**Supporting Information**

# Enantioselective Synthesis of 1-Aryltetrahydroisoquinolines

Sa Wang, M. Burak Onaran, and Christopher T. Seto*

*Department of Chemistry, Brown University, 324 Brook Street Box H*

*Providence, Rhode Island 02912*

Christopher_Seto@brown.edu

## Table of Contents

**General Methods.** Arylzinc reactions were conducted using oven-dried glassware and standard syringe techniques under a nitrogen atmosphere. Reactions were monitored by TLC. TLC plates were visualized using CAM (ceric ammonium molybdate), PMA (phosphomolybdic acid) or ninhydrin staining solution, or UV at 254 nm. Solvent removal was performed by rotary evaporation at water aspirator pressure. Dichloromethane, toluene, tetrahydrofuran and triethylamine were used from a dry solvent dispensing system. All other reagents were used as received.

NMR spectra were recorded at either 300 MHz or 400 MHz using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm and were referenced to residual protonated solvent for $^1H$ NMR (δ 7.26 ppm for $CHCl_3$) and $CDCl_3$ for $^{13}C$ NMR (δ 77.16 ppm). Data are represented as follows: chemical shift (multiplicity [br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], integration, coupling constants in Hz). High-resolution mass spectra were obtained using fast atom bombardment ionization methods. Enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column (0.46 cm i.d. × 25 cm) with UV detection at 219 nm. 2-Propanol and hexanes were used as solvents, and the flow rate was set at 1.0 mL/min. Optical rotations were obtained with a digital polarimeter at ambient temperature and at a wavelength of 589 nm (c = g/100 mL).

**Preparation of Arylzinc Reagents.** The pinacolyl boronic ester (1.4 equiv, 0.28 mmol) or boroxine (0.47 equiv, 0.093 mmol) was weighed, placed in an oven-dried vial, and flushed with a slow stream of $N_2$. Dry toluene (0.5 mL) was added, followed by the addition of a solution of $Et_2Zn$ (4.2 equiv, 86 μL, 0.84 mmol) in dry toluene (0.4 mL) using a gas-tight syringe. The

resulting reaction mixture was heated at 60 $^{o}$C for boroxines or 70 $^{o}$C for boronic esters under an $N_2$ atmosphere for 12 h and then cooled to rt.

**Addition of Arylzinc Reagents to 3,4-Dihydroisoquinoline *N*-Oxide.** The nitrone (1.0 equiv, 29.4 mg, 0.20 mmol) and ligand **2a** (1.3 equiv, 74.5 mg, 0.26 mmol) were placed into an oven-dried vial, and the vial was flushed with $N_2$. Dry dichloromethane (1.0 mL) was added and the solution was cooled to -30 $^{o}$C. $Et_2Zn$ (1.3 equiv, 27 μL, 0.26 mmol) in dry toluene (1.0 mL) was slowly added, resulting in a clear yellow solution. The arylzinc reagent mixture prepared above was then transferred into the solution over 15 min at –30 °C with the help of a syringe pump. The reaction was slowly warmed to –20 °C and kept at this temperature for 24-36 h. Finally the reaction was quenched with MeOH and warmed to rt. The resulting suspension was filtered and the filtrate was concentrated *in vacuo*. Gradient flash column chromatography (0.25% to 0.4% methanol in dichloromethane) gave the purified product.

**Compound 3a.** Compound **3a** (41.5 mg, 0.184 mmol, 92% yield) was prepared as a white solid from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (57.1 mg, 0.28 mmol) according to the general procedure. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H), 7.12-7.06 (m, 2H), 7.00-6.96 (m, 1H), 6.61 (d, $J$ = 7.8 Hz, 1H), 6.53 (s, 1H), 4.77 (s, 1H), 3.27-3.32 (m, 1H), 3.18-3.10 (m, 1H), 3.03-2.96 (m, 1H), 2.89-2.84 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.4, 137.1, 133.6, 130.2, 128.7, 128.3, 127.9, 127.6, 126.5, 126.0, 73.8, 54.1, 28.7; HRMS-FAB ($M + Na^+$) calcd for $C_{15}H_{15}NONa$ 248.1051, found 248.1056; 98% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0

mL/min and detected at 219 nm), $t_R$ = 10.2 min for (*S*) and $t_R$ = 18.0 min for (*R*); $[\alpha]^{24}_D$ = +79.6 $^o$ (c = 0.421, $CH_2Cl_2$).

**Compound 3b.** Compound **3b** (37.9 mg, 0.158 mmol, 79% yield) was prepared as a colorless oil from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (61.1 mg, 0.28 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.19-7.11 (m, 6H), 7.05-7.01 (m, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.40 (s, 1H), 4.79 (s, 1H), 3.37-3.33 (m, 1H), 3.24-3.16 (m, 1H), 3.08-3.02 (m, 1H), 2.96-2.90 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.3, 137.3, 133.6, 130.0, 129.0, 128.7, 127.9, 126.5, 126.0, 73.5, 54.1, 28.7, 21.2; HRMS-FAB (M + $H^+$) calcd for $C_{16}H_{18}NO$ 240.1388, found 240.1396; 98% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R$ = 15.6 min for (*S*) and $t_R$ = 21.4 min for (*R*); $[\alpha]^{24}_D$ = +80.2 $^o$ (c = 0.363, $CH_2Cl_2$).

**Compound 3c.** Compound **3c** (40.7 mg, 0.17 mmol, 85%) was prepared as a white foam from the nitrone (29.4 mg, 0.20 mmol) and the corresponding arylboroxine (33.0 mg, 0.093 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.21-7.14 (m, 4H), 7.12-7.11 (m, 2H), 7.02-6.98 (m, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 5.54 (s, 1H), 5.07 (s, 1H), 3.47-3.43 (m, 1H), 3.30-3.21 (m, 1H), 3.12-3.06 (m, 1H), 2.95-2.90 (m, 1H), 2.33 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.8, 137.5, 133.5, 130.6, 127.8, 127.4, 126.4, 126.1, 126.0, 71.3, 55.0, 29.1, 19.8; HRMS-FAB (M + $Na^+$) calcd for $C_{16}H_{17}NONa$ 262.1208, found 262.1210; 97% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol

(99:1) at 1.0 mL/min and detected at 219 nm), $t_R$ = 16.1 min for (*S*) and $t_R$ = 20.4 min for (*R*); $[\alpha]^{25}_D$ = +81.8° (c = 0.565, $CHCl_3$).

**Compound 3d.** Compound **3d** (47.4 mg, 0.195 mmol, 97%) was prepared as a white powder from the nitrone (29.4 mg, 0.20 mmol) and the corresponding arylboroxine (34.1 mg, 0.093 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (m, 2H), 7.16-7.11 (m, 2H), 7.04-6.99 (m, 3H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 4.78 (s, 1H), 3.31-3.26 (m, 1H), 3.21-3.13 (m, 1H), 3.07-3.00 (m, 1H), 2.93-2.87 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.5, 161.1, 138.2, 136.9, 133.6, 131.7, 131.6, 128.6, 128.0, 126.7, 126.0, 115.2, 115.0, 73.0, 54.3, 28.8; HRMS-FAB ($M + Na^+$) calcd for $C_{15}H_{14}FNONa$ 266.0957, found 266.0966; 93% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 9.2 min for (*S*) and $t_R$ = 13.8 min for (*R*); $[\alpha]^{25}_D$ = +60.8° (c = 0.625, $CHCl_3$).

**Compound 3e.** Compound **3e** (49.1 mg, 0.189 mmol, 95% yield) was prepared as a white crystalline solid from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (66.8 mg, 0.28 mmol) according to the general procedure. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 6H), 7.03 (m, 1H), 6.60 (d, *J* = 6.0 Hz, 1H), 6.36 (s, 1 H), 4.77 (s, 1H), 3.30 (m, 1H), 3.19 (m, 1H), 3.04 (dt, *J* = 9.0, 3.0 Hz, 1H), 2.90 (dt, *J* = 15.0, 3.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 141.1, 136.6, 133.5, 133.4, 131.5, 128.5, 128.4, 128.0, 126.8, 126.1, 73.1, 54.4, 28.8; HRMS-FAB ($M + H^+$) calcd for $C_{15}H_{15}ClNO$ 260.0842, found 260.0846; 97% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and

detected at 219 nm), $t_R$ = 9.3 min for (*R*) and $t_R$ = 14.7 min for (*S*); $[\alpha]^{24}_D$ = +81.2 $^o$ (c = 0.468, $CH_2Cl_2$).

**Compound 3f.** Compound **3f** (56.5 mg, 0.186 mmol, 93%) was prepared as a white powder from the nitrone (29.4 mg, 0.20 mmol) and the corresponding arylboroxine (51.2 mg, 0.093 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.15-7.10 (m, 4 H), 7.04-7.00 (m, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.52 (br s, 1H), 4.75 (s, 1H), 3.29-3.25 (m, 1H), 3.21-3.12 (m, 1H), 3.05-2.99 (m, 1H), 2.92-2.86 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.6, 136.5, 133.5, 131.9, 131.4, 128.5, 128.0, 126.8, 126.1, 121.6, 73.1, 54.5, 28.8; HRMS-FAB ($M + Na^+$) calcd for $C_{15}H_{14}BrNONa$ 326.0156, found 326.0160; 91% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R$ = 16.4 min for (*S*) and $t_R$ = 27.7 min for (*R*); $[\alpha]^{26}_D$ = +70.9 $^o$ (c = 0.501, $CH_2Cl_2$).

**Compound 3g.** Compound **3g** (50.5 mg, 0.166 mmol, 83%) was prepared as a colorless oil from the nitrone (29.4 mg, 0.20 mmol) and the corresponding arylboroxine (51.2 mg, 0.093 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.28-7.23 (m, 2H), 7.16-7.12 (m, 3H), 7.04-7.01 (m, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 5.46 (s, 1H), 3.50 (m, 1H), 3.28-3.19 (m, 2H), 2.96-2.92 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.1, 136.5, 133.4, 132.7, 131.4, 129.0, 128.1, 128.0, 127.8, 126.7, 126.2, 126.0, 72.2, 54.9, 28.9; HRMS-FAB ($M + H^+$) calcd for $C_{15}H_{15}BrNO$ 304.0377, found 304.0345; 84% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99.5:0.5) at 1.0 mL/min and

detected at 219 nm), $t_R$ = 30.5 min for (*S*) and $t_R$ = 36.9 min for (*R*); $[\alpha]^{26}{}_D$ = +135.3 $^o$ (c = 0.272, $CH_2Cl_2$).

**Compound 3h.** Compound **3h** (54.5 mg, 0.198 mmol, 99% yield) was prepared as a white foam from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (71.2 mg, 0.28 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.85-7.77 (m, 4H), 7.52-7.46 (m, 2H), 7.35-7.32 (m, 1H), 7.15 (d, *J* = 4.0 Hz, 2H), 7.02-6.97 (m, 1H), 6.64 (d, *J* = 7.8 Hz, 2H), 6.11 (s, 1H), 4.96 (s, 1H), 3.43-3.38 (m, 1H), 3.30-3.22 (m, 1H), 3.14-3.07 (m, 1H), 2.94-2.89 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.0, 133.6, 133.1, 133.0, 129.5, 128.7, 128.2, 127.9, 127.7, 127.3, 126.6, 126.1, 126.01, 125.99, 74.2, 54.4, 29.0; HRMS-FAB (M + $Na^+$) calcd for $C_{19}H_{17}NONa$ 298.1208, found 298.1216; 97% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 15.4 min for (*S*) and $t_R$ = 29.9 min for (*R*); $[\alpha]^{24}{}_D$ = +155.9 $^o$ (c = 0.272, $CH_2Cl_2$).

**Compound 4a.** Compound **4a** (42.8 mg, 0.129 mmol, 65% yield) was prepared as a white solid from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (86.9 mg, 0.28 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46-7.31(m, 5H), 7.24-7.22 (m, 2H), 7.16-7.11 (m, 2H), 7.05-7.01 (m, 1H), 6.97-6.95 (m, 2H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.58 (s, 1H), 5.07 (s, 3H), 4.78 (s, 1H), 3.47-3.44 (m, 1H), 3.30-3.21 (m, 1H), 3.13-3.06 (m, 1H), 2.95-2.91 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 158.3, 137.4, 137.0, 134.8, 133.6, 131.1, 128.7, 128.6, 128.0, 127.9, 127.5, 126.5, 125.9, 114.6, 73.4, 70.0, 54.2, 28.8; HRMS-FAB (M + $Na^+$) calcd for $C_{22}H_{21}NO_2Na$ 354.1470, found 354.1476; 99% ee

by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 25.9 min for (*S*) and $t_R$ = 37.6 min for (*R*); $[\alpha]^{24}_D$ = +65.4 $^o$ (c = 0.315, $CH_2Cl_2$).

**Compound 4b.** Compound **4b** (49.6 mg, 0.180 mmol, 90% yield) was prepared as a colorless oil from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (73.4 mg, 0.28 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01-7.98 (m, 2H), 7.49-7.39 (m, 2H), 7.16-7.11 (m, 2H), 7.03-6.99 (m, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 4.87 (s, 1H), 3.90 (s, 3H), 3.38-3.35 (m, 1H), 3.29-3.21 (m, 1H), 3.12-3.05 (m, 1H), 2.94-2.88 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.2, 136.6, 134.6, 133.5, 131.2, 130.3, 129.0, 128.5, 128.4, 128.0, 126.8, 126.1, 73.8, 54.8, 52.1, 29.0; HRMS-FAB (M + $Na^+$) calcd for $C_{17}H_{17}NO_3Na$ 306.1106, found 306.1102; 98% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 11.4 min for (*S*) and $t_R$ = 15.5 min for (*R*); $[\alpha]^{23}_D$ = +65.2 $^o$ (c = 0.310, $CH_2Cl_2$).

**Compound 4c.** Compound **4c** (41.2 mg, 0.191 mmol, 96% yield) was prepared as a white solid from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (54.3 mg, 0.28 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41-7.40 (m, 2H), 7.19-7.08 (m, 3H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.27 (s, 1H), 4.88 (s, 1H), 3.42-3.39 (m, 1H), 3.17-3.08 (m, 2H), 3.00-2.96 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.2, 142.6, 135.5, 133.4, 128.2, 128.1, 126.8, 126.0, 110.4, 64.8, 53.4, 27.9; HRMS-FAB (M + $Na^+$) calcd for $C_{13}H_{13}NO_2Na$ 238.0844, found 238.0850; 99% ee by HPLC analysis (Chiralcel OD-H column

eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 13.1 min for (*S*) and $t_R$ = 23.3 min for (*R*); $[\alpha]^{23}_D$ = -0.6 $^o$ (c = 0.319, $CH_2Cl_2$).

**Compound 4d.** Compound **4d** (46.9 mg, 0.191 mmol, 96% yield) was prepared as a white foam from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (62.8 mg, 0.28 mmol) according to the general procedure. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.18-7.07 (m, 4H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.74 (s, 1H), 6.60-6.59 (m, 1H), 5.09 (s, 1H), 3.43-3.41 (m, 1H), 3.12-2.95 (m, 3H), 2.43 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.1, 140.3, 136.0, 133.2, 128.6, 128.1, 126.9, 125.9, 124.3, 68.4, 52.7, 27.7, 15.4; HRMS-FAB (M + $Na^+$) calcd for $C_{14}H_{15}NOSNa$ 268.0772, found 268.0778; 97% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 10.9 min for (*S*) and $t_R$ = 16.0 min for (*R*); $[\alpha]^{25}_D$ = -0.8 $^o$ (c = 0.383, $CHCl_3$).

**Compound 4e.** Compound **4e** (50.8 mg, 0.139 mmol, 70% yield) was prepared as a white solid from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (96.1 mg, 0.28 mmol) according to the general procedure. A side product corresponding to addition of an ethyl group to the nitrone starting material (9.3 mg, 0.052 mmol, 26% yield) was also isolated as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.50 (s, 1H), 7.25-7.22 (m, 1H), 7.12 (d, *J* = 4.0 Hz, 2H), 7.01-6.97 (m, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 3.7 Hz, 1H), 5.90 (s, 1H), 4.89 (s, 1H), 3.48-3.43 (m, 1H), 3.31-3.23 (m, 1H), 3.14-3.07 (m, 1H), 2.97-2.92 (m, 1H), 1.66 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.8, 137.7, 136.8, 134.7, 133.5, 130.6, 128.8, 127.9, 126.5, 126.3, 126.1, 125.9, 122.5, 115.1, 107.4, 83.7, 74.1, 54.3, 29.0, 28.2; HRMS-FAB (M + $Na^+$) calcd for

$C_{22}H_{24}N_2O_3Na$ 387.1685, found 387.1696; 99% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 10.4 min for (*S*) and $t_R$ = 15.7 min for (*R*); $[\alpha]^{24}{}_D$ = +88.6 $^o$ (c = 0.405, $CH_2Cl_2$).

**Compound 4f.** Compound **4f** (23.6 mg, 0.069 mmol, 35% yield) was prepared as a white solid from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (89.7 mg, 0.28 mmol) according to the general procedure. A side product corresponding to addition of an ethyl group to the nitrone starting material (13.2 mg, 0.074 mmol, 37% yield) was also isolated as a yellow crystalline solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.14-7.10 (m, 4H), 7.03-6.99 (m, 1H), 6.82 (br s, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.80 (s, 1H), 3.20-3.09 (m, 2H), 3.02-2.96 (m, 1H), 2.88-2.84 (m, 1H), 1.56 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.9, 150.5, 139.9, 136.8, 133.6, 131.2, 128.7, 127.9, 126.6, 126.0, 121.0, 83.5, 73.1, 54.2, 28.7, 27.7; HRMS-FAB (M + $Na^+$) calcd for $C_{20}H_{23}NO_4Na$ 364.1525, found 364.1530; 97% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 9.0 min for (*S*) and $t_R$ = 11.2 min for (*R*); $[\alpha]^{24}{}_D$ = +55.7 $^o$ (c = 0.278, $CH_2Cl_2$).

**Compound 4g.** Compound **4g** (30 mg, 0.105 mmol, 53% yield) was prepared as a white solid from the nitrone (29.4 mg, 0.20 mmol) and the corresponding pinacolyl boronic ester (74 mg, 0.28 mmol) according to the general procedure. A side product corresponding to addition of an ethyl group to the nitrone starting material (11.3 mg, 0.063 mmol, 32% yield) was also isolated as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.15-7.11 (m, 2H), 7.05-7.01 (m, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 2.3 Hz, 2H), 6.40 (t, *J* = 2.3 Hz, 1H), 6.29 (s, 1H), 4.74 (s,

1H), 3.75 (s, 6H), 3.47-3.42 (m, 1H), 3.12-3.06 (m, 1H), 3.12-3.06 (m, 1H), 2.95-2.91 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ160.7, 144.7, 136.7, 133.3, 128.5, 127.9, 126.6, 126.0, 107.8, 99.7, 74.2, 55.3, 54.3, 28.7; HRMS-FAB (M + $H^+$) calcd for $C_{17}H_{20}NO_3$ 286.1443, found 286.1268; 99% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 17.0 min for (*S*) and $t_R$ = 22.5 min for (*R*); $[\alpha]^{24}{}_D$ = +101.0 $^o$ (c = 0.358, $CH_2Cl_2$).

**Synthesis of Solifenacin (YM905)**

**Compound 5.** 1) Zn-dust （510 mg, 7.80 mmol） was added to a solution of $Cu(OAc)_2$ (31 mg, 0.156 mmol) in acetic acid (6 mL), and the mixture was stirred at room temperature for 15 min under an $N_2$ atmosphere. A solution of compound **3a** (98% ee, 351 mg, 1.56 mmol) in acetic acid (18 mL) and water (6 mL) was added to the above mixture. The resulting suspension was heated at 70 ℃ for 2 h and then cooled to rt. EDTA (1.74 g, 4.68 mmol) was added. The solution was basified to pH 10 using 3 M NaOH. The aqueous phase was separated and extracted with three portions of dichloromethane. The combined organic layers were washed with an aqueous saturated EDTA solution and brine, dried over $NaSO_4$, and concentrated *in vacuo*. The crude amine product could be used directly in the next step without further purification. Gradient flash column chromatography of 3 to 5% MeOH in dichloromethane gave (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline as an off-white solid (310 mg, 1.48 mmol, 95% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 7.18-7.17 (m, 2H), 7.09-7.04 (m, 1H), 6.78 (d, *J* = 10.2 Hz, 1H), 5.13 (s, 1H), 3.35-3.26 (m, 1H), 3.17-3.03 (m, 2H),

2.91-2.82 (m, 1H), 2.06 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 144.9, 138.3, 135.4, 129.1, 129.0, 128.4, 128.1, 127.4, 126.3, 125.6, 62.1, 42.3, 29.8; HRMS-FAB ($M + H^+$) calcd for $C_{15}H_{16}N$ 210.1283, found 210.1286; $[\alpha]^{22}_D = +36.1^{o}$ (c = 0.735, $CH_2Cl_2$).

2) In an oven dried flask (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (152 mg, 0.73 mmol) was dissolved in dry THF (10 mL). $Et_3N$ (112 μL, 0.80 mmol) was added and the reaction mixture was cooled to 0 °C. A solution of *p*-nitrophenyl chloroformate (161 mg, 0.80 mmol) in dry THF (10 mL) was added dropwise at a rate that maintained the internal temperature of the reaction at 0 °C. The solution was then slowly warmed to 25 °C, and stirred at this temperature for 16 h. During this time, a precipitate of triethylammonium chloride formed in the solution. The solution was filtered, and the solvent was evaporated *in vacuo* to give the crude product. Flash column chromatography using 10 % EtOAc in hexanes provided a white solid (251 mg, 0.67 mmol, 92% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 8.30-8.27 (m, 2H), 7.34-7.22 (m, 10H), 7.11 (d, *J* = 16.1 Hz, 1H), 6.52 (d, *J* = 9.6 Hz, 1H), 4.27-4.22 (m, 1H), 3.54-3.42 (m, 1H), 3.20-3.10 (m, 1H), 2.96-2.88 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.3, 152.6, 152.4, 144.9, 141.8, 134.6, 134.4, 129.0, 128.9, 128.6, 128.5, 128.2, 127.9, 127.4, 126.5, 125.1, 122.4, 58.8, 58.2, 39.1, 38.8, 28.6, 28.2; HRMS-FAB ($M + Na^+$) calcd for $C_{22}H_{18}N_2O_4Na$ 397.1164, found 397.1150; $[\alpha]^{23}_D = +213.5^{\circ}$ (c = 0.207, $CH_2Cl_2$).

**Compound 1f (Solifenacin).** To a solution of (*R*)-quinuclidin-3-ol (95 mg, 0.75 mmol) and 18-crown-6 (254 mg, 0.96 mmol) in dry toluene (20 mL) was added NaH (39 mg, 0.96 mmol, 60 % dispersion in mineral oil) under Ar. A white suspension formed, and a solution of compound **5** (199 mg, 0.53 mmol) in toluene (20 mL) was added dropwise to the above mixture at ambient

temperature, which resulted in a yellow suspension. The mixture was heated to reflux at 110 ℃ under an Ar atmosphere. After 18 h, the reaction mixture was cooled to rt, poured into brine, and extracted with ethyl acetate. The organic layer was separated, washed three times with 5% aq $Na_2CO_3$ and twice with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. Gradient flash column chromatography using 0.3:2.7:97 to 0.5:4.5:95 10% aqueous $NH_4OH$:MeOH:$CH_2Cl_2$ provided a colorless oil (142.8 mg, 0.39 mmol, 74% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31-7.10 (m, 8H), 7.11 (d, $J$ = 7.6 Hz, 1H), 6.48-6.26 (m, 1H), 4.84-4.82 (m, 1H), 4.11-4.03 (m, 1H), 3.34-3.26 (m, 2H), 3.06-2.98 (m, 1H), 2.89-2.72 (m, 6H), 2.07-2.06 (m, 1H), 1.90-1.82 (m, 1H), 1.76-1.67 (m, 1H), 1.62-1.55 (m, 1H), 1.48-1.41 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.2, 142.7, 135.4, 135.0, 128.9, 128.3, 127.9, 127.4, 127.1, 126.2, 72.1, 58.2, 57.6, 56.0, 47.5, 46.5, 38.5, 28.5, 25.5, 24.6, 19.9; HRMS-FAB (M + $H^+$) calcd for $C_{23}H_{27}N_2O_2$ 363.2073, found 363.2080; $[\alpha]^{23}_D$ = +141.7 $^o$ (c = 0.247, $CH_2Cl_2$).

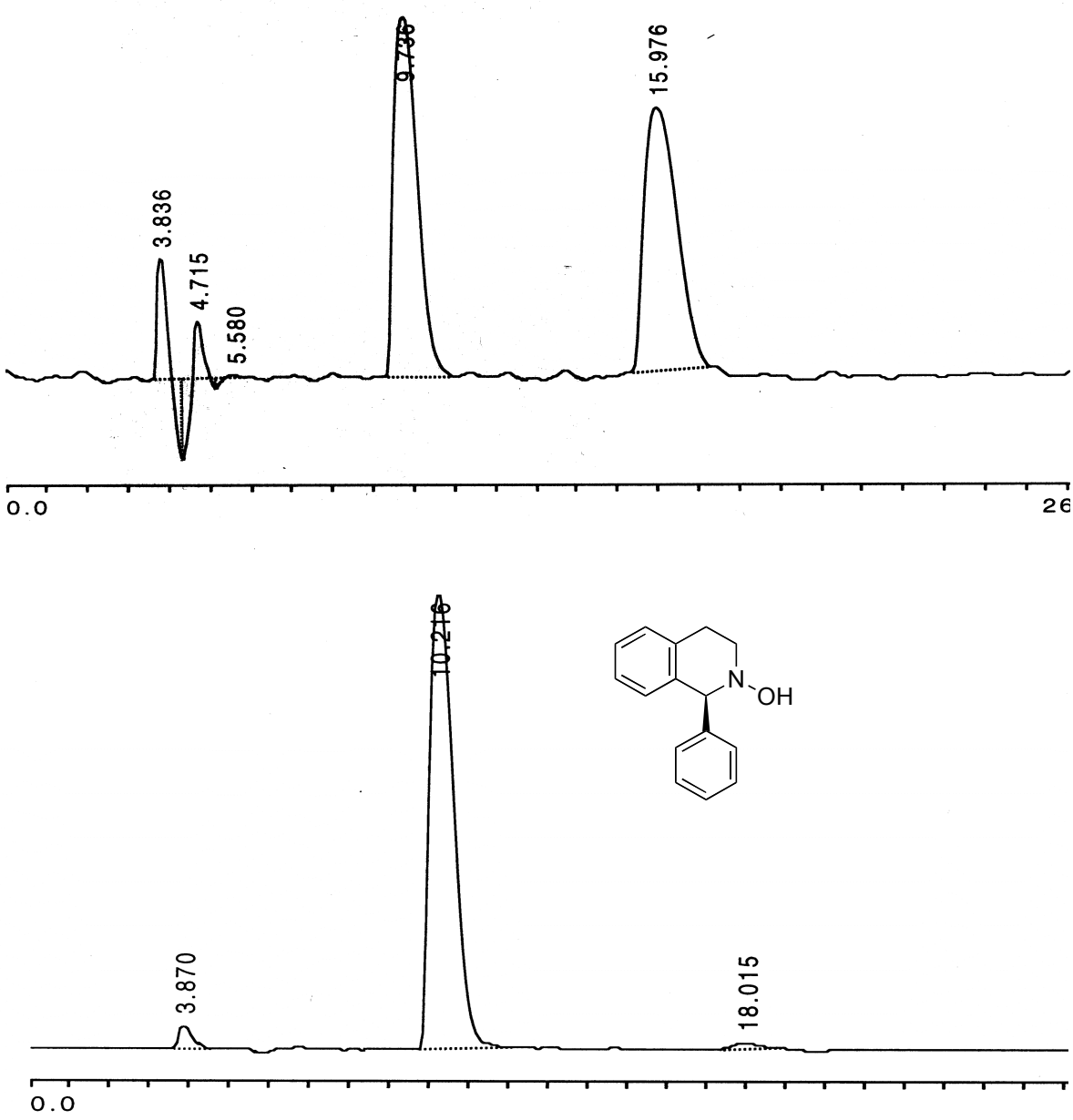


**Figure S1.** HPLC analysis of compound **3a**; 98% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 10.2 min for (*S*) and $t_R$ = 18.0 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

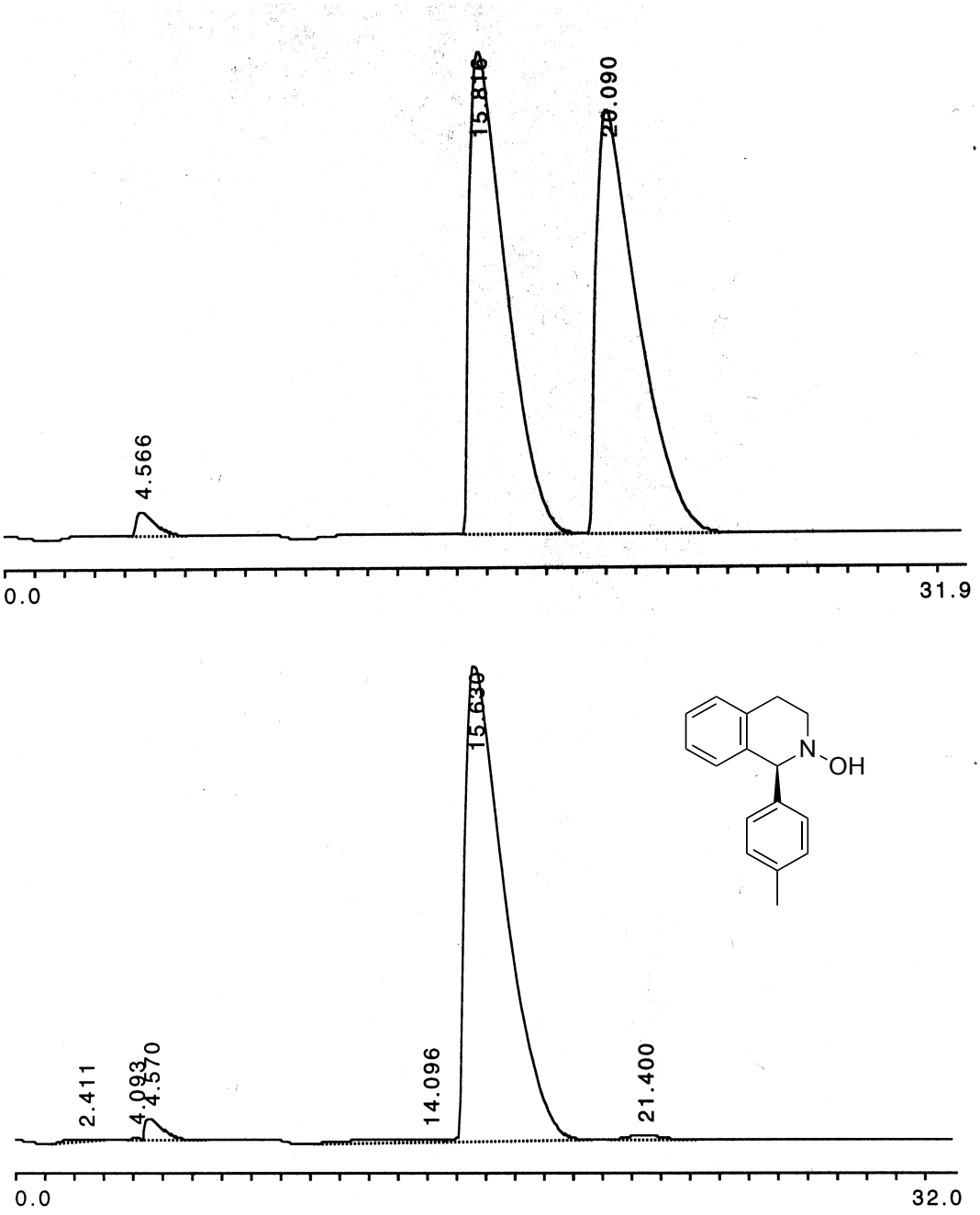


**Figure S2.** HPLC analysis of compound **3b**; 98% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R$ = 15.6 min for (*S*) and $t_R$ = 21.4 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

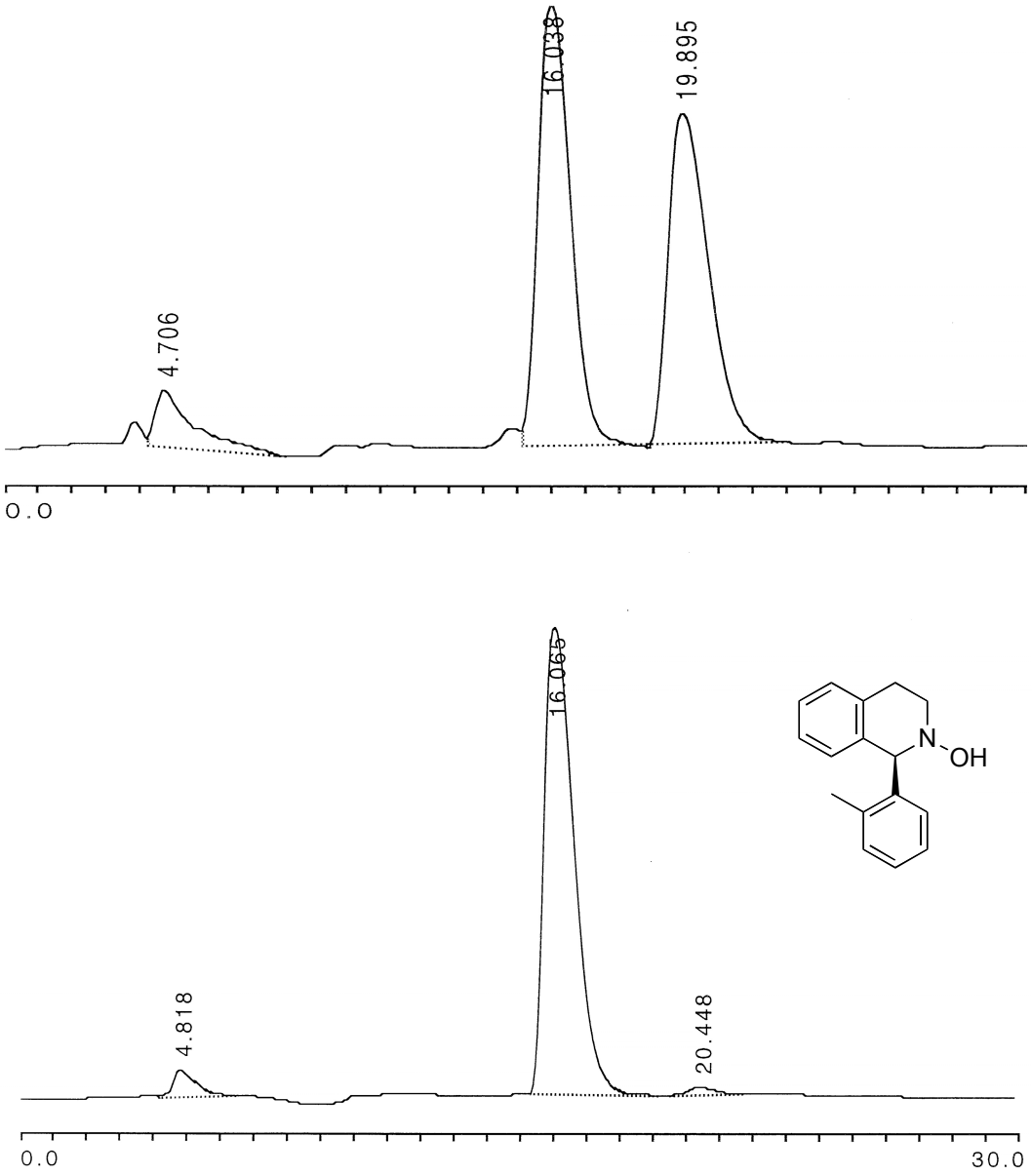


**Figure S3.** HPLC analysis of compound **3c**; 97% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R$ = 16.1 min for (*S*) and $t_R$ = 20.4 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

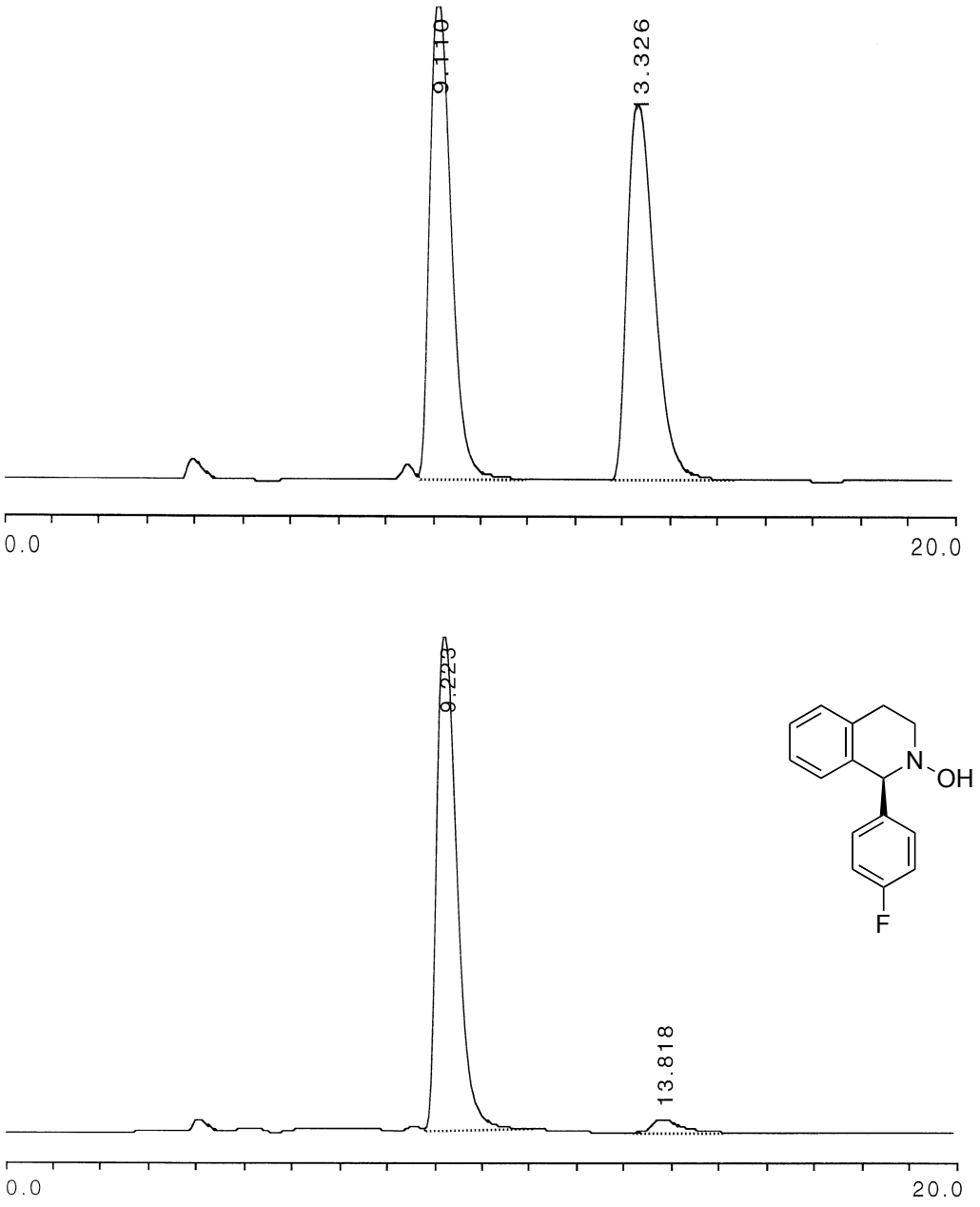


**Figure S4.** HPLC analysis of compound **3d**; 93% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 9.2 min for (*S*) and $t_R$ = 13.8 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

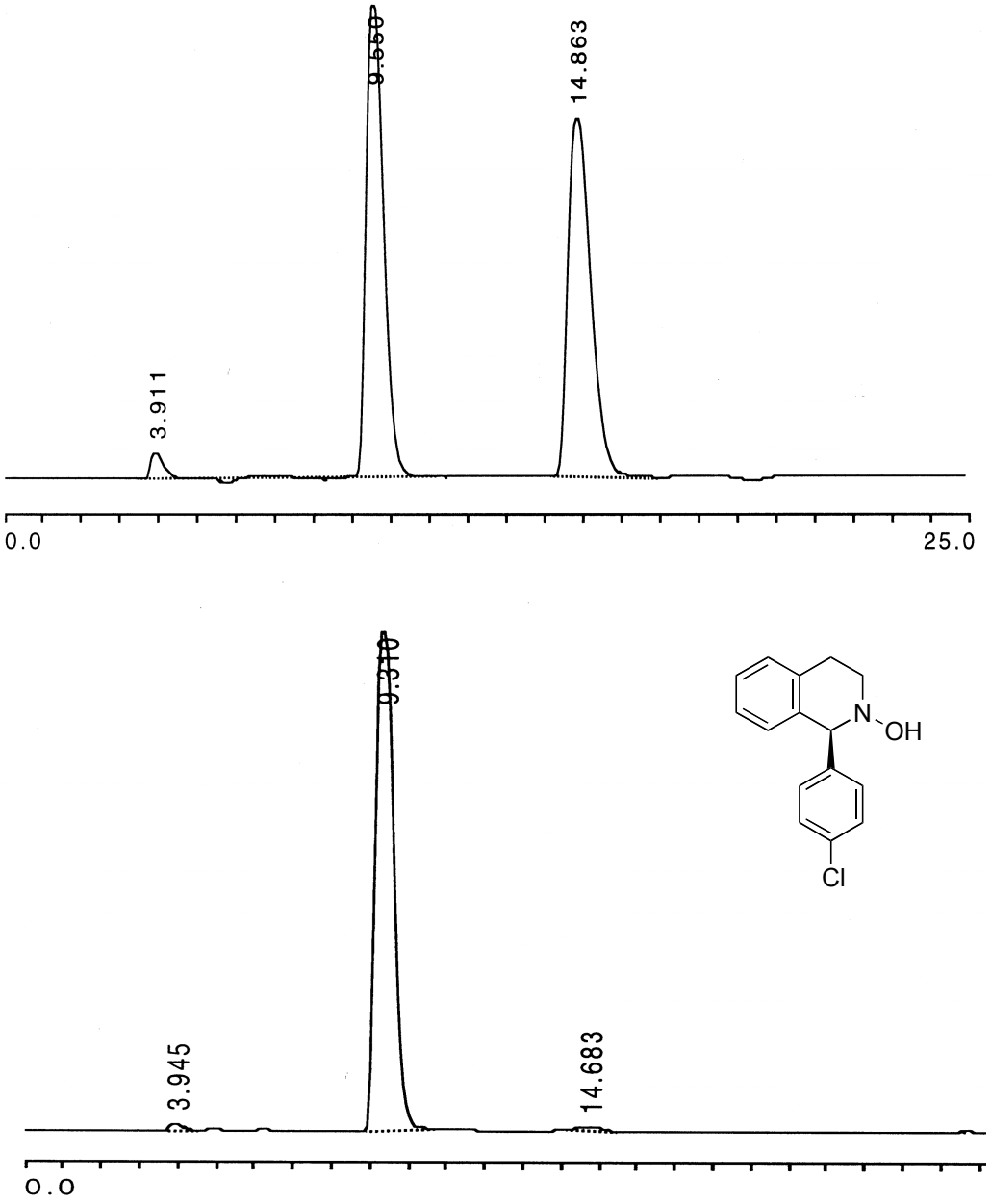


**Figure S5.** HPLC analysis of compound **3e**; 97% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 9.3 min for (*R*) and $t_R$ = 14.7 min for (*S*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

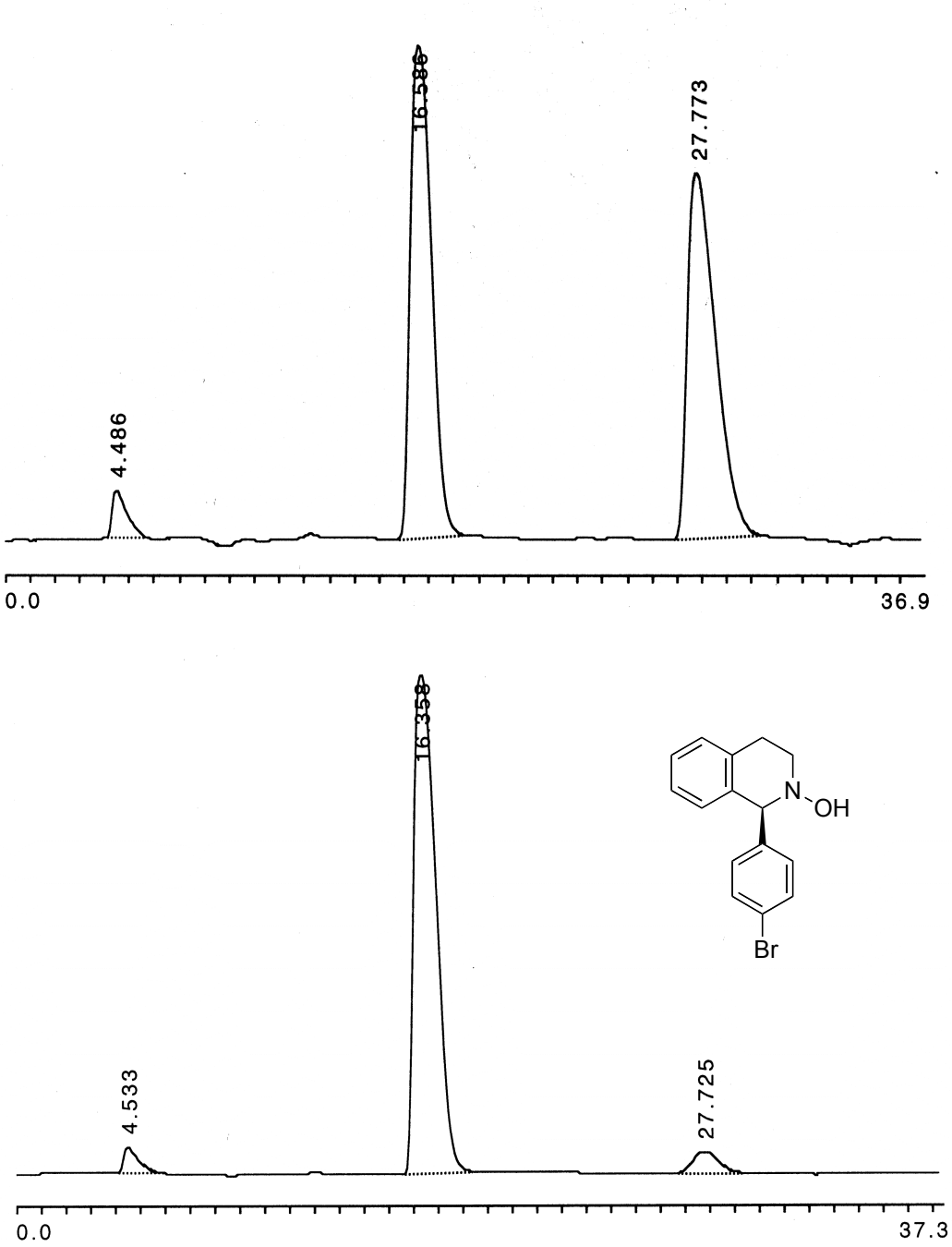


**Figure S6.** HPLC analysis of compound **3f**; 91% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R$ = 16.4 min for (*S*) and $t_R$ = 27.7 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

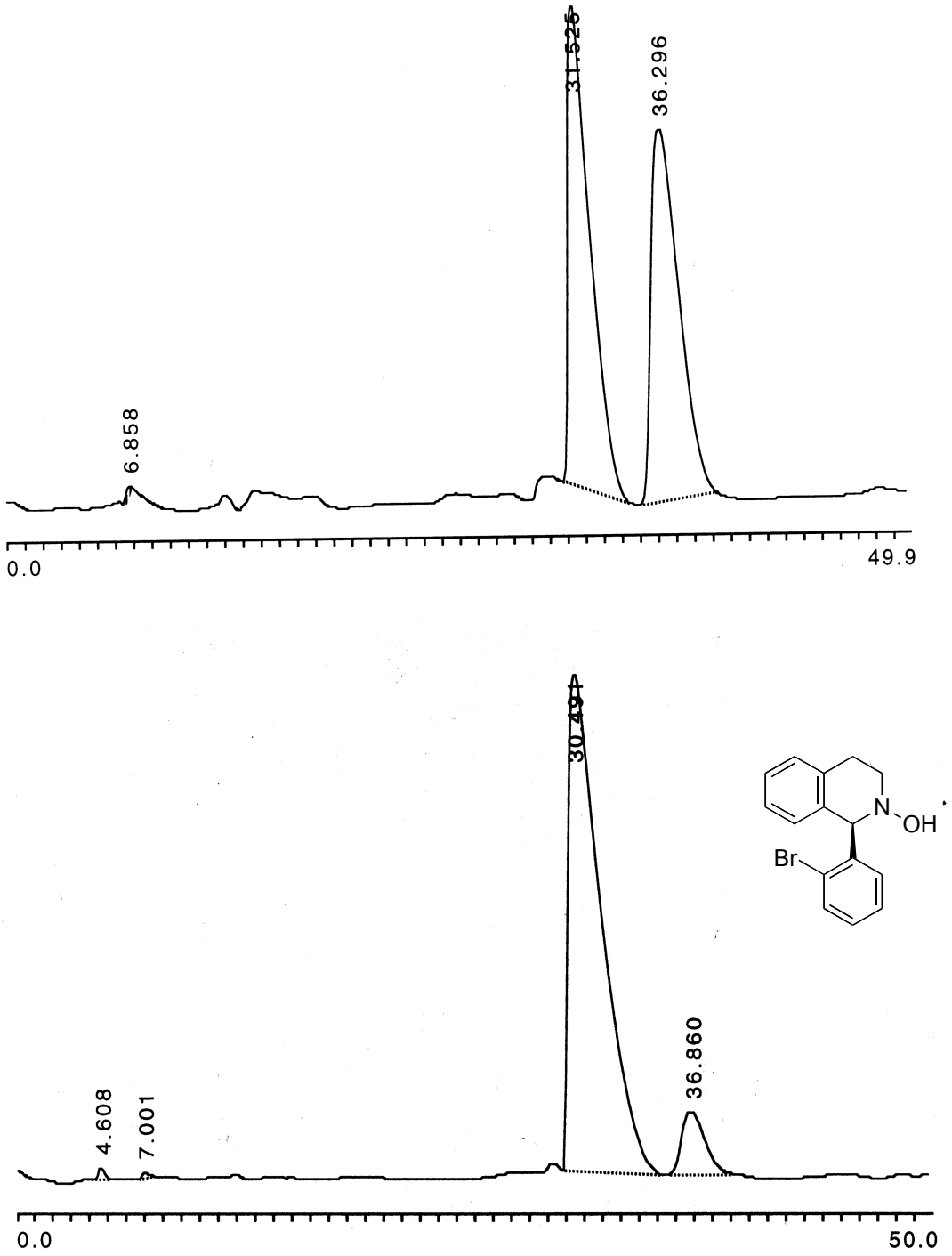


**Figure S7.** HPLC analysis of compound **3g**; 84% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (99.5:0.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 30.5 min for (*S*) and $t_R$ = 36.9 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

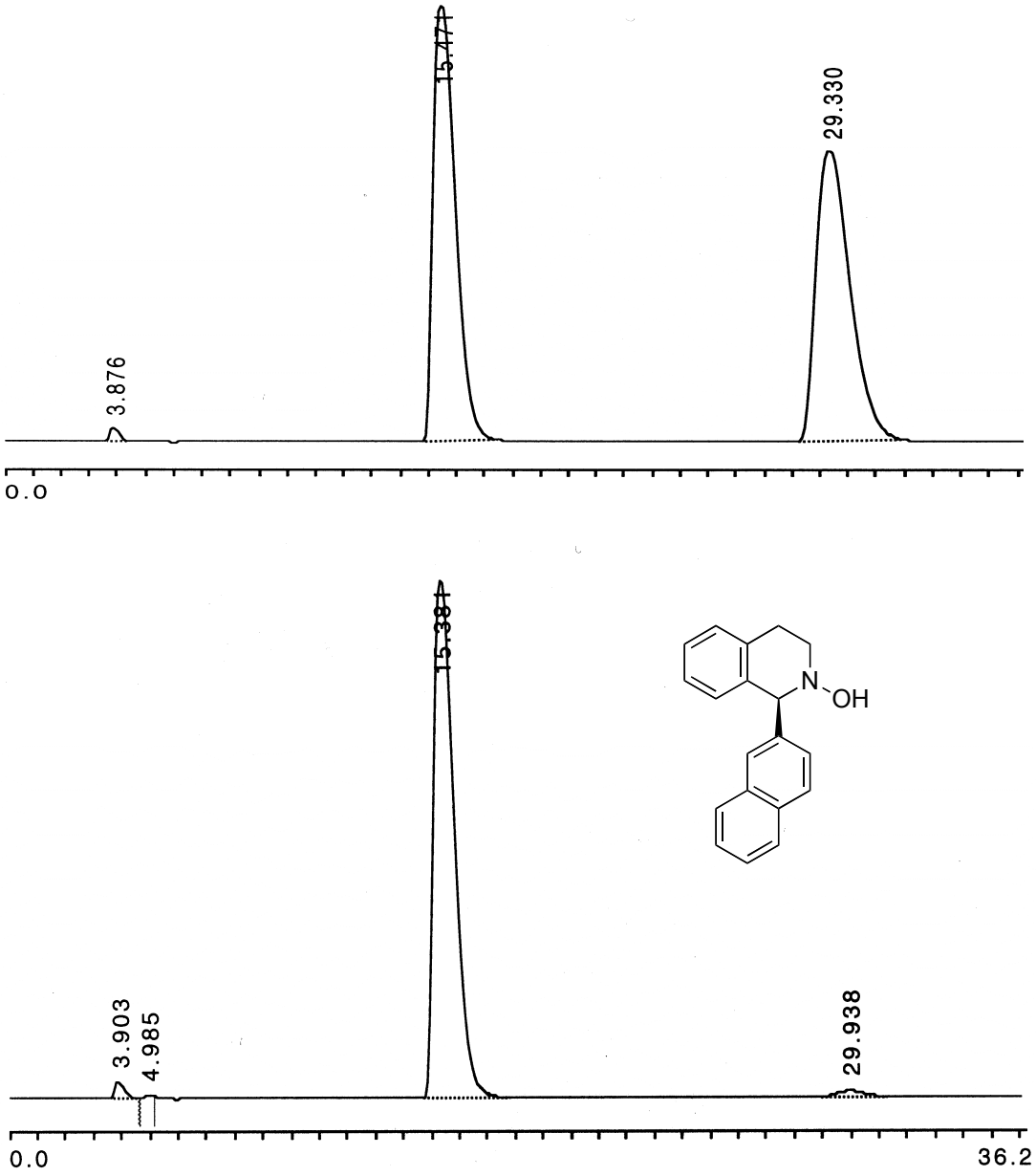


**Figure S8.** HPLC analysis of compound **3h**; 97% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 15.4 min for (*S*) and $t_R$ = 29.9 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

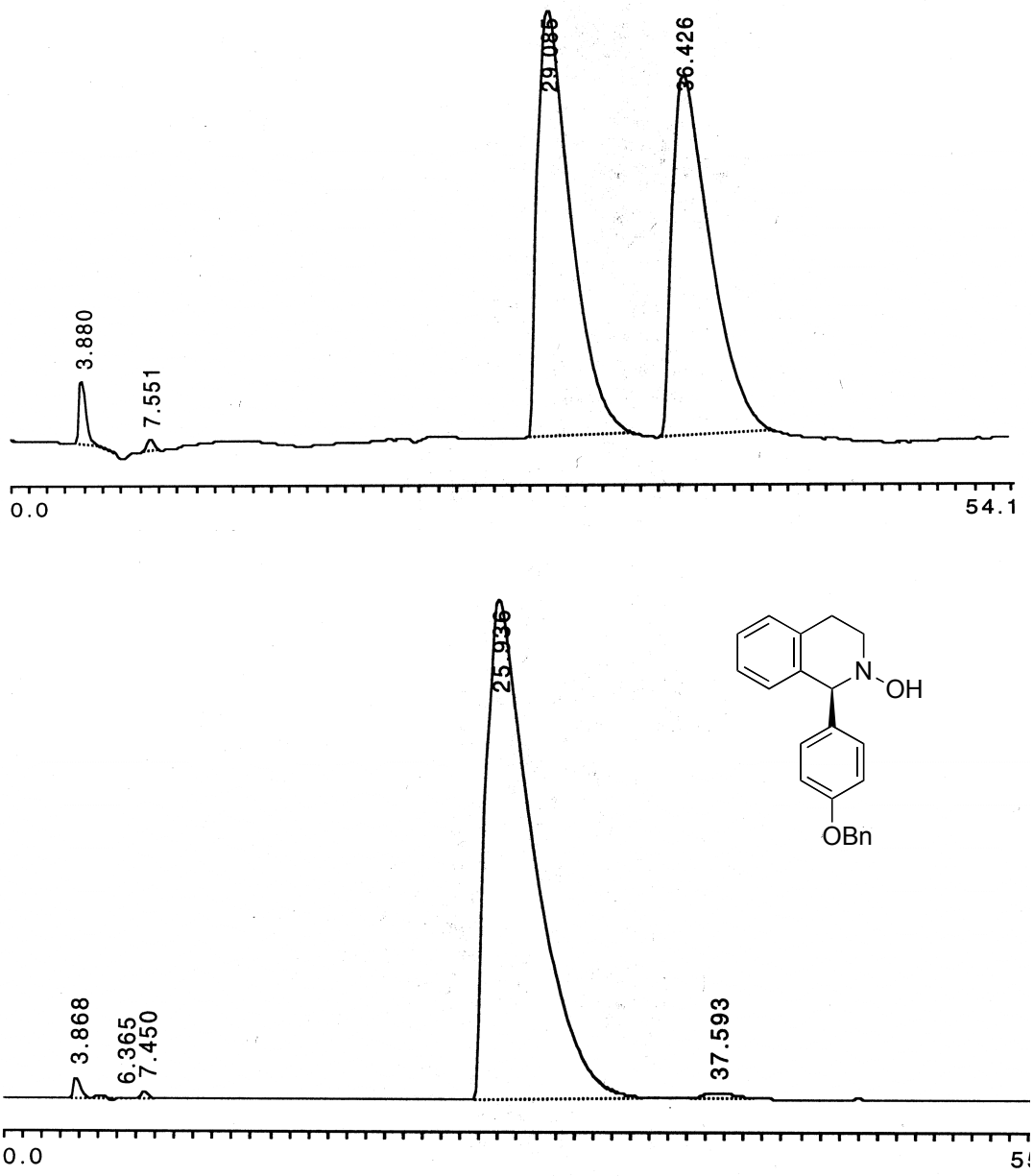


**Figure S9.** HPLC analysis of compound **4a**; 99% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 25.9 min for (*S*) and $t_R$ = 37.6 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

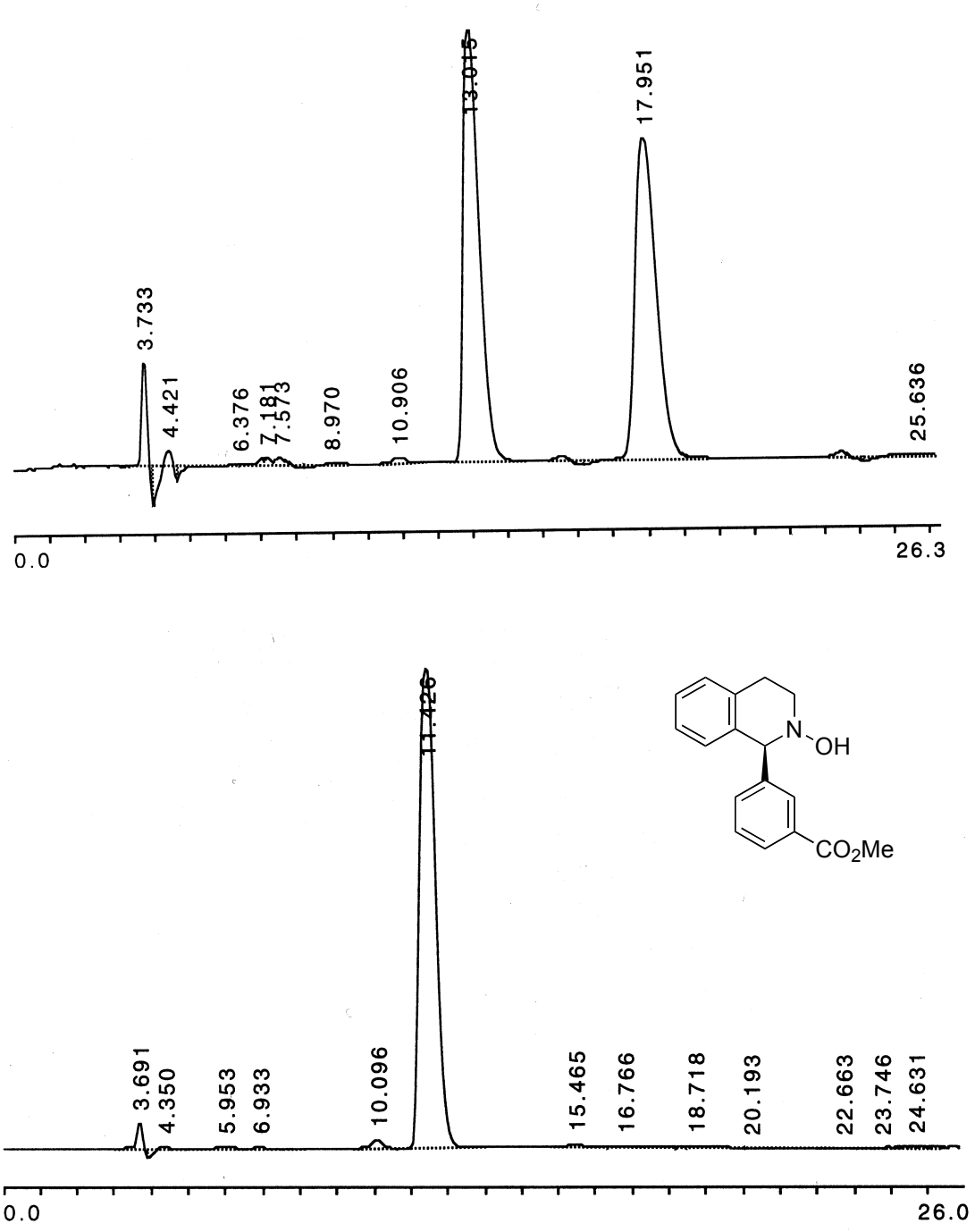


**Figure S10.** HPLC analysis of compound **4b**; 98% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 11.4 min for (*S*) and $t_R$ = 15.5 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

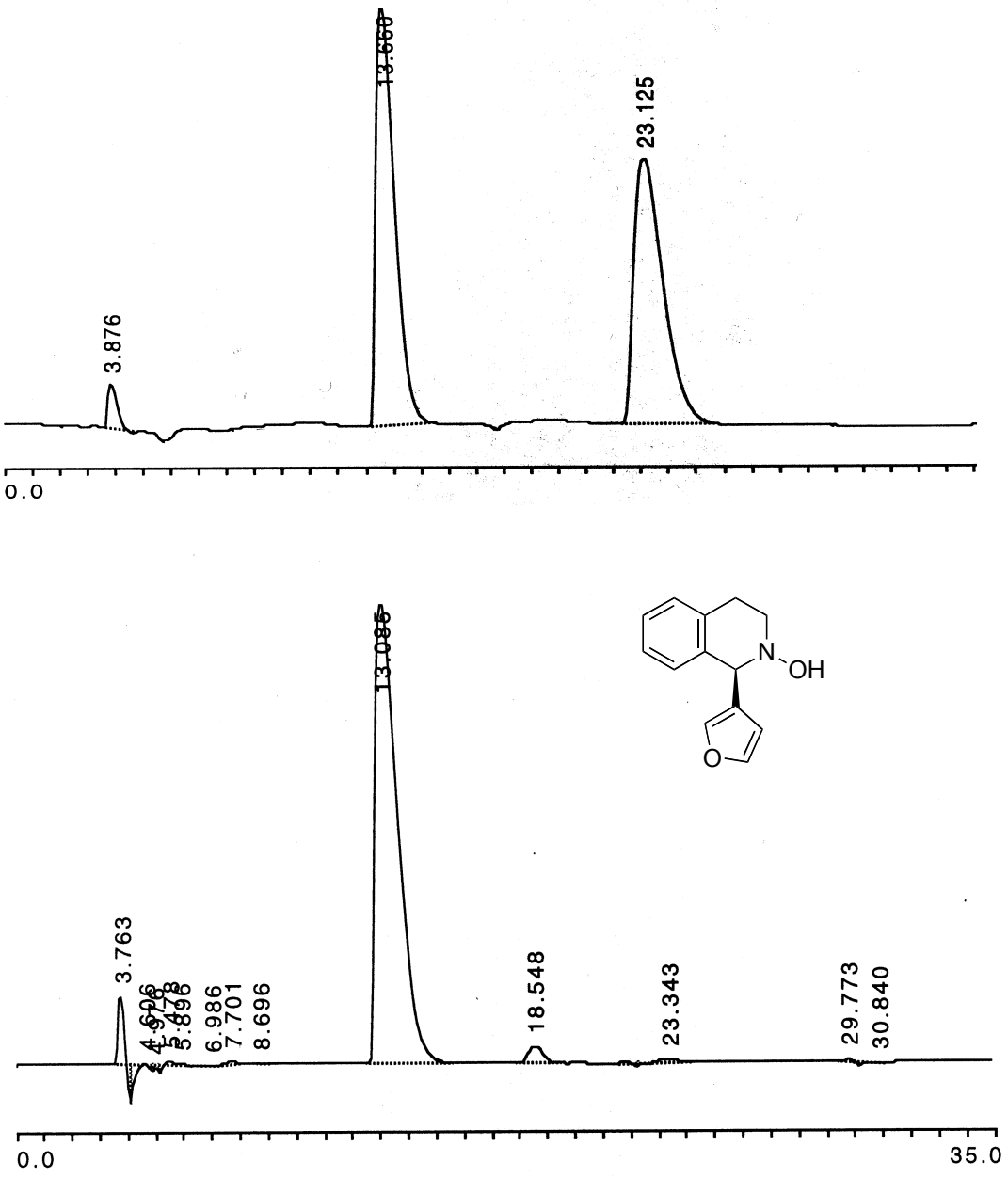


**Figure S11.** HPLC analysis of compound **4c**; 99% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 13.1 min for (*S*) and $t_R$ = 23.3 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

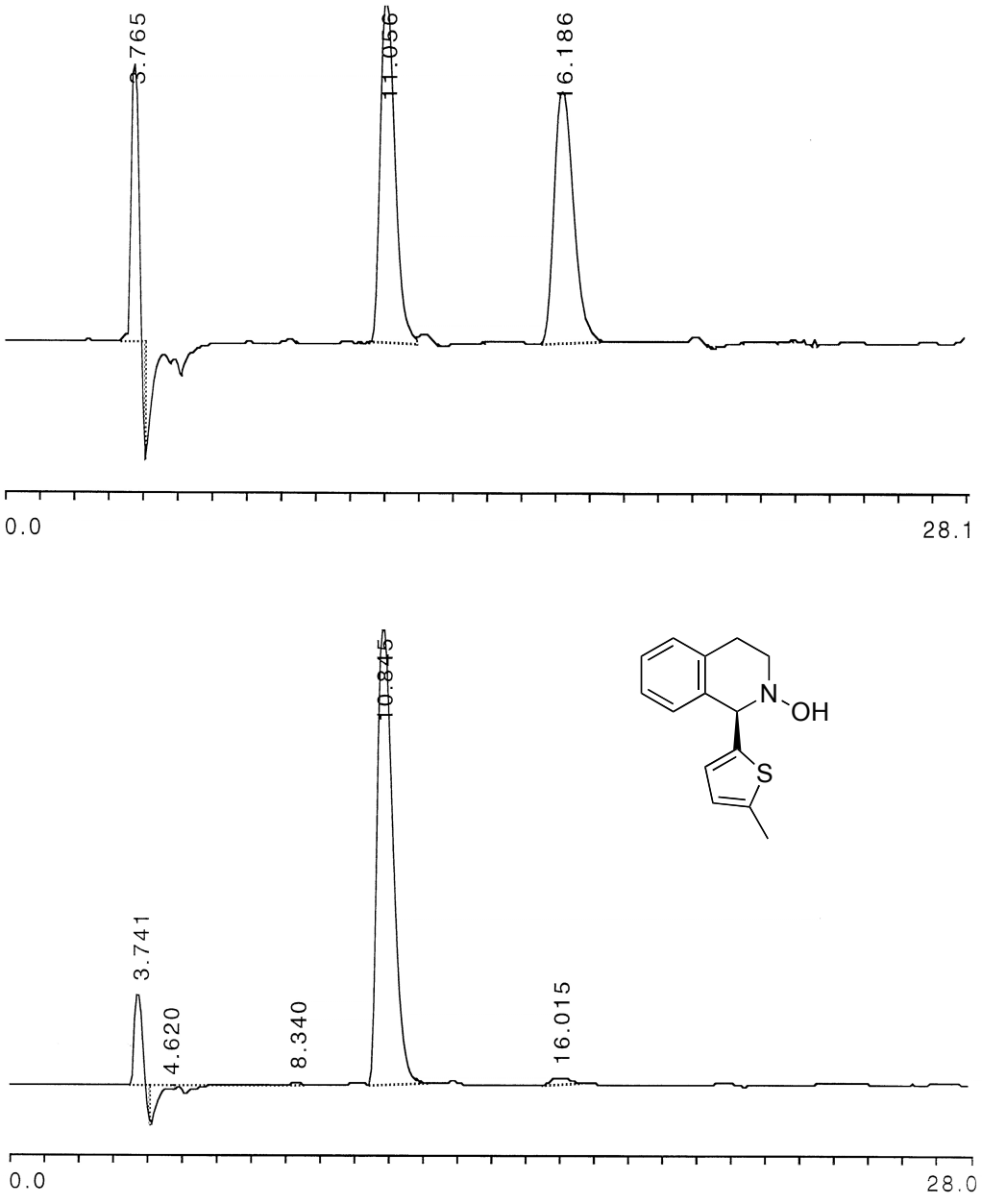


**Figure S12.** HPLC analysis of compound **4d**; 97% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 10.9 min for (*S*) and $t_R$ = 16.0 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

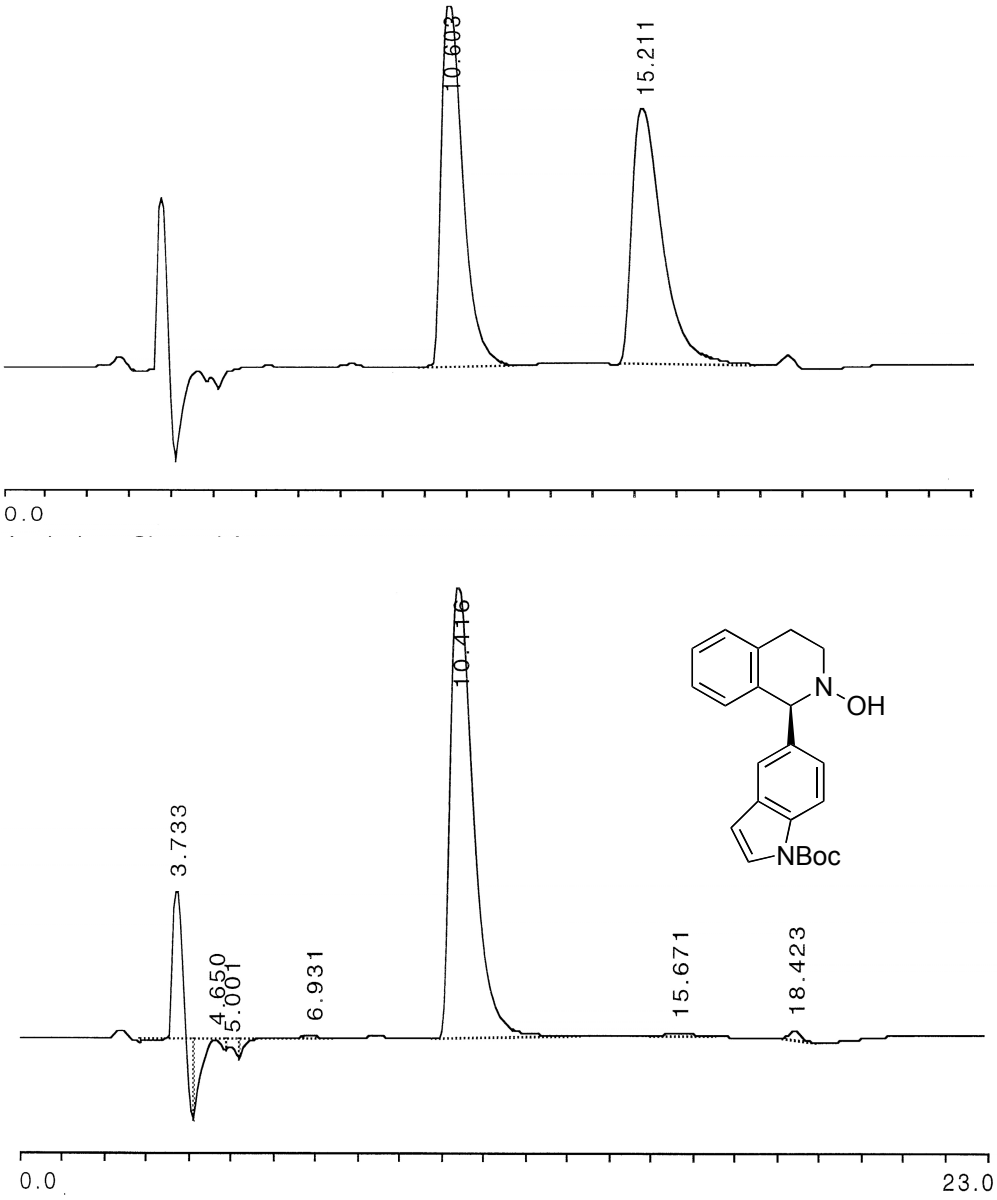


**Figure S13.** HPLC analysis of compound **4e**; 99% (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 10.4 min for (*S*) and $t_R$ = 15.7 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

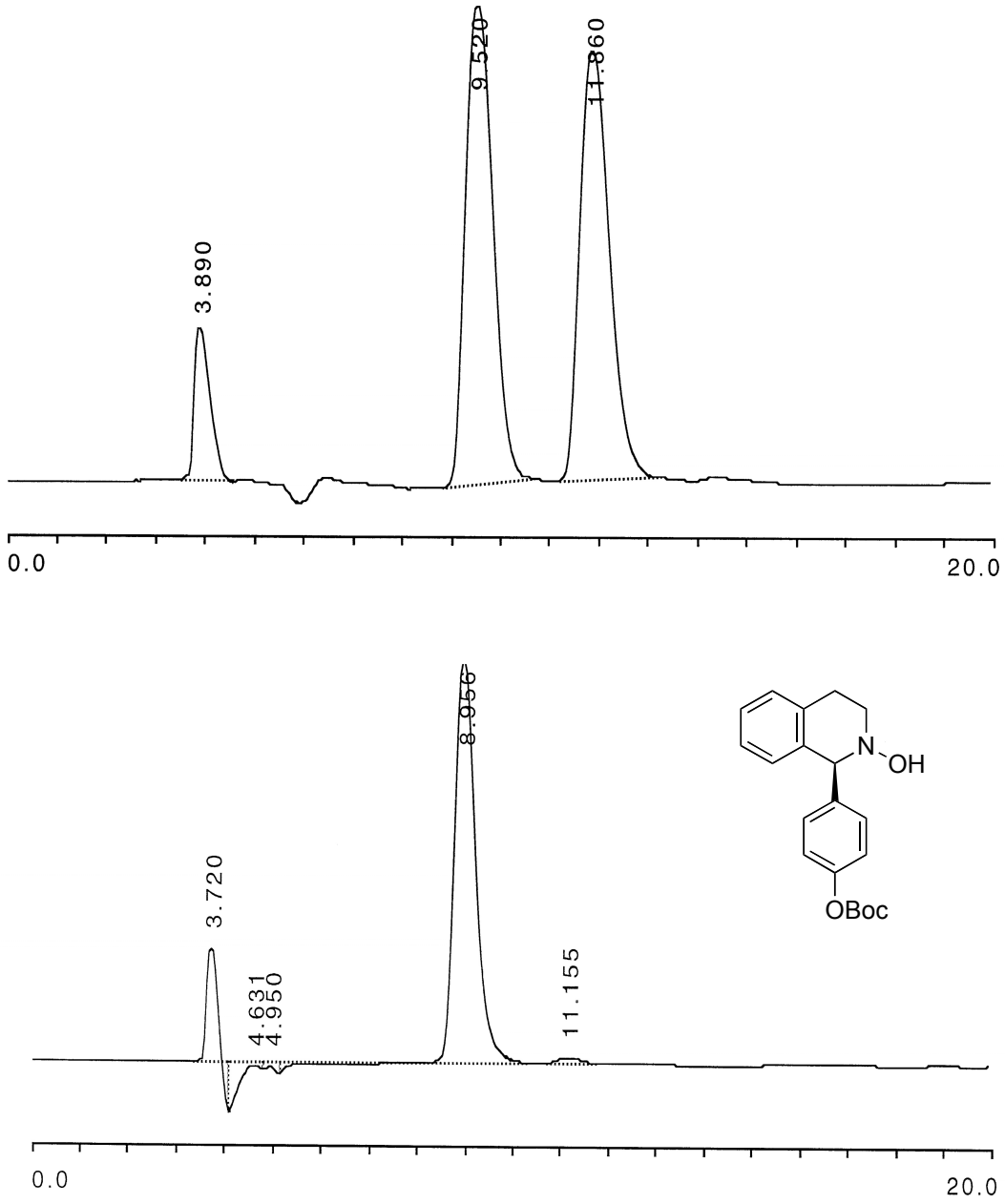


**Figure S14.** HPLC analysis of compound **4f**; 97% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 9.0 min for (*S*) and $t_R$ = 11.2 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

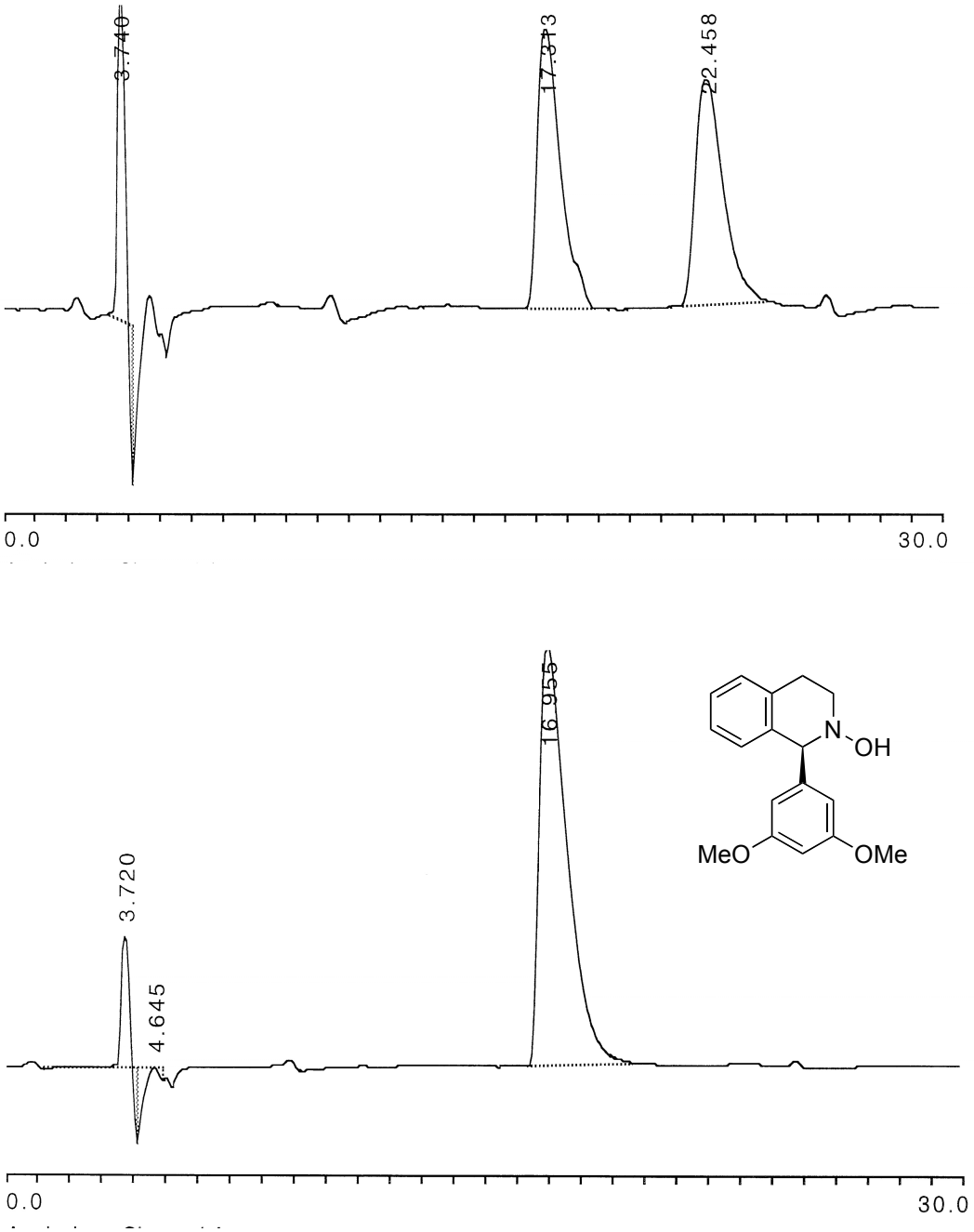


**Figure S15.** HPLC analysis of compound **4g**; 99% ee (Chiralcel OD-H column eluted with hexanes:2-propanol (97.5:2.5) at 1.0 mL/min and detected at 219 nm), $t_R$ = 17.0 min for (*S*) and $t_R$ = 22.2 min for (*R*). Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

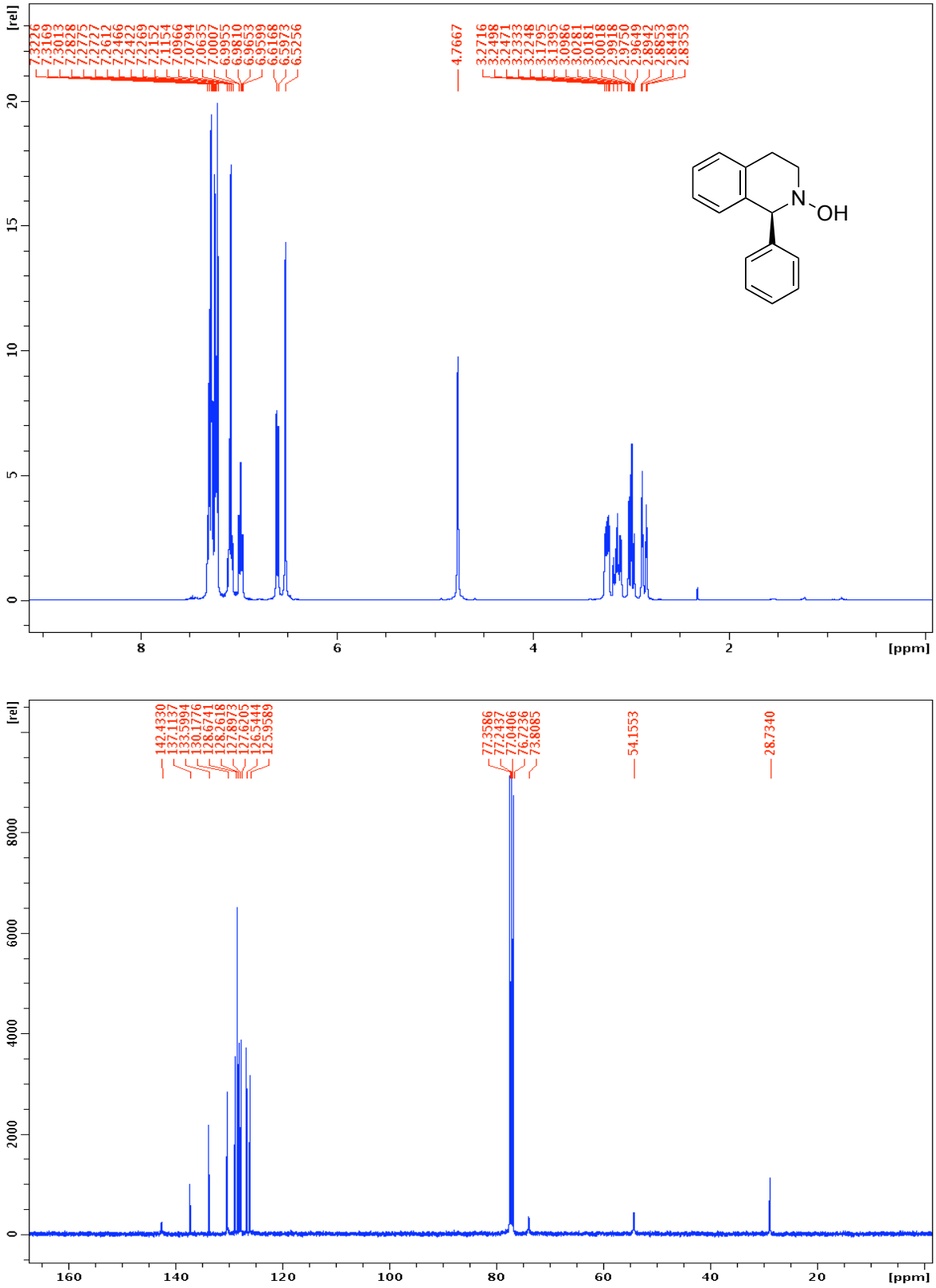


**Figure S16.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3a**.

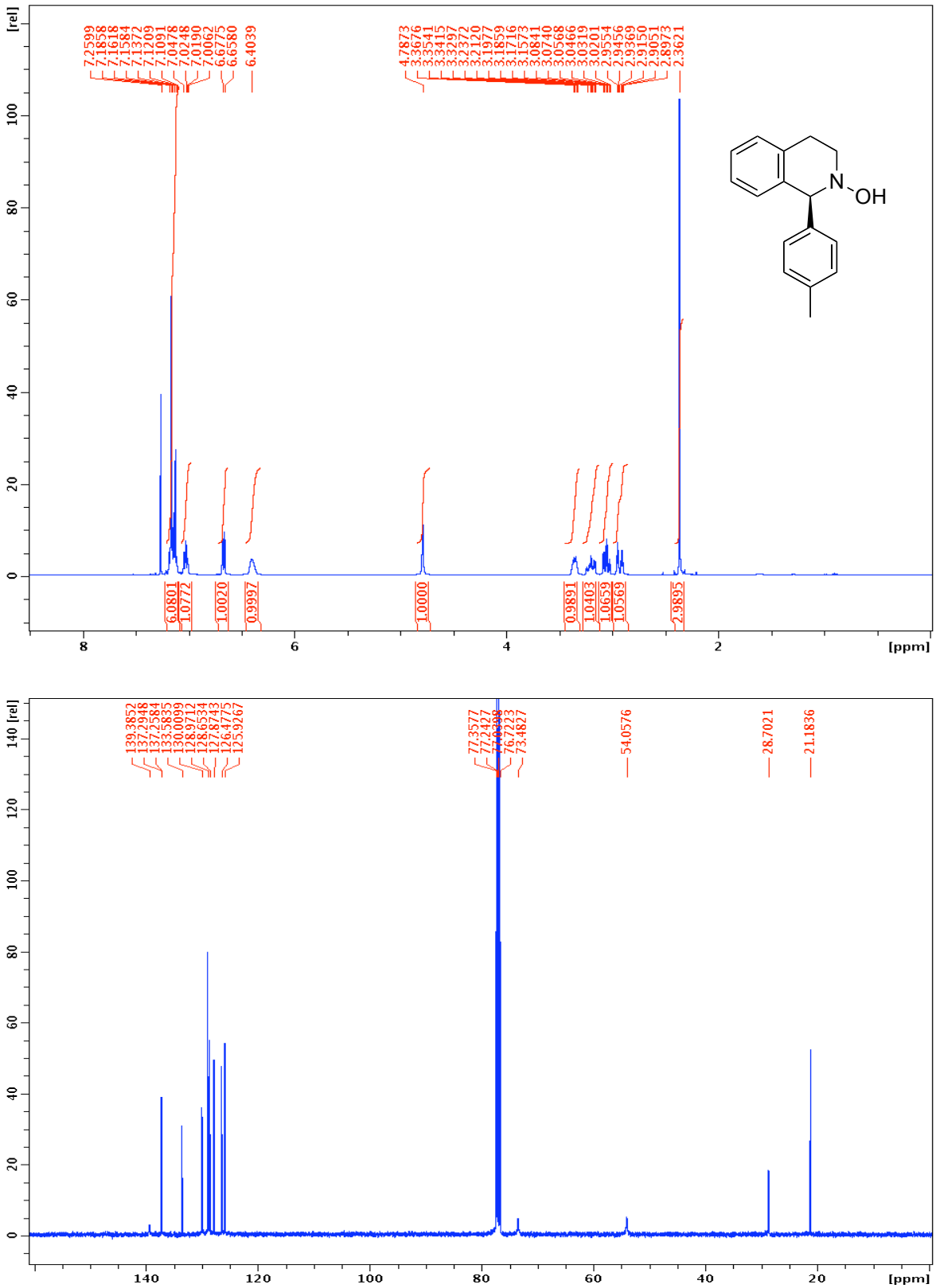


**Figure S17.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3b**.

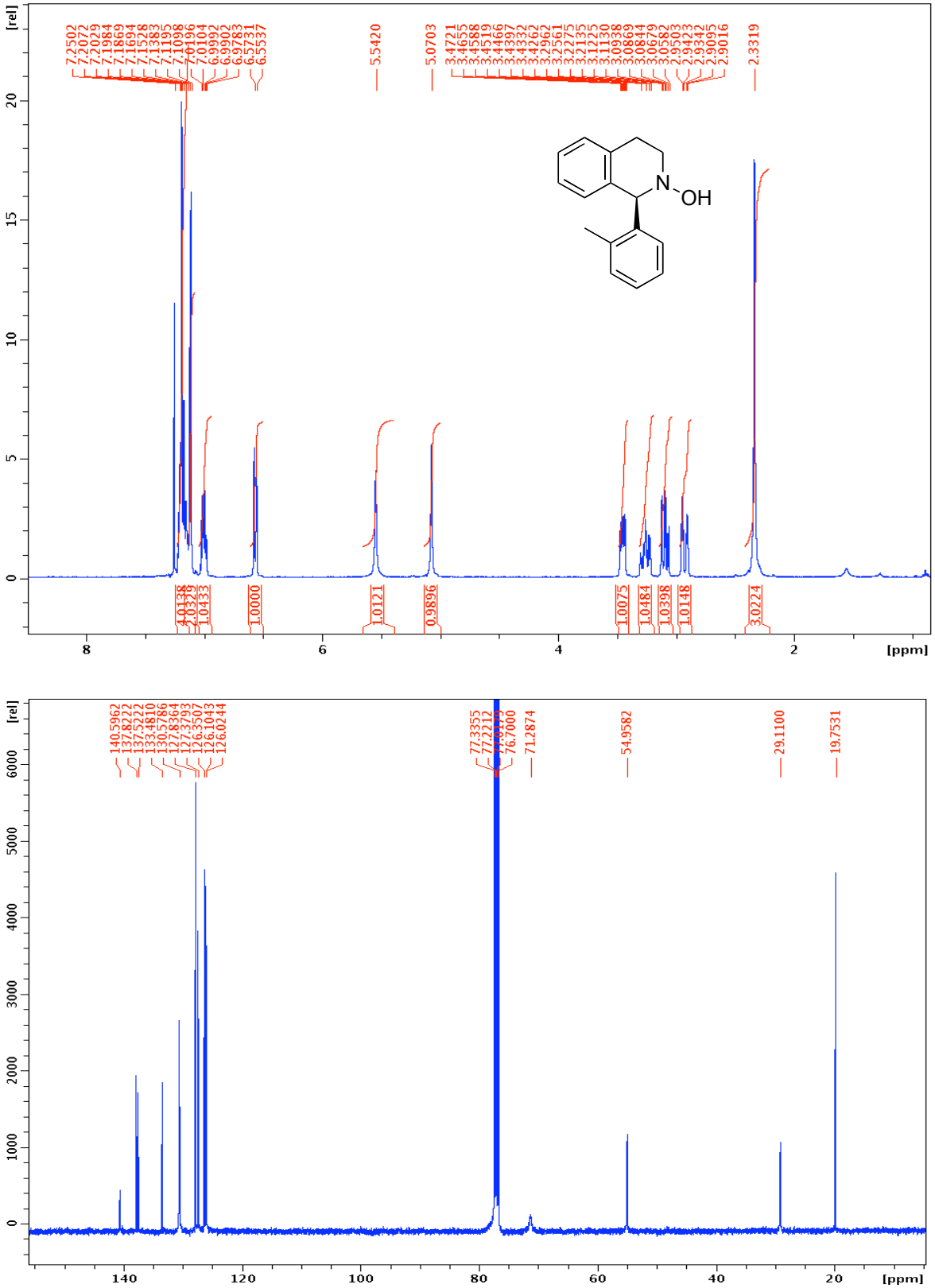


**Figure S18.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3c**.

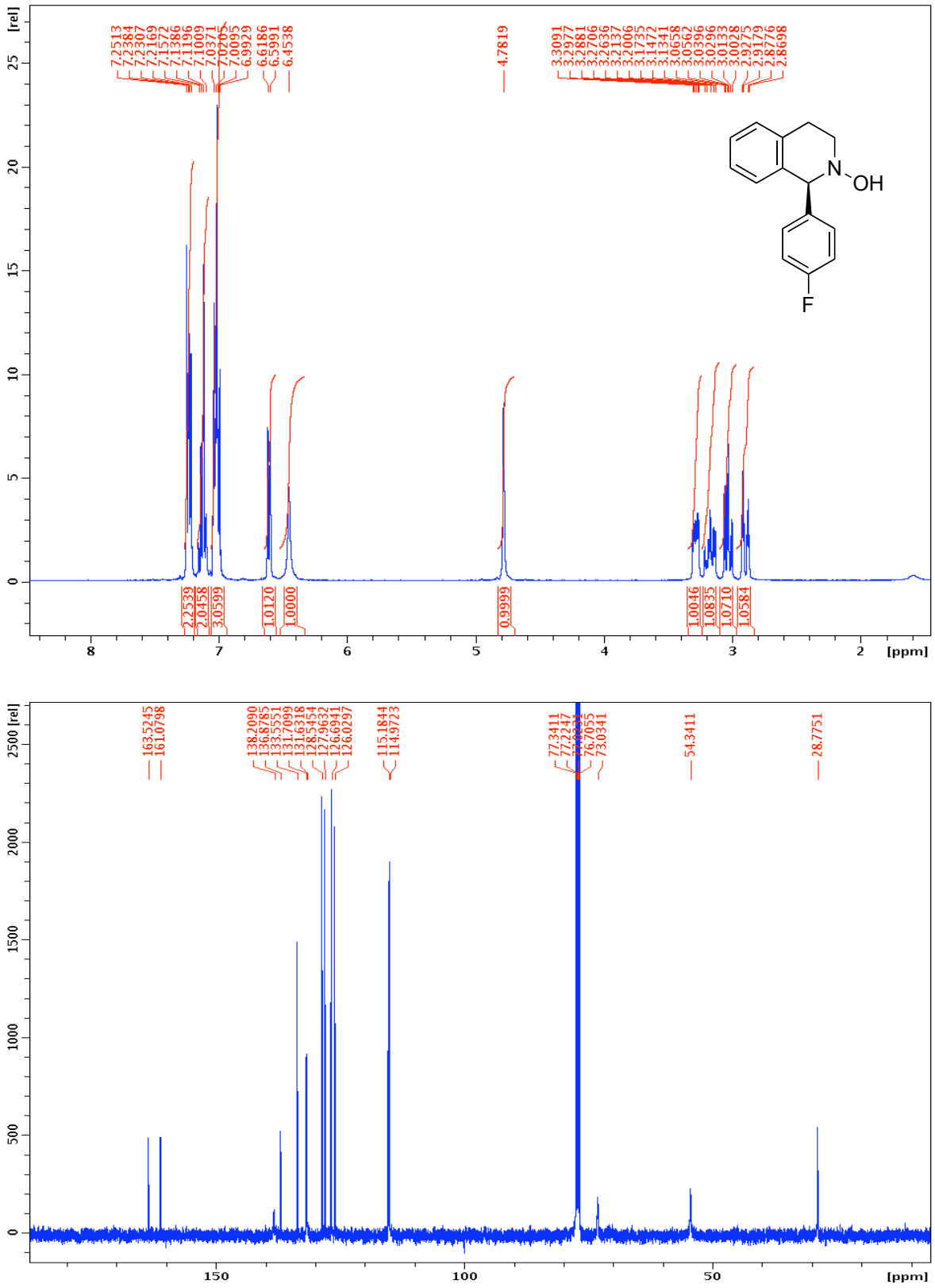


**Figure S19.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3d**.

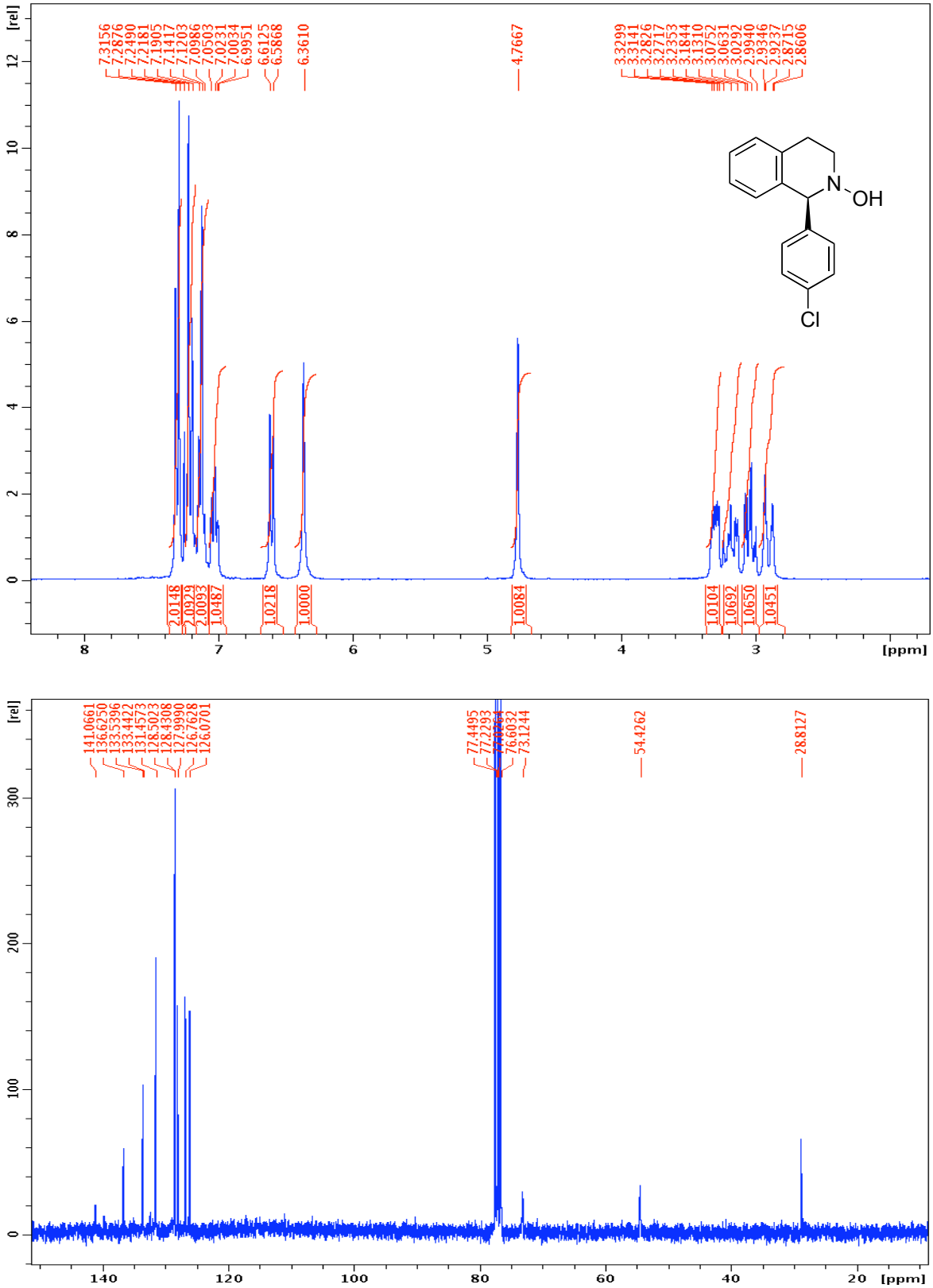


**Figure S20.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3e**.

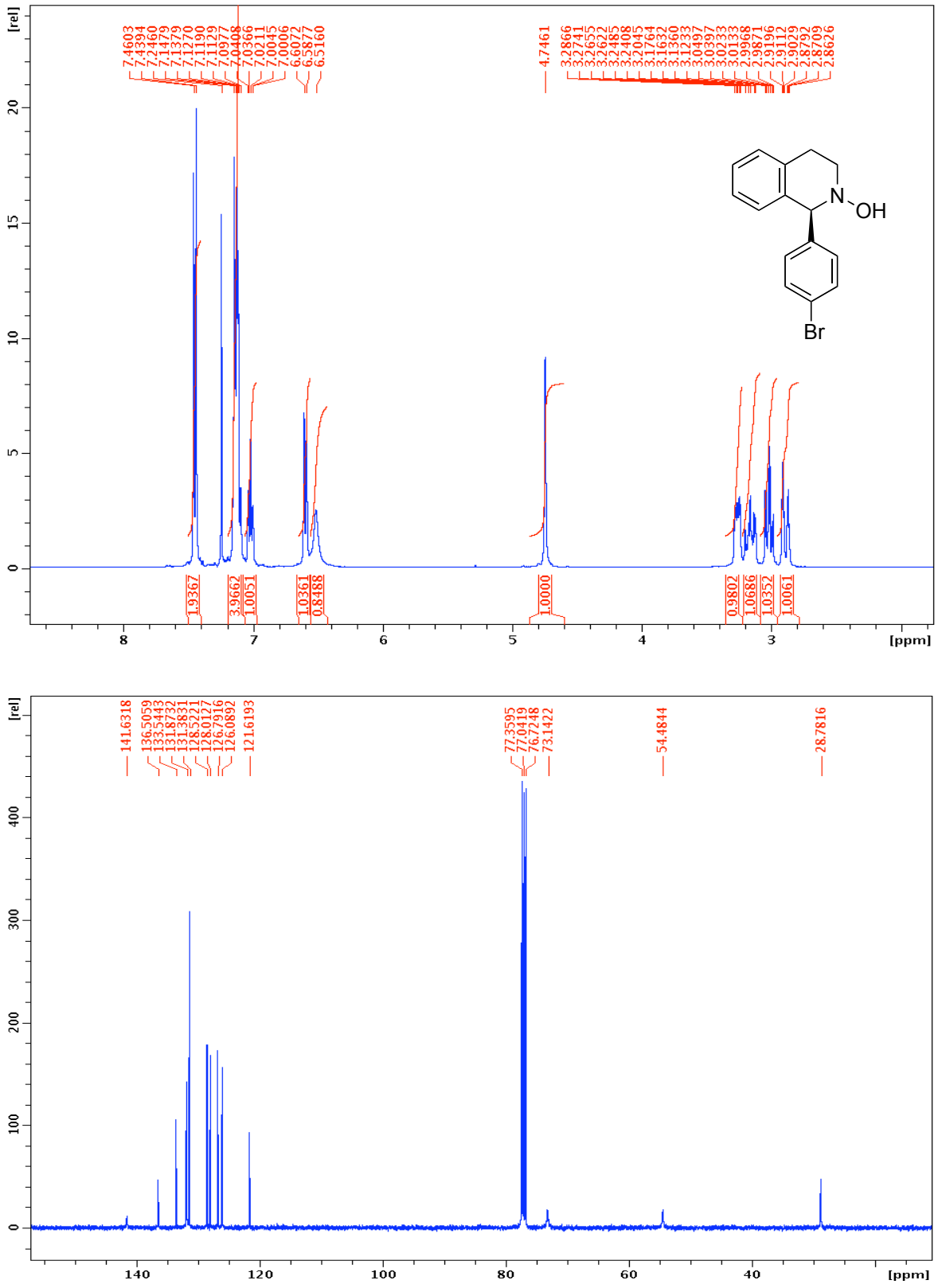


**Figure S21.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3f**.

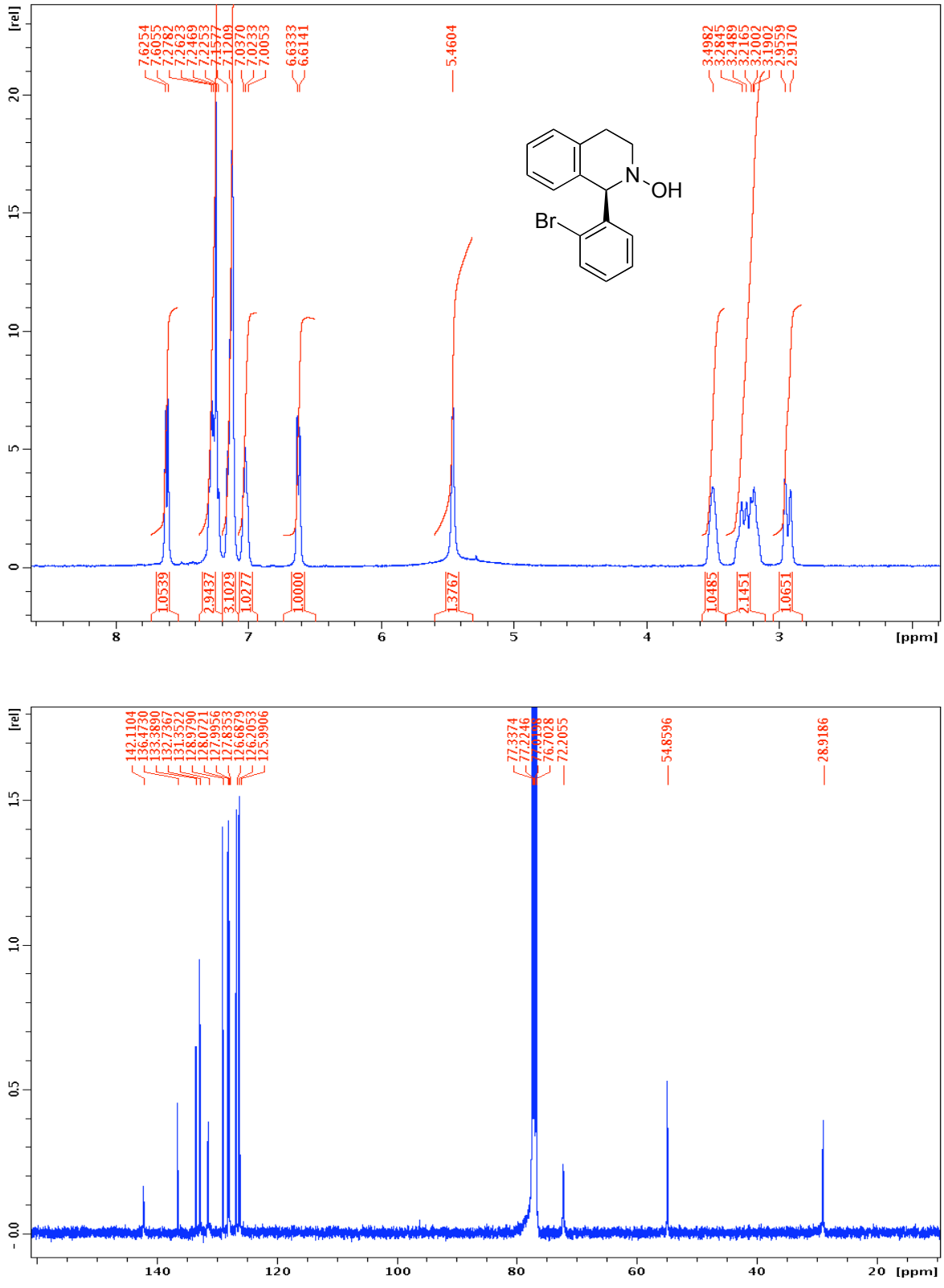


**Figure S22.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3g**.

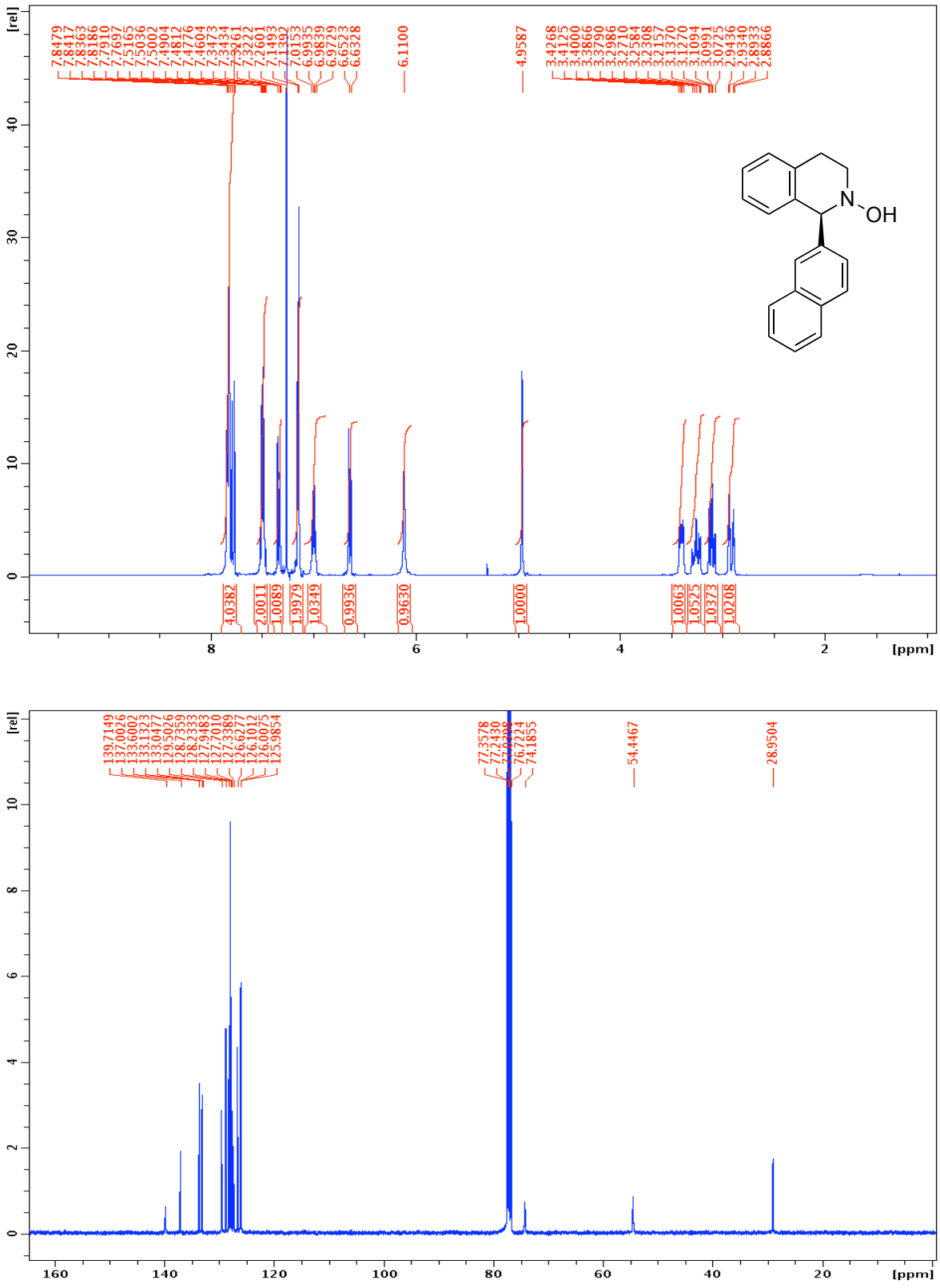


**Figure S23.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3h**.

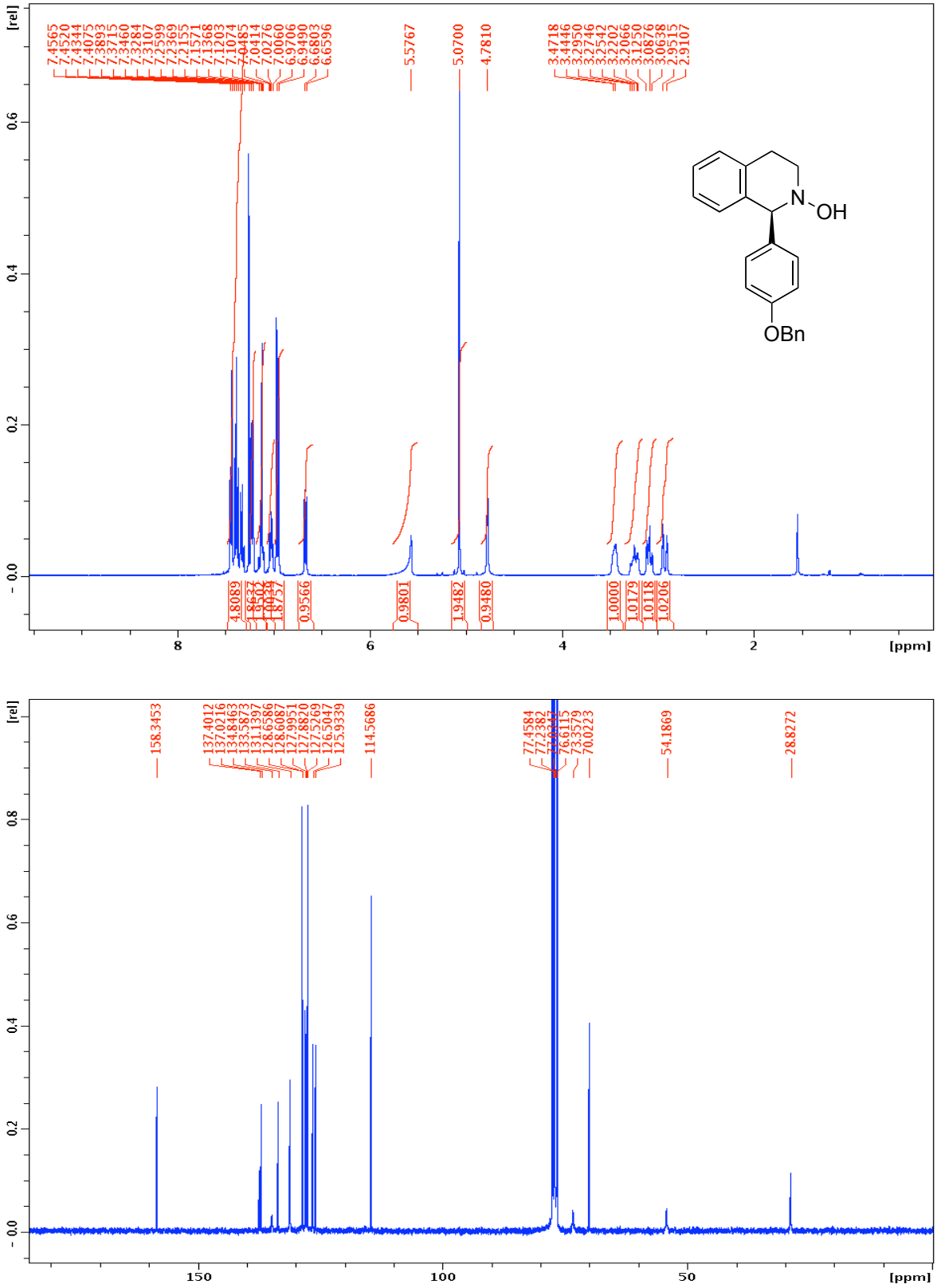


**Figure S24.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4a**.

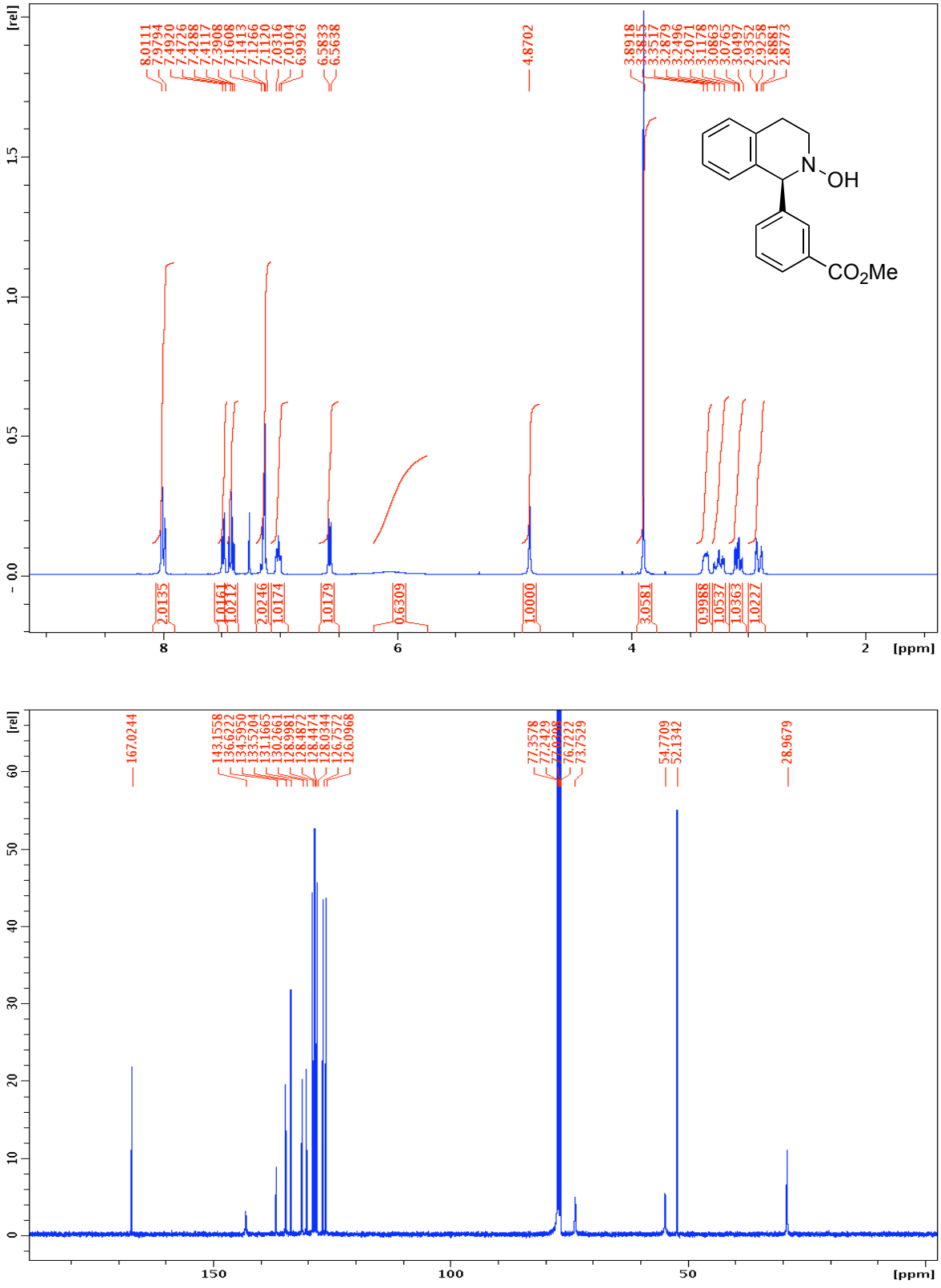


**Figure S25.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4b**.

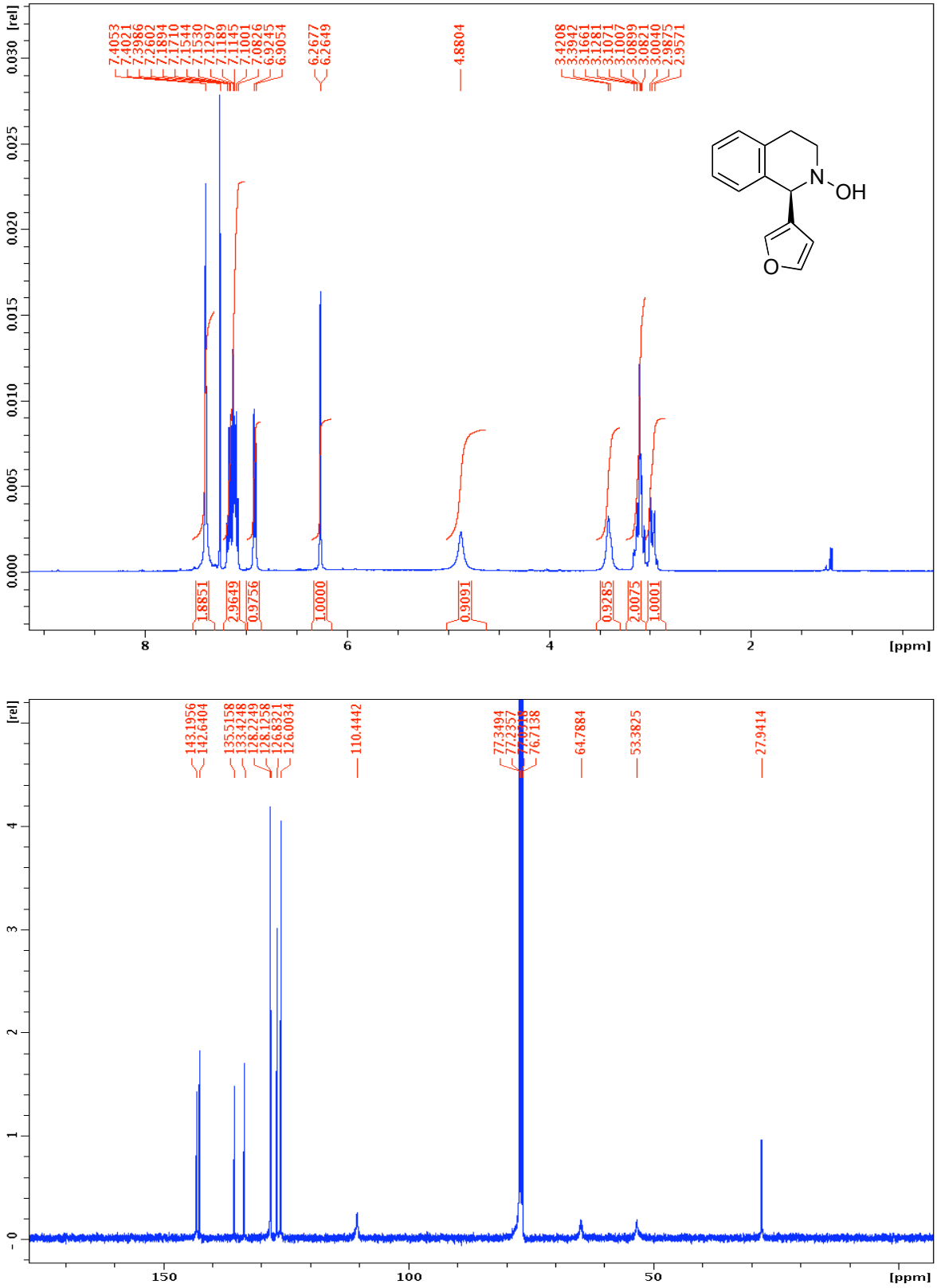


**Figure S26.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4c**.

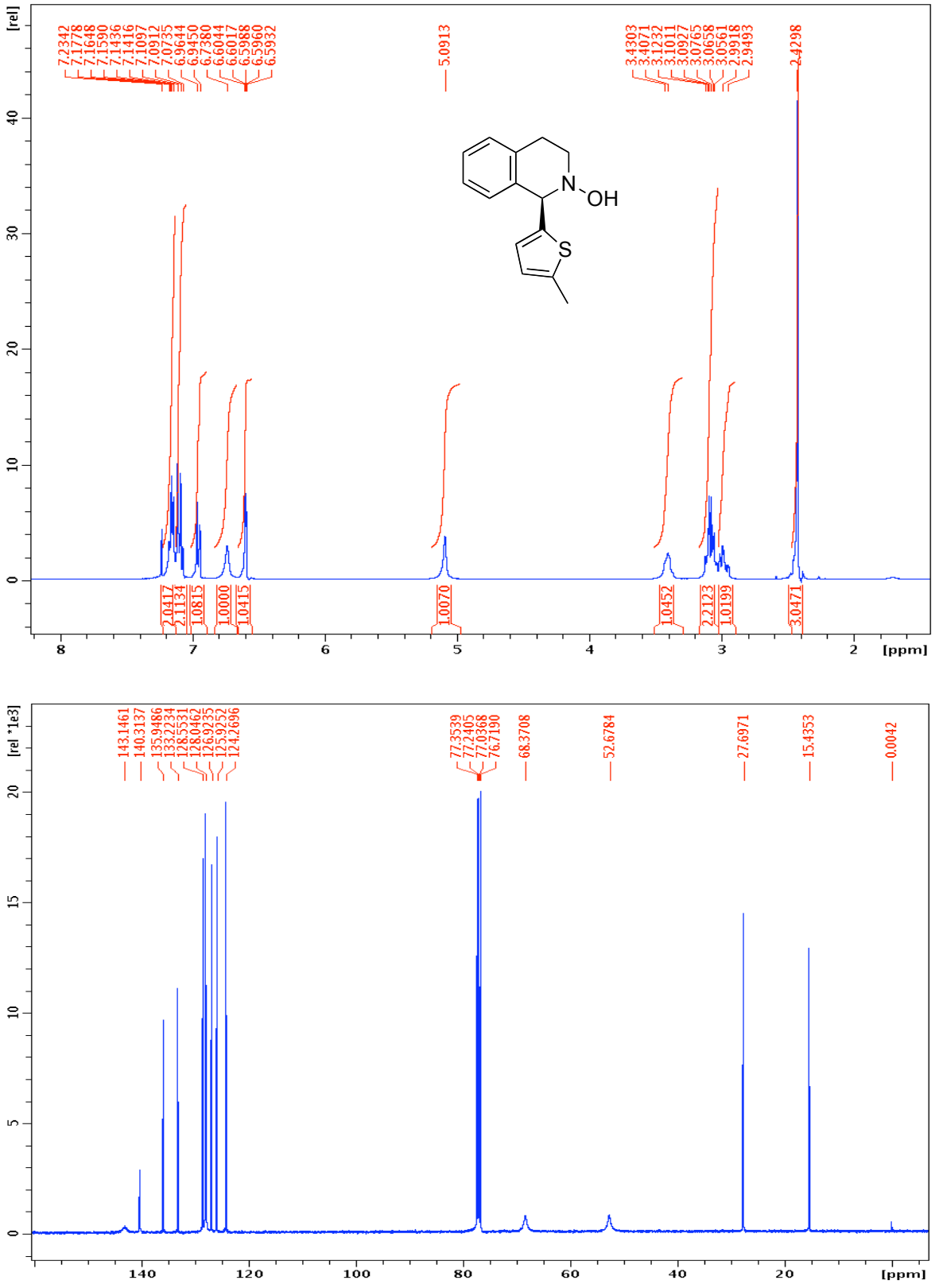


**Figure S27.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4d**.

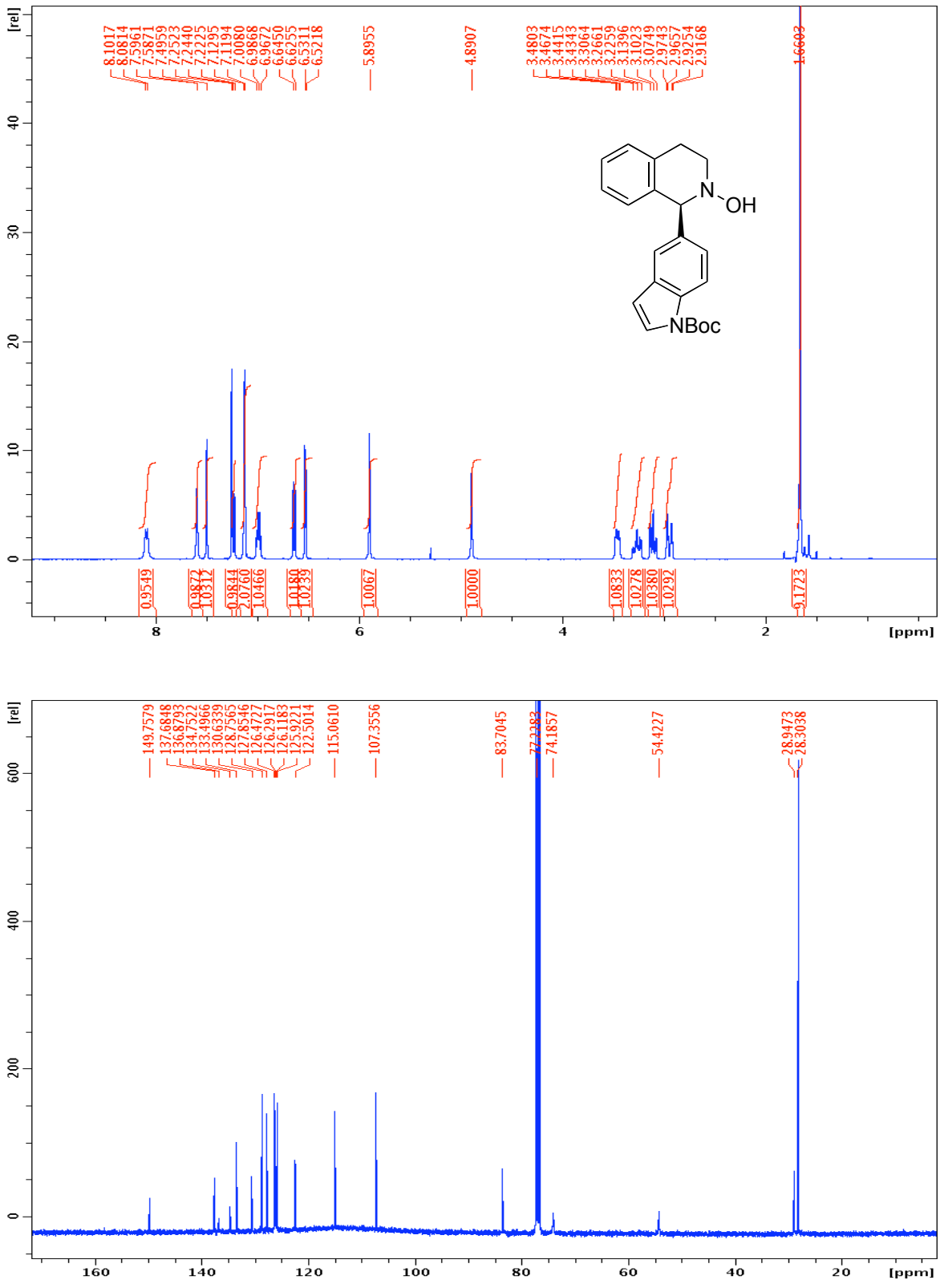


**Figure S28.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4e**.

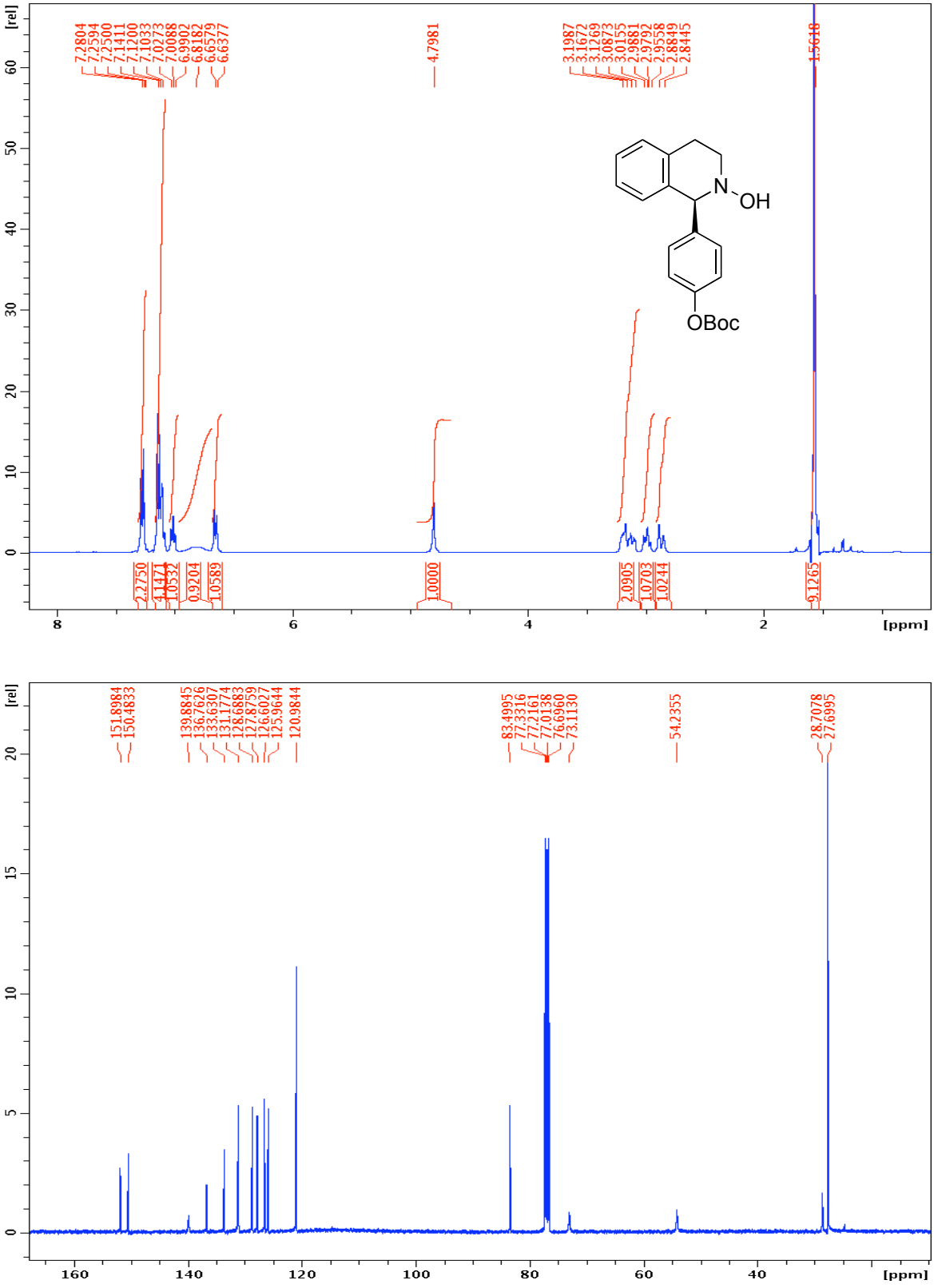


**Figure S29.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4f**.

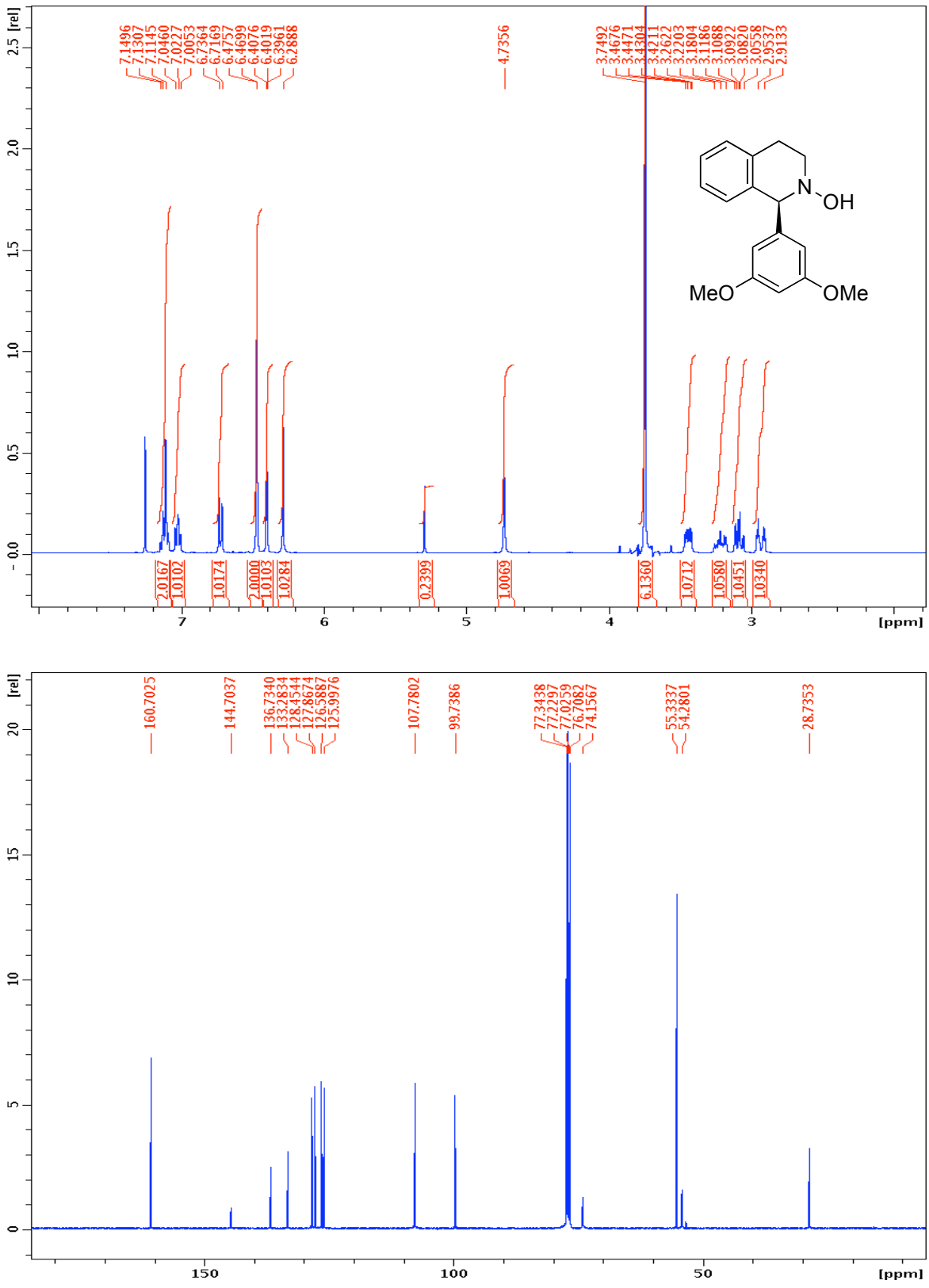


**Figure S30.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4g**.

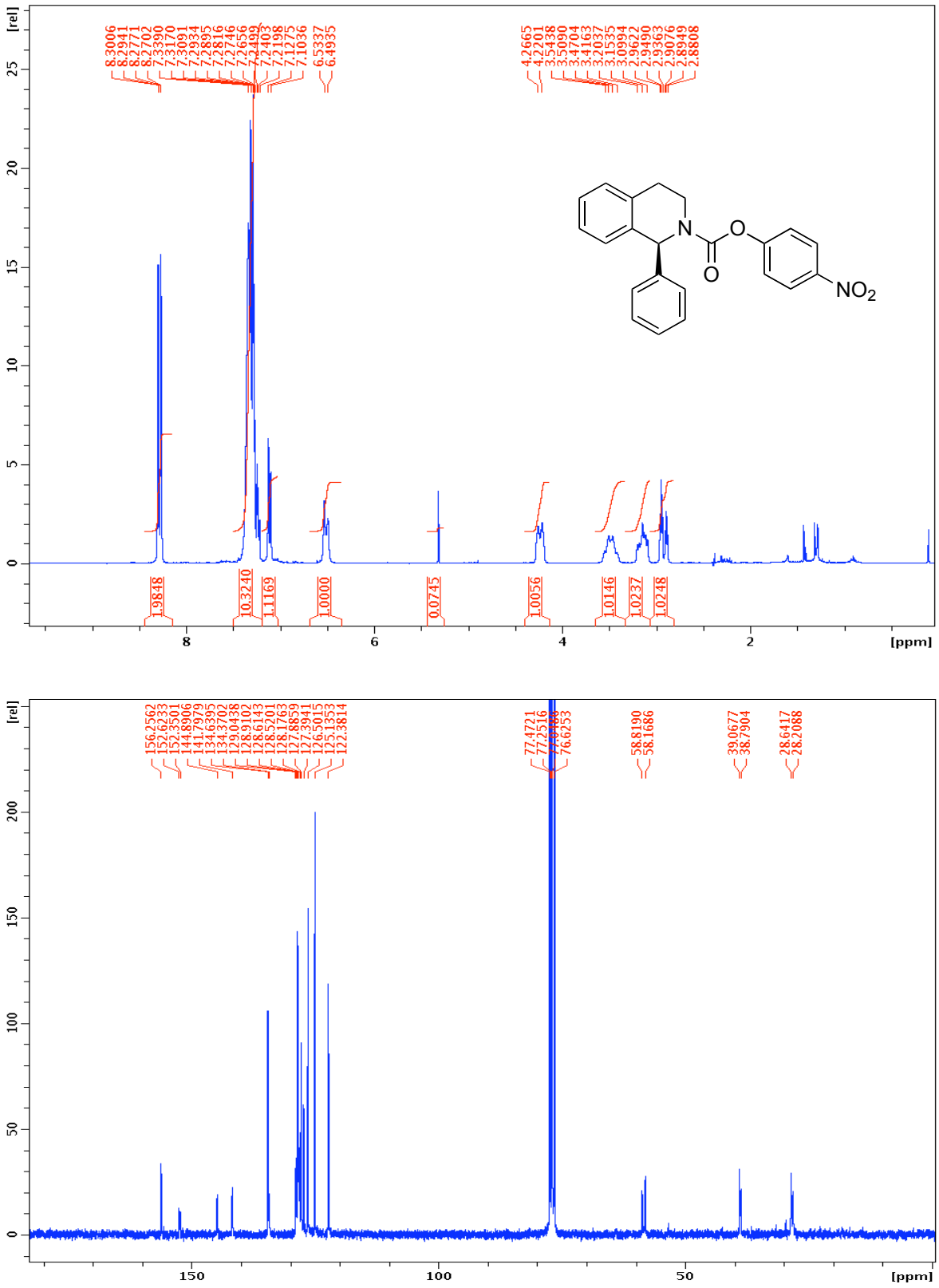


**Figure S31.** $^{1}H$ and $^{13}C$ NMR spectra of compound **5**.

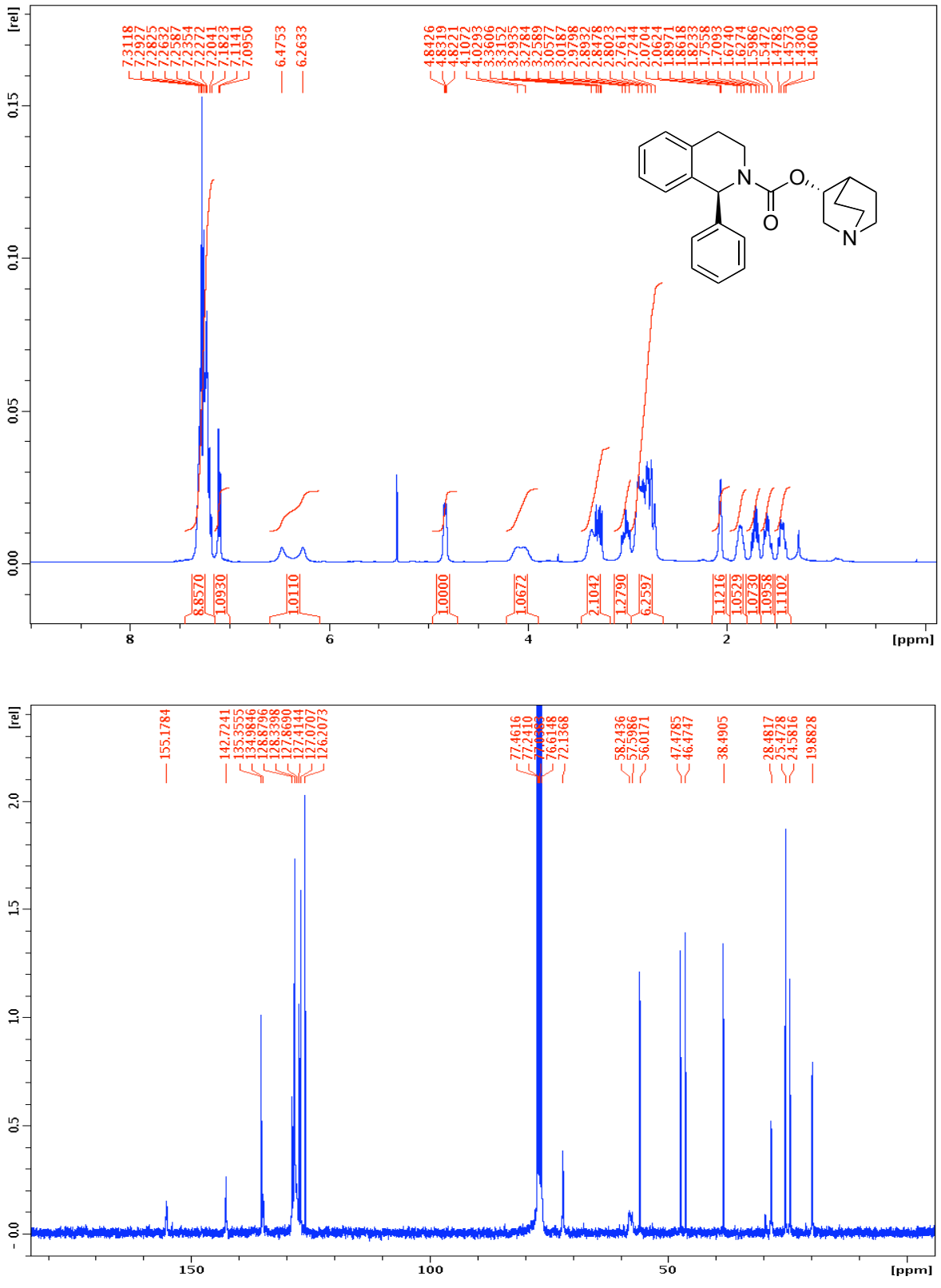


**Figure S32.** $^{1}H$ and $^{13}C$ NMR spectra of compound **1f**.