Studies on the Configurational Stability of 3-(2-Piperidyl)indoles

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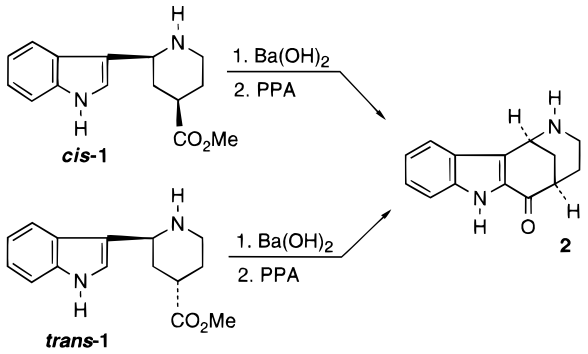
Some years ago we reported that both *cis* and *trans* isomers of 2-(3-indolyl)piperidine-4-carboxylic esters **1** could be converted into tetracyclic ketone **2** in similar yields (38%) by hydrolysis of the ester group with Ba(OH)$_2$, followed by PPA-induced cyclization of the resulting amino acid (Scheme 1).[1] This result was accounted for in terms of an epimerization at the C-4 position of the piperidine ring during the saponification of the ester group because both pure 3-(2-piperidyl)indoles *cis*-**1** and *trans*-**1** were independently converted into an identical epimeric *cis*/*trans* mixture (6:1 ratio) of esters **1** after alkaline hydrolysis followed by treatment of the resulting mixture of amino acids with diazomethane.[1]

In the context of our recent formal syntheses of *Strychnos* and uleine-type alkaloids,[2] we unexpectedly observed that, after alkaline hydrolysis and cyclization with PPA, pure all-*cis* 3-(2-piperidyl)indole **3a** led to a 4:1 mixture of the expected tetracyclic ketone **4a** (the alkaloid nordasycarpidone), bearing an ethyl substituent equatorial with respect to the piperidine ring, and the corresponding C-20[3] epimer **4b**, in which the ethyl substituent is axial with respect to the piperidine ring (Scheme 2).[4]

This unexpected epimerization at the piperidine 3-position (C-20) might be *a priori* accounted for in the same manner as in similar tetracyclic derivatives lacking the 16-oxo substituent:[5,6] protonation at the indole 3-position in the initially formed tetracycle **4a** followed by a retro-Pictet−Spengler reaction with opening of the C ring would lead to an iminium cation in equilibrium with the corresponding enamine (a 3-ethyl-1,4,5,6-tetrahydropyridine). Protonation of the enamine moiety with subsequent cyclization would provide a mixture of epimeric tetracycles **4a** and **4b**. However, this interpretation has proved not to be correct because both **4a** and **4b** are recovered unchanged after being independently treated with PPA at 90 °C under the conditions used in the cyclization step. Consequently, formation of **4b** seems to involve epimerization at both the C-2 and C-4 piperidine positions.

This result prompted us to study the cyclization of pure all-*cis* 3-(2-piperidyl)indole **5a**, and again a mixture (approximate ratio 4:1) of tetracyclic ketones, **6a** and its

Scheme 1



C-20 epimer **6b**, was obtained. Taking into account that it is hard to conceive that C-20 could undergo epimerization in compounds **5a** or **6a**, the formation of the unexpected epimer **6b** can only be rationalized by considering that two epimerizations, at C-2 and C-4 of the piperidine ring, have again occurred, either under the alkaline conditions of the saponification step or under the acidic conditions required for the cyclization.

In order to investigate these epimerizations, the piperidine-4-carboxylic acids resulting from saponification of esters **3a** and **5a** were independently reesterified with excess diazomethane. Surprisingly, in both cases mixtures of the starting esters, **3a** or **5a**, and the corresponding C-2 epimers, **3b** or **5b**, were obtained (approximate ratio 4:1). This result indicates that *C-2 of the piperidine ring, rather than C-4, has undergone epimerization during the alkaline hydrolysis of the ester group* to give mixtures of 2,4-*cis* and 2,4-*trans* piperidine-4-carboxylic acids and that the second epimerization, at C-4 of the piperidine ring, occurs from the above 2,4-*trans* amino acids during the PPA treatment required for the cyclization step. As could be expected from the above results, when pure 2,4-*trans* piperidine **3b** was subjected to saponification [Ba(OH)$_2$] and then treated with PPA, cyclization did take place, and a mixture of epimeric tetracycles **4a** and **4b** (approximate ratio 2:1) was obtained.

A similar epimerization at the piperidine 2-position was observed when the all-*cis* piperidines **3a** and **5a** were heated at 140 °C for 24 h in a sealed tube in anhydrous dioxane containing anhydrous K_2CO_3: epimeric mixtures of **3a** and **3b** (9:1 ratio) and **5a** and **5b** (5:1 ratio) were obtained. Similarly, alkylation of **5a** with bromoacetaldehyde dimethyl acetal under the above conditions led also to an epimeric mixture (10:1 ratio) of the expected all-*cis N*-substituted piperidine **7a** and its C-2 epimer **7b**. However, piperidine **3a** was recovered unchanged after being refluxed for 10 h in anhydrous methanolic HCl solution.

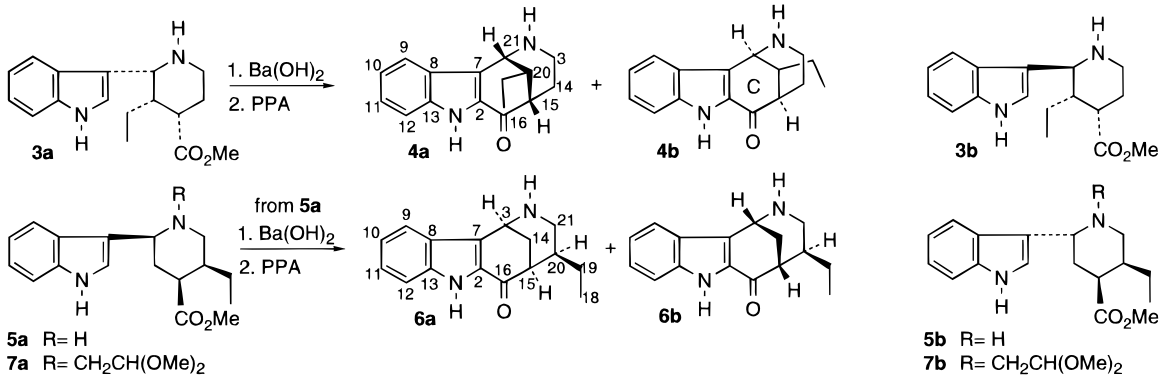
The stereochemical assignments of piperidines **3**, **5**, and **7** were effected from their NMR data, in particular by comparison of the ^{13}C NMR chemical shifts of **3a**/**b** and **5a**/**b** with those of the deethyl compounds *cis*-**1** and *trans*-**1**.[1]

The above epimerizations at the piperidine 2-position can be explained by considering that 3-(2-piperidyl)-indoles are gramine-type systems: cleavage of the C_2−N_b bond,[7] with subsequent recyclization of the resulting

(1) Bosch, J.; Rubiralta, M.; Domingo, A.; Bolós, J.; Linares, A.; Minguillón, C.; Amat, M.; Bonjoch, J. *J. Org. Chem.* **1985**, *50*, 1516.
(2) Amat, M.; Sathyanarayana, S.; Hadida, S.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 7123.
(3) The biogenetic numbering is used for tetracyclic structures: Le Men, J; Taylor, W. I. *Experientia* **1965**, *21*, 508.
(4) Compounds **1**−**7** are racemic. Compounds **3a**−**7a** have been drawn in the same enantiomeric series as the natural products: **3a** and **4a** as both the uleine-type and the *Strychnos* alkaloids with the aspidospermatan skeletal type and **5a**−**7a** as the *Strychnos* alkaloids with the strychnan skeletal type.
(5) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939.
(6) The presence of a 16-oxo substituent seems to preclude the epimerization: Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, 2738.
(7) For a similar ring opening under alkaline conditions, see: Bosch, J.; Amat, M.; Domingo, A. *Heterocycles* **1984**, *22*, 561.

S0022-3263(95)02251-1 CCC: $12.00

Scheme 2

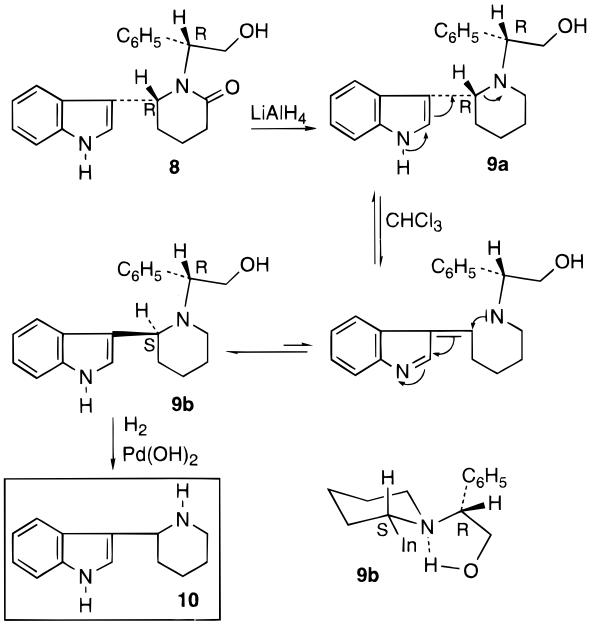


3-alkylideneindolenines, results in the formation of epimeric mixtures at C-2.

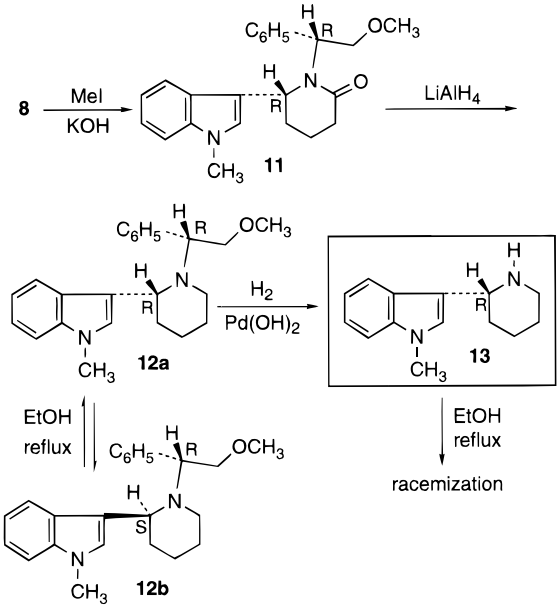
At this point we felt that the easy epimerization of the piperidine 2-position in 3-(2-piperidyl)indoles deserved further study because this moiety is present in a large number of indole alkaloids belonging to different skeletal types (strychnan, aspidospermatan, plumeran, uleine group),[8] and its configurational integrity is essential for the stereocontrolled synthesis of alkaloids of these groups.[9] For this study we selected the enantiomerically pure 3-(2-piperidyl)indole **9a**, which was prepared by $LiAlH_4$ reduction of lactam **8**.[10] Interestingly, a solution of the (α*R*,2*R*) isomer **9a** in $CHCl_3$ at room temperature was almost completely converted after 48 h to the thermodynamically more stable (α*R*,2*S*) epimer **9b**, presumably by way of the intermediate alkylideneindolenine depicted in Scheme 3. Formation of a hydrogen bond allows **9b** to adopt a stable conformation in which the phenyl group does not interact with the equatorial indolyl substituent. Removal of the benzylic chiral auxiliary of **9b** by hydrogenolysis led to the 3-(2-piperidyl)indole **10** as a racemic mixture; in this case the equilibration at the piperidine 2-position involves racemization.

Then, we studied the effect of the substitution at the indole nitrogen. 1-Methyl-3-(2-piperidyl)indole **12a** was prepared by methylation of **8** followed by $LiAlH_4$ reduction of the resulting amide **11** (Scheme 4). When a solution of piperidylindole **12a** in CH_2Cl_2 was stirred at room temperature, no change in the optical rotation was observed after 90 h. Similarly, no epimerization at C-2 was observed after stirring a 2 N HCl−EtOH solution of **12a** for 24 h at room temperature. However, when a solution of **12a** in EtOH was heated at reflux, a nearly equimolecular mixture of **12a** and **12b** was formed (^{1}H NMR). On the other hand, hydrogenolysis of **12a** afforded the N_a-methyl derivative **13**, whose optical rotation value ($[\alpha]^{22}_D = +35.0$) did not change after 7 days of stirring in ethanolic solution at room temperature. When this solution was heated at reflux for 24 h, a complete loss of optical activity was again observed. Therefore, alkylation of the indole nitrogen in 3-(2-piperidyl)indoles affords a higher configurational stability to the piperidine 2-position. The above results are reminiscent of an observation made over 30 years ago regarding a gramine-type system with a stereogenic center α to the nitrogen

Scheme 3



Scheme 4

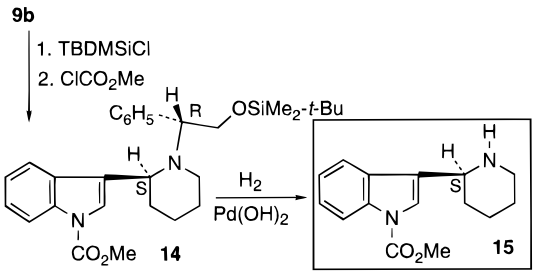


(8) Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Vol. 1, Chapter 5.

(9) For related epimerizations in octahydropyrido[3,2-*c*]carbazoles bearing an acyl substituent on the piperidine nitrogen, see: (a) Gallagher, T.; Magnus, P. *Tetrahedron* **1981**, *37*, 3889. (b) Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, *17*, 111.

(10) (a) Prepared by reaction of (3*R*,8a*S*)-5-oxo-3-phenyl-2,3,6,7,8,-8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine[10b] with indole in the presence of $TiCl_4$. The absolute configuration of **8** was determined by X-ray crystallography. (b) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1995**, *35*, 2223.

Scheme 5



atom: whereas attempts to resolve 3-[1-(dimethylamino)-ethyl]indole were unsuccessful, the corresponding *N*-methyl indole derivative could be resolved without difficulty.[11]

In contrast with the results observed in the *N*-unsubstituted and *N*-methyl indole series, protection of the indole nitrogen with an electron-withdrawing group prevents the undesirable epimerization (or racemization) at the piperidine 2-position. Indeed, both N_a-methoxycarbonyl derivatives **14** and **15**, prepared as outlined in Scheme 5, showed configurational stability under a variety of conditions (for **14**: CH_2Cl_2, rt, 120 h; 2 N HCl/EtOH, rt, 30 h; EtOH, reflux, 24 h; for **15**: EtOH, reflux, 24 h).

In conclusion, attention must be paid to the possibility of epimerization (or racemization) in 3-(2-piperidyl)-indoles, which are frequently used as intermediates in the synthesis of indole alkaloids. The use of an electron-withdrawing protecting group, such as methoxycarbonyl,[12] on the indole nitrogen provides a solution to this synthetic problem.

Experimental Section

General. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, and coupling constants are expressed in hertz. Melting points were determined in a capillary tube and are uncorrected. Optical rotations were measured using a 1 dm cell with a total volume of 1 mL. TLC was carried out on SiO_2, and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2. Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished with a rotatory evaporator. Microanalyses were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

(±)-Nordasycarpidone (4a) and (±)-20-Epinordasycarpidone (4b). A 4% aqueous solution of $Ba(OH)_2$ (35 mL) was added to a solution of methyl *c*-3-ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinecarboxylate (**3a**)[2] (1.0 g, 3.5 mmol) in dioxane (30 mL). The mixture was refluxed for 24 h, cooled, saturated with CO_2, and filtered. The solution was evaporated to dryness, and the residue was dried over P_2O_5. The resulting crude mixture was finely powdered and treated with an excess of PPA. After vigorous stirring at 85−90 °C for 1 h, the reaction mixture was cooled, poured into ice−water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. Evaporation of the dried extracts gave a foam which was purified by chromatography (95:5 Et_2O−diethylamine) affording **4a**[5] (320 mg, 36%) and **4b**[2] (80 mg, 9%).

(±)-Norisodasycarpidone (6a) and (±)-20-Epinorisodasycarpidone (6b). Operating as above, from methyl *c*-5-ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinecarboxylate (**5a**)[2] (0.4 g, 1.4 mmol), an epimeric mixture of **6a** and **6b** (120 mg, 32%) was obtained after chromatography (95:5 Et_2O−diethylamine). Compounds **6a**[5,13] and **6b**[13] were identified by comparison (TLC, ^1H NMR, and ^{13}C NMR) with authentic samples previously prepared in our laboratory. **6b**: ^{13}C NMR ($CDCl_3$, 75 MHz) 11.5 (CH_3), 23.2 (CH_2), 30.3 (CH_2), 37.7 (CH), 40.0 (CH_2), 44.3 (CH), 45.4 (CH), 112.7 (CH), 120.0 (CH), 120.3 (CH), 123.3 (C), 125.0 (C), 126.3 (CH), 132.1 (C), 138.0 (C), 194.3 (C).

Hydrolysis and Reesterification of 3a. The finely powdered mixture of amino acids (100 mg, 0.37 mmol), obtained as described above from **3a**, was dissolved in dry MeOH (5 mL) and treated with an excess of freshly prepared diazomethane in Et_2O for 4 h at room temperature. The reaction mixture was concentrated, dissolved in CH_2Cl_2, and washed with water. The resulting organic solution was dried over Na_2SO_4 and concentrated to give a 5:1 epimeric mixture of esters **3a**[2] and **3b** (78 mg, 74%), respectively, which were separated by careful column chromatography (9:1 EtOAc−MeOH). **3b**: ^1H NMR ($CDCl_3$, 300 MHz) 0.73 (t, J = 7.5, 3 H), 1.15 and 1.26 (2m, 2 H), 1.88−2.3 (m, 3 H), 2.97 (dt, J = 12.0, 3.8, 1 H), 3.06 (q, J = 4.3, 1 H), 3.18 (m, 1 H), 3.71 (s, 3 H), 4.48 (d, J = 10.0, 1 H), 7.04−7.18 (m, 2 H), 7.14 (s, 1 H), 7.30 (d, J = 8.0, 1 H), 7.73 (d, J = 7.7, 1H), 9.00 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.6 (CH_3), 22.5 (CH_2), 28.4 (CH_2), 40.3 (CH), 42.4 (CH_2), 45.4 (CH), 51.2 (CH_3), 53.6 (CH), 111.2 (CH), 117.8 (C), 119.1 (CH), 119.5 (CH), 121.7 (CH), 122.3 (CH), 126.8 (C), 136.1 (C), 175.0 (C).

Hydrolysis and Reesterification of 5a. Operating as described above, from the crude amino acids (100 mg, 0.37 mmol) obtained by hydrolysis of **5a**, a 4:1 epimeric mixture of esters **5a** and **5b** (83 mg, 79%), respectively, was obtained. Compounds **5a**[2] and **5b** were separated by chromatography (9:1 Et_2O−diethylamine). **5b:** ^1H NMR ($CDCl_3$, 300 MHz) 0.97 (t, J = 7.5, 3 H), 1.40 (m, 2 H), 1.83 (m, 1 H), 1.94 (ddd, J = 13.6, 11.5, 5.0, 1 H), 2.26 (dt, J = 13.6, 2.7, 1 H), 2.96 (m, 1 H), 3.02 (dd, J = 11.5, 4.0, 1H), 3.17 (t, J = 11.5, 1 H), 3.73 (s, 3 H), 4.54 (dd, J = 11.5, 2.7, 1 H), 7.06−7.25 (m, 2 H), 7.16 (s, 1 H), 7.35 (d, J = 8.0, 1 H), 7.69 (d, J = 7.7, 1 H), 8.25 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.7 (CH_3), 24.1 (CH_2), 35.6 (CH_2), 40.1 (CH), 41.8 (CH), 47.7 (CH_2), 48.9 (CH), 51.1 (CH_3), 111.3 (CH), 118.7 (C), 118.8 (CH), 119.1 (CH), 120.9 (CH), 121.8 (CH), 126.0 (C), 136.3 (C), 174.9 (C).

Methyl 1-(2,2-Dimethoxyethyl)-*c*-5-ethyl-*r*-2-(3-indolyl)-*c*-4-piperidinecarboxylate (7a) and Its C-2 Epimer 7b. A solution of indolylpiperidine **5a** (2.0 g, 7.0 mmol) and bromoacetaldehyde dimethyl acetal (8.3 mL, 70 mmol) in dioxane (40 mL) containing K_2CO_3 (2.9 g, 21 mmol) and NaI (546 mg, 3.3 mmol) was heated at 140 °C in a sealed tube for 24 h. The reaction mixture was concentrated, and the residue was dissolved in CH_2Cl_2. The organic solution was washed with brine, dried, and evaporated. The resulting residue was purified by column chromatography (1:1 AcOEt−hexane) affording **7a** (2.1 g, 81%) and **7b** (0.2 g, 8%). **7a**: ^1H NMR ($CDCl_3$, 300 MHz) 1.02 (t, J = 7.0, 3H), 1.25 (m, 1H), 1.81 (dm, J = 13.9, 1H), 2.10 (m, 2H), 2.07 (dd, J = 13.8, 5.6, 1H), 2.28 (d, J = 12.3, 1H), 2.36 (q, J = 13.9, 1H), 2.70 (dm, J = 13.1, 1H), 2.77 (dd, J = 13.8, 4.8, 1H), 2.92 (s, 3H), 3.27 (s, 3H), 3.40 (m, 2H), 3.65 (s, 3H), 4.25 (apparent t, J = 5.1, 1H), 7.04−7.20 (m, 3H), 7.30 (d, J = 7.4, 1H), 7.85 (d, J = 7.2, 1H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 12.2 (CH_3), 19.8 (CH_2), 31.6 (CH_2), 38.7 (CH), 45.8 (CH), 51.4 (CH_3), 52.4 (CH_3), 54.5 (CH_3), 55.7 (CH_2), 56.4 (CH_2), 61.0 (CH), 104.6 (CH), 111.1 (CH), 118.5 (C), 119.0 (CH), 120.4 (CH), 121.8 (CH), 122.3 (CH), 126.0 (C), 136.6 (C), 174.9 (C). Anal. Calcd for $C_{21}H_{30}N_2O_4 \cdot H_2O$: C, 64.28; H, 8.16; N, 7.14. Found: C, 64.24; H, 7.72; N, 7.07. **7b**: ^1H NMR ($CDCl_3$, 300 MHz) 0.98 (t, J = 7.4, 3H), 1.41 (q, J = 7.4, 2H), 2.02 (m, 2H), 2.19 (m, 1H), 2.25 (dd, J = 13.6, 5.0, 1H), 2.61 (t, J = 11.6, 1H), 2.85 (m, 2H), 2.99 (s, 3H), 3.09 (dd, J = 11.6, 3.7, 1H), 3.23 (s, 3H), 3.69 (s, 3H), 4.04 (dd, J = 11.1, 3.0, 1H), 4.33 (t, J = 5.2, 1H), 7.11 (m, 3H), 7.32 (d, J = 7.3, 1H), 7.84 (d, J = 7.7, 1H), 8.23 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 11.8 (CH_3), 24.2 (CH_2), 36.2 (CH_2), 39.9 (CH), 41.2 (CH), 50.9 (CH_3), 52.3 (CH_3), 54.0 (CH_3), 55.2 (CH_2), 55.8 (CH), 56.3 (CH_2), 103.5 (CH), 111.1 (CH), 117.7 (C), 118.7 (CH), 119.9 (CH), 121.6 (CH), 122.4 (CH), 126.3 (C), 136.3 (C), 174.9 (C). Anal. Calcd for $C_{21}H_{30}N_2O_4.H_2O$: C, 64.28; H, 8.16; N, 7.14. Found: C, 64.46; H, 7.83; N, 7.11.

(11) Albright, J. D.; Snyder, H. R. *J. Am. Chem. Soc.* **1959**, *81*, 2239.
(12) The preparation of some enantiomerically pure 1-(benzenesulfonyl)-3-(2-piperidyl)indoles has recently been described and no epimerization at the piperidine 2-position has been reported: Miguel, D.; Diez, A.; Blache, Y.; Luque, J.; Orozco, M.; Remuson, R.; Gelas-Mialhe, Y.; Rubiralta, M. *Tetrahedron* **1995**, *51*, 7527.
(13) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.
(14) Van Tamelen, E. E.; Knapp, G. G. *J. Am. Chem Soc.* **1955**, *77*, 1860.

(2*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-(3-indolyl)piperidine (9a). A solution of lactam **8**[10] (300 mg, 0.90 mmol) in anhydrous THF (3 mL) was slowly added to a stirred slurry of $LiAlH_4$ (170 mg, 4.5 mmol) in refluxing anhydrous Et_2O (100 mL). After being refluxed for 1 h, the mixture was cooled to 0 °C, and 15% aqueous NaOH (10 mL) and water (15 mL) were added. The solids were removed by filtration through a Celite pad, and the solution was washed with brine, dried, and evaporated. The resulting residue was purified by column chromatography (AcOEt) affording compound **9a** (230 mg, 80%) impurified with a small amount (<5%) of the C-2 epimer **9b**. **9a**: ^{1}H NMR ($CDCl_3$, 300 MHz) 1.70−2.08 (m, 5 H), 2.02 (m, 1 H), 2.52 (ddd, *J* = 11.5, 9.4, 3.3, 1 H), 2.92 (dd, *J* = 11.5, 3.4, 1 H), 3.95−4.10 (m, 3 H), 4.16 (dd, *J* = 10.0, 3.0, 1 H), 7.13−7.33 (m, 9 H), 7.89 (d, *J* = 10.6, 1 H), 8.04 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 24.7 (CH_2), 26.6 (CH_2), 35.0 (CH_2), 47.4 (CH_2), 57.7 (CH), 59.5 (CH_2), 63.7 (CH), 111.2 (CH), 119.2 (C), 119.4 (CH), 120.2 (CH), 122.0 (CH), 122.2 (CH), 127.6 (C), 127.9 (CH), 128.4 (CH), 129.6 (CH), 136.3 (C), 140.3 (C).

(2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-(3-indolyl)piperidine (9b). A solution of compound **9a** (40 mg) in CH_2Cl_2 (20 mL) was stirred at room temperature until no change was observed in the ratio **9a**/**9b** (15 days; the ^{1}H NMR spectra showed less than 5% of epimer **9a**). **9b**: $[\alpha]_D^{22} = -123.4$ (*c* 1.0, EtOH); IR (NaCl) 3300−3000 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.65−1.85 (m, 6 H), 1.92 (td, *J* = 11.3, 3.0, 1 H), 3.17 (dm, *J* = 11.3, 1 H), 3.40 (dd, *J* = 11.0, 5.0, 1 H), 3.65 (dd, *J* = 11.0, 3.0, 1 H), 4.05 (t, *J* = 11.0, 1 H), 4.27 (dd, *J* = 11.0, 5.0, 1 H), 7.05−7.29 (m, 8 H), 7.38 (d, *J* = 7.4, 1 H), 7.78 (d, *J* = 7.2, 1 H), 8.50 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 25.0 (CH_2), 26.4 (CH_2), 36.4 (CH_2), 46.3 (CH_2), 57.7 (CH), 59.4 (CH_2), 61.8 (CH), 111.5 (CH), 118.2 (C), 119.4 (CH), 119.6 (CH), 122.1 (CH), 122.7 (CH), 126.0 (C), 127.6 (CH), 127.8 (CH), 129.6 (CH), 134.7 (C), 136.5 (C); mp 87−90 °C (Et_2O−hexane). Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.54; N, 8.34. Found: C, 78.31; H, 7.94; N, 7.99.

(±)-3-(2-Piperidyl)indole (10). A suspension of **9b** (225 mg, 0.7 mmol) and activated $Pd(OH)_2$ (135 mg) in MeOH (20 mL) was hydrogenated until the disappearance of the starting compound was observed by TLC (5 h). The catalyst was removed by filtration through Celite, and the solvent was evaporated. The resulting residue was dissolved in CH_2Cl_2 and extracted with aqueous HCl. The combined aqueous extracts were basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic solution was dried and evaporated to give a residue which, after purification by chromatography (9:1 Et_2O−diethylamine), afforded pure piperidylindole **10** (80 mg, 57%) as a racemic mixture: IR (film) 3500, 2925 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.50−1.78 and 1.88−2.10 (2m, 6 H), 2.65 (br s, 1 H), 2.83 (td, *J* = 11.0, 3.0, 1 H), 3.20 (dm, *J* = 11.0, 1 H), 3.98 (dd, *J* = 10.4, 2.0, 1H), 7.07−7.24 (m, 3 H), 7.30 (d, *J* = 7.9, 1 H), 7.66 (d, *J* = 7.4, 1 H), 8.70 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 25.2 (CH_2), 25.8 (CH_2), 33.7 (CH_2), 47.5 (CH_2), 54.2 (CH), 111.4 (CH), 118.6 (CH), 119.0 (CH), 119.4 (C), 120.9 (CH), 121.7 (CH), 126.0 (C), 136.2 (C); mp 119−121 °C (AcOEt) (lit.[14] mp 121.5−122.0 °C).

(6*R*)-1-[(1*R*)-2-Methoxy-1-phenylethyl]-6-(1-methyl-3-indolyl)-2-piperidone (11). Indolylpiperidone **8** (500 mg, 1.5 mmol) was added to a suspension of KOH (335 mg, 6.0 mmol) in DMSO (8 mL), and the mixture was stirred at room temperature for 1.5 h. Then, a solution of MeI (0.18 mL, 3.0 mmol) in DMSO (0.7 mL) was added and the stirring was continued for 2 h. The mixture was poured into ice−water and extracted with Et_2O. Evaporation of the dried organic extracts, followed by chromatography (95:5 AcOEt−EtOH), afforded pure compound **11** (365 mg, 66%): $[\alpha]_D^{22} = -44.6$ (*c* 0.57, EtOH); IR (NaCl) 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.60−1.80 (m, 4 H), 2.50−2.70 (m, 2 H), 3.11 (s, 3H), 3.59 (dd, *J* = 9.8, 7.0, 1 H), 3.64 (dd, *J* = 9.8, 7.0, 1 H), 3.77 (s, 3 H), 4.79 (br s, 1 H), 6.10 (t, *J* = 7.0, 1 H), 6.95 (s, 1 H), 7.10−7.31 (m, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 16.5 (CH_2), 29.8 (CH_2), 31.5 (CH_2), 32.7 (CH_3), 50.6 (CH), 56.4 (CH), 58.2 (CH_3), 70.9 (CH_2), 109.3 (CH), 115.2 (C), 118.4 (CH), 118.9 (CH), 121.6 (CH), 125.4 (C), 127.0 (CH), 127.5 (CH), 127.6 (CH), 128.2 (CH), 136.9 (C), 137.7 (C), 170.8 (C). Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.72. Found: C, 75.83; H, 7.33; N, 7.54.

(2*R*)-1-[(1*R*)-2-Methoxy-1-phenylethyl]-2-(1-methyl-3-indolyl)piperidine (12a). Operating as described in the preparation of **9a**, starting from indolylpiperidone **11** (260 mg, 0.72 mmol), pure compound **12a** (150 mg, 60%) was obtained after column chromatography (4:6 AcOEt−hexane): $[\alpha]_D^{22} = -15.6$ (*c* 1.0, EtOH); IR (NaCl) 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.35−1.65, 1.80, and 2.04 (3m, 6 H), 2.36 (td, *J* = 11.0, 3.0, 1 H), 2.88 (dm, *J* = 11.0, 1 H), 3.26 (s, 3 H), 3.72 (s, 3 H), 3.80 (dd, *J* = 9.7, 7.3, 1 H), 3.88 (dd, *J* = 9.7, 5.0, 1 H), 4.10 (m, 2 H), 7.00 (s, 1 H), 7.00−7.26 (m, 7 H), 7.37 (d, *J* = 7.5, 1 H), 7.94 (d, *J* = 7.9, 1 H); ^{13}C MNR ($CDCl_3$, 75MHz) 25.7 (CH_2), 26.8 (CH_2), 32.6 (CH_3), 35.9 (CH_2), 47.2 (CH_2), 58.2 (CH), 58.8 (CH_3), 59.3 (CH), 69.7 (CH_2), 109.1 (CH), 117.8 (C), 118.5 (CH), 120.8 (CH), 121.4 (CH), 126.0 (CH), 126.8 (CH), 127.6 (CH), 127.8 (C), 128.0 (CH), 137.3 (C), 142.0 (C). Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.07; H, 8.09; N, 8.03. Found: C, 78.69; H, 8.49; N, 7.80.

A solution of compound **12a** (10 mg) in EtOH (10 mL) was refluxed for 24 h. After this time a nearly equimolecular mixture of **12a** and **12b** was formed (^{1}H NMR). The most significant signals in the ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) of the epimer **12b** are 3.03 (dm, *J* = 10.2, 1 H), 3.14 (s, 3 H), 3.50 (dd, *J* = 10.6, 3.0, 1 H), 3.80 (s, 3 H), 3.90 (dd, *J* = 9.6, 4.7, 1 H), 4.37 (dd, *J* = 7.6, 7.0, 1 H), 7.06 (s, 1 H), 7.08−7.40 (m, 8 H), 7.90 (d, *J* = 8.0, 1 H).

(2*R*)-2-(1-Methyl-3-indolyl)piperidine (13). Operating as described for the preparation of **10**, starting from pure indolylpiperidine **12a** (150 mg, 0.43 mmol), followed by chromatography (95:5 Et_2O−diethylamine), compound **13** (53 mg, 57%) was obtained: $[\alpha]_D^{22} = +35.0$ (*c* 0.6, EtOH); IR (NaCl) 3200−3300 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.53−1.67 (m, 4 H), 1.90 (m, 1 H), 2.00 (dm, *J* = 11.5, 1 H), 2.27 (br s, 1 H), 2.83 (td, *J* = 11.4, 3.0, 1 H), 3.18 (dm, *J* = 11.4, 1 H), 3.72 (s, 3 H), 3.97 (dd, *J* = 10.7, 2.2, 1 H), 7.04 (s, 1 H), 7.07−7.29 (m, 3 H), 7.67 (d, *J* = 7.9, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 25.4 (CH_2), 26.1 (CH_2), 32.6 (CH_3), 34.2 (CH_2), 47.8 (CH_2), 54.2 (CH), 109.2 (CH), 118.7 (CH), 119.0 (C), 119.1 (CH), 121.5 (CH), 125.3 (CH), 126.4 (C), 136.8 (C); mp 108−110 °C (Et_2O). Anal. Calcd for $C_{14}H_{18}N_2 \cdot {}^1/_2H_2O$: C, 75.43; H, 8.50; N, 12.09. Found: C, 75.72; H, 8.48; N, 11.69.

(2*S*)-1-[(1*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylethyl]-2-[1-(methoxycarbonyl)-3-indolyl]piperidine (14). A solution of indolylpiperidine **9b** (500 mg, 1.6 mmol), *tert*-butyldimethylsilyl chloride (274 mg, 1.8 mmol), and imidazole (265 mg, 3.9 mmol) in anhydrous DMF was stirred at room temperature for 10 h. The mixture was poured into brine and extracted with Et_2O. The combined organic extracts were dried and concentrated under vacuum affording 650 mg of an oil. To an ice-cold solution of this oil in CH_2Cl_2 (15 mL) were added 50% aqueous NaOH (14.3 mL) and tetrabutylammonium hydrogen sulfate (66 mg, 0.2 mmol). Then, a solution of methyl chloroformate (0.68 mL, 9 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the above mixture, and stirring was continued for 2 h at 0 °C. The mixture was poured into aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organic extracts were dried and concentrated under vacuum to give an oil. Flash chromatography (2:8 AcOEt−hexane) afforded pure compound **14** (573 mg, 70%): IR (NaCl) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) −0.18 (s, 3 H), −0.10 (s, 3 H), 0.75 (s, 9 H), 1.66−1.92 (m, 7 H), 3.09 (dm, *J* = 11.3, 1 H), 3.53 (dd, *J* = 10.6, 3.0, 1 H), 3.96−4.16 (m, 3 H), 4.07 (s, 3 H), 7.10−7.40 (m, 7 H), 7.60 (s, 1 H), 8.00 (m, 1 H), 8.12 (br d, *J* = 7.5, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) −5.6 (CH_3), 18.1 (C), 24.7 (CH_2), 25.7 (CH_3), 25.9 (CH_2), 35.3 (CH_2), 48.0 (CH_2), 53.6 (CH_3), 58.0 (CH), 63.5 (CH), 63.6 (CH_2), 115.0 (C), 115.1 (CH), 121.3 (CH), 122.6 (CH), 122.9 (CH), 124.6 (CH), 127.3 (CH), 127.6 (CH), 128.0 (C), 129.6 (CH), 136.0 (C), 141.5 (C), 151.5 (C). Anal. Calcd for $C_{29}H_{40}N_2O_3Si$: C, 70.69; H, 8.18; N, 5.08. Found: C, 70.42; H, 8.55; N, 5.05.

(2*S*)-2-[1-(Methoxycarbonyl)-3-indolyl]piperidine (15). Operating as described for the preparation of **10**, starting from pure indolylpiperidine **14** (400 mg, 0.81 mmol), followed by chromatography (97:3 Et_2O−diethylamine), compound **15** (90 mg, 43%) was obtained: $[\alpha]_D^{22} = -51.2$ (*c* 0.2, CH_2Cl_2); IR (KBr) 3200−3100, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 1.54−2.01 (m, 6 H), 2.85 (td, *J* = 11.5, 2.7, 1 H), 3.23 (dm, *J* = 11.8, 1 H), 3.91 (dm, *J* = 9.6, 1 H), 4.01 (s, 3 H), 7.23−7.36 (m, 4 H), 7.60 (s, 1 H), 7.65 (d, *J* = 7.7, 1 H), 8.11 (br d, *J* = 7.5, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) 25.2 (CH_2), 26.2 (CH_2), 33.6 (CH_2), 47.7 (CH_2), 53.6 (CH), 53.9 (CH_3), 115.2 (CH), 119.4 (CH), 119.6 (C), 121.3 (CH), 122.6 (CH), 124.6 (CH), 125.9 (C), 135.0 (C), 151.0 (C); mp 193−194 °C (Et_2O).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **3b**, **5b**, **9a**, and **15** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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