First Total Synthesis of (±)-Melinonine-E and (±)-Strychnoxanthine Using a Radical Cyclization Process as the Core Ring-Forming Step

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Received June 24, 1997

The first total synthesis of (±)-melinonine-E and (±)-strychnoxanthine is described. The key common step for the synthesis of both alkaloids is the elaboration of the 2-azabicyclo[3.3.1]nonane nucleus (D and E rings) by a radical carbocyclization, using an α-carbamoyldichloromethyl radical as a donor. The closure of the C ring by a Bischler−Napieralski cyclization, followed by an epimerization process to gain the axial nitrile **20**, and appropriate reduction transformations afforded pentacyclic alcohol **23**. This alcohol was converted into either (±)-melinonine-E (**1**) or (±)-strychnoxanthine (**2**) by means of a palladium black dehydrogenation of the C ring or a SeO_2 oxidation of the corresponding acetate **25**, respectively.

Introduction

Melinonine-E (**1**) and strychnoxanthine (**2**) are two quaternary alkaloids with a pentacyclic ring system unprecedented among natural or synthetic products, consisting of a *β*-carbolinium moiety fused to a 2-azabicyclo[3.3.1]nonane nucleus.[1] Furthermore, these two alkaloids are rare examples of the relatively small collection of biogenetically and theoretically interesting zwitterionic alkaloids with a core of indolo[2,3-*a*]quinolizidine.[2] The isolation of melinonine-E from the bark of *Strychnos melinoniana* was reported for the first time in 1957,[3] but its structural elucidation was not carried out until 1984.[4] Strychnoxanthine is the 14-oxo derivative of melinonine-E isolated from the root bark of *Strychnos gossweileri*.[5] Biogenetically, it can be envisaged that both alkaloids might arise from the tetracyclic bases of the antirhine group,[6] which have an unusual *β*-configuration at C-15, by closure of the E ring (bond formed C-17/C-18)[7] and aromatization of the C ring. Consequently, these alkaloids can be classified as a new group of the Vallesiachotaman class of monoterpenoid indole alkaloids characterized by both the presence of a bond between N-4 and C-17 and the unit C-2/C-3/C-14.[8]

In this paper, we describe the first synthesis of alkaloids **1** and **2**, using a common precursor. The strategy we have developed for assembling the pentacyclic ring system of these alkaloids involves the construction of an appropriately substituted and functionalized 2-azabicyclo[3.3.1]nonane **II**, incorporating rings D and E, and the final closure of the C ring by a Bischler−Napieralski cyclization.[9] The required 2-azabicyclo[3.3.1]-nonane[10] **II** was prepared from radical precursor **I**, which incorporates all carbon atoms of targets **1** and **2**, in a process involving the closure of the piperidine ring by attack of an α-carbamoylmethyl radical upon an α,*β*-unsaturated nitrile moiety[11] (Scheme 1). This process affords a *δ*-lactam unit that enables the next ring closure to achieve pentacycle **III**.

Results and Discussion

Preliminary Studies. Our initial attention was focused on the preparation of acetamides **5a**,**b** (Scheme 2). According to our plan, they should be converted into cyclohexene derivatives, precursors of type **I** radicals, in which an additional carbon (C-21 atom in the target alkaloids) has been incorporated. Model studies using an *N*-benzyl derivative analogue of **I**, such as cyclohexenecarbonitrile **6**, showed that monohaloacetamides are incapable of carrying out the cyclization process to

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(3) Bächli, E.; Vamvacas, C.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1957**, *40*, 1167−1187. A yohimbine-type structure had been proposed earlier but not verified later by synthesis: Albright, J. D.; Mitscher, L. A.; Goldman, L. *J. Heterocycl. Chem.* **1970**, *7*, 623−627.

(4) Borris, R. P.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 455−460.

(5) Coune, C.; Tavernier, D.; Caprasse, M.; Angenot, L. *Planta Med.* **1984**, *50*, 93−95.

(6) Lounasmaa, M.; Tolvanen, A. The Corynantheine-Heteroyohimbine Group. In *Monoterpenoid Indole Alkaloids*, supplement to part 4; Saxton, J. E., Ed.; In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: Chichester, 1994; Vol. 25, pp 57−159.

(7) Biogenetic numbering is used throughout this paper for tetracyclic and pentacyclic compounds. Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508−510.

(8) Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; pp 211−376.

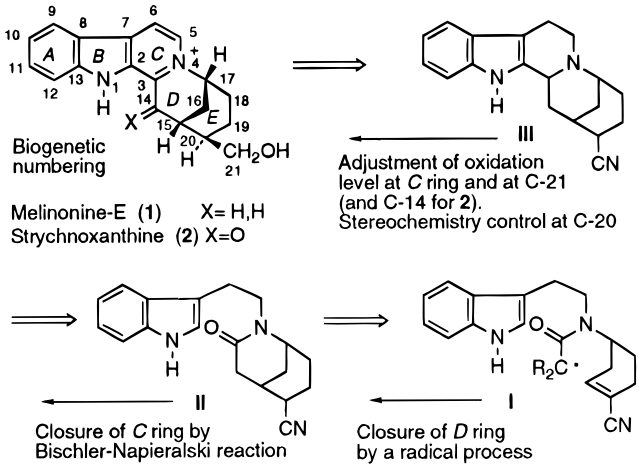
(9) For some recent syntheses of indole alkaloids involving a Bischler−Napieralski process in the elaboration of the tetrahydro-*β*-carboline unit, see: (a) Lögers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139−9150. (b) Aubé, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009−9018. (c) Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947−2949.

(10) For previous synthetic approaches to 2-azabicyclo[3.3.1]nonanes starting from carbocyclic compounds involving the formation of C-4/C-5 bond in the ring closure, see: (a) Alkylation of an enolate, Boger, D. L.; Patel, M.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4559−4562. (b) Aldol condensation, Teuber, H.-J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann. Chem.* **1990**, 781−787. (c) Pummerer rearrangement followed by cationic cyclization, Magnus, P.; Coldham, I. *J. Am. Chem. Soc.* **1991**, *113*, 672−673. (d) Heck reaction, Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695−1698.

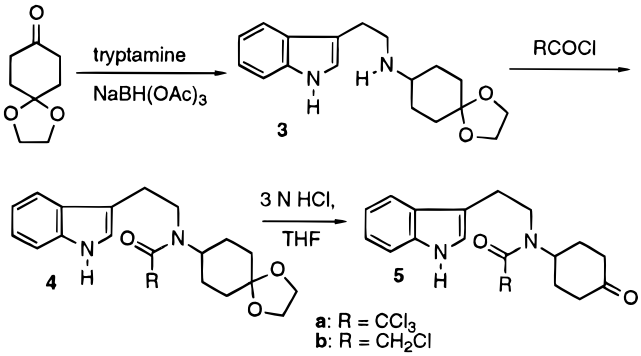
(11) Before our work in this area,[1,12] there was only one precedent for the synthesis of six-membered nitrogen heterocycles from α-carbamoyl radicals:[13] Hirai, Y.; Hagiwara, A.; Terada, T.; Yamazaki, T. *Chem. Lett.* **1987**, 2417−2418. See also: Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723−727.

S0022-3263(97)01148-1 CCC: $15.00
Published on Web 01/27/1998

Scheme 1. Synthetic Strategy



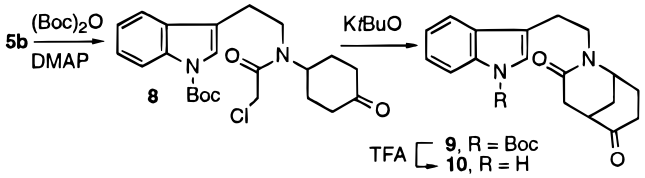
Scheme 2



bridged DE ring systems,[12] and consequently, compound **5b** was discarded for this purpose. An experiment on iodoacetamide **6**, using Bu_3SnD as a radical process promoter, resulted in the isolation of deuterated acetamide **7**,[14] showing that the inefficiency in the cyclization is due to a direct reduction of the carbamoylmethyl radical, not to a 1,5-hydrogen atom transfer followed by reduction.[15]

Next, we examined the possibility that chloroacetamide **5b**, after protection of indole as its *N*-Boc derivative **8**, might prove useful in gaining access to the bridged azabicyclo nucleus through an ionic cyclization (Scheme 3). Nevertheless, treatment of **8** with K-*t*-BuO furnished azabicyclic derivative **10** in low yield,[16,17] and its applicability to the synthesis of melinonine-E was discarded.

Scheme 3



Synthesis of 2-Azabicyclo[3.3.1]nonane II by a Radical Cyclization Process. At this point we turned our attention to trichloroacetamide **5a**, which was prepared in good yield by reductive amination of tryptamine and 1,4-cyclohexanedione monoethylene acetal in the presence of sodium triacetoxyborohydride,[18] followed by trichloroacetylation and further chemoselective hydrolysis of **4a**. The existence of two rotational isomers around the acyl−nitrogen bond in trichloroacetamides **4a** and **5a** caused line broadening of some peaks in the ^1H NMR, but two separate signals in the ^{13}C NMR specta were not observed, thus indicating that the coalescence temperature is close to that of the registration of NMR spectra.[19]

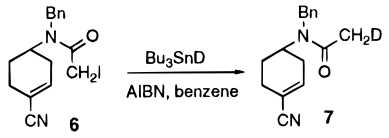
For the purpose of the one-carbon homologation (C-21), ketone **5a** was converted to cyanohydrin **12** by treatment of **5** with trimethylsilyl cyanide and ZnI_2, followed by hydrolysis of *O*-silylcyanohydrin intermediate **11**.[20] The reaction was stereoselective, only the trans isomer being formed, whereas when acetone cyanohydrin and base were used, a mixture of cis−trans isomers of **12** was isolated. α,β-Unsaturated nitrile **13**, the precursor of radical **I**, was obtained by dehydration of **12** at room temperature or in a more straightforward manner by treatment of the intermediate **11** with $POCl_3$ at benzene reflux temperature[21] (Scheme 4).

Our synthetic approach to azabicyclo **II** implies an intramolecular alkylation of the suitably 4-substituted cyclohexenecarbonitrile **13** by means of a reductive radical cyclization, using an α-carbamoyldichloromethyl radical (**I**, R = Cl) as a promoter.[22] When compound **13** was treated with tris(trimethylsilyl)silane (TMS_3SiH)[23] (3.5 equiv), as the radical mediator, and 0.2 equiv of AIBN in refluxing benzene (0.12 M), the expected cyclization to the 2-azabicyclo[3.3.1]nonane ring system took place to give a mixture of **16** (44%) and its C-14 chloro- and dichloro-substituted derivatives **15** (14%) and **14** (11%), respectively. From the synthetic standpoint, the best results were achieved when the above crude

(12) Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391−1402.

(13) For some recent examples of synthesis of six-membered rings using nitrogen-containing radicals, see: (a) Esch, P. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 4659−4676. (b) Martin, S. F.; Tso, H.-H. *Heterocycles* **1993**, *35*, 85−88. (c) Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198−4199. (d) Ihara, M.; Setsu, F.; Shohda, M.; Taniguchi, N.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 5317−5323. (e) Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 417−420. (f) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623−5626. (g) Khim, S.-K.; Cederstrom, E.; Ferri, D. C.; Mariano, P. S. *Tetrahedron* **1996**, *52*, 3195−3222. (h) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063−3064.

(14) *N*-Benzyl-*N*-(4-cyano-3-cyclohexenyl)-2-deuterioethanamide (**7**) was the only product isolated (62%) when iodoacetamide **6** (52 mg, 0.13 mmol) was treated with tributyltin deuteride (0.08 mL, 0.3 mmol) and AIBN (4 mg, 0.026 mmol) in benzene (1 mL) at 80 °C for 8 h.



(15) For 1,5-hydrogen-transfer reactions, see: Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051−6059.

(16) (a) An analogous cyclization in the decahydroisoquinolone series proceeds with good yield,[16b] but in the bridged 2-azabicyclo[3.3.1]-nonane series, a related intramolecular alkylation occurs in low yield.[10a] (b) Sapi, J.; Dridi, S.; Laronze, J.; Sigaut, F.; Patigny, D.; Laronze, J.-Y.; Lévy, J. *Tetrahedron* **1996**, *52*, 8209−8222.

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

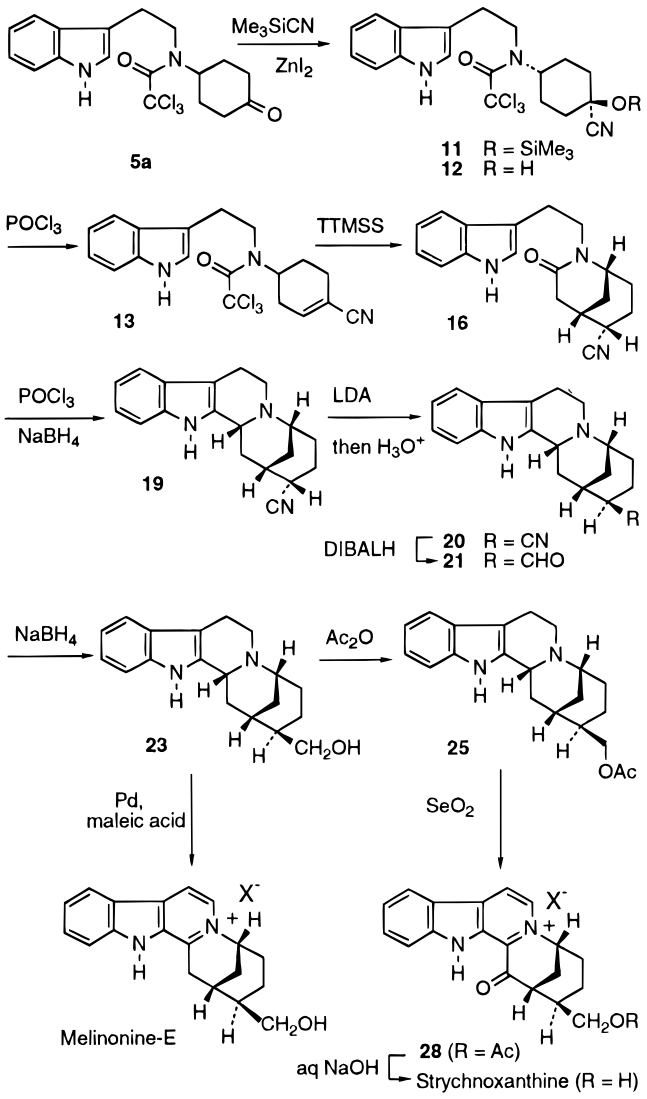
(18) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849−3862.

(19) The same behavior was observed in the other trichloroacetamides (**11**−**13**) synthesized in this work. In contrast, chloroacetamides **4b** and **5b** showed by NMR two sets of signals corresponding to both rotamers at this temperature. For the influence of steric factors on the energy barrier to rotation about the C−N amide bonds, see: Johnson, R. A. *J. Org. Chem.* **1968**, *33*, 3627−3632.

(20) Gassman, P. G.; Talley, J. J. *Org. Synth.* **1981**, *60*, 14−18.

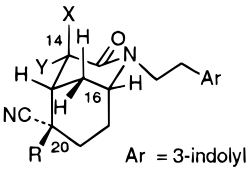
(21) Oda, M.; Yamamuro, A.; Watabe, T. *Chem. Lett.* **1979**, 1427−1430.

Scheme 4



mixture, without isolation of components, was treated in situ with Bu_3SnH−AIBN, which brought about the hydrogenolysis of the remaining C−Cl bonds and allowed the isolation of lactam **16** in 64% overall yield. Attempts to obtain the *all*-dechlorinated compound **16** using only TMS_3SiH were unsuccessful.[24] On the other hand, when the cyclization was conducted in the presence of 3.2 equiv of Bu_3SnH, the cyclized product **16** was obtained directly but in lower yield (46%).

The radical cyclization which allows the preparation of the valuable intermediate **16** is stereoselective. The relative configuration at C-20 in compound **16** (equatorial cyano group) was deduced from its ^{1}H NMR spectrum, in which the multiplicity (qd, J = 13.5, 4 Hz) of H-19$_{ax}$ indicates the axial disposition for the proton at C-20. On the other hand, the equatorial disposition of the chlorine atom at C-14 in azabicyclo **15** was revealed by comparing ^{13}C NMR chemical shifts of C-16 in compounds **14** and **15** (see Table 1), which shows the lack of compression at C-16 in the monochloro derivative **15**.[25] The relative configuration at C-20 in compounds **14**−**16** and at C-14 in **15** is the expected one, taking into account that hydrogen abstraction by radicals in cyclic systems occurs from the most accessible face.[26]



	R	X	Y
14	H	Cl	Cl
15	H	H	Cl
17	D	Cl	Cl
18	D	D	Cl

The above cyclization of trichloroacetamidocyclohexene **13** not only provides a new synthetic entry to the 2-azabiciclo[3.3.1]nonane ring system[10,12] but also constitutes one of the scarce examples of synthetically useful 6-exo-trig cyclization from 3-aza-6-heptenyl radicals.[11,27] The success of the cyclization using trichloroacetamides (i.e., **13**) can be explained by the presence of bulky substituents on the nitrogen, which prevent a restricted rotation around the carbonyl group of the amide, and three chloro atom substituents α to the carbonyl group, which increase the stability of the radical intermediate. These factors change the course of the reaction as compared with the process that uses monohaloacetamides, in which premature irreversible hydrogen abstraction from the stannane by the α-carbamoylmethyl radical is the preferred pathway (see, for example, the failure in cyclization of iodoacetamide **6**). To gain more knowledge, the radical cyclization of **13** was also carried out using 1.1 equiv of tributyltin deuteride. Monodeuterated compound **17** and dideuterated monochloro derivative **18** were isolated, and no uncyclized reduced product was detected. These results indicate that the cyclizing ability of trichloroacetamides to give six-membered lactams does not lie in the three opportunities of carbamoylmethyl radicals to cyclize but in the stability that the two additional chlorine atoms confer to the initially generated α-carbamoyldichloromethyl radical,[28] whose lifetime is long enough to allow it to undergo cyclization even upon a deactivated double bond.[29]

Synthesis of (±)-Melinonine-E and (±)-Strychnoxanthine. With an efficient procedure for the elabo-

(22) (a) Radical cyclizations of trichloroacetamides leading to five-membered lactams have been accomplished using ruthenium-[22b] or copper-catalyzed[22c] processes, nickel−acetic acid,[22d] or tributylstannane.[22e] In contrast, few processes of this type leading to six-membered lactams have been reported so far.[11] (b) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682−1689. (c) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464−470. Seijas, J. A.; Vázquez-Tato, M.-P.; Castedo, L.; Estévez, R. J.; Ónega, M.-G.; Ruíz, M. *Tetrahedron* **1992**, *48*, 1637−1642. (d) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 5629−5632. (e) Goodall, K.; Parsons, A. F. *Tetrahedron* **1996**, *52*, 6739−6758.

(23) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194.

(24) For runs with long reaction times (6 h), adding AIBN every 2 h gave **16** (56%) and **15** (14%). Moreover, treatment of monochloro derivative **15** with TTMSS (1.5 equiv) and AIBN (0.2 equiv) gave 48% of reduced compound **16** and 36% of the starting material, whereas the same process using Bu_3SnH (1.1 equiv) and AIBN (0.2 equiv) furnished exclusively **16** in 80% yield.

(25) For ^{13}C NMR assignments of 2-azabicyclo[3.3.1]nonanes, see: Casamitjana, N.; Bonjoch, J.; Gràcia, J.; Bosch, J. *Magn. Reson. Chem.* **1992**, *30*, 183−185.

(26) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (b) Apeloig, Y.; Nakash, M. *J. Am. Chem. Soc.* **1994**, *116*, 10781−10782. (c) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067−4079.

(27) For reviews about radical cyclization reactions, see: (a) Curran, D. P. Radical cyclization reactions and sequential radical reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 779−831. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856.

(28) For radical stabilization energies, see: Bordwell, F. G.; Lynch, T.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558−7562.

Table 1. ^{13}C NMR Data (δ) of Tetra- and Pentacyclic Derivatives[a−c]

carbon	**1**[d,e]	**2**[d,e]	**10**	**14**	**15**	**16**	**19**	**20**	**21**[f]	**22**[f]	**23**	**24**	**25**	**26**	**27**[d,e]	**28**[d]	**29**[d]	**30**[d,e]
C-2	136.0	135.9	122.1	122.5	122.3	122.1	135.8	135.8	135.9	135.9	135.9	135.9	135.9	135.9	135.0	135.9	135.7	135.6
C-3	131.9	127.7	168.1	163.5	165.8	169.7	49.1	49.1	49.6	49.1	50.1	49.4	49.9	49.4	132.0	127.4	127.6	127.8
C-5	132.5	134.7	47.8	48.6	48.5	47.7	51.5	51.2	51.3	51.5	51.6	51.7	51.5	51.7	133.5	134.5	134.5	134.8
C-6	116.5	121.9	23.6	22.9	23.2	23.3	22.9	22.8	22.9	22.9	22.9	23.0	22.9	23.0	117.0	122.1	122.1	122.0
C-7	142.4	139.5	113.0	112.3	112.9	112.0	108.5	108.3	108.1	108.1	108.2	108.4	108.2	108.3	142.3	139.6	139.6	139.5
C-8	121.5	120.6	127.4	127.0	127.3	127.1	127.1	127.0	127.1	127.1	127.3	127.3	127.3	127.3	121.3	120.5	120.5	120.5
C-9	123.8	124.7	118.7	118.5	118.6	118.2	118.0	117.9	117.8	117.8	117.9	117.9	118.0	117.9	123.9	124.7	124.7	124.7
C-10	122.4	124.1	119.4	119.6	119.6	118.8	119.4	119.3	119.1	119.1	119.2	119.2	119.3	119.2	122.9	124.1	124.1	124.1
C-11	132.0	134.5	121.9	122.2	121.9	121.5	121.4	121.1	121.0	121.0	121.0	121.1	121.1	121.1	132.5	134.5	134.5	134.5
C-12	114.5	114.7	111.2	111.3	111.3	111.2	110.8	110.6	110.7	110.7	110.7	110.6	110.6	110.6	113.9	114.7	114.7	114.6
C-13	146.7	147.6	136.2	136.3	136.2	136.1	136.0	135.9	136.4	136.4	135.9	136.9	136.8	136.8	145.2	147.5	147.5	147.5
C-14	33.0[g]	196.9	35.1	84.2	57.2	33.4	31.2	33.7	34.6	31.2	35.7	28.7	35.6	28.9	26.5	196.0	195.0	195.3
C-15	25.8	42.8	44.1	46.7	36.0	29.2	27.9	28.2	24.4	25.2	25.9	25.9	23.4	26.2	*h*	36.5	39.4	43.6
C-16	25.6	25.9	31.9	29.9	32.4	30.3	27.7	24.6	25.2	28.2	28.3	29.1	26.4	29.0	31.3	26.0	31.6	31.9
C-17	62.4	64.3	52.0	52.8	52.3	51.5	52.7	53.1	53.8	54.1	54.6	54.6	54.3	54.4	62.6	64.0	63.8	64.2
C-18	29.3	27.7	30.4	28.3	28.3	27.7	30.9	28.5	29.3	30.9	29.7	32.0	28.0	31.9	33.9	27.7	32.3	32.6
C-19	18.5	19.3	33.9	20.1	20.2	20.1	20.8	19.5	16.3	17.1	18.2	19.9	18.1	19.9	20.7	19.5	21.7	21.9
C-20	*h*	39.7	211.1	32.8	31.3	32.6	33.3	32.5	53.7	53.9	43.2	43.8	39.2	40.3	44.1	43.0	43.7	43.1
C-21	63.3	62.4		120.0	119.6	120.7	122.1	122.6	205.4	205.3	64.3	65.3	65.9[i]	66.5[i]	65.1	64.6[i]	66.8[i]	64.6

[a] In $CDCl_3$ (75.5 MHz). [b] Biogenetic numbering is used in this table. [c] Assignments were aided by HMQC spectrum. [d] In CD_3OD. [e] Assignments were aided by HMBC spectrum. [f] Registered from a mixture of equatorial and axial aldehydes (**21** and **22**) in a 7:3 ratio. [g] This signal appears as a triplet in the proton noise-decoupled ^{13}C NMR spectrum due to a partial deuteration of the methylene at C-14 (see ref 4). [h] The resonances for C-15 (δ 26.3 and 26.4) in **27** and C-20 (δ 43.1 and 43.2) in **1** appear as two lines, indicating the presence of two rotamers about C-20/C-21 bond (see ref 4). [i] Ac: δ 21.1 and 171.0 for **25** and **26**; δ 20.8 and 172.6 for **28** and **29**.

ration of the ABDE tetracyclic framework of the target alkaloids, we proceeded to the closure of the C ring (Scheme 4). Cyclization to the desired pentacyclic system was achieved by the Bischler−Napieralski reaction. Thus, treatment of lactam **16** with phosphorus oxychloride, followed by $NaBH_4$ reduction, stereoselectively led to the pentacyclic amine **19**, which showed spectroscopic data in agreement with both a 3-Hβ relative configuration and a trans C/D ring conformation for the quinolizidine system[30] (δ 22.9 for C-6 and δ 3.95, dd, J = 12, 4 Hz for H-3). It is noteworthy that the cis relationship between H-3 and H-15 implies a boat conformation for the D ring. This feature was made evident by the ^{1}H NMR spectrum of **19**, in which the vicinal coupling between protons H-14$_{eq}$ and H-15$_{eq}$ ($J \sim 12$ Hz) corresponds to a dihedral angle near 0°.

At this point, three operations were required to complete the synthesis: epimerization of the C-20 equatorial cyano group to the axial position, adjustment of the functionalization at C-21, and aromatization of the β-carboline unit. The epimerization at C-20 was partially accomplished by deprotonation of nitrile **19** with LDA, followed by quenching of the resulting stabilized anion with diluted hydrochloric acid at −78 °C.[31] A mixture of pentacyclic nitriles **19** and **20** (2:3 ratio), the latter with the natural relative stereochemistry at C-20, was obtained.[32] It is worth mentioning that the major epimer **20** arises from the equatorial protonation of the exocyclic α-cyano carbanion to leave an axial cyano substituent.[33] Both isomers were separated by column chromatography, and the wrong minor epimer **19** was reused. The relative configuration at C-20 in nitriles **19** and **20** was established from their ^{13}C NMR data by considering the existence or absence of γ-effects upon C-14, C-16, or C-18.[25]

DIBALH reduction of nitrile **20**, followed by hydrolysis of the intermediate imine, afforded the corresponding aldehyde **21** without appreciable epimerization.[34] This aldehyde was immediately reduced ($NaBH_4$) to the alcohol **23**, which is stereochemically homogeneous. Finally, treatment of **23** with palladium black and maleic acid[35] in boiling water for 20 h caused the dehydrogenation of the C ring to give melinonine-E (**1**) in 63% yield. The ^{1}H and ^{13}C NMR data of our synthetic (±)-melinonine-E chloride were shown to be virtually superimposable on those recorded for the natural product.[4] The R_f values of the corresponding picrates were also coincident.[36]

Strychnoxanthine (**2**) possesses a greater oxidation level than melinonine-E (**1**), incorporating a ketone group at C-14. Therefore, it was of interest to introduce this functionality at the same time in which the aromatization process takes place, using the pentacyclic alcohol **23** as the precursor as above. For this purpose, after protection of the hydroxyl group of **23**, the acetate **25** was oxidized with SeO_2.[37] In this manner, acetate **28** was obtained, and after saponification, (±)-strychnoxanthine (**2**) was isolated. The IR, UV, ^{1}H and ^{13}C NMR, and R_f values of

(29) It is noteworthy that dichloromethylcarbamoyl radicals, generally considered to have an electrophilic nature, undergo cyclization on electron-poor double bonds with good yields. Recently, we have noted that these radicals also undergo cyclization on simple alkenes and alkenes with electron-donating groups: Quirante, J.; Escolano, C.; Bonjoch, J. XVI Spanish Symposium on Organic Chemistry, Ciudad Real, Spain, 1997.

(30) (a) Gribble, G. W.; Nelson, R. B.; Johnson, J. L.; Levy, G. C. *J. Org. Chem.* **1975**, *40*, 3720−3725. (b) Tourwé, D.; Van Binst, G. *Heterocycles* **1978**, *9*, 507−533. (c) Lounasmaa, M.; Jokela, R.; Hanhinen, P.; Miettinen, J.; Salo, J. *Tetrahedron* **1994**, *50*, 9207−9222 and references therein.

(31) For a review on kinetic protonation of enols, enolates, and analogues, see: Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263−268.

(32) Attempts to induce the epimerization of nitrile **19** using LDA and quenching with *tert*-butyl bromide or 2,6-di-*tert*-butyl-4-methylphenol, or using KHMDS and quenching with HCl (0.5 N), were less fruitful.

(33) For protonation of cyclohexyl anions, see: Lüning, U.; Baumgartner, H.; Manthey, C.; Meynhardt, B. *J. Org. Chem.* **1996**, *61*, 7922−7926. See also: Klein, J. *Tetrahedron* **1974**, *30*, 3349−3353. Hoz, S.; Azran, C.; Sella, A. *J. Am. Chem. Soc.* **1996**, *118*, 5456−5461.

(34) Aldehydes **21** and **22** (coming from nitrile **19**) epimerized either in $CDCl_3$ solution or by column chromatography (SiO_2) to a 3:7 mixture of **21** and **22**, respectively. The reduction of this mixture afforded alcohols **23** and **24**, which we could not separate.

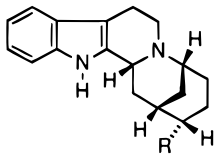
(35) Fujii, T.; Ohba, M.; Ohashi, T. *Tetrahedron* **1993**, *49*, 1879−1890.

(36) We thank Professor M. Hesse (Universität Zürich) for a sample of natural melinonine-E (picrate form).

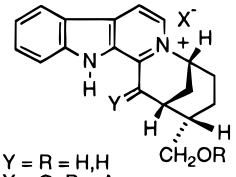
(37) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907−913.

synthetic (±)-**2** proved to be virtually identical with those obtained with a natural sample of strychnoxanthine.[5,38] The NMR spectra data for alkaloids **1** and **2** have been unambiguously assigned, aided by HMQC, HMBC, and NOESY experiments.

On the other hand, in a parallel sequence of reactions, the nitrile **19** was converted into (±)-20-epimelinonine-E (**27**) and (±)-20-epistrychnoxanthine (**30**) (see the Experimental Section).



22 R = CHO
24 R = CH_2OH
26 R = CH_2OAc



27 Y = R = H,H
29 Y = O, R = Ac
30 Y = O, R = H

In summary, the first synthesis of (±)-melinonine-E and (±)-strychnoxanthine from an advanced common intermediate (i.e., alcohol **23**) has been accomplished. The synthesis starts from tryptamine and, in the key steps, makes use of a radical cyclization process to generate the 2-azabicyclo[3.3.1]nonane DE ring system and a Bischler−Napieralski cyclization to achieve the pentacyclic skeleton. The final steps require the adjustment of the stereochemistry and functionality at C-20/C-21 and the oxidation of the C ring.

Experimental Section

General. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution, using Me_4Si as internal standard. Chemical shifts are reported in ppm (δ) downfield from Me_4Si, and coupling constants are expressed in hertz (Hz). NMR peak assignments are given only when they are derived from definitive two-dimensional NMR experiments (500 MHz). The ^{13}C NMR spectra (50 or 75 MHz), when an unambiguous assignation is not available, are reported as follows: chemical shift (multiplicity determined from DEPT spectra). Only noteworthy IR absorptions (cm^{-1}) are listed. Melting points were determined in a capillary tube. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with iodoplatinate reagent or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230−240 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvent was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by the Centro de Investigación y Desarrollo (CSIC), Barcelona, Spain.

***N*-[4,4-(Ethylenedioxy)cyclohexyl]tryptamine (3).** To a solution of tryptamine (13.2 g, 82.4 mmol) in 1,2-dichloroethane (1.5 L) at rt were added 1,4-cyclohexanedione monoethylene acetal (12.1 g, 77.5 mmol), sodium triacetoxyborohydride (25.0 g, 117.9 mmol), and glacial acetic acid (4.4 mL, 77.1 mmol). After stirring for 24 h, the mixture was concentrated and the residue was taken up with CH_2Cl_2 (700 mL). The organic solution was washed with saturated aqueous Na_2CO_3 and water, dried, and concentrated. The resulting crude was recrystallized from CH_2Cl_2 to give **3** (20.2 g, 87%) as a white solid: mp 138−139 °C; IR (KBr) 3167, 1105; ^1H NMR (200 MHz) 1.45 (qd, J = 12, 3, 2 H), 1.54 (td, J = 12, 3, 2 H), 1.67−1.90 (m, 4 H), 2.55 (tt, J = 10, 3, 1 H), 2.98 (s, 4 H), 3.91 (s, 4 H), 7.02 (d, J = 2.5, 1 H), 7.10 (td, J = 7, 1.5, 1 H), 7.19 (td, J = 7, 1.5, 1 H), 7.34 (d, J = 7.5, 1 H), 7.62 (dt, J = 7.5, 1 H), 8.30 (br s, 1 H); ^{13}C NMR 26.0 (t), 30.2 (t, 2C), 33.0 (t, 2C), 47.1 (t), 55.2 (d), 64.2 (t, 2C), 108.7 (s), 111.1 (d), 113.7 (s), 118.8 (d), 119.1 (d), 121.1 (d), 121.9 (d), 127.4 (s), 136.4 (s); MS (EI) *m*/*z* 170 (100), 171, 144, 143, 141, 131, 130, 108, 99, 97, 56, 55. Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 72.00; H, 8.05; N, 9.33. Found: C, 72.23; H, 8.10; N, 9.35.

***N*-[4,4-(Ethylenedioxy)cyclohexyl]-*N*-(trichloroacetyl)tryptamine (4a).** To a solution of **3** (9.20 g, 30.7 mmol) in CH_2Cl_2 (45 mL) were added pyridine (2.60 mL, 32.2 mmol) and dropwise trichloroacetyl chloride (5.3 mL, 47 mmol) in CH_2Cl_2 (4.5 mL). The mixture was stirred at rt for 12 h and then concentrated. The residue was dissolved in CH_2Cl_2 and washed with aqueous HCl (1 N), saturated aqueous Na_2CO_3, and brine. The organic phase was dried and concentrated, and the residue was chromatographed (CH_2Cl_2) to give trichloroacetamide **4a** (12.1 g, 88%) as a yellow solid: mp 163−165 °C (CH_2Cl_2); IR (KBr) 3357, 1663, 1103; ^1H NMR (200 MHz) 1.5−2.1 (m, 8 H), 3.06 and 3.57 (2m, AA′BB′ system, 4 H), 3.95 (s, 4 H), 4.45 (m, 1 H), 7.03 (d, J = 2, 1 H), 7.13 (td, J = 7, 1.5, 1 H), 7.20 (td, J = 7, 1.5, 1 H), 7.35 (dd, J = 7, 1.5, 1 H), 7.81 (dd, J = 7, 1.5, 1 H), 8.13 (br s, 1H); ^{13}C NMR 24.0 (t), 27.2 (t, 2C), 33.8 (t, 2C), 46.1 (t), 57.5 (d), 64.3 (t), 64.5 (t), 93.8 (s), 107.0 (s), 111.0 (d), 112.9 (s), 119.2 (d), 119.4 (d), 122.0 (d, 2C), 127.3 (s), 136.2 (s), 159.9 (s); MS (EI) *m*/*z* 446 (2, M^+), 168, 144, 143 (100), 131, 130, 115, 99, 97, 86, 77, 55. Anal. Calcd for $C_{20}H_{23}Cl_3N_2O_3$: C, 53.88; H, 5.20; N, 6.28. Found: C, 53.47; H, 5.19; N, 6.26.

***N*-(Chloroacetyl)-*N*-[4,4-(ethylenedioxy)cyclohexyl]tryptamine (4b).** A suspension of **3** (0.5 g, 1.66 mmol), magnesium oxide (0.17 g, 4.16 mmol), and chloroacetyl chloride (0.13 mL, 1.66 mmol) in dioxane was stirred at rt for 24 h. After filtration of the magnesium oxide, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The dried extracts were concentrated to give **4b** (0.41 g, 68%) as a pale yellow solid: IR (KBr) 3258, 1644; ^1H NMR (200 MHz) (3:2 mixture of *E* and *Z* rotamers) 1.50−2.20 (m, 8 H), 3.05 and 3.55 (2m, AA′BB′ system, 4 H), 3.65 (m, 0.6 H), 3.88 (s, 0.8 H), 3.96 and 3.97 (2s, 4 H), 4.17 (s, 1.2 H), 4.45 (m, 0.4 H), 7.0−7.9 (m, 5 H), 8.15, 8.30 (2br s, 1 H); ^{13}C NMR (*E* rotamer) 28.3 (t), 27.3 (t, 2C), 33.8 (t, 2C), 41.8 (t), 43.6 (t), 56.8 (d), 64.2 (t, 2C), 107.1 (s), 111.0 (d), 113.0 (s), 119.4 (d), 119 (d), 122.1 (d), 121.7 (d), 127.3 (s), 136.2 (s), 166.2 (s); ^{13}C NMR (*Z* rotamer) 24.7 (t), 27.3 (t, 2C), 33.8 (t, 2C), 41.4 (t), 44.6 (t), 53.5 (d), 64.2 (t, 2C), 107.6 (s), 111.5 (d), 113.0 (s), 118.0 (d), 119.0 (d), 122.1 (d), 122.2 (d), 126.7 (s), 136.2 (s), 167.0 (s). Anal. Calcd for $C_{20}H_{25}ClN_2O_3 \cdot {}^3/_4H_2O$: C, 61.53; H, 6.84; N, 7.18. Found: C, 61.30; H, 6.51; N, 7.21.

***N*-(4-Oxocyclohexyl)-*N*-(trichloroacetyl)tryptamine (5a).** To a solution of **4a** (5 g, 12.4 mmol) in THF (5 mL) was added aqueous HCl (3 N, 30 mL), and the mixture was heated at 65 °C for 5 h. After THF evaporation, the aqueous phase was extracted with CH_2Cl_2. The dried extracts were concentrated and chromatographed (CH_2Cl_2) to give cyclohexanone **5a** (3.8 g, 85%) as a white solid and starting material **4a** (0.3 g, 6%). **5a**: mp 170−171 °C (CH_2Cl_2); IR (KBr) 3370, 1718, 1664; ^1H NMR (COSY) 1.93−2.03 (m, 2 H, H-2_{ax} and H-6_{ax}), 2.15 (dm, J = 13, 2 H, H-2_{eq} and H-6_{eq}), 2.41−2.48 (m, 4 H), 3.08 (ddd, J = 8, 7, 1, 2 H, CH_2Ar), 3.52 (ddd, J = 8, 7, 1, 2 H, CH_2N), 4.88 (tt, J = 12, 3.5, 1 H, H-1_{ax}), 7.03 (d, J = 2.5, 1 H, H-2), 7.13 (td, J = 7.5, 1, 1 H, H-5), 7.19 (td, J = 7.5, 1, 1 H, H-6), 7.35 (d, J = 8.5, 1 H, H-7), 7.70 (d, J = 8, 1 H, H-4), 8.00 (br s, 1 H, NH); ^{13}C NMR (HMQC) 23.8 (CH_2), 29.1 (C-2′, C-6′), 39.6 (C-3′, C-5′), 46.2 (CH_2N), 56.6 (C-1′), 93.7 (CCl_3), 111.2 (C-7), 112.4 (C-3), 118.8 (C-4), 119.6 (C-5), 122.1 (C-2 and C-6), 127.1 (C-3a), 136.1 (C-7a), 159.9 (CO), 208.1 (CO); MS (EI) *m*/*z* 199, 144, 143, 131, 130 (100), 115, 77, 69, 55. Anal. Calcd for $C_{18}H_{19}Cl_3N_2O_3$: C, 53.82; H, 4.77; N, 6.97; Cl, 26.48. Found: C, 53.85; H, 4.88; N, 6.82; Cl, 26.95.

***N*-(Chloroacetyl)-*N*-(4-oxocyclohexyl)tryptamine (5b).** To a cold (0 °C) solution of **4b** (100 mg, 0.28 mmol) in THF (0.64 mL) were added TFA (0.68 mL, 8.8 mmol) and water (0.6 mL). The reaction mixture was stirred at rt for 24 h. THF

(38) We thank Professor L. Angenot (Université de Liège) for a sample of natural strychnoxanthine (chloride form). The NMR spectra of (±)-**2**·HCl were recorded in either D_2O or CD_3OD.

was evaporated, and the residue was taken up with CH_2Cl_2. The organic solution was washed with brine, dried, and concentrated. Chromatography (1% MeOH in CH_2Cl_2) gave ketone **5b** (60 mg, 64%): mp 110−111 °C (EtOAc); IR (film) 3400, 1715, 1642; ^{1}H NMR (300 MHz) (3:2 mixture of *Z* and *E* rotamers) 1.9−2.2 (m, 4 H), 2.49 (t, *J* = 5.5, 4 H), 3.05 (dd, *J* = 8, 7, 2 H), 3.49 (m, 1 H), 3.58 (t, *J* = 7, 1 H), 3.91 (s, 1.2 H), 4.15 (m, 0.4 H), 4.24 (s, 0.8 H), 4.64 (quint, *J* = 7.5, 0.6 H), 7.02 (d, *J* = 2, 1H), 7.11−7.25 (m, 2 H), 7.36 (d, *J* = 8, 0.4 H), 7.40 (d, *J* = 8, 0.6 H), 7.55 (d, *J* = 8, 0.6 H), 7.72 (d, *J* = 8, 0.4 H), 8.25 (br, 0.4 H), 8.45 (br, 0.6 H); ^{13}C NMR (*Z* rotamer) 27.2 (t), 29.2 (t, 2C), 39.9 (t, 2C), 41.5 (t), 45.8 (t), 53.7 (d), 111.3 (s), 111.6 (d), 118.0 (d), 119.8 (d), 122.0 (d), 122.2 (d), 126.6 (s), 136.2 (s), 167.1 (s), 209.4 (s); ^{13}C NMR (*E* rotamer) 24.6 (t), 30.3 (t, 2C), 39.7 (t, 2C), 41.8 (t), 43.8 (t), 55.9 (d), 111.2 (d), 112.8 (s), 118.4 (d), 118.8 (d), 121.4 (d), 121.9 (d), 127.2 (s), 136.1 (s), 166.2 (s), 208.2 (s). Anal. Calcd for $C_{18}H_{21}ClN_2O_2 \cdot {}^3/_4H_2O$: C, 62.42; H, 6.55; N, 8.08. Found: C, 62.29; H, 6.19; N, 7.98.

1-(*tert*-Butoxycarbonyl)-*N*-(chloroacetyl)-*N*-(4-oxocyclohexyl)tryptamine (8). To a solution of ketone **5b** (604 mg, 1.8 mmol) in CH_2Cl_2 (6 mL) at rt were added DMAP (24.1 mg, 0.19 mmol) and di-*tert*-butyl dicarbonate (475 mg, 2.17 mmol). After stirring for 18 h, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 and extracted with aqueous $KHSO_4$ (1 M). The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, and brine. The dried organic extracts were concentrated to give **8** (580 mg, 77%) as a white solid: mp 130−131 °C (EtOAc); IR ($CHCl_3$) 1725, 1640; ^{1}H NMR (200 MHz) (3:2 mixture of *E* and *Z* rotamers) 1.68 and 1.70 (2s, 9 H), 1.95−2.25 (m, 4 H), 2.4−2.6 (m, 4 H), 3.0 and 3.55 (2m, AA′BB′ system, 4 H), 3.65 (m, 0.6 H), 4.06 (s, 0.8 H), 4.25 (s, 1.2 H), 4.60 (m, 0.4 H), 7.10−7.80 (m, 5 H), 8.15 (br s, 1 H); ^{13}C NMR (*E* rotamer) 24.3 (t), 28.0 (q), 30.2 (t, 2C), 39.5 (t, 2C), 41.7 (t), 42.7 (t), 55.8 (d), 83.4 (s), 115.0 (d), 117.5 (s), 119.1 (d), 122.5 (d), 122.9 (d), 124.3 (d), 129.5 (s), 135.3 (s), 149.4 (s), 166.1 (s), 207.9 (s); ^{13}C NMR (*Z* rotamer) 26.9 (t), 28.0 (q), 29.0 (t, 2C), 39.7 (t, 2C), 41.4 (t), 44.8 (t), 53.5 (d), 83.8 (s), 115.4 (d), 116.0 (s), 118.1 (d), 122.7 (d), 122.9 (d), 124.7 (d), 130.1 (s), 135.3 (s), 149.4 (s), 166.6 (s), 209.0 (s). Anal. Calcd for $C_{22}H_{29}ClN_2O_4$: C, 62.78; H, 6.94; N, 6.66. Found: C, 62.89; H, 6.95; N, 6.67.

2-[2-(3-Indolyl)ethyl]-2-azabicyclo[3.3.1]nonane-3,6-dione (10). To a solution of chloroacetamide **8** (100 mg, 0.23 mmol) in toluene (2 mL) was added freshly sublimed potassium *tert*-butoxide (52 mg, 0.46 mmol), and the reaction mixture was stirred at reflux for 3 h. Then, CH_2Cl_2 (13 mL) and aqueous HCl (2 N, 5 mL) were added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. Chromatography (EtOAc) gave **2-[2-[1-(*tert*-butoxycarbonyl)-3-indolyl]ethyl]-2-azabicyclo[3.3.1]-nonane-3,6-dione (9)** (10 mg, 11%): IR (NaCl) 1712, 1650, 1638; ^{1}H NMR (300 MHz) 1.56 (s, 9 H), 1.5−2.7 (m, 8 H), 2.75 (br s, 1 H), 2.90−3.25 (m, 3 H), 3.40 (br s, 1 H), 4.15−4.35 (m, 1 H), 7.00−7.35 (m, 3 H), 7.37 (d, *J* = 7, 1 H), 7.70 (d, *J* = 7, 1 H).

TFA (0.01 mL, 0.14 mmol) was added to a stirred solution of **9** (10 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL) at rt. After 6 h, the mixture was poured into saturated aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2. The dried organic extracts were concentrated, dried, and purified by chromatography (1% MeOH in CH_2Cl_2) to give dione **10** (6 mg, 80%): IR (KBr) 3404, 1712, 1620; ^{1}H NMR[7] (COSY) 1.72 (tdd, *J* = 13.5, 5.5, 2, 1 H, H-18$_{ax}$), 1.86 (*apparent* 2s, 2 H, H-16), 2.16 (dm, *J* = 13, 1 H, H-18$_{eq}$), 2.31 (dd, *J* = 16, 5, 1 H, H-19$_{eq}$), 2.41 (ddd, *J* = 16, 13, 7, 1 H, H-19$_{ax}$), 2.44 (d, *J* = 17.5, 1 H, H-14$_{eq}$), 2.70 (dd, *J* = 18, 8, 1 H, H-14$_{ax}$), 2.73 (br s, 1 H, H-15$_{eq}$), 3.06−3.23 (m, 3 H), 3.39 (m, $W_{1/2}$ = 8, 1 H, H-17$_{eq}$), 4.25 (m, 1 H, H-5), 7.07 (d, *J* = 2, 1 H, H-2), 7.13 (td, *J* = 8, 1, 1 H, H-10), 7.20 (td, *J* = 8, 1, 1 H, H-11), 7.37 (d, *J* = 8, 1 H, H-12), 7.66 (d, *J* = 8, 1 H, H-9), 8.08 (br s, 1 H, NH); ^{13}C NMR, Table 1. Anal. Calcd for $C_{18}H_{20}N_2O_2 \cdot {}^3/_4H_2O$: C, 69.77; H, 6.91; N, 9.04. Found: C, 69.53; H, 6.89; N, 9.02.

***N*-[*trans*-4-Cyano-4-[(trimethylsilyl)oxy]cyclohexyl]-*N*-(trichloroacetyl)tryptamine (11).** To a solution of **5a** (4.0 g, 9.96 mmol) in CH_2Cl_2 (28 mL) were added anhydrous (freshly sublimed) zinc iodide (260 mg, 0.8 mmol) and trimethylsilyl cyanide (1.46 mL, 19.9 mmol). The mixture was heated at 65 °C for 2 h and concentrated to give **11** (3.47 g, 74%) which was pure enough for further transformations. Chromatography (CH_2Cl_2) followed by recrystallization from CH_2Cl_2 yielded a highly pure sample of **11** as white crystals: mp 209−210 °C; IR (KBr) 3403, 1668; ^{1}H NMR (300 MHz) 0.26 (s, 9 H), 1.60−2.07 (m, 6 H), 2.25 (d, *J* = 12, 2 H), 3.08 and 3.58 (2m, AA′BB′ system, 4 H), 4.40 (m, 1 H), 7.05 (d, *J* = 1.5, 1 H), 7.15 (td, *J* = 7, 1, 1 H), 7.20 (td, *J* = 7, 1, 1 H), 7.36 (d, *J* = 7.5, 1 H), 7.80 (d, *J* = 7.5, 1 H), 8.04 (br s, 1 H); ^{13}C NMR 1.38 (q), 24.0 (t), 26.7 (t, 2C), 38.4 (t, 2C), 46.3 (t), 56.7 (d), 70.2 (s), 93.6 (s), 111.1 (d), 112.6 (s), 119.2 (d), 119.7 (d), 120.6 (s), 122.1 (d), 122.2 (d), 127.2 (s), 136.2 (s), 159.9 (s). Anal. Calcd for $C_{22}H_{28}Cl_3N_3O_2Si \cdot {}^2/_3H_2O$: C, 51.51; H, 5.76; N, 8.19. Found: C, 51.27; H, 5.46; N, 8.16. HRMS calcd for $C_{22}H_{28}Cl_3N_3O_2Si$ 499.1016, found 499.1029.

***N*-(4-Cyanocyclohex-3-en-1-yl)-*N*-(trichloroacetyl)-tryptamine (13). Method A.** To a solution of crude **11** (7.5 g, 14.9 mmol) in benzene (6 mL) were added pyridine (23 mL) and $POCl_3$ (4 mL, 43.8 mmol), and the mixture was heated at reflux for 5 h. The mixture was concentrated, and the residue was taken up with CH_2Cl_2. The organic solution was washed with aqueous HCl (1 N) and brine, dried, and concentrated. Chromatography (CH_2Cl_2) gave α,β-unsaturated nitrile **13** (3.4 g, 46% overall yield from ketone **5a**) as a white power: mp 192−194 °C ($CHCl_3$); IR (KBr) 3383, 2325, 1674; ^{1}H NMR (200 MHz) 1.70−2.60 (m, 6 H), 3.12 and 3.52 (2m, AA′BB′ system, 4 H), 4.61 (m, 1 H), 6.51 (br s, 1 H), 7.04 (d, *J* = 2.5, 1 H), 7.10−7.30 (m, 2 H), 7.38 (d, *J* = 7, 1 H), 7.71 (d, *J* = 7, 1 H), 8.02 (br s, 1 H); ^{13}C NMR 23.7 (t), 25.8 (t), 27.0 (t), 29.1 (t), 46.1 (t), 53.5 (s), 93.3 (s), 111.2 (d), 112.2 (s), 112.5 (s), 118.5 (s), 118.8 (d), 119.6 (d), 120.0 (d), 122.2 (d), 127.2 (s), 136.2 (s), 142.2 (d), 160.1 (s); MS (EI) *m*/*z* 144, 143, 131, 130 (100), 103, 77, 69, 57, 55. Anal. Calcd for $C_{20}H_{21}Cl_3N_2O_3$: C, 55.56; H, 4.42; N, 10.23; Cl, 25.90. Found: C, 55.29; H, 4.34; N, 10.06; Cl, 26.17.

Method B. To a solution of crude **11** in THF (4 mL) was added aqueous HCl (3 N, 2.5 mL). The resulting solution was heated at 65 °C for 1 h. After separation of the two phases, the aqueous one was extracted with Et_2O. The combined organic extracts were dried and concentrated, and the residue was chromatographed (CH_2Cl_2) to give ***N*-(*trans*-4-cyano-4-hydroxycyclohexyl)-*N*-(trichloroacetyl)tryptamine (12**; 3.0 g, 70%)[39] as a white solid: mp 210 °C dec; IR (KBr) 3476, 3356, 1670; ^{1}H NMR (200 MHz, CD_3OD) 1.60−2.40 (m, 8 H), 3.10 and 3.58 (2m, AA′BB′ system, 4 H), 4.40 (m, 1 H), 7.07 (d, *J* = 2, 1 H), 7.14 (td, *J* = 7, 1.5, 1 H), 7.20 (td, *J* = 7, 1.5, 1 H), 7.36 (dd, *J* = 7, 1.5, 1 H), 7.79 (d, *J* = 7, 1 H), 8.00 (br s, 1 H); ^{13}C NMR 24.8 (t), 27.6 (t, 2C), 37.7 (t, 2C), 47.5 (t), 58.3 (d), 69.8 (s), 94.7 (s), 112.2 (d), 112.5 (s), 119.6 (d), 119.9 (d), 121.0 (s), 122.4 (d), 123.7 (d), 128.6 (s), 138.0 (s), 161.4 (s); MS *m*/*z* 199, 198, 170, 144, 143, 131, 130 (100), 115, 97, 77, 69, 57, 55. Anal. Calcd for $C_{19}H_{20}Cl_3N_3O_2 \cdot {}^1/_3H_2O$: C, 52.50; H, 4.79; N, 9.67. Found: C, 52.66; H, 4.71; N, 9.44. HRMS calcd for $C_{19}H_{20}Cl_3N_3O_2$ 427.0621, found 427.0632.

To a cold (0 °C) solution of **12** (2.8 g, 6.6 mmol) in pyridine (17 mL) was slowly added $POCl_3$ (4 mL, 43.8 mmol), and the mixture was stirred at rt for 5 h. The mixture was concentrated, and the residue was taken up with CH_2Cl_2. The organic solution was washed with aqueous HCl (1 N) and brine, dried, and concentrated. Chromatography (CH_2Cl_2) gave **13** (1.7 g, 63%, 44% overall yield from **5a**).

(1*RS*,5*SR*,6*SR*)-2-[2-(3-Indolyl)ethyl]-3-oxo-2-azabicyclo-[3.3.1]nonane-6-carbonitrile (16). To a boiling solution of **13** (1.6 g, 3.9 mmol) and AIBN (200 mg, 1.2 mmol) in benzene (32 mL) was added TMS_3SiH (4.2 mL, 13.6 mmol) dropwise, and the mixture was heated under reflux for 3 h. Bu_3SnH

(39) This compound was also obtained from **5a**, but as a mixture of cis−trans isomers, when using acetone cyanohydrin and aqueous K_2CO_3: ^{13}C NMR ($CDCl_3$) (cis isomer) 23.4 (t), 29.7 (t, 2C), 35.4 (t, 2C), 46.0 (t), 56.7 (d), 64.7 (s), 93.4 (s), 111.2 (d), 112.1 (s), 118.8 (d), 119.4 (d), 120.8 (s), 122.1 (d), 122.2 (d), 127.1 (s), 136.0 (s), 160.0 (s).

(2.3 mL, 8.5 mmol) and AIBN (139 mg, 0.84 mmol) were added to the reaction mixture, and the solution was again refluxed for 3 h. After the solvent had been evaporated off, CH_2Cl_2 was added to the residue and the solution was washed several times with aqueous KF (1 M). The mixture was filtered through Celite and chromatographed (3% MeOH in CH_2Cl_2) to give **16** (764 mg, 64%) as white crystals: mp 196−197 °C (CH_2Cl_2); IR (KBr) 3429, 2240, 1612; ^{1}H NMR[7] (COSY) 1.32 (tq, 1 H, J = 13.5, 2, 1 H, H-18$_{ax}$), 1.51 (dm, J = 13, 1 H, H-16), 1.66 (masked, 1 H, H-16), 1.69 (qd, J = 14, 4, 1 H, H-19$_{ax}$), 1.79 (dm, J = 14, 1 H, H-18$_{eq}$), 1.87 (dm, J = 14.5, 1 H, H-19$_{eq}$), 2.40 (br s, 1 H, H-15$_{eq}$), 2.64−2.70 (m, 3 H, H-14 and H-20$_{ax}$), 2.97−3.14 (m, 3 H, H-5 and H-6), 3.24 (br s, 1 H, H-17$_{eq}$), 4.15 (m, 1 H, H-5), 7.03 (s, 1H, H-2), 7.10 (td, J = 8, 1, 1 H, H-10), 7.17 (td, J = 7, 1, 1 H, H-11), 7.35 (d, J = 8.5, 1 H, H-12), 7.61 (d, J = 8, 1 H, H-9), 8.08 (br s, 1 H, NH); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{21}N_3O$: C, 74.23; H, 6.89; N, 13.68. Found: C, 74.11; H, 6.89; N, 13.56.

Radical Cyclization of 13 with TMS_3SiH. To a boiling solution of **13** (500 mg, 1.21 mmol) and AIBN (210 mg, 1.28 mmol) in benzene (10 mL) was added TMS_3SiH (1.30 mL, 4.23 mmol) dropwise, and the mixture was heated under reflux for 3 h. After the solvent had been evaporated off, the residue was chromatographed (1−3% MeOH in CH_2Cl_2). The first eluate gave **(1*RS*,5*RS*,6*SR*)-4,4-dichloro-2-[2-(3-indolyl)-ethyl]-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (14)** (50 mg, 11%): white solid; mp 207−208 °C (CH_2Cl_2); IR (KBr) 3350, 2247, 1666; ^{1}H NMR[7] (COSY) 1.40 (tm, J = 12, 1 H, H-18$_{ax}$), 1.56 (dt, J = 14.5, 3, 1 H, H-16), 1.82 (qd, J = 14, 4, 1 H, H-19$_{ax}$), 1.85 (masked, 1 H, H-18$_{eq}$), 1.93 (dm, J = 13, 1 H, H-19$_{eq}$), 2.41 (dm, J = 13, 1 H, H-16), 2.90 (dt, J = 12, 3, 1 H, H-20$_{ax}$), 3.07 (br s, 1 H, H-17), 3.15 (m, 1 H, H-15), 3.02−3.23 (m, 3 H, H-6 and H-5), 4.21 (m, 1 H, H-5), 7.08 (d, J = 2, 1 H, H-2), 7.13 (td, J = 7, 1, 1 H, H-10), 7.20 (td, J = 7, 1, 1 H, H-11), 7.37 (d, J = 8, 1 H, H-12), 7.65 (d, J = 7.5, 1 H, H-9), 8.01 (br s, 1 H, NH); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{19}Cl_2N_3O$: C, 60.63; H, 5.05; N, 11.17. Found: C, 60.57; H, 5.03; N, 11.03.

The second eluate gave **(1*RS*,4*SR*,5*RS*,6*SR*)-4-chloro-2-[2-(3-indolyl)ethyl]-3-oxo-2-azabicyclo[3.3.1]nonane-6-carbonitrile (15)** (58 mg, 14%): white crystals; mp 211−212 °C (CH_2Cl_2); IR (KBr) 3306, 2242, 1644; ^{1}H NMR[7] (COSY) 1.38 (tm, J = 12, 1 H, H-18$_{ax}$), 1.63 (dt, J = 14, 3.5, 1 H, H-16), 1.71 (dm, J = 14.5, 1 H, H-16), 1.82 (dm, J = 15, 1 H, H-18$_{eq}$), 1.91 (qd, J = 14, 4, 1 H, H-19$_{ax}$), 1.93 (masked, 1 H, H-19$_{eq}$), 2.77−2.83 (m, 2 H, H-15 and H-20$_{ax}$), 2.99−3.21 (m, 4 H), 4.18 (m, 1 H, H-5), 4.64 (d, J = 6.5, 1 H, H-14$_{ax}$), 7.02 (d, J = 2, 1 H, H-2), 7.10 (td, J = 7, 1, 1 H, H-10), 7.18 (td, J = 7, 1, 1 H, H-11), 7.34 (d, J = 8, 1 H, H-12), 7.60 (d, J = 8, 1 H, H-9), 8.00 (br s, 1 H, NH); ^{13}C NMR, Table 1; MS (EI) *m*/*z* 341 (2, M^+), 144, 143 (100), 130, 98, 97, 85, 83, 81, 73, 71, 69, 67, 57, 55. Anal. Calcd for $C_{19}H_{20}ClN_3O$: C, 66.76; H, 5.85; N, 12.29; Cl, 10.39. Found: C, 66.80; H, 5.83; N, 12.30; Cl, 9.99.

The third eluate gave **16** (164 mg, 44%) which was identical with that obtained above.

Dichlorinated lactam **14** (200 mg, 0.53 mmol) was treated with Bu_3SnH (0.32 mL, 1.2 mmol) and AIBN (59 mg, 0.36 mmol) in benzene (4 mL) at reflux temperature for 5 h. After removal of tin products by chromatography (1% MeOH in CH_2Cl_2), lactam **16** (116 mg, 71%) was isolated. Operating as above from monochlorinated lactam **15** (200 mg, 0.58 mmol), Bu_3SnH (0.16 mL, 0.63 mmol), and AIBN (30 mg, 0.18 mmol), lactam **16** (172 mg, 78%) was isolated.

Cyclization of 13 with Bu_3SnD. To a boiling solution of **13** (300 mg, 0.73 mmol) and AIBN (24 mg, 0.14 mmol) in benzene (6 mL) was added Bu_3SnD (0.2 mL, 0.8 mmol) dropwise, and the mixture was heated under reflux for 8 h. After the solvent had been evaporated off, the residue was chromatographed (1% CH_3OH in CH_2Cl_2). The first eluate gave **17** (89 mg, 32%). In its ^{1}H NMR spectrum the signal at δ 2.86 of analogue **14** is missing, and in its ^{13}C NMR spectrum the signal at δ 32.2 appears as a triplet (J = 20 Hz). The second eluate gave the monochlorinated derivative **18** (57 mg, 23%), in which the incorporation of deuterium on C-14 and C-20 was observed.

(2*RS*,3*RS*,6*SR*,14b*SR*)-2,3,4,5,6,7,8,9,14,14b-Decahydro-2,6-methano-1*H*-azocino[1′,2′:1,2]pyrido[3,4-*b*]indole-3-carbonitrile (19). To a solution of nitrile **16** (1.7 g, 5.5 mmol) in benzene (44 mL) was added $POCl_3$ (7 mL, 74.8 mmol) dropwise very slowly. The reaction mixture was heated at reflux for 75 min. The solvent was evaporated, and the residue was taken up with MeOH (41 mL). To the cooled (0 °C) solution was added $NaBH_4$ (1 g, 26.5 mmol), and it was stirred at this temperature for 1.5 h. Acetone (8.5 mL) was added, and stirring was maintained 10 min. The mixture was concentrated, and the residue was taken up with CH_2Cl_2. The organic solution was washed with water, dried, and concentrated. Chromatography (CH_2Cl_2) gave **19** (850 mg, 53%) as a yellow solid: mp 175−177 °C (CH_2Cl_2); IR (KBr): 3358, 2240; ^{1}H NMR (COSY)[7] 1.16 (tdd, J = 13, 4, 2, 1 H, H-18$_{ax}$), 1.21 (dm, J = 13.5, 1 H, H-16), 1.61−1.66 (m, 2H, H-19$_{eq}$), 1.72 (td, J = 12, 2, 1 H, H-14$_{ax}$), 2.23 (dm, J = 13.5, 1 H, H-16), 2.35 (qd, J = 13, 5, 1 H, H-19$_{ax}$), 2.39 (td, J = 12, 4, 1 H, H-14$_{eq}$), 2.46 (dm, J = 11.5, 1 H, H-15$_{eq}$), 2.54 (dt, J = 12.5, 3.5, 1 H, H-20$_{ax}$), 2.57−2.63 (m, 1 H, H-6), 2.78−2.88 (m, 3 H, H-6, H-5, and H-17$_{eq}$), 2.89−2.96 (m, 1 H, H-5), 3.95 (dd, J = 12, 4, 1 H, H-3$_{ax}$), 7.02 (td, J = 7, 1, 1 H, H-10), 7.07 (td, J = 7, 1, 1 H, H-11), 7.25 (d, J = 8, 1 H, H-12), 7.40 (d, J = 8, 1 H, H-9), 7.65 (br s, 1 H, NH); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.36; H, 7.21; N, 14.42. Found: C, 78.21; H, 7.30; N, 14.40.

Epimerization of Equatorial Nitrile 19 to Axial Nitrile 20. To a solution of **19** (1 g, 3.4 mmol) in THF (90 mL) at −78 °C was added dropwise LDA (7.6 mL, 1.5 M in cyclohexane, 11.3 mmol). After the mixture stirred for 2 h at this temperature, aqueous HCl (0.5 N, 20 mL) was added and the reaction mixture was allowed to warm to rt. THF was evaporated, and the aqueous phase was extracted with CH_2Cl_2. The dried extracts were concentrated and chromatographed (EtOAc). A partial separation afforded 180 mg of nitrile **20**, 352 mg of a mixture of nitriles **20** and **19** (2:1 ratio, from ^{1}H NMR), and 260 mg of nitrile **19**. After a further column of the mixture, **20** was isolated in 41.5% yield, and the starting material **19** was recovered in 37% yield, the latter being submitted to further epimerization reactions.

(2*RS*,3*SR*,6*SR*,14b*SR*)-2,3,4,5,6,7,8,9,14,14b-Decahydro-2,6-methano-1*H*-azocino[1′,2′:1,2]pyrido[3,4-*b*]indole-3-carbonitrile (20): mp 176−178 °C (CH_2Cl_2); IR (KBr) 3409, 2232; ^{1}H NMR[7] (COSY) 1.39 (m, 1 H, H-14$_{ax}$), 1.59 (tdd, J = 14, 3.5, 2, 1 H, H-18$_{ax}$), 1.65 (m, 2 H, H-19$_{eq}$), 1.78 (dm, J = 14, 1 H, H-16), 2.20 (dm, J = 15.5, 1 H, H-16), 2.49 (m, 2 H, H-14$_{eq}$ and H-15), 2.53 (tm, J = 14, 1 H, H-19$_{ax}$), 2.60 (m, 1 H, H-20$_{eq}$), 2.66 (m, 1 H, H-6), 2.88 (m, 2 H, H-5 and H-6), 3.00 (m, 2 H, H-5 and H-17), 4.04 (dm, J = 12, 1 H, H-3$_{ax}$), 7.09 (td, J = 7, 1, 1 H, H-10), 7.13 (td, J = 7, 1, 1 H, H-11), 7.30 (d, J = 8, 1 H, H-12), 7.47 (d, J = 7.5, 1 H, H-9), 7.70 (br s, 1 H, NH); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{21}N_3 \cdot {}^1/_2H_2O$: C, 76.01; H, 7.39; N, 13.99. Found: C, 75.95; H, 7.37; N, 13.60. HRMS calcd for $C_{19}H_{21}N_3$ 291.1735, found 291.1725.

(2*RS*,3*SR*,6*SR*,14b*SR*)- and (2*RS*,3*RS*,6*SR*,14b*SR*)-2,3,4,5,6,7,8,9,14,14b-Decahydro-2,6-methano-1*H*-azocino-[1′,2′:1,2]pyrido[3,4-*b*]indole-3-carbaldehyde (21 and 22). To a solution of equatorial nitrile **19** (430 mg, 1.6 mmol) in toluene (6 mL) at −20 °C was added dropwise DIBALH (2 mL, 1 M in toluene). After the mixture stirred for 1 h, 5% aqueous H_2SO_4 (13 mL) was added and then the mixture was allowed to warm to rt over 2 h. The mixture was basified with aqueous NaOH (2 N) and extracted with CH_2Cl_2. The dried extracts were concentrated to give a residue which was chromatographed (from CH_2Cl_2 to 1% MeOH in CH_2Cl_2) to give aldehyde **22** along with its axial C-3 epimer **21** (175 mg, 40%) in a 7:3 ratio, estimated by ^{1}H NMR. It is worth mentioning that without the chromatographic process the reduction yield is much better, as indicated by the overall yield of reduction to the corresponding alcohol (vide infra). Recrystallization from $CHCl_3$ provided an analytical sample: mp 180 °C dec; IR (KBr) 3500, 1720; ^{1}H NMR[7] (COSY) 1.18−1.38 (m, 2.7 H, H-14$_{ax}$, H-16, H-18$_{ax}$, **22** and H-16, H-18$_{ax}$, **21**), 1.51 (td, J = 12, 2.5, 0.3 H, H-14$_{ax}$, **21**), 1.61 (dm, J = 12.5, 0.3 H, H-18$_{eq}$, **21**), 1.70 (dm, J = 12.5, 0.7 H, H-19$_{eq}$, **22**), 1.77 (dm, J = 12.5, 0.7 H,

H-18$_{eq}$, **22**), 1.86 (dm, J = 12.5, 0.3 H, H-19$_{eq}$, **21**), 2.11 (dm, J = 12.5, 0.3 H, H-16, **21**), 2.16 (masked, 0.3 H, H-20$_{ax}$, **21**), 2.18 (qd, J = 13, 4.5, 0.7 H, H-19$_{ax}$, **22**), 2.28 (dt, J = 10, 3.5, 0.7 H, H-20$_{ax}$, **22**), 2.28−2.38 (m, 1.4 H, H-16 and H-14$_{eq}$, **22**), 2.44 (m, 0.3 H, H-19$_{ax}$, **21**), 2.56 (ddd, 0.3 H, J = 13, 11, 5, H-14$_{eq}$, **21**), 2.60−2.75 (m, 1H, H-6), 2.70 (m, $W_{1/2}$ = 20, 1 H, H-15$_{eq}$), 2.95 (m, 0.7 H, H-17$_{eq}$, **22**), 3.2−3.8 (m, 3.3 H, H-5, H-6, and H-17$_{eq}$, **21**), 3.99 (dm, J = 12, 0.7 H, H-3$_{ax}$, **22**), 4.06 (dm, J = 12, 0.3 H, H-3$_{ax}$, **21**), 7.05 (td, J = 7.25, 1.5, 0.7 H, H-10, **22**), 7.06 (td, J = 7.25, 1.5, 0.3 H, H-10, **21**), 7.09 (td, J = 7.25, 1.5, 0.7 H, H-11, **22**), 7.11 (td, J = 7.25, 1.5, 0.3 H, H-11, **21**), 7.25 (d, J = 8, 0.7 H, H-12, **22**), 7.29 (d, J = 8, 0.3 H, H-12, **21**), 7.43 (d, J = 8, 0.7 H, H-9, **22**), 7.45 (d, J = 8, 0.3 H, H-9, **21**), 7.59 (br s, 0.7 H, NH, **22**), 7.63 (br s, 0.3 H, NH, **21**), 9.56 (s, 0.7 H, CHO, **22**), 9.75 (s, 0.3 H, CHO, **21**);^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.53; H, 7.63; N, 9.45.

(2*RS*,3*SR*,6*SR*,14b*SR*)-3-(Hydroxymethyl)-2,3,4,5,6,7,8,9,14,14b-decahydro-2,6-methano-1*H*-azocino[1′,2′:1,2]pyrido[3,4-*b*]indole (23). To a solution of nitrile **20** (500 mg, 1.71 mmol) in toluene (6.6 mL) at −20 °C was added dropwise DIBALH (2.38 mL, 1 M in toluene). After the mixture stirred at −20 °C for 1 h, 5% aqueous H_2SO_4 (13 mL) was added. The resulting mixture was allowed to warm to rt over 2 h. The reaction mixture was basified with aqueous NaOH (2 N) and extracted with CH_2Cl_2. The dried extracts were concentrated to give aldehyde **21** (430 mg), which was immediately reduced to avoid an epimerization process. To a solution of **21** (430 mg, 1.46 mmol) in MeOH (67 mL) at 0 °C was added $NaBH_4$ (116 mg, 3.07 mmol), and the reaction mixture was stirred at rt for 4 h. Water (6.7 mL) was added, MeOH was evaporated, and the organic phase was extracted with CH_2Cl_2. The dried extracts were concentrated, and the residue was chromatographed (CH_2Cl_2) to give alcohol **23** (332 mg, 67% overall yield from nitrile **20**) as a yellow solid: mp 168−169 °C (EtOAc); IR (KBr) 3418, 2928; ^{1}H NMR (COSY) 1.24−1.36 (m, 2 H, H-18$_{ax}$ and H-19$_{eq}$), 1.42 (dm, J = 13.5, 1 H, H-16), 1.45−1.62 (m, 3 H, H-14$_{ax}$, H-18$_{eq}$, and H-20$_{eq}$), 2.00 (dm, J = 12.5, 1 H, H-16), 2.25 (*apparent* dm, J = 10.5, 1 H, H-15$_{eq}$), 2.36 (tm, J = 13, 1 H, H-19$_{ax}$), 2.53 (td, J = 12, 5.5, 1 H, H-14$_{eq}$), 2.65 (dm, J = 11.5, 1 H, H-6), 2.87 (m, 3 H, H-5, H-6, and H-17$_{eq}$), 3.00 (m, 1 H, H-5), 3.68 (dd, J = 11, 7.5, 1 H, H-21), 3.73 (dd, J = 11, 8, 1 H, H-21), 4.06 (dm, J = 12.5, 1 H, H-3$_{ax}$), 7.03 (td, J = 7.5, 1, 1 H, H-10), 7.11 (td, J = 7.5, 1.5, 1 H, H-11), 7.31 (d, J = 8, 1 H, H-12), 7.46 (d, J = 7.5, 1 H, H-9), 7.75 (br s, 1 H, NH); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{24}N_2O\cdot{}^2/_3H_2O$: C, 73.98; H, 8.28; N, 9.08. Found: C, 73.98; H, 8.00; N, 9.26. HRMS calcd for $C_{19}H_{24}N_2O$ 296.1888, found 296.1878.

(2*RS*,3*RS*,6*SR*,14b*SR*)-3-(Hydroxymethyl)-2,3,4,5,6,7,8,9,14,14b-decahydro-2,6-methano-1*H*-azocino[1′,2′:1,2]pyrido[3,4-*b*]indole (24). Operating as above, nitrile **19** (700 mg, 2.40 mmol) was converted by reduction with DIBALH (3.3 mL, 1 M in toluene) into aldehyde **22** (570 mg). Further reduction with $NaBH_4$ (116 mg, 4.3 mmol) in MeOH (95 mL) gave alcohol **24** (483 mg, 69%) as a yellow solid after chromatography (CH_2Cl_2): mp 161−164 °C (EtOAc); IR (KBr) 3252, 2928; ^{1}H NMR (COSY) 1.15−1.25 (m, 3 H, H-16, H-18$_{ax}$ and H-19$_{eq}$), 1.42 (td, J = 12, 2, 1 H, H-14$_{ax}$), 1.58−1.85 (m, 2 H, H-18 and H-20$_{ax}$), 2.10 (ddd, J = 13, 11, 5, 1 H, H-14$_{eq}$), 2.23−2.30 (m, 3 H, H-15, H-16, and H-19$_{ax}$), 2.62 (m, 1 H, H-6), 2.75−2.87 (m, 2 H, H-6 and H-5), 2.85 (br s, 1 H, H-17$_{eq}$), 2.92 (m, 1 H, H-5), 3.34 (dd, J = 10.5, 6, 1 H, H-21), 3.37 (dd, J = 10.5, 8, 1 H, H-21), 3.95 (dm, J = 10, 1 H, H-3$_{ax}$), 7.01 (td, J = 7.5, 1, 1 H, H-10), 7.04 (td, J = 7, 1, 1 H, H-11), 7.22 (d, J = 8, 1 H, H-12), 7.38 (d, J = 7.5, 1 H, H-9), 7.63 (br s, 1 H, NH); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{24}N_2O\cdot{}^2/_3H_2O$: C, 73.98; H, 8.28; N, 9.08. Found: C, 73.97; H, 8.31; N, 8.85. HRMS calcd for $C_{19}H_{24}N_2O$ 296.1888, found 296.1880.

(±)-Melinonine-E (1) Perchlorate. A stirred mixture of alcohol **23** (70 mg, 0.23 mmol), maleic acid (135 mg, 1.16 mmol), and palladium black (80 mg, 0.75 mmol) in water (7 mL) was heated at reflux for 8.5 h. After cooling (5−10 °C) overnight, a further portion of Pd black (50 mg, 0.46 mmol) was added and the reaction mixture was heated at reflux for 9 h. The catalyst was filtered through a short pad of Celite and washed with hot MeOH. The combined filtrate and washings were concentrated to leave a yellowish solid, which was mixed with water (1.5 mL). The resulting aqueous suspension was neutralized with saturated aqueous $NaHCO_3$, and then a solution of $NaClO_4\cdot H_2O$ (56 mg, 0.40 mmol) in water (1 mL) was added. The precipitate was filtered off and washed with water (1 mL) to give **1** perchlorate (58 mg, 63%). Recrystallization from MeOH−Et_2O (1:1) provided an analytical sample as a yellow solid: mp 254−256 °C; IR (KBr) 3425, 2926, 1635, 623; ^{1}H NMR (CD_3OD, COSY and ROESY) 1.30 (m, 1 H, H-19$_{ax}$), 1.74 (dm, J = 15, 1 H, H-19$_{eq}$), 2.02 (dm, J = 14.5, 1 H, H-18$_{eq}$), 2.12 (m, 1 H, H-20$_{eq}$), 2.28 (tm, J = 14, 1 H, H-18$_{ax}$), 2.32 (dm, J = 14, 1 H, H-16$_{syn}$), 2.52 (dt, J = 14.5, 2.5, 1 H, H-16$_{anti}$), 2.79 (br s, 1 H, H-15$_{eq}$), 3.83 (dd, J = 11, 7.5, 1 H, H-21), 3.92 (dd, J = 11, 8, 1 H, H-21), 5.19 (br s, 1 H, H-17$_{eq}$), 7.55 (m, 1 H, H-10), 7.84−7.92 (m, 2 H, H-11 and H-12), 8.44 (m, 1 H, H-5), 8.48 (m, 1 H, H-9), 8.60 (d, J = 6.5, 1 H, H-6); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{21}ClN_2O_5$: C, 58.15; H, 5.40; N, 7.14. Found: C, 58.11; H, 5.76; N, 6.97.

1 Perchlorate (40 mg) was loaded on a basic anion-exchange resin (Amberlite IRA-400, chloride form) and eluted with MeOH. Evaporation of the solvent quantitatively afforded melinonine-E (**1**) chloride (47 mg), which was identical (mp, IR, UV, ^{1}H NMR, and ^{13}C NMR) with the natural melinonine-E chloride form.[4,36] Melinonine-E (**1**) picrate was prepared from **1** chloride (20 mg, 0.06 mmol) by initial conversion to the corresponding betaine on a basic anion-exchange resin (Amberlite IRA-401, hydroxide form) and elution with MeOH. Treatment of the resulting betaine (13 mg, 0.04 mmol) with an equivalent amount of picric acid (9.5 mg, 0.04 mmol) quantitatively afforded **1** picrate as a yellow solid. R_f values of synthetic picrate and an authentic sample[36] were also coincident.

3-Epimelinonine-E (27) Perchlorate.[40] Operating as in the above axial series, from equatorial alcohol **24** (60 mg, 0.20 mmol), maleic acid (116 mg, 1 mmol), and Pd black (80 mg, 0.75 mmol) in water (7 mL) was prepared 3-epimelinonine-E (**27**) perchlorate (50 mg, 63%) as a yellow solid. Recrystallization from MeOH−Et_2O (1:1) provided an analytical sample: mp 260−265 °C; IR (KBr) 3429, 2924, 1635, 625; ^{1}H NMR (CD_3OD, COSY and ROESY) 0.57 (m, 1 H, H-19$_{ax}$), 1.64 (dm, J = 15, 1 H, H-19$_{eq}$), 2.09 (br s, 1 H, H-20$_{ax}$), 2.16 (m, 2 H, H-18), 2.31 (dm, J = 14, 1 H, H-16$_{anti}$), 2.49 (dm, J = 14.5, 1 H, H-16$_{syn}$), 2.76 (br s, 1 H, H-15$_{eq}$), 3.59 (d, J = 7, 2 H, CH_2O), 3.73−3.79 (m, 1 H, H-14), 5.25 (br s, 1 H, H-17$_{eq}$), 7.54 (td, J = 6, 2, 1 H, H-10), 7.86 (m, 2 H, H-11 and H-12), 8.45 (m, 2 H, H-5 and H-9), 8.57 (d, J = 6.5, 1 H, H-6); ^{13}C NMR, Table 1. Anal. Calcd for $C_{19}H_{21}N_2O_5Cl$: C, 58.02; H, 5.55; N, 7.13; Cl, 9.02. Found: C, 58.02; H, 5.55; N, 7.13; Cl, 8.91.

3-Epimelinonine-E (**27**) chloride was obtained from **27** perchlorate using the preceding procedures described for melinonine-E (**1**) chloride: UV (MeOH), λ (nm) 364, 306, 252, 204; HRMS (FAB) calcd for $C_{19}H_{21}N_2O^+$ 293.1653, found 293.1649. 3-Epimelinonine-E (**27**) picrate was prepared from **27** chloride using the preceding procedures described for melinonine-E (**1**) picrate.

(±)-Strychnoxanthine (2) Chloride. To a solution of alcohol **23** (45 mg, 0.15 mmol) in pyridine (5 mL) was added Ac_2O (3 mL). The mixture was stirred at rt overnight. Removal of excess reagent afforded a residue which was taken up with CH_2Cl_2 and washed with water. The dried extracts were concentrated to give a dark solid which was chromatographed (EtOAc) to afford acetate **25** (28 mg, 55%): IR (KBr) 3373, 2928, 1718; ^{1}H (300 MHz) 1.27 (dm, J = 12.5, 1 H), 1.47 (tm, J = 13, 1 H), 1.71 (m, 1 H), 1.94−2.20 (m, 2 H), 2.07 (s, 3 H), 2.36 (tm, J = 13, 1 H), 2.49 (ddd, J = 13, 11, 4.5, 1 H), 2.65 (dm, J = 11, 1 H), 2.89 (m, 3 H), 2.98 (m, 1 H), 4.04 (dm, J = 12, 1 H), 4.11 (dd, J = 11, 7.5, 1 H), 4.18 (dd, J = 11, 8, 1 H), 7.07 (td, J = 7, 1.5, 1 H), 7.12 (td, J = 7, 1.5, 1 H), 7.30 (dd, J = 7, 1.5, 1 H), 7.47 (dd, J = 7, 1.5, 1 H), 7.72 (br s, 1 H); ^{13}C NMR, Table 1.

To a solution of acetate **25** (28 mg, 0.08 mmol) in dioxane (1.5 mL) was added SeO_2 (73.5 mg, 0.66 mmol), and the mixture was stirred for 45 h at reflux. The selenium that

precipitated from the reaction was filtered through Celite and washed with MeOH. The filtrate and washings were combined and concentrated to give **28** as a yellow solid: ^{1}H NMR (CD_3OD) 1.40 (m, 1 H), 1.63 (dm, J = 15, 1 H), 1.95 (m, 1 H), 2.03 (s, 3 H), 2.33 (m, 1 H), 2.66 (m, 1 H), 3.10 (br s, 1 H), 4.46 (m, 1 H), 4.56 (m, 1 H), 5.30 (br s, 1 H), 7.50−9.20 (m, ArH); ^{13}C NMR, Table 1. HRMS calcd for $C_{21}H_{21}N_2O_3$ 349.1539, found 349.1541.

A solution of acetate **28** in EtOH (1 mL) was treated with aqueous NaOH (2 N, 1 mL), EtOH was evaporated, and the aqueous phase was extracted with CH_2Cl_2. The dried extracts were concentrated to afford a violet residue to which HCl (2.5 N) in MeOH was added. The resulting precipitate was filtered off, washed with MeOH, and dried to give **2** chloride (22 mg, 78%), which was identical (R_f values, IR, UV, ^{1}H NMR, and ^{13}C NMR) with an authentic sample,[5,38] as an orange solid: mp 280 °C dec; ^{1}H NMR (CD_3OD, COSY and NOESY) 1.36−1.45 (m, 1 H, H-19$_{ax}$), 1.73 (dm, J = 15, 1 H, H-19$_{eq}$), 2.06 (dm, J = 15, 1 H, H-18$_{eq}$), 2.22 (m, 1 H, H-20$_{eq}$), 2.38 (tdd, 1 H, J = 14.5, 9, 3, H-18$_{ax}$), 2.66 (dt, 1 H, J = 15, 2.5, H-16$_{anti}$), 2.67−2.81 (m, 1 H, H-16$_{syn}$), 3.27 (br s, 1 H, H-15), 3.80 (dd, J = 11, 6.5, H-21), 3.94 (dd, J = 11, 9, H-21), 5.28 (br s, 1 H, H-17), 7.55 (td, J = 7, 1, 1 H, H-10), 7.88 (td, J = 8.5, 1.5, 1 H, H-11), 7.92 (d, J = 8, H-12), 8.49 (d, J = 8, 1 H, H-9), 8.75 (d, J = 6.5, 1 H, H-5), 8.94 (d, J = 6.5, 1 H, H-6); ^{13}C NMR, Table 1; HRMS calcd for $C_{19}H_{19}N_2O_2$ 307.1446, found 307.1450.

20-Epistrychnoxanthine Chloride (30).[41] Operating as in the above axial series, acetoxy derivative **26** was prepared from equatorial alcohol **24** by the foregoing procedure in 49% yield on an identical molar scale: IR (KBr) 3373, 2928, 1718; ^{1}H NMR (300 MHz) 1.16−1.40 (m, 3 H), 1.48 (td, J = 12, 2, 1 H), 1.60−1.85 (m, 2 H), 2.04 (s, 3 H), 2.13 (ddd, J = 13, 11, 5, 1 H), 2.29−2.36 (m, 2 H), 2.64 (m, 1 H), 2.78−3.04 (m, 3 H), 2.98 (br s, 1 H), 3.81 (dd, J = 11, 5.5, 1 H), 3.92 (dd, J = 11, 8, 1 H), 3.99 (dm, J = 11, 1 H), 7.07 (td, J = 7, 1, 1 H), 7.12 (td, J = 7, 1, 1 H), 7.28 (d, J = 7, 1 H), 7.45 (d, J = 7, 1 H), 7.71 (br s, 1 H); ^{13}C NMR, Table 1.

Treatment of **26** (50 mg, 0.14 mmol) with SeO_2 (128 mg, 1.16 mmol) as above afforded **29**:[42] ^{1}H NMR (CD_3OD) 1.20 (m, 1 H), 1.95 (dm, J = 15, 1 H), 2.16 (s, 3 H), 2.15 (m, 1 H), 2.30−2.75 (m, 4 H), 3.10 (dm, J = 14, 1 H), 4.13 (m, 2 H), 5.52 (br s, 1 H), 7.60−9.10 (ArH); ^{13}C NMR, Table 1; HRMS calcd for $C_{21}H_{21}N_2O_3$ 349.1552, found 349.1551.

From 3-epistrychnoxanthine (**29**) was obtained 3-epistrychnoxanthine chloride (**30**) (40 mg, 77%) as an orange solid: mp 280 °C dec; IR (KBr) 3425, 1690, 1626; ^{1}H NMR (CD_3OD, COSY) 0.92 (qd, J = 14.5, 4.5, 1 H, H-19$_{ax}$), 1.86 (dm, J = 14.5, 1 H, H-19$_{eq}$), 2.22−2.23 (m, 2 H, H-18$_{eq}$ and H-20), 2.37 (tdd, J = 14.5, 5, 3, 1 H, H-18$_{ax}$), 2.54 (dt, J = 14.5, 2.5, 1 H, H-16), 3.00 (dm, J = 14.25, 1 H, H-16), 3.30 (masked, 1 H, H-15), 3.45 (dd, J = 11.5, 7.5, 1 H, H-21), 3.59 (dd, J = 11.25, 7, 1 H, H-21), 5.41 (br s, 1 H, H-17), 7.53 (td, J = 7.5, 1, 1 H, H-10), 7.82−7.91 (m, 2 H, H-11 and H-12), 8.48 (d, J = 8, 1 H, H-9), 8.76 (d, J = 6.5, 1 H, H-5), 8.93 (d, J = 6.5, 1 H, H-6); ^{13}C NMR, Table 1; HRMS calcd for $C_{19}H_{19}N_2O_2$ 307.1446, found 307.1444.

Acknowledgment. Financial support from the DGICYT, Spain (Project PB94-0858), is gratefully acknowledged. Thanks are also due to the Comissionat per a Universitats i Recerca (Generalitat de Catalunya) for Grant SGR95-00045 and a fellowship to C.E.

JO971148C

(40) Systematic name: (2*RS*,3*RS*,6*SR*)-3-(hydroxymethyl)-2,3,4,5,6,14-hexahydro-2,6-methano-1*H*-azocino[1′,2′:1,2]pyrido[3,4-*b*]indol-7-ium perchlorate.

(41) Systematic name: (2*RS*,3*SR*,6*RS*)-3-(hydroxymethyl)-1-oxo-2,3,4,5,6,14-hexahydro-2,6-methano-1*H*-azocino[1′,2′:1,2]pyrido[3,4-*b*]-indol-7-ium chloride.

(42) Compound **29** was also prepared, but in a less satisfactory manner, from 3-epimelinonine E perchlorate (**27**) by acetylation (Ac_2O) followed by oxidation (SeO_2) of crude acetate **26**.