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Article *in* Phytochemistry · May 2001

Impact Factor: 2.55 · DOI: 10.1016/S0031-9422(00)00486-6

PERGAMON

Phytochemistry 56 (2001) 753–757

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

Four alkaloids from *Annona cherimola*

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Received 17 July 2000; received in revised form 26 October 2000

Abstract

Four alkaloids, annocherine A, annocherine B, cherianoine, and romucosine H, along with one known alkaloid, artabonatine B, were isolated from the MeOH extract of the stems of *Annona cherimola*. Their structures were identified on the basis of both analysis of their spectral data and from chemical evidence.

Keywords: *Annona cherimola*; Annonaceae; Annocherine A; Annocherine B; Cherianoine; Romucosine H

1. Introduction

Annona cherimola Mill. (Annonaceae), a subtropical fruit tree indigenous to Ecuador and Peru, is cultivated in southern Taiwan. It has been used in folk medicine for the treatment of skin disease, especially for boils (Kan, 1979). Previously, we isolated 88 compounds, including two novel compounds, cherimoline (Chen et al., 1997a) and cherinonaine (Chen et al., 1998a) and 11 kauranes (Chen et al., 1998c), three lignans (Chen et al., 1998c), eight amides (Chen et al., 1998b), two acetogenins (Chen et al., 1999a), one lactam amide (Chen et al., 1997b), two purines (Chen et al., 1997b, 1999b), nine steroids (Chen et al., 1997b, 1999b), 30 alkaloids (Chen et al., 1997b, 1999b), one *p*-quinone (Chen et al., 1999b), and 19 benzenoids (Chen et al., 1999b) from different parts of this plant. As part of our continuing investigation on the phytochemical and bioactive compounds of Formosan Annonaceous plants, four new alkaloids, annocherine A (**1**), annocherine B (**2**), cherianoine (**3**), and romucosine H (**4**), together with one known alkaloid, artabonatine B, were obtained by systematic extraction and isolation from the stems of *A. cherimola*. Artabonatine B was also isolated for the first time from this source.

2. Results and discussion

Annocherine A (**1**) was obtained as a yellow needles, $[\alpha]_D^{24}$ +135.0° (*c* 0.1, $CHCl_3$), positive to Dragendorff's test. The molecular formula, $C_{17}H_{15}O_4N$, was confirmed by high-resolution EIMS measurement (*m*/*z* 297.1014 $[M]^+$, calc. 297.1001). The presence of a 6,7,4′-oxygenated benzylisoquinoline skeleton in the molecule was deduced by its UV (absorption maxima at λ 260, 300, and 330 nm) (Botega et al., 1993). A bathochromic shift of the UV spectrum with the addition of alkali and the IR absorption at 3400 cm^{-1}, suggested the presence of a phenolic function. The ^1H NMR spectrum (Table 1) indicated the presence of signals at δ 3.94 and 4.45 corresponding to one methoxy group and one benzylic carbinol proton, along with two doublets at δ 8.29 and 7.51 (J = 6.0 Hz, each one proton), and six aromatic protons, including two singlets at δ 7.88 and 7.16 (each one proton), and two doublets at δ 7.01 and 6.65 (J = 8.8 Hz, each two protons). The above mentioned data indicated the presence of a C-6,7,4′ and C-α tetra-*O*-substituted benzylisoquinoline. The complete proton assignments of **1** were established by COSY and NOESY (Fig. 1) experiments. Proton 5 showed significant correlations to OMe-6 and H-4, and H-α displayed correlations with H-8, H-2′ and H-6′ in the NOESY spectrum. The substitution of four oxygen-bearing functional groups was determined and located. According to the literature (Bojadziev et al., 1987; Corey and Helal, 1996), a positive $[\alpha]_D$ value indicates that C-α possesses an *S* configuration. Fifteen aromatic carbon atoms were observed between δ 156.3 and 105.1, a methoxy carbon at δ 56.4, and

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0031-9422/01/$ - see front matter
PII: S0031-9422(00)00486-6

Table 1
^{1}H NMR spectral data of alkaloids **1** and **2** (400 MHz, δ in ppm, J in Hz, $CDCl_3$)

Proton	1	2
3	8.29 (1H, *d*, $J=6.0$)	8.24 (1H, *d*, $J=5.6$)
4	7.51 (1H, *d*, $J=6.0$)	7.46 (1H, *d*, $J=5.6$)
5	7.16 (1H, *s*)	7.03 (1H, *s*)
8	7.88 (1H, *s*)	7.67 (1H, *s*)
2′ and 6′	7.01 (2H, *d*, $J=8.8$)*[a]	7.19 (2H, *d*, $J=8.4$)[a]
3′ and 5′	6.65 (2H, *d*, $J=8.8$)[a]	6.67 (2H, *d*, $J=8.4$)[a]
α	4.45 (1H, *s*)	5.78 (1H, *s*)
OMe-6	3.94 (3H, *s*)	3.96 (3H, *s*)
OMe-α	–	3.36 (3H, *s*)

[a] AA′BB′ system.

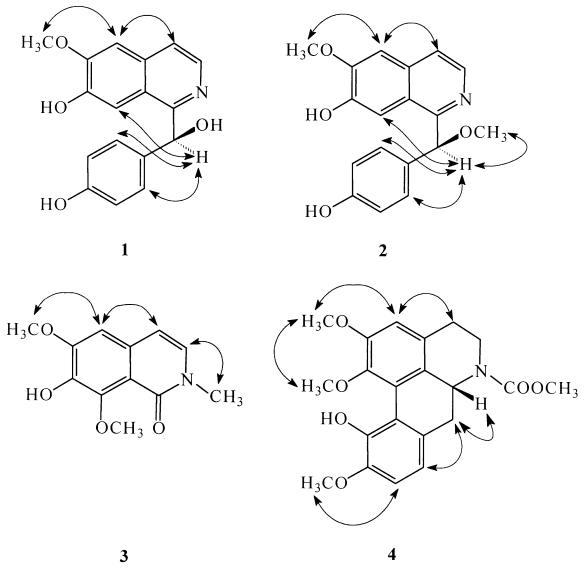


Fig. 1. 2D NOESY correlations for alkaloids **1, 2, 3**, and **4**.

a signal for a methine carbon at δ 74.1 in the ^{13}C NMR spectrum (Table 2) further confirmed the structure of **1**. The EIMS revealed significant key fragments at m/z 174 ($[C_{10}H_7O_2N+H]^+$) and 123 ($[C_7H_6O+OH]^+$), which represented an isoquinoline moiety and a benzyl moiety through cleavage between C-1 and C-α, respectively. Therefore, the structure of **1** was determined as 1(*S*)-hydroxy - *p* - hydroxybenzyl - 6 - methoxy - 7 - hydroxyisoquinoline, which we named annocherine A (**1**). Annocherine A (**1**) is the second example of a C-α hydroxy benzylisoquinoline from natural sources (Botega et al., 1993). Although Botega et al. reported that C-α hydroxy benzylisoquinolines isolated from natural sources were not stable and were oxidized in air to the corresponding ketones (Botega et al., 1993), the new alkaloid **1** is stable and is not oxidized spontaneously in air.

Annocherine B (**2**) was obtained as a yellow amorphous powder, $[\alpha]_D^{24}$ +115.0° (*c* 0.1, $CHCl_3$), positive to Dragendorff's test. The molecular formula, $C_{18}H_{17}O_4N$, was determined by high-resolution EIMS measurement (m/z 311.1174 $[M]^+$, calc. 311.1158). The UV and IR

Table 2
^{13}C NMR spectral data of alkaloids **1** and **2** (100 MHz, δ in ppm, $CDCl_3$)

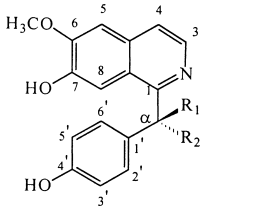
Carbon	1	2
1	156.3 (*s*)	141.5 (*s*)
3	133.3 (*d*)	133.8 (*d*)
4	120.2 (*d*)	120.0 (*d*)
4a	137.3 (*s*)	138.4 (*s*)
5	106.9 (*d*)	107.7 (*d*)
6	151.3 (*s*)	156.4 (*s*)
7	150.2 (*s*)	156.2 (*s*)
8	105.1 (*d*)	106.4 (*d*)
8a	122.3 (*s*)	122.3 (*s*)
1′	130.2 (*s*)	131.0 (*s*)
2′ and 6′	128.5 (*d*)	128.1 (*d*)
3′ and 5′	115.5 (*d*)	115.2 (*d*)
4′	145.3 (*s*)	147.0 (*s*)
α	74.1 (*d*)	85.4 (*d*)
6-OMe	56.4 (*q*)	56.0 (*q*)
α-OMe	–	57.2 (*q*)

absorptions of **2** were very similar to them of **1**. The ^{1}H and ^{13}C NMR spectra of **2** were also similar to those of **1**, except for the presence of a methoxyl signal, as revealed by the signals at δ 3.36 in the ^{1}H NMR (Table 1) and δ 57.2 in the ^{13}C NMR spectra (Table 2). The position of the methoxyl group was confirmed by ^{1}H NMR spectroscopic analysis, in which the α proton was shifted downfield to δ 5.78 as compared to **1**. This indicated that the methoxyl group was at the α carbon. The complete assignments of **2** were established by COSY and NOESY (Fig. 1) experiments. The positive $[\alpha]_D$ value suggested that C-α had an *S* configuration (Bojadziev et al., 1987; Corey and Helal, 1996). The EIMS also revealed significant fragments at m/z 174 ($[C_{10}H_7O_2N+H]^+$) and 137 ($[C_7H_6O+OCH_3]^+$), corresponding to an isoquinoline moiety and a benzylic moiety. Therefore, the structure of **2** was determined as 1(*S*)-methoxy-*p*-hydroxybenzyl-6-methoxy-7-hydroxyisoquinoline and named annocherine B (**2**).

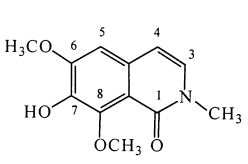
Cherianoine (**3**) was obtained as a white needles from $CHCl_3$. The molecular formula, $C_{12}H_{13}O_4N$, was established by high-resolution EIMS measurement (m/z 235.0845 $[M]^+$, calc. 235.0844). Its UV spectrum (λ_{max} 220, 260, 270 and 300 nm) indicated a 6,7,8-oxygenated isoquinolone skeleton (Castedo et al., 1981). A carbonyl group in the isoquinolone was confirmed by an IR band at 1685 cm^{-1} and a signal at δ 161.3 in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum displayed two typical doublets at δ 7.00 and 6.39 ($J=7.2$ Hz, each one proton) for H-3 and H-4, and an important amidic methyl at δ 3.55. Two methoxyl signals at δ 4.05 and 4.01 (each 3H) and a singlet at δ 6.88 (1H) needed to be assigned. These data indicated the presence of a 6,7,8-tri-*O*-substituted isoquinolone. COSY and NOESY (Fig. 1) experiments established the complete assignments of **3**. Proton 5 displayed significant correlations to OMe-6 and H-4,

and H-3 was correlated with the *N*-methyl and H-4 in the NOESY spectrum. The absence of NOE correlations between the two methoxy groups and a hydrogen bonding signal at δ 10-15 (for an 8-OH group) indicated that the hydroxyl group was positioned at C-7, and the methoxy group at C-8. Eight aromatic carbon atoms between δ 150.6 and 105.4, two methoxy carbons at δ 56.4 and 52.5, an *N*-methyl carbon at δ 37.8, and a carbonyl carbon at δ 161.3 were consistent with structure **3**. The ^{13}C NMR spectrum further supported this assignment. Alkaloid **3** was named cherianoine.

Romucosine H (**4**) was obtained as a brown amorphous powder, $[\alpha]_D^{24}$ −43.0° (*c* 0.01, $CHCl_3$), and was positive to Dragendorff's test. The molecular formula, $C_{21}H_{23}O_6N$, was deduced by high-resolution EIMS measurement (*m*/*z* 385.1532 $[M]^+$, calc. 385.1525). The presence of a 1,2,9,10-oxygenated aporphine skeleton in the molecule was deduced by its UV spectrum (λ_{max} 222, 270 and 310 nm) (Chalandre et al., 1985). IR bands at 3500 and 1630 cm^{-1} and a signal at δ 155.6 in the ^{13}C NMR spectrum indicated that a hydroxyl group and a carbamate moiety were present (Chen et al., 1996). The ^{1}H NMR spectrum indicated the presence of singlets at δ 3.92, 3.89, 3.76, and 3.70 corresponding to three methoxy groups and a *N*-(methoxycarbonyl) group. Three aromatic protons, two doublets at δ 6.88 and 6.84 (J = 8.0 Hz, each 1H), and a singlet at δ 6.73 (1H) were observed. The seven proton signals at δ 4.58 (1H, *dd*, J = 14.0, 4.5 Hz), δ 4.45 (1H, *m*), and δ 3.05-2.63 (5H, *m*) for the aliphatic protons were consistent with the features of an *N*-(methoxycarbonyl) aporphine (Chen et al., 1996; Chang et al., 2000). Two significant downfield signals at δ 4.58 (1H, *dd*) for H-6a and δ 4.45 (1H, *m*) for H-5a indicated an electron-withdrawing group bonded to the nitrogen atom. COSY and NOESY (Fig. 2) experiments were further measured to deduce the structure of **4**. Significant correlated sequences of OMe-1/OMe-2/H-3/H-4/H-5 and H-6a/H-7/H-8/H-9/OMe-10, were observed in the NOESY spectrum. The remaining hydroxyl should therefore be located at 11-position. The ^{13}C NMR spectrum showed 12 aromatic carbons between δ 151.3 and 111.0, three methoxyls at δ 62.0, 56.1, and 55.8, three methylenes at δ 42.6, 38.2, and 29.1, a carbonyl carbon at δ 155.6, a carboxylic methyl carbon at δ 52.6, and a methine at δ 54.0, which were consistent with the structure of **4**. Treatment of (−)-norisocorydine with triethylamine and methyl chlorocarbonate gave a compound that had an mp and TLC, as well as UV, IR, and ^{1}H NMR spectral data identical to **4**. Thus, the structure of **4** was determined as illustrated and named romucosine H.



	R_1	R_2
1	OH	H
2	OCH_3	H



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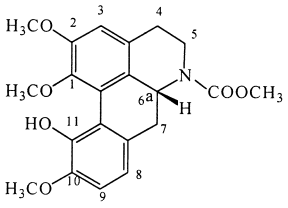

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The identity of the known alkaloid was verified by comparing UV, IR, ^{1}H NMR, ^{13}C NMR and MS spectral data with the published values of artabonatine B (Hsieh et al., 1999).

N-(Methoxycarbonyl) aporphinoid alkaloids like romucosine were shown to have significant antiplatelet aggregation activity (Wu et al., 1998). The *N*-(methoxycarbonyl) aporphinoid alkaloids cathafiline and cathaformine strongly inhibited platelet aggregation induced by AA (arachidonic acid) (Chen et al., 1999b; Wu et al., 1998). The mechanism of antiplatelet aggregation effects of these aporphine alkaloids are apparently different from aspirin, which is known to be a cyclooxygenase inhibitor (Chen et al., 1999b), and will be further investigated.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Melting points were determined using a Yanagimoto micro-melting point apparatus and were uncorrected. The IR spectra were measured on a Hitachi 260-30 spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra (in $CDCl_3$) were recorded with Varian NMR spectrometers, using TMS as internal standard. LRFABMS and LREIMS spectra were obtained with a JEOL JMS-SX/SX 102A mass spectrometer or a Quattro GC/MS spectrometer having a direct inlet system. HRFABMS spectra were measured on a JEOL JMS-HX 110 mass spectrometer. Si gel 60 (Macherey-Nagel, 230-400 mesh) was used for column chromatography, precoated Si gel plates (Macherey-Nagel, SIL G-25 UV_{254}, 0.25 mm) were used for analytical TLC, and precoated Si gel plates (Macherey-Nagel, SIL G/UV_{254}, 0.25 mm) were used for preparative TLC. The spots were detected by spraying with Dragendorff's reagent or 50% H_2SO_4 and then heating on a hot plate.

3.2. Plant material

A. cherimola was collected from Chia-Yi City, Taiwan, in September 1996, and identified by Dr. Hsin-Fu

Yen, National Museum of Natural Science, Taichung, Taiwan. A voucher specimen is deposited in the Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung, Taiwan.

3.3. Extraction and isolation

Fresh stems (4.0 kg) were extracted repeatedly with MeOH at rt. The combined MeOH extracts were evaporated under reduced pressure and partitioned to yield $CHCl_3$ and aq. extracts. The bases in the $CHCl_3$ solution were extracted with 3% HCl to leave the acidic portion (Part A) and $CHCl_3$ solution (Part B). The acidic portion (Part A) was basified with NH_4OH and then extracted with $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to leave a brownish viscous residue (2.0 g). The residue was placed on a silica gel column and eluted with ethyl acetate gradually enriched with MeOH to afford 20 fractions. Fr. 6 (0.3 g) eluted with *n*-hexane–Me_2CO (10:1) was separated using silica gel CC and prep. TLC [*n*-hexane–Me_2CO (15:1)] and gave romucosine H (**4**) (4 mg). Fr. 9 (0.4 g) eluted with $CHCl_3$–MeOH (10:1) was repeatedly subjected to silica gel CC and prep. TLC [$CHCl_3$–MeOH (18:1)] and gave (−)-artabonatine B (6 mg). Cherianoine (**3**) (5 mg) was obtained from Fr. 11 (0.2 g) by means of silica gel CC eluting with $CHCl_3$–MeOH 9:1. Fr. 13 (0.1 g) eluted with $CHCl_3$–MeOH (8:1) was further separated using silica gel CC and prep. TLC [$CHCl_3$–MeOH (12:1)]and gave annocherine A (**1**) (3 mg) and annocherine B (**2**) (5 mg), respectively.

3.3.1. Annocherine A (*1*)

Yellow yellow needles, mp 156–158°C, $[\alpha]_D^{24}$ +135.0° (*c* 0.1, $CHCl_3$). UV λ_{max} (MeOH) nm (log ε): 260 (3.41), 300 (3.10), 330 (3.52). IR (KBr) ν_{max} cm^{-1}: 3400 (OH). EIMS *m/z* (rel. int.): 297 ($[M]^+$, 12), 296 (70), 280 (100), 263 (38), 249 (20), 174 (28), 137 (95), 123 (60), 107 (35). ^1H NMR ($CDCl_3$) δ: see Table 1. ^{13}C NMR ($CDCl_3$) δ: see Table 2. HREIMS *m/z*: 297.1014 (calcd for $C_{17}H_{15}O_4N$ 297.1001).

3.3.2. Annocherine B (*2*)

Yellow amorphous powder, mp 196–198°C, $[\alpha]_D^{24}$ +115.0° (*c* 0.1, $CHCl_3$). UV λ_{max}(MeOH) nm (log ε): 260 (3.32), 300 (3.11), 331 (3.60). IR (KBr) ν_{max} cm^{-1}: 3400 (OH). EIMS *m/z* (rel. int.): 311 ($[M]^+$, 21), 296 (35), 280 (34), 264 (5), 236 (11), 174 (15), 137 (100), 121 (41), 107 (31). ^1H NMR ($CDCl_3$) δ: see Table 1. ^{13}C NMR ($CDCl_3$) δ: see Table 2. HREIMS *m/z*: 311.1174 (calcd for $C_{18}H_{17}O_4N$: 311.1158).

3.3.3. Cherianoine (*3*)

White needles, mp 122–124°C. UV λ_{max} (MeOH) nm (log ε): 220 (4.51), 260 (4.41), 270 (3.35), 330 (3.39). IR (KBr) ν_{max} cm^{-1}: 3200 (OH), 1685 (C=O). EIMS *m/z* (rel. int.): 235 ($[M]^+$, 21), 218 (35), 204 (34), 178 (5), 164 (90), 136 (100), 69 (21), 55 (16). ^1H NMR ($CDCl_3$) δ: 7.00 (1H, *d*, *J* = 7.2 Hz, H-3), 6.88 (1H, *s*, H-5), 6.39 (1H, *d*, *J* = 7.2 Hz, H-4), 4.05 (3H, *s*, OMe-6), 4.01 (3H, *s*, OMe-8), 3.55 (*N*-Me). ^{13}C NMR ($CDCl_3$) δ: 161.3 (*s*, C-1), 150.6 (*s*, C-6), 143.5 (*s*, C-7), 143.1 (*s*, C-8), 132.8 (*s*, C-8a), 131.4 (*s*, C-4a), 131.1 (*d*, C-3), 106.1 (*d*, C-5), 105.4 (*d*, C-4), 56.4 (*q*, OMe-8), 52.5 (*q*, OMe-6), 37.8 (*q*, *N*-Me). HREIMS *m/z*: 235.0845 (calcd for $C_{12}H_{13}O_4N$: 235.0844).

3.3.4. Romucosine H (*4*)

Brown amorphous powder, mp 230–233°C, $[\alpha]_D^{24}$ −43.0° (*c* 0.01, $CHCl_3$). UV λ_{max} (EtOH) nm (log ε): 222 (4.39), 270 (4.19), 310 (3.80). IR (KBr) ν_{max} cm^{-1}: 3500 (OH), 1630 (C=O). EIMS *m/z* (rel. int.): 385 ($[M]^+$, 90), 326 (70), 312 (100), 296 (76), 284 (20), 267 (45), 252 (21), 239 (15). ^1H NMR ($CDCl_3$) δ: 6.88 (1H, *d*, *J* = 8.0 Hz, H-8), 6.84 (1H, *d*, *J* = 8.0 Hz, H-9), 6.73 (1H, *s*, H-3), 4.58 (1H, *dd*, *J* = 14.0, 4.5 Hz, H-6a), 4.45 (1H, *m*, H-5a), 3.92 (3H, *s*, OMe-2), 3.89 (3H, *s*, OMe-10), 3.76 (3H, *s*, *N*-COOMe), 3.70 (3H, *s*, OMe-1). ^{13}C NMR ($CDCl_3$) δ: 155.6 (*s*, *N-CO*OMe), 151.3 (*s*, C-1), 149.4 (*s*, C-2), 144.1 (*s*, C-10), 142.0 (*s*, C-11), 130.2 (*s*, C-7a), 130.1 (*s*, C-3a), 129.8 (*s*, C-11a), 125.6 (*s*, C-3b), 120.1 (*s*, C-11b), 118.8 (*d*, C-3), 111.7 (*d*, C-8), 111.0 (*d*, C-9), 62.0 (*q*, OMe-1), 56.1 (*q*, OMe-10), 55.8 (*q*, OMe-2), 54.0 (*d*, C-6a), 52.6 (*q*, *N*-COO*Me*), 42.6 (*t*, C-5), 38.2 (*t*, C-7), 29.1 (*t*, C-4). HREIMS *m/z*: 385.1532 (calcd for $C_{21}H_{23}O_6N$: 385.1525).

3.3.5. Preparation of N-(methoxycarbonyl) norisocorydine (Romucosine H) (*4*)

(−)-Norisocorydine (20 mg) in dry CH_2Cl_2 (10 ml) was treated with triethylamine (5 μl), with stirring at 0°C, for 10 min, and then methyl chlorocarbonate (2 ml) was slowly added. The reaction mixture was stirred for 10 min, and H_2O was added to quench excess reagent. The mixture was partitioned with $CHCl_3$ and then passed through a disposable pipette (0.6×6 cm) containing silica gel (230–400 mesh) and eluted with 10 ml of $CHCl_3$. Elution with $CHCl_3$ afforded a brown amorphous powder (5 mg) that was identified by comparison with **4** (mixed mp, co-TLC, UV, IR, ^1H and ^{13}C NMR).

3.3.6. Artabonatine B

Yellow powder, $[\alpha]_D^{25}$ −122.4° (*c* 0.80, $CHCl_3$), UV λ_{max}(EtOH) nm (log ε): 214 (4.21), 256 (4.18), 295 (3.85), 325 (3.54). MS, and ^1H and ^{13}C NMR data were identical with published data (Hsieh et al., 1999).

Acknowledgements

This investigation was supported by a grant from the National Science Council of the Republic of China.

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