ^{1}H–^{1}H COSY experiments on **5** indicated the presence of a partial structure shown in the bold line in Fig. 2. In the HMBC experiment, long-range correlations were observed between the following proton and carbon pairs: H_2-2 and C-1, -4; H_2-3 and C-1, -4; H-6 and C-7, -8; H_2-9 and C-5, -8, -10; H_3-12 and C-7, -11 -13; H_3-13 and C-7, -11, -12; H_3-14 and C-1, -5, -9, -10; H_3-15 and C-3, -4; and OCH_3-6 and C-6. Its relative configuration was clarified in a NOESY experiment, in which NOE correlations were observed between the following proton pairs: H-1 and H-6, H-9α, H_3-12, H_3-13; H-5 and H_2-2, H_3-14; H-6 and H_3-13; and H-9β and H_3-14. On the basis of this evidence, the structure of comosone III (**5**) was characterized as shown.

Dimethoxycurcumenone (**6**) was obtained as a colorless oil with negative optical rotation ($[\alpha]_D^{25}$ −10.1°). The molecular formula $C_{17}H_{28}O_3$ of **6** was determined by HR-EI-MS measurement. Its IR spectrum suggested the presence of a carbonyl (1682 cm^{-1}) function. Its UV spectrum showed absorption maxima at 255 nm (log ε 3.59) assignable to an α,β-unsaturated ketone. The signals in the ^{1}H- and ^{13}C-NMR spectra of **6** were found to be very similar to those of curcumenone, with the exception of the presence of a ketal group at the 4-position [δ_C 101.3, 48.0, 48.0; δ_H 3.15 (s), 3.15 (s)] instead of a carbonyl group (Table 1). The planar structure of **6** was confirmed by ^{1}H–^{1}H COSY and HMBC experiments, as shown in Fig. 2. In the NOESY experiment on **6**, NOE correlations were observed between the following proton pairs: H-1 and H-9α; H-5 and H_2-2, H_3-14; and H-9β and H_3-14. Based on those correlations, the relative configuration of **6** was elucidated. Furthermore, treatment of **6** with *p*-TsOH at room temperature (r.t.) yielded curcumenone. On the basis of this evidence, the absolute structure of **6** was determined to be as shown. It is likely that **6** is an artifact produced from curcumenone during the extraction.

Experimental

General Experimental Procedures The following instruments were used to obtain physical data: specific rotations, Horiba SEPA-300 digital polarimeter (l=5 cm); UV spectra, Shimadzu UV-1600 spectrometer; IR spectra, Shimadzu FTIR-8100 spectrometer; EI-MS, CI-MS, and high-resolution CI-MS, JEOL JMS-GCMATE mass spectrometer; FAB-MS and high-resolution MS, JEOL JMS-SX 102A mass spectrometer; ^{1}H-NMR spectra, JNM-LA500 (500 MHz) and JNM-ECA600 (600 MHz) spectrometers; ^{13}C-NMR spectra, JNM-LA500 (125 MHz) and JNM-ECL600 (150 MHz) spectrometers with tetramethylsilane as an internal standard; and HPLC detector, Shimadzu RID-6A refractive index and SPD-10A*vp* UV–VIS detectors. HPLC column, COSMOSIL 5C18-PAQ (250×4.6 mm intra diameter (i.d.) and (250×20 mm i.d.) columns were used for analytical and preparative purposes, respectively.

The following experimental conditions were used for chromatography: ordinary-phase silica gel column chromatography, Silica gel BW-200 (Fuji Silysia Chemical, Ltd., Aichi, Japan, 150—350 mesh); reversed-phase silica gel column chromatography, Chromatorex ODS DM1020T (Fuji Silysia Chemical, Ltd., 100—200 mesh); TLC, precoated TLC plates with Silica gel 60F_{254} (Merck, 0.25 mm) (ordinary phase) and Silica gel RP-18 F_{254S} (Merck, 0.25 mm) (reversed phase); reversed-phase HPTLC, precoated TLC plates with Silica gel RP-18 WF_{254S} (Merck, 0.25 mm); and detection was achieved by spraying with 1% $Ce(SO_4)_2$–10% aqueous H_2SO_4 followed by heating.

Plant Material The rhizomes of *C. comosa* were cultivated in Thailand in July 2006 and identified by one of authors (Yutana Pongpiriyadacha). A voucher specimen (No. T-32) is on file in our laboratory.

Extraction and Isolation The rhizomes of *C. comosa* (4.5 kg) were powdered and extracted three times with methanol (MeOH) under reflux for 3 h. Evaporation of the solvent under reduced pressure gave the methanolic extract (332 g, 7.4%). The MeOH extract (302 g) was partitioned into an EtOAc–H_2O (1 : 1, v/v) mixture, and removal of the solvent *in vacuo* yielded an EtOAc-soluble fraction (174 g, 4.2%) and an aqueous phase. The aqueous phase was further extracted with *n*-BuOH to give an *n*-BuOH-soluble fraction (27 g, 0.7%) and an H_2O-soluble fraction (101 g, 2.5%).

The EtOAc-soluble fraction (166.7 g) was subjected to ordinary-phase silica gel column chromatography [2.5 kg, *n*-hexane–EtOAc (100 : 0→50 : 1→20 : 1→10 : 1→5 : 1→1 : 1, v/v)→$CHCl_3$–MeOH (50 : 1→20 : 1→10 : 1→5 : 1→1 : 1, v/v)→MeOH] to give 11 fractions [Fr. 1 (6.76 g), Fr. 2 (20.74 g), Fr. 3 (12.09 g), Fr. 4 (17.54 g), Fr. 5 (13.11 g), Fr. 6 (26.99 g), Fr. 7 (19.92 g), Fr. 8 (22.43 g), Fr. 9 (4.59 g), Fr. 10 (7.65 g), and Fr. 11 (6.57 g)]. Fr. 3 (12.09 g) was subjected to reversed-phase silica gel column chromatography [360 g, MeOH–H_2O (55 : 45→60 : 40→65 : 35→70 : 30, v/v)→MeOH)] to give 12 fractions [Fr. 3-1 (12 mg), Fr. 3-2 (16 mg), Fr. 3-3 (49 mg), Fr. 3-4 (39 mg), Fr. 3-5 (3386 mg), Fr. 3-6 (652 mg), Fr. 3-7 (484 mg), Fr. 3-8 (918 mg), Fr. 3-9 (1631 mg), Fr. 3-10 (90 mg), Fr. 3-11 (448 mg), and Fr. 3-12 (4192 mg)]. Fr. 3-7 (484 mg) was purified using HPLC [CH_3OH–H_2O (60 : 40, v/v)] to give comosone II (**4**, 32.1 mg, 0.00082%). Fr. 5 (13.11 g) was subjected to reversed-phase silica gel column chromatography [390 g, MeOH–H_2O (40 : 60→45 : 55→50 : 50→55 : 45, v/v)→MeOH)] to give 11 fractions [Fr. 5-1 (28 mg), Fr. 5-2 (34 mg), Fr. 5-3 (79 mg), Fr. 5-4 (66 mg), Fr. 5-5 (259 mg), Fr. 5-6 (207 mg), Fr. 5-7 (131 mg), Fr. 5-8 (662 mg), Fr. 5-9 (3277 mg), Fr. 5-10 (1887 mg), and Fr. 5-11 (6465 mg)]. Fr. 5-9 (3277 mg) was subjected to silica gel column chromatography [100 g, hexane–EtOAc 5 : 1] to give 11 fractions [Fr. 5-9-1 (28 mg), Fr. 5-9-2 (407 mg), Fr. 5-9-3 (84 mg), Fr. 5-9-4 (213 mg), Fr. 5-9-5 (118 mg), Fr. 5-9-6 (503 mg), Fr. 5-9-7 (585 mg), Fr. 5-9-8 (56 mg), Fr. 5-9-9 (113 mg), Fr. 5-9-10 (25 mg), and Fr. 5-9-11 (87 mg)]. Fr. 5-9-4 (213 mg) was purified by silica gel column chromatography [6 g, *n*-hexane–EtOAc 8 : 1] to give dimethoxycurcumenone (**6**, 149.3 mg, 0.0038%). Fr. 5-9-8 (56 mg) was separated by HPLC [CH_3OH–H_2O (60 : 40, v/v)] to give comosone I (**3**, 14.1 mg, 0.00036%). Fr. 5-9-11 (87 mg) was purified by HPLC [CH_3OH–H_2O (40 : 60, v/v)] to give comosone III (**5**, 8.1 mg, 0.00021%). Fraction 7 (19.92 g) was subjected to reversed-phase silica gel column chromatography [600 g, MeOH–H_2O (20 : 80→25 : 75→30 : 70→40 : 60, v/v)→MeOH]] to give 13 fractions [Fr. 7-1 (221 mg), Fr. 7-2 (905 mg), Fr. 7-3 (78 mg), Fr. 7-4 (543 mg), Fr. 7-5 (608 mg), Fr. 7-6 (342 mg), Fr. 7-7 (1112 mg), Fr. 7-8 (753 mg), Fr. 7-9 (618 mg), Fr. 7-10 (5090 mg), Fr. 7-11 (5211 mg), Fr. 7-12 (1374 mg), and Fr. 7-13 (598 mg)]. Fr. 7-12 (302 mg) was purified by HPLC [CH_3OH–H_2O (60 : 40, v/v)] to give (±)-comosol (**1** and **2**, 25.6 mg, 0.0030%).

An Enantiomeric Mixture of (+)- and (−)-Comosol (**1**, **2**): A colorless oil, $[\alpha]_D^{25}$ +1.2° (c=0.8, $CHCl_3$). EI-MS m/z: 236 [M^+] (6), 218 [$M-H_2O$]$^+$ (100). HR-EI-MS m/z: 236.1772 (Calcd for $C_{15}H_{24}O_2$: 236.1776).

Comosone I (**3**): A colorless oil, $[\alpha]_D^{25}$ +15.4° (c=0.80, MeOH). UV λ_{max} (MeOH) nm (log ε): 221 (3.78). IR (film) cm^{-1}: 3430, 1671, 1610, 1377, 1102, 754. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.22, 1.74 (1H each, both m, H_2-2), 1.34, 1.65, 1.92, 1.92 (3H each, all s, H_3-14, 15, 12, 13), 1.92 (2H, m, H_2-3), 1.96 (1H, m, H-1), 2.35 (1H, dd, J=18.3, 1.6 Hz, H-9β), 2.50 (1H, d, J=18.3 Hz, H-9α), 3.74, 5.33 (1H each, both br s, H-6, 5). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: given in Table 1. EI-MS m/z: 234 (M^+) (28), 216 ($M-H_2O$)$^+$ (30), 43 ($M-191$)$^+$ (100). HR-EI-MS m/z: 234.1616 (Calcd for $C_{15}H_{22}O_2$: 234.1620).

Comosone II (**4**): A colorless oil, $[\alpha]_D^{27}$ +10.1° (c=0.70, MeOH). UV λ_{max} (MeOH) nm (log ε): 237 (3.77). IR (film) cm^{-1}: 1665, 1651, 1615, 1439, 1379, 754. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.58, 1.87, 1.93, 2.06 (3H each, all s, H_3-15, 13, 14, 12), 1.82 (2H, m, H_2-3), 1.83, 2.20 (1H each, both m, H_2-2), 2.75 (1H, m, H-1), 3.76 (1H, br s, H-6), 4.92 (1H, br s, H-5), 5.90 (1H, s, H-9). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: given in Table 1. EI-MS m/z: 216 (M^+) (100). HR-EI-MS m/z: 216.1509 (Calcd for $C_{15}H_{20}O$: 216.1514).

Comosone III (**5**): A colorless oil, $[\alpha]_D^{24}$ +23.9° (c=0.5, MeOH). IR (film) cm^{-1}: 1713, 1092; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.79 (1H, ddd, J=8.1, 5.4, 5.4 Hz, H-1), 1.13 (1H, t like, J=*ca.* 5 Hz, H-5), 1.18, 1.21, 1.39, 2.17 (3H each, all s, H_3-12, 14, 13, 15), 1.64, 1.76 (1H each, both m, H_2-2), 2.56 (2H, t, J=7.6 Hz, H_2-3), 2.68, 2.77 (1H each, both d, J=19.9 Hz, H_2-9), 3.43 (3H, s, OCH_3-6), 3.88 (1H, d, J=4.1 Hz, H-6). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: given in Table 1. EI-MS m/z: 280 [M^+] (2), 265 [$M-Me$]$^+$ (3), 139 [$M-141$]$^+$ (100). HR-EI-MS m/z: 280.1676 (Calcd for $C_{16}H_{24}O_4$: 280.1674).

Dimethoxycurcumenone (**6**): A colorless oil, $[\alpha]_D^{25}$ −10.1° (c=1.4, MeOH). UV λ_{max} (MeOH) nm (log ε): 255 (3.59). IR (film) cm^{-1}: 1682, 1601, 1458, 1375, 1055, 853. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.47, 0.66 (1H each, both m, H-1, 5), 1.13, 1.23, 1.79, 2.10 (3H each, all s, H_3-14, 15, 13, 12), 1.34, 1.65 (2H each, both m, H_2-2, 3), 2.51, 2.56 (1H each, both d, J=15.6 Hz, H_2-9), 2.83 (2H, br s, H_2-6), 3.15, 3.15 (3H each, both s, OCH_3-4). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: given in Table 1. EI-MS m/z: 280 [M^+] (3), 85 [$M-195$]$^+$ (100). HR-EI-MS m/z: 280.2046 (Calcd for $C_{17}H_{28}O_3$: 280.2038).

Acetal Formation of (±)-Comosol (1a, 2a) A solution of the mixture of **1** and **2** (14.6 mg, 61.9 mmol) in dry CH_2Cl_2 (1.0 ml) was treated with (*S*)-5-allyl-2-oxabicyclo[3,3,0]oct-8-ene (50 μl, 326.5 μmol) in the presence of a catalytic amount of *p*-TsOH, and the mixture was stirred slowly from 0 °C to r.t. for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The EtOAc extract was successively washed with brine, then dried over $MgSO_4$ powder and filtered. After removal of the solvent under reduced pressure, the residue was purified by normal-phase silica gel column chromatography [0.8 g, *n*-hexane–EtOAc (85 : 1, v/v)] to furnish **1a** (9.1 mg, 27.4%) and **2a** (10.5 mg, 31.7%), respectively.

1a: A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.80, 1.71 (3H each, both s, H_3-14, 13), 1.17, 1.91 (1H each, both m, H_2-10), 1.56, 1.87 (1H each, both m, H_2-3), 1.78 (1H, d, J=13.0 Hz, H-6), [1.84 (1H, dd like), 2.50 (1H, br d, J=*ca.* 13 Hz), H_2-7], [1.89 (1H, dd like), 2.62 (1H, br d, J=*ca.* 13 Hz), H_2-9], 2.09, 2.24 (1H each, both m, H_2-4), 3.54 (1H, dd, J=4.1, 11.7 Hz, H-2), 3.99, 4.11 (1H each, both d, J=10.3 Hz, H_2-12), 4.52, 4.76 (1H each, both br s, H_2-15); H-ALBO′ part δ: 1.44, 1.61 (1H each, both m, H_2-8′), 1.58—1.63 (2H, H_2-7′), 1.60—1.63 (2H, H_2-6′), 1.68—1.74, 1.93—1.96 (1H each, H_2-4′), 2.09, 2.22 (1H each, H_2-9′), [3.77 (1H, dd, J=8.2, 15.8 Hz), 3.81 (1H, m), H_2-3′], 5.01—5.07 (2H, H_2-11′), 5.84 (1H, m, H-10′); H-ALBO″ part δ: 1.47—1.52, 1.55—1.62 (1H each, H_2-6″), 1.58—1.63 (2H, H_2-7″), 1.60, 2.02 (1H each, both m, H_2-8″), 1.68—1.74, 1.93—1.96 (1H each, H_2-4″), 2.08, 2.26 (1H each, H_2-9″), [3.80 (1H, dd, J=8.2, 15.8 Hz), 3.84 (1H, ddd, J=4.1, 8.2, 15.8 Hz), H_2-3″], 5.01—5.07 (2H, H_2-11″), 5.84 (1H, m, H-10″). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 10.9 (C-14), 16.4 (C-13), 25.4 (C-9), 28.2 (C-7), 30.2 (C-3), 34.3 (C-4), 38.6 (C-10), 40.2 (C-1), 48.8 (C-6), 63.6 (C-12), 79.0 (C-2), 106.1 (C-15), 123.2 (C-11), 135.8 (C-8), 149.8 (C-5); C-ALBO′ part δ_C: [21.8 (C-7′), 35.3 (C-8′), 36.7 (C-6′), 38.3 (C-4′), 40.7 (C-9′), 54.9 (C-5′), 66.3 (C-3′), 116.5 (C-1′), 116.7 (C-11′), 136.9 (C-10′)]; C-ALBO″ part δ_C: [21.6 (C-7″), 34.5 (C-8″), 36.9 (C-6″), 38.4 (C-4″), 40.6 (C-9″), 54.2 (C-5″), 65.8 (C-3″), 117.5 (C-1″), 116.7 (C-11″), 137.0 (C-10″)]. EI-MS m/z: 536 [M^+] (1), 200 [$M-336$]$^+$ (100). HR-EI-MS m/z: 536.3871 (Calcd for $C_{35}H_{52}O_4$: 536.3865).

2a: A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.81, 1.72 (3H each, both s, 14, H_3-13), 1.08, 1.93 (1H each, both m, H_2-10), 1.58, 2.29 (1H each, both m, H_2-3), 1.75 (1H, d, J=13.0 Hz, H-6), [1.86 (1H, dd like, J=*ca.* 13 Hz), 2.50 (1H, br d, J=*ca.* 13 Hz), H_2-7], [1.92 (1H, dd like), 2.63 (1H, br d, J=*ca.* 13 Hz), H_2-9], 2.06, 2.24 (1H each, both m, H_2-4), 3.33 (1H, dd, J=4.9, 11.7 Hz, H-2), 3.93, 4.17 (1H each, both d, J=10.3 Hz, H_2-12), 4.52, 4.76 (1H each, both br s, H_2-15); H-ALBO′ part δ: 1.48, 2.03 (1H each, both m, H_2-8′), 1.55—1.63 (2H, H_2-7′), 1.48—1.54, 1.58—1.63 (2H, H_2-

6′), 1.64—1.70, 1.93—1.96 (1H each, H_2-4′), 2.10, 2.27 (1H each, H_2-9′), [3.73 (1H, dd, J=8.2, 15.8 Hz), 3.76 (1H, m), H_2-3′], 5.00—5.08 (2H, H_2-11′), 5.85 (1H, m, H-10′); H-ALBO″ part δ: 1.48—1.54, 1.58—1.63 (1H each, H_2-6″), 1.55—1.63 (2H, H_2-7″), 1.61, 2.09 (1H each, both m, H_2-8″), 1.64—1.70, 1.93—1.96 (1H each, H_2-4″), 2.08, 2.26 (1H each, H_2-9″), [3.78 (1H, dd, J=8.2, 15.8 Hz), 3.84 (1H, ddd, J=4.1, 8.2, 15.8 Hz), H_2-3″], 5.00—5.08 (2H, H_2-11″), 5.85 (1H, m, H-10″). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 10.8 (C-14), 16.6 (C-13), 25.3 (C-9), 28.1 (C-7), 30.9 (C-3), 34.4 (C-4), 39.4 (C-10), 40.3 (C-1), 48.7 (C-6), 63.7 (C-12), 82.0 (C-2), 106.0 (C-15), 123.2 (C-11), 136.0 (C-8), 149.8 (C-5); C-ALBO′ part δ_C: [21.5 (C-7′), 34.6 (C-8′), 37.1 (C-6′), 38.2 (C-4′), 40.8 (C-9′), 54.9 (C-5′), 65.5 (C-3′), 118.1 (C-1′), 116.7 (C-11′), 137.0 (C-10′)]; C-ALBO″ part δ_C: [21.5 (C-7″), 34.4 (C-8″), 36.9 (C-6″), 38.4 (C-4″), 40.7 (C-9″), 54.1 (C-5″), 65.9 (C-3″), 117.5 (C-1″), 116.6 (C-11″), 137.0 (C-10″)]. EI-MS m/z: 536 [M^+] (1), 200 [$M-336$]$^+$ (100). HR-EI-MS m/z: 536.3869 (Calcd for $C_{35}H_{52}O_4$: 536.3865).

Hydrolysis of 1a and 2a To a solution of **1a** (9.1 mg, 17.0 μmol) in aqueous MeOH [MeOH (0.9 ml), H_2O (0.1 ml)] was added a catalytic amount of *p*-TsOH. The solution was left to stand under magnetic stirring at 30 °C for 3 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The EtOAc extract was washed with brine, then dried over $MgSO_4$ powder and filtered. Removal of the solvent under reduced pressure gave a residue, which was purified by normal-phase silica gel column chromatography [1.0 g, *n*-hexane–EtOAc (5 : 1—1 : 1, v/v)] to give **1** (3.3 mg, 82.4%). Using a similar procedure, **2** (3.7 mg, 80.0%) was obtained from **2a** (10.5 mg, 19.6 mmol).

(+)-Comosol (**1**): A colorless oil, $[\alpha]_D^{23}$ +34.7° (c=0.2, $CHCl_3$); IR (film) cm^{-1}: 3420, 2936, 1655, 1541, 754. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.80, 1.79 (3H each, both s, H_3-14, 13), 1.16, 1.99 (1H each, both m, H_2-10), 1.59, 1.82 (1H each, both m, H_2-3), 1.73 (1H, br d, J=*ca.* 12 Hz, H-6), [1.88 (1H, dd, J=13.0, 11.7 Hz), 2.53 (1H, br d, J=*ca.* 13 Hz), H_2-7], [1.94 (1H, dd like, J=13.7 Hz), 2.67 (1H, br d, J=*ca.* 14 Hz), H_2-9], 2.10, 2.32 (1H each, both m, H_2-4), 3.39 (1H, dd, J=11.6, 4.1 Hz, H-2), 4.16 (2H, s, H_2-12), 4.57, 4.82 (1H each, both br s, H_2-15). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: given in Table 1. EI-MS m/z: 236 [M^+] (6), 218 [$M-H_2O$]$^+$ (100). HR-EI-MS m/z: 236.1771 (Calcd for $C_{15}H_{24}O_2$: 236.1776).

(−)-Comosol (**2**): A colorless oil, $[\alpha]_D^{22}$ −32.2° (c=0.2, $CHCl_3$). IR (film) cm^{-1}: 3420, 2936, 1655, 1541, 754. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.80, 1.79 (3H each, both s, H_3-14, 13), 1.16, 1.99 (1H each, both m, H_2-10), 1.59, 1.82 (1H each, both m, H_2-3), 1.73 (1H, br d, J=*ca.* 12 Hz, H-6), [1.88 (1H, dd, J=13.0, 11.7 Hz), 2.53 (1H, br d, J=*ca.* 13 Hz), H_2-7], [1.94 (1H, dd like, J=13.7 Hz), 2.67 (1H, br d, J=*ca.* 14 Hz), H_2-9], 2.10, 2.32 (1H each, both m, H_2-4), 3.39 (1H, dd, J=11.6, 4.1 Hz, H-2), 4.16 (2H, s, H_2-12), 4.57, 4.82 (1H each, both br s, H_2-15). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: given in Table 1. EI-MS m/z: 236 [M^+] (6), 218 [$M-H_2O$]$^+$ (100). HR-EI-MS m/z: 236.1771 (Calcd for $C_{15}H_{24}O_2$: 236.1776).

Pivaloyl Protection of 1 and 2 A solution of **1** (3.3 mg, 14.0 μmol) in dry pyridine (1.0 ml) was treated with pivaloyl chloride (20 μl, 164 mmol) at r.t. for 3 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The EtOAc extract was successively washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and then dried over $MgSO_4$ powder and filtered. After removal of the solvent under reduced pressure, the residue was purified by normal-phase silica gel column chromatography [0.8 g, *n*-hexane–EtOAc (5 : 1, v/v)] to furnish **1b** (3.8 mg, 84.9%). Through a similar procedure, **2b** (4.1 mg, 81.7%) was obtained from **2** (3.7 mg, 15.7 μmol) using pivaloyl chloride (20 μl, 164 μmol).

1b: A colorless oil, $[\alpha]_D^{23}$ +31.5° (c=0.2, $CDCl_3$). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.80, 1.72 (3H each, both s, H_3-14, 13), 1.16, 1.98 (1H each, both m, H_2-10), 1.20 [3H each, all s, –C(CH_3)$_3$], 1.59, 1.82 (1H each, both m, H_2-3), 1.73 (1H, br d, J=*ca.* 12 Hz, H-6), [1.89 (1H, dd, J=13.1, 11.7 Hz), 2.54 (1H, br d, J=13.1 Hz), H_2-7], [1.93 (1H, dd like, J=13.1 Hz), 2.65 (1H, br d, J=*ca.* 13 Hz), H_2-9], 2.10, 2.32 (1H each, both m, H_2-4), 3.39 (1H, dd, J=4.1, 11.7 Hz, H-2), 4.56, 4.81 (1H each, both br s, H_2-15), 4.61 (2H, s, H_2-12). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 9.8 (C-14), 16.3 (C-13), 25.3 (C-9), 27.2 [($\underline{C}H_3$)$_3$C–], 28.1 (C-7), 31.4 (C-3), 34.1 (C-4), 38.1 (C-10), 38.9 [(CH$_3$)$_3\underline{C}$–], 40.5 (C-1), 48.0 (C-6), 65.1 (C-12), 79.1 (C-2), 106.9 (C-15), 121.0 (C-11), 138.2 (C-8), 148.8 (C-5), 178.7 (–$\underline{C}$OO). CI-MS m/z: 321 [$M+H$]$^+$ (4), 201 [$M-120$]$^+$ (100). HR-CI-MS m/z: 321.2435 (Calcd for $C_{20}H_{33}O_3$: 321.2430).

2b: A colorless oil, $[\alpha]_D^{21}$ −36.7° (c=0.2, $CDCl_3$). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.80, 1.72 (3H each, both s, H_3-14, 13), 1.16, 1.98 (1H each, both m, H_2-10), 1.20 [3H each, all s, –C(CH_3)$_3$], 1.59, 1.82 (1H each, both m, H_2-3), 1.73 (1H, br d, J=*ca.* 12 Hz, H-6), [1.89 (1H, dd, J=13.1, 11.7 Hz), 2.54 (1H, br d, J=13.1 Hz), H_2-7], [1.93 (1H, dd like, J=13.1 Hz), 2.65 (1H, br d, J=*ca.* 13 Hz), H_2-9], 2.10, 2.32 (1H each, both m, H_2-4), 3.39 (1H, dd, J=4.1, 11.7 Hz, H-2), 4.56, 4.81 (1H each, both br s, H_2-15), 4.61 (2H, s, H_2-12). ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 9.8 (C-14), 16.3 (C-13), 25.3 (C-9), 27.2 [($\underline{C}H_3$)$_3$C–], 28.1 (C-7), 31.4 (C-3), 34.1 (C-4), 38.1 (C-10), 38.9 [(CH$_3$)$_3\underline{C}$–], 40.5 (C-1), 48.0 (C-6), 65.1 (C-12), 79.1 (C-2), 106.9 (C-15), 121.0 (C-11), 138.2 (C-8), 148.8 (C-5), 178.7 (–$\underline{C}$OO). CI-MS m/z: 321 [$M+H$]$^+$ (4), 201 [$M-120$]$^+$ (100). HR-CI-MS m/z: 321.2432 (Calcd for $C_{20}H_{33}O_3$: 321.2430).

Preparation of the (*R*)- and (*S*)-MTPA Esters (1c, 1d) from 1b A solution of **1b** (2.0 mg, 6.3 mmol) in dry pyridine (1.0 ml) was treated with (+)-MTPA-Cl (20 μl, 107.1 μmol), and the mixture was stirred at r.t. for 3 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The EtOAc extract was successively washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$ powder and filtered. After removal of the solvent, the residue yielded was purified by normal-phase silica gel column chromatography [0.8 g, *n*-hexane–EtOAc (30 : 1, v/v)] to furnish **1c** (2.6 mg, 77.6%). Through a similar procedure, **1d** (2.4 mg, 79.6%) was obtained from **1b** (1.8 mg, 5.6 μmol) using (−)-MTPA-Cl (20 μl, 107.1 μmol).

1c: A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.83, 1.72 (3H each, both s, H_3-14, 13), 1.21, 1.73 (1H each, both m, H_2-10), 1.21 [3H each, all s, –C(CH_3)$_3$], 1.62, 1.99 (1H each, both m, H_2-3), 1.86 (1H, br d, J=*ca.* 12 Hz, H-6), [1.87 (1H, dd, J=13.1, 11.7 Hz), 2.56 (1H, br d, J=*ca.* 13 Hz), H_2-7], [1.90 (1H, dd like, J=13.1 Hz), 2.62 (1H, br d, J=*ca.* 13 Hz), H_2-9], 2.18, 2.35 (1H each, both m, H_2-4), 4.58, 4.61 (1H each, both d, J=11.7 Hz, H_2-12), 4.60, 4.84 (1H each, both br s, H_2-15), 4.82 (1H, dd, J=4.1, 11.0 Hz, H-2). [3.51 (3H, s, –OCH_3), 7.40 (1H, m), 7.41 (2H, dd like), 7.50 (2H, dd like), H-MTPA part]. ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 10.8 (C-14), 16.3 (C-13), 25.1 (C-9), 27.2 [($\underline{C}H_3$)$_3$C–], 27.4 (C-3), 27.8 (C-7), 33.5 (C-4), 37.9 (C-10), 38.9 [(CH$_3$)$_3\underline{C}$–], 39.5 (C-1), 48.0 (C-6), 65.0 (C-12), 83.8 (C-2), 107.8 (C-15), 121.6 (C-11), 137.2 (C-8), 147.4 (C-5), 178.7 (–$\underline{C}$OO), [55.3, 127.5, 127.5, 128.4, 128.4, 129.6, 132.2, 166.3, C-MTPA part].

1d: A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.84, 1.72 (3H each, both s, H_3-14, 13), 1.13, 1.61 (1H each, both m, H_2-10), 1.20 [3H each, all s, –C(CH_3)$_3$], 1.76, 2.03 (1H each, both m, H_2-3), [1.85 (1H, dd like, J=13.1 Hz), 2.56 (1H, br d, J=*ca.* 13 Hz), H_2-9], 1.86 (1H, br d, J=*ca.* 12 Hz, H-6), [1.89 (1H, dd, J=13.1, 11.7 Hz), 2.56 (1H, br d, J=*ca.* 13 Hz), H_2-7], 2.20, 2.38 (1H each, both m, H_2-4), 4.56, 4.60 (1H each, both d, J=11.7 Hz, H_2-12), 4.61, 4.86 (1H each, both br s, H_2-15), 4.87 (1H, dd, J=4.1, 11.0 Hz, H-2). [3.55 (3H, s, –OCH_3), 7.39 (1H, m), 7.40 (2H, dd like), 7.52 (2H, dd like), H-MTPA part]. ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 10.7 (C-14), 16.3 (C-13), 25.0 (C-9), 27.2 [($\underline{C}H_3$)$_3$C–], 27.7 (C-3), 27.8 (C-7), 33.6 (C-4), 37.5 (C-10), 38.9 [(CH$_3$)$_3\underline{C}$–], 39.6 (C-1), 48.0 (C-6), 65.0 (C-12), 83.5 (C-2), 107.9 (C-15), 121.5 (C-11), 137.3 (C-8), 147.4 (C-5), 178.7 (–$\underline{C}$OO), [55.4, 127.3, 127.3, 128.3, 128.3, 129.6, 132.5, 166.0, C-MTPA part].

Preparation of the (*R*)- and (*S*)-MTPA Esters (2c, 2d) from 2b A solution of **2b** (1.9 mg, 5.9 μmol) in dry pyridine (1.0 ml) was treated with (+)-MTPA-Cl (20 μl, 107.1 μmol), and the mixture was stirred at r.t. for 3 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The EtOAc extract was successively washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$ powder and filtered. After removal of the solvent under reduced pressure, the residue was purified by normal-phase silica gel column chromatography [0.8 g, *n*-hexane–EtOAc (30 : 1, v/v)] to furnish **2c** (2.6 mg, 81.7%). Using a similar procedure, **2d** (2.7 mg, 73.3%) was obtained from **2b** (2.2 mg, 6.9 μmol) using (−)-MTPA-Cl (20 μl, 107.1 μmol).

2c: A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.84, 1.72 (3H each, both s, H_3-14, 13), 1.13, 1.61 (1H each, both m, H_2-10), 1.20 [3H each, all s, –C(CH_3)$_3$], 1.76, 2.03 (1H each, both m, H_2-3), [1.85 (1H, dd like, J=13.1 Hz), 2.56 (1H, br d, J=*ca.* 13 Hz), H_2-9], 1.86 (1H, br d, J=*ca.* 12 Hz, H-6), [1.89 (1H, dd, J=13.1, 11.7 Hz), 2.56 (1H, br d, J=*ca.* 13 Hz), H_2-7], 2.20, 2.38 (1H each, both m, H_2-4), 4.56, 4.60 (1H each, both d, J=11.7 Hz, H_2-12), 4.61, 4.86 (1H each, both br s, H_2-15), 4.87 (1H, dd, J=4.1, 11.0 Hz, H-2). [3.55 (3H, s, –OCH_3), 7.39 (1H, m), 7.40 (2H, dd like), 7.52 (2H, dd like), H-MTPA part]. ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 10.7 (C-14), 16.3 (C-13), 25.0 (C-9), 27.2 [($\underline{C}H_3$)$_3$C–], 27.7 (C-3), 27.8 (C-7), 33.6 (C-4), 37.5 (C-10), 38.9 [(CH$_3$)$_3\underline{C}$–], 39.6 (C-1), 48.0 (C-6), 65.0 (C-12), 83.5 (C-2), 107.9 (C-15), 121.5 (C-11), 137.3 (C-8), 147.4 (C-5), 178.7 (–COO), [55.4, 127.3, 127.3, 128.3, 128.3, 129.6, 132.5, 166.0, C-MTPA part].

2d: A colorless oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.83, 1.72 (3H each, both s, H_3-14, 13), 1.21, 1.73 (1H each, both m, H_2-10), 1.21 [3H each, all s, –C(CH_3)$_3$], 1.62, 1.99 (1H each, both m, H_2-3), 1.86 (1H, br d, J=*ca.* 12 Hz,

H-6), [1.87 (1H, dd, J=13.1, 11.7 Hz), 2.56 (1H, br d, J=*ca.* 13 Hz), H_2-7], [1.90 (1H, dd like, J=13.1 Hz), 2.62 (1H, br d, J=*ca.* 13 Hz), H_2-9], 2.18, 2.35 (1H each, both m, H_2-4), 4.58, 4.61 (1H each, both d, J=11.7 Hz, H_2-12), 4.60, 4.84 (1H each, both br s, H_2-15), 4.82 (1H, dd, J=4.1, 11.0 Hz, H-2). [3.51 (3H, s, $-OCH_3$), 7.40 (1H, m), 7.41 (2H, dd like), 7.50 (2H, dd like), H-MTPA part]. ^{13}C-NMR (150 MHz, $CDCl_3$) δ_C: 10.8 (C-14), 16.3 (C-13), 25.1 (C-9), 27.2 [$(\underline{C}H_3)_3C-$], 27.4 (C-3), 27.8 (C-7), 33.5 (C-4), 37.9 (C-10), 38.9 [$(CH_3)_3\underline{C}-$], 39.5 (C-1), 48.0 (C-6), 65.0 (C-12), 83.8 (C-2), 107.8 (C-15), 121.6 (C-11), 137.2 (C-8), 147.4 (C-5), 178.7 ($-\underline{C}OO$), [55.3, 127.5, 127.5, 128.4, 128.4, 129.6, 132.2, 166.3, C-MTPA part].

Hydrolysis of 6 To a solution of **6** (12.5 mg, 44.6 μmol) in aqueous MeOH [MeOH (0.9 ml), H_2O (0.1 ml)] was added a catalytic amount of *p*-TsOH. The solution was stirred at r.t. for 3 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The EtOAc extract was washed with brine, then dried over $MgSO_4$ powder and filtered. Removal of the solvent under reduced pressure gave a residue, which was purified by normal-phase silica gel column chromatography [1.0 g, *n*-hexane–EtOAc (5 : 1, v/v)] to give curcumenone (7.4 mg, 70.8%).

Acknowledgments This research was supported by the 21st COE Program, Academic Frontier Project, and a Grant-in Aid for Scientific Research from MEXT (the Ministry of Education, Culture, Sports, Science and Technology of Japan).

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