Welwitindolinones, Unusual Alkaloids from the Blue-Green Algae *Hapalosiphon welwitschii* and *Westiella intricata*. Relationship to Fischerindoles and Hapalindoles

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Abstract: *N*-Methylwelwitindolinone C isothiocyanate (**7**), the major indole alkaloid in the blue-green algae (cyanobacteria) *Hapalosiphon welwitschii* W. & G. S. West UH IC-52-3 and *Westiella intricata* Borzi UH HT-29-1 (Stigonemataceae), is responsible for some of the multiple-drug-resistance (MDR) reversing activity in *H. welwitschii* and most of the insecticidal activity in *W. intricata*. The oxindole was isolated from the lipophilic extracts of the two cyanophytes and its structure and absolute stereochemistry determined by X-ray crystallography. Fourteen additional alkaloids were isolated from *H. welwitschii* as minor constituents, viz. a novel spiro oxindole, welwitindolinone A isonitrile (**1**), five tetracyclic oxindoles (**1–6**) related to **7**, and eight biogenetically-related fischerindoles (**8–11**) and hapalindoles (**12–15**). In addition to **1**, five other alkaloids were isonitriles and these six compounds collectively accounted for the fungicidal activity of *H. welwitschii*.. The gross structures and relative stereochemistries of **1–6** and **8–15** were elucidated by spectral analysis. The biogenesis of these alkaloids is discussed.

In an ongoing search for potentially useful natural products from blue-green algae (cyanobacteria),[1] we have found that the lipophilic extract of *Hapalosiphon welwitschii* W. & G. S. West (UH strain IC-52-3, Stigonemataceae) is antifungal[2] and reverses P-glycoprotein-mediated multiple-drug-resistance (MDR) in a vinblastine resistant subline (SK-VLB) of a human ovarian adenocarcinoma line (SK-OV-3)[3] and that the lipophilic extract of *Westiella intricata* Borzi (UH strain HT-29-1, Stigonemataceae) exhibits insecticidal activity against blowfly larvae. The extract of *H. welwitschii* contains minor amounts of isonitriles, one of the structually most interesting being welwitindolinone A isonitrile (**1**), which account for the fungicidal activity associated with the cyanophyte. The MDR reversing and larvacidal activities, however, are associated with *N*-methylwelwitindolinone C isothiocyanate (**7**),[3,4] the major indole alkaloid in both algae. We describe here the elucidation of the novel structures, including relative stereochemistries, of **1** and **7**, as well as the structures of 13 other indole alkaloids (**2–6** and **8–15**) from *H. welwitschii* which are biogenetically-related to **1** and **7**.

UH cyanobacterial strains IC-52-3 and HT-29-1 were isolated from Australian and Micronesian soil samples, respectively, and mass cultured using a previously described general procedure.[5] The lipophilic extract (1:1 CH_2Cl_2/2-propanol) of *H. welwitschii* was fractionated by successive size exclusion chromatography on Sephadex LH20 (MeOH elution) and absorption chromatography on silica gel to give **7** (3:1 CH_2Cl_2/isooctane elution) and **1** (9:1 CH_2Cl_2/isooctane elution) in 0.23 and 0.0043% yield, respectively, based on dry weight of alga. The lipophilic *W. intricata* extract was fractionated in a similar manner, except that reversed-phase chromatography steps were carried out before gel filtration and after normal phase chromatography to give **7** in 0.065% yield.

Welwitindolinones. The EIMS of **1** displayed a 3:1 M^+ ion cluster at *m/z* 352/354 and a very strong fragment ion at *m/z* 317 for loss of a chlorine from the molecular ion. High resolution EIMS (*m/z* 352.1360, Δ −1.8 mmu) indicated the molecular formula $C_{21}H_{21}ClN_2O$. The broadband-decoupled and INEPT ^{13}C NMR spectra confirmed the presence of 21 carbons (9C, 7CH, $2CH_2$, and $3CH_3$) and showed that 20 of the 21 hydrogens were nonexchangeable. The remaining proton was exchangeable since the ^1H NMR displayed a broad 1H signal at 7.62 ppm which did not correlate with any of the carbon signals in the HMQC spectrum and the IR spectrum showed a 3250 cm^{-1} band. A ^{13}C signal at 175.8 ppm and an IR absorption at 1705 cm^{-1} had typical δ_C and ν_{max} values for a carbonyl of a γ-lactam group and the UV spectrum and the six ^{13}C signals at 141.8 (s), 129.5 (d), 127.4 (d), 123.1 (s), 121.9 (d), and 110.3 ppm (d) were consistent with its presence in an oxindole system where the benzenoid ring was unsubstituted.[6] The exchangeable proton had to be on the oxindole nitrogen since the remaining heteroatom, a nitrogen, was in a conjugated isocyano functionality as shown by a ^{13}C signal[7] at 167.7 ppm (unconjugated 150–158 ppm) and a sharp intense peak at 2065 cm^{-1} in the IR spectrum.[7] The CC double bond to which the isonitrile group was attached exhibited nonprotonated ^{13}C signals at 119.9 (very broad due to ^{14}N coupling) and 138.09 ppm. A vinyl substituent attached to a quaternary carbon was also present in **1** as shown by methine (δ_C 138.15, δ_H 5.99 ppm) and methylene (δ_C 118.1, δ_H 5.46/5.32

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(1) Patterson, G. M. L.; Larsen, L. K.; Moore, R. E. *J. Appl. Phycol.* **1994**, *6*, 151–7.

(2) Active against *Asperigillus oryzae, Penicillium notatum, Saccharomyces cerevisiae,* and *Trichophyton mentagrophytes.*

(3) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. Manuscript in preparation.

(4) At 20 μM, [^3H]vinblastine accumulation in SK-VLB cells is more than doubled by **7** compared with verapamil. MDR reversal appears to be P-glycoprotein-mediated since **7** inhibits the photoaffinity labeling of P-glycoprotein by [^3H]azidopine at doses of >5 μg/mL. Evaluation of **7** *in vivo* as a MDR-reversing agent is in progress. Interestingly, the corresponding isonitrile **6** is inactive.

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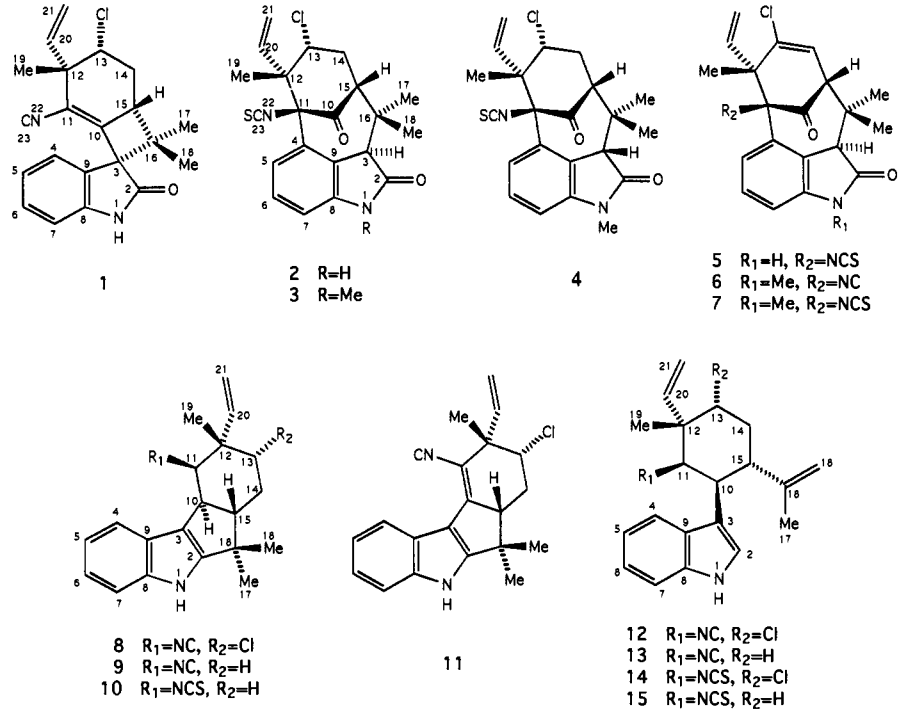
0002-7863/94/1516-9935$04.50/0

Chart 1



1

2 R=H
3 R=Me

4

5 R_1=H, R_2=NCS
6 R_1=Me, R_2=NC
7 R_1=Me, R_2=NCS

8 R_1=NC, R_2=Cl
9 R_1=NC, R_2=H
10 R_1=NCS, R_2=H

11

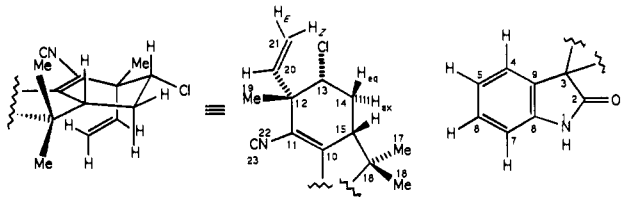
12 R_1=NC, R_2=Cl
13 R_1=NC, R_2=H
14 R_1=NCS, R_2=Cl
15 R_1=NCS, R_2=H

ppm) NMR signals and diagnostic coupling constants.[8] Two additional rings accounted for the remaining units of unsaturation in this tetracyclic alkaloid.

The homonuclear and heteronuclear couplings associated with the ^{1}H signals at 6.92, 7.06, 7.24, and 7.29 ppm confirmed that the benzenoid ring of the oxindole was unsubstituted. HMBC and SINEPT experiments indicated further that C-3 was quaternary since $^3J_{H,C}$-type coupling could be clearly seen between the proton signal at 7.24 ppm (4-H) and the nonprotonated carbon signal resonating at 65.3 ppm (assigned to C-3). Evidence of three-bond coupling between the NH and C-3 signals was not observed. Nevertheless C-3 was definitely disubstituted.

Analysis of the ^{1}H NMR signals at 1.92, 2.03, 3.60, and 4.04 ppm indicated that a $CHCH_2CH$ unit was present. The sizes of the various vicinal couplings associated with these signals strongly suggested that this unit was located in a six-membered ring where the two methine protons were axial. On the basis of chemical shifts, the chlorine was attached to the methine resonating at δ_H 4.04 and δ_C 64.3 (C-13-H), not the one resonating at δ_H 3.60 and δ_C 47.7 (C-15-H). A *gem*-dimethyl group was attached to C-15 since HMBC cross peaks were seen between the 15-H signal and each of the carbon signals at 48.1 (s, C-16), 21.4 (q, C-17), and 23.5 (q, C-18) ppm. The CC double bond bearing the isocyano group also appeared to be connected to C-15 since the HMBC spectrum revealed correlations from δ_H 3.60 (15-H) to δ_C 119.9 (assigned to C-11) and δ_C 138.09 (assigned to C-10 because the 14-H_{eq} signal also shows a cross peak to this carbon signal). A quaternary carbon (47.3 ppm, C-12) bearing the vinyl substituent and the third methyl group (21.5 ppm, C-19) was attached to the chlorine- and isocyano-bearing carbons since HMBC cross peaks were observed between the methyl proton signal at 1.43 ppm (19-H_3) and each of the carbon signals for C-11, C-12, C-13, and C-20. The vinyl group appeared to be in an axial position on C-12 since the 21-H_E signal (5.46 ppm) was a doublet of broad triplets ($J_{20,21E}$ = 10.8 and $J_{gem}/J_{13,21E}$ = 0.5 Hz) showing long-range (zig-zag) coupling to the axial proton on C-13.

To complete the structure of **1**, C-10 of the cyclohexene ring and C-16 of the *gem*-dimethyl group (**1a**) had to both be connected to C-3 of the oxindole (**1b**), resulting in a spiro-fused four-membered ring. 17-H_3/C-3 and 18-H_3/C-3 HMBC correlations confirmed the attachment of C-16 to C-3, but evidence for three-bond coupling between 15-H and C-3 could not be detected in either the HMBC spectrum or a SINEPT experiment. The HMBC spectrum, however, exhibited an unusual $^4J_{H,C}$ coupling between 15-H and C-2, suggesting that 15-H and C-2 might be *cis* to each other on the cyclobutane ring.[9]



1a 1b

A ROESY spectrum supported the proposed relative stereochemistry in the cyclohexene ring of **1**. NOE's were observed between 19-H_3 and 13-H, 13-H and 15-H, 14-H_{ax} and 17-H_3, and 15-H and 18-H_3, denoting that the methyl group on C-12 and the quaternary carbon of the *gem*-dimentyl group on C-15 were both equatorial. A Dreiding model of **1** showed that 4-H was close to 17-H_3 and a confirmatory negative NOE was readily seen in a 1D difference spectrum. Data was not obtained to rigorously establish the absolute stereochemistry as depicted in **1**, but it is probably the same as for the hapalindoles.[10]

The EIMS and FDMS of **7** disclosed a chlorine-containing M^+ ion cluster at *m/z* 412/414 and HREIMS (*m/z* 412.1009, Δ+0.3 mmu) and HRFABMS (*m/z* 413.1118, Δ-2.7 mmu) suggested that its molecular formula was $C_{22}H_{21}ClN_2O_2S$. The presence of 22 carbons and 21 hydrogens (nonexchangeable) in the form of four methyls, one methylene, seven methines, and eleven nonprotonated carbons was confirmed from ^{13}C NMR data. The UV spectrum revealed that **7** was also an oxindole, but NMR analysis (*vide infra*) indicated that the nitrogen was methylated and the benzenoid ring was substituted at C-4. In

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additon to the oxindole carbonyl signal at 174.0 ppm, the ^{13}C NMR spectrum showed a ketone carbonyl signal at 196.3 ppm. The remaining heteroatoms were accounted for by an isothiocyanate group (broad intense band at 2039 cm^{-1} in IR).

Three of the methyls in **7** were attached to quarternary carbons as found in related indole alkaloids (^1H NMR singlets at 1.69, 1.48, and 0.81 ppm). The fourth one, however, appeared to be attached to nitrogen, viz., the oxindole nitrogen (singlet at 3.18 ppm), since **7** did not possess an exchangeable NH. An HMBC experiment showed important $^3J_{H,C}$ correlations from the *N*-methyl protons (3.18 ppm) to the oxindole carbonyl carbon (C-2) and to a non-protonated aromatic carbon at 144.4 ppm (C-8). In addition, the NCH_3 protons showed an unusual $^4J_{H,C}$ correlation to an aromatic methine carbon at 124.6 ppm (C-7). The ^1H NMR spectrum exhibited signals for three adjacent protons (5-H, 6-H, and 7-H) on the benzenoid portion of the oxindole system, the positioning of which was further demonstrated by a strong NOE between the *N*-methyl protons and H-7. Analysis of HMQC and HMBC spectra led to complete assignments for the benzenoid carbon signals and confirmed the structure. A proton appeared to be present on C-3 of the oxindole since couplings could be detected between the 3-H signal (singlet at 3.74 ppm) and the carbon signals for C-2, C-4, C-8, and C-9 in the HMBC spectrum. Again, an unusual $^4J_{H,C}$ correlation was found between the 3-H and C-5 signals.

Alkaloid **7** possessed a vinyl substituent, since the familiar AMX pattern for the three protons of this group could be observed in the 500 MHz ^1H NMR spectrum in $CDCl_3$.[11] NMR data indicated that a trisubstituted double bond (C13=C14) also existed in **7** and the low field chemical shift (138.6 ppm) of the non-protonated carbon (C-13) suggested that chlorine was attached to it. HMBC correlations clearly revealed that the vinyl group was connected to a quaternary carbon (C-12) bearing another quaternary carbon (C-11), a methyl group (C-19), and C-13 of the trisubstituted double bond; for example, cross peaks were visible between the 20-H signal and the carbon signals for C-12, C-13, and C-19 and between the 19-H_3 signal (1.48 ppm) and the carbon signals for C-11 and C-12. Next, inspection of the COSY spectrum showed that the 14-H signal (a doublet at 6.19 ppm) was coupled with another methine proton signal (a doublet at 3.26 ppm, H-15). HMQC and HMBC data then allowed us to connect C-14 successively to C-15, a ketone carbonyl carbon (196.3 ppm, C-10) and C-11 (83.7 ppm). Most importantly, HMBC cross peaks were evident between the 14-H signal and the carbon signals for C-10 and C-15 and between the 15-H signal and the carbon signals for C-10 and C-11, thereby establishing that a cyclohexenone moiety was present.

Additional HMBC correlations revealed unequivocally how the cyclohexenone unit was attached to the oxindole part of the molecule. Since $^3J_{H,C}$-coupling was observed between H-5 and C-11, C-11 must be connected to C-4. Furthermore, since HMBC cross peaks were shown between the H-3 signal and the carbon signals for C-15 and the *gem*-dimethyl group (C-16, C-17, and C-18) and between the H-15 signal and the carbon signals for C-3, C-16, and C-17, C-15 and C-3 had to be bridged via a *gem*-dimethyl group. Therefore, by a process of elimination, the isothiocyano group, having a typical ^{13}C chemical shift of 140.4 ppm, had to be attached to C-11.

Analysis of a ROESY spectrum led us to the total relative stereochemistry. Significant NOE cross peaks were seen between the 5-H and vinyl proton signals, the 3-H and 17-H_3 signals, and the 3-H and 14-H signals and were consistent only with the relative stereochemistery depicted in **7**.

To rigorously establish the relative and absolute stereochemistry, crystals of **7** from MeOH were subjected to an X-ray crystallographic study as described in the Experimental Section.

(11) At 300 MHz in $CDCl_3$, however, the spectral pattern for the three vinyl proton signals of **7** was too complex (ABC type) and coupling constants could not be discerned. In acetone-d_6 at 300 MHz, the vinyl protons exhibited essentially a 3H singlet.

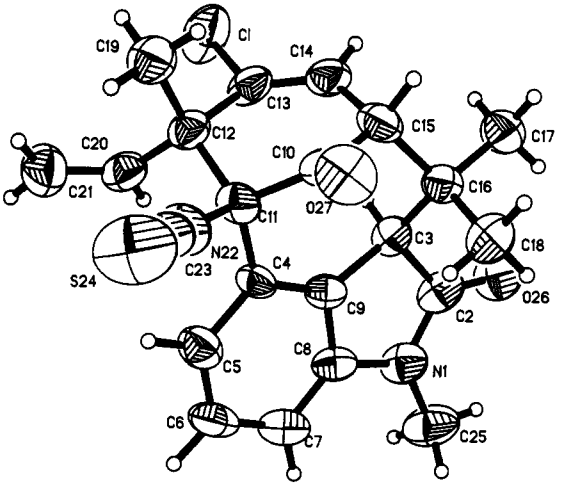


Figure 1. X-ray crystal structure of welwitindolinone **7**.

Table 1. ^1H-NMR Data (500 MHz) for Welwitindolinones **2**–**7** in $CDCl_3$[a]

position	2	3[b]	4[a]	5	6	7[c]
1	8.26	–	7.55	8.50	–	–
3	4.19	4.13	3.25	3.78	3.75	3.74
5	7.23 d	7.25 dd	7.43 dd	7.18 dd	7.29 dd	7.19 dd
6	7.28 dd	7.34 ddd	7.28 ddd	7.26 ddd	7.35 ddd	7.31 ddd
7	6.85 d	6.80 d	6.88 dd	6.86 dd	6.83 dd	6.8 d
13	4.18 t	4.17 t	3.77 dd	–	–	–
14	2.79 t	2.79 t	2.32 q (ax)	6.20 d	6.20 d	6.19 d
	–	–	2.10 ddd (eq)	–	–	–
15	2.96 t	2.96 t	2.83 dd	3.27 d	3.25 d	3.26 d
17	1.62	1.63	1.00	1.68	1.70	1.69
18	0.89	0.82	1.66	0.88	0.82	0.81
19	1.48	1.48	1.36	1.49	1.55	1.48
20	6.01 dd	5.99 dd	6.06 dd	5.38 dd	5.37 m	5.36 dd
21*E*	5.21 d	5.19 d	5.50 d	5.30 d	5.37 m	5.28 dd
21*Z*	5.18 d	5.17 d	5.37 d	5.28 d	5.37 m	5.27 dd
NMe	–	3.20	–	–	3.20	3.18

[a] Spectrum of **4** recorded in CD_2Cl_2; *J*(H,H) in hertz for **4**: 5,6 = 8.8; 6,7 = 7.7; 5,7 = 0.8; 13ax,14ax = 12.8; 13ax,14eq = 2.9; 14ax,14eq = −13.8; 14ax,15ax = 11.9; 14eq,15ax = 7.3; 20,21*E* = 10.7; 20,21*Z* = 17.4. [b] *J*(H,H) in hertz for **3**: 5,6 = 8.2; 6,7 = 7.6; 5,7 = 0.7; 13,14 = 6.3; 14,15 = 7.1; 20,21*E* = 11.0; 20,21*Z* = 17.5; the coupling constants for **2** are within ±0.2 Hz of the values for **3**. [c] *J*(H,H) in hertz for **7**: 5,6 = 8.3; 6,7 = 7.3; 5,7 = 0.9; 14,15 = 4.3; 20,21*E* = 10.4; 20,21*Z* = 16.8; 21*E*,21*Z* = 1.1; the coupling constants for **5** and **6** are within ±0.2 Hz of the values for **7**.

Figure 1 is a computer-generated perspective drawing of the final X-ray model.[12]

High resolution EIMS established the elemental compositions of welwitindolinone B isothiocyanate (**2**, $C_{21}H_{21}ClN_2O_2S$), *N*-methylwelwitindolinone B isothiocyanate (**3**, $C_{22}H_{23}ClN_2O_2S$), welwitindolinone C isothiocyanate (**5**, $C_{21}H_{19}ClN_2O_2S$), and *N*-methylwelwitindolinone C isonitrile (**6**, $C_{22}H_{21}ClN_2O_2$). All four alkaloids exhibited ^1H-NMR (Table 1) and ^{13}C NMR spectra that were comparable to the ones for **7**.

The ^1H and ^{13}C NMR spectra of **5** lacked the signals for the *N*-methyl group found in **7** and the ^1H NMR spectrum displayed an additional broad singlet for an exchangeable proton. Since all of the other ^1H and ^{13}C signals showed virtually identical chemical shifts and patterns with those for **7**, **5** differed from **7** only in lacking the methyl group on N-1. Difference NOE experiments confirmed that **5** and **7** had the same relative stereochemistry. In **5** the irradiation of 3-H led to positive NOEs in the 17-H_3 and 14-H signals and the irradiation of 15-H resulted in positive NOEs in the 14-H, 18-H_3, and 17-H_3 signals. This meant that, within the cycloheptene substructures of **5** and **7**, H-3 and the C-17 methyl group are oriented below the "ring plane" whereas H-15 and the C-18 methyl group lie above the

(12) The absolute configuration of **7** is the same as that found in the hapalindoles.[10,19]

plane. When H-5 was irradiated, a positive NOE was measured in the three protons of the vinyl function (spin diffusion from 21$_Z$-H to 21$_E$-H and 20-H), proving that 21$_Z$-H was close to H-5 and the configuration of C-12 was identical to that shown by **7**.

The only major difference in the ^{13}C-NMR spectra of **6** and **7** was the presence of the resonance at 163.4 ppm for **6**, which was indicative of an isonitrile carbon atom in lieu of an isothiocyanate carbon (140.6 ppm in **7**). Aside from this, **6** displayed virtually the same connectivities in all of its 2D-NMR spectra (COSY, HMQC, HMBC). The IR absorption at 2140 cm^{-1} and the HREIMS of **6** confirmed that it was the isocyano analog of **7**. The relative stereochemistry at C-3, C-11, C-12, and C-15 was found to be identical with that of **7**, as clearly demonstrated by difference NOE experiments.

In comparing the ^{1}H NMR spectrum of **3** with that of **7**, the olefinic signal for 14-H and the doublet signal for 15-H were found to be missing and three characteristic triplets at 4.17, 2.96, and 2.79 ppm were observed instead. Their relative intensities (1:1:2) and the vicinal coupling constants (6.3 and 7.1 ppm) associated with these signals were consistent with the presence of a $CHCH_2CHX$ unit having an electron-withdrawing substituent (X = Cl) attached to the methine showing the δ_H 4.17 signal. Since the ^{13}C NMR data for the indolinone units of **3** and **7** were essentially identical and the mass spectral data indicated that two additional hydrogen atoms were present, **3** had to be the 13,14-dihydro analog of **7**. This was confirmed by $^2J_{C,H}$ and $^3J_{C,H}$ correlations in a HMBC experiment. Welwitindolinone **3** was found to have the same relative stereochemistry as **7** from the following ROESY correlations: (1) The mutual NOEs among 3-H, 17-H$_3$, and 14-H indicated the same relative configurations at C-3 and C-15 and the same prochiral assignments for the methyl groups on C-16. (2) In one-dimensional experiments NOEs were observed between 15-H and 13-H as well as between 13-H and 19-H$_3$, reflecting *syn* relationships for these two pairs on the cyclohexanone ring. (3) The irradiation of 20-H$_Z$ led to positive NOEs in the 3-H and 14-H signals, denoting a boat conformation for the cyclohexanone unit as suggested by a Dreiding model of **3**.

The indolinone nitrogen of welwitindolinone B isothiocyanate (**2**) was found to be unmethylated. Apart from the absence of the *N*-methyl signal and the presence of a broad signal for an exchangeable NH-proton (8.26 ppm), the ^{1}H-NMR spectra of **2** and **3** were virtually identical. The relative stereochemistry proved to be the same as in indolinones **3**–**7**, as indicated by a ROESY experiment. Since the ^{1}H NMR signals for 3-H and 13-H partially overlapped in $CDCl_3$ solutions, the ROESY experiment for **2** had to be determined in CD_2Cl_2.

Comparison of the mass spectral data for 3-*epi*-welwitindolinone B isothiocyanate (**4**) and **2** indicated that the two alkaloids possessed not only the same molecular formulas ($C_{21}H_{21}ClN_2O_2S$), but very similar fragmentation patterns in their EI mass spectra. Characteristic resonances in the ^{13}C spectra for C-2, C-10, and C-11 suggested that **4** was a stereoisomer of **2**. All two-dimensional NMR experiments confirmed this finding. Besides chemical shift differences for 3-H, 17-H$_3$, and 18-H$_3$, the ^{1}H NMR spectra of the two alkaloids differed mainly in the coupling patterns for 15-H, 14-H$_2$, and 13-H. Coupling constants supported the presence of a C(15)H$_{ax}$C(14)H$_{ax}$H$_{eq}$C(13)H$_{ax}$ unit in the six-membered ring. Detailed stereochemical analysis using one-dimensional NOE experiments revealed that **4** differed from **2** by configuration at C-3. This could be deduced from the NOEs observed between 3-H and 18-H$_3$ and between 15-H and 18-H$_3$ which led us to conclude that 3-H, 18-H$_3$, and 15-H were positioned *syn* to one other. Unlike **2**, irradiation of 3-H did not result in a negative NOE in 17-H$_3$ and this indicated that the C-17 methyl group was *anti* to 3-H. Moreover, the C-17 methyl group had to be in close proximity to the equatorial and axial protons of C-14, as indicated by NOEs. A study of a Dreiding model showed that these NOEs could only be achieved if the six-membered ring was in a boat conformation, one that would also account for the observed vicinal coupling constants among 15-H, 14-H$_2$, and 13-H.

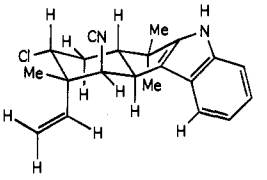
Table 2. ^{1}H-NMR Data (500 MHz) for Fischerindoles 8–11 in CD_2Cl_2

position	8[a]	9[b]	10[b]	11[a]
1	8.06	8.03	8.03	8.38
4	7.41 dd	7.44 d	7.44 d	8.29
5	7.07 ddd	7.14 m	7.07 m	7.18 m
6	7.11 ddd	7.14 m	7.09 m	7.18 m
7	7.36 dd	7.35 dd	7.35 d	7.38 d
10	3.30 dtd[c]	3.17 dtd[c]	3.22 dd	
11	4.53 d	4.37 br s	4.50	–
13eq	–	1.91 dd	1.94 m	–
13ax	4.18 dd	1.71 m	1.60–1.70 m	4.14 m
14eq	2.19 ddd	1.71 m	1.60–1.70 m	2.10 m
14ax	2.08 q	1.62 m	1.60–1.70 m	2.10 m
15	2.45 ddd	2.32 td	2.28 td	3.12 m
17	1.11	1.04	1.04	1.17
18	1.44	1.40	1.40	1.45
19	1.55	1.26	1.13	1.58
20	6.30 dd	5.89 dd	5.92 dd	5.89 dd
21*E*	5.39 d	5.22 d	5.20 d	5.34 d
21*Z*	5.35 d	5.23 d	5.22 d	5.14 d

[a] J(H,H) in hertz for **8**: 4,5 = 7.7; 5,6 = 7.7; 6,7 = 7.7; 4,6 = 1.1; 5,7 = 1.1; 10,11 = 2.7; 10ax,15ax = 10.5, 14eq,15ax = 2.9; 14ax,15ax = 13.4; 13ax,14ax = 12.0; 13ax,14eq = 4.7; 14ax,14eq = –12.5; 20,21*E* = 10.9; 20,21*Z* = 18.0; the coupling constants for **11** are within ±0.5 Hz of the values for **8**. [b] J(H,H) in hertz for **9**: 4,5 = 7.0; 5,6 = 7.0; 6,7 = 7.0; 4,6 = 0.8; 5,7 = 0.8; 10ax,15ax = 11.5, 14eq,15ax = 3.3; 14ax,15ax = 11.5; 13ax,13eq = –12.6; 20,21*E* = 11.0; 20,21*Z* = 17.9; the coupling constants for **10** are within ±0.2 Hz of the values of **9** with the exception of 10ax,11eq = 2.6; 10ax,15ax = 10.4, 14ax,15ax = 10.4 [c] Actually a doublet of a 1:1:1 triplet of doublets where $J_{H,^{14}N}$ = 3.5 Hz.

Fischerindoles. ^{1}H NMR (Table 2) and UV data indicated that **8**–**10** were 2,3-disubstituted indoles of the fischerindole class.[8b] Indeed, 17-H$_3$/C-2 and 18-H$_3$/C-2 HMBC correlations confirmed that C-16 of the *gem*-dimethyl group was connected to C-2 of the indole for each alkaloid. One-dimensional spectral studies coupled with difference NOE experiments, however, revealed that the relative stereochemistry in **8**–**10** differed from that of fischerindole L[8b] at C-10. More definitively, IR and ^{13}C NMR data indicated that **8** and **9** were isonitriles whereas **10** was an isothiocyanate.

The coupling constants in the ^{1}H NMR spectrum of **8** suggested that a C(11)H$_{eq}$C(10)H$_{ax}$C(15)H$_{ax}$C(14)H$_{ax}$H$_{eq}$C(13)H$_{ax}$ unit was present in a six-membered ring as depicted in **8a**. One-



8a

dimensional NOE experiments supported this conclusion and allowed the assignment of relative stereochemistry at C-12. The vinyl group was concluded to be in an axial position, since irradiation of 20-H led to positive NOEs in the 10-H$_{ax}$, 11-H$_{eq}$, and 14-H$_{ax}$ signals. The C-19 methyl group was therefore in an equatorial position and an NOE between 13-H$_{ax}$ and 19-H$_3$ confirmed this assignment. Furthermore, NOEs could be observed from 10-H$_{ax}$ to 4-H and 17-H$_3$. These results clearly showed that 10-H, 11-H, and the vinyl group were located on the same side of the six-membered ring and *syn* to the C-17 methyl group. Positive NOEs were also seen in the 13-H$_{ax}$, 14-H$_{eq}$, and 18-H$_3$ signals when 15-H$_{ax}$ was irradiated. This meant that the C-18 methyl group and H-15 were *syn* to each other on the five-membered ring, and 15-H and 13-H were axially disposed and syn to the C-19 methyl group on the cyclohexane ring. In summary, **8** was found to possess the same relative stereochemistry as the welwitindolinones and differ from fischerindole L[8b] and hapalindole G[10] by configuration at C-12 and C-10, respectively. Indole **8** was therefore 12-*epi*-fischerindole G isonitrile.

Fischerindoles **9** and **10** showed similar NMR spectra. For fischerindole **9**, however, the H-11 signal was broader due to coupling with the isonitrile nitrogen. This type of coupling was not shown by the corresponding isothiocyanate **10**. The ^1H and ^{13}C NMR of both compounds spectra lacked the low field signal for a proton attached to a chlorine-bearing carbon, but otherwise displayed similar resonances and coupling patterns as **8**. The coupling constants $J_{10,15}$ and $J_{14,15}$ confirmed that a C(10)H_{ax}C-(15)H_{ax}C(14)$H_{ax}H_{eq}$ unit in a six-membered ring was present for both compounds. The relative stereochemistry of C-11 and C-12 in the two new fischerindole compounds was determined by differential NOE experiments. Since the irradiation of 10-H induced positive NOEs in 20-H, 11-H, and 17-H_3, the vinyl group had to be *syn* to 11-H_{eq} and 10-H_{ax} and the C-17 methyl group had to be *syn* to 10-H_{ax}. Alkaloids **9** and **10** were therefore 12-*epi*-fischerindole U isonitrile and isothiocyanate, respectively, based on fischerindole L[8b] and hapalindole U[10] nomenclature.

In the ^1H NMR spectrum of **11**, the chemical shifts and coupling patterns for the signals at 3.12, 2.10, and 4.14 ppm denoted the presence of a C(15)HC(14)H_2C(13)HX unit where X had to be chlorine on the basis of the mass spectral data. The downfield shift of the ^{13}C signal for C-22 (164.8 ppm) was consistent with a conjugated isonitrile. The unsubstituted C=C unit (C-11, 113.0 ppm; C-10, 140.7 ppm) attached to the isonitrile was further connected to C-15 and to C-3 of the indole ring, the latter causing C-2 and C-3 to resonate at lower field compared with **8**. Appropriate correlations in the HMBC experiment verified the connections, namely 15-H/C-11, 15-H/C-10, 14-H_2/C-10, 17-H_3/C-2, 18-H_3/C-2, and 4-H/C-3. The relative stereochemistry of **11** was determined by differential NOE spectroscopy. The most diagnostic NOEs, viz. 19-H_3/13-H, 13-H/15-H, and 15-H/18-H_3, showed that the protons on C-13 and C-15 were axial and *syn* to both the C-18 and C-19 methyl groups. Indole **11** was therefore the 10,11-dehydro analog of **8** (12-*epi*-fischerindole I isonitrile[10]).

Hapalindoles. The second most abundant alkaloid in *Hapalosiphon welwitschii* was found to be 12-*epi*-hapalindole E (**12**). This known tricyclic hapalindole had been isolated by Schwartz et al. from another cyanophyte belonging to the Stigonemataceae, *Fischerella* sp. ATCC 53558.[13] In the articles describing the structure determination of **12**, however, the authors have inadvertently presented the wrong stereochemistry at C-10 in the structural drawing. The proton on C-10 of **12** is clearly axial since it shows a large coupling to axial 15-H (J = 12.1 Hz) and a small coupling to equatorial 11-H (J = 2.9 Hz). Minor amounts of three other analogs, viz. 12-*epi*-hapalindole C isonitrile (**13**), 12-*epi*-hapalindole F isothiocyanate (**14**), and 12-*epi*-hapalindole D isothiocyanate (**15**) have been isolated from *H. welwitschii*.

The ^1H NMR data for **13–15** were very similar to the data for **12**. Analysis of the coupling constants (Table 3) led to axial and equatorial assignments for the various protons in the six-membered ring. The coupling constant for $J_{10,15}$ (12.0 Hz) suggested axial orientations for 10-H and 15-H. For **12** and **13**, the H-10 signal displayed an additional *trans* coupling with the nitrogen of the isonitrile (J = 3.2 Hz) that was not observed for the corresponding isothiocyanates **14** and **15**. Difference NOE experiments confirmed that the relative stereochemistry for **12–15** was the same. For each one of these hapalindole isomers, irradiation of the 20-H signal induced NOEs in the signals for the 10-H, 11-H, and 14-H_{ax} protons which indicated that the vinyl group was *syn* to these three protons.

Biogenesis. 12-*epi*-Hapalindole E isonitrile (**12**) is proposed to be the common precursor of the chlorine-containing, isonitrile alkaloids found in *H. welwitschii* (Scheme 1). The biogenesis of **12** may involve a chloronium ion-induced condensation of intermediates derived from geranyl pyrophosphate and tryptophan,[8b] viz. (*Z*)-3,7-dimethyl-1,3,6-octatriene and 3-((*Z*)-2′-isocyanoethenyl)indole.[14] A similar condensation in the presence of a hydrogen ion would lead to 12-*epi*-hapalindole C isonitrile (**13**). Studies on the biosynthesis of hapalindole A suggest that the isonitrile group comes from a tetrahydrofolate (THF) C_1 pool intermediate, possibly 5-formimidoyltetrahydrofolate,[15] and that glycine (C-2 and N-2) and cyanide can serve as precursors of both the carbon and nitrogen of the isonitrile group.[16] The origin of the isothiocyanate group, however, is less clear, but possibly could arise directly from inorganic thiocyanate or indirectly by introduction of a sulfur into an intermediate organic isonitrile. The same organic substrate that accepts the nitrogen end of cyanide from the C_1 pool might accept the nitrogen end of thiocyanate. The isothiocyanate alkaloids found in *H. welwitschii* might then form in an analogous manner as the isonitrile alkaloids, i.e. via 3-((*Z*)-2′-isothiocyanatoethenyl)indole and tricyclic hapalindole **14** intermediates.

12-*epi*-Fischerindole G isonitrile (**8**) is probably formed from **12** by an enzyme-controlled, acid-catalyzed condensation of the isopropenyl group onto C-2 of the indole system. Earlier we had shown that this type of cyclization can proceed nonenzymatically. Hapalindole C formamide (dechlorohapalindole E formamide), for example, is converted to a mixture of fischerindole C formamide and amine in the presence of strong acid, but curiously hapalindole E formamide fails to cyclize under the same conditions.[17] Similar enzyme-controlled cyclizations of **13** and **15** would be expected to lead to 12-*epi*-fischerindole U isonitrile (**9**) and isothiocyanate (**10**), respectively. Cyclization of the isopropenyl group onto C-4 would lead to a tetracyclic hapalindole like those found in *Hapalosiphon fontinalis* V-3-1, viz. 12-*epi*-hapalindole G isonitrile (**16**) in the case of **12** (Scheme 1). Hapalindole **16**, however, could not be detected in *H. welwitschii* IC-52-3.

All of the welwitindolinones (**1–7**) have the same relative stereochemistry as **12**, leading one to speculate that **12** and **14**

Table 3. ^1H-NMR (500 MHz) of 12-epi-Hapalindoles 12–15 in $CDCl_3$

position	12	13	14[a]	15
1	8.12 br	8.08 br s	8.29 br s	8.26 br s
2	7.17 br d	7.19 s	7.11 s	7.12 s
4	7.39 d	7.44 d	7.42 dd	7.47 d
5	7.13 t	7.12 td	7.11 ddd	7.10 td
6	7.20 t	7.20 td	7.19 ddd	7.18 td
7	7.38 d	7.37 d	7.40 dd	7.39 d
10ax	3.63 br dq	3.47 dq	3.67 dd	3.52 dd
11eq	4.02 br s	3.8 br s	4.23 d	3.98 d
13ax	4.34 dd	1.77 m	4.27 dd	1.80 m
13eq	–	1.88 m	–	1.80 m
14ax	2.14 dt	1.81 m	2.23 ddd	1.80 m
14eq	2.23 q	1.67 m	2.17 q	1.69 m
15ax	3.04 td	2.86 ddd	3.02 ddd	2.82 ddd
17	1.51 s	1.47 s	1.53 s	1.48 s
18*E*	4.71 p	4.63 s	4.72 t[b]	4.64 br s
18*Z*	4.85 dq	4.79 s	4.86 m[b]	4.80 br s
19	1.46 s	1.20 s	1.40 s	1.15 s
20	6.45 dd	6.00 dd	6.45 dd	6.04 dd
21*E*	5.59 d	5.40 d	5.57 d	5.38 d
21*Z*	5.45 d	5.31 d	5.45 d	5.31 d

[a] Spectrum recorded in $CDCl_3$; J(H,H) in hertz for **14**: 4,5 = 7.2; 5,6 = 7.2; 6,7 = 7.2; 4,6 = 1.0; 5,7 = 1.0; 10ax,11eq = 2.7; 10ax,15ax = 12.0, 14eq,15ax = 4.5; 14ax,15ax = 11.9; 13ax,14ax = 12.0; 13ax,14eq = 4.6; 14ax,14eq = −13.5; 20,21*E* = 11.4; 20,21*Z* = 17.6; the observable coupling constants for **13** and **15** are within ±0.6 Hz of the values for **14**. For **12** and **13** a ^1H–^{14}N coupling of 3.2 Hz is observed between H-10ax and the isonitrile N. [b] Allylic and geminal coupling (<1 Hz).

(13) (a) Schwartz, R. E.; Hirsch, C. F.; Springer, J. P.; Pettibone, D. J.; Zink, D. L. *J. Org. Chem.* **1987**, *52*, 3706–8. (b) Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113–24.

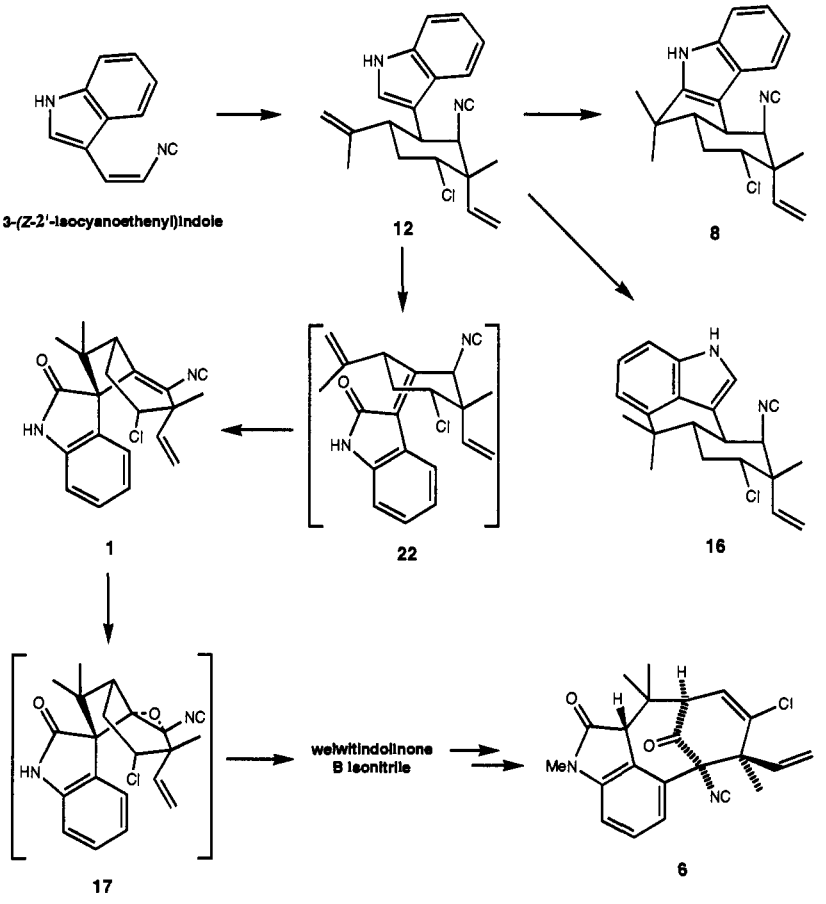
(14) 3-((*Z*)-2′-Isocyanoethenyl)indole (antibiotic B371) has been isolated from a *Pseudomonas* sp. [Evans, J. R.; Napier, E. J.; Yates, P. *J. Antibiotics* **1976**, *19*, 850–2].

(15) Kochi, H.; Kikuchi, G. *J. Biochem.* **1974**, *75*, 1113–27.

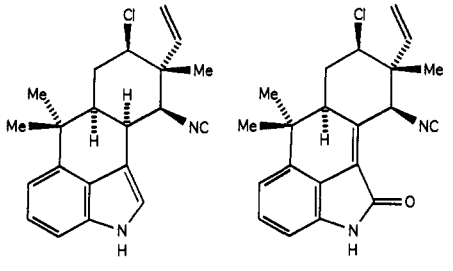
(16) Bornemann, V.; Patterson, G. M. L.; Moore, R. E. *J. Am. Chem. Soc.* **1988**, *110*, 2339–40.

(17) Bonjouklian, R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1988**, *53*, 5866–70.

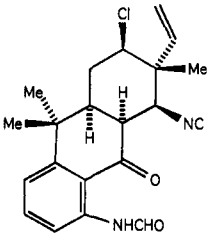
Scheme 1. Biogenesis of Indole Alkaloids in *Hapalosiphon welwitschii*



are biogenetic precursors. The absence of indoles with the same skeletal structure as **2–7** suggests that the oxidation of the indole system in **12** and **14** may occur early and play an important role in the formation of these unusual tetracyclic alkaloids. In the proposed biogenesis of **6** shown in Scheme 1, an isocyano epoxide[18] intermediate **17** generated from **1** might even be involved.


18

19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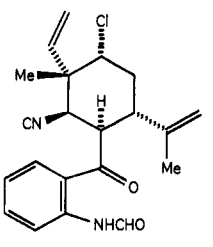
21

Indolinones and other oxidized indoles of hapalindole A (**18**) are present in *H. fontinalis* V-3-1, the major ones being anhydrohapaloxindole A (**19**) and fontonamide.[19] Interestingly, **19** and fontonamide, along with hapalonamides A (**20**) and G, hapalindoles G and I and other products, can be produced by a singlet oxygen oxidation of **18** in MeOH.[19a] A similar $^1O_2$ oxidation of **12**, however, produces essentially a sole product, 12-*epi*-hapalonamide E isonitrile (**21**). Indolinone **22**, having a structure related to **19**, is not formed; however, **22** might serve as an algal intermediate from **12** to **1** (Scheme 1).[20]

Experimental Section

Spectral Analysis. NMR spectra were determined on 11.75 and 7.05-T instruments operating at 500 and 300 MHz for ^1H and 125 and 75 MHz for ^{13}C. ^1H chemical shifts are referenced in $CDCl_3$ and CD_2Cl_2 to residual $CHCl_3$ (7.24 ppm) and $CHDCl_2$ (5.32 ppm); ^{13}C chemical shifts are referenced to the solvent ($CDCl_3$, 77.0 ppm and CD_2Cl_2, 52.8 ppm). A water peak is found near 1.5 ppm in the ^1H spectra presented in the supplementary material. Homonuclear ^1H connectivities were determined by using the 2D double-quantum filtered COSY and 1D decoupling experiments. Homonuclear ^1H NOEs were obtained by difference NOE experiments using a 2 s irradiation period and by 2D ROESY experiments. One-bond heteronuclear ^1H–^{13}C connectivities were determined by 2D proton-detected HMQC experiments; two- and three-bond ^1H–^{13}C connectivities were determined by 2D proton-detected HMBC experiments and 1D carbon-detected SINEPT experiments. Mass spectra, including high resolution mass measurements, were determined in the EI mode. UV spectra were measured in MeOH at 20 °C. Optical rotations were measured in CH_2Cl_2 at 20 °C at the sodium D line (589 nm).

Isolation and Cultivation of Alga. A unialgal, nonaxenic strain of *Hapalosiphon welwitschii* W. & G. S. West, designated UH strain IC-52-3, was isolated from a freshwater sample collected at the Australian Institute of Marine Sciences in Queensland, Australia (19° 17′ 00″ S, 147° 4′ 00″ E) on March 13, 1990 and purified by repeated subculture on solidified media. The cyanophyte was cultured in an autoclaved 20

(18) Fusetani, N.; Wolstenholme, H. J.; Shinoda, K.; Asai, N.; Matsunaga, S.; Onuki, H.; Hirota, H. *Tetrahedron Lett.* **1992**, *33*, 6823–6.

(19) (a) Moore, R. E.; Yang, X-Q. G.; Patterson, G. M. L. *J. Org. Chem.* **1987**, *52*, 3773–7. (b) Moore, R. E.; Yang, X-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A. *Phytochemistry* **1989**, *28*, 1565–7.

(20) The oxidation of **12** with manganese(III) porphin and iodosylbenzene [Saltzman, H.; Sharfkin, J. G. *Org. Synth.* **1963**, *43*, 60–1], a model system for cytochrome P450 oxidation [Hill, C. L.; Schardt, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 6374–5], did not lead to stable products.

L glass carboy containing an inorganic medium (modified BG-11) adjusted to pH 7.0 with MOPS. Cultures were continuously illuminated at an incident intensity of 80–100 μmol photons m^{-2} s^{-1} (photosynthetically active radiation) from banks of cool-white fluorescent tubes and vigorously aerated at a rate of 5 L/min with a mixture of 0.5% CO_2 in air at a temperature of 24 ± 1 °C. After 35 d the alga was harvested by filtration onto Whatman No. 4 paper. The yield of lyophilized cells was 0.45–0.5 g/L.

An edaphic form of *Westiella intricata* Borzi, designated UH strain HT-29-1, was isolated from a soil sample collected on Moen Island, Truk Atoll, Caroline Islands (7° 27′ 9″ N, 151° 51′ 17″ E) on June 29, 1988. The strain was purified and cultivated as described above. After incubation for 20–25 d, the alga was harvested by filtration. The yield of lyophilized cells was 0.17–0.25 g/L.

Isolation of Alkaloids from *Hapalosiphon welwitschii* IC-52-3.[21] Freeze-dried alga (47 g) was extracted twice with 2.5 L portions of 1:1 CH_2Cl_2/2-propanol overnight with stirring. The extracts were combined and evaporated under reduced pressure to a green solid (2 g). This material was dissolved in 20 mL of MeOH and the filtered solution was applied to a column of Sephadex LH20-120 (Fluka, 80 cm x 4.5 cm diameter, flow rate 60 mL/h) equilibrated in MeOH. The first 700 mL of MeOH effluent was discarded and five fractions were collected based on silica-TLC analysis, viz. fraction 1 (700–750 mL, 130 mg), fraction 2 (750–810 mL, 208 mg), fraction 3 (810–855 mL, 130 mg), fraction 4 (855–915 mL, 67 mg), and fraction 5 (915–1050 mL, 36 mg). Fractions 1–3 were flash chromatographed on 33 cm x 2.5 cm columns of silica gel (100–200 mesh, Fisher) with a gradient of CH_2Cl_2/isooctane (C/i-O). Material was eluted by using successively 300 mL amounts of the following solvent mixtures: 65/35, 70/30, 75/25, 80/20, 85/15, and 90/10 C/i-O. Fraction 1 afforded alkaloids **6** (75/25 C/i-O, 47 mg) and **3** (85/15 C/i-O, 5 mg). Fraction 2 gave fraction 2A (65/35 C/i-O, 32 mg) followed by **7** (70/30 C/i-O, 110 mg), additional **3** (75/25 C/i-O, 12 mg), and **1** (90/10 C/i-O, 2 mg). Fraction 2A was chromatographed further on an Econsil C18 HPLC column (250 mm x 10 mm, Alltech) using 61% CH_3CN in H_2O as the mobile phase to give successively **9** (4 mg), **8** (4 mg), **13** (11 mg), and **12** (6 mg). Fraction 3 yielded after flash chromatography fraction 3A (65/35 C/i-O, 6 mg) and additional **12** (70/30 C/i-O, 87 mg). Fraction 3A was further purified by HPLC on a C18 Econosil column (Alltech, mobile phase 65% CH_3CN in H_2O) to give indoles **10** (2 mg) and **15** (1 mg). Similar reversed-phase HPLC purification gave indolinones **2** (10 mg) and **5** (14 mg) from fraction 4 and additional **2** (2 mg), **4** (1 mg), **11** (10 mg), and **14** (4 mg) from fraction 5.

The alkaloids had the following R_f values on silica gel TLC plates with 10:1 CH_2Cl_2/isooctane: **15** (0.71), **10** (0.69), **14** (0.68), **11** (0.49), **8** (0.48), **12** (0.46), **9** (0.45), **13** (0.44), **7** (0.32), **3** (0.26), **6** (0.24), **5** (0.13), **2** (0.11), **4** (0.11), **1** (0.09). The alkaloids had the following HPLC t_R-values in minutes on a 250 × 4.6 mm ODS column (Alltech Econosil, flow rate 1.0 mL/min) using 65% CH_3CN in H_2O as the mobile phase: **2** (9.9), **1** (10.4), **6** (10.6), **4** (12.0), **5** (13.4), **3** (15.5), **9** (16.9), **8** (17.1), **13** (18.7), **11** (19.1), **12** (20.4), **7** (22.2), **10** (33.7), **15** (37.5), **14** (38.8).

Isolation of Alkaloids from *Westiella intricata* HT-29-1. Lyophilized alga (23 g) was stirred in 1.6 L of 1:1 CH_2Cl_2/2-propanol for 16 h at rt and the extract filtered through paper and evaporated to afford 5.8 g of residue. This material was stirred with 80 g of C-18 reverse-phase material in 200 mL of MeOH for 45 min and then 200 mL of water was slowly added to the C-18 suspension over 30 min. The C-18 was captured in a fritted glass funnel and washed with 100 mL of 1:1 MeOH/H_2O. The absorbed organic material was removed from the C-18 by gradual gradient elution and the 90% MeOH/H_2O fraction (A) possessed antibacterial activity. The 500 mg of residue in fraction A was further purified on a 93 cm x 2.25 cm column of Sephadex LH-20 with MeOH to afford 145 mg of fraction B from which the pigments could be removed by silica gel chromatography (15 g, 1.3 cm i.d.) using 2:2:1 cyclohexane/toluene/acetonitrile, resulting in 95 mg of fraction C. Reverse-phase HPLC of fraction C on a 25 mm x 10 cm column of C-18 (Waters PrepPak) using a 5 mL/min linear 50–75% MeOH/H_2O gradient over 20 min, followed by a 100 min 75% MeOH/H_2O elution, and finally a 75–100% MeOH/H_2O gradient over 25 min, gave **7** (15 mg), **5** (8 mg), and 70% pure **2** (5.5 mg).

Welwitindolinone A isonitrile (1): $[\alpha]_D$ +377° (CH_2Cl_2, *c* 0.078); UV (MeOH) λ_{max} nm (ε) 212 (17 200), sh 250 (4000), 290 (900); IR (neat) ν_{max} 3250, 2065, 1705, 1621, 1470 cm^{-1}. EIMS *m/z* 352/354 (3:1 M^+ ion cluster), 317 (M^+ – Cl); high resolution EIMS *m/z* 352.1360 ($C_{21}H_{21}ClN_2O$, Δ-1.8 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2) δ (multiplicity, *J* in hertz, assignment) 7.62 (br s, 1-NH), 7.29 (td, *J* = 7.7/1.2 Hz, 6-H), 7.24 (ddd, *J* = 7.7/1.2/0.6 Hz, 4-H), 7.06 (td, *J* = 7.7/1.2 Hz, 5-H), 6.92 (ddd, *J* = 7.7/1.2/0.6 Hz, 7-H), 5.99 (dd, J_{trans} = 17.3 and J_{cis} = 10.8 Hz, 20-H), 5.46 (d br t, J_{cis} = 10.8 and $J_{gem}/J_{13,21E}$ = 0.5 Hz, 21-H_E), 5.32 (dd, J_{trans} = 17.3 and J_{gem} = 0.5 Hz, 21-H_Z), 4.04 (dd, *J* = 12.5/3.2 Hz, 13-H), 3.60 (dd, *J* = 10.6/7.0 Hz, 15-H), 2.03 (ddd, *J* = –12.5/7.0/3.2 Hz, 14-H_{eq}), 1.92 (td, *J* = 12.5/10.6 Hz, 14-H_{ax}), 1.43 (s, 19-H_3), 1.26 (s, 18-H_3), 1.19 (s, 17-H_3); ^{13}C-NMR (125 MHz, CD_2Cl_2) δ (assignment; ^{1}*H*-HMBC) 175.8 (C-2; *15*), 167.7 (C-23), 141.8 (C-8; *4,6*), 138.15 (C-20; *13,19,21Z*), 138.09 (C-10; *14eq,15*), 129.5 (C-6; *4*), 127.4 (C-4; *5,6*), 123.1 (C-9; *5,7*), 121.9 (C-5; *7*), 119.9 (C-11; *15,19,20*), 118.1 (C-21), 110.3 (C-7; *5*), 65.3 (C-3; *4,17,18*), 64.3 (C-13; *14eq,14ax,19,20,21E,21Z*), 48.1 (C-16; *15,17,18*), 47.7 (C-15; *14eq,14ax,17,18*), 47.3 (C-12; *19,20,21E,21Z*), 29.1 (C-14; *15*), 23.5 (C-18; *15,17*), 21.5 (C-19; *20*), 21.4 (C-17; *15,18*). C-10/15-H HMBC correlation verified by SINEPT.

Welwitindolinone B isothiocyanate (2): UV (MeOH) λ_{max} nm (ε) 210 (23 500), 251 (8720), sh 288 (2430); IR (neat) ν_{max} 2049, 1707 cm^{-1}; EIMS *m/z* 400/402 (3:1 M^+ ion cluster); HREIMS *m/z* 400.1017 ($C_{21}H_{21}ClN_2O_2S$, Δ-0.5 mmu); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C-NMR (125 MHz, $CDCl_3$) δ (assignment) 198.6 (C-10), 176.5 (C-2), 141.1 (C-8), 139.6 (C-22), 136.4 (C-20), 131.6 (C-4), 128.8 (C-6), 124.5 (C-9), 122.6 (C-5), 118.1 (C-21), 110.0 (C-7), 83.5 (C-11), 62.5 (C-13), 60.2 (C-15), 53.7 (C-3), 53.0 (C-12), 39.8 (C-16), 31.5 (C-14), 25.3 (C-17), 24.1 (C-19), 22.6 (C-18).

***N*-Methylwelwitindolinone B isothiocyanate (3):** $[\alpha]_D$ –149° (CH_2Cl_2, *c* 0.071); UV (MeOH) λ_{max} nm (ε) 208 (22 200), 258 (6800); IR (neat) ν_{max} 2050, 1710, 1608, 1461. EIMS *m/z* 414/416 (3:1 M^+ ion cluster); high resolution EIMS *m/z* 414.1166 ($C_{22}H_{23}ClN_2O_2S$, Δ+0.3 mmu); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C-NMR (125 MHz, $CDCl_3$) δ (assignment; ^{1}*H*-HMBC) 198.6 (C-10; *15*), 174.4 (C-2; *3,23*), 144.1 (C-8; *3,6,23*), 139.6 (C-22), 136.4 (C-20; *13,19,21E,21Z*), 131.3 (C-4; *3,6*), 128.8 (C-6), 123.9 (C-9; *3,5,7*), 122.6 (C-5; *7*), 118.1 (C-21), 108.3 (C-7; *5,23*), 83.5 (C-11; *5,13,15,19,20,21E,21Z*), 62.5 (C-13; *14,15,19,20*), 60.1 (C-15; *13,14,17,18*), 53.2 (C-3; *15,17,18*), 52.9 (C-12; *13,14,19,20,21E,21Z*), 39.8 (C-16; *3,14,15,17,18*), 31.5 (C-14; *13*), 26.4 (C-23), 25.4 (C-17; *3,15,18*), 24.1 (C-19; *13,20*), 22.5 (C-18; *3,17*).

***3-epi*-Welwitindolinone B isothiocyanate (4):** EIMS *m/z* 400/402 (3:1 M^+ ion cluster); HREIMS *m/z* 400.1012 ($C_{21}H_{21}ClN_2O_2S$, Δ0.0 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2): see Table 1; ^{13}C-NMR (125 MHz, CD_2Cl_2) δ (assignment, ^{1}*H*-HMBC) 203.9 (C-10; *14ax,14eq,15*), 174.9 (C-2; *3*), 141.7 (C-8; *3,6*), 138.8 (C-20; *13,19*), 132.9 (C-4; *3,6*), 128.4 (C-6), 125.2 (C-5; *3*), 123.9 (C-9; *5,7*), 116.8 (C-21), 110.3 (C-7; *5*), 80.8 (C-11, t (J=6.4 Hz); *15,19,20*), 64.1 (C-13; *14ax,14eq,19*), 59.6 (C-15; *14eq,17,18*), 53.3 (C-12; *14ax,14eq,19,21E,21Z*), 53.1 (C-3; *15,17,18*), 37.0 (C-16; *3,14eq,15,17,18*), 33.3 (C-14; *15*), 29.4 (C-18; *3,15,17*), 21.9 (C-19; *20*), 20.4 (C-17; *3,18*).[22]

Welwitindolinone C isothiocyanate (5): $[\alpha]_D$ –283° (CH_2Cl_2, *c* 0.1475); UV (MeOH) λ_{max} nm (ε) 212 (24 500), 254 (11 200), 292 (2680); IR (neat) ν_{max} 2041, 1710, 1618, 1443 cm^{-1}. EIMS *m/z* 398/400 (3:1 M^+ ion cluster); high resolution EIMS *m/z* 398.0872 ($C_{21}H_{19}ClN_2O_2S$, Δ-1.6 mmu); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C-NMR (125 MHz, $CDCl_3$) δ (assignment) 196.3 (C-10), 176.3 (C-2), 141.5 (C-8), 140.7 (C-22), 138.8 (C-13), 137.1 (C-20), 130.4 (C-4), 128.6 (C-6), 124.6 (C-5), 123.2 (C-14); 122.9 (C-9), 117.7 (C-21), 110.1 (C-7), 83.7 (C-11), 61.7 (C-15), 57.0 (C-12), 53.5 (C-3), 40.8 (C-16), 25.5 (C-17), 22.2 (C-19), 21.4 (C-18).

***N*-Methylwelwitindolinone C isonitrile (6):** $[\alpha]_D$ –117° (CH_2Cl_2, *c* 0.25), UV (MeOH) λ_{max} nm (ε) 218 (26 200), 260 (16 900), sh 292 (4600); IR (neat) ν_{max} 2140, 1712, 1609, 1461, 1342 cm^{-1}; EIMS *m/z* 398/400 (3:1 M^+ ion cluster); high resolution EIMS *m/z* 380.1298 ($C_{22}H_{21}ClN_2O_2$, Δ-0.7 mmu); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C-NMR (125 MHz, $CDCl_3$) δ (assignment; ^{1}*H*-HMBC) 193.5 (C-10; *14,15*), 173.9 (C-2; *3,23*), 144.6 (C-8; *3,6,23*), 163.4 (C-22), 138.4 (C-13; *14,15,19,20*), 136.2 (C-20; *13,19,21*), 128.8 (C-6), 127.7 (C-4, *3,6*), 124.6 (C-5; *7*), 123.3 (C-14; *15*); 122.9 (C-9; *3,5,7*), 118.3 (C-21; *20*), 108.8 (C-7; *5,23*), 81.8 (C-11; *15,19*), 61.6 (C-15; *3,17,18*), 55.6 (C-12; *14,19,21*), 53.2 (C-3; *15,17,18*), 40.7 (C-16; *3,15,17,18*), 26.4 (C-23), 25.6 (C-17; *3,15,18*), 22.6 (C-19; *20*), 21.3 (C-18; *3,17*).

***N*-Methylwelwitindolinone C isothiocyanate (7):** $[\alpha]_D$ –278° (CH_2Cl_2, *c* 0.77); UV (MeOH) λ_{max} nm (ε) 210 (24 300), 258 (8930), 285 (2300); IR (CH_2Cl_2) ν_{max} 2040, 1712, 1608, 1460, 1341 cm^{-1}; EIMS *m/z* 414/416 (3:1 M^+ ion cluster); HREIMS *m/z* 412.1009 ($C_{22}H_{21}ClN_2O_2S$, Δ+0.3 mmu); high resolution negative ion FABMS *m/z* 413.1118 ($C_{22}H_{22}$-

(21) The same alkaloids are present in *H. welwitschii* UTEX B1830 (D. L. Burgoyne, unpublished results).

(22) ^{13}C-Signal for NCS not observed.

ClN_2O_2S, Δ-2.7 mmu); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 1; ^{13}C-NMR (125 MHz, $CDCl_3$) δ (assignment; *^{1}H*-HMBC) 196.3 (C-10; *14,15*), 174.0 (C-2; *3,23*), 144.4 (C-8; *3,6,23*), 140.6 (C-22), 138.6 (C-13; *14,15,20*), 137.1 (C-20; *21*), 130.0 (C-4; *3,6*), 128.5 (C-6), 124.6 (C-5; *7,23*), 123.3 (C-14; *15*); 122.4 (C-9; *3,5,7*), 117.6 (C-21; *20*), 108.4 (C-7; *5,23*), 83.7 (C-11; *15,19,21*), 61.6 (C-15; *3,14,17,18*), 56.9 (C-12; *14,19,20,21*), 53.1 (C-3; *15,17,18*), 40.7 (C-16; *3,14,15,17,18*), 26.3 (C-23), 25.6 (C-17; *3,15,18*), 22.1 (C-19; *14,20*), 21.3 (C-18; *3,17*).

X-ray Crystallography of 7. The alkaloid crystallized from MeOH in the orthorhombic space group $P2_12_12_1$ with a unit cell having the dimensions a = 7.172(2)Å, b = 10.476(3)Å, c = 27.296(7)Å, and a calculated density of 1.337 g/cm^{-3}. A total of 1635 reflections with 2ϕ less than 116.0° was measured on an automated four-circle diffractometer (Siemens R3m-V) using monochromatic copper radiation and the structure was solved by the direct methods (XS) routines of the SHELXTL PLUS (v 4.0) program library. Full-matrix least squares refinement was conducted with anisotropic temperature factors for all atoms except hydrogens, which were included at calculated positions with isotropic temperature factors. The final R-factor of 0.04 was obtained for 1400 observed reflections and no significant features on the final difference Fourier map were noted (largest difference peak and hole was 0.22 e Å^{-3} and –0.22 e Å^{-3}, respectively. The absolute configuration was determined through use of the anomalous dispersion technique (η – 1.02460).

12-*epi*-Fischerindole G isonitrile (8). $[\alpha]_D$ + 67° (CH_2Cl_2, c 0.09); UV (MeOH) λ_{max} nm (ε) 222 (18 600), 278 (5880); IR (neat) ν_{max} 3414, 2962, 2135, 1456, 1261 cm^{-1}; EIMS *m/z* 338/340 (3:1 M$^+$ ion cluster); high resolution EIMS *m/z* 338.1566 ($C_{21}H_{23}ClN_2$, Δ-1.6 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2): see Table 2; ^{13}C-NMR (125 MHz, CD_2Cl_2) δ (assignment; *^{1}H*-HMBC) 160.0 (C-22), 152.4 (C-2; *17,18*), 140.0 (C-8; *4,6*), 138.3 (C-20; *13,21E,21Z*), 124.0 (C-9; *5,7*), 121.3 (C-6; *4*), 120.3 (C-5; *7*), 118.3 (C-4; *6*), 117.5 (C-21), 114.1 (C-3; *4,10,11*), 112.2 (C-7; *5*), 65.2 (C-13; *11,14eq,14ax,19,20*), 64.2 (C-11; *19,20*), 55.3 (C-15; *11,13,14eq,14ax,17,18*), 45.7 (C-12; *11,13,14eq,14ax,20,21E,-21Z*), 41.8 (C-10; *11,14ax,*), 40.9 (C-16; *17,18*), 32.8 (C-14; *13*), 25.1 (C-18; *17*), 24.9 (C-19; *20*), 20.7 (C-17; *18*).

12-*epi*-Fischerindole U isonitrile (9): UV (MeOH) λ_{max} nm (ε) 226 (17 500), 278 (5680); IR (neat) ν_{max} 3401, 3317, 2961, 2139, 1456, 1264 cm^{-1}; EIMS *m/z* 304 (M$^+$); high resolution EIMS *m/z* 304.1913 ($C_{21}H_{24}N_2$, Δ+2.6 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2): see Table 2; ^{13}C-NMR (125 MHz, CD_2Cl_2) δ (assignment; *^{1}H*-HMBC) 158.2 (C-22), 152.9 (C-2; *17,18*), 143.2 (C-20; *11*), 140.0 (C-8; *4,6*), 124.3 (C-9; *5,7*), 121.0 (C-6; *4*), 120.1 (C-5; *7*), 118.4 (C-4; *5,6*), 115.0 (C-3; *10*), 114.7 (C-21), 112.1 (C-7; *5,6*), 62.8 (C-11; *13eq,15,19,20*), 55.6 (C-15; *10,11,14eq,14ax,17,18*), 42.5 (C-10; *11,14ax,15*), 41.2 (C-12; *11,13eq,19,20*), 40.9 (C-16; *15,17,18*), 32.3 (C-13; *11,14,19,20*), 28.2 (C-19; *13eq,15*), 25.2 (C-18; *15,17*), 20.92 (C-14; *13eq,13ax,15*), 20.89 (C-17; *18*).

12-*epi*-Fischerindole U isothiocyanate (10): $[\alpha]_D$ +231° (CH_2Cl_2, *c* 0.035); UV (MeOH) λ_{max} nm (ε) sh 206 (16 300), 228 (23 000), 278 (5240); IR (neat) ν_{max} 3395, 2964, 2105, 1652 cm^{-1}; EIMS *m/z* 336 (M$^+$); high resolution EIMS *m/z* 336.1624 ($C_{21}H_{24}N_2S$, Δ+3.6 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2): see Table 2; ^{13}C-NMR (125 MHz, CD_2Cl_2) δ (assignment; *^{1}H*-HMBC) 152.8 (C-2; *17,18*), 143.5 (C-20; *11,13,19,21E,21Z*), 140.0 (C-8; *4,6*), 132.0 (C-22; *11*), 124.4 (C-9; *5,7*), 121.0 (C-6; *4*), 120.1 (C-5; *7*), 118.4 (C-4; *6*), 115.3 (C-3; *10*), 114.4 (C-21), 112.1 (C-7; *5*), 65.9 (C-11; *13eq,19,20*), 56.3 (C-15; *10,11,13eq,-13ax,17,18*), 43.9 (C-10; *14eq,14ax*), 42.9 (C-12; *13eq,13ax, 14eq,-14ax,19*), 40.7 (C-16; *17,18*), 32.9 (C-13; *11,14ax,19,20*), 28.3 (C-19; *13ax,20,21E,21Z*), 25.4 (C-18; *17*), 21.0 (C-14; *13$_{ax}$*), 20.8 (C-17; *18*).

12-*epi*-Fischerindole I isonitrile (11): EIMS *m/z* 336/338 (3:1 M$^+$ ion cluster); high resolution EIMS *m/z* 336.140045 ($C_{21}H_{21}ClN_2$, Δ –0.7 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2): see Table 2; ^{13}C-NMR (125 MHz, CD_2Cl_2): δ (assignment; *^{1}H*-HMBC) 164.8 (C-22), 159.1 (C-2; *17,18*), 141.1 (C-8; *6*), 141.0 (C-3; *4*), 140.7 (C-10; *14,15*), 138.6 (C-20; *13,19,21Z*), 123.0 (C-6; *4*), 122.5 (C-9; *5,7*), 122.4 (C-4; *6*), 121.6 (C-5; *7*), 117.6 (C-21), 113.0 (C-11; *15*), 112.2 (C-7), 66.1 (C-13; *15,19*), 57.0 (C-15; *14,17,18*), 46.8 (C-12; *14,19,20,21E,21Z*), 41.3 (C-16; *15,17,18*), 29.8 (C-14; *15*), 25.15 (C-18; *17*), 25.01 (C-17; *18*), 22.9 (C-19; *13*).

12-*epi*-Hapalindole E isonitrile (12): $[\alpha]_D$ +42.9° (CH_2Cl_2, *c* 0.3); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 3. The spectral data were identical with the data reported by Schwartz et al.[13]

12-*epi*-Hapalindole C isonitrile (13): $[\alpha]_D$ +10.4° (CH_2Cl_2, *c* 0.54); UV (MeOH) λ_{max} nm (ε) 219 (18 000), 282 (4800); IR (neat) ν_{max} 3419, 2932, 2137, 1458, 740 cm^{-1}; EIMS *m/z* 304 (M$^+$); high resolution EIMS *m/z* 304.1941 ($C_{21}H_{24}N_2$, Δ-0.2 mmu); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 3; ^{13}C-NMR (125 MHz, $CDCl_3$) δ (assignment; *^{1}H*-HMBC) 157.0 (C-22), 147.5 (C-16; *15,17,18*), 142.5 (C-20; *13,19,21*), 135.6 (C-8; *4,6*), 126.6 (C-9; *2,4,5,7,10*), 123.4 (C-2; *7,10*), 121.9 (C-6; *4*), 119.4 (C-5; *7*), 117.3 (C-4; *2,6*), 115.1 (C-21), 114.0 (C-3; *2,10*), 112.1 (C-18; *15,17*), 111.4 (C-7; *5*), 66.4 (C-11; *13eq,13ax,19,20*), 43.3 (C-15; *10,11,13eq,13ax,14eq,14ax,17,18*), 40.2 (C-12; *11,14eq,14ax,19,20,-21E,21Z*), 36.0 (C-10; *11,15*), 30.8 (C-13; *14eq,14ax,19, 20*), 28.45 (C-19; *21*), 28.45 (C-14; *13ax,13eq,15*), 18.7 (C-17; *15,18*).

12-*epi*-Hapalindole F isothiocyanate (14): $[\alpha]_D$ + 102° (CH_2Cl_2, *c* 0.5); UV (MeOH) λ_{max} nm (ε) 222 (21 700), 282 (5160); IR (neat) ν_{max} 3419, 2966, 2094, 1456, 1263, 1098 cm^{-1}; EIMS *m/z* 370/372 (3:1 M$^+$ ion cluster); high resolution EIMS *m/z* 370.1266 ($C_{21}H_{23}ClN_2S$, Δ+0.4 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2): see Table 3; ^{13}C-NMR (125 MHz, CD_2Cl_2) δ (assignment; *^{1}H*-HMBC) 146.3 (C-16; *14$_{ax}$,15,17*), 138.5 (C-20; *13,19,21Z*), 136.1 (C-8; *4,5,6*), 133.0 (C-22; *11*), 126.9 (C-9; *5,7,10*), 124.3 (C-2; *10*), 122.5 (C-6; *4*), 120.0 (C-5; *7*), 118.0 (C-4; *6*), 117.7 (C-21), 113.5 (C-3; *2,4,10*), 113.4 (C-18; *15,17*), 111.8 (C-7; *5*), 70.5 (C-11; *15,19,20*), 64.3 (C-13; *14eq,14ax,15,19,20*), 46.7 (C-12; *11,13,14eq,19,21E,21Z*), 44.8 (C-15; *10,11,14eq, 14ax,17,18*), 39.5 (C-14; *13,15*), 37.6 (C-10; *11,14eq,14ax*), 25.9 (C-19; *13,21*), 18.7 (C-17; *15,18*).

12-*epi*-Hapalindole D isothiocyanate (15): IR (neat) ν_{max} 3419, 2099, 1929, 1456 cm^{-1}; EIMS *m/z* 336 (M$^+$); high resolution EIMS *m/z* 336.1677 ($C_{21}H_{24}N_2S$, Δ-1.7 mmu); ^{1}H-NMR (500 MHz, $CDCl_3$): see Table 3; ^{13}C-NMR (125 MHz, $CDCl_3$) δ (assignment; *^{1}H*-HMBC) 148.3 (C-16; *17*), 143.1 (C-20; *13,19*), 136.1 (C-8; *2,4,6*), 126.9 (C-9; *2,5,7,10*), 124.2 (C-2; *10*), 122.3 (C-6; *4*), 119.8 (C-5; *7*), 118.0 (C-4; *6*), 115.2 (C-21), 114.9 (C-3; *2,4,10*), 112.2 (C-18; *17*), 111.7 (C-7; *5*), 69.1 (C-11; *19,20*), 44.1 (C-15; *10,11,14eq,14ax,17,18*), 42.1 (C-12; *11,13,14,19,20,21E,21Z*), 38.1 (C-10; *11,14eq,15*), 31.7 (C-13; *11,14,19,20*), 28.9 (C-14; *13ax,13eq*), 28.8 (C-19; *21*), 18.9 (C-17; *18*).[22]

$^1O_2$-Oxidation of 12. 12-*epi*-Hapalindole E (**12**, 54 mg) was dissolved in 5 mL of MeOH along with a trace of rose bengal. Oxygen was passed through this solution as it was irradiated at 25 °C with a slide projector lamp. Progress of the oxidation was monitored by TLC (silica/CH_2Cl_2). After 60 h a major product had formed with a R_f-value of 0.19. The MeOH was evaporated and the residue purified on a 0.5 × 30 cm column of silica gel with CH_2Cl_2 to give 11 mg of recovered **12**, 33 mg of 12-*epi*-hapalonamide E isonitrile (**21**), and 2 mg of a mixture of unidentified, highly polar compounds.

Ketoformamide **21** had the following properties: EIMS *m/z* 370/372 (3:1 M$^+$ ion cluster); high resolution EIMS *m/z* 370.1266 ($C_{21}H_{23}ClN_2O_2$, Δ –0.7 mmu); ^{1}H-NMR (500 MHz, CD_2Cl_2) δ (multiplicity, *J* in hertz; assignment) 11.2 (s br; 2-H), 8.76 (d, 8.2 Hz; 7-H), 8.45 (s br, 1-H), 7.67 (dd, 7.85/1.2 Hz; 4-H), 7.62 (t, *J* = 7.85 Hz; 6-H), 7.19 (t, *J* = 7.7 Hz; 5-H), 6.39 (dd, *J* = 17.7/11.3; 20-H), 5.61 (d, *J* = 11.3 Hz; 21-H$_E$), 5.40 (d, *J* = 17.7; 21-H$_Z$), 4.78 (t, *J* = 1.2 Hz; 18-H$_Z$), 4.70 (s br; 18-H$_E$), 4.19 (dd, *J* = 12.6/4.4 Hz; 13-H$_{ax}$), 4.08 (s; 11-H$_{eq}$), 3.55 (t, *J* = 6.7 Hz; 10-H$_{eq}$), 2.99 (td, *J* = 11.9/3.9 Hz; 15-H$_{ax}$), 2.36 (dt, *J* = 13.3/4.2 Hz; 14-H$_{eq}$), 1.89 (q, *J* = 13.3 Hz; 14-H$_{ax}$), 1.79 (t, *J* = 0.7 Hz; 17-H$_3$), 1.43 (s; 19-H$_3$); ^{13}C-NMR (125 MHz, CD_2Cl_2) δ (assignment) 200.3 (C-3), 163.1 (C-22), 159.7 (C-2), 146.2 (C-16), 140.5 (C-8), 137.0 (C-20), 135.3 (C-6), 129.1 (C-4), 123.2 (C-5), 122.3 (C-7), 121.1 (C-9), 118.0 (C-21), 110.8 (C-18), 63.5 (C-11), 62.2 (C-13), 47.0 (C-10), 44.8 (C-12), 40.0 (C-15), 38.1 (C-14), 24.8 (C-19; *13,21*), 21.5 (C-17).

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Supplementary Material Available: 500 MHz ^{1}H NMR spectra of **1–15** and **21**; X-ray crystallographic data for **7** (21 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.