A New Synthesis of Lysergic Acid

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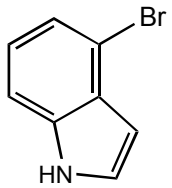
1H and 13C NMR spectra were recorded on a Varian Unity Inova 400 MHz instrument at ambient temperature using TMS as internal standard and $CDCl_3$ as solvent. Mass spectrometry was recorded on the Micromass QUATTRO II instrument. The solvents and reagents were purified by the following methods: diethyl ether, glyme and THF were distilled from sodium with benzophenone as an indicator. DMF, CH_2Cl_2 and xylene were distilled from calcium hydride. Benzene and toluene were distilled from P_2O_5. Methanol and ethanol were dried over magnesium[85]. Triglyme was distilled from $LiAlH_4$. Trimethylamine was distilled from NaOH. Anhydrous $CaCl_2$ has been roasted in a crucible and allowed to cool in a desiccator.

1. **4-Bromo-indole (2a):**

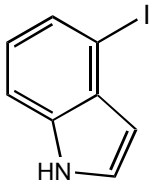


To a solution of 3-methoxycarbonylindole (7.0g, 40.0mmol) in TFA was added Thallium (III) trifluoroacetate (32.6g, 60.0 mmol) in TFA (140 ml), and the mixture was stirred for 2 hours at r.t. After TFA was evaporated *in vacuo*, a dark brown oil was obtained. This oil was dissolved in DMF (100 ml) and $CuBr_2$ (35.8g, 160.0 mmol) was added. The reaction was stirred at 120°C for 1 hour then was cooled and CH_2Cl_2 : MeOH (95 : 5, v/v) (300 ml) was added. Insoluble precipitates were filtered off through a plug of celite. The filtrate was washed with brine (100 ml x 2), and the organic layer was dried over $NaSO_4$. A crystalline material (7.60g) was obtained in 63% yield after the removal of solvent under reduced pressure. This material was directly subjected to decarboxylation for the preparation of 4-bromo-indole in the next step.

To a solution of 4-bromo-indole-3-carboxylic acid methyl ester (5.06g,20.0 mmol) in 200 ml methanol was added 200 ml of 40% aq. NaOH. The reaction was refluxed for 1.5 h with stirring. After evaporation of the solvent, the residue was poured into 200 ml water, and extracted with CH_2Cl_2:MeOH (95 : 5, v/v; 200 ml x 3). The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave a brown oil. Purification by chromatography using hexane : ethyl acetate (6:1) afforded a light colored oil (2.68 g) in 69.1% yield.

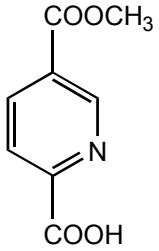
^{1}H NMR ($CDCl_3$): δ 6.62 (t-like m, 1H), 7.05 (dd, 1H, J=8.2, 8.2Hz)), 7.24 (m, 1H,), 7.30 (d, 1H, J=8.2Hz), 7.34(d, 1H, J=8.2Hz), 8.28 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 136.7, 128.2, 125.5, 123.1, 122.9, 115.2, 111.0, 103.5. Mass Spectrum (M+1): Expected for C_8H_6BrN: 195.97. Found: 195.97. Elemental Analysis: Calcd. For C_8H_6BrN: C, 49.01; H, 3.08; N, 7.14. Found: C, 48.83; H, 3.07; N, 7.28.

2. **4-Iodo-indole (2b):**



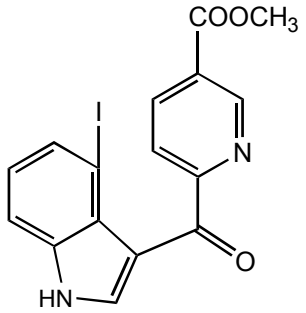
To a solution of 3-methoxycarbonylindole (7.0g, 40.0mmol) in TFA was added Thallium (III) trifluoroacetate (32.6g, 60.0 mmol) in TFA (140 ml), and the mixture was stirred for 2 hours at r.t. After TFA was evaporated in *vacuo*, a dark brown oil was obtained. This oil was suspended in 450 ml H_2O, and KI (19.9 g, 120.0 mmol) was added to this suspension. The reaction was stirred at r. t. for 2 hours. CH_2Cl_2 : MeOH (95 : 5, v/v) (300 ml) was added to the reaction mixture and insoluble precipitates were filtered off through a plug of celite. The organic layer was separated and washed with aq. sodium thiosulfate then brine. Removal of the solvent left a brownish solid. Quick purification by a short plug of silica gel afforded a white solid (8.68g) as 4-iodo-indole-3-carboxylic acid methyl ester in 72.1% yield. This material was used directly in the next step.
To a solution of 4-iodo-indole-3-carboxylic acid methyl ester (6.02g, 20.0 mmol) in 200 ml methanol was added 200 ml of 40% aq. NaOH. The reaction was refluxed for 1.5 h with stirring. After evaporation of the solvent, the residue was poured into 200 ml water, and extracted with CH_2Cl_2:MeOH (95: 5, v/v; 200 ml x 3). The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an off-white solid. Purification by chromatography using hexane : ethyl acetate (6 : 1) afforded a white crystalline solid (3.51g) in 72.3% yield.
^{1}H NMR ($CDCl_3$): δ 8.30 (bs 1H), 7.52 (d, 1H, J=8.4Hz), 7.34 (d, 1H, J=8.4Hz), 7.20 (m, 1H), 6.92 (t, 1H, J=8.4Hz), 6.48 (t-like m, 1H). ^{13}C NMR ($CDCl_3$): δ 135.4, 133.2, 130.1, 125.2, 124.1, 111.8, 107.1, 88.2. Mass Spectrum (M+1): Expected for C_8H_6IN: 243.95. Found: 243.95. Elemental Analysis: Calcd. For C_8H_6IN: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.67; H, 2.59; N, 5.75.

3. **Pyridine-2,5-dicarboxylic acid 5-methyl ester (3)**:



To a solution of pyridine-2,5-dicarboxylic acid dimethyl ester (5.91g, 30 mmol) in 100 ml methanol was added copper(II) nitrate trihydrate (14.5g, 60 mmol) in a 500 ml round bottom flask equipped with a reflux condenser and a stirring bar. The reaction was refluxed for 80 mins. A deep violet-blue precipitation was observed after 20 mins and lasted throughout the course of the reaction. The reaction was cooled to r.t., and the reaction mixture was reduced to 1/3 of its original volume. The deep violet-blue solid was collected by filtration and washed with cold methanol then cold water. This solid material was dissolved in 50 ml glyme, and H_2S gas was bubbled into the solution. The black precipitate was formed in 2 mins, and the deep violet-blue solid disappeared after 15 mins. The black precipitate was filtered out through a plug of celite and the filtrate was concentrated to 20 ml. Excess hexanes were added into this solution, and a white solid was formed. The white solid was collected by filtration. Recrystallization of this solid from acetone afforded 4.83g product in 88.9% yield (mp. 194.1-195.1^{o}C, Lit[6]). ^{1}H NMR ($CDCl_3$): δ 9.21 (s, 1H), 8.60 (d, 1H, J=2.9Hz), 8.23 (d, 1H, J=2.9Hz), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 172.4, 165.3, 154.3, 150.4, 139.2, 129.3, 122.9, 52.3. Mass Spectrum (M+1): Expected for $C_8H_7NO_4$: 182.04. Found: 182.04. Elemental Analysis: Calcd. For $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 52.91; H, 3.88; N, 7.86.

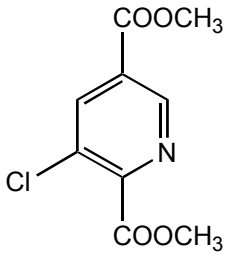
4. **6-(4-Iodo-indole-3-carbonyl)-nicotinic acid methyl ester (4b):**



To a solution of EtMgBr (10 ml, 1.575 M in ether, 15.75 mmol) was added a solution of 4-iodo-1H-indole (3.65g, 15.0 mmol) in ether (anhydrous, 20 ml). The resulting two-phase system was allowed to stand for 15 min under stirring whereupon $ZnCl_2$ (15 ml, 1.0m in ether, 15.0 mmol) was added with stirring. The two-phase system was allowed to stand for 30 min when 6-chlorocarbonyl-nicotinic acid methyl ester (3.14g, 15.75 mmol) in anhydrous ether (10 ml) was added rapidly under vigorous stirring. The reaction mixture was allowed to stand for 2 hours whereupon NH_4Cl (aq. sat. 25 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 ml x 3). The combined organic layer was washed with $NaHCO_3$ (aq. sat. 25 ml) followed by brine (25 ml), and dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded a yellowish solid. Recrystallization of this solid from acetone afforded 4.25g of the desired crystalline product (mp. 245.7-246.8^{o}C) in 69.8% yield.
^{1}H NMR ($CDCl_3$): δ 9.17 (d, 1H, J=1.2Hz), 8.52 (dd,1H, J=8.0, 1.2 Hz), 8.28 (d, 1H, J=2.4Hz), 8.22 (d, 1H, J=8.0Hz), 7.75 (d, 1H, J=8.0Hz), 7.63 (d, 1H, J=8.0Hz), 7.00 (t, 1H, J=8.0Hz). ^{13}C NMR (Acetone-d6): δ 186.1, 164.5, 160.8, 148.8, 142.7, 140.8, 138.2, 137.2, 134.4, 127.7, 123.4, 122.8, 114.9, 111.4, 87.2, 52.2. Mass Spectrum (M+1):

Expected for $C_{16}H_{11}IN_2O_3$: 406.98. Found: 406.98. Elemental Analysis: Calcd. For $C_{16}H_{11}IN_2O_3$: C, 47.31; H, 2.73; N, 6.90. Found: C, 47.50; H, 2.60; N, 6.88.

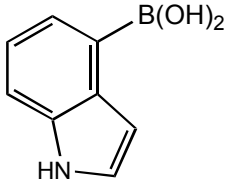
5. **3-Chloro-pyridine-2,5-dicarboxylic acid dimethyl ester (7):**



Pyridine-2,5-dicarboxylic acid (8.35g, 50.0 mmol) was suspended in 250ml 0.2% (w/w) aq. Na_2WO_4 (0.5g) in a 1 liter round bottom flask. To this solution was added H_2O_2 in water (30% w/w, 8.5g, 75.0 mmol). The resulting mixture was stirred and heated at 80-85^oC for 10 hours. The resulting solid was collected by filtration and washed with cold water. Drying the material under vacuum overnight yielded 9.06 g product solid (mp. 253.2-254.1^oC, dec; Lit.[9] 254^oC, dec.) as pyridine-2,5-dicarboxylic acid N-oxide in 99% yield. This solid was used in the next step.

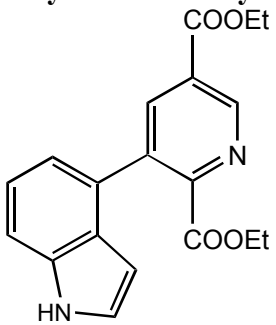
To a solution of thionyl chloride (9.52g, 5.84 ml, 80 mmol) in 200 ml CH_2Cl_2 was added DMF (2 ml) at 0^oC. Pyridine-2,5-dicarboxylic acid N-oxide (3.66g, 20.0 mmol) was added into this mixture portionwise. The resulting mixture was heated at 65^oC for 2 hours. The reaction was cooled to r.t. then placed in an ice-bath. The reaction was quenched with methanol (30 ml) slowly at 0^oC. The solvent was removed *in vacuo* and the crude product was partitioned between CH_2Cl_2 (100 ml) and aq. $NaHCO_3$ (sat. 50 ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (100 ml x 2). The combined organic layer was dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the crude oil through a short plug of silica gel using hexane : ethyl acetate (2 : 1) afforded a white solid (3.73g, mp. 126.0-127.0^oC) in 81.2% yield. ^1H NMR ($CDCl_3$): δ 9.12 (d, 1H, J=1.6Hz), 8.41 (d, 1H, J=1.6Hz), 4.04 (s, 3H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 164.2, 164.0, 151.8, 148.0, 139.9, 131.2, 128.3, 53.2, 53.0. Mass Spectrum (M+1): Expected for $C_9H_8ClNO_4$: 230.01. Found: 230.01. Elemental Analysis: Calcd. for $C_9H_8ClNO_4$: C, 47.08; H, 3.51; N, 6.10. Found: C, 47.21; H, 3.56; N, 6.27.

6. **Indole-4-boronic acid (8):**



To a suspension of KH (4.57 g of a 30% suspension in mineral oil, 32.9mmol) was added a solution of 4-bromo-indole (5.88g, 30.0 mmol) in anhydrous ether (25 ml). The reaction was stirred at r.t. for 30 min under N_2 and the reaction was cooled in an acetone-dry ice bath (-78^{o}C) with stirring. Precooled *t*-BuLi solution in hexane (33.0 ml, 66.0 mmol) was cannulated into the reaction and the reaction was kept stirring for another 20 min. Neat B(*n*-BuO)$_3$ (24.1 ml, 90.0 mmol) was added into the reaction by syringe under vigorous stirring. The reaction mixture became thick when it was allowed to warm to r.t., and more anhydrous ether (30 ml) was added under N_2. The reaction was allowed to stand overnight at r.t. with vigorous stirring. The thick reaction mixture was diluted with more anhydrous ether and then transferred slowly into 1 M aqueous H_3PO_4 (300 ml) at 0^{o}C. The mixture was stirred at r.t. for 40 min, and extracted with ether (100 ml x 30). The combined organic layer was extracted with 1 N NaOH (50 ml x 3). Ether (100 ml) was added to this aqueous solution and the mixture was acidified to pH = 2 using 1M H_3PO_4. The organic layer was separated and the aqueous layer was extracted with ether (100 ml x 2). The combined ether layer was dried over Na_2SO_4 and evaporation of solvent *in vacuo* left a beige solid (4.24g, 88.0%). ^{1}H NMR (acetone-d_6 80% + D_2O 20%): δ 7.56 (dd, 1H, J=7.0, 1.0Hz), 7.53 (dd, 1H, J=8.4, 1.0Hz), 7.34 (d, 1H, J=3.2Hz), 7.21 (dd, 1H, J=8.4, 70Hz), 6.96 (d, 1H, J=3.2Hz). ^{13}C NMR (acetone-d_6 80% + D_2O 20%): 136.2, 132.8, 126.6, 125.5, 124.9, 120.2, 112.8, 103.4

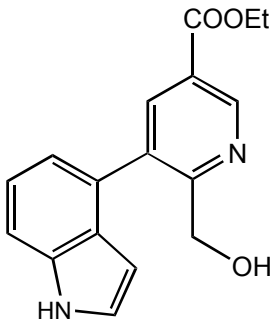
7. **3-(4-indolyl)-pyridine-2,5-dicarboxylic acid diethyl ester (9a):**



Into 500 ml anhydrous toluene in a 1 liter round bottom flask equipped with stirring bar was bubbled in a stream of argon via a needle for 30 min. Pd(PPh$_3$)$_4$ (0.878g, 0.75 mmol) and 3-chloro-pyridine-2,5-dicarboxylic acid dimethyl ester (3.44g, 15.0 mmol) were added into this solvent and the resulting mixture was stirred at r.t. under argon for 1 hour. A solution of indole-4-boronic acid (1.86g, 11.5 mmol) in 50 ml EtOH and a solution of 2M aqueous Na_2CO_3 (11.5 ml) was added into the reaction mixture at r.t. under argon. The mixture was heated under argon with vigorous stirring at 105^{o}C for 8 hours. The reaction mixture was cooled and brine (200 ml) was added. The organic layer was separated and aqueous layer extracted with additional CH_2Cl_2 (100 ml x 2). The combined organic layer was dried over Na_2SO_4 and evaporation of the solvent left a yellowish solid. Purification of the crude material through a short plug of silica gel (hexane : ethyl acetate, 1:2) afforded a yellow solid. The TLC of this material showed it to be a mixture of three different compounds due to ester exchange. This solid was dissolved in 500 ml EtOH and the solution was stirred overnight at r.t. in the presence of cat. HCl in diethyl ether. A single compound (3.54g) was obtained (mp. 212.3-213.0^o C)

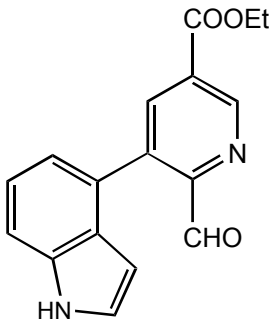
in 91.0% yield. ^{1}H NMR ($CDCl_3$): δ 9.25 (d, 1H, J=1.6Hz), 8.55 (d, 1H, J=1.6Hz), 8.43 (bs, 1H), 7.45 (d, 1H, J=8.4Hz), 7.25-7.30 (m, 2H), 7.08 (d, 1H, J=8.4Hz), 6.34 (m, 1H), 4.42 (q, 2H, J=7.2Hz), 4.06 (q, 2H, J=7.2Hz), 1.41 (t, 3H, J=7.2Hz), 0.90 (t, 3H, J=7.2Hz). ^{13}C NMR ($CDCl_3$): δ 166.4, 164.8, 142.8, 149.0, 140.1, 136.3, 135.8, 129.8, 127.6, 126.4, 125.1, 122.3, 120.2, 111.6, 100.9, 61.1, 61.2, 14.1, 13.7. Mass Spectrum (M+1): Expected for $C_{19}H_{18}N_2O_4$: 339.13. Found: 339.13. Elemental Analysis: Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.64; H, 5.24; N, 8.15.

8. **6-Hydroxymethyl-5-(4-indolyl)-nicotinic acid ethyl ester (9b):**



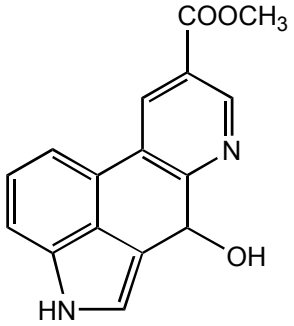
To a solution of 3-(4-indolyl)-pyridine-2,5-dicarboxylic acid diethyl ester (0.34g, 1.0 mmol) in anhydrous EtOH (10 ml) was added $Ba(BH_4)_2$ (24.6mg, 0.65 mmol) followed by $CaCl_2$ (44.3mg, 0.4 mmol) at 0^{o}C. The reaction was warmed to r.t. and stirred for 2 hours. 1 M H_2SO_4 (1 ml) was added to the reaction, and the resulting white precipitation ($CaSO_4$) was filtered out through a plug of celite. The filtrate was concentrated and partitioned between ethyl acetate (20 ml) and $NaHCO_3$ (aq. 15 ml). The organic layer was separated and the aqueous layer was extracted with additional ethyl acetate (20 ml x 2). The combined organic layer was dried over Na_2SO_4, and the solvent was removed. The crude material was purified by silica gel chromatography using hexane-ethyl acetate (3:1 to 1:1). A colorless solid (mp. 198.1-199.0^{o}C) was obtained (231 mg) in 78% yield.
^{1}H NMR ($CDCl_3$): δ 9.22 (d, 1H, J=1.6Hz), 8.72 (bs, 1H), 8.34 (d, 1H, J=1.6Hz), 7.46 (d, 1H, J=8.0Hz), 7.23 (t, 1H, J=8.0Hz), 7.22 (m, 1H), 6.98 (d, 1H, J=8.0Hz), 6.15 (m, 1H), 4.66 (s, 2H), 4.39 (bs, 1H), 4.42 (q, 2H, J=7.2Hz), 1.40 (t, 3H, J=7.2Hz). ^{13}C NMR ($CDCl_3$): δ 165.2, 160.4, 148.0, 138.8, 136.0, 134.2, 128.4, 126.9, 125.4, 125.3, 122.2, 120.3, 111.4, 100.8, 62.4, 60.9, 14.2. Mass Spectrum (M+1): Expected for $C_{17}H_{16}N_2O_3$: 297.12. Found: 297.12. Elemental Analysis: Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.13; H, 5.26; N, 9.33.
Alternatively, the product could also be made using $Ca(BH_4)_2$ as the reducing reagent in the same solvent and temperature for same period of time. The NMR, mass spectrum, elemental analysis and mp. of this product were identical to that of the product obtained by the previous method. The yield of this reaction was 85%.

9. **6-formyl-5-(4-indolyl)-nicotinic acid ethyl ester (9c):**



To a solution of 6-hydroxymethyl-5-(4-indolyl)-nicotinic acid ethyl ester (296 mg, 1.0 mmol) in 5 ml CH_2Cl_2 was added freshly made MnO_2 (870 mg, 10.0 mmol). The reaction was stirred at r.t. for 2 hours then filtered from the solution through a plug of celite, and the solvent was removed *in vacuo*. Purification of the crude material by silica gel chromatography using hexane-ethyl acetate (2 : 1) afforded a yellow solid (271mg, 92%) with mp. 198.4-199.2^oC. ^1H NMR ($CDCl_3$): δ 10.03 (s, 1H), 9.22 (d, 1H, J=1.6Hz), 8.61 (d, 1H, J=1.6Hz), 8.47 (bs, 1H), 7.56 (d, 1H, J=8.0Hz), 7.35-7.25 (m, 2H), 7.08 (d, 1H, J=8.0Hz), 6.26 (m, 1H), 4.42 (q, 2H, J=7.2Hz), 1.42 (t, 3H, J=7.2Hz). ^{13}C NMR ($CDCl_3$): δ 190.8, 164.2, 150.8, 149.6, 140.9, 140.1, 136.7, 128.4, 127.8, 127.2, 126.1, 122.1, 121.9, 112.0, 100.6, 61.7, 14.2. Mass Spectrum (M+1): Expected for $C_{17}H_{14}N_2O_3$: 295.10. Found: 295.10. Elemental Analysis: Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.58; H, 4.83; N, 9.64.

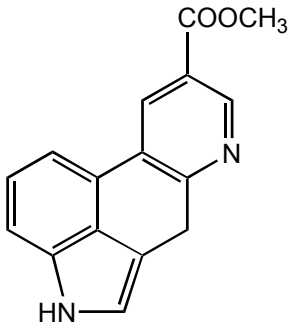
10. **6-Hydroxy-4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic acid methyl ester (10):**



To a solution of 6-formyl-5-(4-indolyl)-nicotinic acid ethyl ester (117.8 mg, 0.4 mmol) in anhydrous methanol (1.0 ml) in a 2 ml conical vial was added 0.5 M NaOMe/MeOH (16.0 μl, 0.008 mmol). The reaction was stirred at r.t. for 2 hours. Solid precipitated out of the solution during the course of the reaction, and the starting material disappeared completely after 2 hours as indicated by TLC. The solution was cooled to 0^oC and the liquid was removed with a pipette. The remaining solid was recrystallized from MeOH to afford 102.0 mg yellow crystalline solid (mp. 234.6-235.8^oC) in 91% yield. ^1H NMR ($CDCl_3$): δ 9.52 (d, 1H, J=1.6Hz), 9.45 (d, 1H, J=1.6Hz), 8.55 (bs, 1H), 7.96 (s, 1H), 7.82 (d, 1H, J=8.0Hz), 7.58 (t, 1H, J=8.0Hz), 6.81 (d, 1H, J=8.0Hz), 6.54 (bs, 1H), 5.22 (bs,

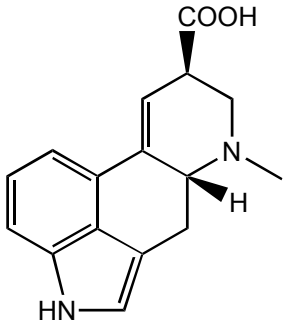
1H), 4.05 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.1, 152.3, 149.4, 148.2, 142.8, 133.8, 131.6, 128.1, 125.9, 123.9, 122.6, 121.0, 111.2, 104.1, 90.4, 52.2. Mass Spectrum (M+1): Expected for $C_{16}H_{12}N_2O_3$: 281.08. Found: 281.08. Elemental Analysis: Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.43; H, 4.48; N, 10.19.

11. **4,6-Dihydro-indolo[4,3-fg]quinoline-9-carboxylic acid methyl ester (11):**



To a solution of 6-hydroxy-4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic methyl ester (90 mg, 0.32mmol) in 10 ml anhydrous THF was added BH_3 in THF (1.0 M, 0.64 ml, 0.64mol) under argon. The resulting mixture was stirred at r.t. for 2 hours. The TLC showed the disappearance of the starting material and a new fluorescent spot under UV on TLC. The solvent was removed *in vacuo* and the crude material was partitioned between CH_2Cl_2 (3 ml) and aq. $NaHCO_3$ (sat., 2 ml). The organic layer was separated and the aqueous was extracted with additional CH_2Cl_2 (3 ml x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel PTLC using CH_2Cl_2:MeOH (98:2). A white solid was obtained (mp. 212.9-213.9^{o}C, 35.2 mg) in 41% yield. ^{1}H NMR ($CDCl_3$): δ 9.44 (d, 1H, J=1.6Hz), 9.40 (d, 1H, J=1.6Hz), 8.07 (bs, 1H), 7.75 (d, 1H, J=8.0Hz), 7.70 (s, 1H), 7.54 (t, 1H, J=8.0Hz), 6.78 (d, 1H, J=8.0Hz), 4.98 (s, 2H), 4.04 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 164.0, 149.6, 147.2, 146.1, 141.0, 135.2, 129.3, 126.4, 124.2, 122.6, 120.9, 119.8, 110.1, 103.6, 55.2, 51.4. Mass Spectrum (M+1): Expected for $C_{16}H_{12}N_2O_2$: 265.09. Found: 265.09. Elemental Analysis: Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.58; H, 4.72; N, 10.68.

12. ±**Lysergic acid (1):**



To a solution of 4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic acid methyl ester (29.2 mg, 0.116 mmol) in CH_2Cl_2 (1ml) was added MeI (33.0 mg, 14.6 μl, 0.24 mmol) at 0°C. The reaction was stirred at 0°C for 2 hours and the starting material disappeared after 2 hours as indicated by TLC. The solvent was removed *in vacuo* and the crude product was dissolved in methanol (1 ml). To that mixture was added $NaBH_4$ (15.2 mg, 0.4 mmol) and the reaction was stirred at r.t. for 5 min. The organic solvent was removed *in vacuo* and the remaining solution was partitioned between CH_2Cl_2 (2 ml) and water (2 ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (3 ml x 2). The organic layers were combined and dried over Na_2SO_4. The solvent was removed and the crude material was purified by PTLC (CH_2Cl_2 : MeOH, 98 : 2). A white solid was obtained (21.4 mg, 65%). ^{1}H NMR showed it to be a mixture of methyl lysergate and methyl isolysergate in 6 : 1 ratio using N-methyl as the integration indicator. ^{1}H NMR ($CDCl_3$) of methyl lysergate: δ 7.90 (bs, 1H), 7.15-7.25 (m, 3H), 6.92 (t, 1H, J=2.0Hz), 6.62 (bs, 1H), 3.78 (s, 3H), 3.75 (m, 1H), 3.52 (dd, 1H, J=14.0, 6.0Hz), 3.29 (br dd, 1H, J=11.0, 5.0Hz), 3.22 (m, 1H), 2.72 (ddd, 1H, J=14.0, 12.0, 2.0Hz), 2.70 (t, 1H, J=11.0Hz), 2.62 (s, 3H). ^{1}H NMR ($CDCl_3$) of methyl isolysergate: δ 7.90 (bs, 1H), 7.15-7.25 (m, 3H), 6.90 (t, 1H, J=2.0Hz), 6.56 (br d, 1H, J=4.0Hz), 3.72 (s, 3H), 3.42 (dd, 1H, J=14.0, 5.0Hz), 3.35 (m, 1H), 3.30 (m, 1H), 3.30 (m, 1H), 3.20 (m, 1H), 2.73 (ddd, 1H, J=14.0, 11.0, 2.0Hz), 2.74 (m, 1H), 2.57 (s, 3H)
These ^{1}H NMR data are in agreement with that of methyl lysergate and methyl isolysergate synthesized by Ninomyia[4c]. Mass Spectrum (M+1): Expected for $C_{17}H_{18}N_2O_2$: 283.14. Found: 283.14. Elemental Analysis: Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.20; H, 6.41; N, 10.05.

To a solution of methyl lysergate & methyl isolysergate (6 : 1 mixture above, 15.6 mg, 0.028 mmol) in ethanol (0.5 ml) was added 1 N NaOH (0.5 ml). The reaction was heated at 35°C for two hours. 0.1 N HCl solution was used to carefully adjust the pH to 6 and the solid material was collected by removing the liquid. The solid was recrystallized from ethanol to afford 12.2 mg, (95%) of lysergic acid. ^{1}H NMR (pyridine-d_5) of ± lysergic acid: δ 7.44 (d, 1H, J=8.4Hz), 7.42 (d, 1H, J=8.4Hz), 7.31 (t, 1H, J=8.4Hz), 7.25 (t, 1H, J=1.6Hz)), 7.20 (bs, 1H), 4.05 (m, 1H), 3.63 (dd, 1H, J=14.4, 6.4Hz), 3.52 (dd, 1H, J=11.2, 5.2Hz), 3.29 (m, 1H), 2.93 (ddd, 1H, J=14.4, 11.2, 2.0Hz), 2.71 (t, 1H, J=11.2Hz), 2.50 (s, 3H). ^{1}H NMR (methanol-d_4) of ±lysergic acid: δ 7.22 (d, 1H, J=8.4Hz), 7.18 (d, 1H, J=8.4Hz), 7.12 (t, 1H, J=8.4Hz), 7.05 (t, 1H, J=2.0Hz), 6.65 (bs, 1H), 4.15 (m, 1H), 3.70 (m, 3H), 3.42 (t, 1H, J=11.2Hz), 2.91 (ddd, 1H, J=14, 12, 2Hz). ^{13}C NMR (pyridine-d_5) : δ 174.9, 137.2, 136.4, 130.2, 128.9, 127.3, 119.8, 119.6, 112.0, 111.5, 111.3, 63.5, 56.1, 43.8, 43.4, 27.3. Mass Spectrum (M+1): Expected for $C_{16}H_{16}N_2O_2$: 269.12. Found: 269.12. Elemental Analysis: Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.54; H, 5.88; N, 10.31.