Mono-, Bi-, and Triphenanthrenes from the Tubers of *Cremastra appendiculata*

Zhen Xue,[†] Shuai Li,[†] Sujuan Wang,[†] Yinhong Wang,[†] Yongchun Yang,[†] Jiangong Shi,*[,†] and Lan He*[,‡]

Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College (Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education), Beijing 100050, People's Republic of China, and Department of Chemistry, Beijing Normal University, Beijing 100875, People's Republic of China

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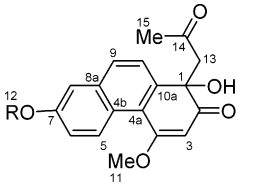
Six newphenanthrene derivatives, including three monophenanthrenes (**1**−**3**), two biphenanthrenes (**4** and **5**), and a triphenanthrene (**6**), have been isolated from an ethanolic extract of the tubers of *Cremastra appendiculata*. Using spectroscopic methods, the structures of compounds **1**−**6** were determined as 1-hydroxy-4,7-dimethoxy-1-(2-oxopropyl)-1*H*-phenanthren-2-one (**1**), 1,7-dihydroxy-4-methoxy-1-(2-oxopropyl)-1*H*-phenanthren-2-one (**2**), 2-hydroxy-4,7-dimethoxyphenanthrene (**3**), 2,7,2′-trihydroxy-4,4′,7′-trimethoxy-1,1′-biphenanthrene (**4**), 2,2′-dihydroxy-4,7,4′,7′-tetramethoxy-1,1′-biphenanthrene (**5**), and 2,7,2′,7′,2″-pentahydroxy-4,4′,4″,7″-tetramethoxy-1,8,1′,1″-triphenanthrene (**6**), respectively. Compounds **1**−**6** and two known compounds, cirrhopetalanthin (**7**) and flavanthrinin (**8**), obtained previously from this plant, were evaluated against six human cancer cells and a normal cell line.

Species of the Orchidaceae are rich sources of aromatic compounds such as simple benzene and bibenzyl derivatives, as well as monomeric and dimeric phenanthrenes, 9,10-dihydrophenanthrenes, phenanthropyrans, and 9,10-dihydrophenanthropyrans.[1−3] The tubers of three orchidaceous plants, *Cremastra appendiculata* (D. Don) Makino, *Pleione bulbocodioides* (Franch.) Rolfe, and *Pleione yunnanensis* Rolfe, are used as "Shan-Ci-Gu" in traditional Chinese medicine for the treatment of various cancers.[4,5] There are only a few reports concerning the secondary metabolites of *C. appendiculata*,[6,7] which has a long history of medicinal utilization in mainland China.[5] Due to the greatly increased use of traditional Chinese medicine in recent years, some species including *C. appendiculata* have became difficult to collect in the wild, and their supply is now carried out by cultivation. As part of a program to assess systematically the chemical and biological diversity of several cultivated traditional Chinese medicines, we have carried out a chemical investigation of the medicinally useful tubers of *C. appendiculata*. In previous papers[8,9] we reported isolation and structural identification of the known compounds blestriarene C[10] (cirrhopetalanthrin,[11] **7**), flavanthrinin (**8**),[12] isohircinol,[13] *p*-hydroxybenzaldehyde, *p*-hydroxyphenylethyl alcohol,[14] 3,4-dihydroxyphenyl ethyl alcohol,[15] 7-hydroxy-4-methoxyphenanthrene-2-*O*-*β*-D-glucoside,[16] 4-(2-hydroxyethyl)-2-methoxyphenyl-1-*O*-*β*-D-glucopyranoside,[17] tyrosol 8-*O*-*β*-D-glucopyranoside,[18] vanilloloside,[19] and the common plant metabolites *β*-sitosterol, daucosterol, sucrose, and adenosine from an ethanolic extract of the tubers of *C. appendiculata*. In a continuation of work on the same material, we report herein the isolation and structural elucidation of six new aromatic compounds including two 1*H*-phenanthren-2-one derivatives with a 2-oxopropyl substituent (**1** and **2**), a monophenanthrene (**3**), two biphenanthrenes (**4** and **5**), and an unusual triphenanthrene (**6**), as well as the cytotoxicity of **1**−**6** and the known compound cirrhopetalanthrin (**7**) against several human cancer cell lines.



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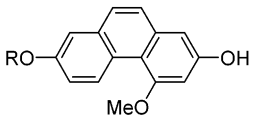

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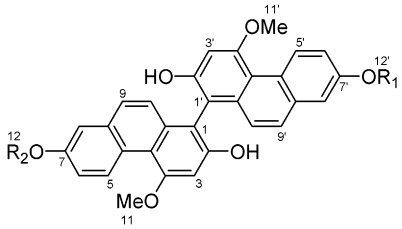

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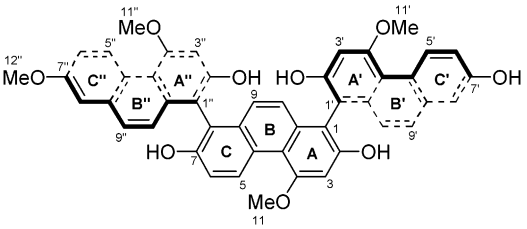
7 R_1 = R_2 = H



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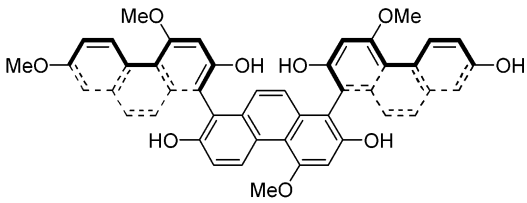

6a

Results and Discussion

An EtOH extract of the tubers of *C. appendiculata* was partitioned between H_2O and EtOAc. After concentration under reduced pressure, the residue of the EtOAc phase was subjected to column chromatography over silica gel by eluting with a gradient of polarity of increasing acetone (5−100%) in petroleum ether, to give 30 fractions. Subsequently, these fractions were further purified by a variety of chromatographic techniques to yield the new compounds **1**−**6**.

Compound **1** was obtained as pale yellowish needles (acetone), mp 155−156 °C. The IR spectrum showed the presence of hydroxyl

* To whom correspondence should be addressed. Tel: 86-10-83154789. Fax: 86-10-63017757. E-mail: shijg@imm.ac.cn.
[†] Institute of Materia Medica.
[‡] Beijing Normal University.

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Table 1. ^{1}H NMR Data of Compounds **1**−**7** and **6a**[a]

proton	**1** (acetone-d_6)	**2** (acetone-d_6)	**3** (acetone-d_6)	**4** (acetone-d_6)	**4** (MeOH-d_4)	**5** ($CDCl_3$)	**6** (MeOH-d_4)	**7** (MeOH-d_4)	**6a** (MeOH-d_4)
1			6.92 d (2.5)						
3	5.77 s	5.75 s	6.83 d (2.5)	7.04 s	6.94 s	7.05 s	7.049 s	6.94 s	7.020s
3′				7.05 s	6.95 s	7.05 s	6.899 s; *6.894 s*[b]	6.94 s	6.927 s; *6.932 s*[b]
3″							6.908 s; *6.912 s*[b]		6.945 s; *6.942 s*[b]
5	9.02 d (9.5)	8.97 d (9.0)	9.42 d (9.5)	9.53 d (9.0)	9.42 d (9.5)	9.57 d (10.0)	9.728 d (9.5)	9.42 d (9.0)	9.728 d (9.5)
5′				9.57 d (9.5)	9.47 d (10.5)	9.57 d (10.0)	9.411 d (9.5)	9.42 d (9.0)	9.390 d (9.5)
5″							9.465 d (9.5)		9.444 d (9.5)
6	7.21 dd (9.5, 2.5)	7.19 dd (9.0, 2.5)	7.17 dd (9.5,2.5)	7.21 dd (9.0, 3.0)	7.05 dd (9.5, 2.5)	7.29 dd (10.0, 3.0)	7.344 d (9.5); *7.347 d (9.5)*[b]	7.05 dd (9.0, 3.0)	7.347 d (9.5); *7.345 d (9.5)*[b]
6′				7.24 dd (9.5, 3.0)	7.12 dd (10.5, 2.5)	7.29 dd (10.0, 3.0)	7.061 dd (9.5, 3.0)	7.05 dd (9.0, 3.0)	7.031 dd (9.5, 3.0)
6″							7.141 dd (9.5, 3.0)		7.111 dd (9.5, 3.0)
8	7.35 d (2.5)	7.23 d (2.5)	7.33 d (2.5)	7.20 d (3.0)	7.01 d (2.5)	7.18 d (3.0)		7.01 d (3.0)	
8′				7.30 d (3.0)	7.13 d (2.5)	7.18 d (3.0)	7.046 d (3.0)	7.01 d (3.0)	7.011 d (3.0)
8″							7.179 d (3.0)		7.142 d (3.0)
9	7.97 d (8.5)	7.84 d (8.5)	7.65 d (8.5)	7.39 d (9.0)	7.24 d (9.0)	7.49 d (8.5)	6.843 d (10.0)	7.25 d (9.5)	6.873 d (10.0)
9′				7.49 d (9.0)	7.34 d (9.0)	7.49 d (8.5)	7.267 d (9.0); *7.278 d (9.0)*[b]	7.25 d (9.5)	7.278 d (9.0); *7.286 d (9.0)*[b]
9″							7.383 d (9.0); *7.373 d (9.0)*[b]		7.386 d (9.0); *7.379 d (9.0)*[b]
10	7.83 d (8.5)	7.77 d (8.5)	7.56 d (8.5)	7.03 d (9.0)	6.94 d (9.0)	7.11 d (8.5)	6.813 d (10.0)	6.94 d (9.5)	6.843 d (10.0)
10′				7.08 d (9.0)	6.98 d (9.0)	7.11 d (8.5)	6.938 d (9.0); *6.978 d (9.0)*[b]	6.94 d (9.5)	6.985 d (9.0); *7.018 d (9.0)*[b]
10″							7.023 d (9.0); *6.983 d (9.0)*[b]		7.060d (9.0); *7.028 d (9.0)*[b]
11	4.16 s	4.13 s	4.09 s	4.21 s	4.12 s	4.22 s	4.245 s	4.12 s	4.245 s
11′				4.22 s	4.12 s	4.22 s	4.095 s	4.12 s	4.112 s
11″							4.090 s		4.097 s
12	3.94 s		3.91 s			3.94 s			
12′				3.91 s	3.82 s	3.94 s			
12″							3.875 s		3.844 s
13	(a) 2.99 d (14.0)	(b) 3.08 d (14.0)	(a) 2.96 d (14.0)	(b) 3.04 d (14.0)					
15	2.08 s	2.06 s							

[a] NMR data were measured at 500 MHz. Proton coupling constants (*J*) in Hz are given in parentheses. The assignments were based on DEPT, ^{1}H−^{1}H COSY, HMQC, HMBC, and phase-sensitive ^{1}H−^{1}H COSY experiments. [b] Data in the same line in italics were assignable to the racemate of **6** with R_{a1},R_{a2}/S_{a1},S_{a2} configurations and **6a** with R_{a1},S_{a2}/S_{a1},R_{a2} configurations.

(3394 cm^{-1}), carbonyl (1707 cm^{-1}), and aromatic ring (1606 and 1502 cm^{-1}) functional groups. The EIMS of **1** exhibited a molecular ion at *m*/*z* 326, and HREIMS gave the molecular formula, $C_{19}H_{18}O_5$. The ^{1}H NMR spectrum of **1** showed three methyl singlets attributed to two aromatic methoxyls at δ 3.94 (3H, s, H_3-12) and 4.16 (3H, s, H_3-11) and an acetyl at δ 2.08 (3H, s, H_3-15), a characteristic AB spin system of an isolated methylene unit at δ 2.99 (1H, d, J = 14.0 Hz, H-13a) and 3.08 (1H, d, J = 14.0 Hz, H-13b), and two singlets assignable to an olefinic proton at δ 5.77 (1H, s, H-3) and a hydroxy proton at δ 4.86 (exchangeable). In addition, two groups of aromatic proton signals could be attributed to a 1,2,3,4-tetrasubstituted benzene moiety [δ 7.83 (1H, d, J = 8.5 Hz, H-10) and 7.97 (1H, d, J = 8.5 Hz, H-9)] and a 1,2,4-trisubstituted benzene moiety [δ 7.21 (1H, dd, J = 9.5 and 2.5 Hz, H-6), 7.35 (1H, d, J = 2.5 Hz, H-8), and 9.02 (1H, d, J = 9.5 Hz, H-5)], respectively. Besides protonated carbon signals corresponding to the above protons, the ^{13}C NMR and DEPT spectra of **1** showed nine quaternary carbon signals assigned to two carbonyls at δ 200.6 (C-2) and 205.2 (C-14), six sp^2 carbons (two oxygenated, δ >150 ppm), and an oxygenated sp^3 carbon at δ 77.7 (C-1). These data, especially the deshielded aromatic proton signal at δ 9.02 (H-5),[11,20] suggested that compound **1** possesses a phenanthrene structure with somewhat unusual substituents.

The structure of **1** was established by a comprehensive analysis of its 2D NMR spectroscopic data. The ^{1}H−^{1}H gCOSY and gHMQC spectra were used to provide unambiguous assignments of the protons and protonated carbons in the NMR spectra of **1** (Tables 1 and 2). In the HMBC spectrum, ^3J correlations from H-3 to C-1 and C-4a, H-5 to C-4a, C-7, and C-8a, H-6 to C-4b and C-8, H-8 to C-4b, C-6, and C-9, H-9 to C-4b, C-8, and C-10a, and H-10 to C-1, C-4a, and C-8a, as well as ^2J correlations from H-3 to C-2 and C-4 (Figure 1), in combination with the chemical shift values of C-1 and C-2, established unequivocally that **1** has the parent structure 1*H*-phenanthren-2-one. Meanwhile, ^3J correlations from H_3-11 to C-4 (δ 172.5) and from H_3-12 to C-7 (δ 158.4) revealed that the two methoxyl groups are located at C-4 and C-7, respectively. In addition, HMBC correlations from the hydroxyl proton to C-1, C-2, C10a, and C-13, from both H-13a and H-13b to C-1, C-2, C10a, C-14, and C-15, and from H_3-15 to both C-13 and C-14 demonstrated the presence of both hydroxy and 2-oxopropyl groups at C-1. Therefore, the structure of **1** was determined as 1-hydroxy-4,7-dimethoxy-1-(2-oxopropyl)-1*H*-phenanthren-2-one.

Compound **2** was obtained as pale yellowish needles (acetone), mp 158−159 °C, and showed UV and IR spectroscopic features similar to those of **1**. The EIMS of **2** gave a molecular ion at *m*/*z* 312, and the HREIMS provided a molecular formula of $C_{18}H_{16}O_5$, with one less CH_2 unit than **1**. The ^{1}H NMR spectroscopic data (Table 1) of **2** were also similar to those of **1** except that a phenolic hydroxy singlet at δ 8.77 (1H, s, exchangeable) of **2** replaced the relatively shielded C-12 methoxyl singlet of **1**, indicating that **2** is the demethyl derivative of **1**, in which the methoxyl attributed to C-7 is replaced by a hydroxyl. This was confirmed by a further comparison of the ^{13}C NMR data of **1** and **2** (Table 2) and by the gHMBC data of **2**, showing long-range correlations from the phenolic hydroxyl proton to C-6, C-7, and C-8. Consequently, the structure of **2** was determined as 1,7-dihydroxy-4-methoxy-1-(2-oxopropyl)-1*H*-phenanthren-2-one.

Compound **3** was obtained as pale yellowish needles (acetone), mp 160−161 °C, with the molecular formula $C_{16}H_{14}O_3$ determined

Table 2. ^{13}C NMR Data of Compounds **1**−**7**[a]

carbon	**1** (acetone-d_6)	**2** (acetone-d_6)	**3** (acetone-d_6)	**4** (acetone-d_6)	**4** (MeOH-d_4)	**5** ($CDCl_3$)	**6** (MeOH-d_4)	**7** (MeOH-d_4)
1	77.7	77.7	105.5	109.6	111.5	105.7	111.4	111.5
1′				109.7	111.5	105.7	111.7	111.5
1″							111.5	
2	200.6	200.8	156.3	154.9	154.8	153.2	154.6	154.6
2′				155.0	154.6	153.2	154.2	154.6
2″							154.7	
3	99.1	99.0	100.3	100.1	100.3	98.5	100.5	100.3
3′				100.1	100.3	98.5	100.3	100.3
3″							100.3	
4	172.5	172.6	160.3	160.0	160.5	160.6	160.7	160.5
4′				159.9	160.5	160.6	160.5	160.5
4″							160.4	
4a	122.9	122.9	115.5	116.3	116.9	116.6	117.3	117.0
4a′				116.1	116.7	116.6	116.8	117.0
4a″							116.8	
4b	125.9	125.3	125.7	125.1	125.8	125.0	126.5	125.8
4b′				125.8	126.5	125.0	125.7	125.8
4b″							126.4	
5	129.9	130.2	129.8	129.9	130.5	129.4	130.4	130.5
5′				129.8	130.4	129.4	130.5	130.5
5″							130.4	
6	120.7	120.6	117.0	117.2	117.3	117.0	117.3	117.3
6′				117.0	117.2	117.0	117.3	117.3
6″							117.1	
7	158.4	156.1	157.6	155.0	155.4	156.9	153.7	155.4
7′				157.3	158.0	156.9	155.3	155.4
7″							158.0	
8	107.8	110.9	109.5	111.7	112.1	108.4	118.4	112.0
8′				108.8	109.3	108.4	112.0	112.0
8″							109.3	
8a	136.8	137.0	134.1	133.8	134.6	133.1	134.1	134.6
8a′				133.6	134.3	133.1	134.5	134.6
8a″							134.3	
9	131.7	131.3	128.6	128.0	128.4	129.1	126.4	128.4
9′				128.3	128.7	129.1	128.3	128.4
9″							128.6	
10	124.9	124.7	127.9	125.2	125.9	123.9	125.9	125.9
10′				125.4	126.1	123.9	125.9	125.9
10″							126.4	
10a	142.3	141.9	135.6	134.8	135.5	133.8	135.2	135.5
10a′				135.0	135.7	133.8	135.0	135.5
10a″							135.6	
11	57.2	57.2	56.0	55.6	56.1	55.8	56.2	56.1
11′				55.7	56.1	55.8	56.0	56.1
11″							56.0	
12	55.7		55.4			55.2		
12′				55.1	55.6	55.2		
12″							55.6	
13	57.5	57.5						
14	205.2	2.5.3						
15	32.0	32.0						

[a] NMR data were measured at 125 MHz. The assignments were based on DEPT, HMQC (or HSQC), and HMBC experiments.

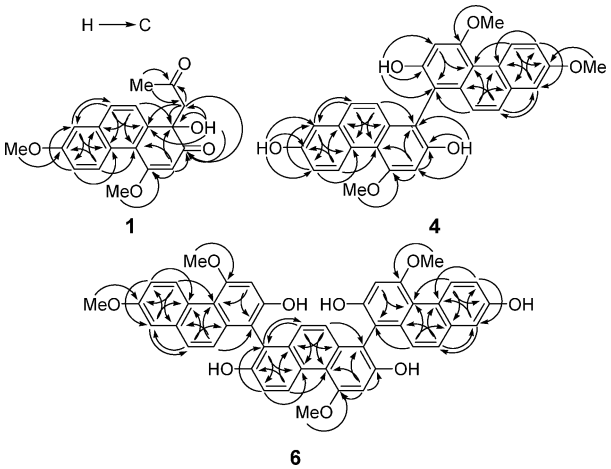

Figure 1. Main HMBC correlations of compounds **1**, **4**, and **6**.

by the HREIMS at *m*/*z* 254.0936 $[M]^+$ (calcd for $C_{16}H_{14}O_3$, 254.0942). The UV, IR, and ^1H NMR data of **3** were similar to those of the co-occurring flavanthrinin (**8**, 2,7-dihydroxy-4-methoxylphenanthrene)[8,12] except for the phenolic hydroxy singlet at δ_H 8.45 (1H, s, O*H*-7) in the ^1H NMR spectrum of flavanthrinin (**8**). This was replaced by a signal attributed to an aromatic methoxyl at δ_H 3.91 (3H, s) in the ^1H NMR spectrum of **3**, indicating that this isolate is the C-7 methoxyl derivative of flavanthrinin (**8**). This was confirmed by comparison of the ^{13}C NMR data of **3** and flavanthrinin and by a gHMBC experiment of **3** showing a long-range correlation from the methoxyl protons to C-7. Thus, the structure of **3** was determined as 2-hydroxy-4,7-dimethoxyphenanthrene.

Compound **4** was obtained as a pale brown amorphous powder (acetone), mp >300 °C. The IR and UV spectroscopic data of **4** closely resembled those of **3**. The EIMS of **4** exhibited a molecular ion at *m*/*z* 492 $[M]^+$, and the HREIMS established the molecular formula as $C_{31}H_{24}O_6$. The ^1H NMR spectrum of **4** in acetone-d_6 showed six pairs of aromatic proton signals consisting of a pair of singlets at δ 7.04 (1H, s, H-3) and 7.05 (1H, s, H-3′), two pairs of doublets attributed to two *ortho*-coupled AB systems at δ 7.03 (1H, d, J = 9.0 Hz, H-10), 7.08 (1H, d, J = 9.0 Hz, H-10′), 7.39 (1H, d, J = 9.0 Hz, H-9), and 7.49 (1H, d, J = 9.0 Hz, H-9′), and three pairs of signals assignable to two *ortho-meta*-coupled ABX systems at δ 9.53 (1H, d, J = 9.0 Hz, H-5), 9.57 (1H, d, J = 9.5 Hz, H-5′), 7.21 (1H, dd, J = 9.0 and 3.0 Hz, H-6), 7.24 (dd, 1H, J = 9.5 and

3.0 Hz, H-6′), 7.20 (1H, d, J = 3.0 Hz, H-8), and 7.30 (1H, d, J = 3.0 Hz, H-8′). In addition, three aromatic methoxyl singlets at δ 3.91 (3H, s, H_3-12′), 4.21 (3H, s, H_3-11), and 4.22 (3H, s, H_3-11′), as well as three exchangeable phenolic hydroxy singlets at δ 7.67, 7.70, and 8.50 (each 1H, s, O*H*-2, O*H*-2′ and O*H*-7), were observed. These data, especially the presence of two deshielded doublets (H-5 and H-5′), suggested that compound **4** is an asymmetrical biphenanthrene derivative with three hydroxyls and three methoxyls as substituents. This deduction was confirmed by the ^{13}C NMR and DEPT spectra of **4**, which displayed carbon signals for six pairs of aromatic methines, five pairs of quaternary aromatic carbons, six oxygenated quaternary aromatic carbons (δ >145 ppm), and three methoxyl carbons (Table 2). The structure of **4** was finally established by 2D NMR experiments. After signals of protons and protonated carbons in the NMR spectra were assigned unambiguously by ^{1}H−^{1}H gCOSY and gHSQC experiments (Tables 1 and 2), the gHMBC data of **4** resulted in the establishment of both the substitution patterns of the two phenanthrene units and their dimerization sites. In the HMBC spectrum, correlations (Figure 1) from H-3 to C-1 and C-4a, H-5 to C-4a, C-7, and C-8a, H-6 to C-4b and C-8, H-8 to C-4b, C-6, and C-9, H-9 to C-4b, C-8, and C-10a, H-10 to C-1, C-4a, and C-8a, H_3-11 to C-4, O*H*-2 to C-1, C-2, and C-3, and O*H*-7 to C-6, C-7, and C-8, in combination with the quaternary nature and chemical shift value of C-1, revealed that one of the phenanthrene units is a 2,7-dihydroxy-4-methoxyphenanthrene-1-yl group. In turn, correlations from H-3′ to C-1′ and C-4′a, H-5′ to C-4′a, C-7′, and C-8′a, H-6′ to C-4′b and C-8′, H-8′ to C-4′b, C-6′, and C-9′, H-9′ to C-4′b, C-8′, and C-10′a, H-10′ to C-1′, C-4′a, and C-8′a, H_3-11′ to C-4′, H_3-12″ to C-7′, and O*H*-2′ to C-1′, C-2′, and C-3′, along with the quaternary nature and chemical shift value of C-1′, demonstrated that the second phenanthrene unit in **4** is a 2-hydroxy-4,7-dimethoxyphenanthrene-1-yl moiety. Accounting for the molecular composition, the two units have to be directly connected through C-1 and C-1′. Therefore, the structure of **4** was established unambiguously as 2,7,2′-trihydroxy-4,4′,7′-trimethoxy-1,1′-biphenanthrene.

Compound **5** was obtained as a pale brown powder (acetone), mp > 300 °C. The EIMS of **5** exhibited a molecular ion at *m*/*z* 506 $[M]^+$ as the base peak, and HREIMS established the molecular formula, $C_{32}H_{26}O_6$. However, the ^{1}H and ^{13}C NMR spectra of **5** exhibited only half the numbers of proton and carbon signals (Tables 1 and 2) expected from the molecular formula. These observations suggested that **5** possesses a symmetrical structure. The UV, IR, and NMR spectra of **5** resembled those of the co-occurring symmetrical phenanthrene dimer, blestriarene C (cirrhopetalanthin) (**7**; several NMR resonances of this compound were incorrectly assigned in the literature;[10,11] hence reassigned data are listed in Tables 1 and 2), except for the appearance of an additional methoxyl signal at δ_H 3.94 and δ_C 55.2 in the NMR spectra of **5**. This indicated that **5** is a derivative of **7** with two additional methoxyls symmetrically substituted at C-7 and C-7′ or C-2 and C-2′. The substitution positions of the methoxyls were established unambiguously by a NOE difference NMR experiment on **5**. Irradiation of the methoxyl signal at δ 3.94 enhanced the *meta*-coupled proton signals at δ 7.29 (dd, J = 10.0 and 3.0 Hz, H-6 and H-6′) and 7.18 (d, J = 3.0 Hz, H-8 and H-8′), demonstrating that the two additional methoxyls are at C-7 and C-7′. These inferences were subsequently corroborated by a comprehensive analysis of the 2D ^{1}H−^{1}H gCOSY, gHSQC, and gHMBC spectra of **5**, resulting in the unequivocal assignment of its NMR data (Tables 1 and 2). Therefore, the structure of **5** was determined as 2,2′-dihydroxy-4,7,4′,7′-tetramethoxy-1,1′-biphenanthrene.

Compound **6** was obtained as a pale brown powder (acetone), mp > 300 °C, and showed UV and IR absorptions similar to those of **4** and **5**. The positive FABMS gave a molecular ion at *m*/*z* 730 $[M]^+$ that was more abundant than the quasi-molecular ion at *m*/*z* 731 $[M + H]^+$ (see Supporting Information). On the basis of the HRFABMS at *m*/*z* 730.2261 $[M]^+$, the molecular formula was established as $C_{46}H_{34}O_9$. Compound **6** is insoluble in acetone and $CHCl_3$ but soluble in MeOH, so the NMR experiments were measured in MeOH-d_4. The ^{1}H, ^{13}C NMR, and DEPT spectra of **6** (Tables 1 and 2) were similar to those of **4** except for the appearance of additional signals assignable to one more phenanthrene unit, suggesting that **6** is a trimeric phenanthrene derivative. In addition, the appearance of four methoxyl signals [δ_H 4.24, 4.10, 4.09, and 3.88 (each 3H, s), δ_C 56.2, 56.0, 56.0, and 55.6] and nine oxygenated quaternary aromatic carbons (δ_C >150 ppm) in the NMR spectra, in combination with the molecular composition, revealed the presence of five phenolic hydroxyls in **6**. The three phenanthrene units were determined unambiguously by a consideration of the ^{1}H−^{1}H gCOSY, HMQC, and HMBC NMR spectra. The ^{1}H−^{1}H COSY spectrum readily distinguished two *ortho-meta*-coupled ABX systems at δ 9.46 (1H, d, J = 9.5 Hz, H-5″), 7.14 (1H, dd, J = 9.5 and 3.0 Hz, H-6″), and 7.18 (1H, d, J = 3.0 Hz, H-8″) and at δ 9.41 (1H, d, J = 9.5 Hz, H-5′), 7.06 (1H, dd, J = 9.5 and 3.0 Hz, H-6′), and 7.05 (1H, d, J = 3.0 Hz, H-8′), and four *ortho*-coupled AB systems at δ 9.73 (1H, d, J = 9.5 Hz, H-5) and 7.34 (1H, d, J = 9.5 Hz, H-6), at δ 7.38 (1H, d, J = 9.0 Hz, H-9″) and 7.02 (1H, d, J = 9.0 Hz, H-10″), at δ 7.28 (1H, d, J = 9.0 Hz, H-9′) and 6.94 (1H, d, J = 9.0 Hz, H-10′), and at δ 6.84 (1H, d, J = 10.0 Hz, H-9) and 6.81 (1H, d, J = 10.0 Hz, H-10), besides three aromatic singlets at δ 7.05 (1H, s, H-3), 6.91 (1H, s, H-3″), and 6.90 (1H, s, H-3′) and the four methoxyls. On the basis of the HMQC spectrum, the protonated carbons in the ^{13}C NMR spectrum of **6** could be assigned (Table 2). In the HMBC spectrum of **6**, correlations from H-3 to C-1, C-2, C-4, and C-4a, H-5 to C-4a, C-7, and C-8a, H-9 to C-4b, C-8, and C-10a, and H-10 to C-1, C-4a, and C-8a, and from the methoxyl protons at δ 4.24 to C-4, in combination with the chemical shift values of C-1, C-2, C-7, and C-8 (δ 111.4, 154.6, 153.7, and 118.4), as well as the quaternary nature of these carbons were used to establish the first unit of **6** as a 1,8-disubstituted 2,7-dihydroxy-4-methoxyphenanthrene moiety. Further, HMBC correlations from H-3′ to C-1′ and C-4′a, H-5′ to C-4′a, C-7′, and C-8′a, H-6′ to C-4′b and C-8′, H-8′ to C-4′b, C-6′, and C-9′, H-9′ to C-4′b, C-8′, and C-10′a, and H-10′ to C-1′, C-4′a, and C-8′a, and from the methoxyl protons at δ 4.10 to C-4′, in combination with the quaternary nature of C-1′ and chemical shift values of C-1′, C-2′, and C-7′ (δ 111.7, 154.2, and 155.3), as well as *ortho-meta* coupling of H-5′, H-6′, and H-8′, revealed the presence of a 2,7-dihydroxy-4-methoxyphenanthren-1-yl unit in **6**. Finally, HMBC correlations from H-3″ to C-1″ and C-4″a, H-5″ to C-4″a, C-7″, and C-8″a, H-6″ to C-4″b and C-8″, H-8″ to C-4″b, C-6″, and C-9″, H-9 to C-4″b, C-8″, and C-10″a, H-10″ to C-1″, C-4″a, and C-8″a, and from the methoxyl at δ 4.09 to C-4″, and the methoxyl at δ 3.88 to C-7″, in combination with the quaternary nature and chemical shift values of C-1″ and C-2″ (δ 111.5 and 154.7), as well as *ortho-meta* coupling relationship of H-5″, H-6″, and H-8″, demonstrated a 2-hydroxy-7,4-dimethoxyphenanthren-1-yl unit in **6**. The NOE difference and NOESY NMR experiments of **6** in MeOH-d_4 further confirmed the presence of the three phenanthrene units, but these experiments did not show any useful information related to the connectivity among the three units. The NOESY spectrum of **6** in DMSO-d_6 showed cross-peaks between H-10 and H-10′ and between H-9 and H-10″, indicating that the 2,7-dihydroxy-4-methoxyphenanthren-1-yl and 2-hydroxy-7,4-dimethoxyphenanthren-1-yl units are located at C-1 and C-8 of the 1,8-disubstitued 2,7-dihydroxy-4-methoxyphenanthrene unit, respectively. Therefore, the planar structure of **6** was proposed as 2,7,2′,7′,2″-pentahydroxy-4,4′,4″,7″-tetramethoxy-1, 8,1′,1″-triphenanthrene.

When the methanol-d_4 solution of **6** was kept at ambient temperature for three weeks, the ^{1}H NMR spectrum clearly indicated that almost half of the compound was converted into **6a** (Supporting Information). Although **6** and **6a** were separable by reversed-phase

(C_{18}) HPLC using MeOH−H_2O (7:3) as mobile phase, it was found that **6a** was easily converted to **6** during the isolation procedure in daylight. Subsequently, **6** and **6a** were carefully separated by a HPLC isolation procedure conducted in the dark. The FABMS and NMR spectroscopic data obtained for **6a** were almost identical to those of **6**. However, the analysis of the ^{1}H NMR data of **6** and **6a** (Table 1; the ^{1}H NMR data of **6** and **6a** are listed to three decimal places for detailed comparison) revealed that proton signals of H-5′, H-5″, H-6′, H-6″, H-8′, H-8″, and H_3-12″ of **6a** are shielded by $\Delta\delta$ 0.020−0.040 ppm compared to those of **6**, whereas H-3′, H-3″, H-9′, H-10′, H-10″, H_3-11′, and H_3-11″ of **6a** are deshielded by $\Delta\delta$ 0.003−0.040 ppm. Construction of a Dreiding model of this triphenanthrene shows that there are two geometric configurations (*E* and *Z* forms), with the most preferred conformation being where the two terminal phenanthrene units remain almost perpendicular to the central phenanthrene unit. On the basis of the known shielding and deshielding effects on phenanthrene units,[1] in the *Z* form of triphenanthrenes, protons of the ring C′ (or C″) of one terminal phenanthrene unit fall in the shielding zone of the magnetic field of ring C″ (or C′) of another terminal monomeric unit. In turn, shielding effects of the magnetic field of the central monomeric unit onto the protons of rings A′ and B′ (or A″ and B″) of one terminal unit may be diminished by the magnetic field of rings A″ and B″ (or A′ and B′) of another terminal unit.[1] However, this situation does not exist in the *E* form. Therefore, the differences between the ^{1}H NMR data of **6** and those of **6a** suggested that **6** (*E* form) and **6a** (*Z* form) are two geometric isomers, as shown.

Interestingly, in the ^{1}H NMR spectra of **6** and **6a**, H-3′, H-3″, H-9′, H-9″, H-10′, and H-10″ appeared as two sets of signals with small differences of chemical shifts, which were confirmed by the phase-sensitive ^{1}H−^{1}H COSY spectra of **6** and **6a** (Supporting Information). The intensities of the two sets of signals were about 4:3 for **6** and 1:1 for **6a** based on the integration of the signals. These indicated that **6** and **6a** are still mixtures. However, we failed to purify these mixtures even using analytical HPLC. Considering the existence of two chiral axes in **6** and **6a**, and the fact that 1,1′-biphenanthrene-2,2′-diol and 1,1′-biphenanthrene-2,7,2′,7′-tetraol undergo rapid photoracemization,[21] it is proposed that two sets of signals of H-3′, H-3″, H-9′, H-9″, H-10′, and H-10″ in the ^{1}H NMR spectra of **6** or **6a** may be attributed to a pair of unseparable diastereomeric racemates (*R*,*R*/*S*,*S* and *R*,*S*/*S*,*R*), respectively. This is supported by the optical inactive nature of both **6** and **6a**. A careful analysis of the two sets of signals in the ^{1}H NMR spectrum of **6** revealed that protons with larger integrations (H-3″, H-9′, and H-10′) were shielded, while H-3′, H-9″, and H-10″ were deshielded, as compared to corresponding protons with the smaller integrations. This suggested that H-3″, H-9′, and H-10′ of the racemate are oriented close to the central unit, whereas H-3′, H-9″, and H-10″ are oriented away from the central unit. Therefore, the set of signals with the larger integrations may be ascribed to the racemate of **6** with the axial configurations R_{a1},S_{a2}/S_{a1},R_{a2}, and the other set of signals with the smaller integrations may be attributed to the racemate of **6** with the axial configurations R_{a1},R_{a2}/S_{a1},S_{a2}. In the same manner, in the ^{1}H NMR spectrum of **6a**, the set of signals including H-3″, H-9′, and H-10′ were shielded, while H-3′, H-9″, and H-10″ were deshielded. These were attributed to the racemate of **6a** with the axial configurations R_{a1},R_{a2}/S_{a1},S_{a2}, and the other set of signals were assigned to the racemate of **6a** with the axial configurations R_{a1},S_{a2}/S_{a1},R_{a2}.

On the basis of the structures of **1** and **2**, it is possible that these compounds are artifacts originating from the oxidative coupling of **3** and flavanthrinin (**8**), respectively, with acetone used as a solvent in the chromatographic isolation procedure. To prove the origin of compounds **1** and **2**, a reisolation procedure without the use of acetone was carried out. A simulated experiment was carried by stirring a mixture of **3** or flavanthrinin (**8**) (3 mg) with silica gel (10 mg) and acetone−petroleum ether (1:1) (5 mL) at 40 °C for 6 h, but this did not yield **1** and **2** as detected by HPLC. In the reisolation procedure starting with a small amount of the plant material (50 g), acetone was replaced by ethyl acetate to yield two fractions, in which the presence of compounds **1** and **2** was clearly detectable by TLC and HPLC-MS^n (Supporting Information). Compounds **1** and **2** were optically inactive and hence racemic, indicating that the biosynthetic formation of the chiral center of **1** and **2** is nonstereoselective. The biphenanthrene derivatives **4**, **5**, and **7** were also obtained in the optically inactive form. They may be photoracemized products obtained during the isolation procedure.[21]

Table 3. Cytotoxicity of Compounds **5**−**7**[a]

	IC_{50} value (μM)[b]						
compound	A549	A2780	Bel7402	BGC-823	HCT-8	MCF-7	WISH
5	11.6	11.0	11.1	9.5	10.7	11.9	5.0
6	11.6	8.1	8.2	8.4	8.0	8.3	>15.0
7	17.8	13.2	8.4	10.5	11.2	12.5	>22.7
topotecan[c]	3.3	1.1	1.2	4.4	1.5	1.9	1.3

[a] Compounds **1**−**4** and **8** were inactive against all cell lines tested (IC_{50} > 5 μg/mL). [b] For cell lines used, see Experimental Section. [c] Positive control.

The ethanolic extract of the tubers of *C. appendiculata* was inactive (IC_{50} > 20 μg/mL) in the preliminary cytotoxic assay against several human cancer cell lines, and thus the compounds reported herein were not isolated by following a specific bioassay-guided separation protocol. However, follow-up cytotoxic screening of the pure compounds obtained (**1**−**8**) against human lung adenocarcinoma (A549), human ovarian cancer (A2780), human hepatoma (Bel7402), human stomach cancer (BGC-823), human colon cancer (HCT-8), and human breast cancer (MCF-7) cell lines, as well as a normal control cell line (human epithelial WISH cell line), was conducted. Compound **5** showed nonselective moderate cytotoxicity against all of the cell lines tested, while compound **6** and cirrhopetalanthrin (**7**) were selectively active against the human cancer cell lines used (Table 3). The other compounds evaluated (**1**−**4**, **8**) were inactive (IC_{50} > 5 μg/mL).

Experimental Section

General Experimental Procedures. Melting points were determined on an XT-4 micro melting point apparatus and are uncorrected. IR spectra were recorded as KBr disks on a Nicolet Impact 400 FT-IR spectrophotometer. 1D- and 2D-NMR spectra were obtained at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, on an INOVA 500 Hz spectrometer in acetone-d_6 or methanol-d_4, with solvent peaks as references. EIMS, HREIMS, FABMS, and HRFABMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. HPLC-MS^n analysis was performed with an Agilent 1100 SL instrument. Column chromatography was performed with silica gel (200−300 mesh) and Sephadex LH-20. HPLC separation was performed on an instrument consisting of a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual λ absorbance detector with an Alltima (250 × 22 mm) preparative column packed with C_{18} (10 μm). TLC was carried out with glass precoated silica gel GF_{254} plates. Spots were visualized under UV light or by spraying with 3% $FeCl_3$ in EtOH or 7% H_2SO_4 in 95% EtOH followed by heating.

Plant Material. The tubers of *Cremastra appendiculata* were collected under cultivation at Xinbang TCM Co., Ltd., Eastsouth District, Qian, Guizhou Province, People's Republic of China, in September 2003. The plant identity was verified by Mr. Ding-Xiang He (Xinbang TCM Co., Ltd.). A voucher specimen (No. 200366) was deposited at the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica, Beijing, People's Republic of China.

Extraction and Isolation. The air-dried and powdered tubers of *C. appendiculata* (5 kg) were extracted with 95% EtOH three times at room temperature for 3 × 48 h. After the solvent was removed under reduced pressure at <45 °C, a dark brown residue (116 g) was obtained. The residue was suspended in water and then partitioned with EtOAc. The EtOAc phase was concentrated to give a residue (37 g). The residue

was separated by column chromatography over silica gel eluting with a gradient of increasing acetone (5−100%) in petroleum ether (60−90 °C) followed by elution with MeOH to give 23 fractions (a_1−a_{23}) on the basis of TLC analysis. Fraction a_7 was chromatographed over Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5:5:1) to give three subfractions. The second subfraction was purified by column chromatography over silica gel eluting with petroleum ether−acetone (8:1) to yield **3** (45 mg), and the third subfraction was purified by column chromatography over silica gel eluting with petroleum ether−acetone (5:1) to yield **1** (13 mg) and **2** (6 mg). Fraction a_{11} was subjected to column chromatography over silica gel eluting with petroleum ether−acetone (3:1) to afford **4** (21 mg), **5** (8 mg), and cirrhopetalanthrin (**7**, 28 mg). Fraction a_{14} was separated into three subfractions by chromatography over Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5:5:1). The third subfraction was rechromatographed over silica gel eluting with petroleum ether−acetone (5:1) to yield flavanthrinin (**8**, 148 mg). Fraction a_{16} was chromatographed over silica gel, eluting with $CHCl_3$−MeOH (8:1), to give a subfraction that was purified by preparative HPLC, using MeOH−H_2O (7:3) as mobile phase, to yield **6** (18 mg). The isolation procedures for the known compounds **7** and **8** have been reported in a preliminary phytochemical investigation of the tubers of *C. appendicula*.[8,9]

1-Hydroxy-4,7-dimethoxy-1-(2-oxopropyl)-1*H*-phenanthren-2-one (1): yellowish needles (Me_2CO); mp 155−156 °C; UV (MeOH) λ_{max} (log ϵ) 214 (4.38), 239 (4.19), 261 (4.13), 343 (3.68) nm; IR (KBr) ν_{max} 3394, 2924, 2852, 1707, 1653, 1606, 1550, 1502, 1477, 1414, 1356, 1230, 1176, 1030, 939, 856, 829 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz), see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz), see Table 2; EIMS *m*/*z* 326 (6) $[M]^+$, 312 (2) $[M - Me]^+$, 270 (18), 269 (17), 268 (8), 255 (10), 242 (14), 241 (47), 240 (100), 226 (10), 209 (9), 197 (12), 185 (6), 182 (12), 169 (24), 152 (7), 139 (15), 126 (17), 113 (5), 58 (11); HREIMS *m*/*z* 326.1158 $[M]^+$ (calcd for $C_{19}H_{18}O_5$, 326.1154).

1,7-Dihydroxy-4-methoxy-1-(2-oxopropyl)-1*H*-phenanthren-2-one (2): yellowish needles (Me_2CO); mp 158−159 °C; UV (MeOH) λ_{max} (log ϵ) 214 (3.82), 237 (3.59), 262 (3.55), 343 (3.03) nm; IR (KBr) ν_{max} 3435, 2922, 2852, 1707, 1650, 1608, 1555, 1501, 1456, 1411, 1359, 1233, 1174, 1034, 939, 879, 821 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz), see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz), see Table 2; EIMS *m*/*z* 312 (4) $[M]^+$, 296 (14), 280 (52), 278 (36), 263 (18), 253 (23), 239 (15), 238 (100), 227 (13), 226 (12), 210 (36), 181 (14), 171 (10), 133 (6), 89 (12), 58 (5); HREIMS *m*/*z* 312.0981 $[M]^+$ (calcd for $C_{18}H_{16}O_5$, 312.0998).

2-Hydroxy-4,7-dimethoxyphenanthrene (3): yellowish needles (Me_2CO); mp 160−161 °C; UV (MeOH) λ_{max} (log ϵ) 209 (4.24), 258 (4.69), 281 (4.13), 291 (4.00), 300 (3.71), 351 (3.29), 368 (3.36) nm; IR (KBr) ν_{max} 3433 (OH), 1616, 1577, 1545, 1500, 1473, 1360, 1277, 1223, 1171, 1140, 1082, 1036, 966, 931, 858, 829, 779, 708, 685, 619, 534 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz), see Table 1; ^{13}C NMR (acetone-d_6, 125 MHz), see Table 2; EIMS *m*/*z* 254 (100) $[M]^+$, 239 (60), 224 (15), 211(25), 196 (15), 168 (20), 152 (10), 139 (15), 127 (10), 58 (20); HREIMS *m*/*z* 254.0936 $[M]^+$ (calcd for $C_{16}H_{14}O_3$, 254.0942).

2,7,2′-Trihydroxy-4,4′,7′-trimethoxy-1,1′-biphenanthrene (4): brown amorphous powder (Me_2CO); mp > 300 °C; UV (MeOH) λ_{max} (log ϵ) 211 (4.57), 263 (4.97), 284 (sh, 4.47), 308 (4.21), 359 (3.81), 375 (3.91) nm; IR (KBr) ν_{max} 3384, 2927, 2850, 1614, 1585, 1533, 1500, 1464, 1352, 1273, 1211, 1155, 1140, 1082, 1041, 951, 864, 829, 781 cm^{-1}; ^1H NMR (acetone-d_6 and MeOH-d_4, 500 MHz), see Table 1; ^{13}C NMR (acetone-d_6 and MeOH-d_4, 125 MHz), see Table 2; EIMS *m*/*z* 492 (100) $[M]^+$, 477 (2) $[M - Me]^+$, 254 (4), 246 (10), 237 (5); HREIMS *m*/*z* 492.1567 $[M]^+$ (calcd for $C_{31}H_{24}O_6$, 492.1573).

2,2′-Dihydroxy-4,7,4′,7′-tetramethoxy-1,1′-biphenanthrene (5): brown amorphous powder (Me_2CO); mp > 300 °C; UV (MeOH) λ_{max} (log ϵ) 210 (4.46), 265 (4.86), 282 (sh, 4.35), 310 (4.01), 361 (3.92), 374 (3.88) nm; IR (KBr) ν_{max} 3500, 3419, 2956, 2927, 2852, 1614, 1585, 1533, 1466, 1437, 1398, 1354, 1270, 1219, 1157, 1082, 1039, 964, 935, 853, 827, 781 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz), see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 2; EIMS *m*/*z* 506 (100) $[M]^+$, 491 (5) $[M - Me]^+$, 254 (3); 253 (22), 237 (11), 225 (7); HREIMS *m*/*z* 506.1719 $[M]^+$ (calcd for $C_{32}H_{26}O_6$, 506.1729).

(*E*)-2,7,2′,7′,2″-Pentahydroxy-4,4′,4″,7″-tetramethoxy-1,8,1′,1″-triphenanthrene (6): brown amorphous powder (Me_2CO); mp > 300 °C; UV (MeOH) λ_{max} (log ϵ) 209 (4.63), 263 (4.99), 309 (4.29), 359 (3.89), 376 (3.97) nm; IR (KBr) ν_{max} 3435, 2931, 2856, 1616, 1596, 1539, 1456, 1354, 1205, 1084, 1041, 968, 866, 829 cm^{-1}; ^1H NMR (MeOH-d_4, 500 MHz), see Table 1; ^{13}C NMR (MeOH-d_4, 125 MHz), see Table 2; FABMS *m*/*z* 731 (10) $[M + H]^+$, 730 (26) $[M]^+$, 530 (8), 391 (24); 338 (47), 279 (6), 246 (6), 137 (68), 115 (45), 107 (25); HRFABMS *m*/*z* 730.2261 $[M]^+$(calcd for $C_{46}H_{34}O_9$, 730.2203).

(*Z*)-2,7,2′,7′,2″-Pentahydroxy-4,4′,4″,7″-tetramethoxy-1,8,1′,1″-triphenanthrene (6a): UV (MeOH) λ_{max} (log ϵ) 209 (4.63), 263 (4.99), 308 (4.27), 360 (3.84), 370 (3.91) nm; ^1H NMR (MeOH-d_4, 500 MHz), see Table 1; FABMS *m*/*z* 731 (9) $[M + H]^+$, 730 (23) $[M]^+$, 530 (8), 391 (25); 338 (50), 279 (4), 246 (6), 137 (64), 115 (44), 107 (25); HRFABMS *m*/*z* 730.2261 $[M]^+$ (calcd for $C_{46}H_{34}O_9$, 730.2203).

Bioassays. Human lung adenocarcinoma (A549), human ovarian cancer (A2780), human hepatoma (Bel7402), human stomach cancer (BGC-823), human colon cancer (HCT-8), and human breast cancer (MCF-7) and the human epithelial WISH cell lines (Susan Hayflick Wistar Institute) were obtained from American Type Culture Collection (ATCC, Rockville, MD). Cells were maintained in RRMI1640 supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin, and 100 μg/mL streptomycin. Cultures were incubated at 37 °C in a humidified 5% CO_2 atmosphere.

A549, A2780, Bel7402, BGC-823, HCT-8, and MCF-7 cells and human epithelial WISH cells were seeded in 96-well microtiter plates at 1200 cells/well. After 24 h, test compounds were added to the cells. After 96 h of drug treatment, cell viability was determined by measuring the metabolic conversion of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) into purple formazan crystals by active cells.[22,23] MTT assay results were read using a MK 3 Wellscan (Labsystem DROGON) plate reader at 570 nm. All compounds were tested at five concentrations and were dissolved in 100% DMSO with a final DMSO concentration of 0.1% in each well. Each concentration of the compounds was tested in three parallel wells. IC_{50} values were calculated using Microsoft Excel software.

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Supporting Information Available: MS and 1D and 2D NMR spectra of compounds **1**−**6** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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