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 CDCl₃ 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, CH₂Cl₂ and xylene were distilled from calcium hydride. Benzene and toluene were distilled from P₂O₅. Methanol and ethanol were dried over magnesium. Trimlyme was distilled from LiAlH₄. Trimethylamine was distilled from NaOH. Anhydrous CaCl₂ 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 CuBr₂ (35.8g, 160.0 mmol) was added. The reaction was stirred at 120°C for 1 hour then was cooled and CH₂Cl₂ : 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 Na₂SO₄. 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 CH₂Cl₂:MeOH (95 : 5, v/v; 200 ml x 3). The extract was washed with brine, dried over Na₂SO₄, 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.
1H NMR (CDCl₃): 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). 13C NMR (CDCl₃): δ 136.7, 128.2, 125.5, 123.1, 122.9, 115.2, 111.0, 103.5. Mass Spectrum (M+1): Expected for C₈H₆BrN: 195.97. Found: 195.97. Elemental Analysis: Calcd. For C₈H₆BrN: C, 49.01; H, 3.08; N, 7.14. Found: C, 48.83; H, 3.07; N, 7.28.

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

![Image of 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 H₂O, and KI (19.9 g, 120.0 mmol) was added to this suspension. The reaction was stirred at r. t. for 2 hours. CH₂Cl₂ : 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 CH₂Cl₂:MeOH (95: 5, v/v; 200 ml x 3). The extract was washed with brine, dried over Na₂SO₄, 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.

1H NMR (CDCl₃): 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). 13C NMR (CDCl₃): δ 135.4, 133.2, 130.1, 125.2, 124.1, 111.8, 107.1, 88.2. Mass Spectrum (M+1): Expected for C₈H₆IN: 243.95. Found: 243.95. Elemental Analysis: Calcd. For C₈H₆IN: 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):

![Image of 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 H₂S 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°C, Lit⁶).

1H NMR (CDCl₃): δ 9.21 (s, 1H), 8.60 (d, 1H, J=2.9Hz), 8.23 (d, 1H, J=2.9Hz), 4.00 (s, 3H).


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 ZnCl₂ (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 NH₄Cl (aq. sat. 25 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (50 ml x 3). The combined organic layer was washed with NaHCO₃ (aq. sat. 25 ml) followed by brine (25 ml), and dried over Na₂SO₄. 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°C) in 69.8% yield.

1H NMR (CDCl₃): 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). 13C 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 C₁₆H₁₁IN₂O₃: 406.98. Found: 406.98. Elemental Analysis: Calcd. For C₁₆H₁₁IN₂O₃: 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):

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\begin{align*}
\text{COOCH}_3 & \quad \text{COOCH}_3 \\
\text{Cl} & \quad \text{N}
\end{align*}
\]

Pyridine-2,5-dicarboxylic acid (8.35g, 50.0 mmol) was suspended in 250ml 0.2% (w/w) aq. Na₂WO₄ (0.5g) in a 1 liter round bottom flask. To this solution was added H₂O₂ in water (30% w/w, 8.5g, 75.0 mmol). The resulting mixture was stirred and heated at 80-85°C 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°C, dec; Lit. 9 254°C, 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 CH₂Cl₂ was added DMF (2 ml) at 0°C. 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°C 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°C. The solvent was removed in vacuo and the crude product was partitioned between CH₂Cl₂ (100 ml) and aq. NaHCO₃ (sat. 50 ml). The organic layer was separated and the aqueous layer was extracted with additional CH₂Cl₂ (100 ml x 2). The combined organic layer was dried over Na₂SO₄ 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°C) in 81.2% yield. ¹H NMR (CDCl₃): δ 9.12 (d, 1H, J=1.6Hz), 8.41 (d, 1H, J=1.6Hz), 4.04 (s, 3H), 4.00 (s, 3H). ¹³C NMR (CDCl₃): 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 C₉H₈ClNO₄: 230.01. Found: 230.01. Elemental Analysis: Calcd. for C₉H₈ClNO₄: 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):

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\begin{align*}
\text{B(OH)}_2 & \quad \text{HN}
\end{align*}
\]
To a suspension of KH (4.57 g of a 30% suspension in mineral oil, 32.9 mmol) was added a solution of 4-bromo-indole (5.88 g, 30.0 mmol) in anhydrous ether (25 ml). The reaction was stirred at r.t. for 30 min under N₂ and the reaction was cooled in an acetone-dry ice bath (-78°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 N₂. 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 H₃PO₄ (300 ml) at 0°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 H₃PO₄. The organic layer was separated and the aqueous layer was extracted with ether (100 ml x 2). The combined ether layer was dried over Na₂SO₄ and evaporation of solvent in vacuo left a beige solid (4.24 g, 88.0%). ¹H NMR (acetone-d₆ 80% + D₂O 20%): δ 7.56 (dd, 1H, J=7.0, 1.0 Hz), 7.53 (dd, 1H, J=8.4, 1.0 Hz), 7.34 (d, 1H, J=3.2 Hz), 7.24 (dd, 1H, J=8.4, 7.0 Hz), 6.96 (d, 1H, J=3.2 Hz). ¹³C NMR (acetone-d₆ 80% + D₂O 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):

![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(PPh₃)₄ (0.878 g, 0.75 mmol) and 3-chloro-pyridine-2,5-dicarboxylic acid dimethyl ester (3.44 g, 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 (1.86 g, 11.5 mmol) in 50 ml EtOH and a solution of 2M aqueous Na₂CO₃ (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°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 CH₂Cl₂ (100 ml x 2). The combined organic layer was dried over Na₂SO₄ 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 (3.54 g) was obtained (mp. 212.3-213.0°C)
in 91.0% yield. \(^1\)H NMR (CDCl\(_3\)): \(\delta 9.25\) (d, 1H, \(J=1.6\)Hz), \(8.55\) (d, 1H, \(J=1.6\)Hz), \(8.43\) (bs, 1H), \(7.45\) (d, 1H, \(J=8.4\)Hz), \(7.25-7.30\) (m, 2H), \(7.08\) (d, 1H, \(J=8.4\)Hz), \(6.34\) (m, 1H), \(4.42\) (q, 2H, \(J=7.2\)Hz), \(4.06\) (q, 2H, \(J=7.2\)Hz), \(1.41\) (t, 3H, \(J=7.2\)Hz), \(0.90\) (t, 3H, \(J=7.2\)Hz). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta 166.4, 164.8, 142.8, 149.0, 140.1, 136.3, 135.8, 129.8, 127.6, 126.4, 125.1, 120.2\). Mass Spectrum (M+1): Expected for C\(_{19}\)H\(_{18}\)N\(_2\)O\(_4\): 339.13. Found: 339.13. Elemental Analysis: Calcd. for C\(_{19}\)H\(_{18}\)N\(_2\)O\(_4\): 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):

![Structure of 6-Hydroxymethyl-5-(4-indolyl)-nicotinic acid ethyl ester (9b)](https://example.com/structure.png)

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°C. The reaction was warmed to r.t. and stirred for 2 hours. 1 M H\(_2\)SO\(_4\) (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\(_2\)SO\(_4\), 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°C) was obtained (231 mg) in 78% yield. \(^1\)H NMR (CDCl\(_3\)): \(\delta 9.22\) (d, 1H, \(J=1.6\)Hz), \(8.72\) (bs, 1H), \(8.34\) (d, 1H, \(J=1.6\)Hz), \(7.46\) (d, 1H, \(J=8.0\)Hz), \(7.23\) (t, 1H, \(J=8.0\)Hz), \(7.22\) (m, 1H), \(6.98\) (d, 1H, \(J=8.0\)Hz), \(6.15\) (m, 1H), \(4.66\) (s, 2H), \(4.39\) (bs, 1H), \(4.42\) (q, 2H, \(J=7.2\)Hz), \(1.40\) (t, 3H, \(J=7.2\)Hz). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta 165.2, 160.4, 148.0, 138.8, 136.0, 134.2, 128.4, 126.9, 125.4, 125.3, 122.2, 120.3, 111.4, 100.8, 62.4, 60.9, 14.2\). Mass Spectrum (M+1): Expected for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_3\): 297.12. Found: 297.12. Elemental Analysis: Calcd. for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_3\): 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 CH₂Cl₂ was added freshly made MnO₂ (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 (271 mg, 92%) with mp. 198.4-199.2°C. ¹H NMR (CDCl₃): 8 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). ¹³C NMR (CDCl₃): 8 190.8, 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 C₁₇H₁₄N₂O₃: 295.10. Found: 295.10. Elemental Analysis: Calcd. for C₁₇H₁₄N₂O₃: 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°C 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°C) in 91% yield. ¹H NMR (CDCl₃): 8 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$_2$O$_3$: 281.08. Found: 281.08. Elemental Analysis: Calcd. for C$_{16}$H$_{12}$N$_2$O$_3$: 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):

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\text{COOCH}_3
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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$_2$Cl$_2$ (3 ml) and aq. NaHCO$_3$ (sat., 2 ml). The organic layer was separated and the aqueous was extracted with additional CH$_2$Cl$_2$ (3 ml x 2). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The crude material was purified by silica gel PTLC using CH$_2$Cl$_2$:MeOH (98:2). A white solid was obtained (mp. 212.9-213.9°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$_2$O$_2$: 265.09. Found: 265.09. Elemental Analysis: Calcd. for C$_{16}$H$_{12}$N$_2$O$_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.58; H, 4.72; N, 10.68.

12. ±Lysergic acid (1):

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\text{COOH}
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To a solution of 4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic acid methyl ester (29.2 mg, 0.116 mmol) in CH₂Cl₂ (1 ml) 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 NaBH₄ (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 CH₂Cl₂ (2 ml) and water (2 ml). The organic layer was separated and the aqueous layer was extracted with additional CH₂Cl₂ (3 ml x 2). The organic layers were combined and dried over Na₂SO₄. The solvent was removed and the crude material was purified by PTLC (CH₂Cl₂ : MeOH, 98 : 2). A white solid was obtained (21.4 mg, 65%). ¹H NMR showed it to be a mixture of methyl lysergate and methyl isolysergate in 6 : 1 ratio using N-methyl as the integration indicator. ¹H NMR (CDCl₃) 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). ¹H NMR (CDCl₃) 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)

To a solution of N-methyl lysergic acid (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. ¹H NMR (pyridine-d₅) 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). ¹H NMR (methanol-d₄) 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).