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SYNTHESIS OF ENANTIOPURE 8-AMINOMETHYLINDOLIZINES FROM GLUTAMINE BY STEREOELECTRONICALLY CONTROLLED CATIONIC CYCLIZATION

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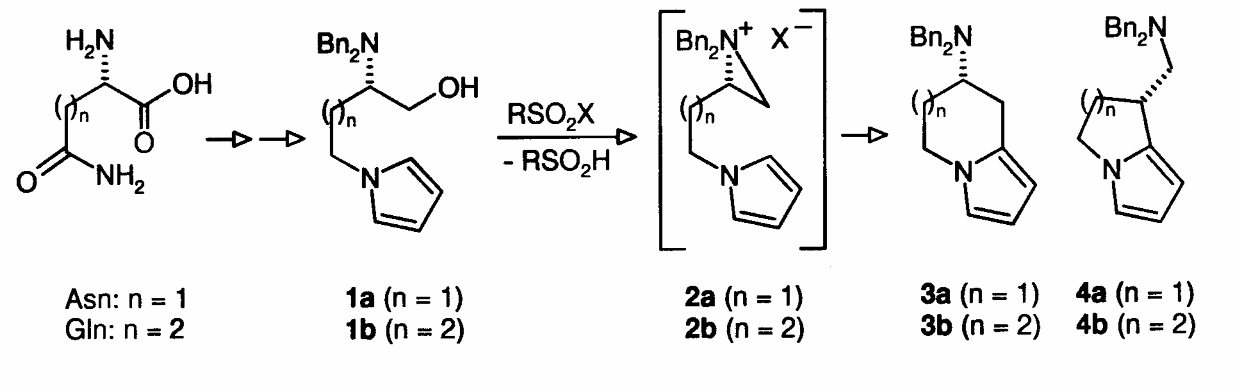
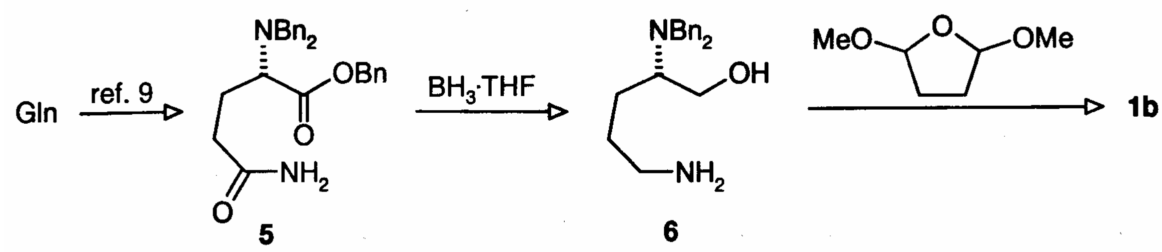
Abstract- Starting from natural glutamine the synthesis of the 8-aminomethylindolizine (**4b**) was accomplished. The construction of the ring system was performed by employing a cationic 6-exo π-cyclization of an intermediate aziridinium salt. Transformation of the *N,N*-dibenzyl protected amine (**4b**) into the pharmacologically relevant target compound (**11**) is also describcd.

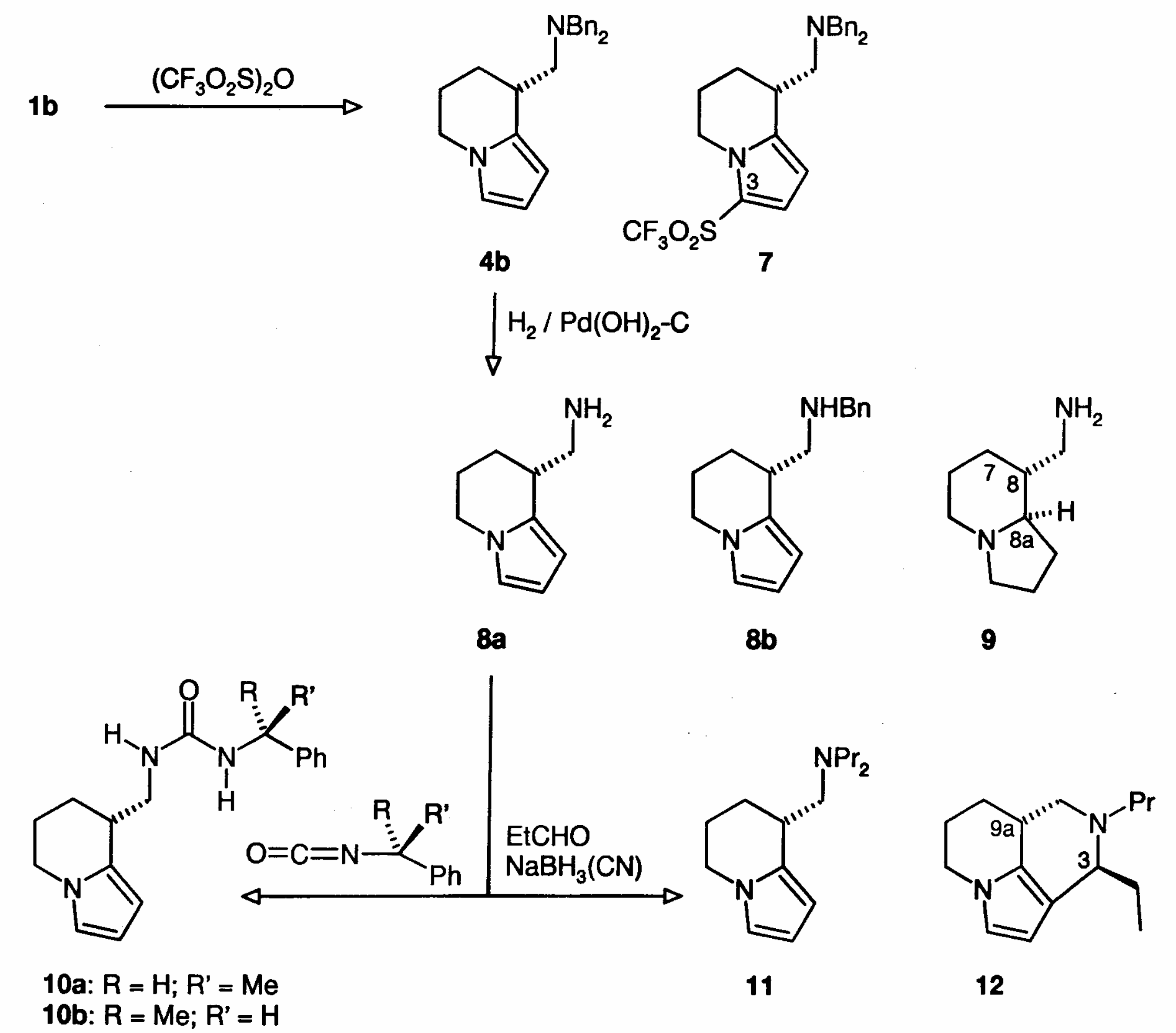
The exploitation of cationic π-cyclizations in the construction of a variety of ring systems has been the object of intense studies in the field of heterocyclic chemistry.[1] Employing *N*-pyrrole-terminated cyclization precursors this strategy gives access to tetrahydroindolizines and tetrahydropyrrolo[1 ,2-*a*]azepines.[2,3] As a part of our ongoing efforts to design selective dopamine D2/D3 autoreceptor agonists[4] which are of potential interest for the treatment of schizophrenia and cocaine craving,[5] we used cationic π-cyclizations for the construction of enantiomerically pure 6- and 7-dipropylaminotetrahydroindolizines revealing highly interesting receptor binding profiles.[6] The ex-chiral pool synthesis of the 7-amino regioisomers was performed by chemoselective functionalization of asparagine (Asn), incorporation of a pyrrole moiety by *Paal-Knorr* reaction to furnish **la** and *O*-activation of the side chain.[7] Since we were aware that sulfonylation of *N,N*-dibenzyl protected 1 ,2-amino alcohols and subsequent intermolecular nucleophilic substitution can result in rearrangements through aziridinium intermediates,[8] we elucidated the structure of the product very carefully. In fact, a 6-endo process leading to the indolizine (**3a**) was observed exclusively. 5-Exo attack of **2a** to give the pyrrolizine derivative (**4a**) could not bc detected. As an extension of our studies, we intended to investigate the synthesis of the homologous 1 ,2-amino alcohol (**1b**) which should bc available from natural glutamine (Gln). After *O*-activation the cyclization behavior of the resulting aziridinium derivative (**2b**) should be examined. Besides the application of the synthesis for extending our structure activity relationship studies, we were intrigued by the question whether the 7-endo process leading to the pyrroloazepine (**3b**) or the 6-exo reaction giving the aminomethylindolizine (**4b**) would be favored.



In practice, natural glutamine (Glu) was transformed into the *N,N*-dibenzyl protected ester (**5**) according to our recently reported protocol.[9] Subsequent borane reduction gave the diamino alcohol (**6**) in 84 % yield which could be readily transformed into the cyclization precursor (**1b**) by *Paal-Knorr* reaction[10] when 2,5-dimethoxytetrahydrofuran was employed as a valuable succinaldehyde equivalent.



Cyclization could be induced by activation of the 1 ,2-amino alcohol (**1b**) with trifluoromethanesulfonic anhydride when the 6-exo reaction pathway was observed, exclusively. Besides the main product (**4b**), we isolated a small amount of a side product which gave very similar ^{1}H NMR and ^{13}C NMR spectra. However, instead of the diagnostic signal for the proton in position 3 trifluoromethanesulfonyl substitution was observed indicating electrophilic attack of Tf_2O to give the side product (7). Although, the diagnostic chemical shifts and coupling patterns of the heterocycles (**4b**) and (7) showed high agreement with those of the tetrahydroindolizines we had prepared earlier,[6,7] the tetrahydropyrrolo[1 ,2-*a*]azepine structure could not be excluded unambiguously on this stage of the synthesis. However, the following reactions, which were performed in order to exchange the *N,N*-dibenzyl protection by the pharmacophoric *N-N*-dipropyl substitution and to investigate the enantiomeric integrity of the synthesis, confirmed our assumption. In detail, hydrogenolysis using $Pd(OH)_2$ as a catalyst afforded a mixture of tbe primary amine (**8a**) (25 %) and the secondary amine (**8b**) (41 %) besides 20 % of the starting material when the hydrogenation was terminated after 45 min. When the reaction was run over night the yield of the target compound (**8a**) could be increased to 59 %. Under these conditions, the octahydroindolizine (**9**) was formed as an easily separable side product. Careful analysis of diagnostic coupling constants in the ^{1}H NMR spectrum followed by H,H-COSY and C,H-COSY as well as NOE experiments clearly proved both the aminomethylindolizine structure and the configuration at the newly generated stereogenic center in position 8a. Especially, the coupling pattern for the exocyclic methylene group (2.58 ppm, dd., J = 12.7, 9.3 Hz and 2.91 ppm, dd, J = 12.7, 4.0 Hz) clearly indicated the N-CH_2-CH substructure. Significant dipolar exchange of magnetism was observed between the axially orientated proton in position 8a and the exocyclic methylene group which showed also a strong NOE with respect to the axial proton in position 7. This reveals that these structural units are located at the same side of the ring indicating (8a*R*)-configuration.



A further interesting side reaction was observed when we transformed the primary amine (**8a**) into the pharmacological test compound (**11**) by reductive alkylation. Besides the expected *N,N*-dipropyl derivative equal amounts of the pyrrolonaphthyridine (**12**) were isolated. Obviously, an iminium typed intermediate gave an intramolecular electrophilic attack resulting in 6-endo trig [11] ring closure. Careful structural analysis including H,H-COSY, C,H-COSY and NOE experiments (significant 1 ,3-diaxial interaction between the axially positioned C1 and C3 protons was observed) clearly proved chair conformations for the 6-membered rings and (*S*)-configuration in position 3.

Finally, examination of the enantiomeric integrity of the synthesis was performed by derivatization of the primary amine (**8a**) with (*S*)- and (*R*)- 1 -phenylethyl isocyanate. NMR analysis of the crude ureas (**10a**) and (**10b**) clearly indicated isomeric purity, when only one set of signals could be observed, respectively. Significant downfleld shift for the NCH_2 protons due to *N*-carbamoylation confirmed the cationic 6-exo ring closure earlier in the synthesis.

EXPERIMENTAL

General: Solvents and reagents were purified and dried by standard procedures. Unless otherwise noted reactions were conducted under dry N_2. Flash chromatography was carried out with 230-400 mesh silica gel. Optical rotation was measured on a Perkin-Elmer Polarimeter 241. IR spectra were recorded on a JASCO FT/IR-410 spectrophotometer. MS and HRMS were run on Finnigan MAT TSQ 70 and 8200 spectrometers, respectivery ^{1}H NMR spectra were obtained on a Bruker AM 360 (360 MHz) spectrometer, if not otherwise stated in $CDCl_3$ relative to TMS; ^{13}C-NMR spectra were run on Bruker AC 250 (63 MHz) or AM 360 (90 MHz) in $CDC1_3$ relative to the solvent resonance (δ = 77.0).

(S)-2-N,N-Dibenzylamino-5-*N*-pyrrolylpentan-1-o1 (1b)

To a mixture of **6** (5.90 g, 19.77 mmol) and NaOAc (32.45 g, 395.12 mmol) in HOAc(300 mL) was added 2,5-dimethoxytetrahydrofuran (2.89 g, 21.87 mmol) at rt. After stirring for 75 min at 70 °C the solution was concentrated. Then, 2N NaOH and Et_2O were added. The organic layer was evaporated and MeOH (200 mL) and K_2CO_3 (100 mL, 8 % in H_2O) were added. After stirring for 24 h at rt the mixture was evaporated and the residue was extracted by Et_2O. The organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether - EtOAc 4: 1) to give pure **lb** (4.50 g, 66 %) as a colorless oil. $[\alpha]_D^{23}$ +68.5°(c = 0.9, $CHC1_3$); IR (NaCl) ν 3600-3200, 3025, 2930, 2860, 1495, 1455, 1280, 1090, 1060, 1030, 750, 725, 700 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.13-1.27 (m, 1H, H-3), 1.61-1.85(m, 3H, H-3 and H-4), 2.71-2.82 (m, 1H, H-2), 2.85-3.03 (br s,1H,OH), 3.39 (d,J = 13.4 Hz,2H, NCH_2Ph), 3.44 (dd, J = l0.6, 9.8 Hz,1H,H-l), 3.49 (dd,J=10.6,5.8 Hz, 1H, H-1), 3.77 (d, J = 13.4Hz, 2H, NCH_2Ph), 3.81-3.88 (m,2H, H-5), 6.14-6.19 (m,2H,$NCHC\underline{H}$) 6.61-6.65 (m 2H $NC\underline{H}CH$), 7.21-7.34 (m, 10H, ar); ^{13}C NMR (63 MHz) δ 22.3 (H_2C-3), 29.0 (H_2C-4), 49.4 (H_2C-5), 53.3 (NCH_2Ph), 58.7 (HC-2), 60.9 (H_2C-1), 108,1 ($NCH\underline{C}H$), 120.4 ($N\underline{C}HCH$), 127.3 (HC-Ar), 128.5 (HC-Ar), 129.0 (HC-Ar), 139.1 (C-Ar); CI-MS (isobutane) *m/z* 349

(M+1)$^+$. *Anal.* Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.17; H, 8.1 1; N, 8.01.

(R)-8-*N,N*-Dibenzylaminomethyl-5,6,7,8-tetrahydroindolizine (4b) and *(R)*-8- *N,N*-Dibenzylaminomethyl-3-trifruormethanesulfonyl-5,6,7,8-tetrahydroindolizine (7)

To a solution of **1b** (6.0 g, 17.22 mmol) in CH_2C1_2 (200 mL) was added Tf_2O (10.0 g, 35.47 mmol) drop by drop at 0 °C. After stirrng for 18 h at rt 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 pure **4b** (1.6 g, 29 %) as colorless crystals (mp 70-72 °C, EtOH) and pure **7** (150 mg, 2 %) as a colorless oil. **4b**: $[\alpha]_D^{23}$ +105.0° (c = 1.0, $CHC1_3$); IR (KBr) ν 3025, 2940, 2855, 2795, 1490, 1450, 1330, 1075, 745, 700 cm^{-1} ; ^{1}H NMR (360 MHz) δ 1.42-1 .55 (m, 1H, H-7$_{ax}$), 1.65-1.83 (m, 2H, H-6$_{ax}$ and H-6$_{eq}$), 2.07-2.18 (m, 1H, H-7$_{eq}$), 2.54 (dd, J = 12.8, l0.6 Hz, 1H, NC$\underline{H}_2$CH), 2.68 (dd, J = 12.8, 4.3 Hz, 1H, NC$\underline{H}_2$CH), 3.00-3.10 (m, 1H, H-8), 3.32 (d, J = 13.7 Hz, 2H, NCH_2Ph), 3.74 (ddd. J = 12.0, 8.6, 5.1 Hz, 1H, H-5$_{ax}$), 3.84-3.91 (m, 1H, H-5$_{eq}$), 3.88 (d, J = 13.7 Hz, 2H, NCH_2Ph), 5.88-5.91 (m, 1H, H-1), 6.07-6.10 (m, 1H, H-2), 6.43-6.46 (m, 1H, H-3), 7.18-7.26 (m, 2H, p-ar), 7.26-7.33 (m, 4H, m-ar), 7.34-7.40 (m, 4H, o-ar); ^{13}C NMR (63 MHz) δ 21.8 (H_2C-6), 25.4 (H_2C-7), 32.2 (HC-8), 45.4 (H_2C-5), 58.5 (N$\underline{C}H_2$CH), 58.8 (NCH_2Ph), 103.4 (HC-1), 107.4 (HC-2), 118.7 (HC-3), 126.8 (HC-Ar), 128.1 (HC-Ar), 128.9 (HC-Ar),131 .7 (C-8a), 139.6 (C-Ar); CI-MS (isobutane) *m/z* 331 (M+1)$^+$. *Anal.* Calcd for $C_{23}H_{26}N_2$: C, 83.58; H, 7.93; N, 8.47. Found: C, 83.69; H, 7.86; N, 8.42.

7: $[\alpha]_D^{23}$ +15.4° (c = 0.6 . $CHC1_3$); IR (NaCl) ν 3030, 2930, 2800, 1360, 1215, 1190, 1115, 745, 700,630cm-^{1}; ^{1}H NMR (360 MHz) δ 1.52-1 .63 (m, IH, H-7$_{ax}$), 1.67-1.82 (m, 2H, H-6$_{ax}$ and H-6$_{eq}$), 1.99-2.09 (m, lH, H-7$_{eq}$), 2,55 (dd, J = 12.7, 9.9 Hz, 1H, NC$\underline{H}_2$CH), 2.70 (dd, J - 12.7, 5.1 Hz, 1H, NC$\underline{H}_2$CH), 3.01-3.11 (m, 1H, H-8), 3.44 (d, J = 13.7 Hz, 2H, NCH_2Ph), 3.80 (d, J = 13.7 Hz, 2H, NCH_2Ph), 3.98 (ddd. J = 13.2, 7.6, 5.6 Hz, 1H. H-5$_{ax}$), 4.16 (ddd, J = 13.2, 5.6, 5.6 Hz, IH, H-5,$_{eq}$), 6.19 (dd, J = 4.1. 0.8 Hz, 1H, H-1), 7.13 (d, J = 4.1 Hz, 1H, H-2), 7.18-7.40 (m, 10H, Ar); ^{13}C NMR (63 MHz) δ 20.6 (H_2C-6), 23.5 (H_2C-7), 33.0 (HC-8), 45.1 (H_2C-5), 58.0 (NC$\underline{H}_2$CH), 59.0 (NCH_2Ph), 108.4 (HC-1), 115.1 (C-3), 120.2 (q, J = 326 Hz, CF_3),125.4 (HC-2), 127. 17 (HC-Ar), 128.3 (HC-Ar), 128.9 (HC-Ar), 139.0 (C-Ar), 145.0 (C-8a); CI-MS (isobutane) *m/z* 463 (M+1)$^+$.

(S)-5-Amino-2-*N,N*-dibenzylaminopentan-1-o1 (6)

To a solution of **5** ^{9} (14.6 g, 35.05 mmol) in THF (300 mL) was added borane-THF (210 mL, 210 mmol, 1.0 M in THF) at 0 °C. After stirring for 1 h at 0 °C the solution was refluxed for 7 h. Then, the pH was adjusted to 1 by 5N HCI and subsequently alkalized to pH 12 by 2N NaOH. After addition of Et_2O the organic layer was dried ($MgSO_4$) and evaporated and the residue was purified by flash chromatography ($CHC1_3$ - MeOH - Et_3N 85: 10:7) to give pure **6** (8.72 g, 84 %) as a colorless oil. $[\alpha]_D^{23}$ +70.5° (c = 1.9. $CHC1_3$); IR (NaCl) ν 3600-2500, 3365, 3025, 2930, 2860, 1600, 1495, 1455, 1365, 1075, 1030, 750, 700 cm^{-1} ; ^{1}H NMR (36MHz) δ 1.22-1.34 (m, 1H, H-3), 1.38-1.51 (m, 2H, H-4), 1.71-1.83 (m, 1H, H-3), 2.27-2.51 (br s, 3H, NH_2 and OH), 2.66-2.83 (m, 3H, H-2 and H-5), 3.45 (d, J = 13.4 Hz, 2H, NCH_2Ph), 3.45-3.55 (m, 2H, H-1), 3.81 (d, J = 13.4 Hz, 2H, NCH_2Ph), 7.19-7.37 (m, 10H, Ar); ^{13}C NMR (63 MHz) δ 22.5 (H_2C-3), 30.6 (H_2C-4), 42.1 (H_2C-5), 53.2 (NCH_2Ph), 58.8 (HC-2), 60.8 (H_2C-1), 127.2 (HC-Ar), 128.4 (HC-Ar), 129.0 (HC-Ar), 139.3

(C-Ar) CI-MS (isobutane) *m/z* 299 $(M+1)^+$. *Anal.* Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.14; H, 8.96; N, 9.34.

(R)-8-Aminomethyl-5,6,7,8-tetrahydroindolizine (8a) and (8*R*,8a*R*)-8-Aminomethyloctahydroindolizine (9)

A mixture of **4b** (871 mg, 2.64 mmol) and 20 % $Pd(OH)_2/C$ (600 mg) in EtOAc (30 mL) and MeOH (30mL) was stirred under H_2 (1 bar) for 16 h at rt. The mixture was filtered and the filtrate evaporated and the residue was purified by flash chromatography (gradient: CH_2C1_2 - MeOH 4:1 to CH_2C1_2 - MeOH - Et_3N 85: 10:7) to give pure **8a** (230 mg, 59 %) as a colorless solid (mp 130 °C, decomp., Et_2O/EtOAc) and pure **9** (34 mg, 9 %) as a colorless oil. **8a**: $[\alpha]_D^{23}$ +36.0° (c = 0.2. MeOH); IR (KBr) ν 3600-2800, 3295, 2945, 1490, 1460, 1330, 1230, 1075, 785, 730, 700 cm^{-1} ; ^1H NMR (CD_3OD, 360 MHz) δ 1.52-1.64 (m, 1H, H-7_{ax}), 1.82-1.94 (m, 1H, H-6_{ax}), 2.00-2.13 (m, 2H, H-6_{eq} and H-7_{eq}), 2.89 (dd, J - 12.2, 7.4 Hz, 1H, $C\underline{H}_2NH_2$), 2.95-3.03 (m, 1H, H-8), 3.07 (dd, J = 12.2, 4.6 Hz, 1H, $C\underline{H}_2NH_2$), 3.86 (ddd, J = 12.0, 9.5, 4.3 Hz, 1H, H-5_{ax}), 3.97 (ddd, J = 12.0, 5.4, 5.3 Hz, 1H. H-5_{eq}), 5.87-5.90 (m, 1H, H-1), 6.02-6.05 (m, 1H, H-2), 6.53-6.56 (m, 1H, H-3); ^{13}C NMR (63 MHz) δ 22.2 (H_2C-6), 25.1 (H_2C-7), 35.9 (HC-8), 45.2 (H_2C-5 and NH:$_2\underline{C}$-CH), 103.9 (HC-1), l07.7 (HC-2), 119.4 (HC-3), 129.7 (C-8a); CI-MS (methane) *m/z* 151 $(M+1)^+$. *Anal.* Calcd for $C_9H_{14}N_2$ (-3/4 H_2O): C, 66.02; H, 9.54; N, 17.11. Found: C, 66.08; H, 9.39; N, 16.88.

9: $[\alpha]_D^{23}$ +26.2° (c = 0.4, MeOH); IR (KBr) ν 3600-2600, 2932, 2794, 1566, 1402, 1328, 1107, 752, 654cm^{-1} ; ^1H NMR (CD_3OD, 360 MHz) δ 1.04 (dddd, J - 12.8, 12.7, 12.7, 4.9 Hz, 1H, H-7_{ax}), 1.39-1.56 (m, 2H, H-l and H-8), 1.56-1.84 (m, 5H, H-8a, H-6 $_{ax}$, H-6 $_{eq}$ and 2H-2) 1.93-2.11 (m, 3H, H-$7_{eq,}$ H-1 and H 5 $_{ax}$), 2.19 (ddd, J = 9.3, 9.3, 9.3 Hz, 1H, H-3), 2.58 (dd, J = 12.7, 9.3 Hz, IH, $C\underline{H}_2NH_2$), 2.91 (dd, J = 12.7, 4.0 Hz, 1H, $C\underline{H}_2NH_2$), 3.03-3.15 (m, 2H. H-3 and H-5 $_{eq}$); ^{13}C NMR (CD_3OD, 90 MHz) δ 21.3 (H_2C-2), 25.6 (H_2C-6),28.9 (H_2C-7), 29.4 (H_2C-1), 42.9 (HC-8), 44.2 (H_2C-NH_2), 53.4 (H_2C-5), 55.0 (H_2C-3), 68.1 (C-8a). HRMS (EI) *m/z* 154.1468 (M^+) calcd for $C_9H_{18}N_2$: 154.1470.

(R)-8-*N*-Benzylaminomethyl-5,6,7,8-tetrahydroindolizine (8b)

A mixture of **4b** (118 mg, 0.36 mmol) and 20 % $Pd(OH)_2/C$ (100 mg) in EtOAc (10 mL) and MeOH (10 mL) was stirred under H_2 (1 bar) for 45 min at rt. The mixture was filtered and the filtrate evaporated and the residue was purified by flash chromatography (gradient: CH_2C1_2- MeOH 97:3 to CH_2C1_2- MeOH 4: 1) to give pure **8b** (35 mg, 41 %) as a colorless oil and pure **8a** (13 mg, 25 %) as a colorless solid besides **4b** (30 mg, 25 %). **8b**: $[\alpha]_D^{23}$ +14.0° (c = 0.2, $CHC1_3$); IR (NaCl) ν3600-3200, 2930, 1455, 1325, 1195, 1115, 1075, 700 cm^{-1} ; ^1H NMR (300 MHz) δ 1.57- 1.68 (m, 1H, H-7_{ax}), 1.81-1.93 (m, 1H, H-6 $_{ax}$), 1.99-2.10 (m, 2H, H-6 $_{eq}$ and H-7 $_{eq}$), 2.78 (dd, J = 11.4, 7.5 Hz, 1H, $NC\underline{H}_2CH$), 2.96 (dd, J = 11.4, 5.5 Hz, 1H, $NC\underline{H}_2CH$), 2.98-3.06 (m, 1H, H-8), 3.80 (d, J - 13.5 Hz, 1H, NCH_2Ph), 3.81-3.91 (m, 1H, H-5 $_{ax}$), 3.86 (d, J = 13.5 Hz, 1H, NCH_2Ph), 3.92-4.00 (m, 1H, H-5_{eq}), 5.90-5.93 (m, 1H, H-1), 6.10-6.13 (m, 1H, H-2), 6.50-6.53 (m, 1H, H-3), 7.22-7.35 (m, 5H, ar); ^{13}C NMR (63 MHz) δ 22.38 (H_2C-6), 25.87 (H_2C-7), 34.52 (HC-8), 45.39 (H_2C-5), 53.70 ($N\underline{C}H_2CH$), 54.05 (NCH_2Ph), 103.6 (HC-1), 107.6 (HC-2), 119.0 (HC-3), 126.9 (HC-ar), 128.1 (HC-Ar), 128.4 (HC-Ar), 131.3 (C-8a), 140.5 (C-Ar); CI-MS (methane) *m/z* 241 (M+1). *Anal.* Calcd for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.87; H, 8.38; N, 11.68.

1-[(1 '*S*)-1 '-Phenylethyl]-3-[(8*R*)-5,6,7,8-tetrahydroindolizin-8-ylmethyl]urea (10a)

To a solution of **8a** (20 mg, 0.13 mmol) in THF (1 mL) and EtOH (0.5 mL) was added *(S)*- 1-phenylethyl isocyanate (20 mg, 0.13 mmol) at 0°C. After stirring for 2 h at rt the mixture was evaporated and the residue was investigated by NMR spectroscopy. For purification, the residue was subjected to flash chromatography (petroleum ether - EtOAc 1:1) to give pure **10a** (32 mg, 83 %) as a colorless solid (mp 126-128°C, hexane/EtOAc). $[\alpha]_D^{23}$ +27.3° (c = 0.9, CHC1^3); IR (NaC1) ν 3335, 2930, 2865, 1630, 1565, 1255, 700 cm^{-1};

^{1}H NMR (360 MHz) δ 1.40-1.53 (m, 1H, H-7$_{ax}$), 1.43 (d, J = 6.4 Hz, 3H, CH$_3$), 1.76-1.91 (m, 2H, H-6$_{ax}$ and H-7$_{eq}$), 1.93-2.03 (m, 1H, H-6$_{eq}$), 2.86-2.95 (m, 1H, H-8), 3.34 (ddd, J = 13.4, 5.8, 5.8 Hz, 1H, NC$\underline{H}_2$CH), 3.45 (ddd, J = 13.4, 5.8, 5.4 Hz, 1H, NC$\underline{H}_2$CH), 3.80 (ddd, J = 11.9, 9.4, 4.7 Hz, 1H, H-5$_{ax}$), 3.92 (ddd, J = 11.9, 5.0, 5.0 Hz, 1H, H-5$_{eq}$), 4.53 (br dd, J = 5.8, 5.8 Hz, 1H, N$\underline{H}$CH$_2$), 4.67-4.76 (m, 2H, CH and N$\underline{H}$CH), 5.71-5.74 (m, 1H, H-1), 6.06-6.09 (m, 1H, H-2), 6.50-6.52 (m,1H, H-3), 7.22-7.36 (m, 5H, ar); EI-MS (70 eV) *m/z* 297 (M$^+$). *Anal.* Calcd for $C_{18}H_{23}N_3O$: C, 72.70; H, 7.80; N, 14.13. Found: C, 72.55; H, 7.70; N, 14.00.

1-[(1'*R*)-1'-Phenylethyl]-3-[(8*R*)-5,6,7,8-tetrahydroindolizin-8-ylmethyl]urea (10b)

Reaction of **8a** with (*R*)- 1 -phenylethyl isocyanate employing conditions as described for **10a** afforded **10b** (33 mg, 84 %) as a colorless oil. $[\alpha]_D^{23}$ +37.8°(c = 1.0, CHC1$_3$); IR (NaCl) ν 3335, 2930, 2865, 1630, 1565, 1255,700cm^{-1}; ^{1}H NMR (360MHz) δ 1.21-1.36(m ,1H ,H-7$_{ax}$), 1.40(d ,J =6 .8Hz ,3H, CH$_3$), 1.71-1.84(m , 2H, H-6 $_{ax}$ and H-7 $_{eq}$), 1.86-1.96 (m, 1H. H-6 $_{eq}$), 2.86-2.95 (m, 1H, H-8), 3.28 (ddd, J = 13.4, 6.3, 4.8 Hz, 1H, NC$\underline{H}_2$CH) 3.55 (ddd, J = 13 .4, 7.5, 4.8 Hz, 1H ,NC$\underline{H}_2$CH), 3.66 (ddd, J = 11.7, 10.5, 4.8 Hz, 1H, H-5 $_{ax}$), 3.87 (ddd, J = 11.7, 4.8, 4.8 Hz, 1H, H-5 $_{eq}$), 4.54 (br-dd, J = 6.3, 4.8 Hz, 1H, N$\underline{H}$CH$_2$), 4.65 (dq, J = 6.8, 6.8 Hz, 1H, CH), 4.78 (br d, J = 6.8 Hz, 1H, N$\underline{H}$CH), 5.84-5.87 (m, 1H, H-1), 6.09-6.12 (m, 1H, H-2), 6.48-6.51 (m, 1H, H-3), 7.19-7.33 (m, 5H, ar); EI-MS (70 eV) *m/z* 297 (M$^+$).

(R)-8-*N,N*-Dipropylaminomethyl-5,6,7,8-tetrahydroindolizine (11) and (3*S*,9a*R*)-3-Ethyl-2-*N*-propyl-2,3,7,8,9,9a-hexahydr0-*1H*-pyrrolo[3,2,1-*ij*] [1,6]naphtyridine (12)

To a solution of **8a** (100 mg, 0.67 mmol) in MeOH (10 mL) were added propionaldehyde (387 mg, 6.66 mmol) and NaBH$_3$(CN) (84 mg, 1 .33 mmol) at 0 °C. After stirring for 15 min at 0 °C the mixture was allowed to warm up to rt. After 18 h 2N HCI was added. Subsequently, the mixture was basified by addition of saturated aqueous NaHCO$_3$. Then, Et$_2$O was added and the organic layer was dried (MgSO$_4$) and evaporated and the residue was purified by flash chromatography (gradient: petroleum ether - EtOAc 9: 1 to petroleum ether - EtOAc 4: 1) to give pure **11** (43 mg, 28 %) and pure **12** (43 mg, 28 %), both as colorless oils. **11**: $[\alpha]_D^{23}$ +118.1° (c = 0.5, CHC1$_3$); IR (NaC1) ν 2955, 2870, 2800, 1465, 1325, 1075, 700 cm^{-1} . ^{1}H NMR (360 MHz) δ 0.88 (t, J = 7.4 Hz, 6H, CH$_3$), 1.37-1.57 (m, 5H. C$\underline{H}_2$CH$_3$ and H-7$_{ax}$, 1.78-1.91 (m, 1H, H-6 $_{ax}$), 1.96-2.14 (m, 2H, H-6$_{eq}$ and H-7$_{eq}$), 2.29-2.49 (m, 5H, NC$\underline{H}_2$CH$_2$ and NC$\underline{H}_2$CH), 2.67 (dd, J = 13.0, 4.8 Hz, 1H, NC$\underline{H}_2$CH), 2.91 (dddd, J= 14.3, 4.8, 4.8, 4.8, 1H, H-8), 3.86 (ddd, J= 12.0, 9.4, 4.6Hz, 1H, H-5$_{ax}$), 3.96 (ddd, J = 12.0, 5,1, 5.1, Hz, 1H, H-5$_{eq}$), 5.96-5.99 (m, 1H, H-1), 6.11-6.14 (m, 1H, H-2), 6.50-6.52 (m,1H, H-3); ^{13}C NMR (63 MHz) δ 12.0 (CH$_3$), 20.4 ($\underline{C}$H$_2$CH$_3$), 22.3 (H$_2$C-6), 26.0 (H$_2$C-7), 33.0 (HC-8), 45.5 (H$_2$C-

5), 56.8 ($N\underline{C}H_2CH_2$), 60.0 ($N\underline{C}H_2CH$), 103.6 (HC-1), 107.4 (HC-2), 118.7 (HC-3), 132.4 (C-8a); CI-MS (isobutane) *m/z* 235 $(M+1)^+$; HRMS (EI) *m/z* 120.0825 $(M-CH_2NPr_2)^+$ (calcd for $C_8H_{10}N$: 120.0813). **12**: $[\alpha]_D^{23}$ +76.4° (c = 0.4, $CHC1_3$); IR (NaCl) ν 2957, 2931, 2868, 2793, 1652, 1464, 1375, 1291, 1201, 690 cm^{-1}; ^{1}H-NMR (360 MHz) δ 0.83 (t, J = 7.4 Hz, 3H, $C\underline{H}_3CH_2CH$), 0.91 (t, J = 7.4 Hz, 3H, $NCH_2CH_2C\underline{H}_3$), 1.12 (dddd, J = 12.1, 12.1, 11.7, 4.1, 1H, H-9_{ax}), 1.38-1.62 (m, 2H, $NCH_2C\underline{H}_2CH_3$), 1.67-1.81 (m, 2H, $CH_3C\underline{H}_2CH$), 1.81-1.90 (m, 1H, H-9_{eq}), 1.91-2.08 (m, 2H, H-8_{eq} and H-8_{ax}), 2.13 (dd, J = 10.3, 10.3, 1H, H-1_{ax}), 2.33-2.46 (m, 1H, $NC\underline{H}_2CH_2CH_3$), 2.62-2.74 (m, 1H, $NC\underline{H}_2CH_2CH_3$), 2.79-2.91 (m, 1H, H-9a), 3.02 (dd, J = 10.3, 4.4, 1H, H-1_{eq}), 3.47-3.53 (m, 1H, CH_3CH_2CH), 3.71 (ddd, J = 11.8, 11.7, 6.2 Hz, 1H, H-7_{ax}), 4.01 (ddd. J = 11.8, 5.3, 2.0 Hz, IH, H-7_{eq}), 5.94 (d, J = 2.7 Hz, 1H, $NCHC\underline{H}$), 6.48 (d, J = 2.7 Hz, 1H, $NC\underline{H}CH$); ^{13}C-NMR (63 MHz) δ 8.5 ($\underline{C}H_3CH_2CH$), 12.0 ($NCH_2CH_2\underline{C}\underline{H}_3$), 20.0 ($NCH_2\underline{C}H_2CH_3$), 23.5 ($H_2C$-8), 24.9 ($H_2C$-9), 26.5 ($CH_3\underline{C}H_2CH$), 33.3 (HC-9a), 44.5 ($H_2C$-7), 55.4 ($H_2C$-1), 55.9 ($N\underline{C}H_2CH_2CH_3$), 60.2 (HC-3), 105.2 ($NCH\underline{C}H$), 116.8 ($NC\underline{C}$), 118.4 ($N\underline{C}HCH$), 129.9 (NC) CI-MS ($NH_3$) *m/z* 233 $(M+1)^+$; HRMS (EL) *m/z* 203.1544 $(M-C_2H_5)^+$ (calcd for $C_{13}H_{19}N_2$: 203.1548).

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