

APPLICATION OF THE MERCURIC ACETATE-EDETIC ACID OXIDATION METHOD TO THE SYNTHESIS OF 11-AZA-1,2,3,4,5,6,7,12b-OCTAHYDROINDOLO[2,3-*a*]QUINOLIZINES

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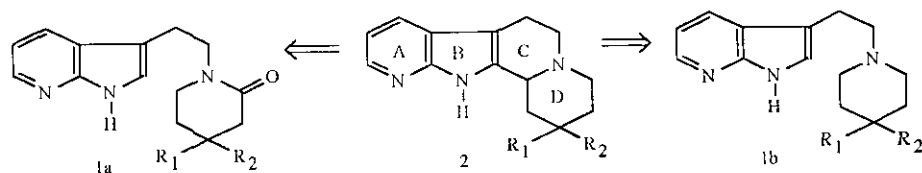
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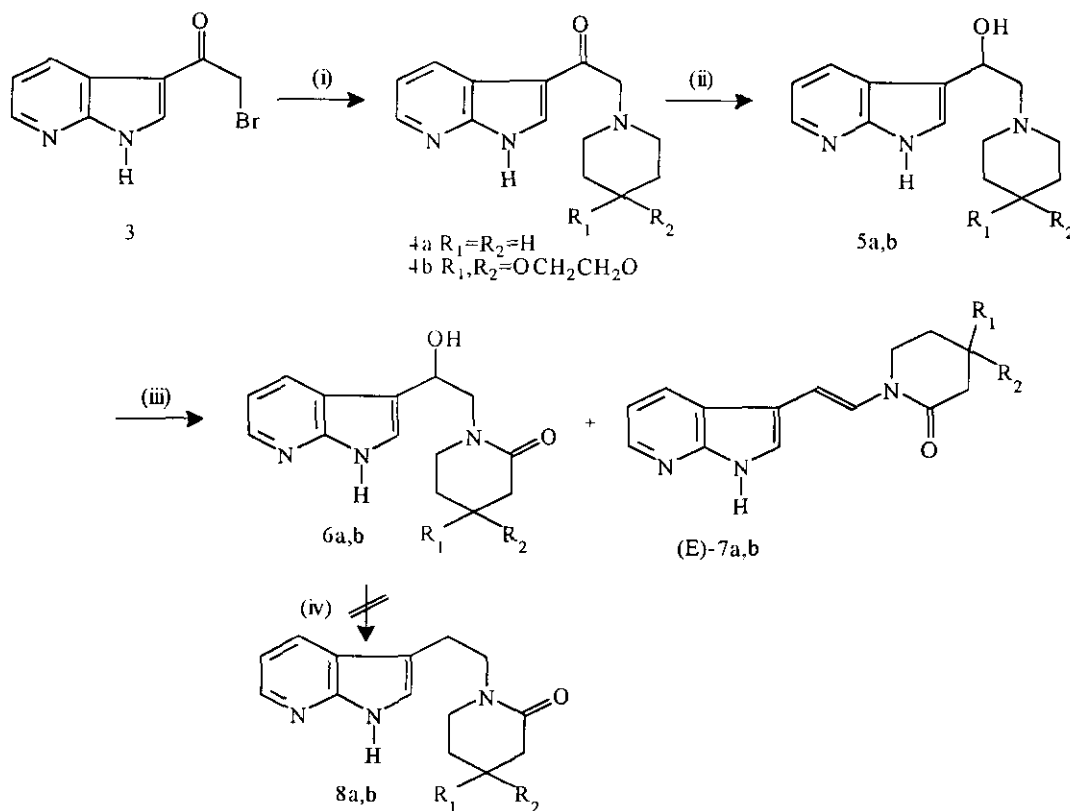
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Abstract- The synthesis of 11-azaindolo[2,3-*a*]quinolizidines such as **2** is reported by cyclisation of lactams (**1a**) or piperidines (**1b**).

Interest in the indolo[2,3-*a*]quinolizidine ring system has increased these last years since this tetracycle is implicated in the synthesis of biological active compounds belonging to the *Yohimban* and *Eburnan* families of indole alkaloids.¹ In addition, number of 2-substituted indoloquinolizidines have been found to be some potent and selective antagonists of α_2 -adrenoreceptors.² As a part of our studies concerning the chemistry of azaindolic structures,³ we developed now a program for the preparation of azaindoloquinolizidine system such as **2**. In this optic, key step was the formation of the C12a-C12b bond. For this purpose two "routes" were investigated: preparation and cyclization of lactams types (**1a**) through a Bischler-Napieralski reaction,⁴ or preparation and cyclization of piperidines types (**1b**) through a "mercuric acetate-edetic acid" procedure.⁵



Our first investigation was to prepare the lactams (**8a,b**). Synthesis of starting 3-bromoacetylazaindole (**3**) was achieved according published methods.⁶ Treatment of **3** with appropriate piperidines yielded the ketones (**4a,b**) which upon a lithium aluminium hydride reduction gave the corresponding alcohols (**5a,b**). Treatment of these two alcohols with mercuric acetate to generate the lactams (**6a,b**) according the Fujii procedure⁷ led to the expected compounds. Presence of the lactam function was made evident by ¹³C-nmr with a carbonyl group at δ 172.1 for **6a** and at δ 169.4 for **6b**. In contrast with previous results obtained by Fujii,^{4,7} no oxazolidine formation was found, but the unsaturated lactams (**7a,b**) were respectively obtained with appreciable amounts. The E-configuration was found in respect to their coupling constant ($J_{1,2}$ = 15.4 Hz for **7a**, and 15.3 Hz for **7b**). Surprisingly, all attempts to reduce the alcohols (**6a,b**) to give **8a,b** failed under various conditions of catalytic hydrogenation (Scheme 1).

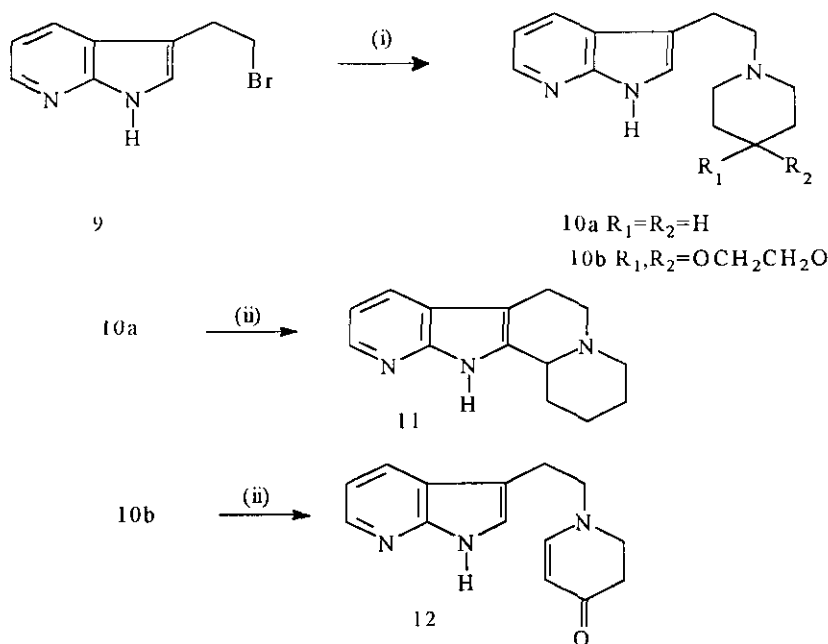


reagents and conditions: (i) piperidines/MeCN/Et₃N/reflux (ii) LiAlH₄/THF/0°C 30 min, 20°C, 2 h (iii) Hg(OAc)₂/EDTA/2N NaOH/reflux (iv) H₂, Pd-C

Scheme 1

This disappointing result led us to investigate the second route starting from 3-bromoethylazaindole (**9**) obtained by reduction of **3**.⁶ Treatment of **9** with appropriate piperidines gave the derivatives (**10a,b**) in good yield. The expected azaindoloquinolizidine (**11**) was obtained when **10a** was treated by mercuric

acetate. Structural determination of **11** was based on ^1H and ^{13}C spectra, ^1H - ^1H , and ^1H - ^{13}C correlations. The *trans* relationship between C and D rings was made evident by the presence of a double doublet in the ^1H -nmr spectra at δ 3.30 for H-12b ($J_{12b-1ax} = 10.7$ Hz and $J_{12b-1eq} = 1.7$ Hz) and by the signals of C-6 and C-4 at δ 53.4 and 55.9 respectively.⁸ Bolhmann bands at $\nu = 2760$ and 2800 cm^{-1} in the infrared spectrum confirmed this analysis.⁹ In contrast, compound (**10b**) treated in the same conditions gave the 2,3-dihydropyridone (**12**). The structure of **12** was easily determined by ^1H and ^{13}C -nmr: ^1H spectra showed two doublets ($J = 7.3$ Hz) at δ 4.81 and 6.80 corresponding to H-5 and H-6, while the ^{13}C -nmr spectrum showed characteristic resonances of such pyridone with δ 97.6 for C-6, δ 154.1 for C-5 and δ 191.2 for the carbonyl group. In attempt the cyclization of **12** into corresponding azaindoloquinolizidinone, we tried divers acidic conditions described for the indolic structure¹⁰ (sulfuric, hydrobromic or trifluoroacetic acids) : in all cases, starting material was recovered (Scheme 2).

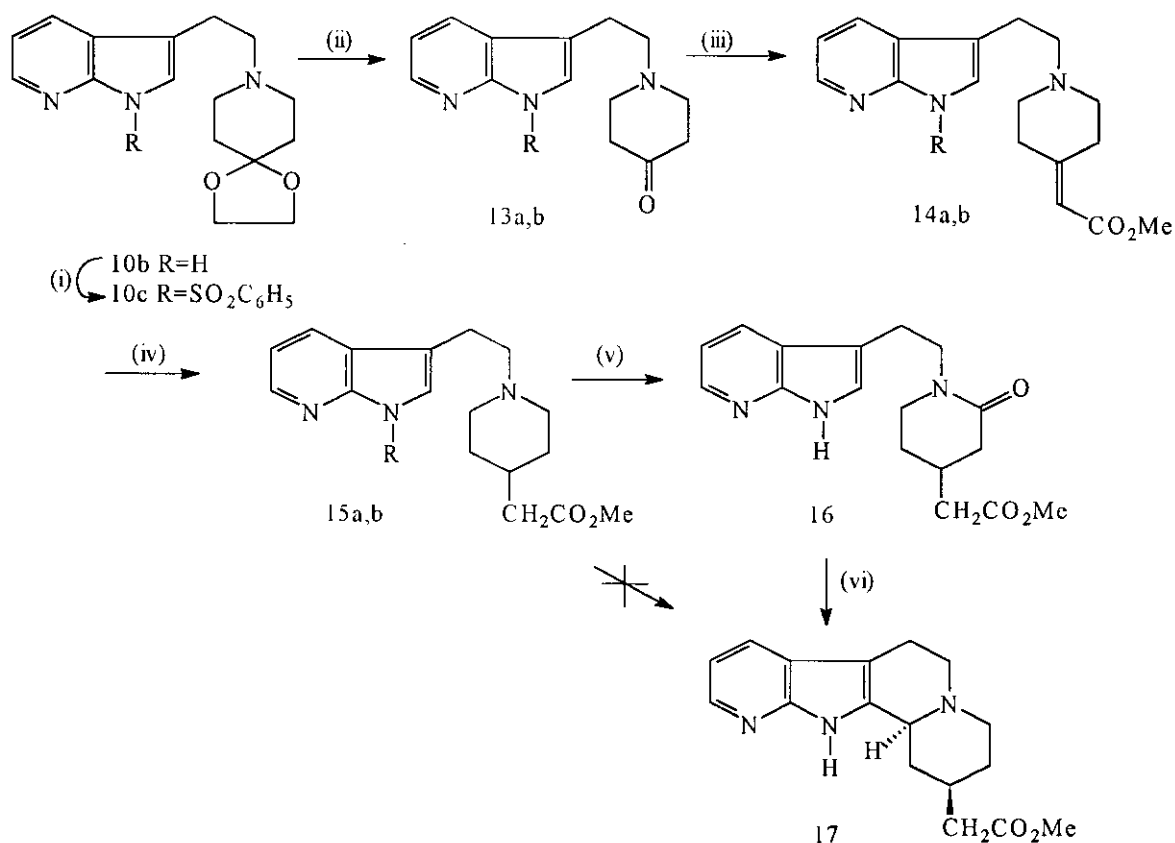


reagents and conditions: (i) piperidines/ $\text{MeCN}/\text{NaHCO}_3/\text{reflux}$
 (ii) a: $\text{Hg}(\text{OAc})_2/\text{EDTA}/\text{H}_2\text{O}, \text{EtOH}$ (2/1) reflux, b: NaBH_4

Scheme 2

From these results, and in our course for the obtention of 2-substituted azaindoloquinolizidines, we have turned our interest to the intramolecular cyclisation of piperidine (**15a,b**). Deprotection of the dioxolane (**10b,c**) under acidic conditions gave the piperidones (**13a,b**) in 95% and 45% yields, respectively. Subsequent Wittig reaction gave **14a,b** in 61% and 39% yields.¹¹ Structural determination of these two last was made by ^{13}C -nmr spectrum with $\delta_{\text{C-4}}$ 159.3 for **14a** and 159.2 for **14b**, $\delta_{\text{C}\alpha}$ 113.3 for **14a** and

113.6 for **14b** and by ^1H -nmr with the exocyclic ethylene proton at δ 5.71 for **14a** and δ 5.68 for **14b**. Catalytic hydrogenation of **14a,b** gave quantitatively the expected piperidines (**15a,b**). The piperidine (**15a**) was unreactive in the conditions cited above ($\text{Hg}(\text{OAc})_2$, 3 eq.), and starting material was recovered, while **15b** led to tar formation. Using 5 equivalent of mercuric acetate, we were able to isolate the lactam (**16**) in 42% yield from **15a**. Structure of **16** was made evident by ^{13}C -nmr with δ 172.1 for the lactam function. Further treatment of **16** with phosphorus oxychloride in refluxed toluene followed by sodium borohydride gave the expected 2-substituted azaindoloquinolizidine (**17**) (Scheme 3).

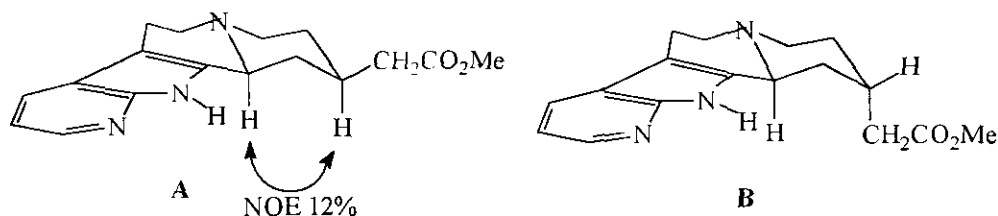


reagents and conditions: (i) a: $\text{BuLi}/\text{THF}/-78^\circ\text{C}$, b: $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$, 2 h, 20°C (ii) 6N HCl/reflux , 6 h (iii) $(\text{C}_6\text{H}_5)_3\text{P}=\text{CHCO}_2\text{Me}/\text{C}_6\text{H}_6/\text{reflux}$ (iv) $\text{H}_2/10\% \text{Pd-C}/\text{MeOH}/1 \text{ atm}$ (v) $\text{Hg}(\text{OAc})_2/\text{EDTA}/\text{H}_2\text{O}, \text{EtOH}(2/1)$ (vi) a: $\text{POCl}_3/\text{toluene}/\text{reflux}$ b: NaBH_4

Scheme 3

Compound (**17**) was isolated as a single diastereoisomer. Determination of the stereochemistry to the C-D *trans*, H12b-H2 *cis* isomer (**A**) was based on its spectral data (ir, ^1H , ^{13}C , ^1H - ^1H and ^1H - ^{13}C correlations). From the ir spectrum, the *trans* relationship between the C and D rings was found by the

presence of the Bolhmann bands at $\nu = 2800$ and 2760 cm^{-1} , and by ^1H -nmr with H-12b at δ 3.39 as a double doublet. The axial position of H-2 was determined by examination of the ^1H - ^1H COSY spectrum which showed H-3ax as a double quadruplet with $J_{3\text{ax}-2\text{ax}} = 12.5\text{ Hz}$. Examination of the ^{13}C -nmr spectrum confirmed this elucidation with C-2 at δ 33.2 as a tertiary carbon. This value is in good agreement with those observed in the 2-substituted octahydroindolo[2,3-*a*]quinolizidines ($\delta_{\text{C-2}}$ (H-2/H-12b *cis*) $31.1 > \delta_{\text{C-2}}$ (H-2/H-12b *trans*) 25.8 when R = methyl).¹² In addition, a NOE experiment clearly indicated this *cis* relationship with a NOE effect of 12% between H-12b_{ax} and H-2_{ax}.



In conclusion, we have described a useful synthesis of 2-substituted azaindoloquinolizidine (17). Influence of the 7-azaindoly on the reactivity of starting piperidines (9,10,12,15) and lactams (6,7) is found to be quite different from those observed for indolyl or phenyl substrates.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Spectral measurements were taken using the following instruments: ^1H and ^{13}C -nmr spectrum were taken on a Brüker AC-100 or a Brüker AC-400; chemical shifts are expressed in ppm downfield δ from TMS. Coupling constants, J , are given in Hz. Mass spectroscopy were recorded on a LKB 2091 spectrometer at 15 eV [$(\theta_{\text{source}}) = 180^\circ\text{C}$] or JEOL DX 300 (FAB). Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier. Possible inversion of two values in the ^{13}C -nmr spectra is expressed by an asterisk.

Procedure for condensations of piperidines with 3-bromoacetylindole (3). A mixture of 5.05 mmol of the appropriate piperidine, 4 mmol of the halogeno derivative, 1.4 g (10.1 mmol) of potassium carbonate in 100 ml of toluene was stirred at reflux for 2 h under a nitrogen stream. After cooling, water (100 ml) was added and the mixture extracted with dichloromethane. Organic layers were dried over sodium sulfate and evaporated *under vacuo*. All compounds were purified by column chromatography on silica gel eluted with dichloromethane.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl]piperidine (4a). Obtained from piperidine and 3; yield

90%; mp 157-159°C (recrystallization solvent: ether); ^1H -nmr (CDCl_3 , 100 MHz) δ 1.51 (m, 6H, H-3,4,5), 2.46 (m, 4H, H-2,6), 3.52 (s, H-1'), 7.18 (dd, $J_{4',5'} = 7.4$, $J_{5',6'} = 4.8$, H-5'), 8.32 (d, $J_{5',6'} = 4.8$, H-6'), 8.50 (s, H-2''), 8.66 (d, $J_{4',5'} = 7.4$, H-4''), 12.76 (s, NH); ^{13}C -nmr (CDCl_3 , 25 MHz) δ 24.0 (C-4), 26.9 (C-3,5), 55.0 (C-2,6), 67.5 (C-1'), 115.0 (C-3''), 118.4 (C-5''), 119.4 (C-3a''), 131.8 (C-2''*), 133.4 (C-4''*), 143.5 (C-6''), 148.9 (C-7a''), 193.8 (CO); *Anal.* Calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}$: C, 69.11; H, 7.04; N, 17.27. Found : C, 69.02; H 4.16; N, 17.19.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl]piperidine-4-ethylene ketal (4b). obtained from 1,4-dioxo-8-azaspiro[4,5]decane and 3; yield 95%; mp 180-182°C (recrystallization solvent: ether); ^1H -nmr (CDCl_3 , 100 MHz) δ 1.83 (m, H-3,5), 2.68 (m, H-2,6), 3.69 (s, 2H, H-1'), 3.95 (s, 4H, -OCH₂CH₂O-), 7.27 (dd, $J_{5',6'} = 4.1$, $J_{4',5'} = 6.9$, H-5''), 8.41 (d, $J_{5',6'} = 4.1$, H-6''), 8.44 (s, H-2''), 8.72 (d, $J_{4',5'} = 6.9$, H-4'') 13.11 (s, NH); ^{13}C -nmr (CDCl_3 , 25 MHz) δ 35.2 (C-3,5), 52.5 (C-2,6), 64.8 (-OCH₂CH₂O-), 66.6 (C-1'), 107.7 (C-4), 115.9 (C-3''), 119.4 (C-5''), 120.4 (C-3a''), 132.8 (C-4''), 134.1 (C-2''), 144.7 (C-6''), 148.8 (C-7a''), 195.5 (CO); *Anal.* Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_3$: C, 63.77; H, 6.36; N, 13.94. Found : C, 63.68; H 6.31; N, 13.99.

Procedure for the reduction of 4a,b. To a cooled solution of lithium aluminium hydride (0.55 g, 14.4 mmol) in 10 ml of THF was slowly added a solution of ketone (2 mmol) in 30 ml of THF. The resulting mixture was stirred at 0°C for 30 min, then at room temperature for 2 h. The mixture was diluted with 5 ml of water and made basic with 15% NaOH. After extraction with dichloromethane and evaporation of solvents, the compounds were chromatographed on neutral alumina eluted with dichloromethane.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]piperidine (5a). Yield 82%; mp 140-142°C (recrystallization solvent: dichloromethane); ms (*m/z*, relative intensity) 245 (7), 227 (44), 147 (12), 98 (100); ^1H -nmr (CDCl_3 , 100 MHz) δ 1.49 (m, 6H, H-3,4,5), 2.28-2.86 (m, 6H, H-2,6,1'), 5.02 (dd, $J = 10.0$ and 3.6 , H-2'), 5.49 (s, OH), 6.92 (dd, $J_{4',5'} = 7.8$, $J_{5',6'} = 4.7$, H-5''), 7.22 (s, H-2''), 7.99 (d, $J_{4',5'} = 7.8$, H-4''), 8.16 (d, $J_{5',6'} = 4.7$, H-6''), 11.89 (s, NH); *Anal.* Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}$: C, 68.54; H, 7.81; N, 17.13. Found : C, 68.49; H 7.76; N, 17.04.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]piperidine-4-ethylene ketal (5b). Yield 97%; mp 150-152°C (recrystallization solvent: dichloromethane); ^1H -nmr (CDCl_3 , 100 MHz) δ 1.80 (m, 4H, H-3,5), 2.59-3.10 (m, 6H, H-2,6, H-1'), 5.04 (dd, $J = 9.5$ and 2.7 Hz, H-2'), 7.07 (dd, $J_{4',5'} = 6.9$, $J_{5',6'} = 4.2$, H-5''), 7.32 (s, H-2''), 8.07 (d, $J_{4',5'} = 6.9$, H-4''), 8.30 (d, $J_{5',6'} = 4.2$, H-6''), 10.86 (s, NH); ^{13}C -nmr (CDCl_3 , 25 MHz) δ 34.9 (C-3,5), 51.4 (C-2,6), 63.8 (C-2'), 64.3 (C-1',

OCH₂CH₂O), 107.0 (C-4), 115.2 (C-3''), 115.5 (C-5''), 118.9 (C-3a''), 122.5 (C-2''), 128.4 (C-4''), 142.6 (C-6''), 149.2 (C-7a''); *Anal.* Calcd for C₁₆H₂₁N₃O₃: C, 63.35; H, 6.98; N, 13.85. Found : C, 63.23; H 7.12; N, 13.78.

Mercuric acetate/EDTA oxidation of 5a,b. A solution of alcohol (5a,b) (2 mmol), EDTA·2H₂O (1.9 g, 5 mmol), Hg(OAc)₂ (1.6 g, 5 mmol), in 12 ml of 1N NaOH was refluxed for 3 h. After being cooled and basified (pH=11), the mixture was extracted with dichloromethane. Organic layers were washed with 10% HCl, dried over sodium sulfate and concentrated *under vacuo*.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]-2-piperidone (6a) and 1-[2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)vinyl]-2-piperidone (7a). Purification of the crude product on silica gel eluted with dichloromethane gave first 6a as an oil; yield 53%; ¹H-nmr (CDCl₃, 100 MHz) δ 1.58 (m, 4H, H-4,5), 2.33 (m, 2H, H-3), 3.10 (m, 2H, H-6), 3.47-3.93 (m, 2H, H-1'), 4.81 (s, OH), 5.27 (m, H-2'), 6.95 (dd, J_{4'',5''} = 7.9, J_{5'',6''} = 4.2, H-5''), 7.25 (s, H-2''), 8.03 (d, J_{4'',5''} = 7.9, H-4''), 8.16 (d, J_{5'',6''} = 4.2, H-6''), 11.31 (s, NH); ¹³C-nmr (CDCl₃, 25 MHz) δ 20.9 (C-4), 23.0 (C-5), 32.1 (C-3), 50.2 (C-6), 55.9 (C-1'), 67.2 (C-2'), 115.5 (C-3''), 116.0 (C-5''), 118.6 (C-3a''), 122.5 (C-2''), 128.3 (C-4''), 142.5 (C-6''), 148.8 (C-7a''), 172.1 (CO). *Anal.* Calcd for C₁₄H₁₇N₃O₂: C, 64.85; H, 6.61; N, 16.20. Found : C, 64.92; H 6.59; N, 16.11. Further elution gave 7a as an oil; yield 12%; ¹H-nmr (CDCl₃, 100 MHz) δ 1.89 (m, H-4,5), 2.54 (t, J = 6.2, H-6), 3.57 (t, J = 5.2, H-3), 6.11 (d, J_{1',2'} = 15.4, H-2'), 7.12 (dd, J_{4'',5''} = 7.6, J_{5'',6''} = 4.7, H-5''), 7.32 (s, H-2''), 8.09-8.32 (m, 3H, H-1',4'',6''), 10.05 (s, NH); *Anal.* Calcd for C₁₄H₁₅N₃O: C, 69.69; H, 6.27; N, 17.41. Found : C, 69.80; H 6.14; N, 17.36.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]-2-piperidone-4-ethylene ketal (6b) and 1-[2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)vinyl]-2-piperidone-4-ethylene ketal (7b). Purification of the crude product on silica gel eluted with dichloromethane gave first 6b; 25%; mp 91-93°C (recrystallization solvent: dichloromethane); ¹H-nmr (CDCl₃, 100 MHz) δ 1.72 (m, 2H, H-5), 2.57 (br s, 2H, H-3), 3.23 (m, 2H, H-6), 3.50-4.00 (m, 6H, H-1', OCH₂CH₂O), 5.24 (m, H-2'), 6.94 (dd, J_{4'',5''} = 6.9, J_{5'',6''} = 4.7, H-5''), 7.22 (s, H-2''), 7.92-8.16 (m, 2H, H-4'',6''), 11.13 (s, NH); ¹³C-nmr (CDCl₃, 25 MHz) δ: 31.9 (C-5), 42.4 (C-3), 46.5 (C-6), 55.0 (C-1'), 64.6 (OCH₂CH₂O), 66.9 (C-2'), 105.8 (C-4), 115.5 (C-3''), 115.8 (C-5''), 118.6 (C-3a''), 122.5 (C-2''), 128.3 (C-4''), 142.5 (C-6''), 148.7 (C-7a''), 169.4 (CO); *Anal.* Calcd for C₁₆H₁₉N₃O₄: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.49; H 6.17; N,

13.26. Further elution gave **7b** as an oil; 5%; ^1H -nmr (CDCl_3 , 100 MHz) δ 2.15 (m, 2H, H-5), 2.78 (s, 2H, H-3), 3.69 (m, H-6), 4.02 (s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 6.20 (d, $J_{1-2} = 15.3$, H-2'), 7.14 (dd, $J_{4-5} = 7.3$, $J_{5-6} = 4.8$, H-5'), 7.34 (s, H-2''), 8.02-8.30 (m, 3H, H-1', 4'', 6''); ^{13}C -nmr (CDCl_3 , 25 MHz) δ 31.5 (C-5), 41.8 (C-3), 42.9 (C-6), 64.9 ($\text{OCH}_2\text{CH}_2\text{O}$), 104.6 (C-1'*), 105.5 (C-4*), 112.3 (C-2'), 116.1 (C-5''), 118.2 (C-3a''), 122.9 (C-2''), 124.8 (C-3''), 128.9 (C-4''), 142.9 (C-6''), 149.1 (C-7a''), 166.3 (CO); *Anal.* Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.12; H 5.87; N, 14.06.

Procedure for condensation of piperidines with 3-bromoethylazaindole (9). A mixture of 8.4 mmol of the appropriate piperidine, 4.2 mmol of **9**, 1.35 g (16.0 mmol) of sodium hydrogenocarbonate in 25 ml of acetonitrile was refluxed under a nitrogen stream for 4 h. After cooling, 100 ml of water was added and the solution was extracted with dichloromethane. Organic layers were dried over sodium sulfate and solvents were removed *under vacuo*. All compounds were purified by chromatography on silica gel eluted with dichloromethane.

1-[2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)ethyl]piperidine (10a). Yield 72%; mp 113-115°C (recrystallization solvent: ether); ^1H -nmr (CDCl_3 , 100 MHz) δ 1.48 (m, 2H, H-4), 1.65 (m, 4H, H-3,5), 2.52 (m, 2H, H-2,6), 2.67 (t, $J_{1-2} = 7.7$, H-1'), 2.97 (t, $J_{1-2} = 7.7$, H-2'), 7.06 (dd, $J_{4-5} = 7.8$, $J_{5-6} = 4.2$, H-5''), 7.16 (s, H-2''), 7.94 (dd, $J_{4-5} = 7.8$, $J_{4-6} = 1.3$, H-4''), 8.30 (d, $J_{5-6} = 4.2$, H-6''), 10.67 (s, NH); ^{13}C -nmr (CDCl_3 , 25 MHz) δ 22.9 (C-2'), 24.4 (C-4), 25.9 (C-3,5), 54.5 (C-2,6), 59.9 (C-1'), 112.6 (C-3''), 114.9 (C-5''), 120.3 (C-3a''), 122.4 (C-2''), 127.3 (C-4''), 142.1 (C-6''), 148.9 (C-7a''); *Anal.* Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.22; H 8.47; N, 18.31.

1-[2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)ethyl]piperidine-4-ethylene ketal (10b). Yield 94%; mp 145-147°C (recrystallization solvent: hexane); ^1H -nmr (CDCl_3 , 100 MHz) δ : 1.81 (t, $J_{2-3} = J_{5-6} = 5.6$, H-3,5), 2.70 (m, H-1',2,6), 2.97 (t, $J_{1-2} = 7.1$, H-2'), 4.00 (s, $\text{OCH}_2\text{CH}_2\text{O}$), 7.06 (dd, $J_{4-5} = 7.8$, $J_{5-6} = 4.5$, H-5''), 7.16 (s, H-2''), 7.93 (d, $J_{4-5} = 7.8$, H-4''), 8.28 (d, $J_{5-6} = 4.5$, H-6''), 9.80 (s, NH); ^{13}C -nmr (CDCl_3 , 25 MHz) δ : 23.3 (C-2'), 34.7 (C-3,5), 51.3 (C-2,6), 58.7 (C-1'), 64.1 ($\text{OCH}_2\text{CH}_2\text{O}$), 107.1 (C-4), 112.4 (C-3''), 114.8 (C-5''), 120.2 (C-3a''), 122.4 (C-2''), 127.2 (C-4''), 142.0 (C-6''), 148.9 (C-7a''); *Anal.* Calcd for $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.72; H 7.41; N, 14.60.

Mercuric acetate/EDTA oxidation of 10a,b. A solution of mercuric acetate (2.2 g, 6.9 mmol), EDTA

(2.57 g, 6.9 mmol) in 60 ml of water was added to a solution of starting heterocycle (2.27 mmol) in 30 ml of ethanol. The whole mixture was refluxed for 4 h. After being cooled and basified with aqueous 30% ammonia (pH=9), sodium borohydride (0.87g, 22.8 mmol) was added and the solution was then stirred for 18 h more. The resulting mixture was acidified with 10% HCl, the precipitate formed was filtered off, the filtrate was basified with 10% NaOH (pH=10) and extracted with dichloromethane. Organic layers were dried over sodium sulfate and evaporated *under vacuo*. All compounds were purified by column chromatography on silica gel eluted with dichloromethane.

1,2,3,4,6,7,12b-Octahydropyrido[2',3':2,3]pyrrolo[4,5-*a*]quinolizine (11). lit.,¹³ Yield 30%, mp 202-204°C (recrystallization solvent: dichloromethane).

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2,3-dihydro-4-pyridone (12). Yield 29%; mp 170-172°C (recrystallization solvent: hexane); ¹H-nmr (CDCl₃, 100 MHz) δ 2.40 (t, J = 7.5 Hz, 2H, H-3), 3.03 (t, J_{1'-2'} = 6.7, H-2'), 3.50 (m, 4H, H-1',2), 4.81 (d, J_{5,6} = 7.3 Hz, H-5), 6.80 (d, J_{5,6} = 7.3 Hz, H-6), 7.15 (dd, J_{4'-5'} = 7.1, J_{5'-6'} = 3.8, H-5'), 7.24 (s, H-2''), 7.98 (d, J_{4'-5'} = 7.1, H-4''), 8.30 (d, J_{5'-6'} = 3.8, H-6''), 11.90 (s, NH); ¹³C-nmr (CDCl₃, 25 MHz) δ 25.1 (C-2'), 35.5 (C-3), 47.0 (C-2), 56.5 (C-1'), 97.6 (C-6), 109.8 (C-3'), 115.4 (C-5'), 119.6 (C-2''), 123.5 (C-3a''), 126.7 (C-4''), 142.7 (C-6''), 149.0 (C-7a''), 154.1 (C-5), 191.2 (CO); *Anal.* Calcd for C₁₄H₁₅N₃O: C, 69.69; H, 6.27; N, 17.41. Found : C, 69.75; H 6.13; N, 17.38.

1-[2-(1-Phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]piperidine-4-ethylene ketal (10c). To a stirred solution of **10b** (1.3 g, 4.5 mmol) in THF (40 ml) at -78°C, was added 3 ml of BuLi (6 mmol) (2M in cyclohexane). After being stirred at 0°C for 15 min, the mixture was cooled again at -78°C and phenylsulfonyl chloride (0.8 ml, 6.2 mmol) was slowly added. After stirring 3 h more at room temperature, the reaction mixture was washed with a 2% solution of sodium carbonate, extracted with ether. Organic layers were dried over sodium sulfate, and solvents removed *under vacuo*. The crude product was chromatographed on silica gel eluted with dichloromethane to give 2.05 g of **10c**; yield 94%; mp 129-131°C (recrystallization solvent: ether); ¹H-nmr (CDCl₃, 100 MHz) δ 1.74 (m, 4H, H-3,5), 2.48-2.95 (m, 8H, H-1',2',2,6), 3.91 (s, 4H, OCH₂CH₂O), 7.12 (dd, J_{4'-5'} = 7.9, J_{5'-6'} = 4.5, H-5'), 7.35 (s, H-2''), 7.44-7.61 (m; 4H, H-2'', H-ar), 8.1-8.25 (m, 3H, H-4'', H-ar), 8.37 (d, J_{5'-6'} = 4.5, H-6''); ¹³C-nmr (CDCl₃, 25 MHz) δ 23.2 (C-2'), 34.9 (C-3,5), 51.4 (C-2,6), 57.4 (C-1'), 64.3 (OCH₂CH₂O), 107.1 (C-4), 117.9 (C-3'), 118.6 (C-5'), 122.9 (C-8''), 123.3 (C-3a''), 127.8 (C-ar), 127.9 (C-4''), 128.9 (C-ar), 133.8 (C-ar), 138.6 (C-ar), 144.9 (C-6''), 147.5 (C-7a''); *Anal.*

Calcd for $C_{22}H_{25}N_3O_4S$: C, 61.81; H, 5.89; N, 9.83. Found : C, 61.75; H 6.03; N, 9.78.

Deprotection of 10b,c. To a solution of ketal (2 g for **10b**, 2.9 g for **10c**, 6.9 mmol) in 50 ml of acetone was added 20 ml of 6N HCl. The mixture was refluxed for 6 h. After being cooled, the solution was diluted with 50 ml of water, basified with Na_2CO_3 (powder) and extracted with dichloromethane. The solvents were removed *under vacuo*. The compounds were purified by chromatography on neutral alumina eluted with dichloromethane.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-4-piperidone (13a). Yield 95%; mp 125-127°C (recrystallization solvent: cyclohexane); 1H -nmr ($CDCl_3$, 100 MHz) δ 2.51 (t, $J = 5.8$, 4H, H-3,5), 2.88 (m, 8H, H-2,6, H-1',2'), 7.09 (m, H-5''), 7.25 (s, H-2''), 7.96 (dd, $J_{4'',5''} = 7.8$, $J_{4'',6''} = 1.4$, H-4''), 8.34 (dd, $J_{5'',6''} = 4.7$, $J_{4'',6''} = 1.4$, H-6''), 10.38 (s, NH); ^{13}C -nmr ($CDCl_3$, 25 MHz) δ 23.7 (C-2'), 41.2 (C-3,5), 53.1 (C-2,6), 58.0 (C-1'), 112.3 (C-3''), 115.1 (C-5''), 120.2 (C-3a''), 122.5 (C-2''), 127.2 (C-4''), 142.4 (C-6''), 149.0 (C-7a''), 209.1 (CO); *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found : C, 69.25; H 7.03; N, 17.38.

1-[2-(1-Phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-4-piperidone (13b). Yield 45%; mp 103-105°C (recrystallization solvent: dichloromethane); 1H -nmr ($CDCl_3$, 100 MHz) δ 2.40 (t, 4H, $J = 5.7$, H-3,5), 2.77 (m, 8H, H-2,6, H-1',2'), 7.15 (m, H-5''), 7.33 (s, H-2''), 7.35-7.60 (m, 3H, H-ar), 7.77 (dd, $J_{4'',5''} = 7.8$, $J_{4'',6''} = 1.3$, H-4''), 8.00-8.20 (m, 2H, H-ar), 8.37 (dd, $J_{4'',6''} = 1.3$, $J_{5'',6''} = 4.8$, H-6''); ^{13}C -nmr ($CDCl_3$, 25 MHz) δ 23.3 (C-2'), 41.1 (C-3,5), 52.9 (C-2,6), 56.5 (C-1'), 117.4 (C-3''), 118.6 (C-5''), 122.9 (C-2''), 123.1 (C-3a), 127.7 (C-4'', C-ar), 128.9 (C-ar), 133.8 (C-ar), 144.9 (C-6''), 147.4 (C-7a''), 208.6 (CO); *Anal.* Calcd for $C_{20}H_{21}N_3O_3S$: C, 62.64; H, 5.52; N, 10.96. Found : C, 62.52; H 5.61; N, 10.88.

Procedure for preparation of 14a,b. A solution of **13a,b** (1.8 mmol) and (carbomethoxymethylene)triphenylphosphine (0.62 g, 1.8 mmol) in 15 ml of benzene was refluxed for 7 h. After cooling, solvent was removed *under vacuo*. The residual oil was dissolved in dichloromethane and chromatographed on neutral alumina eluted with dichloromethane.

Methyl 1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)piperidine- $\Delta^{4,\alpha}$ -acetate (14a). Yielded 61%; mp 104-106°C (recrystallization solvent: ether); 1H -nmr ($CDCl_3$, 100 MHz) δ 2.00-3.40 (m, 12H), 3.74 (s, 3H, CH_3), 5.71 (s, 1H, $CHCO_2CH_3$), 7.09 (dd, $J_{4'',5''} = 7.3$, $J_{5'',6''} = 4.2$, H-5''), 7.22 (s, H-2''), 7.95 (d, $J_{4'',5''} = 7.3$, H-4''), 8.36 (d, $J_{5'',6''} = 4.2$, H-6''), 12.10 (s, NH); ^{13}C -nmr ($CDCl_3$, 25 MHz) δ 22.9 (C-2'),

29.0 (C-3), 36.2 (C-5), 50.6 (CH₃), 53.7 (C-2*), 54.4 (C-6*), 58.3 (C-1'), 111.9 (C-3''), 113.3 (CHCO₂CH₃), 114.6 (C-5''), 120.0 (C-3a''), 122.4 (C-2''), 126.9 (C-4''), 141.7 (C-6''), 148.7 (C-7a''), 159.3 (C-4), 166.6 (CO); *Anal.* Calcd for C₁₇H₂₁N₃O₂: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.01; H 7.14; N, 14.21.

Methyl 1-[2-(1-phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]piperidine-Δ^{4,α}-acetate (14b). Yield 39%; oil; ms (FAB⁺); 440 (100), 438 (51), 285 (10), 168 (40), 131 (20); ¹H-nmr (CDCl₃, 400 MHz) δ 2.40 (m, 2H, H-3*), 2.65 (m, 4H, H-2,6*), 2.72 (t, J = 7.6, H-1'*), 2.92 (t, J = 7.6, H-2'*), 3.07 (m, H-5*), 3.69 (s, CH₃), 7.18 (dd, J_{4',5'} = 7.8, J_{5',6'} = 4.7, H-5''), 7.46 (m, 2H, H-2'', H-ar), 7.55 (m, 2H, H-ar), 7.85 (dd, J_{4',5'} = 7.8, J_{4',6'} = 1.2, H-4''), 8.16 (m, 2H, H-ar), 8.42 (dd, J_{5',6'} = 4.7, J_{4',6'} = 1.2, H-6''); ¹³C-nmr (CDCl₃, 100 MHz) δ 22.9 (C-2'), 29.2 (C-3), 36.5 (C-5), 50.7 (CH₃), 53.9 (C-2*), 54.5 (C-6*), 57.1 (C-1'), 113.6 (CHCO₂CH₃), 117.6 (C-3''), 118.4 (C-5''), 122.8 (C-2''), 123.1 (C-3a''), 127.6 (C-ar), 127.8 (C-4''), 128.8 (C-ar), 133.7 (C-ar), 138.3 (C-ar), 144.7 (C-6''), 147.4 (C-7a''), 159.2 (C-4), 166.7 (CO); *Anal.* Calcd for C₂₃H₂₅N₃O₄S: C, 62.85; H, 5.73; N, 9.59. Found: C, 62.76; H, 5.82; N, 9.51.

Procedure for reduction of 14a,b. A mixture of 14a,b (0.36 mmol), 150 mg of 10% Pd-C, in 10 ml of methanol was hydrogenated at atmospheric pressure during 3 h. After filtration, the solvent was evaporated, and the crude products were used without further purification.

Methyl 1-[2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-piperidineacetate (15a). Yield 97%; mp 85-87°C (recrystallization solvent: ether); ms (FAB⁺) 302 (100), 170 (73), 145 (53); ¹H-nmr (CDCl₃, 400 MHz) δ 1.70-2.10 (m, 5H, H-3,4,5), 2.34 (d, 2H, J = 6.8, CH₂CO₂CH₃), 2.51 (m, 2H, H-2,6), 3.00 (m, 2H, H-2'), 3.26 (m, 2H, H-1'), 3.42 (m, 2H, H-2,6), 3.70 (s, CH₃), 7.10 (dd, J_{4',5'} = 7.6, J_{5',6'} = 4.0, H-5''), 7.19 (s, H-2''), 8.04 (d, J_{4',5'} = 7.6, H-4''), 8.31 (d, J_{5',6'} = 4.0, H-6''), 9.61 (s, NH); ¹³C-nmr (CDCl₃, 100 MHz) δ 22.6 (C-2'), 31.4 (C-3,5), 32.5 (C-4), 40.6 (CH₂CH₃), 51.3 (CH₃), 53.3 (C-2,6), 59.1 (C-1'), 111.9 (C-3'), 114.9 (C-5''), 120.1 (C-3a''), 122.5 (C-2''), 127.1 (C-4''), 142.0 (C-6''), 148.8 (C-7a''), 172.9 (CO); *Anal.* Calcd for C₁₇H₂₃N₃O₂: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.76; H, 7.82; N, 13.91.

Methyl 1-[2-(1-phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-4-piperidineacetate (15b). Yield 97%; mp 140-142°C (recrystallization solvent: ether); ms (FAB⁺): 442 (100), 302 (15), 170 (83), 154 (70), 136 (60); ¹H-nmr (CDCl₃, 250 MHz) δ: 1.90-2.09 (m, 5H, H-3,4,5), 2.38 (d, J = 4.7, 2H, CH₂CO₂CH₃), 2.73 (m, 2H, H-3,5), 3.18 (m, 2H, H-2'), 3.42 (m, 2H, H-1'), 3.69 (m, 5H, H-

2,6,CH₃), 7.23 (dd, $J_{4''-5''} = 7.8$, $J_{5''-6''} = 4.7$, H-5''), 7.49 (m, 2H, H-ar), 7.59 (m, 2H, H-ar), 8.18 (m, 2H, H-ar, H-2''), 8.23 (dd, $J_{4''-5''} = 7.8$, $J_{4''-6''} = 1.4$, H-4''), 8.45 (dd, $J_{5''-6''} = 4.7$, $J_{4''-6''} = 1.4$, H-6''); ¹³C-nmr (CDCl₃, 25 MHz) δ : 20.2 (C-2'), 28.6 (C-3,5), 30.7 (C-4), 39.2 (CH₂CO₂CH₃), 51.6 (CH₃), 52.3 (C-2,6), 55.9 (C-1'), 114.4 (C-3''), 118.9 (C-5''), 122.2 (C-3a''), 123.3 (C-2''), 127.6 (C-ar), 128.5 (C-4''), 128.9 (C-ar), 134.1 (C-ar), 137.8 (C-ar), 145.2 (C-6''), 147.0 (C-7a''), 172.1 (CO); *Anal.* Calcd for C₂₃H₂₇N₃O₄S: C, 62.57; H, 6.16; N, 9.52. Found: C, 62.66; H, 6.22; N, 9.47.

Methyl 1-[2-(1Hpyrrolo[2,3-b]pyridin-3-yl)-2-oxo-4-piperidineacetate (16). This compound is obtained following the procedure used for the preparation of **11,12** using 5 equivalent of Hg(OAc)₂; yield 42%; mp 112-114°C (recrystallization solvent: cyclohexane); ¹H-nmr (CDCl₃, 250 MHz) δ 1.23-1.41 (m, 1H, H-4), 1.78 (m, 1H, H-5), 1.93-2.27 (m, 4H, H-3, CH₂CO₂CH₃), 2.50 (m, H-5), 2.96 (t, $J = 7.4$, H-2'), 3.02-3.20 (m, 2H, H-6), 3.60 (m, 5H, H-1', CH₃), 7.02 (dd, $J_{4''-5''} = 7.9$, $J_{5''-6''} = 4.8$, H-5''), 7.13 (s, H-2''), 7.94 (dd, $J_{4''-5''} = 7.9$, $J_{4''-6''} = 1.5$, H-4''), 8.25 (dd, $J_{5''-6''} = 4.8$, $J_{4''-6''} = 1.5$, H-6''), 10.49 (s, NH); ¹³C-nmr (CDCl₃, 25 MHz) δ 23.2 (C-2'), 28.7 (C-4*), 29.8 (C-5*), 38.2 (C-3), 39.6 (CH₂CO₂CH₃), 47.5 (C-6), 48.1 (C-1'), 51.7 (CH₃), 111.5 (C-3''), 115.3 (C-5''), 120.2 (C-3a''), 122.7 (C-2''), 127.4 (C-4''), 142.6 (C-6''), 148.9 (C-7a''), 168.6 (CO), 172.1 (CO); *Anal.* Calcd for C₁₇H₂₁N₃O₃: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.67; H, 6.82; N, 13.47.

Methyl 1,2,3,4,6,7,12,12b-octahydropyrido[2'3':2,3]pyrrolo[4,5-a]quinolizine-4-acetate (17). A solution of **16** (50 mg, 0.16 mmol), phosphorus oxychloride (1.7 g, 11 mmol) in toluene (5 ml) is refluxed for 2 h. After evaporation of solvent, the residual oil is dissolved in 7 ml of methanol, cooled at 0°C, and NaBH₄ (90 mg, 2.3 mmol) is slowly added. The resulting mixture is then stirred at room temperature for 1.5 h, and 3 ml of acetone are added. After evaporation of the solvents, the crude product was dissolved in water and extracted with dichloromethane. The solvents were removed *under vacuo*. Chromatography on silica gel eluted with dichloromethane/methanol (98/2) gave **17** (45 mg) as a white solid; 95%; mp 158-160°C (recrystallization solvent: ether); ir (KBr); Bolhmann bands 2800 and 2760 cm⁻¹; ms (FAB⁺): 300 (M⁺+1, 46%), 154 (100%); ¹H-nmr (CDCl₃, 400 MHz) δ 1.35 (q, $J = 12.5$, H-1ax), 1.55 (qd, $J = 12.5$, $J = 5$, H-3a), 1.85, (dm, $J = 12.5$, H-3eq), 2.18 (m, H-2ax), 2.36 (d, $J = 7.5$, CH₃), 2.39 (m, H-1eq), 2.5 (td, $J = 12.5$, $J = 2.5$, H-4a), 2.60-2.77 (m, 2H, H-6, H-7), 2.95-3.15 (m, 3H, H-4eq, H-6', H-7'), 3.39 (dd, $J_{12bax-1eq} = 5$, $J_{12bax-1ax} = 1.7$, H-12bax), 3.70 (s, CH₃), 7.05 (dd, $J_{8-9} = 6.0$, $J_{9-10} = 4.8$, H-9), 7.77 (dd, $J_{8-9} = 6.0$, $J_{8-10} = 1.1$, H-8), 8.21 (dd, $J_{9-10} = 4.8$, $J_{8-10} = 1.1$, H-10), 10.7 (s, NH); ¹³C-nmr (CDCl₃, 100 MHz) δ 21.7 (C-7), 32.1 (C-3), 33.2 (C-

2), 36.2 (C-1), 41.1 ($\text{CH}_2\text{CO}_2\text{CH}_3$), 51.7 (CH_3), 53.0 (C-6), 55.4 (C-4), 59.6 (C-12b), 106.4 (C-7a), 115.4 (C-9), 120.4 (C-7b), 126.3 (C-8), 136.0 (C-12a), 141.5 (C-10), 149.3 (C-11a), 173.0 (CO); *Anal.* Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_2$: C, 68.20; H, 7.07; N, 14.04. Found : C, 68.37; H, 7.08; N, 13.98.

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