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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS 95.[1] ATTEMPTED BUILD-UP OF THE ASPIDOSPERMIDINE SKELETON BY [4+2] CYCLOADDITION. SOME UNEXPECTED REACTIONS, AND FORMATION OF A NEW RING SYSTEM

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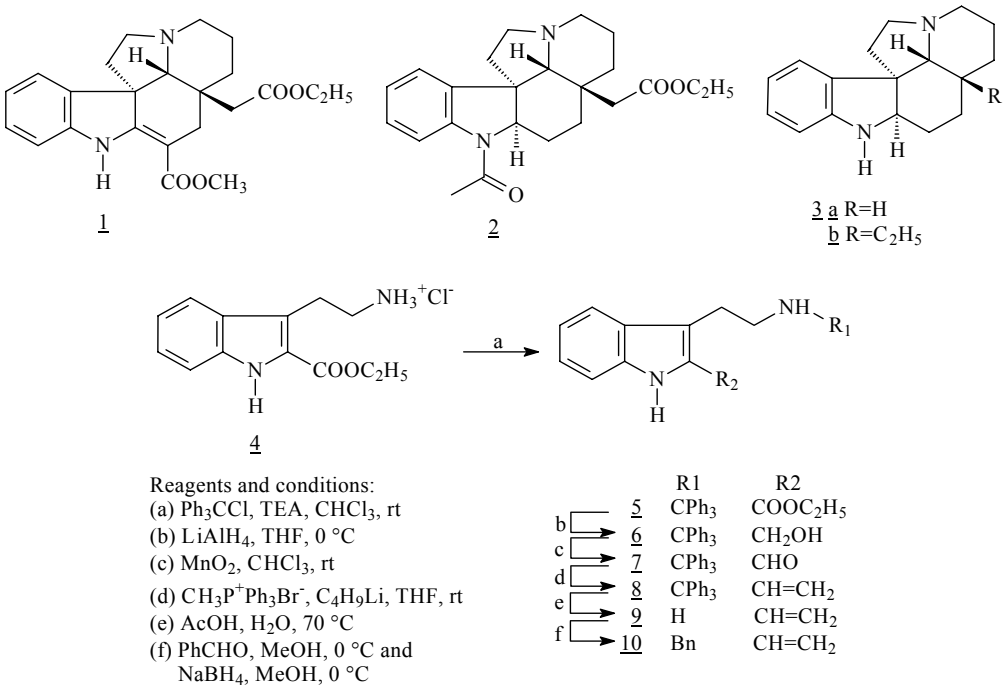
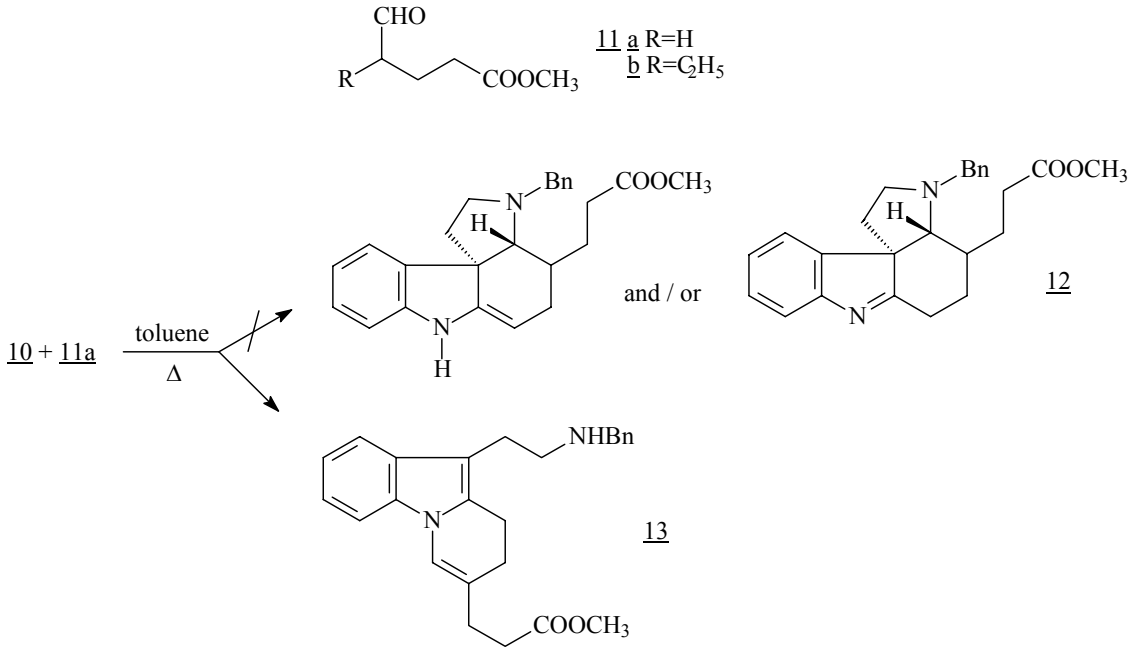
Abstract – The reaction of the 2-vinylindole derivative (**10)** with methyl 4-formylbutanoate (**11a)** gave a pyrido[1,2-*a*]indole (**13),** instead of the expected seco-aspidospermidine (**12)**. Similarly, this cycloaddition reaction failed with the vinyl-enamide (**19),** the products were two 5*H*-pyrido[1',2':1,8]azocino[5,4-*b*]-indole derivatives, (**20** and **21)**.

Using our formerly developed synthetic strategy based on [4+2] cycloaddition reactions,[2] we achieved the synthesis of (±)-19-ethoxycarbonyl-19-demethylvincadifformine (**1**).[3] This alkaloid-like molecule, containing the anilinoacrylate structural unit, had already been converted in several steps by Brennan and Saxton[4] into a natural product, (±)-12-demethoxy-*N*(1)-acetylcylindrocarine (**2**), belonging to the aspidospermine group. Consequently, our synthesis constituted the formal synthesis of this compound. Since the above conversion gave the target molecule only in a moderate yield, we wanted to find a pathway involving the [4+2] cycloaddition reaction, successfully used in the build-up of vincadifformine-tabersonine type of molecules.[5] Our aim was the preparation of deethylaspidospermidine (**3a**), and then of aspidospermidine (**3b**).



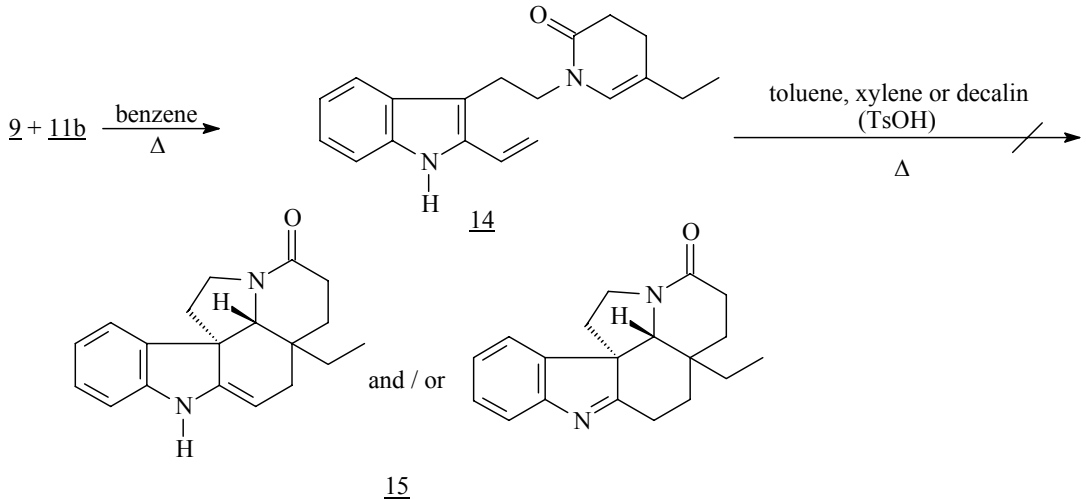
Scheme 1

Starting from 2-ethoxycarbonyltryptamine hydrochloride (**4**),[6] its N_b-trityl derivative (**5**) was prepared in basic medium. **5** was reduced with metal hydride to the alcohol (**6**), which was oxidized with manganese(V) oxide to furnish the aldehyde (**7**). The latter compound, was transformed into the vinyl derivative (**8**) by the help of the ylid derived from triphenylmethylphosphonium bromide. On removal of the protecting group, compound (**9**) was made to react with benzaldehyde, and the resulting Schiff base, without isolation, was converted into the secondary amine (**10**) (Scheme 1).
First, the reaction of **10** with methyl 4-formylbutanoate (**11a**)[7] was tried in the hope of achieving the desired cycloaddition to **12**, by interaction of the diene structural part of **10** – consisting the indole ring and the vinyl group – and the enamine derived from the secondary amine and the aldehyde. It was found, however, that instead of [4+2] cycloaddition the product (**13**) was formed. Very likely the first step was the addition of **11a** to the vinyl group of **10**, followed by enolization of the formyl group. Subsequent dehydration involving the indole-NH group resulted in **13** (Scheme 2).



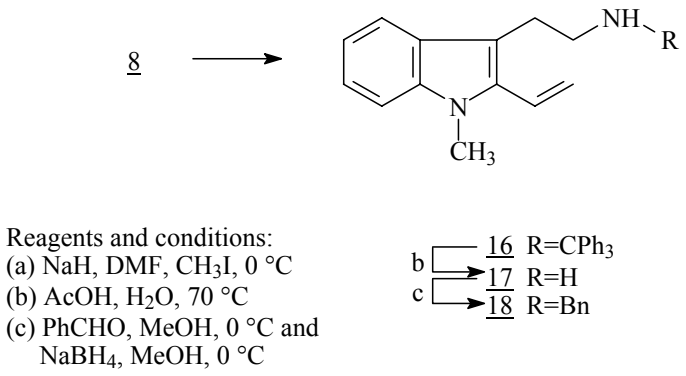
Scheme 2

If the reacting aldehyde had only one hydrogene atom in α-position (**11b**),[8] the reaction gave no definite product. The next notion was to utilise our former experience,[9] i.e. to try to form an enamide unit in the molecule that would readily react with the diene under suitable reaction conditins to furnish the desired [4+2] cycloaddition product.



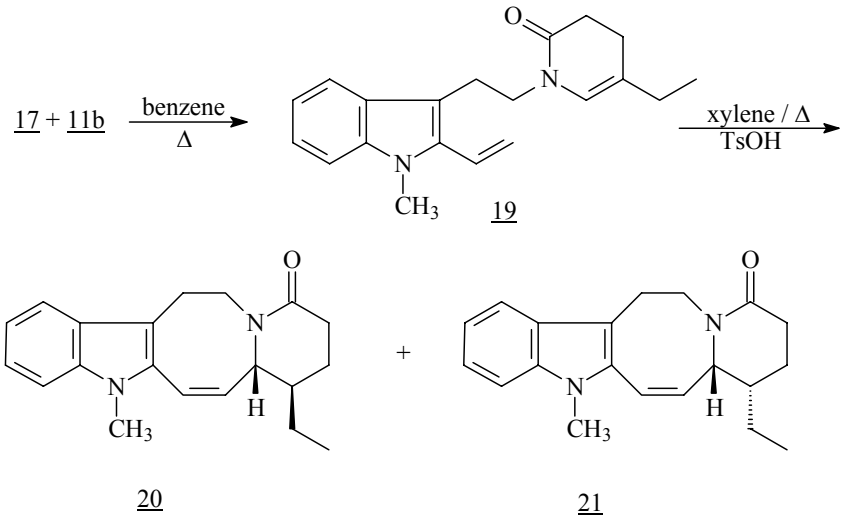
Scheme 3

The interaction of **9** and **11b** was effected at the boiling point of benzene to give the expected compound (**14**), which, however, did not yield the cycloaddition product (**15**) even on refluxing in toluene, xylene or decalin, either in the presence or absence of *p*-toluenesulfonic acid. The starting materials was recovered unchanged (Scheme 3).
In view of the above results, we attributed the failure of the cycloaddition reaction to the presence of the mobile hydrogene atom of the indole ring. Therefore it was substituted by a methyl group, and the reactions described above were carried out with these compounds (Scheme 4).



Scheme 4

The boiling of **18** in toluene, xylene or decalin, with or without *p*-toluenesulfonic acid, neither with **11a** nor with **11b** resulted in a definite product, the starting materials suffered decomposition.
When the primary amine (**17**) was made to react with **11b** in benzene, a well-defined product was obtained. This enamide (**19**) was refluxed in toluene in the presence of *p*-toluenesulfonic acid. This reaction gave two isomeric tetracyclic compounds, representing a new heterocyclic ring system (**20**) and (**21**). The formation of the isomers occurs by addition of the vinyl side chain to the enamide structural part (Scheme 5).



Scheme 5

In conclusion it can be stated that non-activated 2-vinylindole derivatives, in contrast with our earlier experience,[2] do not react as dienes under the given conditions in the reactions described above; they undergo addition reactions of different types instead.

ACKNOWLEDGEMENT

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EXPERIMENTAL

Melting points are uncorrected and were obtained using Hotstage microscope Betius apparatus. IR spectra were obtained using a Specord JR-75 Spectrophotometer. ^{1}H and ^{13}C NMR spectras were recorded on a Varian VXL-400 Spectrometer. Chemical shifts (in ppm) are relative to internal standard tetramethylsilane. Mutual ^{1}H-^{1}H couplings are given only once, at their first occurrences. MS spectra were recorded using a VG-TRIO-2 quadrupol Mass Spectrometer. Column chromatography was accomplished using Merck Kieselgel 60 Mesh. Preparative thin layer chromatography was performed with Silica gel plates F254 (Merck).

3-[2-(Tritylamino)ethyl]-1*H*-indole-2-carboxylic acid ethyl ester (**5**)
To a solution of 17 g (0.061 mol) of tritylchloride in 150 mL of dry chloroform 10.0 g (0.037 mol) of 2-(ethoxycarbonyl)tryptamine hydrocloride was added in one portion. To the resulted suspension 15 mL of triethylamine (0.108 mol) in 30 mL of dry chloroform was added over a period of 1 h. During the addition, the suspension was slowly dissolved. After the addition was complete, the reaction mixture was stirred for 3 h. The solution was extracted with water, dried with magnesium sulfate, concentrated in vacuum. The resulted oil was dissolved in 100 mL of ether. Hydrogen chloride in ether was added to the solution until the pH became acidic. The precipitated salt was filtered, washed with diethyl ether. The hydrochloride salt was suspended in chloroform (200 mL), treated with 2M sodium hydroxide solution and water subsequently. The organic phase was dried with magnesium sufhate, and evaporated in vacuum. The resulted oil was crystallised with methanol as a white powder, 14.7 g (84 %), mp 142-144 ºC; IR (KBr): 3340 (indole-NH), 1680 cm^{-1} (CO). MS m/z (%): 474 (2/30), 397 (14/30), 258 (32/30), 243 (100.0), 165 (25.0), 86 (49.0). ^{1}H NMR δ_H ($CDCl_3$): 1.34 + 4.35 (3H+5H, t+q, J_{vic}=7.0 Hz; COOEt), 1.77 (1H, br s; NH), 2.51 (2H, br t, J=6.8 Hz; $C\underline{H}_2NH$), 3.33 (2H, t, J=6.8 Hz; C3-CH_2), 7.05-7.65 (19H, m; 3xPh+C4-H+C5-H+C6-H+C7-H), 8.78 (1H, br s; indole-NH). ^{13}C NMR δ_C ($CDCl_3$): 14.46($COOCH_2\underline{C}H_3$), 25.82 (C3-$\underline{C}H_2$), 44.31(CH_2NH), 60.71 ($COO\underline{C}H_2CH_3$), 70.87 (NH-$\underline{C}Ph_3$), 111.67 (C7), 120.1 (C4), 121.04 (C5), 122.63 (C3), 123.77 (C3a), 125.59 (C6), 126.12 (3xC4'), 127.68 (3xC2'+3xC6'), 128.39 (C2), 128.59 (3xC3', 3xC5'), 135.82 (C7a), 146.20 (3xC1'), 162.43 (<u>C</u>OOEt). Anal. Calcd for $C_{32}H_{30}N_2O_2$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.90; H, 6.37; N, 6.05.

{3-[2-(Tritylamino)ethyl]-1*H*-indol-2-yl}methanol (**6**)
0.91 g (24 mmol) of $LiAlH_4$ was suspended in 50 mL of dry THF under argon. The suspension was cooled under 5 ºC with an ice bath, than 4.75 g (10 mmol) of **5** in 50 mL of THF solution was added droppwise. After the addition, the reaction mixture was allowed to warm to rt, and was stirred for 1 h. Cooled to 0 ºC, the excess of the $LiAlH_4$ was destroyed with slow addition of 5 mL of 2M sodium hydroxide solution to the reaction mixture. The inorganic salts were separated with filtration, and the filtrate was concentrated in vacuum. The precipitated product was treated with methanol and filtered to yield 3.0 g (69 %) as a white crystal, mp 199-200 ºC; IR (KBr): 3270 (indole-NH) cm^{-1}; MS m/z (%): 258 (18.0), 243 (100.0), 189 (29.0), 165 (54.0), 142 (20.0), 115 (13.0)); ^{1}H NMR δ_H ($CDCl_3$+DMSO-d_6): 2.42 (2H, t, J=6.9 Hz; $C\underline{H}_2NH$), 2.62 (2H, br s; OH+NH), 2.93 (2H, t, J=6.9 Hz; C3-CH_2), 4.76 (2H, s; C2-CH_2), 6.97 (1H, ddd, J_0=7.8 + 7.0, J_m=1.0 Hz; C5-H), 7.06-7.20 (10H, m, 6-H+3xC4'-H+3xC3'-H+3xC5'-H), 7.28-7.40 (8H, m; 3xC2'-H+3xC6'-H+C4-H+C7-H), 9.44 (1H, br s; indole-NH); ^{13}C NMR δ_C ($CDCl_3$+DMSO-d_6): 2.10 (C3-$\underline{C}H_2$), 44.24 (CH_2NH), 55.90 (C2-CH_2), 70.86 (NH-$\underline{C}Ph_3$), 109.44 (C3), 110.79 (C7), 118.59+118.62 (C4+C5), 121.27 (C6), 126.03 (3xC4'), 127.56 (3xC2'), 128.18 (C3a), 128.51 (3xC3'+3xC5'), 135.54+135.62 (C2+C7a), 146.01 (3xC1'). Anal. Calcd for $C_{30}H_{28}N_2O_2$: C, 83.30; H, 6.52; N, 6.48. Found: C, 83.32; H, 6.54; N, 6.49.

3-[2-(Tritylamino)ethyl]-1*H*-indole-2-carbaldehyde (**7**)
To a magnetically stirred solution of 6.0 g (0.014 mol) of **6** in 200 mL of chloroform, manganese dioxide (15 g, 0.17 mol) was added. The suspension was stirred for 2.5 h, flittered. The filtrate was concentrated in vacuum to yield a yellow oil, which was crystallised from methanol to give 5.4 g (90 %) of **7**, mp 187-189 ºC; IR (KBr): 3310 (indole-NH), 1650 cm^{-1} (CHO); MS m/z (%): 243 (100.0), 165 (60.0), 130 (8.0), 115 (8.0), 77 (8.0). ^{1}H NMR δ_H ($CDCl_3$): 1.65 (1H, br s; NH), 2.55 (2H, t J=6.9 Hz; $C\underline{H}_2NH$), 3.26 (2H, t,

J=6.9 Hz; C3-CH_2), 7.05-7.4 (18H, m; 3xPh+C4-H+C5-H+C6-H), 7.61 (1H, m; C7-H), 8.96 (1H, br s; indole-NH), 10.04 (CHO). ^{13}C NMR δ_C ($CDCl_3$): 25.12 (C3-CH_2), 44.84 (CH_2NH), 71.01 (NH-$\underline{C}Ph_3$), 112.26 (C7), 120.57 (C4), 121.68 (C5), 126.30 (3xC4'), 126.97 (C3), 127.54 (C6), 127.73 (C3a), 127.83 (3xC2'+3xC6'), 128.50 (3xC3'+3xC5'), 132.77 (C7a), 137.42 (C2), 145.93 (3xC1'), 180.72 (CHO).). Anal. Calcd for $C_{30}H_{26}N_2O_2$: C, 83.69; H, 6.09; N, 6.51. Found: C, 83.51; H, 6.09; N, 6.4.

Trityl-[2-(2-vinyl-1*H*-indol-3-yl)ethyl]amine (**8**)
To a stirred solution of 1.9 g (1.16 mmol) of methyltriphenylphosphonium bromide in 20 mL of dry THF, 1.9 mL (4.75 mmol) of 2.5 M n-butyllithium was added under argon. After stirring the yellow solution for 30 min, the solution of 0.5 g (1.16 mmol) of **7** in 20 mL of dry THF was added, and the reaction mixture was stirred for 1 h. The THF was removed in vacuum, the residue was dissolved in dichloromethane, washed with water, dried with magnesium sulfate, concentrated in vacuum, to give a yellow residue, which was crystallised from methanol to yield 4.4 g (88 %) as a yellow powder, mp 182-184 ºC decomp.; IR (KBr): 420 (indole-NH), 3060, 2930, 2870, 1640 cm^{-1} (vinyl CH=CH_2); MS m/z (%): 24 (100.0), 194 (10.0), 185 (29.0), 165 (63.0), 156 (56.0), 129 (15.0), 115 (5.0), 91 (8.0), 77 (10.0); HRMS Calcd for MH^+: 429.23306 found 429.233167. ^{1}H NMR δ_H ($CDCl_3$): 1.66 (1H, br s; NH), 2.45 (2H, t, J=7.0 Hz; $C\underline{H}_2NH$), 2.98 (2H, t, J=7.0 Hz; C3-CH_2), 5.25+5.43 (2x1H, 2xdd, J_{gem}=0.8, J_{cis}=11.2 and J_{trans}=17.5 Hz, respectively; CH=$C\underline{H}_2$), 6.90 (1H, dd, J=11.2 and 17.5 Hz; $C\underline{H}$=CH_2), 6.98-7.44 (19H, m, 3xPh+C4-H+C5-H+C6-H, C7-H), 7.99 (1H, br s; indole-NH).). ^{13}C NMR δ_C ($CDCl_3$): 25.27 (C3-$\underline{C}H_2$), 44.10 (CH_2NH), 70.96 (NH-$\underline{C}Ph_3$), 110.46 (C7), 110.87 (CH=$\underline{C}H_2$), 114.13 (C3), 119.37+119.48 (C4+C5), 123.05 (C6), 125.91 ($\underline{C}H$=CH_2), 126.12 (3xC4'), 127.70 (3xC2'+3xC6'), 128.65 (3xC3'+3xC5'), 128.94 (C3a), 132.96 (C7a), 136.20 (C2), 146.24 (3xC1').

[2-(2-Vinyl-1*H*-indol-3-yl)ethyl]amine (**9**)
0.85 g (2 mmol) of **8** was dissolved in the mixture of 20 mL of acetic acid and 0.5 mL of water. The solution was heated under argon at 60 ºC for 1 h, and then allowed to cool to rt. The resulted dark solution was diluted with 200 mL of water, the triphenylmethanol was removed by extraction with ether. The pH of the watery phase was adjusted to a value of 8 with sodium carbonate solution, extracted with dichloromethane, the extract was dried with magnesium sulfate, evaporated to dryness in vacuum. The resulted brown oil, 0.24 g (64 %) was known to be unstable,[10] therefore the product was immediately submitted to the next step without further purification.

Benzyl-[2-(2-vinyl-1*H*-indol-3-yl)ethyl]amine (**10**)
0.3 g (1.6 mmol) of **9**, 0.187 g (1.75 mmol) of benzaldehyde and 3 g of molcular sieve (3A) were allowed to stand overnight in 10 mL of methanol at 5 ºC. The molecular sieve was filtered off, the filtrate was cooled to 0 ºC and 0.15 g (4.0 mmol) of $NaBH_4$ was added. After stirring the reaction mixture for 1 h, acidified with 1 N HCl to pH 1, diluted with water, extracted the excess of benzyl alcohol with diethyl ether. The pH of the watery phase was adjusted to 8 with 25% sodium carbonate solution, extracted with dichloromethane. The extract was dried with magnesium sulfate, and concentrated in vacuum. The purification of the crude product with column chromatography on silica gel, using 10 % methanol in dichloromethane as the eluent gave 0.24 g (54 %) **10** as an unstable yellow oil. IR (neat): 3030, 3070 cm^{-1} (vinyl CH=CH_2); MS m/z (%): 276 (0.15), 261 (9.0), 157 (21.0), 120 (20.0), 91 (100.0), 77 (31.0); HRMS Calcd for M^+: 276.162648 found 276.162530. ^{1}H NMR δ_H ($CDCl_3$): 1.60 (1H, br s; NH), 2.95+3.02 (2x2H, 2xt; J=70 Hz; C3-$C\underline{H}_2C\underline{H}_2NH$), 3.80 (2H, s; NCH_2Ph), 5.22+5.44 (2x1H, 2xdd, J_{gem}=0.8, J_{cis}=11.2 and J_{trans}=17.5 Hz, respectively; CH=$C\underline{H}_2$), 6.87 (1H, dd, J=11.2 and 17.5 Hz; $C\underline{H}$=CH_2), 7.00-7.60 (9H, m; Ph+C4-H+C-5H+C6-H+C7-H), 8.14 (1H, br s; indole-NH). ^{13}C NMR δ_C ($CDCl_3$): 24.68 (C3-$\underline{C}H_2$), 49.92 (CH_2NH), 53.82 ($N\underline{C}H_2Ph$), 110.62 (C7), 111.22 (CH=$\underline{C}H_2$), 113.83 (C3), 119.17+119.57 (C4+C5), 123.11 (C6), 125.59 ($\underline{C}H$=CH_2), 126.83 (C4'), 127.99 (C3'+C5'), 128.35 (C2'C6'), 128.81 (C3a), 132.88 (C7a), 136.29 (C2), 140.29 (C1').

3-[10-(2-Benzylaminoethyl)-8,9-dihydropyrido[1,2-*a*]indol-7-yl]propionic acid methyl ester (**13**)
0.1 g (0.36 mmol) of **10** and 0.05 g (0.38 mmol) of methyl 4-formylbutanoate (**11a**) were heated at reflux for 4 h. The solution was concentrated in vacuum, and the crude product was purified by column chromatography on silica gel, using 50 % acetone in hexane as the eluent, gave 67 mg (48 %) yellowish oil. IR (neat): 1720 cm^{-1} (CO).). MS m/z (%): 388 (2.0), 315 (5.0), 268 (78.0), 194 (35.0), 180 (26.0), 120 (22.0), 91 (100.0). HRMS Calcd for M^+: 388.21508 found 388.21412. ^{1}H NMR δ_H ($CDCl_3$): 2.28 (2H, td, J=7.2 and 1.2 Hz; C8-H_2), 2.52 (4H, s; C7-$C\underline{H}_2C\underline{H}_2$), 2.9-3.0 (6H, m; C9-$H_2$+C10-$CH_2CH_2N$), 3.68 (3H, s; OCH_3), 3.83 (2H, s; N-CH_2Ph), 6.90 (br t, J=1.2 Hz; C6-H), 7.06 (1H, ddd, $J_{1,2}$=7.2, $J_{2,3}$=6.7 and

$J_{2,4}$=1.3 Hz; C2-H), 7.15 (1H, ddd, $J_{3,4}$=7.1 and $J_{1,3}$=1.2 Hz; C3-H), 7.29 (1H, ddd, $J_{1,4}$=0.8 Hz; C4-H), 7.20-7.30 (5H, m; Ph), 7.49 (1H, ddd; C1-H). NOE: 6.90 (C6-H) -> 7.29 (C4-H), 2.52 (C7-CH_2); 2.52 (C7-(CH_2CH_2) -> 6.90 (C6-H), 2.28 (C8-H_2), 3.68 (OCH_3); 7.49 (C1-H) -> 7.06 (C2-H), 2.95 (C10-CH_2). ^{13}C NMR δ_C ($CDCl_3$): 20.33 (C9), 24.17 (C10-CH_2), 24.64 (C8), 29.95 (C7-CH_2), 32.90 (CH_2COOCH_3), 49.08 (CH_2NH), 51.70 (OCH_3), 53.47 ($NHCH_2Ph$), 108.00 (C4), 108.50 (C10), 118.38 (C1), 119.25 (C7), 119.80 (C2), 121.43 (C3), 127.23 (C4'), 128.27 (C3'+C5'), 128.37 (C10a), 128.48 (C2'+C6'), 131.28 (C9a), 133.66 (C4a), 139.0 (C1'), 173.35 ($COOCH_3$).

3-[(3'-Ethyl-4', 5'-dihydro-1*H*-pyridine-6'-on-1'-yl)ethyl]-2-vinylindole (**14**)
0.2 g (1 mmol) of **9** and 0.19 g (1.1 mmol) of ethyl 4-formylhexanoate (**11b**) were heated at refluxed in 50 mL of benzene for 2.5 h. After the reaction mixture was cooled to rt, the solvent was removed in vacuum. Purification of the residue by chromatography on a silica gel column, using 50 % acetone in hexane as eluent, gave 0.2 g of (63 %) **14** as a yellow gum. IR (neat): 3305 (indole-NH), 2920,2965,2870 (vinyl CH=CH_2), 1650 cm^{-1} (CO). MS m/z (%): 294 (12.0), 169 (100.0), 156 (57.0), 138 (14.0), 129 (20.0), 110 (19.0), 39 (30.0). ^{1}H NMR δ_H ($CDCl_3$): 0.84 (3H, t; J=7.5 Hz; C3'-$CH_2\underline{CH_3}$), 1.87 (2H, qtd, J=7.5, 1.0, 1.4 Hz; C3'-$\underline{CH_2}CH_3$), 2.12 (2H, ttd, J=8.0, 1.0 and 1.2 Hz; C4'-H_2), 2.45 (2H, t, J=8.0 Hz; C5'-H_2), 3.06 (2H, t, J=7.0 Hz; C3-CH_2), 3.65 (2H, t, J=7.0 Hz; CH_2N), 5.24+5.48 (2x1H, 2xd, J_{cis}=11.2 and J_{trans}=17.5 Hz, respectively; CH=$C\underline{H_2}$), 5.40 (1H, tt, J=1.4 and 1.2 Hz; C2'-H), 6.83 (1H, dd, J=11.2 and 17.5 Hz; $C\underline{H}$=CH_2), 7.08 (1H, ddd, J_o=7.8 and 7.0, J_m=1.0 Hz; C5-H), 7.17 (1H, ddd, J_o=8.1 and 7.0, J_m=1.3 Hz; C6-H), 7.28 (1H, ddd, J_o=8.1, J_m=1.0, J_p=0.9 Hz; C7-H), 7.59 (1H, ddd, J_o=7.8, J_m=1.3, J_p=0.9 Hz; C4-H), 8.22 (1H, br s; indole-NH). ^{13}C NMR δ_C ($CDCl_3$): 12.30 (C3'-$CH_2\underline{C}H_3$), 23.04 (C3-CH_2), 24.10 (C4'), 26.61 (C3'-$\underline{C}H_2CH_3$), 31.33 (C5'), 47.51 (CH_2N), 110.63 (C7), 111.34 (CH=$\underline{C}H_2$), 112.76 (C3), 118.90+119.62 (C5+C4), 120.81 (C3'), 123.10 (C6), 124.08 (C2'), 125.47 ($\underline{C}H$=CH_2), 128.75 (C3a), 133.17 (C7a), 136.29 (C2), 168.84 (NCO).

[2-(1-Methyl-2-vinyl-1*H*-indol-3-yl)ethyl]tritylamine (**16**)
25 mg (0.6 mmol) of 60 % NaH was suspended in 5 mL of dry DMF, then 0.21 g (0.5 mmol) of **8** was added in a solution of 2 mL DMF. After stirring the dark green solution for 15 min, 0.14 g (1 mmol) of methyliodide was added. The mixture was stirred for an other 30 min. The solvent and the excess of methyliodide was removed in vacuum, the residue was dissolved in dichloromethane, washed with water, dried over magnesium sulfate and evaporated to yield a yellow oil, which was crystallised from acetone-methanol as a yellow powder, 0.137 g (89 %), mp 135-136 ºC decomp. IR (KBr): 3060, 3010, 2920, 1610 cm^{-1} (vinyl CH=CH_2). MS m/z (%):243 (100.0), 199 (27.0), 170 (79.0), 165 (56.0), 154 (12.0), 128 (8.0), 115 (8.0), 91 (6.0), 77 (5.0). ^{1}H NMR δ_H ($CDCl_3$): 1.7 (1H, br s; NH), 2.47 (2H, t, J=7.1 Hz; $C\underline{H_2}NH$), 3.03 (2H, t, J=7.1 Hz; C3-CH_2), 3.69 (3H, s; NCH_3), 5.46+5.55 (2x1H, 2xdd, J_{gem}=1.5, J_{cis}=11.7 and J_{trans}=17.7 Hz, respectively; CH=$C\underline{H_2}$), 6.76 (1H, dd, J=17.7 and 11.7; $C\underline{H}$=CH_2), 7.00-7.50 (19H, m; 3xPh+C4-H+C5-H+C6-H+C7-H). ^{13}C NMR δ_C ($CDCl_3$): 26.06 (C3-CH_2), 30.75 (NCH_3), 44.41 (CH_2NH), 71.04 ($NH\underline{C}Ph_3$), 108.93 (C7), 112.21 (C3), 117.98 (CH=$\underline{C}H_2$), 119.06+119.22 (C4+C5), 122.08 (C6), 126.13 ($\underline{C}H$=CH_2+3xC4'), 127.70 (3xC2'+3xC6'), 127.92 (C3a), 128.69 (3xC3'+3xC5'), 134.96 (C7a), 137.44 (C2), 146.25 (3xC1'). Anal. Calcd for $C_{32}H_{30}N_2$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.76; H, 6.84; N, 6.21.

2-(1-Methyl-2-vinyl-1*H*-indol-3-yl)ethylamine (**17**)
To prepare **17**, the same procedure was used, as in the case of **9**, starting from 0.88 g (2 mmol) of **16**. The resulted crude product, 0.29 g (72 %) was unstable, and used for the next step without further purification.

Benzyl-[2-(1-methyl-2-vinyl-1*H*-indol-3-yl)ethyl]amine (**18**)
For the preparation of **18**, the same procedure was used, as in the case of **10,** starting from 0.13 g (0.65 mmol) of **17**. Chromatographic purification of the crude product gave 0.11 g (58 %) of **17** as an unstable yellow oil. IR (neat): 1610 cm^{-1} (vinyl CH=CH_2). MS m/z (%): 290 (4.0), 275 (5.0), 171 (80.0), 158 (20.0), 120 (26.0), 91 (100.0); HRMS Calcd for M^+: 290.1783 found 290.1779. ^{1}H NMR δ_H ($CDCl_3$): 1.85 (1H, br s; NH), 2.95+3.08 (2x2H, 2xt, J=7.2 Hz; C3-CH_2CH_2NH), 3.72 (3H, s; NCH_3), 3.81 (2H, s; $NH\underline{C}H_2Ph$), 5.49+5.61 (2x1H, 2xdd, J_{gem}=1.5, J_{cis}=11.7 and J_{trans}=17.8 Hz, respectively; CH=$C\underline{H_2}$), 6.79 (1H, dd, J=17.8 and 11.7; $C\underline{H}$=CH_2), 7.05-7.60 (9H, m; Ph+C4-H+C5-H+C6-H+C7-H). ^{13}C NMR δ_C ($CDCl_3$): 25.41 (C3-CH_2), 30.76 (NCH_3), 49.95 (CH_2NH), 53.83 ($NHCH_2Ph$), 109.10 (C7), 112.02 (C3), 118.21 (CH=$\underline{C}H_2$), 119.02+119.2 (C4+C5), 122.19 (C6), 126.02 ($\underline{C}H$=CH_2), 126.85 (C4'), 127.78 (C3a), 128.05 (C3'+C6'), 134.92 (C7a), 137.50 (C2), 140.14 (C1').

5-Ethyl-1-[2-(1-methyl-2-vinyl-1*H*-indol-3-yl)ethyl]-3,4-dihydro-1*H*-pyridin-2-one (**19**)
The same method was used to prepare **19**, as for **14**, starting from 0.2 g (1 mmol) of **17**. The chromatographic purification of the crude product yield 0.22 g (71 %) of **19** as a light gum. IR (neat): 2960, 2910, 2880 (vinyl CH=CH_2) 1660 (CO) cm^{-1}. MS m/z (%): 308 (34.0), 183 (80.0), 170 (100.0), 154 (16.0), 128 (19.0), 115 (12.0), 40 (42.0); HRMS Calcd for MH^+: 309.19669 found 309.19584. ^1H NMR δ_H ($CDCl_3$): 0.90 (3H, t, J=7.3 Hz; C3'-$CH_2C\underline{H}_3$), 1.93 (2H, qtd, J=7.3, 1.0 and 1.4 Hz; C3'-$C\underline{H}_2CH_3$), 2.15 (2H, ttd, J=8.0, 1.0 and 1.2 Hz; C4'-H_2), 2.46 (2H, t, J=8.0 Hz; C5-H_2), 3.11 (2H, t, J=7.4 Hz; C3-CH_2), 3.66 (2H, t, J=7.4 Hz; CH_2N), 3.74 (3H, s; NCH_3), 5.53+5.69 (2x1H, 2xdd, J_{gem}=1.3, J_{cis}=11.8 and J_{trans}=17.8 Hz, respectively; CH=C$\underline{H}_2$), 5.54 (1H, tt, J=1.4 and 1.2 Hz; C2'-H), 6.79 (1H, dd, J=17.8 and 11.8 Hz; C$\underline{H}$=CH_2), 7.10 (1H, ddd, J_o=7.8 and 7.0, J_m=1.2 Hz; C5-H), 7.21 (1H, ddd, J_o=8.2 and 7.0, J_m=1.2 Hz; C6-H), 7.26 (1H, ddd, J_o=8.2, J_m=1.2, J_p=0.8 Hz; C7-H), 7.63 (1H, ddd, J_o=7.8, J_m=1.2, J_p=0.8 Hz; C4-H). ^{13}C NMR δ_C ($CDCl_3$): 12.29 (C3'-$CH_2\underline{C}H_3$), 23.88 (C3-CH_2), 24.14 (C4'), 26.66 (C3'-$\underline{C}H_2CH_3$), 30.75 (NCH_3), 31.82 (C5'), 47.25 (CH_2N), 109.08 (C7), 110.98 (C3), 118.11 (CH=$\underline{C}H_2$), 118.80+119.32 (C4+C5), 120.88 (C3'), 122.24 (C6), 123.93 (C2'), 125.82 ($\underline{C}H=CH_2$), 127.79 (C3a), 134.96 (C7a), 137.49 (C2), 168.77 (NCO).

(±)-(7a*R*,8*R*)-8-Ethyl-5-methyl-7a,8,9,10,13,14-hexahydro-5*H*-pyrido[1',2':1,8]azocino[5,4-*b*]indol-11-one (**20**) and (±)(7a*R*,8*S*)-8-ethyl-5-methyl-7a,8,9,10,13,14-hexahydro-5*H*-pyrido[1',2':1,8]azocino[5,4-*b*]indol-11-one (**21**)
0.2 g (3.2 mmol) of **19** and 20 mg of *p*-toluolsulfonic acid monohydride was dissolved in 20 mL of toluene. The mixture was heated at reflux for 3 h. The solvent was removed in vacuum, and the residue was purified by preparative TLC (eluent: 10% methanol in dichloromethane), which yielded 51 mg (25 %) of **20** as a yellow gum. IR (neat): 3020 (vinyl CH=CH_2) 1630 (CO) cm^{-1}. MS m/z (%): 308 (100.0), 293 (32.0), 279 (45.0), 251 (10.0), 194 (27.0), 182 (64.0), 167 (46.0), 54 (21.0), 39 (22.0); HRMS Calcd for M^+: 308.18886 found 308.18873. ^1H NMR δ_H ($CDCl_3$): 0.88 (3H, t, J=7.5 Hz; C8-$CH_2C\underline{H}_3$), 1.22+1.45 (2x1H, 2xdqd, J_{gem}=13.7, J_{vic}=7.5+8.5 and 7.5+4.8 Hz, respectively; C8-$C\underline{H}_2CH_3$), 1.48 (1H, dddd, J_{gem}=13.5, $J_{9\beta,10\alpha}$=9.0, $J_{9\beta,10\beta}$=6.2, $J_{8\alpha,9\beta}$=8.3 Hz; C9-H_β), 1.64 1H, ddddd, $J_{7a\beta,8\alpha}$=6.2, $J_{8\alpha,9\alpha}$=4.2 Hz; C8-H_α), 2.04 (1H, dddd, $J_{9\alpha,10\alpha}$=6.6, $J_{9\alpha,10\beta}$=5.3 Hz; C9-H_α), 2.35+2.46 (2x1H, 2xddd, J_{gem}=17.5 Hz; C10-H_2), 3.00-3.15 (2H, m; C14-H_2), 3.65 (3H, s; NCH_3), 4.00+4.11 (2x1H, 2xddd, J_{gem}=13.8, $J_{13,14}$=5.8+3.2 and 8.7+3.6 Hz, respectively; C13-H_2), 4.05 (1H, ddd, $J_{7,7a\beta}$=8.0, $J_{6,7a\beta}$=1.2 Hz; C7a-H_β), 5.72 (1H, dd, $J_{6,7}$=11.0 Hz; C7-H), 6.71 (1H, dd, J=11.0 Hz; C6-H), 7.11 (1H, ddd, $J_{1,2}$=7.8, $J_{2,3}$=6.4, $J_{2,4}$=1.7 Hz; C2-H), 7.23 (1H, ddd, $J_{3,4}$=8.2, $J_{1,3}$=1.3 Hz; C3-H), 7.26 (1H, ddd, $J_{1,4}$=0.7 Hz; C4-H), 7.52 (1H, ddd, J=0.7 Hz; C1-H). NOE: 1.64 (C8-H_α) -> 5.72 (C7-H), 4.05 (7a-H_β), 0.87+1.45+1.22 (C8-Et), 2.35 (C10-H_α), 2.04 (C9-H_α); 5.72 (C7-H) -> 6.71 (C6-H), 1.64 (C8-H_α), 2.04 (C9-H_α), 4.05 (C7a-H_β); 6.71 (C6-H) -> 5.72 (C7-H), 3.65 (NCH_3). ^{13}C NMR δ_C ($CDCl_3$): 11.46 (C8-$CH_2\underline{C}H_3$), 23.06 (C9), 25.37 (C8-$\underline{C}H_2CH_3$), 25.40 (C14), 29.86 (NCH_3), 30.61 (C10), 40.20 (C13), 40.89 (C8), 59.33 (C7a), 108.90 (C4), 112.96 (C14a), 118.60 (C1), 119.26 (C2), 122.48 (C3), 122.63 (C6), 127.48 (C14b), 131.95 (C5a), 132.77 (C7), 137.23 (C4a), 170.05 (C11) and 18 mg (9 %) of **21** as a yellow gum. IR (neat): 3020 (vinyl CH=CH_2) 1630 (CO) cm^{-1}. MS m/z (%): 308 (100.0), 293 (36.0), 279 (55.0), 251 (18.0), 194 (30.0), 182 (48.0), 167 (38.0), 54 (27.0), 39 (30.0); HRMS Calcd for M^+: 308.1888 found 308.1888. ^1H NMR δ_H ($CDCl_3$): 0.77 (3H, t, J=7.3 Hz; C8-$CH_2C\underline{H}_3$), 1.20-1.40 (2H, m; C8-$C\underline{H}_2CH_3$), 1.70-1.95 (3H, m; C8-H_β+C9-H_2), 2.40-2.60 (2H, m; C10-H_2), 2.68+3.26 (2x1H, 2xddd, J_{gem}=16.0, $J_{13,14}$=8.8+1.7 and 8.5+1.5 Hz, respectively; C14-H_2), 3.09+4.56 (2x1H, 2xddd, J_{gem}=13.5 Hz; C13-H_2), 3.67 (3H, s; NCH_3), 3.95 (1H, dddd, $J_{7,7a\beta}$=8.6, $J_{7a\beta,8\beta}$=3.8, $J_{6,7a\beta}$=1.0, J_b=1.0 Hz; C7a-H_β), 5.96 (1H, dd, $J_{6,7}$=11.0 Hz; C7-H), 6.72 (1H, dd J=11.0 Hz; C6-H), 7.13 (1H, ddd, $J_{1,2}$=7.9, $J_{2,3}$=6.6, $J_{2,4}$=1.4 Hz; C2-H), 7.25 (1H, ddd, $J_{3,4}$=8.2, $J_{1,3}$=1.2 Hz; C3-H), 7.28 (1H, ddd, $J_{1,4}$=0.7 Hz; C4-H), 7.57 (1H, ddd, J=0.4 Hz; C1-H). NOE: 3.95 (C7a-H_β)-> 1.80 (C8-H_β), 3.09 (C13-H_β), 0.77+1.28 (C8-Et), 3.26 (C14-H_β), 5.96 (C7-H); 5.96 (C7-H) -> 6.72 (C6-H), 1.28 (C8-$C\underline{H}_2CH_3$), 3.95 (C7a-H_β); 3.67 (NCH_3) -> 6.72 (C6-H), 7.28 (C4-H). ^{13}C NMR δ_C ($CDCl_3$): 11.45 (C8-CH_2-$\underline{C}H_3$), 22.73 (C9), 24.79 (C14), 25.21 (C8-$\underline{C}H_2CH_3$), 30.06 (NCH_3), 30.77 (C10), 38.98 (C8), 41.88 (C13), 56.83 (C7a), 108.97 (C4), 113.66 (C14a), 118.58 (C1), 119.30 (C2), 122.38 (C3), 122.58 (C6), 127.42 (C14b), 128.90 (C7), 133.37 (C5a), 137.27 (C4a), 169.77 (C11).

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