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Formal Synthesis of (±)-Physostigmine

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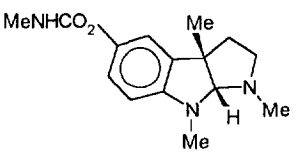
Abstract: The formal synthesis of the indole alkaloid (±)-physostigmine (**1**) from (*Z*)-2-hydroxy-5-methoxyindolenine **9** is described. The key step of the synthesis is a novel diasteroselective conjugated addition of a Grignard reagent to **9**. The relative stereochemistry of the newly formed contiguous chiral centers is established by X-ray crystallography. The stereocontrolled conjugated addition involves the directing effect of the neighboring hydroxyl group to afford **12**. Oxidation of **12** with CrO_3/AcOH leads to oxindole **14**. Decarboxylation of the latter, followed by N-methylation gave 2,3-dihydro-5-methoxy-1,3-dimethyl-2-oxo-1H-indole-3-acetonitrile (**3**), a known precursor for physostigmine (**1**).

(-)-Physostigmine (**1**), an alkaloid isolated from *Physostigma venenosum* Balf is a member of a class of compounds having the hexahydropyrrolo[2,3-b]indole framework. Since this alkaloid has interesting physiological effects, such as anticholinergic and miotic activities, as well as due to its medicinal potential in Alzheimer's disease, new strategies for its synthesis continue to merge.[1] Recently, this alkaloid skeleton has been found to occur in the marine alkaloids from Broyoza *Flustra foliacea* in the flustramines.[2]

RESULTS AND DISCUSSION

As briefly outlined in two preliminary communications,[3] we have succeed in establishing an efficient route to 2,3-dihydro-1,3-dimethyl-2-oxo-1H-indole-3-acetonitrile (**2**) and its 5-methoxy derivative **3**. The last compound is the key intermediate in the synthesis of physostigmine by Julian.[4] In this paper, we wish to report full details of the formal synthesis of (±)-physostigmine (**1**).



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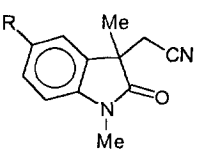
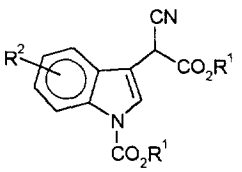


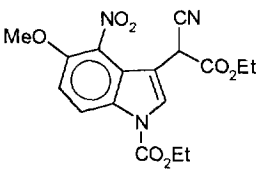
2 R = H
3 R = OMe

Recently, we reported the preparation of (*Z*)-2-hydroxyindolenine **8** by oxidation of indole **4** with nitric acid in acetic acid.[5] Unfortunately, this method is not generally applicable to activated indoles such as the 5-methoxy derivative **5**. In fact, from compound **5** this procedure gives the 4-nitro derivative **7** in 61% isolated

yield. In an alternative method, we found that treatment of **5** with chromium oxide in acetic acid resulted in a high stereoselective oxidation to afford the (*Z*)-2-hydroxy-5-methoxyindolenine **9** in 68% isolated yield (*E*/*Z* ratio 4:96). The (*Z*)-configuration of **9** was determined by detailed ^{1}H and ^{13}C NMR analysis and from the X-ray crystal structure of a (*Z*)-2-hydroxyindolenine.[5] This oxidation procedure seems quite general since it was also successfully applied to indoles **4** and **6** which were transformed, with high stereoselectivity, into the corresponding (*Z*)-2-hydroxyindolenines **8** and **10** in 60 and 51 % yield, respectively. These isolated yields are, however, lower than those obtained *via* the method with nitric acid in acetic acid (85 % for **8**[5] and 87 % for **10**) **Figure 1**. The (*Z*)-2-hydroxyindolenines **8** and **9** were used as the starting material for the preparation of 1,3-dimethyl-2-oxindoles **2** and **3**, respectively.



4 R^1 = Me, R^2 = H
5 R^1 = Et, R^2 = 5-OMe
6 R^1 = Me, R^2 = 6-Br



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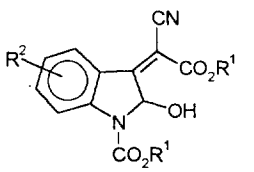
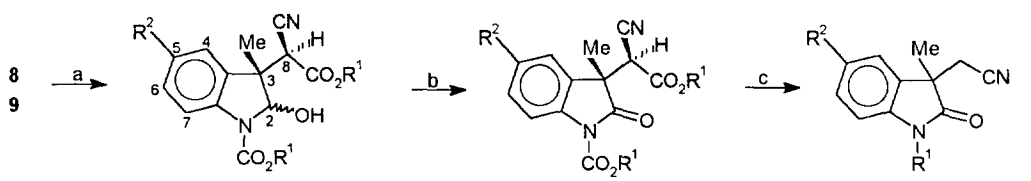


8 R^1 = Me, R^2 = H
9 R^1 = Et, R^2 = 5-OMe
10 R^1 = Me, R^2 = 6-Br

Figure 1

Our synthetic strategy outlined in **Scheme 1** involves the following 4 steps: (i) conjugated addition of methylmagnesium halide to (*Z*)-2-hydroxyindolenines **8** and **9**, to give **11** and **12**; (ii) oxidation of the hydroxy group to form the 2-oxindole derivatives **13** and **14**; (iii) removal of the N-protecting group, hydrolysis of the ester group and subsequent decarboxylation, in a single step, to form **15** and **16**; (iv) N-methylation to give **2** and the key intermediate **3**.



11 R^1 = Me, R^2 = H
12 R^1 = Et, R^2 = OMe

13 R^1 = Me, R^2 = H
14 R^1 = Et, R^2 = OMe

15 R^1 = H, R^2 = H → **2** R^1 = Me, R^2 = H
16 R^1 = H, R^2 = OMe → **3** R^1 = Me, R^2 = OMe

Scheme 1

Reagents and conditions: a) 4 eq. MeMgI/ether, THF, 25 °C, 35 min; b) CrO_3, AcOH, 5°→25 °C, 1 h (for **11**); $Na_2Cr_2O_7/H_2SO_4$-H_2O, ether, 0 °C, 10 min (for **12**); c) NaCN/H_2O, DMSO, 160 °C, 2 h (for **13**) or 1 h (for **14**); d) K_2CO_3, Me_2SO_4, acetone, reflux 10 h (for **15**) or 5 h (for **16**).

In a typical experiment, reaction of (*Z*)-2-hydroxyindolenine **8** with 4 molar equivalents of methylmagnesium iodide, in a solvent mixture of diethyl ether and tetrahydrofuran, at 25 °C, followed by workup with aqueous ammonium chloride, effected the conjugated methyl addition to the prochiral double bond, and led to a 5:4 mixture of only two diastereomeric 3-methylindolines **11a,b** among four possible ones, in

40% yield. The isomers **11a,b** could not be separated by column chromatography on silica gel, however single **11a** could be crystallized from the epimeric mixture (mother liquid contains again **11a** and **11b** in the ratio of *ca* 5:4). In practice, the epimeric mixture was used for the next reaction. As in the previous case, when the 2-hydroxy-5-methoxyindolenine **9** was treated with methylmagnesium iodide, under reaction conditions analogous to those for **8**, it furnished the desired C-3 methylated indoline **12** as a chromatographically inseparable epimeric mixture in 54% yield. Analysis of this mixture by ^{1}H NMR indicated a 5:4 **a/b** ratio. Reaction of **8** and **9** with methylmagnesium chloride at -78 °C also gave 3-methylindolines **11** and **12** as epimeric mixtures in the same **a/b** ratio and with similar yields than those described above. The only advantage was the obtention of a cleaner crude reaction product.

The relative stereochemistries of the two newly produced contiguous stereogenic centers at the C-3 and C-8 positions in the racemic isomers **11a,b** and **12a,b** were unambigously proven by a combination of X-ray crystallographic analysis, spectroscopic properties and subsequent transformations. The X-ray crystal structure[6] of **11a** having the (2R*,3S*,8S*)-stereochemistry is depicted in **Figure 2**.

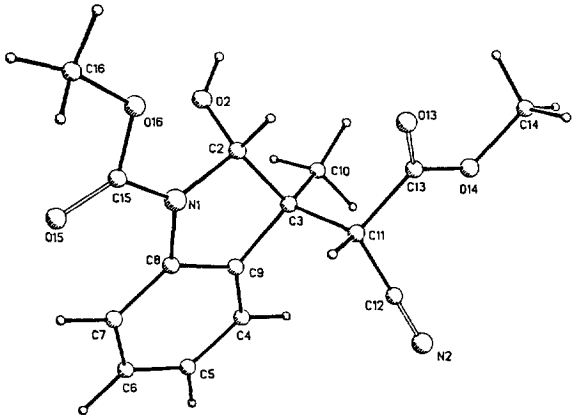
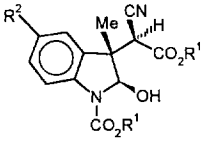
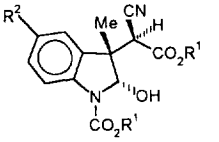


Figure 2. X-Ray crystal structure of 3-methylindoline **11a**, showing crystallographic numbering.

The examination of the ^{1}H NMR spectrum of pure **11a** and the two epimeric mixtures **11a,b** and **12a,b** disclosed diagnostic chemical shifts differences for the H-2 and H-8 proton signals (**Table 1**). Thus, for the **a**-isomers H-2 occur at lower fields than for the **b**-isomers. This situation changed for H-8, which appears for the **a**-isomers at higher field than for the **b**-isomers. In addition, H-2 and H-8 in the **b**-isomers appear as broad signals.

Table 1. ^{1}H NMR chemical shifts[a] (in ppm) of 3-methylindolines **11** and **12**.

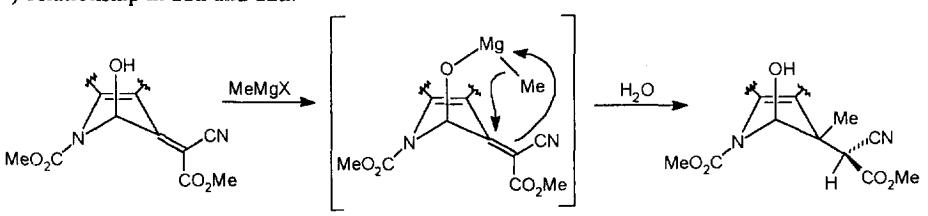




Comp	**a**		**b**[b]	
	H-2	H-8	H-2	H-8
11	6.09(d)	3.52(s)	5.94(br)	3.62(br)
12[b]	6.09(d)	3.53(s)	5.93(br)	3.60(br)

[a]In $CDCl_3$. [b]In a 5:4 **a/b** ratio.

In accord with the stereochemical course of the reaction, the nucleophilic addition can be rationalized by considering an asymmetric induction involving the neighboring alkoxide group as shown in **Scheme 2**. Thus, the (2R*,3S*)-relationship in **11a** and **12a** might result from the initial complexation of the indolenine alkoxide and the Grignard reagent,[7] followed by simultaneous intramolecular electrophilic assistance by the magnesium bond to the oxygen, and the transfer of the methyl group to the nearby C-3 electrophilic center. The high stereoselectivity subsequently achieved in the hydrolysis of the five-membered magnesium ring, yield the (3S*,8S*)-relationship in **11a** and **12a**.

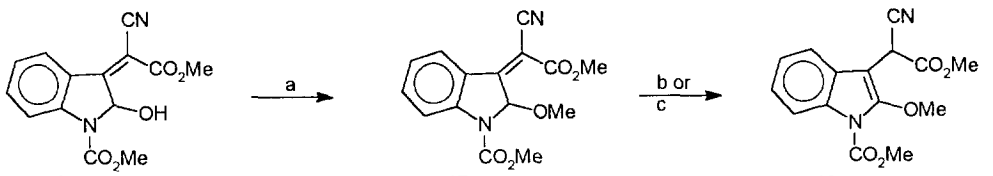


8 **11a**

Scheme 2

Formally, the (2S*,3S*,8S*)-isomers **11b** and **12b** can be obtained by inversion at C-2 of the hemiaminal function in the corresponding **a**-isomers. Effectively, equilibration of **11a** in the presence of a catalytic amount of Et_3N in chloroform at room temperature afforded upon dissolution a 5:4 mixture of **a** and **b** isomers (based on an ^1H NMR spectrum). The observed **a**/**b** ratio of **11** corresponds to that previously obtained from the crude reaction mixture. Such equilibrations involving an aldehyde as the intermediate, are well documented in the literature.[8]

In order to test whether the conjugated addition of the Grignard reagent is dependent on the neighboring alkoxy group, the hydroxy group in **8** was protected as the methyl ether by treatment with gaseous hydrogen chloride in methanol to give **17**.[9] In the reaction of **17** with methylmagnesium iodide, under the reaction conditions described above, we were unable to isolate any products due to nucleophilic addition. Instead, the 2-methoxyindole derivative **18** was isolated in 38% yield (**Scheme 3**). In addition, treatment of **17** with Et_3N in THF at reflux for 6 h also results in the formation of indole **18,** but in this case, in almost quantitative yield. Evidently the alkaline Grignard reaction conditions promote the formation of the rearranged indole **18**. These results support the proposed mechanism involving the key participation of the hydroxy group.



8 **17** **18**

Scheme 3

Reagents and conditions: a) HCl gas, MeOH, reflux 2 h; b) 4 eq. MeMgI/ether, THF, 25 °C, 35 min; c) Et_3N, THF, reflux 6 h.

To continue the synthesis, the epimeric mixture of 3-methylindoline **11** was next subjected to oxidation with chromium oxide in acetic acid at room temperature. As expected, oxidation of such a mixture leads to oxindole **13** as a single isomer, as determined from the ^1H NMR spectrum obtained directly from the reaction mixture. However, this reaction was not successful when extended for the preparation of the 5-methoxy

derivative, since only starting compound **12** was recovered. Fortunately, the epimeric mixture of 3-methyl-5-methoxyindoline **12** was efficiently oxidized with Jones reagent[10] to give the oxindole **14** as a single isomer. These results confirm that the stereochemical difference in the diastereomers **11a,b** and **12a,b** resides in the C-2 hemiaminal center. Oxindoles **13** and **14** were isolated as stable solids in 72 and 67% yield, respectively.

The hydrolysis and subsequent decarboxylation of the carbamate and the ester groups of oxindoles **13** and **14** were performed with sodium cyanide in dimethyl sulfoxide[11] at 160 °C for 2 h, to led the oxindoles **15** and **16** in 93 and 88% yield, respectively. Finally, alkylation of the potassium salt derived from **15** with dimethyl sulfate gives the indole derivative **2** in 80% yield, while the salt derived from **16,** under the same conditions leads to the known 2,3-dihydro-5-methoxy-1,3-dimethyl-2-oxo-1H-indole-3-acetonitrile (**3**) (90% isolated yield), an intermediate in a previous synthesis of (±)-physostigmine (**1**).[4]

We note that the synthesis described here provides a new route to functionalized hexahydropyrrolo[2,3-b]indole alkaloids. Further studies are currently underway to define the scope and limitations of the formation of carbon-carbon bonds and to extend the present approach towards the construction of a variety of related natural products.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. IR spectra were measured on a Nicolet FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian XL300 spectrometer at 300 and 75 MHz, respectively. Electron impact mass spectra were recorded on a Hewlett Packard 5989A spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. Column chromatography was carried out on Merck 60 silica gel (230-400 mesh). Elemental analyses were performed by the Microanalytical Laboratory Elbach, Germany. The X-ray structure was determined using a Nicolet R3m diffractometer. All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Anhydrous solvents were dried and freshly distilled (THF and ether from sodium/benzophenone). Indole derivatives **4**, **5** and **17** were prepared according to literature procedures.[9,12] Compounds **2**[4], **3**[4] and **8**[5,9] are known and they displayed consistent spectral data.

Methyl 6-bromo-3-(1-cyano-2-methoxy-2-oxoethyl)-1H-indole-1-carboxylate (6). It was prepared from 6-bromo-1H-indole-3-acetonitrile and sodium in dimethyl carbonate in 84 % yield, following an analogous procedure to that described in ref. 12; yellow prisms (from hexane-acetone) mp 139-140 °C. IR ($CHCl_3$) 2258, 1754, 1748 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.40(1H, br s, H-7), 7.79(1H, d, J = 0.9 Hz, H-2), 7.52(1H, d, J = 8.5 Hz, H-4), 7.44(1H, dd, J = 8.5, 1.7 Hz, H-5), 4.93(2H, d, J = 0.9 Hz, H-8), 4.08, 3.83(6H, 2s, 2 OMe). ^{13}C NMR ($CDCl_3$) δ 164.5(C-CO_2Me), 150.5(N-CO_2Me), 136.2(C-7a), 127.1(C-5), 126.2(C-3a), 125.6(C-2), 120.2(C-4), 119.7(C-6), 118.9(C-7), 114.5(CN), 110.4(C-3), 54.5, 54.1(2 OMe), 35.3(C-8).

Methyl 3-(1-cyano-2-ethoxy-2-oxoethyl)-5-methoxy-4-nitro-1H-indole-1-carboxylate (7). To a stirred solution of **5** (300 mg, 0.91 mmol) in glacial acetic acid (2.5 ml) was added dropwise HNO_3 (0.2 ml, *d* 1.4) and stirring was continued for 2 h at room temperature. The reaction mixture was poured onto cracked ice and the yellow precipitate which had formed was collected by suction filtration and washed with water (4 x 20 ml). The solid residue was dissolved in AcOEt (60 ml), washed with brine (3x15 ml) and dried over Na_2SO_4. The

solvent was removed under reduced pressure and the residue was recrystallized from $CHCl_3$-hexane to afford **7** as a yellow solid (210 mg, 61%): mp 143-144 °C. IR ($CHCl_3$) 2256, 1748, 1434, 1320 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.43(1H, d, J = 9.3 Hz, H-7), 8.02(1H, d, J = 1.0 Hz, H-2), 7.14(1H, d, J = 9.3 Hz, H-6), 5.22(1H, d, J = 1.0 Hz, H-8), 4.53, 4.23(4H, 2q, J = 7.0 Hz, 2 OCH_2), 3.98(3H, s, OMe), 1.49, 1.28(6H, 2t, J = 7.0 Hz, 2 Me). ^{13}C NMR ($CDCl_3$) δ 164.3 (C-CO_2Et), 149.8(N-CO_2Et), 149.4(C-5), 131.2(C-3a), 129.2(C-2), 121.0(C-4), 119.6(C-7), 115.1(CN), 111.4(C-7), 108.8(C-3), 64.4, 63.8(2 OCH_2), 57.6(OMe), 35.3(C-8), 14.3, 13.8(2 Me). MS (EI) *m/z*: 375(M^+, 100), 302(47), 230(69).

Methyl (*Z*)-3-(1-cyano-2-methoxy-2-oxoethylidene)-2,3-dihydro-2-hydroxy-1H-indole-1-carboxylate (8). To a stirred solution of **4** (200 mg, 0.73 mmol) in glacial acetic acid (3 ml) was added dropwise a solution of chromium oxide (200 mg) in water (1 ml). The reaction mixture was stirred for 1 h at room temperature and then poured onto cracked ice. The precipitate which had formed was collected by suction filtration and washed with water (4 x 20 ml). The solid residue was dissolved in AcOEt (60 ml), washed with brine (3 x 15 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was crystallized from MeOH to afford **8,** as a yellow solid (127 mg, 60%) whose spectral properties[13] were identical to those of a sample prepared by oxidation of **4** with HNO_3 in acetic acid. [5,9]

Ethyl (*Z*)-3-(1-cyano-2-ethoxy-2-oxoethylidene)-2,3-dihydro-2-hydroxy-5-methoxy-1H-indole-1-carboxylate (9). Compound **5** (200 mg, 0.61 mmol) was oxidized with chromium oxide following the same procedure as for **4**, except that **5** was dissolved in only 2 ml of acetic acid. Usual workup and purification by crystallization from methanol afforded **9** as a yellow needles (144 mg, 68%). *E/Z* ratio 4:96; mp 162-164 °C. IR ($CHCl_3$) 3580, 3560, 2220, 1726 cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.77(1H, very broad, H-7), 7.74(1H, d, J = 2.7 Hz, H-4), 7.28(1H, dd, J = 9.0, 2.7 Hz, H-6), 7.27(1H, d, J = 7.8 Hz, OH), 6.62(1H, d, J = 7.8 Hz, H-2), 4.31, 4.26(4H, 2q, J = 7.0 Hz, 2OCH_2), 3.77(3H, s, OMe), 1.33(6H, t, J = 7.0 Hz, 2Me). ^{13}C NMR (DMSO-d_6) δ 162.7, 160.8(C-3, C-CO_2Et), 155.1(C-5), 150.8(N-CO_2Et), 141.4(C-7a), 123.9(C-6), 122.1(C-3a), 116.0(C-7), 115.9(CN), 108.1(C-4), 95.7(C-8), 82.7(C-2), 62.0, 61.7(2 OCH_2), 55.4(OMe), 14.2, 13.8(2 Me). MS (EI) *m/z*: 346(M^+, 3), 69(100). Anal. calc. for $C_{17}H_{18}N_2O_6$: C 58.96, H 5.24, N 8.09, O 27.72. Found C 58.80, H 5.14, N 8.13, O 27.67.

Methyl (*Z*)-6-bromo-3-(1-cyano-2-methoxy-2-oxoethylidene)-2,3-dihydro-2-hydroxy-1H-indole-1-carboxylate (10). **Method a**. Compound **6** (200 mg, 0.57 mmol) was oxidized with chromium oxide following the same procedure as for **4**, except that **6** was dissolved in only 2.5 ml of acetic acid. Usual workup and purification by column chromatography (silica gel 7:3 hexane-acetone) afforded **10** as a yellow solid (107 mg, 51%), mp 198-199 °C from AcOEt. IR ($CHCl_3$) 3568, 2222, 1728 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.16(1H, d, J = 8.6 Hz, H-4), 8.04(1H, very broad, H-7), 7.52(1H, d, J = 7.8 Hz, OH), 7.49(1H, dd, J = 8.6, 1.9 Hz, H-5), 6.70(1H, d, J = 7.8 Hz, H-2), 3.86, 3.84(6H, 2s, 2 OMe). ^{13}C NMR (DMSO-d_6) δ 161.7(C-3), 161.1(C-CO_2Me), 151.4(N-CO_2Me), 147.5(C-7a), 130.3(C-6), 126.7(C-4), 126.6(C-5), 121.0(C-3a), 117.7(C-7), 115.7(CN), 96.2(C-8), 83.1(C-2), 53.3, 53.2(2 OMe), MS (EI) *m/z*: 368[$(M+2)^+$, ^{81}Br, 84], 366(M^+, ^{79}Br, 87), 336(99), 334(100). **Method b**. Compound **6** (300 mg, 0.855 mmol) in glacial acetic acid (3 ml) treated with HNO_3 (1.4 ml, *d* 1.4) for 20 min at 60 °C, afforded, after workup and purification the 2-hydroxyindolenine **10** (273 mg, 87 %).

(2R*,3S*,8S*)- and (2S*,3S*,8S*)-Methyl 3-methyl-3-(1-cyano-2-methoxy-2-oxoethyl)-2,3-dihydro-2-hydroxy-1H-indole-1-carboxylate (11a,b). To a stirred suspension of MeMgI prepared from MeI (986 mg, 6.94 mmol) and Mg turnings (168 mg, 0.007 atom) in dry Et_2O (20 ml) under argon at 25 °C was added a solution of **8** (500 mg, 1.73 mmol) in THF (8 ml) *via* cannula over a period of 20 min. The orange reaction mixture was stirred for additional 15 min at the same temperature. The reaction was quenched with sat. NH_4Cl solution (15 ml) and diluted with AcOEt (80 ml). The organic layer was decanted, washed with brine (2 x 20 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residual brown oil was subjected to column chromatography (silica gel 24:1 CH_2Cl_2-AcOEt). This afforded an epimeric mixture of **11a,b** (ratio 5:4) as a pale yellow oil (210 mg, 40%). Pure **11a** was obtained from this mixture by crystallization from MeOH, whereas isomer **11b** could not be purified in this manner (mother liquid contains **11a** and **11b** in the ration of *ca* 5:4). Note: When compound **8** was treated with MeMgCl at -78 °C for 2 h a slightly increased yield of the epimeric mixture (44 %, 5:4 **a/b** ratio) was obtained.

Compound 11a: slightly greenish crystals from MeOH; mp 152-155 °C. IR ($CHCl_3$) 3591, 3347, 2250, 1746, 1722 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.77(1H, very br, H-7), 7.33(1H, d, J = 7.5 Hz, H-4), 7.31(1H, td, J = 7.5, 1.0 Hz, H-6), 7.08(1H, td, J = 7.5, 1.0 Hz, H-5), 6.09(1H, d, J = 4.5 Hz, H-2), 3.91(3H, br s, N-CO_2Me), 3.62(3H, br s, C-CO_2Me), 3.52(1H, s, H-8), 1.63(3H, s, Me-C3). ^{13}C NMR ($CDCl_3$) δ 164.3(C-CO_2Me), 154.6(N-CO_2Me), 139.6(C-7a), 131.5(C-3a), 129.9(C-6), 124.3(C-4), 123.7(C-5), 114.9(C-7), 114.7(CN), 86.7(C-2), 53.6, 53.2(2 OMe), 49.7(C-3), 46.7(C-8), 16.7(Me-C3). MS (EI) *m/z*: 304(M^+, 16), 146(100). Anal. calc for $C_{15}H_{16}N_2O_5$: C 59.21, H 5.30, N 9.21, O 26.29. Found C 59.21, H 5.32, N 9.14, O 26.40.

Compound 11b: could not be obtained in pure form but was characterized (from the mixture with **11a**) by ^1H and ^{13}C NMR. ^1H NMR ($CDCl_3$) δ 7.77 (1H, very br, H-7), 7.31(1H, td, J = 7.5, 1.0 Hz, H-6), 7.21(1H, d, J = 7.5 Hz, H-4), 7.07(1H, td, J = 7.5, 1.0 Hz, H-5), 5.94(1H, br, H-2), 3.91(3H, br s, N-CO_2Me), 3.68(3H, br s, C-CO_2Me), 3.62(1H, br, H-8), 1.64(3H, s, Me-C3). ^{13}C NMR ($CDCl_3$) δ 164.6 (C-CO_2Me), 154.6(N-CO_2Me), 139.6(C-7a), 131.5(C-3a), 129.9(C-6), 124.3(C-4), 123.7(C-5), 114.9(CN), 114.7(C-9), 86.7(C-2), 53.6, 53.3(2 OMe), 49.8(C-3), 46.7(C-8), 17.0(Me-C3).

(2R*,3S*,8S*)- and (2S*,3S*,8S*)-Ethyl 3-methyl-3-(1-cyano-2-ethoxy-2-oxoethyl)-2,3-dihydro-2-hydroxy-5-methoxy-1H-indole-1-carboxylate (12 a,b). Compound **9** (300 mg, 0.86 mmol) was treated with MeMgI at 25 °C following the procedure described for **8**. Column chromatography (silica gel, 24:1 CH_2Cl_2-AcOEt) afforded an epimeric mixture of **12a,b** (ratio 5:4) as a pale pink oil (166 mg, 54 %) which was used directly for the next step. Note: When compound **9** was treated with MeMgCl at -78 °C for 1 h a slightly reduced yield of the epimeric mixture (48 %, 5:4 **a/b** ratio) was obtained. Epimers **12a,b** did not separate by TLC. IR ($CHCl_3$) 3594, 2250, 1744, 1726 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.70, 7.37 (1H, very br signals, H-7), 6.87(1H, dd, J = 9.0, 2.5 Hz, H-6), 6.80(1H, m, H-4), 6.09, 5.93(1H, d, J = 4.3 Hz and, br signal, H-2), 4.33, 4.09(4H, q, J = 7.0 Hz and br signal, 2 OCH_2), 3.80(3H, s, OMe), 3.60, 3.53(1H, br s and s, H-8), 1.63, 1.62(3H, 2s, Me-C3), 1.39, 1.15(6H, br t, J = 7.0 Hz and br signal, 2 Me). MS (EI) *m/z*: 362(M^+, 87), 316(30), 250(59), 176(100).

(3S*, 8S*)-Methyl 3-methyl-3-(1-cyano-2-methoxy-2-oxoethyl)-2,3-dihydro-2-oxo-1H-indole-1-carboxylate (13). To a stirred solution of the epimeric mixture **11a,b** (100 mg, 0.33 mmol) in AcOH (5 ml) was added at 5

°C a solution of chromium oxide (100 mg) in H_2O (0.5 ml) and stirring continued at room temperature for 1 h. The mixture was poured over cracked ice and extracted with AcOEt (2 x 40 ml). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was crystallized from $CHCl_3$-hexane to afford **13** as white needles (72 mg, 72%); mp 125-126 °C. IR ($CHCl_3$) 2253, 1796, 1752 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.98(1H, d, J = 8.2 Hz, H-7), 7.61(1H, d, J = 7.6 Hz, H-4), 7.40(1H, td, J = 7.6, 1.0 Hz, H-6), 7.23(1H, td, J = 7.6, 1.0 Hz, H-5), 4.31(1H, s, H-8), 4.05(3H, s, N-CO_2Me), 3.57(3H, s, C-CO_2Me), 1.66(3H, s, Me-C3). ^{13}C NMR ($CDCl_3$) δ 175.6(C-2), 163.5(C-CO_2Me), 151.2(N-CO_2Me), 139.0(C-7a), 129.8(C-6), 128.2(C-3a), 125.4(C-5), 122.7(C-4), 115.6(C-7), 114.3(CN), 54.2, 53.8(2 OMe), 47.9(C-3), 44.8(C-8), 24.5(Me-C3). MS (EI) *m/z*: 302(M^+, 43), 204(100). Anal. calc for $C_{15}H_{14}N_2O_5$: C 59.60, H 4.67, N 9.27, O 26.46. Found C 59.64, H 4.57, N 9.25, O 26.34.

(3S*, 8S*)-Ethyl 3-methyl-3-(1-cyano-2-ethoxy-2-oxoethyl)-2,3-dihydro-5-methoxy-2-oxo-1H-indole-1-carboxylate (14). To a stirred solution of the epimeric mixture **12a,b** (220 mg, 0.61 mmol) in Et_2O (2.5 ml) was added at 0 °C a cold solution of Jones reagent[10] (6.4 ml) in two portions. The biphasic mixture was vigorously stirred for additional 6 min at 0 °C, diluted with ether (20 ml) and water (10 ml) and then separated. The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic fractions were washed with 5 % aqueous K_2CO_3 (2 x 15 ml) and brine (3 x 15 ml). The resulting dark red solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 4:1 hexane-AcOEt) to give **14** as a white solid (148 mg, 67 %). Crystallization from Et_2O-hexane gave fine white needles, mp. 89-90 °C. IR ($CHCl_3$) 2252, 1794, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.92(1H, d, J = 9.0 Hz, H-7), 7.16(1H, d, J = 2.7 Hz, H-4), 6.90(1H, dd, J = 9.0, 2.7 Hz, H-6), 4.49(2H, q, J = 7.0 Hz, OCH_2), 4.30(1H, s, H-8), 4.02(2H, m, OCH_2), 3.82(3H, s, OMe), 1.66(3H, s, Me-C3), 1.46, 1.04(6H, 2t, J = 7.0 Hz, 2Me). ^{13}C NMR ($CDCl_3$) δ 175.6(C-2), 162.9(C-CO_2Me), 157.4(C-5), 150.7(N-CO_2Me), 132.3(C-7a), 129.5(C-3a), 116.5(C-7), 114.5(C-6), 114.4(CN), 108.8(C-4), 63.6, 63.3(2 OCH_2), 55.7(OMe), 48.1(C-3), 45.1(C-8), 24.6(Me-C3), 14.2, 13.5(2 Me). MS (EI) *m/z*: 360(M^+, 49), 288(21), 176(100). Anal. calc for $C_{18}H_{20}N_2O_6$: C 59.99, H 5.59, N 7.77, O 26.64. Found C 59.98, H 5.46, N 7.72, O 26.49.

2,3-Dihydro-3-methyl-2-oxo-1H-indole-3-acetonitrile (15). To a solution of **13** (700 mg, 2.32 mmol) in DMSO (7 ml) was added a solution of NaCN (28 mg) in water (0.7 ml) and the resultant mixture heated to 160 °C with stirring for 2 h. DMSO was then removed under reduced pressure and the residue was suspended in AcOEt (80 ml). The AcOEt layer was washed with brine (2 x 15 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting dark residue was subjected to column chromatography (silica gel, 9:1 hexane-AcOEt) to give **15** as a pale yellow oil (400 mg, 93 %), which solidified upon standing at 25 °C. IR ($CHCl_3$) 3434, 3202, 2254, 1724 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.44(1H, br s, NH), 7.44(1H, d, J = 7.5 Hz, H-4), 7.28(1H, td, J = 7.6, 1.0 Hz, H-6), 7.10(1H, td, J = 7.6, 1.0 Hz, H-5), 7.04(1H, d, J = 7.6 Hz, H-7), 2.85, 2.65(2H, AB, J = 16.6 Hz, H-8, 8'), 1.55(3H, s, Me-C3). ^{13}C NMR ($CDCl_3$) δ 180.3(C-2), 140.0(C-7a), 131.5(C-3a), 129.2(C-6), 123.3(C-4), 123.2(C-5), 116.6(CN), 110.7(C-7), 45.4(C-3), 26.1(C-8), 22.1(Me-C3). MS (EI) *m/z*: 186(M^+, 52), 146(100), 128(45).

2,3-Dihydro-5-methoxy-3-methyl-2-oxo-1H-indole-3-acetonitrile (16). Compound **14** (230 mg, 0.64 mmol) was treated following the procedure described for **13**, except that **14** was heated at 160 °C for only 1 h. Column

chromatography (silica gel, 4:1 hexane-AcOEt) afforded **16** as an oil (129 mg, 88%) which was crystallized from $CHCl_3$-hexane as a white solid, mp 126-127 °C. IR ($CHCl_3$) 3436, 3194, 2252, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.31(1H, br s, NH), 7.04(1H, d, J = 2.5 Hz, H-4), 6.91(1H, d, J = 8.5 Hz, H-7), 6.81(1H, dd, J = 8.5, 2.5 Hz, H-6), 3.81(3H, s, OMe), 2.85, 2.65(2H, AB, J = 16.6 Hz, H-8, 8'), 1.55(3H, s, Me-C3). ^{13}C NMR ($CDCl_3$) δ 180.2(C-2), 156.3(C-5), 133.2(C-7a), 132.8(C-3a), 116.5(CN), 113.8(C-6), 111.2(C-7), 110.4(C-4), 55.8(OMe), 45.9(C-3), 26.2(C-8), 22.2(Me-C3). MS (EI) *m/z*: 216(M^+, 26), 176(48), 28(100). Anal. calc for $C_{12}H_{12}N_2O_2$: C 66.65, H 5.59, N 12.95, O 14.80. Found C 66.75, H 5.58, N 12.99, O 14.84.

2,3-Dihydro-1,3-dimethyl-2-oxo-1H-indole-3-acetonitrile (2). To a solution of **15** (700 mg, 3.76 mmol) in anhydrous acetone (10 ml) was added K_2CO_3 (630 mg) and Me_2SO_4 (0.4 ml, 4.21 mmol) and the mixture stirred under reflux for 10 h. The solvent was removed at reduced pressure and the residual slight brown oil was diluted with AcOEt (80 ml). The organic layer was washed with brine (15 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel 9:1 hexane-AcOEt). This afforded **2**[4] as a pale yellow oil (602 mg, 80 %). ^1H NMR ($CDCl_3$) δ 7.48 (1H, ddd, J = 7.5, 1.2, 0.6 Hz, H-4), 7.36(1H, td, J = 7.5, 1.2 Hz, H-6), 7.14(1H, td, J = 7.5, 1.2 Hz, H-5), 6.91(1H, d, J = 7.5 Hz, H-7), 3.25(3H, s, N-Me), 2.28, 257(2H, AB, J = 16.6 Hz, H-8, 8'), 1.53(3H, s, Me-C3). ^{13}C NMR ($CDCl_3$) δ 177.5(C-2), 142.7(C-7a), 131.0(C-3a), 129.2(C-6), 123.3(C-5), 123.1(C-4), 116.6(CN), 108.7(C-7), 44.8(C-3), 26.5(C-8), 26.3(N-Me), 22.2(Me-C3). MS (EI) *m/z*: 200(M^+, 42), 160(100).

2,3-Dihydro-5-methoxy-1,3-dimethyl-2-oxo-1H-indole-3-acetonitrile (3). Compound **16** (100 mg, 0.46 mmol) was methylated with Me_2SO_4 following the same procedure as for **15**, except that **16** was refluxed for only 5 h. Usual workup and purification by column chromatography (silica gel 4:1 hexane-AcOEt) afforded **3** as a colorless oil (96 mg, 90 %). Crystallization from Et_2O-hexane afforded white solid mp 70-72 °C. (Lit.[14] mp 75-76 °C).

Methyl 3-(1-cyano-2-methoxy-2-oxoethyl)-2-methoxy-1H-indole-1-carboxylate (18). **Method a**. Compound **17** (500 mg, 0.16 mmol) was treated with MeMgI at 25 °C following the procedure described for **8**. Column chromatography (silica gel, 95:5 hexane-AcOEt) afforded **18** as a pale yellow oil (190 mg, 38 %) which was crystallized from ether-hexane as a white solid, mp 91-93°C. IR ($CHCl_3$) 2253, 1752 cm^{-1}. ^1H RMN ($CDCl_3$) δ 8.07(1H, m, H-7), 7.60(1H, m, H-4), 7.15(1H, ddd, J = 7.3, 7.3, 1.7, H-6), 7.15(1H, ddd, J = 7.3, 7.3, 1.7, H-5), 5.02(1H, s, H-8), 4.09, 4.05, 3.82(9H, 3s, 3 OMe). ^{13}C NMR ($CDCl_3$) δ 165.0(C-CO_2Me), 150.7, 149.9(N-CO_2Me, C-2), 131.4(C-7a), 124.8(C-6), 124.6(C-3a), 124.0(C-5), 118.3(C-4), 115.6(C-7), 114.6(CN), 96.0(C-3), 64.4, 54.1, 54.0(3 OMe), 32.9(C-8). MS (EI) *m/z*: 302 (M^+, 72), 243(100).
Method b. Compound **17** (100 mg, 0.03 mmol) in THF (5 ml) treated with Et_3N (0.3 ml) for 6 h at reflux, afforded, after workup and purification the 2-methoxyindol **18** in a nearly quantitative yield.

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REFERENCES AND NOTES

1. For reviews, see (a) Takano, S.; Ogasawara, K. *The Alkaloids*; Brossi, A., Ed.; Academic Press; New York, **1989**, *36*, 225. (b) Robinson, B. *The Alkaloids*; Manske, R.H.F., Ed; Academic Press; New York, **1968**, *10*, 398 and *13*, Chapter 4.
2. Carlé, J.S.; Christophersen, C. *J. Org. Chem.* **1980**, *45*, 1586-1589.
3. (a) Morales-Ríos, M.S.; Bucio, M.A.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 881-882. (b) Morales-Ríos, M.S.; Bucio, M.A.; García-Martínez, C.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 6087-6088.
4. (a) Julian, P.L.; Pikl, J.; Boggess, D. *J. Am. Chem. Soc.*., **1934**, *56*, 1797-1801. (b) Julian, P.L.; Pikl, J. *J. Am. Chem. Soc.*, **1935**, *57*, 539-544 and 563-566. (c) Schönenberger, B.; Brossi, A. *Helv. Chim. Acta*, **1986**, *69*, 1486-1487. (d) Yu, Q.-S.; Brossi, A.; *Heterocycl.*, **1988**, *27*, 745-750 and 1709-1712. (d) Lee, T.B.K.; Wong, G.S.K. *J. Org. Chem.*, **1991**, *56*, 872-875.
5. Morales-Ríos, M.S.; Bucio-Vásquez, M.A.; Joseph-Nathan, P. *J. Heterocycl. Chem.*, **1993**, *30*, 953-956.
6. Crystal data for **11a**. $C_{15}H_{16}N_2O_5$, MW = 304.3, monoclinic, space group $P2_1/c$ a = 12.723(5), b = 8.437(3), = 15.114(6) Å, β = 111.51(3)°, V = 1519.42Å^3, D_c = 1.33 gcm^{-3}, F_{000} = 639.89, λ = 1.54178Å, scan type θ-2θ, scan speed variable 4.0 - 29.3, scan limits 3° ≥ 2θ ≥ 110° of the 2166 collected reflections, 1489 [I = 3σ(I)] were considered as observed. The structure was refined to R = 6.65% using 1355 independent reflections. Atomic coordinates, bond lenghts, bond angles, anisotropic thermal parameters, hydrogen coordinates, calculated and observed structure factors and torsion angles are deposited at the Cambridge Crystallographic Data Centre.
7. (a) Swiss, K.A.; Hinkley, W.; Maryanoff, C.A.; Liotta, D.C. *Synthesis*, **1992**, 127-131 and references contained therein. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc. Chem. Commun.* **1987**, 464-466. (c) Larchevêque, M.; Tamagnan, G.; Petit, Y. *J. Chem. Soc. Chem. Commun.*, **1989**, 31-33. (d) Chérest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G. *Tetrahedron Lett.* **1966**, 875-879.
8. (a) Rees, C.W.; Sabet, C.R. *J. Chem. Soc.*, **1965**, 870-875. (b) Buchardt, O.; Lohse, C. *Tetrahedron Lett.* **1966**, 4355-4361. (c) Buchardt, O.; Kumler, P.L.; Lohse, C. *Acta Chem. Scand.*, **1969**, *23*, 1155-1167. (d) Harrison, D.M. *Tetrahedron Lett.* **1984**, *25*, 6063-6064.
9. Morales-Ríos, M.S.; Bucio, M.A.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1993**, *31*, 960-962.
10. Brown, H.C.; Garg, C.P.; Liu, K.-T. *J. Org. Chem.*, **1971**, *36*, 387-390.
11. Krapcho, A.P. *Synthesis*, **1982**, 805-822 and 893-914.
12. Morales-Ríos, M.S.; Joseph-Nathan, P. *Magn. Reson. Chem.*, **1987**, *25*, 911-918.
13. Combined use of long-range C-H coupling constants and long-range chemical shift correlated contour plots allowed to reassign the ^{13}C NMR signals owing to unprotonated C-3 and the carbonyl of the carbamate group (N-CO_2Me) in the series of 2-hydroxyindolenines given in ref.[9] In particular, compound **8** shows in the proton-coupled spectrum the signals at 161.3 and 151.5 ppm as a quartet fine structures caused by long-range coupling with the methyl groups (^3J = 3.8 Hz), whereas the signal at 162.9 ppm appears as a broadened singlet. Irradiation of the H-4 signal at 8.57 ppm sharpened the latter signal which therefore owns to C-3. In addition in the FLOCK spectrum the carbonyl signals at 161.3 (C-CO_2Me) and 151.5(N-CO_2Me) ppm correlate with the methyl singlets at 3.84 and 3.82 ppm, respectively.
14. Robinson, B. *J. Chem. Soc.* **1965**, 3336-3339.

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