Synthesis of analogues of (-)-cytisine for in vivo studies of nicotinic receptors using Positron Emission Tomography

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Supporting Information

General. All reactions were carried out under a nitrogen atmosphere. Palladium-catalyzed reactions were performed in sealed reaction vessels. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Toluene was distilled from CaH_2, dioxane was distilled from sodium. Tetrakis(triphenylphosphine)palladium was prepared according to a known procedure.[1] All other reagents or catalysts were used as obtained from commercial sources (purity > 98% Janssen Chimica, Aldrich or Sigma). Organic layers were washed with water, brine, dried over anhydrous $MgSO_4$ and evaporated at < 50°C under reduced pressure ("standard work up"). Thin layer chromatography was performed on silica gel 60 F-254 plates (0.1 mm, Merck) with iodine and/or UV detection. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 70-230 mesh, Merck). Analytical high performance liquid chromatography (HPLC) was carried out with a Waters instrument [detector 486 and pump 510 or detector M996 (200-400 nm) and pump 600]. All NMR spectra were recorded on a Bruker Avance DPX 250 instrument (250 MHz ^{1}H, 62 MHz ^{13}C, 235 MHz ^{19}F) in $CDCl_3$ unless otherwise indicated. Mass spectral data were obtained on a Nermag R10 (EI, 70 ev) and high resolution mass spectra (HRMS) on a Jeol JMSD 300 or a Jeol AX 500 (University of Rouen). IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrometer. Optical rotations were

measured on a Perkin-Elmer 241 LC polarimeter at $\lambda = 589$ nm. $[\alpha]_D$ values are given in units of 10^{-1}deg.cm^2 g^{-1}. Analytical data were obtained from CNRS Center (Vernaison, France). Melting points were determined on a Gallenkamp apparatus and are uncorrected.

In the radioactive experiments, a "Berthold LB 284/285" instrument was used to detect the radioactive TLC spots. The Sep-Paks were purchased from Millipore Waters. The C-18 cartridges were washed with methanol (5 ml) then water (5 ml) prior to use. High performance liquid chromatographies (HPLC) were performed on a Waters system equipped with an injector U6K and a multiple wavelength u.v. detector (M490, $\lambda = 254$ nm) connected in series with a radioactivity detector (Kipp & Zonen). A μ- Porasil column (10 μm, 6.2 x 300 mm; "column A") was used for preparative conditions. Radiochemical yields were determined with a dose calibrator (Capintec 12 and CRC 15R) and were corrected for decay to the end of bombardment (EOB).

(–)-(1*R*,5*S*)-1,2,3,4,5,6-Hexahydro-1,5-methano-pyrido-[1,2-a][1,5]diazocin-8-one, 1a.[2] *Cytisus* seeds in powder (1000 g, Vilmorin, France), CH_2Cl_2, (1400 mL), MeOH (400 mL) and NH_4OH (150 mL) were stirred for 3 days at RT then filtered. The solids were washed with CH_2Cl_2 and the filtrate was treated with HCl (3N) until pH 1. The aqueous layer was recovered, basified with NH_4OH (28%) and extracted with CH_2Cl_2 (10 times). The combine organic layers were dried then concentrated. The solid was washed with a minimum amount of acetone then collected to give 15 - 18 g (1.5-1.8 %) of (-)-cytisine **1a** as a white solid. $[\alpha]_D^{22} = -76$ (c 1; $CHCl_3$). [litt. -119.6 (c 1; H_2O)]. Mp: 153-154°C (heptane/EtOH) (litt[3]: 155°C). IR (KBr, cm^{-1}): 1540, 1646 (C=O), 3278 (NH); ^{1}H and ^{13}C NMR: identical to those previously described.[4] MS (EI): m/z (relative intensity): 190 ($M^{+\cdot}$, 78), 186 (100), 159 (32), 147

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(42), 146 (53), 57 (43), 44 (52). Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.45; N, 14.72. Found: C, 69.12; H, 7.45; N, 14.52.

(–)-(1*R*,5*S*)-*N*-Acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 1b. A mixture of cytisine **1a** (1g, 5.26 mmol), pyridine (5 mL), 4-dimethylaminopyridine (0.100 g, 0.82 mmol) and acetic anhydride (1.8 mL, 19 mmol) was stirred at RT for 12 h. The volatile compounds were removed under vacuum. Water then NH_4OH (28%), were added and the mixture extracted with dichloromethane. Standard work up gave **1b** (1.22 g, 100%) as a white solid. $[\alpha]_D^{22}$ = -200 (c 1; $CHCl_3$). Mp: 212°C; litt:[5] 208°C. IR (KBr, cm^{-1}) 1238, 1360, 1424, 1452, 1546, 1616 (C=O), 1634 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.67 (s, 2H), 1.98 (br s, 3H), 2.46 (br s, 1H), 2.76 (m, 1H, 2 conformers), 3.03 (s, 1H), 3.34 (m, 1H,1 conformer), 3.72-3.89 (m, 2H, conformers), 4.01 and 4.07 (2 d, *J* = 10.1 Hz, 1H, 2 conformers), 4.60 and 4.72 (2 d, *J* = 13.1 Hz, 1H, 2 conformers), 6.00 (d, *J* = 6.6 Hz, 1H), 6.36 (m, 1H, 2 conformers), 7.24 (m, 1H, 2 conformers). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 19.4, 20.0, 24.7, 24.8, 26.0, 26.3, 33.0, 33.7, 46.2, 47.1, 47.5, 51.2, 52.4, 103.5, 104.6, 116.0, 116.5, 137.1, 137.8, 147.0, 147.2, 161.9, 162.1, 168.3, 168.4. MS (EI): m/z (relative intensity): 232 (100), 190 (25), 147 (87). HRMS (EI) calcd. for $C_{13}H_{16}N_2O_2$ 232.1212, found: 232.1216.

(–)-(1*R*,5*S*)-*N*-methoxycarbonyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 1c. Methyl chloroformate (6.8 mL, 88 mmol) was added dropwise at RT to a mixture of cytisine **1a** (1.67 g, 8.79 mmol), CH_2Cl_2 (50 mL), and NEt_3 (12.2 mL, 88 mmol). After 5 days at RT the volatile compounds were evaporated. The residue was taken in EtOAc (50mL). After filtration, the solvent was evaporated and the crude product was purified by flash chromatography (10% MeOH/CH_2Cl_2) affording **1c** (1.92 g, 88%) as an amorphous solid. $[\alpha]_D^{22}$ = -209 (c 0.775; $CHCl_3$); litt: - 174(EtOH). Mp: 108°C; litt:[6] 109°C. IR (NaCl, cm^{-1}): 1124, 1238, 1448, 1546, 1650 (C=O), 1696 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.99 (m, 2H), 2.47 (br s, 1H), 3.08 (br s, 3H), 3.56 (br s, 3H), 3.86 (dd, *J* = 6.6, 16 Hz, 1H),

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4.14 (d, *J* = 16 Hz, 1H), 4.15 (m, 2H), 6.07 (d, *J* = 6.7 Hz, 1H), 6.43 (d, *J* = 9.1 Hz, 1H,), 7.29 (dd, *J* = 6.7, 9.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.1, 26.6, 33.8, 48.3, 49.6, 50.5, 52.1, 105.0, 116.5, 138.3, 148.4, 155.5, 162.8. MS (EI): m/z (relative intensity): 248 ($M^{+\circ}$, 13), 243 (69.5), 159 (29), 146 (100), 102 (91). Anal. Calcd. $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.89; N, 11.28. Found: C, 62.65; H, 6.74; N, 11.15.

(–)-(1*R*,5*S*)-*N*-nitroso-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 1d. A mixture of cytisine **1a** (10g, 52.6 mmol), sodium nitrite (18.3 g, 260 mmol) and HCl (5M, 50 mL) was stirred at RT for 12h. The mixture was basified with NH_4OH and was extracted with dichloromethane. Standard work up then flash chromatography (10% MeOH/CH_2Cl_2) afforded **1d** (11.5 g, 100%) as a white solid. $[\alpha]^{22}_D$ -310 (c 1; H_2O). Mp: 175°C; litt:[5] 175°C. IR (KBr, cm^{-1}): 1136, 1272, 1370, 1424 (NNO), 1544, 1580, 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.17 (m, 2H), 2.66 (br s, 1H 1 conformer), 2.76-2.85 (m, 2H, 1 conformer), 3.19 and 3.34 (2 s, 1H, 2 conformers), 3.82 (dd, *J* = 6.3, 15.6 Hz, 1H, 1 conformer), 3.85-4.05 (m, 2H), 4.19 (d, *J* = 15.6 Hz, 1H), 4.77 and 4.87 (2 d, *J* = 13.2 Hz, 1H, 2 conformers), 5.08 and 5.15 (2 d, *J* = 14 Hz, 1H, 1 conformer), 6.03 and 6.14 (2 d, *J* = 6.8 Hz, 1H, 2 conformers), 6.39 (m, 1H, 2 conformers), 7.26 (m, 1H, 2 conformers). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 25.3, 25.4, 26.5, 27.1, 33.6, 33.9, 44.2, 45.2, 47.5, 48.0, 54.9, 56.3, 105.7, 132.0, 132.3, 145.7, 145.8, 146.2, 165.2. MS (EI): m/z (relative intensity): 219 (30), 189 (35), 160 (27), 146 (100). HRMS (EI) calcd. for $C_{11}H_{13}N_3O_2$ 219.1008, found: 219.1008.

(–)-(1*R*,5*S*)-9-Nitro-1,2,3,4,5,6-hexahydro-1.5-methano-pyrido[1.2-a][1.5]diazocin-8-one, 6a and (–)-(1*R*,5*S*)-11-nitro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 6a. To a cooled (0°C) solution of cytisine **1a** (1 g, 5.26 mmol) in concentrated sulfuric acid (1.5 mL), was added concentrated nitric acid (1.2 mL, 19 mmol) dropwise. The mixture was stirred at RT for 5 h, cooled to 0°C, quenched by addition of NH_4OH until basic pH and extracted with dichloromethane. The organic layer was dried and the solvents removed.

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Aqueous HCl (12N, 2.5 mL) was added to the residue and the mixture was refluxed for 15 min, cooled, quenched with water then NH_4OH (28%). Standard work up with dichloromethane afforded a mixture of 9-nitro and 11-nitro cytisines **6a** and **7a** which were separated by flash chromatography (1% NH_4OH/10% MeOH/CH_2Cl_2). **6a** (0.950 g, 77%), yellow solid. $[\alpha]^{22}_D$ -66 (c 1; $CHCl_3$). Mp: 211 °C. IR (KBr, cm^{-1}): 1310, 1462, 1550 (NO_2), 1684 (C=O), 2922, 3324 (NH). ^1H NMR ($CDCl_3$): δ 1.61 (1H, NH), 1.98 (s, 2H), 2.42 (br s, 1H), 2.98-3.16 (m, 5H), 3.87 (dd, *J*= 6.5, 16 Hz, 1H), 4.09 (d, *J*= 16 Hz, 1H), 6.12 (d, *J* = 8.1 Hz, 1H), 8.34 (d, *J* = 8.1 Hz, 1H).^{13}C NMR ($CDCl_3$): δ 25.6, 27.4, 36.6, 51.1, 52.8, 53.2, 103.1, 134.2, 137.7, 155.3, 161.0. MS (EI): m/z (relative intensity): 235 (42), 217 (100), 175 (27), 159 (18), 130 (20). HRMS (EI) calcd. for $C_{11}H_{13}N_3O_3$ 235.0957, found: 235.0964.
7a (0.136 g, 11%). $[\alpha]^{22}_D$ -230 (c 1; $CHCl_3$). Mp: 172 °C IR (KBr, cm^{-1}): 1328, 1494, 1546 (NO_2), 1682 (C=O), 3348 (NH). ^1H NMR ($CDCl_3$): δ 1.61 (1H, NH), 1.98 (m, 2H), 2.43 (br s, 1H), 2.97-3.12 (m, 3H), 3.49 (d, *J* = 11.5 Hz, 1H), 3.95-4.12 (m, 3H), 6.48 (d, *J* = 10 Hz, 1H), 8.15 (d, *J* = 10 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.8, 26.9, 31.8, 51.6, 51.8, 53.0, 115.6, 130.6, 135.0, 155.3, 162.3. MS (EI): m/z (relative intensity): 235 (80), 218 (100), 175 (27), 159 (17). HRMS (EI) calcd. for $C_{11}H_{13}N_3O_3$ 235.0957, found: 235.0955.

(–)-(1*R*,5*S*)-9-Amino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 9a. A mixture of 9-nitrocytisine **6a** (1g, 4.25 mmol), MeOH (20 mL) and Pd/C (0.100 g, 10%) was saturated with N_2 and stirred at RT under H_2 atmosphere for 4 h. The suspension was filtered through a pad of celite and the filtrate concentrated to give **9a** (0.870 g, 100%) as a grey solid. $[\alpha]^{22}_D$ -26 (c 1; $CHCl_3$). Mp: 172°C. IR (KBr, cm^{-1}): 1540, 1582, 1640 (C=O), 2924, 3330 (NH). ^1H NMR ($CDCl_3$): δ 1.87 (s, 2H), 2.21 (br s, 1H), 2.75-3.04 (m, 6H), 3.77 - 4.16 (m, 4H), 5.81 (d, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 27.2, 28.1, 35.3, 50.4, 53.3, 54.8, 105.4, 113.7, 135.0, 138.2, 158.8. MS (EI): m/z (relative intensity): 205 (85), 152 (100), 151 (45), 147 (20). HRMS (EI) calcd. for $C_{11}H_{15}N_3O$ 205.1215, found: 205.1213.

(–)-(1*R*,5*S*)-*N*-Acetyl-9-nitro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 6b. Acetylation of 9-nitrocytisine **6a** (0.5 g, 2.13 mmol) was

carried out as described above to give **6b** (0.588 g, 100%) as a yellow solid (two conformers A and B, relative ratio: 33/66). $[\alpha]^{22}_{D}$ = -216 (c 1; $CHCl_3$). Mp 232 °C. IR (KBr, cm^{-1}): 1310, 1420, 1564, 1642 (C=O), 1698 (C=O). ^{1}H NMR ($CDCl_3$): δ Conformer A: 1.78 (s, 3H), 2.08 (s, 2H), 2.64 (br s, 1H), 2.84 (d, *J* = 13.2 Hz, 1H), 3.26 (s, 1H), 3.51 (d, *J* = 13.2 Hz, 1H), 3.91-4.01 (m, 2H), 4.17 (d, *J* = 15 Hz, 1H), 4.80 (d, *J* = 13.2 Hz, 1H), 6.25 (d, *J* = 7.9 Hz, 1H), 8.36 (d, *J* = 7.9 Hz, 1H). Conformer B: 2.04 (s, 3H), 2.08 (s, 2H), 2.64 (br s, 1H), 2.93 (d, *J* = 13.2 Hz, 1H), 3.26 (s, 1H), 3.43 (d, *J* = 13.2 Hz, 1H), 3.91-4.01 (m, 2H), 4.23 (d, *J* = 15 Hz, 1H), 4.74 (d, *J* = 13.2 Hz, 1H), 6.24 (d, *J* = 7.9 Hz, 1H), 8.33 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ Conformer A: 20.8, 24.7, 26.3, 35.2, 46.8, 49.7, 52.1, 102.2, 134.7, 137.2, 154.2, 157.1, 169.0. Conformer B: 20.4, 24.7, 26.7, 34.7, 47.1, 49.6, 51.7, 103.2, 134.5, 137.6, 154.5, 157.1, 169.5. MS (EI): m/z (relative intensity): 277 (100), 217 (90), 175 (35), 159 (20), 130 (25). HRMS (EI) calcd. for $C_{13}H_{15}N_3O_4$: 277.1063, found: 277.1065.

(–)-(1*R*,5*S*)-*N*-Acetyl-9,11-dinitro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 8b. To a solution of acetyl-nitrocytisine **6b** (0.277 g, 1 mmol) in chloroform (3 mL) were added at RT ammonium nitrate (0.24 g, 3 mmol) then trifluoroacetic anhydride (3 mL). The mixture was stirred overnight at RT then was quenched with a saturated solution of $NaHCO_3$. Standard work up and flash chromatography (5% MeOH/CH_2Cl_2) afforded the dinitrocytisine **8b** (0.225 g, 70%) as a light yellow solid. $[\alpha]^{22}_{D}$ = -461 (c 0.1; CH_2Cl_2). Mp: 264°C. IR (KBr, cm^{-1}): 1310, 1356, 1422, 1564, 1644, 1696. ^{1}H NMR ($CDCl_3$): δ 1.85 (s, 1H), 2.05 (s, 3H), 2.15 and 2.2 (m, 1H, 2 conformers), 2.7 (br s, 1H), 2.86 and 3.03 (2 d, *J* = 13 Hz, 1H, 2 conformers), 3.52 (m, 1H), 3.97-4.46 (m, 4H), 4.86 and 5.13 (2 d, *J* = 13.4 Hz, 1H, 2 conformers), 9.11 and 9.14 (2 s, 1H, 2 conformers). ^{13}C NMR (DMSO-d_6): (2 conformers) δ 21, 21.1, 23.8, 23.9, 25.9, 26.3, 31.4, 31.8, 45.4, 46.5, 50.1, 51, 51.7, 51.9, 128.1, 128.5, 132.8, 133.4, 133.7, 153.4, 158.1, 158.9, 169.1, 169.3. MS (EI): m/z (relative intensity): 322 (17), 305 (12), 280 (20), 276 (24), 263 (100), 234 (25), 219 (73), 205 (40), 175 (34).

(–)-(1*R*,5*S*)-*N*-Acetyl-9-amino-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 9b. Reduction of 9-nitrocytisine **6b** (1g, 3.61 mmol) was carried out as previously described to give **9b** (0.890 g, 100 %) as a white solid. $[\alpha]^{22}_{D}$ = -118 (c 1; $CHCl_3$). Mp: 253°C. IR (KBr, cm^{-1}): 1432, 1452, 1538, 1620 (C=O), 1644 (C=O), 3448 (NH_2). ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 2H), 2.00 (s, 3H), 2.49 (br s, 1H), 2.80 (d, *J* = 12.9 Hz, 1H), 3.02 (br s, 1H), 3.36 (d, *J* = 12.9 Hz, 1H), 3.81-4.25 (m, 5H), 4.70 and 4.79 (2 d, *J* = 13 Hz, 1H, 2 conformers), 5.96 (d, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 21.3, 21.8, 27.0, 27.2, 27.7, 28.1, 34.1, 34.8, 47.9, 49.4, 49.6, 53.0, 54.7, 105.4, 106.4, 112.5, 113.8, 135.5, 135.8, 158.6, 170.1, 177.4. MS (EI): m/z (relative intensity): 247 (100), 174 (70), 161 (65), 147 (18). HRMS (EI) calcd. for $C_{13}H_{17}N_3O_2$: 247.1321, found: 247.1310.

(–)-(1*R*,5*S*)-*N*-Acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-8-oxo-pyrido[1,2-a][1,5]diazocine-9-diazonium fluoroborate, 10b. To *N*-acetyl-9-aminocytisine **9b** (0.5 g, 2 mmol) in aqueous tetrafluoroboric acid (50 %, 5 mL) cooled to 0°C, was added sodium nitrite (0.140 g, 2 mmol). The mixture was stirred for 30 min at 0°C and filtered. MeOH (10 mL) and diethylether (25 mL) were added to the filtrate. The precipitated diazonium fluoroborate was collected, washed with diethyl ether (15 mL) then dried at 50°C for 15 h under vacuum (5.10^{-2} mbar) to yield **10b** (0.500 g, 71 %) as a yellow solid. Mp: 215°C (with decomposition). IR (KBr, cm^{-1}): 1002, 1038, 1058, 1096, 1262, 1296, 1324, 1366, 1422, 1460, 1544, 1626 (C=O), 1692 (C=O), 2244 (N_2). ^{1}H NMR (D_2O): δ 1.72 (s, 1H), 1.97 (s, 3H), 1.95-2.13 (m, 1H), 2.66 (br s, 1H), 2.92 and 3.12 (2 d, J = 13.6 Hz, 1H. 2 conformers), 2.46-3.65 (m, 2H), 3.92-4.25 (m, 3H), 4.48 and 4.49 (2 d, *J* = 13.6 Hz, 1H, 2 conformers), 6.82 and 6.88 (2 d, *J* = 8.8 Hz , 1H, 2 conformers), 8.60 and 8.65 (2 d, *J* = 8.8 Hz, 1H, 2 conformers). ^{13}C NMR (D_2O): (2 conformers) δ 19.3, 19.5, 22.3, 25.3, 25.7, 35.6, 35.9, 46.2, 50.2, 50.8, 50.5, 50.7, 94.7, 95.1, 109.9, 110.3, 145.4, 145.8, 156.8, 156.9, 170.0, 170.4, 172.4. ^{19}F NMR (D_2O): δ -150.96. MS (EI): m/z (relative intensity): 250 (56), 232 (100), 208 (28.5), 190 (47), 165 (59).

(–)-(1*R*,5*S*)-*N*-Methoxycarbonyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 11c;
(–)-(1*R*,5*S*)-*N*-methoxycarbonyl-11-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one, 12c and
(–)-(1*R*,5*S*)-*N*-methoxycarbonyl-9,11-dibromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 13c To a solution of *N*-methoxycarbonylcytisine **1c** (0.631 g; 2.54 mmol) in DMF (15 mL) was added dropwise NBS (0.461 g; 2.59 mmol) in DMF (5 mL) at RT. The mixture was stirred for 30 min, diluted with water (30 mL) and extracted with dichloromethane. Standard work up gave the bromo compounds **11c** and **12c** (relative ratio: 78/22) and the dibromo compound **13c** which were separated by chromatography on silica gel (5% MeOH/CH_2Cl_2).

11c: white solid (473 mg, 57%). $[\alpha]^{22}_D$ = -184 (c 1; $CHCl_3$). Mp: 199-200°C. IR (KBr, cm^{-1}): 1448, 1536, 1584, 1642 (C=O), 1696 (C=O).^{1}H NMR ($CDCl_3$): δ 1.91-2.03 (m, 2H), 2.49 (br s, 1H), 2.96-3.10 (m, 3H), 3.57 (br s, 3H), 3.92 (dd, *J* = 6.5, 15.8 Hz, 1H), 4.17 (d, *J* = 15.8 Hz, 1H), 3.95-4.30 (m, 2H), 5.99 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.4, 26.9, 34.2, 50.0, 50.2, 50.8, 52.8, 105.4, 112.5, 140.7, 148.6, 156.0, 159.4. MS (EI): m/z (relative intensity): 328 (19), 326 (21), 226 (28), 224 (30), 102 (100). Anal. Calcd. for $C_{13}H_{15}N_2O_3Br$: C, 47.72; H, 4.62; N, 8.52; O, 14.67. Found (%), C, 47.71; H, 4.61; N, 8.51; O, 14.36.

12c: white solid (141 mg, 17%). $[\alpha]^{22}_D$ = -37 (c 0.5; $CHCl_3$). Mp: 95-96°C. IR (KBr, cm^{-1}): 1448; 1536; 1584; 1642 (C=O); 1696 (C=O. NCOMe).^{1}H NMR ($CDCl_3$): δ 1.98 (br s; 2H), 2.47 (br s; 1H), 2.99-3.11 (m, 2H), 3.49 (br s, 1H), 3.56 (br s, 3H); 3.87 (dd, *J* = 6.5, 15.5 Hz, 1H), 4.13 (d, *J* = 15.5 Hz, 1H), 4.15-4.45 (m, 2H), 6.39 (d, *J* = 9.6 Hz, 1H); 7.43 (d, *J* = 9.6 Hz, 1H).^{13}C NMR ($CDCl_3$): δ 25.8, 26.9, 33.7, 47.8, 49.8, 50.0, 52.8, 99.1, 118.4, 142.6, 145.7, 156.1, 162.2. MS (EI): m/z (relative intensity): 328 (19), 326 (21), 226 (28), 224 (30), 102 (100). Anal. Calcd. for $C_{13}H_{15}N_2O_3Br$: C, 47.72; H, 4.62; N, 8.52; O, 14.67. Found C, 47.32; H, 4.45; N, 8.95; O, 14.79.

13c (20 mg, 2%). $[\alpha]^{22}_{D}$ = -54 (c 0.5; $CHCl_3$). Mp: 156°C. IR (KBr, cm^{-1}): 1236, 1444, 1515, 1570, 1686 (C=O, NCOMe).^{1}H NMR ($CDCl_3$): δ 1.99 (m, 2H), 2.49 (br s, 1H), 2.99-3.11 (m, 2H), 3.47 (br s, 1H), 3.57 (br s, 3H), 3.94 (dd, *J* = 6.5, 15.8 Hz, 1H), 4.17 (d, *J* = 15.8 Hz, 1H), 4.20-4.45 (m, 2H), 7.86 (s, 1H).^{13}C NMR ($CDCl_3$): δ 25.5, 26.7, 33.6, 47.5, 49.6, 51.3, 52.3, 97.9, 113.1, 143.6, 145.5, 155.9, 158.4. MS (EI): m/z (relative intensity): 408 (13), 406 ($M^{+\cdot}$, 33), 404 (15), 306 (11), 304 (21), 302 (10), 102 (100). Anal. Calcd. for $C_{13}H_{14}N_2O_3Br_2$: C, 38.45; H, 3.47; N, 6.89; O, 11.82. Found: C, 38.71; H, 3.63; N, 6.91; O, 11.75

(–)-(1*R*,5*S*)-*N*-Nitroso-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 11d *N*-Bromosuccinimide (1.87 g, 10.5 mmol) was added to *N*-nitroso cytisine **1d** (2 g, 10.5 mmol) in dichloromethane (100 mL) at 0°C. The mixture was stirred for 14 h and water was added. Extraction with dichloromethane and standard work up gave a mixture of **11d** and **12d**. Cristallization in ethyl acetate yielded **11d** (1.57 g, 50 %) as a white solid. $[\alpha]^{22}_{D}$ = -80 (c 0.5; $CHCl_3$). Mp: 252°C (EtOAc). IR (KBr, cm^{-1}): 1344, 1424 (NNO), 1534, 1584, 1654 (C=O).^{1}H NMR ($CDCl_3$): 2.18 (br s, 2H), 2.66 (br s, 1H, 1 conformer), 2.74-2.83 (m, 2H), 3.17 and 3.32 (2 br s, 1H, 2 conformers), 3.80 (dd, *J* = 6.4, 16 Hz, 1H, 1 conformer), 3.88-4.04 (m, 2H), 4.29 (d, *J* = 16 Hz, 1H, 1 conformer), 4.80 and 4.90 (2 d, *J* = 13 Hz, 1H, 2 conformers), 5.10 and 5.17 (2 d, *J* = 13 Hz, 1H, 2 conformers), 5.94 and 6.05 (2 d, *J* = 7.5 Hz, 1H, 2 conformers) 7.63 and 7.69 (2 d, *J* = 7.5 Hz, 1H, 2 conformers). δ^{13}C NMR ($CDCl_3$): (2 conformers) δ 25.9, 26.0, 27.0, 27.6, 33.9, 34.7, 44.8, 45.6, 49.7, 50.1, 55.6, 56.7, 105.5, 105.6, 113.6, 140.7, 146.7, 159.2. MS (EI): m/z (relative intensity): 299 (55), 297 (55), 269 (90), 267 (95), 242 (40), 240 (40), 228 (100), 226 (97). HRMS (EI) calcd. for $C_{11}H_{12}N_3O_2Br$: 297.0113 and 299.0093 found: 297.0110 and 299.0106.

(–)-(1*R*,5*S*)-9-Bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 11a. *N*-nitroso-9-bromocytisine **11d** (0.100 g, 0.337 mmol), hydrochloric acid (36%, 1 mL) were refluxed for 15 min. The mixture was cooled, basified (NH_4OH, 28%) and extracted with dichloromethane. Standard work up

afforded **11a** (0.086 g, 95%) as a yellow solid. $[\alpha]^{22}_{D}$ = -23 (c 1; $CHCl_3$), litt:[7] -56 (c 0.63; MeOH). Mp: 118°C. IR (KBr, cm^{-1}): 1106, 1458, 1540, 1570, 1634 (C=O), 3402 (NH). ^{1}H NMR ($CDCl_3$): δ 1.95 (br s, 2H), 2.05 (br s, 1H), 2.34 (br s, 1H), 2.92 (br s, 1H), 2.96-3.12 (m, 4H), 3.94 (dd, *J* = 6.5, 15.5 Hz, 1H), 4.17 (d, *J* = 15.5 Hz, 1H), 5.93 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 26.5, 28.0, 35.8, 51.5, 53.2, 54.1, 105.3, 112.2, 141.1, 151.5, 160.0. MS (EI): m/z (relative intensity): 270 (85), 268 (90), 227 (100), 225 (100), 189 (24), 187 (25), 82 (67). HRMS (EI) calcd. for $C_{11}H_{13}N_2OBr$: 268.0211 and 270.0192. Found: 268.0210 and 270.0183.

(–)-(1*R*,5*S*)-*N*-Methoxycarbonyl-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 14c. To a mixture of *N*-methoxycarbonylcytisine **1c** (2.5 g, 10.08 mmol) and silver trifluoroacetate (2.78 g, 12.58 mmol) in dichloromethane (100 mL) cooled 0°C, was added iodine (2.55 g, 10.04 mmol). The mixture was stirred for 12h at RT and filtered. The filtrate was washed with sodium thiosulfate (0.1 M) then water. Standard work up gave a crude product which was purified by flash chromatography (AcOEt) to give **14c** (2.07 g, 55%) as a yellow solid. $[\alpha]^{22}_{D}$ = -184 (c 0.5; $CHCl_3$). Mp: 220°C. IR (KBr, cm^{-1}): 1446, 1530, 1580, 1636 (C=O), 1696 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.96 (m, 2H), 2.48 (br s, 1H), 3.05-3.10 (m, 3H), 3.57 (br s, 3H), 3.92 (dd, *J* = 6.5, 15.9 Hz, 1H), 4.17 (d, *J* = 15.9 Hz, 1H), 4.20 (m, 2H), 5.88 (d, *J* = 7.3 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.5, 27.2, 34.2, 50.1, 50.6, 50.8, 52.9, 88.1, 106.8, 147.7, 149.8, 156.1, 160.2. MS (EI): m/z (relative intensity): 374 ($M^{+\cdot}$, 88), 285 (11), 272 (51), 102 (100). Anal. Calcd. for $C_{13}H_{15}N_2O_3I$: C, 41.73; H, 4.04; N, 7.48; O, 12.82. Found: C, 42.01; H, 4.21; N, 7.33; O, 12.71.

(–)-(1*R*,5*S*)-*N*-Nitroso-9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 14d. Under the conditions described for **14c**, *N*-nitrosocytisine **1d** (2 g, 9.13 mmol) gave **14d**: (1.57 g, 50 %) as a yellow solid. $[\alpha]^{22}_{D}$ = -84 (c 0.5; $CHCl_3$). Mp: 239°C (AcOEt). IR (KBr, cm^{-1}): 1342, 1420

(7) O'Neill, B. T. PCT Int. Appl. WO98 18,798, **1998**, *Chem Abstr*., **1998**, *119*, 4774k.

(NNO), 1530, 1580, 1648 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.17 (br s, 2H), 2.65-2.82 (m, 2H), 3.17 and 3.32 (2 s, 1H, 2 conformers), 3.88-4.04 (m, 2H), 4.27 (d, *J* = 16 Hz, 1H, 1 conformer), 4.80 and 4.90 (2 d, *J* = 13 Hz, 1H, 2 conformers), 5.10 and 5.17 (2 d, *J* = 13 Hz, 1H, 2 conformers), 5.83 and 5.95 (2 d, *J* = 7.5 Hz, 1H, 2 conformers) 7.86 and 7.93 (2 d, *J* = 7.5 Hz, 1H, 2 conformers). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 25.8, 25.9, 27.2, 27.8, 33.8, 34.6, 44.7, 45.3, 49.9, 50.3, 55.6, 56.7, 106.8, 147.6, 147.9, 155.2, 160.0. MS (EI): m/z (relative intensity): 345 (100), 315 (98), 286 (40), 272 (100), 130 (25). HRMS (EI) calcd. for $C_{11}H_{12}N_3O_2$ 344.9975, found: 344.9979.

(–)-(1*R*,5*S*)-*N*-Nitroso-9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 2d. To a solution of *N*-nitroso-9-bromocytisine **11d** (0.300 g, 1 mmol) in HMPA (1 mL), tetramethyltin (0.400 g, 2.2 mmol) and $ClPdBn(PPh_3)_2$ (0.035 g, 0.046 mmol) were added. The mixture was heated at 120°C for 15 min, cooled, quenched by addition of water and dichloromethane. It was then filtered through a pad of celite. The filtered cake was rinsed with dichloromethane and the filtrate was concentrated. Water (10 mL) was added to the residue and the aqueous layer was extracted with EtOAc. After standard work up, diethyl ether (20 mL) and pentane (20 mL) were poured onto the crude product. *N*-Nitroso-9-methylcytisine **2d** was isolated as a yellow solid (0.19 g, 81%). $[\alpha]^{22}_D$ = -80 (c 0.25; $CHCl_3$). Mp: 175°C. IR (KBr, cm^{-1}): 1344, 1366, 1426 (NNO), 1562, 1598, 1650 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.07 (br s, 3H), 2.16 (br s, 2H), 2.65-2.82 (m, 2H), 3.14 and 3.29 (2 s, 1H, 2 conformers), 3.73-4.03 (m, 3H), 4.27 (d, *J* = 13.9 Hz, 1H, 1 conformer), 4.76 and 4.88 (2 d, *J* = 13.3 Hz, 1H, 2 conformers), 5.09 and 5.17 (2 d, *J* = 13.3 Hz, 1H, 2 conformers), 5.95 and 6.06 (2 d, *J* = 6.9 Hz, 1H, 2 conformers), 7.11-7.16 (2 d, *J* = 6.9 Hz, 1H, 2 conformers). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 17.4, 26.7, 27.3, 27.6, 28.2, 34.2, 35.1, 45.3, 46.5, 48.9, 49.3, 56.2, 57.6, 105.6, 127.4, 127.6, 136.5, 144.2, 163.7. MS (EI): m/z (relative intensity): 233 (60), 203 (40), 174 (55), 160 (100). HRMS (EI) calcd. for $C_{12}H_{15}N_3O_2$: 233.1164, found: 233.1167.

(–)-(1*R*,5*S*)-*N*-Nitroso-9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 5d. To a solution of *N*-nitroso-9-bromocytisine **11d** (0.300 g,

1 mmol) in dioxane (2 mL), tri-n-butylvinyltin (0.476 g, 1.5 mmol) and $Cl_2Pd(PPh_3)_2$ (0.035 mg, 0.046 mmol) were added. The mixture was heated at 120°C for 60 min, cooled and concentrated. Potassium fluoride (saturated solution, 10 mL) was added and the mixture was stirred overnight. After standard work up, and flash chromatography on silica gel (5% MeOH/CH_2Cl_2), *N*-nitroso-9-vinylcytisine **5d** (0.181 g, 74%) was isolated as a white solid. $[\alpha]^{22}_D$ = -194 (c 1; $CHCl_3$). Mp: 150°C. IR (KBr, cm^{-1}): 1364, 1424 (NNO), 1552, 1574, 1610, 1644 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.16 (m, 2H), 2.65-2.83 (m, 2H), 3.17 and 3.33 (2 s, 1H, 2 conformers), 3.73-4.29 (m, 3H), 4.75 and 4.85 (2 d, *J* = 12.7 Hz, 1H, 2 conformers), 5.07 and 5.14 (2 d, *J* = 15.5 Hz, 1H, 2 conformers), 5.27 (d, *J* = 11.3 Hz, 1H), 5.96 (d, *J* = 17.7 Hz, 1H), 6.05 and 6.15 (2 d, *J* = 7.3 Hz, 1H, 2 conformers), 6.76 (dd, *J* = 11.3, 17.7 Hz, 1H), 7.35 and 7.40 (2 d, *J* = 7.3 Hz, 1H, 2 conformers). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 25.2, 25.3, 26.4, 27.0, 31.3, 34.1, 44.1, 45.1, 47.9, 48.3, 55.0, 56.2, 104.9, 115.0, 115.1, 124.8, 124.9, 131.1, 133.9, 145.2, 160.9. MS (EI): m/z (relative intensity): 245 (87), 215 (62), 186 (35), 172 (100), 158 (50), 144 (25). HRMS (EI) calcd. for $C_{13}H_{15}N_3O_2$: 245.1164, found: 245.1171.

(–)-(1*R*,5*S*)-*N*-Nitroso-9-allyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 4d. To a solution of *N*-nitroso-9-bromocytisine **11d** (0.250 g, 0.84 mmol) in HMPA (1.5 mL), tri-n-butylallyltin (0.416 g, 1.26 mmol) and $ClPdBn(PPh_3)_2$ (0.032 mg, 0.042 mmol) were added. The mixture was heated at 120°C for 30 min, cooled, diluted with dichloromethane (10 mL) and water (10 mL) then filtered through a pad of celite. The solid was rinsed with dichloromethane and the filtrate concentrated. Water was added to the residue and the aqueous layer was extracted with EtOAc. After standard work up, the crude product was stirred with KF (saturated solution, 10 mL) for 4 h to yield after flash chromatography on silica gel (5% MeOH/CH_2Cl_2), *N*-nitroso-9-allylcytisine **4d** as a yellow solid (0.120 g, 55%). $[\alpha]^{22}_D$ = -113 (c 0.5; $CHCl_3$). Mp: 112°C. IR (KBr, cm^{-1}): 1332, 1364, 1430 (NNO), 1556, 1590, 1644 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.16 (m, 2H), 2.62-2.83 (m, 2H), 3.15 and 3.31 (2 br s, 1H, 2 conformers), 3.23 (m, 2H), 3.77-4.03 (m, 3H), 4.26 (d, *J* = 15.5 Hz, 1H, 1 conformer), 4.77 and 4.88 (2 d, *J* = 13 Hz, 1H, 2 conformers),

5.06-5.19 (m, 3H), 5.93 (m, 1H), 5.99 and 6.09 (2 d, J = 7 Hz, 1H, 2 conformers), 7.10 and 7.15 (2 d, J = 7 Hz, 1H, 2 conformers). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 26.4, 26.5, 27.5, 28.1, 34.2, 35.1, 34.8, 45.3, 46.5, 48.9, 49.3, 56.2, 57.6, 105.6, 116.9, 117.0, 129.0, 129.1, 135.8, 136.0, 136.1, 144.9, 163.0. MS (EI): m/z (relative intensity): 259 (77), 229 (70), 200 (25), 186 (100), 172 (22), 158 (28). HRMS (EI) calcd. for $C_{14}H_{17}N_3O_2$.259.1321, found: 259.1323.

(–)-(1*R*,5*S*)-*N*-Methoxycarbonyl-9-trimethylstannyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 15c. To a mixture of *N*-methoxycarbonyl-9-iodocytisine **14c** (1.890 g, 5.051 mmol) and $Pd(PPh_3)_4$ (0.290 g, 0.251 mmol) in dry dioxane (100 mL) was added hexamethyldistannane (2.150 g, 6.563 mmol). The mixture was refluxed for 12h, cooled and filtered. The filtrate was concentrated and extracted with ethyl acetate. After standard work up the crude product was purified on a silica gel column (15% MeOH/AcOEt) to give **15c** (0.92 g, 44%) as a white solid. Mp: 215°C. ^{1}H NMR ($CDCl_3$): δ 0.26 (s, J^2_{Sn-H} = 54 Hz, 9H), 1.95 (m, 2H), 2.46 (br s, 1H), 3.06 (m, 3H), 3.56 (br s, 3H), 3.83 (dd, J = 6.4, 15.6 Hz, 1H), 4.10 (d, J = 15.6 Hz, 1H), 4.10-4.40 (m, 2H), 6.09 (d, J = 6.3 Hz, 1H), 7.41 (d, J = 6.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ : -9.7 (J^1_{Sn-C} = 356 Hz), 25.6, 27.2, 34.1, 48.6, 49.9, 51.0, 52.4, 106.2, 131.7, 146.4, 148.7, 156.0, 166.0.

(–)-(1*R*,5*S*)-*N*-Nitroso-9-trimethylstannyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido [1,2-a][1,5]diazocin-8-one, 15d. To a mixture of *N*-nitroso-9-iodocytisine **14d** (2.1 g, 6.09 mmol) and hexamethyldistannane (3.1 g, 9.46 mmol) in dry dioxane (30 mL) was added $Pd(PPh_3)_4$ (0.500 g, 0.432 mmol). The mixture was refluxed for 3h, cooled and filtered. The filtrate was concentrated. Ethyl acetate was added followed by petroleum ether to precipitate **15d** (1.637 g, 70%) as a white solid. Mp: 220°C. $[\alpha]^{22}_D$ = -68 (c 0.5; $CHCl_3$). IR (KBr, cm^{-1}): 1424 (NNO), 1536, 1564, 1630 (C=O), 2922. ^{1}H NMR ($CDCl_3$): δ 0.24 (s, J^2_{Sn-H} = 54 Hz, 9H), 2.15 (m, 2H), 2.60-2.85 (m, 2H), 3.12 and 3.31 (2 s, 1H, 2 conformers), 3.70-4.05 (m, 3H), 4.18 (d, J = 15.8 Hz, 1H), 4.80 and 4.90 (2 d, J = 15.4 Hz, 1H, 2 conformers), 5.09 and 5.13 (2 d, J = 15.4 Hz, 1H, 2 conformers), 6.02 and 6.13 (2 d, J = 6.5 Hz, 1H), 7.35 and 7.40 (2 d, J = 6.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): (2 conformers) δ - 9.5 (J^1_{Sn-C} = 358 Hz), 26.0, 26.1, 57.2, 27.8, 34.8, 34.6, 44.9, 45.9, 48.2, 48.7, 55.7, 57.0,

106.4, 132.6, 132.8, 146.5, 147.0, 165.9. MS (EI): m/z (relative intensity): 388 (15, ^{124}Sn), 386 (12, ^{122}Sn), 384 (82, ^{120}Sn), 383 (32, ^{119}Sn), 382 (62, ^{118}Sn), 381 (25, ^{117}Sn), 380 (35, ^{116}Sn), 372 (18, ^{124}Sn), 370 (16, ^{122}Sn), 368 (100, ^{120}Sn), 367 (39, ^{119}Sn), 366 (75, ^{118}Sn), 365 (31, ^{117}Sn), 364 (45, ^{116}Sn), 220 (40). HRMS (EI) calcd. for $C_{14}H_{22}N_3O_2Sn$: 384.0734 (MH^+), found: 384.0725 (MH^+).

(–)-(1*R*,5*S*)-*N*-Methoxycarbonyl-9-(4'-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one, 3c. To a mixture of *N*-methoxycarbonyl-9-(trimethylstannyl)cytisine **15c** (0.200 g, 0.486 mmol), dioxane (2 mL), $PdCl_2(PPh_3)_2$ (0.034 g, 0.048 mmol) and LiCl (0.100 g, 2.36 mmol) was added 1-bromo-4-fluorobenzene (0.100 mL, 0.910 mmol). The mixture was heated at 120°C for 2 h in a pressure tube, cooled and filtered. The filtrate was concentrated and the crude product purified by chromatography on silica gel (3% MeOH/CH_2Cl_2) to give **3c** (0.120 g, 72 %) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.92-2.03 (m, 2H), 2.49 (br s, 1H), 3.07 (br s, 3H), 3.57 (br s, 3H), 3.93 (dd, *J* = 6.5, 15 Hz, 1H), 4.19 (d, *J* = 15 Hz, 1H), 4.10-4.30 (m, 2H), 6.15 (d, *J* = 6.5 Hz, 1H), 7.06-7.70 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 25.8, 27.3, 34.5, 49.4, 50.2, 51.1, 52.8, 105.6, 114.8 (d, $J^2_{C\text{-}F}$ = 21.4 Hz), 130.2 (d, $J^3_{C\text{-}F}$ = 8.2 Hz), 131.9 (d, $J^4_{C\text{-}F}$ = 1.9 Hz), 133.4, 137.2, 148.1, 156.2, 161.9, 162.1 (d, $J^1_{C\text{-}F}$ = 246.5 Hz). ^{19}F NMR ($CDCl_3$): δ -115.56.

(–)-(1*R*,5*S*)-*N*-Nitroso-9-(4'-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido [1,2-a][1,5]diazocin-8-one, 3d. Under the same conditions *N*-nitroso-9-(trimethylstannyl)cytisine **15d** (0.300 g, 0.781 mmol) gave **3d**: (165 mg, 65 %) as a white solid. $[\alpha]^{22}_D$ = -102 (c 0.25; $CHCl_3$). Mp: 200-201°C. IR (KBr, cm^{-1}): 1428 (NNO), 1470, 1508, 1552, 1638 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.15 (m, 2H), 2.65-2.83 (m, 2H), 3.15 and 3.30 (2 s, 1H, 2 conformers), 3.78 (dd, *J* = 6.4, 15.9 Hz, 1H, 1 conformer), 3.89-4.02 (m, 3H), 4.25 (d, *J* = 15.9 Hz, 1H, 1 conformer), 4.77 and 4.85 (2 d, *J* = 13 Hz, 1H, 2 conformers), 5.13 (m, 1H, 2 conformers), 6.09 and 6.18 (2 d, *J* = 7.3 Hz, 1H, 2 conformers), 7.04 (dd ~ t, J_{HH}, J_{HF} = 8.6 Hz, 2H), 7.35 and 7.40 (2 d, *J* = 7.3 Hz, 1H, 2 conformers), 7.62 (m, 2H). ^{13}C NMR ($CDCl_3$): (2 conformers) δ 26.3, 26.4, 27.6, 28.2, 34.4, 35.3, 45.3, 46.3, 49.2, 49.7, 56.2, 57.4, 106.1, 115.2 (d, $J^2_{C\text{-}F}$ = 21.4 Hz), 127.9, 128.0, 130.6 (d, $J^3_{C\text{-}F}$ = 7.5 Hz), 133.2 (d,

J^4_{C-F} = 1.9 Hz), 137.1, 146.8, 162.1, 162.6 (d, J^1_{C-F} = 245.6 Hz). ^{19}F NMR ($CDCl_3$): -115.18. MS (EI): m/z (relative intensity): 313 (80), 283 (55), 254 (27), 240 (100). HRMS (EI) calcd. for $C_{17}H_{16}N_3O_2F$ 313.1227, found: 313.1223

(–)-(1*R*,5*S*)-9-(4'-Fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5] diazocin-8-one, 3a. *N*-Nitroso-9-(4'-fluorophenyl)cytisine **3d** (0.100 g, 0.32 mmol) and HCl (3M, 1 mL) were refluxed for 15 min, cooled and quenched with water (10 mL). The aqueous layer was washed with dichloromethane, basified (NH_4OH, 28%) and extracted with dichloromethane. Standard work up afforded **3a** (0.086 g, 95 %) as a colorless oil. $[\alpha]^{22}_D$ = -40 (c 0.25, MeOH). IR (KBr, cm^{-1}): 1554, 1632 (C=O), 3420 (NH). ^{1}H NMR ($CDCl_3$): δ 1.57 (br s, 1H), 1.96 (br s, 2H), 2.36 (br s, 1H), 2.92-3.14 (m, 5H), 3.96 (dd, *J* = 6.5, 15.7 Hz, 1H), 4.18 (d, *J* = 15.7 Hz, 1H), 6.09 (d, *J* = 7.2 Hz, 1H), 7.06 (04 (dd ~ t, J_{HH}, J_{HF} = 8.8 Hz, 1H), 7.25-7.48 (m, 2H), 7.68 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 26.2, 27.8, 35.6, 50.1, 52.9, 53.7, 104.8, 114.7 (d, J^2_{C-F} = 21.2 Hz), 126.2, 127.1, 128.2, 130.1 (d, J^3_{C-F} = 7.9 Hz), 133.3 (d, J^4_{C-F} = 3.3 Hz), 136.8, 150.3, 162.4 (d, J^1_{C-F} = 246 Hz), 162.5. ^{19}F NMR ($CDCl_3$): -115.78. MS (EI): m/z (relative intensity): 284 (98), 266 (100), 241 (80), 223 (80), 210 (20), 203 (25), 185 (35). HRMS (EI) calcd. for $C_{17}H_{17}N_2OF$: calcd.: 284.1325, found: 284.1325.

General procedure for the cross coupling reactions of 4-[^{18}F]fluorobromobenzene 16 with 15d. No carrier-added[^{18}F]fluoride was produced *via* the ^{18}O[p,n]^{18}F nuclear reaction using enriched water (90-98%, 1 mL) target by the cyclotron (CGR MeV 325) at the PET centre of Caen (Cyceron). 4-[^{18}F]Fluorobromobenzene **16** was prepared in 25-35% yield (90 min total synthesis time, radiochemical purity > 95%) from [^{18}F]KF/Kryptofix[222] according to a described procedure.[8] The bromide **16** (6-7 MBq, 0.17 - 0.19 mCi) in the solvent (0.5 mL) was transferred into a vessel containing the stannane **15d** (5 mg, 1.3

(8) (a) Allain-Barbier, L.; Lasne, M. C.; Perrio-Huard, C.; Moreau, B.; Barré, L. *Acta. Chem. Scand.* **1998**, *52*, 480. (b) Forngren, T.; Andersson, Y.; Lamm, B.; Langström, B. *Acta Chem. Scand.* **1998**, *52*, 475.

μmol), the catalyst (1.6 μmol) and the solvent (1 mL). The mixture was heated for 10 min at 110°C, cooled, diluted with dichloromethane (2 mL) and filtered through a Sep-Pak (silica gel from Millipore Waters). Elution with dichloromethane (2 x 5 mL) gave 4-[^{18}F]fluorophenylcytisine **[^{18}F]3d** (radiochemical yields: see Table 2).

9-(4'-[^{18}F]-fluorophenyl)cytisine, [^{18}F]3a. Hydrochloric acid (3M, 300 μL) was added to *N*-nitroso-9-(4-[^{18}F]-fluorophenyl)cytisine **[^{18}F]3d**. The vial was sealed under nitrogen, heated to 110°C for 2 min, rapidly cooled to RT and quenched with water (1 mL). The aqueous layer was washed with dichloromethane (2 x 2 mL), basified (NH_4OH), and extracted with dichloromethane (2 x 2 mL). After evaporation of the volatile compounds under nitrogen, the crude product (**[^{18}F]3a**: 75% of the total radioactivity) was purified by HPLC (column A, eluent: 5% B (B = EtOH/H_2O/$EtNH_2$, v:v:v: 100:2:2)/ CH_2Cl_2, flow: 4 mL.min^{-1}, λ = 254 nm] to give **[^{18}F]3a**. Retention time: 15.4 min.