Electronic Supplementary Information

Discovery of 7-hydroxyaporphines as conformational restricted ligands for beta-1 and beta-2 adrenergic receptors†

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Content

1. General Experimental Conditions

All reactions involving air-sensitive reagents were carried out in oven-dried glassware equipped with a magnetic stir bar and fitted with rubber septa under argon unless otherwise stated. All commercially available chemicals and reagent grade solvents were used directly without further purification unless otherwise specified. All reactions were monitored by thin-layer chromatography (TLC) on Baker-flex® silica gel plates (IB2-F) using UV-light (254 and 365 nm) detection or visualizing agents (ninhydrin or phosphomolybdic acid stain). Flash column chromatography was conducted on silica gel (230−400 mesh) using Teledyne Isco CombiFlash® Rf. Melting points were measured using a Thomas Hoover Uni-Melt capillary melting point apparatus and are uncorrected. NMR spectra were recorded at room temperature using a JEOL ECA-500 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or a JEOL ECX-400P (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) with reference to solvent signals [^{1}H-NMR: $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), DMSO-d_6 (2.50 ppm); ^{13}C-NMR: $CDCl_3$ (77.0 ppm), CD_3OD (49.15 ppm), DMSO-d_6 (39.51 ppm)]. Signal patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (J) are given in Hz. High resolution mass spectra (HRMS) were performed by the University of Texas Mass Spectrometry facility using a quadrupole time-of-flight (Q-TOF) mass spectrometer with electrospray ionization (ESI). The spectra were reported as m/z (relative intensity) for the molecular ion [M]. Optical rotations were measured on ATAGO's polarimeter (POLAX-2L). Specific rotation $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

2. Functional Assays

The functional assays were conducted by Eurofins Panlab Discovery Service. Compound **2** was tested for both agonist and antagonist activities of the adrenergic receptor subtypes β_1 and β_2 using conditions described in Table S1. For functional antagonism, the β_1-adrenergic receptor was first agonized with isoproterenol to release cAMP. The agonism, detected by cAMP accumulation, was subsequently blocked through the treatment with either compound **2** (IC_{50} = 0.017 ± 0.014 μM) or the positive control, atenolol (IC_{50} = 0.40 ± 0.003 μM) as shown in Figure S1. Following a similar protocol, **2** and the positive control, ICI-118,551, inhibited the procaterol-induced cAMP increase at the β_2-adrenergic receptor with IC_{50} values of 0.0069 ± 0.0027 μM and 0.00067 ± 0.00012 μM, respectively (Figure S2). In the absence of β_1 or β_2 agonists, compound **2** had no effect.

Table S1. Methods for β_1 and β_2-adrenergic receptor functional assays

	Adrenergic β_1, adenylyl cyclase	**Adrenergic β_2, adenylyl cyclase**
Target	Human CHO-K1 cells	Human CHO cells
Quantitation method	HTRF quantitation of cAMP accumulation	HTRF quantitation of cAMP accumulation
Vehicle	0.40% DMSO	0.40% DMSO
Incubation time/temp	15 minutes @ 37°C	20 minutes @ 37°C
Incubation buffer	HBSS, 5 mM HEPES, 0.1% BSA, 100 μM IBMX, pH 7.4	HBSS, 5 mM HEPES, 0.1% BSA, 100 μM IBMX, pH 7.4

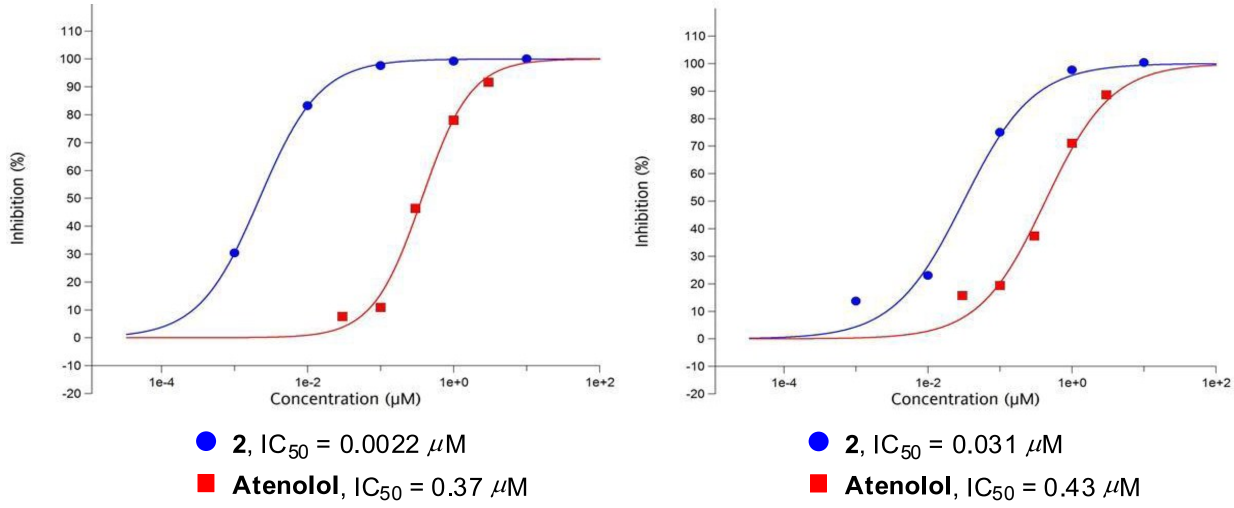
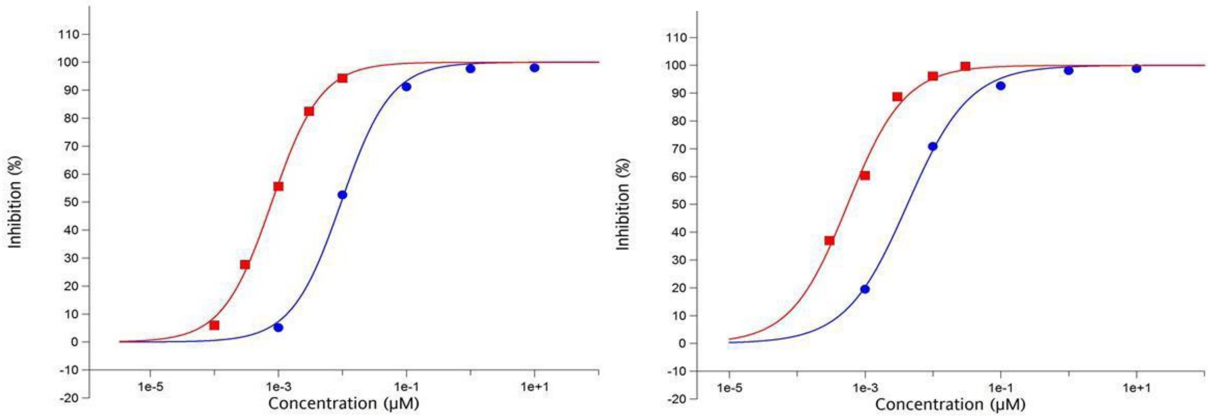


Figure S1. Dose-response curves of **2** and atenolol (positive control) for inhibition of isoproterenol-induced cAMP increase in a β_1-adrenergic receptor functional assay.



● **2**, IC_{50} = 9.53 nM

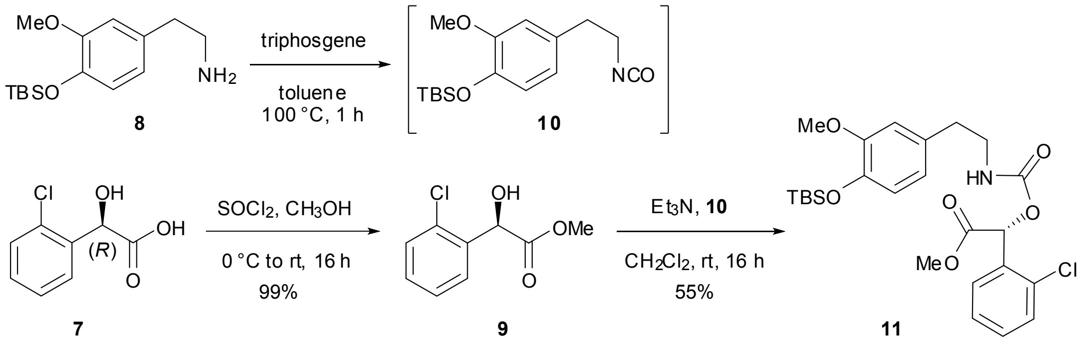
■ **ICI-118,551**, IC_{50} = 0.79 nM

● **2**, IC_{50} = 4.2 nM

■ **ICI-118,551**, IC_{50} = 0.55 nM

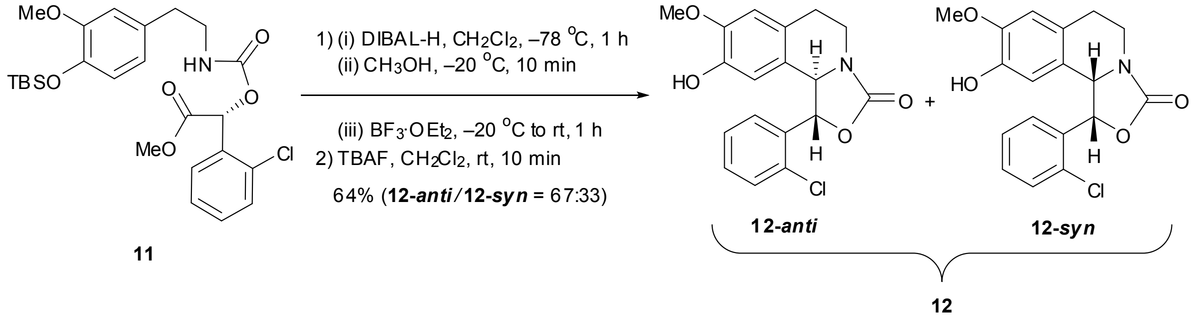
Figure S2. Dose-response curves of **2** and ICI-118,551 (positive control) for inhibition of isoproterenol-induced cAMP increase in a β_2-adrenergic receptor functional assay.

3. Synthetic Procedures



Methyl (*R*)-2-(2-chlorophenyl)-2-hydroxyacetate (9) To a solution of (*R*)-(−)-2-chloromandelic acid (**7**) (7.38 g, 39.5 mmol) in CH_3OH (15 mL) was added $SOCl_2$ (3.2 mL, 44 mmol) at 0 °C under argon. After being stirred at room temperature for 16 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (100 mL). The mixture was then evaporated *in vacuo* to remove CH_3OH. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford **9** (7.9 g, 99%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.40−7.39 (2 H, m), 7.29−7.27 (2 H, m), 5.57 (1 H, s), 3.78 (3 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 173.7, 135.9, 133.5, 130.0, 129.8, 128.8, 127.2, 70.3, 53.2; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + Na]^+$ calculated for $C_9H_9ClO_3Na$ 223.0132; found 223.0132. The crude product was used directly in the next step.

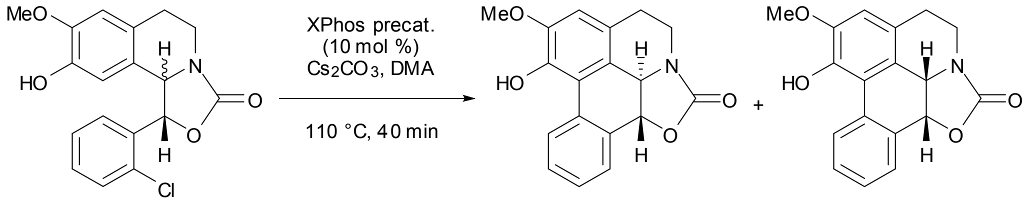
Methyl (*R*)-2-(((4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenethyl)carbamoyl)oxy)-2-(2-chlorophenyl)acetate (11) To a solution of triphosgene (630 mg, 2.1 mmol) in anhydrous toluene (5 mL) was added a solution of **8** (850 mg, 3.0 mmol) in anhydrous toluene (5 mL) under argon. The mixture was stirred at room temperature for 30 min and heated to 100 °C for another 1 h. The resulting mixture was then allowed to cool to room temperature and slowly added into a suspension of **9** (400 mg, 2.0 mmol) and triethylamine (340 μL, 2.4 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon. After being stirred at room temperature for 16 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl, evaporated *in vacuo* to remove excess toluene and CH_2Cl_2, and then partitioned between H_2O and EtOAc. Following neutralization with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 5:95 to 7:93 to 10:90) to afford **11** (560 mg, 55%) as a colorless oil; **$[\alpha]^{24}_D$** −67 (*c* 1.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.43−7.40 (2 H, m), 7.33−7.27 (2 H, m), 6.76 (1 H, d, *J* = 8.0 Hz), 6.67 (1 H, d, *J* = 2.0 Hz), 6.62 (1 H, dd, *J* = 8.0, 2.0 Hz), 6.45 (1 H, s), 4.98 (1H, br, NH), 3.77 (3 H, s), 3.75 (3 H, s), 3.46−3.42 (2 H, m), 2.75 (2 H, t, J = 7.0 Hz), 0.99 (9 H, s), 0.14 (6 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 169.6, 155.0, 150.9, 143.6, 134.1, 132.5, 131.8, 130.4, 129.9, 129.4, 127.1, 120.9, 120.8, 112.6, 71.2, 55.4, 52.7, 42.5, 35.5, 25.7 (3 ×), 18.4, −4.7 (2 ×); **HRMS** (ESI/Q-TOF) *m/z* $[M + Na]^+$ calculated for $C_{25}H_{34}ClNO_6SiNa$ 530.1736; found 530.1740.



To a solution of **11** (308 mg, 0.61 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise a solution of DIBAL-H (25% in toluene, 800 μL, 1.2 mmol) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. Then, CH_3OH (500 μL) was added, and the reaction was stirred at −20 °C for 10 min. Following the addition of $BF_3{\cdot}OEt_2$ (740 μL, 6 mmol), the resulting mixture was stirred at room temperature for another 1 h. This reaction mixture was quenched with H_2O (5 mL), evaporated *in vacuo* to remove excess CH_3OH, and then partitioned between H_2O and EtOAc. After neutralization with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. To the crude mixture in anhydrous CH_2Cl_2 (5 mL) was added TBAF (1.0 M in THF, 470 μL, 4.7 mmol) under argon. After being stirred at room temperature for 10 min, the reaction was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford **12** (132 mg, 64%) as a mixture of diastereomers (*dr* 67:33 for the *anti/syn* isomers). *Anti*-isomer ***12-anti*** could be obtained after several recrystalizations with EtOAc and hexane.

(1*R*,10b*R*)-1-(2-Chlorophenyl)-9-hydroxy-8-methoxy-5,6-dihydro-1*H*-oxazolo[4,3-*a*]isoquinolin-3(10b*H*)-one (12-*anti*) White prisms; **mp** 87−89 °C; **$[\alpha]^{26}_D$** −60 (c 2.4, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.55 (1 H, dd, J = 7.0, 2.5 Hz), 7.47−7.46 (1 H, m), 7.40−7.34 (2 H, m), 6.89 (1 H, s), 6.61 (1 H, s), 5.73 (1 H, d, J = 4.5 Hz), 5.66 (1 H, s, PhOH), 4.82 (1 H, d, J = 4.5 Hz), 4.11 (1 H, ddd, J = 13.0, 6.0, 1.5 Hz), 3.88 (3 H, s), 3.20 (1 H, td, J = 13.0, 4.0 Hz), 3.10 (1 H, td, J = 16.0, 6.0 Hz), 2.61 (1 H, dd, J = 16.0, 4.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 157.6, 146.2, 144.7, 135.7, 132.3, 130.2, 130.2, 128.1, 127.5, 126.3, 125.5, 111.2, 110.9, 79.4, 61.4, 55.9, 39.4, 26.8; **HRMS** (ESI/Q-TOF) *m/z* $[M + H]^+$ calculated for $C_{18}H_{17}ClNO_4$ 346.0841;

found 346.0840.

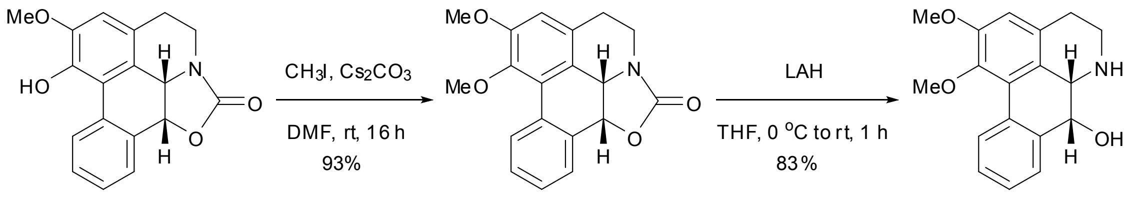


12 (*dr* 67:33) **13-*anti*** (70%) **13-*syn*** (24%)

To **12** (*dr* 67:33) (39 mg, 0.11 mmol), Cs_2CO_3 (111 mg, 0.34 mmol) and XPhos precatalyst (8 mg, 0.011 mmol) was added anhydrous DMA (500 μL) under argon. The reaction was stirred at room temperature for 5 min and then put into a preheated oil bath (110 °C) for another 40 min. After being quenched by the addition of 1 N $HCl_{(aq)}$, the aqueous layer was extracted with EtOAc (2 × 30 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 25:75 to 30:70 to 35:65 to 50:50) to afford **13-*anti*** (24 mg, 70%) and **13-*syn*** (8 mg, 24%) in a combined yield of 94%.

(3^1*R*,12b*R*)-8-Hydroxy-7-methoxy-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de,g*]oxazolo[5,4,3-*ij*]quinolin-2-one (13-*anti*) White prisms; **mp** 218−219 °C; **[α]^{25}$_D$** −103 (*c* 0.97, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.39 (1 H, d, *J* = 8.0 Hz), 7.47 (1 H, d, *J* = 7.5 Hz), 7.43 (1 H, t, *J* = 8.0 Hz), 7.35 (1 H, t, *J* = 7.5 Hz), 6.68 (1 H, s), 6.34 (1 H, s, PhOH), 4.79 (1 H, d, *J* = 13.0 Hz), 4.17 (1 H, d, *J* = 13.0 Hz), 4.01−3.97 (1 H, m), 3.94 (3 H, s), 3.47−3.42 (1 H, m), 3.04−2.97 (1 H, m), 2.94−2.90 (1 H, m); **^{13}C NMR** ($CDCl_3$, 125 MHz) 157.8, 147.3, 142.7, 133.5, 130.4, 129.6, 127.8, 127.7, 121.9, 121.3, 120.1, 116.0, 109.5, 81.6, 56.5, 56.2, 37.8, 26.7; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{18}H_{16}NO_4$ 310.1074; found 310.1079.

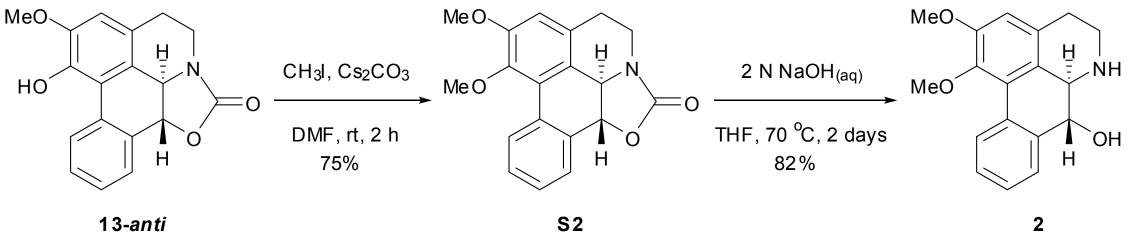
(3^1*S*,12b*R*)-8-Hydroxy-7-methoxy-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de,g*]oxazolo[5,4,3-*ij*]quinolin-2-one (13-*syn*) White prisms; **mp** 237−239 °C; **[α]^{24}$_D$** −80 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.78 (1 H, d, *J* = 8.0 Hz), 7.54−7.50 (2 H, m), 7.35 (1 H, td, *J* = 7.5, 1.0 Hz), 6.76 (1 H, s), 6.45 (1 H, s, PhOH), 5.56 (1 H, d, *J* = 7.0 Hz), 4.70 (1 H, d, *J* = 7.0 Hz), 3.95 (3 H, s), 3.67 (1 H, dd, *J* = 11.0, 7.5 Hz), 3.52 (1 H, td, *J* = 11.0, 6.5 Hz), 2.92−2.80 (2 H, m); **^{13}C NMR** ($CDCl_3$, 125 MHz) 160.4, 146.9, 142.6, 132.1 (2 ×), 130.7, 129.1, 127.7, 126.9, 126.5, 123.6, 115.8, 110.1, 73.2, 56.5, 52.6, 40.4, 27.1; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + Na]^+$ calculated for $C_{18}H_{15}NO_4Na$ 332.0893; found 332.0895.



13-*syn* **S1** **1**

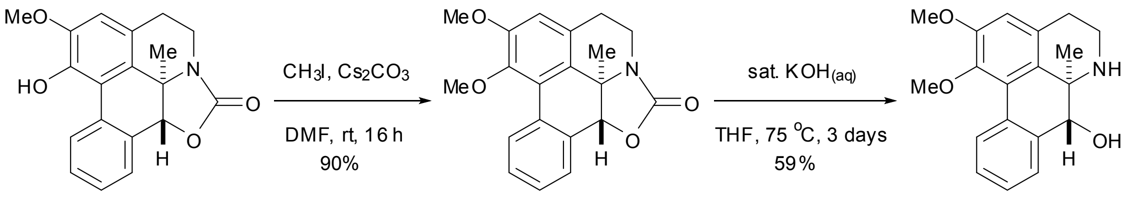
(3^1*S*,12b*R*)-7,8-Dimethoxy-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de,g*]oxazolo[5,4,3-*ij*]quinolin-2-one (S1) To a solution of **13-*syn*** (64 mg, 0.20 mmol) and Cs_2CO_3 (82 mg, 0.25 mmol) in anhydrous DMF (1 mL) was added CH_3I (16 μL, 0.25 mmol) under argon, and the mixture was stirred at room temperature for 16 h. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/CH_2Cl_2, 0:100 to 2:98) to afford **S1** (62 mg, 93%) as a white solid; **mp** 236−237 °C; **$[\alpha]^{24}_D$** −78 (*c* 1.4, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.77 (1 H, d, *J* = 8.0 Hz), 7.53−7.49 (2 H, m), 7.38−7.35 (1 H, m), 6.80 (1 H, s), 5.51 (1 H, d, *J* = 7.5 Hz), 4.67 (1 H, d, *J* = 7.5 Hz), 3.91 (3 H, s), 3.72 (3 H, s), 3.69−3.65 (1 H, m), 3.58−3.52 (1 H, m), 2.93−2.81 (2 H, m); **^{13}C NMR** ($CDCl_3$, 125 MHz) 160.4, 153.7, 146.0, 132.2, 131.9, 131.5, 131.1, 128.7, 128.2, 127.3, 123.4, 123.0, 112.1, 73.1, 60.2, 56.0, 52.5, 40.4, 27.3; **HRMS** (ESI/Q-TOF) *m/z* $[M + Na]^+$ calculated for $C_{19}H_{17}NO_4Na$ 346.1050; found 346.1056.

(6a*S*,7*R*)-1,2-Dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinolin-7-ol (1) To a solution of **S1** (17 mg, 0.053 mmol) in THF (3 mL) was added a solution of lithium aluminum hydride (LAH) (1.0 M in THF, 260 μL) at 0 °C under argon, and the mixture was stirred at room temperature for 1 h. After being quenched with saturated aqueous sodium potassium tartrate (5 mL) for 30 min, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 5:95 to 10:90) to afford **1** (13 mg, 83%) as a pale yellow solid; **mp** 81−82 °C; **$[\alpha]^{22}_D$** −145 (*c* 1.1, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.50 (1 H, d, *J* = 7.0 Hz), 7.43 (1 H, td, *J* = 7.0, 1.5 Hz), 7.38 (1 H, dd, *J* = 7.5, 1.0 Hz), 7.29 (1 H, td, *J* = 7.5, 1.5 Hz), 6.66 (1 H, s), 4.54 (1 H, d, *J* = 2.5 Hz), 3.97 (1 H, s), 3.89 (3 H, s), 3.69 (3 H, s), 3.42 (1 H, dd, *J* = 12.0, 5.0 Hz), 3.13 (1 H, td, *J* = 12.0, 4.0 Hz), 2.99 (1 H, td, *J* = 16.0, 5.0 Hz), 2.70 (1 H, dd, *J* = 16.0, 4.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 152.4, 145.2, 136.3, 131.3, 131.3, 129.4, 129.0, 128.9, 127.8, 125.6, 123.4, 112.1, 71.1, 60.2, 57.1, 55.8, 42.8, 29.0; **HRMS** (ESI/Q-TOF) *m/z* $[M + H]^+$ calculated for $C_{18}H_{20}NO_3$ 298.1438; found 298.1439.



(3^1*R*,12b*R*)-7,8-Dimethoxy-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de,g*]oxazolo[5,4,3-*ij*]quinolin-2-one (S2) To a solution of **13-*anti*** (18 mg, 0.058 mmol) and Cs_2CO_3 (23 mg, 0.07 mmol) in anhydrous DMF (0.5 mL) was added CH_3I (5 µL, 0.07 mmol) under argon, and the mixture was stirred at room temperature for 2 h. After being quenched with H_2O (5 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **S2** (14 mg, 75%) as a white solid; **mp** 196−197 °C; **[α]^{23}$_D$** −70 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.40 (1 H, dd, *J* = 7.0, 1.5 Hz), 7.48 (1 H, d, *J* = 7.0 Hz), 7.44−7.37 (2 H, m), 6.76 (1 H, s), 4.82 (1 H, d, *J* = 13.5 Hz), 4.16 (1 H, d, *J* = 13.5 Hz), 4.03−3.98 (1 H, m), 3.91 (3 H, s), 3.75 (3 H, s), 3.49−3.44 (1 H, m), 3.07−2.94 (2 H, m); **^{13}C NMR** ($CDCl_3$, 125 MHz) 157.7, 153.7, 146.5, 134.0, 130.2, 129.6, 128.2, 128.1, 125.0, 123.7, 121.7, 121.3, 111.6, 81.5, 60.4, 56.2, 56.1, 37.7, 27.0; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{19}H_{18}NO_4$ 324.1230; found 324.1235.

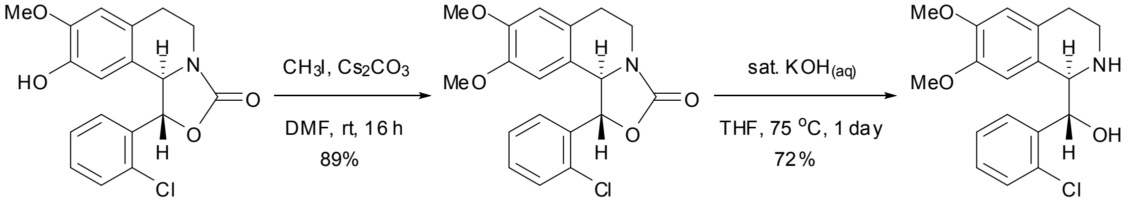
(6a*R*,7*R*)-1,2-Dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinolin-7-ol (2) To a solution of **S2** (10 mg, 0.031 mmol) in THF (2 mL) was added 2 N $NaOH_{(aq)}$ (1 mL), and the mixture was stirred at 70 °C for 2 days. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 5:95 to 10:90) to afford **2** (7.6 mg, 82%) as a pale yellow solid; **mp** 89−91 °C; **[α]^{24}$_D$** +78 (*c* 0.58, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.37−8.35 (1 H, m), 7.73−7.72 (1 H, m), 7.38−7.33 (2 H, m), 6.65 (1 H, s), 4.55 (1 H, d, *J* = 11.5 Hz), 3.88 (3 H, s), 3.67 (1 H, d, *J* = 11.5 Hz), 3.64 (3 H, s), 3.40−3.37 (1 H, m), 3.10−3.03 (1 H, m), 2.98 (1 H, td, *J* = 11.5, 3.5 Hz), 2.73 (1 H, d, *J* = 16.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 152.5, 145.1, 139.0, 130.2, 129.4, 128.1, 127.8, 127.4, 125.9, 124.3, 123.1, 111.8, 72.0, 60.3, 59.0, 55.9, 42.0, 28.9; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{18}H_{20}NO_3$ 298.1438; found 298.1440.



14 **S3** **3**

***rel*-(3^1*S*,12b*S*)-7,8-Dimethoxy-3^1-methyl-3^1,4,5,12b-tetrahydro-2*H*-dibenzo[*de,g*]oxazolo[5,4,3-*ij*]quinolin-2-one (S3)** To a solution of **14** (22 mg, 0.068 mmol) and Cs_2CO_3 (26 mg, 0.08 mmol) in anhydrous DMF (1 mL) was added CH_3I (5 μL, 0.08 mmol) under argon, and the mixture was stirred at room temperature for 16 h. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **S3** (20.7 mg, 90%) as a pale yellow foam; **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.37 (1 H, d, *J* = 8.5 Hz), 7.44−7.37 (3 H, m), 6.74 (1 H, s), 5.07 (1 H, s), 3.92−3.87 (4 H, m), 3.73 (3 H, s), 3.61 (1 H, dt, *J* = 12.5, 7.5 Hz), 3.02−2.99 (2 H, m), 0.95 (3 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 157.2, 153.4, 146.7, 132.6, 130.7, 129.3, 128.2, 128.1, 127.9, 124.6, 123.2, 121.9, 111.7, 84.3, 60.4, 56.3, 56.1, 36.2, 26.6, 16.6; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{20}H_{20}NO_4$ 338.1387; found 338.1390.

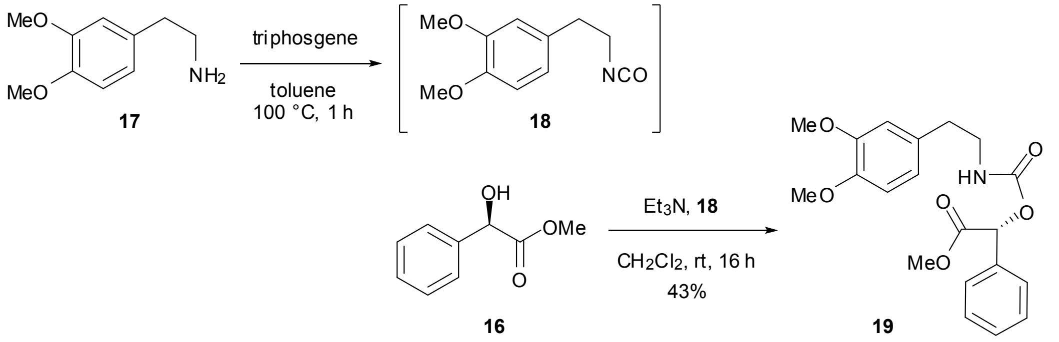
***rel*-(6a*S*,7*S*)-1,2-Dimethoxy-6a-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinolin-7-ol (3)** To a solution of **S3** (22 mg, 0.065 mmol) in THF (1 mL) was added saturated $KOH_{(aq)}$ (1 mL), and the mixture was stirred at 75 °C for 3 days. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 5:95 to 10:90) to afford **3** (12 mg, 59%) as a white solid; **mp** > 250 °C (decomposed); **^{1}H NMR** (CD_3OD, 400 MHz) 8.36−8.33 (1 H, m), 7.64−7.62 (1 H, m), 7.45−7.38 (2 H, m), 6.90 (1 H, s), 4.90 (1 H, s), 3.90 (3 H, s), 3.65 (3 H, s), 3.58−3.50 (2 H, m), 3.28−3.20 (1 H, m), 3.13−3.07 (1 H, m), 1.17 (3 H, s); **^{13}C NMR** (CD_3OD, 100 MHz) 155.3, 147.5, 138.9, 131.1, 129.6 (2 ×), 129.1, 127.4, 126.4, 125.6, 125.3, 113.5, 74.0, 60.9, 60.7, 56.6, 38.0, 26.0, 15.9; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{19}H_{22}NO_3$ 312.1594; found 312.1597.



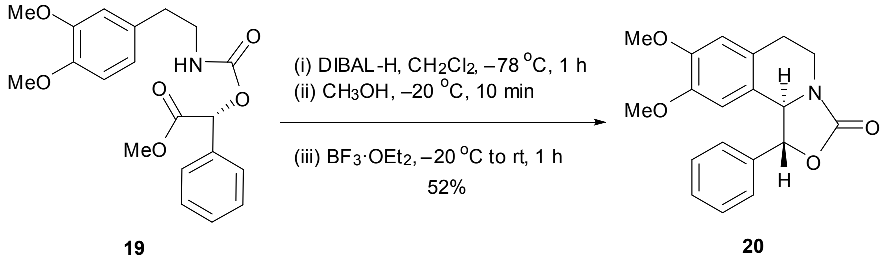
12-*anti* **15** **4**

(1*R*,10b*R*)-1-(2-Chlorophenyl)-8,9-dimethoxy-5,6-dihydro-1*H*-oxazolo[4,3-*a*]isoquinolin-3(10b*H*)-one (15) To a solution of **12-*anti*** (35 mg, 0.10 mmol) and Cs_2CO_3 (39 mg, 0.12 mmol) in anhydrous DMF (1 mL) was added CH_3I (8 μL, 0.12 mmol) under argon, and the mixture was stirred at room temperature for 16 h. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **15** (32 mg, 89%) as a white solid; **mp** 209−210 °C; **$[\alpha]^{24}_{D}$** −138 (*c* 1.3, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.59 (1 H, dd, *J* = 7.5, 1.5 Hz), 7.47 (1 H, dd, *J* = 7.5, 1.5 Hz), 7.43−7.35 (2 H, m), 6.79 (1 H, s), 6.62 (1 H, s), 5.78 (1 H, d, *J* = 5.0 Hz), 4.83 (1 H, d, *J* = 5.0 Hz), 4.15 (1 H, dd, *J* = 12.5, 5.5 Hz), 3.87 (3 H, s), 3.82 (3 H, s), 3.20 (1 H, td, *J* = 12.5, 4.0 Hz), 3.10 (1 H, td, *J* = 16.0, 5.5 Hz), 2.62 (1 H, dd, *J* = 16.0, 4.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 157.5, 148.5, 148.1, 136.1, 131.9, 130.3, 130.1, 128.2, 127.8, 126.0, 125.4, 111.8, 107.9, 79.2, 62.0, 55.9, 55.9, 39.3, 26.7; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{19}H_{19}ClNO_4$ 360.0997; found 360.0997.

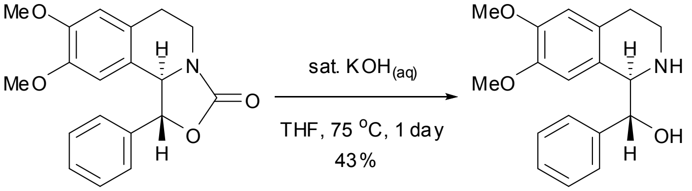
(*R*)-(2-Chlorophenyl)((*R*)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol (4) To a solution of **15** (19 mg, 0.05 mmol) in THF (3 mL) was added saturated $KOH_{(aq)}$ (1 mL), and the mixture was stirred at 75 °C for 1 day. After being quenched with H_2O (10 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 0:100 to 4:96) to afford **4** (12 mg, 72%) as a white foam; **$[\alpha]^{22}_{D}$** +8 (*c* 0.58, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.64 (1 H, d, *J* = 6.4 Hz), 7.37−7.32 (2 H, m), 7.25−7.22 (1 H, m), 6.58 (1 H, s), 6.43 (1 H, s), 5.32 (1 H, d, *J* = 4.0 Hz), 4.16 (1 H, d, *J* = 4.0 Hz), 3.85 (3 H, s), 3.66 (3 H, s), 3.27−3.22 (1 H, m), 3.04−2.98 (1 H, m), 2.89−2.82 (1 H, m), 2.68−2.63 (1 H, m); **^{13}C NMR** ($CDCl_3$, 100 MHz) 147.7, 147.1, 139.8, 132.9, 129.4, 128.6, 128.2, 127.9, 127.0, 126.3, 111.3, 109.4, 71.9, 59.3, 55.8, 55.5, 40.2, 29.1; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{18}H_{21}ClNO_3$ 334.1204; found 334.1207.



(*R*)-Methyl 2-(3,4-dimethoxyphenethylcarbamoyloxy)-2-phenylacetate (19) To a solution of triphosgene (252 mg, 0.85 mmol) in anhydrous toluene (3 mL) was added a solution of 3,4-dimethoxyphenethylamine (**17**) (170 μL, 1.0 mmol) in anhydrous toluene (3 mL) under argon. The mixture was stirred at room temperature for 30 min and heated to 100 °C for another 1 h. The resulting mixture was then allowed to cool to room temperature and slowly added into a suspension of **16** (166 mg, 1.0 mmol) and triethylamine (170 μL, 1.2 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon. After being stirred at room temperature for 16 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl, evaporated *in vacuo* to remove excess toluene and CH_2Cl_2, and then partitioned between H_2O and EtOAc. Following neutralization with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75 to 30:70) to afford **19** (161 mg, 43%) as a colorless oil; **$[\alpha]^{22}_{D}$** −67 (*c* 1.8, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.44−7.36 (5 H, m), 6.79 (1 H, d, $J = 8.0$ Hz), 6.74−6.72 (2 H, m), 5.92 (1 H, s), 5.06 (1 H, br, NH), 3.85 (6 H, s), 3.72 (3 H, s), 3.45−3.42 (2 H, m), 2.78−2.75 (2 H, m); **^{13}C NMR** ($CDCl_3$, 125 MHz) 170.0, 155.2, 148.9, 147.6, 134.1, 130.9, 129.1, 128.7 (2 ×), 127.6 (2 ×), 120.6, 111.8, 111.2, 74.5, 55.8, 55.8, 52.5, 42.4, 35.4; **HRMS** (ESI/Q-TOF) *m/z* $[M + Na]^+$ calculated for $C_{20}H_{23}NO_6Na$ 396.1418; found 396.1413.

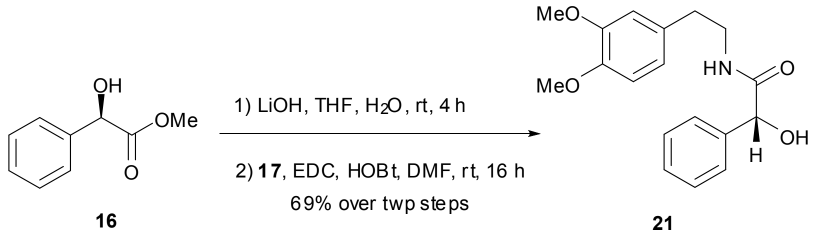


(1*R*,10b*R*)-8,9-Dimethoxy-1-phenyl-5,6-dihydro-1*H*-oxazolo[4,3-*a*]isoquinolin-3(10b*H*)-one (20) To a solution of **19** (130 mg, 0.35 mmol) in anhydrous toluene (10 mL) was added dropwise a solution of DIBAL-H (25% in toluene, 470 μL, 0.7 mmol) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. Then, CH_3OH (280 μL) was added, and the reaction was stirred at −20 °C for 10 min. Following the addition of $BF_3 \cdot OEt_2$ (430 μL, 3.5 mmol), the resulting mixture was stirred at room temperature for another 1 h. This reaction mixture was quenched with H_2O (5 mL), evaporated *in vacuo* to remove excess CH_3OH, and then partitioned between H_2O and EtOAc. After neutralization with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **20** (60 mg, 52%) as a white solid; **mp** 175−176 °C; **$[\alpha]^{22}_D$** −126 (*c* 3.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.52−7.42 (5 H, m), 6.63 (1 H, s), 6.30 (1 H, s), 5.13 (1 H, d, *J* = 7.5 Hz), 4.85 (1 H, d, *J* = 7.5 Hz), 4.17 (1 H, dd, *J* = 13.0, 5.5 Hz), 3.85 (3 H, s), 3.69 (3 H, s), 3.15 (1 H, td, *J* = 13.0, 3.0 Hz), 3.01 (1 H, td, *J* = 16.0, 5.5 Hz), 2.65 (1 H, dd, *J* = 16.0, 3.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 156.6, 148.3, 148.0, 137.7, 129.4, 129.0 (2 ×), 127.0 (2 ×), 125.7, 125.0, 111.9, 107.3, 83.9, 61.5, 55.8, 55.7, 38.5, 27.6; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{19}H_{20}NO_4$ 326.1387; found 326.1393.

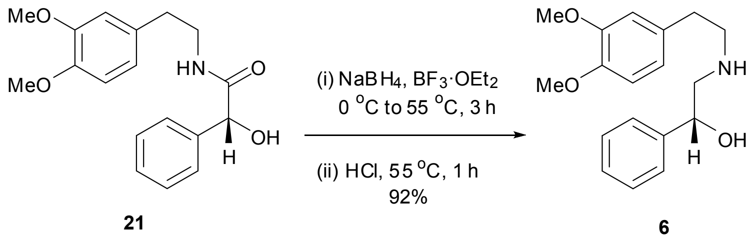


20 **5**

(*R*)-((*R*)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)(phenyl)methanol (5) To a solution of **20** (30 mg, 0.09 mmol) in THF (2 mL) was added saturated $KOH_{(aq)}$ (1 mL), and the mixture was stirred at 75 °C for 1 day. After being quenched with H_2O (10 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 5:95 to 10:90) to afford **5** (12 mg, 43%) as a pale yellow solid; **mp** 142−144 °C; **$[\alpha]^{22}_D$** +30 (*c* 0.83, $CHCl_3$); **^{1}H NMR** (CD_3OD, 500 MHz) 7.38−7.28 (5 H, m), 6.68 (1 H, s), 5.58 (1 H, s), 4.80 (1 H, d, *J* = 8.0 Hz), 4.04 (1 H, d, *J* = 8.0 Hz), 3.76 (3 H, s), 3.46−3.38 (1 H, m), 3.24 (3 H, s), 3.12−3.10 (1 H, m), 2.96−2.91 (1 H, m), 2.84−2.81 (1 H, m); **^{13}C NMR** (CD_3OD, 125 MHz) 149.6, 147.6, 143.6, 129.6 (2 ×), 129.2 (3 ×), 128.1, 125.6, 113.1, 112.8, 75.5, 62.3, 56.4, 55.8, 39.0, 28.5; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{18}H_{22}NO_3$ 300.1594; found 300.1594.

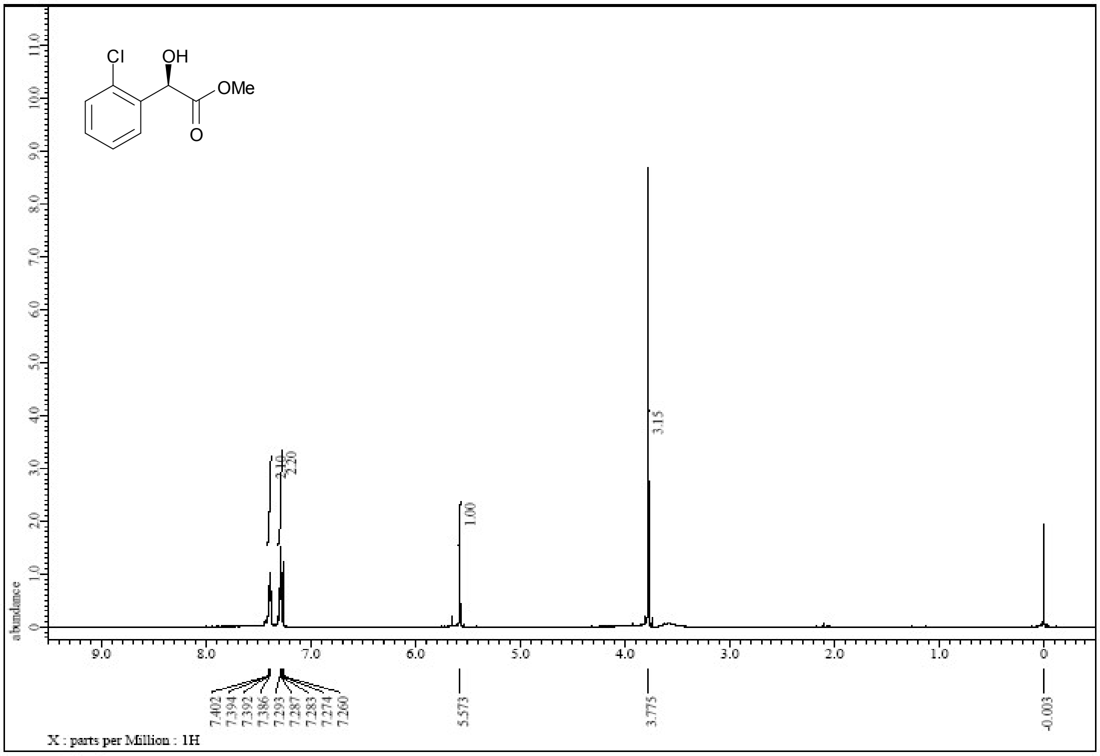


(*R*)-*N*-(3,4-Dimethoxyphenethyl)-2-hydroxy-2-phenylacetamide (21) To a solution of methyl (*R*)-(−)-mandelate (**16**) (332 mg, 2.0 mmol) in THF (3 mL) and H_2O (3 mL) was added $LiOH{\cdot}H_2O$ (672 mg, 16.0 mmol), and the mixture was stirred at room temperature for 4 h. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford the mandelic acid as the crude product. To a solution of this crude product, 3,4-dimethoxyphenethylamine (**17**) (370 μL, 2.2 mmol) and HOBt hydrate (337 mg, 2.2 mmol) in anhydrous DMF (4 mL) was added EDC (422 mg, 2.2 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of 1 N $HCl_{(aq)}$. The aqueous layer was extracted with EtOAc (2 × 20 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 40:60) to afford **21** (433 mg, 69%) as a pale yellow oil; **$[\alpha]^{22}_D$** −39 (*c* 1.9, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.33−7.29 (5 H, m), 6.73 (1 H, d, *J* = 8.4 Hz), 6.62 (1 H, d, *J* = 2.0 Hz), 6.56 (1 H, dd, *J* = 8.4, 2.0 Hz), 6.25 (1 H, br, NH), 4.94 (1 H, s), 3.84 (3 H, s), 3.80 (4 H, s, OCH_3 and OH), 3.51−3.44 (2 H, m), 2.72−2.67 (2 H, m); **^{13}C NMR** ($CDCl_3$, 100 MHz) 172.3, 148.7, 147.4, 139.4, 130.8, 128.4 (2 ×), 128.2, 126.5 (2 ×), 120.5, 111.6, 111.1, 73.8, 55.7, 55.6, 40.3, 34.9; **HRMS** (ESI/Q-TOF) *m/z* $[M + Na]^+$ calculated for $C_{18}H_{21}NO_4Na$ 338.1363; found 338.1360.

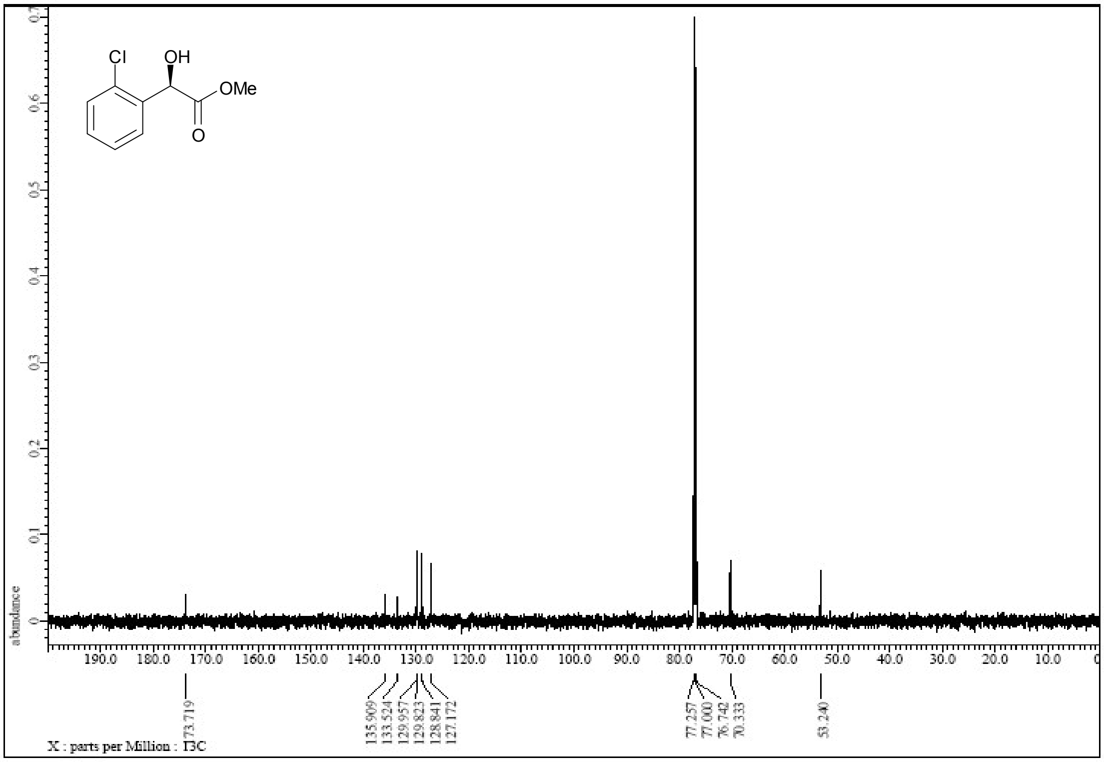


(*R*)-2-(3,4-Dimethoxyphenethylamino)-1-phenylethanol (6) To a solution of **21** (180 mg, 0.57 mmol) in THF (5 mL) was added $NaBH_4$ (45 mg, 1.2 mmol) at 0 °C under argon. Following the addition of $BF_3{\cdot}OEt_2$ (300 μL, 2.4 mmol) dropwise at 0 °C under argon, the resulting mixture was stirred at 55 °C for 3 h. After completion of the reaction, the mixture was cooled to 0 °C, treated with H_2O (5 mL) and 6 N $HCl_{(aq)}$ (5 mL), and then heated at 55 °C for another 1 h. The reaction mixture was cooled to room temperature, treated with 10% $NaOH_{(aq)}$ to adjust the pH value to 10−12, and evaporated *in vacuo* to remove excess THF. After being partitioned between H_2O and CH_2Cl_2, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_3OH/CH_2Cl_2, 5:95 to 10:90) to afford **6** (158 mg, 92%) as a white solid; **mp** 87−88 °C; **$[\alpha]^{22}_{D}$** −38 (*c* 3.9, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.37−7.26 (5 H, m), 6.79 (1 H, d, *J* = 8.0 Hz), 6.74−6.71 (2 H, m), 4.78 (1 H, dd, *J* = 9.0, 3.5 Hz), 3.87 (3 H, s), 3.86 (3 H, s), 3.17 (1 H, br), 3.00−2.89 (3 H, m), 2.82−2.75 (3 H, m); **^{13}C NMR** ($CDCl_3$, 125 MHz) 148.9, 147.5, 142.1, 131.7, 128.4 (2 ×), 127.6, 125.8 (2 ×), 120.6, 111.8, 111.2, 71.3, 56.7, 55.9, 55.8, 50.6, 35.5; **HRMS** (ESI/Q-TOF) *m*/*z* $[M + H]^+$ calculated for $C_{18}H_{24}NO_3$ 302.1751; found 302.1747.

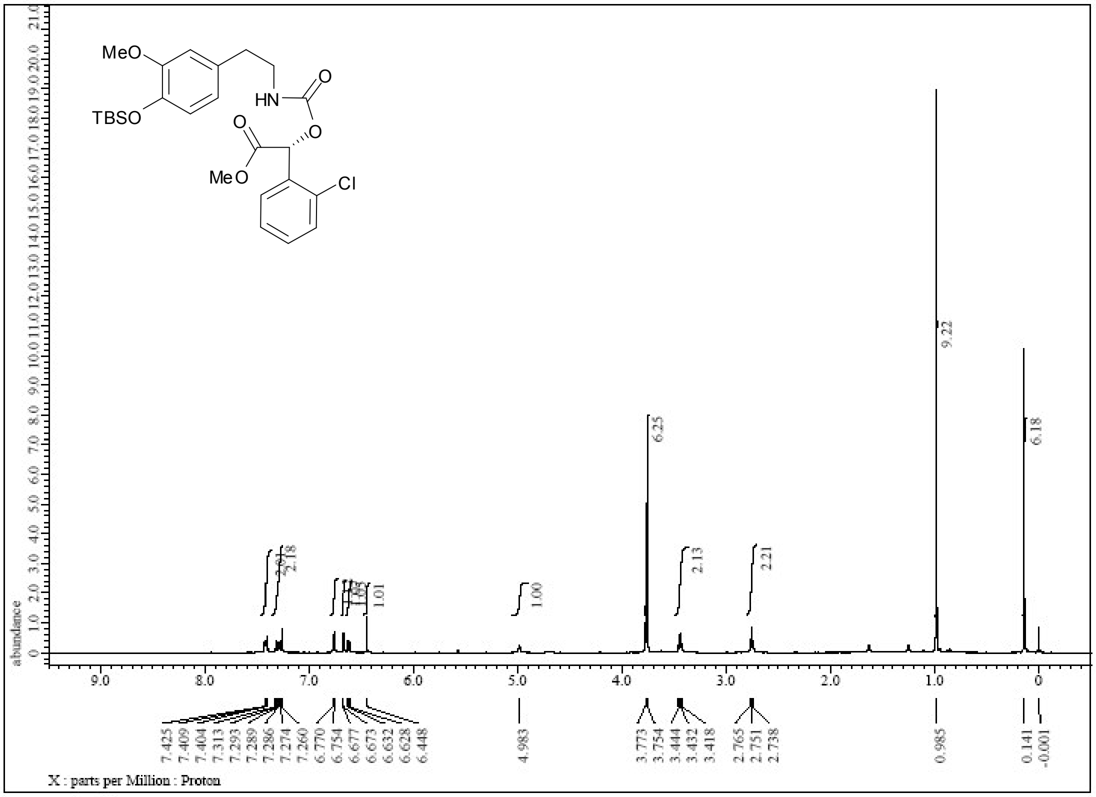
4. Copies of the ^{1}H and ^{13}C NMR spectra



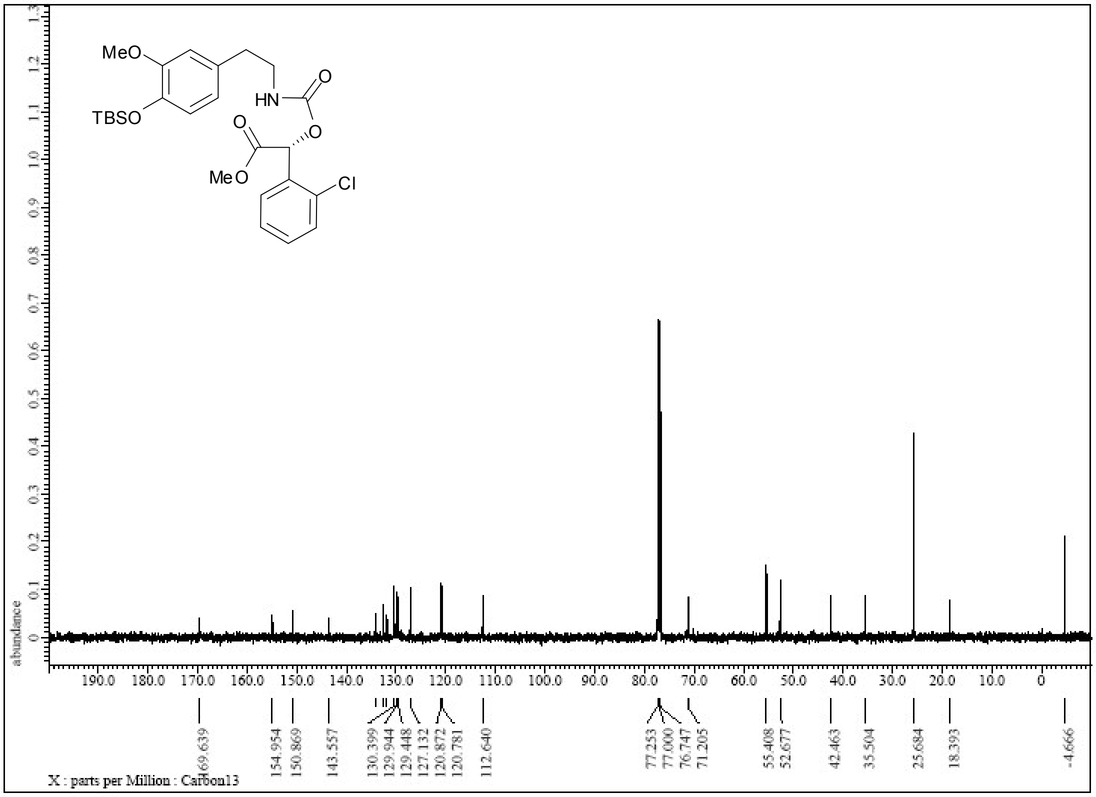
^{1}H NMR (CDCl$_3$, 500 MHz) spectra of **9**



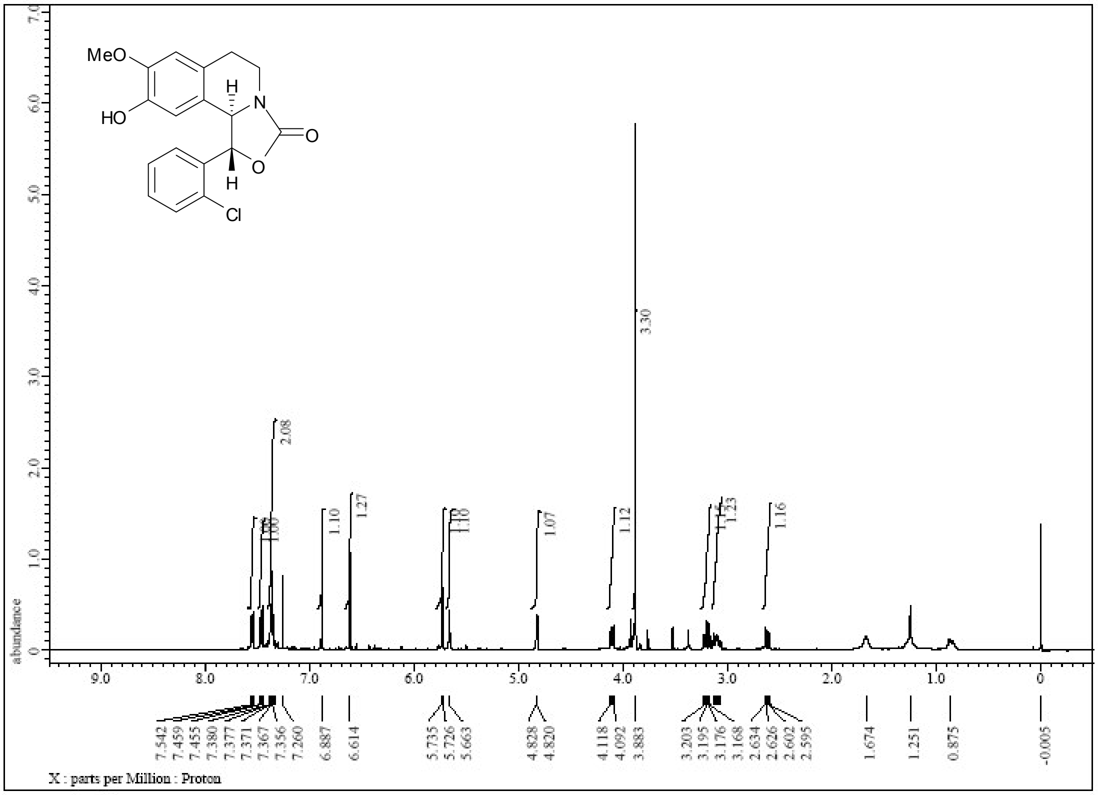
^{13}C NMR (CDCl$_3$, 125 MHz) spectra of **9**



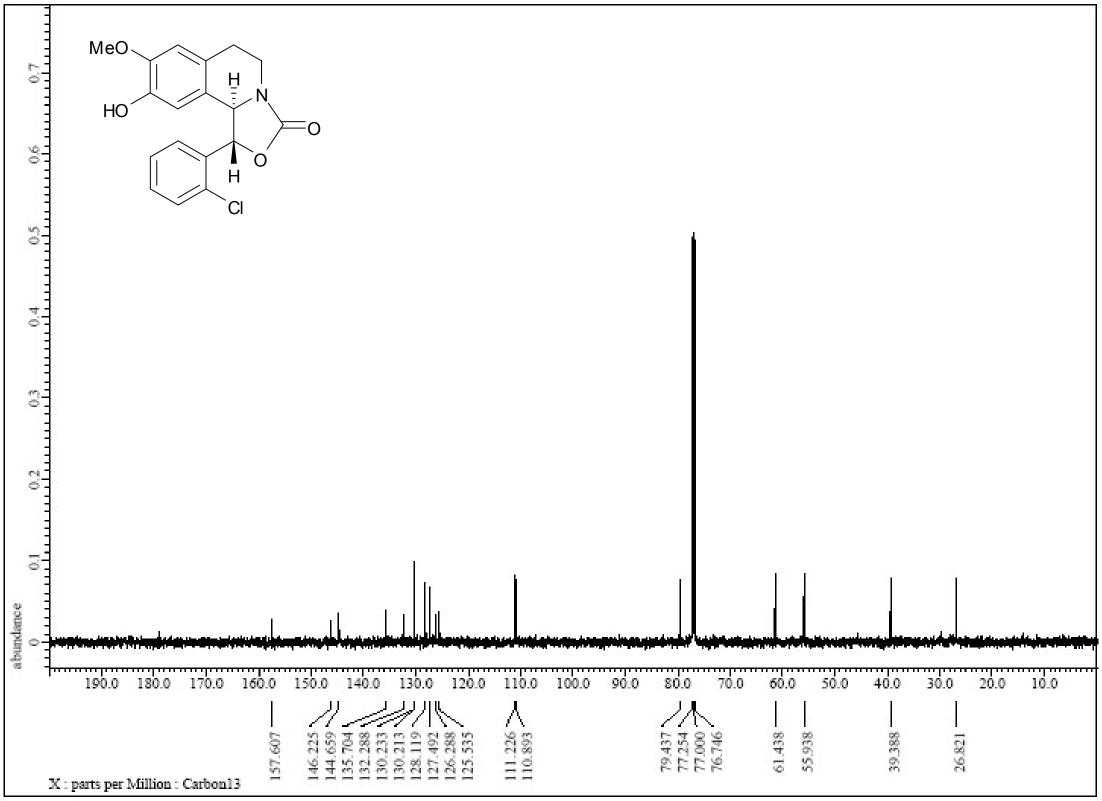
^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **11**



^{13}C NMR (CDCl$_3$, 125 MHz) spectrum of **11**



^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of **12-*anti***



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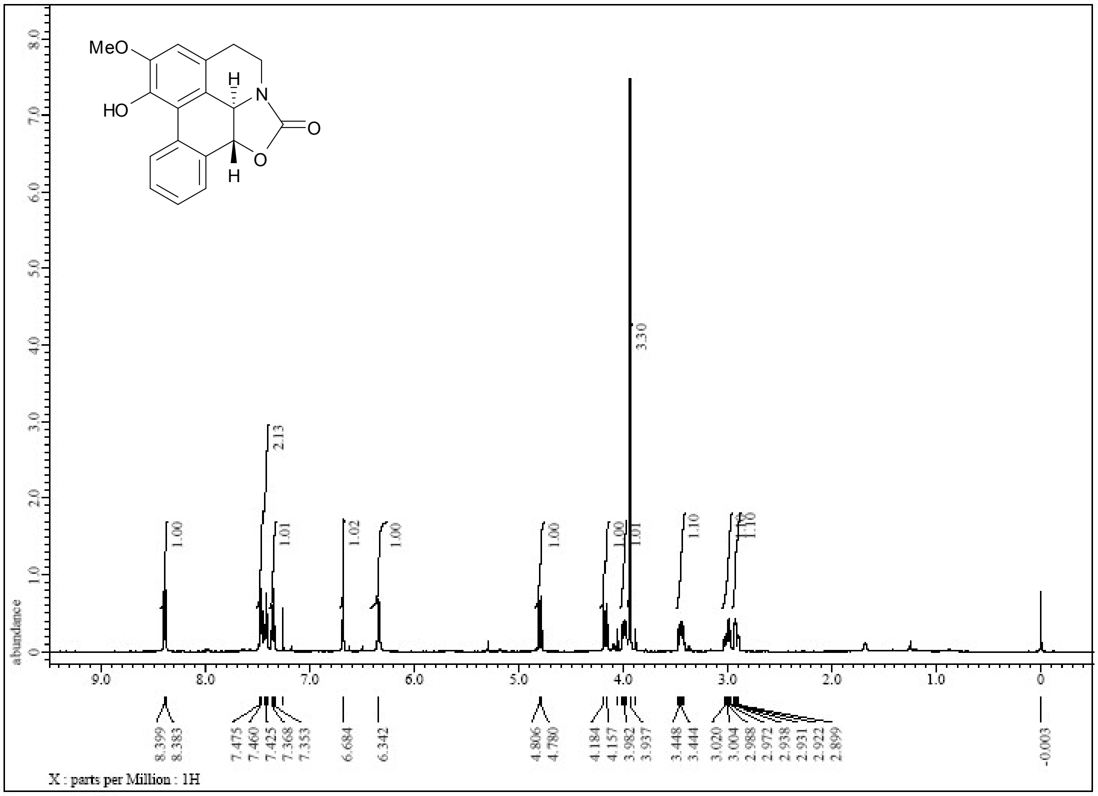
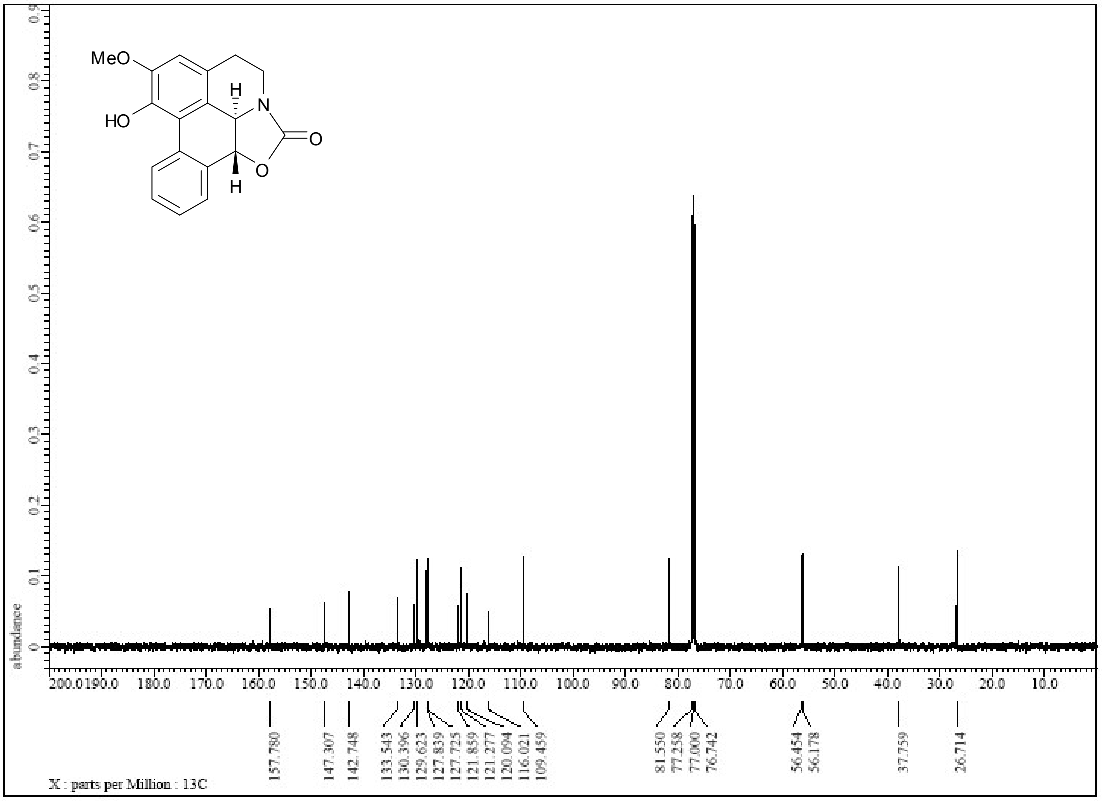
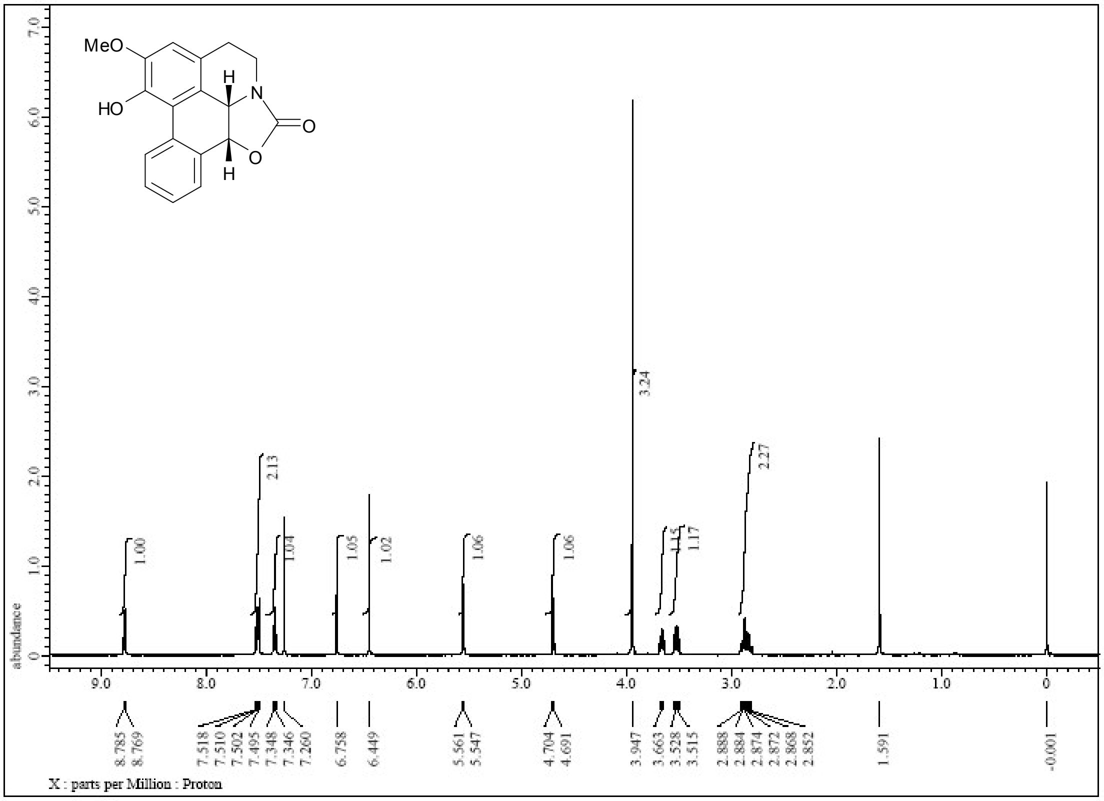


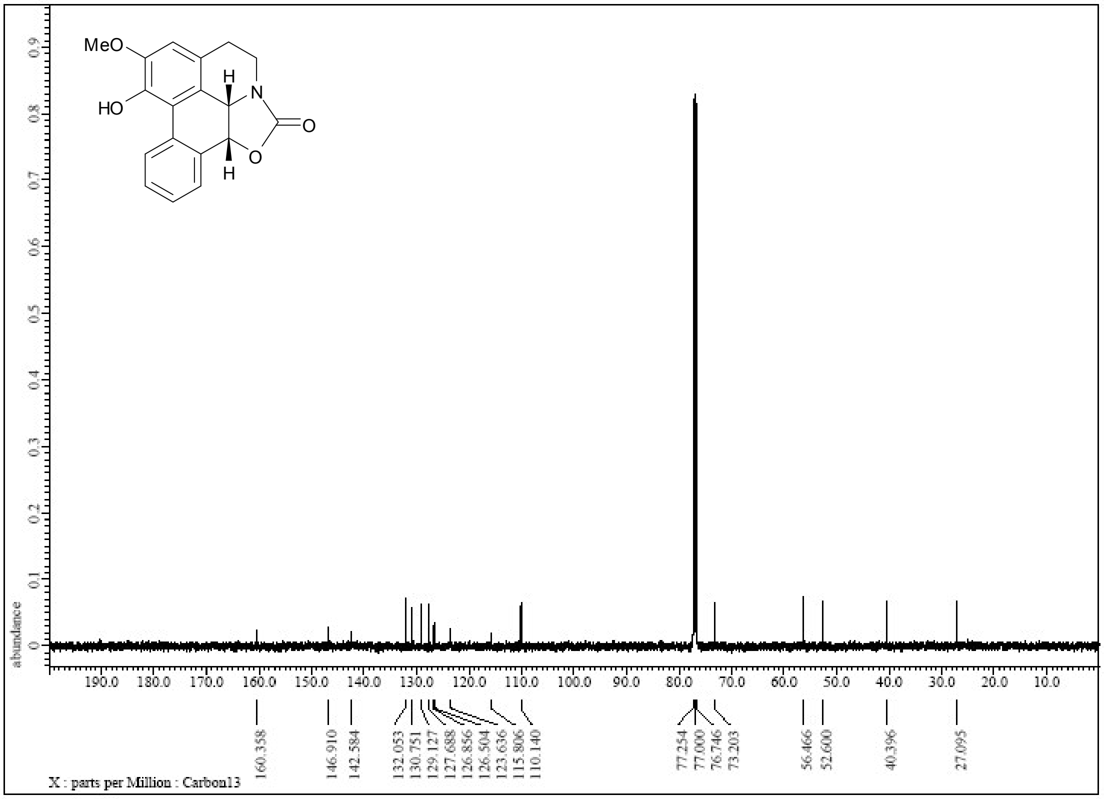
^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **13-*anti***



^{13}C NMR (CDCl$_3$, 125 MHz) spectrum of **13-*anti***



^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **13-*syn***



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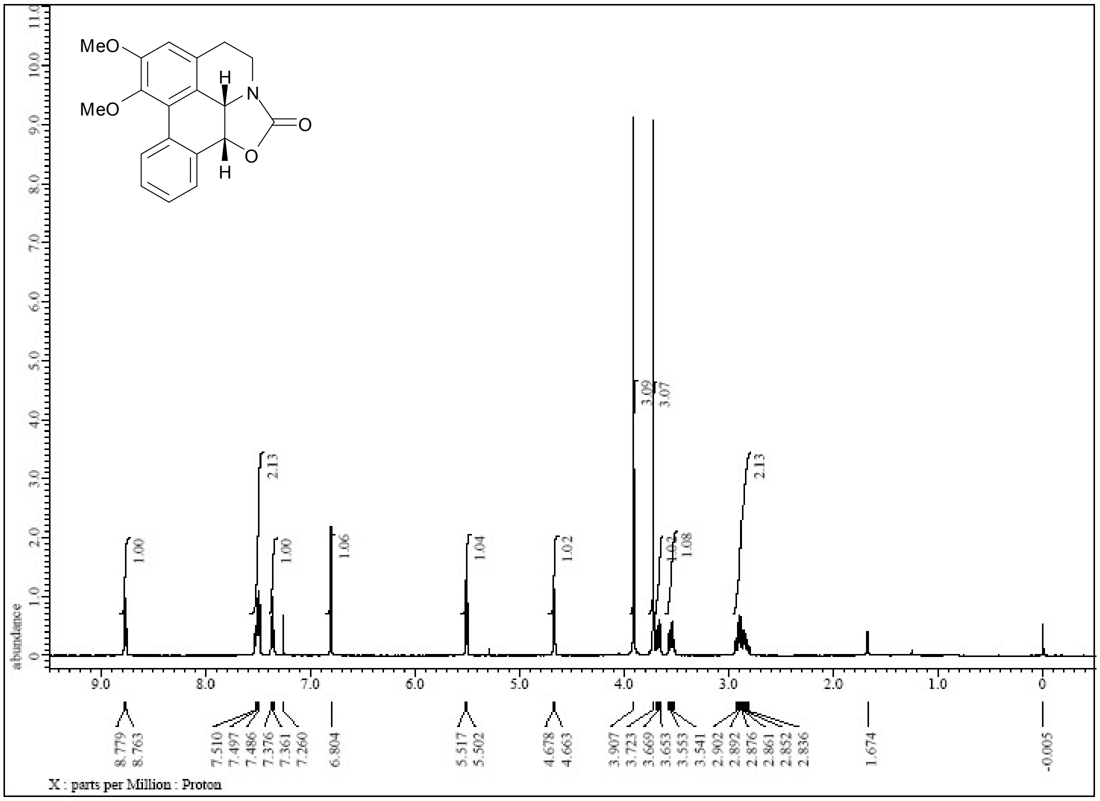
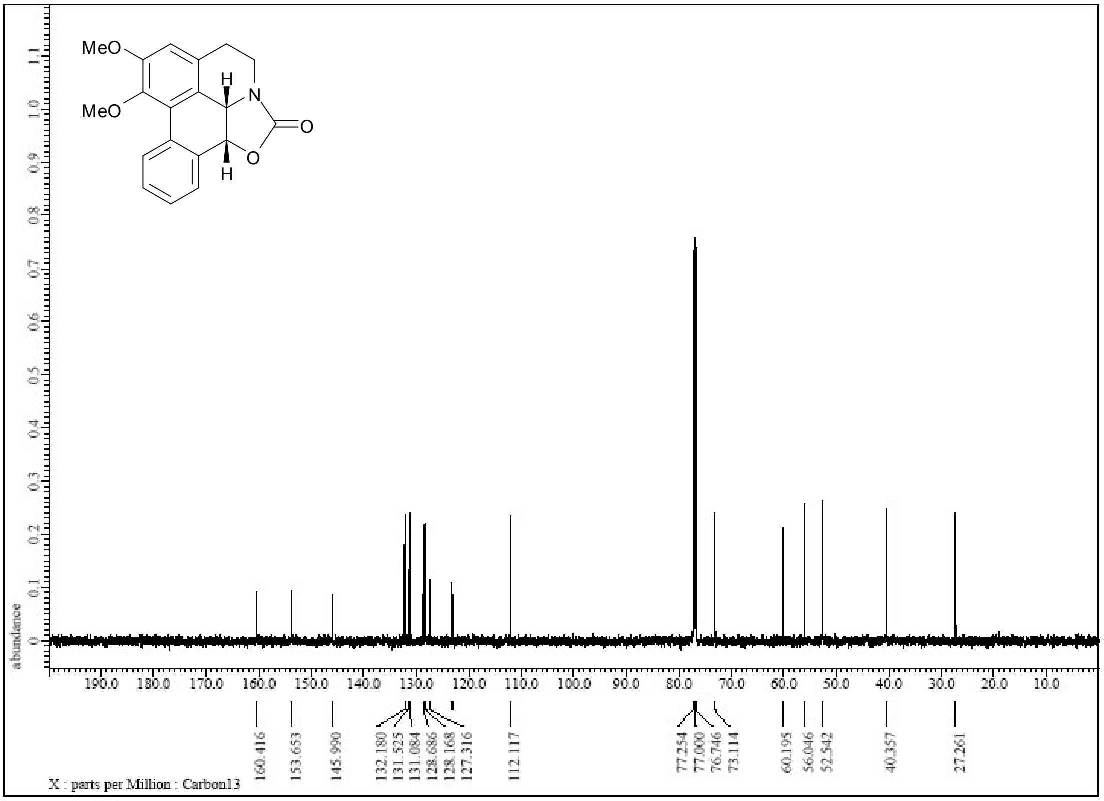
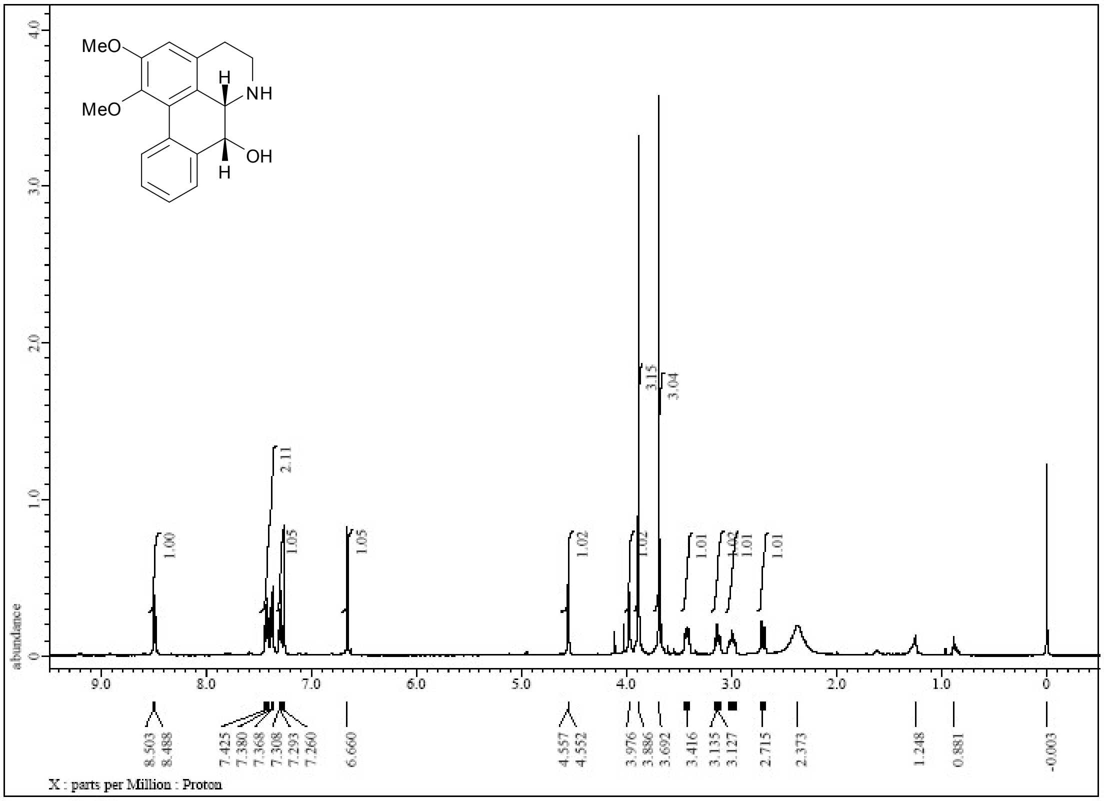


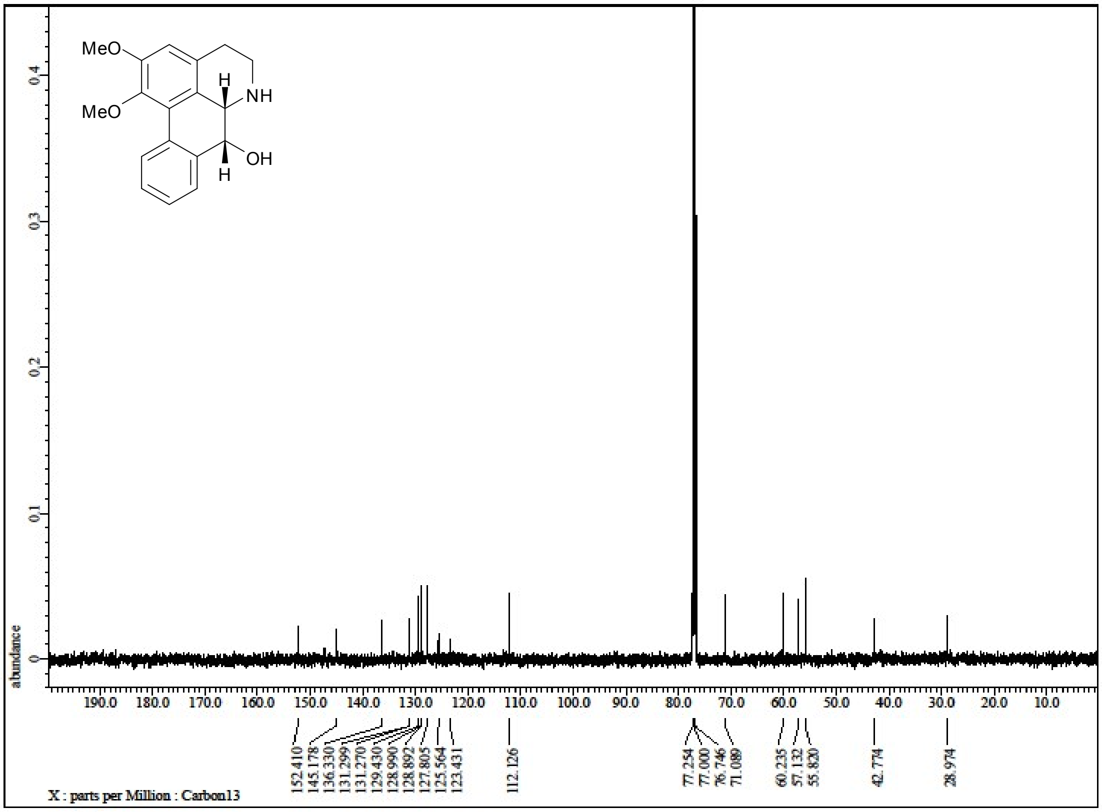
^1H NMR ($CDCl_3$, 500 MHz) spectrum of **S1**



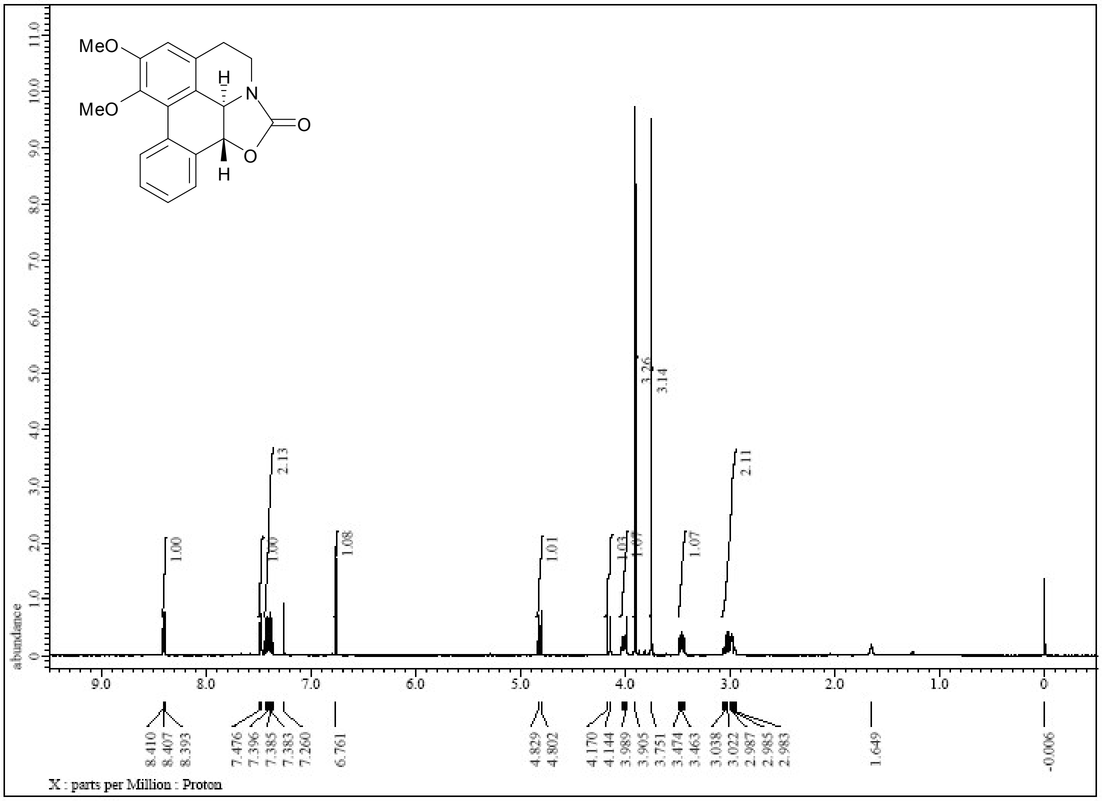
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of **S1**



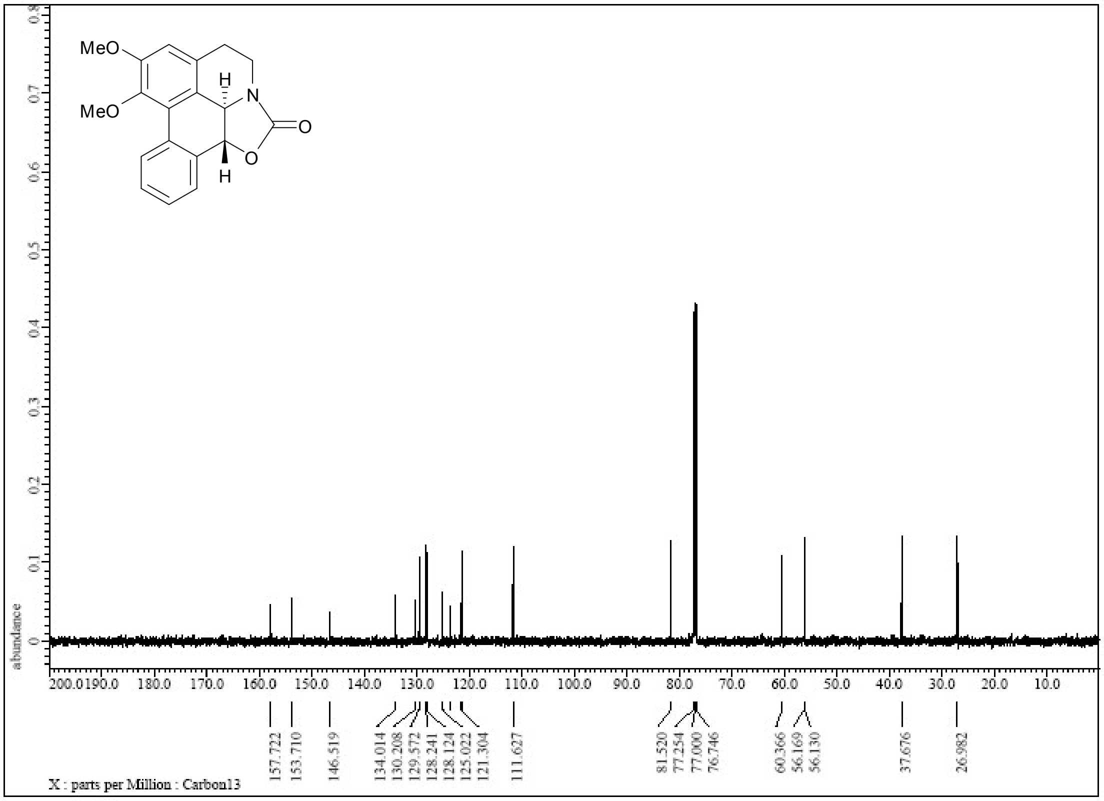
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of **1**



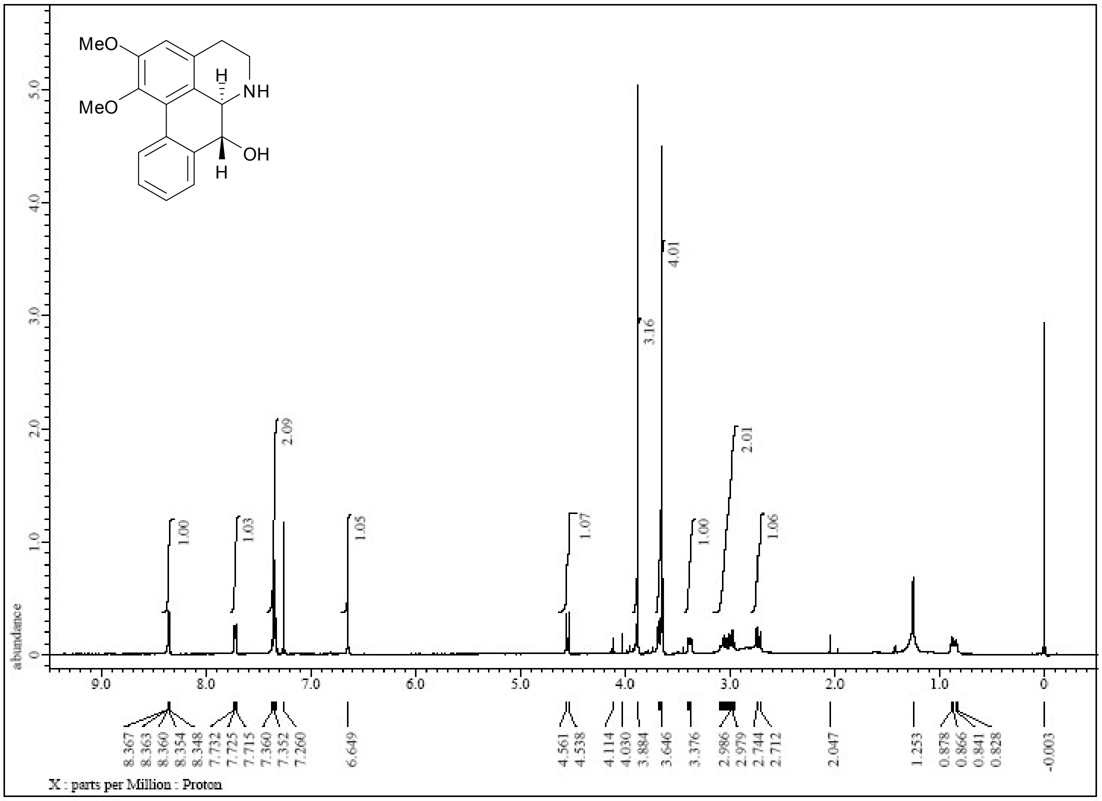
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of **1**



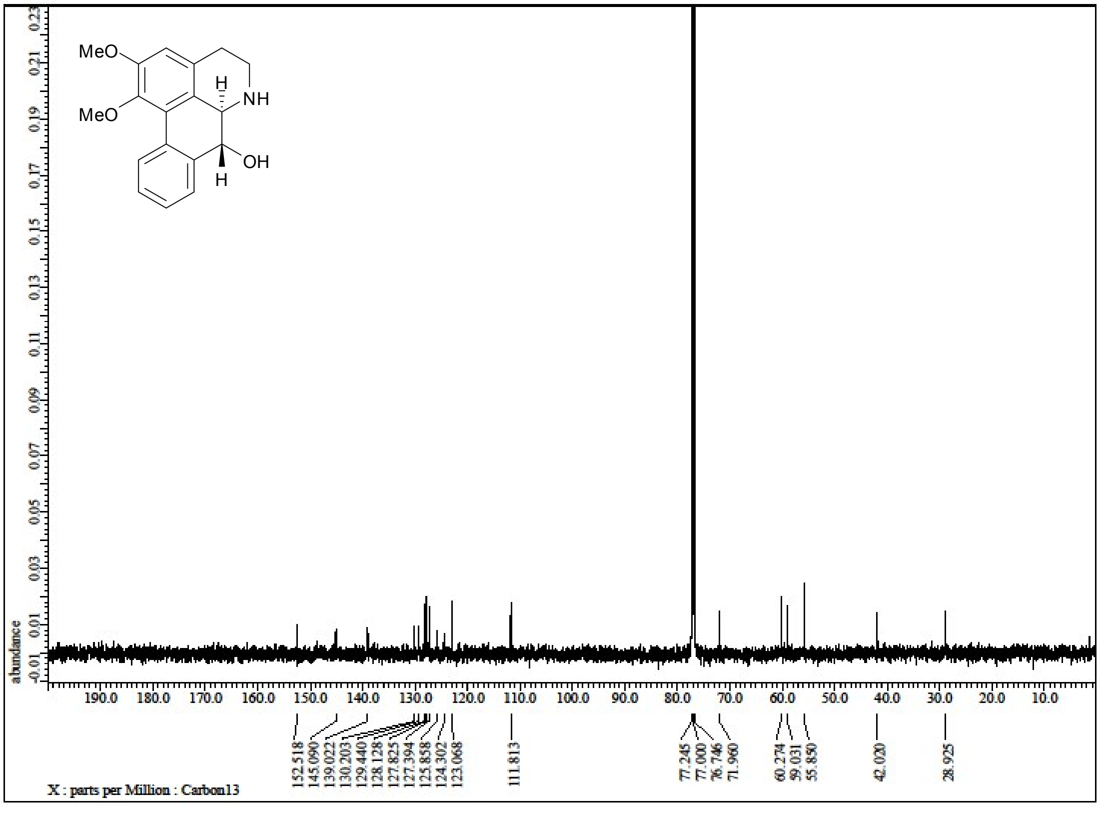
^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **S2**



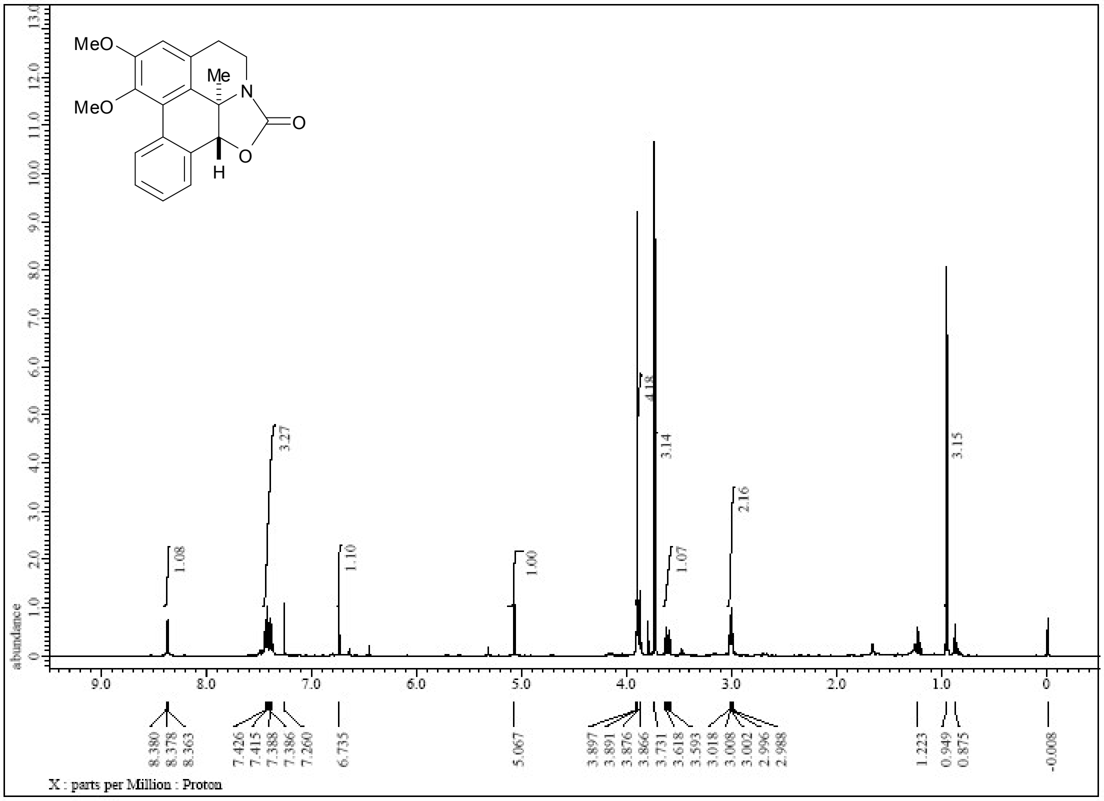
^{13}C NMR (CDCl$_3$, 125 MHz) spectrum of **S2**



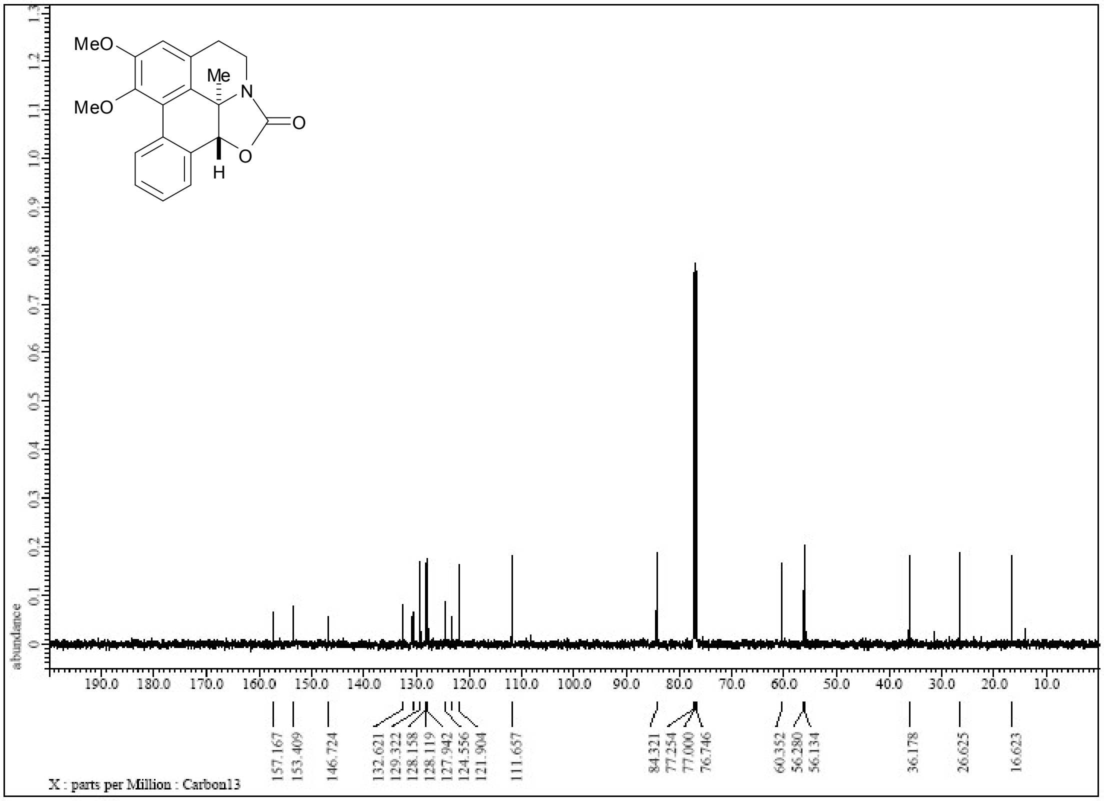
^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **2**



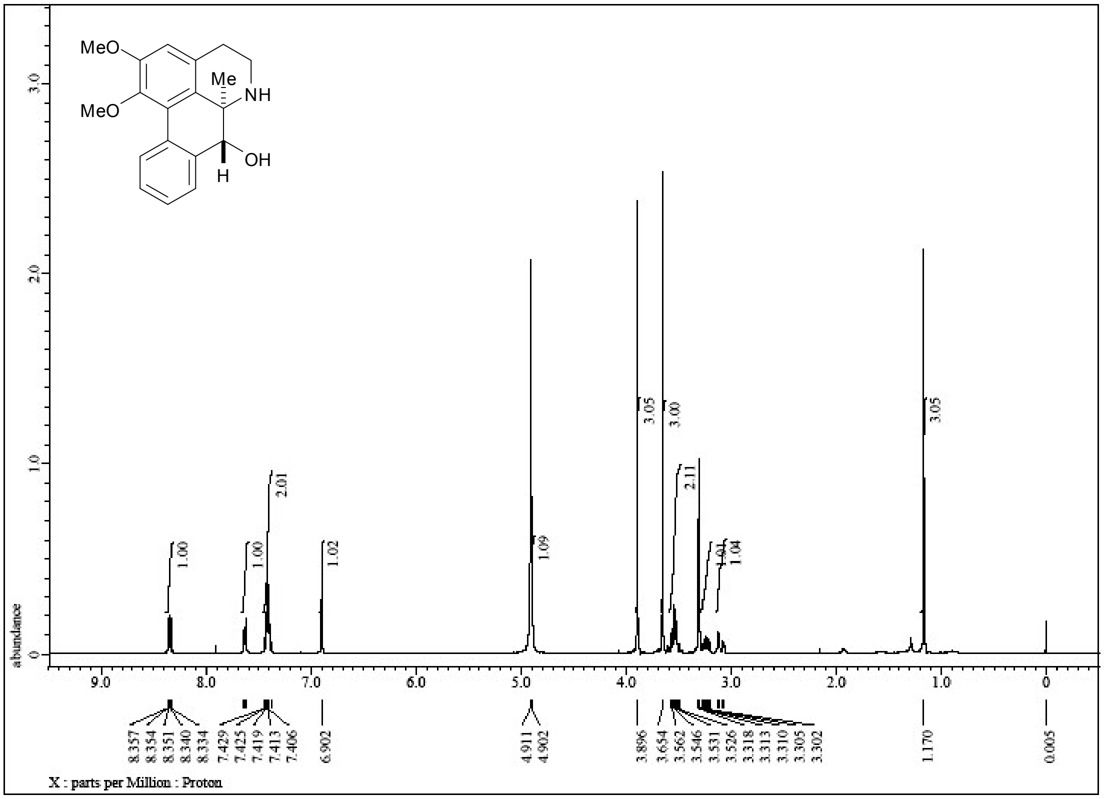
^{13}C NMR (CDCl$_3$, 125 MHz) spectrum of **2**



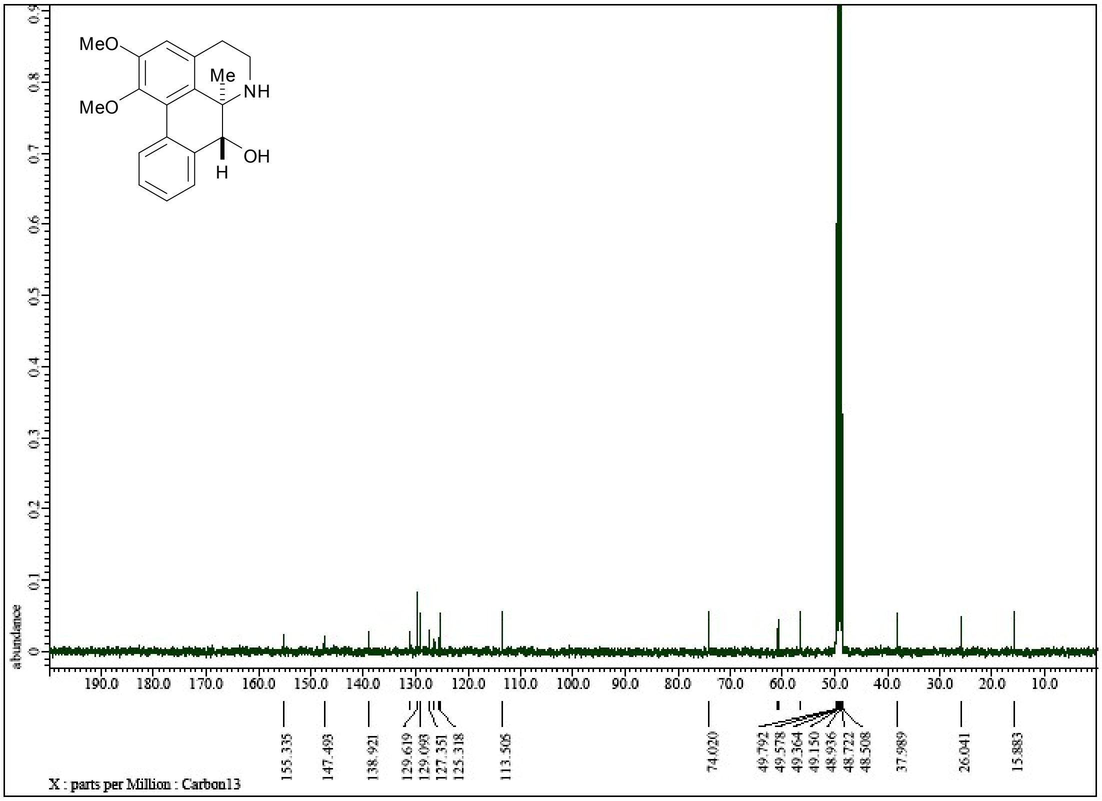
^{1}H NMR ($CDCl_3$, 500 MHz) spectrum of **S3**



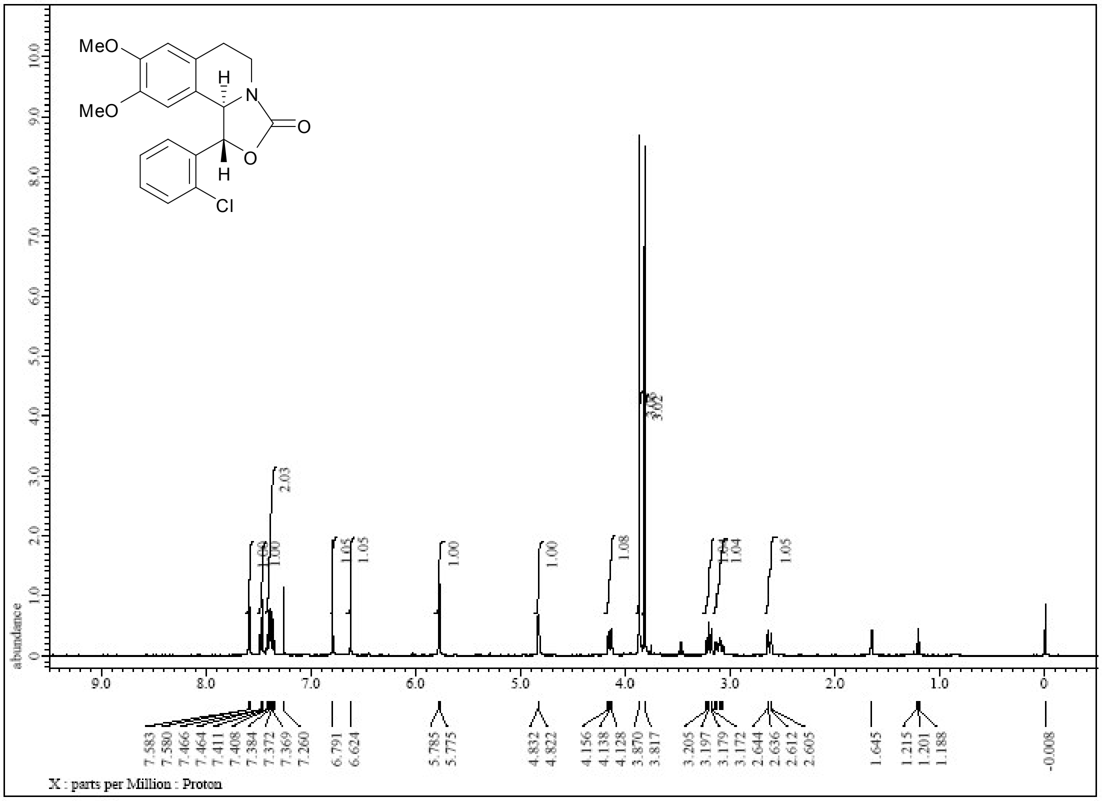
^{13}C NMR ($CDCl_3$, 125 MHz) spectrum of **S3**



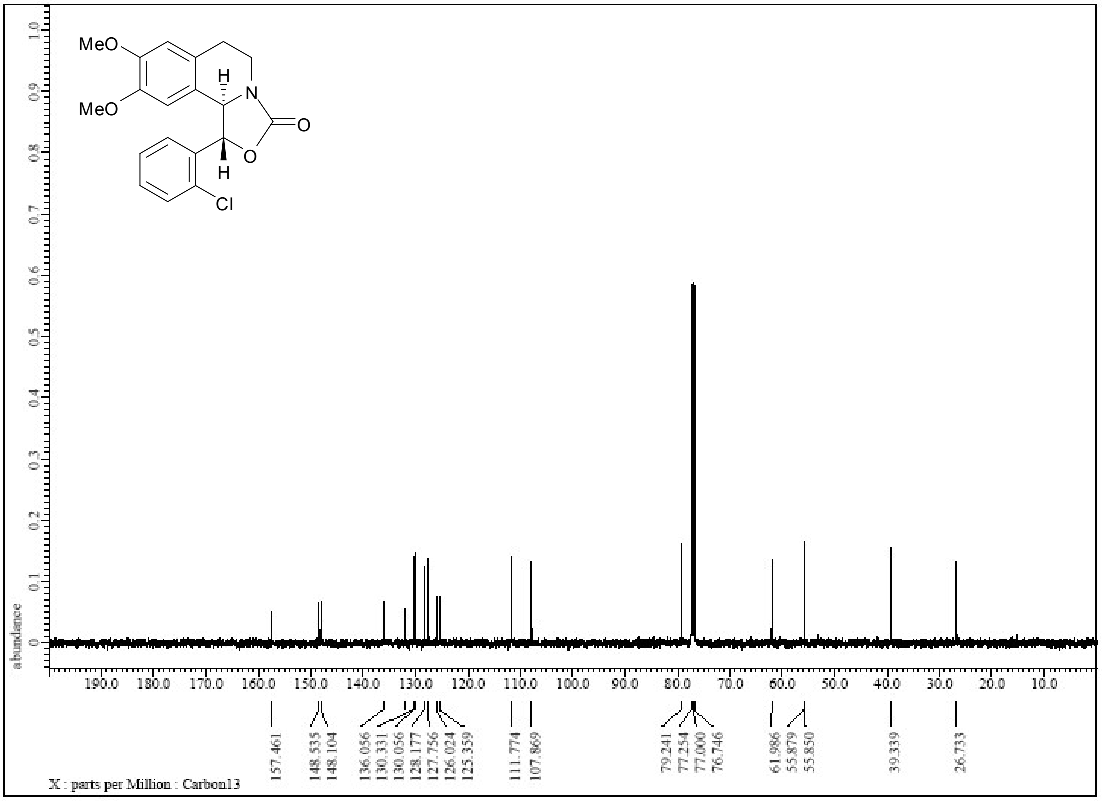
^{1}H NMR (CD$_3$OD, 400 MHz) spectrum of **3**



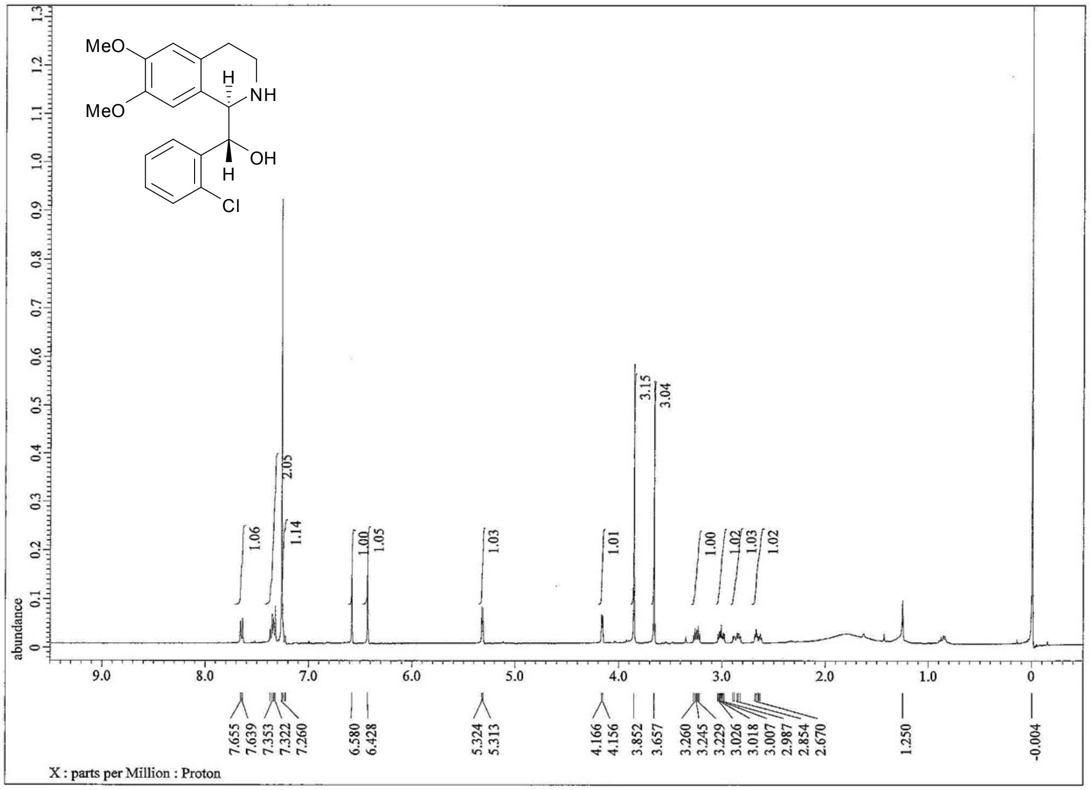
^{13}C (CD$_3$OD, 100 MHz) NMR spectrum of **3**



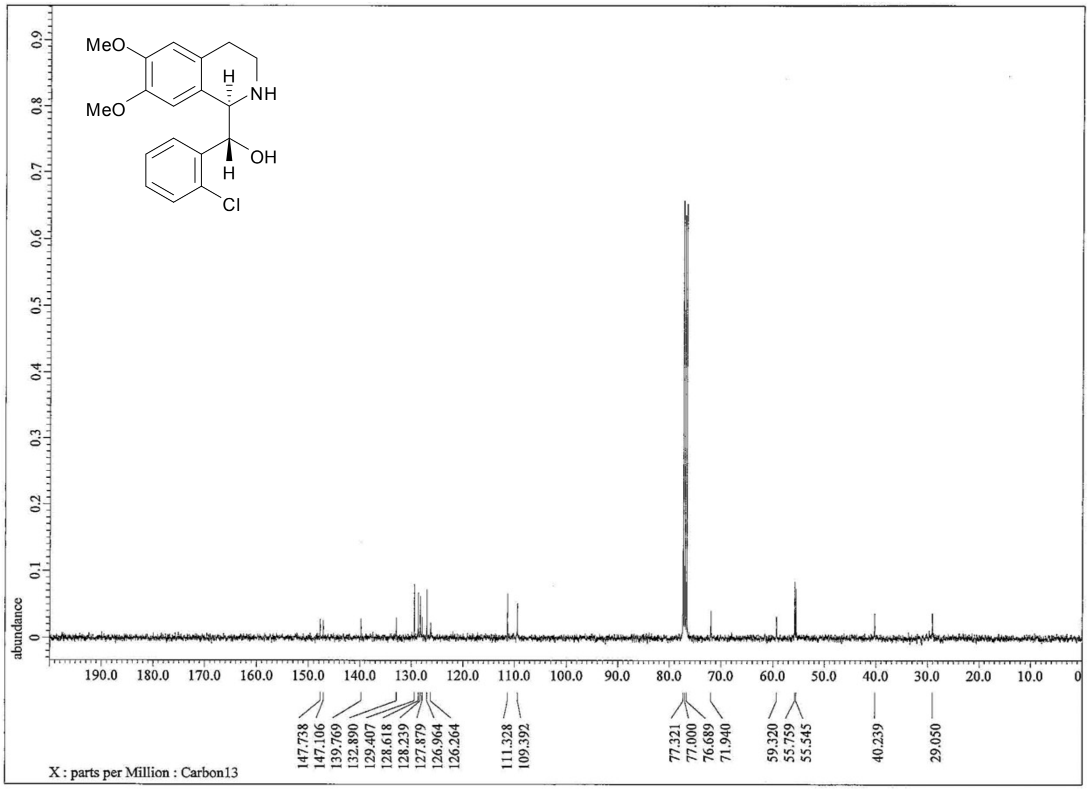
^{1}H NMR (CDCl$_3$, 500 MHz) spectraum of **15**



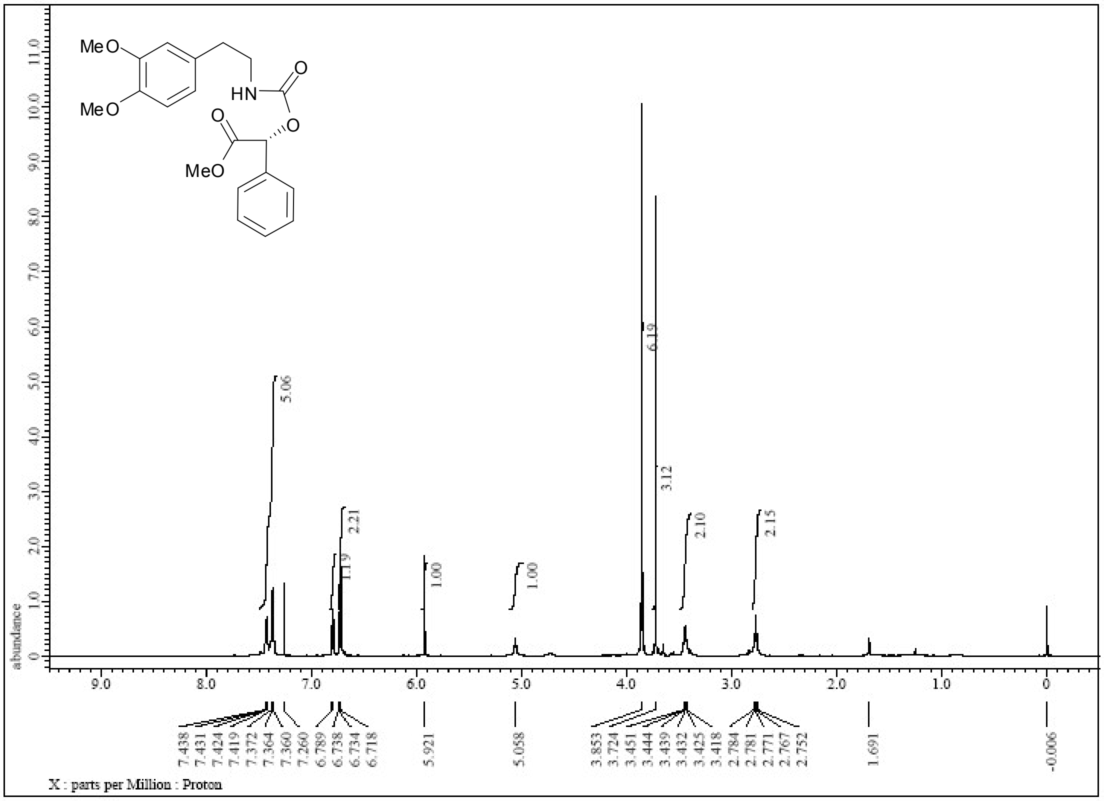
^{13}C NMR (CDCl$_3$, 125 MHz) spectrum of **15**



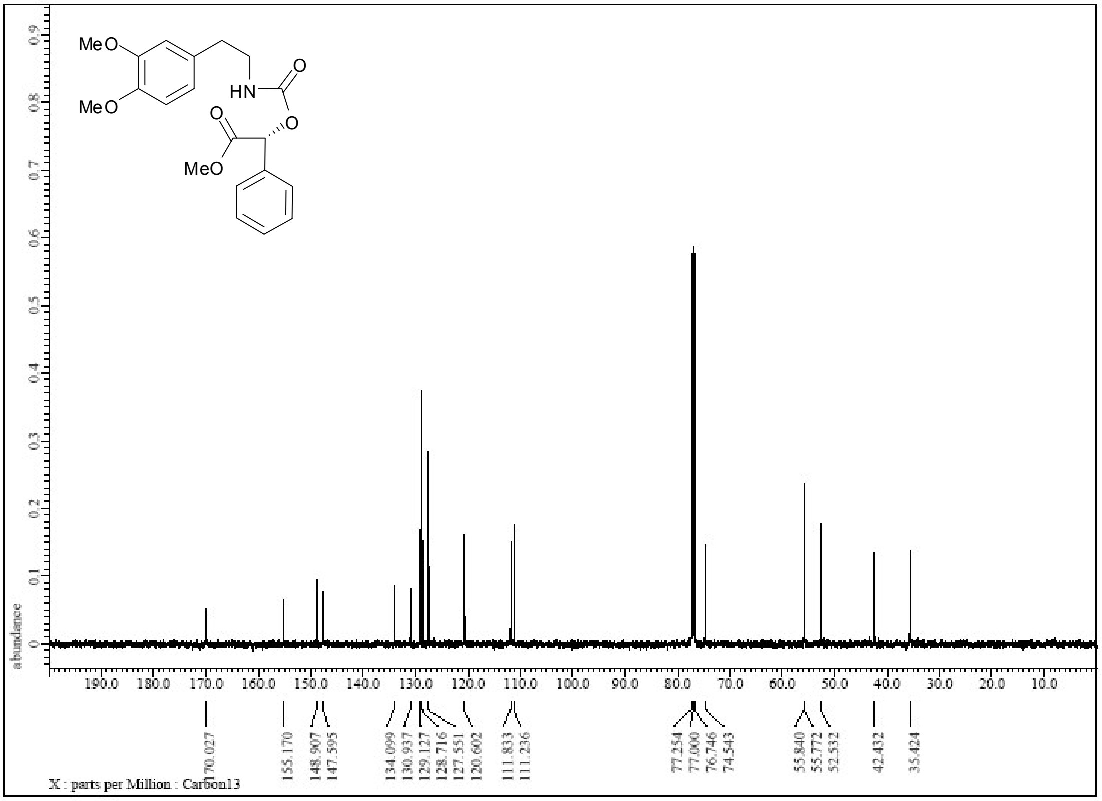
^{1}H NMR (CDCl$_3$, 400 MHz) spectrum of **4**



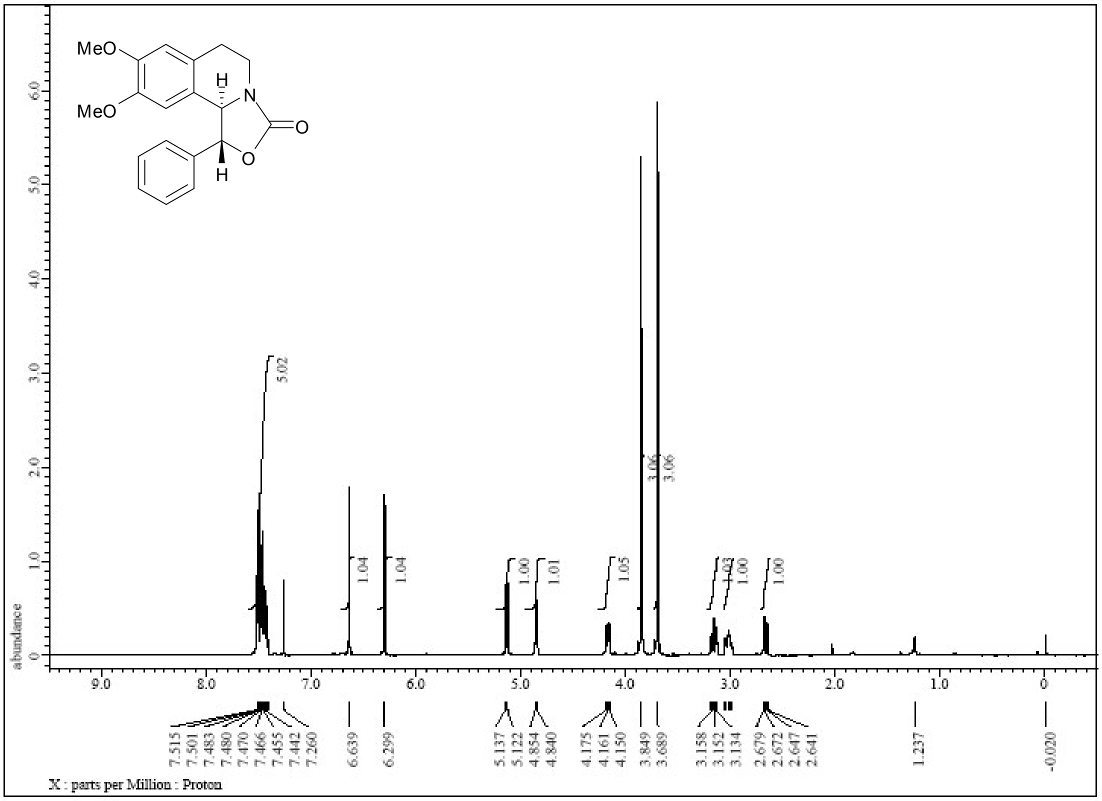
^{13}C NMR (CDCl$_3$, 100 MHz) spectrum of **4**



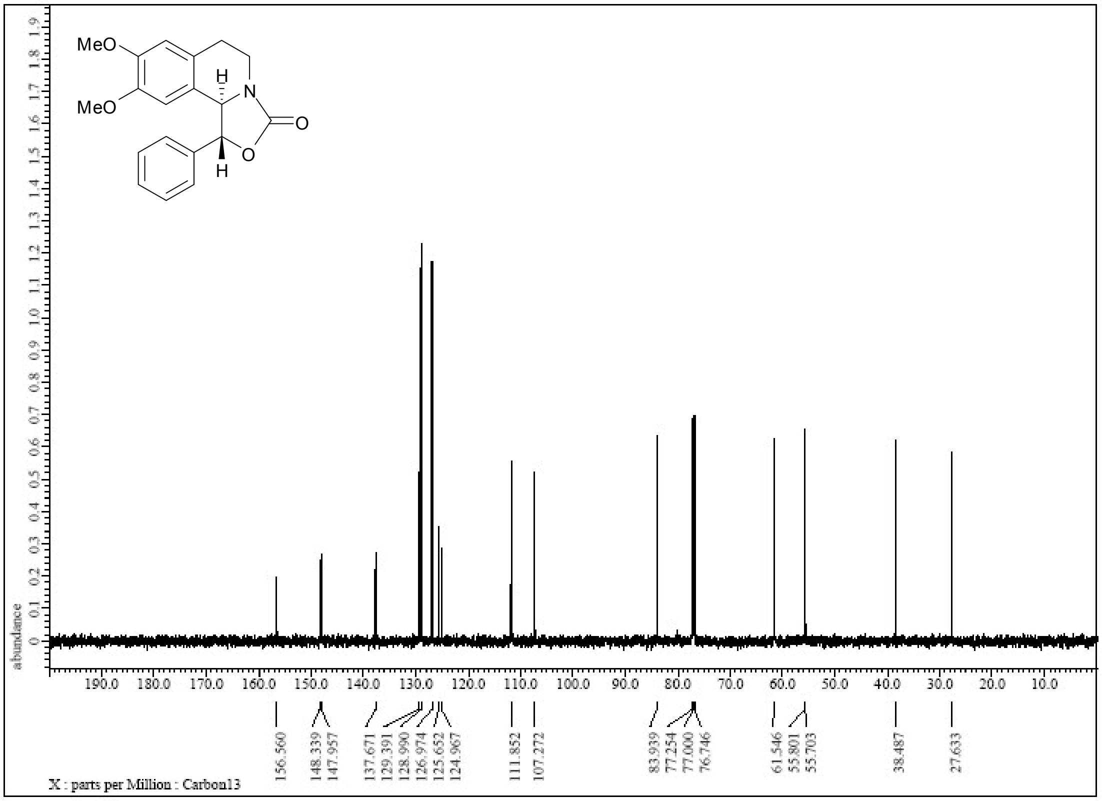
^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **19**



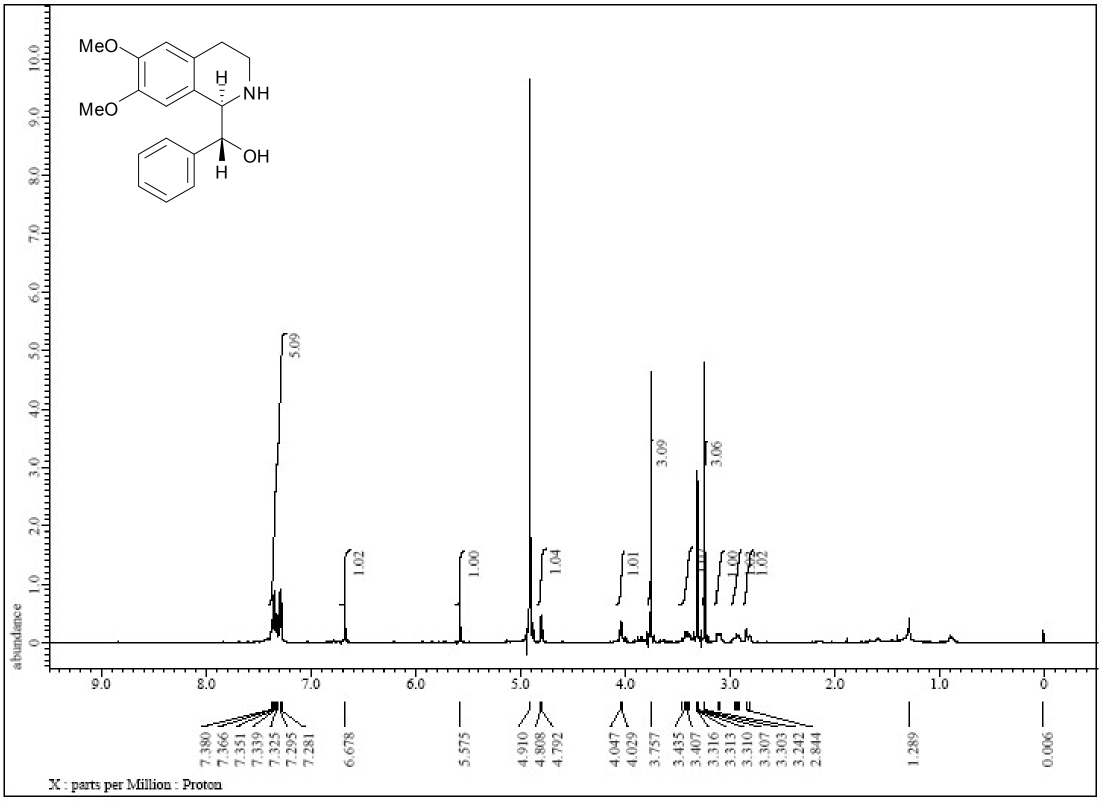
^{13}C NMR (CDCl$_3$, 125 MHz) spectrum of **19**



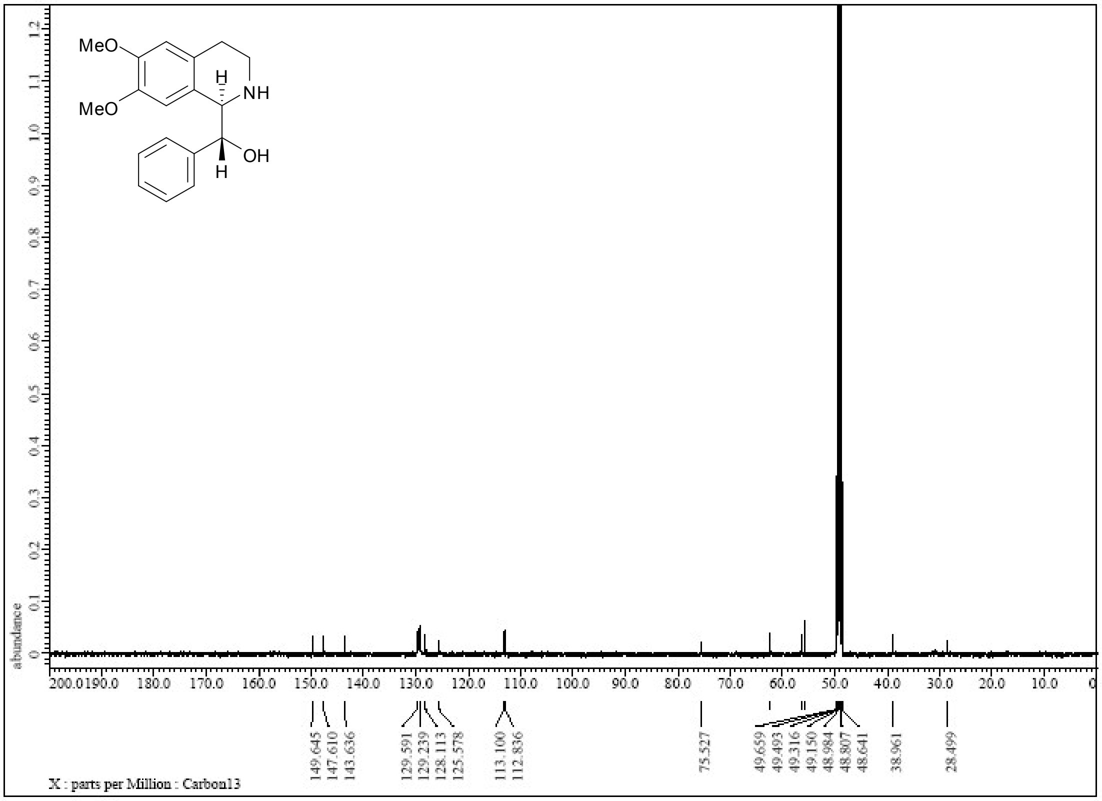
^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **20**



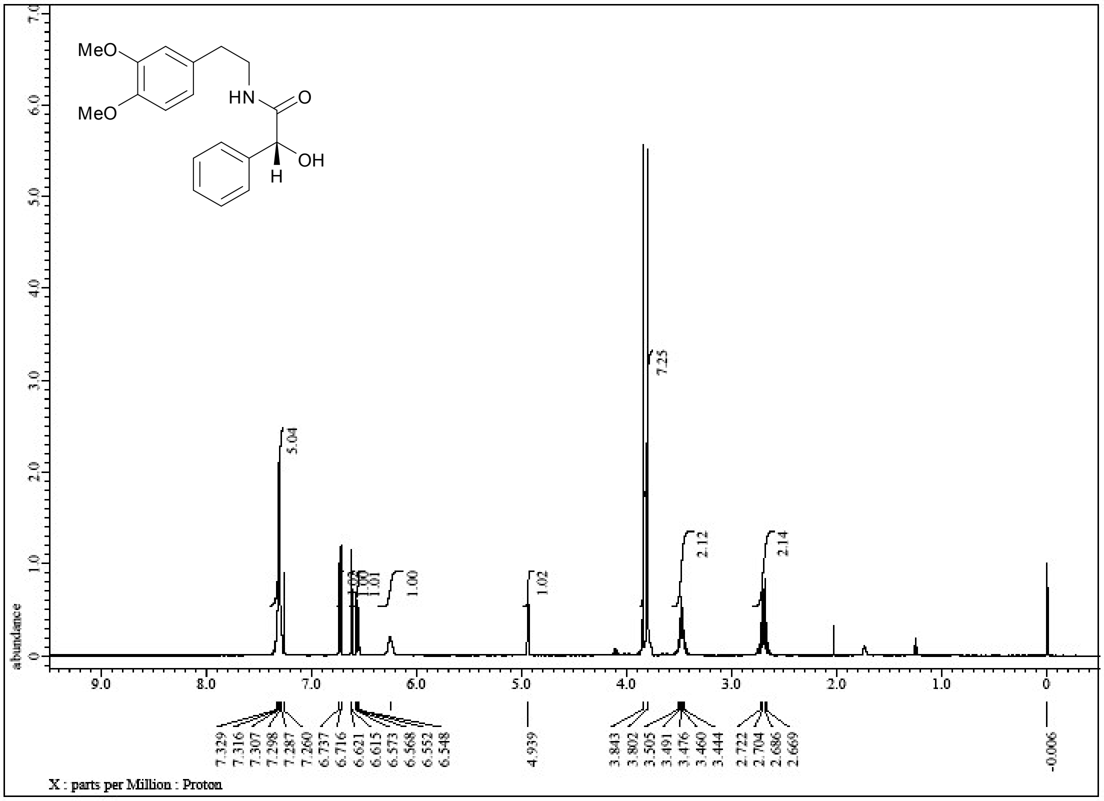
^{13}C NMR (CDCl$_3$, 125 MHz) spectrum of **20**



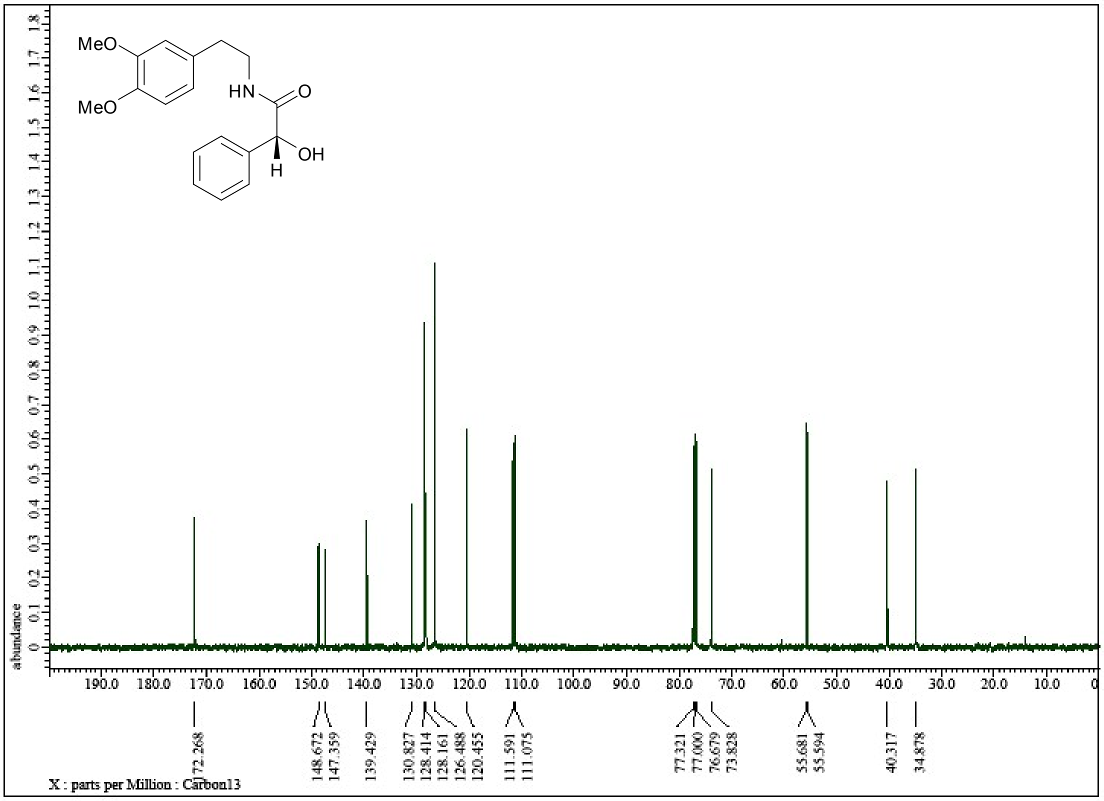
^{1}H NMR (CD$_3$OD, 500 MHz) spectrum of **5**



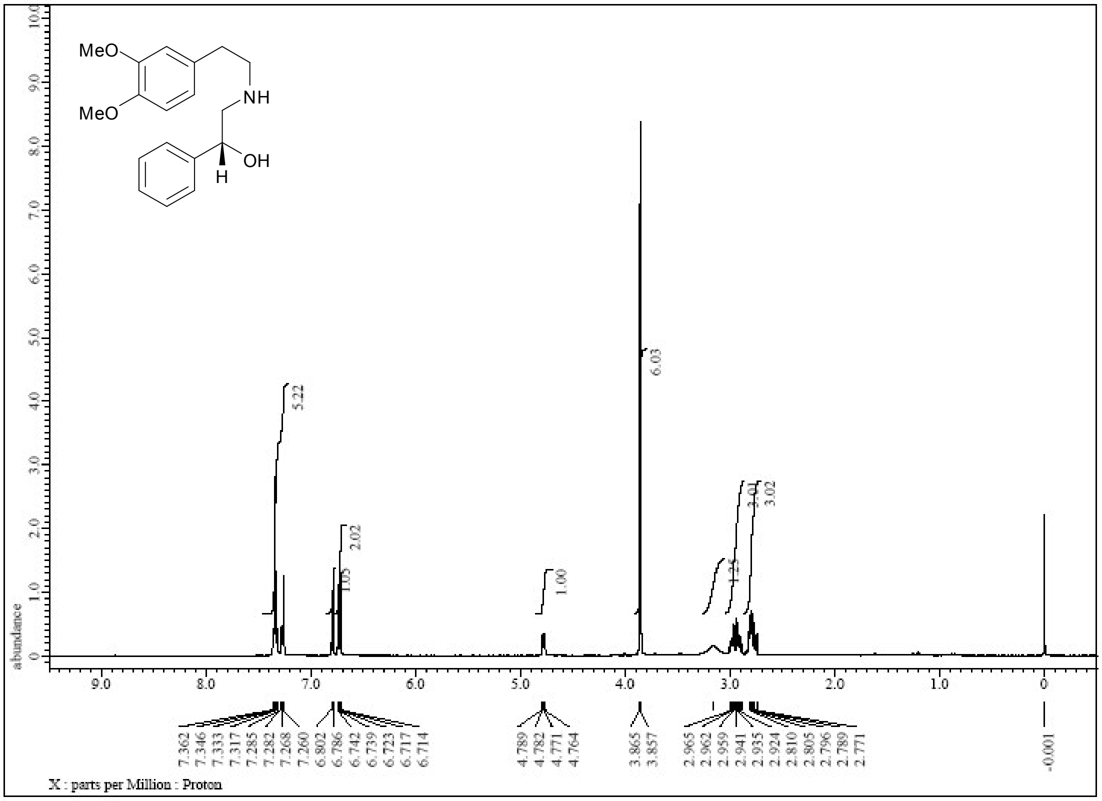
^{13}C NMR (CD$_3$OD, 125 MHz) spectrum of **5**



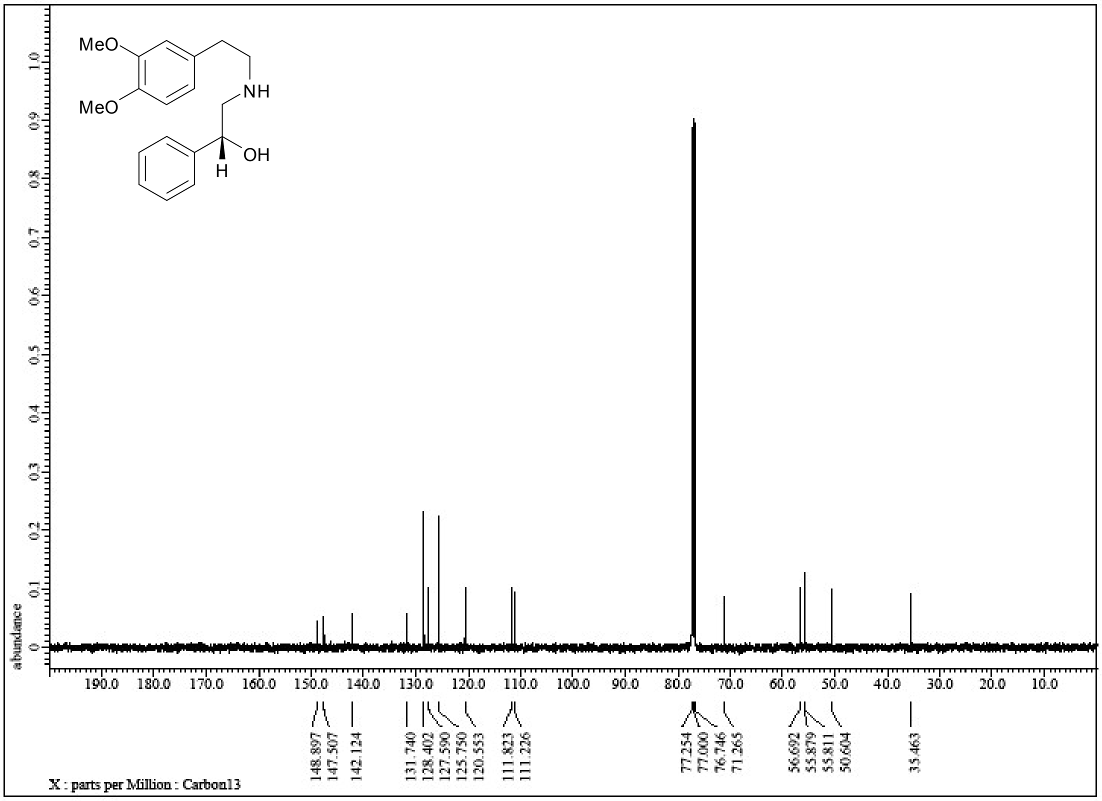
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of **21**



^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of **21**



^{1}H NMR (CDCl$_3$, 500 MHz) spectrum of **6**



^{13}CNMR (CDCl$_3$, 125 MHz) spectrum of **6**