SYNTHESIS OF CHIRAL INDOLIZINES AS BICYCLIC ERGOLINE ANALOGUES

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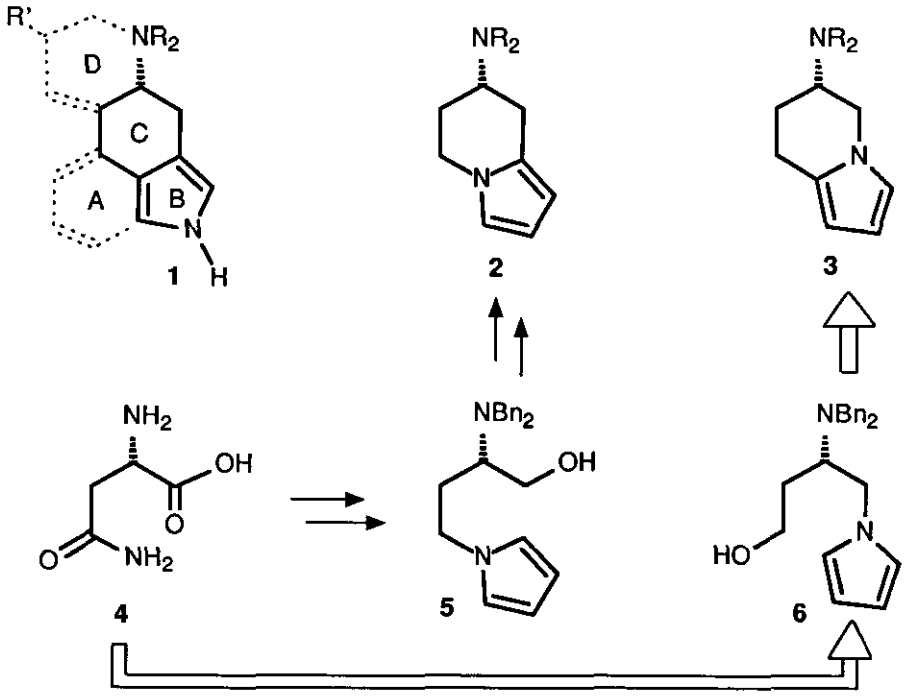
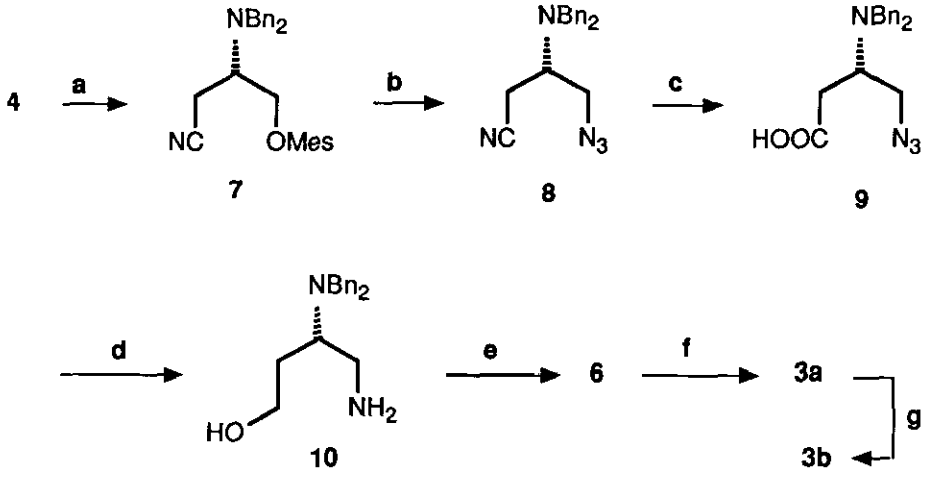
Abstract - An efficient synthesis of the enantiomerically pure aminoindolizine (**3**) by a triflic anhydride assisted cyclization of the 1,3-amino alcohol (**6**) is reported. **6** can be readily derived from L-asparagine (**4**) *via* the O-activated β-homoserine equivalent (**7**).

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-tet[4] 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 preliminarily 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: BH_3 x THF (85 %); e: 1. 2,5-dimethoxytetrahydrofuran, HOAc / NaOAc; 2. NaOH (90 %); f: Tf_2O, CH_2Cl_2 (65 %); g: $Pd(OH)_2$ / C - 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 results [5] 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.

ACKNOWLEDGMENTS

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EXPERIMENTAL PART

General

THF was distilled from $LiAlH_4$ immediately before use, CH_2Cl_2 was distilled from CaH_2. 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 NaN_3 (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 $NaHCO_3$ was added and the mixture was extracted with Et_2O. The extract was dried ($MgSO_4$) 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, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}N_5$: 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}. ^{1}H-Nmr ($CDCl_3$): δ (ppm) 2.29-2.40 (m, 2H), 3.23-3.30 (m, 1H), 3.42 (dd,

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

(R)-**8** ($[\alpha]_D^{23}$ +17.5° (c = 1.0, $CHCl_3$)) 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° (c = 1.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{20}N_2O_2$: 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}H-Nmr ($CDCl_3$): δ (ppm) 2.44 (dd, J = 16.2, 4.6 Hz, 1H), 2.64 (dd, J = 16.2, 10.2 Hz, 1H), 3.36-3.50 (m, 2H), 3.62 (d, J = 13.2 Hz, 2H), 3.62-3.74 (m, 1H), 3.94 (d, J = 13.2 Hz, 2H), 7.25-7.37 (m, 10H).

(R)-**9** ($[\alpha]_D^{23}$ +38° (c = 1.0, $CHCl_3$)) 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 BH_3xTHF (100 ml, 1 molar in THF) at 0°C. After 20 min the mixure 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 ($CHCl_3$ - MeOH - Et_3N 185:10:7) to give 4.85 g (85 %) of pure **10** as a colorless solid; mp 66-68°C. $[\alpha]_D^{23}$ -20° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{24}N_2O$: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}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 Hz, 2H), 3.63 (d, J = 14.2, 2H), 7.21-7.34 (m, 10H).

(R)-**10** ($[\alpha]_D^{23}$ +19.5° (c = 1.0, $CHCl_3$)) 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 x 3 H_2O (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 extraxted 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 $C_{22}H_{26}N_2O$: 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}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° (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°C. $[\alpha]_D^{23}$ -68° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{24}N_2$: 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}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° (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 % $Pd(OH)_2/C$ (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° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_8H_{12}N_2$: 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}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° (c = 1.0, $CHCl_3$)) was prepared from (R)-**3a** following the same procedure.

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