

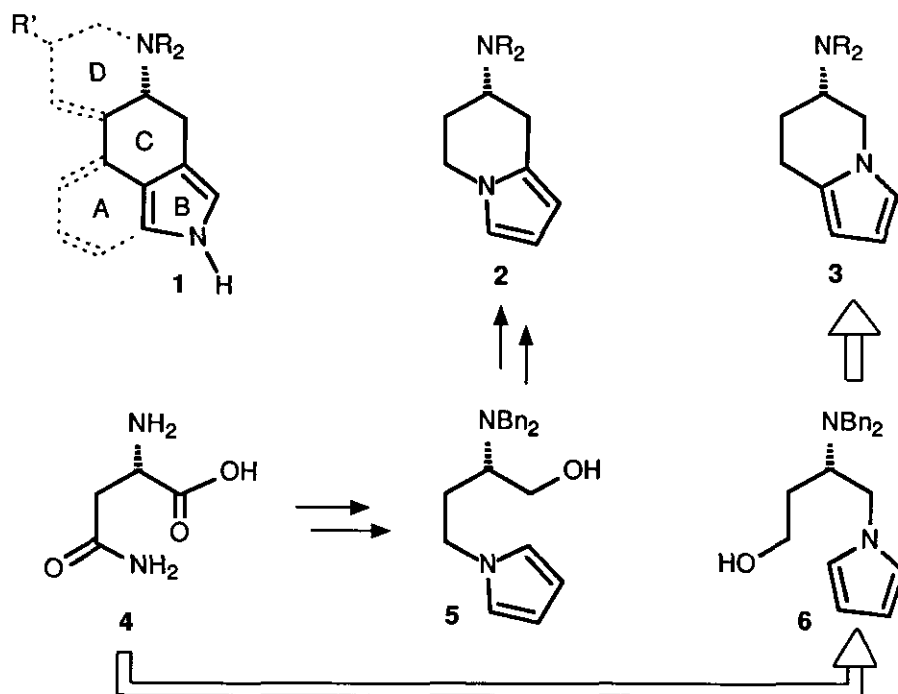
SYNTHESIS OF CHIRAL INDOLIZINES AS BICYCLIC ERGOLINE ANALOGUES

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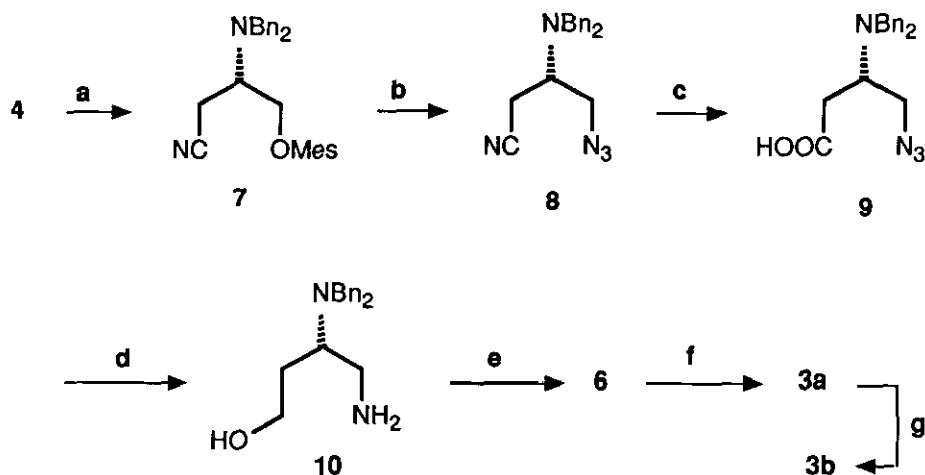
Abstract - An efficient synthesis of the enantiomerically pure aminoindolizine (3) by a triflic anhydride assisted cyclization of the 1,3-amino alcohol (6) is reported. 6 can be readily derived from L-asparagine (4) via the O-activated β -homoserine equivalent (7).

Structure activity relationship (SAR) studies using ergoline congeners as well as their ABC tricyclic and BC bicyclic analogues attract considerable interest.¹ It is proposed, that their dopaminergic activity, which is highly stereospecific, is due to a rigid pyrroleethylamine moiety including an aromatic NH feature as a hydrogen bond donating group.² In fact the isoindole derivative (1) revealed dopaminergic effects *in vivo*.³



We try to investigate, whether the NH subunit is really essential for dopamine activity by using isosteric substrates which are devoid of the NH feature.

Recently we have reported, that 5,6,7,8-tetrahydroindolizine can be prepared very efficiently by a 6-exo-tet⁴ typed cyclization reaction.⁵ Application of this method afforded 7-aminoindolizines (2), when 1,2-amino alcohol (5) - readily derived from L-asparagine (4) - was reacted with trifluoromethanesulfonic anhydride. Since our preliminary studies revealed 2 to be highly CNS active *in vivo*, we intended to elaborate a procedure for the synthesis of 3, as a further regioisomer of 1. In this case the 1,3-amino alcohol (6) was envisaged as the synthetic precursor which should be prepared from an appropriate β -amino acid (9). 9 should be approached by applying our newly developed synthesis of β -amino acids *via* the enantiomerically pure key intermediate (7), which can be readily obtained from L-asparagine (4) in 59 % yield.⁶



a: see ref. 6; b: NaN_3 , DMF (82 %); c: conc. HCl (86 %); d: $\text{BH}_3 \cdot \text{THF}$ (85 %); e:

1. 2,5-dimethoxytetrahydrofuran, HOAc / NaOAc; 2. NaOH (90 %); f: Ts_2O ,

CH_2Cl_2 (65 %); g: $\text{Pd}(\text{OH})_2 / \text{C} - \text{H}_2$, EtOAc - MeOH (75 %).

The *O*-activated β -homoserine equivalent (7) was treated with NaN_3 in DMF to give 8, followed by acidic hydrolysis of the cyano group to afford the N,N -dibenzyl protected β -amino- γ -azido acid (9). Subsequently 9 was reacted with borane / THF to yield the diamino alcohol (10), which was transformed into the envisioned 1,3-amino alcohol (6) by a modified *Paal - Knorr* reaction. Upon treatment of 6 with trifluoromethanesulfonic anhydride ring closure was achieved to afford 3a. In accordance with our recent results⁵ the cyclization reaction was best accomplished when renouncing a proton scavenger as Et_3N . 3a can be debenzylated by catalytic hydrogenation to give the primary amine (3b).

Following the identical protocol the (R)-enantiomers of **3a,b** have been prepared from (R)-**7**, which can be derived from D-asparagine.⁶

The pharmacological properties of the described aminoindolizines are currently investigated.

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EXPERIMENTAL PART

General

THF was distilled from LiAlH₄ immediately before use, CH₂Cl₂ was distilled from CaH₂. All liquid reagents were also purified by distillation. Unless otherwise noted reactions were conducted under dry nitrogen. Evaporations of final product solutions were done under vacuum with a rotatory evaporator. Flash chromatography was carried out with 230-400 mesh silica gel. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmar 881 spectrophotometer. Nmr spectra were measured on a JEOL 400 JNM-GX spectrometer at 400 MHz, when tetramethylsilane was used as an internal standard. Elemental analyses were performed on a Heraeus CHN Rapid instrument.

(S)-4-Azido-3-N,N-dibenzylaminobutanenitrile (8)

To a mixture of **7**⁶ (17.9 g, 50 mmol) in DMF (400 ml) was added NaN₃ (16.25 g, 250 mmol) at room temperature. Then the temperature was slowly raised to 55°C and stirring was continued for 1 h. After being cooled to room temperature saturated aqueous NaHCO₃ was added and the mixture was extracted with Et₂O. The extract was dried (MgSO₄) and evaporated and the residue was purified by flash chromatography (petroleum ether - EtOAc 4:1) to give 12.5 g (82 %) of pure **8** as a colorless oil. $[\alpha]_D^{23}$ -17° (c = 1.1, CHCl₃). Anal. Calcd for C₁₈H₁₉N₅: C, 70.79; H, 6.27; N, 22.93. Found: C, 70.92; H, 6.51; N, 22.67. Ir (NaCl): 3060, 3030, 2930, 2250, 2220, 1600 cm⁻¹. ¹H-Nmr (CDCl₃): δ (ppm) 2.29-2.40 (m, 2H), 3.23-3.30 (m, 1H), 3.42 (dd,

$J = 12.5, 6.6 \text{ Hz, 1H}$), 3.61 (dd, $J = 12.5, 5.9 \text{ Hz, 1H}$), 3.71 (d, 12.9 Hz, 2H), 3.75 (d, $J = 12.9 \text{ Hz, 2H}$), 7.24-7.41 (m, 10H).

(R)-**8** ($[\alpha]_D^{23} +17.5^\circ$ ($c = 1.0, \text{CHCl}_3$)) was prepared from (R)-**7**⁶ following the same procedure.

(S)-4-Azido-3-N,N-dibenzylaminobutanoic acid (9)

A solution of **8** (6.68 g, 20 mmol) in conc. aqueous HCl was stirred at 80°C for 5 h. Then the mixture was concentrated, basified with 2 N NaOH and extracted with Et_2O . The aqueous layer was adjusted to pH 6 with 10 % aqueous citric acid, then extracted with Et_2O and the organic layer was dried (MgSO_4) and evaporated to give 6.1 g (86 %) of pure **9** as a colorless oil. $[\alpha]_D^{23} -38.5^\circ$ ($c = 1.1, \text{CHCl}_3$). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$: C, 66.64; H, 6.22; N, 17.27. Found: C, 66.49; H, 6.39; N, 16.91. Ir (NaCl): 3600-2800, 2105, 1715, 1600 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ (ppm) 2.44 (dd, $J = 16.2, 4.6 \text{ Hz, 1H}$), 2.64 (dd, $J = 16.2, 10.2 \text{ Hz, 1H}$), 3.36-3.50 (m, 2H), 3.62 (d, $J = 13.2 \text{ Hz, 2H}$), 3.62-3.74 (m, 1H), 3.94 (d, $J = 13.2 \text{ Hz, 2H}$), 7.25-7.37 (m, 10H).

(R)-**9** ($[\alpha]_D^{23} +38^\circ$ ($c = 1.0, \text{CHCl}_3$)) was prepared from (R)-**8** following the same procedure.

(S)-4-Amino-3-N,N-dibenzylaminobutanol (10)

To a solution of **9** (6.5 g, 20 mmol) in THF (450 ml) was added $\text{BH}_3\cdot\text{THF}$ (100 ml, 1 molar in THF) at 0°C . After 20 min the mixture was refluxed for 4 h, then cooled to 0°C , when it was quenched with 6 N aqueous HCl. The mixture was basified with 2 N NaOH, extracted with Et_2O and the organic layer was dried (MgSO_4) and evaporated. The residue was purified by flash chromatography ($\text{CHCl}_3 - \text{MeOH} - \text{Et}_3\text{N}$ 185:10:7) to give 4.85 g (85 %) of pure **10** as a colorless solid; mp $66-68^\circ\text{C}$. $[\alpha]_D^{23} -20^\circ$ ($c = 1.0, \text{CHCl}_3$). Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}$: C, 76.02; H, 8.51; N 9.85. Found: C, 75.89; H, 8.65; N, 9.83. Ir (NaCl): 3600-2650, 3030, 1600 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ (ppm) 1.59-1.66 (m, 1H), 2.01-2.09 (m, 1H), 2.56-2.66 (m, 3H), 3.54-3.68 (m, 2H), 3.58 (d, $J = 14.2 \text{ Hz, 2H}$), 3.63 (d, $J = 14.2, 2\text{H}$), 7.21-7.34 (m, 10H).

(R)-**10** ($[\alpha]_D^{23} +19.5^\circ$ ($c = 1.0, \text{CHCl}_3$)) was prepared from (R)-**9** following the same procedure.

(S)-3-N,N-Dibenzylamino-4-N-pyrrolylbutanol (6)

To a mixture of **10** (2.84 g, 10 mmol) and NaOAc $\times 3 \text{ H}_2\text{O}$ (27.2 g, 200 mmol) in acetic acid (150 ml) was added 2,5-dimethoxytetrahydrofuran (1.45 g, 11 mmol) at room temperature. Then the temperature was slowly raised to 70°C and stirring was continued for 2 h. After the mixture was concentrated it was basified with 2 N NaOH and extracted with Et_2O . The organic layer was evaporated and the residue was stirred in a mixture of aqueous NaOH (15 ml, 20 %) and MeOH (45 ml) for 2 h at room temperature, when it was extracted with Et_2O . The organic layer was dried (MgSO_4) and evaporated and the residue was purified by flash

chromatography (petroleum ether - EtOAc 7:3) to give 3 g (90 %) of pure **6** as a colorless oil. $[\alpha]_D^{23}$ -20° ($c = 1.0$, CHCl_3). Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}$: C, 79.00; H, 7.84; N, 8.38. Found: C, 78.63; H, 8.09; N, 8.03. Ir (NaCl): 3600-3200, 3030, 2930, 1600 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ (ppm) 1.32-1.38 (m, 1H), 1.87-2.03 (m, 1H), 3.16-3.22 (m, 1H), 3.42 (d, $J = 13.2$ Hz, 2H), 3.45-3.55 (m, 1H), 3.62-3.66 (m, 1H) 3.73 (dd, $J = 13.6, 8.5$ Hz, 1H), 3.95 (d, $J = 13.2$ Hz, 2H), 4.30 (dd, $J = 13.6, 5.1$ Hz, 1H), 6.14-6.16 (m, 2H), 5.58-5.59 (m, 2H), 7.25-7.36 (m, 10H).

(R)-**6** ($[\alpha]_D^{23} +20^\circ$ ($c = 1.0$, CHCl_3)) was prepared from (R)-**10** following the same procedure.

(S)-6-N,N-Dibenzylamino-5,6,7,8-tetrahydroindolizine (3a)

To a mixture of **6** (2.24 g, 6.7 mmol) in CH_2Cl_2 (90 ml) was added trifluoromethanesulfonic anhydride (3.95g, 14 mmol) at 0°C . After it was stirred for 16 h at room temperature saturated aqueous NaHCO_3 and Et_2O were added. The organic layer was dried (MgSO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether - Et_2O 95:5) to give 1.37 g (65 %) of pure **3a** as a colorless solid; mp $80-82^\circ\text{C}$. $[\alpha]_D^{23} -68^\circ$ ($c = 1.0$, CHCl_3). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.67; H, 7.75; N, 8.80. Ir (NaCl): 3030, 2930, 1600 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ (ppm) 1.75 (ddd, $J = 16.1, 12.4, 5.1$ Hz, 1H), 2.15-2.20 (m, 1H), 2.54-2.63 (m, 1H), 2.92-2.98 (m, 1H), 3.15-3.23 (m, 1H), 3.64 (d, $J = 13.7$ Hz, 2H), 3.79 (d, $J = 13.7$ Hz, 2H), 3.88 (dd, $J = 11.5, 11.5$ Hz, 1H), 4.04 (dd, $J = 11.5, 5.5$ Hz, 1H), 5.77-5.78 (m, 1H), 6.08-6.10 (m, 1H), 6.47-6.48 (m, 1H), 7.23 (d, $J = 7$ Hz, 2H), 7.30 (t, $J = 7$ Hz, 4H), 7.37 (d, $J = 7$ Hz, 4H).

(R)-**3a** ($[\alpha]_D^{23} +67^\circ$ ($c = 1.0$, CHCl_3)) was prepared from (R)-**6** following the same procedure.

(S)-6-Amino-5,6,7,8-tetrahydroindolizine (3b)

A mixture of **3a** (0.95 g, 3 mmol) and 20 % $\text{Pd}(\text{OH})_2/\text{C}$ (0.7 g) in EtOAc (35 ml) and MeOH (35 ml) was stirred under a balloon of H_2 for 5 h at room temperature. The mixture was filtered through celite, the filtrate was evaporated and the residue was purified by flash chromatography (CH_2Cl_2 - MeOH 4:1) to give 0.31 g (76 %) of pure **3b** as a colorless oil. $[\alpha]_D^{23} -75^\circ$ ($c = 1.0$, CHCl_3). Anal. Calcd for $\text{C}_8\text{H}_{12}\text{N}_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.53; H, 9.11; N, 20.35. Ir (NaCl): 3600-3150, 2930 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3): δ (ppm) 1.61-1.71 (m, 1H), 2.00-2.06 (m, 1H), 2.77 (ddd, $J = 16.1, 10.3, 5.9$ Hz, 1H), 2.93 (ddd, $J = 16.1, 5.1, 5.1$ Hz, 1H), 3.30-3.36 (m, 1H), 3.58 (dd, $J = 11.7, 8.8$ Hz, 1H), 4.10 (dd, $J = 11.7, 5.1$ Hz, 1H), 5.84-5.85 (m, 1H), 6.13-6.15 (m, 1H), 6.49-6.50 (m, 1H).

(R)-**3b** ($[\alpha]_D^{23} +76^\circ$ ($c = 1.0$, CHCl_3)) was prepared from (R)-**3a** following the same procedure.

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