# A New Synthetic Entry to Pentacyclic *Strychnos* Alkaloids. Total Synthesis of (±)-Tubifolidine, (±)-Tubifoline, and (±)-19,20-Dihydroakuammicine

Mercedes Amat, Ana Linares, and Joan Bosch*

*Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona-08028, Spain*

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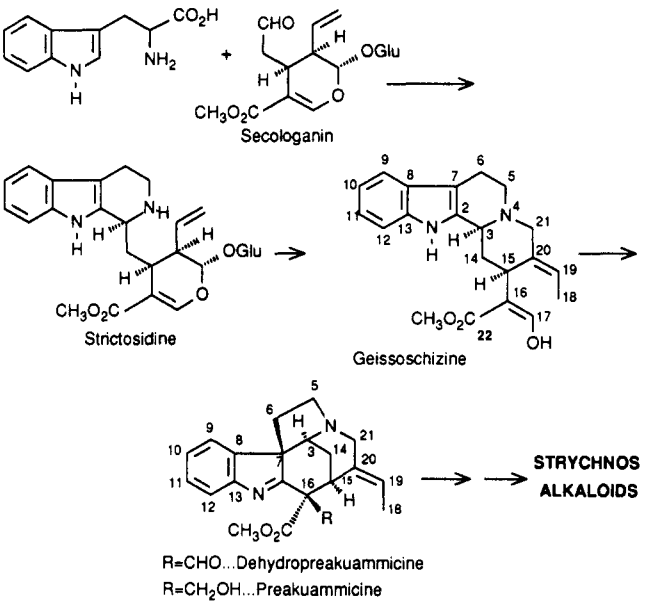
A new strategy for the synthesis of pentacyclic *Strychnos* alkaloids has been developed. It consists in the closure of the five-membered E ring by cyclization upon the indole 3-position from a suitably N-substituted tetracyclic system embodying rings ABCD of the alkaloids. Attempts to effect the key cyclization either by Pummerer rearrangement of sulfinylacetamides **4** and **6**, from chloroacetamide **12**, or from bis(methylthio)acetamide **10b** (exocyclic amide carbonyl group) resulted in failure. In the first case dithioacetals **9** and **10**, respectively, were formed in good yields. Cyclization from alcohol **13** or from the indole-deactivated acetal **15** and dithioacetal **18** were also unsuccessful: noncyclized products coming from the initially formed oxonium or thionium intermediates **16** were obtained. Cyclization was satisfactorily accomplished in 49% yield by treatment of the N-unsubstituted indole dithioacetal **23** with DMTSF. The resulting pentacycle **25** was converted to 20-deethyltubifolidine (**27**). A similar treatment from dithioacetal **41a**, prepared from the secondary amine **32a**, afforded pentacycle **42a**, from which the alkaloids tubifoline, tubifolidine, and 19,20-dihydroakuammicine were synthesized.

The monoterpenoid indole alkaloids belonging to the *Strychnos* type are structurally characterized by the presence of an unrrearranged secologanin unit attached to the indole nucleus by C-7/C-3 (or C-21) and C-2/C-16 bonds.[1] Biogenetically, the *Strychnos* alkaloids are derived from preakuammicine, a precursor which arises from tryptophan and secologanin through strictosidine and geissoschizine, a key intermediate along the biosynthetic pathway of monoterpenoid indole alkaloids. Although several mechanisms have been postulated to interconnect the *Corynanthe* alkaloid geissoschizine with those of the *Strychnos* type,[2] the details of the rearrangement to dehydropreakuammicine and preakuammicine remain still unknown (Scheme I).

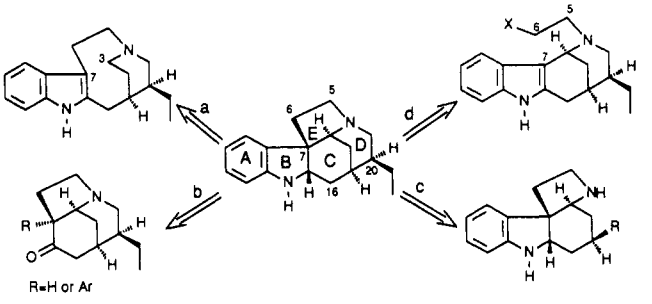
The *Strychnos* alkaloids vary in structural complexity from the pentacyclic alkaloids tubifoline and tubifolidine, lacking the oxidized one-carbon substituent present at C-16 in the greater part of this class of alkaloids, to heptacyclic strychnine which incorporates an additional two-carbon unit arising from acetate.

In contrast with other types of indole alkaloids such as *Aspidosperma*, *Iboga*, *Corynanthe*, or *Yohimbe*, the *Strychnos* alkaloids have received comparatively little attention from a synthetic standpoint.[3] Although four different strategies have been explored for the synthesis of pentacyclic *Strychnos* alkaloids having the octahydro-3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole skeleton (Scheme II),[4] at the beginning of our studies in this field only one of them (disconnection a) had succeeded in the total synthesis of alkaloids of this group.[5] This approach, developed by Harley-Mason,[6] implies the construction of tetracyclic structures having the ring skeleton of stemmadenine and further transannular cyclization with simultaneous formation of C and E rings. Afterwards, a total[7]

**Scheme I. Biosynthesis and Biogenetic Numbering of *Strychnos* Indole Alkaloids**




**Scheme II. Synthetic Strategies**




(1) The biogenetic numbering is used for pentacyclic structures. Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

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

(3) For reviews, see: (a) Husson, H.-P. In *The Chemistry of Heterocyclic Compounds. Indoles Part 4, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Chapter VII. (b) Lounasmaa, M.; Somersalo, P. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: Wien, 1986; Vol. 50, p 27. (c) Massiot, G.; Delaude, C. In *The Alkaloids*; Brossi, A., Ed.; Academic Press, Inc.: San Diego, 1988; Vol. 34, Chapter 5.

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

(5) For pioneering studies, see: van Tamelen, E. E.; Dolby, L. J.; Lawton, R. G. *Tetrahedron Lett.* **1960**, 30.

(6) (a) Dadson, B. A.; Harley-Mason, J.; Foster, G. H. *J. Chem. Soc., Chem. Commun.* **1968**, 1233. (b) Dadson, B. A.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1969**, 665. (c) Harley-Mason, J.; Taylor, C. G. *J. Chem. Soc., Chem. Commun.* **1970**, 812. (d) Crawley, G. C.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1971**, 685. (e) Harley-Mason, J. *Pure Appl. Chem.* **1975**, *41*, 167.

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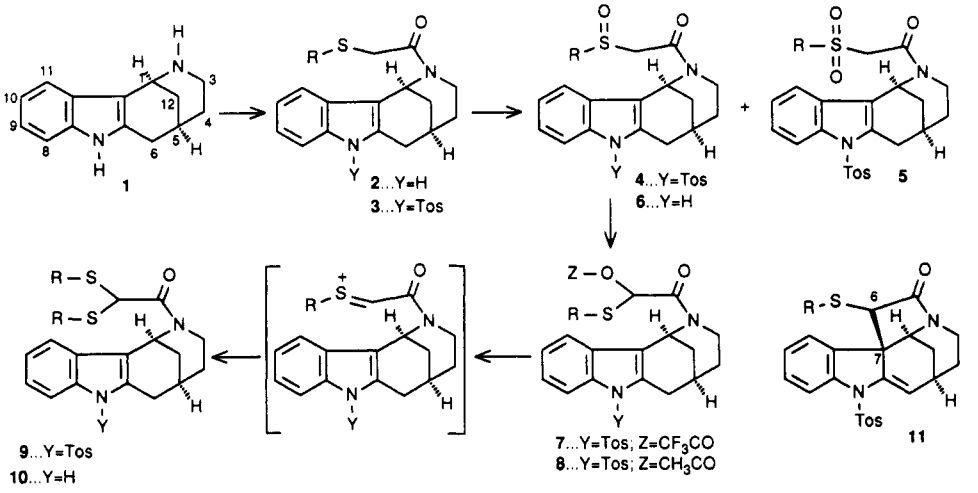
**Scheme III. Pummerer Rearrangement**




a. R=$C_6H_5$; b. R=$CH_3$

and two formal[8] syntheses of tubifoline and tubifolidine, which converge to intermediates used by Harley-Mason, have been reported. Although two other approaches, based on the elaboration of the modified indole nucleus[9] (disconnection b) or the piperidine D ring[10,11] (disconnection c) in the last steps, have also been studied, they have not succeeded so far in obtaining natural products.[12]

In this paper we report a new synthetic entry to the pentacyclic ring system of *Strychnos* alkaloids (disconnection d) which has been successfully applied to the total synthesis of (±)-tubifoline, (±)-tubifolidine, and (±)-19,20-dihydroakuammicine. Our synthetic strategy consists in the closure of the pyrrolidine E ring in the last synthetic steps by intramolecular alkylation of the indole 3-position from an appropriately N-substituted tetracyclic system embodying rings ABCD of *Strychnos* alkaloids. It is worth noting that formation of the C-6/C-7 bond involves closure of a strained five-membered ring[13] with generation of a quaternary carbon center at C-7 and disruption of the aromaticity of the pyrrole nucleus. A similar synthetic approach had been previously developed for the total synthesis of *Aspidosperma* alkaloids from octahydropyrido[3,2-*c*]carbazoles.[14] The best results in this area have been reported by Magnus, who achieved the closure of the five-membered E ring of these alkaloids by means of an intramolecular Pummerer-type reaction from (phenylsulfinyl)acetamides with yields as high as 91%.[14d]

## Results and Discussion

**Model Studies.** The more readily available tetracycle 1,[15] lacking the C-4 two-carbon substituent, was selected as a model starting material to explore a suitable method for the closure of E ring. Taking into account the precedents in the *Aspidosperma* series, we first decided to apply the Pummerer rearrangement to our purpose.[16] The required (phenylsulfinyl)acetamide **4a** was prepared as an equimolecular mixture of diastereomers in three steps from the tetracyclic secondary amine 1, by acylation with (phenylthio)acetyl chloride followed by tosylation of the indole nitrogen in the resulting (phenylthio)acetamide **2a** and oxidation of sulfide **3a** with MCPBA (Scheme III).[17] As a byproduct sulfone **5a** was isolated in 12% yield.

It is known that the Pummerer rearrangement of β-keto sulfoxides with acids or acid anhydrides readily generates thionium ion intermediates, which are electrophilic species able to react with electron-rich aromatic nucleus such as indole.[18] However, treatment of sulfoxides **4a** with TFAA at 0 °C followed by refluxing in chlorobenzene afforded the unexpected dithioacetal **9a** instead of the desired pentacyclic compound **11a**. The formation of dithioacetals from sulfoxides under Pummerer conditions had been previously reported[19] and involves intermolecular attack of the sulfur atom of the initially formed α-acyloxy sulfide at the electrophilic methine carbon of a second molecule, in which the acyloxy group acts as a leaving group. This means that sulfur favorably competes with indole as nucleophile. In fact, when a pure diastereomer of sulfoxide **4a** was exposed to TFAA in $CDCl_3$, the $^1H$ NMR spectrum showed in a few seconds the presence of two singlets (δ 6.23

(7) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657.

(8) (a) Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057. (b) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881.

(9) (a) Bonjoch, J.; Casamitijana, N.; Quirante, J.; Rodriguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267. (b) Quesada, M. L.; Kim, D.; Ahn, S. K.; Jeong, N. S.; Hwang, Y.; Kim, M. Y.; Kim, J. W. *Heterocycles* **1987**, *25*, 283. (c) Bonjoch, J.; Quirante, J.; Rodriguez, M.; Bosch, J. *Tetrahedron* **1988**, *44*, 2087.

(10) (a) Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021. (b) Vercauteren, J.; Bideau, A.; Massiot, G. *Tetrahedron Lett.* **1987**, *28*, 1267.

(11) For an enantioselective approach, see: (a) Henin, J.; Massiot, G.; Vercauteren, J.; Guilhem, J. *Tetrahedron Lett.* **1987**, *28*, 1271. (b) Legseir, B.; Henin, J.; Massiot, G.; Vercauteren, J. *Tetrahedron Lett.* **1987**, *28*, 3573.

(12) However, see ref 3c, p 314.

(13) The strain in the E ring of the *Strychnos* alkaloids is evident from the magnitude of bond lengths and angles, especially those involving C-7. (a) Mostad, A. *Acta Chem. Scand. B* **1985**, *39*, 705. (b) Mostad, A. *Acta Chem. Scand. B* **1986**, *40*, 64.

(14) (a) Husson, H.-P.; Thal, C.; Potier, P.; Wenkert, E. *J. Chem. Soc., Chem. Commun.* **1970**, 480. (b) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146. (c) Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, *17*, 111. (d) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. (e) Wenkert, E.; Hudlický, T. *J. Org. Chem.* **1988**, *53*, 1953.

(15) (a) Feliz, M.; Bosch, J.; Mauleón, D.: Amat, M.; Domingo, A. *J. Org. Chem.* **1982**, *47*, 2435. (b) Bosch, J.; Amat, M.; Sanfeliu, E.; Miranda, M. A. *Tetrahedron* **1985**, *41*, 2557.

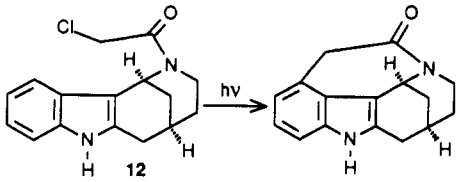
(16) For a preliminary account of this part of the work, see: Bosch, J.; Amat, M. *Tetrahedron Lett.* **1985**, *26*, 4951.

(17) The existence of rotamers due to the restricted rotation of the amide group was observed by $^1H$ NMR. The predominance of the *Z* rotamer (77% for **2a**, 95% for **3a** and **4a**) was inferred from the relative integration of the two apparent triplets due to the C-1 methine proton.

(18) For examples of Pummerer-type cyclizations on indoles, see: (a) Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1972**, 3393. (b) Oikawa, Y.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1479. (c) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118. (d) Gênin, D.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *Heterocycles* **1987**, *26*, 377.

(19) (a) Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1974**, *30*, 2653. (b) Harris, T. D.; Boekelheide, V. *J. Org. Chem.* **1976**, *41*, 2770. See also: ref 18c.

**Scheme IV**



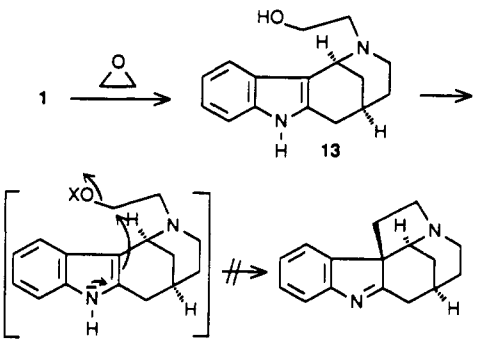

and 6.36) corresponding to the SC*H*CO methine proton of both diastereomers of acyloxy sulfide **7a**.[20] In accordance with the lower leaving group character of the acetoxy group as compared with trifluoroacetoxy, when sulfoxide **4a** was treated with acetic anhydride at 140 °C, acetoxy sulfide **8a** was cleanly obtained in 90% yield as a stable diastereomeric mixture which afforded neither the desired pentacyclic compound **11a** nor the dithioacetal **9a**, even upon heating at 200 °C in nitrobenzene solution. However, heating in the presence of a Lewis acid such as $BF_3$·$Et_2O$, which enhances the ability of the acetoxy group as a leaving group, **8a** gave again dithioacetal **9a**. The above results made evident that the failure in the cyclization could not be attributed to an inefficient procedure in generating a suitable electrophilic species, but probably to electronic or structural factors inherent to the molecule.

In order to assess if the inductive deactivation exerted by the tosyl substituent attached to the indole nitrogen of **4a** prevented the desired cyclization, sulfoxide **6a**, prepared by MCPBA oxidation of sulfide **2a**, was treated with TFAA in the presence of an equimolecular amount of $Et_3N$.[21] The unstable dithioacetal **10a** was obtained as the only identifiable product. The reluctance of sulfoxides **4a** and **6a** to cyclize cannot be attributed either to the steric interactions caused by the bulky phenyl substituent because similar results were obtained from the less sterically demanding (methylsulfinyl)acetamide **4b**, which was prepared similarly as described for sulfoxide **4a**, by acylation of **1** with (methylthio)acetyl chloride, followed by tosylation and MCPBA oxidation. Treatment of **4b** with TFAA at 0 °C in $CH_2Cl_2$ afforded a diastereomeric mixture of $\alpha$-(trifluoroacetoxy)sulfides **7b**[20] in less than 1 min (resonances at $\delta$ 6.03 and 6.16 due to SC*H*CO and at $\delta$ 1.83 and 2.23 due to $CH_3S$ were observed by $^1H$ NMR). However, after heating (135 °C) in chlorobenzene, a dithioacetal (**9b**) was again obtained. The cyclized product **11b** was not detected. As in the phenyl series, reaction of (methylsulfinyl)acetamide **4b** with $Ac_2O$ gave a stable acetoxy sulfide **8b** which, upon treatment with $BF_3$·$Et_2O$, was converted to the corresponding dithioacetal **9b**.

A previous attempt to induce the closure of the five-membered E ring of *Strychnos* alkaloids by cyclization of chloroacetamide **12** had resulted in failure:[15b] cyclization took place upon the indole 4-position to give a pentacyclic seven-membered lactam (Scheme IV).

A common structural feature of sulfoxides **4** and **6** and chloroacetamide **12**, which could account for the failure in the formation of the C-6/C-7 bond, is that the exocyclic carbon atom linked to the piperidine nitrogen is $sp^2$ hybridized; cyclization upon the indole 3-position would imply the disturbance of the planarity of the amide bond.[22,23]

**Scheme V**




Changing the hybridation of this carbon from $sp^2$ to $sp^3$ not only would avoid this possible unfavorable effect but also would reduce the distance between the indole 3-position and the electrophilic carbon atom.[24] Accordingly, we turned our attention to substrates in which the exocyclic carbon attached to the piperidine nitrogen was $sp^3$ hybridized.

First, we tried cyclization of alcohol **13**, which was prepared by reaction of amine **1** with excess of ethylene oxide (Scheme V). However, exposure of this alcohol either to acidic conditions ($BF_3$·$Et_2O$) or to mesyl chloride ($Et_3N$, $K_2CO_3$, or pyridine; $CH_2Cl_2$, THF, or DMF) and then to base (*t*-BuOK) did not produce the expected pentacyclic system. Direct treatment of amine **1** with 1,2-dibromoethane ($Na_2CO_3$, DMF) did not lead to any cyclized product either.

Next, attention was focused upon cyclizations involving trigonally hybridized electrophiles such as oxonium (**16a**) or thionium (**16b**) ions, which would be generated from acetal **15** and dithioacetal **18**,[25] respectively (Scheme VI). Acetal **15** was prepared by alkylation of the secondary amine **1** with bromoacetaldehyde diethyl acetal followed by tosylation of the indole nitrogen in the resulting tertiary amine **14**, whereas dithioacetal **18** was conveniently obtained from **15** by exchange of ethoxy groups by methylthio through treatment with MeSH in the presence of $BF_3$·$Et_2O$. In fact, we expected that 5-*exo-trig*[26] cyclizations from **15** and **18** were less sterically demanding than the above 5-*exo-tet* cyclizations as the latter involved a pseudopentacoordinate transition state which is sterically impeded.[14d] However, cyclization of either acetal **15** or dithioacetal **18** under a variety of acidic conditions failed and pentacycles **17** were never detected.

Thus, heating **15** with *p*-TsOH in refluxing benzene unexpectedly gave the secondary amine **21** in high yield, whereas treatment of **15** with $BF_3$·$Et_2O$ in refluxing $CH_2Cl_2$ afforded a mixture of the unstable aldehyde **19**[27] ($^1H$ NMR: $\delta$ 9.6 t, $J$ = 1.5 Hz) along with minor amounts of **21**. Formation of amine **21** can be rationalized by considering that the oxonium salt **16a**, generated by acid-catalyzed

(20) This compound was stable at room temperature for 24 h under neutral conditions but decomposed in contact with silica gel.

(21) In the absence of $Et_3N$ a complex mixture was formed, probably due to the instability of the *N*-acyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole system under the strong acidic conditions of the Pummerer reaction.

(22) This reason could also explain the failure of the base-promoted cyclization of chloroacetamide **12** under a variety of reaction conditions. For the use of a similar base-promoted cyclization in the *Aspidosperma* series, see ref 14a. However, see also ref 14d.

(23) The differences observed in the Pummerer rearrangement of (phenylsulfinyl)acetamides applied to the closure of the E ring of *Aspidosperma* and *Strychnos* alkaloids could reflect the higher conformational flexibility of the fused tetracyclic precursors of *Aspidosperma* alkaloids in comparison with the conformationally rigid bridged *Strychnos* analogues.

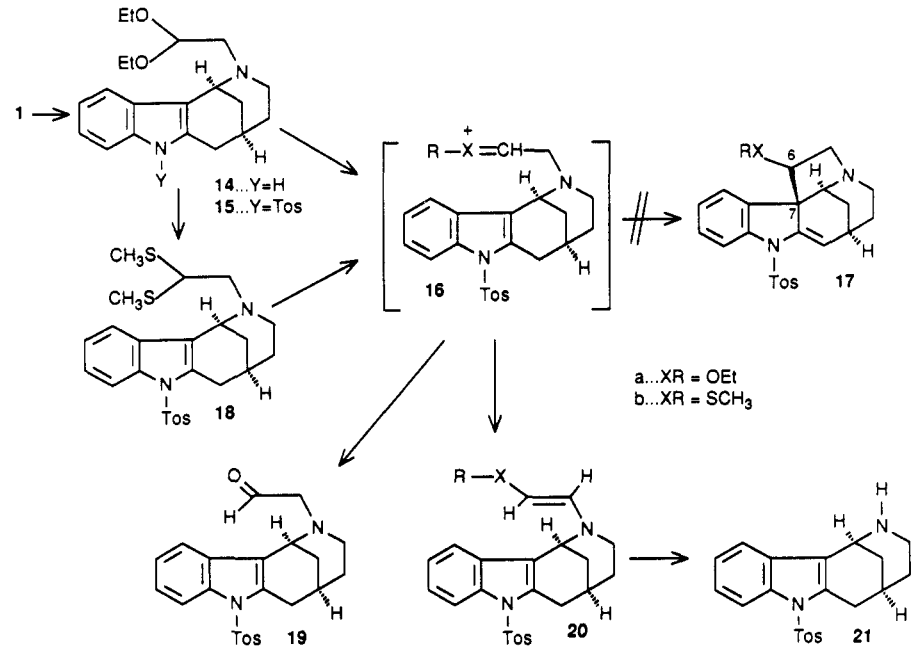
(24) In fact, Dreiding molecular models show that this distance is longer in the *Strychnos* than in the *Aspidosperma* tetracyclic precursors, specially when they have an exocyclic amide carbonyl group.

(25) For the generation of thionium ions from dithioacetals and their use in cyclization reactions, see: Trost, B. M.; Reiffen, M.; Crimmin, M. *J. Am. Chem. Soc.* **1979**, *101*, 257.

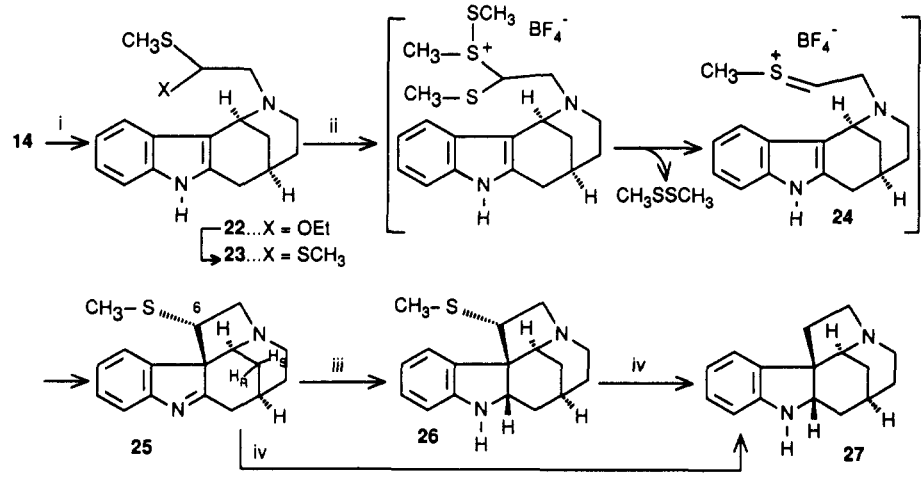
(26) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(27) Aldehyde **19** is formed by hydrolysis of the oxonium intermediate **16a**. However, cyclization of **16a** followed by acid-catalyzed ring opening of the cyclized product **17a** cannot be totally discarded due to the reversibility of the process.

Scheme VI




Scheme VII.[a] Closure of E Ring




[a] Reagents: (i) $CH_3SH$, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 5 °C; (ii) $[(CH_3)_2SSCH_3]^+BF_4^-$, $CH_2Cl_2$, 0 °C; (iii) $LiAlH_4$, THF; (iv) Raney Ni, EtOH.

elimination of ethanol, is in equilibrium, by way of the corresponding enamine **20a**, with an exocyclic iminium ion which is further hydrolyzed.[28] On the other hand, treatment of dithioacetal **18** with excess of $BF_3{\cdot}Et_2O$ (reflux, 45 min) afforded enamine **20b** (a singlet at $\delta$ 1.9 for the MeS group and doublets at $\delta$ 4.5 and 6.5, $J$ = 12.0 Hz, attributable to the two trans olefinic protons were observed by $^1H$ NMR), which was easily hydrolyzable to **21** on standing in $CH_2Cl_2$ or $CDCl_3$ solution. Under milder conditions ($CHCl_3$, reflux, 50 h), the starting dithioacetal was recovered to a considerable extent.

These discouraging results raised the question regarding whether the deactivating effect of the protecting tosyl substituent was responsible for the failure of the above cyclizations. This question could not be solved in the acetal series since acetal **14** gave only polymeric mixtures when it was treated with *p*-TsOH in boiling benzene. However, removal of the indole protecting group was crucial for the success of the cyclization in the dithioacetal series. Thus, when the unprotected dithioacetal **23**, prepared by reaction (5 °C, 48 h)[29] of acetal **14** with MeSH in the presence of excess $BF_3{\cdot}Et_2O$, was treated with 2 equiv of dimethyl(methylthio)sulfonium fluoroborate (DMTSF)[30] in $CH_2Cl_2$ solution at 0 °C, the desired pentacyclic compound **25** was obtained in 49% yield (Scheme VII).[31] A great part of the success of this reaction probably stems from the reagent used to generate the thionium ion since DMTSF is an excellent initiator for the generation

(28) For a similar N-dealkylation of a *N*-(2,2-diethoxyethyl) derivative, see: Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81.

(29) At a higher temperature a complex mixture was formed whereas at shorter reaction times substantial amounts of monothioacetal **22**, which could be further converted to **23**, were isolated.

(30) (a) Meerwein, H.; Zenner, K. F.; Gipp, R. *Justus Liebigs Ann. Chem.* **1965**, *688*, 67. (b) Smallcombe, S. H.; Caserio, M. C. *J. Am. Soc.* **1971**, *93*, 5826.

(31) (a) Methylsulfenylation of tertiary amines by DMTSF to give (methylthio)ammonium ions, which are further hydrolyzed, is a known process[31b,c] that could account for the fact that the best yields were obtained using 2 equiv of DMTSF. When only 1.3 equiv of DMTSF were used, the cyclization took place in 25% yield.[16] (b) Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231. (c) Kim, J. K.; Souma, Y.; Beutow, N.; Ibbeson, C.; Caserio, M. C. *J. Org. Chem.* **1989**, *54*, 1714.

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

| C | 29a | 29b | 30a | 30b | 32a | 32b | 41a | 41b |
|---|---|---|---|---|---|---|---|---|
| C-1 | 50.7 | 51.3 | 50.7 | 51.1 | 44.5 | 44.8 | 52.9 | 53.3 |
| C-3 | 50.7 | 47.3 | 50.3 | 47.1 | 43.5 | 40.5 | 51.2 | 47.9 |
| C-4 | 41.6 | 39.9 | 41.5 | 43.9 | 42.2 | 43.1 | 41.3 | 44.0 |
| C-5 | 45.1 | 46.4 | 28.7 | 30.3 | 29.8 | 29.3 | 28.7 | 30.2 |
| C-6 | 193.1 | 195.3 | 24.5 | 30.9 | 24.9 | 30.7 | 24.6 | 30.8 |
| C-6a | 133.6 | 132.9 | 135.7 | 135.5 | 136.1 | 136.2 | 135.7 | 135.9 |
| C-7a | 138.2 | 138.3 | 136.7 | 136.5 | 136.1 | 136.2 | 136.5 | 136.4 |
| C-8 | 112.8 | 112.9 | 110.4 | 110.3 | 110.6 | 110.5 | 110.4 | 110.3 |
| C-9 | 126.9 | 126.7 | 119.4 | 119.5 | 119.4 | 119.4 | 119.7 | 119.6 |
| C-10 | 122.0 | 122.0 | 120.7 | 120.7 | 121.0 | 121.0 | 120.9 | 120.7 |
| C-11 | 120.8 | 120.9 | 118.4 | 118.4 | 117.3 | 117.4 | 118.2 | 118.2 |
| C-11a | 126.6 | 126.5 | 128.5 | 128.1 | 126.1 | 126.1 | 128.0 | 128.0 |
| C-11b | 122.8 | 122.8 | 106.8 | 107.0 | 110.2 | 110.1 | 109.5 | 107.0 |
| C-12 | 38.3 | 32.4 | 34.3 | 29.2 | 34.2 | 28.3 | 34.2 | 29.0 |
| $CH_2CH_3$ | 24.7 | 24.6 | 22.6 | 25.7 | 22.7 | 25.4 | 22.6 | 25.7 |
| $CH_3CH_2$ | 11.6 | 12.3 | 11.5 | 12.7 | 11.5 | 12.8 | 11.5 | 12.7 |
| $NCH_2$ | 60.2 | 60.2 | 60.5 | 60.6 | | | 61.2 | 60.9 |
| *o*-$C_6H_5$ | 128.5 | 128.2 | 128.8 | 128.4 | | | | |
| *m*-$C_6H_5$ | 128.3 | 128.0 | 128.1 | 128.0 | | | | |
| *p*-$C_6H_5$ | 126.7 | 126.9 | 126.7 | 126.5 | | | | |
| *i*-$C_6H_5$ | 139.2 | 139.5 | 139.4 | 140.0 | | | | |
| SCS | | | | | | | 51.2 | 51.2 |
| $CH_3S$ | | | | | | | 13.2 | 13.0 |
| $CH_3S$ | | | | | | | 12.8 | 12.9 |

[a] In $CDCl_3$ solution.

Table II. $^{13}C$ NMR Data of Pentacyclic *Strychnos*-Type Systems[a]

| C | 25 | 26 | 27 | 42a | 43a | 46[b] | 47[b] |
|---|---|---|---|---|---|---|---|
| C-2 | 189.6 | 66.8 | 64.9 | 190.0 | 66.0 | 190.6 | 168.6 |
| C-3 | 70.2 | 60.0 | 62.3 | 70.1 | 62.5 | 69.8 | 60.8 |
| C-5 | 64.5 | 62.4 | 54.0 | 64.1 | 54.2 | 57.3 | 53.3 |
| C-6 | 47.7 | 56.2 | 42.0 | 47.2 | 42.5 | 33.0 | 42.0 |
| C-7 | 68.3 | 57.6 | 53.2 | 69.0 | 52.6 | 65.7 | 55.5 |
| C-8 | 139.3 | 128.0 | 132.5 | 139.3 | 133.8 | 145.2 | 134.4 |
| C-9 | 124.1 | 126.2 | 122.2 | 124.0 | 122.1 | 120.8 | 119.7 |
| C-10 | 124.8 | 118.2 | 119.1 | 124.7 | 119.0 | 125.3 | 121.2 |
| C-11 | 128.3 | 128.3 | 127.8 | 128.2 | 127.6 | 127.6 | 127.9 |
| C-12 | 119.9 | 109.2 | 109.5 | 119.7 | 109.5 | 119.8 | 109.8 |
| C-13 | 155.1 | 150.4 | 149.7 | 155.0 | 149.2 | 154.4 | 144.2 |
| C-14 | 30.6 | 29.2 | 28.9 | 28.4 | 28.2 | 28.3 | 30.8 |
| C-15 | 28.3 | 23.8 | 23.1 | 32.2 | 27.0 | 32.0 | 30.3 |
| C-16 | 31.1 | 38.3 | 37.4 | 26.0 | 32.6 | 26.1 | 98.6 |
| C-18 | | | | 11.3 | 11.4 | 11.3 | 11.4 |
| C-19 | | | | 24.9 | 25.4 | 24.8 | 25.8 |
| C-20 | 27.3 | 27.1 | 26.5 | 41.4 | 40.3 | 41.5 | 38.7 |
| C-21 | 45.5 | 49.1 | 47.7 | 51.9 | 55.0 | 50.7 | 50.8 |
| $CH_3S$ | 15.3 | 15.0 | | 15.2 | | | |
| C=O | | | | | | | 170.5 |
| $CH_3O$ | | | | | | | 51.5 |

[a] In $CDCl_3$ solution. [b] Bruker AC-300.

of thionium ions from dithioacetals in very mild conditions,[32] compatible with the unprotected indole ring.[33] Methylsulfenylation of one of the methylthio groups of the dithioacetal by DMTSF gaves an alkylthiosulfonium salt which easily dissociates generating the thionium ion **24**[34] and dimethyl disulfide.[35]

Interestingly, a similar DMTSF treatment either from the protected dithioacetal **18** or from bis(methylthio)-acetamide **10b**[36] did not result in cyclization, not even at room temperature after prolonged reaction times. In the former case the aldehyde **19**, resulting from hydrolysis of the intermediate thionium ion **16b**, was the only identifiable product, whereas in the latter a complex mixture was formed, from which no pentacyclic compound could be detected. These failures confirm the unfavorable effect of both the tosyl substituent and the exocyclic amide carbonyl group, which inhibit the cyclization to the *Strychnos* skeleton.

The $^1H$ and $^{13}C$ NMR (Table II) spectra of **25** clearly showed that cyclization had occurred. The most significant signals were a singlet at $\delta$ 1.60 attributable to the MeS protons, a broad singlet at $\delta$ 3.93 for H-3$\alpha$, and three signals at $\delta$ 3.08, 3.50, and 4.08 corresponding to the protons of the tryptamine bridge. The relative configuration at C-6

(32) (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.

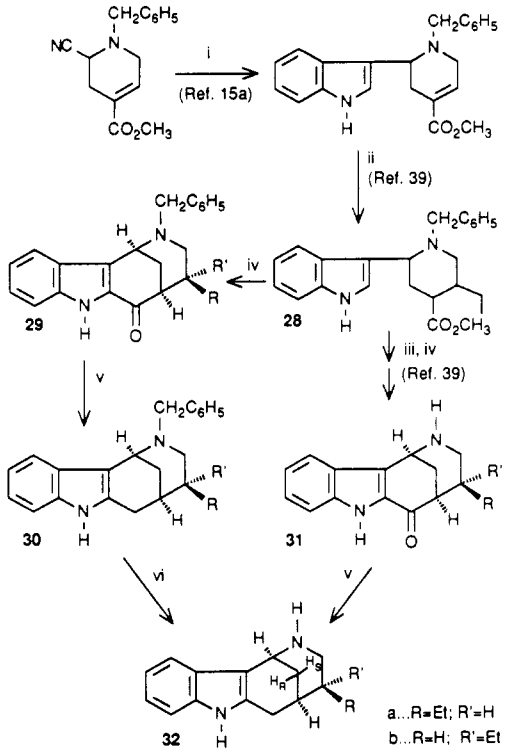
(33) There are no precedents of DMTSF-induced cyclizations of dithioacetals on an aromatic nucleus. For a similar DMTSF-promoted cyclization from a tris(phenylthio)alkyl derivative, via a bis(phenylthio)carbocation, see: bin Manas, A. R.; Smith, R. A. J. *Tetrahedron* **1987**, *43*, 1847.

(34) It is worth noting that thionium ion **24** is also formed as intermediate during the exchange reaction **14** → **23**, in which the cyclized product **25** was not detected. Probably, in the presence of excess $BF_3 \cdot Et_2O$, the N-unsubstituted indole ring is forming an adduct that inhibits cyclization.

(35) Kim, J. K.; Pau, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544.

(36) Amide **10b** was prepared by acylation of amine **1** with bis(methylthio)acetyl chloride (**35**), which was obtained from ethyl diethoxyacetate as depicted in Scheme IX.

**Scheme VIII**[a]



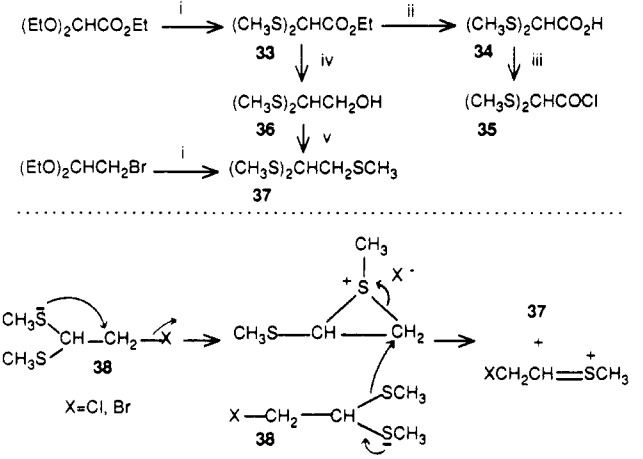

[a] Reagents: (i) indole, 1:1 AcOH–$H_2O$; (ii) EtMgBr–CuI, THF, –30 °C; (iii) $H_2$–Pd–C, HCl–EtOH; (iv) $Ba(OH)_2$, 1:1 dioxane–$H_2O$, reflux; then PPA, 85 °C; (v) $LiAlH_4$, dioxane, reflux; (vi) $H_2$–$Pd(OH)_2$, MeOH.

in **25** as depicted in Scheme VII was inferred from the upfield shift observed for the MeS group ($\delta$ 1.60; compare with $\delta$ 1.9 and $\delta$ 2.0 in dithioacetal **23**), rigidly held over the aromatic ring.

Raney nickel treatment of the cyclized product **25** brought about both desulfurization and simultaneous reduction of the carbon-nitrogen double bond to give 20-deethyltubifolidine (**27**), the fundamental ring system of pentacyclic *Strychnos* indole alkaloids. This transformation was also accomplished, although less efficiently, in two steps, by reduction of indolenine **25** with $LiAlH_4$ and further Raney nickel desulfurization of the resulting indoline **26**. Reduction of the carbon–nitrogen double bond of indolenine **25** induces a conformational change of ring C, from a flattened boat in **25** to a chair in **26**,[37] which also affects ring E causing a stronger anisotropic effect on the MeS group ($\delta$ 1.37).

**Synthesis of Pentacyclic *Strychnos* Alkaloids.** With a method in hand for the elaboration of the fundamental pentacyclic framework of *Strychnos* alkaloids, our next goal was to extend this procedure to the total synthesis of the natural products.[38] First of all, a convenient route to the tetracyclic secondary amine **32a**, having the same relative configuration at C-4 as the alkaloids at the corresponding position (C-20), had to be developed. As we have previously reported, condensation of an appropriate 2-cyano-1,2,3,6-tetrahydropyridine-4-carboxylate ester with indole[15a] followed by conjugate addition of diethylcopper(I)–magnesium bromide to the resulting $\alpha,\beta$-

**Scheme IX**[a]



[a] Reagents: (i) $CH_3SH$, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$; (ii) EtOH–2 N aqueous NaOH; (iii) KOH–$CH_3OH$; then $(COCl)_2$, $C_6H_6$; (iv) $LiAlH_4$, $Et_2O$; (v) $SOCl_2$, $CHCl_3$ or $PBr_3$, $Et_2O$.

unsaturated ester afforded a diastereomeric mixture of 3-(2-piperidyl)indoles **28**, which were further elaborated into tetracycles **31a** (*N*-demethylisodasycarpidone) and **31b**[39] (Scheme VIII). Although reduction of the 2-acylindole carbonyl group of **31a** and **31b** with excess $LiAlH_4$ afforded **32a** and **32b**, an alternative route to these compounds, consisting in saponification of the ester group of **28** followed by PPA cyclization, $LiAlH_4$ reduction of the 2-acylindole moiety in the resulting mixture of C-4 epimeric ketones **29**, and final debenzylation over Pearlman's catalyst, was also developed. It is worth mentioning that, although this second route did not represent a great improvement in the overall yield, the C-4 epimers **30a**[40] and **30b** could be easily separated by column chromatography whereas diastereomeric mixtures of **28**, **29**, **31**, or **32** could not be efficiently separated by chromatographic methods. For this reason, the route **28** → **29** → **30** → **32** was that of choice on a preparative scale.

The above pairs of epimers at C-4 were easily distinguishable from their NMR data. Thus, in series **b** (ethyl axial) the methylene protons of the ethyl substituent appear further downfield ($\delta$ 1.5–1.9) than in series **a** (ethyl equatorial; $\delta$ 1.1–1.5) owing to the anisotropic effect of the piperidine nitrogen lone pair. Other $^1H$ NMR signals of diagnostic value were those corresponding to 3-Hax: a triplet ($J \approx 11.5$ Hz) in series **a** but a doublet of doublets ($J \approx 12.0$ and 4.0 Hz) in series **b**. On the other hand, in the $^{13}C$ NMR spectra, C-12 is shielded in epimers **b** as compared with epimers **a** due to a $\gamma$-effect induced by the axial ethyl group (see Table I). A similar shielding effect

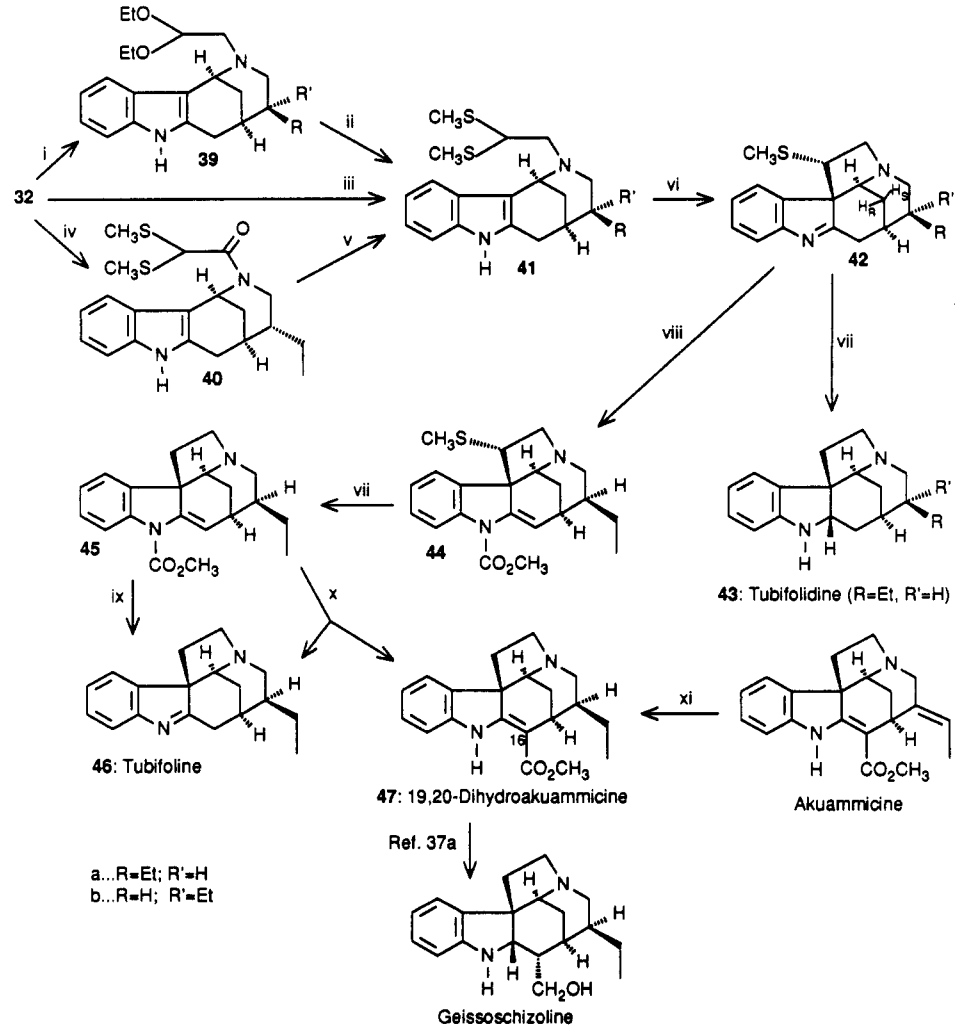
(37) (a) Edwards, P. N.; Smith, G. F. *J. Chem. Soc.* **1961**, 152. (b) Amat, M.; Linares, A.; Muñoz, J.; Bosch, J. *Tetrahedron Lett.* **1988**, *29*, 6373.

(38) For a preliminary report of this part of the work, see: Amat, M.; Linares, A.; Salas, M. L.; Alvarez, M.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1988**, 420.

(39) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516. $^1H$ NMR (200 MHz) data of these compounds have not been previously reported. **31a**: ($CDCl_3$) $\delta$ 1.01 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.15 and 1.40 (2 m, 2 H, $CH_2CH_3$), 1.92 (m, 1 H, H-4$\alpha$), 2.10 (br s, 1 H, $N_b$-H), 2.25 (dt, $J$ = 12.8, 3.2 Hz, 1 H, H-12*R*), 2.34 (t, $J$ = 12.0 Hz, 1 H, H-3$\beta$), 2.55 (dt, $J$ = 12.8, 3.2 Hz, 1 H, H-12*S*), 2.82 (dd, $J$ = 12.0, 4.8 Hz, 1 H, H-3$\alpha$), 2.85 (m, 1 H, H-5$\alpha$), 4.67 (apparent t, 1 H, H-1$\alpha$), 7.15 (t, $J$ = 8.0 Hz, 1 H, H-10), 7.35 (t, $J$ = 8.0 Hz, 1 H, H-9), 7.45 (d, $J$ = 8.0 Hz, 1 H, H-8), 7.70 (d, $J$ = 8.0 Hz, 1 H, H-11). **31b**: ($CDCl_3$) $\delta$ 1.01 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.70–2.10 (m, 3 H, $CH_2CH_3$ and H-4$\beta$), 2.30 (dt, $J$ = 12.6, 3.2 Hz, 1 H, H-12*R*), 2.50 (dt, $J$ = 12.6, 3.5 Hz, 1 H, H-12*S*), 2.59 (d, $J$ = 12.0 Hz, 1 H, H-3$\alpha$), 2.68 (m, 1 H, H-5$\alpha$), 2.80 (dd, $J$ = 12.0, 4.5 Hz, 1 H, H-3$\beta$), 4.64 (apparent t, 1 H, H-1$\alpha$), 7.14 (t, $J$ = 8.0 Hz, 1 H, H-10), 7.40 (t, $J$ = 8.0 Hz, 1 H, H-9), 7.48 (d, $J$ = 8.0 Hz, 1 H, H-8), 7.72 (d, $J$ = 8.0 Hz, 1 H, H-11).

(40) For alternative syntheses of **30a**, see: (a) Bonjoch, J.; Quirante, J.; Linares, A.; Bosch, J. *Heterocycles* **1988**, *27*, 2883. (b) Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5659.

**Scheme X.**[a] **Synthesis of Pentacyclic *Strychnos* Alkaloids**




[a] Reagents: (i) $BrCH_2CH(OEt)_2$, $NaCO_3$, dioxane, reflux; (ii) $CH_3SH$, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 5 °C; (iii) $(CH_3S)_2CHCHO$, $NaBH_3CN$, 1:1 THF–aqueous citric acid/sodium citrate, pH 6; (iv) $(CH_3S)_2CHCOCl$, $CH_2Cl_2$–1 N aqueous NaOH; (v) $LiAlH_4$, dioxane; (vi) $[(CH_3)_2SSCH_3]^+BF_4^-$, $CH_2Cl_2$, 0 °C; (vii) Raney Ni, EtOH, reflux; (viii) $CH_3OCOCl$, NaH, 1,2-dimethoxyethane, 60 °C; (ix) 1 N $NaOCH_3$–$CH_3OH$, reflux; (x) *hν*, $CH_3OH$; (xi) $H_2$–$PtO_2$, EtOH.

was observed upon C-6 in epimers **a**.

As in the above deethyl series, secondary amines **32a** and **32b** were separately alkylated with bromoacetaldehyde diethyl acetal and the resulting acetals **39a** and **39b** converted to dithioacetals **41a** and **41b** in 51% and 43% overall yields, respectively (Scheme X). In order to improve these yields, the introduction of the *N*-bis(methylthio)ethyl chain was explored by two alternative methods. However, reductive alkylation of amine **32b** with bis(methylthio)acetaldehyde and $NaBH_3CN$ for long reaction times afforded dithioacetal **41b** in only 13% yield. This low yield could be attributed to steric factors (axial ethyl group) since the same procedure applied to piperidine gave the corresponding *N*-bis(methylthio)ethyl derivative in 80% yield. Alternatively, acylation of **32b** with bis(methylthio)acetyl chloride (**35**) followed by $LiAlH_4$ reduction of the resulting amide **40** gave **41b** in only 33% overall yield. On the other hand, attempts to obtain the more straightforward alkylating reagents 2-bromo- or 2-chloro-1,1-bis(methylthio)ethane (**38**) failed. Thus, 2,2-bis(methylthio)ethanol **36**, prepared from ethyl diethoxyacetate as depicted in Scheme IX, reacted with $PBr_3$ or $SOCl_2$ to give tris(methylthio)ethane **37** as the only isolable product. The same compound was obtained when bromoacetaldehyde diethyl acetal was treated with MeSH under acetal exchange conditions. Formation of **37** can be explained by considering that the initially formed halo derivative **38** is converted to an episulfonium salt which undergoes intermolecular nucleophilic attack by the sulfur atom of a second dithioacetal molecule (Scheme IX).

The crucial cyclization step was accomplished in 52% yield following the procedure previously developed in the deethyl series, by treatment of dithioacetal **41a** with DMTSF (2 equiv). Further Raney nickel cleavage of the C–S bond with simultaneous reduction of the indolenine double bond in the resulting pentacycle **42a** gave the *Strychnos* alkaloid tubifolidine (**43a**).[41-43] Through a

(41) For the isolation and structural elucidation of this alkaloid, see: Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1497.

(42) For previous total syntheses, see refs 6a and 7. For previous formal syntheses, see ref 8.

(43) (a) Before their isolation, tubifolidine,[43b] tubifoline,[43c-e] and 19,20-dihydroakuammicine[43e-g] were known compounds which had been obtained by partial synthesis in the context of chemical correlations effected for structural elucidation of more complex *Strychnos* alkaloids. (b) Smith, G. F.; Wróbel, J. T. *J. Chem. Soc.* **1960**, 972. (c) Bernauer, K.; Arnold, W.; Weissmann, Ch.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1960**, *43*, 717. (d) Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 1996. (e) Weissmann, Ch.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1961**, *44*, 1877. (f) Aghoramurthy, K.; Robinson, R. *Tetrahedron* **1957**, *1*, 172. (g) Lévy, J.; Le Men, J.; Janot, M.-M. *Bull. Soc. Chim. Fr.* **1960**, 979.

similar two-step sequence, dithioacetal **41b** was converted to (±)-20-epitubifolidine (**43b**).

The synthesis of tubifoline (**46**), a *Strychnos* alkaloid[41] whose most characteristic feature is the presence of an indolenine unit, required the chemoselective hydrogenolysis of the methylthio substituent without affecting the carbon–nitrogen double bond.[44] Although small amounts of (±)-tubifoline were detected in some runs after Raney nickel treatment of **42a**, attempts to efficiently effect this transformation directly from **42a** were unsuccessful. For this reason, in order to avoid the reduction of the indolenine unit, we decided to effect the hydrogenolysis step from the *N*-methoxycarbonyl enamine derivative **44**, which was prepared by treatment of indolenine **42a** with sodium hydride and methyl chloroformate. As expected, careful desulfurization of **44** using not deactivated Raney nickel, followed by methanolysis (NaOMe, MeOH) of the resulting carbamate enamine **45**, afforded racemic tubifoline (**46**) in 24% overall yield from **42a**.[42,43]

The greater part of pentacyclic *Strychnos* alkaloids possess an oxidized one-carbon substituent at C-16.[4] Therefore, it was of interest to introduce this carbon unit on the pentacyclic *Strychnos* skeleton so that our synthetic strategy could constitute a general entry to the alkaloids of this group.[45] For this purpose we took advantage of the pentacyclic intermediate **45** because it is known that *N*-(methoxycarbonyl)enamines photochemically rearrange to vinylogous urethanes.[46–48] Thus, when a methanolic solution of **45** was photolyzed with a high-pressure mercury lamp, a mixture of the alkaloid 19,20-dihydroakuammicine (**47**)[41] and the corresponding decarbomethoxylated product, (±)-tubifoline (**46**), was obtained. In all trials small amounts of the starting material were recovered. Our synthetic 19,20-dihydroakuammicine (**47**) was found to be identical (TLC)[41,43d] with a sample obtained by catalytic hydrogenation[43f,g] of akuammicine.[49] This synthesis constitutes the first total synthesis of 19,20-dihydroakuammicine[43] and, given that this alkaloid had been previously converted into geissoschizoline,[37a] it also represents a formal total synthesis of the latter alkaloid.[50]

## Conclusion

Thus, a new synthetic entry to pentacyclic *Strychnos* alkaloids that has allowed the total synthesis of (±)-tubifolidine, (±)-tubifoline, and (±)-19,20-dihydroakuammicine has been successfully developed. The crucial step of the synthesis consists in the closure of the five-membered E ring (bond formed C-6/C-7) by cyclization upon the indole 3-position from a tetracyclic hexahydro-1,5-methanoazocino[4,3-*b*]indole system having an appropriately functionalized two-carbon substituent on the piperidine nitrogen. The efficiency of DMTSF in this cyclization as initiator for the generation of thionium ions from dithioacetals has been demonstrated. Some structural features in the tetracyclic substrates that inhibit the cyclization to pentacyclic *Strychnos*-type systems have been recognized: (i) the presence of a deactivating tosyl substituent upon the indole nitrogen, (ii) the presence of an amide carbonyl group exocyclic to the piperidine nitrogen, and (iii) the $sp^3$ character of the electrophilic C-6 center during the cyclization step. With methods available for the straightforward introduction of an oxidized one-carbon substituent at C-16 and an ethylidene group at C-20,[51] the strategy developed here provides a general synthetic entry to most of pentacyclic *Strychnos* alkaloids. The extension of this methodology to the total synthesis of more complex *Strychnos* alkaloids is under study.[52]

## Experimental Section

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Varian XL-200 instrument or, when indicated, on a Perkin-Elmer R-24B (60 MHz) or a Bruker AC-300 spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as internal standard. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer, and only noteworthy absorptions are listed. UV spectra were run on a Perkin-Elmer Lambda 5 spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. The HRMS were recorded on a MS-9 AEI mass spectrometer up-dated by VG. Column chromatography was carried out on $SiO_2$ (silica gel 60, 0.063–0.200 mm) or, when indicated, on $Al_2O_3$ (aluminum oxide 90, neutral, activity I, 0.063–0.200 mm). Flash chromatography was carried out on $SiO_2$ (silica gel 60, 0.040–0.063 mm). Thin-layer chromatography was carried out on $SiO_2$ (silica gel 60 $F_{254}$, 0.063–0.200 mm), and the spots were located with iodoplatinate reagent or UV light. Purification of reagents and solvents was effected according to standard methods.[53] All reactions were carried out under nitrogen or argon atmosphere. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ or $Na_2SO_4$ powder. All compounds were synthesized in the racemic series. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Centro de Investigación y Desarrollo (CSIC), Barcelona.

**2-[(Phenylthio)acetyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (2a).** A solution of (phenylthio)acetyl chloride[54] (5.3 g, 28.3 mmol) in $CH_2Cl_2$ (90 mL) was added dropwise to a stirred mixture of **1**[15b] (3.0 g, 14.1 mmol) in $CH_2Cl_2$ (180 mL) and 1 N aqueous NaOH (30 mL). After stirring at room temperature for 3 h the organic solution was separated, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried, and evaporated to give a foam. Purification by column chromatography (alumina, $CHCl_3$) afforded 4.8 g (95%) of pure **2a**: IR (KBr) 3400, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.54–2.18 (m, 4 H, H-4 and H-12), 2.48 (m, 1 H, H-5), 2.68 and 2.70 (2 d, $J$ = 18.0 Hz, 1 H, H-6eq), 2.96 and 2.58 (2 td, $J$ = 14.0, 4.0 Hz, 1 H, H-3ax), 3.14 (dd, $J$ = 18.0, 6.0 Hz, 1 H, H-6ax), 3.44 and 4.28 (2 dd, $J$ = 14.0, 4.8 Hz, 1 H, H-3eq), 3.64 (s, *Z* rotamer, $SCH_2CO$), 4.01 and 4.22 (2 d, $J$ = 14.0 Hz, *E* rotamer, $SCH_2CO$), 5.26 and 6.14 (2 apparent t, 1 H, H-1), 7.00–7.60 (m, 9 H, Ar), 8.16 and 8.34 (2 br s, 1 H, NH); mp 165–167 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{22}H_{22}N_2OS$: C, 72.82; H, 6.12; N, 7.73. Found: C, 72.73; H, 6.22; N, 7.66.

**2-[(Methylthio)acetyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (2b).** Operating as above, from

(44) For a preliminary report about the synthesis of (±)-tubifoline and a detailed discussion of its $^1H$ and $^{13}C$ NMR data, see ref 37b.

(45) For a preliminary report about the synthesis of (±)-19,20-dihydroakuammicine and a detailed discussion of its $^1H$ and $^{13}C$ NMR data, see: Amat, M.; Linares, A.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 2293.

(46) For reviews about the photochemistry of enamides, see: (a) Lenz, G. R. *Synthesis* **1978**, 489. (b) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421.

(47) For the use of this procedure in *Aspidosperma* series, see: (a) Wenkert, E.; Orito, K.; Simmons, D. P.; Kunesh, N.; Ardisson, J.; Poisson, J. *Tetrahedron* **1983**, *39*, 3719. (b) Wenkert, E.; Porter, B.; Simmons, D. P. *J. Org. Chem.* **1984**, *49*, 3733.

(48) For other related methods: (a) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685. (b) Yoshida, K.; Nomura, S.; Ban, Y. *Tetrahedron* **1985**, *41*, 5495. (c) Ladlow, M.; Cairns, P. M.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1986**, 1756.

(49) We are indebted to Professor Georges Massiot (University of Reims) for providing an authentic sample of natural akuammicine.

(50) (a) For previous total syntheses of (±)-geissoschizoline, see refs 6b and 6c. (b) For previous partial syntheses, see: Janot, M.-M. *Tetrahedron* **1961**, *14*, 113. Hymon, J. R.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 2067. See also ref 37a.

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

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1 (2.5 g, 11.8 mmol) in $CH_2Cl_2$ (75 mL), 1 N aqueous NaOH (25 mL), and (methylthio)acetyl chloride[55] (2.9 g, 23.6 mmol) in $CH_2Cl_2$ (25 mL), amide **2b** was obtained in 85% yield after recrystallization from EtOH: IR (KBr) 3400, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz, major rotamer) $\delta$ 2.0 (s, $CH_3S$), 3.1 (s, $SCH_2CO$), 6.0 (apparent t, H-1), 6.7–7.5 (m, 4 H, Ar), 8.6 (br s, NH); mp 160–162 °C (EtOH). Anal. Calcd for $C_{17}H_{20}N_2OS$: C, 67.97; H, 6.71; N, 9.32; S, 10.67. Found: C, 67.80; H, 7.07; N, 9.01; S, 10.87.

**2-[(Phenylthio)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (3a).** A mixture of **2a** (2.0 g, 5.5 mmol) in $C_6H_6$ (100 mL) and 50% aqueous NaOH (30 mL) containing a catalytic amount of tetrabutylammonium hydrogen sulfate (0.2 g, 0.6 mmol) was stirred at room temperature for 10 min. Then, a solution of *p*-toluenesulfonyl chloride (1.6 g, 8.3 mmol) in $C_6H_6$ (45 mL) was added dropwise. Stirring was maintained for 4 h, and the organic layer was separated, washed with brine, dried, and evaporated. Purification of the resulting foam by column chromatography (7:3 $C_6H_6$–$CHCl_3$) furnished 2.1 g (74%) of pure **3a**: IR (KBr) 1630, 1370, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.54–2.06 (m, 4 H, H-4 and H-12), 2.33 (s, 3 H, $CH_3Ar$), 2.42 (m, 1 H, H-5), 2.76 (td, $J$ = 14.0, 4.0 Hz, H-3ax), 3.12 (d, $J$ = 18.0 Hz, 1 H, H-6eq), 3.26 (dd, $J$ = 18.0, 6.0 Hz, 1 H, H-6ax), 3.44 (dd, $J$ = 14.0, 6.0 Hz, H-3eq), 3.62 (s, *Z* rotamer, $SCH_2CO$), 3.94 and 4.12 (2 d, $J$ = 14.0 Hz, *E* rotamer, $SCH_2CO$), 5.16 and 6.02 (2 apparent t, 1 H, H-1), 7.10–7.70 (m, 12 H, Ar), 8.10 (m, 1 H, H-8); mp 53–55 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{29}H_{28}N_2O_3S_2$: C, 67.41; H, 5.46; N, 5.42; S, 12.41. Found: C, 67.69; H, 5.44; N, 5.28; S, 12.25.

**2-[(Methylthio)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (3b).** Operating as above, from **2b** (2.0 g, 6.6 mmol), *p*-toluenesulfonyl chloride (1.9 g, 9.9 mmol), and tetrabutylammonium hydrogen sulfate (0.2 g, 0.6 mmol) in $C_6H_6$ (170 mL) and 50% aqueous NaOH (30 mL), pure **3b** (2.7 g, 91%) was obtained after column chromatography (2:3 $C_6H_6$–$CHCl_3$): IR (KBr) 1630, 1370, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz, major rotamer) $\delta$ 2.0 (s, $CH_3S$), 2.2 (s, $CH_3Ar$), 3.1 (s, $SCH_2CO$), 5.9 (apparent t, H-1), 6.9–7.7 (m, 7 H, Ar), 8.0 (m, 1 H, H-8); mp 132–135 °C ($Et_2O$). Anal. Calcd for $C_{24}H_{26}N_2O_3S_2$: C, 63.41; H, 5.77; N, 6.16; S, 14.11. Found: C, 63.46; H, 5.84; N, 6.07; S, 14.05.

**2-[(Phenylsulfinyl)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (4a).** A solution of *m*-chloroperbenzoic acid (1.4 g, 85% pure, 6.7 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise to a mixture of **3a** (2.3 g, 4.5 mmol) and $NaHCO_3$ (0.8 g, 9.5 mmol) in $CH_2Cl_2$ (20 mL), and the reaction mixture was stirred at room temperature for 5 h. The resulting solution was washed with $H_2O$ and brine, dried, and evaporated to give a solid which was chromatographed. On elution with 9:1 $C_6H_6$–$CHCl_3$, **2-[(phenylsulfonyl)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (5a)** (0.3 g, 12%) was obtained: IR (KBr) 1640, 1370, 1170, 1320, 1160 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.56–2.14 (m, 4 H, H-4 and H-12), 2.33 (s, 3 H, $CH_3Ar$), 2.54 (m, 1 H, H-5), 2.76 (td, $J$ = 14.0, 4.0 Hz, H-3ax), 3.12 (d, $J$ = 18.0 Hz, 1 H, H-6eq), 3.28 (dd, $J$ = 18.0, 6.0 Hz, 1 H, H-6ax), 3.62 (dd, $J$ = 14.0, 6.0 Hz, H-3eq), 4.08 and 4.16 (2 d, $J$ = 14.0 Hz, *Z* rotamer, $SO_2CH_2CO$), 4.26 and 4.78 (2 d, $J$ = 14.0 Hz, *E* rotamer, $SO_2CH_2CO$), 5.28 and 5.94 (2 apparent t, 1 H, H-1), 7.10–7.80 (m, 12 H, Ar), 8.10 (m, 1 H, H-8); mp 92–94 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{29}H_{28}N_2O_5S_2$: C, 63.48; H, 5.14; N, 5.11; S, 11.69. Found: C, 63.46; H, 4.99; N, 5.17; S, 11.44. On elution with 7:3 $C_6H_6$–$CHCl_3$, a pure diastereomer of **4a** was obtained: IR (KBr) 1630, 1370, 1170, 1045 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.50–1.96 (m, 4 H, H-4 and H-12), 2.33 (s, 3 H, $CH_3Ar$), 2.46 (m, 1 H, H-5), 2.74 (td, $J$ = 14.0, 4.0 Hz, H-3ax), 3.08 (d, $J$ = 18.0 Hz, 1 H, H-6eq), 3.24 (dd, $J$ = 18.0, 6.0 Hz, 1 H, H-6ax), 3.36 (dd, $J$ = 14.0, 6.0 Hz, H-3eq), 3.83 (s, *Z* rotamer, $SOCH_2CO$), 3.88 and 4.42 (2 d, $J$ = 14.0 Hz, *E* rotamer, $SOCH_2CO$), 5.14 and 5.94 (2 apparent t, 1 H, H-1), 7.16–7.70 (m, 12 H, Ar), 8.10 (d, 1 H, H-8). On elution with 1:1 $C_6H_6$–$CHCl_3$, a second diastereomer of **4a** was obtained: IR (KBr) 1630, 1370, 1170, 1045 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.50–2.06 (m, 4 H, H-4 and H-12), 2.35 (s, 3 H, $CH_3Ar$), 2.44–2.66 (m, H-3ax and H-5), 3.10 (d, $J$ = 18.0 Hz, 1 H, H-6eq), 3.26 (dd, $J$ = 18.0, 6.0 Hz, 1 H, H-6ax), 3.38 (dd, $J$ = 14.0, 6.0 Hz, H-3eq), 3.60 and 4.00 (2 d, $J$ = 14.0 Hz, *Z* rotamer, $SOCH_2CO$), 4.20 and 4.31 (2 d, $J$ = 14.0 Hz, *E* rotamer, $SOCH_2CO$), 5.00 and 6.06 (2 apparent t, 1 H, H-1), 7.16–7.70 (m, 12 H, Ar), 8.10 (m, 1 H, H-8). Overall yield of **4a**: 74%. For a mixture of diastereomers: mp 76–78 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{29}H_{28}N_2O_4S_2$: C, 65.39; H. 5.30; N, 5.26; S, 12.04. Found: C, 65.09; H, 5.30; N, 5.22; S, 11.75.

**2-[(Methylsulfinyl)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (4b).** A stirred solution of **3b** (2.5 g, 5.5 mmol) in $CH_2Cl_2$ (200 mL) and 10% aqueous $NaHCO_3$ (100 mL) was cooled to 0 °C, and a solution of *m*-chloroperbenzoic acid (1.7 g, 85% pure, 8.2 mmol) in $CH_2Cl_2$ (170 mL) was added dropwise over 2 h. After 2 h of additional stirring at 0 °C, the organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were washed with 5% aqueous $NaHSO_3$ (2 × 60 mL), dried, and evaporated to give a foam which was chromatographed. On elution with 1:1 $C_6H_6$–$CHCl_3$, 0.8 g (22%) of **2-[(methylsulfonyl)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (5b)** was obtained: IR (KBr) 1630, 1370, 1310, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz, major rotamer) $\delta$ 2.3 (s, 3 H, $CH_3Ar$), 3.0 (s, $CH_3SO_2$), 3.9 (br s, $SO_2CH_2CO$), 5.9 (apparent t, H-1), 6.9–7.7 (m, 7 H, Ar), 8.0 (m, 1 H, H-8); mp 152–154 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{24}H_{26}N_2O_5S_2$: C, 59.24; H, 5.38; N, 5.76; S, 13.18. Found: C, 59.16; H, 5.48; N, 5.78; S, 13.09. On elution with 49:1 $CHCl_3$–MeOH, sulfoxide **4b** (2.5 g, 75%) was obtained as a mixture of diastereomers: IR (KBr) 1630, 1370, 1170, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz, major rotamer) $\delta$ 2.0 (s, 3 H, $CH_3Ar$), 2.5 and 2.6 (2 s, $CH_3SO$), 5.9 (apparent t, H-1), 6.9–7.6 (m, 7 H, Ar), 8.0 (m, 1 H, H-8). For a mixture of diastereomers: mp 108–110 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{24}H_{26}N_2O_4S_2$: C, 61.25; H, 5.58; N, 5.95; S, 13.62. Found: C, 61.17; H, 5.81; N, 5.83; S, 13.44.

**2-[(Phenylsulfinyl)acetyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (6a).** Operating as in the above preparation of **4a**, from **2a** (1.2 g, 3.3 mmol), *m*-chloroperbenzoic acid (1.0 g, 85% pure, 4.9 mmol), and $NaHCO_3$ (0.5 g, 6.6 mmol) in $CH_2Cl_2$ (23 mL), an equimolecular diastereomeric mixture of sulfoxides **6a** (0.9 g, 72%) was obtained after column chromatography ($CHCl_3$): IR (KBr) 3400, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.50–2.08 (m, 4 H, H-4 and H-12), 2.34–3.42 (m, 5 H, H-3, H-5, and H-6), 6.98–7.88 (m, 9 H, Ar), 8.25 and 8.40 (2 br s, NH); the most characteristic signals for one diastereomer are 3.60 and 4.01 (2 d, $J$ = 14.0 Hz, *Z* rotamer, $SOCH_2CO$), 4.25 and 4.35 (2 d, $J$ = 14.0 Hz, *E* rotamer, $SOCH_2CO$), 5.06 and 6.14 (2 apparent t, 1 H, H-1); for a second diastereomer are 3.82 and 3.88 (2 d, $J$ = 14.0 Hz, *Z* rotamer, $SOCH_2CO$), 3.95 and 4.46 (2 d, $J$ = 14.0 Hz, *E* rotamer, $SOCH_2CO$), 5.22 and 6.04 (2 apparent t, 1 H, H-1). For a mixture of diastereomers: mp 190–192 °C (acetone). Anal. Calcd for $C_{22}H_{22}N_2OS$: C, 72.82; H, 6.12; N, 7.73. Found: C, 72.73; H, 6.22; N, 7.66.

**Pummerer Rearrangement of 4a. Method A.** To an ice-cold solution of **4a** (500 mg, 0.9 mmol) in $CH_2Cl_2$ (6 mL) was added TFAA (0.17 mL, 1.2 mmol). The mixture was stirred for 10 min, allowed to reach room temperature, and then concentrated with a nitrogen stream. After addition of chlorobenzene (20 mL), the reaction mixture was stirred at 130 °C for 3 h, cooled, poured into 2 N aqueous $NaHCO_3$ solution (30 mL), and extracted with $CH_2Cl_2$. The combined organic extracts were dried and evaporated to give a foam which, after column chromatography (9:1 $C_6H_6$–$CHCl_3$), afforded 190 mg (65%) of **2-[bis(phenylthio)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (9a)**: IR (KBr) 1630, 1370, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major rotamer) $\delta$ 1.54–2.00 (m, 4 H, H-4 and H-12), 2.30 (s, 3 H, $CH_3Ar$), 2.50 (m, 1 H, H-5), 2.66 (td, $J$ = 14.0, 4.0 Hz, H-3ax), 3.12 (d, $J$ = 18.0 Hz, 1 H, H-6eq), 3.26 (dd, $J$ = 18.0, 6.0 Hz, 1 H, H-6ax), 3.56 (dd, $J$ = 14.0, 6.0 Hz, H-3eq), 5.04 (s, SCHS), 5.98 (apparent t, H-1), 6.96–8.10 (m, 18 H, Ar); mp 76–78 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{35}H_{32}N_2O_3S_3$: C, 67.28; H, 5.16; N, 4.48. Found: C, 67.36; H, 5.25; N, 4.48.

**Method B.** A solution of **4a** (250 mg, 0.47 mmol) in freshly distilled $Ac_2O$ (10 mL) was refluxed for 5 h. The cooled reaction mixture was poured into saturated aqueous $Na_2CO_3$ (30 mL) and stirred at room temperature until the $Ac_2O$ was totally hydrolyzed. The resulting solution was extracted with $CH_2Cl_2$. Evaporation of the dried extracts, followed by column chromatography (7:3

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$C_6H_6$–$CHCl_3$) of the residue, left pure **2-[acetoxy(phenylthio)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (8a)** as a mixture of diastereomers (240 mg, 90%): IR ($CHCl_3$) 1740, 1650, 1370, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz, major rotamer for each epimer) $\delta$ 2.05 and 2.10 (2 s, $CH_3CO$), 2.25 (s, $CH_3Ar$), 5.60 and 5.65 (2 apparent t, H-1), 6.00 and 6.10 (2 s, OCHS), 6.60–8.00 (m, Ar). Anal. Calcd for $C_{31}H_{30}N_2O_5S_2 \cdot H_2O$: C, 62.76; H, 5.40; N, 4.72. Found: C, 62.77; H, 5.22; N, 4.95.

**Pummerer Rearrangement of 6a.** To an ice-cold solution of **6a** (200 mg, 0.5 mmol) and triethylamine (0.08 mL, 0.6 mmol) in $CH_2Cl_2$ (8 mL) was added TFAA (0.09 mL, 0.6 mmol). The resulting mixture was stirred at 0 °C for 20 min and at room temperature for 2 h, poured into aqueous $Na_2CO_3$ (10 mL), and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried, and evaporated to give **2-[bis(phenylthio)acetyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (10a)**, which partially decomposed on column chromatography (98:2 $CHCl_3$–MeOH). A similar result was obtained when the reaction was conducted in refluxing benzene (10 mL) for 4 h. **10a**: IR ($CHCl_3$) 3460, 1630 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major rotamer) $\delta$ 1.56–2.22 (m, 4 H, H-4 and H-12), 2.53 (m, 1 H, H-5), 2.72 (d, $J$ = 18.0 Hz, H-6eq), 2.97 (td, $J$ = 14.0, 4.0 Hz, H-3ax), 3.18 (dd, $J$ = 18.0, 6.0 Hz, 1 H, H-6ax), 4.93 (s, SCHS), 6.06 (apparent t, H-1), 7.00–7.56 (m, 14 H, Ar), 8.00 (br s, NH).

**Pummerer Rearrangement of 4b. Method A.** Operating as in the above method A, from sulfoxide **4b** (500 mg, 1.1 mmol) and TFAA (0.4 mL, 2.8 mmol) in $CH_2Cl_2$ (10 mL) and then heating at 130 °C for 5 h in chlorobenzene (40 mL), **2-[bis(methylthio)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (9b)** was obtained (200 mg, 75%): IR (KBr) 1630, 1370, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz, major rotamer) $\delta$ 1.9 and 2.1 (2 s, $CH_3S$), 2.3 (s, $CH_3Ar$), 4.4 (s, SCHS), 5.9 (apparent t, H-1), 6.9–7.7 (m, Ar), 8.0 (m, H-8); mp 180–182 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{25}H_{28}N_2O_3S_3$: C, 59.97; H, 5.64; N, 5.59; S, 19.21. Found: C, 60.16; H, 5.69; N, 5.44; S, 19.40.

**Method B.** Operating as in the above method B, from **4b** (300 mg, 0.64 mmol) and $Ac_2O$ (15 mL), **2-[acetoxy(methylthio)acetyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (8b)** was obtained (300 mg, 92%) after column chromatography (Florisil, $C_6H_6$): IR (KBr) 1740, 1650, 1730, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz, major rotamer for each diastereomer) $\delta$ 1.8 and 2.2 (2 s, $CH_3S$), 2.0 and 2.1 (2 s, $CH_3CO$), 2.3 (s, $CH_3Ar$), 5.9 (apparent t, H-1), 5.9 and 6.0 (2 s, OCHS), 6.9–7.7 (m, Ar), 8.0 (m, H-8). For a mixture of diastereomers: mp 96–98 °C ($C_6H_6$–hexane). Anal. Calcd for $C_{26}H_{28}N_2O_5S_2$: C, 60.92; H, 5.50; N, 5.46; S, 12.51. Found: C, 60.96; H, 5.60; N, 5.37; S, 12.63.

**Dithioacetal 9a from Acetoxy Sulfide 8a.** To a solution of **8a** (230 mg, 0.4 mmol) in $CH_2Cl_2$ (10 mL) was added $BF_3 \cdot Et_2O$ (1 mL, 8.1 mmol), and the resulting mixture was refluxed for 40 h. The reaction mixture was poured into 10% aqueous $Na_2CO_3$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried, and evaporated. The resulting solid was chromatographed (9:1 $C_6H_6$–$CHCl_3$) to give dithioacetal **9a** (94 mg, 76%).

**Dithioacetal 9b from Acetoxy Sulfide 8b.** Operating as above, from **8b** (250 mg, 0.5 mmol) in $CH_2Cl_2$ (15 mL) and $BF_3 \cdot Et_2O$ (1 mL, 8.1 mmol), dithioacetal **9b** was obtained (83 mg, 68%).

**2-(2-Hydroxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (13).** To a solution of amine **1** (1.5 g, 7.1 mmol) in 9:1 THF–MeOH (60 mL) at −20 °C was added an excess of ethylene oxide (ca. 2 g). The resulting mixture was stirred at room temperature in a sealed tube for 66 h. Removal of the solvent, followed by column chromatography (alumina, $CHCl_3$), gave alcohol **13** (1.7 g, 94%) as a colorless foam: IR (KBr) 3400, 3100–3600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$–$CD_3OD$) $\delta$ 1.66 (dm, $J$ = 13.0 Hz, 1 H, H-4eq), 1.90 (dq, $J$ = 12.5, 5.5, 3.0 Hz, 1 H, H-12*R*), 2.02 (m, 1 H, H-4ax), 2.14 (m, 1 H, H-3ax), 2.23 (dt, $J$ = 12.5, 3.5 Hz, 1 H, H-12*S*), 2.28 (m, 1 H, NCH), 2.41 (m, 1 H, H-5), 2.62 (m, 1 H, H-3eq), 2.65 (d, $J$ = 17.0 Hz, 1 H, H-6ax), 2.96 (m, 1 H, NCH), 3.09 (dd, $J$ = 17.0, 8.0 Hz, 1 H, H-6eq), 3.70 (m, 2 H, $CH_2O$), 4.27 (apparent t, 1 H, H-1), 7.05 (m, 2 H, H-9 and H-10), 7.34 (m, 1 H, H-8), 7.45 (m, 1 H, H-11); mp 66–67 °C (EtOH). Anal. Calcd for $C_{16}H_{20}N_2O \cdot H_2O$: C, 70.04; H, 8.02; N, 10.21. Found: C, 70.39; H, 7.63; N, 10.00.

**2-(2,2-Diethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (14).** A stirred solution of amine **1** (5.0 g, 23.6 mmol) and bromoacetaldehyde diethyl acetal (7.0 g, 35.4 mmol) in anhydrous dioxane (300 mL) containing anhydrous $K_2CO_3$ (5.0 g) was refluxed for 20 h. The solvent was evaporated, and the residue was taken up with $CHCl_3$. The resulting solution was washed with 20% aqueous $NaHCO_3$, dried, and evaporated to give a solid which, after column chromatography (97:3 $CHCl_3$–MeOH), afforded **14** (6.2 g, 80%): IR ($CHCl_3$) 3460, 1130, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 1.2 (apparent q, $J$ = 7 Hz, 6 H, $CH_3CH_2O$), 3.5 (m, 4 H, $CH_2O$), 4.2 (apparent t, 1 H, H-1), 4.6 (t, $J$ = 5 Hz, 1 H, OCHO), 6.8–7.2 (m, 3 H, H-8, H-9, and H-10), 7.5 (m, 1 H, H-11), 8.2 (br s, 1 H, NH). For the picrate: mp 128–130 °C (EtOH). Anal. Calcd for $C_{26}H_{31}N_5O_9$: C, 56.01; H, 5.60; N, 12.56. Found: C, 56.06; H, 5.34; N, 13.04.

**2-(2,2-Diethoxyethyl)-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (15).** Operating as described in the preparation of **3a**, from **14** (0.4 g, 1.2 mmol), *p*-toluenesulfonyl chloride (0.35 g, 1.8 mmol), and tetrabutylammonium hydrogen sulfate (41 mg, 0.12 mmol) in a mixture of $C_6H_6$ (30 mL) and 50% aqueous NaOH (15 mL), pure **15** (0.48 g, 82%) was obtained after column chromatography (alumina, 1:1 $C_6H_6$–$CHCl_3$): IR ($CHCl_3$) 1370, 1170, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 1.2 (apparent q, $J$ = 7 Hz, 6 H, $CH_3CH_2O$), 2.3 (s, 3 H, $CH_3Ar$), 3.5 (m, 4 H, $CH_2O$), 4.1 (apparent t, 1 H, H-1), 4.5 (t, $J$ = 5 Hz, 1 H, OCHO), 7.4–8.4 (m, 8 H, Ar). For the picrate: mp 81–83 °C (EtOH). Anal. Calcd for $C_{33}H_{37}N_5O_{11}S$: C, 55.69; H, 5.24; N, 9.84; S, 4.51. Found: C, 55.35; H, 4.95; N, 9.89; S, 4.52.

**2-[2,2-Bis(methylthio)ethyl]-7-tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (18).** Methanethiol was slowly bubbled for 30 min through a solution of **15** (6 g, 12.5 mmol) and $BF_3 \cdot Et_2O$ (25 mL) in $CH_2Cl_2$ (400 mL), and the resulting mixture was stirred at room temperature for 24 h. The solution then poured into 10% aqueous $Na_2CO_3$ and stirred for 30 min. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic extracts were dried and evaporated. The residue was chromatographed ($C_6H_6$) to give **18** (4.8 g, 79%): IR ($CHCl_3$) 1370, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 1.9 and 2.0 (2 s, 3 H each, $CH_3S$), 2.2 (s, 3 H, $CH_3Ar$), 3.7 (t, $J$ = 7 Hz, 1 H, SCHS), 4.0 (apparent t, 1 H, H-1), 6.9–8.0 (m, 8 H, Ar). For the picrate: mp 101–103 °C (EtOH). Anal. Calcd for $C_{31}H_{33}N_5O_9S_3$: C, 52.02; H, 4.65; N. 9.78; S, 13.44. Found: C, 52.29; H, 4.66; N, 9.90; S, 12.86.

**7-Tosyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (21).** A solution of acetal **15** (200 mg, 0.4 mmol) and *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol) in $C_6H_6$ (50 mL) was refluxed with a Dean–Stark condenser for 20 h. The resulting mixture was poured into saturated aqueous $Na_2CO_3$ (50 mL). The organic layer was washed with brine, dried, and evaporated to give a solid which, after column chromatography (9:1 $CHCl_3$–MeOH), afforded pure **21** (120 mg, 79%): IR ($CHCl_3$) 1370, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 2.3 (s, 3 H, $CH_3Ar$), 4.2 (apparent t, 1 H, H-1), 6.9–8.2 (m, 8 H, Ar). For the picrate: mp 218–220 °C (EtOH). Anal. Calcd for $C_{27}H_{25}N_5O_9S$: C, 54.45; H, 4.23; N, 11.76; S, 5.38. Found: C, 54.36; H, 4.16; N, 11.43; S, 5.26.

**2-[2,2-Bis(methylthio)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (23).** An excess of liquid methanethiol was added to a solution of **14** (2.3 g, 7.1 mmol) and $BF_3 \cdot Et_2O$ (13.2 mL, 107 mmol) in $CH_2Cl_2$ (120 mL) maintained at 0 °C. The solution was stirred at 5 °C in a sealed tube for 48 h. The resulting mixture was poured into 10% aqueous $Na_2CO_3$ (300 mL) and stirred for 30 min. The organic layer was dried and evaporated to give a foam which, after column chromatography (1:1 hexane–AcOEt), afforded **23** (1.7 g, 73%): IR ($CHCl_3$) 3420, 1300 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 1.9 and 2.0 (2 s, 3 H each, $CH_3S$), 3.7 (t, $J$ = 7 Hz, 1 H, SCHS), 4.0 (apparent t, 1 H, H-1), 6.6–7.4 (m, 4 H, Ar), 8.1 (br s, 1 H, NH). For the picrate: mp 178–180 °C (EtOH). Anal. Calcd for $C_{24}H_{27}N_5O_7S_2$: C, 51.34; H, 4.80; N, 12.46; S, 11.42. Found: C, 51.32; H, 4.67; N, 12.28; S, 11.41. When the reaction time was shortened to 24 h, **2-[2-ethoxy-2-(methylthio)ethyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (22)** was also isolated by column chromatography (1:3 hexane–AcOEt): IR (KBr) 1110, 1090, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 60 MHz) $\delta$ 1.1 (t, $J$ = 7 Hz, 3 H, $CH_3CH_2$), 2.0 (s, 3 H, $CH_3S$), 4.1 (apparent t, 1 H, H-1), 4.5 (dd, $J$ = 7, 5

Hz, 1 H, OCHS), 6.8–7.4 (m, 4 H, Ar), 7.8 (br s, 1 H, NH); mp 123–124 °C (acetone–hexane). Anal. Calcd for $C_{19}H_{26}N_2OS$: C, 69.05; H, 7.92; N, 8.47; S, 9.70. Found: C, 68.88; H, 8.25; N, 8.49; S, 9.73.

**20-Deethyl-6α-(methylthio)tubifoline (25).** To a suspension of dimethyl(methylthio)sulfonium fluoroborate[30] (DMTSF, 0.6 g, 3.3 mmol) in anhydrous $CH_2Cl_2$ (180 mL) at 0 °C was slowly added a solution of dithioacetal **23** (0.5 g, 1.6 mmol) in anhydrous $CH_2Cl_2$ (30 mL). After a few minutes the solution became purple and a precipitate appeared. The mixture was stirred at 0 °C for 3 h and then poured into 10% aqueous $Na_2CO_3$ (200 mL). After being stirred for 30 min, the organic layer was washed with brine, dried, and evaporated. The residue was chromatographed (Florisil, 99:1 $CHCl_3$–MeOH) to give **25** (211 mg, 49%): IR ($CHCl_3$) 1570 $cm^{-1}$; UV ($Et_2O$) $\lambda_{max}$ 254 nm; $^1H$ NMR ($CDCl_3$) δ 1.06 (dm, $J$ = 14.0 Hz, 1 H, H-14*R*), 1.60 (s, 3 H, $CH_3S$), 1.63 (dm, $J$ = 14.0 Hz, 1 H, H-14*S*), 1.86 (m, 2 H, H-20), 2.50 (br s, 1 H, H-15α), 2.75 (dd, $J$ = 15.0, 2.0 Hz, 1 H, H-16β), 3.08 (t, $J$ = 12.0 Hz, 1 H, H-5α), 3.13 (dd, $J$ = 15.0, 10.5 Hz, 1 H, H-16α), 3.10–3.20 (masked, 1 H, H-21β), 3.34 (ddd, $J$ = 12.0, 5.5, 2.0 Hz, 1 H, H-21α), 3.50 (dd, $J$ = 12.0, 6.0 Hz, 1 H, H-5β), 3.93 (br s, 1 H, H-3α), 4.08 (dd, $J$ = 12.0, 6.0 Hz, 1 H, H-6β), 7.22 (t, $J$ = 7.5 Hz, 1 H, H-10), 7.37 (t, $J$ = 7.5 Hz, 1 H, H-11), 7.44 (d, $J$ = 7.5 Hz, 1 H, H-9), 7.55 (d, $J$ = 7.5 Hz, 1 H, H-12); $^{13}C$ NMR ($CDCl_3$) Table II; MS (*m/e*, relative intensity) 285 ($M^+$ + 1, 19), 284 ($M^+$, 76), 253 (20), 237 (100), 236 (20), 235 (20), 226 (54), 194 (54), 167 (27), 156 (39), 95 (83), 80 (20), 67 (16). Attempts to crystallize **25** as a base or dipicrate failed.

**20-Deethyl-6α-(methylthio)tubifolidine (26).** A solution of indolenine **25** (211 mg, 0.7 mmol) in anhydrous THF (60 mL) was added dropwise to a stirred slurry of $LiAlH_4$ (838 mg, 22.1 mmol) in THF (40 mL), and the resulting mixture was stirred at room temperature for 3 h. After this time, the reaction mixture was cooled with an ice bath and successively treated with $H_2O$ (0.83 mL), 10% aqueous NaOH (0.83 mL), and $H_2O$ (2.50 mL). The solids were filtered off and washed with $CH_2Cl_2$. The combined filtrate and washings were dried and evaporated, and the residue was chromatographed (Florisil, 96:3 $CHCl_3$–MeOH), affording **26** (60 mg, 28%): IR ($CHCl_3$) 3440 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.37 (s, 3 H, $CH_3S$), 1.54 (dm, $J$ = 13.5 Hz, 1 H, H-14*R*), 1.70 (m, 1 H, H-20), 1.80–2.10 (m, 5 H, H-14*S*, H-15, 2 H-16, and H-20), 2.50 (td, $J$ = 12.4, 5.0 Hz, 1 H, H-21β), 2.75 (m, 1 H, H-5), 3.10 (ddd, $J$ = 12.4, 6.0, 2.0 Hz, 1 H, H-21α), 3.40 (m, 2 H, H-5 and H-6β), 3.43 (br s, 1 H, H-3α), 3.75 (dd, $J$ = 9.5, 7.3 Hz, 1 H, H-2β), 6.62 (d, $J$ = 8.0 Hz, 1 H, H-9), 6.82 (t, $J$ = 8.0 Hz, 1 H, H-11), 7.12 (m, 2 H, H-10 and H-12); $^{13}C$ NMR ($CDCl_3$) Table II; MS (*m/e*, relative intensity) 287 ($M^+$ + 1, 3), 286 ($M^+$, 14), 239 (7), 176 (11), 169 (16), 143 (12), 130 (14), 115 (11), 110 (49), 82 (100), 77 (12), 71 (15), 43 (24), 41 (27). For the dipicrate: mp 190–192 °C (EtOH). Anal. Calcd for $C_{29}H_{28}N_8O_{14}S$: C, 46.77; H, 3.78; N, 15.04; S, 4.30. Found: C, 47.06; H, 3.80; N, 14.77; S, 4.20.

**20-Deethyltubifolidine (27). Method A.** To a solution of indoline **26** (100 mg, 0.35 mmol) in EtOH (6 mL) was added Raney Ni (W-2, 3 spatulas). The mixture was refluxed for 2 h, cooled, and filtered through a Celite pad. The solids were well washed with EtOH (80 mL), and the combined ethanolic solutions were evaporated. Chromatography over Florisil (85:15 $CHCl_3$–MeOH) afforded **27** (40 mg, 47%): IR ($CHCl_3$) 3400, 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.50–1.75 (m, 3 H, H-14, H-16, and H-20), 1.80–2.05 (m, 5 H, H-6α, H-14, H-15, H-16, and H-20), 2.42 (dt, $J$ = 13.0, 8.0 Hz, 1 H, H-6β), 2.55 (td, $J$ = 11.4, 5.0 Hz, 1 H, H-21β), 2.90 (ddd, $J$ = 12.0, 8.0, 5.3 Hz, 1 H, H-5β), 3.06 (m, 1 H, H-21α), 3.18 (ddd, $J$ = 12.0, 9.5, 8.0 Hz, 1 H, H-5α), 3.42 (br s, 1 H, H-3α), 3.65 (br s, 1 H, NH), 3.79 (dd, $J$ = 9.5, 7.3 Hz, 1 H, H-2β), 6.65 (d, $J$ = 8.0 Hz, 1 H, H-9), 6.77 (t, $J$ = 8.0 Hz, 1 H, H-11), 7.05 (m, 2 H, H-10 and H-12); $^{13}C$ NMR ($CDCl_3$) Table II; MS (*m/e*, relative intensity) 240 ($M^+$, 32), 212 (10), 171 (16), 167 (11), 158 (17), 143 (30), 130 (31), 115 (15), 110 (100), 96 (16), 77 (16). For the dipicrate: mp 194–195 °C (EtOH). Anal. Calcd for $C_{28}H_{26}N_8O_{14}$: C, 48.14; H, 3.75; N, 16.04. Found: C, 48.13; H, 4.04; N, 15.88.

**Method B.** To a solution of indolenine **25** (100 mg, 0.35 mmol) in acetone (4 mL) was added Raney Ni (W-2, 2 spatulas), and the mixture was refluxed for 3 h. After the usual workup and purification of the reaction mixture by column chromatography, compound **27** (17 mg, 20%) was obtained.

**Ethyl Bis(methylthio)acetate (33).** To an ice-cold solution of ethyl diethoxyacetate (14.9 g, 86.5 mmol) and $BF_3{\cdot}Et_2O$ (52.0 g, 366.2 mmol) in $CH_2Cl_2$ (20 mL) was added an excess of methanethiol (ca. 20-25 mL), and the resulting mixture was stirred at room temperature in a sealed tube for 6 h. The solution was poured into 15% aqueous NaOH (100 mL), and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried, and evaporated to give an oil, which was distilled (bp 77–80 °C (1 mm Hg)). **33** (13.4 g, 86%): IR (NaCl) 1720 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 Mz) δ 1.3 (t, $J$ = 7 Hz, 3 H, $CH_3CH_2$), 2.1 (s, 6 H, $CH_3S$), 4.0 (s, 1 H, SCHS), 4.1 (q, $J$ = 7 Hz, 2 H, $CH_2CH_3$). Anal. Calcd for $C_6H_{12}O_2S_2{\cdot}^1/_2H_2O$: C, 38.09; H, 6.87; S, 33.87. Found: C, 38.15; H, 6.66; S, 33.97.

**2-[Bis(methylthio)acetyl]-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (10b).** A mixture of ester **33** (13.2 g, 73.3 mmol) in EtOH (250 mL) and 2 N aqueous NaOH (250 mL) was refluxed for 24 h. The reaction mixture was cooled, acidified with 12 N HCl, and extracted with $CH_2Cl_2$. The extracts were dried and evaporated affording **bis(methylthio)acetic acid (34)** (11.0 g, 98%) as a white solid: $^1H$ NMR ($CD_3OD$, 60 MHz) δ 2.0 (s, 6 H, $CH_3S$), 4.2 (s, 1 H, SCHS). A solution of this acid (507 mg, 3.3 mmol) and KOH (187 mg, 3.3 mmol) in MeOH (15 mL) was stirred at room temperature for 30 min, and then the solvent was evaporated. The resulting salt was suspended in anhydrous $C_6H_6$ (7 mL) and cooled to 0 °C. To this mixture was added oxalyl chloride (423 mg, 3.3 mmol). After stirring at 20 °C for 15 min and at reflux temperature for 40 min, the mixture was cooled and the solvent was evaporated to give crude **bis(methylthio)acetyl chloride (35)** as an oil which was used without further purification. A solution of this chloride (806 mg, 4.7 mmol) in $CH_2Cl_2$ (10 mL) was added to a solution of **1** (500 mg, 2.4 mmol) in $CH_2Cl_2$ (30 mL) containing 1 N aqueous NaOH (5 mL), and the mixture was stirred at room temperature for 2.5 h. The aqueous phase was separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were dried and evaporated to give amide **10b** (772 mg, 94%) as a foam which partially decomposed on column chromatography: IR ($CHCl_3$) 3460, 1625 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major rotamer) δ 1.65 (dm, $J$ = 12.4 Hz, H-4eq), 2.00 and 2.17 (2 s, $CH_3S$), 1.90–2.10 (m, H-4ax and H-12), 2.50 (m, H-5), 2.74 (d, $J$ = 17.5 Hz, H-6eq), 3.05 (td, $J$ = 14.6, 3.7 Hz, H-3ax), 3.17 (dd, $J$ = 17.5, 6.0 Hz, H-6ax), 3.54 (dd, $J$ = 14.6, 5.7 Hz, H-3eq), 4.50 (s, SCHS), 6.13 (apparent t, H-1), 7.08 (m, H-9 and H-10), 7.30 (m, H-8), 7.60 (m, H-11), 8.30 (br s, NH).

**2-Benzyl-4β(and 4α)-ethyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (29a and 29b).** To a solution of a diastereomeric mixture of **28**[39] (3.4 g, 9.0 mmol) in dioxane (100 mL) was added a 4% aqueous solution of $Ba(OH)_2$ (130 mL). The mixture was refluxed for 24 h, cooled, saturated with $CO_2$, and filtered. The solution was evaporated to dryness, and the residue was dried over $P_2O_5$. The resulting crude amino acid was finely powdered and treated with an excess of PPA. After vigorous stirring at 85–90 °C for 1 h, the reaction mixture was cooled, poured into ice–water, basified with concentrated $NH_4OH$, and extracted with $CH_2Cl_2$. Evaporation of the extracts gave a foam which was purified by flash chromatography (2:3 AcOEt–hexane), affording **29** (1.0 g, 32%) as a C-4 epimeric mixture. Careful column chromatography allowed the isolation and characterization of both epimers. Thus, on elution with 9:1 $C_6H_6$–$CHCl_3$, a pure sample of **29b** was obtained: IR (KBr) 3240, 1630 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.90 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.65–2.15 (m, 3 H, H-4eq and $CH_2CH_3$), 2.18 (dd, $J$ = 12.0, 4.0 Hz, 1 H, H-3ax), 2.28 (dt, $J$ = 12.5, 3.0 Hz, 1 H, H-12*R*), 2.39 (d, $J$ = 12.0 Hz, 1 H, H-3eq), 2.60 (dt, $J$ = 12.5, 3.2 Hz, 1 H, H-12*S*), 2.67 (br s, 1 H, H-5), 3.14 and 3.84 (2 d, $J$ = 13.8 Hz, 2 H, $CH_2C_6H_5$), 4.41 (apparent t, 1 H, H-1), 7.10–7.70 (m, 9 H, Ar), 9.5 (br s, 1 H, NH); $^{13}C$ NMR ($CDCl_3$) Table I. For the picrate: mp 208–210 °C (EtOH). Anal. Calcd for $C_{29}H_{27}N_5O_8$: C, 60.72; H, 4.74; N, 12.21. Found: C, 60.95; H, 4.99; N, 12.28. On elution with 2:3 $C_6H_6$–$CHCl_3$, a pure sample of **29a** was obtained: IR (KBr) 3240, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.02 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.00–1.50 (m, 2 H, $CH_2CH_3$), 1.80 (t, $J$ = 11.6 Hz, 1 H, H-3ax), 2.00 (m, 1 H, H-4ax), 2.35 (dm, $J$ = 12.0 Hz, 1 H, H-12*R*), 2.53 (m, 2 H, H-3eq and H-12*S*), 2.85 (br s, 1 H, H-5), 3.20 and 3.85 (2 d, $J$ = 13.8 Hz, 2 H, $CH_2C_6H_5$), 4.45 (br s, 1 H, H-1), 7.00–7.70 (m, 9 H, Ar), 10.50 (br s, 1 H, NH); $^{13}C$ NMR ($CDCl_3$) Table I.

For the picrate: mp 234–235 °C (EtOH). Anal. Calcd for $C_{29}H_{27}N_5O_8$: C, 60.72; H, 4.74; N, 12.21. Found: C, 60.79; H, 4.67; N, 12.44.

**2-Benzyl-4β(and 4α)-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (30a and 30b).** To a stirred slurry of $LiAlH_4$ (3.6 g, 94.8 mmol) in refluxing anhydrous dioxane (140 mL) was slowly added a solution of ketones **29a,b** (2.2 g, 6.4 mmol) in anhydrous dioxane (60 mL). After refluxing for 17 h, the mixture was cooled to 0 °C, and 15% aqueous NaOH (25 mL) was slowly added. The solids were removed by filtration and washed with dioxane. The combined filtrate and washings were evaporated, and the residue was purified by flash chromatography (2:3 AcOEt–hexane), affording pure **30a** (787 mg, 38%, lower $R_f$) and pure **30b** (780 mg, 37%, higher $R_f$). **30a**: IR (KBr) 3400 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.85 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.15–1.35 (m, 2 H, $CH_2CH_3$), 1.69 (t, $J$ = 11.0 Hz, 1 H, H-3ax), 1.78 (m, 1 H, H-4ax), 1.93 (dt, $J$ = 12.5, 3.8 Hz, 1 H, H-12*R*), 2.20–2.32 (m, 2 H, H-12*S* and H-5), 2.42 (dd, $J$ = 11.0, 3.7 Hz, 1 H, H-3eq), 2.74 (m, 2 H, H-6), 3.20 and 3.94 (2 d, $J$ = 14.0 Hz, 2 H, $CH_2C_6H_5$), 4.28 (apparent t, 1 H, H-1), 7.00–7.50 (m, 9 H, Ar), 8.05 (br s, 1 H, NH); $^{13}C$ NMR ($CDCl_3$) Table I. For the hydrochloride: mp 254–256 °C (EtOH). Anal. Calcd for $C_{23}H_{27}ClN_2 \cdot {}^1/_3C_2H_6O$: C, 74.76; H, 7.64; N, 7.32; Cl, 9.27. Found: C, 73.95; H, 7.33; N, 7.42; Cl, 9.62. **30b**: IR ($CHCl_3$) 3460 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.83 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.30 (m, 1 H, H-4eq), 1.60 and 1.80 (2 m, 2 H, $CH_2CH_3$), 1.65 (dm, $J$ = 12.3 Hz, 1 H, H-12*R*), 2.13 (dd, $J$ = 12.0, 4.0 Hz, 1 H, H-3ax), 2.20 (m, 1 H, H-5), 2.28 (d, $J$ = 12.0 Hz, 1 H, H-3eq), 2.45 (dm, $J$ = 12.3 Hz, 1 H, H-12*S*), 2.57 (d, $J$ = 17.0 Hz, 1 H, H-6eq), 3.10 (dd, $J$ = 17.0, 7.0 Hz, 1 H, H-6ax), 3.13 and 3.92 (2 d, $J$ = 14.0 Hz, 2 H, $CH_2C_6H_5$), 4.20 (br s, 1 H, H-1), 7.00–7.50 (m, 9 H, Ar), 7.90 (br s, 1 H, NH); $^{13}C$ NMR ($CDCl_3$) Table I. For the hydrochloride: mp 229–231 °C (EtOH). Anal. Calcd for $C_{23}H_{27}ClN_2 \cdot {}^1/_2H_2O$: C, 73.48; H, 7.51; N, 7.45. Found: C, 73.18; H, 7.42; N, 7.17.

**4β-Ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (32a).** To a solution of **30a** (787 mg, 2.4 mmol) in MeOH (30 mL) was added 20% $Pd(OH)_2$ (Pearlman's catalyst, 258 mg), and the resulting suspension was hydrogenated until total disappearance of the starting compound was observed by TLC. The catalyst was removed by filtration through a Celite pad, and the solution was concentrated under vacuum. The residue was taken up with $CH_2Cl_2$, and the resulting solution was washed with 10% aqueous $Na_2CO_3$. The organic layer was dried and evaporated to give a solid which, after flash chromatography (2:3 AcOEt–hexane), afforded **32a** (420 mg, 73%): IR ($CHCl_3$) 3460 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.90 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.24 (m, 2 H, $CH_2CH_3$), 1.80 (m, 1 H, H-4ax), 1.97 (dt, $J$ = 12.5, 3.3 Hz, 1 H, H-12*R*), 2.18 (dt, $J$ = 12.5, 3.3 Hz, 1 H, H-12*S*), 2.20 (t, $J$ = 12.0 Hz, 1 H, H-3ax), 2.30 (m, 1 H, H-5), 2.68 (dd, $J$ = 12.0, 4.9 Hz, 1 H, H-3eq), 2.73–2.80 (m, 2 H, H-6), 2.94 (br s, 1 H, $N_bH$), 4.50 (apparent t, 1 H, H-1), 7.11 (m, 2 H, H-9 and H-10), 7.28 (m, 1 H, H-8), 7.52 (m, 1 H, H-11), 8.14 (br s, 1 H, $N_aH$); $^{13}C$ NMR ($CDCl_3$) Table I. For the picrate: mp 223–224 °C (EtOH). Anal. Calcd for $C_{22}H_{23}N_5O_7$: C, 56.31; H, 4.90; N, 14.92. Found: C, 56.36; H, 4.79; N, 14.82.

**4α-Ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (32b).** Operating as above, from **30b** (780 mg, 2.4 mmol) and 20% $Pd(OH)_2$ (250 mg) in MeOH (30 mL), compound **32b** (404 mg, 71%) was obtained: IR ($CHCl_3$) 3460 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.96 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.32 (m, 1 H, H-4eq), 1.55–1.88 (m, 3 H, $CH_2CH_3$ and H-12*R*), 2.05 (m, 1 H, H-5), 2.20–2.35 (m, 1 H, H-12*S*), 2.48 (d, $J$ = 12.0 Hz, 1 H, H-3eq), 2.62 (d, $J$ = 17.0 Hz, 1 H, H-6eq), 2.72 (dd, $J$ = 12.0, 4.2 Hz, 1 H, H-3ax), 3.16 (dd, $J$ = 17.0, 6.3 Hz, 1 H, H-6ax), 4.38 (apparent t, 1 H, H-1), 4.40 (br s, 1 H, $N_bH$), 7.10 (m, 2 H, H-9 and H-10), 7.30 (m, 1 H, H-8), 7.52 (m, 1 H, H-11), 8.10 (br s, 1 H, $N_aH$); $^{13}C$ NMR ($CDCl_3$) Table I. For the picrate: mp 215–217 °C (EtOH). Anal. Calcd for $C_{22}H_{23}N_5O_7$: C, 56.31; H, 4.90; N, 14.92. Found: C, 56.17; H, 5.25; N, 14.62.

**Compounds 32a and 32b by Reduction of 31a,b.** Operating as described in the preparation of **30**, from a C-4 epimeric mixture of ketones **31**[39] (1.0 g, 4.0 mmol) and $LiAlH_4$ (1.5 g, 40.0 mmol) in anhydrous dioxane (60 mL), a mixture of **32a** and **32b** (0.4 g, 66%) was obtained after flash chromatography (70:30:5 $Et_2O$–acetone–DEA). Epimer **32a** showed lower $R_f$ on TLC (70:30:5 $Et_2O$–acetone–DEA).

**2,2-Bis(methylthio)ethanol (36).** To a stirred slurry of $LiAlH_4$ (1.9 g, 50.0 mmol) in anhydrous $Et_2O$ (90 mL) was added a solution of ester **33** (9.0 g, 50.0 mmol) in $Et_2O$ (55 mL). The mixture was refluxed for 1 h and cooled. The solids were filtered off and washed with $Et_2O$. The combined filtrate and washings were dried and evaporated. The resulting residue was distilled (55–58 °C (0.3 mmHg)) to give pure **36** (5.8 g, 83%): IR (NaCl) 3500–3200 $cm^{-1}$; $^1H$ NMR ($CCl_4$, 60 MHz) δ 2.1 (s, 6 H, $CH_3S$), 2.9 (s, 1 H, OH), 3.5 (m, 3 H, H-1 and H-2). Anal. Calcd for $C_4H_{10}OS_2 \cdot {}^1/_2H_2O$: C, 34.16; H, 7.31; S, 45.02. Found: C, 34.08; H, 7.34; S, 45.04.

**1,1,2-Tris(methylthio)ethane (37). Method A.** To a solution of alcohol **36** (0.5 g, 3.6 mmol) in $CHCl_3$ (2 mL) was added a solution of $SOCl_2$ (0.3 mL, 3.8 mmol) in $CHCl_3$ (1 mL). The mixture was stirred at 80 °C for 10 min and then at room temperature for 2 h. The solvent was eliminated, and the residue was distilled to give **37** (220 mg, 72%): bp 66–8 °C (0.5 mmHg) (lit.[56] 68–9 °C (0.5 mmHg)); $^1H$ NMR ($CCl_4$, 60 MHz) δ 2.0 (s, 6 H, $CH_3S$), 2.1 (s, 3 H, $CH_3S$), 2.7 (d, $J$ = 7 Hz, 2 H, $CH_2$), 3.6 (t, $J$ = 7 Hz, 1 H, CH); MS (*m/e*, relative intensity) 168 ($M^+$, 20), 121 (38), 107 (100), 91 (17), 90 (19), 79 (59), 74 (25), 73 (29), 61 (63). **Method B.** To an ice-cold solution of alcohol **36** (1.0 g, 7.2 mmol) in $Et_2O$ (30 mL) was added $PBr_3$ (1.9 g, 7.2 mmol), and the solution was stirred at room temperature for 18 h. The mixture was poured into aqueous $NaHCO_3$, and the organic layer was washed with water, dried, evaporated, and distilled, affording **37** (0.3 g, 42%). **Method C.** Methanethiol was slowly bubbled for 1 h through an ice-cold solution of bromoacetaldehyde diethyl acetal (1.0 g, 5.1 mmol) and $BF_3 \cdot Et_2O$ (0.6 mL) in $CH_2Cl_2$ (30 mL). The mixture was stirred at room temperature for 1 h, poured into aqueous $NaHCO_3$, and extracted with $CH_2Cl_2$. The organic extracts were dried, evaporated, and distilled to give **37** (0.34 g, 40%).

**2-[Bis(methylthio)acetyl]-4α-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (40).** Operating as described in the preparation of **10b**, by addition of acyl chloride **35** (650 mg, 3.8 mmol) in $CH_2Cl_2$ (15 mL) to a mixture of amine **32b** (484 mg, 2.0 mmol) in $CH_2Cl_2$ (20 mL) and 1 N aqueous NaOH (5 mL), amide **40** (550 mg, 73%) was obtained (reaction time 6 h) after purification by flash chromatography (2:3 AcOEt–hexane): IR ($CHCl_3$) 3460, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, major rotamer) δ 0.95 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.40–2.40 (m, 6 H, H-4eq, H-5, H-12, and $CH_2CH_3$), 1.95 and 2.16 (2 s, $CH_3S$), 2.60–2.80 (m, H-3ax and H-6eq), 3.10–3.40 (m, H-3eq and H-6ax), 4.50 (s, SCHS), 6.10 (br s, H-1), 6.90–7.70 (m, 4 H, Ar), 8.50 (br s, NH); $^{13}C$ NMR ($CDCl_3$, major rotamer) 12.8 ($CH_3CH_2$), 12.0 and 13.4 ($CH_3S$), 25.4 ($CH_3CH_2$), 27.3 (C-6), 30.2 (C-5), 30.2 (C-12), 42.0 (C-4), 42.8 (C-1), 43.2 (C-3), 54.6 (SCS), 109.1 (C-11b), 110.6 (C-8), 118.9 (C-11), 119.5 (C-9), 121.3 (C-10), 125.8 (C-11a), 136.0 (C-6a), 136.3 (C-7a), 166.3 (C=O); mp 220–222 °C ($C_6H_6$). Anal. Calcd for $C_{20}H_{26}N_2OS_2$: C, 64.13; H, 6.99; N, 7.47; S, 17.11. Found: C, 64.26; H, 7.03; N, 7.42; S, 17.00.

**2-[2,2-Bis(methylthio)ethyl]-4β-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (41a).** A stirred mixture of **32a** (285 mg, 1.2 mmol), bromoacetaldehyde diethyl acetal (353 mg, 1.8 mmol), and anhydrous $Na_2CO_3$ (252 mg, 2.4 mmol) in anhydrous dioxane (25 mL) was refluxed for 17 h. Removal of the solvent gave a residue which was taken up with $CHCl_3$. The resulting solution was washed with 20% aqueous $Na_2CO_3$, dried, and evaporated to give a solid which was purified by flash chromatography (AcOEt), affording acetal **39a** (274 mg, 65%): $^1H$ NMR ($CDCl_3$, 60 MHz) δ 0.9–1.5 (m, 9 H, $CH_3CH_2$ and $CH_3CH_2O$), 4.2 (apparent t, 1 H, H-1), 4.7 (t, $J$ = 5 Hz, 1 H, OCHO), 6.7–7.5 (m, 4 H, Ar), 8.2 (br s, 1 H, NH). A solution of **39a** (270 mg, 0.76 mmol), $BF_3 \cdot Et_2O$ (1.43 mL, 11.36 mmol), and excess of methanethiol (ca. 25 mL) in $CH_2Cl_2$ (60 mL) was stirred at 5°C in a sealed tube for 48 h. The mixture was poured into 10% aqueous $Na_2CO_3$ (60 mL) and stirred for 30 min. The aqueous phase was extracted with $CH_2Cl_2$, and the combined organic layers were dried and concentrated to give a foam which, after flash chromatography (2:3 AcOEt–hexane), afforded dithioacetal **41a** (215 mg, 79%): IR ($CHCl_3$) 3390 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 0.92 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.27 (m, 2 H, $CH_2CH_3$), 1.76 (t, $J$ = 12.0 Hz, 1 H, H-3ax), 1.82 (m, 1 H, H-4ax),

(56) Schneider, H. J.; Bagnell, J. J.; Murdoch, G. C. *J. Org. Chem.* 1961, *26*, 1987.

1.90 (dt, $J$ = 12.0, 3.0 Hz, 1 H, H-12$R$), 2.00–2.30 (m, 2 H, H-5 and H-12$S$), 2.11 and 2.16 (2 s, 3 H each, $CH_3S$), 2.43 (dd, $J$ = 13.7, 6.6 Hz, 1 H, NCH), 2.56 (dm, $J$ = 12.0 Hz, 1 H, H-3eq), 2.74 (m, 2 H, H-6), 3.08 (dd, $J$ = 13.7, 7.8 Hz, 1 H, NCH), 3.96 (dd, $J$ = 7.8, 6.6 Hz, 1 H, SCHS), 4.18 (apparent t, 1 H, H-1), 7.10 (m, 2 H, H-9 and H-10), 7.25 (m, 1 H, H-8), 7.52 (m, 1 H, H-11), 7.95 (br s, 1 H, NH); $^{13}$C NMR ($CDCl_3$) Table I; MS ($m/e$, relative intensity) 360 ($M^+$, 25), 312 (38), 254 (19), 253 (100), 180 (21), 169 (25), 168 (27), 167 (14); HRMS calcd for $C_{20}H_{28}N_2S_2$ 360.1694, found 360.1694.

**2-[2,2-Bis(methylthio)ethyl]-4α-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (41b). Method A.** Operating as in the series **a**, from **32b** (260 mg, 1.1 mmol), bromoacetaldehyde diethyl acetal (325 mg, 1.7 mmol), and anhydrous $Na_2CO_3$ (234 mg, 2.2 mmol) in dioxane (20 mL), acetal **39b** (227 mg, 58%) was obtained: $^1$H NMR ($CDCl_3$, 60 MHz) δ 0.8–1.5 (m, 9 H, $CH_3CH_2$ and $CH_3CH_2O$), 4.0 (apparent t, 1 H, H-1), 4.5 (t, $J$ = 5 Hz, 1 H, OCHO), 6.8–7.5 (m, 4 H, Ar), 7.7 (br s, 1 H, NH). Operating as in the preparation of **41a**, from acetal **39b** (400 mg, 1.1 mmol), excess methanethiol, and $BF_3Et_2O$ (2.1 mL, 16.8 mmol) in $CH_2Cl_2$ (35 mL), pure dithioacetal **41b** (300 mg, 74%) was obtained after flash chromatography (2:3 AcOEt–hexane): IR ($CHCl_3$) 3460 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.00 (t, $J$ = 7.0 Hz, 3 H, $CH_3CH_2$), 1.38 (m, 1 H, H-4eq), 1.65 (m, 1 H, H-12$R$), 1.80–2.10 (m, 2 H, $CH_2CH_3$), 2.16 and 2.20 (2 s, 3 H each, $CH_3S$), 2.10–2.35 (m, 3 H, H-3ax, H-5, and H-12$S$), 2.40 (dd, $J$ = 13.3, 6.6 Hz, 1 H, NCH), 2.44 (d, $J$ = 12.0 Hz, 1 H, H-3eq), 2.58 (d, $J$ = 17.0 Hz, 1 H, H-6eq), 3.05 (dd, $J$ = 13.3, 7.8 Hz, 1 H, NCH), 3.12 (dd, $J$ = 17.0, 6.8 Hz, 1 H, H-6ax), 3.96 (dd, $J$ = 7.8, 6.6 Hz, 1 H, SCHS), 4.15 (apparent t, 1 H, H-1), 7.12 (m, 2 H, H-9 and H-10), 7.30 (m, 1 H, H-8), 7.54 (m, 1 H, H-11), 8.05 (br s, 1 H, NH); $^{13}$C NMR ($CDCl_3$) Table I; MS ($m/e$, relative intensity) 360 ($M^+$, 24), 312 (70), 254 (20), 253 (100), 180 (12), 169 (25), 168 (18), 167 (10), 144 (11), 110 (23), 107 (25), 84 (14), 74 (10), 73 (10); HRMS calcd for $C_{20}H_{28}N_2S_2$ 360.1694, found 360.1694.

**Method B.** To a stirred slurry of $LiAlH_4$ (50 mg, 1.3 mmol) in anhydrous dioxane (15 mL) was added a solution of **40** (106 mg, 0.3 mmol) in dioxane (10 mL), and the resulting mixture was stirred at room temperature for 16 h. The excess of hydride was decomposed with aqueous dioxane (5 mL) and 15% aqueous NaOH (3 mL). The solids were removed by filtration and washed with dioxane. The combined filtrate and washings were evaporated. The residue was dissolved in 10% aqueous HCl (30 mL), and the solution was washed with AcOEt. The aqueous layer was made alkaline with $Na_2CO_3$ and extracted with $CH_2Cl_2$. The extracts were dried and evaporated, and the residue was purified by flash chromatography (2:3 AcOEt–hexane), affording **41b** (45 mg, 45%).

**Method C.** To a solution of bis(methylthio)methane (7.0 g, 65 mmol) in anhydrous THF (70 mL) at −30 °C was added dropwise $n$-butyllithium (40.6 mL, 1.6 M in hexane, 65 mmol). The mixture was stirred at −20 °C for 1.5 h and then was added dropwise to a solution of anhydrous DMF (19.8 g, 257 mmol) in THF (130 mL) at −30 °C. After stirring at −20 °C for 6 h, the mixture was poured into saturated aqueous $NH_4Cl$ (200 mL) and extracted with AcOEt. The extracts were washed with brine, dried, and evaporated to give bis(methylthio)acetaldehyde[57] as an unstable oil. To a solution of this aldehyde (43 mg, 0.32 mmol) and amine **32b** (50 mg, 0.21 mmol) in THF (1 mL) was added a buffer (citric acid/sodium citrate, pH 6, 1 mL). The mixture was stirred at room temperature for 30 min, and then $NaBH_3CN$ (15 mg, 0.23 mmol) was added. After 72 h, the reaction mixture was acidified (pH 2–3) with 2 N HCl and stirred for 30 min. The resulting mixture was made alkaline with 10% aqueous $Na_2CO_3$ and extracted with AcOEt. The extracts were dried and evaporated to give a residue which, after flash chromatography, afforded dithioacetal **41b** (10 mg, 13%).

**6α-(Methylthio)tubifoline (42a).** Operating as in the preparation of **25**, from DMTSF (1.0 g, 5.6 mmol) in $CH_2Cl_2$ (400 mL) and dithioacetal **41a** (1.0 g, 2.8 mmol) in $CH_2Cl_2$ (50 mL), followed by flash chromatography (93:7 $Et_2O$–DEA), compound **42a** (0.45 g, 52%) was obtained: IR ($CHCl_3$) 1565 cm$^{-1}$; UV ($Et_2O$) $\lambda_{max}$ 253 nm; $^1$H NMR ($CDCl_3$) δ 0.95 (t, $J$ = 7.2 Hz, 3 H, H-18), 1.06 (dm, $J$ = 13.8 Hz, 1 H, H-14$R$), 1.32 (m, 2 H, H-19), 1.58 (s, 3 H, $CH_3S$), 1.63 (m, 1 H, H-14$S$), 1.76 (m, 1 H, H-20α), 2.38 (br s, 1 H, H-15α), 2.62 (t, $J$ = 12.0 Hz, 1 H, H-21β), 2.64 (d, $J$ = 15.0 Hz, 1 H, H-16β), 2.86 (dd, $J$ = 15.0, 10.0 Hz, 1 H, H-16α), 3.04 (t, $J$ = 11.6 Hz, 1 H, H-5α), 3.26 (dd, $J$ = 12.0, 5.0 Hz, 1 H, H-21α), 3.46 (dd, $J$ = 11.6, 6.0 Hz, 1 H, H-5β), 3.88 (br s, 1 H, H-3α), 4.00 (dd, $J$ = 11.6, 6.0 Hz, 1 H, H-6β), 7.20 (t, $J$ = 7.8 Hz, 1 H, H-10), 7.34 (t, $J$ = 7.8 Hz, 1 H, H-11), 7.40 (d, $J$ = 7.8 Hz, 1 H, H-9), 7.52 (d, $J$ = 7.8 Hz, 1 H, H-12); $^{13}$C NMR ($CDCl_3$) Table II. Attempts to crystallize **42a** as a base or dipicrate failed.

**6α-(Methylthio)-20-epitubifoline (42b).** Operating as above, from DMTSF (0.7 g, 3.8 mmol) in $CH_2Cl_2$ (300 mL) and dithioacetal **41b** (0.7 g, 1.9 mmol) in $CH_2Cl_2$ (40 mL), followed by flash chromatography (95:5 $Et_2O$–DEA), compound **42b** (0.30 g, 50%) was obtained: IR ($CHCl_3$) 1565 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.96 (t, $J$ = 7.2 Hz, 3 H, H-18), 1.20–1.60 (m, 2 H, H-19), 1.68 (s, 3 H, $CH_3S$), 1.70 (m, 1 H, H-14$R$), 1.85 (dm, $J$ = 14.4 Hz, 1 H, H-14$S$), 2.00–2.30 (m, 2 H, H-20β and H-15α), 2.77 (d, $J$ = 16.2 Hz, 1 H, H-16β), 2.95 (m, 2 H, H-21), 3.20 (t, $J$ = 11.6 Hz, 1 H, H-5α), 3.26 (dd, $J$ = 16.2, 10.2 Hz, 1 H, H-16α), 3.54 (dd, $J$ = 11.6, 6.0 Hz, 1 H, H-5β), 3.90 (dd, $J$ = 11.6, 6.0 Hz, 1 H, H-6β), 3.95 (br s, 1 H, H-3α), 7.22 (t, $J$ = 7.8 Hz, 1 H, H-10), 7.35 (t, $J$ = 7.8 Hz, 1 H, H-11), 7.40 (d, $J$ = 7.8 Hz, 1 H, H-9), 7.52 (d, $J$ = 7.8 Hz, 1 H, H-12). Attempts to crystallize **42b** as a base or dipicrate failed.

**(±)-Tubifolidine (43a).** To a solution of **42a** (200 mg, 0.64 mmol) in absolute EtOH (6 mL) was added Raney Ni (W-2, 4 spatulas). The mixture was refluxed for 3 h and then filtered through a Celite pad. The solids were well washed with EtOH, and the combined ethanolic solutions were evaporated. Column chromatography (95:5 $Et_2O$–DEA) gave (±)-tubifolidine (**43a**, 34 mg, 20%) as a colorless glass: $^1$H NMR ($CDCl_3$) δ 0.84 (t, $J$ = 7.2 Hz, 3 H, H-18), 1.22 (m, 2 H, H-19), 1.60–1.95 (m, 5 H, H-14, H-16, and H-20), 1.70 (m, 1 H, H-15α), 1.80 (ddd, $J$ = 13.5, 10.0, 3.0 Hz, 1 H, H-6α), 2.10 (t, $J$ = 12.5 Hz, 1 H, H-21β), 2.33 (dt, $J$ = 13.5, 8.5 Hz, 1 H, H-6β), 2.76 (ddd, $J$ = 12.0, Hz, 1 H, 3.0 Hz, 1 H, H-5β), 3.02 (dd, $J$ = 12.5, 6.0 Hz, 1 H, H-21α), 3.11 (ddd, $J$ = 12.0, 10.0, 8.5 Hz, 1 H, H-5α), 3.30 (t, $J$ = 3.0 Hz, 1 H, H-3α), 3.56 (dd, $J$ = 9.5, 7.5 Hz, 1 H, H-2β), 6.56 (d, $J$ = 8.0 Hz, 1 H, H-12), 6.69 (t, $J$ = 8.0 Hz, 1 H, H-10), 6.97 (m, 2 H, H-9 and H-11); $^{13}$C NMR ($CDCl_3$) Table II; HRMS calcd for $C_{18}H_{24}N_2$ 268.1939, found 268.1929. IR, UV, and MS data were identical with those reported for the natural product.[7,41]

**(±)-Epitubifolidine (43b).** Operating as above, from **42b** (86 mg, 0.28 mmol) in EtOH (4 mL) and Raney Ni (W-2, 2 spatulas), (±)-20-epitubifolidine (**43b**, 12 mg, 16%) was obtained: IR ($CHCl_3$) 1600 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.90 (t, $J$ = 7.2 Hz, 3 H, H-18), 2.16 (ddd, $J$ = 14.2, 7.1, 2.5 Hz), 2.55 (dd, $J$ = 14.2, 5.4 Hz), 2.95 (dd, $J$ = 10.5, 3.7 Hz), 3.25 (ddd, $J$ = 10.5, 8.0, 2.5 Hz), 3.65 (br s, 1 H, H-3α), 3.66 (dd, $J$ = 10.0, 7.0 Hz, 1 H, H-2β), 6.65 (d, $J$ = 8.0 Hz, 1 H, H-12), 6.75 (t, $J$ = 8.0 Hz, 1 H, H-10), 7.05 (m, 2 H, H-9 and H-11); MS ($m/e$, relative intensity) 268 ($M^+$, 23), 240 (4), 199 (16), 144 (19), 143 (14), 139 (11), 138 (100), 130 (17), 124 (17), 115 (13), 110 (34); HRMS calcd for $C_{18}H_{24}N_2$ 268.1939, found 268.1940.

**Methyl 2,16-Didehydro-6α-(methylthio)tubifolidine-1-carboxylate (44).** To a solution of **42a** (200 mg, 0.64 mmol) in anhydrous 1,2-dimethoxyethane (5.5 mL) was added a suspension of NaH (37 mg, 50% oil dispersion, 0.77 mmol) in 1,2-dimethoxyethane (0.5 mL). The mixture was stirred at room temperature for 15 min, and then methyl chloroformate (0.1 mL, 1.4 mmol) was added. After stirring at 60 °C for 1 h, $CH_2Cl_2$ (20 mL) was added and the mixture was poured into 10% aqueous $Na_2CO_3$ (15 mL). The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic extracts were washed with brine, dried, and evaporated to give a residue which was purified by flash chromatography (95:5 $Et_2O$–DEA), affording **44** (136 mg, 67%) as a white solid: IR ($CHCl_3$) 1700 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.96 (t, $J$ = 7.2 Hz, 3 H, H-18), 1.32 (m, 2 H, H-19), 1.51 (ddd, $J$ = 12.7, 3.9, 2.7 Hz, 1 H, H-14$R$), 1.66 (s, 3 H, $CH_3S$), 1.78 (m, 1 H, H-20α), 1.94 (dt, $J$ = 12.7, 2.8 Hz, 1 H, H-14$S$), 2.39 (t, $J$ = 11.5 Hz, 1 H, H-21β), 2.53 (m, 1 H, H-15α), 2.77 (dd, $J$ = 12.2, 10.5 Hz, 1H, H-5α), 3.02 (dd, $J$ = 11.5, 4.4 Hz, 1 H, H-21α), 3.31 (dd, $J$ = 12.2, 6.6 Hz, 1 H, H-5β), 3.80 (br s, 1 H, H-3α), 3.82 (dd, $J$ = 10.5, 6.6 Hz, 1 H, H-6β), 3.92 (s, 3 H, $CH_3O$), 6.03 (d, $J$ = 8.0 Hz, 1 H, H-16), 7.05 (td, $J$ = 7.2, 1.0 Hz, 1 H, H-10), 7.12 (dd, $J$ = 7.2, 2.0 Hz,

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1 H, H-9), 7.23 (ddd, $J$ = 7.8, 7.2, 2.0 Hz, 1 H, H-11), 7.69 (d, $J$ = 7.8 Hz, 1 H, H-12).

**Methyl 2,16-Didehydrotubifolidine-1-carboxylate (45).** To a solution of **44** (80 mg, 0.2 mmol) in absolute EtOH (6 mL) was added Raney Ni (W-2, 3 spatulas). After the mixture was refluxed for 1.5 h no trace of **44** was detected by TLC. The solids were removed by filtration and washed with EtOH. Removal of the solvent and purification of the residue by flash chromatography (95:5 $Et_2O$–DEA) gave **45** (28 mg, 45%): IR ($CHCl_3$) 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3 H, H-18), 1.27 (m, 2 H, H-19), 1.48 (ddd, $J$ = 12.8, 3.8, 2.8 Hz, 1 H, H-14$R$), 1.63 (dd, $J$ = 11.3, 7.0 Hz, 1 H, H-6$\alpha$), 1.70 (m, 1 H, H-20$\alpha$), 1.94 (dt, $J$ = 12.8, 2.7 Hz, 1 H, H-14$S$), 2.11 (t, $J$ = 11.6 Hz, 1 H, H-21$\beta$), 2.51 (m, 1 H, H-15$\alpha$), 2.75 (dd, $J$ = 14.6, 7.6 Hz, 1 H, H-5$\beta$), 2.75–3.00 (masked, 1 H, H-6$\beta$), 2.89 (dd, $J$ = 11.6, 4.5 Hz, 1 H, H-21$\alpha$), 3.00 (td, $J$ = 14.6, 7.0 Hz, 1 H, H-5$\alpha$), 3.78 (br s, 1 H, H-3$\alpha$), 3.90 (s, 3 H, $CH_3O$), 5.98 (d, $J$ = 8.0 Hz, 1 H, H-16), 7.04 (td, $J$ = 7.4, 1.2 Hz, 1 H, H-10), 7.11–7.24 (m, 2 H, H-9 and H-11), 7.75 (d, $J$ = 8.0 Hz, 1 H, H-12). Anal. Calcd for $C_{20}H_{24}N_2O_3 \cdot H_2O$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.27; H, 8.00; N, 7.90.

**(±)-Tubifoline (46).** A solution of **45** (32 mg, 0.1 mmol) in 1 N NaOMe in MeOH (0.4 mL) was refluxed for 1 h. The mixture was poured into ice-cold $H_2O$ (5 mL) and extracted with $CH_2Cl_2$. The extracts were washed with brine, dried, and evaporated to give a solid which, after purification by flash chromatography (95:5 $Et_2O$–DEA), afforded (±)-tubifoline (**46**) (21 mg, 80%): $^1H$ NMR ($CDCl_3$) $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3 H, H-18), 1.18 (ddd, $J$ = 13.8, 4.4, 2.4 Hz, 1 H, H-14$R$), 1.31 (m, 2 H, H-19), 1.63 (ddd, $J$ = 13.8, 3.4, 2.2 Hz, 1 H, H-14$S$), 1.75 (m, 1 H, H-20$\alpha$), 1.93 (ddd, $J$ = 13.5, 5.5, 1.3 Hz, 1 H, H-6$\alpha$), 2.36 (m, 1 H, H-15$\alpha$), 2.55 (t, $J$ = 12.5 Hz, 1 H, H-21$\beta$), 2.59 (d, $J$ = 14.6 Hz, 1 H, H-16$\beta$), 2.78 (ddd, $J$ = 13.5, 12.0, 7.0 Hz, 1 H, H-6$\beta$), 2.84 (dd, $J$ = 14.6, 10.5 Hz, 1 H, H-16$\alpha$), 3.10–3.20 (masked, 1 H, H-5$\beta$), 3.14 (dd, $J$ = 12.5, 4.6 Hz, 1 H, H-21$\alpha$), 3.25 (td, $J$ = 12.0, 5.5 Hz, 1 H, H-5$\alpha$), 3.75 (m, 1 H, H-3$\alpha$), 7.18 (t, $J$ = 8.0 Hz, 1 H, H-10), 7.30 (m, 2 H, H-9 and H-11), 7.53 (d, $J$ = 8.0 Hz, 1 H, H-12); $^{13}C$ NMR ($CDCl_3$) Table II. TLC, IR, UV, and MS were identical with those reported for the natural product.[7,41,43d]

**(±)-19,20-Dihydroakuammicine (47).** A solution of **45** (91 mg, 0.3 mmol) in MeOH (40 mL) was photolyzed under argon with a 125-W high-pressure mercury lamp in a quartz immersion well reactor for 1 h. Evaporation of the solvent gave a residue which was chromatographed. On elution with 97:3 $CHCl_3$–MeOH, (±)-tubifoline (**46**, 12 mg, 13%), (±)-19,20-dihydroakuammicine (**47**, 19 mg, 20%), and starting material (**45**, 20 mg) were isolated successively. The $R_f$ of **47** with several solvent mixtures were coincident with those reported[41,43d] for the natural product, and a deep blue color appeared with cerium(IV) sulfate. **47**: $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 (m, 3 H, H-18), 0.95 and 1.25 (2 m, 2 H, H-19), 1.40 (dt, $J$ = 12.5, 3.0 Hz, 1 Hz, H-14$R$), 1.85 (m, 1 H, H-20$\alpha$), 1.95 (dd, $J$ = 12.5, 6.8 Hz, H-6$\alpha$), 2.05 (t, $J$ = 12.5 Hz, 1 H, H-21$\beta$), 2.06 (dt, $J$ = 12.5, 3.0 Hz, 1 H, H-14$S$), 2.80–3.00 (m, 2 H, H-5$\beta$ and H-6$\beta$), 3.00 (dd, $J$ = 12.5, 6.5 Hz, 1 H, H-21$\alpha$), 3.10 (td, $J$ = 12.0, 6.8 Hz, 1 H, H-5$\alpha$), 3.15 (m, 1 H, H-15$\alpha$), 3.75 (s, 3 H, $CH_3O$), 3.95 (br s, 1 H, H-3$\alpha$), 6.80 (d, $J$ = 7.5 Hz, 1 H, H-12), 6.89 (t, $J$ = 7.5 Hz, 1 H, H-10), 7.12 (t, $J$ = 7.5 Hz, 1 H, H-11), 7.15 (d, $J$ = 7.5 Hz, 1 H, H-9), 9.03 (br s, 1 H, NH); $^{13}C$ NMR ($CDCl_3$) Table II.

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**Registry No.** (±)-**1**, 99552-97-3; (±)-**2a**, 101481-26-9; (±)-**2b**, 128902-24-9; (±)-**3a**, 101491-90-1; (±)-**3b**, 128902-25-0; (±)-**4a** (isomer 1), 101481-17-8; (±)-**4a** (isomer 2), 101491-91-2; (±)-**4b** (isomer 1), 101481-29-2; (±)-**4b** (isomer 2), 101481-20-3; (±)-**5a**, 128902-16-9; (±)-**5b**, 128902-26-1; (±)-**6a** (isomer 1), 101481-19-0; (±)-**6a** (isomer 2), 101481-28-1; (±)-**8a** (isomer 1), 128902-17-0; (±)-**8a** (isomer 2), 129029-34-1; (±)-**8b** (isomer 1), 128902-27-2; (±)-**8b** (isomer 2), 128948-97-0; (±)-**9a**, 101481-18-9; (±)-**9b**, 101678-89-1; (±)-**10a**, 101481-21-4; (±)-**10b**, 128902-28-3; (±)-**13**, 128902-18-1; (±)-**14**, 101481-22-5; (±)-**15**, 101481-27-0; (±)-**18**, 101481-24-7; (±)-**21**, 128902-19-2; **22**, 128902-20-5; (±)-**23**, 101481-23-6; (±)-**25**, 101481-16-7; (±)-**26**, 128902-21-6; (±)-**27**, 116787-64-5; **28**, 95533-03-2; (±)-**29a**, 128902-22-7; (±)-**29b**, 128948-94-7; (±)-**30a**, 123718-72-9; (±)-**30b**, 128948-95-8; (±)-**32a**, 116965-66-3; (±)-**32b**, 116965-63-0; **33**, 7023-83-8; **34**, 58925-98-7; **35**, 75272-23-0; **36**, 51534-60-2; **37**, 79414-76-9; (±)-**40**, 128902-23-8; (±)-**41a**, 128948-93-6; (±)-**41b**, 116965-65-2; (±)-**42a**, 122437-63-2; (±)-**42b**, 128948-96-9; (±)-**43a**, 20823-98-7; (±)-**43b**, 117020-72-1; (±)-**44**, 122419-45-8; (±)-**45**, 122419-46-9; (±)-**46**, 20823-97-6; (±)-**47**, 121916-34-5; $PhSCH_2COCl$, 7031-27-8; $BrCH_2CH(OEt)_2$, 2032-35-1; $CH_3SCH_2COCl$, 35928-65-5; $(EtO)_2CHCO_2Et$, 6065-82-3.

# Polar Effects in the Decomposition of Bis(3-alkoxyaroyl) Peroxides. Synthesis of 8-Alkoxy-6*H*-dibenzo[*b*,*d*]pyran-6-ones

Sergio Auricchio,* Attilio Citterio, and Roberto Sebastiano

*Dipartimento di Chimica del Politecnico, P.za L. da Vinci 32, 20133 Milano, Italy*

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The reaction of four substituted bis(3-alkoxybenzoyl) peroxides (**1b–e**) in neat phenols (**2a–e**) affords mainly 8-alkoxy-6*H*-dibenzo[*b*,*d*]pyran-6-ones (**7**) and ortho-benzoyloxylation products (**4**) of the phenol. Diaroyl peroxides without electron-releasing meta substituents afford essentially products **4**. A mechanism involving monoelectronic oxidation of the phenol by the peroxide and biaryl coupling by preferential addition of the phenol radical cation to the ortho positions to the alkoxy group of the diaroyl peroxide is suggested.

Although the oxidation of various phenols with dibenzoyl peroxide has been considerably investigated,[1,2] comparatively little work has been performed on the oxidation of phenols by bis(substituted aroyl) peroxides. The more frequently reported bis(substituted aroyl) peroxide was the strongly electrophilic 4-nitro derivative.[1] This appears surprising in view of the controversy about the mechanism of these reactions.[3]

Until now, the products of the interaction of diaroyl peroxides and phenols have been reported to be the ortho-benzoyloxylated phenols **4** (normally as an equilibrium mixture resulting from trans aroyloxylation) with ortho unsubstituted phenols, and the relatively unstable *o*-

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