yields based on the aldehydes decreased compared to the yields when 5 equiv of the acetates were used. This decrease was because of palladium-catalyzed homocoupling of the acetates.[8] Aromatic and α,β-unsaturated aldehydes can be used in this Pd(0)–Zn system.[9] Further, the aldehyde regioselectively attacked the more substituted allylic position of the π-allylpalladium complex to give a single regioisomer (Scheme II and III).[10] Consequently, the carbonyl allylation exhibits slight diastereoselectivity (syn selectivity) except the cases of 1-phenyl-2-propenyl acetate and 3-phenyl-2-propenyl acetate. Ketones such as 4-*tert*-butylcyclohexanone and acetophenone did not react under the same conditions. As shown in Scheme IV, the allylation of an aldehyde was chemoselectively performed in the presence of a ketone group or an ester group.[2k,q]

Allylic acetates function as synthons of the corresponding allylic carbanions. However, the carbonyl allylation does not exhibit the high diastereoselectivity. Therefore, further investigation for enhancing the selectivity is in progress.

(8) Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1985**, 315.

(9) In this Pd(0)–Zn system, pinacol-type self-coupling products were not detected by thin-layer chromatography. In the Pd(0)–SmI_2 system, which is the only method using allylic acetates in the carbonyl allylation, aromatic and α,β-unsaturated aldehydes cause the pinacol-type self-coupling; see ref 4c.

(10) In the Pd(0)–SmI_2 system, the aldehyde causes the electrophilic attack at the less substituted allylic position; see ref 4c.

(11) For determination of the ratios of syn/anti isomers, see: Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1299.

Yoshiro Masuyama,* Nobuyoshi Kinugawa
Yasuhiko Kurusu
Department of Chemistry
Sophia University
7-1 Kioicho, Chiyoda-ku
Tokyo 102, Japan
Received May 26, 1987

Unusual Cyclopropane-Containing Hapalindolinones from a Cultured Cyanobacterium

Summary: Two structurally unusual indolinones containing a spiro-fused cyclopropane and an isonitrile have been isolated from the cells of a cultured cyanobacterium.

Sir: In a search for inhibitors of arginine vasopressin binding, the unusual indolinones **1A** and **1B** have been isolated from the cells of a cultured cyanobacterium belonging to the genus *Fischerella* (ATCC 53558). The structures were elucidated by IR, NMR, and mass spectral analysis and the stereochemistry and absolute configuration of **1A** established with single-crystal X-ray diffraction analysis.

The producing culture was isolated and purified from an enrichment culture established by using a soil sample obtained from the Everglades, Florida. This cyanobacterium is filamentous and exhibits true branching and a complex developmental cycle. On the basis of its morphological characteristics, this culture appears to be a member of typological group V, as defined by Rippka et al.[1]

(1) Rippka, R.; Deruelles, J.; Waterbury, J. B.; Herdman, M.; Stanier, R. Y. *J. Gen. Microbiol.* **1979**, *111*, 1–66.

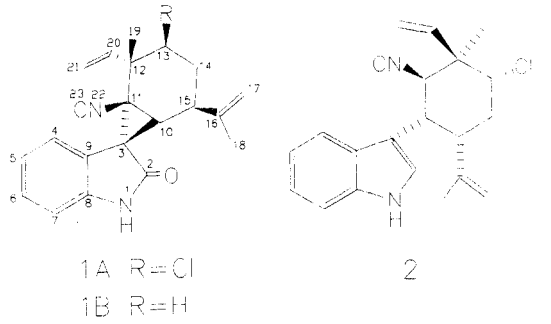

Figure 1.

Cultures were grown axenically in 1 L of BG-11 medium,[2] prepared by using 5 mM of HEPES–NaOH buffer, pH 8.5. Incubation was carried out in a 2800-mL Fernbach flask shaken at 100 rpm and 29 °C at a light intensity of 3500 lux. The headspace of the culture vessel was continuously flushed with humidified 5% (v/v) CO_2 in air at a flow rate of 200 mL/min. After 17 days incubation, the cells (~3.5 g wet w/L) were harvested.

Compounds **1A** and **1B** are related to the hapalindoles[3] and, in particular, hapalindole E (**2**),[4,5] which were also isolated from a cultured cyanobacterium, *Hapalosiphon fontinalis* (ATCC 39694).

Compound **1A** was isolated by MeOH extraction (3×) of the cells obtained from 1 L of the cyanobacterium culture. The MeOH extracts were filtered, combined, concentrated, and partitioned with CH_2Cl_2. The CH_2Cl_2 layer was concentrated and chromatographed on silica gel (CH_2Cl_2) to yield 18 mg of crystalline **1A** (92–96 °C dec) $[\alpha]^{25}_D$ −30°. Compound **1B** was further purified via Sephadex LH-20 (CH_2Cl_2/hexane/MeOH, 10:10:1) chromatography to yield 5 mg of a colorless oil.

Low resolution mass spectra of **1A** indicated the presence of a single Cl while high resolution analysis suggested the formula $C_{21}H_{21}N_2OCl$ (calcd 352.1342, found 352.1347).[6] Comparison showed that compound **1A** had an oxygen and one more unsaturation than hapalindole E (**2**) ($C_{21}H_{23}N_2Cl$). The IR spectrum of **1A** suggested the presence of an isonitrile, an -NH, and a carbonyl group with absorbances at 2125 cm^{-1}, 3420 cm^{-1}, and 1716 cm^{-1}, respectively (Figure 1).

The ^1H NMR data for **1A** (Table I) differed from hapalindole E (**2**) in the absence of signals for the protons on C2 and C11, an upfield shift of 1.3 ppm for the proton on C10, and a downfield shift of 1.3 ppm for the proton on C13. Also, only the proton on C15 was coupled to the proton on C10.

The absence of a proton on C2 and the presence of a carbonyl, as noted in the ^1H NMR and IR spectra, suggested that the indole in **2** was now an indolinone in **1A**. Also, the disappearance of the proton on C11 and the absence of an additional proton on C3, along with the knowledge that **1A** contained another unsaturation site,

(2) Rippka, R.; Waterbury, J. B.; Stanier, R. Y. *The Prokaryotes—A Handbook on Habitats, Isolation and Identification of Bacteria*; Springer-Verlag: New York, 1981; pp 212–220.

(3) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456–6457.

(4) Moore, R. E.; Patterson, G. M. L. Eur. Pat. Appl. 85 305 600.0, 1986.

(5) 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*, 1036–1043.

(6) Mass spectra were obtained on a Finnigan Mat 212 mass spectrometer at 3 kV in the electron impact mode; high resolution data was obtained by using the peak match method with PFK (perfluorokerosene) as the internal standard.

(7) Gassman, P. G.; Gilbert, D. P.; Luh, T. *J. Org. Chem.* **1977**, *42*, 1340–1344.

0022-3263/87/1952-3704$01.50/0

Table I. ^{1}H NMR[a]

	1A	1B	2[4,5]
1	8.41 1 H br s	7.85 1 H br s	8.12 1 H br J(1,2) = 2.2 J(1,10) = 0.3
2			7.17 1 H br d J(2,1) = 2.2
4[b]	7.10–7.20 2 H m	7.10–7.20 2 H m	7.44 1 H ddt J(4,5) = 7.7 J(4,6) = 1.2 J(4,7) = 0.8
5[b]	7.10–7.20 2 H m	7.10–7.20 2 H m	7.13 1 H ddd J(5,6) = 7.1 J(5,7) = 1.1 J(5,4) = 7.7
6[b]	7.32 1 H ddd J(6,4) = 1.9 J(6,5) = 7.4 J(6,7) = 7.7	7.28 1 H ddd J(6,4) = 1.4 J(6,5) = 7.7 J(6,7) = 7.7	7.20 1 H ddd J(6,4) = 1.2 J(6,5) = 7.1 J(6,7) = 8.1
7[b]	6.94 1 H d J(7,6) = 7.7	6.89 1 H d J(7,6) = 7.7	7.38 1 H ddd J(7,4) = 0.8 J(7,5) = 1.1 J(7,6) = 8.1
10	2.29 1 H d J(10,15) = 3.5	2.22 1 H d J(10,15) = 4.0	3.61 1 H br dd J(10,11) = 2.9 J(10,15) = 12.1
11			3.81 1 H br d J(11,10) = 2.9
13[c]	5.75 1 H dd J(13,14) = 9.3 J(13,14) = 6.7	2.86 1 H ddd J(13,13) = –14.0 J(13,14) = 14.0 J(13,14) = 2.6 1.8–2.2 1 H m	4.46 1 H dd J(13,14) = 12.1 J(13,14) = 5.0
14	2.10 2 H m	1.6–2.1 2 H m	2.25 1 H ddd J(14,13) = 5.0 J(14,14) = –13.7 J(14,15) = 4.3 2.15 1 H dt J(14,13) = 12.1 J(14,14) = –13.7 J(14,15) = 12.1
15	3.14 1 H ddd J(15,10) = 3.5 J(15,14) = 8.1 J(15,14) = 8.1	2.95 1 H ddd J(15,10) = 4.0 J(15,14) = 4.0 J(15,14) = 12.7	3.06 1 H td J(15,10) = 12.1 J(15,14) = 12.1 J(15,14) = 4.3
17	4.91 1 H br s	4.85 1 H br s	4.85 1 H dq J(17,17) = 1.5 J(17,18) = 0.8
	4.89 1 H br s	4.82 1 H br t J(17,18) = 1.2	4.72 1 H pent J(17,17) = 1.5 J(17,18) = 1.5
18	1.81 3 H s	1.75 3 H s	1.55 3 H dd J(18,17) = 0.8 J(18,17) = 1.5
19	1.74 3 H s	1.55 3 H s	1.48 3 H s
20	5.98 1 H dd J(21,22) = 17.6 J(21,22) = 10.9	5.84 1 H dd J(21,22) = 17.8 J(21,22) = 10.8	6.05 1 H dd J(21,22) = 17.5 J(21,22) = 10.9
21	5.14 1 H d J(22,21) = 10.9	4.96 1 H d J(22,21) = 10.8	5.30 1 H dd J(22,21) = 10.9 J(22,22) = 0.3
	5.08 1 H d J(22,21) = 17.6	4.92 1 H d J(22,21) = 17.8	5.25 1 H dd J(22,21) = 17.5 J(22,22) = 0.3

[a] Spectra were recorded at 300 MHz in $CDCl_3$; chemical shifts are referenced to $CDCl_3$ at 7.24 ppm. Coupling constants are reported in hertz. [b] Assignment of these protons was based on decoupling and comparison with ^{1}H NMR spectra of published indolinones.[7] These protons are fully resolved in C_6D_6. [c] These coupling constants are significantly different in C_6D_6: C13–6.13 (1 H, dd, J(13,14) = 15.7, J(13,14) = 5.4).

strongly suggested that C3 was bonded to C11 to form a spiro cyclopropane ring fused to a six-membered ring. The large upfield shift of the proton on C10 supported the proposed cyclopropane ring. The large downfield shift of the proton on C13 indicated that the conformation of this unusual ring system placed the C13 proton in the deshielding cone of the carbonyl.

Table II. ^{13}C NMR[a,b]

	IA	IB	2[4,5]
2	173.98 C	173.50 C	123.45
3	40.23 C	38.17 C	111.74
4	122.42 CH J = 163	121.73 CH	116.84
5	123.40 CH J = 161	123.10 CH	119.52
6	128.55 CH J = 162	128.08 CH	122.05
7	109.45 CH J = 163	109.03 CH	111.44
8	139.51 C	139.70 CH	135.50
9	126.03 C	126.64 C	126.23
10	39.76 CH J = 164	40.99 CH	34.71
11	57.36 C	55.50 C	67.04
12	44.85 C	39.64 C	44.54
13	60.50 CH J = 150	24.82 CH_2	60.77
14	34.62 CH_2 J = 132	32.82 CH_2	38.10
15	36.77 CH J = 131	36.09 CH	43.90
16	145.71 C	147.61 C	145.10
17	112.22 CH_2 J = 156	111.16 CH_2	113.36
18	21.28 CH_3 J = 124	22.96 CH_3	18.55
19	20.319 CH_3 J = 120	20.60 CH_3	16.04
20	138.65 CH J = 156	142.81 CH	141.70
21	115.60 CH_2 J = 158	112.61 CH_2	116.06
23	158.06 C	156.73 C	158.45

[a] Spectra were recorded at 75 MHz in $CDCl_3$. Chemical shifts are in ppm referenced to $CDCl_3$ at 77.0 ppm; coupling constants are reported in hertz. [b] Assignments of the carbons in the indolinone portions were based on comparison with ^{13}C NMR spectra of known indolinones.[7]

The ^{13}C NMR spectrum (Table II) corroborated the presence of the carbonyl with an absorbance at 173.98 ppm and the lack of a proton on the isonitrile-bearing carbon (C11) was suggested via an APT[8] experiment. A significant upfield shift for C11, from 67.04 to 57.36 ppm, was consistent with a cyclopropane ring; the presence of the cyclopropane ring was also confirmed by a gated decoupled ^{13}C NMR experiment in which a large and diagnostic (for a cyclopropane) C–H coupling constant of 164 Hz was observed for C10.[9]

Suitable crystals of **1A** for X-ray diffraction studies formed from ethyl acetate with space group symmetry of $P2_1$ and cell constants of a = 13.984 (2) Å, b = 8.950 (2) Å, c = 16.284 (4) Å, and β = 110.63 (2)° for Z = 4 and a calculated density of 1.229 g/cm^3. Of the 2754 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 2564 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[10] The absolute configuration was determined from anomalous scattering with one enantiomer giving an R factor of 0.079 while the other gave 0.085. This difference was significant at the 0.001 level[11] and was confirmed by careful remeasurement of 10 enantiomorph sensitive reflections. Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.054. No abnormally short intermolecular contacts were noted. Tables III, IV, and V containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available

(8) Patt, S. L.; Schoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535–539.
(9) Burke, J. J.; Lauterbur, P. C. *J. Am. Chem. Soc.* **1964**, *86*, 1870–1871.
(10) The following library of crystallographic programs was used: MULTAN 80, P. Main, University of York, York, England (1980); ORTEP-II, C, K. Johnson, Oak Ridge National Laboratory, Oak Ridge, TN (1970); SDP Plus V1.1, Y. Okaya and B. A. Frenz, B. A. Frenz and associates, College Station, TX (1984).
(11) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502–510.

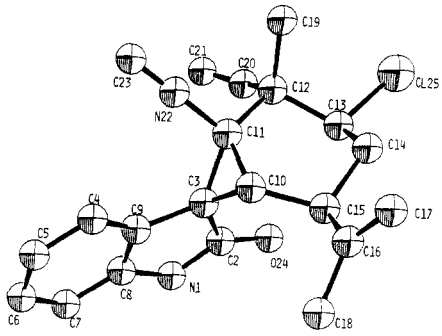

Figure 2. Computer-generated drawing of **1A** derived from the X-ray coordinates with hydrogens omitted for clarity.

as supplementary material. Figure 2 is a computer-generated perspective drawing of **1A** from the final X-ray coordinates showing the absolute stereochemistry of one molecule. The second independent molecule had a similar conformation but is not shown in Figure 2.

Indolinone **1A** has six contiguous asymmetric centers including three contiguous tetrasubstituted carbons. Its four fused rings are centered around a spiro-fused cyclopropane ring and pyrrolidone ring. The indolinone system is essentially planar and is virtually perpendicular to the cyclohexane ring which is in a half-chair conformation. This particular arrangement causes H13 to be 0.36 (0.41) Å[12] from the plane of the carbonyl and 2.33 (2.57) Å from the middle of the carbonyl bond C2–O24, which is consistent with the NMR observations (vide supra) that H13 in **1A** is 1.3 ppm downfield from its position in **2**.[13] Biogenetically, **1A** and **2** may both be thought as derived from tryptophan, two isoprene units and one carbon from the C-1 pool. The absolute stereochemistry of **2** has been assigned by analogy[5] and is opposite to that found for **1A**, except for C11.

The IR spectrum of compound **1B** indicated that it also contained an isonitrile (2135 cm^{-1}), an -NH (3430 cm^{-1}), and a carbonyl (1719 cm^{-1}). The absence of the Cl^- in **1B**, compared to **1A**, is apparent in the ^1H and ^{13}C NMR spectra (C13), as well as the HRMS (found 318.1732, calcd 318.1732 for $C_{21}H_{22}N_2O$).[6] These data indicate that **1B** is the deschloro derivatives of **1A**. We would like to suggest the name hapalindolinone for these indolinone-containing natural products and, in particular, hapalindolinone A and hapalindolinone B for compounds **1A** and **1B**, respectively.

With use of a modification of a procedure described by Bockaert et al.,[14] hapalindolinone A (**1A**) inhibits the binding of [^{3}H]arginine vasopressin to kidney tissue (v_2 receptor) with an IC_{50} of 37.5 ± 7.6 μM (n = 3). This compound also inhibits kidney (v_2) arginine vasopressin stimulated adenylate cyclase with an IC_{50} of 44.6 μM (n = 2).

Acknowledgment. We thank O. Hensens, J. Liesch, and C. Wichmann for valuable suggestions in confirming the reported structures.

Registry No. **1A**, 109151-56-6; **1B**, 109151-57-7.

Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **1A** (5 pages). Ordering information is given on any current masthead page.

(12) The numbers in parentheses are for the second independent molecule in the crystal structure.

(13) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon Press: Oxford, 1969; 2nd ed.; pp 88–92.

(14) Bockaert, J.; Roy, C.; Rajerison, R.; Jard, S. *J. Biol. Chem.* **1973**, *2480S*, 5922–5931.

Robert E. Schwartz,* Charles F. Hirsch
James P. Springer, Douglas J. Pettibone
Deborah L. Zink
Merck, Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065
Received April 2, 1987

A Convergent Total Synthesis of (+)-Phyllanthocin

Summary: A highly convergent, enantioselective total synthesis of (+)-phyllanthocin (**1**), the aglycone of the antineoplastic agent phyllanthoside (**2**), has been achieved by employing a novel strategy that features a stereo- and regioselective dipolar cycloaddition of a nitrile oxide followed by the unmasking of the isoxazoline thus produced to give a key intermediate β-hydroxy ketone that was readily elaborated to the target natural product.

Sir: During the course of screening a variety of plants for potential anticancer agents, Kupchan isolated and characterized (+)-phyllanthocin (**1**), a novel bisabolane sesquiterpene that is the aglycone of the antineoplastic agent phyllanthoside (**2**).[2] In subsequent explorations, a closely related group of natural products known as the phyllanthostatins was discovered.[3] Owing to its promise as a therapeutically useful antitumor agent,[4] phyllanthoside (**2**) as well as the corresponding aglycone **1** have emerged as attractive targets for synthetic investigations.[5-10] It is indeed noteworthy that the absolute configuration of **1** was first ascertained by total synthesis,[5a] although the relative stereochemical relationships were originally established by single-crystal X-ray analysis.[2] Three subsequent accounts of the total synthesis of **1** in optically pure form have been recorded,[6-8] and the naturally occurring glycoside **2** itself has recently succumbed to total synthesis.[9] A highly convergent, enantioselective synthesis of **1** has been completed in our laboratories, and we now disclose the results of those efforts.[10]

The essential elements of our strategy for the asymmetric synthesis of **1** are adumbrated in a retrosynthetic format in Scheme I wherein assembly of the tricycle **3**, which also served as an intermediate in Williams' route

(1) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980–1985.

(2) Kupchan, S. M.; La Voie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199.

(3) (a) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* **1982**, *60*, 544. (b) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P.; Schmidt, J. M. *Ibid.* **1982**, *60*, 939. (c) Pettit, G. R.; Cragg, G. M.; Niven, M. L.; Nassimbeni, L. R. *Ibid.* **1983**, *61*, 2630. (d) Pettit, G. R.; Cragg, G. M.; Suffness, M. I.; Gust, D.; Boettner, F. E.; Williams, M.; Saenz-Renauld, J. A.; Brown, P.; Schmidt, J. M.; Ellis, P. D. *J. Org. Chem.* **1984**, *49*, 4258.

(4) (a) Pettit, G. R.; Cragg, G. M.; Suffness, M. *J. Org. Chem.* **1985**, *50*, 5060. (b) Reference 9.

(5) (a) McGuirk, P. R.; Collum, D. B. *J. Am. Chem. Soc.* **1982**, *104*, 4496. (b) McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984**, *49*, 843.

(6) Williams, D. R.; Sih, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949.

(7) (a) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985**, *50*, 3420. (b) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237.

(8) Smith, A. B., III; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269.

(9) Smith, A. B., III; Rivero, R. *J. Am. Chem. Soc.* **1987**, *109*, 1272.

(10) These results were first presented at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, September 1986; paper ORGN 291.

0022-3263/87/1952-3706$01.50/0