Supplementary Material for:

Total Synthesis of (+/-)-Cytisine

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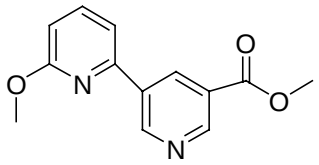
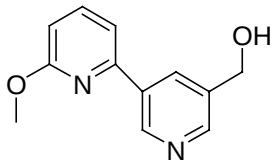
Total Synthesis of (+/-)-Cytisine (**1**)



6-Methoxy-[2,3']bipyridinyl-5'-carboxylic acid methyl ester (**8a**): To a 200 ml round bottom flask was introduced 5.0 gm (26.5 mmol, 1.1 equiv) 2-methoxy-6-bromopyridine (**3**) (commercial or easily prepared by reaction of 2,6-dibromopyridine with sodium methoxide in methanol; see: Comins, D. L., Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69-73), 5.2 gm (24.2 mmol, 1 equiv.) methyl-5-bromonicotinate (**7**) and 12.2 ml (14 gm, 24.2 mmol, 1 equiv.) hexabutyldistannane. The mixture was dissolved in 80 ml of dry DMF and purged of all oxygen by three vacuum / argon cycles. The solution was treated with 1.83 gm (2.4 mmol., 10 mol.%) benzyl bis (triphenylphosphine)palladium (II) chloride followed by one additional vacuum / argon purge cycle. The reaction mixture was plunged into a preheated oil bath at 130 $^{\circ}$ C for one hour and then cooled to ambient temperature. The reaction mixture was filtered through celite and the filtrate was partitioned between 1.0 L of 50 % brine solution (prepared by diluting 500 ml of saturated aqueous brine solution with 500 ml water) and 300 ml of 1:1 /hexane : ethyl acetate solution. The solution was adjusted to pH 8 with saturated carbonate solution. The organic phase was separated and the aqueous phase was extracted with 1:1 / hexane : ethyl acetate until no further product was obtained as evidenced by thin layer analysis. The combined organic layers were washed with brine and then dried and evaporated in vacuo. The residue was partitioned between acetonitrile : pentane to remove alkyl stannane byproducts. The acetonitrile phase was separated and evaporated in vacuo. The residue was quickly passed through a pad of silica gel eluting with 75 : 25 / hexane : ethyl acetate. The procedure afforded 2.38 gm (40 %) of the desired product (**8a**) as a solid after trituration with pentane. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.43 (s, 1H), 9.21 (s, 1H), 8.87 (s, 1H), 7.68 (dd, 1H, J = 8.3 Hz, J = 7.3 Hz), 7.41 (d, 1H, J = 7.3 Hz), 6.77 (d, 1H, J = 8.3 Hz), 4.04 (s, 3H), 3.99 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 164.0, 151.7, 150.8, 150.4, 139.3, 134.7,

134.3, 125.8, 113.1, 110.8, 53.4, 52.5 ppm; ms (m/z) 245 (p+1); HRMS calc'd for H^+/ $C_{13}H_{12}N_2O_3$: 245.0926; found: 245.0917.

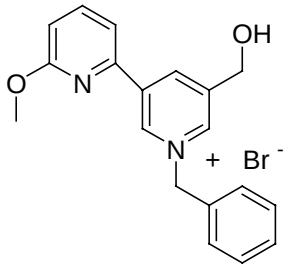
Alternatively, 6-Methoxy-[2,3']bipyridinyl-5'-carboxylic acid methyl ester (**8a**) may be prepared in the following manner: To a dry 50 ml round bottom flask was introduced 3.10 ml (7.8 mmol.) of 2.5 M n-butyllithium in hexanes and the vessel was cooled to – 40 °C. A 10 ml anhydrous ether solution of 1.33 gm (7.1 mmol,) 2-methoxy-6-bromo-pyridine (**3**) (commercial or easily prepared by reaction of 2,6-dibromopyridine with sodium methoxide in methanol; see: Comins, D. L., Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69-73), precooled to –40 °C in a jacketed addition funnel above the reaction, was slowly added into the reaction flask. The reaction mixture was stirred at – 40 °C for 20 minutes. The orange reaction mixture was treated dropwise with 0.881 ml (7.8 mmol) trimethoxyborane The color changed to rose and the temperature increased slightly during addition. The reaction mixture was stirred while at – 40 °C for 30 minutes and allowed to warm to room temperature over 30 minutes. The reaction mixture was transferred to a 125 ml S/N round bottom flask using a small amount of methylene chloride to aid the transfer. The liquid was evaporated in vacuo to afford a foam. In a second flask was combined 1.39 gm (6.4 mmol,) methyl-5-bromonicotinate (**7**) and 372 mg (0.32 mmol) tetrakistriphenylphosphine palladium (0) in 7 ml of dry DME. The mixture was stirred for 15 min and then added to the crude borate residue and additional DME. Total volume; 25 ml DME. The reaction mixture was treated with 2.43 gm (16 mmol) cesium fluoride and a reflux condenser was attached to the flask. The reaction mixture was heated under reflux over 18 hours. The reaction mixture was then partitioned between 220 ml of ethyl acetate and 50 ml water. The organic layer was washed twice with 60 ml of water and then with 90 ml of saturated brine solution. The solution was dried over sodium sulfate and evaporated in vacuo. The residue was taken up in the minimum amount of hot ethyl acetate and cooled to ambient temperature. The solution was treated with hexanes whereupon crystal formation occurred. The solid was chromatographed on silica gel (75 gms) to remove triphenylphosphine eluting with 85:15 / hexane:ethyl acetate. There was obtained 0.85 gms (54 %) of the desired material (**8a**).



(6-Methoxy-[2,3']bipyridinyl-5'-yl)-methanol (**8b**): A solution of 6-Methoxy-[2,3']bipyridinyl-5'-carboxylic acid methyl ester (**8a**) (0.65 gm; 2.5 mmol) in 50 ml of anhydrous ether was cooled to 0 °C. The solution was treated with 3.03 ml (3.03 mmol) of a 1M solution of lithium aluminum hydride in ether. The reaction mixture becomes a bright orange suspension. The ice bath was removed and the mixture was allowed to warm to ambient temperature and then stirred for 2.5 hours. The excess reducing agent was quenched by the sequential addition of 115 ul water, 115 ul 25 % sodium hydroxide solution and 3 X 115 ul water. The bright orange color fades to yellow. After stirring for 20 minutes, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl

acetate. The organic phase was separated, washed with brine solution and then dried over sodium sulfate. The residue after evaporation amounted to 541 mg (100 %) of the desired product (**8b**) which was used without purification.

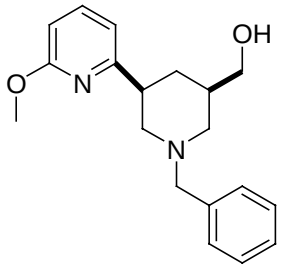
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (s, 1H), 8.47 (s, 1H), 8.30 (s, 1H), 7.57 (dd, 1H, J = 8.3 Hz, J = 7.3 Hz), 7.26 (d, 1H, J = 7.3 Hz), 6.68 (d, 1H, J = 8.3 Hz), 4.76 (s, 2H), 4.42 (br.s, 1H), 3.95 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0, 151.8, 147.8, 146.7, 139.2, 137.0, 134.5, 132.9, 113.0, 110.3, 62.2, 53.3 ppm; ms (m/z) 217 (p+1); HRMS calc'd for H^+ / $C_{12}H_{12}N_2O_2$: 217.0977; found: 217.0998.



1'-Benzyl-5'-hydroxymethyl-6-methoxy-[2,3']bipyridinyl-1'-ium; bromide (**10**): A solution of 87.4 mg (0.4 mmol) (6-Methoxy-[2,3']bipyridinyl-5'-yl)-methanol (**8b**) in 8 ml of dry acetonitrile was treated with 58 ul (0.49 mmol) benzyl bromide. The reaction mixture was heated under reflux for 30 min whereupon a precipitate began to form. Heating continued for a total of 2 hrs and then the mixture was allowed to cool to ambient temperature. Upon filtration there was obtained 115 mg (75 %) of the desired material (**10**) which was used directly in the next transformation.

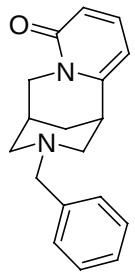
A solution of 404 mg (1.8 mmol) (6-Methoxy-[2,3']bipyridinyl-5'-yl)-methanol (**8b**) in 15 ml of dry acetonitrile was treated with 267 ul (2.2 mmol) benzyl bromide. The reaction mixture was heated under reflux for 5 min whereupon a precipitate began to form. Heating continued for a total of 1.5 hrs and then the mixture was allowed to cool to ambient temperature. Upon filtration there was obtained 494 mg (68 %) of the desired material (**10**).

^{1}H NMR (DMSO-d, 400 MHz) δ 9.78 (s, 1H), 9.11 (s, 2H), 7.95 (dd, 1H, J = 8.3 Hz, J = 7.4 Hz), 7.85 (d, 1H, J = 7.4 Hz), 7.59, (d, 2H, J = 7.6 Hz), 7.42 (m, 3H), 6.99 (d, 1H, J = 8.3 Hz), 5.98 (s, 2H), 5.93 (br.s, 1H), 4.78 (s, 2H), 3.97 (s, 3H) ppm; ^{13}C NMR (DMSO-d, 100 MHz) δ 163.8, 147.0, 144.0, 141.6, 141.4, 140.9, 139.9, 137.5, 134.5, 129.4, 129.3, 129.0, 115.0, 112.6, 63.5, 59.6, 53.5 ppm; ms (m/z) 307 (p-Br^-).



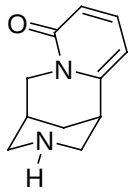
(1'-Benzyl-6-methoxy-1',2',3',4',5',6'-hexahydro-[2,3']bipyridinyl-5'-yl)-methanol (**11**): A solution of 400 mg (1.03 mmol) 1'-Benzyl-5'-hydroxymethyl-6-methoxy-[2,3']bipyridinyl-1'-ium bromide (**10**) in 40 ml of methanol containing 286 ul (2.06 mmol) triethylamine was treated with 40 mg platinum oxide and placed under 50 psi hydrogen pressure and agitated in a Parr Apparatus. After 3.5 hrs, the hydrogenation was halted and the catalyst removed by filtration. The filtrate was evaporated in vacuo and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase was washed with saturated brine solution, separated and then dried over sodium sulfate. The solution was evaporated in vacuo to afford 320 mg (100 %) of an 85 / 15 mixture of cis and trans isomers as measured from the crude ^{1}H NMR spectrum and integration of the individual pyridine protons. The crude material was chromatographed on silica gel eluting with 95:5:1 / methylene chloride: methanol: conc. ammonium hydroxide to afford 250 mg of the less polar cis isomer (**11**).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, 1H, J = 8.3 Hz, J = 7.2 Hz), 7.34 - 7.20 (m, 5 H), 6.68 (d, 1H, J = 7.3 Hz), 6.53 (d, 1H, J = 8.2 Hz), 3.88 (s, 3H), 3.56 (s, 2H), 3.55 - 3.44 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 161.0, 138.7, 137.9, 129.2, 128.1, 127.0, 114.1, 107.7, 66.2, 63.3, 59.0, 56.6, 53.1, 43.6, 39.0, 33.1 ppm; HRMS calc'd for H^+ / $C_{19}H_{24}N_2O_2$: 313.1916; found: 313.1920.



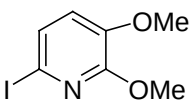
3-Benzyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (N-benzyl cytisine) (**13**): A flame dried round bottom flask was charged with 55 mg (176 mmol) (1'-Benzyl-6-methoxy-1',2',3',4',5',6'-hexahydro-[2,3']bipyridinyl-5'-yl)-methanol (**11**) from above and 3 ml of anhydrous methylene chloride. The solution was cooled to 0° C and was treated with 49 ul (352 mmol) of triethyl amine and 20 ul (265 mmol) mesyl chloride. The reaction mixture was stirred at 0° C for 30 min and then partitioned between 50 ml of methylene chloride and 15 ml of water. The organic phase was washed with 15 ml of saturated brine solution, separated, dried over sodium sulfate and evaporated in vacuo. The crude residue (75 mg) was rapidly passed through a plug of silica gel (2 gm) eluting with 96 : 4 / methylene chloride :

methanol to afford 60 mg (87 %) of the desired mesylate intermediate (**11a**) which was used directly in the next reaction. A flame dried round bottom flask was charged with 60 mg (154 mmol) of the mesylate from above and 10 ml of anhydrous toluene. The solution was heated under reflux for 3 hrs. The reaction mixture was cooled to ambient temperature and evaporated in vacuo. The residue was purified chromatographically on silica gel (3 gm) eluting with 95 : 4 : 1 / methylene chloride : methanol : ammonium hydroxide (aq) to afford 36 mg (84 %) of N-benzyl cytisine (**13**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 – 6.98 (br.m., 6H), 6.46(d, 1H, J = 9Hz), 5.88 (d, 1H, J = 6 Hz), 4.08 (d, 1H, J = 16 Hz) 3.86 (dd, 1H, J = 15 Hz, J = 7 Hz), 3.40 (q, 2H, J = 13 Hz), 2.91 (br.s, 2H), 2.83 (d, 1H, J = 10 Hz), 2.41 (br.s, 1H), 2.32 (dd, 2H, J = 10Hz), 1.83 (q, 2H, J = 13Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 151.7, 138.8, 138.3, 128.4, 127.1, 116.7, 104.8, 104.8, 62.2, 60.2, 60.1, 50.2, 35.7, 28.3, 26.1 ppm. HRMS calc'd for H^+ / $C_{18}H_{20}N_2O$: 281.1654; found: 281.1631.



1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one ((+/-)-cytisine) (**1**): To a flame dried round bottom flask equipped with stir bar and condenser was added 150 mg (0.53 mmol) 3-benzyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (**13**) together with 730 mg (11.6 mmol) ammonium formate and 15 ml of methanol. The solution was treated with 60 mg of Pearlman's catalyst ($Pd(OH)_2$) and heated under reflux for 20 min where upon tlc analysis indicated starting material was consumed (95/4/1 CH_2Cl_2 /MeOH / NH_4OH). The reaction mixture was filtered and concentrated to an oil. The crude material was chromatographed on silica gel eluting with 95:4:1 / CH_2Cl_2 :MeOH : NH_4OH to afford 81 mg of cytisine (**1**) as an off white solid (80 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (dd, 1H, J = 9hz, J = 7Hz), 6.43 (d, 1H, J = 9Hz), 5.97 (d, 1H, J = 7 Hz), 4.11 (d, 1H, J = 16 Hz) 3.87 (dd, 1H, J = 15 Hz, J = 7 Hz), 3.10 - 2.90 (br.m, 5H), 2.88 (br.s, 1H), 2.41 (br.s, 1H), 2.30 (br.s, 1H), 1.93 (br.s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 151.3, 138.9, 116.6, 105.1, 54.1, 53.1, 49.8, 35.6, 27.8, 26.4 ppm. HRMS calc'd for H^+ / $C_{11}H_{14}N_2O$: 191.1184; found: 191.1184. This material displayed identical ^{1}H NMR and ^{13}C NMR spectra when compared with a sample of (-)-cytisine obtained from Austin Chemical Co., Buffalo Grove Il. and The Chengdu Institute of Zhong Hui. China.

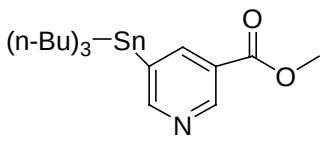
Total Synthesis of (+/-)-9-methoxycytisine (**20**)



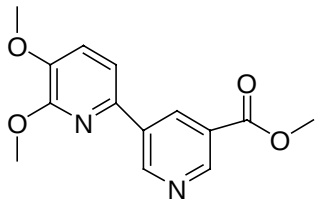
2,3-dimethoxy-6-iodopyridine (**14**): To a 500 ml round bottom flask was introduced 14 gm (80.5 mmol) of 2–bromo-3-hydoxypyridine (commercial), 22.3 gm (161 mmol) potassium carbonate and 180 ml of water. The mixture was treated with 21.0 gm (82.9 mmol) of iodine and was stirred at ambient temperature for 1.5 hrs. The reaction mixture was then cooled to 5 ^{O} C in an ice – water bath and treated with 2N HCl until pH = 7.0 and then carefully continued the addition of 2N HCl until solids began to appear (approx. pH = 6.0). The solids were filtered and dried under N_2 to afford 14.9 gm (58%) of 2 –bromo-6-iodo-3-hydoxypyridine which was used directly in the next transformation. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, 1H, J = 8 Hz), 6.98 (d, 1H, J = 8 Hz), 5.52 (s, 1H) ppm. ms (m/z) = 299, 301 (p+1).

To a 100 ml round bottom flask under nitrogen was introduced 14.9 gm (49.5 mmol) of 2 –bromo-6-iodo-3-hydoxypyridine and 30 ml of DMF. The solution was treated with 6.22 gm (45.1 mmol) of potassium carbonate and 10.77 ml (24.6 gm; 173.3 mmol) methyl iodide and then heated to 100 ^{O} C for 2 hrs. The reaction mixture was allowed to cool to ambient temperature and 100 ml of water was introduced with formation of a precipitate. The mixture was stirred for 30 min and then filtered to afford 14.6 gm (94 %) of solid 2 –bromo-6-iodo-3-methoxypyridine which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, 1H, J = 8 Hz), 6.81 (d, 1H, J = 8 Hz), 3.86 (s, 3H) ppm. ms (m/z) = 314, 316 (p+1).

To a 25 ml round bottom flask under nitrogen was dissolved 4.95 gm (15.77 mmol) of 2–bromo-6-iodo-3-methoxypyridine in 10 ml of DMF. The solution was treated with 1.25 gm (23 mmol) of fresh sodium methoxide and the reaction mixture was heated to 100^{O} C for 1 hr. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate and methylene chloride. The organic phase was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with methylene chloride to afford 3.48 gm (83 %) of 2,3-dimethoxy-6-iodo-pyridine (**14**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (d, 1H, J = 8 Hz), 6.68 (d, 1H, J = 8 Hz), 3.94 (s, 3H), 3.79 (s, 3H) ppm. ms (m/z) = 266 (p+1).

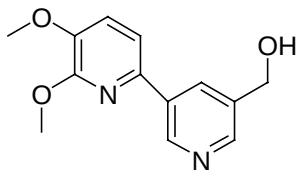


Methyl-5-(tri-n-butyl)stannylnicotinate (**9**): To a flame dried round bottom flask equipped with a condenser and an argon inlet was introduced 10 gm (46.29 mmol) methyl-5-bromonicotinate (**7**), 23.38 ml (26.8 gm; 46.29 mmol) hexabutyldistannane, 1.7 gm (2.3 mmol.) benzyl bis (triphenylphosphine)palladium (II) chloride and 100 ml DMF. The reaction mixture was heated to 130 ^{O} C for 1 hour and then cooled to ambient temperature. The reaction mixture was filtered through celite and the filtrate was partitioned between 1.0 L of 50 % brine solution and 1 liter of 1:1 / hexane : ethyl acetate. The solution was adjusted to pH 8 with saturated bicarbonate solution. The organic phase was separated and the aqueous phase was extracted with 1/1 hexane ethyl acetate until no further product was obtained. The combined organic layers were washed with brine and then dried and evaporated. The residue was partitioned between acetonitrile / pentane to remove alkyl stannane byproducts. The acetonitrile phase was separated and evaporated in vacuo. The residue chromatographed on silica gel eluting with 9/1 hexane / ethyl acetate. The procedure afforded 8.66 gm (44 %) of the desired product (**9**) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.1 (br.s, 1H), 8.72 (br.s, 1H), 8.32 (br.s, 1H), 3.93 (s, 3H), 1.5 (br.m, 6H), 1.3 (br.m, 6H), 1.1 (br.m, 6H), 0.87 (t, 9H, J = 7 Hz) ppm. ms (m/e) 424, 426, 428, (p+1).

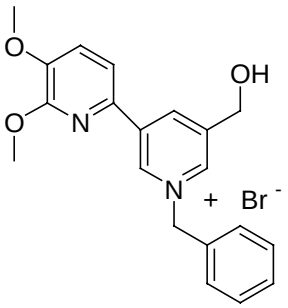


5,6-dimethoxy-[2,3']bipyridinyl-5'-carboxylic acid methyl ester (**15**): To a flame dried round bottom flask equipped with a condenser and an argon inlet was introduced 0.62 gm (2.35 mmol) 2,3-dimethoxy-6-iodo-pyridine (**14**), 1.0 gm (2.35 mmol,) methyl-5-(tri-n-butyl)stannyl-nicotinate (**9**). The mixture was dissolved in 25 ml of dry N-methylpyrrolidinone (NMP) and purged of all oxygen by three vacuum / argon cycles and then heated in an oil bath to 100 ^{o}C. The solution was treated with a solution of 0.089 gm (0.11 mmol.) benzyl bis (triphenylphosphine) palladium (II) chloride in a minimum amount of NMP over a period of 5 min. The reaction mixture heated for one hour and then cooled to ambient temperature. The reaction mixture was filtered through celite and the filtrate was partitioned between 1.0 L of 50 % brine solution and 300 ml of 1:1 / hexane : ethyl acetate. The solution was adjusted to pH 8 with saturated carbonate solution. The organic phase was separated and the aqueous phase was extracted with 1/1 hexane ethyl acetate until no further product was obtained. The combined organic layers were washed with brine and then dried and evaporated. The residue was partitioned between acetonitrile / pentane to remove alkyl stannane byproducts. The

acetonitrile phase was separated and evaporated in vacuo. The residue chromatographed on silica gel eluting with 6 : 4 / hexane : ethyl acetate. The procedure afforded 0.232 gm (36 %) of the desired product (**15**) as a solid after trituration with pentane. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.38 (s, 1H), 9.14 (s, 1H), 8.79 (s, 1H), 7.39 (d, 1H, J = 8 Hz), 7.13 (d, 1H, J = 8 Hz), 4.12 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H) ppm. ms (m/e) 275 (p+1).

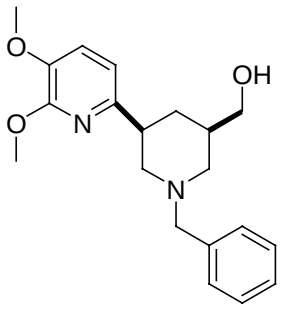


(5,6-dimethoxy-[2,3']bipyridinyl-5'-yl)-methanol (**16**): A solution of 5,6-dimethoxy-[2,3']bipyridinyl-5'-carboxylic acid methyl ester (**15**) (0.373 gm; 1.36 mmol) in 40 ml of anhydrous ether was cooled to 0 ^{O} C. The solution was treated with 1.63 ml (1.63 mmol) of a 1M solution of lithium aluminum hydride in ether. The reaction mixture becomes a bright orange suspension. The ice bath was removed and the mixture was allowed to warm to ambient temperature and then stirred for 2.5 hours. The excess reducing agent was quenched by the sequential addition of 62 ul water, 62 ul 25 % sodium hydroxide solution and 186 ul water. The bright orange color fades to yellow. After stirring for 30 minutes, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The organic phase was separated, washed with brine solution and then dried over sodium sulfate. The residue after evaporation amounted to 315 mg (94 %) of the desired product (**16**) which was used without purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (br.s, 1H), 8.47 (br.s, 1H), 8.26 (br.s), 7.29 (d, 1H, J = 8 Hz), 7.07 (d, 1H, J = 8 Hz), 4.78 (br.s, 2H), 4.08 (s, 3H), 3.90 (s, 3H) ppm. ms (m/e) 247 (p+1).

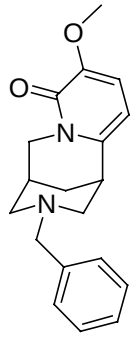


1'-Benzyl-5'-hydroxymethyl-5,6-dimethoxy-[2,3']bipyridinyl-1'-ium bromide (**17**): A solution of 335 mg (1.36 mmol) (5,6-dimethoxy-[2,3']bipyridinyl-5'-yl)-methanol (**16**) in 10 ml of dry acetonitrile was treated with 194 ul (1.63 mmol) benzyl bromide. The reaction mixture was heated under reflux for 0.5 hrs whereupon a precipitate began to form. Heating continued for a total of 1.5 hrs and then the mixture was allowed to cool to ambient temperature. Upon

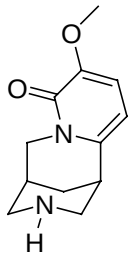
filtration there was obtained 401 mg (71 %) of the desired material (**17**). ^{1}H NMR (DMSO-d, 400 MHz) δ 9.64 (s, 1H), 9.02 (s, 1H), 8.99 (s, 1H), 7.82 (d, 1H, J = 8 Hz), 7.57 (br.d, 2H, J = 8 Hz), 7.49 (d, 1H, J = 8 Hz), 7.42 (m, 3H), 5.92 (s, 2H), 4.75 (d, 2H, J = 5 Hz), 3.98 (s, 3H), 3.85 (s, 3H) ppm. ms (m/e) 337 (p+1).



(1'-Benzyl-5,6-dimethoxy-1',2',3',4',5',6'-hexahydro-[2,3']bipyridinyl-5'-yl)-methanol (**18**): A solution of 440 mg (1.05 mmol) 1'-Benzyl-5'-hydroxymethyl-5,6-dimethoxy-[2,3']bipyridinyl-1'-ium bromide (**17**) from above in 40 ml of methanol containing 300 ul (2.11 mmol) triethylamine was treated with 40 mg platinum oxide and placed under 50 psi hydrogen pressure. After 1.5 hrs, the hydrogenation was halted and the catalyst removed by filtration. The filtrate was evaporated in vacuo and the residue was triturated with ether. The resulting white solids were removed by filtration and the filtrate was evaporated in vacuo to afford 360 mg (100 %) of an 85 / 15 mixture of cis and trans isomers as measured from the crude ^{1}H NMR spectrum and integration of the pyridyl protons (400 MHz NMR). The crude material was chromatographed on silica gel eluting with 95:5:1 methylene chloride: methanol: conc. ammonium hydroxide to afford 220 mg (61 %) of the less polar cis isomer (**18**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (m, 5H), 6.90 (d, 1H, J = 8.0 Hz), 6.61 (d, 1 H, J = 8.0 Hz), 3.96 (s, 3H), 3.80 (s, 3H), 3.55 (m, 2H), 3.55 – 3.45 (m, 2H), 3.06 (d, 2H, J = 10 Hz), 2.90 (m, 1H), 2.11 – 1.92 (m, 4 H), 1.71 (t, 1H, J = 9.0 Hz), 1.27 (q, 1H) ppm. ms (m/z) 343 (p+1). HRMS calc'd for H^+/ $C_{20}H_{26}N_2O_3$: 343.2021; found: 343.2041.



3-Benzyl-9-methoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (N-benzyl –9-methoxycytisine) (**19**): A flame dried round bottom flask was charged with 245 mg (0.72 mmol) (1'-Benzyl-5,6-dimethoxy-1',2',3',4',5',6'-hexahydro-[2,3']bipyridinyl-5'-yl)-methanol (**18**) from above and 10 ml of anhydrous methylene chloride. The solution was cooled to 0° C and was treated with 200 ul (1.44 mmol) of triethylamine and 83 ul (1.07 mmol) mesyl chloride. The reaction mixture was stirred at 0° C for 30 min and then partitioned between 100 ml of methylene chloride and 50 ml of water. The organic phase was washed with 50 ml of saturated brine solution, separated, dried over sodium sulfate and evaporated in vacuo. The crude mesylate (273 mg; 90 %) was used directly in the next reaction. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 - 7.20 (br.m, 5H), 6.91 (d, 1H, J = 8Hz), 6.61 (d, 1H, J = 8Hz), 4.08 (ddd, 2H, J = 10 Hz, J = 7 Hz, J = 6 Hz), 3.96 (s, 3H), 3.81 (s, 3H), 3.56 (s, 2H), 3.03 (overlapping dd, 2H), 2.96 (s, 3H), 2.91 - 2.85 (br.m, 1H), 2.20 (br.s, 1H), 2.10 (t, 1H, J = 11 Hz), 1.97 (br.d, 1H, J = 13 Hz), 1.78 (t, 1H, J = 11 Hz), 1.36 (q, 1H) ppm. ms (m/z) 421 (p+1). A flame dried round bottom flask was charged with 273 mg (0.65 mmol) of the mesylate from above and 80 ml of anhydrous toluene. The solution was heated under reflux for 24 hrs. The reaction mixture was cooled to ambient temperature and evaporated in vacuo. The residue was chromatographically purified on silica gel (3 gm) elulting with 98 / 2 / 1 methylene chloride / methanol / ammonium hydroxide (aq) to afford 300 mg (94 %) of N-benzyl 9-methoxycytisine (**19**). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 – 6.95 (br.m., 5H), 6.58 (d, 1H, J = 8Hz), 5.80 (d, 1H, J = 8 Hz), 4.12 (d, 1H, J = 15 Hz) 3.87 (dd, 1H, J = 15 Hz, J = 6 Hz), 3.79 (s, 3H), 3.35 (s, 2H), 2.84 (br.s, 2H), 2.77 (br. d, 1H, J = 11 Hz), 2.33 (br.s, 1H), 2.24 (d, 2H, J = 11Hz), 1.77 (q, 2H, J = 12Hz) ppm. ms (m/z) 311 (p+1).



9-Methoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (9-methoxy-cytisine) (**20**): To a flame dried round bottom flask equipped with stir bar and condenser was added 180 mg (0.58 mmol) 3-Benzyl-9-methoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one (**19**) from above together with 730 mg (11.6 mmol) ammonium formate and 15 ml of methanol. The solution was treated with 60 mg of Pearlman's catalyst ($Pd(OH)_2$) and heated under reflux for 20 min where upon tlc analysis indicated starting material was consumed (95/4/1 CH_2Cl_2 /MeOH / NH_4OH). The reaction mixture was filtered and concentrated to an oil. The crude material was chromatographed on silica gel eluting with 95/4/1 CH_2Cl_2 /MeOH / NH_4OH to afford 62 mg of **20** as a clear oil (43 %). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.61 (d, 1H, J = 8Hz), 5.89 (d, 1H, J = 8 Hz), 4.17 (d, 1H, J = 15 Hz) 3.90 (dd, 1H, J = 15 Hz, J = 7 Hz), 3.78 (s, 3H), 3.10 - 2.90 (br.m, 4H), 2.84 (br.s, 1H), 2.27 (br.s, 1H), 1.91 (br.s, 2H) ppm. Ms (m/z) 221 (p+1). This material was taken up in methylene chloride and treated with ether saturated with HCl gas. A white precipitate formed.

After stirring for 30 min, the solid was filtered and dried. The material was recrystallized from methanol - ether to afford 63.5 mg of the hydrochloride salt (**20**).