Supporting Information

Identification of an Imine Reductase for Asymmetric Reduction of Bulky Dihydroisoquinolines

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1. General

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (**1g**) was purchased from Acros (Shanghai, China). All other commercial chemicals were purchased from J&K or Sigma-Aldrich (Shanghai, China) in the highest purity and used without further purification. A Shimadzu LC-2010A liquid chromatography equipped with a UV detector was used for determining the conversion of substrates and the enantiomeric excess of products. Chiral HPLC columns Chiracel OD-H (250 mm × 4.6 mm, 5 μm particle size, Daicel) and Chiracel OJ-H (250 mm × 4.6 mm, 5 μm particle size, Daicel) were used for HPLC analysis. A Shimadzu GC-2014 gas chromatography equipped with a flame ionization detector (FID) was used for determining the enantiomeric excess of products. A CP-Chirasil-Dex CB column (25 m × 0.25 mm × 0.39 mm, Varian) was used for GC analysis. ^{1}H NMR and ^{13}C NMR were measured on a Bruker Avance 400 MHz spectrometer. Tetramethylsilane (TMS) was added as internal standard. Optical rotation measurements were taken on a Rudolph Research Analytical Autopol I automatic polarimeter.

2. Cloning, expression, purification and characterization of *Sn*IR

Imine reductase *Sn*IR gene (WP_013019548.1) was cloned into plasmid pET-28a using the primers *Sn*IR-f (5'-GCGGATCCAACTCCAAGAAGTCTCCCGTC-3', *Bam*HI) and *Sn*IR-r (5'-CCCAAGCTTCTACGCCGCCTTCTTCTTGAT-3', *Hind*III) and the recombinant plasmid was transformed into *E. coli* BL21 (DE3) for expression. The methods for recombinant cell culture and enzyme purification were the same as we described previously.[S1]

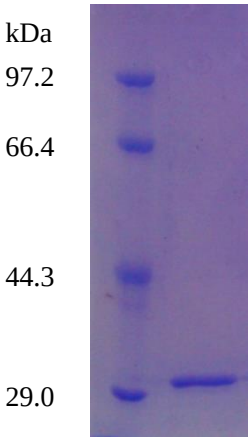


Figure S1. The SDS-PAGE analysis of purified *Sn*IR. Lane 1, protein marker; Lane 2, pure enzyme.

Enzyme activity was assayed by monitoring the decrease in the absorbance of NADPH (ε = 6220 M^{-1} cm^{-1}) at 340 nm using a spectrophotometer. The standard assay mixture (1 mL) contained 1 mM substrate (from a 100 mM stock solution in DMSO), 0.1 mM NADPH, 100 mM potassium phosphate buffer (pH 7.0) and an appropriate amount of enzyme sample. For **1f**, **1g** and

3, the substrate concentration was adjusted to 0.1, 0.1 and 10 mM, respectively. One unit of enzyme activity was defined as the amount of enzyme that catalyzes the oxidation of 1 μmol NADPH per minute.

Table S1. The specific activity of *Sn*IR towards different substrates.[a]

Entry	Substrate	Specific activity (U/mg)	Relative activity (%)
1	**1a**	2.89	100
2	**1b**	2.56	89
3	**1c**	1.56	54
4	**1d**	0.25	8.7
5	**1e**	0.066	2.3
6[b]	**1f**	0.013	0.45
7[b]	**1g**	2.03	70
8	**1h**	0.12	4.2
9[c]	**3**	0.74	26

[a] Specific activity was determined at 30 ℃ and pH 7.0 using purified *Sn*IR;

[b] 0.1 mM substrate concentration;

[c] 10 mM substrate concentration.

The pH optima for both reduction and oxidation activity of *Sn*IR were determined at different pH in the following buffer (100 mM): sodium citrate (pH 3.0-6.0), potassium phosphate (pH 6.0-8.0), Tris-HCl (pH 8.0-9.0) and Gly-NaOH (pH 9.0-11.0). Kinetic parameters were determined at different substrate concentrations and the data was adjusted to uncompetitive inhibition model ($v = (V_{max} \times [S]) / (K_m + [S] + [S]^2 / K_i)$) using Origin 9.0. The effect of additive chemicals and the thermostability of *Sn*IR were also investigated as we described before.[S1]

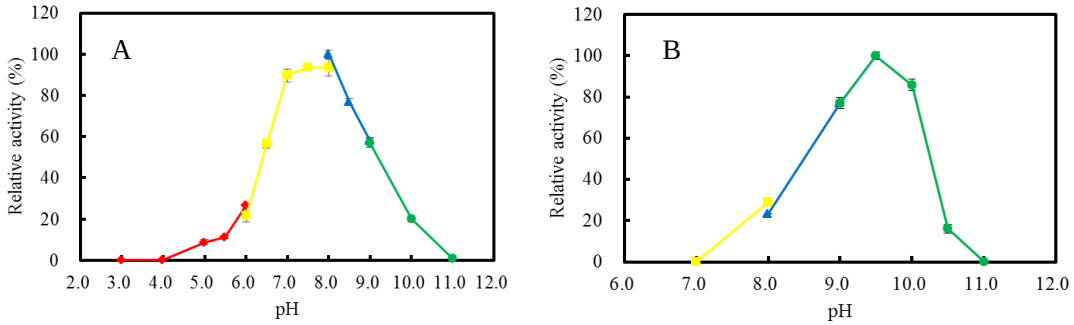


Figure S2. Effect of pH on reduction (A) and oxidation (B) activities of *Sn*IR. Activity-pH profile was determined in the following buffer: (i) citrate buffer (♦, pH 3.0-6.0); (ii) potassium phosphate buffer (■, pH 6.0-8.0); (iii) Tris-HCl buffer (▲, pH 8.0-9.0); (iv) Gly-NaOH buffer (●, pH 9.0-11.0). Relative activity was expressed as a percentage of the maximum activity.

Table S2. Effect of additive chemicals on the activity of *Sn*IR.[a]

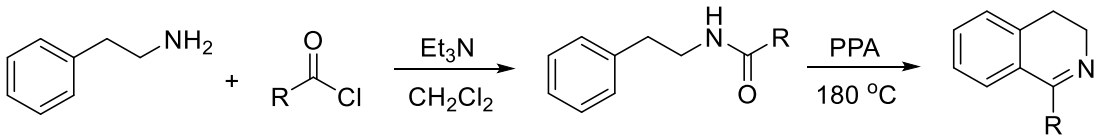
Chemicals	Relative activity (%)	
	1 mM	10 mM
Blank	100.0 ± 1.7	100.0 ± 4.4
Li^{+}	102.5 ± 3.0	96.1 ± 4.0
Ca^{2+}	100.0 ± 3.0	90.4 ± 1.6
Fe^{2+}	93.6 ± 3.0	48.6 ± 1.2
Co^{2+}	100.3 ± 2.7	38.8 ± 1.6
Ni^{2+}	89.6 ± 3.4	18.1 ± 3.6
Zn^{2+}	95.5 ± 1.3	46.5 ± 2.8
Cu^{2+}	33.9 ± 5.4	15.8 ± 2.8
Mg^{2+}	95.8 ± 5.1	93.0 ± 2.8
Mn^{2+}	104.8 ± 5.1	87.3 ± 2.5
Pb^{2+}	100.3 ± 1.7	80.6 ± 1.3
EDTA	100.0 ± 3.6	95.6 ± 3.7

[a] The purified *Sn*IR was incubated in potassium phosphate buffer (100 mM, pH 7.0) containing various chemicals (1 mM or 10 mM) for 1 h, then residual activity was measured.

Table S3. The half-lives of *Sn*IR at different temperatures.

	30 ℃	40 ℃	50 ℃
$t_{1/2}$ (h)	64	8.3	0.018

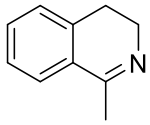
3. Synthesis of 1-alkyl-3,4-dihydroisoquinolines



1-Alkyl-3,4-dihydroisoquinolines (**1a-1f**) were prepared according to literature method.[S2] Twenty mmol 2-arylethylamine and 30 mmol triethylamine were dissolved in 100 mL dichloromethane and a solution of 20 mmol carboxy chloride in dichloromethane was added dropwise at 0 ℃. The reaction mixture was stirred at 30 ℃ for 12 h to afford corresponding *N*-acyl-2-arylethylamine in quantitative yield. Then *N*-acyl-2-arylethylamine and 36 g polyphosphoric acid (PPA) were heated to 180 ℃ for 4 h. The reaction mixture was added into 150 mL water and adjusted the pH to 13 with solid NaOH. The mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was

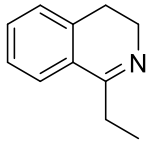
purified by column chromatography eluting with a mixture of ethyl acetate and methanol (10:1) to yield pure imines.

1-Methyl-3,4-dihydroisoquinoline (1a)[S2]



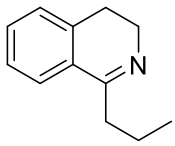
Yield 2.09 g (72%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 1H, *J* = 7.2 Hz), 7.29-7.38 (m, 2H), 7.18 (d, 1H, *J* = 7.6 Hz), 3.67 (td, 2H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 2.71 (d, 2H, *J* = 7.4 Hz), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 137.4, 130.7, 129.5, 127.4, 126.9, 125.4, 46.8, 26.0, 23.2.

1-Ethyl-3,4-dihydroisoquinoline (1b)[S2]



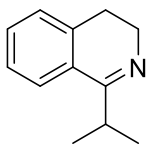
Yield 1.83 g (58%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 1H, *J* = 7.6 Hz), 7.28-7.38 (m, 2H), 7.19 (d, 1H, *J* = 7.6 Hz), 3.68 (t, 2H, *J* = 7.4 Hz), 2.78 (q, 2H, *J* = 7.6 Hz), 2.69 (t, 2H, *J* = 7.4 Hz), 1.23 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 137.8, 130.5, 128.9, 127.6, 126.9, 125.0, 46.7, 28.7, 26.2, 11.3.

1-Propyl-3,4-dihydroisoquinoline (1c)[S3]



Yield 1.66 g (48%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 1H, *J* = 7.2 Hz), 7.35 (t, 1H, *J* = 7.4 Hz), 7.30 (d, 1H, *J* = 7.2 Hz), 7.19 (d, 1H, *J* = 7.2 Hz), 3.67 (t, 2H, *J* = 7.4 Hz), 2.71 (dt, 4H, J_1 = 15.6 Hz, J_2 = 7.6 Hz), 1.69 (h, 2H, *J* = 7.6 Hz), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8, 137.9, 130.6, 128.9, 127.6, 126.9, 125.2, 46.6, 37.8, 26.2, 20.6, 14.0.

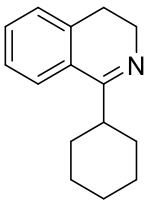
1-Isopropyl-3,4-dihydroisoquinoline (1d)[S2]



Yield 1.77 g (51%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, 1H, *J* = 7.6 Hz), 7.27-7.37 (m, 2H), 7.19 (d, 1H, *J* = 7.2 Hz), 3.67 (t, 2H, *J* = 7.4 Hz), 3.28 (p, 1H, *J* = 6.8 Hz), 2.66 (t, 2H, *J* = 7.4 Hz), 1.22 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 138.3, 130.2, 128.7,

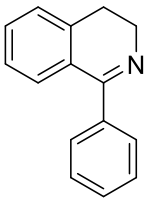
127.6, 126.8, 124.8, 46.7, 31.7, 26.3, 20.8.

1-Cyclohexyl-3,4-dihydroisoquinoline (1e)[S4]



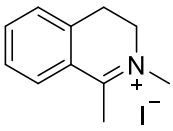
Yield 2.64 g (62%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, 1H, *J* = 7.2 Hz), 7.27-7.37 (m, 2H), 7.19 (d, 1H, *J* = 7.2 Hz), 3.67 (t, 2H, *J* = 7.4 Hz), 2.85-2.96 (m, 1H), 2.65 (t, 2H, *J* = 7.2 Hz), 1.79-1.94 (m, 4H), 1.74 (d, 1H, *J* = 12.4 Hz), 1.27-1.54 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 138.3, 130.3, 128.7, 127.7, 126.8, 124.7, 46.6, 42.1, 31.3, 26.6, 26.3, 26.3.

1-Phenyl-3,4-dihydroisoquinoline (1f)[S4]



Yield 2.10 g (51%), yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58-7.63 (m, 2H), 7.36-7.45 (m, 4H), 7.22-7.29 (m, 3H), 3.86 (t, 2H, *J* = 7.2 Hz), 2.81 (t, 2H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 138.8, 130.8, 129.4, 128.9, 128.7, 128.2, 128.1, 127.4, 126.6, 47.4, 26.3.

1,2-Dimethyl-3,4-dihydroisoquinolin-2-ium iodide (1h)[S5]



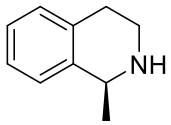
1-Methyl-3,4-dihydroisoquinoline (**1a**, 4 mmol) was dissolved in iodomethane (5 mL, 80 mmol), and the mixture was heated under reflux for 16 h. The precipitate was collected by filtration, washed with diethyl ether and dried under reduced pressure to afford **1h**. Yield 855 mg (74%), yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.10 (d, 1H, *J* = 8.0 Hz), 7.76 (t, 1H, *J* = 7.4 Hz), 7.55 (t, 1H, *J* = 7.8 Hz), 7.51 (d, 1H, *J* = 7.6 Hz), 4.05 (t, 2H, *J* = 7.6 Hz), 3.74 (s, 3H), 3.17 (t, 2H, *J* = 7.6 Hz), 2.83 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 176.0, 137.3, 136.3, 130.7, 128.5, 128.4, 127.8, 52.7, 45.5, 25.3, 19.4.

4. Bioreduction of 1-alkyl-3,4-dihydroisoquinolines

General: The reaction mixture was composed of 1 mmol **1a**, 1.5 mmol glucose, 5 μmol $NADP^+$, 100 mg cell-free extract (free dried cell lysate) of *Sn*IR, 10 mg cell-free extract of *Bm*GDH (100 U), 0.1 mL DMSO and 9.9 mL potassium phosphate buffer (100 mM, pH 7.0) and pH was adjusted to 7.0 by addition of 2 M HCl. The reaction was performed at 30 ℃, 200 rpm and the pH

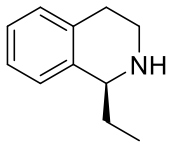
was maintained at 7.0 by titrating with 1 M NaOH. After complete conversion, the reaction was terminated by addition of 1 mL NaOH solution (2 M), and the mixture was extracted with ethyl acetate three times. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was further purified by column chromatography eluting with dichloromethane and methanol (10/1–5/1) to afford pure (*S*)-**2a**.

(*S*)-1-Methyl-1,2,3,4-tetrahydroisoquinoline (2a)[S2]



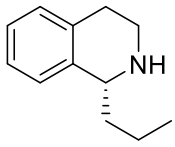
Eluent: DCM/MeOH = 10/1–5/1. Yield 106 mg (72%); yellow oil; 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.05-7.19 (m, 4H), 4.12 (q, 1H, J = 6.8 Hz), 3.28 (dt, 1H, J_1 = 12.4 Hz, J_2 = 5.2 Hz), 2.99-3.07 (m, 1H), 2.84-2.94 (m, 1H), 2.75 (dt, 1H, J_1 = 16.4 Hz, J_2 = 4.8 Hz), 1.47 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.3, 134.2, 129.2, 126.3, 126.1, 125.9, 51.5, 41.4, 29.3, 22.3. $[\alpha]_D^{29}$ = -64.9 (c, 1.0, $CHCl_3$) {ref [S2] $[\alpha]_D^{28}$ = -78.2 (c, 1.0, $CHCl_3$) with 99% ee for (*S*)-**2a**}. HPLC condition for the corresponding acetamide: OD-H column, *n*-hexane/2-propanol = 98/2, 1.0 mL/min at 220 nm and 30 ℃, t_{R1} = 31.4 min (*R*) and t_{R2} = 34.1 min (*S*).

(*S*)-1-Ethyl-1,2,3,4-tetrahydroisoquinoline (2b)[S2]



Eluent: DCM/MeOH = 10/1–5/1. Yield 130 mg (81%); yellow oil; 93% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.05-7.17 (m, 4H), 3.85-4.02 (m, 1H), 3.18-3.32 (m, 1H), 2.94-3.06 (m, 1H), 2.71-2.90 (m, 2H), 2.38 (br s, 1H), 1.86-1.99 (m, 1H), 1.68-1.83 (m, 1H), 1.02 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.3, 135.2, 129.2, 126.2, 125.9, 125.8, 57.1, 41.1, 30.0, 29.0, 10.5. $[\alpha]_D^{30}$ = -67.8 (c, 1.0, CH_2Cl_2) {ref [S2] $[\alpha]_D^{28}$ = -91.7 (c, 1.0, CH_2Cl_2) with 98% ee for (*S*)-**2b**}. HPLC condition for the corresponding acetamide: OD-H column, *n*-hexane/2-propanol = 99/1, 1.0 mL/min at 220 nm and 30 ℃, t_{R1} = 50.4 min (*R*) and t_{R2} = 55.9 min (*S*).

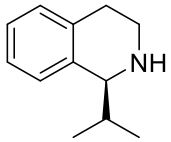
(*R*)-1-Propyl-1,2,3,4-tetrahydroisoquinoline (2c)[S6]



Eluent: DCM/MeOH = 20/1–10/1. Yield 135 mg (77%); yellow oil; 8% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.03-7.18 (m, 4H), 3.97 (dd, 1H, J_1 = 9.2 Hz, J_2 = 3.2 Hz), 3.19-3.28 (m, 1H), 2.93-3.02 (m, 1H), 2.69-2.87 (m, 2H), 1.65-1.87 (m, 3H), 1.39-1.57 (m, 2H), 0.98 (t, 3H, J = 7.4 Hz); ^{13}C

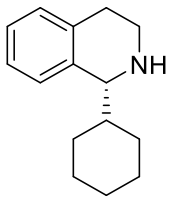
NMR ($CDCl_3$, 100 MHz): δ 139.9, 135.2, 129.2, 126.1, 125.8, 125.7, 55.5, 41.1, 38.8, 30.1, 19.4, 14.2. $[\alpha]_D^{30}$ = +9.4 (c, 1.0, CH_2Cl_2) {ref [S6] $[\alpha]_D^{22}$ = -35 (c, 1.0, $CHCl_3$) with 80% ee for (*S*)-**2c**}. HPLC condition for the corresponding acetamide: OJ-H column, n-hexane/2-propanol = 95/5, 1.0 mL/min at 220 nm and 30 ℃, t_{R1} = 9.3 min (*R*) and t_{R2} = 15.4 min (*S*).

(*S*)-1-Isopropyl-1,2,3,4-tetrahydroisoquinoline (2d)[S2]



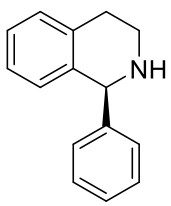
Eluent: DCM/MeOH = 20/1–10/1. Yield 133 mg (76%); yellow oil; 98% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.05-7.19 (m, 4H), 3.95 (d, 1H, *J* = 3.6 Hz), 3.27-3.33 (m, 1H), 2.81-2.97 (m, 2H), 2.67 (dt, 1H, J_1 = 15.2 Hz, J_2 = 3.2 Hz), 2.30-2.39 (m, 1H), 1.85 (br s, 1H), 1.12 (d, 3H, *J* = 6.8 Hz), 0.74 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.7, 136.2, 129.1, 125.9, 125.8, 125.6, 61.0, 42.5, 32.3, 30.4, 20.3, 15.8. $[\alpha]_D^{30}$ = -112.3 (c, 1.0, CH_2Cl_2) {ref [S2] $[\alpha]_D^{28}$ = -118.5 (c, 1.0, CH_2Cl_2) with 96% ee for (*S*)-**2d**}. HPLC condition for the corresponding acetamide: OJ-H column, n-hexane/2-propanol = 95/5, 1.0 mL/min at 220 nm and 30 ℃, t_{R1} = 9.0 min (*R*) and t_{R2} = 9.9 min (*S*).

(*R*)-1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline (2e)[S4, S7]



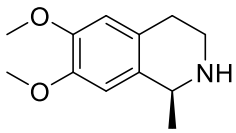
Eluent: DCM/MeOH = 20/1–10/1. Yield 158 mg (73%); yellow oil; 80% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.03-7.21 (m, 4H), 3.97 (d, 1H, *J* = 4.0 Hz), 3.29-3.39 (m, 1H), 2.83-3.00 (m, 2H), 2.70 (dt, 1H, J_1 = 15.6 Hz, J_2 = 3.6 Hz), 1.88-1.99 (m, 1H), 1.79-1.87 (m, 1H), 1.62-1.79 (m, 3H), 1.24-1.46 (m, 3H), 1.08-1.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.6, 135.9, 129.1, 126.1, 125.8, 60.7, 43.0, 42.2, 30.9, 29.8, 27.0, 26.6, 26.5, 26.4. $[\alpha]_D^{30}$ = +46.1 (c, 1.0, EtOH) {ref [S7] $[\alpha]_\lambda^t$ = +90.0 (c, 1.0, EtOH) with 94% ee for (*R*)-**2e**}. HPLC condition for the corresponding acetamide: OJ-H column, *n*-hexane/2-propanol = 98/2, 0.6 mL/min at 220 nm and 30 ℃, t_{R1} = 19.5 min (*R*) and t_{R2} = 22.6 min (*S*).

(*S*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (2f)[S4, S8]



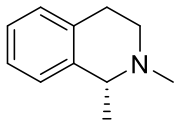
Eluent: PE/EtOAc = 1/2. Yield 170 mg (81%); white solid; 51% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.35 (m, 5H), 7.14 (d, 2H, *J* = 4.0 Hz), 6.99-7.07 (m, 1H), 6.75 (d, 1H, *J* = 8.0 Hz), 5.10 (s, 1H), 3.22-3.31 (m, 1H), 2.98-3.12 (m, 2H), 2.79-2.88 (m, 1H), 2.35 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.7, 138.2, 135.4, 129.1, 129.0, 128.5, 128.2, 127.5, 126.3, 125.7, 62.1, 42.2, 29.7. $[\alpha]_D^{30}$ = +6.9 (c, 1.0, $CHCl_3$) {ref [S8] $[\alpha]_D^{29}$ = +12.3 (c, 1.0, $CHCl_3$) with 99% ee for (*S*)-**2f**}. HPLC condition for the corresponding acetamide: OD-H column, n-hexane/2-propanol = 95/5, 0.8 mL/min at 220 nm and 30 ℃, t_{R1} = 20.7 min (*R*) and t_{R2} = 21.8 min (*S*).

(*S*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2g)[S2]



Eluent: DCM/MeOH = 20/1–10/1. Yield 158 mg (76%); white solid; 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.61 (s, 1H), 6.57 (s, 1H), 4.13 (q, 1H, *J* = 6.5 Hz), 3.85 (s, 3H), 3.85 (s, 3H), 3.54 (br s, 1H), 3.29 (dt, 1H, J_1 = 12.4 Hz, J_2 = 5.2 Hz), 3.01-3.10 (m, 1H), 2.80-2.89 (m, 1H), 2.72 (dt, 1H, J_1 = 16.0 Hz, J_2 = 4.8 Hz), 1.50 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 147.4, 131.2, 126.2, 111.7, 109.0, 56.0, 55.9, 51.1, 41.3, 28.8, 22.4. $[\alpha]_D^{30}$ = -42.0 (c, 1.0, EtOH) {ref [S2] $[\alpha]_D^{28}$ = -50.7 (c, 1.69, EtOH) with 94% ee for (*S*)-**2g**}. HPLC condition for the corresponding acetamide: OD-H column, *n*-hexane/2-propanol = 90/10, 1.0 mL/min at 220 nm and 30 ℃, t_{R1} = 19.4 min (*R*) and t_{R2} = 21.4 min (*S*).

(*R*)-1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline (2h)[S5, S9]



Eluent: DCM/MeOH = 20/1–10/1. Yield 60 mg (75%); yellow oil; 87% *ee*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07-7.20 (m, 4H), 3.73 (q, 1H, *J* = 6.5 Hz), 3.12 (ddd, 1H, J_1 = 12.0 Hz, J_2 = 6.4 Hz, J_3 = 5.0 Hz), 2.83-2.99 (m, 2H), 2.75 (ddd, 1H, J_1 = 12.0 Hz, J_2 = 7.0 Hz, J_3 = 5.0 Hz), 2.54 (s, 3H), 1.46 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.7, 133.3, 128.8, 126.9, 126.2, 126.1, 59.1, 48.7, 42.5, 27.5, 19.7. $[\alpha]_D^{30}$ = +40.5 (c, 1.0, $CHCl_3$) {ref [S9] $[\alpha]_D^{20}$ = +58.6 (c, 1.0, $CHCl_3$) with 98% ee for (*R*)-**2h**}. GC condition: CP-Chirasil-Dex CB column, injector 280 ℃, detector 280 ℃, programmed column temperature 90 ℃ rise to 200 ℃ at 4 ℃/min, t_{R1} = 12.6 min (*S*) and t_{R2} = 13.1 min (*R*).

Reference

[S1] Li, H.; Zhang, G.-X.; Li, L.-M.; Ou, Y.-S.; Wang, M.-Y.; Li, C.-X.; Zheng, G.-W.; Xu, J.-H. *ChemCatChem* **2016**, *8*, 724–727.

[S2] Xie, J.-H.; Yan, P.-C.; Zhang, Q.-Q.; Yuan, K.-X.; Zhou, Q.-L. *ACS Catal.* **2012**, *2*, 561–564.

[S3] Cannon, J. G.; Webster, G. L. *J. Am. Pharm. Assoc. Sci. Ed.* **1958**, *47*, 353–355.

[S4] Chang, M.; Li, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2011**, *50*, 10679–10681.

[S5] Hussain, S.; Leipold, F.; Man, H.; Wells, E.; France, S. P.; Mulholland, K. R.; Grogan, G.; Turner, N. J. *ChemCatChem* **2015**, *7*, 579–583.

[S6] Benmekhbi, L.; Louafi, F.; Roisnel, T.; Hurvois, J.-P. *J. Org. Chem.* **2016**, *81*, 6721–6739.

[S7] Ding, Z.-Y.; Wang, T.; He, Y.-M.; Chen, F.; Zhou, H.-F.; Fan, Q.-H.; Guo, Q.; Chan, A. S. C. *Adv. Synth. Catal.* **2013**, *355*, 3727–3735.

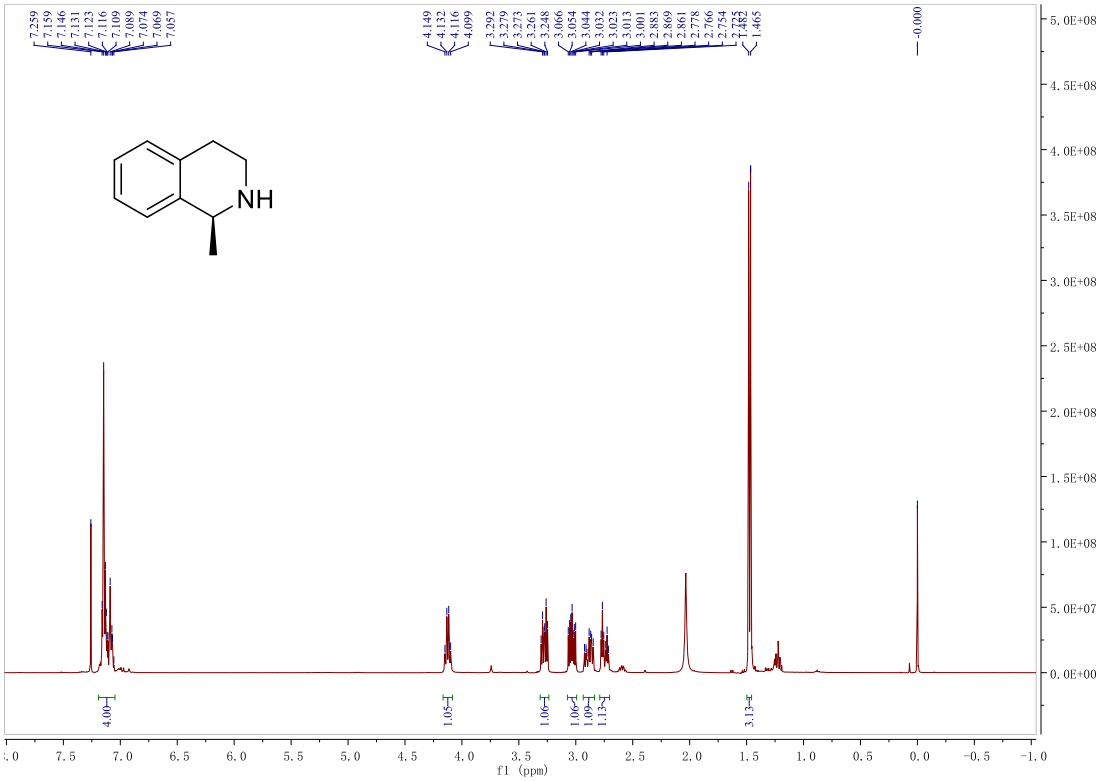
[S8] Ye, Z.-S.; Guo, R.-N.; Cai, X.-F.; Chen, M.-W.; Shi, L.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2013**, *52*, 3685–3689.

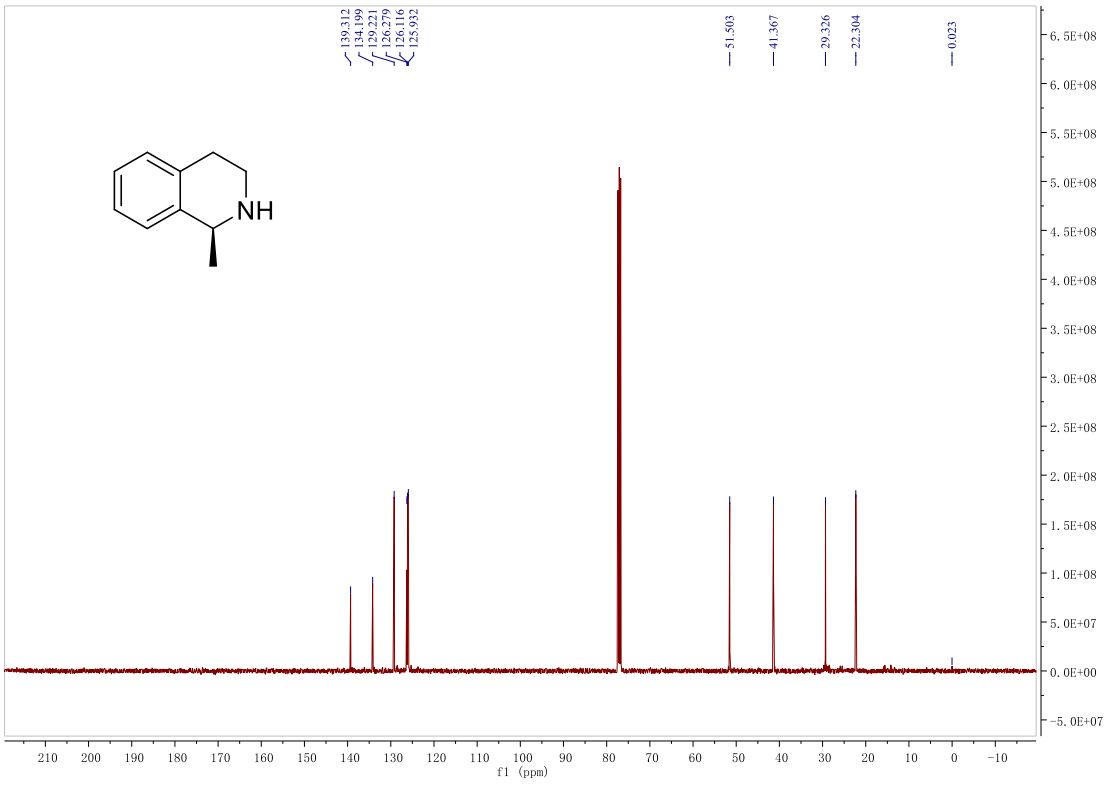
[S9] Yan, P.-C.; Xie, J.-H.; Hou, G.-H.; Wang, L.-X.; Zhou, Q.-L. *Adv. Synth. Catal.* **2009**, *351*, 3243–3250.

[S10] Li, H.; Luan, Z.-J.; Zheng, G.-W.; Xu, J.-H. *Adv. Synth. Catal.* **2015**, *357*, 1692–1696.

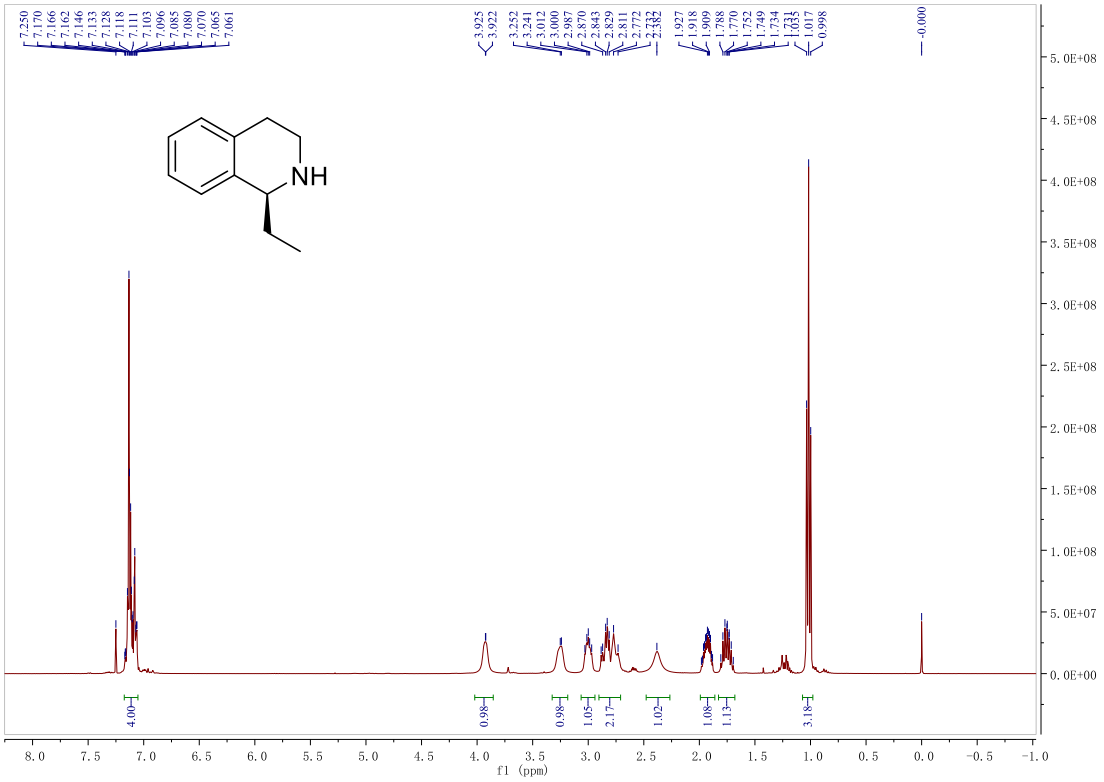
5. NMR spectra

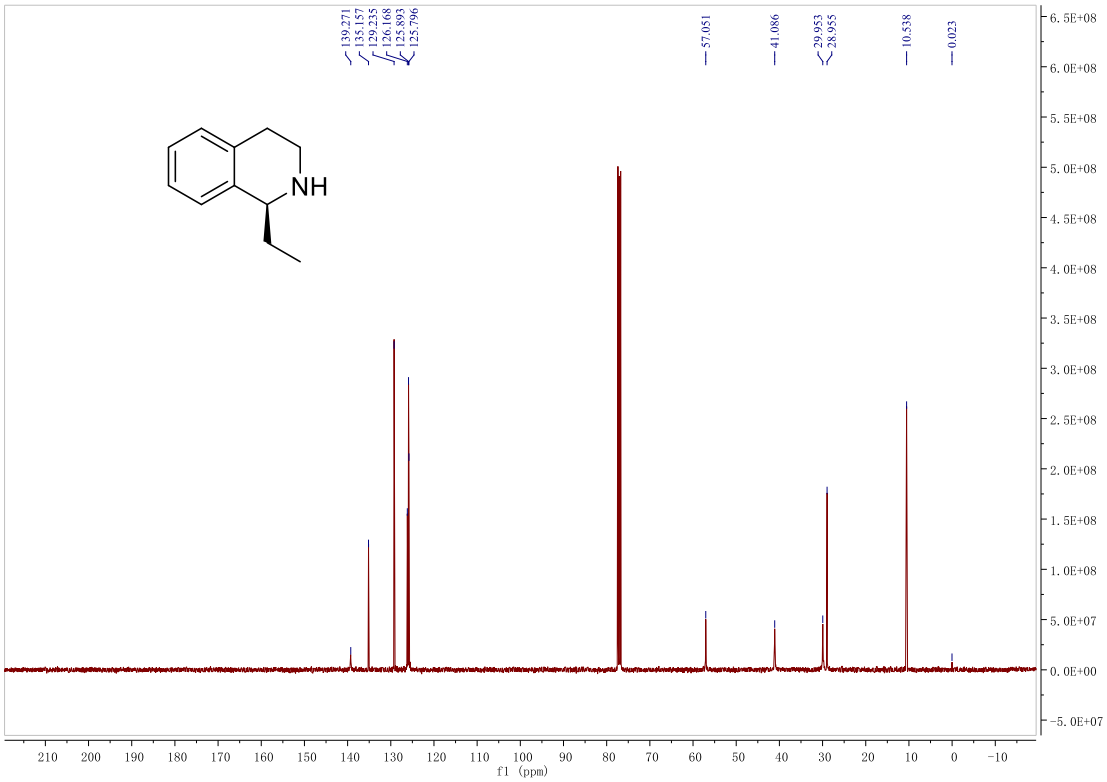
(*S*)-1-Methyl-1,2,3,4-tetrahydroisoquinoline (2a)



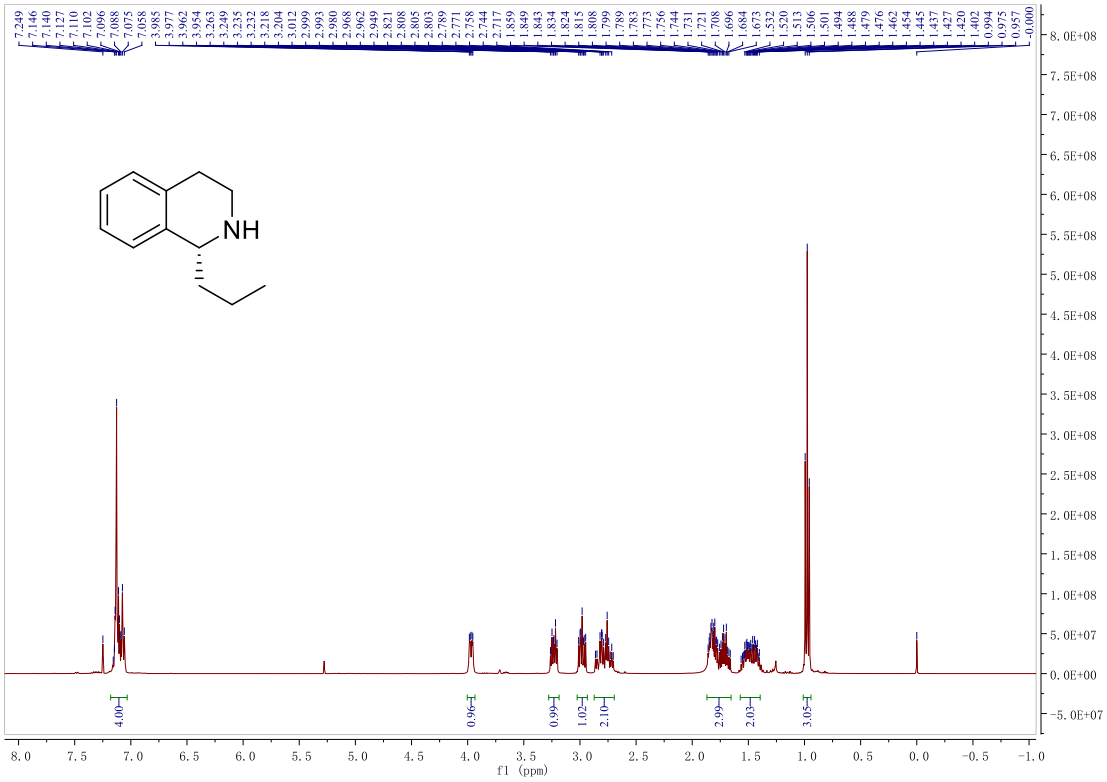


(*S*)-1-Ethyl-1,2,3,4-tetrahydroisoquinoline (2b)

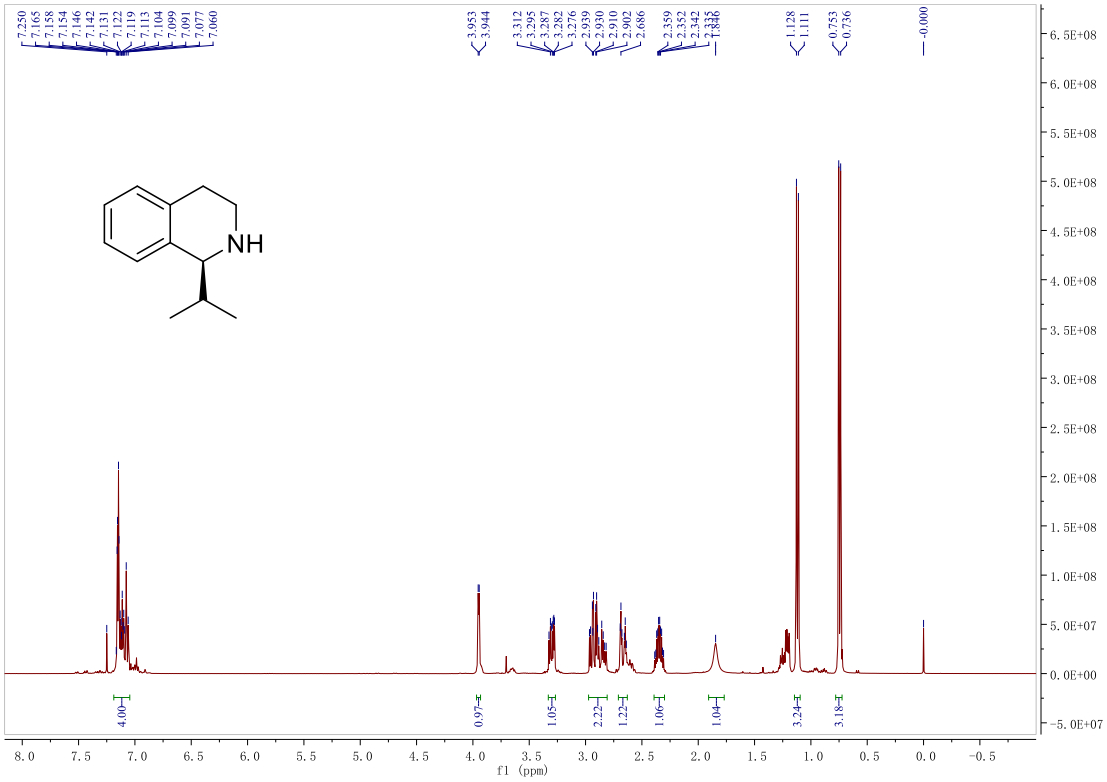


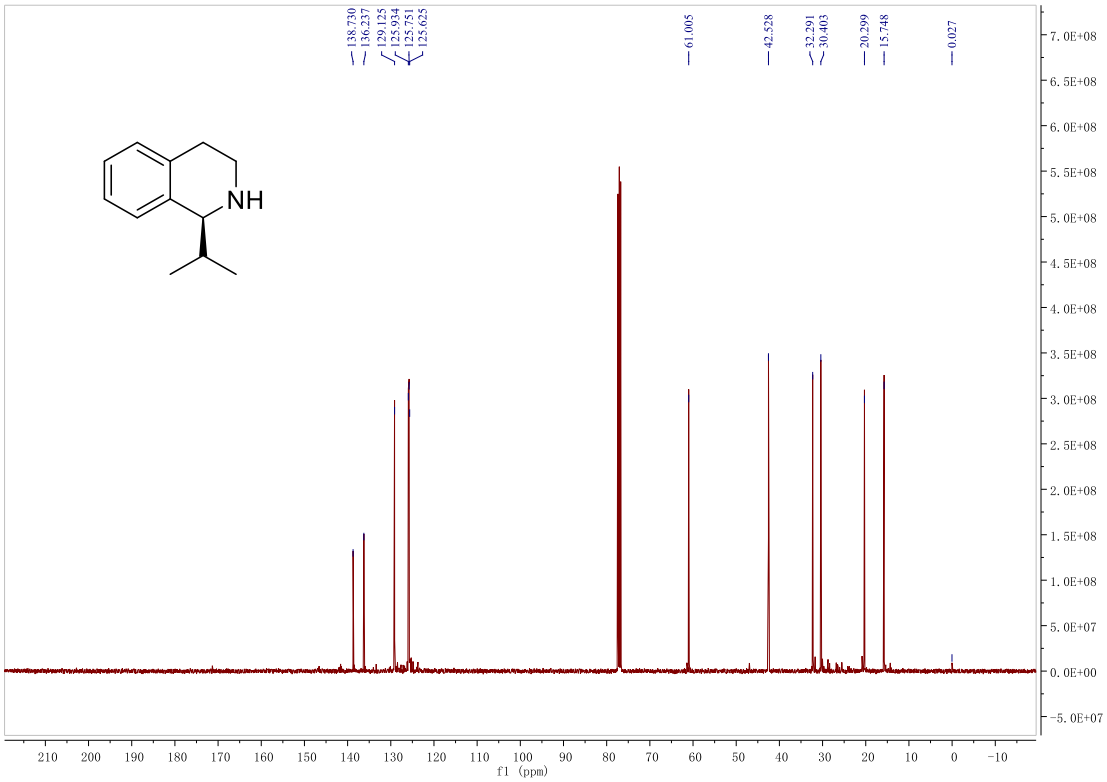


(*R*)-1-Propyl-1,2,3,4-tetrahydroisoquinoline (2c)

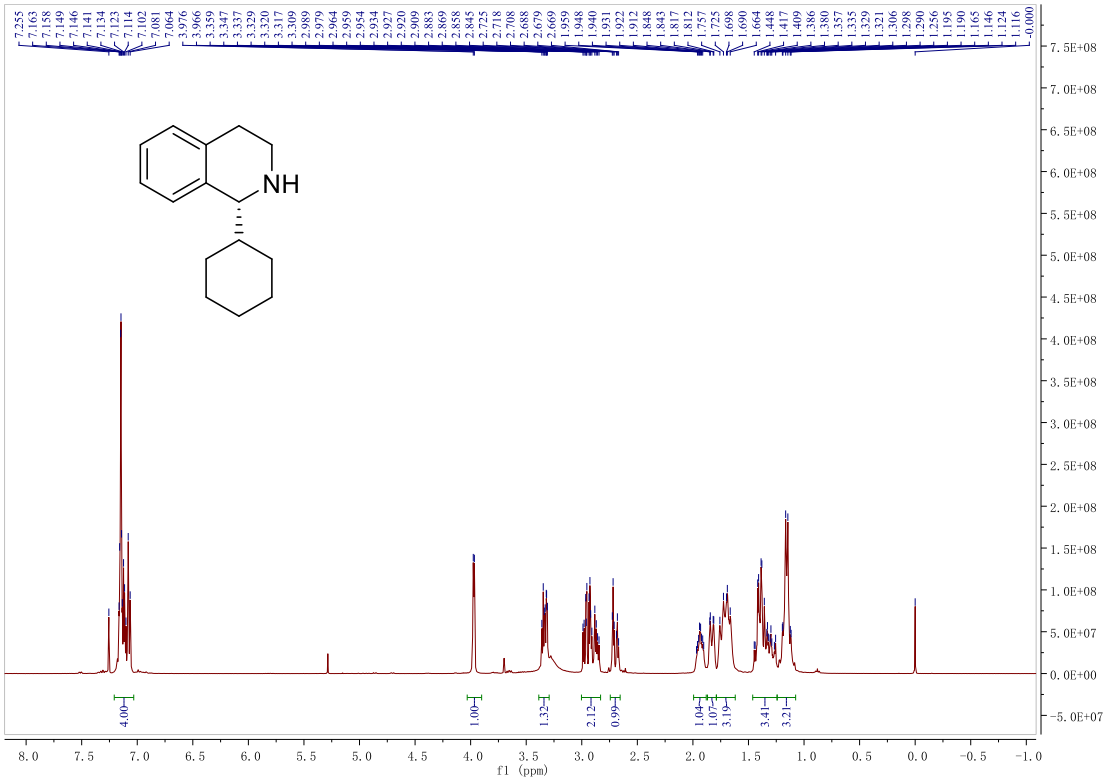


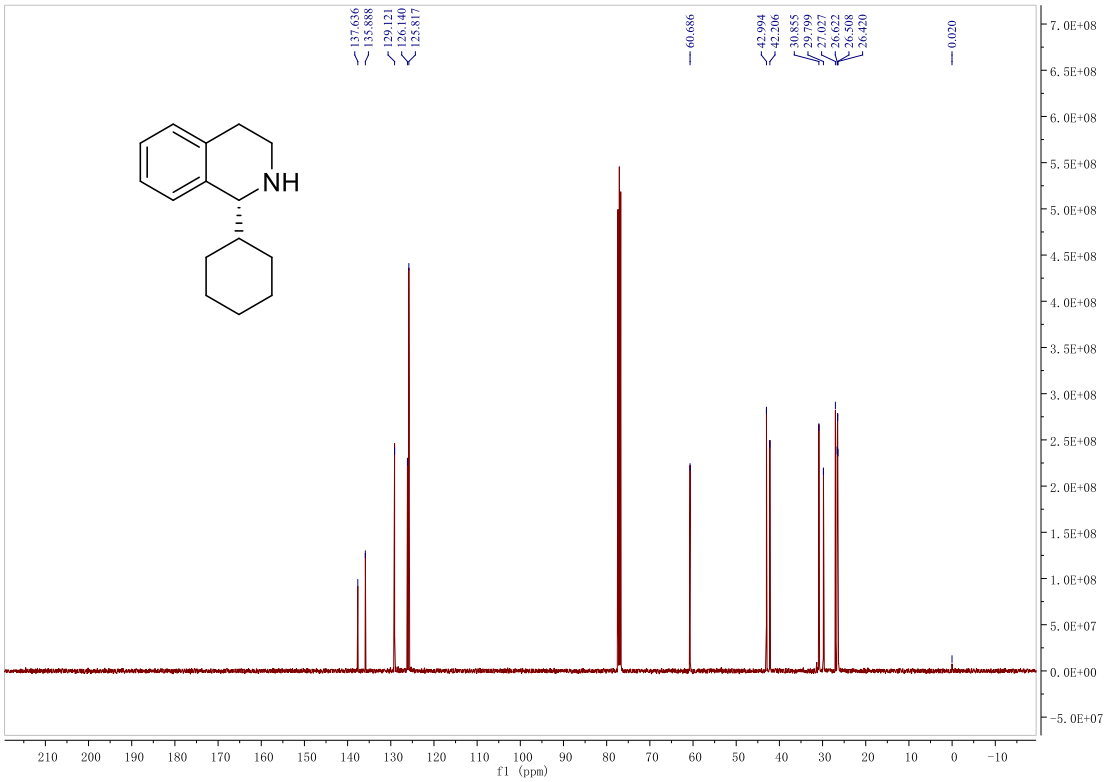
(*S*)-1-Isopropyl-1,2,3,4-tetrahydroisoquinoline (2d)



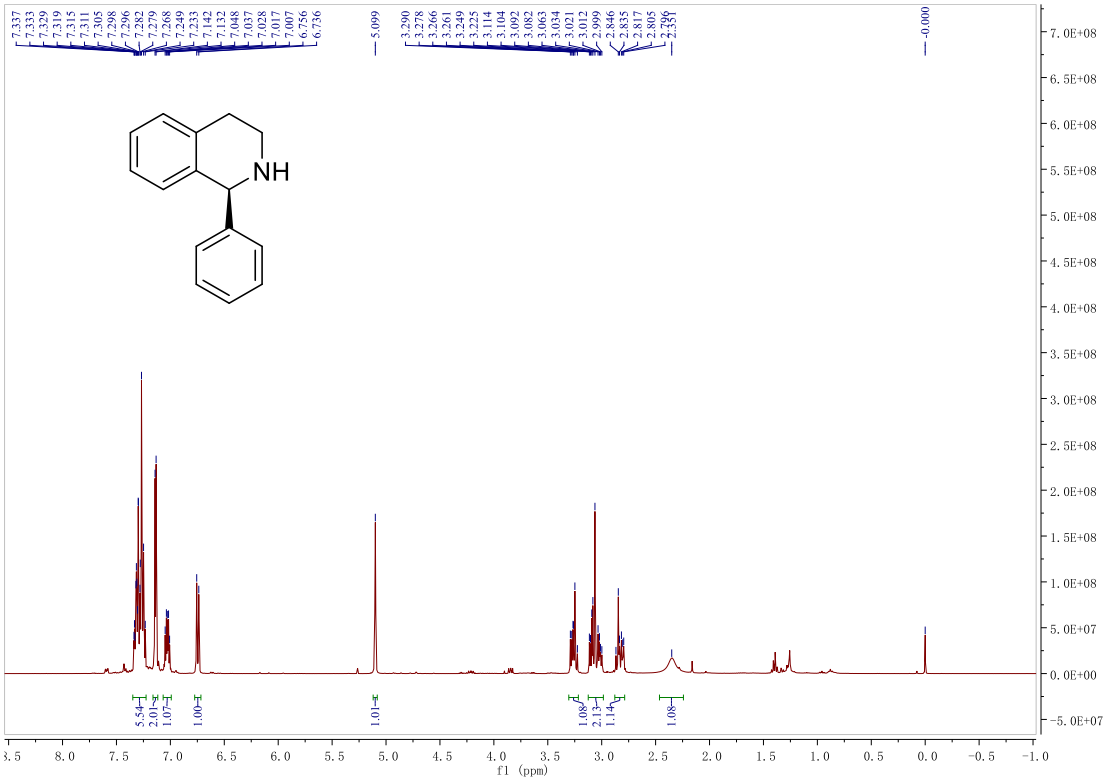


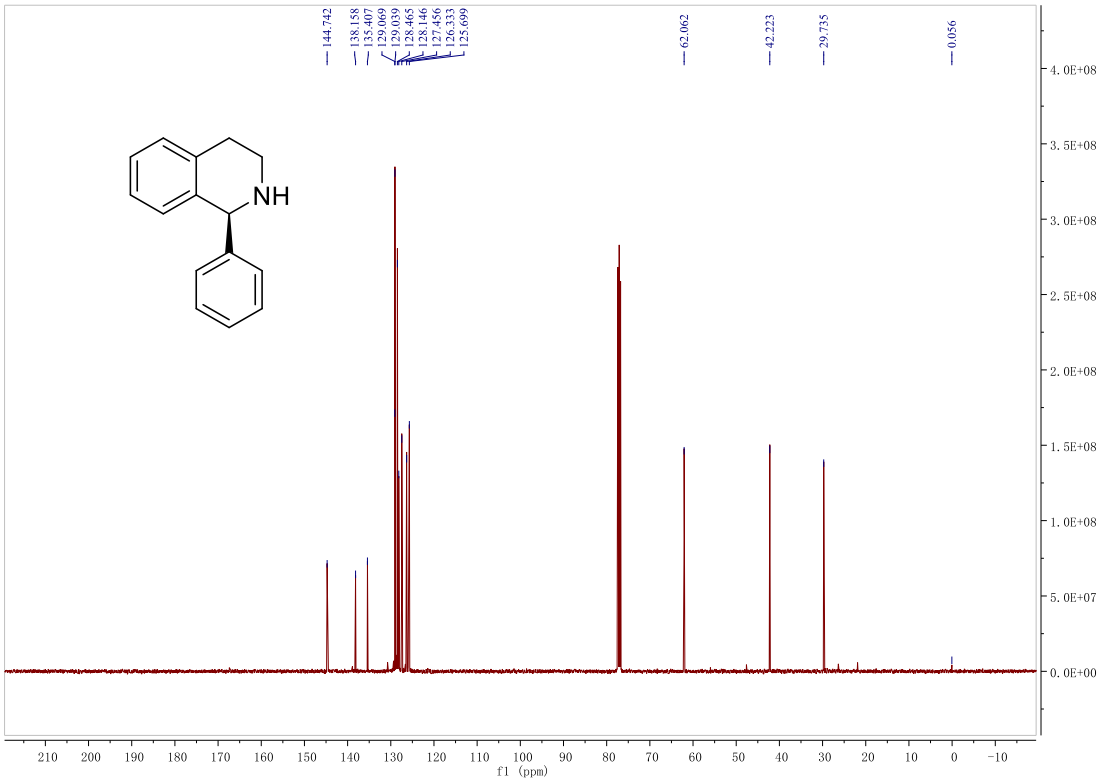
(*R*)-1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline (2e)



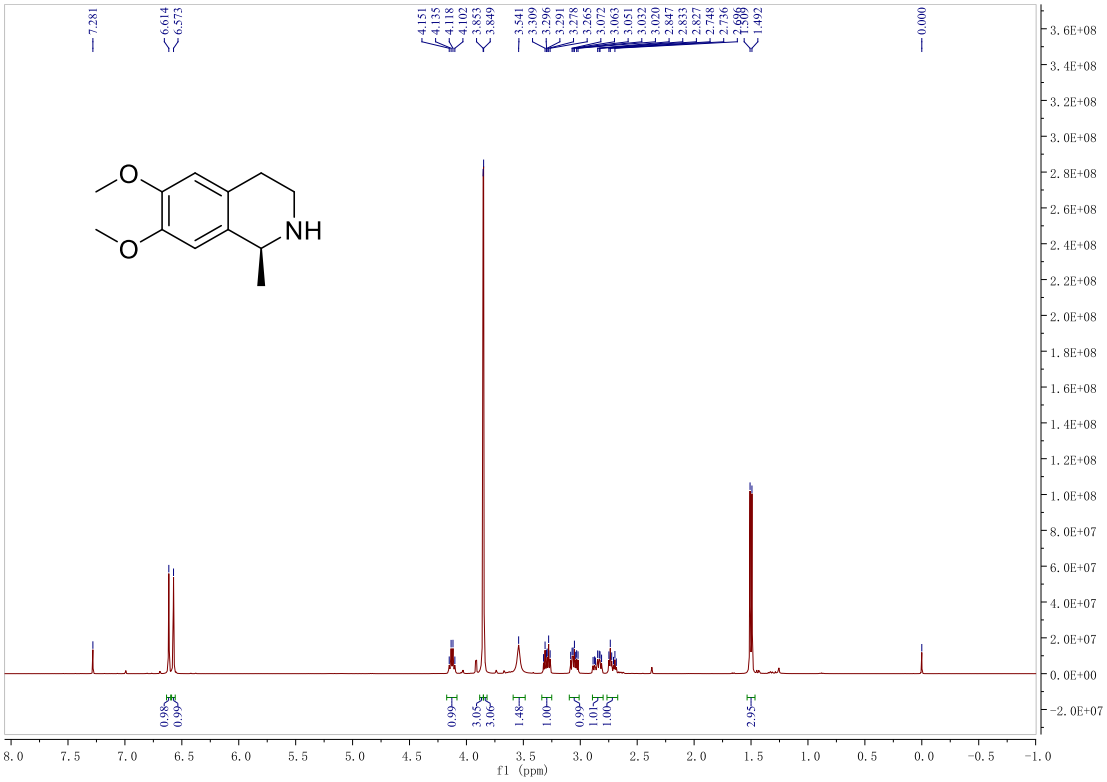


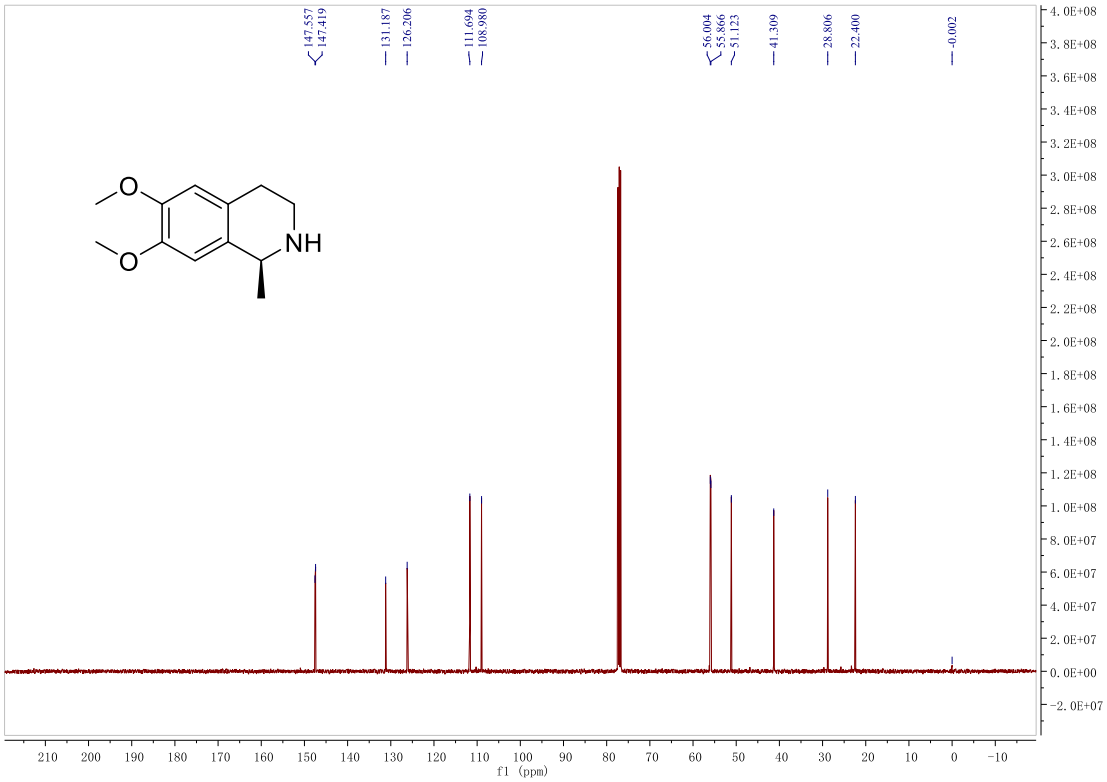
(*S*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (2f)



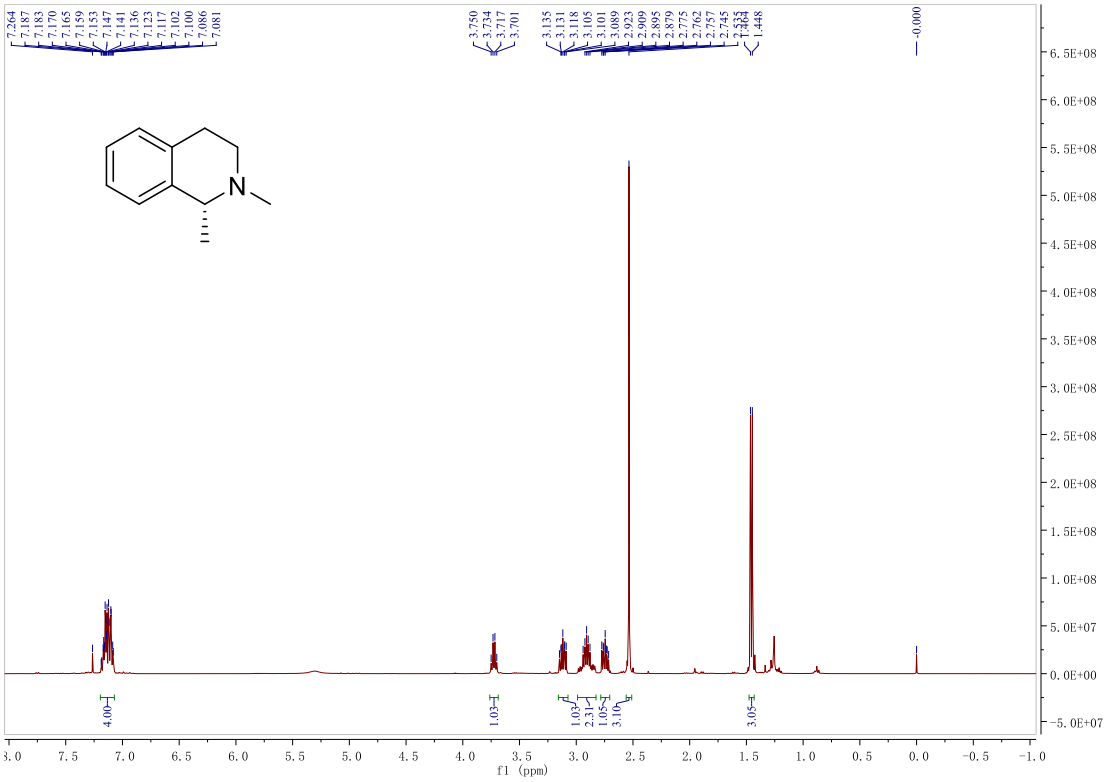


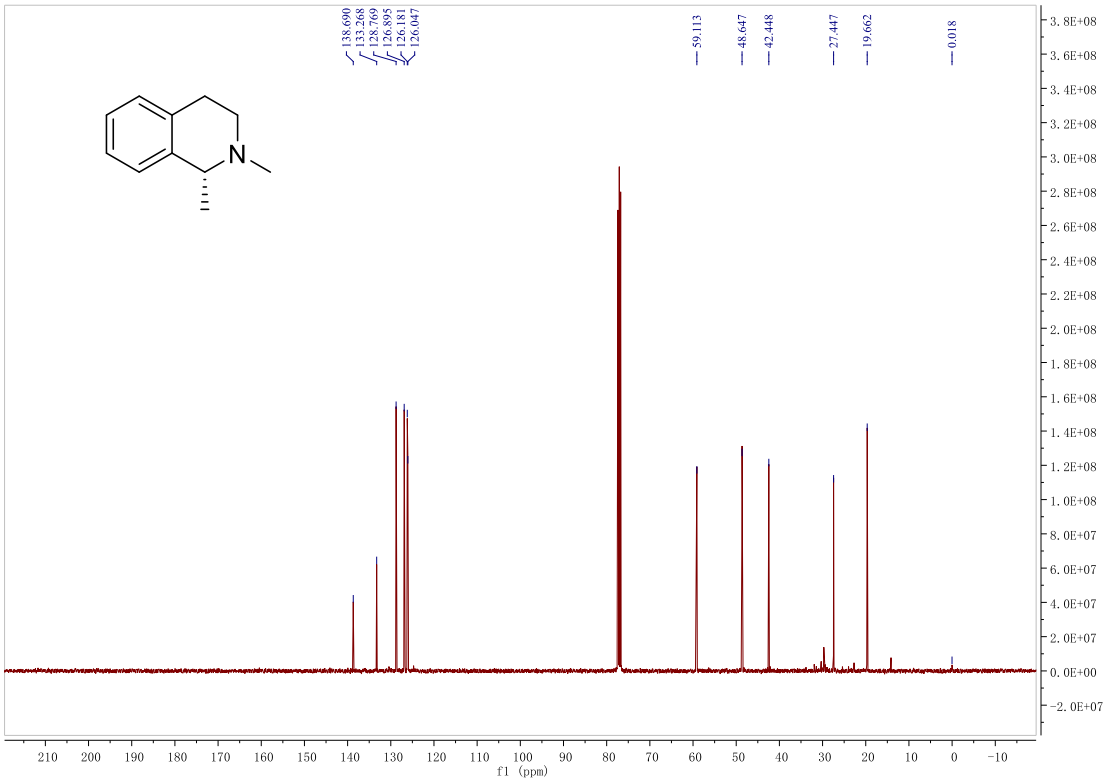
(*S*)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2g)





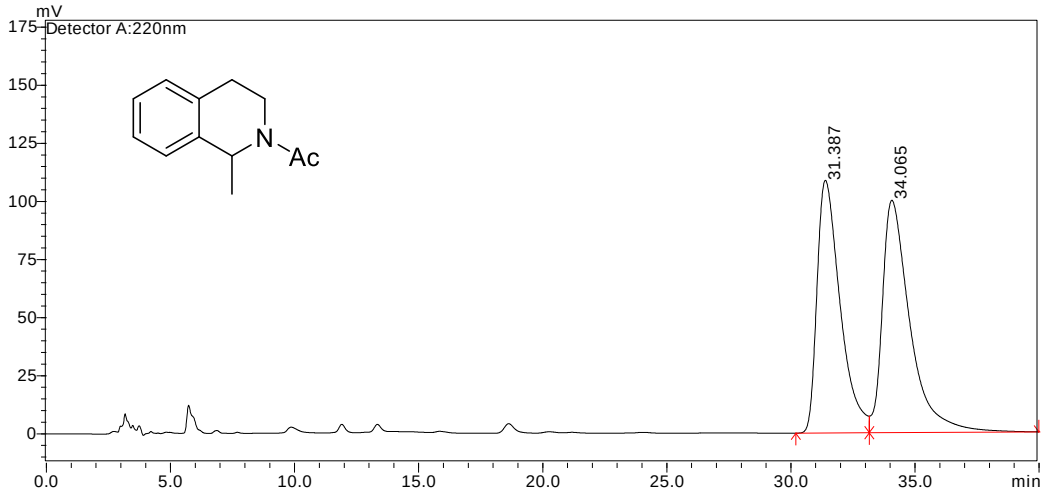
(*R*)-1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline (2h)



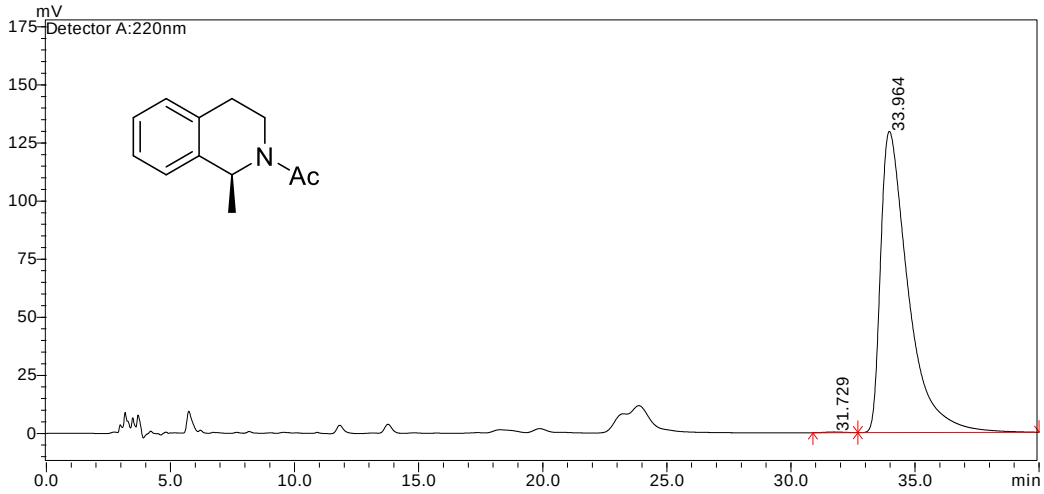


6. HPLC and GC spectra

1-Methyl-1,2,3,4-tetrahydroisoquinoline (2a)

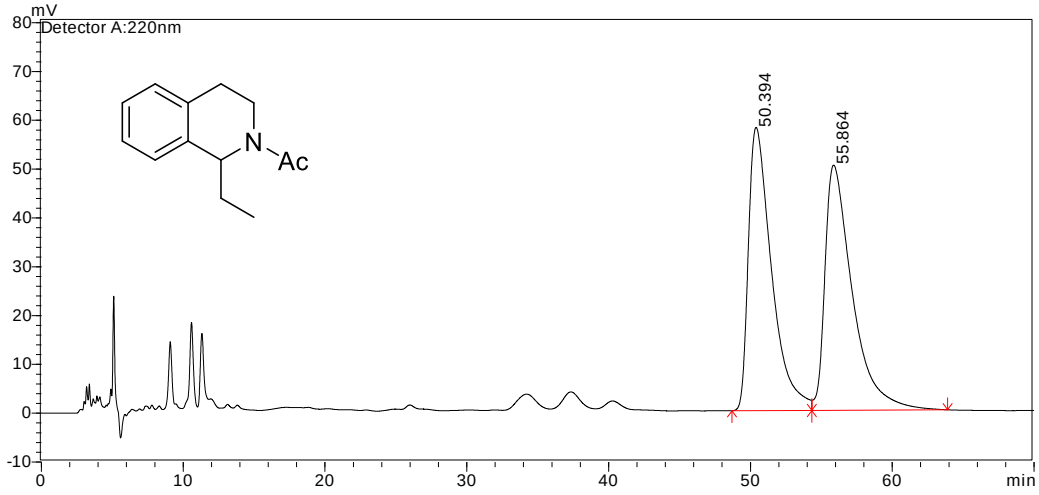


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	31.387	108.755	7051.848	47.6222
2	34.065	100.005	7756.056	52.3778

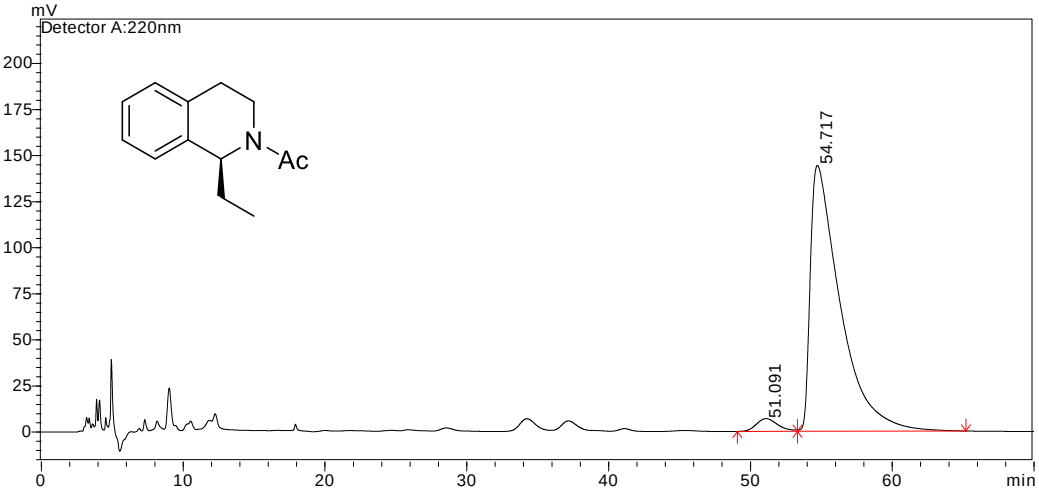


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	31.729	0.308	16.189	0.1611
2	33.964	129.637	10032.849	99.8389

1-Ethyl-1,2,3,4-tetrahydroisoquinoline (2b)

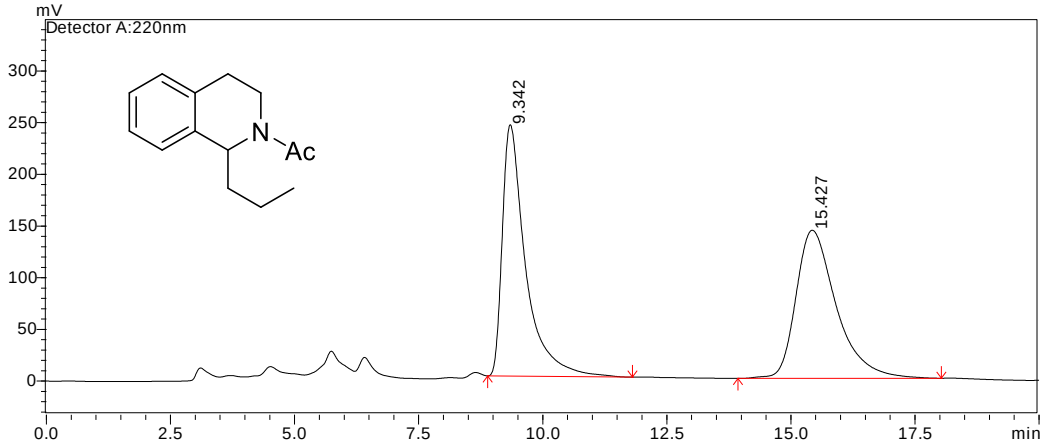


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	50.394	58.012	6593.005	49.4016
2	55.864	50.216	6752.720	50.5984

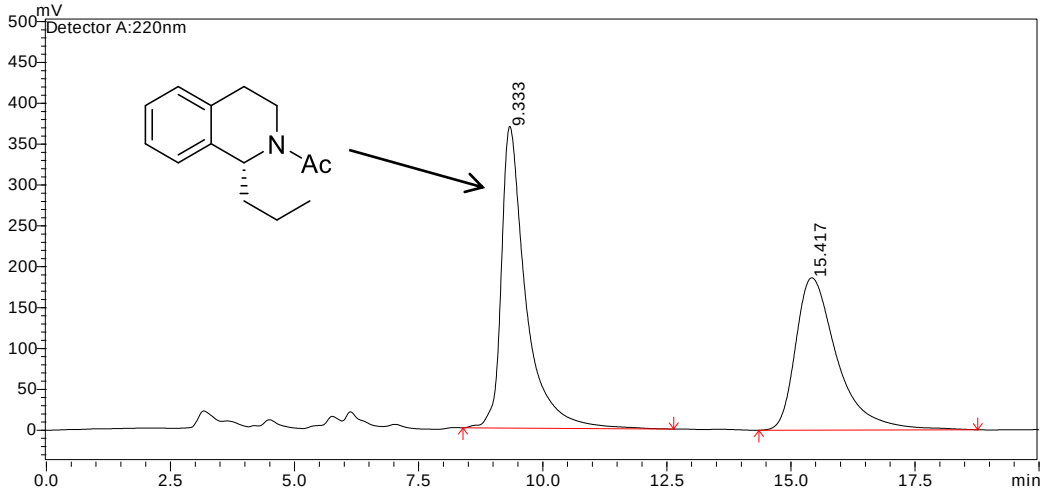


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	51.091	6.896	725.467	3.3145
2	54.717	144.300	21161.987	96.6855

1-Propyl-1,2,3,4-tetrahydroisoquinoline (2c)

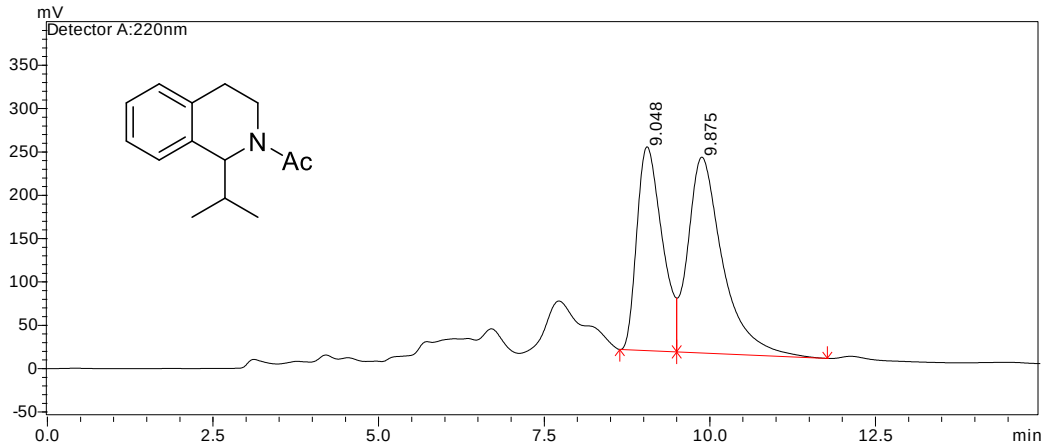


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	9.342	243.342	7959.533	49.545
2	15.427	143.350	8105.729	50.455

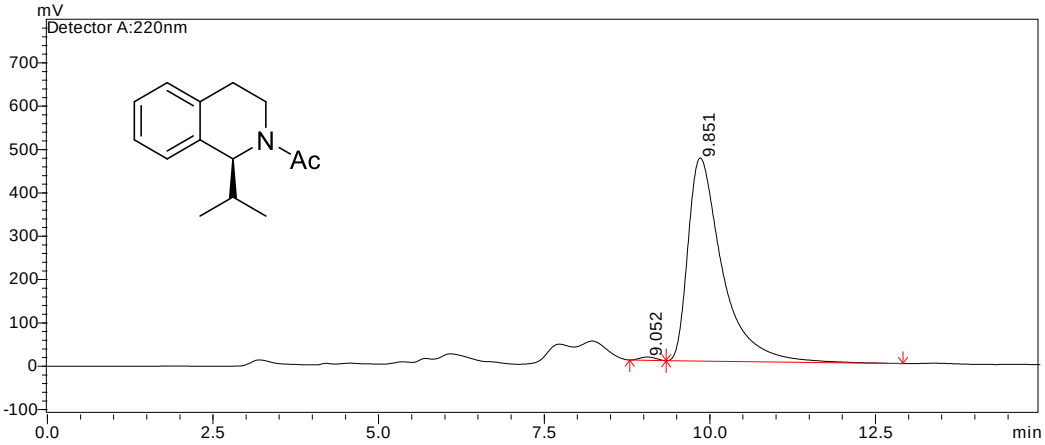


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	9.333	369.258	12716.416	53.9471
2	15.417	186.473	10855.610	46.0529

1-Isopropyl-1,2,3,4-tetrahydroisoquinoline (2d)

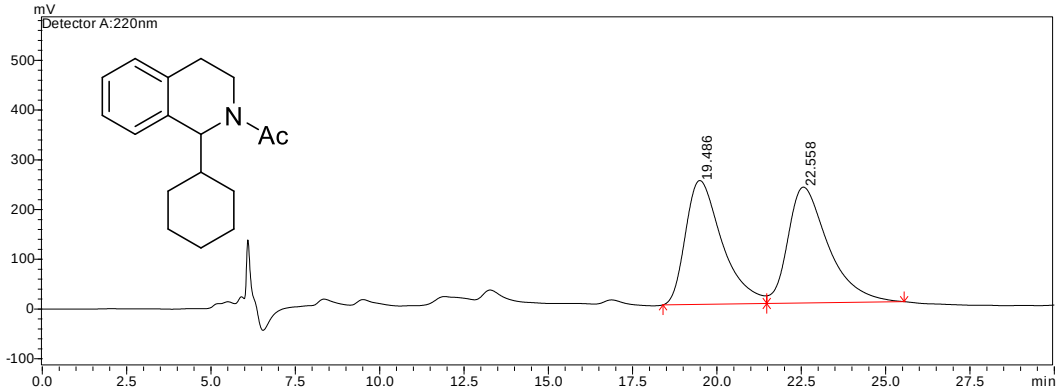


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	9.048	235.331	6281.180	43.1754
2	9.875	226.123	8266.867	56.8246

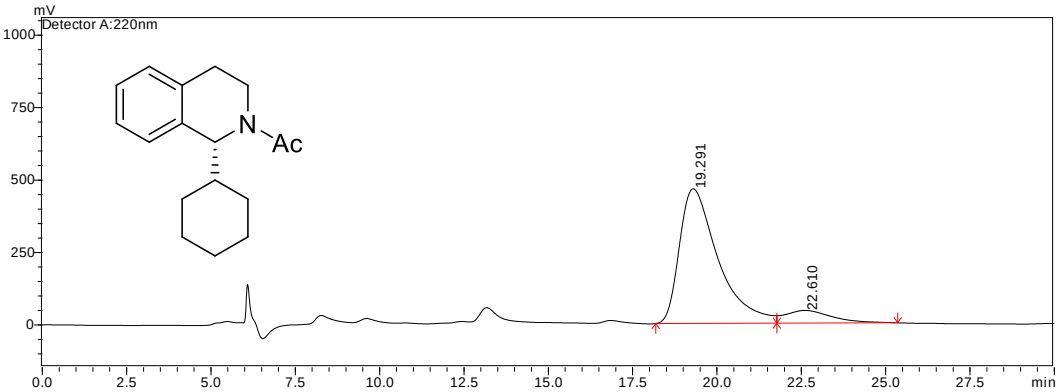


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	9.052	7.703	130.326	0.7643
2	9.851	468.902	16920.955	99.2357

1-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline (2e)

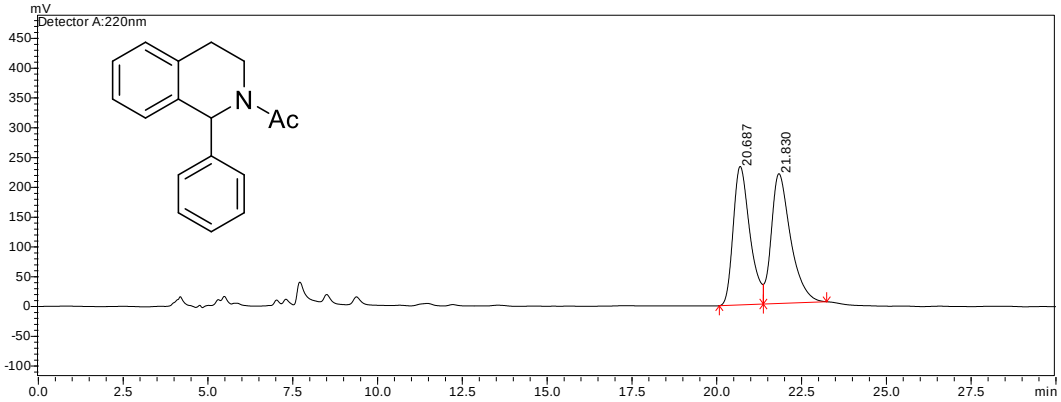


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	19.486	248.916	18817.019	49.1926
2	22.558	232.898	19434.716	50.8074

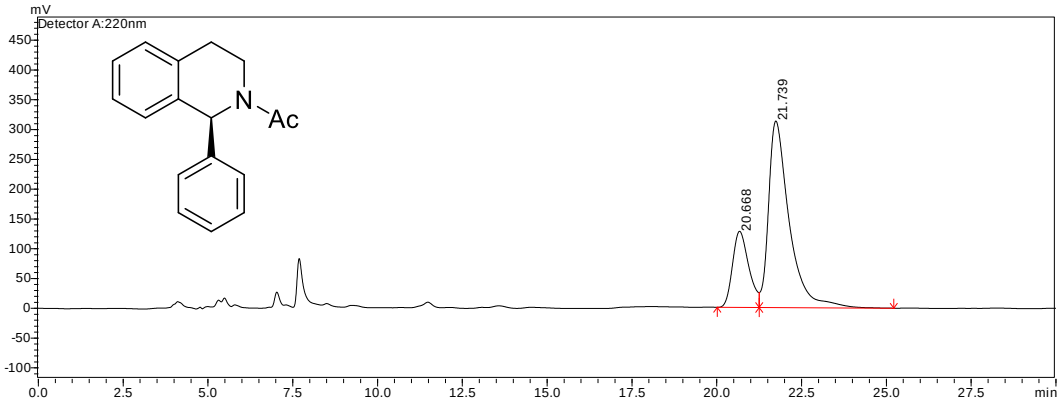


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	19.291	465.005	37138.497	89.8954
2	22.610	43.785	4174.527	10.1046

1-Phenyl-1,2,3,4-tetrahydroisoquinoline (2f)

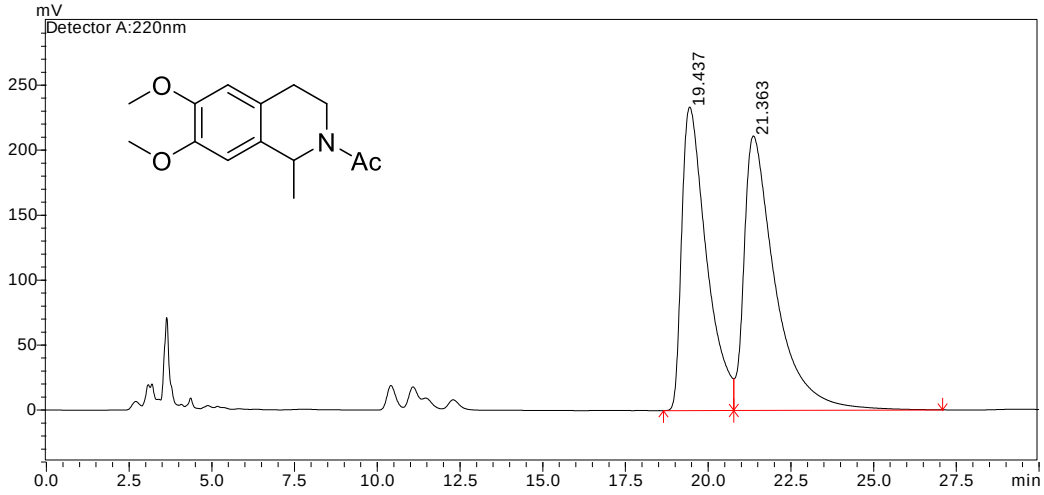


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	20.687	232.551	7990.411	48.0848
2	21.830	217.938	8626.918	51.9152

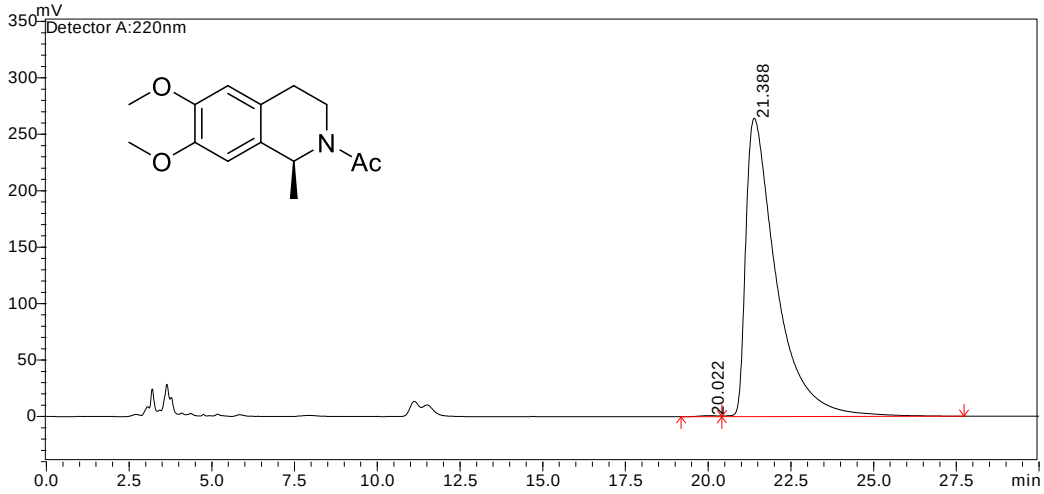


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	20.668	127.854	4279.720	24.3079
2	21.739	313.282	13326.557	75.6921

6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (2g)

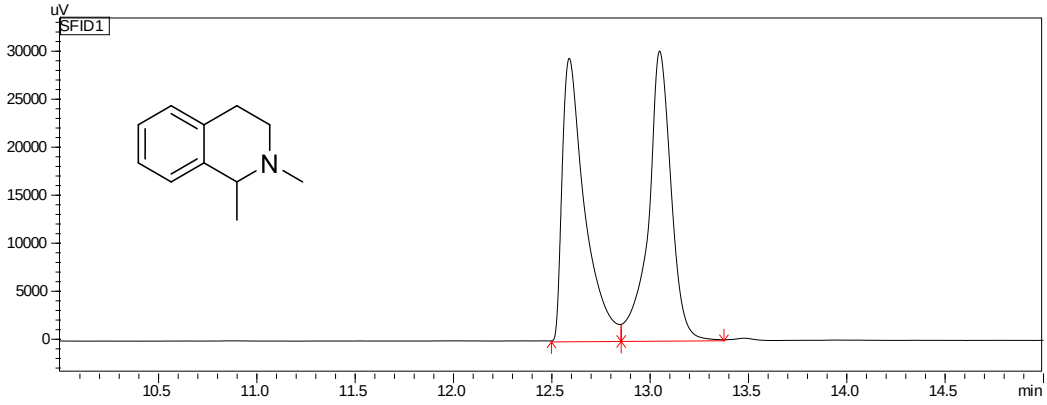


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	19.437	233.555	12213.181	46.7029
2	21.363	211.268	13937.624	53.2971

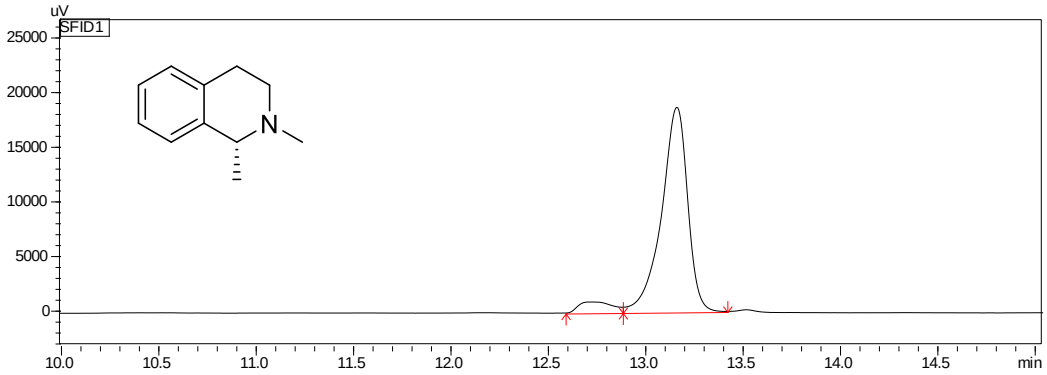


Peak #	Ret. time (min)	Height (mV)	Area (mV*s)	Area (%)
1	20.022	0.902	37.935	0.2221
2	21.388	264.336	17039.156	99.7779

1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline (2h)



Peak #	Ret. time (min)	Height (μV)	Area (μV*s)	Area (%)
1	12.594	29405	233112	49.288
2	13.053	30067	239847	50.712



Peak #	Ret. time (min)	Height (μV)	Area (μV*s)	Area (%)
1	12.712	987	11875	6.355
2	13.165	18701	174980	93.645

2-Methylpiperidine (4)

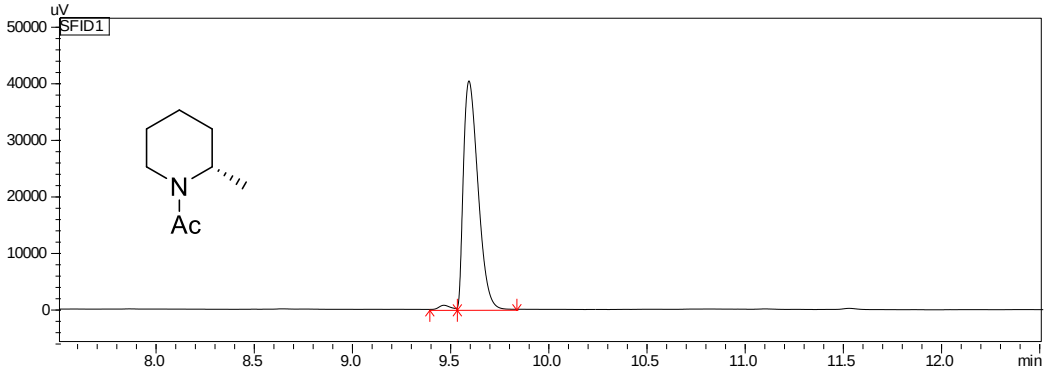


Figure S3. GC analysis of the products formed in the bioreduction of 6-methyl-2,3,4,5-tetrahydropyridine (**3**) by *Sn*IR (GC after acetylation/ CP-Chirasil-Dex CB column, injector: 280 ℃, detector: 280 ℃, programmed column temperature 100 ℃ rise to 160 ℃ at 5 ℃/min).[S10]

Peak #	Ret. time (min)	Height (µV)	Area (µV*s)	Area (%)
1	9.471	724	2774	1.319
2	9.598	40335	207610	98.681