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Stereoselective Synthesis of 1,3,4-Substituted Tetrahydro-β-Carbolines from Indoles Based on Selective Transformations

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Abstract: 1, 3, 4-Substituted tetrahydro β-carbolines **4** have been prepared from indoles **6** by two selective transformations: first, nucleophilic aziridine ring opening with a lower order indolyl magnesium cuprate obtaining the α,β-substituted tryptamines **5** and secondly, a "Pictet-Spengler-like" reaction between azalactones **12** and tryptamines **5**. Under the acidic reaction conditions used, the thermodynamically favoured tetrahydro β-carbolines **4** are obtained due to the conformational restrictions imposed by the tryptamine substituents. © 1997 Elsevier Science Ltd.

The 5-HT_2 family of receptors is comprised of three sub-types, namely 5-HT_{2A}, 5-HT_{2B}, and $5HT_{2C}$.[1] Both rat[2] and human[3] 5-HT_{2B} receptors have been recently cloned, allowing the study of the binding affinity of receptor agonists and antagonists. The search for selective 5-HT_{2B} receptors antagonists have led to indole derived compounds such as **1**[4] and **2**[5] (Figure 1). Recently it has been shown that 1-arylmethyltetrahydro-β-carbolines (**3**) display a potent and selective $5HT_{2B}$ receptor antagonist activity,[6] being able to discriminate among the 5-HT_2 family of serotonin receptors, based upon radioligand binding and functional assays. The potential therapeutic interest of these agents in the treatment of anxiety,[7] migraine[8] and other disorders, has led us to undertake the synthesis of 1,3,4-substituted tetrahydro-β-carbolines (**4**). The introduction of substituents at C-3 and C-4 will produce a conformational restriction on the C-1 substituent which could provide a useful insight into the ligand recognition requirements for the receptor subtypes.

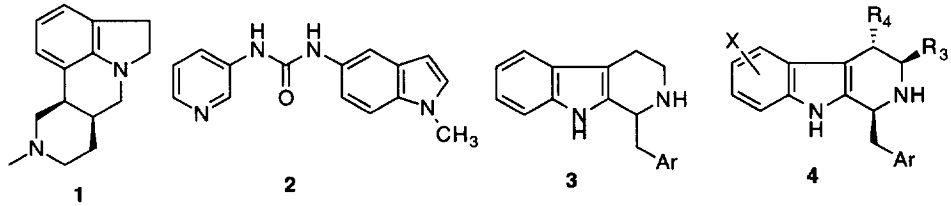
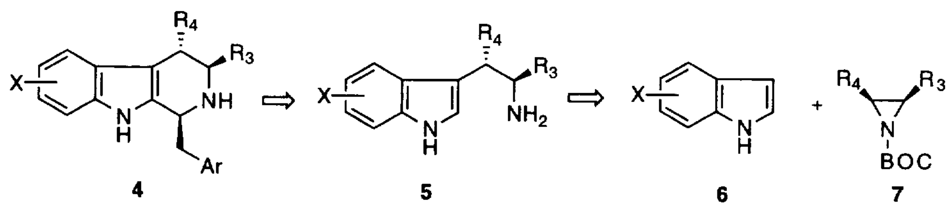


Figure 1

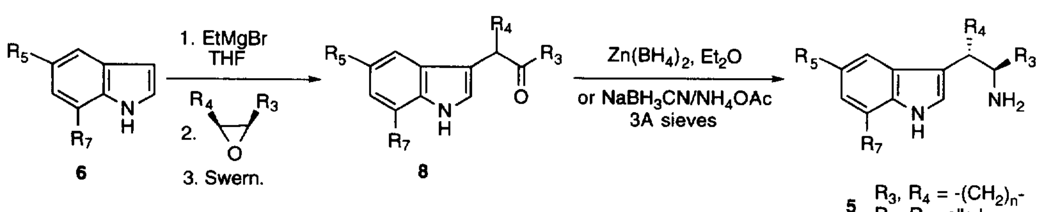
In this paper we report on the synthesis of the 1-arylmethyltetrahydro-β-carbolines **4**[9] from indoles based on two stereoselective transformations: firstly, the synthesis of α,β-substituted tryptamines **5**[10]

(Scheme 1) by nucleophilic ring opening of the *N*-Boc-aziridines **7** with a "lower order" magnesium cuprate, generated from the corresponding indolylmagnesium bromide derived from **6**, and secondly, by a modified "Pictet-Spengler" reaction[11] using azalactones as "arylacetaldehyde equivalents". With this methodology a wide variety of THBC's, with different substitution patterns can be prepared, since substituted indoles **6**[12] and aziridines **7**[13] are readily available and easy to prepare.



Scheme 1

The stereoselective synthesis of the THBC's **4** requires the preparation of the α,β-substituted triptamines **5**. Traditionally, in the case of cycloalkyl derivatives,[14] (Scheme 2) (R_3, R_4 =-$(CH_2)_n$-, n=3,5) these compounds have been accomplished by the reaction of indolylmagnesium bromide with a cycloalkene epoxide, followed by Swern oxidation of the corresponding 3-(2-hydroxycycloalkyl)indole to the ketone **8**. Reductive amination of **8**, using the Danheiser conditions,[15] gave the *trans* isomers of **5** (R_3, R_4 =-$(CH_2)_n$-, n=3) as the major product in the reaction mixture, with different ratios, depending of the reduction agent used [$Zn(BH_4)_2$ 4.2:1 ratio,[14c] $NaBH_3CN$ 9:1 ratio[14b]]. On the other hand, the conversion of the ketone to the enamine under $TiCl_4$ catalysis, followed by reduction with $NaBH_3CN$ yielded the *cis* tryptamine counterpart.[14b]

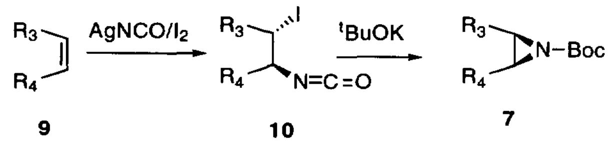


Scheme 2

As this reductive amination approach was not completely diasteroselective for the *trans* derivatives, we decided to develop a new synthetic route by means of *N*-Boc aziridine nucleophilic ring opening,[10] allowing an easy access for both cyclic and acyclic **5** derivatives.

The activated aziridines **7** (Table 1) were prepared by addition of iodine isocyanate to the corresponding alkenes **9**. Subsequent treatment with potassium *tert*-butoxide in DMF of the corresponding *trans* 2-iodo-1-isocyanates **10** gave rise to the *N*-Boc aziridines **7**. The use of ᵗBuOK as a base, instead of the NaH used by Hassner[13] makes the preparation of **7** easier, as the Boc protecting group is generated during the nucleophilic attack of the *tert*-butoxide to the isocyanate with concomitant aziridine formation. This preparation protocol was applied to both cyclic and acyclic alkenes, obtaining the corresponding aziridines in good yields. Moreover, the presence of an urethane protecting group avoids all the problems associated with the cleavage of the aziridine activating group after its reaction with nucleophiles.[16]

Table 1



Entry	R_3	R_4	10 (yield %)	7 (yield %)
a	$-(CH_2)_3-$		95	75
b	$-(CH_2)_4-$		90	85
c	$-(CH_2)_5-$		97	70
d	CH_3	CH_3	94	75

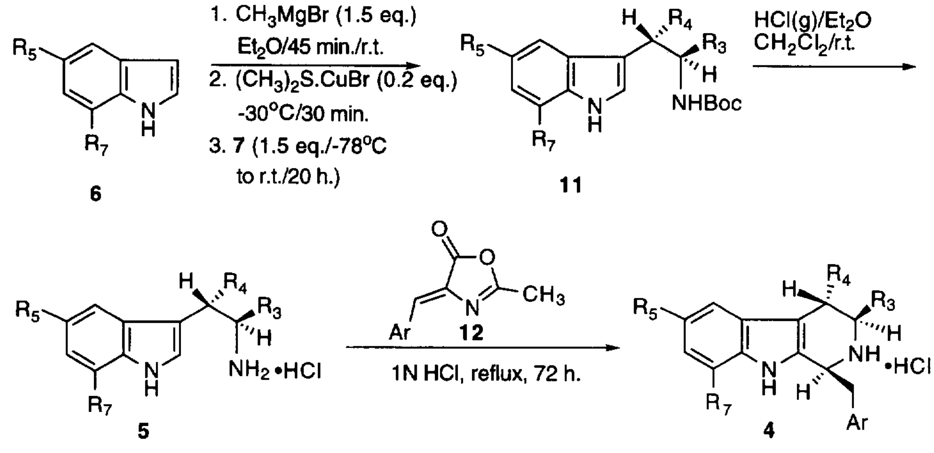
Polarized *N*-urethane activated aziridines have been reacted with indole under Lewis acid catalyst, for the synthesis of several tryptophanes and other derivatives.[17] The activated aziridines **7** were reacted with a "lower order" magnesium cuprate,[18] generated from the corresponding indolylmagnesium bromides and 0.2 equivalents of $(CH_3)_2S{\bullet}CuBr$ (Table 2), resulting in the formation of the *trans* α,β-substituted tryptamines **5** after urethane deprotection. The reaction resulted to be completely stereoselective and yields were dependent, not only on the substituents present in the reacting indole,[10] but also on the reacting aziridine. Thus, cycloheptane aziridine **7c** gave lower yields, compared with the cyclopentane **7a**, cyclohexane **7b** or 2,3-dimethyl aziridine **7d** counterparts, due to the lower aziridine ring strain.

One of the most convenient means to prepare tetrahydro-β-carbolines (THBC's) is the well known Pictet-Spengler (P-S) reaction.[19] Recently, Audia *et al.*[11] have shown that the azalactones **12** can be used as "arylacetaldehyde equivalents" in a modified P-S reaction under hydrolytic and thermal conditions. Thus, tryptamines **5** were reacted with the azalactones **12**[20] in refluxing 1N HCl for 72 h. giving rise to the THBC's **4** in good to moderate yield, which were isolated as hydrochlorides. The cycloalkyl tryptamines (**5a,b,e,f,i**) gave *exclusively* the THBC's **4** as single diastereomers at the C-1 position, regardless the nature of the azalactone **12** . This is not the case of the less conformationally constrained tryptamines **5j** and **5k**, where different diastereomeric mixtures were obtained depending of the tryptamine substitution pattern. While *trans* α, β-dimethyltryptamine **5j** gave **4j** as a major diasteromer in a 6:1 diastereomeric mixture, the α-methyltryptamine **5k** gave rise to a 3:1 mixture where **4k** could not be separated by flash chromatography.

The stereochemistry of the newly created sterogenic center of **4** was established by NMR methods. Thus, full ^1H and ^{13}C assignments were obtained using DQF-COSY and HMQC experiments. The large (*c.* 10Hz) H-1 to NH-2_{ax} and H-3 to NH-2_{ax} couplings provided indirect evidence for a *trans* relationship between these pairs of protons (Scheme 3). Further evidence of the spacial groups relationship was ascertained by nOe difference experiments.[9]

As it can be seen in Table 2, the THBC formation proceeds with complete stereocontrol at the C-1 stereogenic center when cycloalkyl derived aziridines were used, being the *cis* (the term *cis* and *trans* refer to the spacial disposition of substituents at C-1 and C-3 stereogenic centers according to the β-carboline numbering convention) the only isolated product in the reaction mixture. An explanation of the observed stereoselectivity was necessary, since the reaction conditions used in this modified P-S reaction (acidic and thermal conditions) would predict the formation of the *trans* diastereoisomer.[19]

Table 2



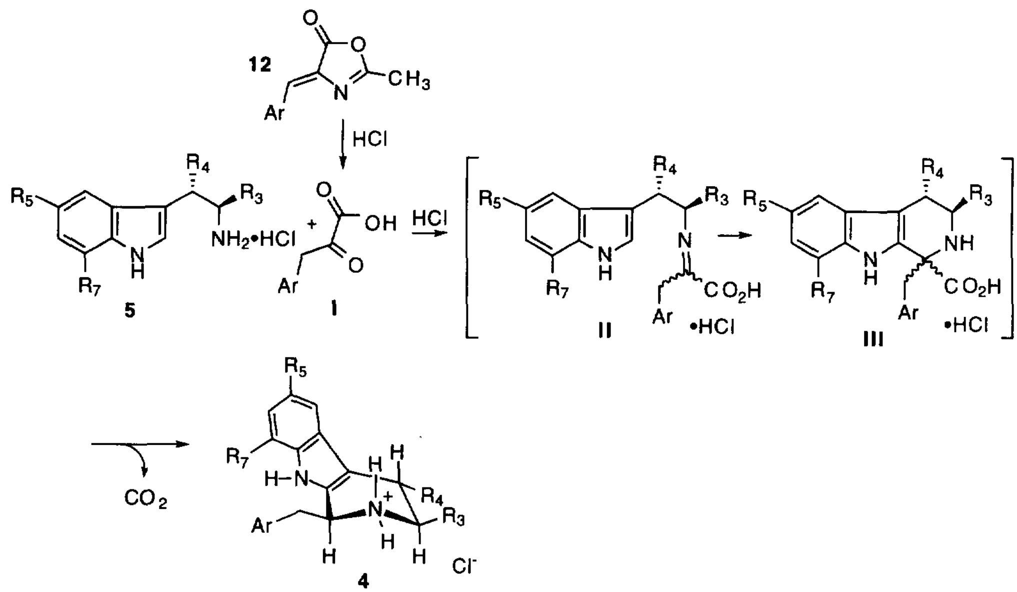
Entry	R3	R4	R5	R7	5 (yield %)	Ar	4 (yield %)
a	-(CH2)3-		CH3	H	85	3,4-di-CH3OC6H3	88
b	-(CH2)4-		CH3	H	80	3,4-di-CH3OC6H3	65
c	-(CH2)3-		CH3	H	–	1-Naphthyl	75
d	-(CH2)4-		CH3	H	–	1-Naphthyl	76
e	-(CH2)3-		CH3	CH3	63	3,4-di-CH3OC6H3	30
f	-(CH2)4-		CH3	CH3	45	3,4-di-CH3OC6H3	42
g	-(CH2)3-		CH3	CH3	–	1-Naphthyl	65
h	-(CH2)4-		CH3	CH3	–	1-Naphthyl	44
i	-(CH2)5-		CH3	H	10	3,4-di-CH3OC6H3	40
j	CH3	CH3	CH3	H	71	3,4-di-CH3OC6H3	40[a]
k	CH3	H	H	H	–[b]	1-Naphthyl	53[c]

[a]Isolated yield from a 6:1 mixture. [b]Commercially available(Aldrich). [c]Yield from a non-separable 3:1 mixture.

It is accepted that the P-S reaction between (L)-tryptophan esters and aldehydes can be controlled under kinetic conditions to give the desired relative and absolute stereochemistry. Thus, under kinetic reaction conditions the *cis* diastereoisomer is the major component in the reaction mixture. On the other hand, the *trans* diastereoisomer is the thermodynamically favoured.[21] Furthermore, recently Cook *et al.*[22] have given futher evidence of this stereochemical reaction outcome on N_b-substituted tryptophanes where the thermodynamically favoured *trans* diastereoisomers are obtained in refluxing benzene. The thermodynamic stability of these compounds was also proved by equilibration experiments, in acidic medium, of the *cis* congeners. This stereochemical control also applies to β-methyltryptophan, giving rise to the corresponding *trans* THBC[23] in a P-S reaction with benzaldehyde under thermodynamic reaction control.

To perform the P-S reaction with the azalactones **12** we require acidic (HCl) and thermal (reflux) conditions to generate the arylpyruvic acid **I** (Scheme 3). Its reaction with the tryptamine **5** gives rise to the imine hydrochloride intermediate **II** which readly cyclises to form the THBC carboxylic acid intermediate

III. Under the reaction conditions, III decarboxylates yielding the corresponding THBC 4 with the arylmethyl substituent oriented in an equatorial position.



Scheme 3

The β-orientation of the substituent at C-1 position must be the result of the higher thermodynamical stability of the final THBC, which is imposed by the conformational constraints induced by other substituents present in the molecule. Thus, the β-projection of the C-1 substituent avoids the unfavoured 1,3-diaxial interaction that would have its α-C-1 epimer. This steric demand imposed by substituents present in the tryptamine (R_3, R_4) can be rationalised analysing the results depicted in Table 2. Thus, the more conformationally constrained cycloalkyl tryptamines (Table 2, entries a-i) account for the total stereocontrol observed at the C-1 position. On the other hand, the less steric demanding tryptamines **5j** and **5k** give different product distribution, directly related with the steric hinderance imposed by the substituents. Therefore, while the observed *cis:trans* diastereomeric ratio for the α,β-dimethyltryptamine **5j** was 6:1, this ratio was 3:1 for the less sterically demanding α-methyltryptamine **5k**. In all the cases studied, the lowest energy conformation of the substituted THBC's **4**, is that where all the substituents locked in the energetically favoured equatorial orientation.

We can conclude that the Pictet-Spengler-like reaction of substituted tryptamines and azalactones under acidic and thermal conditions proceeds with a high degree of stereocontrol due to the conformational restrictions imposed by the tryptamine substituents. 1,3,4-trisubstituted THBC's can be stereoselectively prepared in a two steps sequence starting from readily available reagents, indoles and *N*-Boc aziridines, and using the azalactones **12** as a source of arylpyruvic acid.

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EXPERIMENTAL

General Procedures. Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. ^{1}H NMR were recorded on a Varian Unity 300 spectrometer and were referenced to TMS. IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. Microanalyses were performed on a Heraeus CHN Rapid analyzer and MS were obtained on a Hewlett-Packard 5988 A spectrometer. Positive FAB-MS mass spectra were recorded using 3-nitrobenzylic alcohol matrix on a VG AutoSpec mass spectrometer. Chromatography was performed on silica gel 60 (230-400 meshs). All reagents were obtained from commercial sources and were used as adquired. Solvents were dried before using. Azalactones **12** were obtained following the procedure reported by Audia *et al.*[11]

Synthesis of *N*-Boc-aziridines 7. General Procedure.

To a -30°C cooled solution of silver isocyanate (15 mmol) in dry Et_2O (20 mL) the corresponding alkene was added under argon atmosphere (15 mmol). After stirring for 5 min, iodine (4.19 g, 16.5 mmol) was added and the resulting suspension was stirred at 0°C for 2 h and then at room temperature for 1 h. The inorganic salts were separated by filtration and washed with dry Et_2O (5x10 mL). The filtrate and washes were evaporated under reduced pressure to give a dark oil which was dry under vacuum. The oil was dissolved in dry DMF (10 mL) and added to a 0°C cooled suspension of ^{t}BuOK (1.85 g, 16.5 mmol) in 10 dry DMF (10 mL) under Ar. The mixture was stirred at 0°C for 30 min and then at room temperature for 1 h. The reaction mixture was treated with H_2O (10 mL), extracted with CH_2Cl_2 (3x35 mL) and the organic phase dried over Na_2SO_4. After evaporation of the solvent under reduced pressure the aziridines were obtained as brown oils and purified by reduced pressure distillation.

***N-tert*-Buthoxycarbonyl-6-azabicyclo[3.1.0]hexane (7a).** Colourless oil. Yield: 75%. B.p.: 40°C/0.25 mm Hg. IR (KBr; υ_{max}): 3022, 2974, 1696, 1372, 1316, 1145, 1046, 692. ^{1}H-NMR (CD_3OD, δ): 2.89 (s, 2H), 2.10-2.00 (m, 2H), 1.66-1.46 (m, 3H), 1.42 (s, 9H), 1.28-1.10 (m, 1H).

***N-tert*-Buthoxycarbonyl-7-azabicyclo[4.1.0]hexane (7b).** Colourless oil. Yield: 85%. B.p.: 73°C/0.80 mm Hg. IR (KBr; υ_{max}): 3021, 2973, 1704, 1141, 1084, 878, 691. ^{1}H-NMR (CD_3OD, δ): 2.54 (m, 2H), 1.95-1.84 (m, 2H), 1.82-1.70 (m, 2H), 1.52-1.34 (m, 2H), 1.43 (s, 9H), 1.30-1.15 (m, 2H).

***N-tert*-Buthoxycarbonyl-8-azabicyclo[5.1.0]hexane (7c).** Colourless oil. Yield: 70%. B.p.: 58°C/0.15 mm Hg. IR (KBr; υ_{max}): 3022, 2974, 2927, 1699, 1304, 1253, 1137, 1046, 691. ^{1}H-NMR (CD_3OD, δ): 2.51 (m, 2H), 1.96-1.84 (m, 2H), 1.82-1.66 (m, 2H), 1.60-1.22 (m, 6H), 1.43 (s, 9H).

***N-tert*-Buthoxycarbonyl-2,3-dimethylazyridine (7d).** Colourless oil. Yield: 75%. B.p.: 33°C/0.80 mm Hg. IR (KBr; υ_{max}): 3019, 2982, 1706, 1455, 1368, 1299, 1215, 1156, 760, 668. ^{1}H NMR (CD_3OD, δ): 2.44 (m, 2H), 1.43 (s, 9H), 1.18 (d, J = 1.5Hz, 6H).

Synthesis of *trans* -tryptamines 5. General Procedure.

The indole **6** (5 mmol) in Et_2O (10 mL) was placed in a oven-dried flask under Ar. A 3M solution of methyl magnesium bromide (7.5 mmol) in Et_2O was added dropwise and the mixture was stirred at room temperature for 45 min. The resulting Grignard reagent was added to a -30°C cooled suspension of $CuBr_2 \cdot Me_2S$ (206 mg, 1 mmol) in dry Et_2O (5 mL) and stirring is maintained for 30 min. The reaction mixture was cooled to -78°C, the corresponding aziridine **7** (7.5 mmol) in dry Et_2O (10 mL) was added and the reaction mixture was allowed to reach room temperature gradually and stirred for 20 h. Then, the reaction mixture was slowly treated with a saturated solution of NH_4Cl (10 mL) and the aqueous phase was extracted with Et_2O/EtOAc (1:1, 3x50 mL). The organic phases were dried over Na_2SO_4 and the solvent evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1). After evaporation to dryness, **11** was dissolved in CH_2Cl_2 (10 mL) and diluted with Et_2O (10 mL). The resulting solution was saturated with HCl(g) and stirred for 16 h. The residue obtained after evaporation of the solvent under reduced pressure was triturated with a mixture of CH_2Cl_2/Et_2O to give the corresponding tryptamines **5** as white solids.

***Trans*-3-(2-aminocyclopentil)-5-methylindole hydrochloride (5a).** Yield: 85%. Mp 272-273°C. IR (KBr; υ_{max}): 3304, 2963, 1593, 1510, 1481, 1423, 1102 cm^{-1}. ^{1}H-NMR (CD_3OD, δ): 7.38 (s, 1H), 7.25 (d, J=8 Hz, 1H), 7.15 (s, 1H), 6.95 (d, J=8 Hz, 1H), 3.75 (c, J=8.4 Hz, 1H), 3.30 (m, 1H), 2.41 (s, 3H), 2.40-2.20 (m, 2H), 2.10-1.90 (m, 3H), 1.90-1.74 (m, 1H) ppm. ^{13}C-NMR (CD_3OD, δ): 137.0, 129.0, 127.8, 124.3, 123.1, 119.0, 114.2, 112.4, 58.6, 43.9, 33.1, 31.3, 23.1, 21.7 . MS (EI, *m/z*, rel. int.): 214 ($[M-HCl]^+$, 45), 196 (16), 171 (23), 158 (26), 156 (21), 145 (83), 144 (100), 128 (14), 115 (13), 56 (53) ppm. HRMS (FAB) calcd for $C_{14}H_{18}N_2$: 214.1470; found: 214.1472

***Trans*-3-(2-aminociclohexyl)-5-methylindole hydrochloride (5b).** Yield: 80%. Mp 289-290°C. IR (KBr; υ_{max}): 3400, 3283, 3020, 2936, 2860, 1590, 1491, 1453 cm^{-1}. ^{1}H-NMR (CD_3OD, δ): 7.44 (d, J=1.2 Hz, 1H), 7.27 (d, J=8.3 Hz, 1H), 7.18 (s, 1H), 6.95 (dd, J=8.3 Hz and J=1.2 Hz, 1H), 3.50-3.35 (m, 1H), 2.86 (dd, J=11.2 Hz and J=4 Hz), 2.42 (s, 3H), 2.25-2.10 (m, 1H), 2.10-1.80 (m, 4H), 1.70-1.40 (m, 3H) ppm. ^{13}C-NMR (CD_3OD, δ): 137.0, 129.1, 127.7, 124.4, 123.7, 119.1, 114.8, 112.5 , 56.2, 41.6, 34.7, 32.4, 26.9, 25.8, 21.7 ppm. MS (EI, *m/z*, rel. int): 228 ($[M-HCl]^+$, 39), 211 (20), 185 (21), 170 (17), 157 (31), 145 (43), 144 (100), 131 (14), 115 (12), 56 (50) ppm. HRMS (FAB) calcd for $C_{15}H_{20}N_2$: 228.1626; found: 228.1628

***Trans*-3-(2-aminocyclopentyl)-5,7-dimethylindole hydrochloride (5e).** Yield: 63%. Mp 191-193°C; IR (KBr; υ_{max}): 3264, 2961, 1599, 1510, 1317, 1232, 1171, 1101, 1033 cm^{-1}. ^{1}H-NMR (CD_3OD, δ): 7.20 (s, 1H), 7.14 (s, 1H), 6.76 (s, 1H), 3.75 (q, J=8 Hz, 1H), 3.30 (m, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.40-2.20 (m, 2H), 2.10-1.90 (m, 3H), 1.90-1.70 (m, 1H). ^{13}C-NMR (CD_3OD; δ): 135.7, 128.5, 126.8, 124.2, 122.3, 121.1, 116.0, 113.9, 57.9, 43.4, 32.4, 30.7, 22.4, 21.1, 16.3. MS (EI, *m/z*, rel. int): 228 ($[M-HCl]^+$, 68), 211 (63), 196 (15), 184 (30), 172 (25), 159 (72), 158 (100), 128 (47), 70 (17), 56 (51). HRMS (FAB) calcd for $C_{15}H_{20}N_2$: 228.1626; found: 228.1626.

***Trans*-3-(2-aminocyclohexyl)-5,7-dimethylindole hydrochloride (5f).** Yield: 45%. Mp 276-278°C. IR (KBr; υ_{max}): 3420, 3279, 3013, 2934, 2860, 1615, 1504, 1457, 1125 cm^{-1}. ^{1}H-NMR (CD_3OD, δ): 7.27 (s, 1H), 7.18 (s, 1H), 6.77 (s, 1H), 3.50-3.30 (m, 1H), 2.85 (dd, J=11.2 Hz and J=4.0 Hz, 1H), 2.44 (s, 3H), 2.39 (s, 3H), 2.30-2.10 (m, 1H), 2.10-1.80 (m, 4H), 1.70-1.40 (m, 3H) ppm. ^{13}C-NMR (CD_3OD, δ): 136.4, 129.4, 127.4, 125.0, 123.6, 121.9, 116.8, 115.2, 56.3, 41.7, 34.7, 32.4, 26.9, 25.8, 21.7, 16.9. MS (EI, *m/z*, rel. int): 242 ([M-HCl]$^+$, 65), 225 (25), 199 (22), 184 (19), 171 (33), 159 (47), 158 (100), 145 (18), 128 (10), 115 (9). HRMS (FAB) calcd for $C_{16}H_{22}N_2$: 242.1783; found: 242.1785.

***Trans*-3-(2-aminocicloheptyl)-5-methylindole hydrochloride (5i).** Yield: 10%. Mp 167-170°C (dec.) .IR (KBr, υ_{max}): 3246, 2929, 1692, 1600, 1484, 1379, 1208, 1104, 1046 cm^{-1} ^{1}H-NMR (CD_3OD, δ): 7.37 (d, J=1.3 Hz, 1H), 7.27 (d, J= 8.3 Hz, 1H), 7.17 (s, 1H), 6.96 (dd, J=8.3 Hz and J=1.3 Hz, 1H), 3.70-3.50 (m, 1H), 3.02 (dd, J=10.3 Hz and J=3.2 Hz, 1H), 2.42 (s, 3H), 2.20-1.60 (m, 10H) ppm. ^{13}C-NMR (CD_3OD, d): 137.1, 129.2, 127.3, 124.5, 123.2, 119.1, 116.9, 112.5, 58.5 , 44.1, 34.3, 32.7, 28.5, 27.3, 24.1, 21.7 ppm. MS (EI, *m/z*, rel. int): 242 ([M-HCl]$^+$, 18), 225 (12), 170 (22), 157 (33), 145 (58), 144 (100), 130 (26), 115 (17), 56 (88). HRMS (FAB) calcd for $C_{16}H_{22}N_2$: 242.1783; found: 242.1781.

***Trans*-3-[(2-amino-1-methyl)propyl]-5-methylindole hydrochloride (5j).** Yield: 71%. Mp 229-230 °C; IR (KBr, υ_{max}): 3272, 2987, 1582, 1512, 1481, 1450, 1104 cm^{-1}. ^{1}H-NMR (CD_3OD, δ): 7.40 (s, 1H,), 7.27 (d, J=8.4 Hz, 1H), 7.14 (s, 1H), 6.95 (d, J=8.4 Hz, 1H), 3.61 (q, J=7 Hz, 1H), 3.23 (q, J=7.3 Hz, 1H), 2.41 (s, 3H), 1.43 (d, J=7.3 Hz, 3H), 1.33 (d, J=7 Hz, 3H) ppm. ^{13}C-NMR (CD_3OD, δ): 136.6, 128.9, 127.4, 124.2, 123.4, 118.8, 115.1, 112.2, 53.3, 36.4, 21.5, 16.8, 16.2 ppm. MS (EI, *m/z*, rel. int): 202 ([M-HCl]$^+$, 3), 160 (36), 159 (100), 158 (98), 144 (51), 143 (33), 128 (11), 115 (13), 77 (8). HRMS (FAB) calcd for $C_{13}H_{18}N_2$: 202.1470; found: 202.1466.

Synthesis of tetrahydro-β-carbolines (THBC's) 4. General Procedure.

A mixture of the corresponding tryptamine hydrochloride **5** (2 mmol) and the azalactone **12** (2.4 mmol) in 10 mL of 1N HCl was heated to reflux under Ar for 72 h. The reaction mixture was allowed to cool to room temperature, the precipitate formed was isolated by filtration and washed with H_2O, EtOH and Et_2O and dried under *vacuo* to yield the tetrahydro-β-carbolines **4** as green-yellowish hydrochlorides, which showed decomposition when attempted recrystallization from different solvents.

***Trans*-5-(3,4-dimethoxybenzyl)-9-methyl-1,2,3,4,4a,5,6,10c-octahydrocyclopenta[a]pyrido[3,4-*b*] indole hydrochloride (4a).** Yield: 88%. Mp 220-221°C. IR (KBr, υ_{max}): 3437, 3236, 2941, 1518, 1483, 1263, 1248, 1193, 1022 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 11.28 (s, 1H), 10.09 (q, 1H), 9.26 (bd, 1H), 7.29 (d, J=8 Hz, 1H), 7.26 (s, 1H), 7.22 (s, 1H), 7.00 (d, J= 7.6 Hz, 1H), 6.98 (d, J=7.6 Hz, 1H), 6.96 (d, J= 8 Hz, 1H), 4.86 (bs, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.68 (d, J=14 Hz, 1H), 3.30 (m, 1H), 3.12 (t, J=14 Hz, 1H), 3.00 (m, 1H), 2.51 (m, 1H), 2.37 (s, 3H), 2.20-1.70 (m, 4H), 1.42 (m, 1H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 148.7, 147.9, 134.4, 130.2, 128.2, 127.6, 125.4, 123.0, 121.8, 118.4, 113.7, 112.0, 111.3, 110.6 , 62.0, 57.5, 55.5, 38.2, 37.5, 25.6, 25.1, 21.3, 20.7 ppm. MS (EI, *m/z*, rel. int): 376 ([M-HCl]$^+$, 3), 372 (11), 357 (10), 225 (100), 198 (50), 184 (31), 170 (22), 157 (14), 151 (32), 144 (35). HRMS (FAB) calcd for $C_{24}H_{29}N_2O_2$: 377.2229; found: 377.2234.

***Trans*-6-(3,4-dimethoxybenzyl)-10-methyl-2,3,4,4a,5,6,7,11c-octahydro-1H-indolo[2,3-*c*] quinoline hydrochloride (4b).** Yield: 65%. Mp 164-167°C. IR (KBr; υ_{max}): 3439, 2936, 1516, 1464, 1452, 1265, 1170, 1150, 1027 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 11.15 (s, 1H), 9.46 (c, 1H), 8.82 (bd, 1H), 7.42 (s, 1H), 7.29 (d, J=8 Hz, 1H,), 7.07 (s, 1H), 7.02 (d, J=7.5 Hz, 1H), 6.96 (d, J=7.5 Hz, 1H), 6.94 (d, J=8 Hz, 1H), 4.84 (bs, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.65 (d, J=15.0 Hz, 1H), 3.17 (m, 1H), 3.05 (t, J=15.0 Hz, 1H), 2.95 (m, 1H), 2.85 (m, 1H), 2.36 (s, 3H), 2.13 (m, 1H), 2.00-1.60 (m, 2H), 1.60-1.20 (m, 4H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 148.7, 147.9, 134.9, 129.7, 127.8, 127.5, 125.4, 122.9, 121.8, 119.4, 113.6, 111.9, 111.3, 109.4, 60.0, 55.5, 55.4, 37.1, 36.6, 29.5, 28.2, 24.9, 24.4, 21.3. MS (EI, *m/z*, rel. int): 390 ([M-HCl]$^+$, 2), 239 (100), 222 (6), 183 (5), 149 (32), 105 (5), 91 (8), 73 (6), 69 (10), 57 (26) ppm. HRMS (FAB) calcd for $C_{25}H_{31}N_2O_2$: 391.2386; found: 391.2383.

***Trans*-9-methyl-5-(1-naphthylmethyl)-1,2,3,4,4a,5,6,10c-octahydrocyclopenta[a]pyrido[3,4-*b*] indole hydrochloride (4c).** Yield: 75%. Mp 217-218°C. IR (KBr, υ_{max}): 3445, 3231, 2949, 2876, 2779, 1667, 1603, 1458, 1310 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 11.66 (s, 1H), 10.45 (q, 1H), 9.03 (bd, 1H), 8.47 (d, J=7.8 Hz, 1H), 8.10-7.80 (m, 3H) 7.80-7.40 (m, 3H), 7.40-7.30 (m, 2H), 6.98 (d, J=8 Hz, 1H), 5.00 (bs, 1H), 4.39 (d, J=13.0 Hz, 1H), 3.56 (t, J=13.0 Hz, 1H), 3.30 (m, 1H), 3.01 (m, 1H), 2.52 (m, 1H), 2.40 (s, 3H), 2.00-1.60 (m, 4H), 1.41 (m, 1H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 134.0, 133.3, 131.1, 130.7, 129.3, 128.5, 128.2, 127.4, 127.2, 125.7, 125.3, 125.1, 124.9, 123.4, 122.5, 117.8, 110.6, 110.4 , 61.1, 55.1, 36.8, 34.5, 24.8, 24.4, 20.6, 19.9 ppm. MS (EI, *m/z*, rel. int): 366 ([M-HCl]$^+$, 2), 362 (9), 347 (15), 225 (100), 198 (30), 184 (17), 170 (11), 155 (10), 141 (25), 115 (20). HRMS (FAB) calcd for $C_{26}H_{26}N_2$: 367.2174; found: 367.2173.

***Trans*-10-methyl-6-(1-naphthylmethyl)-2,3,4,4a,5,6,7,11c-octahydro-1*H*-indolo[2,3-*c*]quinoline hydrochloride (4d).** Yield: 76%. Mp 253-255°C. IR (KBr, υ_{max}): 3447, 3235, 2936, 2856, 1615, 1598, 1462, 1403 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 11.00 (s, 1H), 10.40 (q, 1H), 8.40 (d, J=7.8 Hz, 1H), 8.20 (bd, 1H), 8.02 (d, J=7.8 Hz, 1H), 7.93 (d, J=8.2 Hz, 1H), 7.77 (d, J=8.2 Hz, 1H), 7.63 (t, J=7.8 Hz, 1H), 7.60 (t, J=7.8 Hz, 1H), 7.52 (t, J=8.2 Hz, 1H), 7.46 (s, 1H), 7.35 (d, J=8.3 Hz, 1H), 6.97 (d, J=8.3 Hz, 1H), 4.98 (bs, 1H), 4.36 (d, J=13.1 Hz, 1H), 3.20 (t, J=13.1 Hz, 1H), 3.16 (m, 1H), 2.98 (m, 1H), 2.84 (m, 1H), 2.38 (s, 3H), 2.10-1.20 (m, 7H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 135.1, 134.9, 133.8, 131.8, 131.3, 129.4, 128.9, 128.1, 127.6, 126.3, 125.9, 125.8, 125.4, 124.0, 123.1, 119.5, 111.3, 109.6, 59.7, 54.0, 36.7, 35.3, 29.5, 28.4, 24.9, 24.4, 21.3 ppm.MS (EI, *m/z*, rel. int): 380 ([M-HCl]$^+$, 2), 239 (100), 209 (6), 183 (9), 157 (9), 150 (11), 141 (28), 128 (8), 115 (20), 91 (6). HRMS (FAB) calcd for $C_{27}H_{28}N_2$: 381.2331; found: 381.2334.

***Trans*-5-(3,4-dimethoxybenzyl)-7,9-dimethyl-1,2,3,4,4a,5,6,10c-octahydrocyclopenta[a]pyrido [3,4-b]indole hydrochloride (4e).** Yield: 30%. Mp 231-232°C. IR (KBr, υ_{max}): 3588, 3566, 3524, 3509, 3447, 2934, 1513, 1456, 1275, 1048 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 10.95 (s, 1H), 9.65 (q, 1H), 9.26 (bd, 1H), 7.15 (s, 1H), 7.09 (s, 1H), 7.08-6.95 (m, 2H), 6.74 (s, 1H, Hz), 4.83 (bs, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.40-2.90 (m, 4H), 2.44 (s, 3H), 2.32 (s, 3H), 2.00-1.30 (m, 5H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 148.7, 147.9, 134.0, 130.0, 128.3, 127.8, 125.1, 123.8, 121.7, 120.4, 116.0, 113.6, 111.9, 111.2, 61.9, 57.6, 55.5, 37.9, 37.6, 25.6, 25.2, 21.3, 20.7, 17.1 ppm. MS (EI, *m/z*, rel. int): 386 ([M-HCl-4]$^+$, 11), 253

(17), 239 (100), 165 (11), 151 (18), 105 (13), 91 (15), 77 (19), 69 (31), 56 (93). HRMS (FAB) calcd for $C_{25}H_{31}N_2O_2$: 391.2386; found: 391.2395.

***Trans*-6-(3,4-dimethoxybenzyl)-8,10-dimethyl-2,3,4,4a,5,6,7,11c-octahydro-1*H*-indolo[2,3-*c*] quinoline hydrochloride (4f).** Yield: 42%. Mp 210-211°C. IR (KBr, υ_{max}): 3453, 2936, 1516, 1464, 1452, 1263, 1240, 1178, 1164, 1023 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 10.88 (s, 1H), 9.81 (q, 1H), 8.78 (bd, 1H), 7.27 (s, 1H), 7.17 (s, 1H), 7.01 (d, J=8.5 Hz, 1H), 6.95 (d, J=8.5 Hz, 1H), 6.75 (s, 1H), 4.82 (t, 1H), 3.77 (d, J=12 Hz, 1H), 3.76 (s, 6H), 3.15 (m, 1H), 3.12 (t, J= 12 Hz, 1H), 2.95 (m, 1H), 2.85 (m, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 2.14 (m, 1H), 1.83 (m, 1H), 1.79 (m, 1H), 1.68 (m, 1H), 1.40 (m, 1H), 1.32 (m, 1H), 1.19 (m, 1H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 147.9, 147.2, 133.7, 128.8, 127.4, 126.9, 124.4, 123.2, 121.4, 119.6, 116.6, 113.1, 111.5, 109.3, 59.4, 55.3, 55.0, 36.7, 36.2, 29.0, 27.8, 24.5, 23.9, 21.3, 16.6 ppm. MS (EI, *m/z*, rel. int): 404 ($[M-HCl]^+$, 1), 253 (100), 236 (4), 223 (3), 209 (3), 197 (5), 182 (2), 151 (11), 106 (4), 65 (3) ppm. HRMS (FAB) calcd for $C_{26}H_{33}N_2O_2$: 405.2542; found: 405.2549.

***Trans*-7,9-dimethyl-5-(1-naphthylmethyl)-1,2,3,4,4a,5,6,10c-octahydrocyclopenta[a]pyrido[3,4-*b*] indole hydrochloride(4g).** Yield: 65%. Mp 221-222°C. IR (KBr, υ_{max}): 3413, 3196, 3044, 2951, 2733, 2350, 1434, 1302, 1048 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 11.18 (s, 1H), 10.23 (c, 1H), 8.97 (bd, 1H), 8.54 (d, J=8.3 Hz, 1H), 8.02 (d, J=8.3 Hz, 1H), 7.95-7.92 (m, 2H), 7.67 (t, J=8.3 Hz, 1H), 7.60 (t, J=8.3 Hz, 1H), 7.52 (t, J=7.7 Hz, 1H), 7.14 (s, 1H), 6.79 (s, 1H), 5.04 (bs, 1H), 4.58 (d, J= 14.4 Hz, 1H), 3.51 (t, J=14.4 Hz, 1H), 3.37 (m, 1H), 3.00 (t, 1H), 2.56 (m, 1H), 2.54 (s, 3H), 2.35 (s, 3H), 1.95-1.70 (m, 4H), 1.39 (m, 1H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 133.6, 133.3, 131.1, 130.7, 129.0, 128.6, 128.2, 127.4, 127.3, 125.6, 125.3, 125.2, 124.6, 123.8, 123.4, 119.9, 115.5, 110.0, 61.2, 55.3, 36.9, 34.6, 24.9, 24.5, 20.6, 20.1, 16.6 ppm. MS (EI, *m/z*, rel. int): 376 ($[M-HCl-4]^+$, 4), 361 (4), 239 (100), 212 (14), 198 (9), 158 (14), 141 (31), 128 (7), 115 (23), 56 (6).HRMS (FAB) calcd for $C_{27}H_{29}N_2$: 381.2331; found: 381.2342.

***Trans*-8,10-dimethyl-6-(1-naphthylmethyl)-2,3,4,4a,5,6,7,11c-octahydro-1*H*-indolo[2,3-c] quinoline hydrochloride (4h).** Yield: 44%. Mp 250-251°C. IR (KBr; υ_{max}): 3449, 2934, 2858, 2791, 1647, 1448, 1353 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 11.12 (s, 1H), 10.11 (q, 1H), 8.52 (d, J= 8.3 Hz, 1H), 8.35 (bd, 1H), 8.02 (d, J=8.3 Hz, 1H), 7.93 (d, J=7.8 Hz, 1H), 7.83 (d, J=7.8 Hz, 1H), 7.68 (t, J=8.3 Hz, 1H), 7.60 (t, J=8.3 Hz, 1H), 7.51 (t, J=7.8 Hz, 1H), 7.30 (s, 1H), 6.79 (s, 1H), 5.01 (t, 1H), 4.57 (d, J=13.3 Hz, 1H), 3.34 (t, J=13.3 Hz, 1H), 3.24 (m, 1H), 2.97 (m, 1H), 2.87 (m, 1H), 2.53 (s, 3H), 2.36 (s, 3H), 2.00 (m, 1H), 1.79 (m, 1H), 1.80 (m, 1H), 1.60 (m, 1H), 1.46 (m, 1H), 1.27 (m, 1H), 1.19 (m, 1H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 134.6, 133.9, 131.9, 131.4, 129.3, 129.1, 128.8, 128.0, 127.7, 126.2, 125.9, 125.8, 125.1, 124.5, 123.9, 119.5, 117.1, 110.2, 59.6, 54.0, 36.7, 35.2, 29.5, 28.3, 24.9, 24.3, 21.3, 17.3 ppm. MS (EI, *m/z*, rel. int): 390 ($[M-HCl-4]^+$, 11), 375 (14), 250 (17), 149 (61), 128 (63), 115 (45), 84 (44), 73 (44), 69 (52), 57 (100). HRMS (FAB) calcd for $C_{28}H_{31}N_2$: 395.2487; found: 395.2484.

***Trans*-7-(3,4-dimethoxybenzyl)-11-methyl-1,2,3,4,5,5a,6,7,8,12a-decahydrocyclohepta[a]pyrido [3,4-*b*] indole hydrochloride (4i).** Yield: 40%. Mp 220-222°C. IR (KBr, υ_{max}): 3414, 3343, 2932, 2858, 2382, 1516, 1475, 1265, 1252, 1035 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ): 10.92 (s, 1H), 9.56 (bs, 2H), 7.27 (d, J=8 Hz, 1H), 7.25 (s, 1H), 6.90 (d, J=7.8 Hz, 1H), 6.80 (d, J=7.8 Hz, 1H), 6.63 (s, 1H), 6.57 (d, J=8.0 Hz, 1H), 4.75 (m, 1H), 3.66 (s, 3H), 3.43 (s, 3H), 3.38 (m, 2H), 2.94 (t, J= 9.0 Hz, 1H), 2.77 (m, 1H), 2.35 (s, 3H), 2.23 (m, 1H), 1.80-1.20 (m, 8H), 0.8 (m, 1H) ppm. ^{13}C-NMR (DMSO-d_6, δ): 148.6, 147.9, 135.1, 128.8, 128.0, 127.3, 125.3, 123.1, 121.7, 118.9, 113.3, 111.8, 111.3, 110.5, 55.6, 55.1, 55.0, 51.5, 37.0, 36.2, 32.7, 31.9, 26.4, 24.9, 24.1, 21.3 ppm. MS (EI, *m/z*, rel. int): 404 ([M-HCl]$^+$, 2), 400 (26), 385 (22), 253 (46), 151 (100), 107 (28), 91 (22), 77 (31), 65 (22), 55 (21). HRMS (FAB) calcd for $C_{26}H_{33}N_2O_2$: 405.2542; found: 405.2547.

***Trans*-1-(3,4-dimethoxybenzyl)-3,4,6-trimethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-b]indole hydrochloride (4j).** This compound was isolated from a 6:1 mixture by flash columm chromatography (CH_2Cl_2/MeOH, 10%) yielding a 40% yield of **4j**. Mp 198-199°C. IR (KBr, υ_{max}): 3437, 2936, 1518, 1464, 1342, 1265, 1242, 1178, 1163, 1025 cm^{-1}. ^{1}H-NMR (DMSO-d_6, δ) 11.13 (s, 1H), 9.30 (q, 1H), 8.87 (bd, 1H), 7.38 (s, 1H), 7.29 (d, J=8 Hz, 1H), 7.04 (s, 1H), 7.00-6.90 (m, 3H), 4.85 (bs, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.60-3.50 (m, 2H), 3.18-3.00 (m, 2H), 2.36 (s, 3H), 1.44 (d, J=5.5 Hz, 3H), 1.38 (d, J=5.5 Hz, 3H). ^{13}C-NMR (DMSO-d_6, δ) 148.6, 147.9, 135.0, 129.2, 127.4, 125.4, 123.0, 121.8, 119.1, 113.6, 111.9, 111.2 , 110.3, 57.3, 55.4, 55.3, 54.6, 36.4, 32.6, 21.2, 17.1, 15.9. MS (EI, *m/z*, rel. int): 364 ([M-HCl]$^+$, 2), 227 (5), 213 (100), 197 (11), 183 (16), 168 (7), 151 (26), 128 (4), 107 (10), 77 (7).

3-Methyl-1-(1-naphthymethyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-b]indole hydrochloride (4k). This compound was identified from a 3:1 mixture, which could not be separated by chromatographical means.
Yield: 53% IR (KBr; υ_{max}): 3443, 3191, 3052, 2936, 2720, 1451, 1383, 1317 cm^{-1}. MS (EI, m/z, rel. int): 324 ([M-HCl-2]$^+$, 1), 186 (14), 185 (100), 169 (15), 168 (12), 141 (30), 128 (7), 115 (27), 89 (3), 77 (5).

Major componet (**4k**): ^{1}H-NMR (DMSO-d_6; δ): 11.63 (s, 1H), 10.05 (bq, 1H), 8.47 (bd, 1H), 8.42 (d, J= 8.4 Hz, 1H), 8.02 (d, J= 8.4 Hz, 1H), 7.94 (d, J= 8.2 Hz, 1H), 7.80 (d, J= 8.2 Hz, 1H), 7.70-7.40 (m, 5H), 7.17 (t, J= 8.4 Hz, 1H) 7.06 (t, J= 8.2 Hz, 1H), 4.96 (bt, 1H), 4.40 (dd, J= 4.6 Hz, J= 2.3 Hz, 1H), 3.50-3.42 (m, 2H), 3.00 (dd, J=15.6 Hz, J= 4.3 Hz, 1H), 2.98-2.90 (m, 1H), 1.41 (d, J= 6.4 Hz, 3H). ^{13}C-NMR (DMSO-d_6; δ): 135.9 , 134.1 , 131.9 , 131.8 , 129.1, 128.8, 128.5 , 128.2, 127.5, 126.6, 125.4 , 125.2, 124.3 , 122.8, 120.0, 118.4, 110.9, 108.4 , 53.9 , 53.1 , 36.7, 27.1 , 19.1.

Minor component: ^{1}H-NMR (DMSO-d_6; δ): 11.13 (s, 1H), 9.60 (m, 1H), 9.40 (m, 1H), 8.40-7.00 (m, 11H), 4.89 (m, 1H), 4.06 (dd, J= 14.3 Hz, J= 5.4 Hz, 1H), 3.98 (bq , 1H,), 3.75 (m, 1H), 3.19 (dd, J=16 Hz, J= 5 Hz, 1H), 2.73 (dd, J= 16 Hz, J= 6.7 Hz, 1H), 1.31 (d, J= 6.7 Hz, 3H). ^{13}C-NMR (DMSO-d_6; δ): 136.1 , 134.0 , 131.7 , 131.3 , 129.0 , 128.9, 128.7 , 128.0, 127.2, 126.4 , 125.7 , 125.1, 123.9, 122.7, 119.8 , 118.3, 111.0, 106.9 , 51.2, 47.8 , 36.9, 26.7, 18.3.

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