Faurine and *O*-Methylfaurine, Two Novel Benzyl−Aporphine Dimers from *Thalictrum fauriei*[1]

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Two new benzyl−aporphine dimers, faurine (**1**) and its *O*-methyl ether (**2**), were obtained from *Thalictrum fauriei* and their structures determined by spectral and chemical methods. Faurine (**1**), the first dimer with the diphenyl ether connection at C-1 of the aporphine, did not undergo a Hofmann degradation, yet formed a chiral phenanthrene product (**6**) with cyanogen bromide. Two nondimeric chiral aporphine alkaloids, *O*-acetylisocorydine and *O*-methylisocorydine, gave the corresponding phenanthrene products **7** and **8**, respectively, under the same conditions, but only compound **7** was optically active.

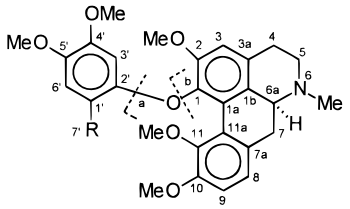
The perennial plant, *Thalictrum fauriei* Hayata (Ranunculaceae), grows to about 4.5 dm and is widely distributed in Taiwan, especially in wet mountain regions.[2] Previous work with this species gave the four aporphine alkaloids oconovine, corydine, isocorydine, and magnoflorine; two protoberberines, thalifaurine and dehydrodiscretine; and one morphinan, ocobotrine.[3−5] Reported herein are the isolation and structure elucidation studies of the major alkaloid, faurine (**1**) and its methyl ether, *O*-methylfaurine (**2**), members of a small group of dimeric alkaloids formed from an aporphine and a substituted phenyl unit joined by an ether oxygen. Several naturally occuring examples are hernandaline[6] from *Hernandia ovigera* L. (Hernandiaceae), thaliadine[7] from *Thalictrum minus* L. var. *adiantifolium* Hort., and natalamine[8] from *Berberis empetrifolia* Lam. (Berberidaceae), while others have been prepared from known benzylisoquinoline−aporphine dimers by oxidation.[9−12]

Results and Discussion

Faurine (**1**) was isolated from the Et_2O-soluble nonphenolic alkaloid fraction of the entire plant obtained by the reported solvent partition scheme[13] followed by Si gel column separations. The optically active amber solid has the molecular formula $C_{29}H_{33}NO_7$ (HRMS, M^+ 507), a UV spectrum (269, 293 shld, and 310 nm shld) suggestive of an aporphine with a substituent at the 11-position,[14] and the IR region showed hydroxyl absorption (3500 cm^{-1}). Acetylation produced monoacetate **3**, and lack of a bathochromic shift in the UV spectrum of the parent compound under alkaline conditions eliminated the consideration of a phenolic hydroxyl. Oxidation of faurine (**1**) with MnO_2 produced an aromatic aldehyde (^{1}H-NMR 10.65 ppm, IR 1660 cm^{-1}) with structure **4**, as will follow. The hydroxyl is therefore a primary alcohol.

The ^{1}H-NMR spectrum of **1** showed five *O*-methyl groups and one *N*-methyl group, as well as five protons in the aromatic region, two of which form an AB quartet with spin-coupling (J = 8.1 Hz) for ortho positioning. The remaining three protons are singlets, one of which is considerably shielded (5.53 ppm), but none is located near 8 ppm—a diagnostic position for H-11. All but two of the nine aliphatic protons are clearly resolved into first-order spin patterns at 270 MHz or higher, and consequently were completely analyzed and assigned.

To establish definitely an aporphine component for **1**, a Hofmann degradation was attempted. The anticipated phenanthrene product (now formulated as **5**) was not obtained, but instead *O*-methylfaurine (**2**) was obtained. This transformation constitutes a synthesis of *O*-methylfaurine (**2**) from faurine (**1**). Exhaustive methylation (MeI/MeOH, room temperature) apparently produced *N*,*O*-dimethylfaurine,[15] but the basic conditions (ethanolamine, 160 °C)[16] that usually generate the phenanthrene caused only *N*-demethylation. The quaternary aporphine magnoflorine, for example, under the same conditions of base treatment yielded the expected phenanthrene product, but the details of this experiment are not recorded here. Presumably, the methylated faurine is unable to twist C-7 down sufficiently to produce a trans orientation between H-7α and N-6 in the transition state, for elimination of the dimethylaminoethyl unit to form the C-6a to C-7 olefin. The inability to obtain the Hofmann product was important in suggesting the location for the benzylic substituent.



1 R=CH_2OH
2 R=CH_2OMe
3 R=CH_2OAc
4 R=CHO

A phenanthrene derivative was obtained from **1**, however, by treatment with cyanogen bromide[17] in the von Braun degradation.[18] The characteristic UV spectrum of phenanthrenes[19] was observed in this product, as well as the appearance of two additional aromatic protons in the ^{1}H-NMR spectrum as an AB quartet (7.51 and 7.47 ppm, J = 9.1 Hz) for H-6a and H-7.[20] Spectral

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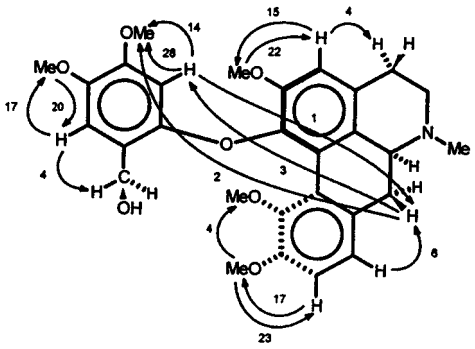


Figure 1. NOED enhancements (in percent) for faurine (**2**) at 270 MHz.

data, which included extensive 1D and 2D NMR results, in particular the NOE studies—not detailed here—led to the formulation of structure **6**, when taken with the results from similar studies with faurine (**1**) (see below).

With the aporphine ring established for **1** and with fragment ion peaks *a* and *b* (see structure **1**) at *m/z* 340 and 324 in the HRMS, the aporphine part must contain three methoxyls and three aromatic protons. The substituted phenyl unit, therefore, contains two methoxyls, two aromatic protons, and a hydroxymethyl. The strong positive specific rotation indicates the *S*-configuration for C-6a,[21] as does the positive Cotton effect curve of high intensity at 237 nm.[22,23]

Placement of the substituents on the aporphine nucleus was made from NOE studies by difference spectroscopy[24] and is summarized in part in Figure 1. The two aliphatic proton-coupled units (H_2-4 to H_2-5 and H-6a to H_2-7) served as reference points. For example, irradiation of the aromatic proton at 6.79 ppm gave relaxation to the aliphatic proton at 2.79 ppm, a component of the four-spin system, and irradiation of aromatic proton at 6.91 ppm gave relaxation to the aliphatic proton at 3.09 ppm, a member of the three-spin system. These protons must be, respectively, H-3 and H-4α in the first irradiation and H-8 and H-7α in the second.[25] Both aliphatic protons would be pseudoequatorially disposed, as clearly seen from CPK space-filling models. The stereospecific proton assignments for both spin systems were now possible from the spin-coupling constants, homonuclear decoupling, and CH-correlations. Upon irradiation, H-7β (2.33 ppm) relaxed to an aromatic one-proton (5.54 ppm) singlet and a methoxyl (3.38 ppm); and these last two units also relaxed to each other upon separate irradiations. This can only occur if they are on the non-aporphine benzylic component. Also, this result established the specific orientation of the benzylic ring to the aporphine system. A benzylic proton (H-7′, 4.43 ppm) was located by NOED from relaxation of the third aromatic singlet (6.75 ppm). This experiment also located the fifth methoxyl (3.746 ppm).

The CH-correlation 2D NMR experiment located the proton-bearing carbons of **1**, and the COLOC experiment (two- to four-bond heteronuclear coupling) located the quaternary carbons. The methoxyl-bearing carbons were identified without ambiguity, as were the aporphine quaternary carbons, except for C-1a and C-11a. These carbons, however, were differentiated by the fully proton-coupled ^{13}C-NMR spectral data. For example, C-1a has only one proton three bonds away, while C-11a has three. Thus, the sharp singlet at δ 126.3 must be

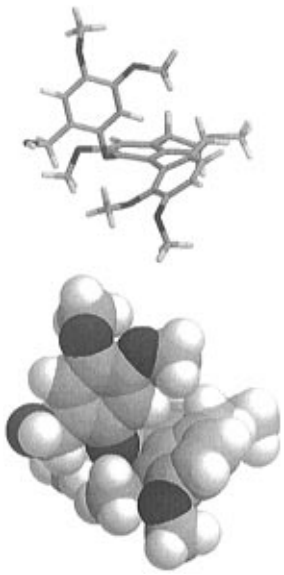


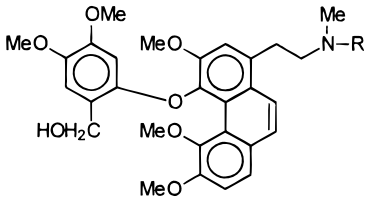
Figure 2. Dreiding-type (top) and space-filling (bottom) stereochemical projections for faurine (**1**).

C-1a, and the triplet (dd) with J = 6.1 Hz at δ 124.7, must be C-11a. Also, the diphenyl ether-bearing carbon (C-1) showed a sharp doublet pattern at 139.4 ppm, (J = 7.6 Hz), from coupling to only one proton, H-3.

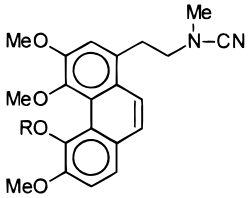
From the described studies, faurine was formulated as **1** and is the first reported dimer having the diphenyl ether at C-1 of the aporphine unit. Its conformational structure is shown in Figure 2 and is a consequence of stereochemical ordering at four locations. First, C-6a has the *S*-configuration, which in turn creates at the second location, the diphenyl system in a right-handed twist. The third location, the diphenyl ether oxygen, positions the benzylic ring above, rather than below, the general plane of the aporphine ring, with the orientation of the benzylic ring, the fourth position, essentially perpendicular to that unit and with H-3′ and MeO-4′ located over the diphenyl system. The shielding from the diphenyl ring currents is responsible for the sizeable upfield shifts of those protons. For example, comparing the chemical shifts of these protons with the equivalent ones in 2,4,5-trimethoxybenzyl alcohol showed upfield chemical shift changes of 0.98 and 0.49 ppm, respectively. The other substituents, H-6′ and H_2-7′, on the other hand, showed only 0.10 (upfield) and 0.14 ppm (downfield and averaged) changes, respectively.

The substituted benzylic moiety of faurine (**1**) is located in a crowded and rotationally restricted position, as evidenced, for example, by the chemical shift difference of 0.6 ppm for the benzylic protons (H_2-7′). This steric crowding would be expected to preserve the chiral twist in the phenanthrene product **6** of the von Braun reaction. Indeed, this product is optically active (specific rotation +7°) with a positive Cotton effect curve at 235 nm. Chiral phenanthrenes have been known for some time,[26] and are said to possess molecular helicity and have led to hexahelicene and helicene chemistry.[27] However, the methyl substituted phenanthrenes (substituted at positions 1, 3a, 8, and 11 using the aporphine numbering) were resolved at −40° and rapidly came to enantiomeric equilibrium at +15°.[28] To test the enantiomeric stability of the aporphine-derived phenanthrenes, two other aporphine alkaloids, *S*-(+)-acetylisocorydine and *S*-(+)-*O*-methylisocorydine were subjected

to the von Braun reaction and gave the corresponding phenanthrenes **7** and **8**, respectively. Only phenanthrene **7** was optically active (specific rotation +2°). Apparently, the more bulky acetate group was able to prevent enantiomeric equilibration from occurring at room temperature. We believe this study is the first report of chiral phenanthrenes from aporphine alkaloids.



5 R=Me
6 R=CN



7 R=Ac
8 R=Me

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher-Johns apparatus; optical rotations, with a Perkin-Elmer 241 photoelectric polarimeter; UV spectra, with a Beckman Spectrophotometer Model UV 5260; CD spectra, with a JASCO Model J-500A spectropolarimeter and reported as molar ellipticities; MS, with VG Kratos MS-30 or DuPont model 21-491 mass spectrometers at 70 eV; and NMR spectra, with Bruker WP-80DS, HX-90E, WM-300, AM-500, IBM AF-270, or GE NT-500 instruments. The NOE and 2D experiments were run using the pulse programs from the manufacturer. Dragendorff's spray reagent was used for alkaloid detection. The Rotation Locular Countercurrent Chromatography (RLCC) apparatus was from the Tokyo Rikakikai Co. Ltd.

Plant Material. The entire *T. fauriei* plant was collected during November and December 1980 (4 kg, air dried) and 1982 (3.6 kg) in Taiwan. A herbarium specimen is on deposit at the College of Pharmacy, The Ohio State University, and was authenticated by M.-T. Kao of the Department of Botany, National Taiwan University.

Extraction and Initial Isolation Procedure. The powdered, air-dried plant was percolated with EtOH until the extract gave a negative Dragendorff's test. After evaporation of solvent at reduced pressure, the 1980 collection left 442 g of residue. The fractionation scheme[13] afforded 1.43 g of the Et_2O-soluble tertiary phenolic alkaloids, 1.69 g of Et_2O-soluble tertiary nonphenolic alkaloids, and 1.85 g of the $CHCl_3$-soluble alkaloids. The 1982 collection gave in the same order 2.19 g, 1.43 g, and 1.67 g of the alkaloid fractions.

Chromatography of the Et_2O-Soluble Nonphenolic Alkaloids. (**A**) The 1.69 g from the 1980 collection was separated on a 70-g Si gel column with MeOH in $CHCl_3$ solvent mixtures (0.5% to 20%). Effluent fractions (12 mL) were monitored by TLC on Si gel with PhMe−Me_2CO−NH_4OH (25:25:1) as solvent system. The 1% MeOH in $CHCl_3$ fractions yielded in order: oconovine (290 mg); isocorydine (50 mg); followed by isooconovine, corydine, and faurine as a mixture (744 mg); and then faurine (**1**) (68 mg). The 744-mg mixture was chromatographed on 15 g of Si gel with 0.8% MeOH in $CHCl_3$. Isooconovine (66 mg after preparative TLC) was eluted first, and then corydine (10 mg), and finally faurine, which, with a fraction from the first column, yielded 285 mg of pure material after a repeated Si gel (24 g) column separation.

(**B**) The 2.2 g of the 1982 collection was separated by RLCC (11-mL fractions) with the aqueous phase as the mobile phase of solvent systems $CHCl_3$−MeOH−acetate buffer (5:5:3) with the acetate buffer[29] component at pH 3.0 (fractions 1−190), 2.54 (fractions 191−272), and 2.26 (fractions 273−354). The following alkaloids were obtained: ocobotrine, corydine, isocorydine, isooconovine, oconovine, faurine (**1**), and *O*-methylfaurine (**2**) in that order, using TLC to monitor the fractions. Fractions 311−342 (800 mg), containing oconovine, faurine, and *O*-methylfaurine, were chromatographed on Si gel (75 g) with mixtures of PhH−$CHCl_3$ (9:1, 0.10 L, 4:1, 0.36 L, 7.3, 1.1 L, and 3:7, 0.5 L) to give, in order, homogeneous oconovine (264 mg), *O*-methylfaurine (**2**, 79 mg), and faurine (**1**, 260 mg).

Faurine (1): amorphous solid, $[\alpha]^{25}_D$ +155° (*c* 0.8, $CHCl_3$); CD ($C = 1.34 \times 10^{-4}$ M, MeOH) (deg) $[\Theta]_{314}$ +8980, $[\Theta]_{292}$ −7960, $[\Theta]_{282}$ −6230 (min), $[\Theta]_{277}$ −6520, and $[\Theta]_{237}$ +300 000; UV (MeOH) λ max (log ϵ) 220 (5.06), 269 (4.85), 293 (sh, 463), and 310 (sh, 4.43) nm; IR ($CHCl_3$) ν max 3500 (OH), 3003, 1513, 1467, 1445, 1262, 1192, 1182, and 1141 cm^{-1}; HRMS *m/z* 507.2245 (21, M^+, $C_{29}H_{33}NO_7$, −1.2 mmu from the calcd value), 492.1977 (20, M − Me, −4.6), 476.2030 (100, M − OMe, −4.3), 340.1497 (3, M − $C_9H_{11}O_3$, −5.2), 324.1546 (9, M − $C_9H_{11}O_4$, −3.6); and ^{1}H- and ^{13}C-NMR in Tables 1 and 2, respectively.

***O*-Methylfaurine (2):** amorphous solid, $[\alpha]^{25}_D$ +244° (*c* 1.2, MeOH); UV (MeOH) λ max (log ϵ) 220 (4.56), 270 (4.34), 296 sh (4.12), and 310 sh (3.90) nm; IR ($CHCl_3$) ν max 3000, 1510, 1463, 1445, 1404, 1190, 1136, and 1076 cm^{-1}; HRMS *m/z* 521.2382 (25, M^+, $C_{30}H_{35}NO_7$, −3.1 mmu), 506.2201 (100, M − Me, $C_{29}H_{32}NO_7$, +2.2), 490.2275 (86, M − MeO, $C_{29}H_{32}NO_6$, +4.5), 324.1647 (9, $C_{20}H_{22}NO_3$, +4.7), 181.0826 (3, $C_{10}H_{13}O_3$, −4.1), and 166.0685 (9, $C_9H_{10}O_3$, +5.5); and ^{1}H- and ^{13}C-NMR in Tables 1 and 2, respectively.

Acetylfaurine (3). Faurine (**1**) (14 mg) was mixed with 4 drops each of Ac_2O and pyridine and reacted overnight at room temperature. The reaction solution was evaporated to dryness, with aid of PhMe, and the residue was chromatographed on 3 g of Si gel with 0.3% MeOH in $CHCl_3$ to give 7.4 mg of acetate **3** as an amorphous solid: $[\alpha]^{24}_D$ +251° (*c* 0.54, $CHCl_3$); UV (MeOH) λ max (log ϵ) 220 (4.97), 271 (4.44), and 292 shld (4.27) nm; IR ($CHCl_3$) ν max 1735 (acetate C=O), 1520, 1470, 1265−1210, 1197, 1145, and 1035 cm^{-1}; HRMS *m/z* 549.2302 (26, M^+, $C_{31}H_{35}NO_8$, −6.0 mmu), 534.2106 (6, M − Me, −2.2) 518.2324 (7, M − OMe, +1.9), 506.2201 (17, M − Ac, +2.3), 490.2179 (5, M − AcO, −5.0), 43.0189 (100, Ac, +0.6), and 42.0111 (11, C_2H_2O, +0.6); and ^{1}H-NMR in Table 1.

Table 1. ^{1}H-NMR Data for Compounds 1−4[a]

proton	compound 1	2[c]	3	4
MeO-2	3.77	3.77	3.76	3.77
H-3	6.79	6.84	6.78	6.78
H-4	2.79 α dd (16.5, 3.3), 3.24 β ddd (16.9, 12.4, 5.8)	2.76 α dd (16.4, 2.6), 3.20 β ddd (17.1, 11.0, 5.8)	2.76 α dd (16.5, 3.3), 3.20 β ddd (15.7, 12.1, 6.0)	2.79 α dd (16.2, 1.4), 3.22 β ddd (16.2, 12.0, 6.0)
H-5	2.59 α ddd (12.5, 12.5, 3.0), 3.08 β hm [dd] (12.5, 5.8)	2.58 α ddd (12.0, 12.0, 3.5), 3.06 β hm	2.58 α ddd (12.0, 12.0, 4.1), 3.06 β hm	2.59 α ddd (11.7, 11.7, 3.7), 3.07 β hm
MeN	2.58	2.56	2.56	2.57
H-6a	2.95 br d (11.7)	2.94 br d (11.9)	2.94 br d (11.7)	2.95 br d (12.5)
H-7	3.09 α hm [dd] (13.5, 3.3), 2.33 β dd (12.4, 12.4)	3.07 α hm [dd] (13.4, 3.4), 2.33 β dd (13.0, 13.0)	3.08 hm [dd] (13.5, 3.3), 2.33 β dd (12.8, 12.8)	3.09 hm [dd] (13.2, 3.5), 2.30 β dd (12.9, 12.9)
H-8	6.91 br d[b] (8.2)	6.88 d (8.1)	6.88 dd (8.0, 0.7)	6.89 d (8.1)
H-9	6.72 d (8.2)	6.73 d (8.0)	6.73 d (8.0)	6.74 d (8.1)
MeO-10	3.751	3.75	3.75	3.73
MeO-11	3.65	3.67	3.68	3.66
H-3′	5.54	5.68	5.70	5.69
MeO-4′	3.38	3.41	3.42	3.48
MeO-5′	3.746	3.71	3.74	3.80
H-6′	6.75	6.73	6.73	7.22
H-7′	4.43 dd (11.7, 9.4), 5.04 dd (11.7, 4.4)	4.69 d (12.6), 4.78 d (12.6)	5.34 d (11.7) 5.43 d (12.1)	10.65 s
Misc	4.26 (HO) dd (9.4, 4.3)	3.42 (MeO-7′)	2.10 (AcO)	

[a] Taken at 300 MHz in $CDCl_3$ or stated otherwise with data point resolution of 0.4 Hz and chemical shift (δ) in ppm as referenced to TMS with residual solvent peak ($CHCl_3$) taken as internal standard at 7.26 ppm. Spin-coupled patterns are designated as follows: singlets unmarked, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened, and h = hidden or overlapped. The spin-coupling constant (J) is given in parenthesis in Hz. Some hidden patterns were clarified by homonuclear decoupling and NOE studies are given in brackets. [b] In some experiments further splitting by 0.6−0.8 Hz was observed. [c] At 500 MHz.

Table 2. ^{13}C-NMR Data for Compounds 1, 2 and 4[a]

carbon	compound 1[b]	multiplicity	2[d]	4
C-1	139.4	s	140.8	139.4
C-1a	126.3	s	127.0	126.5
C-1b	129.2	s	129.2	130.1
C-2	151.5	s	151.8	151.6
C-3	112.4	d	112.6	112.1
C-3a	129.4	s	129.5	130.2
C-4	29.0	t	29.2	29.1
C-5	52.8	t	52.8	52.9
C-6a	63.0	d	63.0	63.1
C-7	35.9	t	36.3	36.0
C-7a	129.9	s	130.7	129.4
C-8	122.2	d	121.6	122.0
C-9	112.7	d	113.3	113.7
C-10	151.9	s	152.1	152.2
C-11	147.1	s	148.5	148.0
C-11a	124.7	s	125.0	124.5
C-1′	120.9	s	118.6	117.8
C-2′	150.3	s	150.1	157.3
C-3′	97.7	d	99.1	98.1
C-4′	148.8	s	148.5	155.0
C-5′	142.9	s	143.6	144.0
C-6′	114.0	d	112.2	108.0
C-7′	61.2	t	68.6	189.1 d
MeO-2	56.3[c]	q	56.4	56.3
MeO-10	56.4[c]	q	56.6	56.8
MeO-11	60.9	q	60.7	60.9
MeO-4′	55.7	q	55.9	55.8
MeO-5′	56.5	q	56.6	56.2
MeN	43.8	q	44.0	43.9
MeO-7′			57.9 q	

[a] Taken at 75 MHz in $CDCl_3$ unless stated otherwise with multiplicities determined by SFORD and chemical shifts (in ppm) relative to TMS using the solvent peak (center) as reference at 77.2 ppm. Abbreviations are as follows: s = singlet, d = doublet, t = triplet, and q = quartet. [b] At 67.9 MHz. [c] May be interchanged. [d] Taken at 20 MHz.

Dehydrofaurine (4). Faurine (**1**) (45 mg) in 2 mL of CH_2Cl_2 was passed into a 13.5-g column of MnO_2-diatomaceous earth (1:2) and followed by 10 mL of CH_2Cl_2. After 1 h, the column was eluted with 200 mL of Me_2CO. The residue (36 mg) from the effluent was chromatographed on 3 g of Si gel $CHCl_3$ (100 mL) and 2% MeOH in $CHCl_3$ to give 28 mg of dehydrofaurine as an amorphous solid: $[\alpha]^{26}_D$ +192° (*c* 0.82, $CHCl_3$); UV (MeOH) λ max (log ϵ) 223 (4.96), 2.70 (4.65), 309 (4.24), and 337 (4.19) nm; IR ($CHCl_3$) ν max 3010, 1672 (C=O), 1615, 1515, 1470, 1280, 1180, and 1145 cm^{-1}; HRMS *m/z* 506.2168 (41, MH^+, $C_{29}H_{32}O_7$, −1.1), 505.2123 (100, M^+, $C_{29}H_{31}NO_7$, +2.2), 490.1818 (25, M − Me, −4.8), 340.1416 (13, $C_{20}H_{22}NO_3$, −3.3), and 182.0596 (18, $C_9H_{10}O_4$, +1.7); and ^{1}H- and ^{13}C-NMR in Tables 1 and 2, respectively.

Formation of *O*-Methylfaurine (2). The attempted Hofmann degradation of faurine (**1**) gave the *O*-methyl derivative **2**. Faurine (54 mg) was treated overnight with 2.5 mL of MeI in 2 mL of MeOH at room temperature. The starting material was gone (by TLC). One-half of the product (26 mg) was added to 0.1 mL of ethanolamine and heated for 30 min at 166−167 °C; then partitioned between H_2O (50 mL) and $CHCl_3$ (2 × 50 mL). The $CHCl_3$ residue (21 mg) was chromatographed on 3 g of Si gel with $CHCl_3$ (72 mL) and 0.2% MeOH in $CHCl_3$ to give with the last solvent, 8.2 mg of *O*-methylfaurine (**2**), identical (^{1}H-NMR, specific rotation, TLC mobility) with the compound isolated from *T. fauriei*.

BrCN Cleavage of Faurine (1). Faurine (25 mg) and BrCN (5.5 mg) were stirred in 2 mL of $CHCl_3$ for 5 h at room temperature, then evaporated to dryness under vacuum. The residue was separated by preparative TLC on Si gel (1 mm) with Me_2CO−PhMe−NH_4OH (18:18:1). The lower band was starting material (12 mg). The upper band was rechromatographed on a Si gel (5 g) column with 5% MeOH in $CHCl_3$ to give 13.2 mg of the phenanthrene **6**: $[\alpha]^{24}_D$ +7° (*c* 0.48, MeOH); CD (*C* 2.4 × 10^{-5}M, MeOH) (deg) $[\Theta]_{220}$ 0, $[\Theta]_{235}$ +15 080, and $[\Theta]_{245}$ 0; UV (MeOH) λ max (log ϵ) 235 (4.55), 265 (4.70), 303 (4.14), 317 (4.24), and 331 (4.26) nm; IR ($CHCl_3$) ν max 3460 (OH), 3005, 2210 (CN), 1615, 1600, 1592, 1508, 1458, 1280, 1190, 1180, 1150,

854, and 820 cm^{-1}; HRMS *m/z* 532.2259 (61, M^+, $C_{30}H_{32}N_2O_7$, +4.9), 297.1118 (22, $C_{18}H_{17}O_4$, −0.8), 166.0632 (18, $C_9H_{10}O_3$, +0.2), 69.0582 (78, CH_2═N(CN)-Me, +12.9), and 55 (100, C_3H_5N); and ^{1}H-NMR in Table 1.

Isolation of Isocorydine. The chromatographic fraction (133 mg) of the 1980 collection gave from Me_2-CO 50 mg of colorless needles: mp 185−186 °C: $[\alpha]^{25}_D$ +147° (*c* 0.3, $CHCl_3$); CD (*C* 3.3 × 10^{-5} M, MeOH) (deg) $[\Theta]_{233}$ +279 000, $[\Theta]_{248}$ 0, $[\Theta]_{268}$ −42 300, $[\Theta]_{300}$ (sh) −4800, and $[\Theta]_{320}$ +2500; comparison of the ^{1}H- and ^{13}C-NMR spectra to the literature values established its identity.[30,31]

***O*-Methylisocorydine (*O,O*-Dimethylcorytubercine).** Isocorydine (20 mg) in 1.0 mL of MeOH was treated with 12 mL of 1.5% CH_2N_2 in Et_2O for 4 days at 4 °C. The residue after solvent removal was purified by preparative TLC on basic Al_2O_3 (0.5 mm) with Et_2O-PhH (1:1), and two developments, followed by chromatography on a Si gel (3 g) column with 0.5% (50 mL) and 2% (40 mL) MeOH in $CHCl_3$. The amorphous product gave $[\alpha]^{25}_D$ +222° (*c* 1.0, $CHCl_3$) and ^{1}H-NMR[32] ($CDCl_3$, 500 MHz) δ 6.95 (1 H, d, J = 8.1 Hz, H-8), 6.84 (1 H, d, J = 8.1 Hz, H-9), 6.66 (1 H, s, H-3), 3.88 (3 H, s, MeO-10), 3.87 (3 H, s, MeO-2), 3.72 (3 H, s, MeO-1 or MeO-11), 3.64 (3 H, s, MeO-11 or MeO-1), 3.16 (1 H, ddd, J = 15.7, 12.3, 6.0 Hz, H-4β), 3.03 (1 H, dd, J = 11.6, 6.4 Hz, H-5β), 3.01 (1 H, J = 13.5, 3.4 Hz, H-7α), 2.89 (1 H, br d, J = 11.3 Hz, H-6a), 2.69 (1 H, dd, J = 16.4, 3.6 Hz, H-4α), 2.53 (1 H, hm, H-5α), 2.54 (3 H, s, MeN), and 2.38 (1 H, dd, J = 13.0, 13.0 Hz, H-7β).

BrCN Treatment of Acetylisocorydine. The acetate derivative was prepared from 49 mg of isocorydine, 3 mL of Ac_2O, and 1 mL of pyridine at room temperature overnight. The clean product (Ac at 2.24 ppm in $CDCl_3$ at 90 MHz) was dissolved in 3 mL of $CHCl_3$ and stirred magnetically with 44 mg of BrCN in 2 mL of $CHCl_3$ for 4 h under N_2. After workup as given for faurine (**1**), 16 mg of the phenanthrene product **7** was obtained showing: $[\alpha]^{25}_D$ +2° (*c* 0.5, MeOH); CD (*C* 2.7 × 10^{-5} M, MeOH) (deg) $[\Theta]_{222}$ 0, $[\Theta]_{235}$ +10 390, and $[\Theta]_{243}$ 0; UV (MeOH) λ max (log ϵ) 240 sh (4.60), 258 (4.79), 297 sh (4.14), 311 (4.35), and 323 (4.37) nm; IR ($CHCl_3$ ν max 3010, 2220 (CN), 1768 (C═O), 1608, 1595, 1463, 1431, 1289, 1197, 1156, 1064, 1023, and 825 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 (1 H, d, J = 8.7 Hz, H-8), 7.50 (1 H, d, J = 9.0 Hz, H-6α), 7.47 (1 H, d, J = 9.0 Hz, H-7), 7.37 (1 H, d, J = 8.7 Hz, H-9), 7.26 (1 H, s, H-3), 4.04 (3 H, s, MeO-2), 3.96 (3 H, s, MeO-10), 3.42 (3 H, s, MeO-1), 3.40 (2 H, m, H_2-4), 3.29 (2 H, m, H_2-5), 2.84 (3 H, s, MeN-6), and 2.38 (3 H, s, AcO-11); NOED (300 MHz, $CDCl_3$) δ 7.70 (H-8) relaxed to 7.47 (H-7, 12%) and 7.37 (H-9, 17%), 4.04 (MeO-2) relaxed to 7.26 (H-3, 14%), 3.96 (MeO-10) relaxed to 7.37 (H-9, 17%), and 2.84 (MeN-6) relaxed to 3.29 (H_2-5, 1%); HRMS *m/z* 408.1653 (7, M^+, $C_{23}H_{24}N_2O_5$, −3.2), 366.1524 (26, M − C_2H_2O, $C_{21}H_{22}N_2O_4$, −5.6) 297.1091 (23, M − C_2H_2O − $C_3H_5N_2$, $C_{18}H_{17}O_4$, −3.5), 69.0684 (100, CH_2N(Me)CN, +12.0), 43.9922 (20, CO_2, +2.4), and 43.0194 (23, CH_3CO, +1.0).

BrCN Treatment of *O*-Methylisocorydine. *O*-Methylisocorydine (20 mg) in 3 mL of $CHCl_3$ was treated with 20 mg of BrCN in 2 mL of $CHCl_3$ as described for acetylisocorydine to give 8 mg of phenanthrene **8**: optically inactive ($[\alpha]_D$, CD); UV (MeOH) λ max (log ϵ) 245 sh (4.56), 264 (4.82), 302 sh (4.21), 318 (4.33), and 329 (4.36) nm; IR ($CHCl_3$) ν max 3004, 2208 (CN), 1592, 1504, 1460, 1418, 1385, 1278, 1152, 1063, 1032, and 820 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 7.48 (1 H, d, J = 8.6 Hz, H-8), 7.45 (2 H, s, H-6a and H-7), 7.30 (1 H, d, J = 8.6 Hz, H-9), 7.21 (1 H, s, H-3), 4.02 (3 H, MeO), 4.01 (3 H, MeO), 3.67 (3 H, MeO), 3.66 (3 H, MeO), 3.25−3.40 (4 H, m, H_2-4 and H_2-5), and 2.84 (3 H, MeN); HRMS *m/z* 380.1733 (88, M^+, $C_{22}H_{24}N_2O_4$, +0.3), 311.1284 (100, M − CH_2C(Me)CN, −0.1), 279.1008 (12, M − 69 − MeOH), 265.0848 (24, M − 69 − Me_2O, +16), 69.0448 (25, CH_2N(Me)CN, +0.5), and 42.0345 (4, C_2H_4N, −0.1).

2,4,5-Trimethoxybenzyl alcohol: prepared from 2,4,5-trimethoxybenzaldehyde (Aldrich Chemical Co.) by $NaBH_4$ reduction;[33] mp 72−74 °C from Et_2O (lit.[34] mp 70°); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.85 (1 H, s, H-6), 6.52 (1 H, s, H-3), 4.60 (2 H, s, CH_2), 3.87 (3 H, s, MeO-4), 3.82 (6 H, s, MeO-2 and MeO-5), and 2.33 (1 H, br s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.8 (s, C-2), 149.3 (s, C-4), 143.1 (s, C-5), 120.9 (s, C-1), 113.5 (d, C-6), 97.6 (d, C-3), 61.5 (t, CH_2), 56.8 (q, MeO-2 or MeO-5), 56.4 (q, MeO-4), 56.3 (q, MeO-2 or MeO-5). The NMR assignments were made from NOED, DEPT, CH-correlation, and COLOC studies.

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