

Supporting information

**Synthesis and evaluation of nuciferine and roemerine enantiomers as 5-HT₂ and α_1
receptor antagonists**

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General information

Column chromatography and analytical thin-layer chromatography (TLC) were performed using silica gel 60 (230–400 mesh) and pre-coated aluminum silica gel sheets (Kieselgel 60 F-254) from Merck (Darmstadt, Germany), respectively. Melting points were determined on a Mel-Temp II melting point instrument. ¹H and ¹³C NMR spectra were obtained using a Jeol ECA 400 (400 MHz) spectrometer at room temperature with TMS as the internal standard. Chemical shifts are reported in parts per million relative to CDCl₃ or TMS. Data for ¹H NMR are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quartet, m = multiplet), coupling constants and integration. ¹³C NMR spectra were recorded with complete proton decoupling. MS analysis was performed on an Agilent 6500 series accurate mass Q-TOF. Optical rotations were recorded on a Jasco P-1020 polarimeter (Tokyo, Japan) at 589 nm. Enantiomeric purity was determined by chiral HPLC analysis on a Chiralcel OD-H column (150 x 4.6 mm, 5 μ m, Daicel, Osaka, Japan), eluting with acetonitrile/isopropanol (gradient from 100% acetonitrile

to 90% acetonitrile over 5 min) at a flow rate of 0.6 mL min⁻¹. The sample injection volume was 20 µL. The detection wavelength was set at 270 nm and the total analysis time was 10 min. Chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) or Merck (Darmstadt, Germany) and were of analytical grade.

Experimental procedures and spectral data

2-(2-Bromophenyl)-*N*-(3,4-dimethoxyphenethyl)acetamide (**6a**)¹

2-bromophenylacetic acid (0.215 g, 1 mmol) and oxalyl chloride (2.0 M solution in dichloromethane, 0.6 mL, 1.2 mmol) in dry dichloromethane (0.25 M) were stirred at room temperature in a flask attached to a bubbler. To this solution was added one drop of *N,N*-dimethylformamide and the solution was stirred for 2 h (or until the effervescence ceased). The solution was concentrated and then added dropwise to a solution of 2-(3,4-dimethoxyphenyl)ethanamine (0.181 g, 1 mmol) and triethylamine (0.28 mL, 2 mmol) in dry dichloromethane (5.0 mL) at 0°C. The reaction mixture was stirred at room temperature overnight and then quenched with brine and extracted with dichloromethane. The combined organic extracts were dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc) to give the product as a pale yellow solid (0.340 g, 90 % yield); mp 130–131 °C (CH₂Cl₂), lit 127–129 °C (CHCl₃).

N-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-2-(2-bromophenyl)acetamide (**6b**)²

This compound was prepared from 2-(benzo[d][1,3]dioxol-5-yl)ethanamine according to the procedure described for compound **6a** to give the product as a pale yellow solid (0.271 g, 75 % yield); mp 130–132 °C (CH₂Cl₂), lit 129.1–131.8 °C (CHCl₃).

(*S*)-1-(2-Bromobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9a**)¹

To a solution of amide **6a** (0.378 g, 1 mmol) in dichloromethane (5.0 mL) in a round-bottomed flask equipped with a magnetic stirrer and a condenser was added phosphorus oxychloride (0.37 mL, 4 mmol) and the resulting mixture was refluxed for 8 h. The reaction mixture was then cooled to 0 °C and neutralised with saturated sodium carbonate solution. The resulting mixture was extracted with Et₂O to afford imine **7a**. This compound was used immediately without further purification. A solution of dimeric dichloro(*p*-cymene)ruthenium(II) (18 mg, 0.03 mmol), 1,2-(*R,R*)-*N*-tosyl-1,2-diphenylethylenediamine **12** (23 mg, 0.062 mmol), and NEt₃ (7 µL, 0.05 mmol) in DMF (1.0 mL) was stirred under

nitrogen for 1 h at 80 °C. The warm solution was added to the imine **7a** in DMF (2.0 mL) and the mixture was cooled to 0 °C. A formic acid-triethylamine azeotropic mixture (5:2, 0.5 mL) was then added dropwise and the reaction mixture was stirred for 2 h at room temperature. Saturated potassium carbonate solution was added to the reaction mixture, which was then diluted with water and extracted with ethyl acetate. The combined organic phases were dried (Na₂SO₄) and evaporated under reduced pressure. The brown residue was purified by column chromatography on silica gel (EtOAc/NEt₃, 100:1 or CH₂Cl₂/MeOH, 10:1) to give the product as a yellow oil (0.326 g, 90 % yield).

(S)-5-(2-Bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (9b)²

This compound was prepared from amide **6b** according to the procedure described for compound **9a** to give the product as a pale yellow oil (0.277 g, 80 % yield).

(S)-Methyl 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (10a)²

Methyl chloroformate (0.15 mL, 2 mmol) was added slowly to a solution of tetrahydroisoquinoline **9a** (0.362, 1 mmol), diisopropylethylamine (0.33 mL, 2 mmol) and 1 mg of 4-(dimethylamino)pyridine in CH₂Cl₂ (5.0 mL) and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then quenched by adding saturated ammonium chloride solution and extracted with CH₂Cl₂. The combined organic phases were purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give the product as a brown solid (0.344 g, 82 % yield); mp 172–173 °C (CH₂Cl₂); lit 173–175 °C (CHCl₃).

(S)-Methyl 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate (10b)

This compound was prepared from tetrahydroisoquinoline **9b** according to the procedure described for compound **10a** to give the product as a brown solid (0.364 g, 90 % yield); mp 185–187 °C (CH₂Cl₂). NMR analysis revealed the presence of two rotamers present in a 2.3:1 ratio. ¹H NMR (600 MHz, CDCl₃): δ = 2.58 (m, 1H), 2.65–3.39 (m, 4H), 3.09 (s, 3H), 4.18 (m, 1H), 5.26 (dd, J = 10.5, 3.6 Hz, 1H), 5.81 (d, J = 4 Hz, 2H), 6.49 (s, 1H), 6.66 (s, 1H), 6.95–7.02 (m, 3H), 7.46 (d, J = 7.6 Hz, 1H); minor rotamer: 2.55 (m, 1H), 2.65–3.39 (m, 4H), 3.49 (s, 3H), 3.81 (m, 1H), 5.33 (dd, J = 8.4, 5.6 Hz, 1H), 5.78 (d, J = 9.5 Hz, 2H), 6.42 (s, 1H), 6.66 (s, 1H), 7.07–7.12 (m, 3H), 7.42 (d, J = 8.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃):

δ = 28.6, 37.1, 42.8, 52.1, 54.1, 100.9, 106.8, 108.6, 125.1, 127.3, 127.4, 128.2, 129.6, 131.6, 132.4, 137.7, 146.2, 146.5, 155.8; minor rotamer: 28.6, 38.7, 42.0, 52.6, 55.0, 100.8, 107.3, 108.3, 125.4, 127.1, 127.5, 128.2, 129.6, 131.5, 132.6, 137.6, 145.9, 146.5, 155.8; HRMS: $[M+Na]^+$ calcd for $C_{19}H_{18}BrNNaO_4$: 426.0317 (100%), 428.0296 (97.3%), found: 426.0330, 428.0313.

(S)-Methyl 1,2-dimethoxy-6a,7-dihydro-4H-dibenzo[de,g]quinoline-6(5H)-carboxylate (12a)²

$Pd(OAc)_2$ (11 mg, 0.05 mmol), KOAc (0.196 g, 2 mmol), DavePhos **11** (38 mg, 0.1 mmol) and tetrahydroisoquinoline **10a** (0.42g, 1 mmol) were placed in a round-bottomed flask with a magnetic stirrer bar. The flask was purged for 5 min with nitrogen. DMA was then added (2.0 mL) and the resulting mixture was heated to 130 °C overnight. The reaction mixture was then concentrated and purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to give the product as a grey white solid (0.237 g, 70 % yield); mp 176–177 °C ($CHCl_3$), lit 176–177 °C ($CHCl_3$).

(S)-Methyl 7a,8-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinoline-7(6H)-carboxylate (12b)³

This compound was prepared from tetrahydroisoquinoline **10b** according to the procedure described for compound **12a** to give the product as a white solid (0.21 g, 65 % yield); mp 150–152 °C ($CHCl_3$), lit 152–153 °C ($CHCl_3$).

(S)-nuciferine (3a)⁴

$LiAlH_4$ (2.0 M in THF, 0.6 mL, 1.2 mmol) was added to a stirred solution of tetrahydroisoquinoline **12a** (0.339 g, 1 mmol) in dry THF (5 mL) at 0 °C under nitrogen and the resulting mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was slowly hydrolysed with water and extracted with diethyl ether, dried, filtered, evaporated and then purified by chromatography on silica gel (acetone or $CH_2Cl_2/MeOH$, 10:1) to give the product as a white solid (0.265 g, 90 % yield); mp 169–170 °C ($CHCl_3$), lit 165–167 °C (MeOH); $[\alpha]_D^{23} +149.5$ (c 2, CH_2Cl_2), lit $[\alpha]_D^{21} +165$ (c 0.26, EtOH); 1H NMR ($CDCl_3$, 400 MHz) δ = 2.57 (s, 3H), 2.66–2.72 (m, 3H), 3.06–3.11 (m, 2H), 3.13–3.20 (m, 2H), 3.65 (s, 3H), 3.88 (s, 3H), 6.63 (s, 1 H), 7.21–7.30 (m, 3H), 8.35 (d, J = 8.0, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 29.2, 35.1, 43.9, 53.3, 55.9, 60.2, 62.4, 111.3,

126.9, 127.0, 127.3, 127.9, 128.0, 128.3, 128.7, 132.2, 136.5, 145.2, 152.0; HRMS: $[M+H]^+$ calcd for $C_{19}H_{22}NO_2$: 296.1651, found: 296.1655.

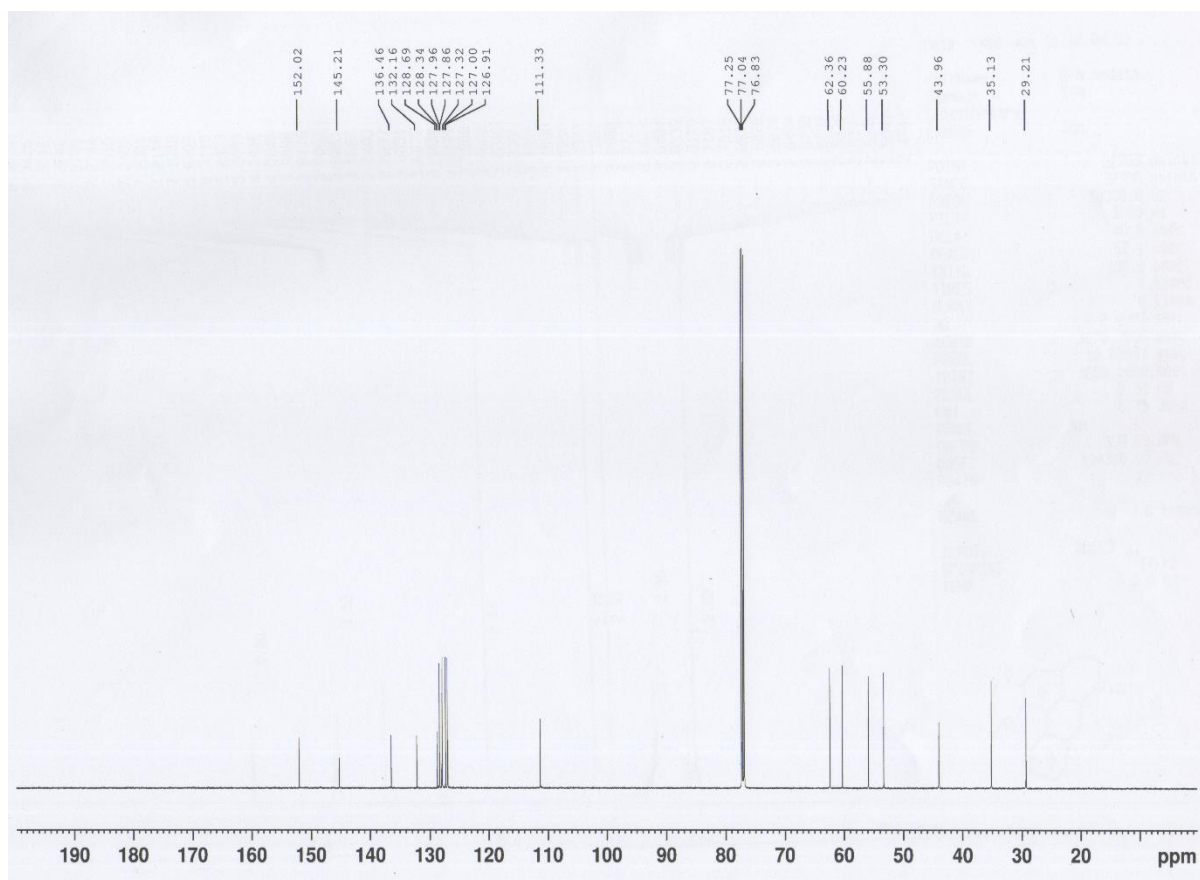
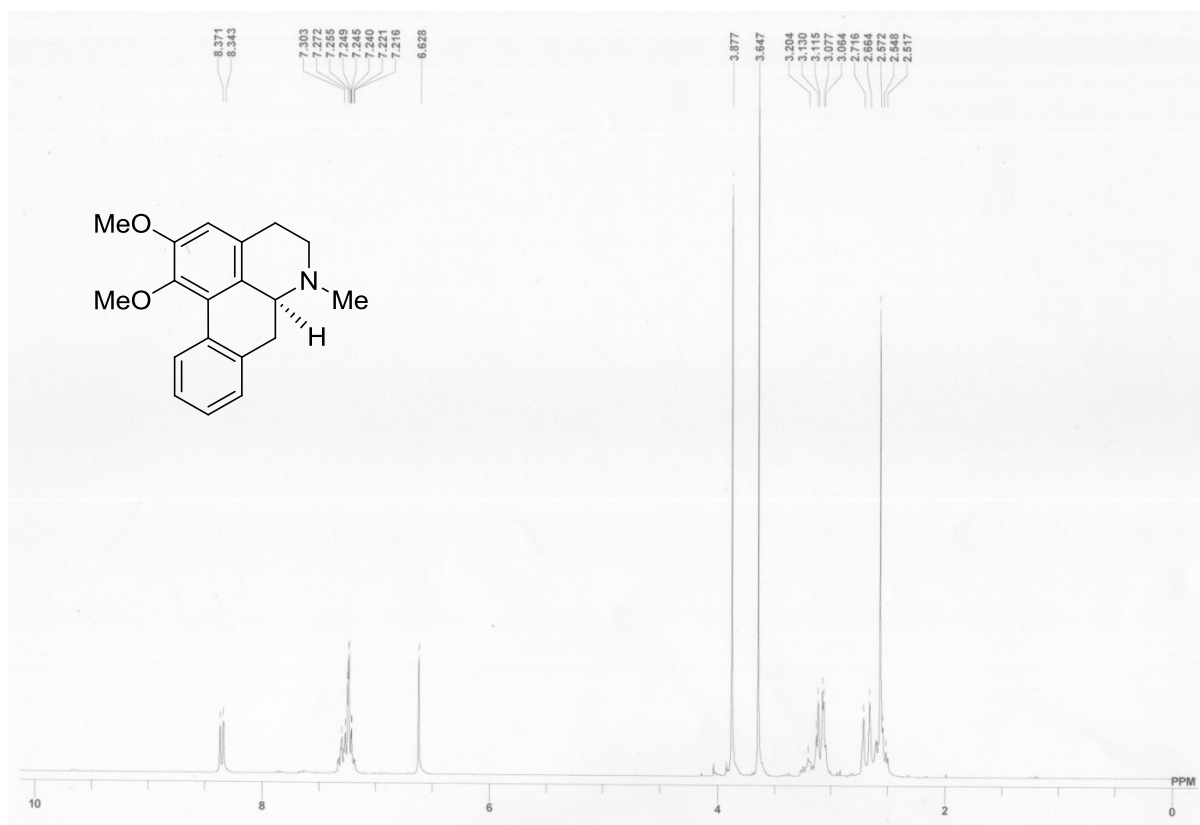
(S)-roemerine (3b)^{5,6}

This compound was prepared was prepared from tetrahydroisoquinoline **12b** according to the procedure described for compound **3a** to give the product as a white solid (0.251 g, 90 % yield); mp 100–102 °C (CH_2Cl_2), lit⁵ 102–103 °C (Et_2O /pet ether); $[\alpha]_D^{23}$ +44.0 (c 0.2, CH_2Cl_2), lit⁶ $[\alpha]_D^{20}$ +69 (c 0.17, $CHCl_3$); ¹H NMR ($CDCl_3$ + MeOH- d_4 , 400 MHz) δ = 2.53 (s, 3H), 2.71–2.57 (m, 4H), 3.22–3.02 (m, 3H), 5.86 (d, J = 1.2, 1H), 6.01 (d, J = 1.2, 1H), 6.49 (s, 1H), 7.26–7.16 (m, 3H), 7.99 (d, J = 7.6, 1H); ¹³C NMR ($CDCl_3$ + MeOH- d_4 , 100 MHz) δ = 27.0, 32.5, 42.2, 54.0, 63.6, 102.8, 108.4, 117.3, 121.5, 124.9, 128.2, 129.0, 129.4, 129.5, 131.1, 132.7, 145.1, 150.0; HRMS: $[M+H]^+$, calcd for $C_{18}H_{18}NO$ 280.1338, found: 280.1330.

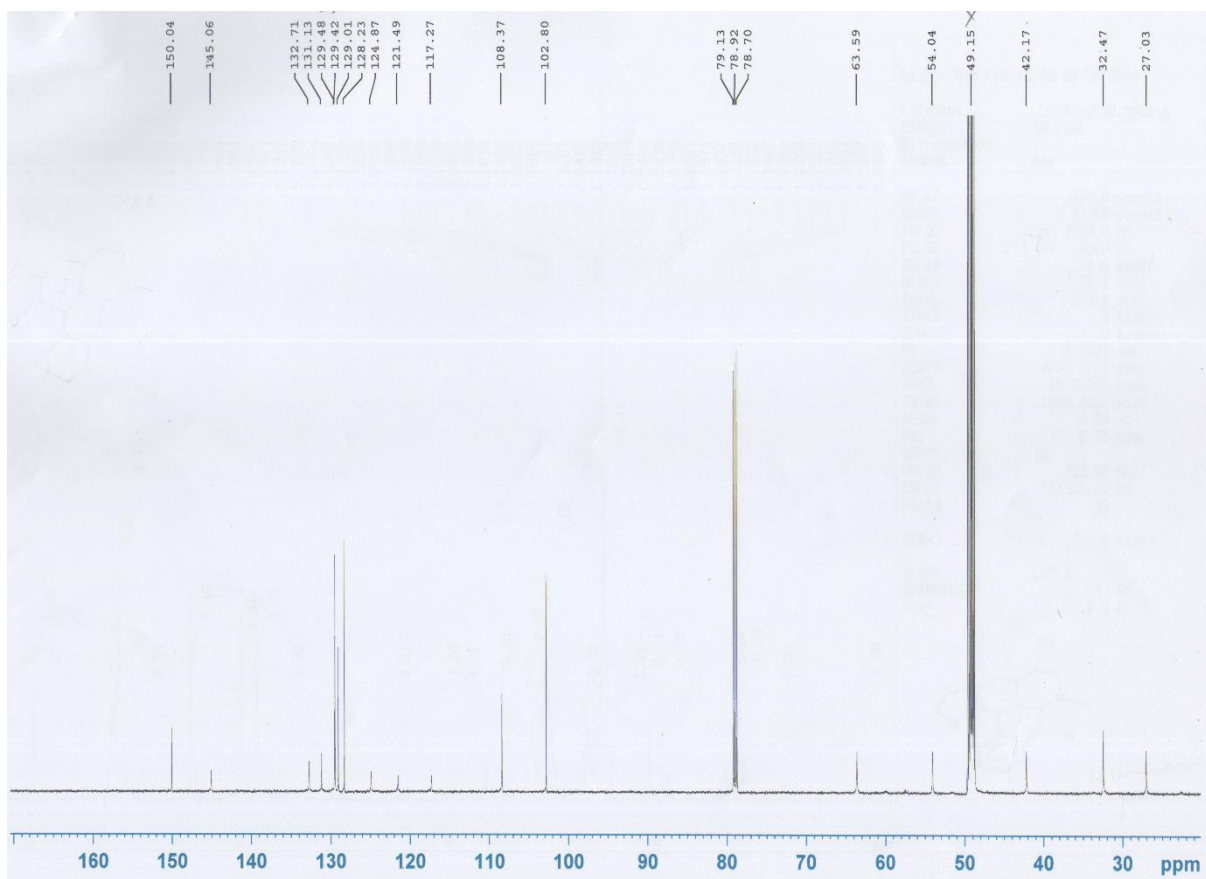
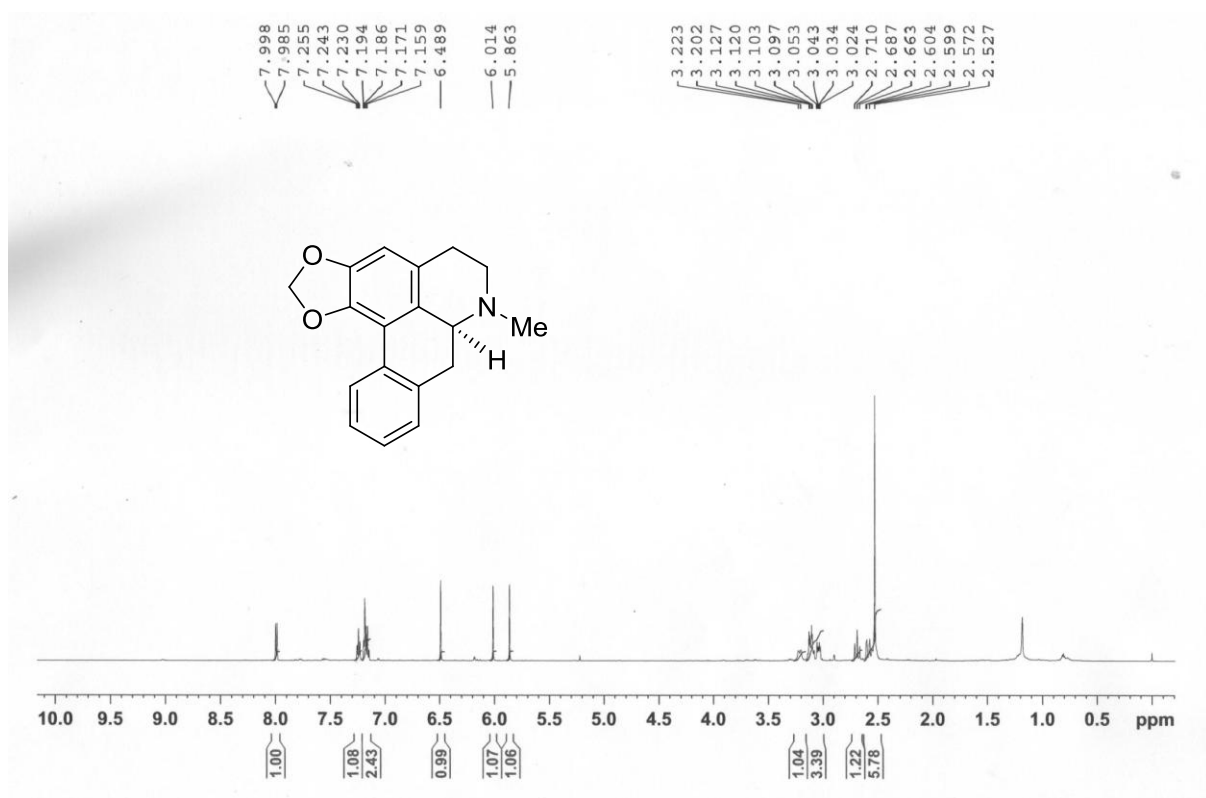
References for supporting information

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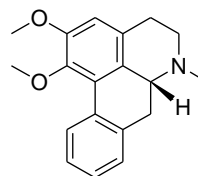
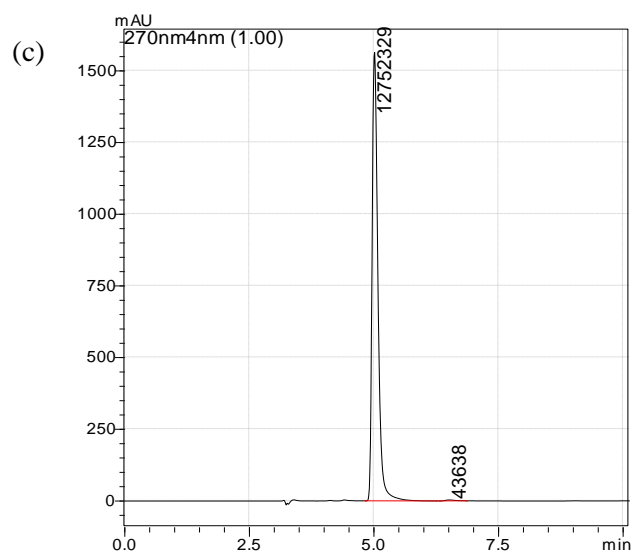
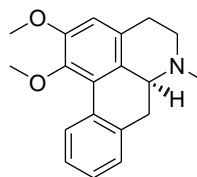
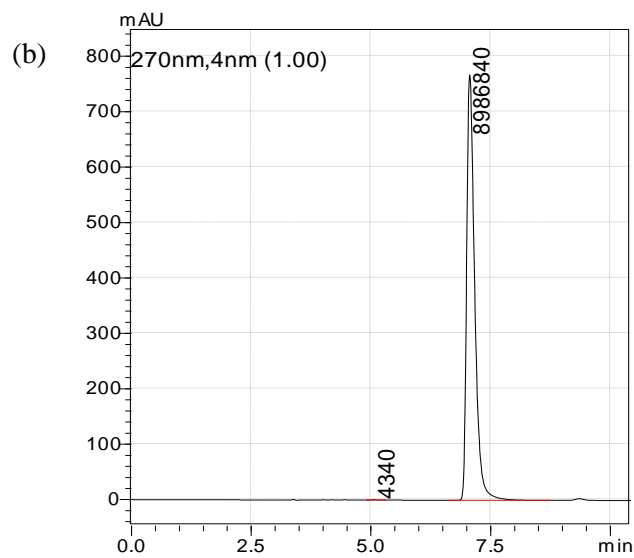
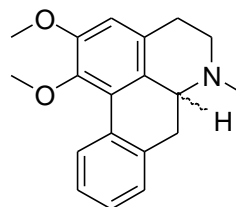
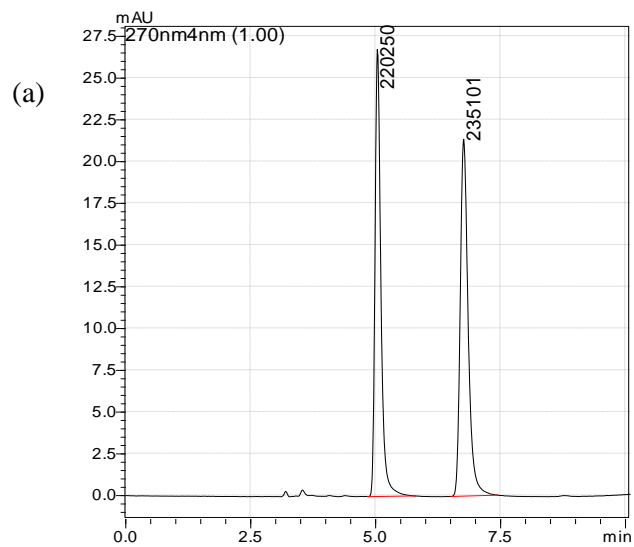
^1H and ^{13}C NMR spectra of (*S*)-nuciferine (3a)



^1H and ^{13}C NMR spectra of (*S*)-roemerine (3b)



HPLC chromatograms of (a) synthesised (\pm)-nuciferine, (b) synthesised (*S*)-nuciferine 99.9% ee and (c) commercial (*R*)-nuciferine 99.3% ee



HPLC chromatograms of (a) synthesised (\pm)-roemerine, (b) synthesised (*S*)-roemerine 96.3% ee and (c) commercial (*R*)-roemerine 99.8% ee

