# Obovamine, a New Indole Alkaloid from *Stemmadenia obovata*

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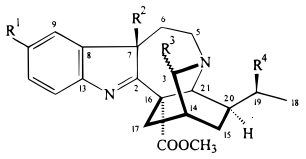
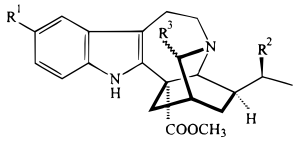
The stem bark of the Panamanian plant *Stemmademia obovata* has afforded a new ibogaine-type alkaloid, obovamine (**1**), whose structure was determined by a combination of spectral interpretation and chemical correlations. Ten known alkaloids, coronaridine, coronaridine hydroxyindolenine, voacangine, voacangine hydroxyindolenine, (19*S*)-heyneanine, (19*S*)-heyneanine hydroxyindolenine, (19*S*)-voacristine, (19*S*)-voacristine hydroxyindolenine, ajmalicine, and ajmalicinine, were also isolated. Voacangine was the main alkaloid constituent.

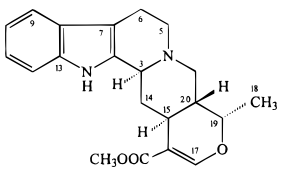
In a previous work, we reported the isolation of obovatine, bis[11-hydroxycoronaridin-12-yl]-11-hydroxycoronaridine, and voacristine from the leaves[1] and $N^1$-methyl-11-hydroxymacusine A from the stem bark[2] of *Stemmadenia obovata*. Here we report the study of the organic-soluble stem bark fraction. The acidic and neutral crude alkaloidal fractions of the EtOH extract afforded the new iboga indolenine alkaloid obovamine (**1**) and the known alkaloids voacangine[3] (**2**), voacangine hydroxyindolenine[4] (**3**), coronaridine,[5] coronaridine hydroxyindolenine[6] (**4**), (19*S*)-heyneanine,[7] (19*S*)-heyneanine hydroxyindolenine,[8] (19*S*)-voacristine,[7] (19*S*)-voacristine hydroxyindolenine,[9] ajmalicine[10] (**5**), and an epimeric mixture of ajmalicinine[11] (**6**) and 17-*epi*-ajmalicinine (**7**). The known compounds were identified by comparison of their spectral data with those reported in the literature.



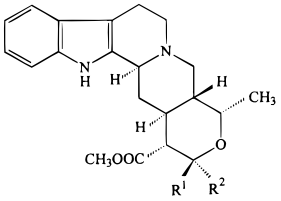


| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| **1** | $OCH_3$ | —O— | | H |
| **3** | $OCH_3$ | OH | H | H |
| **4** | H | OH | H | H |
| **9** | $OCH_3$ | OAc | H | H |
| **10** | $OCH_3$ | OH | OH | H |

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **2** | $OCH_3$ | H | H |
| **8** | $OCH_3$ | H | OH |



**5**



| | $R^1$ | $R^2$ |
|---|---|---|
| **6** | OH | H |
| **7** | H | OH |
| **11** | OAc | H |

## Results and Discussion

Obovamine (**1**), a minor alkaloid, was isolated as an amorphous compound by a combination of adsorption column chromatography and preparative TLC. The UV maxima at 224 and 286 shown by **1** are similar to those of a 10-methoxy-7-hydroxyindolenine chromophore.[4] The IR spectrum showed an absorption band belonging to a carbonyl ester (1731 $cm^{-1}$) and strong bands (1155, 1090 $cm^{-1}$) attributable to an ether functionalization. The mass spectrum displayed a molecular ion at *m*/*z* 382, two amu less than for voacangine hydroxyindolenine (**3**), and the fragments at *m*/*z* 367, $[M - 15]^+$ 353, $[M - 29]^+$, and 323 $[M - 59]^+$ corresponding to the loss of an ethyl side chain and a carbomethoxy group, respectively. Noteworthy is the absence of the prominent peak at $[M - 17]^+$ found in hydroxyindolenines of the iboga series such as **3** and **4**.[4,6] The $^1H$ NMR spectrum showed the following significant signals (Table 1): the absence of the NH broad singlet belonging to an indole chromophore, a typical splitting pattern in the aromatic region of a C-10 or C-11 oxygen function, two singlets attributable to an aromatic methoxyl, and a carbomethoxy group and the characteristic signals of an ethyl side chain. However, the key feature is the sharp doublet at 5.09 ppm ($J$ = 5.4 Hz), which together with the lack of the $[M - 17]^+$ peak in the EIMS spectrum of **1** indicates that obovamine is probably an Iboga indolenine alkaloid with an ether bridge between C-7 and C-3. The molecular formula ($C_{22}H_{26}O_4N_2$) was deduced for **1**, taking into account the signals found in the $^{13}C$ NMR spectrum (Table 2), the molecular ion, and the spectral evidence of four oxygen atoms in the molecule. The structure of **1** was substantiated by comparison of its $^{13}C$ NMR data with those of **3** (Table 2) where the normal α, $\beta$, and $\gamma$ effects on C-3 ($\Delta\delta$ = 40.2), C-14 ($\Delta\delta$ = 5.1), C-15 ($\Delta\delta$ = −2.5), and C-17 ($\Delta\delta$ = −5.0), respectively, derived from the introduction of the O−C(3) bond in **1** were evident. Selective decoupling and proton−carbon chemical shift correlation HMQC and HMBC (Tables 3 and 4) accomplished by

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**Table 1.** $^1$H NMR (400 MHz) Data of Compounds **1**, **3**, and **9** in $Cl_3CD$[a]

| | compound | | | | | |
|---|---|---|---|---|---|---|
| | **1** | | **3** | | **9** | |
| proton | $\delta$ (ppm) | $J$ (Hz) | $\delta$ (ppm) | $J$ (Hz) | $\delta$ (ppm) | $J$ (Hz) |
| H-3*R* | | | 2.72 s | | 2.72 s | |
| H-3*S* | 5.09 d | 5.4 | 2.72 s | | 2.72 s | |
| H-5*R* | 3.44 m | | 2.95 dm | 14.5 | 3.01 dd | 15.0, 3.2 |
| H-5*S* | 3.14 ddd | 12,1, 13.5, 3.3 | 3.48 ddd | 12.4, 11.9, 4.5 | 3.43 ddd | 13.9, 13.8, 3.0 |
| H-6*R* | 1.82[b] m | | 1.94 br d | 15.6 | 1.97 br d | 15.0 |
| H-6*S* | 2.16 ddd | 12.1, 13.5, 3.2 | 1.86[b] ddd | 12.1, 12.5, 3.1 | 1.83[b] ddd | 12.8, 15.1, 4.7 |
| H-9 | 6.88 d | 2.5 | 6.90 d | 2.5 | 6.68 d | 2.5 |
| H-11 | 6.78 dd | 8.4, 2.6 | 6.80 dd | 8.4, 2.5 | 6.80 dd | 8.4, 2.5 |
| H-12 | 7.33 d | 8.4 | 7.35 d | 8.3 | 7.47 d | 8.4 |
| H-14 | 2.26 q | 4.1 | 1.90 br s | | 1.91 br s | |
| H-15*R* | 1.71[b] | | 1.71 ddd | 10.6, 11.0, 4.6 | 1.76 ddd | 10.6, 11.0, 4.6 |
| H-15*S* | 1.01 br m | | 1.08 br m | | 1.07 br m | |
| H-17*R* | 1.82[b] | | 2.47 dm, AB | 13.2 | 2.73[b] dm, AB | 15.0 |
| H-17*S* | 2.37 d, AB | 13.9 | 2.70[b] d, AB | 12.3 | 2.53 d, AB | 14.0 |
| Me-18 | 0.87 t | 7.0 | 0.86 t | 6.9 | 0.92 t | 7.0 |
| H2-19 | 1.38 m | | 1.41 m | | 1.41 m | |
| H-20 | 1.38[b] | | 1.41[b] | | 1.41[b] | |
| H-21 | 3.37 s | | 3.76 s | | 3.71 s | |
| ArOMe | 3.80 s | | 3.81 s | | 3.80 s | |
| COOMe | 3.87 s | | 3.70 s | | 3.61 s | |
| OAc | | | | | 2.09 s | |

[a] Assignments were aided by selective decoupling experiments. [b] Signals (partly) overlapped. The Hanson system for prochirality is used to identify the protons.[23]

**Table 2.** $^{13}$C NMR Data of Compounds **1**, **3**, and **9** in $CDCl_3$ (100 MHz)

| | compound | | | | | |
|---|---|---|---|---|---|---|
| | **1** | | **3** | | **9** | |
| carbon | $\delta_C$ | DEPT | $\delta_C$ | DEPT | $\delta_C$ | DEPT |
| 2 | 188.2 | C | 186.8 | C | 180.6 | C |
| 3 | 88.8 | CH | 48.6 | CH2 | 48.7 | CH2 |
| 5 | 45.7 | CH2 | 49.1 | CH2 | 49.4 | CH2 |
| 6 | 32.3 | CH2 | 34.2 | CH2 | 37.0 | CH2 |
| 7 | 86.4 | C | 88.3 | C | 90.6 | C |
| 8 | 141.3 | C | 144.4 | C | 145.1 | C |
| 9 | 108.8 | CH | 107.9 | CH | 107.0 | CH |
| 10 | 158.6 | C | 159.1 | C | 158.8 | C |
| 11 | 114.2 | CH | 113.7 | CH | 112.7 | CH |
| 12 | 121.5 | CH | 121.3 | CH | 121.8 | CH |
| 13 | 146.9 | C | 144.8 | C | 141.8 | C |
| 14 | 32.1 | CH | 27.0 | CH | 27.4 | CH |
| 15 | 29.5 | CH2 | 32.0 | CH2 | 31.9 | CH2 |
| 16 | 58.7 | C | 58.5 | C | 57.8 | C |
| 17 | 29.5 | CH2 | 34.5 | CH2 | 33.6 | CH2 |
| 18 | 11.3 | CH3 | 11.5 | CH3 | 11.5 | CH3 |
| 19 | 26.2 | CH2 | 26.5 | CH2 | 26.5 | CH2 |
| 20 | 36.3 | CH | 37.5 | CH | 38.4 | CH |
| 21 | 60.0 | CH | 58.5 | CH | 56.5 | CH |
| ArOMe | 55.7 | CH3 | 55.7 | CH3 | 55.6 | CH3 |
| COOMe | 52.7 | CH3 | 53.1 | CH3 | 52.4 | CH3 |
| COOMe | 172.0 | C | 173.8 | C | 172.0 | C |
| OAc | | | | | 21.0 | CH3 |
| OAc | | | | | 168.1 | C |

**Table 3.** HMQC Correlations of Compounds **1** and **3** [$\delta$ (ppm), $CDCl_3$]

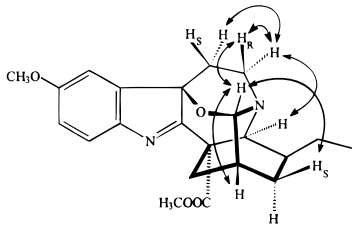
| | compound | | | |
|---|---|---|---|---|
| | **1** | | **3** | |
| position | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ |
| 3 | 88.8 | 5.09 sharp d | 48.6 | 2.72 (2H, s) |
| 5 | 45.7 | 3.14 ddd, 3.44 m | 49.0 | 2.95 dm, 3.48 ddd |
| 6 | 32.3 | 1.82[a] m, 2.16 ddd | 34.2 | 1.86[a] ddd, 1.94 br |
| 9 | 108.8 | 6.88 d | 107.9 | 6.90 d |
| 11 | 114.2 | 6.80 dd | 113.7 | 6.80 dd |
| 12 | 121.5 | 7.33 d | 121.3 | 7.35 d |
| 14 | 32.1 | 2.26 q | 27.0 | 1.90 br s |
| 15 | 29.5 | 1.01 br m, 1.71[a] | 32.0 | 1.08 br m, 1.76 ddd |
| 17 | 29.5 | 1.82,[a] 2.37, d | 34.5 | 2.47 dm, 2.70[a] d |
| 18 | 11.3 | 0.87 t | 11.5 | 0.86 t |
| 19 | 26.1 | 1.38 m | 26.5 | 1.41 m |
| 20 | 36.4 | 1.38[a] | 37.5 | 1.41[a] |
| 21 | 60.0 | 3.37 s | 58.5 | 3.76 s |
| $OCH_3$(Ar) | 55.7 | 3.80 s | 55.7 | 3.81 s |
| COOMe | 52.7 | 3.87 s | 53.1 | 3.70 s |

[a] Signals (partly) overlapped.

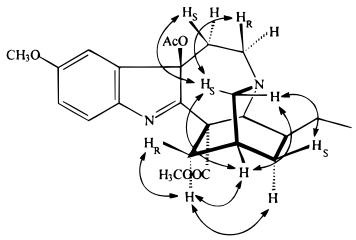
selective NOE experiments (Figure 1) permitted us to assign unambiguously all proton and carbon resonances to the proposed structure. Noteworthy is the unusual chemical shift for the carbomethoxy group at $\delta_H$ 3.87 ppm, which is probably due to the deshielding influence of the neighboring aromatic nucleus. The absolute configuration and further confirmation of structure **1** was proven by chemical correlation with voacangine (**2**), whose identity was deduced by $^{13}$C NMR and optical rotation data.[12,13] Obovamine (**1**) was obtained in 6% yield by oxidation of **2** with lead tetraacetate in an approximately molar ratio 1:3. Moreover, when a molar ratio of 1:1 was used, an epimeric mixture of 3-hydroxyvoacangine (**8**) was isolated in 52% yield and no trace of **1** was found. Compound **8** was not isolated previously as a natural compound and was identified by chemical correlation and by comparison of its spectroscopic data with those given for related compounds such as 3-hydroxyconopharyngine.[14,15] Thus, reduction of **8** with sodium borohydride gave compound **2** in accordance with the presence of a carbon carbinolamine in **8**. The fact that **1** was obtained only with an excess of the oxidizing agent indicates that it is probably an oxidation product from **8**. Indeed, obovamine was recovered in a 6% yield when **8** was treated with lead tetraacetate. Noteworthy is the fact that 3-oxovoacangine was not detected from the reaction mixture in this step. Thus, it seems that the first equivalent of lead tetraacetate oxidizes the most susceptible C-3 position in the iboga skeleton to a carbinolamine and the excess of reagent subsequently attacks the indole nucleus but does not continue at C-3 to give the lactam. Previous studies about the lead tretraacetate oxidation in yohimbinoid alkaloids[16] suggests that the O−C(7) bond in **1** would be formed through an intramolecular nucleophilic sub-

**Table 4.** Selected HMBC Correlations of **1** and **3** [$\delta$ (ppm), $CDCl_3$]

| | 1 | | 3 | |
|---|---|---|---|---|
| position | $\delta_H$ | correlated C | $\delta_H$ | correlated C |
| 3 | 5.09 | 88.8 (C-7), 29.5 (C-15/C-17) | 2.72 | 32.0 (C-15), 34.5 (C-17) |
| 9 | 6.88 | 146.9 (C-13) | 6.90 | 144.8 (C-13), 113.7 (C-11) |
| 11 | 6.78 | 146.9 (C-13), 108.8 (C-9) | 6.80 | 144.8 (C-13), 107.9 (C-9) |
| 12 | 7.33 | 158.6 (C-10), 141.3(C-8) | 7.35 | 159.1 (C-10), 144.4 (C-8) |
| COOMe | 3.87 | 172.0 (C=O) | 3.69 | 173.9 (C=O) |
| ArOMe | 3.80 | 158.6 (C-10) | 3.81 | 159.2 (C-10) |



**1**



**9**

**Figure 1.** Enhancements observed in NOE studies with **1** and **9**.

stitution over the indole oxidation intermediate of the 3(*S*)-hydroxyvoacangine epimer.

Despite the fact that the absolute configuration of iboga alkaloids is known,[17] the absolute stereochemistry at C-7 in the corresponding hydroxyindolenines is still undetermined. On the basis of mechanistic considerations, Wenkert et al. proposed a 7*S* absolute configuration for voacangine hydroxyindolenine.[18] However, a close inspection of the $^1$H NMR data for compound **3** and its acetoxyindolenine derivative, voacangine acetoxyndolenine (**9**) (Table 1), suggests that **3** would display the opposite 7*R* configuration. Thus, three chemical shifts for the protons H-9, $H_R$-17, and $H_S$-17 differ greatly when both $^1$H NMR spectra are compared, such differences being attributable to the diamagnetic anisotropy from the carbonyl group of the acetate. The molecular model of **9** points to the fact that the first of these could be observed if the acetate displays either an $\alpha$ or $\beta$ orientation. However, the last two can only be explained if the acetate lies over the two $H_2$-17 protons, as occur solely when the acetate displays a $\beta$ orientation or an *R* absolute configuration at C-7. A complete NMR study for an iboga hydroxyindolenine-type alkaloid is reported here for the first time. The assignments of all proton resonances in **3** and **9** (Table 1) were made on the basis of a single line decoupling and bidimensional HMQC and HMBC experiments on **3** (Tables 3 and 4), with the spatial relationships being established by NOE studies (Figure 1). Thus, a long-range *W* coupling $H_S$-15/$H_R$-17 together with an NOE between $H_R$-3 and $H_S$-15 inequivocally causes a difference between $H_R$-17 and $H_S$-17 in compounds **3** and **9**.

The hydroxyindolenines from iboga alkaloids are considered to be artifacts derived from air exposure.[9,19] Thus, the fact that a corresponding hydroxyindolenine was isolated for each parent iboga alkaloid present in the plant suggests that this fact can be related with a long extraction step (see the Experimental Section), and then obovamine (**1**) might also be an autooxidation compound from voacangine (**2**). In order to verify this hypothesis, an air stream was bubbled through a chloroform solution of voacangine illuminated by solar radiation. Two weeks later, obovamine (**1**) was isolated in 5% yield from the reaction mixture together with voacangine hydroxyindolenine (**3**), an epimeric mixture of 3-hydroxyvoacangine (**8**) and the unreacted voacangine (**2**). However, although **1** and **3** were isolated as natural products from the plant, no traces of **8** were detected. Since the carbinolamines readily react with the alcohols to form alkoxy compounds, the isolation of compound **8** from the reaction mixture suggests a genesis for **1**. Thus, the intermediate **10** has the appropriate orientation of the alcoholic group at C-7 for the formation of the internal ether bond as is the case in 3,19-oxidocoronaridine.[20] The formation of compounds such as **10** is feasible in view of the easy photooxidation at C-3 and C-7, and similar compounds have been previously isolated as artifacts from *Tabernamontana* species.[14]

Heteroyohimbine-type alkaloids, widely distributed in the *Rauwolfia genera*, are very rare in the *Apocinaceae* species known to produce iboga alkaloids.[12,21] Thus, the isolation of the ajmalicinoid alkaloids ajmalicine (**5**) and the epimeric mixture **6** and **7** is being reported for the first time from the genus *Stemmadenia*. Ajmalicinine (**6**) proved to be in equilibrium with its C-17 epimer, 17-*epi*-ajmalicinine (**7**), which had not been previously described. This epimeric mixture gave a single spot in TLC in various elution systems. However, the $^1$H NMR (400 MHz) spectrum revealed the presence of two doublets signals at 5.50 ppm ($J$ = 3.50 Hz) and 5.11 ppm ($J$ = 9.4 Hz) as well as other duplicated signals in an aproximately 1:9 ratio at 25 °C and corresponded to the H-17$\beta$ equatorial and H-17$\alpha$ axial protons in both anomers, respectively. The $^{13}$C NMR spectrum showed two well-defined sets of signals displaying similar chemical shifts except for the C-16, C-15, and C-18 atoms that can be rationalized by the dependence of the $\beta$, $\gamma$, and $\delta$ effects, respectively, against the orientation of the alcholic group at C-17.[22] The assignments of the $^1$H NMR and $^{13}$C NMR signals were aided by DEPT and carbon−proton correlation HMQC experiments (see Experimental Section). The acetylation of the isolated epimeric mixture yielded a single acetate (**11**) in accordance with the less steric hindrance of the equatorial alcoholic group in the H-17$\alpha$ epimer, whereas treatment with *p*-toluensulfonyl chloride in pyridine gave **5**.

## Experimental Section

**General Experimental Procedures.** Melting points (uncorrected) were determined on a Reichert Thermovar apparatus. NMR spectra were recorded in $CDCl_3$ for $^1H$ NMR at 400 and 200 MHz and for $^{13}C$ NMR at 100 and 50.32 MHz on a Bruker AMX-400 spectrometer or a Bruker WP-200 SY, respectively. Mass spectra were run on a VG Micromass ZAB-2F spectrometer at 70 eV. The UV spectrum was obtained on a Hewlett-Packard HP-8254-A diode array UV spectrophotometer using EtOH. The IR spectra were taken on a Nicolet 5PC FT-IR spectrometer. $R_f$'s were measured on $Al_2O_3$ 60 $F_{254}$ neutral, type E (Merck), using *n*-hexane−EtOAc (7:3) as the mobile phase. The alkaloids were detected with an UV lamp, Dragendorff, and $FeCl_3/HClO_4$ spray reagents. Si gel 60 $PF_{254+366}$, Art. 7748 (Merck) and $Al_2O_3$ 150 neutral Typ T, Art. 1101 (Merck) were used for purification of alkaloids in column chromatography or preparative TLC.

**Plant Material.** *Stemmadenia obovata* Benth (*Apocynaceae*) was collected in Oct 1993 at Monagre, Los Santos, Panama, by Mrs. C. Galdames and identified by Prof. Mireya Correa (Curator of the Herbarium of the University of Panama). A voucher specimen (No. 1283) is deposited at the Herbarium of the University of Panama.

**Extraction and Isolation.** Dried powdered stem bark (3.21 kg) of *S. obovata* was extracted repeatedly at room temperature with 80% ethanol over 3 months. The combined alcoholic extracts were freed of solvent under reduced pressure below 60 °C (181.6 g). HCl (0.5 N, 500 mL) was added to the viscous residue, which was left to stand for 24 h with stirring. After filtration, the solution was subjected to a pH gradient extraction to obtain acidic (A, 4.12 g), neutral (B, 1.87 g), and weakly basic (C, 1.73 g) crude alkaloidal residues. $Na_2CO_3$ and NaOH were used to basify the aqueous layer to pH 7 and 10, respectively. The organic layers were dried with $Na_2SO_4$, and the residues A and B were combined and chromatographed on a Si gel column (6 × 33 cm) with *n*-hexane−EtOAc mixtures of increasing polarity. The fraction eluted with *n*-hexane−EtOAc (8:2) yielded coronaridine (200 mg), **4** (50 mg), and **2** (1.2 g). The fraction eluted with *n*-hexane−EtOAc (7:3) yielded a mixture of two compounds of similar polarity that was subjected to a repeated preparative TLC over $Al_2O_3$ using *n*-hexane−EtOAc (7:3) as the mobile phase to finally obtain **1** (10 mg) and **3** (500 mg). Compound **5** (70 mg) crystallized from the fraction eluted with *n*-hexane−EtOAc (6:4). Further elution with *n*-hexane−EtOAc (1:1) gave (19*S*)-heyneanine (200 mg) and (19*S*)-voacristine (600 mg), elution with EtOAc (100%) gave (19*S*)-heyneanine hydroxindolenine (25 mg) and (19*S*)-voacristine hydroxindolenine (35 mg), and elution with EtOAc−MeOH (9:1) gave **6** and **7** (50 mg). The alkaloids were purified by preparative TLC.

**Obovamine (1)**: amorphous; $[\alpha]^{25}_D$ +134°(*c* 0.10, $CHCl_3$); TLC $R_f$ 0.52, yellow-brown with $FeCl_3/HClO_4$ reagent; UV (EtOH) $\lambda$ max (log $\epsilon$) 224 (4.02), 286 (3.62), 312 (sh, 3.45) nm; IR $\nu$ max ($CHCl_3$) 3378, 2966, 2931, 2860, 1731, 1601, 1466, 1437, 1349, 1302, 1243, 1155, 1090 $cm^{-1}$; EIMS (70 eV) *m/z* $[M]^+$ 382 (100), 367 (11), 353 (11), 323 (58), 215 (58), 189 (32), 151 (74), 122 (13); $^1H$ NMR, see Table 1; $^{13}C$ NMR, see Table 2.

**Epimeric mixture of 6 and 7 (9:1)**: $[\alpha]^{25}_D$ −25.7° (*c* 5.45, $CHCl_3$); gray with $FeCl_3/HClO_4$ reagent. For **6**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.80 (1H, brs, NH), 7.46 (1H, d, $J$ = 7.6 Hz, H-9), 7.28 (1H, d, $J$ = 7.6 Hz, H-12), 7.10 (2H, m, H-10 and H-11), 5.11 (1H, d, $J$ = 9.4 Hz, H-17), 4.22 (1H, m, $J_{19-20}$ = 3.3 Hz, H-19), 3.81 (3H, s, COOMe), 3.30 (1H, brd, $J$ = 12.8 Hz, H-3), 3.08 (1H, m, H-5$\beta$), 2.96 (1H, brm, H-6$\beta$), 2.86 (1H, brd, $J$ = 7.7 Hz, H-21$\beta$), 2.72 (1H, brdd, $J$ = 13.8, 2.7 Hz, H-6α), 2.62 (1H, ddd, $J$ = 13.8, 13.8, 4.3 Hz, H-5α), 2.20 (1H, t, $J$ = 9.7 Hz, H-16), 2.10 (3H, m, H-21α, H-20 and H-15), 2.00 (1H, dt, $J$ = 13.8, 13.8, 3.1 Hz, H-14α), 1.43 (1H, q, $J$ = 10.48 Hz, H-14$\beta$), 1.24 (1H, d, $J$ = 6.88 Hz, $CH_3$-18); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 172.9 (s, MeOC=O), 136.0 (s, C-13), 133.7 (s, C-2), 127.3 (s, C-8), 121.5 (d, C-11), 119.5 (d, C-10), 118.2 (d, C-9), 110.8 (d, C-12), 108.4 (s, C-7), 90.9 (d, C-17), 71.9 (d, C-19), 59.5 (d, C-3), 56.7 (t, C-21), 56.0 (d, C-16), 53.2 (t, C-5), 52.1 (q, COOMe), 41.2 (d, C-20), 34.7 (d, C-15), 33.9 (t, C-14), 21.6 (t, C-6), 14.2 (q, C-18). For **7**: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.97 (1H, brs, NH), 5.50 (1H, d, $J$ = 3.5 Hz, H-17), 4.05 (1H, m, $J_{19-20}$ = 5.1 Hz, H-19), 3.76 (3H, s, COOMe), 3.40 (1H, brd, $J$ = 11.6 Hz, H-3), 2.48 (1H, dd, $J$ = 13.9, 3.6 Hz, H-16), 1.38 (3H, d, $J$ = 7.9 Hz, $CH_3$-18); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 171.6 (s, MeOC=O), 136.0 (s, C-13), 134.1 (s, C-2), 127.3 (s, C-8), 121.4 (d, C-11), 119.4 (d, C-10), 118.1 (d, C-9), 110.8 (d, C-12), 108.1 (s, C-7), 91.7 (d, C-17), 70.3 (d, C-19), 59.9 (d, C-3), 56.9 (t, C-21), 53.2 (t, C-5), 51.9 (q, COOMe), 51.4 (d, C-16), 41.7 (d, C-20), 34.0 (t, C-14), 27.7 (d, C-15), 21.6 (t, C-6), 19.2 (q, C-18).

**Oxidation of 2 to 1.** $Pb(OAc)_4$ (90 mg) was added slowly with stirring to a solution of **2** (30 mg) in 3 mL of $Cl_2CH_2$ (molar ratio 1:2.5). After 45 min, the solution was poured into ice cold 10% aqueous $NaHCO_3$ and extracted with $Cl_2CH_2$. The mixture was purified by preparative TLC on Si gel with *n*-hexane−EtOAc (7:3) as mobile phase to give **1** (2 mg).

**Oxidation of 2 to 8.** The same procedure described above was carried out with $Pb(OAc)_4$ (321 mg) and **2** (266 mg) in 3 mL of $Cl_2CH_2$ (molar ratio 1:1). After extraction with $Cl_2CH_2$, the mixture gave a crude residue (270 mg) that was chromatographed on a column of $Al_2O_3$ (3 × 3.5 cm), elution being effected with *n*-hexane−EtOAc (7:3) to yield unreacted **2** (54 mg) and **8** (116 mg) in an approximately 2:3 *R*/*S* molar ratio: EIMS (70 eV) *m/z* 382 ($M^+$ − 2, 100), 368($M^+$ − 16, 36), 366 ($M^+$ − 18, 43), 353 (24), 307 (11), 244 (38), 225 (31), 185 (33), 124 (22); $^1H$-NMR ($CDCl_3$, 200 MHz) $\delta$ 7.69 (br s, NH, *RS*), 7.15 (d, $J$ = 8.7 Hz, H-12, *RS*), 6.93 (d, $J$ = 2.39 Hz, H-9, *RS*), 6.82 (dd, $J$ = 8.0, 2.4 Hz, H-11, *RS*), 4.43 (br d, $J$ = 8.3 Hz, H-3, *S*), 4.01 (d, $J$ = 2.2 Hz, H-3, *R*), 3.85 (s, Ar-OMe, *RS*), 3.70 (s, COOMe, *RS*), 2.71 (d, $J$ = 11.7 Hz, $H_S$-17, *RS*), 0.93 (t, $J$ = 7.0 Hz, $H_3$-18, *S*) 0.91 (t, $J$ = 7.0 Hz, $H_3$-18, *R*); $^{13}C$ NMR ($CDCl_3$, 50.32 MHz) $\delta$ 174.8 (s, MeOC=O, *RS*), 154.0 (s, C-10, *RS*), 137.6 (s, C-2, *RS*), 130.6 (s, C-13, *RS*), 128.7 (s, C-8, *RS*), 112.0 (d, C-11, *RS*), 111.2 (d, C-12, *RS*), 109.8 (s, C-7, RS), 100.6 (d, C-9, *RS*), 95.8 (d, C-3, *R*), 86.0 (d, C-3, *S*), 56.2 (q, ArOMe, *R*), 56.0 (q, ArOMe, *S*), 55.5 (d, C-21, *RS*), 54.1 (s, C-16, *RS*), 52.7 (q, COOMe, *RS*), 51.2 (t, C-5, *RS*), 37.7 (d, C-20, *RS*), 35.5 (t, C-17, *RS*), 34.4 (d, C-14, *S*), 29.9 (d, C-14, *R*), 26.8 (t, C-19, *S*), 26.6 (t, C-19, *R*), 24.9 (t, C-15, *R*), 24.6 (t, C-15, *S*), 21.8 (t, C-6, *RS*), 11.6 (q, C-18, *RS*).

**Oxidation of 8 to 1.** The same procedure described above was carried out with $Pb(OAc)_4$ (58 mg) and **8** (49 mg) in 1 mL of $Cl_2CH_2$ (molar ratio 1:1). After extraction with $Cl_2CH_2$, the mixture gave a crude residue (45 mg) that was chromatographed on a column of $Al_2O_3$ (3 × 3.5 cm), elution being effected with *n*-hexane−EtOAc (7:3) to yield unreacted **8** (6 mg) and **1** (3 mg).

**Voacangine Acetoxyindolenine 9.** $Ac_2O$ (1 mL) was added to a solution of **3** (10 mg) in pyridine (1 mL) and the mixture stirred at room temperature for 20 days. Excess pyridine was removed under high vacuum pressure to give a residue (12 mg). Analytical TLC revealed a mixture of **3** and **9**. The mixture was crystallized in EtOH to give pure **9** (6 mg): colorless prisms; mp 190−192 °C from EtOH; TLC $R_f$ 0.48, yellow with $FeCl_3/HClO_4$; IR $\nu$ max ($CHCl_3$) 2955, 2860, 1754, 1731, 1601, 1474, 1242, 1200 $cm^{-1}$; EIMS (70 eV) *m*/*z* $[M]^+$ 426 (11), 411 (4), 397 (3), 384 (7), 383 (5), 367 (100), 337 (10), 258 (12), 201 (57), 122 (52); $^1H$ NMR, see Table 1; $^{13}C$ NMR see Table 2.

**Air Oxidation of Voacangine 2.** Compound **2** (230 mg) in 25 mL of $CHCl_3$ was exposed to solar radiation while air was bubbled through the solution, with $CHCl_3$ being periodically added to maintain the volume. After 2 weeks, the solution was chromatographed on a column of Si gel (3 × 5 cm) and eluted with *n*-hexane−EtOAc (7:3) to give unreacted voacangine (200 mg) and a mixture that was further purified by preparative TLC over $Al_2O_3$ using *n*-hexane−EtOAc (7:3) as mobile phase to yield **1** (1 mg), **3** (18.7 mg), and **8** (5.5 mg) in an approximately 2:10 *R*/*S* molar ratio.

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