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Synthesis of *Vinca* Alkaloids and Related Compounds, LXXI[1]

Synthesis of (±)-Cuanzine, (±)-Decarbomethoxy-apocuanzine, and Some of Their Epimers

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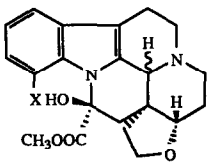
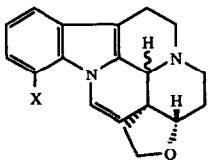
Abstract: *Starting from 7-methoxytryptamine (7) with the use of the method we developed earlier, (±)-cuanzine (1), (±)-decarbomethoxyapocuanzine (4), and their epimers 5 and 22 were synthesized.*

The indole alkaloid cuanzine (**1**) and its side-alkaloid, decarbomethoxy apocuanzine (**4**), were isolated[2] in the 1970s from the root bark of *Voacanga chalotiana* collected in Angola. Their structure elucidation were carried out mainly by high resolution mass spectrometry, high field proton and carbon-13 NMR spectroscopy, and some chemical transformations[3,4]. However, later the configuration of cuanzine at C14 was revised[5] to give the correct structure **1**. These alkaloids structurally belong to a subgroup of eburnanes having an oxygen bridge between the



1 H : α, X = OCH_3
2 H : β, X = OCH_3
3 H : α, X = H

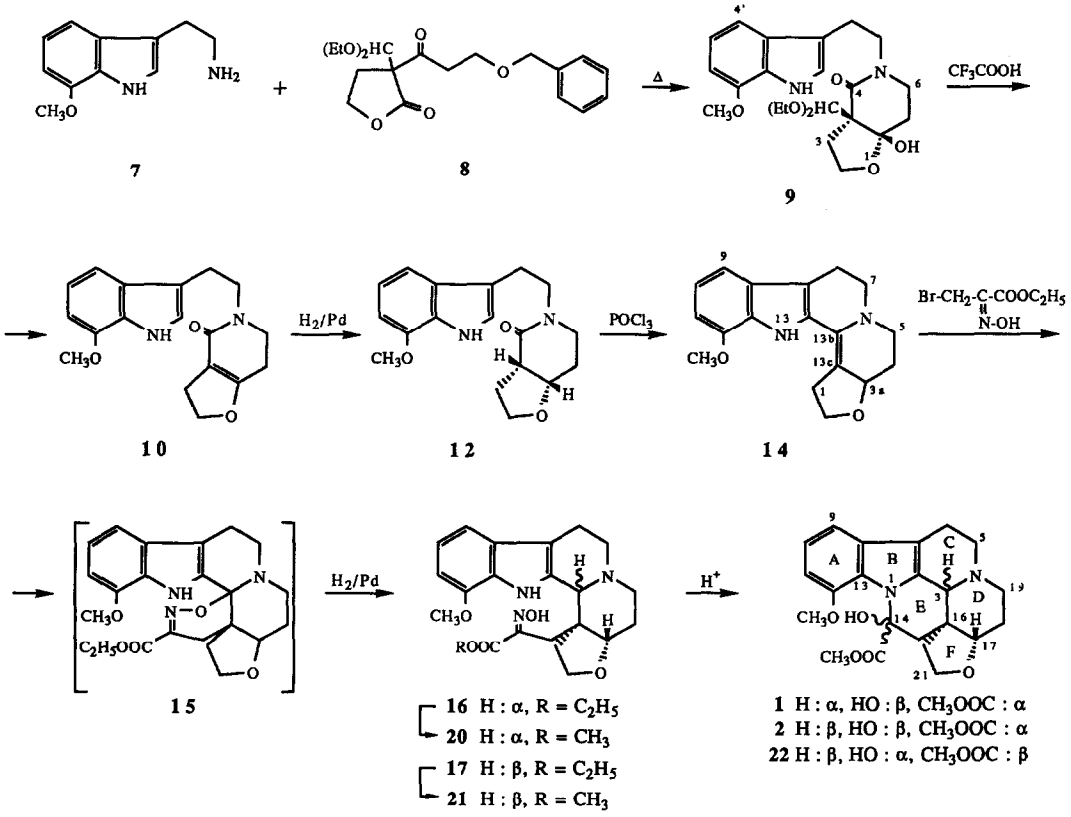


4 H : α, X = OCH_3
5 H : β, X = OCH_3
6 H : α, X = H

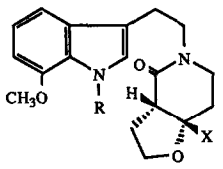
C17 and C21 carbon atoms forming a *cis*-fused tetrahydrofuran ring attached to the D-ring. This structure moiety is rare but can be found in biogenetically related *Aspidosperma* alkaloids (e. g., beninine[6], modestanine[7], vobtusine[8], and related indole alkaloids). Cuanzine was intensively studied in the 1970s for its antiarrhythmic, vasodilatory, and antihypertensive activities[9].

The (±)-desmethoxy analogues of cuanzine and decarbomethoxyapocuanzine (**3** and **6**, respectively) were synthesized by us[10,11] and others[12] using different approaches. A Japanese team reported[13] a formal total synthesis of (±)-desmethoxy-cuanzine. Later (±)-cuanzine was also synthesized by Italian[14] and French[15] researchers.

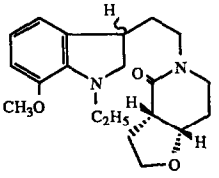
Starting from 7-methoxytryptamine (**7**)[16], we formed the fused C- and D-rings by condensing with (±)-3-(3-benzyloxypropionyl)-3-(diethoxymethyl)-butyrolactone (**8**) using the method[10] we developed earlier. In compound **9**, the *cis*-orientation of the hydroxyl and diethoxymethyl groups were verified by NOE experiments. From compound **9**, by treatment with trifluoroacetic acid in chloroform solution, we easily prepared the expected furopyridone derivative **10** with a small amount of ethanol



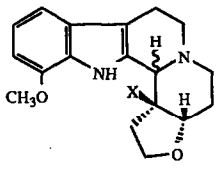
addition product **11**. The preirradiation of the C3a-H signal (δ 2.91 ppm) in this by-product resulted in NOE on one of the methylene protons of C7a-O-$CH_A\underline{H_B}$-CH_3 (δ 3.52), and this unambiguously proved the *cis*-fusion of the rings. The same by-product was formed in small amount at the catalytic hydrogenation of compound **10**



11 R = H, X = OC_2H_5
13a R = C_2H_5, X = H



13b H : α
13c H : β



18 H : α, X = CH_2-C(=N-O-CH_2-C(=N-OH)-$COOC_2H_5$)-$COOC_2H_5$
19 H : β, X = OH

in ethanol solution. In this case, the *cis*-fusion of the main product (**12**) was proved by NOE measurements, but the isolation of any epimer of it failed. In addition to compound **11**, we isolated another "by-product" (**13**), but according to NMR investigations, it turned out to be a mixture of compounds **13a**, **13b**, and **13c**, in about 1:1:1 ratio. The separation of this mixture has failed. The ethylation of the indole nitrogen atom during catalytic hydrogenation in ethanol solution at room temperature and ambient pressure is rather unusual, although at higher temperature, in the presence of Raney nickel catalyst a similar phenomenon was described[17].

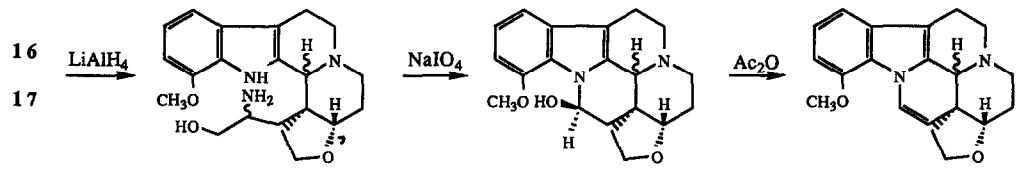
Compound **12** was cyclised without any difficulty by warming with $POCl_3$ in chloroform solution. The formed enamine **14** was pure enough to be condensed with the oxime of ethyl bromopyruvate[18] according to our earlier method[19], although the obtained oxazino-derivative **15** was not isolated because of the very poor solubility of the pure product, but was directly hydrogenated over palladium/charcoal catalyst in dimethylformamide solution. The components of the product were separated by column chromatography. The main products were the C13b-H_α (**16**) and the C13b-H_β (**17**) epimers, and as by-products, we isolated a small amount of compound **18** and a rather small quantity of compound **19**. The latter compound was evidently formed by water addition on the enamine **14** during the condensation.

The *cis*-oxime **16** and the *trans*-oxime **17** were transesterified by boiling in methanol solution in the presence of catalytic amount of sodium-methylate to the methyl esters **20** and **21**, respectively. Their cyclisation to the aimed **1** and **2** was carried out by boiling in aqueous acetic acid solution with sulfuric acid in the presence of sodium metabisulfite. The transesterification and the cyclisation of the *trans*-derivatives were slower than those of the *cis*-ones and needed much longer reaction times. The synthetic and the natural cuanzines (**1**) proved to be identical by their TLC data and by direct comparison of their MS, NMR, and IR (in chloroform

solution) spectra. Their IR spectra in KBr pellets showed some differences which can be rationalized in terms of their different crystal structures. This may be due to the fact that the natural cuanzine is optically active while the synthetic one was a racemic mixture. In the synthetic (±)-cuanzine, the relative configurations of C3, C14, C16, and C17 atoms, were confirmed by detailed NOE measurements which unambiguously indicated the β-orientation of the C17-H and C14-O atoms and the α-orientation of C3-H and C20 atoms. These results are in full accord with the three-dimensional structure of cuanzine determined by X-ray diffraction[5].

The optically active *trans*-cuanzine (**2**) was prepared earlier by Italian researchers[3] from natural cuanzine (**1**) by inverting the configuration at C3 with chromite oxydation and catalytic reduction. However, the above mentioned attempted synthesis of (±)-*trans*-cuanzine (**2**) by cyclisation of the *trans*-oximino derivative **21** using the same procedure what was used at the synthesis of (±)-cuanzine (**1**) has failed. The only product we could isolate from the reaction mixture was its 14-epimer, the (±)-14-epi-*trans*-cuanzine (**22**). The (±)-*trans*-cuanzine (**2**) may be formed in a very small amount (<1 %), or epimerised to **22** during the reaction or at the work up. The stereochemistry of the (±)-14-epi-*trans*-cuanzine (**22**) was unambiguously determined by NOE experiments in $CDCl_3$ and C_6D_6 solutions by proving the β-orientation of the C17-H, C3-H, and $COOCH_3$ atoms and the α-orientation of the C14-O and C20 atoms.

(±)-Desmethoxydecarbomethoxyapocuanzine (**6**) was synthesized earlier by us[11], and now we report the synthesis of (±)-decarbomethoxyapocuanzine (**4**) and of its *trans*-epimer (**5**). Reduction of the *cis*- and *trans*-ethylesters (**16** and **17**,



23 H : α
24 H : β

25 H : α
26 H : β

4 H : α
5 H : β

respectively) by lithium aluminum hydride yielded the amino-alcohols **23** and **24**, respectively. According to NMR investigations, they constituted a diastereomer mixture in about 2:1 ratio. Both of the amino-alcohols, **23** and **24**, were oxidized by periodate, and the alcohols **25** and **26** were formed, respectively, presumably through an intermediate aldehyde or *via* its iminium derivative. The relative β-orientation of the C14-OH groups in both compounds was verified by NOE experiments. We were not able to isolate their α-epimers. From compounds **25** and **26**, (±)-decarbomethoxyapocuanzine (**4**) and its *trans*-epimer (**5**) were prepared by water elimination carried out by heating with acetic anhydride. The NMR, MS, and IR

data of **4** were identical with the data of natural decarbomethoxyapocuanzine. In the case of compound **5**, the NOE experiments demonstrated the spatial proximity of the protons on the C3 and C17 carbon atoms, while the *trans*-annellation of the C- and D-rings was proved by the presence of Bohlmann-bands in its IR spectra.

The members of the *cis*- and *trans*-series are clearly distinguishable by MS because the molecule-ion stability of the *trans*-derivatives is greater and the loss of H from the molecule-ion is more significant than in the *cis*-isomers.

ACKNOWLEDGEMENTS

The authors are deeply grateful to professor Bruno Danieli (University of Milano, Milano, Italy) for the authentic specimen of natural cuanzine. This research was supported by the Hungarian Research Fundation (OTKA), Grant No. 1760.

EXPERIMENTAL

Mass spectra were recorded on an AEI MS-902 mass spectrometer (70 eV, ion source temperature, where is not indicated, was 170 °C). Under 20 % and under 100 m/z, only the significant peaks were reported in the Experimental. Infrared spectra were recorded with a Nicolet 7199 Fourier transform spectrometer at 4 cm^{-1} resolution and the frequencies (cm^{-1}) of the most significant absorption bands are reported. The NMR spectra were run, where it is not stated otherwise, in deuteriochloroform solutions at ambient temperature using a Varian XL-400 instrument for conventional and 2D experiments. Chemical shifts are given in ppm relative to internal TMS standard. Mutual ^1H-^1H couplings are given only once at their first occurrence in the Experimental. At NMR assignment, the numbering of the carbon atoms of the main ring corresponds to its numbering at naming, and at compounds having isolated rings, the figures with an apostrophe refer to the secondary ring. The chemical shift values signed with identical symbols are interchangeable. Selective ^1H-{^1H} NOE measurements were performed in the difference mode. Thin layer chromatography was carried out on silica gel layer (Macherey-Nagel, Polygram® SIL G/UV_{254}) and column chromatography also on silica gel (Aldrich, 70-230 mesh). Mps were determined with an Uni-Melt® Capillary Melting Point Apparatus (Thomas-Hoover), and they are uncorrected.

(±)-3aβ-Diethoxymethyl-7aβ-hydroxy-5-[2-(7-methoxy-indol-3-yl)-ethyl]-2,3,3a,6,7,7a-hexahydrofuro[3,2-c]pyridin-4(5H)-one (9)

A solution of 7-methoxytryptamine[16] (**7**, 11.40 g, 0.060 mole) and (±)-3-(3-benzyloxypropionyl)-3-diethoxymethyl-4,5-dihydro-3*H*-furan-2-one[10] (**8**, 21.00 g, 0.060 mole) in a mixture of chlorobenzene (270 ml) and N,N-diisopropylethylamine

(60 ml) was stirred and heated under reflux for 2.5 hours in argon atmosphere, and then the solvents were removed by evaporation at 40 °C *in vacuo*. The residue was purified by column chromatography on silica gel (1 kg, ethyl acetate, R_f = 0.41) to give pure **9** (14.01 g, 54 %) as a slowly crystallizing thick oil, mp: 108-111 °C. MS (m/z, %): 432 (M^+, 7), 386 (M-46, 12), 312 (M-120, 19), 260 (M-172, 3), 174 (37), 173 (100), 160 (56), 153 (23), 140 (20), 103 (22); IR (KBr, ν, cm^{-1}): 3410 (s, br, νNH), 3320 (s, br, νOH), 2975, 2955, and 2892 (νCH, ethoxy groups), 1630 (vs, νC=O, lactam), 1259 (s, νC-O, methoxy), 1100 and 1055 (s, νC-O, ketal group), 782 and 730 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.18 and 1.29 (2x3H, t, J = 7.0 Hz, 2xO-CH_2-$\underline{CH_3}$), 2.12 (1H, ddd, $J_{7A,7B}$ = -13.5, $J_{6A,7A}$ = 2.2, $J_{6B,7A}$ = 4.3 Hz, C7-H_A), 2.34 (1H, ddd, $J_{3A,3B}$ = -12.6, $J_{2A,3A}$ = 7.7, $J_{2B,3A}$ = 4.9 Hz, C3-H_A), 2.44 (1H, ddd, $J_{2A,3B}$ = 7.5, $J_{2B,3B}$ = 8.4 Hz, C3-H_B), 2.44 (1H, ddd, $J_{6A,7B}$ = 5.6, $J_{6B,7B}$ = 12.4 Hz, C7-H_B), 2.95 + 3.02 (2x1H, 2xddd, J_{gem} = -13.8, J_{vic} = 9.6, 6.3 and 9.2, 5.6 Hz, respectively, C3'-CH_2), 3.18 (1H, ddd, $J_{6A,6B}$ = -11.8 Hz, C6-H_A), 3.42 (1H, ddd, C6-H_B), 3.56 + 3.83 and 3.66 + 3.94 (2x2H, dq, J_{gem} = -9.2, J_{vic} = 7.0 Hz, 2x$\underline{CH_2}$-CH_3), 3.59 + 3.70 (2x1H, 2xddd, J_{gem} = -13.0, J_{vic} = 6.3, 9.2 and 5.6, 9.5 Hz, respectively, N-CH_2), 3.70 (1H, ddd, $J_{2A,2B}$ = -8.2 Hz, C2-H_A), 3.95 (3H, s, OCH_3), 4.03 (1H, ddd, C2-H_B), 5.19 (1H, s, C3a-CH), 5.89 (1H, s, C7a-OH), 6.65 (1H, d, $J_{5',6'}$ = 7.8 Hz, C6'-H), 7.02 (1H, d, J = 2.5 Hz, C2'-H), 7.05 (1H, dd, $J_{4',5'}$ = 7.8 Hz, C5'-H), 7.31 (1H, d, C4'-H), 8.24 (1H, br s, NH). NOE: 5.19 (C3a-CH) → 5.89 (C7a-OH).

5-[2-(7-Methoxy-indol-3-yl)-ethyl]-2,3,6,7-tetrahydrofuro[3,2-c]pyridin-4(5H)-one (10) and by-product (±)-7aβ-Ethoxy-5-[2-(7-methoxy-indol-3-yl)-ethyl]-2,3,3aβ,6,7,7a-hexahydrofuro[3,2-c]pyridin-4(5H)-one (11)

To a solution of compound **9** (14.01 g, 0.032 mole) in dry dichloromethane (400 ml), trifluoroacetic acid (7.5 ml, 0.097 mole) was added and allowed to stand in dark at room temperature for 24 hours in argon atmosphere. The solution was washed successively with 1M ammonium hydroxide solution (200 ml), with water (25 ml), with 1M hydrochloric acid solution (2x25 ml), and again with 1M ammonium hydroxide solution (25 ml). The organic layer was dried ($MgSO_4$) and evaporated at room temperature *in vacuo* . The residue was treated with dry toluene (50 ml), and the crystallized material was filtered after 2 hours of crystallization, washed with dry toluene (5x10 ml), and dried *in vacuo* giving the pure **10** (5.63 g, 56 %) as white crystals, mp: 201-203.5 °C. From the residue of the evaporated combined mother liquors, we got an additional amount of pure **10** (3.51 g, 35 %) by column chromatographic purification on silica gel (500 g, benzene-diethylamine 9-1 v/v, R_f = 0.42). MS (m/z, %): 312 (M^+, 21), 173 (100), 160 (17), 152 (M-160, 31); IR (KBr, ν, cm^{-1}): 3240 (br, νNH), 1670 (vs, νC=C, in F-ring, conjugated with C=O), 1614 (vs, νC=O, conjugated lactam), 1576 and 1482 (s, methoxy substd. A-ring), 1260 (s, νC-O,

methoxy), 1058 (m, νC-O, in F-ring), 785 and 729 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 2.31 (2H, tt, J = 7.2 and 2.2 Hz, C7-H_2), 2.90 (2H, tt, J = 9.3 and 2.2 Hz, C3-H_2), 3.00 (2H, t, J = 7.2 Hz, C3'-CH_2), 3.32 (2H, t, J = 7.2 Hz, C6-H_2), 3.71 (2H, t, J = 7.2 Hz, N-CH_2), 3.95 (3H, s, OCH_3), 4.56 (2H, t, J = 9.3 Hz, C2-H_2), 6.65 (1H, d, $J_{5',6'}$ = 7.8 Hz, C6'-H), 7.04 (1H, dd, $J_{4',5'}$ = 7.8 Hz, C5'-H), 7.29 (1H, d, C4'-H), 8.21 (1H, br s, NH). Anal. Calcd. for $C_{18}H_{20}N_2O_3$ (312.35): C 69.21, H 6.45, N 8.97 %. Found: C 69.27, H 6.48, N 8.97 %.

At the chromatographic purification of **10** we isolated the by-product **11** (0.45 g, 4 %, R_f = 0.49), as white crystals, mp: 130-133 °C. MS (m/z, %): 358 (M^+, 8), 313 (M-45, 5), 173 (100), 160 (18); IR (KBr, ν, cm^{-1}): 3420 (s, νbr, νNH), 1630 (vs, νC=O), 1579 and 1498 (methoxy substd. A-ring), 1260 (s, νC-O, methoxy), 781 and 730 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.15 (3H, t, J = 7.0 Hz, O-CH_2-$\underline{CH_3}$), 1.82 (1H, ddd, $J_{7A,7B}$ = -13.4, $J_{6A,7A}$ = 4.6, $J_{6B,7A}$ = 10.6 Hz, C7-H_A), 2.08 (1H, ddd, $J_{6A,7B}$ = 4.4, $J_{6B,7B}$ = 3.5 Hz, C7-H_B), 2.08 (1H, m, C3-H_A), 2.52 (1H, dddd, $J_{3A,3B}$ = -12.6, $J_{3a,3B}$ = 9.4, $J_{2,3B}$ = 5.2 and 6.8 Hz, C3-H_B), 2.91 (1H, dd, $J_{3a,3A}$ = 5.4 Hz, C3a-H), 3.00 (2H, t, J = 7.2 Hz, C3'-CH_2), 3.07 (1H, ddd, $J_{6A,6B}$ = -12.5 Hz, C6-H_A), 3.21 (1H, ddd, C6-H_B), 3.43 + 3.52 (2H, 2xdq, J_{gem} = -9.0, J_{vic} = 7.0 Hz, O-$\underline{CH_2}$-CH_3), 3.68 + 3.70 (2H, 2xdt, J_{gem} = -13.0, J_{vic} = 7.2 Hz, N-CH_2), 3.85 (2H, m, C2-H_2), 3.95 (3H, s, OCH_3), 6.65 (1H, d, $J_{5',6'}$ = 7.8 Hz, C6'-H), 7.00 (1H, d, J = 2.5 Hz, C2'-H), 7.04 (1H, dd, $J_{4',5'}$ = 7.8 Hz, C5'-H), 7.26 (1H, d, C4'-H), 8.29 (1H, br s, NH); NOE: 2.91 (C3a-H) → 3.52 (C7a-O-$CH_A\underline{H_B}$-CH_3).

(±)-5-[2-(7-Methoxy-indol-3-yl)-ethyl]-2,3,3aβ,6,7,7aβ-hexahydro-furo[3,2-c]pyridin-4(5H)-one (12) and by-products 11 and "13"

Compound **10** (4.68 g, 0.015 mole) was hydrogenated in ethanol (325 ml) over palladium/carbon catalyst (10 %, 9.3 g) at ambient temperature and pressure. When the hydrogen consumption ceased (22.5 hours, 400 ml, 0.017 mole) the catalyst was removed and washed with boiling ethanol (12x15 ml) and the combined solutions were evaporated *in vacuo*. The residue (3.92 g) was purified by column chromatography on silica gel (250 g, benzene-diethylamine 9-1 v/v, R_f = 0.38) to give pure **12** (3.58 g, 76 %) as white crystals, mp: 194-199 °C. MS (m/z, %): 314 (M^+, 11), 173 (100), 160 (20); IR (KBr, ν, cm^{-1}): 3280 and 3220 (νNH), 1621 (vs, νC=O, lactam), 1577 and 1496 (s, methoxy substd. A-ring), 1235 (νC-O, methoxy), 1050 (νC-O, in F-ring), 782 and 731 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.77 (1H, dddd, $J_{7A,7B}$ = -13.8, $J_{6A,7A}$ = 4.5, $J_{6B,7A}$ = 10.3, $J_{7A,7a}$ = 3.5 Hz, C7-H_A), 1.84 (1H, dddd, $J_{6A,7B}$ = 4.7, $J_{6B,7B}$ = 3.6, $J_{7B,7a}$ = 4.5 Hz, C7-H_B), 2.09 (1H, dddd, $J_{3A,3B}$ = -12.6, $J_{2,3A}$ = 7.5 and 7.3, $J_{3A,3a}$ = 5.7 Hz, C3-H_A), 2.38 (1H, dddd, $J_{2,3B}$ = 7.1 and 5.2, $J_{3B,3a}$ = 9.2 Hz, C3-H_B), 2.99 (1H, m, C3a-H), 2.99 (1H, ddd, $J_{6A,6B}$ = -12.5 Hz, C6-H_A), 3.01 (2H, t, J = 7.2 Hz, C3'-CH_2), 3.36 (1H, ddd, C6-H_B), 3.66 + 3.73 (2H, 2xdt, J_{gem} = -13.0, J_{vic} = 7.0 and 7.5 Hz, respectively, N-CH_2), 3.68 (1H, ddd, J_{gem} = -8.5 Hz, C2-H_A), 3.83 (1H, ddd, C2-

H_B), 3.94 (3H, s, OCH_3), 4.14 (1H, ddd, $J_{3a,7a}$ = 7.0 Hz, C7a-H), 6.64 (1H, d, $J_{5',6'}$ = 7.5 Hz, C6'-H), 7.01 (1H, d, J = 2.4 Hz, C2'-H), 7.04 (1H, dd, $J_{4',5'}$ = 8.0 Hz, C5'-H), 7.26 (1H, d, C4'-H), 8.33 (1H, br s, NH). NOE: 4.14 (C7a-H) → 2.99 (C3a-H).

At the chromatographic purification of **12** we isolated the by-products **11** (0.025 g, 0.5 %, R_f = 0.49) and "**13**" (0.058 g, 1.1 %, R_f = 0.55) as a thick oil. MS (180 °C, m/z, %): 344 (61), 342 (14), 202 (22), 201 (100), 190 (32), 188 (51), 176 (22), 173 (16). According to ^1H and ^{13}C NMR investigations, compound "**13**" is a mixture of compounds **13a**, **13b**, and **13c** in about 1:1:1 ratio, and it was possible to determine the chemical shift values of compound **13a** and of the epimeric mixture of **13b** and **13c**.

For compound **13a** ^1H NMR (δ, ppm) 1.37 (N-CH_2-C$\underline{H}_3$), 1.90 + 1.96 (C7-H_2), ~2.07 + 2.36 (C3-H_2), 2.97 (2H, C3'-CH_2), ~2.98 (C3a-H), ~3.00 + ~3.37 (C6-H_2), 3.61 + 3.71 (N-CH_2), 3.71 + 3.84 (C2-H_2), 3.93 (OCH_3), 4.15 (C7a-H), 4.36 (N-C$\underline{H}_2$-CH_3), 6.62 (C6'-H), 6.85 (C2'-H), 6.98 (C5'-H), 7.21 (C4'-H); ^{13}C NMR (δ, ppm): 17.55 (N-CH_2-$\underline{C}H_3$), 23.33 (C3'-$\underline{C}H_2$), 27.57 (C7), 31.97 (C3), 43.66 (C6), 43.90 (N-$\underline{C}H_2$-CH_3), 44.73 (C3a), 48.76 (N-CH_2), 55.28 (OCH_3), 67.43 (C2), 75.47 (C7a), 102.26 (C6'), 111.59 (C3'), 111.62 (C4'), 119.23 (C5'), 125.63 (C3a'), 126.29 (C2'), 135.33 (C7a'), 147.51 (C7'), 170.83 (C4).

For epimeric mixture **13b** + **13c** ^1H NMR (δ, ppm): 1.10 (N-CH_2-C$\underline{H}_3$), ~1.69 + ~1.97 (C3'-C$\underline{H}_2$), 1.75-2.0 (C7-H_2), ~2.09 + ~2.36 (C3-H_2), ~2.98 (C3a-H), 3.07 + 3.53 (C2'-H_2), ~3.12 + ~3.53 (C6-H_2), ~3.16 (C3'-H), 3.2-3.7 (N-CH_2), 3.40 + 3.49 (N-C$\underline{H}_2$-CH_3), 3.71 + 3,89 (C2-H_2), 3.79 (OCH_3), ~4.19 (C7a-H), ~6.69 (C4'-H), ~6.69 (C6'-H), ~6.73 (C5'-H); ^{13}C NMR (δ, ppm): 12.22 + 12.24 (N-CH_2-$\underline{C}H_3$), 27.61 + 27.63 (C7), 31.97 + 32.12 (C3), 32.06 + 32.09 (C3'-$\underline{C}H_2$), 38.70 + 38.83 (C3'), 42.77 + 42.79 (C6), 44.77 + 44.79 (C3a), 45.33 (N-$\underline{C}H_2$-CH_3), 45.52 + 45.58 (N-CH_2), 55.66 (OCH_3), 58.82 + 58.87 (C2'), 67.47 + 67.49 (C2), 75.44 (C7a), 111.41 + 111.42 (C6'), 116.60 + 116.63 (C5'), 119.27 + 119.29 (C4'), 130.27 (C3a'), 139.82 (C7a'), 146.51 (C7'), 170.77 + 170.80 (C4).

(±)-12-Methoxy-1,2,3a,4,5,7,8,13-octahydrofuro[3,2-a]indolo[3,2-h]-quinolizine (14)

To a solution of compound **12** (3.14 g, 0.010 mole) in dry chloroform (100 ml), phosphorus oxychloride (18.6 ml, 0.20 mole) was added and heated under reflux for 1 hour in argon atmosphere. The mixture was evaporated at 40 °C *in vacuo*, and the residue was treated with ice water (100 g) and decanted. The insoluble residue was treated three times with a mixture of water (3x12.5 ml) and concentrated hydrochloric acid (3x2.5 ml). The combined aqueous solutions were basified with 15 % aqueous sodium hydroxide solution (50 ml) and extracted with dichloromethane (4x25 ml). The combined extracts were dried ($MgSO_4$) and evaporated at 40 °C *in vacuo* giving the pure **14** (2.64 g, 89 %) as an orange foam, R_f = 0.70 (toluene-diethylamine 9-1 v/v). MS (m/z, %): 297 (20), 296 (M^+, 100), 295 (49), 268 (M-28,

56), 267 (20), 266 (23), 265 (26): IR (KBr, ν, cm^{-1}): 3496 (s, νNH, free), 1660 (νC=C, in D-ring), 1626 (νC=C, in B/C-ring), 1579 and 1499 (s, methoxy substd. A-ring), 1255 (vs, νC-O, methoxy), 1097 and 1015 (s, νC-O, in F-ring), 782, 739, and 732 (γCH, 1,2,3-trisubstd. A-ring). ^{1}H NMR (δ, ppm): 1.91 + 2.35 (2x1H, 2xm, C4-H_2), 2.90 + 3.00 (2x1H, 2xm, C1-H_2), 2.8-32 (5H, m, C7-H_2 + C8-H_2 + C5-H_A), 3.27 (1H, ddd, $J_{5A,5B}$ = -11.8, J_{vic} = 3.6 and 3.4 Hz, C5-H_B), 3.93 (1H, m, C2-H_A), 3.96 (3H, s, OCH_3), 4.23 (1H, ddd, $J_{2A,2B}$ = -8.5, J_{vic} = 8.8 and 3.0 Hz, C2-H_B), 4.41 (1H, m, C3a-H), 6.65 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = ~1 Hz, C11-H), 7.03 (1H, dd, $J_{9,10}$ = 7.8 Hz, C10-H), 7.13 (1H, br d, C9-H), 8.14 (1H, br s, NH).

13b-Epimers of Ethyl (±)-3-(12-Methoxy-1,2,3aβ,4,5,7,8,13,13b,13c-decahydrofuro[3,2-a]indolo[3,2-h]quinolizin-13cβ-yl)-2-(hydroxyimino)-propionate (16 and 17), and by-products Ethyl (±)-3-(12-Methoxy-1,2,3aβ,4,5,7,8,13,13bα,13c-decahydrofuro[3,2-a]indolo[3,2-h]quinolizin-13cβ-yl)-2-[(3-ethoxy-2-hydroxyimino-3-oxo-propoxy)-imino]-propionate (18) and (±)-12-Methoxy-13cβ-hydroxy-1,2,3aβ,4,5,7,8,13,13bβ,13c-decahydrofuro[3,2-a]indolo[3,2-h]quinolizine (19)

To a stirred solution of compound **14** (2.49 g, 8.4 mmole) and catalytic amount of benzyltributylammonium chloride (0.15 g) in dichloromethane (15 ml), an aqueous sodium hydroxide solution (0.390 g, 9.7 mmole in 5.5 ml of water) and a solution of ethyl bromopyruvate oxime[17] (1.94 g, 9.3 mmole) in dichloromethane (5.5 ml) were added simultaneously at -5 °C in 30 minutes. After the addition was complete, the stirring was continued for 2 hours at -5 °C. After separation, the aqueous phase was extracted with dichloromethane (3x5 ml), the combined organic phases were dried ($MgSO_4$), and evaporated *in vacuo*. From the residue (4.11 g) the ethyl (±)-12-methoxy-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 (**15**) was not isolated, but the residue was directly hydrogenated in dimethylforamide solution (65 ml) over palladium/charcoal (3.0 g) at ambient temperature and pressure. When the hydrogen consumption ceased, (45 hours, 235 ml, 9.7 mmole), the catalyst was filtered and washed with dimethylformamide (3x8 ml). The combined solutions were evaporated at 50 °C *in vacuo* to give a mixture of epimers **16** and **17** and compounds **18** and **19** which were separated by repeated column chromatography on silica gel (500 g, cyclohexane-diethylamine 7-3 v/v, R_f = 0.36, 0.29 0.16 and 0.45, respectively).

Compound **16**, the 13bα-epimer (0.98 g, 27%), the analytical sample was crystallized by solving in isopropanol and diluting with sixfold of cyclohexane, mp: 165-167 °C (decomp.); MS (m/z, %): 427 (M^+, 25), 410 (20), 336 (20), 227 (29), 215 (23), 214 (77), 200 (20), 84 (100), 56 (93); IR (KBr, ν, cm^{-1}): 3418 and 3336 (νNH, H-

bonded), 2932 and 2848 (νCH_2), 3000-2400 (vbr, νOH, oxime, H-bonded), 1709 and 1697 (vs, νC=O, ester, conjugated with C=N), 1628 (νC=C, in B/C-ring), 1578 and 1500 (methoxy substd. A-ring), 1257 (vs, νC-O, methoxy), 1024, 1005 (νC-O, νN-O), 779 and 734 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 1.31 (3H, t, J = 7.0 Hz, COO-CH_2-C<u>H</u>$_3$), 1.91 (1H, m, C4-H_e), 2.01 (1H, ddd, $J_{1A,1B}$ = -12.8, $J_{1A,2}$ = 9.8 and 7.5 Hz, C1-H_A), 2.30-2.42 (2H, m, C1-H_B + C4-H_a), 2.56-2.72 (3H, m, C7-H_a + C5-H_a + C8-H_A), 2.64 + 2.99 (2x1H, 2xd, J_{gem} = -13.6 Hz, C13c-CH_2), 2.78 (1H, ddd, J_{gem} = -11.3, J_{vic} = 5.2 and 2.0 Hz, C5-H_e), 2.96 (1H, m, C8-H_B), 3.09 (1H, ddd, J_{gem} = -11.2, J_{vic} = 5.7 and ~1 Hz, C7-H_e), 3.49 (1H, br s, C13b-H), 3.66 (1H, dd, J = 2.8 and 2.7 Hz, C3a-H), 3.82 (1H, ddd, $J_{2A,2B}$ = -8.5, $J_{1,2A}$ = 9.8 and 4.2 Hz, C2-H_A), 3.96 (3H, s, OCH_3), 4.05 (1H, ddd, $J_{1,2B}$ = 7.8 and 7.5 Hz, C2-H_B), 4.26 (2H, q, J = 7.0 Hz, COO-C<u>H</u>$_2$-CH_3), 6.62 (1H, dd, $J_{10,11}$ = 7.7, $J_{9,11}$ = 0.9 Hz, C11-H), 6.99 (1H, dd, $J_{9,10}$ = 7.9 Hz, C10-H), 7.06 (1H, dd, C9-H), 8.63 (1H, br s, indole-NH), 12.23 (1H, br s, N-OH), it contains cyclohexane as impurity. Anal. Calcd. for $C_{23}H_{29}N_3O_5$ + 0.25 C_6H_{12} (427.51 + 21.04): C 65.61, H 7.19, N 9.37 %. Found: C 65.58, H 7.29, N 9.28 %.

Compound **17**, the 13bβ-epimer (1.01 g, 28 %), the crystalline material was washed with dichloromethane, mp: 212-214 °C (decomp.); MS (m/z, %): 427 (M^+, 38), 410 (27), 337 (23), 336 (72), 295 (20), 227 (27), 214 (100), 200 (20), 104 (34); IR (KBr, ν, cm^{-1}): 3418 (s, νNH), 2950, 2892, and 2848 (νCH and νCH_2), 3000-2400 (vbr, νOH, oxime, H-bonded), 1720 (vs, νC=O, ester, conjugated with C=N), 1630 (w, νC=C, in B/C-ring), 1574 and 1503 (m, methoxy substd. A-ring), 1310 (s, ν_{as}C-O-C, conjugated ester), 1252 (νC-O, methoxy), 986 (νN-O), 729 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 1.35 (3H, t, J = 7.0 Hz, COO-CH_2-C<u>H</u>$_3$), 1.65-1.87 (4H, m, C1-H_2 + C4-H_2), 2.39 (1H, ddd, J_{gem} = -12.2, J_{vic} = 12.0 and 3.6 Hz, C5-H_a), 2.63-2.74 (2H, m, C7-H_a + C8-H_A), 2.89 + 3.51 (2x1H, 2xd, J_{gem} = -13.7 Hz, C13c-CH_2), 2.88-3.03 (2H, m, C5-H_e + C8-H_B), 3.14 (1H, m, C7-H_e), 3.46 (1H, br s, C13b-H), 3.66-3.82 (2H, m, C2-H_2), 3.98 (3H, s, OCH_3), 4.02 (1H, dd, J = 9.8 and 6.7 Hz, C3a-H), 4.30 + 4.32 (2x1H, 2xdq, J_{gem} = -10.8, J_{vic} = 7.0 Hz, COO-C<u>H</u>$_2$-CH_3), 6.59 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = 0.8 Hz, C11-H), 6.96 (1H, dd, $J_{9,10}$ = 7.9 Hz, C10-H), 7.04 (1H, dd, C9-H), 10.00 (1H, br s, indole-NH), 12.78 (1H, br s, N-OH), it contains dichloromethane as impurity. Anal. Calcd. for $C_{23}H_{29}N_3O_5$+ 0.25 CH_2Cl_2 (427.51 + 21.23): C 62.23, H 6.63, N 9.36 %. Found: C 62.51, H 6.69, N 9.24 %.

Compound **18** (0.133 g, 2.8 %), the crystalline material was washed with isopropanol, mp: 172-173 °C (decomp.); MS (m/z, %): 427 (31), 411 (22), 410 (33), 337 (22), 336 (41), 227 (50), 215 (45), 214 (100), 200 (36), 199 (20); IR (KBr, ν, cm^{-1}): 3468 (s, νNH), 2800-2300 (vbr, νOH, oxime, H-bonded), 1742 (νC=O, ester), 1710 (νC=O, conjugated ester), 1307 (s, ν_{as}C-O-C, conjugated ester), 1258 (vs, νC-O, methoxy, and ν_{as}C-O-C, ester), 1040, 1024, 1010, and 972 (νC-O and νN-O, in side chain), 730 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.29 and 1.31 (2x3H, 2xt, J = 7.0 Hz,

2xCOO-CH_2-CH_3), 1.82-1.92 (2H, m, C1-H_A + C4-H_e), 2.18-2.33 (2H, m, C4-H_a + C1-H_B), 2.60 + 3.00 (2x1H, 2xd, J_{gem} = -13.5 Hz, C13c-CH_2), 2.59-2.70 (3H, m, C5-H_a + C7-H_a + C8-H_A), 2.81 (1H, ddd, J_{gem} = -11.2, J_{vic} = 4.8 and 2.0 Hz, C5-H_e), 2.99 (1H, m, C8-H_B), 3.15 (1H, m, C7-H_e), 3.51 (1H, br s, C13b-H), 3.61 (1H, dd, J = 2.8 and 2.6 Hz, C3a-H), 3.79 (1H, m, C2-H_A), 3.95 (3H, s, OCH_3), 3.96 (1H, m, C2-H_B), 4.2-4.35 (4H, m, 2xCOO-CH_2-CH_3), 5.17 + 5.21 (2x1H, 2xd, J_{gem} = -11.3 Hz, O-CH_2-C=N), 6.62 (1H, dd, $J_{10,11}$ = 7.3, $J_{9,11}$ = 1.4 Hz, C11-H), 7.00 (1H, dd, $J_{9,10}$ = 7.9 Hz, C10-H), 7.03 (1H, dd, C9-H), 8.60 (1H, br s, indole-NH), 11.6 (1H, br, N-OH), it contains isopropanol as impurity. Anal. Calcd. for $C_{28}H_{36}N_4O_8$ + 0.25 C_3H_8O (556.62 + 15.02): C 60.41, H 6.70, N 9.80 %. Found: C 60.17, H 6.69, N 9.81 %.

Compound **19** (0.066 g, 2.5 %), the crystalline material was washed with toluene, mp: 176-180 °C (decomp.); MS (m/z, %): 315 (20), 314 (M^+, 100), 313 (75), 296 (M-18, 3), 283 (M-31, 6), 227 (36), 215 (23), 214 (63), 201 (48), 200 (20), 199 (20), 173 (33); IR (KBr, ν, cm^{-1}): 3458 (vs, νNH), 3375 (νOH, H-bonded), 2802 and 2755 (w, Bohlmann-bands, C/D *trans*-anellation), 1577 and 1498 (methoxy substd. A-ring), 1259 (vs, νC-O, methoxy), 774 and 731 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.69 (1H, dddd, J_{gem} = -13.2, $J_{3a,4\alpha}$ = 10.5, $J_{4\alpha,5\beta}$ = 12.5, $J_{4\alpha,5\alpha}$ = 4.6 Hz, C4-H_α), 1.73 (1H, dddd, J_{gem} = -13.5, J_{vic} = 8.0 and 3.5, $J_{1A,3a}$ = 1.0 Hz, C1-H_A), 1.92 (1H, dddd, $J_{3a,4\beta}$ = 7.0, $J_{4\beta,5\beta}$ = 2.5, $J_{4\beta,5\alpha}$ = 2.6 Hz, C4-H_β), 2.30 (1H, ddd, J_{vic} = 10.1 and 8.5 Hz, C1-H_B), 2.45 (1H, ddd, J_{gem} = -11.8 Hz, C5-H_β), 2.66 (1H, m, C7-H_β), 2.70 (1H, m, C8-H_β), 2.80 (1H, br s, OH), 2.93 (1H, ddd, C5-H_α), 2.96 (1H, m, C8-H_α), 3.09 (1H, m, C7-H_α), 3.51 (1H, dd, $J_{13b,8\alpha}$ = 2.5, $J_{13b,8\beta}$ = 1.3 Hz, C13b-H_β), 3.86 (1H, ddd, C3a-H_β), 3.95 (3H, s, OCH_3), 4.03 (1H, ddd, J_{gem} = -8.6, J_{vic} = 10.1 and 3.5 Hz, C2-H_A), 4.09 (1H, ddd, J_{vic} = 8.5 and 8.0 Hz, C2-H_B), 6.62 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = 0.8 Hz, C11-H), 7.01 (1H, dd, $J_{9,10}$ = 7.5 Hz, C10-H), 7.11 (1H, dd, C9-H), 8.99 (1H, br s, indole-NH); NOE: 3.51 (C13b-H) → 3.86 (C3a-H), 2.45 (C5-H_a), and 2.66 (C7-H_a); ^{13}C-NMR (δ, ppm): 22.03 (C8), 29.52 (C4), 32.21 (C1), 52.79 (C7), 52.82 (C5), 55.25 (OCH3), 63.37 (C13b), 65.72 (C2), 82.20 (C13c), 83.56 (C3a), 101.60 (C11), 109.26 (C8a), 110.90 (C9), 119.42 (C10), 125.91 (C12a), 127.85 (C8b), 132.43 (C13a), 145.98 (C12).

Methyl (±)-3-(12-Methoxy-1,2,3aβ,4,5,7,8,13,13bα,13c-decahydrofuro-[3,2-a]indolo[3,2-h]quinolizin-13cβ-yl)-2-(hydroxyimino)-propionate (20)

A solution of compound **16** (0.256 g, 0.60 mmole) in dry methanol (7.2 ml) containing catalytic amount of sodium methylate (0.12 mmole) was boiled in argon atmosphere overnight (21 hours). After cooling, it was acidified with acetic acid (0.01 ml) and evaporated *in vacuo* at 30 °C. The residue was treated with aqueous sodium carbonate solution (5 %, 3 ml) and extracted with dichloromethane containing 20 % of methanol (3x5 ml). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* at 30 °C giving the pure **20** (0.243 g, 98 %) as a light yellow foam, R_f = 0.32

(cyclohexane-diethylamine 7-3 v/v). MS (m/z, %): 413 (M^+, 33), 396 (M-17, 20), 354 (M-59, 6), 336 (M-59-18, 11), 297 (M-116, 14), 227 (28), 215 (23), 214 (100), 200 (20); IR (KBr, ν, cm^{-1}): 3420 (br, νNH), 3400-2400 (vbr, νOH, oxime), 1720 (s, νC=O, conjugeted ester), 1576 and 1500 (methoxy substd. A-ring) 1256 (vs, ν_{as} Ar-O-CH_3), 775 and 730 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.91 (1H, m, C4-H_e), 2.04 (1H, m, C1-H_A), 2.25-2.4 (2H, m, C1-H_B + C4-H_a), 2.6-2.75 (3H, m, C5-H_a + C7-H_a + C8-H_A), 2.65 + 3.07 (2x1H, 2xd, J_{gem} = -13.6 Hz, C13c-CH_2), 2.80 (1H, m, C5-H_e), 2.99 (1H, m, C8-H_B), 3.13 (1H, m, C7-H_e), 3.55 (1H, br s, C13b-H), 3.64 (1H, dd, J = 2.8 and 2.7 Hz, C3a-H), 3.81 (3H, s, $COOCH_3$), 3.83 (1H, m, C2-H_A), 3.94 (3H, s, C12-OCH_3), 4.05 (1H, m, C2-H_B), 6.64 (1H, dd, $J_{10,11}$ = 7.7, $J_{9,11}$ = 0.9 Hz, C11-H), 7.02 (1H, dd, $J_{9,10}$ = 7.9 Hz, C10-H), 7.09 (1H, dd, C9-H), 8.42 (1H, br s, indole-NH), 10.6 (1H, br s, N-OH).

Methyl (±)-3-(12-Methoxy-1,2,3aβ,4,5,7,8,13,13bβ,13c-decahydrofuro-[3,2-a]indolo[3,2-h]quinolizin-13cβ-yl)-2-(hydroxyimino)-propionate (21)

Compound **21** was prepared from compound **17** in 99 % yield as a white crystalline material, mp: 132-137 °C, according to the procedure of *cis*-analogue (**20**), but 2.3 times as much as methanol and 70 hours of boiling were used. R_f = 0.24 (cyclohexane-diethylamine 7-3 v/v); MS (m/z, %): 414 (32), 413 (M^+, 90), 412 (50), 396 (M-17, 44), 354 (M-59, 18), 336 (M-59-18, 48), 297 (M-116, 43), 295 (21), 227 (68), 215 (60), 214 (100), 200 (57), 199 (50), 186 (26); IR (KBr, ν, cm^{-1}): 3405 (νNH), 2800-2500 (νOH, oxime, in intramolecular H-bond), 1725 (νC=O, conjugated ester), 1630 (νC=N), 1251 (s, νC-O, methoxy); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 1.66-1.8 (2H, m, C1-H_2), 1.8-1.9 (2H, m, C4-H_2), 2.39 (1H, ddd, J_{gem} = -12.2, J_{vic} = 12.0 and 3.6 Hz, C5-H_a), 2.65-2.75 (2H, m, C7-H_A + C8-H_A), 2.89 + 3.54 (2x1H, 2xd, J_{gem} = -13.7 Hz, C13c-CH_2), 2.85-3.05 (2H, m, C5-H_e + C8-H_B), 3.14 (1H, m, C7-H_B), 3.47 (1H, br s, C13b-H), 3.70 + 3.77 (2x1H, 2xm, C2-H_2), 3.85 (3H, s, $COOCH_3$), 3.98 (3H, s, C12-OCH_3), 4.03 (1H, dd, J = 9.8 and 6.7 Hz, C3a-H), 6.60 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = 0.8 Hz, C11-H), 6.98 (1H, dd, $J_{9,10}$ = 7.9 Hz, C10-H), 7.07 (1H, dd, C9-H), 9.88 (1H, br s, indole-NH), 12.49 (1H, br s, N-OH).

Methyl (±)-17α,21-Epoxy-14,15-dihydro-14β-hydroxy-12-methoxy-3α,16α-eburnamenine-14α-carboxylate [(±)-Cuanzine] (1)

To a mixture of sulfuric acid (0.06 ml), water (0.6 ml), and acetic acid (0.12 ml), first a solution of sodium metabisulfite (0.380 g, 2.0 mmole) in water (1.4 ml), and after that compound **20** (0.214 g, 0.5 mmole) was added, and this mixture was stirred and boiled in argon atmosphere in an oil bath at 120 °C for 12 hours. After cooling, the reaction mixture was diluted with ice water (2 ml), basified with concentrated ammonium hydroxide solution (0.5 ml), and extracted with dichloromethane containig 15 % of methanol (5x5 ml). The combined extracts were

dried ($MgSO_4$) and evaporated *in vacuo* at 40 °C. The residue (0.155 g) was chromatographed twice on silica gel (25 g, toluene-diethylamine 9-1 v/v, R_f = 0.48) to give the analytically pure **1** (0.088 g, 44 %) as light yellow cristals, mp: 198-200 °C. In direct comparison with natural cuanzine by TLC, MS, IR, and NMR, they proved to be identical except that the natural compound is optically active while the synthetic product was a racemic mixture. MS (m/z, %): 399 (25), 398 (M^+, 100), 397 (42), 380 (M-18, 4), 339 (M-59, 66), 311 (M-87, 26), 296 (M-102, 51), 254 (46); IR (KBr/$CDCl_3$, ν, cm^{-1}): 3480/3530 (br, νOH and 2νC=O), 1750/1747 (vs, νC=O, ester), 1618 (νC=C, in B/C-ring), 1574/1574 and 1494/1495 (methoxy substd. A-ring), 1262/1262 (vs, νC-O, Ar-O-CH_3 and ν_{as}C-O-C, methyl ester), 1066 (νC-O, in F-ring), 725 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.59 (1H, ddd, J_{gem} = -12.4, J_{vic} = 7.5 and 3.7 Hz, C20-H_A), 1.62 (1H, dddd, J_{gem} = -12.8, $J_{17\beta,18\beta}$ = 6.5, $J_{18\beta,19}$ = 3.0 and 2.8 Hz, C18-H_β), 1.70 (1H, dddd, $J_{17\beta,18\alpha}$ = 10.5, $J_{18\alpha,19}$ = ~8.5 and ~8.5 Hz, C18-H_α), 2.02 (1H, d, J_{gem} = -14.1 Hz, C15-H_α), 2.52 (2H, m, C19-H_2), 2.59 (1H, m, C6-H_A), 2.66 (1H, d, C15-H_β), 2.81 (1H, ddd, J_{vic} = 10.3 and 9.0 Hz, C20-H_B), 2.93 (1H, m, C6-H_B), 3.32 (2H, m, C5-H_2), 3.77 (3H, s, $COOCH_3$), 3.88 (3H, s, C12-OCH_3), 4.02 (2H, m, C21-H_2), 4.36 (1H, dd, J_{lr} = 2.4 and 2.1 Hz, C3-H_α), 4.42 (1H, dd, C17-H_β), 4.53 (1H, br d, J_{lr} = ~1 Hz, C14-OH), 6.66 (1H, d, C11-H), 7.07 (1H, dd, C10-H), 7.14 (1H, d, C9-H); NOE: 4.36 (C3-H_α) → 2.02 (C15-H_α), 2.81 + 1.59 (C20-H_2), and 3.32 (C5-H_α); 4.42 (C17-H_β) → 1.62 (C18-H_β), 2.52 (C19-H_β), and 2.66 (C15-H_β); 4.53 (C14-OH) → 4.42 (C17-H_β), 2.66 (C15-H_β), 3.88 (C12-OCH_3), and 3.77 ($COOCH_3$).

Methyl (±)-17α,21-Epoxy-14,15-dihydro-14α-hydroxy-12-methoxy-3β,16α-eburnamenine-14β-carboxylate [(±)-14-epi-trans-Cuanzine] (22)

To a mixture of sulfuric acid (0.06 ml), water (0.6 ml), and acetic acid (0.37 ml), first a solution of sodium metabisulfite (0.380 g, 2.0 mmole) in water (1.4 ml), and after that, compound **21** (0.140 g, 0.34 mmole) was added, and the mixture was stirred and boiled in argon atmosphere in an oil bath at 120 °C for 42 hours. After cooling the mixture was diluted with ice water (2.5 ml), basified with concentrated ammonium hydroxide solution (1.0 ml), and extracted with dichloromethane containing 15 % of methanol (5x5 ml). The combined extracts were dried ($MgSO_4$) and evaporated at 30 °C *in vacuo*. The residue (0.073 g) was repeatedly chromatographed with cyclohexane-diethylamine (8-2 v/v, R_f = 0.29) and toluene-isopropanol (9-1 v/v, R_f = 0.46) on silica gel (25 and 10 g, respectively) to yield pure **22** (0.014 g, 10 %), as light yellow crystals, mp: 173-177 °C. MS (m/z, %): 399 (24), 398 (M^+, 100), 397 (M-1, 79), 383 (M-15, 11), 380 (M-18, 16), 339 (M-59, 86), 337 (34), 336 (31), 296 (M-102, 73), 295 (25), 268 (28); IR (KBr/$CHCl_3$, ν, cm^{-1}): 3460/3495 (νOH), 2818/2808 and 2756/2750 (Bohlmann-bands, C/D *trans*-anellation), 1739/1748 (νC=O, ester), 1637/1637 (νC=C, in B/C-ring), 1575/1573 and 1497/1496 (methoxy-

substd. A-ring), 1274/1265, 1256 (vs, ν_{as}C-O-C, methyl ester and νC-O, methoxy group), 1077/1077 (νC-O, in F-ring), 1020/1020 and 1012/1011 (νC-O, alcohol), 788 and 738 (γCH, 1,2,3-trisubstd. A-ring); ^{1}H NMR (δ, ppm): 1.8-1.95 (2H, m, C18-H_2), 2.07 (1H, ddd, J_{gem} = -10.4, $J_{15\beta,20A}$ = 1.5, $J_{15\beta,OH}$ = 1.7 Hz, C15-H_β), 2.21 (1H, dddd, J_{gem} = -12.5, J_{vic} = 9.6 and 9.4 Hz, C20-H_A), 2.25 (1H, ddd, J_{vic} = 7.9 and 3.5 Hz, C20-H_B), 2.34 (1H, dm, J_{gem} = -11.5 Hz, C19-H_β), 2.60 (1H, ddd, J_{gem} = -11.0, $J_{5\beta,6\alpha}$ = 11.5, $J_{5\beta,6\beta}$ = 4.4 Hz, C5-H_β), 2.68 (1H, d, C15-H_α), 2.74 (1H, dddd, J_{gem} = -15.0, $J_{5\alpha,6\beta}$ = 1.0, $J_{3\beta,6\beta}$ = 2.0 Hz, C6-H_β), 2.95 (1H, dddd, $J_{5\alpha,6\alpha}$ = 5.6, $J_{3\beta,6\alpha}$ = 2.5 Hz, C6-H_α), 3.01 (1H, m, C19-H_α), 3.14 (1H, dd, C3-H_β), 3.15 (1H, ddd, C5-H_α), 3.74 (1H, dd, J_{vic} = 9.2 and 7.6 Hz, C17-H_β), 3.76 (3H, s, $COOCH_3$), 3.90 (3H, s, C12-OCH_3), 4.0-4.15 (2H, m, C21-H_2), 5.08 (1H, br d, C14-OH), 6.67 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = ~1 Hz, C11-H), 7.06 (1H, dd, $J_{9,10}$ = 7.7 Hz, C10-H), 7.14 (1H, dd, C9-H); NOE ($CDCl_3$): 2.07 (C15-H_β) → 2.68 (C15-H_α), 3.14 (C3-H_β), and 3.74 (C17-H_β); 3.90 (C12-OCH_3) → 6.67 (C11-H), 5.08 (C14-OH), and 3.76 ($COOCH_3$); 2.60 (C5-H_β) → 3.15 (C5-H_α), 3.14 (C3-H_β), 2.34 (C19-H_β), and 2.74 (C6-H_β); 5.08 (C14-OH_α) → 3.90 (C12-OCH_3), 2.68 (C15-H_α), 3.76 ($COOCH_3$), and 2.21 + 2.25 (C20-H_2); NOE (C_6D_6): 3.55 (C17-H_β) → 1.64 (C18-H_β), 2.05 (C15-H_β), 2.94 (C3-H_β), and 1.90 (C19-H_β); 2.05 (C15-H_β) → 2.91 (C15-H_α), 2.94 (C3-H_β), and 3.55 (C17-H_β); 5.36 (C14-OH_α) → 3.22 (C12-OCH_3), 2.91 (C15-H_α), 2.49 (C20-H_B), and 3.27 ($COOCH_3$).

(±)-13cβ-(2-Amino-3-hydroxypropyl)-12-methoxy-1,2,3aβ,4,5,7,8,13, 13bα,13c-decahydrofuro[3,2-a]indolo[3,2-h]quinolizine (23)

To a stirred suspension of lithium aluminum hydride (0.38 g, 10 mmole) in dry tetrahydrofuran (15 ml) a solution of compound **16** (0.428 g, 1.0 mmole) in dry tetrahydrofuran (25 ml) was slowly added and then the suspension was boiled for 3 hours. The excess hydride was carefully decomposed at ice cooling and strong stirring by successively adding water (0.6 ml), 15 % aqueous sodium hydroxide solution (0.6 ml), and again water (1.8 ml). After 30 minutes of additional stirring it was filtered and washed thoroughly with tetrahydrofuran (5x5 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield **23** (0.356 g, 96 %) as a light yellow foam which was pure enough for the next step. According to NMR examinations, it was an epimeric mixture in the ratio of about 2:1. MS (160 °C, m/z, %): 372 (25), 371 (M^+, 96), 370 (24), 340 (M-31, 13), 312 (23), 311 (M-60, 100), 296 (M-75, 18), 268 (M-103, 7), 227 (38), 215 (65), 214 (28), 205 (23), 200 (28), 199 (27), 196 (28); ^{1}H NMR (δ, ppm): 3.49 and 3.42 (C13b-H), 3.72 and 3.69 (dd, J_{vic} = 3.0 and 2.6 Hz, C3a-H), 3.930 and 3.926 (s, C12-OCH_3), 6.5-7.1 (3H, aromatic protons), 8.39 and 9.04 (br s, indole NH); ^{13}C NMR (δ, ppm): 21.53 and 21.56 (C8), 26.96 and 25.48 (C4), 38.82^x and 33.58^o (C13c-$\underline{C}H_2$), 40.16^x and 35.38^o (C1), 46.39 and 45.10 (C13c), 49.92 and 50.37 (CH-NH_2), 51.05 and 50.62 (C5), 54.37 (C7), 55.22 and 55.27 (OCH_3), 64.41 and 65.04 (C13b), 65.62 and 66.05 (C2), 67.83 and 68.66 (CH_2OH), 81.00

and 79.93 (C3a), 102.03 and 101.89 (C11), 110.87 and 110.83 (C9), 112.03 and 112.22 (C8a), 120.04 and 119.79 (C10), 126.44 and 126.62 (C12a), 128.15 and 128.44 (C8b), 132.42 and 132.89 (C13a), 145.87 and 146.04 (C12).

(±)-13cβ-(2-Amino-3-hydroxypropyl)-12-methoxy-1,2,3aβ,4,5,7,8,13,13bβ,13c-decahydrofuro[3,2-a]indolo[3,2-h]quinolizine (24)

Compound **24** was prepared in 89 % yield as a light yellow foam from compound **17** according to the procedure of *cis*-analogue (**23**). It was pure enough for the next step. According to NMR examinations, it was an epimeric mixture in a ratio of about 2:1. MS (m/z, %): 372 (44), 371 (M^+, 100), 370 (42), 340 (M-31, 28), 338 (20), 312 (26), 311 (M-60, 70), 310 (23), 296 (M-75, 37), 268 (M-103, 24), 227 (43), 220 (37), 215 (64), 214 (44), 205 (66), 200 (38), 199 (36), 186 (31), 140 (30); ^{1}H NMR (δ, ppm): 1.81 + 1.91 (2x1H, 2xdd, J_{gem} = -15.3, J_{vic} = 6.0 and 2.5 Hz, respectively, C13c-CH_2), 3.12 and 3.25 (1H, m, C<u>H</u>-NH_2), 3.43 + 3.59 (2x1H, 2xdd, J_{gem} = -10.4, J_{vic} = 7.2 and 4.8, respectively, C<u>H</u>$_2$OH), 3.71 and 3.66 (1H, br s, C13b-H), 3.81 and 3.83 (1H, dd, J = 8.3 and 10.6 Hz, C3a-H), 3.93 and 3.92 (3H, s, OCH_3), 6.60 (C11-H), 6.98 (C10-H), 7.10 (C9-H), 11.43 and 10.35 (1H, br s, indole-NH); ^{13}C NMR (δ, ppm): 22.57 and 22.32 (C8), 28.14 and 27.78 (C4), 33.07 and 32.70 (C1), 41.41 and 41.89 (C13c-<u>C</u>H_2), 48.94 and 49.60 (CH-NH_2), 49.62 and 48.53 (C13c), 52.53^x and 52.40^o (C5), 53.07^x and 53.27^o (C7), 55.40 and 55.46 (OCH_3), 61.13 and 62.23 (C13b), 65.72 and 65.57 (C2), 69.58 and 68.63 (CH_2OH), 80.11 and 81.59 (C3a), 101.40 and 101.62 (C11), 110.82 (C9), 110.96 and 111.03 (C8a), 119.19 and 119.34 (C10), 126.75 and 126.58 (C12a), 128.48 and 128.00 (C8b), 134.00 and 133.30 (C13a), 146.22 and 146.05 (C12).

(±)-17α,21-Epoxy-14α,15-dihydro-14β-hydroxy-12-methoxy-3α,16α-eburnamenine (25)

To a solution of compound **23** (0.316 g, 0.85 mmole) in dichloromethane (8.5 ml), an aqueous solution (8.5 ml) of sodium periodate (0.218 g, 1.02 mmole) was added and stirred for 30 minutes at room temperature. After separation, the aqueous phase was extracted with dichloromethane (3x5 ml), and the combined extracts were dried ($MgSO_4$), and evaporated. From the residue (0.281 g), the pure compound **25** (0.086 g, 30 %) as a light yellow foam was isolated by column chromatography on SiO_2 (25 g, cyclohexane-diethylamine 8-2 v/v, R_f= 0.31). MS (160 °C, m/z, %): 341 (22), 340 (M^+, 100), 339 (68), 311 (20), 296 (M-44, 15), 227 (23), 226 (20), 215 (M-125, 61); IR (KBr, ν, cm^{-1}): 3550-3200 (vbr, νOH, H-bonded), 2928 and 2840 (νCH_2), 1616 (νC=C, in B/C-ring), 1572 and 1494 (methoxy substd. A-ring), 1255 (vs, νC-O, methoxy), 1060 (νC-O, in F-ring), 775 and 727 (γCH, 1,2,3-trisubstd A-ring); ^{1}H-NMR (δ, ppm): 1.56-1.76 (3H, m, C20-H_A + C18-H_2), 1.97 (1H, br dd, J_{gem} = -14.8, $J_{14\alpha,15\alpha}$ = 4.8 Hz, C15-H_α),

2.5-2.65 (4H, m, C15-H_β + C19-H_2 + C6-H_A), 2.77 (1H, ddd, J_{gem} = -12.4, J_{vic} = ~9.5 and ~9.5 Hz C20-H_B), 2.93 (1H, m, C6-H_B), 3.25-3.37 (2H, m, C5-H_2), 3.88 (1H, br d, $J_{OH,14\alpha}$ = 3.0, $J_{OH,15\alpha}$ = ~1 Hz, C14-OH), 4.00 (3H, s, OCH_3), 4.00-4.08 (2H, m, C21-H_2), 4.28 (1H, br d, J_{lr} = 2.4 and 2.0 Hz, C3-H_α), 4.46 (1H, dd, J_{vic} = 10.5 and 6.5 Hz, C17-H_β), 6.19 (1H, ddd, $J_{14\alpha,15\beta}$ = ~1Hz, C14-H_α), 6.69 (1H, dd, $J_{10,11}$ = 7.8, $J_{9,11}$ = 1.0 Hz, C11-H), 7.06 (1H, dd, $J_{9,10}$ = 7.8 Hz, C10-H), 7.13 (1H, dd, C9-H).

(±)-17α,21-Epoxy-14α,15-dihydro-14β-hydroxy-12-methoxy-3β,16α-eburnamenine (26)

Compound **26** was prepared from compound **24** according to the procedure of the *cis*-analogue (**25**), but with 2 hours reaction time. The yield of the slowly crystallizing glass-like material, R_f = 0.41 (cyclohexane-diethylamine 8-2 v/v) was 26 %. MS (m/z, %): 341 (30), 340 (M^+, 100), 339 (96), 296 (M-44, 7); IR (KBr, ν, cm^{-1}): 3485 (νOH), 1070 (s, νC-OH); ^{1}H NMR (δ, ppm): 1.25 (1H, ddd, J_{gem} = -12.5, J_{vic} = 6.5 and 4.2 Hz, C20-H_A), 1.75-1.95 (2H, m, C18-H_2), 1.86 (1H, ddd, J_{gem} = -14.0, $J_{14\alpha,15\beta}$ = 8.5, $J_{15\beta,20B}$ = 2.0 Hz, C15-H_β), 2.18 (1H, dddd, J_{vic} = 9.7 and 9.5 Hz, C20-H_B), 2.36 (1H, ddd, J_{gem} = -11.5, $J_{18\alpha,19\beta}$ = 12.7, $J_{18\beta,19\beta}$ = 3.3 Hz, C19-H_β), 2.57 (1H, ddd, J_{gem} = -11.1, $J_{5\beta,6\alpha}$ = 11.3, $J_{5\beta,6\beta}$ = 4.3 Hz, C5-H_β), 2.69 (1H, dd, $J_{14\alpha,15\alpha}$ = 6.4 Hz, C15-H_α), 2.71 (1H, m, C6-H_β), 2.91 (1H, dddd, J_{gem} = -15.2, $J_{5\alpha,6\alpha}$ = 5.7, $J_{3\beta,6\alpha}$ = 2.5 Hz, C6-H_α), 2.98 (1H, ddd, $J_{18\alpha,19\alpha}$ = 5.0, $J_{18\beta,19\alpha}$ = 2.4 Hz, C19-H_α), 3.10 (1H, ddd, $J_{5\alpha,6\beta}$ = 1.2 Hz, C5-H_α), 3.24 (1H, dd, $J_{3\beta,6\beta}$ = 2.0 Hz, C3-H_β), 3.83 (1H, dd, J_{vic} = 9.7 and 6.8 Hz, C17-H_β), 4.03 (3H, s, OCH_3), 4.0-4.1 (2H, m, C21-H_2), 5.16 (1H, br s, C14-OH), 6.02 (1H, dd, C14-H_α), 6.70 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = ~1 Hz, C11-H), 7.05 (1H, dd, $J_{9,10}$ = 7.8 Hz, C10-H), 7.14 (1H, dd, C9-H); NOE: 3.24 (C3-H_β) → 1.86 (C15-H_β), 2.36 (C19-H_β), 2.57 (C5-H_β), and 3.83 (C17-H_β); 5.16 (C14-OH) → 6.02 (C14-H_α), and 4.03 (C12-OCH_3); 6.02 (C14-H_α) → 1.25 (C20-H_A), 2.69 (C15-H_α), 5.16 (C14-OH), and 4.03 (C12-OCH_3); ^{13}C NMR (δ, ppm): 21.67 (C6), 26.73 (C20), 28.74 (C18), 38.61 (C15), 46.34 (C16), 52.03 (C5), 53.54 (C19), 55.90 (OCH_3), 61.37 (C3), 65.93 (C21), 76.57 (C14), 80.02 (C17), 102.42 (C11), 105.49 (C7), 112.24 (C9), 120.29 (C10), 125.63 (C13), 130.43 (C8), 134.03 (C2), 145.69 (C12).

(±)-17α,21-Epoxy-12-methoxy-3α,16α-eburnamenine [(±)-Decarbomethoxyapocuanzine] (4)

A solution of compound **25** (0.076 g, 0.22 mmole) in acetic anhydride (0.5 ml) was stirred at 100 °C for 30 minutes in argon atmosphere. After cooling, it was poured onto crushed ice (10 g), basified with sodium hydrogen carbonate (1 g), and extracted with dichloromethane (3x3 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography on SiO_2 (10 g, cyclohexane-diethylamine 8-2 v/v, R_f = 0.46) to yield pure **4** (0.032 g, 45 %); mp: 190-194 °C; MS (m/z, %): 322 (M^+, 63), 278 (M-44, 33), 238 (23), 237 (M-85,

100), 236 (42); IR (KBr, ν, cm^{-1}): 1636 (s, νC=C, in E-ring), 740 (γCH, *cis* -HC=CH-); ^{1}H-NMR (δ, ppm): 1.63-1.78 (2H, m, C18-H_2), 1.98 (1H, ddd, J_{gem} = -12.1, J_{vic} = 7.1 and 3.5 Hz, C20-H_A), 2.53 (1H, dddd, J_{gem} = -16.0, $J_{5\alpha,6\alpha}$ = 5.1, $J_{5\beta6\alpha}$ = ~1, $J_{3\alpha6\alpha}$ = 2.0 Hz, C6-H_α), 2.61 (1H, ddd, J_{gem} = -11.6, $J_{18,19\alpha}$ = 3.7 and 3.5 Hz, C19-H_α), 2.65 (1H, ddd, J_{vic} = 9.6 and 9.5 Hz, C20-H_B), 2.77 (1H, ddd, $J_{18,19\beta}$ = 11.8 and 3.2 Hz, C19-H_β), 2.94 (1H, dddd, $J_{5\alpha,6\beta}$ = 11.4, $J_{5\beta,6\beta}$ = 5.9, $J_{3\alpha,6\beta}$ = 2.7 Hz, C6-H_β), 3.28 (1H, ddd, J_{gem} = -13,7 Hz, C5-H_α), 3.36 (1H, ddd, C5-H_β), 3.64 (1H, dd, J_{vic} = 10.5 and 6.6 Hz, C17-H_β), 3.95 (3H, s, OCH_3), 4.03-4.15 (2H, m, C21-H_2), 4.59 (1H, dd, C3-H_α), 5.10 (1H, d, $J_{14,15}$ = 7.8 Hz, C15-H), 6.68 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = 1.0 Hz, C11-H), 7.02 (1H, dd, $J_{9,10}$ = 7.7 Hz, C10-H), 7.07 (1H, dd, C9-H), 7.51 (1H, d, C14-H).

(±)-17α,21-Epoxy-12-methoxy-3β,16α-eburnamenine [(±)-trans-Decarbomethoxyapocuanzine] (5)

Compound **5** was prepared from compound **26** according to the procedure of *cis*-analogue (**4**) in 31 % yield as light yellow crystals, mp: 125-129 °C, R_f = 0.53 (cyclohexane-diethylamine 8-2 v/v). MS (m/z, %): 323 (20), 322 (M^+, 96), 321 (100), 293 (M-1-28, 33); IR (KBr, ν, cm^{-1}): 2794 and 2735 (m, Bohlmann-bands, C/D *trans*-anellation), 1653 (m, νC=C, in E-ring), 1606 (νC=C, in B/C-ring), 1431 (vs, δCH, *cis* -HC=CH-), 1258 (vs, ν_{as} Ar-O-CH_3), 740 (γCH, *cis* -HC=CH-), 723 (s, γCH, 1,2,3-trisubstd. A-ring), 681 (m, γCH, *cis* -HC=CH-); ^{1}H NMR (δ, ppm): 1.38 (1H, dd, J_{gem} = -12.0, $J_{20A,21A}$ = 7.6, $J_{20A,21B}$ = 2.5 Hz, C20-H_A), 1.81 (1H, dddd, J_{gem} = -13.8, $J_{17\beta,18\alpha}$ = 9.5, $J_{18\alpha,19\alpha}$ = 5.5, $J_{18\alpha,19\beta}$ = 12.8 Hz, C18-H_α), 1.93 (1H, dddd, $J_{17\beta,18\beta}$ = 6.8, $J_{18\beta,19\alpha}$ = 2.3, $J_{18\beta,19\beta}$ = 3.4 Hz, C18-H_β), 2.34 (1H, ddd, J_{gem} = -11.5 Hz, C19-H_β), 2.59 (1H, ddd, J_{gem} = -11.1, $J_{5\beta6\alpha}$ = 11.0, $J_{5\beta,6\beta}$ = 4.0 Hz, C5-H_β), 2.67 (1H, ddd, $J_{20B,21A}$ = 9.8, $J_{20B,21B}$ = 9.9 Hz, C20-H_B), 2.69 (1H, dddd, J_{gem} = -15.2, $J_{5\alpha,6\beta}$ = 1.5, $J_{3\beta,6\beta}$ = 1.7 Hz, C6-H_β), 2.99 (1H, ddd, C19-H_α), 3.01 (1H, dddd, $J_{5\alpha,6\alpha}$ = 5.4, $J_{3\beta,6\alpha}$ = 2.7 Hz, C6-H_α), 3.16 (1H, ddd, C5-H_α), 3.27 (1H, dd, C3-H_β), 3.94 (1H, ddd, J_{gem} = -8.3 Hz, C21-H_A), 3.95 (3H, s, OCH_3), 4.02 (1H, dd, C17-H_β), 4.04 (1H, ddd, C21-H_B), 5.52 (1H, d, $J_{14,15}$ = 7.5 Hz, C15-H), 6.67 (1H, dd, $J_{10,11}$ = 7.6, $J_{9,11}$ = 1.0 Hz, C11-H), 7.02 (1H, dd, $J_{9,10}$ = 7.7 Hz, C10-H), 7.08 (1H, dd, C9-H), 7.45 (1H, d, C14-H); NOE: 3.27 (C3-H_β) → 2.34 (C19-H_β), 2.59 (C5-H_β), and 4.02 (C17-H_β).

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