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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XLVII[1]
SYNTHESIS OF (+)- AND (-)-DEETHYLCATHARANTHINE

Csaba Szántay[a*], Hedvig Bolcskei[b], Eszter Gács-Baitz[a], and Tibor Keve[b]

[a)] Central Research Institute for Chemistry Hungarian Academy of Sciences H-1525 Budapest, P O Box 17, Hungary [b)] Chemical Works of Gedeon Richter Ltd. H-1475 Budapest, P.O.Box 27, Hungary

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Abstract. Synthesis of optically active deethylcatharanthine (1) was performed in a few steps. While studying various approaches and reaction conditions new rearrangements (7 ⟶ 8 ⟶ 9 and 4b ⟶ 12) and new heterocyclic systems (e.g. 8,9,12,14) were discovered.

Coupling of racemic 20-deethylcatharanthine[2] (1) with vindoline by the fragmentative method yields 20'-deethylanhydro-vinblastine which shows significant antitumor activity[3]. In addition to its biological interest, synthesis of 1 may serve as a model study for preparing (+)-catharanthine, an alkaloid of eminent importance (see following paper).

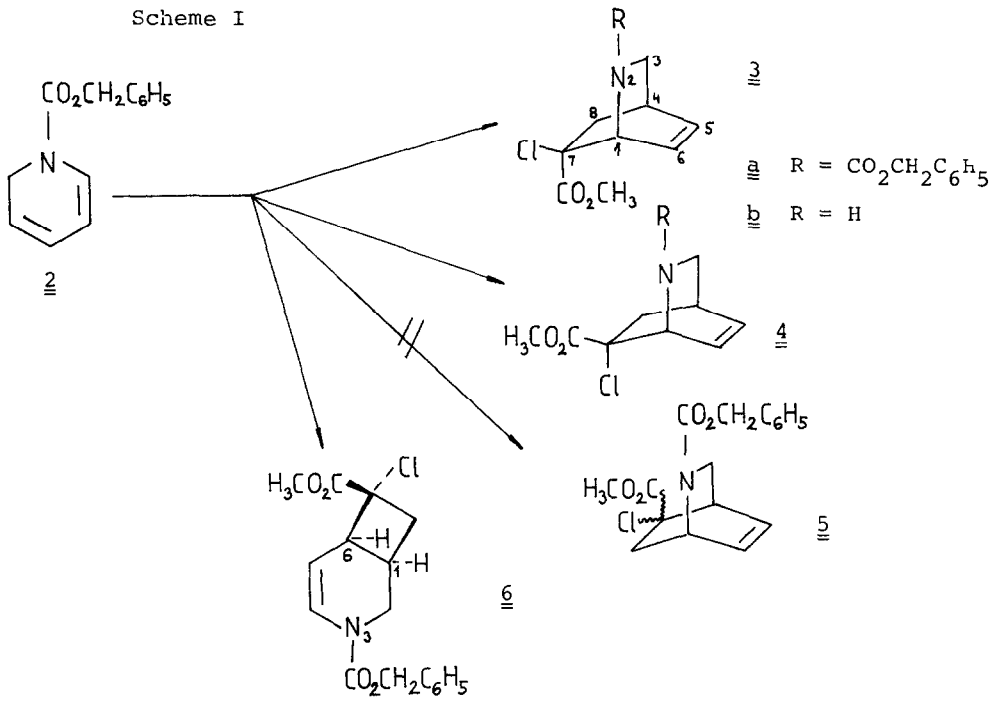
We have already outlined our synthesis of racemic 1 in a preliminary communication[4], now we also report the preparation of the pure enantiomers.

One key step of our synthesis is the construction of the isoquinuclidine ring which we carried out by cycloaddition at room temperature between 2-chloroacryloyl chloride and the dihydropyridine derivative 2[5]. The reaction was monitored by UV spectroscopy and TLC. After completion the reaction was quenched with metnanol and the product isolated as two epimeric methylesters i.e. 3a (20 %) and 4a (5 %). Note that no isomer 5 was formed, but a small amount (~ 1 %) of the cyclobutane derivative 6 was isolated as the product of a [2 + 2] cycloaddition.

The presence of the isoquinuclidine skeleton in both 3a and 4a is apparent from the ^{1}H and ^{13}C NMR data. The small differences in the proton chemical shifts between compounds 3a and 4a (see Experimental) were interpreted by the analogy of 6-chloro-6-cyano-bicyclo[2.2.2]oct-2-enes analysed by Rouillard et al[6]. This established the stereochemistry at C7 as depicted in the formulas.

The structure elucidation of compound 6 was accomplished by one- and two-dimensional NMR methods (Table II) The proton assignments were based

Scheme I



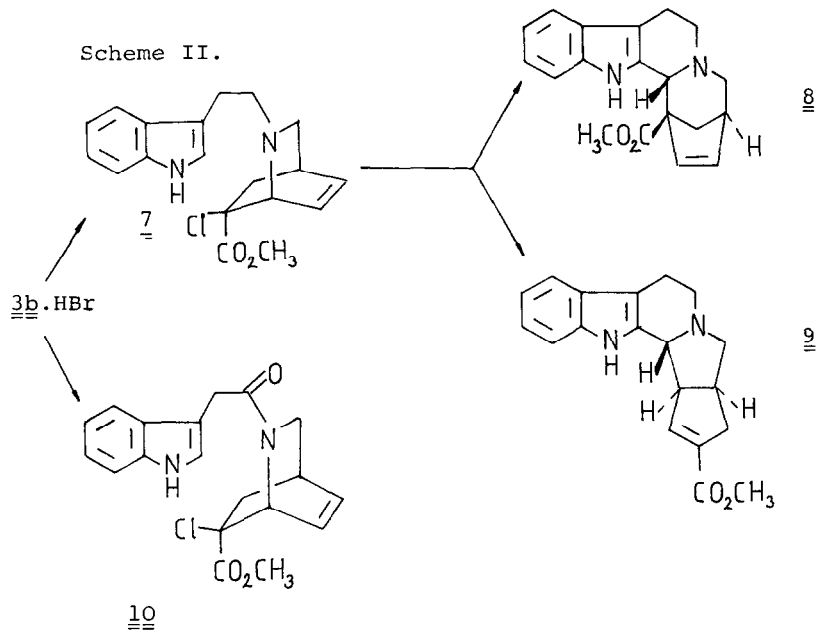
on extensive spin-decoupling experiments. Connectivities between identified protons and protonated carbons were obtained by HETCOR experiment Both the proton and the carbon spectrum measured in $CDCl_3$ solution at ambient temperature was complicated by the presence of two conformers due to restricted rotation about the amide bond.

The cis-fused stereostructure was concluded on the basis of differential NOE experiments. Some of the measurements were repeated in deuterobenzene solution also, where unfavourable overlapping of some of the multiplets was avoided. NOE experiments turned out most convincing in those cases too, when it was impossible to distinguish between vicinal and long range cross-ring (w) couplings (1.5 - 4.4 Hz range). Selective irradiation of the H-6 signal showed enhancement on the resonances for H-1 and H-5, while saturation of H-2β enhanced the resonance on H-1, which demonstrated that these protons were on the same face of the molecule and the sequence of the vicinally related protons is H-5 - H-6 - H-1 - H-2 Saturation of H-6 had no effect on the H-8 protons, thus the coupling between H-6 and $H8_{\alpha}$ must be of long range origin.

Removal of the benzyloxycarbonyl protecting group by hydrogenation was precluded by the presence of the double bond Acid treatment was more successful, using hydrogen bromide in acetic acid and in this way 3b and 4b were obtained

from 3a and 4a respectively in high yield

Scheme II.



First we attempted to reach our target compound (1) by simple intramolecular alkylation using 7 readily obtained by alkylation of 3b with tryptophyl bromide

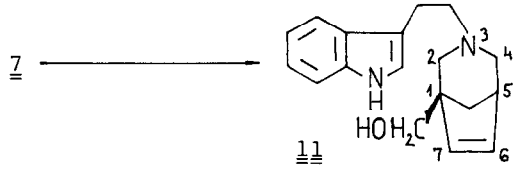
For this an S_N2 type reaction is not very promising because of steric reasons, but there is precedence in the literature for alkylation with a carbocation.

Thus in his approach to catharanthine Buchi[7] used solvolytic conditions to a similar ring-closure. However his compound contained two methoxy groups at the same carbon (C-7) at which we have the chlorine and methoxycarbonyl substituents. Thus in Buchi's case the developing carbocation was stabilized by electron-donating groups.

Creary[8] has shown, that solvolytically generated α-oxo-cations are also viable and can derive significant stabilization by a conjugative interaction. In our case an additional stabilizing factor should be the presence of the C=C bond, which, as known from the classical work of Winstein, can enhance the rate of solvolytic reactions by several orders of magnitude Thus the formation of a carbocation from 7 at C-7 seemed to be feasible.

Although the carbocation was formed indeed under solvolytic conditions, fast rearrangement took place and 8 was formed, which then itself underwent second rearrangement yielding 9. The mechanism of this reaction sequence and the stereostructure of compounds 8 and 9 have been discussed earlier[9].

It is noteworthy that the isoquinuclidine moiety of 7 underwent the same type of rearrangement on reduction with litnium-aluminium-hydride at room temperature giving rise to 11.

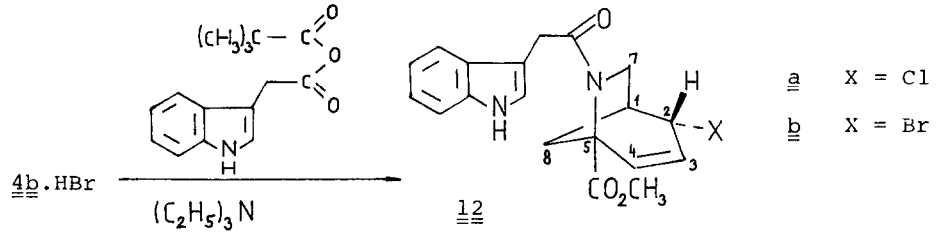


11

The structural assignment of 11 was made on the basis of ^{1}H and ^{13}C cnemical shifts and coupling patterns of the ring protons (Table III) and spectral analogies to 8, a compound of known structure[9]. Corroboration of the structure was obtained through NOE difference spectroscopy. Saturation of CH_2OH protons resulted in enhancement of protons H-2α, H-2β, H-8α, H-8β and H-7, which is in accord with the spatial arrangement of the alluded protons, as studied on Dreiding models.

After trying several modifications (saturation of the C=C bond, protection the double bond by halolactonization, adding catalysts, etc.) we turned instead of alkylation to acylation of the nitrogen of 3b to be followed by homolytic cleavage of the C-Cl bond. Acylation was performed with the mixed anhydride of indole-3-acetic acid and trimethyl acetic acid giving 10.

It has to be mentioned that acylation of the endo-chloro-derivative 4b.HBr gave the rearranged products 12a and 12b. Their structures were established by NMR.



4b.HBr $\xrightarrow[(C_2H_5)_3N]{}$ 12

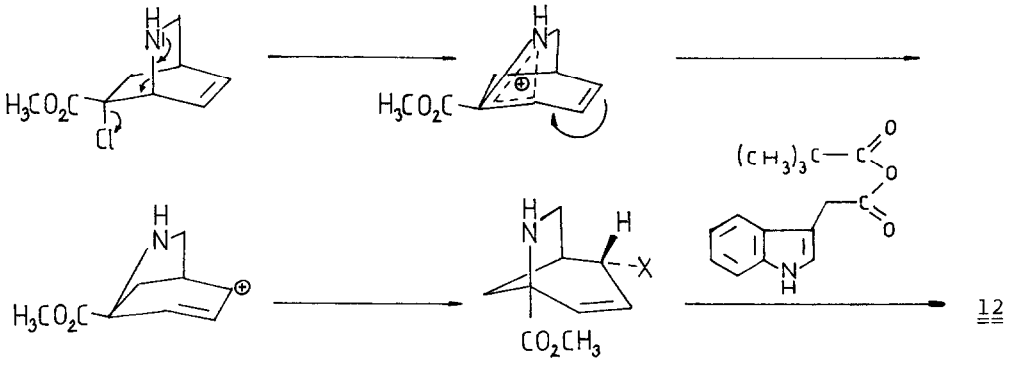
a X = Cl

b X = Br

We have performed elaborate high-field (400 MHz) NOE, and two-dimensional heterocorrelated NMR studies to justify the structure of the rearranged products. Details of the NMR work will be reported elsewhere, together with the NMR data of other compounds with the same skeleton. Some of the characteristic NMR features of the 6-azabicyclo[3.2.1]oct-3-ene ring systems (compounds 12a, 12b and 20), 2-azabicyclo[2.2.2]oct-5-ene ring systems (e.g. compound 7) and 3-azabicyclo[3.2.1]oct-6-ene ring systems (e.g. compound 11) are collected in Table V Of particular note is the value of the olefinic coupling increasing together with the ring size.

It is to be emphasized that the reaction sequence 4b ⟶ 12a,b is entirely different from the one involving the exo-chloro-derivative 7 ⟶ 8 ⟶ 9. One possible mechanism of the new rearrangement is the following. In case of 4b stereoelectronic factors favour the detachment of a chlorine anion being assysted by and synchronized with the formation of a delocalized cation followed by establishment of the new C-N bond (Scheme III). The carbocation is then stabilized by nucleophilic attack of the halide anion. A subsequent acylation yields 12. The fact that both 12a and 12b were isolated, substantiates this mechanism.

Scheme III.



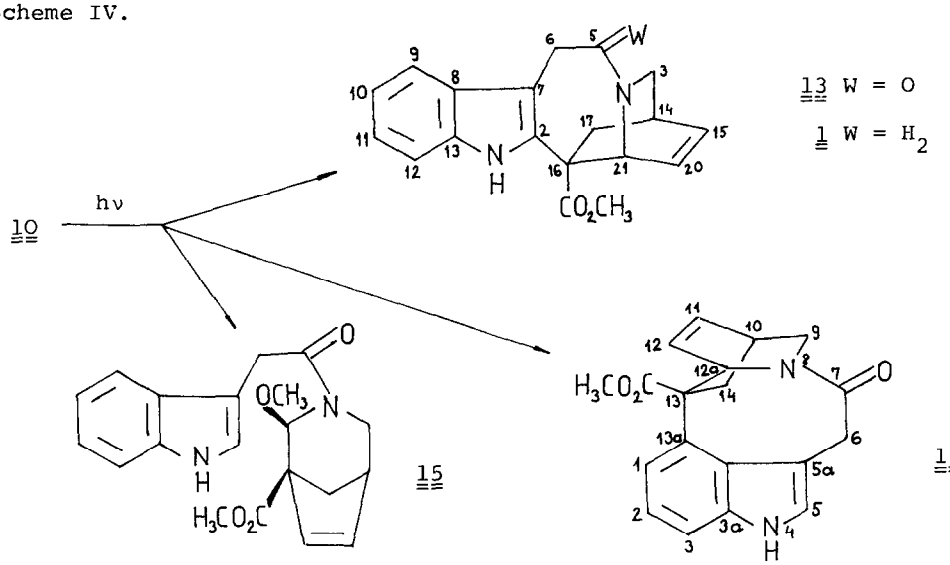
X = Cl or Br

An intermediate, similar to 12 but not isolated was postulated by French authors[10] in the reaction of catharanthinic acid with mercuric acetate. Our finding supports their hypothesis.

Irradiation of 10 in methanol-water gave in fact the desired (±)-5-oxo--20-deethylcatharantine (13) and its isomer 14 in a ratio of about 1:1 (16 % yield). Thus ring closure took place not only at the indole 2 but also in the indole 4 position. Compound 13 obtained in this reaction proved to be identical by spectral (IR, NMR, MS) and TLC comparison with authentic material[11]. Structure 14 was confirmed by spectral data (IR, NMR, MS) and X-Ray analysis

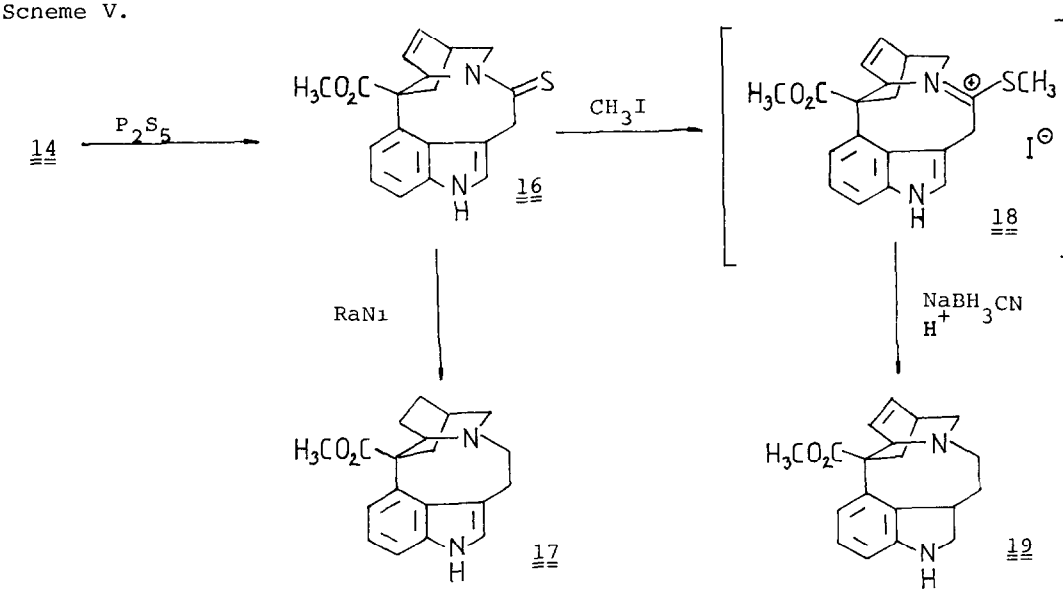
Because the indole-azocine-derivative 14 has a new ring system, we prepared some derivatives from it After reacting of 14 with P_2S_5 it was transformed to 5-thioxo-derivative 16 Desulfurisation (RaNi) of 16 in boiling ethanol gave compound 17. The thiolactam 16 was also converted to the salt 18 and reduced with $NaBH_3CN$ in aqueous methanol containing acetic acid. In this case the double bond of the pyrrole ring was saturated as well, resulting in 19. (see 12).

Scheme IV.



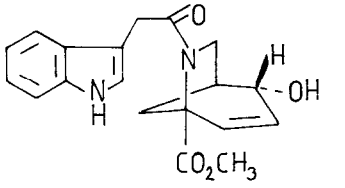
Among the products of photolysis carried out in methanol or in methanol/water an uncyclised, rearranged product (15) was obtained probably formed by similar reaction sequence as involving 7.

Scheme V.



The structure and stereochemistry of 15 was deduced on the basis of NMR spectral comparison with the afore-mentioned compounds 11 and 8[9] (Table III). Although the proton and carbon spectra of 15 were complicated by signal splittings due to amide rotational isomerism, the occurence and location of a methoxy substituent was evident from the NMR data. The singlet of one proton intensity at 6.05 ppm (and at 5.48 ppm in the other amide isomer) must belong to an isolated proton on the six-membered ring, and is therefore assigned to H-2. The stereochemistry of the C2-methoxy group is most probably β (pseudoaxial). This orientation, via γ-gauche effect, may be one factor which causes an upfield shift on C-8, in comparison with its value in compound 11.

The photoreaction is solvent dependent E.g. in aqueous tetrahydrofurane irradiation of 10 led to the cyclised products 13 and 14 and to an uncyclised by-product 20 with a rearranged skeleton. Its structure was elucidated by NMR. Complete NMR discussion, together with that of 12a, 12b and other related compounds will be the subject of a forthcoming paper.



20

To generate carbon radicals the tributyltin hydride combined with azo--bis-isobutyronitrile (AIBN) or UV irradiation is a known method. In our case the first method (n Bu_3SnH + AIBN) only reduced the compound 10.

Irradiating compound 10 in methanol in presence of catalytic amount of tributyltin hydride the yield of 5-oxo-20-deethylcatharanthine 13 increased to 20-22 % and the reaction proved to be faster (1-2 hours)

The above synthesis constitutes a short and simple procedure for preparing (±)-5-oxo-20-deethylcatharanthine. For the removal of the oxo group we developed a one-step method, while Sundberg removed it in three steps via the thiolactam[2a]. Our $BF_3.Et_2O/NaBH_4$ system reduced 13 to 1 in almost quantitative yield

In order to prepare the optically active derivatives we initially performed the resolution of 3b with dibenzoyl-L-tartaric acid Acylation of the pure diastereomeric salt, as was done with the racemic compound gave the dextrorotatory indolyl-acetyl derivative (+)-10. Photochemical ring closure of (+)-10 followed by selective reduction led as shown by CD (Fig.1), to a product [(16S)-20-deethyl-catharanthine] possessing the opposing absolute configuration as natural (+)-catharantnine.

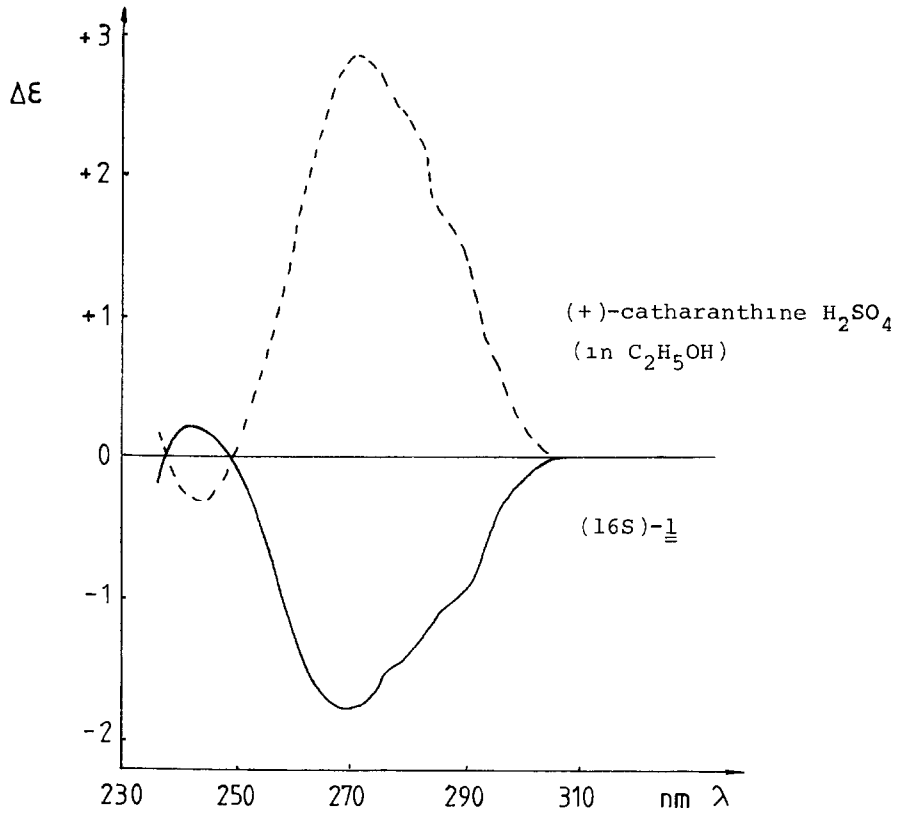


Figure 1. CD curves of (+)-catharanthine H_2SO_4 and (16S)-1 in H_2SO_4/C_2H_5OH.

By a similar sequence, but using dibenzoyl-D-tartaric acid gave (-)-7, selective reduction of which, gave (16R)-20-deethylcatharanthine.

Experimental Section

Melting points were determined on a hot stage microscope and are uncorrected. Infrared spectra were recorded on Specord 75 IR (Carl Zeiss Jena). The NMR spectra were obtained with a Varian XL-100 and Varian XL-400 instrument, Mass spectra were determined on a AEI MJ-902 (70 eV) instrument. Thin layer chromatograms (TLC) were made with DC-Alufolien Kieselgel 60 F_{254} Merck 5554. Column chromatography separations were carried out on silicagel (0.063-0.200; Merck 7734).

(+)-2-(Benzyloxycarboryl)-7-exo-chloro-2-azabicyclo[2 2 2]oct-5-ene-7--endo-carboxylic Acid Methyl Ester 3a, (+)-2-(Benzyloxycarbonyl)-7-endo--chloro-2-azabicyclo[2 2.2]oct-5-ene-7-exo-carboxylic Acid Methyl Ester 4a

and (±)-3-(Benzyloxycarbonyl)-7-chloro-3-azabicyclo[4.2.0]oct-4-ene-7--carboxylic Acid Methyl Ester 6. To a solution of dry pyridine (47.5 g, 0.6 mol) in 1L of dry methanol at -65 °C 22.7 g (0.6 mol) of $NaBH_4$ then dropwise 91 mL (102.4 g = 0.6 mol) of benzyl chloroformate were added. The mixture was stirred for an additional hour at -65 °C and the solvent was evaporated in vacuo. The reaction was checked by TLC (toluene.ethylacetate = = 10:2); pyridine R_f = 0.1; 1-(benzyloxycarbonyl)-1,2-dihydropyridine R_f = 0.65, and by UV spectrum of the residue in methanol λ_{max} = 305 nm, 1,2--dihydropyridine, λ_{max} = 260-270 nm unchanged pyridine; λ_{max} = 230-240 nm 1,4-dihydropyridine . The residue was dissolved in chloroform and water. The organic extract was dried (Na_2SO_4) and evaporated in vacuo. The residue (127.0 g = 100 % yield) was solved in dry acetonitrile to which 74.9 g (0.6 mol) of 2-chloro-acryloyl-chloride was added and stirred at room temperature for one day. The cycloaddition was monitored by UV spectroscopy. The peak at λ = 305 nm disappeared at the end of the reaction. After the addition of methanol (160 mL) the reaction mixture was stirred for one day. Then it was made basic p_H = 8-9 with triethylamine and evaporated in vacuo The residue was solved in benzene and washed with water. The benzene fraction was dried (Na_2SO_4) and evaporated in vacuo The residue was separated on a silica gel column with toluene. ethylacetate = 10:1 as the eluent. The eluted product was evaporated and crystallised from ethyl-acetate-hexane to give 38 8 g (116 mmol, 19 3 %) 3a mp 85-86 °C. IR. (KBr) 1752 cm^{-1} (ester C=O), 1700 cm^{-1} (amide C=O). ^1H NMR (100 MHz, $CDCl_3$, 60 °C): δ 1.98 (dd, 1H, J = 14 + 2Hz, H-8β), 2.72 (m, 1H, J = 14 + 2.5 + 2Hz, H-8α), 2.81 (m, 1H, H-4), 3.05 (m, 1H, J = 10 + 2.5 + 2Hz, $H\text{-}3_A$), 3.49 (dd, 1H, J = 10 + 2Hz, $H\text{-}3_B$), 3.74 (s, 3H, $COOCH_3$), 5.19 (s, 2H, $-COOCH_2-$), 5.26 (dd, 1H, J = 6 + 1 Hz, H-1), 6.36 (m, 1H, J = 8 + 6 + 1.5 Hz, H-6), 6.45 (m, 1H, J = 8 + 6 + 1Hz, H-5), 7.34 (m, 5H, aromatics). See Table I. for ^{13}C NMR data. Anal Calcd. for $C_{17}H_{18}Cl\,NO_4$: C: 60.80; H, 5 40; Cl, 10.56, N, 4.17. Found: C, 61.03; H, 5.31, Cl, 10 54; N, 4.16. MS, m/e 337[1], 336[1], 335 (M^+), 304, 300, 216[1], 215, 171[1], 170, 137, 91, 80, 65. The mother liquor of 3a and the fractions containing 4a and 6 were together evaporated and the residue was purified through a silica column with hexane:ethylacetate:triethylamine = = 6 1:1 as eluant. The fractions containing 4a and 6 were evaporated separately and crystallised at -70 °C from hexane yielding 4a (9.7 g, 28.9 mmol, 4 8 %) and 6 (1 8 g, 5.4 mmol, 0.9 %) 4a mp 38-42 °C, IR (KBr) 1742 cm^{-1} (ester C=O), 1700 cm^{-1} (amide C=O) ^1H NMR (100 MHz, $CDCl_3$, 60 °C). δ 1.94 (m, 1H, J = 14 + 2 5 + 2Hz, H-8α), 2.86 (m, 1H, J = 10 + 2 5 + 2 Hz, $H\text{-}3_A$), 2.90 (m, 1H, H-4), 3 04 (dd, 1H, J = 14 + 2.5 Hz, H-8β), 3 22 (dd, 1H,

1 isotopic peak

J = 10 + 2Hz, H-3_B), 3.63 (s, 3H, $COOCH_3$), 5.10 (s, 2H, $-COOCH_2-$), 5.24 (dd, 1H, J = 6 + 1.5 Hz, H-1), 6.48 - 6 55 (multiplets, 2H, H-5 and H-6), 7.32 (m, 5H, aromatics). H-8α was identified by its long-range (w) coupling with H-3_A in both 3a and 4a compounds The upfield shift of H-8α and the downfield shift of H-8β in the proton spectrum of 4a relative to that of 3a confirmed the exo stereostructure of the carbomethoxy substituent in 4a. See Table I. for ^{13}C NMR data. Anal. Calcd. for $C_{17}H_{18}ClNO_4$; see 3a C, 60.80; H. 5.40; N, 4.17, Cl, 10.56. Found: C, 61.12; H, 5 64; N, 4.01; Cl, 10.40. MS m/e 337[1], 336[1], 335 (M^+), ^{35}Cl , 216[1], 215, 171[1], 170, 91, 80, 65. 6 mp. 61-63 °C. IR· (KBr) 1740 cm^{-1} (ester C=O), 1700 cm^{-1} (amide C=O). See Table II. for ^1H and ^{13}C NMR data S, m/e 337[1], 336[1], 335 (M^+), 334, 292[1], 290, 216[1], 215, 171[1], 170, 91, 80, 65.

(±)-7-Exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester Hydrogen Bromide Salt 3b. A solution of 3a (10.0 g, 29 78 mmol) in 1 5 N hydrogen bromide in acetic acid (90 mL) was stirred for ten minutes. After all the starting material reacted as it was proved by TLC the reaction mixture was evaporated The residual oil was solved in 5 mL of acetone and crystallized from ether giving 8.4 g product (29 72 mmol, 99.8 %) 3b mp. 188-189 °C; IR; (KBr) 1745 cm^{-1} (ester C=O), 2400-2900 cm^{-1} ($\geq NH_2^+$). ^1H NMR (100 MHz, $CDCl_3$, 50 °C)· δ 2.20 (dd, 1H, J = 13.5 + 2 Hz, H-8β), 2.72 (m, 1h, J = 13.5 + 2.5 + 2 Hz, H-8α), 3 04 (m, 1H, H-4), 3.09 (m, 1H, J = 10.5 + + 2 + 2 Hz, H-3_A), 3.60 (dd, 1H, J = 10.5 + 1 5 Hz, H-3_B), 3.80 (s, 3H, $COOCH_3$), 4.81 (dd, J = 6 + 1 Hz, H-1), 6.43 (m, 1h, J = 8 + 6 + 1 Hz, H-6), 6.72 (m, 1H, J = 8 + 6 + 1 Hz, H-5), 6 9 (b, 1H, NH) See Table I. for ^{13}C NMR data Anal. Calcd. for $C_9H_{13}BrClNO$: C, 38.25, H, 4.63; Br, 28.28, Cl, 12 55; N, 4.96. Found C, 38.14; H, 4 63; Br, 28.30; Cl, 12.47; N, 4.92.

(±)-7-Endo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-exo-carboxylic Acid Methyl Ester Hydrogen Bromide Salt 4b. A similar reaction of 4a (10.0 g) was carried out with HBr/CH_3CO_2H The obtained 4b was crystallized from hexane. 8.0 g (28.31 mmol, 95 1 %) mp. 190-191 °C; IR: (KBr) 1765 cm^{-1} (ester C=O) 2400-2900 cm^{-1} ($\geq NH_2^+$) ^1H NMP (100 MHz, $CDCl_3$, 50 °C): δ 2.05 (m, 1H, J = 14 + 2.5 + 2.5 Hz, H-8α), 2.92 (dd, 1H, J = 14 + 1.5 Hz, H-8β), 3.05 (m, 1h, H-4), 3.10 (m, 1H, J = 10 5 + 2.5 + 2 Hz, H-3_A), 3.41 (dd, 1H, J = 10 5 + + 1 5 Hz, H-3_B), 4.0 (s, 3H, $COOCH_3$), 4.88 (dd, 1H, J = 6 + 1 Hz, H-1), 6.55 (m, 1H, J = 8 + 6 + 1 Hz, H-6), 6.79 (m, 1H, J = 8 + 6 + 1 Hz, H-5), 9.0 (b, 1H, NH). See Table I for ^{13}C NMR data Anal. Calcd see 3b., Found· C 38.56, H, 4 86, Br, 28.57, Cl, 12.30, N, 5.22

1: isotopic peak

(±)-2-{1-[2-(Indol-3-yl)-1-oxo-ethyl]}-7-exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester 10. To a stirred solution of indole-3-acetic acid (5 8 g, 33.1 mmol) and 4.6 mL (3.3 g, 32.8 mmol) of triethylamine in dimethylformamide 4.1 mL (4.01 g, 33.2 mmol) of trimethylacetyl chloride was added dropwise between -5 °C and -10 °C. After 20 minutes stirring at room temperature a thick suspension was obtained, to which a solution of 8.0 g (28.4 mmol) of hydrogen bromide salt 3b and 4.6 mL of triethylamine in dimethylformamide was dropped between 0 ° and -5 °C. Then the reaction mixture was stirred at room temperature for an additional hour. The precipitated triethylamine hydrogen bromide and hydrogen chloride salts were filtered and washed with ethylacetate. The mother liquor was evaporated. The residual oil was dissolved in ethylacetate, washed twice with water and dried over sodium sulfate. The ethylacetate solution was evaporated to give 10 as white crystals which were filtered (8.5 g, 23 8 mmol, 83.8 %). Recrystallization from chloroform-methanol yielded the analytical sample, mp. 201-202 °C IR (KBr) 1630 cm^{-1} (amide C=O), 1725 cm^{-1} (ester C=O), 3250 cm^{-1} (indole NH) ^1H NMR (100 MHz, $CDCl_3$, RT): δ 1.95 + 2.00 (dd each, 1H, J = 13 + 2 Hz, H-8β), 2.76 (m, 1F, J = 13 + 3 + 2 Hz, H-8α), 2.86 (m, 1H, H-4), 3 15 + 3.17 (m each, 1H, J = 11 + 3 + 2 Hz, $H-3_A$), 3.58 (dd, 1H, J = 11 + ? Hz, $H-3_B$), 3.73 + 3.75 (s, each, 3H, $COOCH_3$), 3.89 (d, 1H, J = 15.5 Hz, C3'C-H_A), 4.10 (d, 1H, J = 15.5 Hz, C3'C-H_B), 5.04-5.88 (dd each, 1H, J = 6 + 1 5 Hz, H-1), 5.98 (m, 0.5 H, J = 8 + 6 +1.5 Hz, H-6), 6.3 - 6.5 (m, 1.5 H, H-6 and H-5), 7 1 - 7.65 (m, 5H, aromatics), 8 2 (b, 1H, NH) The presence of two conformers is due to restricted rotation about the amide bond. See Table IV. for ^{13}C NMR data. Anal Calcd. for $C_{19}H_{19}ClN_2O_3$: C, 63 60, H, 5 34, Cl, 9.88; N, 7.81. Found: C, 63 40, H, 5.57; Cl, 10.17, N, 7.79. MS m/e 360[1], 358 (M^+), 324[1], 322, 301, 299, 238, 157, 130, 121, 119, 117, 103, 93, 91, 81, 80, 77.

(±)-3-{1-[2-(Indol-3-yl)-ethyl]}-1-(hydroxy-methyl)-3-azabicyclo[3.2 1]oct-6-ene 11. 1.0 g (2 9 mmol). Of 7 was dissolved in 50 mL of dry THF, to which litnium aluminium hydride (0.5 g) was added at -20 °C and then stirred at r.t for 2 hours at which point TLC showed that all the starting material nad been consumed. The mixture was cooled while water was added in small portions After a half hour stirring the mixture was filtered and then evaporated The residue was crystallized from ethylacetate to give 11 (489 mg, 1 73 mmol, 59.7 %), mp. 77-82 °C IR (KBr) 3390 cm^{-1} (indole NH), 3570 cm^{-1} (-OH), See Table III for ^1H and ^{13}C NMR data. MS m/e 283[1], 282 (M^+), 281, 220, 205, 152, 144, 143, 130, 115, 105, 103, 93, 91, 81, 79, 77, 58, 44, 42

(±)-6-(1-[2-(Indol-3-yl)-1-oxo-ethyl])-2α-chloro-6-azabicyclo[3.2.1]oct-3-ene-5-carboxylic Acid Methyl Ester **12a** and (±)-6-(1-[2-Indol-3-yl)-1--oxo-ethyl])-2α-bromo-6-azabicyclo[3.2.1]oct-3-ene-5-carboxylic Acid Methyl Ester **12b**. Method A. Acylation with indole-3-acetic anhydride in CH_2Cl_2. To a stirred solution of **4b** hydrogen bromide salt (622 mg, 2.2 mmol) and 0.6 mL (435.6 mg 4 3 mmol) of triethylamine in dry dichloromethane, 1464 mg (4.404 mmol) of indole-3-acetic acid anhydride dissolved in 100 mL of dichloromethane was added. The reaction solution was stirred at room temperature for 4 days. The CH_2Cl_2 solution was washed with water and dried (Na_2SO_4) and evaporated in vacuo. The residual oil was purified by silicagel column chromatograpny (eluant. toluene:aceton = 2:1) to give a mixture of **12a** and **12b** which was crystallized from aceton-hexane. mp. 181-184 °C. IR: (KBr) 1650 cm^{-1} (amide C=O), 1750 cm^{-1} (ester C=O). **12a** ^{1}H NMR (400 MHz, $CDCl_3$, RT): 2.1 - 2 3 (m, 2H), 2.90 (m, 1H), 3.3 - 3.9 (m, 4H), 3.78 (s, 3H), 4.39 (m, 1H), 5.69 (m, 1H), 6.88 (m, 1H), 7 05 - 7.52 (m, 5H), 9 25 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, RT): δ 32.02, 34.68, 41 70, 50.61, 52.45, 58.09, 62 63, 107.07, 111.43, 118 42, 118.94, 121.64, 122.90, 126.59, 127.07, 133.00, 136.35, 169.21, 170.56. **12b** ^{1}H NMR (400 MHz, $CDCl_3$, RT). 2.1 - 2.4 (m, 2H), 2.99 (m, 1H), 3.3 - 3.85 (m, 4H), 3.73 (s, 3H), 4.59 (m, 1H), 5.79 (m, 1H), 6 79 (m, 1H), 7.04 - 7 51 (m, 5H), 9.30 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, RT). δ 31 40, 34.68, 41 71, 50 68, 51.30, 51.96, 62 20, 107.06, 111.28, 118 36, 118.57, 121.62, 123.22, 127.14, 127 72, 131.92, 136.21, 168 61, 170.26 MS m/e 404 (M^+ **12b** ^{82}Br), 402 (M^+ **12b** ^{80}Br), 373, 371, 360, (M^+ **12a** ^{37}Cl), 358 (M^+ **12a** ^{35}Cl), 324, 323, 322, 308, 295, 196, 157, 156, 130, 105, 96, 94, 93, 91, 77, 51, 50, 44, 38, 36. Anal. Calcd. for $C_{19}H_{19}ClN_2O_3$: C, 63.60; H, 5.34; Cl: 9.88, N, 7.81, for $C_{19}H_{19}BrN_2O_3$: C, 56.59, H, 4.75, Br, 19.81; N, 6 95 Found: C, 60.78; H, 5.45; Br, 11.99, Cl, 3.45, N, 6.98 Method B: Acylation with indole-3-acetic acid and trimethylacetic acid mixed anhydride **12a** and **12b** were obtained from **4b** in a similar way as in case of **10** starting from **3b**. Yield: 19.3 %. Anal. Calcd see above. Found: C, 61.53; H, 5.35, Br, 5.57; Cl, 7 48; N, 7 27. mp. 171-174 °C.

(±)-5-Oxo-20-deethylcatharanthine **13**, (±)-3-(1-[2-(Indol-3-yl)-1-oxo--ethyl])-2-methoxy-3-azabicyclo[3.2 1]oct-6-ene-1-carboxylic Acid Methyl Ester **15** and (±)-10,13-Methano-4H-pyrido[2,1-b]pyrrolo-[4,3,2-f,g][3]benz-azocine-13 (9H)-carboxylic acid, 6,7,10,12a-tetrahydro-7-oxo Metnyl Ester **14**, photolysis of **10**. 1.0 g, (2.79 mmol) Of **10** was dissolved in a mixture of 2.2 L methanol and 300 mL water, to which 1 6 g of sodium hydrogen carbonate was added. The reaction mixture was stirred, purged with nitrogen and irradiated by a low pressure mercury lamp (Tungsram Hg-LI 250 W) in an immersion quartz tube for 4-6 hours The reaction was followed by TLC (eluant:

toluene:acetone:triethylamine = 40.20:1). Then the methanolic solution was evaporated. The residue was dissolved between chloroform and water. The organic layer was dried over sodium sulfate and evaporated. The residue was purified by column chromatography (eluant: chloroform: ethylacetate: triethylamine = 30:8:1) which afforded three compounds listed in order of increasing polarity: (a) 148 mg oil (4.59 mmol, 16.5 %) containing 13 5-oxo-20-deethyl-catharanthine which was crystallized from acetone-hexane mp. 295-298 °C. IR: (KBr) 1640 cm^{-1} (lactam C=O), 1740 cm^{-1} (ester C=O), 3300 cm^{-1} (indole NH). ^{1}H-NMR (400 MHz, $CDCl_3$, RT): δ 1.79 (dd, 1H, J = = 13.4 + 1.8 Hz, H-17$_\beta$), 2.65 (m, 1H, J = 13.4 + 4 + 2.2 Hz, H-17$_\alpha$), 2.94 (m, 1H, H-14), 3.00 (m, 1H, J = 10.7 + 2.2 + 2Hz, H-3$_A$), 3.59 (dd, 1H, J = 10.7 + 3 Hz, H-3$_B$), 3.67 (s, 3H, $COOCH_3$), 3 78 (d, 1H, J = 15.6 Hz, C7-H$_A$), 4.17 (d, 1H, J = 15.6 Hz, C7-H$_B$), 5.33 (dd, 1H, J = 6.3 + 0.9 Hz, H-21), 6.49 (m, 1H, J = 8 + 6.3 + 1.7 Hz, H-15), 6.69 (m, 1H, J = 8 + 6.5 + + 0.9 Hz, H-20), 7.13 (m, 1H, J = 7 8 + 7 + 1.2 Hz, H-10), 7.18 (m, 1H, J = 7 8 + 7 + 1.3 Hz, H-11), 7.27 (m, 1H, J = 7.8 + 1.2 + 0 8 Hz, H-12), 7.56 (m, 1H, J = 7.8 + 1 3 + 0 8 Hz, H-9), 8.09 (b, 1H, NH). See Table IV. for ^{13}C NMR data. Anal Calcd for $C_{19}H_{18}N_2O_3$ C, 70.79; H, 5.62; N, 8.69. Found: C, 70 64; H, 5.49; N, 8 65. MS, m/e 322 (M^+), 243, 215, 214, 201, 182, 154, 121, 93, 81, 80. (b) 90 mg (0.25 mmol) oil containing 15, which was crystallized from acetone-hexane, mp 135-137 °C. IR. (KBr) 1640 cm^{-1} (amide C=O), 1735 cm^{-1} (ester C=O), 3380 cm^{-1} (indole NH). See Table III. for ^{1}H and ^{13}C NMR data. Anal. Calcd. for $C_{20}H_{22}N_2O_4$. C, 67.78, H, 6.26, N, 7.90 Found. C, 67.70; H, 6.22, N, 7 87. MS, m/e 354 1572 (M^+), $C_{20}H_{22}N_2O_4$, 353, 352, 340, 339, 325, 324, 323, 322, 295, 291, 224, 197, 157.0525 ($C_{10}H_7NO$), 130 (c) 130 mg of recovered 10 (0.36 mmol, 13.0 %). (d) The chromatography was followed with the eluant. $CHCl_3$.acetone = 1.1 The fourth product was 147 mg oil (0.456 mmol, 164 %) containing 14 which was crystallized from acetone-hexane mp. 295-296 °C. IR. (KBr) 1630 cm^{-1} (amide C=O), 1715 cm^{-1} (ester C=O), 3300 cm^{-1} (indole NH) ^{1}H NMR (100 MHz, $CDCl_3$, RT): δ 1 80 (dd, 1H, J = 13 + 1.5 Hz, H-14$_A$), 2.90 (m, 1H, H-10), 3.0-3.6 (m, 4H, H-14$_B$, C9-H_2 and H-6$_A$), 3.52 (s, 3H, $COOCH_3$), 4.28 (dd, 1H, J = 15 + + 1.5 Hz, H-6$_B$), 5.72 (dd, 1H, J = 6 + 1.5 Hz, H-12a), 6.40 (m, 1H, J = 7 5 + 6 + 1 Hz, H-12), 6.64 (m, 1H, J = 7 5 + 6.2 + 1.5 Hz, H-11), 6.9 (dd, 1H, J = 3 + 1 5 Hz, H-5), 7.0-7.25 (m, 3H, H-1, H-2 and H-3), 8.8 (b, 1H, NH). See Table VI. for ^{13}C NMR data Anal. Calcd for $C_{19}H_{18}N_2O_3$ see 13. Found: C, 70 68; H, 5.63; N, 8 39 MS, m/e 322 (M^+), 263, 243, 215, 214, 211, 206, 201, 184, 155, 154, 81, 80, 71, 57, 43

(±)-6-[1-[2-(Indol-3-yl)-1-oxo-ethyl]]-2α-hydroxi-6-azabicyclo[3.2.1] oct-3-ene-5-carboxylic Acid Methyl Ester 20 by photolysis of 10. Compound 10

(2.0 g, 5.57 mmol) was dissolved in 1.5 mL of tetrahydrofurane and 300 mL of water and irradiated for 2 hours in a similar way. After the usual workup and chromatography the following products were isolated. (a) 13 202 mg (0 627 mmol, 11.3 %), (b) recovered 10 (102 mg, 0 284 mmol, 5.1 %), (c) 261 mg of unknown product MS, m/e 312.1481 (M^+, $C_{18}H_{20}N_2O_3$), 281, 253, 187.088 ($C_{11}H_{11}N_2O$), 174, 157, 130, 103, 79, 77; IR, ($CHCl_3$) 1660 cm^{-1} (amide C=O), 1740 cm^{-1} (ester C=O), 3420 cm^{-1} (indole NH). (d) 14 494 mg (1.533 mmol, 27.5 %) (e) 162 mg oil (0.476 mmol, 8.5 %) containing 20, which was crystallized from acetone-hexane mp. 224-228 °C; IR: (KBr) 1630 cm^{-1} (amide C=O), 1730 cm^{-1} (ester C=O), 3400 and 3460 cm^{-1} indole NH and OH; ^1H NMR (400 MHz, $CDCl_3$, RT). δ 1.9-2.15 (m, 2H), 2.63 (m, 1H), 3.2-3.8 (m, 4 H), 3.70 (s, 3H), 3.93 (m, 1H), 4 98 (d, J = 5.6 Hz, 1H), 5.65 (m, 1H), 6.74 (m, 1H), 7.04-7.48 (m, 5H), 10.30 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, RT): δ 31.52, 34.79, 40.28, 49.35, 51.72, 62.52, 68.95, 107.45, 111.28, 118.33, 118 61, 121.04, 123.18, 127.27, 129.09, 131.88, 136.27, 168.74, 171.01. MS, m/e 340 (M^+), 309. 210, 178, 157, 130

(±)-10,13-Methano-4H-pyrido[2,1-b]pyrrolo[4.3,2-f,g][3]benzazocine-13(9H)-carboxylic acid, 6,7,10,12a-tetrahydro-7-thioxo Methyl Ester 16. Compound 14 (1.092 g, 3.39 mmol) was refluxed with 1.680 g of phosphorus pentasulfide in 150 mL of benzene for 5 hours. The reaction was followed by TLC (eluent. chloroform acetone = 1:1). After all the starting material was reacted, phosphorus pentasulfide was filtered, washed with chloroform twice. The organic solvent was washed with aqueous bicarbonate and water, dried over sodium sulfate, evaporated in vacuo. The residual oil was crystallized from acetone-hexane to give 881 mg of 16 (2 60 mmol, 76.6 %), mp. 279-280 °C. IR. (KBr) 1730 cm^{-1} (ester C=O), 3270 cm^{-1} (indole NH); ^1H NMR (100 MHz, $CDCl_3$ + Me_2SO-d_6, RT): δ 1.83 (dd, 1H, J = 13 + 1.5 Hz, H-14_A), 3.02 (m, 1H, H-10), 3 1-3.7 (m, 3H, H-14_B and C9-H_2), 3 50 (s, 3H, $COOCH_3$), 4.20 (d, J = 15 Hz, H-6_A), 4.68 (dd, 1H, J = 15 + 1 5 Hz, H-6_B), 6.16 (dd, 1H, J = 5.5 + 1 Hz, H-12a), 6.42 (m, 1H, J = 7.5 + 5 5 + 1 Hz, H-12), 6 74 (m, 1H, J = 7.5 + + 6 5 + 1 Hz, H-11), 6.94 (dd, 1H, J = 2 + 1.5 Hz, H-5), 6.95-7 35 (m, 3H, H-1, H-2 and H-3), 7 71 (b, 1H, NH). See Table VI. for ^{13}C NMR data MS, m/e 338 (M^+), 279, 226, 214, 211, 206, 204, 201, 200, 199, 167.

(±)-10,13-Methano -4H-pyrido[2,1-b]pyrrolo[4,3,2-f,g][3]benzazocine-13-(9H)-carboxylic acid, 6,7,10,11,12,12a-hexahydro Methyl Ester, 17. 1.206 g (3.57 mmol) Of 16 was refluxed with about 5 g freshly prepared Raney nickel in dry ethanol for 4 hours If the starting material could not have been showed by TLC (eluent toluene.acetone.triethylamine = 40·20 1), the nickel was removed and washed many times with ethanol and chloroform. The organic solvent was evaporated in vacuo to give crystals which were filtered and

washed with hexane Yield: 762 mg of 17 (2.45 mmol, 68.8 %), mp. 246-249 °C; IR. (KBr) 1730 cm^{-1} (ester C=O), 3400 cm^{-1} (indole NH); ^1H NMR (100 MHz, $CDCl_3$ + Me_2SO-d_6, FT): δ1.5-3.1 (m, 13H, C6-H_2, C7-H_2, C9-H_2, C11-H_2, C12-H_2, C14-H_2, H-10), 3.51 (s, 3H, $COOCH_3$), 4.0 (t, 1H, J = 2.5 + 2 Hz, H - 12a), 6.90 (dd, 1H, J = 7 + 1.5 Hz, H-3), 6.95 (dd, 1H, J = 8 + 7.5 Hz, H-2), 7.05 (d, J = 2 Hz, H-5), 7.20 (dd, J = 8 + 1.5 Hz, H-1), 7.83 (b, 1H, NH). See Table VI. for ^{13}C NMR data. MS, m/e 310 (M^+), 309, 295, 251, 224, 214, 171, 170, 168, 167, 155, 154, 108, 107, 96, 94, 83, 82.

(±)-10,13-Methano-4H-pyrido[2,1-b]pyrrolo[4.3.2-f,g][3]benzazocine-13(9H)-carboxylic acid, 5,5a,6,7,10,12a-hexahydro Methyl Ester 19. The solution of 16 (300 mg, 0.887 mmol) was stirred in 30 mL of methyl iodide under argon for 1 hour and then evaporated in vacuo. The residue was dissolved in 30 mL of dry methanol to which 500 mg of sodium cyanoborohydride was added. After 5 minutes stirring 30 mL of water-acetic acid = 1.1 was added and stirred for 1 hour. 300 mL of water was added and the pH was brought to 1 by addition of 18 % hydrochloric acid and was extracted with ether. This ether fraction contained recovered starting material. The aqueous fraction was made basic (pH = 9) with ammonium hydroxide and extracted with ether three times. The ether layer was dried over sodium sulfate and evaporated to give 19 (102 mg, 0.328 mmol, 37.0 %) as white crystals, mp. 191-195 °C IR: (KBr) 1720 cm^{-1} (ester C=O), 3380 cm^{-1} (dihydro indole NH); ^1H NMR (100 MHz, $CDCl_3$ + Me_2SO-d_6, RT): δ 1.90 (dd, 1H, J = 12.5 + 2 Hz, H-14$_A$), 2.0-3.9 (m, 11H, H-5$_A$, H-5a, C6-H_2, C7-H_2, C9-H_2, H-10, H-14$_B$), 3.51 (s, 3H, $COOCH_3$), 4.22 (m, 1H, H-5$_B$), 5.01 (dd, 1H, J = 6 + 1 Hz, H-12a), 6.25-6.65 (m, 4H, H-11, H-12, H-1, H-3), 6.93 (dd, 1H, J = 8 + 7 Hz, H-2) See Table VI. for ^{13}C NMR data MS, m/e 310.1700 (M^+), $C_{19}H_{22}N_2O_2$, 309, 295, 292, 279, 273, 258, 231, 230, 170, 144, 142, 134, 133, 115, 106, 93, 80.

(±)-20-Deethylcatharanthine 1 by reduction of 13 Lactam 13 (100 mg, 0.310 mmol) was dissolved in 15 mL of fresnly distilled dry THF, to which 510 mg of sodium borohydride and dropwise 2.4 mL of boron trifluoride etherate were added After 3 hours stirring the reaction mixture was evaporated. The residue was dissolved in chloroform and to this water was slowly added The organic layer was dried over sodium sulfate and evaporated in vacuo resulting in 1 as a white foam 91 mg (0.295 mmol, 95.2 %). This was purified by preparative TLC on a silica plate for the analytical sample (eluant.chloroform:acetone = 1 1). IR. ($CHCl_3$) 1720 cm^{-1} (ester C=O), 3380 cm^{-1} (indole NH), ^1H NMR (400 MHz, $CDCl_3$, RT). δ 1.83 (dd, 1H, J = = 13 + 2 Hz, H-17$_\beta$), 2.69 (m, 1H, J = 13 + 3 + 2.5 Hz, H-17$_\alpha$), 2.76 (m, 1H, H-14), 2.85-3.60 (m, 5H, H-3$_B$, N-CH_2 and C7-CH_2), 2.90 (m, 1H, J = 10 + 3 +

+ 2.5 Hz, H-3_A), 3.75 (s, 3H, $COOCH_3$), 4.39 (dd, J = 6.2 + 1 Hz, H-21), 6.37 (m, 1H, J = 7.6 + 6 2 + 1 2 Hz, H-15), 6.59 (m, 1H, J = 7.6 + 6.5 + 1 Hz, H-20), 7.10 (m, 1H, J = 7.5 + 7 + 1 Hz, H-10), 7.15 (m, 1H, J = 7.5 + 7 + + 1 Hz, H-11), 7.25 (dd, 1H, J = 7.5 + 1 Hz, H-12), 7.49 (dd, J = 7 5 + 1 Hz, H-9), 7.74 (b, 1H, NH). See Table IV. for ^{13}C NMR data. MS, m/e 308 (M^+), 293, 277, 229, 228, 214, 197, 170, 169, 168, 154, 124, 107, 94, 93, 79.

(+)-2-{1-[2-(Indol-3-yl)-1-oxo-ethyl]}-7-exo-chloro-2-azabicyclo[2.2.2] oct-5-ene-7-endo-carboxylic Acid Methyl Ester (+)-10. 10.5 g (37 2 mmol) of 3b hydrogen bromide salt was partitioned between 600 mL of chloroform and 200 ml of water Then it was made basic p_H = 8-9 with ammonium hydroxide. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residual oil was dissolved in ethylacetate (285 mL) to which a solution of 14.04 g (37.3 mmol) of dibenzoyl-L-tartaric acid monohydrate $[\alpha]_L^{25}$ = -108.3° (c = 5 ethanol) in 60 mL of methanol was added. After 1 hour standing the obtained white crystals were filtered and washed with some cold ethylacetate. Yield: 8.98 g (16.0 mmol, 86.3 %) of (1S,7R)-3a dibenzoyl-L-tartaric acid salt, mp 152-155 °C. $[\alpha]_D^{25}$. -62.2 ° (c = 1 methanol).

To a stirred solution of 3.6 g (20.6 mmol) of indole-3-acetic acid and 3.2 mL (23.1 mmol) of triethylamine in 48 mL of dimethylformamide 3.9 mL (32.8 mmol) of trimethylacetyl chloride was added dropwise between -5 °C and -10 °C. After 20 minutes stirring at room temperature a thick suspension was obtained, to which a solution of the above obtained 3a dibenzoyl-L--tartarate salt in 6.0 mL (43.4 mmol) of triethylamine and 48 mL of dimethyl-formamide were added and stirred for 3 days. After the usual workup (see above 10) 4.9 g (13.66 mmol, 85.1 %) of (+)-10 purified material was obtained which was crystallized from acetone-hexane, mp. 155-157 °C. IR and NMR data were identical with those of (±)-10. $[\alpha]_D^{25}$: + 104.4 ° (c = 1.5 in $CHCl_3$-methanol 1.1).

(-)-2-{1-[2-(Indol-3-yl)-1-oxo-ethyl]}-7-exo-chloro-2-azabicyclo[2 2.2] oct-5-ene-7-endo-carboxylic Acid Methyl Ester (-)-10. The same method was applied for the resolution of 10.5 g of 3a hydrogen bromide salt with dibenzoyl-D-tartaric acid monohydrate $[\alpha]_D^{20}$: + 110° (c = 5 ethanol). Yield: 10 1 g (18 mmol, 97.1 %)(1R,7S)-3a dibenzoyl-D-tartarate, mp. 148-151°C, $[\alpha]_D^{25}$ = = + 61.75° (c = 1.5 methanol). 9.0 g of the above obtained salt was acylated in the same way. Yield 5.0 g (13.93 mmol, 86 8 %), mp. 173-176 °C. $[\alpha]_D^{25}$:-106.65° (c = 1.5 in $CHCl_3$-methanol 1:1). IR and NMR date see (±)-10.

Photolysis of (+)-10. 2 0 g of (+)-10 was dissolved in 2.5 L of methanol to which 225 mg (5.8 mmol) of sodium borohydride and 0.3 mL of tributyltin chloride were added. The solution was irradiated for 2 hours. After the usual workup the following products were isolated. (a) 388 mg (1.203 mmol, 21 4 %)

of (16S)-5-oxo-20-deethylcatharanthine (16S)-13 mp. 295-300 °C; $[\alpha]_D^{25}$ = + 8.1 ° (c = 1 5 chloroform); (b) 312 mg (0.929 mmol, 16 6 %) of (-)-15, mp. 135-140 °C, $[\alpha]_D^{25}$ = - 105 35 ° (c = 1.5 chloroform); (c) 198 mg (0.615 mmol, 19.1 %) of (-)-14, mp 156-160 °C, $[\alpha]_D^{25}$ = -30.3 ° (c = 1 chloroform) IR, NMR spectra were the same as those the corresponding racemic compounds

Photolysis of (-)-10. Starting from 2 0 g of (-)-10 using the above procedure the following products were obtained. (a) 402 mg (1.248 mmol, 22.3 %) of (16R)-13, mp. 273 °C, $[\alpha]_D^{25}$ = -10 6 ° (c = 1.5 chloroform); (b) 282 mg (0 796 mmol, 14 2 %) of (+)-15 mp 130-138 °C, $[\alpha]_D^{25}$ + 108.5 ° (c = 1.5 chloroform), (c) 323 mg (1.003 mmol, 16.2 %) of(+) -14, mp. 168-170 °C; $[\alpha]_D^{25}$ = + 31 0 ° (c = 1 5 cnloroform). IP, NMR spectra see at the racemic compounds

(16S)-20-Deethylcatharanthine, (16S)-1 Starting from (16S)-13 use of the same procedure as for racemic deethylcatharanthine (16S)-1 (94.1 %) was obtained as white crystals, from ether mp 132-136 °C. See Fig. 1. for CD curves.

(16R)-20-Deethylcatharanthine, (16R)-1. Starting from (16R)-13 the above procedure yielded (16R)-1 (93 6 %). mp 124-131 °C.

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Table I. ^{13}C NMR Chemical Shifts[a]

	3a[b,c]	4a[d,e]	3b[b]	4b[b]
C1	52.95 + 53.41	52.71	53.45	51.33
C3	46.72 + 47.09	45.54	42.65	42.07
C4	31.09 + 30.85	31.15	28.66	28.77
C5	136.33 + 136.59	135.22	139.08	137.00
C6	130.34 + 129.95	129.64	127.11	127.37
C7	68.14	66.67	63.48	63.20
C8	37.60	37.96	37.23	37.10
COO	169.69	170.40	f	168.93
OMe	53.13	53.04	53.91	55.16
N-CO	155 85 + 155.22	154.78	-	-
O-CH_2	67.01	67.03	-	-
C1'	136.79	136.87	-	-
C2'+C6'	127.88	127.99	-	-
C3'+C5'	128.41	128.47	-	-
C4	127.72	127.75	-	-

[a] In δ ppm from internal TMS. [b] In $CDCl_3$ at ambient temperature. [c] A mixture of amide rotational isomers. [d] In $CDCl_3$ + Me_2SO-d_6. [e] Measured at elevated temperature (80 °C). [f] Signal was not observable due to the low concentration of solution.

Table II. ^{1}H and ^{13}C NMR data of 6 in $CDCl_3$ at ambient temperature[a].

position no.	^{1}H NMR			^{13}C NMR
1	3.17 + 3.21		(9.5+8.3+7.5+3.5+2.0+1.5)	27.88 + 27.72
2	3.05 + 3.10	α	(13.5 + 3.5)	41.87 + 42.12
	3.98 + 3.88	β	(13.5 + 2.0 + 1.5)	
4	6.95 + 7.02		(8.6 + 1.5)	127.91 + 128.11
5	4.85 + 4.98		(8.6 + 3.8 + 1.5)	102.70 + 102.91
6	3.15		(8.3 + 4.4 + 3.8)	43.89 + 43.76
7	-			65.69
8	2.35	α	(13 + 7.5 + 4.4)	34.48 + 34.54
	2.71	β	(13 + 9.5)	
$-OCH_2$	5.16 + 5.25		(12)	68.03 + 67.91
$-OCH_3$	3.75			52.66
-COO	-			168.97 + 168.89
-NCO	-			153.81 + 154.23
1'				135.71
2',6'	7.35			128.36
3',5'				128.59
4'				128.12

[a] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively. Chemical shifts are reported as δ values, and J values are given in hertz in parentheses.

Table III ^1H and ^{13}C NMR Data of 11 and 15[a,b]

atom no	^1H	11[c]	^{13}C	^1H	15[d]	^{13}C
1	-		49 71	-		58 37 + 58 62
2	2 18 β	(d, 10 5)	54 54	-		81 09 + 85 19
	2 94 α	(dd, 10 5 + 2)		6 05 + 5 48	(s)	
4	2 24 β	(dd, 10 5 + 1 5)	51 91	3 30 + 2 84	(dd, 12 5 + 1 5)	44 07 + 45 88
	2 92 α	(m, 10 5 + 3 + 2)		4 18 + 3 47	(m, 12 5 + 3 + 2)	
5	2 72	(m, 5 + 3 + 3 + 1 5)	39 16	2 62 + 2 71	(m, 5 + 3 + 3 + 1 5)	39 42 + 39 59
6	6 08	(dd, 5 8 + 3)	132 66	5 60 + 5 71	(dd, 5 5 + 3	134 53 + 133 55
7	5 97	(d, 5 8	134 29	5 91 + 5 07	(d, 5 5	135 20 + 135 77
8	1 30	(d, 9 5	45 15	2 25 + 2 30	(d, 10	37 08 + 38 28
	1 94 α	(m, 9 5 + 5 + 2 + 2)		2 12 + 2 09	(m, 10 + 5 + 2	
2'	7 02	(d, 2)	120 53*	7 02 + 7 11	(d, 2)	123 08 + 123 54*
3'	-		112 71	-		108 15 + 108 71
3a'	-		126 76	-		127 14 + 127 28
4'	7 58	dd, 7 6 + 1)	117 82°	7 57 + 7 64	(dd, 7 5 + 1)	118 58 + 118 95
5'	7 06	(m, 7 6 + 7 2 + 0 8)	117 90°	7 1 - 7 2	(m)	119 45
6'	7 12	(m, 7 5 + 7 2 + 1)	121 38*	7 1 - 7 2	(m)	122 04*
7'	7 35	(dd, 7 5 + 0 8)	110 70	7 35 + 7 34	dd, 7 8 + 0 8)	111 48 + 111 39
7a'	-		135 66	-		136 43 + 136 39
3'-CH_2	2 8-3 0	(m)	21 35	3 78 + 4 00	(d, 15 5	32 24 + 32 10
N-CH_2	2 8-3 0	(m)	57 98	-		-
N-CO	-		-	-		172 52 + 173 01
CH_2OH	3 59 + 3 63	(d,11)	65 56	-		-
NH	9 12	(b	-	8 28	(b)	-
OH	3 29	(b	-	-		-
2-OCH_3	-		-	3 37 + 3 34	s)	57 44 + 55 66
COO	-		-	-		174 12
OCH_3	-		-	3 75 + 3 65	(s)	52 04

[a] ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, at ambient temperature Chemical shifts are reported in δ ppm from internal TMS, J values are given in hertz in parentheses [b] Signals marked with identical symbols are interchangeable [c] In $CDCl_3$ + Me_2SO-d_6 solution [d] In $CDCl_3$ solution Most signals exhibit splittings due to amide rotational isomerism

Table IV. ^{13}C NMR Chemical Shifts[a,b]

	7[c]	10[d]	10[e]	13[c]	1[c]	
C1	60.61	50.08+54.89	53.09	51.52	56.77	C21
C3	57.82*	47.05+46.39	46.86	50.14	52.66	C3
C4	31.55	30.93+31.18	30.99	31.68	30.71	C14
C5	135.39	137.17+137.43	137.20	137.99	135.13*	C20
C6	128.64	129.63+128.96	129.46	129.48	133.20*	C15
C7	69.82	68.26+69.00	69.11	53.49	55.45	C16
C8	36.04	37.37+37.26	37.71	33.28	38.22	C17
3'-CH_2	24.04	30.16+30.62	30.87	32.66	21.27	C6
C2'	121.60$^{\Delta}$	123.43	123.63	134.32°	134.79°	C2
C3'	114.26	107.54+107.90	108.11	103.98	110.65	C7
C3a'	127.52	127.35+127.22	127.57	127.59	128.99	C8
C4'	118.60°	118.35+118.61	118.56	118.59	118.19	C9
C5'	118.93°	118.45	118.56	119.99	119.47	C10
C6'	121.77$^{\Delta}$	121.01	121.16	122.51	121.88	C11
C7'	110.92	111.31	111.41	110.82	110.49	C12
C7a'	136.06	136.24	136.58	135.41°	135.93°	C13
N-CH_2	54.86*	-	-	-	48.79	-
COO	170.52	170.24+170.16	170.57	174.53	174.73	COO
N-CO	-	169.33+169.07	169.43	173.46	-	N-CO
OCH_3	52.83	53.12+53.25	53.09	52.86	53.01	OCH_3

[a] In δ ppm from internal TMS. [b] Signals marked with identical symbols are interchangeable. [c] In $CDCl_3$ at ambient temperature. [d] In $CDCl_3$ + Me_2SO-d_6 at ambient temperature. Most signals exhibit splittings due to amide rotational isomerism. [e] In Me_2SO-d_6 at elevated temperature (120 °C). The numbering of compounds 1 and 13 are different from 7 and 10. See the right column. The corresponding carbon atoms are in the same lines.

Table V. Partial comparison of NMR data

		11		7		12a	12b	20
olefinic protons[a]	H-6	6.08	H-6	6.15	H-3	5.69	5.79	5.65
	H-7	5.97	H-5	6.45	H-4	6.88	6.79	6.74
olefinic couplings[b]		5.8		8.0		9.5	9.5	9.3
allylic protons[a]	H-5	2.72	H-4	2.63	H-2	4.39	4.59	3.93
		-	H-1	3.96		-	-	-
allylic carbons[a]	C-5	39.16	C-4	31.55	C-2	58.09	51.30	68.95
	C-1	49.71[c]	C-1	60 61	C-5	62.63[c]	62.20[c]	62.52[c]

a/ Chemical shifts in ppm. b/ Coupling constants in Hz.
c/ Quaternary carbons.

Table V1. ^{13}C NMR Chemical Shifts ($CDCl_3$+Me_2SO-d_6)[a,b]

	14	16	17	19
C1	120.60*	119.82*	118.71*	117.71
C2	121.23*	121.04*	120.62*	127.33
C3	111.11	111.02	110.01	107.38
C3a	135.16	134.48	139.13Δ	152.53
C5	126.09	126.56	124.93	55.50*
C5a	108.59	109.43	112.68	40.30
C6	35.87	44.80	27.94	33.19
C7	171.41	199.07	48.59○	52.33*
C9	48.28	55.90	53.40○	54.99*
C10	30.28	30.02	26.79	30.47
C11	136.95	138.09	23.70	135.17
C12	129.76	128.94	19.73	131.80
C12a	52.33	55.08	46.15	52.93
C13	59.31	58.25	55.88	56.65
C13a	139.39	138.87	141.90Δ	140.80
C13b	121.50	121.68	124.35	127.61
C14	36.24	35.39	38.81	36.90
COO	173.86	173.17	176.36	173.76
OMe	52.25	52.36	51.59	51.91

[a] The δ values are in ppm from internal TMS.

[b] Signals marked with identical symbols are interchangeable.

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