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Nucleophilic Additions to Pyridinium Salts. Reduction of the Intermediate Dihydropyridines[#]

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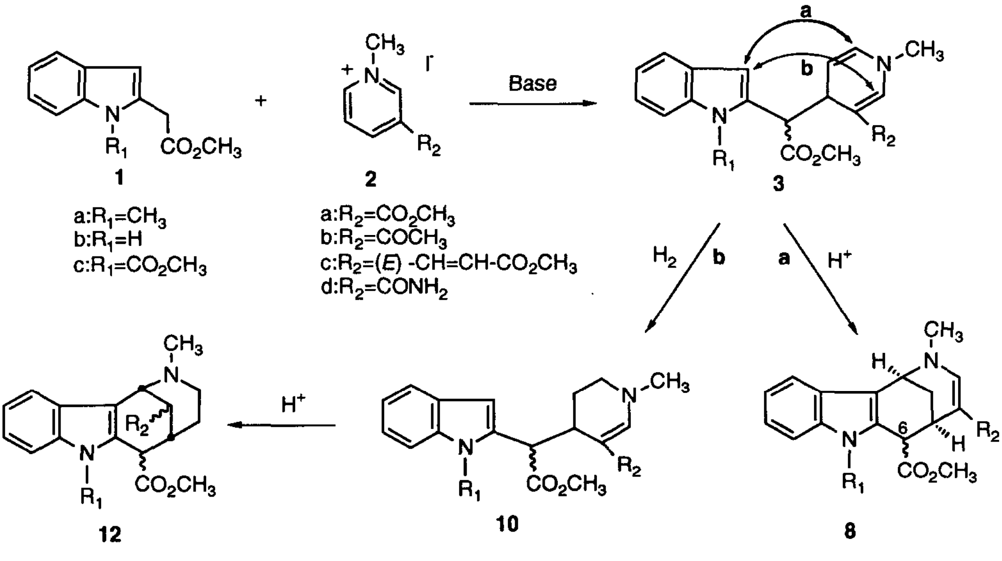
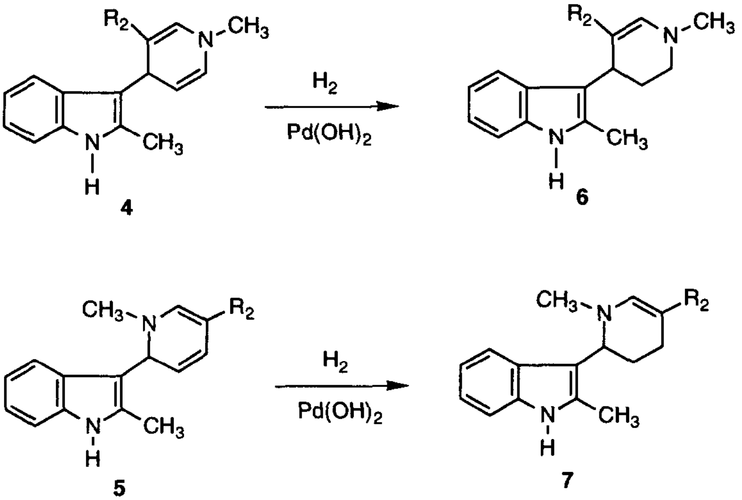
Abstract: Reduction of indolyldihydropyridines **4** and **5** satisfactorily gave the corresponding tetrahydropyridines **6** and **7**. A similar reduction of 4-(2-indolylmethyl)-1,4-dihydropyridines **3** was inefficient. In contrast, dihydropyridine **19** was reduced to **23** and then cyclized to pentacycle **24**. Direct cyclization of **19** resulted in the formation of imide **21**.

The nucleophilic addition of enolates to pyridinium salts bearing an electron-withdrawing substituent at the β position, followed by acid cyclization of the resulting 1,4-dihydropyridine upon an indole nucleus ("Wenkert's procedure") constitutes a general method for the synthesis of indole alkaloids.[1] The interaction of indole-2-acetic esters **1** and salts **2** allows the preparation of tetracyclic compounds **8**, and this strategy has proved to be useful for the total synthesis of pentacyclic *Strychnos* alkaloids.[2] The extension of this methodology to the preparation of alkaloids having the Aspidospermatan type (*i.e.*, tubotaiwine) by the use of a 3,5-disubstituted pyridinium salt met with problems.[3] The results presented in this paper deal with a new approach to the target Aspidospermatan skeleton, involving the reduction of the intermediate dihydropyridine **3** and subsequent cyclization of the resulting tetrahydropyridine **10** upon the indole β-position.

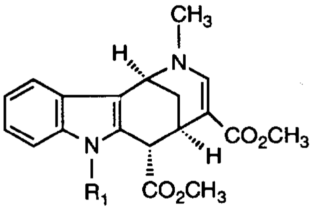


Model studies were undertaken in order to test the feasibility of the aforementioned idea. Pyridinium salt **2d**[4] was prepared by reaction of nicotinamide with excess methyl iodide. Model "irreversible" dihydropyridines **4a** and **5a** were prepared as reported in the literature.[5] Similarly, **4b** and **5b** were prepared by addition of 2-methylindole to pyridinium salt **2d**. Regioselective syntheses were achieved by the proper choice of the solvent.[5] Thus, addition of the indole in sodium methoxide - methanol afforded 1,2-dihydropyridine **5b** in good yield, whereas carrying out the reaction in dioxane with sodium hydride as the base the isomeric 1,4-dihydropyridine **4b** was obtained.[6] The hydrogenation of the unsubstituted dihydropyridine double bond was performed using palladium hydroxide as the catalyst. The resulting tetrahydropyridines **6a,b** and **7a,b** were isolated and characterized by spectroscopic methods and elemental analysis. As expected, 1,2-dihydropyridines **5a,b** underwent smooth catalytic hydrogenation to give compounds **7a,b** satisfactorily, whereas the isomeric 1,4-dihydropyridines **4a,b** reacted to afford **6a,b** in lower yields.[7] The partially reduced pyridines **4**, **5**, **6** and **7** thus prepared show close structural relationships with known bioactive and therapeutic agents.[8]

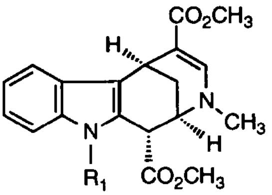


a: R_2= CO_2CH_3
b: R_2= $CONH_2$

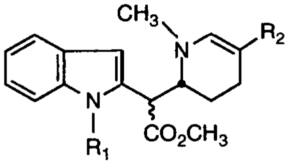
After the model studies gave satisfactory results for the reduction of "irreversible" 1,4-dihydropyridines, experiments were started from reversible dihydropyridines produced by the nucleophilic addition of an ester enolate to a pyridinium salt. Very few cases are reported in the literature on the manipulation of these very reactive intermediates in reactions different from acid-promoted cyclizations.[1b, 9] As expected, interaction between the enolates derived from esters **1a**,[2a] **1b**,[10] and **1c** [2b] and pyridinium salt **2a**,[4] followed by acid cyclization of the resulting mixture of unstable dihydropyridines, afforded tetracycles **8a-c** as mixtures of epimers at C-6, thus confirming the formation of intermediate 1,4-dihydropyridines **3** and their ability to survive mild reaction conditions. Minor amounts of regioisomeric tetracycles **9**, formed by cyclization of the corresponding 1,2-dihydropyridines, were also formed. However, hydrogenation of dihydropyridines **3** [R_2= CO_2CH_3] in the presence of activated palladium hydroxide led to complex reaction mixtures, the main components being the starting esters **1**, thus reflecting the reversibility of the addition process. Careful purification of the mixtures allowed the isolation of tetrahydropyridines **10**[13] and **11**,[14] although in low yields, as mixtures of stereoisomers. The chemical shift of the methine carbon in the piperideines was of diagnostic value; thus, C4 appeared around 30 ppm in **10**, whereas C2 appeared around 58 ppm in **11**. When the reactions were performed from salt **2a**, tetrahydropyridine **16**[15] was isolated, showing again the reversibility of the addition process, which going backward afforded some pyridinium salt that was reduced by hydrogenation. Also in the reaction of ester **1b** with salt **2a**, 1,2-dihydropyridine **17**[16], arising from an α-attack of the indole ring,[17] was isolated and, after reduction, the corresponding tetrahydropyridine **18**[18] was detected. The use of palladium with hydrogen or cyclohexadiene was ineffective, whereas "in situ" sodium borohydride reduction (in MeOH-THF or THF solutions) of dihydropyridines **3** [R_1= Me or H, R_2= methyl (*E*)-acrylate][2a] afforded tetrahydropyridine **14**[12] and the alcohols **15a**[19] or **15b**.[20] Similar results were obtained when sodium cyanoborohydride was used as reducing agent in the presence of an equimolecular amount of trifluoroacetic acid. Finally, acid cyclization of the crude tetrahydropyridines **10** and **11** with hydrogen chloride in methanol resulted in the formation of very complex mixtures from which tetracyclic compounds **12** and **13** could be detected. The major problems found in this approach are: a) the instability of the intermediate dihydropyridines, rendering their purification difficult and lowering the yields, and b) the reversibility of the addition process, especially taking place during reduction of the dihydropyridines **3**.



8a : R_1=CH_3
b : R_1=H
c : R_1=CO_2CH_3



9a : R_1=CH_3
b : R_1=H



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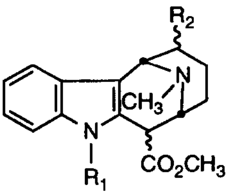

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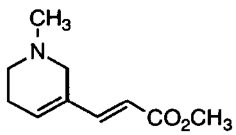

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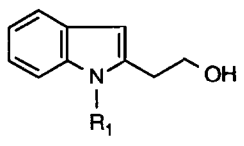
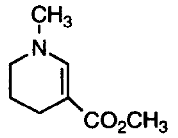


15
a:R_1=CH_3
b:R_1=H



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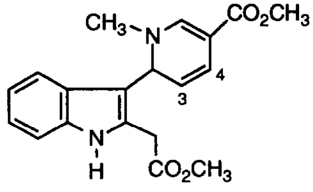
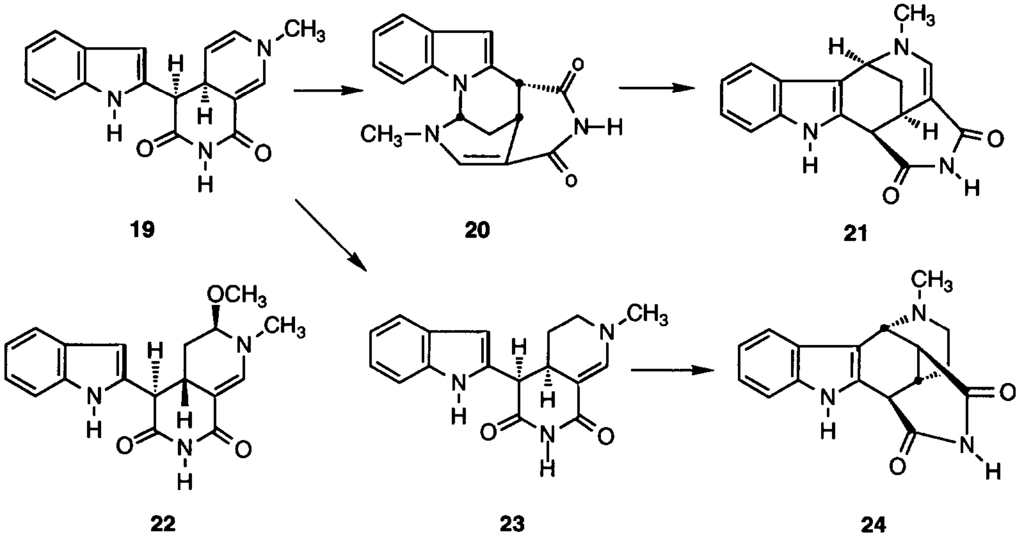
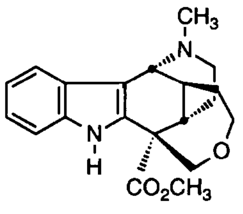


17
18 : 3,4-dihydro

To solve these problems, we turned our attention to an "intramolecular approach", knowing the improvement on the stability of dihydropyridines when they arise from an intramolecular nucleophilic addition.[1b] On the other hand, the presence of cyclic structures would allow a high degree of stereocontrol. Indeed, the addition of the enolate of ester **1c** to pyridinium salt **2d** took place with simultaneous closure of the imide ring under the basic reaction medium to give dihydropyridine **19**,[21] having a *cis* relationship between the hydrogens at the stereogenic centers, in 57% yield. Minor amounts of the *trans* isomer were also detected. Dihydropyridine **19** could be chromatographed over neutral alumina and stored at -20°C without significant decomposition. When the crude mixture was treated with a solution of hydrogen chloride in benzene, the resulting iminium ion underwent a cyclization upon the indole nitrogen affording **20** in 43% yield.[22] This compound isomerized on heating to pentacycle **21**. The rigidity of the pentacyclic systems **20** and **21** only allows the existence of one stereoisomer (see Dreiding^R stereomodels). In fact, the minor *trans* isomer of dihydropyridine **19** did not cyclize and underwent the addition of methanol during column chromatography to give **22**. As expected, in contrast with the above results from 4-(2-indolylmethyl)-1,4-dihydropyridines, catalytic hydrogenation of 1,4-dihydropyridine **19** cleanly afforded tetrahydropyridine **23** in 64% yield,[23] and acid cyclization of **23** yielded the pentacyclic compound **24** in good yield. Its structural elucidation was established with the aid of a ^1H-^1H homocorrelation NMR experiment. It should be noted that pentacycle **24** presents the unusual structural feature of having a cyclohexene ring with two consecutive bridges.[24]

In conclusion, the reduction of "intramolecular" dihydropyridines and subsequent acid cyclization constitutes a useful method for the construction of structures related to the Aspidospermatan skeleton with high overall yield and stereocontrol. This methodology also complements the "classical" Wenkert's procedure, allowing the regioselective alkylation either at the α or α' positions of the pyridinium salt. Studies toward the total synthesis of natural products, for instance the indole alkaloid undulifoline,[25] based on this strategy are under way in our laboratory.





undulifoline

EXPERIMENTAL PART

General. All solvents were dried by standart methods. All reagents were of commercial quality from freshly opened containers. Prior to concentration, under reduced pressure, all organic extracts were dried with anhydrous sodium sulphate. Column chromatography was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm) or on Al_2O_3 (aluminium oxide 90, neutral, activity I, Merck 0.063-0.200 mm). TLC was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm) and the spots were located with UV light or iodine vapors. Melting points were taken using a Büchi apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba 1106 analyzer by Centro de Investigaci6n y Desarrollo (CSIC), Barcelona. ^1H and ^{13}C spectra were obtained using a Varian XL-200 instrument in $CDCl_3$ with TMS as an internal reference unless otherwise specified. Homocorrelation was obtained using a Varian VXR 500 spectrometer. IR spectra were recorded on a Perkin Elmer 1600 series FTIR spectrophotometer. UV spectra were obtained using an Hitachi u-2000 apparatus in MeOH. Low resolution e.i mass spectra were recorded on a Hewlett-Packard 5989A spectrometer. High resolution e.i. mass spectra were determined on a Autospec-VG apparatus.

3-Carbamoyl-1-methylpyridinium Iodide (2d). A solution of methyl iodide (15.3 ml, 246 mmol) in anhydrous benzene (15 ml) was added dropwise to a solution of nicotinamide (10 g, 81.9 mmol) in anhydrous acetone (30 ml), and the mixture was stirred at room temperature for 3 days. The resulting precipitate was filtered, washed with anhydrous ether, and dried in a dissecator under reduced pressure to yield **2d** (19.9 g, 92%); ^1H NMR (DMSO-d_6) : 4.42 (s, 3H, CH_3), 8.16 (s, 1H, NH), 8.27 (m, J=8.0 and 6.0 Hz, H-5), 8.53 (s, 1H, NH), 8.92 (d, J=8.0 Hz, 1H, H-4), 9,12 (d, J=6.0 Hz, 1H, H-6), 9.41 (s, 1H, H-2). ^{13}C NMR (DMSO-d_6) : 48.6 (CH3), 127.7 (C-5), 139.4 (C-3), 143.1 (C-4), 145.8 (C-6), 147. 4 (C-2), 163.1 (C=O). IR (KBr) : 3326 and 3254 (N-H), 1684 (C=O). UV, λ_{max} nm (log ε) : 223 (4.35), 282 (3.79), 348 (3.57). Mp 203-205°C (Lit.[4] 202-203°C).

1-Methyl-4-(2-methyl-3-indolyl)-1,4-dihydropyridine-3-carboxamide (4b). A solution of 2-methylindole (1 g, 7.6 mmol) in anhydrous dioxane (10 ml) was slowly added to a suspension of sodium hydride (60% in oil w/w, 765 mg, 19.1 mmol) in anhydrous dioxane (40 ml) at room temperature under nitrogen atmosphere. Stirring was continued for 30 min at 70°C, and the flask was cooled to room temperature. Pyridinium salt **2d** (2.42 g, 9.2 mmol) was added all at once and stirring was continued for 24 h. The precipitate formed was filtered, water (100 ml) was added, and the resulting suspension was extracted with ethyl acetate. The organic extract was dried and evaporated to yield 1.93 g (95%) of pure **4b**. ^1H NMR (DMSO-d_6): 2.31 (s, 3H, CH_3), 3.10 (s, 3H, N-CH_3), 4.52 (dd, J=7.7 and 4.7 Hz, 1H, H-5), 4.67 (d, J=4.7 Hz, 1H, H-4), 5.97 (d, J=7.7 Hz, 1H, H-6), 6.18 (bs, 2H, NH_2), 6.80-6.95 (m, 2H, H-5 indole and H-6 indole), 7.01 (s, 1H, H-2), 7.18 (d, J=7.6 Hz, 1H, H-7 indole), 7.43 (d, J=7.1 Hz, 1H, H-4 indole), 10.68 (s, 1H, NH indole). ^{13}C NMR (CD_3OD): 11.5 (CH_3), 30.0 (C-4), 41.2 (N-CH_3), 102.6 (C-3), 107.9 (C-5), 111.5 (C-7 indole), 112.6 (C-3 indole), 128.7 (C-3a indole), 118.7 (C-6 indole), 119.7 (C-5 indole), 121.5 (C-4 indole), 128.3 (C-6), 133.3 (C-2 indole), 137.1 (C-7a indole), 140.7 (C-2), 174.0 (C=O). IR (KBr): 3412 (N-H), 1677, 1625 (amide), 1558 (C=C). UV, λ_{max} nm (logε): 219 (4.3), 265 (3.6). MS (m/z, %): 267 (M^+, 100), 252 (48), 223 (45), 137 (56). Mp 192-194°C (acetone-MeOH). Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.91; H, 6.37; N, 15.73. Found: C, 72.14; H, 6.45; N, 15.78.

1-Methyl-2-(2-methyl-3-indolyl)-1,2-dihydropyridine-5-carboxamide (5b). To a solution of sodium methoxide (12 mmol) in methanol (30 ml), kept under nitrogen atmosphere, was added a solution of 2-methylindole (500 mg, 3.8 mmol) in methanol (5 ml). Stirring was continued at room temperature for 30 min, and a solution of pyridinium salt **2d** (1.1 g, 4.2 mmol) in methanol (10 ml) was added. The solution was stirred at room temperature for 24 h. The precipitate was filtered, washed with anhydrous diethyl ether, and dried under reduced pressure. The filtrate was concentrated and allowed to crystallize to yield a second crop of dihydropyridine. Total weight 2.0 g (87%). ^{1}H NMR (DMSO-d_6) : 2.38 (s, 3H, CH_3), 2.62 (s, 3H, N-CH_3), 4.79 (dd, J=9.9 and 3.7 Hz, 1H, H-3), 5.54 (bd, J=3.7 Hz, 1H, H-2), 6.33 (bd, J=9.9 Hz, 1H, H-4), 6.42 (bs, 2H, NH_2), 6.87-7.04 (m, 2H, H-5 indole and H-6 indole), 7.26 (d, J=7.4 Hz, 1H, H-7 indole), 7.29 (s, 1H, H-6), 7.52 (d, J=7.7 Hz, 1H, H-4 indole), 10.98 (s, 1H, N-H indole). ^{13}C NMR (DMSO-d_6) : 11.4 (CH_3), 40.6 (N-CH_3), 55.1 (C-2), 96.9 (C-5), 110.9 (C-3), 112.4 (C-3 indole), 112.7 (C-7 indole), 118.8 (C-4), 118.9 (C-6 indole), 120.5 (C-4 indole), 120.6 (C-5 indole), 127.1 (C-3a indole), 133.0 (C-2 indole), 135.7 (C-7a indole), 144.8 (C-6), 168.1 (C=O). IR (KBr) : 3473, 3383, 3328, 3193 (N-H), 1645, 1591 (amide). UV, λ_{max} nm (logε) : 218 (4.2), 269 (4.3), 364 (3.8). MS (m/z, %) : 267 (M^+, 100), 223 (62), 137 (41). Mp 189-190°C (MeOH). Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.91; H, 6.37; N, 15.73. Found: C, 71.63; H, 6.31; N, 15.48.

General Procedure for the Preparation of Tetrahydropyridines 6a,b and 7a,b. A solution of the corresponding dihydropyridine **4a,b** or **5a,b** (2 mmol) in ethyl acetate (50 ml) was hydrogenated over activated palladium hydroxide (250 mg) at atmospheric pressure for 4-8h. The progress of the reaction was monitored by TLC (silica gel; 95:3:2 ether-acetone-diethylamine). When the spot of starting material disappeared, the reaction was stopped. The catalyst was filtered off, and the filtrate was evaporated to give a foam which was chromatographed over silica-gel. On elution with hexanes - ethyl acetate, pure tetrahydropyridines were obtained.

Methyl 1-Methyl-4-(2-methyl-3-indolyl)-1,2,3,4-tetrahydropyridine-5-carboxylate (6a). Operating as above, product **6a** (43%) was obtained after chromatography (elution with 1:1 hexanes - ethyl acetate). ^{1}H NMR: 1.80-2.05 (m, 2H), 2.27 (s, 3H, CH_3), 2.90-3.10 (m, 2H), 3.08 (s, 3H, N-CH_3), 3.56 (s, 3H, O-CH_3), 4.18 (m, 1H, H-4), 6.90-7.10 (m, 2H, H-5 indole and H-6 indole), 7.18 (d, J=7.1 Hz, 1H, H-7 indole), 7.46 (d, J=7.5 Hz, 1H, H-4 indole), 7.62 (s, 1H, H-6), 8.0 (bs, 1H, NH indole). ^{13}C NMR (Acetone-d_6): 12.1 (CH_3), 27.9 (C-4), 29.8 (C-3), 42.9 (N-CH_3), 45.6 (C-2), 50.3 (O-CH_3), 96.5 (C-5), 110.9 (C-7 indole), 115.6 (C-3 indole), 118.9 (C-5 indole), 119.0 (C-4 indole), 120.5 (C-6 indole), 129.5 (C-3a indole), 131.9 (C-2 indole), 136.0 (C-7a indole), 147.6 (C-6), 169.5 (C=O). IR (KBr): 3325 (N-H), 1663 (C=O), 1614 (C=C). UV, λ_{max} nm (logε): 204 (4.2), 225 (4.4), 290 (4.3). MS (m/z, %): 284 (M^+, 50), 251 (13), 223 (15), 154 (100). Mp 180-182°C (acetone). Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.83; H, 7.04; N, 9.86. Found: C, 72.02; H, 7.03; N, 9.88.

1-Methyl-4-(2-methyl-3-indolyl)-1,2,3,4-tetrahydropyridine-5-carboxamide (6b). Operating as above, product **6b** (40%) was obtained after chromatography (elution with 96:4 ethyl acetate - methanol). ^{1}H NMR: 1.90-2.20 (m, 2H), 2.36 (s, 3H, CH_3), 2.90-3.10 (m, 2H), 3.06 (s, 3H, N-CH_3), 3.97 (m, 1H, H-4), 5.21 (bs, 2H, NH_2), 6.98-7.15 (m, 2H, H-5 indole and H-6 indole), 7.27 (d, J=7.0 Hz, 1H, H-7 indole), 7.55 (d, J=7.8 Hz, 1H, H-4 indole), 7.66 (s, 1H, H-6), 8.29 (bs, 1H, NH indole). ^{13}C NMR (CD_3OD): 12.0 (CH_3), 29.0

(C-4), 31.1 (C-3), 43.0 (N-CH_3), 48.1 (C-2), 98.2 (C-5), 111.4 (C-7 indole), 113.7 (C-3 indole), 119.0 (C-5 indole), 119.5 (C-4 indole), 121.4 (C-6 indole), 129.4 (C-3a indole), 133.2 (C-2 indole), 136.9 (C-7a indole), 147.4 (C-6), 174.1 (C=O). IR (KBr): 3394 (N-H), 1644, 1562 (amide). UV, λ_{max} nm (logε): 225 (5.0), 291 (4.9). MS (m/z, %): 269 (M^+, 67), 252 (32), 251 (31), 223 (38), 139 (100).

Methyl 1-Methyl-2-(2-methyl-3-indolyl)-1,2,3,4-tetrahydropyridine-5-carboxylate (7a). Operating as above, product **7a** (56%) was obtained after column chromatography (elution with 1:1 hexanes - ethyl acetate). ^1H NMR: 1.90-2.42 (m, 4H), 2.38 (s, 3H, CH_3), 2.78 (s, 3H, N-CH_3), 3.72 (s, 3H, O-CH_3), 4.46 (dd, J=7.0 and 4.4 Hz, 1H, H-2), 7.00-7.19 (m, 2H, H-5 indole and H-6 indole), 7.29 (d, J=6.8 Hz, 1H, H-7 indole), 7.48 (d, J=8.4 Hz, 1H, H-4 indole), 7.56 (s, 1H, H-6), 7.91 (bs, 1H, NH indole). ^{13}C NMR: 11.8 (CH_3), 19.2 (C-4), 29.1 (C-3), 40.8 (N-CH_3), 50.6 (O-CH_3), 53.9 (C-2), 94.3 (C-5), 110.4 (C-7 indole), 110.8 (C-3 indole), 118.5 (C-5 indole)119.5 (C-4 indole), 121.1 (C-6 indole), 126.9 (C-3a indole), 131.9 (C-2 indole), 135.1 (C-7a indole), 147.9 (C-6), 169.3 (C=O). IR (KBr): 3407 (N-H), 1658 (C=O), 1612 (C=C). UV, λ_{max} nm (logε): 207 (4.3), 221 (4.4), 291 (4.3). MS (m/z, %): 284 (M^+, 41), 253 (12), 170 (16), 157 (100). Mp 86-88°C (acetone). Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.83; H, 7.04; N, 9.86. Found: C, 71.67; H, 6.95; N, 9.57.

1-Methyl-2-(2-methyl-3-indolyl)-1,2,3,4-tetrahydropyridine-5-carboxamide (7b). Opertaing as above, essentially pure product **7b** (90%) was obtained. ^1H NMR (DMSO-d_6): 1.80-2.34 (m, 4H), 2.31 (s, 3H, CH_3), 2.63 (s, 3H, N-CH_3), 4.38 (m, 1H, H-2), 6.30 (bs, 2H, NH_2), 6.85-6.99 (m, 2H, H-5 indole and H-6 indole), 7.23 (d, J=8.1 Hz, 1H, H-7 indole), 7.30 (s, 1H, H-6), 7.34 (d, J=8.0 Hz, 1H, H-4 indole), 10.88 (s, 1H, NH indole). ^{13}C NMR (DMSO-d_6): 11.6 (CH_3), 19.8 (C-4), 29.4 (C-3), 40.0 (N-CH_3), 53.2 (C-2), 97.9 (C-5), 110.7 (C-3 indole), 110.8 (C-7 indole), 118.1 (C-5 indole), 118.7 (C-4 indole), 120.2 (C-6 indole), 126.9 (C-3a indole), 132.6 (C-2 indole), 135.3 (C-7a indole), 145.2 (C-6), 169.5 (C=O). IR (KBr): 3395 (N-H), 1646, 1629 (amide), 1548 (C=C). UV, λ_{max} nm (logε): 220 (4.4), 291 (4.2). MS (m/z, %): 269 (M^+, 89), 238 (21), 157 (100). The picrate showed a mp 125-126°C (acetone). Anal. Calcd. for $C_{22}H_{22}N_6O_8$: C, 53.01; H, 4.42: N, 16.87. Found: C, 53.38; H, 4.80; N, 16.80.

General Procedure for the Condensation of Esters 1 with Pyridinium Salts 2. A solution of ester **1** (5 mmol) in anhydrous THF (40 ml) was slowly added to a solution of LDA (6.5 mmol for esters **1a** and **1c**; 13 mmol for **1b**) in anhydrous THF (20 ml) cooled to -70°C, and the resulting solution was stirred at -70°C for 1 h. The pyridinium iodide **2** (6 mmol) was added all at once, and the mixture was allowed to rise to -30°C and stirred at this temperature for 2 h. Enough of a saturated benzene solution of dry HCl was added dropwise to bring the pH to 2.5-3, and the mixture was stirred at 0°C for 2 h. The reaction mixture was poured into a saturated Na_2CO_3 solution and extracted with ethyl acetate. Evaporation of the dried organic extracts gave a residue which was chromatographed over silica-gel.

Interaction of Ester 1a with Salt 2a. Operating as above , on elution with 2:8 hexanes-ethyl acetate, **methyl (1*RS*, 5*SR*, 6*RS*)-6-methoxycarbonyl-2,7-dimethyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-carboxylate (8a)** (33%) was obtained. ^1H-NMR: 7.61 (d, J=7 Hz, 1H, H-11); 7.26 (s, 1H, H-3); 7.28-7.11 (m, 3H, H-8, H-9 and H-10); 4.54 (bs, 1H, H-1); 4.03 (d, J=1.7 Hz, 1H, H-6); 3.76 (s, 3H, OCH_3); 3.69 (s, 3H, OCH_3); 3.58 (s, 3H, N_{ind}-CH_3); 3.54 (m, 1H, H-5); 3.17 (s, 3H, N-CH_3); 2.33 and 1.90 (2 dt, 2H, H-12). ^{13}C-NMR: 171.9 (C=O); 167.9 (C=O); 145.8 (C-3); 137.2 (C-7a); 133.7 (C-6a); 125.5 (C-11a); 121.4

(C-10); 119.5 (C-9); 118.0 (C-11); 110.4 (C-11b); 109.1 (C-8); 96.9 (C-4); 52.3 (OCH_3); 50.5 (OCH_3); 48.8 (C-1); 45.7 (C-6); 42.2 (N-CH_3); 29.9 (N_{ind}-CH_3, C-5); 25.9 (C-12). IR ($CHCl_3$): 1730 (C=O); 1667 (C=O); 1611 (C=C). UV, λ_{max} nm (log ε): 282 (4.2); 252 (4.0); 224 (4.4). MS (m/z, %): 354 (M^+, 27); 322 (100); 263 (59); 239 (45). Mp 190-191°C (acetone). Anal. Calcd. for $C_{20}H_{22}N_2O_4$ x $1/3H_2O$: C, 66.65; H, 6.33; N, 7.77. Found: C, 66.89; H, 6.29; N, 7.70. On elution with 1:9 hexanes-ethyl acetate, the C-6 epimer **8a'** (5%) was obtained. ^{1}H-NMR: 7.62 (d, J=7 Hz, 1H, H-11); 7.39 (s, 1H, H-3); 7.30-7.05 (m, 3H, H-8, H-9 and H-10); 4.51 (bs, 1H, H-1); 4.21 (d, J=5 Hz, 1H, H-6); 3.75 (s, 3H, OCH_3); 3.70 (s, 3H, OCH_3); 3.62 (s, 3H, N_{ind}-CH_3); 3.40 (m, 1H, H-5); 3.22 (s, 3H, N-CH_3); 2.00 (m, 2H, H-12). ^{13}C-NMR: 173.0 (C=O); 168.4 (C=O); 145.8 (C-3); 138.6 (C-7a); 133.6 (C-6a); 125.5 (C-11a); 121.7 (C-10); 119.7 (C-9); 117.8 (C-11); 111.3 (C-11b); 109.1 (C-8); 94.9 (C-4); 52.4 (OCH_3); 50.5 (OCH_3); 49.3 (C-1); 48.6 (C-1); 42.2 (N-CH_3); 30.5 (N_{ind}-CH_3); 29.2 (C-12); 28.8 (C-5). IR ($CHCl_3$): 1732 (C=O); 1673 (C=O); 1613 (C=C). UV, λ_{max} nm (log ε): 281 (4.4); 224 (4.6). MS (m/z, %): 354 (M^+, 64); 322 (87); 295 (25); 263(100); 239 (59); 235 (48). On elution of ethyl acetate, **methyl (1*RS*, 2*SR*, 6*SR*)-5-methoxycarbonyl-3,11-dimethyl-1,2,3,6-tetrahydro-2,6-methanoazocino[4,5-*b*]indole-5-carboxylate (9a)** (7%) was obtained. ^{1}H-NMR: 8.00 (d, J=7 Hz, 1H, H-7); 7.29 (s, 1H, H-4); 7.20-7.00 (m, 3H, H-8, H-9 and H-10); 4.30 (m, 1H, H-2), 4.27 (s, 1H, H-1); 3.82 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 3.62 (m, 1H, H-6); 3.51 (s, 3H, N_{ind}-CH_3); 3.02 (N-CH_3); 2.20 and 1.90 (2 dt, 2H, H-12). IR ($CHCl_3$): 1726 (C=O); 1677 (C=O); 1613 (C=C). UV, λ_{max} nm (log ε): 280 (4.2); 227 (4.5); 203 (4.4). MS (m/z, %): 354 (M^+, 61); 295 (22); 281 (33); 263 (34); 152 (100). Minor amounts of the C-1 epimer were also detected.

Interaction of Ester 1b with Salt 2a. Operating as above, on elution with ethyl acetate, **methyl (1*RS*, 5*SR*, 6*RS*)-6-methoxycarbonyl-2-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-carboxylate (8b)** (37%) was obtained. ^{1}H-NMR: 8.70 (bs, 1H, N-H); 7.55 (m, 1H, H-8); 7.28 (m, 1H, H-11); 7.25 (s, 1H, H-3); 7.15-7.00 (m, 2H, H-9 and H-10); 4.45 (bs, 1H, H-1); 3.97 (d, J=1.4 Hz, 1H, H-6); 3.67 (s, 6H, OCH_3); 3.40 (m, 1H, H-5); 3.14 (s, 3H, N-CH_3); 2.32 and 1.95 (2 dt, 2H, H-12). ^{13}C- NMR: 171.3 (C=O); 168.0 (C=O); 146.0 (C-3); 136.0 (C-7a); 131.3 (C-6a); 125.8 (C-11a); 121.8 (C-10); 119.7 (C-9); 117.8 (C-11); 111.5 (C-11-b); 111.1 (C-8); 96.8 (C-4); 52.0 (OCH_3); 50.5 (O-CH_3); 48.5 (C-1); 46.2 (C-6); 42.1 (NCH_3); 28.0 (C-5); 26.6 (C-12). IR ($CHCl_3$): 3400 (N-H); 1730 (C=O); 1666 (C=O); 1610 (C=C). UV, λ_{max} nm (log ε): 279 (4.1); 220 (4.2). MS (m/z, %): 340 (M^+, 15); 308 (40); 225 (100); 193 (84); 152 (32). Mp 196-198°C. Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.82; H, 5.91; N, 8.27. Minor amounts of the C-6 epimer **8b'** and the regioisomers **9** were also detected.

Interaction of Ester 1c with Salt 2a. Operating as above, on elution with 1:9 hexanes - ethyl acetate, **methyl (1*RS*, 5*SR*, 6*RS*)-6,7-bis(methoxycarbonyl)-2-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-carboxylate (8c)** (82%) was obtained. ^{1}H-NMR: 8.10 (d, J=6.5 Hz, 1H, H-8), 7.55 (m, 1H, H-11); 7.30-7.00 (m, 3H, H-3, H-9 and H-10); 4.45 (bs, 1H, H-1); 4.33 (d, J=1.5 Hz, 1H, H-6); 3.94 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 3.69 (s, 3H, OCH_3); 3.41 (bs, 1H, H-5); 3.14 (s, 3H, NCH_3); 2.21 and 1.82 (2 dt, 2H, H-12). ^{13}C-NMR: 172.5 (C=O); 171.1 (C=O); 167.5 (C=O); 145.4 (C-3); 136.2 (C-7a); 133.9 (C-6a); 127.9 (C-11a); 124.6 (C-10); 123.1 (C-9); 118.7 (C-11); 115.4 (C-8); 115.2 (C-11b); 98.0 (C-4); 55.8 (C-6); 53.6 (OCH_3); 52.5 (OCH_3); 50.7 (OCH_3); 48.9 (C-1); 42.4 (NCH_3); 29.8 (C-5); 24.6 (C-12). IR ($CHCl_3$): 1732 (C=O); 1673 (C=O); 1615 (C=C). UV, λ_{max} nm (log ε): 292 (3.9); 284 (4.0); 264.5 (4.2); 226 (4.2). MS (m/z,

%): 398 (M+, 56); 366 (64); 325 (50); 279 (30); 219 (44); 152 (100). Mp 208-210°C (acetone-ether). Anal. Calcd. for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.56; N, 7.03. Found: C, 63.36; H, 5.53; N, 7.05.

Interaction of Ester 1c with Salt 2d. Method A. The reaction was performed as in the above general procedure, but using 18 mmol of LDA and stirring at room temperature for 4 h. On elution with ethyl acetate, compound **20** (43%) was obtained. ^{1}H-NMR: 10.30 (s, 1H, NH); 7.55 (d, J=7 Hz, 1H, H-4 indole); 7.43 (d, J=6.5 Hz, 1H, H-7 indole); 7.30-7.10 (m, 2H, H-5 and H-6 indole); 6.96 (s, 1H, H-6 pyr); 6.56 (s, 1H, H-3 indole); 5.73 (m, 1H, H-2 pyr); 4.13 (d, J=4 Hz, 1H, H-6), 3.25 (m, 1H, H-4 pyr); 3.23 (s, 3H, NCH_3), 2.43 (m, 2H, H-12). IR ($CHCl_3$): 3360 (N-H); 1688 (C=O); 1661 (C=O); 1617 (C=C). UV, λ_{max} nm (log ε): 317 (3.9); 283 (4.0); 218 (4.5). MS (m/z, %): 293 (M+, 100); 249 (21); 221 (20); 167 (36); 137 (48). HRMS: Calcd. for $C_{17}H_{15}N_3O_2$= 293.1161. Found = 293.1168. On elution with 95:5 ethyl acetate - methanol, compound **22** (3%) was obtained. ^{1}H-NMR (DMSO-d_6): 11.05 (s, 1H, NH); 10.32 (s, 1H, NH); 7.45 (d, J=7.5 Hz, 1H, H-4 indole); 7.44 (s, 1H, H-6 pyr); 7.30 (d, J=7.7 Hz, 1H, H-7 indole); 7.03-6.93 (m, 2H, H-5 and H-6 indole); 6.27 (s, 1H, H-3 indole); 4.41 (bs, 1H, H-2 pyr); 3.67 (d, J=10 Hz, 1H, H-6); 3.20 (s, 3H, OCH_3); 3.14 (s, 3H, NCH_3); 2.95 (m, 1H, H-4-pyr); 1.60 and 1.25 (2 m, 2H, H-3 pyr). ^{13}C-NMR (DMSO-d_6): 172.1 (C=O); 165.4 (C=O); 144.6 (C-6 pyr); 136.6 (C-7a indole); 135,1 (C-2 indole); 127.9 (C-3a indole); 120.8 (C-6 indole); 119.7 (C-5 indole); 117.8 (C-4 indole); 111.1 (C-7 indole); 101.8 (C-3 indole); 96.5 (C-5 pyr); 86.0 (C-2 pyr); 55.0 (OCH_3); 47.1 (C-6); 42.0 (NCH_3); 31.4 (C-3 pyr); 27.6 (C-4 pyr). IR ($CHCl_3$): 3500 (N-H); 3400 (N-H); 1704 (C=O); 1675 (C=O); 1601 (C=C). UV, λ_{max} nm (log ε): 313 (4.0); 289 (3.9); 218 (4.4); MS (m/z, %): 325 (M+, 4); 293 (56); 163 (26); 137 (100). HRMS: Calcd. for $C_{18}H_{19}N_3O_3$ = 325.1422. Found = 325.1429.

Method B. The reaction was performed as above, but omitting the addition of the hydrogen chloride-benzene solution. The organic extract, once dried and evaporated under reduced pressure, was chromatographed over alumina. On elution with ethyl acetate, dihydropyridine **19** (57%) was obtained. ^{1}H-NMR: 8.80 (s, 1H, NH); 8.45 (s, 1H, NH); 7.53 (d, J=7.5 Hz, 1H, H-4 indole); 7.32 (d, J=7.5 Hz, 1H, H-7 indole); 7.14 (s, 1H, H-2 pyr); 7.20-7.05 (m, 2H, H-5 and H-6 indole); 6.60 (s, 1H, H-3 indole); 5.58 (d, J=8 Hz, 1H, H-6 pyr); 4.63 (bd, J=8 Hz, 1H, H-5 pyr); 4.34 (bs, 1H, H-4 pyr); 3.97 (d, J=5.3 Hz, 1H, H-6); 3.85 (s, 3H, NCH_3). ^{13}C-NMR: 171.1 (C=O); 167.5 (C=O); 142.8 (C-2 pyr); 136.1 (C-7a indole); 131.2 (C-2 indole); 130.6 (C-6 pyr); 124.8 (C-3a indole); 120.4 (C-5 indole); 120.0 (C-6 indole); 119.8 (C-4 indole); 110.9 (C-7 indole); 104.9 (C-5 pyr); 103.0 (C-3 indole); 94.1 (C-3 pyr); 47.2 (C-6); 41.2 (NCH_3); 32.2 (C-4 pyr). IR (KBr): 3403 (N-H); 3333 (N-H); 1681 (C=O); 1645 (C=O); 1566 (C=C). UV, λ_{max} nm (log ε): 369 (4.3); 282 (4.8); 221 (5.0). MS (m/z, %): 293 (M+, 15); 292 (32); 291 (100); 237 (21); 149 (38).

Isomerization of 20. A solution of compound **20** (52 mg, 0.18 mmol) in DMSO (5 ml) was heated at 95°C for 10h. After the solvent was removed under reduced pressure, compound **21** was obtained (50 mg, 96%). ^{1}H-NMR (DMSO-d_6): 10.90 (s, 1H, NH); 10.20 (s, 1H, NH); 7.50 (d, J=7 Hz, 1H, H-4 indole); 7.31 (d, J=6.5 Hz, 1H, H-7 indole); 7.25-7.00 (m, 2H, H-5 and H-6 indole); 6.93 (s, 1H, H-6 pyr); 4.62 (m, 1H, H-2 pyr); 4.04 (d, J=4 Hz, 1H, H-6); 3.30 (m, 1H, H-4 pyr); 3.11 (s, 3H, NCH_3); 2.05 (m, 2H, H-12). ^{13}C-NMR (DMSO-d_6): 173.9 (C=O); 167.1 (C=O); 146.2 (C-3); 136.9 (C-7a indole); 131.5 (C-2 indole); 126.3 (C-3a indole); 121.4 (C-6 indole); 119.7 (C-5 indole); 118.3 (C-4 indole); 112.2 (C-7 indole); 108.2 (C-3 indole); 98.1 (C-4); 49.1 (C-1); 47.8 (C-6); 41.7 (NCH_3); 29.2 (C-12); 28.0 (C-5). IR ($CHCl_3$): 3370 (N-H); 3250 (N-

H); 1692 (C=O); 1650 (C=O); 1592 (C=C). UV, λ max nm (log ε): 277 (3.8); 218 (4.1). MS (m/z, %): 293 (M$^+$, 100); 167 (49).

Tetrahydropyridine 23. A solution of dihydropyridine **19** (93 mg, 0.32 mmol) in ethyl acetate (50 ml) was hydrogenated over palladium hydroxide (250 mg) at atmospheric pressure. The progress of the reaction was monitored by TLC (silica gel; 95:3:2 ether-acetone-diethylamine). When the spot of starting material disappeared, the reaction was stopped. The catalyst was filtered off, and the filtrate was evaporated to give a foam which was chromatographed over silica-gel. On elution with ethyl acetate, pure tetrahydropyridine **23** (60 mg, 64%) was obtained. ^{1}H-NMR: 8.90 (s, 1H, NH); 8.20 (s, 1H, NH); 7.70 (s, 1H, H-6 pyr); 7.45 (d, J=7.5 Hz, 1H, H-4 indole); 7.30 (d, J=7.5 Hz, 1H, H-7 indole); 7.25-7.00 (m, 2H, H-5 and H-6 indole); 6.42 (s, 1H, H-3 indole); 3.95 (d, J=5.4 Hz, 1H, H-6); 2.98 (s, 3H, NCH_3). IR ($CHCl_3$): 3500 (N-H); 3420 (N-H); 1706 (C=O); 1688 (C=O); 1596 (C=C). UV, λ max nm (log ε): 321 (4.1); 282 (4.1); 218 (4.6). MS (m/z, %): 295 (M$^+$, 70); 273 (28); 251 (82); 139 (100). HRMS: Calcd. for $C_{17}H_{17}N_3O_2$ = 295.1320; Found = 295.1313.

Acid Cyclization of 23 to 24. A solution of tetrahydropyridine **23** (75 mg, 0.25 mmol) in anhydrous methanol (10 ml) was added dropwise to a methanol solution of hydrogen chloride (2.5 M, 10 ml), and the resulting solution was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in saturated aqueous sodium carbonate and extracted with ethyl acetate. Evaporation of the dried organic extracts gave a residue which was chromatographed over silica-gel. Elution with ethyl acetate gave **24** (57 mg, 76%). ^{1}H-NMR: 8.67 (s, 1H, NH); 7.49 (d, J=7.5 Hz, 1H, H-4 indole); 7.32 (d, J=8 Hz, 1H, H-7 indole); 7.17 (m, J=8 Hz, 7 and 1 Hz, 1H, H-6 indole); 7.10 (m, J=7.5, 7 and 1 Hz, 1H, H-5 indole); 4.47 (d, J=2.5 Hz, 1H, H-1); 3.75 (d, J=1.5 Hz, 1H, H-6); 3.41 (bs, 1H, H-12); 3.05 (s, 1H, NH); 2.76 (m, 1H, H-5); 2.50 (dd, J=11.5 and 6.5 Hz, 1H, H-3ax); 2.38 (s, 3H, NCH_3); 2.18 (m, 1H, H-4ax); 2.05 (dm, J=11.5, 1H, H-3eq); 1.85 (dm, J= 12 Hz, 1H, H-4eq). ^{13}C-NMR: 173.6 (C=O); 173.5 (C=O); 136.2 (C-7a indole); 131.5 (C-2 indole); 127.4 (C-3a indole); 122.2 (C-6 indole); 120.1 (C-5 indole); 119.1 (C-4 indole); 111.3 (C-7 indole); 102.9 (C-3 indole); 54.3 (C-1); 45.7 (C-6); 45.5 (C-3); 44.3 (NCH_3); 43.8 (C-12); 29.5 (C-4); 27.4 (C-5). IR ($CHCl_3$): 3550 (N-H); 3400 (N-H); 1702 (C=O); 1652 (C=O). UV, λ max nm (log ε): 266 (3.1); 217 (4.7). MS (m/z, %): 295 (M$^+$, 100); 238 (22); 180 (29); 167 (58). HRMS: Calcd. for $C_{17}H_{17}N_3O_2$ = 295.1320; Found = 295.1326.

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13. For instance: compound **10** (R_1=R_2=CO_2CH_3, major stereoisomer), (9%). ^{1}H- NMR ($CDCl_3$): 8.02 (d, J=7 Hz, 1H, H-7 indole); 7.54 (d, J=6.5 Hz, 1H, H-4 indole); 7.46 (s, 1H, H-6 pyr); 7.30-7.20 (m, 2H, H-5 and H-6 indole); 6.84 (s, 1H, H-3 indole); 4.47 (d, J=9 Hz, 1H, H-α); 3.99 (s, 3H, OCH_3); 3.67 (s, 3H, OCH_3); 3.64 (s, 3H, OCH_3); 2.99 (s, 3H, NCH_3). ^{13}C-NMR ($CDCl_3$); 171.0 (C=O); 167.5 (C=O); 146.8 (C-6 pyr); 137.5 (C-7a indole); 135.2 (C-2 indole); 129.5 (C-3a indole); 124.3 (C-6 indole); 123.3 (C-5 indole); 120.6 (C-4 indole); 115.7 (C-7 indole); 110.3 (C-3 indole); 98.5 (C-5 pyr); 53.4 (OCH_3); 52.0 (OCH_3); 50.6 (OCH_3); 49.8 (C-α); 43.5 (C-2 pyr); 42.8 (NCH_3); 31.5 (C-4 pyr); 24.0 (C-3 pyr). IR ($CHCl_3$): 1739 (C=O); 1675 (C=O); 1623 (C=C). UV, λ_{max} nm (log ε): 292 (3.94); 282 (3.74); 258 (4.03); 226 (4.26).
14. For instance: compound **11** (R_1=R_2=CO_2CH_3, major stereoisomer), (7%). ^{1}H- NMR ($CDCl_3$): 8.1 (d, J=6.5 Hz, 1H, H-7 indole); 7.50 (d, J= 6.5 Hz, 1H, H-4 indole); 7.35 (s, 1H, H-6 pyr); 7.30-7.20 (m, 2H, H-5 and H-6 indole); 6.75 (s, 1H, H-3 indole); 4.80 (d, J=9 Hz, 1H, H-2 pyr); 4.05 (s, 3H, OCH_3); 3.69 (s, 3H, OCH_3); 3.68 (s, 3H, OCH_3); 3.06 (s, 3H, NCH_3); 2.25-1,50 (m, 4H, H-3 and H-4 pyr). ^{13}C-NMR ($CDCl_3$): 172.4 (C=O); 168.7 (C=O); 152.1(C=O); 145.2 (C-6 pyr); 136.1 (C-7a indole); 134.8 (C-2 indole); 128.8 (C-3a indole); 124.7 (C-6 indole); 123.3 (C-5 indole); 120.6 (C-4 indole); 115.7 (C-7 indole); 111.0 (C-3 indole); 95.8 (C-5 pyr); 59.0 (C-2 pyr); 53.8 (OCH_3); 52.5 (OCH_3); 50.6 (OCH_3); 46.2 (C-α); 42.2 (NCH_3); 22.4 (C-3 pyr); 16.4 (C-4 pyr). IR ($CHCl_3$): 1733 (C=O); 1676 (C=O); 1622 (C=C). UV, λ_{max} nm (log ε): 292 (4.51); 286 (4.43); 266 (4.30); 225 (4.62). MS (m/z, %): 400 (M^+, 1); 369 (2); 155 (12); 154 (100).
15. Wenkert, E.; Dave, K.G.; Haglid, F.; Lewis, R.G.; Oishi, T.; Stevens, R.V.; Terashima, M. *J. Org. Chem.* **1968**, *33*, 747.

16. Compound **17**: ^{1}H- NMR ($CDCl_3$): 8.9 (bs, 1H, NH); 7.65 (d, J=6.5 Hz, 1H, H-4 indole); 7.36 (s, 1H, H-6 pyr); 7.40-7.00 (m, 3H, H-5, H-6 and H-7 indole); 6.38 (d, J=10 Hz, 1H, H-4 pyr); 5.62 (m, 1H, H-2 pyr); 4.95 (dd, J=10 Hz and 3 Hz, 1H, H-3 pyr); 3.89 (s, 2H, CH_2); 3.78 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 2.73 (s, 3H, NCH_3). IR ($CHCl_3$): 3550 (N-H); 1734 (C=O); 1672 (C=O). UV, λ_{max} nm (log ε): 290 (3.90); 283 (3.90); 217 (4.16). MS (m/z, %): 340 (M^+, 11); 295 (13); 283 (12); 267 (17); 215 (40); 154 (100).

17 For a similar reaction, see: Alvarez, M.; Lavilla, R.; Bosch, J. *Heterocycles*, **1989**, *29*, 237.

18. Compound **18**: ^{1}H-NMR ($CDCl_3$): 9.00(bs, 1H, NH); 7.52 (s, 1H, H-6 pyr); 7.49 (d, J=6.0 Hz, 1H, H-4 indole); 7.35-7.00 (m, 3H, H-5, H-6 and H-7 indole); 4.49 (m, 1H, H-2 pyr); 3.80 (s, 2H, CH_2); 3.39 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 2.75 (s, 3H, NCH_3); 2.40-1.90 (m, 4H, H-3 and H-4 pyr).

19. Bahadur, G.A.; Bailey, A.S.; Middleton, N.W.; Peach, J.M. *J. Chem. Soc., Perkin I*, **1980**, 1688.

20. Bergman, J.; Pelcman, B. *Tetrahedron* **1988**, *44*, 5215. ^{1}H-NMR ($CDCl_3$): 8.80 (bs, 1H, NH indole); 7.42 (d, J=6.6 Hz, 1H, H_4 indole); 7.20-6.90 (m, 3H, H-5, H-6 and H-7 indole); 6.14 (s, 1H, H-3 indole); 3.80 (t, J=6 Hz, 2H, $-CH_2O-$); 3.00 (bs, 1H, OH); 2.85 (t, J=6 Hz, 2H, $-CH_2-C$).

21. a) A similar reaction has been reported: Wanner, M.J.; Koomen, G.J.; Pandit, U.K. *Tetrahedron* **1983**, *39*, 3673; b) Although presumably the formation of the carbon - carbon bond precedes the closure of the imide ring, the term "intramolecular" is used because of the reversibility of the first step.

22. For related cyclizations see: a) Jackson, A.; Wilson, N.V.D.; Gaskell, A.J.; Joule, J.A. *J. Chem. Soc. (C)* **1969**, 2738; b) Hashimoto, C.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 4563; c) ref. 2a.

23. For catalytic hydrogenations of "intramolecular" dihydropyridines, see: a) Weller, D.D; Stirchak, E.P.; Weller, D.L. *J. Org. Chem.* **1983**, *48*, 4597; b) Rosenberg, S.H.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 56.

24. For a recent example of a doubly bridged system, see: Woudenberg, R.H.; Lie, T.-S.; Maat, L. *J. Org. Chem.* **1993**, *58*, 6139.

25. Massiot, G.; Boumendjel, A.; Nuzillard, J.M.; Richard, B.; Le Men-Olivier, L.; David, B.; Hadi, H.A. *Phytochemistry* **1992**, *31*, 1078.

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