Ambiguine Isonitriles, Fungicidal Hapalindole-Type Alkaloids from Three Genera of Blue-Green Algae Belonging to the Stigonemataceae

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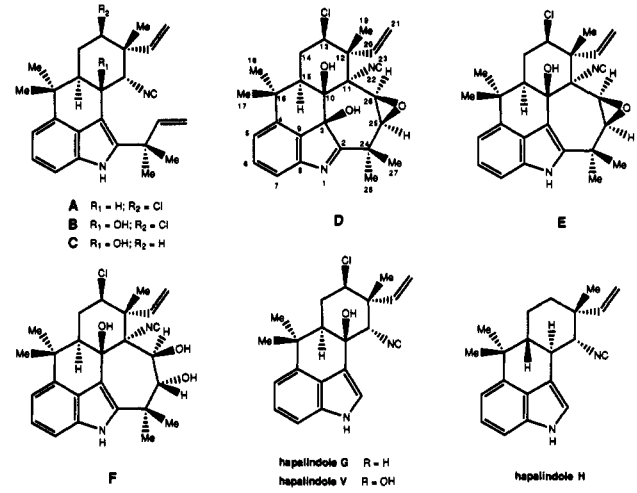
The isolation and structural elucidation of ambiguine isonitriles A–F from the terrestrial cyanophytes *Fischerella ambigua* UTEX 1903, *Hapalosiphon hibernicus* BZ-3-1, and *Westiellopsis prolifica* EN-3-1 are described. The structures of A–F were determined by spectroscopic methods and confirmed for indolenine D by X-ray crystallography. The new alkaloids are characterized by an additional isoprene unit attached to C-2 of the indole moiety. In ambiguines D–F the isoprenyl substituent is further fused to the isonitrile-bearing carbon.

Hapalindoles are moderately potent fungicides that were first found in the terrestrial blue-green alga *Hapalosiphon fontinalis*.[1] The most common one is hapalindole A, a chlorine and isonitrile-containing tetracyclic indole alkaloid that appears to be biosynthesized from precursors derived from tryptophan and geraniol pyrophosphate. Related compounds, the hapalindolinones, have been isolated from a *Fischerella* sp. which belongs to the same family, the Stigonemataceae (Stigonematales).[2] In examining other species of blue-green algae belonging to the Stigonemataceae for fungicidal activity, the extracts of three species, viz. *F. ambigua* (Nageli) Gomont (UTEX 1903), *H. hibernicus* W. & G. S. West (UH isolate BZ-3-1), and *Westiellopsis prolifica* Janet (UH isolate EN-3-1) inhibited the growth of five test fungi, viz. *Aspergillus oryzae*, *Candida albicans*, *Penicillium notatum*, *Saccharomyces cerevisiae*, and *Trichophyton mentagrophytes*, in a soft-agar disc-diffusion assay (250 μg, 10–22-mm zones of inhibition). The algae were mass cultivated and the extracts subjected to successive gel filtration, reversed-phase column chromatography, and normal-phase thin-layer chromatography to obtain a new series of fungicidal hapalindole-related alkaloids, the ambiguines (Table I). Six ambiguine isonitriles (A–F) and two known hapalindoles G and H were isolated from *F. ambigua*. Two ambiguine isonitriles were isolated from each of the other two cyanophytes, viz. A and E from *H. hibernicus* and D and E from *W. prolifica*.

Ambiguine A Isonitrile. The field-desorption mass spectrum of A exhibited a 3:1 molecular ion cluster at m/z 406/408, and a high-resolution mass measurement of the MH^+ ion in the FAB mass spectrum, coupled with NMR information, established the elemental composition $C_{26}H_{31}ClN_2$. A exhibited a typical indole UV spectrum [λ_{max} nm (ϵ) 225 (32 400), 282 (7600), sh 295 (6500)] and IR and ^{13}C NMR peaks [ν_{max} 2142 cm^{-1}; δ_c 158.6] characteristic of an isonitrile. Inspection of the ^1H and ^{13}C NMR data strongly suggested that A was hapalindole G substituted



at C2 with a 1,1-dimethyl-2-propenyl group. The ^1H NMR spectrum of A showed the same signals as hapalindole G, but with somewhat different chemical shifts (Table II). The signal for a proton on C2 of the indole moiety, however, was absent, and additional signals could be seen for the presence of a second vinyl group and a second *gem*-dimethyl group. Most important were the coupling constants associated with the six signals in the 1.9–4.7 ppm region which were consistent only with the presence of a $CH_{ax}CH_{ax}H_{eq}CH_{ax}CH_{ax}CH_{eq}$ segment in a cyclohexane ring in A. The isocyano group had to be attached to the right side of this segment since the CH_{eq} signals (δ_C 66.2; δ_H 4.67) showed coupling to the isonitrile ^{14}N. The chloro group was therefore connected to the left side of the segment since the CH_{ax} chemical shifts (δ_C 62.8; δ_H 4.41) agreed with its placement here. Finally, HMBC and NOESY experiments confirmed the proposed structure; for example, (1) couplings between the C20 carbon and the protons on C13, C19, and C21 and NOEs between the C19 methyl protons and the protons on C10, C11, C14 (axial only), C20, and 21 (*Z* only) agreed with the placement of an equatorial vinyl group and an axial methyl group on C12, (2) couplings between the C16 carbon and the protons on C5, C14, C15, C17, and C18 and NOEs between the C18 methyl protons and the protons on C5, C14 (equatorial only), C15, and C17 established the presence of a *gem*-dimethyl group between C15 of the cyclohexane ring and C4 of the indole, and (3) couplings between C2 and the protons on N1, C10, C25, C27, and C28 and NOEs between H1 and the protons on C27 and C28 were consistent with the presence of a 1,1-dimethyl-2-propenyl group on C2 and the attachment

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Table I. MIC Values (μg/mL) of Ambiguine Isonitriles A–F, Hapalindoles G and H, and Two Clinically Used Fungicides Against Test Organisms in Vitro

compd	*C. albicans*	*T. mentagrophytes*	*A. fumigatus*
A	2.5[a,b]	10;[a] >20[b]	80[a,c]
B	1.25[a,b]	>80;[a] 2.5[b]	20[a,c]
C	2.5,[a] 1.25[b]	>80;[a] 0.625[b]	>80[a,c]
D	1.25[a,b]	>80;[a] 0.625[b]	>80[a,c]
E	5.0;[a] 2.5[b]	5;[a] 2.5[b]	>80[a,b]
F	1.25[a,b]	>80;[a] 1.25[b]	>80[a,c]
G	10.0[b]	2.5[b]	
H	10.0[b]	1.25[b]	
amphotericin B	0.312;[a] 0.156[b]		1.25[a,c]
tolnaftate		<0.02[a,b]	

[a] Tested in Sabouraud dextrose broth. [b] Tested in RPMI broth supplemented with 10% fetal calf serum. [c] Not tested in RPMI.

Table II. ^{1}H NMR Data for Ambiguine Isonitriles A–F and Hapalindoles G and V in $CDCl_3$

	A[a]	B[a]	C[a]	D[b]	E[b]	F[c]	G[d]	V[d]
1	8.03	8.18	8.15		7.99	8.08	8.04	8.14
2							6.89	7.07
5	7.00	7.07	7.06	7.12	7.06	7.08	7.04	7.10
6	7.12	7.17	7.15	7.31	7.19	7.15	7.18	7.24
7	7.13	7.15	7.13	7.32	7.09	7.21	7.20	7.18
10	3.22						3.32	
11eq	4.67	4.68	4.49				4.24	4.11
13ax	4.41	4.41	1.93	4.09	4.45	4.53	4.43	4.40
13eq			1.64					
14ax	2.44	2.53	2.11	2.47	2.62	2.61	2.41	2.51
14eq	1.94	2.30	1.88	2.17	2.33	2.32	2.01	2.29
15	2.22	2.41	2.21	1.64	2.34	2.46	2.11	2.29
17	1.05	1.23	1.21	1.39	1.40	1.37	1.17	1.36
18	1.53	1.54	1.51	1.35	1.51	1.53	1.52	1.52
19	1.34	1.53	1.42	1.68	1.74	1.84	1.39	1.57
20	6.07	6.04	5.94	5.96	6.16	6.08	6.14	6.09
21*E*	5.34	5.31	5.08	5.53	5.59	5.54	5.39	5.36
21*Z*	5.27	5.26	5.06	5.37	5.44	5.43	5.34	5.33
25	6.21	6.33	6.36	3.11	3.13	4.22		
26	5.21 (*E*)	5.28 (*E*)	5.28 (*E*)	3.55	3.77	4.65		
	5.24 (*Z*)	5.36 (*Z*)	5.37 (*Z*)					
27	1.52	1.62	1.63	1.72	1.67	1.43		
28	1.58	1.64	1.67	1.73	1.62	1.60		
3-OH				2.91				
10-OH		1.67	1.62	4.26	3.69	3.61		
24-OH						2.55		
25-OH						4.01		

[a] $J_{H,H}$ (Hz) for A: 5,6 = 7.4; 5,7 = 0.8; 6,7 = 7.9; 10,11 = 2.3; 10,15 = 11.2; 13,14ax = 12.5; 13,14eq = 4.4; 14ax,14eq = −13.0; 14ax,15 = 12.5; 14eq,15 = 2.8; 20,21*E* = 11.1; 20,21*Z* = 17.6; 21*E*,21*Z* = 0, 25,26*E* = 10.6; 25,26*Z* = 17.6; 26*E*,26*Z* = 0.9. All of the coupling constants for B and C are within ±0.5 Hz of these values (see Experimental Section). [b] $J_{H,H}$ (Hz): 25,26 = 4.3 for D and 4.5 for E. All of the other coupling constants for D and E are within ±0.5 Hz of the values for A (see Experimental Section). [c] $J_{H,H}$ (Hz) for F: 25,26 = 1.8; 25,OH = <1; 26,OH = 5.0. All of the other coupling constants are within ±0.5 Hz of the values for A (see Experimental Section). [d] $J_{H,H}$ (Hz) for G: 1,2 = 2.2; 2,10 = 1.6; 5,6 = 7.2; 5.7 = 0.6; 6,7 = 8.2; 10,11 = 3.1; 10,15 = 10.4; 13,14ax = 11.9; 13,14eq = 4.5; 14ax,14eq = −12.5; 14ax,15 = 11.9; 14eq,15 = 3.0; 20,21*E* = 10.9; 20,21*Z* = 17.4; 21*E*,21*Z* = 0.5. Most coupling constants for V are within ±0.5 Hz of the values for G. The 10-OH signal for V was not observed.

of C10 of the cyclohexane ring to C3 of the indole.

Ambiguine Isonitriles B and C. Arguments similar to those presented above for the structure of A were used to deduce the structures of B and C.

Mass spectrometry coupled with NMR analysis established the molecular formula for B as $C_{26}H_{31}ClN_2O$, differing from A's by the addition of an oxygen atom. Compared with the ^{1}H NMR spectrum of A, B's lacked a signal for H10 (the only major difference if one ignores the differences in chemical shift) but possessed a signal at δ 1.67 for a hydroxyl proton. On this basis, we conjectured that B might simply by A substituted at C10 with an OH group. This proposed structure was supported by two- and three-bond HMBC correlations between the OH proton signal and the C3, C10, C11, C15 carbon signals. The OH group on C10 had to be axial since the chemical shifts for the axial proton on C14 and the protons of the axial methyl groups on C12 and C16 were shifted downfield significantly and NOEs could be observed between the OH proton and the protons on C11, C14 (axial only), C19, C25, and C26 (*E* only). Isonitrile B was therefore hapalindole V substituted at C2 with a 1,1-dimethyl-2-propenyl group.

The elemental composition of C was found to be $C_{26}H_{32}N_2O$ by mass spectrometry and NMR analysis. Comparison of NMR data (Table II) suggested that C was the deschloro derivative of B. COSY data and coupling constants (Table II) clearly indicated that C13 to C15 was a $CH_2CH_2\dot{C}H_{ax}$ unit. Again, HMBC and NOESY experiments established that the OH on C10 was axially oriented.

Ambiguine D Isonitrile. NMR analysis indicated that D possessed 26 carbons and 29 hydrogens. Twenty-six signals could be observed in the ^{13}C NMR spectrum for five methyl, two methylene, eight methine, and 11 quaternary carbons. In a HMQC experiment the 15 protonated-carbon signals correlated with 17 of the 19 proton signals in the ^{1}H NMR spectrum. The two remaining proton signals (2.91 and 4.26 ppm) were assigned to two exchangeable protons. Since the FAB mass spectrum showed a 3:1 protonated molecular ion cluster at *m/z* 453/455, D had to have single chlorine atom along with two nitrogen atoms and three oxygen atoms to account for the multiplicity of the ion cluster and the remaining mass units. A high-resolution mass measurement confirmed the molecular formula $C_{26}H_{29}ClN_2O_3$ which required 13 units of unsaturation.

Only 10 signals were present in the 100–200 ppm region of the ^{13}C NMR spectrum. Six peaks were assigned to the carbons of a trisubstituted benzenoid ring, two more to the carbons of a vinyl group, and another to an isonitrile carbon. The remaining signal (δ 187.4) was consistent with an imino carbon and suggested that D might be an indolenine. Compound D did not exhibit the typical UV spectrum of an indole, and the NMR spectra lacked signals for an sp^2-type C3 and an indole NH. Also consistent with an indolenine structure were the lower field chemical shifts for H5, H6, and H7 (Table II). Since only seven of the 13 units of unsaturation could be accounted for by π-bonds, D had to be hexacyclic.

Two of the oxygens were in hydroxyl groups (δ_H 2.91 and 4.26) attached to quaternary carbons (δ_C 83.0 and 77.7). The third oxygen was in a disubstituted epoxide ring (δ_H 3.11 and 3.55; δ_C 64.6 and 60.3).

It was obvious from comparison of NMR data, especially coupling constants (Table II) and HMBC/NOESY correlations (see Experimental Section), that indolenine D had essentially the same structure as indole B from C4 to C21, differing only by the absence of a proton on C11. The H15 proton, however, had an appreciably different chemical shift (1.64 ppm) compared with other ambiguines and the hapalindoles (2.11–2.46 ppm). This could only be explained after the structure of D had been determined (see below). The hydroxyl group on C10 was axial since NOEs could be seen between the OH proton and the axial methyl groups on C12 and C16. A hydroxyl group was also present on C3 and syn to the OH on C10 since (1) NOEs were visible between the two OH protons and between the OH proton on C3 and the axial methyl group on C16 and (2) HMBC correlations were found between the OH proton

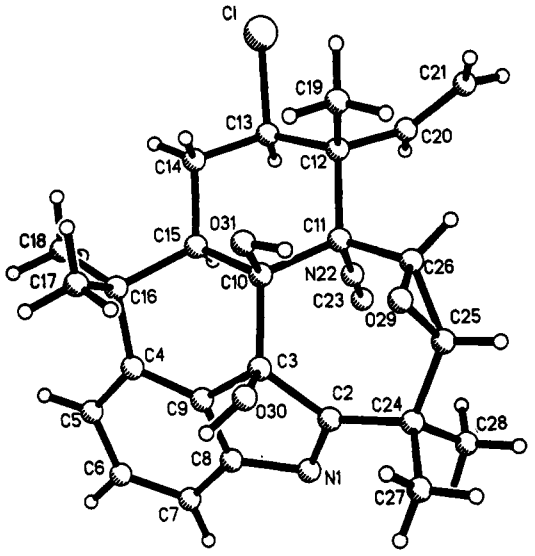

Figure 1.

signal and the C2, C3, C9, and C10 signals. As in indoles A, B, and C, a *gem*-dimethyl group was attached to C2 since HMBC correlations were observed between the protons of the two methyl groups (1.72 and 1.73 ppm) and C2. The only atoms remaining were those of a 1,2-disubstituted epoxide ring which had to be connected to the *gem*-dimethyl group and C11 since HMBC correlations were found between H26 and C10, C11, C12, C24, and C25 and between H25 and C24, C27, and C28. In D, therefore, C26 of the five-carbon substituent on C2 of A–C was fused to C11 and an epoxide oxygen attached to C25 and C26. Finally, we could conclude that the protons on the epoxide ring were oriented as depicted in D on the basis of NOEs between (1) H25 and the protons on C26 and C27 and (2) H26 and the protons on C19, C21 (*E* only), and C25.

Inspection of a Dreiding model of indolenine D revealed that H15 was located above the plane of the indole system, resulting in shielding and a diamagnetic shift of its proton signal relative to the chemical shifts of H15 in other ambiguine isonitriles and the hapalindoles in general.

The gross structure and relative stereochemistry of D were confirmed by X-ray crystallography. Figure 1 is a computer-generated perspective drawing of the final X-ray model.

Ambiguine E Isonitrile. The gross structure and relative stereochemistry of E was solved using essentially the same kind of arguments as those used for the structure elucidation of D. High-resolution mass spectrometry, coupled with NMR analysis, revealed an elemental composition of $C_{26}H_{29}ClN_2O_2$ for E, differing from D's formula by one less oxygen. Inspection of the ^1H and ^{13}C NMR spectra, in particular those from HMBC and NOESY experiments, indicated that the structure of E was similar to the one for D. In the ^1H NMR spectrum of E, however, the 3-OH proton signal was missing, but an indole NH signal was present at 7.99 ppm. The indole system was also established by the UV spectrum.

Ambiguine F Isonitrile. The FD and FAB mass spectra showed overlapping 3:1 M^+ and MH^+ ion clusters at m/z 454/456 and 455/457, and high-resolution FABMS agreed with the molecular formula $C_{26}H_{31}ClN_2O_3$. The UV spectrum and a NH signal at 8.08 ppm in the ^1H NMR spectrum were consistent with an indole. An examination of the NMR data showed that F was similar in structure to E, the major difference being that the epoxide ring was missing and replaced by a trans diol unit. The ^1H NMR spectrum displayed methine proton signals at 4.22 (H25) and 4.65 (H26) ppm which were vicinally coupled to each other (1.8 Hz) and to hydroxyl proton signals at 2.55 (*J* not determined) and 4.01 ppm (5 Hz), respectively. An HMBC experiment proved that this 25,26-diol unit was connected to C11 and C24, since cross peaks were present between the H26 signal and the signals for C10, C11, C12, C24, and C25. A NOESY experiment established that the OH group on C26 was pseudoaxial and syn to the methyl group on C12 and the OH group on C10, since NOEs could be seen between (1) and the 26-OH proton and the protons of 10-OH, the axial methyl group on C12 (C19), and the *pro-R* methyl group on C24 (C27) and (2) H26 and the *Z* proton on C21. The NOESY experiment also suggested that the OH group on C25 was pseudoaxial and trans to the OH group on C26 because NOEs could be seen between (1) H26 and H25 (agrees with small coupling constant), (2) the C27 methyl protons and the 10-OH and 26-OH protons, indicating that this methyl group was pseudoaxial with respect to these hydroxyl groups, and (3) the C28 methyl protons and the NH and H25 protons only (not 25-OH).

In the ^1H NMR spectrum the 10-OH and 26-OH signals were found to be sharper and at lower field compared with the broader 25-OH signal, presumably because of intramolecular hydrogen bonding between the former hydroxyl groups and consequently slower proton exchange with the small amount of H_2O in the solvent. In the NOESY experiment, the 25-OH signal showed a large cross peak with the H_2O signal at 1.63 ppm whereas the 10-OH and 26-OH signals exhibited small cross peaks to the H_2O signal, much smaller cross peaks than the ones denoting NOEs. The 25-OH signal showed small cross peaks to the 10-OH and 26-OH signals reflecting the proton exchange via H_2O; however, cross peaks from the 10-OH and 26-OH signals to the 25-OH signal were not observed.

Absolute Stereochemistry. The X-ray crystallographic study reported in this paper did not lead to the absolute stereochemistry of ambiguine D isonitrile. However, the CD spectra of ambiguine isonitriles A, B, C, E, and F and hapalindole G are roughly similar in shape (all six spectra show a negative minimum at 228–235 nm and a generally positive maximum at 220–225 nm), suggesting that the absolute stereochemistry of the ambiguines and the hapalindoles is probably the same. Since the absolute stereochemistry of hapalindole G is known,[9] the ambiguines may have the total structures depicted in the drawings.

Experimental Section

General. ^1H and ^{13}C NMR chemical shifts are referenced to solvent peaks: δ_H 7.26 (residual $CHCl_3$) and δ_C 77.0 for $CDCl_3$ and δ_H 3.30 (residual CHD_2OD) and δ_C 49.0 for methanol-d_4. Nonprotonated methine, methylene, and methyl carbons were identified by comparison of refocused INEPT and broad-band decoupled ^{13}C NMR spectra. Homonuclear ^1H connectivities were determined with COSY experiments, and heteronuclear ^1H–^{13}C connectivities were determined by HMQC[3] and HMBC[4] experiments. Exchangeable proton signals, which showed no carbon correlations in the HMQC experiment, were further identified by their chemical shift sensitivity to sample concentration and temperature. Homonuclear ^1H NOEs were obtained by difference NOE experiments using a 3-s irradiation period and NOESY spectra. Optical rotations were determined in a 5-cm microcell. R_f values pertain to TLC on silica gel with 3:1 toluene–EtOAc.

Culture Conditions. *F. ambigua* (Nageli) Gomont was obtained from the University of Texas Collection (UTEX 1903). Cultures of UTEX 1903 were grown in liquid medium (modified

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A_3M_7) in 20-L glass bottles using the procedure described for *H. fontinalis*.[1b] After 25–30 days, the axenic alga was harvested by filtration and freeze-dried. Yields of lyophilized alga were typically 0.39 g/L.

Mass cultivation of *H. hibernicus* W. & G. S. West (UH strain BZ-3-1) and *W. prolifica* Janet (UH strain EN-3-1) was carried out as described elsewhere.[5-7]

Isolation. Lyophilized *F. ambigua* UTEX 1903 (83 g) was extracted with CH_2Cl_2/2-propanol. The extract (4.07 g) was chromatographed on a 1.1 m × 5 cm column of Sephadex LH-20 using MeOH as the eluant. The fractions that were active against *C. albicans* by disk assay were combined into two pools and evaporated. The residue from pool 1 (242 mg) was dissolved in 50 mL of MeOH and filtered through 10 g of C18 silica. The filtrate (202 mg) was then chromatographed on a 30 cm × 2.5 cm column of C18 silica (Chromegabond M, ES Industries) using a linear gradient of 80–100% MeOH in water. The fungicidal fractions from this column were combined and evaporated to give A (11.3 mg, R_f 0.83) and a residue (38 mg). Further purification of the residue by preparative TLC on silica gel with 3:1 toluene/EtOAc gave D (21 mg, R_f 0.47) and a mixture of B (R_f 0.75) and C (R_f 0.77). The mixture was separated into pure B (4 mg) and C (7 mg) by preparative silica TLC with 3:2 hexane/dioxane. The residue from pool 2 (338 mg) was chromatographed in a similar manner as the pool 1 material to give E (25 mg, R_f 0.67) and F (8.5 mg, R_f 0.21) along with small amounts of hapalindoles G (10.5 mg) and H (12.5 mg, $[\alpha]_D$ +217.7°).

Using a similar procedure, ambiguine isonitriles A (138 mg) and E (180 mg) were isolated as the major fungicides from the extract (7:3 EtOH/H_2O, 4.72 g) of lyophilized *H. hibernicus* BZ-3-1 (25 g) and ambiguine isonitrile E (32 mg) was isolated as the major fungicide from the extract (7:3 EtOH/H_2O, 3.5 g) of lyophilized *W. prolifica* EN-3-1 (17.3 g). Minor amounts of other hapalindole-type compounds were present, but ambiguine isonitrile D from *W. prolifica* EN-3-1 was the only one that was identified conclusively by ^{1}H NMR and TLC analysis.

Ambiguine A isonitrile: white needles (hexane–CH_2Cl_2), mp >300 °C dec; $[\alpha]_D$ −37.0° (MeOH, *c* 0.1); CD (MeOH) λ nm [θ] 225 (20 800), 236 (−11 000), sh 255 (−6800), 280–292 (−1300), 300–310 (−4700); UV (MeOH) λ_{max} nm (ε) 225 (32 400), 282 (7600), sh 295 (6500); IR (KBr) ν_{max} 3620, 3487, 2975, 2142, 1602, 1467, 1445, 1231, 1046, 924 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz; assignment; *^{1}H NOE's*) 8.03 (br s; 1-NH; *7, 27, 28*), 7.00 (dd, *J* = 7.4 and 0.7 Hz; H-5; *6, 18*), 7.12 (m, *J* = 7.9 and 7.4 Hz; H-6; *5, 7*), 7.13 (m, *J* = 7.9 and 0.7 Hz; H-7; *1-NH, 6*), 3.22 (dd, *J* = 11.2 and 2.3 Hz; H-10; *11, 14ax, 17, 19*), 4.67 (br d, *J* = 2.3 Hz; H-11; *10, 19, 25, 26Z, 27, 28*), 4.41 (dd, *J* = 12.5 and 4.4 Hz; H-13; *14eq, 15*), 2.44 (ddd, *J* = −13.0, 4.4, and 2.8 Hz; H-14eq; *13, 14ax, 15, 18*), 1.94 (q, |*J*| = 13.0 Hz; H-14ax; *10, 14eq, 17, 19*), 2.22 (ddd, *J* = 12.5, 11.2 and 2.8 Hz; H-15; *13, 14eq, 18*), 1.05 (s; H_3-17; *10, 14ax, 18*), 1.53 (s; H_3-18; *5, 14eq, 15, 17*), 1.34 (s; H_3-19; *10, 11, 14ax, 20, 21Z*), 6.07 (dd, *J* = 17.6 and 11.1 Hz; H-20; *13, 19, 21Z, 21E*), 5.27 (d, *J* = 17.6 Hz; H-21Z; *19, 20*), 5.34 (d, *J* = 11.1 Hz; H-21E; *20*), 6.21 (dd, *J* = 17.6 and 10.6 Hz; H-25; *11, 26Z, 26E, 27, 28*), 5.24 (dd, *J* = 17.6 and 0.9 Hz; H-26Z; *11, 25, 27, 28*), 5.21 (dd, *J* = 10.6 and 0.9 Hz; H-26E; *25*), 1.52 (s; H_3-27;[8] *1-NH, 11, 25, 26Z*), 1.58 (s; H_3-28;[8] *1-NH, 11, 25, 26Z*); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, position; *^{1}H HMBC*) 137.0 (s, C2; *1-NH, 10, 25, 27, 28*), 105.4 (s, C3; *1-NH, 10, 11*), 139.7 (s, C4; *5, 6, 7, 17, 18*), 112.6 (d, C5; *6, 7*), 122.2 (d, C6; *none*), 107.8 (d, C7; *5*), 132.2 (s, C8; *1-NH, 5, 6, 7*), 127.0 (s, C9; *1-NH, 5, 6, 7*), 34.5 (d, C10; *11, 14eq, 14ax, 15*), 66.2 (d, C11; *15, 19, 20*), 44.8 (s, C12; *10, 11, 13, 14eq, 14ax, 19, 20, 21Z, 21E*), 62.8 (d, C13; *11, 14eq, 14ax, 19, 20*), 33.0 (t, C14; *10, 13, 15*), 44.6 (d, C15; *10, 11, 14eq, 14ax, 17, 18*), 36.5 (s, C16; *5, 14eq, 14ax, 15, 17, 18*), 24.8 (q, C17; *15, 18*), 23.9 (q, C18; *17*), 16.2 (q, C19; *11, 13, 20*), 142.4 (d, C20; *13, 19, 21Z, 21E*), 115.9 (t, C21; *none*), 158.6 (s, C23; *11*), 38.7 (s, C24; *25, 26Z, 26E, 27, 28*), 146.2 (d, C25; *26Z, 27, 28*), 113.1 (t, C26; *none*), 29.3 (q, C27;[8] *25, 28*), 27.6 (q, C28;[8] *25, 27*); FDMS *m/z* 406/408 (3:1 M^+ ion cluster); FABMS *m/z* 407/409 (3:1 MH^+ ion cluster), 380/382 (MH^+ − HCN); HRFABMS *m/z* 407.2207 ($C_{28}H_{32}ClN_2$, Δ +4.7 mmu), 380.2112 ($C_{25}H_{31}ClN$, Δ +3.3 mmu).

Ambiguine B isonitrile: amorphous solid; $[\alpha]_D$ −44.3° (MeOH, *c* 0.1); CD (MeOH) λ nm [θ] 224 (−7000), 229 (−25 000), 242 (−8700), 255 (−8900), 291 (−5000), 295 (−5300); UV (MeOH) λ_{max} nm (ε) 223 (40 700), 281 (9400), 291 (7700); IR (KBr) ν_{max} 3486, 2976, 2144, 1442, 1227, 999, 936 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz; assignment; *^{1}H NOE's*) 8.18 (br s; 1-NH; *7, 27, 28*), 7.07 (dd, *J* = 7.3 and 0.8 Hz; H-5; *6, 18*), 7.17 (m, *J* = 8.1 and 7.3 Hz; H-6; *5, 7*), 7.15 (m, *J* = 8.1 and 0.8 Hz; H-7; *1-NH, 6*), 4.68 (s; H-11; *10-OH, 19, 20, 21Z, 25, 26Z, 26E, 27, 28*), 4.41 (dd, *J* = 12.2 and 4.1 Hz; H-13; *14eq, 15, 20, 21Z*), 2.30 (ddd, *J* = −13.1, 4.1, and 2.3 Hz; H-14eq; *13, 14ax, 15, 18*), 2.53 (q, |*J*| = 12.7 Hz; H-14ax; *11, 14eq, 17, 19*), 2.41 (ddd, *J* = 12.7 and 2.3 Hz; H-15; *13, 14eq, 18*), 1.23 (s; H_3-17; *10-OH, 14ax, 18*), 1.54 (s; H_3-18; *5, 14eq, 15, 17*), 1.53 (s; H_3-19; *10-OH, 11, 14ax, 20, 21Z*), 6.04 (dd, *J* = 17.6 and 10.9 Hz; H-20; *11, 13, 19, 21Z, 21E*), 5.26 (d, *J* = 17.6 Hz; H-21Z; *11, 13, 19, 20, 21E*), 5.31 (d, *J* = 10.9 Hz; H-21E; *20, 21Z*), 6.33 (dd, *J* = 17.6 and 10.4 Hz; H-25; *10-OH, 11, 26Z, 26E, 27, 28*), 5.36 (d, *J* = 17.6 Hz; H-26Z; *10-OH, 11, 25, 26E, 27, 28*), 5.28 (d, *J* = 10.4 Hz; H-26E; *11, 25, 26Z*), 1.62 (s; H_3-27;[8] *1-NH, 11, 25, 26Z, 28*), 1.64 (s; H_3-28;[8] *1-NH, 11, 25, 26Z, 27*), 1.67 (s; 10-OH; *11, 14ax, 19, 25, 26E*); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, position; *^{1}H HMBC*) 138.8 (s, C2; *1-NH 25, 27, 28*), 111.4 (s, C3; *1-NH, 10-OH, 11*), 139.8 (s, C4; *6, 17, 18*), 114.4 (d, C5; *6, 7*), 122.9 (d, C6; *none*), 107.6 (d, C7; *5*), 131.8 (s, C8; *1-NH, 6*), 125.4 (s, C9; *1-NH, 5, 7*), 73.8 (s, C10; *11, 14eq, 14ax, 15, 10-OH*), 68.5 (d, C11; *15, 19, 20, 10-OH*), 45.3 (s, C12; *11, 13, 14eq, 14ax, 19, 20, 21Z, 21E*), 63.9 (d, C13; *11, 14eq, 14ax, 15, 19, 20*), 29.1 (t, C14; *13, 15*), 48.0 (d, C15; *10-OH, 11, 13, 14eq, 14ax, 17, 18*), 36.7 (s, C16; *5, 14eq, 14ax, 15, 17, 18*), 26.5 (q, C17; *15, 18*), 27.1 (q, C18; *15, 17*), 18.5 (q, C19; *11, 13, 20*), 144.2 (d, C20; *13, 19, 21Z*), 115.5 (t, C21; *none*), 159.0 (s, C23; *11*), 39.0 (s, C24; *25, 26Z, 26E, 27, 28*), 146.8 (d, C25; *26Z, 27, 28*), 112.7 (t, C26; *none*), 28.9 (q, C27;[8] *25, 28*), 27.6 (q, C28;[8] *25, 27*); FDMS *m/z* 421/423 (3:1 $[M - H]^+$ ion cluster); FABMS *m/z* 423/425 (3:1 MH^+ ion cluster); HRFABMS *m/z* 423.2197 ($C_{26}H_{32}ClN_2O$, Δ +0.6 mmu).

Ambiguine C isonitrile: amorphous solid; $[\alpha]_D$ −9.5° (MeOH, *c* 0.1); CD (MeOH) λ nm [θ] 223 (12 600), 230 (−21 200), 241 (−4100), 251 (−6700), sh 270 (−3400), sh 282 (−2400), 291 (−2100), 295–305 (−3600); UV (MeOH) λ_{max} nm (ε) 223 (36 000), 281 (8400), 291 (6800); IR (KBr) ν_{max} 3486, 2970, 2146, 1700, 1603, 1441, 999, 935 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ (multiplicity, *J* in Hz; assignment; *^{1}H NOE's*) 8.15 (br s; 1-NH; *7, 27, 28*), 7.06 (dd, *J* = 7.4 and 0.6 Hz; H-5; *6, 18*), 7.15 (dd, *J* = 8.1, and 7.4 Hz; H-6; *5, 7*), 7.13 (dd, *J* = 8.1 and 0.6 Hz; H-7, *1-NH, 6*), 4.49 (s; H-11; *10-OH, 19, 20, 25, 26Z, 26E, 27, 28*), 1.93 (ddd, *J* = −13.1, 12.7, and 3.6 Hz; H-13; *13eq, 14eq*), 1.64 (ddd, *J* = −13.1, 3.6, and 3.2 Hz; H-13; *13ax, 14eq*), 1.88 (dtd, *J* = −12.7, 3.6, and 2.3 Hz; H-14eq; *13ax, 13eq, 14ax, 15, 18*), 2.11 (qd, |*J*| = 13.0 and 3.2 Hz; H-14ax; *14eq, 17, 19*), 2.21 (dd, *J* = 12.7 and 2.3 Hz; H-15; *14eq, 18*), 1.21 (s; H_3-17; *14ax, 18*), 1.51 (s; H_3-18; *5, 14eq, 15, 17*), 1.42 (s; H_3-19; *11, 14ax, 20, 21Z*), 5.94 (dd, *J* = 17.6 and 10.9 Hz; H-20; *11, 19, 21Z, 21E*), 5.06 (d, *J* = 17.6 Hz; H-21Z; *19, 20, 21E*), 5.08 (d, *J* = 10.9 Hz; H-21E; *20, 21Z*), 6.36 (dd, *J* = 17.6 and 10.4 Hz; H-25; *11, 26Z, 26E, 27, 28*), 5.37 (dd, *J* = 17.6 and <1 Hz; H-26Z; *11, 25, 26E, 27, 28*), 5.28 (dd, *J* = 10.4 and <1 Hz; H-26E; *11, 25, 26Z*), 1.63 (s; H_3-27;[8] *1-NH, 11, 25, 26Z, 28*), 1.67 (s; H_3-28;[8] *1-NH, 11, 25, 26Z, 27*), 1.62 (s; 10-OH; *11*); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, position; *^{1}H HMBC*) 138.5 (s, C2; *1-NH, 25, 27, 28*), 112.6 (s, C3; *1-NH, 10-OH, 11*), 140.6 (s, C4; *5, 6, 15, 17, 18*), 114.2 (d, C5; *7*), 122.6 (d, C6; *5*), 107.3 (d, C7; *5*), 131.7 (s, C8; *1-NH, 5, 6*), 125.7 (s, C9; *1-NH, 5, 7*), 74.2 (s, C10; *10-OH, 11, 14eq, 14ax, 15*), 67.2 (d, C11; *10-OH, 15, 19, 20*), 40.6 (s, C12; *11, 13eq, 14eq, 14ax, 19, 20, 21Z, 21E*), 31.6 (t, C13; *11, 14eq, 14ax, 15, 19, 20*), 17.7 (t, C14; *13ax, 15*), 47.0 (d, C15; *10-OH, 11, 13ax, 14eq, 14ax, 17, 18*), 36.5 (s, C16; *5, 14eq, 15, 17, 18*), 26.6 (q, C17; *15, 18*), 27.0 (q, C18; *15, 17*), 24.1 (q, C19; *11, 13ax, 20*), 147.5 (d, C20; *11, 13ax, 19, 21Z*), 111.9 (t, C21; *none*), 157.0 (s, C23; *11*), 39.0 (s, C24; *25, 26Z, 26E, 27, 28*), 147.1 (d, C25; *26Z, 27, 28*), 112.6 (s, C26; *none*), 28.9 (q, C27;[8] *25, 28*), 27.8 (q, C28;[8] *25, 27*); FDMS *m/z* 388 (M^+);

(5) Patterson, G. M. L.; Baldwin, C. L.; Bolis, C. M.; Caplan, F. R.; Karuso, H.; Larsen, L. K.; Levine, I. A.; Moore, R. E.; Nelson, C. S.; Tschappat, K. D.; Tuang, G. D.; Furusawa, E.; Furusawa, S.; Norton, T. R.; Raybourne, R. B. *J. Phycology* **1991**, *27*, 530–536.

(6) Prinsep, M. R.; Caplan, F. R.; Moore, R. E.; Patterson, G. M. L.; Honkanen, R. E.; Boynton, A. L. *Phytochemistry*, in press.

(7) Prinsep, M. R.; Moore, R. E.; Levine, I. R.; Patterson, G. M. L. *J. Nat. Prod.*, in press.

(8) Methyl assignments may be reversed.

(9) Moore, R. E.; Yang, X.-Q. G.; Patterson, G. M. L. *J. Org. Chem.* **1987**, *52*, 3773–3777.

FABMS m/z 389 (MH^+); HRFABMS m/z 389.2590 ($C_{26}H_{33}N_2O$, Δ +0.3 mmu).

Ambiguine D isonitrile: crystals ($MeOH/H_2O$), mp >300 °C dec; $[\alpha]_D$ −30.3° (MeOH, c 0.1); CD (MeOH) λ nm [θ] 228 (−30 200), 248 (1000), 272 (−11 000), 303 (18 100); UV (MeOH) λ_{max} nm (ϵ) 227 (13 900), 301 (2170); IR (KBr) ν_{max} 3500, 3007, 2977, 2933, 2123, 1391, 1371, 1188, 1043, 1003, 937 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (multiplicity, J in Hz; assignment; *NOE's*) 7.12 (dd, J = 7.3 and 0.7 Hz; H-5; *6, 18*), 7.31 (m, J = 7.8 and 7.3 Hz; H-6; *5, 7*), 7.32 (m, J = 7.8 and 0.7 Hz; H-7; *6*), 4.09 (dd, J = 12.3 and 3.9 Hz; H-13; *14eq, 15, 20*), 2.17 (ddd, J = −12.8, 3.9, and 2.7 Hz; H-14eq; *13, 14ax, 15, 18*), 2.47 (q, $|J|$ = 12.8 Hz; H-14ax; *14eq, 17, 19*), 1.64 (br ddd, J = 12.8, 2.7 and 1.2 Hz; H-15; *13, 14eq, 18*), 1.39 (s; H_3-17; *3-OH, 10-OH, 14ax*), 1.35 (s; H_3-18; *5, 14eq, 15*), 1.68 (s; H_3-19; *10-OH, 14ax, 21Z, 26*), 5.96 (dd, J = 17.3 and 11.1 Hz; H-20; *13, 21Z, 21E*), 5.37 (d, J = 17.3 Hz; H-21*Z*; *19, 20, 21E, 26*), 5.53 (d, J = 11.1 Hz; H-21*E*; *20, 21Z*), 3.11 (d, J = 4.3 Hz; H-25; *26, 27*), 3.55 (d, J = 4.3 Hz; H-26; *19, 21Z, 25*), 1.72 (s; H_3-27; *25*), 1.73 (s; H_3-28; *none*), 2.91 (s; OH on C-3; *10-OH, 17*), 4.26 (d, J = 1.2 Hz; OH on C-10; *3-OH, 17, 19*); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, position; *^1H HMBC*) 187.4 (s, C2; *3-OH, 25, 27, 28*), 83.0 (s, C3; *3-OH, 10-OH*), 147.1 (s, C4; *5, 6, 7, 15, 17, 18*), 120.0 (d, C5; *6, 7*), 130.7 (d, C6; *5*), 118.8 (d, C7; *5*), 152.0 (s, C8; *5, 6, 7*), 135.8 (s, C9; *3-OH, 5, 7*), 77.7 (s, C10; *3-OH, 10-OH, 14eq, 14ax, 26*), 68.1 (s, C11; *10-OH, 19, 20, 25, 26*), 51.2 (s, C12; *13, 14eq, 14ax, 19, 20, 21Z, 21E, 26*), 63.8 (d, C13; *14eq, 14ax, 15, 19, 20*), 29.0 (t, C14; *13, 15*), 53.3 (d, C15; *13, 14eq, 14ax, 17, 18, 10-OH*), 38.8 (s, C16; *5, 15, 17, 18*), 25.6 (q, C17; *15, 18*), 26.3 (q, C18; *17*), 13.9 (q, C19; *13, 20*), 140.5 (d, C20; *13, 19, 21Z*), 120.3 (t, C21; *none*), 164.5 (s, C23; *none*), 39.1 (s, C24; *25, 26, 27, 28*), 64.6 (d, C25; *26, 27, 28*), 60.3 (d, C26; *none*), 26.6 (q, C27; *25, 28*), 30.6 (q, C28; *25, 27*); FABMS m/z 453/455 (3:1 MH^+ ion cluster); HRFABMS m/z 453.1953 ($C_{26}H_{30}ClN_2O_3$, Δ −0.8 mmu).

Ambiguine E isonitrile: white needles (hexane–CH_2Cl_2); mp >300 °C dec; $[\alpha]_D$ −59.7° (MeOH, c 0.1); CD (MeOH) λ nm [θ] 220 (23 200), 231 (−13 400); UV (MeOH) λ_{max} nm (ϵ) 223 (36 000), 272 (7100), 279 (6800); IR (KBr) ν_{max} 3691, 3618, 2976, 2130, 1604, 1448, 1046, 944, 876 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (multiplicity, J in Hz; assignment; *NOE's*) 7.99 (br s; 1-NH; *7, 27, 28*), 7.06 (dd, J = 7.2 and 0.7 Hz; H-5; *6, 18*), 7.19 (dd, J = 8.1 and 7.2 Hz; H-6; *5, 7*), 7.09 (dd, J = 8.1 and 0.7 Hz; H-7; *1-NH, 6*), 4.45 (dd, J = 12.7 and 3.6 Hz; H-13; *14eq, 15, 20*), 2.33 (ddd, J = −12.7, 3.6, and 2.7 Hz; H-14eq; *13, 14ax, 15, 18*), 2.62 (q, $|J|$ = 12.7 Hz; H-14ax; *14eq, 17, 19*), 2.34 (dd, J = 12.7 and 2.7 Hz; H-15; *13, 14eq, 18*), 1.40 (s; H_3-17; *10-OH, 14ax, 18*), 1.51 (s; H_3-18; *5, 14eq, 15, 17*), 1.74 (s; H_3-19; *10-OH, 14ax, 20, 21Z, 26*), 6.16 (dd, J = 17.6 and 10.9 Hz; H-20; *13, 19, 21Z, 21E, 26*), 5.44 (d, J = 17.6 Hz; H-21*Z*; *19, 20, 21E, 26*), 5.59 (d, J = 10.9 Hz; H-21*E*; *21Z*), 3.13 (d, J = 4.5 Hz; H-25; *26, 27, 28*), 3.77 (d, J = 4.5 Hz; H-26; *19, 21Z, 25*), 1.67 (s; H_3-27; *1-NH, 25, 28*), 1.62 (s; H_3-28; *1-NH, 25, 27*), 3.69 (s; OH on C-10; *17, 19*); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, position; *^1H-HMBC*) 133.5 (s, C2; *1-NH, 25, 27, 28*), 109.6 (s, C3; *1-NH*), 139.7 (s, C4; *6, 17, 18*), 114.5 (d, C5; *7*), 123.2 (d, C6; *5, 7*), 107.0 (d, C7; *5*), 133.6 (s, C8; *1-NH, 6*), 124.1 (s, C9; *1-NH, 5, 7*), 75.0 (s, C10; *10-OH, 14eq, 14ax, 15, 26*), 68.6 (s, C11; *19, 20, 25, 26*), 50.4 (s, C12; *13, 14eq, 14ax, 19, 20, 21Z, 21E, 26*), 64.4 (d, C13; *14eq, 14ax, 15, 19, 20*), 28.9 (t, C14; *13, 15*), 48.4 (d, C15; *10-OH, 13, 14eq, 14ax, 17, 18*), 37.8 (s, C16; *5, 14eq, 14ax, 15, 17, 18*), 26.5 (q, C17; *15, 18*), 28.4 (q, C18; *15, 17*), 13.1 (q, C19; *13, 20*), 141.3 (d, C20; *13, 19, 21Z*), 120.0 (t, C21; *none*), 161.5 (s, C23; *none*), 36.1 (s, C24; *25, 26, 27, 28*), 65.9 (d, C25; *26, 27, 28*), 61.4 (d, C26; *25*), 29.8 (q, C27; *25, 28*), 27.3 (q, C28; *25, 27*); FDMS m/z 436/438 (3:1 M^+ ion cluster); FABMS m/z 437/439 (3:1 MH^+ ion cluster); HRFABMS m/z 437.1990 ($C_{26}H_{30}ClN_2O_2$, Δ +0.7 mmu).

Ambiguine F isonitrile: amorphous solid; $[\alpha]_D$ −18.2° (MeOH, c 0.1); CD (MeOH) λ nm [θ] 221 (31 300), 231 (−18 000), 268 (1500), 300 (−2500); UV (MeOH) λ_{max} nm (ϵ) 224 (36 000), 280 (7200), 290 (5500); IR (KBr) ν_{max} 3020, 2131, 1701, 1445, 1250, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (multiplicity, J in Hz; assignment; *^1H NOE's*) 8.08 (br s; 1-NH; *7, 28*), 7.08 (dd, J = 7.2 and 0.7 Hz; H-5; *6, 18*), 7.15 (dd, J = 7.7 and 0.7 Hz; H-6; *5, 7*), 7.21 (dd, J = 7.7 and 7.2 Hz; H-7; *1-NH, 6*), 4.53 (dd, J = 12.7 and 3.6 Hz; H-13; *14eq, 15, 20*), 2.32 (ddd, J = −12.7, 3.6, and 2.7 Hz; H-14eq; *13, 14ax, 15, 18*), 2.61 (q, $|J|$ = 12.7 Hz; H-14ax; *14eq, 17, 19*), 2.46 (br dd, J = 12.7 and 2.7 Hz; H-15; *13, 14eq, 18*), 1.37 (s; H_3-17; *10-OH, 14ax, 18*), 1.53 (s; H_3-18; *5, 14eq, 15, 17*), 1.84 (s; H_3-19; *10-OH, 14ax, 21Z, 26, 26-OH*), 6.08 (dd, J = 17.2 and 11.1 Hz, H-20; *13, 21Z, 21E, 26*), 5.43 (d, J = 17.2 Hz; H-21*Z*; *19, 20, 21E, 26*), 5.54 (d, J = 11.1 Hz; H-21*E*; *20, 21Z*), 4.65 (dd, J = 5.0 and 1.8 Hz; H-26; *19, 21Z, 25, 26-OH*), 4.22 (br s; H-25; *26, 28*), 1.43 (s; H_3-27; *26-OH*), 1.60 (s; H_3-28; *1-NH, 25*), 3.61 (s; OH on C-10, *17, 19, 26-OH, 27*), 2.55 (br s; OH on C-25; *10-OH, 26-OH* by exchange with H_2O), 4.01 (d, J = 5.0 Hz; OH on C-26; *10-OH, 19, 26, 27*); ^{13}C NMR (125 MHz, $CDCl_3$) δ (multiplicity, position; *^1H HMBC*) 136.9 (s, C2; *1-NH, 27, 28*), 110.4 (s, C3; *1-NH*), 139.3 (s, C4; *6, 17, 18*), 114.7 (d, C5; *7*), 123.1 (d, C6; *none*), 107.3 (d, C7; *5*), 133.0 (s, C8; *1-NH, 6*), 124.7 (s, C9; *1-NH, 5, 7*), 77.8 (s, C10; *10-OH, 14eq, 14ax, 15, 26*), 70.3 (s, C11; *10-OH, 19, 20, 26, 26-OH*), 50.7 (s, C12; *13, 14eq, 14ax, 19, 20, 21Z, 21E, 26*), 65.4 (d, C13; *14eq, 14ax, 15, 19, 20*), 29.0 (t, C14; *13, 15*), 49.4 (d, C15; *10-OH, 13, 14eq, 14ax, 17, 18*), 37.6 (s, C16; *5, 15, 17, 18*), 26.6 (q, C17; *15, 18*), 28.8 (q, C18; *15, 17*), 13.2 (q, C19; *13, 20*), 141.3 (d, C20; *13, 19, 21Z*), 120.2 (t, C21; *none*), 163.0 (s, C23; *none*), 40.4 (s, C24; *26, 27, 28*), 73.9 (d, C25; *26, 27, 28*), 80.7 (d, C26; *26-OH*), 27.0 (q, C27; *25, 28*), 28.1 (q, C28; *27*); FDMS and FABMS m/z 454/455/456/457 (overlapping 3:1 M^+ and MH^+ ion clusters); HR FABMS m/z 454.2009 ($C_{26}H_{31}ClN_2O_3$, Δ +1.4 mmu).

X-ray Crystallographic Analysis of Ambiguine D Isonitrile. The compound crystallized from MeOH/water in the monoclinic space group $P2_1$ with a unit cell having the dimensions a = 7.492 (2) Å, b = 12.418 (3) Å, c = 13.686 (6) Å, β = 94.55 (3) Å and a calculated density of 1.27 g cm^{-3}. A total of 1803 reflections with 2θ less than 116.0 was measured on a Siemens R3m-V X-ray diffractometer using copper radiation. The structure was solved using direct methods and was refined by least squares with anisotropic temperature factors for all atoms except hydrogen. All hydrogen atoms were included at calculated positions. The final R factor was 0.06 for 1668 unique observed reflections.

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Supplementary Material Available: 500-MHz ^1H NMR spectra in $CDCl_3$ of ambiguine isonitriles A–F; CD spectra in MeOH of A–F and hapalindole G; tables of atomic coordinates and equivalent isotropic displacement coefficients, bond lengths, bond angles, anisotropic displacement coefficients, and hydrogen atom coordinates and isotropic displacement coefficients for ambiguine D isonitrile (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.