Total Syntheses of (±)-Deethylibophyllidine Using a Crisscross Annulation: Ring Cleavage of Octahydroindolo[2,3-*a*]quinolizines Followed by Tandem Cyclizations of Octahydroazecino[5,4-*b*]indoles

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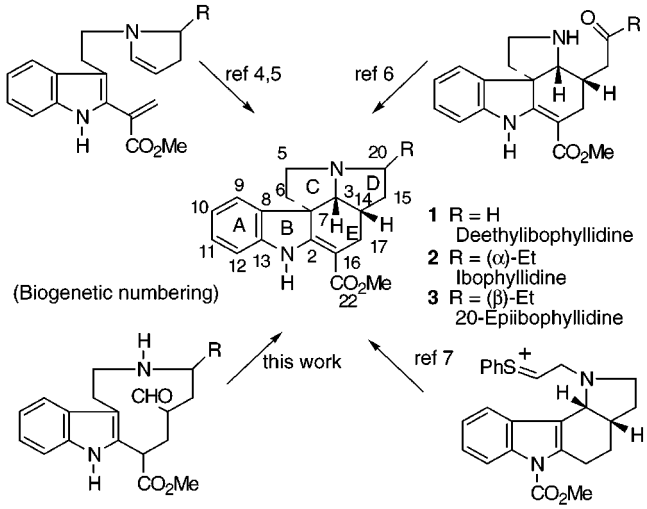
The total synthesis of (±)-deethylibophyllidine (**1**) is described. Three different sequences provide this pentacyclic alkaloid using a common strategy involving a crisscross annulation. Key steps include (i) C/D ring cleavage of a 2-formyloctahydroindolo[2,3-*a*]quinolizine to obtain octahydroazecino[5,4-*b*]indoles, via either a chloroformate induced process or a quaternary ammonium salt formation followed by treatment with lithium, and (ii) a tandem process consisting of an intramolecular Pictet−Spengler double cyclization upon a *β*-indole position of a 2,3-disubstituted indole to generate the quaternary spiro center of the pentacyclic skeleton of ibophyllidine alkaloids. Attempts to extend the procedure to the construction of the pentacyclic framework of (±)-ibophyllidine result in very low yield.

Introduction

The ibophyllidine alkaloids[1] are a type of pentacyclic monoterpenoid indole alkaloids belonging to the Ibogan biogenetic class.[2] They have been synthesized using the strategies depicted in Scheme 1, in which the crucial step is the formation of the spiro stereocenter at C-7[3] to generate the characteristic 2,3,3-trisubstituted indoline unit. Kuehne,[4] and later Das,[5] used an intramolecular Diels−Alder process to form the strategic bonds. Later Kuehne reported a modification of his first approach, elaborating the D ring at the end of the synthesis by a reductive amination.[6] In the more recent example from our laboratory,[7] a Pummerer rearrangement/thionium ion-mediated indole cyclization was employed to elaborate the C ring in the key step.[8] The ibophyllidine alkaloids have a skeleton which lacks the C-21 biogenetic carbon, implying the presence of a pyrrolidine D ring instead of the piperidine ring found in the structurally related *Aspidosperma* and *Strychnos* alkaloids. Nevertheless, since all of them possess a pyrrolo[2,3-*d*]carbazole moiety (ABCE rings) as a common structural feature, the development of a new synthetic strategy to the ibophyllidine alkaloids can also open new perspectives for the synthesis of the aforementioned related alkaloid types.[9]

Scheme 1. Synthetic Strategies for the Synthesis of Ibophyllidine Alkaloids



In this paper we describe a new, straightforward synthetic entry to 2,3,3-trisubstituted indole alkaloids embodying the pyrrolo[2,3-*d*]carbazole skeleton based on the transannular Pictet−Spengler cyclization (bond formed C-3/C-7) of an iminium ion generated intramolecularly

(1) Saxton, J. E. The Ibogamine-Catharanthine Group in *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C. Ed.; Wiley: New York 1994; Supplement to Vol. 25, Part 4, pp 487−521.

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(3) The biogenetic numbering (Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508−509) is used throughout this paper, but the systematic nomenclature has been used in the tables and Experimental Section.

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(7) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106−7115.

(8) For other synthetic approaches leading to derivatives with the pyrrolizino[1,7-*cd*]carbazole skeleton, see: (a) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335−1343. (b) Kuehne, M. E.; Wang, T.; Seaton, P. J. *J. Org. Chem.* **1996**, *61*, 6001−6008. (c) Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, *61*, 7873−7881.

(9) Syntheses of *Aspidosperma* and *Strychnos* alkaloids through formation of E-,[10] D-,[11] and C-ring[12] by the strategies shown in Scheme 1 have also been reported.

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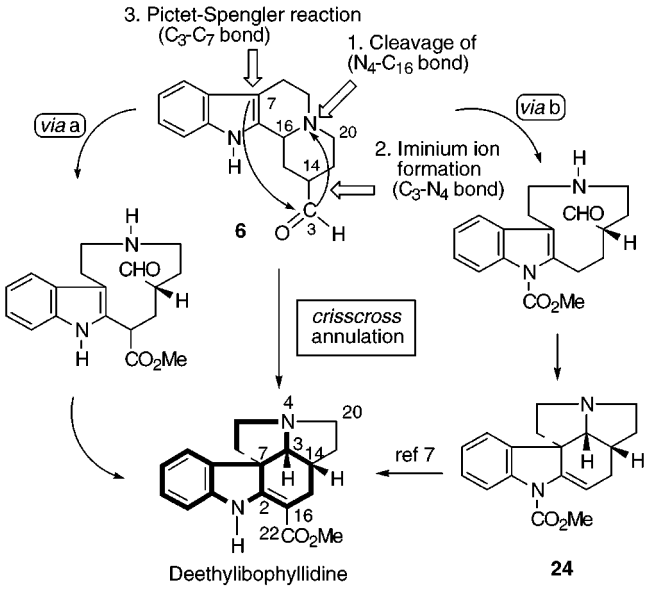
Scheme 2. Retrosynthetic Plan for the Synthesis of Deethylibophyllidine



(bond formed C-3/N-4) from an appropriately substituted azecino[5,4-*b*]indole. The usefulness of this strategy is exemplified by the three routes developed for the synthesis of the alkaloid deethylibophyllidine. Our approach constitutes a *crisscross*-type annulation,[13] in which the key octahydro azecino[5,4-*b*]indole intermediate is prepared by ring cleavage (bond cleaved N-4/C-16) of a readily accessible 2-formyloctahydroindolo[2,3-*a*]quinolizine (Scheme 2). Beginning with the pioneering work of Dolby and Sakai[14] in 1964, a number of procedures have been reported for the cleavage of zero bridged single bonds in tetra- or pentacyclic indole compounds incorporating a tetrahydro-β-carboline unit (i.e. **6**).[15−17] The most common procedure involves the use of chloroformate esters.[18,19] Less common procedures to the cleavage are the reactions with cyanogen bromide[20] or anhydrides.[21] Other approaches have utilized the formation of a quaternary ammonium salt, which is then treated with an alkali metal[22] or cyanide ions.[23]

With the aforementioned strategy to synthesize ibophyllidine alkaloids, two different tactics can be envisaged to introduce the C-22 exocyclic carbon (Scheme 2). Thus, the C-22 can be introduced before the double ring closure, which would allow the pentacyclic skeleton of the targets to be built (via a), taking advantage of the functionalization present in C-16 when the ring cleavage was conducted in solvolytic conditions. On the other hand, the C-22 can be introduced later to the tandem process (via b), taking advantage of the formation of the known ene carbamate **24**, which has been previously converted to (±)-deethylibophyllidine.[7]

Results and Discussion

Total Synthesis of (±)-Deethylibophyllidine: The First Approach.[24] According to our synthetic plan we

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(12) (a) Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4750−4757. (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299−6312.

(13) This name was suggested by Prof. B. M. Trost, see: Ohnuma, T.; Tabe, M.; Shiiya, K.; Ban, Y.; Date, T. *Tetrahedron Lett.* **1983**, *24*, 4249−4252.

(14) Dolby, L. J.; Sakai, S. *J. Am. Chem. Soc.* **1964**, *86*, 5362−5363.

(15) The most significant methods in this field are depicted in the following figure.

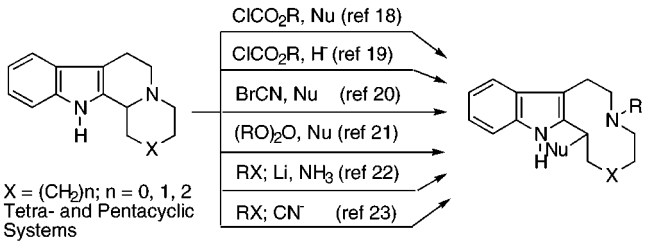

Figure 1.

(16) For a review on synthetic approaches to anticancer alkaloids, using this type of cleavage, see: Atta-ur-Rahman, Iqbal, Z.; Nasir, H. *Stud. Nat. Prod. Chem.* **1994**, *14*, 805−884.

(17) For reviews about the synthesis of medium sized rings by ring expansion reactions, see: (a) Hesse, M. *Ring Enlargement in Organic Synthesis*; VHC: Weinheim, 1991. (b) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749−10784.

(18) (a) Sakai, S.; Yamanaka, E.; Dolby, L. J. *Heterocycles* **1976**, *4*, 981−984. (b) Calverley, M. J.; Harley-Mason, J.; Quarrie, S. A.; Edwards, P. D. *Tetrahedron* **1981**, *37*, 1547−1556. (c) Liu, C.; Sun, S.; Yu, Q. *J. Org. Chem.* **1983**, *48*, 44−47. (d) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327−1336. (e) Schill, G.; Priester, C. U.; Windhövel U. F.; Fritz, H. *Tetrahedron* **1990**, *46*, 1211−1220 and previous papers in this series. (f) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232−10245. (g) Takayama, H.; Tominaga, Y.; Kitajuma, M.; Aimi, N.; Sakai, S.-I. *J. Org. Chem.* **1994**, *59*, 4381−4385 and previous papers in this series. (h) Mahboobi, S.; Wagner, W.; Burgemeister, T.; Wiegrebe, S. *Arch. Pharm. (Weinheim)* **1994**, *327*, 463−465. Mahboobi, S.; Wagner, W.; Burgemeister, T. *Arch. Pharm. (Weinheim)* **1995**, *328*, 371−376.

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(22) For ring cleavage of indolo[2,3-*a*]quinolizidine N_b-metho salts by an alkali metal in ammonia, see: (a) Harley-Mason, J.; Atta-ur-Rahman, Beisler, J. A. *J. Chem. Soc., Chem. Commun.* **1966**, 743. (b) Herbst, D.; Rees, R.; Hughes, G. A.; Smith, H. *J. Med. Chem.* **1966**, *9*, 864−868. (c) Dolby, L. J.; Gribble, G. W. *J. Org. Chem.* **1967**, *32*, 1391−1398. For the same procedure with other heterocyclic related systems, see (d) Wenkert, E.; Garratt, S.; Dave, K. G. *Can. J. Chem.* **1964**, *42*, 489−490. (e) Kutney, J. P.; Abdurahman, N.; Le Quesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1966**, *88*, 3656−3657. (f) Kutney, J. P.; Beck, J.; Bylsma, F.; Cook, J.; Cretney, W. J.; Fuji, K.; Imhof, R.; Treasurywala, A. M. *Helv. Chim. Acta* **1975**, *58*, 1690−1719 and preceding paper. (g) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881−884. (h) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517−521.

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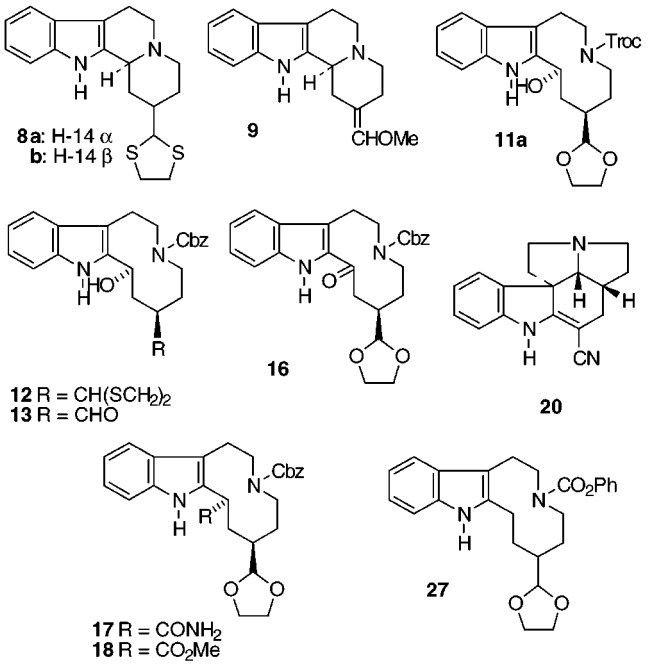

Figure 2.

needed as starting material the indoloquinolizine **6**, which was synthesized by a slight modification of the protocol described by Massiot,[25] who used the method developed by Joule[26] for the synthesis of octahydroindolo-[2,3-*a*]quinolizines by means of acid isomerization of tetrahydropyridine derivatives with an electron-withdrawing substituent at C-4. Compound **6** is available from the pyridinium salt **4** through $NaBH_4$ reduction and acetic acid treatment of the tetrahydropyridine **5**. The latter process brought about deprotection of the acetal function, isomerization of the double bond, which gave an enamine, and cyclization via an iminium ion. Aldehyde **6** was isolated as a 7:2 mixture of epimers and, without purification, was protected as an ethylene acetal using Amberlyst-15[27] or $BF_3{\cdot}Et_2O$[28] as the catalyst. The resulting acetals **7a** and **7b** were separated by column chromatography (the first in this reaction sequence). Although this separation is not strictly necessary from the synthetic standpoint, since C-16 (corresponding to C-12b in the indolo[2,3-*a*]quinolizidine system) is not a stereogenic center in the final product, it is convenient from the practical point of view due to the slightly different reactivity of both epimers (see below).

To test the following ring cleavage, thioacetals **8** and enol ether **9**[29] were also prepared (Figure 2). Interestingly, the *trans*-indoloquinolizine **6b** shows different conformational behavior from **7b** and **8b**. The preferred conformation of aldehyde **6b** was trans (C/D juncture), while that of acetal **7b**, as well as thioacetal **8b**, was cis (see Table 1 for ^{13}C NMR data).[31]

Acetals **7a** and **7b** were independently submitted to C/D ring cleavage with benzyl chloroformate and excess water in THF in the presence of Na_2CO_3[18e] to stereospecifically give the respective epimeric alcohols **10a** (72%) and **10b** (40%). The stereochemical assignment for **10a** was based upon a comparison of its ^{13}C NMR data with those of a model compound lacking the substituent at C-14 and possessing the same CBC conformation for the azecino ring on the basis of the diagnostic ^1H NMR upfield shift of the proton H-15 (δ 0.55).[32] The relative configuration of **10a** also agrees with mechanistic considerations.[18b]

When the ring cleavage was effected with chloroformates other than benzyl, such as vinyl, *p*-nitrophenyl, or α,α,α-trichloroacetyl, the yields were lower, the 54% yield of carbamate **11a** in the Sakai conditions (MgO, TrocCl)[18g] being the most significant. Using other starting materials for this cleavage, the seco derivative **12** was isolated from thioacetal **8a** in 30% yield, and azecinoindole **13** was isolated operating from aldehyde **6** or enol ether **9**, in 10% and 40% yields, respectively. Clearly, these results are lower than those observed in the acetal series, and as a consequence acetal **10a** was chosen as the advanced intermediate for the final steps.

For the introduction of the additional carbon (C-22), alcohol **10a** was converted to the corresponding acetate **14a** (92%) and then treated with NaCN in DMSO.[33] A nearly equimolecular mixture of epimeric nitriles **15** (88%) was obtained, thus suggesting that the S_N1 process is preponderant.[34] Operating in a similar manner from alcohol **10b**, a mixture of nitriles **15** was also obtained, although in lower overall yield (40%). Attempts to obtain esters **18** from nitriles **15**, via amides **17** (i, H_2O_2, NaOH; ii, MeOH, Amberlyst-15), resulted in low yield. When we attempted this conversion in acid medium,[35] to our pleasant surprise we found a transformation that additionally overcomes the crucial difficulty of the synthesis, involving the simultaneous formation of rings CDE by an intramolecular Pictet−Spengler reaction. The alkaloid deethylibophyllidine, which was identified by comparison with a sample prepared by an alternative route,[7] was directly obtained. Thus, when the mixture of nitriles **15** was treated with HCl in methanol, followed by in situ acid hydrolysis, a double transannular cyclization took place satisfactorily leading to a 1:1 mixture of **1** and **19** in a combined yield of 60%. This expeditious

(24) (a) Prior syntheses of (±)-deethylibophyllidine: refs 4a, 5a, 6a, and 7. (b) For a preliminary account of this part of the work, see: Fernàndez, J. C.; Valls, N.; Bosch, J.; Bonjoch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 2317−2318.

(25) Massiot, G.; Cherif, A. *Bull. Soc. Chim. Fr.* **1990**, 648−655.

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(27) Stenberg, V. I.; Vesley, G. F.; Kubik, D. *J. Org. Chem.* **1971**, *36*, 6, 2550−2551.

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(29) Compound **9** was prepared from octahydroindolo[2,3-*a*]quinolizine-2-one[30] by a Wittig-type process [$(C_6H_5)_2POCH_2OCH_3$, LDA] as described in the Supporting Information.

(30) Synthesized from either Szántay or Kuehne protocol: (a) Blaskó, G.; Honty, K.; Novák, L.; Szántay, C. *Acta Chim. Acad. Sci. Hung.* **1979**, *99*, 35−41. (b) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701−2712.

(31) For conformational analysis of 2-substituted octahydroindolo-[2,3-*a*]quinolizines, see: Lounasmaa, M.; Jokela, R. *Tetrahedron* **1989**, *45*, 3975−3991.

(32) The NMR spectra of all octahydroazecinoindoles synthesized in this work are very complicated due to the conformational flexibility of medium sized rings and the duplicity of signals caused by the restricted rotation of the carbamate bond. For a conformational analysis of simple octahydroazecino[5,4-*b*]indoles, see: Bonjoch, J.; Fernàndez, J.-C.; Valls, N. *Eur. J. Org. Chem.*, submitted to be published.

(33) Dadson, B. A.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1969**, 665.

(34) In one run with longer reaction times (24 h), ketone **16** was formed.

(35) For conversion of nitriles to methyl esters, via imidates, see: (a) Mandal, A. N.; Raychaudhuri, S. R.; Chatterjee, A. *Synthesis* **1983**, 727−729. (b) Brussee, J.; Loos, W. T.; Kruse, C. G.; Van Der Gen, A. *Tetrahedron* **1990**, *46*, 979−986.

Table 1. ^{13}C NMR of Octahydroindolo[2,3-*a*]quinolizines (δ ppm, $CDCl_3$)[a]

	C-1	C-2	C-3	C-4	C-6	C-7	C-7a	C-7b	C-8	C-9	C-10	C-11	C-11a	C-12a	C-12b	other	other
6a[b]	29.3	48.3	25.3	54.4	52.9	21.6	108.2	127.1	118.1	119.3	121.3	110.9	136.1	134.1	58.7	203.3	
6b[c]	28.2	44.8	24.5	53.4	51.7	21.0									56.4	204.7	
7a	30.7	40.3	26.9	54.8	53.1	21.7	108.1	127.3	118.1	119.3	121.3	110.7	136.0	134.7	59.1	65.0	106.8
7b	29.1	35.5	26.5	47.7	52.2	19.0	108.0	127.5	118.0	119.3	121.3	110.8	135.7	133.7	54.3	64.9[d]	105.8
8a	35.1	44.0	31.4	55.1	52.8	21.6	108.1	127.3	118.1	119.3	121.3	110.8	135.9	134.4	59.4	38.4	59.4
8b	33.1	39.8	30.7	46.5	51.3	18.1	108.0	127.4	118.0	119.5	121.5	111.0	135.8	132.7	53.9	38.4	58.0
9	29.3	113.4	29.3	56.2	52.9	21.4	107.9	127.1	117.9	119.0	121.0	111.7	135.9	134.6	59.3	140.3	59.5
25a-1[e]	30.7	35.9	20.2	64.2	51.7	17.6	101.0	125.0	117.9	119.7	122.7	111.6	136.4	129.0	64.7	64.9	104.0
25a-2[f]	22.6	37.3	20.6	62.3	61.4	17.5	104.2	125.9	118.6	119.6	122.2	111.9	136.6	127.9	66.0	64.7[d]	104.8
32a-1[g]	31.3	35.7	23.0	76.4	45.9	17.3	102.0	125.0	118.2	119.7	122.5	111.7	136.1	129.6	66.8	64.8	103.9

[a] Values for compounds **6a**, **7a**, **7b**, **8a**, and **8b** were assigned on the basis of HMQC spectra. [b] See also ref 25. [c] Values taken from an NMR spectrum of a mixture of **6a** and **6b**. [d] Two peaks. [e] In $CDCl_3$ + CD_3OD: NMe δ 49.9. [f] In DMSO-d_6: NMe δ 37.4. [g] Et: δ 11.6, 24.6. NMe: δ 47.4.

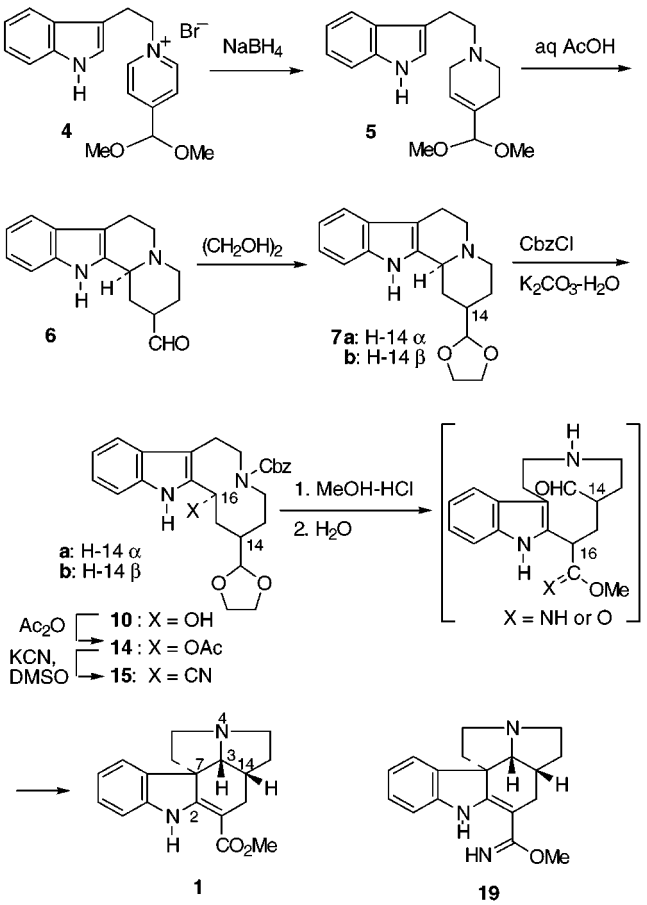
one-pot transformation involves seven chemical processes: formation of an imidate from the cyano group, cleavage of the carbamate protecting group, hydrolysis of the acetal, generation of an iminium salt, hydrolysis of the imidate, and finally, cyclization upon the substituted indole β-position with isomerization of the resulting indolenine double bond to give the α-anilinoacrylate moiety. It is worth mentioning the isolation of the pentacyclic imidate **19** (a vinylogous *O*-methylurea), which could not be further hydrolyzed[36] to deethylibophyllidine, thus suggesting that hydrolysis of the imidate occurs before cyclization.

A Different Tactic. A Second Way to (±)-Deethylibophyllidine. As we have mentioned in the Introduction, a second tactic with a *crisscross* strategy (via b, Scheme 2) to achieve the synthesis of (±)-deethylibophyllidine can also be envisaged. Although the reductive cleavage of **7a** (CbzCl, $NaCNBH_3$)[19d] allowed us to obtain the azecinoindole **21** in only 27% yield, this intermediate was obtained in improved yield by reduction ($NaCNBH_3$, AcOH) of the hydroxy derivative **10a** (Scheme 4).

The formation of the required protected indole **22** was achieved in good yield (95%) using LDA as a base and methyl cyanoformate as the acylating agent. The methoxycarbonyl group not only ensures the stability of the product in the cyclization step but will also allow the elaboration of the anilinoacrylate moiety in the last stage of the synthesis. On the contrary, the deactivation of the nucleophilicity of the indole nucleus did not allow the double ring closure (**22** → **24**) at room temperature in the same conditions used in the first series (**15** → **1**). The best results for the tandem intramolecular iminium salt formation/Pictet−Spengler cyclization were obtained when azecinoindole **23**[37] was treated with TFA at toluene reflux temperature. Under these experimental conditions the crucial quaternary center at C-7 was formed in a satisfactory manner and the pentacyclic derivative **24** was obtained in high yield. The final stage in the synthesis involving the rearrangement of the methoxycarbonyl group to give (±)-deethylibophyllidine has been previously described in our laboratory.[7]

Synthetic Studies toward (±)-Ibophyllidine. After successful results in the deethyl series, we became interested in developing, using the same strategy, the synthesis of more complex alkaloids with the same skeletal-type and bearing a C-20 substituent.[3,38] Attempts to induce the C/D ring cleavage reaction with benzyl chloroformate and excess water in tetrahydrofuran in the presence of sodium carbonate on the mixture of amino acetals **31**[39] were unsuccessful. The unreactivity of **31** is probably due to the fact that the nitrogen is rather more hindered than in **7**, probably by the steric crowding on the nitrogen atom exerted by the adjacent ethyl group. At this point, to obtain the required azecino[5,4-*b*]indole system, we chose a method that implied in the first instance the irreversible formation of a carbon−nitrogen bond instead of the reversible formation that

Scheme 3. Synthesis of (±)-Deethylibophyllidine



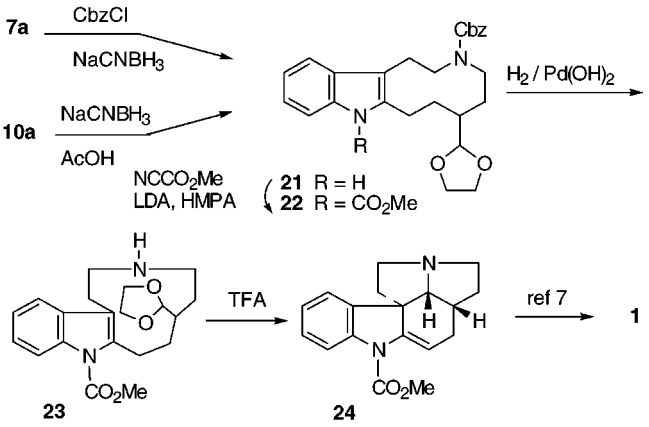
(36) For an alkaloid related to **19** with the same stability under hydrolysis, see: Nuzillard, J.-M.; Thépenier, P.; Jacquier, M.-J.; Massiot, G.; Le Men-Olivier, L.; Delaude, C. *Phytochemistry* **1996**, *43*, 897−902.

(37) The removal of the benzyloxycarbonyl group in **22** by means of hydrogenation was reluctant and the secondary amine **23** was only isolated in 35% yield (no other reagents were tested to attempt this decarbamation).

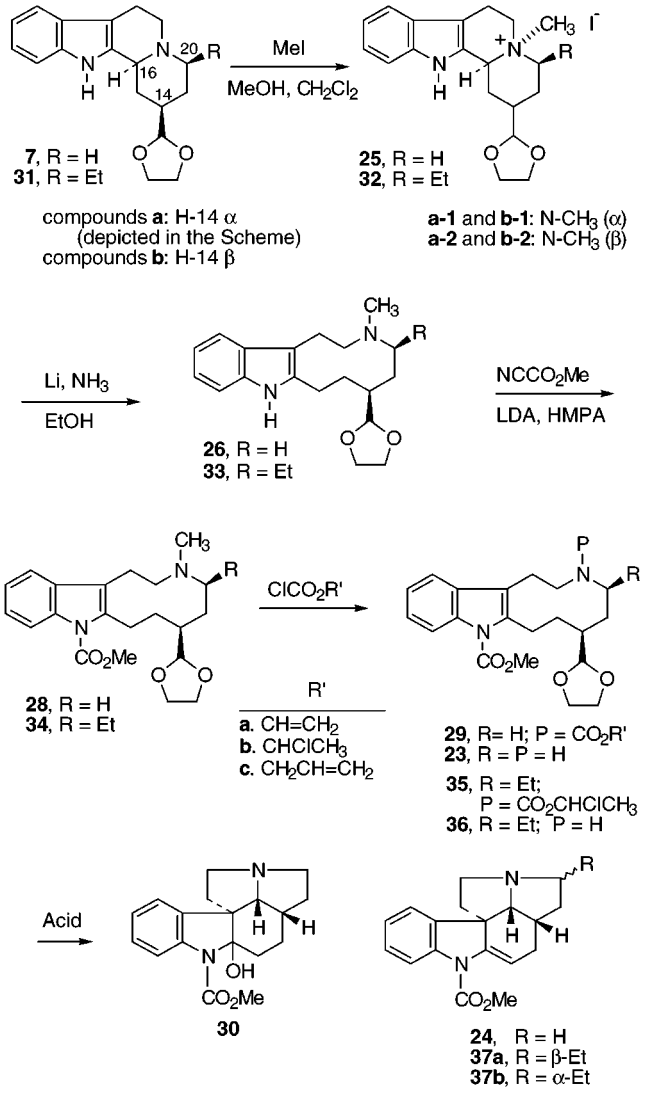
(38) Ibophyllidine and 20-epiibophyllidine: Husson, H.-P.; Jacquemin, H.; Kan, S.-K.; Lounasmaa, M. *Tetrahedron Lett.* **1980**, *21*, 55−58.

(39) Bonjoch, J.; Fernàndez, J.-C.; Terricabras, D.; Valls, N. *Tetrahedron* **1997**, *53*, 9407−9414.

Scheme 4. Synthesis of (±)-Deethylibophyllidine



Scheme 5. Studies in the Synthesis of (±)-20-Epiibophyllidine



occurs in the carbamate path. Thus, we focused on the reductive cleavage of a substrate possessing a quaternary ammonium salt functionality.[22] To test the feasibility of this procedure, we initially carried out a model study in the deethylibophyllidine series (Scheme 5).

Treatment of amine **7a** with methyl iodide yielded in nearly quantitative yield a mixture of epimers **25a-1** and **25a-2** in a 7:3 ratio.[40,41] When the ammonium salts **25a-1** and **25a-2** were treated with Li in ammonia, the C/D ring cleavage occurred satisfactorily,[42] giving the azecinoindole **26**, from which we needed to remove the *N*-alkyl substituent to pursue the synthesis. To ensure a greater stability for the indole nucleus, the indole nitrogen of **26** was first protected as an *N*(1)-methoxycarbonyl derivative.[43] Treatment of amine **28** with vinyl chloroformate provided the carbamate **29a**, which, by means of treatment with hydrogen chloride and then methanol at reflux, gave the secondary amine **23**, which had been converted into target compound **1**, as shown in Scheme 4. The best results for the demethylation process of **28** and double ring closure were obtained working in a one-pot sequence in which amine **28** was treated wirth α-chloroethyl chloroformate, the resulting carbamate **29b** was heated at methanol reflux, and the secondary amine **23** was heated overnight with TFA−MeOH. This process gave in 55% overall yield a mixture of pentacyclic deivatives **24** and **30**,[44] the latter, under dehydration conditions, quantitatively rendering the enecarbamate **24**, which had been converted to deethylibohyllidine such as has been indicated previously.

With these good results, we attempted to repeat the sequence starting from indoloquinolizidine **31a**,[39,45] which incorporates an ethyl substituent in the C-20 biogenetic position. Treatment of **31a** with methyl iodide furnished a mixture of metho salts, **32a-1** being the major isomer as can be inferred from NMR data (δ 3.26 and 47.4 for the *N*-Me group), indicating that the *N*-methyl group and the H-16 are in a cis relationship.[40] Reduction of **32** with Li in ammonia furnished a 5:1 mixture of **33a** and **33b**, after the usual reoxidation step (see Experimental Section). After N(1)-methoxycarbonylation as above, we attempted the demethylation process. Both **34a** and **34b** were considered a priori to be good substrates for conversion into ibophyllidine alkaloids. However, the reluctance shown by these tertiary amines toward demethylation at N(4) made clear that the sequence would not work.[46] Under usual conditions, **34** failed to react with chloroformates, due to the low nucleophilicity of the nitrogen atom, or suffered decomposition processes. After exhaustive attempts to induce demethylation in **34** using several types of chloroformates, only α-chloroethyl chloroformate gave a significant result operating without solvent and with long reaction times. When the crude **35** thus obtained was heated at methanol reflux and then treated with trifluoroacetic acid in toluene at reflux, we could isolate in 8% overall yield a mixture of ibophylli-

(40) For the stereoselectivity in the preparation of indolo[2,3-*a*]-quinolizidine N_b-metho salts and NMR data of these compounds, see: Lounasmaa, M.; Tamminen, T. *Heterocycles* **1991**, *32*, 1527−1535.

(41) When the same reaction was carried out with **7b** a mixture of **25b-1** and **25b-2** was obtained (6:1 ratio, 89% overall yield, see Supporting Information).

(42) To obtain a pure indolo derivative **26**, the crude reaction mixture, in which a dihydroindole derivative appeared, was kept in an oxygen atmosphere in order to reoxidize the over-reduced product.

(43) Attempts to form the carbamate from the unprotected indole **26** operating with several chloroformates gave lower yields, the best result being with phenyl chloroformate, which gave carbamate **27** in 36% yield.

(44) The same compound **30** was isolated in 33% overall yield when allyl chloroformate **29c** was treated initially with $Pd(PPh_3)_4$/AcOH, Bu_3SnH/CH_2Cl_2, and then with 1 N aqeous HCl.

(45) Accompanied by a low percentatge of **31b** and other isomers, all of them synthetically useful.

(46) For some examples of steric hindrance in dealkylation processes via carbamates, see: (a) Torisawa, Y.; Nakagawa, M.; Hosaka, T.; Tanabe, K.; Lai, Z.; Ogata, K.; Nakata, T.; Oishi, T.; Hino, T. *J. Org. Chem.* **1992**, *57*, 5741−5747. (b) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797−11810.

dine-type pentacyclic derivatives **37a** and **37b**, in 9:1 ratio determined by GC-MS analysis.[47] Unfortunately, this process was erratic and did not give enough material to complete the synthesis of 20-epiibophyllidine (**3**). At this point, we decided not to pursue this line of research any longer, concluding that the ring-opening/reclosure strategy starting from octahydroindoloquinolizines does not appear amenable for the synthesis of members of the ibophyllidine family other than **1**.[48]

In summary, total syntheses of (±)-deethylibophyllidine (**1**) are described, proceeding in eight steps (Scheme 3) or nine steps (Scheme 5) from the dimethyl acetal of 4-pyridinecarbaldehyde with nearly 6% overall yield in both cases, results similar to those derived from our first approach.[7] We were unable to extend our crisscross annulation strategy to the synthesis of crowded compounds leading to 20-substituted alkaloids.

Experimental Section

General. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 50.3 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. NMR peak assignments are given only when they are derived from definitive two-dimensional NMR experiments. The ^{13}C NMR spectra, when an unambiguous assignation was not available, are reported as follows: chemical shift (multiplicity determined from DEPT spectra). Only noteworthy IR absorptions (cm^{-1}) are listed. TLC plates were visualized with UV illumination and then developed with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230−400 mesh ASTM) unless otherwise noted. 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 and HRMS were performed by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

4-(Dimethoxy)methyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine (5). To a solution of 4-(dimethoxy)methyl-1-[2-(3-indolyl)ethyl]pyridinium bromide (**4**)[39] (23.5 g, 65 mmol) in MeOH (150 mL) was added $NaBH_4$ (1.3 g, 32 mmol) portionwise at room temperature. Additional $NaBH_4$ (650 mg, 16 mmol) was added three times at 2 h intervals, and 30 min after the last addition, the solvent was evaporated, H_2O (100 mL) was added, and the aqueous basic solution was extracted with $CHCl_3$ (3 × 75 mL). The organic extracts were washed with brine, dried, and concentrated to give, in a quantitative form (19.2 g), the tetrahydropyridine **5**, whose NMR data are the same as those previously reported.[39]

***cis*- and *trans*-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine-2-carbaldehyde (6a and 6b).** A solution of tetrahydropyridine **5** (19 g, 63 mmol) in 30% aqueous AcOH (350 mL) was heated at reflux overnight and then concentrated. The residue was dissolved with CH_2Cl_2, and the mixture was basified with 2 N aqueous NaOH in an ice bath. The organic layer was separated off, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated to give 12.8 g (80%) of crude **6** as a brown solid, which was used for the next reaction without purification. An analytical sample of a mixture of aldehydes **6a** and **6b** (3:1 ratio by ^{1}H NMR analysis) was obtained by chromatography (Florisil, EtOAc): R_f 0.45 (Al_2O_3, 1:1 hexane/EtOAc); mp 115−120 °C; IR (KBr) 3400, 2810, 2735, 1719, 1717. For the major isomer **6a**: ^{1}H NMR (500 MHz, COSY) 1.60 (q, J = 12.5 Hz, 1H, H-1_{ax}), 1.77 (qd, J = 12.5, 4.5 Hz, 1H, H-3_{ax}), 2.03 (d, J = 12.5 Hz, 1H, H-3_{eq}), 2.36 (d, J = 12.5 Hz, 1H, H-1_{eq}), 2.44 (m, 1H, H-2_{ax}), 2.49 (td, J = 12, 4.5 Hz, 1H, H-4_{ax}), 2.67 (m, 1H, H-6_{ax}), 2.74 (br d, J = 17 Hz, 1H, H-7_{eq}), 2.98 (m, 1H, H-7_{ax}), 3.11 (dd, J = 10, 5 Hz, 1H, H-6_{eq}), 3.16 (br d, J = 12 Hz, 1H, H-4_{eq}), 3.32 (br d, J = 10.5 Hz 1H, H-12b), 7.07 (td, J = 7.5, 1 Hz, 1H, H-9), 7.13 (td, J = 7.5, 1 Hz, 1H, H-10), 7.30 (d, J = 7.5 Hz, 1H, H-11), 7.44 (d, J = 7.5 Hz, 1H, H-8), 7.90 (br s, 1H, NH), 9.64 (s, 1H, CHO). Minor signals for the minor isomer **6b** were also observed in the ^{1}H NMR spectrum: 3.43 (brd, J = 10.5 Hz 1H, H-12b), 7.92 (brs, 1H, NH), 9.74 (s, 1H, CHO); ^{13}C NMR, Table 1; HRMS calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1430.

***cis*- and *trans*-2-[2-(1,3-Dioxolanyl)]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (7a and 7b). Method A.** A solution of crude **6** (254 mg, 1 mmol) in glacial AcOH (6.5 mL) and ethylene glycol (0.45 mL, 8 mmol) was warmed at 35−40 °C. Then, freshly distilled $BF_3{\cdot}Et_2O$ (0.63 mL, 5 mmol) was added slowly. The mixture was stirred at room temperature for 15 min. $CHCl_3$ (30 mL) was added to the resulting suspension, and the mixture was basified with 2 N aqueous NaOH. The organic layer was separated off, and the aqueous layer was extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were washed with brine, dried, evaporated, and chromatographed (Al_2O_3). On elution with EtOAc, **7a** (146 mg, 48%) was obtained as a yellowish solid. On elution with 5% MeOH in EtOAc, **7b** (40 mg, 13%) was isolated as a brown solid.

7a: mp 150−152 °C; R_f 0.7 (Al_2O_3, EtOAc); IR (KBr) 3400, 2809, 2747 (Bohlmann bands); ^{1}H NMR (500 MHz, COSY) 1.39 (q, J = 12.5 Hz, 1H, H-1_{ax}), 1.59 (qd, J = 12, 4 Hz, 1H, H-3_{ax}), 1.75 (m, 1H, H-2_{ax}), 1.78 (brd, J = 12 Hz, 1H, H-3_{eq}), 2.14 (qd, J = 12.5, 2.5 Hz, 1H, H-1_{eq}), 2.34 (td, J = 12, 2.5 Hz, 1H, H-4_{ax}), 2.55 (td, J = 11.5, 4.5 Hz, 1H, H-6_{ax}), 2.65 (brd, J = 15 Hz, 1H, H-7_{eq}), 2.93 (m, 1H, H-7_{ax}), 3.03 (m, 2H, H-6_{eq} and H-4_{eq}), 3.17 (brd, J = 10.5 Hz, 1H, H-12b), 3.81−3.93 (m, OCH_2), 4.59 (d, J = 5.5 Hz, 1H, OCHO), 7.00 (td, J = 7.5, 1 Hz, 1H, H-9), 7.05 (td, J = 7.5, 1 Hz, 1H, H-10), 7.20 (d, J = 7.5 Hz, 1H, H-11), 7.39 (d, J = 7.5 Hz, 1H, H-8), 7.80 (br s, 1H, NH); ^{13}C NMR, Table 1. HRMS calcd for $C_{18}H_{22}N_2O_2$ 298.1681, found 298.1687. **7b**: TLC R_f = 0.2 (Al_2O_3, EtOAc); IR (KBr) 3407; ^{1}H NMR (500 MHz, COSY) 1.68 (m, 1H, H-2_{ax}), 1.70 (qd, J = 9, 3 Hz, 1H, H-3_{ax}), 1.81 (m, 1H, H-3_{eq}), 2.07 (dd, J = 6, 5 Hz, 1H, H-1_{ax}), 2.14 (qd, J = 12.5, 2.5 Hz, 1H, H-1_{eq}), 2.63 (d, J = 17 Hz, 1H, H-7_{ax}), 2.73 (m, 1H, H-4_{ax}), 2.81 (m, 1H, H-4_{eq}), 3.01 (m, 2H, H-6_{ax} and H-7_{eq}), 3.01 (m, 1H,), 3.22 (dd, J = 12, 6 Hz, 1H, H-6_{eq}), 3.81−3.93 (m, OCH_2), 4.18 (brd, J = 10.5 Hz 1H, H-12b), 4.81 (d, J = 5.5 Hz, 1H, OCHO), 7.07 (td, J = 7.5, 1 Hz, 1H, H-9), 7.12 (td, J = 7.5, 1 Hz, 1H, H-10), 7.31 (d, J = 7.5 Hz, 1H, H-11), 7.44 (d, J = 7.5 Hz, 1H, H-8), 8.14 (br s, 1H, NH); ^{13}C NMR, Table 1; HRMS calcd for $C_{18}H_{22}N_2O_2$ 298.1681, found 298.1671.

Method B. To a solution of crude **6** (3 g, 11.8 mmol) in ethylene glycol (20 mL) were added Amberlyst 15 (3 g; activated previously under reduced pressure at 100 °C) and anhydrous calcium chloride (2 g, 13 mmol; activated previously under reduced pressure at 200 °C). The mixture was stirred at 31 °C for 3 days. CH_2Cl_2 (50 mL) was added, and after stirrring for 10 min the mixture was basified with 2 N aqueous NaOH and filtered through cotton, washing copiously with CH_2Cl_2 (10 × 75 mL). The two phases were separated, and the organic phase was washed with brine, dried, and concentrated. The residue was chromatographed (Al_2O_3, CH_2Cl_2) yielding 1.24 g (35%) of **7a** and 328 mg (10%) of **7b** (45% overall yield).

(6*RS*,8*RS*)-3-Benzyloxycarbonyl-6-[2-(1,3-dioxolanyl)]-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indol-8-ol (10a). To a solution of **7a** (260 mg, 0.9 mmol) in THF (20 mL) was added Na_2CO_3 (462 mg, 4.4 mmol). The solution was cooled to 0 °C, and benzyl chloroformate (0.4 mL, 2.75 mmol) was introduced dropwise. The mixture was stirred for 1 h at 0 °C and for 1 h at room temperature· H_2O (2.2 mL, 120 mmol) was added, and the mixture was warmed to 50 °C. Three hours later, the addition of reagents was repeated in the same

(47) As occurs in the 20-epiibophyllidine syntheses,[4b,5] the stereoselectivity observed in this cyclization can be ascribed to selective addition of the indole to the iminium salt intermediate of the D ring on the side which is not shielded by the ethyl substituent.

(48) It has been noted that our early strategy[7] did not allow access to these alkaloids either: Bonjoch, J.; Catena, J.; Terricabras, D.; Fernàndez, J.-C.; López-Canet, M.; Valls, N. *Tetrahedron: Asymmetry* **1997**, *8*, 3143−3151.

Table 2. ^{13}C NMR of Octahydroazecino[5,4-*b*]indoles (δ ppm, $CDCl_3$)[a]

	10a	10b	12a	13	14a	14b	15a	15b	17a	18a	21	22	23	26	28	29a	34a	34b
C-1	25.4	24.9	25.2	17.6	25.1	25.4	25.4	25.7	24.4	24.6	24.7	25.1	24.3	22.9	23.5	25.0	24.2	22.9
C-2	50.7	48.9	51.2	46,3	50.3	48.4	50.5	48.5	51.9	52.3	50.0	48.2	46.4	51.1	55.4	48.5	51.5	51.5
C-4	47.7	47.9	47.8	44.9	48.2	48.4	47.8	48.1	47.5	47.6	48.3	47.9	45.2	56.0	51.2	48.0	65.7	54.8
C-5	27.0	28.1	31.6	29.2	26.9	28.0	27.5	26.2	27.6	27.6	27.6	27.7	30.0	28.5	29.0	27.6	32.6	33.3
C-6	35.0	35.0	37.1	23.8	35.4	34.6	29.2	34.6	38.0	38.1	38.8	38.2	35.3	34.2	35.1	38.6	37.1	33.7
C-7	36.2	33.8	38.5	38.4	33.5	32.0	32.3	31.3	31.2	31.9	27.6	26.6	27.2	29.6	28.9	27.1	29.0	29.7
C-8	67.6	66.4	67.1	66.6	69.7	67.5	29.2	27.5	43.4	43.1	25.6	26.0	24.9	24.2	25.5	26.0	24.6	25.4
C-8a	136.1	134.9	136.2	135.2	133.4	132.4	136.2	136.0	133.1	131.6	135.8	135.7	136.2	135.2	136.2	135.9	136.1	136.3
C-9a	137.4	136.9	137.1	136.2	136.8	136.0	136.2	136.0	136.8	137.0	135.8	138.8	137.5	135.7	136.9	137.6	137.4	136.9
C-10	111.2	110.8	111.0	110.7	110.0	110.9	111.2	111.1	111.2	111.1	110.4	115.7	115.7	110.2	115.5	115.8	115.5	115.5
C-11	122.1	121.1	121.9	121.8	122.6	122.2	123.0	121.6	121.8	122.3	121.2	123.7	123.6	120.6	123.5	123.9	123.4	123.4
C-12	119.1	119.2	118.9	119.7	119.4	119.6	119.9	119.7	119.0	119.4	119.0	122.6	122.7	118.6	122.4	122.8	122.4	122.4
C-13	118.3	118.6	118.2	118.7	118.7	119.3	118.6	119.4	118.0	118.3	118.2	118.2	118.4	117.8	118.0	118.2	117.8	118.0
C-13a	127.3	128.8	127.1	128.0	127.2	127.6	127.2	127.0	127.2	127.6	128.0	129.5	129.4	128.4	129.9	129.5	130.6	129.8
C-13b	111.6	111.1	113.3	111.5	112.9	111.1	113.3	111.7	112.3	111.1	111.7	110.3	117.7	111.1	118.9	117.8	119.3	119.2
C−C(6)	106.2	106.1	59.1	201.2	106.4	105.6	105.7	105.1	106.0	106.6	106.6	106.6	107.8	108.3	108.4	106.9	108.3	108.8
other	*b,c*	*b,c*	*b,d*	*b*	*b,c,e*	*b,c,e*	*b,c,f*	*b,c,f*	*b,c,g*	*b,c,h*	*b,c*	*b,c,i*	*c,i*	*c,j*	*c,i,j*	*c,i,k*	*c,i,l*	*c,i,m*

[a] Values for compounds **10a**, **12a**, **14a**, **28**, and **29a** were assigned on the basis of HMQC spectra. All compounds, except **26**, **28**, and **34**, show duplicate signals. In this table the values corresponding to the major rotamer have been indicated. [b] CO_2CH_2Ar: δ 156.8 (±0.8), 66.8 (±0.7). [c] OCH_2: δ 64.9 (±0.2). [d] SCH_2: 38.4. [e] OAc: δ 169.6 (±0.1), 21.0. [f] CN: δ 119.8. [g] $CONH_2$: δ 176.1. [h] CO_2Me: δ 174.4, 52.3. [i] NCO_2Me: δ 152.3 (±0.1), 53.3 (±0.1). [j] NMe: 43.6 (±0.2). [k] $CO_2CH{=}CH_2$: δ 153.8, 142.4, 95.1. [l] Et: δ 12.3, 22.3. NMe: δ 35.4. [m] Et: δ 12.3, 20.6. NMe: δ 35.4.

quantities, and the stirring was maintained at 50 °C for 2 h. The solvent was evaporated, $CHCl_3$ was added, and the resulting solution was washed with 2 N aqueous NaOH, brine, dried, and concentrated to give a residue that was purified by chromatography. On elution with 95:5 CH_2Cl_2−EtOAc, alcohol **10a** (286 mg, 73%) was obtained as a yellowish solid: R_f 0.75 (4% MeOH in EtOAc); mp 168−170 °C; IR (KBr) 3408, 3340, 1677; ^1H NMR (500 MHz, COSY) 0.55 (t, J = 14 Hz, 1H, H-5), 1.10 (tm, J = 16 Hz, 1H, H-5), 1.6−1.9 (m, 2H, H-6 and H-7), 2.14 (d, J = 12 Hz, 1H, H-7), 2.31 (t, J = 11 Hz, 1H, H-4), 2.6−2.9 (m, 2H, H-2 and H-1), 3.0−3.2 (m, 1H, H-1), 3.6−4.0 (m, 5H, H-4 and OCH_2), 4.2−4.4 (m, 1H, H-2), 4.60 and 4.83 (2 d J = 3 Hz, 1H, OCHO), 4.76 (2 dd, J = 12, 3 Hz, 1H, H-8), 5.08 and 5.12 (2d, J = 14 Hz, 1H each, CH_2Ar), 5.17 (s, CH_2-Ar other rotamer), 7.10 (t, J = 7.1 Hz, 1H, H-12), 7.18 (t, J = 7 Hz, 1H, H-11), 7.3−7.4 (m, 7H), 8.50 (br s, 1H, NH); ^{13}C NMR, Table 2. Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.66; N, 6.22. Found: C, 69.33; H, 6.67; N, 6.16.

Ring Cleavage of 7b. Operating as above, but carrying out the workup with an acid−base treatment of the $CHCl_3$ solution, from acetal **7b** (95 mg, 0.3 mmol), alcohol **10b** was obtained (50 mg, 35%, 50% based on recovered **7b**) as a yellow solid after chromatography (5% EtOAc in CH_2Cl_2). From the acid aqueous phase, after being basified and extracted with $CHCl_3$, 29 mg of **7b** was recovered: R_f 0.75 (4% MeOH in EtOAc); mp 150 °C; IR (KBr) 3400, 3287, 1682; ^1H NMR 1.5−1.9 (m, 2H), 2.04−2.2 (m, 3H), 2.5−3.3 (m, 3H), 3.45 (d, J = 17 Hz, 1H), 3.6−4.0 (m, 5H), 4.05−4.2 (m, 1H), 4.37and 4.68 (br s and d J = 3 Hz,1H), 4.42 and 4.48 (2 brs, 1H), 4.8−5.2 (m, 2H), 7.08 (t, J = 7 Hz, 1H), 7.12 (t, J = 7 Hz, 1H), 7.2−7.4 (m, 6H), 7.50 (d, J = 7 Hz, 1H), 8.70 (br s, 1H); ^{13}C NMR, Table 2. Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.66; N, 6.22. Found: C, 69.47; H, 6.79; N, 6.13.

(6*RS*,8*RS*)-8-Acetoxy-3-benzyloxycarbonyl-6-[2-(1,3-dioxolanyl)]-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (14a). To a solution of **10a** (1.3 g, 2.8 mmol) in CH_2Cl_2 (35 mL) were added DMAP (85.5 mg, 0.7 mmol), pyridine (3.8 mL), and Ac_2O (1.5 mL). After 2 h at room temperature, the excess of reagents was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 1 N HCl and saturated aqueous $NaHCO_3$. The dried organic extract was concentrated and chromatographed (CH_2Cl_2) to give **14a** (1.25 g, 92%) as a white solid: R_f 0.75 (5% EtOAc in CH_2Cl_2); mp 88−90 °C; IR (KBr) 3324, 1736, 1678; ^1H NMR (500 MHz, COSY) 0.69 (t, J = 11.5 Hz, 1H, H-5), 1.36 and 1.20 (2 br d, J = 10.5 Hz, 1H, H-5), 1.80−1.90 (m, 2H, H-6 and H-7), 2.04 (s, 3H, CH_3CO), 2.09−2.10 (td, J = 9, 2.5 Hz, 1H, H-7), 2.55 (dd, J = 8.5, 2.0 Hz, 1H, H-4), 2.86 (t, J = 7 Hz, 1H, H-2), 2.90−3.00 (m, 1H, H-1), 3.10−3.20 (m, 1H, H-1), 3.6−4.0 (m, 5H, H-4 and OCH_2), 4.29−4.36 (m, 1H, H-2), 4.58 and 4.83 (2 br s,1H, OCHO), 5.11−5.24 (m, 2H, CH_2Ar), 5.87 (t, J = 10.5 Hz, 1H, H-8), 7.11 (td, J = 7.0, 4.5 Hz, 1H, H-12), 7.21 (t, J = 7 Hz, 1H, H-11), 7.3−7.4 (m, 7H), 7.46 i 7.51 (2d, J = 8 Hz, 1H, H-13), 8.50 (br s, 1H, NH); ^{13}C NMR, Table 2. Anal. Calcd for $C_{28}H_{32}N_2O_6\cdot{}^1/_4H_2O$: C, 67.67; H, 6.54; N, 5.63. Found: C, 67.65; H, 6.53; N, 5.56.

Acetylation of 10b. Operating as above, from alcohol **10b** (90 mg, 0.2 mmol) was obtained **14b** (65 mg, 66%) as a white solid: R_f 0.72 (5% EtOAc in CH_2Cl_2); mp 80−82 °C; IR (KBr) 3327, 1736, 1682; ^1H NMR 1.47−2.0 (m, 4H), 2.03 (s, 3H), 2.06−2.15 (m, 1H), 2.47−3.45 (m, 4H), 3.6−4.0 (m, 5H), 4.26−4.46 (m, 1H), 4.54 and 4.60 (2 d, J = 12 Hz, 1H), 4.9−5.2 (m, 2H), 6.2−6.3 (m, 1H), 6.9 (t, J = 7 Hz, 1H), 7.09−7.4 (m, 7H), 7.52 (d, J = 7 Hz, 1H), 8.2 (brs, 1H); ^{13}C NMR, Table 2. Anal. Calcd for $C_{28}H_{32}N_2O_6\cdot H_2O$: C, 65.88; H, 6.66; N, 5.49. Found: C, 66.11; H, 6.43; N, 5.45.

3-Benzyloxycarbonyl-6-[2-(1,3-dioxolanyl)]-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole-8-carbonitrile (15). From 14a. A mixture of acetate **14a** (956 mg, 1.9 mmol), NaCN (2.5 g, 50.6 mmol), and NaI (18.2 mg, 0.12 mmol) in DMSO (20 mL) was kept at 90−100 °C for 7 h. After cooling, brine was added and the solution was extracted with CH_2Cl_2. The organic extract was washed with brine, dried, and concentrated to give a residue, which was chromatographed. On elution with CH_2Cl_2 800 mg (88%) of nitriles **15**, in a nearly equimolecular ratio, was obtained as a white solid. R_f(**15a**) 0.41; R_f(**15b**) 0.37 (5% EtOAc in CH_2Cl_2); mp 98−100 °C (of the mixture); IR (KBr) 3307, 2241, 1679−1692. **15a**: ^1H NMR 0.6−0.8 (m, 1H), 1.2−1.8 (m, 1H), 1.7−2.0 (m, 2H), 2.2−2.5 (m, 2H), 2.6−2.8 (m, 2H), 3.1−3.3 (m, 1H), 3.6−4.0 (m, 6H), 4.2−4.4 (m, 1H), 4.55 and 4.80 (2d, J = 3 Hz, 1H), 5.18 (s, 2H), 7.03−7.30 (m, 3H), 7.4−7.5 (m, 6H), 8.60 (brs, 1H); ^{13}C NMR, Table 2. **15b**: ^1H NMR 1.50−1.75 (m, 3H), 1.90−2.05 (m, 1H), 2.3 (t, J = 12.4 Hz, 1H), 2.93−3.01 (m, 2H), 3.12−3.30 (m, 2H), 3.8−4.0 (m, 6H), 4.21(dd, J = 11.3, 4.4 Hz, 1H), 4.45 and 4.56 (t, J = 12.5 Hz, and brs 1H), 4.93 and 4.98 (2s, 2H), 7.0 (t, J = 7 Hz, 1H), 7.1−7.4 (m, 7H), 7.5 (d, J = 7 Hz, 1H), 8.60 (br s, 1H); ^{13}C NMR, Table 2. Anal. Calcd for $C_{27}H_{29}N_3O_4\cdot{}^1/_2H_2O$: C, 69.23; H, 6.41; N, 8.97. Found: C, 69.29; H, 6.41; N, 8.68.

Operating as above from acetate **14b** (56 mg, 0.1 mmol), NaCN (145 mg, 3 mmol), and NaI (1 mg, 0.01 mmol) in DMSO (3 mL), an equimolecular mixture of **15a** and **15b** (30 mg, 70%) was obtained after chromatography.

(±)-Deethylibophyllidine (1). Dry HCl was bubbled through a solution of a mixture of nitriles **15** (67 mg, 0.15 mmol) in MeOH (5 mL) at 0−5 °C until saturation (1 h 30 min). The mixture was then allowed to stand at 4 °C for 16 h and poured into ice/water (20 mL). After standing at room temperature for 1 h 30 min, the mixture was extracted with

CH_2Cl_2 and the aqueous phase was basified at 0 °C with NaOH (pellets) and extracted with CH_2Cl_2 (3 × 50 mL). The organic extract was washed with brine (3 × 50 mL), dried, and concentrated, and the residue was chromatographed. Elution with 5:1 EtOAc−MeOH gave deethylibophyllidine (**1**, 13 mg, 30%) and imidate **19** (12 mg, 29%). IR and ^{1}H and ^{13}C NMR data of (±)-deethylibophyllidine were identical with those we had previously reported.[7] TLC: R_f 0.17 (1:1 EtOAc−MeOH).

Methyl 1,2,2a,3,5,10,11,12a-octahydropyrrolizino[1,7-*cd*]carbazole-4-carboximidate (19): R_f 0.06 (50% MeOH in EtOAc); mp 125 °C (dec); UV (EtOH) λ_{max} (log ϵ) 224 (3.9), 298 (3.1), 328 (2.7); IR (KBr) 3421, 1652, 1605; ^{1}H NMR (500 MHz, COSY) 1.76 (dd, J = 12.5, 5.5 Hz, 1H, H-10$_\beta$), 1.81 (dd, J = 12.5, 5.5 Hz, 1H, H-2$_\alpha$), 1.89 (dd, J = 15, 12 Hz, 1H, H-3$_\alpha$), 2.10 (td, J = 13, 5 Hz, 1H, H-10$_\alpha$), 2.14 (m, 1H, H-2a), 2.20 (td, J = 14, 7 Hz, 1H, H-2$_\beta$), 2.69 (dd, J = 15, 5.5 Hz, 1H, H-3$_\beta$), 2.75 (m, 1H, H-1$_\alpha$), 2.93 (dd, J = 12.5, 7 Hz, 1H, H-11$_\alpha$), 3.45 (t, J = 6 Hz, 1H, H-1$_\beta$), 3.47 (t, J = 5.5 Hz, 1H, H-11$_\beta$), 3.75 (s, 3H, OCH_3), 3.90 (d, J = 7 Hz, 1H, H-12a), 6.78 (d, J = 7.5 Hz, 1H, H-16), 6.83 (td, J = 7.5, 1 Hz, 1H, H-8), 7.12 (td, J = 7.5, 1 Hz, 1H, H-7), 7.35 (dd, J = 7.5, 1 Hz, 1H, H-9); ^{13}C NMR (HMQC) 26.7 (C-3), 31.8 (C-2), 38.5 (C-2a), 3.8 (C-10), 51.5 (OCH_3), 51.8 (C-11), 54.7 (C-1), 56.5 (C-9b), 72.8 (C-12a), 93.2 (C-4), 108.8 (C-6), 120.3 (C-8), 122.5 (C-9), 128.1 (C-7), 135.8 (C-9a), 144.1 (C-5a), 156.5 (O−C=NH). 167.1 (C-4a); HRMS calcd for $C_{18}H_{21}N_3O$ 295.1684, found 295.1687.

In one run, small amounts of **1,2,2a,3,5,10,11,12a-octahydropyrrolizino[1,7-*cd*]carbazole-4-carbonitrile** (**20**) were isolated: IR (KBr) 3390, 2187, 1646, 1614; ^{1}H NMR 1.70 (dd, J = 12.5, 5 Hz, 1H, H-10$_\beta$), 1.80 (dd, J = 11.5, 6 Hz, 1H, H-2$_\alpha$), 1.9−2.2 (m, 4H), 2.38 (dd, J = 13, 4 Hz, 1H), 2.76 (m, 1H, H-1$_\alpha$), 2.94 (dd, J = 12, 7.5 Hz, 1H, H-11$_\alpha$), 3.28−3.40 (m, 2H), 3.80 (d, J = 6.5 Hz, 1H, H-12a), 6.84 (d, J = 7.5 Hz, 1H, H-6), 6.92 (td, J = 7.5, 1 Hz, 1H, H-8), 7.19 (td, J = 7.5, 1 Hz, 1H, H-7), 7.32 (d, J = 7.5, 1H, H-9), 7.43 (br s, 1H, NH); ^{13}C NMR 28.1 (C-3), 31.1 (C-2), 37.8 (C-2a), 38.5 (C-10), 51.6 (C-11), 54.4 (C-1), 56.1 (C-9b), 72.8 (C-12a), 91.0 (C-4), 109.2 (C-6), 119.7 (CN), 121.1 (C-8), 122.3 (C-9), 128.6 (C-7), 135.0 (C-9a), 143.5 (C-5a), 164.8 (C-4a).

3-Benzyloxycarbonyl-6-[2-(1,3-dioxolanyl)]-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (21). Method A. To a cooled (−78 °C) solution of alcohol **10a** (50 mg, 0.1 mmol) in glacial AcOH (1 mL) were added $NaCNBH_3$ (21 mg, 0.3 mmol) and then TFA (0.01 mL, 0.16 mmol). The resulting mixture was stirred at room temperature for 15 min and sequentially basified with 6 N aqueous NaOH and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried, and concentrated, and the residue was chromatographed (CH_2Cl_2) to give **21** (26 mg, 53%) as a yellow solid. On elution with 4:1 CH_2Cl_2−EtOAc, unreacted alcohol **10a** (6 mg, 11%) was recovered. **21:** R_f 0.85 CH_2Cl_2/EtOAc (4:1); mp 72−74 °C; IR (KBr) 3405, 3340, 1676−1682; ^{1}H NMR 1.0−1.3 (m, 1H), 1.3−1.5 (m, 2H), 1.7−1.8 (m, 1H), 1.85−1.99 (m, 1H), 2.55−2.70 (m, 2H), 2.81−3.00 (m, 3H), 3.01−3.15 (m, 1H), 3.6−4.0 (m, 5H), 4.25−4.40 (m, 1H), 4.55 and 4.85 (2 d J = 3 Hz, 1H), 4.70 (brd, J = 15 Hz, 1H), 5.2 (m, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.24−7.49 (m, 7H), 7.84 (br s, 1H); ^{13}C NMR, Table 2. Anal. Calcd for $C_{26}H_{30}N_2O_4 \cdot {}^1/_2H_2O$: C, 70.42; H, 6.99; N, 6.32. Found: C, 70.34; H, 6.92; N, 6.20.

Method B. To a cooled (−78 °C) solution of amine **7a** (100 mg, 0.34 mmol) in THF (10 mL) was slowly added benzyl chloroformate (0.25 mL, 1.7 mmol). The mixture was stirred at −78 °C for 1 h and then 64 mg (1 mmol) of $NaCNBH_3$ in THF (5 mL) was added. After 1 h, the reaction mixture was allowed to warm to room temperature and the stirring was maintained for 16 h. Evaporation of the solvent gave a residue which was stirred with CH_2Cl_2 and filtered. The filtrate was washed with 2 N aqueous NaOH and brine, dried, and concentrated, and the residue was chromatographed (CH_2Cl_2) to give **21** (38 mg, 27%). The starting material as its aminoborane adduct (23 mg, 20%) was also isolated.

3-Benzyloxycarbonyl-6-[2-(1,3-dioxolanyl)]-9-methoxycarbonyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (22). To a solution of indole **21** (100 mg, 0.23 mmol) in a 10:1 mixture of THF−HMPA (3.3 mL) at −78 °C was added LDA (1.5 M in cyclohexane, 0.3 mL, 0.45 mmol). This solution was allowed to warm slowly to room temperature, stirred for 30 min, and returned to −78 °C when methyl cyanoformate (0.1 mL, 1.6 mmol) was added. After 2 h at −78 °C, the ice bath was removed. The temperature was raised to room temperature, and stirring was maintained overnight. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc (3 × 50 mL). The organic phase was washed with brine (10 × 50 mL), dried, and concentrated. Chromatography (CH_2Cl_2) afforded **22** as a pale yellow solid (105 mg. 95%): R_f 0.88 (CH_2Cl_2/EtOAc 4:1); IR (neat) 1736, 1690; ^{1}H NMR 1.15−1.60 (m, 3H), 1.65−1.80 (m, 1H), 1.85−2.01 (m, 1H), 2.50−2.72 (m, 1H), 2.8−3.2 (m, 4H), 3.2−3.5 (m, 1H), 3.6−4.0 (m, 5H), 4.02 (s, 3H), 4.25−4.50 (m, 1H), 4.55 and 4.85 (2 d J = 3 Hz, 1H), 5.0−5.1 (m, 2H), 7.02−7.6 (m, 9H), 8.1 (d, J = 8.5 Hz, 1H); ^{13}C NMR, Table 2. Anal. Calcd for $C_{28}H_{32}N_2O_6$: C, 68.27; H, 6.55; N, 5.68. Found: C, 68.01; H, 6.61; N, 5.59.

6-[2-(1,3-Dioxolanyl)]-9-methoxycarbonyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (23). Benzyl carbamate **22** (86 mg, 0.2 mmol), MeOH (2.5 mL), and activated $Pd(OH)_2$ (18 mg) were stirred under 1 atm of H_2 until the disappearance of the starting compound was observed by TLC (3 days). Additional $Pd(OH)_2$ (8 mg) was added after the second day. The mixture was filtered through Celite, the retained solid was rinsed with MeOH, and the combined solvent was evaporated and the residue chromatographed (2% MeOH in EtOAc) to provide amine **23** (22 mg, 35%) as a yellowish solid: R_f 0.55 EtOAc/ MeOH/TEA (8:2:0.1); IR (Film) 3405, 1735; ^{1}H NMR 1.36−1.63 (m, 5H), 2.30 (ddd, J = 13, 7, 0.8 Hz, 1H), 2.74−2.95 (m, 3H), 3.2−3.4 (m, 2H), 3.74−4.00 (m, 4H), 4.05 (s, 3H), 4.64 (d, J = 3 Hz, 1H), 7.19−7.30 (m, 2H), 7.45 (dd, J = 7.5, 1.5 Hz, 1H), 8.09 (dd, J = 7.5, 1.5 Hz, 1H); ^{13}C NMR, Table 2; HRMS calcd for $C_{20}H_{26}N_2O_4$ 358.1893, found 358.1885.

Methyl 2,4,5,5a,6,7,8,12a-Hexahydro-1*H*-pyrrolizino-[1,7-*cd*]carbazole-8-carboxylate (24). To a solution of **23** (10 mg, 0.03 mmol) in toluene (1 mL) was added TFA (0.02 mL, 0.3 mmol). The mixture was heated at reflux for 9 h. A saturated aqueous Na_2CO_3 solution was added, and the solution was extracted with EtOAc. After concentration, crude **24** (8 mg, 90%) was obtained as a brown solid: R_f 0.5, (Al_2O_3, 3:2:drops CH_2Cl_2/EtOAc/DEA); IR (film) 1717, 1610; ^{1}H NMR (500 MHz, COSY) 1.70 (ddd, J = 12.4, 5.7, 2, H-10$_\beta$), 1.75−1.83 (m, H-2$_\beta$), 1.82 (dt, J = 11.5, 3.2, H-3$_\alpha$), 2.04 (td, J = 11.6, 5.1, H-3$_\beta$), 2.10 (m, H-2a), 2.18 (dd, J = 11.4, 7, H-10$_\alpha$), 2.34 (dddd, J = 14.3, 8.2, 5.2, 1, H-2$_\alpha$), 2.81 (m, H-1$_\alpha$), 2.87 (ddd, J = 12.2, 7.5, 2, H-11$_\alpha$), 3.30 (t, J = 8.5, H-1$_\beta$), 3.32 (td, J = 12, 5.5, H-11$_\beta$), 3.76 (d, J = 6, H-12a), 3.95 (s, CO_2Me), 6.23 (dd, J = 8, 3, H-4), 7.07 (td, J = 7.5, 1, H-7), 7.24 (td, J = 7.5, 1, H-8), 7.34 (dd, J = 7.5, 1, H-9), 7.81 (dd, J = 7.5, 1, H-6); ^{13}C NMR (HMQC) 27.8 (C-2), 32.1 (C-3), 38.1 (C-2a), 40.1 (C-10), 52.1 (C-1), 52.7 (OCH_3), 53.5 (C-9b), 54.6 (C-11), 74.0 (C-12a), 106.5 (C-4), 115.2 (C-6), 122.3 (C-9), 123.7 (C-8), 127.6 (C-7), 137.9 (C9a), 144.3 (C4a), 140.2 (C-5a), 153.1 (CO); HRMS calcd for $C_{18}H_{20}N_2O_2$ 296.1525, found 296.1517. 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.

2-[2-(1,3-Dioxolanyl)]-5-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizinium Iodide (25). To a solution of **7a** (470 mg, 1.6 mmol) in a 1:1 mixture of CH_2Cl_2 and MeOH (4 mL) was added methyl iodide (0.8 mL, 12.6 mmol). The mixture was warmed at 65 °C for 30 min. The metho salt **25a-2** was collected by filtration as a white solid (225 mg, 32%). Concentration of the resulting filtrate and crystallization (EtOH−EtOAc) of the resulting solid gave metho salt **25a-1** (410 mg, 58%). **25a-1**: ^{1}H NMR ($CDCl_3$ + drops of CD_3OD) 1.80 (q, J = 12.5 Hz, 1H), 1.95−2.13 (m, 2H), 2.4−2.6 (m, 2H), 3.19−3.22 (m, 2H), 3.36 (s, 3H), 3.63 (m, 2H), 3.84−4.05 (m, 7H), 4.76 (d, J = 4.8 Hz, 1H), 5.25 (dd, J = 12.5, 2.5 Hz, 1H), 7.05 (td, J = 7.5, 0.5 Hz, 1H), 7.14 (td, J = 7.5, 0.5 Hz, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{25}IN_2O_2$: C, 51.81; H, 5.68; N, 6.36. Found: C, 51.73; H, 5.71; N, 6.29. **25a-2**: mp 280−282 °C; IR (KBr) 3170; ^{1}H NMR (DMSO-d_6) 1.78 (q, J = 12.5 Hz, 1H), 1.95−2.13 (m, 3H), 2.61 (brd, J = 14.5 Hz, 1H), 2.91 (s, 3H), 3.01−3.15 (m, 2H), 3.60−3.79 (m, 3H), 3.84−3.99 (m, 5H),

4.81 (d, J = 5.2 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 7.05 (t, J = 7 Hz, 1H), 7.14 (t, J = 7 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 11.29 (s, 1H); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{25}IN_2O_2$: C, 51.81; H, 5.68; N, 6.36. Found: C, 51.70; H, 5.73; N, 6.31.

From the synthetic standpoint, a mixture of acetals **7a** and **7b** can be used for the preparation of **25** (see Supporting Information).

6-[2-(1,3-Dioxolanyl)]-3-methyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (26). A cold (−78 °C) solution of **25** (181 mg, 0.4 mmol), as a mixture of diastereoisomers, in THF (15 mL), EtOH (0.42 mL), and liquid NH_3 (80 mL) was treated with lithium metal (43 mg, 6.2 mmol) until a blue color persisted. After 15 min, the reaction mixture was allowed to warm to room temperature. After NH_3 was evaporated, the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried, and concentrated. The residue was chromatographed (Al_2O_3, CH_2Cl_2) to give **26** (79 mg, 60%) and a dihydro derivative (26 mg, 20%). The latter was rearomatized by stirring a solution of it in the minimum quantity of CH_2Cl_2 under an oxygen atmosphere (1 day, quantitative). From the aqueous phase of the workup process, the starting material **25** can be recovered by extraction with $CHCl_3$ in a 10−15% yield: R_f 0.83 (Al_2O_3, 3:2 CH_2Cl_2/EtOAc); mp 62 °C; IR (KBr) 3400; ^{1}H NMR 1.19−1.35 (m, 1H), 1.54−1.82 (m, 2H), 1.90−2.10 (m, 3H), 2.06 (s, 3H), 2.50−2.60 (m, 1H), 2.70−3.10 (m, 6H), 3.70−3.90 (m, 4H), 4.59 (d, J = 6 Hz, 1H), 7.01−7.15 (m, 2H), 7.25 (dd, J = 8, 1.5 Hz, 1H), 7.44 (dd, J = 8, 1.5 Hz, 1H), 7.81 (br s, 1H). ^{13}C NMR, Table 2. Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.61; H, 8.28; N, 8.92. Found: C, 72.50; H, 8.28; N, 8.79.

6-[2-(1,3-Dioxolanyl)]-3-methyl-8-metoxycarbonyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (28). Operating as in the preparation of **22**, from indole **26** (190 mg, 0.60 mmol), LDA (0.8 mL, 1.21 mmol), and methyl cyanoformate (0.3 mL, 4 mmol) in a 1:10 mixture of HMPA−THF (3.3 mL), indole **28** (210 mg, 94%) was obtained after chromatography (CH_2Cl_2): R_f 0.25 (3:2 CH_2Cl_2/EtOAc), R_f 0.85 (Al_2O_3, 3:2 CH_2Cl_2/EtOAc); IR (film) 1736; ^{1}H NMR (500 MHz, COSY) 1.12−1.18 (m, 1H, H-5), 1.36−1.43 (m, 1H, H-7), 1.62−1.67 (m, 1H, H-5), 1.82 (t, J = 10 Hz, 1H, H-6), 1.93−1.96 (m, 1H, H-4), 2.06 (s, 3H, NCH_3), 2.20 (ddd, J = 13.5, 6, 1.5 Hz, 1H, H-7), 2.46 (dt, J = 11.5, 3.5 Hz, 1H, H-2), 2.67−2.77 (m, 2H, H-1 and H-4), 2.78−2.87 (m, 2H, H-2 and H-1), 3.07 (dt, J = 14.5, 5 Hz, 1H, H-8), 3.19 (dq, J = 14.5, 3 Hz, 1H, H-8), 3.65−3.80 (m, 4H, OCH_2), 4.01 (s, 3H, OCH_3), 4.49 (d J = 4 Hz, 1H, OCHO), 7.11 (dt, J = 7.5, 1.5 Hz, 1H, H-12), 7.15 (dt, J = 7.5, 1.5 Hz, 1H, H-11), 7.45 (dd, J = 7.5, 0.5 Hz, 1H, H-13), 7.98 (dd, J = 8, 0.5 Hz, 1H, H-10); ^{13}C NMR, Table 2; HRMS calcd for $C_{21}H_{28}N_2O_4$ 372.2049, found 372.2068.

Conversion of Tricyclic Derivative 28 to Pentacyclic-Derivative 24. A. Via Carbamate 29a. Vinyl chloroformate (0.1 mL, 1.1 mmol) was slowly added to amine **28** (40 mg, 0.1 mmol) at room temperature. The mixture was heated at reflux for 24 h and then partitioned between CH_2Cl_2 and 1 N HCl. The organic layer was dried, concentrated, and chromatograped (Al_2O_3, CH_2Cl_2) to give vinyl carbamate **29a** (38 mg, 82%): R_f 0.86 (3:2 CH_2Cl_2/EtOAc); IR (film) 1736, 1712; ^{1}H NMR (500 MHz, COSY) 1.11−1.49 (m, 3H, H-5 and H-7), 1.68 (dt, J = 9, 2 Hz, 1H, H-6), 1.94−2.02 (m, 1H, H-7), 2.59−2.67 (m, 1H, H-4), [2.76 (t, J = 13 Hz), 2.82−2.90 (m), 3.35 (m), 3.38 (m), 5H, H-8, H-1 and H-6], 3.74−3.92 (m, 4H, OCH_2), 4.02 (s, 3H, OCH_3), [4.04 (m) and 4.20 (d, J = 5.5 Hz), 4.3−4.4 (m), 4H, H-4, C=CH_2, H-2)], 4.68 and 4.78 (2 d, J = 4 Hz, 1H, OCHO), 6.95 and 7.13−7.25 (2m, 3H, OCH=C, H-10 and H-11), 7.32 and 7.35 (2dd, J = 7.5, 2 Hz, 1H, H-13), 8.02 (2dd, J = 7.5, 2 Hz, 1H, H-10); ^{13}C NMR, Table 2; HRMS calcd for $C_{23}H_{28}N_2O_6$ 428.1947, found 428.1950.

Dry HCl was bubbled through a solution of **29a** (30 mg, 0.1 mmol) in CH_2Cl_2 (5 mL) for 20 min. After the solution was concentrated, MeOH (2 mL) was added to the residue and the solution was heated at reflux for 30 min. The solvent was removed, the residue was taken up with CH_2Cl_2, and the resulting solution was washed with an aqueous Na_2CO_3 solution. Chromatography (Al_2O_3, CH_2Cl_2) yielded 15 mg (60%) of secondary amine **23** (see above for NMR data).

B. Via Carbamate 29b. 1-Chloroethyl chloroformate (0.6 mL, 5.4 mmol) was added dropwise to compound **28** (200 mg, 0.54 mmol) at room temperature. After being heated at 130 °C for 6 h, the reaction mixture was concentrated, diluted with CH_2Cl_2, and washed with 1 N HCl. After drying and concentration, the resulting solid was dissolved in MeOH (5 mL) and the solution was heated at reflux for 8 h. Without purification, the brownish solid was dissolved in MeOH (2 mL) and TFA (0.2 mL) was added. The resulting mixture was heated at reflux overnight. After being cooled to room temperature, the mixture was basified with aqueous Na_2CO_3 solution and extracted with CH_2Cl_2. Evaporation of the solvents gave a residue that was chromatographed (Al_2O_3, CH_2Cl_2). Initially, starting amine **28** (22 mg) was recovered. Further elution gave methyl didehydrodeethylibophyllidine-1-carboxylate (**24**, 47 mg, 29%), identical in all respects to the previously synthesized from **23**. Finally, methyl 4a-hydroxy-1,2,2a,3,4,4a,5,10,11,12a-decahydropyrrolizino[1,7-*cd*]carbazole-5-carboxylate (**30**, 48 mg, 30%) was obtained: IR (neat) 1698−1702; R_f 0.35; ^{1}H NMR (500 MHz, COSY) 1.36 (t, J = 13 Hz, 1H, H-3$_\alpha$), 1.41 (t, J = 13.5 Hz, 1H, H-4$_\beta$), 1.53 (q, J = 6 Hz, 1H, H-3$_\beta$), 1.83 (dd, J = 12.5, 5 Hz, 1H, H-2$_\beta$), 1.89 (dt, J = 12, 7 Hz, 1H, H-10$_\beta$), 2.01 (sextet, J = 6 Hz, 1H, H-2a), 2.23 (dt, J = 12.5, 7 Hz, 1H, H-2$_\alpha$), 2.28 (m, 1H, H-4$_\alpha$), 2.64 (dddd, J = 12.5, 9, 6, 3.5 Hz, 1H, H-1$_\beta$), 2.77 (m, 1H, H-11$_\beta$), 2.83 (dd, J = 12.2, 5.5, 1H, H-10$_\alpha$), 3.13 (dd, J = 13, 7.5 Hz, 1H, H-1$_\alpha$), 3.14 (dd, J = 12, 8 Hz, 1H, H-11$_\alpha$), 3.89 (s, 3H, OCH_3), 4.05 (d, J = 6.5 Hz, 1H, H-12a), 7.01 (td, J = 7.5, 1 Hz, 1H, H-7), 7.14 (td, J = 7.5, 1.5 Hz, 1H, H-8), 7.24 (dd, J = 7, 0.5 Hz, 1H, H-9), 7.41 (br s, 1H, H-6); ^{13}C NMR (HMQC) 22.8 (C-3), 32.9 (C-4), 35.4 (C-2a), 35.9 (C-2), 42.8 (C-10), 52.3 (C-1), 52.7 (OCH_3), 53.2 (C-9b), 56.0 (C-11), 71.2 (C-12a), 95.2 (C-4a), 114.5 (C-6), 122.8 (C-9), 123.7 (C-8), 127.8 (C-7), 135.1 (C-9a); HRMS calcd for $C_{18}H_{20}N_2O_3$ 314.6304, found 314.1628.

Treatment of **30** (48 mg) with TsOH (1.1 equiv) in a benzene solution at reflux for 1 day with a Dean−Strak apparatus gave ene carbamate **24** (42 mg) in 92% yield.

C. Via Carbamate 29c. A mixture of **28** (60 mg, 0.16 mmol) and allyl chloroformate (0.2 mL, 1.6 mmol) was heated at reflux for 20 h. After evaporation of excess reagent, the residue was taken up on CH_2Cl_2 and the solution washed with 1 N HCl. The dried organic phase was chromatographed (Al_2O_3, CH_2Cl_2) to give carbamate **29c** (38 mg, 54%): R_f 0.87 (3:2 CH_2Cl_2/EtOAc); IR (film) 1736, 1697; ^{1}H NMR 1.18−1.53 (m, 3H), 1.76 (t, J = 9.5 Hz, 1H), 2.04 (q, J = 9.5 Hz, 1H), 2.63−2.69 (m, 1H), 2.78−3.44 (m, 5H), 3.6−4.16 (m, 5H), 4.03 (s, 3H), 4.34−4.47(m, 1H), 4.59 (brs, 2H), 4.72 and 4.85 (2 d, J = 3 Hz, 1H), 5.11−5.34 (m, 2H), 5.72 and 5.92 (2m, 1H), 7.21−7.27 (m, 2H), 7.39 (dd, J = 6.5, 2 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H); ^{13}C NMR (two rotamers) 24.8, 25.3, 25.8, 26.1, 26.5, 26.9, 28.0, 28.7, 37.3, 38.7, 47.4, 48.0, 48.3, 49.8, 53.4, 65.0, 65.9, 66.1, 106.8, 115.8, 117.0, 117.2, 118.3, 118.4, 119.1, 122.7, 122.8, 123.8, 124.0, 129.7, 133.2, 136.0, 137.6, 152.4, 156.9, 156.5; HRMS calcd for $C_{24}H_{30}N_2O_6$ 442.2103, found 442.2106.

To a solution of carbamate **29c** (30 mg, 0.1 mmol), $Pd(PPh_3)_4$ (7.9 mg, 6.8×10^{-3} mmol), and AcOH (0.02 mL, 0.3 mmol) in CH_2Cl_2 (2 mL) was added Bu_3SnH (0.04 mL). After 16 h at room temperature, the solvent was evaporated and the residue partitioned between CH_2Cl_2 and 1 N HCl. The aqueous acid phase, after being washed with ether and hexane, was kept standing for 48 h and then basified with a saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 to give crude **30** (7 mg, 33%). For conversion of **30** to **24**, see above.

2-[2-(1,3-Dioxolanyl)]-4-ethyl-5-methyl-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-*a*]quinolizinium Iodide (32). To a solution of **31a**[39] (474 mg, 1.45 mmol) in the minimum quantity of a 5:1 mixture of CH_2Cl_2 and MeOH was added MeI (0.72 mL, 1.45 mmol). The mixture was heated at 65 °C until the disappearance of the starting compound was observed by TLC (2−3 h). The solvent was evaporated to give, as a dark powder, metho salt **32** (620 mg) as a mixture of diastereoisomers. For the major isomer **32a-1**: ^{1}H NMR 1.08 (t, J = 7 Hz, 3H), 3.23,

(s, 3H), 5.35 (d, J = 12 Hz, 1H); ^{13}C NMR, see Table 1. Anal. Calcd for $C_{21}H_{29}IN_2O_2 \cdot H_2O$: C, 51.85; H, 6.37; N, 5.76. Found: C, 51.85; H, 6.20; N, 5.77.

6-[2-(1,3-Dioxolanyl)]-4-ethyl-3-methyl-8-methoxycarbonyl-2,3,4,5,6,7,8,9-octahydro-1*H*-azecino[5,4-*b*]indole (34). The procedure described above for the preparation of **26** was carried out with crude metho salts **32** (440 mg, 0.9 mmol), this time addying MeOH (1 mL for each mmol of **32**), to afford, after chromatography (Al_2O_3, CH_2Cl_2), **33** (188 mg, 66% overall yield from **31**) as a mixture of epimers. From the aqueous phase of the workup, the starting material **32** can be recovered in a 10−20% yield, by extraction with $CHCl_3$: R_f 0.85 (Al_2O_3, 3:2 CH_2Cl_2/EtOAc); ^{1}H NMR (200 MHz) 0.81 and 0.91 (2t, J = 8 Hz, CH_3), 1.91 and 2.26 (2s, NCH_3), 3.7−3.9 (m, 4H, OCH_2), 4.59 and 4.65 (2 d, J = 6 Hz, OCHO), 7.05−7.15 (m, 2H, H-10 and H-11), 7.26 (d, J = 8 Hz, 1H, H-12), 7.45 (d, J = 8 Hz, 1H, H-9), 7.78 (br s, 1H, NH). The procedure described above for methoxycarbonylation of indole **21** was carried out with indole **33** (320 mg, 0.93 mmol). Chromatography (CH_2Cl_2) afforded 289 mg (79%) of indole **34** as a mixture of epimers in a 4:1 ratio (GC-MS analysis): R_f 0.25 (3:2 CH_2Cl_2/EtOAc); IR (film) 1734. Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 68.74; H, 8.30; N, 6.78.

34a: ^{1}H NMR 0.90 (t, J = 7.3 Hz, 3H), 1.05−1.14 (m, 1H), 1.20−1.60 (m, 4H), 1.78−1.83 (m, 1H), 2.02−2.14 (m, 1H), 2.20−2.32 (m, 1H), 2.27 (s, 3H), 2.60−3.38 (m, 6H), 3.72−3.88 (m, 4H), 4.02 (s, 3H), 4.63 (d, J = 3.8 Hz, 1H) 7.18−7.24 (m, 2H), 7.42 (m, 1H), 8.06 (m, 1H); ^{13}C NMR, Table 2. **34b**: ^{1}H NMR 0.84 (t, J = 7.2 Hz, 3H), 1.92 (s, 3H), 4.02 (s, 3H), 4.55 (d, J = 3.7 Hz, 1H); ^{13}C NMR, Table 2.

Methyl 1-Ethyl-1,2,2a,3,5,10,11,12a-octahydropyrrolizino[1,7-*cd*]carbazole-5-carboxylate (37). 1-Chloroethyl chloroformate (0.24 mL, 2 mmol) was added dropwise to compound **34** (60 mg, 0.15 mmol) at room temperature. After being stirred at 130 °C for 6 h, the reaction mixture was concentrated, taken up with CH_2Cl_2, and washed with 1 N HCl. The organic phase was dried and concentrated. After the residue was dissolved in MeOH (5 mL), the solution was heated at reflux for 5 h. MeOH was removed, toluene (2 mL) and TFA (0.2 mL) were added, and the mixture was heated at reflux for 24 h. After being cooled to room temperature, the mixture was diluted with EtOAc, washed with an aqueous Na_2CO_3 solution, and dried. After concentration, purification by chromatography (Al_2O_3, CH_2Cl_2) gave 20 mg of the starting amine **34** and 4 mg (8%) of **37** as a mixture of diastereomers in a 1:9 ratio, according to a GC-MS analysis: R_f 0.7 (Al_2O_3, 3:2 CH_2Cl_2/EtOAc); IR (film) 1718, 1602. For the major isomer **37a**: ^{1}H NMR (200 MHz) 0.88 (t, J = 7.5 Hz, 3H), 3.95 (s, 3H), 6.23 (dd, J = 8, 3 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.24−7.34 (m, 2H), 7.81 (d, J = 7.5 Hz, 1H); ^{13}C NMR 11.6 (CH_3), 27.1 (CH_2), 29.5 (C-2), 36.9 (C-3), 36.2 (C-2a), 38.9 (C-10), 70.0 (C-1), 53.1 (OCH_3), 51.5 (C-9b), 49.7 (C-11), 74.5 (C-12a), 106.5 (C-4), 115.4 (C-6), 123.6 (C-9), 125.0 (C-8), 129.1 (C-7), 133.7 (C-9a), 141.8 (C-4a), 143.8 (C-5a), 152.9 (CO); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1838, found 324.1823.

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Supporting Information Available: Experimental details for the preparation and characterization data for **8a**, **8b**, **9**, **11a**, **12a, 13**, **17a**, **17b**, **18a**, **18b**, **25b-1**, **25b-2** and **28** and NMR data for **16**. MS data of compounds described in the Experimental Section (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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