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SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS LV[1] SYNTHESIS OF (±)-DESMETHOXY CUANZINE[2]

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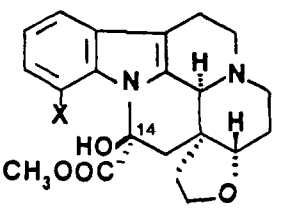
Abstract *Through the key intermediate enamine* (**28**) (±)*-desmethoxy cuanzine* (**2**) *was synthesised.*

The indole alkaloid cuanzine (**1**) isolated[3] from the root bark of *Voacanga chalotiana* and collected in Angola, has antiarrhythmic, vasodilatory, and antihypertensive activity on the cardiovascular system[4].



1 x = OCH_3
2 x = H

Its formula was thought to be determined by chemical transformations and instrumental investigations[5] but very recently the configuration at C-14 was revised[6] to give the corrected structure **1**. Owing to its significant pharmacological effects combined with a substantial structural challenge, cuanzine has emerged as a highly attractive target for synthetic investigations.

Palmisano et al.[7] have just recently reported their studies on the attempted synthesis of cuanzine (**1**).

In order to determine the importance of the methoxy group concerning the biological effects, as well as to gain experience with a model compound,

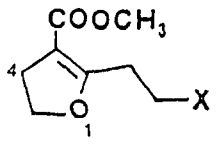
firstly we aimed at the synthesis of desmethoxy cuanzine (2)[8].

PREPARATION OF THE KEY INTERMEDIATE

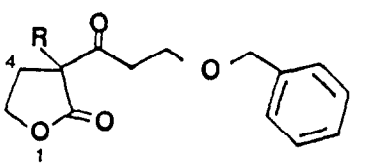
Starting from the commercially easily available 2-acetylbutyrolactone, at the outset a pathway leading through a suitably substituted furan derivative (3) was investigated.

To begin with, the side chain of 2-acetylbutyrolactone was elongated[9] *via* bis-anion and the obtained compound (4) was converted[10] into the dihydrofurane derivative 3 in methanol containing catalytic amount of hydrochloric acid. Using larger excess of hydrochloric acid or longer reaction time also the benzyloxy group was substituted by methoxy group (5) as well.

The benzyloxy group can easily be replaced by chlorine (6) with hydrogen chloride in dioxane, but despite all our efforts we failed to saturate the double bond with hydrogen. The only product we were able to isolate was the hydroxy derivative (7), and therefore our first approach was abandoned.



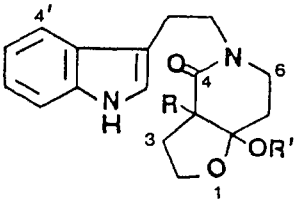
	X
3	OBn
5	CH_3O
6	Cl
7	OH

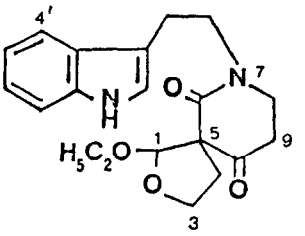


	R
4	H
8	$CH(OEt)_2$
9	$(CH_2)_2COOEt$

Following the alternative pathway, first an aldehyde function or a side chain ($-CH_2CH_2COOC_2H_5$) was attached to the α-carbon of 4. The obtained compounds (8 and 9, respectively) were reacted with tryptamine at elevated temperature. In both cases furo[3,2-*c*]-pyridin-4(2*H*)-one derivatives (10 and 11, respectively) were formed, presumably through a vinyl ketone derivative generated by loss of benzyl alcohol.

When starting from 8 in addition to 10 the spiroketone 12 was obtained as a by product from the ketolactam intermediate by intramolecular transacetalisation.

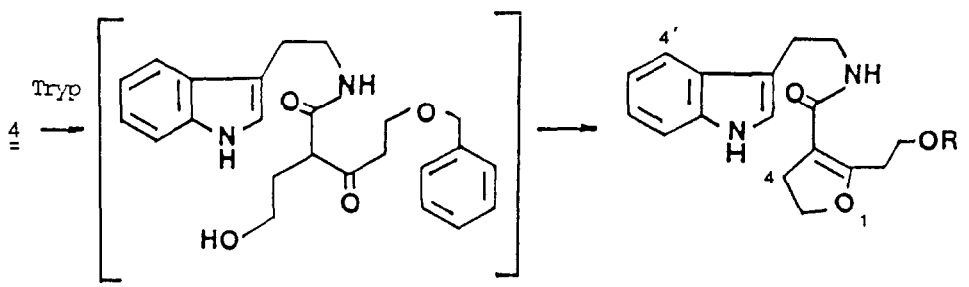




12

	R	R′
10	$CH(OEt)_2$	H
11	$(CH_2)_2COOEt$	H
16	$CH(OMe)_2$	Me
17	H	Me
18	H	Et
19	$(CH_2)_2COOMe$	Me

In contrast to the foregoings the reaction of α-(2-benzyloxy-propionyl)-butyrolactone (4) with tryptamine under the same conditions proceeded in an entirely different way producing amide 14, presumably through intermediate 13.



13

14 R = Ph

15 R = H

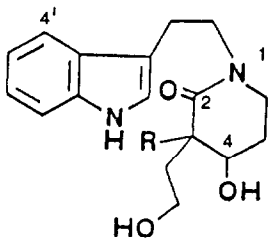
Unfortunately the attempted saturation of the dihydrofuran ring of 14 failed, alcohol 15 was the only product formed. Cyclization of the latter to a dihydro-β-carboline did not occur.

The furopyridones are reactive but stable compounds. The attempted opening of the lactame ring of 10 and a subsequent Pictet-Spengler cyclization in acidic media was unsuccessful. Under milder conditions in alcoholic solution only the hydroxyl group was etherified, accompanied by transacetalisation (16) while using methanol. Under forced conditions the diethoxymethyl group was cleaved (17).

A similar hydrolysis and cyclization of spiroketone 12 also failed to provide a useful intermediate and compound 18 was the only isolable

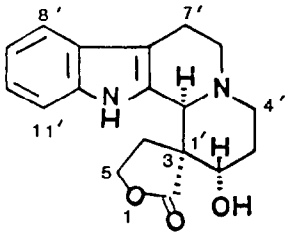
product. Starting from 11, an etherification with contingent transesterification took place (19) as well.

On reduction of furopyridones 10 and 11 with sodium borohydride the hemiketal ring opened up and the reaction resulted in 1,4-diols 20 and 21, respectively. In the case of 11 the ester group was also reduced to some extent.

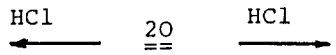


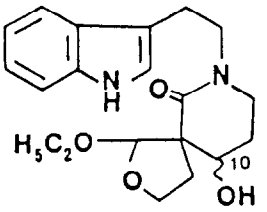
	R
20	$CH(OEt)_2$
21	$(CH_2)_3$-OH

Boiling compound 20 with hydrogen chloride in ethanol gave the indolo[2,3-*a*]quinolizine 22 through opening of the lactam ring and subsequent Pictet-Spengler cyclization.



22





	OH
23	β
24	α

Unfortunately, in compound 22 the configuration of the spiro ring is opposite to that necessary to synthesize cuanzine.

Under milder conditions, at room temperature the lactam ring did not open up and the isomers 23 and 24 (OH β and α, respectively) were formed The same isomers with great predominance of 23 over 24 were formed by the reduction of spiroketone 12.

TRANSFORMATION OF FUROPYRIDONE 10 INTO DESMETHOXY CUANZINE (2)

Taking into account all these experiments, the furopyridone 10 appeared to be the most promising intermediate compound. Treatment of 10 by trifluoroacetic acid in methylene chloride at room temperature for 16 h, furnished the furopyridone derivative 25 in nearly quantitative yield.

As to the mechanism of this reaction, it is presumed that in acidic medium the hemiketal ring opens up and the diethoxymethyl group hydrolyzes yielding a formyl group. The resulting unstable lactam loses a formyl group and thereafter the reaction sequence is concluded by the formation of the dihydrofuran ring as a result of water elimination.

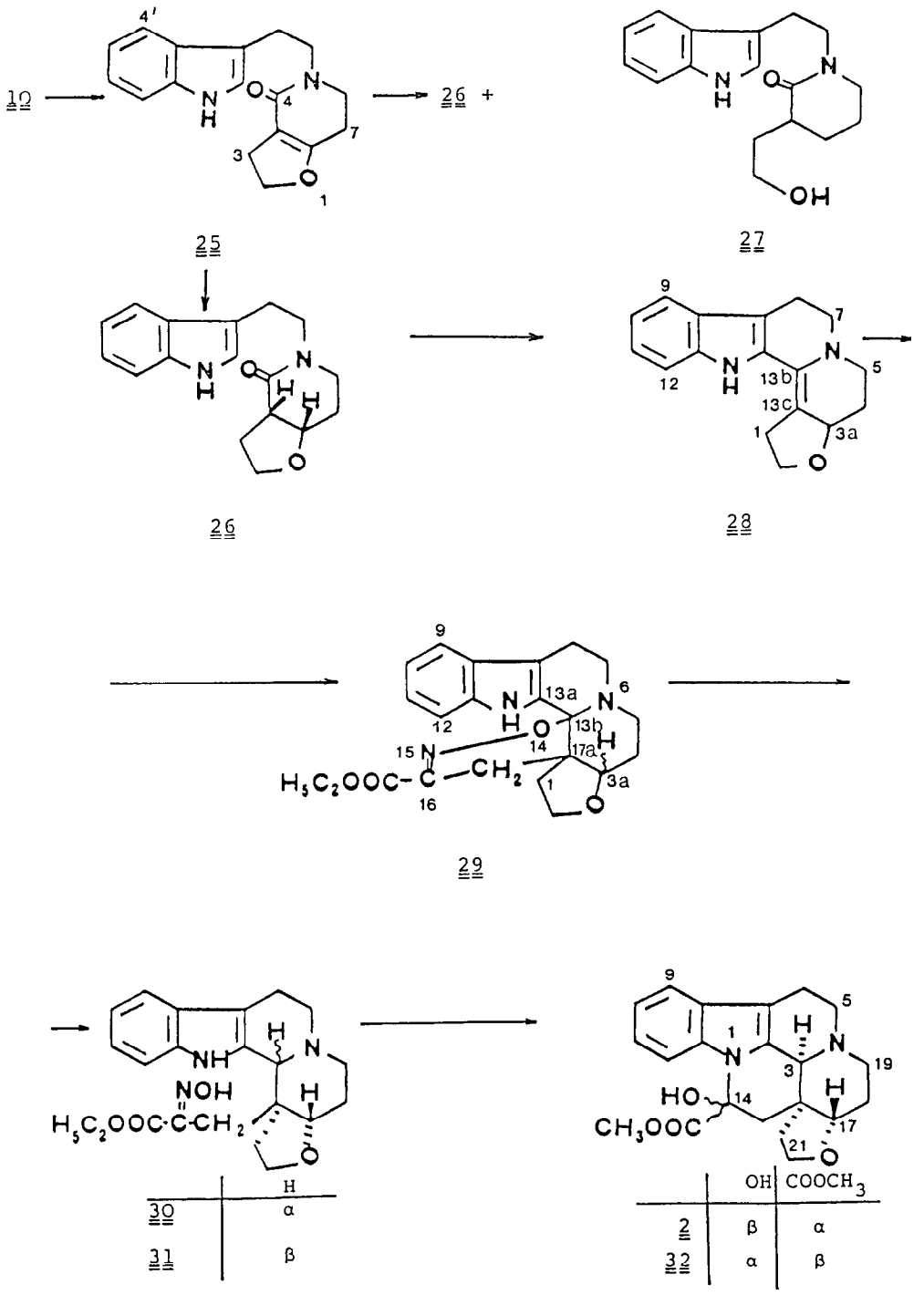
Contrary to its open analogues (14 and 15) the double bond of the dihydrofuran ring of 25 could be easily saturated by catalytic reduction over Pd/C owing to its annelation position. It is worth noting that on chemical reduction of 25 by $NaBH_4$ + $NiCl_2/CH_3OH$ system, in addition to 26 the open chain compound 27 was also formed.

Bischler-Napieralski ring closure of compound 26 by phosphorus oxychloride in chloroform and subsequent basification resulted in the enamine 28 which proved to be the key-intermediate of the synthesis. The absence of the indole α-proton signal in the proton NMR spectrum and that of the amide carbonyl signal in the carbon NMR spectrum of the product was indicative of an intramolecular ring closure.

The enamine 28 was reacted with the oxime of bromopyruvic acid ethyl ester[1], giving the oxazine 29.

Without any purification, on catalytic reduction the latter compound yielded both the *cis* (30, 40 %) and the *trans* (31) epimers. Unequivocal evidence for the relative configuration at C13b in 31 was readily available from selective ^1H-{^1H}NOE difference experiments. Preirradiation of the H-3a signal resulted in NOEs on H-13b, $H\text{-}5_{ax}$ and one of the protons of the C13c-CH_2 methylene group, while preirradiation of H-13b gave rise to enhanced signal intensities on H-3a, $H\text{-}5_{ax}$, $H\text{-}7_{ax}$ and one of the C13c-CH_2 methylene protons. The configuration of the other isomer 30 followed from the comparison of the carbon chemical shift values of C1, C3a and the C13c-CH_2 methylene carbons for both compounds.

Transesterification of the *cis* isomer (30) by boiling it in methanol/ sodium methoxide and subsequent treatment with sodium metabisulfite and sulfuric acid in aqueous acetic acid gave the epimers 2 (35 %) and 32 (14 %). The assignment of the configuration at C14 was accomplished by comparison of the proton and carbon spectra of these epimers with those of Vincamine[11].


10
25
26 +
27
26
28
29
30
31
2
32
H
α
β
OH
COOCH3

Consequently the synthesis of desmethoxy cuanzine was accomplished. Our experiments applying the above strategy for the cuanzine itself are currently in progress

EXPERIMENTAL PART

Mass spectra were recorded on an AEI MS-902 mass spectrometer (70 eV, ion source temp. 200°C, direct inlet). Infrared spectra were recorded on a Nicolet 7199 Fourier transform spectrometer and the frequencies (cm^{-1}) of significant peaks are reported. The NMR spectra were run, where it is not indicated, on deuteriochloroform solutions at ambient temperature using a Varian Associates model XL-100 for lowfield and model XL-400 instrument for high field conventional and 2D experiments. Chemical shifts are in ppm relative to internal TMS Selective ^{1}H-{^{1}H}NOE measurements were performed in the difference mode. Mutual ^{1}H-^{1}H couplings are given only once, at their first occurrence in the Experimental Part. At NMR assignation the numbering of the carbon atoms of the main ring corresponds to its numbering at naming, at compounds having isolated rings the figures with one apostrophe refer the indole ring, while with two apostrophes to a contingent third ring. The chemical shift values signed with identical symbols are interchangeable. The thin layer chromatography was carried out on silica gel layer (Macherey-Nagel, Polygram SIL G/UV_{254}) and the column chromatography also on silica gel (Merck, Geduran SI 60, 0.063 - 0.200 mm). Mps are uncorrected.

(±)-3-(3-Benzyloxy-propionyl)-4,5-dihydro-3*H*-furan-2-one (4)

Sodium hydride, as a 77 % paraffin oil dispersion (5.3 g, 0 17 mole), was washed with pentane and added to a four-necked 500 ml round-bottomed flask fitted with a gas inlet tube, addition funnel, magnetic stirring bar and thermomether. Dry THF (120 ml) was added, the slurry was stirred under argon at -10°C and a solution of 2-acetylbutyrolactone (19.2 g, 0.15 mole) in dry THF (100 ml) was added dropwise After addition was complete, the mixture was stirred for 20 min, 100 ml (0.16 mole) of a 1.6 M solution of n-butyllithium in hexane was added dropwise, and the dianion solution was stirred for 15 min at -10°C. A solution of benzyl chloromethyl ether (23.5 g, 0.15 mole) in dry THF (20 ml) was then added, and the mixture was stirred at 0°C for 2 h and then poured into 300 ml of saturated NaCl solution The mixture was acidified with 10 % HCl and the organic layer

separated. The aqueous solution was extracted twice with 75 ml portions of ether, and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 36 4 g of a brown oil. The material was purified by colurn chromatography on SiO_2 (1 kg, cyclohexane-ethyl acetate 6.4 v/v, R_f 0 42) to give (4) (15.7 g 42 %) as a colourless oil, bp· 156°C (0.06 mmHg) with partial decomp, n_D^{20}: 1 5235, MS (m/z, %). 248 (M^+, 0.13), 230 (23), 142 (13), 113 (18), 107 (26), 92 (12), 91 (100), 86 (26); IR (KBr, ν, cm^{-1}). 3090, 3065 and 3035 (phenyl CH), 2918 and 2870 (CH_2), 1768 (5-membered lactone C=O), 1720 (ketone C=O), 1105 (C-O-C), 741 and 700 (phenyl); ^{1}H-NMR (δ, ppm): 2.27 (1H, dddd, J_{gem} = -13.2 Hz, J_{vic} = 9.5, 7.5, 6.5 Hz, C4-H_A), 2.76 (1H, dddd, J_{vic} = 7.8, 6.8, 6.8 Hz, C4-H_B), 3.06 (2H, t, J = 6.0 Hz, CO-C$\underline{H}_2$-CH_2-O), 3.72 (1H, dd, J_{vic} = 9.5, 6.8 Hz, C3-H), 3.80 (2H, t, J = 6 0 Hz, CO-CH_2-C$\underline{H}_2$-O), 4.1-4.5 (2H, m, C5-H_2), 4.52 (2H, s, O-C$\underline{H}_2$-Ph), 7 2-7.5 (5H, m, Ph), Anal. Calcd. for $C_{14}H_{16}O_4$ (248.27): C 67.73, H 6.50. Found: C 67.58, H 6.65.

Methyl 2-(2-Benzyloxy-ethyl)-4,5-dihydrofuran-3-carboxylate (3)

5 M solution of HCl in dry dioxane (0.1 ml, 0.5 mmole) was added to a solution of 4 (1.24 g, 5 mmole) in dry methanol (5 ml) and the reaction mixture was allowed to stand at room temperature for 10 h. Then it was poured into 50 ml of 1 % $KHCO_3$ solution and extracted with CH_2Cl_2 (5x10 ml) After drying ($MgSO_4$) and evaporation the residue (1.32 g) was purified by column chromatography on SiO_2 (125 g, toluene ethyl acetate 9:1 v/v, R_f: 0.53) to give 3 (0.74 g, 56 %) as a colourless thick oil. MS (m/z, %): 262 (M^+, 7.3), 156 (38), 154 (21), 105 (23), 91 (100), 77 (13), 55 (11), IR (KBr, ν, cm^{-1}): 3090, 3064 and 3032 (phenyl CH), 1722 and 1698 (C=O in conjugation with C=C and O), 1643 C=C in conjugation with C=O and O), 1104 and 1090 (C-O-C, ether), 742 (C=O), 715 and 699 (phenyl), ^{1}H-NMR (δ, ppm)· 2 88 (2H, t, J_{vic} = 9 5 Hz, C4-H_2), 2.98 (2H, t, J_{vic} = 6 8 Hz, C2-C$\underline{H}_2$-CH_2-O), 3 70 (2H, t, J_{vic} = 6 8 Hz, C2-CH_2-C$\underline{H}_2$-O), 3.71 (3H, s, OCH_3), 4.40 (2H, t, J_{vic} = 9.5 Hz, C5-H_2), 4.53 (2H, s, O-C$\underline{H}_2$-Ph), 7.2-7.4 (5H, m, Ph), Anal Calcd. for $C_{15}H_{18}O_4$ (262.29): C 68.68, H 6.92 Found: C 68.80, H 7.05

Methyl 2-(2-Methoxy-ethyl)-4,5-dihydrofuran-3-carboxylate (5)

6 M solution of HCl in dry dioxane (0.2 ml, 1.2 mmole) was added to a

solution of 4 (0.25 g, 1 mmole) in dry methanol and the reaction mixture was allowed to stand at room temperature for 4 days. Then it was poured into 5 ml of 5 % $KHCO_3$ solution and extracted with ether (4x3 ml). After drying ($MgSO_4$) and evaporation the residue (0.24 g) was purified by column chromatography on SiO_2 (20 g, toluene-isopropanol 95:5 v/v, R_f: 0.52) to give 5 (0.085 g, 46 %) as a colourless oil. ^{1}H-NMR (δ, ppm): 2.88 (2H, t, J_{vic} = 9.6 Hz, C4-H_2), 2.94 (2H, t, J_{vic} = 6.8 Hz, C2-CH_2-CH_2-O), 3.34 (3H, s, OCH_3), 3.60 (2H, t, J_{vic} = 6.8 Hz, C2-CH_2-CH_2-O), 3.71 (3H, s, $COOCH_3$), 4.41 (2H, t, J_{vic} = 9.6 Hz, C5-H_2).

Methyl 2-(2-Chloro-ethyl)-4,5-dihydrofuran-3-carboxylate (6)

0.17 g (0.65 mmole) of 3 was solved in 5M solution of HCl in dry dioxane (1.3 ml, 6.5 mmole) and allowed to stand at room temperature for 10 min. Then it was carefully poured into 20 ml of cold 20 % $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x10 ml). After drying ($MgSO_4$) and evaporation the residue was purified by column chromatography on SiO_2 (20 g, toluene-isopropanol 95:5 v/v, R_f: 0.59) to give 6 (0.093 g, 75 %) as a colourless oil. ^{1}H-NMR (δ, ppm): 2.91 (2H, m, C4-H_2), 3.12 (2H, m, C2-CH_2-CH_2-Cl), 3.70 (2H, m, C2-CH_2-CH_2-Cl), 3.72 (3H, s, $COOCH_3$), 4.41 (2H, t, J = 9.8 Hz, C5-H_2)

Methyl 2-(2-Hydroxy-ethyl)-4,5-dihydrofuran-3-carboxylate (7)

Compound 3 (0.26 g, 1 mmole) was hydrogenated in ethanol (8 ml) over 10 % Pd/C (0.25 g) at ambient temperature and pressure. When the hydrogen consumption ceased (5 h, 27 ml), the catalyst was removed, the solvent evaporated and the raw product (0.16 g) purified by column chromatography on SiO_2 (20 g, toluene-isopropanol 95:5 v/v, R_f: 0.29) to give (7) (0.13 g, 75 %) as a colourless very thick oil. ^{1}H-NMR (δ, ppm): 2.91 (2H, m, C4-H_2), 2.93 (2H, m, C2-CH_2-CH_2OH), 3.72 (3H, s, $COOCH_3$), 3.82 (2H, m, C2-CH_2-CH_2OH), 3.8 (1H, br s, OH), 4.45 (2H, m, C5-H_2).

(±)-3-(3-Benzyloxy-propionyl)-3-diethoxymethyl-4,5-dihydro-3*H*-furan-2-one (8)

A mixture of 4 (27.8 g, 0.112 mole), triethyl orthoformate (12.0 g, 0.196 mole) and acetic anhydride (28.6 g, 0 28 mole) was heated for 1 h

in an oilbath at 120°C then the mixture was evaporated in *vacuo* at 50°C. The residue (40.0 g) was purified by column chromatography on SiO_2 (1 kg, toluene-ethyl acetate 9:1 v/v, R_f: 0.54) to give 8 (30.6 g, 78 %) as a colourless oil. MS (m/z, %): 350 (M^+, 0.03), 143 (35), 103 (100), 91 (56), 75 (29), 55 (11), 47 (25); IR (KBr, ν, cm^{-1}): 3090, 3064 and 3032 (phenyl CH), 1762 (5-membered lactone C=O), 1718 (ketone C=O), 1105 and 1061 (O-C-O), 740 and 699 (phenyl); ^{1}H-NMR (δ, ppm): 1.13 + 1. 21 (2x 3H, t, J = 7.0 Hz, 2x OCH_2-CH_3), 2.63 (1H, ddd, J_{gem} = -13.0 Hz, J_{vic}= 8.5, 7.5 Hz, C4-H_A), 2 84 (1H, ddd, J_{vic} = 7.8, 5 5 Hz, C4-H_B), 2.89 (1H, d t, J_{gem} = -17.4 Hz, J_{vic} = 6.5 Hz, CO-CH_AH_B), 3.20 (1H, ddd, J_{vic} = 6.8, 6 0 Hz, CO-CH_AH_B), 3.4-4.0 (4H, m, 2x OCH_2CH_3), 3.77 (2H, t, J = 6.5 Hz, CO-CH_2-CH_2-O), 4.0-4.5 (2H, m, C5-H_2), 4.51 (2H, s, O-CH_2-Ph), 5.21 (1H, s, OCHO), 7.2-7.4 (5H, m, Ph); Anal. Calcd. for $C_{19}H_{26}O_6$ (350.40): C 65.12, H 7.48. Found: C 64.93, H 7.62.

(±)-3-(3-Benzyloxy-propionyl)-3-3(2-ethoxycarbonyl-ethyl)-4,5-dihydro-3*H*-furan-2-one (9)

A solution of sodium (5.6 mg, 0.25 mmole) in dry ethanol (0.75 ml) was added to a mixture of 4 (2.48 g, 10 mmole) and ethyl acrylate (1.10 g, 11 mmole), and the mildly exothermic reaction mixture was allowed to stand at room temperature overnight. After evaporation at 40°C the residue was purified by column chromatography on SiO_2 (200 g, cyclohexane-ethyl acetate 6:4 v/v, R_f: 0.54) to give 9 (2.19 g, 6.3 %) as a colourless thick oil. MS (m/z, %). 348 (M^+, 0.34), 195 (13), 186 (22), 141 (16), 140 (78), 139 (10), 122 (39), 112 (12), 105 (54), 99 (24), 91 (35), 77 (28), 73 (12), 55 (100), 43 (12), 27 (19); IR (KBr, ν, cm^{-1}): 1768 (5-membered lactone C=O), 1733 (ester C=O), 1718 (ketone C=O), 1180 (C-O-C, ester), 716 and 687 (phenyl); ^{1}H-NMR (δ, ppm): 1.23 (3H, t, J = 7.0 Hz, COO-CH_2-CH_3), 2.03 (1H, ddd, J_{gem} = -13.0 Hz, J_{vic} = 8.5, 8.5 Hz, C4-H_A), 2.05-2.5 (4H, m, C3-CH_2-CH_2), 2.88 (1H, ddd, J_{vic} = 6.8, 4.0 Hz, C4-H_B), 2.95 (2H, t, J = 6.0 Hz, CO-CH_2-CH_2-O), 3.74 (2H, t, J = 6.0 Hz, CO-CH_2-CH_2-O), 4.11 (2H, q, COO-CH_2-CH_3), 3.9-4.4 (2H, m, C5-H_2), 4.48 (2H, s, O-CH_2-Ph), 7.2-7.4 (5H, m, Ph). ^{13}C-NMR (δ, ppm): 14.15 (COO-CH_2-CH_3), 29.02 + 29 53 + 29.59 (C4 + C3-CH_2-CH_2), 38.09 (CO-CH_2-CH_2-O), 60 40 (C3), 60.78 (COO-CH_2-CH_3), 65.09 (CO-CH_2-CH_2-O) 66.07 (C5), 73.26 (CH_2-Ph), 127.61 (C2' + C4' + C6'), 128.38 (C3' + C5'), 138 02 (C1'), 172.04 (COO-Et), 175.14 (C2), 202.85 (C3-CO-); Anal. Calcd. for $C_{19}H_{24}O_6$ (348.38): C 65.50, H 6.94. Found: C 65.75, H 6 77.

(±)-3a-Diethoxymethyl-7a-hydroxy-5-[2-2(indol-3-yl)-ethyl]-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(2*H*)-one (**10**) and

(±)-1-Ethoxy-7-[2-(indol-3-yl)-ethyl]-2-oxa-7-azaspiro[4,5]decan-6,10-dione (**12**)

A mixture of **8** (2.20 g, 6.3 mmole) tryptamine (1.01 g, 6.3 mmole) chlorobenzene (30 ml) and N,N-diisopropylethylamine (6 ml) was stirred and heated under reflux for 2.5 h, and then the solvents were removed by evaporation at 40°C in *vacuo*. The residue was separated by column chromatography on SiO_2 (400 g, toluene-diethylamine 9:1 v/v, R_f: 0.36 for **10** and R_f: 0.47 for **12**) to give the pure compounds.

Compound **10** (1.56 g, 62 %) is a colourless glass-like material; MS (m/z, %): 402 (M^+, 2.5), 143 (100), 140 (22), 130 (30); IR (KBr, ν, cm^{-1}): 3320 (br, OH, indole NH), 1626 (amide-I), 1100 (C-OC_2H_5), 1055 (C-O, ether in 5-membered ring), 745 (o-disubstd. A ring); ^{1}H-NMR (400 MHz, δ, ppm): 1.18 and 1.29 (2x 3H, t, J = 7.0 Hz, 2x O-CH_2-$\underline{C}H_3$), 2.12 (1H, ddd, $J_{7A,7B}$ = -13.5 Hz, $J_{6A,7A}$ = 2.2 Hz, $J_{7A,6B}$ = 4.3 Hz, C7-H_A), 2.34 (1H, ddd, $J_{3A,3B}$ = -12.8 Hz, $J_{2A,3A}$ = 7.7 Hz, $J_{3A,2B}$ = 5.0 Hz, C3-H_A), 2.44 (1H, ddd, $J_{3B,2A}$ = 7.5 Hz, $J_{2B,3B}$ = 8.2 Hz, C3-H_B), 2.45 (1H, ddd, $J_{7B,6A}$ = 5.6 Hz, $J_{6B,7B}$ = 12.0 Hz, C7-H_B), 2.97 (1H, ddd, J_{gem} = -14.0 Hz, J_{vic} = 9.5 and 6.3 Hz, C3'-$\underline{C}H_AH_B$), 3.04 (1H, ddd, J_{vic} = 9.2 and 5.6 Hz, C3'-$CH_A\underline{H}_B$), 3.19 (1H, ddd, $J_{6A,6B}$ = -12.0 Hz, C6-H_A), 3.43 (1H, ddd, C6-H_B), 3.56 + 3.83 and 3.66 + 3.94 (2x 2H, J_{gem} = -9.3 Hz, J_{vic} = 7.0 Hz, 2x O-$\underline{C}H_2$-CH_3), 3.62 + 3.70 (2H, m, N-CH_2), 3.69 (1H, ddd, $J_{2A,2B}$ = -8.8 Hz, C2-H_A), 4.03 (1H, ddd, C2-H_B), 5.19 (1H, s, $\underline{C}H(OEt)_2$), 5.90 (1H, br s, C7a-OH), 7.04 (1H, d, J = 2.4 Hz, C2'-H), 7.13 (1H, dd, $J_{5',6'}$ = 7.0 Hz, $J_{4',5'}$ = 7.6 Hz, C5'-H), 7.19 (1H, dd, $J_{6',7'}$ = 7.8 Hz, C6'-H), 7.36 (1H, d, C7'-H), 7.70 (1H, d, C4'-H), 8.20 (1H, br s, NH); ^{13}C-NMR (δ, ppm): 15.27 + 67.27 (OEt), 15.40 + 67.53 (OEt), 23.07 (C3'-$\underline{C}H_2$), 32.01 (C7), 33.15 (C3), 44.69 (C6), 48.94 (N-CH_2), 60.10 (C3a), 64.54 (C2), 103.66 (C7a), 107.08 ($\underline{C}H(OEt)_2$), 111.16 (C7'), 112.88 (C3'), 118.81 (C4'), 119.39 (C5'), 121.89 (C2'), 122.05 (C6'), 127.32 (C3a'), 136.27 (C7a'), 170.33 (C4); Anal. Calcd. for $C_{22}H_{30}N_2O_5$ (402.47): C 65.65, H 7.51, N 6.96. Found: C 65.81, H 7.70, N 6.78.

Compound **12** (0.18 g, 8 %) mp: 138-140°C; MS (m/z, %); 356 (M^+, 7), 153 (16), 152 (11), 144 (20), 143 (100), 130 (34); IR (KBr, ν, cm^{-1}); 3298 (indole NH), 1727 (C=O, ketone), 1646 (amide-I), 1101 (C-OC_2H_5), 1052 (C-O, ether in 5-membered ring), 748 (o-disubstd. A-ring), 690 (C=O, ketone); ^{1}H-NMR (δ, ppm): 1.02 (3H, t, J = 7.0 Hz, O-CH_2-$\underline{C}H_3$), 2.0-2.8

(4H, m, C4-H_2 + C9-H_2), 3.0-4.2 (10H, m, C3'-CH_2-CH_2-N + C8-H_2 + C3-H_2 + O-CH_2-CH_3), 4.93 (1H, s, C1-H), 7.02 (1H, d, J = 2 Hz, C2'-H), 7.05-7.45 (3H, m, C5'-H + C6'-H + C7'-H), 7.64 (1H, m, C4'-H), 8.30 (1H, br s, NH); ^{13}C-NMR (δ, ppm): 14.87 (O-CH_2-CH_3), 23.28 (C3'-CH_2), 27.26 (C9), 37.10 (C4), 42.98 (C8), 49.25 (N-CH_2), 63.72 (O-CH_2-CH_3), 68.09 (C3), 70.35 (C5), 106.01 (C1), 111.54 (C7'), 112.05 (C3'), 118 33 (C4'), 119.44 (C5'), 122.04 (C6'), 122.56 (C2'), 127.36 (C3a'), 136.35 (C7a'), 168.47 (C6), 200.95 (C10); Anal. Calcd. for $C_{20}H_{24}N_2O_4$ (356.41): C 67.40, H 6.79, N 7.86. Found: C 67.33, H 6.85, N 7.77.

At longer reaction time the yield of **12** increased to the detriment of **10**.

(±)-3a-(2-Ethoxycarbonyl-ethyl)-7a-hydroxy-5-[2-(indol-3-yl)-ethyl]-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(2*H*)-one (**11**)

A mixture of **9** (0.87 g, 2.5 mmole), tryptamine (0.40 g, 2.5 mmole), chlorobenzene (12.5 ml) and N,N-diisopropylethylamine was stirred and heated under reflux for 4 h and then the solvents were removed by evaporation at 40°C in *vacuo*. The residue was purified by column chromatography on SiO_2 (12 0 g, toluene-diethylamine 7:3 v/v, R_f: 0.61) to give **11** (0.86 g, 86 %) as a colourless glass-like material; MS (m/z, %): 400 (M^+, 4.5), 144 (17), 143 (100), 130 (21); IR (KBr, ν, cm^{-1}): 3400 (OH), 3312 (indole NH, H-bonded), 1730 and 1707 (C=O, ester, partly H-bonded), 1615 (amide-I), 740 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.24 (3H, t, J = 7.0 Hz, COO-CH_2-CH_3), 1.8-2.8 (8H, m, C3-H_2 + C7-H_2 + C3a-CH_2-CH_2), 2.5 (1H, br s, OH), 3.02 (2H, m, C3'-CH_2), 2.9-4.2 (6H, m, C6-H_2 + N-CH_2 + C-H_2), 4.13 (2H, q, COO-CH_2-CH_3), 7.04 (1H, d, J = 2.0 Hz, C2'-H), 7.1-7.4 (3H, m, C5'-H + C6'-H + C7'-H), 7.65 (1H, m, C4'-H), 8.25 (1H, br s, NH); ^{13}C-NMR (δ, ppm): 14.24 (COO-$CH_2$$CH_3$), 23.02 (C3'-$CH_2$), 28.86$^+$ (C3a-CH_2-CH_2), 30.88$^+$ (C3a-CH_2), 30.97 (C7), 35.25 (C3), 44.07 (C6), 48.44 (N-CH_2), 56.28 (C3a), 60.51 (COO-CH_2-CH_3), 65.64 (C2), 102.79 (C7a), 111.22 (C7'), 112.70 (C3'), 118.68 (C4'), 119.33 (C5'), 121.97^x (C2'), 122.19^x (C6'), 127.36 (C3a'), 136.27 (C7a'), 171.63 (C4), 173 85 (COOEt); Anal.Calcd. for $C_{22}H_{28}N_2O_5$ (400.46): C 65.98, H 7.05, N 7.00. Found. C 66 13, H 7.18, N 6.87.

2-(2-Benzyloxy-ethyl)-N-[2-(indol-3-yl)-ethyl]-4,5-dihydrofuran-3-carboxamide (**14**)

A mixture of **4** (0 124 g, 0.5 mmole), tryptamine (0.080 g, 0.5 mmole),

chlorobenzene (2.5 ml) and N,N-diisopropylethylamine (0.5 ml) was stirred and heated under reflux for 3 h, and then the solvents were removed by evaporation at 40°C in *vacuo*. The residue was purified by column chromatography on SiO_2 (25 g, toluene-diethylamine 9:1 v/v, R_f: 0.41) to give 14 (0.092 g, 51 %) mp: 124-127°C (toluene); MS (m/z, %): 390 (M^+, 2.3), 152 (17), 144 (20), 143 (100), 140 (12), 131 (19), 130 (66), 108 (25), 107 (21), 91 (50); IR (KBr, ν, cm^{-1}): 3420 (indole NH, H-bonded), 3210 (amide NH), 1658 (C=C in conjugation with C=O and O), 1600 (amide-II), 742 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 2.50 (2H, t, J = 7.0 Hz, C2-CH_2), 2.76 (2H, t, J = 7.8 Hz, C4-H_2), 2.98 (2H, t, J = 6.7 Hz, C3'-CH_2), 3.51 (2H, t, J = 7.0 Hz, C2-CH_2-CH_2-O), 3.52 (2H, td, J = 6.7 and 5.8 Hz, NH-CH_2), 4.20 (2H, t, J = 7.8 Hz, C5-H_2), 4.43 (2H, s, O-CH_2-Ph), 7.05 (1H, d, J = 2 Hz, C2'-H), 7.05-7.45 (3H, m, C5'-H + C6'-H + C7'-H), 7.30 (5H, s, Ph), 7.55 (1H, m, C4'-H), 8.2-8.5 (2H, br, amide-NH + indole-NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 26.18^x (C3'-CH_2), 26.61^x (C4), 30.88 (C2-CH_2), 43.54 (NH-CH_2), 65.12 (C5), 66.94 (C2-CH_2-CH_2-O), 73.03 (O-CH_2-Ph), 85.31 (C3), 111.48 (C7'), 111.67 (C3'), 118.28 (C4'), 119.03 (C5'), 121.68° (C2'), 122.96° (C6'), 127.01 (C3a'), 127.53 (C2" + C6"), 127.70 (C4"), 128.38 (C3" + C5"), 136.44 (C7a'), 137.82 (C1"), 157.51 (C2), 174.28 (CO-NH), Anal.Calcd. for $C_{24}H_{26}N_2O_3$ (390.46): C 73.82, H 6.71, N 7.17. Found: C 73.77, H 6.90, N 7.09.

2-(2-Hydroxy-ethyl)-N-[2-(indol-3-yl)-ethyl]-4,5-dihydrofuran-3-carboxamide (15)

Compound 14 (0.072 g, 0.2 mmole) was hydrogenated in dry DMF (10 ml) over 10 % Pd/C (0.1 g) at ambient temperature and pressure. When the hydrogen consumption ceased (6 h, 6 ml) the catalyst was removed by filtration, the solvent evaporated and the residue purified by column chromatography on SiO_2 (10 g, cyclohexane-isopropanol-diethylamine 7:2:1 v/v/v, R_f: 0.28) to give 15 (0.022 g, 37 %) as a colourless glass-like material. ^{1}H-NMR (δ, ppm): 2.3 (1H, br s, OH), 2.46 (2H, t, J = 6.8 Hz, C2-CH_2), 2.78 (2H, t, J = 7.8 Hz, C4-H_2), 2.99 (2H, t, J = 6.6 Hz, C3'-CH_2), 3.54 (2H, td, J = 6.6 and 6 Hz, NH-CH_2), 3.70 (2H, t, J = 6.8 Hz, CH_2OH), 4.20 (2H, t, J = 7.8 Hz, C5-H_2), 6.9-7.6 (5H, m, aromatic protons), 8.1-8 6 (2H, br, amide NH + indole NH).

(±)-3a-Dimethoxymethyl-5-[2-(indol-3-yl)-ethyl]-7a-methoxy-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(2*H*)-one (16)

To a solution of 10 (0.032 g, 0.08 mmole) in dry methanol (0.3 ml) 0.08 ml (0.4 mmole) of 5M solution of HCl in dry dioxane was added and allowed to stand at room temperature for 3 h. Then it was poured into 3 ml of 10 % $KHCO_3$ solution and extracted with CH_2Cl_2 (3x2 ml). After drying ($MgSO_4$) and evaporation the residue was purified by column chromatography on SiO_2 (20 g, cyclohexane-diethylamine 8:2 v/v, R_f: 0.13) to give 16 (0.018 g, 58 %) as a colourless glass-like material; MS (m/z, %): 388 (M^+, 3.6), 246 (14), 154 (13), 143 (52), 75 (100); IR (KBr, ν, cm^{-1}): 3300 (indole NH, H-bonded), 2844 and 2827 (OCH_3), 1629 (amide-I), 1078 (O-C-O), 738 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 2.0-4.0 (12H, m, C2-H_2 + C3-H_2 + N-CH_2 + C3'-CH_2 + C6-H_2 + C7-H_2), 3.25 (3H, s, C7a-OCH_3), 3.48 and 3.57 (2x 3H, s, 2x OCH_3), 4.71 (1H, s, C<u>H</u>(OMe)$_2$), 7.07 (1H, d, J = 2 Hz, C2'-H), 7.05-7.45 (3H, m, C5'-H + C6'-H + C7'-H), 7.71 (1H, m, C4'-H), 8.16 (1H, br s, NH).

(±)-5-[2-(Indol-3-yl)-ethyl]-7a-methoxy-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(2*H*)-one (17)

To a solution of 10 (0.100 g, 0.25 mmole) in dry methanol (2 ml) 0.25 ml (1.25 mmole) of 5M solution of HCl in dry dioxane was added and heated under reflux for 4 h. After evaporation the residue was treated with 10 % $KHCO_3$ solution (5 ml) and extracted with CH_2Cl_2 (2x5 ml). After drying ($MgSO_4$) and evaporation the residue was purified by column chromatography on SiO_2 (10 g, cyclohexane-diethylamine 7:3 v/v, R_f: 0.30) to give 17 (0.024 g, 31 %) as a colourless glass-like material; MS (m/z, %). 314 (M^+, 4.2), 144 (16), 143 (100), 130 (22); IR (KBr, ν, cm^{-1}): 3270 (indole NH, H-bonded), 1628 (amide-I), 1081 and 1031 (C-O-C, ether), 744 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.6-2.7 (5H, m, C3-H_2 + C7-H_2 + C3a-H), 2.8-3.4 (2H, m, C6-H_2), 3.03 (2H, m, C3'-CH_2), 3.20 (3H, s, OCH_3), 3.72 (2H, m, N-CH_2), 3.75-3.95 (2H, m, C2-H_2), 7.02 (1H, d, J = 2 Hz, C2'-H), 7.1-7.4 (3H, m, C5'-H + C6'-H + C7'-H), 7.65 (1H, m, C4'-H), 8.30 (1H, br s, NH); ^{13}C-NMR (δ, ppm): 23.39 (C3'-<u>C</u>H$_2$), 29.00 (C7), 30.17 (C3), 44.65 (C6), 48.38 (OCH_3), 48.43 (N-CH_2), 51.52 (C3a), 66.82 (C2), 106.55 (C7a), 111.34 (C7'), 112.63 (C3'), 118.62 (C4'), 119.22 (C5'), 121.89 (C2'), 122.21 (C6'), 127.45 (C3a'), 136.45 (C7a'), 170.75 (C4).

(±)-7a-Ethoxy-5-[2-(indol-3-yl)-ethyl]-2,3,6,7-tetrahydrofuro[3,2-*c*] pyridin-4(2*H*)-one (18)

To a solution of 12 (0.167 g, 0.47 mmole) in dry ethanol (4.7 ml) 2.3 ml (11.5 mmole) of 5M solution of HCl in dry dioxane was added and allowed to stand at room temperature for 21 h. Then it was diluted with CH_2Cl_2 (10 ml) and poured slowly into 5 ml of cold cc. NH_4OH at strong stirring. After separation the aqueous phase was extracted with CH_2Cl_2 (2x5 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on SiO_2 (20 g, cyclohexane-diethylamine 7:3 v/v, R_f: 0.39) to give 18 (0.055 g, 36 %) as a colourless very thick oil; MS (m/z, %): 328 (M^+, 4.1), 144 (17), 143 (100), 130 (20); IR (KBr, ν, cm^{-1}): 3265 (indole NH), 2975, 2930 and 2885 (OC_2H_5), 1627 (amide-I), 1075 and 1028 (C-O-C, ether), 741 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.15 (3H, t, J = 7.0 Hz, O-CH_2-CH_3), 1.6-2.7 (4H, m, C3-H_2 + C7-H_2), 2.8-3.4 (3H, m, C6-H_2 + C3a-H), 3.04 (2H, m, C3'-CH_2), 3.35-3.65 (2H, m, O-CH_2-CH_3), 3.72 (2H, m, N-CH_2), 3.75-3.95 (2H, m, C2-H_2), 7.02 (1H, br s, C2'-H), 7.1-7.4 (3H, m, C5'-H + C6'-H + C7'-H), 7.65 (1H, m, C4'-H), 8.42, br s, NH); ^{13}C-NMR (δ, ppm): 15.71 (O-CH_2-CH_3), 23.38 (C3'-CH_2), 29.78 (C7), 30.29 (C3), 44.65 (C6), 48.39 (N-CH_2), 51.71 (C3a), 56.36 (OCH_2-CH_3), 66.71 (C2), 106.42 (C7a), 111.35 (C7'), 112.49 (C3'), 118.58 (C4'), 119.15 (C5'), 121.81 (C2'), 122.25 (C6'), 127.41 (C3a'), 136.42 (C7a'), 170.87 (C4).

(±)-5-[2-(Indol-3-yl)-ethyl]-7a-methoxy-3a-(2-methoxy-carbonyl-ethyl)-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(2*H*)-one (19)

To a solution of 11 (0.100 g, 0.25 mmole) in dry methanol (2.5 ml) 0.25 ml (1.25 mmole) of 5M solution of HCl in dry dioxane was added and allowed to stand at room temperature for 4h. Then it was poured into 2.5 ml of 20 % $KHCO_3$ solution and extracted with CH_2Cl_2 (3x2 ml). After drying ($MgSO_4$) and evaporation the residue was purified by column chromatography on SiO_2 (10 g, toluene-diethylamine 9:1 v/v, R_f: 0.48) to yield 19 (0.096 g, 96 %), mp: 102-104°C; MS (m/z, %) 400 (M^+, 6.8), 144 (17), 143 (100), 130 (10); IR (KBr, ν, cm^{-1}): 3270 (indole NH), 1733 (C=O, ester), 1629 (amide-I), 743 (o-disubstituted A-ring); ^{1}H-NMR (δ, ppm): 1.6-2.7 (8H, m, C3-H_2 + C7-H_2 + C3a-CH_2-CH_2), 2.9-3.4 (4H, m, C3'-CH_2 + C6-H_2), 3.20 (3H, s, C7a-OCH_3), 3.4-3.95 (4H, m, N-CH_2 + C2-H_2), 3.66 (3H, s, COO-CH_3), 7.03 (1H, d, J = 2.0 Hz, C2'-H), 7.1-7.4 (3H, m, C5'-H + C6'-H + C7'-H), 7.65 (1H, m, C4'-H), 8.18 (1H, br s, NH).

(±)-3-Diethoxymethyl-4-hydroxy-3-(2-hydroxy-ethyl)-1-[2-(indol-3-yl)-ethyl]-3,4,5,6-tetrahydropyridin-2(1*H*)-one (**20**)

To a stirred solution of **10** (3.05 g, 7.6 mmole) in dry ethanol (100 ml) sodium borohydride (1.44 g, 38 mmole) was added in small portions. After the addition was complete (1 h), stirring was continued for 5 h. To the mixture acetone (40 ml) was added, then it was stirred (1 h) and evaporated to dryness *in vacuo*. The residue treated with water (75 ml) and extracted with $CHCl_3$ (2x40 ml). The organic layer was dried ($MgSO_4$) and evaporated to yield the pure **20** (3.04 g, 99 %), mp: 180-183°C (96 % aq. ethanol), R_f 0.41 (toluene-diethylamine 8:2 v/v); MS (m/z, %): 404 (M^+, 5.5), 216 (12), 170 (43), 143 (100), 130 (13); IR (KBr, ν, cm^{-1}): 3440 (indole NH), 3325 and 3230 (OH), 1610 (amide-I), 1107, 1054 and 1053 (O-C-O), 742 (o-disubstd A-ring); ^{1}H-NMR (δ, ppm): 1.18+1.25 (2x 3H, t, J = 7.0 Hz, 2x O-CH_2-CH_3), 1.7-2.1 (4H, m, C3-CH_2 + C5-H_2), 2.8-3.2 (4H, m, C3-CH_2-CH_2-N), 3.4-4.0 (9H, m, 2x O-CH_2-CH_3 + C6-H_2 + CH_2-OH), 4.11 (1H, dd, J_{vic} = 5.5 and 3.0 Hz, C4-H), 4.72 (1H, br s, OH), 5.21 (1H, s, $CH(OEt)_2$), 7.06 (1H, d, J = 2 Hz, C2-H), 7.05-7.45 (3H, m, C5-H + C6'-H + C7'-H), 7.68 (1H, m, C4'-H), 8.30 (1H, br s, indole NH); ^{13}C-NMR (δ, ppm): 15.33 and 15.60 (2x O-CH_2-CH_3), 22.92 (C3'-CH_2), 25.89 (C5), 37.65 (C3-CH_2), 44.24 (C6), 48.71 (N-CH_2), 52.13 (C3), 59.05 (CH_2-OH), 65.83 and 68.76 (2x O-CH_2-CH_3), 69.90 (C4), 108.26 ($CH(OEt)_2$), 111.32 (C7'), 112.63 (C3'), 118.64 (C4'), 119.25 (C5'), 121.88 (C2'), 122.38 (C6'), 127.42 (C3a'), 136.42 (C7a'), 171.90 (C2). Anal. Calcd. for $C_{22}H_{32}N_2O_5$ (404.49): C 65.32, H 7.97, N 6.93. Found: C 65.19, H 8.11, N 6.90.

(±)-4-Hydroxy-3-(2-hydroxy-ethyl)-3-(3-hydroxy-propyl)-1-[2-(indol-3-yl)-ethyl]-3,4,5,6-tetrahydropyridin-2(1*H*)-one (**21**)

To a stirred solution of **11** (0.101 g, 0.25 mmole) in dry ethanol (5 ml) sodium borohydride (0.095 g, 2.5 mmole) was added in small portions. After the addition was complete (30 min), stirring was continued for 5 h. To the mixture acetone (5 ml) was added, then it was stirred (20 min) and evaporated to dryness *in vacuo*. The residue was treated with water (5 ml) and thoroughly extracted with CH_2Cl_2 (25x5 ml). The organic layer was dried ($MgSO_4$) and evaporated. The residue (0.056 g) was purified by column chromatography on SiO_2 (10 g, toluene-isopropanol-diethylamine 7:2:1 v/v/v, R_f: 0.28) to give **21** (0.038 g, 42 %) as a colourless very thick oil;

^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6 + D_2O, δ, ppm): 1.45-1.6 (2H, m, C3-CH_2-$\underline{CH}_2$-CH_2OH), 1.72 + 1.79 (2H, m, C3-$\underline{CH}_2$-CH_2-CH_2OH), 1.82 + 1.87 (2H, m, C3-$\underline{CH}_2$-CH_2-OH), 1.85-2.0 (2H, m, C5-H_2), 2.9-3.0 (2H, m, C3'-CH_2), 3.15 + 3.32 (2H, m, C6-H_2), 3.45-3.55 (2H, m, C3-$(CH_2)_2$-$\underline{CH}_2OH$), 3.55 + 3.59 (2H, m, C3'-CH_2-$\underline{CH}_2$-N), 3.62 + 3.67 (2H, m, C3-CH_2-$\underline{CH}_2$-OH), 3.85 (1H, dd, J = 6.0 and 5.0 Hz, C4-H), 7.03 (1H, ddd, $J_{4',5'}$ = 7.8 Hz, $J_{5',6'}$ = 7.0 Hz, $J_{5',7'}$ = 1.0 Hz, C5'-H), 7.06 (1H, s, C2'-H), 7.09 (1H, ddd, $J_{6',7'}$ = 8.0 Hz, $J_{4',6'}$ = 1.2 Hz, C6'-H), 7.36 (1H, dd, C7'-H), 7.61 (1H, dd, C4'-H), 10.20 (1H, br s, indole NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 22.81 (C3'-$\underline{CH}_2$), 26.06 (C5), 27.12 (C3-CH_2-$\underline{CH}_2$-CH_2OH), 27.24 (C3-$\underline{CH}_2$-CH_2-CH_2OH), 37.27 (C3-$\underline{CH}_2$-CH_2OH), 44.35 (C6), 48.34 (C3'-CH_2-$\underline{CH}_2$-N), 48.46 (C3), 58.30 (C3-CH_2-$\underline{CH}_2OH$), 62.35 (C3-CH_2-CH_2-$\underline{CH}_2OH$), 69.09 (C4), 111.43 (C7'), 111.78 (C3'), 118.36 (C4'), 118.51 (C5'), 121.14 (C6'), 122.62 (C2'), 127.27 (C3a'), 136.40 (C7a'), 174.03 (C2).

(±)-[1'R*:2'S*:12b'S*]-Spiro[(3*H*-4,5-dihydrofuran-2-one)-3,1'-(1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-ol)] (22)

To a solution of 20 (0.404 g, 1.0 mmole) in ethanol (4 ml) 19 % hydrochloric acid (4 ml) was added and boiled for 1 h. After cooling the reaction mixture was diluted with water (20 ml), basified with cc. NH_4OH (8 ml) and extracted with CH_2Cl_2 (3x10 ml). The organic phase was dried ($MgSO_4$) and evaporated. The residue (0.227 g) was purified by column chromatography on SiO_2 (25 g, cyclohexane-diethylamine 8:2 v/v, R_f: 0.31) to give 22 (0.074 g, 24 %), amorphous; MS (m/z, %): 312 (M^+, 100), 311 (81), 295 (16), 198 (29), 197 (92), 171 (19), 170 (98), 169 (46); IR ($CHCl_3$, ν, cm^{-1}): 3604 (OH), 3390 (indole NH), 1744 (C=O, 5-membered lactone, H-bonded); ^{1}H-NMR (400 MHz, δ, ppm): 1.70 (1H, dddd, J_{gem} = -12.3 Hz, $J_{2'a,3'a}$ = 11.4 Hz, $J_{3'a,4'a}$ = 12.5 Hz, $J_{3'a,4'e}$ = 4.9 Hz, C3'-H_a), 1.75 (1H, dddd, $J_{2'a,3'e}$ = 5.4 Hz, $J_{3'e,4'a}$ = 4.3 Hz, $J_{3'e,4'e}$ = 2.5 Hz, C3'-H_e), 2.61 (1H, dddd, J_{gem} = -16.2 Hz, $J_{7'e,6'a}$ = 5.7 Hz, $J_{6'e,7'e}$ = 0.8 Hz, $J_{7'e,12b'}$ = 1.8 Hz, C7'-H_e), 2.65 (1H, ddd, J_{gem} = -12.0 Hz, C4'-H_e), 2.79 (1H, ddd, J_{gem} = -13.2 Hz, J_{vic} = 9.6 and 8.2 Hz, C4-H_A), 2.82 (1H, ddd, J_{vic} = 7.4 and 4.0 Hz, C4-H_B), 2.92 (1H, ddd, C4'-H_a), 3.03 (1H, dddd, $J_{6'a,7'a}$ = 11.7 Hz, $J_{6'e,7'a}$ = 6.9 Hz, $J_{7'a,12b'}$ = 2.4 Hz, C7'-H_a), 3.23 (1H, ddd, J_{gem} = -13.7 Hz, C6'-H_a, 3.32 1H, ddd, C6'-H_e), 4.14 (1H, dd, C2'-H_a), 4.41 (1H, dd, C12b'-H), 4.45 + 4.49 (2x 1H, 2x ddd,

J_{gem} = -9.0 Hz, C5-H_2), 7.09 (1H, ddd, $J_{8',9'}$ = 7.8 Hz, $J_{9',10'}$ = 7.0 Hz, $J_{9',11'}$ = 1.0 Hz, C9'-H), 7.16 (1H, ddd, $J_{10',11'}$ = 8.0 Hz, $J_{8',10'}$ = 1.3 Hz, C10'-H), 7.37 (1H, ddd, $J_{8',11'}$ = 0.8 Hz, C11'-H), 7.47 (1H, dm, C8'-H), 9.92 (1H, br s, NH); ^{13}C-NMR (δ, ppm): 17.34 (C7'), 27.76 (C3'), 30.34 (C4), 43 22 (C4'), 51.35 (C6'), 54.18 (C1' ≡ C3), 58.32 (C12b'), 66.85 (C5), 67.26 (C2'), 108.67 (C7a'), 111.45 (C11'), 117.85 (C8'), 119.13 (C9'), 121.74 (C10'), 126.44 (C7b'), 129.68 (C12a'), 135.31 (C11a'), 181.57 (C2); Anal. Calcd. for $C_{18}H_{20}N_2O_3$ (312.35): C 69.21, H 6.45, N 8.97. Found: C 69.19, H 6.51, N 8.95.

10-Epimers of 1-Ethoxy-10-hydroxy-7-[2-(indol-3-yl)-ethyl]-2-oxa-7-azaspiro[4,5]decan-6-one (23 and 24)

a.) To a solution of 20 (0.081 g, 0.2 mmole) in ethanol (2 ml) 19 % hydrochloric acid (1 ml) was added and allowed to stand at room temperature for 16 h. After cooling the solution was basified with cc. NH_4OH solution to pH 10 and extracted with CH_2Cl_2 (3x5 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give a mixture of 23 and 24 (0.067 g), which were separated by column chromatography on SiO_2 (10 g, cyclohexane-isopropanol-diethylamine 7:2:1 v/v/v, R_f: 0.57 and 0.36, respectively) to give the pure epimers.

Compound 23 (0.018 g, 25 %), mp: 166-170°C; MS (m/z, %): 358 (M^+, 4.3), 216 (3.6), 170 (13), 143 (100), 130 (17); IR (KBr, ν, cm^{-1}): 3560 (OH), 3500-3200 (OH, H-bonded), 3330 (indole NH), 1633 (amide-I), 1092 and 1044 (C-O-C), 740 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.23 3H, t, J = 7.0 Hz, O-CH_2-$\underline{CH_3}$), 1.7-2.2 (4H, m, C4-H_2 + C9-H_2), 2.9-3.3 (3H, m, C3'-CH_2 + C8-H_A), 3.35-4.0 (6H, m, C8-H_B + N-CH_2 + O-$\underline{CH_2}$-CH_3 + OH), 3.9-4.2 (3H, m, C3-H_2 + C10-H_e), 5.37 (1H, s, C1-H), 7.05 (1H, d, J = 2 Hz, C2'-H), 7.05-7.45 (3H, m, C5'-H + C6'-H + C7'-H), 7.63 (1H, m, C4'-H), 8.26 (1H, br s, NH); ^{13}C-NMR (δ, ppm): 15.23 (O-CH_2-$\underline{CH_3}$), 22.78 (C3'-$\underline{CH_2}$), 27.02 (C9), 35.39 (C4), 43.69 (C8), 48.48 (N-CH_2), 58.27 (C5), 63.42 (O-$\underline{CH_2}$-CH_3), 66.77 (C3), 69.38 (C10), 106.47 (C1), 111.17 (C7'), 113.00 (C3'), 118.78 (C4'), 119.25 (C5'), 121.90 (C6'), 122.08 (C2'), 127.48 (C3a'), 136.19 (C7a'), 171.50 (C6), Anal. Calcd. for $C_{20}H_{26}N_2O_4$ (358.42): C 67.02, H 7.31, N 7.82. Found: C 66.93, H 7.40, N 7.75.

Compound 24 (0.010 g, 14 %), mp: 178-194°C; MS (m/z, %): 358 (M^+, 3.3), 216 (18), 170 (51), 143 (100), 130 (19); IR (KBr, ν, cm^{-1}): 3500-3200 (OH), 3352 (indole NH), 1624 (amide-I), 1071 and 1027 (C-O, ether and alcohol), 740 (o-disubst. A-ring); ^{1}H-NMR (400 MHz, δ, ppm): 1.20 (3H, t,

J = 7.0 Hz, O-CH_2-$C\underline{H}_3$), 1.98 (1H, dddd, J_{gem} = -13.0 Hz, $J_{9a,10a}$ = 11.5 Hz, $J_{8a,9a}$ = 10.5 Hz, $J_{8e,9a}$ = 7.0 Hz, C9-H_a), 2.05 (1H, ddd, J_{gem} = -12.0 Hz, J_{vic} = 9.5 and 8.2 Hz, C4-H_A), 2.09 (1H, dddd, $J_{8a,9e}$ = 6.0 Hz, $J_{8e,9e}$ = 2.8 Hz, $J_{9e,10a}$ = 4.5 Hz, C9—H_e), 2.1 (1H, br s, OH), 2.72 (1H, ddd, J_{vic} = 6.7 and 2.5 Hz, C4-H_B), 2.94 (1H, dddd, J_{gem} = -14.0 Hz, J_{vic} = 9.6 and 5.8 Hz, J_{1r} = 0.7 Hz, C3'-$C\underline{H}_A\underline{H}_B$), 3.08 (1H, dddd, J_{vic} = 9.4 and 5.7 Hz, J_{1r} = 0.7 Hz, C3'-$CH_A\underline{H}_B$), 3.20 (1H, ddd, J_{gem} = -12.3 Hz, C8-H_a), 3.31 (1H, ddd, C8-H_e), 3.33 (1H, ddd, J_{gem} = -13.0 Hz, N-$C\underline{H}_A\underline{H}_B$), 3.52 + 3.83 (2x 1H, 2x dq, J_{gem} = -9.8 Hz, O-$C\underline{H}_2$-CH_3), 3.85 (1H, dd, C10-H_a), 3.90 (1H, ddd, N-$CH_A\underline{H}_B$), 4.04 + 4.30 (2x 1H, 2x ddd, J_{gem} = -8.0 Hz, C3-H_2), 5.25 (1H, s, C1-H), 7.05 (1H, d, J = 2.3 Hz, C2'-H), 7.12 (1H, ddd, $J_{4',5'}$ = 7.7 Hz, $J_{5',6'}$ = 7.0 Hz, $J_{5',7'}$ = 1.0 Hz, C5'-H), 7.18 (1H, ddd, $J_{6',7'}$ = 8.0 Hz, $J_{4',6'}$ = 1.3 Hz, C6'-H), 7.36 (1H, ddd, $J_{4',7'}$ = 0.8 Hz, C7'-H), 7.68 (1H, dm, C4'-H), 8.13 (1H, br s, NH); ^{13}C-NMR (δ, ppm): 15.20 (O-CH_2-$\underline{C}H_3$), 22.71 (C3'-$\underline{C}H_2$), 28.99 (C9), 32.82 (C4), 44.50 (C8), 48.71 (N-CH_2), 59.55 (C5), 64.41 (O-$\underline{C}H_2$-CH_3), 68.17 (C3), 70.01 (C10), 104.30 (C1), 111.15 (C7'), 113.31 (C3'), 118.83 (C4'), 119.26 (C5'), 121.96 (C6'), 122.00 (C2'), 127.39 (C3a'), 136.22 (C7a'), 168.70 (C6).

b.) To a stirred solution of 22 (0.214 g, 0.6 mmole) in dry ethanol (12 ml) sodium borohydride (0.228 g, 6.0 mmole) was added in small portions. After the addition was complete (30 min), stirring was continued for 5 h. To the mixture acetone (10 ml) was added then it was stirred (1 h), and evaporated to dryness in *vacuo*. The residue treated with water (10 ml) and extracted with CH_2Cl_2 (4x5 ml). The organic layer was dried ($MgSO_4$) and evaporated to give pure 23 (0.190 g, 88 %) which was contaminated by compound 24 only in trace amount.

5-[2-(Indol-3-yl)-ethyl]-2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-one (25)

To a solution of 10 (12.1 g, 30 mmole) in CH_2Cl_2 (350 ml) trifluoroacetic acid (6.9 ml 90 mmole) was added and allowed to stand at room temperature for 16 h. The solution was washed successively with 1M solution of ammonium hydroxide (200 ml), with water (20 ml), with 1M solution of hydrochloric acid (2x25 ml) and again with 1M solution of ammonium hydroxide (25 ml). The organic layer was dried ($MgSO_4$) and evaporated to yield the pure 25 (8.3 g, 98 %); mp: 177-179°C (toluene); R_f: 0.46 (toluene-diethylamine 8:2 v/v); MS (m/z, %): 282 (M^+, 17), 152 (55), 144 (14.5), 143 (100), 140 (13), 130 (18); IR (KBr, ν, cm^{-1}): 3200 (indole NH, intramol. H-bonded), 1669 (lactam C=O), 1607 (C=C in conjugation with C=O and O),

745 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 2.32 (2H, tt, J = 7.2 and 7.0 Hz, C7-H_2), 2.90 (2H, tt, J = 9.2 and 2.0 Hz, C3-H_2), 3.04 (2H, t, J = 7.2 Hz, C3'-CH_2), 3.36 (2H, t, J = 7.2 Hz, C6-H_2), 3.74 (2H, t, J = 7.2 Hz, N-CH_2), 4.56 (2H, t, J = 9.2 Hz, C2-H_2), 7.07 (1H, d, J = 2.0 Hz, C2'-H), 7.05-7.5 (3H, m, C5'-H + C6'-H + C7'-H), 7.69 (1H, m, C4'-H), 8.16 (1H, br s, indole NH); ^{13}C-NMR (δ, ppm): 23.35 (C3'-$\underline{C}H_2$), 24 21 (C3), 27.30 (C7), 45.83* (N-CH_2), 47.06* (C6), 73.24 (C2), 105.89 (C3a), 111.24 (C7'), 113.32 (C3'), 118.80 (C4'), 119 21 (C5'), 121.89 (C2'), 122.11 (C6'), 127.53 (C3a'), 136.40 (C7a'), 165.99^{+} (C4), 167.16^{+} (C7a).

(±)-5-[2-(Indol-3-yl)-ethyl]-2,3,3a,6,7,7a-hexahydrofuro[3,2-*c*]pyridin-4(5*H*)-one (26)

Compound 25 (0.423 g, 1.5 mmole) was hydrogenated in ethanol (20 ml) over 10 % Pd/C (0.63 g) at ambient temperature and pressure. When the hydrogen consumption ceased (20 h, 43 ml) the catalyst was removed and washed with ethanol (3x5 ml), the combined solutions were evaporated and the raw product (0.35 g) purified by column chromatography on SiO_2 (25 g, toluene-diethylamine 8:2 v/v, R_f: 0.40) to give 26 (0.258 g, 61 %) as a light brown glass-like material; MS (m/z, %): 284 (M^+, 6.8), 154 (3.5), 143 (100), 130 (23); IR (KBr, ν, cm^{-1}): 3410 and 3260 (indole NH, inter- and intramol. H-bonded), 1624 (lactam C=O), 1073 (C-O-C), 742 (o-disubstd. A ring); ^{1}H-NMR (δ, ppm): 1.7-2.6 (4H, m, C3-H_2 + C7-H_2), 3.03 (2H, t, J = 7.2 Hz, C3'-CH_2), 2.75-3.55 (3H, m, C6-H_2 + C3a-H), 3.70 (2H, t, J = 7.2 Hz, N-CH_2), 3.5-4.0 (2H, m, C2-H_2), 4.13 (1H, dt, J = 6.7 and 4.0 Hz, C7a-H), 7.01 (1H, d, J = 2 Hz, C2'-H), 7.05-7.4 (3H, m, C5'-H + C6'-H + C7'-H), 7 64 (1H, m, C4'-H), 8.46 (1H, br s, indole NH); ^{13}C-NMR (δ, ppm): 23.32 (C3'-$\underline{C}H_2$), 27.49 (C3), 31.88 (C7), 43.63 (C6), 44.75 (C3a), 48.77 (N-CH_2), 67.34 (C2), 75.42 (C7a), 111.38 (C7'), 112.43 (C3'), 118 56 (C4'), 119.07 (C5'), 121.74 (C2'), 122.27 (C6'), 127.43 (C3a'), 136.43 (C7a'), 171.03 (C4).

(±)-1,2,3a,4,5,7,8,13-Octahydrofuro[3,2-*a*]indolo[3,2-*h*]quinolizine (28)

To a solution of 26 (0.128 g, 0.45 mmole) in $CHCl_3$ (4.5 ml) $POCl_3$ (0.4 ml, 4.5 mmole) was added and heated under reflux for 1 h. After evaporation at 40°C the residue was treated with ice water (10 g) and decanted. The insoluble residue was treated again with water (2x10 ml) and decanted. The combined aqueous solutions were basified with 15 % aqueous

NaOH solution (1.8 ml) and extracted with CH_2Cl_2 (3x5 ml). The combined extracts were dried ($MgSO_4$) and evaporated at 40°C to yield the pure 28 as a yellow foam (0.100 g, 84 %); R_f: 0.56 (toluene-diethylamine 9:1 v/v); MS (m/z, %): 266 (M^+, 100), 265 (54), 238 (60), 237 (27), 236 (46), 235 (38), 209 (23); IR (KBr, ν, cm^{-1}): 3360 (indole NH, H-bonded), 1646 (C=C), 1056 (C-O-C), 745 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.92 (1H, dddd, J_{gem} = -12.0 Hz, J_{vic} = 11.8, 10.2 and 4.8 Hz, C4-H_a), 2.32 (1H, dddd, J_{vic} = 6.9, 3.0 and 3.0 Hz, C4-H_e), 2.6-3.4 (8H, m, C1-H_2 + C5-H_2 + C7-H_2 + C8-H_2), 3.90 (1H, ddd, J_{gem} = -8.5 Hz, J_{vic} = 8.0 and 8.0 Hz, C2-H_A), 4.18 (1H, ddd, J_{vic} = 7.5 and 4.2 Hz, C2-H_B), 4.38 (1H, dddd, J_{vic} = 10.2 and 6.0 Hz, J_{lr} = 2 and 2 Hz, C3a-H), 7.0-7.6 (4H, m, aromatic protons), 8.05 (1H, br s, indole NH); ^{13}C-NMR (δ, ppm): 21.80 (C8), 27.63 (C4), 29.53 (C1), 48.54* (C5), 50.68* (C7), 67.59 (C2), 76.03 (C3a), 107.60 (C13c), 110.85 (C12), 111.18 (C8a), 118.30 (C9), 119.48 (C10), 122.24 (C11), 126.32 (C8b), 128.96+ (C13b), 129.88+ (C13a), 136.70 (C12a).

Ethyl (±)-3a*H*,7*H*,17*H*-1,2,4,5,8,13-hexahydrofuro[3,2-*a*]indolo[3,2-*h*][1,2]oxazino[6,5-*j*]quinolizine-16-carboxylate (29)

To the stirred solution of 28 (2.13 g, 8 mmole) in CH_2Cl_2 (12 ml) aqueous NaOH (0.37 g in 4.8 ml water, 9.2 mmole) and solution of oxime of ethyl bromopyruvate (1.85 g, 8.8 mmole) in CH_2Cl_2 (4.8 ml) were added simultaneously at -5°C in 30 min, After the addition was complete the stirring was continued for 2 h at -5°C. After separation, the aqueous phase was extracted with CH_2Cl_2 (3x5 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield 29 (3.06 g, 97 %) as an orange foam which was pure enough for the next step. The analytical sample was purified by column chromatography on SiO_2 (cyclohexane-diethylamine 8:2 v/v, R_f: 0.36); MS (m/z, %): 395 (M^+, 24) 322 (24), 306 (100), 284 (24), 265 (98), 199 (20), 184 (20), 152 (22), 115 (66); IR (KBr, ν, cm^{-1}): 3400 (indole NH, H-bonded), 1718 (ester C=O, conjugd. with C=N), 1685 (C=N), 1282 (C-O-C), 745 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.30 (3H, t, J = 7.0 Hz, COO-CH_2-$\underline{C}H_3$), 4.32 (2H, q, COO-$\underline{C}H$-CH_3), 7.0-7 6 (4H, m, aromatic protons); ^{13}C-NMR (δ, ppm): 13.92 (COO-CH_2-$\underline{C}H_3$), 21.90 (C8), 27.59 (C4), 31.41 (C17), 34.70 (C1), 43.19 (C17a), 45.83* (C5), 48.17* (C7), 62.28 (COO-$\underline{C}H_2$-CH_3), 64.72 (C2), 79.78 (C3a), 96 (C13b), 112.14 (C12), 113.81 (C8a), 118.71 (C9), 119.86 (C10), 123.04 (C11), 125.62 (C8b), 131.93 (C13a), 137.47 (C12a), 145.40 (C16), 164.28 ($\underline{C}OOC_2H_5$).

13b-Epimers of Ethyl (±)-3-{1,2,3a3,4,5,7,8,13,13b,13c-decahydrofuro[3,2-*a*]-indolo[3,2-*h*]quinolizin-13cβ-yl}-2-hydroxyimino-propionate (30 and 31)

Compound 29 (2.96 g, 7.5 mmole) was hydrogenated in DMF (40 ml) over 10 % Pd/C (2.0 g) at ambient temperature and pressure. When the hydrogen consumption ceased (4 h, 180 ml), the catalyst was filtered and washed (DMF, 3x 5 ml). The combined solutions were evaporated at 50°C in *vacuo* to give a mixture of epimers. Compounds 30 and 31 were separated by column chromatography on SiO_2 (400 g, cyclohexane-diethylamine 7:3 v/v, R_f: 0.30 and 0.24 respectively.)

Compound 30, the 13bα epimer (1.19 g, 40 %); mp: 190-195°C decomp; MS (m/z, %): 397 (M^+, 20), 396 (10), 380 (21), 306 (14), 197 (36), 184 (100), 170 (27), 169 (84); IR (KBr, ν, cm^{-1}): 3400 (indole NH), 2700-2400 (NOH, very strong H-bond), 1712 (ester C=O, conjugd. with C=N), 742 (o-disubstd. A ring); ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ, ppm): 1.25 (3H, t, J = 7.0 Hz, $COO-CH_2-C\underline{H}_3$), 1.80 (1H, dddd, J_{gem} = -14.0 Hz, $J_{3aH,4e}$ = 2.2 Hz, $J_{4e,5e}$ = 2.0 Hz, $J_{4e,5a}$ = 2.8 Hz, C4-H_e), 1.92 (1H, ddd, J_{gem} = -13.4 Hz, $J_{1A,2A}$ = 9.8 Hz, $J_{1A,2B}$ = 8.0 Hz, C1-H_A), 2.29 (1H, dddd, $J_{3a,4a}$ = 3.4 Hz, $J_{4a,5a}$ = 12.5 Hz, $J_{4a,5e}$ = 5.5 Hz, 4-H_a), 2.50 (1H, d, J_{gem} = -13.2 Hz, C13c-$C\underline{H}_AH_B$), 2.52 (1H, ddd, $J_{1B,2A}$ = 3.7 Hz, $J_{1A,2B}$ = 7.5 Hz, C1-H_B), 2.55 (1H, ddd, J_{gem} = -10.5 Hz, $J_{7a,8a'}$ = 11.2 Hz, $J_{7a,8e'}$ = 3.6 Hz, C7-H_a), 2.61 (1H, dddd, J_{gem} = -14.5 Hz, $J_{7e,8e'}$ = ~ 1Hz, $J_{8e',13bH}$ = ~ 2 Hz, C8-H_e,), 2.62 (1H, ddd, J_{gem} = -11.0 Hz, C5-H_a), 2.73 (1H, ddd, C5-H_e), 2.87 (1H, dddd, $J_{7e,8a'}$ = 5.1 Hz, $^7_{8a,13bH}$ = 2 2 Hz, C8-H_a,), 2.97 (1H, d, C13c-$CH_A\underline{H}_B$), 3.02 (1H, ddd, C7-H_e), 3.50 (1H, br s, C13b-H), 3.505 (1H, dd, C3a-H), 3.77 (1H, ddd, J_{gem} = -8.2 Hz, C2-H_A), 4.00 (1H, ddd, C2-H_B), 4.14 + 4.16 (2x 1H, dq, J_{gem} = -10.5 Hz, J_{vic} = 7.0 Hz, $COO-C\underline{H}_2-CH_3$), 6.97 (1H, ddd, $J_{9,10}$ = 7.5 Hz, $^7_{10,11}$ = 7.0 Hz, $J_{10,12}$ = 1.0 Hz, C10-H), 7.04 (1H, ddd, $J_{11,12}$ = 7.8 Hz, $^7_{9,11}$ = 1.4 Hz, C11-H), 7.36 (1H, br s, C9-H), 7.39 (1H, br d, C12-H), 9.76 (1H, br s, indole NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 13.92 ($COO-CH_2-\underline{C}H_3$), 21.65 (C8), 24.36 (C13c-$\underline{C}H_2$), 25.29 (C4), 34.20 (C1), 47.42 (C13c), 50.98 (C5), 53.66 (C7), 60.90 ($COO-\underline{C}H_2-CH_3$), 63.06 (C13b), 64.75 (C2), 79.04 (C3a), 111.03 (C8a), 111.40 (C12), 117.50 (C9), 118.51 (C10), 120.73 (C11), 126.46 (C8b), 133.02 (C13a), 136.85 (C12a), 150.10 (C=NOH), 164.66 ($\underline{C}OO-C_2H_5$).

Compound 31. the 13bβ epimer (0.51 g, 17 %) was a light yellow foam; MS (m/z, %): 397 (M^+, 22), 396 (10), 380 (17), 306 (68), 197 (25), 184 (100), 170 (20), 169 (20); IR (KBr, ν, cm^{-1}): 3362 (indole NH, H-bonded), 2805 and 2750 (Bohlmann bands), 1720 (ester C=O, conjugd. with C=N), 1685

(C=N), 740 (o-disubstd. A-ring); ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ, ppm): 1.34 (3H, t, J = 7.0 Hz, COO-CH_2-$\underline{CH_3}$), 1.65-1.8 (3H, m, C4-H_2 + C1-H_A), 1.85 (1H, ddd, J_{gem} = -13.0 Hz, J_{vic} = 10.0 and 7.5 Hz, C1-H_B), 2.41 (1H, ddd, J_{gem} = -11.5 Hz, J_{vic} = 9.8 and 4.3 Hz, C5-H_a), 2.66 (1H, ddd, J_{gem} = -11 Hz, J_{vic} = 12 and 4 Hz, C7-H_a), 2.69 (1H, m, C8-H_e), 2.91 (1H, ddd, J_{vic} = 4.4 and 4.1 Hz, C5-H_e), 2.95 (1H, d, J_{gem} = -13.6 Hz, C13c-$\underline{CH_A}H_B$), 2.95 (1H, m, C8-H_a), 3.13 (1H, m, C7-H_e), 3.39 (1H, d, C13c-$CH_A\underline{H_B}$), 3.49 (1H, t, J = 1.8 Hz, C13b-H), 3.67 (1H, ddd, J_{gem} = -8.5 Hz, J_{vic} = 8.2 and 7.5 Hz, C2-H_A), 3.76 (1H, ddd, J_{vic} = 10.0 and 4.2 Hz, C2-H_B), 3.99 (1H, dd, J_{vic} = 9.3 and 6.7 Hz, C3a-H), 4.28 + 4.30 (2x1H, dq, J_{gem} = -10.8 Hz, J_{vic} = 7.0 Hz, COO-$\underline{CH_2}$-CH_3), 7.01 (1H, ddd, $J_{9,10}$ = 7.6 Hz, $J_{10,11}$ = 7.0 Hz, $J_{10,12}$ = 1.0 Hz, C10-H), 7.08 (1H, ddd, $J_{11,12}$ = 7.9 Hz, $J_{9,11}$ = 1.3 Hz, C11-H), 7.30 (1H, ddd, $J_{9,12}$ = 0.8 Hz, C12-H), 7.40 (1H, br d, C9-H), 9.90 (1H, br s, indole NH); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 14.09 (COO-CH_2-$\underline{CH_3}$), 21.73 (C8), 27.15 (C4), 29.77 (C1), 34.89 (C13c-$\underline{CH_2}$), 49.07 (C13c), 51.67 (C5), 53.64 (C7), 61.23 (COO-$\underline{CH_2}$-CH_3), 64.73 (C13b), 65.11 (C2), 83.06 (C3a), 110.04 (C8a), 111.01 (C12), 117.61 (C9), 118.86 (C10), 121.11 (C11), 126.50 (C8b), 133.38 (C13a), 136.10 (C12a), 151.21 (C=NOH), 164.47 ($\underline{C}OO-C_2H_5$).

Methyl (±)-17β,21-Epoxy-14,15-dihydro-14β-hydroxy-eburnamenine-14α-carboxylate [(±)-Desmethoxy cuanzine] (2) and its 14-Epimer (32)

Compound 30 (0.139 g, 0.35 mmole) was added to a 0.1 M solution of CH_3ONa in dry CH_3OH (2 ml) and boiled under argon for 4 h. After cooling the solution was treated with acetic acid (0.05 ml) and evaporated in vacuo at 40°C. To the residue acetic acid (0.07 ml), water (1.1 ml), conc. H_2SO_4 (0.04 ml) and $Na_2S_2O_5$ (0.247 g, 1.3 mmole) were added and boiled under argon in an oil-bath at 120°C for 7 h. After cooling the solution was diluted with water (1.5 ml), basified with conc. NH_4OH (0.25 ml) to pH 9 and extracted with dichloromethane-methanol (9:1 v/v, 5x2 ml). The combined organic phases were dried ($MgSO_4$) and evaporated to give a mixture of 14-epimers (0.085 g). The analytical pure 2 and 32 were obtained by column chromatography on SiO_2 (10 g, cyclohexane-dietnylamine 8:2 v/v, R_f 0.56 and 0.31, respectively).

Compound 2 (0.045 g, 35 %); mp: 204-208°C; MS (m/z, %): 368 (M^+, 100), 367 (47), 266 (48), 265 (18), 224 (79); IR (KBr, ν, cm^{-1}): 3500-2400 (OH, very strong H-bond), 1740 (C=O), 1074 (C-O-C), 736 (o-disubstd. A ring); ^{1}H-NMR (400 MHz, δ, ppm): 1.62 (1H, ddd, J_{gem} = -12.5 Hz, J_{vic} = 8.3 and

3 5 Hz, C2O-H_β), 1.65 (1H, ddd, J_{gem} = -13 Hz, $J_{17\beta,18\beta}$ = 6.5 Hz, $J_{18\beta,19\alpha}$ = 3.O Hz, $J_{18\beta,19\beta}$ = 2.8 Hz, C18-H_β), 1.72 (1H, dddd, $J_{17\beta,18\alpha}$ = 1O.5 Hz, $J_{18\alpha,19\alpha}$ = 5.4 Hz, $J_{18\alpha,19\beta}$ = 11.5 Hz, C18-H_α), 2.26 + 2.48 (2x 1H, d J_{gem} = -14.2 Hz, C15-H_2), 2.56 (1H, ddd, J_{gem} = -11.6 Hz, C19-H_α), 2.59 (1H, ddd, C19-H_β), 2.6O (1H, dddd, J_{gem} = -16.O Hz, $J_{5\alpha,6\alpha}$ = 4.5 Hz, $J_{5\beta,6\alpha}$ = 2.O Hz, $J_{3\alpha,6\alpha}$ = 2.3 Hz, C6-H_α), 2.84 (1H, ddd, J_{vic} = 1O.5 and 8.5 Hz, C2O-H_α), 2.95 (1H, dddd, $J_{5\alpha,6\beta}$ = 1O.5 Hz, $J_{5\beta,6\beta}$ = 7.5 Hz, $J_{3\alpha,6\beta}$= 2.5 Hz, C6-H_β), 3.25-3.4O (2H, m, C5-H_2), 3.86 (3H, s, COO-CH_3), 3.95-4.1 (2H, m, C21-H_2), 4.42 (1H, dd, C3-H_α), 4.49 (1H, dd, C17-H_β), 4.65 (1H, br s, OH), 7.O5-7.55 (4H, m, aromatic protons); ^{13}C-NMR (δ, ppm): 17.28 (C6), 27.76 (C18), 34.45 (C2O), 42.62 (C19), 42.86 (C15), 43.68 (C16), 5O.71 (C5), 54.22 (COO-$\underline{C}H_3$), 56.35 (C3), 63.91 (C21), 74.36 (C17), 82.11 (C14), 1O6 11 (C7), 11O.49 (C12), 118.68 (C9), 12O 53 (C1O), 121.99 (C11), 128.87 (C8), 131.27 (C2), 134.5O (C13), 173.88 ($\underline{C}$OO-CH_3).

Compound 32 (0.O18 g, 14 %); amorphous; MS (m/z, %): 368 (M^+, 1OO), 367 (43), 266 (38), 265 (26), 224 (42); IR (KBr, ν, cm^{-1}): 3220 (br, OH, H-bonded), 1748 (C=O), 126O (C-O-C), 1O82 (C-O-C), 745 (o-disubstd. A-ring); ^{1}H-NMR (4OO MHz, δ, ppm): 1.63 (1H, dddd, J_{gem} = -13 Hz, $J_{17\beta,18\beta}$ = 6.5 Hz, $J_{18\beta,19\alpha}$ = 3 1 Hz, $J_{18\beta,19\beta}$ = 3.O Hz, C18-H_β), 1.64 (1H, dad, J_{gem} = -12.5 Hz, J_{vic} = 8.O and 3.5 Hz, C2O-H_β), 1.7O (1H, dddd, $J_{17\beta,18\alpha}$= 1O.2 Hz, $J_{18\alpha,19\beta}$ = 12.O Hz, $J_{18\alpha,19\alpha}$ = 4 5 Hz, C18-H_α), 2.16 (1H, d, J_{gem} = -14.8 Hz, C15-H_A), 2 56 (1H, ddd, J_{gem} = -11.6 Hz, C19-H_α), 2.59 (1H, dddd, J_{gem} = -16.O Hz, $J_{5\alpha,6\alpha}$ = 5.6 Hz, $J_{5\beta,6\alpha}$ = ~ 1 Hz, $J_{3\alpha,6\alpha}$ = 2.2 Hz, C6-H_α), 2.63 (1H, ddd, C19-H_β), 2.8O (1H, ddd, J_{vic} = 1O.2 Hz and 8.6 Hz, C2O-H_α), 2.81 (1H, d, C15-H_β), 2.96 (1H, dddd, $J_{5\alpha,6\beta}$ = 11.5 Hz, $J_{5\beta,63}$ = 6.5 Hz, $J_{3\alpha,6\beta}$ = 2.5 Hz, C6-H_β), 3 26 (1H, ddd, J_{gem} = -13.6 Hz, C5-H_α), 3.34 (1H, ddd, C5-H_β), 3.71 (3H, s, COO-$\underline{C}H_3$), 3.91 (1H, dd, C17-H_β), 3.9-4.O (2H, m, C21-H_2), 4.35 (1H, dd, C3-H_α), 7.1-7.5 (4H, m, aromatic protons); ^{13}C-NMR (δ, ppm): 17.18 (C6), 28.O8 (C18), 35.33 (C2O), 42.74 (C19), 44.98 (C16), 45.22 (C15), 5O 99 (C5), 53.76 (COO-$\underline{C}H_3$), 55.91 (C3), 63.76 (C21), 74.14 (C17), 82.2O (C14), 1O6.28 (C7), 111.6O (C12), 118.42 (C9), 12O.53 (C1O), 121.9O (C11), 128.64 (C8), 132.13 (C2), 135.75 (C13), 172.77 ($\underline{C}$OO-CH_3).

(±)-3-[2-Hydroxy-ethyl]-1-[2-(indol-3-yl)-ethyl]-3,4,5,6-tetrahydropyridin-2,1H)-one (27)

To a stirred solution of 25 (O.1OO g, O.35 mmole) in dry methanol (5 ml) nickel(II) chloride hexahydrate (O.O12 g, O.O5 mmole) and then

sodium borohydride (0.083 g, 2.2 mmole) was added in small portions. After the addition was complete (2 h), stirring was continued for 1 h. To the mixture acetone (2 ml) was added, then it was stirred (30 min) and evaporated to dryness in *vacuo*. The residue was treated with water (5 ml) and extracted with CH_2Cl_2 (3x5 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a mixture of 26 and 27 which were separated by column chromatography on SiO_2 (10 g, cyclohexane-diethylamine 8:2 v/v, R_f: 0.40 and 0.26, respectively) to yield 26 (0.047 g, 47 %) and 27 (0.024 g, 27 %).

Compound 27 was a light brown glass-like material; MS (m/z, %): 286 (M^+, 4.8), 144 (21), 143 (100), 130 (17); IR (KBr, ν, cm^{-1}): 3400 (indole NH, sh, H-bonded), 3270 (OH, H-bonded), 1612 (lactam C=O), 743 (o-disubstd. A-ring); ^{1}H-NMR (δ, ppm): 1.0-2.2 (7H, m, C4-H_2 + C5-H_2 + C3-H_2 + OH), 2.48 (1H, m, C3-H), 2.8-3.9 (8H, m, C6-H_2 + N-CH_2 + C3'-CH_2 + CH_2-OH), 7.02 (1H, d, J=2 Hz, C2'-H), 7.05-7.45 (3H, m, C5'-H + C6'-H + C7'-H), 7.64 (1H, m, C4'-H), 8.40 (1H, br s, indole NH); ^{13}C-NMR (δ, ppm): 21.77 (C5), 22.93 (C3'-CH_2), 28.44 (C4), 35.56 (C3-CH_2), 41.17 (C3), 48.83 (C6 + N-CH_2), 61.70 (CH_2-OH), 111.20 (C7'), 112.52 (C3'), 118.41 (C4'), 118.96 (C5'), 121.62 (C2'), 122.11 (C6'), 127.32 (C3a'), 136.22 (C7a'), 173.29 (C2).

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