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REACTIONS WITH INDOLE DERIVATIVES - LV.
AN ENANTIODIVERGENT ROUTE TO BOTH VINCAMINE ENANTIOMERS[1]

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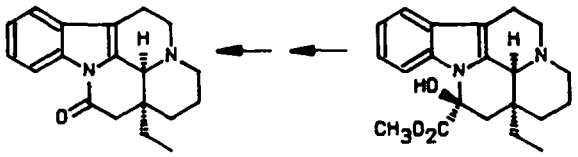
Abstract: The enantioselective synthesis of the tetracyclic lactam 4 is reported which by enantiodivergent techniques is converted into (+)- as well as (-)-vincamine via the corresponding eburnamonine enantiomers.

The natural occurence of both enantiomers is one of the special features of the group of vinca alkaloids. (-)-Eburnamonine (1) obtained on degradation of the alkaloid vincamine[2] (2) turned out to be the enantiomer of (+)-eburnamonine (1') isolated from Hunteria eburnea.[3] As this situation calls for an enantioselective approach to both pure enantiomers we accordingly considered an enantiocomplementing synthesis from a common optical pure intermediate.

As the cyclopropane carboxaldehyde 3 had served well already for a total synthesis of racemic eburnamonine[4] we considered this compound an ideal starting material for an enantiodivergent approach to both enantiomers.

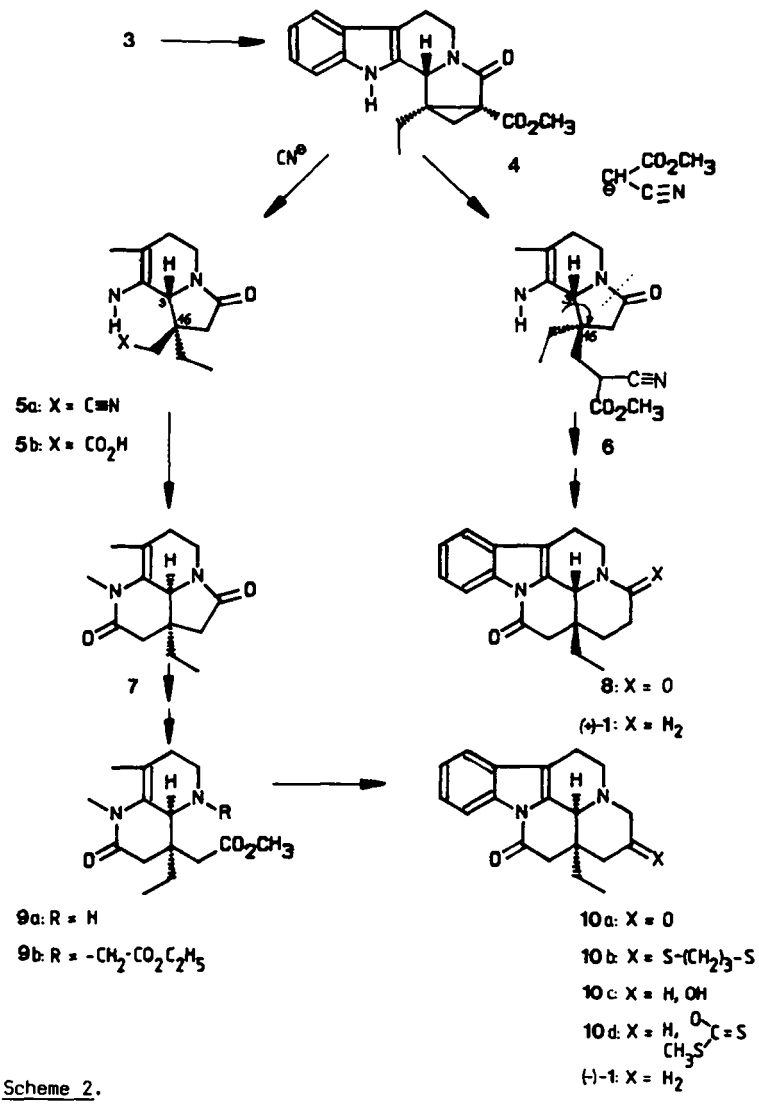


(-)-1 2

(+)-1 3

Scheme 1.

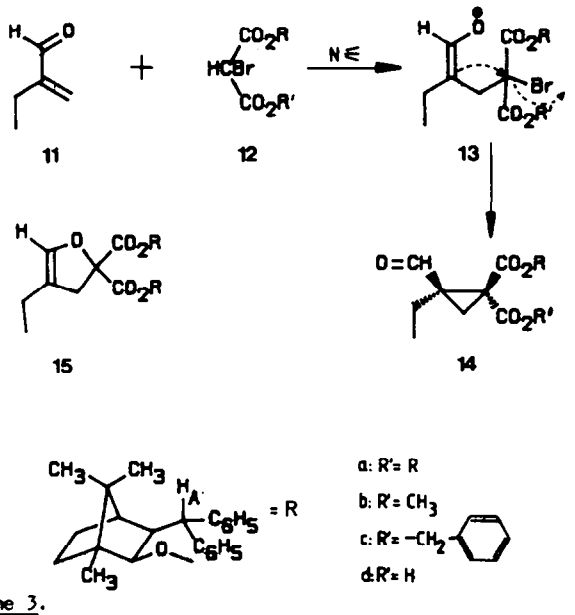
The Pictet-Spengler cyclization of this aldehyde with tryptamine had been shown to be highly stereoselective in the racemic series already. Lactam 4 is formed with high preference (85 : 15) and offers good opportunities to arrive at both pure enantiomers by applying the selected inversion principle.



Scheme 2.

As nucleophilic ring opening reactions accompanied by decarboxymethylation have been shown to generate lactams 5[5] and 6[6] it was decided to focus on lactam 5 for C_3-inversion. In our synthesis of noreburnamonine[6] it was shown a few years ago already that isomerisation at C_3 takes place on proton catalyzed cyclization to form acyl indole 7. The hydrindane-like ring combination of this pentacyclic lactam obviously prefers the thermodynamically more stable cis-configuration. Opening of the γ-lactam, alkylation with methyl bromo-acetate and subsequent Dieckmann cyclization should after decarboxylation generate ketone 10a showing the absolute configuration of (-)-1. Treatment with methyl-cyano-acetate however, in an alternate ring-opening decarboxylation sequence converts lactam 4 into lactam 6. On opening of this γ-lactam and subsequent rotation - which amounts to a formal inversion at C_{16} - this intermediate recyclizes to the pentacyclic lactam 8 with the (+)-1 configuration - reason enough to look for an enantioselective preparation of lactam 4, as these enantiodivergent processes mentioned above hold good promise to provide both pure enantiomers from this particular intermediate.

This lactam being easily available from cyclopropane-aldehyde 3, formation of this cyclopropane ring from bromo-malonate 12 and the corresponding unsaturated aldehyde 11 in a base catalyzed Michael-addition cyclisation sequence via 13 obviously becomes the decisive enantioselective key step.



Scheme 3.

For high diastereoselectivity we choose the symmetric bromo-malonate 12a which indeed gave rise, with excellent selectivity (85%), to an easily purified product.+

This good selectivity in contrast to other cyclizations was, however, only obtained with the sodium hydride/toluene reagent in the presence of HMPA. Without this additive the main reaction product with this particular sterically hindered diester proved to be the unwanted dihydrofuran 15.

Accordingly this crowded diester however, caused enormous difficulties in the later trans-esterification to form the corresponding dimethylester 3 and we therefore subsequently, with the additional aim of gaining some insight into the details of the reaction, switched over to the non symmetric diester 12b. This ester of course can in principle give rise to cis-trans isomers in the cyclopropane product, but we were pleased to note that again one diester aldehyde proved to be by far the most abundant reaction product. As a similar result was obtained with the corresponding benzylester 12c we used this compound for the determination of the relative configuration of the cyclization product.

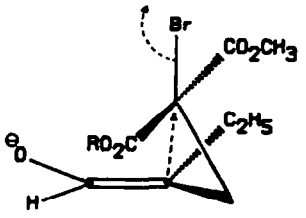
As mild hydrogenolysis generated the aldehyde acid 14d showing no indication of any lactol formation and a very clear aldehyde signal in its NMR spectrum, the benzylester group as given in formula 14 has to be orientated trans to the aldehyde carbonyl group.

On trans-esterification both diesters 14b and 14c both gave rise to the same optically pure (see Experimental) dimethylester 3++ and as diazomethane converted the acid 14d into 14b these

+ The chiral alcohol (see R in Scheme III) was prepared according to Oppolzer[7] (no detailed work-up given). The material obtained by us in contrast to Oppolzer's assignment proved to be the cis-exo compound (see formula in Scheme III) as a strong Overhauser effect (17.5%) was measured for proton H_A and one of the geminal methyl groups. Very probably, endo-alkylation takes place as expected but epimerisation of the kinetic controlled product may occur under reaction or work-up conditions.

++ The absolute configuration of aldehyde 3 and the products resulting from it was of course unknown at this stage and no efforts were made to determine it. The configuration drawn in Scheme I was derived from the fact that the C_3-epimerisation route (see below) did give rise to the absolute configuration of natural vincamine.

transformations also prove the relative configuration of this diester. These results, without however establishing the detailed conformation of the transition state, can be taken as an indication for an arrangement like 16 with the very bulky configuration inducing ester group being held in a space sector minimizing interactions with other substituents.



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As noticed in the racemic series the Pictet-Spengler cyclization with 3 and tryptamine gave rise to mainly one tetracyclic lactam 4, which however did not crystallize as readily as its racemic counterpart. However, after purification by flash chromatography crystals of one very pure enantiomer were also obtained eventually in this case but these proved to be much more soluble and additionally less stable than the corresponding racemic mixture on which we reported earlier.[8]

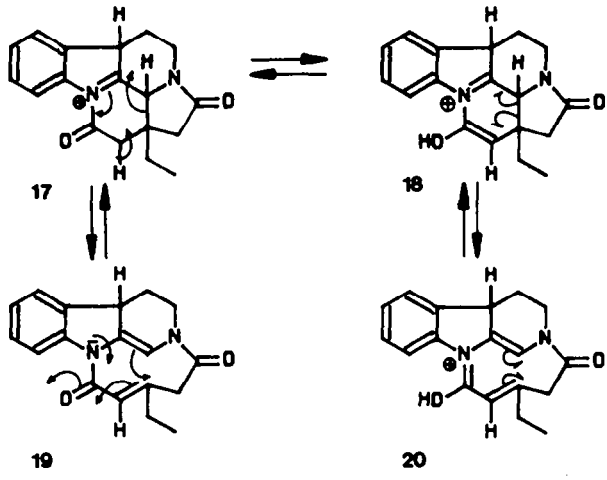
This is in our experience a very general phenomenon which is also noticed with lactams 7 and 8, and which turned out to be extremely helpful in the preparation of optical pure lactam 7 (see below). As similar observations were also made with other lactams the formation of quite different crystal structures from these two species may be an acceptable explanation.

Nucleophilic ring-opening and decarboxymethylation uneventfully generated lactams 5a and 6 as described in the racemic series.[4,5] For the crucial cyclisation the nitrile 5a was hydrolyzed to the corresponding acid 5b which according to earlier results cyclized readily on treatment with trifluoroacetic acid anhydride. To our surprise in contrast to the lactam behaviour mentioned above a small amount of crystals was obtained directly from this cyclization. The surprise was even greater when shift-reagent as well as rotation measurements proved these crystals to be the racemic mixture well known from former work. Luckily the bulk of the material from the cyclization again was oily at the beginning and could easily be proven to be one pure enantiomer. The appearance of the small amount of crystals however, raised the suspicion that in one of the reactions racemisation does occur at least to a small extent, particularly as the optical purity of aldehyde 3 and lactam 4 had been checked again and again very thoroughly.

As carbon-16 is a quarternary centre and racemisation therefore was thought to be quite improbable we first of all checked the optical purity of acid 5b and the corresponding methylester just to find out that both represented pure enantiomers. These findings leave no doubt that partial racemisation occurs in the cyclization step, without however giving any indication on the mechanistic details. Possible explanations that can be offered at the moment first of all rely on the fact that protonation of the indole system is highly probable under the reaction conditions (see 17). Starting from 17 racemisation may result either from a retro-Michael process (see 19) or an electrocyclic ring opening of the corresponding enol (18).[+] Configurational identity may be lost in both ring open intermediates 19 as well as 20 by conformational changes.

Of course the high insolubility of the racemic mixture is very helpful in this situation and offers an opportunity to gain pure enantiomers in spite of this unexpected process.

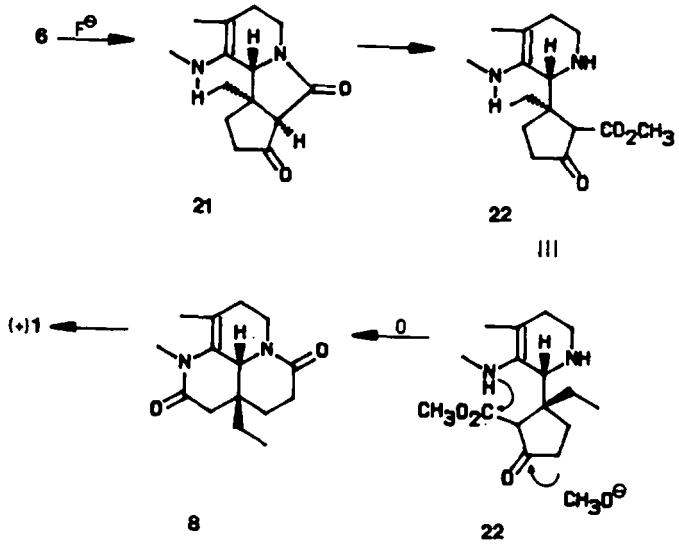
[+] This second explanation was forwarded by Professor Dr. L.Overman at a discussion in Hannover.



Scheme 4.

Treatment with Meerwein reagent and subsequent methanolysis generates aminoester 9a from 7 which after alkylation with bromoacetate (9b) smoothly underwent Dieckmann cyclization to form after decarboxylation the pentacyclic ketone 10a in more than 80% yield. Removal of the keto group can be achieved either by Raney-Nickel desulfurisation of thioketal 10b or via xanthogenate 10d which is easily obtained from the borohydride reduction product 10c and gives rise to (-)-eburnamonine on tributyl-tin-hydride reduction.[9]

For the production of the (+)-enantiomer opening of the δ-lactam in compound 6 is mandatory; but it had been shown in the racemic series already[4] that to achieve this, extra strain has to be put on the molecule by closing a further 5-membered ring in a fluoride anion catalysed Dieckmann cyclization, to form the pentacyclic ketolactam 21.



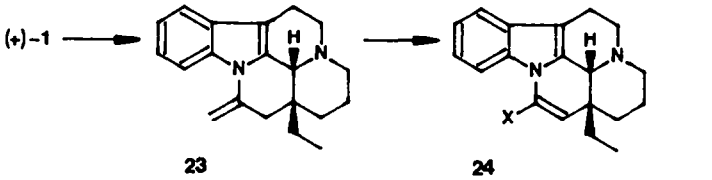
Scheme 5.

Sequential treatment of this ketolactam with Meerwein reagent and methanol gives rise to β-keto-ester 22 which after refluxing with sodium methanolate in methanol and subsequent treatment with trifluoro-acetic acid is smoothly converted into oxoeburnamonine 8. Using the Borch reduction[10] one can easily transform this compound into (+)-1 identical in all details with the natural occuring eburnamonine enantiomer.

Until this stage we had relied completely on well established procedures[11] via the cyanohydrin from (-) or (+)-1 for further elaboration to optical pure vincamine. Unfortunately, in our hands this technique did not work at all and after additionally a whole series of C_1-nucleophiles[12] had

proven also to be completely useless, we formed the impression that steric hindrance might be the explanation for these failures. This was the reason for attempting a methylenation process that had been worked out by Lombardo[13] on the basis of the Nozaki reagent[14] and had proven to be particularly useful with sterically hindered ketones.

Using this reagent the exo-methylene compound 23 was easily obtained in 85% yield without any problems.+ Having arrived at this olefin the remaining transformations were uneventful. Radical bromination (24a) followed by acetate substitution and hydrolysis led to 24c via 24b oxidation with manganese dioxide gave smoothly rise to apovincaminal 24d which on further oxidation was easily converted into apovincamine 24e. As the apovincamine-vincamine conversion is a well established process[4b] this enantioselective synthesis is providing easy access to both enantiomers of eburnamonine as well as vincamine.



23 24

a: X = CH_2Br b: X = CH_2OAc
c: X = CH_2OH d: X = CH=O
e: X = CO_2CH_3

Scheme 6.

Constant and generous support by the Deutsche Forschungsgemeinschaft and the Fonds of Chemical Industry is gratefully acknowledged.

EXPERIMENTAL

^1H NMR spectra were taken on the following instruments: 60 MHz (Varian EM 360), 90 MHz (Bruker WH 90), 200 MHz (Bruker WP 200), 400 MHz (Bruker WH 400). ^{13}C NMR data were measured with Bruker WP 200. IR: Perkin-Elmer 457 and 590. MS: Finnigan MAT 312 (70 eV). UV: Beckman 3600 (CH_3OH). Rotations: Perkin-Elmer 241 ($CHCl_3$, 589 nm, 18 °C). C,H Determinations: Heraeus-CHN Rapid. Flash Chromatography: Merck Silica (0.02 - 0.063 mm).

Preparation of benzyl[exo-diphenyl]-isobornyl-malonate: 150 g mono-benzylmalonate is transformed into the acid chloride by treatment with 138 g thionylchloride at room temp. After 30 h under reflux the surplus thionylchloride is evaporated and 90 g (0.46M) of the crude acid chloride is slowly added to a solution of 65 g (0.2M) exo-diphenylmethyl-isoborneol and 13 ml Hünig base in 130 ml dry dioxan (as the temperature of the mixture may rise sharply, for large scale operations cooling with ice water is recommended). After 3 h the mixture is poured into dilute aqueous acid and extracted with ether. The combined extracts are washed with soda solution and with brine. After evaporation of the solvent filtration over silica gel (petroleum ether/ether 7 : 1) yields 85 g (84%, last step) of the pure mixed malonate. ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.76 [6] s, 1.22 [3] s, 0.95 - 1.7 [5] m, 2.71 [2] s, 2.80 [1] dd, J = 13 Hz, J = 8 Hz, 4.22 [1] d, J = 13 Hz, 5.11 [2] q, J = 12 Hz, 5.19 [1] d, J = 8 Hz, 7.0 - 7.4 [15] m. MS (80 °C): M^+ 496 m/e (1%), 302 (20), 206 (19), 167 (72), 107 (63), 91 (100).

Bis[exo-diphenylmethyl]-isobornyl-malonate: 7.20 g of the above mixed malonate is dissolved in 50 ml dioxan. 1 g Pd/C (10%) is added and the mixture is shaken with hydrogen for 3 h (TLC). After filtration the solvent is evaporated and 4 g of the remaining acid is dissolved in 50 ml dry dichloromethane. 4.8 g exo-Diphenylmethyl-isoborneol is added and this mixture slowly (1.5 h) treated with a solution of 3.4 g DCCI in 50 ml dry dichloromethane. The solution is filtered, the filtrate washed with soda solution and brine and the solvent evaporated. The residue after purification yielded by flash chromatography (petroleum ether/ether 10 : 1) 4.28 g (81%, last step) of colourless crystals, m.p. 185 °C. IR ($CHCl_3$): 1750, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.77 [12] s, 1.24 [6] s, 0.78 - 1.70 [10] m, 2.74 [2] dd, J = 8 Hz, J = 13 Hz, 4.20 [2] d, J = 13 Hz, 5.12 [2] d, J = 8 Hz, 7.1 - 7.3 [20] m. ^{13}C NMR: 165.36 s, 145.39 s, 144.59 s, 129.05 d, 128.90 d, 128.54 d, 128.41 d, 128.04 d, 127.53 d, 127.04 d, 126.51 d, 126.01 , 125.77 d, 125.49 d, 81.43 d, 52.91 d, 51.95 d, 50.40 s, 47.68 d, 47.39 s, 39.69 tr, 32.83 tr, 30.06 tr, 21.85 q, 21.60 q, 11.34 q. MS (170 °C): M+ 708 m/e (1%), 302 (27), 206 (21), 193 (9), 167 (100), 165 (21), 152 (16), 91 (24). - $C_{49}H_{56}O_4$ (708.99) Calc. C 83.01, H 7.96; Found C 82.74, H 8.14.

+ A systematic study of the reaction times later revealed that the 48 hour waiting period suggested by Lombardo for optimum efficiency of the reagent was not necessary in our case. Best results were obtained after 24 hours.

2-Ethyl-2-formyl-1,1-cyclopropane-dicarboxylic acid-bis[exo-diphenylmethyl]-isobornylester (14a): 1 g (14.1 mmol) of the above ester and 0.1 ml Br_2 in 7.5 ml chloroform is treated with 750 mg sodium fluoride at 70 °C for 10 min. Another 0.1 ml Br_2 is added and heating is continued for 10 min. The reaction mixture is diluted with ether, the inorganic salts are filtered off and the solvent is evaporated. 750 mg of the remaining bromomalonate and 420 mg HMPA is dissolved in 8 ml toluene and added to 450 mg sodium hydride (50% oil suspension). Immediately after that 2.5 g α-ethylacrolein is added under rapid stirring. After 30 min the reaction mixture is poured into dilute aqueous acid. After extraction with dichloromethane and evaporation of the solvent 0.4 g (53%) of colourless crystals are obtained from ether. m.p. 155 °C. IR ($CHCl_3$): 1730, 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.37 [1] d, J = 7 Hz, 0.70 - 0.82 [12], 1.03 [3] s, 1.16 [3] s, 1.28 [3] s, 0.9 - 1.7 [13] m, 2.65 - 2.95 [2] dddd, J = 13 Hz, J = 8 Hz, 4.20 [1] d, J = 13 Hz, 4.28 [1] d, J = 13 Hz, 5.26 [1] d, J = 8 Hz, 5.38 [1] d, J = 8 Hz, 6.95 [1] s, 7.0 - 7.4 [20] m. ^{13}C NMR ($CDCl_3$): 196.44 d, 167.42 s, 165.29 s, 146.37 s, 146.31 s, 144.95 s, 144.56 s, 128.75 d, 128.67 d, 128.61 d, 128.48 d, 127.40 d, 127.18 d, 126.35 d, 126.05 d, 84.81 d, 83.64 d, 52.46 d, 52.38 d, 52.10 d, 51.93 s, 51.25 d, 50.37 d, 48.22 d, 47.41 s, 74.25 s, 43.83 d, 42.52 s, 33.79 tr, 33.44 tr, 30.38 tr, 30.16 tr, 22.29 tr, 22.27 q, 21.84 q, 21.55 q, 20.94 q, 17.43 q, 12.53 q, 12.35 q, 11.89 q. MS (200 °C): no molecular ion M^+ 302 m/e (21%), 206 (15), 193 (7), 181 (9), 167 (100), 165 (23), 152 (16). $C_{54}H_{62}O_5 \cdot 0.5\ H_2O$ (800.1) Calc. C 81.06, H 7.93; Found C 80.98, H 7.96.

4-Ethyl-2,3-dihydro-2,2-furandicarboxylic acid-bis[exo-diphenylmethyl]-isobornylester (15): 100 mg of the bromomalonate as prepared under 14a dissolved in 1 ml cyclohexane is treated with 100 mg sodium hydride (80% oil suspension) and a solution of 150 mg ethylacrolein in cyclohexane for 30 min at room temp., work-up as above yields 42 mg (42%) of dihydrofuran 15. IR ($CHCl_3$): 1740, 1600, 1500, 1095, 1035. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.70 [3] s, 0.74 [3] s, 0.80 [3] s, 0.85 [3] s, 1.23 [3] s, 1.19 [3] s, 1.10 [3] tr, J = 7 Hz, 1.25 - 1.85 [14] m, 2.74 [2] dddd, J = 8 Hz, J = 13 Hz, 4.15 [1], J = 13 Hz, 4.24 [1], J = 13 Hz, 5.35 [1], J = 8 Hz, 5.37 [1], J = 8 Hz, 5.70 [1] s, 7.0 - 7.3 [20] m. ^{13}C NMR ($CDCl_3$): 167.78 s, 167.42 s, 146.38 s, 146.32 s, 144.10 s, 137.34 d, 128.52 d, 128.40 d, 128.29 d, 128.19 d, 127.46 d, 127.24 d, 125.91 d, 125.85 d, 125.46 d, 114.66 s, 87.58 s, 83.00 d, 82.34 d, 52.92 d, 52.83 d, 51.59 s, 51.41 s, 50.95 d, 50.78 d, 48.23 d, 48.13 d, 47.41 s, 39.40 tr, 33.22 tr, 32.94 tr, 30.24 tr, 21.85 q, 21.78 q, 21.73 q, 21.60 q, 19.18 tr, 12.11 q, 11.80 q, 11.60 q. MS (220 °C): M^+ 790 m/e (1%), 304 (14), 206 (12), 193 (15), 181 (11), 167 (100), 165 (23), 152 (13), 91 (25). As this product obviously is useless for the synthetic procedure no further characterization was undertaken.

2-Ethyl-2-formyl-1,1-cyclopropane-dicarboxylic acid[exo-diphenylmethyl]-isobornylbenzylester (14c): the bromoester 12c is prepared as described above (see 14a) and 6.3 g (10.9 mmol) of this compound as well as 1.83 g (21.2 mmol) of ethylacrolein is dissolved in 20 ml cyclohexane. This solution is quickly added to 800 mg sodium hydride (50%, oil suspension) and the resulting mixture is stirred for 15 min at room temp. For work-up it is poured into dilute ice cold aqueous acid and extracted with dichloromethane. The same solvent is used for the subsequent filtration on silica gel and the resulting crude product is dissolved in petroleum ether/ether (1 : 1) from this solution 1.6 g (25%) of one pure diastereomer crystallize spontaneously. Further material can be obtained from mother liquors on chromatography. m.p. 123 °C; α_{589} = -68.6° (c = 1.85). IR ($CHCl_3$): 1740, 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.75 [3] s, 0.79 [3] s, 1.25 [3] s, 0.87 - 1.90 [12] m, 2.82 [1] dd, J = 13 Hz, J = 8 Hz, 4.12 [1], J = 13 Hz, 5.18 [2] AB-q, J = 12 Hz, 5.25 [1] d, J = 8 Hz, 7.44 [5] s, 6.9 - 7.32 [10] m, 8.71 [1] s. ^{13}C NMR ($CDCl_3$): 197.39 d, 166.61 s, 165.94 s, 134.79 s, 128.91 d, 128.86 d, 128.78 d, 128.46 d, 128.31 d, 128.08 d, 127.19 d, 126.33 d, 125.99 d, 82.99 d, 68.25 tr, 53.18 d, 51.60 s, 50.81 s, 47.91 d, 47.46 s, 53.93 d, 41.40 s, 32.82 tr, 30.17 tr, 23.68 tr, 22.97 tr, 21.76 q, 21.29 q, 11.44 q, 11.05 q. MS (80 °C): M^+ 578 m/e (1%), 302 (51), 206 (27), 193 (8), 181 (6), 167 (73), 91 (100), 86 (28), 84 (43). $C_{38}H_{42}O_5$ (578.8) Calc. C 78.66, H 7.32; Found C 78.64, H 7.35.

ent-2-Ethyl-2-formyl-1,1-cyclopropane-dicarboxylic aciddimethylester (3): a solution of 24.3 g (4.20 mmol) of the mixed diester 14c in 240 ml ether and 60 ml dichloromethane is cooled to -20 °C and at this temperature a solution of 36 g (642 mmol) KOH in 240 ml methanol is added slowly. After 5 days at -20 °C the saponification is complete. The reaction mixture is concentrated, water is added and neutral components are extracted with ether from which the chiral isoborneol can be regained. The remaining aqueous phase is acidified with sulfuric acid and again extracted with ether. This ether solution is esterified with diazomethane and evaporated to yield 7.5 g (83%) of the enantiomerically pure [α_{589} = 15.5° (c = 3.3)] aldehyde 3 which in every spectroscopic detail was completely identical to the racemic mixture reported earlier.[8] In shift reagent experiments with $Eu(tfc)_3$ this product however, in contrast to the racemic mixture gave rise to only one set of resonance signals (ratio aldehyde to $Eu(tfc)_3$: 8.4 mmol/3.4 mmol). To additionally prove the configurational stability of the cyclopropane compound it is refluxed for 24 h in xylene without any change in rotation values.

2-Ethyl-2-formyl-1,1-cyclopropane-dicarboxylic acid-8-[exo-diphenylmethyl]-isobornylester (14d): 50 mg (0.087 mmol) of diester 14c is after addition of 50 mg Pd/C (10%) hydrogenated in dioxan. After 2 h the solution is filtered and the solvent is evaporated to yield 35 mg (83%) of the acid 14d which does not form any lactol ⟶ see NMR data. ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.78 [3] s, 0.8 [3] s, 1.26 [3] s, 0.85 - 2.03 [12] m, 2.86 [1] dd, J = 13 Hz, J = 8 Hz, 4.25 [1] d, J = 13 Hz, 5.37 [1] d, J = 8 Hz, 7.1 - 7.4 [10] m, 9.03 [1] s.

ent-10-Ethyl-4-oxo-1,2,3,4,6,7,12,12b-octahydro-1,3-cycloindolo[2,3-a]quinolizin-3b-carboxylic acidmethylester (4): 4.9 g tryptamine (30.6 mmol) is dissolved in 40 ml warm toluene and 7.2 g (33.6 mmol) of aldehyde 3 dissolved in 5 ml toluene is added after 2 h at room temp. the solvent is evaporated i.vac. and the remaining oil is dissolved in 40 ml acetic acid and left at room temp. for one week (TLC control!). Water is added and the reaction products are extracted with dichloromethane. The organic phase is washed with sodium hydrogencarbonate solution and brine, dried ($MgSO_4$) and evaporated. The crude product is purified by flash chromatography to yield 5 g (50%) of lactam[8] 4. All pure enantiomers of this series did create problems with crystallization in contrast

to their racemic counterparts which are readily crystallizing compounds of low solubility. All spectroscopic data were in complete agreement.
$C_{19}H_{20}O_3N_2$ (324.1) Calc. 324.1473; Found 324.1473 (MS) α_{589} = -32.3° (c = 3.07).

ent-10-Cyanmethyl-1α-ethyl-3-oxo-2,3,5,6,11,11bβ-hexahydroindolo[8,7-b]indole (5a): 2 g (6.17 mmol) of lactam 4 is dissolved in 80 ml dry dimethylformamide, 1.6 g potassium cyanide and 400 mg lithium iodide are added. The mixture is refluxed for 2 h, poured into sodium hydrogencarbonate solution and extracted with dichloromethane. After evaporation of the solvent, chromatography with dichloromethane/ether (1 : 1) yields 900 mg (50%) of nitrile 5a. Acidification of the aqueous phase and extraction provided the rest of the materialas an acid which on subsequent esterification give rise to lactam 4 again, thus improving the efficiency of this transformation. Again spectral data of the nitrile corresponds perfectly to those of the racemic mixture.
$C_{18}H_{19}N_3O$ (293.2) Calc. 293.1528; Found 293.1528 (MS) α_{589} = +95.8° (c = 0.95).

ent-D-Noreburnamonine-18-one (7): 6 g of nitrile 5a is added to a solution of 30 g potassium hydroxide in 50 ml methanol and 30 ml water. After addition of 2 ml hydrogen peroxide (35%) this mixture is heated for 3 h at 80 °C, diluted with aqueous acid and under still alkaline conditions neutral by-products are extracted with ether. Subsequently the solution is acidified and extracted with dichloromethane to yield after evaporation 5.6 g of the crude acid 5b. To reduce oxidation products formed in the process this product is dissolved in 60 ml dichloromethane and treated with 1 g tetraethylammoniumtetrahydridoborate for 30 min. For work-up the mixture is shaken with dilute acid. The organic phase is dried ($MgSO_4$), evaporated and 4.2 g of the acid prepared this way is left in 135 ml trifluoro acetic acid at room temp. for 15 h. After evaporation the residue is dissolved in dichloromethane and washed with soda solution and brine. On evaporation of the dichloromethane 1.92 g (49%) of dilactam[6] 7 is obtained. (Leaving this product in ether at low temperature led to the formation of crystals of the racemic mixture. After complete removal of these crystals the mother liquor proved to be one pure enantiomer and can be used as such.)
$C_{18}H_{18}N_2O_2$ (294.1) Calc. 294.1368; Found 294.1368 (MS) α_{589} = -228° (c = 0.64).

ent-4,18-seco-D-Noreburnamonine-18-carboxylic acidethylester (9a): 500 mg of lactam 7 are dissolved in 10 ml dry dichloromethane and a solution of 1 g triethyloxoniumhexafluorophosphate in 15 ml dry dichloromethane is added. After 15 h at room temp. this mixture is treated with 5 ml dry methanol and left at room temp. for another 4 h. The dichloromethane is extracted with dilute aqueous acid and this water phase is extracted a few times with ether which is discarded. After adjusting to pH 8 by the addition of soda the ester[6] 9a is extracted with dichloromethane and spectral data obtained after evaporation of the solvent proves to be completely identical to those published already.[6]

ent-18-oxo-Eburnamonine (10a): to a solution of 200 mg of ester 9a in 6 ml acetonitrile 1 ml of Hünig base and 2 ml of bromoacetic acidethylester is added and the mixture stirred under reflux for 3 h under argon. Dichloromethane is added and the solution is washed with aqueous sodium hydrogencarbonate, dried and evaporated to yield 240 mg (96%) of diester 9b. This material is redissolved in 5 ml dry dioxin 250 mg sodium hydride (50% oil suspension) is added and the resulting mixture is treated with eight drops of ethanol. After 15 min water is added and the β-ketoester is extracted with dichloromethane. After evaporation of the solvent the residue is refluxed for 4.5 h in a solution of 400 mg lithium iodide in 40 ml dimethylformamide and again evaporated. The residue is dissolved in dichloromethane and washed with dilute acid, sodium hydrogencarbonate, and brine. After evaporation and purification by chromatography (ether) a yield of 50% of the ketone 10a is obtained. m.p. 181 °C, α_{589} = -134.0° (c = 0.6). IR (KBr): 1710 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 1.0 [3] tr, J = 7.5 Hz, 1.65 - 1.80 [2] m, 2.20 [2] ABq, J = 14 Hz, 2.73 [4] ABq, J = 17 Hz, 2.91 - 3.50 [4] m, 4.23 [1] s, 7.28 - 7.50 [3] m, 8.30 - 8.43 [1] m. MS (110 °C): M^+ 308 m/e (100%), 279 (39), 167 (39), 168 (33), 180 (39), 222 (35), 224 (57), 251 (32). $C_{19}H_{20}N_2O_2$ (308.2) Calc. 308.1524; Found 308.1524 (MS). Calc. C 73.99, H 6.54, N 9.09; Found C 73.69, H 6.55, N 9.07.

(-)-Eburnamonine (-)-1: route A: 10 mg of ketone 10a dissolved in 1 ml chloroform is treated with 220 mg 1,3-propanethiol and a few drops of borontrifluorate etherate. After 17 h at room temp. dichloromethane is added and this solution is washed with sodium hydrogencarbonate, dried and evaporated to yield 9 mg (70%) of thioketal 10b. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.03 [3] tr, J = 7.5, 1.22 - 1.40 [2] m, 1.6 - 2.1 [2] m, 2.25 [1] m, 2.50 - 3.05 [10] m, 3.14 - 3.24 [1] m, 3.40 - 3.50 [2] m, 4.10 [1] s, 7.25 - 7.47 [3] m, 8.33 - 8.40 [1] m. MS (140 °C): M^+ 398 m/e (77%), 369 (8), 341 (8), 323 (16), 292 (11), 266 (11), 263 (15), 251 (11), 219 (100), 196 (23), 184 (30), 180 (20), 178 (45), 177 (48), 154 (27). $C_{22}H_{26}N_2O_1S_2$ (398.1) Calc. 398.1486; Found 398.1484 (MS).
This thioketal is stirred in acetone with Raney-Ni, filtered and evaporated to yield 5 mg (70%) (-)-eburnamonine identical with a sample from natural sources.

Route B: 40 mg of ketone 10a is dissolved in 1.5 ml dry dichloromethane, taken to -78 °C and treated with 0.2 ml of a 1M solution of L-selectride. After 15 min 1 ml methanol is added and the mixture is taken at room temp. and diluted with dichloromethane. This solution is washed with sodium hydrogencarbonate, dried and evaporated to yield 39 mg (97%) of alcohol 10c. $C_{19}H_{22}N_2O_2$ (310.2) Calc. 310.1681; Found 310.1680 (MS).
22 mg of this alcohol 10c is dissolved in 3 ml dry tetrahydrofuran, 50 mg sodium hydride (50% oil suspension) is added and after 10 min at room temp. this mixture is treated with 0.3 ml of carbon disulfide and 0.4 mol methyl iodide. After 1 h at room temp. the mixture is hydrolyzed with dilute acid, extracted with ether (which is discarded), brought to pH 8 with soda solution and extracted with dichloromethane. After evaporation of the solvent 24 mg (85%) of the xanthogenate 10d is obtained.

Eburnamonine-17α-xanthogenate 10d: IR ($CHCl_3$): 1700, 1060 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.95 [3] tr, J = 7.5 Hz, 1.20 - 1.45 [3] m, 1.55 - 1.75 [1] m, 2.10 - 2.45 [2] m, 2.58 [3] s, 2.60 - 2.80 [3] m, 2.80 - 3.04 [1] m, 3.31 - 3.41 [2] m, 4.19 [1] s, 5.67 [1] s, 7.25 - 7.45 [3] m, 8.30 - 8.40 [1] m. MS (130 °C): M^+ 400 m/e (9%), 293 (100), 292 (44), 279 (80), 263 (31), 229 (12), 224 (86), 196 (13), 180 (21), 168 (26), 167 (33), 149 (16), 125 (19), 123 (16), 111 (31).

$C_{21}H_{24}N_2O_2S_2$ (400.1) Calc. 400.1279; Found 400.1278 (MS). 10 mg of xanthogenate 10d is dissolved in 3 ml toluene and after addition of 1 ml tributyl-tin hydride and a few mg of AIBN refluxed for 90 min, taken to dryness and purified by TLC (dichloromethane/methanol 20 : 1). 4 mg (59%) of pure (-)-eburnamonine is obtained this way.

14-Methylene-desoxy-eburnamine (23): to a solution of 3.1 ml dibromomethane in 80 ml tetrahydrofuran 8.8 g zinc dust is added and the mixture is cooled to -78 °C. 3.7 ml titanium tetrachloride is added and stirring is continued at 0 °C for 24 h. To the resulting gray suspension 1.53 g (-)-eburnamonine dissolved in 7 ml dichloromethane is added and the mixture left with stirring for 72 h. The reaction mixture is poured into aqueous soda solution and the base is extracted with dichloromethane. After evaporation of the solvent the crude reaction product is purified by chromatography (dichloromethane/methanol 50 : 1) and 1.07 g (70%) of the vinylindole is obtained. m.p. 120 °C. UV (CH_3OH): 305, 294, 250 nm. IR ($CHCl_3$): 1615, 1645 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.92 [3] tr, J = 8 Hz, 1.0 - 1.9 [4] m, 1.95 - 2.15 [1] m, 2.3 - 2.65 [6] m, 2.83 - 3.05 [1] m, 3.15 - 3.40 [2] m, 3.92 [1] s, 4.50 [1] s, 5.23 [1] s, 7.1 - 7.3 [2] m. α_{589} = -116° (c = 0.83). $C_{20}H_{24}N_2$ (292.4) Calc. C 82.15, H 8.27, N 9.58; Found C 82.52, H 8.05, N 9.66.

(+)-Apovincaminal (24d): 400 mg of vinalindole 23 is dissolved in 15 ml dry tetrahydrofuran and after addition of 250 mg N-bromo-succinimide stirred at room temp. for 90 min. Sodium hydrogencarbonate is added and the reaction product is extracted with dichloromethane. Evaporation of the solvent and chromatography (dichloromethane/methanol 100 : 1) yields 270 mg (53%) of the unstable bromo compound 24a which is immediately transformed into the acetate 24b by refluxing for 3 h in a solution of 2 g potassium acetate in 30 ml acetic acid. After evaporation, redissolving in dichloromethane and washing with aqueous soda solution, removal of the solvent and subsequent chromatography (dichloromethane/methanol 50 : 1) gives rise to 230 mg (92%) of acetate 24b. ^1H NMR ($CDCl_3$), 200 MHz): δ = 1.0 [3] tr, J = 8 Hz, 2.92 - 3.14 [1] m, 3.23 - 3.40 [3] m, 4.21 [1] s, 4.55 [2] ABq, J = 12 Hz, 5.22 [1] s, 7.08 - 7.30 [2] m, 7.44 - 7.53 [1] m, 7.6 - 7.68 [1] m. MS (170 °C): M^+ 350 m/e (36%), 321 (100), 291 (19), 280 (88), 278 (17), 260 (34), 235 (10), 221 (14). Room temp. hydrolysis (4% potassium hydroxide in methanol, 20 min) provided a 90% yield of vincaminol which by standard manganese dioxide oxidation (dichloromethane, room temp., 30 min) yields 75% of apovincaminal[15] 24d. UV (CH_3OH): 312, 271, 257, 235 nm (qualitative). IR ($CHCl_3$): 1600, 1635, 1700 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ = 1.05 [3] tr, J = 7.5 Hz, 1.16 - 2.15 [6] m, 2.33 - 2.77 [3] m, 2.77 - 3.44 [3] m, 4.13 [1] s, 6.18 [1] s, 7.10 - 7.33 [2] m, 7.33 - 7.70 [2] m, 9.54 [1] s. MS (70 °C): M^+ 306 m/e (38%), 277 (100), 247 (19), 230 (92), 228 (18), 220 (11), 193 (16). α_{589} = +348.3° (c = 0.6).
Further treatment as described by H.Najer and Y.Pascal[15] generates apovincamine which has been transformed into vincamine by W.Oppolzer et al.[4b]

(+)-Eburnamonine (+)-1 is prepared from lactam 4 according to the procedure described in lit.[5] The following intermediates are characterized as pure enantiomers.

ent-α-Cyan-1α-ethyl-3-oxo-2,3,5,6,11,11β-hexahydro-1H-indolizino[8,7-b]indole-1β-propionic acid-methylester (6): $C_{21}H_{23}O_3N_3$ (365.2) Calc. 365.1739; Found 365.1735 (MS) α_{589} = +95.4° (c = 1.54).

ent-12cα-Ethyl-1,2,3aα,4,6,7,12,12bβ-decahydrocyclopent[1,2]indolizino[8,7-b]indole-3,4-dione (21): $C_{12}H_{20}N_2O_2$ (308.2) Calc. 308.1524; Found 308.1524 (MS) α_{589} = -65.9° (c = 1.72).

ent-2α-Ethyl-5-oxo-2-(1β,2,3,4-tetrahydro-β-carboline-1-yl)-cyclopentane-carboxylic acidmethylester (22): $C_{21}H_{26}N_2O_3$ (354.2) Calc. 354.1943; Found 354.1943 (MS) α_{589} = +29.5° (c = 0.79).

ent-19-oxo-Eburnamonine (8): $C_{19}H_{20}O_2N_2$ (308.2) Calc. 308.1524; Found 308.1524 (MS) α_{589} = +194.1° (c = 0.7).

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