The Alkaloids of *Artabotrys uncinatus*

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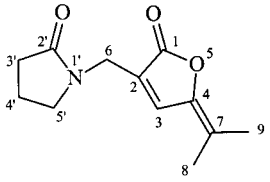
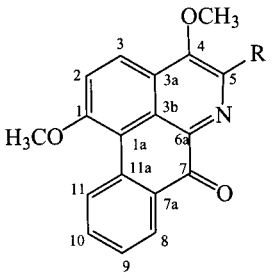
A novel type of α,β-butenolide alkaloid, uncinine (**1**), two novel oxoaporphines, artabonatine C (**2**) and artabonatine D (**3**), a new oxazoloaporphine, artabonatine E (**4**), and a new 7,7′-bisdehydroaporphine, artabonatine F (**5**), along with 25 known alkaloids, were isolated from *Artabotrys uncinatus*. The structures of **1**−**5** were determined using NMR and mass spectral data. Atherospermidine and squamolone exhibited cytotoxicity against hepatocarcinoma cancer cell lines (Hep G_2 and 2,2,15), and the activity of some of the alkaloids in an antithrombin assay is also discussed.

Hepatocarcinoma and nasopharyngeal carcinoma (NPC) are the most important cancers in Taiwan. *Artabotrys uncinatus* (Lam) Merr. (Annonaceae) was used for treatment of human NPC as a traditional folk medicine.[1] In previous studies,[2,3] we reported the structures and cytotoxicities of liriodenine, atherospermidine, and nine known alkaloids from the stems and unripe fruits of *A. uncinatus* against KB cells. To further understand the chemotaxonomy and continue searching for novel bioactive agents from Annonaceous plants, *A. uncinatus* was chosen for further phytochemical investigation. In this paper, we report the isolation and structural determination of a novel type of α,β-butenolide alkaloid, uncinine (**1**), two novel oxoaporphines, artabonatine C (**2**) and artabonatine D (**3**), a new oxazoloaporphine, artabonatine E (**4**), and a new 7,7′-bisdehydroaporphine, artabonatine F (**5**), along with 25 known alkaloids.[2−16] Several compounds were evaluated for their cytotoxicity against hepatocarcinoma cancer cell lines (Hep G_2 and 2,2,15) and for antithrombin activity.



1



R

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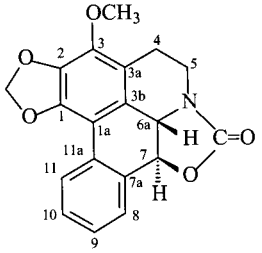
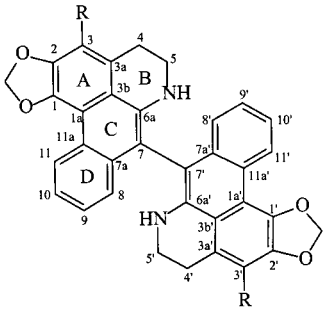
3 OH



4



R

5 OCH_3

6 H

Results and Discussion

Uncinine (**1**) was obtained as a white amorphous powder. Its molecular formula was established as $C_{12}H_{15}O_3N$ by HREIMS. The UV spectrum showed maximal absorption at 291 nm, which suggested that **1** possessed a 4-isopropylidene-cyclobutenolide moiety.[17] The presence of two carbonyl groups was substantiated by IR (1739 and 1676 cm^{-1}) and EIMS (*m*/*z* 193 $[M - 28]^+$ and 165 $[M - 56]^+$) spectra. The ^1H NMR spectrum of **1** showed signals corresponding to one methine, four methylene (one methylene signal was significantly downfield shifted and seen as a singlet at δ 4.18), and two methyl groups, respectively.

The ^{13}C NMR and DEPT spectra confirmed that **1** contained 12 carbons, including two methyls, four methylenes, one methine, and five quaternary carbons (including two carbonyls at δ 170.2 and 175.2), respectively. The sequential correlations of methylenes of C-3′, C-4′, and C-5′ were proven by the COSY spectrum. The NOESY spectrum showed correlations between H-5′/H-6, H-6/H-3, and H-3/CH_3-8, as well as CH_3-8/CH_3-9. The above data indicated that **1** was a 4-isopropylidene-cyclobutenolide, in agreement with other reported compounds with a 2′-oxo-1′-pyrolidinylmethyl side chain.[17] Further confirmation of the structural assignment was obtained by means of an HMBC experiment. The two methyl signals at δ 1.90 and 2.00, correlated to each carbon at δ 18.5 and 18.6 and to the quaternary carbons at δ 124.1 and 144.6, which required them to be geminal, and confirmed their placement in an isopropylidene group. The H-3 signal revealed ^2J coupling to C-2 and C-4 and ^3J coupling to C-1. The H-6 proton at δ 4.18 showed ^3J correlation to C-1, C-3, C-2′, and C-5′ at δ 170.2, 136.7, 175.2, and 47.7, and ^2J correlation to C-2 at δ 126.8, which revealed the connection between γ-lactam

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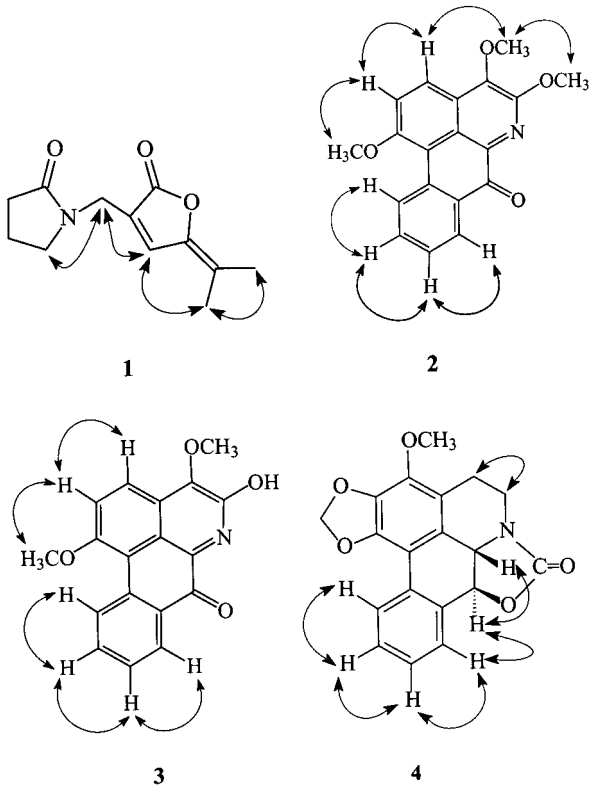

Figure 1. NOESY correlations of **1**−**4**.

and α,β-unsaturated γ-lactone moieties. Three methylene proton signals were placed at C-3′, C-4′, and C-5′, which revealed HMBC correlations with the carbon already assigned to C-2′ (δ 175.2). The above results supported the structure of **1** as a novel 2-(2′-oxo-1′-pyrolidinylmethyl)-4-isopropylidene-cyclobutenolide, which was named uncinine.

Artabonatine C (**2**) was isolated as a green amorphous powder. HREIMS revealed a molecular formula of $C_{19}H_{15}O_4N$. The EIMS revealed fragments at *m/z* 321 $[M]^+$, 306 $[M - 15]^+$, and 291 $[M - 30]^+$. The UV spectrum of **2** showed intense absorption bands at λ 268, 436, and 592 nm, and the IR spectrum of **2** exhibited absorption bands at ν_{max} 1655 cm^{-1}, indicating an oxoaporphine carbonyl group.[5] The ^1H NMR spectrum showed singlets at δ 4.02, 4.31, and 4.36 (each 3H) corresponding to three methoxy groups. The six aromatic protons displayed an AB pattern at δ 7.36 (1H, d, $J = 7.2$ Hz) and 7.55 (1H, d, $J = 7.2$ Hz) and an AA′BB′ pattern at δ 8.97 (1H, dd, $J = 8.4$, 1.1 Hz), 8.24 (1H, dd, $J = 8.4$, 1.7 Hz), 7.71 (1H, td, $J = 8.4$, 1.7 Hz), and 7.45 (1H, td, $J = 8.4$, 1.1 Hz), respectively. These signals suggested that compound **2** has a D-ring similar to that of *O*-methylmoschatoline.[5] The remaining AB pattern of **2** at δ 7.36 (1H, d, $J = 7.2$ Hz) and 7.55 (1H, d, $J = 7.2$ Hz) revealed significant differences in chemical shift and coupling constant, when compared to those of *O*-methylmoschatoline at δ 8.23 (1H, d, $J = 5.2$ Hz, H-4) and 8.97 (1H, d, $J = 5.2$ Hz, H-5).[5]

Various 2D NMR spectra further supported the structure of **2**. The proton relationships of **2** were determined by analyzing its NOESY data (Figure 1). The NOESY spectrum indicated correlations between OMe-1/H-2, H-2/H-3, H-3/OMe-4, and OMe-4/OMe-5, as well as H-8/H-9, H-9/H-10, and H-10/H-11. A singlet at δ 4.31 (3H, s) was assigned to OMe-1, and signals at δ 4.02 and 4.36 were assigned to OMe-4 and OMe-5, respectively. In the ^{13}C NMR spectrum of **2**, the 15 aromatic carbon atoms between δ 169.0 and 111.5, a carbonyl carbon atom at δ 180.5, and three methoxy carbon atoms at δ 47.0, 59.7, and 60.5 were consistent with structure **2**. The ^{13}C NMR data of C- and D-rings displayed a similar pattern when compared with those of *O*-methylmoschatoline.[4,5] To completely assign and confirm the structure of **2**, the HMBC technique was employed. A methoxy signal at δ 4.02 showed ^3J correlation to the C-4 (δ 140.9). The H-8 was assigned at δ 8.24, as it revealed ^3J interactions with the carbon assigned to C-7 (δ 180.5), and H-11 was assigned at δ 8.97, as it revealed ^3J interactions with the carbon assigned to C-1a at δ 115.3. The H-9 proton (δ 7.45) showed ^2J correlation to C-10 (δ 134.6) and ^3J correlation to C-11 at δ 128.3, which provided an assignment of the oxoaporphine. While it is rare to find an oxygen-bearing group at C-4 or C-5 of oxoaporphines,[10] **2** possesses unusual 4,5-dioxygen-bearing substitutions in the oxoaporphine skeleton. Although C-2 and C-3 unsubstituted aporphines had been synthesized in previous studies,[18] **2** is a novel alkaloid that represents the first example of a naturally occurring C-2 and C-3 unsubstituted oxoaporphine.

Artabonatine D (**3**) was obtained as a red amorphous powder. The EIMS spectrum revealed fragments at *m/z* 307 $[M]^+$ and 291 $[M - H - 15]^+$.[9] The UV spectrum of **3** showed intense absorption bands at λ 204, 280, and 506 nm. An IR band at 1641 cm^{-1} and a signal at δ 179.0 in the ^{13}C NMR spectrum confirmed that a carbonyl moiety was present.[5] The ^1H and ^{13}C NMR spectra of **3** were similar to those of **2** except for the disappearance of a methoxy signal. The ^1H NMR spectrum of **3** contained two protons at δ 7.56 (1H, d, $J = 7.0$ Hz) and 7.42 (1H, d, $J = 7.0$ Hz) and four protons at δ 8.31 (2H, dd, $J = 8.0$, 1.6 Hz), 7.70 (1H, td, $J = 8.0$, 1.6 Hz), and 7.40 (1H, td, $J = 8.0$, 1.6 Hz), in the aromatic region, accounting for six protons. Significant correlations between OMe-1/H-2 and H-2/H-3, as well as H-8/H-9, H-9/H-10, and H-10/H-11, were observed in the NOESY spectrum (Figure 1). A singlet at δ 4.38 (3H, s) was assigned to OMe-1, and the signal at δ 4.02 was assigned to OMe-4. In the HMBC spectrum two methoxy signals (δ 4.38 and 4.02) showed ^3J correlation to C-1 and C-4 at δ 130.8 and 136.8. The signals at δ 7.40 and 7.70 were assigned to H-9 and H-10, as they revealed ^3J interactions with the carbons assigned to C-7a (δ 131.8) and C-11a (δ 136.6), respectively. H-3 (δ 7.56) revealed ^2J coupling to C-2 (δ 135.8) and ^3J coupling to C-4 (δ 136.8). The H-8 and H-11 protons (δ 8.31) showed ^3J correlation to C-7 (δ 179.0) and C-1a (δ 100.2) and ^2J correlation to C-7a and C-11a at δ 131.8 and 136.6, respectively. The above information indicated that compound **3** contained a hydroxyl group at C-5 instead of the methoxy group of compound **2**. Thus, the structure of **3** was determined as illustrated. Compound **3**, named artabonatine D, is also a novel 1,4,5-substituted oxoaporphine.

Artabonatine E (**4**) was obtained as a white amorphous powder. It displayed UV, IR, and mass spectra similar to those of artabonatine A.[3] The ^1H NMR spectrum of **4** contained a signal at δ 8.24 for H-11, a multiplet at δ 7.51−7.45 for H-8 and H-10, and a signal at δ 7.34 for H-9 in the aromatic region, in addition to two signals characteristic of aporphine methylenedioxy protons at δ 6.01 and 6.13.[3] A singlet at δ 4.02 (3H, s) was assigned to OMe-3, and two significant downfield signals at δ 4.66 (H-6a) and 5.60 (H-7) indicated that an electron-withdrawing group was bonded to the nitrogen and C-7.[3] The coupling constant between H-6a and H-7 ($J = 7.6$ Hz) indicated a *trans* relationship.[3] Complete assignments and the relative configuration of aliphatic and aromatic protons of **4** were established by NOESY experiment. Significant correlations between H-4 and H-5, as well as H-6a/H-7, H-7/H-8, H-8/

H-9, H-9/H-10, and H-10/H-11, were observed in the NOESY spectrum (Figure 1). Accordingly, compound **4** contained a methoxy group at C-3 instead of a proton as in artabonatine A.[3] Thus, the structure of **4** was elucidated as shown. It is the second example of oxazoloaporphine-type alkaloids from a natural resource.[3]

Artabonatine F (**5**) was isolated as a white amorphous powder. The EIMS showed fragments at *m/z* 584 $[M]^+$ and an $[M/2 + H]^+$ peak at *m/z* 293, which suggested a dimeric structure for **5**. HREIMS revealed a $[M]^+$ ion at *m/z* 584, indicating molecular formula $C_{36}H_{28}O_6N_2$. The UV spectrum of **5** showed intense absorption bands at λ 244, 264, and 324 nm, indicating a dehydroaporphine system linking the C-7 and C-7′ positions.[19−21] The IR spectrum of **5** exhibited absorption bands at ν_{max} 1050 and 938 cm^{-1}, indicating a methylenedioxy group.[19−21] It was apparent from the ^1H NMR spectrum that **5** was closely related to unonopsine (**6**)[21] and that it was characteristic of a 7,7′-bisdehydroaporphine system. Thus, its monomeric unit exhibited four aryl proton signals at δ 7.11 (dd, J = 8.4, 1.2 Hz, H-8), 7.20 (td, J = 8.4, 0.8 Hz, H-9), 7.32 (td, J = 8.0, 1.2 Hz, H-10), and 9.01 (dd, J = 8.0, 0.8 Hz, H-11), suggesting a D-ring with no substitution. The lack of any further aromatic protons and the appearance of a methoxy signal at δ 4.11 and a methylenedioxy group at δ 6.28 indicated that the A-ring was fully substituted.[19−21] The ^1H NMR pattern suggested substitution where the methylenedioxy group was placed at the 1,2-position, and thus, the singlet at δ 4.11 could be assigned to OMe-3.[19−21] The aliphatic methylene H-4 and H-5 resonances appeared as two signals between δ 3.14 and 3.33.[19−21] Compound **5** is similar to 7-dehydronorstephalagine, but lacks H-7. The fact that no singlet signal appeared near δ 6.60, as would be expected for protons at C-7 or C-7′, revealed that **5** was a symmetrical dimer of two 7-dehydronorstephalagine units (e.g., two dehydroaporphine moieties) linked between C-7 and C-7′.[19−22] In the ^{13}C NMR spectrum of **5**, two methylenedioxy carbons at δ 101.2, two methoxy carbons at δ 59.7, and four signals for methylene carbons at δ 23.1 and 39.9 were consistent with structure **5**.[19,21] 7,7′-Bisdehydroaporphines readily decompose when exposed to air, and thus, compounds of this type are rare. The ^{13}C NMR assignments were directly compared with the known compound 7,7′-bisdehydro-*O*-methylisopiline[19] (these data are detailed in the Experimental Section) and a number of other 7,7′-bisdehydroaporphines that have been isolated from Annonaceous plants.[19−21] Thus, the above results indicated the structure of **5** to be a new 7,7′-bisdehydroaporphine, which we named artabonatine F.

Besides these five new alkaloids, 25 known alkaloids, including liriodenine,[2,3] atherospermidine,[2] *O*-methylmoschatoline,[4,5] oxoasimilobine,[6] (−)-anonaine,[7] (−)-romerine,[6] (−)-*N*-acetylnorstephalagine,[8] (−)-norstephalagine,[6,8] (−)-stephalagine,[8,9] (−)-isopiline,[10] (−)-*N*-methylisopiline,[10] (−)-asimilobine,[7] (−)-norushinsunine,[7] artacinatine,[2] (+)-isocorydine,[11] (−)-nornuciferine,[12] (+)-norisocorydine,[11] (−)-*O*-methyl-*N*-norlirinine,[13] (−)-cissaglaberrimine,[14] (−)-10-*O*-demethyldiscretine,[15] (−)-salutaridine,[16] (+)-flavinantine,[16] (+)-stepharine,[12] (+)-reticuline,[7] and squamolone,[11] were isolated and identified by means of spectroscopic methods and by comparing literature data.[2−16] Nineteen of these alkaloids were obtained from this plant for the first time. The alkaloids isolated from the roots, stems, leaves, and unripe fruits[3] of *A. uncinatus* are shown in the table of Supporting Information. Seven compounds were evaluated for their cytotoxicity against two hepatocarcinoma cancer cell lines, Hep G_2 and 2,2,15. Atherospermidine and squamolone showed significant activity against both Hep G_2 and 2,2,15 cell lines (Table 1).

Table 1. In Vitro Cytotoxicity Data of **1**, Atherospermidine, (−)-*N*-Acetylnorstephalagine, (−)-Salutaridine, (+)-Flavinantine, Squamolone, and Artabonatine B

compound	cell lines[a]/IC_{50} (μg/mL)	
	Hep G_2	Hep 2,2,15
1	6.1	7.4
atherospermidine[2]	0.8	2.2
(−)-*N*-acetylnorstephalagine[8]	9.8	9.3
(−)-salutaridine[16]	10.2	10.4
(+)-flavinantine[16]	9.3	9.7
squamolone[11]	2.8	1.6
artabonatine B[3]	9.1	11.0

[a] Cell lines: Hep G_2, human hepatoma cell; Hep 2,2,15, Hep G_2 cell line transfected with hepatitis B virus (HBV).

Platelets play an important role in the hemostatic process, and their aggregation can cause arterial thrombosis. In previous studies, we had demonstrated that liriodenine possessed marked antiplatelet activity by ADP and collagen and vasorelaxing effects. Also, 7-hydroxydehydrothalicsimidine was found to be strongly active against platelet aggregation induced by thrombin, PAF, collagen, and AA.[22] Therefore, isoquinoline alkaloid **5** and several others were also assayed for thrombin activity inhibition, which catalyzes the conversion of fibrinogen to fibrin. None of the alkaloids tested were inhibitory.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. UV spectra were obtained in MeOH using a JASCO V-530 spectrophotometer. Melting points were determined using a Yanagimoto micro-melting point apparatus and are uncorrected. The IR spectra were measured on a Hitachi 260-30 spectrophotometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra (all in $CDCl_3$) were recorded with Varian NMR spectrometers, using TMS as an internal standard. LRFABMS and LREIMS spectra were obtained with a JEOL JMS-SX/SX 102A mass spectrometer or a Quattro GC−MS spectrometer with a direct inlet system. HREIMS and HRFABMS were measured on a JEOL JMS-HX 110 mass spectrometer. Silica gel 60 (Merck, 230−400 mesh) was used for column chromatography. Precoated silica gel plates (Merck, Kieselgel 60 F-254, 0.20 mm) were used for analytical TLC, and precoated silica gel plates (Merck, Kieselgel 60 F-254, 0.50 mm) were used for preparative TLC. Spots were detected by spraying with Dragendorff's reagent or 50% H_2SO_4 and then heating on a hot plate. Thrombin (human, 10 NIH units per vial) and fibrinogen (Type IV, from bovine) were purchased from Sigma Chem. Co. Heparin (1000 IU/mL) was purchased from Leo Pharmaceutical Co. (Denmark).

Plant Material. The roots, stems, and leaves of *A. uncinatus* were collected from Pingtung City, Taiwan, in September 1997. A voucher specimen was characterized by Dr. Hsin-Fu Yen and deposited in the Graduate Institute of Natural Products, Kaohsiung Medical University (voucher number: Annona 12), Kaohsiung, Taiwan.

Extraction and Isolation. The roots (3.0 kg) of *A. uncinatus* were extracted repeatedly with MeOH at room temperature. The combined MeOH extracts were evaporated and partitioned to yield $CHCl_3$ and aqueous extracts. The $CHCl_3$ solution was extracted with 3% HCl. The acidic portion was basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to leave a brownish viscous residue. The crude alkaloid portion (3.0 g) was chromatographed over silica gel ($CHCl_3$−MeOH) to obtain 15 fractions. Fraction 4 was rechromatographed on silica gel ($CHCl_3$−MeOH (20:1)) to afford liriodenine (6 mg), atherospermidine (20 mg), and *O*-methylmoschatoline (3 mg). Fraction 6, eluted

from *n*-hexanes−EtOAc (1:2), was further chromatographed on silica gel eluting with EtOAc−MeOH (15:1) to obtain **5** (5 mg), (−)-anonaine (10 mg), (−)-*N*-acetylnorstephalagine (2 mg), and (−)-norstephalagine (15 mg). Fraction 7 was separated on silica gel ($CHCl_3$−MeOH (10:1)) to afford (−)-isopiline (7 mg), (+)-isocorydine (3 mg), and (−)-nornuciferine (2 mg). Further purification of fraction 8 by preparative TLC yielded the alkaloid **4** (1 mg). Fraction 10 was purified by silica gel chromatography ($CHCl_3$−MeOH, 8:1) to obtain (−)-norushinsunine (2 mg), (+)-norisocorydine (3 mg), and (+)-flavinantine (5 mg). Fraction 12, eluted with EtOAc−MeOH (8:1), was further chromatographed on silica gel to afford (−)-asimilobine (5 mg), (−)-10-*O*-demethyldiscretine (6 mg), (−)-salutaridine (7 mg), (+)-stepharine (9 mg), and (+)-reticuline (2 mg).

The stems (15.0 kg) of *A. uncitaus* were extracted using the same procedures as for roots. The crude alkaloid portion (3.5 g) was chromatographed over silica gel ($CHCl_3$−MeOH) to obtain 13 fractions. Fraction 3 was further chromatographed on silica gel to afford liriodenine (6 mg), atherospermidine (5 mg), *O*-methylmoschatoline (2 mg), and squamolone (2 mg). Fraction 5, eluted from *n*-hexanes−EtOAc (1:2), was rechromatographed on silica gel to afford (−)-romerine (7 mg), (−)-stephalagine (5 mg), (−)-*N*-methylisopiline (6 mg), and artacinatine (1 mg). Compounds **2** (5 mg) and **3** (4 mg) were isolated from fraction 6. Fraction 8 was purified by silica gel chromatography to obtain (−)-anonaine (12 mg), (−)-norstephalagine (17 mg), (−)-isopiline (9 mg), and (−)-*O*-methyl-*N*-norlirinine (4 mg). Fraction 10 was separated on silica gel to afford (+)-norisocorydine (6 mg), (−)-salutaridine (3 mg), and (+)-flavinantine (4 mg). Fraction 11, eluted using EtOAc−MeOH (6:1), afforded (−)-cissaglaberrimine (1 mg), (−)-asimilobine (7 mg), (+)-stepharine (2 mg), and (+)-reticuline (9 mg). The same separation methods were used on leaves (10.0 kg). The crude alkaloid portion (1.8 g) was chromatographed over silica gel using $CHCl_3$/MeOH as eluent to obtain 12 fractions. Fraction 4 was further chromatographed on silica gel elution ($CHCl_3$−MeOH (15:1)) to afford liriodenine (2 mg) and oxoasimilobine (1 mg). Compound **1** (5 mg), (−)-anonaine (6 mg), and (−)-nornuciferine (4 mg) were isolated from the column using EtOAc−MeOH (8:1) as the solvent system (fraction 6). Fraction 8 was purified by silica gel chromatography ($CHCl_3$−MeOH, 8:1) to obtain (−)-asimilobine (8 mg) and (−)-salutaridine (4 mg). Fraction 10 afforded (−)-cissaglaberrimine (2 mg), (+)-stepharine (3 mg), and (+)-reticuline (7 mg).

Uncinine (**1**): white amorphous powder; UV (EtOH) λ_{max} (log ϵ) 204 (3.76) and 291 (4.27) nm; IR (neat) ν_{max} 2915, 2847, 1739, and 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, s, H-3), 4.18 (1H, s, H-6), 3.48 (2H, m, H-5′), 2.40 (2H, m, H-3′), 2.07 (2H, m, H-4′), 2.00 (3H, s, H-9), 1.90 (3H, s, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2 (s, C-2′), 170.2 (s, C-1), 144.6 (s, C-4), 136.7 (d, C-3), 126.8 (s, C-2), 124.1 (s, C-7), 47.7 (s, C-5′), 37.3 (t, C-6), 30.6 (t, C-3′), 18.5 (q, C-8), 18.6 (q, C-9), 18.0 (s, C-4′); EIMS *m/z* 221 $[M]^+$ (37), 193 (21), 165 (64), 84 (100); HREIMS *m/z* $[M]^+$ 221.1050 ($C_{12}H_{15}O_3N$, calcd 221.1048).

Artabonatine C (**2**): green amorphous powder; UV (EtOH) λ_{max} (log ϵ) 268 (3.34), 436 (3.42), and 592 (4.62) nm; IR (neat) ν_{max} 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (1H, dd, J = 8.4, 1.1 Hz, H-11), 8.24 (1H, dd, J = 8.4, 1.7 Hz, H-8), 7.71 (1H, td, J = 8.4, 1.7 Hz, H-10), 7.55 (1H, d, J = 7.2 Hz, H-3), 7.45 (1H, td, J = 8.4, 1.1 Hz, H-9), 7.36 (1H, d, J = 7.2 Hz, H-2), 4.36 (3H, s, OMe-5), 4.31 (3H, s, OMe-1), 4.02 (3H, s, OMe-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5 (s, C-7), 169.0 (s, C-5), 162.0 (s, C-6a), 140.9 (s, C-4), 135.5 (d, C-2), 134.8 (s, C-11a), 134.6 (d, C-10), 134.3 (d, C-7a), 131.0 (s, C-3b), 130.2 (s, C-1), 128.8 (d, C-9), 128.3 (s, C-11), 127.4 (d, C-8), 115.3 (s, C-1a), 111.7 (s, C-3a), 111.5 (d, C-3), 60.5 (q, OMe-5), 59.7 (q, OMe-4), 47.0 (q, OMe-1); FABMS *m/z* 322 $[M + 1]^+$ (89), 306 (62), 289 (9), 242 (36), 176 (19), 154 (89), 136 (100); EIMS *m/z* 321 $[M]^+$ (83), 320 (70), 306 (62), 291 (15), 278 (21), 263 (9), 235 (82), 206 (31), 153 (40), 69 (52); HREIMS *m/z* $[M]^+$ 321.0994 ($C_{19}H_{15}O_4N$, calcd 321.1001).

Artabonatine D (**3**): red amorphous powder; UV (EtOH) λ_{max} (log ϵ) 204 (3.04), 280 (3.71), and 506 (4.52) nm; IR (neat) ν_{max} 3401 and 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (1H, dd, J = 8.0, 1.6 Hz, H-11), 8.31 (1H, dd, J = 8.0, 1.6 Hz, H-8), 7.70 (1H, td, J = 8.0, 1.6 Hz, H-10), 7.56 (1H, d, J = 7.0 Hz, H-3), 7.42 (1H, d, J = 7.0 Hz, H-2), 7.40 (1H, td, J = 8.0, 1.6 Hz, H-9), 4.36 (3H, s, OMe-5), 4.31 (3H, s, OMe-1), 4.02 (3H, s, OMe-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0 (s, C-7), 164.8 (s, C-5), 149.4 (s, C-6a), 136.8 (s, C-4), 136.6 (s, C-11a), 135.3 (d, C-2), 133.9 (d, C-10), 132.3 (s, C-3b), 131.8 (s, C-7a), 130.8 (s, C-1), 128.3 (d, C-11), 125.9 (d, C-9), 123.8 (d, C-8), 119.3 (s, C-3a), 110.2 (d, C-3), 100.2 (s, C-1a), 59.7 (q, OMe-4), 47.1 (q, OMe-1); EIMS *m/z* 307 $[M]^+$ (4), 306 (11), 291 (8), 289 (8), 263 (9), 236 (8), 219 (11), 69 (100).

Artabonatine E (**4**): white amorphous powder; $[\alpha]^{24}_D$ −116.7° (*c* 0.8, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 250 (3.94), 280 (3.76), and 325 (2.64) nm; IR (neat) ν_{max} 1740, 1060, and 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (1H, dd, J = 8.2, 1.2 Hz, H-11), 7.51−7.45 (2H, m, H-8 and H-10), 7.34 (1H, td, J = 8.1, 1.2 Hz, H-9), 6.13 and 6.01 (each 1H, d, J = 1.6 Hz, OCH_2O), 5.60 (1H, d, J = 7.6 Hz, H-7), 4.66 (1H, d, J = 7.6 Hz, H-6a), 4.03 (3H, s, OMe-3), 3.66 (1H, m, H-5b), 3.41 (1H, m, H-5a), 2.40 (1H, m, H-4b), 2.38 (1H, m, H-4a); EIMS *m/z* 337 $[M]^+$ (100), 309 (1), 293 (47), 265 (23), 163 (33), 89 (45); HREIMS *m/z* $[M]^+$ 337.0948 ($C_{19}H_{15}O_5N$, calcd 337.0950).

Artabonatine F (**5**): white amorphous powder; UV (EtOH) λ_{max} (log ϵ) 244 (4.11), 264 (3.94), and 324 (3.76) nm; IR (neat) ν_{max} cm^{-1} 3375, 1050, and 938; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (2H, dd, J = 8.0, 0.8 Hz, H-11 and H-11′), 7.32 (2H, td, J = 8.0, 1.2 Hz, H-10 and H-10′), 7.20 (2H, td, J = 8.4, 0.8 Hz, H-9 and H-9′), 7.11 (2H, dd, J = 8.4, 1.2 Hz, H-8 and H-8′), 6.28 (4H, s, OCH_2O), 4.11 (6H, s, OMe-3 and OMe-3′), 3.24 (4H, d, J = 6.4 Hz, H-5 and H-5′), 3.15 (4H, d, J = 6.4 Hz, H-4 and H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.8 (d, C-8 and C-8′), 126.6 (d, C-9 and C-9′), 124.1 (d, C-10 and C-10′), 123.4 (d, C-11 and C-11′), 101.2 (t, OCH_2O), 59.7 (q, OMe), 39.9 (t, C-5 and C-5′), 23.1 (t, C-4 and C-4′); EIMS *m/z* 584 $[M]^+$ (100), 554 (55), 293 (19), 276 (19); HREIMS *m/z* $[M]^+$ 584.1946 ($C_{36}H_{28}O_6N_2$, calcd 584.1947).

Cytotoxicity Assay. The cytotoxicity assay was carried out according to the literature.[23,24]

Thrombin Activity Assay. The thrombin activity assay was carried out as represented in the literature.[25−27]

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Supporting Information Available: Table of alkaloids isolated from *A. uncinatus*. This material is available free of charge via the Internet at http://pubs.acs.org.

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