The Constituents of the Leaves of *Aristolochia heterophylla* Hemsl.

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Received January 5, 1999; accepted February 18, 1999

Investigation of the fresh leaves of *Aristolochia heterophylla* resulted in the isolation of three new compounds, madolin-N (1), madolin-O (2) and aristophyll-C(3), together with 42 known compounds. Their structures were determined by spectral method.

Key words *Aristolochia heterophylla*; Aristolochiaceae; madolin-N; madolin-O; aristophyll-C

The genus *Aristolochia* is found in a wide area from the tropics to temperate zones and consists of about 400 species. The fruits and roots of the plant of *Aristolochia* genus have been used in traditional Chinese medicine as anodynes, antiphlogistics, antitussives, expectorants, antiasthmatics, and also for the treatment of snakebite and lung inflammation.[1,2] Aristolochic acids have often been isolated from the plant of genus *Aristolochia* for their cytotoxicity.[3] We are interested in the constituents of *A. heterophylla* due to the broad spectrum of pharmacological action of related species of the genus. We report herein the isolation and structural elucidation of three new compounds together with 42 known compounds from the leaves of *A. heterophylla*.

Results and Discussion

Madolin-N (**1**) was isolated as an optically active colorless oil. Its molecular formula was determined as $C_{15}H_{20}O_3$ by high-resolution mass spectrometry (HR-MS), which indicated six unsaturated degrees in the molecule. Compound **1** contained 15 distinct signals attributable to four quaternary carbons, four methines, six methylenes and one methyl from distortionless enhancement by polarization transfer (DEPT) experiments in the ^{13}C-NMR spectrum. The ^{1}H-NMR spectrum of **1** displayed a disubstituted-α, β-unsaturated aldehyde moiety at δ 9.30 (s) and 6.32 (1H, d, J=9.1 Hz), which was confirmed by the IR bands at 1676 (C=O), 1629 (C=C) cm^{-1}, the UV absorption at 261 nm and the ^{13}C-NMR signals at δ 193.5 (d), 153.0 (d) and 143.9 (s). A terminal methylene group and one carbonyl group appeared at δ_H 5.70 (2H, s) and δ_C 150.2 (s), 125.9 (t) and 203.8 (s). In addition, the presence of a 1-hydroxymethyl-1-methylcyclopropyl moiety in the molecule was inferred by the ^{1}H-NMR signals at δ 1.06 (1H, t, J=9.1 Hz), 1.22 (3H, s), 1.61 (1H, t, J=9.1 Hz), 3.40 (1H, d, J=11.0 Hz) and 3.49 (1H, d, J=11.0 Hz) and ^{13}C-NMR signals at δ 11.3 (q), 25.0 (d), 34.0 (d), 29.3 (s) and 71.7 (t) together with a long-range correlation between H-12 and H-13 with C-6 and C-7 in the heteronuclear multiple-bond correlation spectroscopy (HMBC) experiment (Table 1). The above results showed compound **1** to be a bicyclic germacrane skeleton . To confirm the structure of **1**, two-dimensional shift correlation spectroscopy (2D-COSY) and the long-range ^{13}C–^{1}H correlation in the HMBC experiment were conducted. The above spectral evidence disclosed the plane structure of madolin-N as **1**. The 9.1 Hz coupling constant and nuclear Overhauser effect (NOE) between H-6 and H-7 (Table 1) indicated a *cis* configuration of cyclopropane moiety.[4,5] In addition, the NOE correlations between H-12 and H-6, H-7 determined that the 12-hydroxy methyl group is α configuration. The stereochemistry of madolin-N was determined by the nuclear Overhauser enhancement spectroscopy (NOESY) experiment (Table 1). Based on the above spectral analyses, madolin-N was assigned as **1**.

Madolin-O (**2**) was also obtained as an optically active colorless oil. The high resolution mass spectrum of **2** exhibited a molecular ion at *m/z* 250.1571 in agreement with a molecular formula $C_{15}H_{22}O_3$. Considering the molecular formula and signals in the ^{13}C-NMR spectrum of **2**, the existence of three quarternary carbons, five methines, five methylenes and two methyls shown by DEPT spectra suggested a tricyclic sesquiterpene structure. The presence of a partial structure –CH=C–CHO in this molecule was inferred by the appearance of IR bands at 1670 and 1628 cm^{-1}, a UV absorption band at 262 nm and ^{1}H-NMR signals at δ 9.38 (1H, s), 6.48 (1H, d, J=9.6 Hz) together with ^{13}C-NMR signals at δ 193.7 (d), 152.9 (d) and 144.7 (s). The NMR signals also showed the presence of a 1-hydroxymethyl-1-methylcyclopropane ring [δ_H: 1.86 (1H, t, J=9.6 Hz), 1.17 (1H, m), 1.33 (3H, s), 3.45 (1H, d, J=10.8 Hz) and 3.54 (1H, d, J=10.8 Hz); δ_C: 29.7 (s)] and a long-range correlation of H-6 and H-7 to C-13 and C-12; a tertiary methyl [δ_H: 0.94 (3H, s); δ_C: 17.3 (q)] and an epoxide ring [δ_H: 2.96 (1H, dd, J=11.6, 3.2 Hz); δ_C: 62.8 (d), and 59.9 (s)]. This sesquiterpene was believed to have a germacrane skeleton. To confirm the structure of **2**, 2D-COSY and the long-range ^{13}C–^{1}H correlation in the HMBC experiment (Table 1) were conducted. The results showed the plane structure of modolin-O as **2**. The stereochemistry of **2** was unambiguously determined by the NOESY experiment (Table 1). On the basis of the above results, the structure of madolin-O was assigned as **2**.

Aristophyll-C (**3**) was obtained as a grayish green solid. It exhibited a *pseudo*-molecular ion peak at *m/z* 843 $[M+1]^+$, corresponding to a quasi-molecular formula of $C_{53}H_{71}N_4O_5$ by FAB mass spectrometry. The UV spectrum showed absorptions of a chlorophyll derivative at 225 (sh), 277, 361, 408, 480, 508, 546, 642 and 698 nm[6] The ^{1}H-NMR spectrum of **3** showed the presence of the following signals: three olefinic methyl groups; one vinyl group; one ethyl group; three olefinic protons; two aliphatic protons; one secondary methyl group; a $-CH_2CH_2C$ (=O)– group and a phytyl group. The ^{13}C-NMR spectrum of **3** displayed three carbonyl carbon signals at δ 177.6, 176.6 and 173.2. The ^{1}H-NMR and ^{13}C-NMR spectra of **3** closely matched that of purpurin-18 methyl ester (**4**).[7] The difference of the ^{1}H-NMR and ^{13}C-

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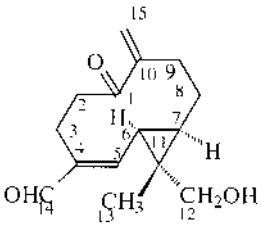
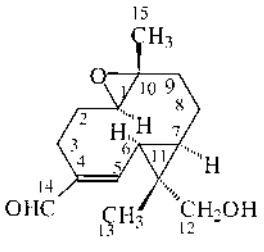
Table 1. NOE Correlations and ^2J,^3J-correlations of HMBC of madolin-N(**1**), -O(**2**)

H	**1**		H	**2**	
	NOESY cross peaks	HMBC correlated carbons		NOESY cross peaks	HMBC correlated carbons
2α	H-2β, H-6α, H-15	C-3, C-4	1α	H-2α, H-3α, H-7α, H-9α	C-2
2β	H-2α, H-15		2α	H-2β, H-1α, H-3β	C-10
3α	H-3β, H-6α	C-2, C-4, C-14	2β	H-2α, H-3β, H-3α, H-9β	
3β	H-3α	C-1	3α	H-3β, H-6α, H-1α, H-2β	C-1, C-2, C-14
5	H-13, H-14	C-3, C-11, C-14	3β	H-3α, H-2α, H-2β	C-1
6α	H-2α, H-3α, H-7α, H-12	C-4, C-7, C-12	5	H-14, H-13	C-3, C-11, C-14
7α	H-6α, H-8α, H-9α	C-8, C-12	6α	H-3α, H-7α, H-12	C-4, C-7, C-12
8α	H-7α, H-8β, H-9α, H-9β		7α	H-1α, H-6α, H-12	
8β	H-8α		8α	H-8β	
9α	H-7α, H-8α, H-9β, H-15		8β	H-8α, H-9β	C-10
9β	H-8α, H-9α, H-15		9α	H-9β, H-1α	C-7, C-8, C-10
12	H-6α, H-7α, H-13	C-6, C-7, C-11, C-13	9β	H-9α, H-8β, H-2β	C-1, C-7
13	H-5, H-12	C-6, C-7, C-11, C-12	12	H-6α, H-7α, H-13	C-6, C-7, C-11, C-13
14	H-5	C-3, C-4	13	H-5, H-12	C-6, C-11, C-12
15	H-2α, H-2β, H-9α, H-9β	C-1, C-9, C-10	14	H-5	C-3, C-4
			15		C-1, C-9, C-10



1



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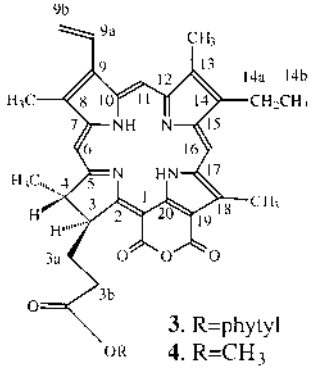

3. R=phytyl
4. R=CH_3

NMR spectra between **3** and **4**, a methyl ester signal at δ_H 3.77 (s) and δ_C 51.63 (q) in **4** were replaced by the characteristic signals of phytyl in **3** at δ_H: 5.20 (H-p2) and 4.51 (H-p1); δ_C: 117.8 (C-p2), 61.4 (C-p1) and 142.7 (C-p3). Thus, **3** was the phytyl ester of purpurin-18. From the above results, the structure of aristophyll-C was proposed as **3**.

The known compounds madolin-A (**5**),[8] (+)-isobicyclogermacrenal (**6**),[5] stigmast-4-en-3,6-dione (**7**),[9] methyl aristolate (**8**),[10] 13^2-hydroxy-(13^2-5)pheophytin-a (**9**),[11] β-sitosterol (**10**),[12] stigmasterol (**11**),[12] piperolactam-A (**12**),[13] aristolactam-AII (**13**),[3] 4-hydroxybenzoic acid (**14**),[3] benzoic acid (**15**),[14] indole-3-carboxylic acid (**16**),[15] aristolic acid (**17**),[10] aristolodione (**18**),[16] cepharadione-A (**19**),[3] aristoliukine-B (**20**),[17] β-sitosteryl-β-D-glucoside (**21**),[17] 4,5-dioxodehydroasimilobine (**22**),[17] aristolochic acid-VIIa (**23**),[18] aristofolin-B (**24**),[17] picrorhizin (**25**),[19] uracil (**26**),[20] caffeic acid (**27**),[3] aristolactam-*N*-β-D-glucoside (**28**),[3] syringic acid (**29**),[19] sodium aristofolin-A (**30**),[10] sodium aristolochate-C (**31**),[21] 4-hydroxycinnamic acid (**32**),[3] aristolochic acid-C (**33**),[3] kaempferol-3-*O*-β-D-6″-(*p*-coumaroyl)glucopyranoside (**34**),[22] kaempferol-7-*O*-β-D-6″-(*p*-coumaroyl)glucopyranoside (**35**),[23] isorhamnetin-3-*O*-β-D-6″-(*p*-coumaroyl)glucopyranoside (**36**),[24] aristolochic acid-IVa (**37**),[17] sodium aristolochate-I (**38**),[17] cepharanone-A-*N*-β-D-glucoside (**39**),[3] aristolactam-IIIa (**40**),[17] -AIII (**41**),[25] -AIIIa (**42**),[17] kaempferol-3-*O*-β-D-glucoside (**43**),[17] isorhamnetin (**44**),[26] vanillic acid (**45**)[17] and *N*-*p*-coumaroyltyramine (**46**),[3] were also isolated and characterized by comparison of their spectroscopic data (UV, IR, NMR and mass spectrometry) with literature values.

Experimental

Melting points (Yanagimoto apparatus) are uncorrected. Optical rotations were recorded on a Jasco DIP-370 digital polarimeter. UV spectra of MeOH solutions were obtained on a Hitachi UV-3210 spectrophotometer. IR spectra of KBr discs were recorded on a Shimadzu FT-IR DR-8011 spectrophotometer. Mass and high resolution mass spectra were measured on a VG-70-250S spectrometer having a direct inlet system. ^{1}H-NMR and ^{13}C-NMR spectra were determined on Bruker AMX-400 and Varian Unity plus 400 spectrometers. Chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as internal standard.

Plant Material *Aristolochia heterophylla* Hemsl. was collected from Tsueg Feng , Nantou Hsien, Taiwan, in May, 1992 and verified by Prof. C.-S. Kuoh. A voucher specimen [Kuoh 017116] is deposited in the Herbarium of National Cheng Kung University, Taiwan.

Extraction and Separation The leaves (1.3 kg) of *Aristolochia heterophylla* Hemsl. were extracted with MeOH and concentrated under reduced pressure to give a deep brown syrup. The MeOH extract was partitioned between $CHCl_3$, *n*-BuOH and H_2O. The $CHCl_3$ extract was directly subjected to chromatography on silica gel column and eluted with a gradient of *n*-hexane : Me_2CO (9 : 1) to afford 9 fractions. Fraction 1 was rechromatographed on silica gel and eluted with *n*-hexane : $CHCl_3$ (5 : 1) to give madolin-N (**1**) (3 mg), -O (**2**) (2 mg), -A (**5**) (2 mg) and (+)-isobicyclogermacrenal (**6**) (4 mg). Fraction 2 was subjected to column chromatography on silica gel using *n*-hexane : Me_2CO (6 : 1) to afford stigmast-4-en-3,6-dione (**7**) (23 mg). Fractions 3 and 4 were combined and separated by column chromatography on silica gel using *n*-hexane : EtOAc (6 : 1) to give aristophyll-C (**3**) (6 mg), methyl aristolate (**8**) (2 mg), 13^2-hydroxy-(13^2-5)pheophytin-a (**9**) (46 mg), β-sitosterol (**10**) (156 mg) and stigmasterol (**11**)

(52 mg). Fractions 6 and 7 were also combined and underwent column chromatography on silica gel and were eluted with a gradient of iso-Pr_2O : Me_2CO (19 : 1) to give piperolactam-A (**12**) (1 mg), aristolactam-AII (**13**) (9 mg), 4-hydroxybenzoic acid (**14**) (2 mg), benzoic acid (**15**) (1 mg) and indole-3-carboxylic acid (**16**) (2 mg). Fraction 8 was rechromatographed on silica gel and were eluted with iso-Pr_2O : MeOH (9 : 1) to give aristolic acid (**17**) (26 mg), aristolodione (**18**) (1 mg), cepharadione-A (**19**) (8 mg), β-sitosteryl-β-D-glucoside (**21**) (15 mg) and 4,5-dioxodehydroasimilobine (**22**) (5 mg). Fraction 9 was chromatographed on sephadex LH-20 using H_2O : MeOH to afford aristolochic acid-VIIa (**23**) (2 mg) and aristofolin-B (**24**) (3 mg). The BuOH layer underwent column chromatography on sephadex LH-20 and was eluted with a gradient of H_2O : MeOH give 14 fractions. Fractions 2 and 3 were combined and chromatographed on silica gel using C_6H_6 : EtOAc : MeOH : H_2O (3 : 5 : 1 : 1 drop) to afford picrorhizin (**25**) (4 mg) and uracil (**26**) (11 mg). Fraction 8 also underwent column chromatography on silica gel using $CHCl_3$: Me_2CO : MeOH (5 : 1 : 1) to give caffeic acid (**27**) (6 mg). Fractions 9 and 10 were separated by column chromatography on silica gel using $CHCl_3$: EtOAc : MeOH : H_2O (4 : 1 : 1 : 0.1) to afford aristolactam-*N*-β-D-glucoside (**28**) (8 mg), syringic acid (**29**) (5 mg) and sodium aristofolin-A (**30**) (2 mg). Fraction 11 was rechromatographed on silica gel and eluted with $CHCl_3$: MeOH : H_2O (5 : 1 : 0.1) to give sodium aristolochate-C (**31**) (3 mg) and 4-hydroxycinnamic acid (**32**) (5 mg). Fraction 12 was also separated by column chromatography on silica gel using EtOAc : MeOH (9 : 1) to give aristolochic acid-C (**33**) (5 mg) and kaempferol-3-*O*-β-D-6″-(*p*-coumaroyl)glucopyranoside (**34**) (1 mg). Fraction 13 was separated by column chromatography on silica gel using EtOAc : MeOH (9 : 1) to give kaempferol-7-*O*-β-D-6″-(*p*-coumaroyl)glucopyranoside (**35**) (2 mg), isorhamnetin-3-*O*-β-D-6″-(*p*-coumaroyl)glucopyranoside (**36**) (4 mg) , aristolochic acid-IVa (**37**) (60 mg). Fraction 14 was rechromatographed on silica gel and eluted with $CHCl_3$: MeOH : H_2O (5 : 1 : 0.1) to give sodium aristolochate-I (**38**) (90 mg), cepharanone-A-*N*-β-D-glucoside (**39**) (6 mg), aristolactam-IIIa (**40**) (5 mg), -AIII (**41**) (2 mg), -AIIIa (**42**) (4 mg), aristoliukin-B (**20**) (2 mg), kaempferol-3-*O*-β-D-glucoside (**43**) (1 mg), isorhamnetin (**44**) (1 mg), vanillic acid (**45**) (1 mg) and *N*-*p*-coumaroyltyramine (**46**) (3 mg).

Madolin-N (**1**): Colorless oil; $C_{15}H_{20}O_3$; $[\alpha]_D$ +224.4° (c=0.392, $CHCl_3$); UV λ_{max}^{MeOH} (log ε) nm: 220 (3.98), 261 (4.06); IR ν_{max}^{KBr} cm^{-1}: 2927, 2860, 1676, 1629, 1514, 1199; EI-MS *m/z* (rel. int.): 248 (M^+,16), 230 (11), 217 (46), 199 (13), 189 (19), 173 (24), 161 (27), 147 (35), 131 (33), 121 (45), 105 (62), 91 (100); HR-EI-MS *m/z* 248.1410 (Calcd for $C_{15}H_{20}O_3$ 248.1412); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.98 (1H, m, H-8), 1.06 (1H, t, J=9.1 Hz, H-7), 1.22 (3H, s, 13-CH_3), 1.61 (1H, t, J=9.1 Hz, H-6), 1.90 (1H, dt, J=12.3, 3.5 Hz, H-8), 2.46 (1H, dt, J=12.3, 3.5 Hz, H-9), 2.56 (1H, td, J=12.3, 3.5 Hz, H-9), 2.69 (1H, td, J=12.6, 4.3 Hz, H-3), 2.70 (1H, dt, J=12.6, 4.3 Hz, H-2), 2.80 (1H, dt, J=12.6, 4.3 Hz, H-3), 2.95 (1H, td, J=12.6, 4.3 Hz, H-2), 3.40 (1H, d, J=11.0 Hz, H-12), 3.49 (1H, d, J=11.0 Hz, H-12), 5.70 (2H, s, H-15), 6.32 (1H, d, J=9.1 Hz, H-5), 9.30 (1H, s, CHO); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 11.3 (C-13), 23.1 (C-3), 25.0 (C-6), 25.4 (C-8), 29.3 (C-11), 31.7 (C-9), 34.0 (C-7), 35.8 (C-2), 71.7 (C-12), 125.9 (C-15), 143.9 (C-4), 150.2 (C-10), 153.0 (C-5), 193.5 (C-14), 203.8 (C-1).

Madolin-O (**2**): Colorless oil; $C_{15}H_{22}O_3$; $[\alpha]_D$ +1019° (c=0.107, $CHCl_3$); UV λ_{max}^{MeOH} (log ε) nm: 262 (4.10); IR ν_{max}^{KBr} cm^{-1}: 2928, 2864, 1670, 1628, 1452, 1064, 1030; EI-MS *m/z* (rel. int.): 250 (M^+,4), 235 (4), 219 (35), 201 (7), 191 (11), 175 (21), 161 (21), 147 (35), 133 (33), 121 (37), 105 (75), 91 (100); HR-EI-MS *m/z* 250.1571 (Calcd for $C_{15}H_{22}O_3$ 250.1569); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.94 (3H, s, H-15), 1.14 (1H, m, H-9), 1.17 (1H, m, H-7), 1.22 (1H, m, H-8), 1.28 (1H, m, H-2), 1.33 (3H, s, H-13), 1.86 (1H, t, J=9.6 Hz, H-6), 1.92 (1H, m, H-8), 2.19 (1H, dd, J=12.0, 5.4 Hz, H-9), 2.25 (1H, dq, J=13.2, 3.2 Hz, H-2), 2.41 (1H, td, J=13.2, 3.2 Hz, H-3), 2.77 (1H, dt, J=13.2, 3.2 Hz, H-3), 2.96 (1H, dd, J=11.6, 3.2 Hz, H-1), 3.45 (1H, d, J=10.8 Hz, H-12), 3.54 (1H, d, J=10.8 Hz, H-12), 6.48 (1H, d, J=9.6 Hz, H-5), 9.38 (1H, s, CHO); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 11.4 (C-13), 17.3 (C-15), 20.6 (C-3), 21.8 (C-8), 25.2 (C-6), 27.7 (C-2), 29.7 (C-11), 34.1 (C-7), 39.8 (C-9), 59.9 (C-10), 62.8 (C-1), 71.5 (C-12), 144.7 (C-4), 152.9 (C-5), 193.7 (C-14).

Aristophyll-C (**3**): Grayish-green solid; $C_{53}H_{70}N_4O_5$; mp: 247—249°; UV λ_{max}^{MeOH} (log ε) nm: 225 (sh, 4.36), 277 (4.05), 361 (4.45), 408 (4.80), 480 (3.54), 508 (3.68), 546 (4.12), 642 (3.77), 698 (4.40); IR ν_{max}^{KBr} cm^{-1}: 2957, 2928, 2864, 1742, 1726, 1562, 1309, 1161; FAB-MS *m/z* (rel. int.): 843 ($(M+1)^+$, 67), 842 (60), 565 (58), 503 (55), 491 (46), 154 (100), 136 (94), 107 (54); HR-FAB-MS *m/z* 843.5424 (Calcd for $C_{53}H_{71}N_4O_5$ 843.5419); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: −0.16 (1H, br s, NH), 0.11 (1H, br s, NH), 0.78 (3H, d, J=7.2 Hz, CH_3), 0.80 (3H, d, J=7.2 Hz, CH_3), 0.84 (6H, d, J=6.8 Hz, 2×CH_3), 1.00—1.60 (m, 21H), 1.61 (3H, t, J=7.4 Hz, H-14b), 1.62 (3H, s, CH_3), 1.74 (3H, d, J=7.2 Hz, 4-CH_3), 2.04 (1H, m, H-3a), 2.46 (2H, m, H-3a, 3b), 2.74 (1H, m, H-3b), 3.10 (3H, s, 13-CH_3), 3.34 (3H, s, 8-CH_3), 3.55 (2H, q, J=7.4 Hz, H-14a), 3.72 (3H, s, 18-CH_3), 4.40 (1H, m, H-4), 4.51 (2H, m, H-p1), 5.20 (2H, m, H-3, H-p2), 6.18 (1H, d, J=11.6 Hz, H-9b), 6.28 (1H, d, J=17.6 Hz, H-9b), 7.87 (1H, dd, J=17.6, 11.6 Hz, H-9a), 8.56 (1H, s, H-6), 9.28 (1H, s, H-11), 9.43 (1H, s, H-16); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 177.6 (C=O), 176.6 (C-5), 173.2 (C=O), 164.1 (C-20), 159.3 (C-2), 156.1 (C-12), 149.9 (C-15), 145.9 (C-14), 144.1 (C-7), 142.7 (C-p3), 139.9 (C-17), 139.1 (C-17), 137.7 (C-9), 136.6 (C-13), 131.8 (C-8), 131.5 (C-18), 129.9 (C-9a), 128.3 (C-9b), 117.8 (C-p2), 111.4 (C-19), 107.5 (C-16), 103.0 (C-11), 95.0 (C-6), 92.9 (C-1), 61.4 (C-p1), 55.0 (C-3), 49.2 (C-4), 39.8, 39.3, 37.4, 37.3, 37.2, 36.6, 32.7, 32.6 (C-3b), 31.2 (C-3a), 29.3, 27.9, 25.0, 24.8, 24.4, 23.8, 22.7 (4-CH_3), 22.6, 19.7 (C-14a), 19.7, 19.3, 17.4, 16.3 (C-14b), 12.3 (18- CH_3), 12.0 (8- CH_3), 11.0 (13-CH_3).

Acknowledgments We thank the National Science Council, R. O. C. (NSC grant 86-2113-M-006-008), for support of this research. We also thank Professor C. S. Kuoh for plant identification.

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