which separated the two aqueous phases. The outer aqueous phase (I) contained specified concentrations of metal picrate in pure water (6 mL), and the inner aqueous phases (II) contained pure water (6 mL). The $CHCl_3$ layer (25 mL) lay below these aqueous phases and bridged them across the separation by way of the central glass tube. The organic layer contained the crown ethers as the carrier and was stirred at a constant speed (60 rpm) with a magnetic stirring bar (30-mm length) at 25 ± 1 °C. Transport of metal picrates was followed by monitoring the absorbance at 357 nm of the aqueous phase (II).

Acknowledgment. This research was partially supported by grant from the Ministry of Education, Japan (454153).

Registry No. 5, 14187-32-7; **6**, 2144-40-3; (+)-**7**, 81370-88-9; (−)-**7**, 81370-89-0; (−)-**8**, 81340-19-4; (−)-**9**, 81370-90-3; **10**, 81370-91-4; **11**, 81370-92-5; **12**, 81370-93-6; (±)-**13**, 81340-20-7; (+)-**13**, 81370-94-7; (+)-**13** (+)-2-(1-aminoethyl)naphthalene, 81370-95-8; (−)-**13**, 81370-96-9; (−)-**13** (+)-2-(1-aminoethyl)naphthalene, 81370-97-0; (±)-**14**, 81340-21-8; (+)-**14**, 81370-98-1; (−)-**14**, 81370-99-2; (+)-**15**, 81371-00-8; (−)-**15**, 81371-01-9; (+)-**16**, 81340-22-9; (+)-**17**, 81422-48-2; **18**, 2240-81-5; **19**, 1472-01-1; **20**, 1472-00-0; **21**, 21645-25-0; **22**, 81340-23-0; **23**, 81340-24-1; **24**, 81371-02-0; (−)-**25**, 81371-03-1; pyrocatechol, 120-80-9.

Synthetic Applications of 2-Cyano-1,2,3,6-tetrahydropyridines. Improved Synthesis of the Fundamental Tetracyclic Framework of Dasycarpidone[1]

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2-Cyano-1,2,3,6-tetrahydropyridines **2b–d**, with a functionalized C-4 substituent, were prepared from the corresponding pyridinium salts by sodium borohydride reduction in the presence of sodium cyanide. Reaction of these 2-cyanotetrahydropyridines with indolylmagnesium iodide afforded 3-(1,2,3,6-tetrahydro-2-pyridyl)indoles **3b–d**. Alternatively, **3c** and **3d** were prepared in excellent yield by condensation of 2-cyanotetrahydropyridines **2c** and **2d** with indole in acetic acid medium. Deethyldasycarpidone was obtained from **3b** in poor or moderate yields by three alternative procedures and from **3c** in a three-step sequence. The preparation of deethyldasycarpidone from 2-cyanotetrahydropyridine **2c** via the (tetrahydropyridyl)indole **3c** constitutes an improved synthesis of this tetracyclic ring system. Similarly, 20-deethyl-4-demethyldasycarpidone was obtained from (tetrahydropyridyl)indole **3d**.

The main synthetic applications of α-amino nitriles are based on their ability to form iminium salts by loss of cyanide ion.[2] Specifically, 2-cyano-1,2,3,6-tetrahydropyridines, easily accessible from the corresponding pyridinium salts,[3] are versatile synthetic intermediates since they constitute masked 2,5-dihydropyridinium salts[3-5] which are able to react with activated aromatic rings such as indole. This property has been applied to the preparation of hexahydroindolo- and hexahydrobenzo[*g*]indolo[2,3-*a*]quinolizines,[6] the alkaloids containing these nuclei deplancheine[7] and dihydrogambirtannine,[8] and 6*H*-pyrido[4,3-*b*]carbazole[9] systems such as ellipticine.[10] Similarly, Husson et al.[11] have shown that 2-cyano-1,2,5,6-tetrahydropyridines are potential 2,3-dihydropyridinium salts from which they synthesized 20-epiuleine[12] and the fundamental tetracyclic framework of the indole alkaloid ervitsine.[13] In addition, 2,5-dihydropyridinium salts resulting from 2-cyano-1,2,3,6-tetrahydropyridines can isomerize in acidic medium to 2,3-dihydropyridinium salts,[3,4] and this behavior has found application to the stereospecific synthesis of β-benzo-[4,14] and β-naphthomorphans.[15,16] On the other hand, 2-cyano-1,2,3,6-tetrahydropyridines, via the corresponding iminium salts, can undergo substitution of the cyano group by Grignard reagents[17] such as benzyl-,[16] thenyl-, or benzo[*b*]thienylmethylmagnesium halides,[19] which constitutes the key step of the most straightforward synthesis of 6,7-benzomorphans[18] and thienomorphans.[19,20]

In previous papers we described the reaction of 2-cyano-1,2,3,6-tetrahydropyridines with the indole Grignard reagent,[19] as well as with the indole lithium or potassium salts,[21] to give 3-(tetrahydro-2-pyridyl)indoles. These systems can be considered as precursors of the characteristic 3-(2-piperidyl)indole moiety[22] common to the most

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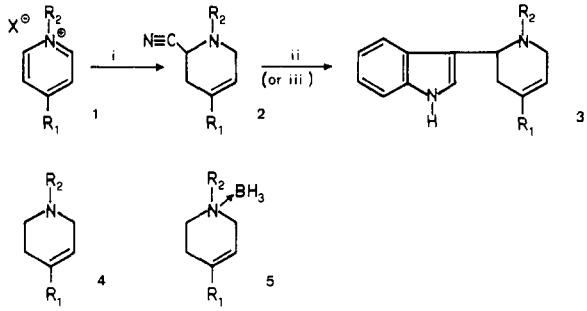
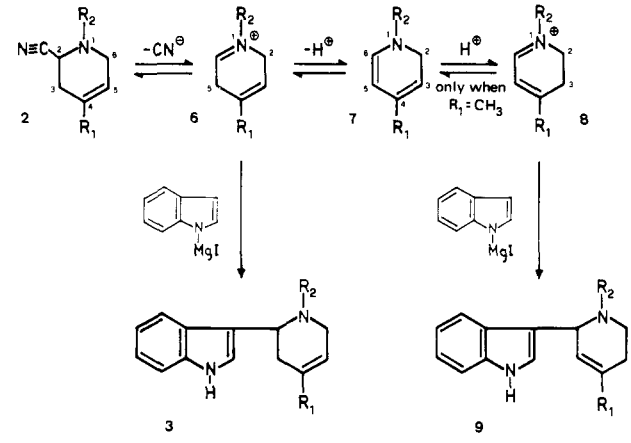
0022-3263/82/1947-2435$01.25/0

Scheme I [a,b]



[a] a, $R_1 = R_2 = CH_3$; b, $R_1 = CH(OEt)_2$, $R_2 = CH_3$; c, $R_1 = COOCH_3$, $R_2 = CH_3$; d, $R_1 = COOCH_3$, $R_2 = CH_2C_6H_5$. [b] (i) $NaBH_4$, NaCN, (ii) indolylmagnesium iodide, Et_2O-CH_2Cl_2, (iii) indole, AcOH-H_2O (1:1), room temperature.

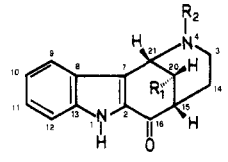
Scheme II [a]



[a] a, $R_1 = R_2 = CH_3$; b, $R_1 = CH(OEt)_2$, $R_2 = CH_3$; c, $R_1 = COOCH_3$, $R_2 = CH_3$; d, $R_1 = COOCH_3$, $R_2 = CH_2C_6H_5$.

of *Strychnos* (uleine, dasycarpidone, strychnine) and *Aspidosperma* (aspidospermine, vindoline) alkaloids. The above results prompted us to extend the procedure to the preparation of similar systems bearing functionalized substituents on the C-4 position of the tetrahydropyridine ring so that later synthetic steps would permit the elaboration of the fundamental tetracyclic framework of dasycarpidone,[23] an alkaloid isolated[24] from *Aspidosperma dasycarpon* (Apocynaceae) containing an indole nucleus condensed between the C-7 and C-8 positions of the 2-azabicyclo[3.3.1]nonane system.[25]

In order to prepare the requisite (tetrahydropyridyl)-indoles, we selected the 2-cyano-1,2,3,6-tetrahydropyridines **2b–d**, in which the diethoxymethyl and methoxycarbonyl substituents are suitable for their subsequent transformation into a carboxyl group. Cyclization of a carboxyl group upon the indole 2-position constitutes the last step in one of the most common approaches to the tetracyclic ring system of dasycarpidone.[22f-i] The *N*-benzyl sub-



R_1 = Et, R_2 = CH_3 dasycarpidone

R_1 = H, R_2 = CH_3 20-deethyldasycarpidone

$R_1 = R_2$ = H 20-deethyl-4-demethyldasycarpidone

stituent of **2d** must allow, after hydrogenolysis, the preparation of 20-deethyl-4-demethyldasycarpidone,[26] a secondary amine that can represent a synthetic entry to the pentacyclic ring system present in several *Strychnos* alkaloids[27] such as tubifoline and condyfoline.

2-Cyanotetrahydropyridines **2b–d** were prepared by quaternization of the appropriate 4-substituted pyridine followed by treatment of the resulting pyridinium salts **1b-d** with sodium borohydride in the presence of a large excess of sodium cyanide.[3] As usual in these reactions, tetrahydropyridines (as **4d**) or amine–borane complexes (as **5b** and **5c**) were isolated as byproducts,[28] the latter being transformed into tetrahydropyridines **4b** and **4c** in refluxing ethanol and methanol, respectively[29] (Scheme I).

Transformation of 2-cyanotetrahydropyridines **2** into the corresponding 3-(tetrahydro-2-pyridyl)indoles **3** was initially carried out by condensation with indolylmagnesium iodide in ether–dichloromethane solution, according to our previously developed procedure.[19] Yields were close to 80% for **3b** and to 50% for **3c** and **3d**. In the last two cases the corresponding 1,2-dihydropyridines **7c** and **7d** were isolated in small amounts.

In contrast to the reaction between the indole Grignard reagent and the 2-cyanotetrahydropyridine **2a**, in which a mixture of the expected condensation product **3a** (Δ^4 isomer) and the isomeric 3-(1,2,5,6-tetrahydro-2-pyridyl)indole **9a** (Δ^3 isomer) was obtained,[19] formation of (Δ^3-tetrahydropyridyl)indoles **9** has not been detected in the condensations described in the present work (see Scheme II). This result is interpreted by considering that

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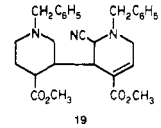
(27) Two synthetic routes to these systems have been described: (a) Harley-Mason, J. *Pure Appl. Chem.* **1975**, *41*, 167. (b) Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057. **Note Added in Proof**: (c) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. (d) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, 881.

(28) In the preparation of 2-cyanotetrahydropyridine **2d**, dimer **19** was also isolated as a minor byproduct. Its formation can be explained by Michael attack of dienamine **7d** upon tetrahydropyridine **4d** followed by cyanide addition to the resulting iminium salt.



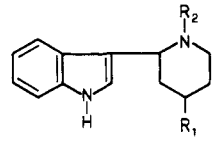
19

(29) Tetrahydropyridine **4b** was identical with that obtained by sodium borohydride reduction of the pyridinium salt **1b** (see Experimental Section).

the equilibrium between the initially formed 2,5-dihydropyridinium salts **6** and the conjugated 2,3-dihydropyridinium salts **8** is not established since protonation of dihydropyridines **7** occurs exclusively at the C-5 ring position. In fact, it is well known[5,30] that protonation of dienamines is faster at the central position (C-5) than at the terminal one (C-3). In our case, protonation at C-3, which would lead to 2,3-dihydropyridinium salts **8** and therefore to (tetrahydropyridyl)indoles **9**, is additionally disfavored by the electron-withdrawing effect of the C-4 substituent. Irreversible attack of indolylmagnesium iodide on the C=N bond of the 2,5-dihydropyridinium salts **6** leads to (Δ^4-tetrahydropyridyl)indoles **3**.

Recovery of dihydropyridine in condensations with **2c** and **2d** and the high yield described for the reaction between indole and 2-cyano-4-[1,1-(ethylenedioxy)ethyl]-1-methyl-1,2,5,6-tetrahydropyridine in the presence of acetic acid[12] prompted us to attempt condensations between 2-cyanotetrahydropyridines **2c** and **2d** and indole in aqueous acetic acid medium. Results were excellent, the corresponding 3-(tetrahydro-2-pyridyl)indoles **3c** and **3d** being isolated in yields higher than 95%.

Conversion of (tetrahydroyridyl)indole **3b** into the acid **13** required for cyclization to deethyldasycarpidone was accomplished by reduction of the tetrahydropyridine double bond, ketal hydrolysis, and oxidation. Double bond hydrogenation was effected in the presence of platinum oxide to afford an approximately equimolecular mixture of the diastereomeric piperidylindoles *cis*-**10** and *trans*-**10**.



10, R_1 = $CH(OEt)_2$; R_2 = CH_3

11, R_1 = CHO ; R_2 = CH_3

12, R_1 = CH=NOH ; R_2 = CH_3

13, R_1 = COOH ; R_2 = CH_3

14, R_1 = CH_2OH ; R_2 = CH_3

15, R_1 = C≡N ; R_2 = CH_3

16, R_1 = $COOCH_3$; R_2 = CH_3

17, R_1 = $COOCH_3$; R_2 = H

18, R_1 = COOH ; R_2 = H

Ketal hydrolysis, by means of 2 N hydrochloric acid in acetone–water at room temperature, was carried out directly upon the 1:1 mixture obtained by hydrogenation since the easy epimerization in alkaline medium of aldehydes **11** made the separation unnecessary. Thus, when the reaction mixture after hydrolysis was basified with potassium carbonate or sodium acetate, an approximately 4:1 mixture[31,32] of aldehydes *cis*-**11** and *trans*-**11** was obtained, from which the thermodynamically most stable cis isomer could be characterized as its oxime (*cis*-**12**). Oxidation of the aldehyde mixture **11** was carried out either with silver(I) oxide or with silver(II) oxide,[33] and the resulting amino acid **13** was treated without further purification with polyphosphoric acid (PPA),[22g] leading to deethyldasycarpidone in 10% yield from aldehydes **11**. Deethyldasycarpidone was identified by its melting point and spectroscopic data, in agreement with those previously reported,[22g,23b] and by chromatographic comparison with an authentic sample.[34]

Alternatively, hydrolysis of ketal **3b** to α,β-unsaturated aldehyde **3e** (**3**; R_1 = CHO, R_2 = CH_3) followed by catalytic hydrogenation gave a diastereomeric mixture of alcohols *cis*-**14** and *trans*-**14**, identical to that resulting from lithium aluminum hydride reduction of the above 4:1 mixture of aldehydes **11**. Oxidation of the major isomer *cis*-**14** with Jones reagent[35] followed by cyclization with PPA[22g] led to deethyldasycarpidone in similar yields.

The main limitation of the above sequences is the low yield in the oxidation step. However, this inconvenience could be overcome by the indirect transformation of aldehydes **11** into acids **13**, via the corresponding nitriles. Thus, nitrile *cis*-**15** was obtained either in one step from aldehydes **11** by means of *N,O*-bis(trifluoroacetyl)-hydroxylamine[36] or in two steps by dehydration of oxime *cis*-**12**[37] with 99% formic acid. Alkaline hydrolysis of nitrile *cis*-**15** followed by PPA cyclization[22g] led to deethyldasycarpidone in 30% yield.

Additionally, 3-(tetrahydro-2-pyridyl)indole **3c** allows a more direct synthetic route to deethyldasycarpidone. Thus, catalytic hydrogenation of tetrahydropyridine **3c** with palladium on charcoal or platinum oxide afforded a 6:1 diastereomeric mixture of esters *cis*-**16** and *trans*-**16**, which could be separated by column chromatography. Transformation of isomer *cis*-**16** into deethyldasycarpidone by saponification followed by PPA cyclization of the resulting amino acid **13** has already been described[22g] and takes place in 36% yield. Comparable results were obtained when cyclization of amino acid **13** was carried out with PPE.[40] Due to its simplicity and the few synthetic steps (four steps from **2c** in 22% overall yield) this synthesis of deethyldasycarpidone improves those previously reported.[22g,23b]

Finally, hydrogenation of 3-(tetrahydropyridyl)indole **3d** with palladium on charcoal brought about both tetrahydropyridine double bond reduction and benzyl group hydrogenolysis, leading to a 5:1 mixture of isomeric esters *cis*-**17** and *trans*-**17**. Saponification to amino acid **18** followed by PPA cyclization afforded 20-deethyl-4-demethyldasycarpidone[26] in 25% yield. The most significant spectroscopic data of this tetracyclic system are an IR absorption at 1645 cm^{-1} due to the indole conjugated carbonyl group and an apparent triplet at δ 4.45 in its NMR spectrum due to the bridgehead C^{21}–H proton.[26]

The syntheses of deethyldasycarpidone and its demethyl analogue described in this paper confirm the usefulness of 2-cyano-1,2,3,6-tetrahydropyridines in the synthesis of structures related with indole alkaloids.

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(31) The ratio was calculated by NMR from the integration of the aldehyde proton singlet in each isomer (δ_{cis} 9.60, δ_{trans} 9.80).

(32) Mixtures (4:1) of aldehydes *cis*-**11** and *trans*-**11** were also obtained when hydrolysis followed by potassium carbonate treatment was effected separately upon each of the starting diastereomeric ketals **10**.

(33) (a) Hammer, R. N.; Kleinberg, J. *Inorg. Synth.* **1953**, *4*, 12. (b) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616. (c) Thomason, S. C.; Kubler, D. G. *J. Chem. Educ.* **1968**, *45*, 546.

(34) We are grateful to Professor J. A. Joule of the Manchester University, who provided us with an authentic sample of this compound.

(35) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.

(36) Pomeroy, J. H.; Craig, C. A. *J. Am. Chem. Soc.* **1959**, *81*, 6340.

(37) By both procedures the minor isomer *trans*-**15** was also isolated. The stereochemical assignation of cis and trans isomers, which were separated by column chromatography, was effected by NMR from the chemical shift of the axial proton on the 2-position of the piperidine ring (δ 3.10 in the major isomer; δ 3.60 in the minor one). This difference of the chemical shift agrees in magnitude and sign with the calculated from McConnell equation[38] for a group with axial symmetry such as cyano group.[39]

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(40) Pollmann, W.; Schramm, G. *Biochem. Biophys. Acta* **1964**, *80*, 1.

Experimental Section

NMR spectra were determined in $CDCl_3$ solution (except where noted) with a Perkin-Elmer R-24B (60 MHz) instrument using internal Me_4Si (δ 0) as a reference. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer. Melting points were determined on a Büchi apparatus and are uncorrected. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ powder. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck, 63-200 μm), and the spots were located with UV light or iodoplatinate reagent. The mass spectrum was determined on a Hewlett-Packard 5930A mass spectrometer. Microanalyses were performed by Instituto de Quimica Bio-Orgânica, Barcelona.

4-(Diethoxymethyl)-1-methyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (2b). A solution of ICH_3 (85.4 g, 0.60 mol) in 180 mL of anhydrous benzene was added dropwise at 0–5 °C to a stirred solution of 4-(diethoxymethyl)pyridine[41] (100 g, 0.55 mol) in 150 mL of anhydrous acetone. The mixture was stirred at room temperature for 3 h and allowed to stand at 5 °C overnight. The hygroscopic methiodide **1b** (160 g, 86%) was collected by filtration: NMR δ 1.25 (t, J = 8 Hz, 6 H, CH_3), 3.65 (q, J = 8 Hz, 4 H, CH_2), 4.68 (s, 3 H, NCH_3), 5.77 (s, 1 H, OCHO), 8.17 (d, J = 6 Hz, 2 H, pyridine H_β), 9.50 (d, J = 6 Hz, 2 H, pyridine H_α).

Hydrochloric acid (6 N, 120 mL) was added dropwise to a stirred solution of 84.8 g (1.73 mol) of NaCN in 230 mL of H_2O, layered with 330 mL of Et_2O, and kept below 15 °C. To this mixture were added 160 g (0.49 mol) of the methiodide **1b** and then 22 g (0.58 mol) of $NaBH_4$ portionwise. The mixture was stirred at room temperature for 4 h, the Et_2O was decanted, and the aqueous layer was extracted with Et_2O. The evaporation of the whole ethereal extract gave 108 g of an oil which was chromatographed. On elution with benzene, **4-(diethoxymethyl)-1-methyl-1,2,3,6-tetrahydropyridine–borane (5b**; 10 g, 10%) was obtained: mp 60–62 °C (hexane); IR (KBr) 2260–2400 cm^{-1} (BH); NMR δ 1.20 (t, J = 8 Hz, 6 H, CH_3), 2.55 (s, 3 H, NCH_3), 3.30–3.80 (2 q, 2 H each, OCH_2), 4.80 (br s, 1 H, OCHO), 5.90 (br s, 1 H, =CH). Anal. Calcd for $C_{11}H_{24}BNO_2$: C, 61.99; H, 11.34; N, 6.57. Found: C, 61.91; H, 11.49; N, 6.65. Elution with $CHCl_3$ gave 72 g (66%) of **2b**: IR ($CHCl_3$) 2230 (CN), 1690 (C=C) cm^{-1}; NMR δ 1.20 (t, J = 8 Hz, 6 H, CH_3), 2.40 (s, 3 H, NCH_3), 3.30–3.70 (2 q, 2 H each, OCH_2), 3.85 (dd, 1 H, NCHCN), 4.70 (s, 1 H, OCHO), 5.90 (br s, 1 H, =CH). Methiodide: mp 108–110 °C (acetone–Et_2O). Anal. Calcd for $C_{13}H_{23}IN_2O_2$: C, 42.63; H, 6.33; N, 7.65; I, 34.65. Found: C, 42.32; H, 6.39; N, 7.60; I, 34.56.

The amine–borane complex **5b** was refluxed in EtOH for 24 h. The residue after evaporation was dissolved in H_2O and extracted with Et_2O to afford **4-(diethoxymethyl)-1-methyl-1,2,3,6-tetrahydropyridine (4b)**: NMR δ 1.20 (t, J = 8 Hz, 6 H, CH_3), 2.30 (s, 3 H, NCH_3), 2.80 (br s, 2 H, C^2H_2), 3.45 (m, 4 H, OCH_2), 4.70 (s, 1 H, OCHO), 5.80 (br s, 1 H, =CH). Methiodide: mp 182–184 °C (acetone). Anal. Calcd for $C_{12}H_{24}INO_2$: C, 42.23; H, 7.10; N, 4.10; I, 37.18. Found: C, 42.13; H, 7.34; N, 4.11; I, 37.26. The same tetrahydropyridine **4b** was obtained in 88% yield, after the usual workup, by treatment of the pyridinium salt **1b** (1.5 g, 4.6 mmol) with $NaBH_4$ (0.3 g, 8 mmol) in MeOH (10 mL) and NaOH (0.1 N, 15 mL) at reflux for 4 h.

Methyl 2-Cyano-1-methyl-1,2,3,6-tetrahydropyridine-4-carboxylate (2c). 1-Methyl-4-(methoxycarbonyl)pyridinium iodide (**1c**)[42] (30 g, 0.10 mol) was allowed to react as above with NaCN and $NaBH_4$. The final extracts were acidified with 10% ethanolic HCl, and the precipitate of **2c** hydrochloride was collected by filtration; mp 180–181 °C (acetone). Anal. Calcd for $C_9H_{13}ClN_2O_2$: C, 49.89; H, 6.04; N, 12.93; Cl, 16.36. Found: C, 49.80; H, 6.12; N, 12.59; Cl, 16.02. From the hydrochloride was obtained the nitrile **2c**: 13 g (72%); IR ($CHCl_3$) 2200 (CN), 1710 (CO) cm^{-1}; NMR δ 2.35 (s, 3 H, NCH_3), 2.70 (m, 2 H, C^3H_2), 3.10–3.30 (m, 2 H, C^6H_2), 3.65 (s, 3 H, OCH_3), 3.90 (t, 1 H, NCHCN), 6.90 (br s, 1 H, =CH). The mother liquor from the precipitation of the hydrochloride were basified with aqueous K_2CO_3 solution and extracted with Et_2O to give an oil (3.0 g) which was chromatographed. On elution with 1:1 benzene–$CHCl_3$, **1-methyl-4-(methoxycarbonyl)-1,2,3,6-tetrahydropyridine–borane (5c)** was obtained: 1.5 g (8%); mp 109–110 °C (Et_2O); IR (KBr) 2280–2370 (BH), 1705 (CO) cm^{-1}; NMR δ 2.50 (m, 2 H, C^3H_2), 2.60 (s, 3 H, NCH_3), 3.00 (m, 2 H, C^2H_2), 3.50 (m, 2 H, C^6H_2), 3.70 (s, 3 H, OCH_3), 6.75 (br s, 1 H, =CH). Anal. Calcd for $C_8H_{16}BNO_2$: C, 56.85; H, 9.54; N, 8.28. Found: C, 56.63; H, 9.63; N, 8.36. A solution of the complex **5c** (0.2 g, 1.18 mmol) in MeOH (30 mL) was refluxed for 20 h and then evaporated. The residue was distributed between Et_2O and H_2O. The organic layer afforded 0.15 g (82%) of **methyl 1-methyl-1,2,3,6-tetrahydropyridine-4-carboxylate (4c)**: IR ($CHCl_3$) 1705 cm^{-1} (CO); NMR δ 2.37 (s, 3 H, NCH_3), 2.40–2.60 (m, 4 H, C^2H_2 and C^3H_2), 3.10–3.30 (m, 2 H, C^6H_2), 3.70 (s, 3 H, OCH_3), 6.87 (br s, 1 H, =CH).

Methyl 1-Benzyl-2-cyano-1,2,3,6-tetrahydropyridine-4-carboxylate (2d). A solution of methyl isonicotinate[43] (35 g, 0.26 mol), benzyl chloride (35.5 g, 0.28 mol), and absolute MeOH (80 mL) was refluxed for 24 h. After evaporation, the residue was digested twice with boiling Et_2O and dried to give 66 g (94%) of the highly hygroscopic pyridinium chloride **1d**: IR ($CHCl_3$) 1740 cm^{-1} (CO); NMR δ 3.90 (s, 3 H, OCH_3), 6.47 (s, 2 H, CH_2), 7.05–7.35 (m, 3 H, phenyl C^3H, C^4H, and C^5H), 7.55–7.95 (m, 2 H, phenyl C^2H and C^6H), 8.32 (d, J = 6 Hz, 2 H, pyridine H_β), 10.15 (d, J = 6 Hz, 2 H, pyridine H_α).

Hydrochloric acid (6 N, 86 mL) was added dropwise to a stirred solution of NaCN (28 g, 0.57 mol) in H_2O (300 mL), keeping the temperature below 15 °C. To the resulting solution were added 300 mL of Et_2O, 600 mL of MeOH, 15 g (57 mmol) of **1d**, and 2.15 g (57 mmol) of $NaBH_4$ sequentially. The homogeneous mixture was stirred at room temperature for 1 h, and then H_2O was added until two layers appeared. The aqueous phase was extracted with Et_2O, and the combined ether layers were washed with 1 N HCl, dried, and evaporated to give 7.5 g (51%) of **2d**: IR (NaCl) 2225 (CN), 1710 (CO), 1660 (C=C) cm^{-1}; NMR δ 2.75 (br s, 2 H, C^3H_2), 3.20–3.50 (m, 2 H, C^6H_2), 3.68 (s, 5 H, OCH_3 and NCH_2Ph), 3.88 (t, 1 H, C^2H), 6.87 (br s, 1 H, =CH), 7.25 (s, 5 H, C_6H_5). An analytical sample was purified by column chromatography (eluent benzene–$CHCl_3$, 1:1). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.08; H, 6.29; N, 10.60. The hydrochloric extracts were basified with aqueous Na_2CO_3 solution and extracted with Et_2O. Evaporation gave an oil (5.4 g) which was digested with MeOH to afford 3.6 g (13%) of **methyl 1-benzyl-2-cyano-3-[1-benzyl-4-(methoxycarbonyl)-3-piperidyl]-1,2,3,6-tetrahydropyridine-4-carboxylate (19)**: mp 150–152 °C (MeOH); IR (KBr) 2220 (CN), 1735 (CO), 1705 (CO), 1625 (C=C) cm^{-1}; NMR δ 1.5–2.8 (complex signal, 7 H), 2.8–3.9 (complex signal, 9 H, $ArCH_2$, NCH_2C=, NCH and NCH_{eq}), 3.63 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, $=CCO_2CH_3$), 7.11 (s, 5 H, Ar H), 7.18 (s, 5 H, Ar H), 6.9–7.2 (masked signal, 1 H, =CH); mass spectrum, m/e (relative intensity) 229 (1), 228 (2), 170 (1), 138 (9), 106 (8), 92 (15), 91 (100), 78 (8), 65 (11), 51 (4). Anal. Calcd for $C_{29}H_{33}N_3O_4$: C, 71.43; H, 6.82; N, 8.62. Found: C, 71.69; H, 6.47; N, 8.60. The methanolic solution was evaporated to give 1.8 g (13%) of **methyl 1-benzyl-1,2,3,6-tetrahydropyridine-4-carboxylate (4d)**: bp 175–180 °C (0.1 mmHg; oven temperature); IR (NaCl) 1710 (CO), 1655 (C=C) cm^{-1}; NMR δ 2.3–2.6 (m, 4 H, C^2H_2, C^3H_2), 3.00 (q, 2 H, C^6H_2), 3.48 (s, 2 H, NCH_2Ph), 3.58 (s, 3 H, OCH_3), 6.70 (br s, 1 H, =CH), 7.12 (s, 5 H, C_6H_5).

3-[4-(Diethoxymethyl)-1-methyl-1,2,3,6-tetrahydro-2-pyridyl]indole (3b). A solution of **2b** (62 g, 0.28 mol) in anhydrous CH_2Cl_2 (500 mL) was added dropwise under N_2 to a stirred solution of indolylmagnesium iodide (0.29 mol) in an anhydrous 1:1 Et_2O–CH_2Cl_2 mixture (600 mL) maintained at −10 °C. The resulting mixture was stirred at −10 °C for 4 h, poured into an ice-cooled saturated NH_4Cl solution, made alkaline with concentrated NH_4OH, and extracted with Et_2O. Evaporation of the dried ethereal extracts gave an oil which on column chromatography ($CHCl_3$–EtOH, 95:5) and further crystallization (Et_2O) afforded 70 g (79%) of **3b**: mp 119–120 °C (Et_2O); IR ($CHCl_3$) 3480 (NH), 1620 (C=C) cm^{-1}; NMR δ 1.18 (t, J = 8 Hz, 6 H, CH_3), 2.12 (s, 3 H, NCH_3), 3.5 and 3.6 (2 q, J = 8 Hz, 2 H each, OCH_2), 4.73 (s, 1 H, OCHO), 5.95 (br s, 1 H, =CH), 6.9–7.4 (m, 4 H,

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indole), 7.6–7.9 (m, 1 H, indole C^7H), 9.25 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.38; H, 8.24; N, 9.08.

Methyl 2-(3-Indolyl)-1-methyl-1,2,3,6-tetrahydropyridine-4-carboxylate (3c). Method A. A solution of **2c** (10.7 g, 59 mmol) in anhydrous CH_2Cl_2 (160 mL) was added dropwise under N_2 to a stirred solution of indolylmagnesium iodide (89 mmol) in 100 mL of anhydrous Et_2O and 100 mL of CH_2Cl_2 (temperature 0 °C). The resulting mixture was stirred at room temperature for 4 h, poured into ice-cooled saturated NH_4Cl solution, basified with concentrated NH_4OH, and extracted with Et_2O. The ethereal layer was extracted with 1 N HCl, and the acidic aqueous solution was basified with concentrated NH_4OH and extracted with Et_2O. The ethereal extract was evaporated to afford an oil which was chromatographed. On elution with $CHCl_3$–EtOH (99:1) dihydropyridine **7c** (yield lower than 8%) was obtained: IR (film) 1715 (CO), 1640 (C=C) cm^{-1}; NMR δ 2.7–3.2 (m, 2 H, C^2H_2), 2.53 (s, 3 H, NCH_3), 3.71 (s, 3 H, OCH_3), 4.28 (d, J = 8 Hz, 1 H, C^5H), 5.69 (d, J = 8 Hz, 1 H, C^6H), 7.05 (m, 1 H, C^3H). Elution with 95:5 $CHCl_3$–EtOH gave 8 g (50%) of **3c** as a pale yellow oil: IR ($CHCl_3$) 3480 (NH), 1710 (CO) cm^{-1}; NMR δ 2.25 (s, 3 H, NCH_3), 3.80 (s, 3 H, OCH_3), 6.9–7.4 (m, 5 H, indole and =CH), 7.4–7.9 (m, 1 H, indole C^7H), 8.30 (br s, 1 H, NH). Hydrochloride: mp 221–222 °C (acetone). Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.12; Cl, 11.57. Found: C, 62.49; H, 6.24; N, 8.90; Cl, 11.95.

Method B. A solution of **2c** hydrochloride (8.75 g, 40 mmol), indole (9.46 g, 80 mmol), AcOH (100 mL), and H_2O (100 mL) was stirred at room temperature for 24 h. After addition of concentrated HCl (2 mL), the solution was extracted with benzene, made alkaline with 15 N NaOH (ice cooling), and extracted with CH_2Cl_2. Evaporation of the dried extracts gave 10.45 g (96%) of pure **3c**.

Methyl 1-Benzyl-2-(3-indolyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (3d). Method A. Cyanotetrahydropyridine **2d** (6 g, 23 mmol) was allowed to react as indicated in the above method A with indolylmagnesium iodide (35 mmol). The reaction mixture was poured into an ice-cooled saturated NH_4Cl solution, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. The evaporation afforded an oil (8.2 g) which was dissolved in a 1:1 mixture of MeOH–aqueous 10% HCl and extracted with benzene. The aqueous solution was reduced to one-third of its volume, made alkaline with concentrated NH_4OH, and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by chromatographic purification (eluent $CHCl_3$) afforded 4.1 g (51%) of **3d**: IR ($CHCl_3$) 3480 (NH), 1710 (CO) cm^{-1}; NMR δ 2.7–2.9 (m, 2 H, C^3H_2), 3.0–4.1 (m, 5 H, C^6H_2, C^2H and NCH_2Ph), 3.63 (s, 3 H, OCH_3), 6.7–7.3 (m, 10 H, indole, C_6H_5, and =CH), 7.6–7.9 (m, 1 H, indole C^7H), 8.15 (br s, 1 H, NH). Picrate: mp 180–182 °C dec (EtOH). Anal. Calcd for $C_{28}H_{25}N_5O_9$: C, 58.43; H, 4.38; N, 12.17. Found: C, 58.48; H, 4.40; N, 12.01. Dihydropyridine **7d** was obtained in yield lower than 6% on elution with 1:4 benzene–$CHCl_3$: NMR δ 2.8–3.3 (m, 2 H, C^2H_2), 3.56 (s, 2 H, $ArCH_2$), 3.72 (s, 3 H, OCH_3), 4.31 (d, J = 8 Hz, 1 H, C^5H), 5.81 (d, J = 8 Hz, 1 H, C^6H), 6.9–7.2 (masked signal, 1 H, C^3H), 7.12 (s, 5 H, Ar H).

Method B. Compound **2d** (4.6 g, 18 mmol) and indole (4.2 g, 36 mmol) were allowed to react for 30 h as in the above method B, affording 6.0 g (97%) of pure **3d**.

3-[4-(Diethoxymethyl)-1-methyl-2-piperidyl]indole (10). A solution of **3b** (20 g, 63 mmol) in absolute EtOH (200 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 (1 g). When the absorption ceased, the catalyst was filtered off, and the solution was evaporated to give a crude 1:1 mixture of *cis*-**10** and *trans*-**10** (19.6 g), from which each isomer was separated by column chromatography ($CHCl_3$ and 9:1 $CHCl_3$–EtOH as eluents) followed by crystallization. *cis*-**10** (higher R_f value on TLC with 95:3:2 ether–acetone–diethylamine as eluent): mp 117–119 °C (Et_2O); NMR δ 1.10 and 1.20 (2 t, J = 8 Hz, 3 H each, CH_3), 2.10 (s, 3 H, NCH_3), 3.0–3.9 (m, 5 H, OCH_2 and NCH), 4.20 (br s, 1 H, OCHO), 6.7–7.5 (m, 4 H, indole), 7.6–7.9 (m, 1 H, indole C^7H), 9.55 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.10; H, 8.91; N, 8.85. Found: C, 72.22; H, 8.84; N, 8.81. *trans*-**10** (lower R_f value on TLC): mp 96–97 °C (hexane–Et_2O); NMR δ 1.18 and 1.22 (2 t, J = 8 Hz, 3 H each, CH_3), 2.15 (s, 3 H, NCH_3), 3.3–3.9 (m, 5 H, OCH_2 and NCH), 4.75 (d, J = 7 Hz, 1 H, OCHO), 6.9–7.5 (m, 4 H, indole), 7.6–7.9 (m, 1 H, indole C^7H), 8.85 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.10; H, 8.91; N, 8.85. Found: C, 72.26; H, 8.80; N, 9.18.

2-(3-Indolyl)-1-methylpiperidine-4-carbaldehyde (11) and Its Oxime (12). Hydrochloric acid (2 N, 200 mL) was added dropwise to a solution of the above 1:1 mixture of acetals **10** (19 g, 60 mmol) in 200 mL of acetone. The resulting solution was stirred at room temperature for 2 h, poured into ice–water, made alkaline with K_2CO_3, and extracted with Et_2O. Evaporation of the solvent gave 12.4 g (85%) of a 4:1 mixture of *cis*-**11** and *trans*-**11**: IR 3480 (NH), 1720 (CO) cm^{-1}; NMR δ 2.00 and 2.05 (2 s, 3 H, NCH_3 cis and trans, respectively), 9.60 (s, 0.8 H, HCO cis), 9.80 (s, 0.2 H, HCO trans).

The above mixture (12.4 g, 51 mmol) was dissolved in 200 mL of EtOH, and solutions of hydroxylamine hydrochloride (12 g, 0.17 mol) in EtOH (100 mL) and of NaOAc (22 g) in H_2O (100 mL) were added. The resulting suspension was heated in a water bath at 90–100 °C for 3 h, made alkaline (pH 8–9) with aqueous Na_2CO_3, and evaporated to dryness. Column chromatography of the residue ($CHCl_3$–EtOH, 8:2) followed by crystallization afforded the oxime *cis*-**12**: 10 g (76%); mp 216–218 °C (EtOH); NMR (Me_2SO-d_6) δ 2.00 (s, 3 H, NCH_3), 6.8–7.5 (m, 5 H, indole and =CH), 7.6–7.8 (m, 1 H, indole C^7H), 11.50 and 11.74 (2 br s, 1 H each, NH and OH). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.22; H, 7.36; N, 16.46.

2-(3-Indolyl)-1-methyl-1,2,3,6-tetrahydropyridine-4-carbaldehyde (3e). Acetal **3b** (5.2 g, 16 mmol) was hydrolyzed by the above procedure to give 3.4 g (88%) of **3e**: IR ($CHCl_3$) 3480 (NH), 1680 (CO), 1660 (C=C) cm^{-1}; NMR δ 2.10 (s, 3 H, NCH_3), 3.65 (t, 1 H, NCH), 6.70 (br s, 1 H, =CH), 6.8–7.4 (m, 4 H, indole), 7.6–8.0 (m, 1 H, indole C^7H), 9.25 (br s, 1 H, NH), 9.50 (s, 1 H, HCO). Oxime: mp 209–210 °C (EtOH); NMR (Me_2SO-d_6) δ 2.10 (s, 3 H, NCH_3), 3.70 (dd, 1 H, C^2H), 6.10 (br s, 1 H, =CH), 6.8–7.5 (m, 4 H, indole), 7.6–7.9 (m, 1 H, indole C^7H), 7.8 (s, 1 H, HC=N), 11.0 (s, 2 H, OH and NH). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.49; H, 7.06, N, 16.61.

2-(3-Indolyl)-1-methylpiperidine-4-methanol (14). Method A. A solution of **3e** (3.4 g, 14 mmol) in EtOH (100 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 (300 mg). When the absorption ceased, the catalyst was filtered off, and the solution was evaporated. The oily residue (3.2 g, 92%) was crystallized from acetone to give the major isomer *cis*-**14**: mp 167–168 °C (acetone–Et_2O); IR (KBr) 2300–3500 cm^{-1} (OH); NMR ($CDCl_3$–CD_3OD) δ 2.10 (s, 3 H, NCH_3), 3.45 (br s, 2 H, CH_2O), 6.8–7.5 (m, 4 H, indole), 7.5–7.8 (m, 1 H, indole C^7H). Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.46. Found: C, 73.67; H, 8.06; N, 11.23.

Method B. To a stirred suspension of $LiAlH_4$ (0.2 g, 5.2 mmol) in anhydrous Et_2O (50 mL) was added under N_2 a solution of the 4:1 mixture of aldehydes **11** (1 g, 4.1 mmol) in anhydrous Et_2O (50 mL). The resulting mixture was refluxed for 5 h, and then 50 mL of H_2O was added dropwise (ice bath). The ethereal layer was removed, and the aqueous one was extracted with Et_2O. The whole ethereal extract left, on evaporation, 0.6 g (60%) of an oil which on crystallization from acetone gave pure *cis*-**14**.

2-(3-Indolyl)-1-methylpiperidine-4-carbonitrile (15). Method A. A solution of oxime *cis*-**12** (7 g, 27.2 mmol) in 99.9% HCOOH (49 mL) was heated in a water bath at 90–100 °C for 2 h. The mixture was cooled, poured into ice–water, rendered basic with aqueous K_2CO_3 solution, and extracted with $CHCl_3$. Evaporation gave a crude oil which was chromatographed. Elution with 96:4 $CHCl_3$–EtOH afforded 3.6 g (55%) of *cis*-**15**: mp 155–156 °C (Et_2O); IR ($CHCl_3$) 3480 (NH), 2240 (CN) cm^{-1}; NMR δ 2.00 (s, 3 H, NCH_3), 3.10 (m, 2 H, C^6H_{eq} and C^2H_{ax}), 6.8–7.4 (m, 4 H, indole), 7.6–7.9 (m, 1 H, indole C^7H), 8.6 (br s, 1 H, NH). Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.55. Found: C, 75.13; H, 7.16; N, 17.17. On elution with 9:1 $CHCl_3$–EtOH, *trans*-**15** (0.2 g, 3%) was obtained: IR ($CHCl_3$) 3480 (NH) 2240 (CN) cm^{-1}; NMR δ 2.10 (s, 3 H, NCH_3), 3.60 (dd, 1 H, C^2H), 7.0–7.5 (m, 4 H, indole), 7.6–7.9 (m, 1 H, indole C^7H), 8.5 (br s, 1 H, NH). Hydrochloride: mp 198–200 °C (acetone). Anal. Calcd for $C_{15}H_{18}ClN_3$: C, 65.33; H, 6.58; N, 15.23; Cl, 12.85. Found: C, 65.46; H, 6.78; N, 15.19; Cl, 12.68.

Method B. To a stirred solution of the 4:1 mixture of aldehydes **11** (8 g, 33 mmol) in anhydrous benzene (200 mL) were added *N,O*-bis(trifluoroacetyl)hydroxylamine[36] (8 g, 38 mmol) and anhydrous pyridine (6 mL). The mixture was refluxed for 4 h, cooled,

poured into ice–water, and extracted with 10% HCl solution. The aqueous phase was made alkaline with concentrated NH_4OH and extracted with Et_2O. Evaporation of the solvent gave 5.4 g (68%) of a 9:1 *cis*-**15**/*trans*-**15** mixture.

Methyl 2-(3-Indolyl)-1-methylpiperidine-4-carboxylate (16). A solution of **3c** (10.4 g, 38.4 mmol) in EtOH (100 mL) was hydrogenated over 1 g of 10% Pd/C catalyst, affording, after filtration and evaporation, 9.8 g of a 6:1 *cis*-**16**/*trans*-**16** mixture. Pure cis isomer (6.7 g, 63%) was separated by column chromatography on elution with 98:2 $CHCl_3$–EtOH: IR ($CHCl_3$) 3460 (NH), 1720 (CO) cm^{-1}; NMR δ 2.10 (s, 3 H, NCH_3), 3.60 (s, 3 H, OCH_3), 6.9–7.4 (m, 4 H, indole), 7.5–7.9 (m, 1 H, indole C^7H), 9.10 (br s, 1 H, NH). Hydrochloride: mp 232–234 °C (acetone). Anal. Calcd for $C_{16}H_{21}ClN_2O_2$: C, 62.23; H, 6.85; N, 9.06; Cl, 11.48. Found: C, 62.54; H, 6.68; N, 8.93; Cl, 11.46. On elution with 9:1 $CHCl_3$–EtOH pure *trans*-**16** (lower R_f value on TLC) was obtained: 1.1 g (10%); IR ($CHCl_3$) 3480 (NH), 1725 (CO) cm^{-1}; NMR δ 2.20 (s, 3 H, NCH_3), 3.75 (s, 3 H, OCH_3), 7.0–7.5 (m, 4 H, indole), 7.6–7.9 (m, 1 H, indole C^7H), 8.95 (br s, 1 H, NH).

Methyl 2-(3-Indolyl)piperidine-4-carboxylate (17). A solution of **3d**·HCl (5.34 g, 14 mmol) in MeOH (200 mL) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (0.8 g). When the absorption ceased, the catalyst was filtered off, the solvent was removed, and the residue was dissolved in 10% Na_2CO_3 solution. The alkaline solution was extracted with Et_2O, and the ethereal extracts were dried and evaporated to give an oil (3.55 g, a mixture of the cis and trans isomers) which was chromatographed. On elution with 96:4 $CHCl_3$–MeOH, pure *cis*-**17** (2.13 g, 59%) was obtained: IR ($CHCl_3$) 3480 (NH), 1725 (CO) cm^{-1}; NMR δ 1.5–4.1 (complex signal, 9 H, piperidine), 3.51 (s, 3 H, OCH_3), 6.7–7.1 (m, 4 H, indole), 7.3–7.6 (m, 1 H, indole C^7H), 9.1 (br s, 1 H, NH). Picrate: mp 226–228 °C (EtOH). Anal. Calcd for $C_{21}H_{21}N_5O_9$: C, 51.75; H, 4.34; N, 14.37. Found: C, 51.79; H, 4.37; N, 14.06. On elution with 91:9 $CHCl_3$–MeOH, pure *trans*-**17** (0.43 g, 12%) was obtained: IR ($CHCl_3$) 3480 (NH), 1725 (CO) cm^{-1}; NMR δ 1.5–3.7 (complex signal, 8 H, piperidine), 3.62 (s, 3 H, OCH_3), 4.15 (dd, 1 H, C^2H), 6.9–7.3 (m, 4 H, indole), 7.4–7.7 (m, 1 H, indole C^7H), 8.5–9.5 (br s, 1 H, NH).

Deethyldasycarpidone. Method A. Freshly prepared AgO[33a] (8 g, 64 mmol) was added to a solution of the 4:1 mixture of aldehydes **11** (4 g, 16 mmol) in THF (90 mL) and H_2O (10 mL), and the resulting suspension was stirred at 50–60 °C for 5 h (a silver mirror appeared). After being cooled, the mixture was filtered, and the residue was digested several times with boiling EtOH. The combined filtrate and washes were evaporated to dryness, and the resultant crude acid **13** was vigorously stirred in the presence of PPA (9 g) under N_2 at 100 °C for 1 h 40 min. The mixture was cooled, poured into ice–water, made alkaline with concentrated NH_4OH, and extracted with Et_2O. Evaporation of the dried extracts followed by column chromatography ($CHCl_3$ as eluent) of the residue gave 0.4 g (10%) of deethyldasycarpidone, mp 215–217 °C (EtOH) (lit. 214–216 °C;[22g] 215–216 °C[23b]).

Method B. A solution of CrO_3 (0.6 g, 6 mmol) in H_2O (3 mL) and concentrated H_2SO_4 (0.9 mL) was added dropwise to a stirred solution of *cis*-**14** (0.7 g, 2.8 mmol) in acetone (30 mL). The mixture was stirred at room temperature for 3 h, quenched with *i*-PrOH, neutralized with aqueous K_2CO_3, and evaporated to dryness. The resulting solid residue was digested several times with boiling EtOH, and the extracts were evaporated to yield a solid (0.9 g), which was treated with PPA (8 g) as described above. Deethyldasycarpidone (70 mg, 10%) was obtained by column chromatography.

Method C. A solution of *cis*-**15** (1.5 g, 6.2 mmol), KOH (5 g), EtOH (100 mL), and H_2O (50 mL) was refluxed for 5 h. The mixture was cooled, poured into ice–water, acidified to pH 6–7 with 10% HCl solution, and evaporated to dryness. The residue was digested several times with boiling EtOH, the solvent was removed, and the residue (1.5 g) was treated with PPA as above. Pure deethyldasycarpidone (0.55 g, 30%) was obtained after column chromatography.

Method D. According to a described procedure,[22g] from 2.8 g (10.2 mmol) of *cis*-**16** was obtained 0.9 g (36%) of deethyldasycarpidone.

Method E. A solution of amino esters **16** (5.0 g, 18.3 mmol) and KOH (18 g) in 1:1 EtOH–H_2O (360 mL) was refluxed for 5 h. After cooling, the mixture was neutralized with concentrated HCl and evaporated. The resulting residue was dried over P_2O_5 and digested several times with boiling EtOH. The ethanolic extracts were evaporated. The crude amino acid **13** thus obtained was mixed with PPE[40] (74 g) and heated at 100 °C for 2 h with stirring. The mixture was worked up in the usual way to afford deethyldasycarpidone (1.21 g, 28%).

20-Deethyl-4-demethyldasycarpidone.[26,44] To a solution of the mixture of esters **17** (4 g, 15.5 mmol) in EtOH (150 mL) was added aqueous 10% KOH (150 mL). After 4 h of refluxing, the mixture was cooled, brought to pH 7 with 6 N HCl solution, and evaporated to dryness. The residue was dried over P_2O_5 and digested several times with boiling absolute EtOH. The solvent was removed, and the residue was dried over P_2O_5. The crude amino acid **18** thus obtained (3.8 g) and PPA (15 g) were stirred under N_2 at 85–90 °C for 1.5 h. The cooled mixture was poured into ice–water, basified with concentrated NH_4OH, and extracted with CH_2Cl_2. Evaporation of the extracts gave a solid which on column chromatography (eluent $CHCl_3$–MeOH, 97:3) afforded 0.88 g (25%) of 20-deethyl-4-demethyldasycarpidone: mp 234–236 °C (EtOH); IR (KBr) 3310 (indole NH), 1645 (CO) cm^{-1}; NMR (Me_2SO-d_6) δ 1.5–2.8 (complex signal, 8 H alicyclic), 4.45 (t, 1 H, $C^{21}H$), 6.8–7.8 (m, 4 H, indole), 11.7 (br s, 1 H, indole NH). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.32; H, 6.24; N, 12.38. Found: C, 73.98; H, 6.30; N, 12.01.

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Registry No. 1b, 75306-40-0; **1c**, 7630-02-6; **1d**, 80845-43-8; **2b**, 80845-44-9; **2b** methiodide, 80845-45-0; **2c**, 80845-46-1; **2c**·HCl, 80845-47-2; **2d**, 80845-48-3; **3b**, 80845-49-4; **3c**, 80845-50-7; **3c**·HCl, 80845-51-8; **3d**, 80845-52-9; **3d** picrate, 80845-53-0; **3d**·HCl, 80845-54-1; **3e**, 80845-55-2; **4b**, 80845-56-3; **4b** methiodide, 80845-57-4; **4c**, 59097-06-2; **4d**, 80845-58-5; **5b**, 80846-16-8; **5c**, 80846-17-9; **7c**, 80845-59-6; **7d**, 80845-60-9; *cis*-**10**, 80845-61-0; *trans*-**10**, 80845-62-1; *cis*-**11**, 80845-63-2; *trans*-**11**, 80845-64-3; *cis*-**12**, 80845-65-4; **13**, 80845-66-5; *cis*-**14**, 80845-67-6; *cis*-**15**, 80845-68-7; *trans*-**15**, 80845-69-8; *trans*-**15**·HCl, 80845-70-1; *cis*-**16**, 80845-71-2; *cis*-**16**·HCl, 80845-72-3; *trans*-**16**, 80845-73-4; *cis*-**17**, 80845-74-5; *cis*-**17** picrate, 80845-75-6; *trans*-**17**, 80845-76-7; **18**, 80845-77-8; **19**, 80845-78-9; 4-(diethoxymethyl)pyridine, 27443-40-9; methyl isonicotinate, 2459-09-8; iodoindole, 26340-47-6; indole, 120-72-9; **3e** oxime, 80865-83-4; deethylasycarpidone, 25490-47-5; 20-deethyl-4-demethyldasycarpidone, 80845-79-0.

(44) Systematic name: 2-methyl-6-oxo-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole.