Anthrone and Oxanthrone *C*-Glycosides from *Picramnia latifolia* Collected in Peru

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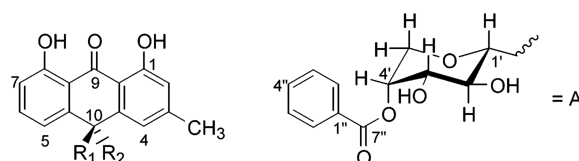
Received October 30, 2003

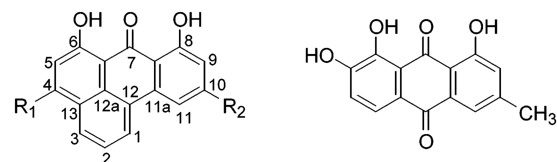
Cytotoxicity-based, bioassay-guided fractionation of the chloroform-soluble extracts of both the roots and leaves of *Picramnia latifolia* led to the isolation of two new anthrone *C*-glycosides, picramniosides G (**1**) and H (**2**), two new oxanthrone *C*-glycosides, mayosides D (**3**) and E (**4**), and a new benzanthrone natural product, 6,8-dihydroxy-10-methyl-7*H*-benz[*de*]anthracen-7-one (**5**), together with 10 known compounds, 6,8-dihydroxy-4-methyl-7*H*-benz[*de*]anthracen-7-one (**6**), nataloe-emodin (**7**), chrysophanein, chrysophanol, 1,5-dihydroxy-7-methoxy-3-methylanthraquinone, pulmatin, 7-hydroxycoumarin, 7-hydroxy-6-methoxy-coumarin, β-sitosterol, and β-sitosterol glucoside. The structures of **1**–**5** were established by spectroscopic methods, including 1D and 2D NMR, HRMS, and CD data interpretation. The cytotoxic activity of all isolates was evaluated in a small panel of human cancer cell lines. Compound **7** exhibited significant in vitro cytotoxic activity in the tested cell lines, but no significant activity was observed with an in vivo hollow fiber model at doses of 6.25, 12.5, 25, and 50 mg/kg/injection.

Picramnia latifolia Tul. (Picramniaceae) is the most common of the about 90 species of the genus *Picramnia* found in tropical America.[1] In Central America, this species is found abundantly only in Costa Rica and Panama and is less common in Honduras. It is also found sporadically in Mexico.[2] The ethnobotanical and ethnomedical information, as well as the chemical constituents of *P. latifolia*, have not been reported to date. A number of anthraquinone and structurally related anthracene derivatives have been reported from other species in the genus *Picramnia*.[3–6] Recently, the genera *Picramnia* and *Alvaradoa* were placed out of the family Simaroubaceae and moved into a new family, Picramniaceae.[7] Phytochemically, the family Simaroubaceae *sensu lato* has been characterized by the production of quassinoids.[8,9] In contrast, species of the genera *Picramnia* and *Alvaradoa* are characterized by the production of anthraquinone and anthracenone derivatives, rather than quassinoids,[1,3–6,10] providing an important argument to support the exclusion of these two genera from the Simaroubaceae.

As part of an ongoing collaborative search for novel antineoplastic agents of plant origin,[11–14] cytotoxicity-based, bioassay-guided fractionation of the separate chloroform-soluble extracts of the roots and leaves of *P. latifolia*, collected in Peru, led to the isolation of two new anthrone *C*-glycosides, picramniosides G (**1**) and H (**2**), two new oxanthrone *C*-glycosides, mayosides D (**3**) and E (**4**), and a new benzanthrone natural product, 6,8-dihydroxy-10-methyl-7*H*-benz[*de*]anthracen-7-one (**5**), along with several compounds of known structure. In this paper, the isolation and the structure elucidation of compounds **1**–**5**, as well as the cytotoxic activity of all isolates against a human cancer cell line panel, and the evaluation of nataloe-emodin (**7**) in an in vivo hollow fiber model are described.



1 R_1 = A R_2 = H
2 R_1 = H R_2 = A
3 R_1 = OH R_2 = A
4 R_1 = A R_2 = OH



5 R_1 = H R_2 = CH_3
6 R_1 = CH_3 R_2 = H

7

Results and Discussion

Bioassay-guided chromatographic purification of the methanol extracts of the separated roots and leaves of *P. latifolia* allowed the isolation of four new anthrone and oxanthrone *C*-glycosides (**1**–**4**), a new benzanthrone natural product (**5**), and 10 known compounds, 6,8-dihydroxy-4-methyl-7*H*-benz[*de*]anthracen-7-one (**6**),[15] nataloe-emodin (**7**),[16] chrysophanol,[17,18] 1,5-dihydroxy-7-methoxy-3-methylanthraquinone,[19] pulmatin,[20] chrysophanein,[20] 7-hydroxycoumarin,[21] 7-hydroxy-6-methoxycoumarin,[22] β-sitosterol,[23] and β-sitosterol glycoside.[24] The structures of the known compounds were identified by comparison of their spectroscopic data with those values reported previously.

The negative-ion mode HRESIMS of compound **1** exhibited a molecular ion peak at m/z 475.1386 $[M - H]^-$,

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10.1021/np030479j CCC: $27.50 © 2004 American Chemical Society and American Society of Pharmacognosy
Published on Web 01/29/2004

Table 1. ^{1}H and ^{13}C NMR Data of Compounds **1**–**4** in $CDCl_3$[a]

position	**1**		**2**		**3**		**4**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		162.4 s		162.0 s		162.6 s		162.1 s
1a		115.7 s		115.4 s		114.6 s		114.6 s
2	6.83, br s	116.5 d	6.74, br s	116.5 d	6.89, br s	118.0 d	6.79, br s	117.7 d
3		146.7 s		147.7 s		147.3 s		148.1 s
4	6.86, br s	121.1 d	6.84, br s	119.9 d	7.18, br s	118.8 d	7.30, br s	117.5 d
4a		141.3 s		144.5 s		141.3 s		144.3 s
5	7.02, d (7.5)	118.7 d	7.04, d (7.5)	119.8 d	7.43, d (7.5)	116.4 d	7.35, d (7.6)	117.2 d
5a		144.4 s		141.2 s		147.1 s		146.6 s
6	7.47, t (7.9)	135.7 d	7.49, t (8.0)	134.7 d		136.4 s		135.0 s
7	6.93, d (8.3)	116.1 d	7.01, d (8.3)	116.3 d	6.96, d (8.3)	117.9 d	7.07, d (8.3)	117.4 d
8		161.9 s		162.2 s		161.8 s		161.7 s
8a		117.5 s		117.9 s		117.5 s		116.4 s
9		193.8 s		193.8 s		193.0 s		192.6 s
10	4.59, br s	44.5 d	4.59, br s	44.4 d		76.5 s		76.2 s
CH_3-3	2.40, s	22.3 q	2.37, s	22.2 q	2.43, s	23.0 q	2.42, s	22.5 q
1′	3.47, dd (9.2, 1.9)	85.1 d	3.45, t (7.7)	85.0 d	3.27, d (8.6)	84.2 d	3.30, m[b]	83.8 d
2′	3.66, t (9.2)	68.6 d	3.67, t (9.1)	68.5 d	3.69, t (8.9)	69.7 d	3.68, t (8.9)	69.6 d
3′	3.76, dd (9.2, 2.8)	74.2 d	3.76, d (7.0)	74.2 d	3.77, m[b]	73.9 d	3.79, m[c]	73.3 d
4′	5.21, br s	71.6 d	5.18, br s	71.6 d	5.18, br s	71.2 d	5.18, br s	70.8 d
5′	3.88, dd (13.1, 1.8)	67.9 t	3.84, br d (11.7)	67.8 t	3.77, m[b]	68.2 t	3.79, m[c]	67.9 t
	3.37, d (13.1)		3.84, d (13.0)		3.30, d (12.6)		3.30, m[b]	
1″		129.4 s		129.3 s		129.6 s		129.2 d
2″/6″	7.58, m	129.6 d	7.57, m	129.7 d	7.56, m	129.9 d	7.56, m	129.6 d
3″/5″	7.39, t (7.7)	128.4 d	7.38, t (7.8)	128.5 d	7.40, m	128.8 d	7.40, m	128.5 d
4″	7.58, m	133.5 d	7.57, m	133.5 d	7.56, m	133.9 d	7.56, m	133.5 d
7″		166.4 s		166.4 s		166.6 s		166.6 s
OH-1	12.10, s		12.09, s		11.94, s		12.05, s	
OH-8	11.99, s		11.96, s		11.89, s		11.85, s	

[a] Spectra taken at 360 and 90 MHz for proton and carbon, respectively; chemical shift values were assigned based on the observed 2D NMR correlations and presented in ppm with TMS as the internal standard; *J* values given in Hz in parentheses. [b,c] Overlapping signals in the same column.

indicating a molecular formula of $C_{27}H_{24}O_8$ (calcd for $C_{27}H_{23}O_8$, 475.1393). The UV spectrum of **1** showed the absorption bands (361, 268, 260, 252, 220, 208 nm) characteristic of a highly conjugated anthracenone system,[25] which was confirmed by the presence of IR absorption maxima indicating the presence of hydroxyl (3466 cm^{-1}), chelated carbonyl (1612 cm^{-1}), and ester carbonyl (1712 cm^{-1}) groups. The ^{1}H NMR spectrum (Table 1) of compound **1** showed three well-defined regions, with the first of these being the downfield region for the two intramolecularly hydrogen-bonded phenolic groups observed at δ 12.10 and 11.99, which were attached to carbons C-1 and C-8, respectively. The second region consisted of 10 aromatic proton NMR signals from δ 7.58 to 6.83 in three different spin systems: a benzoyl group at δ_H 7.58 (3H, m, H-2″/H-6″, H-4″) and 7.39 (2H, t, $J = 7.7$ Hz, H-3″/H-5″), a 1,2,3-trisubstituted aromatic ring at δ_H 7.47 (1H, t, $J = 7.9$ Hz, H-6), 7.02 (1H, d, $J = 7.5$ Hz, H-5), and 6.93 (1H, d, $J = 8.3$ Hz, H-7), and two *meta*-coupled aromatic protons at δ_H 6.86 (1H, br s, H-4) and 6.83 (1H, br s, H-2). The third well-defined region was constituted by the signals observed for the oxygenated methines and methylenes in the range of δ_H 5.21 to 3.37. These proton signals were correlated with the carbon signals of δ_C 85.1 (C-1′, CH), 74.2 (C-3′, CH), 71.6 (C-4′, CH), 68.6 (C-2′, CH), 67.9 (C-5′, CH_2), and 44.5 (C-10, CH). The observed HMBC correlations from two aromatic proton signals at δ_H 6.86 (H-4) and 7.02 (H-5) to the methine resonance at δ_C 44.5 (C-10) indicated that compound **1** is an anthrone derivative.[4,26] The remaining oxygenated methine and methylene signals suggested the presence of a *C*-glycopyranosyl unit in the molecule of **1**. The relative stereochemistry of the sugar moiety was established on the basis of the magnitude of the coupling constants of the observed protons. Thus, the coupling constant between H-1′ and H-2′ (9.2 Hz) indicated a *trans*-diaxial configuration, and the values between H-2′ and H-3′ (9.2 Hz) and H-3′ and H-4′ (2.8 Hz) indicated a *trans*-diaxial and an axial–equatorial configuration, respectively. This relative configuration assignment suggested the sugar moiety of compound **1** to be an α-arabinopyranoside unit.[27] The location of the sugar was assigned at C-10 on the basis of the observed HMBC correlations from the anomeric proton at δ_H 3.47 (H-1′) to the carbon resonances at δ_C 68.6 (C-2′), 67.9 (C-5′), 141.3 (C-4a), and 144.4 (C-5a) and from δ_H 4.59 (H-10) to δ_C 85.1 (C-1′), 121.1 (C-4), and 118.7 (C-5). The HMBC spectrum showed cross-peaks from the proton signals at δ_H 5.21 (1H, br s, H-4′) and 7.58 (3H, m, H-2″/H-6″, H-4″) to the carbonyl carbon at δ_C 166.4, which permitted the position of the benzoate moiety to be established at C-4′. All of the experimental values of the coupling constants of the protons in the sugar moiety were in good agreement with those calculated for the vicinal coupling constants (^{3}J) (Table S1), based on the dihedral angles (ϕ) in the most stable conformation of the structure of compound **1** obtained with the use of the CS Chem3D computational molecular modeling package. The structure with the most stable calculated conformation is given in the Supporting Information (Figure S6). Finally, the absolute stereochemistry of C-10 was determined as *S* by comparison of the circular dichroism (CD) spectral data of compound **1** ($\Delta\epsilon_{375}$ +0.39, $\Delta\epsilon_{345}$ +0.31, $\Delta\epsilon_{298}$ +0.50, $\Delta\epsilon_{271}$ −0.49, $\Delta\epsilon_{257}$ +0.66, $\Delta\epsilon_{222}$ −3.00 nm) with the values previously reported for other anthrone *C*-glycosides.[4,5,26] Therefore, picramnioside G (**1**) was assigned structurally as (10*S*)10-*C*-(4-*O*-benzoyl-α-arabinopyranosyl)-1,8-dihydroxy-3-methylanthracen-9(10*H*)-one. The complete assignments of the ^{1}H and ^{13}C NMR spectral data of compound **1** were undertaken on the basis of 2D COSY, HMQC, and HMBC NMR experiments.

The HRESIMS of compound **2** exhibited a molecular ion peak at *m*/*z* 475.1397 $[M - H]^-$ (calcd for $C_{27}H_{23}O_8$, 475.1393), indicating a molecular formula of $C_{27}H_{24}O_8$, the

same as that of **1**. The NMR (Table 1), UV, and IR spectral data of compound **2** were also nearly identical to those of **1** and suggested that these two compounds are diastereoisomers. Further interpretation of the 2D NMR spectral data of **2** enabled the same gross structure to be proposed for this isolate as that of **1**, 10-*C*-(4-*O*-benzoyl-α-arabinopyranosyl)-1,8-dihydroxy-3-methylanthracen-9(10*H*)-one. Hence, the difference between compounds **1** and **2** was evident only in the stereochemistry at C-10. This was confirmed from the CD spectrum, in which opposite Cotton effects in the regions 270−380 and 215−225 nm allowed the absolute configuration of C-10 of compound **2** to be proposed as *R* instead of *S* as in compound **1**.[4,26,27] Accordingly, picramnioside H (**2**) was assigned structurally as (10*R*)10-*C*-(4-*O*-benzoyl-α-arabinopyranosyl)-1,8-dihydroxy-3-methylanthracen-9(10*H*)-one. Compounds **1** and **2** have been assigned the trivial names picramniosides G and H, respectively, following a previous convention.[4−6]

The HRESIMS of compounds **3** and **4** gave the same sodiated molecular ion peaks at *m*/*z* 515.1332 $[M + Na]^+$ (calcd for $C_{27}H_{24}O_9Na$, 515.1318), indicating the molecular formulas to be $C_{27}H_{24}O_9$, one oxygen atom more than those of picramniosides G (**1**) and H (**2**). The UV, IR, and NMR (Table 1) spectral data of compounds **3** and **4** were very similar to those of **1** and **2**. The presence of the same 4-*O*-benzoyl-α-arabinopyranosyl structural unit in the molecules of **3** and **4** could be assigned by analysis of their 1D and 2D NMR spectral data and by comparison of these data with those of **1** and **2**. In the ^{1}H NMR spectra of compounds **3** and **4**, the broad singlet exhibited by H-10, as in picramniosides G (**1**) and H (**2**), was not present. In the ^{13}C NMR spectra of **3** and **4**, the oxygenated quaternary carbon signals were observed at δ_C 76.5 (C-10) and 76.2 (C-10), respectively, while the aliphatic methine chemical shifts at δ_C 44.5 and 44.4 (C-10) as in **1** and **2** were absent. This observation suggested that mayosides D (**3**) and E (**4**) are oxanthrone derivatives,[5,26] which was confirmed by the observed HMBC correlations from the aromatic proton signals H-4 and H-5 to the oxygenated quaternary carbon signal C-10 for both isolates. The same gross structure of 10-*C*-(4-*O*-benzoyl-α-arabinopyranosyl)-3-methyl-1,8,10-trihydroxyanthracen-9-one could be determined for both **3** and **4** by further interpretation of their 1D and 2D NMR spectral data. As carried out for picramniosides G (**1**) and H (**2**), CD spectral results permitted the absolute stereochemistry of C-10 to be established as *S* and *R* for mayosides D (**3**) and E (**4**), respectively.[4,28] The trivial names of **3** and **4** were assigned following a previous convention.[3−6]

Compound **5** was isolated initially as a mixture with its 4-methyl positional isomer, compound **6**, by normal-phase silica gel column chromatography. This mixture was then successfully purified by reversed-phase HPLC. The HRESIMS of compound **5** provided a molecular formula of $C_{18}H_{12}O_3$ (*m*/*z* 275.0701, calcd for $C_{18}H_{11}O_3$, 275.0708, $[M - H]^-$), indicating 13 degrees of unsaturation. Except for the signals of an aromatic methyl at δ_H 2.53 and δ_C 23.1, two chelated hydroxyl groups at δ_H 14.49 and 12.92, and a conjugated ketone at δ_C 190.3, all other signals were present in the aromatic region in the ^{1}H NMR and ^{13}C NMR spectra of compound **5**. The chemical shifts of the conjugated ketone and the chelated hydroxyl groups were closely comparable to those observed for the above-described anthrone and oxanthrone *C*-glycosides **1**−**4**, which suggested that compound **5** might be another anthrone derivative. In addition to the carbons of the basic skeleton of anthrone and the methyl group, only three aromatic methines remained. However, it can be inferred that these three carbons should provide three degrees of unsaturation based on the molecular formula. Thus, another ring and two more double bonds should be present in the molecule of **5**, and therefore this compound was considered to be a benzanthrone metabolite.[15] The assignment of the position of the aromatic methyl group in compound **5** was carried out using a 2D HMBC NMR experiment. This methyl proton signal at δ_H 2.53 ppm showed long-range correlations with two methine carbons at δ_C 117.0 (C-9) and 115.1 (C-11) and with a quaternary carbon at δ_H 147.7 (C-10). Cross-peaks were also observed from the signals at δ_H 7.76 (1H, br s, H-11) and 6.89 (1H, br s, H-9) to this aromatic methyl carbon. Thus, the position of the methyl group was confirmed at carbon C-10. Other important HMBC correlations to confirm the structure were observed from H-4 to C-3 and C-6 and from H-2 and H-5 to C-13. On the basis of these observations, the structure of compound **5** was established as 6,8-dihydroxy-10-methyl-7*H*-benz[*de*]anthracen-7-one.

By interpretation of the HRMS, 1D, and 2D NMR spectral data, and by comparison of these data with those of **5**, the structure of compound **6** was characterized as 6,8-dihydroxy-4-methyl-7*H*-benz[*de*]anthracen-7-one, an isomer of **5**. Benzanthrone derivatives are rare natural metabolites, and compound **6** was initially isolated from the Thai medicinal plant *Cassia garrettiana*,[15] and was recently identified from an *Aloe* species.[29] Although compound **5** was previously reported as a semisynthetic compound,[15] this is the first report of its isolation from a natural source. Thus, compound **5** is proposed here as a new natural product.

The cytotoxic activity of all compounds obtained in the present study was evaluated against the human lung cancer (Lu1), human hormone-dependent prostate cancer (LNCaP), human breast carcinoma (MCF-7), and human umbilical vein endothelial cell (HUVEC) lines.[14] The results indicated that the known compound nataloe-emodin (**7**) mediated a marginal cytotoxic response ($ED_{50} \le 5$ μg/mL) against the tested cell lines (ED_{50} values were 3.0, 3.6, 4.7, and 5.0 μg/mL for Lu1, LNCaP, MCF-7, and HUVEC, respectively), while all other isolates were considered to be inactive ($ED_{50} > 5$ μg/mL). Interestingly, both nataloe-emodin (**7**) and chrysophanol ($ED_{50} > 20$ μg/mL) were isolated from the active fractions of the chloroform extracts of both the leaves and the roots of *P. latifolia*. Accordingly, nataloe-emodin appears to be the major secondary metabolite responsible for the cytotoxic activity exhibited by the chloroform-soluble extracts of both part plants studied in this investigation.

Since nataloe-emodin (**7**) exhibited a significant cytotoxic response, it was of interest to further evaluate this compound with the in vivo hollow fiber test.[30,31] Doses of 6.25, 12.5, 25, and 50 mg/kg body weight/injection (i.p.) were administrated daily for 4 days, using these same three cell lines. It was found that compound **7** did not mediate significant growth inhibition with cells implanted at either the i.p. or s.c. sites of the mice. Using these regimens, no significant weight loss nor overt toxicity was observed during the test period.

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were obtained using a Perkin-Elmer 241 polarimeter. UV spectra were measured on a Beckman DU-7 spectrometer. IR spectra were obtained with an ATI Mattson FT-IR spectrometer. NMR spectra were

recorded with TMS as internal standard, using either Nicolet-360 or Bruker DRX-500 NMR spectrometers (360 or 500 MHz, respectively). HREIMS and LREIMS were recorded on a Finnigan MAT 95 mass spectrometer (70 eV), while HR-FABMS and LRFABMS were recorded on a VG70E-HF mass spectrometer. Column chromatography was carried out on silica gel 60 (Merck, Darmstadt, Germany; 63−200 and 230−400 mesh). Preparative TLC was performed on Kieselgel 60 F_{254} (Merck) plates (silica gel, 1.0 mm layer thickness). Thin-layer chromatography (TLC) was performed on precoated 0.25 mm thick Merck silica gel F_{254} aluminum-backed plates. Fractions were monitored by TLC with visualization under UV light (254 and 365 nm) and by dipping the plates into a solution of 10% (v/v) H_2SO_4 in EtOH.

Plant Material. The roots and leaves of *Picramnia latifolia* Tul. were collected in July 1998 and November 1997, respectively, in the Department of Ucayali, Province of Coronel Portillo, District of Yarinacocha, Peru, by J.A.G. and J.S.V. These collections were identified by Dr. W. W. Thomas at the New York Botanical Garden, Bronx, New York. Voucher specimens (J. A. Graham and J. Schunke Vigo 495 and 362) representing these collections have been deposited in the John G. Searle Herbarium, Field Museum of Natural History, Chicago, IL, and duplicates of each were provided to the New York Botanical Garden, Bronx, New York.

Extraction and Isolation. Separately, roots (1.16 kg) and leaves (1.83 kg) of *P. latifolia* were air-dried, ground, and extracted with MeOH (5 × 2.0 L and 3 × 5.0 L, respectively) in a percolator. Further treatments for the roots and leaves of *P. latifolia* were carried out independently, but in a similar manner. Briefly, the methanolic extracts from each plant part were combined and concentrated in vacuo at 40 °C. The concentrated extract was suspended in 90% (1 L) MeOH and partitioned successively with petroleum ether, chloroform, and ethyl acetate, following a modification of a published partition scheme.[12] The obtained extracts were evaluated for cytotoxicity against a small panel of human cancer cell lines.[11,14] Only the chloroform-soluble extracts of both parts showed cytotoxic activity (ED_{50} < 20 μg/mL) against the cell lines tested, and therefore, these extracts were selected for further study.

Purification of the $CHCl_3$-Soluble Extract of the Roots. The extract (5.9 g) was chromatographed over a silica gel column (100 × 5 cm; 300 g, 70−230 mesh), eluted with a gradient mixture of petroleum ether−$CHCl_3$, and finally washed with pure MeOH. Fractions were pooled into eight fractions (F005−F012), according to their chromatographic profiles observed on TLC plates.

Fraction F006, eluted with petroleum ether−$CHCl_3$ (4:1), was subjected to purification over a silica gel column (30.0 × 1.0 cm), using hexane−EtOAc (9:1), to give chrysophanol (223 mg) and β-sitosterol (12 mg). Fraction F007, eluted with petroleum ether−$CHCl_3$ (7:3), was chromatographed over a reversed-phase C_{18} silica gel column (22.0 × 2.0 cm), eluted with MeOH−H_2O (7:3 to 9:1), to yield seven subfractions (F013−F019). Fine yellowish needles (2.9 mg) were obtained from F015 and were identified as 1,5-dihydroxy-7-methoxy-3-methylanthraquinone. Subfraction F016 was purified by reversed-phase HPLC, eluted with pure MeOH, to give compounds **5** (1.0 mg, t_R = 17.4 min) and **6** (1.8 mg, t_R = 18.5 min). Fraction F010, eluted with $CHCl_3$−MeOH (4:1), was further purified over a silica gel column (5.0 × 50 cm) using $CHCl_3$−MeOH (10:1 to 1:1) for elution and afforded 7-hydroxycoumarin (3.0 mg), nataloe-emodin (**7**, 3.0 mg), a mixture of two isomers, and β-sitosterol glucoside (8.0 mg), in order of polarity. This mixture was then purified by reversed-phase HPLC, eluted with MeOH−H_2O (containing 0.1% TFA) (1:1), to afford pulmatin (6.0 mg, t_R = 19.9 min) and chrysophanein (6.0 mg, t_R = 21.5 min).

Purification of the $CHCl_3$-Soluble Extract of the Leaves. The extract (22.3 g) was subjected to silica gel column (100 × 5 cm; 300 g, 70−230 mesh) chromatography, eluting in turn with petroleum ether−$CHCl_3$ (1:1), $CHCl_3$, and $CHCl_3$−EtOAc (6:1 to 2:3), and finally washed with EtOAc. Seven combined fractions were obtained based on the TLC profiles (F004−F010).

An orange precipitate, nataloe-emodin (**7**, 955 mg), was obtained from a hexane−$CHCl_3$ (1:1) solution of F005. Fraction F006, eluted with $CHCl_3$−EtOAc (6:1), was subjected to purification over a silica gel column (50.0 × 5.0 cm), eluting with petroleum ether−EtOAc (9:1 to 7:3), $CHCl_3$, and then $CHCl_3$−EtOAc (9:1 to 1:1), to yield nine subfractions (F011−F019). Subfraction F018 was purified by reversed-phase HPLC, eluted with CH_3CN−H_2O (containing 0.1% HOAc) (45:55), to give compounds **1** (3.0 mg, t_R = 71.6 min) and **2** (5.0 mg, t_R = 78.8 min). Subfraction F019 was chromatographed over a reversed-phase silica gel column (22.0 × 2.0 cm), eluted with CH_3CN−H_2O (containing 0.1% HOAc) (7:3 to 9:1), and yielded scopoletin (7.0 mg) and a mixture. The mixture was then finally purified by reversed-phase HPLC, eluted with CH_3CN−H_2O (containing 0.1% HOAc) (45:55), and yielded compounds **3** (3.0 mg, t_R = 45.7 min) and **4** (2.2 mg, t_R = 49.5 min) and additional amounts of compounds **1** (4.4 mg, t_R = 71.6 min) and **2** (1.1 mg, t_R = 78.8 min).

Picramnioside G (1): yellow-brown gum; $[\alpha]^{20}_D$ −18.8° (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ϵ) 361 (4.03), 268 (3.93), 260 (3.83), 252 (3.81), 220 (4.43), 208 (4.47) nm; CD (*c* 84.0 μM, MeOH) nm $\Delta\epsilon_{375}$ +0.39, $\Delta\epsilon_{345}$ +0.31, $\Delta\epsilon_{298}$ +0.50, $\Delta\epsilon_{271}$ −0.49, $\Delta\epsilon_{257}$ +0.66, $\Delta\epsilon_{222}$ −3.00; IR (dried film) ν_{max} 3466, 1712, 1612, 1460, 1274, 1105 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; LRESIMS *m/z* 475.3 $[M - H]^-$; HRESIMS *m/z* 475.1386 $[M - H]^-$ (calcd for $C_{27}H_{23}O_8$, 475.1393).

Picramnioside H (2): yellow-brown gum; $[\alpha]^{20}_D$ −6.7° (*c* 0.09, MeOH); UV (MeOH) λ_{max} (log ϵ) 358 (3.93), 297 (3.82), 268 (3.81), 260 (3.72), 221 (4.31), 209 (4.35) nm; CD (*c* 71.4 μM, MeOH) nm $\Delta\epsilon_{353}$ −0.05, $\Delta\epsilon_{340}$ −0.63, $\Delta\epsilon_{301}$ −2.48, $\Delta\epsilon_{252}$ +0.86, $\Delta\epsilon_{231}$ −0.71, $\Delta\epsilon_{215}$ +0.75; IR (dried film) ν_{max} 3466, 1713, 1648, 1556, 1045 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; LRESIMS *m/z* 475.3 $[M - H]^-$; HRESIMS *m/z* 475.1397 $[M - H]^-$ (calcd for $C_{27}H_{23}O_8$, 475.1393).

Mayoside D (3): brown gum; $[\alpha]^{20}_D$ −48.4° (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ϵ) 375 (3.24), 306 (3.20), 271 (3.32), 263 (3.21), 231 (3.57) nm; CD (*c* 126.0 μM, MeOH) nm $\Delta\epsilon_{375}$ +0.58, $\Delta\epsilon_{338}$ −0.62, $\Delta\epsilon_{296}$ +0.49, $\Delta\epsilon_{269}$ −1.10, $\Delta\epsilon_{234}$ +0.96; IR (dried film) ν_{max} 3460, 1696, 1648, 1611, 1291 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; ESIMS *m/z* 515.1 $[M + Na]^+$; HRESIMS *m/z* 515.1332 $[M + Na]^+$ (calcd for $C_{27}H_{23}O_9Na$, 515.1318).

Mayoside E (4): brown gum; $[\alpha]^{20}_D$ −137.9° (*c* 0.16, MeOH); UV (MeOH) λ_{max} (log ϵ) 367 (4.15), 301 (3.99), 269 (4.07), 226 (4.56) nm; CD (*c* 117.8 μM, MeOH) nm $\Delta\epsilon_{375}$ +0.82, $\Delta\epsilon_{345}$ −0.29, $\Delta\epsilon_{300}$ −2.26, $\Delta\epsilon_{249}$ +1.65, $\Delta\epsilon_{226}$ −0.71; IR (dried film) ν_{max} 3460, 1696, 1648, 1556, 1045 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; LRESIMS *m/z* 515.1 $[M + Na]^+$; ESIMS *m/z* 515.1332 $[M + Na]^+$ (calcd for $C_{27}H_{23}O_9Na$, 515.1318).

6,8-Dihydroxy-10-methyl-7*H*-benz[*de*]anthracen-7-one (5): yellow needles; mp 191−192 °C ($CHCl_3$) [lit. 188−192 °C ($CHCl_3$)[15]]; UV (MeOH) λ_{max} (log ϵ) 374 (3.79), 356 (3.77), 337 (3.92), 288 (3.91), 279 (3.98), 250 (4.07), 236 (4.51), 225 (4.65), 209 (4.87) nm; IR (dried film) ν_{max} 3314, 1650, 1556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 14.49 (1H, s, OH-6), 12.92 (1H, s, OH-8), 8.58 (1H, d, J = 7.6 Hz, H-1), 8.16 (1H, d, J = 9.0 Hz, H-4), 7.96 (1H, d, J = 7.8 Hz, H-3), 7.76 (1H, br s, H-11), 7.62 (1H, dd, J = 7.7, 7.7 Hz, H-2), 7.30 (1H, d, J = 9.0 Hz, H-5), 6.89 (1H, br s, H-9), 2.53 (3H, s, Me-10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3 (C-7), 168.7 (C-6), 163.8 (C-8), 147.7 (C-10), 140.3 (C-4), 137.7 (C-13), 131.2 (C-3), 127.6 (C-12a), 127.2 (C-11a), 126.5 (C-1), 125.3 (C-12), 124.8 (C-2), 120.6 (C-5), 117.0 (C-9), 115.1 (C-11), 113.7 (C-8a), 109.2 (C-7a), 23.1 (Me-10); HRESIMS *m/z* 275.0701 $[M - H]^-$ (calcd for $C_{18}H_{11}O_3$, 275.0708).

Bioassay Evaluation Procedures. The cytotoxic activity of extracts, chromatographic fractions, and pure compounds was evaluated against a panel of human cancer cell lines, according to the established protocols.[14]

In Vivo Evaluation of Compound 7. Nataloe-emodin (**7**) was evaluated for biological potential in the in vivo hollow fiber model, as described previously.[30,31]

Acknowledgment. This investigation was supported by grant U19-CA-52956, funded by the National Cancer Institute, NIH, Bethesda, MD. We thank Dr. W. W. Thomas at the New York Botanical Garden, Bronx, NY, for identifying the plant material used in this investigation. We thank Dr. J. A. Anderson and Dr. Yan Wang (Research Resources Center, University of Illinois at Chicago) for obtaining the mass spectral data. We are grateful to the Nuclear Magnetic Resonance Laboratory of the Research Resources Center, University of Illinois at Chicago, for the provision of the NMR facilities used in this research. F.D. thanks the Colombian Institute for Science and Technology Development "Francisco Jose De Caldas" COLCIENCIAS (Colombia), and the University of Cartagena, Cartagena (Colombia), for a doctoral fellowship.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**−**5** in $CDCl_3$, a representation of the most stable conformation of picramnioside G (**1**) obtained using the CS Chem3D computational molecular modeling program, and the calculated and observed vicinal coupling constants ($3J$) based on the dihedral angles (ϕ) of the most stable conformation of picramnioside G (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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NP030479J