Palladium(0)-Catalyzed Heteroarylation of 2- and 3-Indolylzinc Derivatives. An Efficient General Method for the Preparation of (2-Pyridyl)indoles and Their Application to Indole Alkaloid Synthesis

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Palladium(0)-catalyzed coupling of (1-(benzenesulfonyl)-2-indolyl)zinc chloride (**1**) and (1-(*tert*-butyldimethylsilyl)-3-indolyl)zinc chloride (**6**) with diversely substituted (alkyl, methoxy, methoxycarbonyl, nitro, hydroxy) 2-halopyridines gives the corresponding 2- and 3-(2-pyridyl)indoles [**4** and **7** (or **8**), respectively] in excellent yields. A series of other 3-(heteroaryl)indoles (pyrazinyl, furyl, thienyl, indolyl) have been similarly prepared from **6**. The potential of some of these (2-pyridyl)indoles in alkaloid synthesis is demonstrated. Thus, from 2-(2-pyridyl)indole **4b**, a new synthetic entry to the indolo[2,3-*a*]quinolizidine system, involving stereoselective hydrogenation of the pyridine ring with subsequent electrophilic cyclization upon the indole 3-position from an appropriately N_b-substituted 2-(2-piperidyl)indole, is reported. For this purpose, Pummerer cyclizations have been extensively studied. Whereas the indole-unprotected sulfoxide **17** gives the corresponding indoloquinolizidine **19** in low yield and mainly undergoes an abnormal Pummerer cyclization that ultimately leads to sulfide **18**, the N_a-protected sulfoxides **24a** and **24b** afford the respective indoloquinolizidines **25a,b** in 70% yield. On the other hand, the conversion of 3-(2-pyridyl)indole **8k** into tetracyclic ketone **35** by stereoselective hydrogenation, followed by cyclization of the resulting *all-cis*-3-(2-piperidyl)indole **34**, represents a formal synthesis of *Strychnos* alkaloids with the strychnan skeletal type (tubifoline, tubifolidine, 19,20-dihydroakuammicine). A similar conversion of **8j** into nordasycarpidone constitutes a formal synthesis of the alkaloids of the uleine group. Reduction of nordasycarpidone leads to tetracycle **37**, an advanced intermediate in a previous synthesis of tubotaiwine, a *Strychnos* alkaloid with the aspidospermatan skeletal type. Finally, piperidylindole **34** was transformed into tetracycle **41**, an ABDE substructure of akuammiline alkaloids, by a sequence involving the skeletal rearrangement of an intermediate spiroindolenine as the crucial step.

The monoterpenoid indole alkaloids have a common biogenetic origin, being formed from tryptamine or tryptophan and a C_9- or C_{10}-monoterpene moiety derived from secologanin.[1] In spite of the enormous variation in the terpenoid structure of these alkaloids, a close examination reveals that they have some structural features in common. In particular, a 2-piperidyl unit linked to the 2- or 3-position of an indole or modified indole ring (indoline, indolenine) can be recognized in six of the eight different skeletal types of Hesse's classification.[2] For instance, the tetracyclic indolo[2,3-*a*]quinolizidine alkaloids (*e.g.*, corynantheidine) and the pentacyclic alkaloids of the akuammiline group (*e.g.*, strictamine), both of them with the corynanthean skeletal type, incorporate a 2-(2-piperidyl)indole moiety, whereas the tetracyclic alkaloids of the uleine group and the more complex *Strychnos* alkaloids, with either the strychnan (*e.g.*, akuammicine) or the aspidospermatan (*e.g.*, tubotaiwine) skeletal variations, embody a 3-(2-piperidyl)indole fragment (Figure 1).

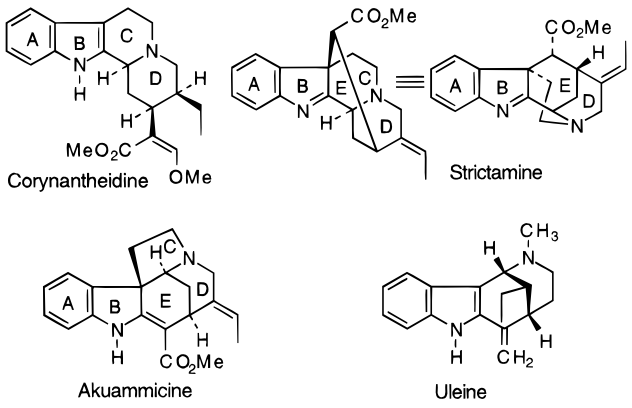

Figure 1.

These similarities prompted us to explore a general synthetic strategy for the synthesis of indole alkaloids from appropriately substituted 2- and 3-(2-piperidyl)-indoles, which, in turn, would be easily accessible by stereoselective reduction of the pyridine ring from the corresponding (2-pyridyl)indoles. Although several methods for the preparation of (2-pyridyl)indoles have been described,[3,4] most of them have some limitations because

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of their low yields, incompatibilities with functional groups, or specific structural requisites. For this reason, in order to develop a simple, general, and efficient methodology for assembling 2- and 3-(2-pyridyl)indoles, we focused our attention on the palladium(0)-catalyzed cross-coupling reactions,[5] in particular on those between halopyridines and *N*-protected 2- and 3-indolylzinc halides,[6] a novel class of indole metal derivatives that, at the beginning of our studies,[7] had received very little attention.[8−10]

The use of palladium complex chemistry has been extensively explored for the synthesis and functionalization of indoles.[11] However, with the exception of a few early examples employing (1-methyl-2-indolyl)lithium[12] or the corresponding magnesio[13] or trialkylborate[14] derivatives, the intermolecular arylation at the 2- and 3-positions of the indole nucleus by Pd-catalyzed cross-coupling reactions of organometal indole derivatives and aryl or heteroaryl halides[15] has only been extensively developed during the last 3 years, using either indolylstannanes[16] or indolylzinc halides.[9,17]

Preparation of *N*-Protected 2- and 3-Indolylzinc Chlorides. Synthesis of 2- and 3-(2-Pyridyl)indoles. For the generation of the required 2- and 3-indolylzinc halides, we selected the procedure based on the transmetalation of the respective lithioindoles. In this manner, 2-indolylzinc chloride **1** was easily attainable by metalation of 1-(benzenesulfonyl)indole with LDA,[18] followed by treatment of the resulting 2-lithioindole with anhydrous $ZnCl_2$. However, attempts to prepare (1-(benzenesulfonyl)-3-indolyl)zinc chloride from the corresponding 3-lithioindole were unsuccessful due to the easy rearrangement of the latter to the 2-lithio isomer.[18−20] For this reason, we decided to use the bulky *tert*-butyldimethylsilyl group as the indole protecting group. It is known that silyl groups bearing bulky alkyl substituents on the silicon atom provide lateral protection of the indole 2-position due to their steric requirements and noncoordinating abilities[21] and that the corresponding 3-lithio-1-silylindoles are stable species, which do not rearrange to the 2-lithio isomers even at room temperature.[22] As expected, the (1-silyl-3-indolyl)zinc derivative **6** could be satisfactorily prepared from 3-bromo-1-(*tert*-butyldimethylsilyl)indole (**5**), by halogen−metal exchange with *tert*-butyllithium, followed by transmetalation of the resulting 3-lithioindole with $ZnCl_2$.

Cross-coupling reactions of **1** and **6** (1.5 equiv) with 2-bromopyridine (**2a**) or 2-chloropyridine (**3a**) in the presence of 2 mol % of a catalyst prepared from $PdCl_2(PPh_3)_2$ and DIBAH (2 equiv) in refluxing THF (Negishi method)[23] afforded the corresponding (2-pyridyl)indoles **4a** and **7a**, respectively, in good yields. Further treatment of the silylated 3-(2-pyridyl)indole **7a** with a refluxing ethanolic solution containing a catalytic amount of *p*-TsOH yielded the deprotected derivative **8a** in nearly quantitative yield. However, from the synthetic standpoint, to avoid partial desilylation during purification by column chromatography, it was more convenient to immediately desilylate the crude reaction mixture as described above. In contrast with the success of direct Pd(0)-catalyzed cross-coupling reactions between chloropyrazines and indoles,[15] 1-(benzenesulfonyl)indole did not react with halopyridines **2a** and **3a** in the presence of $Pd(PPh_3)_4$ (3 mol %) under several reaction conditions.

In order to evaluate the scope of the process, we studied the above cross-coupling reactions with a variety of 2-chloro- and 2-bromopyridines bearing substituents of different electronic nature, either electron-releasing (alkyl, methoxy, hydroxy) or electron-withdrawing (nitro, methoxycarbonyl). The results are given in Table 1. The reaction seems to be general, and the yields ranged from

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(7) (a) This part of the work was presented in a preliminary form at the Eight European Symposium on Organic Chemistry (ESOC-8), Sitges, Spain, August 1993. For preliminary reports, see: (b) Amat, M.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1993**, *34*, 5005. (c) Amat, M.; Hadida, S,; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 793.

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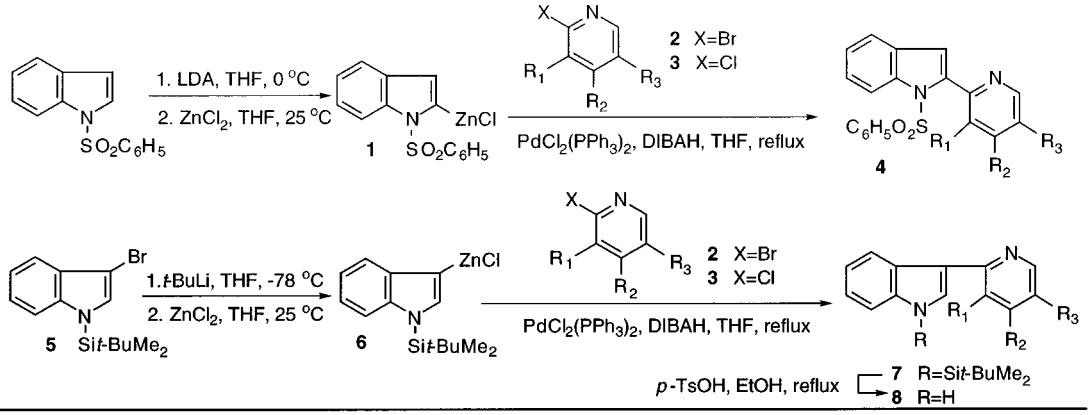
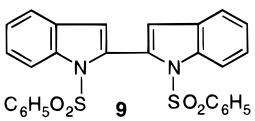
Table 1. The Palladium(0)-Catalyzed Coupling of Indolylzinc Derivatives with Halopyridines

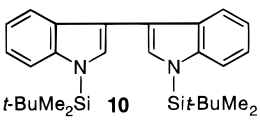


Series	R_1	R_2	R_3	Halopyridine	From 2-indolylzinc **1** 2-(2-Pyridyl)indole (Yield)	From 3-indolylzinc **6** 3-(2-Pyridyl)indole (Yield)
a	H	H	H	**2a**	**4a** (78%)	**8a** (95%)
				3a	**4a** (75%)	**7a** (80%), **8a** (84%)
b	H	Me	H	**2b**	**4b** (92%)	**7b** (93%), **8b** (93%)
				3b	**4b** (40%)	**8b** (52%)
c	Et	Me	H	**2c**	**4c** (94%)	**8c** (88%)
d	H	Me	Et	**2d**	**4d** (89%)	**8d** (89%)
e	OMe	H	H	**2e**	**4e** (80%)	**8e** (77%)
f	OH	H	H	**2f**	**4f** (40%)	**8f** (63%)
g	CO_2Me	H	H	**3g**	**4g** (80%)	**8g** (90%)
h	H	CO_2Me	H	**3h**	**4h** (95%)	**8h** (95%)
i	H	H	CO_2Me	**3i**	**4i** (83%)	**8i** (97%)
j	Et	CO_2Me	H	**3j**		**8j** (42%)[a]
k	H	CO_2Me	Et	**3k**		**8k** (43%)[a]
l	H	H	NO_2	**3l**	**4l** (97%)	**8l** (89%)
m	NO_2	H	NO_2	**3m**	**4m** (70%)	**8m** (80%)

[a] Operating from a 1:1 mixture of halopyridines **3j** and **3k**.

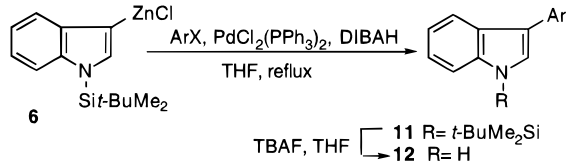
good to excellent. In all cases the corresponding 2,2′- or 3,3′-biindole (**9** and **10**, respectively) was formed in approximately 10−15% yield (based on the starting indole). The most significant conclusions are as follows: (i) in 2-chloropyridines **3**, the presence of an electron-releasing substituent, such as methyl, decreases the yield (entry **b**), whereas with electron-withdrawing substituents (entries **g**−**m**) the cross-coupling products are formed in excellent yield; (ii) in contrast, in the case of 2-bromopyridines **2**, the nature of the substituent on the pyridine ring has practically no effect on the yield (entries **a**−**e**); (iii) there is no substantial difference in the behavior of 2- and 3-indolylzinc halides; (iv) the reaction works in the presence of ester groups (entries **g**−**k**) or acidic protons, although in the latter case the yields are lower (entry **f**).

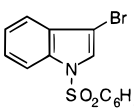




The heteroarylation at the indole 3-position using 3-indolylzinc chloride **6** was extended to heteroaryl halides other than halopyridines, derived from both π-excedent and π-deficient heterocycles (Table 2). Thus, Pd(0)-catalyzed cross-coupling of 2-chloropyrazine and 3-indolylzinc chloride **6**, followed by deprotection of the indole nitrogen as in the above pyridyl series, afforded 3-(pyrazinyl)indole **12a** in 91% yield. However, bromides

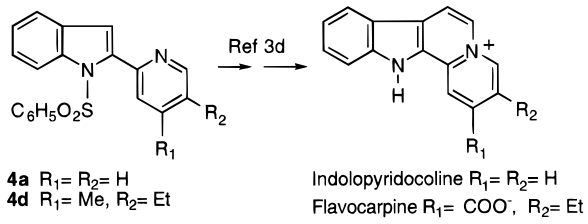
Table 2. The Palladium(0)-Catalyzed Coupling of 3-Indolylzinc 6 with Heteroaryl Halides



ArX	Ar	3-(Heteroaryl)indole **11** (Yield)	**12** (Yield)
	2-pyrazinyl		**12a** (91%)
	2-thienyl	**11b** (50%)	**12b** (78%)
	3-thienyl	**11c** (45%)	**12c** (80%)
	3-furyl	**11d** (12%)	**12d** (65%)
	1-(benzenesulfonyl) -3-indolyl	**11e** (55%)	**12e** (78%)

derived from π-excedent heterocycles such as thiophene, furan, and indole gave lower yields. Moreover, the corresponding 1-silyl-3-(heteroaryl)indoles **11b**−**e** were resistant to hydrolysis under acidic conditions, and in

Scheme 1

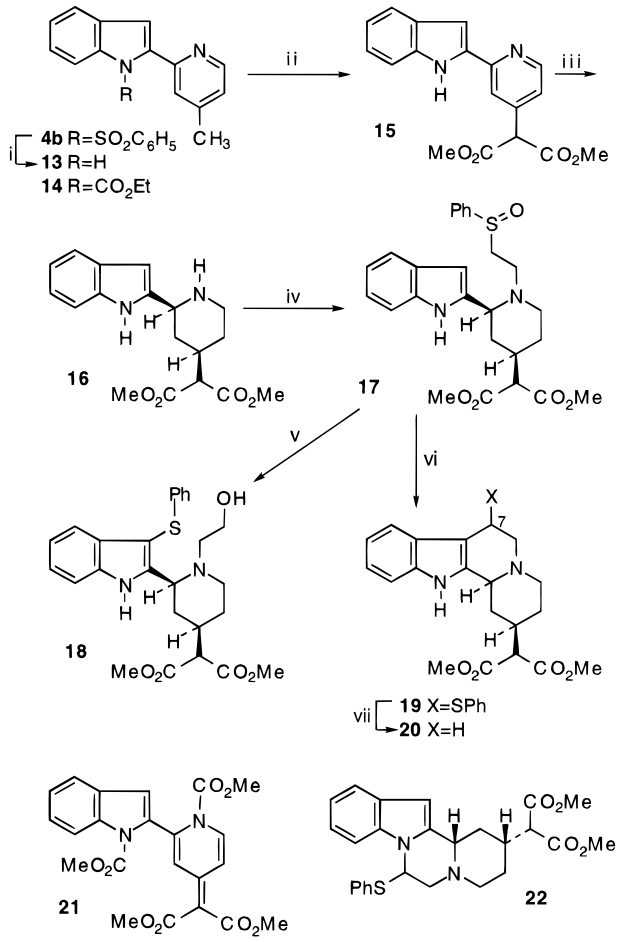


these cases, deprotection of indole had to be carried out, after purification of **11**, by treatment with tetrabutylammonium fluoride.

A New Synthetic Entry to the Indolo[2,3-*a*]quinolizidine System from 2-(2-Pyridyl)indoles. For the construction of the indolo[2,3-*a*]quinolizidine ring system from pyridylindoles **4**, we devised a route involving catalytic hydrogenation of the pyridine ring, introduction of an appropriately functionalized two-carbon chain on the piperidine nitrogen, and finally, closure of ring C by cyclization on the indole 3-position. Although a number of synthetic approaches have been developed for assembling the indolo[2,3-*a*]quinolizidine ring system,[24] the strategy based on the elaboration of ring C by formation of the C_7-C_{7a} bond from 2-(2-piperidyl)indoles has been little explored.[25] A related strategy involving the closure of the C ring by the formation of the N_b-C_6 bond had already been employed[3d] in the conversion of pyridylindoles **4a** and **4b** to the zwitterionic indolo[2,3-*a*]quinolizine alkaloids[26] indolopyridocoline and flavocarpine, respectively (Scheme 1). For the key ring closure we decided to investigate electrophilic cyclizations of thionium ions generated either by Pummerer reaction[27] of a sulfoxide or by treatment of a dithioacetal with dimethyl(methylthio)sulfonium fluoroborate (DMTSF),[28] procedures that we had successfully used in the context of the synthesis of *Strychnos* alkaloids.[29,30]

The required sulfoxide **17** was prepared from pyridylindole **4b** as outlined in Scheme 2. Thus, after deprotection of the indole nucleus and conversion of the methyl group at the pyridine 4-position to a malonate moiety[31] (corresponding to C_{16}, C_{17}, and C_{22} in the biogenetic numbering[32]), the pyridine ring of **15** was stereoselectively hydrogenated to the *cis*-2,4-disubstituted piperidine **16**, which was then treated with phenyl vinyl sulfoxide to afford **17** as an epimeric mixture at the sulfur atom. Both isomers could be easily separated by column chromatography.

Scheme 2[a]



[a] Key: (i) NaOH, H_2O, EtOH, reflux, 96%; (ii) LDA, $ClCO_2Me$, THF, −78 °C, 64%; (iii) H_2, PtO_2, HCl, MeOH, 60%; (iv) $C_6H_5S(O)CH{=}CH_2$, MeOH, reflux, 89%; (v) TFAA, CH_2Cl_2, 25 °C, then chlorobenzene, reflux, 73%; (vi) TFAA, CH_2Cl_2, 25 °C, 20%; (vii) Bu_3SnH, AlBN, benzene, reflux, 72%.

When a solution of amino sulfoxides **17** in CH_2Cl_2 was treated with TFAA at rt, the expected tetracycle **19** (mixture of epimers at C_7) was obtained in only 20% yield. In some runs the secondary amine **16**, resulting from hydrolysis of the exocyclic iminium ion formed through the equilibria thionium ion ⇄ vinyl sulfide (enamine) ⇄ iminium ion, was also isolated.[33] The reversibility of the Pummerer cyclization when the indole ring is not deactivated could favor this undesirable process. To avoid the above *N*-dealkylation, the TFAA-induced Pummerer cyclization was carried out in the presence of either TFA or $BF_3{\cdot}Et_2O$, as it was expected that the formation of a

(24) For reviews, see: (a) Brown, R. T. In *Indoles, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4, Chapter 3. (b) Saxton, J. E. *Ibid*., Chapter 9. (c) Lounasmaa, M.; Tolvanen, A. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4, Chapter 3. (d) Szántay, C. *Ibid*., Chapter 9.

(25) (a) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591. (b) Rubiralta, M.; Diez, A.; Vila, C. *Tetrahedron* **1990**, *46*, 4443.

(26) For a review, see: Gribble, G. W. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed; Elsevier: Amsterdam, 1988; Vol. 1, pp 123−168.

(27) (a) De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157. (b) Grierson, D. S.; Husson, H.-P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed; Pergamon Press: Oxford, 1991; Vol. 6, Chapter 4.7. (c) Kennedy, M.; McKervey, M. A. *Ibid*., Vol. 7, Chapter 2.4.

(28) (a) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. (b) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. (c) Trost, B. M.; Murayama, E. *Tetrahedron Lett.* **1982**, *23*, 1047. (d) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719.

(29) (a) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (b) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792.

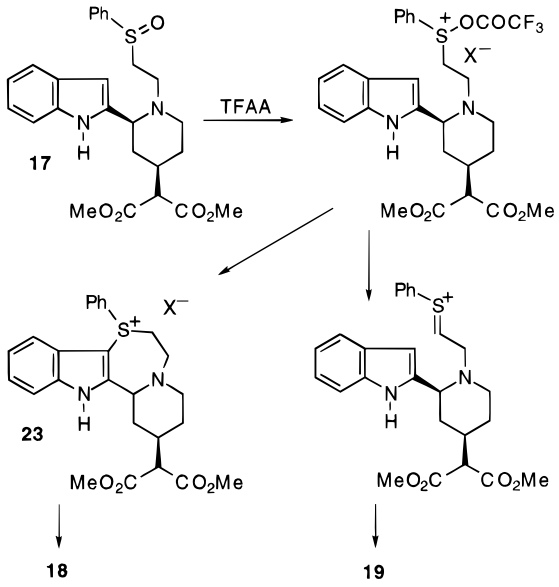
(30) For a preliminary report of this part of the work, see: Amat, M.; Hadida, S.; Sathyanarayana, S; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 3071.

(31) Minor amounts (<5%) of compound **21** were isolated. All attempts to introduce the alkoxycarbonyl substituent from **4b** were unsuccessful. Using NaH and CO_3Et_2 in refluxing toluene, the *N*-ethoxycarbonyl derivative **14** was formed.

(32) Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(33) Similar *N*-dealkylations have been observed from *β*-amino sulfoxides under Pummerer reaction conditions: see ref 29b. For related *N*-dealkylations of aminoacetaldehyde derivatives, see: (a) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. (b) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185. (c) Valls, N.; Segarra, V. M.; Maillo, L. C.; Bosch, J. *Tetrahedron* **1991**, *47*, 1065. (d) Bosch, J.; Salas, M.; Amat, M.; Alvarez, M.; Morgó, I.; Adrover, B. *Tetrahedron* **1991**, *47*, 5269. See also ref 29a.

Scheme 3

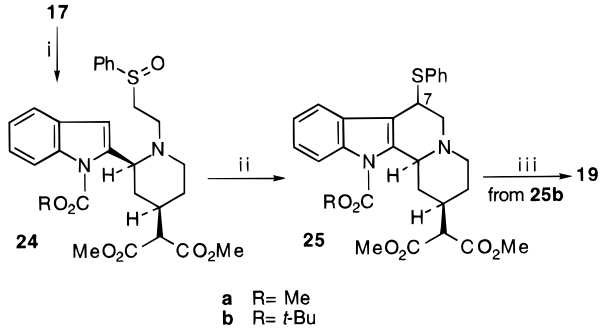


piperidine salt or a piperidine−BF_3 adduct[34] would prevent the formation of the exocyclic iminium ion. However, under these conditions the desired indoloquinolizidine **19** was not isolated.

Surprisingly, when the crude reaction mixture resulting from treatment of **17** under the usual Pummerer reaction conditions (TFAA, rt) was heated in chlorobenzene for 2 h, sulfide **18** was obtained in 73% yield. The use of nonacidic conditions did not improve the situation: TFAA−Hünig's base led to mixtures of **18** (major component) and the secondary amine **16**, whereas TMSOTf−Hünig's base promoted cyclization upon the indole nitrogen to give tetracycles **22** (57% yield; two C_6 epimers). In the latter case, only minor amounts of indoloquinolizidines **19** were detected from the reaction mixture.

Formation of sulfide **18**[35] can be rationalized as depicted in Scheme 3, by considering the nucleophilic displacement of the acyloxy group by the indole ring in the initially formed (acyloxy)sulfonium intermediate to give sulfonium salt **23**, which undergoes a subsequent ring cleavage due to an external nucleophile attack ($CF_3CO_2^-$ or OH^-) on the α-carbon. This process involves the formation of a seven-membered C ring intermediate rather than the expected closure of a six-membered ring by electrophilic cyclization of the intermediate thionium ion on the indole 3-position.[36] In accordance with this interpretation, it was possible to isolate **23** as its conjugate base[37] from the most polar fractions of the chromatographic purification of the crude mixture resulting from the reaction of sulfoxide **17** with TFAA (CH_2Cl_2, rt) and then to transform this material into sulfide **18** by heating it in chlorobenzene in the presence of TFAA.

Scheme 4[a]



[a] Key: (i) $NCCO_2Me$, DMAP, acetonitrile, reflux, ∼85% or $(Boc)_2O$, DMAP, CH_2Cl_2, 25 °C, 97%; (ii) TMSOTf, DIPEA, CH_2Cl_2, 25 °C, ∼70%; (iii) HCO_2H, 25 °C, 65%.

The following two reasons could explain the abnormal course of the above Pummerer reactions: (a) the generation of the thionium ion by abstraction of an α-proton from the (acyloxy)sulfonium intermediate derived from *β-amino* sulfoxide **17** is slower than that in activated sulfoxides such as *β*-keto sulfoxides, (b) the indole ring is not deactivated by an electron-withdrawing group that would diminish its nucleophilic character. Under these circumstances, substitution at the sulfur in the (acyloxy)-sulfonium intermediate by attack of the indole ring is faster than generation of the thionium ion required in the normal Pummerer cyclization.

In order to verify the latter interpretation, we decided to study related Pummerer cyclizations from 2-(2-piperidyl)indoles bearing an electron-withdrawing protecting group on the indole nitrogen. The required *N*-protected sulfoxides **24a** and **24b** were prepared in excellent yields from **17** (Scheme 4) by treatment with methyl cyanoformate and di-*tert*-butyl dicarbonate, respectively, in the presence of DMAP.[38] In fact, this protection could be effected separately for each epimer of the starting sulfoxide **17** to give the two separate epimers at the sulfur atom of both **24a** and **24b**.

Pummerer cyclization of the indole-protected amino sulfoxide **24a** was initially tried with TFAA (4 equiv) in the presence of TFA (4 equiv). Under these conditions indoloquinolizidine **25a** was obtained in 45% yield as a separable mixture of C_7 epimers. The use of TMSOTf in the presence of Hünig's base gave higher yields (∼70%). Similarly, the N_a-Boc sulfoxides **24b** underwent smooth cyclization on treatment with TMSOTf−Hünig's base to give indoloquinolizidine **25b** also in approximately 70% yield (two C_7 epimers). Products arising from either *N*-dealkylation or the above abnormal Pummerer rearrangement were not isolated. In the N_a-Boc series, the use of TFAA−TFA was not successful because of the easy deprotection of the N_a-Boc group under acidic conditions: a mixture of sulfide **18** and indoloquinolizidines

(34) There are very few examples of normal Pummerer cyclizations from *β-amino* sulfoxides: (a) Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932. (b) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1992**, *48*, 7803. (c) Takano, S.; Iida, H.; Inomata, K.; Ogasawara, K. *Heterocycles* **1993**, *35*, 47. (d) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106. See also ref 29b.

(35) For a preliminary communication of this and a related abnormal Pummerer cyclization on the indole ring, see: Amat, M.; Bennasar, M.-L.; Hadida, S.; Sufi, B. A.; Zulaica, E.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 5217.

(36) (a) For a similar migration of an arylthio group to an electron-rich aromatic ring under Pummerer reaction conditions, see: Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1994**, *50*, 13501. For related processes, see: (b) Kaneko, T. *J. Am. Chem. Soc.* **1985**, *107*, 5490. (c) Terauchi, H.; Tanitame, A.; Tada, K.; Nishikawa, Y. *Heterocycles* **1996**, *43*, 1719. (d) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1996**, *61*, 3375. (e) Bravo, P.; Capelli, S.; Meille, S. V.; Seresini, P.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2321.

(37) For the isolation of 3-(dimethylsulfonio)indolides, see: (a) Daves, G. D., Jr.; Anderson, W. R., Jr.; Pickering, M. V. *J. Chem. Soc., Chem. Commun.* **1974**, 301. (b) Hocker, J.; Ley, K.; Merten, R. *Synthesis* **1975**, 334. (c) Park, K. H.; Gray, G. A.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 7475.

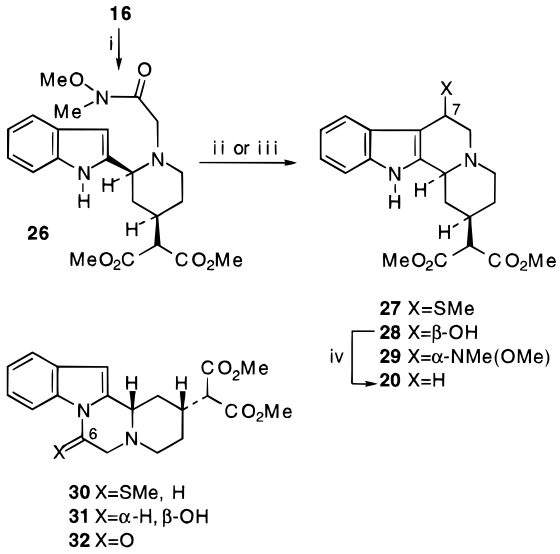
(38) Methoxycarbonylation of **17** under the conditions reported in the preliminary communication ($NCCO_2Me$, NaH, THF, TMDA, 25 °C)[30] gave barely reproducible results, and in most runs, methoxycarbonylation also occurred at the methine carbon of the malonate moiety.

19 and **25b** was obtained. As could be expected, the individual epimeric sulfoxides of each pair **24a-1**/**24a-2** and **24b-1**/**24b-2** behaved similarly under the Pummerer reaction conditions, giving similar C_7 epimeric mixtures of the respective indoloquinolizidines **25a** and **25b**. Deprotection of the indole ring was accomplished by treatment of **25b** with formic acid at room temperature: a nearly equimolecular C_7 epimeric mixture of indoloquinolizidines **19** was obtained starting from either of the two C_7 epimers of **25b**. In accordance with this observation, each C_7 epimer of **19** was separately equilibrated to a 1:1 mixture of C_7 epimers after being stirred in formic acid for 12 h. This epimerization involves protonation at the indole 3-position, followed by cleavage of the C_7-C_{7a} bond and subsequent recyclization of the resulting thionium ion. Finally, desulfurization of **19**, either with Raney Ni or with $Bu_3SnH-AIBN$, led to the known[39] indoloquinolizidine **20**.

The above results not only indicate that the abnormal Pummerer cyclization on the indole 3-position can be avoided if the indole nitrogen bears an electron-withdrawing substituent but also expand the scope of Pummerer cyclizations on the indole ring: this reaction can now be used for the synthesis of *b*-annulated indoles starting from 2-substituted indoles.[40] To our knowledge, the above cyclizations constitute the first examples of synthetically useful Pummerer cyclizations on the indole 3-position in 3-unsubstituted indoles.[41] In contrast, Pummerer cyclizations upon either the indole 2-position[42] or the indole 3-position in 3-substituted indoles[43] have received considerable synthetic attention.

The second method we had planned to study for the construction of the C ring of indolo[2,3-*a*]quinolizidines from 2-(2-piperidyl)indole **16** required the introduction of a 2,2-bis(methylthio)ethyl chain on the piperidine nitrogen. This was attempted by alkylation of **16** with *N*-methoxy-*N*-methylchloroacetamide (Scheme 5), followed by partial reduction of the resulting amide **26** to the corresponding aldehyde[44] and subsequent dithioacetalization. However, when **26** was treated with Red-Al and then with methanethiol in the presence of $BF_3\cdot Et_2O$, a mixture of indoloquinolizidines **27** (17%; two epimers at C_7) and tetracycles **30** (15%; two epimers at C_6) was obtained instead of the expected dithioacetal. Presumably, the intermediate thionium ion formed during dithioacetalization undergoes cyclization, on either C_3 or the nitrogen of the indole ring. When the treatment with methanethiol was omitted, the reduction of **26** led to hydroxyindoloquinolizidine **28** (30%) and tetracyclic alcohol **31** (30%), which arise from cyclization of the initially formed aldehyde, probably promoted by the alane generated during the process.[45] Minor amounts of indoloquinolizidine **29** (12%), formed by cyclization of the intermediate iminium cation generated during the reduction, and lactam **32** (4%) were also isolated. This route was not optimized given the satisfactory results obtained in the above Pummerer cyclizations. Reduction of alcohol **28** with $Et_3SiH-TFA$ gave the same indoloquinolizidine **20** previously prepared from sulfide **19**.

Scheme 5[a]



[a] Key: (i) $ClCH_2CON(OMe)Me$, NaI, K_2CO_3, CH_3CN, 45 °C, 92%; (ii) Red-Al, toluene, THF, −25 °C, then MeSH, $BF_3\cdot Et_2O$, CH_2Cl_2, 0 °C: **27** (17%) and **30** (15%); (iii) Red-Al, toluene, THF, −25 °C: **28** (30%), **29** (12%), **31** (30%), and **32** (4%); (iv) Et_3SiH, TFA, CH_2Cl_2, 70%.

The strategy developed here to build the indolo[2,3-*a*]-quinolizidine system, combined with the flexible method for the preparation of the starting 2-(2-pyridyl)indoles, provides a short, general synthetic entry to this tetracyclic system that may be applicable to the synthesis of *Corynanthe* alkaloids.

Formal Syntheses of Alkaloids of the Uleine and *Strychnos* Groups from 3-(2-Pyridyl)indoles. A common structural feature of the alkaloids of the uleine and *Strychnos* groups, with either the aspidospermatan or the strychnan skeletan type, is the presence of a 3-(2-piperidyl)indole moiety included in a bridged polycyclic system, in which all the piperidine substituents are *cis*. Stereoselective hydrogenation of the pyridine ring of 3-(2-pyridyl)indoles **8j** and **8k**, followed by cyclization of the resulting *all-cis*-3-(2-piperidyl)indoles (**36** and **34**, respectively) would provide rapid access to the hexahydro-1,5-methanoazocino[4,3-*b*]indole system, characteristic of these alkaloids.[46]

The required pyridylindoles **8j** and **8k** had efficiently been obtained (85% overall yield) by Pd(0)-catalyzed heteroarylation of 3-indolylzinc chloride **6** with a 1:1 mixture of methyl 2-chloro-3-(and 5)ethylisonicotinate (**3j** and **3k**, respectively), as indicated in Table 1, followed by chromatographic separation. Alternatively, although less efficiently, they were prepared in approximately 60% overall yield from pyridylindoles **8c** and **8d**, as outlined in Scheme 6, through a four-step sequence involving protection of the indole nucleus as a *N*-benzenesulfonyl derivative, oxidation of the methyl substituent at the pyridine 4-position, deprotection of the indole ring, and, finally, esterification of the resulting isonicotinic acid.[47]

(39) Grierson, D. S.; Vuilhorgne, M.; Husson, H.-P. *J. Org. Chem.* **1982**, *47*, 4439.

(40) For a recent application of these concepts to the synthesis of geissoschizine, see: Bennasar, M.-L.; Jiménez, J.-M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 9105.

(41) For previous unsuccessful attempts, see: Bennasar, M.-L.; Zulaica, E.; Sufi, B. A.; Bosch, J. *Tetrahedron* **1996**, *52*, 8601. See also ref 42.

(42) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118.

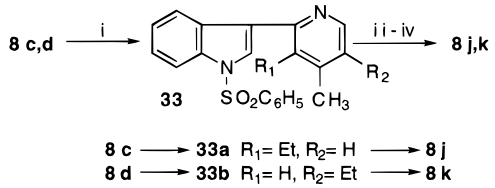
(43) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. See also refs 29b and 34d.

(44) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(45) For related cyclizations of *N*-(2-oxoethyl)piperidine derivatives in the construction of the seven-membered C ring of *Iboga* alkaloids, see: (a) Sundberg, R. J.; Amat, M.; Fernando, A. *J. Org. Chem.* **1987**, *52*, 3151. (b) Sundberg, R. J.; Gadamasetti, K. G. *Tetrahedron* **1991**, *47*, 5673.

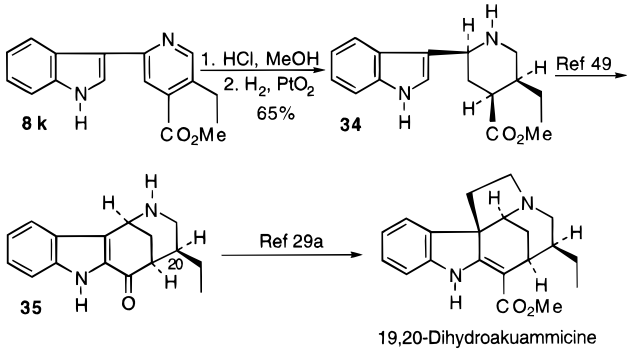
(46) For a preliminary report of this part of the work, see: Amat, M.; Sathyanarayana, S.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 7123.

Scheme 6[a]



[a] Key: (i) $C_6H_5SO_2Cl$, *n*-$Bu_4N^+HSO_4^-$, NaOH, H_2O, benzene, 96%; (ii) SeO_2, pyridine, 95 °C; (iii) NaOH, H_2O, EtOH, reflux; (iv) MeOH, H_2SO_4, ~60% from **33**.

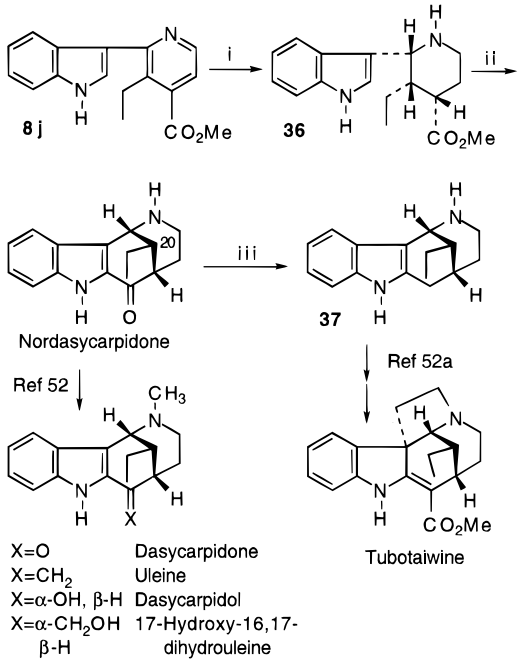
Scheme 7



As expected, catalytic hydrogenation of **8k** hydrochloride stereoselectively provided piperidine **34**, with the natural *all-cis* relative configuration[48] (Scheme 7). The cyclization of piperidine ester **34** to tetracyclic ketone **35**[49,50] and the conversion of **35** to the *Strychnos* alkaloids (strychnan skeletal type) tubifoline, tubifolidine, and 19,20-dihydroakuammicine[29a] by construction of the five-membered C ring had previously been effected in our laboratory.[51]

In a similar way, the 2,3,4-trisubstituted pyridine isomer **8j** was hydrogenated to the *all-cis*-piperidylindole **36**[48] and then cyclized[49a] to the alkaloid nordasycarpidone[4e,50] (Scheme 8). Taking account of previous correlations,[4e,52] this constitutes a formal synthesis of the alkaloids dasycarpidone, dasycarpidol, uleine, and 17-hydroxy-16,17-dihydrouleine as well as a notable improvement on previous syntheses of the alkaloids of the uleine group.[53] On the other hand, $LiAlH_4$ reduction of nordasycarpidone gave tetracycle **37**, from which we have

Scheme 8[a]



[a] Key: (i) HCl, MeOH, then H_2, PtO_2, MeOH, 60%; (ii) $Ba(OH)_2$, H_2O, dioxane, reflux, then PPA, 85−90 °C, 36%; (iii) $LiAlH_4$, dioxane, reflux, 33%.

reported the synthesis of tubotaiwine,[52a] a *Strychnos* alkaloid with the aspidospermatan skeletal type.

In summary, formal total syntheses of alkaloids of the uleine and *Strychnos* groups, the latter belonging to either the strychnan or the aspidospermatan skeletal series, have been accomplished from 3-(2-pyridyl)indoles **8j** and **8k**.

A Synthetic Entry to the Tetracyclic ABDE Core of Akuammiline Alkaloids. The akuammiline alkaloids constitute a subgroup of corynanthean indole alkaloids that remain synthetically inaccessible to date, which are characterized by the presence of a C_7-C_{16} bond,[32] giving an additional ring E.[54] Consequently, they incorporate a 1,5-methanoazocino[3,4-*b*]indole system (rings ABDE) (Figure 1). In order to further illustrate the synthetic potential of the above 3-(2-piperidyl)indoles, *e.g.*, **34**, we decided to study the intramolecular alkylation of the indole nucleus from derivatives bearing a good leaving group on the substituent at the 4-position of the piperidine ring.

$LiAlH_4$ reduction of ester **34**, followed by protection of the piperidine nitrogen with benzyl chloroformate and mesylation of the resulting alcohol **39**, led to the key mesylate **40** in satisfactory overall yield. Treatment of

(47) All attempts to directly oxidize the methyl substituent of **8c** were unsuccessful.

(48) The stereochemical assignment of *all-cis*-piperidines **34** and **36** was effected by comparison of their ^{13}C NMR data with the data of the *cis* and *trans* isomers of methyl 2-(3-indolyl)-4-piperidinecarboxylate: see ref 46.

(49) (a) Amat, M.; Hadida, S.; Llor, N.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 3878. For the cyclization of a mixture of **34** and other stereoisomers, see: (b) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516.

(50) Minor amounts of the C-20 epimer were also isolated. For a detailed discussion of this epimerization and related epimerizations in 3-(2-piperidyl)indoles, see ref 49a.

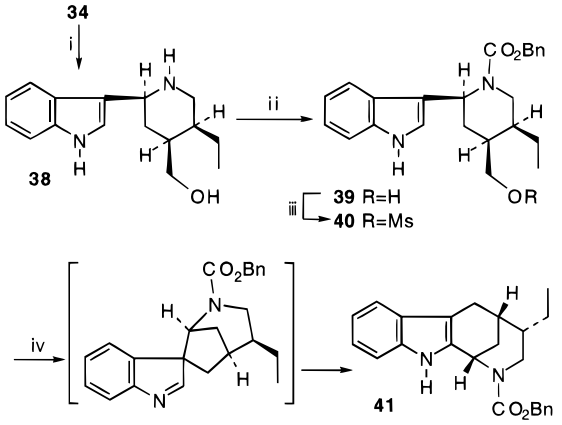
(51) For recent reviews on the *Strychnos* alkaloids, see: (a) Sapi, J.; Massiot, G. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4, Chapter 7. (b) Bosch, J.; Bonjoch, J.; Amat, M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1996; Vol. 48, pp 75−189.

(52) (a) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939. (b) Blechert, S. *Liebigs Ann. Chem.* **1985**, 2073. (c) Borris, R. P.; Lankin, D. C.; Cordell, G. A. *J. Nat. Prod.* **1983**, *46*, 206. (d) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. (C)* **1969**, 2738. (e) Joule, J. A.; Ohashi, M.; Gilbert, B.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1717.

(53) For reviews, see: (a) Joule, J. A. In *Indoles, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4, Chapter 6. (b) Alvarez, M.; Joule, J. A. In *Monoterpenoid Indole Alkaloids;* Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4, Chapter 6.

(54) For reviews, see: (a) Joule, J. A. In *Indoles, The Monoterpenoid Indole Alkaloids:* Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4, pp 244−264. (b) Alvarez, M.; Joule, J. In *Monoterpenoid Indole Alkaloids;* Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4, pp 248−259. For more recent work, see: (c) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239. (d) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 6611.

Scheme 9[a]



[a] Key: (i) $LiAlH_4$, THF, −30 °C, 95%; (ii) $ClCO_2CH_2C_6H_5$, K_2CO_3, $CHCl_3$, 25 °C, 43%; (iii) $MeSO_2Cl$, pyridine, 25 °C, 90%; (iv) *t*-BuOK, THF, 25 °C, 50%.

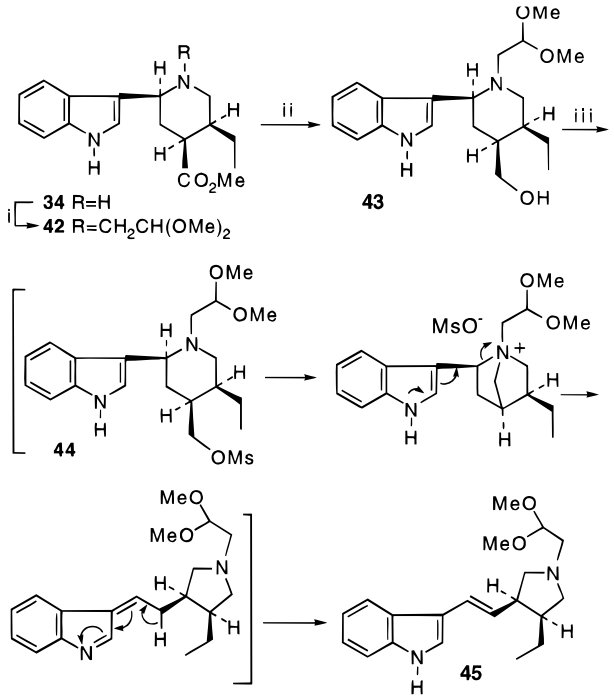
40 with potassium *tert*-butoxide directly afforded the akuammiline-type tetracycle **41** in 50% yield (Scheme 9).[55,56] The isomeric tetracycle with the [4,3-*b*] fusion characteristic of uleine and *Strychnos* alkaloids was not detected. The above result corroborates that the intramolecular alkylation at C_2 in 3-alkylindoles proceeds through the intermediacy of a spiroindolenine, with subsequent Wagner−Meerwein-like 1,2-shifts.[57] The higher migratory aptitude of an aminoalkyl group, as compared with an alkyl group,[58] in the initially formed spiroindolenine, accounts for the observed regioselective formation of **41**.

Protection of the piperidine nitrogen is necessary for the success of this approach to tetracyclic ABDE substructures of akuammiline alkaloids. Thus, attempted preparation of the *N*-alkylpiperidine mesylate **44** (Scheme 10) resulted in the unexpected formation of pyrrolidine **45**. This result can be rationalized by considering an intramolecular alkylation[59] of the piperidine nitrogen in the initially formed mesylate **44**, followed by a gramine-type fragmentation of the resulting quaternary salt involving cleavage of the piperidine ring.

Experimental Section

Melting points were determined in a capillary tube and are uncorrected. NMR spectra were recorded at 200, 300, or 500 MHz (^{1}H) and 50.3 or 75 MHz (^{13}C). Only noteworthy IR absorptions are listed. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck, 0.063−0.200 mm), and the spots were located with iodoplatinate reagent. Column chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.060−0.2 mm). Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.040−0.060 mm). Drying of the organic extracts during the workup of reactions was performed over Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. All compounds were synthesized in the racemic series.

Scheme 10[a]



[a] Key: (i) $BrCH_2CH(OMe)_2$, dioxane, K_2CO_3, NaI, 140 °C, 24h, 81%; (ii) $LiAlH_4$, Et_2O, −30 °C to 25 °C, 90%; (iii) $MeSO_2Cl$, pyridine, 25 °C, 35%.

2-Bromo-3-ethyl-4-methylpyridine (2c) and 2-Bromo-5-ethyl-4-methylpyridine (2d). 3-Ethyl-4-methylpyridine (100 mL, 780 mmol) was slowly added to a suspension of $NaNH_2$ (91 g, 2.3 mmol) in *N*,*N*-dimethylaniline (152 mL), and the resulting mixture was heated at reflux for 12 h. The temperature was lowered to 25 °C, and water (50 mL) was added dropwise. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were dried and concentrated to give an oil. Distillation (106 °C, 3 mmHg) afforded a 1:3 mixture of aminopyridines (56 g, 53%), which were difficult to separate. Column chromatography (hexane−AcOEt, increasing polarity) gave a pure sample of each isomer. **2-Amino-3-ethyl-4-methylpyridine** (minor isomer): IR ($CHCl_3$) 3401 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, J = 7.5 Hz, 3 H), 2.22 (s, 3 H), 2.45 (q, J = 7.5 Hz, 2 H), 4.88 (br s, 2 H), 6.42 (d, J = 5.1 Hz, 1 H), 7.77 (d, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.7 (CH_3), 18.6 (CH_3), 20.1 (CH_2), 116.9 (CH), 120.9 (C), 144.9 (CH), 145.4 (C), 157.3 (C). Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.73; H, 8.53; N, 20.68. **2-Amino-5-ethyl-4-methylpyridine** (major isomer): IR ($CHCl_3$) 3403 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.5 Hz, 3 H), 2.17 (s, 3 H), 2.48 (q, J = 7.5 Hz, 2 H), 4.83 (br s, 2 H), 6.29 (s, 1 H), 7.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 18.4 (CH_3), 22.5 (CH_2), 109.5 (CH), 128.2 (C), 146.6 (CH), 147.0 (C), 157.0 (C); mp 61−62 °C (Et_2O−hexane). Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.66; H, 8.82; N, 20.61. Bromine (11.1 mL, 216 mmol) and a solution of $NaNO_2$ (12.7 g, 184 mmol) in water (28 mL) were added to a solution of the above mixture of aminopyridines (10 g, 73 mmol) in 48% HBr (36 mL) maintained at −10 °C, and the mixture was stirred at this temperature for 1 h 30 min. Then, a solution of NaOH (70 g) in water (100 mL) was added, and the stirring was continued for 1 h at 25 °C. The mixture was extracted with Et_2O, and the organic solution was dried and concentrated to give an oil. Distillation (120 °C, 1 mmHg) afforded a mixture of 2-bromopyridines **2c** and **2d** (14

(55) For a preliminary report on this part of the work, see: Amat, M.; Hadida, S.; Bosch, J. *An. Quim., Int. Ed.* **1996**, *92*, 62.

(56) For precedents on the synthesis of hexahydro-1,5-methanoazocino[3,4-*b*]indoles, see: (a) Dolby, L. J.; Nelson, S. J. *J. Org. Chem.* **1973**, *38*, 2882. (b) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990,** *55*, 1156. See also ref 54c.

(57) (a) Jackson, A. H.; Naidoo, B. *J. Chem. Soc., Perkin Trans. 2* **1973**, 548 and previous papers in this series. (b) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439. (c) Diez, A.; Vila, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta, M. *Tetrahedron Lett.* **1993**, *34*, 733.

(58) For a review, see: Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089.

(59) For related processes, see: (a) Wenkert, E.; Halls, T. D. J.; Kwart, L. D.; Magnusson, G,; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017. (b) Kalaus, G.; Malkieh, N.; Katona, I.; Kajtár-Peredy, M.; Koritsánszky, T.; Kálmán, A.; Szabó, L.; Szántay, C. *J. Org. Chem.* **1985**, *50*, 3760.

g, 96%), which were difficult to separate. Flash chromatography (CH_2Cl_2) gave pure samples of both isomers. **2c**: ^{1}H NMR ($CDCl_3$) δ 1.69 (t, J = 7.5 Hz, 3 H), 2.37 (s, 3 H), 2.80 (q, J = 7.5 Hz, 2 H), 7.02 (d, J = 4.8 Hz, 1 H), 8.04 (d, J = 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3), 19.5 (CH_3), 25.2 (CH_2), 125.2 (CH), 138.9 (C), 144.9 (C), 147.0 (CH), 147.8 (C). Anal. Calcd for $C_8H_{10}NBr$: C, 48.03; H, 5.09; N, 7.00; Br, 39.93. Found: C, 47.82; H, 5.09; N, 6.88; Br, 39.99. **2d**: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.5 Hz, 3 H), 2.28 (s, 3 H), 2.58 (q, J = 7.5 Hz, 2 H), 7.22 (s, 1 H), 8.07 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 18.1 (CH_3), 22.7 (CH_2), 128.5 (CH), 137.2 (C), 139.3 (C), 148.3 (C), 149.1 (CH). Anal. Calcd for $C_8H_{10}NBr\cdot{}^1/_3H_2O$: C, 46.62; H, 5.19; N, 6.79; Br, 39.93. Found: C, 46.60; H, 5.19; N, 6.49.

General Procedure for the Preparation of 2-(2-Pyridyl)indoles 4. A solution of LDA (1.5 M in cyclohexane, 1.1 equiv) was slowly added to a 0.6 M solution of 1-(benzenesulfonyl)indole in anhydrous THF at 0 °C, and the resulting mixture was stirred for 30 min at this temperature. Then, a 0.45 M solution of anhydrous $ZnCl_2$ (it was used after fusion by flame-drying under reduced pressure) (1.1 equiv) in THF was added, and the stirring was continued for 30 min at 25 °C. In a separate flask, a 0.8 M solution of the 2-halopyridine **2** or **3** in anhydrous THF was added to a solution containing 2 mol % of a catalyst prepared by reaction of a 0.027 M solution of $Cl_2Pd(PPh_3)_2$ in anhydrous THF with 2 equiv of diisobutylaluminum hydride (1.0 M in hexane), and the mixture was stirred at 25 °C for 10 min. The resulting solution was transferred via canula to the solution of (1-(benzenesulfonyl)-2-indolyl)zinc chloride (**1**) prepared above. The mixture was heated at reflux for 4 h, cooled, and poured into saturated aqueous Na_2CO_3. The aqueous phase was extracted with Et_2O, and the organic extracts were concentrated to give a residue, which was chromatographed (CH_2Cl_2).

1-(Benzenesulfonyl)-2-(2-pyridyl)indole (4a). Following the above procedure, from 2-bromopyridine (**2a**) (920 mg, 5.8 mmol) and 1-(benzenesulfonyl)indole (2.3 g, 8.7 mmol) were obtained [1,1′-bis(benzenesulfonyl)]-2,2′-biindole[3b] (**9**) (220 mg, 10%) and pyridylindole **4a** (1.5 g, 78%). **4a**:[3d] IR (KBr) 1448, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 1 H), 7.23−7.53 (m, 7 H), 7.68 (dm, J = 7.8 Hz, 2 H), 7.74 (ddd, J = 8.0, 1.7, 1.1 Hz, 1 H), 7.82 (td, J = 8.0, 1.7 Hz, 1 H), 8.23 (d, J = 7.5 Hz, 1 H), 8.71 (ddd, J = 5.0, 1.7, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 114.8 (CH), 115.8 (CH), 121.1 (CH), 122.7 (CH), 124.1 (CH), 125.1 (CH), 125.7 (CH), 126.5 (CH), 128.3 (CH), 129.9 (C), 133.2 (CH), 135.1 (CH), 137.6 (C), 140.7 (C), 148.4 (CH), 150.9 (C). Operating as above, from 2-chloropyridine (**3a**) (660 mg, 5.8 mmol) and 1-(benzenesulfonyl)indole (2.2 g, 8.7 mmol) were obtained dimer **9** (220 mg, 10%) and pyridylindole **4a** (1.45 g, 75%).

1-(Benzenesulfonyl)-2-(4-methyl-2-pyridyl)indole (4b). Following the general procedure, from 2-bromo-4-methylpyridine (**2b**)[60] (700 mg, 4.0 mmol) and 1-(benzenesulfonyl)indole (1.5 g, 6.0 mmol) were obtained **9** (160 mg, 10%) and **4b** (1.3 g, 92%). **4b**: IR (KBr) 1610, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 6.85 (s, 1 H), 7.17 (d, J = 5.0 Hz, 1 H), 7.20−7.35 (m, 5 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.53 (s, 1 H), 7.69 (dm, J = 7.5 Hz, 2 H), 8.20 (d, J = 8.1 Hz, 1 H), 8.54 (d, J = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 115.0 (CH), 116.2 (CH), 121.3 (CH), 124.2 (CH), 124.4 (CH), 125.3 (CH), 127.0 (CH), 128.7 (CH), 130.4 (C), 133.6 (CH), 137.1 (C), 138.1 (C), 141.2 (C), 146.7 (C), 148.6 (CH), 151.2 (C); mp 110 °C (Et_2O). Anal. Calcd for $C_{20}H_{16}N_2S$: C, 68.95; H, 4.63; N, 8.04. Found: C, 68.91; H, 4.63; N, 7.90. Operating as above, from 2-chloro-4-methylpyridine (**3b**)[61] (637 mg, 5.0 mmol) and 1-(benzenesulfonyl)indole (1.9 g, 7.5 mmol) were obtained dimer **9** (194 mg, 10%) and pyridylindole **4b** (700 mg, 40%).

1-(Benzenesulfonyl)-2-(3-ethyl-4-methyl-2-pyridyl)indole (4c). Following the general procedure, from 2-bromo-3-ethyl-4-methylpyridine (**2c**) (500 mg, 2.5 mmol) and 1-(benzenesulfonyl)indole (964 mg, 3.7 mmol) were obtained **9** (106 mg, 11%) and **4c** (884 mg, 94%). **4c**: IR ($CHCl_3$) 1450, 1373, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.5 Hz, 3 H), 2.44 (s, 3 H), 2.67 (q, J = 7.5 Hz, 2 H), 6.68 (s, 1 H), 7.20 (d, J = 4.9 Hz, 1 H), 7.40 (m, 6 H), 7.95 (dm, J = 6.6 Hz, 2 H), 8.12 (d, J = 8.2 Hz, 1 H), 8.41 (d, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 19.0 (CH_3), 22.8 (CH_2), 111.8 (CH), 114.7 (CH), 121.1 (CH), 123.7 (CH), 124.7 (CH), 126.0 (CH), 127.3 (CH), 128.7 (CH), 129.7 (C), 133.5 (C), 135.9 (C), 137.8 (C), 139.0 (C), 139.2 (C), 145.6 (CH), 150.5 (C); mp 136−138 °C (Et_2O−hexane). Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.18; H, 5.35; N, 7.44; S, 8.51. Found: C, 70.16; H, 5.38; N, 7.42; S, 8.52.

1-(Benzenesulfonyl)-2-(5-ethyl-4-methyl-2-pyridyl)indole (4d). Following the general procedure, from 2-bromo-5-ethyl-4-methylpyridine (**2d**) (550 mg, 2.7 mmol) and 1-(benzenesulfonyl)indole (1.1 g, 4.1 mmol) were obtained **9** (100 mg, 10%) and **4d**[3d] (920 mg, 89%). **4d**: IR ($CHCl_3$) 1450, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 2.39 (s, 3 H), 2.72 (q, J = 7.5 Hz, 2 H), 6.83 (s, 1 H), 7.31 (m, 7 H), 7.68 (dm, J = 7.8 Hz, 2 H), 8.18 (d, J = 8.1 Hz, 1 H), 8.42 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 18.6 (CH_3), 23.5 (CH_2), 114.6 (CH), 116.1 (CH), 121.1 (CH), 124.3 (CH), 124.7 (CH), 126.9 (CH), 127.2 (CH), 128.5 (CH), 130.4 (C), 133.4 (CH), 136.9 (C), 137.4 (C), 137.8 (C), 141.2 (C), 144.5 (C), 145.6 (C), 148.0 (CH).

1-(Benzenesulfonyl)-2-(3-methoxy-2-pyridyl)indole (4e). Following the general procedure, from 2-bromo-3-methoxypyridine (**2e**)[62] (940 mg, 5.0 mmol) and 1-(benzenesulfonyl)indole (1.9 g, 7.4 mmol) were obtained **9** (200 mg, 10%) and **4e** (1.5 g, 80%). **4e**: IR (KBr) 1370, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3 H), 6.80 (s, 1 H), 7.15−7.42 (m, 7 H), 7.48 (dm, J = 7.7 Hz, 1 H), 7.73 (dm, 2 H), 8.11 (d, J = 8.1 Hz, 1 H), 8.32 (dd, J = 4.6, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.5 (CH_3), 113.3 (CH), 115.1 (CH), 117.7 (CH), 121.3 (CH), 123.8 (CH), 124.7 (CH), 124.9 (CH), 126.8 (CH), 128.7 (CH), 130.2 (C), 133.4 (CH), 136.7 (C), 137.4 (C), 137.8 (C), 140.5 (CH), 155.5 (C); mp 108 °C (Et_2O). Anal. Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.92; H, 4.43; N, 7.69; S, 8.80. Found: C, 65.90; H, 4.39; N, 7.75; S, 8.55.

1-(Benzenesulfonyl)-2-(3-hydroxy-2-pyridyl)indole (4f). Following the general procedure, from 2-bromo-3-hydroxypyridine (**2f**) (500 mg, 2.9 mmol) and 1-(benzenesulfonyl)indole (1.9 g, 7.4 mmol) were obtained **9** (200 mg, 11%) and **4f** (400 mg, 40%). **4f**: IR (KBr) 3400−3600, 1369, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.74 (s, 1 H), 7.14−7.46 (m, 9 H), 7.70 (dm, J = 8.0 Hz, 2 H), 8.08 (d, J = 8.3 Hz, 1 H), 8.18 (dd, J = 3.9, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 114.7 (CH), 115.2 (CH), 121.4 (C), 123.5 (CH), 123.9 (CH), 125.1 (CH), 126.8 (CH), 128.7 (CH), 130.1 (C), 133.6 (C), 136.5 (C), 136.8 (C), 137.2 (C), 139.5 (C), 153.3 (C); mp 202−203 °C (acetone−hexane). Anal. Calcd for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 8.00; S, 9.15. Found: C, 64.95; H, 4.01; N, 7.87; S, 9.17.

Methyl 2-(1-(Benzenesulfonyl)-2-indolyl)-3-pyridinecarboxylate (4g). Following the general procedure, from methyl 2-chloro-3-pyridinecarboxylate (**3g**)[63] (858 mg, 5.0 mmol) and 1-(benzenesulfonyl)indole (1.9 g, 7.4 mmol) were obtained **9** (180 mg, 9%) and **4g** (1.6 g, 80%). **4g**: IR (KBr) 1723, 1368 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3 H), 6.77 (s, 1 H), 7.20−7.50 (m, 6 H), 7.51 (dd, J = 8.0, 5.0 Hz, 1 H), 7.75 (dm, J = 7.5 Hz, 2 H), 8.08 (d, J = 8.2 Hz, 1 H), 8.40 (dd, J = 8.0, 1.7 Hz, 1 H), 8.84 (dd, J = 5.0, 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.4 (CH_3), 112.7 (CH), 114.5 (CH), 121.3 (CH), 123.3 (CH), 123.7 (CH), 125.0 (CH), 126.9 (CH), 128.8 (CH), 129.6 (C), 133.5 (CH), 136.1 (C), 137.7(C), 138.8 (C), 151.0 (CH), 151.4 (C), 165.6 (C); mp 135 °C (Et_2O). Anal. Calcd for $C_{21}H_{16}N_2O_4S$: C, 64.26; H, 4.11; N, 7.13; S, 8.17. Found: C, 64.87; H, 4.17; N, 7.14; S, 7.89.

Methyl 2-(1-(Benzenesulfonyl)-2-indolyl)-4-pyridinecarboxylate (4h). Following the general procedure, from methyl 2-chloro-4-pyridinecarboxylate (**3h**)[64] (858 mg, 5.0 mmol) and 1-(benzenesulfonyl)indole (1.9 g, 7.4 mmol) were

(60) (a) Bosch, J.; Canals, C.; Granados, R. *An. Quim.* **1978**, *74*, 985. (b) Case, F. H. *J. Am. Chem. Soc.* **1946**, *68*, 2574.

(61) Seide, O. *Chem. Ber.* **1924**, *57*, 791.

(62) **2e** was prepared in nearly quantitative yield by methylation of 2-bromo-3-hydroxypyridine with CH_2N_2.

(63) Esters **3g** and **3i** were prepared by methylation of the corresponding acids with CH_2N_2 in 78% and 95% yields, respectively.

(64) Chloropyridine **3h** was prepared in 95% yield by treatment (reflux, 12 h) of methyl isonicotinate *N*-oxide (4.6 g, 30 mmol)[4d] with $POCl_3$ (11 mL) in $CHCl_3$ (11 mL).

obtained **9** (200 mg, 10%) and **4h** (1.9 g, 95%). **4h**: IR (NaCl) 1732, 1373 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (s, 3 H), 6.92 (s, 1 H), 7.20−7.42 (m, 5 H), 7.48 (dm, J = 7.8 Hz, 1 H), 7.65 (dm, J = 7.5 Hz, 2 H), 7.90 (dd, J = 5.1, 1.5 Hz, 1 H), 8.20 (d, J = 8.1 Hz, 1 H), 8.27 (d, J = 1.5 Hz, 1 H), 8.83 (d, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.7 (CH_3), 115.9 (CH), 116.2 (CH), 121.5 (CH), 122.1 (CH), 124.5 (CH), 125.2 (CH), 125.6 (CH), 126.9 (CH), 128.6 (CH), 130.2 (C), 133.6 (CH), 136.8 (C), 136.9 (C), 138.1 (C), 140.1 (C), 149.6 (CH), 152.3 (C), 165.3 (C); mp 113−115 °C (Et_2O). Anal. Calcd for $C_{21}H_{16}N_2O_4S$: C, 64.26; H, 4.11; N, 7.13; S, 8.17. Found: C, 64.32; H, 4.04; N, 7.19; S, 7.98.

Methyl 2-(1-(Benzenesulfonyl)-2-indolyl)-5-pyridinecarboxylate (4i). Following the general procedure, from methyl 2-chloro-5-pyridinecarboxylate (**3i**)[63] (858 mg, 5.0 mmol) and 1-(benzenesulfonyl)indole (1.9 g, 7.4 mmol) were obtained **9** (190 mg, 10%) and **4i** (1.6 g, 83%). **4i**: IR (KBr) 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (s, 3 H), 7.00 (s, 1 H), 7.25−7.40 (m, 3 H), 7.35 (dm, J = 7.5 Hz, 2 H), 7.48 (dm, J = 8.8 Hz, 1 H), 7.62 (dm, J = 7.5 Hz, 2 H), 7.83 (d, J = 8.3 Hz, 1 H), 8.21 (d, J = 8.2 Hz, 1 H), 8.38 (dd, J = 8.3, 2.0 Hz, 1 H), 9.28 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.3 (CH_3), 116.5 (CH), 117.0 (CH), 121.8 (CH), 124.8 (CH), 124.9 (C), 125.7 (CH), 126.1 (CH), 127.0 (CH), 128.8 (CH), 130.2 (C), 133.8 (CH), 136.5 (CH), 138.2 (C), 140.5 (C), 150.2 (CH), 154.9 (C), 165.8 (C); mp 105 °C (Et_2O). Anal. Calcd for $C_{21}H_{16}N_2O_4S$: C, 64.26; H, 4.11; N, 7.13; S, 8.17. Found: C, 64.24; H, 4.56; N, 6.72; S, 7.85.

1-(Benzenesulfonyl)-2-(5-nitro-2-pyridyl)indole (4l). Following the general procedure, from 2-chloro-5-nitropyridine (**3l**) (792 mg, 5.0 mmol) and 1-(benzenesulfonyl)indole (1.9 g, 7.4 mmol) were obtained **9** (220 mg, 11%) and **4l** (1.8 g, 97%). **4l**: IR (KBr) 1519, 1352, 1173, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (s, 1 H), 7.15−7.56 (m, 6 H), 7.61 (dm, J = 7.0 Hz, 2 H), 7.98 (d, J = 8.6 Hz, 1 H), 8.23 (d, J = 8.3 Hz, 1 H), 8.58 (dd, J = 8.6, 2.6 Hz, 1 H), 9.51 (d, J = 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 116.5 (CH), 118.6 (CH), 122.0 (CH), 125.0 (CH), 125.9 (CH), 126.6 (CH), 127.0 (CH), 128.7 (CH), 130.1 (C), 130.4 (CH), 133.9 (CH), 136.1 (C), 138.9 (C), 139.2 (C), 143.0 (C), 144.3 (CH), 156.2 (C); mp 174−176 °C (acetone). Anal. Calcd for $C_{19}H_{13}N_3O_4S$: C, 60.15; H, 3.45; N, 11.08; S, 8.45. Found: C, 60.18; H, 3.38; N, 11.14; S, 8.42.

1-(Benzenesulfonyl)-2-(3,5-dinitro-2-pyridyl)indole (4m). Following the general procedure, from 2-chloro-3,5-dinitropyridine (**3m**) (407 mg, 2.0 mmol) and 1-(benzenesulfonyl)-indole (771 mg, 3.0 mmol) were obtained **9** (100 mg, 13%) and **4m** (595 mg, 70%). **4m**: IR (KBr) 1594, 1526, 1343 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (s, 1 H), 7.27−7.51 (m, 6 H), 7.59 (d, J = 7.0 Hz, 2 H), 8.09 (d, J = 8.4 Hz, 1 H), 9.22 (d, J = 2.3 Hz, 1 H), 9.72 (d, J = 2.3 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.1 (CH), 117.5 (CH), 122.9 (CH), 125.2 (CH), 127.1 (CH), 128.8 (CH), 129.7 (C), 129.9 (CH), 134.5 (C), 135.3 (CH), 135.8 (C), 136.8 (C), 144.0 (C), 145.6 (C), 147.8 (CH), 149.1 (C); mp 184−186 °C (acetone−hexane). Anal. Calcd for $C_{19}H_{12}N_4O_6S$: C, 53.77; H, 2.85; N, 13.20; S, 7.55. Found: C, 53.52; H, 2.70; N,13.01; S, 7.46.

3-Bromo-1-(*tert*-butyldimethylsilyl)indole (5). To a solution of indole (8g, 68 mmol) in anhydrous THF (200 mL) at −78 °C was slowly added a solution of *n*-BuLi in hexane (47 mL of a 1.6 M solution, 75 mmol), and the temperature was raised to −10 °C. After 15 min the reaction mixture was cooled to −50 °C, and a solution of TBDMSCl (11.6 g, 77 mmol) in anhydrous THF (60 mL) was added dropwise. After the mixture was stirred at 0 °C for 3 h, the temperature was lowered to −70 °C, and freshly crystallized NBS (12.2 g, 68.4 mmol) was added. After 2 h the temperature was raised to 25 °C, and hexane (100 mL) and pyridine (1 mL) were added. The resulting suspension was filtered through a Celite pad, and the filtrate was concentrated to give a residue which was purified by column chromatography (hexane) affording pure **5** (17.8 g, 84%) as a colorless solid: ^1H NMR ($CDCl_3$) δ 0.60 (s, 6 H), 0.93 (s, 9 H), 7.17 (s, 1 H), 7.20 (m, 2 H), 7.48 (m, 1 H), 7.54 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.0 (CH_3), 19.3 (C), 26.2 (CH_3), 93.6 (C), 114.0 (CH), 119.1 (CH), 120.5 (CH), 122.5 (CH), 129.6 (CH), 129.8 (C), 140.2 (C). Anal. Calcd for $C_{14}H_{20}BrNSi$: C, 54.18; H, 6.50; Br, 25.75; N, 4.51. Found: C, 54.21; H, 6.60; Br, 25.52; N, 4.62.

General Procedure for the Preparation of 3-(2-Pyridyl)indoles 7 and 8. A solution of *t*-BuLi (1.7 M in pentane, 2.0 equiv) was slowly added to a 0.8 M solution of 3-bromo-1-(*tert*-butyldimethylsilyl)indole (**5**) in anhydrous THF at −78 °C, and the resulting mixture was stirred for 10 min at this temperature. Then, a 0.35 M solution of $ZnCl_2$ (it was used after fusion by flame-drying under reduced pressure) (1.1 equiv) in THF was added to this solution, and the stirring was continued for 30 min at 25 °C. In a separate flask, a 0.54 M solution of the 2-halopyridine **2** or **3** in anhydrous THF was added to 2 mol % of a catalyst prepared by reaction of a 0.014 M solution of $Cl_2Pd(PPh_3)_2$ in anhydrous THF with 2 equiv of diisobutylaluminum hydride (1.0 M in hexane), and the mixture was stirred at 25 °C for 5 min. The resulting mixture was transferred via canula to the solution of the indolylzinc chloride **6** (1.5 equiv) prepared as described above, and the solution was heated at reflux for 4 h, cooled, and poured into saturated aqueous Na_2CO_3. The aqueous phase was extracted with Et_2O, and the organic extracts were dried and concentrated. The residue was chromatographed (CH_2Cl_2) to afford **7**. Alternatively, the above crude residue was dissolved in EtOH, and a catalytic amount of TsOH was added. This mixture was heated at reflux until the disappearance of the starting material was observed by TLC. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2. The solution was washed with saturated aqueous Na_2CO_3, dried, and concentrated, and the resulting residue was chromatographed to afford **8**.

1-(*tert*-Butyldimethylsilyl)-3-(2-pyridyl)indole (7a). Following the general procedure, from 2-chloropyridine (**3a**) (500 mg, 4.4 mmol) and 3-bromo-1-(*tert*-butyldimethylsilyl)indole (**5**) (2.0 g, 6.6 mmol) were obtained 1,1′-bis(*tert*-butyldimethylsilyl)]-3,3′-biindole (**10**) (200 mg, 13%) and pyridylindole **7a** (1.1 g, 80%). **10**: IR (KBr) 2950−2850, 1451, 1139, 1004 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (s, 12 H), 0.99 (s, 18 H), 7.19 (m, 4 H), 7.44 (s, 2 H), 7.57 (dm, J = 7.2 Hz, 2 H), 7.78 (dm, J = 7.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ −3.8 (CH_3), 19.6 (C), 26.4 (CH_3), 112.7 (C), 114.0 (CH), 119.8 (CH), 120.0 (CH), 121.7 (CH), 128.3 (CH), 130.3 (C), 141.5 (C); mp 197−198 °C (hexane). Anal. Calcd for $C_{28}H_{35}N_2Si_2$: C, 73.04; H, 8.69; N, 6.08. Found: C, 73.01; H, 8.85; N, 6.19. **7a**: ^1H NMR ($CDCl_3$) δ 0.61 (s, 6 H), 0.92 (s, 9 H), 7.04 (ddd, J = 7.5, 5.0, 1.8 Hz, 1 H), 7.20 (m, 2 H), 7.53 (m, 1 H), 7.62 (td, J = 7.5, 1.8 Hz, 1 H), 7.69 (dm, J = 7.5 Hz, 1 H), 7.75 (s, 1 H), 8.28 (m, 1 H), 8.63 (ddd, J = 5.0, 2.8, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.6 (CH_3), 18.8 (C), 25.8 (CH_3), 113.7 (CH), 118.9 (C), 119.7 (CH), 129.9 (CH), 120.4 (CH), 120.7 (CH), 121.5 (CH), 128.3 (C), 130.8 (CH), 135.7 (CH), 141.7 (C), 149.0 (CH), 154.4 (C).

1-(*tert*-Butyldimethylsilyl)-3-(4-methyl-2-pyridyl)indole (7b). Following the general procedure, from 2-bromo-4-methylpyridine (**2b**)[60] (370 mg, 2.1 mmol) and 3-bromoindole (**5**) (1.0 g, 3.2 mmol) were obtained dimer **10** (70 mg, 10%) and pyridylindole **7b** (630 mg, 93%). **7b**: IR(NaCl) 1603, 1545, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (s, 6 H), 0.97 (s, 9 H), 2.41 (s, 3 H), 6.95 (dm, J = 5.1 Hz, 1 H), 7.23 (m, 2 H), 7.55 (s, 1 H), 7.56 (dm, J = 8.0 Hz, 1 H), 7.75 (s, 1 H), 8.28 (m, 1 H), 8.53 (d, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.1 (CH_3), 19.2 (CH_3), 21.0 (CH_3), 26.2 (C), 114.3 (CH), 119.5 (C), 120.8 (CH), 120.9 (CH), 121.5 (CH), 121.9 (CH), 128.9 (C), 131.4 (CH), 142.3 (C), 147.3 (C), 149.5 (CH), 154.9 (C).

3-(2-Pyridyl)indole (8a). Following the general procedure, from 2-bromopyridine (**2a**) (450 mg, 3.1 mmol) and 3-bromoindole **5** (1.5 g, 4.7 mmol), after reflux of the crude mixture in EtOH (31 mL) containing TsOH for 4 h and purification by column chromatography, were obtained dimer **10** (eluent CH_2Cl_2, 130 mg, 12%) and pyridylindole **8a** (eluent 98:2 CH_2Cl_2−EtOH, 580 mg, 95%). **8a**: IR (KBr) 3200−2700, 1602, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (dd, J = 8.8, 4.9 Hz, 1 H), 7.24 (m, 2 H), 7.39 (m, 1 H), 7.71 (m, 2 H), 7.77 (d, J = 2.8 Hz, 1 H), 8.30 (dm, J = 7.0 Hz, 1 H), 8.66 (dm, J = 4.9 Hz, 1H), 8.85 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 111.7 (CH), 116.2 (C), 120.0 (CH), 120.2 (CH), 120.5 (CH), 121.0 (CH), 122.1 (CH), 125.0 (CH), 125.2 (C), 136.8 (CH), 148.9 (CH), 154.8 (C); mp 138−140 °C (Et_2O) [lit.[4h] mp 150−154 °C (benzene)]. Anal. Calcd

for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.31. Found: C, 80.48; H, 5.23; N, 14.31. Operating as above, from 2-chloropyridine (**3a**) (500 mg, 4.4 mmol) and 3-bromoindole **5** (2.0 g, 6.6 mmol) were obtained dimer **10** (200 mg, 13%) and pyridylindole **8a** (717 mg, 84%).

3-(4-Methyl-2-pyridyl)indole (8b). Following the general procedure, from 2-bromo-4-methylpyridine (**2b**)[60] (369 mg, 2.1 mmol) and 3-bromoindole **5** (1.0 g, 3.2 mmol), after reflux of the crude mixture in EtOH (21 mL) containing TsOH for 12 h and purification by column chromatography, were obtained dimer **10** (eluent CH_2Cl_2, 104 mg, 14%) and pyridylindole **8b** (eluent 98:2 CH_2Cl_2−EtOH, 416 mg, 93%). **8b**: IR (KBr) 3200−2800, 1608 cm^{-1}; ^1H NMR ($CDCl_3$−CD_3OD) δ 2.39 (s, 3 H), 6.96 (d, J = 5.1 Hz, 1 H), 7.21 (m, 2 H), 7.44 (m, 1 H), 7.58 (s, 1 H), 7.75 (s, 1 H), 8.12 (m, 1 H), 8.39 (d, J = 5.1 Hz, 1 H), 10.46 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.6 (CH_3), 111.7 (CH), 115.7 (C), 119.7 (CH), 120.2 (CH), 121.3 (CH), 121.8 (CH), 124.4 (CH), 125.1 (CH), 125.3 (C), 136.9 (C), 148.2 (C), 148.4 (CH), 154.6 (C); mp 142−146 °C (EtOH). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.77; H, 5.77; N, 13.46. Found: C, 80.93; H, 5.95; N, 13.11. Operating as above, from 2-chloro-4-methylpyridine (**3b**)[61] (400 mg, 3.1 mmol) and 3-bromoindole **5** (1.5 g, 4.7 mmol) were obtained dimer **10** (130 mg, 12%) and pyridylindole **8b** (340 mg, 52%).

3-(3-Ethyl-4-methyl-2-pyridyl)indole (8c).[65] Following the general procedure, from 2-bromo-3-ethyl-4-methylpyridine (**2c**) (790 mg, 3.9 mmol) and 3-bromoindole **5** (1.8 g, 5.9 mmol), after reflux of the crude mixture in EtOH (40 mL) containing TsOH for 28 h and purification by column chromatography, were obtained dimer **10** (eluent CH_2Cl_2, 190 mg, 14%) and pyridylindole **8c** (eluent 98:2 CH_2Cl_2−EtOH, 820 mg, 88%). **8c**: IR (KBr) 3200−2800, 1585, 1443 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3 H), 2.41 (s, 3 H), 2.71 (q, J = 7.5 Hz, 2 H), 6.90 (br s, 1 H), 7.06 (d, J = 5.0 Hz, 1 H), 7.04−7.14 (m, 3 H), 7.60 (m, 1 H), 8.45 (d, J = 5.0 Hz, 1 H), 9.5 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 19.3 (CH_3), 22.4 (CH_2), 111.4 (CH), 115.1 (C), 119.5 (CH), 119.7 (CH), 121.4 (CH), 123.7 (CH), 124.1 (CH), 127.2 (C), 136.0 (C), 137.3 (C), 145.8 (CH), 145.9 (C), 153.7 (C); mp 170−172 °C (EtOH) (lit.[4c] mp 117−119 °C). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.32; H, 6.92; N, 11.85.

3-(5-Ethyl-4-methyl-2-pyridyl)indole (8d).[65] Following the general procedure, from 2-bromo-5-ethyl-4-methylpyridine (**2d**) (310 mg, 1.5 mmol) and 3-bromoindole **5** (720 mg, 2.3 mmol), after reflux of the crude mixture in EtOH (15 mL) containing TsOH for 6 h and purification by column chromatography, were obtained dimer **10** (eluent CH_2Cl_2, 50 mg, 10%) and pyridylindole **8d** (eluent 98:2 CH_2Cl_2−EtOH, 310 mg, 89%). **8d**: IR (KBr): 3200−2800, 1607, 1551 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 2.37 (s, 3 H), 2.67 (q, J = 7.5 Hz, 2 H), 7.12 (m, 2 H), 7.36 (m, 1 H), 7.50 (s, 1 H), 7.69 (d, J = 2.7 Hz, 1 H), 8.26 (m, 1 H), 8.41 (s, 1 H), 8.85 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 18.8 (CH_3), 23.3 (CH_2), 111.7 (CH), 116.4 (C), 120.3 (CH), 121.9 (CH), 122.1 (CH), 124.6 (CH), 125.2 (C), 134.6 (C), 137.0 (C), 145.5 (C), 148.4 (CH), 152.6 (C); mp 140−142 °C (Et_2O) (lit.[4c] mp 119−120 °C). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.40; H, 6.89; N, 11.86.

3-(3-Methoxy-2-pyridyl)indole (8e). Following the general procedure, from 2-bromo-3-methoxypyridine (**2e**)[62] (500 mg, 2.7 mmol) and 3-bromoindole **5** (1.2 g, 4.0 mmol), after reflux of the crude mixture in EtOH (26 mL) containing TsOH for 24 h and purification by column chromatography (eluent CH_2Cl_2), were obtained dimer **10** (90 mg, 10%) and pyridylindole **8e** (460 mg, 77%). **8e**: IR (KBr) 3600−2800, 1449 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 3 H), 7.10 (dd, J = 8.2, 4.6 Hz, 1 H), 7.23 (m, 3 H), 7.39 (m, 1 H), 8.05 (d, J = 2.7 Hz, 1 H), 8.36 (dd, J = 4.6, 1.4 Hz, 1 H), 8.40 (br s, 1 H), 8.70 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.1 (CH_3), 111.0 (CH), 112.7 (C), 117.0 (CH), 120.1 (CH), 120.4 (CH), 122.0 (CH), 122.5 (CH), 126.5 (C), 127.4 (CH), 135.9 (C), 140.5 (CH), 145.4 (C), 152.5 (C); mp 136−138 °C (Et_2O). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.98; H, 5.40; N, 12.48.

3-(3-Hydroxy-2-pyridyl)indole (8f). Following the general procedure, from 2-bromo-3-hydroxypyridine (**2f**) (500 mg, 2.9 mmol) and 3-bromoindole **5** (2.2 g, 7.2 mmol), after reflux of the crude mixture in EtOH (28 mL) containing TsOH for 24 h and purification by column chromatography (AcOEt), were obtained dimer **10** (240 mg, 15%) and pyridylindole **8f** (380 mg, 63%). **8f**: IR (KBr) 3800−2800, 1455 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.04 (dd, J = 8.0, 4.6 Hz, 1 H), 7.17 (m, 2 H), 7.34 (dd, J = 8.0, 1.4 Hz, 1 H), 7.50 (m, 1 H), 8.28 (dd, J = 4.6, 1.4 Hz, 1 H), 8.40 (d, J = 2.7 Hz, 1 H), 8.92 (dm, J = 7.0 Hz, 1 H), 9.15 (br s, 1 H), 10.50 (br s, 1 H); ^{13}C NMR (acetone-d_6) δ 111.8 (CH), 113.7 (C), 120.4 (CH), 120.6 (CH), 122.5 (CH), 124.0 (CH), 127.7 (C), 128.9 (CH), 137.2 (C), 140.4 (CH), 145.1 (C), 151.1 (C); mp 145−147 °C (benzene−CH_2Cl_2). Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74,27; H, 4.79; N, 13.32. Found: C, 74.36; H, 4.51; N, 13.36.

Methyl 2-(3-Indolyl)-3-pyridinecarboxylate (8g). Following the general procedure, from methyl 2-chloro-3-pyridinecarboxylate (**3g**)[63] (500 mg, 2.9 mmol) and 3-bromoindole **5** (1.35 g, 4.36 mmol), after reflux of the crude mixture in EtOH (30 mL) containing TsOH for 12 h and purification by column chromatography (CH_2Cl_2), were obtained dimer **10** (100 mg, 10%) and pyridylindole **8g** (660 mg, 90%). **8g**: IR (KBr) 3200−2800, 1712, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 3 H), 7.21 (m, 2 H), 7.26 (dd, J = 7.8, 4.8 Hz, 1 H), 7.43 (dm, J = 7.0 Hz, 1 H), 7.62 (d, J = 2.8 Hz, 1 H), 7.81 (dm, J = 7.0 Hz, 1 H), 8.08 (dd, J = 7.8, 1.8 Hz, 1 H), 8.45 (br s, 1 H), 8.80 (dd, J = 4.8, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.4 (CH_3), 111.6 (CH), 115.7 (C), 119.3 (CH), 120.0 (CH), 120.4 (CH), 122.1 (CH), 125.8 (CH), 126.0 (C), 126.4 (C), 136.2 (C), 137.8 (CH), 151.2 (CH), 153.4 (C), 169.0 (C); mp 140 °C (EtOH). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.43; H, 4.79; N, 11.10. Found: C, 71.50; H, 4.80; N, 11.11.

Methyl 2-(3-Indolyl)-4-pyridinecarboxylate (8h). Following the general procedure, from methyl 2-chloro-4-pyridinecarboxylate (**3h**)[64] (368 mg, 2.1 mmol) and 3-bromoindole **5** (1.0 g, 3.2 mmol), after reflux of the crude mixture in EtOH (20 mL) containing TsOH for 12 h and purification by column chromatography (CH_2Cl_2), were obtained dimer **10** (75 mg, 10%) and pyridylindole **8h** (515 mg, 95%). **8h**: IR (NaCl) 3400−2800, 1729, 767−746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (s, 3 H), 7.23 (m, 2 H), 7.59 (d, J = 5.5 Hz, 1 H), 7.60 (m, 1 H), 8.19 (s, 1 H), 8.40 (dm, J = 8.0 Hz, 1 H), 8.74 (d, J = 5.5 Hz, 1 H), 9.67 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 53.2 (CH_3), 112.3 (CH), 116.6 (C), 119.5 (CH), 120.2 (CH), 121.4 (CH), 121.6 (C), 123.2 (CH), 125.7 (C), 126.1 (CH), 137.6 (C), 138.2 (CH), 150.6 (CH), 156.8 (C), 166.7 (C); mp 163 °C (MeOH−Et_2O) [lit.[4a] mp 161−162 °C (Et_2O)]; MS, m/e (relative intensity) 252 (M^+, 40), 194 (21), 166 (12), 139 (11), 97 (6), 69 (33), 43 (100).

Methyl 2-(3-Indolyl)-5-pyridinecarboxylate (8i). Following the general procedure, from methyl 2-chloro-5-pyridinecarboxylate (**3i**)[63] (500 mg, 2.9 mmol) and 3-bromoindole **5** (1.3 g, 4.4 mmol), after reflux of the crude mixture in EtOH (30 mL) containing TsOH for 12 h and purification by column chromatography (CH_2Cl_2), were obtained dimer **10** (120 mg, 12%) and pyridylindole **8i** (710 mg, 97%). **8i**: IR (KBr) 3368, 1719 cm^{-1}; ^1H NMR ($CDCl_3$−CD_3OD) δ 3.99 (s, 3 H), 7.29 (m, 2 H), 7.50 (m, 1 H), 7.84 (dd, J = 8.4, 0.8 Hz, 1 H), 7.95 (s, 1 H), 8.26 (m, 1 H), 8.32 (dd, J = 8.4, 2.2 Hz, 1 H), 9.21 (dd, J = 2.2, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 51.9 (CH_3), 111.8 (CH), 115.2 (C), 119.4 (CH), 120.1 (CH), 120.8 (CH), 121.3 (C), 122.2 (CH), 124.8 (C), 126.8 (CH), 137.1 (C), 137.3 (CH), 150.1 (CH), 158.9 (C), 166.1 (C); mp 184−186 °C (EtOH) (lit.[4c] mp 203−206 °C). Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.43; H, 4.79; N, 11.10. Found: C, 71.33; H, 4.88; N, 10.99.

Methyl 3-Ethyl-2-(3-indolyl)-4-pyridinecarboxylate (8j) and Methyl 5-Ethyl-2-(3-indolyl)-4-pyridinecarboxylate (8k). Following the general procedure, from an equimolecular mixture of methyl 2-chloro-3-ethyl-4-pyridinecarboxylate (**3j**)

(65) From the synthetic standpoint it was more convenient to use a mixture of bromopyridines **2c** and **2d** in the cross-coupling reaction, because pyridylindoles **8c** and **8d** could be separated by column chromatography (AcOEt) much more efficiently than **2c** and **2d**.

and methyl 2-chloro-5-ethyl-4-pyridinecarboxylate (**3k**)[66] (5.8 g, 29.0 mmol), and 3-bromoindole **5** (13.5 g, 43.6 mmol), after reflux of the crude mixture in EtOH (435 mL) containing TsOH for 12 h and purification by column chromatography (1:1 AcOEt−hexane), were obtained dimer **10** (1.0 g, 10%) and pyridylindoles **8k** (3.5 g, 43%) and **8j** (3.4 g, 42%). **8j**: IR (KBr) 3800−2800, 1737, 1450, 1293, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3 H), 3.00 (q, J = 7.5 Hz, 2 H), 3.97 (s, 3 H), 7.08−7.30 (m, 3 H), 7.12 (d, J = 2.5 Hz, 1 H), 7.51 (d, J = 5.0 Hz, 1 H), 7.63 (dm, J = 6.5 Hz, 1 H), 8.63 (d, J = 5.0 Hz, 1 H), 9.05 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 15.9 (CH_3), 23.1 (CH_2), 52.6 (CH_3), 111.3 (CH), 115.6 (C), 120.1 (CH), 120.3 (CH), 121.2 (CH), 122.3 (CH), 124.1 (CH), 127.1 (C), 135.9 (C), 137.5 (C), 138.8 (C), 146.8 (CH), 155.6 (C), 167.8 (C); mp 184−186 °C [lit.[4f] mp 185−186 °C (MeOH−Et_2O)]. **8k**: IR (KBr) 3800−2600, 1714, 1249, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 2.94 (q, J = 7.5 Hz, 2 H), 3.96 (s, 3 H), 7.20−7.40 (m, 3 H), 7.73 (d, J = 2.7 Hz, 1 H), 8.06 (s, 1 H), 8.35 (m, 1 H), 8.60 (s, 1 H), 8.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.8 (CH_3), 24.5 (CH_2), 52.4 (CH_3), 111.6 (CH), 116.3 (C), 120.0 (CH), 120.7 (CH), 120.8 (CH), 122.5 (CH), 124.6 (CH), 125.2 (C), 135.2 (C), 136.9 (C), 151.5 (CH), 153.4 (C), 167.2 (C); mp 100−102 °C [lit.[4f] mp 99−100 °C ($CHCl_3$−hexane)].

3-(5-Nitro-2-pyridyl)indole (8l). Following the general procedure, from 2-chloro-5-nitropyridine (**3l**) (500 mg, 3.1 mmol) and 3-bromoindole **5** (1.5 g, 4.7 mmol), after reflux of the crude mixture in EtOH (30 mL) containing TsOH for 2 h and purification by column chromatography (CH_2Cl_2), were obtained dimer **10** (140 mg, 13%) and pyridylindole **8l** (670 mg, 89%). **8l**: IR (KBr) 3371, 1590, 1540, 1336, 1278 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 2 H), 7.46 (m, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 8.0 (s, 1 H), 8.37 (m, 1 H), 8.43 (dd, J = 8.8, 2.6 Hz, 1 H), 9.43 (d, J = 2.6 Hz, 1 H), 10.0 (br s, 1 H); ^{13}C NMR (acetone-d_6) δ 112.9 (CH), 116.1 (C), 119.5 (CH), 122.1 (CH), 122.9 (CH), 123.6 (CH), 126.4 (C), 129.8 (CH), 131.7 (CH), 138.5 (C), 141.4 (C), 145.9 (CH), 162.0 (C); mp 174−176 °C (acetone). Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.40; H, 3.81; N, 17.44.

3-(3,5-Dinitro-2-pyridyl)indole (8m). Following the general procedure, from 2-chloro-3,5-dinitropyridine (**3m**) (500 mg, 2.4 mmol) and 3-bromoindole **5** (1.1 g, 3.6 mmol), after reflux of the crude mixture in EtOH (24 mL) containing TsOH for 1 h and purification by column chromatography (97:3 $CHCl_3$−EtOH), were obtained dimer **10** (75 mg, 9%) and pyridylindole **8m** (550 mg, 80%). **8m**: IR (KBr) 3361, 1540, 1328, 1241 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.27 (m, 2 H), 7.59 (m, 1 H), 7.98 (s, 1 H), 8.20 (m, 1 H), 9.00 (d, J = 2.4 Hz, 1 H), 9.65 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (acetone-d_6) δ 111.7 (C), 113.2 (CH), 122.3 (CH), 122.7 (CH), 124.2 (CH), 126.7 (C), 128.4 (CH), 130.6 (CH), 137.8 (C), 140.6 (C), 143.4 (C), 147.3 (CH), 152.6 (C); mp 267−269 °C (acetone). Anal. Calcd for $C_{13}H_8N_4O_4 \cdot {}^1/_3C_3H_6O$: C, 55.34; H, 3.29; N, 18.45. Found: C, 54.72; H, 3.14; N, 18.45.

3-(2-Pyrazinyl)indole (12a). Following the above general procedure, from 2-chloropyrazine (438 mg, 3.8 mmol) and 3-bromoindole **5** (1.8 g, 5.7 mmol), after reflux of the crude mixture in EtOH (38 mL) containing TsOH for 2.5 h and purification by column chromatography (CH_2Cl_2), were obtained dimer **10** (198 mg, 15%) and pyrazinylindole **12a** (680 mg, 91%). **12a**: IR (KBr) 3600−2800, 1545, 1511, 1131, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 2 H), 7.42 (m, 1 H), 7.83 (d, J = 2.8 Hz, 1 H), 8.35 (d, J = 2.6 Hz, 1 H), 8.39 (m, 1 H), 8.60 (dd, J = 2.6, 1.6 Hz, 1 H), 8.80 (br s, 1 H), 9.00 (d, J = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 111.6 (CH), 113.5 (C), 120.8 (CH), 121.1 (CH), 122.7 (CH), 124.9 (C), 125.4 (CH), 136.8 (C), 139.8 (CH), 141.6 (CH), 144.0 (CH), 151.6 (C); mp 157−160 °C (Et_2O). Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.81; H, 4.77; N, 21.39.

1-(*tert*-Butyldimethylsilyl)-3-(2-thienyl)indole (11b). Following the general procedure for the preparation of **7**, from 2-bromothiophene (500 mg, 3.1 mmol) and 3-bromoindole **5** (1.4 g, 4.6 mmol) were obtained 2,2′-bithiophene (eluent hexane, 70 mg, 27%), thienylindole **11b** (eluent hexane, 470 mg, 50%), and dimer **10** (eluent 3:1 hexane−AcOEt, 330 mg, 31%). **11b**: ^1H NMR ($CDCl_3$) δ 0.63 (s, 6 H), 0.96 (s, 9 H), 7.11 (dd, J = 5.1, 3.4 Hz, 1 H), 7.17−7.25 (m, 3 H), 7.27 (dd, J = 3.4, 1.0 Hz, 1 H), 7.36 (s, 1 H), 7.52 (m, 1 H), 7.96 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −3.9 (CH_3), 19.4 (C), 26.3 (CH_3), 113.7 (C), 114.2 (CH), 119.8 (CH), 120.5 (CH), 122.1 (CH), 122.5 (CH), 127.5 (CH), 128.7 (CH), 128.9 (C), 137.6 (C), 141.7 (C).

1-(*tert*-Butyldimethylsilyl)-3-(3-thienyl)indole (11c). Operating as above, from 3-bromothiophene (500 mg, 3.1 mmol) and 3-bromoindole **5** (1.4 g, 4.6 mmol) were obtained 3,3′-bithiophene (eluent hexane, 64 mg, 25%), thienylindole **11c** (eluent hexane, 430 mg, 45%), and dimer **10** (eluent 3:1 hexane−AcOEt, 310 mg, 29%). **11c**: ^1H NMR ($CDCl_3$) δ 0.75 (s, 6 H), 1.08 (s, 9 H), 7.32 (m, 2 H), 7.46 (s, 1 H), 7.48−7.58 (m, 3 H), 7.68 (m, 1 H), 8.04 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.0 (CH_3), 19.3 (C), 26.2 (CH_3), 114.1 (CH), 115.3 (CH), 118.5 (CH), 119.7 (CH), 120.2 (CH), 121.8 (CH), 125.3 (CH), 127.2 (CH), 128.4 (CH), 129.1 (C), 135.7 (C), 141.7 (C).

1-(*tert*-Butyldimethylsilyl)-3-(3-furyl)indole (11d). Operating as above, from 3-bromofuran (500 mg, 3.4 mmol) and 3-bromoindole **5** (1.6 g, 5.1 mmol) were obtained furylindole **11d** (eluent hexane, 121 mg, 12%) and dimer **10** (eluent 3:1 hexane−AcOEt, 420 mg, 36%). **11d**: ^1H NMR ($CDCl_3$) δ 0.63 (s, 6 H), 0.96 (s, 9 H), 6.71 (br s, 1 H), 7.20 (m, 2 H), 7.26 (s, 1 H), 7.52 (m, 2 H), 7.76 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ −3.9 (CH_3), 19.4 (C), 26.3 (CH_3), 109.9 (CH), 110.9 (C), 114.1 (CH), 114.5 (C), 119.7 (CH), 120.1 (CH), 121.8 (CH), 128.1 (CH), 129.1 (C), 137.6 (CH), 141.7 (C), 142.8 (CH).

1-(Benzenesulfonyl)-1′-(*tert*-butyldimethylsilyl)-3,3′-biindole (11e). Operating as above, from 1-(benzenesulfonyl)-3-bromoindole (500 mg, 1.5 mmol) and 3-bromoindole **5** (693 g, 2.2 mmol) were obtained biindole **11e** (400 mg, 55%) and dimer **10** (200 mg, 39%) after column chromatography (95:5 hexane−AcOEt). **11e**: ^1H NMR ($CDCl_3$) δ 0.59 (s, 6 H), 0.98 (s, 9 H), 7.10−7.78 (m, 10 H), 7.44 (s, 1 H), 7.81 (s, 1 H), 7.93 (dm, J = 8.4 Hz, 2 H), 8.10 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.1 (CH_3), 19.3 (C), 26.1 (CH_3), 110.3 (C), 113.7 (CH), 114.1 (CH), 119.6 (CH), 120.2 (CH), 120.7 (CH), 122.1 (CH), 122.1 (CH), 123.4 (CH), 124.8 (CH), 126.5 (CH), 129.0 (CH), 129.3 (CH), 130.3 (C), 130.8 (C), 133.6 (CH), 135.5 (C), 137.9 (C), 141.4 (C).

General Procedure for the Desilylation of Heteroarylindoles 11. A 1.0 M solution (1.1 equiv) of tetra-*n*-butylammonium fluoride (TBAF) in THF was added to a 1.0 M solution of heteroarylindole **11** in THF. The mixture was stirred at 25 °C for 10 min and poured into saturated aqueous Na_2CO_3. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried and concentrated to give a residue, which was chromatographed (1:1 AcOEt−hexane).

3-(2-Thienyl)indole (12b). Following the above general procedure, from thienylindole **11b** (440 mg, 1.4 mmol) and TBAF (1.6 mL, 1.6 mmol) was obtained compound **12b**[67] (218 mg, 78%): IR (KBr) 1455, 744, 691 cm^{-1}; ^1H NMR ($CDCl_3$) 7.12 (dd, J = 5.1, 3.3 Hz, 1 H), 7.25 (m, 4 H), 7.40 (m, 1 H), 7.41 (d, J = 2.5 Hz, 1 H), 7.98 (m, 1 H), 8.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 111.4 (CH), 119.7 (C and CH), 120.5 (CH), 121.9 (CH), 122.4 (CH), 122.5 (CH), 125.1 (C), 127.5 (CH), 136.1 (C), 137.5 (C).

3-(3-Thienyl)indole (12c). Following the above general procedure, from thienylindole **11c** (430 mg, 1.3 mmol) and TBAF (1.5 mL, 1.5 mmol) was obtained compound **12c** (220 mg, 80%): ^1H NMR ($CDCl_3$) δ 7.23 (m, 2 H), 7.41 (m, 5 H), 7.94 (m, 1 H), 8.10 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 111.4 (CH),

(66) Chloropyridines **3j** and **3k** were prepared from methyl 3-ethylisonicotinate[52d] by treatment (reflux, 12 h) of the corresponding *N*-oxide[4f] (58 g, 320 mmol) with $POCl_3$ (113 mL) in $CHCl_3$ (113 mL). Distillation (112 °C, 2.5 mmHg) gave a nearly equimolecular mixture of **3j** and **3k** (43 g, 67%), which could not be separated. **3j** (from the mixture): ^1H NMR ($CHCl_3$) δ 1.24 (t, J = 7.5 Hz, 3 H), 2.93 (q, J = 7.5 Hz, 2 H), 3.95 (s, 3 H), 7.52 (d, J = 4.9 Hz, 1 H), 8.32 (d, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.0 (CH_3), 29.6 (CH_2), 52.2 (CH_3), 122.0 (CH), 137.6 (C), 139.6 (C), 146.4 (CH), 152.6 (C), 165.4 (C). **3k** (from the mixture): ^1H NMR ($CHCl_3$) δ 1.24 (t, J = 7.5 Hz, 3 H), 2.93 (q, J = 7.5 Hz, 2 H), 3.95 (s, 3 H), 7.70 (s, 1 H), 8.36 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 29.6 (CH_2), 52.2 (CH_3), 123.5 (CH), 137.1 (C), 138.5 (C), 151.3 (CH), 151.6 (C), 164.6 (C).

(67) Bergman, J. *Acta Chem. Scand.* **1971**, *25*, 1277.

113.1 (C), 118.4 (CH), 119.7 (CH), 120.2 (CH), 121.8 (CH), 122.3 (CH), 125.5 (C and CH), 127.0 (CH), 135.7 (C), 136.3 (C); mp 133−135 °C (Et_2O). Anal. Calcd for $C_{12}H_9NS$: C, 72.33; H, 4.35; N, 7.03; S, 16.09. Found: C, 72.21; H, 4.53; N, 7.09; S, 15.90.

3-(3-Furyl)indole (12d). Following the above general procedure, from 3-(3-furyl)indole **11d** (100 mg, 0.34 mmol) and TBAF (370 μL, 0.37 mmol) was obtained compound **12d** (40 mg, 65%): ^{1}H NMR ($CDCl_3$) δ 6.70 (dm, J = 1.8 Hz, 1 H), 7.20 (m, 2 H), 7.30 (d, J = 2.5 Hz, 1 H), 7.40 (m, 1 H), 7.51 (d, J = 1.8 Hz, 1 H), 7.78 (m, 1 H), 7.80 (s, 1 H), 8.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 109.1 (C), 109.8 (CH), 111.4 (CH), 119.6 (C), 119.8 (CH), 120.2 (CH), 121.4 (CH), 122.5 (CH), 125.7 (C), 136.5 (C), 137.7 (C), 142.9 (C); MS, *m/e* (relative intensity) 183 (M^+, 10), 149 (13), 83 (100), 57 (72), 55 (76).

1-(Benzenesulfonyl)-3,3′-biindole (12e). Following the above general procedure, from 3,3′-biindole **11e** (400 mg, 0.83 mmol) and TBAF (910 μL, 0.91 mmol) was obtained compound **12e** (240 mg, 78%) after column chromatography (2:1 hexane−AcOEt): IR (KBr) 3426, 1447, 1371, 1187 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10−7.50 (m, 9 H), 7.55−7.79 (m, 2 H), 7.91 (dm, J = 8.4 Hz, 2 H), 8.05 (d, J = 7.8 Hz, 1 H), 8.30 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 108.5 (C), 111.4 (CH), 113.8 (CH), 117.6 (C), 119.8 (CH), 120.3 (CH), 120.8 (CH), 122.2 (CH), 122.6 (CH), 122.7 (CH), 124.9 (CH), 126.1 (C), 126.7 (CH), 129.2 (CH), 130.3 (C), 133.7 (CH), 135.4 (C), 136.2 (C), 138.0 (C); mp 214−216 °C ($EtOH-CH_2Cl_2$). Anal. Calcd for $C_{22}H_{16}N_2SO_2 \cdot CH_2Cl_2$: C, 60.39; H, 3.96; N, 6.12; S, 7.01. Found: C, 59.99; H, 4.36; N, 6.35; S, 7.40.

2-(4-Methyl-2-pyridyl)indole (13). A solution of compound **4b** (2.0 g, 5.8 mmol) in EtOH (343 mL) and 10% aqueous NaOH (34 mL) was heated at reflux for 12 h. The resulting mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (100 mL). The organic solution was washed with water and aqueous Na_2CO_3, dried, and concentrated. Column chromatography (CH_2Cl_2) of the residue afforded pure **13** (1.2 g, 96%): IR ($CDCl_3$) 3440, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3 H), 6.91 (d, J = 5.0 Hz, 1 H), 7.00 (d, J = 1.2 Hz, 1 H), 7.05−7.15 (m, 2 H), 7.22 (d, J = 7.8 Hz, 1 H), 7.61 (br s, 1 H), 7.64 (d, J = 6.8 Hz, 1 H), 8.43 (d, J = 5.0 Hz, 1 H), 10.89 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 100.5 (CH), 111.5 (CH), 120.0 (CH), 120.9 (CH), 121.1 (CH), 122.9 (CH), 123.3 (CH), 129.1 (C), 137.0 (C), 137.1 (C), 148.1 (C), 148.8 (CH), 150.6 (C); mp 164−165 °C (Et_2O). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.85; H, 5.80; N, 13.43.

Ethyl 2-(4-Methyl-2-pyridyl)-1-indolecarboxylate (14). A suspension of pyridylindole **4a** (200 mg, 0.6 mmol), NaH (230 mg, 5.8 mmol, 60% oil dispersion), and diethyl carbonate (3 mL) was heated at reflux for 7 h. The resulting mixture was poured into saturated aqueous NH_4Cl and extracted with AcOEt. The combined organic extracts were dried and concentrated, and the residue was chromatographed (CH_2Cl_2) to give pure compound **14** (90 mg, 56%): ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3 H), 2.43 (s, 3 H), 4.68 (q, 2 H, J = 7.1 Hz, 2 H), 6.84 (s, 1 H), 7.05 (d, J = 5.1 Hz, 1 H), 7.13 (td, J = 7.0, 1.1 Hz, 1 H), 7.25 (td, J = 8.2, 1.1 Hz, 1 H), 7.42 (d, J = 8.2 Hz, 1 H), 7.55 (s, 1 H), 7.66 (d, J = 7.0 Hz, 1 H), 8.55 (d, J = 5.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.4 (CH_3), 21.0 (CH_3), 39.3 (CH_2), 103.4 (CH), 109.9 (CH), 119.6 (CH), 120.9 (CH), 122.2 (CH), 122.7 (CH), 124.1 (CH), 127.7 (C), 138.0 (C), 138.3 (C), 147.4 (C), 148.7 (C), 152.3 (CH); MS, *m/e* (relative intensity) 280 (M^+, 31), 189 (45), 179 (33), 149 (41), 140 (46), 115 (32), 113 (53), 106 (30), 100 (36), 94 (58), 92 (31), 88 (33), 86 (36), 83 (33), 76 (32), 75 (39), 73 (31), 65 (58), 63 (40), 57 (100), 53 (41), 51 (30), 50 (31), 48 (36), 46 (74).

Dimethyl 2-(2-Indolyl)-4-pyridinemalonate (15). A solution of LDA (1.5 M in cyclohexane, 22.4 mL, 33.7 mmol) was slowly added to a solution of pyridylindole **13** (2.0 g, 9.6 mmol) in anhydrous THF (60 mL) at −78 °C, and the mixture was stirred for 30 min. Then, a solution of methyl chloroformate (3.7 mL, 48 mmol) in anhydrous THF (10 mL) was added dropwise, and the solution was stirred at −78 °C for 30 min and at 25 °C for 3 h. The mixture was diluted with Et_2O and washed with aqueous Na_2CO_3. The organic layer was dried and concentrated, and the resulting oil was crystallized (EtOH) to give pure malonate **15** (2.0 g, 64%): IR (KBr) 3417, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 6 H), 4.71 (s, 1 H), 7.06 (s, 1 H), 7.10−7.25 (m, 2 H), 7.24 (d, J = 5.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 7.8 Hz, 1 H), 7.83 (s, 1 H), 8.54 (d, J = 5.0 Hz, 1 H), 9.93 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 53.1 (CH_3), 56.8 (CH), 101.2 (CH), 111.5 (CH), 120.2 (CH), 120.6 (CH), 121.3 (CH), 122.5 (CH), 123.4 (CH), 129.1 (C), 136.4 (C), 136.8 (C), 141.9 (C), 149.5 (CH), 151.1 (C), 167.5 (C); mp 130 °C (EtOH). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.96; H, 4.93; N, 8.52. From the mother liquors, **1-(methoxycarbonyl)-2-[1-(methoxycarbonyl)-2-indolyl]-4-[bis(methoxycarbonyl)methylene]-1,4-dihydropyridine (21)** was isolated in less than 5% yield: IR (KBr) 1556, 1602, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.95 (s, 3 H), 6.72 (s, 1 H), 7.15 (dd, J = 8.3, 2.5 Hz, 1 H), 7.20 (d, J = 2.5 Hz, 1 H), 7.27 (td, J = 7.5, 2.1 Hz, 1 H), 7.38 (td, J = 7.8, 2.1 Hz, 1 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.76 (d, J = 8.3 Hz, 1 H), 8.08 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 51.6 (CH_3), 53.8 (CH_3), 54.9 (CH_3), 104.9 (C), 111.1 (CH), 112.0 (CH), 115.6 (CH), 117.2 (CH), 121.3 (CH), 123.5 (CH), 125.6 (CH), 128.8 (C), 131.4 (CH), 134.6 (C), 135.7 (C), 136.1 (C), 144.3 (C), 150.5 (C), 151.7 (C), 167.6 (C). Anal. Calcd for $C_{22}H_{20}N_2O_8$: C, 59.99; H, 4.57; N, 6.36. Found: C, 60.10; H, 4.75; N, 6.38.

Dimethyl *cis*-2-(2-Indolyl)-4-piperidinemalonate (16). A solution of pyridylindole **15** hydrochloride (1.5 g, 4.3 mmol) in MeOH (100 mL) was stirred at 25 °C under hydrogen for 24 h in the presence of PtO_2 (100 mg). The catalyst was removed by filtration, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, and the solution was washed with aqueous Na_2CO_3, dried, and concentrated. Column chromatography (97:3 AcOEt−EtOH) of the residue gave pure piperidine **16** (851 mg, 60%): IR (KBr) 3458, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (m, 1 H), 1.42 (q, J = 11.7 Hz, 1 H), 1.75 (dm, J = 12.7 Hz, 1 H), 2.02 (dm, J = 11.7 Hz, 1 H), 2.35 (m, 1 H), 2.84 (td, J = 12.2, 2.6 Hz, 1 H), 3.20 (dm, J = 12.2 Hz, 1 H), 3.25 (d, J = 9.0 Hz, 1 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 3.93 (dd, J = 11.3, 2.6 Hz, 1 H), 6.34 (s, 1 H), 7.00−7.20 (m, 2 H), 7.32 (d, J = 7.8 Hz, 1 H), 7.54 (d, J = 7.3 Hz, 1 H), 8.73 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_2), 36.3 (CH), 36.8 (CH_2), 45.9 (CH_2), 52.4 (CH_3), 54.6 (CH), 57.2 (CH), 98.6 (CH), 110.9 (CH), 119.7 (CH), 120.4 (CH), 121.6 (CH), 128.0 (C), 136.0 (C), 141.0 (C), 168.8 (C); mp (picrate) 156−158 °C (EtOH). Anal. Calcd for $C_{24}H_{25}N_5O_{11} \cdot C_2H_6O$: C, 51.57; H, 5.16; N, 11.56. Found: C, 51.61; H, 5.24; N, 11.44.

Dimethyl *cis*-2-(2-Indolyl)-1-[2-(phenylsulfinyl)ethyl]-4-piperidinemalonate (17). A solution of indolylpiperidine **16** (2.1 g, 6.4 mmol) and phenyl vinyl sulfoxide (1.1 mL, 8.3 mmol) in MeOH (31 mL) was heated at reflux for 48 h. The mixture was cooled and concentrated, and the residue was chromatographed (from 1:1 hexane−AcOEt to AcOEt) to give two epimeric sulfoxides **17** (2.0 g and 975 mg; 89% overall yield). **17** (major epimer, oil): ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 2 H), 1.90 (m, 2 H), 2.27 (td, J = 11.8, 2.4 Hz, 1 H), 2.38 (m, 2 H), 2.80 (m, 2 H), 3.11 (m, 1 H), 3.22 (d, J = 9.2 Hz, 1 H), 3.30 (dt, J = 11.8, 3.0 Hz, 1 H), 3.60 (dd, J = 11.3, 2.7 Hz, 1 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 6.31 (s, 1 H), 7.00−7.17 (m, 2 H), 7.42−7.58 (m, 7 H), 9.95 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.2 (CH_2), 36.1 (CH), 39.4 (CH_2), 47.0 (CH_2), 51.5 (CH_2), 52.3 (CH_3), 54.5 (CH_2), 56.8 (CH), 61.5 (CH), 100.1 (CH), 111.5 (CH), 119.2 (CH), 119.6 (CH), 121.1 (CH), 123.8 (CH), 128.0 (C), 129.0 (CH), 130.7 (CH), 136.5 (C), 140.3 (C), 143.6 (C), 168.4 (C). **17** (minor epimer): ^{1}H NMR ($CDCl_3$) δ 1.42 (qd, J = 12.5, 3.8 Hz, 1 H), 1.59 (q, J = 12.0 Hz, 1 H), 1.69 (dm, J = 12.5 Hz, 1 H), 1.88 (dm, J = 12.0 Hz, 1 H), 2.26 (m, 2 H), 2.56 (m, 2 H), 2.80 (m, 2 H), 3.14 (dm, J = 11.6 Hz, 1 H), 3.17 (d, J = 9.1 Hz, 1 H), 3.44 (dd, J = 11.4, 2.7 Hz, 1 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 6.28 (d, J = 1.6 Hz, 1 H), 7.08 (m, 1 H), 7.16 (m, 1 H), 7.31 (m, 5 H), 7.37 (d, J = 7.9 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 9.15 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.1 (CH_2), 35.9 (CH), 37.6 (CH_2), 48.3 (CH_2), 52.3 (CH_3), 53.0 (CH_2), 54.8 (CH_2), 56.8 (CH), 61.2 (CH), 100.5 (CH), 111.1 (CH), 119.4 (CH), 119.9 (CH), 121.4 (CH), 123.6 (CH), 127.8 (C), 128.8 (CH), 130.6 (CH), 136.0 (C), 139.6 (C), 143.3 (C), 168.3 (C). MS, *m/e* (relative intensity) 483 (M^+ + 1, 38), 482 (M^+, 9), 357 (57), 352 (31), 314 (31), 182 (91), 144 (90), 143 (54), 141 (42), 127 (59), 126 (34), 111 (61), 109 (100); mp 155−156 °C. Anal. Calcd for

$C_{26}H_{30}N_2O_5S \cdot {}^1/_2H_2O$: C, 63.52; H, 6.35; N, 5.70; S, 6.52. Found: C, 63.40; H, 6.32; N, 5.60; S, 6.30.

Pummerer Cyclization of Sulfoxide 17. Method A. TFAA (257 μL, 1.82 mmol) was added to a solution of sulfoxides **17** (440 mg, 0.91 mmol) in CH_2Cl_2 (18 mL) at 0 °C, and the mixture was stirred at 25 °C for 2 h. The solution was poured into aqueous Na_2CO_3, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (1:1 AcOEt−hexane) to give 17 mg of **dimethyl *cis*-7-(phenylthio)indolo[2,3-*a*]quinolizidine-2-malonate** (**19**) as a C_7 epimeric mixture and 70 mg of pure α-PhS epimer (20% overall yield): IR ($CHCl_3$) 3400, Bohlmann bands, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (q, J = 12.0 Hz, 1 H), 1.44 (qd, J = 12.0, 4.5 Hz, 1 H), 1.64 (dm, J = 12.0 Hz, 1 H), 2.13 (dm, J = 12.0 Hz, 1 H), 2.27 (m, 1 H), 2.38 (td, J = 12.0, 2.0 Hz, 1 H), 2.61 (dd, J = 11.7, 10.0 Hz, 1 H), 2.90 (dm, J = 12.0 Hz, 1 H), 3.20 (dd, J = 11.7, 6.0 Hz, 1 H), 3.20 (d, J = 8.4 Hz, 1 H), 3.25 (d, J = 12.0 Hz, 1 H), 3.68 (s, 3 H), 3.70 (s, 3 H), 4.75 (ddd, J = 10.0, 6.0, 2.0 Hz, 1 H), 7.00−7.40 (m, 8 H); 7.83 (br s, 1 H), 7.93 (dm, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.3 (CH_2), 33.4 (CH_2), 35.8 (CH), 42.2 (CH), 52.6 (CH_3), 54.2 (CH_2), 57.0 (CH), 58.8 (CH), 60.4 (CH_2), 107.7 (C), 110.8 (CH), 119.7 (CH), 120.6 (CH), 121.8 (CH), 126.5 (C), 126.9 (CH), 128.8 (CH), 132.1 (CH), 134.7 (C), 136.0 (C), 136.1 (C), 168.6 (C); MS, *m*/*e* (relative intensity) 465 (M^+ + 1, 1), 358 (21), 357 (92), 356 (38), 355 (24), 133 (43), 111 (100), 101 (75). Anal. Calcd for $C_{26}H_{28}N_2O_4S$: C, 67.22; H, 6.07; N, 6.03. Found: C, 67.18; H, 6.46; N, 5.69. When the column was washed with 70:30:5 Et_2O−acetone−DEA, the conjugate base of **23** (275 mg, 65%) was isolated: ^1H NMR ($CDCl_3$) δ 0.63 (qd, J = 12.3, 3.9 Hz, 1 H), 1.20 (q, J = 12.0 Hz, 1 H), 1.50 (dm, J = 12.3 Hz, 1 H), 2.20 (m, 1 H), 2.29 (dm, J = 12.0 Hz, 1 H), 2.57 (td, J = 11.2, 2.4 Hz, 1 H), 2.80 (dt, J = 11.2, 3.4 Hz, 1 H), 2.95 (dd, J = 15.0, 5.5 Hz, 1 H), 3.00 (d, J = 8.0 Hz, 1 H), 3.28 (ddd, J = 15.0, 12.0, 3.7 Hz, 1 H), 3.61 (m, 1 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 3.80 (m, 1 H), 4.02 (dd, J = 11.3, 3.1 Hz, 1 H), 7.10 (m, 2 H), 7.49 (m, 6 H), 7.72 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.5 (CH_2), 35.5 (CH), 37.2 (CH_2), 48.3 (CH_2), 51.3 (CH_2), 52.2 (CH_3), 52.4 (CH_3), 53.9 (CH_2), 56.8 (CH), 66.5 (CH), 67.4 (C), 114.0 (CH), 118.2 (CH), 119.4 (CH), 119.5 (CH), 125.9 (CH), 129.4 (CH), 130.1 (CH), 133.0 (C), 137.4 (C), 147.8 (C), 158.8 (C), 168.2 (C); MS, *m*/*e* (relative intensity) 464 (M^+, 10), 451 (45), 432 (45), 355 (54), 342 (39), 341 (100), 251 (77), 218 (72), 217 (41), 200 (34), 182 (52), 174 (45), 173 (25), 168 (25), 130 (28). Anal. Calcd for $C_{26}H_{28}N_2O_4S \cdot {}^3/_2H_2O$: C, 63.52; H, 6.36; N, 5.70; S, 6.52. Found: C, 63.55; H, 6.30; N, 5.89; S, 6.27.

Method B. TFAA (785 μL, 5.6 mmol) was added to a solution of sulfoxide **17** (670 mg, 1.4 mmol) in CH_2Cl_2 (28 mL) at 0 °C. The resulting mixture was stirred at 25 °C for 2.5 h and concentrated under vacuum. Chlorobenzene (30 mL) was added, and the solution was heated at reflux for 2 h and concentrated. The residue was dissolved in CH_2Cl_2, and the organic solution was washed with aqueous Na_2CO_3, dried, and concentrated. Column chromatography of the residue (AcOEt) afforded **dimethyl *cis*-1-(2-hydroxyethyl)-2-[3-(phenylthio)-2-indolyl]-4-piperidinemalonate** (**18**): 490 mg, 73%; IR (NaCl) 3400, 3100, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (qd, J = 12.0, 3.5 Hz, 1 H), 1.64 (q, J = 12.0 Hz, 1 H), 1.72−1.85 (m, 2 H), 2.10 (dm, J = 13.5 Hz, 1 H), 2.23 (td, J = 12.0, 3.0 Hz, 1 H), 2.30 (m, 1 H), 2.72 (ddd, J = 13.5, 10.0, 4.5 Hz, 1 H), 3.18 (d, J = 8.5 Hz, 1 H), 3.28 (dm, J = 12.0 Hz, 1 H), 3.41 (dt, J = 11.8, 4.0 Hz, 1 H), 3.55 (s, 3 H), 3.68 (s, 3 H), 3.71 (dm, J = 11.8 Hz, 1 H), 4.03 (dd, J = 11.5, 2.8 Hz, 1 H), 6.98−7.22 (m, 7 H), 7.33 (dm, J = 8.0 Hz, 1 H), 7.55 (dm, J = 7.6 Hz, 1 H), 9.90 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.4 (CH_2), 35.9 (CH), 37.6 (CH_2), 52.3 (CH_2), 52.4 (CH_3), 56.4 (CH_2), 56.7 (CH), 58.4 (CH_2), 59.3 (CH), 99.7 (C), 111.6 (CH), 119.1 (CH), 120.6 (CH), 122.8 (CH), 124.6 (CH), 125.5 (CH), 128.7 (CH), 129.7 (C), 135.8 (C), 139.0 (C), 144.3 (C), 168.2 (C), 168.4 (C); MS, *m*/*e* (relative intensity) 482 (M^+, 27), 451 (36), 342 (39), 341 (100), 238 (18), 200 (21); HRMS calcd for $C_{26}H_{30}N_2O_5S$ 482.1870, found 482.1870. Anal. Calcd for $C_{26}H_{30}N_2O_5S \cdot {}^1/_2H_2O$: C, 63.52; H, 6.35; N, 5.70; S, 6.52. Found: C, 63.82; H, 6.44; N, 5.71; S, 6.26.

Method C. TMSOTf (435 μL, 2.4 mmol) was added to a solution of sulfoxides **17** (330 mg, 0.685 mmol) in CH_2Cl_2 (9 mL) containing DIPEA (410 μl, 2.4 mmol), and the mixture was stirred at rt for 30 min. The solution was poured into $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried and evaporated, and the residue was chromatographed (1:2 AcOEt−hexane) to give the separate C_6 epimers of **dimethyl *cis*-6-(phenylthio)-6,7,10,-11,12,12a-hexahydro-9*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*b*]-indole-11-malonate** (**22**). **α-PhS epimer**: 80 mg (25%); IR (KBr) 1754, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (q, J = 12.0 Hz, 1 H), 1.45 (qd, J = 12.5, 4.0 Hz, 1 H), 1.71 (dt, J = 13.0, 2.5 Hz, 1 H), 2.17−2.38 (m, 3 H), 2.98 (dt, J = 11.2, 3.0 Hz, 1 H), 3.10 (dd, J = 12.0, 3.0 Hz, 1 H), 3.23 (d, J = 9.0 Hz, 1 H), 3.25 (dm, J = 10.4 Hz, 1 H), 3.37 (dd, J = 12.0, 1.4 Hz, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 5.61 (dd, J = 3.0, 1.4 Hz, 1 H), 6.16 (s, 1 H), 7.12 (m, 2 H), 7.20−7.36 (m, 6 H), 7.52 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.3 (CH_2), 34.1 (CH_2), 35.6 (CH), 52.4 (CH_3), 52.5 (CH_3), 54.5 (CH_2), 57.2 (CH), 59.3 (CH), 59.6 (CH_2), 61.6 (CH), 96.8 (CH), 110.8 (CH), 120.2 (CH), 121.0 (CH), 128.1 (CH), 128.7 (CH), 128.8 (C), 134.0 (C), 134.6 (C), 135.1 (C), 137.2 (C), 168.6 (C). ***β*-PhS epimer**: 100 mg (32%); IR (KBr) 1753, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24−1.49 (m, 2 H), 1.60 (m, 1 H), 1.70 (dt, J = 13.0, 3.0 Hz, 1 H), 2.14−2.32 (m, 2 H), 2.68 (dd, J = 12.4, 10.0 Hz, 1 H), 2.90 (dm, J = 10.0 Hz, 1 H), 2.98 (dt, J = 11.3, 3.0 Hz, 1 H), 3.23 (d, J = 8.5 Hz, 1 H), 3.43 (dd, J = 12.4, 6.6 Hz, 1 H), 3.73 (s, 3 H), 3.78 (s, 3 H), 5.65 (dd, J = 10.0, 6.6 Hz, 1 H), 6.18 (s, 1 H), 7.04 (dm, J = 8.2 Hz, 2 H), 7.12−7.34 (m, 5 H), 7.55 (dm, J = 7.0 Hz, 1 H), 7.93 (dm, J = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.0 (CH_2), 34.1 (CH_2), 35.3 (CH), 52.5 (CH_3), 52.6 (CH_3), 54.2 (CH_2), 57.0 (CH), 58.6 (CH_2), 58.9 (CH), 59.4 (CH), 97.2 (CH), 112.9 (CH), 120.3 (CH), 120.4 (CH), 121.1 (CH), 128.7 (CH), 128.9 (CH), 134.9 (CH), 139.4 (C), 168.6 (C).

Dimethyl *cis*-2-[1-(Methoxycarbonyl)-2-indolyl]-1-[2-(phenylsulfinyl)ethyl]-4-piperidinemalonate (24a). Methyl cyanoformate (200 μL, 2.5 mmol) was added to a solution of sulfoxide **17** (major epimer, 140 mg, 0.29 mmol) in acetonitrile (2 mL) containing DMAP (40 mg, 0.32 mmol), and the mixture was heated at reflux for 5 h. Water was added, and the aqueous layer was extracted with AcOEt. The combined organic extracts were dried and concentrated, and the residue was chromatographed (15:1 Et_2O−MeOH) to give pure sulfoxide **24a-1** (139 mg, 89%): ^1H NMR ($CDCl_3$) δ 1.40 (q, J = 11.4 Hz, 1 H), 1.51 (m, 1 H), 1.70 (dm, J = 11.4 Hz, 1 H), 2.04 (dm, J = 12.5 Hz, 1 H), 2.27−2.49 (m, 3 H), 2.70−2.75 (m, 2 H), 3.19 (m, 2 H), 3.20 (d, J = 8.8 Hz, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 4.07 (s, 3 H), 4.24 (dd, J = 10.7, 2.0 Hz, 1 H), 6.63 (s, 1 H), 7.20 (m, 8 H), 8.00 (d, J = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.5 (CH_2), 36.3 (CH), 36.9 (CH_2), 46.1 (CH_2), 52.3 (CH_3), 52.8 (CH_2), 53.6 (CH_3), 55.2 (CH_2), 56.9 (CH), 59.5 (CH), 108.4 (CH), 115.4 (CH), 120.5 (CH), 123.1 (CH), 123.7 (CH), 124.1 (CH), 128.9 (CH), 130.5 (CH), 136.0 (C), 142.5 (C), 143.8 (C), 152.2 (C), 168.5 (C). Operating as above, from **17** (minor epimer, 140 mg) was obtained pure sulfoxide **24a-2** (83%): ^1H NMR ($CDCl_3$) δ 1.34 (q, J = 11.3 Hz, 1 H), 1.42 (qd, J = 11.7, 2.7 Hz, 1 H), 1.68 (dm, J = 11.7 Hz, 1 H), 1.98 (dm, J = 11.3 Hz, 1 H), 2.25 (m, 2 H), 2.48 (m, 1 H), 2.77 (m, 3 H), 3.11 (dm, J = 12 Hz, 1 H), 3.12 (d, J = 9.2 Hz, 1 H), 3.61 (s, 3 H), 3.66 (s, 3 H), 3.96 (s, 3 H), 4.18 (dd, J = 10.5, 2.0 Hz, 1 H), 6.56 (s, 1 H), 7.12−7.32 (m, 7 H), 7.40 (d, J = 7.3 Hz, 1 H), 7.95 (d, J = 7.4 Hz, 1 H). Anal. Calcd for $C_{28}H_{32}N_2O_7S$: C, 62.20; H, 5.97; N, 5.18; S, 5.93. Found: C, 62.09; H, 6.11; N, 5.28; S, 5.90.

Dimethyl *cis*-2-[1-(*tert*-Butoxycarbonyl)-2-indolyl]-1-[2-(phenylsulfinyl)ethyl]-4-piperidinemalonate (24b). A mixture of **17** (major epimer, 200 mg, 0.42 mmol), DMAP (10 mg, 0.08 mmol), and di-*tert*-butyl dicarbonate (229 mg, 1.05 mmol) in anhydrous CH_2Cl_2 (4 mL) was stirred under Ar at 25 °C for 10 h. Evaporation followed by chromatography (12:1 Et_2O−MeOH) gave pure sulfoxide **24b-1** (235 mg, 97%): ^1H NMR ($CDCl_3$) δ 1.43 (m, 2 H), 1.70 (m, 1 H), 1.70 (s, 9 H), 2.02 (dm, J = 12.3 Hz, 1 H), 2.24−2.53 (m, 3 H), 2.71 (m, 2 H), 3.13 (m, 2 H), 3.20 (d, J = 9.0 Hz, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 4.34 (dd, J = 11.0, 2.4 Hz, 1 H), 6.64 (s, 1 H), 7.20−7.50 (m, 8 H), 8.10 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.2 (CH_3), 28.5 (CH_2), 36.3 (CH), 36.8 (CH_2), 46.2 (CH_2), 52.4 (CH_3),

52.9 (CH_2), 55.3 (CH_2), 57.1 (CH), 59.4 (CH), 84.3 (C), 107.7 (CH), 115.4 (CH), 120.4 (CH), 122.7 (CH), 123.6 (CH), 123.7 (CH), 128.9 (CH), 130.6 (CH), 136.4 (C), 142.5 (C), 143.8 (C), 150.2 (C), 168.4 (CH). Anal. Calcd for $C_{31}H_{38}N_2O_7S$: C, 63.90; H, 6.57; N, 4.81; S, 5.50. Found: C, 64.02; H, 6.84; N, 4.72; S, 5.31. Operating as above, from **17** (minor epimer, 200 mg) was obtained pure sulfoxide **24b-2** (236 mg, 98%): ^{1}H NMR ($CDCl_3$) δ 1.36 (q, J = 12.3 Hz, 1 H), 1.48 (qd, J = 12.3, 3.6 Hz, 1 H), 1.70 (s, 9 H), 1.76 (dm, J = 12.3 Hz, 1 H), 2.03 (dm, J = 12.3 Hz, 1 H), 2.26 (m, 1 H), 2.34 (td, J = 11.8, 2.3 Hz, 1 H), 2.59 (m, 1 H), 2.87 (m, 3 H), 3.18 (d, J = 9.0 Hz, 1 H), 3.20 (dm, J = 11.8 Hz, 1 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 4.25 (dd, J = 11.0, 2.7 Hz, 1 H), 6.60 (s, 1 H), 7.10−7.40 (m, 7 H), 7.43 (d, J = 7.5 Hz, 1 H), 8.05 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.0 (CH_3), 29.2 (CH_2), 36.0 (CH), 38.5 (CH_2), 47.3 (CH_2), 52.2 (CH_3), 53.0 (CH_2), 54.4 (CH_2), 56.9 (CH), 59.7 (CH), 84.3 (C), 107.6 (CH), 115.5 (CH), 120.2 (CH), 122.6 (CH), 123.5 (CH), 128.7 (CH), 130.6 (CH), 136.2 (C), 143.0 (C), 143.2 (C), 149.9 (C), 168.3 (C). Anal. Calcd for $C_{31}H_{38}N_2O_7S$: C, 63.90; H, 6.57; N, 4.81; S, 5.50. Found: C, 63.55; H, 6.71; N, 4.71; S, 5.10.

Dimethyl *cis*-12-(Methoxycarbonyl)-7-(phenylthio)indolo[2,3-*a*]quinolizidine-2-malonate (25a). TMSOTf (200 μL, 1.01 mmol) was added under Ar to a solution of sulfoxide **24a-1** (130 mg, 0.24 mmol) and DIPEA (194 μL, 1.13 mmol) in anhydrous CH_2Cl_2 (1 mL), and the mixture was stirred at 25 °C for 15 min. The solution was poured into aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were dried and concentrated, and the residue was chromatographed (1:1 AcOEt−hexane) to give two epimeric indoloquinolizidines **25a**. **α-PhS epimer**: 60 mg (48%); IR (KBr) 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 3 H), 1.97 (dm, J = 12.3 Hz, 1 H), 2.45 (m, 1 H), 2.85 (dd, J = 12.3, 3.0 Hz, 1 H), 3.15 (m, 1 H), 3.20 (d, J = 8.3 Hz, 1 H), 3.21 (m, 1 H), 3.45 (dd, J = 12.3, 3.5 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 4.06 (s, 3 H), 4.43 (dd, J = 10.7, 1.6 Hz, 1 H), 4.58 (t, J = 3.2 Hz, 1 H), 7.20 (m, 5 H), 7.53 (m, 2 H), 7.63 (dm, J = 7.2 Hz, 1 H), 8.13 (dm, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.1 (CH_2), 30.1 (CH_2), 36.9 (CH), 42.5 (CH), 51.0 (CH_2), 52.4 (CH_3), 53.7 (CH_3), 54.3 (CH_2), 57.1 (CH), 57.2 (CH), 115.0 (C), 115.6 (CH), 119.3 (CH), 123.1 (CH), 124.5 (CH), 127.1 (CH), 128.0 (C), 129.0 (CH), 132.0 (CH), 135.8 (C), 136.4 (C), 138.4 (C), 151.7 (C), 168.5 (C). Anal. Calcd for $C_{28}H_{30}N_2O_6S$: C, 64.35; H, 5.79; N, 5.36; S, 6.14. Found: C, 64.31; H, 5.74; N, 5.35; S, 6.03. ***β*-PhS epimer**: 32 mg (25%); IR (KBr) Bohlmann bands, 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (q, J = 11.0 Hz, 1 H), 1.45−1.65 (m, 2 H), 2.08 (dm, J = 12.5 Hz, 1 H), 2.38 (m, 1 H), 2.77 (td, J = 12.5, 3.5 Hz, 1 H), 3.05 (dm, J = 12.5 Hz, 1 H), 3.14 (d, J = 8.5 Hz, 1 H), 3.12−3.20 (m, 2 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 3.85 (dm, J = 11.0 Hz, 1 H), 4.03 (s, 3 H), 4.43 (m, 1 H), 7.20−7.35 (m, 5 H), 7.42 (m, 2 H), 7.75 (dm, J = 7.2 Hz, 1 H), 8.12 (dm, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.8 (CH_2), 33.6 (CH_2), 36.9 (CH), 42.7 (CH), 52.4 (CH_3), 53.8 (CH_3), 54.5 (CH_2), 55.7 (CH_2), 57.4 (CH), 59.1 (CH), 115.3 (CH), 115.6 (C), 119.7 (CH), 123.1 (CH), 124.6 (CH), 127.3 (CH), 128.0 (C), 128.8 (CH), 132.9 (CH), 135.1 (C), 136.7 (C), 138.2 (C), 151.9 (C), 168.7 (C). Anal. Calcd for $C_{28}H_{30}N_2O_6S$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.11; H, 6.13; N, 5.42. A similar result was obtained operating from sulfoxide **24a-2**.

Dimethyl *cis*-12-(*tert*-Butoxycarbonyl)-7-(phenylthio)-indolo[2,3-*a*]quinolizidine-2-malonate (25b). TMSOTf (956 μL, 4.8 mmol) was added under Ar to a solution of sulfoxide **24b-1** (700 mg, 1.2 mmol) and DIPEA (904 μL, 5.25 mmol) in anhydrous CH_2Cl_2 (4 mL), and the mixture was stirred at 25 °C for 15 min. Workup as above, followed by chromatography (1:1 AcOEt−hexane), gave two epimeric indoloquinolizidines **25b**. **α-PhS epimer**: 326 mg (48%); IR (NaCl) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 2 H), 1.68 (s, 9 H), 1.70 (m, 1 H), 1.94 (dm, J = 12.3 Hz, 1 H), 2.45 (m, 1 H), 2.84 (dd, J = 12.4, 2.3 Hz, 1 H), 3.13 (dm, J = 13.0 Hz, 1 H), 3.19 (d, J = 9.3 Hz, 1 H), 3.25 (td, J = 13.0, 3.0 Hz, 1 H), 3.48 (dd, J = 12.4, 3.5 Hz, 1 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 4.55 (m, 2 H), 7.20−7.40 (m, 5 H), 7.55 (m, 2 H), 7.63 (dm, J = 7.3 Hz, 1 H), 8.20 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.5 (CH_2), 28.0 (CH_3), 29.3 (CH_2), 36.4 (CH), 42.5 (CH), 49.7 (CH_2), 52.4 (CH_3), 54.1 (CH_2), 56.4 (CH), 57.5 (CH), 84.4 (C), 114.0 (C), 115.8 (CH), 118.9 (CH), 122.8 (CH), 124.3 (CH), 127.1 (CH), 127.8 (C), 129.0 (CH), 131.9 (CH), 136.0 (C), 136.7 (C), 138.6 (C), 149.8 (C), 168.5 (C); mp 139−140 °C. Anal. Calcd for $C_{31}H_{36}N_2O_6S$: C, 65.94; H, 6.43; N, 4.96; S, 5.68. Found: C, 65.78; H, 6.49; N, 4.89; S, 5.58. ***β*-PhS epimer**: 112 mg (17%); IR (NaCl) Bohlmann bands, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (q, J = 12.0 Hz, 1 H), 1.56 (m, 2 H), 1.67 (s, 9 H), 2.10 (dm, J = 12.0 Hz, 1 H), 2.40 (m, 1 H), 2.80 (td, J = 12.4, 2.5 Hz, 1 H), 3.02 (dm, J = 12.4 Hz, 1 H), 3.06 (dd, J = 12.0, 4.2 Hz, 1 H), 3.12 (d, J = 9.4 Hz, 1 H), 3.17 (dd, J = 12.0, 4.4 Hz, 1 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.95 (dm, J = 10.0 Hz, 1 H), 4.45 (br s, 1 H), 7.20−7.35 (m, 5 H), 7.41 (m, 2 H), 7.75 (d, J = 7.3 Hz, 1 H), 8.11 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.7 (CH_2), 28.0 (CH_3), 33.1 (CH_2), 36.3 (CH), 42.7 (CH), 52.3 (CH_3), 52.4 (CH_3), 54.3 (CH_2), 55.5 (CH_2), 57.6 (CH), 58.7 (CH), 84.4 (C), 115.4 (CH), 115.7 (C), 119.6 (CH), 122.7 (CH), 124.2 (CH), 127.1 (CH), 127.9 (C), 128.7 (CH), 132.7 (CH), 135.3 (C), 136.9 (C), 138.8 (C), 150.0 (C), 168.5 (C); mp 122−123 °C. Anal. Calcd for $C_{31}H_{36}N_2O_6S$: C, 65.94; H, 6.43; N, 4.96; S, 5.68. Found: C, 65.77; H, 6.33; N, 5.02; S, 5.57. Operating as above, from sulfoxide **24b-2** (150 mg) was obtained compound **25b** (71%) as a 2:1 mixture of C_7 epimers.

Dimethyl *cis*-7-(Phenylthio)indolo[2,3-*a*]quinolizidine-2-malonate (19). Compound **25b** (major epimer, 130 mg, 0.23 mmol) was dissolved in formic acid (20 mL), and the solution was stirred under Ar at 25 °C for 24 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with 10% aqueous Na_2CO_3. The organic solution was dried and concentrated, and the resulting residue was chromatographed. Elution with Et_2O successively afforded the β-PhS and α-PhS epimers of **19** in an approximate ratio of 1:1 (70 mg, 65% overall yield). A similar result was obtained starting from the minor epimer of **25b**. **19** (β-PhS epimer): IR (NaCl) 3400, Bohlmann bands, 1750, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (q, J = 12.0 Hz, 1 H), 1.64 (qd, J = 12.0, 4.0 Hz, 1 H), 1.70 (m, 1 H), 2.15 (dm, J = 12.0 Hz, 1 H), 2.33 (m, 1 H), 2.40 (td, J = 11.5, 3.3 Hz, 1 H), 2.90 (dd, J = 12.3, 3.5 Hz, 1 H), 2.98 (dt, J = 11.2, 3.2 Hz, 1 H), 3.16 (dd, J = 12.5, 1.0 Hz, 1 H), 3.21 (d, J = 11.5 Hz, 1 H), 3.26 (d, J = 9,0 Hz, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 4.56 (m, 1 H), 7.10−7.20 (m, 2 H), 7.25−7.30 (m, 4 H), 7.49 (m, 2 H), 7.62 (m, 1 H), 7.97 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.5 (CH_2), 33.5 (CH_2), 36.0 (CH), 42.7 (CH), 52.5 (CH_3), 54.6 (CH_2), 57.1 (CH), 58.9 (CH and CH_2), 107.6 (C), 111.0 (CH), 118.9 (CH), 119.8 (CH), 121.8 (CH), 126.2 (C), 126.7 (CH), 126.8 (CH), 133.0 (CH), 135.9 (C), 136.5 (C), 136.7 (C), 168.7 (C), 168.8 (C).

Dimethyl *cis*-2-(2-Indolyl)-1-[(*N*-methoxy-*N*-methylcarbamoyl)methyl]-4-piperidinemalonate (26). A mixture of indolylpiperidine **16** (1.0 g, 3.0 mmol), K_2CO_3 (460 mg, 3.3 mmol), NaI (213 mg, 1.4 mmol), and *N*-methoxy-*N*-methylchloroacetamide (460 mg, 3.3 mmol) in acetonitrile (33 mL) was stirred at 45 °C for 2 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2. The solution was washed with aqueous Na_2CO_3, dried, and concentrated to give an oil which, after column chromatography (8:2 AcOEt−hexane), afforded compound **26** (1.2 g, 92%): IR (NaCl) 3391, 1734, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48−1.82 (m, 3 H), 1.91 (dm, J = 12.8 Hz, 1 H), 2.30 (m, 1 H), 2.48 (td, J = 11.6, 2.4 Hz, 1 H), 3.05 (d, J = 16.2 Hz, 1 H), 3.08 (s, 3 H), 3.20 (dt, J = 11.6, 3.7 Hz, 1 H), 3.23 (d, J = 9.1 Hz, 1 H), 3.40 (s, 3 H), 3.43 (d, J = 16.2 Hz, 1 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 3.78 (dd, J = 11.1, 2.7 Hz, 1 H), 6.36 (d, J = 1.4 Hz, 1 H), 7.10 (m, 2 H), 7.33 (d, J = 8.1 Hz, 1 H), 7.53 (d, J = 7.5 Hz, 1 H), 9.03 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.3 (CH_2), 31.8 (CH_3), 36.0 (C), 38.0 (CH_2), 52.3 (CH_3), 53.1 (CH_2), 54.1 (CH_2), 56.9 (CH), 59.9 (CH), 60.9 (CH_3), 100.6 (CH), 111.0 (CH), 119.5 (CH), 120.1 (CH), 121.6 (CH), 128.0 (C), 136.0 (C), 140.1 (C), 168.7 (C); mp 131−133 °C (Et_2O). Anal. Calcd for $C_{22}H_{29}N_3O_6$: C, 61.24; H, 6.77; N, 9.74. Found: C, 61.27; H, 7.05; N, 9.56.

Reductive Cyclization of *N*-Methoxyamide 26. Method A. A solution of Red-Al (3.4 M in toluene, 332 μL, 1.2 mmol) was added to a solution of amide **26** (180 mg, 0.42 mmol) in toluene (15 mL) and THF (4 mL) at −40 °C. The mixture was stirred at −25 °C for 2 h, and the reaction was quenched with saturated Rochelle's salt solution (7.5 mL). To this solution were added sequencially CH_2Cl_2 (7.5 mL), 10% aqueous HCl

(7.5 mL), and saturated aqueous Na_2CO_3 (19 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. To the above solution were added MeSH (excess, 1.0 mL) and $BF_3{\cdot}Et_2O$ (53 μL, 0.42 mmol), and the mixture was stirred at 0 °C for 3.5 h, poured into water, and basified with Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. Column chromatography (1:1 AcOEt−hexane) of the residue successively afforded **30** (α-MeS; 11 mg, 7%), **27** (*β*-MeS; 20 mg, 12%), **30** (*β*-MeS; 13 mg, 8%), and **27** (α-MeS; 8 mg, 5%). **Dimethyl *cis*-7-(methylthio)indolo[2,3-*a*]quinolizidine-2-malonate** (**27**, *β*-MeS epimer): IR($CHCl_3$) 3392, 2800−2700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (q, J = 12.0 Hz, 1 H), 1.53−1.80 (m, 2 H), 2.08 (s, 3 H), 2.20 (dm, J = 12.0 Hz, 1 H), 2.30−2.54 (m, 2 H), 3.00 (dd, J = 12.2, 3.7 Hz, 1 H), 3.06 (dm, J = 11.6 Hz, 1 H), 3.20 (dm, J = 12.2 Hz, 1 H), 3.23 (masked, 1 H), 3.27 (d, J = 8.8 Hz, 1 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.11 (br s, 1 H), 7.12 (m, 2 H), 7.30 (dm, J = 7.4 Hz, 1H), 7.68 (dm, J = 7.4 Hz, 1H), 7.95 (br s, 1 H); MS, *m/e* (relative intensity) 402 (M^+, 3), 356 (29), 355 (100), 223 (35). **27** (α-MeS epimer): IR($CHCl_3$) 3400, 2800−2700, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (q, J = 12.0 Hz, 1 H), 1.50−1.80 (m, 2 H), 1.88 (s, 3 H), 2.25 (dm, J = 12.0 Hz, 1 H), 2.35 (m, 1 H), 2.47 (td, J = 11.6, 2.7 Hz, 1 H), 2.65 (dd, J = 11.4, 10.5 Hz, 1 H), 3.05 (dm, J = 11.6 Hz, 1 H), 3.20−3.35 (m, 2 H), 3.30 (d, J = 8.3 Hz, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.35 (m, 1 H), 7.16 (m, 2 H), 7.32 (dm, J = 7.4 Hz, 1 H), 8.03 (dm, J = 7.4 Hz, 1 H), 8.00 (br s, 1 H); MS, *m/e* (relative intensity) 402 (M^+, 1), 356 (28), 355 (100), 354 (29), 353 (41), 223 (71), 221 (25), 219 (34), 169 (20), 168 (21), 59 (21). **Dimethyl *cis*-6-(methylthio)-6,7,10,11,12,12a-hexahydro-9*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*a*]indole-11-malonate** (**30**, *β*-MeS epimer): IR($CHCl_3$) 3000−2700, 1752, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (m, 1 H), 1.79 (s, 3 H), 1.68−1.88 (m, 2 H), 2.26−2.44 (m, 3 H), 2.81 (dd, J = 12.5, 10.5 Hz, 1 H), 3.05 (dm, J = 11.0 Hz, 1 H), 3.28 (d, J = 8.6 Hz, 1 H), 3.30 (masked, 1 H), 3.40 (dd, J = 12.5, 6.5 Hz, 1 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 5.39 (dd, J = 10.5, 6.5 Hz, 1 H), 6.24 (s, 1 H), 7.14 (m, 2 H), 7.54 (dm, J = 7.4 Hz, 1 H), 8.00 (d, J = 7.4 Hz, 1 H); MS, *m/e* (relative intensity) 402 (M^+, 2), 355 (61), 354 (96), 353 (59), 293 (13), 223 (100), 221 (51), 169 (34), 168 (56), 101 (25), 69 (20), 59 (44), 55 (29). **30** (α-MeS epimer): IR($CHCl_3$) 2920, 2800−2700, 1752, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (q, J = 11.4 Hz, 1 H), 1.55 (masked, 1 H), 1.78 (m, 1 H), 1.91 (s, 3 H), 2.22−2.44 (m, 3 H), 3.07 (dm, J = 11.0 Hz, 1 H), 3.19 (dd, J = 12.1, 3.5 Hz, 1 H), 3.29 (d, J = 9.0 Hz, 1 H), 3.35 (d, J = 12.1 Hz, 1 H), 3.36 (masked, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 5.34 (br s, 1 H), 6.20 (s, 1 H), 7.16 (m, 2 H), 7.48 (m, 1 H), 7.55 (dm, J = 7.4 Hz, 1 H); MS, *m/e* (relative intensity) 402 (M^+, 12), 356 (30), 355 (100), 354 (31), 353 (22), 223 (62), 221 (20), 169 (16), 168 (19).

Method B. Operating as described above, from amide **26** (1.8 g, 4.2 mmol) and Red-Al (2.8 mL, 9.7 mmol, 3.4 M in toluene), but omitting the final treatment with MeSH, compounds **32** (70 mg, 4%), **29** (180 mg, 12%), **31** (460 mg, 30%), and **28** (470 mg, 30%) were successively obtained after column chromatography (AcOEt). **Dimethyl *cis*-7*β*-hydroxyindolo-[2,3-*a*]quinolizidine-2-malonate** (**28**): IR (KBr) 3800−3400, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (q, J = 12.0 Hz, 1 H), 1.56 (qd, J = 12.0, 4.1 Hz, 1 H), 1.73 (dm, J = 11.5 Hz, 1 H), 2.22 (dm, J = 12.0 Hz, 1 H), 2.37 (m, 1 H), 2.48 (td, J = 11.5, 2.8 Hz, 1 H), 2.73 (dd, J = 12.0, 2.6 Hz, 1 H), 3.00 (dm, J = 11.5 Hz, 1 H), 3.10 (dd, J = 12.0, 1.8 Hz, 1 H), 3.20 (dd, J = 11.5, 2.2 Hz, 1 H), 3.25 (d, J = 8.5 Hz, 1 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.88 (br s, 1 H), 7.15 (m, 2 H), 7.30 (m, 1 H), 7.68 (m, 1 H), 8.00 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.4 (CH_2), 33.1 (CH_2), 35.8 (CH), 52.5 (CH_3), 54.5 (CH_2), 56.7 (CH), 59.3 (CH), 61.5 (CH_2), 62.0 (CH), 110.8 (C), 111.1 (CH), 118.4 (CH), 120.0 (CH), 121.8 (CH), 126.2 (C), 136.0 (C), 136.5 (C), 168.7 (C). Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.49; H, 6.51; N, 7.44. **Dimethyl *cis*-7α-(*N*-methoxy-*N*-methylamino)indolo[2,3-*a*]quinolizidine-2-malonate** (**29**): IR($CHCl_3$) 3300, 2800−2700, 1759, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (q, J = 12.0 Hz, 1 H), 1.42−1.75 (m, 2 H), 2.14 (dm, J = 12.0 Hz, 1 H), 2.37 (m, 1 H), 2.57 (s, 3 H), 2.61 (masked, 1 H), 2.74 (dd, J = 11.3, 8.8 Hz, 1 H), 3.07 (dm, J = 11.5 Hz, 1 H), 3.18 (dd, J = 11.3, 5.4 Hz, 1 H), 3.26 (d, J = 8.6 Hz, 1 H), 3.45 (dm, J = 12.0 Hz, 1 H), 3.54 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.60 (m, 1 H), 7.10 (m, 2 H), 7.30 (m, 1 H), 7.85 (dm, J = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.5 (CH_2), 32.7 (CH_2), 35.9 (CH), 39.2 (CH_3), 51.2 (CH_2), 52.4 (CH_3), 54.6 (CH_2), 56.9 (CH), 58.3 (CH), 59.3 (CH), 59.8 (CH_3), 108.4 (C), 110.6 (CH), 119.4 (CH), 121.0 (CH), 121.4 (CH), 126.9 (C), 136.0 (C), 136.7 (C), 168.7 (C). Anal. Calcd for $C_{22}H_{29}N_3O_5{\cdot}{}^1/_2H_2O$: C, 62.25; H, 7.12; N, 9.89. Found: C, 62.58; H, 6.95; N, 9.58. **Dimethyl *cis*-6*β*-hydroxy-6,7,10,11,12,12a-hexahydro-9*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*b*]indole-11-malonate** (**31**): IR (KBr) 3800−3400, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (q, J = 12.0 Hz, 1 H), 1.50 (masked, 1 H), 1.60 (m, 1 H), 2.19 (dm, J = 13.5 Hz, 1 H), 2.28−2.44 (masked, 1 H), 2.32 (m, 1 H), 2.38 (dd, J = 12.0, 8.2 Hz, 1 H), 2.80 (dm, J = 12.0 Hz, 1 H), 3.00 (dm, J = 12.0 Hz, 1 H), 3.20 (d, J = 8.7 Hz, 1 H), 3.34 (dm, J = 12.0 Hz, 1 H), 3.40 (dd, J = 12.0, 5.0 Hz, 1 H), 3.75 (s, 3 H), 3.78 (s, 3 H), 5.72 (m, 1 H), 6.20 (s, 1 H), 7.13 (m, 2 H), 7.50 (dm, J = 7.0 Hz, 1 H), 7.64 (dm, J = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.5 (CH_2), 34.4 (CH_2), 35.4 (CH), 52.5 (CH_3), 54.3 (CH_2), 56.9 (CH), 59.0 (CH), 60.0 (CH_2), 75.8 (CH), 96.8 (CH), 111.8 (CH), 120.0 (CH), 120.3 (CH), 121.4 (CH), 128.6 (C), 136.1 (C), 138.1 (C), 168.7 (C); MS, *m/e* (relative intensity) 373 (M^+ + 1, 23), 372 (M^+, 100), 371 (M^+ − 1, 44), 355 (32), 354 (81), 353 (34), 241 (88), 239 (35), 223 (86), 197 (24), 169 (31), 168 (48), 130 (36), 69 (35), 59 (32), 57 (42), 55 (65). Anal. Calcd for: $C_{20}H_{24}N_2O_5{\cdot}{}^1/_4H_2O$: C, 63.73; H, 6.55; N, 7.43. Found: C, 63.74; H, 6.60; N, 7.41. **Dimethyl *cis*-6-oxo-6,7,9,10,12,12a-hexahydro-9*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*b*]indole-11-malonate** (**32**): IR (KBr) 3200−2700, 1754, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (q, J = 11.0 Hz, 1 H), 1.64−1.86 (m, 2 H), 2.31 (td, J = 11.7, 2.5 Hz, 1 H), 2.30−2.50 (m, 2 H), 3.05 (dm, J = 11.7 Hz, 1 H), 3.23 (d, J = 16.8 Hz, 1 H), 3.32 (d, J = 8.4 Hz, 1 H), 3.32 (masked, 1 H), 3.72 (d, J = 16.8 Hz, 1 H), 3.77 (s, 3 H), 3.81 (s, 3 H), 6.35 (s, 1 H), 7.30 (m, 2 H), 7.50 (m, 1 H), 8.38 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.0 (CH_2), 33.3 (CH_2), 35.1 (CH), 52.6 (CH_3), 54.0 (CH_2), 56.9 (CH), 57.4 (CH), 59.4 (CH_2), 103.6 (CH), 116.1 (CH), 120.3 (CH), 124.2 (CH), 124.6 (CH), 129.6 (C), 134.3 (C), 138.8 (C), 165.6 (C), 168.5 (C).

Dimethyl *cis*-Indolo[2,3-*a*]quinolizidine-2-malonate (20). A. From Sulfide 19. A mixture of **19** (33 mg, 0.084 mmol), Bu_3SnH (38 μl, 0.143 mmol), and AIBN in benzene (5 mL) was heated at reflux for 5 h. The mixture was concentrated, and the resulting residue was chromatographed (Et_2O) to give indoloquinolizidine **20**[39] (20 mg, 72%).

B. From Alcohol 28. Triethylsilane (135 μL, 0.85 mmol) and TFA (0.2 mL, 2.6 mmol) were added to a solution of compound **28** (93 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (5 mL), and the mixture was heated at reflux for 24 h. Aqueous K_2CO_3 was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a residue which, after column chromatography (AcOEt), afforded pure **20**[39] (62 mg, 70%): IR (KBr) 3600−3400, 2800−2700, 1748, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (q, J = 11.7 Hz, 1 H), 1.60 (qd, J = 12.0, 4.3 Hz, 1 H), 1.75 (dm, J = 12.0 Hz, 1 H), 2.22 (dm, J = 11.7 Hz, 1 H), 2.36 (m, 1 H), 2.46 (td, J = 11.7, 3.0 Hz, 1 H), 2.56−2.80 (m, 2 H), 2.90−3.15 (m, 3 H), 3.29 (d, J = 8.7 Hz, 1 H), 3.30 (masked, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 7.11 (m, 2 H), 7.32 (m, 1 H), 7.46 (dm, J = 7.4 Hz, 1 H), 7.82 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.6 (CH_2), 29.6 (CH_2), 33.7 (CH_2), 36.0 (CH), 52.6 (CH_3), 52.8 (CH_2), 54.9 (CH_2), 57.0 (CH), 59.3 (CH), 108.1 (C), 110.7 (CH), 118.0 (CH), 119.3 (CH), 121.3 (CH), 127.2 (C), 134.1 (C), 135.9 (C), 168.7 (C).

1-(Benzenesulfonyl)-3-(3-ethyl-4-methyl-2-pyridyl)indole (33a). Tetrabutylammonium hydrogenosulfate (16 mg), 50% aqueous NaOH (2.2 mL), and benzenesulfonyl chloride (0.8 mL, 6.1 mmol) were added to a suspension of pyridylindole **8c** (0.9 g, 3.8 mmol) in benzene (6.2 mL), and the resulting mixture was stirred at 25 °C for 24 h. Water was added, and the aqueous layer was extracted with AcOEt. The combined organic extracts were dried and concentrated to give compound **33a** (1.3 g, 98%) as a yellow solid: IR (KBr) 1579, 1363, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.5 Hz, 3 H), 2.41 (s, 3 H), 2.65 (q, J = 7.5 Hz, 2 H), 7.09 (d, J = 5.0 Hz, 1 H), 7.70 (s,

1 H), 7.92 (dm, J = 7.1 Hz, 2 H), 8.05 (d, J = 8.1 Hz, 1 H), 8.40 (d, J = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 19.2 (CH_3Ar), 22.4 (CH_2), 113.3 (CH), 121.1 (CH), 122.6 (C), 123.7 (CH), 124.1 (CH), 124.7 (CH), 124.9 (CH), 126.7 (CH), 129.2 (CH), 130.7 (C), 133.8 (CH), 134.7 (C), 137.5 (C), 138.0 (C), 146.6 (CH), 150.7 (C); mp 106−108 °C (benzene). Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44; S, 8.52. Found: C, 70.20; H, 5.37; N, 7.53; S, 8.46.

1-(Benzenesulfonyl)-3-(5-ethyl-4-methyl-2-pyridyl)indole (33b). Operating as above, from pyridylindole **8d** (2.3 g, 9.9 mmol) was obtained compound **33b** (3.6 g, 96%): IR (KBr) 1363, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3 H), 2.37 (s, 3 H), 2.67 (q, J = 7.5 Hz, 2 H), 7.45 (s, 1 H), 7.20−7.60 (m, 5 H), 7.92 (dm, J = 7.0 Hz, 2 H), 8.04 (m, 1 H), 8.30 (m, 1 H), 8.42 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 18.4 (CH_3), 23.4 (CH_2), 113.4 (CH), 122.1 (CH), 122.6 (CH), 123.0 (C), 123.8 (CH), 124.3 (CH), 124.9 (CH), 126.7 (CH), 128.8 (C), 129.2 (C), 133.8 (CH), 135.5 (C), 136.3 (C), 137.9 (C), 145.4 (C), 149.0 (CH), 150.2 (C); mp 164−166 °C (benzene). Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44; S, 8.52. Found: C, 69.91; H, 5.31; N, 7.40; S, 8.30.

Methyl 3-Ethyl-2-(3-indolyl)-4-pyridinecarboxylate (8j). A mixture of pyridylindole **33a** (3.8 g, 10.2 mmol) and SeO_2 (1.7 g, 15.3 mmol) in anhydrous pyridine (40 mL) was stirred at 95 °C for 12 h. The resulting suspension was filtered through a Celite pad, and the solution was concentrated. The residue was dissolved in EtOH (600 mL) and 10% aqueous NaOH (60 mL). The mixture was heated at reflux for 12 h, neutralized with 6 N HCl, and concentrated to give a solid, which was dried at 90 °C under vacuum overnight and digested with absolute EtOH (3 × 250 mL). The ethanolic solution was concentrated, and the residue was dissolved in MeOH (160 mL) and H_2SO_4. The mixture was stirred at 25 °C for 3 h, poured into ice water, basified with Na_2CO_3, and extracted with Et_2O. The combined organic extracts were dried and concentrated, and the resulting oil was chromatographed (AcOEt) to afford pure compound **8j** (2.8 g, 60%).

Methyl 5-Ethyl-2-(3-indolyl)-4-pyridinecarboxylate (8k). Operating as above, from pyridylindole **33b** (2.5 g, 6.6 mmol) was obtained pure compound **8k** (1.2 g, 64%) after purification by column chromatography (AcOEt).

Methyl *c*-5-Ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinecarboxylate (34). A solution of indolylpyridine **8k** hydrochloride (5.1 g, 16.1 mmol) in MeOH (30 mL) containing PtO_2 (0.3 g) was hydrogenated at 400 psi at 25 °C. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in AcOEt and washed with aqueous Na_2CO_3. The organic solution was dried and concentrated, and the residue was chromatographed (9:1 Et_2O−DEA) to give indolylpiperidine **34**[49b] (3 g, 65%): IR (NaCl) 3400, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3 H), 1.20 (m, 1 H), 1.75 (m, 1 H), 1.83−2.10 (m, 4 H), 2.81 (m, 1 H), 2.93 (dd, J = 12.5, 1.8 Hz, 1 H), 3.25 (dd, J = 12.5, 1.8 Hz, 1 H), 3.69 (s, 3 H), 3.96 (dd, J = 10.0, 4.4 Hz, 1 H), 7.00−7.20 (m, 3 H), 7.30 (dm, J = 7.0 Hz, 1 H), 7.70 (dm, J = 6.6 Hz, 1 H), 8.32 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3), 19.1 (CH_2), 29.9 (CH_2), 37.6 (CH), 46.2 (CH), 48.6 (CH_2), 51.4 (CH_3), 53.6 (CH), 111.2 (CH), 119.1 (CH), 119.1 (CH), 119.3 (C), 120.9 (CH), 121.8 (CH), 126.0 (C), 136.3 (C), 175.1 (C).

Methyl *c*-3-Ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinecarboxylate (36). Operating as above, from indolylpyridine **8j** hydrochloride (5.6 g, 17.7 mmol) and PtO_2 (0.3 g) was obtained pure indolylpiperidine **36**[4e] (3.1 g, 60%) after column chromatography (9:1 Et_2O−DEA): IR (NaCl) 3450, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.30 (t, J = 7.5 Hz, 3 H), 1.20 (m, 1 H), 1.50 (m, 1 H), 1.70−2.00 (m, 3 H), 2.36 (m, 1 H), 2.78−2.89 (m, 2 H), 3.27 (ddd, J = 12.0, 4.3, 2.3 Hz, 1 H), 3.69 (s, 3 H), 4.20 (d, J = 2.5 Hz, 1 H), 7.10−7.25 (m, 3 H), 7.38 (dm, J = 7.0 Hz, 1 H), 7.68 (dm, J = 6.6 Hz, 1 H), 8.18 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 17.8 (CH_2), 22.9 (CH_2), 42.8 (CH), 46.4 (CH), 46.6 (CH_2), 51.4 (CH_3), 58.6 (CH), 111.2 (CH), 117.9 (C), 118.9 (CH), 119.2 (CH), 120.9 (CH), 121.9 (CH), 125.8 (C), 136.2 (C), 175.2 (C).

(±)-Nordasycarpidone. Ester **36** was converted to the alkaloid nordasycarpidone in 36% yield following the previously reported procedure.[49a]

(1*RS*,5*RS*,12*SR*)-12-Ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (37). A solution of nordasycarpidone (254 mg, 1.0 mmol) in anhydrous THF (10 mL) was slowly added to a stirred slurry of $LiAlH_4$ (380 mg, 10.0 mmol) in refluxing anhydrous THF (40 mL). After being refluxed for 4 h, the mixture was cooled to 0 °C, and the excess of $LiAlH_4$ was destroyed with 15% aqueous NaOH. The resulting suspension was filtered through a Celite pad, and the filtrate was concentrated to give a residue which, after column chromatography (93:7 Et_2O−DEA), afforded pure compound **37**[52a] (80 mg, 33%) as a foam.

***c*-5-Ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinemethanol (38).** A solution of ester **34** (286 mg, 1.0 mmol) in anhydrous THF (25 mL) was added dropwise to a suspension of $LiAlH_4$ (114 mg, 3.0 mmol) in anhydrous THF (20 mL) at −60 °C. The reaction mixture was stirred at −30 °C for 90 min and at 25 °C for 2 h. The excess of $LiAlH_4$ was destroyed with 5% aqueous NaOH (10 mL), and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with aqueous Na_2CO_3, dried, and concentrated to give amino alcohol **38** (245 mg, 95%): IR ($CHCl_3$) 3400−3200, 2930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3 H), 1.30 (m, 2 H), 1.50−1.85 (m, 3 H), 2.01 (m, 1 H), 2.85 (dd, J = 12.2, 1.7 Hz, 1 H), 3.26 (dd, J = 12.2, 1.7 Hz, 1 H), 3.56 (m, 2 H), 4.00 (dd, J = 11.0, 2.7 Hz, 1 H), 7.06−7.21 (m, 3 H), 7.31 (dm, J = 7.0 Hz, 1 H), 7.73 (dm, J = 7.0 Hz, 1 H), 8.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 16.6 (CH_2), 31.6 (CH_2), 36.1 (CH), 42.7 (CH), 48.6 (CH_2), 54.0 (CH), 64.8 (CH_2), 111.3 (CH), 118.8 (CH), 120.9 (CH), 121.5 (CH), 125.8 (C), 136.3 (C).

1-((Benzyloxy)carbonyl)-*c*-5-ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinemethanol (39). A suspension of amino alcohol **38** (100 mg, 0.4 mmol), benzyl chloroformate (80 μL, 0.6 mmol), and K_2CO_3 (138 mg, 1.0 mmol) in $CHCl_3$ (10 mL) was stirred at 25 °C for 2 h. Water (10 mL) was added, and the mixture was stirred for 20 min. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were dried and concentrated. Column chromatography (9:1 Et_2O−DEA) of the residue afforded pure carbamate **39** (65 mg, 43%): IR ($CHCl_3$) 3400, 2931, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.2 Hz, 3 H), 1.22 (m, 3 H), 1.78−2.10 (m, 3 H), 2.56 (dm, J = 13.2 Hz, 1 H), 2.88 (t, J = 13.5 Hz, 1 H), 3.19−3.44 (m, 2 H), 4.14 (dd, J = 13.5, 5.0 Hz, 1 H), 5.16 (d, J = 10.0 Hz, 1 H), 5.15 (d, J = 10.0 Hz, 1 H), 5.67 (br s, 1 H), 6.86 (s, 1 H), 7.02−7.33 (m, 8 H), 7.62 (d, J = 7.3 Hz, 1 H), 8.40 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.5 (CH_3), 22.5 (CH_2), 29.2 (CH_2), 36.8 (CH), 42.4 (CH_2), 49.0 (C), 60.7 (CH_2), 67.0 (CH_2), 111.4 (CH), 116.1 (C), 119.0 (CH), 120.9 (CH), 121.7 (CH), 125.1 (C), 127.4 (CH), 127.7 (CH), 128.2 (CH), 136.6 (C), 136.7 (C), 155.9 (C); MS, m/e (relative intensity) 392 (M^+, 10), 257 (100), 189 (41), 167 (20), 144 (36), 143 (55), 142 (24), 140 (69), 130 (70), 118 (25), 117 (30), 116 (20), 115 (27), 105 (22). Under acidic conditions (CH_2Cl_2 and a drop of concd HCl, 2 min) carbamate **39** was converted into the corresponding C_2 epimer: IR ($CHCl_3$) 3365, 2950, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (br, 3 H), 1.25 (m, 2 H), 1.51 (m, 1 H), 1.75 (m, 2 H), 2.10 (br d, J = 13.5 Hz, 1 H), 2.32 (br s, 1 H), 2.85 (dd, J = 13.7, 2.3 Hz, 1 H), 3.52 (m, 2 H), 4.11 (m, 1 H), 5.22 (dd, J = 10.0 Hz, 1 H), 5.23 (dd, J = 10.0 Hz, 1 H), 5.87 (br s, 1 H), 6.97−7.36 (m, 9 H), 7.53 (br s, 1 H), 8.25 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.4 (CH_3), 16.1 (CH_2), 26.8 (CH_2), 37.4 (CH), 37.6 (CH), 41.8 (CH_2), 48.4 (CH), 65.2 (CH_2), 67.3 (CH_2), 111.2 (CH), 114.3 (C), 119.4 (CH), 119.6 (CH), 121.8 (CH), 122.7 (CH), 126.3 (C), 128.0 (CH), 128.4 (CH), 136.4 (C), 136.7 (C), 156.0 (C); MS, m/e (relative intensity) 392 (M^+, 13), 347 (6), 301 (7), 283 (20), 258 (20), 257 (100), 245 (38), 144 (28), 143 (47), 140 (48), 130 (55).

(1*RS*,4*RS*,5*RS*)-2-((Benzyloxy)carbonyl)-4-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole (41). Methanesulfonyl chloride (50 μL, 0.6 mmol) was added to a solution of alcohol **39** (120 mg, 0.3 mmol) in anhydrous pyridine (2.5 mL) at 0 °C, and the resulting mixture was stirred at 25 °C for 1 h. The solvent was evaporated, and the residue was taken up with CH_2Cl_2 (50 mL). The solution was washed with saturated aqueous Na_2CO_3, dried, and concentrated to give crude mesylate **40** (130 mg, 90%): IR ($CHCl_3$) 3000, 1674, 1174 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.26 (q, J = 7.5 Hz, 2 H), 1.83−2.32 (m, 2 H), 1.99 (s, 3

H), 2.68 (dm, J = 14.0 Hz, 1 H), 2.91 (m, 2 H), 3.76 (t, J = 9.0 Hz, 1 H), 4.00 (dd, J = 9.0, 5.1 Hz, 1 H), 4.22 (dd, J = 14.0, 4.5 Hz, 1 H), 5.15 (d, J = 10.0 Hz, 1 H), 5.16 (d, J = 10.0 Hz, 1 H), 5.73 (d, J = 4.5 Hz, 1 H), 6.83 (s, 1 H), 7.02−7.32 (m, 8 H), 7.61 (d, J = 7.3 Hz, 1 H), 8.92 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.4 (CH_3), 23.1 (CH_2), 29.2 (CH_2), 34.3 (CH), 35.3 (CH_3), 39.3 (CH), 42.2 (CH), 67.1 (CH_2), 68.3 (CH_2), 111.4 (CH), 116.4 (C), 119.5 (CH), 120.3 (CH), 122.1 (CH), 125.3 (C), 127.5 (CH), 127.8 (CH), 128.3 (CH), 136.6 (C), 137.0 (C), 155.8 (C). A mixture of **40** (100 mg, 0.2 mmol) and freshly sublimed potassium *tert*-butoxide (36 mg, 0.3 mmol) in anhydrous THF (5 mL) was stirred at 25 °C for 2 h, and the solvent was evaporated under vacuum. The residue was dissolved in $CHCl_3$, and the solution was washed with water, dried, and concentrated. Column chromatography (3:2 hexane−AcOEt) of the residue afforded tetracycle **41** (40 mg, 50%): IR ($CHCl_3$) 3400, 3000, 1675 cm^{-1}; ^{1}H NMR (major rotamer, $CDCl_3$) δ 0.94 (t, J = 7.0 Hz, 3 H), 1.30 (m, 2 H), 1.70 (m, 1 H), 2.00 (dm, J = 12.6 Hz, 1 H), 2.16 (dm, J = 12.6 Hz, 1 H), 2.30 (t, J = 13.0 Hz, 1 H), 2.34 (m, 1 H), 2.70−2.88 (m, 2 H), 3.72 (dd, J = 13.0, 5.0 Hz, 1 H), 5.08 (d, J = 10.0 Hz, 1 H), 5.12 (d, J = 10.0 Hz, 1 H), 5.42 (m, 1 H), 7.05−7.55 (m, 9 H), 8.12 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.4 (CH_3), 19.8 (CH_2), 24.1 (CH_2), 28.4 (CH), 33.0 (CH_2), 41.2 (CH), 43.2 (CH_2), 44.8 (CH), 67.0 (CH_2), 111.2 (CH), 111.7 (C), 118.3 (CH), 119.1 (CH), 121.9 (CH), 126.3 (C), 127.5 (CH), 127.8 (CH), 128.4 (CH), 135.8 (C), 136.7 (C), 156.2 (C); MS, m/e (relative intensity) 374 (M^+, 41), 169 (100), 168 (39), 91 (59); mp 108−110 °C (hexane). Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.81; H, 7.15; N, 7.37.

Methyl 1-(2,2-Dimethoxyethyl)-*c*-5-ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinecarboxylate (42) was prepared in 81% yield from piperidylindole **34** following the procedure previously reported.[49a]

1-(2,2-Dimethoxyethyl)-*c*-5-ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinemethanol (43). A solution of ester **42** (650 mg, 1.7 mmol) in anhydrous Et_2O (60 mL) was slowly added to a suspension of $LiAlH_4$ (140 mg, 5.2 mmol) at −60 °C, and the mixture was stirred at −30 °C for 90 min and at 25 °C for 2 h. The excess of hydride was destroyed with 15% aqueous NaOH (10 mL) and water (10 mL), and the suspension was filtered through a Celite pad. The filtrate was dried and concentrated, and the residue was chromatographed (98:2 AcOEt−MeOH) to give pure **43** (542 mg, 90%) as a colorless oil: IR (NaCl) 3600, 2958 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3 H), 1.34 (m, 1 H), 1.62 (m, 1 H), 1.72−2.00 (m, 4 H), 2.08 (dd, J = 13.6, 5.4 Hz, 1 H), 2.20 (dd, J = 11.4, 2.6 Hz, 1 H), 2.79 (dd, J = 13.6, 4.8 Hz, 1 H), 2.92 (s, 3 H), 3.28 (s, 3 H), 3.30−3.65 (m, 4 H), 4.29 (t, J = 5.2 Hz, 1 H), 7.11(m, 3 H), 7.29 (d, J = 7.2 Hz, 1 H), 7.87 (d, J = 7.4 Hz, 1 H), 8.22 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 17.8 (CH_2), 33.4 (CH_2), 37.2 (CH), 42.5 (CH), 52.3 (CH_3), 54.4 (CH_3), 56.0 (CH_2), 56.8 (CH_2), 61.7 (CH), 65.1 (CH_2), 104.6 (CH), 111.1 (CH), 118.8 (CH), 119.0 (C), 120.5 (CH), 121.7 (CH), 122.2 (CH), 126.0 (C), 136.6 (C). Anal. Calcd for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.27; H, 8.81; N, 7.81.

(*E*)-*cis*-1-(2,2-Dimethoxyethyl)-3-ethyl-4-[2-(3-indolyl)-vinyl]pyrrolidine (45). Methanesulfonyl chloride (360 μL, 4.6 mmol) was added to a solution of alcohol **43** (800 mg, 2.3 mmol) in anhydrous pyridine (4.0 mL) at 0 °C, and the resulting mixture was stirred at 25 °C for 90 min. The solvent was evaporated, and the residue was taken up with CH_2Cl_2 (40 mL). The solution was washed with saturated aqueous Na_2CO_3, dried, and concentrated, and the residue was chromatographed (95:5 Et_2O−DEA) to give pyrrolidine **45** (260 mg, 35%) as an oil: IR (NaCl) 3450, 1660, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 3 H), 1.34 (m, 1 H), 1.63 (m, 1 H), 1.90 (m, 1 H), 2.40−2.80 (m, 4 H), 2.74 (dd, J = 12.8, 5.5 Hz, 1 H), 2.91 (td, J = 11.8, 3.0 Hz, 2 H), 3.39 (s, 6 H), 4.52 (t, J = 5.5 Hz, 1 H), 6.14 (dd, J = 16.0, 8.5 Hz, 1 H), 6.55 (d, J = 16.0 Hz, 1 H), 7.10−7.26 (m, 3 H), 7.38 (dm, J = 6.8 Hz, 1 H), 7.84 (dm, J = 6.7 Hz, 1 H), 8.30 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3), 26.6 (CH_2), 46.8 (CH), 49.4 (CH), 53.4 (CH_3), 53.6 (CH_3), 58.3 (CH_2), 60.7 (CH_2), 61.5 (CH), 103.3 (CH), 111.3 (CH), 114.6 (C), 119.8 (CH), 122.1 (CH), 122.4 (CH), 122.9 (CH), 125.4 (CH), 129.5 (CH), 136.7 (C); HRMS calcd for $C_{20}H_{28}N_2O_2$ 328.2153, found 328.2153.

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