Efficient Formal Total Synthesis of Physostigmine and Physovenine: Conformational Analysis of Key Intermediates[1]

Martha S. Morales-Ríos, Norma F. Santos-Sánchez, and Pedro Joseph-Nathan*

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México, D.F., 07000 México

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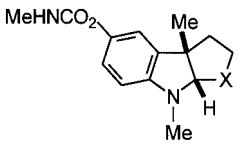
An efficient route for the formal total synthesis of physostigmine (**1**) and physovenine (**2**), alkaloids from 5-methoxyindole-3-acetonitrile, through a Grignard reagent 1,4-addition, is described. 2-Hydroxyindolenine **5**, the key advanced intermediate for the synthetic targets, was converted either to esermethole (**12**) via a high-yielding (28%) seven-step sequence or to the C-ring oxygenated analogue **15** in a five-step sequence and 23% overall yield. ^{1}H NMR and molecular modeling analyses of esermethole (**12**) and the furoindolines **13** and **15** were used to deconvolute weighted time-average vicinal coupling constants to provide definite solution-state conformational preferences in CD_2Cl_2 solvent.

The *Physostigma* genus (Fabaceae) produces a group of indole alkaloids which include physostigmine (**1**) as the main basic constituent. Alkaloid **1** was first isolated in 1864 from the seeds of *Physostigma venenosum* and was structurally characterized in 1925.[2] One of the minor alkaloids of the same plant, physovenine (**2**), a C-ring oxygenated analogue of physostigmine, was in turn structurally characterized in 1964.[3] During the last four decades, a number of other physostigmine-like alkaloids were isolated from diverse biological origins, including the A-ring brominated alkaloids the flustramines and flustraminols, isolated in very small amounts from a cheilostome bryozoan, namely, *Flustra foliacea*.[4] Pseudophrynamines, a class of 3a-prenyl pyrrolo[2,3-*b*]indoles, were isolated from the skin extracts of the frog *Pseudophryne coriacea*.[5] The recently disclosed mollenines A and B also display close structural similarity to physostigmine and were isolated from the fungus *Eupenicillium molle*.[6] These alkaloids are of interest from biological and pharmacological viewpoints. The most widely studied of these alkaloids, physostigmine (**1**), is an acetylcholinesterase inhibitor which seems useful for treating cholinergic disorders. More recently, analogues of **1** have shown promise as therapeutic agents for Alzheimer's disease.[7]



1: X = NMe
2: X = O

After the pioneering synthesis of racemic physostigmine by Julian in 1935,[8] numerous researchers have been challenged by the chemical synthesis of these alkaloids. The goal of our program was to devise a new general strategy for the syntheses of furo- and pyrrolo[2,3-*b*]indole alkaloids, including those occurring in the Calabar bean *Physostigma venenosum* and in the marine bryozoan *Flustra foliacea*, that would allow a simple entry to any of the alkaloids of both families starting from a common advanced intermediate. We recognized that most members of these groups differ in the functionality at C-3a and N-8a, and thus, we attempted to devise a strategy with the flexibility to allow for the variations in these positions of the molecules. We developed one facile entry to this target in which a Grignard reagent 1,4-addition to 2-hydroxyindolenines has been exploited as the key construction intermediate.[9] The versatility of the strategy lies in the fact that, by using the Grignard reagent, a variety of alkyl groups can be introduced into the C-3 position of the appropriately substituted 2-hydroxyindolenine.[10] Recently, we have described the successful application of this strategy to the synthesis of a series of marine *Flustra foliacea* alkaloids.[11] To further develop our method, in this paper we applied the above synthetic strategy to the formal synthesis of the acetylcholinesterase inhibitors physostigmine (**1**) and physovenine (**2**), demonstrating that this protocol is a general and efficient approach for the synthesis of 3a-alkylated furo- and pyrrolo[2,3-*b*]indole alkaloids.

Results and Discussion

According to Scheme 1, the starting material for the formal syntheses of physostigmine (**1**) and physovenine (**2**), the dialkoxycarbonylindole derivative **4**, was prepared in high yield by reaction of 5-methoxyindole-3-acetonitrile (**3**)[12] with dimethyl carbonate in the presence of sodium hydride at room temperature. When sodium was used instead of sodium hydride, only the corresponding *N*-monoalkoxycarbonylindole derivative was formed even heating at reflux. Oxidation of **4** with chromium oxide in acetic acid at 0 °C gave the *N*-protected 2-hydroxyindolenine **5**, as the (*Z*)-alkene isomer in 82% yield. The (*Z*)-alkene stereochemistry of **5** was deduced from the H-2 and H-4 NMR chemical shifts.[10] Using our standard conditions,[9b] the synthesis of **1** (Scheme 1) involves the 1,4-addition of methylmagnesium iodide to 2-hydroxyindolenine **5** to give 3-methylindoline **6** in a reasonable isolated yield (50%). This method was previously applied, through an analogous synthesis of **5**, for the preparation of Julian's oxindole.[9a] After several reaction conditions were screened, lactonization of **6** was effected by treatment with 6% aqueous potassium hydroxide at room temperature to afford furoindolinone **7** as the only observable product, regardless of the *N*-carbomethoxy leaving group, in a quantitative yield. It might be noted that the effectiveness of this strategy as compared with those also based on the construction of

* To whom correspondence should be addressed. Tel: (52-55) 5747-7112. Fax: (52-55) 5747-7137. E-mail: pjoseph@nathan.chem.cinvestav.mx.

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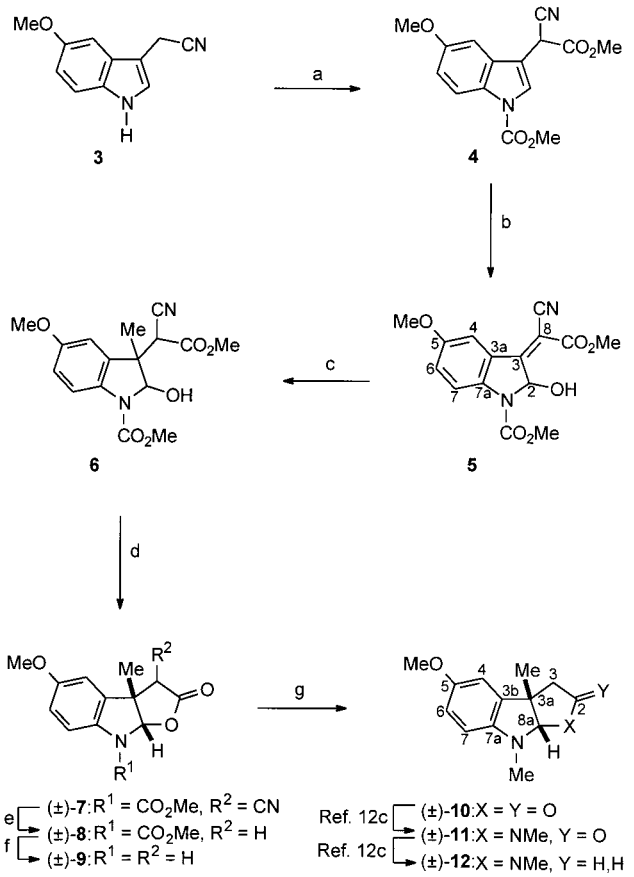
Scheme 1[a]

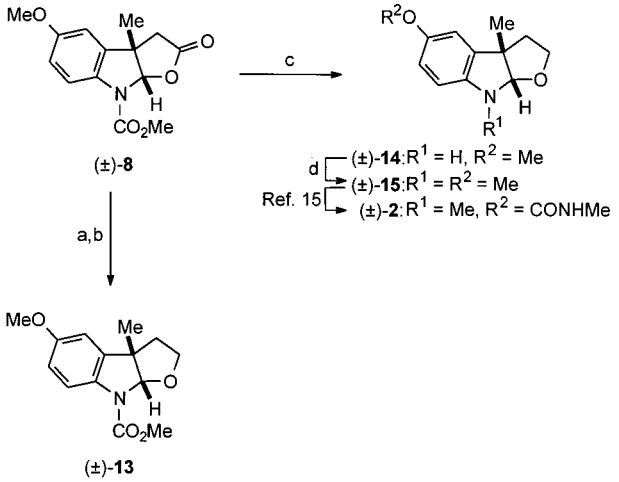


[a] (a) $NaH-Me_2CO_3$, rt, 12 h, 87%; (b) CrO_3-H_2O, AcOH, 0 °C, 1 h, 82%; (c) 4 equiv MeMgI, Et_2O–THF, 1:1, rt, 15 min, 50%; (d) 6% aq KOH, THF, rt, 20 min, quant.; (e) Al_2O_3, 10% aq THF, reflux, 0.5 h, 75%; (f) NaOMe–MeOH, reflux, 1 h, >95%; (g) K_2CO_3, Me_2SO_4, acetone, reflux, 6 h, 78% from **8**.

furoindolinone-type intermediates,[13] to produce the physostigmine alkaloids, lies in the simplicity of the lactone formation.

With a viable route to the furo[2,3-*b*]indoline system established, it remained to remove both the *N*-protective group and the cyano group at C-3 to demonstrate the utility of this strategy in the synthesis of the Calabar bean (*P. venenosum*) alkaloids. Using a decyanation protocol that was recently developed,[14] furoindolinone **7** was easily and efficiently decyanated with neutral alumina in refluxing 10% aqueous THF for 0.5 h to produce compound **8**, the key divergent intermediate in our syntheses, in 75% yield. After an extensive survey of reaction conditions, it was found that sodium methoxide in methanol was optimal for effecting the desired removal of the *N*-protective group. Thus, refluxing compound **8** for 1 h furnished the unstable product **9** in an excellent yield (>95% as determined by ^{1}H NMR in CD_2Cl_2 of the crude reaction mixture). *N*-Methylation of the potassium salt derived from **9** was achieved with dimethyl sulfate in refluxing acetone for 6 h to give **10** in 78% yield. This result compares favorably to a previous report,[13c] where **10** was obtained from **9** in only 25% yield. Conversion of **10** into esermethole (**12**) has been described previously in a two-step sequence including treatment with methylamine and reduction of the resulting lactam **11** with LAH in quantitative yield for the two steps.[13c] Thus, our route to esermethole provides this compound in 28% overall yield from 2-hydroxyindolenine **5**. Since esermethole (**12**) has previously been converted into physostigmine (**1**) by demethylation with boron tribromide and treatment of the resulting phenol with methyl isocyanate,[15] the preparation of **12** constitutes a formal total synthesis of **1**. The rather rigid structure of esermethol (**12**) facilitated the diagnosis of its conformational preference in solution, based on careful inspection of the ^{1}H NMR spectral data and molecular modeling (vide infra).

Scheme 2[a]



[a] (a) $AlH_3NEt(Me)_2$, THF, −10 °C, 1 h; (b) *p*-TsOH, catalytic amount, benzene, 2.5 h, reflux, 72% from **8**; (c) 3.5 equiv LAH, ether–THF, rt, 10 min, 96%; (d) 35% aq CH_2O, MeCN, rt, overnight, $NaCNBH_3$, rt, 30 min, 64%.

In light of the synthesis outlined in Scheme 2, the first objective for the preparation of physovenine (**2**) was to access the *N*-carbomethoxylated furoindoline **13** by reduction of the key divergent intermediate **8**. Initially, this reduction was effected at room temperature using BH_3 in THF, albeit in 21% yield. It was therefore decided to adopt a new procedure in which reduction of **8** was performed in two steps. In the first step, **8** was subjected to reduction with the alane–*N*,*N*-dimethylethylamine complex to give, as assigned by ^{1}H NMR analysis of the crude product, a mixture of the 1,4-diol arising from the γ-lactone cleavage and small amounts of furoindoline **13**. The resulting mixture was fully converted to **13** (72% for the two steps) on exposure to a catalytic amount of *p*-toluenesulfonic acid.

Compound **13** and the *N*(8)-carbomethoxylated derivatives **7** and **8** showed very broad H-7 and N(8)-CO_2Me proton signals in the ^{1}H NMR spectra at room temperature, as well as very broad N(8)-CO_2Me, C-7a, C-3b, and C-3a carbon signals in their ^{13}C NMR spectra. Hindered rotation about the N(8)–CO_2Me single bond in these compounds is responsible for such broad signals.[12] This was further tested at higher temperatures (70 °C in DMSO-d_6), where the rotation barrier was exceeded and sharp signals in both the ^{1}H and the ^{13}C NMR spectra were obtained.

Attempting, in one step, to reduce and deprotect the key divergent intermediate **8** to afford directly furoindoline **14**, it was found that when **8** was stirred in the presence of 2 equiv of LAH at room temperature for 2 h, decomposition products were obtained, along with some recovery of **8** (10%). After evaluating a variety of reaction conditions, optimum results were found using 3.5 equiv of LAH in ether–THF at room temperature for 10 min to provide the unstable furoindoline **14** in essentially quantitative yield (>95% as determined by ^{1}H NMR in CD_2Cl_2 of the crude reaction mixture). This one-step procedure was found to be a great improvement over the four-step sequence used previously for the conversion of **8** to the deprotected furoindoline **14** (62% based on **8**).[13d]

Although conversion of the furoindoline **14** to the corresponding tertiary amine **15** was previously reported[16]

Table 1. ^{1}H NMR Data (δ in ppm from TMS), Coupling Constants (J in Hz),[a] and Torsion Angles (ϕ in deg), of the C-Ring of **12**, **13**, and **15** (300 MHz, CD_2Cl_2, at 295 K)

	^{1}H chemical shifts					coupling constants (torsion angles)					
	H-2		H-3		H-8a	$^2J_{2,2}$	$2J_{3,3}$	$^3J_{2,3}$			
compd	*exo*	*endo*	*exo*	*endo*	*exo*	*exo-endo*	*exo-endo*	*exo-exo*	*exo-endo*	*endo-endo*	*endo-exo*
12[b]	2.55	2.68	1.88	1.91	4.03	9.1	12.0	6.8 (37)	8.4 (141)	6.9 (40)	3.6 (−54)
13[c]	3.35	3.85	2.11	2.02	5.57	8.6	12.0	4.7 (43)	11.9 (167)	7.3 (39)	1.3 (−100)
15[d]	3.39	3.89	2.10	2.02	4.99	8.4	12.0	5.1 (41)	11.2 (158)	7.4 (39)	1.5 (−63)

[a] From LAOCN3 simulated spectra. [b] $^4J_{2-exo,8a-exo} \cong 0.4$ Hz. [c] $^4J_{3-exo,8a-exo} \cong 0.5$ Hz. [d] $^4J_{3-exo,8a-exo} \cong 0.6$ Hz.

utilizing a modified Borch procedure, we were unable to reproduce this transformation under the reported reaction conditions. The inconvenience was solved after using the original Borch conditions[17] detailed in the Experimental Section. The spectroscopic data of **15** were identical with those reported in the literature,[13b] thus confirming that its precursor **14** has the correct structure. Since the furo[2,3-*b*]indole **15** was previously transformed into physovenine (**2**),[16,18] the present procedure constitutes a formal total synthesis. The conformational analysis of furoindolines **13** and **15** was now firmly established by ^{1}H NMR and molecular modeling analysis (vide infra).

Conformational Analysis. Although it is known that five-membered rings are flexible and may exist as equilibrium mixtures,[19] the reduced conformational flexibility of esermethole (**12**) and the furoindolines **13** and **15** facilitated their conformational assignment. The most diagnostic data derive from the measurements of vicinal ^{1}H−^{1}H coupling constants ($^3J_{2,3}$, Table 1), computer simulated spectra, detection of specific NOE contacts, and structural simulation. NOESY and ^{1}H NMR analysis of esermethole (**12**) in CD_2Cl_2 at 295 K established the *cis* orientation between H-8a and the substituents at N-8 and C-3a and, therefore, their *exo* stereochemistry. A pseudoequatorial-coplanar disposition for H-8a at 4.02 ppm and H-2 at 2.55 ppm was deduced from the observed *W* long-range coupling constant between these protons. Thus, the pseudoequatorial and pseudoaxial H-2 protons are clearly differentiated as H-2-*exo* and H-2-*endo*, respectively. Starting from the H-2-*exo* resonance, the vicinal coupling constant values obtained from a LAOCN3 simulated spectrum allowed the assignments of the proton C-ring signals. As summarized in Table 1, the Karplus type rules that link the ^3J coupling constants with the torsion angle (ϕ)[20] allowed the deduction that esermethole (**12**) exists in a conformational equilibrium in solution, and thus only the weighted time-average vicinal coupling constants ($^3J_{obs}$) between protons H-2 and H-3 can be obtained. The spectra obtained at variable low temperature in CD_2Cl_2 were not significantly different down to −65 °C.

According to theoretical calculations using molecular mechanics (MMX force field[21]) method, compound **12** has four low-energy conformations resulting from the C-ring inversion (**A**, **B**) and the nitrogen (N-1) inversion (**A′**, **B′**). The fused rings introduce a conformational rigidity in this compound with the pyrrolidine ring fused to the benzene ring in an almost flat conformation. The computed structures of **12** are collected in Figure 1, and the corresponding relative energies are listed in Table 2.

The lower energy conformer **A** corresponds to structure C-2-*endo*/C-3-*exo* with H-2-*exo* in a quasi-equatorial position. The two conformations **A′** and **B′**, in which the N(1)−CH_3 group is on the *exo* face, are essentially isoenergetic and are predicted to be only slightly less stable (≤1.6 kcal mol^{-1}) than the **A** conformation. The nitrogen inversion in **A′** and **B′** causes no appreciable change of the geometry of ring C, as deduced from the theoretical $^3J_{2,3}$ coupling

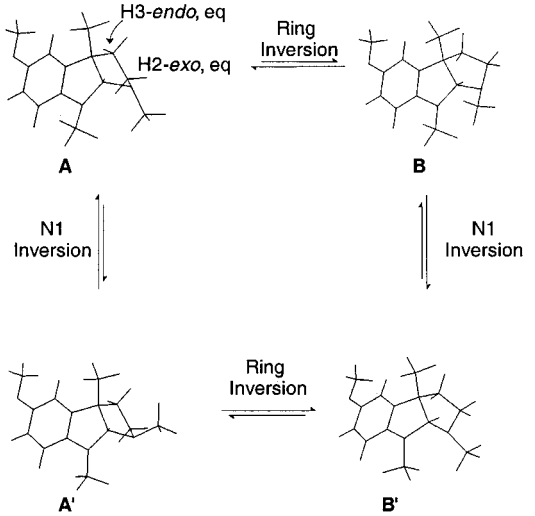


Figure 1. Computed geometries of **12** fully optimized at the MMX level.

Table 2. Calculated Relative Energies (kcal mol^{-1})[a] of Principal Conformers of **12**, **13**, and **15**

conformer	**12**	**13**	**15**
A	0.0	0.0	0.0
A′	1.6		
B	5.5	1.0	1.5
B′	1.2		

[a] Energies are relative to the **A** conformers.

Table 3. Theoretical C-Ring Coupling Constants (J in Hz), and Torsion Angles (ϕ in deg), of Principal Conformers of **12**, **13**, and **15**

			$^3J_{2,3}$			
compd	conformer		*exo-exo*	*exo-endo*	*endo-endo*	*endo-exo*
12	**A**	J	6.7	0.6	5.4	12.0
		ϕ	−41.6	78.3	−44.4	−164.3
	A′	J	7.4	0.5	6.6	11.2
		ϕ	−37.6	81.4	−38.5	−157.4
	B	J	6.9	11.0	7.7	0.4
		ϕ	36.6	156.0	36.3	−83.1
	B′	J	6.4	11.5	7.5	0.4
		ϕ	39.4	159.6	37.2	−82.9
13	**A**	J	6.9	0.3	4.4	11.8
		ϕ	−41.6	79.3	−44.7	−165.6
	B	J	4.4	11.8	7.3	0.3
		ϕ	44.6	165.6	39.8	−81.2
15	**A**	J	6.9	0.3	4.4	11.8
		ϕ	−41.9	79.0	−44.9	−165.8
	B	J	4.6	11.8	7.1	0.3
		ϕ	43.5	164.3	40.5	−80.5

constants (Table 3), and is therefore not expected to affect the NMR parameters of this part of the molecule to any significant extent. The **B** conformer, in which 1,3 nitrogen lone pair repulsion is involved, is the least stable one by 5.5 kcal mol^{-1}. The interconversion of the **A** and **B′** conformations through **A′** results in a dynamic process

involving exchange of the methylene protons between quasi-axial and quasi-equatorial environments (Figure 1).

Inserting the observed coupling constants ($^3J_{obs}$) and the corresponding computed conformer couplings (Table 3) arising from the energy-minimized structures **A** and **B′** $\{J_{2e,3e} + J_{2a,3a}\}$, $\{J_{2e,3a} + J_{2a,3e}\}$, $\{J_{2a,3a} + J_{2e,3e}\}$, and $\{J_{2a,3e} + J_{2e,3a}\}$ into eqs 1 and 2, where $n_{\mathbf{A}}$ and $n_{\mathbf{B}'}$ are the mole fractions of the pseudoequatorial and pseudoaxial conformations (with respect to specified proton), allows for the deduction of conformer populations owing to the C-ring inversion. A 28:72 ratio was calculated in favor of conformer **B′** at the fast exchange limit (FEL) for nitrogen inversion,[22] with all averaged vicinal ^{1}H−^{1}H coupling constants ($^3J_{2,3}$, see Table 1) consistently fitting the experimental values. In addition, the estimated small value of the weighted time-average long-range *W* coupling, $^4J_{2-exo,8a-exo} \cong 0.4$ Hz, is in agreement with the **A** and **B′** relative populations. Our calculations have been carried out in the absence of solvent, and since the calculated energy difference between the **A** and **B′** conformations is relatively small, it is reasonable to expect that solvatation effects might result in a bias of one over the other.[23]

$$^3J_{obs} = n_{\mathbf{A}}(^3J_{2,3})_{\mathbf{A}} + n_{\mathbf{B}'}(^3J_{2,3})_{\mathbf{B}'} \quad (1)$$

$$n_{\mathbf{A}} + n_{\mathbf{B}'} = 1 \quad (2)$$

The conformation of five-membered rings can be described by the concept of pseudorotation.[24] Using this, the values of *P* (phase angle) and ϕ (puckering amplitude) for structure **A** are 292.5° and 47.2° and for **B′** are 100.2° and 48.6°, respectively. These values of *P* refer to approximate pyrrolidine ring puckers of N-1-*exo*, C-2-*endo* and N-1-*endo*, C-2-*exo*, respectively. In structures **A** and **B′**, the C-ring was in a close twisted ^{2}T$_1$ and enveloped-twisted ^{1}E-^{1}T$_2$ conformations, respectively (Figure 1).

Concerning furoindolines **13** and **15**, a notable variation in the conformation of the tetrahydrofuran frame within the constructors is evidenced with respect to the pyrrolidine ring in **12**. Thus, whereas a *W* long-range coupling constant exists between H-8a-*exo* and H-2-*exo* in **12**, in the furoindolines **13** and **15** a *W* long-range coupling constant was detected between H-8a-*exo* and H-3-*exo* protons (Table 1). This fact allowed us to establish a pseudoequatorial-coplanar disposition for these protons. The small magnitude of the $^3J_{2-endo,3-exo}$ of around 1.4 Hz, which corresponds to a torsion angle in the vicinity of −64°, is consistent with the observed *W* long-range $^4J_{8a-exo,3-exo}$ coupling constants in **13** and **15**. Analysis of the vicinal ^{1}H−^{1}H coupling constants and the calculated torsion angles suggested that **13** and **15** adopt a single solution-state conformation. This is interesting because analogue compound **12** (vide supra) exists in a dynamic equilibrium in solution.

The theoretical geometries of **13** and **15** were evaluated at the same basis set as **12** and revealed two low-energy conformations, **A** and **B**, resulting from the C-ring inversion. The **B** conformation in **13** and **15** was predicted to be slightly less stable (≤1.5 kcal mol^{-1}) than the **A** conformation. The computed structures of **13** and **15** are represented in Figure 2, and the corresponding relative energies are listed in Table 2. The theoretical vicinal ^{1}H−^{1}H coupling constants for conformer **B**, listed in Table 3, show excellent agreement with the available experimental data (Table 1), the main difference appearing in the $^3J_{2-endo,3-exo}$ with a deviation of ca. 1 Hz.

Molecular mechanics calculations predict that the C-ring in **13** was blocked in an enveloped $_2$E conformation with *P* = 125.0° and τ_m = 40.4° (Figure 2), while in furoindoline

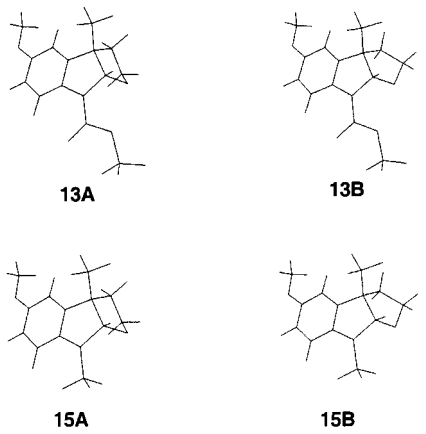


Figure 2. Computed geometries of **13** (top) and **15** (bottom) optimized at the MMX level.

15 the C-ring adopts an enveloped-twisted $_2$T^1-$_2$E conformation with *P* = 117.7° and τ_m = 41.9° (Figure 2). These values of *P* refer to approximate tetrahydrofuran ring puckers of C-2-*exo*.

Experimental Section

General Experimental Procedures. Melting points were obtained on a Fisher-Johns melting point apparatues and are uncorrected. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrophotometer. NMR spectra were recorded on Varian Mercury spectrometers working at 300 and 75.4 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane. NOESY spectra were acquired using mixing times of 800 ms. Standard library pulse sequences were used for all NMR experiments. LREIMS were obtained on Varian Saturn 2000 or Hewlett-Packard 5989A spectrometers. HRMS were measured on a JEOL JMS-SX 102A spectrometer. Flash chromatography was performed using Si gel 60 (230−400 mesh) from Aldrich. Analytical thin-layer chromatography (TLC) was performed on Si gel 60 F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Dry THF and ether were obtained by distillation over sodium. All the commercial grade reagents were used without further purification. Esermethol (**12**) and its precursor **11** were prepared according to the methods described previously.[13c] For properties, constants, and spectroscopic data of **11** and **12**, see refs 13b and 25. For MMX force field calculations,[21] the PCMODEL program was used from Serena Software (Bloomington, IN, 1990).

Methyl 3-(1-Cyano-2-methoxy-2-oxoethyl)-5-methoxy-1*H*-indole-1-carboxylate (4). To a solution of 5-methoxyindole-3-acetonitrile (**3**)[12] (3.78 g, 20.3 mmol) in dimethyl carbonate (40 mL) was added sodium hydride (1.05 g, 44.0 mmol), and it was stirred at room temperature for 12 h under an argon atmosphere. The reaction mixture was cooled in an ice bath, treated with 10% aqueous HCl to reach pH 6, and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was crystallized from EtOAc to afford 4.63 g of **4**. Flash chromatography of the mother liquors afforded a further 0.71 g of the same compound (87% overall yield) as a pale yellow solid: mp 128−129 °C (EtOAc); R_f = 0.34 (1:1:3 EtOAc−$CHCl_3$−hexane); IR ($CHCl_3$) ν_{max} 3028, 1740, 1482, 1250 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.01 (1H, d, *J* = 9.0 Hz, H-7), 7.85 (1H, s, H-2), 7.14 (1H, d, *J* = 2.6 Hz, H-4), 7.04 (1H, dd, *J* = 9.0, 2.6 Hz, H-6), 5.98 (1H, s, H-8), 3.98 (3H, s, *O*-CH_3), 3.80 (3H, s, *O*-CH_3), 3.77 (3H, s, *O*-CH_3); ^{13}C NMR (DMSO-d_6) δ 165.3, 155.8, 150.4, 129.3, 128.3, 126.0, 115.9, 115.8, 113.7, 110.5, 102.0, 55.4, 54.3, 53.8, 34.2; EIMS *m*/*z* 302 $[M]^+$ (90), 243 (100); HRFABMS (positive mode) *m*/*z* 302.0907 (calcd for $C_{15}H_{14}N_2O_5$, 302.0903).

Methyl (*Z*)-3-(1-Cyano-2-methoxy-2-oxoethylidene)-2,3-dihydro-2-hydroxy-5-methoxy-1*H*-indole-1-carboxylate (5). To a precooled (0 °C) stirred solution of **4** (3.9 g, 12.9 mmol) in glacial acetic acid (40 mL) was added dropwise a solution of chromium oxide (4.5 g) in water (25 mL). The reaction mixture was stirred for 1 h at 0 °C and then poured onto cracked ice. The precipitate that had formed was collected by suction filtration and washed with water (3 × 25 mL). The solid residue was dissolved in EtOAc (200 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was crystallized from EtOAc to afford **5**, as a yellow solid (3.37 g, 82%): mp 173−174 °C (EtOAc−hexane); R_f = 0.26 (4:6 EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3570, 3030, 2220, 1724 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.75 (1H, br s, H-7), 7.71 (1H, d, J = 2.6 Hz, H-4), 7.35 (1H, d, J = 7.9 Hz, OH), 7.27 (1H, dd, J = 9.1, 2.6 Hz, H-6), 6.55 (1H, d, J = 7.9 Hz, H-2), 3.84 (3H, s, *O*-CH_3), 3.79 (3H, s, *O*-CH_3), 3.75 (3H, s, *O*-CH_3); ^{13}C NMR (DMSO-d_6) δ 162.8, 161.2, 155.2, 151.3, 141.3, 124.1, 122.1, 116.0, 115.9, 108.0, 95.4, 82.8, 55.5, 53.0, 52.9; EIMS m/z 318 $[M]^+$ (100), 286 (41), 258 (40); HRFABMS (positive mode) m/z 318.0871 (calcd for $C_{15}H_{14}N_2O_6$, 318.0852).

Methyl 3-Methyl-3-(1-cyano-2-methoxy-2-oxoethyl)-2,3-dihydro-2-hydroxy-5-methoxy-1*H*-indole-1-carboxylate (6). To a stirred suspension of MeMgI prepared from MeI (3.56 g, 25.1 mmol) and Mg turnings (0.61 g, 0.025 g-atom) in dry ether (60 mL) under argon at 25 °C was added dropwise a solution of **5** (2.0 g, 6.3 mmol) in THF (70 mL) over a 15 min period. The reaction was completed in 15 min, quenched with saturated NH_4Cl solution (50 mL), and diluted with EtOAc (150 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, concentrated, and chromatographed (1.5:3.0:5.5 EtOAc−CH_2Cl_2−hexane) to give **6** as a white solid (1.05 g, 50%): mp 162−164 °C (EtOAc−hexane); R_f = 0.21 (6:4 EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3592, 2250, 1748, 1698, 1276 cm^{-1}; ^1H NMR (DMSO-d_6) diastereomeric 1:1 equilibrated ratio δ 7.54 (2H, br s, H-7), 6.92 (1H, d, J = 2.7 Hz, H-4), 6.90−6.84 (3H, m, H-4, 2 H-6), 6.83 (1H, d, J = 6.6 Hz, OH), 6.80 (1H, d, J = 6.5 Hz, OH), 5.82 (1H, d, J = 6.6 Hz, H-2), 5.71 (1H, d, J = 6.5 Hz, H-2), 4.39 (1H, s, H-8), 4.33 (1H, s, H-8), 3.77 (6H, s, 2 *O*-CH_3), 3.73 (6H, s, 2 *O*-CH_3), 3.59 (3H, s, *O*-CH_3), 3.54 (3H, s, *O*-CH_3), 1.45 (6H, br s, 2 C3a-CH_3); ^{13}C NMR (DMSO-d_6) δ 165.0, 155.5, 152.6, 133.7 (br), 116.0, 115.7, 115.0 (br), 114.1, 113.9, 110.9, 110.2, 86.9, 86.5, 55.6, 55.5, 53.2, 52.6, 49.8, 46.0, 45.9, 16.7, 16.6; EIMS m/z 334 $[M]^+$ (72), 236 (46), 176 (100); HRFABMS m/z 334.1170 (calcd for $C_{16}H_{18}N_2O_6$, 334.1165).

Methyl 3-Cyano-5-methoxy-3a-methyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (7). To a precooled (0 °C) stirred solution of **6** (387 mg, 1.15 mmol) in THF (10 mL) was added 6% aqueous KOH (1.3 mL) at once. The resulting mixture was stirred at room temperature for 20 min, then treated with 10% aqueous HCl to reach pH 4−5, and extracted with EtOAc (2 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Recrystallization of the crude reaction mixture gave **7** as a white solid (348 mg, quant.): mp 212−214 °C ($CHCl_3$−hexane); R_f = 0.32 (4:6 EtOAc−hexane); IR ($CHCl_3$) ν_{max} 2958, 2258, 1802, 1728, 1602, 1452 cm^{-1}; ^1H NMR (DMSO-d_6) diastereomeric 3:1 *endo*/*exo* ratio, δ (*endo* isomer) 7.65 (1H, br s, H-7), 7.16, (1H, d, J = 2.6 Hz, H-4), 7.00 (1H, dd, J = 8.9, 2.6 Hz, H-6), 6.42 (1H, s, H-8a), 5.18 (1H, s, H-3), 3.85 (3H, br s, *O*-CH_3), 3.75 (3H, s, *O*-CH_3), 1.57 (3H, s, C3a-CH_3); δ (*exo* isomer) 7.65 (1H, br s, H-7), 7.19 (1H, d, J = 2.6 Hz, H-4), 6.91 (1H, dd, J = 8.9, 2.6 Hz, H-6), 6.53 (1H, s, H-8a), 5.04 (1H, s, H-3), 3.84 (3H, br s, *O*-CH_3), 3.75 (3H, s, *O*-CH_3), 1.62 (3H, s, C3a-CH_3); ^{13}C NMR (DMSO-d_6) δ (*endo* isomer) 166.8, 156.1, 152.0 (br), 132.5 (br), 131.6 (br), 115.6, 114.9, 114.0, 111.3, 96.5, 55.5, 53.4 (br), 50.4 (br), 42.9, 22.9; δ (*exo* isomer) 166.8, 156.5, 152.0 (br), 132.5 (br), 131.6 (br), 115.6, 115.0, 113.8, 110.2, 96.5, 55.5, 53.3 (br), 50.4 (br), 42.2, 21.3; EIMS m/z 302 $[M]^+$ (100), 199 (44); HRFABMS m/z 302.0919 (calcd for $C_{15}H_{14}N_2O_5$, 302.0903).

Methyl 5-Methoxy-3a-methyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (8). A mixture of **7** (132 mg, 0.44 mmol) and alumina (1.18 g) in 10% aqueous THF (6 mL) was stirred at reflux until TLC analysis showed complete loss of starting material (0.5 h). The alumina was filtered off and washed with EtOAc (5 × 20 mL). The filtrate and the eluates were combined and concentrated, yielding the crude product, which was purified by flash chromatography on Si gel (2:8 EtOAc−hexane) to give **8** as white solid (91 mg, 75%): mp 136−137 °C ($CHCl_3$−hexane); R_f = 0.31 (4:6 EtOAc−hexane); IR ($CHCl_3$) ν_{max} 3018, 1784, 1722, 1212 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (1H, br s, H-7), 6.83 (1H, br dd, J = 8.9, 2.3 Hz, H-6), 6.73 (1H, d, J = 2.3 Hz, H-4), 6.12 (1H, br s, H-8a), 3.90 (3H, br s, *O*-CH_3), 3.80 (3H, s, *O*-CH_3), 2.99 (1H, d, J = 17.9 Hz, H-3), 2.84 (1H, d, J = 17.9 Hz, H-3′), 1.52 (3H, s, C3a-CH_3); ^{13}C NMR ($CDCl_3$) δ 173.4, 157.0, 152.6 (br), 136.0 (br), 133.1 (br), 116.2, 114.0, 109.4, 97.5, 55.8, 53.2 (br), 48.1 (br), 41.3, 24.9; EIMS m/z 277 $[M]^+$ (100), 232 (20), 218 (26); HRFABMS m/z 277.0957 (calcd for $C_{14}H_{15}NO_5$, 277.0950).

5-Methoxy-3a,8-dimethyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (10). To a solution of **8** (260 mg, 0.94 mmol) in MeOH (5 mL) at room temperature was added Na (60 mg, 2.61 mmol). The mixture was heated at reflux for 1 h, treated with 10% aqueous HCl to reach pH 4−5, and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product **9**, which was used in the next step without purification. EIMS m/z 219 $[M]^+$ (78), 174 (100). To a solution of crude compound **9** in anhydrous acetone (5 mL) was added K_2CO_3 (160 mg, 1.16 mmol) and dimethyl sulfate (0.1 mL, 1.1 mmol). The reaction mixture was heated to reflux for 6 h and concentrated under reduced pressure. After dilution of the residue with water (20 mL), the reaction mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated, yielding the crude product, which was purified by flash chromatography on Si gel (1:1:3 CH_2Cl_2−EtOAc−hexane) and crystallized (ether hexane) to give **10** as a white solid (165 mg, 78%): R_f = 0.40 (4:6 EtOAc−hexane). Physical and spectral data were identical with those reported in the literature.[13b]

Methyl 5-Methoxy-3a-methyl-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (13). A solution of **8** (100 mg, 0.36 mmol) in dry THF (10 mL) was cannulated into a precooled (−10 °C) stirred solution of alane−*N*,*N*-dimethylethylamine complex (0.8 mL of a 0.5 M solution in toluene) over a 5 min period. The resulting mixture was maintained at −10 °C for 1 h, quenched with 8% aqueous NaOH (2 mL), stirred at room temperature until all the aluminum salts had dissolved (30 min), and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the crude diol, which was used directly in the next step. To a solution of diol in benzene (15 mL) was added a catalytic amount of *p*-TsOH (5 mg). The reaction mixture was heated at reflux for 2.5 h in a flask equipped with a Dean−Stark apparatus. After the benzene was removed under reduced pressure, the residue was diluted with EtOAc (100 mL), washed with brine, dried over Na_2SO_4, and concentrated, yielding the crude product, which was purified by flash chromatography on Si gel (1:2:7 EtOAc−CH_2Cl_2−hexane) to give **13** as pale yellow oil (68 mg, 72% for the two steps); R_f = 0.40 (2:3 EtOAc−hexane); ^1H NMR (CD_2Cl_2) δ 7.60 (1H, br s, H-7), 6.67 (1H, d, J = 2.6 Hz, H-4), 6.66 (1H, dd, J = 9.7, 2.6 Hz, H-6), 5.57 (1H, br s, H-8a), 3.74 (3H, br s, *O*-CH_3), 3.69 (3H, s, *O*-CH_3), 1.39 (3H, s, C3a-CH_3), for the methylene protons data (H-2 and H-3) see Table 1; ^{13}C NMR (CD_2Cl_2) δ 156.8, 153.6 (br), 137.9 (br), 136.0 (br), 115.1, 113.2, 109.7, 99.6, 68.1, 56.0, 52.9 (br), 52.4 (br), 41.6, 25.2. The remaining spectral data were identical with those reported in the literature.[16]

5-Methoxy-3a,8-dimethyl-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (15). A solution of **8** (70 mg, 0.25 mmol) in dry THF (5 mL) was added to a suspension of LAH (34 mg, 0.89 mmol) in dry ether. The resulting mixture was stirred at room temperature for 10 min, then quenched with EtOAc, diluted with water, treated with 5% aqueous KOH (2 mL), and stirred until two layers separated. The water layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were

washed with brine, dried over Na_2SO_4, and concentrated to give the crude product **14**, which was immediately used in the next step without purification. EIMS *m*/*z* 205 $[M]^+$ (100), 190 (42), 174 (40). To a solution of **14** (50 mg, 0.24 mmol) in acetonitrile (1.5 mL) was added 37% aqueous formaldehyde (0.1 mL, 1.23 mmol). After stirring at room temperature overnight, sodium cyanoborohydride was added (25 mg, 0.39 mmol) to the reaction mixture. The reaction was stirred for 15 min at room temperature to form a homogeneous brownish solution, and then glacial acetic acid was added dropwise until the solution tested neutral on wet pH paper. After stirring for another 15 min, aqueous 2 N KOH (10 mL) was added. The mixture was extracted with Et_2O (3 × 25 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated, yielding the crude product, which was purified by flash chromatography on Si gel (1:9 EtOAc−hexane) to give **15** as a colorless oil (34 mg, 64%); R_f = 0.66 (2:3 EtOAc−hexane); ^{1}H NMR (CD_2Cl_2) δ 6.68 (1H, d, J = 2.6 Hz, H-4), 6.63 (1H, dd, J = 8.3, 2.6 Hz, H-6), 6.23 (1H, br d, J = 8.3 H-7), 4.99 (1H, br s, H-8a), 3.72 (3H, br s, *O*-CH_3), 2.84 (3H, br s, *N*-CH_3), 1.42 (3H, s, C3a-CH_3), for the methylene protons data (H-2 and H-3) see Table 1; ^{13}C NMR (CD_2Cl_2) δ 153.1, 145.4, 136.6, 112.5, 110.7, 105.9, 105.5, 67.6, 56.3, 52.8, 41.8, 31.8, 24.7. The remaining spectral data were identical with those reported in the literature.[16]

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References and Notes

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