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SECO-ALDEHYDES FROM DIDROVALTRATUM[1]

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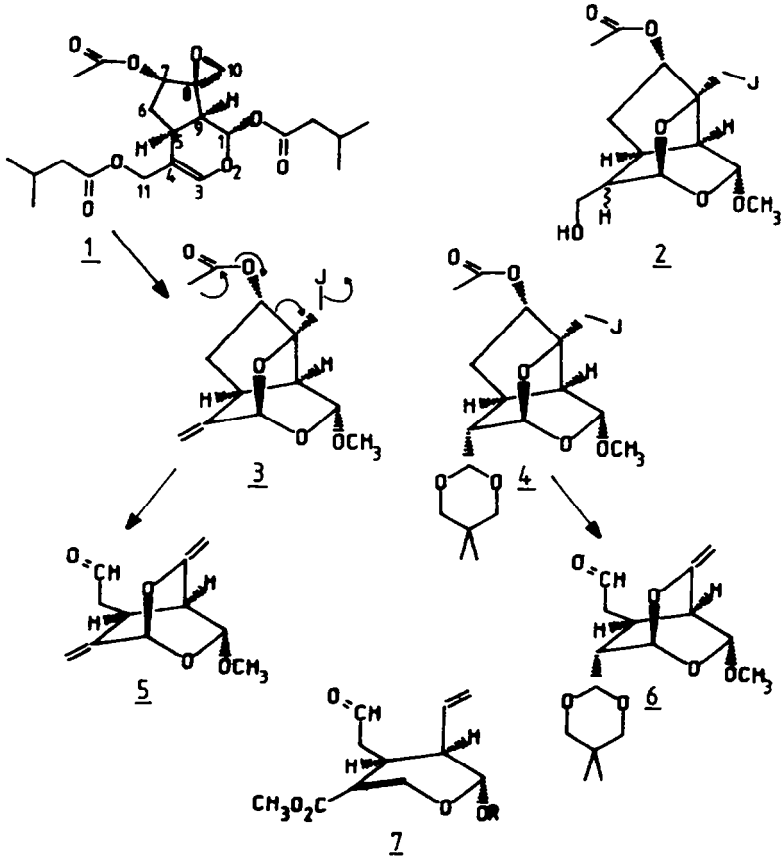
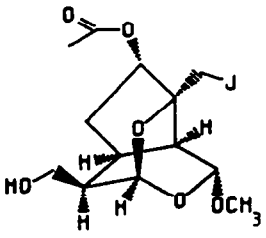
Abstract - Primary iodides, obtained from didrovaltratum (1) on treatment with hydriodic acid in methanol, are transformed into seco-aldehydes 5 and 6 in a fragmentation reaction. Both aldehydes very similar to secologanine yield various condensation products with tryptamine under Pictet-Spengler conditions. The relative and absolute configuration of the crucial intermediate 4 was secured by X-ray structure analysis.

A few years ago the epoxide ring opening process of didrovaltratum 1, which is easily available from valeriana wallichii or v.officinalis, with hydriodic acid in methanol was reported to give rise to the iodide 3.[2]

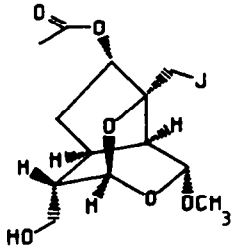


This compound on treatment with sodium methanolate in methanol in a fragmentation process smoothly gives rise to the corresponding seco-aldehyde 5, which proves to be quite similar to seco-loganine 7, the biogenetic iridoid precursor of indole alkaloids. As 5 similar to 7 could be converted into Pictet-Spengler cyclization products with tryptamine (see below) we realized that early transformation of C_{11} into the equivalent of a carbonyl group (see 4) would after fragmentation lead to compound 6, which as seco-loganine is providing a masked 1,3-dicarbonyl group at C_3 and C_{11}, thus representing an easily and in quantity available chiral building block for various types of indole alkaloids.

Electrophilic attack at the exocyclic 4/11 double bond offered itself as the method of choice to functionalize C_{11} but this double bond turned out to be quite unreactive under standard conditions. Reagents like N-iodosuccinimide, m-chloroperbenzoic acid as well as bromine in aqueous methanol left the molecule completely unchanged. Treatment with the borane-THF complex however, resulted even at 0°C in the quick formation of the corresponding borane adduct, which on subsequent oxydation with alkaline H_2O_2 gave rise to the 1 : 1 mixture of the epimeric primary carbinoles 2a and 2b in 73% yield.



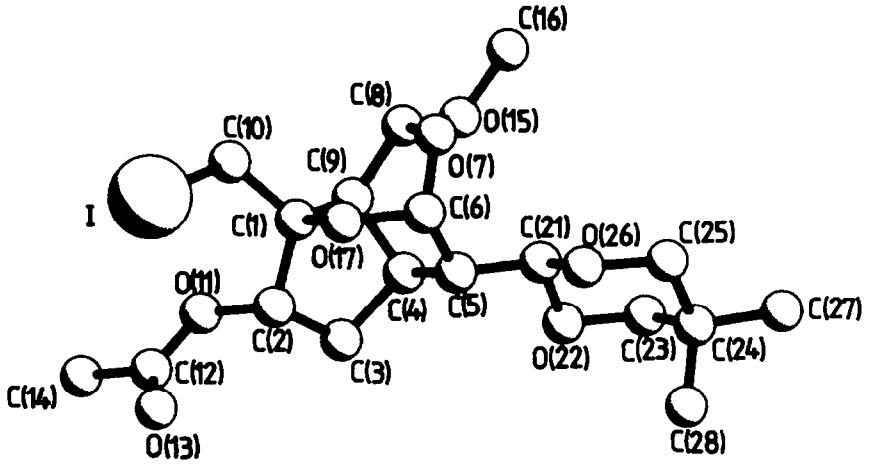
2a



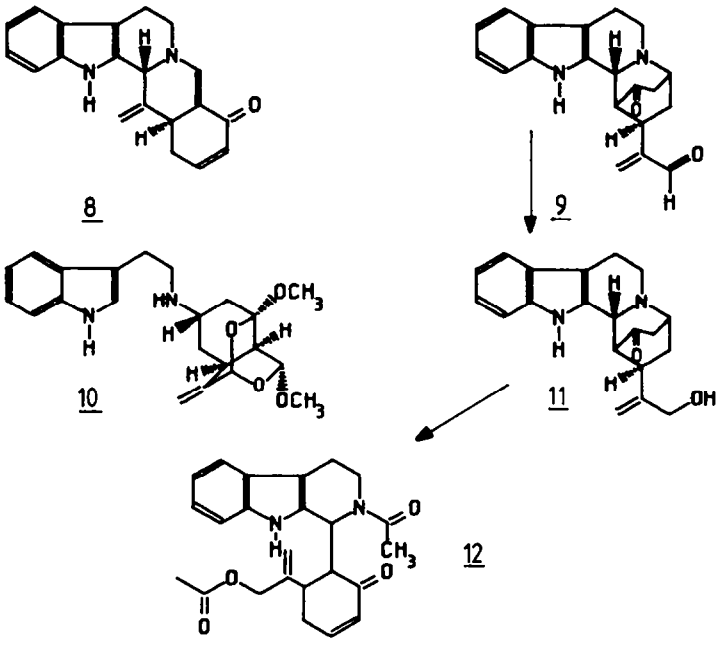
2b

As according to the Karplus-Conroy[3]-rule the α-proton at C_4 does show a very small coupling to the acetal proton at C_3 we assigned configuration 2a to the less polar carbinole and configuration 2b to the more polar one. Subsequently both alcohols were transformed into their corresponding MEM-ethers for further characterization. The 1 : 1 ratio of these epimeric compounds proves the attack of the borane to occur at comparable rates to both sides of the exocyclic double bond. For preparative use the kinetically controlled mixture of boranes was directly oxidized to the aldehyde by PCC and immediately protected as the neopentyl acetal 4. This particular protection was chosen deliberately to ensure increased acid stability in the final polycarbonyl compound 6 which contains four aldehyde groups in differing states of protection. Although the 1 : 1 mixture of diastereomeric boranes was used in the oxydation process this acetal again turned out to be a single pure stereoisomer and a close TLC investigation of the oxydation process proves the initial formation of two aldehydes which can be separated on TLC and are intensely coloured by a 2,4-dinitrophenyl-hydrazine spraying reagent; one of them later being isomerized however, under oxydation conditions. The single pure aldehyde is then transformed into acetal 4, which accordingly is referred to as the thermodynamic stable isomer and as the acetal proton at C_3 in this compound too is showing a 3 Hertz coupling constant as seen with compound 2b the exo configuration 4 was assumed for this intermediate. As 4 does represent a very crucial intermediate en route to aldehyde 6 its configuration was secured beyond any doubt by an X-ray structure determination disclosing configuration 4 as shown in the computer plot.

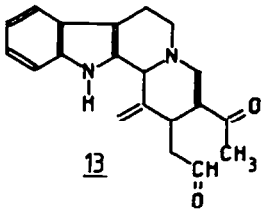
The X-ray structure determination could ascertain the relative and absolute configuration in compound 4. The atomic coordinates of the two crystallographically independent molecules are given in Table 1. No significant structural differences between the two independent molecules are observed. Bond lengths and angles (C-I 217.5 (15) and 215.3 (15) pm) are in the usually found range. The dioxacyclohexane ring C(21) - O(26) displays chair conformation and that of the five-membered ring is between the twist and envelope form. The non-hydrogen substituents at the rings are - as far as possible - in equatorial positions. Short intermolecular contacts are not observed.



Having 4 available in a few steps only, fragmentation was studied under conditions as worked out for iodide 2 and it was rewarding to note that this more complex educt provided even a slightly higher yield of aldehyde 6. Both aldehydes, 4 as well as 6 are crowded with functionality at different stages of protection and can be expected to react with nucleophiles like tryptamine and other amines. Experiments even under very mild conditions proved this to be the case.



Just by leaving the more simple aldehyde 5 with tryptamine in aqueous acetic acid at room temperature the nicely crystallizing, non basic yellow coloured vinylogue amide 8 was obtained in 25% non optimized yield. Spectral data as well as the knowledge of the starting materials quickly indicated constitution 8 for this compound, the formation of which may be explained by a combination of Pictet-Spengler and aldol cyclizations (e.g.13) the sequence however being uncertain as products of type 10 (aldol cyclization first) readily might loose tryptamine and later recombine with the amine in a Pictet-Spengler cyclization.



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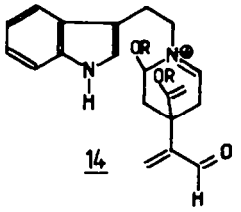


14

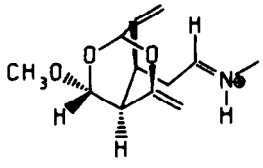
Reduction of the 1,9 double bond was achieved very efficiently and selectively by the well established procedure using borohydride in acetic acid[4] and the UV spectrum of this reduction is clearly showing normal indole absorption.

Under the condensation conditions obviously quite a number of different reactions take place, - it is certain however, that the unprotected aldehyde group in 5 does not initiate the reaction sequence -, in this case. In another experiment just this unprotected aldehyde group was however converted into a Schiff base with tryptamine by using aprotic conditions (heating in toluene) leaving the three remaining carbonyl groups protected. Without isolation the Pictet-Spengler cyclization was subsequently triggered by acid treatment. This way a completely different reaction product was isolated, which according to spectral data was assigned aldehyde structure 9. Borohydride at room temperature almost exclusively attacked the less hindered aldehyde group giving rise to a 60% yield of the allylic alcohol 11, which on treatment with acetic acid anhydride in a structure revealing sequence of retro-Michael reaction and bis-acetylation is transformed into 12 with the very characteristic spectroscopic data of an unsaturated ketone and an allylic acetate (see Experimental).

Structure 9 proves the free aldehyde group to have been combined with the basic nitrogen in this case, the bicyclic ketone obviously being due to an intramolecular Mannich cyclization (see 14).

To get a more clear picture of the sequence of reactions leading to 9 even milder conditions were tried and in the event a new basic product was obtained on reacting aldehyde 5 with tryptamine hydrochloride at 60°C. As non hydrolytic conditions are secured, one is not surprised to find no carbonyl absorption in the infrared spectrum of this material and according to NMR data (see Experimental) this product does represent a 10 : 1 mixture of the two epimeric amines 10a and 10b.

Clearly under these conditions the enolether has won the race of the donor groups indole system and enolether double bond for the electron accepting iminium group, and as transition state 15 with the equatorial orientation of the imine should be more favoured in comparison with the more crowded one (16), the product ratio is meeting expectations.



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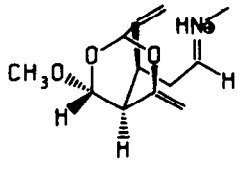
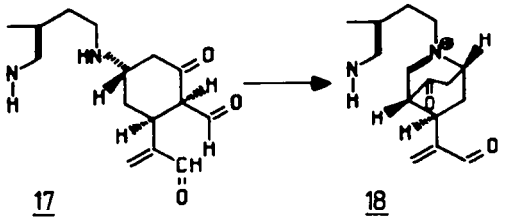


16

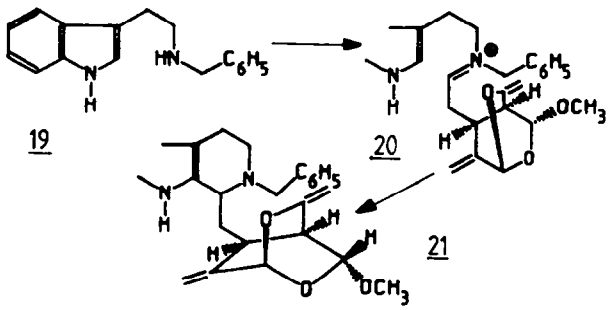
On treatment with aqueous acid 10a is cleanly converted into 9, intermediates 17 and 18 probably being involved.



17 18

These results prove the bicyclic ketone 9 to be generated in a multistep sequence starting with imines 15 and 16, followed by a Mannich cyclization (10), demasking of the aldehyde groups and a final Pictet-Spengler cyclization.

As the formation of 10 as shown in 15 and 16 does need a nucleophile for the enolether capture (CH_3OH, CH_3COOH or even $(CH_3)_3COH$), we hoped for cyclization with the indole system if nucleophiles would be banned from the reaction mixture completely. Unfortunately, these reaction conditions did not yield any cyclization products whatsoever and accordingly to improve the electron acceptor capacity of the imine we changed over to N-benzyl-tryptamine 19, hoping for higher reactivity in the iminium salt 20.



19 20 21

On treatment of aldehyde 5 with this tryptamine derivative the formation of two C-epimeric cyclization products (21a,b) was easily proven by lack of the α-indole proton in the ^1H NMR-spectra of these compounds, which after TLC separation and isolation were shown to have formed in a 2.5 : 1 ratio respectively. As these diastereomers are formed in a Pictet-Spengler cyclization and as a number of experiments with more simple aldehydes have shown this process to be very efficiently directed by the combined action of the N_b substituent and the ester group of tryptophane[5] we decided, after having found the correct reaction conditions and a sufficiently reactive tryptamine derivative, to switch over to N-benzyl-tryptophane esters for further experiments in this field.

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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. ^1H 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.

14-Methylen-3β-yohimba-17,20-dien-19-on 8:

0.5 g sodium was dissolved in 250 ml dry methanol and to this solution 6 g (15.8 mmol) of iodide 3 was added at room temperature. This mixture was stirred for 1.5 h at 60°C under nitrogen and subsequently 180 ml of the solvent was evaporated in vacuo. The residue was treated with 100 ml of a saturated aqueous solution of ammonium sulfate and extracted five times with 100 ml of ether. The combined ether extracts were washed with brine, dried with magnesium sulfate and evaporated in vacuo. The raw aldehyde (86% pure by NMR - aldehyde proton at 0.89 δ) was dissolved in 50 ml dioxane, 3.4 g tryptamine hydrochloride was added and after a few minutes this solution was treated with a mixture of 25 ml water and 25 ml acetic acid. After three days at room temperature the mixture was diluted with dilute aqueous citric acid and extracted with ether. This neutral material was not investigated and after addition of aqueous soda solution the bases were extracted with methylene chloride. After evaporation and quick filtration over silica the more polar yellow coloured fractions were combined, evaporated and the residue was crystallized from ethyl acetate to yield 1.2 g (25%) of the pentacyclic vinylogue amide 8, m.p.249°C (decomposition); $[\alpha]_D^{20}$: +632°; UV (CH_3OH): λ_{max} (ε) 220 (4.5), 275 (3.78), 2.87 (3.70), 367 (3.98); IR ($CHCl_3$): 3460, 1720, 1645, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): δ 2.28 - 2.65 [2] m, 2.81 [1] dd, J = 16 Hz, J = 4 Hz, 2.90 - 3.06 [1] m, 3.30 - 3.40 [1] m, 3.55 [1] d,tr, J = 16 Hz, J = 6 Hz, 3.88 [1] d,tr, J = 16 hz, J = 6 Hz, 5.21 [1] s, 6.02 [1] dd, J = 10 Hz, J = 3.5 Hz, 6.65 - 6.75 [1] m, 7 - 7.5 [4] m, 7.63 [1] d, J = 2 Hz, 7.82 [1] s broad; MS (210°C): *m/e* 302 (M^+, 100%), 287 (10), 285 (8), 273 (30), 258 (13), 245 (7), 234 (44), 218 (6), 204 (8), 180 (6), 169 (19), 144 (30), 130 (13). Found: 302.1417 (mass spectroscopy). Calc.for $C_{20}H_{18}N_2O$: 302.1419. Found: C, 79.44; H, 6.00; N, 9.26. Calc.: C, 79.75; H, 6.15; N, 9.21.

23-Oxo-3β-14ζ,21ζ-ethano-18,19-dinor-coryn-16-en-16-carbaldehyd 9:

2.9 g aldehyde prepared as described above was dissolved in 20 ml toluene and 1.7 g tryptamine was also dissolved in 50 ml hot toluene. The warm solutions were combined and left overnight. After evaporation the residue was dissolved in 100 ml dry methanol and treated with 1 ml glacial acetic acid. After 15 h more acetic acid was added (20 ml) and the mixture was left at room temperature for another 15 h. Subsequently the solution was diluted with aqueous citric acid and neutral substances were extracted with ether and set aside. The aqueous phase was treated with concentrated aqueous soda solution and after reaching ph8 was extracted with methylene chloride. The residue after evaporation of the solvent for hydrolysing any ketals was left in a mixture from 50 ml methanol, 50 ml water and 2 ml trifluoro acetic acid for 5 days at room temperature. The solution then was poured into concentrated aqueous soda solution and extracted with methylene chloride. After washing with brine and drying over magnesium sulfate the solvent was evaporated and the residue purified by flash chromatography (ether/4% methanol). Pale yellow crystals were obtained from ether, yield 33%, m.p. 180°C (decomposition); [α] +40°; UV (CH_3OH): indole absorption; IR (KBr): 3400, 1725, 1685, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.35 [1] dd, J = 12 Hz, J = 8 Hz, 2.31 [1] tr, J = 3 Hz, 3.59 [1] tr, J = 9 Hz, 4.74 [1] s broad, 6.0 [1] s, 6.18 [1] d, J = 2 Hz, 6.89 - 7.50 [4] m, 7.98 [1] s broad, 9.46 [1] s; MS (120°C): m/e 320 (M^+, 80%), 291 (20), 277 (9), 265 (20), 249 (8), 237 (29), 222 (20), 209 (36), 196 (100), 180 (18), 169 (76), 154 (30), 144 (22), 130 (18). Found: 320.1515 (mass spectroscopy). Calc.for $C_{20}H_{20}N_2O_2$: 320.1525. Found: C, 73.19; H, 6.56; N, 8.70. Calc.: C, 72.93; H, 6.42; N, 8.50.

Keto-aldehyde 9 (procedure B), starting from 10a: 82 mg (0.21 mmol) amine 10a was dissolved in 10 ml CH_3OH:H_2O (1 : 1), 1 ml TFA was added. After standing for 72 hours, neutralisation with $NaHCO_3$, evaporation of CH_3OH, organic material was taken up in chloroform, the chloroform solution washed with water, dried ($MgSO_4$), filtrated and evaporated to give 63 mg of crude, almost pure 9. Further purification was achieved by short column (5% CH_3OH/ether) filtration and crystallization from diethylether to yield 35 mg (51%) pure 9. The product was identical to the one obtained under procedure A. Spectral data see above.

5-[1-Acetoxymethyl-vinyl]-6-[2-acetyl-2,3,4,9-tetrahydro-1H-β-carbolin-1-yl]-cyclohex-2-enon 12:

Treatment of 250 mg 9 with 100 mg sodiumborohydride in 25 ml isopropanol for 30 min at 0° C gave after work up a quantitative yield of a keto-carbinol (11). UV (CH_3OH): Indole absorption; IR (KBr): 3500, 3400, 1725, 1650 cm^{-1}; ^1H NMR (DMSO, 90 MHz): δ 2.3 - 2.8 [4] m, 3.0 - 3.5 [8] m, 3.95 [2] s broad, 4.55 [1] m, 4.83 [1] s, 5.02 [1] s, 6.9 - 7.1 [2] m, 7.2 - 7.4 [2] m, 10.65 [1] s broad; MS (270°C): m/e 322 (M^+, 75%), 266 (18), 198 (100), 169 (50).
For further characterization this compound was transformed into diacetate 12 by heating in acetic acid anhydride (70°C, 1 h), evaporation under reduced pressure and crystallization from acetone. Yield 85%, m.p. 194°C; UV (CH_3OH): indole absorption; IR (KBr): 3400, 1735, 1665, 1650, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ 1.83 [3] s, 2.13 [3] s, 2.8 - 3.0 [3] m, 3.03 - 3.23 [3] m, 3.8 - 4.2 [3] m, 4.52 [2] A,B-quartet, J = 12 Hz, 4.95 [1] s, 5.10 [1] s, 6.10 [3] m, 6.85 [1] m, 7.0 - 7.5 [4] m, 8.65 [1] s broad; MS (170°C): m/e 406 (M^+, 10%), 363 (15), 213 (100), 170 (80), 169 (32). Calc. for $C_{24}H_{26}O_4N_2$ (406.5): C, 70.91; H, 6.44; N, 6.89. Found: C, 70.44; H, 6.58; N, 6.40.

Epimeric primary carbinols 2a and 2b: 100 mg (0.26 mmol) of iodide 3 was dissolved in 3 ml of dry ether under dry N-atmosphere and cooled to 0°C. 0.35 ml (0.35 mmol) of a 1m BH_3 THF complex solution in THF (purchased from Aldrich and used from freshly opened bottles only) was added by syringe with magnetic stirring. The mixture was stirred magnetically for 3 h at 0°C and for 1 h at r.t. 3 drops of water, 3 drops of 3N NaOH and 5 drops of a 30% H_2O_2 solution were added by Pasteur pipette and stirring was continued for further 20 min. The yellowish solution was diluted with 100 ml of ether, washed with 0.1M $Na_2S_2O_3$ solution and water, dried ($MgSO_4$), filtered and evaporated in vacuo to yield 100 mg of a crude oil, containing 2a, 2b, and a third, not further investigated, non polar material. TLC yielded 40 mg (38%) of 2a and 37 mg (35%) of 2b. 2a and 2b were characterized as MEM ethers by a general procedure of Corey[6].

Non polar carbinol 2a: IR ($CHCl_3$): 3620 (w), 1735 (s); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 [1] ddd, J_1 = 15 Hz, J_2 = 7 Hz, J_3 = 3 Hz, 2.32 [1] dd, J_1 = 15 Hz, J_2 = 7 Hz, 1.65 [1] s broad with H/D-exchange, 2.08 [3] s, 2.47 [1] dd, J_1 = 6 Hz, J_2 = 4 Hz, 2.54 [1] ddd, J_1 = J_2 = J_3 = 8 Hz, 2.9 [1] ddd (J_1 = J_2 = J_3 = 7 Hz, 3.42 and 3.45 [5] ds, 3.55 - 3.7 [2] m, 4.82 [1] dd (J_1 = 7 Hz, J_2 = 3 Hz, 4.99 and 5.01 [2] d, J = 3 Hz and s.

Polar carbinol 2b: IR ($CHCl_3$): 3620 (w), 1740 (s); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.68 [1] ddd, J_1 = 14 Hz, J_2 = 8 Hz, J_3 = 3.5 Hz, 2.25 [1] dd, J_1 = 14 Hz, J_2 = 8 Hz, 1.75 [1] s broad with H/D-exchange, 1.85 [1] tr broad, J = 7 Hz, 2.08 [3] s, 2.33 [1] dd, J_1 = 5 Hz, J_2 = 2 Hz, 2.43 [1] tr broad, J = 6 Hz, 3.4 - 3.5 [5] s and ds, 3.68 [1] dd, J_1 = 11 Hz, J_2 = 7 Hz, 3.83 [1] dd, J_1 = 11 Hz, J_2 = 7 Hz, 4.9 - 5.0 [2] two doubletts, 5.12 [1] d, J = 3.6 Hz.

MEM-Ethers of 2a/2b: IR (CCl_4): 1750 (s), 1240 (vs), 1250 (vs); ^1H NMR (90 MHz, $CDCl_3$): δ = 2.08 [3] s broad, 3.42 and 3.45 [8] two plus one singulett, 3.5 - 3.75 [6] m, 4.7 [2] s broad, 4.83 [1] dd (J_1 = 7 Hz, J_2 = 4 Hz, 4.9 - 5.1 [2] m. Found: C, 41.96; H, 5.45; Calc.for $C_{17}H_{27}IO_8$: C, 41.98; H, 5.60.

Neopentyl acetal 4: 10.7 g (28.1 mmol) of iodide 3 was dissolved in 500 ml of dry ether under dry N_2-atmosphere and cooled to 0°C. 37 ml of 1M BH_3·THF complex solution/THF (Aldrich from freshly opened bottle) was added by syringe with magnetic stirring. After 3 h at 0°C and 1 h at r.t., subsequent evaporation in vacuo, the crude boranes were dissolved in 100 ml dry CH_2Cl_2 and added slowly by dropping funnel to a vigorously stirred suspension of 25 g (116 mmol) of pyridinium chlorochromate (PCC) in 100 ml of dry CH_2Cl_2 and refluxed 2 h at 60 - 65°C. After addition of 500 ml diethylether and filtration through a short "flurisil" (Aldrich)-column, 8.17 g of crude aldehyde was obtained on evaporation, immediately dissolved in 150 ml of dry CH_2Cl_2 and stirred magnetically with 3.4 g (34 mmol) of neopentylglycole in the presence of 100 mg p-toluene sulfonic acid and 5 g $MgSO_4$ for 36 h under N_2-atmosphere. Filtration, concentration, short column-filtration (20% ethylenacetate/petrolether), concentration and crystallization from CH_3OH yielded 4.5 g (35% overall) of 4. m.p.: 159°C; $[\alpha]_D^{20}$ = +18°C; IR (KBr): 1740 (s), 1240 (s), 1100 (vs),

1080 (vs), 1030 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73 [3] s, 1.18 [3] s, 1.69 [1] ddd, J_1 = 14 Hz, J_2 = 7 Hz, J_3 = 3 Hz, 2.25 [1] dd, J_1 = 14 Hz, J_2 = 7 Hz, 1.85 [1] d broad, J = 9 Hz, 2.08 [3] s, 2.32 [1] m, 2.68 [1] tr broad, J = 7 Hz, 3.3 - 3.4 and 3.55 - 3.65 [6] m, 3.47 [3] s, 4.6 [1] d, J = 8 Hz, 4.9 - 5.0 [2] two partly overlapping ds, 5.10 [1] d, J = 3 Hz; MS (120°C): m/e 482 (M^+, 0.1%), 355 (0.8), 323 (6), 263 (4), 249 (2), 176 (5), 172 (3), 163 (3), 157 (7), 149 (8), 137 (5), 129 (7), 128 (1), 121 (5), 115 (100), 69 (61). Found: C, 44.72; H, 5.74. Calc.for $C_{18}H_{27}IO_7$: C, 44.83; H, 5.64.

C$_7$-Epimeric amines 10a and 10b: In analogy to the previously described procedure, 2 g of crude seco-aldehyde 5 were prepared from 4 g (10.5 mmol) iodide 3. The yellowish oily 5 was immediately dissolved in a solution of 2 g tryptamine hydrochloride (ca. 10 mmol) in 100 ml of dry CH_3OH and stirred magnetically for 3.5 h at 60°C under N_2-atmosphere. The appearance of two non polar indolic bases (positive Schlittler test) was detected by TLC. On evaporation of CH_3OH, addition of an excess of saturated Na_2CO_3, extraction with CH_2Cl_2, drying over $MgSO_4$, filtration and evaporation, ca. 4 g of a reddish material was obtained. Purification by flash-chromatography (5% $CH_3OH/CHCl_3$) yielded 890 mg (22% overall) of non polar 10a as a colourless foam. The polar by-product 10b had to be re-purified to homogenity by TLC (5% $CH_3OH/CHCl_3$) to yield 125 mg (3.1% overall).

7s-Amine 10a: $[\alpha]_d^{20}$ = +3.3°; UV: indole chromophor; IR (KBr): 3400 (m), 1610 (vw), 1160 (vs), 1120 (vs), 740 (m); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.08 [1] dd, J_1 = J_2 = 12 Hz, 1.3 [1] ddd, J_1 = J_2 = 12 Hz, J_3 = 4 Hz, 2.05 [1] m, 2.07 [1] tr, J = 3 Hz, 2.50 [1] dd, J_1 = 12 Hz, J_2 = 4 Hz, 2.65 - 2.80 [1] m, 3.0 [4] s, 3.18 [1] s broad, 3.32 [3] s, 3.40 [3] s, 4.89 [1] d, J = 2, 5.02 [1] d, J = 2 Hz, 5.13 [1] d, J = 3 Hz, 5.18 [1] s, 7.02 [1] d, J = 3 Hz, 7.08 - 7.22 [2] m, 7.38 [1] d, J = 8 Hz, 7.61 [1] d, J = 8 Hz, 8.15 [1] s broad - slow H/D-exchange; MS (130°C): 384 (M^+, 4%), 383 (11), 352 (11), 253 (43), 221 (21), 192 (27), 179 (42), 175 (9), 144 (11), 131 (100). Found: 384.2048 (mass spectroscopy). Calc.for $C_{22}H_{28}N_2O_4$: 384.2049.

7r-Amine 10b: UV: indole chromophor; IR (KBr): 3400 (m), 1620 (vw), 1120 (vs), 1060 (vs), 740 (m); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.48 [1] dd, J_1 = 16 Hz, J_2 = 6 Hz, 1.68 [1] ddd, J_1 = 16 Hz, J_2 = J_3 = 6 Hz, 2.05 [1] tr, J = 3 Hz, 2.42 [1] d broad, J = 16 Hz, 2.68 [1] d broad, J = 16 Hz, 3.2 [3] s, 3.31 [3] s, 4.22 [1] s broad, 4.3 [1] s broad, 4.78 [1] d, J ≤ 1 Hz, C_1-H: 5.02 [1] d, J = 3 Hz, 7.05 - 7.25 [3] m, 7.4 [1] d, J = 8 Hz, 7.6 [1] d, J = 8 Hz, 8.45 [1] s broad; MS (110°C): 384 (M^+, 7%), 353 (8%), 254 (100), 242 (12), 222 (27), 196 (28), 166 (38), 144 (28), 130 (52). Found: 384.2048 (mass spectroscopy). Calc.for $C_{22}H_{28}N_2O_4$: 384.2049.

(17R,21R)-4-Benzyl-17,19;17,21-diepoxy-21-methoxy-16-methylen-3ζ-4,21-seco-corynan 21:

Starting from 350 mg (0.92 mmol) of iodide 3, 190 mg of crude seco-aldehyde 5 was prepared and immediately reacted with 230 mg (0.92 mmol) N_b-benzyl-tryptamine in 14 ml dry toluene in the presence of 1.4 g $MgSO_4$ for 12 h at 60°C under N_2 with magnetical stirring. The formation of two non polar indolic products were detected by TLC. On filtration, evaporation in vacuo, 386 mg of orange material was obtained. Preliminary purification by filtration on 10 g silica (30% ether/petrolether) gave 241 mg which was further purified by PTC to 82 mg non polar 21a (20%) and 33 mg polar 21b (8%) as colourless foams, crystalizing on trituration with ether.

Non polar epimer 21a: m.p.: 141°C; UV: indole-chromophor: IR ($CHCl_3$): 3460 (m), 1670 (m), 1600 vbr (m), 1110 (s), 1060 (s); ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.66 - 2.0 [3] m with tr at 1.96, J = 3 Hz, 3.1 - 3.28 [2] m, 3.49 [3] s, 3.69 [1] s broad, 4.33 [1] s broad, 3.78 [2] m, 4.86 [1] d, J = 2.5 Hz, 5.02 [1] d, J = 2.5 Hz, 4.72 [1] d, J = 3 Hz, 5.25 [1] s, 7.05 - 7.6 [10] m; MS (120°C): 442 (M^+, 6%), 411 (3), 351 (4), 261 (100), 169 (9), 91 (26). Found: 442.2256 (mass spectroscopy). Calc.for $C_{28}H_{30}N_2O_3$: 442.2256.

Polar epimer 21b: m.p.: 187°C; UV: indole-chromophor; IR ($CHCl_3$): 3460 (m), 1670 vbr (m), 1600 vbr (m), 1110 (s), 1065 (s); ^1H NMR (90 MHz, $CDCl_3$): δ = 2.8 [1] tr, J = 3 Hz, 3.5 [3] s, 3.78 [4] s broad, 4.28 [1] d, J = 2 Hz, 4.97 [2] m, 4.65 [1] d, J = 2 Hz, 5.26 [1] s, 7.0 - 7.58 ca. 9] m, 7.8 [1] s broad; MS (160°C): 442 (M^+, 4%), 441 (6), 411 (2), 451 (6), 261 (100), 210 (11), 169 (10), 91 (34). Found: 442.2256 (mass spectroscopy). Calc.for $C_{28}H_{30}N_2O_3$: 442.2256.

X-ray analysis: Crystals of 4 obtained by recrystallization from have orthorhombic symmetry, space group $p2_12_12_1$. The unit cell which has parameters a = 1410.2(3), b = 1077.5(1), c = 2678.9(3) pm, contains 8 molecules yielding a calculated density of 1.570 g/cm^3. The data were collected on a Syntex $P2_1$ diffractometer using graphite-monochromated Cu-K (154.178 pm) radiation in the -2 mode in the range 3°=2 =135° at a scan speed between 2.93 and 29.30°/min depending on the intensity of the reflection.

The data were corrected for Lorentz, polarisation and absorption effects (=128.35 cm^{-1} for Cu-K radiation). The structure was solved by Patterson and difference-Fourier syntheses. The refinement using 2424 out of 3172 measured independent reflections (I=2.0 (I)) converged at R=0.064. A final difference map displayed no electron density higher than 0.67 e/A^3.

Table 1

Site-Parameters of Atoms

	x/a	y/b	z/c	U -eq
I	-0.1351 (1)	-0.7969 (1)	0.0364 (1)	53 (1)
C(1)	-0.2099 (13)	-0.6003 (12)	-0.0367 (5)	30 (10)
C(2)	-0.3151 (14)	-0.6408 (16)	-0.0281 (5)	41 (11)
C(3)	-0.3756 (15)	-0.5613 (18)	-0.0632 (5)	58 (12)
C(4)	-0.3011 (14)	-0.4900 (14)	-0.0954 (4)	37 (10)
C(5)	-0.2610 (14)	-0.5728 (14)	-0.1398 (5)	36 (10)
C(6)	-0.1704 (13)	-0.6198 (15)	-0.1239 (5)	36 (11)
O(7)	-0.0994 (8)	-0.5265 (10)	-0.1196 (3)	35 (7)
C(8)	-0.1289 (15)	-0.4286 (13)	-0.0861 (5)	38 (10)
C(9)	-0.2186 (13)	-0.4709 (15)	-0.0585 (5)	36 (10)
C(10)	-0.1423 (15)	-0.6096 (14)	0.0063 (5)	48 (11)
O(11)	-0.3446 (9)	-0.6188 (10)	0.0230 (3)	42 (7)
C(12)	-0.3951 (14)	-0.7081 (22)	0.0446 (6)	57 (13)
O(13)	-0.4084 (12)	-0.8101 (14)	0.0286 (5)	79 (11)
C(14)	-0.4335 (15)	-0.6618 (19)	0.0961 (5)	62 (13)
O(15)	-0.1485 (9)	-0.3176 (10)	-0.1107 (3)	42 (7)
C(16)	-0.0695 (15)	-0.2663 (16)	-0.1356 (6)	58 (13)
O(17)	-0.1751 (7)	-0.6820 (9)	-0.0769 (3)	32 (6)
C(21)	-0.2585 (14)	-0.5011 (15)	-0.1871 (4)	34 (10)
O(22)	-0.3517 (9)	-0.4549 (10)	-0.1972 (3)	42 (7)
C(23)	-0.3506 (15)	-0.3889 (18)	-0.2432 (5)	55 (12)
C(24)	-0.3254 (14)	-0.4697 (15)	-0.2858 (5)	36 (10)
C(25)	-0.2260 (14)	-0.5206 (17)	-0.2731 (5)	45 (12)
O(26)	-0.2275 (8)	-0.5815 (10)	-0.2248 (3)	40 (7)
C(27)	-0.3197 (16)	-0.3898 (15)	-0.3334 (5)	53 (11)
C(28)	-0.3927 (16)	-0.5809 (17)	-0.2939 (8)	69 (15)
I'	-0.1830 (1)	-0.6928 (1)	-0.4308 (1)	55 (1)
C(1)'	-0.2325 (13)	-0.9057 (15)	-0.3591 (5)	33 (10)
C(2)'	-0.3405 (14)	-0.8927 (14)	-0.3673 (5)	40 (12)
C(3)'	-0.3890 (14)	-0.9965 (15)	-0.3345 (5)	43 (11)
C(4)'	-0.3025 (15)	-1.0376 (14)	-0.3010 (4)	39 (10)
C(5)'	-0.2802 (12)	-0.9426 (13)	-0.2589 (4)	24 (9)
C(6)'	-0.1914 (13)	-0.8741 (14)	-0.2737 (5)	29 (10)
O(7)'	-0.1153 (9)	-0.9495 (10)	-0.2772 (3)	40 (7)
C(8)'	-0.1206 (14)	-1.0476 (15)	-0.3131 (5)	38 (10)
C(9)'	-0.2229 (12)	-1.0378 (13)	-0.3378 (4)	23 (9)
C(10)'	-0.1728 (14)	-0.8818 (15)	-0.4053 (5)	46 (11)
O(11)'	-0.3642 (9)	-0.9134 (9)	-0.4201 (3)	37 (6)
C(12)'	-0.4266 (18)	-0.8355 (20)	-0.4393 (7)	63 (15)
O(13)'	-0.4636 (14)	-0.7540 (16)	-0.4184 (6)	119 (15)
C(14)'	-0.4332 (14)	-0.8514 (20)	-0.4966 (6)	64 (13)
O(15)'	-0.1230 (10)	-1.1634 (10)	-0.2871 (3)	44 (7)
C(16)'	-0.0302 (15)	-1.1968 (20)	-0.2697 (6)	62 (13)
O(17)'	-0.2060 (8)	-0.8170 (10)	-0.3217 (3)	40 (6)
C(21)'	-0.2695 (13)	-1.0045 (14)	-0.2081 (4)	32 (10)
O(22)'	-0.2530 (9)	-0.9109 (9)	-0.1723 (3)	41 (6)
C(23)'	-0.2429 (14)	-0.9618 (16)	-0.1233 (5)	39 (10)
C(24)'	-0.3382 (14)	-1.0246 (16)	-0.1101 (5)	45 (11)
C(25)'	-0.3568 (14)	-1.1296 (13)	-0.1502 (4)	43 (10)
O(26)'	-0.3574 (9)	-1.0655 (8)	-0.1982 (3)	34 (6)
C(27)'	-0.4193 (15)	-0.9349 (17)	-0.1063 (6)	54 (13)
C(28)'	-0.3256 (15)	-1.0950 (17)	-0.0597 (5)	55 (12)

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