2-Hydroxy-1-substituted-1,2,3,4-tetrahydro-β-carbolines. The Pictet–Spengler Reaction of *N*-Hydroxytryptamine with Aldehydes

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The Pictet–Spengler reaction of *N*-hydroxytryptamine (6) with various aldehydes was examined. Reduction of 3-(2-nitroethyl) indole (5) with aluminum amalgam gave 6, which was not so stable and was readily oxidized to the azoxy compound (10) in solution under an oxygen atmosphere. Reaction of 6 with saturated aldehydes gave the corresponding nitrones (11b, c) without an acid catalyst at room temperature, while the reaction with α,β-unsaturated aldehydes provided nitrones (11d, e, f) in the presence of trifluoroacetic acid. Cyclization of the nitrones with trifluoroacetic acid in methylene chloride gave the 2-hydroxy-1,2,3,4-tetrahydro-β-carbolines (2) in good yields. The cyclization of the saturated nitrones proceeded rapidly, whereas the similar reaction of the unsaturated nitrones was slow. Direct Pictet–Spengler reaction of 6 with aldehydes in methylene chloride in the presence of trifluoroacetic acid gave 2a, b, c in excellent yields. Dehydration of the 2-hydroxy-β-carboline (2b) with trifluoroacetic anhydride in benzene gave the 3,4-dihydro-β-carboline (15). 6-Bromo-5-methoxy-*N*-hydroxytryptamine (25) was prepared from 3-bromo-4-methoxyaniline (17) *via* the indole (22). The Pictet–Spengler reaction of 25 with isovaleraldehyde gave the 2-hydroxy-tetrahydro-β-carboline (26).

Keywords 1-substituted-2-hydroxy-tetrahydro-β-carboline; Pictet–Spengler reaction; *N*-hydroxytryptamine; nitrone; 3-(2-nitroethyl)-indole; cyclization; eudistomin; Fischer indolization; indole; aldehyde

Since eudistomins (1), anti-viral marine alkaloids, were isolated in 1984,[1] synthesis of 2-hydroxy-1-substituted tetrahydro-β-carbolines, which are partial structure of eudistomins, has been reported by two groups. Cava and his coworkers[2] reported the Pictet–Spengler (P–S) reaction of *N*-hydroxytryptamine with some aldehydes to give 2-hydroxy-β-carbolines (2) via the nitrones. Ottenheijm and his coworkers[3] reported a modified P–S reaction of an *N*-hydroxytryptophan ester with acetals to form 3.

We describe here a similar P–S reaction of *N*-hydroxytryptamine with various aldehydes which were not used by Cava's group, giving the 2-hydroxy-1-substituted-β-carbolines (2), as a part of our synthetic approaches to eudistomins.[4] We have prepared 3-(2-nitroethyl) indole (5) as the precursor of *N*-hydroxytryptamine (5) by two different methods. Michael addition of indole to nitroethylene[5] gave 5 in 57% yield. On the other hand, condensation of 3-indolecarboxyaldehyde with nitromethane in the presence of ammonium acetate[6] gave 3-(2-nitrovinyl) indole (8) in 92% yield. Reduction of 8 with $NaBH_4$ in methanol gave 5 in 91% yield.[7] Partial reduction of 5 with Zn–NH_4Cl in aqueous ethanol[8] afforded the desired *N*-hydroxytryptamine (6) in 46% yield. The oxime (9) has been reported as a by-product of the reduction.[8] The same by-product, mp 148—149 °C, was also isolated by us, but its structure should be revised to the azoxy compound (10) based on the following evidence. The by-product showed a molecular ion peak at *m/z* 332 in the mass spectrum (MS). Its ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum showed four triplets at 3.08, 3.42, 3.75, and 4.46 ppm due to two sets of side chain methylene groups. Furthermore, no strong absorption was observed in the region of 1650—1680 cm^{-1} due to the C=N double bond of the oxime (9) in its infrared (IR) spectrum, but a band was observed at around 1330 cm^{-1} due to an azoxy group.[9] Reduction of 5 with aluminum amalgam[2] gave a better result (64%). Direct reduction of the nitrovinylindole (8) to 6 with BH_3–tetrahydrofuran (THF)–$NaBH_4$[10] and reduction of the nitronate of 5 to 6 with BH_3–THF[11] were not successful.

The *N*-hydroxytryptamine (6) can be obtained as crystals and purified by careful recrystallization, but it readily decomposed during silica gel chromatography. When 6 in methylene chloride was stirred under air in the presence or absence of silica gel, it gradually oxidized to the azoxy

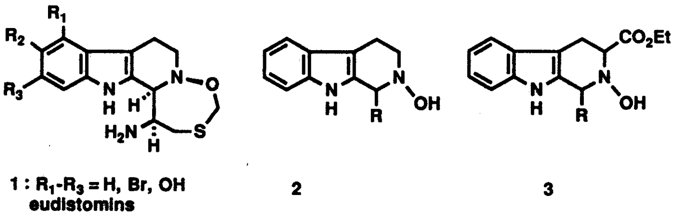

Chart 1

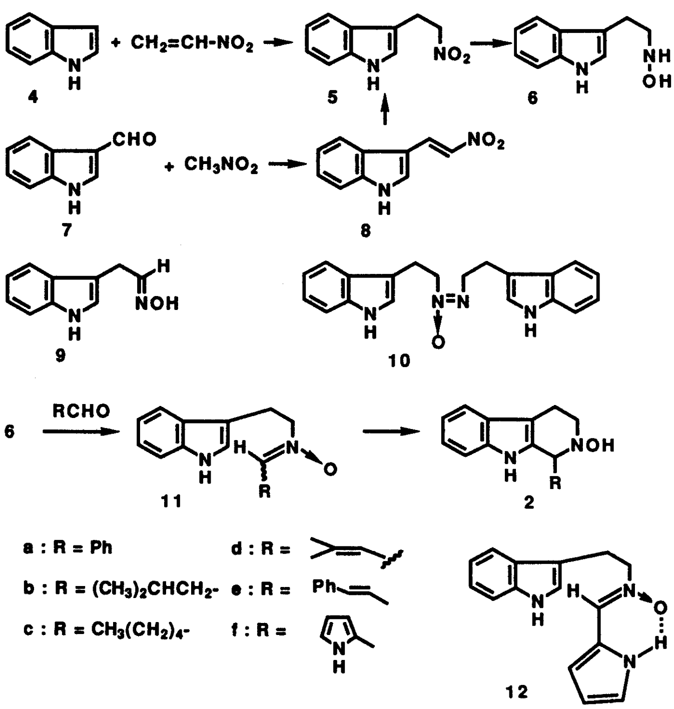

Chart 2

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TABLE I. Reaction of *N*-Hydroxytryptamine (**6**) with Aldehydes to Give the Nitrone (**11**)

R–CHO R	Solvent	Acid	Conditions	Nitrone **11** Yield (%)	NMR HC=N→O ppm (*J*, Hz)
Ph[a]	Benzene		2 h, reflux	**11a**, 90.0	7.07[s]
$(CH_3)_2CHCH_2$–[b]	CH_2Cl_2		1 min, r.t.	**11b**, 89.5	6.33[t] (5.8)
$CH_3(CH_2)_4$–[a]	CH_2Cl_2		1 min, r.t.	**11c**, 84.3	6.32[t] (5.8)
$(CH_3)_2C=CH$–[a]	CH_2Cl_2	TFA	20 min, r.t.	**11d**, 79.0	6.54[d] (9.9) or 6.91[d] (9.9)
PhCH=CH–[a]	CH_2Cl_2	TFA	1 h, r.t.	**11e**, 55.0	6.91[d] (9.6)
2-pyrrolyl (pyrrole ring, N–H)[a]	CH_2Cl_2	TFA	1.5 h, reflux	**11f**, 92.6	6.95[d] (2.7)

a) 1.5 mol eq of the aldehyde with respect to **6** was used. *b*) 1.0 mol eq of the aldehyde with respect to **6** was used.

TABLE II. Ring Closure of the Nitrone (**11**) to the *β*-Carboline (**2**)[a]

11	Reaction temp.	Reaction time	**2** Yield	**2** mp (°C)
a	r.t.	2 h	82.6	184—185
b	r.t.	10 min	88.3	159.5—160.5
c	r.t.	15 min	91.7	Caramel
d	Reflux	6 h	63.4	155—156.5
e	Reflux	6.5 h	64.5	182.5—184
f[b]	r.t.	3 h	89.0	194—195

a) The reaction was carried out in CH_2Cl_2 with 3 mol eq of TFA with respect to **11**. *b*) The reaction was carried out in TFA.

compound (**10**).

We next examined the P–S reaction of **6** with aldehydes. Refluxing of **6** with benzaldehyde in benzene gave the nitrone (**11a**), mp 130—131.5 °C, in 90% yield, but not the *β*-carboline (**2a**). Similar reactions of **6** with aliphatic aldehydes proceeded quickly to form the nitrone (**11b, c**) at room temperature in CH_2Cl_2. On the other hand, the similar reaction of **6** with *α,β*-unsaturated aldehydes did not proceed in CH_2Cl_2 at room temperature, but gave **11d, e** on the addition of trifluoroacetic acid (TFA). The reaction with 2-pyrrolecarboxyaldehyde afforded the nitrone (**11f**) in refluxing methylene chloride in the presence of TFA. These results are summarized in Table I. These nitrones (**11**) were obtained as a single isomer, and the another isomer could not be isolated. The NMR spectra of **11** showed a peak at 6.3—7.1 ppm due to the methine proton of the nitrone group, but the stereochemistry, *syn* or *anti*, could not be established. However, the hydrogen-bonded NH proton of pyrrole in **11f** was observed at 11.98 ppm in its NMR spectrum, suggesting that the stereochemistry of **11f** is *syn* as shown in **12**.

The subsequent ring-closure of the nitrone (**11**) to the 2-hydroxy-tetrahydro-*β*-carboline (**2**) was carried out in methylene chloride in the presence of TFA (3 eq). The reaction proceeded at room temperature for **11a, b, c**, while refluxing was required for **11d, e**. In the case of **11f**, the reaction in TFA at room temperature gave the best result (see Table II). The structures of these *β*-carbolines (**2**) were confirmed by their spectral data and elemental analysis.

The 2-hydroxy-tetrahydro-*β*-carbolines (**2**) were also obtained by the direct P–S reaction of **6** with aldehydes in the presence of TFA (3 eq) in methylene chloride. Yields were

TABLE III. The Pictet–Spengler Reaction of **6** with Aldehydes[a]

Aldehyde R–CHO (R=)	Reaction temperature	Reaction time	**2** Yield (%)
Ph	r.t.	1.5 h	90.9
$(CH_3)_2CHCH_2$–	r.t.	20 min	89.1
$CH_3(CH_2)_4$–	r.t.	30 min	80.0
$(CH_3)_2C=CH$–	r.t.	3 h	23.3
PhCH=CH–	Reflux	5.5 h	26.7

a) All reactions were carried out with 1.5 mol eq of aldehyde and 3 mol eq of TFA in CH_2Cl_2.

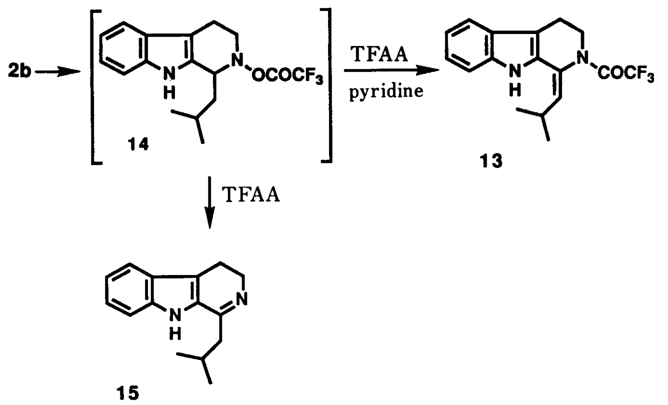

Chart 3

excellent (80—90%) for **2a**, **b**, **c**, but **2d** and **2e** were obtained in low yields. However, the yields of **2d**, **e** were improved by using a two step procedure (see Table III). It is interesting to note that the P–S reaction of tryptamine with senecialdehyde was successful only with tosyl chloride, but not with a proton acid.[12]

Acetylation of **2** (R=*p*-methoxyphenyl) with acetic anhydride-pyridine was reported[2] to give the 2-acetoxy-*β*-carboline, and the dehydration did not occur under the conditions used. However, reaction of **2b** with trifluoroacetic anhydride (TFAA)–pyridine gave 1-isobutylene-2-trifluoroacetyl-*β*-carboline (**13**), mp 186—188 °C, which may be formed by elimination of trifluoroacetic acid from **14** followed by trifluoroacetylation. On the other hand, reaction of **2b** with TFAA in boiling benzene gave 3,4-dihydro-*β*-carboline (**15**), which was probably formed from **14**.

We next prepared 6-bromo-5-methoxy-3-(2-nitroethyl)-indole (**23**) which is a potential intermediate for the synthesis of eudistomin C. Reduction of 3-bromo-4-methoxy-nitrobenzene (**16**)[13] with Sn–HCl–MeOH gave the aniline (**17**)[14] in excellent yield. The Japp–Klingemann reaction of **17** with ethyl methylacetoacetate gave **18** (79%), which was converted to the phenylhydrazone (**19**) on acid treatment. The hydrazone can be separated into two isomers, and a crystalline isomer, mp 83.5—84 °C, was assigned as the *Z*-isomer (**19a**) from the NMR spectrum.[15] A singlet at 2.14 ppm due to the methyl protons and a broad singlet at 11.97 ppm due to the NH proton were observed in **19a**, while a singlet at 2.05 ppm and a broad singlet at 7.75 ppm were observed in **19b**. Fischer indolization of **19** (a mixture of isomers) in boiling $BF_3 \cdot Et_2O$–$CHCl_3$ gave the 6-bromoindole (**20a**, 51.5%) and the 4-bromo isomer (**21**, 27.4%) along with recovered **19** (17%). The reaction with $BF_3 \cdot Et_2O$–AcOH,[16] and $TiCl_4$–CH_2Cl_2 gave poor results.

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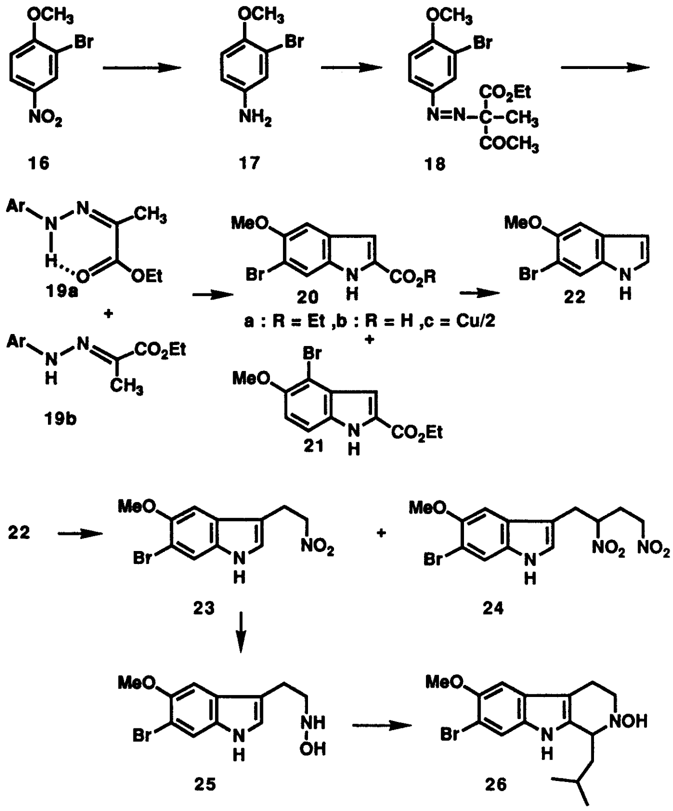

Chart 4

Hydrolysis of the ester group in **20** followed by decarboxylation[17] in quinoline in the presence of the copper salt (**20c**) gave the indole **22** in 65% yield.

Michael addition of **22** to nitroethylene in benzene gave the nitroethylindole (**23**) in 53% yield and the 1 : 2 adduct (**24**) in 31% yield. The nitroethylindole (**23**) was also obtained by the Vilsmeier formylation of **22** followed by condensation with nitromethane, and reduction with $NaBH_4$–MeOH. Aluminum amalgam reduction of **23** afforded the hydroxylamine (**25**), which was too unstable to be purified. Therefore, P–S reaction of crude **25** with isovaleraldehyde in TFA–CH_2Cl_2 was carried out to verify the formation of **25**. The 2-hydroxy-β-carboline (**26**), mp 192—194.5 °C, was obtained in 50% yield from **23**.

In conclusion, *N*-hydroxytryptamines (**6**, **25**) were readily prepared from 3-nitroethylindoles and their P–S reactions with aldehydes provided 2-hydoxy-tetrahydro-β-carbolines, as with tryptamines. We have recently reported the total synthesis of eudistomin L and debromoeudistomin L from **6** with D-cysteine.[18] Syntheses of other eudistomins form **25** and **21** are in progress.

Experimental

Melting points were measured on a Yamato MP-1 apparatus or a Yanagimoto micromelting point apparatus and are not corrected. The ultraviolet (UV) spectra were taken with Hitachi 323 and 340 spectrophotometers, and the IR spectra with Hitachi 260-10 and 295 spectrophotometers. The MS were recorded on Hitachi M-60 and 7M spectrometers, and the NMR spectra in $CDCl_3$ solution on JEOL JNM-FX-270 and GX-270 apparatus using tetramethylsilane as an internal standard. Kieselgel 60 (70—230 mesh, Merck) or Silica gel BW-820 MH (Fuji-Davison) was used for silica gel column chromatography. Aluminiumoxide 90 standardisiert (Aktivitättsstufe II-III, 70-230 mesh, Merck) was used for alumina column chromatography. Kieselgel GF_{254} type 60 (Merck) or DC-Fertigplatten SILG-50 UV_{254} was used for preparative thin layer chromatography (TLC).

Reduction of 3-Nitroethylindole (5) to *N*-Hydroxytryptamine (6) 1) By Zn–NH_4Cl[8]: Zn powder (6.54 g, 100 mmol) was added to a solution of 3-nitroethylindole[5] (**5**, 9.51 g, 50 mmol) in EtOH (100 ml), and NH_4Cl (3.08 g, 57.5 mmol) in H_2O (50 ml) at 40 °C during 10 min, and the mixture was stirred for 1 h at 40 °C. The EtOH was evaporated off *in vacuo* to leave a brown oil, which was solidified on addition of a small amount of CH_2Cl_2. Filtration of the mixture gave **6** (4.08 g, 46.3%). Recrystallization of **6** from benzene gave a colorless powder, mp 111—112 °C (reported mp[8] 113—115 °C). The CH_2Cl_2 filtrate obtained above was chromatographed on a silica gel column (50 g, AcOEt–benzene (1 : 2)) to give **5** (2.07 g, 21.7%) and **10** (1.82 g, 21.8%). Recrystallization of **10** from benzene gave colorless leaflets, mp 148—149 °C. **6**: UV λ_{max}^{EtOH} nm: 223, 275^{sh}, 283, 291. IR (KBr) cm^{-1}: 3400 (NH, OH). MS *m/z* (rel. intensity): 176 (15, M^+), 130 (100). ^1H-NMR δ: 3.04 (2H, t, J=6.6 Hz, $\underline{CH_2}CH_2NHOH$), 3.26 (2H, t, J=6.6 Hz, $\underline{CH_2}NHOH$), 2.40—4.20 (2H, br, $N\underline{H}O\underline{H}$, exchangeable), 7.05 (1H, d, J=2.3 Hz, indole C_2-H), 7.09—7.23 (2H, m, indole C_5, C_6-H), 7.35—7.38 (1H, m, indole C_4 or C_7-H), 7.62 (1H, d, J=7.9 Hz, indole C_4 or C_7-H), 8.01 (1H, br s, NH, exchangeable).

10: UV λ_{max}^{EtOH} nm (ε): 221.5 (74200), 274.5^{sh} (12100), 281.5 (12900), 290.5 (10600). IR (KBr) cm^{-1}: 3410 (NH), 1330 (N=NO). MS *m/z* (rel. intensity): 332 (4, M^+), 130 (100). ^1H-NMR δ 3.08 (2H, t, J=7.2 Hz, $ON=NCH_2\underline{CH_2}$), 3.42 (2H, t, J=7.3 Hz, $ONCH_2\underline{CH_2}$), 3.75 (2H, t, J=7.2 Hz, $ON=N\underline{CH_2}$), 4.46 (1H, t, J=7.3 Hz, $ON\underline{CH_2}$), 6.72 (1H, d, J=2.5 Hz, arom-H), 6.86 (1H, d, J=2.1 Hz, arom-H), 7.08—7.24 (4H, m, arom-H), 7.32 (2H, d, J=7.9 Hz, arom-H), 7.60 (2H, d, J=7.9 Hz, arom-H), 7.80 (2H, br s, NH × 2, exchangeable). *Anal.* Calcd for $C_{20}H_{20}N_4O$: C, 72.27; H, 6.06; N, 16.86. Found: C, 72.29; H, 6.09; N, 16.75.

2) Reduction with Aluminum Amalgam: Al–Hg (prepared from Al (5.0 g) and 0.5% $HgCl_2$), was added to a solution of **5** (1.90 g, 10 mmol) in THF (100 ml) and H_2O (20 ml) at 0 °C under stirring. After 10 min, the mixture was filtered through Celite 545, and washed with EtOH. The filtrate and washings were evaporated to leave a residue, which was dissolved in AcOEt. The AcOEt solution was washed with saturated NaCl solution and dried. Evaporation of the solvent left a colorless solid (1.95 g), which gave *N*-hydroxytryptamine (**6**, 0.96 g, 54.5%) on trituration with CH_2Cl_2. Further **6** (0.16 g, total 1.12 g, 63.6%) was obtained by concentration of the CH_2Cl_2 solution. This sample was identical with **6** obtained above (TLC, UV).

Reduction of 3-Nitroethyleneindole (8) to 5 $NaBH_4$ (1.54 g, 43.1 mmol) was added gradually to a solution of **8**[6] (2.7 g, 14.4 mmol) in MeOH (200 ml) at room temperature. The mixture was stirred for 20 min at room temperature until **8** was no longer detected on TLC of the mixture. The solvent was evaporated off to leave a residue, which was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O and saturated NaCl solution, and then dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (80 g, hexane–AcOEt (3 : 1—1 : 1)) to give **5** (2.02 g, 74%). The sample was identical with the sample prepared by Michael reaction of indole with nitroethylene.[5]

Stability of 6 A solution of **6** (3 mg, 0.017 mmol) in CH_2Cl_2 (10 ml) was stirred for 4 d under an oxygen atmosphere at room temperature. The TLC of the mixture showed disappearance of **6** and appearance of **10**. Similar TLC behavior was observed in the reactions under air and in the presence of silica gel under air. Residues obtained from three reactions were combined and separated by preparative TLC (SiO_2, AcOEt–hexane (1 : 1)) to give **10** (7 mg), which was identical with the sample of **10** obtained above.

Reaction of 6 with Aldehydes: Formation of Nitrones (11) 1) Without Acid Catalyst: A solution of **6** (200 mg, 1.135 mmol) and benzaldehyde (181 mg, 1.70 mmol) in benzene (12 ml) was refluxed for 1 h. The solvent was evaporated off to leave a residue (326 mg), which was chromatographed on a silica gel column (10 g, CH_2Cl_2) to give benzaldehyde (24 mg) and the nitrone (**11a**, 270 mg, 90%). Recrystallization from benzene gave colorless scales, mp 130.5—131.5 °C. UV λ_{max}^{EtOH} nm (ε): 221.5 (42300), 284 (20400), 295 (20900), 303 (13700). IR (KBr) cm^{-1}: 3200 (NH), 1140 (NO). MS *m/z* (rel. intensity): 264 (1, M^+), 143 (100). ^1H-NMR δ: 3.47 (2H, t, J=6.7 Hz, $\underline{CH_2}CH_2NO$), 4.18 (2H, t, J=6.7 Hz, CH_2NO), 7.01 (1H, d, J=2.4 Hz, indole C_2-H), 7.07 (1H, s, ON=CH), 7.10—7.23 (2H, m, arom-H), 7.33—7.40 (4H, m, arom-H), 7.64 (1H, d, J=7.9 Hz, arom-H), 8.11—8.16 (3H, m, arom-H, NH, 1H is exchangeable). *Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.31; H, 6.12; N, 10.54.

Similar reactions with isovaleraldehyde and hexylaldehyde in CH_2Cl_2 gave **11b** and **11c**. (Table I). **11b** (colorless caramel), UV λ_{max}^{EtOH} nm: 222, 274, 282, 290. MS *m/z* (rel. intensity): 244 (1, M^+), 143 (100). ^1H-NMR δ: 0.76 (6H, d, J=6.7 Hz, CH_3 × 2), 1.59—1.74 (1H, m, $C\underline{H}(CH_3)_2$), 2.28

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(2H, d, J=7.0 Hz, ON=CHCH_2), 3.38 (2H, t, J=6.7 Hz, CH_2CH_2NO), 4.03 (2H, t, J=6.7 Hz, CH_2NO), 6.33 (1H, t, J=5.8 Hz, ON=CH), 7.05 (1H, d, J=2.1 Hz, indole C_2-H), 7.10—7.24 (2H, m, indole C_5, C_6-H), 7.37 (1H, d, J=7.9 Hz, indole C_4 or C_7-H), 7.62 (1H, d, J=7.6 Hz, indole C_4 or C_7-H), 8.15 (1H, br s, NH, exchangeable).

11c (colorless caramel), UV λ_{max}^{EtOH} nm: 222, 275, 282, 291. MS m/z (rel. intensity): 258 (1, M^+), 143 (100). ^{1}H-NMR δ: 0.83 (3H, t, J=6.7 Hz, CH_3), 1.09—1.36 (6H, m, $(CH_2)_3CH_3$), 2.37 (2H, td, J=6.1, 7.3 Hz, ON=$CHCH_2$), 3.38 (2H, t, J=6.4 Hz, CH_2CH_2NO), 4.01 (2H, t, J=6.7 Hz, CH_2NO), 6.32 (1H, t, J=5.8 Hz, ON=CH), 7.04 (1H, d, J=2.5 Hz, indole C_2-H), 7.08—7.23 (2H, m, indole C_5, C_6-H), 7.38 (1H, d, J=7.9 Hz, indole C_4 or C_7-H), 7.60 (1H, d, J=7.6 Hz, indole C_4 or C_7-H), 8.47 (1H, br s, NH, exchangeable).

2) With TFA: TFA (582 mg, 5.10 mmol) was added to a solution of **6** (300 mg, 1.70 mmol) and senecialdehyde (215 mg, 2.55 mmol) in CH_2Cl_2 (50 ml) at room temperature. The mixture was stirred for 20 min, and then diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ and NaCl solutions, and dried. Evaporation of the solvent gave a residue (552 mg), which was chromatographed on a silica gel column (30 g, AcOEt–MeOH (15 : 1)) to give **11d** (326 mg, 79%) as colorless caramel. Similar reactions with cinnamaldehyde and pyrrolealdehyde gave **11e**, **f** (Table I). **11d** (amorphous solid), UV λ_{max}^{EtOH} nm: 221, 286. MS m/z (rel. intensity): 242 (3, M^+), 143 (100). ^{1}H-NMR δ: 1.59 (3H, s, CH_3), 1.85 (3H, s, CH_3), 3.39 (2H, t, J=6.9 Hz, CH_2CH_2NO), 4.04 (2H, t, J=6.9 Hz, CH_2NO), 6.54 (1H, d, J=9.9 Hz, CH), 6.99 (1H, d, J=2.3 Hz, indole C_2-H), 7.09—7.22 (2H, m, indole C_5, C_6-H), 7.38 (1H, d, J=7.9 Hz, indole C_7-H), 7.60 (1H, d, J=7.9 Hz, indole C_4-H), 8.63 (1H, br s, NH, exchangeable). HR-MS Calcd for $C_{15}H_{18}N_2O$: 242.1420. Found: 242.1437.

11e (yellow amorphous solid): UV λ_{max}^{EtOH} nm: 222, 238^{sh}, 241^{sh}, 285, 291, 333. IR (KBr) cm^{-1}: 3400 (NH), 1170 (NO). MS m/z (rel. intensity): 290 (4, M^+), 130 (100). ^{1}H-NMR δ: 3.41 (2H, t, J=6.6 Hz, CH_2CH_2NO), 4.07 (2H, t, J=6.6 Hz, CH_2NO), 6.76 (1H, d, J=16.2 Hz, CHPh), 7.03 (1H, d, J=2.3 Hz, indole C_2-H), 7.11—7.44 (9H, m, indole C_5, C_6, C_7-H, CH=CHC_6H_5), 7.62 (1H, d, J=7.6 Hz, indole C_4-H), 8.35 (1H, br s, NH, exchangeable). HR-MS Calcd for $C_{19}H_{18}N_2O$: 290.1420. Found 290.1432.

11f (slightly purple needles), mp 194.0—195.0 °C (from benzene). UV λ_{max}^{EtOH} nm (ε): 221 (38200), 247.5^{sh} (8300), 285^{sh} (10800), 292^{sh} (13300), 316 (26000), 325^{sh} (23700). IR (KBr) cm^{-1}: 3350. MS m/z (rel. intensity): 253 (2, M^+), 143 (100). ^{1}H-NMR δ: 3.43 (2H, t, J=6.7 Hz, CH_2CH_2NO), 4.09 (2H, t, J=6.7 Hz, CH_2NO), 6.26—6.37 (2H, m, pyrole CH × 2), 6.95 (1H, d, J=2.7 Hz, ON=CH), 6.97 (1H, d, J=2.4 Hz, indole C_2-H), 7.06—7.24 (3H, m, indole C_5, C_6 pyrole NCH), 7.36 (1H, d, J=7.9 Hz, indole C_7-H), 7.62 (1H, d, J=7.9 Hz, indole C_4-H), 8.09 (1H, br s, NH, exchangeable), 11.98 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.87; H, 6.07; N, 16.47.

Cyclization of 11 to 1-Substituted-2-hydroxy-1,2,3,4-tetrahydro-β-carbolines (2) General Procedure Exemplified with **11e**: TFA (306 mg, 2.69 mmol) was added to a solution of **11e** (260 mg, 0.90 mmol) in CH_2Cl_2 (20 ml) at room temperature, and the mixtue was stirred for 6.5 h at room temperature. The mixture was diluted with CH_2Cl_2 and the CH_2Cl_2 solution was washed with saturated $NaHCO_3$ and NaCl solutions, and dried. Evaporation of the solvent gave a residue (294 mg), which was purified by preparative TLC to give **2e** (168 mg, 64.5%). Recrystallization from benzene gave a yellowish powder, mp 182.5—184 °C (Table II). **2e**: UV λ_{max}^{EtOH} nm (ε): 207 (38500), 210.5 (38500), 219.5 (38100), 225 (38300), 253 (22500), 273^{sh} (13100), 283 (11900), 292 (9800). IR (KBr) cm^{-1}: 3450 (OH). MS m/z (rel. intensity): 290 (4, M^+), 245 (100). ^{1}H-NMR δ: 2.81—3.05 (2H, m, C_4-H), 3.15—3.24 (1H, m, C_3-H), 3.57—3.64 (1H, m, C_3-H), 4.58 (1H, d, J=6.7 Hz, C_1-H), 6.36 (1H, dd, J=8.7, 15.7 Hz, CH=CHPh), 6.53 (1H, br s, NOH), 6.81 (1H, d, J=15.9 Hz, CHPh) 7.07—7.18 (2H, m, C_6, C_7-H), 7.25—7.49 (7H, m, C_5, C_8-H, C_6H_5), 7.67 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{19}H_{18}N_2O$: C, 78.59: H, 6.25; N, 9.65. Found: C, 78.59; H, 6.31; N, 9.62.

2a (colorless prism), mp 184.0—185.0 °C (from acetone–hexane). UV λ_{max}^{EtOH} nm (ε): 225.5 (40800), 275 (8200), 282.5 (8500), 291 (7100). IR (KBr) cm^{-1}: 3390 (OH). MS m/z (rel. intensity): 264 (28, M^+), 218 (100). ^{1}H-NMR δ: 2.91—2.93 (1H, m, C_4-H), 2.99—3.22 (2H, m, C_3, C_4-H), 3.40—3.46 (1H, m, C_3-H), 4.88 (1H, s, C_1-H), 7.07—7.20 (3H, m, C_6, C_7 Ph-H), 7.25—7.26 (2H, m, C_8-H, NH, one proton is exchangeable), 7.34—7.40 (4H, m, Ph-H × 4), 7.48—7.52 (1H, m, C_5-H). *Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.21; H, 6.14; N, 10.57.

2b (colorless cotton-like needles), mp 159.5—160.5 °C (from benzene). UV λ_{max}^{EtOH} nm (ε): 226.5 (35700), 276 (7300), 282 (7500), 290 (6500). IR (KBr) cm^{-1}: 3370 (OH). MS m/z (rel. intensity): 244 (44, M^+), 187 (100). ^{1}H-NMR δ: 1.00 (3H, d, J=6.5 Hz, CH_3), 1.06 (3H, d, J=6.5 Hz, CH_3), 1.55—2.05 (3H, m, CH_2CH), 2.92 (2H, br s, C_4-H), 3.25—3.44 (1H, m, C_3-H), 3.45 (1H, br s, C_3-H), 4.14 (1H, br s, C_1-H), 4.90—5.20 (1H, br, NOH, exchangeable), 7.06—7.18 (2H, m, C_6, C_7-H), 7.32 (1H, d, J=7.2 Hz, C_5 or C_8-H), 7.49 (1H, d, J=6.9 Hz, C_5 or C_8-H), 7.71 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.78; H, 8.24; N, 11.39.

2c (colorless caramel): UV λ_{max}^{EtOH} nm: 227, 275^{sh}, 283, 290. MS m/z (rel. intensity): 258 (26, M^+), 171 (100). ^{1}H-NMR δ: 0.90 (3H, t, J=6.7 Hz, CH_3), 1.23—1.56 (6H, m, CH_2 × 3), 1.84—1.98 (2H, m, CH_2), 2.90 (2H, br s, C_4-H), 3.23 (1H, td, J=6.7, 11.9 Hz, C_3-H), 3.48—3.54 (1H, m, C_3-H), 4.04 (1H, br s, C_1-H), 4.65 (1H, br, NOH, exchangeable), 7.06—7.17 (2H, m, C_6, C_7-H), 7.30—7.36 (1H, m, C_5 or C_8-H), 7.48 (1H, d, J=7.0 Hz, C_5 or C_8-H), 7.71 (1H, br s, NH, exchangeable).

2d (colorless powder), mp 155.5—156.5 °C (from benzene). UV λ_{max}^{EtOH} nm (ε): 226.5 (38400), 275 (7300), 281.5 (7500), 290.5 (6000). IR (KBr) cm^{-1}: 3340 (OH). MS m/z (rel. intensity): 242 (10, M^+), 182 (100). ^{1}H-NMR δ: 1.90 (3H, d, J=2.1 Hz, CH_3), 1.91 (3H, d, J=1.5 Hz, CH_3), 2.82—2.87 (1H, m, C_4-H), 2.90—3.05 (1H, m, C_4-H), 3.13—3.23 (1H, m, C_3-H), 4.68 (1H, m, C_1-H), 5.35 (1H, d, J=8.9 Hz, CH), 6.77 (1H, br s, NOH, exchangeable), 7.05—7.16 (2H, m, C_6, C_7-H), 7.29 (1H, d, J=7.0 Hz, C_8-H), 7.46 (1H, d, J=7.0 Hz, C_5-H), 7.60 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found C, 74.40; H, 7.48; N, 11.57.

2f (slightly orange powder), mp 194.0—195.0 °C (from benzene). UV λ_{max}^{EtOH} nm (ε): 226.5 (40800), 275^{sh} (8000), 281.5 (8400), 290.5 (7100). IR (KBr) cm^{-1}: 3320 (OH). ^{1}H-NMR δ: 2.87—2.93 (1H, m, C_4-H), 3.00—3.08 (1H, m, C_4-H), 3.09—3.25 (1H, m, C_3-H), 3.52—3.60 (1H, m, C_3-H), 5.00 (1H, br s, C_1-H), 6.18—6.21 (1H, m, pyrole-CH), 6.29 (1H, br s, pyrole-CH), 6.72—6.74 (1H, m, pyrole-CH), 7.07—7.18 (2H, m, C_6, C_7-H), 7.24 (1H, d, J=7.0 Hz, C_8-H), 7.50 (1H, d, J=6.7 Hz, C_5-H), 7.56 (1H, br s, NH, exchangeable), 8.54 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.35; H, 6.02; N, 16.55.

Pictet–Spengler Reaction of 6 with Aldehydes General procedure exemplified by the reaction with isovaleraldehyde. TFA (0.38 ml, 5.1 mmol) was added to a solution of **6** (300 mg, 1.7 mmol) and isovaleraldehyde (220 mg, 2.55 mmol) in CH_2Cl_2 (20 ml) at room temperature under cooling. The mixture was stirred for 20 min at room temperature and then diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$ and NaCl solutions, and dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (10 g, AcOEt–hexane (1 : 1)) to give the β-carboline (**2b**, 370 mg, 89%). This was identical with the sample obtained above (UV, TLC). See Table III for other examples.

Reaction of 2b 1) Reaction with TFAA–Pyridine: TFAA (187 mg, 0.89 mmol) was added to a solution of **2b** (218 mg, 0.89 mmol) in pyridine (20 ml) at room temperature. The mixture was stirred for 2 h at room temperature, and further TFAA (1 ml, excess) was added. The reaction mixture was diluted with AcOEt, washed with 10% HCl, H_2O, and saturated NaCl solution, and then dried. Evaporation of the solvent gave a residue (249 mg), which was chromatographed on a silica gel column (10 g, AcOEt–hexane (1 : 3)) to give **13** (234 mg, 82%). Recrystallization from aqueous MeOH gave colorless prisms, mp 186—188 °C. UV λ_{max}^{EtOH} nm (ε): 217 (24800), 228^{sh} (24100), 303.5 (22200), 311 (22000). IR (KBr) cm^{-1}: 3330 (NH). MS m/z (rel. intensity): 322 (55, M^+), 307 (100). ^{1}H-NMR δ: 1.09 (6H, d, J=6.1 Hz, CH_3 × 2), 2.34—2.48 (1H, m, $CH(CH_3)_2$), 2.71—2.96 (2H, m, $CH_2CH_2NCOCF_3$), 3.12—5.04 (2H, m, CH_2NCOCF_3), 5.55 (1H, d, J=9.8 Hz, C=CH), 7.07—7.23 (2H, m, arom-H), 7.27 (1H, d, J=6.1 Hz, arom-H), 7.42 (1H, d, J=7.9 Hz, arom-H), 7.92 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{17}H_{17}F_3N_2O$: C, 63.35; H, 5.32; N, 8.69. Found: C, 63.25; H, 5.26; N, 8.68.

2) Reaction with TFAA–Benzene: TFAA (55 mg, 0.26 mmol) was added to a solution of **2b** (64 mg, 0.26 mmol) in benzene (10 ml), and the mixture was stirred for 2 h at room temperature and for 10 min under reflux. The mixture was diluted with AcOEt and washed with saturated $NaHCO_3$ and NaCl solution, and then dried. Evaporation of the solvent gave a residue (44 mg), which was purified by preparative TLC (silica gel, AcOEt–hexane (2 : 1)) to give **15** (15 mg, 26%) as pale yellow caramel. UV λ_{max}^{EtOH} nm: 237, 242^{sh}, 318; $\lambda_{max}^{EtOH-HCl}$ nm: 247, 355. MS m/z (rel. intensity): 226 (29, M^+), 184 (100). ^{1}H-NMR δ: 1.00 (6H, d, J=6.7 Hz, CH_3 × 2), 2.11—2.24 (1H, m, CH), 2.54 (2H, d, J=7.3 Hz, CH_2CH), 2.86 (2H, t, J=8.2 Hz, CH_2CH_2N), 3.89 (2H, t, J=8.2 Hz, CH_2N), 7.12—7.30 (2H, m, arom-H), 7.40 (1H, d, J=8.2 Hz, arom-H), 7.60 (1H, d, J=7.9 Hz, arom-H).

Ethyl 4-Bromo-5-methoxyindole-2-carboxylate (20a) and Ethyl 6-Bromo-5-methoxyindole-2-carboxylate (21) 1) Japp–Klingemann Reac-

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tion of **17**: $NaNO_2$ (0.30 g, 0.56 mmol) was added to a solution of **17**[14] (1.02 g, 0.5 mmol) in concentrated HCl (1.26 ml, 1.5 mmol), H_2O (2 ml), and ice (10 g) at −5 °C during 1 h. AcONa (0.55 g) was added to adjust the pH to 3 (solution A) and the mixture was kept at −5 °C. KOH (0.37 g) in H_2O (0.5 ml) was added to a solution of ethyl α-methylacetoacetate (0.77 g, 0.56 mmol) in EtOH (5 ml) and kept at −5 °C (solution B). Solution A was added to solution B gradually to keep the temperature under 0 °C. The reaction mixture was stirred for 2 h and extracted with AcOEt. The extract was washed with saturated $NaHCO_3$, H_2O, and NaCl solution, and dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (50 g, AcOEt–hexane (1 : 2)) to give **18** (1.43 g, 79.4%) as reddish-yellow caramel. UV λ_{max}^{EtOH} nm: 241, 317. ^{1}H-NMR (60 MHz $CDCl_3$) δ: 1.25 (3H, t, J=8 Hz, $CH_2\underline{CH_3}$), 1.60 (3H, s, CH_3), 2.30 (3H, s, $COCH_3$), 3.92 (3H, s, OCH_3), 4.23 (2H, q, J=8 Hz, CH_2), 6.93 (1H, d, J=9 Hz, arom-H), 7.72 (1H, dd, J=3, 9 Hz, arom-H), 7.94 (1H, d, J=3 Hz, arom-H).

2) Hydrazones (**19**): A solution of **18** (376 mg) in 3 N HCl–EtOH (10 ml) was refluxed for 20 min. The mixture was extracted with CH_2Cl_2 and the extract was washed with saturated $NaHCO_3$ and NaCl solutions, and then dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (30 g, AcOEt–hexane (1 : 4)) to give **19a** (116 mg, 34.9%) as a solid and **19b** (139 mg, 41.9%) as a pale red caramel. Recrystallization of **19a** from aqueous MeOH gave yellow fine needles, mp 83.5—84.0 °C. UV λ_{max}^{EtOH} nm (ε): 204 (19800), 237 (10000), 317 (9900), 355 (17200). IR (KBr) cm^{-1}: 3240 (NH), 1670 (C=O). MS m/z (rel. intensity): 316, 314 (87, 88, M$^+$), 201 (100), 199 (96). ^{1}H-NMR δ: 1.35 (3H, t, J=7.3 Hz, $CH_2\underline{CH_3}$), 2.14 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 4.27 (2H, q, J=7.3 Hz, $\underline{CH_2}$), 6.84 (1H, d, J=8.6 Hz, arom-H), 7.00 (1H, dd, J=2.8, 8.9 Hz, arom-H), 7.47 (1H, d, J=2.4 Hz, arom-H), 11.97 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{12}H_{15}BrN_2O_3$: C, 45.73; H, 4.80; N, 8.89. Found: C, 45.65; H, 4.78; N, 8.83.

19b: UV λ_{max}^{EtOH} nm: 220^{sh}, 309, 336. IR (KBr) cm^{-1}: 3300 (NH), 1695 (C=O). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.35 (3H, t, J=8 Hz, $CH_2\underline{CH_3}$), 2.05 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.28 (2H, q, J=8 Hz, $\underline{CH_2}$), 6.76 (1H, d, J=9 Hz, atom-H), 7.11 (1H, dd, J=3, 9 Hz, atom-H), 7.41 (1H, d, J=3 Hz, atom-H), 7.75 (1H, br s, NH, exchangeable).

3) Fischer Indolization: Formation of **20a** and **21**. $BF_3 \cdot Et_2O$ (161 mg, 1.14 mmol) was added to a solution of **19** (358 mg, 1.14 mmol, a mixture of **19a** and **b**) in $CHCl_3$ (10 ml) and the mixture was refluxed for 20 h. The mixture was diluted with CH_2Cl_2 and washed with H_2O, saturated $NaHCO_3$ solution, and H_2O, and then dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (30 g, AcOEt–hexane (1 : 3)) to give **19a** (36 mg, 10%), **20a** (158 mg, 51.5%), **21** (84 mg, 27%), and **19b** (26 mg, 7%) in that order of elution. Recrystallization of **20a** from benzene gave colorless needles, mp 164—165 °C. Recrystallization of **21** from AcOEt–hexane gave pale yellow needles, mp 179—180 °C. **20a**: UV λ_{max}^{EtOH} nm (ε): 210.5 (31900), 293.5 (18500), 302 (22000). IR (KBr) cm^{-1}: 3310 (NH), 1700 (C=O). MS m/z (rel. intensity): 299, 297 (75, 76, M$^+$), 253 (98), 251 (100). ^{1}H-NMR δ: 1.41 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.93 (3H, s, OCH_3), 4.41 (2H, q, J=7.0 Hz, CH_2), 7.10 (1H, s, C_4-H), 7.12 (1H, d, J=2.1 Hz, C_3-H), 7.64 (1H, s, C_7-H), 8.82 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.35; H, 4.07; N, 4.83.

21: UV λ_{max}^{EtOH} nm (ε): 225.5 (25500), 290.5^{sh} (13600), 300.5 (15200). IR (KBr) cm^{-1}: 3330 (NH), 1705 (C=O). MS m/z (rel. intensity): 299, 297 (77, 77, M$^+$), 253 (97), 251 (100). ^{1}H-NMR δ: 1.43 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.94 (3H, s, OCH_3), 4.42 (2H, q, J=7.0 Hz, CH_2), 7.07 (1H, d, J=8.9 Hz, C_6-H), 7.23 (1H, d, J=2.1 Hz, C_3-H), 7.33 (1H, d, J=8.9 Hz, C_7-H), 8.94 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.31; H, 4.05; N, 4.80.

A solution of **19** (1.345 g, 3.37 mmol) in 3 N HCl EtOH (5 ml) was refluxed for 4 h. Work-up as above gave **19a** (314 mg, 26%), **20a** (87 mg, 8%), **21** (42 mg, 4%), and **19b** (357 mg, 30%).

6-Bromo-5-methoxyindole (22) i) The 2-Indolecarboxylic Acid (**20b**): A suspension of **20a** (2.98 g, 10 mmol) in KOH (1.168 g, 30 mmol) solution in H_2O (100 ml) was refluxed for 3 h. The mixture was extracted with AcOEt and the alkaline aqueous solution was acidified with 5% HCl to pH 1 to give **20b** (2.68 g, 99%), mp 282—285 °C (dec.). UV λ_{max}^{EtOH} nm: 295^{sh}, 301, 323^{sh}, 340^{sh}. IR (KBr) cm^{-1}: 3400 (NH), 3200—2800 (OH), 1670 (C=O).

ii) Cu Salt of the Acid (**20c**): A suspension of **20a** (500 mg, 1.68 mmol) in Na_2CO_3 (98.8 mg) solution in H_2O (30 ml) was refluxed for 8 h, then allowed to cool. After cooling $CuSO_4 \cdot 5H_2O$ (233 mg, 0.93 mmol) in H_2O (30 ml) was added to the mixture. The precipitate was collected by filtration and washed with H_2O and EtOH to give **20c** (303 mg, 54%).

iii) Decarboxylation: A suspension of **20b** (2.00 g, 7.41 mmol) and **20c** (0.50 g) in quinoline (50 ml) was heated at 220—230 °C (bath temperature) for 1 h under an argon atmosphere. The mixture was poured into 10% HCl solution, and extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ and NaCl solutions, and dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (150 g, AcOEt–hexane (1 : 3)) to give **22** (1.34 g, 65%). Recrystallization from benzene–hexane gave colorless needles, mp 127—127.5 °C. UV λ_{max}^{EtOH} nm (ε): 220 (28000), 281 (8000), 299^{sh} (7000), 310.5^{sh} (4400). IR (KBr) cm^{-1}: 3400 (NH). MS m/z (rel. intensity): 227, 225, (100, 99, M$^+$). ^{1}H-NMR δ: 3.92 (3H, s, OCH_3), 6.46—6.48 (1H, m, C_3-H), 7.14 (1H, s, C_5-H), 7.17 (1H, dd, J=2.6, 3.2 Hz, C_2-H), 7.59 (1H, s, C_8-H), 8.04 (1H, br s, NH, exchangeable). ^{13}C-NMR δ: 56.8 (q, CH_3), 102.4 (d, C_{3a}), 102.8 (d, C_4), 107.3 (s, C_6), 115.4 (d, C_{7a}), 125.4 (d, C_2), 127.6 (s, C_{3b}), 131.2 (s, C_{7b}), 150.1 (s, C_5). *Anal.* Calcd for C_9H_8BrNO: C, 47.82; H, 3.57; N, 6.20. Found: C, 47.68; H, 3.62; N, 6.05.

6-Bromo-5-methoxy-3-(2-nitroethyl)-indole (23) Nitroethylene[19] (2.90 g, 39.7 mmol) was added to a solution of **22** (4.50 g, 19.9 mmol) in benzene (50 ml) and the mixture was stirred for 14 d at room temperature under an argon atmosphere. The solvent and an excess of nitroethylene were evaporated off *in vacuo* to leave a residue, which was chromatographed on a silica gel column (280 g, CH_2Cl_2–hexane (2 : 1)) to give **23** (3.17 g, 53.3%) and **24** (2.23 g, 31.3%). Recrystallization of **23** from AcOEt—hexane gave yellow prisms, mp 120—121.5 °C. UV λ_{max}^{EtOH} nm (ε): 221.5 (30300), 288 (8000), 301 (7700), 311 (5100). IR (KBr) cm^{-1}: 3430 (NH), 1540 (NO_2), 1380 (NO_2). MS m/z (rel. intensity): 300, 298, (84, 86, M$^+$), 253 (100), 251 (96). ^{1}H-NMR δ: 3.45 (2H, t, J=7.0 Hz, $\underline{CH_2}CH_2NO_2$), 3.95 (3H, s, OCH_3), 4.65 (2H, t, J=7.0 Hz, CH_2NO_2), 7.00 (1H, s, C_4-H), 7.04 (1H, d, J=2.8 Hz, C_2-H), 7.57 (1H, s, C_7-H), 7.98 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{11}H_{11}BrN_2O_3$: C, 44.17; H, 3.71; N, 9.37. Found: C, 44.25; H, 3.59; N, 9.46.

Recrystallization of **24** from AcOEt–hexane gave a pale yellow powder, mp 130—131 °C. UV λ_{max}^{EtOH} nm (ε): 220 (32400), 288 (8000), 301 (7800), 311 (5300). IR (KBr) cm^{-1}: 3460 (NH), 1550 (NO_2), 1390 (NO_2). MS m/z (rel. intensity): 373, 371 (49, 50, M$^+$), 240 (94), 238 (100). ^{1}H-NMR δ: 2.58—2.67 (2H, m, $\underline{CH_2}CH_2NO_2$), 3.30 (1H, dd, J=6.6, 15.0 Hz, $\underline{CH_2}CH(NO_2)CH_2$), 3.49 (1H, dd, J=7.3, 15 Hz, $\underline{CH_2}CH(NO_2)CH_2$), 3.96 (3H, s, OCH_3), 4.39—4.55 (2H, m, CH_2NO_2), 4.87—4.97 (1H, m, $CHNO_2$), 6.98 (1H, s, C_4-H), 7.03 (1H, d, J=2.4 Hz, C_2-H), 7.59 (1H, s, C_7-H), 8.04 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{13}H_{14}BrN_3O_5$: C, 41.95; H, 3.79; N, 11.29. Found: C, 41.99; H, 3.81; N, 11.28.

6-Bromo-*N*-hydroxy-5-methoxytryptamine (25) Al–Hg, prepared from Al (0.5 g), was added to a solution of **23** (100 mg, 0.33 mmol) in THF (10 ml) and H_2O (2 ml) at 0 °C. The mixture was stirred for 20 min at 0 °C and filtered through Celite-545. The solid material was washed with EtOH. The filtrate and washing were conbined and evaporated *in vacuo* to leave a residue, which was separated by preparative TLC (SiO_2, AcOEt) to give crude **25** (63 mg) as a yellow caramel. Further purification was not successful due to decomposition during preparative TLC. UV λ_{max}^{EtOH} nm: 226, 293, 301, 312^{sh}. MS m/z (rel. intensity): 286, 284 (6, 22, M$^+$), 240 (100), 238 (98). ^{1}H-NMR δ: 2.98 (2H, t, J=6.7 Hz, $\underline{CH_2}CH_2NHOH$), 3.23 (2H, t, J=6.4 Hz, $\underline{CH_2}NHOH$), 3.91 (3H, s, OCH_3), 3.30—4.55 (*ca.* 2H, br, NHOH), 7.00 (1H, d, J=2.5 Hz, C_2-H), 7.07 (1H, s, C_7-H), 7.55 (1H, s, C_4-H), 8.09 (1H, br s, NH, exchangeable).

7-Bromo-2-hydroxy-1-isobutyl-6-methoxy-1,2,3,4-tetrahydro-β-carboline (26) Crude **25** prepared from **23** (500 mg, 1.67 mmol) as above was dissolved in CH_2Cl_2 (20 ml), and isovaleraldehyde (216.0 mg, 2.50 mmol) was added to the solution. A new spot corresponding to the nitrone was observed on TLC of the mixture. TFA (0.57 ml, 5.0 mmol) was added to the mixture and the whole was stirred for 20 min. The mixture was diluted with CH_2Cl_2, and washed with saturated $NaHCO_3$, H_2O, and NaCl solutions, and then dried. Evaporation of the solvent gave a residue, which was chromatographed on a silica gel column (20 g, AcOEt–hexane (1 : 1)) to give **26** (294 mg, 50% from **23**). Recrystallization from benzene gave a colorless powder, mp 192—194.5 °C. UV λ_{max}^{EtOH} nm (ε): 230.5 (29900), 297.5^{sh} (10600), 301.5 (11000), 311^{sh} (8100). IR (KBr) cm^{-1}: 3360 (OH). MS m/z (rel. intensity): 354, 352 (28, 34, M$^+$), 297 (90), 295 (100). ^{1}H-NMR δ: 0.99 (3H, d, J=6.4 Hz, CH_3), 1.05 (3H, d, J=6.4 Hz, CH_3), 1.59—2.05 (3H, m, CH_2CH), 2.80—2.99 (2H, m, C_4-H), 3.28—3.66 (2H, m, C_3-H), 3.93 (3H, s, OCH_3), 4.06—4.19 (1H, m, C_1-H), 5.40—5.70 (1H, br, OH), 6.95 (1H, s, arom-H), 7.50 (1H, s, arom-H), 7.64 (1H, br s, NH, exchangeable). *Anal.* Calcd for $C_{16}H_{21}BrN_2O_2$: C, 54.40; H, 5.99; N, 7.93. Found: C, 54.33; H, 5.99; N, 8.16.

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