Notes

Dimeric Guaianolides and Sesquiterpenoids from *Artemisia anomala*

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A new dimeric guaianolide (**8**) and a new glaucolide (**3**), a *seco*-guaiaretic acid (**4**), two guaianolides (**6** and **7**), and five known sesquiterpene lactones (**1**, **2**, **5**, **9**, and **10**) were isolated from the aerial part of *Artemisia anomala*. Their structures were determined on the basis of chemical and spectroscopic analysis. In addition, their cytotoxic activities against five human cancer cell lines and anti-COX-2 effects in vitro were evaluated.

Artemisia anomala S. Moore (Chinese name Nan-Liu-Ji-Nu), one species of the genus *Artemisia*, belongs to the Compositae family. As a perennial herbaceous plant, it has been used for centuries in Chinese folk medicines for its function as an analgesic and antibiotic and for curing wounds.[1] However, only a few papers have reported on the chemical constituents of *A. anomala*.[2−4] In addition to flavonoids and coumarins, several sesquiterpene lactones including germacranolides, guaianolides, and unusual dimeric guaianolides were isolated.

In our continuous investigation of bioactive natural products derived from Traditional Chinese Medicines, a systematic phytochemical investigation on *A. anomala* resulted in the isolation of 10 sesquiterpenes, including five new compounds (**3**, **4**, **6**−**8**). In this paper, we describe the isolation, structural elucidation, and evaluation of the antitumor and anti-inflammatory activities of these compounds.

The EtOH extract of *A. anomala* was suspended in H_2O and partitioned with petroleum ether, EtOAc, and *n*-BuOH, successively. The EtOAc fraction was subjected to silica gel and Sephadex LH-20 column chromatography. Terpene-containing fractions were then purified using preparative HPLC and recrystallization to obtain five new compounds: artanomalide A (**3**), artanomalic acid (**4**), artanomalide B (**6**), artanomalide C (**7**), and artanomalide D (**8**), along with five known compounds, armexifolin (**1**),[5] eudesmaafraglaucolide (**2**),[6] *seco*-tanapartholide A (**5**),[7] 8-*O*-acetylarteminolide (**9**),[8] and artanomaloide (**10**).[4] The structures of the new compounds were elucidated on the basis of spectroscopic data.

Compound **3** has a molecular formula of $C_{19}H_{24}O_7$ as established by HRESIMS ($[M + H]^+$, m/z 365.1595), which indicated eight degrees of unsaturation. The IR spectrum of **3** showed absorption bands at 3436 and 1750 cm^{-1}, ascribable to hydroxy and α,β-unsaturated γ-lactone functions. The ^1H and ^{13}C NMR (DEPT) and HSQC data (Table 1) revealed the presence of four methyl, three methylene, five methine, and seven quaternary carbons, including one tetrasubstituted and two trisubstituted double bonds, a lactone, and two *O*-acetyl groups. The two *O*-acetyl groups could be assembled by an HMBC experiment, where a methine proton signal at δ_H 4.96 (H-3) was correlated with the C-1′ acetyl carbon, and the methylene protons at δ_H 4.82 and 4.89 (H_2-13) were correlated with the C-1″ acetyl carbon. The proton at δ_H 4.35 and the carbon at δ_C 65.6 were respectively assigned to H-1 and C-1. Considering the eight degrees of unsaturation and extensive investigation of the HMBC spectrum, compound **3** has considerable structure similarity to 1α-hydroxyisoafraglaucolide.[6] The difference between compound **3** and 1α-hydroxyisoafraglaucolide is probably due to different configurations at some stereogenic centers. The NOESY experiment gave strong cross-peaks between H-14 and H-9, indicating a *Z*-double bond between C-9 and C-10. The correlation between H-15 and H-6 required a preferred conformation with the C-15 methyl group above the plane.[6] The cross-peaks between H-1 and H-3, H-15 and H-3, and H-15 and H-1 indicate that H-1 and H-3 are at the *cis* position. Furthermore, one proton of H-8 at δ_H 2.94 showed correlations with H-6 and H-1, while the other proton at δ_H 3.31 gave no cross-peaks with H-1 or H6. Therefore, compound **3** was elucidated as (*rel*)-1α-hydroxy-3α,13-diacetoxygermacra-4,7(11),9-trien-12,6α-olide and named artanomalide A.

Compound **4** has a molecular formula of $C_{15}H_{18}O_5$ as established by HRESIMS ($[M + H]^+$, m/z 279.1227), which indicated seven degrees of unsaturation. Its IR spectrum showed absorption bands at 3426, 1740, and 1701 cm^{-1}, suggesting the existence of hydroxy, carbonyl, and double-bond functions. The ^1H and ^{13}C NMR (DEPT) and HMQC data (Table 1) revealed the presence of two methyl, five methylene, one methine, and seven quaternary carbons, including one exocyclic methylene (H_2-13) and one tetrasubstituted double bond (C-4 and C-5), three ketone carbonyl carbons (C-1, -3, -10), and one carboxylic carbon (C-12). $^1H-^1H$ COSY data indicated the presence of a partial structure (C-6 to C-9) shown as a bold line in Figure 1. In the HMBC spectrum, long-range correlations between H_2-2 and C-1, C-3 and between H_3-15 and C-3, C-5 established the cyclopentenedione fragment. Key correlations between H_2-6 and C-1, C-5, C-7; H_2-7 and C-5, C-8, C-11, C-13; H_2-8 and C-6, C-9, C-10; and H_3-14 and C-9, C-10 linked the fragments. Further analysis of spectroscopic data confirmed that compound **4** has the same basic skeleton as mandassidione.[9,10] The configuration of C-7 could not be established. The structure of compound **4** was elucidated as a *seco*-guaiaretic acid, named artanomalic acid.

Compound **6** has a molecular formula of $C_{15}H_{19}O_5Cl$, which was established by HRESIMS ($[M + NH_4]^+$, m/z 332.1259), indicating six degrees of unsaturation. The IR spectrum of **6** showed absorption bands at 3493 and 1761 cm^{-1}, ascribable to hydroxy and α,β-unsaturated γ-lactone carbonyl groups. The ^1H and ^{13}C NMR (DEPT) and HMQC data (Table 1) revealed the presence of two methyl, three methylene, five methine, and five quaternary carbons.

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Table 1. NMR Data of Compounds **3**, **4**, **6**, and **7** in $CDCl_3$

	3[a]		**4**[a]		**6**[b]		**7**[a]	
position	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)
1	65.6, CH	4.35, dd (5.5, 11.0)	200.5, qC		75.1, qC		68.0, CH	2.65, s
2	33.1, CH_2	2.00, m; 2.18, m	40.9, CH_2	2.82, s	63.2, CH	3.95, s	203.8, qC	
3	75.2, CH	4.96, dd (7.0, 10.5)	200.3, qC		63.6, CH	4.03, s	131.7, CH	6.06, d (1.5)
4	136.4, qC		157.3, qC		80.3, qC		177.8, qC	
5	125.2, CH	4.99, d (10.0)	157.6, qC		50.9, CH	2.44, d (11.1)	82.4, qC	
6	80.3, CH	5.48, d (10.5)	29.6, CH_2	2.67, dd (6.5, 13.0); 2.72, dd (8.0, 13.0)	77.2, CH	4.33, dd (10.2, 10.8)	86.0, CH	4.41, d (9.5)
7	165.5, qC		39.6, CH	2.91, m	44.5, CH	2.98, m	41.0, CH	3.41, m
8	26.1, CH_2	2.94, t (12.0); 3.31, ddd (1.5, 5.0, 13.0)	27.6, CH_2	1.88, m	22.1, CH_2	1.70, m; 2.22, m	22.5, CH_2	1.80−2.00[c]
9	123.7, CH	5.07, dd 4.0, 10.5)	41.2, CH_2	2.43, dd (7.0, 8.0)	35.5, CH_2	1.90, m	38.6, CH_2	1.80−2.00[c]
10	137.7, qC		208.1, qC		69.8, qC		71.6, qC	
11	122.9, qC		141.0, qC		139.5, qC		139.1, qC	
12	172.3, qC		170.8, qC		169.0, qC		169.5, qC	
13	55.5, CH_2	4.82, d (13.0); 4.89, d (13.0)	129.0, CH_2	5.68, s; 6.36, s	119.9, CH_2	5.43, d (3.0); 6.16, d (3.6)	120.1, CH_2	5.54, d (3.0); 6.21, d (3.5)
14	17.0, CH_3	1.77, s	30.0, CH_3	2.13, s	21.9, CH_3	1.40, s	32.7, CH_3	1.60, s
15	11.5, CH_3	1.92, s	9.5, CH_3	1.98, s	24.0, CH_3	1.51, s	16.2, CH_3	2.29, d (1.5)
1′	169.9, qC							
2′	21.1, CH_3	2.06, s						
1″	170.6, qC							
2″	20.8, CH_3	2.11, s						

[a] ^{1}H and ^{13}C NMR data were recorded at 500 and 125 MHz. [b] ^{1}H and ^{13}C NMR data were recorded at 300 and 75 MHz. [c] Overlapped signals.

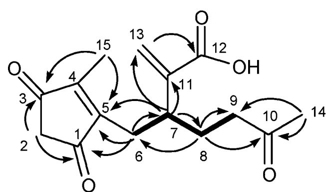


Figure 1. HMBC correlations (arrows) and ^{1}H−^{1}H COSY (bold lines) used in determining the structure of **4**.

The ^{1}H and ^{13}C NMR spectra were similar to those of 3α-chloro-4β,10α-dihydroxy-1β,2β-epoxy-5α,7αH-guai-11(13)-en-12,6α-olide,[11] except some resonances at C-5, C-7, and C-14. The *trans* disposition of H-5, H-6, and H-7 was deduced from the large vicinal coupling constants ($J_{5,6}$ = 11.1 Hz and $J_{6,7}$ = 10.2 Hz), while the relative α-orientations of the methyl groups at C-14 and C-15 were evident from NOE interactions between H-5/H_3-14 and H-5/H_3-15. The strong NOE correlation between H-3 and H-5 revealed their *cis* relationship, corresponding to the 3β-Cl orientation. The coupling constant between H-2 and H-3α (<1 Hz) implied a dihedral angle near 90°. Thus, H-2 was β-oriented and the 1,2-epoxy group was α-oriented.[11,12] Therefore, the structure of compound **6** was elucidated as (*rel*)-3β-chloro-4β,10β-dihydroxy-1α,2α-epoxy-5α,7αH-guai-11(13)-en-12,6α-olide and named artanomalide B.

Compound **7** has a molecular formula of $C_{15}H_{18}O_5$, as established by HRESIMS ([M + H]$^+$, m/z 279.1227), which indicated seven degrees of unsaturation. The IR spectrum of **7** showed absorption bands at 3432 and 1770 cm^{-1}, ascribable to hydroxy and α,β-unsaturated γ-lactone functions. The ^{1}H and ^{13}C NMR and HSQC data (Table 1) revealed the presence of two methyl, three methylene, four methine, and six quaternary carbons, including an exocyclic methylene (H_2-13), a cyclic olefinic bond (C-3 and C-4), and a ketone carbonyl carbon (C-1). The overall appearance of the ^{1}H and ^{13}C NMR spectra showed similarity to those of 5α,10α-dihydroxy-1αH-dehydroleucodin.[13] The major difference between the two compounds was the configuration at C-10. A strong NOE between H-1 and H_3-14 revealed their *cis* relationship, corresponding to a 10α-Me orientation. Thus, the structure of compound **7** was elucidated as (*rel*)-5α,10β-dihydroxy-1αH-dehydroleucodin, named artanomalide C.

Compound **8** has a molecular formula of $C_{32}H_{36}O_8$, as established by HRESIMS ([M + H]$^+$, m/z 549.2483), which indicated 15 degrees of unsaturation. The IR spectrum of **8** showed absorption bands at 3437, 1765, and 1647 cm^{-1}, ascribable to hydroxy, α,β-unsaturated γ-lactone, and olefinic groups. The ^{1}H and ^{13}C NMR (DEPT) and HSQC data (Table 2) revealed the presence of five methyl, five methylene, 10 methine, and 12 quaternary carbons including four carbonyl carbons. The overall appearance of the ^{1}H and ^{13}C NMR spectra were very similar to those of compound **9** (8-*O*-acetylarteminolide),[8] except for signals around C-8 and C-10′. The NOE correlation between the methyl of the acetyl group and

Table 2. NMR Data of Compound **8** in $CDCl_3$

position	δ_C, mult.	δ_H (J in Hz)	HMBC[a]
1	134.0, qC		
2	194.8, qC		
3	136.1, CH	6.19, t (1.0)	1, 2, 4, 5, 15
4	170.2, qC		
5	52.0, CH	3.26, t (10.0)	1, 3, 4, 6, 7
6	80.1, CH	4.02, dd (10.0, 11.0)	1
7	59.4, CH	2.68, t (11.0)	5, 6, 8, 9, 11, 13, 4′
8	68.0, CH	4.78, dt (2.5, 11.0)	
9	44.4, CH_2	2.31, dd (5.0, 13.5); 2.47, dd (11.0, 13.5)	1, 7, 8, 10, 14
10	143.9, qC		
11	61.9, qC		
12	178.7, qC		
13	39.7, CH_2	2.04, d (12.0); 2.52, d (12.0)	7, 12, 1′, 2′, 4′, 5′, 6′, 10′, 14′
14	20.5, CH_3	2.39, s	1, 9, 10
15	20.2, CH_3	2.33, s	3, 4, 5
1′	63.2, qC		
2′	138.5, CH	6.29, d (5.5)	11, 1′, 4′, 5′
3′	134.9, CH	5.81, d (5.5)	11, 13, 1′, 2′, 5′, 15′
4′	58.2, qC		
5′	66.6, CH	2.86, d (10.0)	11, 2′, 3′, 6′, 7′
6′	78.0, CH	4.06, t (10.0)	8′
7′	43.3, CH	2.76, m	
8′	23.0, CH_2	1.56, m	7′, 10′, 11′
9′	37.0, CH_2	1.74, q (7.0)	1′, 7′, 8′, 10′
10′	72.8, qC		
11′	140.1, qC		
12′	169.6, qC		
13′	119.2, CH_2	5.36, d (3.0); 6.08, d (3.0)	7′, 11′, 12′
14′	23.7, CH_3	1.45, s	1′, 9′, 10′
15′	17.0, CH_3	1.48, s	11, 3′, 4′, 5′
1″	169.3, qC		
2″	21.5, CH_3	2.01, s	1″

[a] HMBC NMR data were recorded at 600 and 150 MHz.

H-6′ indicated that the *O*-acetyl group is substituted at C-10′. The relative configuration of **8** was determined by analysis of the NOESY spectrum. The strong NOE correlation between H-6 and H-8 and between H-6 and H_3-15′ indicated that they are cofacial and were randomly assigned to a β-orientation, while the correlation between H-2′, H-3′ and H-6′ and between H-2″ and H-6′ indicated the β-orientation of H-6′ and the 10′ *O*-acetyl group. A strong NOE correlation was found between H-14′ and H-7′, confirming the 10′β-*O*-acetyl orientation. Thus, compound **8** was identified as an isomer of compound **9** and named artanomalide D.

The structures of the five known sesquiterpene lactones (**1**, **2**, **5**, **9**, and **10**) (Chart 1) were determined by comparison of their spectroscopic data with literature data.[4−8]

The cytotoxicity of the sesquiterpenes against HCT-8, Bel-7402, BGC-823, A549, and A2780 cells was assayed. The dimeric guaianolide artanomalide D (**8**) showed strong inhibition of the growth of all cell lines except A549. The IC_{50} values against HCT-8, Bel-7402, BGC-823, and A2780 were 1.9, 3.0, 8.5, and 1.8 μM, respectively. Compounds **4**, **6**, and **8** showed strong anti-inflammatory activities in the COX-2 inhibition test at 50 μM, with inhibitory rates of 98.2%, 98.4%, and 99.5%, respectively.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer 243B polarimeter in $CHCl_3$ at 25 °C. UV data were recorded on a Shimadzu UV-2401 spectrophotometer. IR spectra were determined with a Nicolet Avatar FT-IR spectrophotometer. NMR spectra were obtained on Varian INOVA-500 and JEOL JNM-A 300 spectrometers, and the chemical shifts are given in δ (ppm) values with reference to TMS. The coupling constants (*J* values) are reported in Hz. ESIMS and HRESIMS were carried out on Applied-Biosystems QSTAR ESI-TOF and Bruker APEX II mass spectrometers, respectively. Analytical HPLC was conducted using an Agilent 1100 liquid chromatograph system, which was set up with a quaternary pump, a diode array detector, and Waters NovaPak HR C_{18} column (4.6 mm i.d. × 250 mm, 5 μm). Semipreparative HPLC was performed using a Waters Prep. NovaPak HR C_{18} column (7.8 mm i.d. × 300 mm, 6

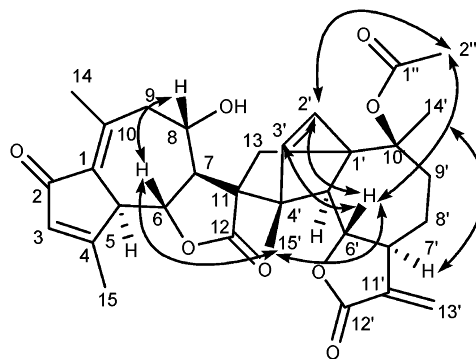
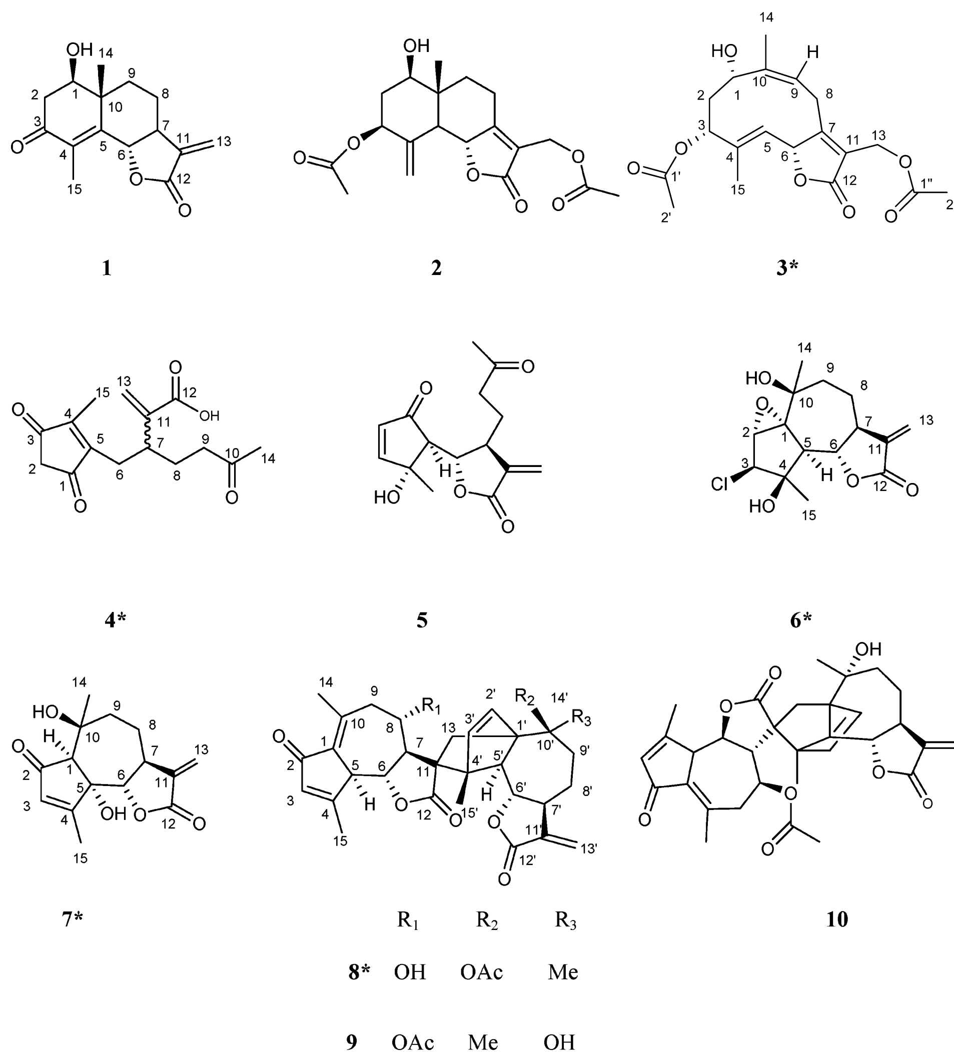


Figure 2. NOE cross-peaks observed in the NOESY spectrum of **8**.

Chart 1. Structures of Compounds **1**−**10**[a]



	R1	R2	R3
8*	OH	OAc	Me
9	OAc	Me	OH

[a] New compounds marked with star.

μm), Waters 2487 dual-λ absorbance detector, and detection wavelength of 210 and 254 nm. Silica gel (200−300 mesh, Qingdao Marine Chemical Co. Ltd.) and ODS (Fuji Silysia Chemical Ltd.) were used in open column chromatography fractionations. All solvents used for isolation were of analytical grade.

Plant Material. The aerial part of *A. anomala* was collected from Zhejiang Province, China, in 2005 and identified by Prof. Peng-Fei Tu of Peking University Health Science Center. A voucher specimen (No. 20070315) has been deposited at the Herbarium of Modern Research Center for Traditional Chinese Medicine, Peking University.

Extraction and Isolation. The air-dried aerial part of *A. anomala* (15 kg) was refluxed with 95% EtOH (3 × 90 L) at 60 °C. The combined extract was concentrated under vacuum; the residue (150 g) was suspended in H_2O and partitioned with petroleum ether, EtOAc, and *n*-BuOH successively. The EtOAc extract (60 g) was subjected to column chromatography (200−300 mesh silica gel, 500 g). Fractions 1−6 were obtained through gradient elution with $CHCl_3$−MeOH (100:1 to 1:1) on the basis of TLC analysis. Fraction 4 was subjected to column chromatography (CC) (Sephadex LH-20, $CHCl_3$−MeOH, 1:1) and then to semipreparative HPLC (MeOH−H_2O, 70:30) to give **9** (5.2 mg) and **6** (13.6 mg). Fraction 5 was subjected to CC (Sephadex LH-20, $CHCl_3$−MeOH, 1:1) and subsequently to ODS open column chromatography (MeOH−H_2O, 15:85 to 65:45) to afford fractions 5-1 to 5-3. Fraction 5-1 was further purified by semipreparative HPLC (MeOH−H_2O, 32:68) to give **1** (15.2 mg) and **7** (7.4 mg). Fraction 5-2 was purified by semipreparative HPLC (MeOH−H_2O, 28:72) to give **4** (12.6 mg) and **5** (23.2 mg). Fraction 5-3 was purified by semipreparative HPLC (MeOH−H_2O, 52:48) to afford **8** (25.6 mg) and **10** (12.3 mg). Fraction 6 was purified by semipreparative HPLC (MeOH−H_2O, 60:40) to afford **2** (93.6 mg) and **3** (11.0 mg).

Artanomalide A (3): colorless gum; $[\alpha]^{25}_{D}$ +118.2 (*c* 0.11, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 248.2 (3.46) nm; IR (KBr) ν_{max} 3436, 1750, 1680 cm^{-1}; ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data, see Table 1; HRESIMS $[M + H]^+$ *m*/*z* 365.1595 (calcd for $C_{19}H_{25}O_7$, 365.1588).

Artanomalic acid (4): colorless gum; $[\alpha]^{25}_{D}$ −46.8 (*c* 0.19, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 246.2 (4.26) nm; IR (KBr) ν_{max} 3426, 1740, 1701 cm^{-1}; ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data, see Table 1; HRESIMS $[M + H]^+$ *m*/*z* 279.1227 (calcd for $C_{15}H_{19}O_5$, 279.1230).

Artanomalide B (6): yellowish gum; $[\alpha]^{25}_{D}$ −52.6 (*c* 0.19, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 242 (4.32) nm; IR (KBr) ν_{max} 3493, 3439, 1761, 1702 cm^{-1}; ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectroscopic data, see Table 1; HRESIMS $[M + NH_4]^+$ *m*/*z* 332.1259 (calcd for $C_{15}H_{23}O_5ClN$, 332.1260).

Artanomalide C (7): colorless, amorphous solid; $[\alpha]^{25}_{D}$ −8.0 (*c* 0.10, CH_3OH); UV (CH_3OH) λ_{max} (log ε) 205.2(3.62) nm; IR (KBr) ν_{max} 3432, 1770, 1687 cm^{-1}; ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data, see Table 1; HRESIMS $[M + H]^+$ *m*/*z* 279.1227 (calcd for $C_{15}H_{19}O_5$, 279.1238).

Artanomalide D (8): colorless gum; $[\alpha]^{25}_{D}$ +35.3 (*c* 0.15, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 251.8 (4.52) nm; IR (KBr) ν_{max} 3437, 2923, 1765, 1691, 1647, 1617, 1261, 1140, 1033 cm^{-1}; ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectroscopic data, see Table 2; HRESIMS $[M + H]^+$ *m*/*z* 549.2483 (calcd for $C_{32}H_{37}O_8$, 549.2470).

Bioassays. Human tumor cell lines HCT-8, Bel-7402, BGC-823, A549, and A2780 were maintained in RPMI 1640 medium (Gibco/BRL) supplemented with 10% (v/v) fetal bovine serum, 100 IU/mL penicillin, and 100 IU/mL streptomycin. Cells were cultured in 96-well microtiter plates for the assay. Appropriate dilutions (10^{-2} to 10^2 μM) of the test compounds were added to the cultures. After 72 h incubation in humidified air containing 5% CO_2 at 37 °C, growth inhibitions of the cancer cells were evaluated by the MTT method.[14] Results are expressed as the mean value of triplicate data points. Taxol was used as a positive control.

The procedure described by Hu et al.[15] was used for the measurement of COX-2 inhibitory activity.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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