Biomimetic Total Synthesis of Ervitsine and Indole Alkaloids of the Ervatamine Group *via* 1,4-Dihydropyridines

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Addition of the enolate derived from 2-acetylindole **1a** to pyridinium salt **2** followed by *in situ* trapping of the initially formed 1,4-dihydropyridine **3a** with Eschenmoser's salt gives tetracycle **5a**. Subsequent elaboration of the exocyclic methylene and *E*-ethylidene substituents leads to N_a-methylervitsine (**17a**). A similar sequence from the N_a-protected 2-acetylindole **1c** establishes the first total synthesis of the 2-acylindole alkaloid ervitsine. Alternatively, dihydropyridine **3a** is trapped with BrSePh to give the tetracyclic selenide **7a**, which is then converted to N_a-methylervitsine by way of selenoxide **20**. The synthesis of the alkaloids of the ervatamine group starts with the addition of the enolate derived from 2-acetyl-1-benzylindole (**1g**) to pyridinium salt **24** and the conversion of the resulting 1,4-dihydropyridine to 3,5-diacylated dihydropyridine **26g**. Chemoselective reduction of the vinylogous amide moiety of **26g**, followed by deprotection of the indole ring and $LiEt_3BH$ reduction leads to diol **37b**. On sequential treatment with Eschenmoser's salt, methyl iodide, $NaCNBH_3$, and MnO_2, **37b** is converted to the tetracyclic 2-acylindole **39**, from which the first total synthesis of 19,20-didehydroervatamine and 20-epiervatamine is accomplished by manipulation of the 1-hydroxyethyl chain. The above syntheses can be considered as biomimetic, as cyclization of the key intermediates **I** and **II** mimics the key steps of the biosynthesis of the title alkaloids.

The ervitsine−ervatamine alkaloids[1] constitute a group of 2-acylindole alkaloids of the Corynanthean[2] type, with an unusual skeleton in which the tryptamine carbon atoms (C_5−C_6)[3] are in a rearranged situation, forming C_5−C_{16} and C_6−C_{16} bonds. In ervitsine, a minor alkaloid isolated from *Pandaca boiteaui*,[4] there is an additional link between C-5 and the indole 3-position (C-7) and, consequently, this bridged alkaloid incorporates a seven-membered C ring and a piperidine moiety bearing two different (16-methylene and 20*E*-ethylidene) exocyclic double bonds. On the other hand, in the alkaloids of the ervatamine group (19,20-didehydroervatamine,[5] ervatamine,[5] methuenine,[6] and silicine[7]) the indole 3-position is attached to C-6; the seven-membered C ring is now included in a cis-fused[8] bicyclic system bearing an ethyl or *E*-ethylidene group at C-20 and a methoxycarbonyl group at C-16, which is not present in the methuenine−silicine series.

The structural similarities between ervitsine and the alkaloids of the ervatamine group are a consequence of their common biogenetic origin from a vobasine *N*-oxide equivalent, as illustrated in Scheme 1.[9] Thus, 19,20-didehydroervatamine would be derived from the intermediate **A** by closure of the C ring by cyclization of the enamine moiety upon the 3-methyleneindoleninium cation (bond formed C_6−C_{16}), followed by reduction of the resulting iminium cation **B**.[10] Hydrolysis of **B** would give rise to acid **C**, the decarboxylation of which can account for the biogenetic formation of both ervitsine and the C-16 unsubstituted ervatamine alkaloids: decarboxylative fragmentation of **C** followed by cyclization of the resulting conjugated iminium cation **D** on the indole 3-position (1,2-addition) would result in the formation of ervitsine (bond formed C_5−C_7), whereas either simple decarboxylation of **C** or cyclization of **D** via a 1,4-addition, followed by reduction, would lead to methuenine.[11]

These alkaloids have received little attention from the synthetic standpoint: total syntheses of only (±)-6-oxosilicine[12] and (±)-6-oxo-16-episilicine[13] have been reported so far. Additionally, several synthetic approaches to simplified analogs of ervitsine[14] and the

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1997.

(1) (a) Joule, J. A. 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 232−239. (b) Alvarez, M.; Joule, J. 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 234−236.

(2) Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Chapter 5.

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

(4) Andriantsiferana, M.; Besselièvre, R.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1977**, 2587.

(5) Knox, J. R.; Slobbe, J. *Aust. J. Chem.* **1975**, *28*, 1813 and 1825.

(6) Bui, A.-M.; Debray, M.-M.; Boiteau, P.; Potier, P. *Phytochemistry* **1977**, *16*, 703.

(7) Vecchietti, V.; Ferrari, G.; Orsini, F.; Pelizzoni, F.; Zajotti, A. *Phytochemistry* **1978**, *17*, 835.

(8) The trans C/D ring junction is present in isomethuenine (16-epimethuenine), 6-oxo-16-episilicine, and 16-episilicine: Clivio, P.; Richard, B.; Nuzillard, J.-M.; Zèches-Hanrot, M. *Phytochemistry* **1995**, *40*, 987.

(9) Atta-ur-Rahman; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, 1983.

(10) The biogenetic relationship between the alkaloids of the vobasine and ervatamine groups through an intermediate like **A** has been demonstrated: (a) Husson, A.; Langlois Y.; Riche, C.; Husson, H.-P.; Potier, P. *Tetrahedron* **1973**, *29*, 3095. (b) Thal, C.; Dufour, M.; Potier, P.; Jaouen, M.; Mansuy, D. *J. Am. Chem. Soc.* **1981**, *103*, 4956.

(11) Ervitsine and a methuenine-type compound have been correlated *in vitro*: see reference 4.

(12) Husson, H.-P.; Bannai, K.; Freire, R.; Mompon, B.; Reis, F. A. M. *Tetrahedron* **1978**, *34*, 1363.

(13) Bennasar, M.-L.; Vidal, B.; Bosch, J. *Chem. Commun.* **1996**, 2755.

(14) (a) Grierson, D. S.; Harris, M.; Husson, H.-P.; *Tetrahedron* **1983**, *39*, 3683. (b) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516. (c) Bosch, J.; Rubiralta, M.; Bolós, J. *Tetrahedron* **1987**, *43*, 391. (d) Salas, M.; Joule, J. A. *J. Chem. Res. (M)* **1990**, 664. (e) Rubiralta, M.; Marco, M.-P.; Bolós, J.; Trapé, J. *Tetrahedron* **1991**, *47*, 5585.

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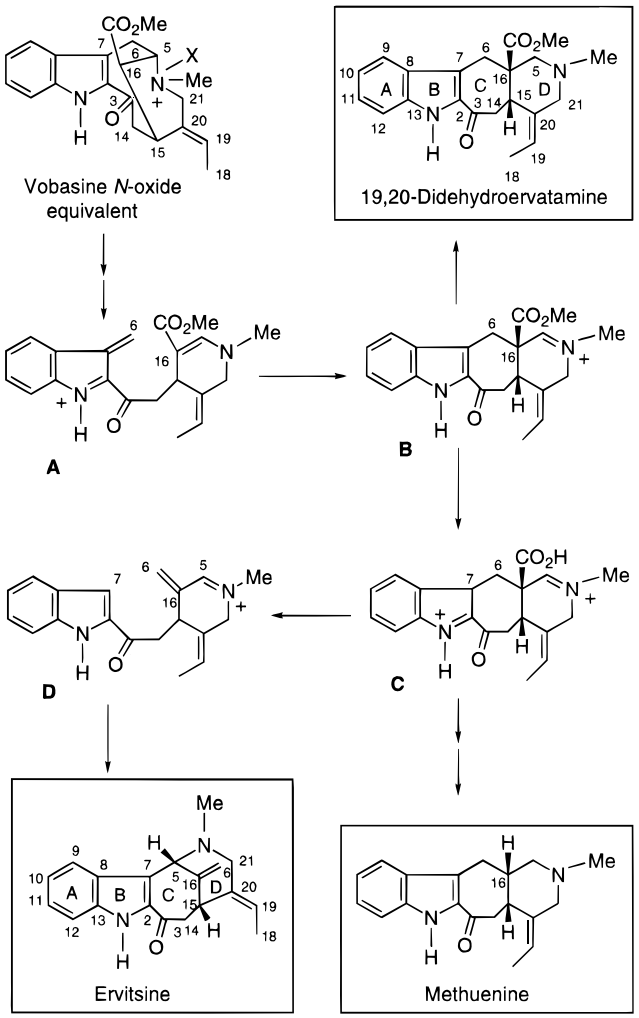
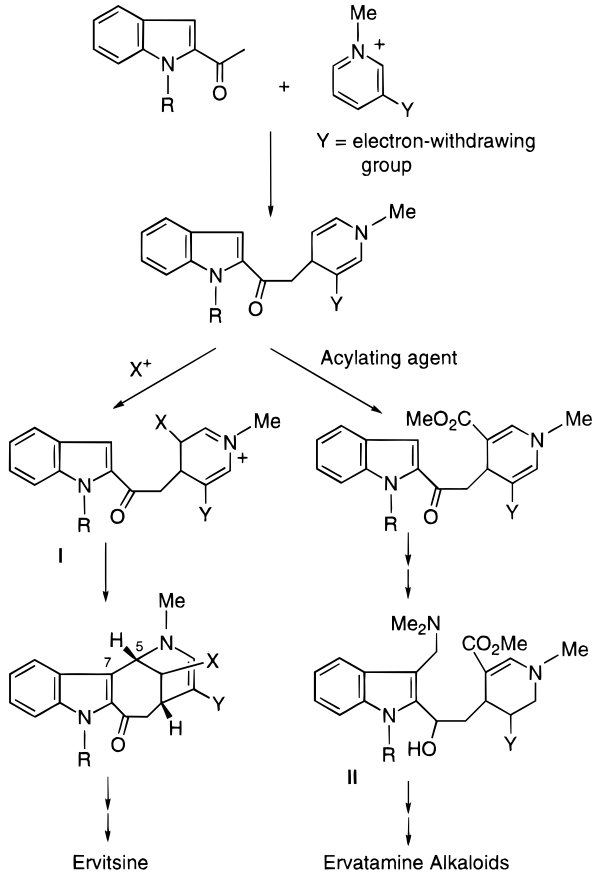
Scheme 1. Biosynthesis and Biogenetic Numbering



Scheme 2. Synthetic Strategy



synthesis of tetracyclic structures related to ervatamine alkaloids,[15] including a N_a-methyl-16-epi-20-epi derivative of ervatamine,[12] have been described.

In this paper we report a synthetic entry to the tetracyclic ring systems of ervitsine and ervatamine alkaloids based on biomimetic considerations[9,16] as well as the first total syntheses of the alkaloids ervitsine, 19,20-didehydroervatamine, and 20-epiervatamine.

The synthesis of ervitsine was planned through dihydropyridinium cations **I**, which were envisaged as synthetic equivalents of the biogenetic intermediate **D** as they incorporate (i) a substituent X that either constitutes a latent exocyclic methylene group or can allow a later introduction of this group, and (ii) an electron-withdrawing substituent Y that can be elaborated into the *E*-ethylidene substituent present in the alkaloid (Scheme 2). On the other hand, the C_6-C_{16} seco derivatives **II** were considered as synthetic equivalents of the key intermediate **A** in the biogenetic pathway to ervatamine alkaloids: the 3-[(dimethylamino)methyl]indole moiety is a latent 3-methyleneindoleninium cation whereas the substituent Y could again be transformed into the C-20 ethylidene (or ethyl) chain present in these natural products.

Both biomimetic key intermediates **I** and **II** would be prepared by taking advantage of the general procedure for the generation of 4-substituted 1,4-dihydropyridines based on the addition of stabilized carbon nucleophiles (in this case enolates derived from 2-acetylindoles) to pyridinium salts bearing an electron-withdrawing substituent at the β-position. Reaction of the resultant 1,4-dihydropyridines with an electrophile (X^+) would promote cyclization to the bridged tetracyclic ring system of ervitsine through dihydropyridinium cations **I**. On the other hand, reaction of the above intermediate dihydropyridines with an acylating agent would result in the formation of 4-substituted 3,5-diacyl-1,4-dihydropyridines, from which we could have access to the required enamines **II** by partial reduction of the dihydropyridine ring followed by aminoalkylation at the indole 3-position.

Results and Discussion

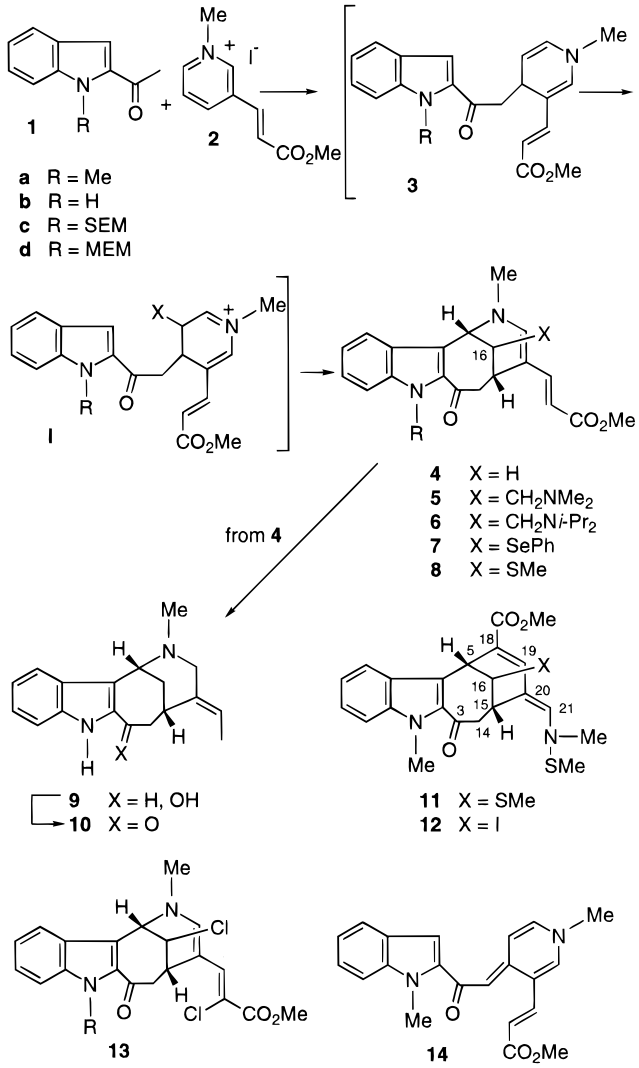
Synthesis of Ervitsine. The tandem nucleophilic addition of an indole-containing enolate to a pyridinium salt−acid cyclization of the intermediate 1,4-dihydropyridine has been successfully used for the synthesis of bridged indole alkaloids[17] belonging to several structural types.[18] In previous work we had employed enolates derived from indoleacetic esters, which give rise to tetracyclic systems bearing a six-membered C ring.[19] The

(15) (a) Langlois, Y.; Potier, P. *Tetrahedron* **1975**, *31*, 423. (b) Grierson, D. S.; Bettiol, J.-L.; Buck, I.; Husson, H.-P.; Rubiralta, M.; Díez, A. *J. Org. Chem.* **1992**, *57*, 6414.

(16) Husson, H.-P. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 10.

(17) (a) For a review, see: Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587. For more recent work, see: (b) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239. (c) Bennasar, M.-L.; Zulaica, E.; Sufi, B. A.; Bosch, J. *Tetrahedron* **1996**, *52*, 8601. (d) Bennasar, M.-L.; Jiménez, J.-M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 9105.

Scheme 3. Synthesis of (±)-16-Demethyleneervitsine (10) and Functionalization at C-16



aim of our first experiments in the ervitsine field was to evaluate if, starting from a 2-acetylindole enolate, this nucleophilic addition−cyclization sequence could be used for the construction of the bridged tetracyclic 1,5-methanoazonino[4,3-*b*]indole skeleton characteristic of ervitsine.[20]

Thus, whereas exposure of pyridinium salt **2** to the enolate derived from acetylindole **1a** and then to acid ($HCl-C_6H_6$) had led to the expected tetracycle **4a** through dihydropyridine **3a** in 20% yield, the procedure could not be satisfactorily extended to the preparation of the N_a-unsubstituted tetracycle **4b**, which was isolated in a yield lower than 5% (Scheme 3).[21] For this reason, we then studied the use of *N*-protected 2-acetylindoles **1c** and **1d**. The best results were obtained from **1c**, with the isolation of N_a-SEM protected tetracycle **4c** in 15% yield. From acetylindole **1d**, the corresponding tetracycle **4d** was obtained in a lower yield (7%).

The exocyclic *E*-ethylidene substituent was incorporated in a stereoselective manner by taking advantage of the *β*-(tetrahydro-3-pyridyl)acrylate moiety of tetracycles **4**.[22] Thus, treatment of **4c** with refluxing 4 N HCl brought about the hydrolysis and decarboxylation of the acrylic portion, with simultaneous deprotection of the indole ring, to give an iminium ion, which was then reduced with $NaBH_4$. The resulting alcohol **9** was reoxidized with MnO_2 to give **10**, the 16-demethylene analog of ervitsine, in 38% overall yield from **4c**. A similar sequence from the N_a-unsubstituted tetracycle **4b**, which was conveniently prepared (48% yield) by deprotection of **4c** (BF_3-Et_2O, Triton B), led to (±)-16-demethyleneervitsine (**10**) in 50% yield.

The extension of these studies to the synthesis of ervitsine required the functionalization at C-16 in order to then incorporate the exocyclic methylene substituent. This was achieved by a slight modification of the above methodology, consisting of the trapping of the initially formed 1,4-dihydropyridine **3** with an electrophile other than a proton to generate the key dihydropyridinium cation **I** necessary for the cyclization.[23] Reactions of the model dihydropyridine **3a** (incorporating a N_a-methyl substituent) with several one-carbon electrophiles were first investigated. However, reaction of **3a** either with formaldehyde or with several alkyl halides ($ClCH_2SPh$, $ClCH_2SO_2Ph$, and $BrCH_2SePh$) under a variey of experimental conditions resulted in failure. In all cases, the only identifiable product was the anhydro base **14** resulting from oxidation of **3a**. The desired functionalization at C-16 was achieved when dihydropyridine **3a** was treated with *N*,*N*-dimethylmethyleneiminium iodide (Eschenmoser's salt).[24] The best results were obtained when lithium cyclohexylisopropylamide (LICA) was used as the base to generate the enolate derived from **1a**: under these conditions tetracycle **5a** was obtained in 18% yield. The use of LDA gave this tetracycle in lower yield (14%) along with minor amounts of tetracycle **6a**, probably formed by reaction of **3a** with $CH_2{=}N^+(i\text{-}Pr)_2$, which would result from the interaction of LDA or diisopropylamine with Eschenmoser's salt.

As could be expected from the results obtained in the above nucleophilic addition−acid cyclization sequence when using the dianion derived from acetylindole **1b**, interaction of this dianion with salt **2** followed by *in situ* treatment of the resulting 1,4-dihydropyridine **3b** with Eschenmoser's salt gave the C-16 substituted tetracycle **5b** in only 5% yield. The use of the SEM-protected 2-acetylindole **1c** gave a better result, tetracycle **5c** being obtained in 15% yield. Although this is clearly not a high chemical yield,[25] it must be noted that the construction of the bridged tetracycles **5** involves the formation of

(18) The addition of stabilized carbon nucleophiles to *N*-alkyl-*β*-acylpyridinium salts for alkaloid synthesis was first used by Wenkert: (a) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. (b) Wenkert, E.; Guo, M.; Pestchanker, M. J.; Shi, Y.-J.; Vankar, Y. D. *J. Org. Chem.* **1989**, *54*, 1166 and refs cited therein. See also: (c) Spitzner, D.; Arnold, K.; Stezowski, J. J.; Hildenbrand, T.; Henkel, S. *Chem. Ber.* **1989**, *122*, 2027. (d) Amann, R.; Arnold, K.; Spitzner, D.; Majer, Z.; Snatzke, G. *Liebigs Ann. Chem.* **1996**, 349.

(19) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156.

(20) For a preliminary report of this part of the work, see: Bennasar, M.-L.; Zulaica, E.; Vidal, B.; Bosch, J. *Tetrahedron Lett.* **1992**, *33*, 3895.

(21) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1995**, *60*, 4280.

(22) For a review, see: Bosch, J.; Bennasar, M.-L. *Heterocycles* **1983**, *20*, 2471.

(23) For a preliminary report of this part of the work, see: Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 5340.

(24) There are few examples of aminomethylation of cyclic enamines: (a) Barnett, C. J.; Copley-Merriman, C. R.; Maki, J. *J. Org. Chem.* **1989**, *54*, 4795. (b) Mitch, C. H.; Zimmerman, D. M.; Snoddy, J. D.; Reel, J. K.; Cantrell, B. E. *J. Org. Chem.* **1991**, *56*, 1660.

(25) The moderate or low yields usually associated with the nucleophilic addition−cyclization sequence leading to bridged tetracyclic indole-containing systems are due both to the reversibility of the first step and to the fact that polymerization occurs to some extent during cyclization.

three new C−C bonds on the pyridine ring by successive γ-nucleophilic, β-electrophilic, and α-nucleophilic attacks in a one-pot, three-step sequence.

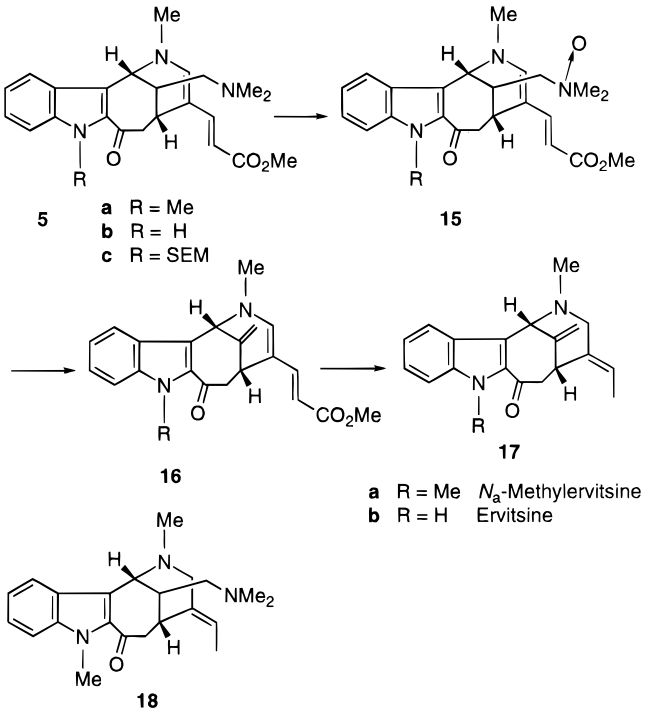
At this point we decided to explore the reactivity of the intermediate 1,4-dihydropyridines **3** toward heteroatom-centered electrophiles in order to develop alternative procedures for the generation of the biomimetic intermediate **I**. However, dihydropyridine **3a** did not react with $ClP(OEt)_2$, $ClPO(OEt)_2$, or Me_3SiCl,[26] whereas on treatment with $[Me_2SSMe]^+$ BF_4^- (DMTSF)[27] it led to a mixture of the expected C-16 functionalized tetracycle **8a** (6%) and the rearranged sulfenamides **11** and **12** (12% overall yield). Formation of these sulfenamides can be rationalized by considering that a further methylthiolation on the tetrahydropyridine nitrogen[28] of **8a** promotes the opening of the tetrahydropyridine ring to give a 3-alkylideneindoleninium cation that undergoes recyclization by nucleophilic attack of C-18 to C-5.[29] Reaction of **3a** with NCS was not chemoselective either, as the 16,18-dichloro tetracycle **13** was obtained (6%) as the only isolable product. More interestingly from the synthetic standpoint (*vide infra*), interaction of **3a** with BrSePh led to the C-16 functionalized tetracycle **7a** in 20% yield as the only isolable product.

The relative configuration at C-16 in tetracycles **5**−**8** and **13** was inferred from the multiplicity of 5-H in the ^{1}H NMR spectra. This proton appears as a singlet, as expected from the approximate dihedral angle (90°) formed by the H−C_5−C_{16}−H bond system when 5-H and 16-H are located *trans* with respect to the partially reduced pyridine ring (see Dreiding stereomodels).

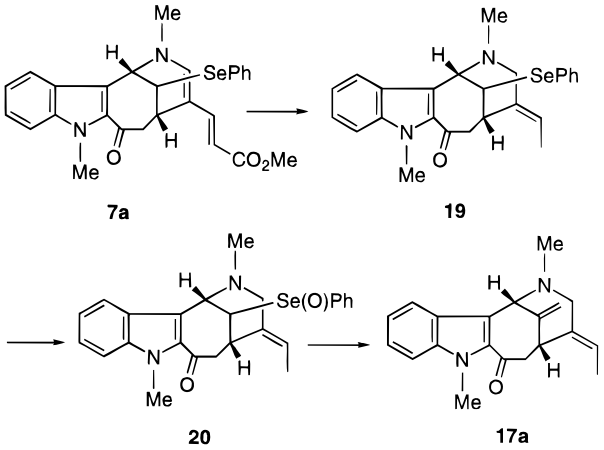
With a method in hand for the construction of tetracyclic ervitsine-type systems **5** bearing latent methylene and *E*-ethylidene substituents at C-16 and C-20, respectively, we next studied the formation of the two exocyclic double bonds. Initially, tetracycle **5a** was stereoselectively converted into the *E*-ethylidene derivative **18** (Scheme 4) by the usual hydrolysis−decarboxylation−reduction sequence, although in this case reduction of the intermediate iminium cation was chemoselectively accomplished without reduction of the 2-acylindole carbonyl group by using only a slight excess of $NaBH_4$. Alternatively, the (dimethylamino)methyl group of **5a** was first converted into the exocyclic C-16 methylene substituent by Cope elimination of the corresponding *N*-oxide, and then the doubly vinylogous urethane moiety was elaborated as above into the 20*E*-ethylidene group. Thus, oxidation of **5a** with *m*-CPBA (63% yield), followed by heating of the resulting *N*-oxide **15a** in refluxing toluene gave (79%) tetracycle **16a**, which was converted (55% yield) into (±)-N_a-methylervitsine (**17a**) by treatment with 4 N HCl and then with $NaBH_4$.

As expected, the successive formation of the exocyclic 16-methylene and 20*E*-ethylidene substituents from the N_a-protected C-16 functionalized tetracycle **5c**, as in the above **a** series, gave **16c** (through **15c**; overall yield 45%) and then the target alkaloid ervitsine (**17b**, 65%). Clearly, deprotection of the indole ring took place under the hydrolytic conditions of the latter step. The ^{1}H NMR and MS data of synthetic ervitsine were identical to those reported for the natural product,[4] whereas the ^{13}C NMR spectrum was in full agreement with the one expected for this structure.

Scheme 4. Synthesis of (±)-Ervitsine and (±)-N_a-Methylervitsine



Scheme 5. Alternative Synthesis of (±)-N_a-Methylervitsine



The biomimetic synthesis of ervitsine here reported constitutes the first total synthesis of this alkaloid. The complex structure of ervitsine has been assembled in a straightforward sequence from very accessible starting products, acetylindole **1c** and pyridinium salt **2**.

In order to demonstrate the versatility of the above methodology for the synthesis of ervitsine, an alternative synthesis of (±)-N_a-methylervitsine (**17a**) was completed from the 16-selenenyl tetracycle **7a** (Scheme 5).[30] Thus, after **7a** was stereoselectively converted (60% yield) into the C-20 *E*-ethylidene derivative **19** by the usual treatment, the phenylseleno group of **19** allowed the introduction of the exocyclic C-16 methylene substituent by

(26) 4-Alkylidene-1,4-dihydropyridine **14** and tetracycle **4a** were formed in some runs.

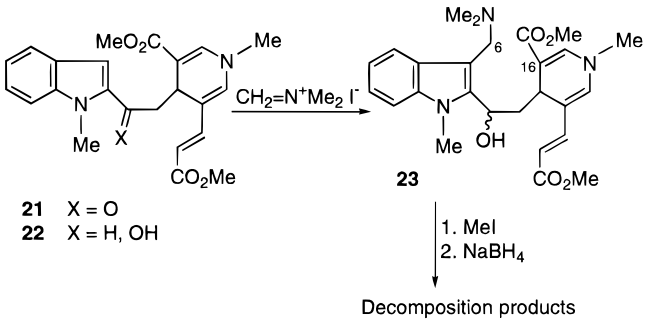
(27) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 3, pp 2102−2104.

(28) (a) Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231. (b) Kim, J. K.; Souma, Y.; Beutow, N.; Ibbeson, C.; Caserio, M. C. *J. Org. Chem.* **1989**, *54*, 1714.

(29) A DMTSF-promoted displacement of the C-16 methylthio group by iodide ion can account for the formation of the C-16 iodo derivative **12**.

(30) For a preliminary report of this part of the work, see: Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 125.

Scheme 6



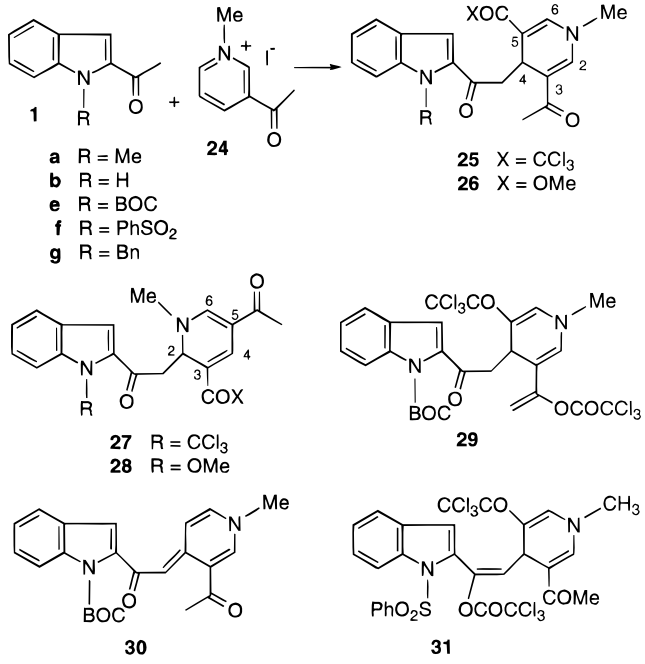
oxidation with *m*-CPBA, followed by methylation (LDA, MeI) at the α-position of the resulting selenoxide **20** and subsequent thermal elimination (30% overall yield from **19**).

Synthesis of Ervatamine Alkaloids. We have recently reported a procedure for the preparation of 3-(methoxycarbonyl)-4-[(2-indolylcarbonyl)methyl]-1,4-dihydropyridines bearing an additional electron-withdrawing substituent at the 5-position.[21] The method consists of the nucleophilic addition of a 2-acetylindole enolate to a 3-acylpyridinium salt, with trapping of the initially formed 1,4-dihydropyridine with trichloroacetic acid anhydride (TCAA) and subsequent conversion of the trichloroacetyl group to methoxycarbonyl by treatment with MeONa in MeOH. According to our synthetic plan, these dihydropyridines were considered to be potential precursors of the C_6-C_{16} seco derivatives (**II**, Scheme 2) required for the synthesis of ervatamine alkaloids.

In order to evaluate if the biomimetic cyclization by formation of C_6-C_{16} bond could be effected at the dihydropyridine stage, we first studied the aminoalkylation of dihydropyridines **21**[21] and **22**, the latter prepared by $NaBH_4$ reduction of **21** (Scheme 6). Whereas no reaction was observed when 2-acylindole **21** was treated with Eschenmoser's salt,[31] most probably as a consequence of the deactivation exerted by the carbonyl group, alcohol **22** did react (CH_2Cl_2, rt) with this reagent to give gramine **23**. However, all attempts to induce cyclization, either directly (rt, 24 h) or through the corresponding methiodide (CH_3I, rt, 48 h), gave only decomposition products.

For this reason we then focused our efforts on the generation of gramine−tetrahydropyridine derivatives **II**. This required the preparation of a suitable 3,5-disubstituted 4-[(indolylcarbonyl)methyl]-1,4-dihydropyridine, the chemoselective reduction of one of the dihydropyridine double bonds, and finally the introduction of the (dimethylamino)methyl substituent at the 3-position of the indole ring. Whereas the methoxycarbonyl group at one of the dihydropyridine β-positions would correspond to the characteristic C-16 methoxycarbonyl substituent of ervatamine alkaloids, we selected the acetyl group as the substituent Y, precursor of the two-carbon C-20 appendage of these alkaloids. Consequently, 3-acetylpyridinium salt **24** was used as the starting pyridinium salt. However, although the nucleophilic addition−TCAA acylation sequence from the enolate derived from acetylindole **1a** and salt **24** had satisfactorily led to (trichloroacetyl)-dihydropyridine **25a**, which was then efficiently converted into dihydropyridine ester **26a**[21] (Scheme 7), the extension of the procedure to the N_a-unsubstituted acetylindole **1b** proved to be unsuccessful. This result

Scheme 7. Synthesis of 3,5-Diacyldihydropyridines



made evident that, as in the above synthesis of ervitsine, it was necessary to operate with *N*-protected acetylindoles.

More satisfactorily, interaction of the *N*-Boc acetylindole **1e** with salt **24** followed by treatment with TCAA gave the expected 1,4-dihydropyridine **25e** (13%) together with the corresponding enol trichloroacetate **29** (11%) and 4-alkylidene-1,4-dihydropyridine **30** (12%). However, reaction of **25e** or **29** (or a mixture of **25e** and **29**) with MeONa in MeOH to simultaneously promote the haloform-type reaction[32] and the deprotection of the indole ring gave a mixture of the expected 1,4-dihydropyridine **26b** and the regioisomeric 1,2-dihydropyridine **28b**. Clearly, under the reaction conditions, equilibration of the initially formed 1,4-dihydropyridine to a mixture of 1,2- and 1,4-dihydropyridines had occurred. Protection of the indole nitrogen with a phenylsulfonyl group was not synthetically useful either: after the addition−trichloroacetylation sequence from acetylindole **1f** and salt **24**, the desired 1,4-dihydropyridine **25f** was obtained in only 7% yield along with trace amounts of the bis(trichloroacetyl) product **31** and, in several runs, 1,2-dihydropyridine **27f**. The best results were obtained when using a benzyl group as the indole protecting group:[33] reaction of the enolate derived from *N*-benzyl-2-acetylindole (**1g**) with pyridinium salt **24**, followed by *in situ* treatment with TCAA, gave a 2:1 mixture of dihydropyridines **25g** and **27g** in 21% overall yield. Subsequent treatment of **25g** with MeONa in MeOH accomplished the conversion of the trichloroacetyl group to methoxycarbonyl to give dihydropyridine **26g** in 91% yield.

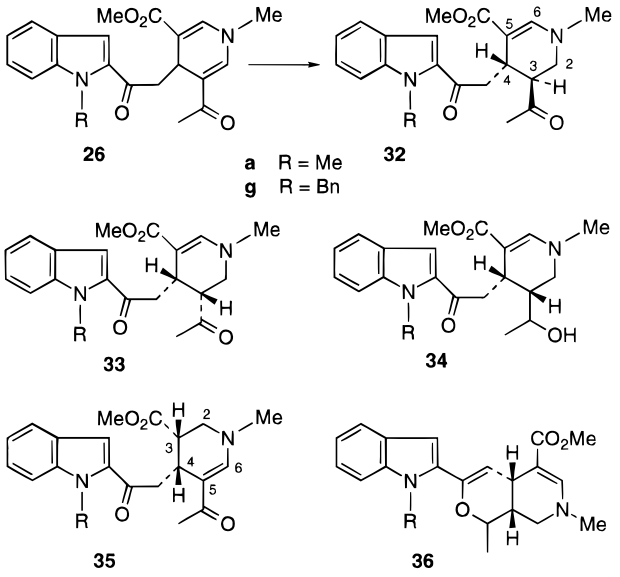
Although the reduction of 1,4-dihydropyridines to the corresponding tetrahydropyridines or piperidines is a

(31) For the aminomethylation of indoles with $[CH_2{=}NMe_2]^+$ Cl^-, see: Kozikowski, A. P.; Ishida, H. *Heterocycles* **1980**, *14*, 55.

(32) (a) Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618. (b) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259.

(33) For the debenzylation of *N*-benzyl-2-acylindoles with $AlCl_3$, see: (a) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738. (b) Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1152.

Table 1. Catalytic Hydrogenation of 1,4-Dihydropyridines 26



entry	dihydro-pyridine	conditions	products (yield, %)
1	**26a**	MeOH, 12 h	**32a** (7), **33a** (25), **34a** (30), **35a** (20)
2	**26a**	MeOH, 24 h	**32a** (7), **34a** (55), **35a** (20)
3	**26g**	MeOH, 18 h	**32g** (6), **34g** (40), **35g** (13)
4	**26g**	1:1 MeOH−THF, 10 h	**32g** (6), **33g** (45), **35g** (13)

known process,[34] there are few examples of the reduction of 1,4-dihydropyridines generated by addition of stabilized carbanions to pyridinium salts,[35] probably due to the reversibility of the addition. In our case, the higher stability of the 3,5-diacyl substituted 1,4-dihydropyridines **26a** and **26g** made their catalytic hydrogenation possible.[36,37] The results are given in Table 1. Favorable to our synthetic interest, hydrogenation of these dihydropyridines using platinum as the catalyst took place predominantly on the vinylogous amide moiety to give the α,β-unsaturated esters **33** and **34**, with a *cis* relative configuration between the tetrahydropyridine substituents. Only minor amounts of the *trans* isomers **32** were formed. Reduction of the vinylogous urethane double bond leading to the α,β-unsaturated ketones **35** occurred to a lesser extent. On prolonged reaction times the acetyl group of **33** undergoes a further reduction to give alcohols **34** (a single stereoisomer of undetermined stereochemistry at C-19 in each series), whose manipulation was difficult since traces of acid caused their transformation into the corresponding enol ethers **36**. Interestingly, reduction of **26g** could be stopped at the acetyl stage using a 1:1 MeOH−THF mixture as the solvent.

The *cis* relative configuration of tetrahydropyridines **33**−**35** is the result of the hydrogen uptake from the most accessible face of the dihydropyridine ring and implies the pseudoaxial disposition of the bulky C-4 substituent (to relieve the steric $A^{1,2}$ interactions[38] with C-5 acyl group) and the equatorial disposition of the acetyl (or hydroxyethyl) substituent. Of diagnostic value from the stereochemical standpoint was the ^{1}H NMR signal attributable to 2-H_{ax}, which appears as a triplet with $J \sim 12$ Hz due to the geminal and vicinal (with 3-H_{ax}) couplings in the *cis* isomers **33**−**35**. In contrast, in the *trans*-tetrahydropyridines **32**, 2-H_{ax} appears as a doublet of doublets ($J \sim$13 and 4 Hz) as a result of the axial disposition of the acetyl group. The above stereochemical assignments agree with the shielding of C-5 in the ^{13}C NMR spectra of *trans*-tetrahydropyridines **32**, as compared with **33**−**35**, due to the γ-effect induced by the axial acetyl group.

Both *cis*-tetrahydropyridines **33g** and **34g** were considered *a priori* to be good substrates for conversion into ervatamine alkaloids. However, the reluctance shown by 2-acylindoles toward aminoalkylation at C-3 and the tendency of alcohols **34** to undergo cyclodehydration to give enol ethers **36** made evident that reduction of the 2-acylindole carbonyl group was necessary for the success of our synthetic plan. The synthetic possibilities of alcohol **34g** were first investigated. In a model study with the N_a-methyl derivative **34a** we were able to convert this unstable alcohol into diol **37a** (one diastereomer of undetermined stereochemistry at C-3 and C-19) in 75% yield by reduction with $LiBEt_3H$. The same reaction applied to alcohol **34g** gave a single diol **37g** in 83% yield (Scheme 8).

As expected, treatment of **37g** with Eschenmoser's salt gave the key intermediate **II** (R = Bn), which underwent a biomimetic cyclization after activation of the dimethylamino group as a methiodide.[39] Further $NaCNBH_3$ reduction of the resulting iminium salt gave the ervatamine-type tetracycle **38g** in 40% overall yield. Unfortunately, all attempts to regenerate the 2-acylindole carbonyl group by MnO_2 oxidation were unsuccessful, probably due to the presence of the bulky N_a-benzyl group.

This result clearly indicated that the benzyl group had to be removed prior to the key cyclization step. Taking into account the sensitivity of alcohols **34** to acids, we turned our attention to ketone **33g**.[40] Deprotection of the indole ring of **33g** with $AlCl_3$[33] gave (75%) the N_a-unsubstituted indole **33b**, which was then stereoselectively reduced with $LiBEt_3H$ to give (72%) diol **37b**. Biomimetic cyclization as above, by successive treatment of **37b** with Eschenmoser's salt, methyl iodide, and $NaCNBH_3$, gave tetracycle **38b**, which could be chemoselectively oxidized to the tetracyclic 2-acylindole **39** with MnO_2 in 25% overall yield from **37b**. The relative stereochemistry of **39** was determined from its ^{1}H and ^{13}C NMR data, with the aid of 2D experiments (^{1}H−^{1}H COSY and HMQC). The triplet (J = 11.5 Hz) corresponding to 21-H_{ax} was of diagnostic value as it indicates that the vicinal hydroxyethyl substituent is equatorial. Taking into account the 15-H/20-H *cis* relationship (*vide*

(34) (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Stout, D.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 233. (c) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291. (d) Rosentreter, U. *Synthesis* **1985**, 210.

(35) (a) Lounasmaa, M.; Koskinen, A. *Tetrahedron Lett.* **1982**, *23*, 349. (b) Lavilla, R.; Gotsens, T.; Gullón, F.; Bosch, J. *Tetrahedron* **1994**, *50*, 5233.

(36) However, fragmentation to the starting products was the only process observed when dihydropyridine **21** was treated with Et_3SiH−TFA, Et_3SiH−AcOH, *n*-Bu_3SnH−TFA, or $NaBH_3CN$−AcOH under the conditions reported for the reduction of the carbon−carbon double bond in vinylogous urethanes: Rosentreter, U.; Born, L.; Kurz, J. *J. Org. Chem.* **1986**, *51*, 1165.

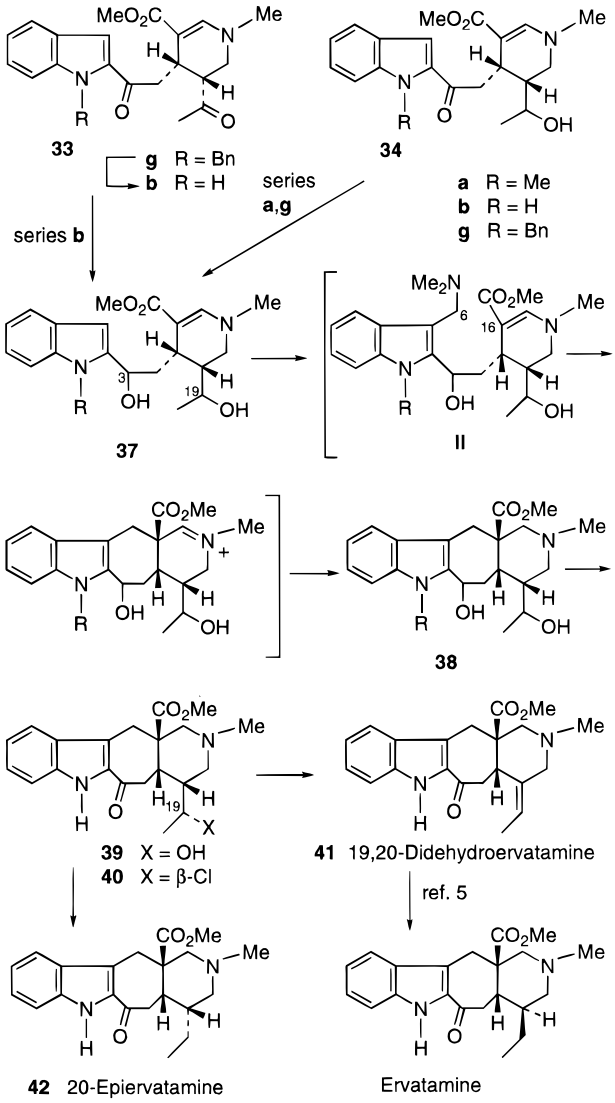
(37) For related hydrogenations, see: Bennasar, M.-L.; Vidal, B.; Lázaro, A.; Kumar, R.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 3541.

(38) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(39) For examples of alkylation of enamines with gramines, see: (a) Sundberg, R. J.; Ligon, W. V.; Lin, L.-S. *J. Org. Chem.* **1971**, *36*, 2471. (b) Sainsbury, M. *Synthesis* **1977**, 437, and references cited therein.

(40) For a preliminary report of this part of the work, see: Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1916.

Scheme 8. Synthesis of Ervatamine Alkaloids



supra), this equatorial disposition is only compatible with a *cis* C/D ring junction. This stereochemistry was the expected one by considering the stereochemical outcome of the cyclization of the key biogenetic intermediate **A** (Scheme 1).[41]

Finally, treatment of the mesylate derived from alcohol **39** with DBU afforded (±)-19,20-didehydroervatamine (**41**) in 70% yield. The stereoselective formation of an *E*-ethylidene double bond in this *anti* elimination allowed the relative stereochemistry at C-19 in alcohols **37b**, **38b**, and **39** to be established.[42] On the other hand, reduction of chloride **40**, obtained in 71% yield from alcohol **39** via the corresponding mesylate, with *n*-Bu_3SnH-AIBN gave (±)-20-epiervatamine (**43**) in 73% yield. Given that 19,20-didehydroervatamine had previously been converted into ervatamine by catalytic hydrogenation,[5] the above synthesis also constitutes a formal synthesis of the latter alkaloid. The ^1H and ^{13}C NMR spectra of our synthetic ervatamines were completely identical to those reported[43] for the natural products.

In summary, we have completed biomimetic total syntheses of the 2-acylindole alkaloids ervitsine, 19,20-didehydroervatamine, and 20-epiervatamine. The key synthetic intermediates **I** (X = CH_2NMe_2; Y = $CH{=}CHCO_2Me$) and **II** (Y = CHOHMe) (Scheme 2) mimic the biogenetic intermediates **D** and **A** (Scheme 1), respectively, and undergo biomimetic cyclizations that reproduce the key steps of the biosynthesis of these alkaloids. The results here reported significantly expand the scope and potential of the methodology for indole alkaloid synthesis based on the reactivity of *N*-alkyl-3-acylpyridinium salts with indole-containing enolates. After the initial nucleophilic attack on the γ-position, the intermediate 1,4-dihydropyridine is further functionalized to ultimately lead to tetracyclic ervitsine- or ervatamine-type systems.

Experimental Section

Melting points were determined in a capillary tube and are uncorrected. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ solution at 200, 300, or 500 MHz (^1H) and 50.3 or 75 MHz (^{13}C). Only noteworthy IR absorptions (cm^{-1}) 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 organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HMRS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. All compounds were synthesized in the racemic series. The biogenetic numbering is used to describe the ^{13}C NMR spectra of tetracyclic compounds **11**, **12**, **17b**, and **39**.

2-Acetylindole (1b). MeLi (1.6 M in Et_2O, 30 mL, 48 mmol) was slowly added to a suspension of lithium indole 2-carboxylate (4 g, 24 mmol) in anhydrous DME (300 mL) cooled at 0 °C, and the mixture was refluxed for 1 h. Additional MeLi (1.6 M in Et_2O, 30 mL, 48 mmol) was added at rt, and the mixture was refluxed for 7 h. The reaction was quenched by addition of saturated aqueous NH_4Cl, diluted with Et_2O, and extracted with Et_2O. The organic extracts were washed with H_2O, dried, and evaporated to give acetylindole **1b**[44] after column chromatography (CH_2Cl_2): 3.7 g (97%); ^1H NMR (200 MHz) 2.59 (s, 3 H), 7.00−7.40 (m, 3 H), 7.45 (d, J = 8 Hz, 1 H), 7.69 (d, J = 8 Hz, 1 H), 9.70 (br s, 1 H); ^{13}C NMR (50.3 MHz) 25.7, 110.1, 112.4, 120.9, 123.0, 126.4, 127.5, 135.4, 137.7, 191.1.

2-Acetyl-1-{[2-(trimethylsilyl)ethoxy]methyl}indole (1c). A solution of 2-acetylindole (**1b**, 2 g, 12.5 mmol) in DMF (32 mL) was added dropwise to a suspension of NaH (55%, 0.6 g, 13.8 mmol) in anhydrous THF (3 mL), and the resulting mixture was stirred at rt for 1 h. [2-(Trimethylsilyl)ethoxy]-methyl chloride (2.2 mL, 12.5 mmol) was slowly added at 0 °C, and the resulting solution was stirred at rt for 1 h. The reaction mixture was poured into H_2O−ice and extracted with Et_2O. The organic extracts were washed with H_2O, dried, and evaporated to give a residue which was chromatographed (85:15 hexane−AcOEt) to give **1c** as an oil: 3.4 g (93%); IR (film) 1667; ^1H NMR (200 MHz) −0.15 (s, 9 H), 0.82 (t, J = 8 Hz, 2 H), 2.57 (s, 3 H), 3.48 (t, J = 8 Hz, 2 H), 5.98 (s, 2 H), 7.10−7.40 (m, 3 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.65 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) −1.8, 17.4, 27.7, 65.3, 72.9, 111.5, 114.0, 121.4, 122.7, 126.4, 126.1, 134.6, 140.2, 191.3. Anal. Calcd for $C_{16}H_{23}NO_2Si$: C, 66.39; H, 8.01; N, 4.83. Found: C, 66.48; H, 8.23; N, 4.98.

2-Acetyl-1-[(2-methoxyethoxy)methyl]indole (1d). Operating as above, from acetylindole **1b** (1.5 g, 9.4 mmol) and

(41) A related $Me_2N^+{=}CH_2$-induced cyclization from a 19-deoxo analog of 2-acylindole **33a** has been reported to lead to the *trans* C/D ring junction: see ref 12.

(42) This relative stereochemistry is the one predicted by Cram and Felkin−Anh models for the reduction of the acetyl group of **33b**.

(43) Clivio, P.; Richard, B.; Zeches, M.; Le Men-Olivier, L.; Goh, S. H.; David, B.; Sevenet, T. *Phytochemistry* **1990**, *29*, 2693.

(44) (a) Chastrette, F. *Bull. Soc. Chem. Fr.* **1970**, 1151. (b) Bhandari, K. S.; Snieckus, V. *Can. J. Chem.* **1971**, *49*, 2354.

(2-methoxyethoxy)methyl chloride (1.1 mL, 9.4 mmol) was obtained acetylindole **1d** (1.7 g, 73%) as an oil after column chromatography (3:7 hexane−AcOEt): IR (film) 1664; ^{1}H NMR (200 MHz) 2.60 (s, 3 H), 3.31 (s, 3 H), 3.45 and 3.58 (2 m, 4 H), 6.07 (s, 2 H), 7.15−7.50 (m, 3 H), 7.58 (d, J = 8.4 Hz, 1 H), 7.68 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) 27.7, 58.6, 66.9, 71.3, 73.7, 111.5, 114.2, 121.5, 122.7, 126.1, 126.5, 134.5, 140.2, 191.5. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.07; H, 7.02; N, 5.69.

Methyl 2-Methyl-7-oxo-8{[2-(trimethylsilyl)ethoxy]-methyl}-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (4c). LDA (2.5 mmol) was slowly added under N_2 to a solution of acetylindole **1c** (0.7 g, 2.4 mmol) in anhydrous THF (45 mL) cooled at −70 °C, and the resulting solution was stirred at −70° C for 30 min. Then, pyridinium iodide **2**[45] (0.74 g, 2.4 mmol) was added in portions, and the mixture was allowed to rise to 0 °C, stirred at this temperature for 3 h 30 min, and cooled to −30 °C. Enough of a saturated C_6H_6 solution of dry HCl was added dropwise to bring the pH to 3.5−4, and the mixture was allowed to rise to rt. After being stirred at rt for 2 h, the reaction mixture was poured into saturated aqueous Na_2CO_3 and extracted with Et_2O. Evaporation of the dried extracts followed by column chromatography (85:15 hexane−AcOEt) gave tetracycle **4c**: 0.17 g (15%); mp 162 °C (MeOH−Et_2O); IR (KBr) 1577, 1640, 1690; ^{1}H NMR (200 MHz) 0.00 (s, 9 H), 0.92 (t, J = 7.6 Hz, 2 H), 2.65 (m, 2 H), 2.90 (s, 3 H), 3.05 (m, 2 H), 3.42 (dd, J = 15 and 6.6 Hz, 1 H), 3.54 (t, J = 7.6 Hz, 2 H), 3.80 (s, 3 H), 5.01 (t, 1 H), 5.50 (d, J = 15 Hz, 1 H), 5.72 and 6.00 (2d, J = 10 Hz, 2 H), 6.39 (s, 1 H), 7.30−7.50 (m, 3 H), 7.62 (d, J = 8 Hz, 1 H), 7.87 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) −1.7 (CH_3), 17.5 (CH_2), 26.6 (CH), 31.4 (CH_2), 41.6 (CH_3), 47.7 (CH_2), 50.4 (CH), 50.7 (CH_3), 65.7 (CH_2), 73.1 (CH_2), 103.2 (CH), 106.3 (C), 111.6 (CH), 119.9 (C), 120.1 (CH), 121.7 (CH), 126.2 (CH), 126.6 (C), 133.2 (C), 138.4 (C), 143.7 (CH), 146.6 (CH), 169.2 (C), 196.5 (C). Anal. Calcd for $C_{26}H_{34}N_2O_4Si$: C, 66.92; H, 7.34; N, 6.00. Found: C, 67.01; H, 7.45; N, 5.97.

Methyl 8-[(2-Methoxyethoxy)methyl]-2-methyl-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (4d). Operating as above, from acetylindole **1d** (0.5 g, 2 mmol) and pyridinium iodide **2** (0.62 g, 2 mmol) was obtained tetracycle **4d** (60 mg, 7%) after column chromatography (75:25 hexane−AcOEt): mp 134 °C (acetone−Et_2O); IR (KBr) 1567, 1661,1687; ^{1}H NMR (200 MHz) 2.56 (m, 2 H), 2.83 (s, 3 H), 2.98 (m, 2 H), 3.32 (s, 3 H), 3.50 (m, 5 H), 3.72 (s, 3 H), 4.91 (t, 1 H), 5.44 (d, J = 15 Hz, 1H), 5.70 and 5.93 (2d, J = 10 Hz, 2 H), 6.32 (s, 1 H), 7.20−7.45 (m, 3 H), 7.59 (d, J = 8 Hz, 1H), 7.77 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) 26.5 (CH), 31.3 (CH_2), 41.6 (CH_3), 47.6 (CH_2), 50.4 (CH), 50.7 (CH_3), 58.8 (CH_3), 67.2 (CH_2), 71.5 (CH_2), 74.0 (CH_2), 103.2 (CH), 106.3 (C), 111.7 (CH), 120.0 (CH), 121.5 (C), 121.7 (CH), 126.3 (CH), 126.6 (C), 133.2 (C), 138.5 (C), 143.7 (CH), 146.6 (CH), 169.2 (C), 196.5 (C). Anal. Calcd for $C_{24}H_{28}N_2O_5\cdot H_2O$: C, 65.15; H, 6.83; N, 6.33. Found: C, 64.80; H, 6.68; N, 6.10.

Methyl 2-Methyl-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (4b). $BF_3\cdot Et_2O$ (0.1 mL, 0.85 mmol) was added to a solution of tetracycle **4c** (50 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (7 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 10 min and at rt for 30 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. After evaporation of the organic extracts, the residue was dissolved in CH_3CN (7 mL) and treated with Triton B (40% MeOH, 2 drops). The resulting solution was refluxed for 2 h and partitioned between H_2O and Et_2O. The organic extracts were washed with H_2O, dried, and evaporated to give tetracycle **4b**[21] (16 mg, 48%).

4(*E*)-Ethylidene-2-methyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole [(±)-16-Demethyleneervitsine, 10]. Method A. From Tetracycle 4b. A solution of **4b** (92 mg, 0.27 mmol) in 4 N HCl (11 mL) was refluxed for 3 h and then evaporated. The residue was dissolved in MeOH (10 mL), treated with $NaBH_4$ (0.1 g, excess) at 0 °C, and stirred at 0 °C for 1 h. The solvent was removed, and the residue was partitioned between H_2O and Et_2O. The organic extracts were dried and evaporated to give crude alcohol **9**: 50 mg; ^{1}H NMR (200 MHz) 1.71 (dd, J = 6.7 and 1.7 Hz, 3 H), 1.80−3.50 (m, 8 H), 2.14 (s, 3 H), 4.37 (br s, 1 H), 5.20 (dd, J = 4.8 and 12 Hz, 1 H), 5.53 (q, J = 6.7 Hz, 1 H), 7.10−7.40 (m, 3 H), 7.65 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) 12.1 (CH_3), 29.3 (CH), 36.3 (CH_2), 42.3 (CH_2), 43.0 (CH_3), 53.4 (CH), 57.2 (CH_2), 67.6 (CH), 105.5 (C), 110.8 (CH), 118.2 (CH), 119.5 (CH), 121.2 (CH), 121.6 (CH), 130.5 (C), 133.6 (C), 135.6 (C), 140.7 (C). A suspension of alcohol **9** (50 mg, 0.17 mmol) and MnO_2 (0.3 g, 3.5 mmol) in $CHCl_3$ (20 mL) was stirred at rt for 16 h. The mixture was filtered and evaporated to give ketone **10** (38 mg, 50% overall yield from **4b**) after column chromatography (AcOEt): mp 210 °C (acetone); IR (KBr) 1637, 3450; ^{1}H NMR (200 MHz) 1.66 (dd, J = 6.8 and 1.4 Hz, 3 H), 2.08 (s, 3 H), 2.20−3.30 (m, 7 H), 4.65 (dd, J = 5.5 and 1.5 Hz, 1 H), 5.45 (q, J = 6.8 Hz, 1 H), 7.10−7.40 (m, 3 H), 7.76 (d, J = 8 Hz, 1 H), 9.20 (br s, 1 H); ^{13}C NMR (50.3 MHz) 12.0 (CH_3), 28.8 (CH), 34.4 (CH_2), 43.7 (CH_3), 49.0 (CH_2), 53.5 (CH), 54.2 (CH_2), 112.1 (CH), 116.6 (C), 120.8 (CH), 122.0 (CH), 126.4 (CH), 134.7 (C), 136.1 (C), 136.3 (C). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.88; H, 7.18; N, 9.89.

Method B. From Tetracycle 4c. Operating as above, from **4c** (70 mg, 0.15 mmol) was obtained ketone **10**: 16 mg (38%).

Methyl (1*RS*,5*RS*,13*SR*)-13-[(Dimethylamino)methyl]-2,8-dimethyl-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (5a). *n*-BuLi (1.6 M in hexane, 2.7 mL, 4.3 mmol) was added under N_2 to a solution of isopropylcyclohexylamine (0.73 mL, 4.3 mmol) in anhydrous THF (7 mL) cooled at −70 °C, and the resulting solution was stirred at −70 °C for 30 min. A solution of acetylindole **1a**[46] (0.5 g, 2.89 mmol) in anhydrous THF (40 mL) was slowly added, and stirring was continued at −70 °C for 45 min. Then, pyridinium iodide **2** (0.88 g, 2.89 mmol) was added in portions, and the mixture was allowed to rise to −30 °C and stirred at this temperature for 1 h 30 min. *N*,*N*-Dimethylmethyleneiminium iodide (Eschenmoser's salt, 1.6 g, 8.6 mmol) was added, and the mixture was stirred at 0 °C for 4 h. Workup as in the preparation of **4c** gave a residue, which was chromatographed (hexane−AcOEt, increasing polarity and 95:5 AcOEt−MeOH) to give **5a**: 210 mg (18%); mp 227 °C (acetone); IR (KBr) 1575, 1643, 1695; ^{1}H NMR (200 MHz) 2.29 (s, 6 H), 2.30 (m, 2 H), 2.65 (m, 2 H), 2.85 (s, 3 H), 2.90 (dd, J = 15 and 2.5 Hz, 1 H), 3.35 (dd, J = 15 and 5 Hz, 1 H), 3.71 (s, 3 H), 3.88 (s, 3 H), 4.98 (br s, 1 H), 5.42 (d, J = 15.5 Hz, 1 H), 6.26 (s, 1 H), 7.20−7.42 (m, 4 H), 7.88 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (50.3 MHz) 30.4 (CH), 32.0 (CH_3), 38.9 (CH), 41.8 (CH_3), 45.8 (CH_3), 47.8 (CH_2), 50.7 (CH_3), 51.7 (CH), 63.6 (CH_2), 102.9 (CH), 104.6 (C), 110.5 (CH), 118.6 (C), 120.5 (CH), 120.8 (CH), 125.8 (CH), 126.2 (C), 133.6 (C), 138.2 (C), 142.7 (CH), 147.2 (CH), 169.3 (C), 195.9 (C). Anal. Calcd for $C_{24}H_{29}N_3O_3$: C, 70.90; H, 6.95; N, 10.34. Found: C, 70.53; H, 7.10; N, 10.04.

When LDA instead of LICA was used as the base, tetracycles **5a** (14%) and **6a** (4%) were obtained after column chromatography. **6a**: IR (KBr) 1581, 1656, 1698; ^{1}H NMR (200 MHz) 1.00 and 1.07 (2d, J = 6.6 Hz, 12 H), 2.40 (m, 2 H), 2.55 (m, 1 H), 2.75 (m, 1 H), 2.78 (s, 3 H), 2.90 (dd, J = 14.3 and 3 Hz, 1 H), 3.07 (m, 2 H), 3.38 (dd, J = 14.3 and 5.7 Hz, 1 H), 3.73 (s, 3 H), 3.88 (s, 3 H), 5.02 (s, 1 H), 5.42 (d, J = 15.1 Hz, 1 H), 6.28 (s, 1 H), 7.20−7.42 (m, 4 H), 7.78 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (50.3 MHz) 19.9 (CH_3), 21.9 (CH_3), 30.0 (CH), 32.2 (CH_3), 40.0 (CH), 41.7 (CH_3), 47.8 (CH), 48.2 (CH_2), 50.7 (CH_3), 50.8 (CH), 102.7 (CH), 104.9 (C), 110.5 (CH), 118.9 (C), 120.0 (CH), 120.8 (CH), 125.6 (CH), 126.1 (C), 133.7 (C), 138.0 (C), 142.7 (CH), 147.1 (CH), 169.1 (C), 196.1 (C).

Methyl (1*RS*,5*RS*,13*SR*)-13-[(Dimethylamino)methyl]-2-methyl-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (5b). Operating as above, from acetylindole **1b** (0.5 g, 3.14 mmol) and LDA (7.9 mmol) was obtained tetracycle **5b**: 50 mg (4%); mp 275 °C (*i*-Pr_2O−

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(46) Diels, O.; Köllisch, A. *Chem. Ber.* **1911**, *44*, 263.

MeOH); IR (KBr) 1571, 1647, 1690, 3440; ^{1}H NMR (200 MHz) 2.20 (m, 2 H), 2.27 (s, 6 H), 2.55 (m, 2 H), 2.80 (dd, J = 15 and 2.5 Hz, 1 H), 2.96 (s, 3 H), 3.45 (dd, J = 15 and 5 Hz, 1 H), 3.71 (s, 3 H), 4.98 (s, 1 H), 5.45 (d, J = 15 Hz, 1 H), 6.24 (s, 1 H), 7.15−7.40 (m, 4 H), 7.88 (d, J = 7.5 Hz, 1 H), 9.40 (br s, 1 H); ^{13}C NMR (50.3 MHz) 29.6 (CH), 38.9 (CH), 42.4 (CH_3), 44.8 (CH_2), 46.0 (CH_3), 50.9 (CH_3), 51.9 (CH), 63.6 (CH_2), 103.2 (CH), 105.1 (C), 112.2 (CH), 118.3 (C), 120.8 (CH), 121.3 (CH), 126.5 (CH), 127.5 (C), 132.3 (C), 136.1 (C), 142.5 (CH), 147.2 (CH), 169.0 (C), 193.4 (C). Anal. Calcd for $C_{23}H_{27}N_3O_3\cdot{}^1/_2H_2O$: C, 68.13; H, 7.01; N, 10.44. Found: C, 68.98; H, 6.99; N, 10.20.

Methyl (1*RS*,5*RS*,13*SR*)-13-[(Dimethylamino)methyl]-2-methyl-7-oxo-8-{[2-(trimethylsilyl)ethoxy]methyl}-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (5c). Operating as above, except for the temperature and reaction time with the pyridinium salt (0 °C, 3 h), from acetylindole **1c** (0.5 g, 1.73 mmol) and LICA (2.6 mmol) was obtained tetracycle **5c** as an oil: 136 mg (15%); IR ($CHCl_3$) 1580, 1650; ^{1}H NMR (200 MHz) 0.00 (s, 9 H), 0.85 (t, J = 8.5 Hz, 2 H), 2.20 (m, 2 H), 2.33 (s, 6 H), 2.65 (m, 2 H), 2.86 (s, 3 H), 2.95 (dd, J = 15 and 2.5 Hz, 1 H), 3.40 (dd, J = 15 and 5 Hz, 1 H), 3.47 (m, 2 H), 3.71 (s, 3 H), 4.99 (s, 1 H), 5.42 (d, J = 15.3 Hz, 1 H), 5.65 and 5.93 (2 d, J = 10 Hz, 2 H), 6.27 (s, 1 H), 7.20−7.60 (m, 4 H), 7.90 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (50.3 MHz) −1.5 (CH_3), 17.7 (CH_2), 30.8 (CH), 38.8 (CH), 41.8 (CH_3), 45.6 (CH_3), 47.8 (CH_2), 50.8 (CH_3), 51.8 (CH), 63.7 (CH_2), 65.7 (CH_2), 73.1 (CH_2), 103.3 (CH), 104.4 (C), 111.4 (CH), 120.2 (C), 120.3 (CH), 121.5 (CH), 126.1 (CH), 126.6 (C), 133.0 (C), 138.3 (C), 142.4 (CH), 146.8 (CH), 168.9 (C), 195.5 (C). Anal. Calcd for $C_{29}H_{41}N_3O_4\cdot{}^1/_2H_2O$: C, 65.38; H, 7.94; N, 7.88. Found: C, 65.39; H, 8.13; N, 7.48.

Methyl (1*RS*,5*RS*,13*RS*)-2,8-Dimethyl-7-oxo-13-(phenylseleno)-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (7a). Acetylindole **1a** (0.5 g, 2.89 mmol) in anhydrous THF (40 mL) was allowed to react with LDA (2.89 mL, 4.3 mmol) and then with pyridinium iodide **2** (0.88 g, 2.89 mmol) at −30 °C for 1 h 30 min. PhSeBr (2 g, 8.67 mmol) was slowly added to the mixture, and stirring was continued at 0 °C for 3 h. Workup as above gave a crude residue, which was chromatographed (hexane−AcOEt, increasing polarity) to give tetracycle **7a**: 285 mg (20%); mp 240−242 °C (acetone); IR (KBr) 1588, 1650, 1690; ^{1}H NMR (200 MHz) 2.84 (s, 3 H), 2.92 (dd, J = 14.4 and 2.7 Hz, 1 H), 3.10 (m, 1 H), 3.32 (dd, J = 14.4 and 5.8 Hz, 1 H), 3.72 (s, 3 H), 3.86 (s, 3 H), 4.19 (s, 1 H), 4.93 (s, 1 H), 5.40 (d, J = 15.2 Hz, 1 H), 6.33 (s, 1 H), 7.10−7.70 (m, 10 H); ^{13}C NMR (50.3 MHz) 32.6 (CH_3), 33.6 (CH), 42.0 (CH_3), 44.7 (CH_2), 48.0 (CH_2), 50.9 (CH_3), 55.4 (CH), 103.9 (CH), 110.6 (CH), 117.1 (C), 119.7 (CH), 121.1 (CH), 125.4 (C), 125.8 (CH), 133.2 (C), 138.1 (C), 142.3 (CH), 146.4 (CH), 168.8 (C), 194.6 (C). Anal. Calcd for $C_{27}H_{26}N_2O_3Se\cdot{}^1/_2H_2O$: C, 63.03; H, 5.28; N, 5.44. Found: C, 62.98; H, 5.13; N, 5.33.

Interaction of Acetylindole 1a with Pyridinium Iodide 2 and DMTSF. Operating as above but using DMTSF (1.13 g, 5.8 mmol) instead of PhSeBr, from acetylindole **1a** (0.5 g, 2.89 mmol) was obtained a crude residue, which was chromatographed (hexane−AcOEt, increasing polarity). On successive elution the following compounds were isolated. Tetracycle **12**: 90 mg (6%); ^{1}H NMR (500 MHz, assignments aided by ^{1}H−^{1}H COSY and HMQC) 2.28 (s, 3 H, SMe), 2.90 (s, 3 H, NMe), 3.08 (dd, J = 14.5 and 3 Hz, 1 H, 14-H), 3.24 (dd, J = 14.5 and 6 Hz, 1 H, 14-H), 3.75 (s, 3 H, OMe), 3.84 (s, 3 H, NMe), 4.55 (m, 1 H, 15-H), 5.06 (t, J = 2 Hz, 1 H, 5-H), 5.21 (t, J = 2 Hz, 1 H, 16-H), 6.58 (s, 1 H, 19-H), 7.20−7.40 (m, 3 H, indole), 7.58 (s, 1 H, 21-H), 7.68 (d, J = 8 Hz, 1 H, 9-H); ^{13}C NMR (75 MHz, assignments aided by HMQC) 20.3 (SMe), 26.4 (C-16), 32.2 (NMe), 39.2 (C-15), 42.5 (NMe), 50.8 (C-14), 52.1 (OMe), 60.2 (C-5), 104.6 (C-18), 108.7 (C-20), 110.8 (C-12), 115.7 (C-7), 119.6 (C-9), 121.4 (C-10), 125.0 (C-8), 126.0 (C-11), 133.0 (C-2), 138.1 (C-13), 145.9 (C-19), 148.9 (C-21), 168.5, 195.8 (CO); MS, m/z (rel intensity) 522 (M^+, 1), 396 (1); HRMS calcd for $C_{22}H_{23}N_2O_3SI$ 522.0473, found 522.0435. **Methyl (1*RS*,5*RS*,13*RS*)-2,8-Dimethyl-13-(methylthio)-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (8a):** 70 mg (6%); mp 168−169 °C (acetone); IR (KBr) 1578, 1663, 1690; ^{1}H NMR (200 MHz) 2.31 (s, 3 H), 2.88 (s, 3 H), 2.95 (dd, J = 14 Hz and 1.5 Hz, 1 H), 3.05 (m, 1 H), 3.40 (dd, J = 14 and 15 Hz, 1 H), 3.60 (br s, 1 H), 3.72 (s, 3 H), 3.88 (s, 3 H), 4.93 (s, 1 H), 5.43 (d, J = 15.3 Hz, 1 H), 6.30 (s, 1 H), 7.20−7.50 (m, 4 H), 7.80 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (50.3 MHz) 15.2 (CH_3), 32.2 (CH_3), 33.1 (CH), 42.1 (CH_3), 47.7 (CH_2), 48.5 (CH), 50.9 (CH_3), 55.4 (CH), 103.8 (CH), 110.4 (C), 110.6 (CH), 117.1 (C), 119.9 (CH), 121.1 (CH), 125.7 (C), 125.9 (CH), 133.5 (C), 138.2 (C), 142.1 (CH), 146.6 (CH), 168.8 (C), 194.5 (C). Anal Calcd for $C_{22}H_{24}N_2O_3S\cdot{}^1/_2H_2O$: C, 65.16; H, 6.21; N, 6.90; S, 7.90. Found: C, 65.48; H, 6.14; N, 6.84; S, 7.69. Tetracycle **11**: 78 mg (6%); ^{1}H NMR (500 MHz, assignment aided by ^{1}H−^{1}H COSY and HMQC) 2.29 and 2.32 (2s, 6 H, SMe), 2.85 (s, 3 H, NMe), 3.02 (dd, J = 14.5 and 3.5 Hz, 1 H, 14-H), 3.47 (dd, J = 14.5 and 6 Hz, 1 H, 14-H), 3.67 (t, J = 1.5 Hz, 1 H, 16-H), 3.74 (s, 3 H, OMe), 3.85 (s, 3 H, NMe), 4.30 (m, 1 H, 15-H), 4.92 (t, J = 1.5 Hz, 1 H, 5-H), 6.50 (s, 1 H, 19-H), 7.20−7.40 (m, 3 H, indole), 7.54 (s, 1 H, 21-H), 7.75 (d, J = 8 Hz, 1 H, 9-H); ^{13}C NMR (75 MHz, assignments aided by HMQC) 15.3 and 19.8 (SMe), 32.2 (NMe), 33.4 (C-15), 42.5 (NMe), 48.6 (C-16), 50.6 (C-14), 52.1 (OMe), 55.6 (C-5), 105.3 (C-18), 108.0 (C-20), 110.8 (C-12), 117.1 (C-7), 119.7 (C-9), 121.2 (C-10), 125.8 (C-8), 125.9 (C-11), 133.1 (C-2), 138.0 (C-13), 146.5 (C-19), 149.1 (C-21), 168.5 and 196.4 (CO); MS, m/z (rel intensity) 442 (M^+, 100), 395 (M − 47, 20), 364 (20); HRMS calcd for $C_{23}H_{26}N_2O_3S_2$ 442.1384, found 442.1386.

Methyl (1*RS*,5*RS*,13*RS*)-13-Chloro-2,8-dimethyl-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4-(α-chloro)acrylate (13). Operating as above, but using NCS (695 mg, 5.2 mmol) as electrophile, from acetylindole **1a** (0.3 g, 1.73 mol) was obtained tetracycle **13** (43 mg, 6%) after column chromatography (hexane−AcOEt, increasing polarity): mp 230 °C (i-Pr_2O−MeOH); IR (KBr) 1561, 1648, 1694; ^{1}H NMR (300 MHz) 2.92 (s, 3 H), 3.13 (dd, J = 14.8 and 3 Hz, 1 H), 3.38 (dd, J = 14.8 and 6.1 Hz, 1 H), 3.78 (s, 3 H), 3.87 (s, 3 H), 3.98 (m, 1 H), 4.97 and 5.00 (2 t, J = 2 Hz, 2 H), 6.64 (s, 1 H), 7.26 (m, 1 H), 7.40 (m, 3 H), 7.75 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 32.2 (CH_3), 37.1 (CH), 42.3 (CH_3), 50.3 (CH_2), 52.5 (CH_3), 57.6 (CH), 57.8 (CH), 101.5 (C), 107.1 (CH), 110.8 (CH), 115.0 (C), 119.6 (CH), 121.5 (CH), 125.6 (C), 126.1 (CH), 133.0 (C), 138.2 (C), 139.2 (CH), 144.9 (CH), 165.2 (C), 195.2 (C). Anal. Calcd for $C_{21}H_{20}N_2O_3Cl_2$: C, 60.15; H, 4.81; N, 6.68. Found: C, 59.87; H, 4.90; N, 6.38.

3-[(*E*)-2-(Methoxycarbonyl)vinyl]-1-methyl-4-[[(1-methyl-2-indolyl)carbonyl]methylene]-1,4-dihydropyridine (14). This compound was obtained when dihydropyridine **3a** failed to react with electrophiles ($PhSCH_2Cl$, $PhSeCH_2Br$, HCHO): mp 249 °C (acetone−MeOH); IR (KBr) 1523, 1636, 1703; ^{1}H NMR (200 MHz) 3.54 (s, 3 H), 3.78 (s, 3 H), 4.11 (s, 3 H), 5.87 (s, 1 H), 6.19 (d, J = 15 Hz, 1 H), 7.00 (s, 1 H), 7.10−7.40 (m, 6 H), 7.63 (d, J = 8 Hz, 1 H), 9.01 (d, J = 9.8 Hz, 1 H); ^{13}C NMR (50.3 MHz) 31.8, 42.8, 51.6, 90.7, 105.3, 110.0, 114.8, 117.4, 120.1, 121.7, 122.4, 123.8, 126.5, 130.8, 139.4, 139.5, 140.5, 141.8, 151.8, 167.8. Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.31; H, 5.81; N, 8.06.

Methyl 2,8-Dimethyl-13-methylene-7-oxo-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (16a). A. *m*-CPBA (246 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **5a** (270 mg, 0.66 mmol) in CH_2Cl_2 (20 mL) at −10 °C, and the mixture was stirred at −10 °C for 2 h. Na_2CO_3 (excess) was then added, and the reaction mixture was allowed to stand for 15 min at rt, filtered over Celite, and evaporated. The resulting residue was chromatographed (flash, 7:3 CH_2Cl_2−MeOH) to give *N*-oxide **15a** as a foam: 177 mg (63%); ^{1}H NMR (200 MHz) 2.75 (m, 1 H), 2.90 (s, 3 H), 3.10−3.50 (m, 5 H), 3.35 and 3.50 (2s, 6 H), 3.70 (s, 3 H), 3.90 (s, 3 H), 5.45 (d, J = 15 Hz, 1 H), 5.55 (s, 1 H), 6.40 (s, 1 H), 7.20−7.50 (m, 4 H), 7.90 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) 32.1 (CH_3), 33.6 (CH), 36.3 (CH), 41.8 (CH_3), 47.1 (CH_2), 50.8 (CH_3), 54.6 (CH), 57.7 (CH_3), 61.1 (CH_3), 75.1 (CH_2), 103.3 (C), 103.5 (CH), 110.3 (CH), 117.7 (C), 120.6 (CH), 120.9 (CH), 125.8 (CH), 126.2 (C), 133.0 (C), 138.0 (C), 143.7 (CH), 146.3 (CH), 168.6 (C), 194.5 (C).

B. A solution of *N*-oxide **15a** (100 mg, 0.24 mmol) in anhydrous toluene (30 mL) was refluxed for 1 h. The mixture

was poured into H_2O and extracted with Et_2O. Evaporation of the organic extracts followed by flash chromatography (3:2 hexane−AcOEt) gave **16a**: 68 mg (79%); mp 235 °C (acetone); IR (KBr) 1580, 1642, 1680; ^{1}H NMR (200 MHz) 2.83 (s, 3 H), 3.02 (m, 1 H), 3.44 (m, 2 H), 3.72 (s, 3 H), 3.87 (s, 3 H), 5.19 and 5.26 (2s, 2 H), 5.25 (s, 1 H), 5.44 (d, J = 15.3 Hz, 1 H), 6.29 (s, 1 H), 7.20−7.40 (m, 4 H), 7.81 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (50.3 MHz) 32.3 (CH_3), 36.4 (CH), 41.3 (CH_3), 48.6 (CH_2), 50.8 (CH_3), 58.1 (CH), 103.4 (CH), 105.6 (C), 110.6 (CH), 111.7 (CH_2), 117.6 (C), 119.9 (CH), 121.0 (CH), 125.4 (C), 125.8 (CH), 133.1 (C), 138.3 (C), 142.5 (C), 143.4 (CH), 145.5 (CH), 168.9 (C), 195.2 (C). Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.94; H, 6.16; N, 7.65.

Methyl 2-Methyl-13-methylene-7-oxo-8-{[2-(trimethylsilyl)ethoxy]methyl}-2,5,6,7-tetrahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole-4(*E*)-acrylate (16c). A. Operating as above, from tetracycle **5c** (250 mg, 0,48 mmol) was obtained *N*-oxide **15c** as a foam: 155 mg, 60%; ^{1}H NMR (200 MHz) 0.00 (s, 9 H), 1.05 (t, J = 7.5 Hz, 2 H), 2.90 (m, 1 H), 3.05 (s, 3 H), 3.20−3.70 (m, 7 H), 3.50 and 3.60 (2s, 6 H), 3.90 (s, 3 H), 5.59 (d, J = 15 Hz, 1 H), 5.70 (s, 1 H), 5.80 and 6.15 (2d, J = 10 Hz, 2 H), 6.60 (s, 1 H), 7.30−7.75 (m, 4 H), 8.05 (d, J = 8 Hz, 1H); ^{13}C NMR (50.3 MHz) −1.5 (CH_3), 17.5 (CH_2), 33.8 (CH), 36.2 (CH), 41.9 (CH_3), 47.2 (CH_2), 50.9 (CH_3), 54.6 (CH), 57.5 (CH_3), 61.3 (CH_3), 65.7 (CH_2), 73.0 (CH_2), 75.1 (CH_2), 103.3 (C), 103.8 (CH), 111.2 (CH), 119.6 (C), 120.6 (CH), 121.4 (CH), 126.3 (CH), 126.5 (C), 132.7 (C), 138.3 (C), 143.8 (CH), 146.3 (CH), 168.7 (C), 194.5 (C).

B. Operating as above, from *N*-oxide **15c** (90 mg, 0,17 mmol) was obtained tetracycle **16c** (60 mg, 75%) as a foam after flash chromatography (4:1 hexane−AcOEt): IR (film) 1584, 1611, 1660, 1695; ^{1}H NMR (200 MHz) 0.00 (s, 9 H), 0.91 (t, J = 8 Hz, 2 H), 2.94 (s, 3 H), 3.10 (m, 1 H), 3.50 (m, 4 H), 3.82 (s, 3 H), 5.25 and 5.37 (2s, 2 H), 5.36 (s, 1 H), 5.55 (d, J = 15.3 Hz, 1 H), 5.74 and 6.01 (2d, J = 10.6 Hz, 2 H), 6.40 (s, 1 H), 7.30−7.70 (m, 4 H), 7.90 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) −1.5 (CH_3), 17.8 (CH_2), 36.5 (CH), 41.2 (CH_3), 48.7 (CH_2), 50.9 (CH_3), 58.1 (CH), 65.8 (CH_2), 73.3 (CH_2), 103.8 (CH), 105.7 (C), 111.7 (CH), 111.9 (CH_2), 119.4 (C), 119.9 (CH), 121.8 (CH), 125.9 (C), 126.3 (CH), 133.0 (C), 138.6 (C), 142.3 (C), 143.2 (CH), 145.5 (CH), 168.9 (C), 195.3 (C); HRMS calcd for $C_{27}H_{34}N_2O_4Si$ 478.2287, found 478.2290.

(1*RS*,5*RS*,13*SR*)-13-[(Dimethylamino)methyl]-4(*E*)-ethylidene-2,8-dimethyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (18). A solution of tetracycle **5a** (330 mg, 0.81 mmol) in EtOH (18 mL) and 4 N HCl (30 mL) was refluxed for 2 h. The solvents were removed, and the residue was dissolved in MeOH (40 mL). The resulting solution was treated with $NaBH_4$ (38 mg, 1 mmol) at 0 °C and stirred at 0 °C for 1 h. The solvent was evaporated, and the residue was partitioned between H_2O and Et_2O. Evaporation of the organic extracts followed by flash chromatography (98:2 Et_2O−DEA) gave **18** as a foam: 150 mg (53%); IR (KBr) 1648; ^{1}H NMR (200 MHz) 1.67 (d, J = 6.6 Hz, 3 H), 1.98 (s, 3 H), 2.27 (s, 6 H), 2.30−3.20 (m, 7 H), 3.24 (m, 1 H), 3.93 (s, 3 H), 4.50 (s, 1 H), 5.52 (q, J = 6.6 Hz, 1 H), 7.17 (m, 1 H), 7.36 (m, 2 H), 7.80 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) 12.1 (CH_3), 32.1 (CH_3), 33.6 (CH), 42.1 (CH), 43.6 (CH_3), 46.2 (CH_3), 51.9 (CH_2), 54.8 (CH_2), 56.9 (CH), 64.4 (CH_2), 110.3 (CH), 116.4 (C), 120.6 (CH), 121.3 (CH), 121.9 (CH), 125.4 (CH), 127.4 (C), 134.6 (C), 135.5 (C), 138.2 (C), 197.5 (C). Anal. Calcd for $C_{22}H_{29}N_3O\cdot{}^1/_3H_2O$: C, 73.91; H, 8.36; N, 11.75. Found: C, 73.94; H, 8.28; N, 11.38.

(±)-N_a-Methylervitsine (17a). Operating as above, from tetracycle **16a** (130 mg, 0.36 mmol) was obtained **17a** as a foam after flash chromatography (AcOEt): 60 mg (55%); IR (KBr) 1647; ^{1}H NMR (200 MHz) 1.62 (dd, J = 6.9 and 1.9 Hz, 3 H), 2.08 (s, 3 H), 2.88 (m, 4 H), 3.70 (t, J = 4 Hz, 1 H), 3.84 (s, 3 H), 4.94 (s, 1 H), 4.98 and 4.99 (2s, 2 H), 5.36 (q, J = 6.9 Hz, 1 H), 7.14 (m, 1 H), 7.30 (m, 2 H), 7.72 (d, J = 8 Hz, 1 H); ^{13}C NMR (50.3 MHz) 12.6 (CH_3), 32.8 (CH_3), 40.6 (CH), 43.0 (CH_3), 53.4 (CH_2), 54.3 (CH_2), 62.0 (CH), 110.8 (CH), 110.9 (CH_2), 116.7 (C), 121.2 (CH), 121.5 (2 CH), 126.3 (CH), 127.6 (C), 135.4 (2 C), 139.3 (C), 146.7 (C), 196.8 (C); HRMS calcd for $C_{20}H_{22}N_2O$ 306.1732, found 306.1729.

(±)-Ervitsine (17b). Operating as above, from tetracycle **16c** (80 mg, 0.17 mmol) was obtained **17b**: 32 mg (65%); mp 173 °C (acetone); IR (KBr) 1638, 3400; ^{1}H NMR (500 MHz, assignments aided by ^{1}H−^{1}H COSY and HMQC) 1.68 (dd, J = 6.5 and 2.5 Hz, 3 H, 18-H), 2.23 (s, 3 H, NMe), 2.80 (d, J = 14.5 Hz, 1 H, 21-H), 2.93 (dd, J = 17 and 4 Hz, 1 H, 14-H), 2.98 (dd, J = 17 and 5 Hz, 1 H, 14-H), 3.06 (br d, J = 14.5 Hz, 1 H, 21-H), 3.76 (dd, J = 4 and 5 Hz, 1 H, 15-H), 4.94 (s, 1 H, 5-H), 5.07 and 5.08 (2s, 2 H, 6-H), 5.38 (qd, J = 6.5 and 2 Hz, 1 H, 19-H), 7.16 (m, 1 H, 10-H), 7.35 (m, 2 H, 11-H and 12-H), 7.78 (dd, J = 8.5 and 1 Hz, 1 H, 9-H), 9.06 (br s, 1 H, NH); ^{13}C NMR (75 MHz, assignments aided by HMQC) 12.0 (C-18), 38.9 (C-15), 42.6 (NMe), 50.2 (C-14), 53.4 (C-21), 61.7 (C-5), 111.2 (C-6), 112.1 (C-12), 117.1 (C-7), 120.8 (C-10), 121.0 (C-19), 121.7 (C-9), 126.5 (C-11), 127.8 (C-8), 133.9 (C-2), 135.2 (C-20), 136.5 (C-13), 145.6 (C-16), 193.9 (C-3); HRMS calcd for $C_{19}H_{20}N_2O$ 292.1575, found 292.1577.

(1*RS*,5*RS*,13*RS*)-4(*E*)-Ethylidene-2,8-dimethyl-7-oxo-13-(phenylseleno)-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (19). Operating as above, from tetracycle **7a** (265 mg, 0.52 mmol) was obtained **19** after flash chromatography (95:5 hexane−AcOEt): 141 mg (60%); mp 113 °C (acetone), IR (KBr) 1650; ^{1}H NMR (200 MHz) 1.67 (dd, J = 6.8 and 1.8 Hz, 3 H), 2.03 (s, 3 H), 2.80 (m, 4 H), 3.45 (m, 1 H), 3.93 (s, 3 H), 4.08 (t, J = 2 Hz, 1 H), 5.00 (d, J = 2 Hz, 1 H), 5.65 (q, J = 6.8 Hz, 1 H), 7.10−7.80 (m, 9 H); ^{13}C NMR (50.3 MHz) 12.2 (CH_3), 32.1 (CH_3), 37.0 (CH), 43.5 (CH_3), 50.6 (CH), 51.8 (CH_2), 54.4 (CH_2), 59.5 (CH), 110.3 (CH), 114.8 (C), 120.6 (CH), 120.9 (CH), 122.8 (CH), 125.6 (CH), 127.5 (C), 133.7 (C), 135.3 (C), 138.3 (C), 196.2 (C). Anal. Calcd for $C_{25}H_{26}N_2OSe$: C, 66.81; H, 5.83; N, 6.23. Found: C, 66.82; H, 5.86; N, 6.18.

(±)-N_a-Methylervitsine (17a) from Tetracycle 19. A. *m*-CPBA (60 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was added to a solution of tetracycle **19** (0.1g, 0.22 mmol) in CH_2Cl_2 (10 mL) at −70 °C, and the resulting mixture was stirred at −70 °C for 20 min. K_2CO_3 (excess) was added, and the mixture was allowed to stand at rt for 15 min, diluted with H_2O, and extracted with CH_2Cl_2. Evaporation of the organic extracts gave crude selenoxide **20**: 85 mg (82%).

B. LDA (0.4 mL, 0.60 mmol) was slowly added to a solution of **20** (50 mg, 0.11 mmol) in anhydrous THF (10 mL) cooled at −70 °C, and the resulting solution was stirred at −70 °C for 45 min. Then, MeI (0.048 mL, 0.77 mmol) in anhydrous THF (1 mL) was added, and the mixture was allowed to rise to rt and stirred at rt for 1 h. Glacial AcOH (0.05 mL, 0.88 mmol) and diisopropylamine (0.6 mL, 4.4 mol) were consecutively added, and the mixture was refluxed for 1 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The organic extracts were evaporated to give **17a** (12 mg, 35%) after flash chromatography (AcOEt).

2-Acetyl-1-(*tert*-butoxycarbonyl)indole (1e). DMAP (0.19 g, 1.57 mmol) and di-*tert*-butyl dicarbonate (4.1 g, 18.5 mmol) were added to a solution of acetylindole **1b** (2.5 g, 15.7 mmol) in CH_3CN (50 mL). The mixture was stirred at rt for 2.5 h, poured into H_2O, and extracted with Et_2O. The organic extracts were dried and evaporated. Flash chromatography (hexane−AcOEt, increasing polarity) of the residue gave **1e**: 3.3 g (80%); mp 59 °C (cyclohexane); IR (KBr) 1677, 1735; ^{1}H NMR (300 MHz) 1.62 (s, 9 H), 2.56 (s, 3 H), 7.08 (s, 1 H), 7.26 (td, J = 8 and 0.9 Hz, 1 H), 7.42 (td, J = 8 and 1.3 Hz, 1 H), 7.61 (d, J = 8 Hz, 1 H), 8.04 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 27.7, 28.7, 84.7, 114.4, 114.7, 122.4, 123.3, 127.2, 127.4, 138.2, 138.8, 149.6, 191.3. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.55; H, 6.60; N, 5.41.

Interaction of Acetylindole 1e with Pyridinium Salt 24 and TCAA. Acetylindole **1e** (0.5 g, 2 mmol) was allowed to react with LDA (1.45 mL, 2.18 mmol) at −70 °C for 30 min and then with pyridinium iodide **24**[47] (0.5 g, 2 mmol) at −30 °C for 3 h 30 min. TCAA (1.1 mL, 6 mmol) was slowly added, and the mixture was stirred at 0 °C for 3 h. The reaction mixture was poured into saturated aqueous Na_2CO_3 and extracted with Et_2O. The organic extracts were dried and

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evaporated. Column chromatography (hexane−AcOEt, increasing polarity) of the residue gave the following compounds on successive elution. **4-{[1-(*tert*-Butoxycarbonyl)-2-indolyl]carbonylmethyl}-1-methyl-5-[1-(trichloroacetoxy)-vinyl]-3-(trichloroacetyl)-1,4-dihydropyridine (29):** 146 mg (11%); ^{1}H NMR (200 MHz) 1.60 (s, 9 H), 3.01 and 3.10 (2 dd, J = 12.5 and 5 Hz, 2 H), 3.25 (s, 3 H), 4.45 (t, J = 5 Hz, 1 H), 5.10 and 5.40 (2 d, J = 3 Hz, 2 H), 6.33 (s, 1 H), 7.05 (s, 1 H), 7.20−7.40 (m, 2 H), 7.60 (d, J = 8 Hz, 1 H), 7.74 (s, 1 H), 7.99 (d, J = 8 Hz, 1 H). **3-Acetyl-4-{[[1-(*tert*-butoxycarbonyl)-2-indolyl]carbonyl]methyl}-1-methyl-5-(trichloroacetyl)-1,4-dihydropyridine (25e):** 140 mg (13%); ^{1}H NMR (300 MHz) 1.59 (s, 9 H), 2.25 (s, 3 H), 3.05 and 3.15 (2 dd, J = 12.6 and 5 Hz, 2 H), 3.31 (s, 3 H), 4.49 (t, J = 5 Hz, 1 H), 6.90 (s, 1 H), 7.02 (s, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 7.40 (t, J = 7.5 Hz, 1 H), 7.60 (d, J = 7.5 Hz, 1 H), 7.70 (s, 1 H), 7.93 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz) 24.8 (CH_3), 27.7 (CH_3), 29.0 (CH), 42.4 (CH_3), 43.9 (CH_2), 84.4 (C), 96.0 (C), 104.7 (C), 114.4 (CH), 115.4 (CH), 118.6 (C), 122.5 (CH), 123.2 (CH), 127.0 (CH), 127.4 (CH), 137.9 (C), 139.0 (C), 139.8 (CH), 145.9 (CH), 149.4 (C), 178.7 (C), 192.7 (C), 194.8 (C). **3-Acetyl-4-{[[1-(*tert*-butoxycarbonyl)-2-indolyl]carbonyl]methylene}-1-methyl-1,4-dihydropyridine (30):** 95 mg (12%); ^{1}H NMR (200 MHz) 1.62 (s, 9 H), 2.44 (s, 3 H), 3.58 (s, 3 H), 5.60 (s, 1 H), 6.80 (s, 1 H), 7.10−7.60 (m, 4 H), 7.90 (s, 1 H), 8.05 (d, J = 8 Hz, 1 H), 8.90 (d, J = 9.5 Hz, 1 H).

Interaction of Acetylindole 1f with Pyridinium Salt 24 and TCAA. Operating as above, from acetylindole **1f**[48] (250 mg, 0.84 mmol) were isolated the following compounds. **3-Acetyl-1-methyl-4-{[[1-(phenylsulfonyl)-2-indolyl]carbonyl]methyl}-5-(trichloroacetyl)-1,4-dihydropyridine (25f):** 34 mg (7%); ^{1}H NMR (300 MHz) 2.26 (s, 3 H), 2.92 (dd, J = 13.4 and 4.6 Hz, 1 H), 3.18 (dd, J = 13.4 and 5.3 Hz, 1 H), 3.31 (s, 3 H), 4.56 (dd, J = 5.3 and 4.6 Hz, 1 H), 6.95 (d, J = 1 Hz, 1 H), 7.29 (t, J = 8 Hz, 1 H), 7.45−7.65 (m, 7 H), 7.68 (s, 1 H), 8.04 (m, 2 H), 8.16 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 24.9 (CH_3), 29.7 (CH), 42.6 (CH_3), 43.9 (CH_2), 104.2 (C), 115.4 (CH), 118.2 (C), 119.9 (CH), 123.1 (CH), 124.0 (CH), 127.8 (C), 127.9 (CH), 138.9 (C), 139.4 (C), 139.9 (CH), 146.1 (CH), 178.8 (C), 194.9 (C), 191.0 (C). **3-Acetyl-1-methyl-4-{2-[1-(phenylsulfonyl)-2-indolyl]-2-(trichloroacetoxy)vinyl}-5-(trichloroacetyl)-1,4-dihydropyridine (31):** 18 mg (3%); ^{1}H NMR (300 MHz) 2.35 (s, 3 H), 3.38 (s, 3 H), 5.03 (d, J = 9 Hz, 1 H), 6.10 (d, J = 9 Hz, 1 H), 6.79 (s, 1 H), 7.03 (s, 1 H), 7.18−7.67 (m, 8 H), 7.78 (s, 1 H), 8.13 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 25.1 (CH_3), 29.1 (CH), 42.8 (CH_3), 89.7 (C), 95.6 (C), 105.5 (C), 115.9 (CH), 117.3 (CH), 118.2 (C), 121.5 (CH), 124.4 (CH), 125.8 (CH), 128.0 (C, CH), 136.6 (C), 137.6 (C), 138.4 (CH), 138.8 (C), 144.4 (CH), 158.9 (C), 178.6 (C), 195.1 (C).

Interaction of Acetylindole 1g with Pyridinium Salt 24 and TCAA. Operating as above, from acetylindole **1g**[33a] (0.75 g, 3 mmol) were isolated the following compounds. **5-Acetyl-2-[[(1-Benzyl-2-indolyl)carbonyl]methyl]-1-methyl-3-(trichloroacetyl)-1,2-dihydropyridine (27g):** 110 mg (7%); ^{1}H NMR (300 MHz) 2.32 (s, 3 H), 2.94 (dd, J = 14.4 and 3.5 Hz, 1 H), 3.03 (s, 3 H), 3.20 (dd, J = 14.4 and 7.6 Hz, 1 H), 5.28 (m, 1 H), 5.72 and 5.82 (2 d, J = 16 Hz, 2 H), 7.00−7.40 (m, 8 H), 7.45 (s, 1 H), 7.74 (d, J = 8 Hz, 1 H), 7.82 (s, 1 H), 7.99 (s, 1 H); ^{13}C NMR (75 MHz) 24.6 (CH_3), 43.5 (CH_2), 44.0 (CH_3), 48.0 (CH_2), 56.4 (CH), 96.2 (C), 98.8 (C), 110.7 (CH), 113.9 (CH), 120.0 (C), 121.2 (CH), 123.1 (CH), 126.0 (C), 126.2 (CH), 126.5 (CH), 126.9 (CH), 128.3 (CH), 133.8 (C), 134.6 (CH), 137.9 (C), 140.3 (C), 155.0 (CH), 175.7 (C), 189.8 (C), 195.0 (C). **3-Acetyl-4-[[(1-benzyl-2-indolyl)carbonyl]-methyl]-1-methyl-5-(trichloroacetyl)-1,4-dihydropyridine (25g):** 230 mg (14%); mp 141 °C (Et_2O); IR (KBr) 1649; ^{1}H NMR (300 MHz) 2.21 (s, 3 H), 2.89 (dd, J = 12.7 and 5.6 Hz, 1 H), 2.99 (dd, J = 12.7 and 5.8 Hz, 1 H), 3.09 (s, 3 H), 4.56 (t, J = 5.7 Hz, 1 H), 5.71 and 5.77 (2 d, J = 16.2 Hz, 2 H), 6.86 (s, 1 H), 7.05−7.30 (m, 8 H), 7.54 (s, 1 H), 7.63 (s, 1 H), 7.75 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 24.9 (CH_3), 29.9 (CH), 42.2 (CH_3), 45.0 (CH_2), 48.0 (CH_2), 96.0 (C), 105.2 (C), 110.7 (CH), 113.7 (CH), 119.0 (C), 120.7 (CH), 123.3 (CH), 126.0 (CH), 126.4 (CH), 126.7 (CH), 126.8 (C), 128.3 (CH), 134.8 (C), 138.7 (C), 139.3 (CH), 140.1 (C), 145.2 (CH), 178.8 (C), 192.0 (C), 194.6 (C). Anal. Calcd for $C_{27}H_{23}N_2O_3Cl_3$: C, 61.20; H, 4.37; N, 5.28. Found: C, 61.10; H, 4.49; N, 5.18.

3-Acetyl-4-[[(1-benzyl-2-indolyl)carbonyl]methyl]-5-(methoxycarbonyl)-1-methyl-1,4-dihydropyridine (26g). A solution of dihydropyridine **25g** (0.5 g, 0,94 mmol) in MeOH−THF (1:1, 40 mL) was slowly added to a solution of MeONa (2.8 mmol) in MeOH (20 mL), and the resulting mixture was stirred at rt for 3 min. The solvents were removed, and the residue was partitioned between H_2O and Et_2O. Evaporation of the dried extracts gave a crude residue which was chromatographed (flash, 8:2 hexane−AcOEt and AcOEt) to give **26g**: 380 mg (91%); mp 155 °C (hexane−AcOEt); IR (KBr) 1568, 1644, 1699; ^{1}H NMR (300 MHz) 2.19 (s, 3 H), 2.93 (d, J = 6 Hz, 2 H), 3.02 (s, 3 H), 3.64 (s, 3 H), 4.49 (t, J = 6 Hz, 1 H), 5.77 and 5.82 (2 d, J = 16.5 Hz, 2 H), 6.86 (s, 1 H), 7.02 (s, 1 H), 7.03−7.30 (m, 8 H), 7.54 (s, 1 H), 7.75 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 24.6 (CH_3), 29.9 (CH), 41.3 (CH_3), 46.4 (CH_2), 47.9 (CH_2), 51.2 (CH_3), 107.1 (C), 110.7 (CH), 113.4 (CH), 116.3 (C), 120.6 (CH), 123.1 (CH), 125.8 (CH), 126.0 (C), 126.1 (CH), 126.3 (CH), 128.2 (CH), 135.0 (C), 138.5 (C), 139.4 (CH), 139.9 (C), 141.3 (CH), 166.7 (C), 192.5 (C), 194.7 (C). Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92; N, 6.33. Found: C, 73.22; H, 5.92; N, 6.32.

Catalytic Hydrogenation of Dihydropyridine 26a. A solution of **26a**[21] (0.2 g, 0.5 mmol) in MeOH (15 mL) was hydrogenated over PtO_2 (40 mg) for 12 or 24 h. The catalyst was filtered off, and the solution was evaporated to give a crude residue which was chromatographed (hexane−AcOEt, increasing polarity and 9:1 AcOEt−MeOH). The results are given in Table 1.

***trans*-3-Acetyl-5-(methoxycarbonyl)-1-methyl-4-[[(1-methyl-2-indolyl)carbonyl]methyl]-1,2,3,4-tetrahydropyridine (32a):** ^{1}H NMR (300 MHz) 2.20 (s, 3 H), 2.72 (dd, J = 15.6 and 11.0 Hz, 1 H), 2.89 (m, 1 H), 3.07 (s, 3 H), 3.22 (dd, J = 13.2 and 4.1 Hz, 1 H), 3.48 (ddd, J = 13.2, 2.4, and 1.7 Hz, 1 H), 3.58 (dd, J = 15.6 and 3.2 Hz, 1 H), 3.71 (s, 3 H), 3.82 (dm, J = 11.0 Hz, 1 H), 4.12 (s, 3 H), 7.20 (m, 1 H), 7.39 (s, 1 H), 7.42 (m, 2 H), 7.56 (s, 1 H), 7.65 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 27.1 (CH_3), 29.3 (CH), 32.2 (CH_3), 43.0 (CH_2), 43.1 (CH_3), 46.2 (CH_2), 47.4 (CH), 50.5 (CH_3), 93.1 (C), 110.2 (CH), 112.3 (CH), 120.7 (CH), 123.1 (CH), 125.8 (C), 126.0 (CH), 134.5 (C), 140.1 (C), 146.7 (CH), 168.0 (C), 193.1 (C), 207.3 (C).

***cis*-3-Acetyl-5-(methoxycarbonyl)-1-methyl-4-[[(1-methyl-2-indolyl)carbonyl]methyl]-1,2,3,4-tetrahydropyridine (33a):** IR (NaCl) 1622, 1666, 1704; ^{1}H NMR (300 MHz) 2.36 (s, 3 H), 2.90 (m, 4 H), 3.03 (s, 3 H), 3.42 (t, J = 12.1 Hz, 1 H), 3.53 (s, 3 H), 3.90 (m, 1 H), 4.02 (s, 3 H), 7.12 (m, 1 H), 7.21 (s, 1 H), 7.38 (m, 3 H), 7.68 (dm, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 28.9 (CH), 30.2 (CH_3), 32.1 (CH_3), 42.8 (CH_3), 43.6 (CH_2), 44.5 (CH_2), 48.5 (CH), 50.6 (CH_3), 97.8 (C), 110.2 (CH), 110.9 (CH), 120.4 (CH), 122.8 (CH), 125.7 (C), 125.6 (CH), 134.9 (C), 140.0 (C), 145.9 (CH), 167.8 (C), 192.0 (C), 209.2 (C). Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.47; H, 6.57; N, 7.61.

***cis*-3-(1-Hydroxyethyl)-5-(methoxycarbonyl)-1-methyl-4-[[(1-methyl-2-indolyl)carbonyl]methyl]-1,2,3,4-tetrahydropyridine (34a):** mp 58−60 °C (cyclohexane−Et_2O); IR (KBr) 1620, 1660, 3400; ^{1}H NMR (300 MHz, acetone-d_6) 1.29 (d, J = 6.1 Hz, 3 H), 1.82 (m, 1 H), 2.65 (dd, J = 14.5 and 4 Hz, 1 H), 3.08 (masked, 2 H), 3.09 (s, 3 H), 3.35 (dd, J = 14.5 and 5 Hz, 1 H), 3.40 (s, 3 H), 3.69 (m, 2 H), 4.07 (s, 3 H), 7.15 (m, 1 H), 7.34 (s, 1 H), 7.40 (m, 1 H), 7.55 (d, J = 7.5 Hz, 1 H), 7.65 (s, 1 H), 7.67 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) 22.6 (CH_3), 29.4 (CH), 32.3 (CH_3), 42.7 (CH_3), 44.6 (CH_2), 45.8 (CH), 47.0 (CH_2), 50.8 (CH_3), 66.6 (CH), 98.3 (C), 111.2 (CH), 112.1 (CH), 121.0 (CH), 123.5 (CH), 126.0 (CH), 126.9 (C), 136.2 (C), 141.0 (C), 146.7 (CH), 167.9 (C), 195.3 (C). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.92; H, 7.19; N, 7.46. In the presence of trace amounts of acid, tetrahydropyridine **34a** was rapidly converted into enol ether **36a**: ^{1}H NMR (300 MHz, acetone-d_6) 1.54 (d, J = 6.6 Hz, 3 H), 2.10 (m, 1 H), 3.07 (s, 3 H), 3.16 (m, 2 H), 3.42 (dd, J = 5.8 and 2 Hz, 1 H), 4.47 (qd, J = 6.6 and 2 Hz,

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1 H), 5.28 (m, 1 H), 6.49 (s, 1 H), 7.04 (t, J = 8 Hz, 1 H), 7.18 (t, J = 8 Hz, 1 H), 7.38 (d, J = 8 Hz, 1 H), 7.42 (s, 1 H), 7.53 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) 18.4, 25.6, 31.6, 34.5, 42.6, 48.5, 50.3, 73.1, 96.7, 102.3, 106.3, 110.2, 120.1, 121.1, 122.5, 128.2, 137.7, 139.0, 141.0, 147.0, 168.3.

***cis*-5-Acetyl-3-(methoxycarbonyl)-1-methyl-4-[[(1-methyl-2-indolyl)carbonyl]methyl]-1,2,3,4-tetrahydropyridine (35a):** IR (NaCl): 1647, 1733; ^{1}H NMR (300 MHz) 2.10 (s, 3 H), 2.89 (m, 3 H), 3.10 (s, 3 H), 3.25 (ddd, J = 13.5, 4.7 and 1.6 Hz, 1 H), 3.54 (t, J = 13.5 Hz, 1 H), 3.66 (s, 3 H), 4.02 (masked, 1 H), 4.02 (s, 3 H), 7.12 (m, 1 H), 7.24 (s, 1 H), 7.36 (m, 2 H), 7.47 (s, 1 H), 7.70 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 23.8 (CH_3), 29.2 (CH), 32.0 (CH_3), 40.9 (CH), 43.2 (CH_3), 43.7 (CH_2), 44.9 (CH_2), 51.8 (CH_3), 110.2 (CH), 111.1 (C), 111.5 (CH), 120.5 (CH), 122.9 (CH), 125.4 (CH), 125.9 (C), 135.0 (C), 139.9 (C), 147.6 (CH), 172.4 (C), 191.7 (C), 192.4 (C). Anal. Calcd for $C_{21}H_{24}N_2O_4 \cdot H_2O$: C, 65.27; H, 6.78; N, 7.25. Found: C, 66.54; H, 6.57; N, 7.29.

Catalytic Hydrogenation of Dihydropyridine 26g. A solution of dihydropyridine **26g** (0.44 g, 1 mmol) in MeOH (35 mL) or 1:1 MeOH−THF (50 mL) was hydrogenated over PtO_2 (90 mg) for 18 or 10 h. The catalyst was filtered off, the solution was evaporated, and the residue was purified as above. The results are given in Table 1.

***trans*-3-Acetyl-4-[[(1-benzyl-2-indolyl)carbonyl]methyl]-5-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (32g):** mp 58 °C (Et_2O); IR (KBr) 1624, 1650, 1668, 1710; ^{1}H NMR (300 MHz) 1.95 (s, 3 H), 2.38 (m, 1 H), 2.54 (dd, J = 14.6 and 11.3 Hz, 1 H), 3.00 (s, 3 H), 3.10 (dd, J = 13.2 and 4.1 Hz, 1 H), 3.30 (dm, J = 13.2 Hz, 1 H), 3.57 (dd, J = 14.6 and 3.3 Hz, 1 H), 3.68 (masked, 1 H), 3.69 (s, 3 H), 5.80 (d, J = 16 Hz, 1 H), 5.92 (d, J = 16 Hz, 1 H), 7.00−7.40 (m, 9 H), 7.68 (s, 1 H), 7.78 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 26.8 (CH_3), 29.9 (CH), 42.8 (CH_2), 43.0 (CH_3), 46.4 (CH_2), 46.8 (CH), 47.9 (CH_2), 50.4 (CH_3), 93.0 (C), 110.6 (CH), 113.6 (CH), 120.9 (CH), 123.3 (CH), 125.9 (CH), 126.1 (C), 133.9 (C), 140.1 (C), 146.6 (CH), 167.9 (C), 192.9 (C), 206.9 (C). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30. Found: C, 72.88; H, 6.33; N, 6.33.

***cis*-3-Acetyl-4-[[(1-benzyl-2-indolyl)carbonyl]methyl]-5-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (33g):** IR (KBr) 1620, 1665, 1703; ^{1}H NMR (300 MHz) 2.20 (s, 3 H), 2.90 (m, 4 H), 3.00 (s, 3 H), 3.39 (t, J = 12.6 Hz, 1 H), 3.52 (s, 3 H), 3.93 (m, 1 H), 5.74 (d, J = 16.2 Hz, 1 H), 5.85 (d, J = 16.2 Hz, 1 H), 7.05−7.30 (m, 8 H), 7.32 and 7.37 (2 s, 2 H), 7.69 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 28.4 (CH), 30.0 (CH_3), 42.7 (CH_3), 43.4 (CH_2), 44.5 (CH_2), 48.2 (CH_2), 48.3 (CH), 50.5 (CH_3), 97.7 (C), 110.8 (CH), 111.9 (CH), 120.8 (CH), 122.9 (CH), 125.9 (CH), 126.1 (C), 134.3 (C), 139.8 (C), 145.9 (CH), 167.8 (C), 191.4 (C), 209.2 (C); HRMS calcd for $C_{27}H_{28}N_2O_4$ 444.2049, found 444.2040.

***cis*-4-[[(1-Benzyl-2-indolyl)carbonyl]methyl]-3-(1-hydroxyethyl)-5-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (34g)** was unstable and was immediately used in the next reaction without further manipulation.

***cis*-5-Acetyl-4-[[(1-benzyl-2-indolyl)carbonyl]methyl]-3-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (35g):** mp 108 °C (Et_2O−acetone); IR 1578, 1670, 1736; ^{1}H NMR (300 MHz) 2.09 (s, 3 H), 2.90 (m, 3 H), 3.06 (s, 3 H), 3.19 (ddd, J = 13.4, 4.6 and 1.6 Hz, 1 H), 3.45 (s, 3 H), 3.46 (t, J = 13.4 Hz, 1 H), 4.03 (m, 1 H), 5.69 (d, J = 16.2 Hz, 1 H), 5.89 (d, J = 16.2 Hz, 1 H), 7.05−7.30 (m, 8 H), 7.22 (s, 1 H), 7.57 (s, 1 H), 7.73 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 23.8 (CH_3), 28.7 (CH), 40.8 (CH), 43.1 (CH_3), 43.4 (CH_2), 44.9 (CH_2), 48.2 (CH_2), 51.6 (CH_3), 110.8 (CH), 111.0 (C), 112.4 (CH), 120.7 (CH), 123.1 (CH), 125.8 (CH), 126.1 (C), 134.4 (C), 139.9 (C), 147.4 (CH), 172.4 (C), 191.8 (C), 191.9 (C). Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 72.95; H, 6.35; N, 6.30. Found: C, 72.86; H, 6.38; N, 6.29.

***cis*-3-(1-Hydroxyethyl)-4-[2-hydroxy-2-(1-methyl-2-indolyl)ethyl]-5-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (37a).** A 1 M solution of $LiBEt_3H$ in THF (Super-Hydride, 0.7 mL, 0.7 mmol) was added to a solution of tetrahydropyridine **34a** (61 mg, 0.17 mmol) in THF (4 mL) at −70 °C, and the mixture was stirred at −70 °C for 45 min. The reaction mixture was poured into H_2O and extracted with Et_2O. Evaporation of the organic extracts followed by flash chromatography (AcOEt) of the residue gave diol **37a**: 46 mg (75%); mp 155 °C (CH_2Cl_2); IR (KBr) 1609, 1646, 3380; ^{1}H NMR (300 MHz) 1.26 (d, J = 6 Hz, 3 H), 1.82 (m, 2 H), 2.13 (m, 1 H), 2.55 (m, 2 H), 2.90 (m, 2 H), 3.20 (m, 1 H), 3.62 (s, 3 H), 3.70 (m, 1 H), 3.81 (s, 3 H), 5.10 (dd, J = 9.9 and 4 Hz, 1 H), 6.44 (s, 1 H), 7.05 (t, J = 8 Hz, 1 H), 7.17 (t, J = 8 Hz, 1 H), 7.29 (d, J = 8 Hz, 1 H), 7.36 (s, 1 H), 7.53 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 22.3 (CH_3), 27.1 (CH), 29.8 (CH_3), 39.4 (CH_2), 42.8 (CH_3), 44.9 (CH), 46.6 (CH_2), 50.7 (CH_3), 65.4 (CH), 66.3 (CH), 98.1 (CH), 98.7 (C), 108.8 (CH), 118.9 (CH), 120.4 (CH), 121.1 (CH), 127.1 (C), 137.7 (C), 142.4 (C), 146.5 (CH), 169.6 (C). Anal. Calcd for $C_{21}H_{28}N_2O_4 \cdot {}^1/_2H_2O$: C, 66.12; H, 7.66; N, 7.34. Found: C, 65.81; H, 7.37; N, 7.17.

***cis*-4-[2-(1-Benzyl-2-indolyl)-2-hydroxyethyl]-3-(1-hydroxyethyl)-5-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (37g).** Operating as above, from tetrahydropyridine **34g** (180 mg, 0,4 mmol) was obtained a residue which was chromatographed (flash, 3:7 hexane−AcOEt) to give diol **37g** as a foam: 150 mg (83%); IR (KBr) 1600, 1658, 3300; ^{1}H NMR (300 MHz) 1.07 (d, J = 6 Hz, 3 H), 1.70 (m, 4 H), 1.90 (m, 1 H), 2.78 (m, 2 H), 2.94 (s, 3 H), 3.08 (m, 1 H), 3.24 (m, 1 H), 5.00 (dd, J = 10.2 and 2.5 Hz, 1 H), 5.54 (s, 2 H), 6.53 (s, 1 H), 6.98−7.30 (m, 9 H), 7.58 (dm, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 22.6 (CH_3), 27.6 (CH), 41.0 (CH_2), 42.8 (CH_3), 44.5 (CH), 46.3 (CH_2), 46.6 (CH_2), 50.8 (CH_3), 65.8 (CH), 66.1 (CH), 98.8 (CH), 99.5 (C), 109.5 (CH), 119.4 (CH), 120.6 (CH), 121.5 (CH), 127.6 (C), 138.8 (C), 143.1 (C), 145.8 (CH), 169.4 (C); HRMS calcd for $C_{27}H_{32}N_2O_4$ 448.2362, found 448.2353.

***cis*-3-Acetyl-4-[[(2-indolyl)carbonyl]methyl]-5-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (33b).** Anhydrous $AlCl_3$ (180 mg, 1.35 mmol) was added to a solution of tetrahydropyridine **33g** (100 mg, 0.22 mmol) in anhydrous C_6H_6 (3 mL), and the resulting mixture was stirred at rt for 1 h. Additional anhydrous $AlCl_3$ (120 mg, 0.9 mmol) was then added, and stirring was continued for 2 h. The mixture was poured into H_2O, basified with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic extracts were dried and evaporated, and the residue was chromatographed (flash, hexane−AcOEt, increasing polarity) to give tetrahydropyridine **33b** as a foam: 60 mg (75%); IR (KBr) 1595, 1658, 1715; ^{1}H NMR (300 MHz) 2.34 (s, 3 H), 2.89 (m, 4 H), 3.04 (s, 3 H), 3.43 (t, J = 12.6 Hz, 1 H), 3.54 (s, 3 H), 3.95 (m, 1 H), 7.12−7.45 (m, 5 H), 7.67 (d, J = 8 Hz, 1 H), 7.40 (s, 1 H); ^{13}C NMR (75 MHz) 28.9 (CH), 30.0 (CH_3), 42.1 (CH_2), 42.8 (CH_3), 44.4 (CH_2), 48.5 (CH), 50.6 (CH_3), 97.6 (C), 109.0 (C), 112.1 (C), 120.6 (CH), 122.9 (CH), 125.9 (CH), 127.4 (C), 135.1 (C), 137.3 (C), 146.0 (CH), 167.8 (C), 199.9 (C), 209.0 (C); HRMS calcd for $C_{20}H_{22}N_2O_4$ 354.1579, found 354.1577.

***cis*-3-(1-Hydroxyethyl)-4-[2-hydroxy-2-(2-indolyl)ethyl]-5-(methoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyridine (37b).** Operating as in the preparation of diols **37a** and **37g**, from tetrahydropyridine **33b** (180 mg, 0.51 mmol) and $LiBEt_3H$ 1 M in THF (3.3 mL, 3.3 mmol) was obtained diol **37b** after flash chromatography (Et_2O−DEA, increasing polarity): 30 mg (72%); mp 88−90 °C (Et_2O); IR (KBr) 1614, 3290; ^{1}H NMR (300 MHz) 1.21 (d, J = 6.1 Hz, 3 H), 1.71 (m, 4 H), 2.03 (m, 1 H), 2.90 (m, 2 H), 2.98 (s, 3 H), 3.09 (m, 1 H), 3.65 (s, 3 H), 3.73 (m, 1 H), 5.13 (dd, J = 7.7 and 6.2 Hz, 1 H), 6.33 (d, J = 1 Hz, 1 H), 7.00−7.35 (m, 3 H), 7.32 (s, 1 H), 7.52 (d, J = 8 Hz, 1 H), 9.40 (s, 1 H); ^{13}C NMR (75 MHz) 22.4 (CH_3), 26.7 (CH), 41.7 (CH_2), 42.9 (CH_3), 44.6 (CH), 46.7 (CH_2), 50.8 (CH_3), 66.4 (CH), 67.4 (CH), 96.9 (CH), 98.7 (C), 111.0 (CH), 119.3 (CH), 120.0 (CH), 121.0 (CH), 128.4 (C), 135.4 (C), 143.1 (C), 146.5 (CH), 169.7 (C). Anal. Calcd for $C_{20}H_{26}N_2O_4 \cdot {}^1/_2C_4H_{10}O$: C, 66.81; H, 7.90; N, 7.08; C, 66.49; H, 7.63; N, 6.91.

(4*RS*,4a*SR*,12a*RS*)-7-Benzyl-6-hydroxy-4-(1-hydroxyethyl)-12a-(methoxycarbonyl)-2-methyl-2,3,4,4a,5,6,12,12a-octahydro-1*H*-pyrido[3′,4′:4,5]cyclohepta[1,2-*b*]indole (38g). A. *N*,*N*-Dimethylmethyleneiminium iodide (Eschenmoser's salt, 70 mg, 0.38 mmol) was added to a solution of diol **37g** (75 mg, 0,17 mmol) in CH_2Cl_2, and the mixture was stirred at rt for 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried and evaporated to give crude **II** (R = Bn) as a foam.

B. MeI (26 μL, 0.42 mmol) was added to a solution of the above residue in DMSO (2 mL), and the mixture was stirred at rt for 30 min and at 70 °C for 4 h. After the mixture was cooled at rt, a solution of $NaCNBH_3$ (37 mg, 0.5 mmol) in MeOH (3 mL) was added, and stirring was continued for 45 min. The solvent was evaporated, and the residue was partitioned between H_2O and Et_2O. The organic extracts were dried and evaporated, and the resulting residue was chromatographed (flash, 97:3 Et_2O−DEA) to give tetracycle **38g** as a foam: 31 mg (40%); IR (KBr) 1733 (CO), 3300; ^{1}H NMR (300 MHz) 1.21 (d, J = 6 Hz, 3 H), 1.55 (t, J = 11 Hz, 1 H), 1.80−2.20 (m, 3 H), 1.95 (d, J = 11.5 Hz, 1 H), 2.29 (s, 3 H), 2.54 (dd, J = 11 and 3 Hz, 1 H), 2.72 (d, J = 16 Hz, 1 H), 3.11 (m, 1 H), 3.24 (d, J = 16 Hz, 1 H), 3.38 (d, J = 11.5 Hz, 1 H), 3.63 (s, 3 H), 3.66 (m, 1 H), 5.02 (t, 1 H), 5.45 (d, J = 16.7 Hz, 1 H), 5.75 (d, J = 16.7 Hz, 1 H), 6.95−7.25 (m, 8 H), 7.40 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 22.2 (CH_3), 27.3 (CH_2), 30.4 (CH), 30.5 (CH_2), 45.3 (CH_3), 46.5 (CH), 47.5 (CH_2), 51.4 (C), 52.4 (CH_3), 54.6 (CH_2), 60.8 (CH_2), 66.7 (CH), 67.3 (CH), 106.0 (C), 109.5 (CH), 117.8 (CH), 121.6 (2 CH), 126.2 (CH), 126.9 (CH), 128.5 (CH), 127.7 (C), 137.0 (C), 137.2 (C), 138.7 (C), 176.0 (C); HRMS calcd for $C_{28}H_{34}N_2O_4$ 462.2518, found 462.2532.

(±)-19-Hydroxy-20-epiervatamine (39). Diol **37b** (0.12 g, 0.34 mmol) was allowed to react with *N*,*N*-dimethylmethyleneiminium iodide (0.15 g, 0.83 mmol) and then with MeI (42 μL, 0.67 mmol) and $NaCNBH_3$ (74 mg, 1 mmol) as described above. Crude **38b** was dissolved in $CHCl_3$ (6 mL) and treated with MnO_2 (0.22 g, 2.5 mmol) at rt for 1 h 30 min. The resulting mixture was filtered over Celite and evaporated. Column chromatography (95:5 AcOEt−MeOH) of the residue gave tetracycle **39** as a foam: 30 mg (25%); IR (KBr) 1637, 1718, 3395; ^{1}H NMR (500 MHz, assignments aided by ^{1}H−^{1}H COSY and HMQC) 1.26 (d, J = 6 Hz, 3 H, 18-H), 1.67 (t, J = 11.5 Hz, 1 H, 21-H_{ax}), 1.75 (br s, 1 H, OH), 1.91 (m, 1 H, 20-H), 2.08 (d, J = 12 Hz, 1 H, 5-H), 2.33 (s, 3 H, NMe), 2.52 (dd, J = 15.5 and 10 Hz, 1 H, 14-H), 2.62 (dd, J = 11.5 and 3 Hz, 1 H, 21-H_{eq}), 2.79 (d, J = 15.5 Hz, 1 H, 14-H), 2.80 (d, J = 15.5 Hz, 1 H, 6-H), 3.01 (dd, J = 10 and 4 Hz, 1 H, 15-H), 3.46 (d, J = 12 Hz, 1 H, 5-H), 3.47 (d, J = 15.5 Hz, 1 H, 6-H), 3.65 (s, 3 H, OMe), 3.83 (m, 1 H, 19-H), 7.10 (t, J = 8 Hz, 1 H, 10-H), 7.15−7.30 (m, 2 H, 11-H and 12-H), 7.49 (d, J = 8 Hz, 1 H, 9-H), 9.10 (s, 1 H, NH); ^{13}C NMR (75 MHz, assignments aided by HMQC) 22.5 (C-18), 31.7 (C-6), 33.8 (C-15), 37.3 (C-14), 45.3 (NMe), 46.4 (C-20), 49.1 (C-16), 52.6 (OMe), 54.6 (C-21), 60.2 (C-5), 66.4 (C-19), 112.4 (C-12), 119.2 (C-7), 119.6 (C-9), 120.4 (C-10), 125.9 (C-11), 127.0 (C-8), 132.7 (C-2), 136.6 (C-13), 175.8 (CO), 194.3 (C-3); HRMS calcd for $C_{21}H_{26}N_2O_4$ 370.1893, found 370.1880.

(±)-19,20-Didehydroervatamine (41). A. MsCl (19 μL, 0.24 mmol) and Et_3N (56 μL, 0.40 mmol) were added at 0 °C to a solution of **39** (30 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (2 mL), and the resulting solution was stirred at 0 °C for 1 h. The solution was washed with aqueous $NaHCO_3$, dried, and evaporated to give a crude mesylate.

B. DBU (72 μL, 0.49 mmol) was added to a solution of the above mesylate in DMSO (2 mL) and toluene (2 mL), and the mixture was heated at 80 °C for 3 h. Then, additional DBU (36 μL, 0.24 mmol) was added, and the mixture was heated at 100 °C for 1 h. The mixture was poured into H_2O and extracted with AcOEt. The organic extracts were washed with H_2O, dried, and evaporated. Flash chromatography of the residue (hexane−AcOEt, increasing polarity) gave **41** as a foam: 20 mg (70%); IR (KBr) 1631, 1729, 3313; ^{1}H NMR (300 MHz) 1.58 (dd, J = 6.78 and 1.86 Hz, 3 H), 2.24 (d, J = 11.8 Hz, 1 H), 2.30 (s, 3 H), 2.44 (d, J = 15.9 Hz, 1 H), 2.58 (br d, J = 12.1 Hz, 1 H), 2.88 (d, J = 15.4 Hz, 1 H), 3.08 (dd, J = 15.9 and 11 Hz, 1 H), 3.10 (br d, J = 12.1 Hz, 1 H), 3.44 (br d, J = 11.8 Hz, 1 H), 3.52 (d, J = 11 Hz, 1 H), 3.59 (s, 3 H), 3.62 (d, J = 15.4 Hz, 1 H), 5.42 (qd, J = 6.78 and 1.4 Hz, 1 H), 7.12 (t, J = 8 Hz, 1 H), 7.40 (m, 2 H), 7.58 (d, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz) 12.5 (CH_3), 31.1 (CH_2), 34.1 (CH), 44.0 (CH_2), 45.9 (CH_3), 49.1 (C), 52.4 (CH_3), 61.2 (CH_2), 61.8 (CH_2), 112.3 (CH), 119.7 (C), 120.3 (CH), 120.7 (CH), 121.4 (CH), 126.6 (CH), 127.3 (C), 132.6 (C), 136.1 (C), 136.7 (C), 175.2 (C), 193.5 (C); HRMS calcd for $C_{21}H_{24}N_2O_3$ 352.1787, found 352.1772.

(±)-20-Epiervatamine (42). A. Alcohol **39** (20 mg, 0.054 mmol) was converted into the corresponding mesylate operating as above. LiCl (0.04 g, 0.94 mmol) was added to a solution of this mesylate in acetone (1 mL), and the mixture was refluxed for 1 h. The solvent was evaporated, and the resulting residue was partitioned between H_2O and CH_2Cl_2. Evaporation of the organic extracts followed by flash chromatography (AcOEt) gave chloride **40** as a foam: 15 mg (71%); ^{1}H NMR (300 MHz) 1.42 (d, J = 6 Hz, 3 H), 1.67 (t, J = 11.5 Hz, 1 H), 2.08 (d, J = 12 Hz, 1 H), 2.10 (m, 1 H), 2.27 (s, 3 H), 2.36 (d, J = 15 Hz, 1 H), 2.51 (dd, J = 15 and 10 Hz, 1 H), 2.65 (dd, J = 11.5 and 3 Hz, 1 H), 2.78 (d, J = 15.5 Hz, 1 H), 3.11 (dm, J = 10 Hz, 1 H), 3.40 (d, J = 12 Hz, 1 H), 3.48 (d, J = 15.5 Hz, 1 H), 3.59 (s, 3 H), 3.93 (m, 1 H), 7.10 (t, J = 8 Hz, 1 H), 7.15−7.32 (m, 2 H), 7.49 (d, J = 8 Hz, 1 H), 8.88 (s, 1 H); MS m/z (rel intensity) 390 (M + 2, 20), 388 (M^+, 60), 353 (M − 35, 15), 352 (M − 36, 15), 329 (M − 59, 30).

B. A solution of chloride **40** (15 mg, 0.039 mmol), *n*-Bu_3SnH (31 μL, 0.12 mmol), and AIBN (3 mg, 0.02 mmol) in benzene (15 mL) was refluxed for 1 h. The resulting mixture was poured into H_2O and extracted with Et_2O. The organic extracts were dried and evaporated, and the residue was chromatographed (flash, 98:2 AcOEt−MeOH) to give **42** as a foam: 10 mg (73%); IR (KBr) 1625, 1725, 3300; ^{1}H NMR (300 MHz) 0.87 (t, J = 7.5 Hz, 3 H), 1.36 (m, 2 H), 1.59 (t, J = 11.5 Hz, 1 H), 1.85 (m, 1 H), 2.08 (d, J = 11.8 Hz, 1 H), 2.32 (s, 3 H), 2.53 (m, 2 H), 2.62 (d, J = 15.9 Hz, 1 H), 2.65 (br d, J = 11.5 Hz, 1 H), 2.80 (d, J = 15.6 Hz, 1 H), 3.47 (br d, J = 11.8 Hz, 1 H), 3.49 (d, J = 15.6 Hz, 1 H), 3.63 (s, 3 H), 7.13 (t, J = 8 Hz, 1 H), 7.36 (m, 2 H), 7.55 (d, J = 8 Hz, 1 H), 8.95 (s, 1 H); ^{13}C NMR (75 MHz) 11.4 (CH_3), 23.9 (CH_2), 31.8 (CH_2), 36.2 (CH), 36.6 (CH_2), 39.0 (CH), 46.3 (CH_3), 49.3 (C), 52.5 (CH_3), 57.5 (CH_2), 60.7 (CH_2), 112.3 (CH), 119.5 (C), 120.1 (CH), 120.6 (CH), 126.5 (CH), 127.4 (C), 132.7 (C), 136.6 (C), 175.5 (C), 194.1 (C); HRMS calcd for $C_{21}H_{26}N_2O_3$ 354.1943, found 354.1943.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **16c**, **17a**, **17b**, **33b**, **37g**, **38g**, **39**, **41**, and **42** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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