Lactones from *Angiopteris caudatiformis*

Yong-Ming Yu,[†] Jun-Shan Yang,[†] Chao-Zhong Peng,[†] Valerie Caer,[‡] Pu-Zhu Cong,[†] Zhong-Mei Zou,*[,†] Yang Lu,[§] Shi-Ying Yang,[§] and Yu-Cheng Gu[†,‡]

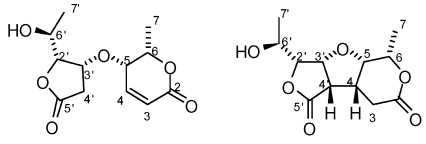
Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100193, People's Republic of China, Syngenta Jealott's Hill International Research Center, Bracknell, Berkshire, RG42 6EY, U.K., and Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, People's Republic of China

Received January 16, 2009

Angiopterlactones A (**1**) and B (**2**), two unique lactones, and three known lactones, osmundalactone (**3**), osmundalin (**4**), and 3,5-dihydroxy-γ-caprolactone (**5**), have been isolated from the rhizome of *Angiopteris caudatiformis*. The structures of **1** and **2** were determined by NMR and MS methods, and the structure of **2** was confirmed by X-ray crystallography. The absolute configurations of **1** and **2** were assigned by application of the CD excitation chirality method and the modified Mosher's method. Compound **1** was slightly cytotoxic against HeLa cells, with an IC_{50} value of 68.8 μM, and compounds **3** and **4** showed moderate insect antifeeding activity against *Plutella xylostella* and *Heliothis virescens*.

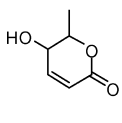
Angiopteris caudatiformis Hieron (Angiopteridaceae) is an ancient fern species that grows mainly in Asia. Its rhizome is known as "ji ma" in Dai folk medicine in China, and it is used to treat infectious diseases such as enteritis, dysentery, and tuberculosis. The rhizomes and fibrous roots of *A. caudatiformis* are also used as ingredients in treatments of cough with lung heat, venomous snake bite, furuncle, and bleeding wounds in Tu folk medicine in China.[1] However, to the best of our knowledge, there has been no previous report of chemical investigation on this species. In our search for new bioactive constituents from the medicinal plants used by the Dai nationality in China, we initiated chemical studies of the rhizome of *A. caudatiformis*.

The air-dried and chopped rhizomes of *A. caudatiformis* (10 kg) were extracted with 95% EtOH (3 × 40 L). After removal of solvent, the aqueous residue was partitioned successively with chloroform and ethyl acetate. The $CHCl_3$ and EtOAc extracts both exhibited significant insect antifeeding activity against *Plutella xylostella* and *Heliothis virescens*. Bioassay-guided fractionation of these extracts led to the isolation of two new metabolites, angiopterlactones A (**1**) and B (**2**), and three known compounds, osmundalactone (**3**),[2] osmundalin (**4**),[3,4] and 3,5-dihydroxy-γ-caprolactone (**5**).[5] Details of the isolation, structure elucidation, and biological activities of these compounds are reported herein.

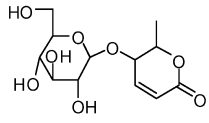


1

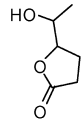
2



3



4



5

Angiopterlactone A (**1**) was obtained as colorless, transparent needles. Its molecular formula was determined to be $C_{12}H_{16}O_6$ by analysis of its HRESIMS (*m/z* 279.0844 $[M + Na]^+$), indicating the presence of five degrees of unsaturation. The IR spectrum of **1** showed absorption bands at 3462 (OH), 1764 (C═O), 1712 (C═O), and 1633 (C═C) cm^{-1}. An α,β-unsaturated-δ-lactone moiety in **1** was indicated by a carbonyl carbon signal at δ_C 162.9 (C-2) and two olefinic carbon signals at δ_C 122.6 and 144.6 in the ^{13}C NMR spectrum. The two oxymethine proton signals at δ_H 4.03 (dd, J = 5.4, 3.0 Hz) and 4.58 (dq, J = 6.6, 3.0 Hz) in the ^1HNMR spectrum were assigned to C-5 and C-6, respectively, on the basis of HMQC data. Analysis of the $^1H-^1H$ COSY NMR data led to the identification of two isolated proton spin systems corresponding to the C-3−C-7 and C-4′−C-7′ (including OH-6′) subunits of **1**. HMBC correlations from H-3 and H-4 to the carboxyl carbon (C-2) led to the connection of C-2 to C-3, while a correlation from H-7 to C-2 established the structure of the α,β-unsaturated-δ-lactone moiety. HMBC cross-peaks from H-3′ to C-5 and from H-5 to C-3′ indicated that C-5 and C-3′ were connected to the same oxygen to form an ether linkage. Although no HMBC correlation was observed between H-2′ and C-5′, a γ-lactone ring was proposed on the basis of the degree of unsaturation requirement of **1** to complete the gross structure of **1** as shown. The proposed structure of **1** was also supported by the fragment ions at *m/z* 212, 167, 129, 111, 84, 68, and 55 in the EIMS spectrum of **1** (Figure S1, Supporting Information). The NOESY correlation of H-3′ with H-5 suggested a *cis* relationship between these protons. A correlation between H_3-7 and H_3-7′ indicated that these two methyl groups were in close proximity. The *cis* relationship between H-3′/H-2′ and H-5/H-6 was also established by relevant NOESY correlations as shown in Figure 1.

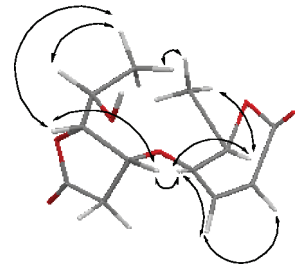


Figure 1. Key NOESY correlations for angiopterlactone A (**1**).

The absolute configuration of **1** was determined by application of the CD excitation chirality method. The CD spectrum of **1** showed a negative Cotton effect ($\Delta\varepsilon$ −2.9) at 221 nm, and according to an empirical observation for the absolute configuration

* To whom correspondence should be addressed. Tel: +86 10 62899756. Fax: +86 10 62899756. E-mail: zmzou@implad.ac.cn.
[†] Institute of Medicinal Plant Development.
[‡] Syngenta Jealott's Hill International Research Center.
[§] Institute of Materia Medica.

10.1021/np900027m CCC: $40.75
Published on Web 04/16/2009

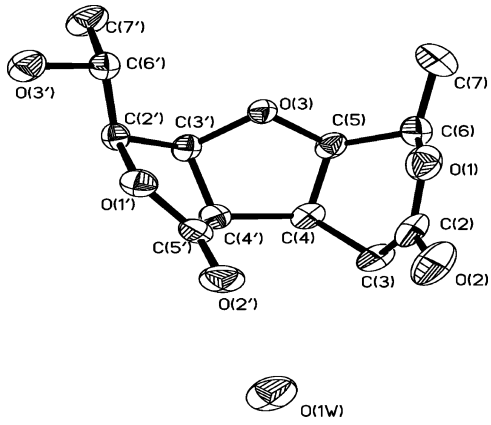


Figure 2. Thermal ellipsoid representation of angiopterlactone B (**2**).

of α,β-unsaturated-δ-lactones, such a negative Cotton effect was consistent with the *S* absolute configuration at C-6.[6] The strong negative value of $\Delta\varepsilon$ −2.9 at 221 nm was due to the overlapped negative Cotton effects resulting from the saturated γ-lactone,[7] leading to the 3′*R* absolute configuration assignment. The absolute configuration of C-6′ was established using the modified Mosher's method.[8] Treatment of **1** with (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chlorides using catalytic DMAP afforded (*S*)- and (*R*)-MTPA esters (**1a** and **1b**), respectively (see Experimental Section). Analysis of the proton chemical shift differences between its (*S*)- and (*R*)-MTPA esters showed negative $\Delta\delta_H$ signs for H_3-7′ (−0.07) and positive signs for H-2′ (+0.01) and H-3′ (+0.01) (Figures S14 and S15, Supporting Information). This distribution of $\Delta\delta$ signs enabled assignment of the *S*-configuration to C-6′. Thus, from the relative configuration, the absolute configuration of **1** was established as 5*S*,6*S*,2′*R*,3′*R*,6′*S*.

Angiopterlactone B (**2**) was obtained as colorless needles. It was assigned the same molecular formula as that of **1** ($C_{12}H_{16}O_6$) on the basis of HRESIMS analysis (*m*/*z* 279.0839 $[M + Na]^+$). The IR spectrum of **2** showed absorption bands at 3612 (OH), 1765 (C=O), and 1735 (C=O) cm^{-1}. Analysis of the ^1H and ^{13}C NMR spectroscopic data of **2** revealed the presence of structural features similar to those of **1**, such as the presence of the same γ-lactone ring and a saturated δ-lactone moiety. The ^{13}C NMR spectrum displayed lactone carbonyl carbon signals at δ_C 169.8 (C-2) and 172.9 (C-5′) and five oxygen-linked carbon signals at δ_C 78.8, 73.3, 84.9, 78.9, and 66.4. However, the absence of olefinic carbon signals in the ^{13}C NMR spectrum of **2** suggested the presence of a saturated δ-lactone in **2** instead of the α,β-unsaturated-δ-lactone present in **1**. From the $^1H-^1H$ COSY spectra, it was observed that a methine signal at δ_H 3.28 (H-4, ddd, J = 9.0 Hz) was coupled with the methylene signals at δ_H 3.33 (d, J = 16.2 Hz) and 2.50 (dd, J = 16.2, 9.0 Hz) and with an oxymethine signal at δ_H 4.15 (H-5, dd). The γ-lactone moiety displayed proton signals similar to those of **1**, except for the appearance of a methine signal at δ_H 3.43 (H-4′) instead of the methylene signals. Furthermore, couplings between H-5 and H-4, H-4 and H-4′, and H-4′ and H-3′ were observed in the $^1H-^1H$ COSY spectrum, suggesting that the δ-lactone ring was coupled to the γ-lactone ring through a tetrahedrofuran ring, which satisfied the degree of unsaturation requirement of **2**. This assignment was supported by relevant HMBC correlations and was consistent with the EIMS fragmentation pattern (Figure S2, Supporting Information). Ultimately, the structure of **2** was confirmed by X-ray crystallographic analysis, and a perspective ORTEP plot is shown in Figure 2.

The absolute configuration of angiopterlactone B (**2**) was determined by the CD excitation chirality method. The δ-lactone ring adopted a boat conformation, which was in agreement with the negative Cotton effect ($\Delta\varepsilon$ −0.6) at 221 nm, suggesting the 4*R* and 3′*R* absolute configurations.[9] The absolute configuration of C-6′ was also determined by the modified Mosher's method. The same methodology as **1a** and **1b** was applied to **2**, which, by analysis of the $\Delta\delta_H$ ($S - R$) values between its (*S*)- and (*R*)-MTPA esters **2a** and **2b** (Figures S16 and S17, Supporting Information), negative $\Delta\delta_H$ signs for H_3-7′ (−0.09) and positive signs for H-2′ (+0.01) and H-4′ (+0.02) were evident, indicating the *S* configuration at C-6′. Therefore, the absolute configuration of angiopterlactone B (**2**) was assigned as 4*R*,5*S*,6*S*,2′*R*,3′*R*,4′*S*,6′*S*.

Angiopterlactones A (**1**) and B (**2**) are unique metabolites possessing dual-lactone skeletons. Compound **1** could be the biosynthetic precursor of **2** by reaction of the α-proton of the γ-lactone ring with the olefin of the α,β-unsaturated-γ-lactone unit, leading to the formation of the previously unreported tricycle system present in **2**. The known compound **3** was isolated for the first time from the genus *Angiopteris*.

Compounds **1**−**5** were tested for insecticidal activity using the *P. xylostella* insect mortality[10] (PLUTMA) and *H. virescens* leaf area eaten (HELIVI) assays.[11] Compounds **3** and **4** displayed antifeeding effects on *P. xylostella* and *H. virescens* at 500 and 1000 ppm, respectively, similar to the antifeeding activity reported for **3** toward yellow butterfly larvae.[12] Compounds **1**−**5** were also evaluated for their in vitro cytotoxicity against HeLa, K562, and KB cell lines using the [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) colorimetric assay.[13] Compound **1** showed minimal cytotoxicity against HeLa cells, with an IC_{50} of 68.8 μM.

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. CD spectra were recorded on a Jasco J-815 spectropolarimeter in CH_3OH. UV absorption was recorded on a Shimadzu UV-2550 spectrophotometer. IR spectra were obtained using a Shimadzu FTIR-8400S spectrophotometer. NMR spectra were recorded using a Bruker AMX 600 spectrometer using the residual $CHCl_3$ (δ_H 7.26/δ_C 77.2) and DMSO-d_6 (δ_H 2.50 /δ_C 39.5) signals as references. The 2D NMR experiments ($^1H-^1H$ COSY, HMQC, HMBC, NOESY) were performed using standard Bruker microprograms. EIMS data were recorded on a GCMS-QP 2010 Shimadzu spectrometer, and HRESIMS data were obtained using a LTQ Orbitrap XL mass spectrometer.

Plant Material. The rhizomes of *A. caudatiformis* were collected from Meng-La County, Yunnan Province, in May 2006. The sample was identified by one of the authors, C.Z.P. A voucher specimen (No. 20060528) has been deposited in the Herbarium of the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Beijing.

Extraction and Isolation. The air-dried and chopped rhizomes of *A. caudatiformis* (10 kg) were extracted with 95% EtOH (3 × 40 L), and the organic solvent was evaporated under vacuum to afford a crude extract (860 g). The extract was suspended in H_2O (5.0 L) and then partitioned successively with $CHCl_3$ and EtOAc (3 × 5.0 L). The $CHCl_3$ extract (80 g) was subjected to silica gel column chromatography (2.4 kg, 100−200 mesh), using petroleum ether−EtOAc gradient elution, and yielded compound **3** (60 g; 0.6%). The EtOAc extract (35 g) was fractionated by silica gel CC (0.7 kg, 100−200 mesh) using $CHCl_3$−MeOH gradient elution (20:1, 10:1, 5:1, 1:1, 0:1) to give eight fractions (I−VIII). Angiopterlactones A (**1**, 230 mg) and B (**2**, 20 mg) were isolated from fraction II (2.8 g) by further chromatography over silica gel (90 g, 15:1 $CHCl_3$−Me_2CO) and purified by Sephadex LH-20 column chromatography using $CHCl_3$−MeOH (1:1) as eluent. Compounds **4** (1.2 g) and **5** (14 mg) were isolated from fraction VII (2.6 g) eluting with petroleum ether−Me_2CO (3:1, 2:1, 1:1, 0:1) over silica gel (80 g, 100−200 mesh).

Angiopterlactone A (1): colorless, transparent needles; mp 160−162 °C; $[\alpha]^{20}_D$ −110 (*c* 0.04, Me_2CO); UV (MeOH) λ max (log ε) 200 (2.75) nm; IR (KBr) ν_{max} 3461, 2916, 1764, 1712, 1633, 1396 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* (% rel int), 212 (6), 167 (10), 129 (32), 111 (66), 84 (100), 68 (28), 55 (51); HRESIMS *m*/*z* 279.0844 $[M + Na]^+$ (calcd for $C_{12}H_{16}O_6Na$, 279.0845).

Table 1. ^{1}H (600 MHz) and ^{13}C (150 MHz) NMR Data for Angiopterlactones A (**1**) (DMSO-d_6) and B (**2**) ($CDCl_3$)

	angiopterlactone A (**1**)			angiopterlactone B (**2**)		
position	δ_C	δ_H (mult, J in Hz)	HMBC	δ_C	δ_H (mult, J in Hz)	HMBC
2	162.9			169.8		
3	122.6	6.09 (d, 9.6)	2, 5	27.9	3.33 (d, 16.2)	2, 4, 5,4′
					2.50 (dd, 16.2, 9.0)	2, 4, 4′
4	144.6	7.17 (dd, 9.6, 5.4)	2, 5, 6	36.6	3.28 (ddd, 9.0, 8.4, 10.2)	3, 6, 5′
5	68.6	4.03 (dd, 5.4, 3.0)	3,4, 3′	78.8	4.15 (br d, 8.4)	3, 6
6	76.0	4.58 (dq, 3.0, 6.6)	5, 7	73.3	4.31 (br q, 6.6)	5, 7
7	15.6	1.32 (d, 6.6)	2,5, 6	16.6	1.46 (d, 6.6)	5, 6
2′	87.0	4.20 (dd, 4.2, 7.2)	6′	84.9	4.21 (m, overlap)	
3′	75.7	4.48 (ddd, 2.4, 5.4, 4.2)	5′, 5	78.9	4.58 (dd, 5.4, 3.0)	5′
4′	37.8	2.88 (dd, 17.4, 5.4)	5′	48.9	3.43 (dd, 10.2, 5.4)	5
		2.47 (dd, 17.4, 2.4)	2′, 3′, 5′			
5′	175.0			172.9		
6′	63.7	3.93 (dq, 7.2, 6.6)	2′	66.4	4.21 (m, overlap)	
7′	19.0	1.10 (d, 6.6)	2′, 6′	17.2	1.31 (d, 6.0)	2′, 6′
OH-6′		4.93 (d, 5.4)			2.45 (s)	

(*S*)-MTPA Ester of 1 (1a): ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.20 (1H, dd, J = 9.6, 5.4 Hz, H-4), 6.13 (1H, d, J = 9.6 Hz, H-3), 5.44 (1H, dq, J = 6.6, 6.0 Hz, H-6), 4.67 (1H, dd, J = 6.0, 5.4 Hz, H-5), 4.63 (1H, dd, J = 5.4, 3.0 Hz, H-2′), 4.63 (1H, dd, J = 5.4, 2.4 Hz, H-3′), 4.12 (1H, dd, J = 5.4, 3.0 Hz, H-6′), 2.90 (1H, dd, J = 17.4, 5.4 Hz, H-4′a), 2.42 (1H, dd, J = 17.4, 2.4 Hz, H-4′b), 1.36 (3H, d, J = 6.6 Hz, H_3-7), 1.29 (3H, d, J = 6.6 Hz, H_3-7′).

(*R*)-MTPA Ester 1 (1b): ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.16 (1H, dd, J = 9.6, 5.4 Hz, H-4), 6.14 (1H, d, J = 9.6 Hz, H-3), 5.45 (1H, dq, J = 6.6, 6.0 Hz, H-6), 4.65 (1H, dd, J = 6.0, 5.4 Hz, H-5), 4.62 (1H, dd, J = 5.4, 3.0 Hz, H-2′), 4.62 (1H, dd, J = 5.4, 2.4 Hz, H-3′), 4.08 (1H, dd, J = 5.4, 3.0 Hz, H-6′), 2.78 (1H, dd, J = 17.4, 6.6 Hz, H-4′a), 2.14 (1H, dd, J = 17.4, 3.6 Hz, H-4′b), 1.38(3H, d, J = 6.6 Hz, H_3-7), 1.36 (3H, d, J = 6.6 Hz, H_3-7′).

Angiopterlactone B (2): colorless needles; mp 200−202 °C; $[\alpha]^{20}_D$ +22 (*c* 0.04, EtOAc); UV (MeOH) λ_{max} (log ε) 203 (2.45) nm; IR (KBr) ν_{max} 3612, 1765, 1735 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* (% rel int), 212 (92), 194 (36), 184 (9), 170 (74), 155 (13), 137 (38), 126 (11), 109 (31), 97 (26), 81 (100), 68 (33), 57 (65); HRESIMS *m*/*z* 279.0839 $[M + Na]^+$ (calcd for $C_{12}H_{16}O_6Na$, 279.0845).

(*S*)-MTPA Ester of 2 (2a): ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.45 (1H, dq, J = 6.6, 6.0 Hz, H-6′), 4.56 (1H, dd, J = 8.4, 4.8 Hz, H-3′), 4.43 (1H, dd, J = 9.0, 3.6 Hz, H-5), 4.30 (1H, dq, J = 7.2, 6.0 Hz, H-6), 4.20 (1H, d, J = 8.4 Hz, H-2′), 3.35 (1H, dd, J = 16.2, 4.8 Hz, H-3a), 3.35 (1H, dd, J = 4.8 Hz, H-4′), 3.31 (1H, dd, J = 8.4, 9.0 Hz, H-4), 2.51 (1H, dd, J = 16.2, 8.4 Hz, H-3b), 1.50 (3H, d, J = 7.2 Hz, H_3-7), 1.40 (3H, d, J = 6.6 Hz, H_3-7′).

(*R*)-MTPA Ester of 2 (2b): ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.48 (1H, dq, J = 6.0, 2.4 Hz, H-6′), 4.57 (br), 4.46 (1H, dd, J = 9.0, 3.6 Hz, H-5), 4.30 (1H, dq, J = 6.6, 6.0 Hz, H-6), 4.19 (1H, d, J = 7.8 Hz, H-2′), 3.34 (1H, dd, J = 16.2, 4.8 Hz, H-3a), 3.33 (1H, dd, J = 4.8 Hz, H-4′), 3.29 (1H, dd, J = 8.4, 9.0 Hz, H-4), 2.50 (1H, dd, J = 16.2, 8.4 Hz, H-3b), 1.51 (3H, d, J = 6.6 Hz, H_3-7), 1.49 (3H, d, J = 6.0 Hz, H_3-7′).

Preparation of MTPA Esters of 1 and 2. To a solution of **1** (1 mg) and *N*,*N*-dimethylaminopyridine (DMAP, a spatula tip, 5 mg) in dry pyridine (2 mL) was added 10 μL of (*S*)-MTPA chloride. The mixture was stirred overnight under N_2 at room temperature. The solvent was removed under vacuum, and the product was purified by HPLC (ODS column) eluting with MeOH−H_2O (65:35) at a flow rate of 2 mL/min to give (*S*)-MTPA ester **1a** in 20% yield (0.2 mg) in 29.2 min. The corresponding (*R*)-MTPA ester (**1b**) was also obtained in 70% yield (0.7 mg) using the same procedure. This procedure was repeated for **2** (2 mg) to obtain the (*S*)-MTPA ester **2a** and (*R*)-MTPA ester **2b** in similar yields.

X-ray Crystallographic Analysis of Angiopterlactone B (2).[14] Crystallization from petroleum ether−EtOAc (1:5) yielded colorless crystals of **1**. A crystal (0.20 × 0.20 × 0.10 mm) was separated from the sample and mounted on a glass fiber, and data were acquired with a MAC DIP-2030K single-crystal X-ray diffractometer with Mo Kα radiation (λ = 0.71071Å) and a graphite monochromator. Structure analysis was made using the SHELXS97 program. Crystal data: $C_{12}H_{16}O_6$ (256 g/mol), space group $P2_12_12_1$; unit cell dimensions a = 5.481(1) Å, b = 9.784(1) Å, c = 24.207(1) Å, orthorhombic, V = 1298.0(1) Å^3, D_c = 1.404 g/cm^3, Z = 4. A total of 30 maps and 2974 independent reflections were collected in the range $0° < \theta < 180°$, of which 2726 were observable reflections [$|F|^2 \geq 2\sigma|F|^2$)], completeness to θ max was 99.7%; non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in Fourier difference maps and refined with idealized geometries and riding constraints. The final indices were R_1 = 0.0347, wR_2 = 0.0965, S = 1.090 [$I > 2\sigma(I)$].

Insecticidal Assay. All compounds were formulated to 500 or 1000 ppm and applied to 96-well assay plates at various volumes to give final concentrations. Two replicates were carried out for each species. Direct contact application was used in the PLUTMA assay. A leaf-dipping means and leaf damage area was applied in the HELIVI assay. A score based on a two-banded scale of 0 and 99 was assigned to each well, where 0 represented no activity and 99 was almost complete control. Different assays were assessed in different ways and at different time points but generally between 5 and 9 days after treatment.

Cytotoxic Assay. The isolated compounds were tested in vitro against HeLa, K562, and KB cell lines. All three cells lines were maintained in RPMI 1640 (Gibco) containing 10% FBS (Gibco), 2 mg/mL sodium bicarbonate, 100 μg/mL penicillin sodium salt, and 100 μg/mL streptomycin sulfate. Cells were grown to 70% confluence, trypsinized with 0.05% trypsin-2 mM EDTA, and plated for experimental use. In all experiments, the cells were grown in RPMI-1640 medium with 10% FBS for 24 h prior to treatment. All compounds were dissolved in DMSO at a concentration of 100 mM, then diluted in tissue culture medium and filtered before use. The cells (1.0×10^4) were seeded in 96-well tissue culture plates, treated with test compounds or vehicle (0.1% DMSO) at various concentrations, and incubated for 48 h followed by MTT assay at 570 nm. The IC_{50} values of the tested compounds against different cell lines were obtained from the concentration−effect curves. Each experiment was repeated at least three times, and the combined data were analyzed using the Student's paired t test.

Acknowledgment. We thank Syngenta for the fellowship to Y.M.Y., and Dr. J. Clough for the proofreading. We gratefully acknowledge financial support from the Major Project of Chinese National Programs for severe infectious diseases such as AIDs and viral hepatitis (Grant No. 2008ZX10003-006). We are also grateful to the Department of Instrumental Analysis, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, for spectroscopic measurements.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of angiopterlactones A (**1**) and B (**2**), proposed MS fragmentation schemes of **1** and **2**, and the cif file of the X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Fang, Z. X.; Zhao, H.; Zhao J. H. *Tu Jia Zu Yao Wu Zhi*; China Medico-Pharmaceutical Science & Technology Publishing House: Beijing, 2006; p 507.
(2) Hollenbeak, K. H.; Kuchne, M. E. *Tetrahedron* **1974**, *30*, 2307–2316.

(3) Hseu, T. H. *Acta Crystallogr.* **1981**, *B37*, 2095–2098.
(4) Ollis, W. D.; Smith, C.; Wright, D. E. *Tetrahedron* **1979**, *35*, 105–127.
(5) Numata, A.; Takahashi, C.; Fujiki, R. *Chem. Pharm. Bull.* **1990**, *38*, 2862–2865.
(6) Riham, S. E. D.; Ali, M. E. H.; Norio, N.; Ma, C. M. *Chem. Pharm. Bull.* **2008**, *56*, 642–646.
(7) Wolf, H. *Tetrahedron Lett.* **1966**, *42*, 5151–5156.
(8) Misong, J.; Kyoung, H. J.; Bora, K.; Bong, H. L.; Byoung, W. C.; Ki-Bong, O.; Jongheon, S. *J. Nat. Prod.* **2008**, *71*, 1714–1719.
(9) Beecham, A. F. *Tetrahedron Lett.* **1968**, *32*, 3591–3594.
(10) Zahid, L.; Thomas, G. H. *J. Nat. Prod.* **1998**, *61*, 614–619.
(11) Kamaraj, C.; Abdul, R. A. *Parasitol. Res.* **2008**, *103*, 1361–1368.
(12) Numata, A.; Hokimoto, K.; Takemura, T. *Chem. Pharm. Bull.* **1984**, *32*, 2815–2820.
(13) Xie, H. G.; Chen, H.; Cao, B.; Zhang, H. W.; Zou, Z. M. *Chem. Pharm. Bull.* **2007**, *55*, 1258–1260.
(14) Crystallographic data for compound **2** have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 724062). Copies of the data can be obtained, free of charge, on application to the director, CCDC 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

NP900027M