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SYNTHETIC APPLICATIONS OF PROTECTED 2-ARYL-4-PIPERIDONES. V.[1,2] SYNTHESIS OF GUETTARDINE AND 15-EPIGUETTARDINE

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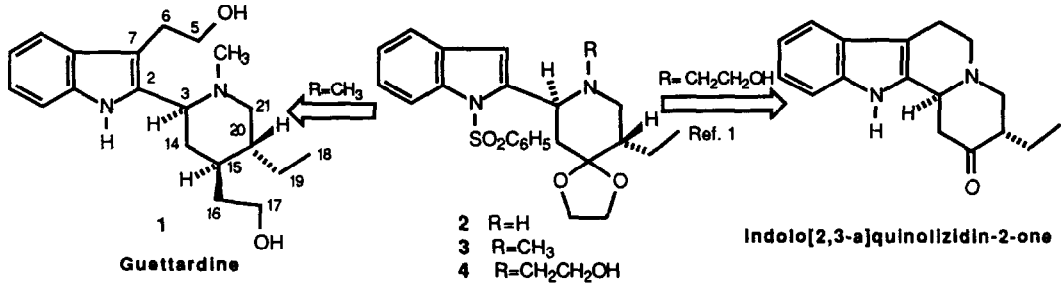
Abstract- The synthesis of indole alkaloid guettardine and its epimer on position 15 is reported, as another synthetic application of 5-ethyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone ethylene acetal (**2**).

Indole alkaloid guettardine **1** was isolated and identified in 1984 from the bark of *Guettarda heterosepala* (Rubiaceae). Its structural interest arises from its free hydroxyethyl chains on positions 7 and 15,[3] which makes it to be considered a probable biogenetic intermediate between the Corynanthe and the Cinchona alkaloids. The stereochemistry of guettardine was established by its transformation into dihydrocorynantheol .[4]

In the context of our studies on the synthesis of alkaloid related compounds containing a 2-arylpiperidine moiety[5] by a synthetic route that implies the use of an easily accesible protected 2-aryl-4-piperidone,[6] we planned to evaluate the effectiveness of this strategy to the synthesis of indole alkaloid guettardine.

We have recently reported[1] the preparation of 5-ethyl-2-(1-phenylsulfonyl-2-indolyl)-4-piperidone ethylene acetal (**2**) and its successful application in the synthesis of indolo[2,3-*a*]quinolizidines *via* intramolecular cyclization of **4** with potassium *tert*-butoxide. Now, we have considered piperidine **2** as the starting product towards guettardine, since the *trans* relative configuration between C-3 and C-5 in **3** is the suitable for our purpose.



1 Guettardine

2 R=H
3 R=CH_3
4 R=CH_2CH_2OH

Indolo[2,3-a]quinolizidin-2-one

Scheme 1

Thus, the functionalisation on the 4-position of piperidine ring was first studied (Scheme 2). Alkylation of **2** with methyl iodide in the presence of an excess of potassium carbonate followed by treatment of the resulting acetal **3** in 4*N* hydrochloric acid led, rather unexpectedly, to a 1:3 mixture of epimeric piperidones **5** (*trans* isomer) and **6** (*cis* isomer), respectively. In the ^{1}H-NMR spectra C-2 methine proton showed to be a doublet of doublets at δ 4.36 (*J*= 11.2 and 4.2 Hz) characteristic of a 2-H axial disposition for **5** (*trans* isomer) but a double

doublet at δ 4.92 (J= 6.3 and 4 Hz) was observed in the spectrum of **6** (*cis* isomer). The abnormal chemical shift observed in the last case is only explainable by considering an equatorial disposition for the C-2 methine proton, deshielded by the *syn* nitrogen lone pair. This observation induces to think that in the preferred conformation of *cis* isomer **6** the indole substituent on C-2 adopts an axial disposition and the ethyl side chain an equatorial one. The preferred conformation in each case was confirmed by ^{13}C-NMR data. Thus, a significant shielding (Δδ=6.3 Hz) on C-6 in **6** was observed when compared to the *trans* isomer **5**, due to the "γ-gauche" effect exerted by the axial indole moiety. Consistently, the fact that **6** was the major isomer made us suppose that some kind of stereoelectronic stabilizing interaction is promoted by the 1-phenylsulfonyl-2-indolyl substituent.[7]

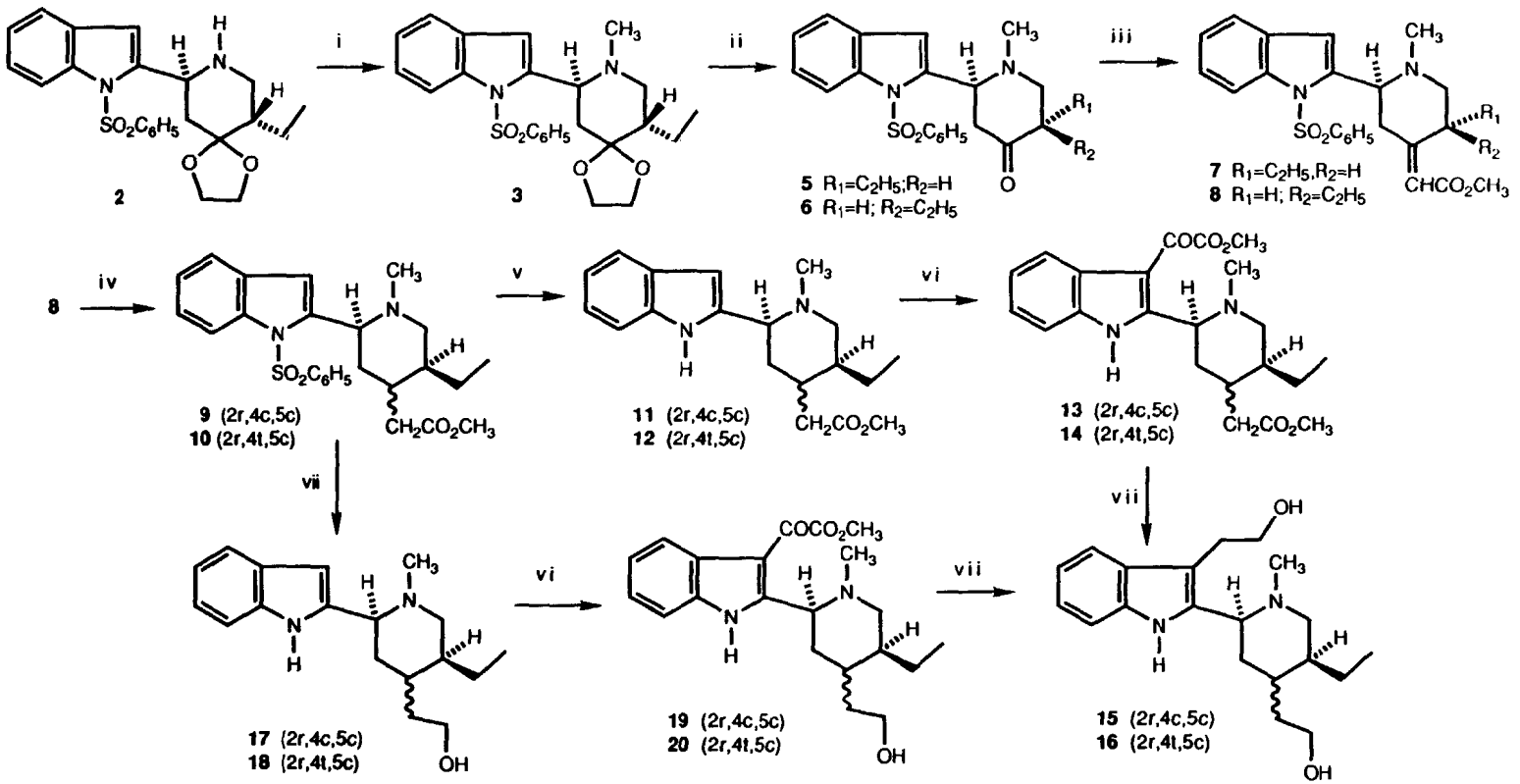
Even though treatment of piperidone **6** with potassium *tert*-butoxide allowed us to recover some *trans* isomer **5**, Wadsworth-Emmons reaction with diethyl methoxycarbonylmethylphosphonate[8] on pure *trans* piperidone **5** provided a 2:1 mixture of olefins **7** and **8**, respectively. The C-2/C-5 *trans* isomer **7** appeared to be only one geometric isomer assigned as *E* due to the $A^{(1,3)}$ steric interaction[9] of the equatorial ethyl group (see spectroscopic data) which favors the *anti* disposition of methoxycarbonyl group.

When the Wadsworth-Emmons condensation was carried out on pure **6** (*cis* isomer), an equimolecular mixture of exocyclic olefins *Z* - and *E* - **8** was obtained. The assignment of the double bond configuration of **8** was inferred from the line width of the vinyl proton signal in the ^{1}H-NMR spectrum (2 and 4 Hz for (*E*)-**8** and (*Z*)-**8**, respectively) taking into account that transoid allylic coupling constants are smaller than cisoid ones.[10] Moreover, the ^{13}C-NMR data for C-6 in both olefins did not show any "γ-gauche" effect (see table 1), which, together with the comparison of the ^{1}H-NMR chemical shift values of C-2 methine proton in **7** and **8** indicate that the conformation in **8** is such that the indolyl group is equatorially oriented and the ethyl chain axial.

Catalytic hydrogenation of **8** over platinum dioxide afforded a (2:1) mixture of C-4 epimeric acetates **9** and **10**, respectively, which is in accordance with the fact that the approach of hydrogen is quicker from the α-face as it lacks the steric interaction of the axial C-5 piperidine ethyl substituent.

Two pathways were studied to obtain the guettardine analogs **15** and **16** from the mixture of piperidine-4-acetates **9** and **10**. The first one consisted in the indole deprotection by treatment with 2*N* sodium hydroxide and the introduction of the hydroxy ethyl chain on indole 3 position in a sequence of two steps.[11-13] Thus, reaction of a mixture of **11** and **12** with oxalyl chloride followed by methanol esterification afforded a mixture of indole-3-oxalates **13** and **14** which was reduced with $LiAlH_4$, obtaining simultaneously the two hydroxyethyl chains. Alternatively, reduction of the C-4 acetate chainnn and indole deprotection followed by introduction of the indole C-3 hydroxyethyl substituent, as previuously indicated, afforded piperidines **15** and **16** in 22% overall yield.

The unsuitable stereochemistry of C-5 ethyl substituent led us to study another strategy consisting in the introduction of the 2-hydroxyethyl chain on indole 3-position before the acetal hydrolysis, in order to control the epimerization observed on C-5 in piperidone **5**. Thus, indole deprotection of **3** with 2*N* sodium hydroxide afforded piperidine **21**, which by the ususal consecutive oxalyl chloride, methanol, and $LiAlH_4$ treatments was converted into **23**.[14] Reaction of ethylene acetal **23** with 2*N* hydrochloric acid in methanol furnished *trans* piperidone **24** in 75% yield, which presents the appropriate stereochemistry on C-5. Only when the reaction time was longer a little proportion of the epimer on C-5 (18% yield) was detected. Wadsworth-Emmons condensation of **24** with the appropriate phosphonoacetate provided a 3:1 mixture of (*E*) and (*Z*) isomers of **25**. In this case, the existence of two equatorial groups on C-2 and C-5 does not permit ring inversion in spite of the $A^{(1,3)}$ strain, and the major

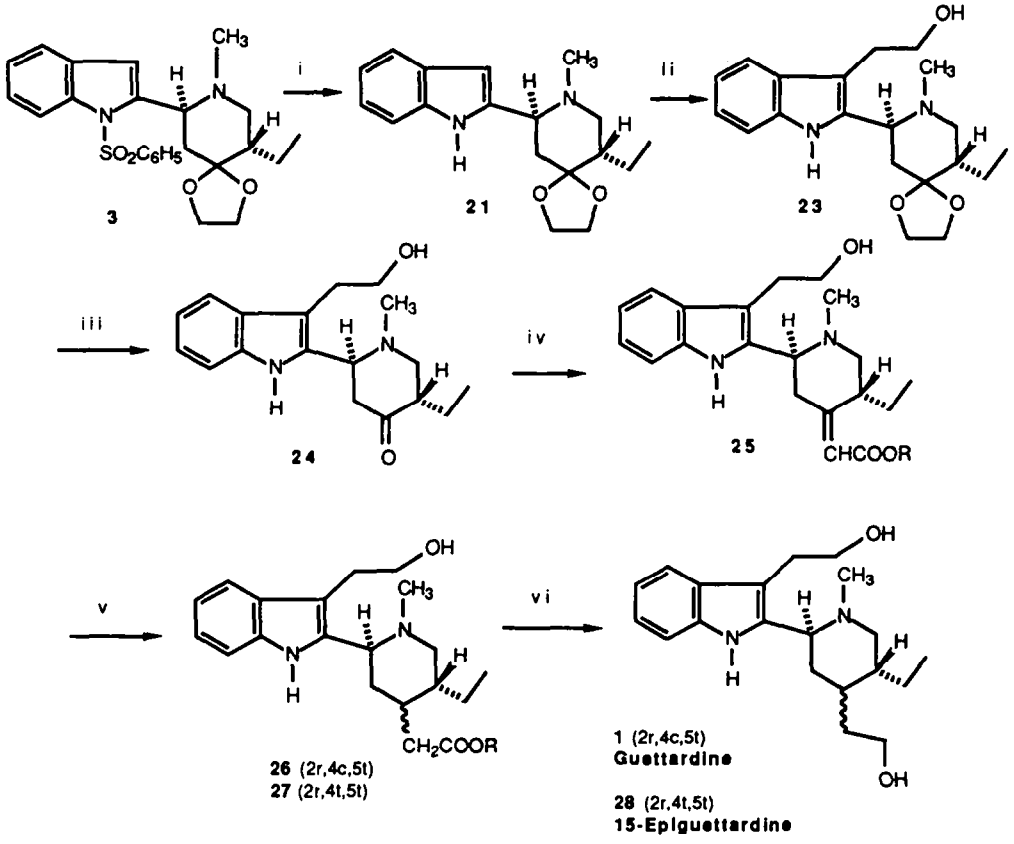


Reagents and conditions. i) CH_3I, acetone, anh. K_2CO_3; ii) 4*N* HCl-CH_3OH, Δ; iii) $(C_2H_5O)_2POCH_2CO_2CH_3$, NaH-DME; iv) H_2, PtO_2/EtOH, 150 psi; v) a. 2*N* NaOH, CH_3OH; b. 4*N* CH_3OH-HCl; vi) a. $(COCl)_2$, CH_2Cl_2; b. CH_3OH, Δ; vii) $LiAlH_4$, THF.

Scheme 2

isomer has equatorial indolyl and ethyl substituents and the *E* double bond geometry, as it presents less interactions with the ethyl substituent.

Unfortunately, the catalytic hydrogenation of **25** leads to a 3:1 mixture of **27** and **26**, respectively, in which the major piperidine-4-acetate results from the addition of hydrogen from the less hindered β side. These



Reagents and conditions. i) aq 10% NaOH, C_2H_5OH; ii) 1. $(COCl)_2$, CH_2Cl_2; 2. CH_3OH; 3. $LiAlH_4$, THF; iii) 4*N* HCl, CH_3OH, Δ, 30 min; iv) $(C_2H_5O)_2POCH_2COOC_2H_5$, NaH, DME; v) H_2, PtO_2/C_2H_5OH, 200 psi; vi) $LiAlH_4$, THF.

Scheme 3

stereochemical differences were clearly shown by ^{13}C-NMR when comparing the chemical shift of the piperidine ring carbon atoms of **26** with those reported for guettardine (see table 1).

Table 1. ^{13}C-NMR Spectral Data of 2-(2-Piperidyl)indoles

Carbon	3	5	6	7-(*E*)	8-(*E*)	8-(*Z*)	9	10	11	12	17	18	21	23	24	25-(*Z*)	25-(*E*)	26	28	1
C-2	59 4	60.6	59.0	61 3	61 3	63 1	62 2	57 2	63 7	58 3	64.3	61 2	60 9	58.5	61.4	62.7	62 8	60.4	57 5	61 1
C-3	43 1	43 4	41.7	36 7	33 8	41 9	37 0	34 7	35 9	32.8	36 1	39 1	43.4	42.1	47.9	39 5	37 5	38.0	36.4	37 4
C-4	108 4	208 2	210 3	160 0	160 1	160.0	36 8	32 0	36 6	32 8	35.9	29.7	108 6	108.4	208 2	160 3	160 7	37 3	29 7	36.9
C-5	45 2	50 5	48 2	45 1	47 4	39 0	39 0	39 0	39 2	38 9	39.3	40 5	45 7	45.6	51.1	38 2	45 4	41.6	39.9	41.8
C-6	59 2	60 4	54 1	61 7	60 7	60 6	59 2	54.6	37 9	37 7	60 0	46 6	58 7	58.7	62.7	62.6	62 4	61 6	53 9	61.7
CH_3CH_2	18 3	19 6	20 3	22 3	25 2	25 2	17 5	25 1	17 7	25 0	17 4	24 9	18 3	18 3	19 3	23.4	21 8	23.5	24 1	23.3
CH_3CH_2	12 0	11 7	11.6	11 7	12.1	11 8	12 6	12 1	12 6	12 0	12.6	12 2	12 0	12.0	11 6	10.7	11.7	10.9	12.1	10.8
NCH_3	42 8	41 1	41.4	42 4	43.5	43 4	41 1	43 8	44 3	43 9	44 5	44 2	42.8	43.3	42 7	43.6	43.3	44.1	46 3	43 9
OCH_2CH_2O	64 7	—	—	—	—	—	—	—	—	—	—	—	65 0	64 9	—	—	—	—	—	—
	64 9	—	—	—	—	—	—	—	—	—	—	—	65 1	65.0	—	—	—	—	—	—
$HOCH_2CH_2$	—	—	—	—	—	—	—	—	—	—	59.1	58 3	—	62.9	61.1	62.9	63.1	63 0	62.8[b]	62.7[b]
$HOCH_2CH_2$	—	—	—	—	—	—	—	—	—	—	35.9	33.1	—	27 7	27.5	27.4	27.7	27.7	27 7[b]	27.7[b]
OCH_3	—	—	—	50 9	—	—	51 4	51 5	51 5	51 5	—	—	—	—	—	—	—	—	—	—
CH_2COOR	—	—	—	—	—	—	—	—	58 7	54 2	—	—	—	—	—	c	d	—	—	—
CO_2R	—	—	—	166.9	166.8	166 6	173.0	173 3	173.1	173.1	—	—	—	—	—	165.6	166.6	173 4	—	—
=C	—	—	—	115.2	115 2	115.0	—	—	—	—	—	—	—	—	—	112.0	111 9	—	—	—
In-C2	142 9	140 9	142.1	143 2	143 9	143.7	144 9	144 2	140 8	139 9	141 3	141.1	139.9	136.5	135.6	136.4	136.4	136.7	135.5	135 5
In-C3	109 2	111 1	110 1	110 3	110.1	109 2	108 9	109 4	100 2	100 3	99.9	100.3	100.5	108.5	109.5	110.9	110 9	110.9	107.3	108.1
In-C3a	129 6	128 6	128 9	129 6	129 7	129 5	129.7	129 6	128 2	128.3	128 1	128 1	128 1	128.3	128.1	127.4	127 4	128.7	128.6	128 4
In-C4	120 7	123 6	121 9	123 7	120.7	120 7	120.7	120 5	121.4	121 4	121 3	121 3	120 2	119.2	118 7	118 4	118 4	118.4	118 1	118.3
In-C5	123 6	121.0	120 9	120 7	123.7	123.7	123 7	123.6	119.5	119 5	119 4	119 6	119 6	118 4	122 2	121 8	121.8	121 7	121 2	121 8
In-C6	124 3	124 9	123.8	124.4	124.5	124 4	124.4	124.1	120 1	120 1	120 0	120 2	121 6	121 7	119.5	119 2	119 2	119.2	119.3	119.1
In-C7	114 9	114 9	115 1	112 5	114.6	114.6	115 0	114 9	110 8	110 8	110 8	110 8	110 8	110 8	110 9	110 8	110 8	110 8	110 5	111 7
In-C7a	137 2	137 5	137 3	137 1	137.2	137 2	137.1	137 3	135.8	135.9	135 9	136 0	136 0	135.5	135 1	135 4	135 4	135.7	136.9	136 6
$(C_6H_5)i$	139 8	140 2	139 4	138.9	139 7	139 2	139 6	139 9	—	—	—	—	—	—	—	—	—	—	—	—
$(C_6H_5)o$	126 5	125 9	132 8	133 6	126 5	126.4	126 4	126 1	—	—	—	—	—	—	—	—	—	—	—	—
$(C_6H_5)m$	129 1	128 8	129 2	129 1	129 2	129 1	129 2	129.1	—	—	—	—	—	—	—	—	—	—	—	—
$(C_6H_5)p$	133 7	133 3	133 8	133 6	133.9	133.7	133 7	133.5	—	—	—	—	—	—	—	—	—	—	—	—

a Recorded at 50 3 MHz in $CDCl_3$ assignments were aided by "off resonance" experiments Chemical shifts are given in δ units (downfield from TMS). b. Chemical shifts of hydroxyethyl pipendine chain CH_2CH_2OH (28 δ 35 9, 1 δ 35 1), CH_2OH (28 δ 62 8, 1 δ 60 5) c Ethyl group CH_2 δ 23 4, CH_3 δ 10 7 d Ethyl group· CH_2 δ 21 8, CH_3 δ 11 7.

Finally, reduction of a mixture of **26** and **27** with $LiAlH_4$ afforded a mixture of **1** and **28** which was separated by successive flash chromatographies, from which compound **28** was isolated as the major product. The comparison of the obtained spectral data with those of guettardine[4] allowed us to identify **1** with guettardine and **28** as 15-epiguettardine. In particular, ^{13}C-NMR chemical shifts for C-2 and C-6 showed a clear "γ-gauche" shielding effect in **28** due to the axial disposition of the C-4 hydroxyethyl chain, while the ^{13}C-NMR date of compound **1** were totally in accordance with those of guettardine.

EXPERIMENTAL SECTION

General Methods. Melting points were determined in a capillary tube on a BÜchi or a CTP-MP 300 hotplate apparatus and are uncorrected. ^1H-NMR spectra were recorded on a Varian XL-200 instrument or, when indicated, on a Perkin-Elmer R-24B (60 MHz) spectrometer. ^{13}C-NMR spectra were recorded with a Varian XL-200 spectrometer. Unless otherwise noted, NMR spectra were registered in $CDCl_3$ and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60, 63-200 mm, Merck) or Al_2O_3 (aluminium oxide 90, neutral, activity I, 63-200 mm, Merck). Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 mm, Macherey-Nagel). TLC was performed on SiO_2 (silica gel 60 F254, Merck) using 99:1 Et_2O-DEA as developing solvent, and the spots were located with UV light or iodoplatinate reagent. Purification of reagents and solvents was effected according to standart methods. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo-Erba 1106 analyzer by the Departament de Química Orgànica Biològica. Barcelona.

5-Ethyl-1-methyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (3). Methyl iodide (3.1 ml, 50.5 mmol) was slowly added to a dispersion of piperidone acetal **2**[1] (21.5 g, 50.5 mmol) and anhydrous K_2CO_3 (15 g) in dry acetone (250 ml). The mixture was stirred at 0°C for 3 h under nitrogen atmosphere, and filtered. Evaporation of the filtrate provided **3** (21.1 g, 95%) after flash chromatography purification (98:2 Et_2O-DEA): mp 108-110 °C (hexane-Et_2O); IR (KBr) 1370, 1170 cm^{-1}; ^1H-NMR 0.92 (t, J=7 Hz, 3H, CH_3CH_2), 1.00-1.20 (m, 1H, CH_ACH_3), 1.58 (dd, J=12.9 and 11.5 Hz, 1H, 3-Ha), 1.60-1.80 (m, 1 H, CH_BCH_3), 1.85-2.00 (m, 1H, 5-Ha), 1.92 (s, 3H, NCH_3), 2.08 (dd, J=12.9 and 2.7 Hz, 1H, 3-He), 2.20 (t, J=11.5 Hz, 1H, 6-Ha), 3.02 (dd, J=11.5 and 4 Hz, 1H, 6-He), 3.80-4.10 (m, 4H, OCH_3), 3.92 (dd, J=12.9 and 2.7 Hz, 1H, 2-Ha), 6.71 (s, 1H, In-3H), 7.20-7.60 (m, 7H, Ar-H), 7.80 (d, J=8 Hz, 1H, In-4H), 8.30 (d, J=8 Hz, 1 H, In-7H); MS (m/z, %) 440 (M^+, 27), 395 (25), 394 (100), 299 (64), 283 (51), 185 (43), 142 (44), 130 (42), 115 (45), 42 (13). Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.40; N, 6.36; S, 7.28. Found: C, 65.42; H, 6.27; N, 6.08; S, 7.21.

5-Ethyl-1-methyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidones (5 and 6). A solution of piperidine **3** (14.5 g, 33 mmol) in methanol (300 ml) and 4*N* HCl (300 ml) was refluxed for 15 h. The reaction mixture was basified with Na_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried and the solvent evaporated to furnish a mixture of piperidones **5** and **6**, which were chromatographied. On elution with hexane-ethyl acetate (8:2) **5** (*trans* isomer) was isolated (1.6 g, 12%): IR (NaCl) 1700 cm^{-1}; ^{1}H-NMR 0.95 (t, *J*=7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.10-1.40 (m, 1H, C*H*$_A$CH$_3$), 1.70-1.95 (m, 2H, C*H*$_B$CH$_3$ and 5-Ha), 2.04 (s, 3H, NCH$_3$), 2.38 (t, *J*=11.2 Hz, 1H, 3-Ha), 2.55 (t, *J*= 11.2 Hz, 1H, 6-Ha), 3.20 (dd, *J*= 11.2 and 5.6 Hz, 1H, 6-He), 4.36 (dd, *J*=11.2 and 4.2 Hz, 1H, 2-Ha), 6.78 (s, 1H, In-3H), 7.20-7.60 (m, 7H, Ar-H), 7.78 (d, *J*=8 Hz, 1H, In-4H), 8.30 (d, *J*=8 Hz, 1H, In-7H); MS (m/z, %) 396 (M^+, 16), 283 (61), 255 (100), 184 (41), 170 (31), 142 (68), 115 (53), 77 (83), 42 (31).The hydrochloride melted at 167-168°C (acetone); ^{1}H-NMR ($CDCl_3$-CD_3OD) 1.04 (t, *J*=7 Hz, 3H, CH$_2$C*H*$_3$), 1.25-1.50 (m, 1H, C*H*$_A$CH$_3$), 1.82-2.10 (m, 2H, C*H*$_B$CH$_3$ and 5-Ha), 2.48 (dd, *J*=14 and 3 Hz, 1H, 3-He), 2.47 (s, 3H, NCH$_3$), 3.15 (t, *J*=12 Hz, 1H, 6-Ha), 3.55 (t, *J*=14 Hz, 1H, 3-Ha), 3.83 (dd, *J*=12 and 5 Hz, 1H, 6-He), 5.45 (br d, *J*=12 Hz, 1H, 2-Ha), 7.30-7.70 (m, 9H, Ar-H), 8.25 (d, *J*=7Hz, 1H, In-7H). Anal. Calcd for $C_{22}H_{25}ClN_2O_3S.H_2O$: C, 58.60; H, 5.99; N, 6.21. Found: C, 58.48; H, 5.59; N, 6.49. On elution with hexane-ethyl acetate (7:3) **6** (*cis* isomer) was obtained (5.3 g, 39%): IR (NaCl) 1700 cm^{-1};^{1}H-NMR 0.85 (t, *J*= 7.4 Hz, 3H, CH$_2$C*H*$_3$), 0.80-1.00 (m, 1H, C*H*$_A$CH$_3$), 1.10-1.30 (m, 1H, C*H*$_B$CH$_3$), 1.70-1.90 (m, 1H, 5-He), 2.30-2.50 (m, 1H, 6-Ha), , 2.48 (s, 3H, NCH$_3$), 2.60 (dd, *J*=12 and 4 Hz, 1H, 3-He), 2.88 (dd, *J*=12 and 4 Hz, 1H, 6-He), 4.92 (dd, *J*=6 and 4 Hz, 1H, 2-He), 6.53 (s, 1H, In-3H), 7.10-7.50 (m, 7H, Ar-H), 7.76 (d, *J*= 8 Hz, 1H, In-7H), 8.21 (d, *J*=8 Hz, 1H, In-4H); MS (m/z,%) 396 (M^+, 16), 283 (48), 255 (66), 184 (28), 170 (27), 142 (46), 115 (40), 77 (100).

To a solution of pure **6** (*cis* isomer) (350 mg, 0.88 mmol) in dry THF (40 m), cooled at 0 °C, recently sublimed K^{t}BuO (98 mg, 0.88 mmol) was added portionwise. The mixture was stirred at 0°C for 2 h, then poured over ice-water and extracted dichloromethane. The organic extracts were dried and evaporated to furnish a 1:1 mixture of **5** and **6**.

Methyl 5-Ethyl-1-methyl-2-[1-(phenylsulfonyl)-2-indolyl]-piperidine-$\Delta^{4,\alpha}$-acetate (7 and 8). Method A. Diethyl methoxycarbonylmethylphosphonate[8] (1.1 g, 5.1 mmol) in dry DME (15 ml) was added to a dispersion of sodium hydride (0.2 g, 4.6 mmol) in dry DME. When the mixture was totally transparent, piperidone **6** (1.6 g, 4 mmol) in DME (15 ml) was added. The mixture was stirred at 70 °C for 3 h, poured over ice-water and extracted with CH_2Cl_2. The organic layer was washed with 20% aqueous Na_2CO_3, dried, and the solvent evaporated yielding an oil which was distilled (120 °C, 0.01 mmHg) to remove the remaining phosphonate. Flash chromatography of the oil (8:2 hexane-ethyl acetate) provided **8** (1.5 g, 85 %) as an equimolecular mixture of *Z* and *E* geometric isomers. (*E*)-**8** (Higher Rf) : IR (NaCl) 1710, 1650, 1370, and 1175 cm^{-1};^{1}H-NMR 0.86 (t, *J*=7Hz, 3H, CH$_2$C*H*$_3$), 1.80 (s, 3H, NCH$_3$), 3.56 (s, 3H, COOCH$_3$), 3.73 (m, 1H, 2-Ha), 5.55 (br s, $W_{1/2}$=2 Hz, 1H, =CH), 6.80 (s, 1H, In-3H), 7.10-7.50 (m, 7H, Ar-H), 7.70-7.90 (m, 1H, In-4H), 8.20-8.30 (m, 1H, In-7H). The hydrochloride melted at 192-195 °C (acetone); ^{1}H-NMR 0.99 (t, *J*=7 Hz, 3H, CH$_2$C*H*$_3$), 2.14 (t, *J*=12 Hz, 3-Ha), 2.00-2.30 (m, 3H, C*H*$_2$CH$_3$ and 5-He), 2.66 (d, *J*=3 Hz, 3H, NCH$_3$), 3.25 (t, *J*=12 Hz, 1H, 6-Ha), 3.65 (d, *J*=12 Hz, 1H, 3-He), 3.76 (s, 3H, COOCH$_3$), 4.08-4.20 (m, 1H, 6-He), 4.95 (br t, *J*=12 Hz, 1H, 2-Ha), 5.68 (s, 1H, =CH), 7.25-7.55 (m, 7H, Ar-H), 7.64 (d, *J*=7 Hz,1H, In-4H), 8.00 (s, 1H, In-3H), 8.25 (d, *J*=7 Hz, In-7H). Anal. Calcd for $C_{25}H_{29}N_2SO_4Cl.1/2H_2O$: C, 60.29; H, 5.87; N, 5.62. Found: C, 60.81; H, 6.17; N, 5.31. (*Z*)-**8** (Lower Rf): IR (NaCl) 1710, 1650, 1370, and 1175 cm^{-1}; ^{1}H-NMR 0.83 (t, *J*=7 Hz, 3H, C*H*$_3$CH$_2$), 1.90 (s, 3H, NCH$_3$), 3.56 (s, 3H, OCH$_3$), 3.96 (m, 1H, 2-Ha),

5.65 (br s, $W_{1/2}$= 4 Hz, =CH), 6.80 (s, 1H, In-3H), 7.60-7.80 (m, 7H, Ar-H), 7.80-7.90 (m, 1H, In-4H), 8.20-8.30 (m, 1H, In-7H); MS (m/z, %) 452 (M^+, 2), 311 (93), 268 (35), 236 (20), 208 (40), 171 (33), 130 (40), 77 (100).

Method B. Operating as above, from sodium hydride (0.4 g, 8.7 mmol) in dry DME (30 ml), diethyl methoxycarbonylmethylphosphonate (2.3 g, 11.3 mmol) in DME (35 ml) and piperidone *trans*-5 (3.5 g, 8.7 mmol) in DME (35 ml), a mixture of *(E)*-7 and *(E)*- and*(Z)* -8, was obtained in a 1:2 proportion, which was flash chromatographied (99.5:0.5 Et_2O-DEA). First, an equimolecular mixture of *(E)* and*(Z)* -8 isomer was obtained (1.7 g, 43 %), followed by pure*(E)*-7 (0.9 g, 23 %); IR (NaCl)1710 and 1645 cm^{-1}; ^{1}H-NMR 0.99 (t, J=7 Hz, 3H, CH_2CH_3), 1.20-1.45 (m, 1H, CH_ACH_3), 1.60-1.80 (m, 1H, CH_BCH_3), 2.02 (s, 3H, NCH_3), 2.10 (t, J=13 Hz, 1H, 3-Ha), 2.35 (br d, J=12 Hz, 1H, 6-Ha), 3.14 (dd, J= 11 and 4 Hz, 1H, 3-He), 3.68 (s, 3H, OCH_3), 4.09 (dd, J=13 and 4 Hz, 1H, 6-He), 4.18 (dd, J=10 and 3 Hz, 1H, 2-Ha), 5.69 (s, 1H, =CH), 6.78 (s, 1H, In-3H), 7.20-7.60 (m, 7H, Ar-H), 7.80 (d, J=7 Hz, 1H, In-4H), 8.26 (d, J=7 Hz, In-7H).The hydrochloride of the*(E)* -7 isomer melted at 220-222 °C (Et_2O-acetone); ^{1}H-NMR 1.09 (t, J=7 Hz, 3H, CH_2CH_3), 1.30-1.50 (m, 2H, CH_ACH_3 and 5-H) , 1.80-2.00 (m, 1H, CH_BCH_3), 2.68 (d, J=3 Hz, 3H, NCH_3), 3.22 (t, J=12 Hz, 1H, 3-Ha), 3.48-3.62 (m, 1H, 6-Ha), 3.76 (s, 3H, OCH_3), 4.62 (dd, J= 13 and 3 Hz, 1H, 6-He), 5.28 (ddd, J=,13, 10 and 3 Hz, 1H, 2-Ha), 5.87 (s, 1H, =CH), 7.2-7.6 (m, 8H, Ar-H), 7.82 (d, J=7 Hz, 1H, In-4H), 8.18 (d, J=7 Hz, 1H, In-7H), 13.0 (br, 1H, N^+H). Anal. Calcd for $C_{25}H_{29}N_2O_4SCl$: H, 61.41; H, 5.93; N, 5.73. Found: C, 61.42; H, 6.14; N, 5.73.

Methyl 5-Ethyl-1-methyl-2-[1-(phenylsulfonyl)-2-indolyl]-piperidine-4-acetates (9 and 10). A dispersion of **8** (570 mg, 1.26 mmol) and PtO_2 (26 mg) in absolute ethanol (80 ml) was hydrogenated under pressure (150 psi), at room temperature, for 24 h. The reaction mixture was filtered and the solvent evaporated to provide a 2:1 mixture of epimers **9** and **10** which was separated by flash chromatography (8:2 hexane-ethyl acetate). Isomer **9** (higher Rf; 310 mg, 54 %); IR (NaCl) 1730, 1370 and 1170 cm^{-1}; ^{1}H-NMR 0.90 (br t, J=7 Hz, 3H, CH_2CH_3), 1.79 (s, 3H, NCH_3), 2.25 (d, J=5Hz, 2H, CH_2CO), 2.91 (br d, J=12 Hz, 1H, 6-He), 3.70 (s, 3H, OCH_3), 3.90-4.20 (m, 1H, 2-Ha), 6.73 (s, 1H, In-3H), 7.20-7.60 (m, 7H, Ar-H), 7.65-7.90 (m, 1H, In-4H), 8.15-8.40 (m, 1H, In-7H); MS (m/z, %) 454 (M^+, 3), 313 (59), 239 (13), 198 (14), 180 (11), 171 (27), 130 (62), 115 (31), 77 (100), 70 (15), 42 (15). Isomer **10** (lower Rf; 150 mg, 26 %): IR (NaCl) 1730, 1370 and 1170 cm^{-1}; ^{1}H-NMR 0.91 (t, J=7 Hz, 3H, CH_3CH_2), 1.20-1.40 (m, 1H, CH_ACH_3), 1.50-1.70-(m, 2H, CH_BCH_3 and 5-He), 1.60 (dd, J=14.8 and 7.4 Hz, 1 H, 3-He), 1.80-1.95 (m, 1H, 6-Ha), 1.91 (s, 3H, NCH_3), 2.10-2.30 (m, 1H, 3-Ha), 2.36 (dd, J=12 and 7.4 Hz, 1H, 6-He), 2.50 (t, J=7 Hz, 1H, 6-Ha), 2.50-2.70 (m, 2H, CH_2CO), 3.70 (s, 3H, OCH_3), 3.96 (dd, J=8.5 and 4.3 Hz, 1H, 2-Ha), 6.75 (s, 1H, In-3H), 7.16-7.56 (m, 7H, Ar-H), 7.74 (br d, J=8 Hz, 1H, In-4H), 8.24 (d, J=8 Hz, 1H, In-7H); MS (m/z, %) 454 (M^+, 2), 313 (43), 198 (15), 183 (7), 168 (17), 130 (39), 115 (17), 77 (100), 42 (17). Anal. Calcd for $C_{25}H_{30}N_2O_4S.1/2\ H_2O$: C, 64.79; H, 6.69; N, 6.04. Found: C, 64.83; H, 6.68; N, 5.69.

Methyl 5-Ethyl-2-(2-indolyl)-1-methylpiperidine-4-acetates (11 and 12). A (2:1) mixture of piperidines **9** and **10** (1 g, 2.21 mmol), 10% aqueous NaOH (10 ml) and EtOH (100 ml) was refluxed for 15 h. The solution was neutralized (pH=6-7) with 10% aqueous HCl and evaporated to dryness. The residue was dissolved in CH_2Cl_2, filtered and the solvent was removed. The mixture of aminoacids thus obtained was reesterified with methanol in 4 N HCl (100 ml), at room temperature for 15 h. Methanol was evaporated, and the residue, solved in an

aqueous Na_2CO_3 solution (pH=8), was extracted with CH_2Cl_2. The organic extracts were dried and evaporated to yield a (2:1) mixture of **11** and **12** (0.5 g, 71%) after a flash chromatography purification (8:2 hexane-ethyl acetate); IR (NaCl) 3300 (NH), 1730 cm^{-1} (CO); ^{1}H-NMR 0.85 (t, J=7 Hz, CH_3CH$_2$), 1.95 and 2.10 (2 s, 3H each, NCH$_3$), 3.65 (br s, OCH$_3$), 6.35 (br s, In-3H), 7.00-7.50 (m, In-H), 8.50-9.00 (2 br s, 1 H each, In-NH); MS (m/z, %) 314 (M^+, 5), 312 (11), 258 (12), 210 (32), 180 (28), 143 (100), 130 (80), 115 (29), 89 (17), 77 (29), 42 (20). Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.6; H, 8.28; N, 8.91. Found: C, 72.10; H, 8.43; N, 8.52.

5-Ethyl-4-(2-hydroxyethyl)-2-(2-indolyl)-1-methylpiperidine (17 and 18). To a mixture of **9** and **10** (1.66 g, 3.65 mmol) in dry THF (100 ml), $LiAlH_4$ (0.6 g, 16.4 mmol) was added at 0°C under nitrogen atmosphere. The reaction mixture was refluxed for 4 h and poured over saturated aqueous sodium-potassium tartrate. The solution was extracted with CH_2Cl_2 the organic layer washed with aqueous 10% $NaHCO_3$, dried and evaporated, yielding a mixture of **17** and **18** (0.93 g, 90 %) which was separated by flash chromatography (99.5:0.5, Et_2O-DEA). Isomer **17** (higher Rf, 0.34 g, 44 %); ^{1}H-NMR 0.92 (t, J=7 Hz, CH$_2$CH_3), 1.20-1.45 (m, 1H, CH_ACH$_3$), 1.55-1.70 (m, 1H, CH_BCH$_3$), 1.80-2.00 (m, 4H, 4-H, 5-H and CH_2CH$_2$OH), 2.07 (s, 3H, NCH$_3$), 2.73 (dd, J=12 and 4 Hz, 1H, 6-He), 3.10 (br s, 1H, OH), 3.35 (dd, J=10 and 5 Hz, 1H, 2-Ha), 3.50-3.80 (m, 2H, CH_2OH), 6.30 (s, 1H, In-3H), 7.07 (t, J=7 Hz, In-5H), 7.12 (t, J=7 Hz, In-6H), 7.28 (d, J=7 Hz, 1H, In-7H), 7.52 (d, J=7 Hz, 1H, In-4H), 9.00 (br s, 1H, In-NH). Isomer **18** (lower Rf, 0.3 g, 38%): IR ($CHCl_3$) 3445 and 3400-3200 cm^{-1}; ^{1}H-NMR 0.90 (t, J=7 Hz, 3H, CH_3CH$_2$), 2.00 (s, 3H, NCH$_3$), 4.00-4.20 (m, 3H, OCH$_2$ and 2-Ha), 6.3 (s, 1H, In-3H), 6.9-7.5 (m, 1H, In-6H), 7.5-7.7 (m, 1H, In-4H), 8.65 (br s, 1H, In-NH); MS (m/z, %) 288 (M^+, 2), 284 (17), 258 (36), 210 (14), 170 (43), 158 (35), 143 (87), 130 (100), 117 (70), 90 (25), 77 (43). Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.46; H, 9.15; N, 9.78. Found: C, 75.02; H, 9.21; N,9.53.

5-Ethyl-4-(2-hydroxyethyl)-2-[3-(2-hydroxyethyl)-2-indolyl]-1-methylpiperidine (15 and 16). Method A: A mixture of piperidines **11** and **12** (0.3 g, 0.95 mmol) in dry CH_2Cl_2 (15 ml) was slowly added on a solution of oxalyl chloride (65 µl, 0.72 mmol) in dry CH_2Cl_2 (10 ml), at 0°C under nitrogen atmosphere. Stirring was maintained at room temperature for 3 h, and reflux for 1 h. Dichloromethane was evaporated, and the residue, was dissolved in absolute methanol (40 ml), was stirred overnight at room temperature. Methanol was removed under vacuum and the residue was treated with CH_2Cl_2 and aqueous Na_2CO_3. The layers were separated, and the aqueous fraction extracted with CH_2Cl_2 . The organic layers, dried and evaporated provided **methyl 5-ethyl-2-(3-methoxyoxalyl-2-indolyl)-1-methylpiperidine-4-acetates (13 and 14)** (0.2 g, 54%) after a flash chromatography purification (99:1 Et_2O-DEA); IR (NaCl) 3400 (NH), 1730 and 1640 cm^{-1} (CO); ^{1}H-NMR 0.90-1.10 (br t, J=7 Hz, 3H, CH$_2$CH_3), 2.10 (s, 3H, NCH$_3$), 2.30 (broad s, 2H, CH$_2$CO), 3.20 (dd, J= 14 and 2 Hz, 1H, 6-He), 3.60-3.90 (m, 1H, 2-Ha), 3.70 (s, 3H, CH$_2$COOCH_3), 4.00 (s, 3H, COCOOCH$_3$), 7.10-7.50 (m, 3H, In-H), 7.80-8.00 (m, 1H, In-4H), 8.80-9.00 (br s, 1H, NH); MS (m/e, %) 400 (M^+, 21), 369 (4), 340 (38), 311 (37), 267 (100), 239 (45), 149 (99), 130 (56), 115 (49).

To the mixture of **13** and **14** (80 mg, 0.2 mmol), in dry THF (20 ml), $LiAlH_4$ (70 mg, 1.8 mmol) was added at 0 °C under nitrogen atmosphere. The reaction mixture was refluxed for 4 h 30 min and poured over saturated aqueous sodium-potassium tartrate. The solution was extracted with CH_2Cl_2, the organic layer washed with aqueous 10%

$NaHCO_3$, dried and evaporated, yielding a (2:1) mixture of **15** and **16** (38 mg, 55 %) after flash chromatography purification (99.5:0.5 Et_2O-DEA); IR ($CHCl_3$) 3440 and 3500-3100 cm^{-1}; ^{1}H-NMR 0.90-1.10 (m, CH_2CH_3), 1.40-1.70 (m, CH_2CH_3 and 5-H), 2.00 and 2.15 (2 s, 3H each, NCH_3), 2.20-2.70 (m, CH_2CH_2OH and 4-H), 2.80-2.90 (t, J=7 Hz, In-CH2), 3.10 (br d, J=12 Hz, 6-He), 3.50-3.80 (m, CH_2OH and 3-H), 7.00-7.15 (m, Ar-H), 7.30 and 7.50 (2d, J=7 Hz, 1H each, In-4H), 9.05 and 9.10 (2 br s, 1H each, In-NH); MS (m/z, %) 330 (M^+, 5), 313 (4), 300 (4), 283 (7), 268 (5), 204 (6), 180 (8), 168 (16), 156 (31), 142 (18), 130 (17), 77 (11), 44 (100). Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.28; H, 9.34; N, 8.13.

Method B: Operating as for the preparation of **13** and **14**, from a mixture of piperidines **17** and **18** (130 mg, 0.45 mmol), oxalyl chloride (0.11 ml, 1.36 mmol), and dry CH_2Cl_2 (40 ml), **5-ethyl-4-(2-hydroxyethyl)-2-(3-methoxyoxalyl-2-indolyl)-1-methylpiperidines** (**19** and **20**; 0.1 g, 80%) were obtained; IR ($CHCl_3$) 1730 and 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.95 (t, J=7 Hz, 3H, CH_2CH_3), 1.20-1.40 (m, 1H, CH_ACH_3), 1.60-1.80 (m, 1H, CH_BCH_3), 1.80-2.10 (m, 4H, 3-H, 5-H and 6-Ha), 2.21 (s, 3H, NCH_3), 2.73 (dd, J=11.7 and 4 Hz, 1H, 6-He), 3.70-3.90 (m, 2H, CH_2OH), 4.30 (br d, J=11.7 Hz, 2-Ha), 7.20-7.30 (m, 2H, In-H), 7.40-7.50 (m, 1H, In-7H), 7.70-7.80 (m, 1H, In-4H). From a solution of **19** and **20** (0.1 g, 0.26 mmol) in dry THF (100 ml), and $LiAlH_4$ (90 mg, 2.3 mmol), **15** and **16** (26 mg, 30 %) were obtained, which were identified by comparison of the spectral data with those previously obtained.

5-Ethyl-2-(2-indolyl)-1-methyl-4-piperidone ethylene acetal (21). A solution of piperidine **3** (6.64 g, 15.1 mmol) in ethanol (400 ml) and aqueous 10% NaOH (75 ml) was refluxed for 12 h. The solvent was removed and the residue, dissolved in water, was extracted with CH_2Cl_2. The dried organic layer was evaporated and purified by flash chromatography (8:2 hexane-ethyl acetate), to give **21** (4.6 g, 70 %): IR (KBr) 3330 cm^{-1}; ^{1}H-NMR 0.94 (t, J=7 Hz, 3H, CH_3CH_2), 1.00-1.20 (m, 1H, CH_ACH_3), 1.60-1.80 (m, 1H, CH_BCH_3), 1.90-2.00 (m, 1H, 5-Ha), 1.92 (t, J=10.4 Hz, 1H, 3-Ha), 2.09 (s, 3H, NCH_3), 2.18 (t, J=11.6 Hz, 1H, 6-Ha), 3.04 (dd, J=11.6 and 4.3 Hz, 1H, 6-He), 3.40 (dd, J=10.4 and 4.6 Hz, 1H, 2-Ha), 3.94-4.05 (m, 4H, OCH_2), 6.35 (s, 1H, In-3H), 7.08 and 7.14 (2 t, J=8 Hz, 1H each, In-5H and In-6H), 7.32 (d, J=8 Hz, 1H, In-7H), 7.54 (d, J=8 Hz, 1H, In-4H), 8.40 (m, 1H, In-NH); MS (m/z, %) 300 (M^+, 26), 241 (13), 184 (12), 171 (45), 143 (100), 130 (54), 115 (48), 99 (35), 90 (16), 42 (22). The hydrochloride melted at 227-228 °C (Et_2O-acetone). Anal. Calcd for $C_{18}H_{25}N_2O_2Cl.1/2H_2O$: C, 62.50; H, 7.52; N, 8.10. Found: C, 62.58; H, 7.57; N, 8.02.

5-Ethyl-2-[3-(2-hydroxyethyl)-2-indolyl]-1-methyl-4-piperidone ethylene acetal (23). Operating as for the preparation of **13** and **14**, from oxalyl chloride (3.38 ml, 39.46 mmol), piperidine **21** (5.92 g, 19.73 mmol) in dry CH_2Cl_2 (60 ml) and then absolute methanol (50 ml) ***trans*-5-ethyl-2-(3-methoxyoxalyl-2-indolyl)-1-methyl-4-piperidone ethylene acetal (22)** was obtained, which was flash chromatographied (Et_2O) (3.60 g, 60 %); IR (NaCl) 3450, 1740 and 1640 cm^{-1}; ^{1}H-NMR 0.94 (t, J= 7 Hz, 3H, CH_2CH_3), 1.00-1.20 (m, 1H, CH_ACH_3), 1.60-1.80 (m, 1H, CH_BCH_3), 1.62 (t, J= 13 Hz, 1H, 3-Ha), 1.80-2.00 (m, 1H, 5-Ha), 2.14 (s, 3H, NCH_3), 2.18 (dd, J=13 and 3 Hz, 1H, 3-He), 2.27 (t, J=12 Hz, 1H, 6-Ha), 3.08 (dd, J=12 and 4 Hz, 1H, 6-He), 3.88 (dd, J=13 and 3 Hz, 1H, 2-Ha), 3.90-4.10 (m, 4H, OCH_2), 4.10 (s, 3H, OCH_3), 7.20-7.30 (m, 2H, In-5H and In-6H), 7.40 (dd, J=8 and 2 Hz, In-7H), 8.00 (dd, J= 8 and 2 Hz, 1H, In-4H); ^{13}C-NMR 11.9 (CH_2CH_3), 18.2 (CH_2CH_3), 41.1 (C-3), 43.6 (NCH_3),

45.1 (C-5), 52.6 (OCH_3), 58.7 (C-6), 59.5 (C-2), 64.8 and 65.1 (OCH_2), 107.6 (C-4), 111.7 (In-C7), 113.1 (In-C3), 121.0 (In-C4), 123.0 (In-C5), 123.9 (In-C6), 126.3 (In-C3a), 135.2 (In-C7a), 149.6 (In-C2), 166.3 (*C*OOMe), 203.0 (*C*OCOOMe); MS (m/z, %) 386 (M^+, 15), 326 (21), 225 (25), 213 (57), 184 (75), 170 (65), 142 (46), 127 (68), 115 (84), 99 (100), 86 (90), 70 (49), 42 (48).

Operating as for the preparation of **15** and **16**, from piperidine **22** (7.67 g, 19.87 mmol), $LiAlH_4$ (6.78 g, 178 mmol) and dry THF (300 ml), piperidine **23** was obtained, which was purified by flash chromatography (95:5 Et_2O-DEA) (3.5 g, 53%): mp 147-150°C (Et_2O-acetone); IR (NaCl) 3500-3100 cm^{-1}; ^{1}H-NMR 0.94 (t, *J*=7 Hz, 3H, CH_3CH_2), 1.00-1.20 (m, 1H, CH_ACH_3), 1.60-1.80 (m, 1H, CH_BCH_3), 1.80-2.00 (m, 1H, 5-Ha), 2.07 (s, 3H, NCH_3), 2.23 (t, *J*= 11 Hz, 3-Ha), 3.03 (t, *J*=8 Hz, 1H, $InCH_2$), 3.06 (dd, *J*=8 and 4 Hz, 1H, 6-He), 3.58 (dd, *J*=11 and 4.8 Hz, 1H, 2-Ha), 3.87 (t, *J*=6 Hz, 2H, CH_2CH_2OH), 3.92-3.97 (m, 4H, OCH_2), 7.00-7.20 (m, 2H, In-5H and In-6H), 7.30 (dd, *J*=7 and 1 Hz, 1H, In-7H), 7.55 (dd, *J*=7 and 1 Hz, 1H, In-4H), 8.65-8.72 (br s, 1H, In-NH); MS (m/z, %) 344 (M^+, 7), 314 (8), 283 (10), 227 (15), 183 (19), 156 (56), 127 (22), 115 (100), 99 (20), 86 (31), 70 (30), 42 (17). Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.83; H, 8.20; N, 8.14. Found: C, 69.64; H, 8.21; N, 8.06.

5-Ethyl-2-[3-(2-hydroxyethyl)-2-indolyl]-1-methyl-4-piperidone (24). Operating as for the preparation of **5** and **6**, from piperidine **23** (2.37 g, 6.88 mmol), ethanol (25 ml), and 4*N* HCl (150 ml), piperidone **24** was obtained. After flash chromatography (92:8 Et_2O-DEA) pure *trans*-**24** was isolated (1.76 g, 75 %): IR (NaCl) 3500-3200 and 1710 cm^{-1}; ^{1}H-NMR 0.96 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.10-1.20 (m, 1H, CH_ACH_3), 1.80-2.00 (m, 1H, CH_BCH_3), 2.14 (s, 3H, NCH_3), 2.22 (dd, *J*=12 and 10.4 Hz, 1H, 3-Ha), 2.49 (dd, *J*=12 and 3 Hz, 1H, 3-He), 2.60-2.80 (m, 1H, 5-Ha), 2.80 (t, *J*=12 Hz, 1H, 6-Ha), 2.99 (t, J=7 Hz, 2H, $InCH_2$), 3.30 (dd, *J*=12 and 6 Hz, 1H, 6-He), 3.66 (dd, *J*=10.4 and 3 Hz, 1H, 2-Ha), 3.80-4.00 (m, 2H, CH_2CH_2OH), 7.05-7.25 (m, 2H, In-5H and In-6H), 7.35 (dd, *J*=7 and 1 Hz, 1H, In-4H), 7.55 (dd, *J*=7 and 1 Hz, 1H, In-7H), 8.60 (br s, 1H, In-NH); MS (m/z, %) 300 (M^+, 18), 257 (9), 215 (32), 187 (22), 183 (56), 172 (18), 168 (24), 156 (100), 154 (23), 144 (23), 130 (29), 115 (30), 86 (12), 70 (29), 42 (22). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 72.06; H, 8.06; N, 9.30. Found: C, 72.23; H, 8.14; N, 9.55. The hydrochloride melted at 177-180 °C (acetone): ^{1}H-NMR 1.01 (t, *J*= 7Hz, 3H, CH_2CH_3), 1.20-1.50 (m, 1H, CH_ACH_3), 1.80-2.00 (m, 1H, CH_BCH_3), 2.71 (d, *J*= 4 Hz, 3H, NCH_3), 2.80 (dd, *J*= 13 and 2.5 Hz, 1H, 3-He), 2.90-3.00 (m, 2H, $InCH_2$), 3.10 (m, 1H, 6-Ha), 3.40-3.60 (m, 1H, 6-He), 3.70-4.00 (m, 2H, CH_2OH), 4.85 (br t, *J*= 12 Hz, 1H, 2-Ha), 7.13 (ddd, *J*= 8, 7, and 1 Hz, 1H, In-5H), 7.27 (td, *J*= 7 and 1 Hz, 1H, In-6H), 7.49 (d, *J*= 8 Hz, 1H, In-4H), 7.54 (br d, *J*= 7 Hz, 1H, In-7H), 10.8 (br s, 1H, NH).

Ethyl 5-Ethyl-2-[3-(2-hydroxyethyl)-2-indolyl]-1-methylpiperidine-$\Delta^{4,\alpha}$-acetate (25). Operating as for the preparation of **8**, from NaH (243 mg, 5.59 mmol), diethyl ethoxycarbonylmethylphosphonate[8] (1.38 g, 6.17 mmol), dry DME (40 ml), and piperidone **24** (1.46 g, 4.86 mmol), a 3:1 mixture of (*E*)- and (*Z*)-**25** which was separated by flash chromatography (90:10 Et_2O-DEA). (*E*)-**25** (Higher Rf; 1.19 g, 66 %): IR ($CHCl_3$) 3430, 3300-3200, 1720 and 1650 cm^{-1}; ^{1}H-NMR 1.00 (t, *J*=7Hz, 3H, CH_2CH_3), 1.20-1.40 (m, 1H, CH_ACH_3), 1.60-1.80 (m, 1H, CH_BCH_3), 1.25 (t, *J*=7 Hz, 3H, OCH_2CH_3), 1.93 (t, *J*=12 Hz, 1H, 3-Ha), 2.07 (s, 3H, NCH_3), 3.00 (m, 2H, $InCH_2$), 3.22 (dd, *J*=11.2 and 4.2 Hz, 1H, 6-He), 3.42 (dd, *J*=12 and 2.8 Hz, 1H, 3-He), 3.85 (m, 2H, CH_2OH), 4.10 (q, *J*=7 Hz, 2H, $COOCH_2CH_3$), 4.20 (dd, *J*=12 and 2.8 Hz, 1H, 2-Ha), 5.65 (s, 1H, =CH), 7.00-7.20 (m, 2H, In-5H and

In-6H), 7.30 (br d, J=7 Hz, 1H, In-7H),7.55 (br d, J=7 Hz, 1H, In-4H), 8.60 (br s, 1H, In-NH). (*Z*)-**25** (Lower Rf; 397 mg, 22 %): IR ($CHCl_3$) 3430, 3340, 1720 cm^{-1}; ^{1}H-NMR 0.97 (t, J=7 Hz, 3H, CH_2CH_3), 2.18 (s, 3H, NCH_3), 3.83 (t, J=7 Hz, 2H, CH_2OH), 4.12 (q, J=7Hz, 2H, $COOCH_2$), 5.45 (s, 1H, =CH), 7.00-7.20 (m, 2H, In-6H and In-5H), 7.31 (br d, J=7 Hz, 1H, In-7H), 7.60 (d, J=7 Hz, 1H, In-4H), 8.80 (br s, 1H, In-NH); MS (m/z, %) 370 (M^+, 11), 325 (8), 296 (12), 283 (16), 208 (23), 180 (30), 144 (30), 130 (36), 115 (17), 77 (27), 44 (91), 42 (100). Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.09; H, 8.43 N, 7.23.

Ethyl 5-Ethyl-2-[3-(2-hydroxyethyl)-2-indolyl]-1-methylpiperidine-4-acetate (26 and 27). Operating as for the preparation of **9** and **10**, from **25** (2.01 g, 5.43 mmol), PtO_2 (200 mg) and absolute ethanol (50 ml), a 1:3 epimeric mixture of **26** and **27** was obtained, which was separated by flash chromatography (99:1 Et_2O-DEA). **27** (Higher Rf; 1.2 g, 61 %): IR ($CHCl_3$) 3460, 3400-3200 and 1720 cm^{-1};^{1}H-NMR 0.97 (br t, J=7 Hz, 3H, CH_2CH_3), 1.28 (t, J= 7 Hz, 3H, $COOCH_2CH_3$), 1.50-1.90 (m, 3H, 5-H and CH_2CH_3), 2.07 (s, 3H, NCH_3), 2.10-2.30 (m, 2H, CH_2CO), 3.03 (br t, J=7 Hz, $InCH_2$), 3.10 (dd, J=13 and 2.5 Hz, 1H, 6-He), 3.30 (m, 1H, 2-Ha), 3.80 (t, J=7 Hz, 2H, CH_2OH), 4.12 (q, J=7 Hz, 2H, $COOCH_2$), 7.07 (t, J=7 Hz, 1H, In-5H), 7.14 (t, J=7 Hz, 1H, In-6H), 7.32 (d, J=7 Hz, In-7H), 7.54 (d, J=7 Hz, 1H, In-4H), 8.85 (br s, 1H, In-NH); MS (m/z, %) 372 (M^+, 20), 354 (37), 310 (16), 267 (21), 253 (10), 212 (22), 184 (15), 168 (39), 156 (94), 130 (15), 115 (20), 86 (27), 70 (20), 42 (10).**26** (Lower Rf, 450 mg, 20 %): IR ($CHCl_3$) 3460, 3400-3200 and 1720 cm^{-1}; ^{1}H-NMR 0.98 (t, J= 7 Hz, 3H, CH_2CH_3), 1.30 (t, J=7 Hz, 3H, $COOCH_2CH_3$), 1.90-2.10 (m, 2H, CH_2COO), 2.01 (s, 3H, NCH_3), 2.20 (t, J=12 Hz, 1H, 3-Ha), 2.60 (dd, J=12 and 4 Hz, 1H, 3-He), 3.05 (t, J=7 Hz, 2H, $InCH_2$), 3.07 (dd, J=12 and 3 Hz, 1H, 6-He), 3.35 (br d, J=12 Hz, 1H, 2-Ha), 3.83 (t, J=7 Hz, CH_2OH), 7.07 (t, J=7 Hz, 1H, In-5H), 7.14 (t, J=7 Hz, 1H, In-6H), 7.32 (d, J=7 Hz, 1H, In-7H), 7.54 (d, J=7 Hz, 1H, In-4H), 8.40 (br s, 1H, In-NH); MS (m/z, %) 372 (M^+, 20), 354 (37), 310 (16), 267 (21), 212 (22), 168 (39), 156 (94), 115 (20), 86 (27), 70 (20). Anal. Calcd for $C_{22}H_{32}N_2O_3$: 70.94; H, 8.66; N, 7.52. Found: C, 70.54; H, 8.97; N, 7.33.

5-Ethyl-4-(2-hydroxyethyl)-2-[3-(2-hydroxyethyl)-2-indolyl]-1-methylpiperidine [guettardine (1) and 15-epiguettardine (28)]. Operating as for the preparation of **17** and **18**, from a solution of piperidines **26** and **27** (1.41 g, 3.7 mmol) in dry THF (100 ml), and $LiAlH_4$ (1.3 g, 33.4 mmol) a 4:1 mixture of compounds **28** and **1**, respectively, was obtained, which was separated by flash chromatography (98:2 to 90:10 Et_2O-DEA). **28** (Higher Rf, 0.4 g, 32 %): IR ($CHCl_3$) 3440 and 3500-3100 cm^{-1}; ^{1}H-NMR 1.00 (t, J=7 Hz, 3H, CH_2CH_3), 1.20-1.90 (m, 5H , CH_2CH_2OH, CH_2CH_3, and 4-H)), 2.08 (s, 3H, NCH_3), 2.95-3.05 (m, 2H, In-CH_2), 3.17 (br d, J= 12 Hz, 6-He), 3.30 (br d, J=12 Hz, 2-Ha), 3.65 (t, J=7 Hz, 2H, CH_2OH), 3.85 (m, 2H, CH_2OH), 7.08 (d, J=7 Hz, 1H, In-5H), 7.17 (t, J=7 Hz, 1H, In-6H), 7.35 (d, J=7 Hz, 1H, In-7H), 7.55 (d, J=7 Hz, 1H, In-4H). The hydrochloride of **28** melted at 218-220 °C (acetone); IR (KBr) 3420, 3240, 2800-2500 and 1460 cm^{-1}; ^{1}H-NMR 1.08 (t, J= 7 Hz, 3H, CH_2CH_3), 1.50-1.70 (m, 1H, CH_ACH_3), 1.70-1.80 (m, 1H, CH_BCH_3), 2.10-2.40 (m, 4H, 5-Ha, 4-Ha and CH_2CH_2OH), 2.65 (s, 3H, NCH_3), 3.00 (t, J= 7 Hz, 3H, $InCH_2$), 3.25 (br d, J= 13 Hz, 6-He), 3.62 (t, J= 7 Hz, 2H, CH_2OH), 3.70-3.90 (m, 2H, CH_2OH), 4.50 (m, 1H, 2-Ha), 7.10 (t, J= 7 Hz, 1H, In-5H), 7.20 (t, J= 7 Hz, 1H, In-6H), 7.48 (d, J= 7 Hz, 1H, In-7H), 7.52 (d, J= 7 Hz, 1H, In-4H); MS (m/z, %) 330 (M^+, 5), 313 (4), 300 (3), 283 (7), 268 (5), 204 (6), 180 (8), 168 (16), 156 (31), 142 (18), 130 (17), 77 (11), 44 (100). Anal. Calcd for $C_{20}H_{31}ClNO_2$:

C, 62.41; H, 8.06; N, 7.28. Found: C, 62.63; H, 8.11; N, 7.00. **1** (lower Rf; 0.1 g, 8 %) was identified by comparison of its spectral data with those of the natural product.[4] ^{1}H-NMR 0.99 (t, J=7 Hz, 3H, CH_2CH_3), 1.20-1.80 (m, 5H, CH_2CH_2OH, CH_2CH_3, and 4-H), 2.05 (s, 3H, NCH_3), 3.01 (br t, J=7 Hz, 2H, $InCH_2$), 3.05 (dd, J=12 and 2 Hz, 1H, 6-He), 3.25 (m, 1H, 2-Ha), 3.63 (t, J=7 Hz, 2H, CH_2OH), 3.80 (br t, J=7 Hz, 2H, CH_2OH), 7.08 (t, J=7 Hz, 1H, In-5H), 7.17 (t, J=7 Hz, 1H, In-6H), 7.34 (d, J=7 Hz, In-7H), 7, 54 (d, J=7 Hz, 1H, In-4H), 8.40-8.60 (br s, 1H, In-NH).

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