Studies on the Synthesis of Mavacurine-Type Indole Alkaloids. First Total Synthesis of (±)-2,7-Dihydropleiocarpamine

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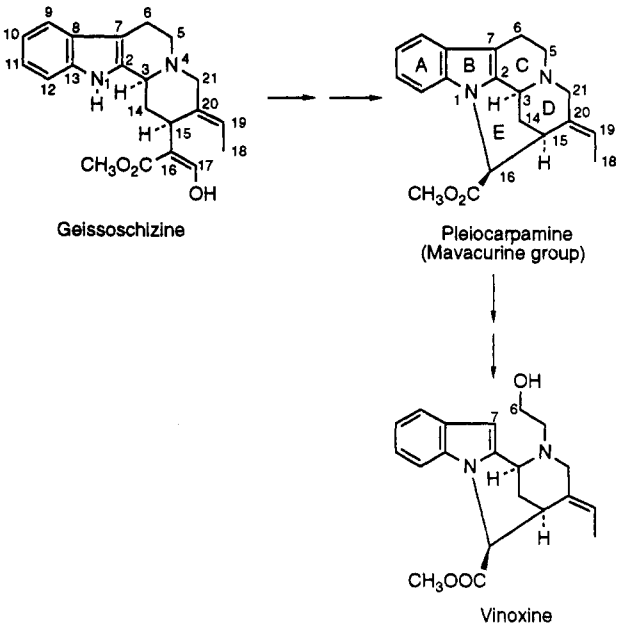
Closure of the six-membered C ring of pentacyclic mavacurine-type alkaloids from suitably substituted tetracyclic substructures embodying rings ABDE of these alkaloids, either by electrophilic cyclization upon the indole 3-position or by intramolecular alkylation of the piperidine nitrogen, failed. In contrast, 6a-homopleiocarpamine (**45**) has been synthesized from dithioacetal **42** by an electrophilic cyclization involving the closure of the seven-membered C ring. The first total synthesis of the alkaloid 2,7-dihydropleiocarpamine (**58**) has been achieved by photocyclization of the tetracyclic chloroacetamide **54** as the key step. The required tetracyclic ABDE ring systems were prepared by a straightforward sequence consisting of nucleophilic addition of a 1-indoleacetatic ester enolate to the γ position of a pyridinium salt, acid cyclization of the resulting 1,4-dihydropyridine, and final elaboration of the (*E*)-ethylidene substituent. An alternative synthesis of the tetracyclic alkaloid vinoxine (**10a**) is also reported.

The mavacurine-type alkaloids[1] (C-mavacurine, pleiocarpamine) constitute a small subgroup of Corynanthean indole alkaloids (C_{4f} skeletal variation, according to the Hesse's classification)[2] and are structurally characterized by the presence of a bond between N-1 and C-16[3] giving an additional ring E. Consequently, they incorporate a bridged pentacyclic 2*H*-2,12-methanoindolo[2,3-*a*]quinolizine system, corresponding to the 1,16-cyclocorynan stereoparent. Other characteristic structural features are the presence of an oxidized one-carbon substituent (CH_2-OH or CO_2CH_3) at C-16 and a two-carbon chain, usually an *E*-configurated ethylidene, at C-20.

Biogenetically the mavacurine alkaloids are formally derived from geissoschizine (Scheme I), a key intermediate along the biosynthetic pathway of monoterpenoid indole alkaloids, although the details of the formation of the key bond N-1/C-16 (closure of the E ring) still remain unknown.[4] The tetracyclic alkaloid vinoxine[5] would be formed by further hydrolytic cleavage of the tryptamine C-6/C-7 bond. Pleiocarpamine also constitutes one half of several bisindole alkaloids.[6]

The additional N-1/C-16 bond causes these molecules to adopt a hemispherical shape. Consequently, the groups inside the sphere (β-face) exhibit strong transannular interactions whereas the α-face is easily accessible to chemical reagents.[1]

Scheme I. Biosynthesis and Biogenetic Numbering



These alkaloids have received little attention from a synthetic standpoint: only the total synthesis of (±)-C-mavacurine, via (±)-16-epipleiocarpamine and (±)-nor-mavacurine, has been reported so far.[7] Additionally, the partial synthesis of (+)-16-epipleiocarpamine from (+)-geissoschizine[8] and several syntheses of pentacyclic model structures[9-11] and 19,20-dihydro analogs[9,12] have been reported. All these synthetic approaches (Scheme II) involve, as the key reaction, the formation of N-1/C-16

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(1) 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.

(2) (a) Kisakürek, M. V.; Hesse, M. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 2. (b) Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *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 tetracyclic and pentacyclic compounds. Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(4) (a) Bisset, N. G. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 3. (b) Atta-ur-Rahman; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, 1983.

(5) Voticky, Z.; Grossmann, E.; Potier, P. *Collect. Czech. Chem. Commun.* **1977**, *42*, 548.

(6) (a) Cordell, G. A.; Saxton, J. E. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1981; Vol. XX, Chapter 1. (b) Cordell, G. A. In *The Chemistry of Heterocyclic Compounds. Indoles Part 4, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter XI.

(7) Calverley, M. J.; Banks, B. J.; Harley-Mason, J. *Tetrahedron Lett.* **1981**, *22*, 1635.

(8) Sakai, S.; Shinma, N. *Heterocycles* **1976**, *4*, 985.

(9) O'Rell, D. D.; Lee, F. G. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1972**, *94*, 3205.

(10) Calverley, M. J.; Harley-Mason, J.; Quarrie, S. A.; Edwards, P. D. *Tetrahedron* **1981**, *37*, 1547.

(11) Calverley, M. J. *J. Chem. Res., Synop.* **1983**, 190.

(12) (a) Sakai, S.; Shinma, N. *Chem. Pharm. Bull.* **1974**, *22*, 3013. (b) Koike, T.; Takayama, H.; Sakai, S. *Chem. Pharm. Bull.* **1991**, *39*, 1677.

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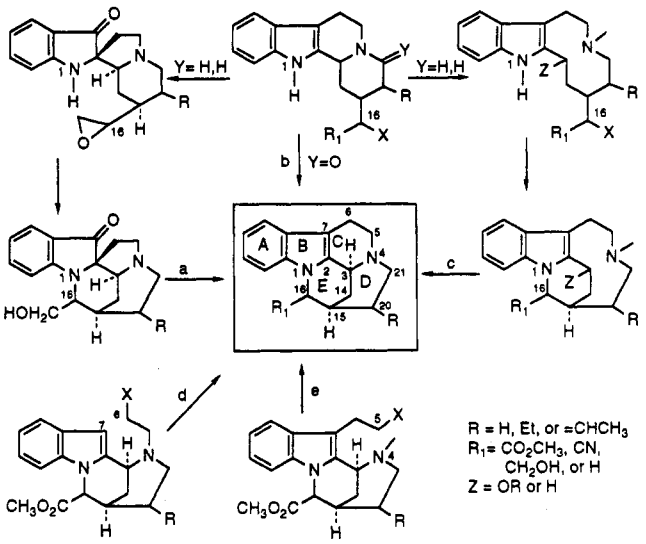
Scheme II. Synthetic Strategies



bond, either from a tetracyclic pseudoindoxyl derivative followed by a skeletal rearrangement of the resulting pentacyclic norfluorocurine system (via a)[9,13] or from an indolo[2,3-*a*]quinolizidine derivative. In the latter case, closure of the E ring can occur either directly (via b)[10] or, in most cases, after C/D ring cleavage (solvolytic[8,10,12] or reductive[7,11]) with final reclosing of the C-3/N-4 bond by transannular cyclization (solvolytic[8,12] or oxidative[7,11]; via c). These syntheses lead to products with a H-15/H-16 trans-relationship, i.e., the same relative stereochemistry as in C-mavacurine but the opposite of pleiocarpamine.

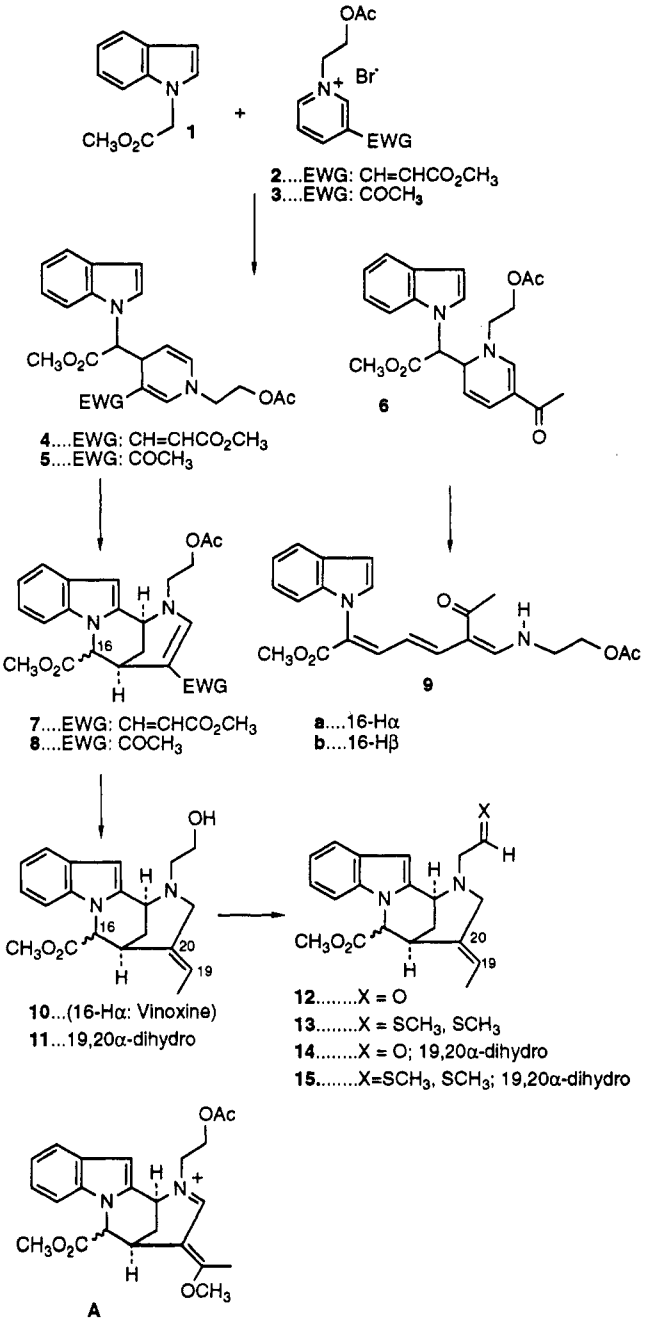
In this paper, we report a new synthetic entry to the alkaloids of the mavacurine group, based on the closure of the C ring in the last synthetic steps from an appropriately N-4-substituted tetracyclic system embodying rings ABDE of the mavacurine alkaloids (bond formed C-6/C-7; via d). We also report the results obtained when developing an alternative strategy consisting in the closure of the C ring in the key step by formation of N-4/C-5 bond (via e).

Results and Discussion

In a previous work we have reported[14] the first total synthesis of the alkaloid vinoxine (**10a**), a tetracyclic analog of pleiocarpamine having a 2-hydroxyethyl chain at the piperidine nitrogen, by reaction of the enolate derived from methyl 1-indoleacetate (**1**) with pyridinium salt **2** followed by acid cyclization of the intermediate 1,4-dihydropyridine **4** and further elaboration of the (*E*)-ethylidene substituent from the resulting tetracyclic compound **7** (Scheme III).[15] This methodology, based on the nucleophilic addition of an indole-containing enolate to the γ-position of a pyridinium salt followed by cyclization of the resulting 1,4-dihydropyridine, has successfully been used for the synthesis of bridged indole alkaloids belonging to several structural types.[14,16,17]

Vinoxine (**10a**) itself or some derivative of this alkaloid with the appropriate functionality at C-6 were envisaged

Scheme III



as immediate precursors of pentacyclic mavacurine alkaloids by formation of the C-6/C-7 bond by means of electrophilic cyclization upon the indole 3-position. For this reason, we initially explored an alternative synthesis of vinoxine based on the above synthetic strategy but using a pyridinium salt bearing an acetyl group, instead of acrylate, as the electron-withdrawing substituent at the β-position.[18] As expected, interaction of ester **1** with pyridinium bromide **3** in the presence of an excess of LDA

(13) For the rearrangement of the norfluorocurine to the normavacurine skeleton, see refs 1 and 10. This rearrangement implies the formation of the C-6/C-7 bond, the β-position of the indole ring (C-7) acting as an electrophilic center.

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

(15) All synthetic compounds are racemic. The schemes depict only the enantiomer bearing the natural configuration at C-15.

(16) Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 5089. (b) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 5340.

(17) Carbanion nucleophile additions to *N*-alkyl-β-acylpyridinium salts for alkaloid synthesis were 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 references cited therein. For a review, see: (c) Bennasar, M.-L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, *27*, 789. For more recent work, see: (d) Spitzner, D.; Arnold, K.; Stezowski, J. J.; Hildenbrand, T.; Henkel, S. *Chem. Ber.* **1989**, *122*, 2027. (e) Amann, R.; Spitzner, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1320. (f) Bennasar, M.-L.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 2835.

(18) For a preliminary report of this part of the work, see: Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 747.

(3 equiv),[19] followed by acidic treatment, afforded a mixture of tetracycle **8b** (25% yield; minor amounts of the corresponding C-16 epimer **8a** could be isolated in several runs) and the polyunsaturated amine **9** (10% yield). When the acidic treatment was omitted, a 3:1 mixture of 1,4-dihydropyridine **5** (which could be further cyclized to **8b**) and amine **9** was obtained in 20% yield. These results made evident that the pyridinium salt had undergone not only the expected γ attack but also, to some extent, α-attack to give a mixture of 1,2- and 1,4-dihydropyridines **6** and **5** respectively. Irreversible ring opening of the former promoted by the excess of base leads to **9**[20] whereas regiospecific acid-promoted cyclization of the latter affords **8**.

The elaboration of the (*E*)-ethylidene substituent[21] was effected in a stereoselective manner taking advantage of the vinylogous amide moiety of tetracycles **8** since it was known that 3-acetyl-2-piperideines can be stereoselectively elaborated into 3(*E*)-ethylidenepiperidines.[22] Thus, treatment of **8b** with $Me_3O^+BF_4^-$ gave the iminium intermediate **A** (not isolated), which was then treated with $NaBH_4$ to bring about 1,4-reduction, subsequent elimination of a methoxide ion, and further reduction of the resulting conjugated carbon-nitrogen double bond.[22a,b] As in its biogenetic origin, the *E*-configuration of the ethylidene chain is a consequence of its formation by reduction of an iminium cation conjugated to an exocyclic double bond. Finally, methanolysis of the acetate group gave (±)-16-epivinoxine (**10b**) in 30% overall yield from **8b**. When the same reaction sequence was carried out from **8a**, (±)-vinoxine (**10a**) was obtained in 20% yield.[23] These synthetic vinoxines were identical in all respects with those obtained by our previous route.[14] The relative configuration at C-16 in the above tetracycles, as well as in all tetracyclic and pentacyclic compounds prepared in this work, was determined from the coupling constants between H-15 and H-16 (3.4–6.6 Hz in series **a** and 0–1.8 Hz in series **b**) and by the shielding of C-14 in series **b** due to the γ-effect induced by the methoxycarbonyl group (Tables I and II).

Closure of the C ring of mavacurine alkaloids by electrophilic cyclization upon the indole 3-position seemed to be *a priori* an easy task.[24] Initially we tried the direct cyclization of vinoxine (**10a**) under acidic conditions (BF_3·Et_2O). However, starting material or polymeric materials were obtained depending on the reaction conditions. Cyclizations involving trigonally hybridized electrophiles generated either from aldehydes **12a,b**, prepared by DMSO–TFAA oxidation of **10a** and **10b**,[25] or from the

Table I. ^{13}C NMR Data of Tetrahydro-2,6-methano[1,4]diazocinoindoles

	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-18	C-19	C-20	C-21	CO_2CH_3	other
8a	136.1	48.4	52.4	61.6	100.1	128.3	120.6	120.8	122.4	110.8	136.6	26.0	26.1	62.9	23.7	192.7	108.6	146.7	52.7, 170.3	20.7, 170.5
8b	134.5	48.9	52.5	61.8	99.5	127.7	120.5	120.8	122.4	109.3	136.8	22.6	27.4	60.3	23.8	192.2	110.5	147.2	52.3, 170.6	20.8, 170.8
19a	134.1	47.1	62.3	27.9	108.6	128.1	119.3	120.1	122.5	110.5	136.7	25.9	27.0	61.9	102.7	145.5	102.8	147.0	50.9, 52.6, 169.5, 171.4	41.2
19b	132.9	47.9	62.1	27.5	108.6	127.8	119.2	120.1	122.6	109.1	136.5	22.6	28.3	59.3	102.7	145.5	105.1	145.7	50.8, 52.4, 169.3, 171.4	41.1
20a	134.1	44.7	63.3	28.1	109.1	127.7	119.3	120.1	122.4	110.5	136.7	26.0	27.4	62.4	103.5	145.3	103.1	147.0	50.8, 52.5, 169.4, 170.3	–5.7, 18.0, 25.6, 57.3
20b	132.8	45.7	63.4	28.4	108.9	127.4	119.4	119.9	122.5	109.0	136.7	22.8	28.7	59.3	103.3	144.8	105.3	145.5	50.8, 52.3, 169.1, 170.3	–5.7, 18.0, 25.6, 57.4
21a	136.7	53.6	63.1	28.3	109.1	129.3	119.2	120.2	121.7	109.5	137.8	24.9	23.4	62.6	104.3	143.9	106.9	145.9	51.0, 52.6, 169.4, 170.0	43.2
21b	136.6	53.9	62.8	28.4	108.8	129.1	119.0	120.3	121.8	108.3	136.9	22.6	23.6	59.0	103.6	143.9	106.2	145.1	51.0, 52.7, 169.3, 170.0	41.0
22a	136.6	50.7	63.8	28.1	109.6	127.5	119.2	120.0	121.6	109.3	137.8	25.5	23.6	62.7	105.7	143.1	107.3	145.9	52.6, 52.7, 169.2, 170.4	–5.7, 18.2, 25.8, 59.4
33a	136.2	47.5	49.8	27.3, 61.2	100.0	128.1	120.7	120.9	122.4	110.6	136.5	25.9	27.6	62.1	103.8	144.8	103.5	146.9	50.9, 52.6, 169.5, 171.2	20.7, 170.1
33b	134.7	48.0	49.7	27.1, 61.2	99.5	127.8	120.6	120.9	122.4	109.1	136.5	22.8	28.9	59.0	103.6	144.8	105.5	145.5	50.9, 52.6, 169.2, 170.9	20.7, 170.9
34a	135.1	47.5	49.6	30.7, 59.0	99.9	128.1	120.5	120.8	122.2	111.5	136.6	25.7	27.5	62.0	102.7	145.4	104.9	147.3	50.8, 52.5, 169.6, 171.0	
34b	135.1	48.1	49.7	30.7, 59.0	99.6	127.8	120.5	120.8	122.4	109.0	136.4	22.8	28.9	58.9	102.7	145.3	104.9	145.8	50.8, 52.5, 169.4, 170.2	
35a	134.4	46.5			100.2	128.0	120.6	120.9	122.3	110.6	136.7	25.7	27.6	62.1	103.8	145.3	105.1	147.0	50.9, 52.5, 169.1, 170.8	56.7
35b	134.4	47.3			99.8	128.0	120.6	120.9	122.4	109.1	136.7	22.7	28.9	59.1	103.8	145.1	105.1	145.6	50.9, 52.5, 169.1, 170.8	56.7
46a	136.3	50.8			97.9	128.7	120.3	120.5	121.3	109.3	140.1	24.8	25.2	62.2	105.5	142.4	109.5	145.1	52.5, 169.0, 169.9	59.3
46b	136.3	51.6			97.9	128.7	120.4	120.5	121.5	108.4	139.1	22.4	25.4	59.7	104.3	142.6	109.4	144.5	52.5, 169.2, 169.7	57.5

(19) The use of stoichiometric quantities of LDA resulted in the recovery of the starting products.

(20) This kind of ring opening has been previously observed: (a) 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. (b) See also ref 14.

(21) 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.

(22) (a) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.* **1980**, *102*, 7971. (b) Mandal, S. B.; Pakrashi, S. C. *Heterocycles* **1987**, *26*, 1557. (c) Hämeilä, M.; Lounasmaa, M. *Acta Chem. Scand.* **1981**, *B35*, 217. (d) Sankar, P. S.; Das, S. K.; Giri, V. S. *Heterocycles* **1991**, *32*, 1109.

(23) (±)-Epivinoxine (**10b**) could be partially epimerized to a 3:2 mixture of **10b** and (±)-vinoxine (**10a**) by treatment with $NaOCH_3$ in refluxing MeOH.

(24) For the synthesis of indolo[2,3-a]quinolizidines using this strategy, see: Rubiralta, M.; Diez, A.; Bosch, J. *J. Org. Chem.* **1989**, *54*, 5591.

(25) The use of DMSO–DCC or DMSO–P_2O_5 proved to be inefficient, whereas under Swern conditions [DMSO–$(COCl)_2$] only products resulting from chlorination at the indole 3-position were detected.[25a] (a) For precedents, see ref 24 and references cited therein. See also: Tidwell, T. T. *Synthesis* **1990**, 857.

Table II. ^{13}C NMR Data of Hexahydro-2,6-methano[1,4]diazocinoindoles and Pentacyclic Mavacurine-Type Systems

	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-18	C-19	C-20	C-21	CO_2CH_3	other
11a	134.0	51.2	56.2	57.6	101.2	128.2	120.1	120.5	121.3	109.9	135.5	33.4	33.4	51.2	12.7	23.1	44.1	50.0	51.9	
11b	132.6	51.1	56.3	57.6	100.6	127.8	120.2	120.7	121.5	108.5	136.1	28.6	32.8	53.8	11.0	23.9	40.5	51.1	52.4, 172.1	
13a	133.3	51.6	59.1	52.1	101.6	128.0	120.2	120.5	121.4	109.9	136.5	30.5	30.7	59.8	12.3	122.1	133.7	55.6	51.9, 170.3	12.6, 12.7
13b	132.0	51.5	59.0	52.1	101.2	127.8	120.3	120.5	120.8	108.5	136.3	27.3	31.4	59.7	12.3	121.7	135.1	55.0	52.3, 171.2	12.6, 12.6
15a	134.2	51.1	59.0	51.8	100.8	128.2	120.1	120.4	121.1	109.8	135.5	33.2	33.2	51.7	12.5	23.1	43.7	50.9	52.3	12.6, 12.6
15b	132.6	51.0	59.0	52.1	100.3	127.8	120.1	120.6	121.4	108.3	136.1	28.3	32.6	53.7	11.0	23.8	40.2	51.8	52.2, 172.1	12.5, 12.6
24a	132.9	51.0	62.7	27.0	110.8	128.2	118.8	119.9	123.0	109.9	136.2	27.9	31.4	60.2	12.3	121.9	132.9	55.9	52.0, 170.2	41.1
25a	132.3	49.8	62.5	27.4	110.5	127.9	118.9	119.9	123.8	109.8	137.6	25.5	31.1	60.0	12.2	122.5	134.0	51.9	51.9, 170.4	56.6
25b	133.3	49.0	62.3	27.5	110.8	127.6	119.6	120.0	122.3	108.7	137.2	21.1	32.0	59.7	12.2	122.1	133.4	51.4	52.5, 171.5	56.3
27a	133.9	43.9	62.0	27.0	109.9	127.8	118.4	119.6	121.5	109.6	135.5	31.6	31.1	59.3	11.8	121.3	135.1	47.5	51.8, 170.2	
28b	133.2	43.2	61.9	27.1	110.0	127.9	118.8	119.8	121.8	108.4	135.6	28.0	32.9	53.4	10.6	23.8	40.8	43.6	52.4, 172.2	
29a	130.9	44.9	44.5	27.0	109.7	127.6	119.2	120.7	122.8	110.4	136.9	30.7	30.2	59.8	12.3	124.5	131.4	48.2	52.3, 170.0	38.2
30b	131.0	44.1	44.6	27.3	109.2	127.6	119.3	120.6	122.8	109.0	136.6	28.5	32.4	53.7	10.8	23.5	40.0	44.6	52.6, 171.6	38.4
36b	130.9	51.4	55.3	27.5, 64.3	101.9	127.7	120.5	120.8	121.5	108.8	136.4	26.8	31.4	59.7	12.4	121.9	134.5	54.6	52.6, 171.1	
37a	131.6	44.1 (46.8)			102.1	128.1	120.9	121.4	122.6	110.0	136.4	29.9	30.8	59.5	12.4	125.0	132.9	49.0 (46.3)	52.4, 170.0	
38a	133.3	50.4			101.8	128.0	120.2	120.5	121.4	109.9	136.5	30.9	30.9	59.9	12.2	121.8	134.2	55.5	51.9, 170.4	59.2
38b	132.0	50.4			101.5	127.1	120.3	120.5	120.7	108.6	136.3	27.6	31.6	59.8	12.3	121.6	135.6	54.9	52.5, 171.3	59.0
42	133.3	51.3	55.6	30.9, 52.1	101.8	128.1	120.3	120.6	121.5	109.9	136.5	32.2	30.9	59.8	12.3	122.2	134.1	52.6	52.1, 170.4	12.3, 12.3
43	133.1	50.7	55.6	29.5, 102.1	103.2	128.0	120.4	120.7	121.6	110.0	136.7	30.9	30.8	59.9	12.4	121.6	134.6	50.4	52.1, 170.5	52.7, 52.8
44	133.4	50.5	53.2	28.7, 64.0	114.4	126.8	118.0	120.2	120.8	110.5	138.2	29.6	31.5	59.9	12.4	123.5	135.2	51.3	51.9, 169.8	
45	133.7	51.8	58.7	22.6, 22.1	114.0	127.5	118.4	119.6	120.5	110.4	136.2	30.4	31.8	60.0	12.3	123.1	135.4	53.2	51.8, 170.1	
47	134.0	42.4 (47.3)	164.3	41.2	100.8	128.3	120.7	121.4	122.2	108.6	136.1	27.3	32.9	53.6	10.9	23.5	40.7	45.7	52.7, 171.7	
49	90.6	51.8	177.1	36.6	47.5	128.5	125.0	118.9	128.4	104.1	147.9	24.2	30.3	53.8	12.3	20.1	39.4	37.0	53.1, 170.9	
50	60.7	48.3	173.4	37.1	37.8	129.7	124.5	116.9	128.2	103.0	149.0	25.3	29.9	53.2	12.5	24.0	39.3	37.7	52.1, 171.0	
52	58.8	49.5	50.4	30.4	38.5	134.5	123.3	117.4	127.3	104.5	147.8	25.0	31.2	52.9	11.4	21.3	40.7	50.0	51.8, 173.4	
53	134.9	41.6 (47.4)	168.2	21.8	100.3	128.3	120.5	121.2	121.9	108.5	135.9	27.6	33.1	53.7	11.1	24.0	41.0	46.0 (40.9)	52.8, 171.7	
54	131.8	42.7 (47.6)	164.6	41.2	101.4	128.2	120.7	121.3	122.9	109.9	136.3	29.9	30.8	59.6	12.4	124.3	134.2	49.7 (45.5)	52.3, 170.2	
55	92.1	51.4	170.3	36.2	45.8	129.7	124.7	118.5	127.6	107.9	147.8	23.1	31.0	57.6	13.0	120.7	134.3	41.6	51.7, 170.9	
56	67.0	48.3	170.3	36.2	36.9	132.3	124.3	118.6	127.7	107.4	149.8	29.4	31.7	61.9	13.1	121.2	134.3	42.0	51.9, 171.4	
58	63.1	50.4	49.8	20.2	37.7	131.0	123.6	119.5	127.5	108.9	147.7	31.2	31.2	60.6	12.6	123.5	133.6	49.8	52.1, 170.1	

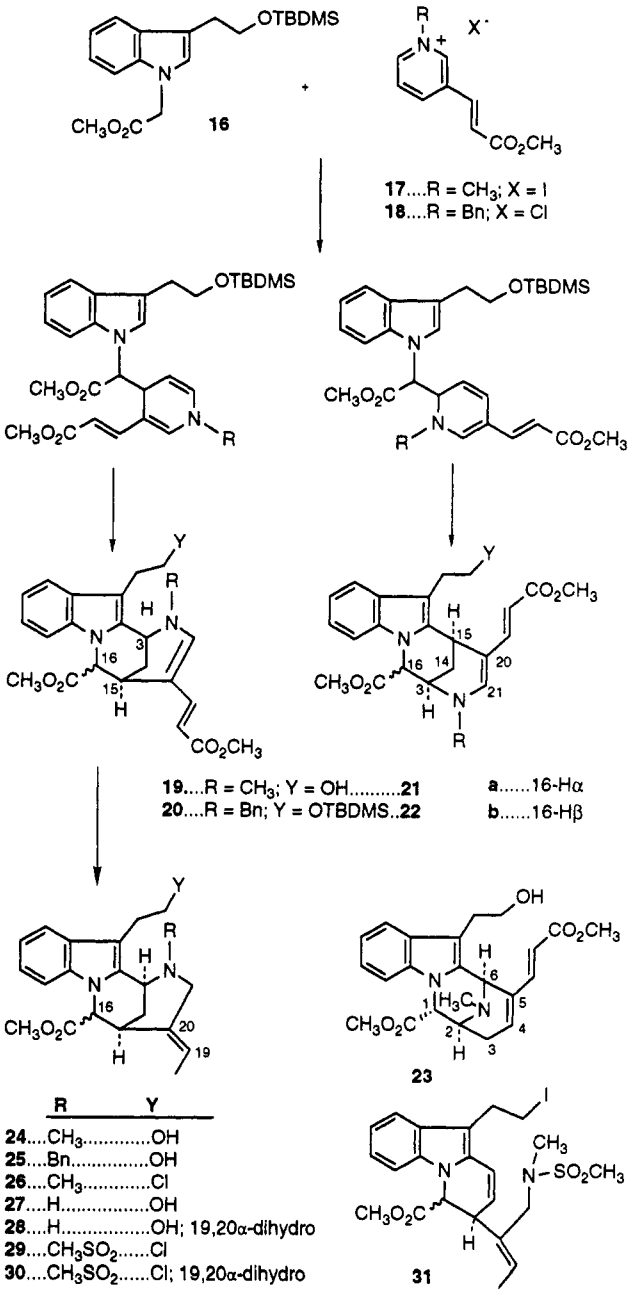
corresponding dithioacetals **13a,b** also failed. Thus, treatment of the crude aldehydes **12a** or **12b** with BF_3·Et_2O, $TiCl_4$,[26] or AcOH–HCl[27] at several temperatures and reaction times only gave polymeric material. Similar discouraging results were obtained when dithioacetals **13a** or **13b** were treated under several reaction conditions with dimethyl(methylthio)sulfonium fluoroborate (DMTSF),[28] which is an excellent initiator for the generation of thionium ions from dithioacetals in very mild conditions.[29,30] In this case, the only isolable products were the aldehydes **12a** or **12b** coming from the hydrolysis of the intermediate thionium ion.[31]

With the hope that the conversion of the ethylidene substituent into an ethyl group would increase the conformational flexibility of the piperidine ring, thus favoring the formation of C-6/C-7 bond, we also tried the cyclization of C-20 ethyl-substituted dithioacetals **15a,b**, which were independently prepared by catalytic (PtO_2) hydrogenation of either (±)-vinoxine (**10a**) or (±)-16-epivinoxine (**10b**), followed by DMSO–TFAA oxidation of the resulting 19,20α-dihydro derivatives (**11a** and **11b**, respectively) and further dithioacetalization. It is worth mentioning that, in both cases, hydrogenation of the ethylidene group took place stereoselectively from the less hindered α-face of the molecule and that hydrogenation of **10a** took a longer time due to the steric interactions between the ethyl and methoxycarbonyl substituents, showing a 1,3-diaxial relationship. Unfortunately, treatment of both **15a** and **15b** with DMTSF did not lead to any cyclized product either.

The above unsuccessful results prompted us to study an alternative mode of constructing the six-membered C ring, by formation of N-4/C-5 bond from tetracyclic derivatives having a functionalized two-carbon chain at the indole 3-position.[32] Our attention was focused on the functionalized 4,5-seco derivatives **24** and **25** (Scheme IV). For their preparation we took advantage of the straightforward three-step sequence (nucleophilic addition, cyclization, and final elaboration of the (*E*)-ethylidene substituent) we had developed for the synthesis of vinoxine.

Thus, interaction of the enolate of the silylated tryptophol ester **16** with pyridinium salt **17**, followed by acid cyclization, gave the desired tetracyclic compounds **19a,b** (35% yield) as a nearly equimolecular mixture of C-16 epimers and the unnatural regioisomers **21a,b** (15%; 1:1 mixture of C-16 epimers) and **23** (5% yield). A similar reaction from pyridinium salt **18** led to tetracycles **20a,b** (29% yield; nearly equimolecular mixture of C-16 epimers) and **22a** (7% yield). These results show that pyridinium salts **17** and **18** undergo both α- and γ-attacks to give a mixture of 1,2- (minor) and 1,4-dihydropyridines. Further

Scheme IV



protonation, followed by cyclization of the resulting dihydropyridinium salts, leads to the isolated tetracycles.[33] The structures of the unexpected tetracycles **21** and **22** (and **46**, Scheme V) were established by comparison of their spectroscopic data with those corresponding to the mavacurine-type systems **19** and **20**. Thus, C-3 and C-15 appear more shielded (see Table I), but H-3 and H-15 are more deshielded, in those regioisomers where these carbons are adjacent to the indole nucleus.

Tetracycles **19a,b** and **20a,b** were stereoselectively elaborated into the corresponding (*E*)-ethylidene derivatives **24a,b** (40% yield; 3:1 epimeric mixture at C-16) and **25a,b** (39% yield; 2:1 epimeric mixture at C-16) by a one-pot, three-step sequence consisting of treatment with refluxing aqueous HCl to bring about hydrolysis of ester groups and decarboxylation of the resulting acrylic acid

(26) For similar cyclizations in the *Iboga* series, see: (a) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52*, 315. (b) Sundberg, R. J.; Gadamasetti, K. G. *Tetrahedron* **1991**, *47*, 5673.

(27) Mashimo, K.; Sato, Y. *Tetrahedron* **1970**, *26*, 803.

(28) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826.

(29) (a) Trost, B. M.; Murayama, E.; *J. Am. Chem. Soc.* **1981**, *103*, 6529. (b) Trost, B. M.; Murayama, E. *Tetrahedron Lett.* **1982**, *23*, 1047. (c) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719.

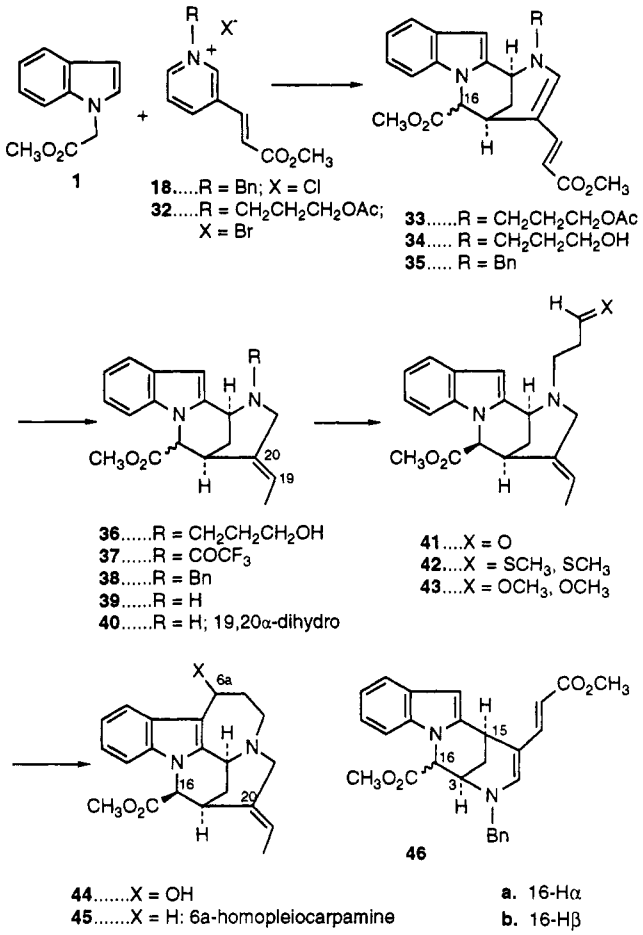
(30) DMTSF-induced cyclizations upon the indole 3-position have been successfully applied to the synthesis of pentacyclic *Strychnos* alkaloids: (a) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (b) Gràcia, J.; Bonjoch, J.; Casamitjana, N.; Amat, M.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1991**, 1687.

(31) For a preliminary report of this part of the work, see: Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. *Nat. Prod. Lett.* **1992**, *1*, 15.

(32) For the use of this strategy in the synthesis of *Iboga* alkaloids, see: (a) Marazano, C.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 37. (b) Marazano, C.; Le Goff, M.-T.; Fourrey, J.-L.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 389.

(33) For precedents of nucleophilic α-attack to the pyridinium ring and further acid cyclization of the resulting 1,2-dihydropyridine, see refs 14 and 17f. See also: Alvarez, M.; Bosch, J.; Granados, R.; López, F. *J. Heterocycl. Chem.* **1978**, *15*, 193. Bennasar, M.-L.; Zulaica, E.; Vidal, B.; Bosch, J. *Tetrahedron Lett.* **1992**, *33*, 3895.

Scheme V. Synthesis of 6a-Homopleiocarpamine



moiety, reesterification of the C-16 carboxy group, and finally $NaBH_4$ reduction of the carbon–nitrogen double bond.[21,34]

Closure of the C ring was attempted under several conditions. Thus, reaction of **24a** with mesyl chloride followed by heating in DMF led to chloride **26a** as the only identifiable product, whereas sequential treatment of **24a** or **24b** with mesyl chloride and then with NaI in refluxing acetonitrile gave the respective piperidine-cleaved products **31a** or **31b** in *ca.* 35% yield. On the other hand, hydrogenolysis [$Pd(OH)_2$ or Pd/C] of the mesylate derived either from **25a** or **25b** resulted in intractable mixtures. Alternatively, direct debenzylation of **25a,b** by hydrogenolysis [$Pd(OH)_2$] afforded a mixture of the secondary amines **27a** and **28b** (80% yield), the latter resulting from the concomitant reduction of the ethylidene substituent.[35] However, treatment of either **27a** or **28b** with mesyl chloride followed by heating in DMF led to the sulfonamides **29a** (46% yield) and **30b** (50% yield), respectively. Finally, cyclization of **27a** via the corresponding bromide under a variety of conditions (HBr–AcOH or Ph_3P–CBr_4) also failed, and the expected cyclized product (pleiocarpamine) was never detected.

The reluctance of the above tetracyclic intermediates (**10–15** and **24–28**) to close the six-membered C ring of the mavacurine alkaloids could be attributed to the fact that the distance between the indole 3-position (or the piperidine nitrogen) and the electrophilic carbon is not favorable for bond formation because the piperidine ring is included in a rigid bridged system.

In order to verify this interpretation we examined the cyclization of tetracyclic compounds (**41–43**) with a functionalized three-carbon chain at the piperidine nitrogen, where the distance C-6a/C-7 is more favorable for bond formation (see Dreiding stereomodels). The new ring thus formed would be seven-membered, resulting in less strain than in pleiocarpamine.

For the preparation of the required tetracycles **41–43** we initially extended our methodology for the synthesis of tetracyclic ABDE ring substructures of mavacurine alkaloids by using a pyridinium salt **32** which bears a 3-acetoxypropyl substituent at the piperidine nitrogen (Scheme V). As was expected, exposure of salt **32** to the enolate of ester **1** and then to acid afforded tetracycles **33a,b** (15% yield; nearly equimolecular mixtures of C-16 epimers), which were elaborated by the usual procedure[34] into the (*E*)-ethylidene derivatives **36a,b** in 38% yield. However, oxidation of amino alcohols **36a,b** was unsuccessful under a variety of conditions. Starting material was recovered under Moffat conditions, whereas trifluoroacetamides **37a,b**[36] were obtained with DMSO–TFAA. In order to avoid the above fragmentation we tried the oxidation of alcohols **34a,b**, which were easily obtained by methanolysis of acetates **33a,b**. However only minor amounts of the corresponding aldehyde could be detected after DMSO–TFAA treatment.

At this point we turned our attention to the N-4 unsubstituted tetracycle **39**, which would allow further introduction of an appropriately functionalized three-carbon chain on the piperidine nitrogen. With this aim, the nucleophilic addition–acidic cyclization sequence was carried out from ester **1** and pyridinium salt **18**, which incorporates an easily removable *N*-benzyl group. In this way tetracycles **35a,b** were obtained in 33% yield as a nearly equimolecular mixture of C-16 epimers along with the unnatural regioisomers **46a,b** (30%) coming from an initial nucleophilic attack to the α-position of the pyridine ring.[33] Tetracycles **35a,b** were converted in the usual manner into a 3:2 epimeric mixture of the (*E*)-ethylidene derivatives **38a,b** (34%), which were separated. Debenzylation of the major epimer **38a** by hydrogenolysis [$Pd(OH)_2$] was accomplished in almost quantitative yield, and the resulting secondary amine **39a** was then elaborated (41%) into dithioacetal **42**[38] by reaction with acrolein followed by dithioacetalization of the aldehyde **41**.

(34) For the use of this procedure in the synthesis of (*E*)-ethylidene bearing indole alkaloids, see: Besselièvre, R.; Cosson, J.-P.; Das, B. C.; Husson, H.-P. *Tetrahedron Lett.* **1980**, *21*, 63. See also refs 14, 16b, 17b, 20a, and 22a.

(35) As has already been observed in the hydrogenation of **10a,b**, reduction of the ethylidene substituent occurs faster in the **b** series, *i.e.*, when the methoxycarbonyl group at C-16 is in the α-face.

(36) Their formation can be explained by considering a Grob-type fragmentation of the intermediate alcoxysulfonium promoted by the nitrogen lone pair, followed by hydrolysis of the resulting iminium ion and further acylation.[37]

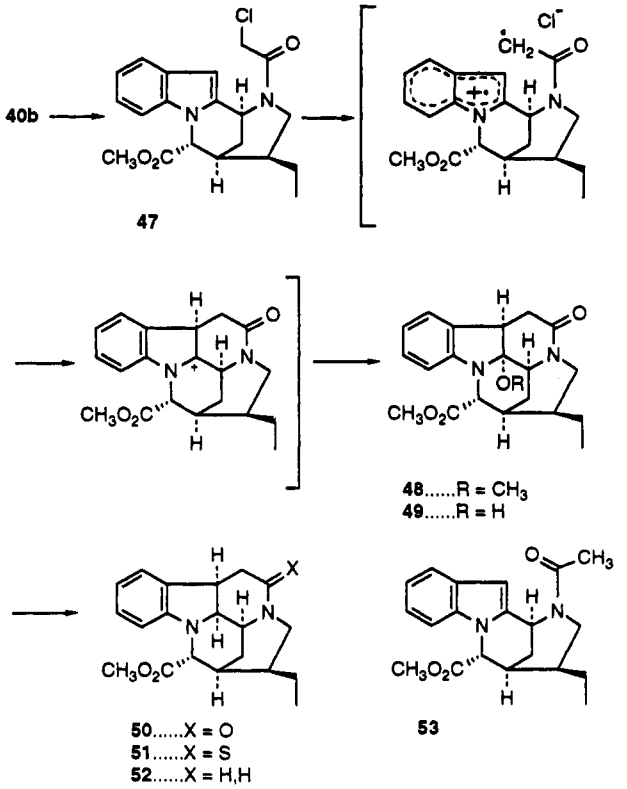
(37) For a similar fragmentation observed in the context of the synthesis of homo analogs of *Iboga* alkaloids, see: Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028.

(38) Direct alkylation of **39a** with 3,3-bis(methylthio)propylmethanesulfonate[39] failed under a variety of experimental conditions whereas, although alkylation of **39a** with 3-bromopropionaldehyde dimethyl acetal gave the acetal **43** in moderate yield (33%), only unrecognizable products were formed in the attempts to convert **43** into dithioacetal **42**.

(39) (a) Prepared by reaction of 3,3-bis(methylthio)-1-propanol[39b] with MsCl (CH_2Cl_2, Et_3N, 0 °C). (b) Brandsma, L.; Vermeer, P.; Kooijman, J. G. A.; Boelens, H.; Maessen, J. T. M. *Rec. Trav. Chim. Pays-Bas* **1972**, *91*, 729.

(40) Cyclization of the thionium ion generated from **42** should afford a pentacyclic thioether (X = SCH_3).[30] However, in the presence of an excess of DMTSF, the methylthio substituent undergoes hydrolytic cleavage of the C_{6a}–sulfur bond, promoted by the indole nitrogen, leading to **44**.

Scheme VI. Closure of C Ring: Chloroacetamide Photocyclization



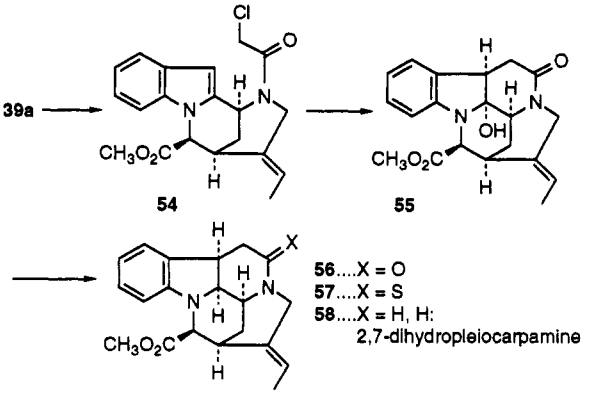
As expected, dithioactal **42** did cyclize after treatment with DMTSF to give the pentacyclic alcohol **44**[40] (38% yield; undetermined stereochemistry at C-6a) which was then converted (80% yield) into 6a-homopleiocarpamine (**45**) by reduction with Et_3SiH–TFA.[41] Cyclization to **44** also occurred, although in lower yield (10%), when acetal **43** was treated with 1.2 N hydrochloric acid (rt, 12 h).

The above successful closure of the seven-membered C ring in the C-homo series provides a support for the geometrical origin of the failure of similar electrophilic cyclizations leading to natural mavacurine systems having a six-membered C ring. In this respect, it is worth mentioning that 6a-homopleiocarpamine (**45**) shows a fairly normal indole UV spectrum rather than the perturbed indolic chromophore typical of the strained mavacurine systems.[1]

In view of the aforementioned results, we decided to study the photocyclization of an appropriate tetracyclic chloroacetamide[42] as a mechanistically different approach for the closure of the six-membered C ring of mavacurine alkaloids. In this case the key C-6/C-7 bond would be formed by diradical coupling instead of by electrophilic cyclization.

Preliminary studies were done with chloroacetamide **47**, a model compound with a β-ethyl group at C-20 and a relative configuration at C-16 opposite to that of pleiocarpamine. This chloroacetamide was prepared in 60% overall yield by debenzylation of **38b** with simultaneous hydrogenation of the ethylidene substituent[35] and further acylation of the resulting secondary amine **40b** (Scheme VI). To our delight, photocyclization of **47** in a diluted 1:1 MeOH–H_2O solution in the presence of Na_2CO_3 gave the pentacyclic 2-hydroxyindoline **49** in 25% yield along with trace amounts of 2-methoxyindoline **48**. No pentacyclic indole-containing compounds were detected. The use of H_2O-CH_3CN mixtures as the solvent afforded **49** as the only isolable product but in lower yield (15%), whereas the use of a methanolic solution gave **48** in only 10% yield.[43] Formation of indolines **48** and **49** implies that, after coupling of the initially formed diradical cation[42] (bond formed C-6/C-7), the resulting cation undergoes nucleophilic attack instead of aromatization, probably due to the strain associated with the pentacyclic mavacurine system.[44] This successful cyclization is in sharp contrast with the failure of the six-membered C ring to close by electrophilic cyclization. The different nature of the actual species involved in the cyclization step, an indolyl radical cation rather than a normal indole ring, with the consequent differences in geometry, could account for this result.[45]

Scheme VII. Synthesis of (±)-2,7-Dihydropleiocarpamine



Hydroxyindoline **49** proved to be very sensitive and, as could be expected from the above result, reluctant to undergo dehydration under several acid (TFA, TsOH, or $HClO_4$) or neutral (Martin's sulfurane) conditions. Attempted reduction of the lactam carbonyl (BH_3–SMe_2, BH_3–THF, or Lawesson's reagent) also resulted in failure. However **49** could be reduced to the indoline **50** by treatment with Et_3SiH–TFA (70% yield) and then elaborated into tetrahydro-16-epipleiocarpamine (**52**) by conversion into the thiolactam **51** (73%) followed by desulfurization with nickel boride[46] (60%).

With a method in hand for the construction of the pentacyclic ring system of mavacurine alkaloids, our efforts were then directed toward the extension of the above synthetic sequence from chloroacetamide **54** (Scheme VII), the final goal being the synthesis of 2,7-dihydropleiocarpamine, an indole alkaloid isolated in 1973 from *Alstonia muelleriana*.[47,48] The requisite chloroacetamide **54** was prepared by acylation of the secondary amine **39a** (61% yield) and then photocyclized under similar reaction

(41) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

(42) For a review, see: Sundberg, R. J. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1983; Vol. 6, Chapter 2. See also ref 26a.

(43) Methoxyindoline **48** could not be purified since it slowly changed in solution to hydroxyindoline **49**.

(44) The strain associated with these systems accounts for the occurrence of alkaloids of this group with an indoline moiety, both monomeric (2,7-dihydro or 2,7-dihydroxy) and dimeric (linked by C-2 and C-7), and the smooth addition reaction on the C-2/C-7 double bond of pleiocarpamine in its conversion to the bisindole alkaloid villalstonine.[6]

(45) Accordingly, radical cyclization of chloroacetamide **47** by means of nBu_3SnH/AIBN failed, and the acetyl derivative **53** was isolated in nearly quantitative yield.

(46) (a) Dikshit, D. K.; Panday, S. K. *J. Org. Chem.* **1992**, *57*, 1920. (b) Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407.

(47) Burke, D. E.; Cook, G. A.; Cook, J. M.; Haller, K. G.; Lazar, H. A.; LeQuesne, P. W. *Phytochemistry* **1973**, *12*, 1467.

(48) For a preliminary report of this part of the work, see: Jiménez, J.-M.; Zulaica, E.; Bennasar, M.-L.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1993**, 732.

conditions as used for **47** to give the pentacyclic hydroxyindoline **55** (18% yield). Reduction of **55** with Et_3SiH–TFA provided indoline **56** (50% yield), which was transformed into (±)-2,7-dihydropleiocarpamine (**58**) as in the above 19,20-dihydro series by way of the corresponding thiolactam **57** (overall yield 30%). The ^1H NMR spectrum of our synthetic material **58** was identical to that reported[1,47] for the natural product.

Although 2,7-dihydropleiocarpamine had been previously obtained by reduction of natural pleiocarpamine[1] and by reductive cleavage of bisindole alkaloids,[6] the synthesis here reported constitutes the first total synthesis of this alkaloid as well as the first synthesis of an alkaloid of the mavacurine group with a H-15/H-16 cis stereochemistry.

Experimental Section

Melting points were determined in a capillary tube and are uncorrected. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50.3 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, and coupling constants are expressed in hertz. 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. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. All compounds were synthesized in the racemic series. The biogenetic numbering[3] is used to describe the NMR spectra of tetracyclic and pentacyclic compounds.

1-(2-Acetoxyethyl)-3-acetylpyridinium Bromide (3). A mixture of 3-acetylpyridine (2 g, 16.5 mmol) and 2-bromoethyl acetate (2.75 g, 16.5 mmol) was heated at 80–100 °C for 2 h. The reaction mixture was diluted with Et_2O, and the resulting precipitate was filtered to give **3** (hygroscopic): 3.88 g (82%); mp 114–115 °C (acetone–MeOH–Et_2O); IR (KBr) 1690, 1735 (CO); ^1H NMR ($CDCl_3$–DMSO-d_6, 60 MHz) 1.9 and 2.7 (2 s, 6 H), 4.5 (m, 2 H), 5.3 (m, 2 H), 8.1 (m, 1 H), 8.8 (d, J = 8, 1 H), 9.5 (d, J = 6, 1 H), 10.2 (s, 1 H).

Reaction of Ester 1 with Pyridinium Salt 3. A. A solution of ester **1**[14] (1 g, 5.29 mmol) in THF (60 mL) was slowly added to a solution of LDA (15.8 mmol) in THF (10 mL) under N_2 cooled at −70 °C, and the resulting solution was stirred at −70 °C for 1 h. Then, pyridinium bromide **3** (1.52 g, 5.29 mmol) was added in portions, and the mixture was allowed to rise to a temperature of −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 mixture was permitted to rise to room temperature. After being stirred at room temperature for 2 h, the reaction mixture was poured into saturated aqueous Na_2CO_3 and extracted with Et_2O. Evaporation of the dried extracts gave a crude residue which was chromatographed (flash, Et_2O and 95:5 Et_2O–DEA). On successive elution, the following compounds were isolated. **Methyl 7-[(2-acetoxyethyl)amino]-6-acetyl-2-(1-indolyl)-2,4,6-heptatrienoate (9)**: 0.21 g (10%); IR (KBr) 1640, 1700, 1730 (CO); ^1H NMR 1.88 and 2.21 (2 s, 6 H), 3.34 (m, 2 H), 3.71 (s, 3 H), 4.05 (t, J = 5.8, 2 H), 5.70 (dd, J = 15, 11, 1 H), 6.62 (d, J = 4, 1 H), 6.96–7.25 (m, 6 H), 7.60 (dm, J = 8, 1 H), 7.70 (d, J = 11, 1 H); ^{13}C NMR 20.5, 27.4, 48.1, 52.1, 63.1, 102.9, 106.2, 110.7, 112.3, 120.0, 120.8, 122.1, 128.4, 129.5, 135.2, 137.2, 141.3, 141.7, 153.4, 165.6, 170.4, 196.9. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 66.28; H, 6.07; N, 6.83. **Methyl 5-(2-acetoxyethyl)-3-acetyl-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-a]indole-1α-carboxylate (8b)**: 0.52 g (25%); mp 186–187 °C (acetone–Et_2O), IR (KBr) 1735, 1600 (CO); ^1H NMR 1.81 (dt, J = 13.9, 3.4, 1 H), 2.10 and 2.14 (2 s, 6 H), 2.44 (dt, J = 13.9, 2.6, 1 H), 3.35 and 3.67 (2 m, 2 H), 3.75 (s, 3 H), 3.80 (br, 1 H), 4.20 and 4.45 (2 m, 2 H), 4.64 (t, 1 H), 5.05 (d, J = 1. 74, 1 H), 6.43 (s, 1 H), 7.10–7.25 (m, 3 H), 7.18 (s, 1 H), 7.55 (dd, J = 7.2, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.06. Found: C, 66.34; H, 6.26; N, 6.92. The C-16 epimer **8a** was isolated in some runs (yield <5%): ^1H NMR 1.93 (dt, J = 12.5, 3.6, 1 H), 2.09 and 2.12 (2 s, 6 H), 2.10 (masked, 1 H), 3.40 and 3.70 (2 m, 2 H), 3.81 (s, 3 H), 4.07 (br s, 1 H), 4.15 and 4.50 (2 m, 2 H), 4.65 (dd, J = 3.6, 3, 1 H), 4.86 (d, J = 4.8, 1 H), 6.41 (s, 1 H), 7.05–7.20 (m, 3 H), 7.13 (s, 1 H), 7.56 (dm, J = 7, 1 H); ^{13}C NMR, Table I.

B. When the acidic treatment was omitted, a 3:1 mixture of 1,4-dihydropyridine **5** and amine **9** was obtained: 0.4 g (20%). Both compounds were separated by column chromatography (2:3 hexane–AcOEt). **Methyl α-[1-(2-acetoxyethyl)-3-acetyl-1,4-dihydro-4-pyridyl]-1-indoleacetate (5)**: IR (KBr) 1570 (C=C), 1630, 1670, 1735 (CO); ^1H NMR 1.88 and 1.90 (2s, 6 H), 3.13 (t, J = 5.4, 2 H), 3.77 (s, 3 H), 3.84 (m, 2 H), 4.55 (dd, J = 4.8, 4.6, 1 H), 4.95 (dd, J = 7.8, 4.8, 1 H), 5.61 (d, J = 4.6, 1 H), 5.90 (br d, J = 7.8, 1 H), 6.38 (d, J = 3.3, 1 H), 6.56 (br s, 1 H), 6.90–7.10 (m, 3 H), 7.43 (d, J = 3.3, 1 H), 7.50 (br d, J = 7, 1 H); ^{13}C NMR 20.4, 23.7, 38.2, 52.1, 52.5, 59.5, 62.9, 101.7, 104.0, 108.8, 109.1, 119.1, 120.5, 121.0, 127.3, 127.7, 130.9, 137.5, 143.7, 169.7, 170.1, 195.2.

(±)-16-Epivinoxine (10b). Trimethyloxonium fluoroborate (0.138 g, 0.932 mmol) in CH_2Cl_2 (2 mL) was slowly added under N_2 to a solution of **8b** (0.25 g, 0.62 mmol) in CH_2Cl_2 (12 mL), and the resulting solution was stirred at room temperature for 2 h. The solvent was removed, and the resulting residue was dissolved in MeOH (12 mL) and treated with $NaBH_4$ (0.1 g, 2.5 mmol) at 0 °C for 1 h and at room temperature for 1 h. The solvent was removed, and the residue was dissolved in H_2O and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by flash chromatography (9:1 Et_2O–DEA) gave (±)-16-epivinoxine (**10b**): 62 mg (30%). The ^1H and ^{13}C NMR spectra of **10b** were identical with those previously reported.[14]

(±)-Vinoxine (10a). Operating as above, from **8a** (0.1 g, 0.25 mmol) was obtained (±)-vinoxine (**10a**): 17 mg (20%). The ^1H and ^{13}C NMR spectra of **10a** were identical with those previously reported for this alkaloid.[5]

(±)-19,20α-Dihydrovinoxine (11a). (±)-Vinoxine (**10a**, 0.2 g, 0.58 mmol) in MeOH (30 mL) was hydrogenated over PtO_2 (60 mg) at atmospheric pressure for 48 h. The catalyst was filtered off, the solvent was removed, and the residue was diluted with aqueous Na_2CO_3 and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by column chromatography (9:1 AcOEt–MeOH) gave **11a**: 0.12 g (60%); IR (KBr) 1720 (CO), 3300 (OH); ^1H NMR 0.96 (t, J = 7, 3 H), 1.10–1.50 (m, 3 H), 1.90 (m, 1 H), 2.01 and 2.25 (2 dt, J = 13, 3, 2 H), 2.30–3.00 (m, 4 H), 3.50–3.70 (m, 2 H), 3.84 (br s, 3 H), 4.11 (t, 1 H), 4.90 (d, J = 6, 1 H), 6.29 (s, 1 H), 6.80–7.30 (m, 3 H), 7.60 (m, 1 H); ^{13}C NMR, Table II; MS m/e (rel intensity) 342 (M^+, 26), 311 (100), 283 (10), 268 (45), 251 (13), 168 (48), 167 (99). The hydrochloride melted at 220 °C (MeOH). Anal. Calcd for $C_{20}H_{27}N_2O_3Cl$: C, 63.40; H, 7.18; N, 7.39; Cl, 9.35. Found: C, 63.30; H, 7.19; N, 7.30; Cl, 9.37.

(±)-19,20α-Dihydro-16-epivinoxine (11b). (±)-16-Epivinoxine (**10b**, 0.7 g, 2.06 mmol) in MeOH (70 mL) was hydrogenated over PtO_2 (140 mg) at atmospheric pressure for 24 h. Workup as above and column chromatography (95:5 AcOEt–MeOH) gave **11b**: 0.4 g (56%); IR (KBr) 1730 (CO), 3320 (OH); ^1H NMR 1.03 (t, J = 7, 3 H), 1.20–1.70 (m, 3 H), 1.95 (m, 1 H), 2.10 (dt, J = 13, 2, 1 H), 2.32 (m, 2 H), 2.55 (m, 2 H), 2.77 (m, 1 H), 3.01 (br, 1 H), 3.50–3.70 (m, 2 H), 3.67 (s, 3 H), 4.00 (t, 1 H), 4.96 (s, 1 H), 6.27 (s, 1 H), 7.10–7.20 (m, 3 H), 7.59 (d, J = 8, 1 H); ^{13}C NMR, Table II; MS m/e (rel intensity) 342 (25, M^+), 311 (85), 283 (14), 268 (25), 251 (19), 168 (50), 167 (100). The hydrochloride melted at 218 °C (MeOH). Anal. Calcd for $C_{20}H_{27}N_2O_3Cl$: C, 63.40; H, 7.18; N, 7.39; Cl, 9.35. Found: C, 63.40; H, 7.25; N, 7.36; Cl, 9.30.

Methyl 5-[2,2-Bis(methylthio)ethyl]-3(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-a]indole-1β-carboxylate (13a). TFAA (0.08 mL, 0.52 mmol) in CH_2Cl_2 (0.5 mL) was slowly added under N_2 to a solution of DMSO (0.05 mL, 0.7 mmol) in CH_2Cl_2 (0.5 mL) cooled at −50 °C. After the mixture was stirred at −50 °C for 15 min, (±)-vinoxine (**10a**, 0.12 g, 0.35 mmol) in CH_2Cl_2 (15 mL) was added, and the mixture was stirred at −50 °C for 1 h 30 min. Then, Et_3N (0.14 mL, 1.05 mmol) was added dropwise, and the mixture was allowed to rise to room temperature, quenched with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extracts were dried and evaporated to give crude aldehyde **12a**. The residue coming from two

reactions as above was dissolved in CH_2Cl_2 (30 mL) and allowed to react with an excess of CH_3SH (9 mL) and $BF_3{\cdot}Et_2O$ (0.36 mL, 2.93 mmol) at 0 °C for 12 h. The organic solution was washed with 5% aqueous NaOH, dried, and evaporated to give an oil. Column chromatography (8:2 hexane–AcOEt) gave dithioacetal **13a**: 0.18 g (62%); mp 122–123 °C (Et_2O); IR (KBr) 1730 (CO); ^1H NMR 1.65 (dd, J = 6.8, 1.7, 3 H), 2.04 (dm, J = 12.8, 1 H), 2.12 and 2.15 (2 s, 6 H), 2.30 (dm, J = 12.8, 1 H), 2.58 (dd, J = 13.4, 7, 1 H), 3.01 (m, 3 H), 3.71 (s, 3 H), 3.70 (masked, 1 H), 3.89 (dd, J = 7, 7.3, 1 H), 4.17 (t, 1 H), 4.99 (d, J = 6, 1 H), 5.52 (q, J = 6.8, 1 H), 6.35 (s, 1 H), 6.80–7.25 (m, 3 H), 7.60 (m, 1 H); ^{13}C NMR, Table II. Anal. Calcd for $C_{22}H_{28}N_2O_2S_2$: C, 63.42; H, 6.77; N, 6.72. Found: C, 63.34; H, 6.86; N, 6.70.

Dithioacetal 13b. Operating as above, from (±)-16-epivinoxine (**10b**, 0.1 g, 0.29 mmol) was obtained dithioacetal **13b** after column chromatography (7:3 hexane–AcOEt): 0.14 g (58%); ^1H NMR 1.76 (dd, J = 6.8, 1.8, 3 H), 2.12 and 2.15 (2 s, 6 H), 2.13 (masked, 1 H), 2.27 (dt, J = 12.7, 2.8, 1 H), 2.50 (m, 2 H), 2.89 (dd, J = 13.4, 7.7, 1 H), 3.08 (d, J = 13, 1 H), 3.53 (t, 1 H), 3.70 (s, 3 H), 3.87 (dd, J = 7.7, 7.3, 1 H), 4.13 (t, 1 H), 4.83 (s, 1 H), 5.45 (q, J = 6.8, 1 H), 6.35 (s, 1 H), 6.98–7.25 (m, 3 H), 7.60 (m, 1 H); ^{13}C NMR, Table II.

Methyl 5-[2,2-Bis(methylthio)ethyl]-3β-ethyl-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β-carboxylate (15a). Operating as above, from **11a** (0.1 g, 0.29 mmol) was obtained dithioacetal **15a**: 0.14 g (58%); IR (film) 1740 (CO); ^1H NMR 0.93 (t, J = 7, 3 H), 2.12 and 2.15 (2 s, 6 H), 3.70 (br s, 3 H), 3.91 (t, J = 7, 1 H), 4.09 (t, 1 H), 4.87 (d, J = 5.5, 1 H), 6.27 (s, 1 H), 6.80–7.30 (m, 3 H), 7.65 (m, 1 H); ^{13}C NMR, Table II. The hydrochloride melted at 183–184 °C (CH_2Cl_2–Et_2O). Anal. Calcd for $C_{22}H_{31}N_2O_2S_2Cl{\cdot}1/2H_2O$: C, 56.93; H, 6.95; N, 6.03; S, 13.81. Found: C, 57.10; H, 6.93; N, 5.87; S, 13.77.

Dithioacetal 15b. Operating as above, from **11b** (0.15 g, 0.44 mmol) was obtained dithioacetal **15b**: 0.175 g (47%); mp 112–113 °C (Et_2O); IR (KBr) 1740 (CO); ^1H NMR 1.01 (t, J = 7, 3 H), 2.11 and 2.16 (2 s, 6 H), 3.65 (s, 3 H), 3.86 (t, J = 7.5, 1 H), 4.03 (t, 1 H), 4.95 (s, 1 H), 6.27 (s, 1 H), 7.10–7.20 (m, 3 H), 7.57 (dm, J = 8, 1 H); ^{13}C NMR, Table II. Anal. Calcd for $C_{22}H_{30}N_2O_2S_2{\cdot}1.5H_2O$: C, 59.29; H, 7.36; N, 6.28. Found: C, 59.29; H, 6.96; N, 6.23.

Methyl 3-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]indole-1-acetate (16). A solution of tryptophol (4.5 g, 28 mmol), TBDMSCl (5.1 g, 33 mmol), and imidazole (4.7 g, 70 mmol) in DMF (10 mL) was heated at 35 °C for 10 h. The reaction mixture was poured into aqueous Na_2CO_3 and extracted with Et_2O. The extract was dried and evaporated to give **3-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]indole**: 7.2 g (92%). This compound (7.2 g, 26 mmol) in THF (100 mL) was slowly added to a suspension of NaH (55%, 3.35 g, 82 mmol) in THF (250 mL) and HMPA (35 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 45 min. Then, methyl bromoacetate (7.2 mL, 81 mmol) was added, and the mixture was stirred at room temperature overnight, poured into ice–H_2O, and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated. Flash chromatography (Et_2O) gave **16**: 6.6 g (72%); IR (film) 1735 (CO); ^1H NMR (60 MHz) 0.9 (s, 9 H), 2.8 (t, J = 7, 2 H), 3.4 (s, 3 H), 3.7 (t, J = 7, 2 H), 4.4 (s, 2 H), 6.5 (s, 1 H), 6.6–6.9 (m, 3 H), 7.3 (m, 1 H). Anal. Calcd for $C_{19}H_{28}NO_3Si$: C, 65.86; H, 8.13; N, 4.04. Found: C, 66.02; H, 8.34; N, 3.97.

Reaction of Ester 16 with Pyridinium Iodide 17. Operating as in the preparation of tetracycles **9**, from ester **16** (1 g, 2.88 mmol), LDA (5.76 mmol), and pyridinium iodide **17**[49] (0.58 g, 1.90 mmol) was obtained a crude residue which was chromatographed (flash, 7:2:1 Et_2O–EtOH–DEA and 4:1 Et_2O–DEA). On successive elution the following compounds were isolated. **Methyl 7-(2-hydroxyethyl)-1β(and 1α)-(methoxycarbonyl)-3-methyl-1,2,3,6-tetrahydro-2,6-methano[1,4]diazocino[4,5-*a*]indole-5(*E*)-acrylate (21a and 21b)**: 0.12 g (equimolecular mixture, 15%); mp 211–214 °C (acetone–Et_2O); IR (KBr) 1575 (C=C), 1670, 1750 (CO), 3300–3600 (OH); ^1H NMR (**21a**) 1.92 (m, 2 H), 2.99 (s, 3 H), 3.20 (m, 2 H), 3.72 and 3.82 (2 s, 6 H), 3.70 (m, 2 H), 4.15 (t, 1 H), 4.25 (m, 1 H), 4.89 (d, J = 5.1, 1 H), 5.83 (d, J = 15, 1 H), 6.49 (s, 1 H), 6.90–7.30 (m, 4 H), 7.60 (m, 1 H); ^1H NMR (**21b**) 1.90 and 2.30 (2 m, 2 H), 3.14 (s, 3 H), 3.20 (m, 2 H), 3.67 and 3.72 (2 s, 6 H), 3.70 (m, 2 H), 3.90 (m, 1 H), 4.09 (t, 1 H), 5.13 (d, J = 1.4, 1 H), 5.80 (d, J = 15, 1 H), 6.40 (s, 1 H), 6.90–7.30 (m, 4 H), 7.60 (m, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{23}H_{26}N_2O_5$ (mixture of diastereomers): C, 67.30; H, 6.38; N, 6.82. Found: C, 67.33; H, 6.32; N, 6.70. **Methyl 7-(2-hydroxyethyl)-1α-(methoxycarbonyl)-12-methyl-1,2,3,6-tetrahydro-2,6-iminoazocino[1,2-*a*]indole-5(*E*)-acrylate (23)**: 39 mg (5%); IR ($CHCl_3$) 1640 (C=C), 1700–1740 (CO), 3200–3600 (OH); ^1H NMR 2.22 (dd, J = 19, 5.2, 1 H), 2.48 (s, 3 H), 2.91 (t, J = 5, 2 H), 3.73 and 3.77 (2 s, 6 H), 3.85 (t, J = 5, 2 H), 4.23 (s, 1 H), 4.41 (dd, J = 5.2, 0.95, 1 H), 4.82 (d, J = 0.95, 1 H), 6.10 (d, J = 16.2, 1 H), 6.22 (br s, 1 H), 7.02–7.24 (m, 3 H), 7.20 (d, J = 16.2, 1 H), 7.52 (d, J = 7.1, 1 H); ^{13}C NMR 27.7, 28.0, 40.8, 50.4, 51.7, 52.8, 56.0, 57.3, 62.2, 105.3, 108.7, 115.9, 118.6, 119.8, 121.4, 128.0, 130.8, 135.0, 136.0, 136.8, 144.6, 167.2, 170.5. The picrate melted at 186–187 °C (CH_2Cl_2–MeOH). Anal. Calcd for $C_{29}H_{29}N_5O_{12}$: C, 54.46; H, 4.57; N, 10.91. Found: C, 54.02; H, 4.39; N, 10.51. **Methyl 7-(2-hydroxyethyl)-1β(and 1α)-(methoxycarbonyl)-5-methyl-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3(*E*)-acrylate (19a and 19b)**: 0.27 g (equimolecular mixture, 35%); mp 208–209 °C (acetone–Et_2O); IR (KBr) 1575 (C=C), 1685, 1735 (CO), 3100–3600 (OH); ^1H NMR (**19a**) 2.02 (m, 2 H), 3.02 (m, 2 H), 3.07 (s, 3 H), 3.55 (br s, 1 H), 3.70 and 3.73 (2 s, 6 H), 3.80 (m, 2 H), 4.55 (t, 1 H), 4.90 (d, J = 5.6, 1 H), 5.38 (d, J = 14.5, 1 H), 6.52 (s, 1 H), 6.90–7.30 (m, 4 H), 7.55 (dm, J = 7.5, 1 H); ^1H NMR (**19b**) 1.98 and 2.25 (2 m, 2 H), 2.99 (s, 3 H), 3.02 (m, 2 H), 3.25 (br s, 1 H), 3.69 and 3.73 (2 s, 6 H), 3.70 (m, 1 H), 4.65 (t, 1 H), 5.04 (d, J = 0.8, 1 H), 5.63 (d, J = 14.5, 1 H), 6.39 (s, 1 H), 6.90–7.30 (m, 4 H), 7.55 (dm, J = 7.5, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{23}H_{26}N_2O_5$ (mixture of diastereomers): C, 67.30; H, 6.38; N, 6.82. Found: C, 67.33; H, 6.52; N, 6.57.

1-Benzyl-3-[(*E*)-2-(methoxycarbonyl)vinyl]pyridinium Chloride (18). This compound was prepared as described for **3**, starting from methyl (*E*)-3-(3-pyridyl)acrylate[50] (5 g, 30 mmol) and benzyl chloride (3.8 mL, 4.17 g, 33 mmol): 8 g (92%); mp 164–165 °C (acetone–MeOH); IR (KBr) 1720 (CO); ^1H NMR (DMSO-d_6) 3.76 (s, 3 H), 5.94 (s, 2 H), 7.14 (d, J = 16, 1 H), 7.41 (m, 3 H), 7.64 (m, 2 H), 7.79 (d, J = 16, 1 H), 8.22 (dd, J = 7.5, 5.2, 1 H), 8.97 (d, J = 7.5, 1 H), 9.32 (d, J = 5.2, 1 H), 9.98 (s, 1 H). Anal. Calcd for $C_{16}H_{16}NO_2Cl$: C, 66.32; H, 5.56; N, 4.83; Cl, 12.23. Found: C, 66.36; H, 5.56; N, 4.78; Cl, 12.31.

Reaction of Ester 16 with Pyridinium Chloride 18. Operating as above, from ester **16** (1 g, 2.88 mmol), LDA (2.88 mmol), and pyridinium chloride **18** (0.55 g, 1.92 mmol) was obtained a crude residue which was chromatographed (flash, 1:1 hexane–Et_2O and Et_2O). On successive elution the following compounds were isolated. **Methyl 5-benzyl-7-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1α-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3(*E*)-acrylate (20b)**: 0.18 g (16%); IR ($CHCl_3$) 1575 (C=C), 1680, 1730 (CO); ^1H NMR 0.89 (s, 9 H), 1.93 (dt, J = 12.5, 2.5, 1 H), 2.30 (dm, J = 12.5, 1 H), 3.10 (m, 2 H), 3.35 (br s, 1 H), 3.74 and 3.77 (2 s, 6 H), 3.90 (m, 2 H), 4.31 and 4.60 (2d, J = 15, 2 H), 4.69 (t, 1 H), 5.11 (s, 1 H), 5.75 (d, J = 15.4, 1 H), 6.60 (s, 1 H), 7.10–7.50 (m, 9 H), 7.65 (d, J = 8, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{35}H_{44}N_2O_5Si$: C, 69.96; H, 7.38; N, 4.66. Found: C, 69.68; H, 7.34; N, 4.47. **Epimer 20a**: 0.15 g (13%); IR ($CHCl_3$) 1575 (C=C), 1680, 1715, 1740 (CO); ^1H NMR 0.89 (s, 9 H), 2.06 (m, 2 H), 3.06 (m, 2 H), 3.70 (masked, 1 H), 3.77 and 3.79 (2 s, 6 H), 3.90 (m, 2 H), 4.43 and 4.66 (2 d, J = 15.7, 2 H), 4.72 (t, 1 H), 4.99 (d, J = 5.2, 1 H), 5.51 (d, J = 15, 1 H), 6.81 (s, 1 H), 7.00–7.50 (m, 9 H), 7.65 (m, 1 H); ^{13}C NMR, Table I. **Methyl 3-benzyl-7-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-1β-(methoxycarbonyl)-1,2,3,6-tetrahydro-2,6-methano[1,4]diazocino[4,5-*a*]indole-5(*E*)-acrylate (22a)**: 80 mg (7%); mp 170–171 °C (Et_2O); IR (KBr) 1580 (C=C), 1690, 1750 (CO); ^1H NMR 0.89 (s, 9 H), 1.70 (dm, J = 12.5, 1 H), 1.90 (dt, J = 12.5, 2, 1 H), 3.15 (m, 2 H), 3.70 and 3.89 (2 s, 6 H), 3.80 (m, 2 H), 4.19 (t, 1 H), 4.35 (m, 1 H), 4.23 and 4.40 (2d, J = 15, 2 H), 4.95 (d, J = 5.5, 1 H), 5.95 (d, J = 15, 1 H), 6.72 (s, 1 H), 6.80–7.40 (m, 9 H), 7.60 (m, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{35}H_{44}N_2O_5Si$: C, 69.96; H, 7.38; N, 4.66. Found: C, 70.15; H, 7.44; N, 4.64.

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

(50) 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.

Methyl 3(*E*)-Ethylidene-7-(2-hydroxyethyl)-5-methyl-1,2,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β(and 1α)-carboxylate (24a and 24b). A suspension of tetracycles **19a,b** (0.4 g, 0.97 mmol) in 4 N aqueous HCl (30 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 (30 mL) and stirred at room temperature overnight. The solvent was removed, and the residue was dissolved in MeOH (30 mL), treated with $NaBH_4$ (0.3 g, 9 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 organic extracts were dried and evaporated to give a 3:1 mixture of **24a** and **24b** (0.14 g, 40%). Column chromatography (AcOEt–MeOH, increasing polarity) allowed the isolation of pure **24a**: IR (KBr) 1750 (CO), 3200–3600 (OH); ^{1}H NMR 1.67 (dd, J = 6.8, 2, 3 H), 1.80 (dm, J = 13.4, 1H), 2.43 (s, 3 H), 2.75 (d, J = 14, 1 H), 2.90 and 3.10 (2 m, 2 H), 3.36 (m, 1 H), 3.70 (s, 3 H), 3.80 (m, 2 H), 4.12 (t, 1 H), 5.03 (d, J = 6, 1 H), 5.47 (qd, J = 6.8, 1.4, 1 H), 7.02–7.30 (m, 3 H), 7.60 (m, 1 H); ^{13}C NMR, Table II. The picrate melted at 229–230 °C (acetone–Et_2O). Anal. Calcd for $C_{27}H_{29}N_5O_{10}$: C, 55.57; H, 5.00; N, 12.00.. Found: C, 56.18; H, 5.16; N, 11.69.

Methyl 5-Benzyl-3(*E*)-ethylidene-7-(2-hydroxyethyl)-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β(and 1α)-carboxylate (25a and 25b). Operating as above, from tetracycles **20a,b** (0.4 g, 0.66 mmol) was obtained a 2:1 mixture of **25a** and **25b** (0.11 g, 39%). Both isomers were separated by column chromatography (CH_2Cl_2–MeOH, increasing polarity). **25a**: IR (KBr) 1735 (CO), 3400 (OH); ^{1}H NMR 1.70 (d, J = 6.8, 3 H), 1.80 and 2.60 (2 dm, J = 13.2, 2 H), 2.77 (d, J = 14.5, 1 H), 2.90 and 3.10 (2 m, 2 H), 3.40 (br d, J = 14.5, 1 H), 3.70 (s, 3 H), 3.80 (m, 4 H), 4.27 (t, 1 H), 5.07 (d, J = 5.9, 1 H), 5.39 (q, J = 6.8, 1 H), 6.90–7.70 (m, 9H); ^{13}C NMR, Table II. The picrate melted at 137–138 °C (acetone–Et_2O). Anal. Calcd for $C_{33}H_{33}N_5O_{10}$·1.5H_2O: C, 57.72; H, 5.06; N, 10.20. Found: C, 57.38; H, 4.98; N, 9.99. **25b**: IR (KBr) 1740 (CO), 3350 (OH); ^{1}H NMR 1.81 (dd, J = 6.8, 1.9, 3 H), 2.05 (dt, J = 12.5, 2, 1 H), 2.45 (dm, J = 12.5, 1 H), 3.05 (m, 5 H), 3.76 (s, 3 H), 3.70 (m, 4 H), 4.28 (t, 1 H), 4.85 (s, 1 H), 5.40 (q, J = 6.8, 1 H), 6.90–7.50 (m, 8 H), 7.56 (m, 1 H); ^{13}C NMR, Table II.

Attempted Cyclization of 24a. A. A solution of **24a** (0.22 g, 0.62 mmol), mesyl chloride (0.07 mL, 0.93 mmol), and Et_3N (0.15 mL, 1.1 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C under N_2 for 2 h. The solvent was removed, and the residue was dissolved in DMF (10 mL). After the solution was heated at 90 °C overnight, the solvent was removed and the residue was dissolved in H_2O and extracted with Et_2O. The ethereal extract was dried and evaporated. Column chromatography (AcOEt) gave **methyl 7-(2-chloroethyl)-3(*E*)-ethylidene-5-methyl-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β-carboxylate (26a)**: 20 mg (8%); IR ($CHCl_3$) 1750 (CO); ^{1}H NMR 1.69 (dd, J = 6.8, 1.6, 3 H), 2.02 (dt, J = 13.2, 3.1, 1 H), 2.40 (masked, 1 H), 2.42 (s, 3 H), 3.30 (m, 2 H), 3.70 (m, 2 H), 3.75 (s, 3 H), 4.35 (t, 1 H), 5.00 (d, J = 6.2, 1 H), 5.60 (q, J = 6.8, 1 H), 6.90–7.20 (m, 3 H), 7.60 (m, 1 H); MS m/e (rel intensity) 374 (30), 372 (M^+, 100), 336 (89), 313 (65).

B. Alcohol 24a (90 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was allowed to react with mesyl chloride (0.032 mL, 0.44 mmol) and Et_3N (0.06 mL, 0.44 mol) at −20 °C under N_2 for 2 h. The solution was washed with 5% aqueous $NaHCO_3$, dried, and evaporated. NaI (56 mg, 0.37 mmol) was added to the resulting residue in CH_3CN (2 mL), and the mixture was heated at 70 °C for 3 h. Workup followed by flash chromatography (95:5 Et_2O–MeOH)) gave **methyl *cis*-5-(2-iodoethyl)-2-[1-[(*N*-methylmethanesulfonamido)methyl]-1(*E*)-propenyl]-1,2-dihydropyrido-[1,2-*a*]indole-1-carboxylate (31a)**: 50 mg (37%); IR ($CHCl_3$) 1150, 1330 (SO_2N), 1730 (CO); ^{1}H NMR 1.80 (d, J = 7.4, 3 H), 2.83 and 2.84 (2 s, 6 H), 3.20–4.01 (m, 6 H), 3.50 (s, 3 H), 4.20 (m, 1 H), 5.25 (d, J = 8.2, 1 H), 5.83 (q, J = 7.4, 1 H), 5.96 (dm, J = 10, 1 H), 6.75 (dt, J = 10, 3.2, 1 H), 7.10–7.30 (m, 3 H), 7.50 (dm, J = 8, 1 H); ^{13}C NMR 5.7, 14.8, 27.8, 34.1, 35.2, 38.4, 52.0, 55.9, 56.4, 108.8, 113.1, 116.7, 118.6, 120.3, 122.9, 124.9, 128.6, 129.8, 131.1, 136.8; MS m/e (rel intensity) 542 (M^+ 9), 483 (3), 415 (36), 232 (100), 180 (85).

C. Operating as above, from alcohol **24b** (0.11 g, 0.31 mmol) was obtained sulfonamide **31b** after flash chromatography (Et_2O): 60 mg (35%); IR ($CHCl_3$) 1150, 1330 (SO_2N), 1735 (CO); ^{1}H NMR 1.88 (dt, J = 7, 1.6, 3 H), 2.50 and 2.53 (2 s, 6 H), 3.20–3.90 (m, 6 H), 3.66 (s, 3 H), 4.30 (d, J = 6, 1 H), 4.93 (d, J = 1.5, 1 H), 5.79 (m, 2 H), 6.84 (m, 1 H), 7.10–7.30 (m, 3 H), 7.50 (dm, J = 8, 1 H); ^{13}C NMR 7.7, 13.2, 27.4, 34.7, 34.9 , 37.6, 51.4, 52.8, 57.7, 108.5, 110.0, 118.7, 119.5, 120.2, 122.1, 123.2, 1242, 128.5, 131.9, 133.5, 137.5, 170.7; MS m/e (rel intensity) 542 (M^+, 6), 483 (2), 415 (32), 232 (58), 180 (100).

Debenzylation of 25a,b. A mixture of tetracycles **25a,b** (0.32 g, 0.74 mmol) in MeOH (30 mL) was hydrogenated over $Pd(OH)_2$ (25%, 80 mg) at atmospheric pressure for 24 h. The usual workup gave a residue which was chromatographed. Elution with 9:1 CH_2Cl_2–MeOH gave **methyl 3β-ethyl-7-(2-hydroxyethyl)-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1α-carboxylate (28b)**: 63 mg (25%); IR (KBr) 1748 (CO), 3300 (OH, NH); ^{1}H NMR 1.02 (t, J = 7, 3 H), 1.39 (m, 2 H), 2.00–2.50 (m, 4 H), 2.70 (m, 1 H), 2.80–3.20 (m, 3 H), 3.73 (s, 3 H), 3.90 (m, 2 H), 4.57 (t, 1 H), 5.01 (s, 1 H), 7.10–7.30 (m, 3 H), 7.60 (d, J = 8, 1 H); ^{13}C NMR, Table II. Elution with 8:2 CH_2Cl_2–MeOH gave **methyl 3(*E*)-ethylidene-7-(2-hydroxyethyl)-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β-carboxylate (27a)**: 139 mg (55%); IR (KBr) 1731, 1755 (CO), 3330 (NH, OH); ^{1}H NMR 1.65 (dd, J = 6.8, 1.8, 3 H), 2.16 (m, 2 H), 2.80–3.40 (m, 3 H), 3.50 (d, J = 15, 1 H), 3.66 (m, 1 H), 3.71 (s, 3 H), 3.86 (m, 2 H), 4.47 (t, 1 H), 5.11 (d, J = 6 .1, 1 H), 5.45 (q, J = 6.8, 1 H), 6.80–7.30 (m, 3 H), 7.60 (d, J = 8, 1 H); ^{13}C NMR, Table II.

Attempted Cyclization of 27a. Operating as in the preparation of **26a**, from **27a** (90 mg, 0.26 mmol) sulfonamide **29a** was obtained after column chromatography (7:3 hexane–AcOEt): 50 mg (46%); IR (KBr) 1150, 1335 (SO_2N), 1748 (CO); ^{1}H NMR 1.72 (dd, J = 6.8, 1.7, 3 H), 2.06 and 2.30 (2 dm, J = 13, 2 H), 2.77 (s, 3 H), 3.40 (m, 3 H), 3.72 (m, 2 H), 3.79 (s, 3 H), 3.82 (m, 2 H), 5.04 (d, J = 6.3, 1 H), 5.57 (t, 1 H), 5.60 (q, J = 6.8, 1 H), 6.90–7.30 (m, 3 H), 7 .60 (d, J = 8, 1 H); ^{13}C NMR, Table II.

Attempted Cyclization of 28b. Operating as above, from **28b** (0.11 g, 0.32 mmol) was obtained sulfonamide **30b**: 70 mg (50%); IR (KBr) 1150, 1330 (SO_2N), 1748 (CO); ^{1}H NMR 1.08 (t, J = 7, 3 H), 1.50 (m, 2 H), 2.01–2.69 (m, 4 H), 2.70 (s, 3 H), 3.50 (m, 4 H), 3.67 (s, 3 H), 3.78 (m, 2 H), 5.04 (s, 1 H), 5.48 (t, 1 H), 7.10–7.30 (m, 3 H), 7.60 (d, J = 8, 1 H); ^{13}C NMR, Table II.

1-(3-Acetoxypropyl)-3-[(*E*)-2-(methoxycarbonyl)vinyl]-pyridinium Bromide (32). This salt was prepared as described for **3**, starting from methyl (*E*)-3-(3-pyridyl)acrylate (4.9 g, 29 mmol) and 3-bromopropyl acetate[51] (6.5 g, 35 mmol): 8.6 g (86%); mp 106–107 °C (MeOH); IR (KBr) 1720 (CO); ^{1}H NMR (DMSO-d_6) 1.89 (s, 3 H), 2.31 (t, 2 H), 3.77 (s, 3 H), 4.09 (t, 2 H), 4.70 (t, 2 H), 7.10 (d, J = 16, 1 H), 7.78 (d, J = 16, 1 H), 8.21 (dd, J = 7.7, 5.5, 1 H), 8.94 (d, J = 7.7, 1 H), 9.12 (d, J = 5. 5, 1 H), 9.58 (s, 1 H). Anal. Calcd for $C_{14}H_{18}NO_4Br$·1/4H_2O: C, 48.22; H, 5.34; N, 4.01; Br, 22.91. Found: C, 48.14; H, 5.32; N, 4.00; Br, 29.93.

Methyl 5-(3-Acetoxypropyl)-1β(and 1α)-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3(*E*)-acrylate (33a and 33b). Operating as in the preparation of tetracycles **9**, from ester **1** (1 g, 5.29 mmol), LDA (6.34 mmol), and pyridinium bromide **32** (1.18 g, 3.42 mmol) was obtained a nearly equimolecular mixture of tetracycles **33a,b** (0.23 g, 15%) after column chromatography (hexane–AcOEt, increasing polarity). Both isomers were separated by additional column chromatography (hexane–AcOEt, increasing polarity). **33a**: mp 95–96 °C (*i*-Pr_2O); IR (film) 1570 (C=C), 1680, 1720 (CO); ^{1}H NMR 1.83 (m, 4 H), 2.06 (s, 3 H), 3.30 and 3.50 (2 m, 2 H), 3.68 (s, 6 H), 3.70 (masked, 1 H), 4.15 (m, 2 H), 4.51 (t, 1 H), 4.97 (d, J = 5.2, 1 H), 5.40 (d, J = 15, 1 H), 6.38 (s, 1 H), 6.57 (s, 1 H), 6.90–7.30 (m, 4 H), 7.60 (m, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{25}H_{28}N_2O_6$·1/2H_2O: C, 65.06; H, 6.33; N, 6.07. Found: C, 64.63; H, 6.14; N, 5.94. **33b**: ^{1}H NMR 1.99 (m, 3 H), 2.02 (s, 3 H), 2.40 (dt, J = 13, 2.3, 1 H), 3.20 and 3.50 (2 m, 2 H), 3.33 (br s, 1 H), 3.73 and 3.78 (2 s, 6 H), 4.14 (m, 2 H), 4.53 (t, 1 H), 5.05 (s, 1 H), 5.69 (d, J = 15, 1 H), 6.40 (s, 1 H), 6.45 (s, 1 H), 7.00–7.30 (m, 4 H), 7.58 (d, J = 8, 1 H); ^{13}C NMR, Table I.

Methyl 5-(3-Hydroxypropyl)-1β(and 1α)-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3(*E*)-acrylate (34a and 34b). A mixture of tetracycles

(51) Prepared by reaction of 3-bromopropanol with Ac_2O (80 °C, 1.5 h).

33a,b (0.75 g, 1.65 mmol) was stirred overnight at room temperature with a 1 N MeOH solution of dry HCl (25 mL). After workup and column chromatography (hexane–AcOEt, increasing polarity), a mixture of tetracycles **34a,b** was obtained: 0.4 g (59%); mp 139–140 °C (*i*-Pr_2O–acetone); ^1H NMR (**34a**) 1.90 (m, 4 H), 3.30 and 3.50 (2 m, 2 H), 3.70 (s, 6 H), 3.70 (masked, 3 H), 4.55 (t, 1 H), 4.95 (d, J = 5, 1 H), 5.40 (d, J = 15, 1 H), 6.40 (s, 1 H), 6.70 (s, 1 H), 6.90–7.30 (m, 4 H), 7.60 (d, J = 8, 1 H); ^1H NMR (**34b**) 1.90 (m, 3 H), 2.40 (dt, J = 13, 2, 1 H), 3.20 and 3.50 (2 m, 2 H), 3.35 (br s, 1 H), 3.70 and 3.80 (2 s, 6 H), 3.70 (masked, 2 H), 4.55 (t, 1 H), 5.05 (s, 1 H), 5.70 (d, J = 15, 1 H), 6.40 (s, 1 H), 6.50 (s, 1 H), 7.00–7.30 (m, 4 H), 7.60 (d, J = 8, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{23}H_{26}N_2O_5 \cdot 1/2H_2O$ (mixture of diastereomers): C 65.84; H, 6.49; N, 6.68. Found: C, 65.58; H, 6.41; N, 6.41.

Methyl 3(*E*)-Ethylidene-5-(3-hydroxypropyl)-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β(and 1α)-carboxylate (36a and 36b). Operating as in the preparation of compounds **24**, from a mixture of tetracycles **33a,b** (0.5 g, 1.1 mmol) a nearly equimolecular mixture of **36a,b** (0.15 g, 38%) was obtained. Column chromatography (hexane–AcOEt, increasing polarity) allowed the isolation of pure **36b**: mp 123–124 °C (Et_2O); IR (KBr) 1740 (CO), 3400 (OH); ^1H NMR 1.78 (dd, J = 6.7, 2.1, 3 H), 2.07 (dt, J = 13, 3.5, 1 H), 2.20–2.90 (m, 6 H), 3.17 (d, J = 13, 1 H), 3.55 (br s, 1 H), 3.73 (s, 3 H), 3.83 (m, 2 H), 4.27 (t, 1 H), 4.84 (s, 1 H), 5.50 (qd, J = 6.7, 1.6, 1 H), 6.37 (s, 1 H), 7.00–7.30 (m, 3 H), 7.60 (d, J = 8, 1 H); ^{13}C NMR , Table II. Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.90. Found: C, 71.29; H, 7.55; N, 7.76.

Methyl 3(*E*)-Ethylidene-5-(trifluoroacetyl)-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β(and 1α)-carboxylate (37a and 37b). A mixture of alcohols **36a,b** (0.1 g, 0.28 mmol) was treated with TFAA (0.13 mL, 0.84 mmol), DMSO (0.08 mL, 1.12 mmol), and Et_3N (0.22 mL, 1.68 mmol) as described in the oxidation of **10a**. The usual workup gave **37a,b**: 35 mg (32%). Flash chromatography (Et_2O) allowed the isolation of pure **37a**: mp 107–109 °C (MeOH); IR (KBr) 1675, 1735 (CO); ^1H NMR 1.63 and 1.65 (2dd, J = 7.2, 3 H), 2.15 (m, 2 H), 3.60 (m, 1 H), 3.69 (s, 3 H), 3.84 (m, 1 H), 4.01 (m, 2 H), 4.58 (d, J = 15, 1 H), 5.06 and 5.07 (2dd, J = 6.1, 2.8, 1 H), 5.43 and 6.05 (2 t, 1 H), 5.55 and 5.60 (2 q, J = 7, 1 H), 6.45 and 6.49 (2 s, 1 H), 6.90–7.30 (m, 3 H), 7.63 (dd, J = 8, 1.5, 1 H); ^{13}C NMR, Table II. Anal. Calcd for $C_{20}H_{19}N_2O_3F_3$: C, 61.22; H, 4.88; N, 7.14. Found: C, 61.29; H, 4.90; N, 7.09.

Reaction of Ester 1 with Pyridinium Chloride 18. Operating as in the preparation of tetracycles **9**, from ester **1** (1 g, 5.29 mmol), LDA (6.34 mmol), and pyridinium chloride **18** (1 g, 3.45 mmol), a residue was obtained and then chromatographed (hexane–AcOEt, increasing polarity). The initial elution gave **methyl 5-benzyl-1β(and 1α)-(methoxycarbonyl)-1,2,5,6-tetrahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-3(*E*)-acrylate (35a and 35b)**: 0.5 g (equimolecular mixture, 33%); mp 97–98 °C (*i*-Pr_2O–acetone); IR (KBr) 1578 (C=C), 1690, 1730 (CO); ^1H NMR (**35b**) 1.97 (dt, J = 13, 3.6, 1 H), 2.35 (dt, J = 13, 2.5, 1 H), 3.35 (br s, 1 H), 3.75 and 3.76 (2 s, 6 H), 4.2 0 and 4.47 (2 d, J = 15, 2 H), 4.44 (t, 1 H), 5.07 (s, 1 H), 5.70 (d, J = 15, 1 H), 6.38 (s, 1 H), 6.54 (s, 1 H), 7.05–7.40 (m, 9 H), 7.60 (d, J = 8, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{27}H_{26}N_2O_4.1/2H_2O$ (mixture of diastereomers): C, 71.82; H, 6.02; N, 6.20. Found: C, 71.45; H, 5.95; N, 5.97. Further elution gave a nearly equimolar mixture of **methyl 3-benzyl-1β(and 1α)-(methoxycarbonyl)-1,2,3,6-tetrahydro-2,6-methano[1,4]diazocino[4,5-*a*]indole-5(*E*)-acrylate (46a and 46b)**: 0.45 g (30%); mp 218–219 °C (*i*-Pr_2O–acetone); IR (KBr) 1582 (C=C), 1693, 1748 (CO); ^1H NMR (**46a**) 1.70 (dt, J = 13, 3, 1 H), 1.96 (dt, J = 13, 2.5, 1 H), 3.73 and 3.85 (2 s, 6 H), 3.98 (br s, 1 H), 4 .10 and 4.40 (2 d, J = 15, 2 H), 4.30 (t, 1H), 5.07 (d, J = 5.7, 1 H), 5.85 (d, J = 15, 1 H), 6.38 (s, 1 H), 6.65 (s, 1 H), 6.90–7.50 (m, 9 H), 7.55 (m, 1 H); ^1H NMR (**46b**) 1.85 (dt, J = 13, 3, 1 H), 2.35 (dt, J = 13, 2, 1 H), 3.63 and 3.73 (2s, 6 H), 3.98 (br s, 1 H), 4.10 and 4.40 (2 d, J = 15, 2 H), 4.34 (t, 1 H), 5.02 (s, 1 H), 5.80 (d, J = 15, 1 H), 6.38 (s, 1 H), 6.50 (s, 1 H), 7.05–7.50 (m, 9 H), 7.52 (m, 1 H); ^{13}C NMR, Table I. Anal. Calcd for $C_{27}H_{26}N_2O_4 \cdot 1/4H_2O$ (mixture of diastereomers): C, 72.54; H, 5.97; N, 6.26. Found: C, 72.61; H, 6.00; N, 6.28.

Methyl 5-Benzyl-3(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β(and 1α)-carboxylate (38a and 38b). Operating as in the preparation of **24**, from a mixture of tetracycles **35a,b** (0.5 g, 1.13 mmol) was obtained a 3:2 mixture of **38a** and **38b** (0.15 g, 34%). Both isomers were separated by column chromatography (hexane–AcOEt, increasing polarity). **38a**: mp 192–194 °C (*i*-Pr_2O); IR (KBr) 1748 (CO); ^1H NMR 1.65 (d, J = 6.7, 3 H), 2.03 (dt, J = 13, 3, 1 H), 2.25 (dt, J = 13, 3.5, 1 H), 3.30–3.80 (m, 5 H), 3.72 (s, 3 H), 4.10 (t, 1 H), 5.02 (d, J = 6, 1 H), 5.45 (q, J = 6.7, 1 H), 6.34 (s, 1 H), 6.90–7.50 (m, 8 H), 7.60 (m, 1 H); ^{13}C NMR, Table II. Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.24. Found: C, 77.41; H, 7.03; N, 6.95. **38b**: ^1H NMR 1.76 (dd, J = 6.7, 2, 3 H), 2.10 (dt, J = 13, 3, 1 H), 2.26 (dt, J = 13, 2.5, 1 H), 2.50 (br d, J = 13.5, 1 H), 2.95 (d, J = 13.5, 1 H), 3.30–3.60 (m, 3 H), 3.68 (s, 3 H), 4.06 (t, 1 H), 4.84 (s, 1 H), 5.39 (q, J = 6.7, 1 H), 6.36 (s, 1 H), 7.05–7.50 (m, 8 H), 7.65 (m, 1 H); ^{13}C NMR, Table II.

Methyl 5-[3,3-Bis(methylthio)propyl]-3(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β-carboxylate (42). Tetracycle **38a** (0.4 g, 1 mmol) was hydrogenated over $Pd(OH)_2$ (25%, 90 mg) at atmospheric pressure for 24 h. The usual workup gave crude **39a** (0.3 g) which was used without further purification. A stirred solution of amine **39a** (0.3 g, 1 mmol) in MeOH (30 mL) was allowed to react under N_2 with acrolein (0.13 mL, 2 mmol) and Et_3N (0.26 mL, 2 mmol) at room temperature for 3 h. The solvent was removed, and the residue was dissolved in H_2O and extracted with Et_2O. Evaporation of the organic extract gave crude aldehyde **41**, which was dissolved in CH_2Cl_2 (30 mL) and treated with an excess of CH_3SH (3 mL) in the presence of $BF_3 \cdot Et_2O$ (0.32 mL) at −30 °C for 3 h. Workup and column chromatography (3:7 hexane–AcOEt) gave **42**: 0.178 g (41%); ^1H NMR 1.67 (dd, J = 6.8, 3 H), 2.10 (m, 4 H), 2.11 and 2.13 (2 s, 6 H), 2.47 (m, 1 H), 2.70–3.05 (m, 3 H), 3.70 (masked, 1 H), 3.73 (s, 3 H), 3.81 (t, J = 7, 1 H), 4.15 (t, 1 H), 5.01 (d, J = 6.1, 1 H), 5.53 (q, J = 6.8, 1 H), 6.37 (s, 1 H), 6.90–7.20 (m, 3 H), 7.62 (m, 9-H); ^{13}C NMR, Table II. The hydrochloride melted at 124–126 °C (acetone–Et_2O). Anal. Calcd for $C_{23}H_{31}N_2O_2S_2Cl \cdot H_2O$: C, 56.94; H, 6.85; N, 5.77; S, 13.21. Found: C, 56.74; H, 6.63; N, 5.52; S, 13.32.

Methyl 5-(3,3-Dimethoxypropyl)-3(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole-1β-carboxylate (43). A solution of crude **39a** (90 mg, 0.3 mmol) and 3-bromopropanaldehyde dimethyl acetal (0.06 mL, 0.45 mmol) in anhydrous dioxane (9 mL) containing Na_2CO_3 (64 mg, 0.6 mmol) was refluxed under N_2 for 24 h. The solvent was evaporated, and the residue was dissolved in H_2O and extracted with Et_2O. Evaporation of the organic extract gave **43** after column chromatography (AcOEt): 40 mg (33%); ^1H NMR 1.68 (dd, J = 6.8, 1.8, 3 H), 1.80–2.70 (m, 6 H), 2.90 (br d, J = 13, 1 H), 3.05 (d, J = 13, 1 H), 3.33 and 3.35 (2 s, 6 H), 3.73 (s, 3 H), 3.75 (m, 1 H), 4.20 (t, 1 H), 4.50 (m, 1 H), 5.03 (d, J = 6, 1 H), 5.54 (q, J = 6.8, 1 H), 6.37 (s, 1 H), 6.90–7.20 (m, 3 H), 7.65 (m, 1 H); ^{13}C NMR, Table II.

(±)-6a-Homopleiocarpamine (45). To a solution of DMTSF[28] (76.5 mg, 0.39 mmol) in CH_2Cl_2 (40 mL) at −70 °C was slowly added under N_2 a solution of dithioacetal **42** (80 mg, 0.18 mmol) in CH_2Cl_2 (2 mL). The mixture was allowed to rise to −30 °C and stirred at this temperature for 1.5 h and at 0 °C for 3 h. The reaction mixture was quenched with 10% aqueous Na_2CO_3 (50 mL) and stirred at room temperature for 30 min. The organic layer was dried and evaporated, and the residue was chromatographed (8:2 AcOEt–DEA) to give alcohol **44**: 25 mg (38%); ^1H NMR 1.59 (dd, J = 6.9, 2, 3 H), 1.70–2.10 (m, 4 H), 2.90 (m, 3 H), 3.60 (s, 3 H), 3.72 (m, 1 H), 3.98 (br t, J = 12, 1 H), 4.88 (t, 1 H), 5.17 (d, J = 5.4, 1 H), 5.24 (dd, J = 5.4, 2.5, 1 H), 5.47 (q, J = 6.9, 1 H), 6.90–7.20 (m, 3 H), 7.55 (m, 1 H); ^{13}C NMR, Table II.

A solution of alcohol **44** (30 mg, 0.085 mmol), TFA (0.075 mL, 0.97 mmol), and Et_3SiH (0.05 mL, 0.3 mmol) in CH_2Cl_2 (3 mL) and refluxed under N_2 for 2 h. The mixture was poured into ice–H_2O, basified with solid Na_2CO_3, and extracted with CH_2Cl_2. Evaporation of the dried extracts gave a residue which was chromatographed (flash, 97:3 AcOEt–DEA) to give **45**: 23 mg (80%); IR ($CHCl_3$) 1732, 1759 (CO); UV (EtOH) λ max 201, 226, 277 nm; ^1H NMR 1.50 (m, 2 H), 1.61 (dd, J = 6.8, 2, 3 H), 2.20 (m, 2 H), 2.70–3.50 (m, 6 H), 3.60 (s, 3 H), 3.72 (m, 1 H), 4.50 (t, 1 H), 5.17 (d, J = 5.4, 1 H), 5.47 (q, J = 6.8, 1 H), 6.90–7.20 (m, 3 H), 7.52 (m, 1 H); ^{13}C NMR, Table II; MS m/e (rel intensity)

336 (M^+, 100), 277 (35), 180 (25); HRMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1816.

Methyl 5-(Chloroacetyl)-3β-ethyl-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-a]indole-1α-carboxylate (47). Tetracycle **38b** (1 g, 2.59 mmol) was hydrogenated over $Pd(OH)_2$ as described for **38a** to give the crude amine **40b** (0.75 g). Chloroacetyl chloride (0.25 mL, 2.83 mmol) in CH_2Cl_2 (20 mL) was slowly added to a solution of **40b** (0.75 g, 2.52 mmol) and Et_3N (0.63 mL, 5 mmol) in CH_2Cl_2 (10 mL), and the resulting solution was stirred at room temperature for 2 h. The mixture was washed with 10% aqueous Na_2CO_3 solution, dried, and evaporated. Column chromatography (1:1 hexane–AcOEt) of the resulting residue gave chloroacetamide **47** (0.58 g, 60%): mp 109–110 °C (Et_2O); IR (KBr) 1647, 1750 (CO); ^1H NMR 1.09 (t, J = 7, 3 H), 1.49 (m, 2 H), 1.97 (dt, J = 13.6, 3.7, 1 H), 2.10 (m, 1 H), 2.37 (dt, J = 13.6, 3.3, 1 H), 2.56 (dd, J = 13.4, 12.6, 1 H), 2.70 (m, 1 H), 3.55 (dd, J = 13.4, 6, 1 H), 3.72 (s, 3 H), 3.95, 4.05, 4.20, and 4.30 (4 d, J = 12, 2 H), 5.05 (s, 1 H), 5.32 and 6.09 (2 t, 1 H), 6.47 (s, 1 H), 7.09–7.30 (m, 3 H), 7.60 (d, J = 8, 1 H); ^{13}C NMR, Table II. Anal. Calcd for $C_{20}H_{23}N_2O_3Cl$: C, 64.08; H, 6.18; N, 7.47. Found: C, 64.06; H, 6.18; N, 7.55.

(±)-2α-Hydroxy-5-oxo-2α,7α,19,20α-tetrahydro-16-epipleiocarpamine (49). A solution of chloroacetamide **47** (0.1 g, 0.267 mmol) in MeOH–H_2O (1:1, 200 mL) containing $NaHCO_3$ (0.16 g) was irradiated under N_2 at room temperature for 45 min using a 125-W medium-pressure mercury lamp in a quartz immersion well reactor. The reaction mixture was evaporated to dryness, and the residue was chromatographed (flash, 9:1:1 Et_2O–EtOH–DEA) to give alcohol **49**: 24 mg (25%); IR (film) 1656, 1735 (CO), 3400 (OH); ^1H NMR 0.94 (t, J = 7, 3 H), 1.20 (m, 3 H), 2.05 (m, 2 H), 2.30–2.70 (m, 2 H), 2.90 (m, 2 H), 3.60 (br d, J = 7, 1 H), 3.82 (s, 3 H), 3.87 (br d, J = 4.5, 1 H), 3.98 (dd, J = 13, 1.3, 1 H), 4.33 (s, 1 H), 6.25 (d, J = 8, 1 H), 6.71 (t, J = 8, 1 H), 7.11 (m, 2 H); ^{13}C NMR, Table II; MS m/e (rel intensity) 338 (59, M − 18), 279 (100), 180 (84).

When MeOH was used as the solvent, methoxyindoline **48** (δ3.75, 3 H) was isolated in 10% yield after column chromatography (flash, 95:5 AcOEt–DEA).[43]

(±)-5-Oxo-2α,7α,19,20α-tetrahydro-16-epipleiocarpamine (50). Operating as in the preparation of **45**, from alcohol **49** (225 mg, 0.63 mmol), TFA (0.55 mL, 6.7 mmol), and Et_3SiH (0.39 mL, 2.2 mmol) was obtained a residue, which was chromatographed (flash, 9:0.5:0.5 Et_2O–EtOH–DEA) to give **50**: 150 mg (70%); IR (KBr) 1656, 1735 (CO); ^1H NMR 0.96 (t, J = 7, 3 H), 1.20 (m, 3 H), 2.05 (m, 2 H), 2.28 (dm, J = 14, 1 H), 2.50 (m, 3 H), 2.95 (dd, J = 14, 7.4, 1 H), 3.70 (s, 3 H), 3.84 (br d, J = 5. 1, 1 H), 4.08 (dd, J = 14, 1.4, 1 H), 4.24 (s, 1 H), 4.43 (dd, J = 10, 1.4, 1 H), 6.12 (d, J = 8, 1 H), 6.53 (t, J = 8, 1 H), 6.98 (m, 2 H); ^{13} NMR, Table II; MS m/e (rel intensity) 340 (M^+, 31), 281 (100); HRMS calcd for $C_{20}H_{24}N_2O_3$ 340,1787, found 340,1781.

(±)-2α,7α,19,20α-Tetrahydro-16-epipleiocarpamine (52). A solution of amide **50** (0.1 g, 0.294 mmol) and Lawesson's reagent (68 mg, 0.17 mmol) in dry toluene (30 mL) was refluxed for 2 h. The solution was evaporated, and the resulting residue was chromatographed (flask, 9:0.5:0.5 Et_2O–EtOH–DEA) to give thioamide **51**: 75 mg (73%); ^1H NMR 1.00 (t, J = 7, 3 H), 1.30 (m, 3 H), 2.10 (m, 2H, 2 H), 2.40 (dt, J = 14, 3, 1 H, 1 H), 2.65 (br s, 1 H), 2.95 (dd, J = 15, 6, 1 H), 3.25 (dd, J = 14, 5, 1 H), 3.50 (dd, J = 16, 1.3, 1 H), 3.75 (s, 3 H), 3.85 (br s, 1 H), 4.29 (s, 1 H), 4.55 (d, J = 15, 1 H), 5.24 (d, J = 14, 1 H), 6.17 (d, J = 8, 1 H), 6.60 (t, J = 8, 1 H), 7.06 (m, 2 H).

$NaBH_4$ (0.31 g, 8.4 mmol) was slowly added to a solution of thioamide **51** (125 mg, 0.35 mmol) and $NiCl_2·6H_2O$ (0.66 g, 2.8 mmol) in MeOH–THF (1:1, 80 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The solvents were removed and the resulting residue was digested with hot CH_2Cl_2. Evaporation of the organic solution followed by flash chromatography (9:1:1 Et_2O–EtOH–DEA) gave **52**: 70 mg (60%); IR (KBr) 1737 (CO); ^1H NMR 0.97 (t, J = 7, 3 H), 1.45 (m, 4 H), 1.93 (m, 3 H), 2.26 (br s, 1 H), 2.57 (dd, J = 11, 6, 1 H), 3.05 (m, 3-H), 3.69 (s, 3 H), 3.70 (masked, 1 H), 4.21 (s, 1 H), 6.25 (d, J = 7, 1 H), 6.64 (t, J = 7, 1 H), 7.07 (m, 2 H); ^{13}C NMR, Table II; MS m/e (rel intensity) 326 (M^+ + 21), 267 (100); HRMS calcd for $C_{20}H_{26}N_2O_2$ 326.1994, found 326.1998.

Methyl 5-Acetyl-3β-ethyl-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-a]indole-1α-carboxylate (53). A solution of chloroacetamide **47** (50 mg, 0.13 mmol), Bu_3SnH (0.1 mL, 0.39 mmol), and AIBN (catalytic amount) in toluene (50 mL) was refluxed for 1 h. The solvent was removed, and the resulting residue was chromatographed (flash, 9:0.5:0.5 Et_2O–EtOH–DEA) to give acetamide **53**: 43 mg (98%); mp 134 °C (acetone–Et_2O); IR (KBr) 1629, 1742 (CO); ^1H NMR 1.08 (t, J = 7, 3 H), 1.45 (m, 2 H), 1.85 (m, 3 H), 2.02 and 2.30 (2 s, 3 H), 2.50 (dd, J = 13, 12.8, 1 H), 2.66 (m, 1 H), 3.48 and 4.40 (2 dd, J = 12.8, 4, 1 H), 3.70 and 3.72 (2 s, 3 H), 5.03 (s, 1 H), 5.22 and 6.16 (2 t, 1 H), 6. 39 and 6.45 (2 s, 1 H), 7.10–7.25 (m, 3 H), 7.60 (dm, J = 8, 1 H); ^{13}C NMR, Table II. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.10; N, 8.23. Found: C, 70.71; H, 7.06; N, 8.56.

Methyl 5-(Chloroacetyl)-3(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-2,6-methano[1,4]diazocino[1,2-a]indole-1β-carboxylate (54). Operating as described for **47**, from amine **39a** (0.72 g, 2.43 mmol), chloroacetyl chloride (0.25 mL, 2.68 mmol), and Et_3N (0.62 mL, 4.83 mmol) was obtained chloroacetamide **54**: 0.59 g (61%); mp 168–170 °C (i-Pr_2O); IR (KBr) 1646, 1752 (CO); ^1H NMR 1.69 (dd, J = 6.8, 1, 3 H), 2.12 (m, 2 H), 3.55 (br d, J = 14, 1 H), 3.74 (s, 3 H), 3.88 (br, 1 H), 4.02 (m, 3 H), 5.12 (d, J = 6.1, 1 H), 5.40 and 6.16 (2 t, 1 H), 5.62 (q, J = 6.8 , 1 H), 6.53 (s, 1 H), 6.94–7.25 (m, 3 H), 7.60 (d, J = 7, 1 H); ^{13}C NMR, Table II. Anal. Calcd for $C_{20}H_{21}N_2O_3Cl·1/2H_2O$: C, 62.91; H, 5.80; N, 7.33. Found: C, 62.95; H, 5.75; N, 7.04.

(±)-2α-Hydroxy-5-oxo-2α,7α-dihydropleiocarpamine (55). Operating as described in the preparation of pentacycle **49** except for the irradiation time (15 min), from chloroacetamide **54** (0.1 g, 0.269 mmol) was obtained pentacycle **55**: 17 mg (18%); IR (KBr) 1632, 1732, 1758 (CO), 3400 (OH); ^1H NMR 1.52 (dd, J = 7, 1, 3 H), 2.05 (dm, J = 13.6, 1 H, 1 H), 2.51 (d, J = 15.7, 1 H), 2.77 (dm, J = 13.6, 1 H), 2.86 (dd, J = 15.7, 9.8, 1 H), 3.27 (d, J = 9.8, 1 H), 3.45 (br d, J = 16.6, 1 H), 3.56 (br, 1 H), 3.60 (s, 3 H), 4.02 (d, J = 4.3, 1 H), 4.49 (d, J = 5, 1 H), 4.85 (d, J = 16.6, 1 H), 5.38 (q, J = 7, 1 H), 6.05 (d, J = 7, 1 H), 6.70 (t, J = 7, 1 H), 7.05 (m, 2 H); ^{13}C NMR, Table II.

(±)-5-Oxo-2α,7α-dihydropleiocarpamine (56). Operating as in the preparation of **50**, from alcohol **55** (190 mg, 0.536 mmol) was obtained **56**: 90 mg (50%); IR (KBr) 1649, 1732, 1755 (CO); ^1H NMR 1.52 (dd, J = 7, 1.3, 3 H), 2.01 (dm, J = 14, 1 H), 2.36 (dm, J = 14, 1 H), 2.45 (d, J = 15.8, 1 H), 2.66 (dd, J = 15.8, 10, 1 H), 3.50 (m, 3 H), 3.66 (s, 3 H), 3.80 (d, J = 8, 1 H), 4.01 (m, 2 H), 5.00 (d, J = 16.6, 1 H), 5.45 (q, J = 7, 1 H), 6.00 (d, J = 8, 1 H), 6.64 (t, J = 8, 1 H), 7.01 (m, 2 H); ^{13}C NMR, Table II; MS m/e (rel intensity) 338 (M^+, 45), 279 (100); HRMS calcd for $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1628.

(±)-2α,7α-Dihydropleiocarpamine (58). Amide **56** (90 mg, 0.26 mmol) was treated with Lawesson's reagent (60 mg, 0.15 mmol) and then worked up as described for **51** to give crude thioamide **57**: 60 mg (64%).

Thioamide **57** (30 mg, 0.084 mmol) and $NiCl_2·6H_2O$ (140 mg, 0.58 mmol), in MeOH–THF (1:1, 20 mL), were treated with $NaBH_4$ (67 mg, 1.76 mmol) at −30 °C for 5 min. Workup followed by flash chromatography (9:0.5:0.5 Et_2O–EtOH–DEA) gave **58**: 12 mg (45%); ^1H NMR 1.53 (dd, J = 6.7, 2, 3 H), 1.90 and 2.10 (2 m, 4 H), 2.80–3.10 (m, 4 H), 3.15 (m, 2 H), 3.25 (m, 1 H), 3.67 (s, 3 H), 4.00 (d, J = 3.4, 1 H), 4.40 (dm, J = 12.4, 1 H), 5.45 (qd, J = 6.7, 2, 1 H), 6.12 (d, J = 8, 1 H), 6.69 (t, J = 8, 1 H), 7.02 (m, 2 H); ^{13}C NMR, Table II; MS m/e (rel intensity) 324 (M^+, 30), 265 (70), 135 (100); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324,1838, found 324,1824.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds (43 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.