CHEMISTRY OF INDOLES CARRYING A BASIC FUNCTION. PART IV[1] SYNTHESIS OF D-NORERGOLINE AND ERGOLINE RING BY STOBBE REACTION

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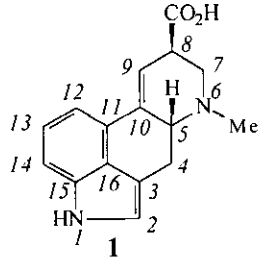
Abstract — Starting from Uhle's ketone (**2**), pentacyclic lactone derivatives with D-norergoline ring (**13** and **14**) have been prepared by an unusual intramolecular Stobbe reaction of a succinic diester derivative (**3a**). The preparation of ergoline ring (**1**) itself was also achieved through modification of the reaction conditions.

INTRODUCTION

Before the first successful synthesis of lysergic acid (**1**) by the Woodward-Kornfeld group in 1956,[2] two pioneering researchers had attempted to reach this goal by applying a legendary starting material - Uhle's ketone (**2**). Uhle's approach was described in a preliminary communication,[3] but the final version has never been published. In Uhle's synthesis the key intermediate was supposed to be a diethyl succinate derivative (**3b**), which should have been appropriate for an intramolecular Stobbe condensation. The second approach starting from **2** was elaborated by the directions of Stoll as follows. Compound (**2**) was transformed into Schiff-base (**4**),[4] then **4** allegedly afforded the desired cyclised ergolene derivative (**5**). *Two years later* the structures of **4** and **5** were corrected.[5] Instead of an intramolecular Stobbe reaction an internal acylation occurred in the side chain, and the end-product proved to be a pyrrolidone derivative (**6**).



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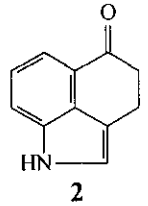

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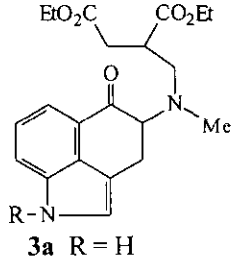
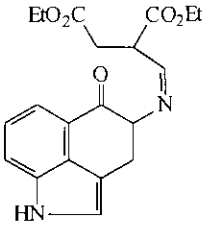


3a R = H
3b R = Ac



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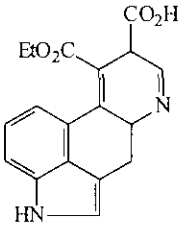

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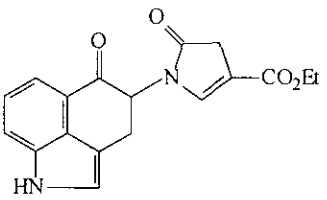


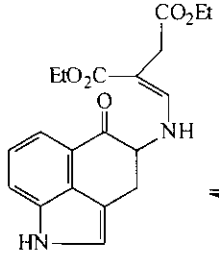
6

Early in the seventies Bowman *et al.*[6] reinvestigated a few results of Uhle's synthesis. They established that one of the key steps, alkylation of several types of amines with the 4-bromo derivative of **2** had always failed but for one case. Only aniline afforded a C-N bond but at the same time the C-ring was oxidized into an α,β-unsaturated ketone on the air.

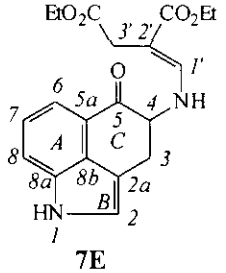
In connection with our attempt to find reasonable total synthesis of **1** we wished to reinvestigate the ring D cyclisation *via* intramolecular Stobbe condensation of succinic diester derivative (**3a**). Because of the dubiuos results found in the course of alkylation of appropriate amines with 4-bromo derivatives of Uhle's ketone, in the preparation of intermediate (**3a**) useful elements of the Stoll's approach was applied.

RESULTS AND DISCUSSION

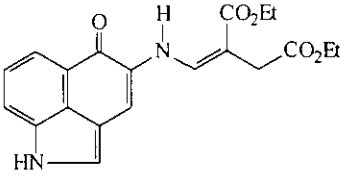
Our starting material (**2**) was prepared by Goto's method.[7] In a one-pot reaction **2** was allowed to react with *n*-amyl nitrite then the α-nitroso ketone (or oxime) formed was reduced into amine. [A very recent report of Rapoport *et al.*[8] shows the continued interest in this amino ketone as an important intermediate of ergoline derivatives]. In the final step the latter was condensed with diethyl formylsuccinate.[9] After working up the reaction mixture, enamine (**7**)[10] was obtained as an isomeric mixture. The dominant **7Z**-isomer was separeted in nearly pure form as pale pink crystals in 20% yield, but after a few days it isomerized in $CDCl_3$ (during NMR examination) to **7E**-isomer and the ratio of **7Z**:**7E** in the equilibrium turned out to be about 3:2. Similar ratio can also be observed in the NMR spectrum of the crude, pure product which was obtained after a chromatographic purification (36% yield). In the hope of obtaining any kind of cyclization, **7** was treated with KO^{t}Bu in a mixture of ^{t}BuOH and EtOH for 45 min at room temperature. Nevertheless, we were able to isolate neither the cyclized product (**5**), nor (**6**) or any other tetracyclic compound, only the C-ring oxidized derivative (**8**) was obtained in 27% yield as red crystals.



7Z



7E



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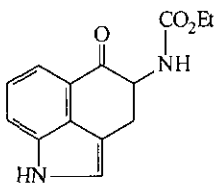
The driving force of the oxidation is probably the low energy of the fully conjugated ABC-ring with carbonyl group (see later). The same oxidized product (**8**) was formed in 38% yield, when enamine (**7**) was tried to convert into the corresponding *N*-methyl derivative with iodomethane (MeI, K_2CO_3; 4 h, rt).
For further transformations we decided to protect the nitrogen atom of enamine as carbamate *via* acylation with ethyl chloroformate (THF + H_2O + $KHCO_3$; 24 h, rt). The acylation proceeded smoothly, however, the diester side chain was eliminated from the molecule to yield **9** in 54% yield.
As an other branch of transformations of **7**, a few reductive methods were examined to saturate the enamine function. Catalytic hydrogenation (H_2, 10% Pd/C, rt, H_2O + AcOH or DMF) gave an unseparable complex mixture. The NMR spectra gave only limited structural information: the double bond of enamine remained intact, however, the carbonyl function was reduced into hydroxyl group (**10**).



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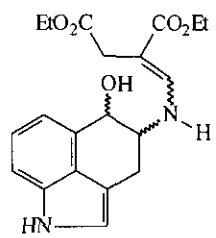

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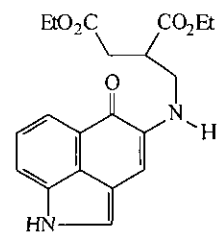

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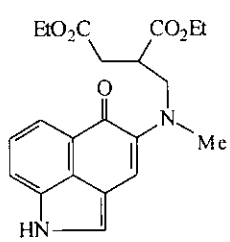
When the enamine mixture (**7**) was treated with $NaCNBH_3$ (THF + MeOH + HCl or acetic acid) the successful reduction of the double bond was accompanied by undesired oxidation of ring C leading to **11**, which might have occurred during the work-up by air oxidation. This oxidation process could be avoided, if the $NaCNBH_3$ reduction was performed in acetonitrile and acetic or formic acid, and the mixture - without isolation - was treated with aqueous formaldehyde (30 min). After a simple work-up (extraction, column chromatography) compound (**3a**) was obtained as diastereomeric mixture in 70% yield. Our derivative (**3a**) proved to be the *N*-desacetyl analog of Uhle's key intermediate (**3b**).
In order to obtain the ergolene ring by intramolecular Stobbe condensation, about a dozen of bases (e.g. KO^{t}Bu/^{t}BuOH, NaH/benzene + EtOH, K_2CO_3/DMF, KF/Al_2O_3, TlOEt/THF, etc.) were tried without any success. All runs afforded compound (**12**) as a red oil (yield: 20-40%).



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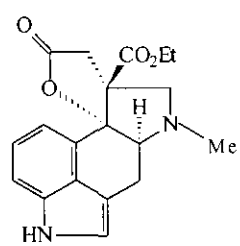
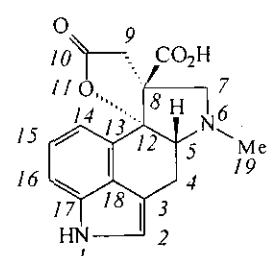


13



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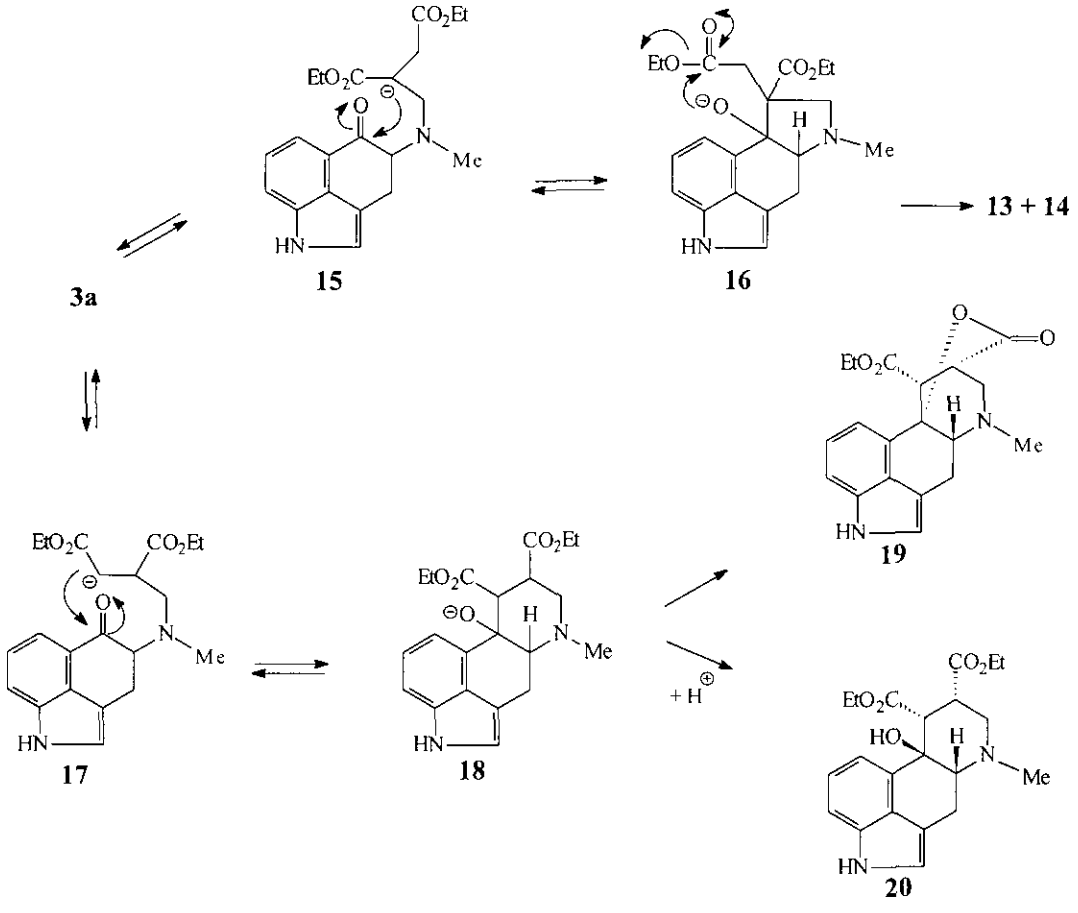
However, treatment of **3a** with KH (14 equivalents) in the presence of 18-crown-6 (8 equivalents) in THF (30 min, 0 °C) afforded two isomeric pentacyclic lactones (**13**,[11] yield: 18%; **14**, yield: 16%) after work-up

and subsequent column chromatography. Compound (**12**) was also isolated in 15-20% yield. The acid derivative (**14**) was presumably formed by hydrolysis during the work-up of the reaction mixture.

Based on the generally accepted mechanism of Stobbe condensation,[12] a possible reaction sequence leading to lactones (**13** and **14**) may be the following. In the first step carbanion (**15**) is formed, then in the first cyclization step this anion reacts with the carbonyl function. The formed alkoxide anion (**16**) attacks at the carbonyl group of the ester, affording lactone isomers. Because of the lack of hydrogen at the carbon bearing the carboxyl or carboxylate group, the reaction stops in the lactone phase, which is generally an intermediate of Stobbe condensation leading to unsaturated half-ester.



In order to rationalize some of the chemical behaviors described in this paper, we performed some calculations. The question is, why only the five membered lactones (**13** and **14**) were formed, and not the expected six membered lactone (e.g. **19**)? Is it a big energy barrier between the two possible reaction routes? Assuming a product-like transition state we calculated the relative stability of **13** and **19** by the AM1,[13] MNDO[14] and PM3[15] methods. Calculations revealed that **19** is less stable by 1-2 kcal/mol than **13** at *each* semiempirical level. This relatively small energy difference does not explain why we could not find the expected **19** or its half-ester derivatives at all, thus we intend to study the problem later on.

Being aware of the mechanism of the Stobbe condensation,[12] as a working hypothesis we assume that equilibrium among compounds **15-18** is pushed irreversibly towards **13** and **14**. Since the OLi bond is much stronger (81.4 kcal/mol) than the OK or ONa bonds (66.0 and 61.3 kcal/mol, respectively)[16] we tried to stabilize the intermediate **18** as its Li salt. Therefore the so called superbase (a mixture of *n*-BuLi solution and KO^{t}Bu) was used in THF at -70 °C. After work-up we could, although in moderate yield (22%), indeed isolate the expected compound **20** as a result of an intramolecular aldol-type reaction.
The optimisation of the reaction conditions and transformation of **20** into natural products having ergoline skeleton are in progress.

Structure elucidation

1) IR spectra were taken on a NICOLET Magna 750 spectrometer, using KBr pellets. 128 scans at 4 cm^{-1} resolution were accumulated, water vapour and carbon dioxide bands were substracted. As C=O groups of esters and ketones, C=C groups of olefinic and aromatic systems absorb in a fairly narrow frequency range, considerable overlaps occured, which needed a proper decomposition. In order to determine the number of bands the second derivative of the spectrum has been used. For the calculation of band positions, intensities and bandshapes a least-squares band fitting program has also been applied in some cases.
To distinguish between the diethoxycarbonyl-1′-propylamine and diethoxycarbonyl-1′-propenylamine derivatives two characteristic spectral data have been found. Although C1'=C2' stretching resulted in a fairly weak absorbtion at *ca.* 1615 cm^{-1}, the "unexpectedly" low frequency (1680 cm^{-1}) of ester C=O group, caused by conjugation with C1′= C2′, proved the existence of the C=C double bond. This νC=O ester band was detected using second derivative and curve fitting techniques, as the ketone νC=O appaered in the close neigbourhood of it. For the recognition of compounds with a fully conjugated ABC ring with ketone group the νC=O frequency of the α,β-unsaturated ketone proved to be the best marker. Its frequency was lowered by 50 cm^{-1} due to the conjugation with the newly formed double bond in ring C. Compering the spectra of the compound with different C ring (with or without double bond) three characteristic bands, referring to the fully conjugated ABC ring system has been found at around 1590, 1560 and 1520 cm^{-1}. Compounds (**13**) and (**14**) had completely new spectral features, the bands at 1767 cm^{-1} and 1762 cm^{-1}, respectively, appeared due to the formation of γ-lactone structures in the molecules.
2) The proton and carbon assignments (see Experimental) were made by one- and two-dimensional NMR (proton-proton decoupling, COSY, HETCOR and HMBC) methods. The stereochemistry of the double bond in products (**7Z**, **7E** and **8**) was identified by NOE experiments.
Isomeric lactones (**13** and **14**) gave characteristically different proton and carbon spectra. In both compounds presence of two (fused) pentacyclic rings as well as their anellation with ring C was deduced from characteristic long-range carbon-proton correlations appearing in the INEPT long-range and HMBC experiments. From the long-range hetero-correlations those of C-8 with H-5, H-7 and H-9, morover the connections between C-12 and H-4, H-5, H-7, H-9, H-14 protons are of diagnostic value. In addition, correlations of the carboxylic carbon with H-7 and H-9 are also of interest. In both products the *cis* junction of the pentacyclic rings are established by observing the sizeable NOE effect between H-9α and H-7α

protons. Inspection of the Dreiding models reveals that in this stereochemistry the H-9β and H-7β hydrogens are in W-arrangement which is in accord with the observed long-range couplings (1.2 and 1.0 Hz in **13** and **14**, respectively). The noteworthy difference in the chemical shift of the H-5 proton in compounds (**13**) and (**14**) (3.79 and 2.88 ppm, respectively) indicates the different orientation of this proton. The deshielding influence of the nitrogen lone pair may be responsible for the sizeable downfield shift of H-5 in **13** compared to its position in **14**. This stereochemistry is consistent with the presence of an NOE connection between the H-9β and H-14 protons in **13**. Moreover, the rather highfield resonance of the ester methyl protons in this compound (0.36 ppm) can be ascribed to the fact that these protons are positioned above the plane of aromatic rings A and B.

The NOE effects and the carbon chemical shifts suggest that the N-Me group is equatorially (i.e. β) oriented in both **13** and **14**. Due to the γ-gauche interaction between C-4 and N-Me carbons in **13** the ^{13}C values (17.20 and 36.01 ppm, respectively) are shifted upfield in comparison with the corresponding values of **14** (21.99 and 39.60 ppm) where no such interaction exists. The molecular model also reveals a γ-gauche relation between C-4 and C-7 carbons in compound (**13**). As a result the chemical shift of C-7 is upfield compared to its value in **14** (63.72 and 68.62 ppm, respectively). All these observations corroborate that the two compounds are isomers at the C-5 chiral centre.

The formation of a six-membered D ring in compound (**20**) was deduced from the H-7, H-8, H-9 proton sequence in the ^{1}H NMR spectrum and from the long-range heterocorrelations of these protons with carbons C-10 and C-5. Similarly, the correlation of H-5 proton with C-7, C-9 and C-11 carbons corroborates the presence and size of ring D. The diequatorial orientation of carbethoxy substituents at C-8 and C-9 follows from the coupling constant of H-8 and H-9 protons (12.1 Hz). The $J_{4,5}$ coupling values (5.9 + 10.5 Hz) reflect the axial orientation of the H-5 proton with respect to ring C. *Cis* C/D ring anellation was found on the basis of the NOE effects of the C10-OH with H-5, H-8 and H-12 protons. An NOE correlation was also found between H-9 and H-7_{α} (axial) protons. The equatorial position of the N-Me group follows from the NOE effect of the methyl and H-4 protons. Finally, the γ-gauche effect of C-4 carbon with C-7 and C-9 carbons causes an upfield shift (14.32 ppm) in comparasion with the corresponding carbons in related compounds.

EXPERIMENTAL SECTION

Mps are uncorrected. Mass spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos MS-902 mass spectrometer. NMR measurements were carried out on a Varian Unity Inova (400 MHz) instrument. Chemical shifts are given relative to TMS = 0.00 ppm.

Calculations

Calculations were carried out by the Gaussian 94 package.[17] Geometries were optimized at the HF/6-31G* level. Calculation of the second derivatives ensured that real minima were obtained on the potential

energy surface. Improved energies were obtained at the MP2/6-31G*//HF/6-31G* level. The NMR shielding tensors (in ppm) were calculated by GIAO scheme with the 6-311+G** basis HF/6-31G* optimized geometries. Semiempirical calculations were carried out by using the AM1, MNDO and PM3 Hamiltonians.

Synthesis

Z and E N-(5-Oxo-1,3,4,5-tetrahydrobenz[c,d]indol-4-yl)-2',3'-diethoxycarbonyl-1'-propenylamine (7Z and 7E)

To a solution of ketone (**2**) (1.2 g; 7.0 mmol) in ^{t}BuOH (24 mL) at rt, KO^{t}Bu (0.84 g; 7.0 mmol) was added, and the mixture was stirred for 15 min at 60 °C. After cooling to rt *n*-amyl nitrite (1.5 mL; 12.8 mmol) was added to the mixture and the mixture was stirred for 0.5 h. (After a few mins precipitation of yellow crystals could be observed). The mixture was cooled to 0 °C with ice-bath and diluted with a mixture of water (22.5 mL) and acetic acid (12 mL), then tin powder (2.25 g; 20.0 mmol) was added and the mixture stirred for 15-20 min. While stirring and cooling $NaOAc{\cdot}3H_2O$ (22.5 g; 165.3 mmol) and diethyl formylsuccinate (1.5 mL; 7.4 mmol) were added to the reaction mixture. The temperature was allowed to warm up rt and the mixture was stirred for 2 h. The reaction mixture was poured to a mixture of ethyl acetate (300 mL), water (75 mL) and saturated $NaHCO_3$ solution (25 mL). After extraction the phases were separated and the organic phase was washed with brine (2x100 mL) and water (3x50 mL), dried (Na_2SO_4) and evaporated. The residue was treated (decantation) with hexane (3x50 mL) to remove the excess of aldehyde reagent then the residue was chromatographed (eluent: hexane - ethyl acetate 2:1; adsorbent: silicagel, Merck 9385). The pure oil (0.93g, 36%) was crystallised from a mixture of hexane + ethyl acetate + *i*-propanol (10 + 10 + 2 mL) to give **7Z** (0.53 g, 20.4%), mp 135-136 °C [lit., mp[4] 135-137 °C]. IR (KBr): 3387 (νNH indole), 3315 (νNH enamine), 1726 (νC=O unconjugated ester), 1683 (νC=O conjugated ester), 1677 (νC=O ketone), 1615 (νC=C), 1610, 1458 (νC_{Ar}-C_{Ar}), 1235 (ν_{as}COC ester), 1040 cm^{-1} (ν_sCOC ester). MS (*m/z*, %): 370 (71.7, M^+), 297 (100), 251 (15.9), 221 (10.6), 197 (48.6), 169 (60.1), 130 (23.8), 115 (17.6). ^{1}H NMR ($CDCl_3$), δ: 1.26 (6H, t, *J*= 7.0 Hz, $CO_2CH_2CH_3$), 3.04 (1H, d, *J*=16.3 Hz, H3'-A), 3.10 (1H, m, *J*=15.3 + 10.5 + 1.6 Hz, H3-A), 3.17 (1H, d, *J*=16.3 Hz, H3'-B), 3.48 (1H, dd, *J*=15.3 + 6.9 Hz, H3-B), 4.15 (1H, m, H-4), 4.19 (4H, m, $CO_2CH_2CH_3$), 6.68 (1H, d, *J*=13.1 Hz, H-1'), 7.10 (1H, dd, *J*=1.6 + 1.7 Hz, H-2), 7.25 (1H, dd, *J*=7.3 + 7.8 Hz, H-7), 7.55 (1H, d, *J*=7.8 Hz, H-8), 7.59 (1H, d, *J*=7.3 Hz, H-6), 8.32 (1H, dd, *J*=13.1 + 6.5 Hz, NH), 8.82 (1H, br s, H-1); NOE: 6.11 (NH) → 3.04 (H3'-A), 3.17 (H3'-B), 4.15 (H-4). ^{13}C NMR ($CDCl_3$) δ: 14.27+14.40 ($CO_2CH_2CH_3$), 29.12 (C-3), 35.99 (C-3'), 59.29+60.50 ($CO_2CH_2CH_3$), 62.66 (C-4), 89.96 (C-2'), 107.79 (C-2a), 116.53 (C-8), 116.71 (C-6), 121.49 (C-2), 123.20 (C-7), 124.20 (C-5a), 131.18 + 134.55 (C-8a + C-8b), 150.31 (C-1'), 169.29 + 173.51 ($CO_2CH_2CH_3$), 194.54 (C-5).

The NMR data of minor isomer **7E** was determined in the equilibrium of the solution.

^{1}H NMR ($CDCl_3$), δ: 1.26 (6H, t, *J*= 7.0 Hz, $CO_2CH_2CH_3$), 3.05 (1H, m, *J*=15.1 + 10.2 + 1.4 Hz, H3-A), 3.34 (1H, d, *J*=16.0 Hz, H3'-A), 3.39 (1H, d, *J*=16.0 Hz, H3'-B), 3.55 (1H, dd, *J*=15.2 + 7.0 Hz, H3-B), 4.25 (1H, m, H-4), 4.10-4.20 (4H, m, $CO_2CH_2CH_3$), 6.11 (1H, dd, *J*=14.0 + 4.9 Hz, NH), 7.12 (1H, dd, *J*=1.4 + 1.7 Hz, H-2), 7.28 (1H, dd, *J*=7.7 + 7.2 Hz, H-7), 7.55 (1H, d, *J*=14.0 Hz, H-1'), 7.55-7.60 (2H,

m, H-6 + H-8), 8.90 (1H, br s, H-1); NOE: 6.11 (NH) → 4.25 (H-4), 7.55 (H-1′). ^{13}C NMR ($CDCl_3$), δ: 14.21 + 14.58 ($CO_2CH_2CH_3$), 29.69 (C-3), 30.99 (C-3′), 59.72 + 60.88 ($CO_2CH_2CH_3$), 61.90 (C-4), 93.78 (C-2′), 107.66 (C-2a), 116.53 (C-8), 116.74 (C-6), 121.53 (C-2), 123.20 (C-7), 124.10 (C-5a), 131.30 + 134.52 (C-8a + C-8b), 146.05 (C-1′), 168.80 + 172.06 ($CO_2CH_2CH_3$), 194.54 (C-5).

N-(5-Oxo-1,5-dihydrobenz[c,d]indol-4-yl)-2′,3′-diethoxycarbonyl-1′-propenylamine (**8**)

To a solution of **7** (37 mg; 0.1 mmol) in a mixture of ^{t}BuOH (2 mL) and EtOH (8 mL) at rt, KO^{t}Bu (33 mg; 0.27 mmol) was added and the mixture was stirred for 45 min. (The color of the mixture turned into red in a moment). The mixture was treated with a few drops of acetic acid (pH 5-6), then the solvents were evaporated under reduced pressure. The residue was dissolved in a mixture of chloroform (50 mL) and water (20 mL) and the pH was adjusted to 8-9 with saturated $NaHCO_3$ solution. The phases were separated and the organic phase was washed with water (2x5 mL), dried (Na_2SO_4) and evaporated. The residue (31 mg) was chromatographed (eluent: chloroform - MeOH 100:2.5) to yield **8** as red crystals (10 mg; 27%), mp 185-186 °C [lit., mp[4] 238-240 °C].

IR (KBr): 3350 (sh, νNH indole), 3159 (νNH enamine, H-bonded), 1734 (νC=O unconjugated ester), 1682 (νC=O conjugated ester), 1633 (νC=O conjugated ketone), 1612 (νC=C), 1589, 1560, 1522 (νC_{Ar}-C_{Ar}), 1205, 1180 (ν_{as}COC ester), 1100 cm^{-1} (ν_sCOC ester). MS (*m/z*, %): 368 (100, M^+), 295 (77.6, M-73), 265 (8.9), 249 (23.2), 221 (64.3, M-73-74), 195 (41.9), 169 (19.6), 140.0 (14.3), 110 (6.2). ^{1}H NMR ($CDCl_3$), δ: 1.35 + 1.40 (6H, t, *J*= 7.0 Hz, $CO_2CH_2CH_3$), 3.22 (2H, br s, H-3′), 4.2-4.35 (4H, m, $CO_2CH_2CH_3$), 6.80 (1H, br s, H-3), 6.98 (1H, d, *J*=10.3 Hz, H-1′), 7.47 (1H, dd, *J*=7.7 + 7.2 Hz, H-7), 7.52 (1H, br s, H-2), 7.68 (1H, d, *J*=7.7 Hz, H-8), 8.08 (1H, d, *J*=7.2 Hz, H-6), 9.68 (1H, br s, H-1), 10.22 (1H, br d, *J*=10.3 Hz, NH); NOE: 6.98 (H-1′) → 3.22 (H-3′), 6.80 (H-3).

Ethyl 5-oxo-1,3,4,5-tetrahydrobenz[c,d]indol-4-ylcarbamate (**9**)

To a solution of **7** (37 mg; 0.1 mmol) in a mixture of THF (5 mL) and aqueous $KHCO_3$ solution (0.1 mL, 0.5N) at rt, ethyl chloroformate (0.1 mL; 1.3 mmol) was added and the mixture was stirred for 2 h then a further portion of reagent (0.1 mL) was added. The mixture was stirred overnight then evaporated. The residue was dissolved in a mixture of chloroform (20 mL) and water (5 mL) and the pH was adjusted to 8-9 with aqueous $KHCO_3$ solution (0.5N). After extraction the two phases were separated, the organic phase was washed with water (2x5 mL), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (eluent: hexane - ethyl acetate 7:3). The collected fractions were evaporated to about 2 mL under reduced pressure. The precipitated product was filtered, washed with the eluent to afford **9** (14 mg; 54%), mp 179-182 °C (from a mixture of hexane - ethyl acetate, 7:3).

IR (KBr): 3361 (νNH indole), 3300 (sh, νNH carbamate), 1715 (νC=O carbamate), 1673 (νC=O ketone), 1527 (νCN + δNH carbamate), 1235 (ν_{as}COC ester), 1056 (ν_sCOC ester), 753 cm^{-1} ($\gamma C_{Ar}H$). ^{1}H NMR ($CDCl_3$ + DMSO-d_6), δ: 1.35 (3H, t, *J*=6.8 Hz, $CO_2CH_2CH_3$), 4.23 (2H, q, *J*=6.8 Hz, $CO_2CH_2CH_3$), 7.51 (1H, dd, *J*=7.7 + 7.2 Hz, H-7), 7.77 (1H, d, *J*=7.2 Hz, H-8), 7.78 (1H, d, *J*=2.0 Hz, H-3), 8.00 (1H, br, H-2), 8.10 (1H, d, *J*=7.7 Hz, H-6), 8.48 (1H, br, NH), 11.6 (1H, br, H-1). Anal. Calcd. for $C_{14}H_{14}N_2O_3$; C, 65.10, H, 5.46, N, 10.84. Found C, 65.02, H, 5.33, N, 10.79.

***N-(5-Hydroxy-1,3,4,5-tetrahydrobenz[c,d]indol-4-yl)-2′,3′-diethoxycarbonyl-1′-propenylamine* (10)**

Enamine (**7**) (74 mg; 0.2 mmol) was dissolved in a mixture of acetic acid (10 mL) and water (5 mL) and 10% Pd/C catalyst (about 20 mg) was added and the mixture was hydrogenated according to the standard pro-cedure. After 4 h the catalyst was filtered off and the filtrate was diluted with chloroform (50 mL) and cold water (10 mL). The mixture was alkalized to pH 8 by adding concentrated aqueous ammonium hydroxide solution (6-7 mL). The organic layer was separated, washed with water (3x10 mL) and dried (Na_2SO_4). The filtrate was evaporated *in vacuo* and the residue (51 mg) was chromatographed on silicagel (eluent: hexane-ethyl acetate 6:4). The solvent was evaporated under reduced pressure to give **10** (28 mg; 38.8%) as an orange-coloured oil.

IR (KBr): 3400 (sh, νOH), 3395 (νNH indole), 3321 (νNH enamine), 1733 (νC=O unconjugated ester), 1677 (νC=O conjugated ester), 1613 (νC=C), 1221, 1178 (ν_{as}COC ester), 1096, 1031 cm^{-1} (ν_sCOC ester). ^{1}H NMR ($CDCl_3$), δ: 1.18-1.35 (6H, m, $CO_2CH_2CH_3$), 3.10-3.20 (1H, m, H-3_A), 3.12-3.25 (2H, d, J_{gem}=16.5 Hz, H-3′), 3.65 + 3.72 (1H, m, H-3B), 3.95-4.05 (1H, m, H-4), 4.00-4.20 (2H, m, $CO_2CH_2CH_3$), 5.02 + 5.28 (1H, m, H-5), 6.78 + 7.62 (1H, d, *J*=12 Hz, H-2′), 6.90 (1H, br d, H-2), 7.07 (1H, dd, *J*=7.8 + 7.2 Hz, H-7), 7.15-7.25 (2H, m, H-6 + H-8), 7.92-8.00 (1H, br d, H-1), 8.15 (1H, br d, *J*=12 Hz, NH). ^{13}C NMR ($CDCl_3$), δ: 13.83 + 13.93 + 13.96 + 14.27 ($CO_2CH_2CH_3$), 25.87 + 25.99 + 30.65 + 31.14 (C-3), 35.46 + 35.53 + 35.54 + 36.02 (C-3′), 58.77 + 60.43 ($CO_2CH_2CH_3$), 69.99 + 70.14 + 70.15 + 72.57 (C-5), 88.66 + 92.21 (C-2′), 109.28 + 109.31 + 109.95 + 110.60 (C-2a), 115.06 - 118.97 (C-8 + C-6), 122.95 + 123.02 + 123.06 + 123.07 (C-7), 125.63 + 130.07 + 130.30 + 133.90 (C-5a + C-8a + C-8b), 147.75 + 147.79 + 150.97 + 151.48 (C-1′), 162.25 + 168.22 + 168.98 + 171.79 + 173.13 ($CO_2CH_2CH_3$). Anal. Calcd. for $C_{20}H_{24}N_2O_5$; C, 64.50, H, 6.49, N, 7.52. Found C, 64.38, H, 6.53, N, 7.60.

***N-(5-Oxo-1,5-dihydrobenz[c,d]indol-4-yl)-2′,3′-diethoxycarbonyl-1′-propylamine* (11)**

To a cold (5-10 °C) solution of **7** (185 mg; 0.5 mmol) in acetic acid (10 mL) $NaCNBH_3$ (126 mg; 2.0 mmol) was added and stirred for 15 min. The reaction mixture was diluted with water (20 mL) and the pH was adjusted to about 7-8 with saturated aqueous Na_2CO_3 solution. The solution was extracted with chloroform (50 mL), the organic phase was washed with water (20 mL), and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure, the residue was chromatographed (eluent: hexane - ethyl acetate 6:4). The solvent was evaporated *in vacuo*, the residue (70 mg; 38%) was recrystallized from ether to give **11** as red crystals, mp 105-108 °C.

IR (KBr): 3376 (νNH indole), 3300 (sh, νNH enamine), 1730 (νC=O unconjugated ester), 1714 (νC=O conjugated ester), 1630 (νC=O conjugated ketone), 1602, 1576, 1526 (νC_{Ar}-C_{Ar}), 1214, 1182 (ν_{as}COC ester), 1083 cm^{-1} (ν_sCOC ester). MS (*m/z*, %): 370.1524 (calcd.: 370.1529, $C_{20}H_{22}N_2O_5$, 30.0, M^+), 324 (31.6), 251 (32.5), 197 (100), 156 (11.6). ^{1}H NMR ($CDCl_3$), δ: 1.20 + 1.35 (6H, m, $CO_2CH_2CH_3$), 2.61 (1H, dd, *J*=16.6 + 6 Hz, H-3′A), 2.81 (1H, m, *J*=16.6 + 7.8 Hz, H-3′B), 3.28 (1H, m, *J*=6.0 + 7.8 + 6.9 Hz, H-2′), 4.08-4.25 (2H, m, $CO_2CH_2CH_3$), 5.40 (1H, br s, NH), 6.55 (1H, s, H-3), 7.38 (1H, d, *J*=2 Hz, H-2), 7.44 (1H, t, *J*=7.6 Hz, H-7), 7.52 (1H, br s, H-2), 7.60 (1H, d, *J*=7.6 Hz, H-8), 8.10 (1H, d, *J*=7.6 Hz, H-6), 8.90 (1H, br d, *J*=2 Hz, H-1).

N-Methyl-N-(5-oxo-1,3,4,5-tetrahydrobenz[c,d]indol-4-yl)-2′,3′-diethoxycarbonyl-1′-propylamine (**3a**)

Enamine (**7**) (185 mg; 0.5 mmol) was dissolved in acetonitrile (7 mL) and cooled to 0 °C. To the solution acetic acid (2 mL) was added and stirred for 3-5 min, then $NaCNBH_3$ (126 mg; 2.0 mmol) was added and the mixture stirred for 15 min at the above temperature. The mixture was treated with formaldehyde (3 mL, 37% solution in water) and stirred for 30 min. The mixture was diluted with water (10 mL) and the pH was adjusted to 7-8 with saturated aqueos Na_2CO_3 solution. The mixture was extracted with chloroform (100 mL) and the organic phase was washed with water (20 mL), and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure. The residue was chromatographed (eluent: chloroform - methanol 10:1, then hexane - ethyl acetate 1:2) to give **3a** (130 mg; 68%) as a colorless oil.

IR (KBr): 3369 (νNH indole), 1731 (νC=O unconjugated ester), 1683 (νC=O ketone), 1602, 1449, (νC_{Ar}-C_{Ar}), 1177 (ν_{as}COC ester), 1103 (ν_sCOC ester), 753 cm^{-1} (γC_{Ar}-H). ^{1}H NMR ($CDCl_3$), δ: 1.10 + 1.30 (6H, m, $CO_2CH_2CH_3$), 2.45 + 2.58 (3H, s, NCH_3), 2.64 + 2.67 (2H, m, H-3′), 2.85-3.00 (2H, m, H-1′), 3.06 (1H, m, H-2′), 3.15-3.30 (2H, m, H-3), 3.84 (1H, dd, *J*=9.8 + 7.8 Hz, H-4), 4.10-4.25 (4H, m, $CO_2CH_2CH_3$), 7.02 (1H, br s, H-2), 7.20-7.30 (1H, m, H-7), 7.48 + 7.60 (1H, d, *J*=7.2 Hz, H-8), 7.54 + 8.10 (1H, d, *J*=7.8 Hz, H-6), 7.92 + 8.22 (1H, br s, H-1). ^{13}C NMR (C_6D_6), δ: 14.17 + 14.26 ($CO_2CH_2CH_3$), 26.38 + 26.76 (C-3), 34.76 + 34.84 (C-3′), 3.76 + 39.03 (C-2′), 42.19 (NCH_3), 57.32 + 57.57 (C-1′), 59.98 + 60.22 + 60.31 + 60.34 ($CO_2CH_2CH_3$), 70.43 + 70.56 (C-4), 110.83 + 110.89 (C-2a), 115.35 (C-8), 118.84 (C-6), 120.42 (C-2), 123.18 (C-7), 123.80 (C-5a), 131.84 + 135.17 (C-8a + C-8b), 169.91 + 171.96 + 174.03 174.08 ($CO_2CH_2CH_3$), 197.68 + 197.73 (C-5). Anal. Calcd. for $C_{21}H_{26}N_2O_5$; C, 65.27, H, 6.78, N, 7.24. Found C, 65.34, H, 6.73, N, 7.30.

N-(5-Oxo-1,5-dihydrobenz[c,d]indol-4-yl)-2′,3′-diethoxycarbonyl-1′-propylamine (**12**)

To a solution of **3a** (119 mg; 0.3 mmol) in DMF (2 mL) dry K_2CO_3 (40 mg; 0.3 mmol) was added at rt and stirred for overnight. Two further portions of reagent (K_2CO_3; 2x40 mg) was added during 8 h, then the reaction mixture was diluted with ether (100 mL) and water (10 mL). After extraction the organic layer was separated and washed with water (3x10 mL), dried (Na_2SO_4), filtered and the filtrate was evaporated in reduced pressure. The residue was chromatographed (eluent: hexane - ethyl acetate 1:2) to give **12** (40 mg; 34%) as an oil.

IR (KBr): 3232 (νNH indole), 1731 (νC=O unconjugated ester), 1635 (νC=O conjugated ketone), 1599, 1569, 1509 (νC_{Ar}-C_{Ar}), 1174 (ν_{as}COC ester), 1093 cm^{-1} (ν_sCOC ester). MS (*m/z*, %): 384.1688 (calcd.: 384.1685, $C_{21}H_{24}N_2O_5$, 15.8, M^+), 339 (2.5, M-CO_2H), 310 (1.6, M-HCO_2Et), 211 (100). ^{1}H NMR (DMSO-d_6), δ: 1.05 + 1.15 (6H, t, *J*=7.0 Hz, $CO_2CH_2CH_3$), 2.58 + 2.69 (2H, m, H-3′), 2.76 (3H, s, NCH_3), 3.11 (1H, m, H-2′), 3.42 (2H, d, *J*=7.2 Hz, H-1′), 3.88 - 4.05 (4H, m, $CO_2CH_2CH_3$), 7.11 (1H, s, H-2), 7.48 (1H, dd, *J*=7.6 + 7.3 Hz, H-7), 7.77 (1H, d, *J*=7.6 Hz, H-8), 7.87 (1H, d, *J*=7.3 Hz, H-6), 7.91 (1H, s, H-3), 11.80 (1H, br s, H-1). ^{13}C NMR (DMSO-d_6), δ: 13.76 + 13.90 ($CO_2CH_2CH_3$), 33.87 (C-3′), 39.50 (C-2′), 54.05 (C-1′), 59.89 + 59.99 ($CO_2CH_2CH_3$), 109.94 (C-2a), 115.81 (C-2), 116.59 (C-8), 119.90 (C-6), 123.94 (C-7), 124.74 (C-5a), 125.96 + 135.30 + 145.71 (C-4, C-8a, C-8b), 171.32 + 173.45 ($CO_2CH_2CH_3$), 180.34 (C-5).

***(±)-6-Methyl-8β-carbethoxy-10-oxo-[8H,9H,12H]-furano[c]1,4,5α,6,7,8-hexahydroindolo[4,3-ef] indole* (13) *and* *(±)-6-Methyl-8β-carboxy-10-oxo-[8H,9H,12H]-furano[c]1,4,5β,6,7,8-hexahydroindolo [4,3-ef]indole* (14)**

Potassium hydride (813 mg; 7 mmol, 35% in oil) was suspended in THF (20 mL) and cooled to 0 °C. To this suspension 18-crown-6 (1.096 g; 4.15 mmol) was added and the mixture was stirred for 4-5 min, then a solution of compound (**3a**) (190 mg; 0.517 mmol) in THF (10 mL) was poured. The reaction mixture was stirred for 30 min. at the above temperature. The pH was adjusted to about 4-5 with dry HCl/MeOH. The precipitated potassium chloride was filtered off and the filtrate evaporated in reduced pressure. The residue was suspended in methanol (20 mL) and decanted from the oil. The solution was evaporated *in vacuo* and the residue was washed with ether (5x30 mL). The combined organic phase was evaporated in reduced pressure and the residue was chromatographed (eluent: ethyl acetate - hexane 4:1) to give **12** (27 mg; 15%) as an red oil.

The residue was washed with ether and chromatographed (eluent: ethyl acetate - hexane 4:1) to give **13** (30 mg; 18%), mp 175-178 °C (from a mixture of ehyl acetate - hexane, 4:1).

IR (KBr): 3411 (νNH indole), 1769 (νC=O γ-lactone), 1727 (νC=O ester), 1450 ($\beta_s CH_2$+ νC_{Ar}-C_{Ar}), 1240 (ν_{as}COC ester), 1100 (ν_sCOC ester), 756 cm^{-1} (γC_{Ar}-H). MS (*m/z*, %): 340.1414 (calcd.: 340.1423, $C_{19}H_{20}N_2O_4$, 47.5, M^+), 311 (5.8, M-29), 284 (5.0), 267 (5.0, M-73), 223 (8.3), 170 (100), 142 (10.8), 115 (5.8). ^{1}H NMR ($CDCl_3$), δ: 0.36 (3H, t, *J*=7.3 Hz, $CO_2CH_2CH_3$), 2.55 (3H, s, NCH_3), 2.80 (1H, d, J=18.4 Hz, H-9α), 2.98 (1H, d, *J*=10.0 Hz, H-7α), 3.06-3.21 (2H, m, H-4), 3.30-3.52 (2H, m, $CO_2CH_2CH_3$), 3.74 (1H, dd, *J*=10.0 + 1.2 Hz, H-7β), 3.79 (1H, dd, *J*=10.5 + 7.8 Hz, H-5), 4.03 (1H, dd, J=18.4 + 1.2 Hz, H-9 β), 6.91 (1H, d, *J*=7.4 Hz, H-14), 6.95 (1H, br, H-2), 7.17 (1H, t, *J*=7.4 Hz, H-15), 7.25 (1H, d, *J*=7.4 Hz, H-16), 8.03 (1H, br, H-1); NOE: 2.55 (NCH_3) → 2.98 (H-7α), 3.17 (H-4β), 3.7 -3.8 (H-7β + H-5); 2.98 (H-7α) → 2.55 (NCH_3), 2.80 (H-9α), 3.7 - 3.8 (H-7β + H-5); 4.03 (H-9β) → 2.80 (H-9α), 6.91 (H-14). ^{13}C NMR ($CDCl_3$), δ: 12.60 ($CO_2CH_2CH_3$), 17.20 (C-4), 36.08 ($N\text{-}CH_3$), 40.15 (C-9), 60.20 (CO_2CH_2 CH_3), 61.56 (C-8), 63.72 (C-7), 67.29 (C-5), 95.94 (C-12), 109.54 (C-3), 110.75 (C-16), 115.67 (C-14), 119.42 (C-2), 122.91 (C-15), 126.02 (C-13), 127.18 (C-18), 133.39 (C-17), 170.41 ($CO_2CH_2CH_3$), 175.30 (C-10).

The oil (after separation of methanol and the oil) was purified with column chromatography (eluent: chloroform - methanol 10:1, then 1:1) to yield **14** (24 mg; 16%) as semisolid crystals.

IR (KBr): 3531 (νOH lattice water), 3313 (νNH indole), 3500-2500 (νOH carboxylic acid), 1762 (νC=O γ-lactone), 1660 (sh, νC=O carboxylic acid), 1615 (νC_{Ar}-C_{Ar}), 1450 ($\beta_s CH_2$ + νC_{Ar}-C_{Ar}), 934cm^{-1} (γOH carboxylic acid) . FAB-MS (*m/z*, %): 313 (MH^+), 307.1; 289.1; 154.0; 137.0; 107.0; 89.0. ^{1}H NMR (DMSO-d_6), δ: 2.30 (3H, s, NCH_3), 2.61 (1H, m, H-4α), 2.87 (1H, dd, *J*=11.6 + 4.5 Hz, H-5), 2.88 (1H, d, J=18.1 Hz, H-9α), 2.98 (1H, dd, *J*=9.8 + 1.0 Hz, H-7β), 3.11 (1H, dd, *J*=14.1+4.5 Hz, H-4β), 3.30 (1H, d, *J*=9.8 Hz, H-7α), 3.69 (1H, dd, J=18.1 + 1.0 Hz, H-9β), 6.90 (1H, d, *J*=7.4 Hz, H-14), 7.02 (1H, t, J=7.4 Hz, H-15), 7.14 (1H, br, H-2), 7.33 (1H, d, *J*=7.4 Hz, H-16), 10.85 (1H, br, H-1); NOE: 2.30 (NCH_3) → 2.87 (H-5), 2.98 (H-7β), 3.30 (H-7α); 2.61 (H-4α) → 3.11 (H-4β), 7.14 (H-2), no NOE with H-5; 3.31 (H-7α) → 2.30 (NCH_3), 2.88 (H-9α), 2.98 (H-7β); due to overlaps of the signals NOE effect between H-5 and H-7β was not detectable. ^{13}C NMR (DMSO-d_6), δ: 21.99 (C-4), 39.60 ($N\text{-}CH_3$), 39.60 (C-9), 53.81

(C-8), 68.62 (C-7), 71.51 (C-5), 93.40 (C-12), 109.07 (C-3), 111.96 (C-16), 112.56 (C-14), 120.65 (C-2), 121.70 (C-15), 121.08 (C-13), 127.42 (C-18), 134.00 (C-17), 173.31 (CO_2H), 173.71 (C-10).

***(±)-8α,9α-Dicarboethoxy-10β-hydroxyergoline (5β-H)* (20)**

To a suspension of KO^{t}Bu (0.435g, 3.9 mmol) in THF (10 mL) at -70 °C *n*-BuLi solution (5 mL, 8.0 mmol, 1.6 mol/L, in hexane) was added. (The suspension turned into a yellow solution). To this solution compound (**3a**) (500 mg, 1.29 mmol) was added in THF (5 mL) and was stirred for 15 min at the above temperature. The mixture was treated with acetic acid (pH ≈ 6) and allowed to warm up to rt. The precipitated potassium acetate was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was chromatographed (eluent: hexane - ethyl acetate 1:1) to yield **20** (109 mg, 22.0 %), mp 186-187 °C (from a mixture of hexane - ethyl acetate, 1:1).

IR (KBr): 3400 (νNH indole), 3365 (νOH), 1730, 1716 (νC=O ester, both unconjugated), 1200, 1184 (ν_{as} COC, ester), 1039, 1030 (ν_s COC, ester) cm^{-1}. MS (*m/z*, %): 386.1795 (calcd.: 386.1842, $C_{21}H_{26}N_2O_5$, 75.3, M^+), 368 (13.3), 341 (17.5), 313 (12.5), 295 (19.1), 267 (9.1), 239 (25.8), 213 (21.6), 170 (100), 130 (20.8), 115 (15.8).

^{1}H NMR ($CDCl_3$), δ: 0.92 (3H, t, *J*=6.9 Hz, OCH_2CH_3), 1.22 (3H, t, *J*=6.9 Hz, OCH_2CH_3), 2.57 (3H, s, NCH_3), 2.77 (1H, dd, *J*=12.4 + 11.9 Hz, H-7α), 2.91 (1H, d, *J*=12.1 Hz, H-9), 2.96-3.09 (3H, m, H-4α + H-4β + H-7β), 3.21 (1H, dd, *J*=10.5 + 5.9 Hz, H-5), 3.55 (1H, m, *J*=12.1 + 11.9 + 5.2 Hz, H-8), 3.88-4.02 (2H, m, OCH_2CH_3), 4.04-4.15 (2H, m, OCH_2CH_3), 4.26 (1H, s, O*H*), 6.92 (1H, br s, H-2), 7.03 (1H, dd, *J*= 7.0 + 0.6 Hz, H-12), 7.14 (1H, dd, *J*=7.0 + 8.1 Hz, H-13), 7.22 (1H, dd, *J*= 8.1 + 0.6 Hz, H-14), 8.06 (1H, br s, N*H*), NOE: 2.57 (NCH_3) → 2.77 (H-7α), 2.96-3.09 (H-4α + H-4β + H-7β), 3.21 (H-5); 2.77 (H-7α) → 2.57 (NCH_3), 2.91 (H-9), 3.05 (H-4), 3.07 (H-7β); 2.91 (H-9) → 2.77 (H-7α), 3.05 (H-4); 3.21 (H-5) → 2.57 (NCH_3), 3.0 (H-4), 4.26 (OH); 3.55 (H-8) → 3.07 (H-7β), 4.26 (OH); 4.26 (OH) → 3.21 (H-5), 3.55 (H-8), 7.03 (H-12). ^{13}C NMR ($CDCl_3$), δ: 13.76 (OCH_2CH_3), 14.06 (OCH_2CH_3), 14.32 (C-4), 41.18 (C-8), 42.82 (NCH_3), 48.05 (C-7), 48.50 (C-9), 60.40 (OCH_2CH_3), 60.95 (OCH_2CH_3), 66.12 (C-5), 72.12 (C-10), 109.20 (C-3), 109.70 (C-14), 114.56 (C-12), 118.81 (C-2), 122.75 (C-13), 124.83 (C-16), 132.92 (C-11), 133.79 (C-15), 172.44 ($CO_2CH_2CH_3$), 172.49 ($CO_2CH_2CH_3$).

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