# 9. Synthesis of Enantiomeric Pure E-Nor-15-azayohimbines

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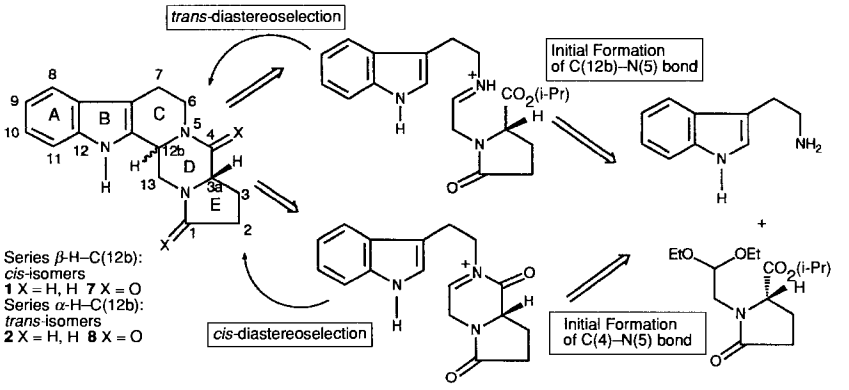
A stereodivergent synthesis of enantiomerically pure E-nor-15-azayohimbines *via* condensation of tryptamine with derivatives of pyroglutamate **4** is reported. When the *Pictet-Spengler* reaction was induced in refluxing aqueous AcOH a nearly equimolar ratio of lactams **7** and **8** was obtained, whereas under kinetic control (TFA, room temperature) the *trans*-derivative **8** was the major product. In contrast, cyclization of amido acetal **12** with TsOH gave the *cis*-derivative **7** as preponderant component.

**1. Introduction.** – The synthesis of pharmacologically active tetra- and pentacyclic compounds embodying the 2-(piperazin-2-yl)indole moiety has recently received considerable attention [1–5]. Nevertheless, in all cases the products have been obtained in the racemic form.

In this paper, we report the synthesis of enantiomerically pure pyrrolo[1″,2″:4′,5′]-pyrazino[1′,2′:1,2]pyrido[3,4-*b*]indoles **1** and **2**, which are derivatives of a new heterocyclic system with the aforementioned moiety (*Scheme 1*). Compounds **1** and **2** can be

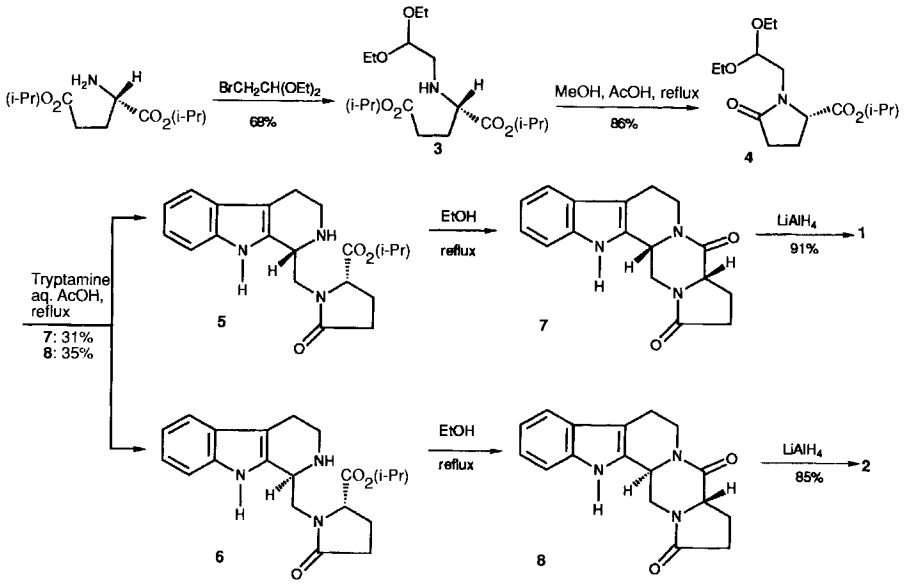
*Scheme 1*




considered E-nor-15-azayohimban derivatives, and their skeletons are constitutional isomers of the pyrrolo-pyrazino-pyrido-indole framework present in several tremorgenic mycotoxins [6].

In designing the synthesis of **1** and **2**, it must be considered that the *Pictet-Spengler* condensation between tryptamine and α-amino acetals to give 1-(aminomethyl)tetra-

*Scheme 2*




hydro-β-carbolines proceeds in very low yields due to a competitive fragmentation process [5]. For this reason, acetal **4** was chosen as the starting material for the synthesis of **1** and **2** (*Scheme 2*). Compound **4** incorporates ring E, with one chiral center of known configuration, a chain suitable for the *Pictet-Spengler* reaction with tryptamine without risk of fragmentation, and an ester group to induce the closure of ring D by lactamization. The order in which the acetal and the ester chains react with the tryptamine N-atom as well as the reaction conditions allow a different stereocontrol in the formation of the tetrahydro-β-carboline unit.

**2. Results.** – 2.1. *Synthesis of the Target Compounds.* A common solution to the problem of synthesizing optically active molecules is to take recourse to educts derived from naturally occurring α-amino acids [7]. Accordingly, we used L-glutamic acid as a readily available, optically pure starting material.

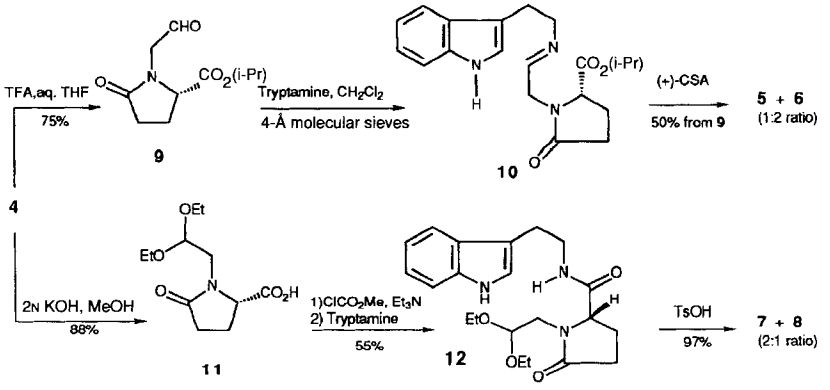
Alkylation of the isopropyl diester of L-glutamic acid [8] with bromoacetaldehyde diethyl acetal followed by lactamization of the resulting amino diester **3**, either by heating in MeOH/AcOH or by pyrolysis at 170°, gave the enantiomerically pure lactam **4** (*Scheme 2*). The optical purity of **4** was established by comparison of its $^1$H- and $^{13}$C-NMR spectra, recorded in presence of the chiral shift reagent Eu(hfc)$_3$ [9], with those of (±)-**4**, which was prepared following the same reaction sequence starting from (±)-glutamic acid. Lactam **4** showed only one set of signals, while (±)-**4** gave two sets of signals.

During the formation of the tetrahydro-β-carboline moiety by *Pictet-Spengler* reaction between acetal **4** and tryptamine, a new chiral center is formed[1]). However, when the

[1]) For the synthesis of 1-substituted 1,2,3,4-tetrahydro-β-carbolines in a diastereoselective manner starting from tryptophan derivatives, see [10]; for an enantioselective *Pictet-Spengler* reaction in the tetrahydroisoquinoline series, see [11].

condensation was effected in refluxing aqueous AcOH, mixtures containing nearly equal amounts of the *cis*- and *trans*-lactams **7** and **8**, or the corresponding tetrahydro-$\beta$-carboline intermediates **5** and **6**, were formed. Interestingly, lactamization occurs faster starting from **6** (1*S*), to give the *trans*-lactam **8**, than starting from **5** (1*R*). In contrast, when the reaction was conducted under anhydrous conditions in the presence of $CF_3COOH$ [12] at room temperature (kinetic control), a significant degree of diastereoselectivity was observed, and a mixture of *trans* (**8**) and *cis* (**5** and **7**) derivatives was isolated in a 2:1 ratio. A similar diastereoselectivity was obtained, when the *Pictet-Spengler* cyclization was effected upon imine **10** in the presence of (+)-camphorsulfonic acid (*Scheme 3*). The

*Scheme 3*




required imine **10** was prepared by chemoselective hydrolysis [13] of acetal **4**, followed by condensation of the resulting aldehyde **9** with tryptamine under mild conditions (room temperature, molecular sieves). That the observed *trans*-diastereoselectivity is the result of the kinetic trapping of the intermediate iminium salt was evident, because separate treatment of either **5** or **6** with $CF_3COOH$ or (+)-camphorsulfonic acid for 24 h under the *Pictet-Spengler* reaction conditions did not lead to epimerization at C(1)[2]).

On the other hand, changing the order of the reactions resulted in an inversion of the diastereoselectivity. Thus, coupling of acid **11**, which was obtained by saponification of ester **4** under conditions that prevent racemization [8], with tryptamine by the mixed-anhydride method, followed by treatment of the resulting acetal **12** with TsOH at room temperature, led to a mixture of pentacycles **7** and **8** in which the *cis*-isomer **7** predominated (2:1 ratio). The observed diastereoselection reflects a kinetically controlled intramolecular *Pictet-Spengler* cyclization of the indolyl group upon the $\alpha$-acyliminium ion [16].

Finally, $LiAlH_4$ reduction of **7** and **8** afforded the target pentacycles **1** and **2** in excellent yields.

To ensure that the chiral center C(3a) had not undergone epimerization either during the *Pictet-Spengler* condensation or during the subsequent lactamization or reduction

[2]) The *Pictet-Spengler* reaction of *N*(b)-benzyltryptophan esters with aldehydes in $CF_3COOH/CH_2Cl_2$ at room temperature provides tetrahydro-$\beta$-carbolines *via* thermodynamic control [14], whereas the same reaction with tryptophan methyl ester is a kinetically controlled process [15].

Table 1. *$^1$H-NMR Data*[a]) *of Pentacyclic E-Nor-15-azayohimbane-Type Compounds*

| | **1**[b]) | **2**[b]) | **7**[c]) | **8**[c]) |
|---|---|---|---|---|
| $H_\alpha$–C(1) | 3.01 (*m*) | 3.01 (*m*) | – | – |
| $H_\beta$–C(1) | 2.32 (br. *t*, *J* = 9.5) | 2.12 (br. *t*, *J* = 10.5) | – | – |
| $H_\alpha$–C(2) | 1.70 (*m*) | 1.70–1.79 (*m*) | 2.12 (*ddd*, *J* = 16.5, 10.0, 2.5) | 2.29 (*m*) |
| $H_\beta$–C(2) | 1.75 (*m*) | 1.70–1.79 (*m*) | 2.34 (*dt*, *J* = 16.5, 9.5) | 2.38 (*m*) |
| $H_\alpha$–C(3) | 1.50 (*m*) | 1.31 (*qd*, *J* = 10.0, 6.5) | 2.25 (*dddd*, *J* = 12.5, 9.5, 8.0, 2.5) | 2.38 (*m*) |
| $H_\beta$–C(3) | 1.75 (*m*) | 1.66 (*tt*, *J* = 10.0, 3.0) | 2.0 (*dddd*, *J* = 12.5, 10.5, 9.5, 8.0) | 1.95 (*m*) |
| H–C(3a) | 2.38 (br. *t*, *J* = 9.5) | 2.12 (br. *t*, *J* = 10.0) | 4.34 (*t*, *J* = 8.0) | 4.25 (*t*, *J* = 8.0) |
| $H_{eq}$–C(4) | 2.80 (*dd*, *J* = 11.0, 3.5) | 3.01 (*dd*, *J* = 10.0, 2.5) | – | – |
| $H_{ax}$–C(4) | 2.74 (*ddd*, *J* = 11.0, 9.5, 1.0) | 2.18 (*t*, *J* = 10.0) | – | – |
| $H_{eq}$–C(6) | 3.24 (*ddd*, *J* = 13.0, 6.0, 1.0) | 3.02 (*ddd*, *J* = 10.5, 6.5, 2.5) | 4.61 (*ddd*, *J* = 12.5, 4.7, 2.6) | 4.89 (*dm*, *J* = 11.0) |
| $H_{ax}$–C(6) | 3.13 (*td*, *J* = 12.5, 4.5) | 2.55 (*td*, *J* = 11.0, 4.0) | 3.03 (*ddd*, *J* = 12.5, 10.0, 6.5) | 2.81 (*td*, *J* = 12.0, 4.0) |
| $H_{eq}$–C(7) | 2.59 (*ddd*, *J* = 15.0, 5.0, 2.0) | 2.60 (*ddd*, *J* = 15.0, 6.5, 4.0) | 2.72 | 2.76 (*dm*, *J* = 15.0) |
| $H_{ax}$–C(7) | 3.03 (*dddd*, *J* = 15.0, 13.0, 6.0, 2.5) | 2.77 (*dddd*, *J* = 15.0, 11.0, 6.0, 2.5) | 2.72 (*m*) | 2.65 (*dddd*, *J* = 15.0, 12.5, 6.0, 2.5) |
| H–C(8) | 7.45 (*d*, *J* = 7.5) | 7.33 (*d*, *J* = 8.0) | 7.41 (*d*, *J* = 8.0) | 7.43 (*d*, *J* = 8.0) |
| H–C(9) | 7.07 (*td*, *J* = 8.0, 1.0) | 6.93 (*t*, *J* = 8.0) | 7.00 (*t*, *J* = 8.0) | 6.99 (*t*, *J* = 8.0) |
| H–C(10) | 7.12 (*td*, *J* = 7.5, 1.5) | 7.00 (*t*, *J* = 8.0) | 7.08 (*t*, *J* = 8.0) | 7.08 (*t*, *J* = 8.0) |
| H–C(11) | 7.30 (*dt*, *J* = 8.0, 1.0) | 7.26 (*d*, *J* = 8.0) | 7.34 (*d*, *J* = 8.0) | 7.30 (*d*, *J* = 8.0) |
| H–N(12) | 7.88 (br.) | 10.73 (*s*) | | 11.17 (*s*) |
| H–C(12b) | 4.10 (br. *s*) | 3.37 (*ddd*, *J* = 10.5, 3.0, 2.0) | 5.16 (*t*, *J* = 6.0) | 4.90 (*ddd*, *J* = 12.0, 5.0, 1.5) |
| $H_{eq}$–C(13) | 3.23 (br. *dd*, *J* = 11.0, 3.5) | 3.59 (*dd*, *J* = 10.5, 3.0) | 3.79 (*dd*, *J* = 18.0, 6.0) | 4.83 (*dd*, *J* = 13.0, 5.0) |
| $H_{ax}$–C(13) | 2.75 (*dd*, *J* = 11.5, 3.8) | 2.02 (*t*, *J* = 10.5) | 3.82 (*dd*, *J* = 18.0, 6.0) | 2.99 (*ddd*, *J* = 12.0, 11.5, 1.0) |

[a]) Chemical shifts in ppm relative to TMS; coupling constants *J* [Hz]. Recorded at 500 MHz.

[b]) In $CDCl_3$.

[c]) In $(D_6)$DMSO.

steps, the $^1$H- and $^{13}$C-NMR spectra of amines **1** and **2** were recorded as their (*S*)-MTPA salts [17], both in the optically active and in the racemic series. Whereas in (±)-**1** and (±)-**2** the signals appeared duplicate, the spectra of the corresponding optically active samples indicated no diastereoisomeric contamination.

In summary, pentacyclic E-nor-15-azayohimbanes can easily be obtained in enantiomerically pure form in five steps from L-glutamic acid.

2.2. *Structure of the Cyclization Products.* The assignment of the relative configurations of pentacycles **1**, **2**, **7**, and **8**, as well as their preferred conformation, if any, was accomplished on the basis of the NMR data ($^1$H, $^{13}$C, and 2D-COSY), taking into account the available data in the 15-azayohimbane series [18]. Thus, in the $^1$H-NMR spectrum of **1**, the H–C(12b) signal at 4.10 ppm appears as a br. *s*, which is characteristic of a *cis*-C/D fusion, whereas in compound **2** the chemical shift (3.3 ppm) and multiplicity (see *Table 1*) of the H–C(12b) signal indicate a *trans*-C/D conformation and axial disposition of this proton. The *trans*-D/E fusion and consequently the axial orientation of H–C(3a) in **1** and **2** were established on the basis of the multiplicity (br. *t*) and coupling constants ($J \approx 10$) of the signal due to this proton, which was unambiguously assigned from the corresponding 2D-NMR spectra and decoupling experiments. The $^{13}$C-NMR data corroborate the above-mentioned assignments (*Table 2*); isomer **1** shows a larger shielding for C(4), C(7), and C(12b) than isomer **2**, a characteristic feature for yohimboid compounds of the *pseudo*-series, which have a *cis*-configuration, and a *cis*-C/D, *trans*-D/E conformation [19]. These assignments are in agreement with the configuration of the precursors **7** and **8**, in spectra of which the signal H–C(3a) appears at a lower field and is easy recognizable.

Table 2. *$^{13}$C-NMR Chemical Shifts*[a]) *of Pentacyclic E-Nor-15-azayohimbane-Type Compounds*

| C-Atom | **1**[b]) | **2**[b]) | **7**[c]) | **8**[c]) | C-Atom | **1**[b]) | **2**[b]) | **7**[c]) | **8**[c]) |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 51.9 | 52.7 | 173.2 | 172.8 | C(8) | 117.9 | 118.1 | 118.3 | 118.4 |
| C(2) | 20.9 | 21.5 | 30.1 | 30.4 | C(9) | 119.2 | 119.2 | 119.2 | 119.3 |
| C(3) | 26.1 | 26.9 | 21.3 | 22.7 | C(10) | 121.2 | 121.9 | 121.8 | 121.8 |
| C(3a) | 61.3 | 62.3 | 56.6 | 57.0 | C(11) | 111.1 | 110.9 | 111.8 | 111.7 |
| C(4) | 53.8 | 58.6 | 170.5 | 168.0 | C(11a) | 136.1 | 136.2 | 136.6 | 136.9 |
| C(6) | 51.2 | 52.3 | 40.6 | 39.0 | C(12a) | 132.6 | 132.7 | 131.8 | 131.2 |
| C(7) | 18.8 | 20.9 | 20.3 | 20.8 | C(12b) | 55.3 | 58.2 | 51.6 | 52.9 |
| C(7a) | 108.0 | 108.5 | 108.9 | 108.3 | C(13) | 52.3 | 54.5 | 41.9 | 40.7 |
| C(7b) | 127.5 | 127.3 | 126.8 | 126.2 | | | | | |

[a]) In ppm relative to TMS. Recorded at 50.3 MHz.
[b]) In $CDCl_3$.
[c]) In $(D_6)$DMSO.

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## Experimental Part

*General.* For TLC, *E. Merck* silica gel was used, and for FC ( = flash chromatography) silica gel (230–400 mesh) *SDS* was used. M.p.: *CTP-MP 300* hot-plate apparatus; uncorrected. Optical rotations were measured with a *Perkin-Elmer 241* polarimeter. IR spectra [$cm^{-1}$]: *Perkin-Elmer 1600* FT-IR spectrometer. NMR spectra: *Varian VXR-500* or *Varian Gemini-200*; chemical shifts in $\delta$ [ppm] relative to internal TMS; unless otherwise specified, in $CDCl_3$, $J$ in Hz. All $^{13}$C-NMR spectra were determined at 50.3 MHz. MS [*m*/*z* (rel %)]: *Hewlett-Packard HP-5988 A* spectrometer.

1. *Diisopropyl (S)-N-(2,2-Diethoxyethyl)glutamate* (**3**). To a stirred soln. of bromoacetaldehyde diethyl acetal (12.0 ml, 77.3 mmol) in DMF (70 ml), anh. $K_2CO_3$ (29.9 g, 216 mmol) was added, followed by diisopropyl (*S*)-glutamate [7] (17.9 g, 77.7 mmol). Stirring was continued at 85–90° for 22 h. Then, the soln. was cooled, diluted with $H_2O$ (200 ml) and benzene (200 ml), and the phases were separated. The aq. phase was extracted with benzene (3 × 200 ml), and the combined org. phases were washed with brine, dried, filtered, and evaporated. The residue was purified by FC ($Et_2O$/EtOH 40:1): **3** (18.2 g, 68%) and recovered diester (1.27 g).

*Data of* **3**. $[\alpha]_D^{20} = -4.4$ (*c* = 2.0, MeOH). IR (film): 3420, 3320, 1720. $^1$H-NMR (200 MHz): 1.1–1.3 (*m*, 18 H); 1.7–2.0 (*m*, 2 H–C(3)); 2.39 (*t*, *J* = 7.8, 2 H–C(4)); 2.56 (*dd*, *J* = 10.4, 4.9, $NCH_AH_B$); 2.78 (*dd*, *J* = 10.4, 6.4, $NCH_AH_B$); 3.22 (*dd*, *J* = 7.2, 6.2, H–C(2)); 3.4–3.8 (*m*, 2 $CH_2O$); 4.56 (*dd*, *J* = 6.4, 4.9, OCHO); 4.9–5.1 (2 *sept.*, 2 CH). $^{13}$C-NMR: 15.7 ($CH_3CH_2O$); 22.2, 22.4 ($(CH_3)_2CH$); 28.6 (C(3)); 31.4 (C(4)); 50.5 ($CH_2N$); 61.2 (C(2)); 61.8, 62.7 ($CH_2O$); 68.1, 68.8 (CH); 102.6 (OCHO); 173.4, 174.9 (CO). Anal. calc. for $C_{17}H_{33}NO_6$ (347.43): C 58.76, H 9.57, N 4.03; found: C 58.87, H 9.72, N 4.03.

2. *Isopropyl (S)-1-(2,2-Diethoxyethyl)-5-oxopyrrolidine-2-carboxylate* (**4**). 2.1. A soln. of **3** (7 g, 20.2 mmol) in MeOH (170 ml) and AcOH (70 ml) was refluxed for 3 h and then evaporated. The resulting oily residue was submitted to FC ($Et_2O$/EtOH 40:1): **4** (4.98 g, 86%). $[\alpha]_D^{20} = +0.15$ (*c* = 2.0, MeOH). IR (film): 1730, 1690. $^1$H-NMR (200 MHz): 1.1–1.3 (*m*, 12 H); 2.0–2.5 (*m*, 2 H–C(3), 2 H–C(4)); 3.00 (*dd*, *J* = 15.6, 6.6, $NCH_AH_B$); 3.4–3.8 (*m*, 2 $CH_2O$); 3.90 (*dd*, *J* = 15.6, 4.0, $NCH_AH_B$); 4.40 (*m*, H–C(2)); 4.56 (*dd*, *J* = 6.6, 4.0, OCHO); 5.07 (*sept.*, *J* = 6.4, CH). $^{13}$C-NMR: 15.7 ($CH_3CH_2O$); 22.1 ($(CH_3)_2CH$); 23.7 (C(3)); 29.8 (C(4)); 44.8 ($CH_2N$); 61.3 (C(2)); 63.2, 63.7 ($CH_2O$); 69.6 (CH); 101.5 (OCHO); 172.5 (COO); 176.5 (C(5)). Anal. calc. for $C_{14}H_{25}NO_5$ (287.34): C 58.52, H 8.77, N 4.87; found: C 58.51, H 8.86, N 4.85.

2.2. Compound **3** (4.5 g, 13.0 mmol) was heated at 175° in an oil bath for 6 h. Purification as above gave **4** (2.6 g, 70%) and unchanged **3** (1.16 g). Yield based on recovered starting material: 93%.

3. *Determination of the Optical Purity of* **4**. Racemic **4** (100 mg), obtained by the same procedure as the optically active compound but starting from racemic glutamic acid, was dissolved in $CDCl_3$ (0.7 ml) in a NMR tube to which small portions (10 mg each, 2.5 mol-%) of tris[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato]-europium (III) were added. Optimal separation of the two *sept.* (5.160 and 5.174) due to OCH was achieved with 20 mg, 5 mol-% Eu(hfc)$_3$. The same experiment was repeated with optically active **4**, using 5 mol-% Eu(hfc)$_3$. Only one *sept.* (5.16) appeared in this experiment, with no observable indication for the presence of the other enantiomer. For the $^{13}$C-NMR analyses, 20 mol-% Eu(hfc)$_3$ was used: racemic **4** showed two sets of signals for the majority of C-atoms, whereas optically pure **4** displayed only one.

4. *Condensation between Tryptamine and* **4**. 4.1. *In Aq. AcOH Followed by Lactamization.* A mixture of **4** (3 g, 10.5 mmol) and tryptamine (2.2 g, 13.8 mmol) in AcOH (32 ml) and $H_2O$ (11 ml) was refluxed for 6 h under $N_2$. After evaporation, the crude product was dissolved in abs. EtOH (35 ml), and the mixture was refluxed for 22 h. The solid was filtered and crystallized from EtOH to give the *trans*-derivative **8**. The combined mother liquors were evaporated and submitted to FC ($Et_2O$/EtOH 2:1) to give additional **8** (1.09 g, 35% overall yield) and the *cis*-derivative **7** (960 mg, 31%), both of them as white solids.

*Data of (3aS,12bR)-2,3,3a,4,6,7,12b,13-Octahydro-1,4-dioxo-1*H,*12*H*-pyrrolo[1″,2″:4′,5′]pyrazino-[1′,2′:1,2]pyrido[3,4-b]indole* (**7**). M.p. 258–259° (EtOH). $[\alpha]_D^{20} = +104.5$ (*c* = 1.0, MeOH). IR (KBr): 3280, 1675, 1665. $^1$H- and $^{13}$C-NMR: see *Tables 1* and *2*. Anal. calc. for $C_{17}H_{17}N_3O_2$ (295.31): C 69.14, H 5.80, N 14.22; found: C 69.05, H 5.89, N 14.31.

*Data of (3aS,12bS)-2,3,3a,4,6,7,12b,13-Octahydro-1,4-dioxo-1*H,*12*H*-pyrrolo[1″,2″:4′,5′]pyrazino-[1′,2′:1,2]pyrido[3,4-b]indole* (**8**). M.p. 280–281° (EtOH). $[\alpha]_D^{20} = -71.4$ (*c* = 1.0, DMSO). IR (KBr): 3200, 1660. $^1$H- and $^{13}$C-NMR: see *Tables 1* and *2*. Anal. calc. for $C_{17}H_{17}N_3O_2$ (295.31): C 69.14, H 5.80, N 14.22; found: C 69.13, H 5.71, N 14.17.

Lactams (±)-**7** and (±)-**8** were identical with the optically pure derivatives in all respects except for the IR, m.p., and [α].

4.2. *In Aq. AcOH.* A mixture of **4** (600 mg, 2.09 mmol) and tryptamine (438 mg, 2.73 mmol) in AcOH (6 ml) and $H_2O$ (2 ml) was refluxed for 3 h under $N_2$ and then evaporated. The crude product was chromatographed (FC; $Et_2O$/EtOH 2:1): *(1R)-1,2,3,4-tetrahydro-1-{[(2S)-2-(isopropoxycarbonyl)-5-oxopyrrolidin-1-yl]methyl}-β-carboline* (**5**, 255 mg, 34%) and a mixture of **6**/**8** (260 mg, 38%).

*Data of* **5**. M.p. 54–56°. IR (film): 3440, 3290, 1720, 1670. $^1$H-NMR (200 MHz): 1.15, 1.16 (2*d*, *J* = 6.2, 2 $CH_3$); 1.94 (*s*, NH); 1.9–2.5 (*m*, 2 H–C(3′), 2 H–C(4′)); 2.7 (*m*, 2 H–C(4)); 2.9–3.2 (*m*, 2 H–C(3)); 3.25 (*dd*, *J* = 15.0, 8.1, $NCH_AH_B$); 4.06 (*dd*, *J* = 15.0, 3.2, $NCH_AH_B$); 4.30 (br. *dd*, *J* = 8.1, 3.2, H–C(1)); 4.45 (*m*, H–C(2′)); 4.96 (*sept.*, *J* = 6.2, OCH); 6.9–7.4 (*m*, 4 H, indole); 9.5 (*s*, NH, indole). $^{13}$C-NMR: 21.6 ($CH_3$); 21.9 (C(4)); 23.1 (C(3′)); 29.5 (C(4′)); 40.4 ($NCH_2$); 45.6 (C(3)); 52.6 (C(1)); 61.9 (C(2′)); 69.4 (OCH); 108.9 (C(4a));

111.2 (C(8)); 117.9 (C(5)); 119.1 (C(6)); 121.7 (C(7)); 126.8 (C(4b)); 132.4 (C(9a)); 135.9 (C(8a)); 171.6 (COO); 176.6 (C(5')). Anal. calc. for $C_{20}H_{25}N_3O_3$ (355.40): C 67.40, H 7.07, N 11.78; found: C 67.26, H 6.81, N 11.81.

*Data of* **6**. M.p. 62–63°. $[\alpha]_D^{20} = -33.5$ ($c = 1.3$, MeOH). IR (KBr): 3284, 1734, 1683. $^1$H-NMR (200 MHz): 1.26, 1.27 (2*d*, $J = 6.2$, 2 $CH_3$); 1.9 (*m*, 1 H); 2.1–2.5 (*m*, 3 H); 2.73 (*m*, 2 H–C(4)); 3.02 (*ddd*, $J = 12.5$, 8.5, 5, H–C(3)); 3.26 (*dt*, $J = 12.5$, 5, H–C(3)); 3.60 (*dd*, $J = 14.7$, 3, $NCH_AH_B$); 3.91 (*dd*, $J = 14.7$, 6.2, $NCH_AH_B$); 4.35 (*m*, H–C(1), H–C(2')); 5.08 (*sept.*, $J = 6.2$, OCH); 7.06 (*td*, $J = 7$, 1.6, H–C(6)); 7.13 (*td*, $J = 7$, 1.6, H–C(7)); 7.34 (*dd*, $J = 7$, 1.6, H–C(8)); 7.46 (*dd*, $J = 7$, 1.6, H–C(5)); 9.1 (br. *s*, NH, indole). $^{13}$C-NMR: 21.5 ($CH_3$); 21.8 (C(4)); 23.2 (C(3')); 29.2 (C(4')); 42.2 (C(3)); 45.4 ($NCH_2$); 52.8 (C(1)); 61.6 (C(2')); 69.0 (OCH); 109.6 (C(4a)); 111.3 (C(8)); 117.9 (C(5)); 119.1 (C(6)); 121.6 (C(7)); 127.3 (C(4b)); 132.9 (C(9a)); 136.2 (C(8a)); 172.1 (COO); 177.1 (C(5')). Anal. calc. for $C_{20}H_{25}N_3O_3 \cdot C_2H_6O$ (401.47): C 65.81, H 7.78, N 10.46; found: C 65.52, H 7.47, N 10.11.

When the reaction time was 72 h, lactamization of **5** and **6** occurred *in situ*, and lactams **7** and **8** were isolated (60%, *ca.* 1:1 ratio) after workup, FC ($Et_2O$/EtOH 3:1), and crystallization (EtOH).

4.3. *Under Anh. Conditions*. To a stirred soln. of **4** (555 mg, 1.9 mmol) and tryptamine (305 mg, 1.9 mmol) in $CH_2Cl_2$ (10 ml), $CF_3COOH$ (0.4 ml, 5.7 mmol) was added dropwise. The mixture was stirred for 72 h, basified with $NH_4OH$, and extracted with $CH_2Cl_2$. The org. phase was washed with brine, dried, and evaporated. FC ($Et_2O$/EtOH 2:1) gave **8** (218 mg, 39%) and a mixture **7**/**5** (*ca.* 1:1, 123 mg, 20%).

5. *Isopropyl (S)-1-(Formylmethyl)-5-oxopyrrolidine-2-carboxylate* (**9**). To a soln. of **4** (1 g, 3.48 mmol) in THF (8 ml) at 0°, $CF_3COOH$ (8.5 ml) was added dropwise, followed by $H_2O$ (3.8 ml). The mixture was stirred at r.t. for 7 h. Most of the THF was then evaporated, and the remaining mixture was extracted with $CH_2Cl_2$. The combined org. extracts were washed with brine and aq. $Na_2CO_3$ soln., dried, and evaporated. The oily residue was submitted to FC (AcOEt/$CH_2Cl_2$ 2:1): **9** (566 mg, 75%). $[\alpha]_D^{20} = -13.3$ ($c = 2.0$, MeOH). IR (film): 1733, 1702, 1680. $^1$H-NMR (200 MHz): 1.27 (*d*, $J = 6.3$, 2 $CH_3$); 2.50 (*m*, 2 H–C(3), 2 H–C(4)); 4.30 (*m*, H–C(2)); 4.01, 4.42 (2*d*, $J = 19$, 1 H each, $NCH_2CHO$); 5.07 (*sept.*, $J = 6.3$, OCH); 9.61 (*s*, CHO). $^{13}$C-NMR: 21.3 ($CH_3$); 22.6 (C(3)); 28.5 (C(4)); 51.8 ($NCH_2$); 60.0 (C(2)); 69.4 (OCH); 171.0 (COO); 175.8 (C(5)); 197.4 (CO). Anal. calc. for $C_{10}H_{15}NO_4 \cdot 1/2\ H_2O$ (222.23): C 54.04, H 7.25, N 6.29; found: C 53.67, H 7.26, N 6.39.

6. *Isopropyl (S)-1-{2-{[2-(Indol-3-yl)ethyl]imino}ethyl}-5-oxopyrrolidine-2-carboxylate* (**10**). A soln. of **9** (570 mg, 2.66 mmol) and tryptamine (426 mg, 2.66 mmol) in $CH_2Cl_2$ (10 ml) containing molecular sieves (4 Å) was stirred at 25° for 15 h, then filtered, and evaporated: **10** (> 95% pure by NMR). IR (film): 3300, 1733, 1682. $^1$H-NMR (200 MHz): 1.24, 1.25 (2*d*, $J = 6.2$, 2 $CH_3$); 2.0 (*m*, 1 H); 2.2–2.5 (*m*, 3 H); 3.04 (*t*, $J = 7$, 2 H–C–C(3')); 3.6–3.7 (*m*, 3 H); 4.04 (*dd*, $J = 8.5$, 3.5, H–C(2)); 4.37 (*dd*, $J = 16.5$, 2.5, 1 H, $NCH_2$); 5.04 (*sept.*, $J = 6.2$, COOH); 6.98 (*s*, H–C(2')); 7.14 (*m*, 2 H); 7.35 (*d*, $J = 2.5$, H–C=N); 7.36 (*d*, $J = 7.5$, H–C(7')); 7.58 (*d*, $J = 7.5$, H–C(4')); 8.15 (br., NH). $^{13}$C-NMR: 21.3 ($CH_3$); 22.6 (C(3)); 26.1 (*C*–C(3')); 28.8 (C(4)); 45.3 (*C*–N=C); 59.6 ($NCH_2$); 60.9 (C(2)); 69.1 (OCH); 111.2 (C(7')); 113.0 (C(3')); 118.6 (C(4')); 118.9 (C(5')); 121.6 (C(6')); 122.4 (C(2')); 127.3 (C(3'a)); 136.3 (C(7'a)); 159.3 (C=N); 171.5 (CO); 176.7 (C(5)).

7. *Acid Treatment of* **10**. A stirred soln. of **10** (230 mg, 0.68 mmol) and (+)-camphorsulphonic acid (204 mg, 0.88 mmol) in MeCN (10 ml) was stirred at r.t. for 2½ h. The mixture was evaporated, $CH_2Cl_2$ was added, and the resulting soln. was washed with aq. $Na_2CO_3$. The org. phase was dried and evaporated to give an oil which was chromatographed (FC, $Et_2O$/EtOH 3:1) to give **5**/**6** (50%, *ca.* 1:2).

8. *(S)-1-(2,2-Diethoxyethyl)-5-oxopyrrolidine-2-carboxylic Acid* (**11**). To a stirred soln. of **4** (1 g, 3.48 mmol) in dioxane (13 ml) was added at r.t. 2N KOH (7 ml) and MeOH (10 ml). After 1 h, the soln. was cooled, acidified to pH 4 with $H_3PO_4$, and filtered. The mother liquid was evaporated and extracted with $CH_2Cl_2$. The resulting oil was chromatographed (FC, $Et_2O$/EtOH 2:1): **11** (755 mg, 88%). $[\alpha]_D^{20} = +7.0$ ($c = 2.0$, MeOH). $^1$H-NMR (200 MHz): 1.20 (2*t*, $J = 7$, 2 $CH_3$); 2.1–2.5 (*m*, 2 H–C(3), 2 H–C(4)); 3.17 (*dd*, $J = 14.3$, 6.2, $NCH_AH_B$); 3.55, 3.70 (2*m*, 2 $CH_2O$); 3.85 (*dd*, $J = 14.3$, 4.0, $NCH_AH_B$); 4.48 (*dd*, $J = 8.5$, 2.8, H–C(2)); 4.57 (*dd*, $J = 6.2$, 4.0, OCHO); 8.5 (br. *s*, OH). $^{13}$C-NMR: 14.9 (2 peaks, 2 $CH_3$); 23.1 (C(3)); 29.0 (C(4)); 44.3 ($CH_2N$); 60.6 (C(2)); 62.3, 63.0 (2 $CH_2O$); 100.5 (OCHO); 174.6 (CO); 177.1 (C(5)).

9. *(S)-1-(2,2-Diethoxyethyl)-N-[2-(indol-3-yl)ethyl]-5-oxopyrrolidine-2-carboxamide* (**12**). A soln. of methyl chloroformate (106 mg, 1.12 mmol) in $CH_2Cl_2$ (20 ml) was added dropwise to an ice-cooled soln. of **11** (250 mg, 1.02 mmol) and $Et_3N$ (154 mg, 1.52 mmol) in $CH_2Cl_2$ (30 ml). The mixture was stirred at r.t. for 2 h. Then, tryptamine (179 mg, 1.18 mmol) was added and the mixture stirred overnight at r.t. The soln. was successively washed with aq. $Na_2CO_3$, 2N HCl, and brine. After evaporation and FC ($Et_2O$/EtOH 2:1), **12** (215 mg, 55%) was obtained. IR (film): 3300, 1680. $^1$H-NMR (200 MHz): 1.12, 1.13 (2*t*, $J = 7.1$, 2 $CH_3$); 2.0 (*m*, 1 H); 2.1–2.5 (*m*, 3 H); 2.99 (*t*, $J = 7$, 2 H–C–C(3')); 3.3–3.7 (*m*, 8 H); 4.17 (*dd*, $J = 8.6$, 3.2, H–C(2)); 4.61 (*dd*, $J = 5.8$, 4.3, OCHO); 6.70 (*t*, $J = 6$, CONH); 7.00 (*d*, $J = 2$, H–C(2')); 7.09 (*td*, $J = 7.5$, 1.1, H–C(6')); 7.17 (*td*, $J = 7.5$, 1.1, H–C(5')); 7.35

(*d*, $J = 7.5$, H–C(7′)); 7.58 (*d*, $J = 7.5$, H–C(4′)); 8.90 (br. *s*, NH). $^{13}$C-NMR: 14.9 ($CH_3$); 23.5 (C(3)); 24.9 (*C*–C(3′)); 29.2 (C(4)); 39.5 ($CH_2$NH); 44.6 ($CH_2$N); 62.5 (C(2)); 62.9 ($CH_2$O); 100.3 (OCHO); 111.4 (C(7′)); 112.2 (C(3′)); 118.4 (C(4′)); 119.2 (C(5′)); 122.0 (C(6′)); 122.3 (C(2′)); 127.2 (C(3a)); 136.5 (C(7a)); 171.5 (CO); 176.7 (C(5)). MS: 387 (5, $M^+$), 341 (35), 296 (7), 199 (57), 154 (34), 143 (100), 130 (75), 103 (88), 75 (42), 47 (23). Anal. calc. for $C_{21}H_{29}N_3O_4\,C_2H_6O$ (433.51): C 63.72, H 8.14, N 9.69; found: C 63.40, H 7.77, N 9.84.

10. *Acid Treatment of* **12**. A mixture of **12** (150 mg, 0.39 mmol), TsOH hydrate (81 mg, 0.42 mmol), and benzene (30 ml) was stirred at r.t. for 1 h. The solvent was evaporated and the residue chromatographed (FC, $Et_2O$/EtOH 2:1): **8** (37 mg, 32%) and **7** (75 mg, 65%). Both compounds were identical in all respects, including the optical purity, with those obtained from **4**.

11. *(3a*S*,12b*R*)-2,3,3a,4,6,7,12b,13-Octahydro-1*H*,12*H*-pyrrolo[1″,2″:4′,5′]pyrazino[1′,2′:1,2]pyrido-[3,4-*b*]indole* (**1**). To a suspension of **7** (879 mg, 2.98 mmol) in anh. THF (100 ml) was added $LiAlH_4$ (1 g, 26.3 mmol) under $N_2$. The mixture was refluxed for 24 h. After cooling, $H_2O$ and a sat. soln. of sodium potassium tartrate (70 ml) were slowly added. The aq. phase was separated and extracted with THF. Evaporation of the combined org. phases, followed by FC ($Et_2O$/EtOH 1:1), gave **1** (723 mg, 91%) as an amorphous solid. M.p. 115–117°. $[\alpha]_D^{20} = +11.3$ ($c = 1.0$, $CH_2Cl_2$). IR (KBr): 3200, 2820, 2780, 2730. $^1$H- and $^{13}$C-NMR: see *Tables 1* and *2*.

*Data of* **1**·*2 HCl*. M.p. 235 236° (hexane/EtOH). $[\alpha]_D^{20} = +44.7$ ($c = 1.0$, $H_2O$). Anal. calc. for $C_{17}H_{21}N_3 \cdot 2\,HCl \cdot H_2O$ (358.27): C 56.99, H 7.03, N 11.72; found: C 56.97, H 6.91, N 11.63.

12. *(3a*S*,12b*S*)-2,3,3a,4,6,7,12b,13-Octahydro-1*H*,12*H*-pyrrolo[1″,2″:4′,5′]pyrazino[1′,2′:1,2]pyrido-[3,4-*b*]indole* (**2**). Operating as above, from **8** (1.09 g, 3.69 mmol), *trans*-derivative **2** was obtained (838 mg, 85%), after FC ($Et_2O$/EtOH 2:1), as a white solid. M.p. 198–199° (EtOH). $[\alpha]_D^{20} = -81.4$ ($c = 1.0$, $CH_2Cl_2$). IR (KBr): 3200, 2830, 2820, 2780. $^1$H- and $^{13}$C-NMR: see *Tables 1* and *2*. *Data of* **2**·*2 HCl*. M.p. 244–245° (EtOH). $[\alpha]_D^{20} = -25$ ($c = 2.2$, $H_2O$). Anal. calc. for $C_{17}H_{21}N_3 \cdot 2$ HCl (340.27): C 60.00, H 6.80, N 12.34; found: C 59.60, H 6.82, N 12.08.

13. *Assay of the Enantiomeric Purity of* **1** *and* **2**. The racemic and optically active samples (100 mg, 0.37 mmol) were individually complexed with (–)-(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (173 mg, 0.74 mmol) in $CDCl_3$ (0.7 ml). THe $^1$H- and $^{13}$C-NMR spectra were examined at 200 and 50.3 MHz, respectively.

## REFERENCES


[1] N. Valls, V.-M. Segarra, J. Bosch, *Heterocycles* **1986,** *24,* 943.
[2] I. Jirkovsky, G. Santroch, R. Baudy, G. Oshiro, *J. Med. Chem.* **1987,** *30,* 388.
[3] N. Valls, V.-M. Segarra, X. López, J. Bosch, *Heterocycles* **1989,** *29,* 231.
[4] S. Misztal, M. Dukat, J.L. Mokrosz, *J. Chem. Soc., Perkin Trans. 1* **1990,** 2311.
[5] N. Valls, V.-M. Segarra, L.-C. Maillo, J. Bosch, *Tetrahedron* **1990,** *47,* 1065.
[6] S. Kodato, M. Nakagawa, M. Hongu, T. Kawate, T. Hino, *Tetrahedron* **1988,** *44,* 359.
[7] G.M. Coppola, H.F. Schuster, 'Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids', John Wiley, New York, 1987.
[8] T.F. Buckley III, H. Rapoport, *J. Org. Chem* **1983,** *48,* 4222.
[9] R.R. Fraser, M.A. Petit, I.K. Saunders, *J. Chem. Soc. D* **1971,** 1450.
[10] F. Ungemach, M. DiPierro, R. Weber, J.M. Cook, *J. Org. Chem.* **1981,** *46,* 164; G. Massiot, T. Mulamba, *J. Chem. Soc., Chem. Commun.* **1983,** 1147; S.A. Boyd, W.J. Thompson, *J. Org. Chem.* **1987,** *52,* 1790.
[11] D.L. Comins, M.M. Badawi, *Tetrahedron Lett.* **1991,** *32,* 2995.
[12] R. Plate, R.H.M. Van Hout, H. Behm, H.C.J. Ottenheijm, *J. Org. Chem.* **1987,** *42,* 555; J. Sandrin, S.P. Hollinshead, J.M. Cook, *ibid.* **1989,** *54,* 5636.
[13] E.G. Baggiolini, G. Pizzolato, M.R. Uskokovic, *Tetrahedron* **1988,** *44,* 3203.
[14] L. Deng, K. Czerwinski, J.M. Cook, *Tetrahedron Lett.* **1991,** *32,* 175.
[15] P.D. Bailey, N.R. McLay, *Tetrahedron Lett.* **1991,** *32,* 3895.
[16] H. Hiemstra, W.N. Speckamp, *The Alkaloids* **1988,** *32,* 271.
[17] F.J. Villani, Jr., M.J. Costanzo, R.R. Inners, M.S. Mutter, D.E. McClure, *J. Org. Chem.* **1986,** *51,* 3715.
[18] N. Valls, V.-M. Segarra, J. Bonjoch, *Magn. Reson. Chem.* **1991,** *29,* 985.
[19] E. Wenkert, C.-J. Chang, H.P.S. Chawla, D.W. Cochran, E.W. Hagaman, J.C. King, K. Orito, *J. Am. Chem. Soc.* **1976,** *98,* 3645.