Syntheses of (*RS*)- and (*S*)-(–)-Nazlinin and (*RS*)- and (+)-6-Azacyclodeca[5,4-*b*]indol-1-amine

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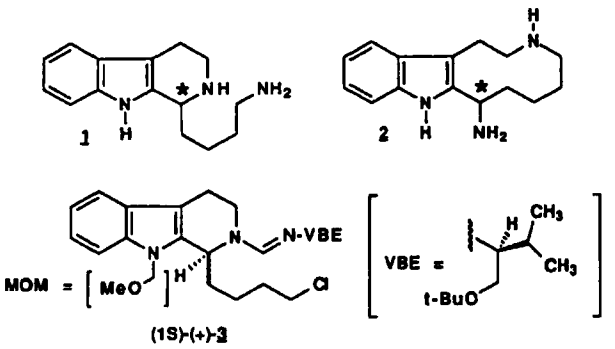
(*RS*)-1-(4-Aminobutyl)-1,2,3,4-tetrahydro-β-carboline ((*RS*)-**1**) was synthesized in two different ways. The preparation of (*S*)-(–)-**1** was performed both by asymmetric reduction with ≥ 95% ee and by synthesis from (*S*)-(+)-**3**. From this compound also (+)-6-azacyclodeca[5,4-*b*]indol-1-amine ((+)-**2**) was prepared with high enantioselectivity.

Synthesen von (*RS*)- und (*S*)-(–)-Nazlinin sowie von (*RS*)- und (+)-6-Azacyclodeca[5,4-*b*]indol-1-amin

(*RS*)-1-(4-Aminobutyl)-1,2,3,4-tetrahydro-β-carboline ((*RS*)-**1**) wurde auf zwei verschiedenen Wegen synthetisiert. Die Darstellung von (*S*)-(–)-**1** gelang sowohl durch asymmetrische Reduktion mit ≥ 95% ee, als auch durch Synthese ausgehend von (*S*)-(+)-**3**. Dieses diente auch als Edukt zur Darstellung von (+)-6-Azacyclodeca[5,4-*b*]indol-1-amin ((+)-**2**) mit hoher Enantioselektivität.

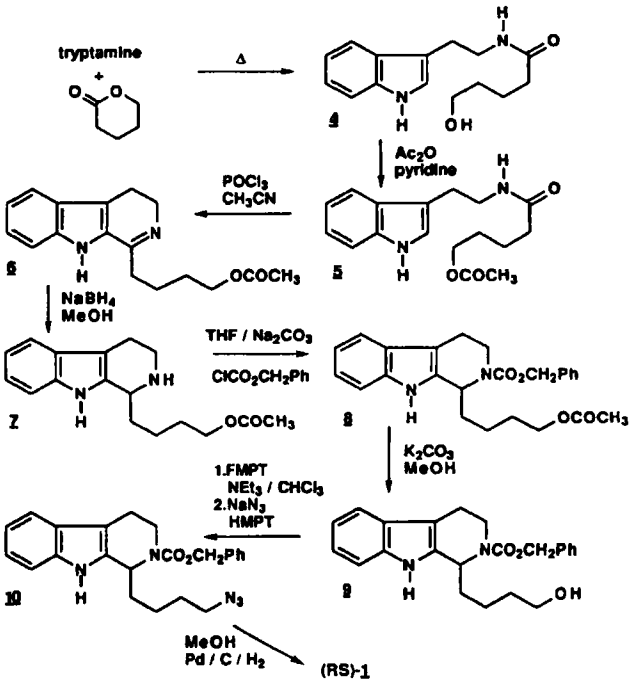


Scheme 1

Nitraria species are an important source of various piperidine alkaloids [1a]. Besides spiropiperidine and tripiperidine alkaloids numerous indole alkaloids were isolated, *inter alia* the racemic alkaloid nazlinin ((*RS*)-**1**) which shows serotonergic activity. In the first place structure **2** was postulated for nazlinin [2], isolated from *Nitraria schoberi* (*Zygophyllacae*). According to *Koomen et al.* [1b,c], however, ^{1}H-NMR data of (*RS*)-**1** (CD_3OD + > 2 equiv. of F_3C-CO_2D), prepared from tryptamine and piperideine, agree with those published by *Üstünes et al.* [2] for nazlinin. The data of (*RS*)-6-azacyclodeca[5,4-*b*]indol-1-amine ((*RS*)-**2**), however, are strikingly different [3]. Most probably, the alkaloid isolated from *Nitraria schoberi* is protonated (*RS*)-**1**. An acid-catalyzed rearrangement of (*RS*)-**1**, however, could not be excluded from the outset. In order to study the stability of (*RS*)-**1** under acidic conditions we have developed new syntheses for (*RS*)-**1**, including the possibility of preparing the enantiomers of alkaloids **1** and **2**. (*1S*)-(+)-**3** was used as the precursor for the enantioselective synthesis of either (–)-**1** or (+)-**2**.

Syntheses

Heating of tryptamine with δ-valerolactone and subsequent acetylation of the amide **4** by acetic anhydride/pyridine afforded the ester **5** which could be cyclized according to *Bischler-Napieralski* leading to the imine **6**. The yield, however, was low. Imine **6** could not, moreover, be purified sufficiently for subsequent enantioselective reduction, but reduction of crude **6** under achiral conditions led to the amine **7** which was converted to the carbamate **8** and deacetylated to the alcohol **9**. Cpd. **9** was in turn transformed to the azide **10** using 2-fluoro-1-methylpyridinium tosylate (FMPT) and NaN_3/HMPT according to *Mukaiyama* [4]. Hydrogenolysis



Scheme 2

[+] Dedicated to Prof. Dr. *K. Bernauer* (Basel) on the occasion of his 70th birthday.

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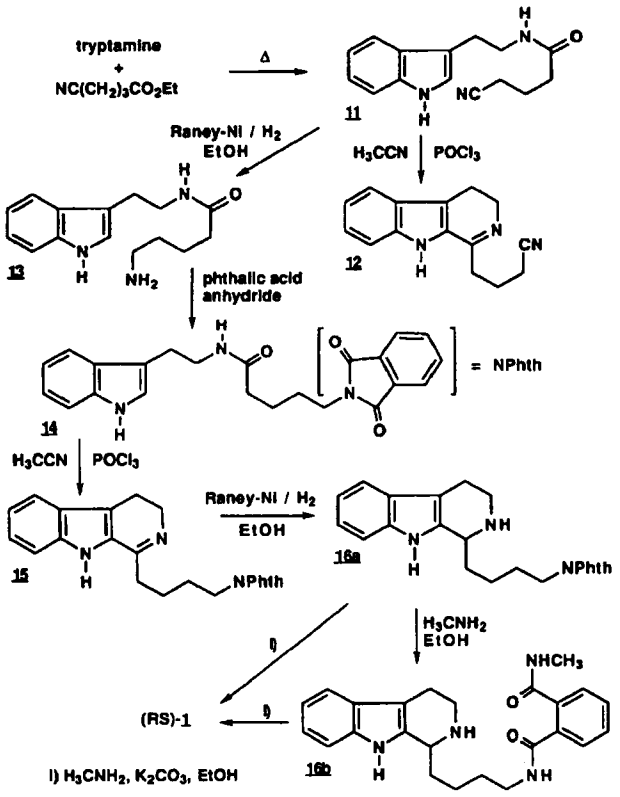
($Pd/C/H_2$) of the urethane and reduction of the azide were performed in one step, affording (***RS*)-1** as a colourless powder (18% yield, eight steps, Scheme 2).

The ^{1}H-NMR-data of (***RS*)-1** in CD_3OD and in CD_3OD + 3 equiv. F_3C-CO_2D, respectively, are identical with those reported [1b,c]. After neutralization of the acidic solution with Na_2CO_3 we obtained the same ^{1}H-NMR-data as before acidification, indicating that (***RS*)-1** is stable under the conditions used for NMR-measurements. In order to obtain imine analogues which can be purified correctly (*vide supra*) we have synthesized further 3,4-dihydro-β-carbolines. Analogously to the preparation of amide **4** we have condensed tryptamine with ethyl ω-cyanobutyrate to the amide **11**, but again cyclization of **11** to the imine **12** gave poor yields only. We therefore protected the amine **13**, obtained by reduction of the nitrile **11**, as its phthalimide **14**. Cyclization of **14** with $POCl_3$ led to the imine **15** in high yield. Hydrogenation with *Raney*-Ni afforded the tetrahydro-β-carboline **16a**. Whereas deprotection of **16a** by hydrazine hydrate led to a deteriorated product, cleavage of the imide by H_3CNH_2 according to *Wolfe* [5] produced the amide **16b**. From this cpd. or directly from **16a** (***RS*)-1** could easily be prepared by reaction with K_2CO_3 and H_3CNH_2 (39% yield, six steps, Scheme 3).



Scheme 3

As the yield in the cyclization step is high, imine **15** was reduced asymmetrically by (*S*)-*N*-benzoxycarbonylprolinate-borane-complex using a modified procedure [6a–c] of *Iwakuma's* reduction [6d]. The 400 MHz ^{1}H-NMR spectrum of the phthalimide **(–)-16a**, measured in the presence of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (*Pirkle* alcohol [7]) indicated an ee of > 95% (Fig. 1). **(–)-16a** was transformed to **(–)-1** as described for the racemate (Scheme 4). The *S*-configuration of **(–)-1** was established later (Scheme 6).

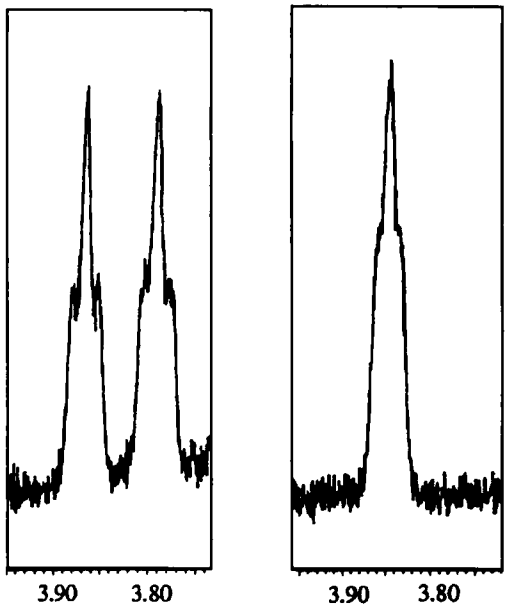
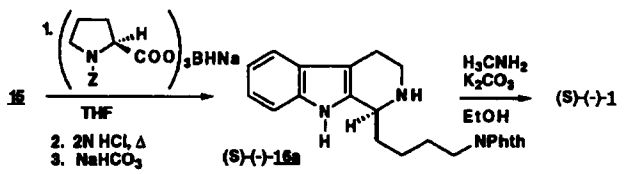
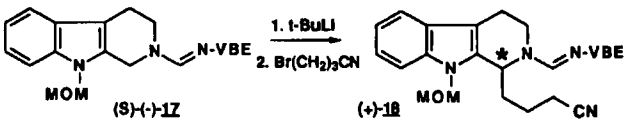


Fig. 1: 400 MHz ^{1}H-NMR spectra of (***RS*)-16a** and (*S*)-(–)-**16a**) (CD_3OD + about 3 equiv. *Pirkle* alcohol)



Scheme 4

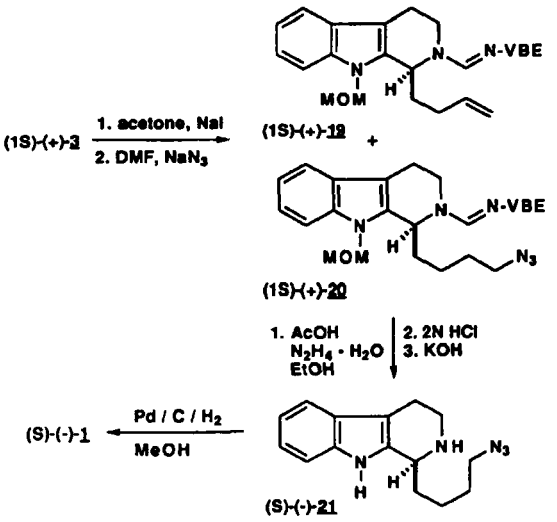
In parallel with this enantioselective reduction, we have tried to prepare (*S*)-(–)-**1** from the formamidine (*S*)-(–)-**17** by reaction with *tert*-butyl-Li and 4-bromopropionitrile according to *Meyers* [8a–d], affording nitrile **(+)-18**. The yield, however, was low (Scheme 5).



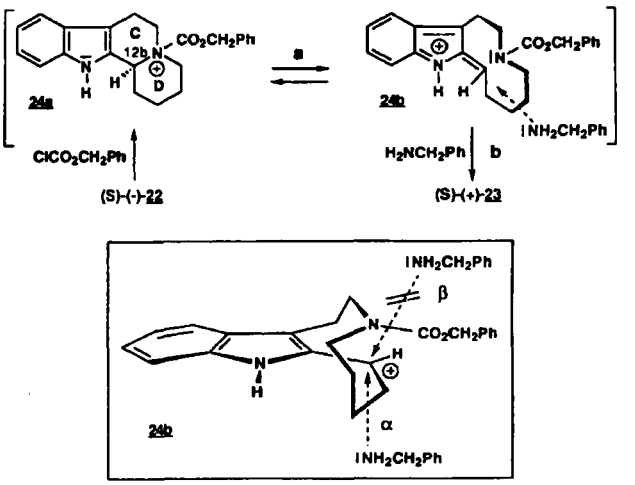
Scheme 5

The prim. amine-function of (*S*)-(–)-**1** was introduced *via* the pertinent azide. (*1S*)-(+)-**3**, easily obtained from (*S*)-(–)-**17** by reaction with *tert*-butyl-Li and 1-bromo-4-chlorobutane in high chemical yield (> 83% ee) as described by *Meyers* [8a], was transformed to the azide (*1S*)-(+)-**20** by twofold substitution with NaI/acetone and NaN_3/DMF, respectively. (*1S*)-(+)-**19** was produced by elimination as a side product. Removing of the chiral auxiliary in (*1S*)-(+)-**20** with AcOH/hydrazine and deprotection with 2N HCl led to (*S*)-(–)-**21** which was easily hydrogenated to (*S*)-(–)-**1** by $Pd/C/H_2$ (Scheme 6).

In order to check the degree of enantioselectivity of the C/D ring cleavage in **22** [3] ((***RS*)-22** has been isolated from *Nitraria* species [1a]), (*1S*)-(+)-**3** (Scheme 1) was deprotected to (*S*)-(–)-**22** (> 83% ee) [8a], which was treated first with benzyl chloroformate and then with an excess of benzylamine, af-

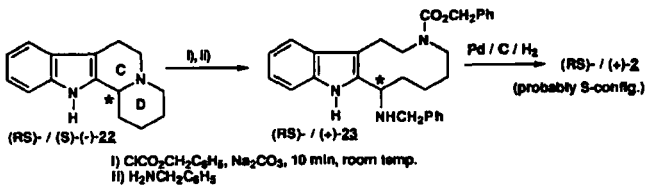


Scheme 6



Scheme 8: Explanation of the high enantioselectivity of the cleavage of rings C and D in (S)-(–)-22 according to *Harley-Mason* [9a]

fording (+)-23 in > 83% ee, as indicated by comparison of the 400 MHz ^{1}H-NMR spectra of (*RS*)-23 (which was synthesised by the same method) and (+)-23 using (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (*Pirkle* alcohol [7]) as a shift reagent. The structure of (*RS*)-23 was confirmed by ^{13}C-NMR, ^{1}H/^{1}H- and ^{1}H/^{13}C-COSY- and ^{13}C-DEPT-NMR experiments and so the 400 MHz ^{1}H-NMR spectrum could be interpreted in a wide range. Hydrogenolytic deprotection of (+)-23 (or (*RS*)-23) with Pd/C/H_2 led to (+)-2 (or to (*RS*)-2), as described in the Experimental Part (Scheme 7).



Scheme 7

Concerning the rather high ee, the β-side of the delocalized carbenium ion at C-12b of **24b**, being formed from **24a**, seems to be protected against nucleophilic attack by the bridge formed by the urethane part of the ten-membered ring (Scheme 8). This has been concluded by *Harley-Mason* [9a] from similar stereospecific reactions. If these assumptions are correct, the total reaction of (*S*)-(–)-22 should create *S* configuration in (+)-23 (Scheme 8). Delocalized cations as intermediates like **24b** were also described by *Magnus* [9b]. Quaternary urethanes as intermediates are established by *Böhme* [10a] and by *Lee* [10b].

Discussion

Undoubtedly the alkaloid nazlinin, isolated from *Nitraria schoberi*, has structure (*RS*)-1 and is stable under acidic conditions. Most probably it was isolated from the plant in a multiply protonated state, as indicated by the spectroscopic data [1b,2].

The synthesis of (*S*)-(–)-1 by asymmetric reduction using a chiral borane (Scheme 4) is – in our case – the more effective route than the laborious method of internal chiral induction (Scheme 5). Since the chiral catalyst of the externally induced reduction can be recycled, this method can be superior to internal induction. The limiting steps for the reductive enantioselective preparation of tetrahydro-β-carbolines with chiral C-1 are, however, the formation and the stability of the imine precursors. In our hands, the best way for the preparation of the enantiomers of nazlinin (1) is shown in Schemes 3 and 4.

The less stable azacyclodeca[5,4-*b*]indole **2** [3] can be easily prepared from the indolo[2,3-*a*]quinolizine **22** (Scheme 7) which might be a biological precursor of **2**. The high enantioselectivity of the ring cleavage of (*S*)-(–)-22 could not only be useful for the preparation of (+)- and (–)-2, but most probably also for the enantioselective syntheses of 9-, 10-, and 11-membered rings with a chiral C-atom at the common position of pertinent rings C and D.

We thank Prof. Dr. *W. Wiegrebe* for helpful discussions.

Experimental Part

General remarks: α values: Perkin Elmer 241 polarimeter (length: 10 cm, solvent: MeOH).– m.p.: Büchi 512, uncorrected.– IR: FT Nicolet 510.– ^{1}H-NMR: Varian EM 390 (90 MHz), Bruker AC-250 (250 MHz), Bruker ARX 400 (400 MHz); solvent: $CDCl_3$, if not stated otherwise; *cis/trans* isomers of amides and urethanes (rotamers) could be distinguished in the 400 MHz-spectra only.– ^{13}C-NMR: Bruker ARX 400 (100.61 MHz).– MS: Varian MAT 112 S/SS, 70 eV.– Column chromatography (cc): SiO_2/flash.– All reactions were performed under N_2.– Solutions were dried over Na_2SO_4.

3-[2-N-(5-Hydroxy-1-oxopentyl)aminoethyl]indole (4)

A mixture of 3.00 g (18.7 mmole) tryptamine and 2.60 g δ-valerolactone was heated to 130 °C for 5 h. After cooling the brown mixture was purified by cc (CH_2Cl_2/MeOH, 9/1): 4.36 g (89%) colourless crystals, m.p. 84-85 °C (i-Pr_2O/i-PrOH). - $C_{15}H_{20}N_2O_2$ (260.3) calcd. C 69.2 H 7.69 N 10.8 found C 68.9 H 7.73 N 10.7.– IR (KBr): $\tilde{\nu}$ = 3294; 2937; 1646 cm^{-1}.– ^{1}H-NMR (90 MHz) (CD_3OD): δ (ppm) = 1.42–1.83 (m; 4H, 2 × CH_2), 2.03–2.35 (m; 2H, CH_2), 2.84–3.11 (m; 2H, CH_2), 3.42–3.72 (m; 4H, 2 × CH_2), 7.03–7.79 (m; 5 aromat. H).– MS (70 eV): m/z = 260 ($M^{+\bullet}$, 7 %), 143 (100), 130 (54).

3-[2-N-(5-Acetoxy-1-oxopentyl)aminoethyl]indole (5)

30 ml acetic anhydride (*pro analysi*) were added dropwise to a solution of 19.8 g (76.2 mmole) 4 in 100 ml absol. pyridine. After stirring for 4 h at room temp. the reaction was terminated by addition of 20 g $NaHCO_3$, 200 ml Et_2O,

and 300 ml H_2O. After shaking, the org. phase was washed several times with 2N HCl and dried. Evaporation of the solvent led to a brown oil.– Purification by cc (EtOAc): 20.3 g (88%) colourless oil.– IR (film): $\tilde{\nu}$ = 3400; 2960; 1737; 1648 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 1.43–1.73 (m; 4H, 2 × CH_2), 1.90–2.21 (m; 2H, CH_2), 1.97 (s; 3H, CH_3), 2.76–3.07 (m; 2H, CH_2), 3.36–3.73 (m; 2H, CH_2), 3.88–4.12 (m; 2H, CH_2), 6.08–6.30 (m; 1H, NH), 6.87–7.69 (m; 5 aromat. H), 9.28 (br. s; 1H, indole-NH).– MS (70 eV): m/z = 302 ($M^{+\bullet}$, 7%), 143 (100).

1-(4-Acetoxybutyl)-3,4-dihydro-β-carboline (6)

A solution of 1.51 g (5.00 mmole) **5** in 20 ml absol. CH_3CN was cooled to 0 °C, and 8.90 g freshly distilled $POCl_3$ in 10 ml absol. CH_3CN were added slowly. After 2 h stirring at room temp. the reaction was stopped by addition of 3 g $NaHCO_3$, 10 ml CH_2Cl_2, and 20 ml H_2O in the ice bath. The org. phase was separated, dried, filtered, and evaporated *in vacuo* at 30 °C: 0.85 g (60%) brownish oil which was directly reduced to **7** without purification.– 50 mg **6** were purified by cc (EtOAc/MeOH, 18/1): 38 mg (46%) colourless oil.– IR (film): $\tilde{\nu}$ = 1737 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) 1.60–1.95 (m; 4H, 2 × CH_2), 2.02 (s; 3H, CH_3), 2.62–3.07 (m; 4H, 2 × CH_2), 3.78–4.20 (m; 4H, 2 × CH_2), 7.03–7.76 (m; 4 aromat. H), 9.77(br. s; 1H, indole-NH).

1-(4-Acetoxybutyl)-1,2,3,4-tetrahydro-β-carboline (7)

1.00 g (3.52 mmole) **6** were dissolved in 10 ml absol. MeOH and mixed with 1.0 g $NaBH_4$ at 0 °C. After 2 h stirring at 0 °C, 20 ml CH_2Cl_2 and 20 ml brine were added and stirring was continued for 30 min at room temp. The org. phase was dried and filtered. Evaporation led to a brown oil.– Purification by cc (EtOAc/MeOH, 9/1): 0.92 g (91%) red oil.– IR (film): $\tilde{\nu}$ = 1733 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 1.10–2.51 (m; 7H, NH, 3 × CH_2), 1.98 (s; 3H, CH_3), 2.59–4.33 (m; 7H, CH, 3 × CH_2), 6.61–7.53 (m; 4 aromat. H), 8.49 (br. s.; 1H, indole-NH).– MS (70 eV): m/z = 286 ($M^{+\bullet}$, 13%), 225 (15), 171 (100).

1-(4-Acetoxybutyl)-2-benzoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (8)

To 1.20 g (4.20 mmole) **7**, dissolved in 10 ml absol. THF, were added at 0 °C firstly 3 g Na_2CO_3, then 0.79 g $ClCO_2CH_2Ph$. The suspension was stirred for 1 h at room temp. and then poured on to 10 g ice, 2 g $NaHCO_3$, and 20 ml CH_2Cl_2. The org. phase was separated, filtered, and evaporated: brown oil.– Purification by cc (EtOAc/CH_2Cl_2, 4/1): 1.23 g (70%) yellow oil. - IR (film): $\tilde{\nu}$ = 1739; 1698; 1683 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 1.35–3.53 (m; 8H, 4 × CH_2), 2.00 (s; 3H, CH_3), 3.87–4.13 (m; 2H, CH_2), 4.26–4.70 (m; 2H, OCH_2), 5.05–5.50 (m; 3H, OCH_2Ph, CH), 6.98–7.61 (m; 9 aromat. H), 8.12 (br. s; 1H, indole-NH).– MS (70 eV): m/z = 420 ($M^{+\bullet}$, 8%), 305 (17), 285 (26), 225 (10), 171 (33), 91 (100).

2-Benzoxycarbonyl-1-(4-hydroxybutyl)-1,2,3,4-tetrahydro-β-carboline (9)

1.10 g (2.62 mmole) **8** were dissolved in a suspension of 2 g K_2CO_3 and 10 ml MeOH and stirred for 1 h at room temp. After addition of 20 ml Et_2O and 10 ml H_2O the org. phase was separated, dried, and evaporated: 0.93 g (93%) colourless oil.– IR (film): $\tilde{\nu}$ = 1699 cm^{-1}.– ^{1}H-NMR (400 MHz): δ (ppm) = 1.44–1.69 (m; 4H, 2 × CH_2), 1.73–2.11 (m; 3H, CH_2, OH), 2.65–2.92 (m; 2H, CH_2), 3.12–3.30 (m; 1H, C*H*H, part of an ABX-system), 3.52–3.69 (m; 2H, CH_2), 4.36–4.58 (m; 1H, CH*H*, part of an ABX-system), 5.05–5.43 (m; 3H, OCH_2Ph, CH), 7.04–7.52 (m; 9 aromat. H), 8.11 (br. s; 1/3 indole-NH, *cis/trans*-isomer), 8.60 (br. s; 2/3 indole-NH, *cis/trans*-isomer).– MS (70 eV): m/z = 378 ($M^{+\bullet}$, 12%), 243 (32), 171 (42), 91 (100).

1-(4-Azidobutyl)-2-benzoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (10)

At room temp. a solution of 30 mg (0.079 mmole) **9** and 19 mg absol. Et_3N in 3 ml absol. $CHCl_3$ was added dropwise to a suspension of 52 mg 2-fluoro-1-methylpyridinium tosylate (FMPT) in 2 ml absol. $CHCl_3$. After stirring for 1 h at room temp. the solvent was blown off by dry N_2. The remaining turbid oil was dissolved in 1 ml absol. HMPT together with 14 mg NaN_3. After stirring for 1 h at 80 °C the solution was cooled and the reaction was terminated by addition of 5 ml Et_2O and 10 ml H_2O. The org. phase was separated, multiply washed with brine, dried, and filtered. Evaporation afforded a yellow oil.– Purification by cc (CH_2Cl_2): 29 mg (91 %) colourless oil.– IR (film): $\tilde{\nu}$ = 2097; 1683 cm^{-1}.– ^{1}H-NMR (400 MHz): δ (ppm) = 1.46–1.73 (m; 4H, 2 × CH_2), 1.78–1.92 (m; 2H, CH_2), 2.67–2.93 (m; 2H, CH_2), 3.12–3.33 (m; 3H, C*H*H, part of an ABX system, CH_2), 4.38–4.61 (m; 1H, CH*H*, part of an ABX system), 5.08–5.45 (m; 3H, CH_2, CH), 7.08–7.53 (m; 9 aromat. H), 7.72 (br. s; 1/3 indole-NH, *cis/trans*-isomer), 7.89 (br. s; 2/3 indole-NH, *cis/trans*-isomer).– MS (70 eV): m/z = 403 ($M^{+\bullet}$, 6%), 91 (100).

(RS)-1-(4-Aminobutyl)-1,2,3,4-tetrahydro-β-carboline ((RS)-1)

40 mg (0.10 mmole) **10** were dissolved in 2 ml absol. MeOH and hydrogenated at 10 bar H_2 for 15 min over 40 mg Pd/C (5%) at room temp. The catalyst was filtered off over celite and washed several times with warm MeOH. Evaporation of the solvent at 30 °C at the oil pump afforded a brown oil.– Purification by twofold cc (1. EtOAc/*i*-PrOH/conc. NH_3, 55/30/15; 2. EtOAc/MeOH (satd. with NH_3 gas), 4/1): 22 mg (91%) colourless powder.– NMR data: ref. [1b].

3-[2-N-(4-Cyano-1-oxobutyl)aminoethyl]indole (11)

10.0 g (6.25 mmole) tryptamine were heated with 10.6 g ethyl ω-cyanobutyrate for 12 h at 110 °C. After cooling the brown mixture was purified by cc (EtOAc):13.9 g (87%) yellow oil.– IR (film): $\tilde{\nu}$ = 3402; 3298; 2939; 2248; 1652; 1534; 745 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 1.64–2.35 (m; 6H, 3 × CH_2), 2.71–2.96 (m; 2H, CH_2), 3.31–3.65 (m; 2H, CH_2), 6.01 (m; 1H, NH), 6.87–7.53 (m; 5 aromat. H), 8.77 (br. s; 1H, indole-NH).– MS (70 eV): m/z = 255 ($M^{+\bullet}$, 9%), 143 (100), 130 (45).

1-(3-Cyanopropyl)-3,4-dihydro-β-carboline (12)

At 0 °C a solution of 1.7 g freshly distilled $POCl_3$ in 2 ml absol. CH_3CN was added dropwise to a solution of 0.23 g (0.96 mmole) **11** in 4 ml absol. CH_3CN. The reaction mixture becomes black. After stirring overnight at room temp. the mixture was poured onto 10 g ice, 5 ml CH_2Cl_2, 1 ml acetone, and 1 g $NaHCO_3$. The org. phase was washed with brine, dried, and filtered. Evaporation led to a black oil.– Purification by twofold cc (EtOAc): 16 mg (7%) yellow oil.– IR (film): $\tilde{\nu}$ = 3321; 2943; 2248; 1709 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 1.65–1.93 (m; 2H, CH_2), 2.41– 3.87 (m; 8H, 4 × CH_2), 7.07–7.92 (m; 4 aromat. H), 9.56 (br. s; 1 H, NH).

3-[2-N-(5-Amino-1-oxobutyl)aminoethyl]indole (13)

At room temp. a solution of 2.00 g (7.80 mmole) **11** in 10 ml absol. EtOH was hydrogenated for 48 h over *Raney* Ni (from 10 g Ni/Al alloy) and 20 bar H_2. The catalyst was removed by filtration over celite and washed with warm MeOH. The solvent was evaporated at 30 °C at the oil pump, the residue was distributed between 20 ml CH_2Cl_2 and 20 ml brine. The org. phase was dried, filtered, and the solvent was removed *in vacuo*: yellow oil which was converted directly to **14**.

3-[2-N-(5-Phthalimido-1-oxobutyl)aminoethyl]indole (14)

1.80 g crude **13**, 1.03 g phthalic acid anhydride, and 0.5 ml absol. NEt_3 were suspended in 30 ml absol. toluene and refluxed for 16 h at a water trap. After cooling, the mixture was purified by cc (EtOAc): 2.67 g (88%, over two steps) yellow crystals, m.p. 142-143 °C (MeOH).– $C_{23}H_{23}N_3O_3$ (389.3) calcd. C 70.9 H 5.91 N 10.8 found C 70.8 H 6.04 N 10.8.– IR (KBr): $\tilde{\nu}$ = 3429; 3305; 1702; 724 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 1.43– 1.80 (m; 4H, 2 × CH_2), 1.93–2.21 (m; 2H, CH_2), 2.75–3.05 (m; 2H, CH_2), 3.47–3.72 (m; 4H, 2 × CH_2), 5.73 (m; 1H, NH), 6.91–7.83 (m; 5 aromat. H), 8.56 (br. s; 1H, indole-NH).– MS (70 eV): m/z = 389 ($M^{+\bullet}$, 5%), 143 (100), 130 (45).

1-(4-Phthalimidobutyl)-3,4-dihydro-β-carboline (15)

At 0 °C a solution of 5.0 g freshly distilled $POCl_3$ in 20 ml absol. CH_3CN was added drop by drop to a suspension of 1.00 g (2.57 mmole) **14** in 20 ml absol. CH_3CN, producing a black mixture. After refluxing for 2 h the mixture was allowed to cool and poured on to 100 g ice, 10 g $NaHCO_3$, and 50 ml CH_2Cl_2. Separation of the org. phase, washing, and evaporation led to a brown oil.– Purification by cc (EtOAc/MeOH, 9/1): 0.81 g (84%) yellow oil.– IR (film): $\tilde{\nu}$ = 3359; 2941; 1769; 1710 cm^{-1}.– ^{1}H-NMR (90 MHz): δ

(ppm) = 1.50–1.99 (m; 4H, 2 × CH_2), 2.58–2.99 (m; 4H, 2 × CH_2), 3.79–4.04 (m; 4H, 2 × CH_2), 7.00–7.92 (m; 8 aromat. H), 9.45 (br. s; 1H, indole-NH).– MS (70 eV): m/z = 371 ($M^{+\bullet}$, 22%), 184 (100).

(RS)-1-(4-Phthalimidobutyl)-1,2,3,4-tetrahydro-β-carboline ((*RS*)-16a)

To 0.20 g (0.54 mmole) **15** in 3 ml absol. EtOH were added some drops of EtOH satd. with NH_3 gas and *Raney* Ni (from 2 g Ni/Al alloy). After stirring for 5 h at room temp. and 10 bar H_2 the mixture was filtered over celite, and the solvent was evaporated at 30 °C at the oil pump: brown oil.– Purification by cc (EtOAc/MeOH, 4/1) and stirring in 5 ml i-Pr_2O and 5 ml $CHCl_3$ at 30 °C, filtration and washing with a little H_2O, acetone and Et_2O: 0.14 g (72%) colourless powder.– Precipitation from EtOH/HCl: 0.15 g (71%) colourless powder, m.p. (hydrochloride) 254–255 °C ($CHCl_3$/i-Pr_2O). $C_{23}H_{23}N_3O_2$•HCl (409.5) calcd. C 67.4 H 5.86 N 10.3 found C 67.3 H 5.86 N 10.3.– Spectroscopic data of the free base: IR (KBr): $\tilde{\nu}$ = 3398; 2939; 1713 cm^{-1}.– ^{1}H-NMR (250 MHz): δ (ppm) = 1.42–1.99 (m; 6H, 3 × CH_2), 1.61 (m; 1H, NH), 2.66–2.78 (m; 2H, CH_2), 2.95–3.10 (m; 1H, C*H*H, part of an ABX-system), 3.28–3.92 (m; 1H, CH*H*, part of an ABX-system), 3.69–3.83 (m; 2H, CH_2), 4.04–4.14 (m; 1H, CH), 7.01–7.89 (m; 8 aromat. H), 8.07 (br. s; 1H, indole-NH). - ^{1}H-NMR (400 MHz) (only 1-H): δ (ppm) = 4.11 (m; 1H, CH).– ^{1}H-NMR (400 MHz) (+ about 3 equiv. *Pirkle* alcohol, only 1-H, Fig. 1): δ (ppm) = 3.83, Δδ (ppm) = 0.08 (ratio of integrals 1/1).– MS (70 eV): m/z = 373 ($M^{+\bullet}$, 7%), 171 (100).

(RS)-1-[4-N-[2'-(Methylaminocarbonyl)benzoyl]aminobutyl]-1,2,3,4-tetrahydro-β-carboline ((*RS*)-16b)

At 0 °C 0.20 g (0.54 mmole) (*RS*)-16a were dissolved in 5 ml absol. EtOH and mixed with 2 ml H_3CNH_2 (30% solution in EtOH). After stirring for 1 h at room temp. the solution was diluted with much H_2O and thoroughly extracted with EtOAc. The org. phase was washed with brine and the solvent was evaporated *in vacuo*: yellow oil. Purification by cc (EtOAc/MeOH (satd. with NH_3 gas), 9/1): 0.21 g (96%) colourless foam.– IR (KBr): $\tilde{\nu}$ = 3255; 2831; 1627 cm^{-1}.– ^{1}H-NMR (400 MHz): δ (ppm) = 0.92–1.09 (m; 1H), 1.48–1.77 (m; 5H), 2.24–2.37 (m; 1H), 2.41 (m; 3H), 2.64– 2.72 (m; 2H), 2.95–3.16 (m; 2H), 3.32–3.40 (m; 1H), 4.00– 4.13 (m; 1H), 4.26–4.35 (m; 2H), 6.32–7.83 (m; 9H, 8 aromat. H, NH), 8.75 (br. s; 1H, indole-NH).– MS (70 eV): m/z = 404 ($M^{+\bullet}$, 3%), 373 (3), 243 (31), 171 (100).

(RS)-1-(4-Aminobutyl)-1,2,3,4-tetrahydro-β-carboline ((*RS*)-1)

At 0 °C a solution of 0.20 g (0.54 mmole) (*RS*)-16a (or 0.50 mmole (*RS*)-16b) in 5 ml absol. EtOH was mixed with 0.2 g K_2CO_3 and 5 ml H_3CNH_2 (30% solution in EtOH). After 12 h stirring at room temp. the mixture was diluted with water and extracted with EtOAc. The org. phase was washed with brine, dried, and evaporated at the oil pump: yellow oil.– Purification by twofold cc (1. EtOAc/i-PrOH/conc. NH_3, 55/30/15; 2. EtOAc/MeOH (satd. with NH_3 gas), 4/1): 0.11 g (85%, 88% from (*RS*)-16b) colourless powder.– NMR data: ref. [1b].

(S)-(–)-1-(4-Phthalimidobutyl)-1,2,3,4-tetrahydro-β-carboline ((*S*)-(–)-16a)

At 0 °C a suspension of 0.21 g (5.68 mmole) $NaBH_4$ in 10 ml absol. THF was mixed with 5.82 g (23.3 mmole) *N*-benzoxycarbonyl-L-(+)-proline (Janssen). After stirring at room temp. until the $NaBH_4$ had reacted completely (about 2 h) the solvent was removed by a stream of N_2 and the residue was dried at the oil pump: colourless foam which was dissolved in 20 ml absol. CH_2Cl_2 and cooled to 0 °C. A solution of 1.00 g (2.70 mmole) **15** in 10 ml absol. CH_2Cl_2 was then added dropwise and stirring was continued overnight at room temp. The solvent was removed by a stream of N_2, the yellowish residue was stirred with 20 ml 2N HCl for 4h at 70–80 °C and after cooling mixed with 20 ml CH_2Cl_2 and 20 ml H_2O. After neutralization by $NaHCO_3$ the mixture was thoroughly extracted with CH_2Cl_2. The org. phase was dried, filtered, and evaporated at the oil pump: yellow oil which was stirred at 30 °C in 10 ml i-Pr_2O and 5 ml $CHCl_3$. Filtration and washing with H_2O, acetone, and Et_2O: 0.81 g (80%) colourless powder.– Analytical data: (*RS*)-16a.– $[\alpha]_D^{20}$ = –22° (c = 0.2, poorly soluble).– ^{1}H-NMR (400 MHz) (only 1-H): δ (ppm) = 4.11 (m; 1H, CH).– ^{1}H-NMR (400 MHz) (+ about 3 equiv. *Pirkle* alcohol, Fig. 1): δ (ppm) = 3.85 (m; 1H, CH).– ee ≥ 95%.

(S)-(–)-1-[4-N-[2'-(Methylaminocarbonyl)benzoyl]aminobutyl]-1,2,3,4-tetrahydro-β-carboline ((*S*)-(–)-16b)

Preparation and analytical data: (*RS*)-16b.– $[\alpha]_D^{20}$ = -32° (c = 1).

(S)-(–)-1-(4-Aminobutyl)-1,2,3,4-tetrahydro-β-carboline ((*S*)-(–)-1)

Preparation and analytical data: (*RS*)-1.– $[\alpha]_D^{20}$ = -33.4° (c = 0.3).

(S)-(–)-2-[N-(1-tert-Butoxy-3-methylbut-2-yl)iminomethyl]-9-methoxymethyl-1,2,3,4-tetrahydro-β-carboline ((*S*)-(–)-17): *Ref.* [8b–d].

(+)-2-[N-(1-tert-Butoxy-3-methylbut-2-yl)iminomethyl]-1-(3-cyanopropyl)-9-methoxymethyl-1,2,3,4-tetrahydro-β-carboline ((+)-18)

Preparation from (*S*)-(–)-17 [8a,d] according to the synthesis of (*1S*)-(+)-3 (ref.[8a,b,d]). Purification by twofold cc (1. EtOAc/MeOH, 3/2; 2. pentane/NEt_3, 4/1): 20% colourless oil.– $[\alpha]_D^{20}$ = +7.6° (c = 2.6).– IR (film): $\tilde{\nu}$ = 2970; 2230; 1648 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 0.74–1.01 (m; 6H, 2 × CH_3), 1.01–1.28 (m; 9H, 3 × CH_3), 1.62–2.10 (m; 4H, 2 × CH_2), 2.52–4.06 (m; 10H, 2 × CH, 4 × CH_2), 3.21 (s; 3H, OCH_3), 5.43 (br. s; 2H, NCH_2), 6.21 (m; 1H, CH), 7.04–7.60 (m; 5H, 4 aromat. H, 1 methine-H).– MS (70 eV): m/z 452 ($M^{+\bullet}$, 9%), 385 (5), 294 (100).

(1S)-(+)-2-[N-(1-tert-Butoxy-3-methylbut-2-yl)iminomethyl]-1-(4-chlorobutyl)-9-methoxymethyl-1,2,3,4-tetrahydro-β-carboline ((*1S*)-(+)-3)

Preparation from (*S*)-(–)-17 as described in ref. [8a] (neither spectroscopic data nor statements about enantiomeric purity were given in this ref.).– Purification by twofold cc (1. EtOAc/MeOH, 3/2; 2. pentane/NEt_3, 4/1): 84% colourless oil.– $[\alpha]_D^{20}$ = +34° (c = 1).– IR (film): $\tilde{\nu}$ = 2971; 1652 cm^{-1}.– ^{1}H-NMR (90 MHz): δ (ppm) = 0.74–1.20 (m; 15H, 5 × CH_3), 1.40–2.10 (m; 8H, 4 × CH_2), 2.50–4.10 (m; 9H, 3 × CH, 3 × CH_2), 3.28 (*s*; 3H, OCH_3), 5.18–5.61 (m; 2H, NCH_2), 7.06–7.60 (m; 5H, 4 aromat. H, 1 methine-H).– MS (70 eV): m/z = 475 ($M^{+\bullet}$, 19%), 213 (96),45 (100).

(1S)-(+)-1-(3-Butenyl)-2-[N-(1-tert-butoxy-3-methylbut-2-yl)-iminomethyl]-9-methoxymethyl-1,2,3,4-tetrahydro-β-carboline ((*1S*)-(+)-19 *and (1S)-(+)-(4-Azidobutyl)-2-[N-(1-tert-butoxy-3-methylbut-2-yl)iminomethyl]-9-methoxymethyl-1,2,3,4-tetrahydro-β-carboline* ((*1S*)-(+)-20)

0.20 g (0.42 mmole) (*1S*)-(+)-3 were dissolved in 10 ml absol. acetone and refluxed with 0.25 g NaI for 48 h. After removal of acetone the residue was mixed with H_2O and CH_2Cl_2, 10 ml each. The org. phase was dried, filtered, and evaporated: yellow oil which was dissolved in 10 ml absol. DMF and mixed with 0.11 g NaN_3. After stirring for 24 h at room temp. the suspension was distributed between H_2O and $CHCl_3$, 10 ml each. The org. phase was washed with H_2O, dried, filtered, and evaporated: yellow oil.– Purification by twofold cc (1. pentane/NEt_3, 18/1; 2. EtOAc/MeOH (satd. with NH_3 gas), 18/1).–

(*1S*)-(+)-19: 0.10 g (55%) colourless oil.– $[\alpha]_D^{20}$ = +49° (c = 1).– IR (film): $\tilde{\nu}$ = 2971; 1648 cm^{-1}.– ^{1}H-NMR (250 MHz): δ (ppm) = 0.61–0.79 (m; 6H, 2 × CH_3), 1.04 (br. *s*; 9H, 3 × CH_3), 1.72–1.85 (m; 2H, CH_2), 1.89–2.01 (m; 2H, CH_2), 2.22–2.34 (m; 2H, CH_2), 2.61–3.51 (m; 7H, 3 × CH, 2 × CH_2), 3.26 (*s*; 3H, OCH_3), 5.01–5.18 (m; 2H, =CH_2), 5.30 (d; 1H, J = 11.1 Hz, part of an AB-system, NC*H*H), 5.47 (d; 1H, J = 11.1 Hz, part of an AB-system, NCH*H*), 5.83–6.02 (m; 1H, =CH), 7.08–7.51 (m; 5H, 4 aromat. H, 1 methine-H).– MS (70 eV): m/z = 439 ($M^{+\bullet}$, 55%), 398 (62), 229 (100).

(*1S*)-(+)-20: 81 mg (40%) colourless oil.– $[\alpha]_D^{20}$ = +44° (c = 0.4).– IR (film): $\tilde{\nu}$ = 2929; 2097; 1646 cm^{-1}.– ^{1}H-NMR (250 MHz): δ (ppm) = 0.80–0.89 (m; 6H, 2 × CH_3), 1.01 (br. s; 9H, 3 × CH_3), 1.53–2.02 (m; 8H, 4 × CH_2), 2.62–3.5 8 (m; 9H, 3 × CH, 3 × CH_2), 3.28 (s; 3H, OCH_3), 5.31 (d; 1H, J = 11.1 Hz, part of an AB-system, NC*H*H), 5.45 (d; 1H, J = 11.1 Hz, part of an AB-system, NCH*H*), 7.08–7.51 (m; 5H, 4 aromat. H, 1 methine-H).– MS (70 eV): m/z = 482 ($M^{+\bullet}$, 100%).

(S)-(–)-1-(4-Azidobutyl)-1,2,3,4-tetrahydro-β-carboline ((S)-(–)-21)

Preparation according to ref.[8a].– 100 mg (0.21 mmole) **(1S)-(+)-20** were stirred for 2 h in 67 ml EtOH, 8 ml H_2O, 8 ml AcOH, and 17 ml hydrazine hydrate. The mixture was then diluted with H_2O and extracted with EtOAc. The combined org. phases were dried, filtered, and evaporated *in vacuo* at 30 °C. The residue was shaken with 5 ml Et_2O and 10 ml 2N HCl for 30 min at room temp. followed by basification with dilute KOH. The org. phase was separated, dried, filtered, and evaporated *in vacuo* at 30 °C: yellow oil.– Purification by cc (EtOAc/MeOH (satd. with NH_3 gas), 9/1): 50 mg (89%) colourless oil.– $[\alpha]_D^{20} = -41°$ (c = 1).– IR (film): $\tilde{\nu}$ = 3284; 2937; 2097 cm^{-1}.– ^{1}H-NMR (250 MHz): δ (ppm) = 1.39–2.08 (m; 7H, NH, 3 × CH_2), 2.56–3.48 (m; 6H, 3 × CH_2), 3.91–4.18 (m; 1H, CH), 7.05–7.60 (m; 4 aromat. H), 7.90 (br. s; 1H, indole-NH).– MS (70 eV): m/z = 269 ($M^{+\bullet}$, 9%),171 (100).

(S)-(–)-1-(4-Aminobutyl)-1,2,3,4-tetrahydro-β-carboline ((S)-(–)-1)

40 mg (0.15 mmole) **(S)-(–)-21** were dissolved in 2 ml absol. MeOH and hydrogenated over 40 mg Pd/C (5%) at 15 bar H_2 for 10 min at room temp. The catalyst was filtered off over celite and washed several times with warm MeOH. Evaporation at 30 °C at the oil pump left a yellow oil.– Purification by twofold cc (1. EtOAc/i-PrOH/conc. NH_3, 55/30 15; 2. EtOAc/MeOH (satd. with NH_3 gas), 4/1): 31 mg (85%) colourless powder.– $[\alpha]_D^{20} = -29°$ (c = 0.3).– NMR data: ref. [1b].

(RS)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine ((RS)-22): Ref. [3]

(S)-(–)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine ((S)-(–)-22)

Preparation: ref. [8a].– m.p. 145–146 °C.– $[\alpha]_D^{20} = -70°$ (c = 1).– ee > 83% (calcd. from $[\alpha]_D^{20}$). (Ref. [8c,d]: $[\alpha]_D^{20} = -81°$ (c = 1, MeOH), ee = 96%, m.p. 144–146 °C.– Ref. [11]: $[\alpha]_D^{20} = -84°$ (c = 1, MeOH), m.p. 149–151 °C).

(RS)-1-Benzamino-6-benzoxycarbonyl-6-azacyclodeca[5,4-b]indole ((RS)-23)

At 0 °C first 0.40 g Na_2CO_3 then 0.16 g $ClCO_2CH_2Ph$ were added to a solution of 0.20 g (0.88 mmole) **(RS)-22** in 10 ml absol. THF. After 10 min stirring at room temp., 0.4 g benzylamine were quickly added and the mixture was stirred for 30 min at room temp. The reaction was stopped by addition of H_2O and Et_2O, 10 ml each. The org. phase was washed with H_2O, dried, and evaporated at 30 °C *in vacuo*: brown oil.– Purification by cc (CH_2Cl_2/EtOAc, 3/2): 0.31 g (75%) colourless oil.– IR (film): $\tilde{\nu}$ = 3330; 2929; 1690 cm^{-1}. ^{1}H-NMR (400 MHz) (*cis/trans*-, or *trans/cis*-isomers appeared in the ratio 1/2, they were marked as **A** and **B**): δ (ppm) = 0.68–0.79 (m; 1H, 4-H_a (**A**)), 0.85–1.00 (m; 1H, 4-H_a (**B**)), 1.24–1.29 (m; 1H, 4-H_b (**A**)), 1.30–1.51 (m; 5H, 4-H_b (**B**), 3-$H_{a/b}$ (**A**, **B**)), 1.62–1.75 (m; 4H, 2-$H_{a/b}$ (**A**, **B**)), 2.57–2.66 (m; 1H, 5-H_a (**A**)), 2.76–2.95 (m; 3H, 7-H_a or 8-H_a (**A**, **B**), 5-H_a (**B**)), 3.05–3.28 (m; 3H, 7-H_b and/or 8-H_b (2 × **A**, **B**), 3.40–3.61 (m; 3H, 5-H_b (**A**, **B**), 8-H_a or 7-H_a (**B**)), 3.44 (d; 2H, J = 13.4 Hz, part of an AB-system, NCH_2Ph (**A**,**B**)), 3.57 (d; 2H, J = 13.4 Hz, part of an AB-system, NCH_2Ph (**A**,**B**)), 3.81–3.96 (m; 3H, 1-H (**A**, **B**), 8-H_b or 7-H_b (**B**)), 4.20–4.29 (m; 1H, 8-H_a or 7-H_a (**A**)), 4.72 (d; 1H, J = 12.4 Hz, part of an AB-system, OCH_2Ph (**B**)), 5.07 (d; 1H, J = 12.4 Hz, part of an AB-system, OCH_2Ph (**B**), the right peak of this d was used for the determination of ee), 5.10 (d; 1H, J = 13.8 Hz, part of an AB-system, OCH_2Ph (**A**)), 5.14 (d; 1H, J = 13.8 Hz, part of an AB-system, OCH_2Ph (**A**)), 7.03–7.52 (m; 28 aromat. H, (**A**,**B**)), 8.50 (br. s; 2H, indole-N, (**A**,**B**)).– ^{13}C-NMR ($CDCl_3$) (only sp^3-area, with relative intensities of ^{13}C-DEPT- experiment): δ (ppm) = 21.20 (C-3, **B**, –262), 21.47 (C-3, **A**, –158), 24.92 (C-5, **A**, –134), 25.77 (C-5, **B**, –400), 26.43 (C-4, **B**, –228), 26.51 (C-4, **A**, –99), 34.92 (C-2, **B**, –252), 35.17 (C-2, **A**, –154), 47.81 (C-7 or C-8, **A**, –180), 48.20 (C-7 or C-8, **B**, –297), 49.04 (C-7 or C-8, **B**, –297), 50.50 (C-7 or C-8, **A**, –162), 51.50 (NCH_2Ph, – 412), 54.50 (C-1, **B**, +301), 55.71 (C-1, **A**, +193), 66.78 (OCH_2Ph, **B**, –330), 66.94 (OCH_2Ph, **A**, –156).– ^{1}H-NMR (400 MHz) (+ about 3 equiv. *Pirkle* alcohol, only signals used for determination of ee): δ (ppm) = 5.02, Δδ (ppm) = 0.01 (ratio of integrals 1/1).– MS (70 eV): m/z = 467 ($M^{+\bullet}$, 14%), 376 (61), 225 (38),91 (100).

(+)-1-Benzamino-6-benzoxycarbonyl-6-azacyclodeca[5,4-b]indole ((+)-23)

Preparation and analytical data: **(RS-23**.– $[\alpha]_D^{20} = +114°$ (c = 0.4).– ^{1}H-NMR (400 MHz) (+ about 3 equiv. *Pirkle* alcohol, only signal used for determination of ee): δ (ppm) = 5.01, Δδ (ppm) = 0.01 (ratio of integrals 11/1).– ee ≥ 83%.

(RS)-6-Azacyclodeca[5,4-b]indol-1-amine ((RS)-2)

20 mg (0.42 mmole) **(RS)-23** were dissolved in 2 ml absol. MeOH and hydrogenated over 20 mg Pd/C (5%) at 20 bar H_2 for 24 h at room temp. Filtration over celite, washing the catalyst several times with warm MeOH, and evaporation of the solvent at 30 °C *in vacuo*: yellow oil. - Purification by cc (EtOAc/MeOH (satd. with NH_3 gas), 4/1): 78 mg (76%) colourless oil.– NMR data: ref. [3].

(+)-6-Azacyclodeca[5,4-b]indol-1-amine ((+)-2)

Preparation: **(RS)-2**.– NMR-data: ref. [3].– $[\alpha]_D^{20} = +38°$ (c = 0.3).

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