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INDOLE-ALKALOID ANALOGUES FROM DIDROVALTRATUM[1]

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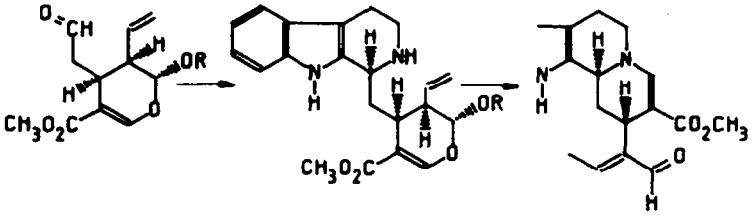
Abstract - The condensation products of secoaldehydes 4 and 16 with N-benzyl-tryptophane-methylester can be easily transformed into pentacyclic indole-alkaloid analogues.

The combination of a highly functionalized C_{10}-terpene unit with a tryptophane or tryptamine residue is a very typical and unique structural feature of all important indole-alkaloids.[2] As the decisive steps leading to very early biogenetic intermediates like strictosidine 1 look like a very normal Pictet-Spengler reaction, followed by demasking of hidden aldehyde groups and subsequent cyclization reactions, it is very tempting to look for naturally occuring chiral C_{10}-building blocks that may be available in quantity and could be used as a cycloaliphatic C_{10} unit for various indole-alkaloids. Secologanin (1) itself for instance has been used as starting material in biomimetic synthesis,[3] but due to the high reactivity of the malonic-semi-aldehyde moiety (C_3;C_{11}) there is a high tendency to the formation of vallesiachotamine (3) in vitro. 3 unfortunately, does represent a biosynthetic as well as a synthetic dead end. By using N-benzyl-tryptamine this particular cyclization can be blocked but in the subsequent hydrogenolytic deprotection the for further development extremely important 8/10 double bond is hydrogenated too.

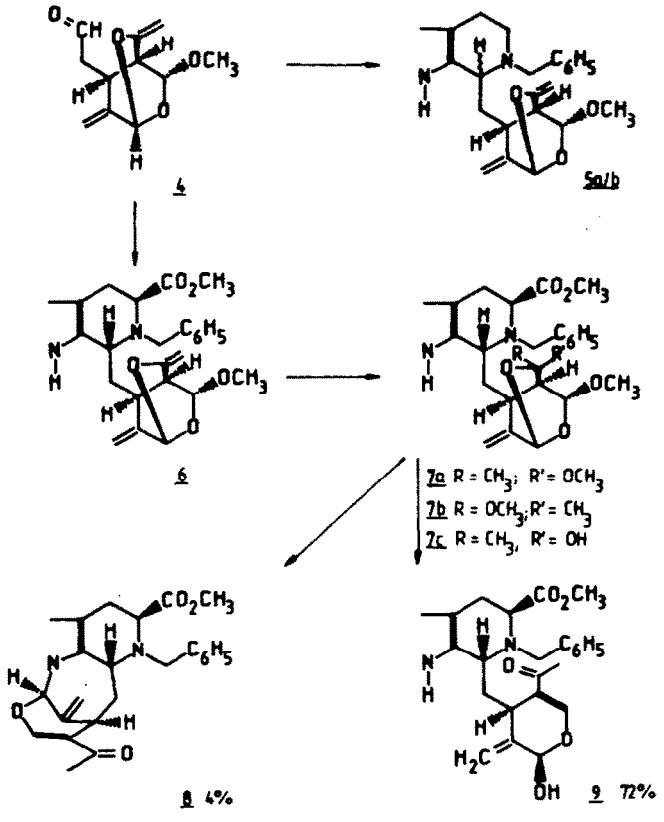


1 2 3

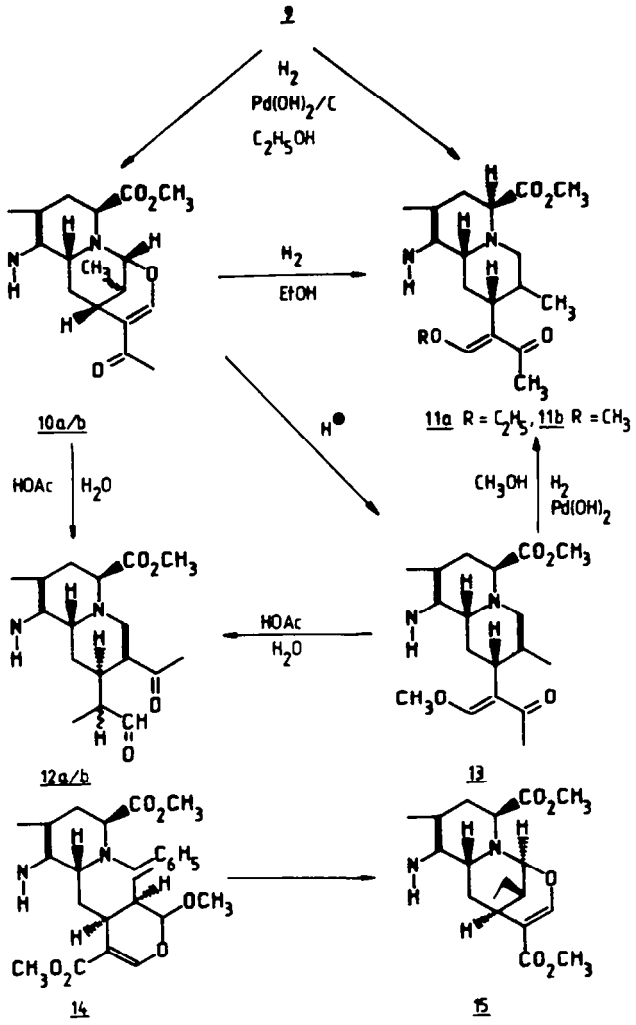
By choosing a building-block from the iridoid group of terpenes one would at any rate make sure however for the synthetically very important short chemical distance between educt and natural product and there additionally would be the guarantee to work with and to arrive at pure enantiomers with the correct absolute configuration. Following this strategy and realising the crucial role of the semi-malonic-aldehyde moiety in diverting the non-enzymatic reaction of strictosidine into the dead end vallesiachotamine, one has to look for secologanin resembling iridoids either completely missing this particular functionality or at least enclosing it in a less reactive form, as a synthetic substitute for non-enzymatic conversions. By subsequently simulating well known or sometimes obvious or easy to guess biosynthetic transformations various alkaloid analogues may be easily available.

This was the reason to investigate the formation as well as the subsequent Pictet-Spengler reactions of tryptamine derived Schiff bases generated from aldehydes 4 and 16. In both although showing close similarity to secologanin (1) the crucial 8/10 double bond turns out to be protected as part of a 1,3-dicarbonyl system. Additionally 4 is available in large amounts from didro-valtratum the main iridoid from valeriana wallichii (see preceeding paper) which is cultivated in Northern Germany; the iridoid terpenes being isolated and purified by using the in this area well established sugar beet technology. The reaction product 5 formed with N-benzyl-tryptamine and aldehyde 4, which was chosen for first generation model experiments, as far as constitution goes looks like a strictosidine analogue, but if it comes to configuration it unfortunately turns out to be a non-satisfying 2.5 : 1 mixture of diastereomers.

Obviously there is not sufficient diastereoselectivity in the cyclization step and thus for further experiments tryptophane ester was chosen, as this molecule by virtue of its space demanding ester group can be expected to direct the C_3-configuration and to additionally enhance the synthetic flexibility as this particular type of ester group was shown to be a synthetic equivalent of the corresponding iminium salt.[3] Following reaction conditions as developed for 5 the tryptophane ester gave rise indeed to just one pure diastereomer, and configuration 6 is indicated for this product,[4] NMR as well as mass-spectroscopy clearly proving its structure.



To now study the behaviour of the crucial 8/10 double bond the acid catalyzed addition of methanol was investigated and as expected the epimeric methanol adducts 7a and 7b were obtained in high yield and easily separated. On employing water as the nucleophile one is not surprised to observe immediate ring opening of the semi-acetal 7c under the reaction conditions, followed by elimination of methanol to form the vinylogue ester 9 as the main product of hydrolysis (72%), which is accompanied by only a small amount (~4%) of a less polar by-product (8) obviously formed by nucleophilic attack of the indole-nitrogen on acetal carbon atom-3. As one is unable to convert 9 into 8 and vice versa, the formation of the seven membered ring has to preceed elimination. Interestingly this type of N,O-acetal formation generating a seven membered ring does find parallels in indole-alkaloid biosynthesis.[5]

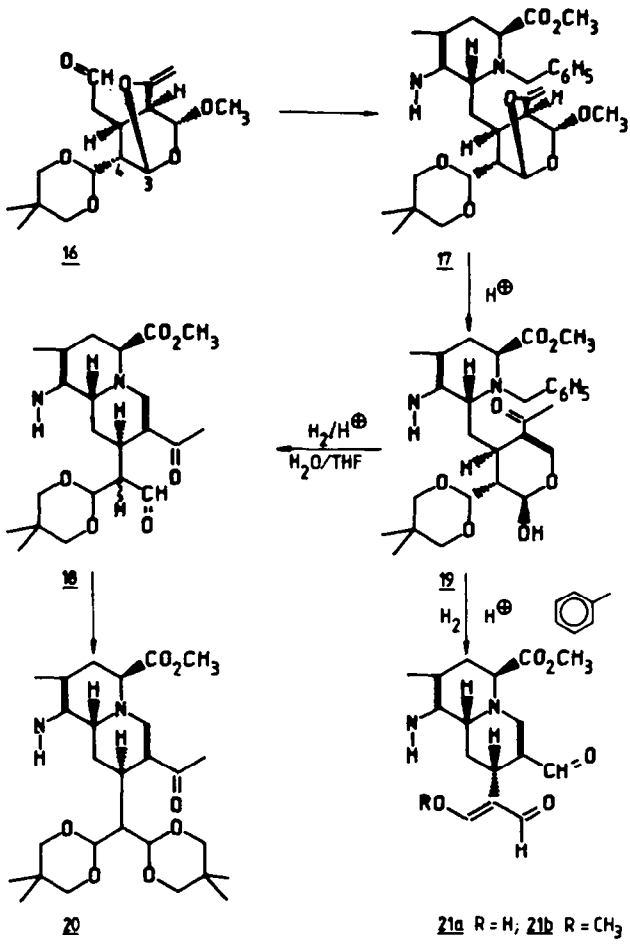


As the vinylogue ester group in 9 can be expected to protect this double bond against hydrogenation, the demasking of the benzylamine was studied next und depending on hydrogenation conditions two substances can be isolated. If the hydrogenation (solvent: ethanol) is stopped immediately after disappearance of starting material 9 (TLC!) one gets roughly a 2 : 1 mixture of the debenzylated tetrahydro product 10 - stabilized again as a bicyclic acetal - and the ethyl enolether 11a of the hexahydro product. Formation of 10 is in a way resembling the generation of 5Θ-carbomethoxy-dihydromancunin 15 on hydrogenation of the protected amine 14 as reported by R.T.Brown.[6] Stereochemically 10 however, is representing a C_3-epi-dihydromancunin with cis-orientation of hydrogens at C_3 and C_{15} thus arguing against any interference of 3-epi-dihydromancunin type intermediates in indole-alkaloid biosynthesis.[7] On continued hydrogenation in ethanol the hexahydro product 11a proves to be the only final reaction product.

These experiments prove clearly that functionality at C_8 being part of the 1,3-dicarbonyl system is untouched, even in a hexahydro product. Of course the 4/11 double bond is saturated under these conditions but this is meeting expectations and for the second generation of synthetic intermediates early transformation of this double bond had been taken care of already (see 16).

Prior to starting his series however, we did investigate acid catalyzed solvolysis of N,O-acetal 10. On treatment with a trace of sulfuric acid in methanol at room temperature the enamine 13 is formed which for chemical structure proof is hydrogenated to the vinylogue ester 11b which as the corresponding ethyl derivative had been obtained from 9 already. Subsequent hydrolysis leads to the vinylogues amide 12 which may also be obtained from the cyclic N,O-acetals 10a,b directly.

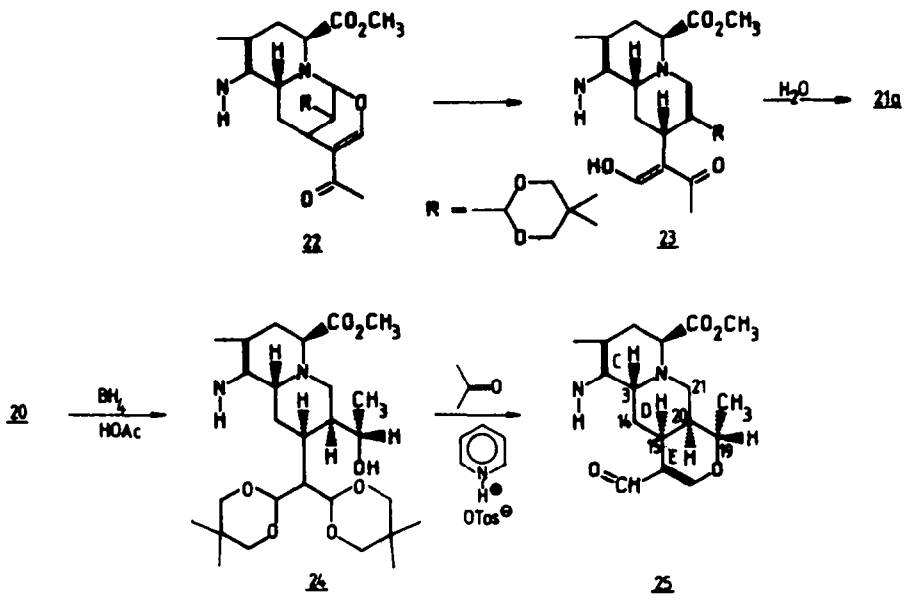
This last hydrolysis smoothly gives rise to a very interesting corynanthe type substitution pattern and clearly application of this sequence to an aldehyde like 16 would open the road to alkaloid analogues.



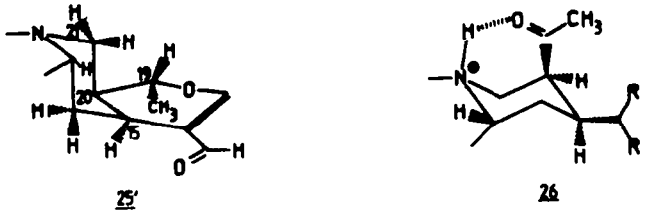
Although 16 is crowded with functionality, on applying the mild reaction conditions, worked out for 5, to this aldehyde the Pictet-Spengler product 17 is obtained in an even higher yield than in the model series. This is also true for the subsequent hydrolysis which yields 80% of the vinylogue ester 19, containing no functionality that could suffer from the hydrogenation step. As three different aldehyde equivalents are ready for electrophilic attack to the nucleophilic centre to be generated we decided not to isolate the hydrogenation product, but to "in situ" demask the aldehyde groups by aqueous and non-aqueous acid treatment. As expected the molecule responded quite differently to these reagents.

In aqueous tetrahydrofuran the epimeric aldehydes 18a,b are the main reactions products. To prove this assignment the stereoconvergent acetalisation with neopentyl glykole, converting a centre of chirality into a pro-chiral carbon atom, was shown to generate the homogeneous bis-acetal 20. Under non-aqueous conditions employing trifluoro-acetic acid in toluene the vallesia-chotamine type aldehyde 21 is isolated as the only reaction product and these results hint to an O,N-acetal intermediate 22 similar to 10, that could be isolated in the model series but in this case in a very quick elimination reaction generates enamine 23 which representing the acetal of a vinylogue amide is expected to hydrolyse even under neutral conditions.[8]

20 looks very promising for a highly selective borohydride reduction and in the event the Djerassi conditions provided hydroxy compound 24 as a single pure stereoisomer, the configuration of which could not be deduced from the alcohol itself but was assigned from NMR data, including decoupling experiments of the pentacyclic aldehyde 25 which is obtained on acid catalyzed trans-



ketalization. These data do show strong similarity with those of well known pentacyclic hetero-yohimbine alkaloids prepared by us before[9] and left no doubt as far as the vinylogue ester group is concerned. A cis-quinolizidine structure with an axial hydrogen atom at C_3 is indicated by lack of Bohlmann bands in the infra-red and a broad 11 Hz coupling to the axial proton at C_{14}. A small H_{14} - H_{15} coupling is in line with the cis-D/E juncture having the axial substituent at C_{15} and this is supported by a 12 Hz H_{20} - H_{12ax} coupling and a corresponding 5 Hz H_{20} - H_{21eq} coupling, proving the equatorial C_{20} substituent (see 25').



The 8-19 hydrogen is indicated by a small 2 Hz coupling to the proton at C_{20} in connection with a downfield shift (4.35 ppm) which is due to the in-plane position of this hydrogen-atom with the vinylogue ester moiety,[10] a phenomen which is visible in the corresponding akuammigin (19BH) - isoraunicin (19H) pair of stereoisomers too.

The high stereoselectivity of the reduction at C_{20} is remarkable but has been observed by us many years ago in other very similar cases too.[11] As the reduction of the keto group definitely is the last step in the acetic acid borohydride reduction sequence we explain this result by a hydrogen bridge fixing the carbonyl conformation as shown in 26 and allowing only for Re-attack of the hydride donor, the Si-sector being efficiently shielded by the bulky bis-acetale at C_{15}.

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EXPERIMENTAL

Melting points were determined on a Kofler bank. Infrared spectra were taken on Perkin-Elmer 457 and 580. UV spectra on Beckman 3600 and DB GT. ^{1}H NMR spectra with TMS as internal standard were recorded on the following instruments: AT 80 MHz on a Varian CFT 20; at 90 MHz on Bruker WH 90 and HX 90; at 270 MHz on Bruker WH 270; at 300 MHz on a Nicolet WB 2000 respectively ^{13}C NMR spectra were taken on the Bruker WH 270 instrument at 67.89 MHz. Critical assignments were in any case confirmed by extensive spin-spin decoupling and NOE experiments. Mass spectra were recorded on a Finnigan MAT 312 instrument at 70 eV. Preparative TLC (PTC) separations were run on self coated 0.5 mm thick plates (100 mg/20 cm). For conventional column chromatography "Woelm SiliTech" (63 - 200 µm) and for flash chromatography at 0.5 kp/cm^2 "Silica Woelm" 32 - 63 (32 - 63 µm) were used. Temperatures refer to bath temperatures.

Pictet-Spengler cyclization product 6: 3.68 g (9.7 mmol) of iodide 3 (cf. preceding paper) were transformed into 2 g of seco-aldehyde 4 (cf. preceding paper). 4 was subjected to reaction with 2 g (6.5 mmol) N_b-benzyl-L(-)-tryptophane-methylester in 35 ml of dry toluene in the presence of 15 g $MgSO_4$ at 60°C for 12 hrs and at 70-75°C for 48 hrs under N_2-atmosphere. On filtration, washing with CH_2Cl_2, evaporation in vacuo 4.3 g of a reddish foam was obtained. Purification by conventional column chromatography on 120 g (gradual elution with 5-20% ether/petrolether) yields 1.2 g (25% overall yield based on the iodide) of 6 as a colourless foam. $[\alpha]_D^{20}$ = -29.1; UV: indole chromophor; IR ($CHCl_3$): 3480 (m), 1730 (s), 1675 (m), 1120 (s), 1070 (s); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.62 [1] tr (J = 4 Hz), 1.65 - 1.8 [1] m, 1.82-1.98 [1] m, 3.0-3.25 [2] m, 3.31 [1] d_{AB} broad, (J = 12 Hz), 3.4 [1] d (J = 12 Hz), 3.48 [3] s, 3.63 [1] s broad, 3.7 [1] dd (J_1 = 12 Hz, J_2 = 4 Hz), 3.88 [3] s, 3.90 [1] (J_{AB} = 12 Hz), 4.13 [1] dd (J_1 = 12 Hz, J_2 = 4 Hz), 4.3 [1] s broad, 4.6 [1] d (J = 4 Hz), 5.02 [1] d (J = 2 Hz), 5.25 [1] s, 7.1-7.22 [2] m, 7.26-7.45 [6] m, 7.55 [1] d (J = 8 Hz), 7.58 [1] s broad, with H/D exchange; ^{13}C NMR: δ = 20.07, 27.8, 38.1, 40.1, 52.0, 52.1, 53.0, 55.5, 56.5, 86.2, 96.8, 100.1, 107.2, 109.5, 110.8, 118.1, 119.8, 121.9, 127.1, 128.3, 130.1, 134.1, 136.1, 139.4, 146.5, 173.3; MS (130°C): m/e 500 (M^+, 7%), 499 (16), 468 (3), 456 (6), 441 (9), 410 (14), 332 (5), 319 (100), 259 (8), 220 (4), 184 (4), 169 (11), 156 (6), 91 (36).

Methanol adducts 7a and 7b: 60 mg (0.12 mmol) of 6 was dissolved in 6 ml of dry CH_3OH and stirred for 35 min after addition of one drop of conc. HCl. After neutralization with $NaHCO_3$, evaporation in vacuo all organic material was taken up in CH_2Cl_2, filtrated, and concentrated. Separation by TLC (10% CH_2Cl_2/30% ether / petrolether) yielded 22 mg (35%) of non polar epimer 7a and 25 mg (39%) of polar epimer 7b as colourless foams.

Non polar epimer 7a: UV: indole chromophor; IR ($CHCl_3$): 3450 (m), 1730 (s), 1600 (vw), 100 (vs), 1020 (vs9; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.5 [3] s, 1.73 [1] dd (J_1 = 15 Hz, J_2 = 10 Hz), 2.19 [1] ddd (J_1 = 15 Hz, J_2 = 8 Hz, J_3 = 2 Hz), 2.9-3.13 [2] m + d (J = 7 Hz, partly overlapped), 3.38 [3] s, 3.45 [3] s, 3.78 [1] d (J = 7 Hz), 3.84 [3] s, 4.05 [1] dd (J_1 = 10 Hz, J_2 = 7 Hz), 4.9-5.1 [3] m, 5.2 [1] s broad, 7.0-7.6 [9] m, 8.25 [1] s broad; MS (140°C): m/e 532 (M^+, 12%), 502 (2), 474 (3), 458 (1), 442 (6), 410 (5), 397 (3), 338 (5), 319 (100), 306 (7), 259 (5), 250 (9), 219 (16), 184 (2), 169 (8), 156 (7), 91 (42). Found: 532.2572 (mass spectroscopy). Calc.for $C_{31}H_{36}N_2O_6$: 532.2573.

Polar epimer 7b: UV: indole chromophor; IR ($CHCl_3$): 3650 (m), 1730 (s), 1620 (vw), 1090 (vs), 1020 (vs); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.5 [3] s, 1.68 [1] ddd (J_1 = 18 Hz, J_2 = 8 Hz, J_3 = 2 Hz), 1.9-2.32 [1] m, 3.42 [3] s, 3.45 [3] s, 3.84 [3] s, 4.05 [1] dd (J_1 = 10 Hz, J_2 = 6 Hz), 4.9-5.1 [2] m, 5.11 [1] s broad, 5.34 [1] s, 7.05-7.58 [9] m, 8.18 [1] s broad; MS (150°C): m/e 532 (M^+, 15%), 501 (4), 473 (3), 441 (7), 409 (3), 319 (100), 261 (3), 181 (1), 169 (3), 156 (4), 91 (13). Found: 532.2578 (mass spectroscopy). Calc.for $C_{31}H_{36}N_2O_6$: 532.2573.

Acid hydrolysis of 6: 200 mg (0.65 mmol) 6 was dissolved in 25 ml THF/H_2O (1 : 1), 18 drops of concentrated HCl were added and the batch is stirred for 60 min at r.t. After neutralisation with $NaHCO_3$, evaporation of THF in vacuo, extraction with $CHCl_3$, drying ($MgSO_4$), and evaporation 191 mg of crude mixture (containing a minor non polar and a major polar product according to TLC) was obtained. TLC (10% CH_2Cl_2/30% ether/petrolether) yields 7 mg (~4%) of non polar polycyclic 8

(after crystalization from acetone/ether) and 141 mg (72%) of rather polar vinylogue ester 9 as a colourless foam.

Polycycle 8: m.p.: 173°C; $[\alpha]_D^{20}$ = -94°C; UV: 292 (3.49), 282 (3.78), 258 (3.98), 225 (4.20); IR ($CHCl_3$): 1730 (s), 1660 (m), 1620 (vs); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.88 and 1.93 [3] s, 2.98 [1] dd (J_1 = 16 Hz, J_2 = 4 Hz), 3.12 [1] ddd (J_1 = 16 Hz, J_2 = 10 Hz, J_3 = 1 Hz), 3.52 [1] d (J = 14 Hz), 3.77 [3] s, 5.05 [1] s, 5.08 [1] s, 6.45 [1] s broad, 7.12-7.37 [7] m, 7.4 [1] s; MS (130°C): m/e 468 (M^+, 35%), 453 (2), 440 (32), 425 (23), 409 (43), 397 (30), 383 (12), 377 (82), 370 (10), 349 (14), 344 (7), 319 (27), 290 (19), 276 (14), 262 (12), 259 (12), 247 (17), 233 (25), 218 (20), 206 (18), 193 (17), 180 (9), 168 (19), 154 (7), 136 (10), 91 (100). Found: 468.2048 (mass spectroscopy). Calc.for $C_{29}H_{28}N_2O_4$: 468.2049.

(17R,20E)-4-Benzyl-17,21-epoxy-17-hydroxy-16-methylen-19-oxo-3β-4,21-seco-coryn-20-en-5β-carbonsäure-methylester 9:

$[\alpha]_D^{20}$ = +84°C; UV: 290 (3.93), 278 sh (4.08), 258 (4.24), 225 (4.64) - on addition of 0.1n-NaOH: λ_{max} = 285 (5.0); IR (KBr): 3390 (m), 1730 (s), 1650 (m), 1610 (vs), 740 (m), 700 (m); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.55-1.72 [1] m, 1.90 [1] dtr (J_1 = 13 Hz, J_2 = 2 Hz), 2.10 [3] s, 2.81 [1] d broad (J = 9 Hz), 3.0 [1] dd (J_1 = 16 Hz, J_2 = 4.5 Hz), 3.18 [1] dd (J_1 = 16 Hz, J_2 = 9 Hz), 3.46 [1] d (J = 14 Hz), 3.75 [1] d (J = 14 Hz), 3.78 [1] broad - H/D exchange -, 3.85 [3] s, 3.9-4.02 [2] m, 4.18 [1] d broad (J = 9 Hz), 4.7 [1] d broad (J = 12 Hz), 7.1-7.3 [7] m, 7.32 [1] d (J = 8 Hz), 7.53 [1] (J = 8 Hz), 7.43 [1] s, 8.35 [1] s broad, 9.03 [1] s broad; ^{13}C NMR: δ = 19.65, 24.8, 37.4, 52.2, 53.4, 57.0, 61.6, 107, 111, 118.2, 118.9, 119.5, 121.8, 126.8, 127.8, 128.5, 128.8, 134.1, 136.7, 138.5, 158.2, 196.3, 200.5; MS (190°C): m/e 486 (M^+, 5%), 485 (8), 467 (5), 426 (7), 409 (5), 395 (40), 377 (10), 319 (63), 259 (12), 184 (9), 169 (16), 156 (13), 91 (100). Found: 486.2156 (mass spectroscopy). Calc.for $C_{29}H_{30}N_2O_5$: 486.2155.

Hydrogenolysis of vinylogue ester 9: 100 mg (0.205 mmol) of vinylogue ester 9 was hydrogenated in 20 ml ethanol over 27 mg $Pd(OH)_2/C$ ("Pearlman" catalyst) at a pressure of 1000 mm H_2O with magnetic stirring until all starting material disappeared on TLC (ca. 7 hrs). Filtration through a cellite-pad (CH_2Cl_2 wash!) and evaporation yielded 80 mg of yellowish material. By TLC (3% CH_3OH/$CHCl_3$) 15 mg (18%) of non polar ethyl enolether 11a (colourless solid) and 31 mg (39%) of polar polycyclic N,O-acetal 10 (unstable yellowish foam) are isolated.

Ethyl enolether 11a: UV: 290 sh, 258, 215 (main peak); IR ($CHCl_3$): 3480 (m), "Bohlmann" bands: 2870-2750 (vw), 1740 (s), 1650 (m), 1625 (vs); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.66 [3] d (J = 6 Hz), 1.25 [ca.3] tr (J = 7 Hz), 3.0-3.33 [2] m, 3.54 [3] s, 3.82 [1] m, 3.98 [2] q (J = 7 Hz), 4.11-4.45 [1] m, 6.92-7.45 [4] m, 7.27 [1] s, 7.72 [1] s broad; MS (120°C): m/e 410 (M^+, 56%), 395 (5), 381 (27), 365 (4), 351 (100), 323 (12), 309 (6), 295 (6), 269 (4), 242 (5), 237 (4), 222 (4), 209 (4), 197 (3), 183 (8), 169 (21), 156 (8), 130 (7). Found: 410.2205 (mass spectroscopy). Calc.for $C_{24}H_{30}N_2O_4$: 410.2206.

Polycyclic N,O-acetals 10a/b: (Diastereomeric mixture of C-20 epimers). UV: 288 (sh), 280 (sh), 268, 226 (main peak), on addition of concentrated NaOH a strong absorption at 285 nm is detected; IR (CCl_4): 3470 (m), 1740 (s), 1640 (s), 1605 (vs); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.85 [3] d (J = 7 Hz), 1.41 and 1.72 [3] s (ratio 1 : 3 due to integration), 2.79 [1] s (v br), 3.22-3.45 [2] m, 3.69 [3] s, 4.32 [1] dd (J_1 = 6 Hz, J_2 = 3 Hz), 4.61-4.83 [1] m (v br), 4.99 [1] s broad, 6.95 and 7.11 [1] s, 7.0-7.58 [4] m, 8.35 and 8.53 [1] s broad; MS (110°C): m/e 380 (M^+, 52%), 365 (6), 351 (9), 323 (15), 321 (26), 295 (10), 293 (16), 290 (14), 269 (100), 242 (18), 233 (17), 221 (10), 209 (32), metastable peak: 190 (5), 183 (16), 169 (20), 156 (20), 130 (15). Found: 380.1725 (mass spectroscopy). Calc.for $C_{22}H_{24}N_2O_4$: 380.1736.

(16)-16-Methyl-17,19-dioxo-3β-coryn-20-en-5β-carbonsäure-methylester 12:

Variant A: 25 mg (0.09 mmol) of 10 are stirred in 2 ml of glacial acetic acid/water (1 : 1) for 1.5 hrs. The appearance of a characteristic vinylogous amide chromophor is detected. On dilution with CH_2Cl_2, neutralisation with $NaHCO_3$ (ice bath), filtration, and evaporation, 22 mg of crude material was obtained. Purification by TLC (30% petrolether/ethyl acetate) and crystalization from

ether yields 14 mg (56%) of colourless crystals.

Variant B: (without purification of 10). 100 mg (0.205 mmol) of vinylogue ester 9 was hydrogenated as described above. The crude yellowish material was stirred in 7 ml glacial acetic acid/water (1 : 1) and worked up in analogy to variant A to yield 13 mg (15% overall) non polar ethylenolether 11a and 27 mg (29% overall) of vinylogous amides 12. m.p.: 132°C; UV: 298 (4.27), 290 sh (4.25), 255 (4.31); IR ($CHCl_3$): 3460 (m), 2720 (vw), 1735 (s), 1715 (s), 1600 sh (s), 1585 (vs); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.12 and 1.21 [3] d (J = 5 Hz), 1.69 [1] ddd (J_1 = J_2 = 12 Hz, J_3 = 5 Hz), 2.22 and 2.25 [3] s, 2.69 [1] ddd (J_1 = 12 Hz, J_2 = 7 Hz, J_3 = 2.5 Hz), 3.0-3.5 [3] m, 3.68 [3] two s with Δδ = 1 Hz, 4.48 [1] d broad (J = 5.5 Hz), 4.61-5.0 [1] m (broad triplett habitus), 7.0-7.62 [4] m, 7.47 [1] s broad, 8.33 [1] s broad, 9.67 and 9.83 [1] d (J = 2 Hz); MS (150°C): m/e 380 (M^+, 100%), 368 (10), 365 (9), 352 (11), 352 (11), 337 (13), 323 (94), 321 (98), 309 (30), 297 (31), 293 (20), 279 (12), 263 (31), 249 (14), 237 (11), 221 (16), 207 (11), 195 (10), 183 (13), 169 (29), 156 (25), 149 (16), 143 (14), 130 (29), 111 (28), 97 (45), 83 (47), 71 (42), 69 (44), 57 (48). Found: 380.1733 (mass spectroscopy). Calc.for $C_{22}H_{24}N_2O_4$: 380.1735.

(16E)-16-Acetyl-17-methoxy-3β,15α-18-nor-coryna-16,20-dien-5α-carbonsäure-methylester 13:

25 mg (0.09 mmol) of 10 was dissolved in 4 ml of dry CH_3OH, a trace of concentrated H_2SO_4 was added and the reaction was stirred for 8 hrs under N_2 atmosphere. The reddish reaction mixture was neutralized with $NaHCO_3$, evaporated and all organic material was taken up in 100 ml CH_2CL_2 (small portions), washed with water, dried ($MgSO_4$) and purified by TLC (50% ethyl acetate/petrolether). Yield: 18 mg (69%) of amorphous, yellowish solid. UV: 287, 280 (sh), 256, 225 (main absorption); IR (CCl_4): 3480 (m), 1740 (s), 1660 (m), 1630 (s); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.43 [3] s broad, 2.25 [3] s, 3.1-3.3 [2] m, 3.59 [3] s, 3.82 [3] s, 3.95-4.2 [1] m, 4.5-4.78 [1] m, 5.83 [1] s broad, 7.0-7.56 [4] m, 7.28 [1] s, 7.78 and 7.93 [1] s broad; MS (250°C): m/e 394 (M^+, 100%), 379 (50), 363 (53), 337 (73), 335 (93), 319 (75), 393 (87), 235 (85), 233 (80), 221 (33), 209 (53), 183 (33), 169 (93), 156 (72), 143 (28), 130 (33). Found: 394.1887 (mass spectroscopy). Calc.for $C_{23}H_{26}N_2O_4$: 394.1692.

Hydrogenation of 13: 10 mg (0.02 mmol) enamine 13 was hydrogenated in 5 ml of ethanol over 3 mg of 10% Pd/C under normal pressure until TLC indicates complete disappearance of starting material. After ca. 3 hrs the catalyst was removed by cellite filtration, the filtrate taken to dryness and subjected to TLC (ethylacetate/petrolether 1 : 1). The saturated indolochinolizidine 11b crystalizes immediately on trituration with acetone. Yield: 6 mg (60%). m.p.: 144°C; UV: 290 (3.67), 280 (3.85), 258 (4.08), 225 (4.35); IR (KBr): 3370 (s), "Bohlmann"-bands: 2800 (w), 2740 (vw), 1730 (s), 1710 (s), 1650 (m), 1620 (vs), 740 (m); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.72 [3] d (J = 6 Hz), 2.25 [3] s, 3.1-3.33 [2] m, 3.7-3.92 [1] m, 3.8 [3] s, 4.1-4.25 [1] m, 7.0-7.2 [2] m, 7.2-7.55 [ca.3] m, 7.68 [1] s broad; MS (130°C): m/e 395 (M^+, 56%), 381 (37), 365 (13), 353 (6), 351 (6), 337 (100), 323 (26), 309 (20), 295 (20), 281 (10), 261 (11), 242 (10), 235 (20), 219 (20), 207 (16), 197 (15), 195 (16), 183 (28), 169 (42), 156 (16), 154 (19), 142 (10), 129 (16). Found: 396.2048 (mass spectroscopy). Calc.for $C_{23}H_{28}N_2O_4$: 396.2049.

(16S,17R,21R)-4-Benzyl-16-[5,5-dimethyl-[1,3]dioxan-2-yl]-17,19;17,21-diepoxy-21-methoxy-3β,20βH-4,21-seco-coryn-18-en-5α-carbonsäure-methylester 17:

A sodium methylate solution is prepared by adding 2 g of sodium in small portions to 165 ml of CH_3OH and 5.7 g (11.8 mmol) of neopentyl-acetal 4 (cf.preceding paper) was added and stirred for 1.5 hrs at 60°C (bath temperature) under dry N_2-atmosphere. After concentration to 1/3 of the initial volume, 500 ml of ether was added, the solution transferred to a separating funnel and this organic layer washed twice with a saturated $(NH_4)_2SO_4$ solution (NH_3!), water dried ($MgSO_4$), filtrated and evaporated in vacuo to yield 3.7 g of yellow oily crude neopentyl-seco-aldehyde 16 which was used immediately without further purification. 16 was dissolved in 60 ml dry toluene, 3.7 g (12 mmol) Nb-benzyl-L(-)-tryptophane-methylester and 25 g $MgSO_4$ was added, stirred for 24 hrs at 60°C and further 24 hrs at 80°C (bath temperature) under N_2-atmosphere. Filtration, evaporation in vacuo (7.3 g crude

material) and purification by flash chromatography (0.5% CH_3OH/CH_2Cl_2) yielded 2.62 g (37%) of pure 17 as a colourless foam. $[\alpha]_D^{20}$ = -42°C; UV: indole-chromophor; IR ($CHCl_3$): 3480 (m), 1740 (s), 1675 (m), 1090 (vs), 1020 (vs); ^1H NMR (270 MHz, $CDCl_3$): δ = 0.7 [3] s, 1.0 [3] s, 1.55-1.65 [1] m, 1.7-1.8 [1] m, 1.9-2.0 [1] m, 2.02 [1] tr (J = 3 Hz), 2.55-2.7 [1] m, 2.95-3.2 [2] m, 3.35-3.65 [8] m with a s at 3.48, 3.7-3.9 [6] m with a s at 3.8, 4.15 [1] dd (J_1 = 12 Hz, J_2 = 5 Hz), 4.28 [1] s broad, 4.48 [1] d (J = 8 Hz), 4.75 [1] d (J = 3 Hz), 5.24 [1] d (J = 3 Hz), 7.1-7.4 [ca.9], 7.55 [1] d (J = 7 Hz), 8.27 [1] s broad; MS (250°C): m/e 602 (M^+, 1%), 601 (2), 543 (2), 511 (2), 395 (1), 332 (2), 319 (100), 273 (2), 259 (12), 220 (4), 218 (4), 183 (5), 169 (30), 156 (5), 140 (4), 130 (4), 115 (27), 91 (80). Found: 602.2983 (mass spectroscopy). Calc.for $C_{35}H_{42}N_2O_7$: 602.2992.

(16S,17S,20E)-4-Benzyl-16-[5,5-dimethyl-[1,3]dioxan-2-yl]-17,21-epoxy-17-hydroxy-19-oxo-3β-4,21-seco-coryn-20-en-5β-carbonsäure-methylester 19:

1.4 g (2.32 mmol) of Pictet-Spengler product 17 was suspended in 60 ml THF/H_2O (1 : 1), 46 drops of concentrated HCl (ca. 17 mmol) were added and stirred for 60 min at r.t. (17 dissolved immediately). Neutralisation with $NaHCO_3$, extraction with $CHCl_3$, washing with water, drying ($MgSO_4$), and evaporation yielded 1.4 g of crude 19, which was purified by TLC on 4 large plates (1% ether/chloroform). 1.09 g (80%) of 19 was obtained as a colourless foam. $[\alpha]_D^{20}$ = +137°C; UV: 290 (3.88), 2.85 (3.97), 262 (4.14), 225 (4.62); IR (CCl_4): 3460 (m), 3350 br (m), 1740 (vs), 1650 (m), 1615 (vs); ^1H NMR (90 MHz, $CDCl_3$): δ = 0.73 and 0.78 [3] s (rotamers), 1.22 and 1.27 [3] s (rotamers), 2.18 [3] s, 3.0-3.25 [2] m, 3.76 [3] s, 3.9-4.2 [2] m, 4.45 [1] d (J = 8 Hz), 5.17 [1] dd (J_1 = 12 Hz, J_2 = 2 Hz, on H/D exchange d, J = 2 Hz), 6.0 [1] d (J = 12 Hz), 7.05-7.62 [9] m, 7.48 [1] s, 9.05 [ca.1] s broad; MS (190°C): m/e 588 (M^+,ca.0.5%), 570 (M-18, 1), 542 (2), 527 (2), 511 (2), 498 (3), 479 (5), 455 (4), 398 (4), 394 (5), 369 (4), 347 (17), 319 (40), 307 (6), 259 (29), 247 (7), 219 (7), 206 (3), 193 (3), 184 (7), 169 (17), 156 (10), 151 (9), 140 (5), 130 (3), 115 (22), 91 (100). Found: 570.2731 (mass spectroscopy). Calc.for $C_{34}H_{40}N_2O_7$-H_2O: 570.2729.

Hydrogenolysis of 19: 183 mg (0.31 mmol) of 19 was hydrogenated in 18 ml ethanol over 65 mg 30% $Pd(OH)_2/C$ ("Pearlman"-catalyst) for 2 hrs at 1000 mm H_2. The formation of a very unstable polar product is completed within 2 hrs (TLC). After filtration through cellite the filtrate is concentrated to 15 ml and 15 ml H_2O was added and the solution was stirred for 6 hrs at r.t. (appearance of a characteristic vinylogous amide chromophor). On removing ethanol in vacuo, extraction with $CHCl_3$, drying ($MgSO_4$), filtration and evaporation, 130 mg of material was obtained. TLC (10% ether/ethylacetate yields 10 mg (7%) non polar vinylogue amide 18a, 48 mg (32%) polar vinylogue amide 18b, and 14 mg (11%) very polar vinylogue acid 21a.

(16)-16-[5,5-Dimethyl-]1,3 dioxan-2-yl -17,19-dioxo-3β-coryn-20-en-5β-carbonsäure-methylester 18a:

(colourless foam): UV: 298.221 (vinylogue amide spectrum); IR (KBr): 3390 (m), 1735 (s), 1720 (s), 1615 (s), 1575 (vs), 1200 (vs), 1120 (s), 1020 (s), 740 (m); ^1H NMR (270 MHz, $CDCl_3$): δ = 0.72 [3] s, 1.22 [3] s, 1.70 [1] ddd (J_1 = J_2 = 12 Hz, J_3 = 5 Hz), 2.2 [3] s, 2.49 [1] dd (J_1 = 12 Hz, J_2 = 5 Hz), 2.88 [1] m, 3.23 [1] ddd (J_1 = 15 Hz, J_2 = 5 Hz, J_3 = 2 Hz), 3.4-3.65 [6] m, 3.7 [3] s, 4.45 [1] d (J = 5 Hz), 4.82 [1] d broad (J = 12 Hz), 5.08 [1] d (J = 3 Hz), 7.1-7.25 [2] m, 7.35 [1] d (J = 8 Hz), 7.50 [1] d (J = 8 Hz), 7.45 [1] s, 7.85 [1] s broad, 9.79 [1] d (J = 2 Hz); MS (170°C): m/e 480 (M^+, 7%), 479 (24), 466 (8), 437 (19), 425 (5), 409 (4), 407 (4), 380 (47), 365 (4), 352 (14), 337 (14), 323 (100), 321 (100), 309 (17), 297 (27), 281 (30), 279 (53), 263 (57), 261 (40), 249 (31), 236 (20), 229 (16), 219 (36), 206 (16), 202 (17), 194 (10), 183 (14), 169 (28), 160 (16), 156 (11), 143 (10), 129 (13), 115 (32). Found: 480.2260 (mass spectroscopy). Calc.for $C_{27}H_{32}N_2O_6$: 480.2260.

(16)-16- 5,5-Dimethyl- 1,3 dioxan-2-yl -17,19-dioxo-3β-coryn-20-en-5β-carbonsäure-methylester 18b:

(colourless foam): UV: 310.221 (vinylogue amide spectrum); IR (KBr): 3400 (m), 1735 (s), 1720 (s), 1595 (m), 1550 (vs), 1090 (vs), 1060 (vs), 1020 (vs), 740 (m); ^1H NMR (270 MHz, $CDCl_3$): δ = 0.73 [3] s, 1.22 [3] s, 1.72 [1] ddd (J_1 = 13 Hz, J_2 = 11 Hz, J_3 =

5 Hz), 2.37 [3] s, 2.52 [1] d broad (J = 13 Hz), 2.87 [1] m, 3.12 [1] dd (J_1 = 16 Hz, J_2 = 4 Hz), 3.4-3.6 [ca.6] m, 3.68 [3] s, 4.85 [1] d broad (J = 11 Hz), 5.05-5.2 [2] m, 7.08-7.22 [2] m, 7.33 [1] d (J = 8 Hz), 7.50 [1] d (J = 8 Hz), 8.11 [1] s broad, 9.7 [1] s, 9.75 [1] d (J = 2 Hz); MS (180°C): m/e 480 (M^+, 10%), 479 (35), 450 (19), 425 (14), 398 (9), 380 (51), 366 (9), 352 (13), 337 (25), 323 (100), 321 (76), 309 (29), 297 (25), 293 (50), 279 (28), 263 (57), 249 (36), 235 (19), 232 (20), 219 (20), 206 (20), 202 (19), 194 (13), 183 (21), 169 (43), 160 (20), 156 (21), 143 (14), 129 (29), 115 (39). Found: 480.2270 (mass spectroscopy). Calc.for $C_{27}H_{32}N_2O_6$: 480.2260.

Vinylogue acid 23 (colourless crystals from a ketone): m.p.: 212°C; UV: 292 (3.81), 218 (3.95); IR (KBr): 3400 (s), 1740 (s), 1600 (m), 1580 (vs), 740 (m); ^{1}H NMR (90 MHz, DMSO-d_6): δ = 2.11 [3] s v broad, 3.61 [3] s, 4.72 [1] d broad (J = 10 Hz), 5.01 [1] d broad (J = 4 Hz), 6.9-7.1 [2] m, 7.2-7.55 [2] m, 8.76 [1] s broad, 11.0 [1] s; MS (210°C): m/e 394 (M^+, 93%), 378 (8), 365 (34), 351 (56), 335 (15), 323 (35), 309 (65), 279 (50), 249 (98), 235 (50), 219 (100), 206 (30), 194 (17), 183 (13), 169 (44), 156 (53), 129 (38). Found: 394.1530 (mass spectroscopy). Calc.for $C_{22}H_{22}N_2O_5$: 394.1528.

(16E)-16-Formyl-17-hydroxy(methoxy)-19-oxo-3β,15β-18-nor-coryna-16,20-dien-5β-carbonsäure-methylester 21a:

50 mg (0.08 mmol) of vincoside analogue 19 was hydrogenated as described previously in 5 ml ethanol over 15 mg of "Pearlman"-catalyst for 2 hrs, passed through a cellite-pad and evaporated. The crude mixture, containing the unstable compound accompanied with traces of 18a and 18b was immediately dissolved in 5 ml of dry toluene, three drops of THF were added and the batch was stirred for 1 h at r.t. CH_2Cl_2 was added and the mixture was evaporated several times. Trituration with acetone yields 15 mg (45% overall, referred to 19) colourless crystals of 21a.

16-[(E)-Hydroxy(methoxy)methylen]-17,19-dioxo-3β,15β-18,19-seco-yohimb-20-en-5β-carbonsäure-methylester 21b:

22 mg (0.06 mmol) of a vinylogue acid 21a was stirred with an excess of etherical diazomethane. On TLC the formation of polar 21b is detected. Stirring for additional 3 hrs. at r.t., evaporation and TLC (10% CH_3OH/ethylacetate) yields 19 mg (83%) of pure colourless foam. UV: 297 (4.35), 265 (4.05), 221 (4.26); IR ($CHCl_3$): 3470 (m), 2720 (vw), 1740 (s), 1630 (vs), 1600 (vs); ^{1}H NMR (90 MHz, 260°K, $CDCl_3$, split of by rotamers): 2.18 and 2.34 [3] s, 3.11-3.50 [1] m, 3.60 and 3.64 [3] s, 3.73 and 3.91 [3] s, 4.11-4.33 [1] m, 4.50 [1] m, 4.79 [1] d broad (J = 10 Hz), 7.02 [1] s broad, 7.06 [1] s broad, 7.06-7.62 [5] m, 8.84 and 8.88 [1] s, 8.65 and 9.21 [1] s.

Bis-acetal 20: 21 mg (0.044 mmol) of epimeric vinylogue amides 18a/b was dissolved in 2 ml dry CH_2Cl_2, 42 mg (0.4 mmol) neopentylglycol, one crystal of p-toluene-sulfonic acid, some $MgSO_4$ were added and the mixture stirred for 1 week under a dry nitrogen atmosphere. Short column (0.5 x 5 cm) filtration (elution with 50 ml of ethyl acetate) yields 30 mg of crude material. TLC (10% $CHCl_3$/ 30% ethyl acetate/petrolether) gave 1 mg of not further investigated material plus 16 mg (65%) bis-acetal 20 as a colourless foam. UV: 300 (4.64); IR (CCl_4): 3475 (m), 1740 (s), 1692 (vs), 1590 (vs); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.70 [3] s, 0.77 [3] s, 1.20 [3] s, 1.33 [3] s, 1.59 [1] ddd (J_1 = 12 Hz, J_2 = 12 Hz, J_3 = 5 Hz), 2.11-2.33 [4] s (2.22) and m, 3.01 [1] d broad (J = 13 Hz), 4.94-5.11 [2] d m (J = 2 Hz), 7.05-7.55 [4] m, 7.47 [1] s broad, 8.05 [1] s broad; MS (180°C): m/e 566 (M^+, 13%), 523 (2), 507 (2), 480 (1), 466 (10), 451 (2), 423 (2), 376 (4), 359 (5), 322 (100), 279 (40), 261 (47), 249 (19), 236 (22), 219 (32), 206 (9), 194 (7), 183 (6), 169 (10), 156 (8), 154 (8), 143 (6), 131 (10), 129 (8), 115 (19). Found: 566.2995 (mass spectroscopy). Calc.for $C_{32}H_{42}N_2O_7$: 566.2992.

Hydroxy compound 24: 16 mg (0.028 mmol) of bis-acetal 20 was dissolved in 5 ml of dry glacial acetic acid a total of 560 mg (15 mmol) of $NaBH_4$ was added in small portions with magnetical stirring and occasional cooling on a ice bath: Stirring was continued for 30 min after completed addition. The mixture was carefully (CO_2!) added to a solution of 5 g Na_2CO_3 in 15 ml of water. extraction with $CHCl_3$, water wash, drying ($MgSO_4$), filtration, evaporation in vacuo yielded 20 mg

of crude material which gave 8 mg (50%) of crystalline (from ether) hydroxy compound 24 on TLC (20% petrolether/ether). m.p.: 239°C; UV (CCl_4): 3480 (s), 1730 (s), 1260 (vs), 1100 (vs), 1020 (vs); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.70 [3] s, 0.74 [3] s, 1.04 [3] s, 1.19-1.33 [6] s d (J = 6 Hz), 3.11-3.28 [2] m, 3.63 [3] s, 3.71-4.17 [2] m, 4.65 [1] d (J = 8 Hz), 5.0-5.11 [2] m, 7.0-7.33 [3] m, 7.36-7.55 [1] m, 7.9 [1] s broad; MS (170°C): m/e 570 (M^+, 52%), 565 (10), 525 (27), 511 (34), 483 (13), 467 (5), 455 (10), 453 (12), 439 (4), 423 (8), 407 (10), 395 (11), 379 (5), 369 (4), 351 (8), 337 (4), 325 (67), 309 (24), 293 (5), 281 (100), 265 (14), 242 (28), 229 (13), 221 (33), 206 (21), 195 (17), 183 (26), 169 (31), 156 (10), 143 (8), 129 (8), 115 (71), 69 (81), 57 (21), 55 (21), 45 (35). Found: 570.3286 (mass spectroscopy). Calc.for $C_{32}H_{46}N_2O_7$: 570.3305.

Pentacyclic aldehyde 25: 5 mg (0.009 mmol) of hydroxy compound 24 was boiled to reflux in 5 ml of wet acetone in the presence of 5 mg of pyridiniumtosylate (PPTS) for 60 hrs. After evaporation of acetone, the mixture was taken up in CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtrated, evaporated and purified by TLC (20% petrolether/ether). 2 mg (60%) of 25 was isolated as a colourless foam. UV: 290, 280 (sh), 251, 221 (major absorption); IR (CCl_4): 3465 (m), 2720 (vw), 1740 (s), 1675 (s), 1610 (vs), 1190 (s); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.25 [3] d (J = 7 Hz), 1.9-2.0 [1] m, 2.72 [1] dd (J_1 = 12 Hz, J_2 = 5 Hz), 2.88-2.96 [1] m, 3.5 [3] s, 3.72 [1] dd (J_1 = 7 Hz, J_2 = 2 Hz), 4.1 [1] d broad (J = 11 Hz), 4.35 [1] dq (J_1 = 7 Hz, J_2 = 2 Hz), 6.95-7.1 [2] m, 7.25 [1] d (J = 7 Hz), 7.39 [1] d (J = 7 Hz), 7.22 [1] d (J = ca.1.5 Hz), 8.02 [1] s broad, 9.25 [1]s; MS (140°C): m/e 380 (M^+, 80%), 363 (33), 351 (77), 335 (10), 321 (100), 309 (10), 307 (8), 303 (10), 393 (38), 281 (43), 279 (21), 267 (20), 255 (15), 249 (17), 247 (28), 235 (12), 221 (26), 219 (29), 206 (25), 197 (28), 195 (24), 183 (50), 168 (50), 160 (19), 156 (40), 154 (37), 142 (19), 129 (37), 115 (37). Found: 380.1736 (mass spectroscopy). Calc.for $C_{22}H_{24}N_2O_4$: 380.1736.

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