

Four Aristolochic Acid Esters of Rearranged *ent*-Elemene Sesquiterpenes from *Aristolochia heterophylla*

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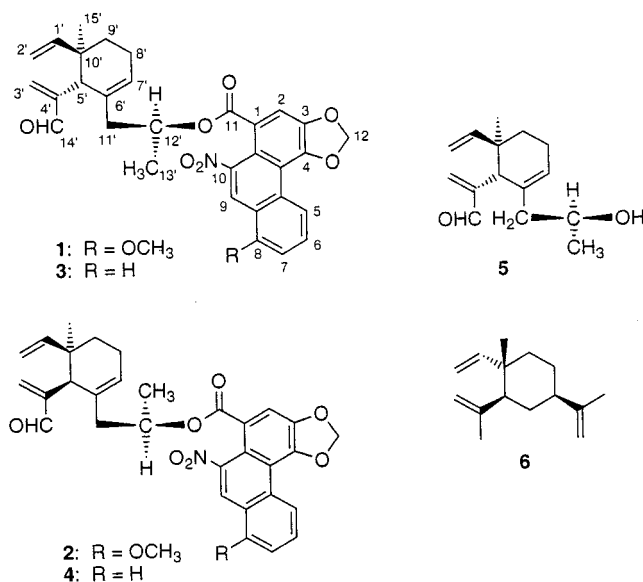
Received August 14, 1998

Four aristolochic acid esters of *ent*-elemene type sesquiterpene having a new carbon skeleton, aristophyllides A (**1**), B (**2**), C (**3**), and D (**4**), were isolated from the stems and roots of *Aristolochia heterophylla*. The esters were characterized by NMR and MS methods and included is a study of absolute configurations using the CD exciton chirality method.

Aristolochia heterophylla Hemsl. (*Aristolochia shimadai* Hayata) (Aristolochiaceae) is a perennial shrub¹ that has been used as an alternative for the famous traditional Chinese medicine "Madouling". It is employed as an expectorant, antitussive, analgesic, and antiasthmatic and also for the treatment of snakebite and lung inflammation.² Previous studies demonstrated that the main constituents of this plant were aristolochic acid and aristolactam.^{3–7} However, these two compounds are not responsible for the many drug actions that the plant possesses. Based on interests in pharmacology and taxonomy, we investigated the constituents of the stems and roots of *A. heterophylla*. The MeOH extract of fresh *A. heterophylla* was partitioned successively between H₂O and CHCl₃, *n*-BuOH. Then, the CHCl₃ layer was subjected to Si gel chromatography to afford four novel aristolochic acid esters of rearranged *ent*-elemene sesquiterpenes: aristophyllides A (**1**), B (**2**), C (**3**), and D (**4**).

Aristophyllide A (**1**) was determined to have the molecular formula C₃₂H₃₁NO₈ by HRFABMS. UV absorptions at 224, 251, 266, 283, 320, and 390 nm suggested the presence of a phenanthrene nucleus.⁸ IR bands at 1705 cm⁻¹ for a carbonyl group and at 1536, 1324 cm⁻¹ for a nitro group suggested that it was an aristolochic acid ester. This conclusion was supported by signals in the ¹H NMR spectrum⁹ and by HMBC and ROESY experiments (Tables 1 and 2). The remaining 15 carbons were shown through COSY, HMQC, and HMBC correlations to be assembled as in **5**, which we name aristophyllene. Aristophyllene (**5**) has a rearranged *ent*-elemene-type sesquiterpene¹⁰ closely related to β -elemene (**6**), but with a new carbon skeleton. The point of connection between aristolochic acid I and **5** to form **1** was established by the downfield ¹H NMR signal of H-12' (δ 5.17). The presence of NOEs of H-2' with H-7', H-3' with H-9', and H-5' with H-15' (Table 2) indicated that the vinyl and vinylidene groups were *pseudo* axial with *trans* geometry on the cyclohexene ring as shown in Figure 2.

The absolute configuration of **1** at C-5' and C-12' was determined by application of the circular dichroic (CD) exciton chirality method.^{11,12} By comparing the UV spectrum of **1** with that of aristolochic acid I, the strong absorption at 224 nm was attributed to the α,β -unsaturated aldehyde chromophore in the **5** moiety. The possible chiral



exciton couplings between the cyclohexene double bond and the unsaturated aldehyde chromophores with a *trans* geometry to the vinyl group are shown in Figure 1 (**I** and **II**). The observation of a positive Cotton effect at 221 nm ($\Delta\epsilon +2.28$) indicated a clockwise configuration (**I**) between the double bond and the unsaturated aldehyde, which led us to conclude the *R* configuration at C-5'. In addition, the stereochemistry at C-12' of **1** was also assigned based on the ROESY and CD spectral analysis. The observed NOE correlation between H-5' and H-12' as well as H-7' and H-13' suggested that compound **1** can adopt two possible conformations, **I** and **II**, as shown in Figure 2. Conformer **I** was expected to be more stable than conformer **II** because the steric interaction between the C-5' unsaturated aldehyde and the C-6' side chain is serious in conformer **II**. On the other hand, the CD spectrum of **1** exhibited a negative Cotton effect at 266 nm ($\Delta\epsilon -1.78$). Considering that the UV absorption around 260 nm may be assigned to the transition due to the 3,4-methylenedioxybenzoate part of the aristolochic acid-I chromophore,¹³ the observed Cotton effect was caused by the exciton interaction between the 3,4-methylenedioxybenzoate part and the ring double bond. In the case of the stable conformer **I**, the exciton transitions of these two chromophores constitute a negative chirality, which is in agreement with the observed negative Cotton effect at 266 nm. Therefore, the absolute configuration of

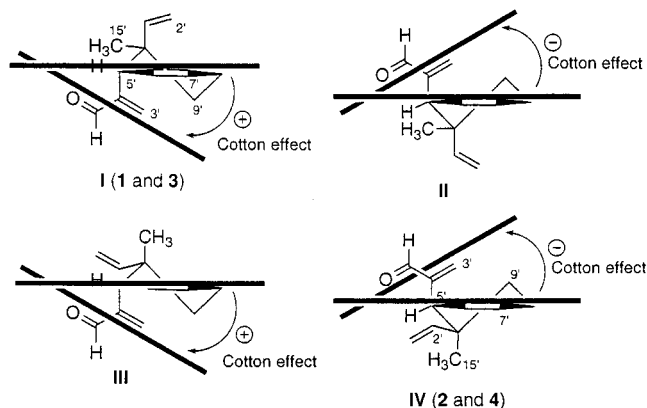
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Table 1. HMBC Correlations for **1** and **2** (CDCl₃)

carbon	HMBC of 1	HMBC of 2
C-3	H-12	H-2, H-12
C-4	H-2, H-12	H-2, H-12
C-4a	H-5	H-5
C-4b	H-5, H-6, H-9	H-6, H-9
C-5	H-7	H-7
C-6	H-5	
C-7	H-5	H-5
C-8	H-6, H-7, H-9, 8-OMe	H-6, H-9, 8-OMe
C-8a	H-5	H-5
C-10	H-9	H-9
C-10a	H-2, H-9	
C-11	H-2	H-2
C1'	H-2', H-5', H-9', H-15'	H-15'
C-3'	H-5'	H-5'
C-4'	H-3', H-5', H-14'	H-5', H-14'
C-5'	H-3', H-7', H-11', H-15'	H-3', H-15'
C-6'	H-5', H-11'	H-5', H-8'
C-7'	H-5', H-9', H-11'	H-5'
C-8'	H-7', H-9'	
C-9'	H-5', H-7', H-15'	H-15'
C-10'	H-1', H-2', H-5', H-9', H-15'	H-2', H-5', H-15'
C-11'	H-5', H-13'	H-13'
C-12'	H-11', H-13'	H-13'
C-13'	H-11'	
C-14'	H-3', H-5'	H-3'

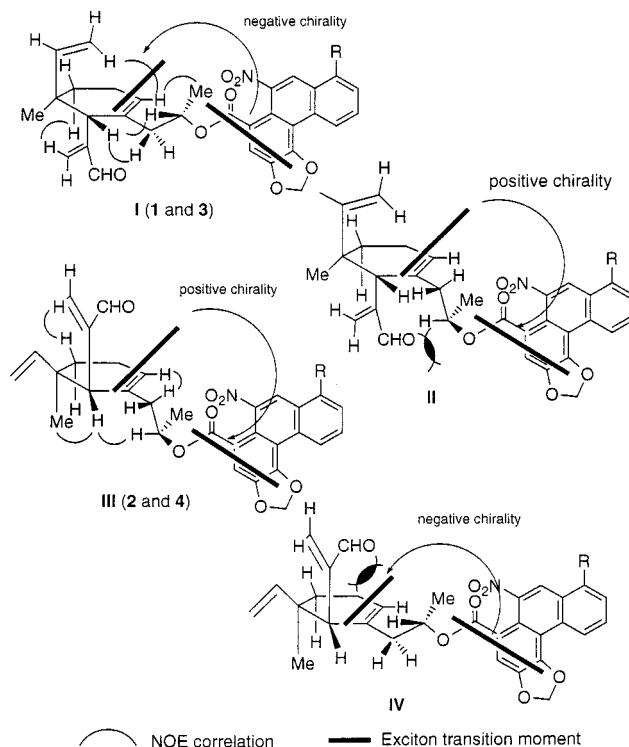
**Figure 1.** The possible exciton chirality at C-5' and sign of α, β -unsaturated aldehyde for **1-4**.

C-12' was assigned to be *S*. On the basis of these results, aristophyllide A is **1**.

The UV and IR spectra of **1** and **2** were practically superimposable. The ¹H and ¹³C NMR spectra of **2** markedly resembled those of **1**, but the CD spectrum showed clearly opposite characteristics, suggesting that **2** would

Table 2. ROESY Correlations for **1-4** (CDCl₃)

proton	1	2	3	4
H-5	H-6	H-6	H-6	H-6
H-6	H-5, H-7	H-5, H-7	H-5	H-5, H-7
H-7	H-6, 8-OMe	H-6, 8-OMe	H-8	H-6, 8-OMe
H-8 or 8-OMe	H-7	H-7	H-7, H-9	H-7, H-9
H-9			H-8	H-8
H-1'	H-2'	H-2'	H-2', H-12'	H-2', H-5', H-12'
H-2'	H-1', H-7'	H-1'	H-1', H-7'	H-1', H-5'
H-3'	H-9', H-14'	H-9', H-14'	H-9', H-14'	H-9', H-14'
H-5'	H-11', H-12', H-15'	H-12', H-15'	H-11', H-12', H-15'	H-1', H-2', H-11', H-12', H-15'
H-7'	H-2', H-8', H-11', H-13'	H-8', H-11'	H-2', H-8', H-11', H-13'	H-2', H-8', H-11', H-13'
H-8'	H-7', H-9'	H-7', H-9'	H-7', H-9'	H-7', H-9'
H-9'	H-3', H-8'	H-3', H-8'	H-3', H-8'	H-3', H-8'
H-11'	H-5', H-7'	H-7'	H-5', H-7'	H-5', H-7', H-12', H-13'
H-12'	H-5'	H-5', H-13'	H-1', H-5'	H-1', H-5', H-11', H-13'
H-13'	H-7'	H-12'	H-7'	H-11', H-12'
H-14'	H-3'	H-3'	H-3'	H-3'
H-15'	H-5'	H-5'	H-5'	H-5'

**Figure 2.** The NOE correlations and the possible exciton interactions between the ring double bond and C-6' side chain for **1-4**.

be stereoisomeric to **1**. Some minor differences were observed in ROESY correlations (Table 2). The NOEs between H-5' and H-15' and between H-3' and H-9' and the absence of NOE between H-2' and H-7' showed the vinyl and the vinylidene groups to be *pseudo* equatorial and *pseudo* axial, respectively, with *cis* geometry. The CD spectral analysis as above revealed a negative Cotton effect at 227 nm ($\Delta\epsilon -1.22$), leading to the *S* configuration at C-5' (Figure 1, **IV**) and a positive Cotton effect at 261 nm ($\Delta\epsilon +0.33$) led to the *R* configuration at C-12' (Figure 2, **III**). Consequently, aristophyllide B is proposed to be **2**.

The HRMS of **3** established the molecular formula C₃₁H₂₉NO₇, which was 30 mass units less than that of **1**. The ¹H NMR data of **3** were closely related to those of **1** but indicated an ester of an aristophyllene sesquiterpene alcohol and aristolochic acid II,¹⁰ which has no methoxyl at C-8. The CD spectrum was also similar to that of **1**. Thus, the positive Cotton effect at 218 nm ($\Delta\epsilon +3.57$) led to an *R* configuration at C-5', and the negative Cotton effect

at 247 nm ($\Delta\epsilon -2.09$) led to an *S* configuration at C-12'. Therefore, aristophyllide C is concluded to be **3**.

Aristophyllide D (**4**) had spectral data very similar to those of **3**. However, a totally opposite CD spectrum to that of **3** was obtained. The negative Cotton effect at 225 nm ($\Delta\epsilon -2.18$) and the positive Cotton effect at 244 nm ($\Delta\epsilon +3.37$) were correlated to the *S* configuration at C-5' and the *R* configuration at C-12', respectively. Therefore, aristophyllide D is **4**.

The IC₅₀ values of **1–4** against hepatoma G2,2,2,15 cells were 5.1, 9.4, 6.2, and 13.2 μ M, respectively. Evaluation of other biological activities are under investigation.

Experimental Section

General Experimental Methods. Melting points were not corrected. UV spectra were obtained in MeOH solution. IR spectra were measured as solid dispersions in KBr. NMR spectra were recorded at 200 or 400 MHz for ¹H and 50 or 100 for ¹³C; all chemical shifts are reported in parts per million (ppm, δ) from TMS as an internal standard. Mass spectra were performed in the EI or FAB mode.

Plant Material. *Aristolochia heterophylla* Hemsl. was collected from Tsueg Feng, Natou Hsien, Taiwan, in May 1992, and verified by Prof. C. S. Kuoh. A specimen of this plant was deposited in the herbarium (Kuoh 017116) of National Cheng Kung University, Tainan, Taiwan.

Extraction and Isolation. Fresh stems and roots of *A. heterophylla* were extracted with MeOH ($\times 10$) at room temperature and concentrated to give a deep brown syrup. This MeOH extract was partitioned successively between H₂O and CHCl₃, and then *n*-BuOH. The CHCl₃ layer was subjected to chromatography on Si gel, eluting with a gradient of CHCl₃ and MeOH to afford eight fractions. Fraction 2 was chromatographed on Si gel eluting with hexane–EtOAc (19:1) to give **1** (8.5 mg), **2** (3.2 mg), **3** (6.6 mg), and **4** (1.0 mg).

Aristophyllide A (1): obtained as yellow needles; mp 226–228 °C; $[\alpha]_D^{+120}$ (*c* 0.0245, CHCl₃); UV λ_{\max} nm (log ϵ) 224 (4.34), 251 (4.16), 266 (4.07), 283 (3.86), 320 (3.82), 390 (3.59); IR ν_{\max} cm⁻¹ 2855, 1705, 1693, 1536, 1324; ¹H NMR (CDCl₃, 400 MHz) δ 9.63 (1H, s, H-14'), 8.79 (1H, s, H-9), 8.64 (1H, d, *J* = 8.0 Hz, H-5), 7.72 (1H, s, H-2), 7.68 (1H, t, *J* = 8.0 Hz, H-6), 7.07 (1H, d, *J* = 8.0 Hz, H-7), 6.36 (1H, d, *J* = 1.2 Hz, H-12), 6.35 (1H, d, *J* = 1.2 Hz, H-12), 6.24 (1H, s, H-3'), 6.19 (1H, s, H-3'), 5.81 (1H, dd, *J* = 17.6, 10.8 Hz, H-1'), 5.77 (1H, m, H-7'), 5.17 (1H, m, H-12'), 4.98 (1H, d, *J* = 17.6 Hz, H-2'), 4.79 (1H, d, *J* = 10.8 Hz, H-2'), 4.05 (3H, s, 8-OMe), 3.42 (1H, s, H-5'), 2.33 (1H, dd, *J* = 14.4, 8.0 Hz, H-11'), 2.11 (2H, br s, H-8'), 1.95 (1H, br d, *J* = 14.4 Hz, H-11'), 1.38 (3H, d, *J* = 6.0 Hz, H-13'), 1.36 (2H, m, H-9'), 0.71 (3H, s, H-15'); ¹³C NMR (CDCl₃, 100 MHz) δ 194.2 (d, C-14'), 166.3 (s, C-11), 156.8 (s, C-8), 150.6 (s, C-4'), 146.3 (s, C-4), 145.9 (s, C-3), 145.7 (s, C-10), 145.5 (d, C-1'), 137.4 (t, C-3'), 133.4 (s, C-6'), 130.7 (s, C-4b), 130.7 (d, C-6), 126.0 (d, C-7), 124.1 (s, C-1), 120.8 (d, C-9), 120.1 (s, C-8a), 119.1 (d, C-5), 118.4 (s, C-4a), 118.3 (s, C-10a), 112.7 (d, C-2), 111.9 (t, C-2'), 107.8 (d, C-7), 102.3 (t, C-12), 71.1 (d, C-12'), 55.9 (q, 8-OMe), 43.5 (d, C-5'), 42.3 (t, C-11'), 38.3 (s, C-10'), 27.9 (t, C-9'), 25.9 (q, C-15'), 22.8 (t, C-8'), 20.1 (q, C-13'); EIMS *m/z* (rel int): 557 (M⁺, 6), 341 (49), 295 (100); HRFABMS calcd for C₃₂H₃₂NO₈, *m/z* 558.2128 [M + H]⁺, found 558.2123; CD (4.65 $\times 10^{-5}$ M, CHCl₃) $\Delta\epsilon_{206}$ 8.62, $\Delta\epsilon_{221}$ 2.28, $\Delta\epsilon_{236}$ 0.54, $\Delta\epsilon_{240}$ 0, $\Delta\epsilon_{250}$ -1.18, $\Delta\epsilon_{266}$ -1.78, $\Delta\epsilon_{286}$ 0, $\Delta\epsilon_{317}$ 2.44, $\Delta\epsilon_{379}$ 0.

Aristophyllide B (2): obtained as yellow needles; mp 229–231 °C; $[\alpha]_D -79$ (*c* 0.0218, CHCl₃); UV λ_{\max} nm (log ϵ) 224 (4.55), 249 (4.40), 268 (4.28), 283 (4.04), 318 (4.04), 390 (3.79); IR ν_{\max} cm⁻¹ 2856, 1707, 1693, 1536, 1342; ¹H NMR (CDCl₃, 400 MHz) δ 9.66 (1H, s, H-14'), 8.81 (1H, s, H-9), 8.68 (1H, d, *J* = 8.2 Hz, H-5), 7.76 (1H, s, H-2), 7.70 (1H, t, *J* = 8.2 Hz, H-6), 7.10 (1H, d, *J* = 8.2 Hz, H-7), 6.37 (1H, d, *J* = 1.5 Hz, H-12), 6.36 (1H, d, *J* = 1.5 Hz, H-12), 6.23 (2H, s, H-3'), 5.86 (1H, dd, *J* = 17.5, 10.8 Hz, H-1'), 5.71 (1H, m, H-7'), 5.09 (1H, q, *J* = 6.5 Hz, H-12'), 5.00 (1H, d, *J* = 17.5 Hz, H-2'), 4.94 (1H, d, *J* = 10.8 Hz, H-2'), 4.05 (3H, s, 8-OMe), 3.43 (1H, s,

H-5), 2.30 (1H, dd, *J* = 14.0, 5.3 Hz, H-11'), 2.09 (2H, m, H-8'), 2.09 (1H, m, H-11'), 1.42 (2H, m, H-9'), 1.34 (3H, d, *J* = 6.5 Hz, H-13'), 0.75 (3H, s, H-15'); ¹³C NMR (CDCl₃, 100 MHz) δ 194.2 (d, C-14'), 166.2 (s, C-11), 156.8 (s, C-8), 150.5 (s, C-4'), 146.4 (s, C-4), 145.9 (s, C-3), 145.9 (s, C-10), 145.6 (d, C-1'), 137.3 (t, C-3'), 133.6 (s, C-6'), 130.8 (s, C-4b), 130.8 (d, C-6), 125.7 (d, C-7'), 124.0 (s, C-1), 120.9 (d, C-9), 120.2 (s, C-8a), 119.1 (d, C-5), 118.4 (s, C-4a), 118.4 (s, C-10a), 112.8 (d, C-2), 111.9 (t, C-2'), 107.8 (d, C-7), 102.3 (t, C-12), 71.7 (d, C-12'), 55.9 (q, 8-OMe), 43.4 (d, C-5'), 42.5 (t, C-11'), 38.3 (s, C-10'), 28.0 (t, C-9'), 25.4 (q, C-15'), 22.9 (t, C-8'), 19.7 (q, C-13'); EIMS *m/z* (rel int) 557 (M⁺, 1), 341 (17), 293 (100); HRFABMS calcd for C₃₂H₃₂NO₈, *m/z* 558.2128 [M + H]⁺, found 558.2130; CD (4.69 $\times 10^{-5}$ M, CHCl₃) $\Delta\epsilon_{211}$ -3.96, $\Delta\epsilon_{227}$ -1.22, $\Delta\epsilon_{244}$ 0, $\Delta\epsilon_{261}$ 0.33, $\Delta\epsilon_{272}$ 0, $\Delta\epsilon_{336}$ -1.32, $\Delta\epsilon_{384}$ 0.

Aristophyllide C (3): obtained as yellow needles; mp 217–219 °C; $[\alpha]_D +113$ (*c* 0.0656, CHCl₃); UV λ_{\max} nm (log ϵ) 218 (4.33), 243 (4.32), 252 (4.37), 266 (4.20), 298 (3.98), 377 (3.48); IR ν_{\max} cm⁻¹ 2860, 1695, 1691, 1525, 1335; ¹H NMR (CDCl₃, 400 MHz) δ 9.64 (1H, s, H-14'), 9.12 (1H, d, *J* = 8.0 Hz, H-5), 8.31 (1H, s, H-9), 7.97 (1H, d, *J* = 8.0 Hz, H-8), 7.79 (1H, t, *J* = 8.0 Hz, H-6), 7.73 (1H, s, H-2), 7.70 (1H, t, *J* = 8.0 Hz, H-7), 6.40 (1H, s, H-12), 6.38 (1H, s, H-12), 6.25 (1H, s, H-3'), 6.20 (1H, s, H-3'), 5.80 (1H, dd, *J* = 17.6, 11.2 Hz, H-1'), 5.78 (1H, m, H-7'), 5.17 (1H, q, *J* = 6.5 Hz, H-12'), 4.99 (1H, d, *J* = 17.6 Hz, H-2'), 4.79 (1H, d, *J* = 11.2 Hz, H-2'), 3.43 (1H, s, H-5'), 2.33 (1H, dd, *J* = 15.0, 8.8 Hz, H-11'), 2.12 (2H, br s, H-8'), 1.95 (1H, br d, *J* = 15.0 Hz, H-11'), 1.38 (3H, d, *J* = 6.4 Hz, H-13'), 1.36 (2H, m, H-9'), 0.66 (3H, s, H-15'); EIMS *m/z* (rel int): 527 (M⁺, 4), 311 (47), 265 (100); HRFABMS calcd for C₃₁H₃₀NO₇, *m/z* 528.2022 [M + H]⁺, found 528.2016; CD (3.54 $\times 10^{-5}$ M, CHCl₃) $\Delta\epsilon_{205}$ 11.83, $\Delta\epsilon_{218}$ 3.57, $\Delta\epsilon_{231}$ 0.76, $\Delta\epsilon_{235}$ 0, $\Delta\epsilon_{247}$ -2.09, $\Delta\epsilon_{255}$ -1.89, $\Delta\epsilon_{278}$ 0, $\Delta\epsilon_{301}$ 3.20, $\Delta\epsilon_{381}$ 0.

Aristophyllide D (4): obtained as yellow needles; mp 220–222 °C; $[\alpha]_D -100$ (*c* 0.0098, CHCl₃); UV λ_{\max} nm (log ϵ) 219 (4.60), 242 (4.55), 252 (4.61), 266 (4.47), 297 (4.19), 355 (3.76), 373 (3.73); IR ν_{\max} cm⁻¹ 28586, 1699, 1649, 1521, 1342; ¹H NMR (CDCl₃, 400 MHz) δ 9.67 (1H, s, H-14'), 9.13 (1H, d, *J* = 8.3 Hz, H-5), 8.33 (1H, s, H-9), 7.98 (1H, d, *J* = 8.3 Hz, H-8), 7.79 (1H, t, *J* = 8.3 Hz, H-6), 7.77 (1H, s, H-2), 7.73 (1H, t, *J* = 8.3 Hz, H-7), 6.40 (1H, d, *J* = 1.4 Hz, H-12), 6.39 (1H, d, *J* = 1.4 Hz, H-12), 6.24 (2H, s, H-3'), 5.85 (1H, dd, *J* = 17.6, 10.8 Hz, H-1'), 5.72 (1H, m, H-7'), 5.10 (1H, q, *J* = 6.4 Hz, H-12'), 5.00 (1H, dd, *J* = 17.6, 0.8 Hz, H-2'), 4.91 (1H, dd, *J* = 10.8, 0.8 Hz, H-2'), 3.42 (1H, s, H-5'), 2.32 (1H, dd, *J* = 14.2, 6.4 Hz, H-11'), 2.10 (2H, m, H-8'), 2.10 (1H, m, H-11'), 1.44 (2H, m, H-9'), 1.35 (3H, d, *J* = 6.4 Hz, H-13'), 0.72 (3H, s, H-15'); EIMS *m/z* (rel int) 527 (M⁺, 10), 311 (23), 265 (56); HRFABMS calcd for C₃₁H₃₀NO₇, *m/z* 528.2022 [M + H]⁺, found 528.2015; CD (4.65 $\times 10^{-5}$ M, CHCl₃) $\Delta\epsilon_{209}$ -7.65, $\Delta\epsilon_{225}$ -2.18, $\Delta\epsilon_{232}$ 0, $\Delta\epsilon_{244}$ 3.37, $\Delta\epsilon_{284}$ 0, $\Delta\epsilon_{310}$ -1.79, $\Delta\epsilon_{338}$ -1.94, $\Delta\epsilon_{384}$ 0.

Acknowledgment. We thank the National Science Council, R. O. C. (NSC 86-2113-M-006-008) for support of this research. We also thank Prof. Y. C. Wu for the cytotoxicity screening.

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NP980354S