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SYNTHETIC APPLICATIONS OF 2-CYANO-1,2,3,6-TETRAHYDROPYRIDINES. 3.[1] SYNTHESIS OF 19,20-ISO-16-DEMETHYLENEERVITSINE[2]

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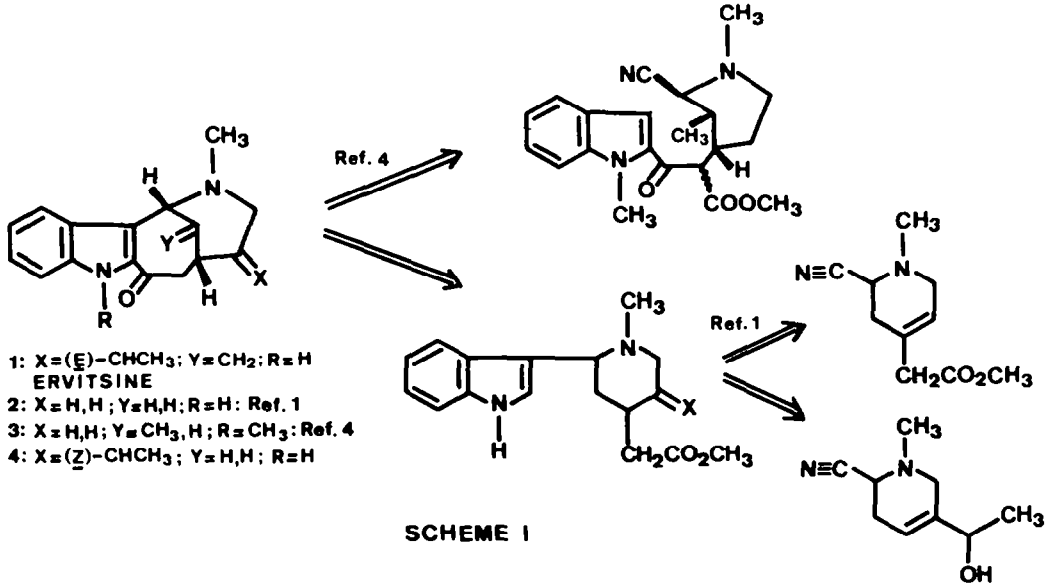
Abstract- The synthesis of 19,20-iso-16-demethyleneervitsine (4), a simplified analogue of the indole alkaloid ervitsine, is reported. The last step of the synthesis consists in the hydrolysis followed by PPA cyclization of methyl (Z)-5-ethylidene-2-indolylpiperidine-4-acetate 8. This key intermediate was prepared from 5-(hydroxyethyl)-2-cyano-1,2,3,6-tetrahydropyridine 6, by condensation with indole followed by orthoester Claisen rearrangement of the resulting allylic alcohol.

2-Cyano-1,2,3,6-tetrahydropyridines constitute a class of compounds easily accessible by reductive cyanation of pyridinium salts by means of sodium borohydride in the presence of a large excess of cyanide ions.[3] These compounds are useful and versatile synthons[4] because they can undergo a variety of synthetic transformations. i) At the cyano group: addition of organolithium reagents gives aryl (or alkyl) tetrahydropyridyl ketones,[5] whereas lithium aluminium hydride reduction leads to 2-(aminomethyl) tetrahydropyridines.[6] ii) At the C-2 position of the tetrahydropyridine ring: the cyano group can be substituted,through the corresponding 2,5-dihydropyridinium salt, by reaction with Grignard reagents[1,5,7,8] or, directly, with activated aromatic rings such as indole.[1,8-14] In this way it is possible to construct the 3-(2-piperidyl)indole moiety common to most of *Strychnos* and *Aspidosperma* indole alkaloids.[15] iii) At the piperidine nitrogen substituent: thus, further hydrogenolysis of N-benzyl group



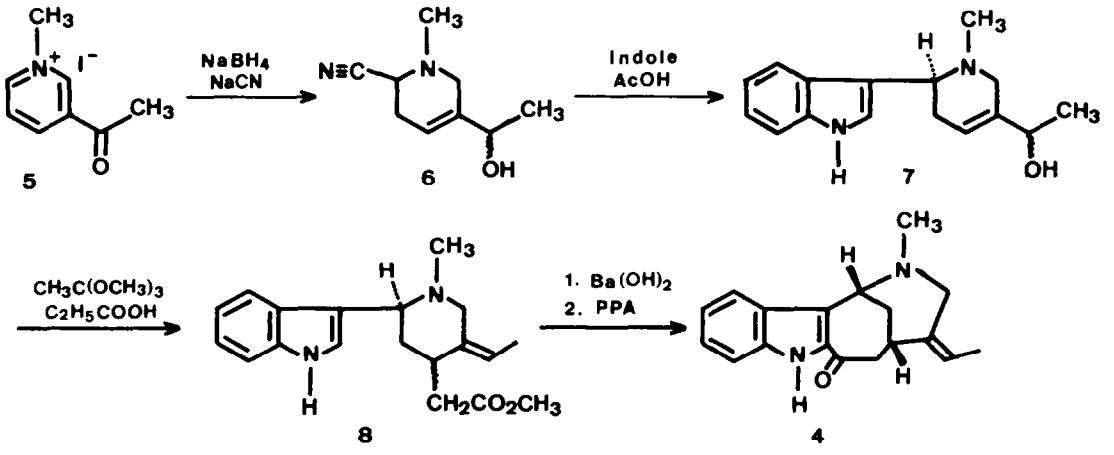
SCHEME I

affords the corresponding *N*-unsubstituted piperidine.[1,8] Such a transformation constitutes one of the steps of a recent synthetic entry to pentacyclic *Strychnos* alkaloids. iv) At the carbon-carbon tetrahydropyridine double bond: this double bond can be suppr sed by hydrogenation to give piperidines,[1,8,13] can be used to promote acid-induced el trophilic cyclizations upon aromatic rings,[3a,5-7] can allow the introduction of an alk substituent at the C-5 piperidine position by means of a conjugate addition,[1] or can b further elaborated[11,14,17] to the ethylidene substituent[18] present in some indole alka loids. The syntheses of 6,7-benzomorphans[7] and heteroaromatic analogues,[5] ß-homobenzomorphans,[1] the indole alkaloid deplancheine,[11] and simplified models of the indole alk loids deplancheine,[17] dasycarpidone,[1,8] ervitsine,[1] strictamine,[13] and vinoxine[13,14] fully illustrate the above aspects.

In this paper we wish to report another synthetic application of 2-cyano-1,2,3,6-tetrahydropyridines. When the substituent at C-5 of the tetrahydropyridine is 1-hydroxyethyl, it is possible to take again advantadge of the tetrahydropyridine carbon-carb double bond once the condensation with indole has been effected. By the use of the orthoester Claisen rearrangement,[19,20] the allylic alcohol moiety simultaneously allows to elaborate an exocyclic ethylidene substituent at the 5-position of the piperidine ring and to introduce a functionalized two-carbon chain at the C-4 position.[21] In this way, we present here a short synthesis of a 16-demethylene analogue (4) of ervitsine (a minor 2-acylindole alkaloid isolated in 1977 from *Pandaca boiteaui*[22] whose most rema kable features are the presence of two exocyclic (16-methylene and 20-ethylidene)[23] pi peridine double bonds. Although two synthetic approaches to the tetracyclic ring syste of ervitsine have been reported,[1,4,24,25] (see Scheme I) no total synthesis for this alkaloid has been described yet.

The required 2-cyanotetrahydropyridine 6, having the 1-hydroxyethyl substituent a the C-5 position of the pyridine ring, was prepared in the usual way by reductive cyan tion of pyridinium salt 5. As expected, reduction of the carbonyl group also occurred to give an equimolecular mixture of diastereomers, which were evidenced from the obser vation of two close set of signals in the ^{1}H- and ^{13}C-NMR[26] spectra. The IR spectrum o 6 showed absorptions at 3400-3500 and 2215 cm^{-1} due to the hydroxy and cyano groups, r pectively, whereas the most significant signals in the ^{1}H-NMR spectrum were a quartet and a doublet attributable to the hydroxyethyl substituent and a doublet of doublets corresponding to the C-2 methine proton.

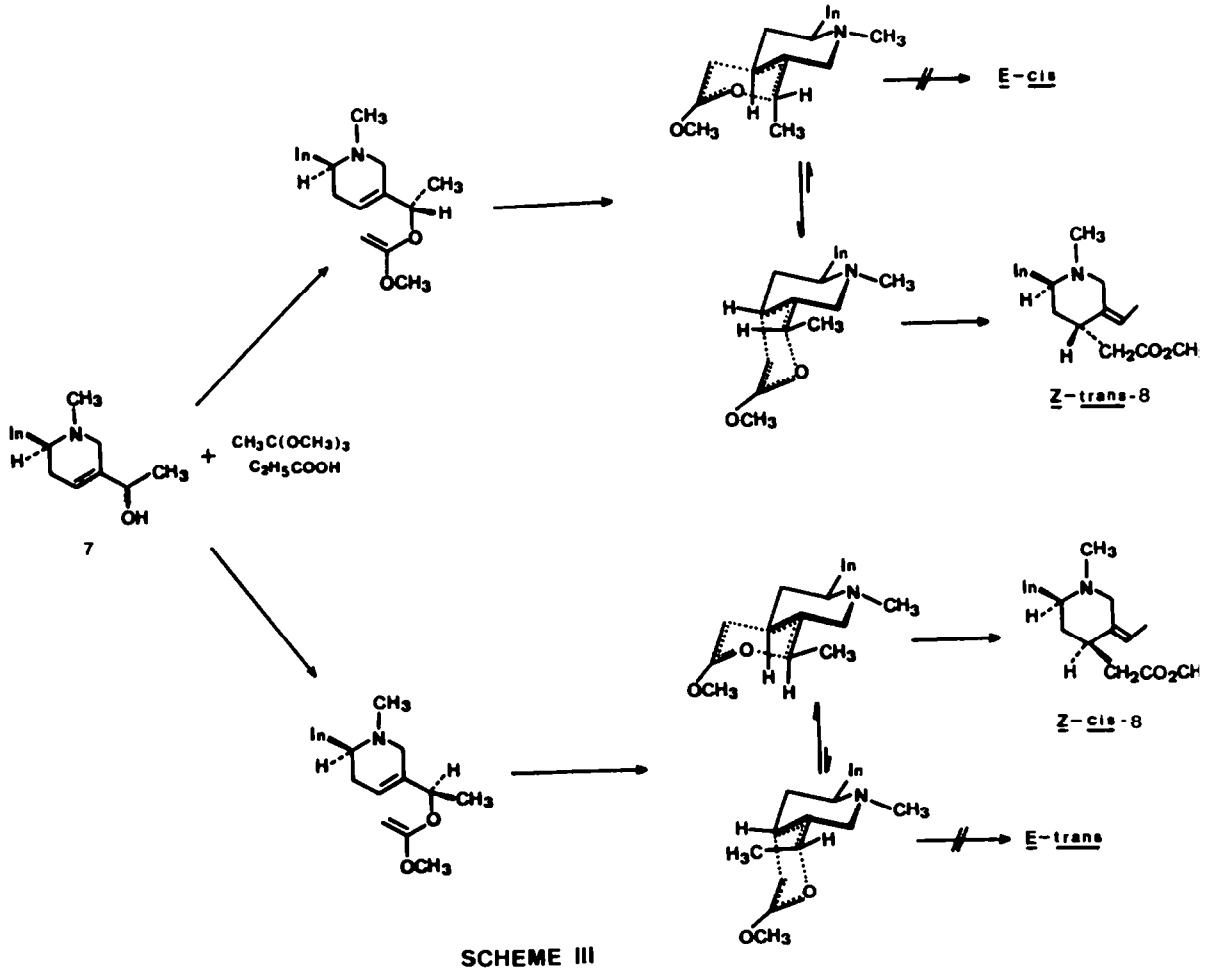
Condensation of the cyanotetrahydropyridine mixture 6 with indole in aqueous acet acid afforded the allylic alcohols 7 as a 1:1 diastereomeric mixture which was submitt to an orthoester Claisen rearrangement with trimethyl orthoacetate and propionic acid.



SCHEME II

A nearly equimolecular C-4 epimeric mixture of amino esters 8, having the unnatural Z configuration for the exocyclic ethylidene substituent, was obtained.[27] The reaction is stereospecific,[28] and each diastereomer in the starting allylic alcohols 7 gives rise to one diastereomeric amino ester 8, as illustrated in Scheme III. The Z double bond configuration follows from the fact that transition states in which the C-methyl group can adopt an equatorial disposition are favoured over those in which the C-methyl group is axial.

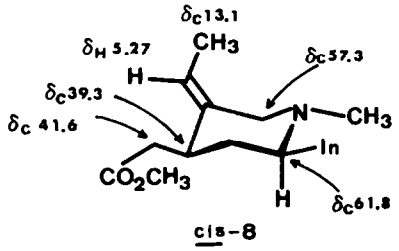
The IR spectrum of isomeric esters 8 showed a strong absorption at 1740 cm^{-1} due t the ester carbonyl group formed in the process. The ^{1}H-NMR spectrum exhibited, as the most significant signals, a doublet and a quartet (J=6.6 Hz) attributable to the ethylidene substituent and singlets due to the methyl and methylene groups of the methyl acetate moiety. The comparison of ^{13}C-NMR spectra of *cis*-8 and *trans*-8 allowed the assignment of the relative stereochemistry at carbons 2 and 4 of the piperidine ring. Thus, in *trans*-8 the axial C-4 substituent produces an upfield γ-effect shift of ∿5 ppm upon the piperidine C-2 and C-6 resonances with respect to isomer *cis*-8. On the other hand, the predictable unnatural Z-configuration of the ethylidene substituent was confirmed by comparing the ^{13}C-NMR chemical shifts of C-4 (δ 39.3) and C-6 (δ 57.3) in *cis*-8 with those of the corresponding deethylidene analogue (δ 33.6 and 56.8, respectively; $\Delta\delta_{C-4}$ 5.7 and $\Delta\delta_{C-6}$ 0.5).[29] The magnitude of the deshielding effect upon the vicinal carbons exerted by the introduction of an ethylidene substituent at the 3-position of a piperidine ring depends on the configuration of the exocyclic double bond.[30] As compared with the corresponding deethylidene analogues, in the Z-isomers carbon 2 under goes a lower downfield shift than carbon 4 as a consequence of the 1,4-gauche interaction between the methyl group and C_2-H, which results in an additional upfield shift.



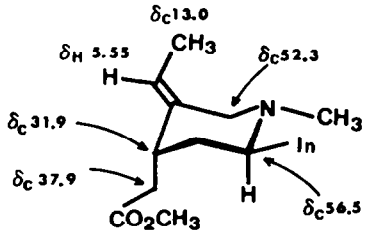
SCHEME III

This interaction does not operate upon C-4. For the same reason, the substitution at the piperidine 3-position by an E-ethylidene group produces a downfield effect higher at C-2 than at C-4.

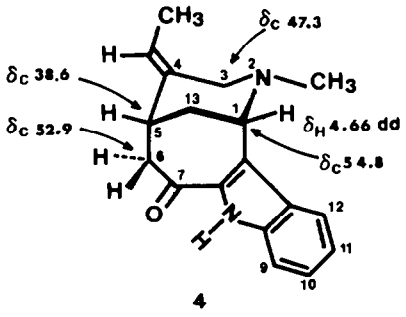
Finally, hydrolysis of the epimeric mixture of amino esters 8 with barium hydroxide solution, followed by PPA cyclization of the resulting amino acids, afforded the 7-membered cyclic ketone 4 in 10% yield. Formation of 2-acylindole moiety was evidenced by an IR absorption at 1630 cm^{-1}. On the other hand, the ^{1}H-NMR spectrum showed a doublet of doublets due to the bridgehead equatorial methine proton adjacent to the indole ring and characteristic signals for the methine and methyl protons of the ethylidene substituent and for the diastereotopic C-6 methylene protons. The Z-configuration of ethylidene group was confirmed as above by ^{13}C-NMR taking into account that the deshielding effect caused by the introduction of the ethylidene substituent is higher upon C-5 ($\Delta\delta$ 11.0) than upon C-3 ($\Delta\delta$ 0.7).[31]



cis-8



trans-8



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SCHEME IV

EXPERIMENTAL

General- Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Varian XL-200 (200 MHz) spectrometer. ^{13}C-NMR spectra were recorded on a Varian XL-200 spectrometer (50.3 MHz). Unless otherwise indicated, NMR spectra were measured in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) downfield from TMS as internal standard. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60, Merck, 63-200 μm). Thin layer chromatography was done on Merck silica gel 60 F_{254} aluminium precoated sheets, and the spots were located with UV light or iodoplatinate reagent. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate. Microanalyses were performed by Instituto de Química Bio-Orgánica, Barcelona.

5-(1-Hydroxyethyl)-1-methyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (6). Hydrochloric acid (6N, 42ml) was added dropwise to a stirred solution of sodium cyanide (28 g, 0.57 mol) in water (400 ml), layered with ether (600 ml), and kept below 15 °C. To this mixture were added the pyridinium iodide[32] 5 (35 g, 0.13 mol) and then sodium borohydride (10 g, 0.26 mol) portionwise. The mixture was stirred at room temperature for 5 h, ether was decanted , and the aqueous layer was extracted with methylene chloride. The combined organic solutions were extracted with aqueous 5% hydrochloric acid,

aqueous solution was basified with sodium carbonate and extracted again with methylene chloride, dried, and evaporated to give 6 (12.4 g, 56%) as an oil. An analytical sampl was obtained by preparative TLC using 1:9 acetone-ether as developing solvent. IR (NaC 3400-3500 (OH) and 2215 (CN) cm^{-1}; ^{1}H-NMR 1.32 and 1.33 (2d, J=6.5 Hz, 3H, CCH_3), 2.38 (br d, J=16 Hz, 1H, 3-H), 2.48 (s, 3H, NCH_3), 2.70 (br d, J=16 Hz, 1H, 3-H), 2.98 (br J=16 Hz, 1H, 6-H), 3.26 and 3.34 (2br d, J=16 Hz, 1H, 6-H),3.83 and 3.84 (2 dd, J=6 an 2 Hz, 1H, 2-H), 4.24 and 4.28 (2q, J=6 Hz, 1H, OCH), 5.68 (m, 1H, =CH); ^{13}C-NMR 21.5 and 21.8 (2q, CCH_3), 29.0 and 29.1 (2t, C-3), 43.6 (q, NCH_3), 48.7 and 49.5 (2t, C-6), 51.4 and 51.45 (2d, C-2), 69.2 and 69.8 (2d, OCH), 115.4 and 114.6 (2d, C-4), 116.3 a 116.2 (2s, C≡N), 140.4 and 140.6 (2s, C-5). (Found: C, 65.15; H, 8.38; N, 16.93. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85).

5-(1-Hydroxyethyl)-2-indolyl-1-methyl-1,2,3,6-tetrahydropyridine (7). A solution of 2-cyanotetrahydropyridine 6 (2.8 g, 17 mmol) and indole (3.4 g, 29 mmol) in acetic acid (60 ml) and water (60 ml) was stirred for 24 h. After addition of concentrated hydrochloric acid (2 ml), the solution was washed with benzene, basified with aqueous sodiu hydroxide solution, and extracted with methylene chloride. Drying and evaporation of the extracts gave a solid (3.4 g) which was purified by column chromatography. On elut with 9:1 chloroform-methanol, 7 (2.4 g, 55%) was obatined as a mixture of isomers. A p re isomer of 7 was obtained from one column fraction and recrystallized from methanol: m.p. 141-142 °C; IR (KBr) 3100-3400 (OH); ^{1}H-NMR 1.36 (d, J=6.5 Hz, 3H, CCH_3), 2.14 (b 1H, OH), 2.22 (s, 3H, NCH_3), 2.43 (br d, J=17 Hz, 1H, 3-H), 2.6-2.8 (m, 1H, 3-H), 3.08 br d, J=16 Hz, 1H, 6-H), 3.54 (br d, J=16 Hz, 1H, 6-H), 3.76 (dd, J=10 and 5 Hz, 1H, 2-4.43 (q, J=6.5 Hz, 1H, OCH), 5.84 (br s, 1H, =CH), 7.1-7.3 (m, 3H, indole), 7.40 (dt, J=7.1 and 1.2 Hz, 1H, 7′-H), 7.72 (dd, J=7.1 and 0.6 Hz, 1H, 4′-H), 8.50 (br, 1H, NH); ^{13}C-NMR 21.1 (q, CCH_3), 33.1 (t, C-3), 42.4 (q, NCH_3), 53.4 (t, C-6), 56.1 (d, C-2), 6 (d, OCH), 115.3 (d, C-7′), 114.2 (s, C-3′), 118.5 (d, =CH), 118.9 (d, C-4′), 119.4 (d, C-6′), 121.4 (d, C-2′), 122.9 (d, C-5′), 127.4 (s, C-3a′), 136.3 (s, C-7a′), 139.2 (s, C-5); MS m/e (relative abundance) 257 (M^++1, 12), 256 (M^+, 53), 241 (13), 239 (9), 223 (4), 211 (17), 209 (5), 159 (21), 158 (100), 157 (72), 130 (41), 118 (18). (Found: C, 74.60; H, 7.95; N, 10.70. Calcd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93).

Methyl (Z)-5-Ethylidene-2-indolyl-1-methylpiperidine-4-acetate (8). A solution of 7 (8.9 35 mmol), trimethyl orthoacetate (40 g, 0.33 mol), and propionic acid (0.26 g, 3.5 mmo in anhydrous DME (200 ml) was refluxed for 1.5 h under nitrogen atmosphere. After evap ration *in vacuo*, the product was purified by column chromatography. Elution with 99:1 t 97:3 methylene chloride- methanol gave 8 (6.1 g, 56%) as an equimolecular mixture of c and *trans*-isomers. Pure *cis*-8 was obtained by recrystallization of a column fraction: m.p. 180-181 °C (acetone); IR (KBr) 1740 (C=O) and 755 (=C-H); ^{1}H-NMR ($CDCl_3$-CD_3OD) 1. br d, J=6.6 Hz, 3H, $=CCH_3$), 1.98 (ddd, J=12, 4, and 3.2 Hz, 1H, 3-He), 2.17 (s, 3H, NC 2.28 (dd, J=17.6 and 10.4 Hz, 1H, 3-Ha), 2.61 (d, J=12.6 Hz, 1H, 6-Ha), 2.70 (apparent s, $OCCH_2$), 3.55 (dd, J=10.4 and 3.2 Hz, 1H, 2-Ha), 3.65 (s, 3H, OCH_3), 3.91 (d, J=12.6 Hz, 1H, 6-He), 5.27 (q, J=6.6 Hz, 1H, =CH), 7.0-7.2 (m, 3H, indole), 7.37 (dt, J=7 and 1 Hz 1H, 7′-H), 7.68 (dd, J=7 and 1 Hz, 1H, 4′-H); ^{13}C-NMR 13.1 (q, $=CCH_3$), 37.1 (t, C-3), 3 (d, C-4), 41.6 (t, $COCH_2$), 43.8 (q, NCH_3), 51.9 (q, OCH_3), 57.3 (t, C-6), 61.8 (d, C-2 111.7 (d, C-7′), 116.3 (d, =CH), 118.7 and 119.2 (2d, C-4′ and C-6′), 121.8 (d, C-2′), 122.7 (d, C-5′), 127.3 (s, C-3a′), 136.4 and 136.9 (2s, C-7a′ and C-5), 174.2 (s, CO MS m/e (relative abundance) 313 (M^++1, 3), 312 (M^+, 11), 239 (20), 197 (15), 182 (18), 158 (15), 157 (16), 124 (53), 122 (25), 86 (37), 84 (59), 73 (34), 66 (57), 58 (100), (63), 42 (37). (Found: C, 72.94; H, 7.94; N, 8.90. Calcd. for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97). *trans*-8 (lower Rf value): ^{1}H-NMR 1.68 (br d, J=6.6 Hz, 3H, $=CCH_3$), 2.2 (s, 3H, NCH_3), 2.35 (apparent s, 2H, $OCCH_2$), 2.70 (br d, J=12 Hz, 1H, 6-Ha), 3.64 (s, 3H, OCH 3.78 (d, J=12 Hz, 1H, 6-He), 5.55 (q, J=7Hz, 1H, =CH), 7.0-7.3 (m, 3H, indole), 7.36 (J=7 Hz, 1H, 7′-H), 7.69 (d, J=7 Hz, 1H, 4′-H), 9.35 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$+CD_3O 13.0 (q, $=CCH_3$), 37.8 (t, C-3), 31.9 (d, C-4), 37.9 (t, $COCH_2$), 43.2 (q, NCH_3), 51.4 (OCH_3), 52.3 (t, C-6), 56.5 (d, C-2), 111.7 (d, C-7′), 117.7 (d, =CH), 118.7 and 119.2 (2d, C-4′ and C-6′), 121.7 (d, C-2′), 122.9 (d, C-5′), 126.9 (s, C-3a′), 136.4 and 136. (2s, C-7′ and C-5), 173.3 (s, COO).

(Z)-4-Ethylidene-2-methyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1H-azonino[4,3-b]indole (4) To a solution of the mixture of esters 8 (450 mg, 1.44 mmol) in dioxane (20 ml) was ad a saturated aqueous solution of barium hydroxide (50 ml). After stirring for 4 h at 80 the dioxane was evaporated *in vacuo*, and solid carbon dioxide was added to the aqueous solution. The precipitate was filtered off and washed with water. The combined aqueous solution and washings were evaporated to dryness. The residue was dried over P_2O_5 to gi 0.43 g of crude amino acid. This amino acid and excess of PPA were vigorously stirred u der nitrogen at 100 °C for 30 min. The mixture was cooled, poured into ice-water, basif with concentrated ammonium hydroxide, and extracted with methylene chloride. Evaporatic of the extracts gave a solid which was purified by preparative TLC (92:5:3 ether-acetor diethylamine as eluent) to give 4 (40 mg, 10% overall yield): m.p. 168-170 °C (acetone-ether); IR ($CHCl_3$) 3450 (NH) and 1630 (C=O); ^{1}H-NMR 1.63 (dd, J=7 and 1.4 Hz, 3H, $=CCH_3$ 1.70 (m, 1H, 5-H), 2.12 (s, 3H, NCH_3), 2.30 (dt , J=13.5 and 1.8 Hz, 1H, 13-He), 2.49 (br d, J=14.4 Hz, 1H, 3-Ha), 2.62 (m, 1H, 13-Ha), 2.86 (ddd, J=18, 3.6, and 1.5 Hz 1H, 6-H), 3.01 (dd, J=18 and 5.4 Hz, 1H, 6-H), 3.29 (d, J=14.4 Hz, 1H, 3-He), 4.66 (dd,

J=5.4 and 1.8 Hz, 1H, 1-H), 5.47 (qd, J = 7 and 1.6 Hz, 1H, =CH), 7.17 (td, J=8 and 1.5 Hz, 1H, 11-H), 7.36 (td, J=8 Hz, 1H, 10-H), 7.42 (d, J =8 Hz, 1H, 9-H), 7.78 (d, J =8 Hz, 1H, 12-H), 9.06 (br, 1H, NH); ^{13}C-NMR (CD_3OD) 12.7 (q, =CCH_3), 35.3 (t, C-13), 38.6 (d, C-5), 43.7 (q, NCH_3), 47.3 (t, C-3), 52.9 (t, C-6), 54.8 (d, C-1), 113.5 (d, C-9), 121. (d, $CHCH_3$), 122.4 (d, C-11), 122.7 (d, C-12), 127.0 (d, C-10), 127.2 (s, C-12a), 137.1 (s, C-7a), 138.0 (s, C-8a), 196.8 (s, C=O); MS *m/e* (relative abundance) 281 (M^++1, 23), 280 (M^+, 100), 265 (23), 252 (30), 239 (40), 221 (37), 196 (53), 169 (30), 168 (57), 16 (60), 143 (30), 122 (40), 121 (30), 115 (47), 84 (37), 42 (63). (Found: C, 76.94; H, 7. N, 9.95. Calcd. for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99).

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