Total Synthesis of (±)-Deethylibophyllidine: Studies of a Fischer Indolization Route and a Successful Approach via a Pummerer Rearrangement/Thionium Ion-Mediated Indole Cyclization

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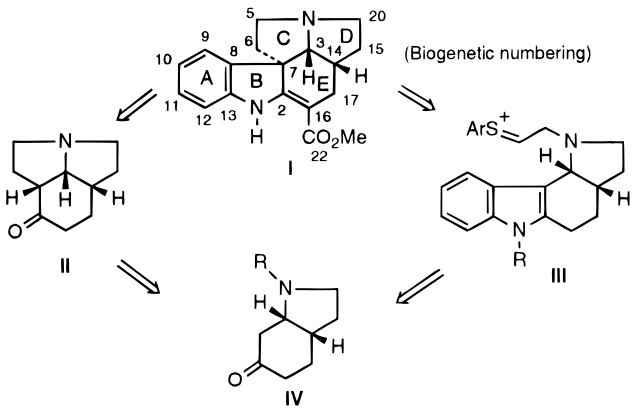
The total synthesis of (±)-deethylibophyllidine is described, proceeding in eight steps from 4-(methoxyphenyl)ethylamine in 5% overall yield (Scheme 6). In terms of sequential annulation, the strategy involves the following operations: E → DE → ABDE → ABCDE (Scheme 1). The key steps in the synthesis are the stereoselective formation of octahydroindol-6-ones by acid treatment of dihydroanisole derivatives, the regioselective Fischer indolization to obtain octahydropyrrolo-[3,2-*c*]carbazoles, and the tandem process consisting of Pummerer rearrangement upon a *β*-amino sulfoxide and thionium ion cyclization upon a *β*-indole position of a 2,3-disubstituted indole to generate the quaternary spiro center. Attempts to effect the construction of the pentacyclic framework by means of Fischer indolization of the octahydropyrrolo[3,2,1-*hi*]indol-6-one resulted in failure (Scheme 2).

Introduction

The pentacyclic system of pyrrolizino[1,7-*cd*]carbazole constitutes the core of ibophyllidine alkaloids.[1] Among the great variety of skeletal types of monoterpenoid indole alkaloids, the ibophyllidine alkaloids are characterized structurally by the presence of a 2,3,3-trisubstituted indole, incorporating the unit of pyrrolo[2,3-*d*]-carbazole (ABCE rings), and the lack of the C-21 biogenetic carbon,[2] which implies a pyrrolidine D ring instead of the piperidine ring usually found in the related alkaloids. Much research has been devoted to the synthesis of alkaloids with the former feature, typified by the *Aspidosperma*[3] and *Strychnos*[4] alkaloids, but far less attention has been given to ibophyllidine alkaloids.[5] We therefore set out to explore some novel synthetic routes to this type of alkaloid and chose deethylibophyllidine (**I**) as the synthetic target.[6]

A retrosynthetic analysis of the pentacyclic structure target **I** is diagrammed in Scheme 1. We are interested in the development of synthetic routes to the scarcely described heterocyclic systems of pyrrolo[3,2,1-*hi*]indole[7]

Scheme 1. Retrosynthetic Plan for the Synthesis of Deethylibophyllidine



II and pyrrolo[3,2-*c*]carbazole[8] **III** types, which embody three and four of the rings of target **I**, respectively, in order to study the elaboration of the desired pentacyclic skeleton by Fischer indolization or else, by ring closure upon the *β*-position of a 2,3-disubstituted indole, respectively. In our project, we envisaged that both heterocyclic systems **II** and **III** might arise from octahydroindol-6-ones derivatives **IV**.

Results and Discussion

The First Approach (Route IV → II → I). According to our initial synthetic plan, azatricyclo **II**, which possesses rings C, D, and E of ibophyllidine alkaloids, was chosen as the key intermediate since it was expected that further indolization would give rise to the pentacyclic framework of these alkaloids.

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1996.

(1) For leading references regarding isolation, characterization, and biosynthesis of ibophyllidine alkaloids, see: (a) Khuong-Huu, F.; Cesario, M.; Guilhem, J.; Goutarel, R. *Tetrahedron* **1976**, *32*, 2539. (b) Kan, C.; Husson, H.-P.; Jacquemin, H.; Kan, S.-K.; Lounasmaa, M. *Tetrahedron Lett.* **1980**, *21*, 55. (c) Kan, C.; Husson, H.-P.; Kan, S.-K.; Lounasmaa, M. *Tetrahedron Lett.* **1980**, *21*, 3363. (d) Kuehne, M. E.; Pitner, J. B. *J. Org. Chem.* **1989**, *54*, 4553. (e) Saxton, J. E. The Ibogamine-Catharanthine Group. In Monoterpenoid Indole Alkaloids, supplement to part 4, Saxton, J. E., Ed. in *The Chemistry of Heterocyclic Compounds*, Taylor, E. C., Ed.; John Wiley: Chichester, 1994; Vol. 25, pp 487−521.

(2) The biogenetic numbering (Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508) is used throughout this paper only for pentacyclic compounds.

(3) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292 and references cited therein.

(4) (a) Bosch, J.; Bonjoch, J. Pentacyclic *Strychnos* Indole Alkaloids. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, pp 31−88. (b) Bosch, J.; Bonjoch, J.; Amat, M. *Strychnos* Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1996; Vol. 48, pp 75−189.

(5) (a) Kuehne, M. E.; Matsko, T. H.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002. (b) Kuehne, M. E.; Bohnert, J. C. *J. Org. Chem.* **1981**, *46*, 3443. (c) Barsi, M.-C.; Das, B. C.; Fourrey, J.-L.; Sundaramoorthi, R. *J. Chem. Soc., Chem. Commun.* **1985**, 88. (d) Jegham, S.; Fourrey, J.-L.; Das, B. C. *Tetrahedron Lett.* **1989**, *30*, 1959.

(6) (a) Prior syntheses of (±)-deethylibophyllidine: refs 1d, 5a, and 5c. (b) Preliminary communication: Catena, J.; Valls, N.; Bosch, J.; Bonjoch, J. *Tetrahedron Lett.* **1994**, *35*, 4433. (c) Recently, we have described another synthetic approach to this target: Fernàndez, J.-C.; Valls. N.; Bosch, J.; Bonjoch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 2317.

(7) For the previous synthesis of perhydropyrrolo[3,2,1-*h,i*]indoles functionalized at the carbocyclic ring, see: (a) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. (b) Valls, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 2508.

(8) For the only previously described synthetic strategy, see: Magnus, P. D.; Exon, C.; Sear, N. L. *Tetrahedron* **1983**, *39*, 3725.

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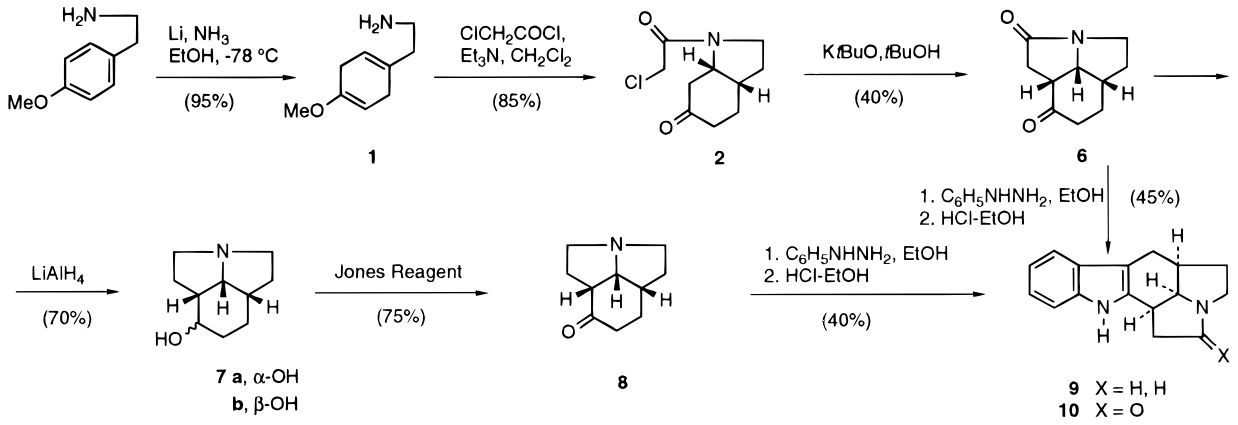
Scheme 2. Attempts to Synthesize the Framework of Ibophyllidine Alkaloids by Fischer Indolization



Our synthetic approach to azatricyclo **8** requires the intramolecular alkylation of a suitably 1-substituted octahydroindol-6-one (Scheme 2). In contrast to the preparation of the 3a-aryloctahydroindol-6-ones, for which many routes have been described since this unit is present in mesembrine and related *Amaryllidaceae* alkaloids,[9] only a few approaches for 3a-unsubstituted derivatives of type **IV** (i.e. **2**) have been reported. Usually, the procedures for the synthesis of *cis*-octahydroindol-6-ones take advantage of the presence of the β-amino ketone moiety for the formation of the last bond in the synthetic step. Thus, either the intramolecular 1,4-addition of an amino group upon an α,β-unsaturated ketone[10,11] or a Mannich process from an adequate pyrroline derivative[12] have allowed access to the target unit.[13]

The octahydroindolone **2**[14] was prepared in two steps from commercially available *O*-methyltyramine in 80% overall yield.[15] The synthesis includes a Birch reduction[16] which allows the formation of dihydrobenzene **1** in excellent yield using lithium in ammonia and ethanol[17] and later acylation with chloroacetyl chloride in the presence of triethylamine in anhydrous medium. Interestingly, the acylation, the conversion of the enol ether into the ketone, the double bond isomerization, and the last 1,4 addition of an amide group into the α,β-unsaturated ketone occurs in a single operation step.[18] The process is stereoselective, the cis isomer of the octahydroindole ring being formed exclusively (a through-space correlation between the H-3a and H-7a is observed in the ROESY spectrum of **2**). Unoptimized attempts to apply the same tandem process using trichloroacetyl chloride with **1** furnished a mixture of enones (**4a**, **4b**) and the cyclized product **5**.

The closure of the C ring was accomplished in moderate yield by treatment of *N*-(chloroacyl)octahydroindolone **2** with K*t*BuO. An analogous cyclization in the *Aspidosperma* field (starting from a decahydroquinolone) proceeds with good yield[19] but in the *Strychnos* series (starting from an azabicyclo[3.3.1]nonanone) was unsuccessful.[20] The different behavior in this cyclization type seems to be related to the tension associated with the carbonyl lactam group in the cyclized product.

To achieve the target tricyclic ketone **8**, keto amide **6** was subjected to LAH reduction followed by Jones oxidation of the resulting mixture of epimeric alcohols **7**. The relative *all-cis* configuration of these perhydropyrrolo[3,2,1-*hi*]indoles was deduced from the multiplicity and coupling constants of H-8b in the ^{1}H NMR spectra. In all cases the signal attributable to this proton appears as a triplet with a *J* value between 4.5 and 7.5 Hz, which implies a non-trans diaxial relationship with any proton at C-5a or C-8a.

The last step of the synthesis was the Fischer indolization with azatricyclo **8** as the ketonic moiety. It is well-known that, in the Fischer indole synthesis of phenylhydrazones derived from unsymmetrical ketones, the use of weak acids promotes cyclization toward the more branched α-carbon atom.[21] However, unfortunately, when **8** phenhylhydrazone was treated with glacial acetic acid, only the nondesired indole **9** coming from cyclization upon the methylene group was obtained. The structure of **9** was ascertained from the NMR spectra, which showed a typical indole pattern, instead of the indolenine

(9) For reviews: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251−376. (b) Lewis, J. R. *Nat. Prod. Rep.* **1992**, *9*, 183.

(10) By Birch reduction of 4-methoxyphenethylamines: (a) Ueda, N.; Tokuyama, T.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012. (b) Sawlewicz, P.; Smulkowski, M.; Sowinski, P.; Borowski, E. *Pol. J. Chem.* **1978**, *52*, 219.

(11) By alkylation of $Fe(CO)_3$ complex of a 2-methoxycyclohexadiene cation: Bös, M.; Burkard, W. P.; Moreau, J.-L.; Schönholzer, P. *Helv. Chim. Acta* **1990**, *73*, 932.

(12) By intramolecular photocycloaddition and retro-Mannich fragmentation of acyclic tertiary vinylogous amides: Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831.

(13) For approaches leading to 1,2,3,3a,4,5-hexahydroindol-6-ones, see: (a) from 1,3-cyclohexanedione, Bryson, T. A.; Gammill, R. B. *Tetrahedron Lett.* **1974**, 3963. (b) From 6-methoxyindoline, Iida, H.; Aoyagi, S.; Kibayashi *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502. Iida, H.; Yuasa, Y.; Kibayashi, C. *Synthesis* **1977**, 879. (c) From pyrrolidine-2-thiones, Michael, J. P.; Howard, A. S.; Katz, R. B.; Zwane, M. I. *Tetrahedron Lett.* **1992**, *33*, 4751. Michael, J. P.; Zwane, M. I. *Tetrahedron Lett.* **1992**, *33*, 4755. For the reduction to octahydroderivatives: Higashiyama, H.; Honda, T.; Otomasu, H.; Kametani, T. *Planta Med.* **1983**, *48*, 268. Ito, K.; Naruma, M.; Furukawa, H. *J. Chem. Soc., Chem. Commun.* **1975**, 681.

(14) All synthetic compounds are racemic. The schemes depict only the enantiomer bearing the natural configuration at C-14.

(15) The synthesis of octahydroindolones by acid treatment of dihydroanisoles derived from tyramine derivatives has been precedented but without experimental details[10b] or else with moderate yields.[10a] For the synthesis of hexahydroindol-6-ones by hypervalent iodine oxidation of tyramine derivatives, see: (a) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435. (b) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996**, *37*, 739.

(16) (a) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, 35−85. (b) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1−334.

(17) For the synthesis of **1**, using sodium as reducing agent, see: Clarke, C. B.; Pinder, A. R. *J. Chem. Soc.* **1958**, 1967.

(18) On the contrary, when the acylation was carried out in the Schotten−Baumann conditions, acylated but not cyclized compound **3** was isolated (see Experimental Section).

(19) (a) Wu, P.-L.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 963. (b) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673.

(20) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodríguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267.

(21) (a) Miller, F. M.; Schinske, W. N. *J. Org. Chem.* **1978**, *43*, 3384. (b) Hugues, D. L.; Zhao, D. *J. Org. Chem.* **1993**, *58*, 228.

Table 1. ^{13}C NMR Data (δ) of Octahydroindol-6-ones[a]

	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	other
2 (*Z*)	45.7	29.3	34.8	23.9	36.5	210.0	41.8	56.3	41.2/164.8
2 (*E*)	45.1	25.8	36.8	23.6	35.7	208.5	43.5	57.4	41.0/164.6
5	43.4	30.7	37.1	24.4	34.7	209.2	40.9	59.4	/158.6
12	52.8	29.2	35.0	26.2	35.8	212.4	41.5	61.2	57.5[b]
15	173.9	36.7	28.6	26.4	36.7	209.4	41.2	55.0	44.0[c]
30a	53.2	29.3	35.2	26.2	36.3	212.1	41.5	62.8	46.3/56.7[d]
30b	52.6	29.3	35.2	26.2	36.1	212.3	41.5	62.0	46.5/56.3[d]

[a] In $CDCl_3$ (50.3 MHz). Values for compounds **2** and **12** were assigned on the basis of HMQC spectra. [b] Phenyl ring carbons were found at 138.9, 128.7, 128.0, and 126.7. [c] Phenyl ring carbons were found at 135.7, 128.7, 128.0, and 127.7. [d] Values for the benzene nucleus: 143.8 (±0.3), 130.9 (±0.1), 129.1 and 124.0 (±0.1).

one.[22] Additionally, Fischer indolization of amido ketone **6** gives pentacyclic derivative **10** which upon reduction leads to the same pyrrolizinocarbazole **9**. The pentacyclic framework of **9** and **10** constitutes a new type of heterocyclic ring system.

The reason for the different behavior in the indolization step of our ibophyllidine series with respect to the results described in the *Aspidosperma* field[23,24] is not clear. Nevertheless, what is remarkable is the different conformation of the azatricyclic unit in **8** in which the fusion of rings CD is cis, as is usual in pyrrolizidine framework,[25] instead of the trans conformation preferred for the indolizidine unit present in the pyrroloquinolone derivatives used in the *Aspidosperma* synthesis. The different conformation for compound **8** and the D-homo derivatives was inferred from the chemical shift of the methine proton adjacent to the nitrogen atom. This proton resonates a δ 3.92 when it is located *syn* to the lone pair of nitrogen as occurs in **8**, whereas it appears at a chemical shift lower than δ 3.2 when it is located *anti*, as occurs in the pyrroloquinolone derivatives.[23e,f] It seems reasonable to assume that the different conformational arrangement of the tricyclic ketones in both series is also present in the corresponding hydrazones. This feature could be the cause of the different regioselectivity observed in the enehydrazine formation-step and consequently in the isolation of indole **9**.[26]

Synthesis of Pyrrolo[3,2-*c*]carbazoles. At this point we decided to examine the sequence in reverse involving the initial formation of the indole nucleus (**III**) starting from an octahydroindol-6-one (**IV**) and then the construction of the pyrrolidine C ring in the key step (Scheme 1). In this context, we explored the Fischer indolization of several types of octahydroindol-6-ones bearing different functionality at the nitrogen atom. The regioselectivity (C-5 *vs* C-7) in the indolization of amides **2** and **5**, the amine **12**, and the lactam **15** were checked.

The required amides **2** and **5** are the same as those we synthesized in our first approach (Scheme 2). The *N*-benzyl derivative **12** was synthesized by sodium borohydride reduction of the imine from amine **1** and benzaldehyde followed by acid treatment of the resulting dihydroanisole **11** in an efficient manner.

Studies using NMR spectroscopy (500 MHz, COSY, HMQC, ROESY experiments) have allowed us to assign the conformational preference of *cis*-octahydroindolone **12**.[27] This compound appears to adopt a preferred conformation which locates the bond C-3a/C-3 axially with respect to the carbocyclic ring (The ROESY experiment for **12** shows, *inter alia* (see Figure 1), interrelations between H-3α and H-5ax as well as H-2β and H-3a, which corroborates this fact). Interestingly, the coupling constants of H-7a with H-3a (9 Hz) and H-7 (4.5 Hz with both protons) suggest that the carbocyclic ring does not adopt a chair conformation. This feature seems to be common for all bicyclic octahydroindol-6-one derivatives synthesized in this work as reflected by their similar ^{13}C NMR data (see Table 1).

The synthesis of lactam **15** was achieved by means of alkylation of an enol ether of 1,3-cyclohexanedione with *N*-benzyliodoacetamide[28] and further reduction of compound **13** with sodium borohydride and later treatment of the resulting enone **14** in acid medium. When the reduction was carried out with lithium aluminum hydride, the benzyl derivative **12** was formed after the final acid treatment.

The different course of the indolization of ketones **2**, **5**, **12**, and **15** is depicted in Scheme 3. From ketone **2**, operating with AcOH, a mixture of indoles **16** and **17** was isolated in 43% yield.[29] The constitution of isomers **16** and **17** was assigned on the basis of the coupling pattern/chemical shift observed for the methine proton adjacent to the nitrogen atom: the ^{1}H spectrum of [3,2-*c*] fused compound **16** displays a δ (J = 6.5 Hz) at 5.40 ppm for H-10c, while the [2,3-*b*] fused compound **17** shows a multiplet at 4.34 ppm for the H-10a hydrogen in the major *Z* rotamer. From amide **5** and lactam **15**, pyrrolo[2,3-*b*]carbazoles were isolated. Only when the nitrogen atom adopts a sp^3 hybridization does the geometry of the molecule favor the formation of the enehydrazine toward

(22) Schripsema, J.; Verpoorte, R. *Stud. Nat. Prod. Chem.* **1991**, *9*, 163−199.

(23) For indolization upon the methine carbon in the *Aspidosperma* series, see: (a) Stork. G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (b) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261. (c) Inoue, I.; Ban, Y. *J. Chem. Soc (C)* **1970**, 602. (d) Klioze, S. S.; Darmory, F. P. *J. Org. Chem.* **1975**, *40*, 1588. (e) Lawton, G.; Saxton, J. E.; Smith, A. J. *Tetrahedron* **1977**, *33*, 1641. (f) Pearson, A. J.; Rees, D. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2467.

(24) For the same regioselectivity in the *Aspidosperma* series, see: Akagi, M.; Oishi, T.; Ban, Y. *Tetrahedron Lett.* **1969**, 2063.

(25) Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109.

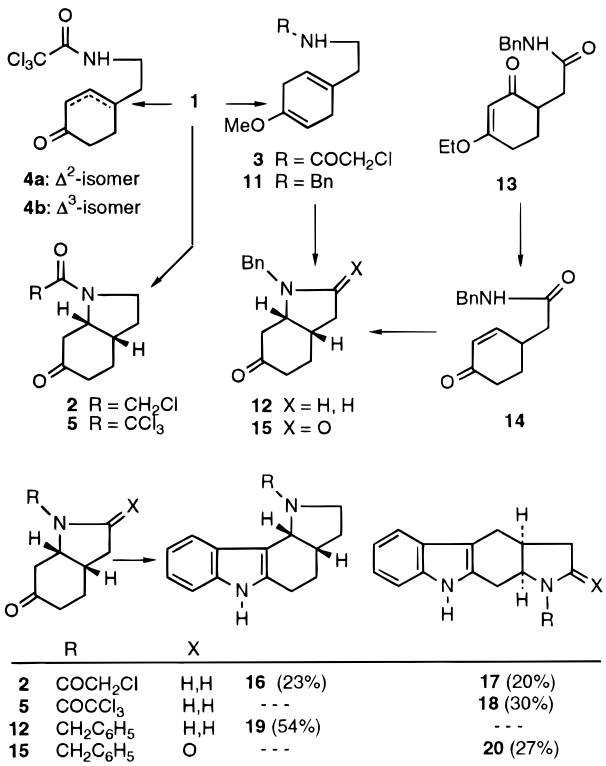
(26) (a) For interesting mechanistic aspects on the Fischer indolization upon β-amino ketones in this field, see: Ban, Y.; Iijima, I. *Tetrahedron Lett.* **1969**, 2523. See also ref 23e. (b) For a discussion about the stereochemical factors influencing the regiochemical course of Fischer indole synthesis, see: Freter, K.; Fuchs, V.; Pitner, T. P. *J. Org. Chem.* **1983**, *48*, 4593.

(27) For conformational analysis of the *cis*-octahydroindole, see: Mokotoff, M.; Hill, S. T. *J. Heterocycl. Chem.* **1988**, *25*, 65. For the conformational preference in 3a-aryloctahydroindol-6-ones (*i.e.* mesembrine), see: Jeffs, P. W.; Hawks, R. L.; Farrier, D. S. *J. Am. Chem. Soc.* **1969**, *91*, 3831. Sánchez, I. H.; Larraza, M.-I.; Flores, H. J.; Díaz, E. *Heterocycles* **1985**, *23*, 593.

(28) *N*-Benzyliodoacetamide was prepared from benzylamine and chloroacetyl chloride and later treatment of the resulting chloroacetamide with sodium iodide in 2-butanone according to Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M.-E.; Troin, Y. *J. Org. Chem.* **1990**, *55*, 5483.

(29) Operating with AcOH/NaOAc or EtOH/HCl instead of AcOH neat, the ratio of indole **17** increases and is the major product in the indolization.

Scheme 3. Synthesis and Fischer Indolization of Hydroindolone Derivatives



	R	X		
2	$COCH_2Cl$	H,H	**16** (23%)	**17** (20%)
5	$COCCl_3$	H,H	- - -	**18** (30%)
12	$CH_2C_6H_5$	H,H	**19** (54%)	- - -
15	$CH_2C_6H_5$	O	- - -	**20** (27%)

C_6-C_7 and consequently the regioselectivity is in line with the desired structure, the pyrrolocarbazole **19** being the only indole derivative isolated (60% yield).[30]

Interestingly, the pyrrolocarbazoles **16** and **19** show different conformational behavior. The unit of *cis*-octahydroindole can exist in two chair conformations, namely c_1 and c_2, which refer to the *N*-outside and *N*-inside conformer, respectively. Whereas amide **16** exhibited c_1 as a preferred conformation, pyrrolocarbazole **19**, as well as all derivatives with an amine nitrogen, showed the c_2 conformation as preferred[31] (see Table 2 for ^{13}C NMR data). In order to obtain additional data about the conformational change of pyrrolocarbazoles when functionality on N(1) varies, we prepared the *N*-Boc derivative **21**.[32] The ^{13}C NMR spectrum reflects the conformational inversion of the hydroindole ring, which adopts a c_1 conformation as did amide **16**, as shown by the shielding in the C-3, C-4, and C-5 carbon atoms.

Synthesis of Deethylibophyllidine (Route IV → III → I). With an efficient procedure for the elaboration of the ABDE tetracyclic framework of ibophyllidine alkaloids, we investigated the synthesis of (±)-deethylibophyllidine by formation of the C ring (Scheme 1). Initial attempts to obtain the pentacyclic framework of ibophyllidine alkaloids by means of photocyclization (CH_3CN-H_2O, *hν* 125 W, 45 min) of *N*-chloroacetyl derivative **16** through coupling of the initially formed diradical cation failed[33] and led instead to an azepinone[34,35] (Scheme 4).

We therefore decided on the formation of the required 2,3,3-trisubstituted indole unit by means of a thionium ion-mediated cyclization. The advanced key thionium ion intermediate **III** (Scheme 1) would arise via Pummerer rearrangement[36] of sulfoxide **25** or else by formation from dithioacetal **28** by dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) treatment.[37]

Compound **25** is available from the *N*-benzyl derivative **19** through methoxycarbonylation of the indole nitrogen[38] ($ClCO_2Me$, NaOH), *N*-debenzylation with Pearlman's catalyst,[39] and addition of phenyl vinyl sulfoxide[40] to the secondary amine **24**.

The good results obtained in the elaboration of the pentacyclic skeleton from the sulfoxide **25** (*vide infra*) induced us to abandon the path which involves dithioacetal **28**, which had been prepared in an unoptimized manner from the benzyl derivative **19**.

Taking into account that in the overall sequence for the synthesis of the key intermediate **25** the benzyl group is introduced (**1** to **11**) and removed (**23** to **24**), we decided to carry out a shorter synthesis of **25** taking advantage of our results in the synthesis of octahydroindol-6-ones and their Fischer indolization (see above). Thus, addition of **1** to phenyl vinyl sulfoxide[40] yielded β-aminoethyl sulfoxide **29** which, without further purification, was treated with 2 N HCl at 90 °C for 3 h. After basification with sodium hydroxide and flash chromatography on silica gel (EtOAc), *cis*-octahydroindolone **30**[41] was obtained in a stereoselective manner in 54% overall yield for the three steps.

(30) For studies on the regioselectivity in the Fischer indolization of β-amino ketones, see: Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Úbeda, M.-C.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 2449.

(31) The influence of the A 1,3 strain (Johnson, F. *Chem. Rev.* **1968**, *68*, 375) caused by the amide linkage in this conformational change was suggested by a reviewer. Also the difference in regioselectivity in the Fischer indole synthesis of hydroindolones could be accounted for considering that it occurs through the enehydrazine that minimizes the A 1,3 strain.

(32) Compound **21** was prepared by hydrogenation of benzyl derivative **19** followed by in situ *tert*-butyloxycarbonylation (H_2, $Pd(OH)_2$, Boc_2O, 87% yield): ^1H NMR (300 MHz, $CDCl_3$): 1.54−1.61 (m, 9H), 1.87 (m, 2H), 2.05 (m, 2H), 2.68 (m, 2H), 2.80 (m, 1H), 3.20 (m, 1H), 3.50 (m, 1H), 5.32 (br s, 1H), 7.06 (t, *J* = 7.5, 1H), 7.12 (t, *J* = 7.5, 1H), 7.25 (d, *J* = 7.5, 1H), 7.80 (br s, 1H), 8,05 (br s amp, 1H); ^{13}C NMR, see Table 2.

(33) For a successful formation of C-6/C-7 bond by this coupling-type in β-unsubstituted indoles, see: Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. *J. Org. Chem.* **1993**, *58*, 7756.

(34) The single product isolated (12%), coming from cyclization upon C-4 indole atom, was identified as the 1,2,3,3a,3,5,6,10c-octahydro-1,-10-ethanopyrrolo[3,2-*c*]carbazol-12-one (**22**): ^1H NMR (300 MHz, $CDCl_3$, COSY): 1.69 (m, H-3), 1.80 (m, H-3), 1.96 (m, H-4), 2.10 (m, H-4), 2.62−2.66 (m, 2H, H-5), 2.78 (m, H-3a), 3.35 (ddd, *J*= 10.5, 10, 6, 1H, H-2), 3.59 (d, *J*= 13.2, 1H, H-11), 3.74 (ddd, *J*= 10, 9, 1.5, 1H, H-2), 4.48 (d, *J*= 13.2, 1H, H-11), 5.24 (d, *J*= 6.3, H-10c), 6.81 (d, *J* = 7.2, H-9), 6.96 (t, *J* = 7.6, H-8), 7.06 (d, *J* = 8, H-7), 7.69 (br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$, HMQC) 18.4 (C-4), 23.6 (C-5), 26.4 (C-3), 29.7 (C-11), 36.7 (C-3a), 46.4 (C-2), 54.8 (C-10c), 109.6 (C-7), 110.0 (C-10b), 119.0 (C-9), 122.7 (C-8), 124.3 (C-10a), 126.2 (C-10), 131.2 (C-5a), 135.2 (C-6a), 170.4 (C-12).

(35) A similar result has been observed in the *Strychnos* series: Bosch, J.; Amat, M.; Sanfeliu, E.; Miranda, M.-A. *Tetrahedron* **1985**, *41*, 2557.

(36) The Pummerer rearrangement has emerged as a versatile and effective method for the generation of cationic reactive intermediates from sulfoxide precursors. For recent reviews, see: (a) Grierson, D. S.; Husson, H.-P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 6, pp 909−947. (b) Kennedy, M.; McKervey, M. A. *Ibid*. Vol. 7, pp 193−216. (c) De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157−405.

(37) (a) Amat, M.; Alvarez, M.; Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Lavilla, R.; Garcías, X.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 3453. (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (c) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939.

(38) Illi, V. O. *Synthesis* **1979**, 136.

(39) Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Ban, Y.; Shibasaki, M. *Heterocycles* **1988**, 27, 1167.

(40) For conjugate addition of secondary[40a,b] or primary amines[40c,d] upon phenyl vinyl sulfoxide, see: (a) Abbott, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 492. (b) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1986**, *27*, 2603. (c) Lee, A. W. M.; Chan, W. H.; Chan, E. T. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 309. (d) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1992**, *48*, 7803.

(41) Compound **30** was a diastereomeric mixture at sulfur, which could not be separated at this stage.

Table 2. ^{13}C NMR Data (δ) of Octahydropyrrolo[3,2-*c*]carbazole Derivatives[a]

	C-2	C-3	C-3a	C-4	C-5	C-5a	C-6a	C-7	C-8	C-9	C-10	C-10a	C-10b	C-10c	N(1)C	other
16[b]	44.8	25.6	36.1	22.7	18.1	134.9	136.0	110.5	120.6	118.4	120.1	126.7	108.3	54.0	165.1	c
19[b]	52.4	28.8	37.3	27.9	23.0	135.9	136.6	110.6	120.9	119.4	118.5	128.4	109.7	61.1	59.8	d
21	45.1	25.7	36.8	22.8	18.3	133.6	135.8	110.1	121.1	119.3	120.0	127.1	110.2	54.0	155.3	e
23	52.1	28.4	36.4	27.7	25.1	135.9	138.3	115.5	123.4	122.8	118.6	130.2	116.5	60.3	59.8	d,f
24	45.8	30.7	36.9	26.0	23.9	135.5	136.7	115.1	123.5	122.7	118.4	129.1	117.2	54.4		f
25a[b]	51.9	28.5	36.4	27.3	25.2	135.7	138.0	115.3	123.4	122.8	117.9	129.8	115.5	60.0	56.6	f,g
25b	51.6	28.2	36.1	27.1	24.7	136.8	138.0	115.5	123.4	123.2	118.4	129.8	115.7	60.7	57.3	f,g
26[h]	45.3	30.8	37.8	25.7	21.6	135.7	135.7	110.4	120.8	119.0	117.8	127.0	109.1	54.4		
27	53.0	29.2	36.6	27.4	22.3	135.9	136.8	110.6	120.4	119.0	118.1	128.1	108.4	61.4	57.7	i
28	51.6	32.7	36.4	28.2	24.1	135.9	136.8	110.5	120.4	119.0	118.1	128.1	108.4	58.9	57.9	j
31a	51.7	28.7	37.1	27.7	22.8	136.1	137.0	110.9	120.2	118.8	117.6	128.0	107.5	60.7	55.9	g
31b[b]	51.8	28.6	37.0	27.7	22.8	136.1	137.1	111.0	120.3	118.7	118.0	128.1	107.6	61.2	55.5	g

[a] In $CDCl_3$ (50.3 MHz). [b] Assignments were aided by HMQC spectrum. [c] CH_2Cl: δ 43.3. [d] Phenyl ring carbons were found at δ 140.4; 128.6, 128.0, and 126.5. [e] $C(CH_3)_3$: δ 78.9, 28.6. [f] CO_2Me: δ 152.3 (±0.1), 53.2 (±0.2). [g] CH_2SOAr: δ 48.3 (±0.1) for **25** and 47.4 (±0.1) for **31**,124.1 (±0.1), 128.6 (±0.2), 130.5 (±0.2), and 142.4 (**25a**), 144.1 (**25b**), 143.7 (**31a**), and 144.7 (**31b**). [h] In $CDCl_3$ + CD_3OD. [i] $CH(OEt)_2$: δ 101.8, 61.1, 15.3, 15.1. [j] $CH(SMe)_2$: δ 44.7, 11.3, 11.1.

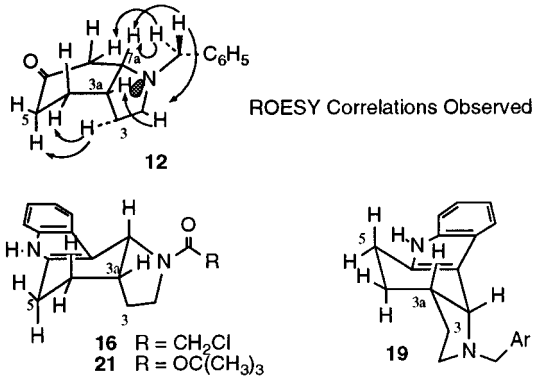
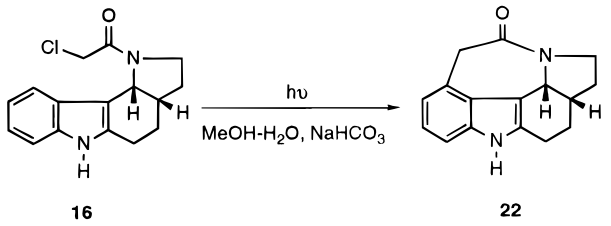


Figure 1. Conformational behavior of hydroindole unit.

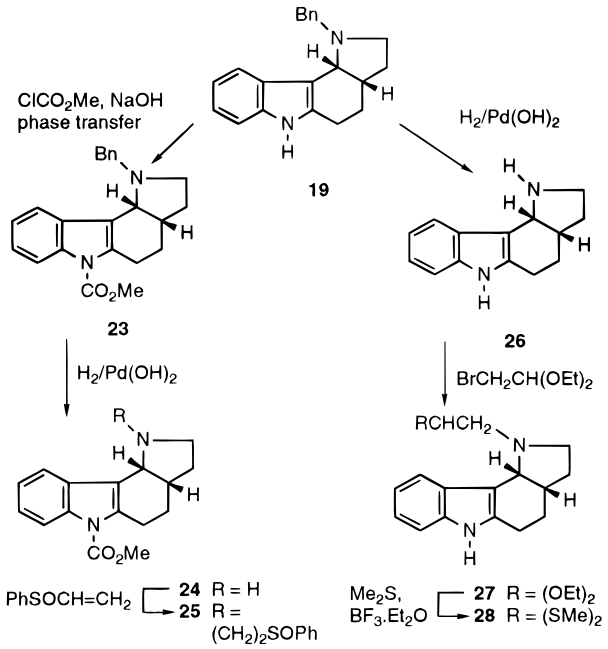
Scheme 4. Photocyclization of Chloroacetamide 16



The Fischer indolization from the phenylhydrazone of ketone **30** took place regioselectively when AcOH was used as an acid catalyst to afford the key tetracyclic derivative **31** (60% yield). The sequence of four steps from *O*-methyltyramine developed here to obtain the pyrrolo[3,2-*c*]carbazole framework, exemplified with the synthesis of compound **19** as well as **31**, constitutes an efficient new entry to this tetracyclic skeleton.[8] It is noteworthy that the sulfoxide group did not undergo Pummerer rearrangement under the acidic conditions required for both the hydrolytic cleavage of the enol ether and the Fischer indolization. The stability of the β-amino sulfoxide moiety is in contrast with the higher reactivity of sulfoxides with an electron-withdrawing substituent at the α-position[34] and constitutes an advantage from the synthetic point of view because the sulfoxide group can be incorporated in an early stage of the synthesis with the required oxidation level at the methylene carbon adjacent to the nitrogen atom.

A limited number of examples of Pummerer reactions from β-amino sulfoxides have been reported so far.[42] In order to carry out the tandem process, the indole nitrogen of **31** was first protected as a N(6)-methoxycarbonyl

Scheme 5. Synthesis of Pyrrolo[3,2-*c*]carbazole Precursors of the Key Thionium Ion III

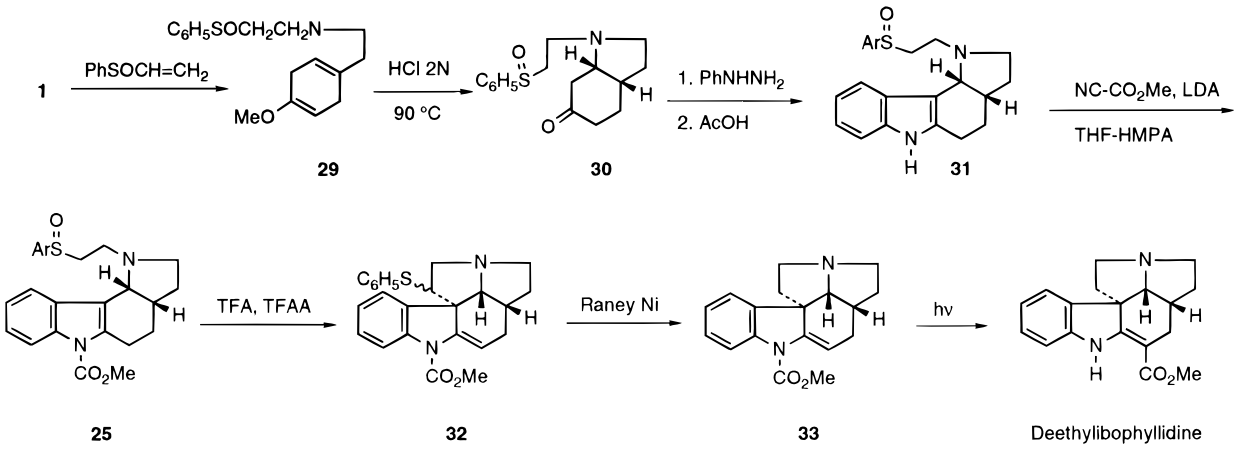


derivative. This methoxycarbonylation was initially troublesome since the use of several standard procedures (LDA, $ClCO_2Me$, or dimethylcarbonic anhydride; $(CO_2Me)_2O$, CH_3CN, DMAP; or NaOH aq, TBAB, $ClCO_2Me$) caused the partial or total formation of carbazole derivatives by way of an additional methoxycarbonylation at N(1) and further gramine-type cleavage.[43] The exclusive formation of the required protected indole **25** was achieved in good yield (76%) using LDA as a base and methyl cyanoformate as the acylating agent. The methoxycarbonyl group not only ensures the stability of the cyclized product but also allows for the elaboration of the anilinoacrylate moiety in the last step of the synthesis. The best results for the tandem Pummerer rearrangement−cyclization were obtained when a mixture of sulfoxides **25** was treated with an equimolecular mixture of TFA

(42) (a) Scarce tandem Pummerer rearrangement−cyclization processes using β-amino sulfoxides have been reported so far: upon the indole 3-position in 2,3-disubstituted indoles,[42b] in 3-unsubstituted indoles,[42c] upon the benzene ring.[42d] (b) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792. (c) Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 3071. (d) Takano, S.; Iida, H.; Inomata, K.; Ogasawara, K. *Heterocycles* **1993**, *35*, 47.

(43) Besselièvre, R.; Husson, H.-P. *Tetrahedron* **1981**, *37*, Suppl. No. 1, 241.

Scheme 6. Synthesis of (±)-Deethylibophyllidine by Pummerer Rearrangement-Induced Cyclization



and TFAA (3 equiv) at 80 °C for 2 h. Under these experimental conditions the crucial quaternary center at C-7[2] was formed in a satisfactory manner[44] and the pentacyclic derivative **32** was obtained in 63% yield as an epimeric mixture at C-6[2] (both epimers gave **33** on desulfurization). Similar results were obtained from the separate epimers **25a** or **25b**.

The final stages in the synthesis involved (i) reductive removal of the sulfur function and (ii) rearrangement of the methoxycarbonyl group. The *N*-(methoxycarbonyl)-enamine function present in **32** allowed us to effect both the chemoselective hydrogenolysis of the phenylthio substituent without affecting the double bond at C-2 and the photochemical rearrangement[45] to the vinylogous carbamate moiety present in the ibophyllidine alkaloids. Thus, desulfurization of **32** using Raney nickel (W-2) in ethanol gave **33** (63% yield), which was then irradiated with a medium-pressure mercury lamp to give (±)-deethylibophyllidine in 50% yield. Our synthetic material was identified by comparing its ^{1}H NMR spectrum (500 MHz) with that of the natural product.[1b] Its ^{13}C NMR spectrum is reported for the first time, and unambiguous assignment, aided by an HMQC spectrum, has been effected. The good yield in the formation of the anilinoacrylate unit in this series contrasts with the moderate yields obtained in analogous photochemical rearrangements in the *Strychnos* series,[46] probably due to the greater coplanarity of the N−C(2)−C(16) unit in the ibophyllidine derivatives.

In summary, a synthesis of (±)-deethylibophyllidine has been achieved. The route requires eight steps from *O*-methyltyramine and proceeds with 5.5% overall yield. The key steps involve stereoselective formation of the octahydroindol-6-one bicyclic system, regioselective Fischer indolization to a tetracyclic ring system, tandem Pummerer rearrangement−thionium ion cyclization operating from a β-aminosulfoxide, in acidic medium, in the three anelation processes, and finally a photo Fries rearrangement for generation of the aminoacrylate function of deethylibophyllidine.

(44) The intramolecular Pummerer reaction has been used to close the crucial C_6-C_7 bond in the synthesis of *Aspidosperma* alkaloids, but using either an exocyclic or an endocyclic amide as the substrate: Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. See also, Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70 and references cited therein.

(45) (a) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesh, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719. (b) Wenkert, E.; Porter, B.; Simmons, D. P. *J. Org. Chem.* **1984**, *49*, 3733.

(46) Solé, D.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 4194. See also ref 37b, 37c.

Experimental Section

General. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50.3 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, and coupling constants are expressed in hertz. The ^{13}C NMR spectra, when an unambiguous assignment was not available, are reported as follows: chemical shift (multiplicity determined from DEPT spectra). Only noteworthy IR absorptions (cm^{-1}) are listed. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230−400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

2-(4-Methoxy-2,5-dihydrophenyl)ethylamine (1). To a solution of *O*-methyltyramine (32 mL, 0.218 mmol) in dry EtOH (150 mL) under argon was added at −78 °C ammonia (200 mL) that was passed through solid NaOH. Lithium (11.1 g, 1.6 g-atom) as small chips was added (*ca.* 3 h) until the solution was a persistent deep blue for 15 min. Then, the cooling bath was removed, the ammonia was allowed to evaporate overnight, and the reaction mixture was evaporated. Brine (200 mL) was added to the residue, and the mixture was extracted with Et_2O (4 × 150 mL). The dried extract was evaporated to give **1**[17] (31.4 g, 94% yield) as a yellowish thick oil that was deemed suitably pure to carry through to subsequent steps without purification: IR (film) 3364, 1696, 1665; ^{1}H NMR 1.71 (s, 2H), 2.15 (t, J = 6.7, 2H), 2.72 and 2.73 (2s, 2H each), 2.78 (t, J = 6.7, 2H), 3.54 (s, 3H), 4.62 (s, 1H), 5.44 (s, 1H); ^{13}C NMR 28.7(two t), 39.4 (t), 40.3 (t), 53.5 (q), 90.1 (d), 119.2 (d), 132.7 (d), 152.9 (d).

1-(Chloroacetyl)octahydroindol-6-one (2). To a solution of crude amine **1** (6 g, 39 mmol) in anhydrous CH_2Cl_2 (18 mL) was added triethylamine (4.8 mL, 42 mmol). A solution of chloroacetyl chloride (4.3 mL, 51 mmol) in CH_2Cl_2 (6 mL) was added dropwise (exothermic), and the solution was stirred for 3 h. The solution was evaporated to dryness, brine was added (40 mL), and the mixture was extracted with CH_2Cl_2 (4 × 50 mL). Chromatography (hexanes−CH_2Cl_2−EtOAc, 1:1:1) of the dried and evaporated organic extract gave chloroacetamide **2** (7.1 g, 85%) as a yellowish oil: IR (film) 1713, 1650; ^{1}H NMR (500 MHz, COSY) (*Z* isomer) 1.86 (dddd, J = 11, 10, 7, 7, 1H, H-4_{ax}), 2.01 (m, H-3), 2.10 (m, H-4_{eq}), 2.17 (m, H-3), 2.22 (ddd, J = 16.5, 8.5, 3, H-5_{ax}), 2.29 (dd, J = 15.5, 9, H-7_{ax}), 2.39 (ddd, J = 16, 8, 6.5, H-5_{eq}), 2.53 (sext, J = 8, H-3a), 2.99 (dd, J = 15.5, 6, H-7_{eq}), 3.60 (ddd, J = 10, 8, 8 H-2_α), 3,69 (ddd, J = 10, 8, 4, H-2_β), 3.97 (s, CH_2Cl), 4.42 (ddd, J = 9, 8.5, 6, H-7a); ^{13}C NMR, Table 1. Anal. Calcd for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.38; H, 6.51; N, 6.38.

When the chloroacetylation was carried out as above but with additional water (1.1 equiv), the acylated dihydroanisole **3** was obtained as a brown solid: IR (film) 3316, 1697, 1664, 1645; ^{1}H NMR 2.24 (t, J = 6.7, 2H), 2.74 (s, 4H), 3.39 (q, J = 6.7, 2H), 3.55 (s, 3H), 4.04 (s, 2H), 4.63 (s, 1H), 5.48 (s, 1H), 6,7 (br s, 1H); ^{13}C NMR 28.7 (t), 28.8 (t), 35.8 (t), 37.2 (t), 42.4 (t), 53.7 (q), 89.9 (d), 120.2 (s), 132.0 (s), 152.8 (s), 165.9 (s). HRMS calcd for $C_{11}H_{16}ClNO_2$ 229.0869, found 229.0861.

Treatment of **3** (100 mg, 0.45 mmol) in 2 N HCl (10 mL) at room temperature for 24 h afforded after workup the cyclized product **2** (70 mg, 60%).

***cis*-1-(Trichloroacetyl)octahydroindol-6-one (5).** Operating as above in the anhydrous form and starting from dihydroanisole **1** (3 g, 19.5 mmol) and trichloroacetyl chloride (3.75 mL, 33 mmol) was obtained octahydroindolone **5** (1.85 g, 34%). In this case, cyclohexenones **4b** (700 mg, 13%) and **4a** (800 mg, 14.5%) were also isolated in the purification step (chromatography, CH_2Cl_2).

Compound **5**: mp 118 °C (EtOAc); IR (KBr) 1709, 1668; ^{1}H NMR 1.9−2.6 (m, 8H), 3.09 (dd, J = 15.4, 6.2, 1H), 3.91−4.16 (m, 2H); 4.53 (dd, J = 15.4, 8.3, 1H); ^{13}C NMR, Table 1. Anal. Calcd for $C_{10}H_{12}Cl_3NO_2$: C, 42.20; H, 4.25; N, 4.92. Found: C, 42.22; H, 4.30; N, 4.90. Compound **4b**: IR (film) 3340, 1712, 1668; ^{1}H NMR 1.54−1.67 (m, 4H), 1.96−1.99 (m, 3H), 2.20 (t, J = 6.2, 1H), 3.42 (t, J = 6.7, 1H); 3,45 (t, J = 6.7, 1H), 5.54 (m, 1H), Compound **4a**: IR (film) 3375, 1698, 1673; ^{1}H NMR 1.54−2.67 (m, 7H), 3.38−3.50 (m, 2H), 5.95 (dd, J = 10, 2.4, 1H), 6.80 (d, J = 10.2, 1H); 7,0 (br s, 1H); ^{13}C NMR 28.1 (t), 33.4 (d), 33.4 (t), 36.4 (t), 38.8 (t), 92.4 (s), 129.2 (d), 153.8 (d), 169.1 (s), 199.5 (s).

(5a*RS*,8a*SR*,8b*SR*)-Octahydropyrrolo[3,2,1-*hi*]indole-2,8-dione (6). To a solution of chloroacetamide **3** (1 g, 4.63 mmol) in *tert*-butyl alcohol (40 mL) was added a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (1 M, 4.7 mL, 4.7 mmol) under Ar, and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed, and the residue was partionated between aqueous $NaHCO_3$ solution (0.1 M, 25 mL) and $CHCl_3$ (25 mL). The aqueous phase was reextracted, and the combined organic extracts were dried and chromatographed (Al_2O_3, CH_2Cl_2−EtOAc 1:1) to give amido ketone **6** (330 mg, 40%) as a white solid: mp 126−127 °C (EtOAc); IR (KBr) 1710, 1676; ^{1}H NMR (500 MHz, COSY) 1.37 (qd, J = 12.5, 3.5, H-6$_{ax}$), 1.8−1.9 (m, H-6$_{eq}$ and H-5$_{ax}$), 2.2−2.4 (m, 4H), 2.8−2.9 (m, 3H), 3.07 (td, J = 10.5, 1.5, H-4), 3.41 (ddd, J = 11, 9, 8.5, H-4), 4.32 (br t, J = 6, H-8b); ^{13}C NMR (HMQC), 24.2 (C-6), 32.1 (C-5), 34.3 (C-5a), 37.3 (C-7), 38.5 (C-1 and C-4), 43.2 (C-8a), 65.0 (C-8b), 172.0 (C-2), 209.9 (C-8). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81. Found: C, 67.00; H, 7.30; N, 7.87.

(5a*RS*,8a*SR*,8b*RS*)-Decahydropyrrolo[3,2,1-*hi*]indol-6-ol (7). To a solution of keto lactam **6** (100 mg, 0.55 mmol) in anhydrous THF (15 mL) was added $LiAlH_4$ (85.4 mg, 2.25 mmol) under N_2. The mixture was heated to reflux for 6 h. After the mixture was cooled, water and a saturated solution of sodium potassium tartrate were slowly added. The aqueous phase was separated and extracted with Et_2O. Evaporation of the combined dried organic extracts gave **7** as a mixture of epimers in a nearly equimolecular ratio. IR (neat) 3350, 1063, 1039; ^{1}H NMR 0.8−3.2 (m, 13H), 3.50 (t, J = 8, 1H, compd **7a**), 3.60 (t, J = 5, 1H, compd **7b**), 3.88 and 3.90 (m, 1H), 4.60 (br s, 1H); ^{13}C NMR alcohol **7a**: 27.3 (t), 31.6 (t), 33.6 (t), 34.8 (d), 35.1 (t), 44.7 (d), 52.5 (t), 53.0 (t), 67.5 (d), 71.7 (d); alcohol **7b**: 23.7 (t), 25.0 (t), 32.9 (t), 33.9 (t), 36.1 (d), 44.3 (d), 56.7 (t), 56.9 (t), 66.1 (d), 69.0 (d).

(5a*RS*,8a*SR*,8b*RS*)-Octahydropyrrolo[3,2,1-*hi*]indol-6-one (8). 1.23 M Jones reagent (1.02 mL, 1.27 mmol) was added at 0 °C to a stirred solution of alcohols **7** (70 mg, 0.42 mmol) in acetone (2 mL), and the mixture was stirred at 25 °C for 45 min. Addition of 10% aqueous $NaHSO_3$ solution (7.5 mL) and 4 N aqueous NaOH (6 mL), followed by extraction with Et_2O (4 × 25 mL), left an oil which was chromatographed (Al_2O_3, $CHCl_3$) to give ketone **8** (50 mg, 75%): IR (film) 1707; ^{1}H NMR 1.5−3.8 (m, 14H), 3.92 (t, J = 7.7, 1H); ^{13}C NMR 24.8 (t), 29.3 (t), 31.7 (t), 35.8 (d), 36.8 (t), 45.7 (d), 52.8 (t), 53.3 (t), 67.6 (d), 213.1 (s). HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1147.

(5a*RS*,11b*SR*,11c*SR*)-1,2,4,5,5a,6,11b,11c-Octahydropyrrolizino[1,7-*ab*] carbazole (9). To a solution of ketone **8** (100 mg, 0.6 mmol) in EtOH (6 mL) were added phenylhydrazine hydrochloride (100 mg, 0.7 mmol) and Na_2CO_3 (76 mg, 0.72 mmol). The mixture was heated at reflux for 1.5 h, filtered, and evaporated. The crude hydrazone was dissolved in glacial AcOH (10 mL) and heated at 95 °C for 1 h. The acid was removed, and the residue was dissolved in CH_2Cl_2 and washed with aqueous Na_2CO_3. Chromatography ($CHCl_3$−MeOH) gave pentacycle **9** (20 mg, 25%); mp 165 °C dec; ^{1}H NMR 1.75−1.92 (m, 2H), 2.06 (td, J = 13, 7.2, 1H), 2.30−2.41 (m, 1H), 2.50 (dd, J = 15, 6.7, 1H), 2.56 (dd, J = 11, 5.4, 1H), 2.60−2.66 (m, 1H), 2.70 (dt, J = 10.5, 7.4, 1H), 2.99 (dd, J = 15.1, 6.2, 1H), 3.06 (dt, J = 10, 5.2, 1H), 3.25 (ddd, J = 10.5, 7.1, 5.2, 1H), 3.42 (dt, J = 8, 5, 1H), 4.00 (dd, J = 8.5, 6.1, 1H), 7.11 (td, J = 7.1, 1.4, 1H); 7.16 (td, J = 7.1,1.4 Hz, 1H), 7.32 (dd, J = 7.4, 1.7, 1H); 7.50 (d, J = 7.3, 1H), 8.41 (br s, 1H); ^{13}C NMR 21.6 (C-6), 32.4 (C-4), 32.9 (C-1), 33.8 (C-5a), 36.0 (C-11b), 52.4 (C-2), 54.0 (C-4), 68.3 (C-11c), 107.1 (C-6a), 111.1 (C-10), 117.9 (C-7), 119.3 (C-8), 121.8 (C-9), 126.7 (C-6b), 132.2 (C-11a), 136.7 (C-10a). Anal. Calcd for $C_{16}H_{18}N_2 \cdot 1/4H_2O$: C: 79.12; H: 7.51; N: 11.42. Found: C: 78.74; H: 7.55; N: 11.30.

(5a*RS*,11b*SR*,11c*SR*)-4,5,5a,6,11b,11c-Hexahydro-1*H*-pyrrolizino[1,7-*ab*] carbazol-2-one (10). Operating as above, from ketone **6** (380 mg, 2.12 mmol), pentacycle **10** was obtained (224 mg, 42%) after chromatography (Al_2O_3, CH_2Cl_2); mp 249−250 °C (hexane−$CHCl_3$). IR (KBr) 3394, 3253, 1667; ^{1}H NMR 2.06−2.39 (m, 4H), 2.46 (d, J = 16.4, 1H), 2.95 (dd, J = 15, 6, 1H), 3.18 (dd, J = 16.4, 9.4, 1H), 3.21−3.27 (m, 1H), 3.63 (m, 2H), 4.35 (dd, J = 7.5, 4.5, 1H), 7.07−7.13 (m, 2H), 7.24−7.28 (m, 1H), 7.43−7.48 (m), 8,2 (br s, 1H); ^{13}C NMR 21.4 (C-6), 29.3 (C-5a), 33.2 (C-5), 34.0 (C-11b), 39.0 (C-1), 41.9 (C-4), 64.8 (C-11c), 108.6 (C-6a), 110.9 (C-10), 117.9 (C-7), 119.2 (C-8), 121.7 (C-9), 126.6 (C-6b), 133.6 (C-11a), 136.7 (C-10a), 172.2 (C-2). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.14; H, 6.36; N, 11.18.

To a solution of **10** (100 mg, 0.4 mmol) in THF (12 mL) was added $LiAlH_4$ (60 mg, 1.6 mmol). The mixture was heated at reflux for 10 h. After cooling, a satutared solution of sodium potassium tartrate (15 mL) was added and the aqueous phase was extracted with Et_2O and EtOAc. Evaporation of the combined dried organic phases, followed by chromatography (Al_2O_3, 10% MeOH in EtOAc), gave **9** (65 mg, 70%) as an amorphous solid.

***N*-Benzyl-2-(4-Methoxy-2,5-dihydrophenyl)ethylamine (11).** To a solution of **1** (10.7 g, 70 mmol) in CH_2Cl_2 (50 mL) were added benzaldehyde (8 mL, 78 mmol) and molecular sieves (4Å). The mixture was stirred at room temperature for 4 h, filtered, and evaporated to give the crude imine (>95% pure by NMR): IR (film) 1702, 1665, 1645; ^{1}H NMR 2.39 (t, J = 7.5, 2H), 2.76 (m, 4H), 3.55 (s, 3H), 3.72 (td, J = 7.5, 1.3, 2H), 4.63 (t, J = 2.8, 1H), 5.46 (t, J = 3.0, 1H), 7.41 (m, 3H), 7.72 (m, 2H), 8.26 (s, 1H); ^{13}C NMR 28.9 (t), 29.6 (t), 37.9 (t), 53.5 (q), 60.0 (t), 90.1 (d), 118.8 (d), 127.8 (d), 128.3 (d), 130.3 (d), 133.1 (s), 136.0 (s), 152.7 (s), 160.9 (d).

To a stirred solution of this imine (15.7 g) in MeOH (40 mL) was slowly added $NaBH_4$ (2.43 g, 64.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, quenched by addition of H_2O (100 mL) and then extracted with CH_2Cl_2 (3 × 100 mL). The organic extract was dried and evaporated to provide **11** (14.8 g, 95%), which was used directly in the next step: IR (film) 3364,1697, 1665; ^{1}H NMR 1.50 (br, 1H), 2.18 (t, J = 7, 2H), 2.71 (t, J = 7, 2H), 2.72 (s, 4H), 3.53 (s, 3H), 3.78 (s, 2H), 4,60 (br s, 1H), 5.43 (br s, 1H), 7.30 (s, 5H); ^{13}C NMR 28.9 (two t), 36.8 (t), 46.7 (t), 53.6 (q), 53.7 (t), 90.1 (d), 118.8 (d), 126.6 (d), 127.9 (d), 128.1 (d), 133.0 (s), 140.2 (s), 152.7 (s).

***cis*-1-Benzyloctahydroindol-6-one (12).** A solution of crude benzyl derivative **11** (13.7 g, 56.3 mmol) in 6 N HCl (70 mL) was heated at reflux for 5 h. The reaction mixture was basified with pellets of NaOH and extracted with CH_2Cl_2. Purification of the dried organic extract by chromatography (1:1 CH_2Cl_2−EtOAc) gave **12** (6.38 g, 50%): IR (film) 1716; ^{1}H NMR (500 MHz, COSY) 1.47 (ddt, J = 12, 10.5, 7.5, H-3$_\alpha$), 1.72 (dddd, J = 13, 6.5, 6, 5, H-4$_{eq}$), 1.91−1.98 (m, 2H, H-3$_\beta$

and H-4_{ax}), 2.05 (td, J = 9, 7, H-2_{β}), 2.18 (ddd, J = 18, 6, 4.5, H-5_{eq}), 2.45 (ddd, J = 18, 10, 4.5, H-5_{ax}), 2.47 (m, H-3a), 2.52 and 2.58 (2 dd, J = 16, 4.5 each, H-7), 2.80 (dt, J = 9, 4.5, H-7a), 2.85 (t, J = 8.5, H-2_{α}), 3.09 and 3.95 (2 d, J = 13 each CH_2Ar), 7.15−7.3 (m, 5H); ^{13}C NMR, Table 1; HRMS calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1478. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.58; H, 8.43; N, 6.12.

6-[(*N*-Benzylcarbamoyl)methyl]-3-ethoxy-2-cyclohexen-1-one (13). To a stirred solution of diisopropylamine (2.5 mL, 18 mmol) in THF (15 mL) was added under nitrogen at −78 °C a 1.6 M solution of *n*-BuLi in hexane (10.6 mL, 17 mmol). After the mixture was stirred for 25 min, a solution of 3-ethoxy-2-cyclohexen-1-one[47] (2 g, 14 mmol) in THF (10 mL) was added slowly. After 30 min at −78 °C, the solution was cannulated into a solution of *N*-benzyliodoacetamide[27] (8.7 g, 28 mmol) in THF (10 mL) stirring at −78 °C. The cold bath was removed upon complete addition, and after a further 6 min, the reaction was quenched by addition of H_2O (15 mL). The aqueous layer was extracted with Et_2O. Combined organic layers were washed with H_2O (3 × 15 mL) and brine (3 × 15 mL). Workup and chromatography (EtOAc−CH_2Cl_2) gave, in order of elution, the starting materials, iodo derivative (2.4 g) and cyclohexenone (520 mg), and **13** (2.1 g, 67%, over consumed starting material). A sample of **13**, crystallized (hexane−CH_2Cl_2), melted at 129−131 °C: IR (KBr) 3310, 1638, 1607; ^{1}H NMR 1.37 (t, J = 7, 3H), 2.1−2.8 (m, 7H), 3.92 (dq, J = 7, 2, 2H), 4.43 (d, J = 6, 2H), 6.5 (br, 1H), 7.25 (m, 5H); ^{13}C NMR 13.8 (q), 27.3 (t), 28.8 (t), 36.7 (t), 42.6 (d), 43.2 (t), 64.3 (t), 101.9 (d), 127.1 (d), 127.5 (d), 128.4 (d), 138.6 (s), 172.0 (s), 177.9 (s), 200.7 (s). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.88; H, 7.34; N, 4.88.

***cis*-1-Benzylhexahydroindole-2,6-dione (15).** To a solution of **13** (700 mg, 2.6 mmol) in MeOH (25 mL) at 0 °C was added $NaBH_4$ (250 mg, 7 mmol) in five portions at 30 min intervals each. The mixture was stirred for 24 h and then quenched by aqueous 30% H_2SO_4, and the stirring was maintained for 4 h at room temperature. The resulting solution was neutralized with solid $NaHCO_3$ and evaporated. Digestion of the dryness residue with $CHCl_3$ furnished a mixture of amido enone **14** and **15** (443 mg, 71%). Compound **14**: IR (KBr) 3282, 1678, 1637; ^{1}H NMR 1.30−2.50 (m, 6H), 3.05 (m, 1H), 4.45 (d, J = 5.8, 2H), 5.97 (dd, J = 10.2, 2.5, 1H), 6.2 (br s, 1H), 6.86 (dt, J = 10.2, 1.2, 1H), 7.27−7.32 (m, 5H); ^{13}C NMR 28.3 (t), 33.1 (d), 36.4 (t), 40.6 (t), 43.7 (t), 127.6 (d), 127.7 (d),128.7 (d), 129.3 (d), 138.2 (s), 153.9 (d), 170.7 (s), 199.8 (s).

A solution of **14** (295 mg, 1.3 mmol) and TsOH (50 mg, 2.26 mmol) in benzene (25 mL) was heated at reflux for 6 h and then concentrated to dryness. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous Na_2CO_3. From the organic extracts ketone **15** was isolated (250 mg, 85%); IR (film) 1721, 1679; ^{1}H NMR 1.4−2.9 (m, 9H), 3.80 (d, J = 12.5, 1H), 3.84 (d, J = 15, 1H), 4.98 (d, J = 15, 1H), 7.1−7.4 (m, 5H); ^{13}C NMR, see Table 1.

Fischer Indolization of Ketone 2. To a solution of ketone **2** (1.02 g, 4.7 mmol) in EtOH (25 mL) were added phenylhydrazine hydrochloride (720 mg, 5 mmol) and anhydrous Na_2CO_3 (550 mg, 5.2 mmol). The mixture was heated at reflux under Ar for 1.5 h and then filtered and evaporated to dryness. A solution of the resulting crude phenylhydrazone (650 mg, 2.1 mmol) in glacial AcOH (20 mL) was heated at 95 °C for 2 h. The solvent was evaporated, saturated aqueous $NaHCO_3$ (15 mL) was added, and then the mixture was extracted with CH_2Cl_2 (4 × 25 mL). Evaporation of the dried extracts followed by chromatography (CH_2Cl_2) gave indole **16** (150 mg, 23%) and indole **17** (120 mg, 20%).

***cis*-1-(Chloroacetyl)-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3,2-*c*]carbazole (16)**: mp 179−180 °C (EtOH); IR (KBr) 3556, 3275, 1651; ^{1}H NMR (500 MHz, DMSO-d_6, COSY) 1.93 (ddd, J = 11, 9, 5, 2H, H-3); 1.98 (dd, J = 8.5, 3.5, 2H, H-4), 2.52 (m, H-3a), 2.66 (dt, J = 17, 3.5, H-5_{eq}), 2.78 (dt, J = 17, 8.5, H-5_{ax}), 3.34 (dt, J = 10, 5, H-2_{α}), 3.60 (ddd, J = 10, 9, 9, H-2_{β}), 4.34 (s, CH_2Cl), 5.40 (d, J = 6.5, H-10c), 6.85 (t, J = 8, H-9), 6.96 (t, J = 8, H-8), 7.21 (d, J = 8, H-7), 7.65 (d, J = 8, H-10), 10.78 (s, NH); ^{13}C NMR, Table 2. Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.46; H, 5.96; N, 9.61.

***cis*-1-(Chloroacetyl)-1,2,3,3a,4,9,10,10a-octahydropyrrolo[2,3-*b*]carbazole (17)**: mp 197−198 °C (EtOH); IR (KBr) 3232, 1649; ^{1}H NMR (COSY, peaks of the major *Z* rotamer) 1.80 (m, H-3_{β}), 2.04 (quint, J = 10.5, H-3_{α}), 2.49 (dd, J = 17, 7.5, H-10_{ax}), 2.56 (m, H-3a), 2.75 (d, J = 17, H-4_{ax}), 2.98 (dd, J = 17, 8, H-4_{eq}), 3.25 (dd, J = 17, 7.5, H-10_{eq}), 3.52 (td, J = 10, 7.5, H-2_{β}), 3.63 (td, J = 9.5, 1.5, H-2α), 4.29 (s, CH_2Cl), 4.34 (m, H-10a), 6.92 (t, J = 7.5, H-6), 6.99 (t, J = 7.5, H-7), 7.24 (d, J = 7.5, H-8), 7.33 (d, J = 7.5, H-5), 10.62 (s, NH); ^{13}C NMR (DMSO-d_6, HMQC) **(*Z*)**: 21.1 (C-4), 24.7 (C-10), 29.6 (C-3), 35.0 (C-3a), 42.9 (CH_2Cl), 44.7 (C-2), 54.3 (C-10a), 105.0 (C-4a), 110.9 (C-8), 117.4 (C-5), 118.3 (C-6), 120.5 (C-7), 127.1 (C-4b), 131.1 (C-9a), 136.4 (C-8a), 164.2 (CO); **(*E*)**: 21.3 (C-4), 25.5 (C-10), 27.2 (C-3), 36.8 (C-3a), 42.7 (CH_2Cl), 44.6 (C-2), 54.8 (C-10a), 105.2 (C-4a), 110.9 (C-8), 117.4 (C-5), 118.3 (C-6), 120.6 (C-7), 127.1 (C-4b), 130.6 (C-9a), 136.4 (C-8a), 163.9 (CO). Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.18; H, 5.92; N, 9.57.

***cis*-1-(Trichloroacetyl)-1,2,3,3a,4,9,10,10a-octahydropyrrolo[2,3-*b*]carbazole (18).** The same procedure described above for indolization of ketone **2** was carried out with ketone **5** (140 mg, 0.49 mmol). Chromatography (CH_2Cl_2) afforded 50 mg (30%) of indole **18**: IR (KBr) 3386, 1665; ^{1}H NMR ($CDCl_3$ + CD_3OD) 1.90−2.12 (m, 2H), 2.50−3.20 (m, 3H), 3.50−3.70 (m, 2H), 3.85−4.20 (m, 2H), 4.65 (dd, 1H), 7.08−7.43 (m, 3H), 7.90 (s, 1H), 8.03 (d, J = 7.5, 1H); ^{13}C NMR 21.1 (C-4), 23.9 (C-10), 30.4 (C-3), 34.8 (C-3a), 48.2 (C-2), 58.4 (C-10a), 105.9 (C-4a), 110.9 (C-8), 117.4 (C-5), 119.0 (C-6), 120.0 (C-7), 127.1 (C-4b), 129.8 (C-9a), 136.3 (C-8a), 159.2 (CO).

***cis*-1-Benzyl-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3,2-*c*]-carbazole (19).** Reaction of **12** (6.3 g, 27.8 mmol) with phenylhydrazine and then with AcOH (115 °C, 3 h), as described for the indolization of **2**, gave **19** (4.5 g, 54%) as a solid after chromatography (2:1, CH_2Cl_2−EtOAc); mp 90−92 °C (EtOH); IR (film) 3420, 3382; ^{1}H NMR (300 MHz, COSY) 1.49 (dddd, J = 11, 8, 8, 2.5, H-3_{α}), 1.74 (dddd, J = 10, 5.5, 3.3, 3.3, H-4_{eq}), 2.08 (dddd, J = 12, 10.5, 2.7, 2.5, H-3_{β}), 2.2 (m, H-4_{ax}), 2.25 (m, H-2_{α}), 2.3 (m, H-3a), 2.66 (ddd, J = 16.5, 10.5, 5.5, H-5_{ax}), 2.74 (ddd, J = 16.5, 5.5, 3, H-5_{eq}), 2.93 (td, J = 9.1, 2.7, H-2_{β}), 3.37 and 4.49 (2d, J = 12.3 each, CH_2Ar), 3.59 (d, J = 4.4, H-10c), 7.06−7.08 (m, H-9, H-8), 7.15−7.29 (m, 5H), 7.65 (t, J = 5, H-10), 7.91 (s, NH); ^{13}C NMR, Table 2. Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26. Found: C: 83.50; H: 7.42; N: 9.29.

***cis*-1-Benzyl-1*H*-3,3a,4,9,10,10a-hexahydropyrrolo[2,3-*b*]carbazol-2-one (20).** The procedure described above for the preparation of **16** was carried out with ketone **15** (222 mg, 0.92 mmol) to afford, after chromatography (CH_2Cl_2), **20** (73 mg, 27%): IR (KBr) 3407, 1667; ^{1}H NMR 2.36 (dd, J = 17, 8.5 Hz, 1H), 2.6−3.1 (m, 6H), 3.88 (dd, J = 8, 5, 1H), 4.17 (d, J = 15, 1H), 4.90 (d, J = 15, 1H), 7.1−7.4 (m, 9H), 7.7 (br s, 1H); ^{13}C NMR 23.3 (t), 25.1 (t), 29.7 (t), 36.8 (d), 43.8 (t), 53.4 (d), 110.7 (d), 118.1 (d), 119.2 (d), 121.6 (d), 127.1 (d). 129.1 (d), 129.7 (d), 172.0 (s).

Methyl *cis*-1-Benzyl-1,2,3,3a,4,5,6,10c-octahydropyrrolo-[3,2-*c*]carbazole-6-carboxylate (23). A 50% aqueous NaOH solution (6.7 mL) was added to a suspension of indole **19** (500 mg, 1.65 mmol) and tetrabutylammonium hydrogen sulfate (10 mg) in toluene (20 mL). The resulting two-phase mixture was vigorously stirred at room temperature for 15 min. Then, a solution of methyl chloroformate (0.2 mL, 2.4 mmol) in toluene (2 mL) was added dropwise. The mixture was stirred for 1 h and additional methyl chloroformate (0.2 mL) in toluene was added. After 15 min, H_2O (40 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 100 mL). After workup and chromatography (CH_2Cl_2), indole **23** (470 mg, 80%) was isolated as a white solid: mp 86 °C (EtOH); IR (KBr) 1735; ^{1}H NMR 1.48−1.60 (m, H-3_{α}), 1.77−1.84 (ddd, J = 12, 5.5, 1.6, H-4_{eq}), 2.04 (m, H-3_{β}), 2.22 (dd, J = 9.5, 4, H-2_{α}), 2.25−2.31 (m, H-3a and H-4_{ax}), 2.92 (dd, J = 18.4, 3.2, H-5_{eq}), 2.93 (td, J = 9, 6, H-2_{β}), 3.26 (ddd, J = 18.4, 5, 4.5, H-5_{eq}), 3.41 and 4.34

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(2d, J = 12.5 each, CH_2Ar), 3.64 (d, J = 4.4, H-10c), 4.02 (s, 3H, CH_3O), 7.20−7.28 (m, 7H). 7.65 (m, H-10), 8.13 (m, H-7); ^{13}C NMR, Table 2. Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.66; H, 6.67; N, 7.64.

Methyl *cis*-1,2,3,3a,4,5,6,10c-Octahydropyrrolo[3,2-*c*]-carbazole-6-carboxylate (24). A suspension of tetracycle **23** (1 g, 2.77 mmol) and activated[39] $Pd(OH)_2$ (100 mg) in MeOH (25 mL) was hydrogenated until the disappearance of the starting compound was observed by TLC (3 days). The catalyst was removed by filtration through Celite, and the solvent was evaporated to give indole **24** (970 mg) as a white solid, which was used in the next step without further purification. A pure sample was obtained by chromatography (1% diethylamine in a 1:10 mixture MeOH−EtOAc): mp 98−100 °C (EtOH); IR (film) 3297, 1720; ^1H NMR 1.50−1.65 (m, 2H), 1.78−1.85 (ddd, J = 13.6, 9.1, 4.4, 1H), 2.02 (m, 1H), 2.31 (m, 1H), 2.52 (br s, 1H), 2.79 (ddd, J = 18, 9.5, 5.8, 1H), 2.96−3.14 (m, 3H), 3.98 (s, 3H), 4.09 (d, J = 5.9, 1H), 7.20−7.24 (m, 2H), 7.59−7.63 (m, 1H), 8.04−8.09 (m, 1H); ^{13}C NMR, Table 2. HRMS calcd for $C_{16}H_{18}N_2$ 270.1368, found 270.1364.

Methyl *cis*-1-[2-(Phenylsulfinyl)ethyl]-1,2,3,3a,4,5,6,-10c-octahydropyrrolo[3,2-*c*]carbazole-6-carboxylate (25). To a solution of amine **24** (400 mg, 1.47 mmol) in MeOH (4 mL) was slowly added phenyl vinyl sulfoxide (0.25 mL, 45 mmol). The reaction mixture was heated to reflux for 18 h. Following evaporation to dryness, chromatography (EtOAc) afforded **25** (400 mg, 65%) as a mixture of diastereoisomers at sulfur. For analytical data, *vide infra*.

***cis*-1,2,3,3a,4,5,6,10c-Octahydropyrrolo[3,2-*c*]carbazole (26).** A suspension of tetracycle **19** (820 mg, 2.71 mmol) and activated[39] $Pd(OH)_2$ (80 mg) in MeOH (80 mL) was hydrogenated until the disappearance of the starting compound was observed by TLC (3 days). The catalyst was removed by filtration through Celite, and the solvent was evaporated to give indole **26** (420 mg, 90%) as a white solid: mp 157−159 °C (EtOH); IR (film) 3398; ^1H NMR 1.53−2.20 (m, 4H), 2.42 (m, 1H), 2.71 (dd, J = 7.2, 5, 2H), 2.96 (ddd, J = 11.2, 8.7, 6.1, 1H), 3.14 (ddd, J = 11.3, 8.8, 6.2, 1H), 3.63 (s, 2H), 4.21 (d, J = 9, 1H), 7.06−7.12 (m, 2H), 7.26−7.33 (m, 1H), 7.62−7.66 (m, 1H); ^{13}C NMR, Table 2. HRMS calcd for $C_{14}H_{16}N_2$ 212.1313, found 212.1304.

***cis*-1-[2,2-Bis(methylthio)ethyl]-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3,2-*c*]carbazole (28).** A stirred mixture of **26** (212 mg, 1 mmol), bromoacetaldehyde diethyl acetal (0.25 mL, 1.5 mmol), and anhydrous K_2CO_3 (200 mg, 1.3 mmol) in dioxane (15 mL) was heated at reflux for 20 h. Removal of the solvent gave a residue which was taken up with CH_2Cl_2. The resulting solution was washed with saturated aqueous Na_2CO_3. After workup, the residue was chromatographed (CH_2Cl_2−EtOAc) to yield acetal **27** (150 mg, 50%): IR (film) 3398; ^1H NMR 0.96 (t, J = 7, 3H), 1.10 (t, J = 7, 3H), 1.50 (m, 1H), 1.60 (m, 1H), 1.90−2.11 (m, 2H), 2.15 (m, 1H), 2.38 (td, J = 9.2, 8, 1H), 2.45 (m, 1H), 2.56 (dd J = 12.5, 5.5, 1H), 3.20−3.35 (m, 3H), 3.39 (dq, J = 10, 7, 2H), 3.51 (d, J = 5.1, 1H), 3.57 (dq, J = 9.5, 7, 2H), 4.57 (t, J = 5.3, 1H), 6.96−7.03 (m, 2H), 7.14 (m, 1H), 7.52 (m, 1H), 8.06 (br s, 1H); ^{13}C NMR, Table 2. A solution of **27** (150 mg, 0,46 mmol), $BF_3{\cdot}Et_2O$ (0.9 mL, 6.9 mmol), and methanethiol (1 mL) in CH_2Cl_2 (10 mL) was stirred at 0 °C in a sealed tube for 6 h. The mixture was poured into 50% aqueous NaOH and extracted with CH_2Cl_2 (3 × 50 mL). After workup and chromatography (1:1, hexane−CH_2Cl_2), thioacetal **28** (50 mg, 34%) was isolated: IR (film) 3398; ^1H NMR 1.58−1.67 (m, 1H), 1.72−1.80 (m, 1H), 1.88 (s, 3H), 1.95 (s, 3H), 2.03−2.22 (m, 2H), 2.23 (m, 1H), 2.38 (td, J = 9, 7, 1H), 2.67−2.72 (m, 2H), 2.85 (dd, J = 12.2, 5.4, 1H), 3.32 (td, J = 8.5, 3.5, 1H), 3.38 (dd, 1H, J = 12.3, 9.8, 1H), 3.60 (d, J = 4.4, 1H), 4.57 (dd, J = 9.7, 5.3, 1H), 7.05−7.11 (m, 2H), 7.22−7.28 (m, 1H), 7.56−7.61 (m, 1H), 7.87 (br s, 1H); ^{13}C NMR, Table 2. HRMS calcd for $C_{18}H_{24}N_2S_2$ 332.1380, found 332.1366.

***cis*-1-[2-Phenylsulfinyl)ethyl]octahydroindol-6-one (30).** To a solution of amine **1** (4.8 g, 31.3 mmol) in absolute EtOH (15 mL) was slowly added phenyl vinyl sulfoxide (5.93 mL, 45 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 18 h. Concentration give a crude ***N*-[2-(phenylsulfinyl)ethyl]-2-(4-methoxy-2,5-dihydrophenyl)-ethylamine (29)**, which was used directly. An aliquot was chromatographed (CH_2Cl_2−EtOAc) and gave a pure **29** as a yellowish oil: IR (film) 3303, 1696, 1664; ^1H NMR 1.63 (br s, 1H), 2.19 (t, J = 7, 2H), 2.71 (t, J = 7, 2H), 2,73 (s, 4H), 2.90−3.17 (m, 4H), 3.54 (s, 3H), 4.62 (s, 2H), 5.43 (s, 1H), 7.50−7.67 (m, 5H); ^{13}C NMR 29.0 (two t), 36.7 (t), 42.8 (t), 47.3 (t), 53.4 (q), 57.4 (t), 90.1 (d), 119.1 (d), 123.7 (d), 129.1 (d), 130.8 (d), 132.8 (s), 143.8 (s), 152.8 (s).

The crude **29** was dissolved in 2 N HCl (100 mL) and warmed at 90 °C for 2 h. The solution was allowed to cool to room temperature and was carefully basified with NaOH pellets. The resulting solution was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts after workup and chromatography (EtOAc) furnished 5.72 g (63%) of **30** (mixture of diastereomers at sulfur atom) as a yellow oil: IR (film) 1713; ^1H NMR 1.50−3.30 (m, 16H); 7.48−7.64 (m, 5H).^{13}C NMR, Table 1. Anal. Calcd for $C_{16}H_{21}NO_2S{\cdot}{}^1/_4H_2O$: C, 64.94; H, 7.32; N, 4.73. Found: C, 64.81; H, 7.42; N, 4.58.

***cis*-1-[2-Phenylsulfinyl)ethyl]-1,2,3,3a,4,5,6,10c-octahydropyrrolo[3,2-*c*]carbazole (31).** The same procedure used for the preparation of **19** from ketone **12** was carried out with the ketone **30** (5.7 g, 19.55 mmol). The indolization step was carried out at 120 °C for 1 h 30 min. Chromatography (Al_2O_3, EtOAc) afforded 4.45 g (60%) of **31** as an epimeric mixture at sulfur. The process allowed isolation of separate pure diastereomers **31a** and **31b**.

31a (less polar isomer): mp 195 °C (EtOAc); IR (film) 3130; ^1H NMR (500 MHz, DMSO-d_6, COSY) 1.48 (dtd, J = 13, 9, 1.5, H-3$_\alpha$), 1.70 (m, H-4$_\beta$), 1.99 (qd, J = 12, 6, H-4$_\alpha$), 2.08 (dtd, J = 12.5, 10, 3, H-3$_\beta$), 2.15 (m, H-3a), 2.23 (td, J = 9, 7.5, H-2$_\beta$), 2.60 and 3.00 (2m, CH_2S), 2.68 (ddd, J = 16.5, 11, 5.5, H-5$_\beta$), 2.75 (ddd, J = 17, 5.5, 2.5, H-5$_\alpha$), 2.88 and 3.02 (2m, CH_2N), 3.26 (td, J = 9, 3, H-2$_\alpha$), 3.32 (d, J = 5.5, H-10c), 6.83 (td, J = 7.5, 1, H-9), 6.96 (td, J = 7.5, 1, H-8), 7.16 (t, J = 7, 2H), 7.19 (d, J = 7.5, H-10), 7.25 (d, J = 7, 1H), 7.26 (d, J = 7.5, H-7), 7.31 (dd, J = 7, 1, 2H), 10.90 (s, H-6); ^{13}C NMR, Table 2. Anal. Calcd for $C_{22}H_{24}N_2OS$: C, 72.49; H, 6.64; N, 7.68. Found: C, 72.34; H, 6.65; N, 7.66.

31b (more polar isomer): mp 205−207 °C (EtOAc); IR (Nujol): 3189−3217; ^1H NMR (500 MHz, DMSO-d_6): 1.45 (ddt, J = 10, 7, 1.5, H-3$_\alpha$), 1.70 (m, H-4$_\beta$), 1.98 (qd, J = 11.5, 5.5, H-4$_\alpha$), 2.04 (dtd, J = 12, 9, 3, H-3$_\beta$), 2.10 (t, J = 8.5, H-2$_\beta$), 2.14 (m, H-3a), 2.40 (ddd, J = 11.5, 7.5, 5, 1H, CH_2S), 2.66 (ddd, J = 17, 11, 5.5, H-5$_\beta$), 2.72 (ddd, J = 17, 6, 3, H-5$_\alpha$), 2.91 (m, 2H, CH_2N), 3.15 (td, J = 9, 2, H-2$_\alpha$), 3.28 (d, J = 6, H-10c), 3.42 (dt, J = 12, 8, 1H, CH_2S); 6,96 (td, J = 7.5, 1, H-8), 7.00 (td, J = 7.5, 1, H-9), 7.26 (d, J = 7.5, H-7), 7.32 (d, J = 7.5, H-10), 7.50−7.58 (m, 5H), 10.88 (s, H-6); ^{13}C NMR, Table 2. Anal. Calcd for $C_{22}H_{24}N_2OS$: C, 72.49; H, 6.64; N, 7.68. Found: C: 72.46; H: 6.64; N: 7.77.

***N*-Methoxycarbonylation of Indole 31.** To a solution of indoles **31** (630 mg, 1.66 mmol) in a 6:1 mixture of THF−HMPA (10 mL) at −78 °C was added 1.6 M LDA in cyclohexane (1.1 mL, 1.7 mmol). The mixture was stirred at this temperature for 1 h. Then, methyl cyanoformate (0.25 mL, 3.15 mmol) was added and the ice bath was removed. The temperature was raised to room temperature and stirring was maintained for 2 h. The reaction was quenched with saturated aqueous Na_2CO_3 (25 mL) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine (10 × 50 mL), dried, and evaporated to dryness. Crystallization of the residue with EtOAc allowed isolation of separate pure diastereomer **25a**. From the mother liquors and by column chromatography (EtOAc), the other carbamate **25b** was isolated in a pure form. The overall yield was 78% (550 mg) in an equimolecular ratio of both carbamates.

Using the same procedure, the less polar diastereomer **31a** gave the related carbamate **25a**, and the more polar diastereomer **31b** gave **25b**.

Methyl *cis*-1-[2-(Phenylsulfinyl)ethyl]-1,2,3,3a,4,5,6,-10c-octahydropyrrolo[3,2-*c*]carbazole-6-carboxylate (25a): mp 138−139 °C (EtOAc); IR (KBr) 1736; ^1H NMR 1.62 (m, 1H), 1.80 (m, 1H), 1.99−2.20 (m, 3H), 2.23 (m, 1H), 2.60−3.00 (m, 4H), 3.17 (m, 1H), 3.27 (m, 1H), 3.40 (m, 1H), 3.41 (d, J = 4, 1H), 4.04 (s, 3H), 6.90−7.30 (m, 8H), 8.10 (d, J = 7.5, 1H); ^{13}C

NMR, Table 2. Anal. Calcd for $C_{24}H_{26}N_2O_3S$: C, 68.22; H, 6.20; N, 6.63. Found: C, 68.16; H, 6.20; N, 6.66.

Methyl *cis*-1-[2-(Phenylsulfinyl)ethyl]-1,2,3,3a,4,5,6,-10c-octahydropyrrolo[3,2-*c*]carbazole-6-carboxylate (25b): ^{1}H NMR 1.50−1.70 (m, 1H), 1.70−1.90 (m, 1H), 1.98−2.10 (m, 3H), 2.24 (m, 1H), 2.44 (m, 1H), 2.70−3.00 (m, 3H), 3.10−3.30 (m, 2H), 3.45 (m, 1H), 3.58 (d, J = 5.1, 1H), 4.02 (s, 3H), 7.23−7.50 (m, 8H), 8.10 (d, J = 7.5, 1H); ^{13}C NMR, Table 2.

Methyl 1-(Phenylthio)-2,4,5,5a,6,7,8,12a-hexahydro-1*H*-pyrrolizino[1,7-*cd*]carbazole-8-carboxylate (32). To a solution of sulfoxides **25** (300 mg, 0.71 mmol) in anhydrous toluene (10 mL) was added at room temperature, in a sequential manner, TFAA (0.3 mL, 2.16 mmol) and TFA (0.18 mL, 2.16 mmol). The solution was warmed at 80 °C for 2 h. The mixture was then cooled and the reaction quenched by addition of aqueous saturated Na_2CO_3 (25 mL). The aqueous mixture was extracted three times with 50 mL portions of CH_2Cl_2. Purification of dried extracts by chromatography (4:1, EtOAc−CH_2Cl_2) afforded 180 mg (63%) of pentacycle **32** as an epimeric mixture at C-6, which could be separated partially by a chromatography: IR (film) 1717.

Compound **32a** (H-6$_\beta$):[2] ^{1}H NMR 1.76 (m, 2H, H-17), 1.94 (ddd, J = 14.5, 11.5, 3, H-15$_\beta$), 2.08−2.25 (m, H-14 and H-15$_\alpha$), 2.31−2.44 (m, H-20$_\beta$), 2.77 (ddd J = 14.5, 9, 5.5, H-20$_\alpha$), 3.18 (dd, J = 12.5, 7.5, H-6), 3.29 (t, J = 11.5, H-5$_\alpha$), 3.65 (dd, J = 12, 7.5, H-5$_\beta$), 3.87 (s, 3H), 3.94 (d, J = 6.5, H-3), 6.25 (dd, J = 7.5, 1, H-16), 7.10−7.40 (m, 8H), 7.83 (d, J = 8, H-12); ^{13}C NMR 30.6 (C-15), 31.6 (C-17), 38.3 (C-14), 53.1 (C-20), 52.6 (O*C*H$_3$), 55.7 (C-6), 56.5 (C-7), 58,0 (C-5), 74.2 (C-3), 107.1 (C-16), 115.2 (C-12), 123.5 (C-9), 123.5 (*p*-Ar), 126.5 (C-10), 128.4 (C-11), 128.6 (*o*-Ar), 131.0 (*m*-Ar), 133.0 (*ipso*-Ar), 135.2 (C-8), 141.8 (C-2), 142.9 (C-13), 152.6 (CO).

Compound **32b** (H-6$_\alpha$):[2] ^{1}H NMR 1.91 (m, H-15$_\beta$), 2.03 (m, 2H, H-17), 2.14 (m, H-14), 2.44 (td, J = 11.3, 2.5, H-15$_\alpha$), 2,72 (t, J = 10, H-5$_\beta$), 3.03 (dt, J = 11, 7, H-20$_\beta$), 3.20 (m, H-20$_\alpha$), 3.59 (dd, J =10, 7, H-5$_\alpha$), 3.87 (d, J = 7, H-3), 3.87 (s, 3H), 3.93 (dd, J = 10, 7, H-6), 6.59 (dd, J = 9, 1.5, H-16), 6.9−7.0 (m, 5H), 7.08 (td, J = 7.5, 1.5, H-11), 7.20 (td, J = 7.5,1.5, H-10), 7.43 (dd, J = 7.5, 1.5, H-9), 7.64 (d, J = 7.5, H-12); ^{13}C NMR 30.6 (C-15), 31.5 (C-17), 37.3 (C-14), 52.6 (C-20), 52.7 (O*C*H$_3$), 55.2 (C-7), 62.9 (C-6), 63.0 (C-5), 75.4 (C-3), 113.0 (C-16), 115.2 (C-12), 121.8 (C-9), 123.7 (*p*-Ar), 126.0 (C-10), 128.0 (C-11), 128.5 (*o*-Ar), 129.9 (*m*-Ar), 135.3 (C-8), 137.1 (*ipso*-Ar), 140.9 (C-2), 141.7 (C-13), 153.2 (CO). HRMS calcd for $C_{24}H_{24}N_2O_2S$ 404.1558, found 404.1558.

Methyl 2,4,5,5a,6,7,8,12a-Hexahydro-1*H*-pyrrolizino-[1,7-*cd*]carbazole-8-carboxylate (33). To a solution of **32** (220 mg, 0.12 mmol) in absolute EtOH (6 mL) was added freshly prepared Raney Ni (W-2, 6 spatulas), and the mixture was heated at reflux for 4 h. The solids were removed by filtration through Celite and washed with EtOH. Removal of the solvent and purification of the residue by chromatography (1% diethylamine in EtOAc) gave **33** as an oil (100 mg, 64%): IR (film) 1717; ^{1}H NMR 1,70 (ddd, J = 12.4, 5.7, 2, H-6$_\beta$), 1.75−1.83 (m, H-15$_\beta$), 1.82 (dt, J = 11.5, 3.2, H-17$_\alpha$), 2.04 (td, J = 11.6, 5.1, H-17$_\beta$), 2.10 (m, H-14), 2.18 (dd, J = 11.4, 7, H-6$_\alpha$), 2.34 (dddd, J = 14.3, 8.2, 5.2, 1, H-15$_\alpha$), 2.81 (m, H-20$_\alpha$). 2.87 (ddd, J = 12.2, 7.5, 2, H-5$_\alpha$), 3.30 (t, J = 8.5, H-20$_\beta$), 3.32 (td, J = 12, 5.5, H-5$_\beta$), 3.76 (d, J = 6, H-3), 6.23 (dd, J = 8, 3, H-16), 7.07 (td, J = 7.5, 1, H-11), 7.24 (td, J = 7.5, 1, H-10), 7.34 (dd, J = 7.5, 1, H-9), 7.81 (dd, J = 7.5, 1, H-12); ^{13}C NMR 27.8 (C-15), 32.1 (C-17), 38.2 (C-14), 40.1 (C-6), 52.1 (C-5), 52.8 (O*C*H$_3$), 53.5 (C-7), 54.6 (C-20), 74.1 (C-3), 106.6 (C-16), 115.3 (C-12), 122.4 (C-10), 123.8 (C-9), 127.8 (C-11), 137.8 (C-8), 140.5 (C-2), 144.2 (C-13), 153.2 (CO). Anal. Calcd for $C_{18}H_{20}N_2O_2{\cdot}H_2O$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.65; H, 6.98; N, 8.76.

(±)-Deethylibophyllidine. A degassed solution of **33** (50 mg, 0.17 mmol) in MeOH (100 mL) was photolyzed under argon with a 125-W medium-pressure mercury lamp in a quartz immersion well reactor for 2.5 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous Na_2CO_3. After workup and chromatography (2% diethylamine in CH_2Cl_2), deethylibophyllidine (25 mg, 50%) in amorphous form was isolated: mp 111−112 °C (reported[5a] mp 110 °C); IR (film) 3500, 1676, 1608; ^{1}H NMR (500 MHz, COSY) 1.68 (dd, J = 12.5, 5, H-6$_\beta$), 1.78 (dd, J = 12.5, 5.5, H-15$_\alpha$), 1.86 (dd, J = 15.5, 12, H-17$_\alpha$), 2.02 (m, H-14), 2.05 (td, J = 12.5, 5.5, H-6$_\alpha$), 2.14 (tt, J = 12.5, 7, H-15$_\beta$), 2,73 (m, H-20$_\alpha$), 2.78 (dd, J = 15.5, 6, H-17$_\beta$), 2.92 (dd, J = 12.5, 7, H-5$_\alpha$), 3.33 (t, J = 8, H-20$_\beta$), 3.38 (td, J = 12.5, 5.5, H-5$_\beta$), 3.75 (s, 3H), 3.79 (d, J = 6, H-3), 6.82 (dd, J = 7.5, 0.5, H-12), 6.88 (td, J = 7.5, 1, H-10), 7.15 (td, J = 7.5, 1, H-11), 7.33 (dd, J = 7.5, 0.5, H-9), 9.05 (s, N*H*); ^{13}C NMR (HMQC) 26.2 (C-17), 31.8 (C-15), 38.7 (C-14), 38.9 (C-6), 51.0 (O*C*H$_3$), 52.4 (C-5), 55.1 (C-20), 57.5 (C-7), 73.0 (C-3), 91.6 (C-16), 109.1 (C-12), 120.9 (C-10), 122.5 (C-9), 128.1 (C-11), 136.6 (C-8), 143.5 (C-13), 164.3 (C-2), 168.5 (CO).

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