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NAPHTHYLISOQUINOLINE ALKALOIDS FROM *ANCISTROCLADUS COCHINCHINENSIS*

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Key Word Index—*Ancistrocladus cochinchinensis*; Ancistrocladaceae; leaves; naphthylisoquinoline alkaloids; 6-*O*-methylhamateine; ancistrocladinine; hamatinine; 6-*O*-methylhamatinine; 6-*O*-demethyl-7-*epi*-ancistrobrevine D; 7-*epi*-ancistrobrevine D; 6-*O*-demethyl-8-*O*-methyl-7-*epi*-ancistrobrevine D; structural elucidation.

Abstract—From the leaves of *Ancistrocladus cochinchinensis*, besides the already known ancistrocladinine, the new naturally occurring alkaloids, 6-*O*-methylhamateine, hamatinine, 6-*O*-methylhamatinine, 6-*O*-demethyl-7-*epi*-ancistrobrevine D, 7-*epi*-ancistrobrevine D and 6-*O*-demethyl-8-*O*-methyl-7-*epi*-ancistrobrevine D have been isolated and their structures elucidated from spectroscopic data and chemical degradation. © Elsevier Science Ltd. All rights reserved

INTRODUCTION

Ancistrocladus cochinchinensis is a large, hooked climber endemic in south Vietnam [1]. It is used in folk medicine as a diuretic, antifebrile and antiphlogistic agent. From the leaves of this species some tetralone derivatives and triterpenes have been isolated recently [2]. In continuation of these studies, the alkaloids 6-*O*-methylhamateine (**1**), ancistrocladinine (**2**), hamatinine (**3**), 6-*O*-methylhamatinine (**4**), 6-*O*-demethyl-7-*epi*-ancistrobrevine D (**5**), 7-*epi*-ancistrobrevine D (**6**) and 6-*O*-demethyl-8-*O*-methyl-7-*epi*-ancistrobrevine D (**7**) have now been isolated and their structures elucidated.

RESULTS AND DISCUSSION

The elemental compositions of alkaloids (**1–7**) were $C_{26}H_{27}NO_4$, $C_{25}H_{27}NO_4$, $C_{25}H_{27}NO_4$, $C_{26}H_{29}NO_4$, $C_{25}H_{29}NO_4$, $C_{26}H_{31}NO_4$ and $C_{26}H_{31}NO_4$, respectively, as deduced by HR mass spectrometry. A weak ion at *m/z* 202 ($C_{13}H_{14}O_2$) is in agreement with the presence of a dimethoxymethylnaphthalene moiety. ^1H and ^{13}C NMR data suggest that **1–7** are naphthylisoquinoline alkaloids well known from the family Ancistrocladaceae [3]. By ruthenium-mediated oxidative degradation [4–6] of alkaloids **2–4** (*S*)-3-aminobutyric acid was obtained, whereas the compounds **5–7** were degraded to (*S*)-3-amino-*N*-methylbutyric acid. This proves the (*S*)-configurations of **2–7** at C-3.

^1H chemical shifts and multiplicities of the naphthalene part of **1–7** clearly indicated the presence of a 2′-methyl-4′,5′-dimethoxynaphthalene ring in each case. This was proved by NOE experiments showing H-3′ to be located in close proximity to both Me-2′ and OMe-4′, on the one hand, and H-6′ spatially close to OMe-5′, on the other hand. Furthermore, protons H-6′, H-7′ and H-8′ form a three spin system (*d*, *dd*, and *d*). Thus, the isoquinoline moiety must be connected to C-1′ of the naphthalene moiety. This was confirmed by the high-field proton shift of Me-2′ (δ 2.22–2.01) found for **1–7**. Therefore, the naphthalene methyl group must be in an *ortho*-position with respect to the biaryl axis.

The lack of resonances for protons at C-1 and C-3 and geminal protons at C-4 in the ^1H NMR spectrum of **1** implies a fully dehydrogenated isoquinoline moiety, which was confirmed by a long-range ^1H, ^{13}C chemical shift (HMBC) experiment. All methyl group protons exhibit HMBC correlations only to low-field (aromatic) ^{13}C signals. The proton singlet at δ 6.43 was assigned to H-4 because of its NOE interaction with Me-3 and Me-2′, whereas the singlet at δ 6.74 shows NOEs with the two methoxyl groups belonging to the isoquinoline moiety; it is therefore assigned to H-7. Consequently, the naphthalene moiety is connected to C-5 of the isoquinoline part. The (*P*)-enanti-

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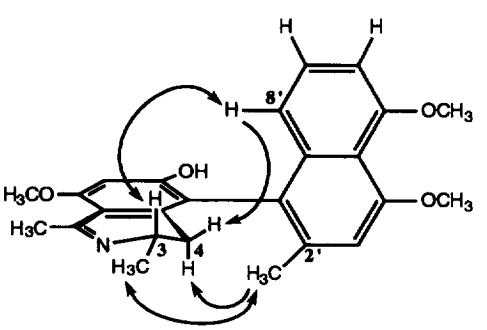
omer of this alkaloid (**1**) has already been obtained by synthesis [7, 8]. The ^{1}H NMR spectra are identical with that of our product (in $CDCl_3$); however, the opposite sign of optical rotation proves different axial chirality. These data confirm **1** as 6-*O*-methylhamateine.

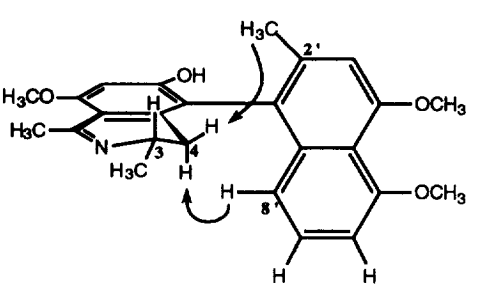
Unfortunately, **2** and **3** could be isolated only as a mixture in a ratio of *ca* 1:1. The ^{1}H NMR spectrum showed two sets of signals with identical coupling patterns but slightly different chemical shifts, supporting the assumption that **2** and **3** represent atropisomers with the same constitution. The methyl group at C-1 appears as a ^{1}H NMR singlet, whereas Me-3 has a coupling with H-3, which also couples with H-4_{eq} and H-4_{ax}. Thus, the isoquinoline parts of **2** and **3** consist of 3,4-dihydroisoquinoline moieties. The coupling constant $^3J_{H\text{-}3/H\text{-}4ax}$ of *ca* 10 Hz indicates a pseudo-axial position of H-3. The high-field shift of H-4_{eq} and H-4_{ax} (δ *ca* 2.0 and 1.7, respectively) and the lack of a NOE from the aromatic singlet at δ 6.10 to H-4_{eq}, prove that the biaryl axis is located at C-5 (and the singlet at δ 6.10 to belong to H-7). One of the methoxyl groups belongs to the isoquinoline part of the molecule. Because of its NOEs on Me-1 and to H-7, this methoxyl function must be located at C-8. Based on the observed NOEs, it is possible to assign all signals of the ^{1}H NMR spectrum of the mixture to compounds **2** and **3**, respectively, as well as to determine the absolute configuration at the biaryl axes (Fig. 1). H-8′ of **2** shows a NOE to H-4_{eq} and H-3, whereas H-8′ of **3** shows a NOE to H-4_{ax} and Me-3. Furthermore, Me-2′ of **2** gives a NOE with H-4_{ax} and Me-3, and Me-2′ of **3** gives a NOE with H-4_{eq}. From these findings, the biaryl axes of **2** and **3** are (*P*)- and (*M*)-oriented, respectively. Thus, **2** is identical with ancistrocladinine [9], whereas **3** represents its hitherto unknown atropisomer, hamatinine.

Mass spectral data, as well as ^{1}H and ^{13}C chemical shifts and multiplicities, reveal **4** to have a constitution similar to **2** and **3**, but with a methoxyl substituent at C-6 instead of a hydroxyl substituent. The NOE between H-8′ and H-4_{ax} confirms the (*M*)-configuration of the biaryl axis of **4**. From the positive exciton couplet at *ca* 220 nm of 6-*O*-methylhamatinine (**4**), the axial (*M*)-configuration is deduced, when the circular dichroism is compared with that of ancistrocladinine [$\Delta\varepsilon_{231} = -24.8$, $\Delta\varepsilon_{207} = +19.9$ (Bringmann, G. *et al.*, unpublished)] which is structurally analogous, but different with regard to the axial configuration.

The ^{1}H NMR spectra of **5**–**7** are very similar, showing, besides the signals of the naphthalene protons, typical resonances of a *N*-methyl-tetrahydroisoquinoline moiety. The high-field shift of H-3 in comparison with naphthyltetrahydroisoquinoline alkaloids with a C-5-C-1′ biaryl axis [3] and the missing NOE between Me-1 and H-3, suggest that the two methyl groups, Me-1 and Me-3, are *cis*-oriented [3]. The vicinal coupling constant $^3J_{H\text{-}3/H\text{-}4ax}$ of *ca* 10 Hz indicates the pseudo-axial orientation of H-3. The aromatic proton singlet of the isoquinoline moiety shows a HMBC correlation with C-4 and is therefore assigned to H-5. Consequently, the biaryl axis is located at C-7. This was confirmed by the low-field shift of H-4_{ax} and H-4_{eq} (δ *ca* 2.9 and 2.7, respectively) compared with naphthylisoquinoline alkaloids with the biaryl axis at C-5, such as **2** and **3**. A small but indubitable NOE [10, 11] between Me-1 and Me-2′, found in each case, reveals that **5**–**7** possess a *cis* spatial relationship between these methyl groups, opposite to that found for ancistrobrevine D [12]. For ancistrobrevine D with the axial (*P*)-configuration, a negative exciton couplet [$\Delta\varepsilon_{231} = -10.9$, $\Delta\varepsilon_{203} = +11.9$ (Bringmann, G. *et al.*, unpublished)] was detected; hence, the positive couplets for the alkaloids **5**–**7** at *ca* 220 nm suggest atropo-diastereomeric axial configurations. Whereas the NMR spectra of **5** display only two methoxyl groups (belonging to the naphthalene part), those of **6** and **7** show a third methoxyl group. In the case of **6**, it is assigned to OMe-6 by its NOE interaction with H-5. For **7**, the methoxyl group is assigned to OMe-8 because of its NOE with Me-1. 7-*epi*-Ancistrobrevine D (**6**) has previously been prepared by total synthesis by the Würzburg group

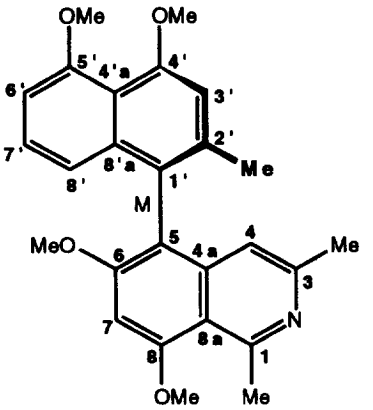


2

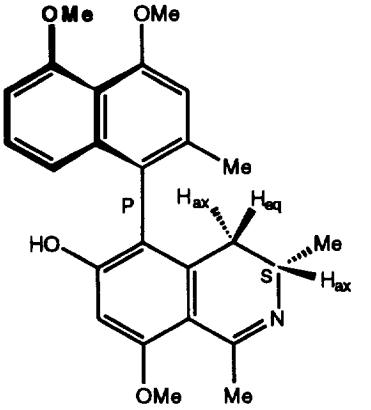


3

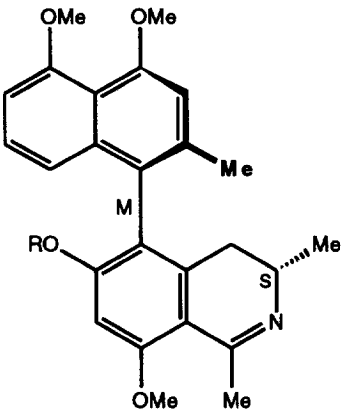
Fig. 1. Relevant NOEs of compounds **2** and **3**.



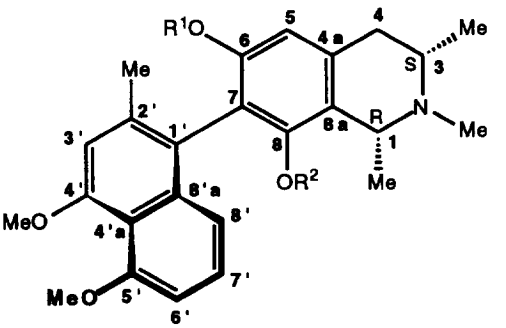
1



2



3: R = H
4: R = Me



5: R^1 = H R^2 = H 7,1'-axis: P
6: R^1 = Me R^2 = H 7,1'-axis: M
7: R^1 = H R^2 = Me 7,1'-axis: P

[12]; the physical data are in full agreement, also in comparison with *ent*-**6**, which has been prepared by partial synthesis, starting from ancistrobrevine C [12].

The correlations found in the ^{1}H, ^{1}H-COSY, HMQC and HMBC spectra and the results of the ID- and 2D NOE experiments allow a complete assignment of all ^{1}H and ^{13}C NMR signals for **1**–**7** (Tables 1 and 2).

EXPERIMENTAL

Spectrometric methods. EIMS were recorded at 70 eV. ^{1}H and 2D NMR experiments were carried out at 500 MHz using a 3 mm microsample inverse-detection probe. ID NOE-difference, 2D ROESY, COSY, HMQC and HMBC spectra were recorded according to standard pulse programs. ^{13}C NMR were recorded at 75.5 MHz using a 5 mm switchable probe.

Plant material and extraction. Leaves of *A. cochinchinensis* Gagn. were collected in Binh Dinh in December 1993. The species was identified by Dr Nguyen Van Tap, Hanoi. A voucher specimen is deposited at the Herbarium of the Institute of Materia Medica, Hanoi. Leaves were dried at 40°, ground and extracted (580 g) with 95% MeOH at room temp. This soln was extracted with *n*-hexane, the MeOH evapd *in vacuo* and the aq. soln extracted with EtOAc followed by *n*-BuOH. *n*-BuOH was evapd *in vacuo*, the residue partitioned between 0.5 N HCl and toluene–Et_2O (1:1). The aq. layer was basified with $KHCO_3$ and extracted with $CHCl_3$–EtOH (2:1). The residue of the EtOAc extract was chromatographed over silica gel with $CHCl_3$ and increasing amounts of MeOH to give crude **1**. The residue of the $CHCl_3$–EtOH extract was chromatographed over silica gel. $CHCl_3$–MeOH (19:1) eluted **6**, $CHCl_3$–MeOH (9:1) eluted **4**, followed by **5**, **7** and a mixt. of **2** and **3**.

6-O-*Methylhamateine* (**1**). Flash CC of crude **1** over silica gel with $CHCl_3$–MeOH (49:1), followed by prep. silica gel TLC with *n*-hexane–EtOAc–$NHEt_2$ (6:4:1),

Table 1. ^{1}H NMR data* of compounds **1**–**7** (solvent: $CDCl_3$)

H	1	2†	3†	4	5	6	7
1	—	—	—	—	3.86 *m*	3.74 *m*	3.81 *m*
1-Me	3.14 *s*	2.20 *s*	2.20 *s*	2.51 *d*	1.53 *d*	1.47 *d*	1.50 *d*
2-Me	—	—	—	—	2.54 *s*	2.52 *s*	2.54 *s*
3	—	2.72 *ddq*	2.64 *ddq*	3.19 *ddq*	2.74 *m*	2.65 *m*	2.70 *m*
3-Me	2.35 *s*	0.78 *d*	0.74 *d*	1.14 *d*	1.33 *d*	1.30 *d*	1.34 *d*
4	6.43 *s*	a:1.76 *dd*	a:1.69 *dd*	a:1.73 *dd*	a:2.87 *dd*	a:2.85 *dd*	a:2.85 *dd*
4	—	e:1.96 *dd*	e:1.99*dd*	e:2.01 *dd*	e:2.66 *dd*	e:2.67 *dd*	e:2.67 *dd*
5	—	—	—	—	6.41 *s*	6.34 *s*	6.59 *s*
6-OMe	3.77 *s*	—	—	3.69 *s*	—	3.60 *s*	—
7	6.74 *s*	6.10 *s*	6.10 *s*	6.51 *s*	—	—	—
8-OMe	4.09 *s*	3.82 *s*	3.82 *s*	3.97 *s*	—	—	3.07 *s*
2′-Me	2.01 *s*	2.10 *s*	2.18 *s*	2.09 *s*	2.21 *s*	2.19 *s*	2.22 *s*
3′	6.87 *s*	6.71 *s*	6.75 *s*	6.81 *s*	6.60 *s*	6.81 *s*	6.82 *s*
4′-OMe	4.05 *s*	3.87 *s*	3.87 *s*	4.01 *s*	3.79 *s*	3.97 *s*	3.98 *s*
5′-OMe	3.99 *s*	3.85 *s*	3.76 *s*	3.97 *s*	3.89 *s*	3.93 *s*	3.95 *s*
6′	6.78 *d*	6.72 *d*	6.63 *d*	6.78 *d*	6.73 *dd*	6.75 *dd*	6.78 *dd*
7′	7.10 *dd*	7.19 *dd*	7.08 *dd*	7.16 *dd*	7.26 *dd*	7.21 *dd*	7.27 *dd*
8′	6.66 *d*	7.00 *d*	6.94 *d*	6.78 *d*	6.99 *dd*	6.92 *dd*	7.06 *dd*

* Typical coupling constants: *J*(H-1/Me-1) 6.3 Hz, *J*(H-3/Me-3) 6.3 Hz, *J*(H-3/H-4a) 10.2 Hz, *J*(H-3/H-4e) 2.8 Hz, *J*(H-4a/H-4e) −15.7 Hz, *J*(H-6′/H-7′) 7.9 Hz, *J*(H-6′/H-8′) 0.9 Hz, *J*(H-7′/H-8′) 8.4 Hz.

† Solvent $CDCl_3$–CD_3OD (19:1).

Table 2. ^{13}C chemical shifts of compounds **1**–**7** (solvent: $CDCl_3$)

C	1*	2*†	3*†	4	5	6	7
1	158.0	165.8	165.8	166.1	57.4	57.3	57.9
1-Me	27.8	23.5	23.5	26.8	22.1	22.1	22.8
2-Me	—	—	—	—	40.9	40.9	41.2
3	150.0	46.6	46.5	50.2	55.1	55.0	55.6
3-Me	23.4	18.1	18.0	20.5	20.6	21.1	20.5
4	114.5	32.3	32.2	31.5	38.8	39.4	37.9
4a	*140*	138.6	138.6	141.1	137.5‡	136.8‡	137.1
5	*114*	123.0	123.0	119.6	106.0	102.3	109.5
6	158.8	165.8	165.8	161.6	151.7	155.8	152.3
6-OMe	56.3	—	—	55.6‡	—	55.7	—
7	94.2	100.3	100.3	93.8	102.2	112.1	116.9
8	160.2	164.1	164.1	159.9	150.2	150.4	155.8
8-OMe	55.5	54.7	54.7	55.5‡	—	—	59.9
8a	114.0	101.8	101.6	111.6	118.4	119.5	124.1
1′	124.0	126.2	126.5	123.9	116.6§	119.8	119.7
2′	136.3	135.7	135.1	135.1	139.6	137.7	138.4
2′-Me	20.4	20.2	20.3	20.4	21.0	20.6	20.7
3′	109.1	109.1	109.2	108.9	108.6	108.9	109.1
4′	156.7	155.8	155.8	156.5	157.7	157.2	157.4
4′-OMe	56.4	56.2	56.2	56.5§	56.0	56.2	56.3
4′a	116.2	116.1	116.1	116.3	116.4§	116.5	116.4
5′	157.5	157.1	157.0	157.5	157.4	157.4	157.6
5′-OMe	56.5	56.2	56.1	56.4§	56.3	56.4	56.4
6′	105.5	105.5	105.2	105.5	106.0	105.8	105.7
7′	126.4	126.3	126.1	126.5	127.7	127.9	127.4
8′	118.6	118.3	118.4	117.5	117.5	118.0	117.9
8′a	137.1	136.4	136.7	136.5	136.9‡	136.9‡	136.4

* Chemical shifts of HMQC and HMBC cross peaks, respectively; values in italic face could only be estimated because of poorly resolved cross peaks.

† Solvent $CDCl_3$–CD_3OD (19:1).

‡,§ May be reversed in the column.

gave pure alkaloid. Crystals from $CHCl_3$–*n*-hexane, mp 233–236°, lit. [7] for (*P*)-isomer 238–240°, yield 0.003%. R_f 0.70 [silica gel, $CHCl_3$–MeOH (9:1)]. $[\alpha]_D^{22} -41.4°$ ($CHCl_3$; *c* 0.46), lit. [7] for (*P*)-isomer +51.0° ($CHCl_3$). CD ($CHCl_3$): $\Delta\varepsilon_{340} = -2.38$, $\Delta\varepsilon_{247} = +30.1$. EI-MS (70 eV) *m/z* (rel. int.): 417.1968 $[M]^+$ ($C_{26}H_{27}NO_4$, calcd 417.1940) (100).

Ancistrocladinine (**2**) *and hamatinine* (**3**). Flash CC of the crude mixt. of **2** and **3** over silica gel with $CHCl_3$–MeOH (9:1), followed by HPLC [Eurosil Bioselect 100-10 C8 column, 250 × 32 mm, 6.6 MPa, 20 ml min^{-1}, detection at 254 nm, elution with buffer soln–MeCN–MeOH (2.3:1:1), buffer soln: 0.1 M $(NH_4)H_2PO_4$–H_3PO_4 added to pH 3. Frs containing alkaloids were basified with aq. $KHCO_3$, MeCN and MeOH evapd *in vacuo*, the aq. soln extracted with $CHCl_3$–EtOH (2:1) and the solvents evapd *in vacuo*, gave a mixt. of **2** and **3** in a ratio of *ca* 1:1. Crystals from $CHCl_3$, mp 286–289°, yield 0.023%. R_f 0.53 [$CHCl_3$–*n*–hexane–$NHEt_2$ (8:2:1)]. EIMS (70 eV) *m/z* (rel. int.): 405.1922 $[M]^+$ ($C_{25}H_{27}NO_4$, calcd 405.1940) (100), 390.1715 $[M-Me]^+$ ($C_{24}H_{24}NO_4$, calcd 390.1705) (31), 202.0988 ($C_{13}H_{14}O_2$, calcd 202.0994) (28).

6-O-*Methylhamatinine* (**4**). Flash CC of crude **4** over silica gel with Me_2CO–MeOH (9:1) gave pure alkaloid. Amorphous, yield 0.20%. R_f 0.68 [*n*-hexane–$CHCl_3$–$NHEt_2$ (6:4:1)]. $[\alpha]_D^{22} +34.1°$ ($CHCl_3$; *c* 1.0). CD (MeOH). $\Delta\varepsilon_{227} = +18.1$, $\Delta\varepsilon_{211} = -25.7$. EI MS (70 eV) *m/z* (rel. int.): 419.2101 $[M]^+$ ($C_{26}H_{29}NO_4$, calcd 419.2096) (100), 404.1901 $[M-Me]^+$ ($C_{25}H_{26}NO_4$, calcd 404.1862) (39), 202.0977 ($C_{13}H_{14}O_2$) calcd 202.0994) (20).

6-O-*Demethyl*-7-epi-*ancistrobrevine D* (**5**). Flash CC of crude **5** over silica gel with $CHCl_3$–MeOH (19:1), followed by prep. silica gel TLC with *n*-hexane–$CHCl_3$–$NHEt_2$ (6:4:1), gave pure alkaloid. Crystals from $CHCl_3$–*n*–hexane, mp 229–232°, yield 0.04%. R_f 0.45 [*n*-hexane–$CHCl_3$–$NHEt_2$ (6:4:1)]. $[\alpha]_D^{22} +51.8°$ ($CHCl_3$; *c* 0.49). CD (MeOH): $\Delta\varepsilon_{235} = +12.7$, $\Delta\varepsilon_{211} = -9.3$. EI MS (70 eV) *m/z* (rel. int.): 407.2102 $[M]^+$ ($C_{25}H_{29}NO_4$, calcd 407.2096) (2), 392.1861 [M-Me]$^+$ ($C_{24}H_{26}NO_4$, calcd 392.1862) (100), 202.0968 ($C_{13}H_{14}O_2$, calcd 202.0994) (4).

7-epi-*Ancistrobrevine D* (**6**). Flash CC of crude **6** over silica gel with $CHCl_3$–MeOH (97:3) gave pure alkaloid. Crystals from $CHCl_3$–*n*-hexane, mp 177–178°, lit. [12] 166°C, lit. for *ent*-**6** [12] 166°; yield 0.02%. R_f 0.75 [*n*-hexane–$CHCl_3$–$NHEt_2$ (6:4:1)]. $[\alpha]_D^{22} +46.1°$ ($CHCl_3$; *c* 1.0), lit. [12] $[\alpha]_D^{20} +46.4°$; lit. for *ent*-**6** [12] −48.9°. CD (MeOH): $\Delta\varepsilon_{235} = +8.6$, $\Delta\varepsilon_{213} = -13.3$. EI MS (70 eV) *m/z* (rel. int.): 421.2241 $[M]^+$ ($C_{26}H_{31}NO_4$, calcd 421.2253) (4), 406.2008 $[M-Me]^+$ ($C_{25}H_{28}NO_4$, calcd 406.2018) (100), 203 (5), 202.0987 ($C_{13}H_{14}O_2$, calcd 202.0994) (2).

6-O-*Demethyl*-8-O-*methyl*-7-epi-*ancistrobrevine D* (**7**). Flash CC of crude **7** over silica gel with $CHCl_3$–MeOH (19:1), followed by prep. silica gel TLC with *n*-hexane–$CHCl_3$–$NHEt_2$ (6:4:1), gave pure alkaloid. Amorphous, yield 0.016%. R_f 0.47 [*n*-hexane–$CHCl_3$–$NHEt_2$ (6:4:1)]. $[\alpha]_D^{22} +51.8°$ ($CHCl_3$; *c* 0.71). CD (MeOH): $\Delta\varepsilon_{239} = +8.8$, $\Delta\varepsilon_{210} = -12.6$. EI MS (70 eV) *m/z* (rel. int.): 421.2240 $[M]^+$ ($C_{26}H_{31}NO_4$, calcd 421.2253) (1), 406.2005 $[M-Me]^+$ ($C_{25}H_{28}NO_4$, calcd 404.2018) (100), 203 (11), 202 (2).

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