Cycloartane Triterpenoids from *Kleinhovia hospita*

Li-She Gan,[†] Gang Ren,[†] Jian-Xia Mo,[†] Xiang-Yi Zhang,[†] Wei Yao,[‡] and Chang-Xin Zhou*[,†]

Institute of Modern Chinese Medicine (IMCM), College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, People's Republic of China, and Zhejiang Chem-Tech Group Co., Ltd., Hangzhou 310023, People's Republic of China

Received January 19, 2009

Four new cycloartane triterpenoids, together with the known gardenolic acid B, were isolated from *Kleinhovia hospita*. The triterpenoids (**1**−**3**) contain a unique 21,23-diacetal side-chain, while compound **4** contains two α,β-unsaturated ketone moieties. Their structures and relative configurations were determined by spectroscopic methods, including 2D NMR and IR. These compounds showed promising hepatoprotective effects on nitrofurantoin-induced cytotoxicity in human liver-derived Hep G2 cells.

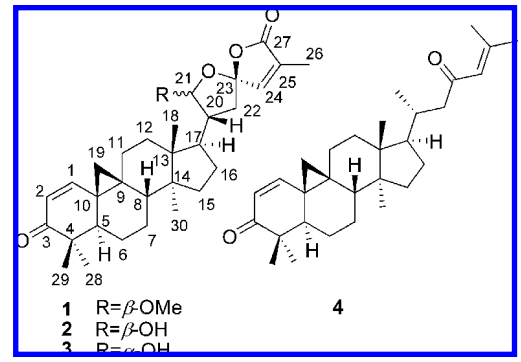
Kleinhovia hospita Linn. (Sterculiaceae) is an evergreen arbor commonly found in tropical areas of Asia, Africa, and Oceania.[1] As the only species representing the genus *Kleinhovia*, it has been used as a folk medicine in parts of Malaya, Indonesia, Papua New Guinea, and China for the treatment of pruritus, tetter, epatitis, and scabies.[2] To date, there are only two phytochemical studies of this species, with several fatty acids and flavonoids identified.[3]

Our interest in searching for novel bioactive natural products from folk medicines prompted us to conduct a chemical investigation of *K. hospita*. Repeated chromatography of the 95% EtOH extract of this plant led to four new cycloartane triterpenoids (**1**−**4**) and the known compound gardenolic acid B. Compounds **1**−**3** are new cycloartane triterpenoids with a unique 21,23-diacetal (bicyclic tetrhydrofuran/furanone) side-chain, while the new **4** possesses two α,β-unsaturated ketone moieties.

Cycloartane triterpenoids, namely, 9,19-cyclotetracyclic triterpenoids, are commonly found throughout the plant kingdom and play a key role in the biosynthesis of steroids.[4] Many of them have been shown to possess various bioactivities such as antitumor, antivirus, and hepatoprotection.[5] Previously, an unsubstituted C-21 methyl was considered to be characteristic of cycloartane triterpenoids.[4a] However, some cycloartane triterpenoids with C-21 oxygenated substitutions were later identified from plants.[6] Uvariastrol, isolated from *Uvariastrum zenkeri* in 1984, was the first cycloartane triterpenoid with a unique 21,23-diacetal side-chain.[6a] The current study is the second report of this type of cycloartane triterpenoids and the first report of this class being isolated from the Sterculiaceae. In this paper, we present the isolation and structure elucidation of five cycloartane triterpenoids from *K. hospita* and their hepatoprotective activities.

Results and Discussion

Compound **1** was isolated as a white, amorphous powder and had a molecular formula of $C_{31}H_{42}O_5$, indicated by a positive HRESIMS pseudomolecular ion peak at *m/z* 495.3111 $[M + H]^+$ (calcd 495.3105). The IR spectrum of **1** showed the presence of an unsaturated ketone (1668 cm^{-1}) and an unsaturated lactone group (1767 cm^{-1}).[7] The five methyls at δ_H 1.94 (3H, d, J = 1.6 Hz), 1.09 (3H, s), 1.04 (3H, s), 0.96 (3H, s), and 0.89 (3H, s), the H-19 doublets at δ_H 0.74 and 1.34 (each, 1H, d, J = 4.8 Hz), and the olefinic proton at δ_H 6.66 (1H, s) observed in the ^{1}H NMR spectrum suggested that **1** is a typical cycloartane triterpenoid with a 21,23-diacetal side-chain.[6a,7] This was further supported by the ^{13}C NMR and DEPT spectra, which showed 30 signals including five methyl, eight methylene, eight methine, and nine quaternary carbons. The α,β-unsaturated ketone moiety was recognized by the NMR signals at δ_C 205.2, 153.5, 126.8 and δ_H 6.79 (1H, d, J = 10.1 Hz), 5.96 (1H, d, J = 10.1 Hz), while the characteristic NMR signals at δ_C 171.2, 144.1, 133.7, 110.7 and δ_H 6.66 (1H, s) demonstrated the existence of the α,β-unsaturated lactone moiety.[6a] In addition, the NMR signals at δ_C 56.2 and δ_H 3.40 (3H, s) indicated a methoxy group. The complete assignments of the overall structure and the ^{1}H and ^{13}C NMR signals of **1** were achieved by a combination of ^{1}H, ^{13}C, DEPT, HSQC, ^{1}H−^{1}H COSY, HMBC, and NOESY experiments. The multiplicities of the carbon and proton signals were obtained from the HSQC spectrum. The ^{1}H−^{1}H COSY spectrum revealed four proton spin systems, as seen in Figure 1. Finally, interpretation of the HMBC spectrum with the aid of HSQC and COSY spectra led to the establishment of the structure skeleton of **1**. As shown in Figure 1, the HMBC correlations of H-1, H_3-28, and H_3-29 with C-3, H_2-19 with C-1, and H-2 with C-10 revealed the presence of ring A, while the correlations of H_2-19 with C-5, C-8, C-9, and C-10 and the transannular correlations of H-1 with C-9 and H_2-6 with C-4 established critical parts of the 9,19-cyclopropyl ring and ring B. Similarly, the structures of rings C and D as well as the 21,23-diacetal side-chain were established by the long-range correlations as shown in Figure 1. A key HMBC correlation of δ_H 3.40 (3H, s) with δ_C 111.7 placed the methoxy group at C-21.



The relative configuration of **1** was determined through NOE correlations. The key correlations of H-19β with H_3-29 and H-8, and H-8 with H_3-18, observed in the NOESY experiment of **1** suggested that these protons were β-oriented, while the NOE correlations of H_3-28/H-5, H-5/H-7α, H-7α/H_3-30, and H_3-30/H-17 revealed their α-orientation (Figure 2). A molecular dynamics study in the MM2 force field (Chem3D 11.0) and a conformational analysis performed in the MMFF94 molecular mechanics force field (SPARTAN 04) showed that the carbon skeleton of **1** was rigid to some extent and only one dominating conformation was found

* To whom correspondence should be addressed. Tel/Fax: 86-571-88208457. E-mail: zhoucx10@zju.edu.cn.
[†] Zhejiang University.
[‡] Zhejiang Chem-Tech Group Co., Ltd.

10.1021/np900029z CCC: $40.75
Published on Web 06/02/2009

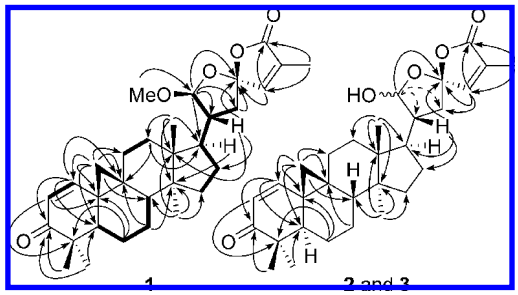


Figure 1. ^{1}H−^{1}H COSY (—) correlations of **1**; key HMBC (→) correlations of **1**−**3** (dashed arrows only observed for **3**).

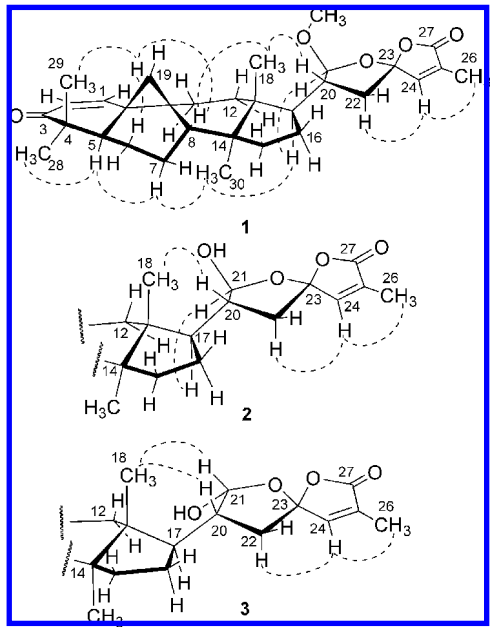


Figure 2. Key NOESY (---) correlations of **1**−**3**.

(Figure 2). The rotation around the C-17−C-20 bond to form various lowest energy conformations was restricted.[8] The NOE correlations of H-20/H_3-18, H-20/H-22β and H-21/H-17, H-22α/H-24, H-24/H_3-26 supported the orientation of these protons and the two oxygen heterocycles. Assuming the same absolute configuration at C-13 and C-20 in **1** as in other cycloartanes based on biogenetic considerations, the overall structure of **1** was therefore determined to be 21*S*,23*R*-21/23,23/27-diepoxy-21-methoxycycloartan-1,24-diene-3,27-dione.

Compounds **2** and **3** were isolated in a mixture and could not be further separated by HPLC under several optimized conditions. The ^{1}H NMR spectrum of the mixture showed that **2** and **3** were in a ratio of about 1:1 as determined by integration values of H-21. This mixture gave the same $[M - H]^-$ ion at *m*/*z* 479.2798 in the HRESIMS (negative ion mode), suggesting **2** and **3** were isomers. The NMR signals of the methoxy group at δ_C 56.2 and δ_H 3.40 (3H, s) in **1** did not appear in **2** and **3**. This, together with the HRESIMS data, indicated the absence of the methoxy group in **2** and **3**. The ^{13}C NMR spectra of compounds **1**, **2**, and **3** were very similar, except for the chemical shifts of C-17, C-20, C-21, and C-22 due to the substitutions and the configuration at C-21. The ^{13}C NMR data allowed for the differentiation of the isomers as the chemical shifts of carbons C-17, C-20, C-21, and C-22 of **2** and **3** displayed significant differences (Table 2). As observed in the NOESY spectrum of the mixture, the key correlations of H-21 with H-17 for **2** and H-21 with H_3-18 for **3** supported the proposed configuration at C-21 for **2** and **3**. The ^{1}H and ^{13}C signals (Tables 1 and 2) of **2** and **3** were unambiguously assigned by detailed analyses of ^{1}H, ^{13}C, DEPT, HSQC, HMBC, and NOESY spectra and by comparison of the ^{1}H and ^{13}C NMR data of **1**. From the above evidence, the structures of **2** and **3** were elucidated as 21*S*,23*R*-21/23,23/27-diepoxy-21-hydroxycycloartan-1,24-diene-3,27-dione and 21*R*,23*R*-21/23,23/27-diepoxy-21-hydroxycycloartan-1,24-diene-3,27-dione, respectively.

Table 1. ^{1}H NMR Data of Compounds **1**−**3** (400 MHz in $CDCl_3$)

H	1	2	3
1	6.79 d (10.1)	6.78 d (10.1)	6.78 d (10.1)
2	5.96 d (10.1)	5.96 d (10.1)	5.96 d (10.1)
5	2.14 dd (12.9, 3.9)	2.14 m	2.14 m
6a	1.35m	1.55m	1.55m
6b	1.11 m	1.10 m	1.10 m
7α	1.24 m	1.25 m	1.25 m
7β	1.40 m1.	60 m	1.60 m
8	2.09 m	2.09 m	2.09 m
11a	1.85 m	1.81 m	1.81 m
11b	1.71 m	1.71 m	1.71 m
12a	1.57 m	1.69 m	1.73 m
12b	1.51 m	1.58 m1.	39 m
15	1.34 m	1.38 m	1.38 m
16a	1.79 m	1.83 m	1.83 m
16b	1.30 m	1.37 m1.	37 m
17	1.93 m	1.91 m	2.17 m
18	1.04 s	1.07 s	1.02 s
19α	0.74 d (4.8)	0.71 d (4.5)	0.70 d (4.5)
19β	1.34 d (4.8)	1.34 (overlap)	1.34 (overlap)
20	2.65 m	2.55 m	2.55 m
21	4.89 d (5.1)	5.30 dd (9.2, 5.0)	5.58 m
22α	1.89 dd (12.9, 11.0)	1.93 m	2.05 m
22β	2.25 dd (12.9, 7.2)	2.27 m	2.23 m
24	6.66 s	6.68 d (1.6)	6.73 d (1.6)
26	1.94 d (1.6)	1.94 d (1.6)	1.92 d (1.6)
28	1.09 s	1.09 s	1.09 s
29	0.96 s	0.96 s	0.96 s
30	0.89 s	0.89 s	0.90 s
other	MeO: 3.40 s	OH: 3.11 d (9.2)	OH: 2.91 d (2.9)

Table 2. ^{13}C NMR Data of Compounds **1**−**4** (100 MHz in $CDCl_3$)

carbon	1	2	3	4
1	153.5	153.6	153.5	154.0
2	126.8	126.8	126.8	126.7
3	205.2	205.4	205.4	205.3
4	45.9	45.8	45.8	45.9
5	43.9	43.8	43.7	44.2
6	19.1	19.0	18.9	19.4
7	22.7	22.6	22.6	23.2
8	42.4	42.2	42.1	43.4
9	24.9	25.0	25.1	24.7
10	30.0	30.1	30.1	29.8
11	27.6	27.7	27.5	27.8
12	30.1	30.1	31.3	32.2
13	45.6	45.6	45.4	49.3
14	49.0	49.0	48.8	45.4
15	34.0	33.9	34.3	34.4
16	27.0	26.8	27.0	28.0
17	49.7	49.7	44.1	52.1
18	17.1	17.2	18.1	16.8
19	28.1	27.8	27.9	29.1
20	45.8	48.5	44.7	33.3
21	111.7	105.2	99.4	19.4
22	41.9	42.4	38.4	51.6
23	110.7	110.8	110.9	201.5
24	144.1	143.9	146.2	124.3
25	133.7	133.9	132.4	154.9
26	10.5	10.5	10.4	27.7
27	171.2	171.2	171.0	20.7
28	21.4	21.3	21.3	21.4
29	19.1	19.1	19.1	19.1
30	18.4	18.4	18.3	18.4
MeO	56.2			

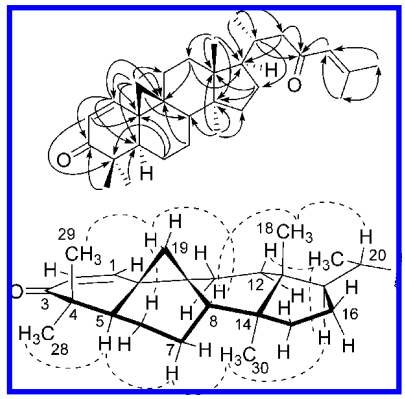


Figure 3. Key HMBC (→) and NOESY (---) correlations of **4**.

Compound **4**, an amorphous powder, exhibited a positive HRESIMS at *m/z* 437.3418 $[M + H]^+$, corresponding to a molecular formula of $C_{30}H_{45}O_2$. The IR spectrum of **4** showed the presence of α,β-unsaturated ketone absorptions (1664 cm^{-1}), similar to that of **1**−**3**. The ^{13}C NMR and DEPT spectra of **4** exhibited 30 carbons including seven methyl, eight methylene, seven methine, and eight quaternary carbons. This, together with the seven methyls at δ_H 2.13 (3H, s), 1.88 (3H, s), 1.08 (3H, s), 0.99 (3H, s), 0.95 (3H, s), 0.88 (3H, s), and 0.88 (3H, d, $J = 5.2$ Hz) and the H-19 doublets at δ_H 0.74, 1.29 (each, 1H, d, $J = 4.5$ Hz) indicated that **4** is a typical cycloartane triterpenoid with a linear side-chain devoid of oxygenation at C-21. The two α,β-unsaturated ketone moieties were indicated by two carbonyl carbons at δ_C 205.3 and 201.5, four olefinic carbon signals at δ_C 154.9, 154.0, 126.7, and 124.3, and three olefinic proton signals at δ_H 6.77 (1H, d, $J = 10.1$ Hz), 5.93 (1H, d, $J = 10.1$ Hz), and 6.05 (1H, s). The assignments of the three olefinic protons H-1, H-2, and H-24 and the two ketones at C-3 and C-23 were made on the basis of the HMBC correlations as shown in Figure 3. The HMBC correlations of H-20/C-16, H-20/C-23, H_3-21/C-17, H_3-21/C-20, H_3-21/C-22, H-22/C-23, H-24/C-23, H_3-26/C-24, and H_3-27/C-24 confirmed part of the linear side-chain. The relative configuration of **4** was concluded from NOEs (Figure 3) obtained from the NOESY spectrum that displayed key correlations of H-5/H_3-28, H-5/H-7α, H-7α/H_3-30, H-8/H_3-18, H-8/H-19β (δ 1.29, d, $J = 4.5$ Hz), H-19β/H_3-29, H-17/H-21, H-17/H-30, and H-18/H-20. The full assignments of ^1H and ^{13}C NMR signals of **4** were based on HSQC, HMBC, and NOESY correlations (Figure 3). Accordingly, compound **4**, a new cycloartane triterpenoid, was determined to be cycloartan-1,24-diene-3,23-dione.

The known compound was identified as gardenolic acid B by analyses of its ^1H, ^{13}C, HSQC, and HMBC spectra and by comparison of the literature data.[9]

The five isolated cycloartane triterpenoids were tested for their hepatoprotective effects on nitrofurantoin-induced cytotoxicity in human hepatoma Hep G2 cells. Compound **1**, the mixture of **2** and **3**, compound **4**, and gardenolic acid B exhibited promising hepatoprotective activities, with EC_{50} values (mean ± SD) of 123.1 ± 15.7, 37.9 ± 5.3, 109.1 ± 16.2, and 66.4 ± 7.1 μM, respectively. Silybin (EC_{50} = 75.7 ± 6.5 μM) was used as positive control.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO p-1030 polarimeter. IR spectra were recorded on a Bruker VECTOR 22 FT-IR spectrometer. UV spectra were recorded on a Hitachi U-4100 spectrometer. NMR spectra were measured on a Varian Inova-400 spectrometer with TMS as internal standard. ESIMS and HRESIMS were measured on a Waters UPLC/MS/MS ACQUITY TQD instrument and a Bruker Daltonics Bio TOF-Q mass spectrometer, respectively. Precoated silica gel GF254 plates (Qingdao Haiyang Chemical Co. Ltd., Qingdao, People's Republic of China) were used for TLC. Silica gel (200−300 mesh), C_{18} reversed-phase silica gel (150−200 mesh, Merck), and MCI gel (CHP20P, 75−150 μm, Mitsubishi Chemical Industries Ltd.) were used for column chromatography. All solvents were analytical grade (Shanghai Chemical Plant, Shanghai, People's Republic of China).

Plant Material. Leaves and twigs of *K. hospita* (8 kg) were collected from Hainan Province, People's Republic of China, in December 2007, and authenticated by Prof. Shi-Man Huang, Department of Biology, Hainan University, People's Republic of China. A voucher specimen has been deposited at the Institute of Modern Chinese Medicine, Zhejiang University (accession number KH-2007-I).

Extraction and Isolation. The dried plant material of *K. hospita* was ground and extracted three times with 95% EtOH for 15 days (5 days for each extraction) at room temperature. The solvent was evaporated under reduced pressure to give a crude extract (288 g). The EtOH extract was suspended in 1.5 L of H_2O and partitioned successively with petroleum ether, EtOAc, and *n*-butanol. The EtOAc fraction (89 g) was then chromatographed over an MCI gel column eluting with a mixture of H_2O and increasing MeOH gradient to give four fractions (A−D). Fraction C was separated by a silica gel column ($CHCl_3/CH_3OH$, 50:1) and then a reversed-phase C_{18} column (70% EtOH in H_2O) to afford gardenolic acid B. Fraction D was subjected to a silica gel column eluting with petroleum ether/EtOAc (8:1) to give six subfractions (D_1−D_6). Compounds **4** (15 mg) and **1** (20 mg) were purified from fractions D_1 and D_5, respectively, over a silica gel column eluting with petroleum ether/Me_2CO (60:1 for **4** and 5:1 for **1**). Fraction D_6 was separated by silica gel chromatography (petroleum ether/Me_2CO, 20:1) and then purified by preparative TLC (silica gel, petroleum ether/Et_2O, 1:1) to furnish a mixture of **2** and **3** (19 mg).

Compound 1: white, amorphous powder; $[\alpha]^{29}_D$ +7.5 (*c* 0.16, CH_3OH); UV (MeOH) λ_{max} (log ε) 270 (3.76), 214 (3.81) nm; IR (KBr disk) ν_{max} 3448, 2956, 1767, 1668, 1458, 1380, 1339, 1100, 948, 605 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Tables 1 and 2; ESIMS (positive) *m/z* 495 $[M + H]^+$; HRESIMS (positive) *m/z* 495.3111 $[M + H]^+$ (calcd for $C_{31}H_{43}O_5$, 495.3105).

Mixture of Compounds 2 and 3: white, amorphous powder; $[\alpha]^{18}_D$ −6.8 (*c* 0.8, CH_3OH); UV (MeOH) λ_{max} (log ε) 266 (3.84), 225 (3.59) nm; IR (KBr disk) ν_{max} 3443, 2944, 2872, 1769, 1667, 1604, 1463, 1129, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz), see Tables 1 and 2; ESIMS (positive) *m/z* 503 $[M + Na]^+$, 481 $[M + H]^+$; ESIMS (negative) *m/z* 479 $[M - H]^-$; HRESIMS (negative) *m/z* 479.2798 $[M - H]^-$ (calcd for $C_{30}H_{39}O_5$, 479.2803).

Compound 4: white, amorphous powder; $[\alpha]^{25}_D$ −23.1 (*c* 0.36, CH_3OH); UV (MeOH) λ_{max} (log ε) 273 (3.43) nm; IR (KBr disk) ν_{max} 3420, 2974, 2949, 2872, 1740, 1689, 1664, 1617, 1598, 1465, 1378, 629 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.77 (1H, d, $J = 10.1$ Hz, H-1), 6.05 (1H, s, H-24), 5.93 (1H, d, $J = 10.1$, H-2), 2.49 (1H, br d $J = 13.4$, H-22a), 2.13 (3H, s, H_3-27), 2.11 (2H, m, H_2-5), 2.07 (1H, m, H-22b), 2.00 (1H, m, H-20), 1.99 (1H, m, H-8), 1.88 (2H, m, H_2-11), 1.88 (3H, s, H_3-26), 1.63 (2H, m, H_2-12), 1.61 (1H, m, H-17), 1.56 (1H, m, H-6a), 1.50 (1H, m, H-7β), 1.29 (2H, m, H_2-15), 1.29 (1H, d, $J = 4.5$ Hz, H-19β), 1.28 (2H, m, H_2-16), 1.26 (1H, m, H-7α), 1.08 (1H, m, H-6b), 1.08 (3H, s, H_3-28), 0.99 (3H, s, H_3-18), 0.95 (3H, s, H_3-29), 0.88 (3H, d, $J = 5.2$, H_3-21), 0.88 (3H, s, H_3-30), 0.74 (1H, d, $J = 4.5$ Hz, H-19α); ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 2; ESIMS (positive) *m/z* 459 $[M + Na]^+$, 437 $[M + H]^+$; HRESIMS (positive) *m/z* 437.3418 $[M + H]^+$ (calcd for $C_{30}H_{45}O_2$, 437.3414).

Hepatoprotective Activity Assay. Human hepatoma Hep G2 (ATCC) cells were maintained at 2×10^5 cells/well in complete medium consisting of RPMI supplemented with 10% heat-inactivated FBS, penicillin G (100 IU/mL), and streptomycin (100 μg/mL) and then incubated at 37 °C in a humidified atmosphere containing 5% CO_2 and 95% air. Cytotoxicity was assessed by the MTT assay after incubating cells for 2 h in the corresponding medium containing 1.7 mM nitrofurantoin or without nitrofurantoin (control).[10] Four concentrations (10, 50, 100, and 150 μM) were tested for each sample, and each experiment was performed in triplicate. The results were expressed as the EC_{50} values (percentage of viability vs control). Silybin was used as the positive control. Data were statistically assessed by using a linear regression model (Origin 7.0).

Acknowledgment. We thank Mr. A. Peoples (NovoBiotic Pharmaceuticals, LLC) for his kind help with the language editing and revision of the manuscript. Financial support from the National Natural Science Foundation of China (No. 30801429), the Zhejiang Provincial Natural Science Foundation (No. Y2080602), and China Postdoctoral Science Foundation (No. 20080441228) is gratefully acknowledged.

Supporting Information Available: Spectroscopic data including 1D and 2D NMR, ESIMS, and IR spectra of **1**, the mixture of **2** and **3**, and **4**. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Editorial Committee of the Chinese Academy of Sciences. *Flora of China (Zhongguo Zhiwu Zhi)*; Science Press: Beijing, China, 1982; Vol.49 (2), pp 142−144.

(2) (a) Latiff, A. In *Plant Resources of South-East Asia*; Faridah, H. I., van der Maesen, L. J. G., Eds.; Prosea Foundation: Bogor, 1997; Vol. 11, pp 166−167. (b) Editorial Committee of the Administration Bureau of Traditional Chinese Medicine. *Chinese Materia Medica (Zhonghua Bencao)*; Shanghai Science & Technology Press: Shanghai, 1999; Vol. 5, pp 387−388.

(3) (a) Dan, S.; Dan, S. S. *Fitoterapia* **1988**, *59*, 348–349. (b) Siddiqi, I. A.; Osman, S. M.; Subbaram, M. R.; Achaya, K. T. *Indian J. Chem.* **1971**, *9*, 209–210.

(4) (a) Boar, R. B.; Romer, C. R. *Phytochemistry* **1975**, *14*, 1143–1146. (b) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; John Wiley & Sons: Chichester, 2002; pp 233−237.

(5) (a) Mohamad, K.; Martin, M. T.; Leroy, E.; Tempête, C.; Sévenet, T.; Awang, K.; Païs, M. *J. Nat. Prod.* **1997**, *60*, 81–85. (b) Tuchinda, P.; Pompimon, W.; Reutrakul, V.; Pohmakotr, M.; Yoosook, C.; Kongyai, N.; Sophasan, S.; Sujarit, K.; Upathum, S. E.; Santisuk, T. *Tetrahedron* **2002**, *58*, 8073–8086. (c) Banskota, A. H.; Tezuka, Y.; Adnyana, I. K.; Xiong, Q.; Hase, K.; Tran, K. Q.; Tanaka, K.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull.* **2000**, *23*, 456–460.

(6) (a) Waterman, P. G.; Mohammad, I. *Phytochemistry* **1984**, *23*, 2077–2079. (b) Nishizawa, M.; Emura, M.; Yamada, H.; Shiro, M.; Chairul; Hayashi, Y.; Tokuda, H. *Tetrahedron Lett.* **1989**, *30*, 5615–5618. (c) Achenbach, H.; Frey, D. *Phytochemistry* **1992**, *31*, 4263–4274.

(7) Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds: Tables of Spectral Data*, 3rd ed.; Springer-Verlag: Berlin, 2000; pp287−294, 176−178.

(8) (a) *Chem3D 11.0*, CambridgeSoft Corporation: MA. (b) *Spartan 04*; Wavefunction Inc.: Irvine, CA. (c) McCann, D. M.; Stephens, P. J. *J. Org. Chem.* **2006**, *71*, 6074–6098.

(9) Xu, R. S.; Qin, G. W.; Zhu, D. Y.; Fan, Z. Y.; Jiang, F. X.; Zhang, B. X.; Wang, J. C.; Wang, Y. L. *Acta Chim. Sin.* **1987**, *45*, 301–304.

(10) Song, E. K.; Cho, H.; Kim, J. S.; Kim, N. Y.; An, N. H.; Kim, J. A.; Lee, S. H.; Kim, Y. C. *Planta Med.* **2001**, *67*, 876–877.

NP900029Z