stirred at room temperature for 20.5 h and then diluted with CH_2Cl_2. The solid was filtered off through Celite and the filtrate was condensed to give a crude product. Flash column chromatography (elution with 20% EtOAc in CH_2Cl_2) afforded 170 mg (83%) of **31** as a colorless oil: $[\alpha]^{25}_D$ -58.0° (*c* 1.21, $CHCl_3$) [lit.[21a] $[\alpha]^{25}_D$ -56.9° (*c* 1.13, $CHCl_3$)]; IR ($CHCl_3$) 1720, 1180, and 1020 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.26 (3 H, t, *J* = 7.0 Hz), 1.27 (3 H, t, *J* = 7.0 Hz), 1.44-2.70 (8 H, m), 2.88-3.32 (1 H, m), 3.26 and 3.53 (2 H, ABq, *J* = 17.1 Hz), 4.13 (2 H, q, *J* = 7.0 Hz), 4.18 (2 H, q, *J* = 7.0 Hz); MS, *m/z* 243 (M^+), 170, 156, 128; HRMS calcd for $C_{12}H_{21}NO_4$ MW 243.1489, found *m/z* 243.1495 (M^+). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.36; H, 8.65; N, 5.94.

Methyl (*R*)-6-oxo-2-piperidineacetate (36a): A mixture of **14** (151 mg, 0.50 mmol) and K_2CO_3 (35 mg, 0.25 mmol) in absolute MeOH (4 mL) was stirred at room temperature for 30 min (the original yellow color of the solution disappared). The solid was filtered off through Celite, and the filtrate was condensed in vacuo to give a residue. Preparative TLC (elution with 33% acetone in $CHCl_3$) of the residue yielded 75 mg (88%) of **36a** as colorless prisms: mp 87-88 °C (recrystallized from Et_2O); $[\alpha]^{21}_D$ -14.1° (*c* 0.41, EtOH); IR ($CHCl_3$) 3375, 1725, 1653, and 1078 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.20-2.10 (4 H, m), 2.20-2.58 (4 H, m), 3.71 (3 H, s), 3.60-4.00 (1 H, m), 6.32 (1 H, br s); MS, *m/z* 171 (M^+), 143, 115, 98 (100), 55. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.22; H, 7.71; N, 8.26.

(*R*)-6-Oxo-2-piperidineacetic acid (36b): A solution of **36a** (34.5 mg, 0.202 mmol) in MeOH (0.5 mL) and 2% aqueous NaOH (0.5 mL) was stirred at room temperature for 5 h. The reaction mixture was acidified with 5% HCl, and the solvent was completely removed. Extraction of the residue with $CHCl_3$, washing with brine, and the usual workup gave 20 mg (63%) of **36b** as colorless needles: mp 131.5-133.5 °C (recrystallized from $CHCl_3$-EtOAc); $[\alpha]^{25}_D$ -19.7° (*c* 0.38, EtOH) [lit.[24] (*S*)-form (≤64% ee) mp 132-134 °C; $[\alpha]^{24}_D$ +11.3° (*c* 1, EtOH)]; IR ($CHCl_3$) 3280, 2450 (br), 1930 (br), 1705 (br), and 1620 (br) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.14-2.20 (4 H, m), 2.20-2.76 (4 H, m), 3.80-4.16 (1 H, m), 7.20-8.10 (1 H, br s), 8.26 (1 H, br s); MS, *m/z* 157 (M^+), 139, 129, 101, 98, 70, 55 (100).

Acknowledgment. We are grateful to Professor M. Benn, The University of Calgary, for sending us an authentic sample of the chiral diester **31** and to Professor M. Ikeda, Kyoto Pharmaceutical University, for providing us with the spectral data of (-)-trachelanthamidine (**17a**). We also thank Dr. S. Aoyagi, Tokyo College of Pharmacy, for his technical assistance in the preparation of some pyrrolidinone derivatives.

Registry No. 1, 76186-04-4; **2**, 110199-16-1; **3a**, 101979-45-7; **3b**, 124201-69-0; **3c**, 111975-21-4; **3d**, 111975-22-5; **3e**, 121929-87-1; **3f**, 121929-88-2; **3g**, 124201-70-3; (±)-**5** *n* = 1, 111975-27-0; (±)-**5** *n* = 2, 111975-28-1; **6**, 121929-83-7; **7**, 124201-72-5; **8**, 111975-23-6; **9**, 111975-24-7; **10**, 111975-25-8; **11**, 111975-26-9; **12**, 121929-84-8; **13**, 121929-85-9; **14**, 124201-73-6; **15**, 112065-91-5; **17a**, 526-64-7; **17b**, 111975-29-2; **17c**, 111975-30-5; **17d**, 112065-89-1; **18a**, 62912-97-4; **18b**, 111975-35-0; **18c**, 111975-36-1; **18d**, 112065-90-4; **19a**, 111975-31-6; **19b**, 111975-32-7; **19d**, 111975-34-9; **20a**, 111975-37-2; **20b**, 111975-38-3; **20d**, 111975-40-7; **21**, 486-71-5; **22**, 71657-68-6; **23**, 111975-41-8; **24**, 124201-74-7; **25a**, 67036-44-6; **25b**, 124201-75-8; **26**, 61884-75-1; **28**, 61884-76-2; **29**, 124201-76-9; **31**, 83455-90-7; **36a**, 67036-45-7; **36b**, 65084-15-3; (±)-6-ethoxy-2-piperidinone, 124201-71-4; 3,4-dihydro-2-pyridone, 57147-25-8.

General Method for the Synthesis of Bridged Indole Alkaloids. Nucleophilic Addition of Indoleacetic Ester Enolates to *N*-Alkylpyridinium Salts

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A short route to tetracyclic ring substructures of C-mavacurine, *Strychnos*, and akuammiline-type alkaloids, based on the addition of methyl 1-, 2-, or 3-indoleacetate anions to *N*-alkylpyridinium salts followed by acid cyclization of the resultant 1,4-dihydropyridines, is reported. Further stereoselective elaboration of the C-20 (*E*)-ethylidene substituent results in the synthesis of the indole alkaloid vinoxine (**7b**) and of 4-ethylidenehexahydro-1,5-methanoazocino[4,3-*b*]- and -[3,4-*b*]indoles **14-17**, **32**, and **35**. Some mechanistic aspects concerning the regiochemistry of the nucleophilic addition to the pyridinium ring are discussed.

The development of general methods for the synthesis of indole alkaloids has been a longtime goal for organic synthesis chemists.[1] The main group of indole alkaloids biogenetically derives from tryptophan and secologanin,[2] geissoschizine being a key early intermediate: oxidative cyclization between C-16[3] and the indole 3-position (C-7) gives formylstrictamine, from which the alkaloids of the akuammiline group are formed; similarly, oxidative ring closure between C-16 and the indole nitrogen affords the alkaloids of the C-mavacurine group. The hydrolytic cleavage of the tryptamine bridge would explain the formation of the tetracyclic alkaloid vinoxine. A skeletal rearrangement (cleavage of C-7/C-16 and C-2/C-3 bonds and formation of C-3/C-7 and C-2/C-16 bonds) interconnects formylstrictamine with *Strychnos* alkaloids (Scheme I).

Despite their apparent skeletal dissimilarity, the indole alkaloids of the C-mavacurine, *Strychnos*, and akuammiline groups have some common structural features due to their common biogenetic origin: (i) an oxidized one-carbon substituent at C-16 (lost in some cases), (ii) a two-carbon chain, usually an *E*-configurated ethylidene, at C-20, (iii) a tryptamine C-5/C-6 unit connecting the indole 3-position and the piperidine nitrogen, (iv) a bond linking indole and piperidine rings, the latter by an α-carbon, and (v) a cis-2,4-disubstituted piperidine ring in-

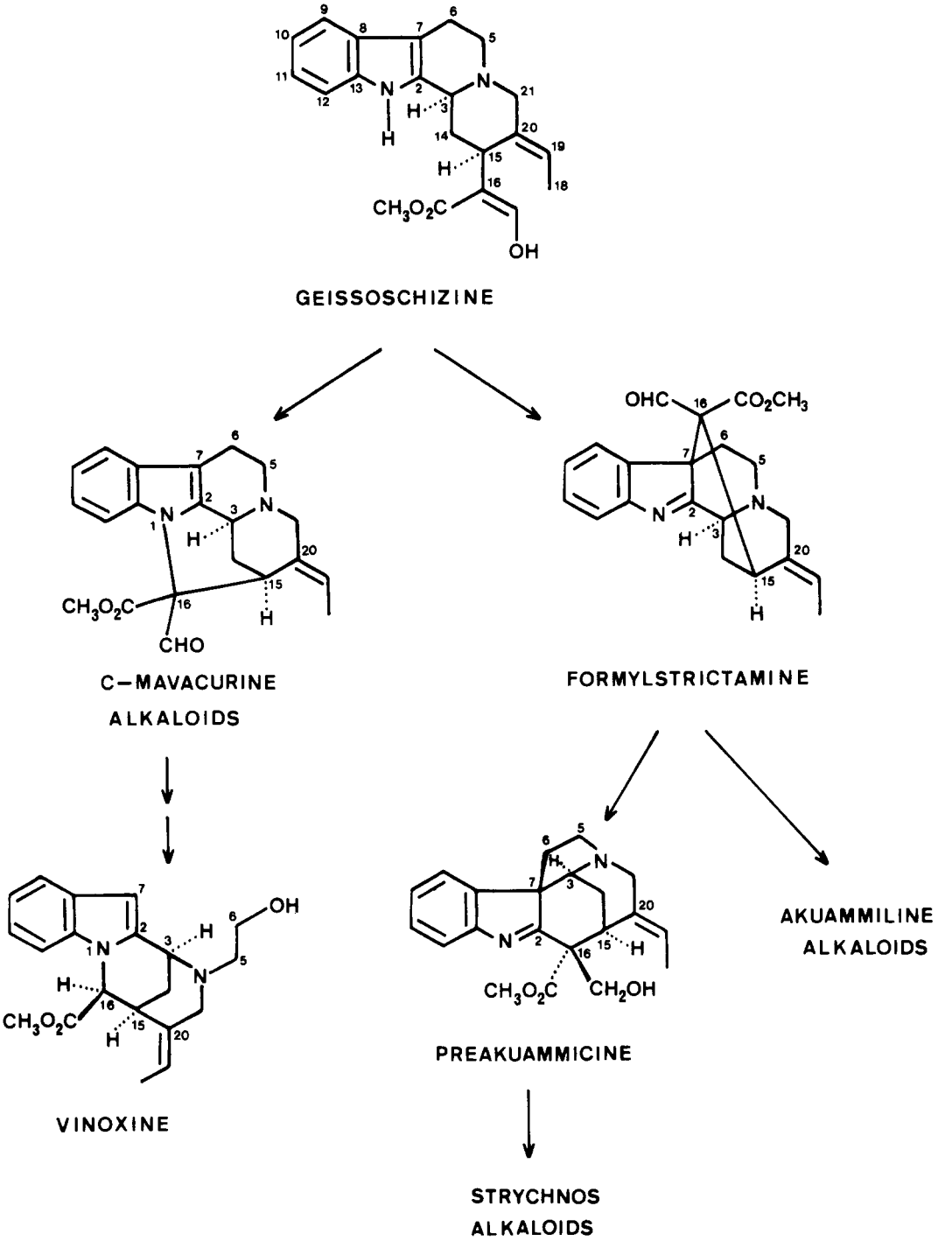
(1) (a) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. (b) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (d) Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021. (e) Kuehne, M. E.; Zebovitz, T. C. *J. Org. Chem.* **1987**, *52*, 4331, and previous papers in this series.

(2) (a) Bisset, N. G. In *Indoles and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 3. (b) Herbert, R. B. In *The Chemistry of Heterocyclic Compounds. Indoles Part 4, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter 1. (c) Atta-ur-Rahman; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, 1983.

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

0022-3263/90/1955-1156$02.50/0

Scheme I



cluded in a bridged polycyclic system.

Because of these structural similarities, we considered the possibility of designing the synthesis of the three above-mentioned groups of alkaloids through a common synthetic strategy in which the key bonds were C-15/C-16, C-2 (or -7)/C-3, and C-6/C-7. The formation of these bonds was envisaged as follows: first, nucleophilic addition of the enolate derived from an indoleacetic ester to the γ-position of a pyridinium salt; second, nucleophilic attack of the indole ring to the α-position of the resulting partially reduced pyridine; third, closure of the tryptamine chain by cyclization of the electrophilic β-carbon of the pyridine nitrogen substituent upon the indole 3-position (Scheme II). Since the formation of the C-6/C-7 bond in the last synthetic steps from appropriately N-substituted tetracyclic systems (third phase of our strategy) is a process that has already been accomplished in the field of the synthesis of *Strychnos*,[4] *Aspidosperma*,[5] *Iboga*,[6] and *Corynanthe*[7] alkaloids, we decided to explore the first two phases, in

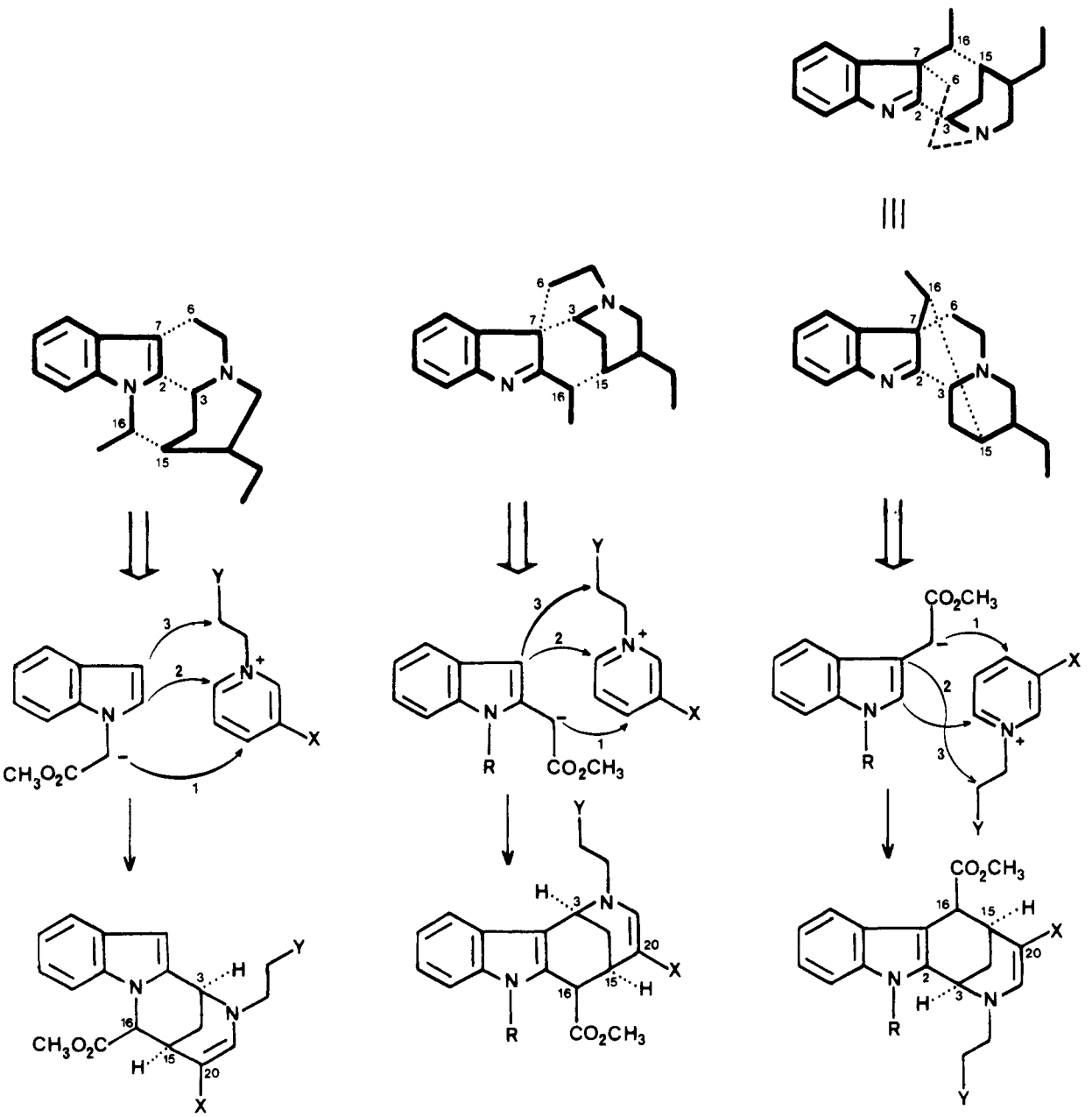
(4) (a) Bosch, J.; Amat, M. *Tetrahedron Lett.* **1985**, *26*, 4951. (b) Amat, M.; Linares, A.; Salas, M.-L.; Alvarez, M.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1988**, 420.

(5) (a) Husson, H.-P.; Thal, C.; Potier, P.; Wenkert, E. *J. Chem. Soc., Chem. Commun.* **1970**, 480. (b) Ziegler, Z. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (c) Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, *17*, 111. (d) Magnus, P.; Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212, and references therein. (e) Wenkert, E.; Hudlický, T. *J. Org. Chem.* **1988**, *53*, 1953.

(6) (a) Rosenmund, P.; Haase, W. H.; Bauer, J.; Frische, R. *Chem. Ber.* **1975**, *108*, 1871. (b) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3882. (c) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52*, 3151.

(7) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591.

Scheme II



which the reactivity of the pyridinium ring plays an essential role.[8]

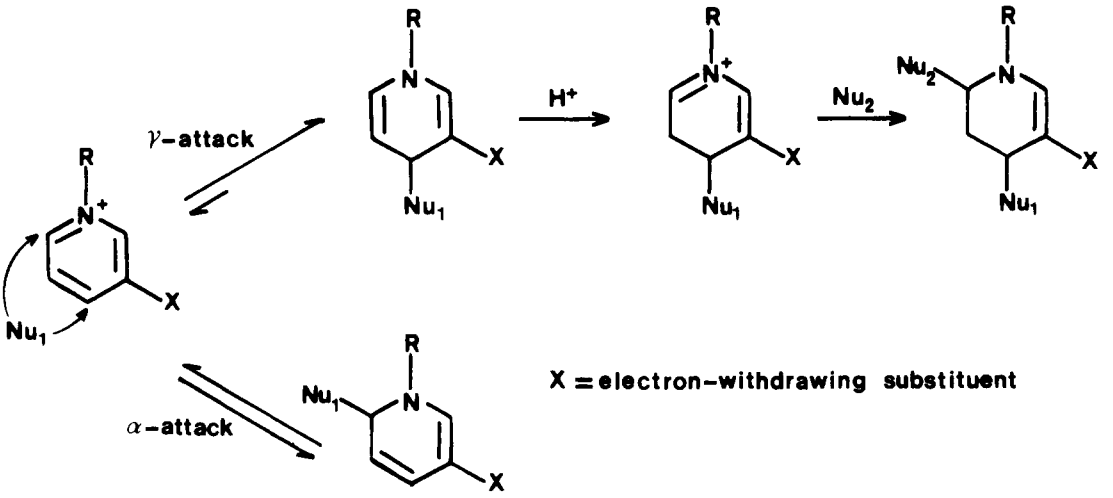
Thus, it is well-known that *N*-alkylpyridinium salts can undergo the addition of nucleophiles at the α- and γ-positions to give 1,2- and 1,4-dihydropyridines, respectively. Under kinetic control conditions the regioselectivity of this kind of addition depends on the hardness of the nucleophile: hard nucleophiles preferentially attack at C-2, whereas soft ones react at C-4. On the other hand, under thermodynamic control, when the nucleophile is sufficiently stable, rapid addition and elimination can lead to an equilibrium in which ultimately the thermodynamically more stable 1,4-dihydropyridine becomes the major product. The presence of an electron-withdrawing substituent at the pyridine β-position exerts three important effects: (i) it causes a stabilizing effect upon the dihydropyridine system, (ii) it increases the electrophilicity of the pyridinium salt, and (iii) it allows the regioselective protonation of the 1,4-dihydropyridine to give, after acidic treatment, a dihydropyridinium cation that can undergo the α-attack of a second nucleophile, affording a 2,4-disubstituted tetrahydropyridine (Scheme III).[9]

The intramolecular version of this simple three-step sequence—nucleophilic γ-attack, protonation, and second nucleophilic attack (cyclization)—using the enolate of an indoleacetic ester as a bis-1,3-nucleophile having two

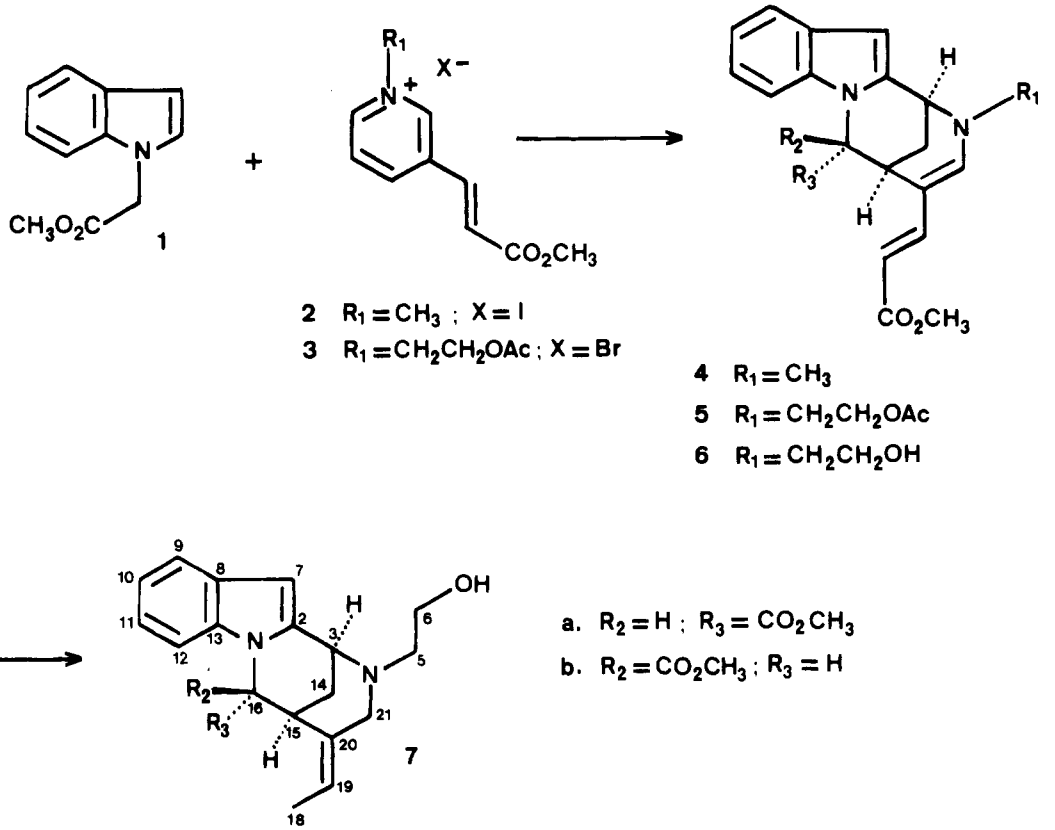
(8) For a review of the application to alkaloid synthesis of the addition of stabilized carbon nucleophiles to *N*-alkylpyridinium salts, see: Bennasar, M.-L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, *27*, 789. For more recent work, see: (a) Spitzner, D.; Zaubitzer, T.; Shi, Y.-J.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 2274. (b) Bieräugel, H.; Brands, K. M. J.; Pandit, U. K. *Heterocycles* **1988**, *27*, 1589.

(9) This reactivity pattern was first used by Wenkert for the construction of the fused indoloquinolizidine moiety common to many indole alkaloids and later applied to the synthesis of variety of *Corynanthe* and *Yohimbe* alkaloids. (a) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645. (b) Wenkert, E.; Halls, T. D. J.; Kunesch, G.; Orito, K.; Stephens, R. L.; Temple, W. A.; Yadav, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 5370. (c) Wenkert, E.; Pyrek, J. S.; Uesato, S.; Vankar, Y. D. *J. Am. Chem. Soc.* **1982**, *104*, 2244.

Scheme III



Scheme IV



differentiated nucleophilic moieties would allow the construction of 2,6-methano[1,4]diazocino[1,2-*a*]-, 1,5-methanoazocino[4,3-*b*]-, and 1,5-methanoazocino[3,4-*b*]-indole systems depending on the position at which the acetate chain is linked to the indole ring in the starting ester (Scheme II). It is worth noting that as a consequence of the mode of cyclization, the required cis relative configuration between the 3 and 15 centers is necessarily attained through this approach.

The above tetracyclic systems would possess four of the five rings of C-mavacurine,[10] *Strychnos*,[11] and akuammiline-type[12] alkaloids, respectively, and incorporate their characteristic C-16 appendage. Moreover, the electron-withdrawing substituent X could be further elaborated into the C-20 two-carbon substituent present in indole alkaloids.

Results and Discussion

Our initial experimental work was focused on the synthesis of vinoxine[13] (**7b**), a tetracyclic indole alkaloid iso-

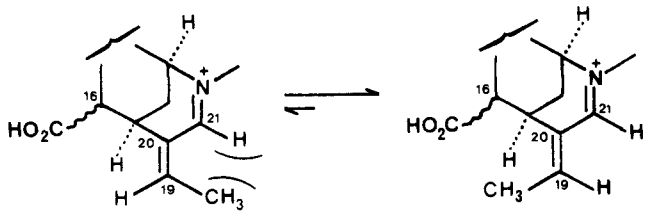
(10) Hesse, M.; Philipsborn, W. v.; Schumann, D.; Spiteller, G.; Spiteller-Friedmann, M.; Taylor, W. I.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1964**, *47*, 878.

(11) For a review about pentacyclic *Strychnos* indole alkaloids, see: Bosch, J.; Bonjoch, J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol I, p 31.

(12) For a review, see: Joule, J. A. In *The Chemistry of Heterocyclic Compounds. Indoles Part 4, the Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; p 244.

(13) (a) Votický, Z.; Grossmann, E.; Tomko, J.; Massiot, G.; Ahond, A.; Potier, P. *Tetrahedron Lett.* **1974**, 3923. (b) Votický, Z.; Grossmann, E.; Potier, P. *Collect. Czech. Chem. Commun.* **1977**, *42*, 548.

Scheme V



(Z)-A (E)-A

lated[14] in 1967 from *Vinca minor* L. that lacks the characteristic tryptamine unit present in the greater part of indole alkaloids.[15,16] In a model experiment, interaction of the enolate derived from ester **1** with *N*-methylpyridinium iodide **2** followed by treatment with dry HCl in C_6H_6 afforded the tetracycle **4a** in 31% yield as the only isolable product[17] (Scheme IV). Formation of **4a** clearly established that the expected γ-attack to the pyridinium salt to give a 1,4-dihydropyridine had occurred and that cyclization had taken place regiospecifically with formation of the C-2/C-3 bond. The latter occurs because protonation takes place at the β-carbon of the unsubstituted enamine function rather than at the doubly vinylogous urethane moiety. When the above two-step sequence was effected from pyridinium salt **3**, tetracycle **5** was obtained in 38% yield as a 5:1 mixture of C-16 epimers **5a** and **5b**, respectively. In several runs, the corresponding *O*-deacylated products **6** were detected. These compounds were also prepared in 93% yield by methanolysis of tetracycles **5**.

A (methoxycarbonyl)vinyl group was selected as the electron-withdrawing substituent at the β-position of the starting pyridinium salt since it was already known[18] that β-(1,4,5,6-tetrahydro-3-pyridyl)acrylates can be stereoselectively elaborated into (3*E*)-ethylidenepiperidines.[19] Thus, treatment of **6a**[20] with refluxing 4 N aqueous HCl brought about both the hydrolysis of ester groups and the decarboxylation of the resulting acrylic acid to give a conjugated iminium ion (A, Scheme V), which, after reesterification of the 16-carboxy group, was reduced with $NaBH_4$. A C-16 epimeric mixture of ethylidene derivatives **7a** [(±)-16-epivinoxine] and **7b** [(±)-vinoxine] was obtained in 30% yield. When the same reaction sequence was effected from **6b**,[20] (±)-vinoxine (**7b**) was isolated as the major product (32%). This synthetic vinoxine was identical in all respects (TLC, IR, ^{1}H NMR, and ^{13}C NMR) except for its chiroptical properties with the natural product.[21] This synthesis constitutes the first total synthesis of the indole alkaloid vinoxine.

The natural *E* configuration of the ethylidene chain in both isomers results, as in its biogenetic origin, from its formation by reduction of an iminium salt conjugated to the exocyclic double bond. The ethylidene substituent in the iminium ion A exists as the more stable *E* configuration since the steric interactions between C-21 H and C-19 H in the *E* isomer are lower than the interactions between C-21 H and the CH_3 group in the *Z* isomer[22] (Scheme V). This configuration in **7a** and **7b** was evident from the observation of a positive NOE effect for the signal corresponding to C-15 H on irradiation of the signal due to C-18 H in the ^{1}H NMR spectrum.[23]

With both vinoxine and 16-epivinoxine in hand, comparison of their ^{1}H NMR spectra with those of the pentacyclic analogues pleiocarpamine[10] and 16-epipleiocarpamine[10] allowed the reassignment of the relative configuration at C-16 in vinoxine. A trans relationship between C-15 H and C-16 H had been proposed for this alkaloid.[13] However, the coupling constants between C-15 H and C-16 H in vinoxine (J = 6.1 Hz) and 16-epivinoxine (J = 1.1 Hz) better correlate with those of pleiocarpamine (J = 4 Hz; C-15 H/C-16 H cis relationship) and 16-epipleiocarpamine (J = 1.5 Hz; C-15 H/C-16 H trans relationship) respectively, two alkaloids with well-established stereochemistry.[10] Accordingly, vinoxine has the same relative configuration at C-16 as pleiocarpamine, so it can be depicted as **7b**. This stereochemical assignment is in good agreement with the shielding of C-14 in 16-epivinoxine (**7a**) and of C-20 in vinoxine (**7b**) in the ^{13}C NMR spectra (Table II) due to γ-effects induced by the methoxycarbonyl group.[23]

The use of the same synthetic strategy from methyl indole-2-acetates allowed the synthesis of tetracyclic systems[24] that incorporate four of the five rings of pentacyclic *Strychnos* alkaloids[25,26] (Scheme VI).

Our first studies in this field were done using ester **8**, having a CH_3 substituent blocking the indole nitrogen.[27] As was expected, exposure of pyridinium salts **2** and **3** to the lithium enolate of ester **8** and then to acid provided the corresponding tetracycles **10a,b** and **11a,b** in 58% and 75% yields, respectively, clearly higher than those obtained in the above series. In both cases, epimeric mixtures, in which the C-15 H/C-16 H trans isomers **10a** and **11a** predominated, were obtained. The extension of this addition–cyclization reaction sequence to the N-unsubstituted indole ester **9** allowed the preparation of the ex-

(14) Mokrý, J.; Kompiš, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2523.

(15) For a preliminary report of this part of the work, see: Bosch, J.; Bennasar, M.-L.; Zulaica, E.; Feliz, M. *Tetrahedron Lett.* **1984**, *25*, 3119.

(16) For the synthesis of tetracyclic analogues of vinoxine, see: (a) Bosch, J.; Mauleón, D.; Feliz, M.; Granados, R. *J. Org. Chem.* **1983**, *48*, 4836. (b) Bosch, J.; Feliz, M.; Bennasar, M.-L. *Tetrahedron* **1984**, *40*, 1419. (c) Bennasar, M.-L.; Bosch, J. *Tetrahedron* **1986**, *42*, 637. (d) Bosch, J.; Bennasar, M.-L.; Zulaica, E. *J. Org. Chem.* **1986**, *51*, 2289.

(17) Trace amounts of the corresponding C-15/C-16 H cis isomer were detected by ^{1}H NMR.

(18) For the use of this procedure in the synthesis of (*E*)-ethylidene bearing indole alkaloids, see: (a) Besselièvre, R.; Cosson, J.-P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 63. (b) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.* **1980**, *102*, 7971. (c) Wenkert, E.; Angell, E. C.; Drexler, J.; Moeller, P. D. R.; Pyrek, J. S.; Shi, Y.-J.; Sultana, M.; Vankar, Y. D. *J. Org. Chem.* **1986**, *51*, 2995.

(19) For a review on the elaboration of the ethylidene substituent in the synthesis of indole alkaloids, see: Bosch, J.; Bennasar, M.-L. *Heterocycles* **1983**, *20*, 2471. For more recent examples, see: (a) Lesma, G.; Palmisano, G.; Tollari, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1593. (b) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986**, *42*, 2903. (c) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108. (d) Overman, L. E.; Robichaud, A. *J. J. Am. Chem. Soc.* **1989**, *111*, 300.

(20) A similar result was obtained starting from the corresponding acetates **5**.

(21) We are indebted to Professor Pierre Potier (Institut de Chimie des Substances Naturelles, Gif-sur-Yvette) for the gift of an authentic sample of natural vinoxine.

(22) Uskoković, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Pruess, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742.

(23) For a more detailed discussion, see: Bosch, J.; Bennasar, M.-L.; Rubiralta, M. *An. Quim.* **1987**, *83C*, 66.

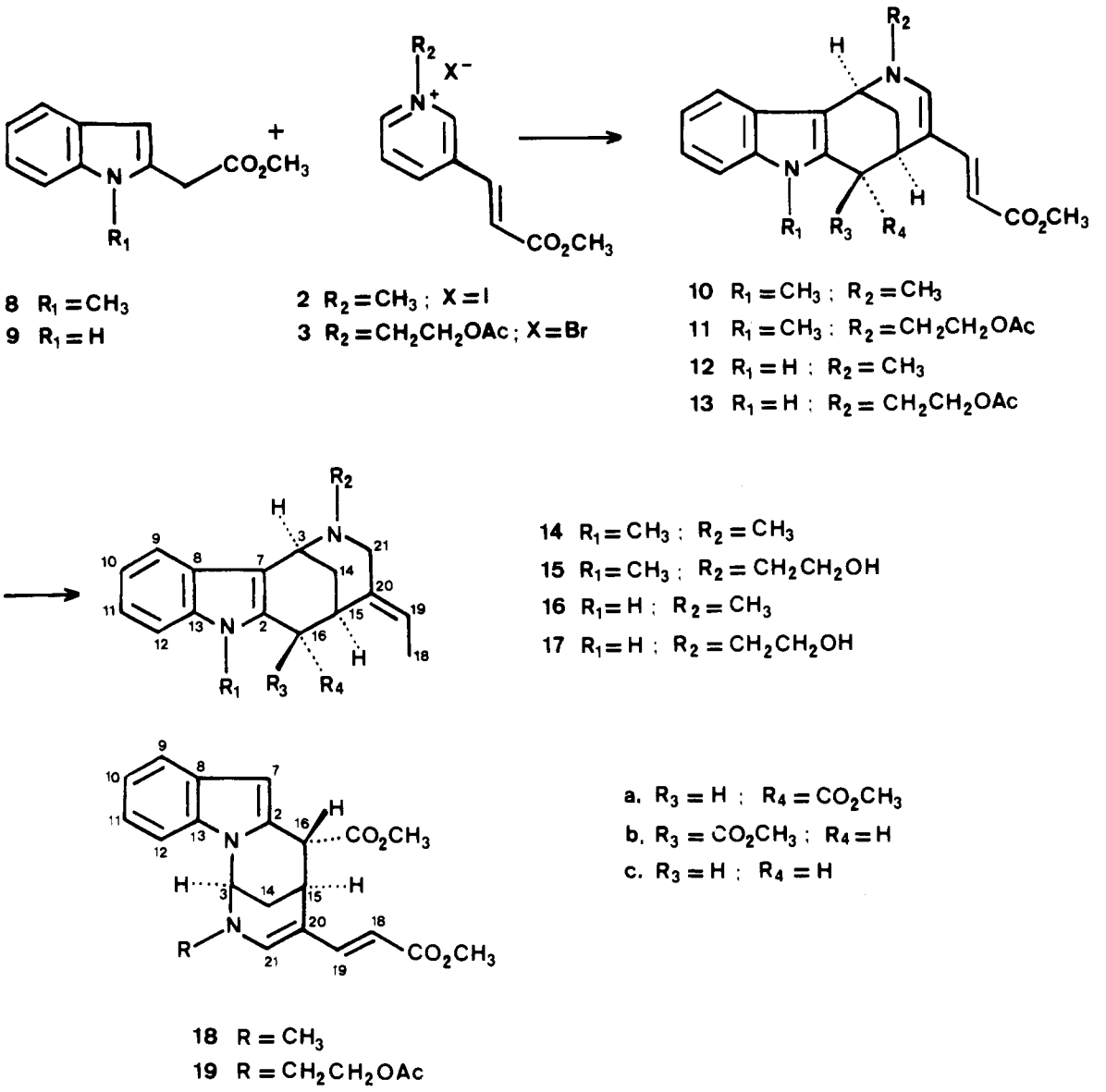
(24) For the synthesis of hexahydro-1,5-methanoazocino[4,3-*b*]indole systems, see: Joule, J. A. In *The Chemistry of Heterocyclic Compounds. Indoles Part 4, the Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter 6. For more recent work, see: (a) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516. (b) Bonjoch, J.; Quirante, J.; Rodriguez, M.; Bosch, J. *Tetrahedron* **1988**, *44*, 2087, and references therein.

(25) For a preliminary report of this part of the work, see: Alvarez, M.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1987**, *28*, 4457.

(26) For a related approach in the context of the synthesis of ellipticine derivatives, see: Wanner, M. J.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1983**, *39*, 3673.

(27) Although this substitution pattern is not usual in *Strychnos* alkaloids, there are some members (e.g., strychnofluorine) having this methyl substituent.

Scheme VI



pected tetracycles **12a**[17] and **13a**[17] in approximately 45% yield. Minor amounts of the regioisomers **18** and **19**, in which cyclization had occurred upon the indole nitrogen, were also formed.[28] Upon heating, compound **18** was easily converted into tetracycle **12a**.

Tetracycles **10a,b** and **11a,b** were stereoselectively elaborated in 30% yield into the corresponding (*E*)-ethylidene derivatives **14a,b** and **15a,b** by the above one-pot, three-step sequence consisting of treatment with refluxing hydrochloric acid, reesterification of the C-16 carboxy group, and finally $NaBH_4$ reduction. In the latter series, decarboxylation of the C-16 carboxy group occurred to some extent during the hydrolytic step, giving the C-16 unsubstituted tetracycle **15c** in 20% yield.[29] The occurrence of this decarboxylation process was more extensive in the N-unsubstituted indole series, in which the decarboxylated ethylidene-bearing tetracycles **16c** (75%) and **17c** (46%) were obtained as the sole isolable products from **12a**[30] and **13a**, respectively.

As a consequence of operating with stabilized carbon nucleophiles, in all examples discussed so far only products coming from a γ-attack to the pyridinium ring were detected. However, in some cases the reaction leads to products coming from an α-attack. The occurrence of such an α-attack was evident when the reaction between pyridinium salt **2** and ester **8** was conducted using an excess of $NaOCH_3$ instead of LDA as the base. Under these conditions, pyridone **20a** was obtained in 59% yield (Figure 1). Its formation can be rationalized by considering that the base promotes the abstraction of the methine proton α to the methoxycarbonyl group, with concomitant ring opening, in the initially formed α-adduct. Further irreversible recyclization of the amide nitrogen with the ester group of the acrylate moiety leads to a pyridone system.[31,32]

(28) For related cyclizations involving the indole nitrogen, see: (a) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, 2738. (b) Hashimoto, C.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 4563.

(29) When the reaction conditions of this step were forced (100 °C, 6 h), the decarboxylated tetracycle **14c** was obtained in 44% yield as the only isolable product from **10a,b**.

(30) Even operating under milder conditions (90 °C, 45 min) during the hydrolytic step, this decarboxylation could not be avoided, though in this case the desired ethylidene derivatives **16a,b** were formed in a yield lower than 10%.

(31) This kind of ring opening was first observed by Wenkert. See ref 18c.

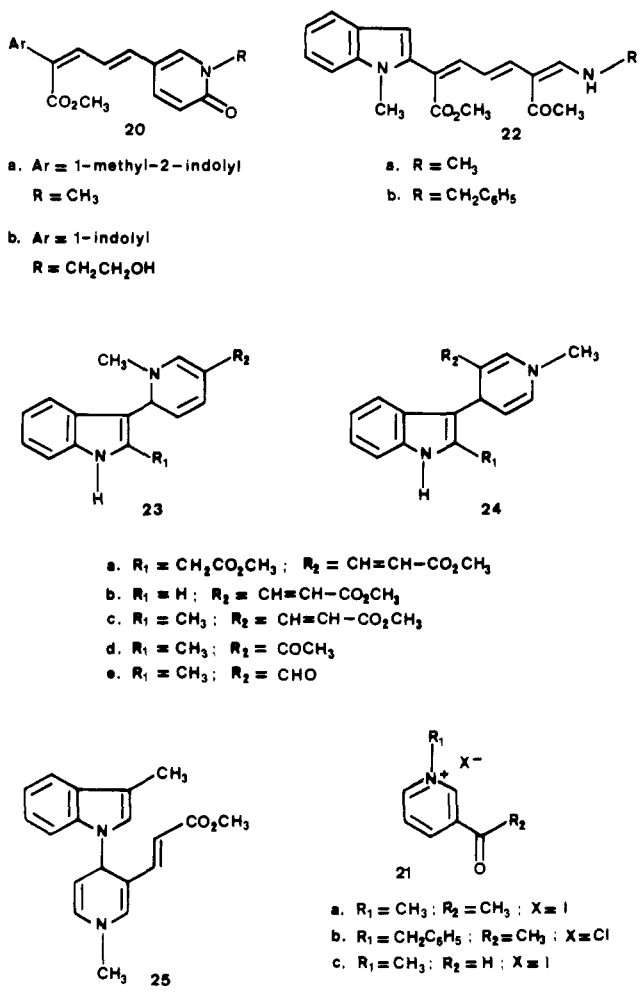


Figure 1.

In this manner, the equilibrium between 1,2- and 1,4-dihydropyridine is shifted to an unusual direction. This kind of ring opening in a 1,2-dihydropyridine system was also observed in the reaction of ester 8 with 3-acetylpyridinium salts **21a** and **21b** in the presence of an excess of $NaOCH_3$. In these cases, recyclization to a pyridone system cannot occur, and the polyunsaturated amines **22a** and **22b**, respectively, were obtained.[31]

In other cases, the appearance of α-addition products is a consequence of a kinetic, irreversible α-attack of the nucleophile to the pyridinium ring. Thus, when the reaction of N-unsubstituted indole ester **9** with pyridinium salt **2** was carried out in MeOH solution in the presence of $NaOCH_3$ as the base, the (dihydropyridyl)indole **23a** was obtained in 61% yield.[33] This result can be explained by taking into account that $NaOCH_3$ is a weaker base than LDA and that, consequently, there is a low concentration of dianion in solution. Kinetic attack by C-3 of the indolyl anion at the α-position of the pyridinium salt followed by rapid aromatization of the indole ring gave 1,2-dihydropyridine **23a**.[34] The latter fact blocks the equilibration of the kinetic α-addition product to the thermodynamic γ-addition product.

The above reaction seems to be quite general and of preparative interest. Thus, treatment of other N-unsubstituted indoles, such as indole itself or 2-methylindole, first with $NaOCH_3$ and then with pyridinium salts **2**, **21a**, or **21c**, having different electron-withdrawing substituents at the 3-position, afforded the corresponding 3-(1,2-dihydro-2-pyridyl)indoles **23b–e** in good yields. In some cases, minor amounts of the corresponding 1,4-dihydropyridines (**24b** and **24e**) were also detected or isolated, thereby indicating that the kinetic attack can also occur to some extent at the γ-position. The use of the same set of reaction conditions from 3-methylindole led to an interesting result: the 1,4-dihydropyridine **25**, having a 1-indolyl substituent, was obtained in 51% yield.[35] This result can be accounted for by considering that, in this case, the attack of the indolyl anion, either by C-3 or by the nitrogen, is reversible and, consequently, leads to the thermodynamically more stable product, i.e., a 1,4-dihydropyridine in which the γ-substituent is 3-methyl-1-indolyl rather than the less stable 3-methyl-3*H*-indol-3-yl (an indolenine) unit.[36]

The application of our common strategy from methyl indole-3-acetates allowed the construction of the hexahydro-1,5-methanoazocino[3,4-*b*]indole fragment[37,38] present in the akuammiline-type alkaloids.

Thus, interaction of the dianion derived from **26** with pyridinium salt **2** followed by the usual acidic treatment gave a 2:1 mixture of the expected model tetracycle **28a**[17] (31%) and the unnatural regioisomer **30**[17] (15%) (Scheme VII). This result evidences that the pyridinium salt **2** has undergone both α- and γ-attacks to give a mixture of 1,2- and 1,4-dihydropyridines. Further protonation, followed by cyclization of the resulting dihydropyridinium salts leads to the isolated tetracycles **28a** and **30**. The formation, in this case, of products coming from an α-attack indicates that the mixture of dihydropyridines is not equilibrated, probably due to the predictably lower ability of the dianion derived from **26** to act as leaving group as compared with those derived from 1- and 2-indoleacetates. Moreover, the lower acidity of the methine proton α to the methoxycarbonyl group in the intermediate 1,2-dihydropyridine could explain the absence of the base-promoted ring-opening process observed in the 2-indoleacetate series.

It could be expected that blocking of the indole nitrogen of **26** increased the ability of the indoleacetic ester moiety to act as a leaving group (it would be a simple enolate instead of a dianion) and, consequently, favored the equilibration of the dihydropyridine adducts to the more stable 1,4-dihydropyridine, which is the precursor of the desired tetracyclic akuammiline-type systems; however, when the above addition–cyclization sequence was effected from ester **27**, a mixture of the regioisomeric tetracycles **29a**[17] and **31**[17] was again obtained (1:1 ratio, 32% yield).

The structures of the unexpected tetracycles **30** and **31**

(32) A related pyridone, **20b**, was obtained as a minor byproduct in the first step of the above synthesis of vinoxine (see the Experimental Section).

(33) For a preliminary report of this part of the work, see: Alvarez, M.; Lavilla, R.; Bosch, J. *Heterocycles* **1989**, *29*, 237.

(34) To our knowledge there are no precedents of nucleophilic additions of indoles to *N*-alkylpyridinium salts. For this kind of addition to *N*-acylpyridinium salts, see: (a) Bergman, J. *J. Heterocycl. Chem.* **1970**, *7*, 1071. (b) Deubel, H.; Wolkenstein, D.; Jokisch, H.; Messerschmitt, T.; Brodka, S.; Dobeneck, H. v. *Chem. Ber.* **1971**, *104*, 705. (c) Ishikura, M.; Terashima, M. *Heterocycles* **1988**, *27*, 203.

(35) Minor amounts of the corresponding 1,2-dihydropyridine were detected by ^1H NMR from the crude reaction mixture.

(36) The reversibility of the nucleophilic attack was evident from the tendency of 1,4-dihydropyridine **25** to undergo fragmentation into the starting materials: (i) all attempts to purify **25** by crystallization or column chromatography resulted in the formation of 3-methylindole and the pyridinium salt **2** and (ii) reduction of **25** with $NaBH_4$ in MeOH gave 3-methylindole and a mixture of methyl (*E*)-1-methyltetrahydropyridine-3-acrylates.

(37) For a preliminary account of this part of the work, see: Bennasar, M.-L.; Zulaica, E.; López, M.; Bosch, J. *Tetrahedron Lett.* **1988**, *29*, 2361.

(38) For previous syntheses of this tetracyclic ring system, see: (a) Dolby, L. J.; Nelson, S. J. *J. Org. Chem.* **1973**, *38*, 2882. (b) References 16a and 16b.

Table I. ^{13}C NMR Data of Tetracycles 4, 6, 10–13, 28–31, 33, and 34

C	4a	6a	6b	10a	10b	11a	11b	12a[a]	13a	28a[a]	29a	30[a]	31	33a[a]	33b[a]	34a
C-2	133.9	135.1	136.3	132.0	132.2	132.7	132.9	131.0	130.5	133.7	137.1	135.4	137.0	134.1	134.6	134.9
C-3	50.3	48.9	48.6	49.1	48.6	46.8	47.0	48.0	48.5	48.9	48.5	53.9	54.9	47.9	47.5	47.8
C-5		55.5	56.1			52.4	52.8		53.2					55.7	55.4	52.7
C-6		60.6	60.6			62.1	61.9		62.3					59.6	59.7	62.7
C-7	99.9	99.5	99.9	110.4	110.4	110.3	112.0	110.1	111.7	107.2	109.1	107.3	107.1	106.6	105.5	110.1
C-8	127.7	127.8	128.1	125.0	125.4	124.7	125.0	125.4	125.4	126.3	125.2	126.8	126.6	126.3	125.7	126.5
C-9	120.4	120.5	120.6	118.2	117.7	118.3	117.6	118.3	117.8	118.4	119.5	117.8	118.5	118.4	118.6	119.6
C-10	120.9	120.9	120.9	119.6	119.8	119.2	119.9	119.2	120.6	118.9	119.8	118.5	119.3	118.9	118.8	119.8
C-11	122.4	122.4	122.2	121.6	121.8	121.2	121.8	121.2	122.3	121.3	122.2	120.2	121.3	121.3	121.0	122.4
C-12	109.0	109.0	110.4	109.2	109.1	109.4	109.3	110.9	111.3	111.4	109.4	111.1	109.3	111.4	111.4	109.4
C-13	136.6	136.6	136.9	137.2	137.0	136.8	137.3	135.8	136.5	135.5	139.0	139.5	139.5	135.5	135.6	137.6
C-14	22.9	22.9	26.0	25.9	29.2	25.6	29.3	25.6	26.8	25.5	26.2	25.4	26.3	25.6	28.6	26.4
C-15	28.9	29.1	27.5	30.3	28.7	30.0	28.9	29.2	28.3	28.8	28.9	24.7	24.3	29.1	28.6	29.3
C-16	59.2	59.1	62.0	44.0	48.2	43.2	47.9	44.1	44.2	42.4	42.9	42.2	42.9	42.3	46.5	42.8
C-18	103.3	103.3	103.1	101.0	101.9	100.4	102.7	99.7	102.6	100.4	103.6	100.5	102.3	100.0	100.2	104.8
C-19	145.4	145.2	145.4	146.2	145.9	145.2	144.9	145.9	144.2	145.9	143.9	145.0	145.3	145.7	146.2	142.3
C-20	105.6	105.4	103.0	107.3	105.1	106.3	105.6	106.3	102.6	105.1	106.9	100.9	101.8	105.2	104.7	107.2
C-21	145.4	145.6	147.0	146.2	148.0	146.3	147.9	146.0	146.4	146.3	146.1	145.3	145.5	146.6	148.5	145.9
$N(4)CH_3$	40.5			42.1	41.9			41.3		40.9	41.9	40.6	41.4			
$N(1)CH_3$				29.7	30.5	29.4	30.4				30.2		30.7			30.2
OCH_3	51.0	51.1	51.0	50.8	50.9	50.3	50.7	50.0	51.0	50.3	50.9	49.9	50.9	50.2	50.1	50.9
	52.6	52.7	52.7	52.5	52.5	52.4	52.3	51.2	52.5	51.7	52.0	51.5	52.1	51.7	51.2	51.9
$COOCH_3$	168.9	169.1	169.3	169.2	169.4	167.9	169.2	167.8	169.1	167.9	169.1	168.2	169.2	168.0	168.2	168.9
	170.7	170.8	170.3	171.8	172.4	170.2	170.5	171.3	170.8	173.0	173.0	171.8	172.3	173.1	173.1	170.5
CH_3CO						171.4	172.3		171.1							173.5
CH_3CO						20.8	20.7		20.9							20.7

[a] In DMSO-d_6 solution.

Table II. ^{13}C NMR Data of Ethylidene Derivatives 7, 14–17, 32, and 35

C	7a	7b	14a	15b	14c	15c	16c	17c	32a	32b	35b
C-2	131.9	133.8		134.9	137.5	137.6		136.5	131.2	130.7	131.1
C-3	51.8	51.8	52.6	51.2	52.1	50.9	51.9	51.4	53.2	53.2	51.3
C-5	56.5	56.5		53.5		53.2		53.1			56.6
C-6	57.9	58.0		57.7		57.8		58.2			59.7
C-7	101.4	101.8		107.3	105.6	105.6		106.0	108.7	109.1	109.2
C-8	127.8	128.1		126.8	128.1	127.5		127.8	126.3	128.3	126.4
C-9	120.7	120.6	119.6	118.5	117.8	117.8	117.5	118.0	119.0	119.0	119.1
C-10	121.8	122.3	121.6	121.9	119.3	119.3	120.5	119.7	119.2	119.4	119.5
C-11	120.3	120.3	120.3	119.7	118.4	118.2	118.5	118.6	119.7	121.0	121.3
C-12	108.6	110.0	109.0	109.0	108.6	108.7	110.4	110.7	111.0	111.1	111.2
C-13	136.3	136.5		137.3	139.1	139.1		138.1	135.5	135.4	135.4
C-14	27.8	31.0	29.9	33.8	33.0	32.8	33.4	33.1	29.9	33.3	33.4
C-15	31.8	31.1	32.4	31.9	27.2	27.8	27.4	27.7	31.4	31.3	31.9
C-16	59.9	60.0	43.7	45.3	28.4	28.6	29.3	29.6	43.2	43.0	44.7
C-18	12.6	12.6	12.5	12.6	12.4	12.4	12.4	12.3	12.5	12.3	12.4
C-19	120.9	121.6	119.3	121.6	120.5	120.6	121.1	121.1	121.8	121.8	121.8
C-20	135.1	133.2	136.2	134.2	138.1	136.8	135.9	135.9	137.2	135.9	135.9
C-21	54.3	55.0	55.0	57.1	55.8	57.2	56.0	57.6	56.0	56.7	55.2
$N(1)CH_3$			29.7	30.3	29.1	29.2					
$N(4)CH_3$			44.8		43.9		44.2		43.4	44.6	
OCH_3	52.7	52.2	51.8	51.9					52.0	51.4	51.5
CO		170.1	172.2	172.2					174.1	173.4	173.6

were established by comparison of their spectroscopic data with those corresponding to **28a** and **29a**. Thus, C-3 and C-15 appear more shielded (see Table I) in those regioisomers in which they are adjacent to the indole nucleus, whereas in the same situation C-3 H and C-15 H resonate at a lower magnetic field.

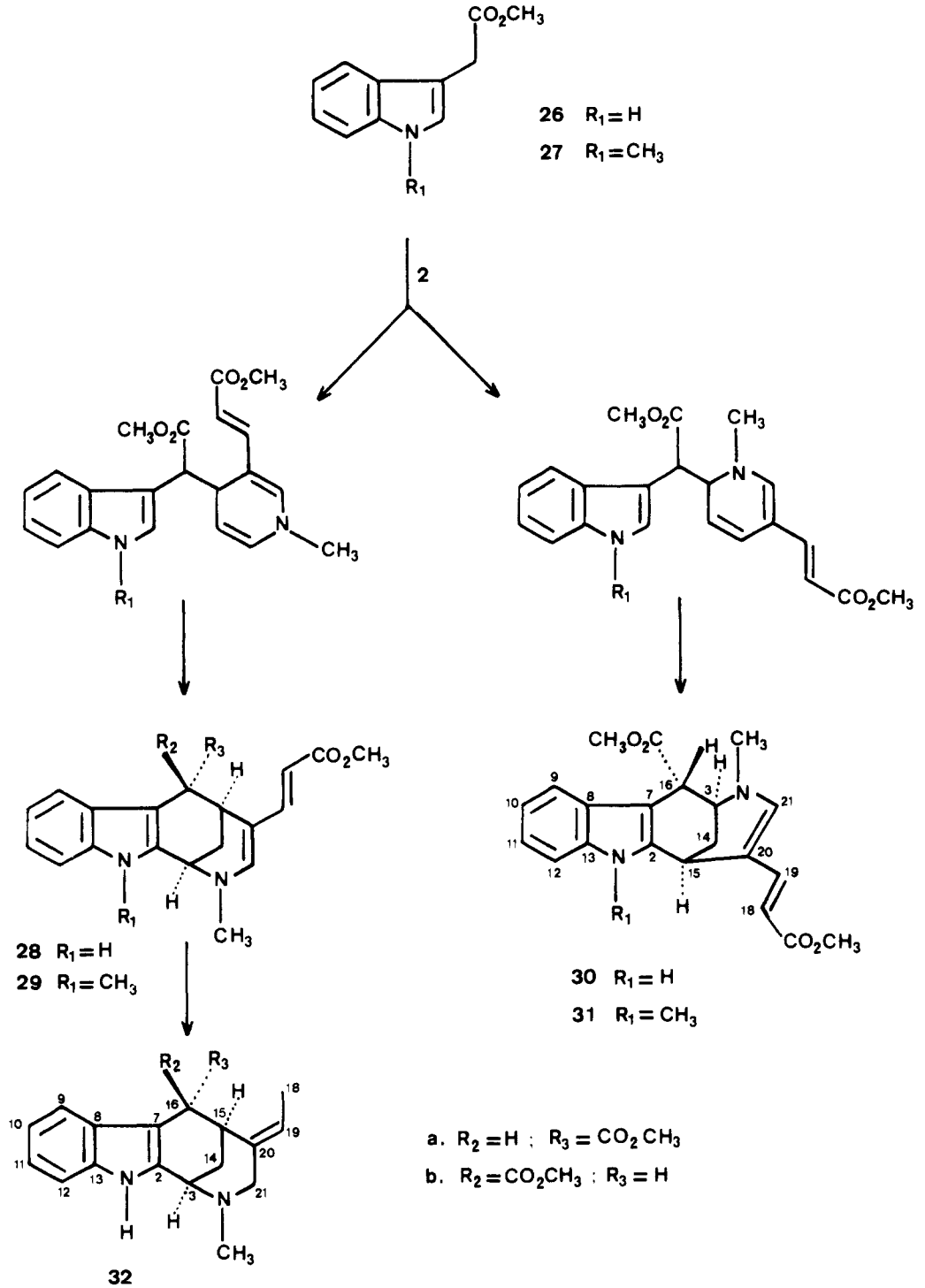
In contrast with the above results, the reactions of the enolates of esters **26** and **27** with pyridinium salt **3**, having a functionalized two-carbon chain (2-acetoxyethyl) at the pyridine nitrogen, provided, although in low yield, only the expected akuammiline-type regioisomers **33** and **34** (epimeric mixtures at C-16), respectively (Scheme VIII). The presence of an N-substituent bulkier than CH_3 could account for the absence of products derived from a kinetic α-attack.

Finally, the stereoselective elaboration of the (*E*)-ethylidene substituent from **28a** was effected in the usual manner to give an epimeric mixture of tetracycles **32a** and **32b** (3:1 ratio) in 40% yield. Similarly, a mixture of tetracycles **33a,b** was converted into **35a,b** in 50% yield.

Conclusion

The addition of indoleacetic ester anions to *N*-alkylpyridinium salts, followed by cyclization of the resulting dihydropyridines, has proved to be a useful tool for the straightforward construction of aza-bridged systems fused to the indole nucleus. This methodology has been successfully applied to the first synthesis of the tetracyclic indole alkaloid vinoxine (**7b**) as well as to that of tetracycles **15a,b** and **35a,b**. These compounds possess four of the five rings of the C-mavacurine, *Strychnos*, and akuammiline-type alkaloids, respectively, and incorporate both their characteristic two-carbon substituent at C-20 and their oxidized one-carbon appendage at C-16. Moreover, the hydroxyethyl chain at the piperidine nitrogen can allow further closure of the tryptamine unit by formation of the C-6/C-7 bond according to a methodology similar to that which we successfully employed[4] for the synthesis of

Scheme VII



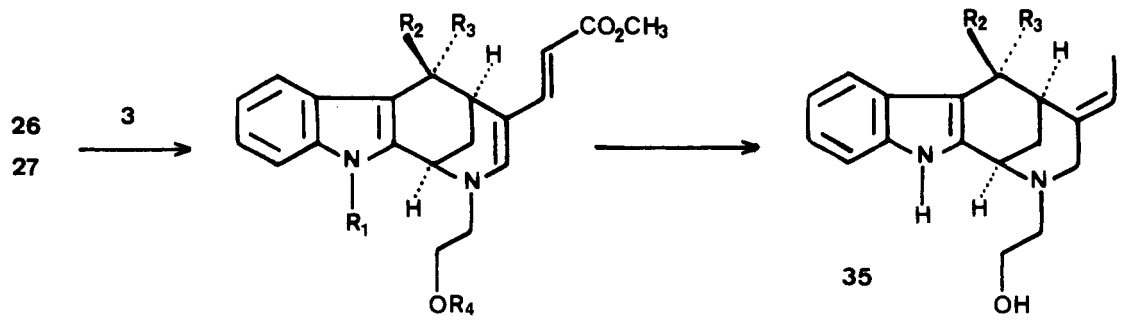
pentacyclic *Strychnos* alkaloids. On the other hand, the loss of the methoxycarbonyl group in the N-unsubstituted 2-indoleacetate series is not a serious inconvenience, not only because this group can be reintroduced after elaboration of the fifth ring[39] but also because tetracycle **17c** can be considered a potential synthetic precursor of the pentacyclic *Strychnos* alkaloids tubifoline and tubifolidine, which lack the oxidized C-16 substituent.

Experimental Section

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Varian XL-200 spectrometer or, when indicated, on a Perkin-Elmer R-24B (60 MHz) or Brüker WH-400 instruments, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. UV spectra were run in EtOH solution on a Perkin-Elmer Lambda 5 spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. 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, Merck, 0.063–0.200 mm) or, when indicated, on Al_2O_3 (aluminum oxide 90, Merck, neutral, activity I, 0.063–0.200 mm). Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 0.040–0.063 mm). Drying of organic extracts during the workup

(39) Amat, M.; Linares, A.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 2293.

Scheme VIII



33 $R_1 = H$; $R_4 = H$

34 $R_1 = CH_3$; $R_4 = COCH_3$

a. $R_2 = H$; $R_3 = CO_2CH_3$

b. $R_2 = CO_2CH_3$; $R_3 = H$

of reactions was performed over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by Departamento de Química Orgánica Biológica (C.S.I.C.), Barcelona.

1-(2-Acetoxyethyl)-3-[(*E*)-2-(methoxycarbonyl)vinyl]-pyridinium Bromide (3). A mixture of methyl (*E*)-3-(3-pyridyl)acrylate[9b] (10 g, 59 mmol) and 2-bromoethyl acetate (12.1 g, 8 mL, 72 mmol) was heated at 90–100 °C for 1 h. The reaction mixture was diluted with Et_2O, and the resulting precipitate was filtered to give **3**: 16.4 g (84%); mp 170–171 °C (acetone–MeOH); IR (KBr) 1715, 1740 (CO); ^1H NMR (DMSO-d_6, 60 MHz) 1.90 (s, 3 H, CH_3CO), 3.65 (s, 3 H, OCH_3), 4.50 (t, 2 H, CH_2O), 4.80 (t, 2 H, CH_2N), 6.80 (d, J = 15 Hz, 1 H, CHCO), 7.15 (d, J = 15 Hz, 1 H, CH), 8.05 (m, 1 H, 5-H), 8.90 (m, 2 H, 4- and 6-H), 9.50 (s, 1 H, 2-H). Anal. Calcd for $C_{13}H_{16}BrNO_4$: C, 47.30; H, 4.88; Br, 24.20; N, 4.24. Found: C, 47.30; H, 4.83; Br, 24.59; N, 4.10.

Methyl (1*RS*,2*SR*,6*SR*)-1-(Methoxycarbonyl)-5-methyl-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3-(*E*)-acrylate (4a). A solution of ester **1**[40] (1 g, 5.3 mmol) in THF (40 mL) was slowly added to a solution of LDA (7.9 mmol) in THF (20 mL) cooled at −70 °C, and the resulting solution was stirred at −70 °C for 1 h. Subsequently, pyridinium iodide **2**[41] (1.6 g, 5.3 mmol) was added in portions, and the mixture was allowed to rise to −30 °C and stirred at this temperature for 1.5 h. Enough of a saturated C_6H_6 solution of dry HCl was added dropwise to bring the pH to 3.5–4, and the reaction mixture was permitted to rise to room temperature. After being stirred at room temperature for 2 h, the reaction mixture was poured into a saturated aqueous Na_2CO_3 solution and extracted with Et_2O. Evaporation of the ethereal extracts afforded a residue, which was purified by flash chromatography (7:3 Et_2O–hexane) to give **4a**: 0.6 g (31%); mp 183–184 °C (acetone–Et_2O); IR (KBr) 1695, 1735 (CO); ^1H NMR 2.03 (dt, J = 13.2 and 3.5 Hz, 1 H, 14-H), 2.40 (dt, J = 13.2 and 2.6 Hz, 1 H, 14-H), 2.99 (s, 3 H, NCH_3), 3.31 (br, 1 H, 15-H), 3.74 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.40 (t, 1 H, 3-H), 5.04 (d, J = 1.3 Hz, 1 H, 16-H), 5.67 (d, J = 15 Hz, 1 H, 18-H), 6.37 (s, 1 H, 7-H), 6.40 (s, 1 H, 21-H), 7.01–7.30 (m, 3 H, indole), 7.22 (d, J = 15 Hz, 1 H, 19-H), 7.60 (dm, J = 9 Hz, 1 H, 9-H); ^{13}C NMR, Table I. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.69; H, 6.00; N, 7.45.

Condensation of Ester 1 with Pyridinium Bromide 3. Operating as above, except for the temperature of the cyclization step (60 °C), from ester **1** (4 g, 21.1 mmol), LDA (21.1 mmol), and pyridinium bromide **3** (4.6 g, 14.1 mmol), a crude residue was obtained. Purification by flash chromatography (CH_2Cl_2) gave a 5:1 mixture of tetracycles **5a** and **5b**: 2.4 g (38%). **Methyl (1*RS*,2*SR*,6*SR*)-5-(2-acetoxyethyl)-1-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3-(*E*)-acrylate (5a)**: mp 100–101 °C (acetone–Et_2O); IR (KBr) 1690, 1740 (CO); ^1H NMR 1.96 (dt, J = 12 and 3.6 Hz, 1 H, 14-H), 2.09 (s, 3 H, CH_3CO), 2.40 (dt, J = 12 and 2.4 Hz, 1 H, 14-H), 3.20 (m, 1 H, 5-H), 3.30 (br, 1 H, 15-H), 3.60 (m, 1 H, 5-H), 3.75 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.10 (m, 1 H, 6-H), 4.40 (m, 1 H, 6-H), 4.60 (t, J = 1 Hz, 1 H, 3-H), 5.05 (d, J = 1.2 Hz, 1 H, 16-H), 5.68 (d, J = 15 Hz, 1 H, 18-H), 6.42 (s, 1 H, 7-H), 6.45 (s, 1 H, 21-H), 7.02–7.16 (m, 3 H, indole), 7.25 (d, J = 15 Hz, 1 H, 19-H), 7.56 (dd, J = 7 and 1 Hz, 1 H, 9-H). Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.97; N, 6.39. Found: C, 65.57; H, 6.11; N, 6.42. **Methyl (1*RS*,2*RS*,6*RS*)-5-(2-acetoxyethyl)-1-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3-(*E*)-acrylate (5b)**: ^1H NMR 1.98 (dt, J = 13 and 2.8 Hz, 1 H, 14-H), 2.07 (s, 3 H, CH_3CO), 2.10 (masked, 1 H, 14-H), 3.40 (m, 1 H, 5-H), 3.73 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.78 (masked, 1 H, 5-H), 4.00 (br, 1 H, 15-H), 4.05 (m, 1 H, 6-H), 4.38 (m, 1 H, 6-H), 4.50 (br, 1 H, 3-H), 5.09 (d, J = 5 Hz, 1 H, 16-H), 5.87 (d, J = 15 Hz, 1 H, 18-H), 6.38 (s, 1 H, 7-H), 6.44 (s, 1 H, 21-H), 7.06–7.22 (m, 3 H, indole), 7.20 (d, J = 15 Hz, 1 H, 19-H), 7.54 (m, 1 H, 9-H).

In several runs, on elution with 98:2 CH_2Cl_2–MeOH, **methyl 5-[1-(2-hydroxyethyl)-2-oxo-1,2-dihydro-5-pyridyl]-2-(1-indolyl)-2,4-pentadienoate (20b)** was obtained: 0.25 g (5%); mp 174–175 °C (acetone–Et_2O); UV λ_{max} 200 nm (log ϵ = 4.92), 265 (4.20), 341 (4.52); IR (KBr) 1610 (C=C), 1650, 1710 (CO), 3200–3600 (OH); ^1H NMR 3.77 (s, 3 H, OCH_3), 3.90 (br t, J = 5 Hz, 2 H, CH_2N), 4.06 (t, J = 5 Hz, 2 H, CH_2O), 6.20 (dd, J = 16 and 11 Hz, 1 H, 4-H), 6.42 (d, J = 9.6 Hz, 1 H, pyridone 3-H), 6.68 (dd, J = 3.2 and 0.8 Hz, 1 H, indole 3-H), 6.74 (d, J = 16 Hz, 1 H, 5-H), 7.02–7.40 (m, 6 H), 7.68 (m, 2 H); ^{13}C NMR 52.5 (OCH_3), 53.0 (NCH_2), 61.1 (OCH_2), 103.5 (indole C-3), 110.5 (indole C-7), 116.0 (C-2), 119.9 (indole C-4), 120.4 (indole C-5), 121.0 (indole C-6 and C-4), 122.4 (pyridone C-3), 125.9 (pyridone C-5), 128.4 (indole C-3a), 129.2 (indole C-2), 136.5 (C-3), 136.9 (C-5), 137.1 (indole C-7a), 138.5 (pyridone C-4), 139.7 (pyridone C-6), 162.6 (pyridone C-2), 165.0 (CO); MS, m/e (rel intensity) 364 (77, M^+), 305 (63), 261 (17), 226 (100). Anal. Calcd for $C_{21}H_{20}N_2O_4 \cdot {}^1/_4H_2O$: C, 68.38; H, 5.56; N, 7.59. Found: C, 68.31; H, 5.42; N, 7.96.

Methyl (1*RS*,2*SR*,6*SR*)- and (1*RS*,2*RS*,6*RS*)-5-(2-Hydroxyethyl)-1-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3-(*E*)-acrylate (6a and 6b). A C-16 epimeric mixture of tetracycles **5a** and **5b** (2.5 g, 5.7 mmol) was treated at room temperature overnight with a 1 N MeOH solution of dry HCl (100 mL). After workup, a mixture of tetracycles **6a** and **6b** (2.1 g, 93%) was obtained. Both isomers were separated by flash chromatography (99:1 CH_2Cl_2–MeOH). **6a**: mp 109–110 °C (acetone–Et_2O); IR and ^1H NMR, see ref 15; ^{13}C NMR, Table I. Anal. Calcd for $C_{22}H_{24}N_2O_5 \cdot H_2O$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.60; H, 6.01; N, 6.54. **6b**: IR and ^1H NMR, see ref 15; ^{13}C NMR, Table I.

Methyl 1-Methylindole-2-acetate (8). A solution of ethyl 1-methylindole-2-glyoxylate[5b] (14 g, 60 mmol), KOH (31.2 g, 0.56 mmol), and 80% hydrazine hydrate (46.8 mL) in EtOH (90 mL) was refluxed under N_2 for 5 h. Additional KOH (31.2 g, 0.56 mmol) was added, the solvent was carefully distilled, and the residue was heated at 170–180 °C for 45 min. The reaction mixture was dissolved in H_2O, acidified with 5% aqueous HCl, and extracted with Et_2O. Evaporation of the organic extracts left a solid, which was treated with an excess of Et_2O–CH_2N_2 to give ester **8**: 10.9 g (97%); mp 50–51 °C (petroleum ether); IR (NaCl) 1730 (CO); ^1H NMR (60 MHz) 3.45 (s, 3 H, NCH_3), 3.50 (s, 3 H,

(40) Prepared by alkylation of indole with methyl bromoacetate followed by esterification of the resulting 1-indoleacetic acid.

(41) Besselièvre, C.; Beugelmans, R.; Husson, H.-P. *Tetrahedron Lett.* **1976**, 3447.

OCH_3), 3.55 (s, 2 H, CH_2), 6.10 (s, 1 H, indole 3-H), 6.75–7.30 (m, 4 H, indole). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.93; H, 6.40; N, 6.85. Found: C, 71.31; H, 6.50; N, 6.85.

Methyl (1*RS*,5*SR*,6*RS*)- and (1*RS*,5*SR*,6*SR*)-6-(Methoxycarbonyl)-2,7-dimethyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-(*E*)-acrylate (10a and 10b). Operating as in the preparation of compound **4a** except for the cyclization conditions (−10 °C, 1.5 h), from ester **8** (1 g, 5 mmol), LDA (5.1 mmol), and pyridinium iodide **2** (1.5 g, 5 mmol) a residue was obtained and then was chromatographed (C_6H_6–$CHCl_3$, increasing polarity) to give a 3:1 mixture of tetracycles **10a** and **10b**: 1.1 g (58%). **10a**: mp 188–190 °C (acetone); IR ($CHCl_3$) 1685, 1720 (CO); ^1H NMR, see ref 25; ^{13}C NMR, Table I. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.47; H, 6.31; N, 7.36. Found: C, 69.73; H, 6.27; N, 7.22. **10b**: IR ($CHCl_3$) 1675, 1725 (CO); ^1H NMR 2.07 (t, 2 H, 14-H), 3.16 (s, 3 H, NCH_3), 3.51 (s, 3 H, NCH_3), 3.66 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 4.28 (d, J = 6 Hz, 1 H, 16-H), 4.51 (t, 1 H, 3-H), 5.36 (d, J = 15 Hz, 1 H, 18-H), 6.49 (s, 1 H, 21-H), 7.05–7.29 (m, 4 H, indole and 19-H), 7.66 (dd, 1 H, 9-H); ^{13}C NMR, Table I.

Methyl (1*RS*,5*SR*,6*RS*)- and (1*RS*,5*RS*,6*SR*)-2-(2-Acetoxyethyl)-6-(methoxycarbonyl)-7-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-(*E*)-acrylate (11a and 11b). Operating as above, from ester **8** (2.5 g, 12 mmol), LDA (13.2 mmol), and pyridinium bromide **3** (4 g, 12 mmol) a 2:1 mixture of tetracycles **11a** and **11b** (4.1 g, 75%) was obtained after purification by column chromatography (C_6H_6–$CHCl_3$, increasing polarity). **11a**: mp 170–172 °C (acetone–Et_2O); IR ($CHCl_3$) 1690, 1740 (CO); ^1H NMR, see ref 25; ^{13}C NMR, Table I. Anal. Calcd for $C_{25}H_{28}N_2O_6 \cdot {}^1/_2H_2O \cdot {}^1/_2C_3H_6O$: C, 64.89; H, 6.53; N, 5.71. Found: C, 64.69; H, 6.66; N, 5.34. **11b**: IR ($CHCl_3$) 1690, 1740 (CO); ^1H NMR 2.04 (m, 2 H, 14-H), 2.09 (s, 3 H, CH_3CO), 3.51 (s, 3 H, NCH_3), 3.66 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 4.24 (d, J = 6 Hz, 1 H, 16-H), 4.68 (t, 1 H, 3-H), 5.40 (d, J = 15 Hz, 1 H, 18-H), 6.51 (s, 1 H, 21-H), 7.10–7.34 (m, 4 H, indole and 19-H), 7.58 (dd, 1 H, 9-H); ^{13}C NMR, Table I.

Condensation of Ester 9 with Pyridinium Iodide 2. Operating as above, from ester **9**[42] (2 g, 10.6 mmol), LDA (21 mmol), and pyridinium iodide **2** (3.2 g, 10.6 mmol), a residue was obtained and chromatographed. Elution with $CHCl_3$ afforded **methyl (1*RS*,5*RS*,6*SR*)-6-(methoxycarbonyl)-2-methyl-1,2,5,6-tetrahydro-1,5-methano[1,3]diazocino[3,4-*a*]indole-4-(*E*)-acrylate (18)**: 4 mg (1%); IR ($CHCl_3$) 1695, 1725 (CO); ^1H NMR, see ref 25. Elution with 99:1 $CHCl_3$–MeOH gave **methyl (1*RS*,5*SR*,6*RS*)-6-(methoxycarbonyl)-2-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-(*E*)-acrylate (12a)**: 1.8 g (46%); mp 272–274 °C (acetone–Et_2O); IR ($CHCl_3$) 1690, 1730 (CO), 3460 (NH); ^1H NMR, see ref 25; ^{13}C NMR, Table I. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.85; H, 6.02; N, 7.65. Found: C, 68.87; H, 6.27; N, 7.32.

Methyl (1*RS*,5*SR*,6*RS*)-2-(2-Acetoxyethyl)-6-(methoxycarbonyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]-indole-4-(*E*)-acrylate (13a). Operating as above, ester **9** (0.5 g, 2.6 mmol) was allowed to react with LDA (9.2 mmol) and then with pyridinium bromide **3** (1 g, 3 mmol) to give a crude residue, which was chromatographed. Elution with 9:1 $CHCl_3$–C_6H_6 afforded tetracycle **13a**: 0.49 g (43%); mp 231–233 °C (acetone–Et_2O); IR (KBr) 1705, 1730 (CO), 3310 (NH); ^1H NMR 1.95 and 2.31 (2 dt, 2 H, 14-H), 2.08 (s, 3 H, CH_3CO), 3.40 (m, 2 H, 15- and 5-H), 3.72 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.88 (d, J = 1 Hz, 1 H, 16-H), 4.15 and 4.45 (2 m, 2 H, 6-H), 4.65 (t, 1 H, 3-H), 5.48 (d, J = 15 Hz, 1 H, 18-H), 6.37 (s, 1 H, 21-H), 7.05–7.48 (m, 4 H, indole and 19-H), 7.52 (dd, 1 H, 9-H), 8.30 (s, 1 H, NH); ^{13}C NMR, Table I. Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.75; H, 5.93; N, 6.39. Found: C, 66.02; H, 6.10; N, 6.36. Minor amounts of compound **19** were detected from some fractions of the chromatography: ^1H NMR 2.17 (s, 3 H, CH_3CO), 2.75 (dt, 1 H, 14-H), 5.65 (d, J = 15 Hz, 1 H, 18-H), 5.80 (t, 1 H, 3-H), 6.30 (s, 1 H, 21-H), 6.40 (s, 1 H, 7-H).

Condensation of Ester 26 with Pyridinium Iodide 2. Operating as in the preparation of compound **4a**, ester **26**[43] (2 g, 10.6 mmol) was treated with LDA (26.5 mmol) and then with pyridinium iodide **2** (3.2 g, 10.6 mmol) to give a crude reaction mixture, which was separated by flash chromatography (7:3:0.5 Et_2O–acetone–DEA). The initial elution afforded **methyl (1*RS*,2*RS*,6*RS*)-1-(methoxycarbonyl)-3-methyl-1,2,3,6-tetrahydro-2,6-methanoazocino[5,4-*b*]indole-5-(*E*)-acrylate (30)**: 0.6 g (15%); mp 269–270 °C (acetone); IR (KBr) 1670, 1720 (CO), 3400 (NH); ^1H NMR, see ref 37; ^{13}C NMR, Table I. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.85; H, 6.02; N, 7.65. Found: C, 68.72; H, 6.11; N, 7.54. Further elution gave **methyl (1*RS*,5*SR*,6*RS*)-6-(methoxycarbonyl)-2-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4-(*E*)-acrylate (28a)**: 1.2 g (31%); mp 288–290 °C (acetone); IR (KBr) 1690, 1725 (CO), 3400 (NH); ^1H NMR, see ref 37; ^{13}C NMR, Table I. Anal. Calcd for $C_{21}H_{22}N_2O_4 \cdot H_2O$: C, 67.19; H, 6.17; N, 7.46. Found: C, 67.10; H, 6.29; N, 7.42.

Condensation of Ester 27 with Pyridinium Iodide 2. Operating as above, from ester **27**[44] (1 g, 4.9 mmol), LDA (7.4 mmol), and pyridinium iodide **2** (1.5 g, 4.9 mmol) a nearly equimolecular mixture of tetracycles **31** and **29a** (0.6 g, 32%) was obtained after purification of the crude product by column chromatography (CH_2Cl_2). Both isomers were separated by flash chromatography (99:1 Et_2O–DEA and 6:1:2 Et_2O–EtOH–DEA). **Methyl (1*RS*,2*RS*,6*RS*)-1-(methoxycarbonyl)-3,7-dimethyl-1,2,3,6-tetrahydro-2,6-methanoazocino[5,4-*b*]indole-5-(*E*)-acrylate (31)**: mp 244–245 °C (acetone); IR (KBr) 1680, 1725 (CO); ^1H NMR 1.88 and 2.60 (2 dm, J = 13 Hz, 2 H, 14-H), 3.09 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.74 (s, 3 H, NCH_3), 3.96 (m, 2 H, 3- and 15-H), 4.06 (d, J = 1.4 Hz, 1 H, 16-H), 5.67 (d, J = 15 Hz, 1 H, 18-H), 6.44 (s, 1 H, 21-H), 7.10–7.30 (m, 4 H, indole and 19-H), 7.50 (d, J = 8 Hz, 1 H, 9-H); ^{13}C NMR, Table I. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.35; N, 7.36. Found: C, 69.45; H, 6.38; N, 7.34. **Methyl (1*RS*,5*SR*,6*RS*)-6-(methoxycarbonyl)-2,11-dimethyl-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4-(*E*)-acrylate (29a)**: mp 205–206 °C (acetone); IR (KBr) 1690, 1710 (CO); ^1H NMR 1.98 (dt, J = 13 and 3.2 Hz, 1 H, 14-H), 2.55 (dt, J = 13 and 2.8 Hz, 1 H, 14-H), 3.11 (s, 3 H, NCH_3), 3.25 (br, 1 H, 15-H), 3.72 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.80 (s, 3 H, NCH_3), 4.01 (d, J = 1 Hz, 1 H, 16-H), 4.42 (t, 1 H, 3-H), 5.65 (d, J = 15 Hz, 1 H, 18-H), 6.29 (s, 1 H, 21-H), 7.10–7.30 (m, 4 H, indole and 19-H), 7.55 (d, J = 7 Hz, 1 H, 9-H); ^{13}C NMR, Table I. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.35; N, 7.36. Found: C, 69.46; H, 6.40; N, 7.31.

Methyl (1*RS*,5*SR*,6*RS*)- and (1*RS*,5*SR*,6*SR*)-2-(2-Hydroxyethyl)-6-(methoxycarbonyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4-(*E*)-acrylate (33a and 33b). Operating as above, from ester **26** (2 g, 10.6 mmol), LDA (26.4 mmol), and pyridinium bromide **3** (3.5 g, 10.6 mmol) a 3:1 mixture of tetracycles **33a** and **33b** (0.5 g, 12%) was obtained after column chromatography (AcOEt). **33a**: ^1H NMR, see ref 37; ^{13}C NMR, Table I. **33b**: mp 220–222 °C (acetone–Et_2O); IR (KBr) 1670, 1725 (CO), 3200 (NH); ^1H NMR, see ref 37; ^{13}C NMR, Table I. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.66; H, 6.10; N, 7.06. Found: C, 66.41; H, 6.25; N, 6.91.

Methyl (1*RS*,5*SR*,6*RS*)-2-(2-Acetoxyethyl)-6-(methoxycarbonyl)-11-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4-(*E*)-acrylate (34a). Operating as above, from ester **27** (2 g, 9.8 mmol), LDA (14.7 mmol), and pyridinium bromide **3** (3.2 g, 9.8 mmol) a nearly equimolecular mixture of tetracycles **34a** and **34b** (0.45 g, 10%) was obtained after flash chromatography (99:1 Et_2O–DEA and 6:1:2 Et_2O–EtOH–DEA). Column chromatography (CH_2Cl_2) allowed the isolation of pure **34a**: IR (KBr) 1690, 1730 (CO); ^1H NMR 1.90 (dt, J = 13 and 3 Hz, 1 H, 14-H), 2.06 (s, 3 H, CH_3CO), 2.55 (dm, J = 13 Hz, 1 H, 14-H), 3.26 (br, 1 H, 15-H), 3.50 (m, 2 H, 5-H), 3.71 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.00 (s, 1 H, 16-H), 4.14 (m, 1 H, 6-H), 4.32 (m, 1 H, 6-H), 4.55 (t, 1 H, 3-H), 5.70 (d, J = 15 Hz, 1 H, 18-H), 6.28 (s, 1 H, 21-H), 7.05–7.25 (m, 4 H, indole and 19-H), 7.48 (d, J = 7.6 Hz, 1 H, 9-H); ^{13}C NMR, Table I. Anal. Calcd for $C_{25}H_{28}N_2O_6 \cdot H_2O$: C, 63.82; H, 6.42; N, 5.95. Found: C, 63.45; H, 6.30; N, 5.76.

(42) (a) Prepared by reaction of 2-indoleacetic acid[42b] with diazomethane. (b) Katritzky, A. R.; Akutagawa, K. *J. Am. Chem. Soc.* **1986**, *108*, 6808.

(43) Jackson, R. W. *J. Biol. Chem.* **1930**, *88*, 660.

(44) Chapman, R. F.; Phillips, N. I. J.; Ward, R. S. *Tetrahedron* **1985**, *41*, 5229.

(±)-Vinoxine (7b) and (±)-16-Epivinoxine (7a). A suspension of tetracycle **6a** (0.35 g, 0.88 mmol) in 4 N aqueous HCl (16 mL) was heated at 100 °C for 2 h and then evaporated. The residue was dissolved in a 1.5 N MeOH solution of dry HCl (24 mL) and stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in MeOH (10 mL), treated with $NaBH_4$ (0.28 g, 8.7 mmol) at 0 °C, and stirred at this temperature for 1 h. The solvent was evaporated, and the residue was dissolved in H_2O and extracted with Et_2O. The ethereal layers were extracted with 5% aqueous HCl, and the acidic aqueous phase was basified with solid Na_2CO_3 and extracted with Et_2O. The organic extracts were dried and evaporated to give a mixture of **7b** and **7a**, 90 mg (30%). Both isomers were separated by column chromatography. Elution with AcOEt gave 16-epivinoxine (**7a**): IR and ^1H NMR, see ref 15; ^{13}C NMR, Table II. Elution with 99:1 AcOEt–DEA gave vinoxine (**7b**): IR and ^1H NMR, see ref 13; ^{13}C NMR, Table II.

Operating as above from tetracycle **6b** (0.27 g, 0.68 mmol), vinoxine (**7b**, 75 mg, 32%) was obtained after purification by column chromatography (99:1 AcOEt–DEA).

Methyl (1*RS*,5*SR*,6*RS*)- and (1*RS*,5*SR*,6*SR*)-4-(*E*)-Ethylidene-2,7-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-6-carboxylate (14a and 14b). Operating as above, from tetracycles **10a,b** (0.5 g, 1.3 mmol), 4 N aqueous HCl (25 mL), 1.5 N MeOH solution of dry HCl (40 mL), and $NaBH_4$ (0.4 g, 12 mmol), a mixture of ethylidene derivatives **14a** and **14b** (0.15 g, 30%) was obtained after purification by column chromatography (AcOEt). **14b**: The picrate melted at 207–210 °C (MeOH); IR and ^1H NMR, see ref 25. Anal. Calcd for $C_{26}H_{27}N_5O_9$: C, 56.42; H, 4.91; N, 12.56. Found: C, 56.37; H, 5.00; N, 12.70.

(*E*)-Ethylidene Derivatives 15b and 15c. Operating as above, from tetracycles **11a,b** (1.5 g, 3.3 mmol), 4 N aqueous HCl (66 mL), 1.5 N MeOH solution of dry HCl (95 mL), and $NaBH_4$ (1 g, 31 mmol) a crude residue was obtained and then was chromatographed. Elution with 99:1 AcOEt–DEA afforded **4-(*E*)-ethylidene-2-(2-hydroxyethyl)-7-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (15c)**: 0.2 g (20%); mp 130–132 °C (acetone–Et_2O); IR ($CHCl_3$) 3100–3600 (OH); ^1H NMR 1.69 (dd, J = 7 and 2 Hz, 3 H, 18-H), 1.92 and 2.16 (2 dt, 2 H, 14-H), 2.60 (d, J = 16 Hz, 1 H, 16-Hβ), 2.74 (dm, J = 13 Hz, 1 H, 21-H_{ax}), 2.90 (d, J = 13 Hz, 1 H, 21-H_{eq}), 3.02 (dd, J = 16 and 6 Hz, 1 H, 16-Hα), 3.38 (m, 1 H, 15-H), 3.62 (s, 3 H, NCH_3), 4.25 (t, 1 H, 3-H), 5.28 (qd, 1 H, 19-H), 7.08–7.25 (m, 2 H, indole), 7.28 (dd, 1 H, 12-H), 7.48 (dd, 1 H, 9-H); ^{13}C NMR, Table II. Anal. Calcd for $C_{19}H_{24}N_2O\cdot{}^1/_3H_2O$: C, 75.49; H, 8.14; N, 9.27. Found: C, 75.31; H, 7.99; N, 9.19. Elution with 95:5 AcOEt–DEA gave a mixture of **methyl (1*RS*,5*SR*,6*RS*)- and (1*RS*,5*SR*,6*SR*)-4-(*E*)-ethylidene-2-(2-hydroxyethyl)-7-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-6-carboxylate (15a and 15b),** 0.4 g (32%). Major component **15b**: IR and ^1H NMR, see ref 25; ^{13}C NMR, Table II. The picrate melted at 95–98 °C (MeOH). Anal. Calcd for $C_{27}H_{29}N_5O_{10}\cdot{}^3/_2H_2O$: C, 53.11; H, 5.24; N, 11.47. Found: C, 53.07; H, 4.86; N, 11.71.

4-(*E*)-Ethylidene-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (16c). Operating as above, from tetracycle **12a** (0.25 g, 0.7 mmol), 4 N aqueous HCl (12 mL), 1.5 N MeOH solution of dry HCl (20 mL), and $NaBH_4$ (0.2 g, 6.2 mmol) tetracycle **16c** was obtained after purification by column chromatography (98:2 AcOEt–DEA): 0.13 g (75%); mp 187–190 °C (acetone); IR (KBr) 3400 (NH); ^1H NMR, see ref 25; ^{13}C NMR, Table II. Anal. Calcd for $C_{17}H_{20}N_2\cdot{}^1/_2H_2O\cdot{}^1/_2C_3H_6O$: C, 76.55; H, 8.26; N, 9.65. Found: C, 76.66; H, 7.90; N, 9.89.

4-(*E*)-Ethylidene-2,7-dimethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (14c). A suspension of tetracycles **10a,b** (2.6 g, 6.8 mmol) in 4 N aqueous HCl (140 mL) was heated at 100 °C for 6 h and then evaporated. The residue was dissolved in MeOH (150 mL), treated with $NaBH_4$ (2 g, 62 mmol) at 0 °C, and stirred at this temperature for 1 h. The usual workup followed by column chromatography (99:1 AcOEt–DEA) gave tetracycle **14c**: 0.88 g (44%); mp 137–140 °C (acetone–Et_2O); ^1H NMR 1.67 (dd, J = 6.8 and 2 Hz, 3 H, 18-H), 1.88 (ddd, J = 12.4, 3, and 2.8 Hz, 1 H, 14-H), 2.12 (ddd, J = 12.4, 3.4, and 3.2 Hz, 1 H, 14-H), 2.28 (s, 3 H, NCH_3), 2.66 (d, J = 17.4 Hz, 1 H, 16-Hβ), 2.64 (dt, J = 12.8 and 2 Hz, 1 H, 21-H_{ax}), 2.83 (d, J = 12.8 Hz, 1 H, 21-H_{eq}), 3.52 (dd, J = 17.4 and 6.6 Hz, 1 H, 16-Hα), 3.33 (m, 1 H, 15-H), 3.58 (s, 3 H, NCH_3), 4.19 (t, 1 H, 3-H), 5.30 (qd, J = 6.8 and 2 Hz, 1 H, 19-H), 7.15 (m, 3 H, indole), 7.55 (dd, 1 H, 9-H); ^{13}C NMR, Table II. Anal. Calcd for $C_{18}H_{22}N_2\cdot{}^1/_3H_2O$: C, 79.41; H, 8.33; N, 10.29. Found: C, 79.30; H, 8.23; N, 10.03.

4-(*E*)-Ethylidene-2-(2-hydroxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (17c). Operating as above, from tetracycle **13a** (90 mg, 0.2 mmol), 4 N aqueous HCl (30 mL), and $NaBH_4$ (0.8 g, 25 mmol), tetracycle **17c** was obtained after column chromatography (95:5 AcOEt–DEA): 27 mg (46%); IR ($CHCl_3$) 3240 (OH), 3460 (NH); ^1H NMR 1.68 (dd, J = 7 and 1.8 Hz, 3 H, 18-H), 1.91 and 2.12 (2 dt, 2 H, 14-H), 2.28 (m, 1 H, 5-H), 2.55 (d, J = 15.5 Hz, 1 H, 16-Hβ), 2.80 (dm, J = 12 Hz, 1 H, 21-H_{ax}), 2.97 (d, J = 12 Hz, 1 H, 21-H_{eq}), 3.04 (m, 1 H, 5-H), 3.17 (d, J = 15.5 Hz, 1 H, 16-Hα), 3.30 (m, 1 H, 15-H), 3.60 (m, 2 H, 6-H), 4.25 (t, 1 H, 3-H), 5.28 (qd, 1 H, 19-H), 7.05–7.35 (m, 3 H, indole), 7.45 (dd, 1 H, 9-H), 8.05 (br s, 1 H, NH); ^{13}C NMR, Table II. The picrate melted at 137–140 °C (acetone–Et_2O). Anal. Calcd for $C_{24}H_{25}N_5O_8\cdot{}^3/_2H_2O$: C, 53.43; H, 5.20; N, 13.01. Found: C, 53.05; H, 4.90; N, 12.91.

Methyl (1*RS*,5*SR*,6*RS*)- and (1*RS*,5*SR*,6*SR*)-4-(*E*)-Ethylidene-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6-carboxylate (32a and 32b). Operating as in the preparation of compounds **7**, from tetracycle **28a** (1.2 g, 3.28 mmol), 4 N aqueous HCl (60 mL), 1.5 N MeOH solution of dry HCl (120 mL), and $NaBH_4$ (1 g, 31 mmol), a 3:1 mixture of ethylidene derivatives **32a** and **32b** (0.4 g, 40%) was obtained after flash chromatography (98:2 AcOEt–DEA). **32a**: IR (KBr) 1710 (CO); ^1H NMR, see ref 37; ^{13}C NMR, Table II. The picrate melted at 197–198 °C (acetone–Et_2O). Anal. Calcd for $C_{25}H_{25}N_5O_9$: C, 55.64; H, 4.67; N, 12.98. Found: C, 55.24; H, 4.32; N, 13.36. **32b**: ^1H NMR, see ref 37; ^{13}C NMR, Table II.

Methyl (1*RS*,5*SR*,6*SR*)-4-(*E*)-Ethylidene-2-(2-hydroxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]-indole-6-carboxylate (35b). Operating as above, from tetracycles **33** (1.2 g, 3 mmol), 4 N aqueous HCl (60 mL), 1.5 N MeOH solution of dry HCl (100 mL), and $NaBH_4$ (1 g, 31 mmol), a mixture of ethylidene derivatives **35a** and **35b** (0.52 g, 51%) was obtained. Flash chromatography (95:5 AcOEt–DEA) allowed the isolation of pure **35b**: IR (KBr) 1710 (CO); ^1H NMR, see ref 37; ^{13}C NMR, Table II. The oxalate melted at 128–129 °C (acetone–MeOH). Anal. Calcd for $C_{22}H_{26}N_2O_7\cdot H_2O$: C, 58.90; H, 6.29; N, 6.20. Found: C, 58.79; H, 5.95; N, 6.03.

Methyl 2-(1-Methyl-2-indolyl)-5-(1-methyl-2-oxo-1,2-dihydro-5-pyridyl)-2,4-pentadienoate (20a). A solution of ester **8** (0.9 g, 4.4 mmol) in THF (20 mL) was added to a suspension of $NaOCH_3$ (22 mmol) in THF (40 mL) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. Then, pyridinium iodide **2** (2 g, 6.5 mmol) was added in portions, and the stirring was continued at room temperature for 2 h. The reaction mixture was quenched with H_2O and extracted with AcOEt. Evaporation of the organic extracts left a residue which was chromatographed ($CHCl_3$) to give pyridone **20a**: 0.9 g (59%); mp 137–139 °C (acetone–Et_2O); UV λ_{max} 200 nm (log ϵ = 4.67), 279 (4.03), 342 (4.37); IR ($CHCl_3$) 1645, 1690 (CO); ^1H NMR (400 MHz) 3.52 (s, 3 H, NCH_3), 3.56 (s, 3 H, NCH_3), 3.77 (s, 3 H, OCH_3), 6.46 (d, J = 0.8 Hz, 1 H, indole 3-H), 6.49 (dt, J = 9.5, 0.5, and 0.5 Hz, 1 H, pyridone 3-H), 6.61 (dd, J = 15.5 and 11 Hz, 1 H, 4-H), 6.73 (dt, J = 15.5, 0.5, and 0.5 Hz, 1 H, 5-H), 7.14 (ddd, J = 7.9, 7, and 0.8 Hz, 1 H, indole 5-H), 7.26 (ddd, J = 8.3, 7, and 1.3 Hz, 1 H, indole 6-H), 7.33 (d, J = 2.6 Hz, 1 H, pyridone 6-H), 7.35 (dq, J = 8.3, 0.8, 0.8, and 0.8 Hz, 1 H, indole 7-H), 7.39 (dd, J = 9.5 and 2.6 Hz, 1 H, pyridone 4-H), 7.64 (ddd, J = 7.9, 1.3, and 0.8 Hz, 1 H, indole 4-H), 7.77 (dd, J = 11 and 0.5 Hz, 1 H, 3-H); ^{13}C NMR 30.4 (indole NCH_3), 37.5 (pyridone NCH_3), 52.0 (OCH_3), 104.1 (indole C-3), 109.3 (indole C-7), 116.0 (C-2), 119.6 (indole C-4), 120.7 (indole C-5), 120.9 (C-4), 121.8 (indole C-6), 122.3 (pyridone C-3), 122.5 (pyridone C-5), 127.7 (indole C-3a), 133.6 (indole C-2), 136.4 (C-3), 136.5 (C-5), 137.7 (indole C-7a), 138.7 (pyridone C-4), 144.7 (pyridone C-6), 162.1 (pyridone C-2), 167.1 (CO); MS, m/e (rel intensity) 348 (69, M^+), 333 (3), 289 (43). Anal. Calcd for $C_{21}H_{20}N_2O_3\cdot C_3H_6O$: C, 70.93; H, 6.34; N, 6.89. Found: C, 70.82; H, 5.95; N, 7.06.

Methyl 6-Acetyl-7-(methylamino)-2-(1-methyl-2-indolyl)-2,4,6-heptatrienoate (22a). Operating as above, from ester **8** (0.9 g, 4.4 mmol), $NaOCH_3$ (22 mmol), and pyridinium

iodide **21a**[45] (2.3 g, 9.1 mmol) compound **22a** was obtained after purification by column chromatography (Al_2O_3, AcOEt): 0.43 g (28%); IR ($CHCl_3$) 1570 (C=C), 1630, 1680 (CO); ^1H NMR 2.23 (s, 3 H, CH_3CO), 2.99 (d, J = 5.2 Hz, 3 H, NCH_3), 3.55 (s, 3 H, OCH_3), 3.73 (s, 3 H, NCH_3), 6.10 (dd, J = 15 and 11 Hz, 1 H, 4-H), 6.43 (d, J = 0.8 Hz, 1 H, indole 3-H), 7.04 (d, J = 15 Hz, 1 H, 5-H), 7.18 (d, J = 14 Hz, 1 H, 7-H), 7.06–7.26 (m, 2 H, indole 5- and 6-H), 7.33 (dm, J = 8 Hz, 1 H, indole 7-H), 7.62 (dm, J = 7.2 Hz, 1 H, indole 4-H), 7.79 (dd, J = 11 and 0.8 Hz, 1 H, 3-H), 10.71 (br s, 1 H, NH); ^{13}C NMR 27.1 (CH_3CO), 30.5 (indole NCH_3), 36.5 (NCH_3), 52.0 (OCH_3), 103.0 (indole C-3), 105.5 (C-6), 109.0 (indole C-7), 113.5 (C-4), 116.8 (C-2), 119.5 (indole C-4), 121.0 (indole C-5), 122.0 (indole C-6), 128.0 (indole C-3a), 135.5 (indole C-2), 138.0 (indole C-7a), 142.5 (C-5), 148.0 (C-3), 155.0 (C-7), 168.2 (CO), 197.0 (CO); MS, m/e (rel intensity) 337 (8, M^+), 322 (9), 307 (2), 277 (1), 217 (0.7).

Methyl 6-Acetyl-7-(benzylamino)-2-(1-methyl-2-indolyl)-2,4,6-heptatrienoate (22b). Operating as above, from ester **8** (0.9 g, 4.4 mmol), $NaOCH_3$ (22 mmol), and pyridinium chloride **21b**[46] (2.2 g, 9.1 mmol), compound **22b** was obtained after purification by column chromatography (Al_2O_3, $CHCl_3$): 0.4 g (22%); IR ($CHCl_3$) 1630, 1670 (CO); ^1H NMR (60 MHz) 2.28 (s, 3 H, CH_3CO), 3.60 (s, 3 H, OCH_3), 3.83 (s, 3 H, NCH_3), 4.50 (d, J = 5.3 Hz, 2 H, CH_2N), 6.16 (dd, J = 15 and 11 Hz, 1 H, 4-H), 6.50 (s, 1 H, indole 3-H), 7.03–7.83 (m, 11 H, Ar-H), 7.89 (d, J = 11 Hz, 3-H); ^{13}C NMR 27.1 (CH_3CO), 30.1 (indole NCH_3), 51.6 (NCH_2), 52.9 (OCH_3), 103.2 (indole C-3), 105.7 (C-6), 109.1 (indole C-7), 114.2 (C-4), 116.9 (C-2), 119.1 (indole C-4), 120.3 (indole C-5), 121.1 (indole C-6), 126.8 and 126.9 (phenyl C-2 and C-4), 127.7 (indole C-3a), 127.8 (phenyl C-3 and C-5), 134.6 (indole C-2), 136.2 (phenyl C-1), 137.3 (indole C-7a), 141.6 (C-5), 147.4 (C-3), 152.7 (C-7), 167.4 (CO), 196.5 (CO); MS, m/e (rel intensity) 414 (3, M^+), 399 (3), 355 (5), 91 (100).

Methyl 3-{5-[(*E*)-2-(Methoxycarbonyl)vinyl]-1-methyl-1,2-dihydro-2-pyridyl}-2-indoleacetate (23a). Ester **9** (1 g, 5.3 mmol) in MeOH (20 mL) was added to a solution of $NaOCH_3$ (11 mmol) in MeOH (20 mL) at 0 °C, and the mixture was stirred at this temperature for 0.5 h. A solution of pyridinium salt **2** (1.34 g, 4.4 mmol) in MeOH (10 mL) was added, and the stirring was continued at room temperature for 16 h. The resulting precipitate was filtered to give **23a**: 0.99 g (61%); mp 157–159 °C (MeOH); IR (KBr) 1670, 1720 (CO), 3350 (NH); ^1H and ^{13}C NMR, see ref 33. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.85; H, 6.01; N, 7.65. Found: C, 68.59; H, 6.19; N, 7.75.

3-{5-[(*E*)-2-(Methoxycarbonyl)vinyl]-1-methyl-1,2-dihydro-2-pyridyl}indole (23b). The sodium salt of indole, prepared from indole (1 g, 8.5 mmol) and $NaOCH_3$ (10 mmol) in MeOH (20 mL), was allowed to react as above with pyridinium iodide **2** (2.6 g, 8.5 mmol) at room temperature for 6 h. The solvent was removed, and the residue was dissolved in H_2O and extracted with AcOEt. Evaporation of the organic extracts left a residue, which was chromatographed (AcOEt) to give **23b** (trace amounts of **24b**): 1 g (50%); IR ($CHCl_3$) 1680 (CO), 3460 (NH); ^1H and ^{13}C NMR, see ref 33; MS, m/e (rel intensity 294 (56, M^+), 279 (56).

3-{5-[(*E*)-2-(Methoxycarbonyl)vinyl]-1-methyl-1,2-dihydro-2-pyridyl}-2-methylindole (23c). Operating as above, from 2-methylindole (1 g, 7.6 mmol), $NaOCH_3$ (10 mmol), and pyridinium iodide **2** (2.3 g, 7.6 mmol) 1,2-dihydropyridine **23c** was obtained after filtration of the reaction mixture: 2.07 g (80%); mp 183–185 °C (MeOH–acetone); IR (KBr) 1670 (CO), 3280 (NH); ^1H and ^{13}C NMR, see ref 33. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.02; H, 6.49; N, 9.09. Found: C, 74.12; H, 6.62; N, 8.93.

3-(5-Acetyl-1-methyl-1,2-dihydro-2-pyridyl)-2-methylindole (23d). The sodium salt of 2-methylindole, prepared from 2-methylindole (0.5 g, 3.8 mmol) and $NaOCH_3$ (9 mmol) in MeOH (20 mL), was allowed to react as above with pyridinium iodide **21a** (1 g, 3.8 mmol) at room temperature for 16 h. Extractive workup with AcOEt gave 1,2-dihydropyridine **23d**: 1 g (95%); mp 185–188 °C (acetone–MeOH); IR (KBr) 1640 (CO), 3250 (NH); ^1H and ^{13}C NMR, see ref 33; MS, m/e (rel intensity) 266 (2.7, M^+), 265 (3.5). Anal. Calcd for $C_{17}H_{18}N_2O \cdot {}^1/_4H_2O$: C, 75.41; H, 6.83; N, 10.35. Found: C, 75.67; H, 6.80; N, 10.18.

Reaction of 2-Methylindole with Pyridinium Iodide 21c. Operating as above, from 2-methylindole (0.5 g, 3.8 mmol), $NaOCH_3$ (4.5 mmol), and pyridinium iodide **21c**[47] a residue was obtained and was chromatographed. Elution with 4:6 C_6H_6-AcOEt gave **3-(3-formyl-1-methyl-1,4-dihydro-4-pyridyl)-2-methylindole (24e)**: 0.14 g (13%); mp 200–203 °C (acetone–MeOH); IR (KBr) 1670 (CO), 3300 (NH); ^1H and ^{13}C NMR, see ref 33. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 76.40; H, 6.40; N, 11.25. Elution with AcOEt gave **3-(5-formyl-1-methyl-1,2-dihydro-2-pyridyl)-2-methylindole (23e)**: 0.24 g (26%); mp 218–220 °C (acetone–MeOH); IR (KBr) 1615 (CO), 3200 (NH); ^1H and ^{13}C NMR, see ref 33. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11: Found: C, 75.88; H, 6.32; N, 10.85.

1-{3-[(*E*)-2-(Methoxycarbonyl)vinyl]-1-methyl-1,4-dihydro-4-pyridyl}-3-methylindole (25). Operating as above, from 3-methylindole (1 g, 7.6 mmol), $NaOCH_3$ (10 mmol), and pyridinium salt **2** (2.3 g, 7.6 mmol), 1,4-dihydropyridine **25** was obtained after filtration of the reaction mixture: 1.2 g (51%); mp 160–162 °C (MeOH); IR (KBr) 1680 (CO); ^1H and ^{13}C NMR, see ref 33. Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.02; H, 6.49; N, 9.09. Found: C, 73.92; H, 6.55; N, 9.05.

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(45) Ginsburg, S.; Wilson, I. B. *J. Am. Chem. Soc.* **1957**, *79*, 481.
(46) Anderson, A. G.; Berkelhammer, G. *J. Am. Chem. Soc.* **1958**, *80*, 992.
(47) Panizzon, L. *Helv. Chim. Acta* **1941**, *24*, 24.