Abieseconordines A and B, Two Novel Norditerpenoids with a 18-Nor-5,10:9,10-disecoabietane Skeleton from *Abies forrestii*

by **Ping Yu**[a]), **Shou-De Zhang**[c]), **Yong-Li Li**[c]), **Xian-Wen Yang***[b]), **Hua-Wu Zeng**[c]), **Hong-Lin Li**[d]), and **Wei-Dong Zhang***[a])[c])

[a]) Department of Natural Product Chemistry, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, P. R. China (phone/fax: +86-21-8187-1244; e-mail: wdzhangy@hotmail.com)

[b]) Key Laboratory of Marine Bio-resources Sustainable Utilization, Guangdong Key Laboratory of Marine Materia Medica, and RNAM Center for Marine Microbes, South China Sea Institute of Oceanology, Chinese Academy of Sciences, 164 West Xingang Road, Guangzhou 510301, P. R. China (phone: +86-20-89023174; fax: +86-20-84451672; e-mail: xwyang@scsio.ac.cn)

[c]) School of Pharmacy, Shanghai Jiao Tong University, Shanghai 200240, P. R. China

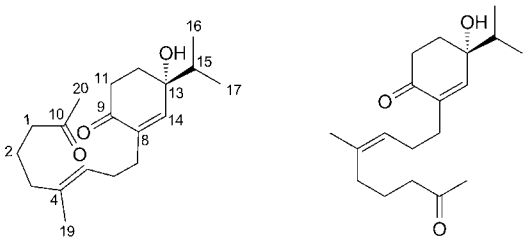
[d]) Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China

A systematic phytochemical investigation on *Abies forrestii* afforded two new and 20 known compounds. Abieseconordines A and B (**1** and **2**) are the first two examples of norditerpenes with a novel 18-nor-5,10:9,10-disecoabietane skeleton. Their structures were established mainly by analysis of 1D- and 2D-NMR spectroscopic data. In addition, electronic circular-dichroism calculations and molecular-orbital analysis were utilized to confirm the absolute configuration of **1**. Both compounds exhibited a potent effect in a bioassay inhibiting LPS-stimulated NO production in RAW264.7 macrophages.

Introduction. – The genus *Abies* is characteristic for structurally fascinating compounds with diverse biological activities [1]. In our recent studies focused on this species indigenous to China, several *Abies* plants were collected for systematic investigations. As a result, many interesting chemical constituents were obtained with remarkable bioactivities [2–15]. In a continuing study, *Abies forrestii*, a tall tree occurring in the northwest of China [16], was harvested for an intensive study, which led to the isolation of two new and 20 known compounds. The new compounds **1** and **2** (*Fig. 1*) are the first two norditerpenoids with a unique 18-nor-5,10:9,10-disecoabietane skeleton. In this study, we describe the isolation and structural elucidation of abieseconordines A (**1**) and B (**2**)[1]).

Results and Discussion. – 1. *Structure Elucidation.* Abieseconordine A (**1**) was obtained as colorless oil with a molecular formula $C_{19}H_{30}O_3$ according to the positive-mode HR-ESI-MS (*m*/*z* 329.2098), requiring five degrees of unsaturation. The IR spectrum of **1** showed OH (3442 cm^{-1}) and C=O (1713 and 1676 cm^{-1}) groups. The

[1]) Trival atom numbering; for systematic names, see *Exper. Part.*



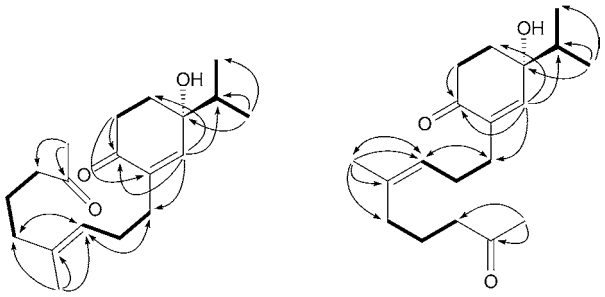
1[1] **2**

Fig. 1. *Abieseconordines A* (**1**) *and B* (**2**) *isolated from* Abies forrestii

Table 1. *^{1}H- and ^{13}C- NMR Data* (600 and 150 MHz, resp.; $CDCl_3$) *of Abieseconordines A* (**1**) *and B* (**2**)[1]). δ in ppm, J in Hz.

	1		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
CH_2(1)	2.37 (*t*, $J = 7.4$)	43.0 (*t*)	2.41 (*t*, $J = 7.2$)	43.3 (*t*)
CH_2(2)	1.65 – 1.68 (*m*)	21.9 (*t*)	1.62 – 1.64 (*m*)	22.1 (*t*)
CH_2(3)	1.95 (*t*, $J = 7.0$)	38.8 (*t*)	1.97 (*t*, $J = 7.2$)	31.1 (*t*)
C(4)		135.0 (*s*)		135.4 (*s*)
H–C(5)	5.06 (*t*, $J = 7.2$)	124.3 (*d*)	5.11 (*t*, $J = 7.2$)	125.2 (*d*)
CH_2(6)	2.09 – 2.12 (*m*)	26.4 (*t*)	2.09 – 2.12 (*m*)	26.6 (*t*)
CH_2(7)	2.20 – 2.25 (*m*)	29.5 (*t*)	2.19 – 2.21 (*m*)	30.0 (*t*)
C(8)		138.8 (*s*)		139.1 (*s*)
C(9)		199.3 (*s*)		199.4 (*s*)
C(10)		209.5 (*s*)		209.4 (*s*)
CH_2(11)	2.68 (*ddd*, $J = 16.8, 10.2, 5.4$), 2.42 (*ddd*, $J = 17.0, 6.2, 4.9$)	34.2 (*t*)	2.68 (*ddd*, $J = 16.8, 10.2, 5.3$), 2.41 – 2.43 (*m*)	34.3 (*t*)
CH_2(12)	2.10 – 2.13 (*m*)	30.7 (*t*)	2.10 – 2.13 (*m*), 1.90 – 1.93 (*m*)	30.8 (*t*)
C(13)		72.2 (*s*)		72.4 (*s*)
H–C(14)	6.45 (*s*)	148.1 (*d*)	6.48 (*s*)	148.3 (*d*)
H–C(15)	1.88 – 1.90 (*m*)	37.0 (*d*)	1.87 – 1.91 (*m*)	37.2 (*d*)
Me(16)	1.01 (*d*, $J = 6.9$)	16.4 (*q*)	1.01 (*t*, $J = 7.0$)	16.5 (*q*)
Me(17)	0.96 (*d*, $J = 6.9$)	17.4 (*q*)	0.96 (*t*, $J = 7.1$)	17.6 (*q*)
Me(19)	1.55 (*s*)	15.8 (*q*)	1.66 (*s*)	23.3 (*q*)
Me(20)	2.13 (*s*)	29.8 (*q*)	2.14 (*s*)	30.1 (*q*)

^{1}H-NMR spectrum (*Table 1*) revealed the presence of a tertiary Me (δ(H) 1.55 (*s*)), an Ac (δ(H) 2.13 (*s*)), and an i-Pr group (δ(H) 0.96 and 1.01 (2*d*, each $J = 6.9$ Hz, 3 H) and 1.88 – 1.90 (*m*, 1 H)). The ^{1}H-, ^{13}C-, and DEPT-NMR spectra showed 19 well-resolved resonances for four Me groups (δ(H) 1.01 (*d*, Me(16)), 0.96 (*d*, Me(17)), 1.55 (*s*, Me(19)), and 2.13 (*s*, Me(20)); δ(C) 16.4 (*q*, C(16)), 17.4 (*q*, C(17)), 15.8 (*q*, C(19)), and 29.8 (*q*, C(20))), seven CH_2 groups, three CH groups including two olefinic ones (δ(H) 5.06 (*t*, $J = 7.2$ Hz, H–C(5)) and 6.45 (*s*, H–C(14)); δ(C) 124.3 (*d*, C(5)) and 148.1 (*d*, C(14))), and five quaternary C-atoms including two ketone groups (δ(C)



1 **2**

Fig. 2. *Key* $^1H,^1H$*-COSY* (—), *HMBC* (H → C), *and NOESY* (H ↔ H) *features for abieseconordines A* (**1**) *and B* (**2**)

199.3 (*s*, C(9)) and 209.5 (*s*, C(10))), two olefinic bonds (δ(C) 135.0 (*s*, C(4)) and 138.8 (*s*, C(8))), and one O-bearing aliphatic C-atom (δ(C) 72.2 (*s*, C(13)). In a $^1H,^1H$-COSY experiment, correlations of $CH_2(1)$ through $CH_2(2)$ to $CH_2(3)$, H–C(5) through $CH_2(6)$ to $CH_2(7)$, $CH_2(11)$ to $CH_2(12)$, and CMe(16) through H–C(15) to CMe(17) suggested the presence of four fragments shown in *Fig. 2*. Further HMBC correlations originated from four Me groups and two vinyl H-atoms connected these fragments into one (*Fig. 2*). Accordingly, the constitutional formula of **1** was established as shown in *Fig. 1*. The (*E*) configuration of the C(4)=C(5) bond was assigned by the ROESY correlation H–C(5)/$CH_2(3)$, which established that $CH_2(3)$ and H–C(5) were cofacial (*Fig. 2*). However, the absolute configuration of **1** could not be readily deduced. The experimental ECD (electronic circular dichroism) spectrum of **1** displayed distinct negative and positive *Cotton* effects (CE) at 239 and 335 nm, respectively. A theoretical calculation of its ECD spectrum by Gaussian 03 [17] was performed as this method has been shown to be effective for determining the absolute configuration of natural products [18].

The (13*R*)-enantiomer **1** was initially optimized by using molecular mechanics, specifically by using the MMFF 94 force field and the program of Maestro7.5, and then geometrically optimized by using DFT at the B3LYP/6-31G** level. On the basis of the above optimization, the ECD spectrum of **1** was calculated at the B3LYP/6-31G**// B3LYP/6-31G** level in the gas phase as well as at the B3LYP-SCRF/6-31G**// B3LYP/6-31G** and B3PW91-SCRF/6-31G**//B3LYP/6-31G** levels with the COMSO model in MeOH solution. As can be noted in *Fig. 3*, the calculated ECD spectra of **1** show diagnostic negative and positive CEs around 239 and 335 nm, which were very close to those of the experimental spectrum.

Molecular orbital (MO) analysis of **1** at the B3PW91-SCRF/6-31G**//B3LYP/6-31G** level with the COSMO model in MeOH, provided a rationalization of the production of the experimentally observed ECD of **1** at a molecular level. The electronic transitions from MO83 to MO85 involving the electrons of the α,β-unsaturated ketone and from MO84 to MO86 of the C=O in the side chain generated positive and negative rotatory strengths at 331 and 230 nm, respectively. This is

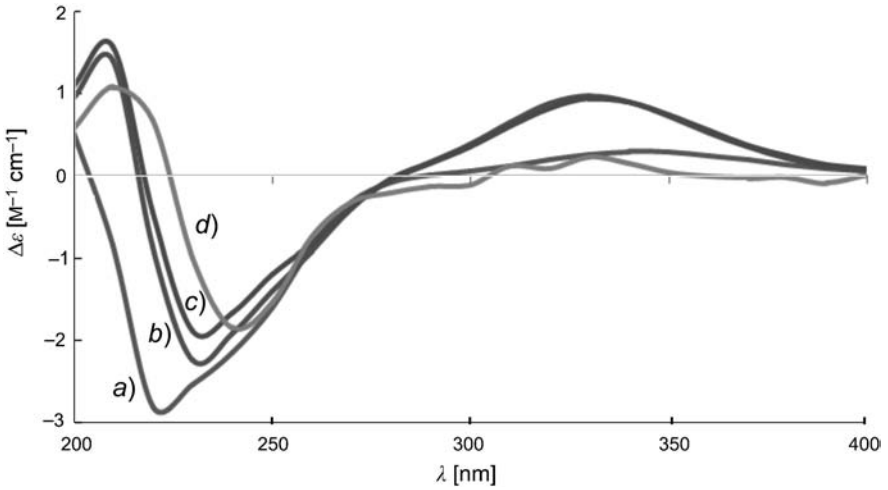


Fig. 3. *Calculated ECD spectra of* **1** *at* a) *the B3LYP/6-31G**//B3LYP/6-31G** level in the gas phase,* b) *the B3LYP-SCRF/6-31G**//B3LYP/6-31G** level with the COSMO model in MeOH, and* c) *the B3PW91-SCRF/6-31G**//B3LYP/6-31G** level with the COSMO model in MeOH.* d) *Experimental ECD spectrum of* **1** *in MeOH*

consistent with the result of the experimental ECD of **1** with the strong positive CE at 336 nm and the negative CE at 239 nm (*Fig. 3*).

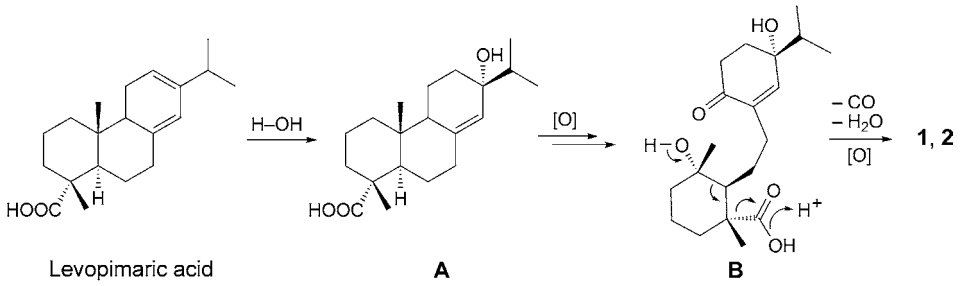
On the basis of the above evidence, the structure of compound **1** was determined as (4*E*,13*R*)-18-nor-5,10 : 9,10-diseco-13-hydroxyabieta-4,8(14)-diene-9,10-dione, and was named abieseconordine A[1]).

Abieseconordine B (**2**) shared the same molecular formula $C_{19}H_{30}O_3$ as **1**. Both compounds exhibited almost the same IR, UV, and ^{1}H-NMR spectra. A close comparison of their ^{13}C-NMR data, however, showed significant differences: C(3) was upfield-shifted by 7.7 ppm, whereas C(19) was downfield-shifted by 7.5 ppm in **2**. This implied that the olefinic C(4)=C(5) bond might be (*Z*)-orientated in **2**. This assumption was confirmed by the ROESY correlations between Me(19) and H–C(5). Accordingly, the structure of compound **2** was determined as (4*Z*,13*R*)-18-nor-5,10 : 9,10-diseco-13-hydroxyabieta-4,8(14)-diene-9,10-dione, and was named abieseconordine B[1]).

Abieseconordines A and B are the first two examples of norditerpenes with a novel 18-nor-5,10 : 9,10-disecoabietane skeleton. A tentative biosynthetic pathway is proposed in the *Scheme*. The precursor, levopimaric acid, is first hydrated to 12,13-dihydro-13-hdroxylevopimaric acid (**A**). Oxidation of this intermediate with opening of ring *B* then leads to 9-oxo-10-hydroxy-9,10-secoabiet-8(14)-en-18-oic acid (**B**). Further elaboration of this precursor finally gives the novel structures of abieseconordines A and B.

Comparing spectroscopic data with those previously published, 20 known chemical constituents were identified as eight diterpenoids, *i.e.*, abieta-7,13-dien-18-oic acid [19], 9,13β-epidioxyabiet-8(14)-en-18-oic acid [20], dehydroabietic acid [21], manool [22], 15-hydroxydehydroabietic acid [21], abieta-8,11,13-triene-15,18-diol [23], 12-hydroxyabietic acid [21], and 15-hydroxy-7-oxoabieta-8,11,13-trien-18-oic acid [24], as two

Scheme. *Proposed Biosynthetic Pathway to Abieseconordines A* (**1**) *and B* (**2**)



triterpenoids, *i.e.*, 23-oxomariesiic acid B [25] and abiesatrine B [3], and as ten phenol derivatives, *i.e.*, (7′*S*,8′*R*)-dihydrodehydrodiconiferyl alcohol [26], rhododendrol [27], 4-(4-hydrophenyl)butan-2-one [28], (+)-pinoresinol [29], (−)-isolariciresinol [30], rhododendrin [31], naringenin [32], kaempferol [33], kaempferol 3-(*β*-D-glucopyranoside) [34], and 4-hydroxy-3-methoxybenzoic acid [35].

2. *Biological Assays.* The capabilities of compounds **1** and **2** to inhibit the LPS-stimulated NO production were measured in RAW264.7 macrophages according to the

Table 2. *Effect of Compounds* **1** *and* **2** *on LPS-Induced NO Production in RAW264.7 Macrophages*

Test compound	Dose [μg/ml]	Inhibition rate [%]
Aminoguanidine[a])	25.0 ([μM])	52.1
Abieseconordine A (**1**)	100.0	72.7
	75.0	23.9
	50.0	0
Abieseconordine B (**2**)	100.0	64.7
	75.0	42.0
	50.0	7.3

[a]) Positive control.

previously reported protocol [36]. Both exhibited potent effects within the tested concentrations (*Table 2*).

The work was supported by the *National Natural Science Foundation of China* (21002110, 30725045), the *Shanghai Leading Academic Discipline Project* (B906), and the *Special Program for New Drug Innovation of the Ministry of Science and Technology*, China (2009ZX09308-005).

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2), *Sephadex LH-20* and *ODS*. Medium pressure liquid chromatography (MPLC): *Büchi Sepacore* system. Optical rotations: *Perkin–Elmer-341* polarimeter. CD and UV Spectra: *Jasco J810* and *Shimadzu-UV-2550* UV/VIS spectrophotometers, resp.; λ ($\Delta\varepsilon$) and λ_{max} ($\log\varepsilon$) in nm, resp. IR Spectra: *Bruker-Vector-22* spectrometer; KBr pellets; in cm^{-1}. NMR Spectra: *Bruker-Avance-600* NMR spectrometer; δ in ppm rel. to Me_4Si as internal standard,

J in Hz. ESI-MS: *Agilent-LC/MSD(Trap)-XCT* mass spectrometer; in *m*/*z*. HR-ESI-MS: *Waters-Q-TOF* micro mass spectrometer; in *m*/*z*.

Plant Material. The twigs, needles, and cones of *A. forrestii* were collected in July 2008 from Linzhi City, Tibet Autonomous Region, China. It was identified by Prof. *Han-Ming Zhang* at the Second Military Medical University. A voucher specimen (200807902) was deposited with the Herbarium of the School of Pharmacy, Second Military Medical University, Shanghai, China.

Extraction and Isolation. The dried powdered sample of *A. forrestii* (7 kg) was extracted three times with 80% EtOH under reflux (3 × 3 h). After evaporation of the solvent, the residue was extracted with AcOEt to give a residue (500 g), which was subjected to CC (SiO_2, gradient $CHCl_3$/MeOH): *Fractions 1–3*. *Fr. 1* underwent further sequential CC (*MCI* gel, MeOH/H_2O 50 → 100%; *ODS*, H_2O/MeOH 70 → 100%; *Sephadex LH-20*, MeOH). Purification by prep. TLC ($CHCl_3$/MeOH 50:1) afforded abieta-7,13-dien-18-oic acid (30.5 mg), 9,13β-epidioxyabiet-8(14)-en-18-oic acid (22.1 mg), and dehydroabietic acid (63.7 mg). *Fr. 2* was also subjected to CC (*MCI* gel, MeOH/H_2O 50 → 100%): *Frs. 2.1–2.3*. *Fr. 2.1* was subjected to CC (*ODS*, H_2O/MeOH 5 → 100%; *Sephadex LH-20*, MeOH). Final purification by prep. TLC ($CHCl_3$/MeOH 20:1) gave 4-(4-hydrophenyl)butan-2-one (12.5 mg), 4-hydroxy-3-methoxybenzoic acid (36.5 mg), naringenin (23.1 mg), and kaempferol (23.1 mg). Similarly, (7′*S*,8′*R*)-dihydrodehydrodiconiferyl alcohol (15.3 mg), rhododendrol (16.7 mg), manool (24.2 mg), abieta-8,11,13-triene-15,18-diol (21.3 mg), 12-hydroxyabietic acid (10.5 mg), and (+)-pinoresinol (30.1 mg) were obtained from *Fr. 2.2*, 23-oxomariesiic acid B (8.1 mg), and 15-hydroxydehydroabietic acid (16.1 mg), abiesatrine B (7.8 mg), and 15-hydroxy-7-oxoabieta-8,11,13-trien-18-oic acid (12.8 mg) from *Fr. 2.3*, and rhododendrin (25.1 mg), kaempferol 3-(β-D-glucopyranoside) (21.7 mg), and (−)-isolariciresinol (13.2 mg) from *Fr. 3*.

Abieseconordine A (=*(4*R*)-4-Hydroxy-4-(1-methylethyl)-2-[(3*E*)-4-methyl-8-oxonon-3-en-1-yl)cyclohex-2-en-1-one*; **1**). Colorless oil. $[\alpha]_D^{20} = -9$ ($c = 0.2$, MeOH). UV (MeOH): 214 (3.87), 230 (3.97). CD (MeOH): 210 (+1.20), 239 (−1.88). IR (KBr): 3442, 2960, 2933, 2875, 1713, 1676, 1443, 1375, 1248, 1175, 1124, 1055, 947. ^{1}H- and ^{13}C-NMR: *Table 1*. ESI-MS (pos.): 329 ($[M+Na]^+$). HR-ESI-MS (pos.): 329.2098 ($[M+Na]^+$, $C_{19}H_{30}NaO_3^+$; calc. 329.2087).

Abieseconordine B (=*(4*R*)-4-Hydroxy-4-(1-methylethyl)-2-[(3*Z*)-4-methyl-8-oxonon-3-en-1-yl)cyclohex-2-en-1-one*; **2**). Colorless oil. $[\alpha]_D^{20} = -10$ ($c = 0.2$, MeOH). UV (MeOH): 214 (4.02), 231 (4.12). CD (MeOH): 213 (+2.05), 240 (−3.79). IR (KBr): 3440, 2972, 2938, 1716, 1679, 1448, 1379, 1189, 1059, 953. ^{1}H- and ^{13}C-NMR: *Table 1*. ESI-MS (pos.): 329 ($[M+Na]^+$). HR-ESI-MS (pos.): 329.2093 ($[M+Na]^+$, $C_{19}H_{30}NaO_3^+$; calc. 329.2087).

Computational Methods. All calculations were performed at 298 K by the Gaussian 03 program package. Ground-state geometries were optimized at the B3LYP/6-31G** level. Excitation energy (in nm) and rotatory strength *R* (velocity form R^{vel} and length form R^{len} in 10^{-40} erg.esu.cm/Gauss) between different states were calculated by the time-dependent density functional theory (TDDFT). The ECD spectra were then simulated by overlapping Gaussian functions for each transition according to *Eqn. 1*, where σ is the width of the band at 1/*e* height and ΔE_i and R_i are the excitation energies and rotatory strengths for transition *i*, resp.: $\sigma = 0.20$ eV and R^{vel} were used in this work.

$$\Delta\varepsilon(E) = \frac{1}{2.297 \times 10^{-39}} \times \frac{1}{\sqrt{2\pi}\sigma} \sum_i^A \Delta E_i R_i e^{-[(E-E_i)/(2\sigma)]^2} \quad (1)$$

Measurement of Nitric Oxide (NO) *in LPS-Activated Macrophages.* According to the reported protocol [36], RAW264.7 macrophages were seeded into 24-well cell-culture plates and co-incubated with tested samples and LPS for 24 h. The amount of NO was assessed by determining the nitrite concentration in the culture supernatants with a microplate reader at 570 nm.

REFERENCES

[1] X.-W. Yang, S.-M. Li, Y.-H. Shen, W.-D. Zhang, *Chem. Biodiversity* **2008**, *5*, 56.

[2] X.-W. Yang, Y.-L. Li, S.-M. Li, Y.-H. Shen, J.-M. Tian, Z.-J. Zhu, L. Feng, L. Wu, S. Lin, N. Wang, Y. Liu, W.-D. Zhang, *Planta Med.* **2011**, *77*, 742.
[3] X.-W. Yang, S.-M. Li, L. Wu, Y.-L. Li, L. Feng, Y.-H. Shen, J.-M. Tian, J. Tang, N. Wang, Y. Liu, W.-D. Zhang, *Org. Biomol. Chem.* **2010**, *8*, 2609.
[4] X.-W. Yang, S.-M. Li, Y.-L. Li, J.-H. Xia, L. Wu, Y.-H. Shen, J.-M. Tian, N. Wang, Y. Liu, W.-D. Zhang, *Eur. J. Org. Chem.* **2010**, 6531.
[5] X.-W. Yang, L. Feng, S.-M. Li, X.-H. Liu, Y.-L. Li, L. Wu, Y.-H. Shen, J.-M. Tian, X. Zhang, X.-R. Liu, N. Wang, Y. Liu, W.-D. Zhang, *Bioorg. Med. Chem.* **2010**, *18*, 744.
[6] L. Wu, Y.-L. Li, S.-M. Li, X.-W. Yang, J.-H. Xia, L. Zhou, W.-D. Zhang, *Chem. Pharm. Bull.* **2010**, *58*, 1646.
[7] X.-W. Yang, Y. Ding, X.-C. Li, D. Ferreira, Y.-H. Shen, S.-M. Li, N. Wang, W.-D. Zhang, *Chem. Commun.* **2009**, 3771.
[8] Y.-L. Li, X.-W. Yang, S.-M. Li, J. Tang, J.-M. Tian, X.-Y. Peng, D.-S. Huang, W.-D. Zhang, *Planta Med.* **2009**, *75*, 1534.
[9] Y.-L. Li, X.-W. Yang, S.-M. Li, Y.-H. Shen, H.-W. Zeng, X.-H. Liu, J. Tang, W.-D. Zhang, *J. Nat. Prod.* **2009**, *72*, 1065.
[10] X.-W. Yang, S.-M. Li, L. Feng, Y.-H. Shen, J.-M. Tian, H.-W. Zeng, X.-H. Liu, L. Shan, J. Su, C. Zhang, W.-D. Zhang, *Tetrahedron Lett.* **2008**, *49*, 3042.
[11] X.-W. Yang, S.-M. Li, L. Feng, Y.-H. Shen, J.-M. Tian, X.-H. Liu, H.-W. Zeng, C. Zhang, W.-D. Zhang, *Tetrahedron* **2008**, *64*, 4354.
[12] Y.-L. Li, X.-W. Yang, W.-D. Zhang, *Biochem. Syst. Ecol.* **2008**, *36*, 932.
[13] Y.-L. Li, L. Wu, D.-W. Ou-Yang, P. Yu, J.-H. Xia, Y.-X. Pan, X.-W. Yang, H.-W. Zeng, X.-R. Cheng, H.-Z. Jin, W.-D. Zhang, *Chem. Biodiversity* **2011**, *8*, 2299.
[14] D.-W. Ou-Yang, L. Wu, Y.-L. Li, P.-M. Yang, D.-Y. Kong, X.-W. Yang, W.-D. Zhang, *Phytochemistry* **2011**, *72*, 2197.
[15] J.-H. Xia, S.-D. Zhang, Y.-L. Li, L. Wu, Z.-J. Zhu, W.-W. Yang, H.-W. Zeng, H.-L. Li, N. Wang, A. Steinmetz, W.-D. Zhang, *Phytochemistry* **2012**, *74*, 178.
[16] W. J. Zheng, L. G. Fu, in'Flora of China', Ed. Z. Y. Wu, Science Press, Beijing, 1978, p. 55.
[17] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. Montgomery, J. A., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian 03 (Revision B.02), *Gaussian, Inc.*, Wallingford, CT, 2004.
[18] Y. Ding, X.-C. Li, D. Ferreira, *J. Nat. Prod.* **2010**, *73*, 435.
[19] E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, A. Tahara, *J. Am. Chem. Soc.* **1964**, *86*, 2038.
[20] A. F. Barrero, J. F. Sanchez, E. J. Alvarez-Manzaneda, R. M. M. Dorado, A. Haidour, *Phytochemistry* **1991**, *30*, 593.
[21] H. T. A. Cheung, T. Miyase, M. P. Lenguyen, M. A. Smal, *Tetrahedron* **1993**, *49*, 7903.
[22] A. Ulubelen, G. Topcu, C. Eri, U. Sönmez, M. Kartal, S. Kurucu, C. Bozok-Johansson, *Phytochemistry* **1994**, *36*, 971.
[23] A. H. Conner, J. W. Rowe, *Phytochemistry* **1977**, *16*, 1777.
[24] T. Matsumoto, S. Imai, Y. Sunaoka, T. Yoshinari, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 723.
[25] S. Hasegawa, T. Miura, N. Kaneko, Y. Hirose, Y. Iitaka, *Tetrahedron* **1987**, *43*, 1775.
[26] M. S. da Silva, J. M. Barbosa-Filho, M. Yoshida, O. R. Gottlieb, *Phytochemistry* **1989**, *28*, 3477.
[27] B. Das, S. Padma Rao, K. V. N. S. Srinivas, J. S. Yadav, *Phytochemistry* **1993**, *33*, 1529.
[28] M. Winter, *Helv. Chim. Acta* **1961**, *44*, 2110.

[29] H. Pan, L. N. Lundgren, *Phytochemistry* **1995**, *39*, 1423.
[30] K. Xiao, L. Xuan, Y. Xu, D. Bai, D. Zhong, *Chem. Pharm. Bull.* **2002**, *50*, 605.
[31] E. Šmite, L. N. Lundgren, R. Andersson, *Phytochemistry* **1993**, *32*, 365.
[32] E. Wenkert, H. E. Gottlieb, *Phytochemistry* **1977**, *16*, 1811.
[33] H. Wagner, V. M. Chari, J. Sonnenbichler, *Tetrahedron Lett.* **1976**, *17*, 1799.
[34] K. R. Markham, B. Ternai, R. Stanley, H. Geiger, T. J. Mabry, *Tetrahedron* **1978**, *34*, 1389.
[35] L. J. Harrison, G.-L. Sia, K.-Y. Sim, H. T.-W. Tan, J. D. Connolly, C. Lavaud, G. Massiot, *Phytochemistry* **1995**, *38*, 1497.
[36] X.-W. Yang, H.-W. Zeng, X.-H. Liu, S.-M. Li, W. Xu, Y.-H. Shen, C. Zhang, W.-D. Zhang, *J. Pharm. Pharmacol.* **2008**, *60*, 937.

Received June 3, 2011