

## Constituents of the Roots and Stems of *Aristolochia mollissima*

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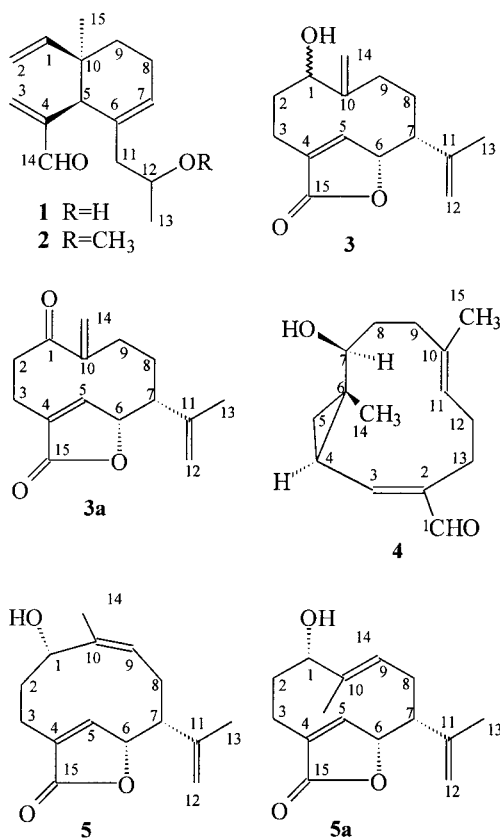
Received June 9, 2000

Five new sesquiterpenes, mandolins R (**1**), S (**2**), U (**3**), W (**4**), and X (**5**), together with 39 known compounds, were isolated from the dried roots and stems of *Aristolochia mollissima*. Their structures were determined by spectroscopic methods.

The genus *Aristolochia* consists of about 400 species distributed widely in areas ranging from the tropics to temperate zones. *Aristolochia mollissima* Hance (Aristolochiaceae) (Chinese name, “Xun Gu Feng”) is found in mainland China. The roots and fruits of this plant are employed as analgesic, anticancer, antimalarial, and anti-inflammatory agents, and also for the treatment of stomach ache, abdominal pain, and rheumatism.<sup>1</sup> Earlier studies of this species described the isolation of several aristolochic acids, aristolactams, sesquiterpenes, and other constituents.<sup>2–11</sup> Recently, we reported a series of new sesquiterpenes (madolins<sup>12</sup> A–O, T, and V) from *Aristolochia* species growing in Taiwan.<sup>13–17</sup> In a continuation of our phytochemical studies on the genus *Aristolochia*, we describe herein the isolation and structure elucidation of five new sesquiterpenes, mandolins R (**1**), S (**2**), U (**3**), W (**4**), and X (**5**), together with 39 known compounds, from the roots and stems of *Aristolochia mollissima*.

### Results and Discussion

Madolin R (**1**) was isolated as an optically active oil, and its molecular formula, C<sub>15</sub>H<sub>22</sub>O<sub>2</sub> (M<sup>+</sup> at *m/z* 234.1618), indicated five degrees of unsaturation. Compound **1** was revealed by the following spectroscopic evidence to be a monocyclic sesquiterpenoid, which contained a formyl group conjugated with a terminal methylene group [ $\lambda_{\max}$  221 nm;  $\nu_{\max}$  1695 cm<sup>-1</sup>;  $\delta_{\text{H}}$  9.64 (1H, s), 6.26 (1H, s), and 6.22 (1H, s);  $\delta_{\text{C}}$  194.2 (d), 150.6 (s), and 137.5 (t)], a vinyl group [ $\delta_{\text{H}}$  5.86 (1H, dd, *J* = 17.6, 11.2 Hz), 5.10 (1H, d, *J* = 17.6 Hz), and 5.02 (1H, d, *J* = 11.2 Hz);  $\delta_{\text{C}}$  145.7 (d) and 112.1 (t)], and another trisubstituted double bond [ $\delta_{\text{H}}$  5.71 (1H, brs);  $\delta_{\text{C}}$  134.6 (s) and 126.9 (d)]. In addition, the <sup>1</sup>H NMR and HMQC spectra revealed the presence of two methine groups at  $\delta$  3.82 (1H, sept., *J* = 6.4 Hz) and 3.44 (1H, br s); three methylene groups at  $\delta$  2.13 (2H, m), 1.83 (2H, dd, *J* = 6.4, 0.8 Hz), and 1.43 (2H, m); and two methyl groups at  $\delta$  1.13 (3H, d, *J* = 6.4 Hz) and 0.75 (3H, s). The COSY spectrum established the presence of the partial structures –CH<sub>2</sub>–CH<sub>2</sub>–CH=C< (**a**) and –CH<sub>2</sub>–CH(O–)–CH<sub>3</sub> (**b**). The skeleton of **1** was constructed from the HMBC spectral data (Table 1). The <sup>2</sup>*J* and <sup>3</sup>*J* correlations of the signal at  $\delta$  3.44 (H-5) with the carbon signals at  $\delta$  150.6 (C-4), 134.6 (C-6), and 38.3 (C-10) and of the signal at  $\delta$  0.75 (H-15) with resonance at  $\delta$  27.7 (C-9), 38.3 (C-10), 41.9 (C-5), and 145.7 (C-1), helped establish the connections of fragment **a** with the vinylidene at C-5, and with the vinyl and the methyl groups at C-10, respectively. Other important correlations in the HMBC spectrum of **1** were observed between  $\delta$  1.83 (H-11) and  $\delta$  134.6 (C-6) and



126.9 (C-7) and suggested that the fragments **a** and **b** were linked at C-6. Therefore, the planar structure of **1** could be established. The relative stereochemistry of madolin R was determined by a NOESY experiment (Table 1). The NOEs observed between H-5 and H-15 and between H-3 and H-9, along the absence of any NOE between H-2 and H-7, showed the vinyl and the vinylidene groups to be pseudoequatorial and pseudoaxial, respectively, with *cis* geometry. Thus, structure **1** was assigned for madolin R, which is 2-[2-(2-hydroxypropyl)-6-methyl-6-vinylcyclohex-2-enyl]prop-2-ene. Although compound **1** is a new sesquiterpene having a rearranged *ent*-elemene-type carbon skeleton, esterified forms of this compound with aristolochic acid have been reported from *A. heterophylla*.<sup>18</sup>

Madolin S (**2**) was isolated as an oil, and HRMS established the molecular formula as C<sub>16</sub>H<sub>24</sub>O<sub>2</sub>, which was 14 mass units more than that of **1**. The spectral data of **2** were similar to those of **1**. The differences observed in the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of **2** compared with those of **1** were the occurrence of signals for H-12 and C-12 at  $\delta_{\text{H}}$  3.34 and  $\delta_{\text{C}}$  74.7 instead of at  $\delta_{\text{H}}$  3.82 and  $\delta_{\text{C}}$  64.3,

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**Table 1.** HMBC Correlations and NOE Interactions for Madolins **1**, **2**, **3**, **4**, and **5**

<b>1</b>			<b>2</b>			<b>3</b>		
H	NOESY	HMBC	H	NOESY	HMBC	H	NOESY	HMBC
1	H-2a		2a		C-10	1	H-2a, H-2b, H-8	
2a	H-1	C-10	2b		C-10	2a	H-1	
3a	H-9	C-5, C-14	3a	H-9a		2b	H-1	
3b	H-14	C-5, C-14	3b	H-14	C-4, C-5	5	H-6	C-6, C-15
5	H-11, H-12, H-15	C-4, C-6, C-10	5	H-11b, H-13, H-15	C-3, C-10	6	H-5, H-7, H-13	
7	H-8, H-11		7	H-11a		7	H-6, H-8, H-9, H-12a	
8	H-7, H-9		8	H-9a, H-9b		8	H-1, H-7	
9	H-3a, H-8, H-15		9a	H-8, H-3a	C-10	9	H-7	
11	H-5, H-12, H-13	C-5, C-6, C-7, C-12	9b	H-8		12a	H-7	C-13
12	H-5, H-11, H-13		11a	H-7, H-11b	C-5, C-7, C-12	12b	H-13	C-7
13	H-11, H-12	C-11, C-12	11b	H-5, H-11a		13	H-6, H-12b	C-7, C-11, C-12
14	H-3b	C-4	12	H-13		14b	H-9	C-1
15	H-5, H-9	C-1, C-5, C-9, C-10	13	H-12	C-11, C-12			
			14	H-3b	C-4, C-5			
			15	H-5	C-1, C-5, C-9, C-10			
<b>4</b>			<b>5</b>					
H	NOESY	HMBC	H	NOESY	HMBC			
1	H-3	C-2, C-13	1 $\beta$	H-7 $\beta$ , H-8 $\beta$				
3	H-1, H-14	C-1, C-13	2a	H-2b				
4	H-7, H-5a		2b	H-2a				
5a	H-4, H-5b, H-7	C-4, C-7	3a	H-3b				
5b	H-5a	C-14	3b	H-3a				C-15
7	H-5a, H-4	C-14	5	H-6 $\beta$				C-6, C-15
8a	H-8b		6 $\beta$	H-5, H-7 $\beta$				
8b	H-8a	C-10	7 $\beta$	H-1 $\beta$ , H-6 $\beta$ , H-8 $\beta$ , H-13				
9a	H-15	C-10	8 $\alpha$	H-8 $\beta$				
9b	H-11, H-15	C-8, C-11, C-5	8 $\beta$	H-7 $\beta$ , H-8 $\alpha$				
11	H-9b, H-12		9	H-14				
12	H-11, H-15		12	H-13				C-7, C-13
13a	H-13b	C-12	13	H-7 $\beta$ , H-12				C-7, C-11, C-12
13b	H-13a	C-12	14	H-9				C-1, C-9, C-10
14	H-3	C-4, C-5, C-6, C-7						
15	H-9a, H-9b, H-12	C-9, C-10, C-11						

respectively. In addition, the presence of a methoxy group in this molecule was implied by the signals at  $\delta_{\text{H}}$  3.27 (3H, s) and  $\delta_{\text{C}}$  56.0. Therefore, the structure of madolin **S** was assigned as **2**, which is 2-[2-(2-methoxypropyl)-6-methyl-6-vinylcyclohex-2-enyl]prop-2-ene, and was supported by COSY, HMQC, HMBC (Table 1), and NOESY (Table 1) experiments.

Madolin **U** (**3**) was isolated as an optically active oil, and its molecular formula,  $\text{C}_{15}\text{H}_{20}\text{O}_3$  ( $\text{M}^+$  at  $m/z$  248.1414), indicated six degrees of unsaturation. The presence of an  $\alpha,\beta$ -unsaturated- $\gamma$ -lactone was implied by the IR band at  $1759\text{ cm}^{-1}$  and confirmed by the signals in the  $^{13}\text{C}$  NMR signals at  $\delta$  174.3 (s), 148.8 (d), 138.2 (s), and 82.8 (d) and the  $^1\text{H}$  NMR resonances at  $\delta$  7.02 (1H, s) and 5.00 (1H, s). The  $^1\text{H}$  NMR and HMQC spectra also indicated two terminal methylene groups [ $\delta$  5.43 (1H, d,  $J = 2.4$  Hz), 5.10 (1H, d,  $J = 2.4$  Hz), 4.93 (1H, s), and 4.83 (1H, s)], as well as a vinylic methyl group [ $\delta$  1.84 (3H, s)]. The presence of a bicyclic ring system in the molecule could be deduced based on the unsaturation values and the unsaturated groups evident, namely, two terminal methylenes and an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone ring. The COSY and HMQC spectra readily established the presence of  $-\text{CH}-\text{CH}_2\text{CH}_2-$  and  $-\text{CH}(\text{O})-\text{CH}_2\text{CH}_2-$  as partial structures. The spectral data of **3** were similar to those of madolin **I** (**3a**)<sup>16</sup> except for the signals of H-1 and C-1 of **3** at  $\delta_{\text{H}}$  3.85 (1H, m) and  $\delta_{\text{C}}$  75.2 (d) instead of the signal of C-1 of **3a** at  $\delta_{\text{C}}$  206.8 (s). Therefore, compound **3** was shown to be a germacrane-type of sesquiterpenes, which possess a hydroxyl function at C-1 instead of a ketone group. On the other hand, the relative stereochemistry of H-6 and H-7 was determined to be syn based on the cross-peak between H-7 ( $\delta$  2.49–2.53) and H-6 ( $\delta$  5.00) in the NOESY experi-

ment (Table 1). Thus, structure **3** was assigned for madolin **U**, which is 4-hydroxy-8-isopropenyl-5-methylene-10-oxabicyclo[7.2.1]dodec-1(12)-en-11-one. The stereochemistry of the OH-1 group has not been resolved.<sup>19</sup>

Madolin **W** (**4**) was isolated as a colorless oil and determined to have the molecular formula  $\text{C}_{15}\text{H}_{22}\text{O}_2$  by HRMS. The presence of an  $\alpha,\beta$ -unsaturated aldehyde was revealed by IR and UV absorption bands at  $1675\text{ cm}^{-1}$  and at 258 nm, respectively, together with  $^{13}\text{C}$  NMR signals at  $\delta$  194.1 (s), 157.0 (d), and 143.3 (s). The signals at  $\delta$  127.1 (d) and 135.6 (s) in the  $^{13}\text{C}$  NMR spectrum, as well as a resonance at  $\delta$  5.26 (1H, br d,  $J = 10.0$  Hz) in the  $^1\text{H}$  NMR spectrum, provided evidence for the presence of a trisubstituted double bond in **4**. The COSY and HMQC spectra helped establish three structural fragments:  $-\text{CH}_2-\text{CH}=\text{CH}=\text{C}-\text{CHO}$  (**a**),  $-\text{O}-\text{CH}-\text{CH}_2-\text{CH}_2-$  (**b**), and  $-\text{CH}_2-\text{CH}_2-\text{CH}=\text{C}-$  (**c**). The skeleton of **4** was elucidated from the HMBC experiment (Table 1). The  $^2J$  and  $^3J$  correlations between H-15 at  $\delta$  1.47 and the carbons at  $\delta$  135.6 (C-10), 127.1 (C-11), and 39.0 (C-9) established the connectivity of fragments **b** and **c** and a methyl group at C-10. Other significant correlations in the HMBC spectrum of **4** observed from  $\delta$  1.23 (H-14) to  $\delta$  82.4 (C-7), 30.9 (C-6), 27.8 (C-4), and 25.3 (C-5), suggested linkages between fragments **a**, **b**, and another methyl group at C-6. The linkage between fragments **a** and **c** was confirmed by the HMBC correlations between  $\delta$  22.9 (C-13) and 6.08 (H-3). Therefore, the planar structure of **4** could be deduced as a 4,6-cyclohumulane-type sesquiterpene.<sup>20</sup> The relative stereochemistry of madolin **W** was determined from a NOESY experiment (Table 1). The NOE correlations between H-1 and H-3 and between H-11 and H-9 established that  $\Delta^{2,3}$  and  $\Delta^{10,11}$  were both in the *E* form. Finally,

the configurations of H-4 with H-7 and H-14 were determined as syn and anti, respectively, due to the appearance of cross-peaks between H-4 and H-7 and between H-3 and H-14. On the basis of above spectral analysis, structure **4** was assigned for madolin W, which is 10-hydroxy-7,11-dimethylbicyclo[9,1,0]dodeca-2,6-diene-3-carbaldehyde.

Madolin X (**5**) was isolated as a colorless oil. The HRMS showed a  $[M]^+$  at  $m/z$  248.1410 and revealed the molecular formula of **5** to be  $C_{15}H_{20}O_3$ , with six degrees of unsaturation. The IR absorption band at  $1739\text{ cm}^{-1}$  and a signal at  $\delta$  174.0 (s) in the  $^{13}\text{C}$  NMR spectrum suggested the presence of a  $\gamma$ -lactone. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **5** indicated the presence of two sets of trisubstituted double bonds ( $\delta_{\text{H}}$  6.77,  $\delta_{\text{C}}$  152.9, 137.5;  $\delta_{\text{H}}$  5.25,  $\delta_{\text{C}}$  136.3, 129.4) and one terminal methylene group ( $\delta_{\text{H}}$  4.91 (2H),  $\delta_{\text{C}}$  146.0, 112.9). The presence of these three double bonds and the one  $\gamma$ -lactone suggested a bicyclic structure for **5**. The COSY and HMQC spectra established  $-\text{CH}-\text{CH}_2-\text{CH}=\text{C}-\text{CH}_3$ ,  $\text{CH}_2=\text{C}-\text{CH}_3$ , and  $-\text{CH}(\text{O}-)-\text{CH}_2-\text{CH}_2-$  as partial structures. The linkage between the partial structures was achieved by HMBC experiment (Table 1). Based on the above information, the planar structure of **5** was the same as versicolactone B (**5a**)<sup>21</sup> and it belongs to the germacran-type of sesquiterpenes, so that compound **5** was seen to be an isomer of **5a**. Some minor differences were observed in their NOESY correlations (Table 1). The presence of NOEs of H-7 with H-1 and H-6 indicated that H-7, H-1, and H-6 have syn configurations. In addition, the NOEs between H-9 and H-14 showed that  $\Delta^{9,10}$  was in the *Z* form. Based on these observations, structure **5** was assigned for madolin X, which is 4-hydroxy-8-isopropenyl-5-methyl-10-oxabicyclo[7,2,1]dodeca-1(12),5-dien-11-one.

The known compounds (+)-isobicyclogermacrenal;<sup>22</sup> aristolactone;<sup>17</sup> saphthulenol;<sup>23</sup> manshurilide;<sup>17</sup> 1,10-epoxylepidozenal;<sup>24</sup> versicolactone B;<sup>21</sup> madolins A,<sup>15</sup> B,<sup>15</sup> H,<sup>14</sup> K,<sup>16</sup> M,<sup>16</sup> T,<sup>17</sup> and V;<sup>17</sup> (-)-lepidozonal,<sup>13</sup> borneol;<sup>17</sup> stigmast-4-en-3-one;<sup>17</sup>  $\beta$ -sitosterol;<sup>17</sup> stigmasterol;<sup>17</sup> aristophyllide A;<sup>18</sup> aristoloterpenate I;<sup>25</sup> aristoloterpenate III;<sup>25</sup> alkyl *trans*-ferulate;<sup>26</sup> alkyl *cis*-ferulate;<sup>26</sup> aristolactam AII;<sup>26</sup> 9-methoxyaristolactam I;<sup>26</sup> aristolactam-*N*- $\beta$ -D-glucoside,<sup>26</sup> aristolactam-*C*-*N*- $\beta$ -D-glucoside,<sup>26</sup> aristolactam AIIIa;<sup>16</sup> cepharadione A;<sup>26</sup> 4,5-dioxodehydroasimilobine;<sup>26</sup> allantoin;<sup>26</sup> isorhamnetin 3-*O*-rutinoside;<sup>26</sup> *N*-*p*-*trans*-coumaroyltyramine;<sup>26</sup> *N*-*p*-*cis*-coumaroyltyramine;<sup>26</sup> aristoliukines A and B;<sup>27</sup> aristolochic acids I and II;<sup>26</sup> and aristolochic acid IVa<sup>26</sup> were also isolated and characterized from the roots and stems of *A. mollissima*. The structures of those known compounds were identified by comparison of their spectroscopic data (UV, IR, NMR, EIMS) with literature values.

## Experimental Section

**General Experimental Procedures.** Optical rotations were recorded on a JASCO DIP-370 digital polarimeter. UV spectra were obtained on a Hitachi UV-3210 spectrophotometer. IR spectra were recorded on a Shimadzu FT-IR DR-8011 spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were determined on Bruker AMX-400 and Varian Unity plus 400 spectrometers. Chemical shifts are shown in  $\delta$  values (ppm) with tetramethylsilane (TMS) as internal standard. LRMS and HRMS were measured on a VG-70-250S spectrometer having a direct inlet system.

**Plant Material.** *A. mollissima* was collected in Jiujiang Hsien, Jiangshi Province, People's Republic of China, in August 1997, and was identified by Prof. C.-S. Kuoh. A voucher specimen (Kuoh 017114) is deposited in the Herbarium of National Cheng Kung University, Tainan, Taiwan.

**Extraction and Isolation.** The combined roots and stems (162 g) of *A. mollissima* were extracted successively with  $\text{Et}_2\text{O}$  and MeOH and concentrated under reduced pressure. The

$\text{Et}_2\text{O}$  extract was chromatographed over Si gel and eluted with *n*-hexane– $\text{Me}_2\text{CO}$  (49:1) to afford (+)-isobicyclogermacrenal (12 mg), aristolactone (25 mg), saphthulenol (4 mg), stigmast-4-en-3-one (3 mg), manshurilide (8 mg), borneol (3 mg),  $\beta$ -sitosterol (20 mg), stigmasterol (5 mg), aristophyllide A (1 mg), aristoloterpenate I (3 mg), aristoloterpenate III (0.8 mg), madolin A (3 mg), madolin M (2 mg), madolin S (1 mg), and madolin T (9 mg). The MeOH extract was partitioned into  $\text{H}_2\text{O}$ - and  $\text{CHCl}_3$ -soluble parts. The  $\text{CHCl}_3$  extract was subjected to chromatography over a Si gel column by eluting with gradients of *n*-hexane– $\text{EtOAc}$  (9:1) to afford 13 fractions. Fraction 2 was rechromatographed on Si gel and eluted with *n*-hexane– $\text{EtOAc}$  (19:1) to give (-)-lepidozonal (0.5 mg). Fraction 4 was subjected to chromatography on Si gel using  $\text{C}_6\text{H}_6$ – $\text{Me}_2\text{CO}$  (49:1) as eluent to afford madolin H (2 mg), alkyl *trans*-ferulate (2 mg), and alkyl *cis*-ferulate (1 mg). Fraction 5 was column chromatographed over Si gel using  $\text{C}_6\text{H}_6$ – $\text{Me}_2\text{CO}$  (49:1) as eluent to give madolin R (1 mg) and 1,10-epoxylepidozenal (0.5 mg). Fractions 7 and 8 were chromatographed on Si gel and eluted with a gradient of *n*-hexane– $\text{EtOAc}$  (1:1) to afford versicolactone B (16 mg), aristolactam AII (1 mg), 9-methoxyaristolactam I (1 mg), cepharadione A (0.5 mg), madolin B (0.5 mg), madolin K (0.5 mg), madolin U (1.5 mg), madolin V (0.9 mg), madolin W (2 mg), and madolin X (1 mg). Fraction 9 was also separated by chromatography on Si gel using  $\text{CHCl}_3$ – $\text{MeOH}$  (17:1) to give 4,5-dioxodehydroasimilobine (0.6 mg). Fraction 10 was separated by chromatography on Si gel using  $\text{EtOAc}$  as eluent to give aristolochic acid I (114 mg). Fraction 11 was purified by chromatography on Si gel with  $\text{EtOAc}$  as eluent to yield aristolactam-*N*- $\beta$ -D-glucoside (25 mg). Fractions 12 and 13 were chromatographed on Si gel and eluted with a gradient of  $\text{CHCl}_3$ – $\text{MeOH}$ – $\text{H}_2\text{O}$  (5:1:0.1) to separate aristolochic acid II (1.6 mg) and aristolochic acid I (0.9 mg). The  $\text{H}_2\text{O}$  layer was passed over a column containing Diaion HP-20, eluted with a gradient of  $\text{H}_2\text{O}$ – $\text{MeOH}$ , to afford eight fractions. Fraction 1 was filtered to give allantoin (83 mg). Fraction 6 was chromatographed on Si gel using a gradient of  $\text{CHCl}_3$ – $\text{MeOH}$ – $\text{H}_2\text{O}$  (5:1:0.1) to purify aristolactam-*C*-*N*- $\beta$ -D-glucoside (1 mg) and isorhamnetin 3-*O*-rutinoside (2 mg). Fraction 7 was also subjected to chromatography on Si gel and eluted with a gradient of  $\text{CHCl}_3$ – $\text{MeOH}$ – $\text{H}_2\text{O}$  (5:1:0.1) to give aristolactam AIIIa (1 mg), *N*-*p*-*trans*-coumaroyltyramine (1 mg), *N*-*p*-*cis*-coumaroyltyramine (1 mg), aristoliukine A (0.5 mg), and aristoliukine B (0.5 mg). Fraction 8 was separated by chromatography on Si gel using  $\text{CHCl}_3$ – $\text{MeOH}$ – $\text{H}_2\text{O}$  (5:1:0.1) as eluent to obtain aristolochic acid IVa (6 mg).

**Madolin R (1):** obtained as a colorless oil;  $[\alpha]_{\text{D}} -63.0^\circ$  (c 0.07,  $\text{CHCl}_3$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 221 (2.66) nm; IR  $\nu_{\text{max}}$  (KBr) 3470, 2918, 2850, 1695, 1460, 1375  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.75 (3H, s, H-15), 1.13 (3H, d,  $J = 6.4$  Hz, H-13), 1.43 (2H, m, H-9), 1.83 (2H, dd,  $J = 6.4, 0.8$  Hz, H-11), 2.13 (2H, m, H-8), 3.44 (1H, br s, H-5), 3.82 (1H, sept.,  $J = 6.4$  Hz, H-12), 5.02 (1H, d,  $J = 11.2$  Hz, H-2b), 5.10 (1H, d,  $J = 17.6$  Hz, H-2a), 5.71 (1H, br s, H-7), 5.86 (1H, dd,  $J = 17.6, 11.2$  Hz, H-1), 6.22 (1H, s, H-3b), 6.26 (1H, s, H-3a), 9.64 (1H, s, H-14);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  22.6 (C-13), 22.8 (C-8), 26.3 (C-15), 27.7 (C-9), 38.3 (C-10), 41.9 (C-5), 46.3 (C-11), 64.3 (C-12), 112.1 (C-2), 126.9 (C-7), 134.6 (C-6), 137.5 (C-3), 145.7 (C-1), 150.6 (C-4), 194.2 (C-14); EIMS  $m/z$  234  $[M]^+$  (16), 217 (16), 216 (49), 201 (16), 189 (11), 188 (43), 175 (32), 161 (33), 146 (69), 131 (50), 119 (39), 107 (93), 91 (100); HREIMS  $m/z$  234.1618 (calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_2$ , 234.1619).

**Madolin S (2):** obtained as a colorless oil;  $[\alpha]_{\text{D}} -41.7^\circ$  (c 0.06,  $\text{CHCl}_3$ ); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 220 (2.67) nm; IR  $\nu_{\text{max}}$  (KBr) 2967, 2929, 2827, 1694, 1455, 1377, 1134, 1085  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  0.74 (3H, s, H-15), 1.06 (3H, d,  $J = 6.0$  Hz, H-13), 1.32 (1H, m, H-9b), 1.42 (1H, m, H-9a), 1.89 (1H, d,  $J = 14.8$  Hz, H-11b), 2.00–2.20 (2H, m, H-8, H-11a), 3.27 (3H, s,  $\text{OCH}_3$ ), 3.34 (1H, m, H-12), 3.41 (1H, br s, H-5), 4.98 (1H, d,  $J = 10.8$  Hz, H-2b), 5.08 (1H, d,  $J = 17.6$  Hz, H-2a), 5.64 (1H, br s, H-7), 5.92 (1H, dd,  $J = 17.6, 10.8$  Hz, H-1), 6.24 (1H, s, H-3b), 6.26 (1H, s, H-3a), 9.64 (1H, s, H-14);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  19.1 (C-13), 22.9 (C-8), 25.6 (C-15), 28.4 (C-9), 38.4 (C-10), 42.6 (C-5), 43.4 (C-11), 56.0 ( $\text{OCH}_3$ ), 74.7 (C-12), 111.7 (C-2), 125.3 (C-7), 128.5 (C-6), 137.3

(C-3), 145.7 (C-1), 152.8 (C-4), 194.4 (C-14); EIMS  $m/z$  248 [M]<sup>+</sup> (21), 233 (5), 219 (10), 217 (10), 216 (32), 201 (6), 189 (7), 188 (10), 161 (9), 151 (26), 136 (29), 121 (37), 112 (100); HREIMS  $m/z$  248.1777 (calcd for C<sub>16</sub>H<sub>24</sub>O<sub>2</sub> 248.1776).

**Madolin U (3):** obtained as a colorless oil; [α]<sub>D</sub> +84.9° (c 0.08, CHCl<sub>3</sub>); UV (MeOH) λ<sub>max</sub> (log ε) 219 (3.86) nm; IR ν<sub>max</sub> (KBr) 3256, 2953, 2917, 2867, 1759, 1647, 1436, 1024 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.46–1.60 (2H, m, H-8), 1.69–1.84 (2H, m, H-9), 1.84 (3H, s, H-13), 2.10 (1H, m, H-2b), 2.25 (1H, m, H-3b), 2.29 (1H, m, H-2a), 2.49–2.53 (2H, m, H-3a, H-7), 3.85 (1H, m, H-1), 4.83 (1H, s, H-12b), 4.93 (1H, s, H-12a), 5.00 (1H, s, H-6), 5.10 (1H, d, *J* = 2.4 Hz, H-14b), 5.43 (1H, d, *J* = 2.4 Hz, H-14a), 7.02 (1H, s, H-5); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 20.2 (C-3), 21.3 (C-13), 24.8 (C-9), 32.2 (C-8), 35.8 (C-2), 52.0 (C-7), 75.2 (C-1), 82.8 (C-6), 112.2 (C-12), 113.6 (C-14), 138.2 (C-4), 147.6 (C-10 or C-11), 148.8 (C-5), 152.2 (C-10 or C-11), 174.3 (C-15); EIMS  $m/z$  248 [M]<sup>+</sup> (100), 231 (51), 230 (60), 215 (18), 203 (52), 202 (43), 189 (12), 185 (50), 176 (25), 159 (31), 147 (50), 138 (66), 131 (43), 119 (83), 105 (68); HREIMS  $m/z$  248.1414 (calcd for C<sub>15</sub>H<sub>20</sub>O<sub>3</sub>, 248.1412).

**Madolin W (4):** obtained as a colorless oil; [α]<sub>D</sub> -83.4° (c 0.1, CHCl<sub>3</sub>); UV (MeOH) λ<sub>max</sub> (log ε) 258 (3.83) nm; IR ν<sub>max</sub> (KBr) 3450, 2930, 2866, 1675, 1481, 1386, 1028 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 0.83 (1H, m, H-5b), 1.20 (1H, m, H-5a), 1.23 (3H, s, H-14), 1.47 (3H, s, H-15), 1.66 (1H, m, H-8b), 2.20–2.00 (6H, m, H-4, H-12a, H-8a, H-9b, H-13b, and H-12b), 2.24 (1H, m, H-9a), 2.80 (1H, dd, *J* = 8.2, 2.8 Hz, H-13a), 2.88 (1H, dt, *J* = 8.0, 1.4 Hz, H-7), 5.26 (1H, br d, *J* = 10.0 Hz, H-11), 6.08 (1H, d, *J* = 11.6 Hz, H-3), 9.31 (1H, s, H-1); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 13.7 (C-14), 15.0 (C-15), 22.9 (C-13), 25.3 (C-5), 27.5 (C-12), 27.8 (C-4), 30.9 (C-6), 30.9 (C-8), 39.0 (C-9), 82.4 (C-7), 127.1 (C-11), 135.6 (C-10), 143.3 (C-2), 157.0 (C-3), 194.1 (C-1); EIMS  $m/z$  234 [M]<sup>+</sup> (9), 219 (22), 205 (13), 191 (26), 163 (23), 149 (34), 135 (31), 121 (42), 107 (74), 91 (100); HREIMS  $m/z$  234.1619 (calcd C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>, 234.1619).

**Madolin X (5):** obtained as a colorless oil; [α]<sub>D</sub> +32.6° (c 0.05, CHCl<sub>3</sub>); UV (MeOH) λ<sub>max</sub> (log ε) 210 (4.00) nm; IR ν<sub>max</sub> (KBr) 3266, 2951, 2916, 1739, 1653, 1436, 1024 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.67–1.56 (1H, m, H-2b), 1.73 (3H, t, *J* = 1.8 Hz, H-14), 1.81 (1H, br d, *J* = 10.8 Hz, H-8β), 1.85 (3H, s, H-13), 2.30–2.17 (2H, m, H-2a, H-3b), 2.41 (1H, dt, *J* = 12.0, 10.8 Hz, H-8α), 2.49 (1H, d, *J* = 10.8 Hz, H-7β), 2.65 (1H, m, H-3a), 4.43 (1H, dd, *J* = 10.6, 5.4 Hz, H-1β), 4.91 (2H, s, H-12), 5.14 (1H, s, H-6β), 5.25 (1H, brd, *J* = 12.0 Hz, H-9), 6.77 (1H, s, H-5); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 16.9 (C-14), 20.7 (C-3), 21.6 (C-13), 23.9 (C-2), 25.6 (C-8), 50.3 (C-7), 66.9 (C-1), 83.3 (C-6), 112.9 (C-12), 129.4 (C-9), 136.3 (C-10), 137.5 (C-4), 146.0 (C-11), 152.9 (C-5), 174.0 (C-15); EIMS  $m/z$  248 [M]<sup>+</sup> (61), 230 (24), 215 (7), 202 (18), 189 (6), 185 (19), 177 (15), 165 (20), 147 (46), 138 (75), 134 (39), 119 (100); HREIMS  $m/z$  248.1410 (calcd for C<sub>15</sub>H<sub>20</sub>O<sub>3</sub>, 248.1412).

**Acknowledgment.** We thank the National Science Council, Republic of China, for financial support of this research (NSC grant 89-2113-M-006-004). We also thank Professor C. S. Kuoh (Department of Biology, National Cheng Kung University, Tainan, Taiwan) for the plant identification and Miss S. Zhang (Institute of Materia Medica, Chinese Academy of Medicinal Sciences, Beijing, People's Republic of China) for the plant collection.

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NP0002886