Synthetic Efforts toward Akuammiline Alkaloids from Tetracyclic 6,7-Seco Derivatives

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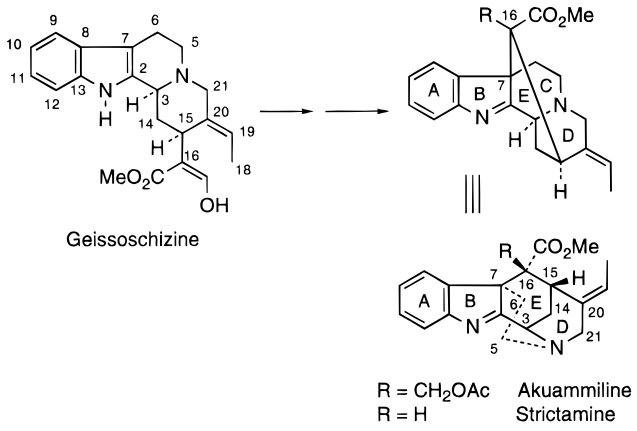
The addition of enolates derived from indole-3-acetic esters **1**−**3** to pyridinium salts **4**, **23**, and **24**, followed by acid cyclization of the resulting 1,4-dihydropyridines, leads to tetrahydro-1,5-methanoazocino[3,4-*b*]indoles **5**−**7**, **25**−**27**, which have been subsequently elaborated into 4*E*-ethylidene(or 4α-ethyl)-hexahydro-1,5-methanoazocino[3,4-*b*]indoles. Closure of the six-membered C ring of akuammiline alkaloids by formation of C-6/C-7 bond from appropriately $N_{(b)}$-substituted derivatives of these tetracyclic ABDE substructures has been extensively investigated. In the *N*-unsubstituted indole series, both cyclization of thionium ions generated either by Pummerer reaction from sulfoxide **16** or by DMTSF treatment of dithioacetal **36** and photocyclization of chloroacetamide **47** occur upon the indole nitrogen to give pentacycles **18**, **38**, and **49**, respectively. When the indole nitrogen is blocked by a substituent, the thionium ions derived from sulfoxides **17** and **43** and dithioacetals **37** and **44** do not cyclize and lead to different products depending on the reaction conditions, whereas chloroacetamides **48** and **51** undergo a reductive photodehalogenation. Attempted radical cyclization of seleno derivatives **53**, **55**, and **56** under a variety of conditions gives the corresponding reduced products. Finally, attempted photoisomerization of 1-acylindole **62** leads to the $N_{(b)}$-methyl tetracycle **63**.

The akuammiline-type alkaloids[1] (*i.e.* akuammiline, strictamine; *Chemical Abstracts* stereoparent: akuammilan) constitute a subgroup of Corynanthean indole alkaloids[2] and are structurally characterized by the presence of a bond between C-7 and C-16,[3] giving an additional ring E. Consequently, they incorporate a bridged pentacyclic 2,7a-methanoindolo[2,3-*a*]quinolizine system, with an *E*-configured ethylidene substituent at C-20 and one or two oxidized one-carbon substituents at C-16. Most of these alkaloids have an indolenine ring (or an equivalent oxidation level), the indoline bases being less frequent. The same carbon skeleton (C-7/C-16 bond) is also found in other structural variations, in which additional epoxy bridges are present (*i.e.* picraline; 2,5-epoxyakuammilan) or bonds with the piperidine nitrogen have been broken or formed (*i.e.* echitamine; 2,4-cyclo-3,4-secoakuammilan).[4]

Scheme 1



Biogenetically, the akuammiline alkaloids are formally derived from geissoschizine (Scheme 1), a key intermediate along the biosynthetic pathway of monoterpenoid indole alkaloids, although the mechanism of the formation of the C-7/C-16 bond still remains unknown.[5,6] These alkaloids also constitute one half of several bisindole alkaloids.[7]

The additional C-7/C-16 bond causes these molecules to possess an unusual and compact ring system, in which rings D and E adopt a boat conformation. Probably due to this complex architecture, these alkaloids, as well as their structural variations, remain synthetically inaccessible to date. In fact, not even model structures embodying the characteristic pentacyclic skeleton of these alkaloids have been synthesized so far. Attempts to close the C-6/C-7 bond from a model, unfunctionalized tetracyclic ABDE substructure met with no success,[8] and the biomimetic construction of the akuammiline alkaloids by formation of the C-7/C-16 bond from a tricyclic C/D ring-cleaved indolo[2,3-a]quinolizidine resulted in failure.[9,10]

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1996.

(1) (a) Joule, J. A. In *Indoles, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4, pp 244−264. (b) Alvarez, M.; Joule, J. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4, pp 248−259.

(2) 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) These structural variations have been chemically correlated with the akuammiline alkaloids: see ref 1.

(5) (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.

(6) Since strictamine was converted *in vitro* into akuammicine, the akuammiline alkaloids have been postulated to be biogenetic precursors of *Strychnos* alkaloids: see ref 5b, pp 76−77.

(7) (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) Sapi, J.; Massiot, G. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4, pp 523−646.

(8) (a) Dolby, L. J.; Esfandiari, Z. *J. Org. Chem.* **1972**, *37*, 43. (b) Dolby, L. J.; Nelson, S. J. *J. Org. Chem.* **1973**, *38*, 2882.

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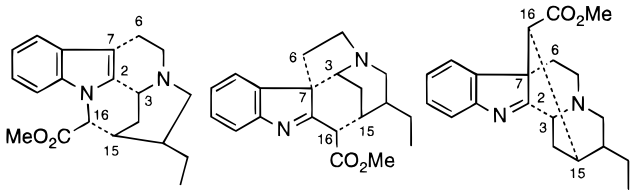


Figure 1.

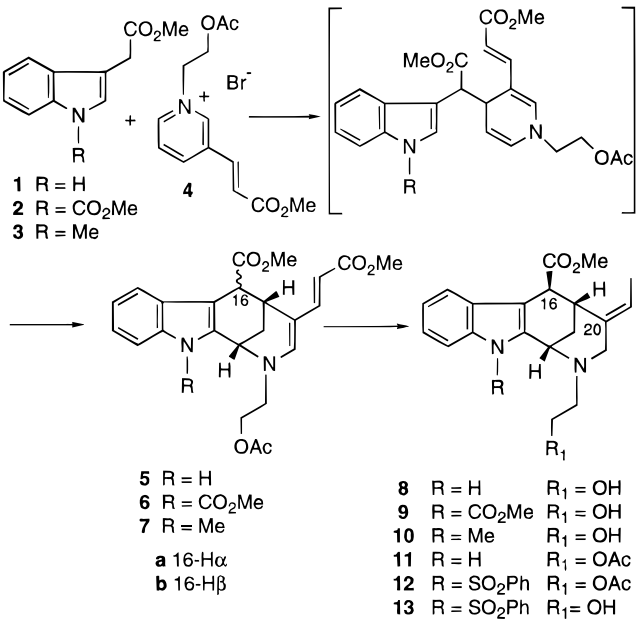
An approach to a tetracyclic ABCE substructure of echitamine including the crucial quaternary C-7 center, by Diels−Alder reaction between a 2-vinyltryptamine and an activated alkene, has recently been reported.[11]

In this paper we present our studies aimed at the synthesis of akuammiline alkaloids. Our approach involves three key bonds: (i) C-15/C-16, (ii) indole/C-3, and (iii) C-6/C-7. These bonds would be formed: the first, by nucleophilic addition of the enolate derived from a 3-indoleacetic ester at the γ-postion of a pyridinium salt; the second, by acid cyclization of the resulting 1,4-dihydropyridine; and the third, by closure of the tryptamine chain, with formation of the quaternary C-7 center, by cyclization upon the indole 3-position from a suitable N-4 substituted tetracyclic system embodying rings ABDE of the akuammiline alkaloids. A conceptually similar strategy has been successfully employed for the synthesis of pentacyclic alkaloids of the mavacurine[12] and *Strychnos*[13] groups, starting from 1- and 2-indoleacetic esters, respectively (Figure 1).[14]

Results and Discussion

The tandem nucleophilic addition of an indole-containing enolate to a pyridinium salt−cyclization of the resulting 1,4-dihydropyridine has successfully been used for the synthesis of bridged indole alkaloids belonging to several structural types.[12−15] Following this methodology, we have previously reported[15e] the synthesis of tetracycle **8** (6,7-secostrictamine)[16] by reaction of the dianion derived from methyl 3-indoleacetate (**1**) with pyridinium salt **4**, followed by acid cyclization of the intermediate 1,4-dihydropyridine and subsequent elaboration of the (*E*)-ethylidene substituent from the resulting tetracyclic compounds **5a**,**b** (Scheme 2).[17]

Scheme 2



Tetracycle **8** was envisaged as a direct precursor of pentacyclic akuammiline alkaloids by formation of the crucial C-6/C-7 bond. However, due to the erratic results observed in the above addition−cyclization sequence leading to **5**, we decided to develop alternative sequences based on the same synthetic strategy but using esters **2** and **3**, bearing either an easily removable methoxycarbonyl group or a methyl substituent[18] blocking the indole nitrogen. As expected, interaction of esters **2** and **3** with pyridinium salt **4** in the presence of LDA, followed by acid treatment, afforded the respective tetracycles **6a** and **7** (2:1 mixture of C-16 epimers **7a** and **7b**) in moderate but reproducible yields. The β-(1,4,5,6-tetrahydro-3-pyridyl)acrylate moiety of tetracycles **6a** and **7a** was stereoselectively elaborated into the corresponding (3*E*)-ethylidenepiperidines **9** (40% yield) and **10** (30% yield) by the usual one-pot, three-step sequence consisting of treatment with refluxing aqueous HCl, reesterification of the C-16 carboxy group, and finally, $NaBH_4$ reduction.[19] When tetracycle **6a** was subjected to alkaline hydrolysis before the above reaction sequence, the ethylidene derivative **8** was obtained in 30% overall yield. 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 [H-16 appears as a singlet in the series **a** (H-15/H-16 trans relationship) but as a doublet of $J = 5.1-6$ Hz in the series **b** (H-15/H-16 cis relationship)] and by the shielding of C-14 in the series **a** due to the γ-effect induced by the methoxycarbonyl group (Tables 1 and 2).

Closure of the six-membered C ring of akuammiline alkaloids was initially attempted by cyclization of alcohol **8** through the corresponding mesylate. However, by

(9) Koike, T.; Takayama, H.; Sakai, S. *Chem. Pharm. Bull.* **1991**, *39*, 1677.
(10) A related approach has been successfully applied to the synthesis of C-mavacurine alkaloids: see ref 9.
(11) Lévy, J.; Sapi, J.; Laronze, J.-Y.; Royer, D.; Toupet, L. *Synlett* **1992**, 601.
(12) Bennasar, M.-L.; Zulaica, E.; Jiménez, J.-M.; Bosch, J. *J. Org. Chem.* **1993**, *58*, 7756.
(13) (a) Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 5089. (b) Amat, M.; Linares, A.; Bosch. J. *J. Org. Chem.* **1990**, *55*, 6299.
(14) For a review, see: Bennasar, M.-L.; Bosch, J. *Synlett* **1995**, 587.
(15) 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) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156. (f) Amann, R.; Spitzner, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1320. (g) Bennasar, M.-L.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 2835. (h) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 5340. (i) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1995**, 125.
(16) For previous syntheses of ABDE substructures of akuammiline alkaloids, 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) Salas, M.; Joule, J. *J. Chem. Res. (M)* **1990**, 664. See also ref 8b.
(17) All synthetic compounds are racemic. The schemes depict only the enantiomer bearing the natural configuration at C-15.
(18) There are some akuammiline alkaloids (cathafoline, strictaminolamine) that incorporate this methyl substituent.
(19) 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. See also refs 12, 13a, 15b,e,g,h.

Table 1. ^{13}C NMR Data of Tetrahydro-1,5(and 2,6)-methanoazocino[3,4-*b*(and 5,4-*b*)]indoles

	6a	7a	25a	26a	26b	27a	27b	34a	34b	35a	35b
C-2	134.1	134.6	134.4	134.9	135.4	134.8	135.4	136.5	136.6	137.0	136.8
C-3	47.8	47.3	47.8	46.4	47.5	46.1	47.5	52.4	52.3	52.0	52.2
C-7	108.6	109.4	*a*	109.2	106.9	108.9	106.9	107.7	108.3	107.5	108.2
C-8	128.8	126.1	*a*	126.4	125.6	126.3	125.6	126.6	125.9	128.0	128.6
C-9	119.5	119.2	119.3	119.4	119.5	119.3	119.5	118.5	118.7	118.5	118.6
C-10	123.5	119.5	123.4	119.7	119.7	119.6	119.7	119.4	119.4	119.3	119.3
C-11	125.3	122.1	125.2	122.2	122.2	122.0	122.2	121.4	121.4	121.3	121.1
C-12	116.3	109.3	116.1	109.4	109.5	109.3	109.4	109.3	109.4	109.3	109.3
C-13	135.5	137.2	135.7	136.4	136.4	137.2	137.2	137.0	136.9	140.0	140.1
C-14	25.9	26.1	25.9	26.3	29.3	26.1	29.3	26.4	28.6	26.4	28.5
C-15	28.6	28.9	28.6	29.1	28.4	29.1	28.5	24.4	24.1	24.5	24.0
C-16[b]	42.6	42.4	42.6	42.8	45.2	42.7	45.1	43.7	48.2	43.6	48.0
C-18[b]	103.8	104.0	103.4	103.9	103.9	103.5	103.7	103.0	103.6	102.7	103.2
C-19	143.5	142.4	143.9	143.4	144.4	143.3	144.3	145.2	145.6	145.0	145.6
C-20	108.8	106.7	108.6	107.0	106.5	106.8	106.3	102.0	102.3	101.9	102.2
C-21	146.1	145.8	146.2	146.1	147.8	146.1	147.9	145.4	145.7	145.4	145.6
$N_{(4)}$-C	52.3	52.4	57.8[d]	58.2[d]	58.1[d]	57.5[e]	57.6[e]	57.2[d]	59.1[d]	56.8[e]	58.6[e]
	62.7[c]	62.5[c]									
$N_{(1)}$-C	50.9	29.9	50.8	30.1	30.0	29.9	30.0	30.7	30.7	30.7	30.6
	152.9		152.7								

[a] Not observed. [b] 16- and 18-CO_2Me carbons were found at (average values) 52.3, 172.6, 51.2, and 169.0. [c] $MeCO_2$ (average values): 20.6 and 173.1. [d] Phenyl ring carbons were found at (average values) 127.3, 128.0, 128.9, and 138.4. [e] *p*-Methoxyphenyl carbons (average values): 55.2, 113.5, 128.1, 128.7, and 159.4.

analogy with the result observed from a model tetracycle,[8b] only polymeric material was obtained when **8** was treated with mesyl chloride (Et_3N, CH_2Cl_2, 0 °C) and then with *t*-BuOK. The same result was obtained when the indole-sulfonylated alcohol **13**, prepared from **8** *via* acetates **11** and **12**, was treated with *t*-BuOK.[20]

Next, attention was focused on cyclizations involving trigonally hybridized electrophiles such as thionium ions, which can be generated by DMTSF treatment of a dithioacetal[21,22] or by Pummerer rearrangement of a sulfoxide.[23,24] Although the former procedure could not be studied from alcohols **8** and **10**, since, in our hands, their oxidation (Swern, Dess−Martin, TPAP−NMO) proved to be an erratic and irreproducible process, alcohol **8** was effectively transformed into sulfoxide **16** (Scheme 3). Thus, treatment of **8** with tributylphosphine−diphenyl disulfide or, alternatively, with mesyl chloride and then with sodium benzenethiolate, followed by MCPBA oxidation of the resulting sulfide **14**, gave sulfoxide **16** as a 2:1 mixture of diastereomers in acceptable overall yield. Pummerer rearrangement of sulfoxide **16** was conducted under the usual conditions (TFAA in CH_2Cl_2). However, when the presumed acyloxy sulfide intermediate was refluxed in 1,2-dichloroethane in the presence of BF_3·Et_2O,[23c] cyclization took place upon the indole nitrogen to give pentacycle **18** as the only isolable product. The structural assignment of **18** was somewhat difficult since its ^{1}H NMR spectrum (see Experimental Section) showed an abnormal shielding of some indole protons, displaying an indoline rather than indole pattern.[25] However, a careful examination of the ^{13}C NMR (Table 2) and 2D NMR (COSY, HMQC, and HMBC) spectra allowed the correct identification to be made. Furthermore, reduction of **18** with nickel boride gave pentacycle **39** (see below).

In order to avoid the above undesired cyclization, we turned our attention to the indole-protected sulfoxide **17**, which was obtained (mixture of diastereomers) by MCPBA oxidation of sulfide **15** along with minor amounts of the corresponding sulfone **19**. Sulfide **15** was prepared either by methoxycarbonylation of **14** or, as above, by exchange of the hydroxy group of alcohol **9** for phenylthio by way of the corresponding mesylate. To our disappointment, Pummerer cyclization of sulfoxide **17** under a variety of conditions did not afford the desired pentacyclic system either. Thus, when the Pummerer reaction was effected under the conditions previously used for sulfoxide **16**, dithioacetal **20** was the only isolable product. The same product was obtained when the cyclization was carried out in CH_2Cl_2, whereas the use of toluene led to sulfide **21**. These results clearly indicated that both the sulfur atom[26] of the initially formed acyloxy sulfide and the solvent toluene favorably compete with indole as nucleophiles to react with the electrophilic carbon of the intermediate thionium ion. On the other hand, when sulfoxide **17** was treated with TFA and TFAA in refluxing toluene,[23d] trifluoroacetamide **22** was isolated in 42% yield. Formation of **22** again makes evident the reluctance of the intermediate thionium ion to undergo cyclization; an equilibrium with an exocyclic iminium ion, via the corresponding vinyl sulfide (an enamine), is established. Hydrolysis of this iminium ion followed by acylation of the resulting secondary amine leads to **22**.[27]

In order to explore alternative procedures for the formation of the C-6/C-7 bond, it was necessary to prepare tetracyclic substrates bearing different functionalized two-carbon chains on the piperidine nitrogen. For this reason, the nucleophilic addition−cyclization sequence from esters **2** and **3** was extended to pyridinium salts **23** and **24**, which incorporate an easily removable *N*-benzyl or *N*-*p*-methoxybenzyl group (Scheme 4). In this way, tetracycle **25a** was obtained as a single dias-

(20) This kind of cyclization has been successfully used for the closure of the C ring of the indolo[2,3-*a*]quinolizidine system from 1-(benzenesulfonyl)-2-[1-(2-hydroxyethyl)-2-piperidyl]indoles: Rubiralta, M.; Díez, A.; Bosch, J. *J. Org. Chem.* **1989**, *54*, 5591.

(21) (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.

(22) For DMTSF-induced cyclizations upon the indole 3-position to generate the quaternary C-7 center of *Strychnos* alkaloids, see ref 13b.

(23) (a) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. (b) Magnus, P.; Sear, N. L.; Kim. C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70, and references cited therein. (c) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792. (d) Catena, J. L.; Valls, N.; Bosch, J.; Bonjoch, J. *Tetrahedron Lett.* **1994**, *35*, 4433.

(24) For a review, see: De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157.

(25) Schripsema, J.; Verpoorte, R. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1991; Vol. 9, pp 163−199.

(26) (a) Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1974**, *30*, 2653. (b) Harris, T. D.; Boekelheide, V. *J. Org. Chem.* **1976**, *41*, 2770.

(27) For related *N*-dealkylations of aminoacetaldehyde derivatives, see ref 23c and references cited therein.

Table 2. ^{13}C NMR Data of Hexahydro-1,5-methanoazocino[3,4-*b*]indoles

	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	other[a]
8	131.2	50.2	56.2	59.6	107.9	126.0	118.6	119.2	119.2	111.1	136.8	29.6	31.5	43.2	12.3	121.5	135.3	54.4	–
9	134.4	51.2	54.5	58.4	117.0	127.8	118.6	119.5	124.5	115.7	135.9	26.5	31.5	43.2	12.0	122.9	135.6	51.9	*b*
10	134.0	50.6	55.0	58.1	108.2	125.6	118.8	119.2	121.5	109.1	137.3	27.5	31.8	43.2	12.2	119.4	136.2	51.8	29.5
12	134.5	52.2	52.7	62.9	119.9	129.2	119.0	124.0	124.9	115.7	137.6	27.2	31.4	43.6	12.3	119.7	136.8	52.6	*c*, 21.0, 171.2
13	134.7	51.2	55.4	58.9	120.2	129.1	119.1	124.2	125.1	115.7	136.9	27.7	31.5	43.6	12.2	119.8	135.8	52.3	*c*
14	130.9	51.1	54.6	31.7	108.8	126.1	118.9	119.5	119.6	111.0	136.2	29.8	31.7	43.3	12.4	121.8	135.4	54.6	*d*
15	133.3	52.2	53.6	31.8	117.3	127.9	118.7	119.2	124.6	115.8	136.4	28.6	31.5	43.4	12.3	123.0	136.4	53.1	*b*,*d*
16	130.4	49.0	55.5	48.3	108.0	126.1	118.9	119.4	119.4	111.6	136.5	28.7	31.6	43.3	12.6	121.8	135.7	55.2	*e*
	130.4	49.0	56.0	45.5	108.3	126.1	119.3	119.5	119.9	111.5	137.1	30.4	31.5	43.4	12.5	121.6	135.6	52.2	*e*
17	133.3	49.8	56.4	47.1	117.3	127.9	118.8	119.0	124.7	115.9	136.3	28.3	31.5	43.9	12.3	123.1	136.2	53.9	*b*,*e*
18[f]	136.3	50.1	57.2	62.2	109.7	128.7	119.3	120.9	121.9	109.8	139.1	27.5	31.0	43.5	12.7	121.4	135.6	55.2	*d*
19	132.8	49.9	54.9	47.5	117.4	128.2	118.8	119.2	123.2	116.0	136.3	28.8	31.3	43.4	12.3	124.8	136.1	53.8	*b*,*c*
20	133.9	52.3	59.9	57.1	118.9	124.5	118.8	119.0	124.7	115.9	136.4	28.2	31.5	43.4	12.3	123.0	134.3	53.8	*b*,*d*
21	*g*	52.2	59.6	53.2	*g*	*g*	118.8	122.9	124.5	115.8	*g*	28.0	31.6	43.5	12.3	126.4	*g*	53.5	*b*,*d*
22	*g*	45.4	–	–	*g*	*g*	119.0	122.5	125.8	115.9	136.6	29.9	31.2	43.5	12.6	123.5	*g*	48.1	*b*
28a	131.7	51.8	–	–	108.9	126.5	119.0	119.8	121.9	111.1	137.6	29.8	31.7	43.4	12.2	119.0	135.7	54.1	*h*
29a	134.8	49.6	–	–	108.2	125.9	119.0	119.3	121.5	109.3	137.3	27.3	32.2	43.6	12.3	119.0	137.4	52.9	*h*, 29.7
29b	134.2	49.5	–	–	108.9	125.9	119.0	119.4	120.9	109.3	137.4	31.7	32.1	44.8	12.4	121.5	135.2	53.9	*h*, 29.8
30a	134.8	49.4	–	–	108.1	125.8	118.9	119.2	121.4	109.2	137.4	27.2	32.1	43.5	12.3	118.9	137.1	52.7	*i*, 29.7
31a	132.4	45.3	–	–	109.7	126.2	118.9	119.5	122.2	111.6	136.4	31.0	32.7	36.9	10.9	24.0	41.5	42.8	–
32a	135.0	44.2	–	–	108.5	125.7	118.8	119.2	125.5	109.1	137.3	32.3	33.5	37.2	11.3	24.5	42.4	43.8	28.8
33b	133.9	44.6	–	–	109.0	125.6	119.1	119.3	120.5	109.3	137.2	35.4	32.2	44.6	12.3	121.6	136.3	47.7	29.0
36	131.5	51.2	60.4	52.8	109.2	126.3	118.7	119.7	121.8	111.2	135.6	31.2	32.6	36.8	11.1	24.0	41.0	51.3	*j*
37	134.3	50.2	59.0	53.1	108.5	125.6	118.5	119.1	121.3	109.2	137.4	29.2	32.6	36.6	10.8	23.7	38.8	49.7	*j*, 29.5
38	136.4	49.0	123.8	129.9	111.2	130.4	119.7	122.1	122.5	112.0	139.5	27.9	31.6	40.8[k]	11.4	24.2	37.4[k]	54.9	–
39	136.6	49.7	51.6	40.4	108.0	128.4	119.4	120.2	121.3	109.6	137.3	28.2	31.7	40.6[k]	11.2	24.0	37.6[k]	53.9	–
40	131.4	50.2	56.5	59.7	108.8	126.2	116.7	119.5	121.7	111.3	135.5	31.9	32.7	36.8	11.4	24.1	41.4	51.1	–
41	136.6	50.1	55.9	57.8	109.3	125.8	118.9	119.5	121.8	109.5	137.8	30.6	32.9	36.9	11.0	23.9	40.3	48.9	29.9
43	134.0	51.5	57.3	46.3	108.6	125.6	118.9	119.2	121.5	109.3	137.2	30.2	32.2	44.5	12.2	121.8	134.5	52.5	*e*, 29.3
	133.0	50.5	56.1	47.5	109.1	125.7	119.0	119.4	121.2	109.3	137.4	32.6	31.7	44.6	12.4	121.6	134.8	53.8	*e*, 30.0
44	134.3	51.2	58.2	53.6	108.5	125.6	118.8	119.0	121.3	109.1	137.1	30.4	32.1	44.4	12.2	121.3	134.6	53.7	*j*, 29.5
45	132.9	51.5	58.3	58.3	118.8	125.7	119.0	119.3	121.6	109.3	*g*	30.5	32.2	44.5	12.3	121.6	*g*	53.8	*d*, 29.6
47[l]	136.6	42.7	165.5	41.5	109.2	125.9	118.9	119.6	122.4	111.6	136.2	30.3	32.5	36.8	11.2	23.8	41.5	45.1	–
48	133.2	41.7	164.2	41.4	108.9	125.6	119.1	119.5	122.2	109.5	137.3	30.7	32.6	36.8	11.1	23.7	40.9	45.2	29.6
49[f]	71.2	50.8	171.3	50.8	90.6	129.6	125.2	121.6	131.8	113.2	150.3	23.3	29.5	47.3	12.0	25.3	41.1	39.7	*m*
50	134.1	41.9	167.9	21.9	108.7	125.7	119.0	119.4	122.0	109.5	137.3	30.9	32.7	36.9	11.2	23.8	40.0	45.3	29.8
51	132.5	40.9	163.9	41.2	108.9	125.2	118.9	119.3	121.9	109.4	136.9	32.7	31.3	43.9	12.3	122.9	132.8	49.2	29.4
53	131.0	50.9	54.4	25.6	108.9	126.1	118.9	119.5	119.7	111.1	136.9	29.8	31.5	43.3	12.5	121.8	135.5	55.2	*d*
54	133.4	50.9	52.8	26.0	117.1	127.9	118.8	119.2	124.7	115.9	136.6	26.6	31.5	43.5	12.4	123.1	136.2	54.4	*b*,*d*
55	130.9	51.6	51.5	26.3	109.0	126.0	118.6	119.6	121.8	111.3	135.6	31.3	32.6	36.8	11.2	24.1	41.2	56.5	*d*, 120.3
56[n]	134.0	51.3	52.9	26.8	109.0	125.6	119.1	119.4	121.7	109.3	137.1	26.8	31.9	44.4	12.3	122.5	134.5	55.6	*d*, 120.2
		52.1	54.0									26.9	32.3		12.4			55.8	
57	131.3	51.1	49.4	13.1	109.0	126.3	119.0	119.3	119.7	110.9	135.5	29.9	31.9	43.4	12.5	121.9	137.2	54.1	–
58	130.6	51.6	50.6	16.6	108.7	125.8	118.4	119.2	121.6	111.2	135.7	31.3	32.6	36.9	11.2	24.1	41.2	50.9	119.3
59	133.9	51.5	49.5	17.9	108.9	125.6	119.1	119.4	121.7	109.3	137.3	30.8	32.1	44.5	12.3	122.0	133.9	53.0	29.5
																			119.0
60	133.4	41.2	165.5	−3.3	108.8	125.6	119.0	119.2	122.1	109.5	137.3	30.5	32.5	36.8	11.1	23.7	40.7	46.2	29.5
61	130.4	50.4	57.5	171.7	109.3	126.1	118.7	119.6	121.8	111.3	135.6	31.0	32.2	36.7	10.9	23.9	41.0	51.8	51.8
62	134.2	50.3	59.7	172.9	115.5	129.7	119.2	124.6	125.2	116.3	135.6	28.1	31.8	40.1[k]	11.4	24.4	38.0[k]	52.0	–
63	130.4	51.9	43.4	–	109.3	126.0	118.7	119.6	121.8	111.2	135.5	31.5	32.4	36.9	11.3	24.2	41.4	52.8	–

[a] 16-CO_2Me carbons (average values): 51.7 and 173.5 [b] $N_{(1)}$−CO_2Me values (± 0.3): 53.3 and 152.2. [c] Phenyl ring carbons were found at (average values) 126.9, 128.8, 133.5, and 139.1. [d] Phenyl ring carbons (average values): 127.3, 128.9, 131.1, and 136.5. [e] Phenyl ring carbons (average values): 124.3, 129.3, 130.9, and 144.1. [f] Assignments were done with the aid of HMQC and HMBC. [g] Not observed. [h] Benzyl carbons (average values): 59.0, 127.2, 128.5, 129.0, and 137.9. [i] PMB group: 55.1, 57.7, 113.6, 129.7, 131.1, and 158.6. [j] For the methylthio group (±0.3): 12.7 and 12.8. [k] May be interchanged. [l] Signals due to the major rotamer. [m] For the CH_2CO bridge: 41.0 and 173.5. [n] Diastereomeric mixture at C-6.

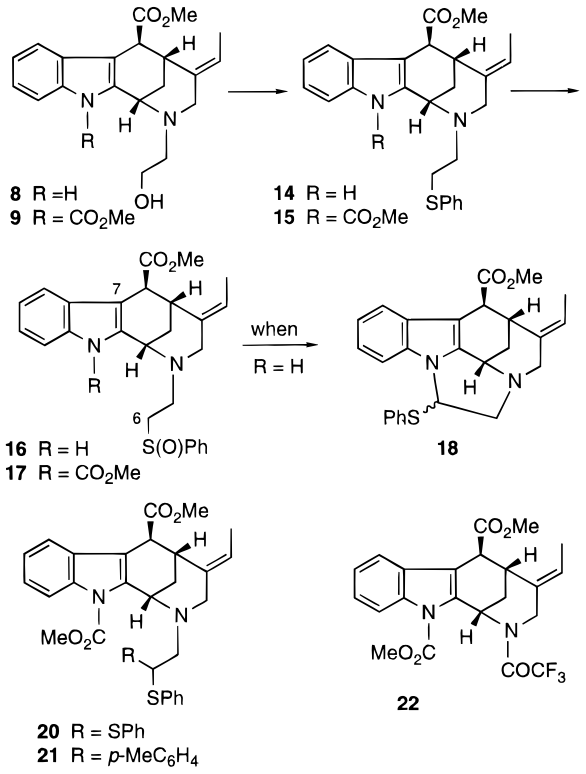
tereomer whereas tetracycles **26a**,**b** and **27a**,**b** were isolated as C-16 epimeric mixtures in which the H-15/H-16 trans isomers (series **a**) predominated. It is worth mentioning that tetracycles **26a**,**b** were formed in 45% yield, the highest observed in our nucleophilic addition−cyclization approach from indole 3-acetic esters. Minor amounts of the unnatural regioisomers **34a**,**b** and **35a**,**b**, coming from an initial nucleophilic attack of the enolate derived from **3** on the α-position of the pyridine ring, were also isolated. Tetracycles **25a**, **26a**,**b**, and **27a**,**b** were converted in the usual manner into the respective ethylidene derivatives **28a**, **29a**,**b**, and **30a**.

Debenzylation of **28a** and **29a** by hydrogenolysis took place with simultaneous hydrogenation of the ethylidene substituent to give the secondary amines **31a** and **32a**, respectively, with an α-ethyl group at C-20. The same result was observed when **29a** was treated under transfer catalytic hydrogenation conditions (Pd−C, ammonium formate). On the other hand, only piperidine-cleaved products were detected when **29a** was allowed to react with α-chloroethyl chloroformate.[28] Unsuccessful results were also obtained in all attempts to cleave the *p*-methoxybenzyl group of **30a** either oxidatively (CAN or DDQ) or by treatment with TFAA.[29] However, as could be expected from our work in the mavacurine series,[12] debenzylation was chemoselectively accomplished in the H-15/H-16 *cis* series (series **b**): the minor isomer **29b** was easily converted by hydrogenolysis (Pd−C, ammonium formate) into the secondary amine **33b**, which preserves intact the C-20 ethylidene substituent.

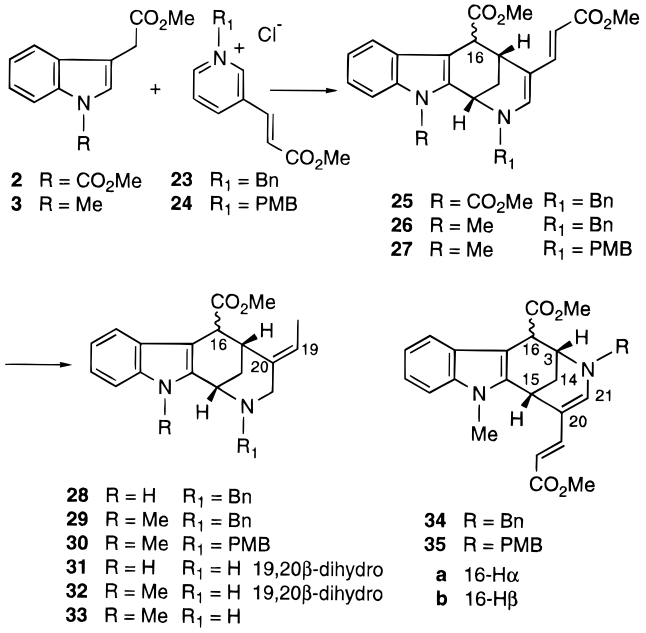
In order to study DMTSF-induced cyclizations, the C-20 ethyl substituted secondary amine **31a** was converted in excellent yield into dithioacetals **36** and **37** by alkylation with bromoacetaldehyde diethyl acetal, followed by exchange of ethoxy groups for methylthio and further alkylation of the indole nitrogen (Scheme 5). However, treatment of dithioacetal **36** with DMTSF in

(28) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195.
(29) Nussbaumer, P.; Baumann, K.; Dechat, T.; Harasek, M. *Tetrahedron* **1991**, *47*, 4591.

Scheme 3

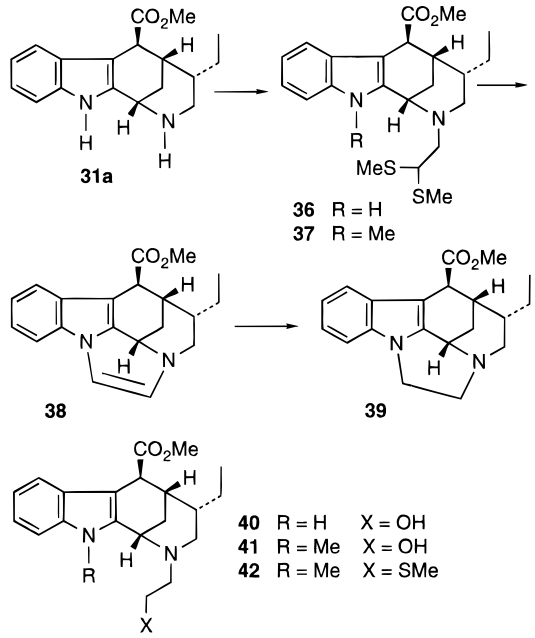


Scheme 4

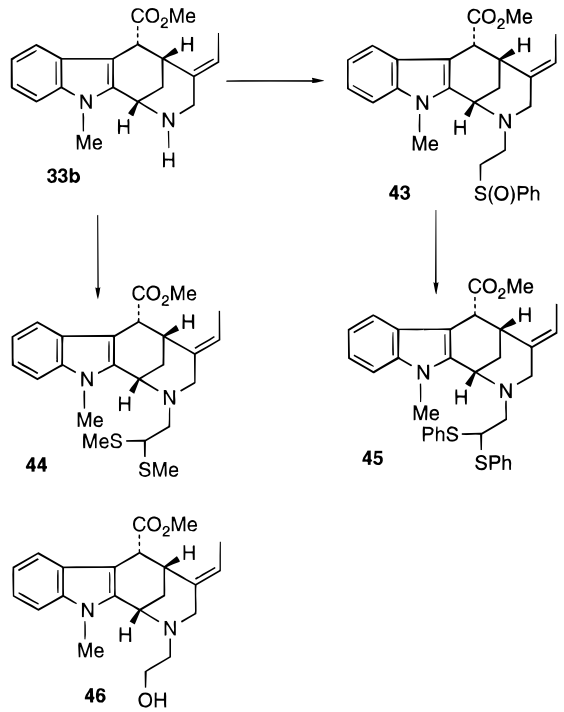


refluxing nitromethane gave the pentacyclic enamine **38** (55%), again arising from cyclization of the thionium ion upon the indole nitrogen, with subsequent elimination of methanethiol. Enamine **38** was easily converted into the pentacyclic amine **39**. When the reaction was carried out under milder conditions (temperature or time) and the mixture was then treated with $NaBH_4$ to reduce the presumed indolenine double bond, alcohol **40** was the only isolable product. Similarly, under these conditions alcohol **41** was obtained from the $N_{(a)}$-methyl substituted dithioacetal **37**. Alcohols **40** and **41** are formed by reduction of the aldehyde resulting from the hydrolysis of the intermediate thionium ion. With the aim of discerning if the failure of the latter cyclization was a consequence of the reversibility of the alkylation at the

Scheme 5



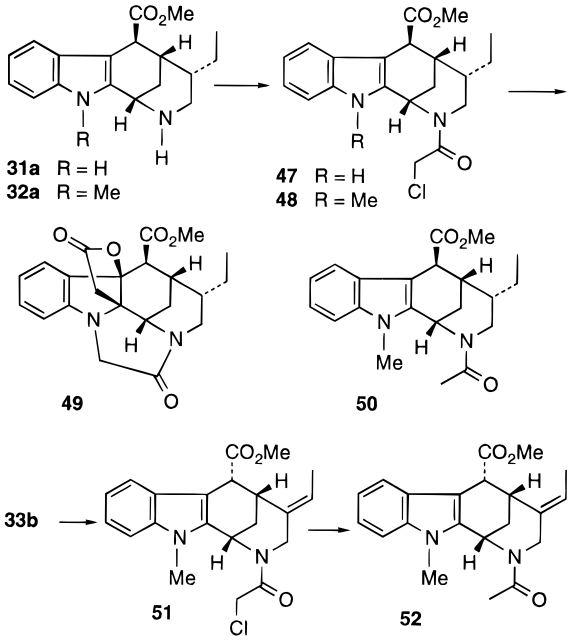
Scheme 6



indole 3-position, in order to trap the initially formed indoleninium ion we tried DMTSF-induced cyclizations from **37**, either in the presence of an external nucleophile (cyanide or acetate ions) or from the corresponding amine−borane complex. However, in the former cases only was the corresponding $N_{(b)}$-dealkylated product **32a** formed, whereas in the latter, sulfide **42**, resulting from an internal reduction of the intermediate thionium ion by the amine−borane, was isolated in 20% yield.

Nor did the desired cyclization upon the indole 3-position occur when operating from the ethylidene-bearing sulfoxide **43** and dithioacetal **44**, which were easily obtained by alkylation of the secondary amine **33b** either with phenyl vinyl sulfoxide or with bromoacetaldehyde diethyl acetal followed by exchange with methanethiol (Scheme 6). Treatment of **43** under the Pummerer reaction conditions previously used from sulfoxide **16** led

Scheme 7

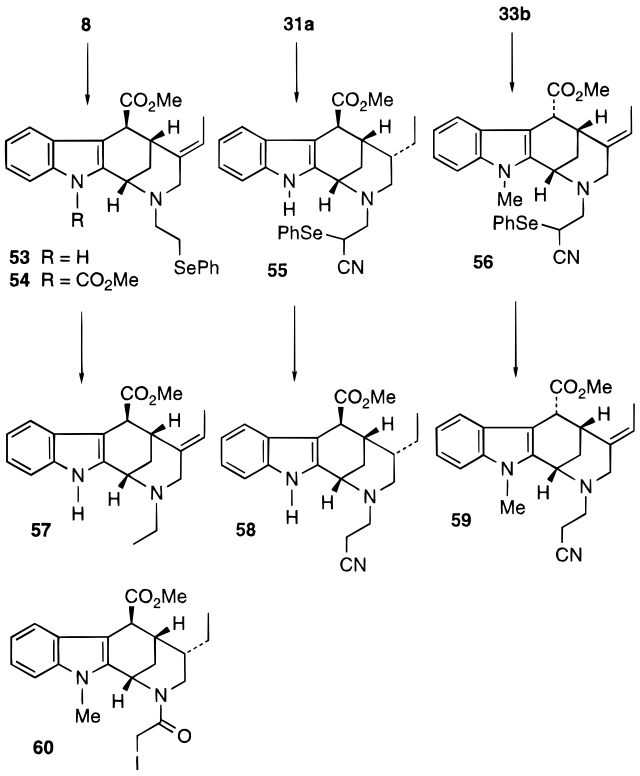


again to a dithioacetal (**45**), whereas the use of a higher boiling point solvent (CH_3NO_2) promoted dealkylation to give the secondary amine **33b**. Dealkylation to the amine **33b** was again the process observed when cyclization of dithioacetal **44** was attempted with DMTSF in the presence of AcOH or with silver trifluoroacetate in refluxing nitromethane.[30] In the latter case, the use of lower temperatures (refluxing CH_2Cl_2) gave alcohol **46** after a reductive workup.

The above unsuccessful but consistent results prompted us to study the photocyclization of a chloroacetamide[31] as a mechanistically different approach for the closure of the C ring of akuammiline alkaloids. In this case the key C-6/C-7 bond would be formed by diradical coupling instead of by electrophilic cyclization. The required chloroacetamides **47**, **48**, and **51** were prepared by acylation of secondary amines **31a**, **32a**, and **33b**, respectively (Scheme 7). Unexpectedly, photocyclization of **47** in a diluted 1:1 MeOH−H_2O solution in the presence of $NaHCO_3$ gave the hexacyclic indoline **49** in 10% yield along with trace amounts of the secondary amine **31a**. The same result was observed when using H_2O−CH_3CN mixtures as the solvent of photocyclization. Formation of hexacycle **49** indicates that cyclization takes place again upon the indole nitrogen[32] and that the resulting pentacyclic lactam undergoes an intermolecular photoalkylation with chloroacetic acid coming from the solvolysis of the starting chloroacetamide.[33] On the other hand, all attempts to induce the photocyclization of the indole-methylated chloroacetamides **48** and **51** met with no success and led to acetamides **50** and **52** resulting from a reductive photodehalogenation.

Formation of the key C-6/C-7 bond by a radical cyclization[34] upon the indole nucleus[35] was also investigated. Initially we studied the Bu_3SnH-mediated nu-

Scheme 8



cleophilic radical cyclization of selenides **53** and **54**, which were prepared by exchanging the hydroxy group of alcohol **8** for phenylseleno through the corresponding mesylate, with subsequent methoxycarbonylation of the indole nitrogen (Scheme 8). However, the desired cyclization did not take place since treatment of **53** with Bu_3SnH−AIBN under conditions (syringe pump techniques)[34] that minimize the effective hydride concentration in the reaction medium afforded the reduced product **57**, whereas only polymeric mixtures were obtained from **54**. The use of an electrophilic radical[36] to induce the cyclization was also unsuccessful: selenides **55** and **56**, obtained by alkylation of secondary amines **31a** and **33b** with 2-(phenylseleno)-2-propenenitrile, again gave the corresponding reduced products **58** and **59**. Reduction of the intermediate radical to give acetamide **50** was also the only observed process operating from iodoacetamide **60** under a variety of conditions [Bu_3SnH−AIBN, Bu_3SnCl−$NaCNBH_3$−AIBN, or $(Bu_3Sn)_2$−AIBN under halogen atom transfer conditions[37]].

Taking into account that cyclizations upon the indole nitrogen occur easily, we thought we could take advan-

(30) (a) Manas, A. R. B.; Smith, R. A. J. *Tetrahedron* **1987**, *43*, 1847. (b) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028.

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

(32) There are few examples of photocyclization of chloroacetamides upon the indole nitrogen: (a) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52*, 3151. (b) Bennasar, M.-L.; Zulaica, E.; Vila, R.; Bosch, J. *Heterocycles* **1989**, *29*, 381. (c) See also ref 20.

(33) For the intermolecular photoalkylation of the indole, see: Naruto, S.; Yonemitsu, O. *Chem. Pharm. Bull.* **1972**, *20*, 2163.

(34) (a) Curran, D. P. *Synthesis* **1988**, 417 and 489. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 779−831.

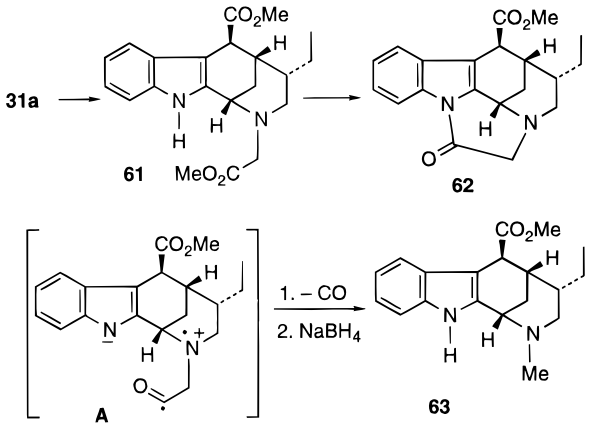
(35) (a) There are few precedents of radical cyclizations upon the indole 3-position: Yang, C.-C.; Chang, H.-T.; Fang, J.-M. *J. Org. Chem.* **1993**, *58*, 3100. Most radical cyclizations upon the indole nucleus involve reaction at the indole 2-position to give pyrrolo[1,2-*a*]indole systems: (b) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479. (c) Ziegler, F. E.; Harran, G. *J. Org. Chem.* **1993**, *58*, 2768. (d) Kraus, G. A.; Kim, H. *Synth. Commun.* **1993**, *23*, 55. (e) Caddick, S.; Aboutayab, K.; West, R. *Synlett* **1993**, 231. (f) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456.

(36) Electrophilic radicals are prone to react with electron-rich alkenes: (a) Renaud, S.; Schubert, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433. (b) Renaud, P. *Tetrahedron Lett.* **1990**, *31*, 4601.

(37) (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (b) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (c) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

(38) This photochemical rearrangement has been applied to the total synthesis of *Strychnos*, *Aspidosperma*, and eburnamine alkaloids: Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657.

Scheme 9



tage of the pentacyclic 1-acylindole **62** (Scheme 9) by promoting an intramolecular photochemical [1,3]-acyl migration to the corresponding 3-acylindolenine.[38] This photo-Fries rearrangement[39] would imply the formation of the C-6/C-7 bond by intramolecular coupling of a diradical species generated by homolytic cleavage of the $N_{(a)}$–CO bond.[40] The required 1-acylindole **62** was easily prepared by alkylation of secondary amine **31a** with methyl bromoacetate followed by $AlMe_3$-mediated intramolecular acylation of the resulting amino ester **61**. However, all attempts to induce the desired photoisomerization of **62** failed, the $N_{(b)}$-methyl derivative **63** being the only isolable product after a reductive workup with $NaBH_4$. The unexpected course of the reaction can be rationalized by taking into account that the rigidity of the pentacyclic system **62** disturbs the conjugation of carbonyl group with the aromatic nucleus. An electronic transfer from the piperidine nitrogen to the 1-acylindole carbonyl group, with subsequent heterolytic cleavage of the $N_{(a)}$–CO bond gives rise to an acyl radical (**A**), which undergoes decarbonylation. Further $NaBH_4$ reduction of the resulting exocyclic iminium salt gives **63**.

The results presented here can be summarized as follows: (a) in the *N*-unsubstituted indole series, cyclization invariably occurs upon the indole nitrogen; (b) when the indole nitrogen is blocked by a substituent, the electrophilic or radical species at C-6 do not cyclize and react depending on the reaction conditions: forming a dithioacetal, reacting with the solvent toluene, or undergoing $N_{(b)}$-dealkylation, reduction, or decarbonylation.

The reluctance of the above tetracyclic intermediates to undergo cyclization in spite of the various procedures we have tried cannot be attributed to geometrical factors since the distance between the indole 3-position and the reactive center at C-6, after a conformational change of ring D to a boat-type conformation, seems to be favorable for bond formation (see Dreiding stereomodels). However, closure of ring C involves the generation of a highly congested quaternary center and an increased rigidity of the polycyclic system, with severe transannular interactions, especially when C-20 is sp^3 hybridized.

In conclusion, formation of the C-6/C-7 bond in the last step from tetracyclic 6,7-seco derivatives does not seem a suitable approach for the synthesis of akuammiline alkaloids, which remains a challenge for synthetic organic chemists.

(39) Miranda, M. A.; García, H. In *The Chemistry of Acid Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1992; Vol. 2, Part 2, Chapter 23.
(40) (a) Lenz, G. R. *Synthesis* **1978**, 489. (b) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421.
(41) Jackson, R. W. *J. Biol. Chem.* **1930**, *88*, 660.

Experimental Section

Melting points were determined in a capillary tube and are uncorrected. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ solution at 200, 300, or 500 MHz (^1H) and 50.3 or 75 MHz (^{13}C). 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. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HMRS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. All compounds were synthetized in the racemic series. The biogenetic numbering is used to describe the ^{13}C NMR spectra of tetracyclic and pentacyclic compounds (Tables 1 and 2) and the ^1H NMR spectra of **18** and **49**.

Methyl 1-(Methoxycarbonyl)-3-indoleacetate (2). A solution of ester **1**[41] (10 g, 53 mmol) in THF (300 mL) was added dropwise to a suspension of NaH (55%, 7.2 g, 0.3 mol) in THF (20 mL) and HMPA (20 mL), and the resulting solution was stirred at rt for 2 h. Methyl chloroformate (10 mL, 0.13 mol) was added, and the mixture was stirred for 2 days at rt. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic extracts were washed with H_2O, dried, and evaporated to give a residue which was chromatographed (flash, 1:1 hexane–Et_2O) to give **2**: 11.12 g (85%); mp 34–35 °C (hexane–Et_2O); IR (NaCl) 1735 (CO); ^1H NMR (200 MHz) 3.70 (s, 5 H), 4.05 (s, 3 H), 7.22–7.58 (m, 3 H), 7.60 (s, 1 H), 8.18 (d, J = 7.5, 1 H); ^{13}C NMR 30.6, 51.9, 53.6, 113.8, 115.0, 118.9, 122.8, 123.8, 124.6, 129.8, 135.2, 151.1, 171.2. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.19; H, 5.31; N, 5.61.

Methyl 2-(2-Acetoxyethyl)-6*β*,11-bis(methoxycarbonyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4(*E*)-acrylate (6a). A solution of ester **2** (1 g, 4 mmol) in THF (50 mL) was slowly added under N_2 to a solution of LDA (6 mmol) in THF (10 mL) cooled at −70 °C, and the resulting solution was stirred at −70 °C for 1 h. Then, pyridinium bromide **4**[15e] (1.3 g, 4 mmol) was added in portions, and the mixture was allowed to rise to a temperature of −40 °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 rt. After being stirred at rt for 2 h, the reaction mixture was poured into saturated aqueous Na_2CO_3 and extracted with Et_2O. Evaporation of the dried extracts gave a residue which was chromatographed (hexane–AcOEt, increasing polarity) to give **6a**: 290 mg (15%); mp 141–142 °C (Et_2O–acetone); IR ($CHCl_3$) 1735 (CO); ^1H NMR (200 MHz) 1.85 (dt, J = 12.5, 2, 1 H), 2.05 (s, 3 H), 2.48 (br d, J = 12.5, 1 H), 3.22 (br s, 1 H), 3.25–3.45 (m, 2 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 3.94 (s, 1 H), 4.08 (s, 3 H), 4.40 (m, 2 H), 5.50 (t, 1 H), 5.67 (d, J = 15, 1 H), 6.40 (s, 1 H), 7.18–7.38 (m, 3 H), 7.33 (d, J = 15, 1 H), 7.97 (d, J = 7.5, 1 H). Anal. Calcd for $C_{26}H_{28}N_2O_8$: C, 62.89; H, 5.68; N, 5.64. Found: C, 62.53; H, 5.62; N, 5.28.

Methyl 2-(2-Acetoxyethyl)-11-methyl-6*β*(and 6α)-(methoxycarbonyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4(*E*)-acrylates (7a and 7b). Operating as above, from ester **3**[42] (1 g, 4.93 mmol) was obtained a 2:1 mixture of tetracycles **7a**,**b** (330 mg, 15%) after flash chromatography (9:1 Et_2O–DEA). Further flash chromatography (CH_2Cl_2) gave pure **7a**: mp 147–149 °C (Et_2O–acetone); IR (KBr) 1730, 1690 (CO); ^1H NMR (200 MHz) 1.90 (dt, J = 13, 3, 1 H), 2.06 (s, 3 H), 2.55 (dm, J = 13, 1 H), 3.26 (s, 1 H), 3.50 (m, 2 H), 3.73 (s, 3 H), 3.75 (s, 6 H), 4.00 (s, 1 H), 4.14 (m, 1 H), 4.32 (m, 1 H), 4.55 (t, 1 H), 5.70 (d, J = 15, 1 H), 6.28 (s, 1 H), 7.05–7.25 (m, 4 H), 7.48 (d, J = 7.5, 1 H). Anal. Calcd for $C_{25}H_{28}N_2O_6 \cdot {}^3/_4H_2O$: C, 64.42; H, 6.37; N, 6.01. Found: C, 64.40; H, 6.19; N, 6.05.

Methyl 4(*E*)-Ethylidene-2-(2-hydroxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxy-

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

late (8). A solution of tetracycle **6a** (0.4 g, 0.9 mmol) in a 1:1 MeOH−10% aqueous KOH solution (60 mL) was stirred at rt for 12 h. The solution was neutralized with aqueous HCl and then evaporated. The resulting residue was dissolved in 4 N aqueous HCl (30 mL), heated at 100 °C for 2 h, and then evaporated. The residue was dissolved in a 1.5 N MeOH solution of dry HCl (60 mL) and stirred at rt overnight. The solvent was removed, and the residue was dissolved in MeOH (80 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. Evaporation of the dried extracts gave a crude residue which was chromatographed (flash, 9:1 Et_2O−DEA) to give **8**: 82 mg (30%); mp 167−168 °C (Et_2O); IR (KBr) 3483 (NH), 3262 (OH), 1706 (CO); ^{1}H NMR (200 MHz) 1.71 (dd, J = 6.8, 2, 3 H), 2.04 (dt, J = 12.8, 2.8, 1 H), 2.44 (m, 2 H), 2.63 (m, 2 H), 2.89 (d, J = 14, 1 H), 3.49 (t, 1 H), 3.71 (s, 1 H), 3.73 (s, 3 H), 3.76 (m, 2 H), 4.11 (t, 1 H), 5.31 (qd, J = 6.8, 1, 1 H), 7.06−7.33 (m, 3 H), 7.56 (d, J = 7.5, 1 H), 8.76 (br s, 1 H). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.55; H, 7.10; N, 8.23. Found: C, 70.22; H, 7.04; N, 8.07.

Methyl 4(*E*)-Ethylidene-2-(2-hydroxyethyl)-11-(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino-[3,4-*b*]indole-6*β*-carboxylate (9). A solution of tetracycle **6a** (0.4 g, 0.9 mmol) in MeOH (10 mL) and 4 N aqueous HCl (20 mL) was refluxed for 3 h and then evaporated. The residue was treated as above with 1.5 N HCl−MeOH and then with $NaBH_4$. Workup followed by flash chromatography (8:2 Et_2O−DEA) gave **9**: 128 mg (40%); IR (film) 3446 (OH), 1736 (CO); ^{1}H NMR (200 MHz) 1.71 (dd, J = 6.8, 2, 3 H), 2.14 (dt, J = 13.5, 3.2, 1 H), 2.23 (dt, J = 13.5, 2.7, 1 H), 2.54 (m, 1 H), 2.76 (d, J = 14.8, 1 H), 2.90 (m, 1 H), 3.03 (dm, J = 14.8, 1 H), 3.49 (s, 1 H), 3.57 (m, 2 H), 3.67 (s, 1 H), 3.72 (s, 3 H), 4.04 (s, 3 H), 4.80 (t, 1 H), 5.28 (qd, J = 6.8, 1.1, 1 H), 7.20−7.50 (m, 3 H), 8.20 (d, J = 7.5, 1H). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.30; H, 6.57; N, 7.04. Found: C, 66.13; H, 6.68; N, 6.92.

Methyl 4(*E*)-Ethylidene-2-(2-hydroxyethyl)-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (10). Operating as above, from tetracycle **7a** (0.4 g, 0.9 mmol) was obtained tetracycle **10** (85 mg, 30%) after column chromatography (8:2 AcOEt−DEA): mp 86−87 °C (Et_2O−acetone); IR (KBr) 3400 (OH), 1732 (CO); ^{1}H NMR (200 MHz) 1.71 (dd, J = 6.8, 2, 3 H), 2.20 (dt, J = 13, 3.4, 1 H), 2.32 (dt, J = 13, 2.7, 1 H), 2.54 (m, 1 H), 2.73−3.00 (m, 4 H), 3.51 (t, 1 H), 3.59 (t, J = 5, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 3.73 (s, 1 H), 4.04 (t, 1 H), 5.28 (q, J = 6.8, 1 H), 7.05−7.35 (m, 3 H), 7.55 (d, J =7.5, 1 H). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.17; H, 7.39; N, 7.91. Found: C, 71.19; H, 7.44; N, 7.89.

Methyl 2-(2-Acetoxyethyl)-4(*E*)-ethylidene-11-(phenylsulfonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (12). Alcohol **8** (250 mg, 0.73 mmol) in pyridine (7 mL) was treated with Ac_2O (1.75 mL, 0.01 mol) at rt overnight. The reaction was quenched with MeOH (2 mL), and the resulting mixture was stirred at rt for 1 h. The solution was diluted with 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and evaporated. The residue was chromatographed (flash 9:1, Et_2O−DEA) to give acetate **11**: 210 mg (78%). LDA (0.33 mmol) was added to a solution of acetate **11** (110 mg, 0.28 mmol), in THF (10 mL) and HMPA (1 mL) cooled at −78 °C, and the mixture was stirred at −78 °C for 30 min. Then, $ClSO_2C_6H_5$ (0.07 mL, 0.56 mmol) was added, and the mixture was allowed to rise to −40 °C and stirred at this temperature for 1 h. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic extracts were carefully washed with H_2O, dried, and evaporated, and the resultant residue was chromatographed (flash, 8:2 Et_2O−hexane) to give **12**: 102 mg (70%); mp 105−107 °C (Et_2O); IR (film) 1737 (CO), 1440, 1370, and 1170 (SO_2); ^{1}H NMR (200 MHz) 1.70 (dd, J = 6.8, 2, 3 H), 2.01 (s, 3 H), 2.19 (m, 2 H), 2.63 (m, 1 H), 2.81 (dm, J = 14, 1 H), 2.94 (d, J = 14, 1 H), 3.30 (m, 1 H), 3.41 (t, 1 H), 3.58 (s, 1 H), 3.60 (s, 3 H), 4.23 (t, J = 5.7, 2 H), 4.87 (t, 1 H), 5.30 (q, J = 6.8, 1 H), 7.17−7.45 (m, 6 H), 7.28 (dm, 2 H), 8.09 (d, J = 7.5, 1 H). Anal. Calcd for $C_{28}H_{30}N_2O_6S$: C, 64.34; H, 5.78; N, 5.36; S, 6.14. Found: C, 64.30; H, 5.76; N, 5.35; S, 6.01.

Methyl 4(*E*)-Ethylidene-2-(2-hydroxyethyl)-11-(phenylsulfonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino-[3,4-*b*]indole-6*β*-carboxylate (13). A solution of acetate **12** (0.46 g, 0.88 mmol) in a 2.5 N MeOH (40 mL) solution of dry HCl was stirred at rt for 18 h. The solvent was removed, and the residue was partitioned between an aqueous Na_2CO_3 solution and Et_2O and extracted with Et_2O. Evaporation of the ethereal extracts followed by flash chromatography (95:5 Et_2O−DEA) gave alcohol **13**: 300 mg (71%); IR (KBr) 3400 (OH), 1734 (CO), 1449, 1369, and 1149 (SO_2); ^{1}H NMR (300 MHz) 1.63 (dd, J = 6.8, 2, 3 H), 2.12 (m, 2 H), 2.48 (m, 1 H), 2.81 (br s, 2 H), 3.14 (m, 1 H), 3.37 (t, 1 H), 3.52 (s, 1 H), 3.54 (s, 3 H), 3.58 (m, 2 H), 4.71 (t, 1 H), 5.23 (q, J = 6.8, 1 H), 7.12−7.40 (m, 6 H), 7.63 (dm, J = 7.5, 2 H), 8.00 (d, J = 7.5, 1 H); HRMS calcd for $C_{26}H_{28}N_2O_5S$ 480.1718, found 480.1720.

Methyl 4(*E*)-Ethylidene-2-[2-(phenylthio)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (14). A. A mixture of alcohol **8** (165 mg, 0.48 mmol), Bu_3P (0.22 mL, 0.87 mmol), and $(C_6H_5S)_2$ (190 mg, 0.87 mmol) in pyridine (4 mL) was heated at 60 °C for 5 h. The resulting mixture was diluted with H_2O and extracted with Et_2O. Evaporation of the ethereal extracts followed by flash chromatography (1:1 hexane−Et_2O) gave sulfide **14**: 125 mg (60%); mp 84−87 °C (Et_2O); IR (NaCl) 3400 (NH), 1720 (CO); ^{1}H NMR (200 MHz) 1.71 (dd, J = 6.8, 1.6, 3 H), 2.03 (dt, J = 12.7, 3.5, 1 H), 2.40−2.81 (m, 4 H), 2.94 (d, J = 12.7, 1 H), 3.13 (m, 2 H), 3.48 (br s, 1 H), 3.67 (s, 1 H), 3.70 (s, 3 H), 4.00 (br s, 1 H), 5.35 (qd, J = 6.8, 1.1, 1 H), 7.15−7.45 (m, 8 H), 7.55 (d, J = 7.5, 1 H), 7.62 (s, 1 H). Anal. Calcd for $C_{26}H_{28}N_2O_2S$: C, 72.18; H, 6.52; N, 6.48; S, 7.42. Found: C, 72.04; H, 6.57; N, 6.44; S, 7.38.

B. Alcohol **8** (70 mg, 0.2 mmol) was allowed to react under N_2 with mesyl chloride (0.029 mL, 0.31 mmol) and Et_3N (0.17 mL, 0.35 mmol) in CH_2Cl_2 (7 mL) at −30 °C for 45 min. The solvent was removed, and C_6H_5SNa (55 mg, 0.41 mmol) was added to the resulting residue dissolved in DMF (5 mL). The mixture was stirred at rt for 2.5 h, diluted with 10% aqueous Na_2CO_3, and extracted with Et_2O. The organic extracts were washed with H_2O and evaporated. Flash chromatography (1:1 hexane−Et_2O) of the residue gave **14**: 52 mg (59%).

Methyl 4(*E*)-Ethylidene-2-[2-(phenylthio)ethyl]-11-(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (15). A. Operating as in the above procedure B, from alcohol **9** (250 mg 0.63 mmol) was obtained sulfide **15**: 170 mg (55%); IR (NaCl) 1735 (CO); ^{1}H NMR (200 MHz) 1.63 (dd, J = 6.6, 1.7, 3 H), 2.02 (dt, J = 12.8, 3.5, 1 H), 2.27 (dt, J = 12.8, 2.3, 1 H), 2.40 (m, 1 H), 2.68 (dm, J = 13, 1 H), 2.79−3.10 (m, 4 H), 3.36 (br s, 1 H), 3.57 (s, 1 H), 3.63 (s, 3 H), 3.86 (s, 3 H), 4.85 (t, 1 H), 5.21 (qd, J = 6.6, 1.1, 1 H), 7.05−7.40 (m, 8 H), 8.05 (d, J = 7.5, 1 H); HRMS calcd for $C_{28}H_{30}N_2O_4S$ 490.1926, found 490.1911.

B. LDA (0.30 mmol) was added to a solution of sulfide **14** (75 mg, 0.17 mmol) in THF (7 mL) and HMPA (0.7 mL) at −70 °C, and the mixture was stirred for 30 min. Then, methyl chloroformate (0.03 mL, 0.40 mmol) was slowly added at −70 °C. The mixture was allowed to rise to rt, stirred at this temperature for 1 h, poured into 10% aqueous Na_2CO_3, and extracted with Et_2O. The extracts were washed with H_2O and evaporated. Flash chromatography (1:1 hexane−Et_2O) of the residue gave sulfide **15**: 60 mg (72%).

Methyl 4(*E*)-Ethylidene-2-[2-(phenylsulfinyl)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (16). TFA (0.05 mL, 0.65 mmol) was slowly added to a solution of sulfide **14** (218 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and the resulting solution was stirred for 30 min. MCPBA (104 mg, 0.60 mmol) in CH_2Cl_2 (4 mL) was slowly added at −60 °C, and the stirring was continued for 2 h at the same temperature. The reaction was quenched with solid K_2CO_3 (excess) and stirred at rt for 2 h. The mixture was filtered, and the filtrate was washed with H_2O, dried, and evaporated. The resulting residue was chromatographed (flash, 8:1:1 Et_2O−EtOH−DEA) to give sulfoxide **16**: 176 mg (78%, 2:1 mixture of diastereomers). Major diastereomer: IR (NaCl) 3200 (NH), 1731 (CO), 1015 (SO); ^{1}H NMR (300 MHz) 1.64 (dd, J = 6.8, 2.2, 3 H), 1.90 (dt, J = 12.8, 2.2, 1 H), 2.43 (dt, J = 12.8, 2, 1 H), 2.79−3.08 (m, 6 H), 3.43 (br s, 1 H), 3.64 (s, 3 H), 3.65 (s, 1 H), 4.13 (t, 1 H), 5.25 (qd, J = 6.8, 1.1, 1 H), 7.05 (m, 2 H), 7.35 (d, J = 7.1, 1 H), 7.50 (m, 4 H), 7.65 (m, 2 H), 9.55 (br s, 1 H); HRMS calcd for $C_{26}H_{28}N_2O_3S$ 448.1820,

found 448.1812. Minor diastereomer: IR (NaCl) 3227 (NH), 1731 (CO), 1014 (SO); ^{1}H NMR (300 MHz) 1.70 (dd, J = 6.8, 2.2, 3 H), 2.00 (dt, J = 12.8, 2.2, 1 H), 2.18 (m, 1 H), 2.56 (dt, J = 12.8, 2, 1 H), 2.65 (dm, J = 13, 1 H), 2.78 (d, J = 13, 1 H), 2.96 (m, 1 H), 3.08 (m, 1 H), 3.34 (m, 1 H), 3.49 (t, 1 H), 3.68 (s, 1 H), 3.71 (s, 3 H), 4.25 (t, 1 H), 5.3 (qd, J = 6.8, 1.1, 1 H), 7.25 (m, 2 H), 7.55 (m, 7 H), 10.24 (br s, 1 H).

Oxidation of 15. Operating as above, from sulfide **15** (200 mg, 0.41 mmol) was obtained a residue, which was chromatographed (Et_2O and 8:2 Et_2O−DEA). On successive elution the following compounds were isolated. **Methyl 4(*E*)-ethylidene-2-[2-(phenylsulfonyl)ethyl]-11-(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (19)**: 23 mg (10%); mp 114−116 °C; IR (NaCl) 1736 (CO), 1313, 1146 (SO_2); ^{1}H NMR (300 MHz) 1.67 (dd, J = 6.8, 1.1, 3 H), 1.8 (dt, J = 12.8, 3.3, 1 H), 2.28 (dt, J = 12.8, 2.7, 1 H), 2.59 (m, 1 H), 2.69 (s, 1 H), 2.89 (m, 1 H), 3.05 (m, 1 H), 3.36 (m, 1 H), 3.51 (m, 1 H), 3.60 (s, 1 H), 3.69 (s, 3 H), 4.07 (s, 3 H), 4.85 (t, 1 H), 5.20 (qd, J = 6.8, 1.1, 1 H), 7.20−7.65 (m, 6 H), 7.91 (d, J = 7.5, 2 H), 8.05 (d, J = 7.5, 1 H). Anal. Calcd for $C_{28}H_{30}N_2O_6S$: C, 64.34; H, 5.78; N, 5.36; S, 6.14. Found: C, 64.38; H, 5.72; N, 5.27; S, 6.05. **Methyl 4(*E*)-ethylidene-2-[2-(phenylsulfinyl)ethyl]-11-(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (17)**: 100 mg (47%, mixture of diastereomers); mp 158−160 °C (Et_2O); IR (NaCl) 1735 (CO), 1045 (SO); ^{1}H NMR (300 MHz, major diastereomer) 1.72 (dd, J = 6.8, 1.8, 3 H), 2.09 (dm, J = 12.8, 1 H), 2.34 (dt, J = 12.8, 3, 1 H), 2.50−3.20 (m, 6 H), 3.45 (t, 1 H), 3.66 (s, 1 H), 3.73 (s, 3 H), 4.09 (s, 3 H), 5.02 (t, 1 H), 5.30 (qd, J = 6.8, 1.1, 1 H), 7.22−7.73 (m, 8 H), 8.07 (d, J = 7.5, 1 H). Anal. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.37; H, 5.97; N, 5.53; S, 6.33. Found: C, 66.32; H, 5.98; N, 5.41; S, 6.19.

Methyl 4(*E*)-Ethylidene-12-(phenylthio)-2,11-ethano-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (18). TFAA (0.075 mL, 0.54 mmol) was added to a solution of sulfoxide **16** (60 mg, 0.134 mmol) in CH_2Cl_2 (2.5 mL), and the mixture was stirred at rt for 3 h. The solvent was evaporated, and the resulting residue was dissolved in 1,2-dichloroethane (25 mL). Then, $BF_3{\cdot}Et_2O$ (0.065 mL, 0.54 mmol) was added, and the mixture was refluxed for 3 h, cooled, poured into 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and evaporated, and the residue was chromatographed (flash, 3:7 Et_2O−hexane) to give pentacycle **18**: 14 mg (24%); IR (NaCl) 1732 (CO); UV (MeOH) λ_{max} 276, 203 nm; ^{1}H NMR (500 MHz) 1.23 (dt, J = 12.9, 2, 1 H, 21-H), 1.62 (dd, J = 6.5, 2, 3 H, 18-H), 1.93 (dm, J = 13.5, 1 H, 14-H), 2.64 (dm, J = 13.5, 1 H, 14-H), 2.66 (d, J = 12.9, 1 H, 21-H), 3.04 (dd, J = 14.5, 8.7, 1 H, 5-H), 3.49 (dd, J = 14.5, 3.9, 1 H, 5-H), 3.51 (br s, 1 H, 15-H), 3.59 (s, 1 H, 16-H), 3.80 (s, 3 H, OCH_3), 4.03 (t, J = 3.4, 1 H, 3-H), 5.16 (qd, J = 6.5, 2, 1 H, 19-H), 5.69 (dd, J = 8.7, 3.9, 1 H, 6-H), 6.45 (d, J = 8.5, 1 H, 12-H), 6.93 (dd, J = 8.5, 7, 1 H, 11-H), 7.07 (dd, J = 7.5, 7, 1 H, 10-H), 7.26 (m, 2 H), 7.34 (m, 1 H), 7.52 (m, 2 H), 7.56 (d, J = 7.5, 1 H, 9-H); MS m/z (rel intensity) 430 (M^+, 1), 321 (100); HRMS calcd for $C_{26}H_{26}N_2O_2S$ 430.1715, found 440.1708.

Pummerer Rearrangement of 17. Method A. Operating as above, from sulfoxide **17** (80 mg, 0.15 mmol) was obtained a residue, which was chromatographed (flash, 1:1 Et_2O−hexane) to give dithioacetal **20**: 35 mg (37%); IR (NaCl) 1737 (CO); ^{1}H NMR (300 MHz) 1.68 (dd, J = 6.8, 2.2, 3 H), 2.05 (dt, J = 12.8, 2, 1 H), 2.27 (dt, J = 12.8, 2, 1 H), 2.65 and 3.10 (2 dd, J = 12.5, 7.5, 2 H), 2.82 (br s, 2 H), 3.42 (t, 1 H), 3.66 (s, 1 H), 3.70 (s, 3 H), 3.92 (s, 3 H), 4.65 (t, J =7.5, 1 H), 4.85 (t, 1 H), 5.15 (q, J = 6.8, 1 H), 7.20−7.50 (m, 13 H), 8.10 (d, J = 7.5, 1 H).

Method B. Sulfoxide **17** (80 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was allowed to react as above with TFAA (0.083 mL, 0.6 mmol). Then, $BF_3{\cdot}Et_2O$ (0.072 mL, 0.60 mmol) was added, and the mixture was refluxed for 3 h. Workup as above gave dithioacetal **20**: 20 mg (21%).

Method C. Operating as in the above method A but using toluene as the solvent instead of 1,2-dichloroethane, from sulfoxide **17** (80 mg, 0.15 mmol) was obtained sulfide **21** after flash chromatography (1:1 hexane−Et_2O): 36 mg (41%, mixture of diastereomers); IR (NaCl) 1736 (CO); ^{1}H NMR (300 MHz, most significant signals) 1.65 (dd, J = 6.8, 1.6, 3 H), 2.28 (s, 3 H), 3.38 (br s, 1 H), 3.69 (s, 3 H), 4.00 (s, 3 H), 4.46 (t, J = 6.5, 1 H), 4.87 (t, 1 H), 5.20 (q, J = 6.8, 1 H), 7.03−7.50 (m, 13 H), 8.05 (d, J = 7.5, 1 H).

Method D. TFA (0.064 mL, 0.46 mmol) and TFAA (0.035 mL, 0.46 mmol) were added to a solution of **17** (80 mg, 0.15 mmol) in toluene (3 mL). After being refluxed for 1.5 h, the mixture was cooled, poured into 10% aqueous Na_2CO_3, and extracted with Et_2O. The organic extracts were dried and evaporated, and the residue was chromatographed (flash, 8:2 Et_2O−DEA) to give trifluoroacetamide **22**: 30 mg (42%); IR (KBr) 1740, 1690 (CO); ^{1}H NMR (300 MHz, most significant signals) 1.75 (dd, J = 6.8, 2, 3 H), 2.03 (dt, J = 12.8, 2.2, 1 H), 2.47 (dt, J = 12.8, 2, 1 H), 3.55 (br s, 1 H), 3.75 (s, 3 H), 3.95 (s, 3 H), 5.45 (q, J = 6.8, 1 H), 6.38 (t, 1 H), 7.20−7.50 (m, 3 H), 8.30 (d, J = 7.5, 1 H).

1-(*p*-Methoxybenzyl)-3-[(*E*)-2-(methoxycarbonyl)vinyl]-pyridinium Chloride (24). A mixture of methyl (*E*)-3-(3-pyridyl)acrylate (2 g, 12 mmol) and *p*-methoxybenzyl chloride (1.84 mL, 13.2 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 **24**: 3.22 g (84%); mp 157−158 °C (Et_2O); IR (film) 1720 (CO); ^{1}H NMR (DMSO-d_6, 200 MHz) 3.75 (s, 3 H), 3.76 (s, 3 H), 6.32 (s, 2 H), 6.84 (d, J = 8.7, 2 H), 7.10 (d, J = 16, 1 H), 7.65 (d, J = 16, 1 H), 7.76 (d, J = 8.7, 2 H), 8.06 (dd, J = 8.2, 5.8, 1 H), 8.43 (d, J = 8.2, 1 H), 9.67 (d, J = 5.8, 1 H), 10.32 (s, 1 H). Anal. Calcd for $C_{17}H_{18}NO_3Cl$: C, 63.84; H, 5.67; N, 4.38. Found: C, 63.70; H, 5.69; N, 4.37.

Methyl 2-Benzyl-6*β*,11-bis(methoxycarbonyl)-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4(*E*)-acrylate (25a). Operating as in the preparation of tetracycle **6a** from ester **2** (1 g, 4 mmol) and pyridinium chloride **23**[12] (1.16 g, 3.4 mmol) was obtained a residue, which was chromatographed (flash, 6:4 hexane−AcOEt) to give **25a**: 250 mg (15%); mp 154−156 °C (MeOH); IR (KBr) 1732 (CO), 1575 (C═C); ^{1}H NMR (200 MHz) 1.70 (dt, J = 12.5, 2.5, 1 H), 2.40 (dm, J = 12.5, 1 H), 3.25 (s, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 1 H), 3.96 (s, 3 H), 4.35 (d, J = 15, 1 H), 4.75 (d, J = 15, 1 H), 5.50 (t, 1 H), 5.70 (d, J = 15, 1 H), 6.52 (s, 1 H), 7.15−7.50 (m, 8 H), 8.00 (dd, J = 7.5, 2.5, 1 H). Anal. Calcd for $C_{29}H_{27}N_2O_6{\cdot}^1/_2H_2O$: C, 68.48; H, 5.53; N, 5.50. Found: C, 68.42; H, 5.43; N, 5.66.

Reaction of Ester 3 with Pyridinium Chloride 23. Operating as above, from ester **3** (1 g, 4.93 mmol) and pyridinium chloride **23** (1.43 g, 4.93 mmol) was obtained a crude residue, which was chromatographed (hexane−Et_2O, increasing polarity). On successive elution the following compounds were isolated. **Methyl 2-benzyl-6*β*(and 6α)-(methoxycarbonyl)-11-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4(*E*)-acrylates (26a and 26b)**: 1 g (2:1 mixture, 45%). Both isomers were separated by a further column chromatography (hexane−Et_2O, increasing polarity). **26a**: mp 215−218 °C (Et_2O); IR (KBr) 1733, 1699 (CO), 1586 (C═C); ^{1}H NMR (200 MHz) 1.85 (dt, J = 12.5, 3.5, 1 H), 2.49 (dt, J = 12.5, 2, 1 H), 3.27 (s, 1 H), 3.65 (s, 3 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 4.03 (s, 1 H), 4.35 (d, J = 16, 1 H), 4.53 (d, J = 16, 1 H), 4.44 (t, 1 H), 5.68 (d, J = 15, 1 H), 6.42 (s, 1 H), 7.03−7.40 (m, 9 H), 7.51 (d, J = 7, 1 H). Anal. Calcd for $C_{28}H_{28}N_2O_4$: C, 73.67; H, 6.18; N, 6.14. Found: C, 73.46; H, 6.15; N, 6.11. **26b**: IR (KBr) 1730, 1694, 1686 (CO), 1584 (C═C); ^{1}H NMR (200 MHz) 1.94 (dt, J = 12.5, 3.3, 1 H), 2.06 (dt, J = 12.5, 2, 1 H), 3.52 (s, 1 H), 3.66 (s, 3 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 4.23 (d, J = 5.2, 1 H), 4.41 and 4.58 (2d, J = 16, 2 H), 4.44 (t, 1 H), 5.51 (d, J = 15, 1 H), 6.63 (s, 1 H), 7.02−7.40 (m, 10 H). **Methyl 3-benzyl-1*β*(and 1α)-(methoxycarbonyl)-7-methyl-1,2,3,6-tetrahydro-2,6-methanoazocino-[5,4-*b*]indole-5(*E*)-acrylates (34a and 34b)**: 250 mg (2:1 mixture, 9%). Both isomers were separated by a further column chromatography (hexane−Et_2O, increasing polarity). **34a**: mp 179−180 °C (Et_2O); IR (KBr) 1739, 1690 (CO), 1576 (C═C); ^{1}H NMR (200 MHz) 1.82 (dm, J = 12.5, 1 H), 2.58 (dm, J = 12.5, 1 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 3.99 (t, 1 H), 4.04 (s, 1 H), 4.06 (s, 1 H), 4.35 and 4.48 (2 d, J = 16, 2 H), 5.73 (d, J = 15, 1 H), 6.60 (s, 1 H), 7.04−7.35 (m, 9 H), 7.47 (d, J = 7, 1 H). Anal. Calcd for $C_{28}H_{28}N_2O_4{\cdot}^1/_3H_2O$: C, 72.71; H, 6.24; N, 6.05. Found: C, 72.73; H, 6.12; N, 5.94. **34b**: IR (KBr) 1731, 1693 (CO), 1594 (C═C); ^{1}H NMR (200

MHz) 1.74 (dm, J = 12, 1 H), 2.09 (dm, J = 12, 1 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 3.88 (s, 3 H), 3.95 (t, 1 H), 4.15 and 4.34 (2 d, J = 16, 2 H), 4.16 (d, J = 5.3, 1 H), 4.28 (t, 1 H), 5.74 (d, J = 15, 1 H), 6.71 (s, 1 H), 7.00−7.34 (m, 10 H).

Reaction of Ester 3 with Pyridinium Chloride 24. Operating as above, from ester **3** (1 g, 4.93 mmol) and pyridinium chloride **24** (1.57 g, 4.93 mmol) was obtained a crude residue, which was chromatographed (hexane−AcOEt, increasing polarity). On successive elution the following compounds were isolated. **Methyl 3-(*p*-methoxybenzyl)-1*β*-(and 1α)-(methoxycarbonyl)-7-methyl-1,2,3,6-tetrahydro-2,6-methanoazocino[5,4-*b*]indole-5(*E*)-acrylates (35a and 35b)**: 190 mg (3:2 mixture, 8%). Both isomers were separated by flash chromatography (hexane−Et_2O). **35a**: mp 186−188 °C (Et_2O−acetone); IR (film) 1732, 1648 (CO), 1574 (C═C); ^{1}H NMR (200 MHz) 1.78 (dm, J = 12.5, 1 H), 2.57 (dm, J = 12.5, 1 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.79 (s, 3 H), 3.97 (t, 1 H), 4.03 (s, 1 H), 4.05 (t, 1 H), 4.29 (d, J = 15, 1 H), 4.39 (d, J = 15, 1 H), 5.70 (d, J = 15, 1 H), 6.60 (s, 1 H), 6.85 (d, J = 10, 2 H), 7.05−7.30 (m, 6 H), 7.45 (d, J = 7.5, 1 H). Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.58; H, 6.21; N, 5.76. Found: C, 71.55; H, 6.25; N, 5.73. **35b**: IR (film) 1744, 1689 (CO), 1577 (C═C); ^{1}H NMR 1.71 (m, 1 H), 2.08 (dm, J = 12.5, 1 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 3.93 (t, 1 H), 4.09 and 4.20 (2d, J = 15, 2 H), 4.15 (masked, 1 H), 4.28 (t, 1 H), 5.72 (d, J = 15.5, 1 H), 6.75 (s, 1 H), 6.90 (d, J = 8.5, 2 H), 7.02−7.35 (m, 7 H). **Methyl 2-(*p*-methoxybenzyl)-6*β*(and 6α)-(methoxycarbonyl)-11-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[3,4-*b*]indole-4(*E*)-acrylates (27a and 27b)**: 850 mg (3.5:1 mixture, 36%). Both isomers were separated by flash chromatography (95:5 Et_2O−DEA). **27a**: mp 222−224 °C (Et_2O−acetone); IR (film) 1730, 1689 (CO), 1577 (C═C); ^{1}H NMR (200 MHz) 1.82 (dt, J = 11.2, 3.5, 1 H), 2.47 (dm, J = 11.2, 1 H), 3.26 (s, 1 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 3.81 (s, 3 H), 4.03 (s, 1 H), 4.40 and 4.47 (2 d, J = 15, 2 H), 4.45 (t, 1 H), 5.65 (d, J = 15, 1 H), 6.40 (s, 1 H), 6.90 (d, J = 8.5, 2 H), 7.05−7.30 (m, 6 H), 7.50 (d, J = 7.5, 1 H). Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.58; H, 6.21; N, 5.76. Found: C, 71.20; H, 6.24; N, 5.66. **27b:** IR (film) 1744, 1696 (CO), 1574 (C═C); ^{1}H NMR (200 MHz) 1.91 (dt, J = 12.5, 3.7, 1 H), 2.06 (dt, J = 12.5, 2.2, 1 H), 3.55 (br s, 1 H), 3.66 (s, 3 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.83 (s, 3 H), 4.24 (d, J = 5.1, 1 H), 4.38 and 4.52 (2 d, J = 15, 2 H), 4.45 (t, 1 H), 5.50 (d, J = 15, 1 H), 6.65 (s, 1 H), 6.94 (d, J = 8.5, 2 H), 7.05−7.30 (m, 7 H).

Methyl 2-Benzyl-4(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (28a). Operating as in the preparation of **8**, from tetracycle **25a** (0.4 g, 0.8 mmol) was obtained pure **28a** after flash chromatography (1:1 hexane−Et_2O): 93 mg (30%); mp 182−183 °C (MeOH); IR (KBr) 1720 (CO); ^{1}H NMR (200 MHz) 1.70 (dd, J = 6.8, 2, 3 H), 2.10 (dt, J = 12.5, 3, 1 H), 2.42 (dt, J = 12.5, 2.8, 1 H), 2.65 (dt, J = 13, 1.8, 1 H), 2.90 (d, J = 13, 1 H), 3.50 (m, 3 H), 3.68 (s, 1 H), 3.71 (s, 3 H), 3.94 (t, 1 H), 5.25 (qd, J = 6.8, 1.5, 1 H), 7.00−7.40 (m, 8 H), 7.55 (dd, J = 7.5, 1, 1 H), 7.85 (s, 1 H). Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.89; H, 6.79; N, 7.26. Found: C, 77.87; H, 6.69; N, 7.19.

Methyl 2-Benzyl-4(*E*)-ethylidene-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*(and 6α)-carboxylate (29a and 29b). Operating as in the preparation of **9**, from tetracycles **26a**,**b** (0.5 g, 1.1 mmol) was obtained a 2:1 mixture of ethylidene derivatives **29a**,**b** (189 mg, 43%). Both isomers were separated by flash chromatography (9:1 hexane−AcOEt). **29a**: mp 193−194 °C (Et_2O); IR (KBr) 1731 (CO); ^{1}H NMR (200 MHz) 1.70 (dd, J = 6.8, 2, 3 H), 2.30 (m, 2 H), 2.70 (d, J = 14, 1 H), 2.89 (dt, J = 14, 2, 1 H), 3.50 and 3.88 (2d, J = 14, 2 H), 3.54 (masked, 1 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 3.66 (s, 1 H), 4.11 (t, 1 H), 5.18 (q, J = 6.8, 1 H), 7.06−7.39 (m, 8 H), 7.56 (d, J = 7.5, 1 H). Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.98; H, 7.04; N, 6.99. Found: C, 77.92; H, 7.13; N, 6.99. **29b**: IR (KBr) 1742 (CO); ^{1}H NMR (200 MHz) 1.65 (dd, J = 6.8, 1, 3 H), 1.90 (dt, J = 12.5, 2.4, 1 H), 2.42 (dt, J = 12.5, 3.4, 1 H), 2.72 (d, J = 13.5, 1 H), 3.16 (dt, J = 13.5, 1.9, 1 H), 3.50 and 3.80 (2 d, J = 13.3, 2 H), 3.66 (2 s, 6 H), 3.72 (m, 1 H), 4.13 (t, 1 H), 4.23 (d, J = 6, 1 H), 5.28 (q, J = 6.8, 1 H), 7.07−7.40 (m, 9 H).

Methyl 4(*E*)-Ethylidene-11-methyl-2-(*p*-methoxybenzyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (30a). Operating as above, from tetracycles **27a**,**b** (0.5 g, 1.03 mmol) was obtained compound **30a** after flash chromatography (8:2 Et_2O−hexane): 244 mg (55%); mp 153−154 °C (Et_2O); IR (film) 1734 (CO); ^{1}H NMR (200 MHz) 1.70 (dd, J = 6.8, 2, 3 H), 2.39 (m, 2 H), 2.69 (d, J = 14, 1 H), 2.84 (dm, J = 14, 1 H), 3.44 and 3.83 (2 d, J = 14, 2 H), 3.55 (br s, 1 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 3.73 (s, 1 H), 3.80 (s, 3 H), 4.10 (t, 1 H), 5.20 (q, J = 6.8, 1 H), 6.85 (d, J = 8.5, 2 H), 7.05−7.30 (m, 5 H), 7.55 (d, J = 7.5, 1 H). Anal. Calcd for $C_{27}H_{30}N_2O_3$: C, 75.31; H, 7.02; N, 6.51. Found: C, 75.35; H, 7.12; N, 6.47.

Methyl 4α-Ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (31a). The hydrochloride of **28a** (0.5 g, 1.3 mmol) in MeOH (50 mL) was hydrogenated over $Pd(OH)_2$ (25%, 125 mg) at atmospheric pressure for 24 h. The catalyst was filtered off, the solvent was removed, and the residue was diluted with 10% aqueous Na_2CO_3 and extracted with Et_2O. Evaporation of the dried extracts followed by flash chromatography (7:2:1 Et_2O−EtOH−DEA) gave **31a**: 0.33 g (85%); mp 122−123 °C (acetone); IR (KBr) 3250−3600 (NH), 1739 (CO); ^{1}H NMR (200 MHz) 0.95 (t, J = 7, 3 H), 1.30 (m, 2 H), 1.75 (m, 1 H), 1.95 (dm, J = 12.5, 1 H), 2.10−2.70 (m, 4 H), 3.70 (s, 3 H), 3.85 (s, 1 H), 4.21 (t, 1 H), 7.10−7.30 (m, 3 H), 7.60 (dd, J = 7.5, 1, 1 H), 9.05 (s, 1 H). Anal. Calcd for $C_{18}H_{22}N_2O_2 \cdot {}^1/_2C_3H_6O$: C, 71.53; H, 7.69; N, 8.50. Found: C, 71.87; H, 7.97; N, 8.39.

Methyl 4α-Ethyl-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (32a). Operating as above, from the hydrochloride of **29a** (0.5 g, 1.25 mmol) was obtained pure **32a**: 210 mg (54%); mp 118−120 °C (Et_2O); IR ($CHCl_3$) 1728 (CO); ^{1}H NMR (200 MHz) 0.95 (t, J = 7, 3 H), 1.26 (m, 2 H), 1.73 (m, 1 H), 2.00 (m, 3 H), 2.50 (m, 3 H), 3.67 (s, 3 H), 3.69 (s, 3 H), 3.85 (s, 1 H), 4.25 (t, 1 H), 7.06−7.31 (m, 3 H), 7.55 (dm, J = 7.5, 1 H). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.04; H, 7.83; N, 8.82.

Methyl 4(*E*)-Ethylidene-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6α-carboxylate (33b). A mixture of **29b** (285 mg, 0.71 mmol), 10% Pd−C (28.5 mg), and NH_4HCO_2 (65 mg, 1 mmol) in MeOH (17 mL) was refluxed for 15 min. Workup followed by flash chromatography (7:3:2 Et_2O−EtOH−DEA) gave **33b**: 185 mg (83%); IR (film) 1740 (CO); ^{1}H NMR (300 MHz) 1.64 (dd, J = 6.8, 2, 3 H), 2.09 (dt, J = 12.8, 2.3, 1 H), 2.18 (dt, J = 12.8, 2.8, 1 H), 2.64 (s, 1 H), 3.03 (d, J = 13.9, 1 H), 3.42 (dt, J = 13.9, 1.1, 1 H), 3.66 (s, 3 H), 3.73 (s, 3 H), 4.26 (d, J = 5.8, 1 H), 4.39 (t, 1 H), 5.38 (qd, J = 6.6, 1.1, 1 H), 7.06−7.34 (m, 4 H); HRMS calcd for $C_{19}H_{22}N_2O_2$ 310.1681, found 310.1694.

Methyl 2-[2,2-Bis(methylthio)ethyl]-4α-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (36). A solution of amine **31a** (280 mg, 0.94 mmol) and 2-bromoacetaldehyde diethyl acetal (0.42 mL, 2.82 mmol) in CH_3CN (25 mL) containing Na_2CO_3 (250 mg, 2.82 mmol) was refluxed for 24 h. The solvent was evaporated, and the residue was dissolved in aqueous Na_2CO_3 and extracted with CH_2Cl_2. Evaporation of the dried extracts gave a residue, which was dissolved in CH_2Cl_2 (50 mL) and treated with CH_3SH (5 mL) in the presence of $BF_3 \cdot Et_2O$ (0.5 mL, 2.04 mmol) at 0 °C for 24 h. Workup followed by flash chromatography (Et_2O) gave **36**: 290 mg (80%); mp 154−155 °C (Et_2O); IR (KBr) 3400 (NH), 1703 (CO); ^{1}H NMR (200 MHz) 0.90 (t, J = 7, 3 H), 1.20 (m, 2 H), 1.55 (t, J = 12.5, 1 H), 1.80 (m, 1 H), 2.05 (masked, 1 H), 2.05 and 2.10 (2 s, 6 H), 2.25−2.55 (m, 4 H), 2.75 (dd, J = 13, 7, 1 H), 3.60 (s, 3 H), 3.75 (s, 1 H), 3.80 (dd, J = 7, 6.5, 1 H), 3.90 (t, 1 H), 7.01−7.30 (m, 3 H), 7.45 (dd, J = 7.5, 1 H), 8.10 (s, 1 H). Anal. Calcd for $C_{22}H_{30}N_2O_2S_2$: C, 63.12; H, 7.22; N, 6.69; S, 15.31. Found: C, 63.10; H, 7.26; N, 6.66; S, 15.11.

Methyl 2-[2,2-Bis(methylthio)ethyl]-4α-ethyl-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (37). LDA (1.05 mmol) was added to a solution of dithioacetal **36** (0.4 g, 95 mmol) in THF (70 mL) and HMPA (7 mL) at −70 °C, and the mixture was stirred at −70 °C for 30 min. Then, MeI (0.08 mL, 1.19 mmol) was added, and the stirring was continued at rt for 5 h. The mixture was poured into H_2O and extracted with Et_2O.

Evaporation of the dried extracts followed by flash chromatography (1:1 hexane−Et_2O) gave **37**: 380 mg (92%); mp 101−102 °C (Et_2O−hexane); IR (KBr) 1735 (CO); ^1H NMR (200 MHz) 0.96 (t, J = 7, 3 H), 1.25 (m, 3 H), 1.88 (m, 2 H), 2.11 and 2.14 (2 s, 6 H), 2.35 (m, 3 H), 2.65 and 3.05 (2 dd, J = 12.5, 7.5, 2 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 3.81 (m, 1 H), 3.84 (s, 1 H), 4.02 (t, 1 H), 7.05−7.30 (m, 3 H), 7.51 (d, J = 7.5, 1 H). Anal. Calcd for $C_{23}H_{32}N_2O_2S_2$: C, 63.85; H, 7.44; N, 6.47; S, 14.82. Found: C, 64.00; H, 7.55; N, 6.53; S, 14.60.

Cyclization of 36. A. A solution of dithioacetal **38** (180 mg, 0.43 mmol) in CH_3NO_2 (10 mL) was slowly added under N_2 to a degassed solution of DMTSF[43] (168 mg, 0.86 mmol) in CH_3NO_2 (65 mL) at −30 °C, and the mixture was refluxed for 12 h. The reaction mixture was quenched with 10% aqueous Na_2CO_3 (50 mL) and stirred at rt for 30 min. The solvent was evaporated, and the residue was dissolved in MeOH (30 mL) and treated with $NaBH_4$ (100 mg, 3 mmol) for 1 h. The mixture was poured into H_2O and extracted with Et_2O. The organic layer was dried and evaporated, and the resultant residue was purified by column chromatography (hexane−AcOEt, increasing polarity) to give pentacycle **38**: 76 mg (55%); IR ($CHCl_3$) 1735 (CO), 1624 (C=C); ^1H NMR (200 MHz) 0.85 (t, J = 7.5, 3 H), 1.10 (m, 2 H), 1.70 (m, 1 H), 2.11 (dm, J = 13.5, 1 H), 2.59−2.75 (m, 4 H), 3.69 (s, 1 H), 3.76 (s, 3 H), 3.84 (t, 1 H), 5.87 (d, J = 5, 1 H), 6.83 (d, J = 5, 1 H), 7.20−7.24 (m, 2 H), 7.44 (m, 1 H), 7.65 (m, 1 H).

Pentacycle **38** (80 mg, 0.24 mmol) in MeOH (50 mL) was hydrogenated over 10% Pd−C (20%, 16 mg) at atmospheric pressure for 24 h. The usual workup followed by flash chromatography (7:2:1 Et_2O−EtOH−DEA) gave **methyl 4α-ethyl-2,11-ethano-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (39)**: 41 mg (50%); mp 135−137 °C (MeOH); IR ($CHCl_3$) 1728 (CO); ^1H NMR (200 MHz) 0.83 (t, J = 7.5, 3 H), 1.10 (m, 2 H), 1.65 (m, 1 H), 2.00 (dt, J = 13, 2, 1 H), 2.10−2.70 (m, 6 H), 3.45 (ddd, J = 13, 7.8, 1.7, 1 H), 3.76 (s, 3 H), 3.77 (s, 1 H), 3.92 (t, 1 H), 4.35 (ddd, J = 13, 8.5, 1.8, 1 H), 7.19 (m, 2 H), 7.34 (m, 1 H), 7.65 (m, 1 H). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.45; N, 8.63. Found: C, 74.07; H, 7.45; N, 8.70.

B. When the above cyclization was effected for shorter reaction times or at lower temperatures (CH_2Cl_2, reflux) **methyl 4α-ethyl-2-(2-hydroxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (40)** was obtained: 20−40%; IR ($CHCl_3$) 3468 (NH), 3397 (OH), 1725 (CO); ^1H NMR (200 MHz) 0.97 (t, J = 7.5, 3 H), 1.31 (m, 2 H), 1.59 (t, J = 12, 1 H), 1.82 (m, 1 H), 2.03 (dt, J = 13, 3.4, 1 H), 2.30−2.70 (m, 5 H), 3.15 (br s, 1 H), 3.70 (s, 3 H), 3.70 (masked, 2 H), 3.82 (s, 1 H), 4.03 (t, 1 H), 7.05−7.35 (m, 3 H), 7.55 (dd, J = 7.5, 1, 1 H), 8.85 (s, 1 H).

Attempted Cyclization of 37. A. Operating as in the aboven cyclization of dithioacetal **36**, from dithioacetal **37** (100 mg, 0.23 mmol) was obtained **methyl 4α-ethyl-2-(2-hydroxyethyl)-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (41)** after flash chromatography (9:1 Et_2O−DEA): 33 mg (40%); mp 104−105 °C (Et_2O); IR ($CHCl_3$) 3400 (OH), 1731 (CO); ^1H NMR (200 MHz) 0.97 (t, J = 7.5, 3 H), 1.26 (m, 3 H), 1.80 (m, 1 H), 2.14 (dt, J = 12.5, 3.3, 1 H), 2.44 (m, 3 H), 2.95 (m, 2 H), 3.60 (m, 2 H), 3.69 (2 s, 6 H), 3.86 (s, 1 H), 4.01 (t, 1 H), 7.01−7.30 (m, 3 H), 7.53 (dm, J = 7.5, 1 H). Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.75; H, 7.91; N, 7.86. Found: C, 70.35; H, 8.02; N, 7.53.

B. Dithioacetal **37** (150 mg, 0.34 mmol) was allowed to react as above with DMTSF (142 mg, 0.68 mmol) in CH_3NO_2 (60 mL) in the presence of either NaCN or AcONa (0.68 mmol). The usual workup gave amine **32a**: 30−40%.

C. $NaBH_4$ (32 mg, 0.83 mmol) and $BF_3{\cdot}Et_2O$ (0.05 mL, 0.42 mmol) were added to a solution of dithioacetal **37** (60 mg, 0.14 mmol) in THF (5 mL), and the resulting solution was stirred at rt for 5 h. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extracts were dried and evaporated. The resulting amine−borane complex (60 mg, 0.13 mmol) was allowed to react with DMTSF as in the above cyclization of **36**. After flash chromatography (9:1 Et_2O−DEA), sulfide **42** was obtained: 10 mg (20%).

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

Methyl 4(*E*)-Ethylidene-2-[2-(phenylsulfinyl)ethyl]-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]-indole-6α-carboxylate (43). A mixture of amine **33b** (125 mg, 0.403 mmol) and phenyl vinyl sulfoxide (0.08 mL, 0.604 mmol) in MeOH (5 mL) was refluxed for 5 h. The solvent was removed, and the residue was diluted with H_2O and extracted with Et_2O. The organic extracts were dried and evaporated to give sulfoxide **43** (138 mg, 80%) as a 1:1 mixture of diastereomers, which were separated by column chromatography (AcOEt). Less polar diastereomer: IR (NaCl) 1740 (CO), 1019 (SO); ^1H NMR (300 MHz) 1.64 (dd, J = 6.8, 1.8, 3 H), 1.85 (dm, J = 12.8, 1 H), 2.31 (dt, J = 12.8, 2, 1 H), 2.69 (d, J = 14, 1 H), 2.90 (m, 2 H), 3.04 (m, 2 H), 3.42 (br d, J = 14, 1 H), 3.66 (s, 3 H), 3.70 (br s, 1 H), 3.77 (s, 3 H), 4.15 (t, 1 H), 4.25 (d, J = 5.8, 1 H), 5.3 (qd, J = 6.8, 1.1, 1 H), 7.05−7.52 (m, 9 H). More polar diastereomer: IR (NaCl) 1737 (CO), 1040 (SO); ^1H NMR (300 MHz) 1.66 (dd, J = 6.8, 2, 3 H), 1.95 (dt, J = 12, 2, 1 H), 2.31 (dt, J = 12, 2.3, 1 H), 2.47 (m, 1 H), 2.79 (d, J = 12.9, 1 H), 2.98 (m, 3 H), 3.29 (m, 1 H), 3.66 (s, 3 H), 3.68 (masked, 1 H), 3.71 (s, 3 H), 4.18 (t, 1 H), 4.22 (d, J = 5.8, 1 H), 5.4 (qd, J = 6.8, 1, 1 H), 7.05−7.65 (m, 9 H); HRMS calcd for $C_{27}H_{30}N_2O_3S$ 462.1977, found 462.1974.

Pummerer Rearrangement of Sulfoxide 43. A. Operating as in the cyclization of sulfoxide **16**, from sulfoxide **43** (80 mg, 0.173 mmol) was obtained dithioacetal **45**: 20 mg (21%); IR (NaCl) 1738 (CO); ^1H NMR (300 MHz) 1.68 (dd, J = 6.8, 2, 3 H), 1.78 (dt, J = 12.8, 2, 1 H), 2.24 (dm, J = 12.8, 1 H), 2.62 (d, J = 14, 1 H), 2.79 (dd, J = 14, 7.2, 1 H), 3.17 (dd, J = 14, 4.8, 1 H), 3.40 (d, J = 14, 1 H), 3.62 (s, 3 H), 3.70 (masked, 1 H), 3.73 (s, 3 H), 4.08 (t, 1 H), 4.21 (d, J = 5.8, 1 H), 4.40 (dd, J = 7.2, 4.8, 1 H), 5.05 (q, J = 6.8, 1 H), 7.05−7.50 (m, 14 H).

B. Operating as above, but using CH_3NO_2 as the solvent instead of 1,2-dichloroethane, from sulfoxide **43** (65 mg, 0.14 mmol) was obtained amine **33b**: 12 mg (28%).

Methyl 2-[2,2-Bis(methylthio)ethyl]-4(*E*)-Ethylidene-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6α-carboxylate (44). Operating as in the preparation of dithioacetal **36**, from amine **33b** (0.35 g, 1.1 mmoll) was obtained dithioacetal **44** after flash chromatography (1:1 hexane−Et_2O): 0.33 g (68%); mp 135−137 °C (hexane−Et_2O); IR (film) 1742 (CO); ^1H NMR (300 MHz) 1.57 (dd, J = 7.5, 2, 3 H), 1.75 (dt, J = 12.6, 2.5, 1 H), 2.07 and 2.08 (s, 6 H), 2.25 (dt, J = 12.6, 3.5, 1 H), 2.61−2.71 (m, 2 H), 3.04 (dd, J = 13.3, 6.2, 1 H), 3.29 (d, J = 13.9, 1 H), 3.57 (s, 3 H), 3.60 (m, 2 H), 3. 73 (s, 3 H), 4.01 (t, 1 H), 4.16 (d, J = 6 Hz, 1 H), 5.30 (q, J = 7.5, 1 H), 7.05 (m, 1 H), 7.10 (m, 1 H), 7.25 (m, 2 H). Anal. Calcd for $C_{23}H_{30}N_2O_2S_2$: C, 64.16; H, 7.02; N, 6.51; S, 14.89. Found: C, 64.10; H, 7.14; N, 6.50; S, 14.57.

Attempted Cyclization of Dithioacetal 44. Method A. Dithioacetal **44** (60 mg, 0.14 mmol) was allowed to react with DMTSF (55 mg, 0.28 mmol) at −30 °C for 30 min. Then AcOH (1 mL) was added, and the mixture was refluxed overnight. The usual workup gave amine **33b**: 20 mg (46%).

Method B. Silver trifluoroacetate (123 mg, 0.56 mmol) was slowly added to a solution of dithioacetal **44** (60 mg, 0.14 mmol) and $BF_3{\cdot}Et_2O$ (0.065 mL, 0.56 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was refluxed for 10 h. The mixture was poured into 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were evaporated, and the residue was dissolved in MeOH (10 mL) and treated with $NaBH_4$ (excess) at 0 °C for 45 min. Workup followed by flash chromatography (7:3:2 Et_2O−EtOH−DEA) gave alcohol **46**: 10 mg (20%); IR (film) 1739 (CO), 3400 (OH); ^1H NMR (300 MHz, most significative signals) 1.59 (dd, J = 6.7, 1.3, 3 H), 1.83 (dm, J = 12.8, 1 H), 2.26 (dm, J = 12.8, 1 H), 2.73 (d, J = 13, 1 H), 2.90 (m, 1 H), 3.59 (m, 2 H), 3.60 (s, 3 H), 3.66 (s, 3 H), 4.02 (t, 1 H), 4.17 (d, J = 6.2, 1 H), 5.30 (q, J = 6.7, 1 H), 7.05−7.35 (m, 4 H); MS m/z (rel intensity) 354 (M^+, 14), 322 (30), 295 (22), 241 (100).

Method C. Dithioacetal **44** (60 mg, 0.14 mmol) in CH_3NO_2 (5 mL) was allowed to react with silver trifluoroacetate (123 mg, 0.56 mmol) and TFA (0.045 mL, 0.56 mmol) at reflux temperature for 18 h. Workup followed by flash chromatography (8:2 Et_2O−DEA) gave amine **33b**: 20 mg (46%).

Methyl 2-(Chloroacetyl)-4α-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (47). Chlo-

roacetyl chloride (0.035 mL, 0.44 mmol) in CH_2Cl_2 (3 mL) was slowly added to a solution of amine **31a** (100 mg, 0.34 mmol) and Et_3N (0.085 mL, 0.68 mmol) in CH_2Cl_2 (3 mL), and the resulting solution was stirred at rt for 2 h. The reaction mixture was washed with 10% aqueous Na_2CO_3 solution, dried, and evaporated. Flash chromatography (Et_2O) of the residue gave chloroacetamide **47**: 98 mg (80%); mp 191−193 °C (Et_2O); IR (KBr) 3250 (NH), 1731 and 1643 (CO); ^{1}H NMR (200 MHz, major rotamer) 1.05 (t, J = 7, 3 H), 1.30 (m, 3 H), 1.96 (m, 1 H), 2.60 (m, 3 H), 3.43 (dm, J = 13.5, 1 H), 3.74 (s, 3 H), 3.93 (s, 1 H), 4.00 and 4.10 (2 d, J = 12, 2 H), 5.87 (t, 1 H), 7.10−7.30 (m, 3 H), 7.61 (d, J = 7.5, 1 H), 8.64 (s, 1 H). Anal. Calcd for $C_{20}H_{23}N_2O_3Cl$: C, 64.09; H, 6.19; N, 7.47. Found: C, 64.12; H, 6.16; N, 7.47.

Methyl 2-(Chloroacetyl)-4α-ethyl-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (48). Operating as above, from amine **32a** (80 mg, 0.26 mmol) was obtained chloroacetamide **48**: 70 mg (70%); mp 152−153 °C (Et_2O); IR (KBr) 1732, 1654 (CO); ^{1}H NMR (200 MHz) 1.02 (t, J = 7, 3 H), 1.35 (m, 3 H), 1.98 (dt, J = 13.5, 2.5, 1 H), 2.60 (m, 3 H), 3.38 (dd, J = 13.5, 5, 1 H), 3.65 and 3.71 (2 s, 6 H), 3.95 (s, 1 H), 4.03 (s, 2 H), 6.02 (t, 1 H), 7.09−7.33 (m, 3 H), 7.59 (d, J = 7.5, 1 H). Anal. Calcd for $C_{21}H_{25}N_2O_3Cl$: C, 64.86; H, 6.47; N, 7.20. Found: C, 64.75; H, 6.52; N, 7.21.

Methyl 2-(Chloroacetyl)-4(*E*)-ethylidene-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-b]indole-6α-carboxylate (51). Operating as above, from amine **33b** (0.3 g, 0.96 mmol) was obtained chloroacetamide **51**: 0.31 g (83%); mp 152−154 °C (acetone−Et_2O); IR (KBr) 1644,1740 (CO); ^{1}H NMR (300 MHz) 1.69 (d, J = 7.5, 3 H), 2.12 (m, 2 H), 3.69 (s, 3 H), 3.71 (s, 3 H), 3.79 (m, 2 H), 3.90 (dt, J = 13, 1, 1H), 4.06 (s, 2 H), 4.32 (d, J = 6.2, 1 H), 5.51 (q, J = 7.5, 1 H), 6.10 (t, 1 H), 7.10 (m, 1 H), 7.30 (m, 3 H). Anal. Calcd for $C_{21}H_{23}N_2O_3Cl$: C, 65.18; H, 5.99; N, 7.25; Cl, 9.17. Found: C, 65.20; H, 6.07; N, 7.17; Cl, 9.04.

Photocyclization of Chloroacetamide 47. A solution of chloroacetamide **47** (75 mg, 0.2 mmol) in MeOH−H_2O (1:1, 150 mL) containing $NaHCO_3$ (120 mg) was irradiated under N_2 at rt for 30 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, Et_2O−DEA) to give **methyl 4α-ethyl-13,16-dioxo-6a*β*,11a*β*-(epoxyethano)-2,11-ethano-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (49)**: 8 mg (10%); IR ($CHCl_3$) 1783, 1733 and 1668 (CO); ^{1}H NMR (500 MHz) 0.78 (t, J = 7.5, 3 H, 18-H), 0.99 (m, 1 H, 19-H), 1.20 (m, 1 H, 19-H), 1.95 (m, 1 H, 20-H), 2.04 (ddd, J = 14.5, 5.5, 1.5, 1 H, 14-H), 2.26 (dd, J = 14.5, 4.5, 1 H, 14-H), 2.70 (m, 1 H, 15-H), 2.84 and 2.93 (2d, J = 18.5, 2 H, CH_2COO), 3.11 (dd, J = 14.5, 8.5, 1 H, 21-H), 3.30 (d, J = 4, 1 H, 16-H), 3.54 (dd, J = 14.5, 4, 1 H, 21-H), 3.76 (s, 3 H, OCH_3), 3.91 (d, J = 5.5, 1 H, 3-H), 3.78 and 4.02 (2 d, J = 16, 2 H, NCH_2CO), 6.77 (d, J = 8.5, 1 H, 12-H), 6.89 (t, J = 8, 1 H, 10-H), 7.20 (d, J = 8, 1 H, 9-H), 7.28 (m, 1 H, 11-H); MS m/z (rel intensity) 396 (M^+, 100), 354 (8), 338 (10); HRMS calcd for $C_{22}H_{24}N_2O_5$ 396.1685, found 396.1684.

Attempted Photocyclization of Chloroacetamide 48. Operating as above, except for the irradiation time (15 min), from chloroacetamide **48** (80 mg, 0.20 mmol) was obtained acetamide **50**: 16 mg (22%); mp 156−158 °C (Et_2O); IR (KBr) 1733, 1637 (CO); ^{1}H NMR (200 MHz) 1.01 (t, J = 7, 3 H), 1.37 (m, 2 H), 1.77 (m, 1 H), 1.93 (dt, J = 14, 2.5, 1 H), 2.06 (s, 3 H), 2.55 (m, 3 H), 3.35 (dd, J = 13.6, 4.5, 1 H), 3.67 and 3.71 (2 s, 6 H), 3.91 (s, 1 H), 6.10 (t, 1 H), 7.08−7.32 (m, 3 H), 7.57 (d, J = 7.5, 1 H). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.17; H, 7.39; N, 7.90. Found: C, 71.14; H, 7.45; N, 7.87.

Attempted Photocyclization of Chloroacetamide 51. Operating as above, from **51** (60 mg, 0.15 mmol) was obtained acetamide **52**: 20 mg (37%); IR (film) 1654, 1738 (CO); ^{1}H NMR (300 MHz, most significant signals) 1.65 (dd, J = 7.5, 3 H), 2.00 (s, 3 H), 3.62 (s, 3 H), 3.66 (s, 3 H), 4.25 (d, J = 6.2, 1 H), 5.40 (q, J = 7.5, 1 H), 6.15 (t, 1 H), 7.05−7.40 (m, 4 H); MS m/z (rel intensity) 352 (M^+, 35), 293 (39), 182 (100).

Methyl 4(*E*)-Ethylidene-2-[2-(phenylseleno)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (53). $NaBH_4$ (13 mg, 0.34 mmol) was added to a solution of diphenyl diselenide (54 mg, 0.17 mmol) in EtOH (6 mL), and the mixture was stirred at rt until the bright yellow solution became colorless (5−10 min). A solution of alcohol **8** (60 mg, 0.18 mmol), mesyl chloride (0.024 mL, 0.27 mmol), and Et_3N (0.15 mL, 1 mmol) in CH_2Cl_2 (6 mL) was stirred at −20 °C under N_2 for 1.5 h. The solvent was removed, and the above solution of C_6H_5SeNa was added to the resulting residue. The mixture was stirred at rt for 2 h, the solvent was removed, and the residue was dissolved in H_2O and extracted with Et_2O. The extracts were dried and evaporated. Flash chromatography (1:1, Et_2O−hexane) gave **53**: 40 mg (46%); mp 134−135 °C (Et_2O); IR (KBr) 3410 (NH), 1719 (CO). ^{1}H NMR (200 MHz) 1.70 (dd, J = 6.8, 2, 3 H), 2.02 (dt, J = 13, 3.5, 1 H), 2.41 (dt, J = 13, 3, 1 H), 2.50−2.90 (m, 3 H), 2.94 (d, J = 13, 1 H), 3.10 (m, 2 H), 3.47 (br s, 1 H), 3.66 (s, 1 H), 3.70 (s, 3 H), 3.96 (t, 1 H), 5.30 (q, J = 6.8, 1 H), 7.00−7.70 (m, 9 H). Anal. Calcd for $C_{26}H_{28}N_2O_2Se$: C, 65.13; H, 5.85; N, 5.84. Found: C, 65.11; H, 5.92; N, 5.80.

Methyl 4(*E*)-Ethylidene-2-[2-(phenylseleno)ethyl]-11-(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (54). Operating as in the preparation of **15** (procedure B), from selenide **53** (60 mg, 0.125 mmol) was obtained selenide **54** after flash chromatography (7:3 hexane−Et_2O): 35 mg (46%); IR (NaCl) 1732, 1733 (CO); ^{1}H NMR (200 MHz) 1.69 (dd, J = 6.7, 1.8, 3 H), 2.10 (dm, J = 13, 1 H), 2.35 (dm, J = 13, 1 H), 2.45−3.15 (m, 6 H), 3.42 (br s, 1 H), 3.66 (s, 1 H), 3.71 (s, 3 H), 3.96 (s, 3 H), 4.91 (t, 1 H), 5.25 (q, J = 6.7, 1 H), 7.21−7.55 (m, 8 H), 8.10 (d, J = 7.5, 1 H); HRMS calcd for $C_{28}H_{30}N_2O_4Se$ 538.1370, found 538.1317.

Methyl 2-[2-Cyano-2-(phenylseleno)ethyl]-4α-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (55). 2-(Phenylseleno)-2-propenenitrile[44] (280 mg, 1.34 mmol) was added to a solution of amine **31a** (0.2 g, 0.67 mmol) and Et_3N (0.2 mL, 2 mmol) in MeOH (20 mL) at rt. The mixture was stirred for 3 h and then evaporated. The residue was dissolved in H_2O and extracted with Et_2O. The organic extracts were dried and evaporated. Flash chromatography of the residue (7:3 hexane−Et_2O) gave **55**: 240 mg (70%); mp 121−123 °C (Et_2O); IR (KBr) 3375 (NH), 2320 (CN), 1709 (CO); ^{1}H NMR (200 MHz) 0.96 (t, J = 7, 3 H), 1.29 (m, 2 H), 1.83 (m, 1 H), 2.05 (dm, J = 12, 1 H), 2.38−2.68 (m, 5 H), 3.01 (dt, J = 13, 3, 1 H), 3.69 (s, 3 H), 3.79 (s, 1 H), 3.84 (masked, 1 H), 3.96 (t, 1 H), 7.06−7.70 (m, 8 H), 7.53 (d, J = 7.5, 1 H), 8.01 (s, 1 H). Anal. Calcd for $C_{27}H_{29}N_3O_2Se$: C, 64.03; H, 5.77; N, 8.30. Found: C, 64.01; H, 5.73; N, 8.31.

Methyl 2-[2-Cyano-2-(phenylseleno)ethyl]-11-methyl-4(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino-[3,4-*b*]indole-6α-carboxylate (56). Operating as above, from amine **33b** (150 mg, 0.48 mmol) was obtained selenide **56**: 0.2 g (40%, diastereomeric mixture); mp 58−60 °C (Et_2O); IR (KBr) 1737 (CO), 2295 (CN); ^{1}H NMR (300 MHz, most significative signals) 1.64 and 1.65 (2 dd, J = 6.7, 3 H), 3.63 and 3.65 (s, 3 H), 3.70 and 3.75 (s, 3 H), 4.05 and 4.15 (2 t, 1 H), 4.23 (d, J = 6, 1 H), 5.25 and 5.35 (2 q, J = 6.7, 1 H), 7.10−7.50 (m, 8 H), 7.73 (m, 1 H). Anal. Calcd for $C_{28}H_{29}N_3O_2Se.1H_2O$: C, 62.68; H, 5.82; N, 7.82. Found: C, 62.57; H, 5.63; N, 8.12.

Attempted Cyclization of Selenide 53. A solution of *n*-Bu_3SnH (0.08 mL, 0.28 mmol) and AIBN (7 mg, 0.042 mmol) in toluene (25 mL) was slowly added (4 h, syringe pump) to a refluxing solution of **53** (70 mg, 0.14 mmol) in toluene (25 mL). The mixture was refluxed for an additional 2 h. The solvent was removed, and the residue was dissolved in H_2O and extracted with Et_2O. Evaporation of the dried extracts followed by column chromatography (hexane−Et_2O−DEA, increasing polarity) of the residue gave **methyl 2-ethyl-4(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (57)**: 10 mg (20%); IR (NaCl) 3200 (NH), 1733 (CO); ^{1}H NMR (200 MHz, most significative signals) 1.20 (t, J = 7, 3 H), 1.72 (dd, J = 6.6, 2, 3 H), 3.01 (d, J = 12.5, 1 H), 3.50 (br s, 1 H), 4.05 (t, 1 H), 5.40 (q, J = 6.6, 1 H), 7.10−7.40 (m, 3 H), 7.60 (d, J = 7.5, 1 H), 8.10 (br s, 1 H); HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.1837, found 324.1833.

(44) Clive, D. L. J.; Boivin, T. L. B.; Angoh, A. G. *J. Org. Chem.* **1987**, *52*, 4943.

Attempted Cyclization of Selenide 55. Selenide **55** (100 mg, 0.20 mmol) in benzene (20 mL) was allowed to react as above with *n*-Bu_3SnH (0.08 mL, 0.30 mmol) and AIBN (9 mg, 0.06 mmol) in benzene (20 mL). Workup followed by flash chromatography (Et_2O) gave **methyl 2-(2-cyanoethyl)-4α-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (58)**: 40 mg (56%); mp 190−192 °C (Et_2O); IR (KBr) 3363 (NH), 2248 (CN), 1722 (CO); ^{1}H NMR (200 MHz) 0.97 (t, J = 7, 3 H), 1.31 (m, 3 H), 1.59 (t, J = 11.5, 1 H), 1.85 (m, 3 H), 2.04 (dt, J = 13.5, 3.3, 1 H), 2.47 (m, 3 H), 2.87 (m, 1 H), 3.69 (s, 3 H), 3.75 (s, 1 H), 3.88 (br, 1 H), 7.06−7.33 (m, 3 H), 7.54 (d, J = 7.5, 1 H), 8.33 (br s, 1 H). Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.77; H, 7.16; N, 11.96. Found: C, 71.65; H, 7.21; N, 11.85.

Attempted Cyclization of Selenide 56. Operating as above, from selenide **56** (80 mg, 0.15 mmol) was obtained **methyl 2-(2-cyanoethyl)-11-methyl-4(*E*)-ethylidene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6α-carboxylate (59)**: 28 mg (50%); mp 135−136 °C (hexane−Et_2O); IR (film) 1740 (CO), 2243 (CN); ^{1}H NMR (300 MHz) 1.66 (dd, J = 6.8, 1.9, 3 H), 1.88 (dd, J = 12.7, 2.5, 1 H), 2.30 (dd, J = 12.7, 3.5, 1 H), 2.50 (m, 2 H), 2.69 (dm, J = 13.9, 1 H), 3.06 (m, 2 H), 3.32 (br d, J = 13.9, 1 H), 3.66 (s, 3 H), 3.71 (m, 1 H), 3.78 (s, 3 H), 4.12 (t, J = 2.5, 1 H), 4.25 (d, J = 6.1, 1 H), 5.37 (qd, J = 6.8, 1.5, 1 H), 7.10 (t, J = 8, 1 H), 7.23 (t, J = 8, 1 H), 7.34 (m, 2 H). Anal. Calcd for $C_{22}H_{25}N_3O_2$: C, 72.71; H, 6.93; N, 11.56. Found: C, 72.71; H, 7.00; N, 11.48.

Methyl 4α-Ethyl-2-(iodoacetyl)-11-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (60). NaI (97 mg, 0.64 mmol) was added to a solution of chloroacetamide **48** (250 mg, 0.64 mmol) in anhydrous acetone (8 mL). The flask was protected from light, and the reaction mixture was stirred at rt for 4 h. After filtration, the solvent was removed, and the residue was taken up in Et_2O, washed with H_2O, dried, and evaporated. Column chromatography (CH_2Cl_2−hexane, increasing polarity) gave **60**: 200 mg (65%); mp 118−120 °C (Et_2O); IR (KBr) 1730 and 1634 (CO); ^{1}H NMR (200 MHz) 1.03 (t, J = 7.5, 3 H), 1.38 (m, 2 H), 1.95 (m, 2 H), 2.50 (m, 3 H), 3.40 (dd, J = 13, 4.7, 1 H), 3.65 and 3.72 (2 s, 6 H), 3.69 (masked, 2 H), 3.92 (s, 1 H), 6.01 (t, 1 H), 7.09−7.32 (m, 3 H), 7.58 (d, J = 7.5, 1H). Anal. Calcd for $C_{21}H_{25}N_2O_3I$: C, 52.51; H, 5.24; N, 5.83. Found: C, 52.50; H, 5.23; N, 5.77.

Attempted Cyclization of Iodoacetamide 60. A. Operating as in the above attempted cyclization of selenide **55**, from iodoacetamide **60** (80 mg, 0.167 mmol) was obtained acetamide **50** after flash chromatography (9:1, Et_2O−DEA): 30 mg (51%).

B. A suspension of iodoacetamide **60** (200 mg, 0.41 mmol), Bu_3SnCl (0.02 mL, 0.06 mmol), $NaCNBH_3$ (54 mg, 0.85 mmol), and AIBN (8 mg, 0.05 mmol) in 4 mL of *t*-BuOH was refluxed for 4 h. The solvent was evaporated, and the residue was partitioned between H_2O and Et_2O and extracted with Et_2O. The organic extracts were dried and evaporated. Flash chromatography (9:1 Et_2O−DEA) of the residue gave **50**: 140 mg (95%).

C. A solution of iodoacetamide **60** (75 mg, 0.16 mmol), $(Bu_3Sn)_2$ (0.11 mL, 0.32 mmol), and AIBN (3 mg, 0.018 mmol) in toluene (8 mL) was irradiated with a 275-W sunlamp for 10 h at reflux temperature. Workup as above gave acetamide **50**: 45 mg (82%).

Methyl 4α-Ethyl-6*β*-(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-2-acetate (61). To a solution of amine **31a** (0.50 g, 1.67 mmol) in CH_3CN (50 mL) containing Na_2CO_3 (0.53 g, 5 mmol) was added methyl bromoacetate (0.3 mL, 3 mmol). The mixture was refluxed for 3 h, poured into H_2O, and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by flash chromatography (9:1 Et_2O−DEA) gave amino ester **61**: 0.39 g (64%); mp 60 °C (Et_2O); IR (NaCl) 3363 (NH), 1735 (CO); ^{1}H NMR (200 MHz) 0.95 (t, J = 7, 3 H), 1.30 (m, 2 H), 1.54 (t, J = 11.5, 1 H), 1.93 (m, 1 H), 2.10 (dt, J = 12.5, 4, 1 H), 2.50 (m, 3 H), 3.03 and 3.12 (2 d, J = 15, 2 H), 3.69 (s, 3 H), 3.77 (s, 3 H), 3.81 (br, 2 H), 7.05−7.30 (m, 3 H), 7.55 (dd, J = 7.5, 1 H), 8.55 (br s, 1 H). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.06; N, 7.56. Found: C, 68.11; H, 7.10; N, 7.39.

Methyl 4α-Ethyl-12-oxo-2,11-ethano-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[3,4-*b*]indole-6*β*-carboxylate (62). Me_3Al (0.13 mL, 0.27 mmol) was added to a solution of **61** (100 mg, 0.27 mmol) in dry toluene (15 mL) cooled at 0 °C. The mixture was refluxed under N_2 for 7 h, diluted with H_2O, and extracted with Et_2O. The extracts were dried and evaporated, and the residue was chromatographed (flash, 9:1 Et_2O−DEA) to give pentacycle **62**: 74 mg (80%); mp 144−146 °C (MeOH−acetone); IR (KBr) 1735 and 1710 (CO); ^{1}H NMR (200 MHz) 0.78 (t, J = 7, 3 H), 0.90 (m, 2 H), 1.70 (m, 1 H), 1.95 (dm, J = 12.5, 1 H), 2.35 (dm, J = 12.5, 1 H), 2.50 (m, 3 H), 3.05 (d, J = 17, 1 H), 3.55 (s, 1 H), 3.68 (s, 3 H), 3.80 (d, J = 17, 1 H), 3.82 (t, 1 H), 7.20 (m, 2 H), 7.57 (m, 1 H), 8.04 (m, 1 H); UV λ_{max} (MeOH) 205, 268. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.87; H, 6.60; N, 8.12.

Attempted Photoisomerization of 62. A solution of pentacyclic lactam **62** (40 mg, 0.1 mmol) in MeOH (100 mL) was irradiated under N_2 at −40 °C for 10 min using a 250 W high pressure mercury lamp, in a quartz inmersion well reactor. The reaction mixture was then treated with $NaBH_4$ (30 mg, 0.9 mmol) for 30 min at 0 °C. The solvent was removed and the resulting residue was chromatographed (flash, 7:2:1 Et_2O−EtOH−DEA) to give tetracycle **63:** (7 mg, 20%); mp 165−167 °C (Et_2O−acetone); IR (KBr) 3354 (NH), 1719 (CO); ^{1}H NMR (200 MHz) 0.97 (t, J = 7, 3 H), 1.25 (m, 2 H), 1.68 (t, J = 10, 1 H), 1.85 (m, 1 H), 2.08 (dm, J = 13, 1 H), 2.75 (s, 3 H), 2.45 (m, 3 H), 3.69 (s, 3 H), 3.78 (t, 1 H), 3.81 (s, 1 H), 7.05−7.35 (m, 3 H), 7.55 (dd, J = 7.5, 2, 1 H), 8.05 (br s, 1 H). Anal. Calcd for $C_{19}H_{24}N_2O_2 \cdot C_3H_6O \cdot {}^1/_2H_2O$: C, 69.63; H, 8.40; N, 7.38. Found: C, 69.81; H, 8.00; N, 7.44.

Operating as above, but using a 125 W mercury lamp at 25 °C for 15 min, tetracycle **63** was isolated in higher yield (70%).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of the synthetic intermediates **13, 15**, **16**, **18**, **33b**, **43**, **49**, and **54** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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