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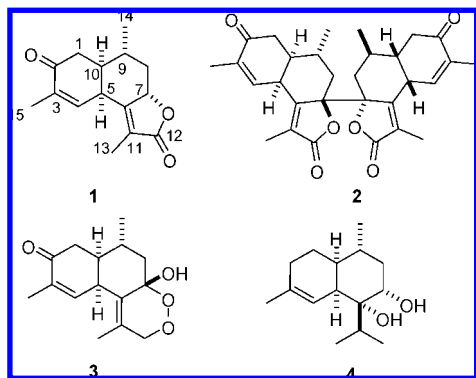
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Received April 16, 2008

Four new cadinane sesquiterpenes (**1–4**), including a dimeric cadinane derivative (**2**) and a peroxide cadinane analogue (**3**), have been isolated from the leaves of *Eupatorium adenophorum*. Their structures including absolute configurations were determined on the basis of spectroscopic data interpretation and single-crystal X-ray crystallography. Compound **4** showed in vitro cytotoxicity against the HCT-8, Bel-7402, and A2780 cancer cell lines.

*Eupatorium adenophorum* Spreng (syn. *Ageratina adenophora* Spreng), belonging to the family Compositae, is a native species of Mexico and Costa Rica and distributed practically all around the world.<sup>1</sup> It is an invasive plant causing some severe problems in forested and cultured areas in mainland China. In order to find a possible pharmaceutical use for this plant, its chemical constituents including alkaloids, coumarins, flavonoids, and sesquiterpenoids, as well as their biological activities, have been investigated.<sup>2–6</sup> In our previous investigation of this plant, a new cadinane sesquiterpene and several known compounds were isolated from the petroleum ether- and chloroform-soluble portions of a methanolic extract of *E. adenophorum*.<sup>7</sup> Due to a continued interest in the minor components of this widely distributed plant, we have carried out an investigation of a re-collection of this species. This paper deals with the isolation and structure elucidation of four new cadinane sesquiterpene derivatives (**1–4**), including a dimeric cadinane derivative (**2**) and a peroxide cadinane analogue (**3**), and their in vitro cytotoxic activities.



Compound **1** was obtained as a colorless gum. Its IR spectrum showed absorption bands for  $\alpha,\beta$ -unsaturated carbonyl ( $1676\text{ cm}^{-1}$ ) and  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone ( $1755\text{ cm}^{-1}$ ) groups. The EIMS of

**1** gave a molecular ion peak at  $m/z$  246  $[M]^+$ , and the molecular formula  $C_{15}H_{18}O_3$  was indicated by HREIMS at  $m/z$  246.1259 (calcd for  $C_{15}H_{18}O_3$ , 246.1256). The  $^1\text{H}$  NMR spectrum of **1** showed signals (Table 1) attributed to a trisubstituted double bond proton at  $\delta$  6.26 (d,  $J = 1.5\text{ Hz}$ , H-4), three methyls at  $\delta$  1.81 (s, H<sub>3</sub>-15), 1.91 (s, H<sub>3</sub>-13), and 1.01 (d,  $J = 6.5\text{ Hz}$ , H<sub>3</sub>-14), and an oxymethine at  $\delta$  4.72 (dd,  $J = 12.0, 6.0\text{ Hz}$ , H-7), in addition to signals with complex coupling patterns attributed to two aliphatic methylenes and two methines. The  $^{13}\text{C}$  NMR and DEPT spectra (Table 2) showed 15 carbon resonances including three methyls, two methylenes, five methines (one olefinic and one oxygenated), and five quaternary carbons (one carbonyl, one carboxyl, and three olefinic). These spectroscopic data indicated **1** to be a cadinane sesquiterpene derivative possessing  $\alpha,\beta$ -unsaturated carbonyl and  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone moieties.<sup>6–8</sup> The location of the functional groups in **1** was elucidated by 2D NMR analysis of **1**. The proton and protonated carbon signals (Tables 1 and 2) were assigned unequivocally by  $^1\text{H}$ – $^1\text{H}$  COSY and HMQC spectroscopic analysis of **1**. In the HMBC spectrum of **1** (Figure S1, Supporting Information), correlations of C-2 with H<sub>2</sub>-1, H-4, and H<sub>3</sub>-15, in combination with the chemical shifts of these protons and carbons, supported the presence of an  $\alpha,\beta$ -unsaturated carbonyl moiety in **1**. Meanwhile, long-range correlations of C-6 and C-11 with H-7 and H<sub>3</sub>-13, and C-12 with H<sub>3</sub>-13, in combination with chemical shifts of these protons and carbons were used to locate the  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone moiety in **1**.

The stereochemistry of **1** was elucidated by a comprehensive analysis of the  $^1\text{H}$  NMR coupling constants, NOESY NMR, and CD data. The large coupling characteristics showed pseudodaxial relationships of H-8b (ddd,  $J_{7,8b} \approx J_{8b,9} \approx J_{8a,8b} \approx 12.0\text{ Hz}$ ) with both H-7 and H-9, together with a NOE correlation between H-7 and H-9 in the NOESY spectrum, and demonstrated that H-7, H-8b, and H-9 occupied pseudoaxial positions and that H-7 and H-9 were oriented on the same side of the ring system in **1**. The NOE correlation of H-10 with H-5 and H-8b indicated these protons were oriented on opposite sides of the ring system in **1**. The CD spectrum of **1** (Figure S2, Supporting Information) showed a split Cotton effect at  $\lambda$  232 nm ( $\Delta\epsilon +32.4$ ) and 200 nm ( $\Delta\epsilon -24.4$ ), centered at 216 nm. This corresponded to the UV maxima of the  $\alpha,\beta$ -unsaturated enone and  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone chromophores and could be interpreted using the exciton chirality method.<sup>9</sup> The positive chirality of **1**, resulting from the dipole–dipole interaction between the electric transition moments of the two chromophores, suggested that the two chromophores are oriented in a clockwise manner. Accordingly, the absolute configurations at the chiral

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**Table 1.**  $^1\text{H}$  NMR Spectroscopic Data for Compounds **1–4**<sup>a</sup>

position	1	2	3	4
1a	2.84 dd (16.5, 2.5)	2.56 dd (15.5, 4.0)	2.82 dd (16.5, 2.0)	1.92 m
1b	2.63 dd (16.5, 4.5)	1.95 dd (15.5, 15.0)	2.58 dd (16.5, 5.0)	1.54 m
2a				1.93 m
2b				1.75 m
4	6.26 d (1.5)	6.60 d (4.5)	6.35 brs	5.34 s
5	4.04 brs	3.99 brs	3.91 brs	2.57 brs
7	4.72 dd (12.0, 6.0)			3.70 dd (11.0, 4.5)
8a	2.40 ddd (12.0, 6.0, 3.0)	2.27 dd (15.0, 13.0)	1.84 dd (13.0, 3.5)	1.62 m
8b	1.05 ddd (12.0, 12.0, 12.0)	2.20 dd (15.0, 3.5)	1.20 dd (13.0, 13.0)	1.47 ddd (12.0, 12.0, 12.0)
9	1.83 m	1.15 m	2.15 m	1.65 m
10	1.85 m	2.36 m	1.86 m	1.67 m
11				2.10 m
12a			4.80 d (16.0)	1.10 d (7.0)
12b			4.17 d (16.0)	
13	1.91 s	1.89 s	1.78 s	1.17 d (7.0)
14	1.01 d (6.5)	1.07 d (6.5)	0.97 d (7.0)	0.94 d (6.0)
15	1.81 s	1.87 s	1.79 s	1.65 s

<sup>a</sup>  $^1\text{H}$  NMR data ( $\delta$ ) were measured in  $\text{CDCl}_3$  at 500 MHz. Proton coupling constants ( $J$ ) in Hz are given in parentheses. The assignments were based on DEPT,  $^1\text{H}$ – $^1\text{H}$  COSY, HMQC, and HMBC experiments.

**Table 2.**  $^{13}\text{C}$  NMR Spectroscopic Data for Compounds **1–4**<sup>a</sup>

position	1	2	3	4
1	40.8 t	40.3 t	41.2 t	24.4 t
2	197.3 s	197.6 s	198.1 s	26.1 t
3	137.4 s	137.4 s	134.6 s	135.6 s
4	141.0 d	140.1 d	147.0 d	119.6 d
5	38.7 d	38.2 d	38.5 d	45.0 d
6	161.9 s	160.9 s	131.1 s	77.0 s
7	78.3 d	91.5 s	97.0 s	72.2 d
8	41.4 t	36.3 t	41.5 t	40.1 t
9	27.6 d	32.9 d	26.1 d	26.4 d
10	44.8 d	44.6 d	44.7 d	36.3 d
11	121.3 s	127.7 s	127.3 s	35.1 d
12	174.1 s	172.4 s	73.0 t	17.8 q
13	8.4 q	9.4 q	13.7 q	19.0 q
14	19.0 q	18.9 q	18.8 q	19.4 q
15	15.6 q	15.7 q	15.6 q	24.1 q

<sup>a</sup>  $^{13}\text{C}$  NMR data ( $\delta$ ) were measured in  $\text{CDCl}_3$  at 125 MHz. The assignments were based on DEPT,  $^1\text{H}$ – $^1\text{H}$  COSY, HMQC, and HMBC experiments.

centers of **1** were assigned as 5*R*, 7*S*, 9*R*, and 10*S*, respectively. Therefore, the structure of **1** was identified as (+)-(5*R*,7*S*,9*R*,10*S*)-2-oxocadinan-3,6(11)-dien-12,7-olide.

Compound **2**, obtained as colorless crystals (acetone), gave IR and NMR spectroscopic features similar to those of **1** (Tables 1 and 2 and Experimental Section). However, the oxymethine carbon (C-7) was replaced by an oxygen-bearing quaternary carbon signal at  $\delta$  91.5 in the  $^{13}\text{C}$  NMR spectrum of **2**. In addition, the EIMS spectrum of **2** exhibited a molecular ion peak at  $m/z$  490 and a base peak at  $m/z$  245, and the HREIMS at  $m/z$  490.2362 indicated the molecular formula as  $\text{C}_{30}\text{H}_{34}\text{O}_6$ . These spectroscopic data suggested that **2** is a symmetrical dimer of **1** at C-7. Furthermore, the similarity of the CD data between **1** and **2** (Figure S2, Supporting Information) indicated that the dipole–dipole interactions between the electric transition moments of the two chromophores of the monomeric moieties in **2** were identical to that of **1**. This suggested that the absolute configurations at C-5, C-9, and C-10 of **2** are the same as those of **1**. The structure and the absolute stereochemistry of **2** were proved by single-crystal X-ray crystallographic analysis of **2** using an anomalous scattering of Cu K $\alpha$  radiation. An ORTEP drawing, with the atom-numbering scheme indicated, is shown in Figure 1, and the configuration at C-7 (C-7') of the monomeric unit in **2** was indicated to be opposite of that of **1**. Therefore, the structure of **2** was determined as (+)-7,7'-bis[(5*R*,7*R*,9*R*,10*S*)-2-oxocadinan-3,6(11)-dien-12,7-olide].

Compound **3**, colorless crystals (acetone), showed absorption bands for hydroxy (3363  $\text{cm}^{-1}$ ) and  $\alpha,\beta$ -unsaturated carbonyl (1651  $\text{cm}^{-1}$ ) groups in its IR spectrum. The EIMS of **3** displayed a

molecular ion peak at  $m/z$  264  $[\text{M}]^+$ , and the molecular formula  $\text{C}_{15}\text{H}_{20}\text{O}_4$  was indicated by the HREIMS at  $m/z$  264.1365. The NMR data (Tables 1 and 2) of **3** were similar to those of **2** except that the carboxyl signal of **2** was replaced by oxymethylene signals at  $\delta_{\text{H}}$  4.80 (d,  $J = 16.0$  Hz, H-12a) and 4.17 (d,  $J = 16.0$  Hz, H-12b) and  $\delta_{\text{C}}$  72.9 (C-12) of **3**. In addition, in the  $^1\text{H}$  NMR spectrum of **3**, the appearance of an exchangeable proton signal at  $\delta_{\text{H}}$  3.09 confirmed the presence of a free hydroxy group in **3**. These data suggested that **3** is another 2-oxocadinan-3,6(11)-diene derivative, which was supported by  $^1\text{H}$ – $^1\text{H}$  COSY, HMQC, and HMBC NMR experiments for **3**. In particular, in the HMBC spectrum of **3** (Figure S1, Supporting Information), long-range correlation of C-2 with H-1a, H-1b, H-4, and H-15 supported the presence of an  $\alpha,\beta$ -unsaturated enone moiety in **3**. In turn, HMBC correlations from H-13 to C-6, C-11, and C-12 and from H-12 to C-11, C-13, and C-6, in combination with chemical shifts of these protons and carbons, were consistent with the occurrence of a double bond between C-6 and C-11, with C-12 being an oxymethylene in **3**. In addition, HMBC correlations from H-8 to C-6, C-7, C-10, and C-14, together with chemical shifts of these protons and carbons, indicated that there were two oxygen atoms attached at C-7. Taking account of the molecular composition, the information above suggested that **3** is a 2-oxocadinan-3,6(11)-diene peroxide with an additional ring bridging through one oxygen atom or an epidioxy bond between C-7 and C-12. In order to determine the form of the additional ring and the relative stereochemistry of **3**, X-ray crystallographic analysis was carried out using graphite-monochromated Mo K $\alpha$  radiation. The result showed that **3** is 7-hydroxy-7,12-epidioxycadinan-3,6(11)-dien-2-one, and an ORTEP drawing, with the atom-numbering scheme indicated, is shown in Figure 2. The CD spectrum of **3** (Figure S2, Supporting Information) showed a split Cotton effect with positive chirality (247 nm,  $\Delta\epsilon +6.9$  and 194 nm,  $\Delta\epsilon -27.5$ ), also similar to that of **1**, indicating an exciton coupling between the  $\pi \rightarrow \pi^*$  transition of the enone chromophore and the  $\pi \rightarrow \pi^*$  transition of the  $\Delta^{7(11)}$  double bond. Therefore, the absolute configurations at C-5, C-9, and C-10 of **3** were assigned as being the same as those of **1**, and **3** was determined as (+)-(5*R*,7*S*,9*R*,10*S*)-7-hydroxy-7,12-epidioxycadinan-3,6(11)-dien-2-one.

Compound **4**, colorless crystals (acetone), showed an IR absorption band for hydroxy groups (3377  $\text{cm}^{-1}$ ). Its molecular formula,  $\text{C}_{15}\text{H}_{26}\text{O}_2$ , was indicated by HREIMS at  $m/z$  238.1935  $[\text{M}]^+$ . The NMR data of **4** (Tables 1 and 2) showed that it is a cadinendiol derivative.<sup>10</sup> The location of the functional groups and NMR data assignments of **4** were assigned unambiguously by HMQC and HMBC spectroscopic analysis. In the HMBC spectrum, long-range correlations of C-6 with H-7, H-11, H-12, and H-13, and C-7

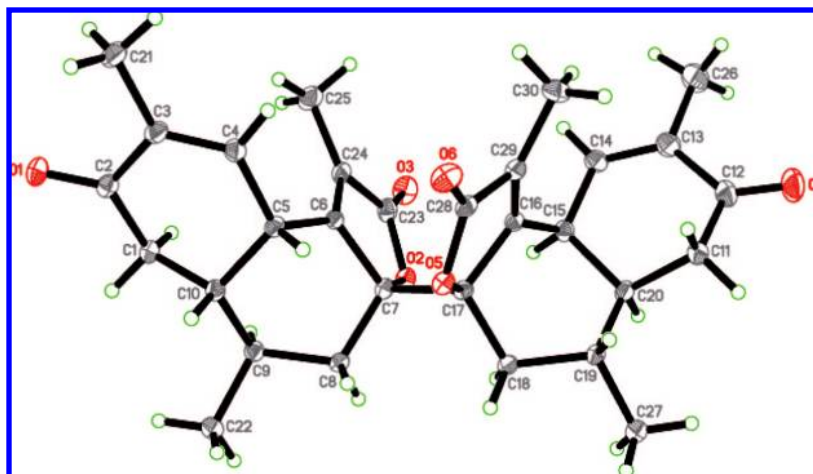


Figure 1. ORTEP diagram of compound 2.

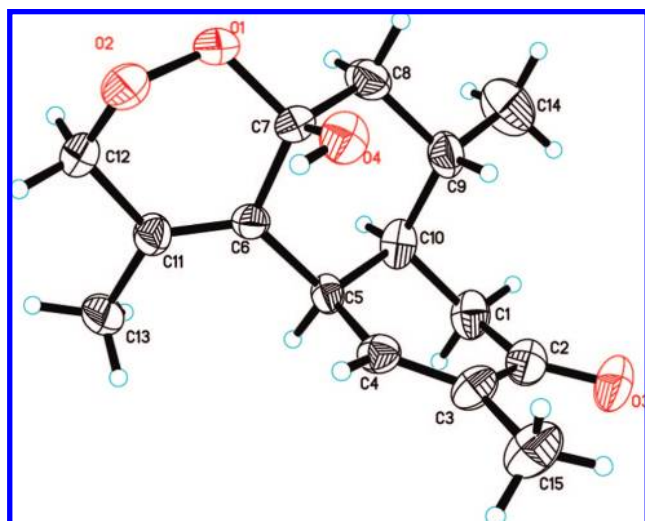


Figure 2. ORTEP diagram of compound 3.

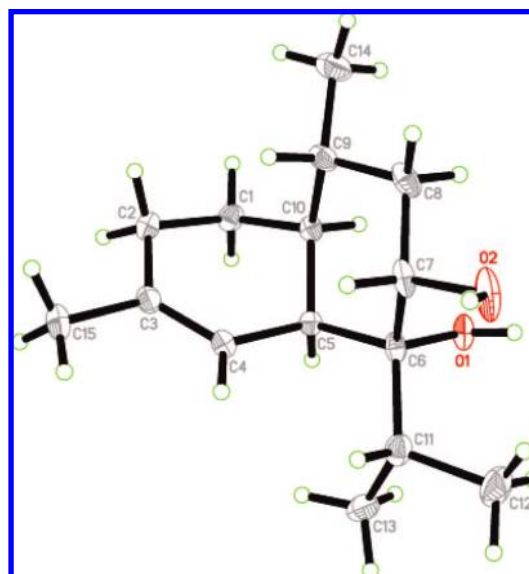


Figure 3. ORTEP diagram of compound 4.

with H<sub>2</sub>-8, in combination with chemical shifts of these protons and carbons, revealed unequivocally that the two hydroxyls are located at C-6 and C-7, respectively. Meanwhile, HMBC correlations of C-3 and C-4 with H<sub>3</sub>-15 and H<sub>3</sub>-2, in combination with chemical shifts of these protons and carbons, were used to locate the double bond between C-3 and C-4. The absolute configurations of the chiral centers were finally determined by X-ray crystallographic analysis of **4** using an anomalous scattering of Cu K $\alpha$  radiation. An ORTEP drawing, with the atom-numbering scheme indicated, is shown in Figure 3. Thus, **4** was determined as (–)-(5*R*,6*R*,7*S*,9*R*,10*S*)-cadinan-3-ene-6,7-diol.

Using the MTT method,<sup>11,12</sup> compounds **1–4** were tested against five human cancer cell lines including colon cancer (HCT-8), hepatoma (Bel 7402), stomach cancer (BGC-823), lung adenocarcinoma (A549), and human ovarian cancer (A2780). Compound **4** showed activities against the HCT-8, Bel-7402, and A2780 cell lines with IC<sub>50</sub> values of 2.0, 1.7, and 1.7  $\mu$ M, respectively, but **1–3** were inactive (IC<sub>50</sub> values >5  $\mu$ M).

## Experimental Section

**General Experimental Procedures.** Melting points were determined on a X-4 digital micromelting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. UV spectra were measured on a Cary 300 spectrophotometer. CD spectra were recorded on a JASCO J-810 spectropolarimeter. IR spectra were recorded on Nicolet 380 FI-IR and Nicolet Avatar 360 FT-IR spectrophotometers. 1D and 2D NMR spectra were obtained at 500

and 125 MHz for <sup>1</sup>H and <sup>13</sup>C, respectively, on a Bruker Avance DRX 500 spectrometer with TMS as internal standard. EIMS and HREIMS data were measured with Waters GCT GC-MS and Thermo Finnigan Trace 2000 GC-MS spectrometers. Column chromatography was performed with silica gel (200–300 mesh, Qingdao Marine Chemical Inc. Qingdao People's Republic of China). TLC was carried out with glass precoated silica gel GF<sub>254</sub> plates. Spots were visualized under UV light or by spraying with 10% sulfuric acid in EtOH followed by heating.

**Plant Material.** The leaves of *Eupatorium adenophorum* were collected in Xichang, Sichuan Province, People's Republic of China, in August 2006. The plant was identified by Prof. A. C. Cao (Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing). A voucher specimen (No. 20060712) was deposited at College of the Chemistry, Beijing Normal University, Beijing 100875, People's Republic of China.

**Extraction and Isolation.** The air-dried leaves of *E. adenophorum* (31 kg) were powdered and extracted with MeOH at room temperature. The methanolic extract was evaporated under reduced pressure to yield a dark residue (8.8 kg). The residue was suspended in H<sub>2</sub>O and then partitioned successively with petroleum ether, chloroform, and ethyl acetate to give three corresponding portions. The petroleum ether portion (675 g) was subjected to column chromatography over silica gel, eluting with a gradient of increasing EtOAc in petroleum ether (0–100%), to give 12 fractions (Fr.<sub>1</sub>–Fr.<sub>12</sub>). Fr.<sub>10</sub> (55 g) was chromatographed on a MCI gel column, using a step-gradient elution of increasing amounts of MeOH in H<sub>2</sub>O (30%–100%), to give seven subfractions (Fr.<sub>10-1</sub>–Fr.<sub>10-7</sub>). Fr.<sub>10-2</sub> (2 g) was recrystallized with acetone to give



4 (83 mg). Fr.<sub>11</sub> (27 g) was chromatographed on a MCI gel column using a step-gradient elution of increasing MeOH in H<sub>2</sub>O (30%–100%) to yield three subfractions (Fr.<sub>11-1</sub>–Fr.<sub>11-3</sub>). Fr.<sub>11-1</sub> (5 g) was separated over a silica gel column, eluting with petroleum ether–acetone (10:1), to give **3** (355 mg). Fr.<sub>11-2</sub> (1 g) was separated over a silica gel column with petroleum ether–acetone (9:1) as an eluent, to yield **1** (66 mg) and **2** (5 mg).

(+)-(5*R*,7*S*,9*R*,10*S*)-2-Oxocadinan-3,6(11)-dien-12,7-olide (**1**): colorless gum;  $[\alpha]_D^{20} +172.0$  (*c* 1.0, CHCl<sub>3</sub>); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 235 (4.23), 213 (4.18) nm; CD (MeOH) 200 ( $\Delta\epsilon$  –24.4), 232 ( $\Delta\epsilon$  +32.4) nm; IR (KBr)  $\nu_{\max}$  2961, 1755, 1676, 1368, 1105, 1086, 1072, 1032, 755 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz), see Table 1; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz), see Table 2; EIMS *m/z* 246 [M]<sup>+</sup> (50), 204 (73), 191 (24), 175 (28), 136 (100), 121 (37), 110 (25), 82 (16); HREIMS *m/z* 246.1259 [M]<sup>+</sup> (calcd for C<sub>15</sub>H<sub>18</sub>O<sub>3</sub>, 246.1256).

(+)-7,7'-Bis[(5*R*,7*R*,9*R*,10*S*)-2-oxocadinan-3,6(11)-dien-12,7-olide] (**2**): colorless crystals (acetone); mp 242–244 °C;  $[\alpha]_D^{20} +228.5$  (*c* 0.1, CHCl<sub>3</sub>); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 236 (4.07) nm; CD (MeOH) 209 ( $\Delta\epsilon$  –20.1), 248 ( $\Delta\epsilon$  +29.4) nm; IR (KBr)  $\nu_{\max}$  2964, 1759, 1683, 1278, 1111, 968, 918, 754 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz), see Table 1; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz), see Table 2; EIMS *m/z* 490 [M]<sup>+</sup> (2), 245 (100), 202 (30), 175 (54), 161 (38), 136 (18), 91 (23); HREIMS *m/z* 490.2362 [M]<sup>+</sup> (calcd for C<sub>30</sub>H<sub>34</sub>O<sub>6</sub>, 490.2355).

(+)-(5*R*,7*S*,9*R*,10*S*)-7-Hydroxy-7,12-epidioxycadinan-3,6(11)-dien-2-one (**3**): colorless crystals (acetone); mp 100–102 °C;  $[\alpha]_D^{20} +124.4$  (*c* 0.9, CHCl<sub>3</sub>); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 241 (4.01), 192 (4.02) nm; CD (MeOH) 194 ( $\Delta\epsilon$  –27.5), 247 ( $\Delta\epsilon$  +6.9) nm; IR (KBr)  $\nu_{\max}$  3363, 2950, 1651, 1371, 1153, 1116, 994, 535 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz), see Table 1; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz), see Table 2; EIMS *m/z* 264 [M]<sup>+</sup> (19), 246 (44), 188 (55), 175 (90), 161 (100), 91 (55), 57 (57), 43 (53); HREIMS *m/z* 264.1365 [M]<sup>+</sup> (calcd for C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>, 264.1362).

(–)-(5*R*,6*R*,7*S*,9*R*,10*S*)-Cadinan-3-ene-6,7-diol (**4**): colorless crystals (acetone); mp 159–160 °C;  $[\alpha]_D^{20} -42.1$  (*c* 0.9, CHCl<sub>3</sub>); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 194 (4.00), 218 (3.04) nm; IR (KBr)  $\nu_{\max}$  3377, 2922, 1449, 1138, 1049, 1012, 997, 934 cm<sup>–1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz), see Table 1; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz), see Table 2; EIMS *m/z* 238 [M]<sup>+</sup> (6), 220 (19), 202 (21), 177 (57), 163 (43), 159 (32), 121 (100), 93 (28); HREIMS *m/z* 238.1935 [M]<sup>+</sup> (calcd for C<sub>15</sub>H<sub>26</sub>O<sub>2</sub>, 238.1933).

**X-ray Crystallography of 2.** C<sub>30</sub>H<sub>34</sub>O<sub>6</sub>, *M* = 490.57, orthorhombic, *P*<sub>2</sub><sub>1</sub><sub>2</sub><sub>1</sub><sub>2</sub><sub>1</sub> (no. 24), *a* = 7.7931(5) Å, *b* = 12.1860(7) Å, *c* = 26.8031(17) Å,  $\alpha = \beta = \gamma = 90^\circ$ , *V* = 2545.4(3) Å<sup>3</sup>, *Z* = 4, *D*<sub>calcd</sub> = 1.280 g cm<sup>–3</sup>,  $\mu$  = 0.088 mm<sup>–1</sup>, 15 264 reflections measured, 4138 reflections independent (*R*<sub>int</sub> = 0.0516), *R* = 0.0443, *wR*<sub>2</sub> = 0.1102, goodness of fit = 1.067, and *T* = 100.0(1) K.

**X-ray Crystallography of 4.** C<sub>15</sub>H<sub>26</sub>O<sub>2</sub>, *M* = 238.36, orthorhombic, *P*<sub>2</sub><sub>1</sub><sub>2</sub><sub>1</sub><sub>2</sub><sub>1</sub> (no. 24), *a* = 5.5549(1) Å, *b* = 14.5774(3) Å, *c* = 17.7586(4) Å,  $\alpha = \beta = \gamma = 90^\circ$ , *V* = 1438.02(5) Å<sup>3</sup>, *Z* = 4, *D*<sub>calcd</sub> = 1.101 g cm<sup>–3</sup>,  $\mu$  = 0.071 mm<sup>–1</sup>, 11 851 reflections measured, 2421 reflections independent (*R*<sub>int</sub> = 0.0403), *R* = 0.0413, *wR*<sub>2</sub> = 0.0995, goodness of fit = 1.076, and *T* = 100.0(1) K.

Compounds **2** and **4** data were collected on a Bruker SMART APEX2 CCD area detector diffractometer with Mo K $\alpha$  radiation ( $\lambda$  = 0.71073 Å) equipped with an Oxford Cryosystem Cobra low-temperature attachment. Cell refinement: APEX2; data reduction: SAINT; programs used to solve structures: SHELXTL;<sup>13</sup> molecular graphics: SHELXTL; software used to prepare material for publication: SHELXTL and PLATON.<sup>14</sup> The structure was solved by direct methods (SHELXTL), and all non-hydrogen atoms were refined anisotropically using the least-squares method on *F*<sup>2</sup> (SHELXTL).<sup>13</sup> Hydroxyl H atoms in compound **4** were located from the difference map and isotropically refined. The remaining H atoms were positioned geometrically and allowed to ride on their parent atoms, with C–H distances in the range 0.93–0.97 Å. The *U*<sub>iso</sub> values were constrained to be 1.5*U*<sub>eq</sub> of the carrier atom for methyl H atoms and 1.2*U*<sub>eq</sub> for the remaining H atoms.

The absolute structures of compounds **2** and **4** were determined by retaking the data and making use of the anomalous scattering of Cu K $\alpha$  X-radiation. The method generally accepted by the International Union of Crystallography is based on the Flack parameter, *x*.<sup>15</sup> This parameter is refined in the least-squares procedure and should give a value close to 0 with a low esd for the correct hand or a value of +1

if the refined structure should be inverted. Flack has indicated that for compounds of known enantiopurity the esd should still be less than 0.12.<sup>16</sup> The crystallographic data (both Cu K $\alpha$  and Mo K $\alpha$  radiations) for the structures of compounds **2** and **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications (CCDC 680150, CCDC 680151, CCDC 681979, and CCDC 681980).

**X-ray Crystal Data of 3.** C<sub>15</sub>H<sub>20</sub>O<sub>4</sub>, *M* = 264.31, crystal dimensions 0.50 × 0.12 × 0.10 mm, hexagonal, space group *P*6(5), *a* = 14.058(2) Å, *b* = 14.058(2) Å, *c* = 15.624(3) Å,  $\alpha = 90^\circ$ ,  $\beta = 90^\circ$ ,  $\gamma = 120^\circ$ , *V* = 2674.1(8) Å<sup>3</sup>, *Z* = 6, *D*<sub>c</sub> = 0.985 mg/m<sup>3</sup>, *F*(000) = 852. The reflection data were collected on a Rigaku RAXIS RAPID IP diffractometer, using graphite-monochromated Mo K $\alpha$  radiation,  $\lambda$  = 0.71073 Å. A total of 16 453 reflections were collected in the range  $2.12^\circ \leq \theta \leq 25.02^\circ$ , of which 1634 unique reflections with *I* > 2 $\sigma$ (*I*) were collected for the analysis. The structure was solved by direct methods using Shelldrick SHELXS-97. The final *R* and *R*<sub>w</sub> factors were 0.0450 and 0.0954, respectively (CCDC 683238).

The X-ray crystal data of **2–4** can be obtained free of charge, by request to the Director, via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

**Cells, Culture Conditions, and Cell Proliferation Assay.** See refs 11, 17, and 18.

**Acknowledgment.** This work was supported by National Natural Science Foundation of China (no. 20772012), The Research Fund for the Doctorate of Higher Education of China (no. 20070027038), and Beijing Natural Science Foundation of China (no. 2073024). H.-K.F. and S.C. also thank the Malaysian Government and Universiti Sains Malaysia for the Scientific Advancement Grant Allocation (SAGA) grant no. 304/PFIZIK/653003/A118.

**Supporting Information Available:** IR, MS, 1D NMR and 2D spectra of **1–4**, CIF data for the crystal studies of **2–4**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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NP800242W