Total Synthesis of Uleine-Type and *Strychnos* Alkaloids through a Common Intermediate

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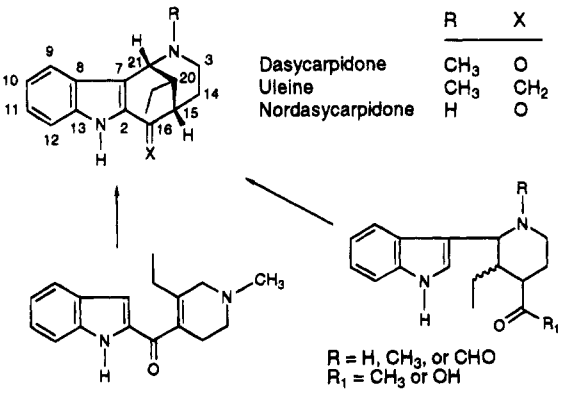
A stereoselective total synthesis of the alkaloids of the uleine group, dasycarpidone, dasycarpidol, and nordasycarpidone, has been accomplished from the tetracyclic intermediate **1**, which has been prepared by two alternative routes, either by Fischer indolization of 2-azabicyclo[3.3.1]nonanone **9** or, more efficiently, by stereocontrolled cyclization of 2-[(2-cyano-3-ethyl-4-piperidyl)methyl]indoles **24a** and **24b**. From the same tetracyclic intermediate **1**, the *Strychnos* alkaloid tubotaiwine was also synthesized, the key step being the construction of the quaternary spiranic center by cyclization of a thionium ion upon the indole β-position.

The indole alkaloids with a nonrearranged secologanin skeleton include several structural types.[1] Among them, the alkaloids of the uleine group[2] (dasycarpidan stereoparent) and the *Strychnos* alkaloids[3] with the Aspidospermatan biogenetic subtype[4] (condyfolan stereoparent) are characterized by the presence of a 1,5-methanoazocino[4,3-*b*]indole fragment bearing a two-carbon chain, usually an ethyl substituent, at the bridge carbon.

Several total syntheses[5–8] for the alkaloids of the uleine group, all of them in the racemic series, have been reported since their structural elucidation in 1965.[9] However, except in Kametani's syntheses in the dasycarpidone series[5,6c] and in Büchi's stereodivergent synthesis of uleine,[7] these syntheses lead to the 20-epi isomer[10] (ethyl group axial with respect to the piperidine ring) as the predominant or exclusive product. In all cases the carbocyclic ring was formed in the last step, either by formation of the C-7/C-21 bond by isomerization of a 4-(indolylcarbonyl)-1,2,5,6-tetrahydropyridine to the corresponding 1,4,5,6-tetrahydropyridine followed by acid treatment[6a] or by formation of the C-2/C-16 bond from 3-(2-piperidyl)indoles. In the latter approach the ring closure occurs with simultaneous formation of the 2-acyl-[5,6b,c] or 2-vinylindole[7,8] units (Scheme 1).[11]

Scheme 1. Previous Syntheses of Alkaloids of the Uleine Group



The *Strychnos* alkaloids with the Aspidospermatan skeletal type have received little attention from a synthetic standpoint.[12–14] After the pioneering work by Harley-Mason,[12a,13] only two different strategies, both involving an intramolecular Diels–Alder process in the key step, have recently culminated in the synthesis of an alkaloid of this group (Scheme 2).[12b,14,15]

With the aim of developing a stereoselective entry to the two above-mentioned groups of indole alkaloids, we envisaged a synthetic strategy that utilizes the metha-

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(1) (a) Atta-ur-Rahman; Basha, A. *Biosynthesis of Indole Alkaloids*; Clarendon Press: Oxford, 1983. (b) Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, pp 211–376.

(2) Joule, J. A. In *Indoles*, Saxton J. E., Ed. in *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4, pp 265–292.

(3) (a) Bosch, J.; Bonjoch, J. Pentacyclic *Strychnos* Indole Alkaloids. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, pp 31–88. (b) Massiot, G.; Delaude, C. African *Strychnos* Alkaloids. In *The Alkaloids*, Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 34, pp 211–329.

(4) Lounasmaa, M.; Somersalo, P. The Condylocarpine Group of Indole Alkaloids. 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, pp 28–56.

(5) Nordasycarpidone: Kametani, T.; Suzuki, T. *Chem. Pharm. Bull.* **1971**, *19*, 1424.

(6) Dasycarpidone and its 20-epimer: (a) Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, 2738. (b) Dolby, L. J.; Biere, H. *J. Org. Chem.* **1970**, *35*, 3843. (c) Kametani, T.; Suzuki, T. *J. Org. Chem.* **1971**, *36*, 1291. (d) See also ref 5.

(7) Uleine: (a) Büchi, G.; Gould, S. J.; Näf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492. (b) See also ref 6a.

(8) 20-Epiuleine: (a) Natsume, M.; Kitagawa, Y. *Tetrahedron Lett.* **1980**, *21*, 839. (b) Harris, M.; Besselièvre, R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1981**, *22*, 331. (c) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683. (d) See also refs 6a,b and 7.

(9) Joule, J. A.; Ohashi, M.; Gilbert, B.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1717.

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

(11) For other procedures for the synthesis of 1,5-methanoazocino-[4,3-*b*]indoles, see the following. (a) Mercuric acetate oxidation of 4-(2-indolylmethyl)piperidines: Bosch, J.; Bonjoch, J.; Diez, A.; Linares, A.; Moral, M.; Rubiralta, M. *Tetrahedron* **1985**, *41*, 1753. (b) Elaboration of the indole nucleus from 2-azabicyclo[3.3.1]nonanes: Bonjoch, J.; Quirante, J.; Rodríguez, M.; Bosch, J. *Tetrahedron* **1988**, *44*, 2087. Teuber, H.-J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann. Chem.* **1992**, 461. (c) Addition of a 2-indoleacetic ester enolate to a pyridinium salt followed by acid cyclization of the resultant 1,4-dihydropyridine: Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156. (d) Treatment of 4-(2-indolylmethyl)-1,2,3,6-tetrahydropyridines with tris(triphenylphosphine)rhodium(I): Salas, M.; Joule, J. A. *J. Chem. Res., Synop.* **1990**, 98. (e) Closure of the piperidine ring from tetrahydrocarbazole derivatives: Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70.

(12) Tubotaiwine: (a) Dadson, B. A.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1969**, 665. (b) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696.

(13) Condylocarpine: Harley-Mason, *J. Pure Appl. Chem.* **1975**, *41*, 167.

(14) 19-Hydroxytubotaiwine: Nkiliza, J.; Vercauteren, J.; Léger, J.-M. *Tetrahedron Lett.* **1991**, *32*, 1787.

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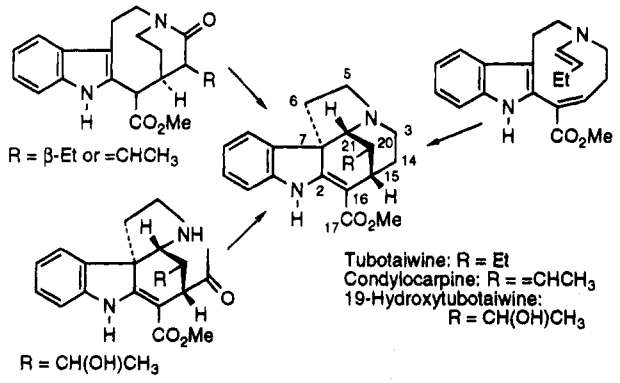
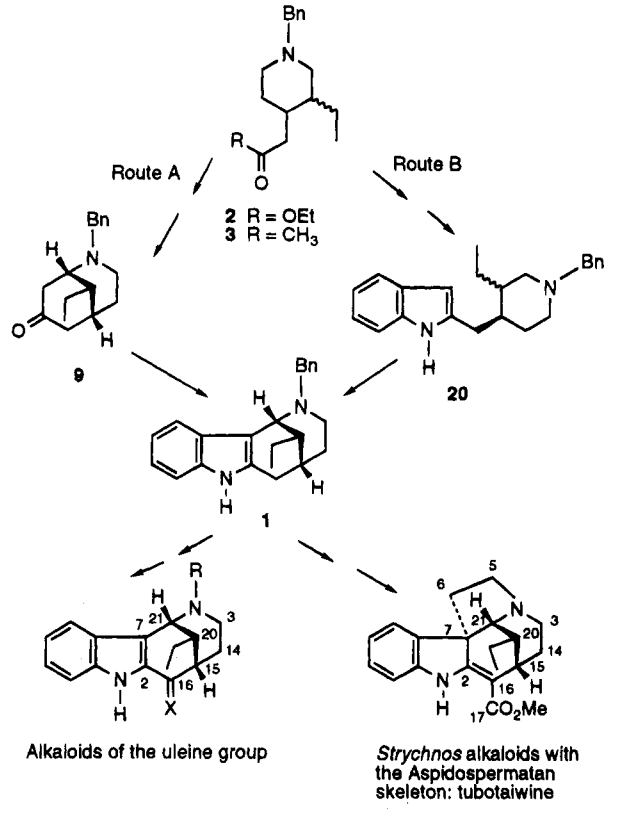
Scheme 2. Previous Syntheses of *Strychnos* Alkaloids with the Aspidospermatan Skeleton



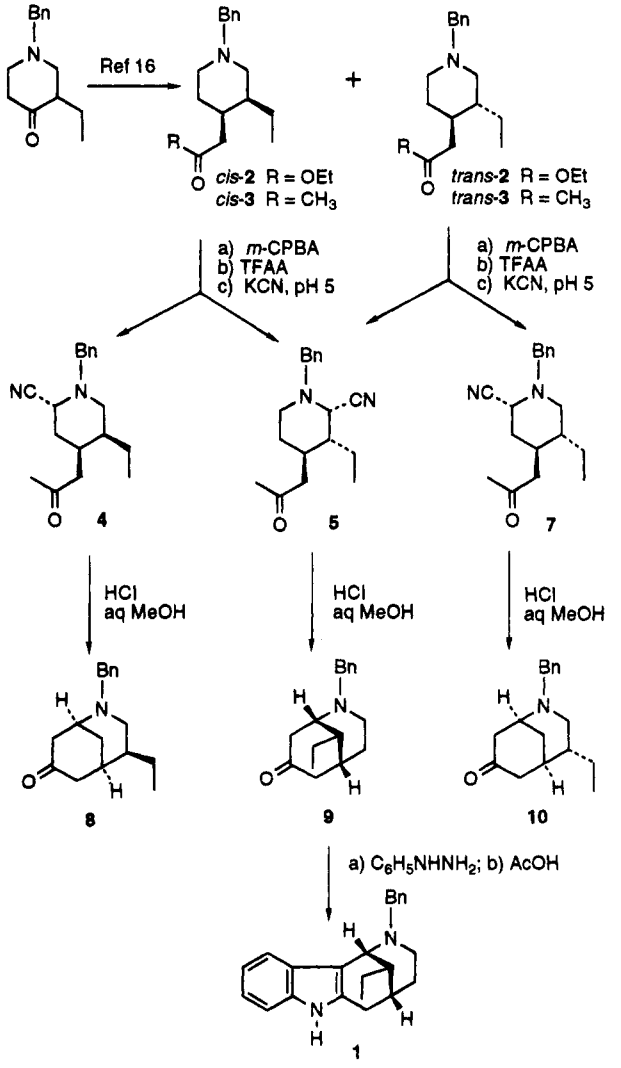
Scheme 3. Synthetic Strategy



noazocinoindole **1** as a common key intermediate. This tetracyclic compound incorporates a C-20 ethyl substituent equatorial with respect to the piperidine ring, *i.e.*, with the same relative stereochemistry as dasycarpidone, uleine, and the Aspidospermatan alkaloids. In the case of the alkaloids of the uleine group, this approach would imply a further oxidation step in order to generate the 2-acylindole moiety, whereas in the synthesis of *Strychnos* alkaloids the crucial step would be the closure of the five-membered ring. Tetracycle **1** could be constructed either by oxidative cyclization of a 4-acetonylpiperidine (**3**) (through the corresponding 2-cyanopiperidine) followed by Fischer indolization of the resulting 2-azabicyclo-[3.3.1]nonanone **9** (route A) or by a reverse sequence (route B) involving the initial elaboration of the indole ring and further oxidative cyclization of the resulting 2-(4-piperidylmethyl)indole **20**, again through the corresponding 2-cyanopiperidine (Scheme 3).

Synthesis of Tetracycle 1 via Fischer Indolization. In a previous work we reported the preparation of 4-piperidineacetates *cis*-**2** and *trans*-**2** from 1-benzyl-3-

Scheme 4. Synthesis of the Target Compound 1 by Fischer Indolization



ethyl-4-piperidone and their conversion to the corresponding 4-acetonylpiperidines **3**.[16] According to our synthetic plan, our first goals were the transformation of piperidine *cis*-**3** into the bridged 2-azabicyclo[3.3.1]-nonane derivative **9** and the Fischer indolization of the latter in order to obtain the target compound **1** (Scheme 4).[17]

Intramolecular reactions of 2,3,4,5-tetrahydropyridinium intermediates have proven to be useful for the synthesis of the 2-azabicyclo[3.3.1]nonane framework when a side chain containing a suitable and properly located nucleophilic carbon atom is attached at C-4.[18] In

(15) For the total synthesis of *Strychnos* alkaloids with the Strychnan skeletal type, see ref 3. For more recent work, see: (a) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (b) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 2064. (c) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966. (d) Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116. (e) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. (f) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490.

(16) Bonjoch, J.; Linares, A.; Guardià, M.; Bosch, J. *Heterocycles* **1987**, *26*, 2165.

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

(18) (a) Bonjoch, J.; Casamitjana, N.; Bosch, J. *Tetrahedron* **1982**, *38*, 2883. (b) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodríguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267. (c) Bonjoch, J.; Casamitjana, N.; Bosch, *Tetrahedron* **1988**, *44*, 1735.

Table 1. ^{13}C NMR Data of 2-Cyanopiperidines[a]

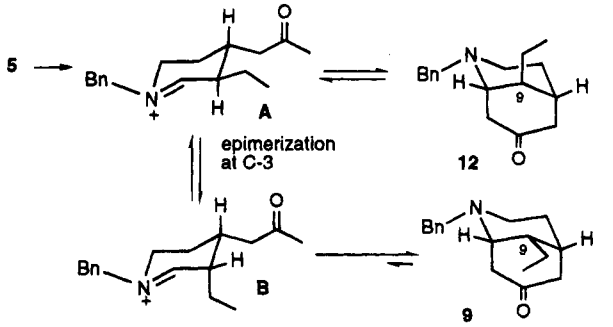
	4	5	6	7	13	23	24a	24b	25
C-2	52.6	56.2	53.8	51.5	51.8	52.8	56.5	53.7	51.5
C-3	29.9	44.0	42.8	34.1	34.3	29.7	45.5	42.6	33.6
C-4	31.9	33.8	31.7	32.9	28.3	35.3	36.7	35.2	36.5
C-5	38.5	31.3	26.9	41.3	31.3	38.8	30.8	26.4	42.4
C-6	50.9	48.7	49.8	54.1	49.3	51.2	49.0	50.0	54.1
CH_2Ph[b]	60.2	60.4	60.1	60.4	60.4	60.2	60.4	60.1	60.1
CN	116.7	115.0	116.5	116.2	116.7	115.7	115.4	115.7	115.3
CH_2	17.4	22.4	17.3	23.4		17.1	22.1	16.8	22.2
CH_3	12.2	11.0	11.6	10.8		12.2	11.4	11.8	10.2
4-CH_2	46.5	47.0	47.2	46.8	49.6	32.8	33.2	33.4	33.0
other[c]	207.6	207.8	207.5	207.4	207.7	150.7[d]	150.7[d]	150.5[d]	150.3[d]
	30.2	30.5	30.2	30.3	30.4	84.0	84.1	84.1	83.8
						28.2	28.3	28.2	28.0

[a] In $CDCl_3$ (50.3 MHz). [b] Phenyl ring carbons were found (±0.3) at 137.0 (for compounds **4**–**7** and **13**), 139.4 (for **23**–**25**), 129.0, 128.7, and 127.8. [c] $COCH_3$ for **4**–**7** and **13**, $NCO_2C(CH_3)_3$ for **23**–**25**. [d] Values (±0.3) for the indole nucleus: 136.6 (C-2), 109.1 (C-3), 128.9 (C-3a), 119.7 (C-4), 122.6 (C-5), 123.3 (C-6), 115.6 (C-7), and 139.5 (C-7a).

the last years we have employed 4-acetonyl-2-piperidinecarbonitriles for this purpose in the synthesis of 5-phenylmorphans[18c] and other 2-azabicyclo[3.3.1]nonane derivatives,[19] taking advantage of the behavior of 2-cyanopiperidines, which react as 2,3,4,5-tetrahydropyridinium salts since under acid conditions the carbon–cyano bond is cleaved, generating an iminium salt in a controlled manner.[20]

The oxidative cyanation[21] of *cis*-**3** was carried out by treatment with *m*-CPBA, formation and subsequent elimination of the corresponding *N*-trifluoroacetate derivative (Polonovski–Potier reaction[22]), and, finally, trapping of the resulting iminium salts with potassium cyanide[23] in a one-pot procedure.[24] Regioisomeric 2-cyanopiperidines **4** and **5**[25] were isolated in 78% overall yield in a 3:2 ratio.[26,27] Remarkably, the 3-ethyl and 4-acetonyl substituents in cyanopiperidine **5** are trans, with the ethyl substituent in an equatorial disposition, thus indicating that an epimerization at C-3 had occurred. This result can be rationalized by considering that the intermediate iminium salt is in equilibrium with the corresponding enamine (pH 4–5)[28] and that the more stable trans-3,4-diequatorial disposition is reached. However, the loss of the cis relationship between the C-3 and C-4 substituents did not constitute a serious problem since a further epimerization took place during the cyclization step (*vide infra*).

Scheme 5



The structural assignment of the above 2-cyanopiperidines, as well as of all 2-cyanopiperidines prepared in this work, was made on the basis of the ^1H and ^{13}C NMR data (Table 1). Thus, the 5-ethyl-substituted compounds show a characteristic deformed triplet due to the methine proton at C-2, while in the 3-ethyl series H-2 appears as a doublet when the ethyl group is equatorially located or as a broad signal when it is in an axial disposition. The chemical shift (δ ~3.8) and coupling patterns of H-2 also corroborate the expected axial disposition of the 2-cyano group.[29] The stereochemical assignment of the ethyl side chain was confirmed by the chemical shift value of its methylene carbon, which resonates at δ ~22 when the ethyl group is equatorial and at δ ~17 when it is axial. This upfield shift is due to the simultaneous crowding between H-5ax and one proton of the CH_2CO group at C-4 with the methylene protons of the ethyl substituent.

As expected, cyclization of 2-cyanopiperidine **5** was accomplished (68% yield) by treatment with HCl in methanol.[30] However, the resulting azabicyclic derivative **9** was found to possess the correct Aspidospermatan-type relative stereochemistry at the bridge carbon, thus pointing out that a further epimerization had taken place during the cyclization step. This epimerization can be rationalized as shown in Scheme 5. Thus, cyclization of

(19) *Inter alia*: (a) Casamitjana, N.; Gràcia, J.; Bonjoch, J.; Bosch, J. *Tetrahedron Lett.* **1992**, *33*, 2055. (b) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Garriga, C.; Bosch, J. *Tetrahedron* **1992**, *48*, 3131.

(20) Fry, E. M. *J. Org. Chem.* **1964**, *29*, 1647. (b) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064. (c) Feliz, M.; Bosch, J.; Mauleón, D.; Amat, M.; Domingo, A. *J. Org. Chem.* **1982**, *47*, 2435. (d) Koskinen, A.; Lounasmaa, M. *Tetrahedron* **1983**, *39*, 1627.

(21) For a preliminary report of this part of the work, see: Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5655.

(22) For a review, see: Grierson, D. *Org. React.* **1991**, *39*, 85.

(23) (a) Groutas, W. C.; Essawi, M.; Portoghese, P. S. *Synth. Commun.* **1980**, *10*, 495. (b) This reaction has been extensively used by the Husson group: see refs 8b,c and 20b.

(24) Lounasmaa, M.; Karvinen, E.; Koskinen, A.; Jokela, R. *Tetrahedron* **1987**, *43*, 2135.

(25) Minor amounts of the nitrile **6** were also formed.

(26) For the regiochemistry of this reaction from 1,3-disubstituted piperidines, see: (a) Jokela, R.; Tamminen, T.; Lounasmaa, M. *Heterocycles* **1985**, *23*, 1707. (b) Jokela, R.; Karvinen, E.; Tolvanen, A.; Lounasmaa, M. *Tetrahedron* **1988**, *44*, 2367.

(27) For other procedures leading to 1,3,4-trisubstituted-2-piperidinecarbonitriles, see the following. (a) Controlled reduction of 2-piperidones followed by cyanation: Glass, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324. (b) Nucleophilic addition to a 2-cyano-1,2,5,6-tetrahydropyridine followed by reintroduction of cyanide ion: ref 8c and references cited therein. See also: Koskinen, A.; Lounasmaa, M. *J. Chem. Soc., Chem. Commun.* **1983**, 821. Chapman, R. F.; Phillips, N. I. J.; Ward, R. S. *Tetrahedron* **1985**, *41*, 5229.

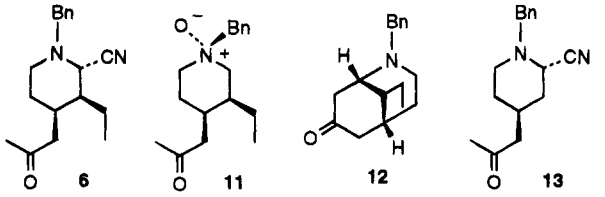
(28) (a) Grierson, D. S.; Vuilhorgne, M.; Husson, H.-P.; Lemoine, G. *J. Org. Chem.* **1982**, *47*, 4439. (b) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227.

(29) (a) Bonin, M.; Romero, J.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392. (b) Compernolle, F.; Saleh, M. A.; Van den Branden, S.; Toppet, S.; Hoornaert, G. *J. Org. Chem.* **1991**, *56*, 2386.

(30) Gnecco Medina, D. H.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1983**, *24*, 2099.

(31) This fact was experimentally proved since a pure sample of **12** was completely converted into the more stable epimer **9** after acid treatment (see Experimental Section). Minor amounts of **12** (~4%), besides **8** and **9**, had been isolated when *N*-oxide **11** was directly cyclized under Polonovski–Potier reaction conditions.[22]

the iminium cation **A**, initially formed from **5**, through a conformation in which both piperidine substituents adopt an axial disposition, would lead to bicyclo **12** (epi series). However, this cyclization not only probably requires a high activation energy but is also reversible because the resulting product is a β-amino ketone that can undergo a retro-Mannich reaction.[31] Under these circumstances, the cation **A** epimerizes, via the corresponding enamine, to **B**, which cyclizes to the more stable product **9**.[32] A similar cyclization from 2-cyanopiperidine **4** gave the anticipated azabicyclo **8** in 69% yield.



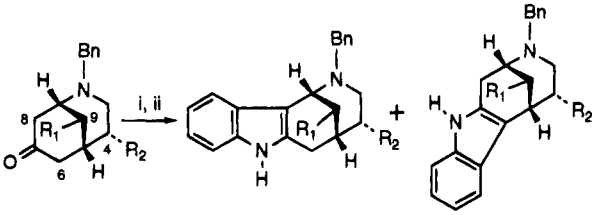
Operating as in the cis series, cyanation of *trans*-**3** gave a mixture of the above 3,4-trans-disubstituted 2-cyanopiperidine **5** and its regioisomer **7** (3:5 ratio, 71% overall yield), whose cyclization afforded a separable mixture of azabicyclic derivatives **9** (27%) and **10** (34%).[33,34] Therefore, the stereochemistry of the starting piperidine **3** is irrelevant, and the desired morphan derivative **9** was obtained starting from either the cis or the trans isomer as a consequence of the easy epimerization of the carbon bearing the ethyl substituent.

The Fischer indolization of ketone **9** was studied using several acid catalysts.[35] From the preparative standpoint, the best result was obtained when the phenylhydrazone derived from **9** was refluxed in AcOH solution. Under these conditions the target tetracycle **1** was obtained as the only isolable product, but in moderate yield. The use of HCl–EtOH or PPA led to mixtures of **1** and the undesired regioisomer **15**, in which **1** was the major product (Scheme 6).

Worthy of mention is the effect of the C-9 ethyl substituent upon the regioselectivity of the Fischer indole synthesis. In contrast with the above result from ketone **9**, when azabicyclic ketones **8**, in which the ethyl substituent is at the C-4 position, and **14**,[36] lacking this substituent, were subjected to Fischer indolization conditions, the unnatural regioisomers **17** or **19** were formed as the major or exclusive products. The *Strychnos*-type tetracycles **16** and **18** were isolated in low yields. These results are summarized in Scheme 6.[37]

In conclusion, although the strategy based on the final Fischer indolization permits the preparation of azocinoindole **1**, it was found to be somewhat inefficient because

Scheme 6. Fischer Indolization of 2-Azabicyclo[3.3.1]nonan-7-ones



ketone		compd	Method and Yield (%)[a] A	B	C	compd	Method and Yield (%)[a] A	B	C
9	R_1 = Et; R_2 = H	**1**	26	30	17	**15**	---	15	10
8	R_1 = H; R_2 = Et[b]	**16**	---	---	14	**17**	20	57	20
14	R_1 = R_2 = H	**18**	13	1	12	**19**	9	40	18

[a] Reagents: (i) $C_6H_5NHNH_2$, EtOH, rfx; (ii) Method A : AcOH; Method B : HCl-EtOH; Method C : PPA. [b] For clarity, compounds **8** and **16** have been depicted in the unnatural enantiomeric series.

of the observed regioselectivity in the oxidative cyanation and the low yield in the indolization step.

Synthesis of Tetracycle 1 via Pictet–Spengler Cyclization. At this point we decided to examine a reverse sequence involving the initial formation of the indole nucleus and the construction of the fused morphan moiety in the key step by cyclization of an iminium salt generated from a 4-(indolylmethyl)-2-cyanopiperidine (Scheme 7).[38] The required (piperidylmethyl)indole *cis*-**20** was prepared either by Fischer indolization of 4-acetonylpiperidine *cis*-**3** or, more efficiently (63% yield), by Smith indole synthesis[39] from 4-piperidineacetate *cis*-**2**.[40]

In order to avoid the formation of unwanted side products during the Polonovski reaction,[8c] the indole nucleus of *cis*-**20** was protected as the *N*-Boc derivative using the phase-transfer technique.[41] When the resulting compound *cis*-**21** was subjected to the usual oxidative cyanation conditions by way of the corresponding *N*-oxide (*cis*-**22**),[42] a 3:3:2 mixture of 2-cyanopiperidines **23**, **24a**, and **24b**, respectively, was obtained in 81% overall yield. As in the above 4-acetonylpiperidine series, epimerization at the piperidine 3-position occurred to a considerable extent in the regioisomer **24**, giving a mixture in which the most stable trans-3,4-diequatorial epimer **24a** predominated. However, it is noteworthy that, in contrast with the regioselectivity observed from 4-acetonylpiperidine *cis*-**3**, the 3-ethyl-substituted products **24** were the predominant regioisomers.[43]

Treatment of the above mixture of 2-cyanopiperidines

(32) From molecular mechanics calculations it was found that the lowest energy conformation in the protonated morphan **9** was 0.6 kcal/mol more stable than in the protonated epimer **12**. Minimizations were carried out with a MM2 (85) force field on a VAX 6610 computer. We acknowledge Prof. Carlos Jaime (Universitat Autònoma de Barcelona) for these results.

(33) The relative configuration at C-4 and C-9 in 2-azabicyclo[3.3.1]-nonan-7-ones **8**–**10** and **12** was easily established by ^{13}C NMR: Casamitjana, N.; Bonjoch, J.; Gràcia, J.; Bosch, J. *Magn. Reson. Chem.* **1992**, *30*, 183.

(34) A common fragmentation pattern, which implies a loss of 57 mass units (the propanone moiety) to give a 2,3-dihydropyridinium ion, was observed in all 2-azabicyclo[3.3.1]nonan-7-ones prepared in this work. For a similar fragmentation, see ref 18b and references therein.

(35) (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley: New York, 1982. (b) For a recent study, see: Hughes, D. L.; Zhao, D. *J. Org. Chem.* **1993**, *58*, 228.

(36) Prepared from 2-cyanopiperidine **13** (see Experimental Section).

(37) (a) For a more detailed discussion, see: Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Ubeda, M.-C.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 2449. (b) For the Fischer indolization of 2-azabicyclo[3.3.1]nonane-3,7-diones, see: Amat, M.; Sanfeliu, E.; Bonjoch, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 3841.

(38) For a preliminary report of this part of the work, see: Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5659.

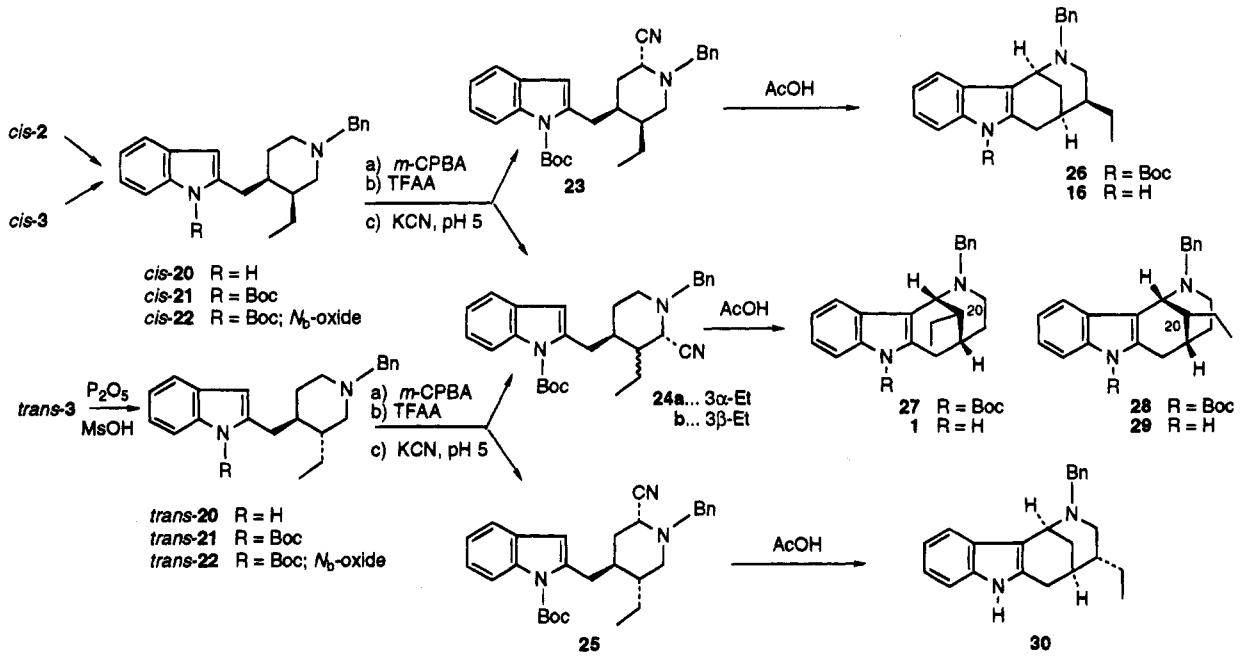
(39) Smith, A. B.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2954.

(40) Bonjoch, J.; Quirante, J.; Linares, A.; Bosch, J. *Heterocycles* **1988**, *27*, 2883.

(41) Illi, V. O. *Synthesis* **1979**, 136.

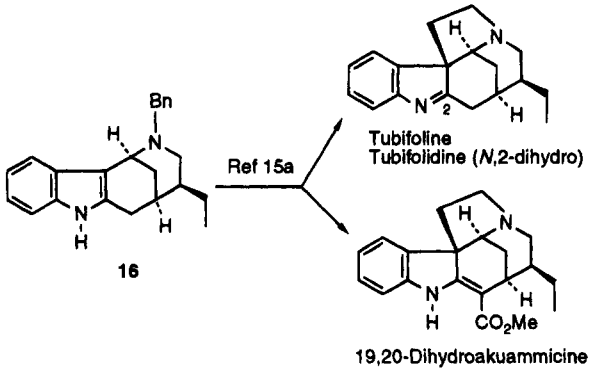
(42) The oxidation of *cis*-**21**, as well as of *cis*-**3** and the corresponding trans derivatives, occurs stereoselectively. According to the NMR data, *N*-oxides **11** and *cis*-**22** adopt a conformation in which both the oxygen atom and the C-4 piperidine substituent are axial. For a stereochemical analysis of *N*-oxide formation in piperidines, see: Shvo, Y.; Kaufman, E. D. *J. Org. Chem.* **1982**, *46*, 2148.

Scheme 7. Synthesis of the Target Compound 1 by Pictet–Spengler Cyclization



23 and 24 with acetic acid in aqueous dioxane[44] for 14 h accomplished both cyclization and deprotection of the indole ring to give a mixture of tetracycles **16** (26%) and **1** (46%), with the Strychnan and Aspidospermatan skeletal types respectively.[45] Minor amounts of the epimer **29**, with the same trans relative stereochemistry as **24a**, were also isolated. The almost exclusive formation of the required stereoisomer **1** (ethyl substituent equatorial with respect to the piperidine ring) from cyanopiperidines **24a** and **24b** made evident that a further epimerization at the carbon bearing the ethyl substituent had taken place during the process. When the cyclization time was shortened (2 h), appreciable amounts of the indole-protected tetracycles **26**, **27**, and **28** were detected (*ca.* 25% yield) by ^{13}C NMR analysis, thereby indicating that cyclization takes place, at least to some extent, before deprotection. Interestingly, under these conditions, tetracycle **28**, coming from cyclization of **24a**, predominated over **27**, a result that implies that epimerization at C-20[10] follows deprotection of the indole ring. Accordingly, the isolated minor epimer **29** was converted to a great extent into **1** after an additional equilibrating acid treatment. This useful epimerization occurs through the equilibrium iminium–enamine, after protonation at the indole 3-position and subsequent opening of the carbocyclic ring, and shows that, when the indole ring is not deactivated, the Pictet–Spengler reaction is reversible.[46] It should be noted that similar cyclizations from *2-acyl*-indole derivatives lead to tetracyclic systems in which the alkyl substituent at the bridge

Scheme 8. Formal Synthesis of *Strychnos* Alkaloids with the Strychnan Skeleton



carbon is axial with respect to the piperidine ring[6a,8c] and that further attempts to induce epimerization failed.[6a]

Taking into account the epimerizable character of the carbon carrying the ethyl substituent, (piperidylmethyl)-indole *trans*-**20**, which was available by Fischer indolization of *trans*-**3**, was also envisaged as a precursor of the target compound **1** through a sequence similar to the one described above for the cis series. Indeed, after protecting the indole nitrogen, *trans*-**20** was converted into a regioisomeric mixture of 2-cyanopiperidines **24a** and **25** (5:4 ratio) and then cyclized to tetracycles **1** and **30**. As expected, tetracycle **30** possesses a trans relationship between the hydrogens at the piperidine C-4 and C-5 positions (no epimerization has occurred), whereas the relative configuration at C-20 in **1** is the opposite of that of its precursor **24a**.

In conclusion, starting from easily accessible piperidine derivatives, using common intermediates, we have obtained the valuable tetracycles **1** and **16** in acceptable yields. The synthesis of **16** here reported represents a formal total synthesis of the *Strychnos* alkaloids with the Strychnan skeletal type, tubifolidine, tubifoline, and 19,-20-dihydroakuammicine[15a] (Scheme 8). The synthesis of **1**, in turn, constitutes a stereocontrolled access to the dasycarpidan framework and opens a new synthetic entry

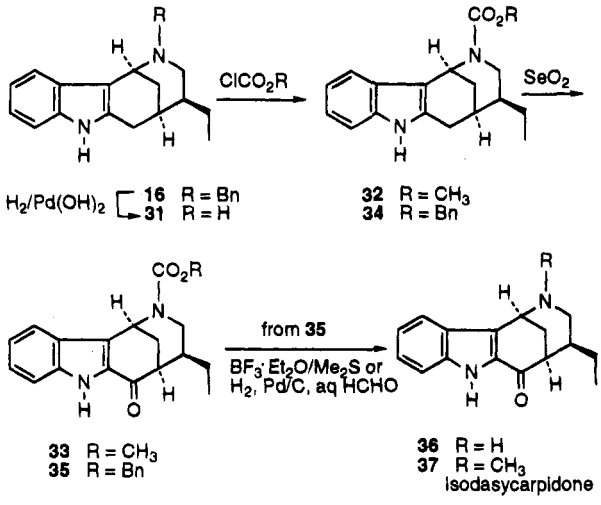
(43) For a remarkable regioselective formation of 2-cyanopiperidines, see: Rubiralta, M.; Torrens, A.; Reig, I.; Grierson, D. S.; Husson, H.-P. *Heterocycles* **1989**, *29*, 2121.

(44) The use of dioxane as cosolvent was crucial in order to achieve a good yield in this cyclization. When it was omitted, the yield was much lower due to the low solubility of the starting material.

(45) It is noteworthy that direct oxidative cyclization of *cis*-**20** with mercuric acetate afforded only tetracycle **16** in low yield (7%), compound **1** not being isolated.[40]

(46) The acid-catalyzed epimerization of compounds containing the tetrahydro-β-carboline structure has been known for a long time: Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053. See also: Wenkert, E.; Moeller, P. D. R.; Shi, Y.-J. *J. Org. Chem.* **1988**, *53*, 2383. Zhang, L.-H.; Gupta, A. K.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 4708.

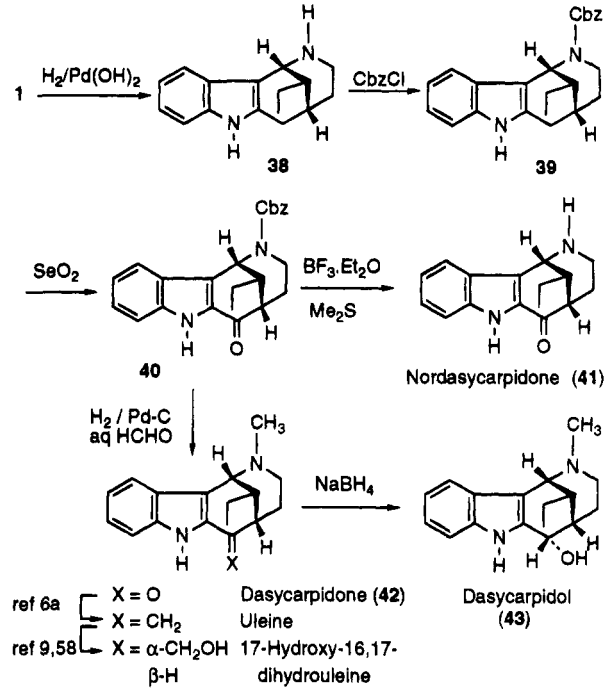
Scheme 9. Oxidation to 2-Acylindole Systems



to the alkaloids of the uleine group and the *Strychnos* alkaloids with the Aspidospermatan skeletal type (*vide infra*).

Synthesis of Alkaloids of the Uleine Group. The conversion of the key tetracyclic derivative **1** to the target natural products required two synthetic transformations: oxidation of the C-16[10] methylene group and exchange (or removal) of the substituent at the piperidine nitrogen. Although the oxidation of 2,3-dialkylindoles is a known process,[47] all attempts[48] to directly convert the tetracyclic amine **16**, used as a model compound, to the corresponding 2-acylindole were unsuccessful and the basic nitrogen had to be protected as a carbamate.[49] Since it is known that gramine-type compounds such as **16** undergo fragmentation when treated with acylating agents,[50] this protection was effected in two steps, by hydrogenolysis of the benzyl group followed by methoxycarbonylation of the resulting secondary amine **31** (Scheme 9). The carbamate **32** was then treated with SeO_2 in dioxane[48c] for a long time to give 2-acylindole **33** in excellent yield. However, removal of the protecting group on the piperidine nitrogen took place in low yield (30% maximum), the most efficient method being the alkaline hydrolysis. This inconvenience was overcome by using the more easily removable benzyloxycarbonyl group. In this manner, SeO_2 oxidation of benzyl carbamate **34** satisfactorily gave (80%) the corresponding 2-acylindole **35**, which was then successfully converted (63%) into the secondary amine **36** (norisodasycarpidone)[15a] by treatment with boron trifluoride/dimethyl sulfide.[51,52] Alternatively, hydrogenolysis of **35** in aqueous formaldehyde medium led to isodasycarpidone (**37**)[53] in 89% yield.

Scheme 10. Synthesis of Alkaloids of the Uleine Group



With a protocol for the conversion of azocinoindoles to the corresponding 2-acylindoles in hand, our efforts were then directed toward the extension of the above synthetic sequence starting from the dasycarpidan-type tetracycle **1** (Scheme 10). Thus, debenzylation of **1** by hydrogenolysis, followed by benzyloxycarbonylation of the resulting unstable secondary amine **38**, gave carbamate **39** in 50% overall yield.[54] As expected, oxidation of **39** with SeO_2 furnished the 2-acylindole **40** without any degree of epimerization at C-20, and cleavage of the benzyl carbamate protecting group, either with BF_3–Me_2S or by hydrogenolysis with *in situ* methylation of the resulting secondary amine, gave the alkaloids nordasycarpidone (**41**) and dasycarpidone (**42**) in 73% and 76% yields, respectively. Our synthetic dasycarpidone was found to be identical with a sample provided by Prof. J. A. Joule. Given that dasycarpidone had been previously converted to uleine,[6a] this synthesis also represents a stereoselective formal synthesis of the latter alkaloid.

Finally, sodium borohydride reduction of dasycarpidone led to a 5:2 mixture of the alkaloid dasycarpidol (**43**) and its C-16 epimer **44**. This constitutes the first total synthesis of dasycarpidol. The lower stereoselectivity in the above reduction, as compared with that observed in the deethyl series,[55] can be attributed to the steric effect of the ethyl substituent, which hinders the approach of the reducing agent to the most accessible, β-face of the carbonyl group.

The NMR spectral data of both the key intermediate **1** and dasycarpidone (**42**) were unambiguously assigned from the ^1H NMR values (500 MHz) and 2D NMR experiments (COSY, TOCSY, and HMQC). These pat-

(47) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; pp 282–315.

(48) (a) I_2O_5: Yoshida, K.; Goto, J.; Ban, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4700. (b) H_5IO_6: Dolby, L. J.; Both, D. L. *J. Am. Chem. Soc.* **1966**, *88*, 1049. (c) SeO_2: Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907. Sambasivarao, K.; Hollinshead, S.; Grubisha, D.; Laib, F.; Bennet, D.; Cook, J. M. *J. Org. Chem.* **1990**, *55*, 3858.

(49) There are few reports about the oxidation of indoles to 2-acylindoles in substrates carrying an unprotected amine function, the yields in such cases being usually low. Sakai, S.; Kubo, A.; Katsuura, K.; Mochinaga, K.; Ezaki, M. *Chem. Pharm. Bull.* **1972**, *20*, 76.

(50) (a) Cohylakis, D.; Hignett, G. J.; Lichman, K. V.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1518. (b) Besselièvre, R.; Husson, H.-P. *Tetrahedron* **1981**, *37 Suppl. No. 1*, 241.

(51) Sánchez, I. H.; López, F. J.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 7640.

(52) Catalytic debenzylation required a long reaction time and provided norisodasycarpidone (**36**) in only 41% yield, probably due to the instability of the product.

(53) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516.

(54) For a preliminary report of this part of the work, see: Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1991**, 1687.

(55) Bosch, J.; Amat, M. *An. Quím.* **1985**, *81C*, 277.

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

	C-1	C-3	C-4	C-5	C-6	C-6a	C-7a	C-8	C-9	C-10	C-11	C-11a	C-11b	C-12	CH_2	CH_3	N-C-	other
1	55.7	43.7	33.8	29.1	25.7	136.1	139.5	110.6	120.6	119.3	118.5	129.5	104.7	43.8	23.7	11.8	60.7	*c*
16[d]	50.7	50.3	41.5	28.7	24.5	135.7	136.7	110.4	120.7	119.4	118.4	128.5	106.8	34.3	22.6	11.5	60.5	*c*
18[e]	52.1	43.7	32.4	25.0	29.1	135.9	136.5	110.8	121.7	119.9	118.1	128.1	105.5	32.1			60.5	*c*
26	50.4	50.1	*f*	29.3	25.5	135.6	*f*	115.4	122.6	123.2	118.2	129.2	115.4	33.0	24.4	11.4	60.4	*c,g*
27[h]	55.4	43.6	33.6	29.2	25.4									42.2	24.2	11.7		
28	52.5	44.4	28.3	29.9	34.5	135.7	138.6	115.3	122.4	122.9	118.4	130.9	114.6	42.6	23.4	12.4	60.8	*c,g*
29	52.6	44.3	28.1	29.6	31.0	136.0	137.2	110.4	120.7	119.4	118.6	128.5	104.7	43.6	23.7	12.2	60.6	*c*
30[i]	51.1	47.1	43.9	30.3	30.9	135.5	136.5	110.3	120.7	119.5	118.4	128.1	107.0	29.2	25.7	12.7	60.6	*c*
31[i]	44.5	43.5	42.2	29.8	24.9	136.1	136.1	110.6	121.0	119.4	117.3	126.1	110.2	34.2	22.7	11.5		
32[j]	43.6	42.1	41.1	28.8	24.0	136.0	136.1	110.6	121.3	119.6	118.9	126.0	108.7	33.4	21.8	11.1	156.0	*k*
33[j]	43.8	42.4	41.2	44.7	192.5	133.2	138.6	113.0	127.9	122.7	121.7	125.1	124.5	36.3	24.3	11.2	156.1	*k*
34[j]	43.6	42.2	41.0	28.8	24.1	136.0	137.1	110.5	121.4	119.7	119.0	127.1	108.9	33.5	21.8	11.1	155.2	*l*
35[j]	43.8	42.5	41.1	44.8	192.5	133.2	138.6	112.8	128.1	122.7	121.3	125.1	124.5	36.3	24.3	11.2	156.1	*l*
36	45.7	43.7	41.4	44.8	193.2	133.6	138.7	113.0	127.0	121.1	120.9	125.9	124.3	37.5	24.7	11.3		
37[m]	52.6	51.9	41.4	44.0	192.8	133.5	138.0	112.8	126.7	121.9	121.0	126.7	121.8	38.1	24.8	11.6	44.8	
38	48.6	37.0	34.2	29.9	25.4	135.9	136.5	110.7	120.7	119.2	117.3	127.0	107.8	43.7	23.8	11.6		
39[j]	47.7	36.5	33.3	29.1	24.8	135.6	137.2	110.4	121.4	119.7	119.1	127.9	107.3	43.4	23.3	11.7	155.5	*l*
40[j]	47.9	36.4	29.8	46.3	193.1	132.4	138.9	112.9	127.4	121.1	121.9	125.3	*f*	47.7	24.6	11.5	155.5	*l*
41	49.0	37.2	30.2	49.0	193.9	132.9	139.0	113.0	127.0	120.8	121.0	125.1	123.8	47.4	25.0	11.5		
42	56.2	46.0	30.1	46.3	193.5	132.9	138.1	112.7	126.9	121.1	119.9	127.8	122.0	49.6	24.8	11.8	44.0	
43	56.0	46.1	25.3	35.4	65.1	136.4	137.1	111.0	121.8	119.7	119.4	128.7	105.0	47.3	23.2	11.8	44.2	
44[n]	55.8	46.1	29.3	39.6	67.5									43.9	22.5	13.6	44.2	
45	55.4	45.2	34.0	29.0	25.8	136.1	136.2	110.3	120.3	119.3	118.8	129.3	104.9	43.6	23.6	11.6	59.4	*o*
46	55.7	44.5	33.7	28.8	25.6	136.0	136.1	110.4	120.6	119.4	118.2	128.9	105.0	43.5	23.5	11.6	61.2	*p*
50(Z)[q]	44.3	39.5	32.5	30.1	24.8	135.8	136.3	110.9	121.7	119.9	118.6	126.7	106.5	43.0	23.1	11.6	160.3	
51	55.6	44.3	33.7	29.1	28.7	136.0	137.7	115.5	123.1	123.5	118.2	130.8	112.1	42.6	23.4	11.5	61.3	*r*
52(Z)[q]	43.4	39.5	32.4	30.2	27.6	136.0	137.6	115.5	123.5	124.3	118.7	128.4	113.1	42.0	23.0	11.5	160.5	*s*

[a] In $CDCl_3$ (50.3 MHz). [b] The systematic numbering is used in this table. [c] Phenyl ring carbons were found at 140.0 (±0.4), 128.7 (±0.3), 128.1 (±0.1), and 126.6 (±0.1). [d] Reference 40. [e] Reference 11a. [f] Not observed. [g] Boc: 150.7, 83.5, 28.3. [h] Signals of aliphatic carbons registered from a mixture of **26** and **27**. [i] Reference 15a. [j] Some signals are duplicated due to the carbamate function. [k] OMe: δ 52.5. [l] Benzyloxy carbons were found (average values) at δ 67.0, 128.7, 128.5, 127.9, and 136.2. [m] Reference 53. [n] Signals of aliphatic carbons registered from a mixture of **44** and **43**. [o] $CH(OEt)_2$: δ 102.4, 61.8, 61.2, 15.2, 15.1. [p] $CH(SMe)_2$: δ 52.9, 12.9, 12.4. [q] The (*E*) rotamer was slightly minor: signals at δ 50.7 (C-1) and 33.8 (C-3). [r] $CH(SMe)_2$: δ 53.0, 13.1, 12.5; CO_2Me: δ 152.7, 53.3. [s] CO_2Me: δ 152.7, 53.5.

terns permitted the assignment of the ^{13}C NMR data of all tetracyclic derivatives synthesized in this work (Table 2).[56] In the NMR spectra of the dasycarpidan-type compounds (**1**, **27**, **38–46**, **50–52**), the most significant feature, confirming that the ethyl substituent is equatorial with respect to the piperidine ring, was the C-14 resonance (C-4 in the systematic numbering, Table 2), which indicates the absence of a γ-effect (compare the values δ ~30 for 2-acylindoles and δ ~34 for 2-alkylindoles with δ 32.4 for the C-20-unsubstituted tetracycle **18** and with δ ~28 for the C-20 epimers **28** and **29**). A notable exception is the lower chemical shift (δ 25.3) in dasycarpidol (**43**) due to 1,3-interactions between H-14eq and the α-hydroxy substituent at C-16. The H-15/H-16 coupling constant (5.7 Hz) in the ^1H NMR spectrum of **43** corroborates the cis relationship between these protons. As could be expected, this coupling constant is lower (<1 Hz) in the C-16 epimer **44**.

On the basis of the above ^{13}C NMR data, it is possible to assign the relative configuration at C-16 in 17-hydroxy-16,17-dihydrouleine, an alkaloid[9,57] identical with the product resulting from hydroboration of uleine.[9,58] The α-disposition of the C-16-hydroxymethyl group can be inferred by comparing the chemical shift of C-14 in this alkaloid (δ 27.3)[58a] with the value (δ 33.8) for the C-16 unsubstituted tetracycle **1**.

Synthesis of the *Strychnos* Alkaloid Tubotaiwine. Our last goal was the synthesis of *Strychnos* alkaloids with the Aspidospermatan skeletal type, *e.g.* tubotaiwine, from the key tetracyclic intermediate **1**.[59] Starting from the debenzylated derivative **38**, the two main problems to overcome were the elaboration of the five-membered ring and the introduction of the C-16 methoxycarbonyl substituent.

The first problem was solved by using the methodology we had developed[15a,60] for the synthesis of *Strychnos* alkaloids of the Strychnan type, based on the closure of the pyrrolidine ring by cyclization upon the indole 3-position of a thionium ion generated by treatment of an appropriate dithioacetal with dimethyl(methylthio)-sulfonium tetrafluoroborate (DMTSF),[61] a reagent that is an excellent initiator for the chemoselective generation of thionium ions from dithioacetals.[62] The required dithioacetal **46** was prepared (57%) by alkylation of **38** with bromoacetaldehyde diethyl acetal followed by BF_3-catalyzed exchange with methanethiol and then was treated with DMTSF in a degassed acetonitrile solution to give the unstable indolenine **47** in 36% yield (Scheme 11). The use of methylene chloride as the solvent, as is usual in similar DMTSF-promoted cyclizations,[60] was less efficient (21%), probably due to the fact that indolenine **47** readily decomposed in the presence of chlorinated

(56) (a) For NMR studies on 2-acylindoles, see: Morales-Ríos, M. S.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1989**, *27*, 155. (b) For ^{13}C NMR studies on the uleine alkaloids, see: Borris, R. P.; Lankin, D. C.; Cordell, G. A. *J. Nat. Prod.* **1983**, *46*, 200.

(57) Garcia, R. F.; Brown, K. S., Jr. *Phytochemistry* **1976**, *15*, 1093.

(58) (a) Borris, R. P.; Lankin, D. C.; Cordell, G. A. *J. Nat. Prod.* **1983**, *46*, 206. (b) Blechert, S. *Liebigs Ann. Chem.* **1985**, 2073.

(59) For a preliminary report of this part of the work, see: Gràcia, J.; Bonjoch, J.; Casamitjana, N.; Amat, M.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1991**, 614.

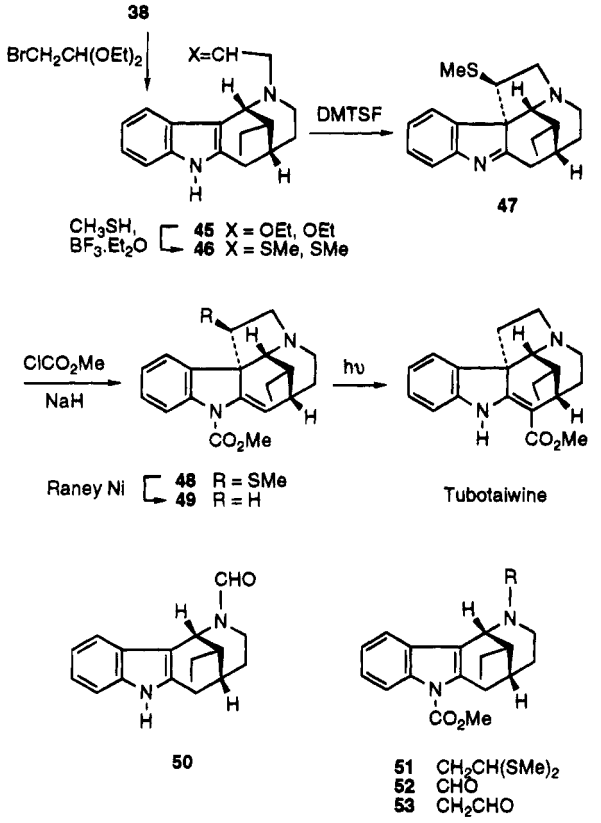
(60) Amat, M.; Alvarez, M.; Bonjoch, J.; Casamitjana, N.; Gràcia, J.; Lavilla, R.; Garcías, X.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 3453.

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

(62) (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.

(63) The tendency of *Strychnos* alkaloids, in particular tubotaiwine, to form adducts with CH_2Cl_2 has been reported: Verpoorte, R. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 5, pp 92–95. See also ref 4, p 33.

Scheme 11. Synthesis of (±)-Tubotaiwine



solvents.[63] Under these conditions significant amounts (19%) of the *N*-formyl derivative **50** were isolated. On the other hand, attempts to induce the cyclization from the N_a-protected dithioacetal **51** failed,[64] and the resulting products were the *N*-formyl derivative **52** and the aldehyde **53**. Due to its instability, the latter was characterized as the corresponding dithioacetal **51**.

The NMR data of the cyclized product **47**, in particular the chemical shifts for C-21 (δ 73.3) and C-14 (δ 34.5; absence of γ-effect), clearly indicated that an epimerization at C-20, similar to that observed in some related pentacyclic indolenines (*e.g.* condyfoline),[65] had not occurred.

The methoxycarbonyl group was first introduced on the indolenine nitrogen and then photochemically rearranged to the C-16 position, taking advantage of the resulting *N*-(methoxycarbonyl)enamine function.[66] Thus, exposure of indolenine **47** to sodium hydride and then to methyl chloroformate gave the *N*-acylated enamine **48** in 50% yield. Chemoselective hydrogenolysis (Raney nickel W-2) of the methylthio substituent of **48**, without affecting the enamine double bond, led to **49**, which was irradiated with a high-pressure mercury lamp to give the alkaloid tubotaiwine in 20% yield. This synthetic material was identified by comparison of its ^{1}H NMR spectral and TLC mobility data with those of the natural product.[67]

In summary, starting from a common tetracyclic intermediate (**1**), we have achieved stereocontrolled total syntheses of tetracyclic alkaloids of the uleine group and pentacyclic *Strychnos* alkaloids possesing the Aspidospermatan skeletal type. Two points deserve a final comment: firstly, the usefulness of 2-cyanopiperidines as synthetic equivalents of iminium ions, allowing the stereochemistry of the α-substituent to be controlled in either Mannich- or Pictet–Spengler-type cyclizations, and secondly, the general character of the synthetic strategy that we had previously developed for the synthesis of pentacyclic *Strychnos* alkaloids with the Strychnan skeletal type, based on the closure of the pyrrolidine ring by formation of the crucial quaternary C-7 center from an appropriate tetracyclic system.

Experimental Section

General. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 200 and 50.3 MHz, respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, and coupling constants are expressed in hertz. Only noteworthy IR absorptions (cm^{-1}) are listed. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–400-mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

Ethyl 1-Benzyl-3-ethyl-4-piperidineacetate (*cis*-2 and *trans*-2). These compounds were prepared from commercially available ethyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (65 g) by the published procedure.[16] Chromatography (gradient of EtOAc–hexane, 15:85 to 30:70) gave 29.1 g (45%) of *cis*-**2**[68] and 8.2 g (13%) of *trans*-**2**.

4-Acetonyl-1-benzyl-3-ethylpiperidines (*cis*-3 and *trans*-3) were prepared in separated runs from *cis*-**2** and *trans*-**2** on a 35-mmol scale in 80% and 78% yields, respectively, by the published procedure.[16]

***t*-4-Acetonyl-1-benzyl-*t*-5-ethyl-*r*-2-piperidinecarbonitrile (4) and *t*-4-Acetonyl-1-benzyl-*c*-3-ethyl-*r*-2-piperidinecarbonitrile (5).** A solution of *m*-chloroperbenzoic acid (85%, 1.72 g, 8.5 mmol) in anhydrous CH_2Cl_2 (32 mL) was slowly added to a stirred solution of *cis*-**3** (2.0 g, 7.7 mmol) in anhydrous CH_2Cl_2 (26 mL) kept at 0 °C. The mixture was stirred at 0 °C for 1 h and then cooled to −15 °C. TFAA (3.8 mL, 27.0 mmol) was added dropwise to the resulting solution, and stirring was continued at −15 °C for 1 h and at room temperature for 15 min. A solution of KCN (1.5 g, 23.1 mmol) in water (12 mL) was then added, and the pH was adjusted to 5 by addition of solid NaOAc. After being vigorously stirred for 30 min at room temperature, the two-phase mixture was basified with 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were washed twice with water, dried, and evaporated to give an oil which was purified by chromatography. Elution with 7:3 hexane–EtOAc afforded 2-cyan-

(64) For a related cyclization upon a deactivated indole ring, see: Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792.

(65) Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 1996.

(66) Wenkert, E.; Porter, B.; Simmons, D. P. *J. Org. Chem.* **1984**, *49*, 3733.

(67) (a) Lounasmaa, M.; Koskinen, A.; O'Connell, J. *Helv. Chim. Acta* **1986**, *69*, 1343. (b) Schripsema, J.; Van Beek, T. A.; Verpoorte, R.; Erkelens, C.; Perera, P.; Tibell, C. *J. Nat. Prod.* **1987**, *50*, 89.

(68) The synthetically equivalent methyl ester was prepared, but in lower overall yields, from methyl 3-ethyl-4-pyridineacetate[69] by two alternative routes: (a) H_2, PtO_2, MeOH, HCl, 400 psi, 54 h, 58%[70] and then $BrCH_2C_6H_5$ (1.2 equiv), K_2CO_3, C_6H_6, reflux, overnight, 64%. (b) $BrCH_2C_6H_5$, acetone, rt, 4 h, 73%[71] and then H_2, PtO_2, AcOH, 42%.

(69) Uskoković, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571.

(70) Methyl *cis*-3-ethyl-4-piperidineacetate:[69] ^{13}C NMR δ 11.9 (br), 19.6 (br), 29.2, 35.0 (br), 35.5 (br), 40.2, 44.6, 47.9, 51.5, 173.7. Minor quantities (5%) of the trans isomer were also isolated: ^{13}C NMR δ 10.6, 23.4, 31.6, 37.1, 38.3, 41.8, 45.6, 49.9, 51.5, 173.5.

(71) (*E*)-1-Benzyl-3-ethyl-4-[(methoxycarbonyl)methylene]-1,4-dihydropyridine: mp 101–102 °C (Et_2O–acetone); IR (film) 1660, 1615; ^{1}H NMR δ 1.14 (t, J = 7.5, 3 H), 2.26 (qd, J = 7.5, 1, 2 H), 3.66 (s, 3 H), 4.78 (s, 2 H), 6.71 (m, 1 H), 6.84 (ddd, J = 8, 2, 1, 1 H), 7.1–7.4 (m, 5 H), 7.34 (d, J = 1, 1H), 7.99 (d, J = 8, 1 H); ^{13}C NMR δ 11.8, 23.6, 49.9, 59.4, 84.0, 111.1, 125.8, 127.2, 128.5, 129.2, 131.8, 134.1, 136.0, 148.6, 169.5. Anal. Calcd for $C_{17}H_{19}NO_2 \cdot 1/4C_3H_6O$: C, 75.10; H, 7.28; N, 4.93. Found: C, 75.21; H, 7.15; N, 5.05.

opiperidine **4** (1.03 g, 47%) as a white solid and 2-cyanopiperidine **5** (0.68 g, 31%) as a pale yellow oil.

Compound **4**: mp 68–69 °C (hexane); IR ($CHCl_3$) 2220 (weak), 1710; ^1H NMR δ 0.77 (t, J = 7, 3 H), 1.20 (m, 1H), 1.45–1.70 (m, 4 H), 2.14 (s, 3 H), 2.20–2.52 (m, 3 H), 2.50 (dd, J = 12.5, 2.5, 1 H), 2.79 (dq, J = 12.5, 2.5, 0.5, 1 H), 3.55 and 3.65 (2d, J = 13, 2 H), 3.78 (apparent t, J = 3.5, 1 H), 7.25–7.35 (m, 5 H);^{13}C NMR, Table 1; MS *m/z* 284 (5, M^+), 283, 193, 135, 92, 91 (100), 65. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.90; H, 8.18; N, 9.54.

Compound **5**: IR ($CHCl_3$) 1710; ^1H NMR δ 0.83 (t, J = 7.5, 3 H), 1.20–1.60 (m, 4 H), 1.70 (dddd, J = 12, 5, 5, 3, 1 H), 1.9 (m, 1 H), 2.14 (s, 3 H), 2.19 (dd, J = 16.5, 8.5, 1 H), 2.45 (td, J = 12, 3, 1 H), 2.66 (dd, J = 16.5, 3.5, 1H), 2.78 (dm, J = 12, 1 H), 3.61 and 3.70 (2d, J = 13, 2 H), 3.86 (dd, J = 4, 0.5, 1 H), 7.25–7.35 (m, 5 H); ^{13}C NMR, Table 1; MS *m/z* 284 (2, M^+), 283, 193, 135, 92, 91 (100), 65. Anal. Calcd for $C_{18}H_{24}N_2O \cdot {}^1/_4C_4H_8O_2$: C, 74.47; H, 8.55; N, 9.14. Found: C, 74.45; H, 8.40; N, 9.16.

In some runs a less polar isomer, ***t*-4-acetonyl-1-benzyl-*t*-3-ethyl-*r*-2-piperidinecarbonitrile (6)**, was isolated in *ca.* 1% yield. For the ^{13}C NMR data, see Table 1.

***t*-4-Acetonyl-1-benzyl-*c*-5-ethyl-*r*-2-piperidinecarbonitrile (7).** Following the same procedure, *trans*-**3** (1.57 g, 6.1 mmol) was converted to a 5:3 mixture (1.21 g, 71%) of cyanopiperidines **7** and **5**, which could not be separated by flash chromatography. Compound **7**: ^1H NMR (taken from a mixture) δ 0.87 (t, J = 7, 3 H), 1.1–2.0 (m, 6 H), 2.14 (s, 3 H), 2.16 (dd, J = 16, 8.5, 1H), 2.2 (masked, 1 H), 2.69 (dd, J = 16, 3.5, 1H), 2.92 (dq, J = 12, 4, 1, 1 H), 3.53 and 3.73 (2d, J = 13, 2 H), 3.71 (deformed t, J = 3, 1 H), 7.25–7.35 (m, 5 H); ^{13}C NMR, Table 1.

(1*RS*,4*RS*,5*SR*)-2-Benzyl-4-ethyl-2-azabicyclo[3.3.1]-nonan-7-one (8). A solution of 2-cyanopiperidine **4** (0.79 g, 2.8 mmol) in MeOH (18 mL) containing 12 N aqueous HCl (2 mL) was refluxed for 40 h. The solvent was evaporated, and the resulting residue was basified with 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. Evaporation of the dried organic extracts followed by chromatography (1:2 petroleum ether–Et_2O) gave ketone **8** (0.49 g, 69%) as a pale yellow oil: IR ($CHCl_3$) 1690; ^1H NMR δ 0.85 (t, J = 7, 3 H), 1.22 (qn, J = 7.5, 2 H), 1.78 (m, $W_{1/2}$ = 18, 1 H), 1.95 (t, J = 12.5, 1 H), 2.00 (m, 2H), 2.11 (dd, J = 17, 5, 1 H), 2.32 (m, 1 H), 2.32 (dd, J = 17, 5, 1 H), 2.57 (dm, J = 17, 1 H), 2.60 (dd, J = 12.5, 4.5, 1 H), 2.88 (dq, J = 17, 4, 2, 1 H), 3.30 (m, 1 H), 3.57 and 3.65 (2d, J = 14, 2 H), 7.25–7.33 (m, 5 H); ^{13}C NMR δ 11.3, 23.9, 32.2, 34.2, 40.5, 40.9, 41.9, 51.2, 53.9, 59.1, 126.9, 128.3, 128.6, 138.8, 211.5; MS *m/z* 257 (21, M^+), 214, 200, 92, 91 (100), 65. The picrate melted at 143–144 °C (Et_2O). Anal. Calcd for $C_{17}H_{23}NO \cdot C_6H_3N_3O_7$: C, 56.79; H, 5.39; N, 11.52. Found: C, 56.74; H, 5.46; N, 11.74.

(1*RS*,5*SR*,9*RS*)-2-Benzyl-9-ethyl-2-azabicyclo[3.3.1]-nonan-7-one (9). 2-Cyanopiperidine **5** (440 mg, 1.5 mmol) was cyclized as above. The crude product was chromatographed (2:1 petroleum ether–Et_2O) to afford ketone **9** (270 mg, 68%) as a yellow solid: mp 88–89 °C (Et_2O); IR (KBr) 1700; ^1H NMR δ 0.97 (t, J = 7, 3 H), 1.48 (qn, J = 7.5, 2 H), 1.60 (dm, J = 13.5, 1 H), 1.8–2.2 (m, 2 H), 2.16 (dd, J = 17.5, 5.5, 1 H), 2.22–2.40 (m, 3 H), 2.56 (dd, J = 17.5, 6, 1 H), 2.60 (m, 1 H), 2.74 (dm, J = 17.5, 1 H), 3.15 (m, $W_{1/2}$ = 10, 1 H), 3.57 and 3.67 (2d, J = 14, 2 H), 7.26–7.32 (m, 5 H); ^{13}C NMR δ 11.7, 23.9, 31.8, 32.7, 35.9, 42.4, 42.6, 44.3, 58.0, 59.4, 126.9, 128.2, 128.5, 139.3, 211.7; MS *m/z* 257 (7, M^+), 214, 200, 92, 91 (100), 65. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.34; H, 9.01; N, 5.44. Found: C, 78.99; H, 9.17; N, 5.21.

(1*RS*,4*SR*,5*SR*)-2-Benzyl-4-ethyl-2-azabicyclo[3.3.1]-nonan-7-one (10). Operating as above, the mixture of 2-cyanopiperidines **5** and **7** (1.22 g, 4.29 mmol) afforded, after purification by chromatography (3:1 petroleum ether–Et_2O), **10** (375 mg, 34%) and **9** (303 mg, 27%). Compound **10**: IR ($CHCl_3$) 1690; ^1H NMR δ 0.82 (t, J = 7, 3 H), 1.35 (m, 1 H), 1.50 (qn, J = 7, 2 H), 1.65–1.80 (m, 2 H), 2.09 (dd, J = 17, 5, 1 H), 2.20–2.30 (m, 2 H), 2.39 (dd, J = 12.5, 3.5, 1 H), 2.44 (dq, J = 17, 4, 2, 1 H), 2.57 (dd, J = 17, 5, 1 H), 2.89 (dq, J = 17, 4, 2, 1 H), 3.28 (m, $W_{1/2}$ = 10, 1 H), 3.49 and 3.63 (2d, J = 13.5, 2 H), 7.27–7.32 (m, 5 H); ^{13}C NMR δ 12.4, 25.4, 28.7, 33.1, 40.1, 41.9, 47.3, 48.5, 54.6, 59.5, 126.8, 128.2, 128.3, 139.3, 211.6; MS *m/z* 257 (21, M^+), 214, 200, 92, 91 (100), 65. Anal. Calcd for $C_{17}H_{23}NO$: C, 79.34; H, 9.01; N, 5.44. Found: C, 79.07; H, 8.92; N, 5.26.

***t*-4-Acetonyl-1-benzyl-*t*-3-ethylpiperidine *r*-1-Oxide (11).** A solution of *m*-CPBA (2.66 g, 85%, 13.1 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a solution of piperidine *cis*-**3** (3.11 g, 12.0 mmol) in CH_2Cl_2 (30 mL). After the mixture was stirred at 0 °C for 1 h and at room temperature for 15 min, an excess of solid K_2CO_3 was added. The mixture was stirred at room temperature for an additional 15 min and filtered through Celite. The solid material was thoroughly washed with CH_2Cl_2. The combined organic solutions were concentrated, and the residue was chromatographed on alumina (1–2% MeOH in CH_2Cl_2). Pure *N*-oxide **11** (2.4 g, 74%) was obtained as a solid: mp 89–90 °C (Et_2O–acetone); IR (KBr) 1700; ^1H NMR δ 0.91 (t, J = 7.5, 3 H), 1.17 (qn, J = 7.5, 2 H), 1.46 (dq, J = 14.5, 1 H), 2.15 (s, 3 H), 2.12–3.38 (m, 9 H), 4.40 (s, 2 H), 7.39–7.55 (m, 5 H); ^{13}C NMR δ 11.1, 22.8, 24.0, 27.7, 30.2, 34.6, 38.4, 58.6, 64.1, 76.0, 128.5, 129.4, 129.7, 132.5, 132.7, 207.8. Anal. Calcd for $C_{17}H_{25}NO_2 \cdot H_2O$: C, 69.59; H, 9.28; N, 4.77. Found: C, 70.02; H, 9.54; N, 4.73.

Polonovski–Potier Reaction from Piperidine *N*-Oxide 11. TFAA (3.0 mL, 21.1 mmol) was added dropwise to a solution of **11** (1.66 g, 6.0 mmol) in CH_2Cl_2 (30 mL) maintained at −15 °C under an N_2 atmosphere. After the mixture was stirred at −15 °C for 1 h and at room temperature for 15 min, MeOH (18 mL) containing 2 mL of concd HCl was added, and CH_2Cl_2 was removed. Additional MeOH (18 mL) containing 2 mL of concd HCl was added, and the resulting solution was refluxed for 24 h. The solvent was evaporated, and the resulting residue was basified with 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. Evaporation of the dried extracts left an oil which was chromatographed (2:1 to 1:1 petroleum ether–Et_2O) to give 60 mg (4%) of **(1*RS*,5*SR*,9*SR*)-2-benzyl-9-ethyl-2-azabicyclo[3.3.1]nonan-7-one (12),** 0.21 g (14%) of **9**, and 0.40 g (26%) of **8**. Compound **12**: ^1H NMR δ 0.89 (t, J = 7.5, 3 H), 1.34 (dm, J = 13, 1 H), 1.6–2.0 (m, 3 H), 2.06 (dd, J = 17, 5, 1 H), 2.10 (m, 1 H), 2.19 (m, 1 H), 2.30 (td, J = 13, 3.5, 1 H), 2.5 (m, 2 H), 2.58 (dd, J = 13, 5.5, 1 H), 2.92 (dm, J =17, 1 H), 3.10 (m, 1 H), 3.56 (s, 2 H), 7.20–7.32 (m, 5 H); ^{13}C NMR δ 12.2, 23.3, 26.4, 32.2, 40.4, 43.1, 44.6, 48.4, 55.9, 59.5, 126.9, 128.2, 128.5, 139.2, 212.8. Anal. Calcd for $C_{17}H_{23}NO \cdot {}^1/_4H_2O$: C, 77.97; H, 9.04; N, 5.35. Found: C, 78.38; H, 9.28; N, 5.41.

Epimerization of 12 to Morphan 9. A solution of **12** (8 mg) in 15 mL of 12 N aqueous HCl–MeOH (1:9) was refluxed for 24 h under N_2. After the usual workup, only morphan **9** was detected by TLC (3:1 petroleum ether–Et_2O).

2-Benzyl-2-azabicyclo[3.3.1]nonan-7-one (14). Operating as in the preparation of the above 2-cyanopiperidines, 4-acetonyl-1-benzylpiperidine[18a] (4.0 g, 17.3 mmol) was converted to ***trans*-4-acetonyl-1-benzyl-2-piperidinecarbonitrile (13**; 3.32 g, 75%): IR (film) 2220, 1715; ^1H NMR δ 1.27 (qd, J = 12, 4.5, 1 H), 1.48 (td, J = 12, 4.5, 1 H), 1.76 (dm, J = 12, 1 H), 1.90 (dm, J = 12, 1 H), 2.05–2.15 (m, 1 H), 2.14 (s, 3 H), 2.37 (d, J = 7.5, 2 H), 2.50 (td, J = 12, 3, 1 H), 2.84 (dm, J = 12, 1 H), 3.55 and 3.71 (2d, J = 13, 2 H), 3.76 (deformed t, J = 4, 1 H), 7.33 (s, 5 H); ^{13}C NMR, Table 1. Cyanopiperidine **13** was cyclized according to the foregoing procedure on a 6.8-mmol scale to provide azabicyclo **14**[18b] (1.4 g, 89%).

General Procedures for the Fischer Indolization of Ketones 8, 9, and 14. Method A. A mixture of ketone **9** (560 mg, 2.2 mmol) and freshly distilled phenylhydrazine (0.24 mL, 2.4 mmol) in absolute EtOH (8 mL) was refluxed under N_2 for 2 h. A solution of the resulting phenylhydrazone (389 mg, 1.1 mmol) in glacial AcOH (7 mL) was heated at 90–95 °C for 50 min. The mixture was cooled, poured into ice–water (40 mL), basified with 50% aqueous NaOH, and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by chromatography (EtOAc) gave **1** (96 mg, 26%). For analytical data *vide infra*. The same procedure was employed for the indolization of ketones **8** and **14**, with the results showed in Scheme 6.

Method B. A mixture of ketone **8** (560 mg, 2.2 mmol) and freshly distilled phenylhydrazine (0.24 mL, 2.4 mmol) in

absolute EtOH (8 mL) was refluxed under N_2 until the disappearance of **8** (IR). This required the addition of more $C_6H_5NHNH_2$ (0.12 mL) and 20 h of reaction. The resulting phenylhydrazone (280 mg, 0.8 mmol) was dissolved in a 2.5 N EtOH solution of dry HCl (1.75 mL) and refluxed for 3 h. The solvent was evaporated, NH_4OH was added to the residue, and the mixture was extracted with Et_2O. After the usual workup and chromatography, tetracycle **17** (150 mg, 57%) was obtained. The same procedure was employed for the indolization of ketones **9** and **14**, with the results shown in Scheme 6.

Method C. A mixture of ketone **14** (1.4 g, 6.1 mmol) and phenylhydrazine (0.66 mL, 6.7 mmol) in absolute EtOH (20 mL) was refluxed under N_2 until the disappearance of the starting ketone (TLC, IR). This required the addition of more $C_6H_5NHNH_2$ (0.3 mL) and 20 h of reaction. After the solvent was removed, an excess of PPA was added to the crude phenylhydrazone (660 mg, 2.1 mmol), and the mixture was mechanically stirred under N_2 at 90 °C for 30 min, poured into crushed ice, basified with NH_4OH, and extracted with CH_2Cl_2. Evaporation of the dried extracts gave a syrup which was chromatographed. Elution with 1:1 hexane–EtOAc left **19** (110 mg, 18%), whereas elution with 2% EtOH in EtOAc gave **18**[11a] (76 mg, 12%). The same procedure was employed for the indolization of ketones **8** and **9**, with the results shown in Scheme 6.

Compound **15**: ^{1}H NMR δ 0.88 (t, J = 7.5, 3 H), 1.22 (qn, J = 7.5, 2 H), 1.6 (m, 1 H), 1.9–2.1 (m, 2 H), 2.20 (td, J = 12, 3, 1 H), 2.47 (dm, J = 12, 1 H), 2.56 (dd, J = 18, 6, 1 H), 3.00 (d, J = 18, 1 H), 3.19 (m, 1 H), 3.28 (m, 1 H), 3.63 and 3.75 (2d, J = 13, 2 H), 7.1–7.4 (m, 9 H), 7.8 (br s, 1 H).

Compound **17**: ^{1}H NMR δ 0.92 (t, J = 7, 3 H), 1.30 (m, 2 H), 1.81 (dt, J = 12 and 3, 1 H), 1.94–1.98 (m, 2 H), 2.16 (dt, J = 12, 3, 1 H), 2.54 (d, J = 8, 1 H), 2.59 (dd, J = 18, 6, 1 H), 3.06 (d, J = 18, 1 H), 3.24 (m, 1 H), 3.34 (m, 1 H), 3.66 and 3.73 (2d, J = 13, 2 H), 7.05–7.45 (m, 9 H), 7.9 (br s, 1 H).

3-Benzyl-1,2,3,4,5,6-hexahydro-2,6-methanoazocino-[4,5-*b*]indole (19): ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.58 (dm, J = 12, 1 H), 1.83 (dq, J = 12, 3, 1 H), 2.04 (tt, J = 12, 3, 1 H), 2.20 (dt, J = 12, 3, 1 H), 2.29 (td, J = 12, 3 , 1 H), 2.52 (dm, J = 12, 1 H), 2.67 (dd, J = 18, 6, 1 H), 3.10 (d, J = 18, 1 H), 3.36 (m, 2 H), 3.70 (s, 2 H), 7.1–7.4 (m, 10 H); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 21.1, 24.6, 29.6, 32.6, 44.6, 51.0, 59.4, 110.6, 112.9, 117.4, 119.0, 120.8, 126.3, 127.2, 128.4, 129.3, 133.9, 136.0, 138.0. Anal. Calcd for $C_{21}H_{22}N_2 \cdot 1/2H_2O$: C, 81.03; H, 7.39; N, 9.00. Found: C, 80.73; H, 7.15; N, 8.88.

2-[(*cis*-1-Benzyl-3-ethyl-4-piperidyl)methyl]indole (*cis*-20) was prepared from ester *cis*-**2** on a 12-mmol scale in 63% yield by the published procedure.[40]

2-[(*trans*-1-Benzyl-3-ethyl-4-piperidyl)methyl]indole (*trans*-20). Phenylhydrazine hydrochloride (4.54 g, 47.1 mmol) and anhydrous Na_2CO_3 (1.73 g, 14.4 mmol) were added to a stirred solution of ketone *trans*-**3** (7.41 g, 28.6 mmol) in absolute EtOH (185 mL). The resulting mixture was refluxed for 8 h and cooled. The solvent was then evaporated, and the residue was partitioned between H_2O and CH_2Cl_2. Evaporation of the dried organic extracts gave crude phenylhydrazone (9.6 g). To this material was added a solution of P_2O_5 in $MeSO_3H$[72] (1:10; 96 g), and the mixture was stirred for 4 days at room temperature, diluted with CH_2Cl_2, and basified with saturated aqueous $NaHCO_3$. The residue obtained after the usual workup was chromatographed (1:1 hexane–EtOAc) to give 1.61 g (19%) of **2-(*trans*-1-benzyl-3-ethyl-4-piperidyl)-3-methylindole (54)** and 3.24 g (37%) of *trans*-**20**.

Compound *trans*-**20**: ^{1}H NMR δ 0.84 (t, J = 7, 3 H), 1.05–1.90 (m, 7 H), 2.36 (dd, J = 12, 8, 1 H), 2.76 (d, J = 12, 1 H), 2.93 (d, J = 10, 1 H), 3.03 (d, J = 16, 2 H), 3.42 and 3.52 (2d, J = 13, 2 H), 6.16 (s, 1 H), 6.9–7.5 (m, 9 H), 8.50 (br s, 1 H); ^{13}C NMR δ 10.8, 23.7, 31.0, 31.8, 40.2, 41.5, 53.3, 58.2, 63.3, 100.7, 110.4, 119.6, 119.7, 121.0, 127.1, 128.3, 129.3, 135.9, 138.2, 138.3. Anal. Calcd for $C_{23}H_{28}N_2 \cdot H_2O$: C, 78.85; H, 8.57; N, 8.00. Found: C, 78.91; H, 8.59; N, 7.74.

Compound **54**: ^{1}H NMR δ 0.68 (t, J = 7, 3 H), 2.28 (s, 3 H), 3.06 (d, J = 10, 1 H), 3.26 (d, J = 10, 1 H), 3.59 and 3.75 (2d, J = 13, 2 H), 6.85–7.75 (m, 9 H), 8.08 (br s, 1 H); ^{13}C NMR: δ 11.1, 12.0, 24.7, 31.9, 39.8, 40.8, 54.2, 59.6, 63.5, 110.2, 118.5, 119.5, 120.3, 127.0, 128.9, 128.1, 129.4, 130.7, 135.2, 137.0, 138.5.

2-[(*cis*-1-Benzyl-3-ethyl-4-piperidyl)methyl]-1-(*tert*-butoxycarbonyl)indole (*cis*-21). A 50% aqueous NaOH solution (16 mL) was added to a suspension of indole *cis*-**20** (2.30 g, 6.9 mmol) and tetrabutylammonium hydrogen sulfate (0.69 g) in toluene (30 mL). The resulting two-phase mixture was vigorously stirred at room temperature until a remarkable increase of viscosity was observed (5 min approximately). Then, a solution of $(Boc)_2O$ (3.02 g, 13.8 mmol) in toluene (15 mL) was added dropwise (15 min). After the mixture was stirred for an additional 10 min, the organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried, and evaporated to give crude carbamate *cis*-**21** (2.71 g, 91%) as a yellow oil which was used in the next step without further purification. An analytical sample was obtained after chromatography (70:30:0.3 hexane–Et_2O–diethylamine):[73] IR ($CHCl_3$) 1720; ^{1}H NMR δ 0.81 (t, 3 H), 1.68 (s, 9 H), 2.88 (dd, J = 15, 8.5, 1 H,), 3.06 (dd, J = 15, 5.5, 1 H), 3.37 and 3.53 (2d, J = 13, 2 H), 6.31 (s, 1 H), 7.15–7.46 (m, 8 H), 8.05 (dm, 1 H); ^{13}C NMR δ 12.2, 19.1, 27.7, 28.3, 31.7, 38.7, 40.2, 53.8, 55.8, 63.3, 83.6, 108.3, 115.4, 119.6, 122.5, 123.1, 126.7, 128.0, 128.9, 129.2, 136.8, 139.2, 140.6, 151.5; MS *m/z* 433 (4, M^+), 215, 214, 200, 199, 187, 186, 185, 172, 159, 145, 130, 124, 120, 118, 110, 92, 91 (100). Anal. Calcd for $C_{28}H_{36}N_2O_2$: C, 77.74; H, 8.39; N, 6.49. Found: C, 77.69; H, 8.59; N, 6.32.

Modified Polonovski Reaction from *cis*-21. Operating as in the preparation of nitriles **4** and **5**,[74] from crude carbamate *cis*-**21** (2.71 g, 6.3 mmol) was obtained a 3:3:2 mixture of 2-cyanopiperidines **23**, **24a**, and **24b** (2.32 g, 81%) as a white foam after a short column chromatography (75:25:0.3 hexane–EtOAc–diethylamine). Individual ratios were calculated from the integration of the CH_2CH_3 protons on the ^{1}H NMR (400 MHz) spectrum of the mixture. Pure samples of **24b** and **24a** were obtained from the first and last fractions, respectively, of an additional chromatography (5% EtOAc in hexane).

2-[(1-Benzyl-*r*-2-cyano-*t*-5-ethyl-*t*-4-piperidyl)methyl]-1-(*tert*-butoxycarbonyl)indole (23): ^{1}H NMR δ 0.79 (t, J = 7, 3 H), 3.60 (s, 2 H), 3.81 (deformed t, 1 H), 6.34 (s, 1 H); ^{13}C NMR, Table 1.

2-[(1-Benzyl-*r*-2-cyano-*c*-3-ethyl-*t*-4-piperidyl)methyl]-1-(*tert*-butoxycarbonyl)indole (24a): ^{1}H NMR δ 0.89 (t, 3 H), 1.70 (s, 9 H), 2.34 (t, J = 12, 1 H), 2.51 (dd, J = 14.5, 10, 1 H), 2.75 (dm, J = 12, 1 H), 3.61 and 3.69 (2d, J = 13.5, 2 H), 3.90 (d, J = 3.5, 1 H), 6.34 (s, 1 H), 7.17–7.46 (m, 8 H), 8.00 (dm, 1 H); ^{13}C NMR, Table 1.

2-[(1-Benzyl-*r*-2-cyano-*t*-3-ethyl-*t*-4-piperidyl)methyl]-1-(*tert*-butoxycarbonyl)indole (24b): ^{1}H NMR δ 0.67 (t, J = 7, 3 H), 1.70 (s, 9 H), 2.83 (dm, J = 12, 1 H), 2.86 (dd, J = 15, 8, 1 H), 3.12 (dd, J = 15, 6, 1 H), 3.47 and 3.71 (2d, J = 13.5, 2 H), 3.70 (br s, 1 H), 6.33 (s, 1 H), 7.17–7.50 (m, 8 H), 8.07 (dm, 1 H); ^{13}C NMR, Table 1.

In some runs, when using *m*-CPBA of lower concentration, *N*-oxide *cis*-**22** was isolated by column chromatography (1:1 CH_2Cl_2–MeOH): ^{1}H NMR δ 0.98 (t, J = 7, 3 H), 1.2–1.5 (m, 2 H), 1.46 (dm, J = 14.5, 1 H), 1.68 (s, 9 H), 2.30–3.45 (m, 9 H), 4.52 (s, 2 H), 6.28 (s, 1 H), 7.2–8.0 (m, 9 H); ^{13}C NMR δ 11.2, 22.7, 23.5, 28.2, 30.9, 35.2, 58.8, 63.8, 76.2, 83.9, 108.6, 115.4, 119.7, 122.7, 123.4, 128.5, 128.9, 129.6, 132.6, 136.0, 140.0, 150.2.

(1*RS*,5*RS*,12*SR*)-2-Benzyl-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (1). A vigorously stirred solution of the mixture of cyanopiperidines **23**, **24a**, and **24b** (2.5 g, 7.5 mmol) in dioxane (20 mL)[44] was heated at 90 °C. Then AcOH (60 mL) and H_2O (20 mL) were added, and the

(72) Zhao, D.; Hughes, D. L.; Bender, D. R.; DeMarco, A. M.; Reider, P. J. *J. Org. Chem.* **1991**, *56*, 3001.

(73) Partial deprotection was observed regardless of the adsorbent material–eluent combination used.

(74) A *m*-CPBA of 95% purity was used in this case. It was obtained by purification of commercial 55% pure *m*-CPBA, following the methodology described: Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

mixture was stirred at 90 °C for 14 h. The resulting mixture was cooled with an ice bath, basified with 25% aqueous NaOH, and extracted with $CHCl_3$. The organic extracts were washed with brine, dried, and evaporated to give a yellow foam which was chromatographed. Elution with 9:1 hexane–EtOAc gave **29** (80 mg, 4%) as a pale yellow foam. Elution with a gradient from 7:3 hexane–EtOAc to 2% diethylamine in EtOAc gave **16**[15a] (0.47 g, 26%) and then **1** (0.83 g, 46%) as pale yellow foams.

Compound **1**: IR ($CHCl_3$) 3450; ^1H NMR (500 MHz) δ 0.88 (t, J = 7.5, 3 H), 1.14 and 1.17 (2m, 1 H each), 1.61 (dq, J = 12, 2.5 1 H), 1.95 (tt, J = 12, 3, 1 H), 2.06 (td, J = 12, 3, 1 H), 2.19 (m, 1 H), 2.26 (m, 1 H), 2.43 (dm, J = 12, 1 H), 2.52 (d, J = 17.5, 1 H), 2.97 (dd, J = 17.5, 7, 1 H), 3.23 and 3.97 (2d, J = 13.5, 1H each), 4.21 (br s, 1 H), 7.08 (t, J = 8, 1 H), 7.13 (t, J = 8, 1 H), 7.23 (t, J = 7, 1 H), 7.29 (d, J = 7, 1 H), 7.32 (d, J = 7, 1 H), 7.37 (d, J = 8, 1 H), 7.95 (br s, 1 H); ^{13}C NMR, Table 2; MS *m/z* 330 (7, M^+), 239, 198, 197, 196, 169, 168, 167, 107, 106, 91 (100). The hydrochloride melted at 246–247 °C (MeOH). Anal. Calcd for $C_{23}H_{27}ClN_2 \cdot CH_3OH$: C, 72.25; H, 7.83; N, 7.02. Found: C, 72.52; H, 7.46; N, 7.32.

Compound **29**: IR ($CHCl_3$) 3450; ^1H NMR δ 1.01 (t, J = 7, 3 H), 1.1–1.4 (m, 2 H), 1.6–1.9 (m, 2 H), 2.0–2.4 (m, 4 H), 2.69 (d, J = 17, 1 H), 3.08 (dd, J = 17, 7, 1 H), 3.22 and 3.83 (2d, J = 14, 2 H), 4.06 (br s, 1 H), 7.0–7.5 (m, 9 H), 7.87 (br s, 1 H); ^{13}C NMR, Table 2.

In some runs, when the reaction time was shortened, the *N*-Boc derivatives **26**, **27**, and **28** were detected in the NMR spectrum of the reaction mixture. See Table 2 for the ^{13}C NMR data.

Tetracycle 1 from Piperidine *trans*-20. Operating as in the above cis series, piperidine *trans*-**20** (1.55 g, 4.6 mmol) was converted into a 5:4 mixture of 2-cyanopiperidines **24a** and **25** by way of the *N*-Boc derivative *trans*-**21** and *N*-oxide *trans*-**22**. This mixture was purified by flash chromatography on alumina (1:1 hexane–EtOAc) and then cyclized as described above. Column chromatography (EtOAc) gave tetracycles **30**[15a] (195 mg, 13% from *trans*-**20**) and **1** (248 mg, 16%, from *trans*-**20**).

Compound *trans*-**21**: IR (film) 1733; ^1H NMR δ 0.89 (t, J =7, 3 H), 1.69 (s, 9 H), 2.91 (dm, J = 11, 1 H), 3.46 and 3,52 (2d, J = 13, 2 H), 3.4–3.7 (masked, 2 H), 6.33 (s, 1 H), 7.0–7.5 (m, 8 H), 8.02 (dm, 1 H); ^{13}C NMR δ 11.2, 23.8, 28.1, 30.7, 33.2, 38.6, 42.5, 53.2, 58.2, 63.4, 83.4, 108.5, 115.3, 119.5, 122.4, 122.9, 126.7, 128.0, 128.9, 129.1, 136.4, 138.4, 140.7, 150.2.

Compound *trans*-**22**: ^1H NMR δ 0.90 (t, J = 7, 3 H), 1.67 (s, 9 H), 3.92 (dm, J = 11, 1 H), 4.85 and 4.91 (2d, J = 12.5, 2 H), 6.33 (s, 1 H), 7.2–8.1 (m, 9 H); ^{13}C NMR δ 10.9, 22.2, 25.3, 28.1, 32.9, 36.8, 37.1, 62.1, 66.0, 74.1, 83.9, 109.5, 115.4, 119.8, 122.6, 123.3, 127.6, 128.6, 129.1, 132.7, 136.1, 137.7, 139.1, 150.2.

Compound **25**: ^{13}C NMR, Table 1.

(1*RS*,4*RS*,5*SR*)-4-Ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (31) was prepared from the benzyl derivative **16** by the published procedure[15a]: ^{13}C NMR, Table 2.

(1*RS*,4*RS*,5*SR*)-4-Ethyl-2-(methoxycarbonyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (32). A solution of methyl chloroformate (0.08 mL, 1 mmol) in $CHCl_3$ (4 mL) was added dropwise to a stirred mixture of amine **31** (160 mg, 0.67 mmol), anhydrous K_2CO_3 (230 mg), and $CHCl_3$ (12 mL). After the mixture was stirred for 90 min, H_2O (5 mL) was added and the stirring was maintained for additional 20 min. The layers were separated, and the aqueous phase was extracted with $CHCl_3$. Evaporation of the dried extract followed by chromatograhy (Et_2O) afforded carbamate **32** (150 mg, 75%) as a solid: IR ($CHCl_3$) 3469, 1679; ^1H NMR δ 0,95 (t, J = 7, 3 H), 1.30 (sext, J = 7, 2 H), 1.6–1.8 (m, 4 H), 1.8–2.1 (m, 2 H), 2.2–2.4 (m, 2 H), 2.80 (m, 2 H), 3.66 and 3.85 (2 s, 1.5 H each, two rotamers), 3.7–3.8 (masked, 1 H), 5.51 and 5.66 (2 br s, 0.5 H each, two rotamers), 6.8–7.8 (m, 4 H), 7.95 (br s, 1 H); ^{13}C NMR, Table 2; MS *m/z* 298 (18, M^+), 169, 168 (100), 167, 59. Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.43; H, 7.43; N, 9.43. Found: C, 72.41; H, 7.51; N, 9.41.

(1*RS*,4*RS*,5*SR*)-2-(Benzyloxycarbonyl)-4-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (34). Operating as above, from benzyl chloroformate (0.22 mL, 1.5 mmol) and amine **31** (250 mg, 1.0 mmol) was obtained carbamate **34** (340 mg, 88%) after chromatography (1:1 hexane–EtOAc): IR ($CHCl_3$) 3469, 1682; ^1H NMR δ 0.92 (t, J = 7, 3H), 1.26 (m, 2H), 1.6–1.8 (m, 1H), 1.8–2.1 (m, 2H), 2.2–2.3 (m, 2H), 2.76 (m, 2H), 3.75 and 3.88 (2 dd, J = 13, 5, 1H, two rotamers), 5.06 and 5.18 (2d, J = 12, 0.45 H each, *Z* rotamer), 5.21 and 5.33 (2d, J = 12 each, 0.55 H each, *E* rotamer), 5.60 and 5.73 (2 apparent t, J = 3, 1H, two rotamers), 6.7–7.8 (m, 9H), 8.03 (br s, 1H); ^{13}C NMR, Table 2; MS *m/z* 153, 151, 142, 136, 134, 126, 125, 93, 69 (100). Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.10; H, 7.04; N, 7.37.

(1*RS*,4*RS*,5*RS*)-4-Ethyl-2-(methoxycarbonyl)-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (33). To a solution of carbamate **32** (280 mg, 0.94 mmol) in anhydrous dioxane (50 mL) was added SeO_2 (160 mg, 1.41 mmol). The mixture was refluxed for 40 h and filtered through Celite. The solid material was thoroughly washed with Et_2O. The filtrate was concentrated, and the residue was chromatographed (Et_2O) to give acylindole **33** (210 mg, 72%) as a solid: IR ($CHCl_3$) 3455, 1687, 1654; UV (MeOH), λ nm 312, 238, 212; ^1H NMR δ 1.06 (t, J = 7, 3H), 0.8–1.5 (m, 2H), 1.96 (m, 1H), 2.16 and 2.22 (2 t, 1H, two rotamers), 2.42 (td, J = 13, 4, 1H), 2.61 (dm, J = 13, 1H), 2.92 (m, 1H), 3.70 and 3,89 (2s, 3H, two rotamers), 3.8–4.1 (masked, 1H), 5.79 and 5.92 (2 br s, 1H, two rotamers), 7.1–8.2 (m, 4H), 10.1 (br, 1H); ^{13}C NMR, Table 2; MS *m/z* 312 (7, M^+), 184, 183, 168, 167, 154, 59, 55, 41, 39, 32, 31 (100), 29. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.19; H, 6.45; N, 9.01. Found: C, 69.33; H, 6.66; N, 9.02.

(1*RS*,4*RS*,5*RS*)-2-(Benzyloxycarbonyl)-4-ethyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (35). Operating as above, from carbamate **34** (340 mg, 0.9 mmol) in anhydrous dioxane (50 mL) and SeO_2 (150 mg, 1.4 mmol) was obtained acylindole **35** (280 mg, 80%) as a solid after chromatography (1:1 hexane–EtOAc): IR ($CHCl_3$) 3454, 1684, 1654; UV (MeOH), λ nm 311, 236, 201; ^1H NMR δ 1.05 (t, J = 7, 3 H), 1.0–1.5 (m, 2 H), 1.8–2.1 (m, 1 H), 2.19 (d, J = 13.5, 1 H), 2.3–2.7 (m, 2 H), 2.92 (br s, 1 H), 3.91 (dd, J = 13.5, 5, 0.5 H, *E* rotamer), 4.06 (dd, J = 13.5, 5, 0.5 H, *Z* rotamer), 5.09 and 5.20 (2d, J = 12, 0.5 H each, *E* rotamer), 5.23 and 5.36 (2d, J = 12, 0.5 H each, *Z* rotamer), 5.80 (apparent t, 0.5 H, *Z* rotamer), 5.95 (apparent t, 0.5 H, *E* rotamer), 6.9–8.0 (m, 9 H), 9.75 (br, 1 H); ^{13}C NMR, Table 2; MS *m/z* 299, 298 (100), 284, 270, 255, 228, 227, 77, 44, 42. Anal. Calcd for $C_{24}H_{24}N_2O_3 \cdot {}^1/_4H_2O$: C, 73.76; H, 6.28; N, 7.13. Found: C, 73.54; H, 6.38; N, 7.01.

(±)-Norisodasycarpidone (36). Method A. A suspension of **35** (120 mg, 0.3 mmol) and 10% Pd/C (15 mg) in MeOH (5 mL) was hydrogenated until the disappearance of the starting compound was observed by TLC (5 days). Additional Pd/C (30 mg) was added during the process. The catalyst was removed by filtration through Celite, and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and washed with saturated aqueous $NaHCO_3$. Evaporation of the dried organic solution gave an oil which was chromatographed (5% diethylamine in EtOAc) to afford the secondary amine **36**[15a,53] (32 mg, 41%): ^{13}C NMR, Table 2.

Method B. To a solution of carbamate **35** (80 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (10 mL) were added dimethyl sulfide (0.46 mL, 6.3 mmol) and $BF_3 \cdot Et_2O$ (0.26 mL, 2.1 mmol), and the mixture was stirred at room temperature until the reaction was complete (3 h, TLC). The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts were dried and evaporated, and the crude product was purified by chromatography (2% diethylamine in Et_2O), affording norisodasycarpidone (**36**; 32 mg, 63%).

(±)-Isodasycarpidone (37). To a mixture of **35** (80 mg, 0.2 mmol) and 10% Pd/C (24 mg) in MeOH (10 mL) was added aqueous formaldehyde (35%, 0.18 mL, 2.1 mmol), and the suspension was hydrogenated until the disappearance of the starting compound was observed by TLC (6 days). Additional Pd/C (16 mg) was added during the process. The catalyst was removed by filtration through Celite, and the solvent was evaporated. Workup and chromatography as in the above method A gave isodasycarpidone (**37**; 49 mg, 89%), which was

identical by IR, ^{1}H NMR, and TLC with a sample prepared by an independent synthesis.[53] ^{13}C NMR, Table 2.

(1*RS*,5*RS*,12*SR*)-2-(Benzyloxycarbonyl)-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (39). A suspension of tetracycle **1** (2.20 g, 6.66 mmol) and activated[75] $Pd(OH)_2$ (1.32 g) in MeOH (150 mL) was hydrogenated until the disappearance of the starting compound was observed by TLC (5 days). Additional $Pd(OH)_2$ (800 mg) was added during the process. The catalyst was removed by filtration through Celite, and the solvent was evaporated. The residue was dissolved in $CHCl_3$ and washed with saturated aqueous $NaHCO_3$. The organic solution was dried and evaporated to give the secondary amine **38** (1.60 g) which, due to its instability, was used in the next step without purification. A pure sample was obtained by chromatography (5% diethylamine in Et_2O): IR ($CHCl_3$) 3410; ^{1}H NMR δ 0.90 (t, J = 7, 3 H), 1.0–1.3 (m, 2 H), 1.63 (dm, J = 13, 1 H), 1.8–2.1 (m, 2 H), 2.27 (m, 1 H), 2.4–2.7 (m, 3 H), 2.99 (dd, J = 17.5, 6.5, 1 H), 4.30 (d, J = 3, 1 H), 7.0–7.6 (m, 4 H), 8.3 (br s, 1 H); ^{13}C NMR, Table 2.

A solution of benzyl chloroformate (0.6 mL, 4.18 mmol) in CH_2Cl_2 (16 mL) was added dropwise to a stirred mixture of amine **38** (670 mg, 2.79 mmol), anhydrous K_2CO_3 (930 mg), and anhydrous CH_2Cl_2 (40 mL). After the mixture was stirred for 90 min, H_2O was added, and the stirring was maintained for additional 20 min. After the usual workup and chromatography (1:1 hexane–Et_2O), carbamate **39** (520 mg, 50% from **1**) was isolated: IR ($CHCl_3$) 3469, 1684; ^{1}H NMR δ 0.90 and 0.92 (2t, J = 7, 3 H, two rotamers), 1.1–1.4 (m, 2 H), 1.5–2.0 (m, 3 H), 2.31 (m, 1 H), 2.54 (d, J = 17.5, 1 H), 2.6–2.8 (m, 1 H), 2.99 and 3.01 (2dd, J = 17.5, 6, 1 H, two rotamers), 3.77 and 3.87 (dd, J = 14, 5, 1H, two rotamers), 5.03 and 5.18 (2d, J = 12, 1.1 H, *E* rotamer), 5.28 (2d, J = 12, 0.9 H, *Z* rotamer), 5.46 and 5.61 (2d, J = 2.5, 1H, *Z* and *E* rotamers), 6.83–7.74 (m, 9 H), 7.98 (br s, 1 H); ^{13}C NMR, Table 2; MS *m/z* 374 (19, M^+), 239, 222, 197, 196, 182, 169, 168, 167, 155, 91 (100). Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.93; H, 7.13; N, 7.23.

(1*RS*,5*SR*,12*SR*)-2-(Benzyloxycarbonyl)-12-ethyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (40). Operating as in the preparation of **35**, indole **39** (130 mg, 0.35 mmol) was converted to acylindole **40** (58 mg, 43%) which showed to be a 3:2 mixture of *E* and *Z* rotamers: IR ($CHCl_3$) 3455, 1686, 1658; UV (MeOH) λ nm 237, 313; ^{1}H NMR δ 0.91 and 0.93 (2t, J = 7.5, 3 H, *Z* and *E* rotamers), 1.2–1.5 (m, 2 H), 1.9–2.3 (m, 3 H), 2.6–2.9 (m, 2 H), 3.8–4.1 (m, 1 H), 5.06 and 5.20 (2d, J = 12, 1.2 H, *E* rotamer), 5.23 and 5.38 (2d, J = 12, 0.8 H, *Z* rotamer), 7.01 (tm, J = 7, 1 H), 7.1–7.6 (m, 7 H), 7.93 (d, J = 8. 1 H), 9.95 (br s, 1 H); ^{13}C NMR, Table 2.

(±)-Nordasycarpidone (41). To a solution of carbamate **40** (75 mg, 0.19 mmol) in CH_2Cl_2 (10 mL) were added dimethyl sulfide (0.42 mL, 5.7 mmol) and $BF_3{\cdot}Et_2O$ (0.24 mL, 1.9 mmol), and the mixture was stirred at room temperature for 2h. Then, more Me_2S was added (0.42 mL), and the stirring was continued overnight. The mixture was poured into a 0.5 N aqueous NaOH solution and extracted with $CHCl_3$ containing a few drops of MeOH. Evaporation of the dried extracts followed by chromatography (1% diethylamine in EtOAc) gave nordasycarpidone (**41**)[5] (36 mg, 73%): ^{1}H NMR δ 0.89 (t, J = 7.5, 3 H), 1.33 (qn, J = 7.5, 2 H), 1.8–2.2 (m, 3 H), 2.30 (tt, J = 7.5, 2.5, 1 H), 2.5–2.9 (m, 2 H), 4.59 (d, J = 2.5, 1 H), 7.18 (td, J = 8, 1, 1 H), 7.39 (td, J = 7, 1, 1 H), 7.51 (d, J = 8, 1 H), 7.72 (d, J = 8, 1 H), 10.22 (br s, 1 H); ^{13}C NMR, Table 2.

(±)-Dasycarpidone (42). Following the same procedure as described for isodasycarpidone (**37**), the carbamate **40** (66 mg, 0.17 mmol) was converted to dasycarpidone (**42**;[6] 35 mg, 76%): ^{1}H NMR (500 MHz) δ 0.82 (t, J = 7.5, 3 H), 1.30 (m, 2 H), 1.92 (dm, J = 12.5, 1 H), 2.09–2.20 (m, 2 H), 2.35 (s, 3 H), 2.42 (m, 1 H), 2.62 (dm, 1 H), 2.70 (m, 1 H), 4.33 (br s, 1 H), 7.21 (tm, J = 7, 1 H), 7.40 (ddd, J = 8.5, 7, 1, 1 H), 7.48 (dt, J = 8, 1, 1 H), 7.70 (d, J = 8, 1 H), 9.19 (br s, 1 H); ^{13}C NMR, Table 2.

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(±)-Dasycarpidol (43). Sodium borohydride (40 mg, 1.06 mmol) was added to a solution of ketone **42** (35 mg, 0.13 mmol) in MeOH (3 mL). The mixture was stirred at room temperature for 5 h. Acetone (0.5 mL) was added, and the stirring was maintained for 15 min. After evaporation of the solvent, the residue was chromatographed (Al_2O_3, 5% diethylamine in EtOAc) to afford the starting ketone (5.4 mg) and a 5:2 epimeric mixture (25 mg) of alcohols **43** and **44**. (±)-Dasycarpidol (**43**):[9] ^{1}H NMR δ 0.91 (t, J = 7, 3 H), 2.28 (s, 3 H), 4.05 (d, J = 1.5, 1 H), 5.07 (d, J = 5.7, 1 H), 7.05–7.65 (m, 4 H), 8.50 (br s, 1 H); ^{13}C NMR, Table 2. (±)-16-Epidasycarpidol (**44**): ^{1}H NMR δ 1.25 (t, J = 7, 3 H), 2.28 (3 H), 4.08 (d, J = 1.5, 1 H), 4.66 (s, 1 H), 7.05–7.65 (m, 4 H), 8.50 (br s, 1 H); ^{13}C NMR, Table 2.

(1*RS*,5*RS*,12*SR*)-2-(2,2-Diethoxyethyl)-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (45). A stirred solution of amine **38** (1.23 g, 5.12 mmol) and bromoacetaldehyde diethyl acetal (1.19 mL, 7.68 mmol) in anhydrous dioxane (40 mL) containing anhydrous Na_2CO_3 (1.09 g) was refluxed for 18 h. The solvent was evaporated, and the residue was taken up with $CHCl_3$. The resulting solution was washed with saturated aqueous $NaHCO_3$, dried, and evaporated to give an oil which, after flash chromatography (Et_2O with 0.5% diethylamine), afforded **45** (1.31 g, 72%): IR ($CHCl_3$) 3469; ^{1}H NMR δ 0.86 (t, J = 7, 3 H), 1.16 (t, J = 7, 3 H), 1.0–1.4 (masked, 2 H), 1.27 (t, J = 7, 3 H), 1.6 (m, 1 H), 2.0–2.6 (m, 5 H), 2.49 (d, J = 17, 1 H), 2.95 (dd, J = 17, 6, 1 H), 3.4–3.8 (m, 6 H), 4.21 (br s, 1 H), 4.73 (deformed t, 1 H), 7.0–7.1 (m, 2 H), 7.2–7.3 (m, 1 H), 7.6–7.7 (m, 1 H), 7.99 (br s, 1 H); ^{13}C NMR, Table 2; MS *m/z* 356 (3, M^+), 311, 254, 253 (100), 240, 223, 222, 197, 196, 194, 169, 168, 167, 103, 75, 47. Anal. Calcd for $C_{22}H_{32}N_2O_2{\cdot}^1/_4H_2O$: C, 73.20; H, 9.07; N, 7.76. Found: C, 73.40; H, 9.07; N, 7.55.

(1*RS*,5*RS*,12*SR*)-2-[2,2-Bis(methylthio)ethyl]-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (46). To a solution of acetal **45** (1.31 g, 3.58 mmol) in anhydrous CH_2Cl_2 (50 mL) cooled at 0 °C were added freshly distilled $BF_3{\cdot}Et_2O$ (6.7 mL, 53.5 mmol) and excess methanethiol. The mixture was stirred at 0 °C in a sealed tube for 4 h, poured into 50% aqueous NaOH (chilled at 0 °C), and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by chromatography (6:4 hexane–Et_2O) gave **46** (1.01 g, 79%): ^{1}H NMR δ 0.87 (t, J = 7.5, 3 H), 1.0–1.2 (m, 2 H), 1.7 (m, 1 H), 2.0–2.3 (m, 4 H), 2.12 and 2.18 (2s, 3H each), 2.47 (dd, J = 13.5, 6, 1 H), 2.50 (d, J = 17.5, 1 H), 2.6 (m, 1 H), 2.97 (dd, J = 17.5, 6, 1 H), 3.07 (dd, J = 13.5, 8, 1 H), 3.93 (deformed t, J = 7, 1 H), 4.05 (br s, 1 H), 7.0–7.1 (m, 2 H), 7.2–7.4 (m, 1 H), 7.5–7.6 (m, 1 H), 7.92 (br s, 1 H); ^{13}C NMR, Table 2.

(1*RS*,3a*SR*,4*RS*,5*SR*,11b*SR*)-4-Ethyl-1-(methylthio)-2,3,-3a,4,5,6-hexahydro-3,5-ethano-1*H*-pyrrolo[2,3-*d*]carbazole (47). To a solution of **46** (280 mg, 0.76 mmol) in degassed anhydrous acetonitrile (150 mL) at −30 °C was added via syringe a solution of dimethyl(methylthio)sulfonium fluoroborate[61] (DMTSF, 300 mg, 1.52 mmol) in the minimum amount of acetonitrile. The mixture was stirred at 0 °C for 3 h and then was evaporated. The residue was dissolved in EtOAc and washed with aqueous Na_2CO_3. The organic layer was dried and evaporated. Chromatography (2% diethylamine in EtOAc) gave indolenine **47** (86 mg, 36%): IR ($CHCl_3$) 1565; ^{1}H NMR (C_3D_6O) δ 0.55 (t, J = 5.5, 3 H), 0.80 (m, 2 H), 1.64 (s, 3 H), 2.40 (m, 1 H), 3.46 (dd, J = 12, 6, 1 H), 3.95 (m, 1 H), 4.18 (dd, J = 12, 6, 1 H), 6.9–7.5 (m, 4 H); ^{13}C NMR (C_3D_6O) δ 12.2 (C-18),[10] 15.2 (SCH_3), 23.3 (C-19), 30.5 (C-16), 32.1 (C-15), 34.5 (C-14), 42.8 (C-20), 46.1 (C-3), 49.8 (C-6), 64.8 (C-5), 67.0 (C-7), 73.3 (C-21), 120.6 (C-12), 124.5 (C-9), 125.3 (C-10), 128.7 (C-11), 143.3 (C-8), 157.1 (C-13), 190.9 (C-2). In some runs the *N*-formyl derivative **50** was isolated in *ca.* 5% yield: IR ($CHCl_3$) 3025,1655; ^{1}H NMR (C_3D_6O) δ 0.97 and 0.98 (2t, J = 7 each, 3 H, two rotamers), 1.33 (m, 2 H), 2.76 (d, J = 18, 1 H), 3.16 (dd, J = 18, 6.5, 1 H), 3.7–4.1 (m, 1 H), 5.05 and 5.77 (2d, J = 3, 1 H, two rotamers), 7.0–7.6 (m, 4 H), 8.05 and 8.51 (2s, 1 H, two rotamers), 10.22 and 10.41 (2 br s, 1 H, two rotamers); ^{13}C NMR, Table 2.

(1*RS*,3a*SR*,4*RS*,5*RS*,11b*SR*)-Methyl 4-Ethyl-1-(methylthio)-2,3,3a,4,5,7-hexahydro-3,5-ethano-1*H*-pyrrolo[2,3-

***d*]carbazole-7-carboxylate (48).** To a solution of **47** (86 mg, 0.28 mmol) in anhydrous DME (6 mL) was added NaH (30 mg, 55% oil dispersion, 0.69 mmol). The mixture was stirred at room temperature for 15 min, and then methyl chloroformate (0.05 mL, 0.62 mmol) was added. After the mixture was stirred at 60 °C for 1h, MeOH was added, and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$. The organic solution was dried and evaporated, and the residue was chromatographed (2% diethylamine in EtOAc) to give **48** (51 mg, 50%): IR ($CHCl_3$) 1700; ^1H NMR δ 0.72 (t, J = 6.5, 3 H), 0.92 (m, 2 H), 1.66 (s, 3 H), 1.5–2.2 (m, 4 H), 2.5–2.7 (masked, 1 H), 2.76 (t, J = 11.5, 1 H), 3.03 (dt, J = 11.5, 3.5, 1H), 3.33 (dd, J = 12, 6.5, 1 H), 3.77 (br s, 1 H), 3.87 (dd, J = 10.5, 6.5, 1 H), 3.93 (s, 3 H), 5.91 (d, J = 8, 1 H), 7.0–7.4 (m, 3 H), 7.71 (d, J = 8, 1 H); ^{13}C NMR δ 11.4 (C-18),[10] 15.6 (SCH_3), 23.5 (C-19), 28.1 (C-14), 31.2 (C-20), 42.0 (C-15), 46.0 (C-3), 52.7 (OCH_3), 54.2 (C-7), 55.7 (C-6), 62.3 (C-5), 64.8 (C-21), 111.2 (C-12), 114.5 (C-16), 122.3 (C-10), 124.1 (C-9), 127.8 (C-11), 133.0 (C-8), 141.4 (C-13), 147.2 (C-2), 153.1 (CO).

(3a*RS*,4*SR*,5*SR*,11b*SR*)-Methyl 4-Ethyl-2,3,3a,4,5,7-hexahydro-3,5-ethano-1*H*-pyrrolo[2,3-*d*]carbazole-7-carboxylate (49). To a solution of **48** (43 mg, 0.12 mmol) in absolute EtOH (6 mL) was added freshly prepared Raney Ni (W-2, 6 spatulas), and the mixture was refluxed for 4 h. The solids were removed by filtration through Celite and washed with EtOH. Removal of the solvent and purification of the residue by chromatography (1% diethylamine in EtOAc) gave **49** (24 mg, 64%): IR ($CHCl_3$) 1700; ^1H NMR (500 MHz) δ 0.66 (t, J = 7.5, 3 H), 0.86 (hept, J = 7.5, 2 H), 1.52–1.75 (m, 3 H), 1.84 (tm, J = 14, 1 H), 2.44–2.48 (m, 1 H), 2.49 (ddd, J = 12, 5.5, 1 H), 2.75 (dd, J = 11, 7.5, 1 H), 2.75 (td, J = 11, 5.5, 1 H), 2.84 (ddd, J = 12, 4.5, 2.5, 1 H), 2.89 (t, J = 7, 1 H), 3.64 (t, J = 2, 1 H), 3.85 (s, 3 H), 5.78 (d, J = 8, 1 H), 6.96 (td, J = 7.5, 1, 1 H), 7.05–7.11 (m, 2 H). 7.6 (d, J = 8, 1 H); ^{13}C NMR δ 11.4 (C-18),[10] 23.8 (C-19), 28.0 (C-14), 31.3 (C-20), 41.4 (C-15), 42.3 (C-6), 45.0 (C-3), 50.5 (C-7), 52.6 (OCH_3), 53.5 (C-5), 65.0 (C-21), 110.3 (C-12), 115.1 (C-16), 119.6 (C-9), 123.8 (C-10), 127.0 (C-11), 137.9 (C-8), 140.1 (C-13), 147.5 (C-2), 153.1 (CO). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.03; H, 7.47; N, 8.64. Found: C, 73.69; H, 7.76; N, 8.45.

(1*RS*, 5*RS*, 12*SR*)-Methyl 2-[2,2-Bis(methylthio)ethyl]-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]-indole-7-carboxylate (51). A 50% aqueous NaOH solution (1.7 mL) was added to a suspension of **46** (150 mg, 0.42 mmol) and tetrabutylammonium hydrogen sulfate (20 mg) in toluene (5 mL). The resulting two-phase mixture was vigorously stirred at room temperature until a remarkable increase of viscosity was observed (10–15 min approximately). Then, a solution of methyl chloroformate (0.05 mL, 0.63 mmol) in toluene (0.5 mL) was slowly added. After the mixture was stirred for 1 h, additional methyl chloroformate (0.05 mL) was added, and stirring was continued for 15 min. The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated. Chromatography (Et_2O–hexane 3:7) of the residue gave **51** (153 mg, 88%): IR ($CHCl_3$) 1735; ^1H NMR δ 0.88 (t, J = 7, 3 H), 1.13 (qn, J = 7, 2 H), 1.65 (m, 1 H), 2.12 and 2.18 (2s, 3 H each), 1.9–2.3 (m, 4 H), 2.48 (dd, J = 13.5, 6, 2 H), 2.6 (m, 1 H), 2.8–3.2 (m, 2 H), 3.88 (deformed t, J = 7, 1 H), 4.01 (br s, 1 H), 4.05 (s, 3 H), 7.25 (m, 2 H), 7.49 (m, 1 H), 8.13 (m, 1 H); ^{13}C NMR, Table 2.

(±)-Tubotaiwine. A degassed solution of **49** (22 mg, 0.07 mmol) in MeOH (70 mL) was photolyzed under argon with a 125-W high-pressure mercury lamp in a quartz immersion well reactor for 30 min. Evaporation of the solvent gave a residue which was chromatographed. Elution with 0.5% diethylamine in EtOAc gave tubotaiwine[12] (4 mg, 20%), which was identical with an authentic sample by ^1H NMR and TLC comparison.[67]

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of the key synthetic intermediates **1**, **4**, **5**, **9**, *cis*-**21**, **29**, **38**–**40**, and **45**–**49** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.