(Aldrich),[38] thiophenol (Aldrich, 99%), and 2-thionaphthol (Aldrich, 99%). Buffer and vesicle solutions were prepared from "steam-distilled" water (distilled, U.S.P., Electrified Water Co., Newark, NJ).

Stock solutions (~0.01 M) of thiols and Ellman's reagent were prepared in EtOH (or in THF for thiocholesterol). These solutions were purged and maintained under nitrogen and stored in the dark. Fresh stock solutions were usually prepared on alternate days.

Vesicle Preparation. All vesicle solutions were created in degassed 0.01 M aqueous KCl at pH 6. *Small vesicles* were generated by sonication with the 108 × 19 (diameter) mm probe of Braunsonic Models 1510 or 2000 sonicators, operated at 40 W. Sonication was carried out at 50 °C for 15 min (Model 1510) or for 6 min (Model 2000). Both procedures gave comparable vesicles (dynamic light scattering). The vesicle solutions were allowed to cool slowly to 25 °C and then filtered through 0.8 μM Millipore filters before use. The vesicle size was 700–800 Å by dynamic light scattering.[39]

Large vesicles were generated by slow (1 mL/h) injection using a Sage Instrument Model 341A syringe pump. Typically, 1 mL of 1×10^{-3} M surfactant in $CHCl_3$ was injected into 20 mL of buffer or water at 68–70 °C. Nitrogen was continuously bubbled through the solution during injection to facilitate the removal of the chloroform. After cooling to 25 °C, dynamic light scattering gave the apparent hydrodynamic diameter of these vesicles as 3000 ± 500 Å.

Kinetic Studies. Faster reactions were followed on a Durrum/Dionex Model D-130 stopped-flow spectrophotometer coupled either to a Tektronix Model 5103N storage oscilloscope or, via a custom-built interface, to a Commodore Model 8032 computer. Slower reactions were monitored on a Gilford Model 250 spectrophotometer coupled to a Gilford Model 6051 recorder. Rate constants were obtained from computer-generated correlations of log $(A_\infty - A_t)$ with time. Temperature (±1 °C) was controlled by a circulating-water bath.

Rate constants are tabulated in Tables I–III. All reactions or reaction phases were followed to >90% completion and showed good first-order kinetics ($r > 0.998$). Reproducibilities of the rate constants were better than ±3% in micellar or buffer solutions. Reproducibilities of ±5% were observed in vesicular kinetics runs when the experiments used vesicle solutions derived from the same vesicle preparation. Kinetic reproducibility was poorer (with deviations up to 20% in k_{obsd}) when different vesicle preparations were employed in repetitive runs.

(38) Aldrich thiocholesterol (95–100%) had mp 93–94 °C (uncorrected) Aldrich catalogue, 1988–89, gives mp 97–99 °C. TLC on precoated silica gel–polyester gave a single spot, R_f 0.62, when developed with 1:5 $CHCl_3$/MeOH, containing 1% glacial acetic acid.

(39) Experimental details for light scattering appear in ref 8.

Acknowledgment. We are grateful to the U.S. Army Research Office and to the Charles and Johanna Busch Fund (Rutgers University) for financial support. We thank Professor Larry Romsted for helpful discussions.

Acid-Catalyzed Reactions of Hapalindoles

Rosanne Bonjouklian*

Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, Indiana 46285

Richard E. Moore* and Gregory M. L. Patterson

Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822

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Tetracyclic hapalindole isonitriles such as hapalindoles A (**1**), G (**2**), H (**3**), and I (**4**) are converted to the corresponding formamides (**5–8**) with 90% aqueous formic acid at 0 °C or amines (**9–11**) with ethanolic hydrochloric acid at reflux. The tricyclic hapalindole isonitriles C (**12**) and E (**13**), however, give predominantly formamides (**14** and **16**) on formic acid treatment and dihydro-β-carbolines (**15** and **17**), resulting from nucleophilic condensation of the isonitrile carbon at the indole C-2, on strong acid treatment. Treatment of the tricyclic hapalindole C formamide with strong acid leads to a hexahydroindeno[2,1-*b*]indole amine (**21**) as well as hapalindole C amine (**18**), but similar treatment of hapalindole E formamide leads only to hapalindole E amine (**19**). The tetracyclic hapalindole isothiocyanate B (**23**) is recovered unchanged on treatment with ethanolic hydrochloric acid, but hapalindole isothiocyanates D (**24**) and F (**30**) readily cyclize to a mixture of γ-thiolactams (**25–29** and **31–35**) resulting from trans addition of the isothiocyanate and isopropenyl groups to the indole Δ^2 double bond; since the electrophilic addition is initiated by the isopropenyl group, an octahydro-7*H*-benzo[*c*]carbazole is formed.

The hapalindoles are responsible for the antibacterial,[1] antimycotic,[1] and antialgal[2] activities associated with the terrestrial blue-green alga *Hapalosiphon fontinalis* (Ag.) Bornet (Stigonemataceae). All of the hapalindoles that have been isolated and identified to date are isonitriles and isothiocyanates.[1] Formamides and amines, which sometimes accompany isonitriles and isothiocyanates in other isonitrile-producing organisms,[3] have not been found in *H. fontinalis* (strain V-3-1), ATCC 39694). The resemblance of the hapalindoles to the ergot alkaloids, however, prompted us to prepare the corresponding formamides and amines for pharmacological evaluation.[4] During the course of our work, the tricyclic hapalindoles were found to un-

(1) Moore, R. E.; Cheuk, C.; Yang, X. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036.

(2) In a preliminary communication [Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456] we reported that our strain of *Hapalosiphon fontinalis* produces an extracellular substance that inhibits the growth of microalgae, including other blue-green algae. The major antialgal substance in this cyanophyte appears to be hapalindole A, which shows antialgal activity in a disk assay (10 μg per 7 mm disk) on an agar plate against *Chlorella vulgaris* and *Aphanocapsa* sp. ATCC 27184.

(3) (a) Sullivan, B. W.; Faulkner, D. J.; Okamoto, K. T.; Chen, M. H. M.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5134. (b) Gulavita, N. K.; de Silva, E. D.; Hagadone, M. R.; Karuso, P.; Scheuer, P. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5136.

(4) The hapalindole formamides and amines possessed markedly reduced antibacterial and antifungal activity in vitro than do the naturally occurring isonitriles and isothiocyanates. In addition, all compounds displayed a very weak ability to block binding of the appropriate agonists to both the serotonin and dopamine central nervous system receptors in vitro and failed to inhibit prolactin release in vivo when compared to the classic ergot alkaloid-derived drugs. These latter tests were performed under the guidance of J. A. Clemens and N. R. Mason in the CNS Research Division of Lilly Research Laboratories. For a review and leading references on CNS agents, see: *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: New York, 1985; Vol. 20, Sect. I, Chapters 1–7, pp 1–60.

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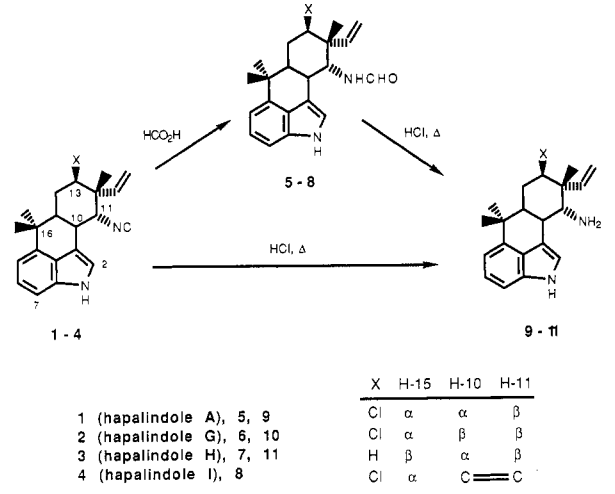
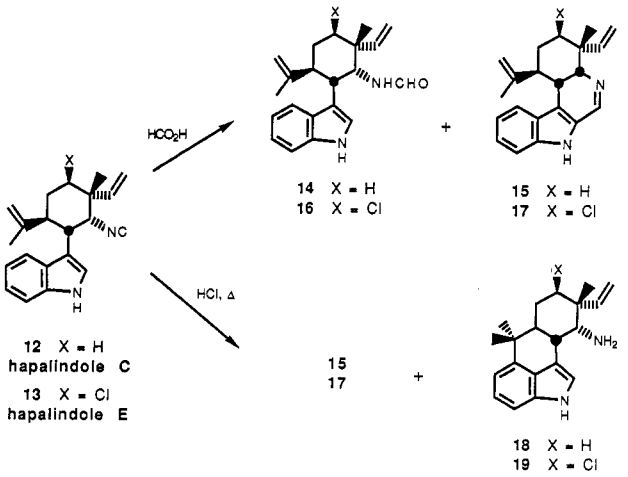
Scheme I



	X	H-15	H-10	H-11
1 (hapalindole A), 5, 9	Cl	α	α	β
2 (hapalindole G), 6, 10	Cl	α	β	β
3 (hapalindole H), 7, 11	H	β	α	β
4 (hapalindole I), 8	Cl	α	C=C	

Scheme II

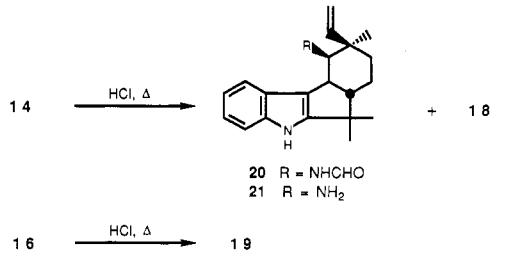


dergo three interesting cyclization reactions. We describe here these three reactions.

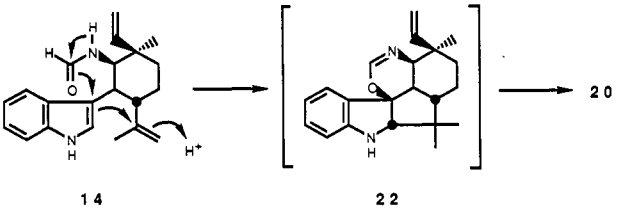
Acid Reaction Studies. Treatment of four representative tetracyclic hapalindole isonitriles, viz. A (**1**), G (**2**), H (**3**), and I (**4**), with 90% aqueous formic acid in tetrahydrofuran at 0 °C for 1–2 h afforded the expected formamides (**5**–**8**) in good yield. Deacylation of formamides **5**–**7** with 1:1 2.5 N hydrochloric acid/ethanol at reflux gave the corresponding amines **9**–**11**. The same amines could also be produced directly from hapalindoles A, G, and H by solvolysis with strong acid (see Scheme I).

The tricyclic hapalindole isonitriles, viz. C (**12**) and E (**13**), however, presented a different picture. Formic acid treatment of **12** generated a 3:1 mixture of the formamide **14** and the 3,4-dihydro-β-carboline **15** (Scheme II). Similarly **13** gave a 3:1 mixture of the formamide **16** and the 3,4-dihydro-β-carboline **17**. When either isonitrile was subjected to a 1:1 mixture of 2.5 N hydrochloric acid and tetrahydrofuran at 0 °C, the dihydro-β-carboline was the sole product.[5] A small amount of hapalindole amine (**18**, **19**), however, was produced along with the dihydro-β-carboline if the isonitrile was heated with a 1:1 mixture of 2.5 N hydrochloric acid and ethanol at reflux.

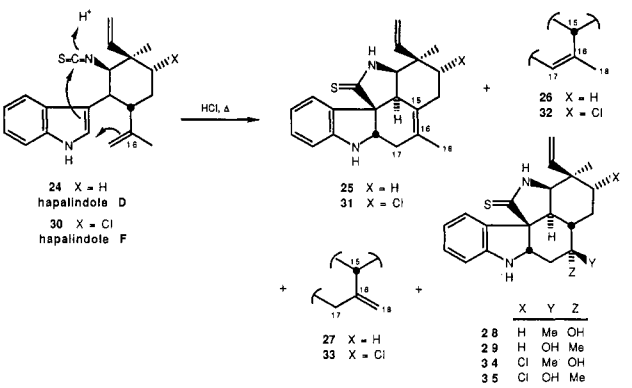
Scheme III



Scheme IV



Scheme V



	X	Y	Z
28	H	Me	OH
29	H	OH	Me
34	Cl	Me	OH
35	Cl	OH	Me

Unexpected products were also formed when hapalindole C formamide (**14**) was heated with strong acid. The hexahydroindeno[2,1-*b*]indole formamide **20** and corresponding amine **21** were obtained, along with hapalindole C amine **18**, in a 2:1:1 ratio (Scheme III). Surprisingly, hapalindole E formamide (**16**) failed to cyclize to a hexahydroindeno[2,1-*b*]indole under identical reaction conditions and gave only hapalindole E amine **19**. Cyclization of **14** to **20** appeared to have proceeded by straightforward electrophilic addition of the indole Δ^2 double bond to the isopropenyl double bond.[6] Cyclization of **16** to a similar hexahydroindeno[2,1-*b*]indole, however, might have failed because solvolysis of **16** to hapalindole E amine (**19**) proceeded faster. It is possible, but unprecedented, that cyclization of **14** to **20** may have been assisted by the formamido group, perhaps via an intermediate pentacyclic indoline **22** that readily decomposes to **20** under the reaction conditions (Scheme IV). Hapalindole C amine was not converted to **21** when resubmitted to strong acid. Nevertheless, it is difficult to explain why the presence of the (equatorial) chloro group in **16** prevented cyclization entirely.

(5) Presumably the dihydro-β-carboline is formed as a result of an acid-catalyzed nucleophilic attack of the isonitrile group at the indole C-2 position. This particular use of isonitriles in heterocyclic synthesis has not been previously described in the literature. Schiff's bases of tryptamine, however, condense to tetrahdyro-β-carbolines under acidic conditions [(a) Abramovitch, R. A.; Spenser, I. D. In *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1964; Vol. 3, pp 78–207. (b) Bobowski, G. *J. Heterocycl. Chem.* **1983**, *20*, 267. (c) Misztal, S.; Cegla, M. *Synthesis* **1985**, 1134]. Isonitriles have been reported to add as nucleophiles to carbocations derived from acetals and similar compounds [Pellissier, H.; Meou, A.; Gil, G. *Tetrahedron Lett.* **1986**, *27*, 3505 and references cited therein].

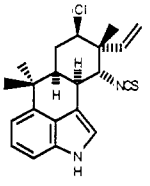
(6) An acid-catalyzed condensation of an alkenyl group with C-2 of an indole has been reported in the synthesis of the alkaloid aristoteline, although in that case a six-membered ring was formed from the synthetic precursors, hobartine and makomakine [Mirand, C.; Massiot, G.; Levy, J. *J. Org. Chem.* **1982**, *47*, 4169].

Table I. ^{1}H NMR Spectral Data for Hapalindole A Formamide in $CDCl_3$

	chemical shifts	
	major conformer[a]	minor conformer[b]
1	8.077 br s	8.100
2	7.069 t	6.957
5	6.928 dd	6.951
6	7.16 t	7.20
7	7.19 dd	7.20
10	3.618 br m	[c]
11	4.938 dd	4.172 d
13	4.182 dd	4.14
14ax	1.568 td	[c]
14eq	2.125 dtd	2.132
15	1.905 ddd	1.970
17	1.525 s	1.536
18	1.135 s	1.152
19	0.986 s	0.962
20	5.797 dd	5.804
21*E*	5.198 dd	5.291
21*Z*	5.203 dd	5.174
22	5.93 br d	6.45 t
23	8.212 d	8.131 d

[a] J(H,H) in Hz: 1,2 = 2; 2,10 = 2; 5,6 = 7.2; 5,7 = 0.6; 6,7 = 8.2; 10,11 = 1.8; 10,14eq = 1.3; 10,15 = 4.7; 11,22 = 9.0; 11,23 = 0.5; 13,14ax = 12.4; 13,14eq = 4.1; 14ax,14eq = −13.1; 14ax,15 = 12.8; 14eq,15 = 3.5; 20,21*E* = 11.0; 20,21*Z* = 17.4; 21*E*,21*Z* = 0.5; 22,23 = 1.6. Ratio of major conformer to minor conformer is 4:1. [b] J(H,H) in Hz: couplings essentially identical with those of major conformer except 10,11 = 0; 11,22 = 10.5; 11,23 = 0; 22,23 = 11.5. [c] Not determined.

Tetracyclic hapalindole isothiocyanates, viz. B (**23**), were recovered unchanged by using conditions that convert hapalindole isonitriles to the corresponding amines. When



23

the tricyclic hapalindole isothiocyanate D (**24**) was heated at reflux with 1:1 2.5 N hydrochloric acid and ethanol, however, five γ-thiolactams were formed by trans addition of the isopropenyl and isothiocyanato groups to the Δ^2 double bond of the indole system, followed by either proton loss from C-15, C-17, or C-18 to give alkenes **25**–**27** in a 20:4:1 ratio or addition of hydroxide (from water) at C-16 to give alcohols **28** and **29** (Scheme V). Hapalindole F (**30**) gave a similar mixture of γ-thiolactams **31**–**35**. In the cyclization of **24** or **30**, electrophilic addition is initiated by the isopropenyl group, resulting in the formation of an octahydro-7*H*-benzo[*c*]carbazole. In the cyclization of **14**, however, electrophilic addition is initiated by the indole Δ^2 double bond which leads to a hexahydroindeno[2,1-*b*]indole.

Structure Determination. ^{1}H NMR analysis indicated that the hapalindole formamides exist in solution as 4:1 mixtures of *Z* and *E* conformational isomers. The couplings between H-22 (NH) and H-23 were found to be 1.6 and 11.5 Hz for the *Z* and *E* conformers of hapalindole A formamide (**5**) (Table I); similar couplings were estimated (unreported) for the *Z* and *E* conformers of all the other hapalindole formamides that were prepared. Other than this, ^{1}H NMR analysis of the hapalindole formamides was straightforward. No difficulty was encountered in the identification of the hapalindole amines.

The UV spectra of **15** and **17** were found to be grossly different from that of an indole, but the intense absorption at 321–323 nm (ϵ >10 000) was consistent with a dihydro-β-carboline chromophore. In the ^{1}H NMR spectra of **15** and **17** a sharp doublet was observed at 8.5 ppm, which showed coupling (3.5 Hz) to the H-11 signal (at 3.30 ppm for **15** and 3.51 ppm for **17**). This coupling strongly suggested that the proton resonating at 8.5 ppm was attached to C-23 (originally the isonitrile carbon in the tricyclic starting material)[7] and that C-23 in turn was attached to C-2. The dihydro-β-carboline structure for **15** was rigorously supported by X-ray crystallography.[8] The X-ray study indicated, as did ^{1}H NMR analysis, that the relative stereochemistry of ring D was identical with that shown by hapalindoles C and E.

Compound **21** exhibited a UV spectrum typical of an indole. In the ^{1}H NMR spectra of **20** and **21** signals could be seen for an indole NH and four adjacent protons on the benzenoid ring. Missing were signals for H-2 and the two terminal methylene protons on C-18.[7] Sharp singlets, however, were present for three methyl groups attached to sp^3-type quaternary carbons. These data strongly suggested that **20** and **21** were hexahydroindeno[2,1-*b*]-indoles.

Mass spectral analysis established the molecular compositions of the γ-thiolactams from hapalindoles D (**24**) and F (**30**) and showed that sulfur was not lost during the reaction. ^{1}H NMR analysis indicated that one of the reaction products from **24** was a 20:4:1 mixture of three alkenes, viz. **25**, **26**, and **27**. The major alkene **25** exhibited a broad NH signal at 7.53 ppm, which was assigned to H-22 (not to H-1).[7] Although the H-22 signal did not show coupling to the adjacent C-11 proton, a strong positive NOE was observed in the H-22 signal on irradiation of H-11. Since the signal for H-15 was missing and the signal for the methyl group on C-16 was a broad singlet at 1.69 ppm, a double bond had to be present between C-15 and C-16 in **25**. Long-range coupling (0.5–1 Hz) from the methyl protons to all of the protons on C-10, C-14, and C-18 supported a double bond at the Δ^{15} position. Minor alkene **26** showed a broad signal at 5.55 ppm for H-18 and a 1:3:3:1 quartet at 1.76 ppm for the methyl group on C-16. The splitting in the latter signal reflected long-range coupling to protons on C-2, C-15, and C-18. Minor alkene **27** exhibited broad singlets at 4.75 and 4.92 ppm for the two terminal methylene protons on C-16. Mass spectrometry and a cursory ^{1}H NMR analysis suggested that a similar mixture of alkenes (**31**–**33**) was formed from **30**.

The ^{1}H NMR spectra of thiolactams **28** and **29** showed some of the features described above for **25**. A broad singlet was present in the 7.6–7.8 ppm region for H-22, but again coupling to H-11 was lacking. A strong NOE, however, could be observed between these two protons. Inspection of the coupling constants for the protons on C-10, C-11, C-13, C-14, and C-15 and the difference NOE spectra from irradiation of H-11 and the methyl group on C-12 confirmed that the relative stereochemistry of ring D was the same as that in hapalindole D. A hydroxy group had to be located on C-16, along with a methyl group, and its stereochemistry accounted for the difference between **28** and **29**. The methyl group on C-16 was axial in **29**, since strong NOEs could be seen in the signals for the axial C-10 and equatorial C-18 protons on irradiation of H_3-**17** and in the signal for the axial C-18 proton on irradiation of H-2. The C-16 methyl group was therefore equatorial in **28**. The ^{1}H NMR spectra of thiolactams **34** and **35** were similar in

(7) The numbering system corresponds to the one used for the hapalindoles.[1]

(8) The X-ray study of compound **15** was carried out by Mr. Jack Deeter at Lilly Research Laboratories.

appearance to those of **28** and **29**.

Experimental Section

General Procedures. Analytical TLC was performed and R_f values were determined on 5 × 10 cm EM silica gel 60 F-254 plates in 20:1 CH_2Cl_2/MeOH and visualized by UV irradiation or sulfuric acid. Preparative TLC was run on 20 × 20 cm (0.25-mm thickness) EM silica gel F-254 plates. Bond-Elut mini silica columns (3 mL) were purchased from Analytichem International, Harbor City, CA. Gravity column chromatographic purification was performed on EM Kieselgel 60 (230–400 mesh).

^{1}H NMR spectra were determined at 300 MHz; all chemical shifts are referenced in chloroform-*d* to the residual chloroform signal (7.25 ppm). ^{13}C NMR spectra were determined at 75 MHz; all chemical shifts are referenced to chloroform-*d* (77.0 ppm). Elemental analyses were performed at Lilly Research Laboratories.

Cultivation. *Hapalosiphon fontinalis* (strain V-3-1) was mass cultured in the laboratory as previously described.[1]

Isolation of Hapalindoles. The hapalindoles used in this study were isolated from *H. fontinalis* as previously described.[1]

Conversion of Hapalindole A to Formamide 5. Hapalindole A (**1**) (1.75 g, 5.2 mmol) was dissolved in 25 mL of tetrahydrofuran. Formic acid (90% in water, 12 mL) was then added slowly to the solution at 0 °C with stirring. After 2 h the reaction mixture was warmed to room temperatute and stirred another 1 h. The mixture was evaporated and the residue dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated aqueous $NaHCO_3$ and then with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to give 2.11 g of crude product. Purification was achieved by flash chromatography using a silica gel column packed with cyclohexane. Formamide **5** was eluted with 2.5:1 cyclohexane/EtOAc (1.76 g, 92%): R_f 0.4; $[\alpha]_D$ −27.4° (CH_2Cl_2, *c* 0.76); IR ($CHCl_3$) ν_{max} 3477, 3430, 1685 cm^{-1}; UV (MeOH) λ_{max} 223 nm (ϵ 35 710), 281 (6090), 291 (5080); ^{1}H NMR (see Table I); FDMS, *m/z* 356, 358 (rel intensity 3:1). Anal. Calcd for $C_{21}H_{25}N_2OCl$: C, 70.44; H, 6.82; N, 7.70. Found: C, 70.67; H, 7.06; N, 7.85.

Similar treatment of hapalindoles G (**2**), H (**3**), and I (**4**) with 90% formic acid led to formamides **6**, **7**, and **8**.

Hapalindole G formamide (6): R_f 0.41; IR ($CHCl_3$) ν_{max} 3391 (br), 1681 cm^{-1}; UV (MeOH) λ_{max} 222 nm (ϵ 29 680), 280 (5550), 291 (4780); ^{1}H NMR of major conformer (ratio *Z*:*E* = 4:1) δ 8.02 (br s, H-1), 6.9–7.2 (m, H-2, H-5, H-6, H-7), 3.46 (dd, H-10ax), 4.92 (dd, H-11eq), 4.2 (dd, H-13ax), 2.41 (dt, H-14eq), 2.10 (m, H-14ax), 1.68 (td, H-15ax), 1.17 (s, H_3-17), 1.51 (s, H_3-18), 1.47 (s, H_3-19), 5.89 (dd, H-20), 5.28 (2 dd, *E* and *Z* H_2-21); FDMS, *m/z* 356, 358 (rel intensity 3:1); high resolution EIMS, *m/z* 356.1654 (calcd for $C_{21}H_{25}N_2ClO$, mmu error −0.1).

Hapalindole H formamide (7): R_f 0.42 and 0.51 for the two conformational isomers; IR ($CHCl_3$) ν_{max} 3298 (br), 1680 cm^{-1}; UV (MeOH) λ_{max} 223 nm (ϵ 37 010), 280 (6180), 291 (5010); ^{1}H NMR of major conformer (ratio *Z*:*E* = 4:1) δ 7.93 (br s, H-1), 6.95–7.3 (m, H-2, H-5, H-6, H-7), 2.93 (br dd, H-10ax), 4.21 (dd, H-11ax), 1.4–2.0 (m, H-13ax, H-14eq, H-14ax, H-15ax), 1.47 (s, H_3-17), 1.23 (s, H_3-18), 1.11 (s, H_3-19), 6.28 (dd, H-20), 5.28 (2 dd, *E* and *Z* H_2-21), 8.48 (d, H-23); FDMS, m/z 322. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.31; H, 7.93; N, 8.56.

Hapalindole I formamide (8): R_f 0.47; IR ($CHCl_3$) ν_{max} 3480, 3350, 1686 cm^{-1}; UV (MeOH) λ_{max} 228 nm (ϵ 28 010), 304 (8610); ^{1}H NMR of major conformer (ratio *Z*:*E* = 4:1) δ 8.32 (br d, H-1), 7.89 (d, H-2), 7.0–7.2 (m, H-5, H-6, H-7), 4.18 (dd, H-13ax), 2.22 (td, H-14ax), 2.38 (ddd, H-14eq), 2.80 (m, H-15ax), 1.54 (s, H_3-17), 1.10 (s, H_3-18), 1.42 (s, H_3-19), 5.77 (dd, H-20), 5.4 (2 dd, *E* and *Z* H_2-21), 6.55 (br d, H-23); FDMS, *m/z* 354, 356 (rel intensity 3.5:1); high resolution EIMS, *m/z* 354.1506 (calcd for $C_{21}H_{23}N_2ClO$, mmu error 0.7).

Conversion of Hapalindole A or Formamide 5 to Amine 9. Formamide **5** (40 mg, 0.11 mmol) or hapalindole A (**1**) (37 mg, 0.11 mmol) was dissolved in 2 mL of MeOH, 2 mL of 2.5 N HCl was added, and the solution was heated to reflux with stirring for 3 h. The reaction mixture was cooled to room temperature and neutralized with 1.0 N NaOH. Dichloromethane was added and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated to give 35 mg (94%) of hapalindole A amine (**9**): R_f 0.3; IR ($CHCl_3$) ν_{max} 3480 cm^{-1}; UV (MeOH) λ_{max} 223 nm (ϵ 34 260), 281 (6570); ^{1}H NMR δ 8.01 (br s, H-1), 6.95–7.2 (m, H-5, H-6, H-7), 3.42 (m, H-10eq), 4.65 (dd, H-11eq), 3.82 (d, H-13ax), 1.5 (m, H-14ax), 2.08 (dtd, H-14eq), 2.35 (ddd, H-15ax), 1.55 (s, H_3-17), 1.19 (s, H_3-18), 0.89 (s, H_3-19), 5.99 (dd, H-20), 5.25–5.28 (2 dd, *E* and *Z* H_2-21); FDMS, *m/z* 328, 330 (rel intensity 3:1). Anal. Calcd for $C_{20}H_{25}N_2Cl$: C, 73.04; H, 7.66; N, 8.52. Found: C, 73.27; H, 7.69; N, 8.39.

Similar treatment of hapalindoles G and H or the corresponding formamides **6** and **7** led to amines **10** and **11**.

Hapalindole G amine (10): R_f 0.30; ^{1}H NMR δ 8.00 (br s, H-1), 6.9–7.2 (m, H-5, H-6, H-7), 3.35 (dd, H-10ax), 4.80 (dd, H-11eq), 3.62 (m, H-13ax), 2.33 (m, H-14eq), 2.03 (m, H-14ax and H-15ax), 1.14 (s, H_3-17), 1.50 (s, H_3-18), 1.36 (s, H_3-19), 6.08 (dd, H-20), 5.28 (2 dd, *E* and *Z* H_2-21), 1.46 (br d, H_2-22); FDMS, *m/z* 328, 330 (rel intensity 3:1); high resolution EIMS, *m/z* 328.1707 (calcd for $C_{20}H_{25}N_2Cl$, mmu error 0.1).

Hapalindole H amine (11): R_f 0.22; ^{1}H NMR δ 7.83 (br s, H-1), 6.9–7.6 (m, H-5, H-6, H-7), 2.52 (d, H-10eq), 2.68 (dd, H-11eq), 1.4–1.8 (m, H-13ax, H-14eq, H-14ax, and H-15ax), 1.38 (s, H_3-17), 1.15 (s, H_3-18 and H_3-19), 6.23 (dd, H-20), 5.14 (2 dd, *E* and *Z* H_2-21); FDMS, *m/z* 294.

Conversion of Hapalindole C to Formamide 14 and Dihydro-β-carboline 15. Hapalindole C (**12**, 19 mg) in 1.0 mL of THF was treated with 0.8 mL of 90% formic acid at 0 °C for 1 h (method A). Workup afforded 14 mg of material that was chromatographed on a Bond-Elut silica column (3 mL) with 100:1 CH_2Cl_2/MeOH to give 9 mg of formamide **14** and 3 mg of dihydro-β-carboline **15**. When hapalindole C was treated with 1:1 2.5 N HCl/THF at 0 °C for 1 h (method B), the dihydro-β-carboline was formed in 80% yield. Using method A, hapalindole E (**13**, 16 mg) afforded 9 mg of formamide **16** and 2 mg of dihydro-β-carboline **17**, whereas method B again led to an 80% yield of the dihydro-β-carboline.

Hapalindole C formamide (14): R_f 0.38; IR ($CHCl_3$) ν_{max} 3478, 1682 cm^{-1}; UV (MeOH) λ_{max} 222 nm (ϵ 27 130), 282 (4740), 290 (4380); ^{1}H NMR of major conformer (ratio *Z*:*E* = 4:1) δ 8.15 (br d, H-1), 6.8–7.6 (m, H-2, H-4, H-5, H-6, H-7), 3.65 (dd, H-10ax), 3.40 (dd, H-11eq), 1.6–1.95 (m, H-13eq, H-13ax, H-14eq, H-14ax), 2.51 (td, H-15ax), 1.52 (s, H_3-17), 4.76 and 4.66 (2 br s, H_2-18), 1.44 (s, H_3-19), 5.77 (dd, H-20), 5.00 (2 dd, *E* and *Z* H_2-21); FDMS, *m/z* 322; high resolution EIMS, *m/z* 322.2029 (calcd for $C_{21}H_{26}N_2O$, mmu error −0.16).

Dihydro-β-carboline 15:[7] mp 210–213 °C dec; R_f 0.3; UV (MeOH) λ_{max} 237 (ϵ 13 700), sh 240, 321 (11 300); ^{1}H NMR ($CDCl_3$) δ 8.50 (d, $J_{11,23}$ = 3.5 Hz, H-23), 8.12 (br s, NH), 7.59 (dd, H-4), 7.33 (dd, H-7), 7.23 (t, H-6), 7.08 (t, H-5), 6.26 (dd, H-20), 5.15 (dd, *E* H-21), 5.13 (dd, *Z* H-21), 4.57 (br s, H-18), 4.50 (br s, H-18), 4.47 (dd, H-13), 3.30 (dd, *J* = 5.5 and 3.5 Hz, H-11), 3.25 (dd, *J* = 12 and 5.5 Hz, H-10), 1.5–2.1 (m, 4 H on C-14 and C-15), 1.60 (s, H_3-17), 1.30 (s, H_3-19); FDMS, *m/z* 304.

Hapalindole E formamide (16): R_f 0.38; IR ($CHCl_3$) ν_{max} 3480, 1685 cm^{-1}; UV (MeOH) λ_{max} 222 nm (ϵ 32 280), 283 (5190), 290 (4650); ^{1}H NMR of major conformer (ratio *Z*:*E* = 4:1) δ 8.16 (br d, H-1), 6.85–7.6 (m, H-2, H-4, H-5, H-6, H-7), 3.71 (dd, H-10ax), 3.54 (dd, H-11eq), 4.25 (dd, H-13ax), 2.21 (m, H-14eq, H-14ax), 2.79 (m, H-15ax), 1.58 (s, H_3-17), 4.8 and 4.7 (2 br s, H_2-18), 1.56 (s, H_3-19), 5.81 (dd, H-20), 5.22 (2 dd, *E* and *Z* H_2-21), 8.01 (d, H-23); FDMS, *m/z* 356, 358 (rel intensity 3:1); high resolution EIMS, *m/z* 356.1651 (calcd for $C_{21}H_{25}N_2ClO$, mmu error −0.4).

Dihydro-β-carboline 17:[7] R_f 0.35; UV (MeOH) λ_{max} 217 nm (ϵ 18 600), 235 (11 540), 323 (10 100); ^{1}H NMR δ 8.47 (d, *J* = 3.5 Hz, H-23), 8.19 (br s, NH), 7.56 (dd, H-4), 7.33 (dd, H-7), 7.24 (t, H-6), 7.08 (t, H-5), 6.55 (dd, H-20), 5.30 (dd, *E* H-21), 5.21 (dd, *Z* H-21), 4.59 (br s, H-18), 4.49 (br s, H-18), 4.47 (dd, *J* = 11.5 and 4.5 Hz, H-13), 3.51 (dd, *J* = 5.5 and 3.5 Hz, H-11), 3.31 (dd, *J* = 11.5 and 5.5 Hz, H-10), 2.18 (m, H-14eq and H-15), 2.02 (m, H-14ax), 1.60 (s, H_3-17), 1.45 (s, H_3-19); ^{13}C NMR δ 151.6 (C-23), 146.2 (C-16), 145.8 (C-20), 136.8 (C-8), 127.8 (C-9), 126.1 (C-2), 124.8 (C-6), 121.9 (C-3), 121.0 (C-5), 120.6 (C-4), 113.8 (C-21), 113.0 (C-18), 112.0 (C-7), 71.3 (C-11), 64.2 (C-13), 45.6 (C-12), 45.2 (C-15), 36.3 (C-14), 33.4 (C-10), 20.9 (C-17), 16.2 (C-19); high resolution EIMS, *m/z* 338.1549 (calcd for $C_{21}H_{23}N_2Cl$, mmu error −0.1).

Conversion of Formamide 14 to Hexahydroindeno[2,1-*b*]indoles 20 and 21 and Amine 18. A solution of hapalindole C formamide **14**, 9 mg) in 1 mL of absolute EtOH and 1 mL of 2.5 N HCl was refluxed for 2 h. The cooled mixture was neutralized and extracted with CH_2Cl_2. The extract (7 mg) was

purified on a Bond-Elut silica column with CH_2Cl_2 to give 4 mg of compound **21** and 1.5 mg of hapalindole C amine (**18**). If the reaction mixture was refluxed for only 1 h, then workup (preparative TLC on silica gel with 20:1 CH_2Cl_2/MeOH) led to compound **20** as the major product with smaller amounts of **18** and **21**. Using the same procedure, hapalindole E formamide (**16**) was converted to hapalindole E amine (**19**); hexahydroindeno[2,1-*b*]indoles could not be detected.

Hapalindole C amine (18): R_f 0.1; IR ($CHCl_3$) ν_{max} 3475 cm^{-1}; ^1H NMR δ 8.15 (br s, H-1), 7.05–7.6 (m, H-2, H-4, H-5, H-6, H-7), 3.59 (dd, H-10ax), 3.03 (m, H-11eq), 1.4–1.9 (m, H-13eq, H-13ax, H-14eq, H-14ax), 2.14 (td, H-15ax), 1.53 (s, H_3-17), 4.80 and 4.63 (2 br s, H_2-18), 1.37 (s, H_3-19), 5.80 (dd, H-20), 5.05 (2 dd, *E* and *Z* H_2-21), 2.01 (br d, H_2-22); FDMS, *m/z* 294; high resolution EIMS, *m/z* 294.2095 (calcd for $C_{20}H_{26}N_2$, mmu error −0.1).

Hapalindole E amine (19): R_f 0.4; ^1H NMR δ 8.07 (br s, H-1), 7.05–7.6 (m, H-2, H-4, H-5, H-6, H-7), 3.63–3.7 (m, H-10ax, H-11eq, and H-13ax), 2.2 (m, H-14eq, H-14ax, H-15ax), 1.59 (s, H_3-17), 4.87 and 4.73 (2 br s, H_2-18), 1.56 (s, H_3-19), 5.95 (dd, H-20), 5.28 (2 dd, *E* and *Z* H_2-21), 1.75 (br d, H_2-22); FDMS, *m/z* 328, 330 (3:1 rel intensity); high resolution EIMS, 328.1697 (calcd for $C_{20}H_{25}N_2Cl$, mmu error −0.9).

Hexahydroindeno[2,1-*b*]indole 20:[7] R_f 0.5; IR (CH_2Cl_2, film) ν_{max} 1680 cm^{-1}; ^1H NMR δ 8.24 and 8.15 (2 d, J = 11.5 and 2, 1:3 rel. intensity, *E* and *Z* H-23), 7.86 (br s, H-1), 7.56 (m, H-4), 7.30 (m, H-7), 7.08 (m, H-5 and H-6), 5.85 and 6.10 (2 dd, 1:3 rel. intensity, *E* and *Z* H-20), 4.03 and 4.94 (2 dd, J = 11 and 4 Hz, 1:3 rel intensity, *E* and *Z* H-11), 3.38 (dd, J = 11 and 4 Hz, *Z* H-10), 1.36/1.30/1.06 and 1.38/1.32/1.10 (3 Me groups of *E* and *Z* conformers); EIMS, *m/z* 322, 277 (M − NHCHOH), 262 (277 − Me); high resolution EIMS, *m/z* 322.2046 (calcd for $C_{21}H_{26}N_2O$, mmu error 0.1).

Hexahydroindeno[2,1-*b*]indole 21:[7] R_f 0.2; UV (MeOH) λ_{max} 227 nm (ϵ 26 860), 279 (5450); ^1H NMR δ 7.90 (br s, H-1), 7.47 (m, H-4), 7.33 (m, H-7), 7.07 (m, H-5 and H-6), 5.99 (dd, H-20), 5.08 (dd, *E* H-21), 5.04 (dd, *Z* H-21), 3.58 (d, J = 4 Hz, H-11), 3.32 (dd, J = 10.5 and 4 Hz, H-10), 2.46 (m, $J_{14ax,15}$ = 12.5 Hz, H-15), 1.94 (ddd, H-13ax), 1.64 (br m, H_2-22, H-13eq, and H-14eq), 1.50 (qt, H-14ax), 1.36 (s, H_3-19), 1.23 and 1.08 (2 s, H_3-17 and H_3-18); EIMS, *m/z* 294, 279, 264; high resolution EIMS, *m/z* 294.2092 (calcd for $C_{20}H_{26}N_2$, mmu error −0.4).

Conversion of Hapalindole D to Pentacyclic Thiolactams 25–29. A mixture of hapalindole D (**24**) (5 mg), 2.5 N HCl (0.5 mL) and absolute EtOH (0.5 mL) was refluxed for 1 h. Workup afforded 5.6 mg of crude product, which was subjected to preparative TLC on 5-mm analytical silica plates with 50:1 CH_2Cl_2/MeOH to give 2.5 mg of thiolactam (R_f 0.7; ^1H NMR analysis indicated to to be a 20:4:1 mixture of **25**, **26**, and **27**, respectively), 1.3 mg of alcohol **28** (R_f 0.5), and 1.0 mg of alcohol **29** (R_f 0.2).

Mixture of 25–27:[7] UV (MeOH) λ_{max} 281 nm; EIMS, *m/z* (rel intensity) 336 (100), 303 (35), 268 (40), 201 (45), 194 (70), 114 (68), 112 (55); high resolution EIMS, *m/z* 336.1645 (calcd for $C_{21}H_{24}N_2S$, mmu error −1.5). ^1H NMR for **25**: δ 4.50 (dd, H-2), 6.98 (br dd, H-4), 6.73 (m, H-5), 7.08 (td, H-6), 6.71 (m, H-7), 2.77 (br m, H-10ax), 3.94 (d, H-11eq), 1.61 (td, H-13ax), 1.46 (dt, H-13eq), 1.97 (br t, H-14ax), 2.60 (dt, H-14eq), 1.69 (br s, H_3-17), 2.41 (br dd, H-18ax), 2.21 (br dd, H-18eq), 1.11 (s, H_3-19), 5.87 (dd, H-20), 5.23 (dd, *E* H-21), 5.14 (dd, *Z* H-21), 7.53 (br s, H-22). J(H,H) in Hz for **25**: 2,18ax = 6.4; 2,18eq = 4; 4,5 = 7.2; 4,6 = 1.1; 5,6 = 7.7; 5,7 = 0.9; 6,7 = 7.7; 10ax,11eq = 5.6; 10ax,17 = <1; 10ax,18ax = <1; 10ax,18eq = 1.3; 11eq,13eq = 1.1; 11eq,22 = 0; 13ax,13eq = −12.8; 13ax,14ax = 4; 13ax,14eq = 4; 13eq,14ax = 4.1; 13eq,14eq = 4; 14ax,14eq = −15.3; 14ax,17 = 1; 14eq,17 = <1; 17,18ax = <1; 17,18eq = 1; 18ax,18eq = −17.8; 20,21*E* = 10.9; 20,21*Z* = 17.6; 21*E*,21*Z* = 0.8. NOE(H,H) for **25**: δ 3.94 → 7.53, 6.98, 5.87, 2.77, 1.11; 1.11 → 5.87, 5.14, 3.94, 2.77, 1.97, 1.46; 1.69 → 2.60, 2.41, 2.21. ^1H NMR for **26**: δ 4.89 (hextet, J = 2 Hz, H-2), 4.14 (d, J = 3.5 Hz, H-11eq), 2.12 (m, H-15), 1.76 (q, J = 2 Hz, H_3-17), 5.55 (br s, H-18), 7.64 (br s, H-22). ^1H NMR for **27**: δ 4.92 (br m, H-17), 4.75 (br m, H-17), 7.75 (br s, H-22).

Thiolactam alcohol 28:[7] UV (MeOH) λ_{max} 278 nm; EIMS, *m/z* (rel intensity) 354 (100), 321 (15), 295 (25), 227 (85); high resolution EIMS, *m/z* 354.1745 (calcd for $C_{21}H_{26}N_2OS$, mmu error −2.1); ^1H NMR δ 4.63 (dd, H-2), 6.91 (dd, H-4), 6.82 (m, H-5), 7.12 (td, H-6), 6.79 (m, H-7), 2.49 (dd, H-10ax), 3.81 (d, H-11eq), 1.37 (m, H-13ax), 1.55 (m, H-13eq), 1.64 (m, H-14ax), 1.31 (m, H-14eq), 1.16 (td, H-15ax), 1.19 (s, H_3-17),1.77 (dd, H-18ax), 2.02 (dd, H-18eq), 1.03 (s, H_3-19), 5.89 (dd, H-20), 5.26 (dd, *E* H-21), 5.18 (dd, *Z* H-21), 7.76 (br s, H-22). J(H,H) in Hz: coupling constants are similar to those of **29**. NOE (H,H): δ 1.03 → 5.89, 5.18, 3.81, 2.49, 1.64, 1.55; 1.19 → 2.02, 1.77; 3.81 → 7.76, 6.91, 5.89, 2.49, 1.03; 4.63 → 2.02, 1.77.

Thiolactam alcohol 29:[7] UV (MeOH) λ_{max} 277 nm; EIMS, *m/z* (rel intensity) 354 (100), 295 (20), 227 (60); high resolution EIMS, *m/z* 354.1755 (calcd for $C_{21}H_{26}N_2OS$, mmu error −1.1); ^1H NMR δ 4.67 (dd, H-2), 6.91 (dd, H-4), 6.69 (m, H-5), 7.08 (td, H-6), 6.67 (m, H-7), 2.20 (dd, H-10ax), 3.87 (d, H-11eq), 1.22 (m, H-13ax), 1.56 (m, H-13eq), 1.67 (m, H-14ax), 1.87 (m, H-14eq), 1.28 (m, H-15ax), 1.32 (s, H_3-17), 1.77 (dd, H-18ax), 1.99 (dd, H-18eq), 1.04 (s, H_3-19), 5.88 (dd, H-20), 5.26 (dd, *E* H-21), 5.18 (dd, *Z* H-21), 7.65 (br s, H-22). J(H,H) in Hz: 2,18ax = 5; 2,18eq = 3.8; 4,5 = 7.7; 4,6 = 1.3; 5,6 = 7.7; 5,7 = 1; 6,7 = 7.7; 10ax,11eq = 4.2; 10ax,15ax = 11.5; 11eq,22 = 0; 13ax,13eq = −12.5; 13ax,14ax = 12.5; 13ax,14eq = 3.2; 13eq,14ax = 3.4; 13eq,14eq = 3.4; 14ax,14eq = −12.5; 14ax,15ax = 11.5; 14eq,15ax = 2.5; 18ax,18eq = −14.2; 20,21*E* = 10.9; 20,21*Z* = 17.6; 21*E*,21*Z* = 0.7. NOE(H,H): δ 1.04 → 5.88, 3.87, 2.20; 1.32 → 2.20, 1.99; 3.87 → 7.65, 6.91, 5.88 (weak), 2.20, 1.04; 4.67 → 1.77.

Under the same reaction conditions, hapalindole B (**23**) was recovered unchanged.

Conversion of Hapalindole F to Pentacyclic Thiolactams 31–35. A mixture of hapalindole F (**30**) (4 mg), 2.5 N HCl (0.5 mL), and absolute EtOH (0.5 mL) was refluxed for 1 h. The crude reaction product was subjected to preparative TLC on 5-mm analytical silica plates with 40:1 CH_2Cl_2/MeOH to give 1.4 mg of a mixture of thiolactams **31–33** (R_f 0.8), 0.9 mg of alcohol **34** (R_f 0.6), and 0.3 mg of alcohol **35** (R_f 0.32).

Mixture of 31–33:[7] FDMS, *m/z* 370 (M^+); ^1H NMR of major isomer **31** δ 5.92 (dd, H-20), 4.53 (dd, H-2), 4.11 (dd, H-13ax), 4.01 (d, H-11eq), 1.75 (br m, H_3-17).

Compound **34**:[7] FDMS, *m/z* 388 (M^+); ^1H NMR δ 4.79 (br d, J = 3 Hz, H-2), 4.15 (br dd, H-13), 4.02 (br d, H-11eq), 2.57 (dd, H-10ax).

Compound **35**:[7] FDMS, *m/z* 388 (M^+); ^1H NMR δ 4.68 (br dd, H-2), 4.20, 4.10.

X-ray Analysis of Dihydro-β-carboline 15. The compound crystallized from CH_2Cl_2/heptane as yellow prisms in the space group *P*222, *Z* = 4, with unit cell dimensions *a* = 10.461 (2), *b* = 11.379 (2), and *c* = 14.570 (4) Å. The calculated density was 1.166 g/cm^{-3}. Over 1000 unique reflections (final *R* factor 0.0863) were measured.

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Registry No. **1**, 92219-95-9; **2**, 102045-13-6; **3**, 101968-75-6; **4**, 101968-76-7; **5**, 117184-31-3; **6**, 117249-41-9; **7**, 117184-32-4; **8**, 117184-33-5; **9**, 117184-34-6; **10**, 117249-42-0; **11**, 117184-35-7; **12**, 101968-71-2; **13**, 101968-73-4; **14**, 117184-36-8; **15**, 117184-37-9; **16**, 117184-38-0; **17**, 117184-39-1; **18**, 117305-53-0; **20**, 117201-63-5; **21**, 117184-40-4; **24**, 101968-72-3; **25**, 117184-41-5; **26**, 117184-42-6; **27**, 117184-43-7; **28**, 117184-44-8; **29**, 117305-54-1; **30**, 101968-74-5; **31**, 117184-45-9; **32**, 117184-46-0; **33**, 117184-47-1; **34**, 117184-48-2; **35**, 117249-43-1.

Supplementary Material Available: ORTEP drawing for dihydro-β-carboline **15**, numbering system used for X-ray analysis, and tables for atom coordinates, temperature factors, bond lengths, bond angles, and anisotropic temperature factors (5 pages). Ordering informing is given on any current masthead page.