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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XLVIII[1]
SYNTHESIS OF (+)-CATHARANTHINE AND (±)-ALLOCATHARANTHINE

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

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 The first synthesis of natural (+)-catnaranthine (1) has been achieved in a few steps and in ~ 20 % overall yield based on indole-3--acetic acid. The isomeric (±)-allocatharanthine was also prepared.

The dimeric Catharanthus alkaloids vincristine and vinblastine are widely used clinical anticancer agents applied routinely for treatment of a number of human cancer[2]. Recently, starting from anhydrovinblastine, a new and effective anticancer drug, NAVELBINE[R] has been developed in France[3].

Catharanthine 1 is a major alkaloid of Catharanthus roseus. On coupling of catharanthine 1 with vindoline antitumor vinblastine derivatives could be obtained[4], thus the total syntheses of the above mentioned three drugs became commercially feasible

Several research groups have synthesized racemic but none the natural (+)-catharanthine[5]. Now we present the first synthesis of optically active catharanthine using fewer steps then previous schemes aimed at the racemic compound.

Allocatharanthine (2) the regioisomer of catharanthine (1) is an artefact obtained from tabersonine by boiling in acetic acid[6]. Recently (±)-16-hydroxy--allo-ibogamine, the first natural member of the allo-iboga class of alkaloids has been isolated from Strychnos ngouniensis by a Frenchgroup[7].

After completion of the synthesis of (±)-20-deethylcatharanthine[8] and the corresponding enantiomers[1] we aimed at the preparation of (+)-catharanthine 1 and allocatharanthine 2 using the same strategy.

At the outset the isoquinuclidines 5 and 6 were prepared starting from 3-ethylpyridine by the Diels-Alder reaction of the dihydropyridine and dienophile

3-Ethylpyridine was reduced by sodium-borohydride in the presence of benzyl chloroformate using Fowler's method[9], by which 1-(benzyloxycarbonyl)--1,2-dihydropyridines can be readily obtained. The unstable dihydropyridines

3 and 4 were reacted without isolation at 20 °C successively with 2-chloroacryloyl chloride and methanol. The regioisomers 5a and 6a were obtained in a ratio of about 55:45 (overall yield 20 % from 3-ethyl-pyridine). From ethylacetate-hexane 6a could be crystallized pure while the remaining mixture of 5a and 6a accompanied by a small amount of 5b and 6b was separated by HPLC on a reversed phase column.

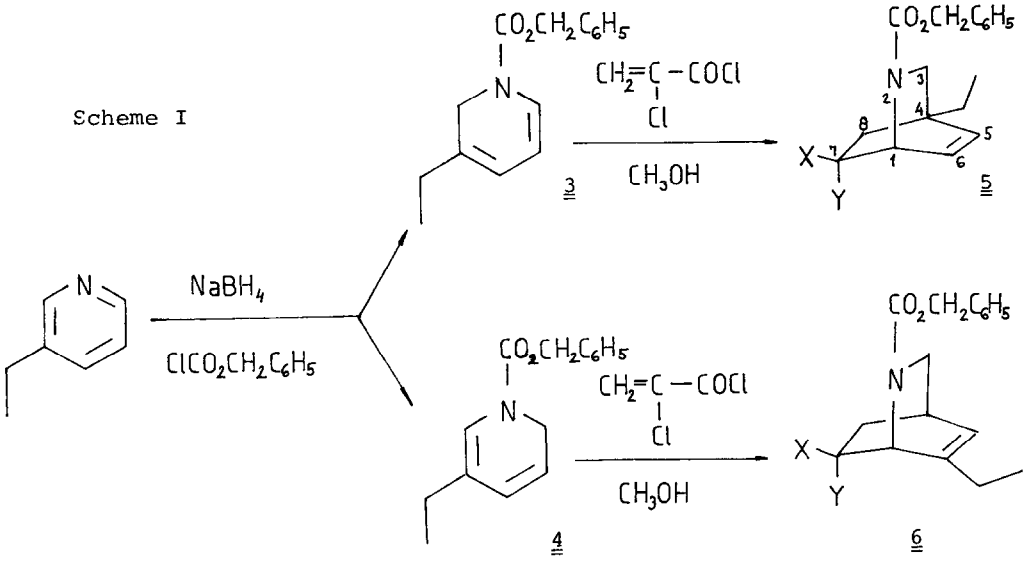
The obtained oil containing both 5a and 6a was treated with HBr/CH_3COOH resulting in a mixture of 10a and 11a. After evaporation of acetic acid the major component, 10a, crystallised from the residue.

When cycloaddition was carried out refluxing the reaction mixture the overall yield raised to ~ 40 %, but the ratio of 5a and 6a shifted to ~ 60:40. From this mixture we could isolate as minor products, the epimers 5b and 6b containing the chlorine atom in endo position (ratio 9:1).

Meanwhile Raucher and Lawrence reported[10] that the application of Fowler's method[9] for 3-ethylpyridine led in their hands only to 1-(methoxycarbonyl)-3-ethyl-1,2-dihydropyridine, i.e. to the regioisomer useless for catharanthine synthesis.

Preparation of 6a was tried also by another sequence with some advantageous modification. Raucher and Lawrence prepared 1-(methoxycarbonyl)--5-ethyl-1,2-dinydropyridine[10] from the corresponding dibromo-compound using $EtAlCl_2$ for dehydrobromination. We synthesised the N-(benzyloxycarbonyl)--dibromo derivative 9 in two different ways

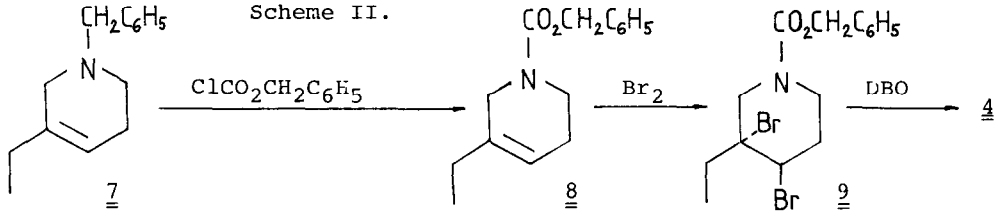
Scheme I



a X = Cl, Y = CO_2CH_3
b X = CO_2CH_3 Y = Cl

Fowler noticed[11] that reduction of 1-(methoxycarbonyl)-3-ethyl-1,2-dihydropyridine with $NaBH_4/CF_3CO_2H$ in benzene led to 1-(methoxycarbonyl)-5-ethyl-1,2,3,6-tetrahydropyridine. The subsequent bromine addition gave the trans-3,4-dibromo-derivative. Double denydrobromination of the latter was carried out with 1,4-diazabicyclo[2.2.2]octane in dimethylformamide at reflux affording 1-(methoxycarbonyl)-5-ethyl-1,2-dihydropyridine. In our hands the analogous series of reactions (3-ethylpyridine → 3 → 8 → 9), gave the desired dibromo derivative 9 after a column chromatography in poor yield. The second procedure for 9 involved reaction of 1-benzyl-3-ethyl-1,2,5,6-tetrahydropyridine (7)[5d] with benzyl chloroformate to give 1-(benzyloxycarbonyl) derivative 8. Treatment of 8 with bromine provided the corresponding dibromide 9 in 72 % overall yield based on 1-benzyl-3-ethylpyridinium chloride In view of the sensitivity of the benzyloxycarbonyl group[12] $EtAlCl_2$ did not seem to be suitable for dehydrobromination of 9, but the desired dihydropyridine 4 was readily available using 1,4-

Scheme II.



-diazabicyclo[2.2 2]octane (DBO) in dimethylformamide or acetonitrile. Raucher et al. reported[5d] that DBO was unsuited for dehydrobromination of 1-(methoxycarbonyl)-trans-3,4-dibromo-3-ethyl-piperidine in DMF. Surprisingly we could perform this transformation using acetonitrile as solvent and obtained 1-(methoxycarbonyl)-5-ethyl-1,2-dihydropyridine.

The cycloaddition between dihydropyridine 4 and 2-chloroacryloyl chloride followed by treatment of the product with methanol led to the crystalline isoquinuclidine 6a in 38 % yield from dibromide 9. Chromatography of the mother liquor, gave more of 6a as well as the corresponding endo-chloro-epimer 6b (15 % for each), meaning 68 % overall yield of 6a and 6b based on dibromide 9.

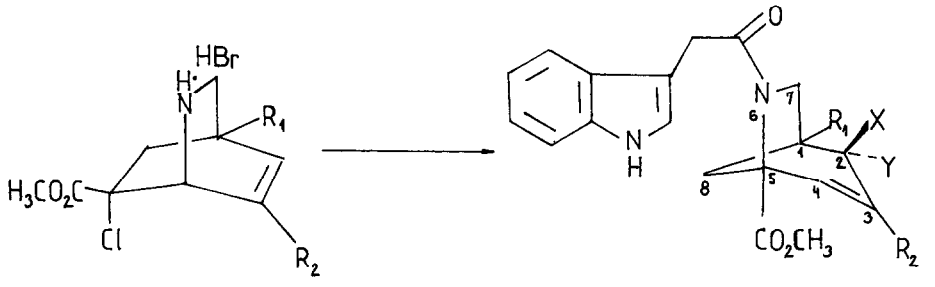
Removal of the benzyloxycarbonyl protecting group proved to be very simple. On treatment of 6a with acetic acid/HBr for 10 minutes at room temperature of 6a the hydrogen bromide salt (11a) was obtained in high yield (98 %).

Acylation of the amines 10a and 11a by the mixed anhydride of indole-3-acetic acid and pivalic acid led to the compounds 12a and 13a respectively.

Acylation of the endo-chloro epimers 10b and 11b under the same

conditions resulted in rearranged products containing 6-azabicyclo[3.2.1]-oct-3-ene skeleton similarly to the corresponding deethyl-derivative[1]. Evidence in favour of the rearranged structures 14 and 15 was provided by one- and two-dimensional NMR techniques. Details of the NMR studies together with those of related compounds will be the subject of a forthcoming paper.

Scheme III.



10b $R_1 = C_2H_5$, $R_2 = H$

11b $R_1 = H$, $R_2 = C_2H_5$

14 $R_1 = C_2H_5$, $R_2 = H$, X = Cl, Y = H

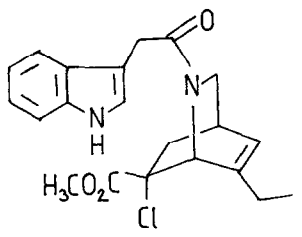
15a $R_1 = H$, $R_2 = C_2H_5$, X = H, Y = Cl

15b $R_1 = H$, $R_2 = C_2H_5$, X = H, Y = Br

We have established previously[1] that a characteristic of the presence of the 6-azabicyclo[3.2.1]oct-3-ene skeleton is the large value of the olefinic coupling between H-3 and H-4 protons. Thus the 9.5 Hz coupling observed on the signals at δ 5.63 and δ 6.85 ppm in the spectrum of 14 is consistent with the rearranged structure.

The signal of the olefinic proton in the ^{1}H NMR spectra of 15a and 15b didn't show the spectral features characteristic for the H-5 proton in the 6-ethyl substituted isoquinuclidine ring. Instead, a broad singlet attributable to an olefinic proton without a vicinal proton partner was found at 6.61 ppm. This and all the other spectral properties are in accord with the structure given for 15a and 15b. It is to be noted, that Raucher et al.[5d] have published the ^{1}H NMR data for a molecule where most of the chemical shifts and the coupling constant values were the same with those of 15a. However, the structure they assigned to this molecule (13b) was not in agreement with the published ^{1}H NMR data. The values given for the olefinic proton (singlets at 6.67 and 6.61 ppm for the two rotamers) markedly differ from those expected for the H-5 proton in the isoquinuclidine ring (~ 6 ppm, J = 6 Hz + long range couplings). Most probably they isolated a molecule

with 6-azabicyclo[3.2.1]oct-3-ene skeleton, which might be the C2 epimer of 15a



13b

In their synthesis of racemic catharanthine published in 1987[5d] Raucher et al. followed our reaction sequence and strategy published in 1983[8] without mentioning that fact. They reproduced our photocyclization of the deethyl-compound 16, but failed to extend it to the ethyl-derivative 13a. So they transformed compound 13a to the corresponding thioamide. Irradiaton of the latter compound resulted in 5-thioxo-catharanthine which was transformed to racemic catharanthine in two steps.

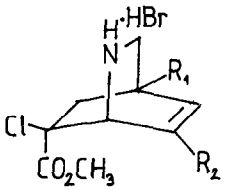
In our hands, using a small amount of tributyl tinhydride in methanol, photolytic ring closure of 12a and 13a led to the products 17 and 18 respectively. The yields (30 and 30 %) fortunately were even higher than in case of the deethyl compound 16.

As with the deethyl compound photocyclisation gave also other products, 19 and 20. The structure and stereochemistry of the molecules were established on the basis of their NMR data in comparison with those of the deethyl analogues[1]. When tributyltin hydride was present as catalyst a small amount of a reduced compound derived from 13a was also obtained containing hydrogen instead of chlorine. If tetrahydrofuran, acetonitrile or ethanol was used as solvent for the photochemical reaction or else the photo-cyclisation took place in methanol in presence of $NaHCO_3$ but without Bu_3SnH the yield of 5-oxo-catharanthine (18) was lower.

Initially the oxo group of 17 and 18 was removed by Sundberg's method[13]. 17 and 18 were transformed to the thioamides 21 and 22 respectively with P_2S_5 and then with methyl iodide to the S-methyl-derivatives 23 and 24. Subsequent reduction with $NaBH_3CN$ yielded catharanthine 1 and allo-catharanthine 2 respectively.

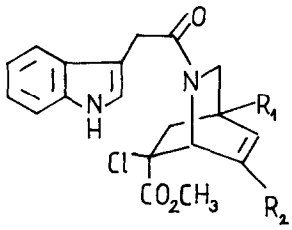
The S-methyl derivatives were very sensitive to water making the above mentioned procedure rather tedious. Of the other methods (e.g. $Et_3O^+.BF_4^-$, CH_2Cl_2 and $NaBH_4$; $POCl_3/NaBH_4$, etc.) tried the boron trifluoride etherate sodium borohydride system proved to be the best. By this 17 and 18 were transformed in one step and in almost quantitative yield to catharanthine 1 and allocatharanthine 2 respectively.

Scheme IV.



10a $R_1 = C_2H_5$, $R_2 = H$

11a $R_1 = H$, $R_2 = C_2H_5$

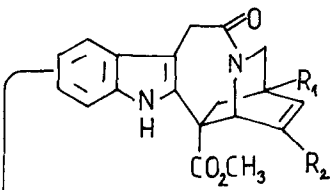


12a $R_1 = C_2H_5$, $R_2 = H$

13a $R_1 = H$, $R_2 = C_2H_5$

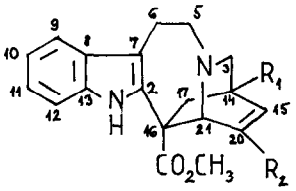
16 $R_1 = R_2 = H$

hν



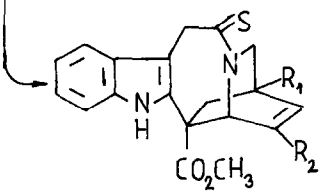
17 $R_1 = C_2H_5$, $R_2 = H$

18 $R_1 = H$, $R_2 = C_2H_5$



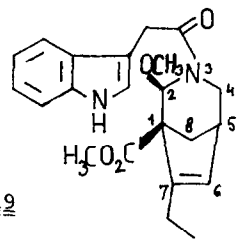
1 $R_1 = H$, $R_2 = C_2H_5$

2 $R_1 = C_2H_5$, $R_2 = H$

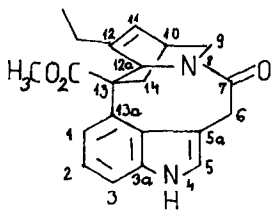


21 $R_1 = C_2H_5$, $R_2 = H$

22 $R_1 = H$, $R_2 = C_2H_5$



19



20

Synthetic and natural catharanthine had superimposable IR, NMR, MS spectra and exhibited identical mobility on TLC plates. Spectral data of synthetic (±)-allocatharanthine (2) and of a sample obtained from tabersonine[6] were identical. Since for us only dihydroallocatharanthine (25) but no allocatharanthine was available, 5-thioxo-allocatharanthine (21) was reduced in ethanol in presence of Raney nickel. The R_f values of the obtained dihydroallocatharanthine 25 and of the authentic sample were identical.

Resolution was performed in good yield (~ 96 %) with isoquinuclidine base 11a using (+)-dibenzoyl-D-tartaric acid. Carrying out the above mentioned reaction sequence acylation, photocyclisation, reduction of the oxo-group (+)-catharanthine was synthesized which proved to be identical with the natural product in every respect.

Thus the reaction sequence (11a ⟶ 13a ⟶ 18 ⟶ 1) provided the desired optically active alkaloid in ~ 20 % combined yield based on indole-3-acetic acid.

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 Specific rotation was measured on Polamat A (Carl Zeiss Jena). Thin layer chromatograms (TLC) were made with DC-Alufolien Kieselgel $60F_{254}$ (Merck 5554). Column chromatography separations were carried out on silicagel (0.063-0.200; Merck 7734).

(±)-2-(Benzyloxycarbonyl)-4-ethyl-7-exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester 5a, (±)-2-(Benzyloxycarbonyl)-4-ethyl-7-endo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-exo-carboxylic Acid Metnyl Ester 5b, (±)-2-(Benzyloxycarbonyl)-6-ethyl-7-exo-chloro-2-azabicyclo-[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester 6a and (±)-2-(Benzyloxycarbonyl)-6-ethyl-7-endo-chloro-2-azabicyclo[2.2 2]oct-5-ene-7-exo-carboxylic Acid Methyl Ester 6b.

Method (a). To a stirred solution of 32.15 g (0.3 mol) 3-ethylpyridine in 600 mL of dry methanol 13 2 g (0.35 mol) $NaBH_4$ and then 50 mL (59.75 g = = 0.35 mol) benzyl chloroformate were dropwise added between -65 °C and -75 °C. The mixture was stirred for an additional hour at the above temperature at which point TLC and UV showed that all starting material had been consumed. Then the solvent was evaporated in vacuo. The residue was dissolved in chloroform and water The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residual oil 72.4 g (298 mmol, 99.0 %) containing both

1-(benzyloxycarbonyl)-3-ethyl-1,2-dihydropyridine 3 and 1-(benzyloxycarbonyl)-5-ethyl-1,2-dihydropyridine 4 (UV: λ_{max} = 305 nm) was dissolved in 150 mL of acetonitrile to which 43.73 g (0.35 mol) 2-chloroacryloyl chloride and 0.1 g hydroquinon were added After 1 day the reaction mixture was made basic (p_H=8-9) with Et_3N and evaporated in vacuo. The residue was dissolved in 200 mL of chloroform washed with water, dried (Na_2SO_4), evaporated. Purification was effected by passing the residual oil through a silica column (eluant:toluene: ethylacetate = 10:2). The fractions containing 5a,b and 6a,b were evaporated in vacuo and crystallized from ethylacetate-hexane to give 6a (3.6 g, 9.89 mmol, 3.3 %), mp. 88-91 °C; IR (KBr) 1695 cm^{-1} (amide C=O), 1740 cm^{-1} (ester C=O); ^1H NMR (100 MHz, $CDCl_3$, 55 °C): δ 0.98 (t, 3H, J = 7 Hz, $-CH_2-\underline{CH_3}$), 1.96 (dd, 1H, J = 13 + 2 Hz, H-8β), 2.15 (qd, 2H, J = 7 + 1 Hz, $\underline{CH_2}$ - CH_3), 2.76 (m, 1H, J = 13 + 2.5 + 2 Hz, H-8α), 2.82 (m, 1H, H-4), 3.02 (m, 1H, J = 10 + 2.5 + 2 Hz, $H\text{-}3_A$), 3.46 (dd, 1H, J = 10 + 1.5 Hz, $H\text{-}3_B$), 3.74 (s, 3H, $COOCH_3$), 5.10 (d, 1H, J = 1.5 Hz, H-1), 5.19 (s, 2H, $COO\underline{CH_2}$), 6.04 (m, 1H, J = 6.5 + 1 + 1 + 1 Hz, H-5), 7.3 - 7.4 (m, 5H, aromatics). See Table I. for ^{13}C NMR data. MS m/e 366[1], 365[1], 364[1], 363(M^+), 284, 243, 198, 196, 166, 133, 122, 121, 108, 107, 91, 79, 77, 65; Anal. Calcd. for $C_{19}H_{22}ClNO_4$; C, 62.72; H, 6.10; Cl, 9.75; N, 3.85, Found. C, 63.09; H, 6.21; Cl, 9.69, N, 3.89. The mother liquor was evaporated in vacuo. The residue (17.55 g, 48.23 mmol, 16.1 %) contained 5a and 6a about in a ratio of 2:1 (measured by ^1H NMR and HPLC) and a small amount of 5b and 6b. IR of the residue: ($CHCl_3$, film) 1695 cm^{-1} (amide C=O), 1740 cm^{-1} (ester C=O); ^1H NMR of 5a (100 MHz, $CDCl_3$, 55 °C) 0.94 (t, 3H, J = 7 Hz, $CH_2-\underline{CH_3}$), 1.68 (q, 2H, J = 7 Hz, $\underline{CH_2}-CH_3$), 1.80 (d, 1H, J = 14 Hz, H-8β), 2.60 (dd, 1H, J = 14 + 2.5 Hz, H-8α), 2.92 (dd, J = 10 + 2.5 Hz, H-3A), 3.27 (d, J = 10 Hz, H-3B), 5.20 (bs, 3H, H-1 + $COOCH_2$), 6.1 - 6.3 (m, 2H, H-5 and H-6), 7.35 (bs, 5H, aromatics). See Table I. for ^{13}C NMR data. MS spectrum of the mixture containing 5a and 6a was indistinguishable from that of 6a

Method (b). The reaction mixture of cycloaddition was refluxed together with 2-chloroacryloyl chloride for ten hours. Apart from this the reaction was carried out under the same conditions as in case of method (a). After the usual workup and column chromatography the fractions containing 5a,b and 6a,b were evaporated in vacuo and crystallized from ethylacetate-hexane to give 3.9 g (10.7 mmol, 3.6 %) of compound 6a comparable purity to the material obtained in part (a) The mother liquor was evaporated in vacuo. The residue (39.5 g, 108.56 mmol, 36.2 %) contained 5a and 6a about in a ratio of 2:1 (measured by ^1H NMR and HPLC) and a small amount of 5b and 6b which could be separated from 5a and 6a by chromatography of the residual oil on a silica column (eluant:toluene.ethylacetate = 10:1). The obtained mixture contained 5b and 6b in a ratio of 9:1 (1.728 g, 4.749 mmol, 1.58 %).

1. isotopic peak

IR of 5b and 6b ($CHCl_3$, film) 1695 cm^{-1} (amide C=O), 1740 cm^{-1} (ester C=O); ^1H NMR of 5b (100 MHz, $CDCl_3$, 55 °C) 0.98 (t, 3H, J = 7 Hz, CH_2-$\underline{CH_3}$), 1.60 (q, 2H, J = 7 Hz, $\underline{CH_2}$-CH_3), 1.75 (dd, 1H, J = 14 + 2.5 Hz, H-8α), 2.75 - 3.1 (m, 3H, H-3A, H-8β and H-3B), 3.62 (s, 3H, $COOCH_3$), 5.10 (s, 2H, $COOCH_2$), 5.20 (dd, 1H, J = 6 + 1.5 Hz, H-1), 6.34 (dd, 1H, J = 8 + 1.5 Hz, H-5), 6.50 (dd, 1H, J = 8 + 6 Hz, H-6), 7.34 (bs, 5H, aromatics). H-8α was identified by its long range (w) coupling with H-3A in both 5a and 5b. The upfield shift of H-8α and the downfield shift of H-8β in the proton spectrum of 5b relative to that of 5a confirmed the exo orientation of the carbomethoxy substituent in 5b. See Table I. for ^{13}C NMR data. MS of 5b and 6b m/e 366^1, 365^1, 364^1, 363 (M^+), 243, 198, 170, 166, 165, 154, 152, 133, 108, 92, 91, 79, 77, 65.

1-(Benzyloxycarbonyl)-trans-3,4-dibromo-3-ethylpiperidine 9

(a) 3-Ethylpyridine (10.7 g, 0.1 mol) was dissolved in 200 mL of absolute methanol. To this solution $NaBH_4$ (3.8 g) and then 15 mL of benzyl chloroformate were added in small portions between -65 °C and -75 °C. The mixture was stirred for an additional hour at the above temperature at which point TLC showed that all starting material had been consumed. Then the reaction mixture was evaporated in vacuo. The residue was dissolved in diethylether, washed with water, dried (Na_2SO_4) and evaporated. The residue was dissolved in 200 mL of dry benzene and 3.8 g (0.1 mol) of $NaBH_4$ and 8 mL of trifluoroacetic acid were added carefully. The reaction mixture was stirred for two hours and then evaporated. The residual oil was partitoned between chloroform and water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on a silica column (eluant:toluene:ethylacetate = 10:2) to give an oil containing 8 which was dissolved in 200 mL of CH_2Cl_2 and 5.3 mL of bromine was added to it. After 1 hour stirring 0.5 g of $Na_2S_2O_3$ and water were added. The organic layer was washed with water, dried (Na_2SO_4), evaporated. Chromatography of the residual oil under the above conditions afforded 9 as an oil (4.58 g, 11.3 mmol, 11.3 %). The analytical sample was crystallized from ether-hexane mp. 66-68°C IR (KBr) 1700 cm^{-1} (C=O). ^1H NMR (100 MHz, $CDCl_3$, 45 °C): δ 1.10 (t, 3H, J = 7 Hz, CH_2-$\underline{CH_3}$), 1.90 (m, 1H, J = 13 + 4 + 2.5 + 2.5 Hz H-5_A), 1.98 (q, 2H, J = 7 Hz, $\underline{CH_2}$-CH_3), 2.76 (m, 1H, J = 13 + 11.5 + 5 + 3 Hz, H-5_B), 3.40 (m, 1H, J = 13.5 + 11.5 + 2.5 Hz, H-6_A), 3.42 (d, 1H, J = 14.5 Hz, H-2_A), 4.10 (m, 1H, J = 13.5 + 5 + 2.5 Hz, H-6_B), 4.12 (d, 1H, J = 14.5 Hz, H-2_B), 4.60 (dd, 1H, J = 4 + 3 Hz, H-4), 5.15 (s, 2H, O-CH_2), 7.32 (bs, 5H, aromatics). MS m/e 403 (M^+), 324, 312, 296, 280, 245, 244, 243, 232, 216, 200, 186, 172, 154, 138, 110, 108, 91, Anal Calcd. for $C_{15}H_{19}Br_2NO_2$: C, 44.47; H, 4.73, Br, 39.45; N, 3.46. Found. C, 44.17; H, 4.76; Br, 39.58; N, 3.39.

1: isotopic peak

(b) To a stirred solution of 1-benzyl-3-ethyl-pyridinium chloride (11.689 g, 50 mmol) in 100 mL of ethanol 7.06 g (187 mmol) of $NaBH_4$ dissolved in 100 mL of ethanol was added at 0 °C and stirred for 24 hours at room temperature. The reaction mixture was evaporated, the residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated. The obtained residual oil was dissolved in dry benzene to which 15.2 ml benzyl chloroformate was added and refluxed for 5 hours and then evaporated in vacuo. To the solution of the residue in 100 mL of CH_2Cl_2 3 mL of bromine was added dropwise. After 1 hour stirring 0.5 g of $Na_2S_2O_3$ and water were added to the reaction mixture. The organic layer was dried (Na_2SO_4), evaporated and the residue was crystallized from acetone-hexane to give white crystals of 9 (7.15 g, 17.66 mmol, 35.3 %) mp. 67-69 °C. Chromatography of the mother liquor afforded additional amounts of 9 (7.88 g, 19.46 mmol, 38.92 %; overall yield. 74.22 %). Spectral data see above.

(±)-2-(Benzyloxycarbonyl)-6-ethyl-7-exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester 6a and (±)-2-(Benzyloxycarbonyl)-6-ethyl-7-endo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-exo-carboxylic Acid Methyl Ester 6b from 9. Dibromo compound 9 (6.400 g, 15.797 mmol), and 8.0 g (71 3 mmol) of 1,4-diazabicyclo[2.2.2]octane in acetonitrile (200 mL) were refluxed together for 5 hours under nitrogen at which point TLC or UV showed that all the starting material had been consumed. Then the reaction mixture was evaporated in vacuo The residue was dissolved in 200 mL of dichloromethane, the precipitated salt of DBO was filtered, washed with CH_2Cl_2. The filtrate was washed with water, dried over Na_2SO_4 and evaporated. The residue was dissolved in acetonitrile (200 mL) to which 2-chloro-acryloyl chloride (24 g, 19.2 mmol) was added. The reaction mixture was stirred for 24 hours, then evaporated. The residue was refluxed in 200 mL of methanol for 5 hours, then evaporated. The residue was dissolved in CH_2Cl_2 washed with water, dried (Na_2SO_4), evaporated and crystallized from ethylacetate-hexane to give 6a (2.210 g, 6.074 mmol, 38.5 %). The mother liquor was evaporated (2.459 g, 6.759 mmol, 42 8 %) and purified by chromatography on a silica column (eluant:hexane:ethylacetate:triethylamine = 15:3:1) to give additional amount of 6a (393 mg, 2.454 mmol, 15.5 %) and 6b (822 mg, 2.259 mmol, 14.3 %). Overall yield of 6a + 6b . 68 3 %. 6b IR: 1695 cm^{-1} (amide C=O), 1740 cm^{-1} (ester C=O), ^1H NMR (100 MHz, $CDCl_3$, 55 °C): δ 1.07 (t, 3H, J = 7 Hz, $-CH_2-CH_3$), 1.94 (m, 1H, J = 13.5 + 2.5 + 2 Hz, H-8α), 2.32 (qd, 2H, J = 7 + 1 Hz, CH_2-CH_3), 2.81 (m, 1H, H-4), 2.90 (m, 1H, J = 10 + 2.5 + 2 Hz, H-3A), 3 00 (dd, 1H, J = 13.5 + 2.5 Hz, H-8β), 3.20 (dd, 1H, J = 10 + 2 Hz, H-3B), 3.63 (s, 3H, $COOCH_3$), 5 12 (bs, 3H, H-1 and $COOCH_2$), 6.07 (m, 1H, J = 6.5 + 1 + 1 + 1 Hz, H-5), 7.3 - 7.4 (m, 5H, aromatics

See Table I. for ^{13}C NMR data. MS m/e 365[1], 364[1], 363 (M^+), 332, 244, 243, 199, 198, 169, 165, 154, 133, 108, 107, 105, 93, 92, 91, 79, 77, 65.

(±)-4-Ethyl-7-exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester Hydrogen Bromide Salt 10a and (±)-6-Ethyl-7-exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester Hydrogen Bromide Salt 11a. An oil containing mixture of 5a and 6a (10.0 g, 27.48 mmol) obtained above by method (a) evaporating mother liquor of 5a was dissolved in 60 mL of 2-3 N hydrogen bromide in acetic acid and stirred for 30 minutes. The solution was evaporated in vacuo to dryness to give a mixture of 10a and 11a (8.4 g, 27.04 mmol, 98.4 %). Crystallization of the residue from diethylether-hexane afforded only a small amount of 10a (1.6 g, 5.15 mmol, 17.74 %); mp. 161-166 °C. IR (KBr) 1740 cm^{-1} (ester C=O), 2300-2750 cm^{-1} ($\geq NH_2^+$); 10a (base) ^1H NMR (100 MHz, $CDCl_3$, 45 °C), δ 0.93 (t, 3H, J = 7 Hz, CH_2-$\underline{CH_3}$), 1.52 (q, 2H, J = 7 Hz, $\underline{CH_2}$-CH_3), 1 78 (d, 1H, J = 14 Hz, H-8β), 2 40 (dd, 1H, J = 9.5 + 3 Hz, H-3_A), 2.58 (dd, 1H, J = 14 + 3 Hz, H-8α), 2.85 (d, 1H, J = 9.5 Hz, H-3_B), 3.74 (s, 3H, $COOCH_3$), 4.93 (dd, 1H, J = 5.5 + 1.5 Hz, H-1), 6.15 - 6.3 (m, 2H, H-5 and H-6). ^{13}C NMR (25.16 MHz, $CDCl_3$, RT): δ 8.4 (-CH_3), 28.1 (-$\underline{CH_2}$-CH_3), 38.8 (C-4), 42.4 (C-8), 49.6 (C-3), 53.0 (OCH_3), 54.9 (C-1), 70 7 (C-7), 130.1 (C-6), 139.1 (C-5), 170.6 (COO). Mother liquor of 10a contained both 10a and 11a.

(±)-6-Ethyl-7-exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester Hydrogen Bromide Salt 11a 5.00 g (13.74 mmol) Of 6a was treated with hydrogen bromide in acetic acid in the former way to give 11a (4 26 g, 13.68 mmol, 99 56 %). The analytical sample was prepared by crystallization from acetone, mp. 157-159 °C. 11a (base) ^1H NMR (100 MHz, $CDCl_3$, 45 °C): δ 1 02 (t, 3H, J = 7 Hz, CH_2-$\underline{CH_3}$), 2.15 (m, 2H, $\underline{CH_2}$-CH_3), 2.19 (dd, 1H, J = 12 + 2 Hz, H-8β), 2.52 (m, 1H, J = 10 + 2 + 2 Hz, H-3_A), 2.66 (m, 1H, H-4), 2 76 (m, 1H, J = 12 + 2.5 + 2.0 Hz, H-8α), 3.03 (dd, 1H, J = 10 + 1 5 Hz, H-3_B), 3.74 (s, 3H, $COOCH_3$), 3.79 (d, 1H, J = 1.2 Hz, H-1), 6.01 (m, 1H, J = 6 + 1.5 + 1.5 + 1 2 Hz, H-5). ^{13}C NMR (25.16 MHz, $CDCl_3$, RT). δ 11.06 (-CH_3), 26.26 ($\underline{CH_2}$-CH_3), 30.54 (C-4), 38.36 (C-8), 45.10 (C-3), 52.74 (OCH_3), 58.71 (C-1), 70.71 (C-7), 126 22 (C-5), 144.78 (C-6), 169.95 (COO). IR (KBr) 1740 cm^{-1} (ester C=O), 2300-2750 cm^{-1} ($\geq NH_2^+$), Anal. Calcd for $C_{11}H_{17}BrClNO_2$. C, 42.53, H, 5.52; Br, 25.73; Cl, 11 41, N, 4.51. Found: C, 42.60, H, 5.53; Br, 25.66: Cl, 11.35, N, 4.47.

Resolution of (±)-11a. Hydrogen bromide salt of 11a (1163 mg, 3.74 mmol) was dissolved in 125 mL of $CHCl_3$ and 125 mL of water and the p_H was made basic (p_H = 9) with ammonium hydroxide. The organic layer was dried (Na_2SO_4), evaporated in vacuo The residue was dissolved in ethylacetate (13 75 mL), to which a solution of dibenzoyl-D-tartaric acid (1411 mg, 3.75 mmol) in

methanol (6.25 mL) was added. After 1 hour the obtained crystals were filtered, washed some ethylacetate to give 11a salt (1058.5 mg, 1.8 mmol, 96 0 %), mp. 166-168 °C.$[\alpha]_D^{25}$= + 63.4 ° (c = 1.5 CH_3OH).

(±)-2-(1-[2-(Indol-3-yl)-1-oxo-ethyl])-4-ethyl-7-exo-chloro-2--azabicyclo[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester 12a. Indole--3-acetic acid (3.60 g, 20.55 mmol) and triethylamine (3 mL, 2.18 g, 21.52 mmol) were dissolved in dimethylformamide (60 mL). The mixture was cooled to -5 °C and -10 °C and stirred to which 2.6 ml (2.55 g, 21.11 mmol) of trimethylacetyl chloride was dropped at the above temperature. After 20 minutes stirring a thick suspension was obtained, to which the solution of 10a HBr salt (5 00 g, 16.096 mmol) and triethylamine 3 ml (2.18 g, 21.52 mmol) in dimethylformamide (60 mL) was dropped between 0 and -5 °C. After 24 hours stirring at room temperature the reaction mixture was evaporated in vacuo The residue was dissolved in ethylacetate. The precipitated salts of triethylamine. HBr and HCl were filtered, washed with ethylacetate. The filtrate was evaporated in vacuo and crystallised from acetone-hexane to give 12a (3 48 g, 9.00 mmol, 55.9 %). mp. 142-144 °C IR. (KBr) 1650 cm^{-1} (amide C=O) 1745 cm^{-1} (ester C=O). ^{1}H NMR (100 MHz, $CDCl_3$, RT): 0 92 + 0.97 (t each, 3H, J = 7 Hz, CH_2-$\underline{CH_3}$) , 1 4-1 65 (m, 2H, $\underline{CH_2}$-CH_3), 1 71 + 1 88 (d each, 1H, J = 13 5 Hz, H-8β), 2.62 - 2 63 (dd, each, 1H, J = 13 5 + 2.5 Hz, H-8α), 3.03 + 3 05 (dd, each, 1H, J = 10 5 + 2.5 Hz, H-3_A), 3.38 (d, 1H, J = 10.5 Hz, H-3_B), 3.72 + 3 74 (s each, 3H, $COOCH_3$), 3 93 (d, 1H, J = 15 Hz, C3'-CH_A), 4.16 (d, 1H, J = 15 Hz, C3'-CH_B), 5.03 + 5 90 (dd each, 1H, J = 5.5 + 1 Hz, H-1), 6 21 (dd, 1H, J = 8 + 1 Hz, H-5), 5.96 + 6.32 (dd each, 1H, J = 8 + 5 5 Hz, H-6), 7.0 - 7 7 (m, 5H, aromatics), 8.22 (bs, 1H, NH) Most signals in the ^{1}H NMR spectrum exhibit splittings due to amide rotational isomerism. See Table I for ^{13}C NMR data. MS m/e 386 (M^+), 351, 220, 130, 108, 77. Evaporating the mother liquor of 12a an additional amount of 12a as oil (1 81 g, 4 68 mmol, 29.1 %) could be isolated.

(±)-2-(1-[2-(Indol-3-yl)-1-oxo-ethyl)-6-ethyl-7-exo-chloro-2-azabicyclo-[2 2 2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester (±)-13a. Crystalline 6a (9 8 g, 27 0 mmol) was stirred at room temperature in 48 mL of 2-3 N hydrogen bromide in acetic acid for 30 minutes and ther evaporated. Using 5 8 g of indole-3-acetic acid the acylating agent was prepared in dimethylformamide as in case of compound 12a to which the solution of the above prepared HBr salt of 11a and triethylamine (4.6 mL, 3 34 g, 33 mmol) in dimethylformamide (98 mL) was dropped between 0 °C and -5 °C. Then the reaction mixture was allowed to come to room temperature, and stirred for an additional hour The precipitated salts of triethylamine HBr and HCl were filtered and washed with ethylacetate The filtrate was evaporated in vacuo and the residual oil

was partitioned between chloroform and water. The organic layer was dried (Na_2SO_4) and evaporated. Chromatography of the residue on a silica column (eluant:toluene:acetone:triethylamine = 40:20:1) afforded (±)-13a as oil (8.12 g, 20.99 mmol, 77.8 %). IR film ($CHCl_3$) 1630 cm^{-1} (amide C=O), 1740 cm^{-1} (ester C=O). ^1H NMR (100 MHz, $CDCl_3$, RT): δ 0.68 + 0.97 (t each, 3H, J = 7 Hz, CH_2-CH_3), 1.5 - 1.9 (m, 1H, H-8β), 1.5 - 2.2 (m, 2H, CH_2-CH_3), 2.68 + 2.88 (m each, 1H, H-4), 2.70 (m, 1H, H-8α), 3.06 (m, 1H, H-3_A), 3.52 (dd, 1H, J = 9.5 + 1.5 Hz, H-3_B), 3.72 + 3.74 (s each, 3H, $COOCH_3$), 3.90 (d, 1H, J = 15 Hz, C3'-CH_A), 4.15 (d, 1H, J = 15 Hz, C3'-CH_B), 4.87 + 5.72 (d each, 1H, J = 1.0 Hz, H-1), 5.97 (m, 1H, J = 6 + 1.5 + 1.5 + 1 Hz, H-5), 7.0 - 7.7 (m, 5H, aromatics), 8.50 (bs, 1H, NH). Most signals in the ^1H NMR spectrum exhibit splittings due to amide rotational isomerism. See Table I. for ^{13}C NMR data. The same MS spectrum was obtained as in case of 12a

(±)-2-(1-[2-(Indol-3-yl)-1-oxo-ethyl])-4-ethyl-7-exo-chloro-2-azabicyclo-[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester 12a, (±)-2-(1-[2-(Indol--3-yl)-1-oxo-ethyl])-6-ethyl-7-exo-chloro-2-azabicyclo[2.2.2]oct-5-ene-7--endo-carboxylic Acid Methyl Ester 13a and (±)-6-(1-[2-(Indol-3-yl)-1-oxo--ethyl])-1-ethyl-2-chloro-6-azabicyclo[3.2.1]oct-3-ene-5-carboxylic Acid Methyl Ester 14. The oil (10.0 g, 27.485 mmol) containing 5a,b and 6a,b prepared by method (b) was treated with hydrogen bromide in acetic acid resulting in the corresponding hydrogen bromide salts which were dissolved in a mixture of dimethyl-formamide (97 ml) and triethylamine (4.7 mL). This solution was dropped between 0 °C and -5 °C to the acylating agent gained from indole 3-acetic acid (5.9 g) in the former way. The reaction mixture was stirred for 24 hours. After a similar workup as in case of compound 13a the residue was purified by passing through a silica column (eluent.hexane· ethylacetate:triethylamine = 3.3:1) and gave a mixture of 12a and 13a in a ratio of about 2:1 as oil (6.85 g, 17.71 mmol, 64.42 %) and compound 14 (921 mg, 2.38 mmol, 8.66 %). The analytical sample of 14 was crystallized from ethylacetate, mp. 171-174 °C. IR (KBr) 1630 cm^{-1} (amide C=O), 1730 cm^{-1} (ester C=O). 3270 cm^{-1} (indole NH). ^1H NMR (400 MHz, $CDCl_3$, PT): δ 0.92 (t, 3H), 1.52 (m, 1H), 1.80 (m, 1H), 2.05 (d, 1H), 2.19 (d, 1H), 3.42 (d, 1H), 3.66 (d, 1H), 3.72 (d, 1H), 3.75 (s, 3H), 4.12 (d, 1H), 4.91 (m, 1H), 5.63 (dd, 1H), 6.85 (dd, 1H), 7.03 (d, 1H), 7.10-7.56 (m, 4H), 8.38 (bs, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, RT): δ 8.68, 27.25, 31.63, 44.58, 49.76, 52.17, 53.06, 63.17, 64.24, 107.02, 111.28, 118.58, 118.59, 121.26, 123.14, 127.17, 127.85, 133.33, 136.33, 168.80, 170.33. MS m/e 388[1], 387[1], 386 (M^+), 355, 352, 351, 350, 258, 256, 228, 196, 165, 164, 157, 149, 133, 131, 130, 105, 103, 77, 53, 50, 38, 36

1· isotopic peak

(-)-2-(1-[2-(Indol-3-yl)-1-oxo-ethyl])-6-ethyl-7-exo-chloro-2-azabicyclo-[2.2.2]oct-5-ene-7-endo-carboxylic Acid Methyl Ester (-)-13a. Starting from 1.055 g (6.022 mmol) of indole-3-acetic acid the acylating agent was prepared in the former way to which a solution of dibenzoyl-D-tartarate of 11a (2.283 g, 3.88 mmol) and triethylamine (1 77 mL, 1.285 g, 12.70 mmol) in dimethylformamide (14 mL) was dropped between 0 and -5 °C. The solution was stirred for 24 hours. After the usual workup the residue was purified by chromatography on a silicagel column (eluant:toluene:acetone = 2:1) to give (-)-13a as an oil (1493 mg, 3.859 mmol, 99.4 %). $[\alpha]_D^{25}$ = -91.4 ° (c = 1.5 $CHCl_3$) The same IR, NMR spectra were obtained as in case of the racemic compound.

(±)-6-(1-[2-(Indol-3-yl)-1-oxo-ethyl])-1-ethyl-2-chloro-6-azabicyclo-[3.2.1]oct-3-ene-5-carboxylic Acid Methyl Ester 14. Starting from 5b (2.00 g, 5.497 mmol) gained by method (b) compound 14 was prepared in the same manner as that described for 13a. Chromatography of the residue (silica column eluant:hexane:ethylacetate: triethylamine = 3:3:1) afforded 14 (406 mg, 1.05 mmol, 19.1 %) and other unidentified products. The analytical sample of 14 was crystallized from ethylacetate-hexane, mp. 160-164 °C. The IR and NMR spectra were indistinguishable from those of the product obtained in the other way.

(±)-6-(1-[2-(Indol-3-yl)-1-oxo-ethyl])-2-chloro-3-ethyl-6-azabicyclo-[3 2 1]oct-3-ene-5-carboxylic Acid Methyl Ester 15a and (±)-6-(1-[2-(Indol--3-yl)-1-oxo-ethyl])-2-bromo-3-ethyl-6-azabicyclo[3.2.1]oct-3-ene-5--carboxylic Acid Methyl Ester 15b Compound 6b (3.921 g, 10.777 mmol) was treated with hydrogen bromide in acetic acid and then acylated by use of the same procedure as for 13a. Chromatography of the residue (silica column, eluant:hexane:ethylacetate:triethylamine = 3 3:1) afforded 1878 mg (4.854 mmol, 45.0 %) of a mixture of 15a and 15b The analytical sample was crystallized from diethylether, mp. 151-156 °C IR (KBr) 1660 cm^{-1} (amide C=O), 1745 cm^{-1} (ester C=O). 15a ^1H NMR (400 MHz, $CDCl_3$,RT) δ 0.92 (t, J = 7.5 Hz, 3H), 2.02 (m, 1H), 2 14 (m, 2H), 2 31 (dd, J = 11 + 1 Hz, 1H), 2.92 (m, J = 5 + 5 + 1.5 Hz, 1H), 3.22 (dd, J = 10 + 1 Hz, 1H), 3.65 (bs, 2H), 3.81 (s, 3H), 3.86 (dd, J = 10 + 5 Hz, 1H), 4.22 (d, J = 1.5 Hz, 1H), 6.61 (bs, 1H), 7.04 (bs, 1H), 7 1 - 7.53 (m, 4H), 8.20 (bs, 1H) ^{13}C NMR (100 6 MHz, $CDCl_3$, RT): δ 11 46, 26 04, 31.96, 35.06, 42.53, 50.39, 52.67, 61 20, 63 06, 108 03, 111.26, 118 53, 119.59, 122.28, 122.54, 126.71, 127.04, 136.16, 138 89, 168.97, 170.94. 15b ^1H NMR (400 MHz, $CDCl_3$, RT): δ 0.89 (t, 3H), 1.98 (m, 1H) 2.15 (m, 2H), 2.39 (dd, 1H), 3.03 (m, 1H), 3.22 (dd, 1H), 3.65 (s, 2H), 3.80 (s, 3H), 3.84 (dd, 1H), 4 44 (d, 1H), 6.61 (bs, 1H), 7.03 (bs, 1H), 7.1-7.54 (m, 4H), 8.2 (bs, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, RT).

δ 11.51, 26.94, 31.96, 35 33, 43.04, 51.02, 52.67, 54.44, 63.20, 107.48, 111 42, 118.40, 119.38, 122.06, 122.83, 126.52, 127.05, 136.23, 139.63, 169.06, 170.94. MS m/e 430 (M^+ 15b), 410, 399, 386 (M^+ 15a), 368, 355, 352, 351, 350, 319, 309, 292, 291, 256, 224, 194, 188, 165, 164, 157, 149, 133, 130, 129, 77. Anal. Calcd. for $C_{21}H_{24}ClN_2O_3$: C, 65.02; H, 6.24, Cl, 9.14; N, 7 22. Calcd. for $C_{21}H_{24}BrN_2O_3$: C, 58 34, H, 6 00; Br, 18.48; N, 6.48. Found: C: 63.46, H, 6.30, Br, 5.18; Cl, 7.41, N, 6.80.

(±)-5-Oxo-catharanthine 18 and (±)-5-oxo-allocatharanthine 17. A mixture of 12a and 13a in a ratio of about 2:1 gained earlier (2.00 g, 5.17 mmol), 139 mg (3.67 mmol) of $NaBH_4$ and 0 17 mL (204 mg, 0.63 mmol) of tributyltin chloride were dissolved in methanol (2.5 L). The solution was purged with N_2 and irradiated with a low pressure mercury lamp (Tungsram 250 W) for 2-3 hours or until TLC showed no remaining starting material. The methanol was evaporated. The residue was partitioned between chloroform and water. The chloroform layer was dried (Na_2SO_4) and evaporated. Chromatography of the residue (silica column, eluant:cnloroform:ethylacetate:triethylamine = = 30:8:1) afforded the following products listed in increasing polarity (a) not ring closured product (M = 382) containing a methoxy group instead of chlorine atom (b) 17 (342 mg, 0.976 mmol, 18.9 %). The analytical sample was crystallised from acetone-hexane, mp. 273-276 °C. IR (KBr) 1620 cm^{-1} (lactam C=O), 1720 cm^{-1} (ester C=O), 3300 cm^{-1} (indole NH), ^1H NMR (100 MHz, $CDCl_3$, 45 °C): δ 0.98 (t, 3H, J = 7 Hz, CH_2-$\underline{CH}_3$), 1 61 (q, 2H, J = 7 Hz, $\underline{CH}_2$-CH_3), 1.70 (d, 1H, J = 13.5 Hz, H-17β), 2.51 (dd, 1H, J = 13.5 + 2 Hz, H-17α), 2.88 (dd, 1H, J = 10.5 + 2 Hz, H-3_A), 3 40 (d, 1H, J = 10.5 Hz, H-3_B), 3.66 (s, 3H, $COOCH_3$), 3.76 (d, 1H, J = 15 5 Hz, H-6_A), 4.18 (d, 1H, J = 15.5 Hz, H-6_B), 5.30 (dd, 1H, J = 4 + 2 Hz, H-21), 6.35-6 55 (m, 2H, H-15 and H-20), 7.05-7.60 (m, 4H, aromatics), 8.06 (bs, 1H, NH). See Table II. for ^{13}C NMR data. MS m/e 350 (M^+), 291, 243, 215, 214, 201, 154, 149, 130, 121, 109, 108. (c) 18 (169 mg, 0 482 mmol, 9.3 %) The analytical sample was crystallized from acetone-hexane, mp. 277-285 °C; IR (KBr) 1620 cm^{-1} (lactam C=O), 1720 cm^{-1} (ester C=O), 3300 cm^{-1} (indole NH) ^1H NMR (100 MHz, $CDCl_3$ + DMSO, 45 °C) δ 1.10 (t, 3H, J = 7 Hz, CH_2-$\underline{CH}_3$), 1 76 (dd, J = 13.5 + 1 Hz, H-17β), 2 29 (m, 2H, J = 7 + 1.5 Hz, $\underline{CH}_2$-CH_3), 2.74 (m, 1H, J = 13 5 + 3 0 + 2.5 Hz, H-17α), 2.90 (m, 1H, H-14), 3.05 (m, 1H, H-3_A), 3.53 (dd, 1H, J = 10 + 2.5 Hz, H-3_B), 3.64 (s, 3H, $COOCH_3$), 3.76 (d, 1H, J = 15 5 Hz, H-6_A), 4.19 (d, 1H, J = 15.5 Hz, H-6_B), 5 13 (d, 1H, J = 1.5 Hz, H-21), 6 28 (m, 1H, J = 6 + 1.5 + 1 5 + 1 5 Hz, H-15), 7 1 - 7 6 (m, 4H, aromatics), 8.46 (bs, 1H, NH) See Table II. for ^{13}C NMR data The same MS spectrum was obtained as in case of 17 (d) not ring closured product with MS spectrum similar to that of compound (a) (M = 382) (e) reduction product, (M = 352) where the chlorine atom was substituted with a hydrogen.

(±)-5-Oxo-catharanthine 18 Compound 13a was irradiated in the former manner resulting in 18 (Yield: 29.3 %).

(±)-5-Oxo-allocatharanthine 17. Irradiating compound 12a in the usual way 17 was obtained (Yield: 28.5 %).

(16R)-5-Oxo-catharanthine, 16R-18, (+)-3-{1-[2-(Indol-3-yl)-1-oxo--ethyl]}-2-methoxy-3-azabicyclo[3.2.1]oct-6-ene-7-ethyl-1-carboxylic Acid Methyl Ester, (+)-19 and (+)-10,13-Methano-4H-pyrido-[2,1b]pirrolo[4.3.2-f,g][3]benzazocine-13 (9H)-carboxylic acid, 12-ethyl, 6,7,10,12a-tetrahydro-7--oxo Methyl Ester, (+)-20 by photolysis of (-)-13a. 1048 mg (2.71 mmol) of (-)-13a was dissolved in 1.5 L of dry methanol to which 70 mg (1.85 mmol) of $NaBH_4$ and 0.08 mL (96 mg, 0.295 mmol) of tributyltin chloride were added. After the usual photochemical reaction and workup chromatography of the residue (silica column, eluant:chloroform:ethylacetate:triethylamine 30:8:1) afforded three main products listed in order of increasing polarity (16R)-18 (281 mg, 0.80 mmol, 29.5 %). The analytical sample was crystallized from acetone-hexane, mp. 285-294 °C. $[\alpha]_D^{25}$: -21.6 ° (c = 1.5 $CHCl_3$). The same IR, NMR spectra were obtained as in case of the corresponding racemic compound (+)-19 (180 mg, 0 471 mmol, 17.4 %). The analytical sample was crystallized from acetone-hexane, mp. 171-177 °C. $[\alpha]_D^{25}$: + 127.83° (c = 1 5 $CHCl_3$) IR(KBr): 1620 cm^{-1} (amide C=O), 1720 cm^{-1} (ester C=O), 3270 cm^{-1} (indole NH). See Table III for ^1H and ^{13}C NMR data of 19. MS m/e 382 (M^+), 367, 351, 350, 323, 319, 265, 252, 225, 220, 199, 198, 194, 193, 157, 137, 130, 103, 91, 77, 73. Chromatography was carried on with eluant. $CHCl_3$·acetone = 1.1 resulting in an additional product (+)-20 (299 mg, 0.85 mmol, 31.5 %). The analytical sample was crystallized from acetone-hexane, mp. 272-289°C. IR (KBr) 1640 cm^{-1} (lactam C=O), 1740 cm^{-1} (ester C=O) 3300 cm^{-1} (indole NH). ^1H NMR (400 MHz, $CDCl_3$ RT): δ 1 09 (t, 3H, J = 7 Hz, CH_2-CH_3), 1.80 (dd, 1H, J = 13 + 1.5 Hz, $H\text{-}14_A$), 2.17 (m, 2H, CH_2-CH_3), 2 88 (m, 1H, H-10), 3.02 (m, 1H, J = 10.5 + + 2.5 + 2 Hz, $H\text{-}9_A$), 3 27 (m, 1H, J = 13 + 4 + 2.5 Hz, $H\text{-}14_B$), 3.36 (dd, 1H, J = 10 5 + 2 5 Hz, $H\text{-}9_B$), 3.51 (s, 3H, $COOCH_3$), 3 56 (dd, 1H, J = 14 + 2 Hz, $H\text{-}6_A$), 4.30 (dd, 1H, J = 14 + 1.5 Hz, $H\text{-}6_B$), 5 53 (d, 1H, J = 1 Hz, H-12a), 6.20 (m, 1H, J = 6 5 + 1 + 1 + 1 Hz, H-11), 6.95 (d, 1H, J = 7.2 Hz, H-3), 6.98 (m, 1H, J = 11 + 2 + 1.5 Hz, H-5), 7 07 (dd, 1H, J = 7.2 + 7.5 Hz, H-2), 7 29 (d, 1H, J = 7.5 Hz, H-1), 9.03 (d, J = 11 Hz, NH). ^{13}C NMR (25 16 MHz, $CDCl_3$, RT): δ 11 55 (CH_2-CH_3), 26.54 (CH_2-CH_3), 30 21 (C10), 36.07 (C6), 36.85 (C14), 48.96 (C9), 52.30 (OMe), 56.72 (C12a), 59 23 (C13), 108 59 (C5a), 111.13 (C3), 120.94 (C1), 121.60 (C2), 121.98 (C13b), 126.25 (C5), 127.86 (C11), 135.73 (C3a), 139.24 (C13a), 144.19 (C12), 171.84 (C7), 173 81 (COO) MS m/e 350 (M^+), 291, 243, 234, 215, 214, 211, 204, 201, 184, 155, 154, 149, 127, 121, 109, 108. $[\alpha]_D^{25}$ + 84 95 ° (c = 2 $CHCl_3$).

(±)-Catharanthine 1. 87 mg (0.248 mmol) of (±)-5-oxo-catharanthine 18 was dissolved in 15 mL of dry THF to which 425 mg (11.23 mmol) of $NaBH_4$ and then dropwise 2.0 mL (2.308 g, 16.26 mmol) of boron trifluoride etherate were added. After stirring for two hours at room temperature the reaction mixture was evaporated in vacuo and the residue was dissolved in $CHCl_3$ to which water was added slowly. The organic layer was dried (Na_2SO_4) and evaporated in vacuo giving (±)-catharanthine (82 mg, 0.243 mmol, 98.3 %). The analytical sample was purified by TLC on a silica plate (eluant:toluene: acetone = 2 1). IR (film, $CHCl_3$) 1720 cm^{-1} (ester C=O). ^1H NMR (100 MHz, $CDCl_3$, 45 °C) δ 1.06 (t, 3H, J = 7 Hz, CH_2-$\underline{CH_3}$), 1 80 (dd, 1H, J = 13 + + 2.5 Hz, H-17β), 2.30 (m, 2H, J = 7 + 1.5 Hz, $\underline{CH_2}$-CH_3), 2.86 (m, 1H, H-14), 2 7 - 3 7 (m, 7H, H-17α, C3-H_2, C5-H_2 and C6-H_2), 3 72 (s, 3H, $COOCH_3$), 4 25 (d, 1H, J = 1.5 Hz, H-21), 5.96 (m, 1H, J = 6 + 1 5 + 1.5 + 1.5 Hz, H-15), 7.05 - 7.55 (m, 4H, aromatics), 7.68 (bs, 1H, NH) MS m/e 337[1], 336, (M^+), 335, 321, 305, 251, 248, 230, 229, 228, 219, 214, 204, 197, 170, 168, 167, 154, 138, 135, 122, 121, 107, 93, 92.

(+)-Catharanthine (+)-1 Starting with (-)-5-oxo-catharanthine the same method as in case of racemic 1 resulted in (+)-catharanthine (yield: 96.2 %) which was identical with the natural product in every respect

(±)-Allocatharanthine 2 Method A (±)-5-Oxo-allocatharanthine 17 (50 mg, 0 143 mmol), 50 mL of dry benzene and 200 mg of phosphorus pentasulfide were refluxed together for 3 h at which point TLC indicated that all the starting material had been consumed The mixture was filtered and washed with excess chloroform. The filtrate was washed with aqueous sodium hydrogen carbonate and water dried over sodium sulfate, and evaporated to dryness to give (+)-5-thioxo-allocatharanthine 21 (51 mg, 0.139 mmol, 97.2 %). MS m/e 366 (M^+), 351, 337, 333, 307, 259, 226, 201, 200, 194, 165, 154, 108 The above obtained thioamide 21 was dissolved in dry methyl iodide (2 mL) and stirred under argon for 1 day at room temperature The solvent was removed and the residue was dissolved in methanol (5 mL) and 300 mg of sodium cyanoborohydride added After 5 min, 5 mL of 1 1 water-acetic acid was added, and the solution was stirred for 3 h. To which 100 mL of water was added and the pH was brought to 1 with 10 % hydrochloric acid The aqueous solution was extracted with ether The aqueous layer was made basic (pH = 9) by addition of ammonium hydroxide and extracted with chloroform The organic fraction was dried over sodium sulfate and evaporated to give 2 as an oil (45 5 mg, 0 1354 mmol, 94.7 %) IR 1720 cm^{-1} (ester C=O), ^1H NMR (100 MHz, $CDCl_3$, 45 °C): δ 0 95 (t, 3H, J = 7 Hz, CH_2-$\underline{CH_3}$), 1 52 (q, 2H, J = 7 Hz, $\underline{CH_2}$-CH_3), 1.66 (d, 1H, J = 13 Hz, H-17β), 2.61 (dd, 1H, J = 13 + 2.5 Hz, H-17α), 2 64 (d, 1H, J = 10 Hz, H-3_A), 2.87 (dd, 1H, J = 10 + 2 5 Hz, H-3_B), 3 0 - 3 7 (m, 4H,

4H, C5-H_2 and C6-H_2), 3.74 (s, 3H, $COOCH_3$), 4.55 (dd, 1H, J = 6 + 1 Hz H-21), 6.20 (dd, 1H, J = 8 + 1 Hz, H-15), 6.57 (dd, 1H, J = 8 + 6 Hz, H-20), 7.05 - 7.60 (m, 4H, aromatics), 7.90 (bs, 1H, NH). MS m/e 336 (M^+), 305, 251, 243, 229, 228, 214, 170, 168, 167, 154, 138, 135, 134, 122, 121, 107, 91. Method B: starting with (±)-17 applying the same procedure as in case of 1, (±)-2 was obtained (yield: 96.8 %).

(±)-15,20-Dihydroallocatharanthine 23. (±)-5-Thioxo-catharanthine (31 mg, 0.0846 mmol) was refluxed in dry ethanol with Raney nickel (300 mg) for 4 hours. The reaction mixture was filtered washed with ethanol. The solution was evaporated to dryness to give 25 mg of a product having TLC behavior identical with that of authentic dihydroallocatharanthine. IR: ($CHCl_3$, film) 1720 cm^{-1}, MS m/e 338 (M^+), 323, 309, 214, 208, 154, 124, 110.

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

	6a[b]	6b[c]	5a[b]	5b[b]	13a[b]	12a[b]
C1	56.83+57.31	56.53	53.41+53.80	52.71+53.34	54.42+59.40	51.12+55.72
C3	47.07+47.48	46.25	50.96+51.29	49.63+49.92	47.35+47.87	50.97+51.97
C4	30 69+30 94	30.84	39.63+39 92	39.65+39.96	30 32+31.15	39.38+40.26
C5	126 86+127.21	124 88	139.69+139.99	138.18+138.41	127.02+127.76	139.80+140.47
C6	144.92+145.44	145.34	129.25+129.64	128.91+129.27	143.93+145.41	128.52+129.63
C7	68.29	66.73	68.01+68.09	66.60+67.27	67.94+68.79	67.70+68.43
C8	38.35	38.40	42.55	42.65+42.75	38.05+38.33	42.43+42.60
COO	169.57	170.63	169.82	170.32+170.73	169.28+169.58	169.78
OCH_3	52 99+53.03	53.09	53 24	53.16+53.26	53 06+53.13	53.24+53.34
N-CO	155.1	154.91	155.78	154.53+154.78	171.19+171.53	171.27+171.33
$O-CH_2$	67.00	67.18	67.09	67.00	-	-
$CH_2-\underline{CH}_3$	11.28	11.40	8.37	8.47+8.50	10.58+11.43	8.28
$\underline{CH}_2-CH_3$	26.21	28.14	27.72+27.77	27.80+27.83	25.02+26.28	27.59+27.70
C1'	136.88	137.00	136.74	136.36+136.59	-	-
C2'+C6'	127.86	128.05	127.70	128.18	-	-
C3'-C5'	128.40	128.53	128.40	128.50	-	-
C4'	127.76	127.94	127.85	127.69	-	-
$3'-CH_2$	-	-	-	-	31.33+31.74	31.32+31.69
C2''	-	-	-	-	123.16+123.25	123.12+123.30
C3''	-	-	-	-	107.85+108.60	107.68+108.35
C3a''	-	-	-	-	127.12+127.29	127.14+127.33
C4''	-	-	-	-	118.40+118.60	118.39+118.57
C5''	-	-	-	-	119.15+119.26	119 16
C6''	-	-	-	-	121.73+121.83	121.71
C7''	-	-	-	-	111.47	111.50
C7a''	-	-	-	-	136 31	136.34

[a] In δ ppm from internal TMS. [b] In $CDCl_3$ at rt. Most of the signals exhibit splittings due to amide rotational isomerism. [c] In $CDCl_3$ at 65 °C.

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

	17	18
C2	134.25*	134.89*
C3	54 17	50.95
C5	174.38	174.67
C6	32.61	32.73
C7	103.76	103.77
C8	127.49	127.53
C9	118.42	118.50
C10	119.91	119.89
C11	122.42	122.41
C12	110.96	110.96
C13	135.35*	135.41*
C14	38.48	31.49
C15	141.10	128.83
C16	53.80	53.29
C17	40.39	33.69
C20	128.89	143.89
C21	51 90	55.95
COO	173.42	173.02
$-\underline{CH}_2-CH_3$	28.10	26.92
$-CH_3$	8.42	11.39
OMe	52.92	52.68

[a] In $CDCl_3$ at room temperature. Chemical shifts are relative to internal TMS. Signals marked with identical symbols are interchangeable.

Table III. ^{1}H and ^{13}C NMR Data of 19[a]

Atom no.	^{1}H	^{13}C
1	-	60.17 + 60.63
2	5.12 + 5.57 (s)	80.32 + 85.11
4	β 3.27 + 2.85 (dd, 12.5 + 1.5)	43.47 + 43.96
	α 4.16 + 3.42 (m, 12.5 + 3 + 1.5)	
5	2.58 + 2.70 (m, 4 + 3 + 2 + 1.5)	38.32 + 38.94*
6	5.14 + 5.36 (m, 2 + 1.5 + 1.5)	125.64 + 126.65
7	-	149.87 + 148.63
8	β 2.21 + 2.29 (d, 10)	38.23 + 38.51*
	α 2.24 + 2.01 (m, 10 + 4 + 1.5)	
2'	7.03 + 7.12 (d, 2)	122.77 + 123.01°
3'	-	108.44 + 108.83
3a'	-	127.06
4'	7.55 + 7.65 (dd, 7.5 + 1)	118.65 + 118.85
5'	7.1 - 7.2 (m)	119.54
6'	7.1 - 7.2 (m)	122.13°
7'	7.36 + 7.34 (dd, 7.8 + 0.8)	111.33
7a'	-	136.33 + 136.37
C3'-CH_2	3.90 + 4.05 (d, 15.5)	32.16 + 31.65
NCO	-	172.48 + 173.0
NH	8.15 (bs)	-
C2-OCH_3	3.39 + 3.49 (s)	57.49 + 56.10
COO	-	173.68
OCH_3	3.74 + 3.75 (s)	51.90
$\underline{CH_2}$-CH_3	2.0 + 1.89 (m, 7 + 1.5)	21.77 + 21.10
CH_2-$\underline{CH_3}$	0.82 + 0.93 (t, 7)	11.43 + 10.84

[a] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solution at room temperature. Chemical shifts are reported in δ ppm from internal TMS, J values are given in hertz in parentheses. Signals marked with identical symbols may be interchanged. Most signals exhibit splittings due to amide rotational isomerism.

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