Photoredox Activation and Anion Binding Catalysis in the Dual Catalytic Enantioselective Synthesis of β-Amino Esters

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Supporting Information

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1. General Information

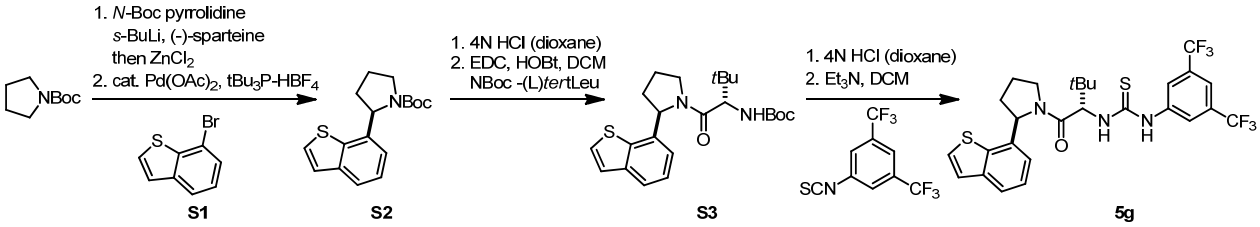
General Laboratory Procedures. All moisture-sensitive reactions were performed under an atmosphere of nitrogen in flame-dried round bottom flasks or glass vials fitted with rubber septa and/or septa equipped screw caps. For reactions run at low temperatures the caps were wrapped with Teflon® tape and parafilm to minimize the introduction of adventitious water. Stainless steel syringes were used to transfer air or moisture-sensitive liquids.

Materials and Instrumentation. All chemicals were purchased from Sigma-Aldrich and were used as received unless otherwise stated. All solvents, excluding methyl *tert*-butyl ether (MTBE), were purchased from Fischer Scientific and further dried using Glass Contour Solvent System by SG Waters USA LLC. Unless stated differently, all reactions were performed under inert atmosphere (Argon) and previously dried using common anhydrous techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with I_2. All compounds were purified via flash column chromatography using 230–400 mesh silica gel. NMR spectra were recorded on Varian Unity Plus 500 and Varian Mercury 400 spectrometers. Chemical shifts for ^{1}H-NMR were reported as δ, parts per million (ppm), relative to the signal of $CHCl_3$ at 7.26(s) ppm. Chemical shifts for ^{13}C-NMR were reported as δ, parts per million, relative to the signal of the $CDCl_3$ 77.0 (t) ppm. Proton and carbon assignments were established using spectral data of similar compounds. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, p, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, pentet, multiplet and broad multiplet, respectively. IR spectra were recorded on an Avatar 360 FT-IR spectrometer. Mass spectra were recorded in the Mass Spectrometry Facility at the Department of Chemistry of Boston University in Boston, MA on a Waters Q-Tof API-US with ESI high-resolution mass spectrometer. The enantiomeric purity was determined by Chiral HPLC analysis performed on a Waters system using either a CHIRALPAK AD-H or a CHIRALCEL OD-H column from CHIRAL TECHNOLOGIES, INC with *i*-PrOH/hexane as the eluent. HPLC traces were compared to racemic samples prepared by performing the Oxidative Mannich Reaction in acetonitrile at room temperature, without the presence of the thiourea catalyst. Optical rotations were measured on a AUTOPOL III automatic polarimeter from RUDOLF RESEARCH ANALYTICAL. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg). 1,2,3,4-Tetrahydroisoquinoline derivatives and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline were prepared according to published literature procedures.[1]

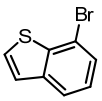
Abbreviations used: ee = enantiomeric excess, HPLC = high pressure liquid chromatography, EDC hydrochloride = *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, Et_3N = triethylamine, EtOAc = ethyl acetate, AcOH = acetic acid, DCM = dichloromethane, HCl = hydrogen chloride, HOBt = 1-Hydroxybenzotriazole hydrate, $NaHCO_3$ = sodium bicarbonate, Boc = tert-butoxycarbonyll, LiCl = lithium chloride, NaOAc = sodium acetate, NaOMe = sodium methoxide, MeOH = methanol, DIPEA = *N*,*N*-diisopropylethylamine, MTBE = methyl *tert*-butyl ether, THF = tetrahydrofuran.

2. Catalyst Preparation and Characterization Data

The catalysts shown in table 1 were synthesized following the general reaction sequence shown below:

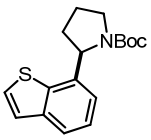


7-bromobenzothiophene (S1).



To a solution of 2.29g (42.31 mmol) NaOMe in 25 mL of MeOH was added 5.0g (26.44 mmol) of 2-bromothiophenol and 3.42 mL of bromoacetoaldehyde dimethylacetal at 0˚C. After 20 minutes at 0˚C, the mixture was refluxed for 4 hours. The mixture was then evaporated to yield a crude oil. Water (50 mL) was added to this residue and the aqueous layer was extracted with 50 mL of Et_2O (3 times). The combined organic layers are washed with brine and subsequently dried using $MgSO_4$ and evaporated. The crude material was then added to a mixture of 0.5g polyphosphoric acid in 50 mL of chlorobenzene and heated to reflux in a pressure tube for 12 hours. After 12 hours, the supernatant of the reaction mixture was separated and evaporated. The residue was purified by column chromatography using hexane as eluent to yield the desired product **S1** (4.03g, 72% yield) as a colorless oil. The spectroscopic data was in agreement with that reported in the literature.[2] **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.73 (dd, *J* = 8.0 Hz, 1H),7.47-7.45 (m, 2H), 7.41 (d, *J* = 5.6 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H); **HRMS** calcd for C_8H_6BrS: 212.9374; found: 212.9378.

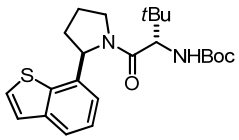
(R)-*tert*-butyl 2-(benzothiophen-7-yl)pyrrolidine-1-carboxylate (S2).



The preparation follows a procedure described by Campos and coworkers for the Palladium-catalyzed α-arylation of *N*-Boc-pyrrolidines.[4] To a solution of *N*-Boc-pyrrolidine (2.0 mL, 11.4 mmol) and (-)-sparteine (2.6 ml, 11.4 mmol) in MTBE (24 mL) at -78˚C was added s-BuLi (9.6 mL, 11.4 mmol, 1.2 M in cyclohexane) via syringe pump over the course of 60 minutes. The resulting solution was stirred at -78˚C for 3 hours. A solution of $ZnCl_2$ (6.4 mL, 6.8 mmol, 1.0 M in Et_2O) was added to the reaction via syringe pump over the course of one hour. Stirring at -78˚C was continued for 30 minutes and the resulting suspension was subsequently warmed to room temperature. Arylbromide **S1** (2.01g, 9.5 mmol) was subsequently added followed by $Pd(OAc)_2$ (102 mg, 0.46 mmol) and tBu$_3$P-HBF$_4$ (164 mg, 0.57 mmol). Stirring at room temperature was continued for 12 hours. NH_4OH solution (1 ml) was then added and stirring was continued for one hour. To this mixture was then added 1M HCl (100 mL) and the aqueous phase was extracted twice with DCM (100 mL). The combined organic phases were washed with brine, dried using Na_2SO_4 filtered and concentrated. The crude material was purified using column chromatography and hexane/EtOAc (4:1) as eluent to yield **S2** (2.04g, 71% yield) as a colorless oil. $[\alpha]_D^{23}$ = + 29.2° (c = 0.50, $CHCl_3$); Compound **S2** is characterized as a mixture of rotamers. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.71 (d, *J* = 7.8 Hz, 2 H), 7.44 - 7.40 (m, 2 H), 7.37 (d, *J* = 5.4 Hz, 2 H), 7.32 (t, *J* = 7.6 Hz, 4 H), 7.13 (d, *J* = 6.8 Hz, 3 H), 5.04 (t, *J* = 6.3

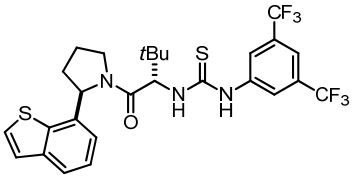
Hz, 2 H), 3.80 - 3.66 (m, 8 H), 3.59 (d, *J* = 7.8 Hz, 1 H), 3.37 - 3.25 (m, 4 H), 2.44 - 2.35 (m, 4 H), 2.07 - 1.88 (m, 13 H), 1.83 (d, *J* = 2.4 Hz, 4 H), 1.52 - 1.38 (m, 28 H), 1.06 - 0.91 (m, 29 H); **^{13}C NMR** (126MHz, $CDCl_3$) δ = 154.9, 154.8, 140.5, 139.2, 136.0, 126.3, 124.5, 124.3, 122.2, 121.1, 79.5, 79.1, 61.4, 47.3, 46.2, 45.9, 34.4, 28.8, 28.3, 28.2, 24.2; **IR** (thin film, cm^{-1}) 2972 (w), 2946 (w), 2881 (w), 1677 (s, C=O), 1412 (m), 1366 (s), 1250 (s), 1159 (m), 1104 (m), 799 (m), 705 (s); **HRMS** calcd for $C_{17}H_{22}NO_2S$: 304.1371; found: 304.1367.

***tert*-butyl((S)-1-((R)-2-(benzothiophen-7-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (S3).**



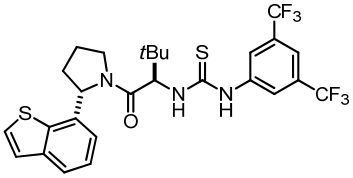
To a solution of (R)-*tert*-butyl 2-(benzothiophen-7-yl)pyrrolidine-1-carboxylate (**S2**) (2.04g, 6.74 mmol) in DCM was added HCl (6.75 mL, 27 mmol, 4N in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH_4OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na_2SO_4, filtered and concentrated. To the resulting oil in DCM was then added EDC hydrochloride (1.36g, 7.08 mmol) and HOBt (1.08g, 7.08 mmol) together with Boc-L-*tert*-leucine (1.73g, 7.08 mmol) and stirring at room temperature was continued for 12 hours. The reaction was quenched by the addition of 50 mL of water and the aqueous phase was extracted with DCM (100 mL, 3 times). The combined organic phases were dried using Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified using column chromatography with hexanes/EtOAc (4:1) as eluent to yield the desired product as a yellow foam (2.52g, 90% yield). $[\alpha]_D^{23}$ = - 7.9° (c = 0.50, $CHCl_3$); Compound **S3** is characterized as a mixture of rotamers. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 7.66 (d, *J* = 7.3 Hz, 2 H), 7.63 - 7.60 (m, 1 H), 7.59 - 7.49 (m, 1 H), 7.41 - 7.38 (m, 2 H), 7.34 (d, *J* = 5.4 Hz, 2 H), 7.32 - 7.31 (m, 1 H), 7.22 (t, *J* = 7.6 Hz, 2 H), 7.01 (d, *J* = 7.3 Hz, 2 H), 5.52 - 5.39 (m, 2 H), 5.30 (d, *J* = 9.8 Hz, 2 H), 4.43 (d, *J* = 9.8 Hz, 2 H), 4.39 - 4.30 (m, 2 H), 4.12 (d, *J* = 7.3 Hz, 1 H), 3.84 - 3.73 (m, 3 H), 2.41 - 2.26 (m, 3 H), 2.10 - 1.96 (m, 9 H), 1.54 - 1.37 (m, 29 H), 1.31 - 1.19 (m, 3 H), 1.05 (s, 23 H), 1.01 - 0.90 (m, 4 H), 0.83 (s, 7 H); **^{13}C NMR** (126MHz, $CDCl_3$) δ = 171.5, 169.3, 156.6, 153.0, 140.6, 136.6, 136.4, 128.6, 128.1, 126.4, 126.3, 126.2, 124.6, 124.5, 122.5, 120.4, 117.1, 111.4, 79.8, 66.3, 60.6, 60.4, 59.1, 48.7, 34.9, 34.7, 32.3, 31.4, 28.6, 28.5, 27.7, 27.3, 26.8, 26.7, 26.3, 25.1, 24.4, 21.3, 14.4; **IR** (thin film, cm^{-1}) 2969 (w), 1778 (s), 1704 (s), 1647 (s), 1498 (w), 1366 (m), 1240 (m), 1185 (m), 918 (s), 801 (s), 745 (s), 702 (s); **HRMS** calcd for $C_{23}H_{32}NO_3SNa$: 439.2031; found: 439.2036.

1-((S)-1-((R)-2-(benzothiophen-7-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (5g).



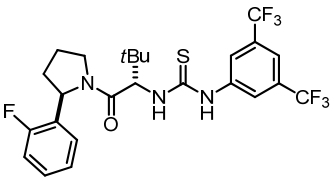
To a solution of amide (**S3**) (2.52g, 6.05 mmol) in DCM was added HCl (6.05 mL, 24.21 mmol, 4N in dioxane) and stirring of the reaction mixture was continued for four hours at room temperature. The solvent was subsequently removed in vacuum and the solid residue was dissolved in DCM. To this reaction mixture was added 50 mL of aqueous NH_4OH and stirring was continued for one hour. The aqueous phase was then extracted with DCM (3 times, 100 mL) and the combined organic phases were dried using Na_2SO_4, filtered and concentrated. The resulting solid was subsequently dissolved in DCM and Et_3N (1.7 mL, 12.1 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.1 mL, 6.05 mmol) was added. Stirring at room temperature was continued for 12 hours. The mixture was then concentrated under reduced pressure and the resulting crude product was purified using column chromatography with hexane/EtOAc (4:1) as eluent to form the desired product **5g** (2.88g, 81% yield) as a colorless foam. $[\alpha]_D^{23}$ = - 56.0° (c = 0.50, $CHCl_3$); Compound **5g** is characterized as a mixture of rotamers. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 9.23 - 9.13 (m, 1 H), 8.92 - 8.75 (m, 2 H), 7.81 - 7.76 (m, 1 H), 7.69 (br. s., 4 H), 7.62 - 7.58 (m, 1 H), 7.54 (s, 2 H), 7.49 - 7.43 (m, 3 H), 7.40 (d, *J* = 5.4 Hz, 1 H), 7.38 - 7.28 (m, 7 H), 7.22 (d, *J* = 5.4 Hz, 2 H), 7.03 - 6.93 (m, 5 H), 6.24 - 6.07 (m, 1 H), 5.56 (d, *J* = 9.3 Hz, 3 H), 5.33 (dd, *J* = 2.0, 7.8 Hz, 3 H), 5.28 - 5.20 (m, 1 H), 4.60 - 4.46 (m, 3 H), 3.89 (d, *J* = 9.8 Hz, 3 H), 3.80 - 3.59 (m, 2 H), 2.39 - 2.22 (m, 4 H), 2.20 - 2.09 (m, 1 H), 2.09 - 1.93 (m, 11 H), 1.91 - 1.79 (m, 1 H), 1.14 (s, 29 H), 0.60 (s, 8 H); **^{13}C NMR** (126MHz, $CDCl_3$) δ = 181.7, 181.2, 173.2, 171.0, 140.9, 140.5, 140.3, 139.6, 136.7, 135.9, 135.8, 132.4, 132.1, 132.1, 131.9, 131.6, 126.8, 125.9, 124.5, 124.4, 124.3, 124.3, 123.5, 123.3, 122.4, 122.3, 122.1, 120.6, 118.8, 118.2, 63.4, 62.3, 61.9, 60.8, 49.0, 48.2, 36.0, 35.9, 33.6, 32.5, 27.2, 27.0, 24.3; **IR** (thin film, cm^{-1}) 1610 (s), 1536 (s), 1439 (m), 1381 (s), 1276 (m), 1172 (m), 1127 (m), 961 (s), 884 (s), 795 (s), 700 (m); **HRMS** calcd for $C_{27}H_{27}F_6N_3OS_2Na$: 610.1397; found: 610.1392.

1-((R)-1-((S)-2-(benzothiophen-7-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (*ent*-5g).



The thiourea catalyst ***ent*-5g** was prepared following the general reaction sequence described above using (+)-sparteine as a chiral ligand in the Palladium-catalyzed α-arylation of *N*-Boc-pyrrolidine. $[\alpha]_D^{23}$ = + 57.4° (c = 0.50, $CHCl_3$); **IR** (thin film, cm^{-1}) 1610 (s), 1536 (s), 1439 (m), 1381 (s), 1275 (m), 1172 (m), 1125 (m), 961 (s), 885 (s), 796 (s), 669 (m), 681 (m); **HRMS** calcd for $C_{27}H_{27}F_6N_3OS_2Na$: 610.1397; found: 610.1392.

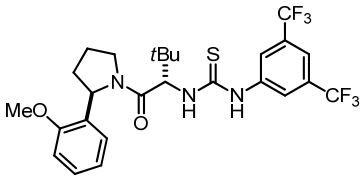
1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(2-fluorophenyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (5e).



The thiourea catalyst **5e** was prepared following the general reaction sequence described above using (-)-sparteine as a chiral ligand in the Palladium-catalyzed α-arylation of *N*-Boc-pyrrolidine. $[\alpha]_D^{24}$ = + 10.9° (c = 0.50, $CHCl_3$); Compound **5e** is characterized as a mixture of rotamers. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 8.85 - 8.68 (m, 1 H), 8.67 - 8.47 (m, 2 H),

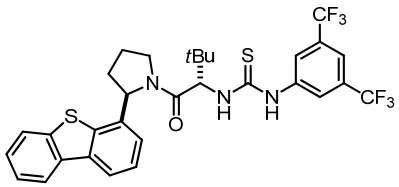
7.90 - 7.82 (m, 1 H), 7.78 (s, 4 H), 7.65 (s, 2 H), 7.40 - 7.29 (m, 1 H), 7.03 (d, *J* = 7.3 Hz, 8 H), 6.90 - 6.75 (m, 4 H), 5.43 (d, *J* = 9.3 Hz, 2 H), 5.35 (d, *J* = 7.3 Hz, 2 H), 4.47 (s, 3 H), 3.79 (d, *J* = 10.3 Hz, 4 H), 2.24 (s, 3 H), 1.96 (td, *J* = 3.5, 7.6 Hz, 9 H), 1.17 - 1.02 (m, 26 H), 0.71 (s, 5 H); **^{13}C NMR** (126MHz, $CDCl_3$) δ = 181.7, 172.3, 170.7, 160.5, 158.5, 139.9, 132.7, 132.4, 132.1, 131.9, 130.1, 129.4, 128.7, 128.6, 128.4, 128.3, 126.7, 126.7, 126.5, 124.3, 123.9, 123.7, 123.7, 122.1, 120.0, 118.9, 115.4, 115.2, 63.4, 62.0, 58.6, 56.2, 56.2, 48.8, 47.7, 36.0, 35.8, 34.6, 32.9, 27.2, 27.0, 26.8, 23.5, 22.4; **IR** (thin film, cm^{-1}) 1614 (s), 1254 (s), 1456 (m), 1383 (2), 1275 (s), 1174 (s), 1126 (s), 885 (s), 759 (s), 681 (s); **HRMS** calcd for $C_{25}H_{27}F_7N_3OS$: 550.1763; found: 550.1765.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(2-methoxyphenyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (5f).



The thiourea catalyst **5f** was prepared following the general reaction sequence described above using (-)-sparteine as a chiral ligand in the Palladium-catalyzed α-arylation of *N*-Boc-pyrrolidine. $[\alpha]_D^{24}$ = + 15.4° (c = 0.50, $CHCl_3$); Compound **5f** is characterized as a mixture of rotamers. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 9.60 - 9.43 (m, 1 H), 9.36 - 9.18 (m, 2 H), 8.15 (s, 2 H), 7.88 (s, 4 H), 7.61 (s, 3 H), 7.38 (br. s., 3 H), 7.06 - 6.96 (m, 2 H), 6.91 (t, *J* = 7.6 Hz, 2 H), 6.88 - 6.78 (m, 3 H), 6.63 (d, *J* = 7.8 Hz, 2 H), 6.58 (t, *J* = 7.6 Hz, 3 H), 5.93 - 5.76 (m, 1 H), 5.55 (d, *J* = 9.3 Hz, 2 H), 5.33 (d, *J* = 6.8 Hz, 3 H), 4.44 (br. s., 2 H), 3.85 (s, 3 H), 3.79 (d, *J* = 9.3 Hz, 3 H), 3.63 (s, 10 H), 2.17 (s, 3 H), 2.03 - 1.76 (m, 11 H), 1.17 - 1.02 (m, 25 H), 0.71 (s, 10 H); **^{13}C NMR** (126MHz, $CDCl_3$) δ = 181.8, 181.4, 172.3, 170.6, 156.6, 155.9, 141.3, 140.4, 132.5, 132.2, 132.1, 131.9, 131.9, 131.7, 131.6, 130.7, 129.3, 129.2, 127.9, 126.6, 125.6, 124.6, 124.4, 123.8, 122.9, 122.4, 122.2, 120.5, 120.0, 118.4, 117.5, 111.2, 110.3, 63.1, 61.2, 57.3, 55.6, 55.2, 49.2, 47.8, 36.3, 36.0, 33.7, 32.5, 32.2, 29.9, 29.9, 29.6, 27.2, 27.2, 23.3, 22.9, 14.4; **IR** (thin film, cm^{-1}) 1610 (s), 1523 (s), 1449 (m), 1275 (s), 1240 (s), 1173 (s), 1127 (m), 883 (s), 755 (s), 6819s); **HRMS** calcd for $C_{26}H_{29}F_6N_3O_2SNa$: 584.1782; found: 584.1776.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(dibenzo[b,d]thiophen-4-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (S4).



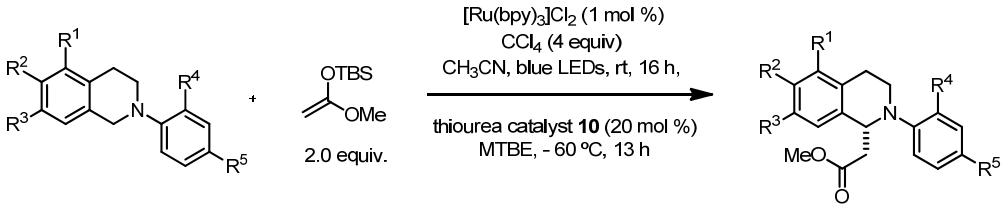
The thiourea catalyst **S4** was prepared following the general reaction sequence described above using (-)-sparteine as a chiral ligand in the Palladium-catalyzed α-arylation of *N*-Boc-pyrrolidine. $[\alpha]_D^{24}$ = - 13.1° (c = 0.50, $CHCl_3$); Compound **S4** is characterized as a mixture of rotamers. **^{1}H NMR** (500MHz, $CDCl_3$) δ = 9.24 - 9.00 (m, 1 H), 8.86 - 8.51 (m, 2 H), 8.21 - 8.14 (m, 1 H), 8.13 - 8.07 (m, 1 H), 8.07 - 7.92 (m, 4 H), 7.79 (d, *J* = 6.3 Hz, 6 H), 7.58 (br. s., 5 H), 7.54 - 7.31 (m, 13 H), 7.11 (br. s., 5 H), 6.22 - 6.01 (m, 1 H), 5.59 (d, *J* = 9.3 Hz, 3 H), 5.36 - 5.19 (m, 3 H), 4.56 (d, *J* = 2.9 Hz, 3 H), 3.97 - 3.83 (m, 3 H), 3.70 - 3.35 (m, 2 H), 2.41 - 2.18 (m, 4 H), 2.18 - 1.91 (m, 11 H), 1.19 - 1.01 (m, 30 H), 0.62 (s, 6 H); **^{13}C NMR** (126MHz, $CDCl_3$) δ = 181.7, 171.1, 139.6, 139.5, 139.2, 136.9, 136.3, 135.6, 135.4,

135.3, 132.2, 132.0, 127.3, 127.0, 124.8, 124.7, 124.7, 124.2, 124.1, 123.6, 123.5, 123.0, 122.8, 122.0, 121.9, 121.8, 120.2, 118.8, 63.3, 61.1, 49.1, 36.1, 35.9, 32.8, 27.2, 27.1, 26.7, 24.4, 24.2; **IR** (thin film, cm^{-1}) 1614 (s), 1528 (s), 1443 (s), 1382 (s), 1276 (s), 1175 (s), 1128 (s), 884 (s), 752 (s), 702 (s), 681 (s); **HRMS** calcd for $C_{31}H_{29}F_6N_3OS_2Na$: 660.1554; found: 660.1557.

3. Substrate Preparation

All substrates were either commercially available and used without further purification or were prepared according to literature procedures.[4, 5]

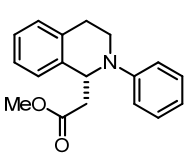
4. General Reaction Procedure



A mixture of tetrahydroisoquinoline (0.05 mmol), $[Ru(bpy)_3]Cl_2$ (0.32 mg, 1 mol%) and acetonitrile (0.5 mL) was degassed by three cycles of freeze-pump-thaw. CCl_4 (19.4 μL, 0.2 mmol, 4 equiv) was added and the mixture was stirred overnight under an inert atmosphere at room temperature while irradiated by blue LEDs (at a distance of approximately 10 cm so that the reaction mixture did not heat up during the reaction). Full conversion of the tetrahydroisoquinoline was ensured by either TLC or analyzing an aliquot of the reaction mixture with ^{1}H-NMR. The reaction mixture with the so formed iminium specie was transferred to a glass vial equipped with a septum screw cap using additional acetonitrile (1 mL) to assure complete transfer. The solution (or suspension depending on which tetrahydroisoquinoline derivative was used) was concentrated with stirring under high vacuum at -30 °C. The solid residue was kept under high vacuum for approximately 30 minutes at room temperature, which produced a red glassy solid. To the solid was added the thiourea catalyst ***ent*-5g** (5.9 mg, 0.01 mmol, 20 mol %) whereupon the glass vial was sealed and then evacuated and refilled with argon thr*ee* times. MTBE (1 mL) was added and the mixture was agitated with a vortex for a few seconds. The reaction mixture was then stirred at -60 °C for 30 minutes before the addition of the nucleophile, 1-(tert-butyldimethylsilyloxy)-1-methoxyethylene (21.8 μL, 0.1 mmol, 2 equiv). The reaction mixture was stirred overnight (16 h) and was then filtered through a plug of silica gel using DCM (3 x 2 mL) and a mixture of DCM/Et_2O (1:1, 3 x 2 mL). The product was isolated by Flash chromatography using 10% Et_2O in hexanes as eluent.

5. Characterization of Products

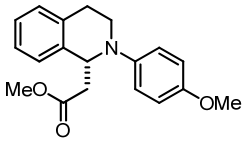
(*R*)-methyl 2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3a).



The synthesis of **3a** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (10% diethyl ether in

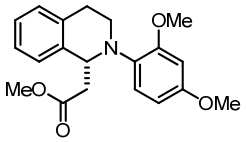
hexanes), using I_2 for TLC visualization, as a colorless oil (10.1 mg, 72% yield) in 95% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =4.6 min, t_R(minor) = 6.7 min; $[\alpha]_D^{26}$ = + 46.7° (c = 0.51, DCM); **IR** (thin film, cm^{-1}) 2953 (w), 2904 (w), 2841 (w), 1737 (s, C=O), 1588 (m), 1490 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.24-7.21 (2H, m), 7.17-7.10 (4H, m), 6.95 (2H, d, J = 8.35 Hz), 6.74 (1H, t, J = 7.2 Hz), 5.31 (1H, t, J = 7.1 Hz), 3.64-3.52 (2H, m), 3.60 (3H, s), 3.04 (1H, ddd, J = 16.1, 9.0, 5.6 Hz), 2.96 (1H, dd, J = 14.9, 7.1 Hz), 2.79 (1H, dt, J = 16.1, 4.9), 2.66 (1H, dd, J = 15.0, 7.0); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 171.9, 148.8, 137.4, 134.6, 129.3, 128.8, 127.0, 126.7, 126.1, 118.1, 114.6, 56.3, 51.7, 41.5, 41.3, 27.0; **HRMS** calcd for $C_{18}H_{20}N_1O_2$: 282.1494; found: 282.1492.

(*R*)-methyl 2-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3b).



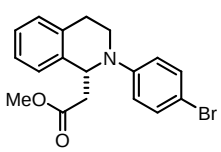
The synthesis of **3b** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (15% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (9.3 mg, 60% yield) in 84% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =9.0 min, t_R(minor) = 14.7 min; $[\alpha]_D^{26}$ = + 19.7° (c = 0.37, DCM); **IR** (thin film, cm^{-1}) 2949 (w), 2905 (w), 2833 (w), 1733 (s, C=O), 1509 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.19-7.11 (4H, m), 6.96-6.93 (2H, m), 6.84-6.81 (2H, m), 5.20 (1H, t, J = 7.0 Hz), **3.75** (3H, s), 3.61 (3H, s), 3.59-3.46 (2H, m), 3.04 (1H, ddd, J = 16.4, 10.1, 6.2 Hz), 2.92 (1H, dd, J = 14.9, 7.6 Hz), 2.74 (1H, dt, J = 16.4, 3.9 Hz), 2.66 (1H, dd, 14.8, 6.5); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 ˚C) **δ** 172.1, 153.1, 143.7, 137.5, 134.5, 129.0, 126.7, 126.1, 118.1, 114.6, 57.3, 55.6, 51.6, 42.2, 41.1, 26.7; **HRMS** calcd for $C_{19}H_{22}N_1O_3$: 312.1600; found: 312.1586.

(*R*)-methyl 2-(2-(2,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3c).



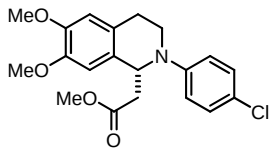
The synthesis of **3c** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (20% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (8.9 mg, 52% yield) in 96% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(minor) =9.9 min, t_R(major) = 16.0 min; $[\alpha]_D^{26}$ = + 31.0° (c = 0.42, DCM); **IR** (thin film, cm^{-1}) 2998 (w), 2948 (w), 2835 (w), 1735 (s, C=O), 1507 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.17-7.10 (4H, m), 6.81 (1H, br d, J = 8.6 Hz), 6.47 (1H, d, J = 2.9 Hz), 6.37 (1H, dd, J = 8.6, 2.7 Hz), 5.18 (1H, t, J = 6.6 Hz), 3.83 (3H, s), 3.76 (3H, s), 3.48 (3H, s), 3.46-3.33 (2H, m), 2.99 (1H, ddd, J = 16.8, 10.8, 6.2 Hz), 2.83 (1H, dd, J = 14.9, 7.8 Hz), 2.74 (1H, d, J = 16.1 Hz), 2.58 (1H, dd, J = 15.0, 5.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 172.4, 156.4, 154.3, 138.4, 134.5, 133.3, 129.1, 126.8, 126.4, 125.8, 122.5, 103.6, 100.1, 56.7, 55.6, 55.5, 51.4, 43.1, 40.3, 27.8; **HRMS** calcd for $C_{20}H_{24}N_1O_4$: 342.1705; found: 342.1695.

(*R*)-methyl 2-(2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3d).



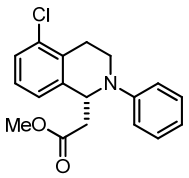
The synthesis of **3d** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (10% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (12.5 mg, 69% yield) in 86% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(minor) =8.5 min, t_R(major) = 14.0 min; $[\alpha]_D^{26}$ = + 30.6° (c = 0.5, DCM); **IR** (thin film, cm^{-1}) 2950 (w), 2901 (w), 2841 (w), 1734 (s, C=O), 1589 (m), 1494 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.33-7.30 (2H, m), 7.21-7.13 (4H, m), 6.86-6.83 (2H, m), 5.27 (1H, t, J = 7.1 Hz), 3.64 (3H, s), 3.62-3.53 (2H, m), 3.05 (1H, ddd, J = 15.9, 8.6, 5.9 Hz), 2.96 (1H, dd, J = 15.0, 7.2 Hz), 2.82 (1H, dt, J = 16.2, 5.0 Hz), 2.69 (1H, dd, J = 15.0, 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 171.7, 147.9, 137.1, 134.4, 132.0, 128.2, 127.2, 126.7, 126.3, 116.2, 110.2, 56.3, 51.2, 41.6, 41.3, 26.8; **HRMS** calcd for $C_{18}H_{19}Br_1N_1O_2$: 288.0388; found: 288.0221.

(*R*)-Methyl 2-(2-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3e).



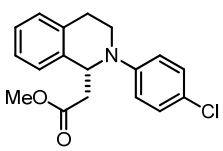
The synthesis of **3e** followed the general reaction procedure described above. The product was obtained in 44% yield and in 42% *ee*. The product yield is reported as a ^{1}H-NMR determined yield obtained using 2,5-dimethylfuran as internal standard. Chiral HPLC (CHIRALCEL OD-H, 3% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =14.3 min, t_R(minor) = 19.2 min; $[\alpha]_D^{26}$ = N/A; All spectral data in agreement with the racemic product (see below).

(*R*)-methyl 2-(5-chloro-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3f).



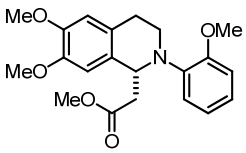
The synthesis of **3f** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (10% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (9.2 mg, 58% yield) in 92% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =4.7 min, t_R(minor) = 5.4 min; $[\alpha]_D^{26}$ = + 32.2° (c = 0.41, DCM); **IR** (thin film, cm^{-1}) 2950 (w), 2898 (w), 2841 (w), 1738 (s, C=O), 1599 (m), 1504 (m); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.26-7.22 (3H, m), 7.12-7.06 (2H, m), 7.00-6.98 (2H, m), 6.79 (1H, tt, J = 7.2, 1.1 Hz), 5.34 (1H, t, J = 7.1 Hz), 3.78 (1H, dddd, J = 13.6, 6.2, 3.3, 1.1 Hz), 3.62 (3H, s), 3.53 (1H, ddd, J = 13.6, 10.5, 4.8 Hz), 3.03 (1H, ddd, J = 17.1, 10.6, 6.1 Hz), 2.96 (1H, dd, J = 15.0, 7.7 Hz), 2.84 (1H, ddd, J = 17.4, 4.9, 3.4), 2.7 (1H, dd, J = 15.2, 6.4); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 171.7, 148.8, 139.6, 134.4, 132.7, 129.3, 127.7, 126.9, 125.2, 118.9, 115.5, 56.4, 51.8, 41.0, 40.5, 24.5; **HRMS** calcd for $C_{18}H_{19}Cl_1N_1O_2$: 316.1104; found: 316.1107.

(*R*)-methyl 2-(2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3g).



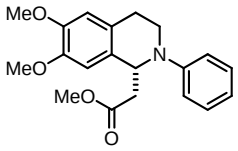
The synthesis of **3g** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (10% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (8.6 mg, 54% yield) in 77% *ee*. Chiral HPLC (CHIRALCEL OD-H, 3% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(minor) =8.0 min, t_R(major) = 13.3 min; $[\alpha]_D^{26}$ = + 33.1° (c = 0.32, DCM); **IR** (thin film, cm^{-1}) 2951 (w), 2917 (w), 2850 (w), 1736 (s, C=O), 1597 (m), 1497 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.21-7.17 (4H, m), 7.16-7.13 (2H, m), 6.90-6.88 (2H, m), 5.27 (1H, t, J = 7.1 Hz), 3.63 (3H, s), 3.62-3.53 (2H, m), 3.05 (1H, ddd, J = 16.1, 9.0, 5.9), 2.96 (1H, dd, J = 14.9, 7.3 Hz), 2.82 (1H, dt, J = 16.3, 4.8 Hz), 2.69 (1H, dd, J = 14.9, 6.8); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 171.8, 147.5, 137.1, 134.4, 129.1, 128.8, 127.1, 126.7, 126.3, 122.9, 115.8, 56.4, 51.8, 41.7, 41.3, 26.8; **HRMS** calcd for $C_{18}H_{19}Cl_1N_1O_2$: 316.1104; found: 316.1093.

(*R*)-Methyl 2-(6,7-dimethoxy-2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3h).



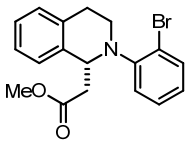
The synthesis of **3h** followed the general reaction procedure described above. The product was obtained in 11% yield and in 79% *ee*. The product yield is reported as a ^{1}H-NMR determined yield obtained using 2,5-dimethylfuran as internal standard. Chiral HPLC (CHIRALCEL OD-H, 3% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =16.9 min, t_R(minor) = 19.9 min; $[\alpha]_D^{26}$ = N/A; All spectral data in agreement with the racemic product (see below).

(*R*)-methyl 2-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3i).



The synthesis of **3i** followed the general reaction procedure described above. The product was obtained in 14% yield and in 67% *ee*. The product could not be separated from the thiourea catalyst via flash chromatography and thus is the yield reported as a ^{1}H-NMR determined yield obtained using 2,5-dimethylfuran as internal standard. Chiral HPLC (CHIRALPAK AD-H, 1% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =52.4 min, t_R(minor) = 56.4 min; $[\alpha]_D^{26}$ = N/A; All spectral data in agreement with the racemic product (see below).

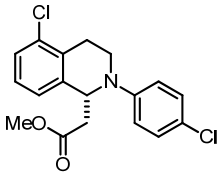
(*R*)-methyl 2-(2-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3j).



The synthesis of **3j** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (10% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (12.3 mg, 69% yield) in 97% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =5.2 min, t_R(minor) = 8.1 min; $[\alpha]_D^{26}$ = + 40.0° (c = 0.39, DCM); **IR** (thin film, cm^{-1}) 3026 (w), 2950 (w), 2837 (w), 1736 (s, C=O), 1599 (s), 1505 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.26-7.23

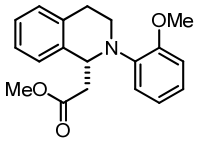
(2H, m), 7.19-7.12 (4H, m), 6.98-6.96 (2H, m), 6.76 (1H, t, J = 7.3 Hz), 5.33 (1H, t, J = 7.1 Hz), 3.66-3.62 (1H, m), 3.62 (3H, s), 3.59-3.54 (1H, m), 3.06 (1H, ddd, J = 16.1, 8.8, 5.6 Hz), 2.98 (1H, dd, J = 14.9, 7.1 Hz), 2.82 (1H, dt, J = 16.1, 4.9 Hz), 2.68 (1H, dd, J = 14.9, 7.1 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 171.9, 148.9, 137.5, 134.7, 129.3, 128.8, 127.0, 126.7, 126.2, 118.1, 114.6, 56.3, 51.7, 41.5, 41.3, 27.0; **HRMS** calcd for $C_{18}H_{19}Br_1N_1O_2$: 360.0599; found: 360.0608.

(*R*)-methyl 2-(5-chloro-2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3k).



The synthesis of **3k** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (7.5% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (8.4 mg, 48% yield) in 82% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =6.9 min, t_R(minor) = 7.7 min; $[\alpha]_D^{26}$ = + 25.0° (c = 0.32, DCM); **IR** (thin film, cm^{-1}) 2924 (w), 2855 (w), 1736 (s, C=O), 1596 (m), 1498 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.27-7.26 (1H, m), 7.20-7.17 (2H, m), 7.12 (1H, t, J = 7.8 Hz), 7.07 (1H, dd, J = 7.8, 0.7 Hz), 6.93-6.90 (2H, m), 5.28 (1H, t, J = 6.8 Hz), 3.73 (1H, dddd, J = 13.6, 6.1, 3.3, 0.7 Hz), 3.64 (3H, s), 3.53 (1H, ddd, J = 13.6, 10.5, 4.8 Hz), 3.01 (1H, ddd, J = 17.1, 10.7, 6.0 Hz), 2.94 (1H, dd, J = 15.2, 7.8 Hz), 2.84 (1H, dt, J = 16.9, 4.2), 2.7 (1H, dd, J = 15.2, 6.4 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 171.6, 147.5, 139.2, 134.4, 132.5, 129.1, 127.8, 127.0, 125.2, 123.7, 116.7, 56.5, 51.2, 41.0, 40.7, 24.3; **HRMS** calcd for $C_{18}H_{18}Cl_2N_1O_2$: 350.0715; found: 350.0714.

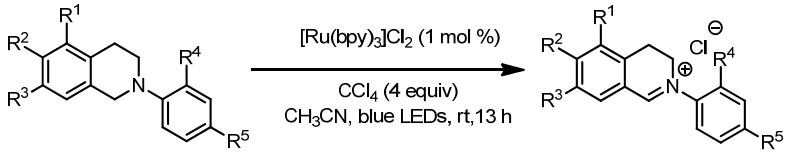
(*R*)-methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3l).



The synthesis of **3l** followed the general reaction procedure described above. The product was isolated via flash chromatography on silica gel (15% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless oil (9.7 mg, 62% yield) in 99% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =6.5 min, t_R(minor) = 10.4 min; $[\alpha]_D^{26}$ = + 41.8° (c = 0.39, DCM); **IR** (thin film, cm^{-1}) 2949 (w), 2832 (w), 1737 (s, C=O), 1594 (w), 1501 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.18-7.15 (3H, m), 7.14-7.10 (1H, m), 6.98 (1H, ddd, J = 9.0, 7.1, 2.0 Hz), 6.91-6.83 (3H, m), 5.32 (1H, dd, J = 7.7, 5.7 Hz), 3.86 (3H, s), 3.51-3.49 (2H, m), 3.46 (3H, s), 3.05-2.98 (1H, m), 2.86 (1H, J = 14.9, 7.8 Hz), 2.74 (1H, dt, J = 16.6, 2.9 Hz), 2.61 (1H, dd, J = 14.9, 5.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 172.3, 153.1, 139.7, 138.2, 134.4, 129.2, 126.8, 126.5, 125.9, 123.2, 121.65, 120.8, 112.0, 56.2, 55.6, 51.4, 42.5, 40.4, 27.8; **HRMS** calcd for $C_{19}H_{22}N_1O_3$: 312.1600; found: 312.1587.

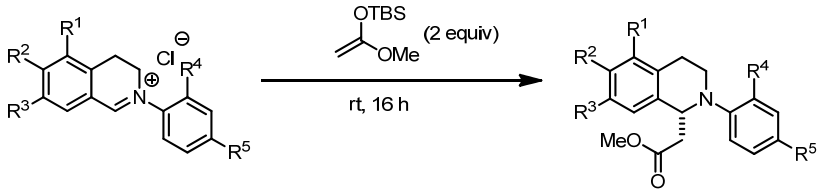
6. Generation of Racemic Reference Compounds

Racemic material of all products was prepared as reference for *ee* determination using HPLC. The transformation was performed in two steps; visible light mediated photoredox activation conducted at room temperature followed by nucleophillic addition also conducted at room temperature.



Step 1. Oxidative activation:

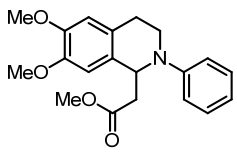
A mixture of tetrahydroisoquinoline (0.05 mmol), $[Ru(bpy)_3]Cl_2$ (0.32 mg, 1 mol%) and MeCN (0.5 mL) was degassed by three cycles of freeze-pump-thaw. CCl_4 (19.4 µL, 0.2 mmol, 4 equiv) was added and the mixture was stirred over night under an inert atmosphere at room temp while irradiated by blueLEDs (at a distance of approximately 10 cm so that the reaction mixture did not heat up during the reaction). Full conversion of the tetrahydroisoquinoline was ensured by either TLC or analyzing an aliquot of the reaction mixture with ^{1}H-NMR.



Step 2: Nucleophilic addition:

To the reaction mixture with the so formed iminium species was added the nucleophile, 1-(tert-butyldimethylsilyloxy)-1-methoxyethylene (21.8 µL, 0.1 mmol, 2 equiv). The reaction mixture was stirred over night (16 h) and was then filtered through a plug of silica using DCM (3 x 2 mL) and a mixture of DCM/Et_2O (1:1, 3 x 2 mL). The product was isolated by Flash chromatography using a mixture of Et_2O in hexanes as eluent.

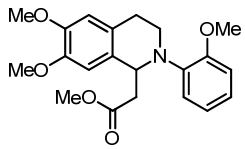
Methyl 2-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (*rac*-3i).



The reaction was performed following the general conditions described above. **IR** (thin film, cm^{-1}) 2952 (w), 2849 (w), 1736 (s, C=O), 1599 (w), 1516 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.25 (2H, dd, J = 9.1, 7.1 Hz), 6.98 (2H, d, J = 8.1 Hz), 6.77 (1H, t, J = 7.2 Hz), 6.66 (1H, s), 6.61 (1H, s), 5.25 (1H, t, J = 7.0 Hz), 3.85 (3H, s), 3.84 (3H, s), 3.70-3.47 (2H, m), 3.63 (3H, s), 3.03-2.94 (2H, m), 2.73-2.66

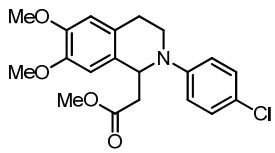
(2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 172.2, 149.0, 148.0, 147.3, 129.33, 129.25, 126.6, 118.3, 115.0, 111.5, 109.7, 56.1, 56.0, 55.9, 51.7, 41.4, 41.2, 26.4; **HRMS** calcd for $C_{20}H_{24}NO_4$: 342.1705; found: 342.1707.

Methyl 2-(6,7-dimethoxy-2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (*rac*-3h).



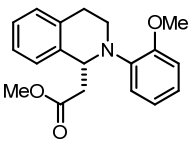
The reaction was performed following the general conditions described above. **IR** (thin film, cm^{-1}) 2950 (w), 2835 (w), 1734 (s, C=O), 1593 (w), 1514 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 6.98 (1H, ddd, J = 8.1, 7.1, 1.7 Hz), 6.90-6.83 (3H, m), 6.66 (1H, s), 6.58 (1H, s), 5.21 (1H, t, J = 6.9 Hz), 3.86 (3H, s), 3.85 (3H, s), 3.85 (3H, s), 3.49-3.46 (2H, m), 3.47 (3H, s), 2.92 (1H, ddd, J = 16.6, 10.5, 7.1 Hz), 2.84 (1H, dd, J = 14.9, 7.6 Hz), 2.64-2.59 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 172.6, 153.0, 147.8, 147.3, 139.7, 130.0, 126.3, 123.2, 121.6, 120.8, 112.0, 111.6, 109.5, 56.0, 55.8, 55.7, 51.4, 42.5, 40.5, 27.2; **HRMS** calcd for $C_{21}H_{26}NO_5$: 372.1811; found: 372.1810.

Methyl 2-(2-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (*rac*-3e).



The reaction was performed following the general conditions described above. **IR** (thin film, cm^{-1}) 2956 (w), 2951 (w), 2836 (w), 1733 (s, C=O), 1595 (w), 1498 (s); **^{1}H NMR** (400 MHz, $CDCl_3$, 20 °C) **δ** 7.19-7.16 (2H, m), 6.91-6.88 (2H, m), 6.64 (2H, s), 6.61 (2H, s), 5.18 (1H, t, J = 7.0 Hz), 3.85 (3H, s), 3.84 (3H, s), 3.64 (3H, s), 3.64-3.59 (1H, m), 3.54-3.49 (1H, m), 2.98 (1H, ddd, J = 16.1, 9.8, 5.6 Hz), 2.93 (1H, dd, J = 14.9, 7.3 Hz), 2.72-2.66 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$, 20 °C) **δ** 172.0, 148.1, 147.7, 147.4, 129.0, 128.9, 126.4, 123.1, 116.2, 111.5, 109.6, 56.2, 56.0, 55.9, 51.8, 41.5, 41.2, 26.2; **HRMS** calcd for $C_{20}H_{23}ClNO_4$: 376.1316; found: 376.1317.

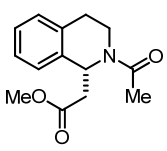
(*R*)-Methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3l).



The reaction was performed following the general conditions described above with the following exceptions; the reaction was performed on a 0.25 mmol scale and the enantioselective addition was conducted at – 40 °C for a reaction time of 48 h. The product was isolated via flash chromatography on silica gel (15% diethyl ether in hexanes), using I_2 for TLC visualization, as a colorless semisolid (48.3 mg, 62% yield) in 95% *ee*. Chiral HPLC (CHIRALPAK AD-H, 2% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(major) =6.5 min, t_R(minor) = 10.4 min.

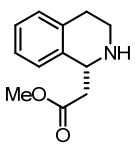
7. Determination of Absolute Configuration

(*R*)-methyl 2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (7)[7]



A solution of CAN (169.9 mg, 0.31 mmol, 5 eq) and H_2O (3 mL) was added to a solution of $[Fe(bpy)_3](PF_6)_2$ (252.4 mg, 0.31 mmol, 5 equiv) in MeCN (3 mL). The resulting blue solution was added dropwise to a solution of methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (19.3 mg, 0.062 mmol), MeCN (2 mL) and water (1 mL) at room temperature. The reaction immediately turned red. The reaction was allowed to stir for 45 minutes and was then quenched with sat. Na_2CO_3 (10 mL). The resulting mixture was extracted with EtOAc (3 x 15 mL) and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The so obtained solid crude was dissolved in a minimum amount of DCM (approx. 1 mL) followed by addition of Et_2O (5 mL) to precipitate the metal salts. The crude dearylated product was obtained by filtration using a cotton plugged pipette followed by evaporation of the solvent.

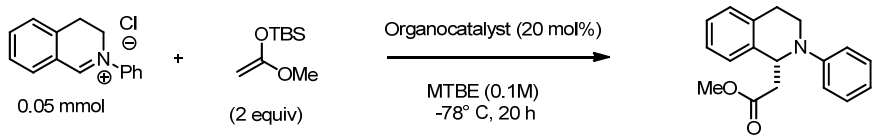
AcCl (7 µL, 0.093 mmol, 1.5 equiv) was added to a solution of the crude amine and pyridine (3 mL) at ambient temperature. The reaction mixture was stirred for 2 h and then quenched with H_2O (10 mL). The mixture was extracted with DCM (10 times 3 mL) and the combined organic phases was dried over Na_2SO_4 and then concentrated in vacuo. The crude was triturated with Et_2O and the suspension was allowed to rest at -18 °C over night. The solvent was decanted and concentrated in vacuo to give the acetylated product as a white solid in 87% yield (13 mg) and 95% *ee*. Chiral HPLC (CHIRALCEL OD-H, 15% IPA in hexanes, 1.0 mL/min, **λ** = 254 nm) t_R(minor) =6.7 min, t_R(major) = 9.6 min; $[\alpha]_D^{26}$ = + 32.7° (c = 0.36, DCM). All spectral data was in accordance with published data.

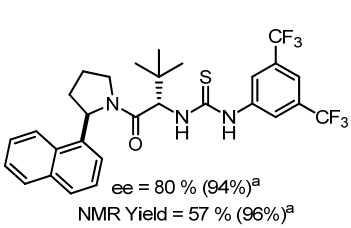


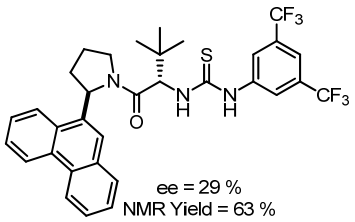
(*R*)-methyl 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetate was isolated from an aliquot of the crude reaction mixture in the oxidative dearylation of (*R*)-Methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (**6**) utilizing reverse phase chromatography (GILSON PLC 2020 system with a SunFire prep C18 ODB™ column). Comparing with the literature $[\alpha]_D^{26}$ value for (+)-methyl (*R*)-2-(1,2,3,4-tetrahydroisoquinolin-1-yl)acetate confirmed the absolute configuration of the tetrahydroisoquinoline derivative to be *R*-enantiomer.[8] $[\alpha]_D^{26}$ = + 40.7° (c = 0.1, DCM, 95% *ee*). Literature: $[\alpha]_D^{26}$ = + 95.2° (c = 1.0, $CHCl_3$, 95% *ee*)

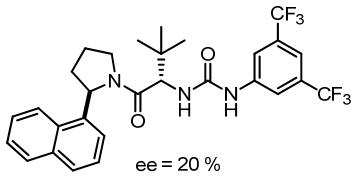
8. Additional Catalyst Optimization Data

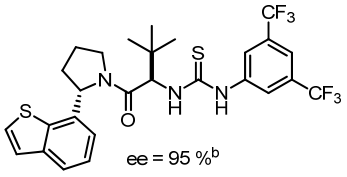
Enantioselectivities of selected additional catalysts in the enantioselective oxidative Mannich reaction following the general reaction conditions at -78˚C.

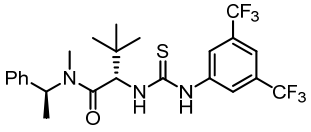


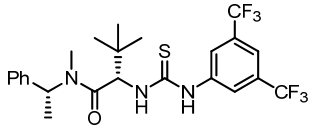

ee = 80 % (94%)[a]
NMR Yield = 57 % (96%)[a]

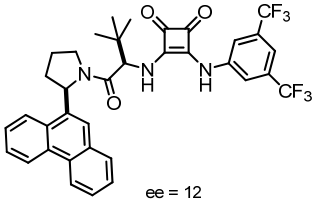

ee = 29 %
NMR Yield = 63 %

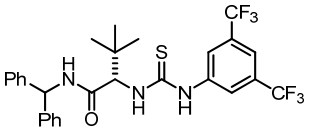

ee = 20 %
NMR Yield = 67 %

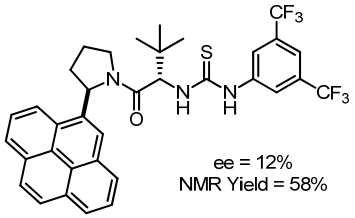

ee = 95 %[b]
NMR Yield = 70 %

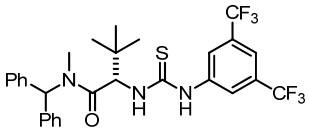

ee = 3 %
NMR Yield = 72 %

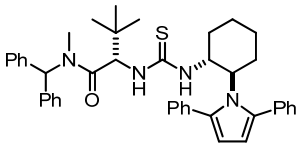

ee = 16 %
NMR Yield = 70 %

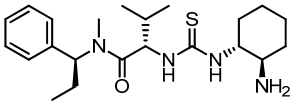

ee = 12
NMR Yield = 87 %

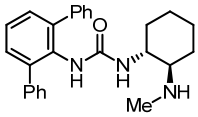

ee = 10 %
NMR Yield = 75 %

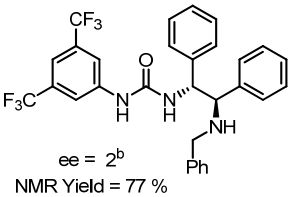

ee = 12%
NMR Yield = 58%

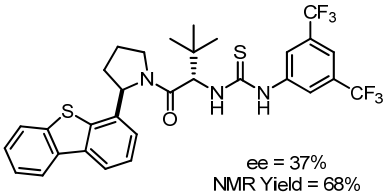

ee = 11 %
NMR Yield = 74 %


ee = 4 %
NMR Yield = 72 %


ee = 2 %
NMR Yield = 77 %

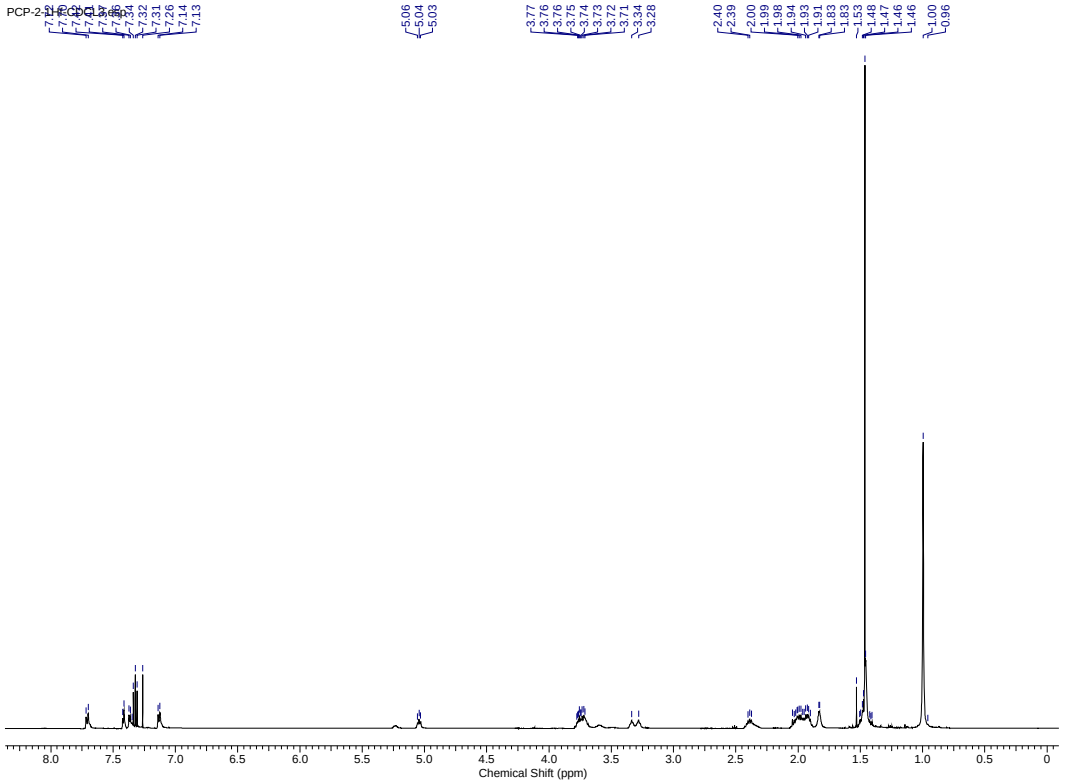

ee = 2 %
NMR Yield = 62 %

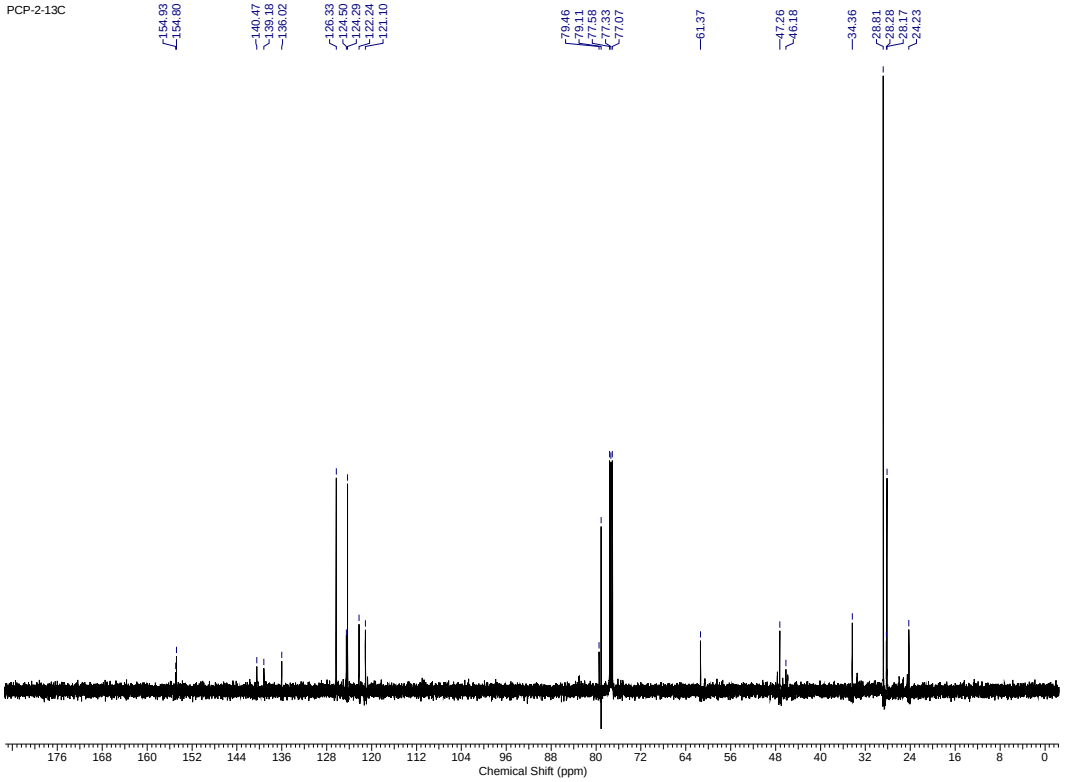

ee = 2[b]
NMR Yield = 77 %


ee = 37%
NMR Yield = 68%

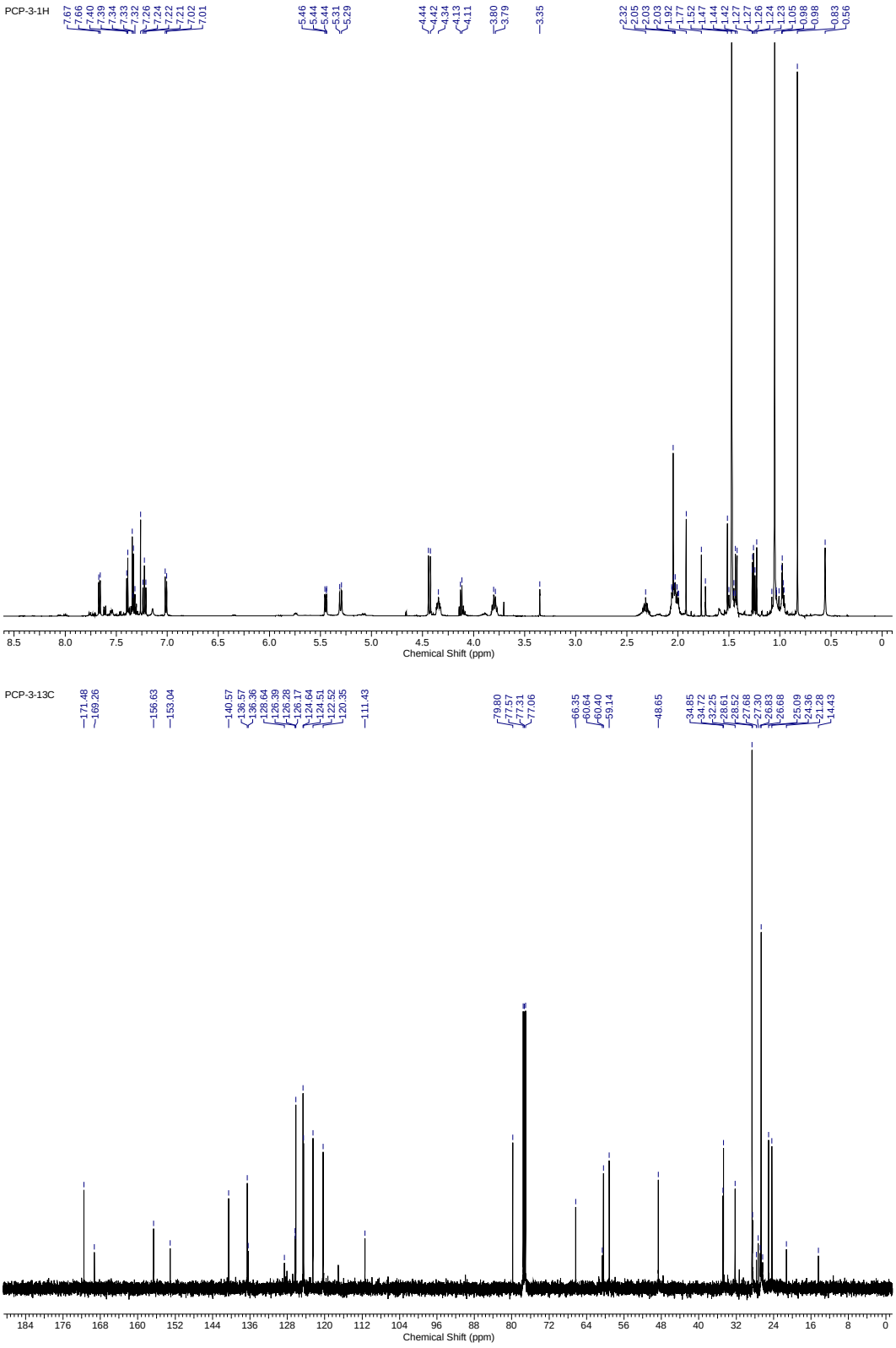
9. NMR Spectra and HPLC Traces

(R)-*tert*-butyl 2-(benzothiophen-7-yl)pyrrolidine-1-carboxylate (S2)

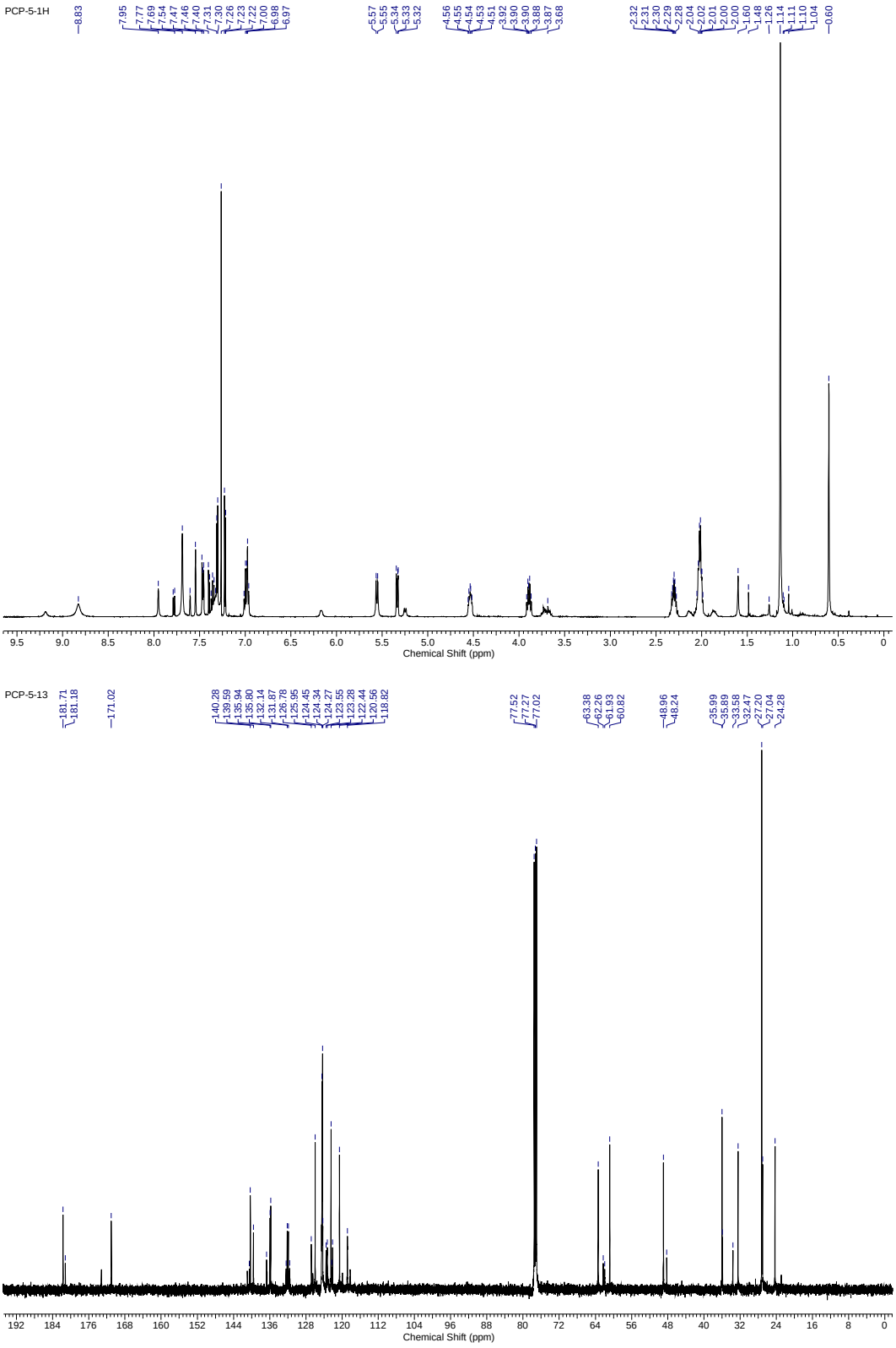




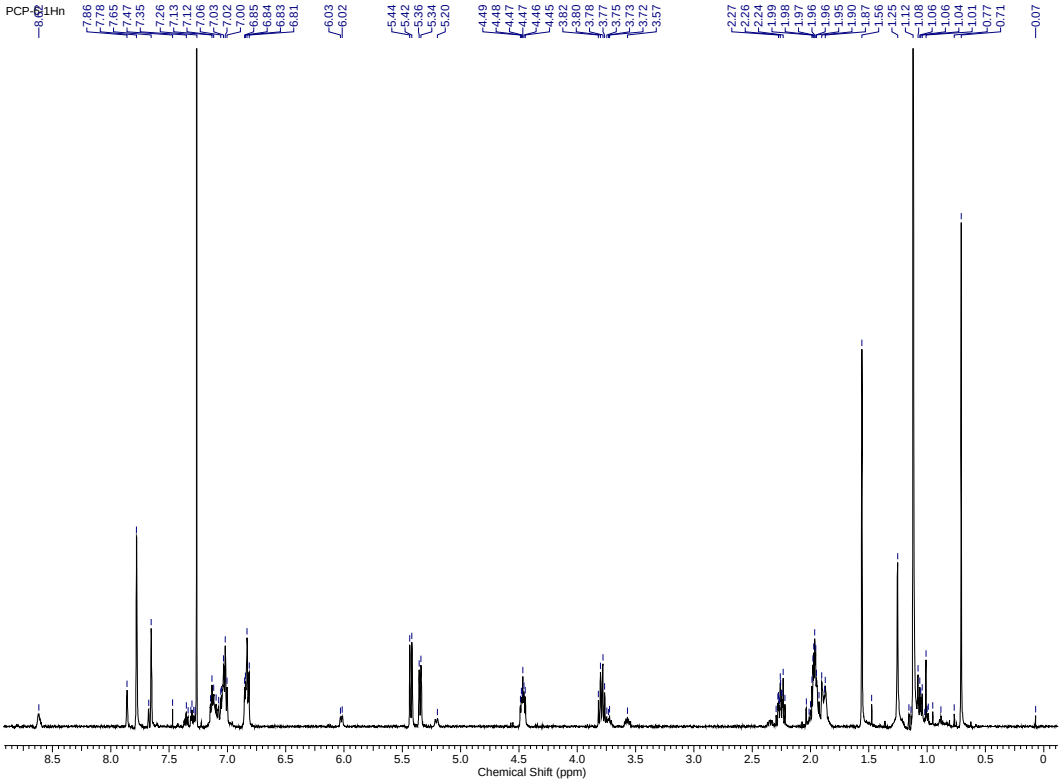
tert-butyl((S)-1-((R)-2-(benzothiophen-7-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl) carbamate (S3)

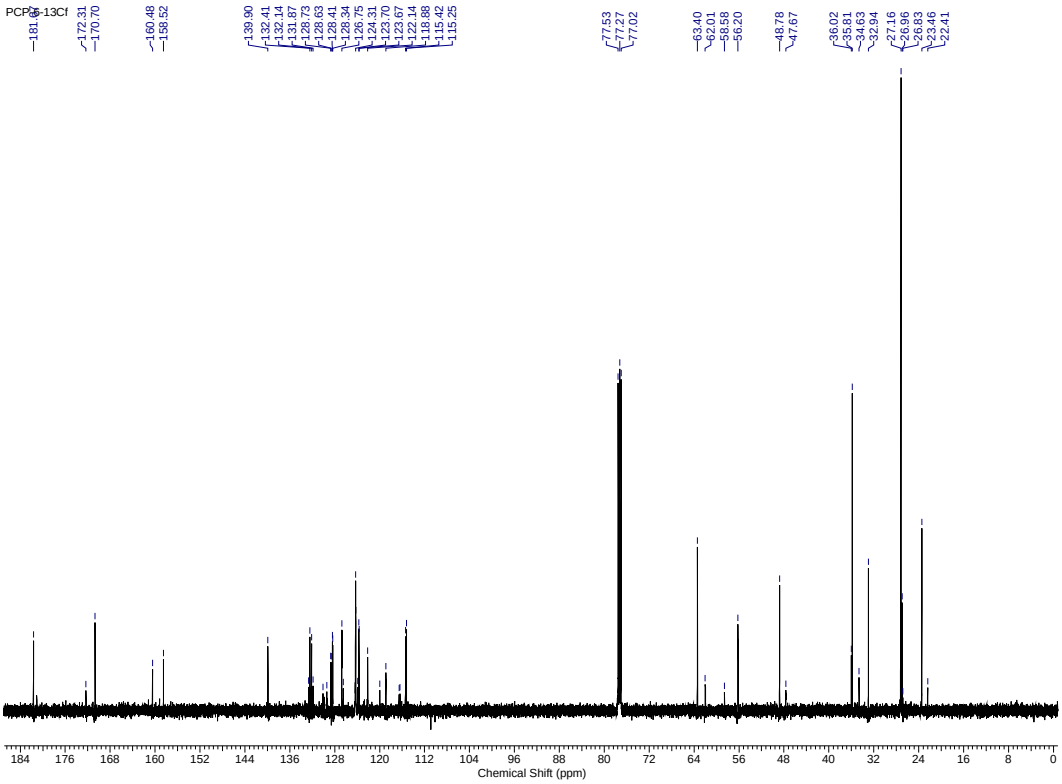


1-((S)-1-((R)-2-(benzothiophen-7-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (5g).

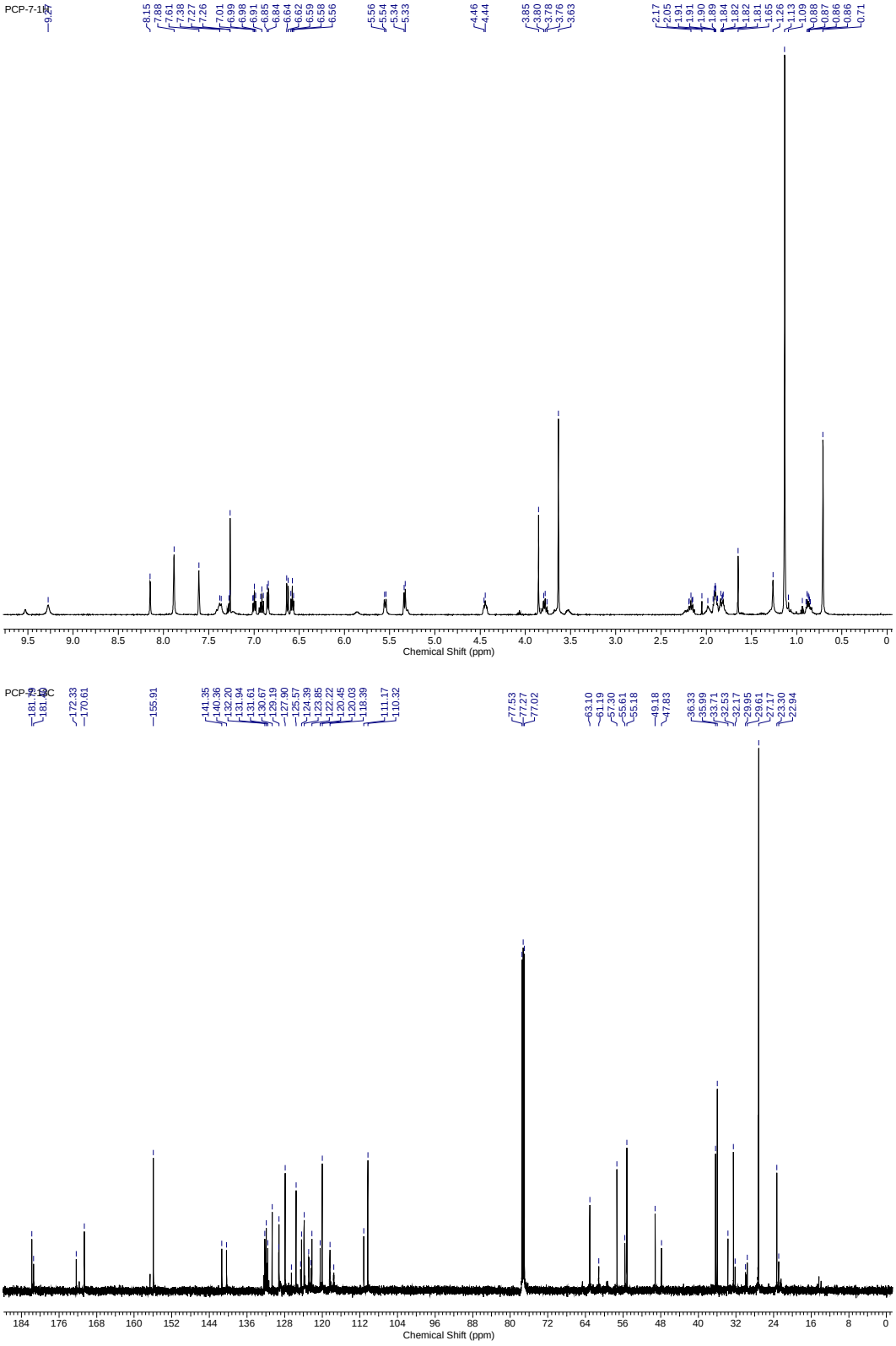


1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(2-fluorophenyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (5e).

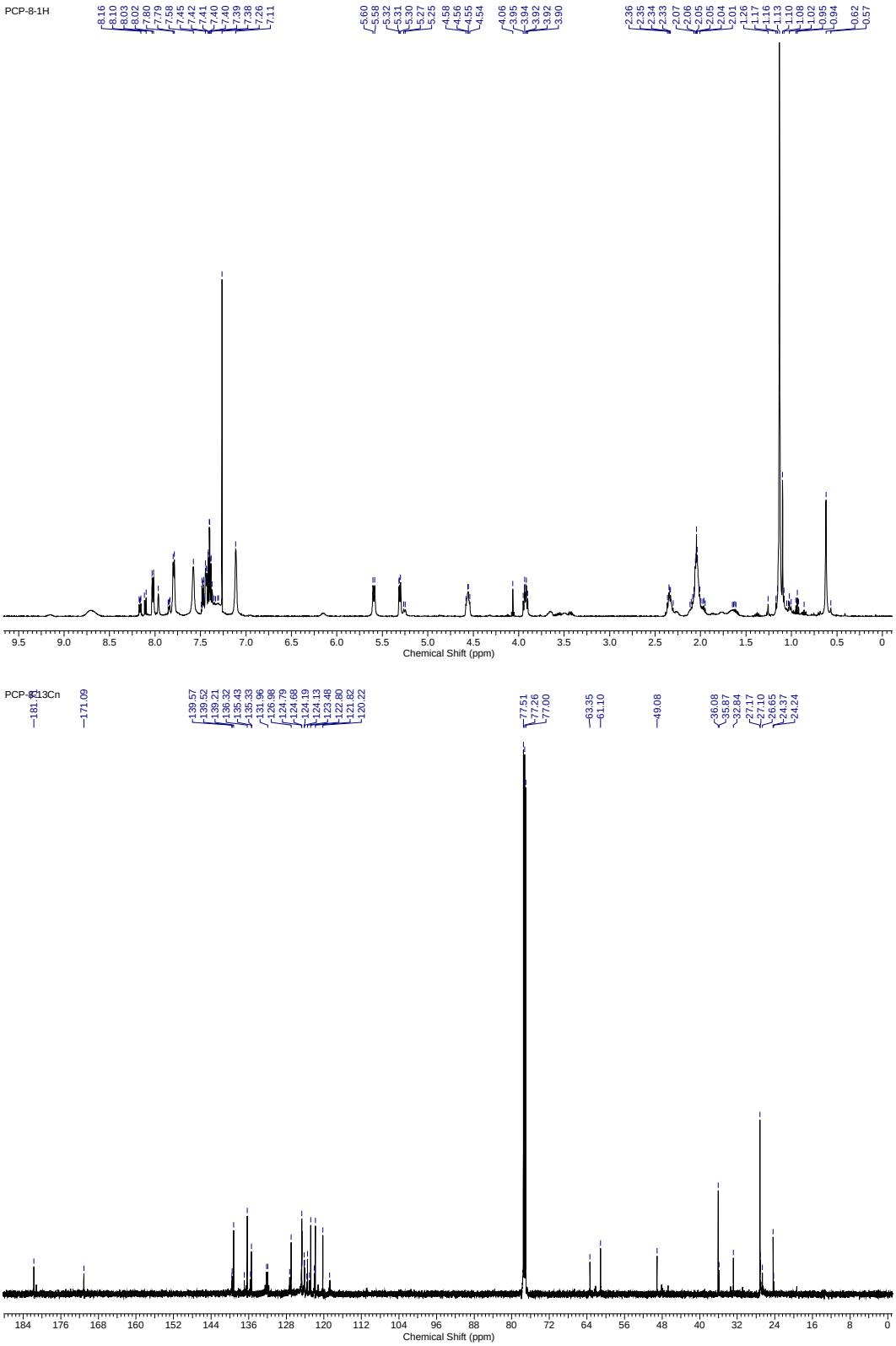




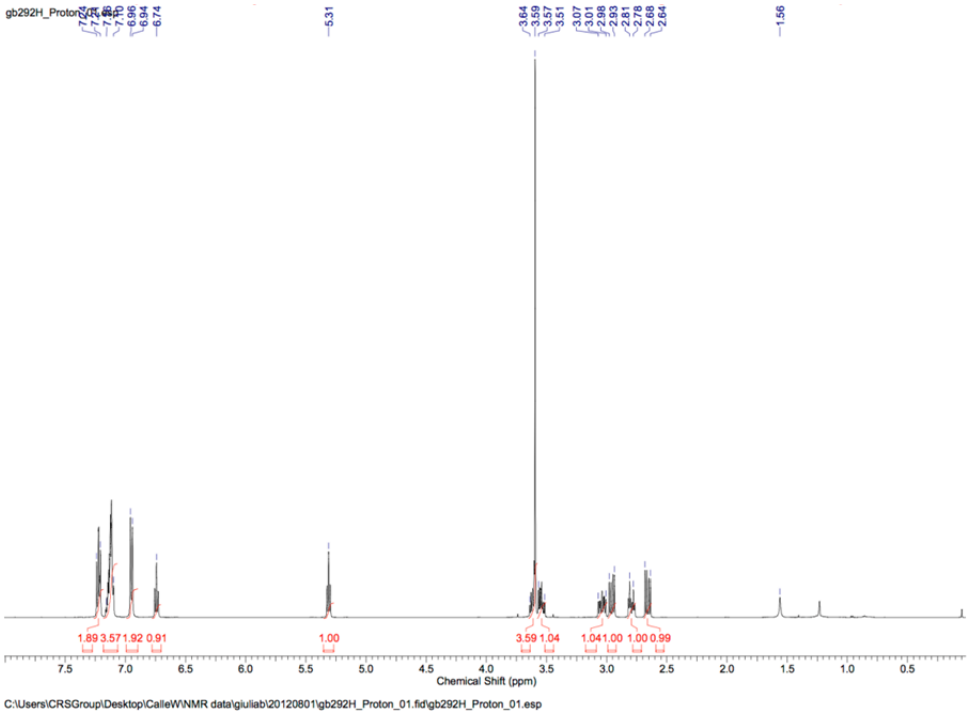
1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(2-methoxyphenyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (5f).

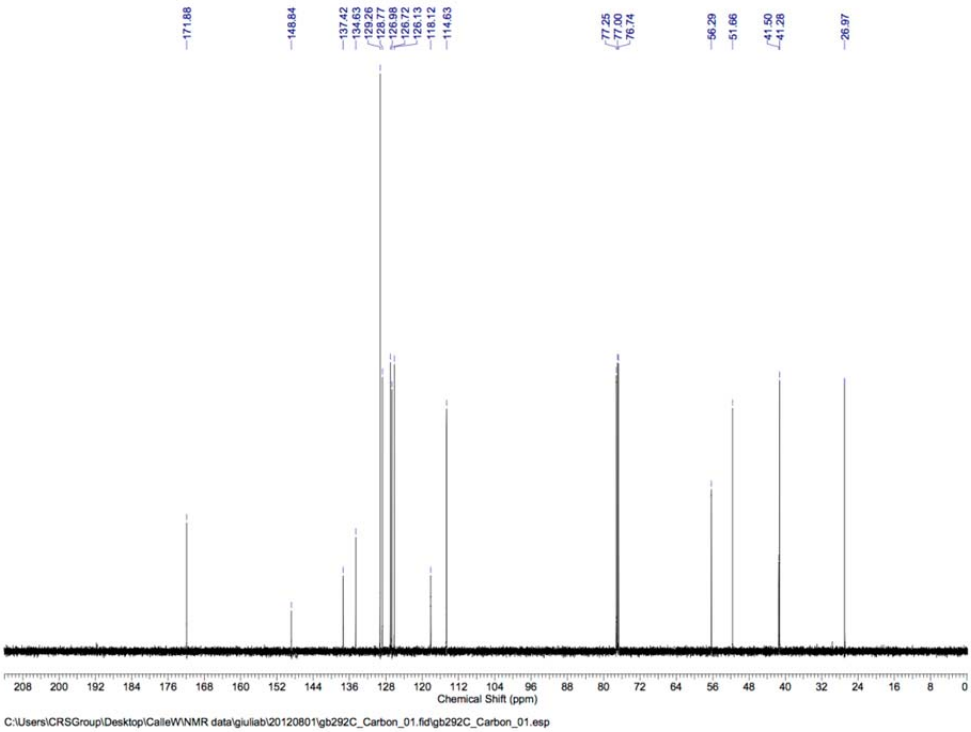


1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-1-((R)-2-(dibenzo[b,d]thiophen-4-yl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)thiourea (S4).

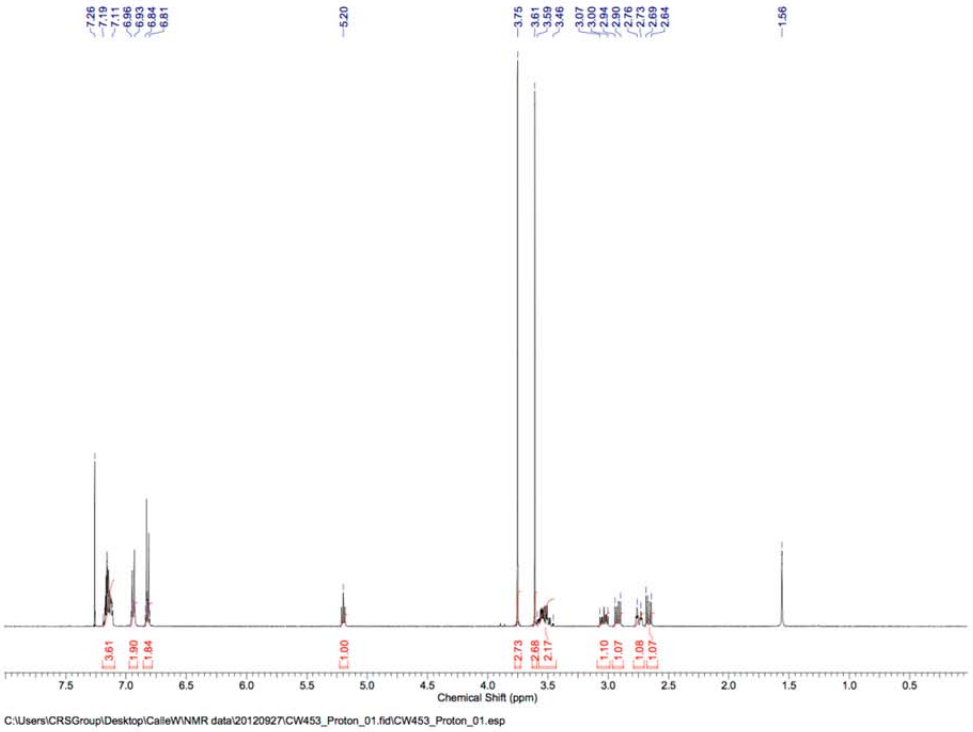


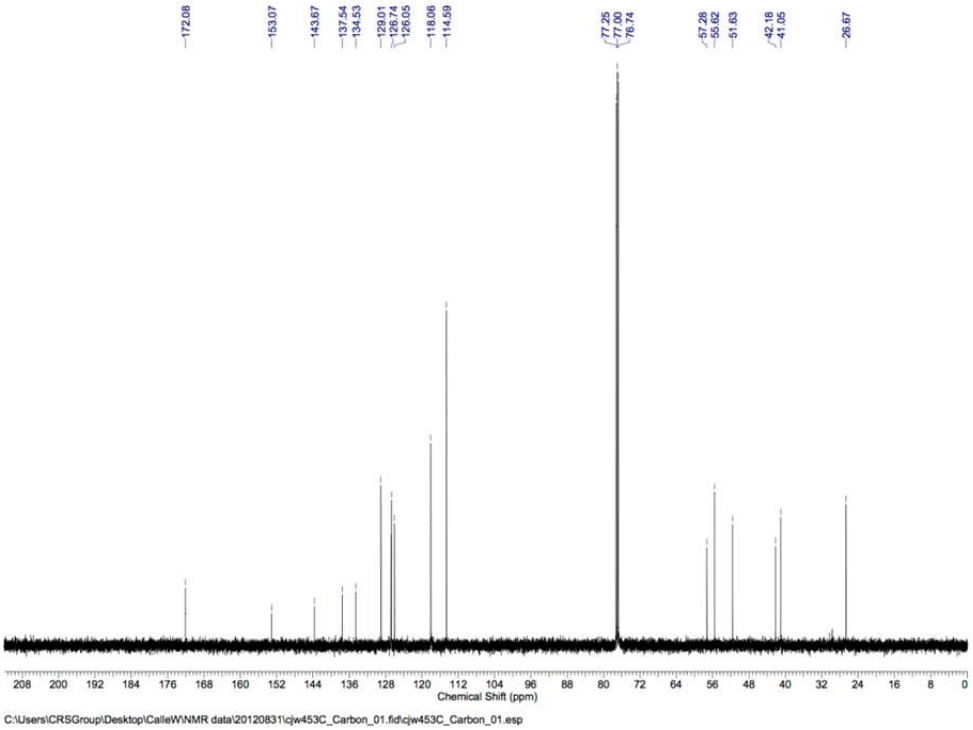
(*R*)-methyl 2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3a).



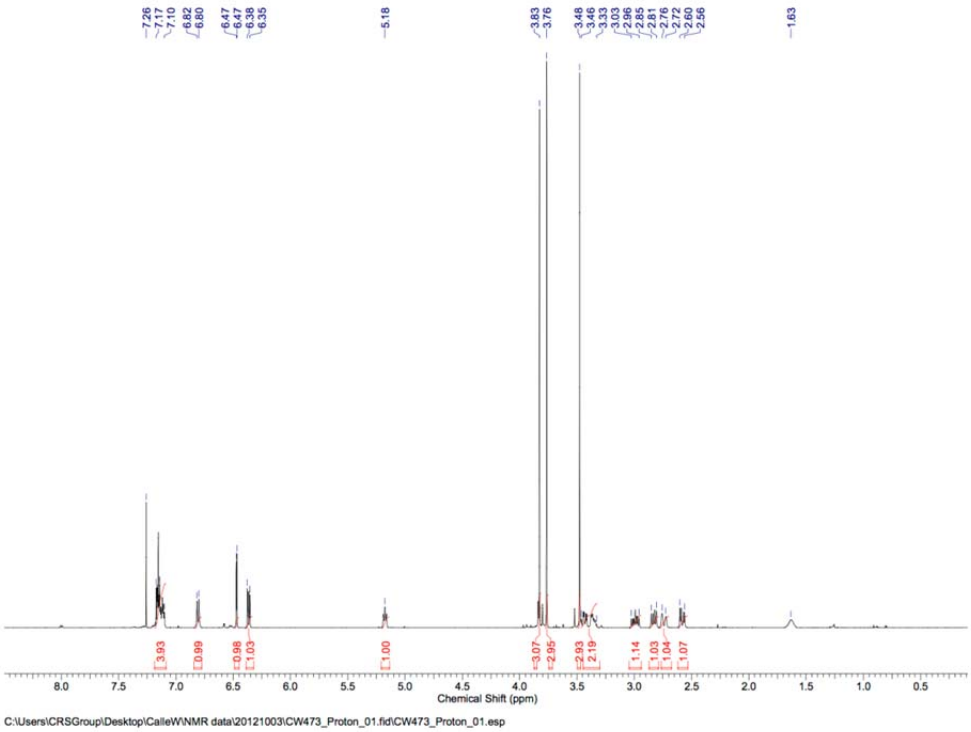


(*R*)-methyl 2-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3b).

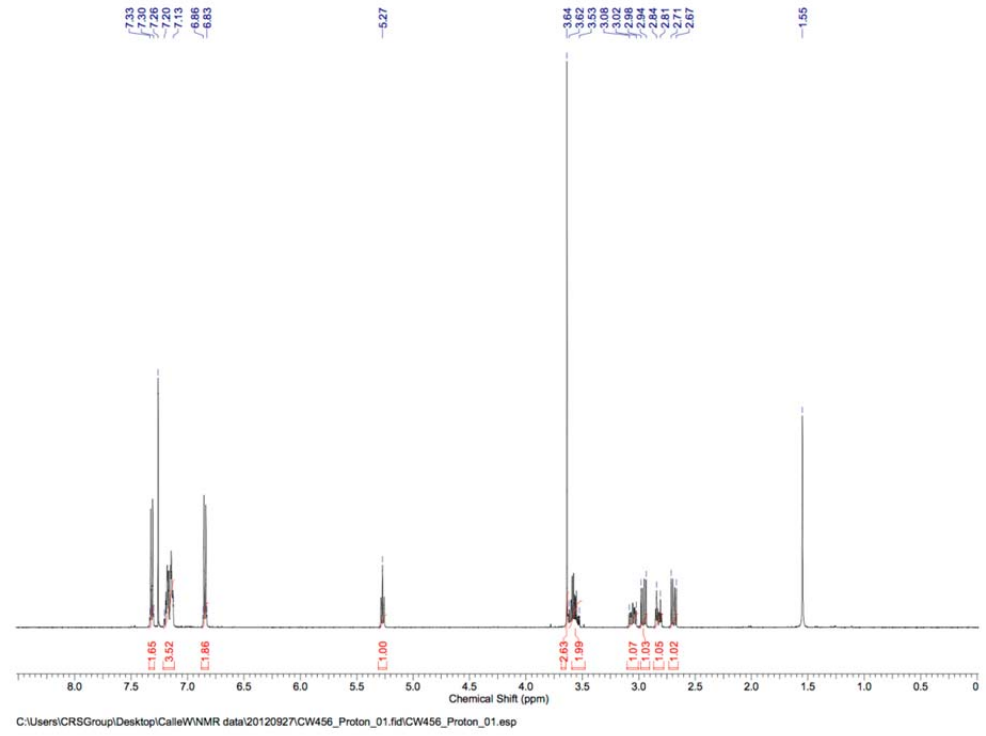


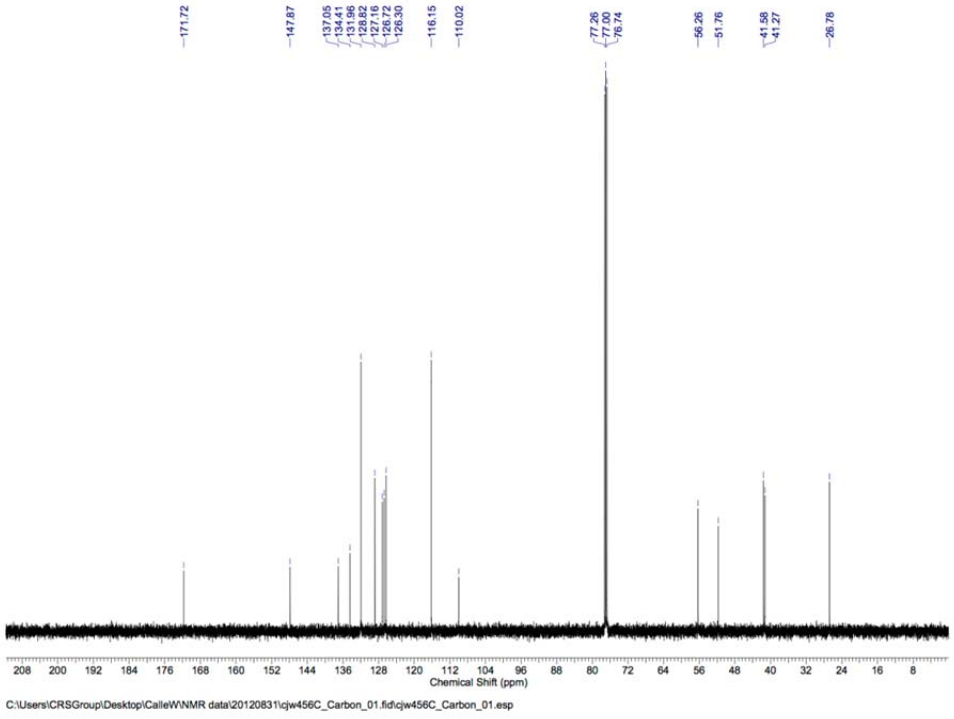


(*R*)-methyl 2-(2-(2,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3c).

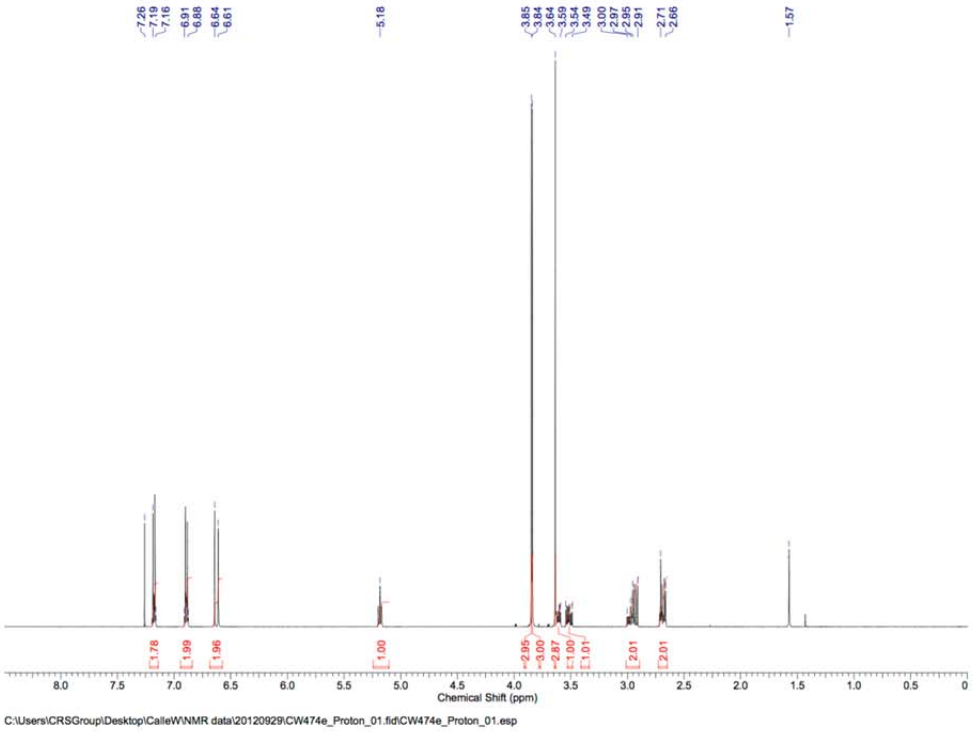


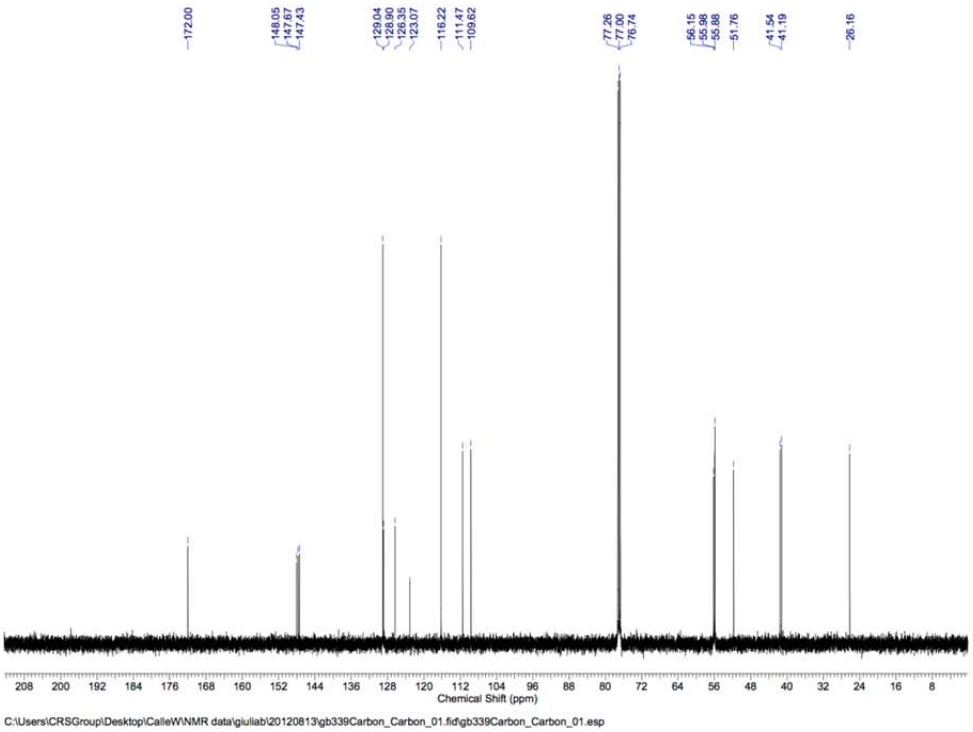
(*R*)-methyl 2-(2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3d).



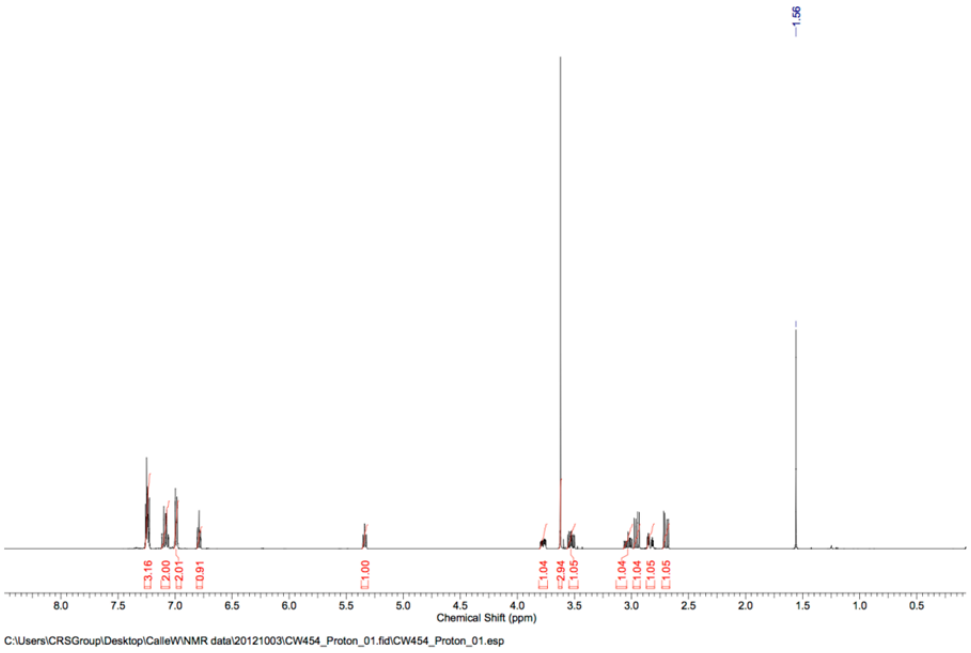


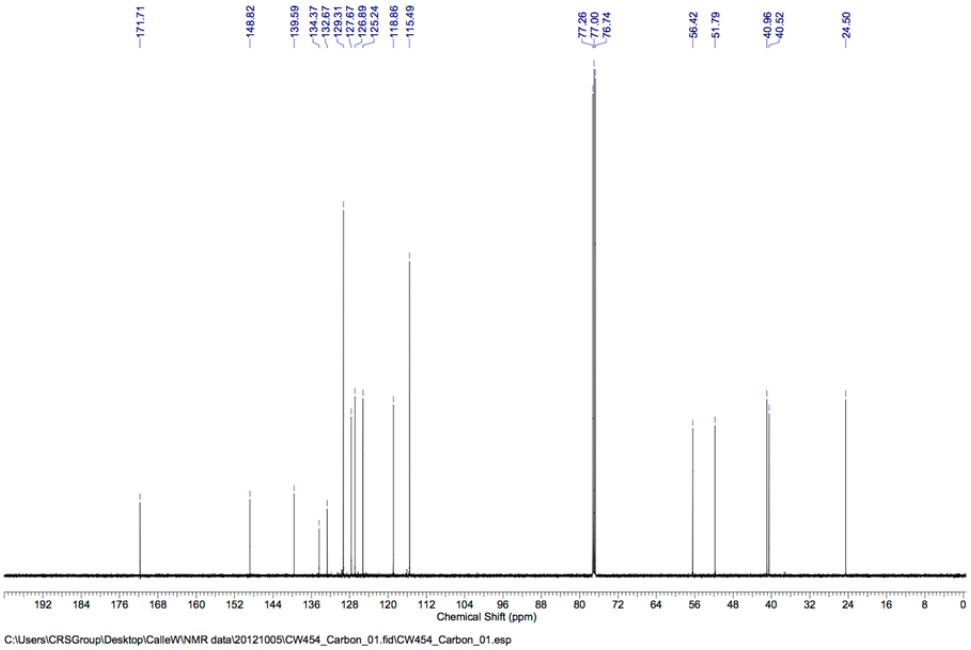
(*R*)-Methyl 2-(2-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3e).



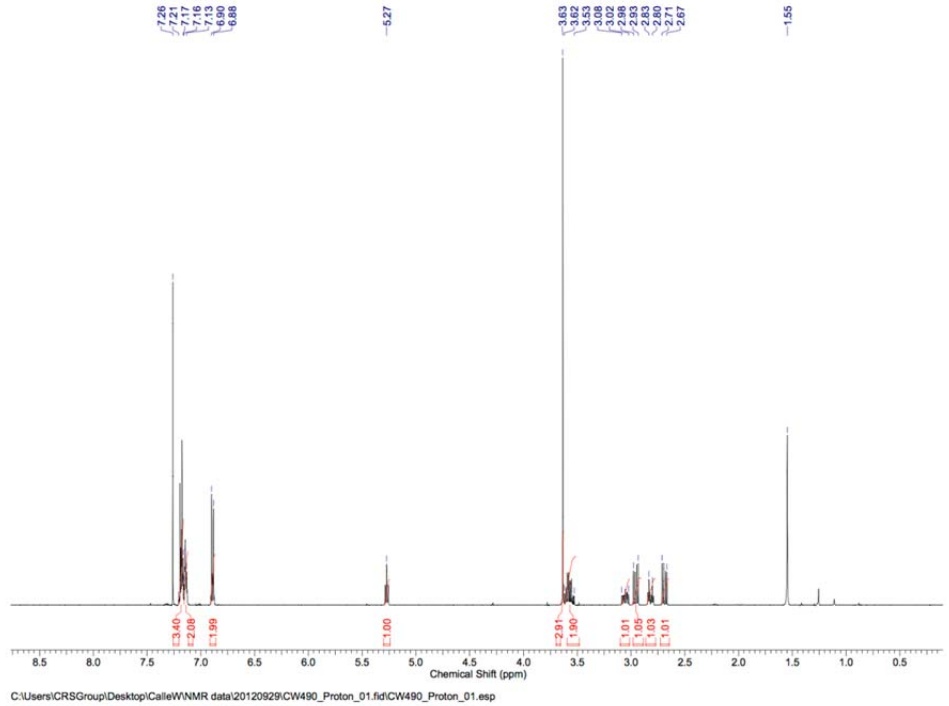


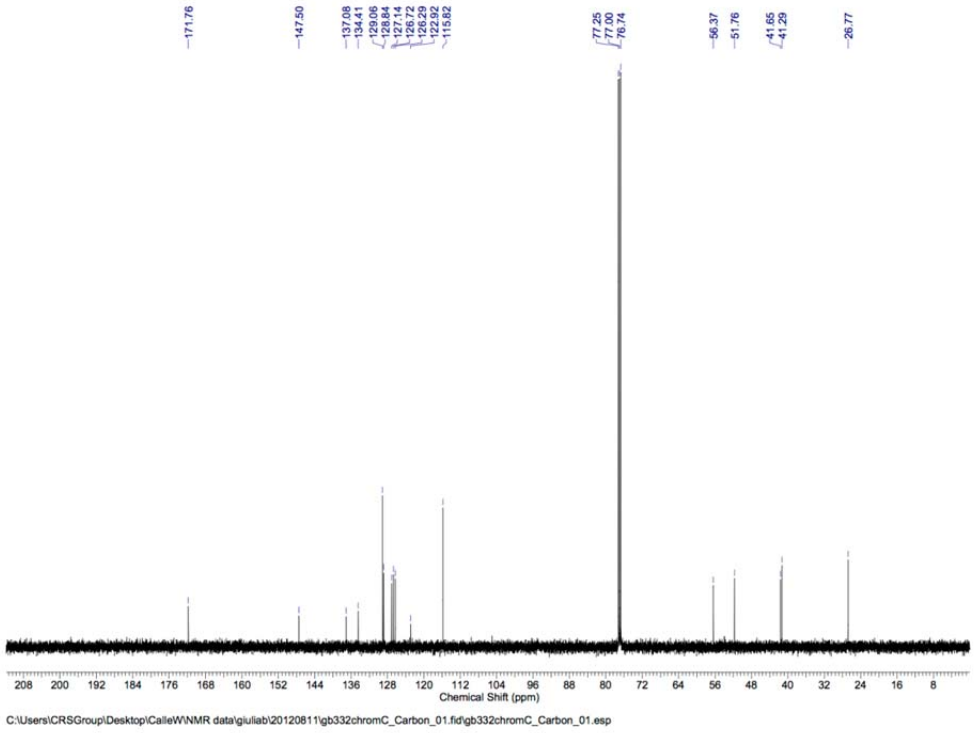
(*R*)-methyl 2-(5-chloro-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3f).



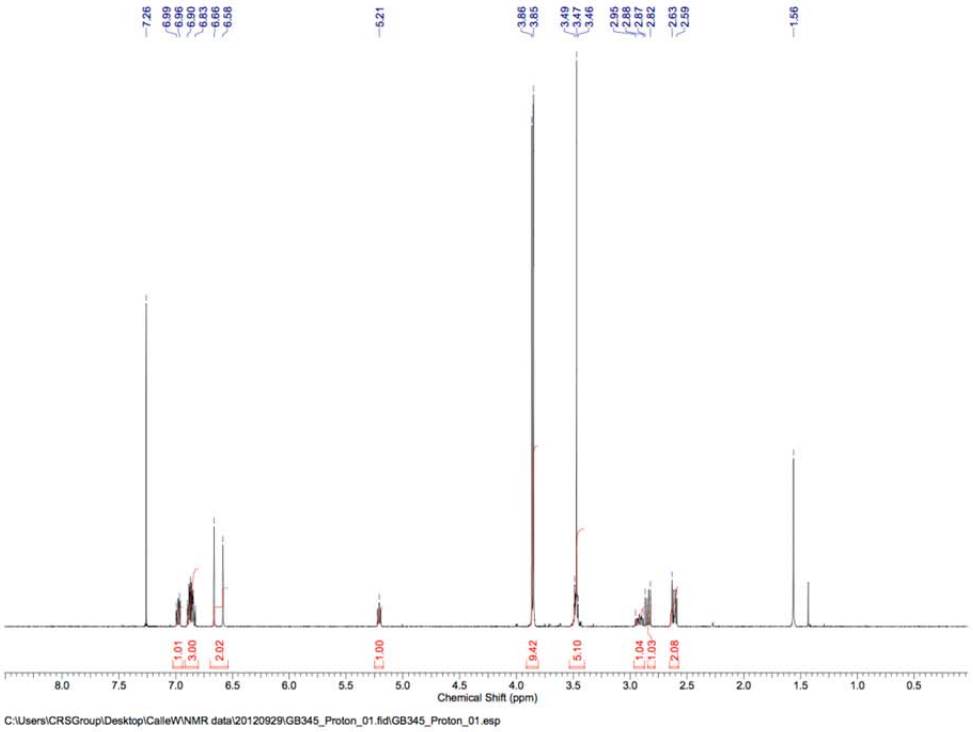


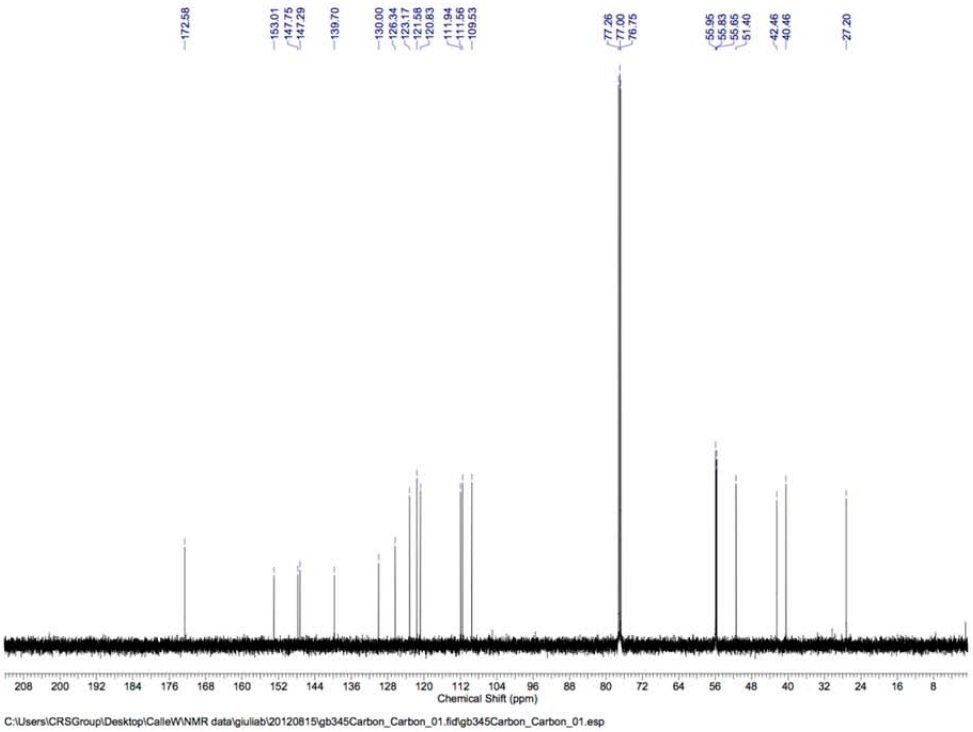
(*R*)-methyl 2-(2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3g).



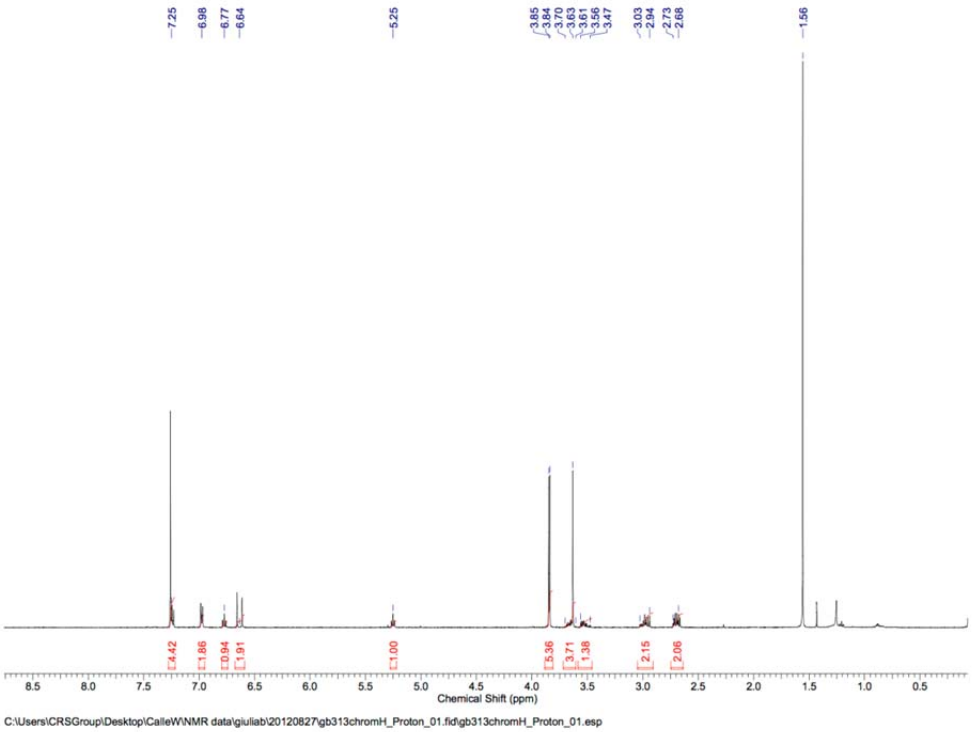


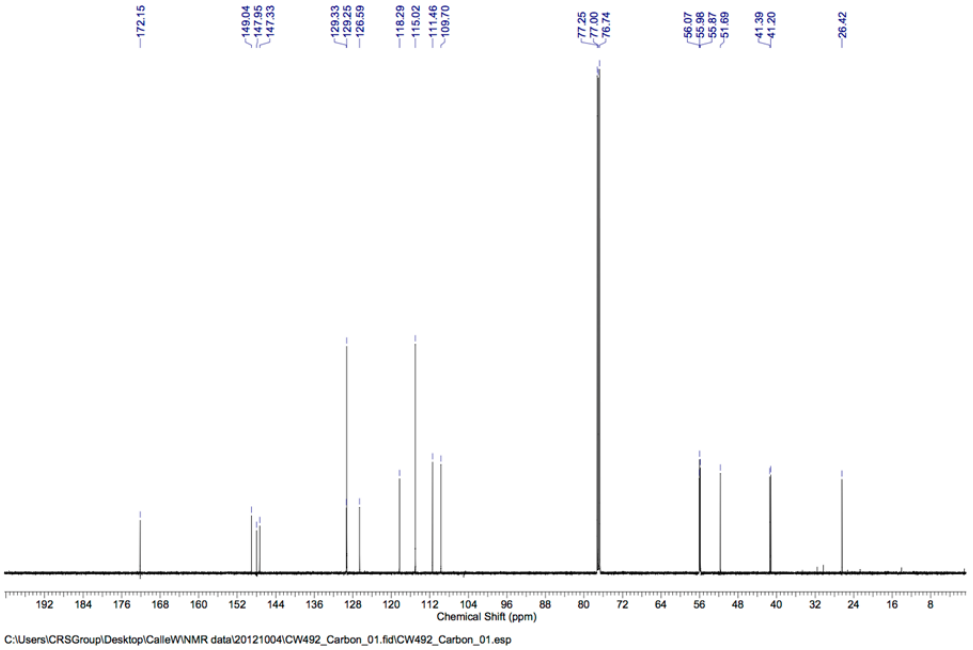
(*R*)-Methyl 2-(6,7-dimethoxy-2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3h).



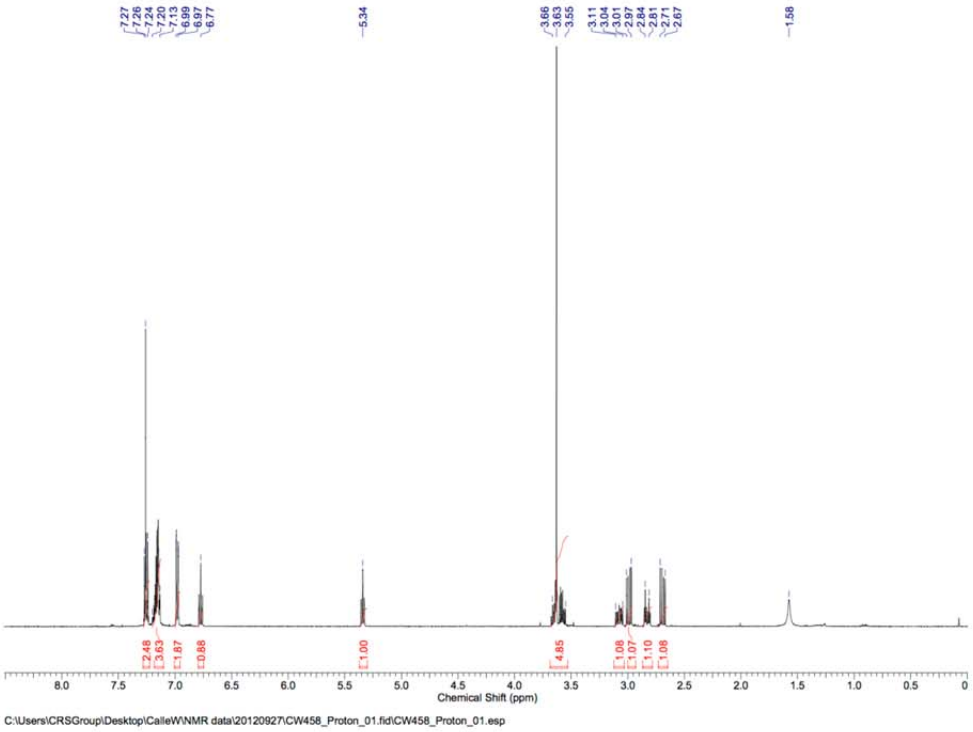


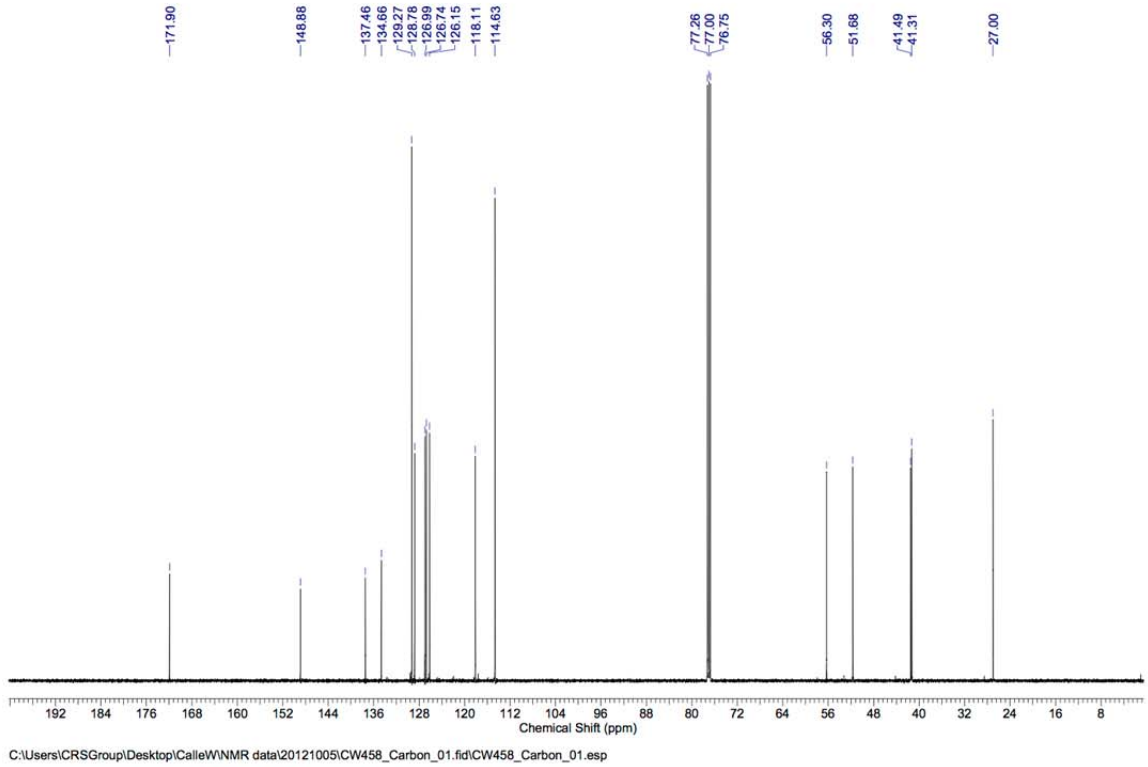
(*R*)-methyl 2-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3i).



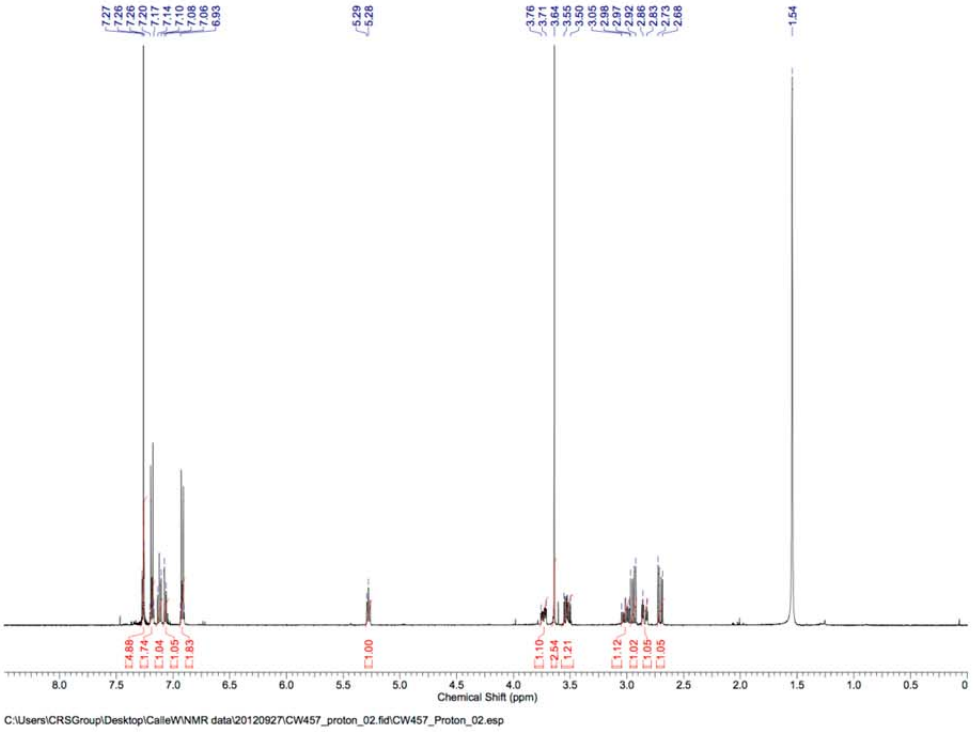


(*R*)-methyl 2-(2-(2-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3j).

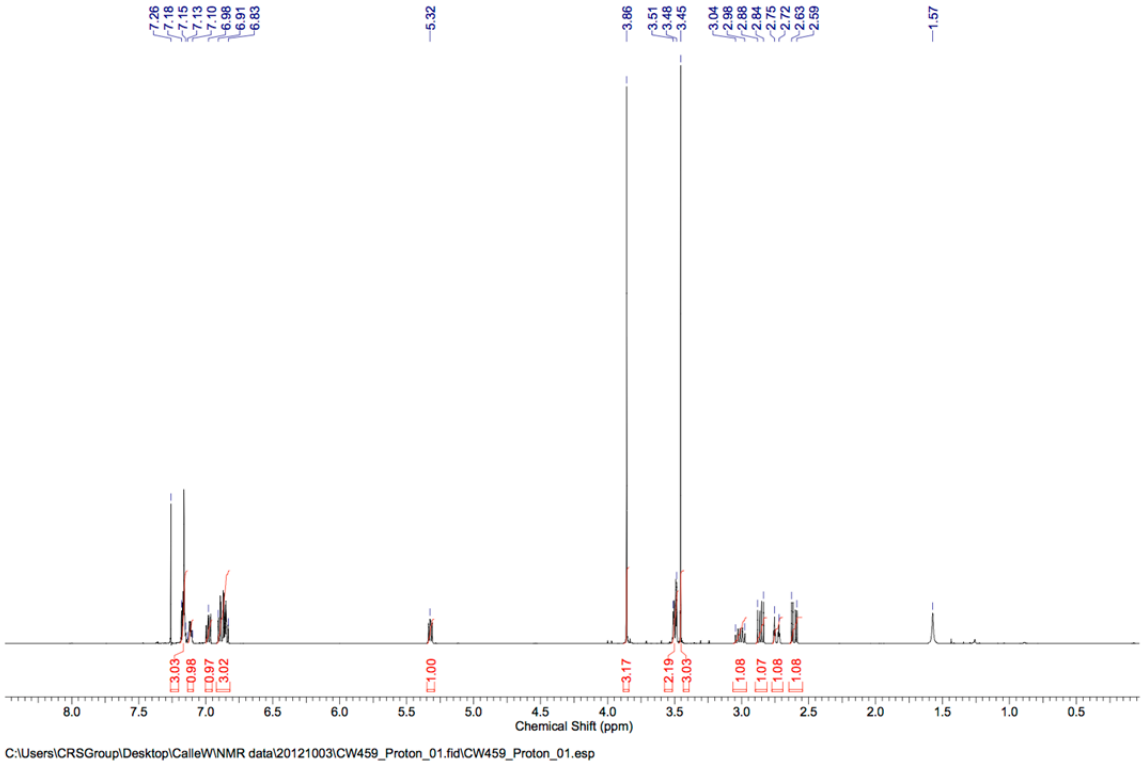


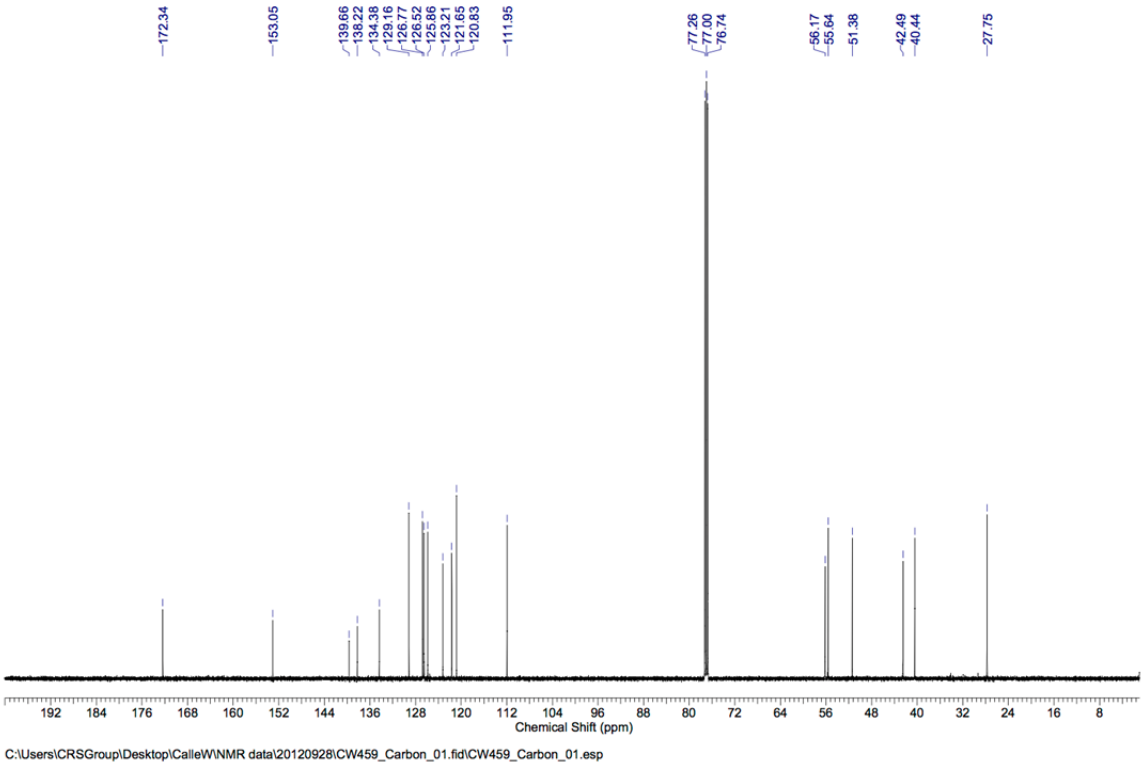


(*R*)-methyl 2-(5-chloro-2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3k).

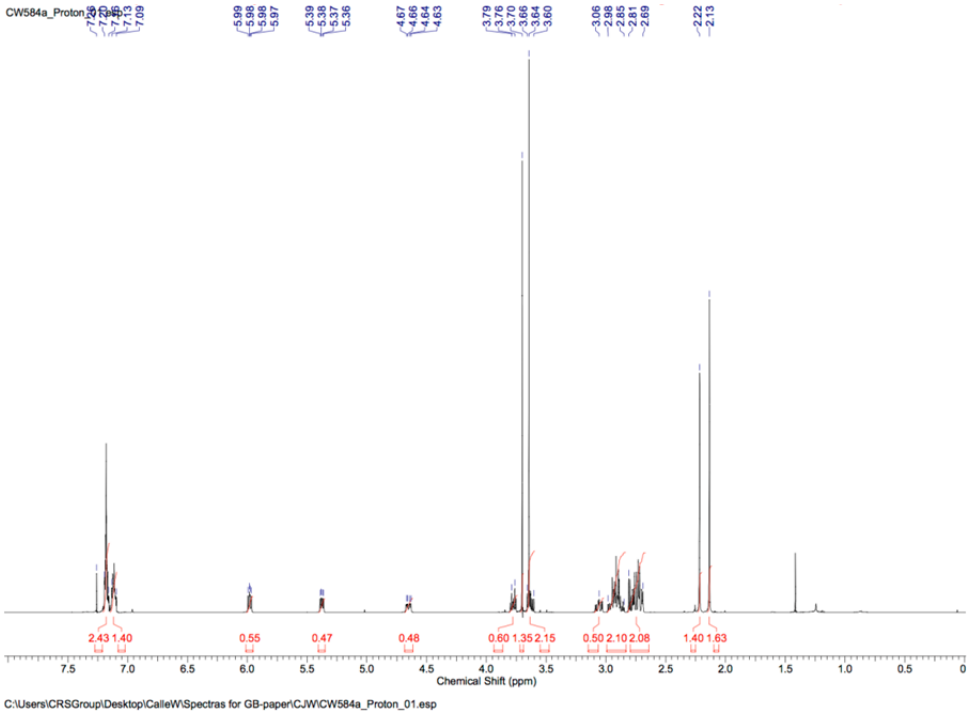


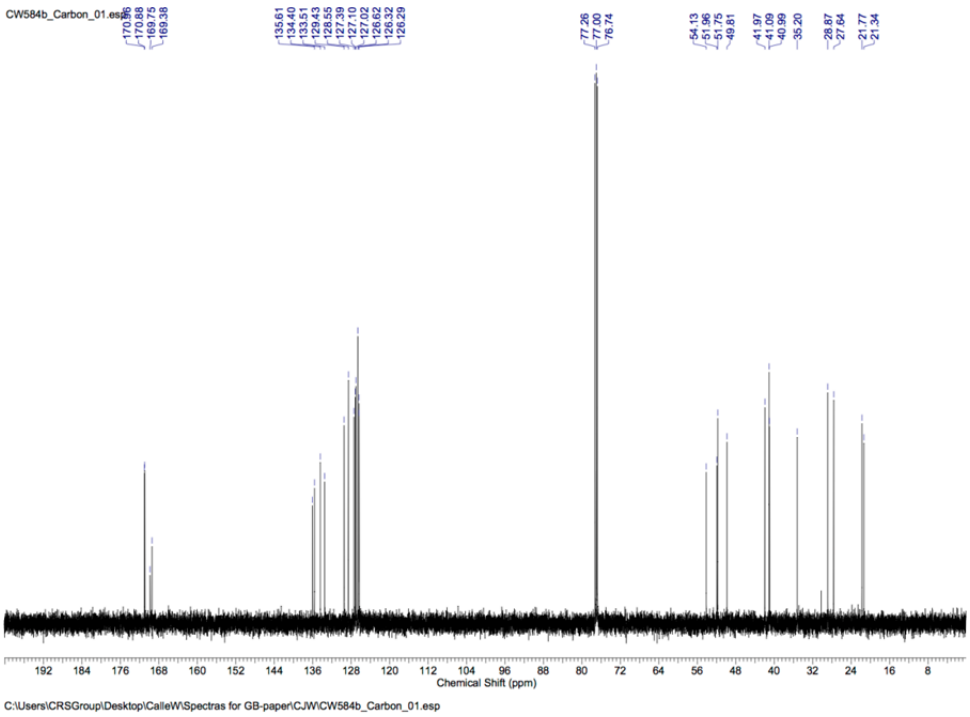
(*R*)-methyl 2-(2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (3l).



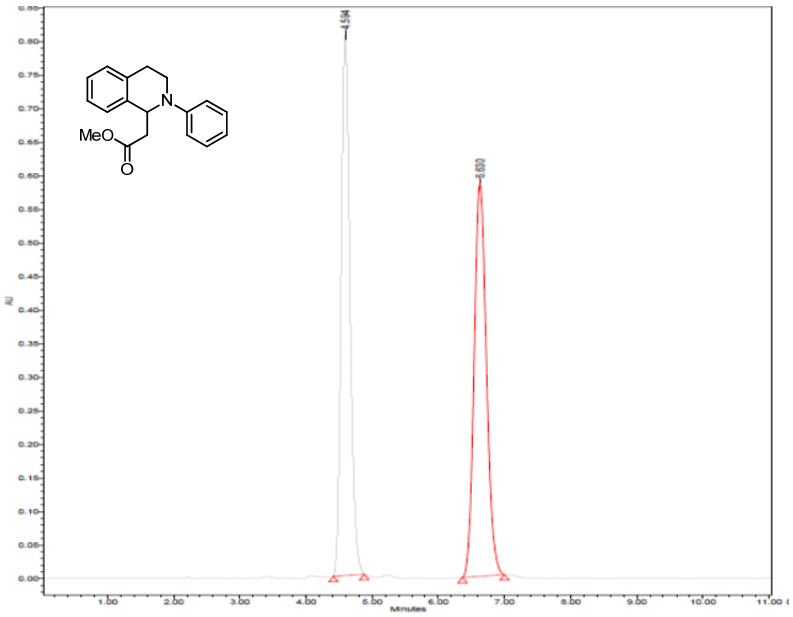


(*R*)-methyl 2-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (7)[7]

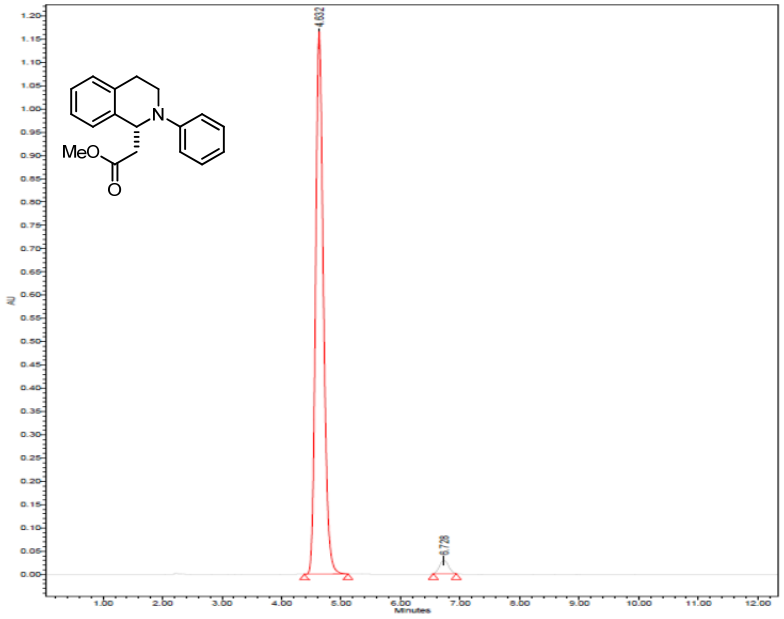




HPLC Traces



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	4.594	7489149	49.86	809641
2	6.630	7531195	50.14	586084



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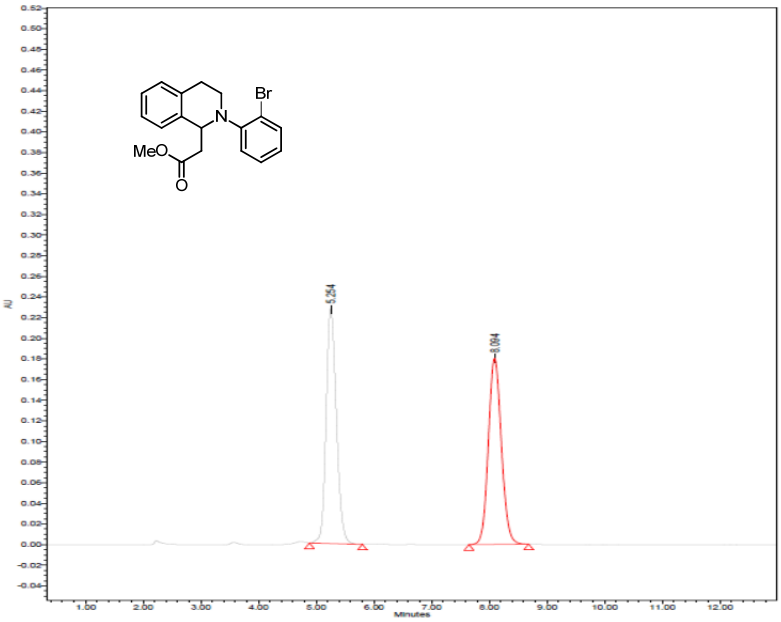
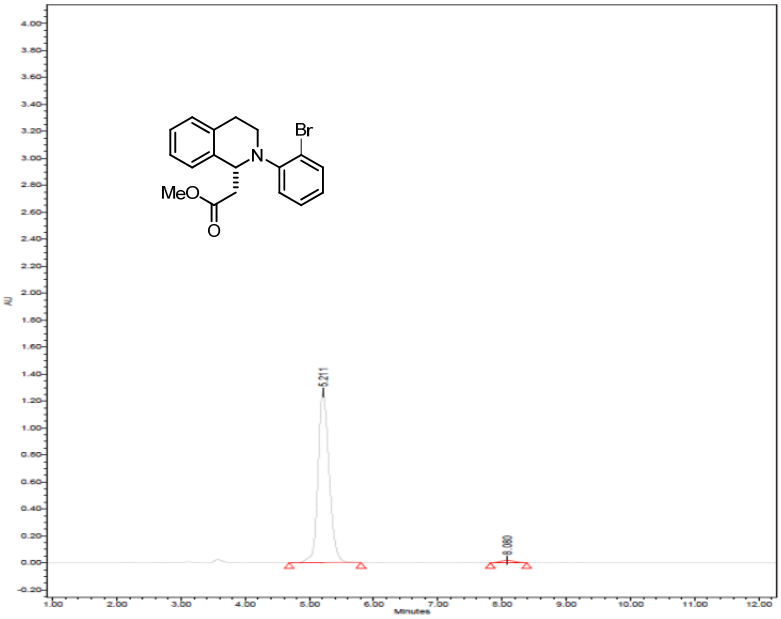
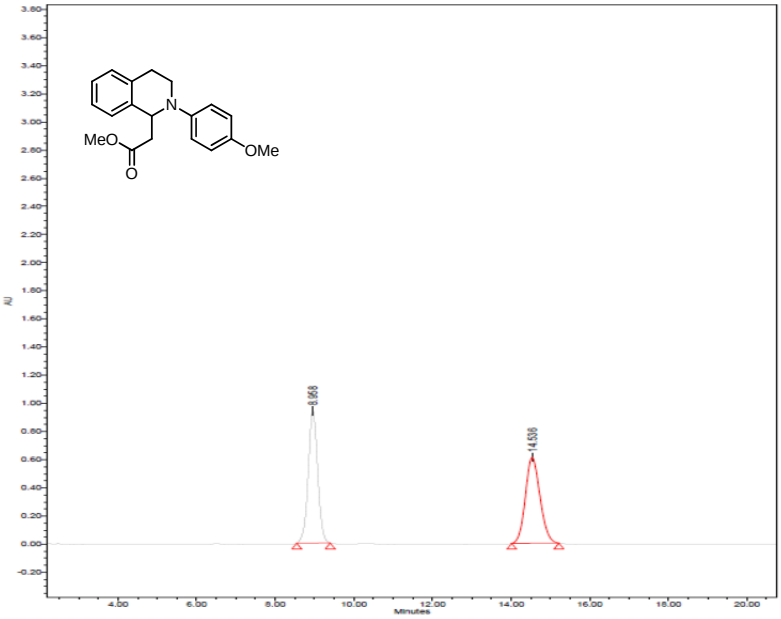
1	4.632	10724780	97.27	1163554
2	6.728	301095	2.73	28121



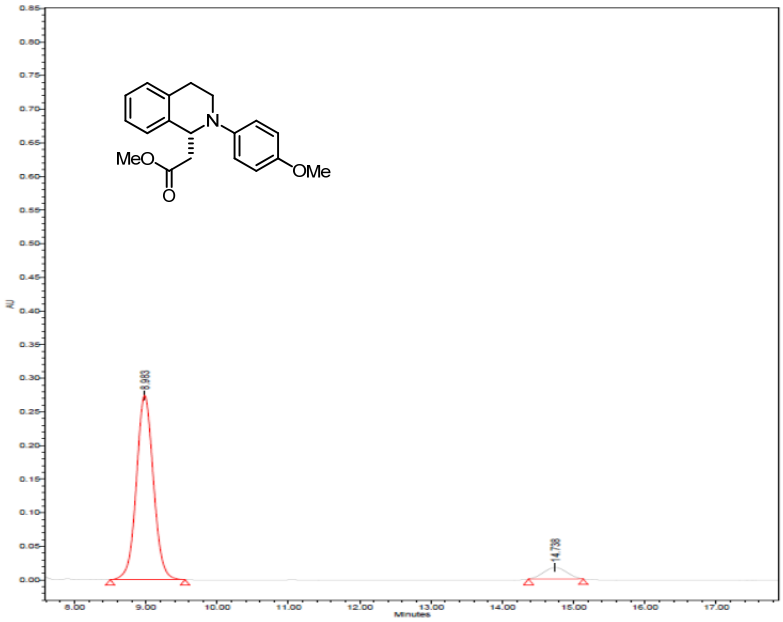
	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	5.254	2825790	50.08	227606
2	8.094	2816598	49.92	180550



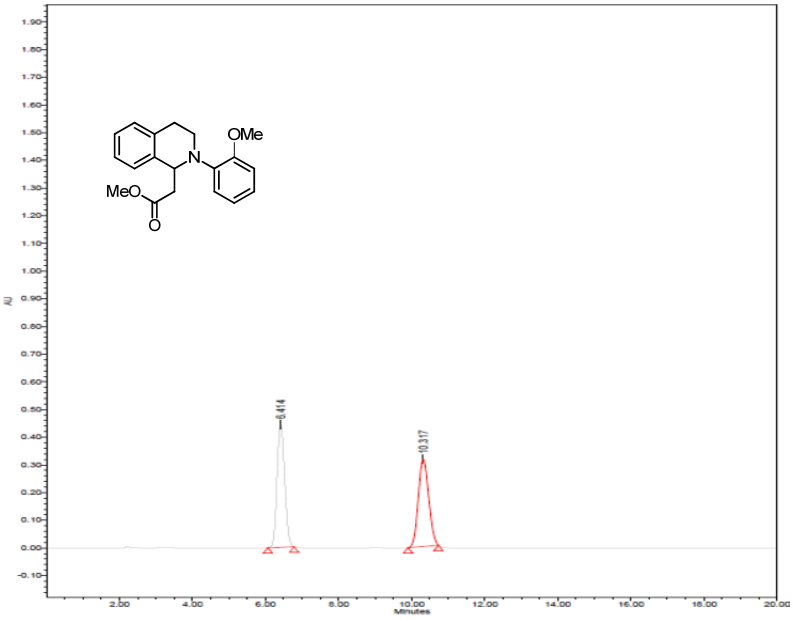
	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	5.211	15207365	98.34	1265587
2	8.080	256677	1.66	17906



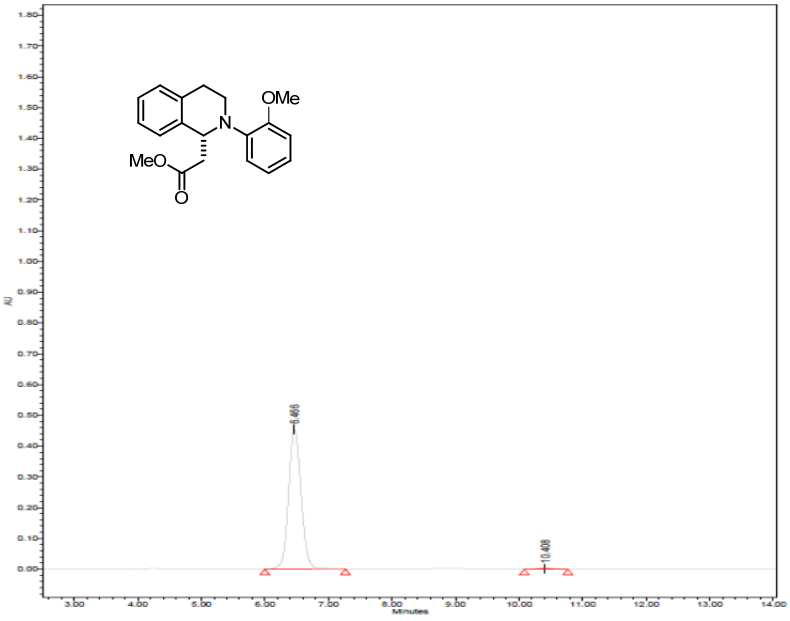
	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	8.958	15746312	49.94	940626
2	14.536	15783337	50.06	610745



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	8.983	4534707	92.23	274005
2	14.738	382049	7.77	16940



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	6.414	6421127	50.81	443628
2	10.317	6216617	49.19	314618



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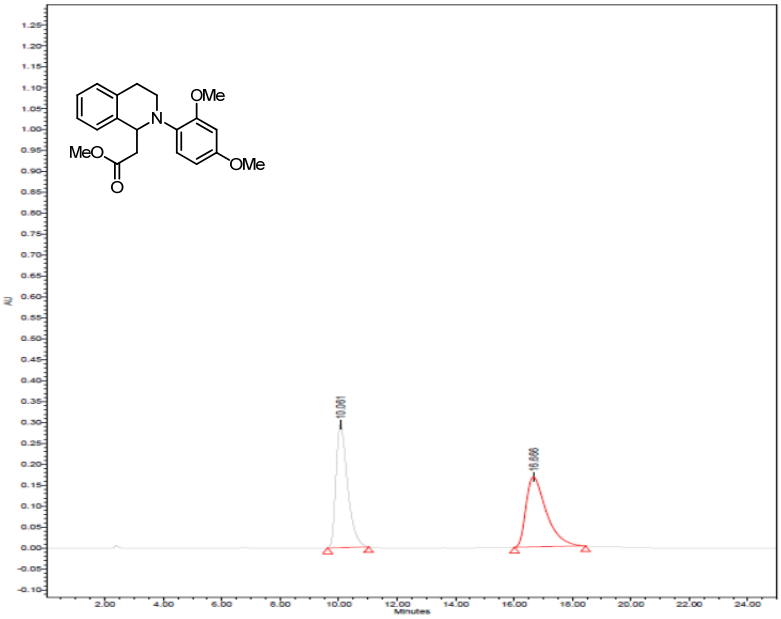
1	6.466	6185087	99.51	453860
2	10.408	30678	0.49	1651



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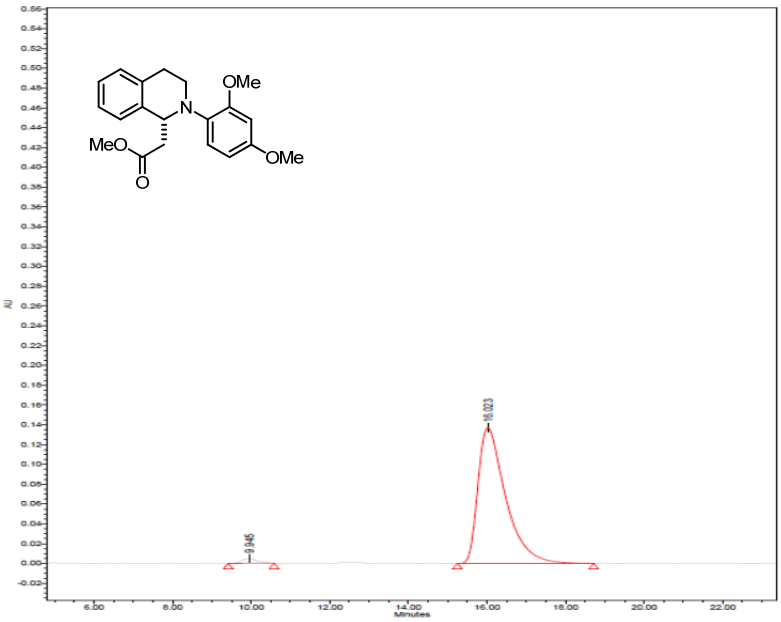
1	10.061	8098544	50.07	294068
2	16.666	8076053	49.93	167227



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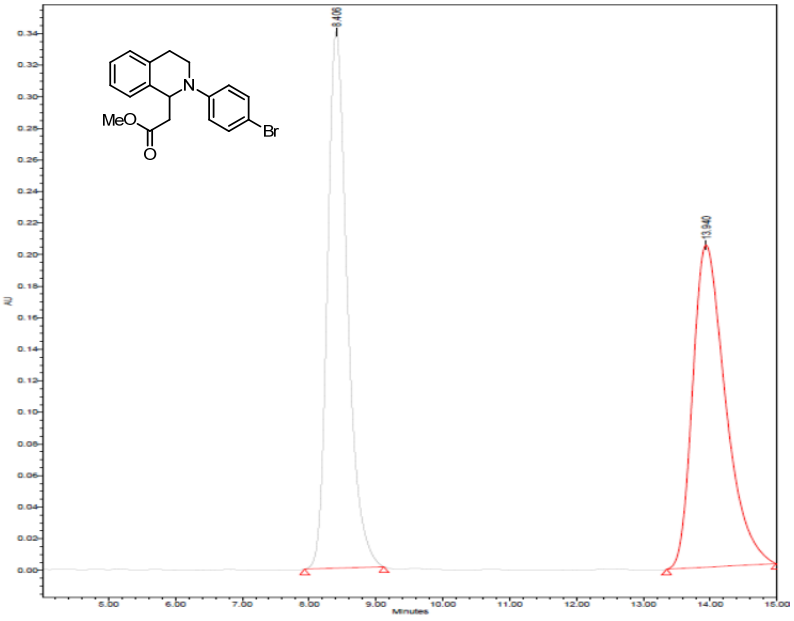
1	9.945	123438	1.82	4580
2	16.023	6669787	98.18	136819



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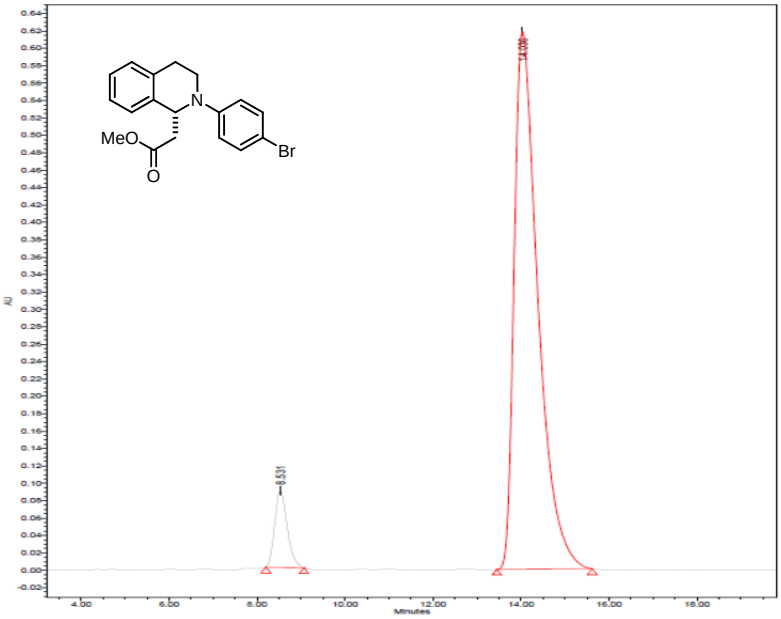
1	8.406	7065124	50.33	340359
2	13.940	6971147	49.67	204197



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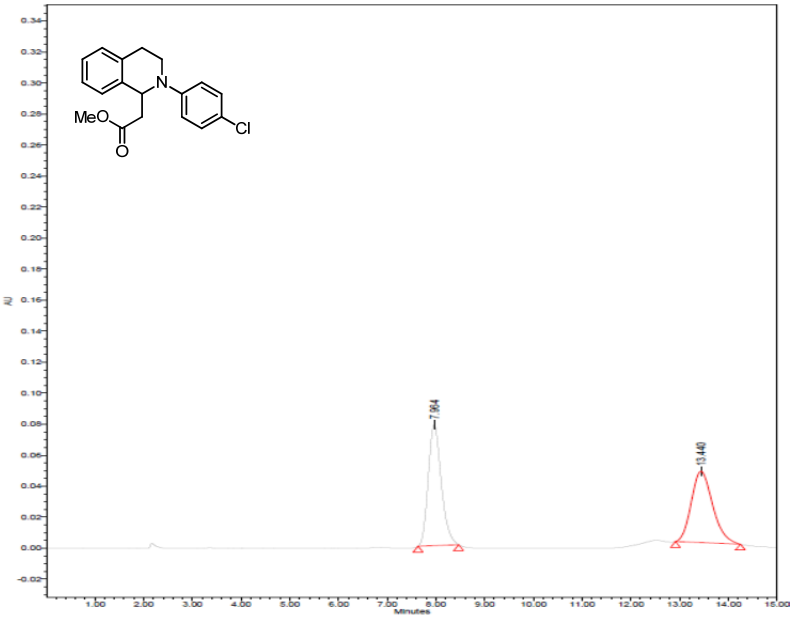
1	8.531	1748770	7.02	88463
2	14.036	23159500	92.98	618354



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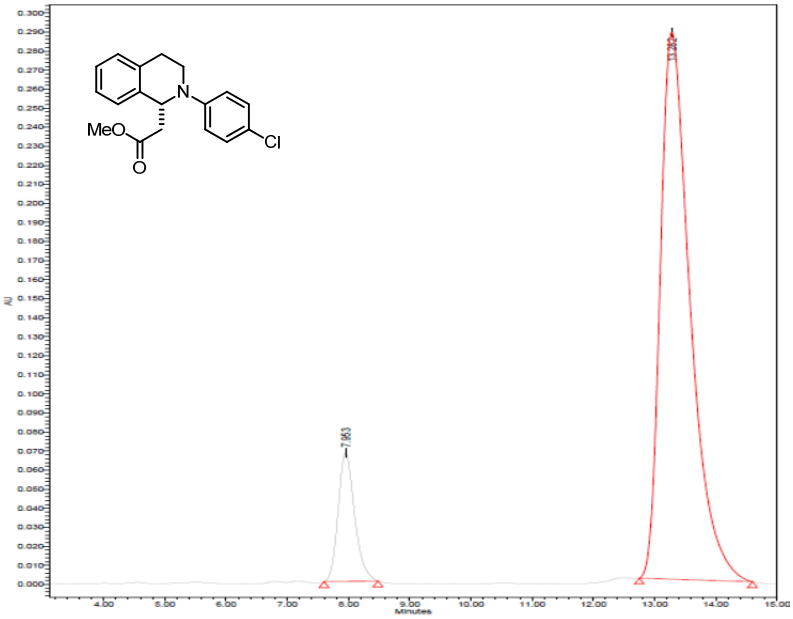
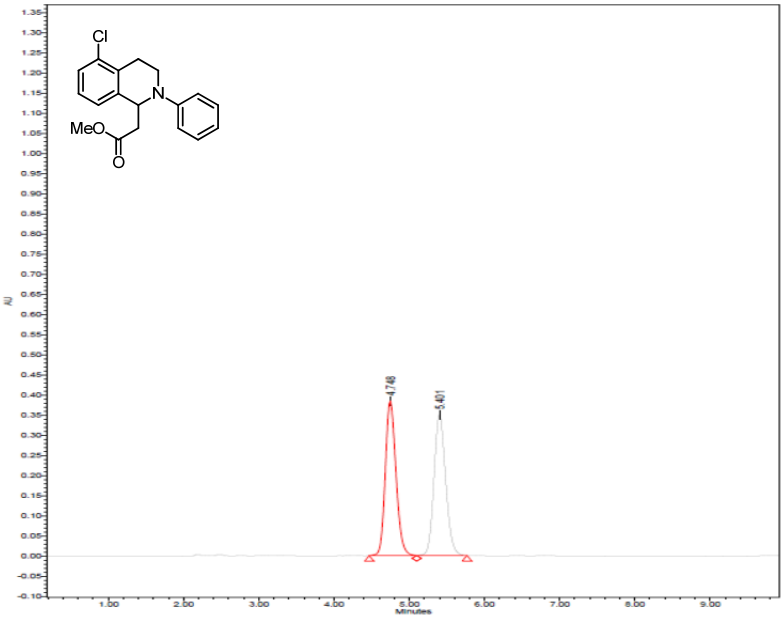
1	7.964	1450342	50.78	78066
2	13.440	1405873	49.22	46058



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	7.953	1263593	11.49	67583
2	13.282	9730553	88.51	287191



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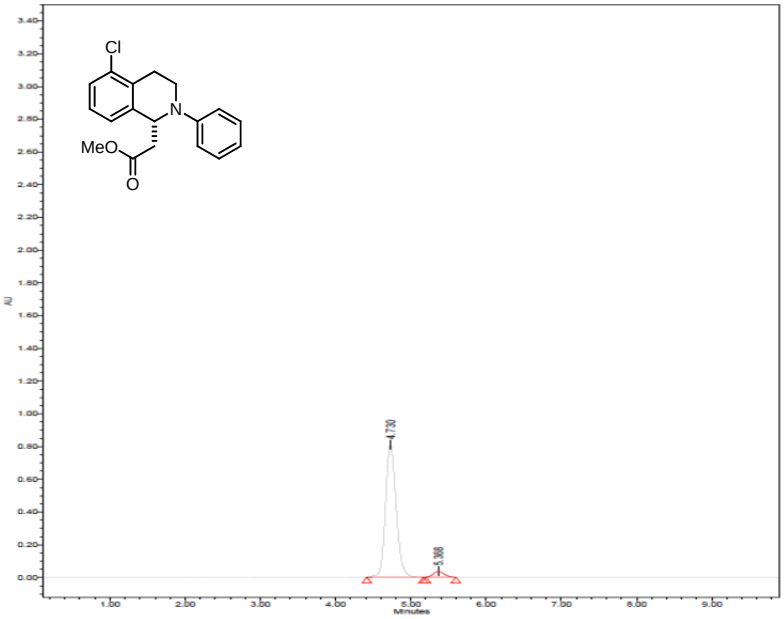
1	4.748	3778515	50.07	384399
2	5.401	3767958	49.93	349204



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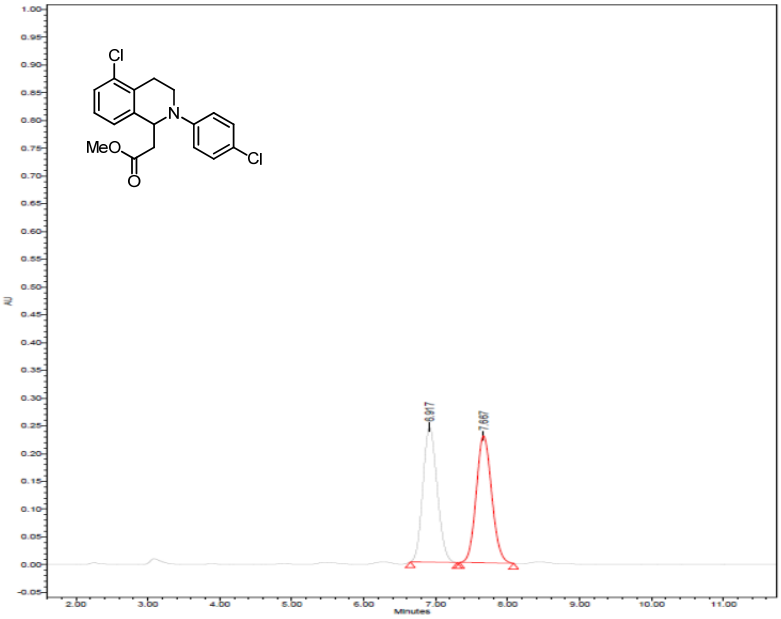
1	4.730	7938444	95.83	812181
2	5.368	345291	4.17	34546



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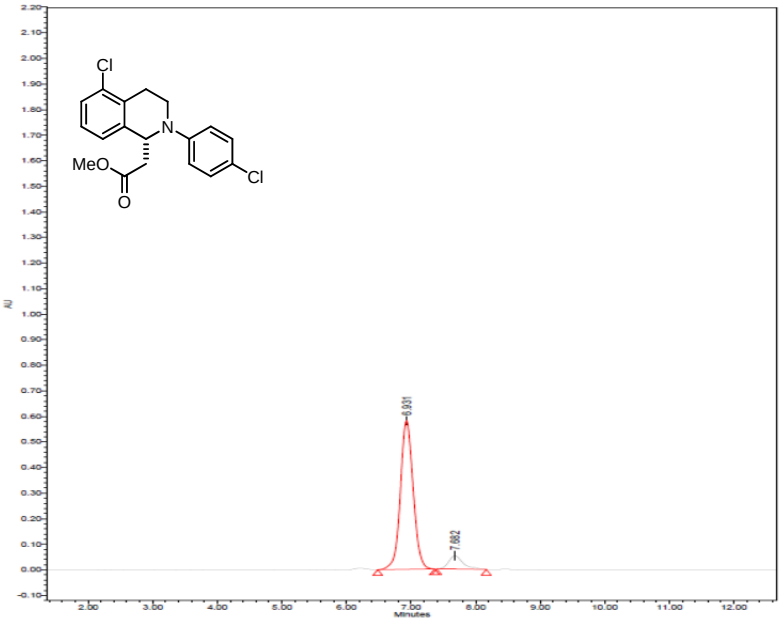
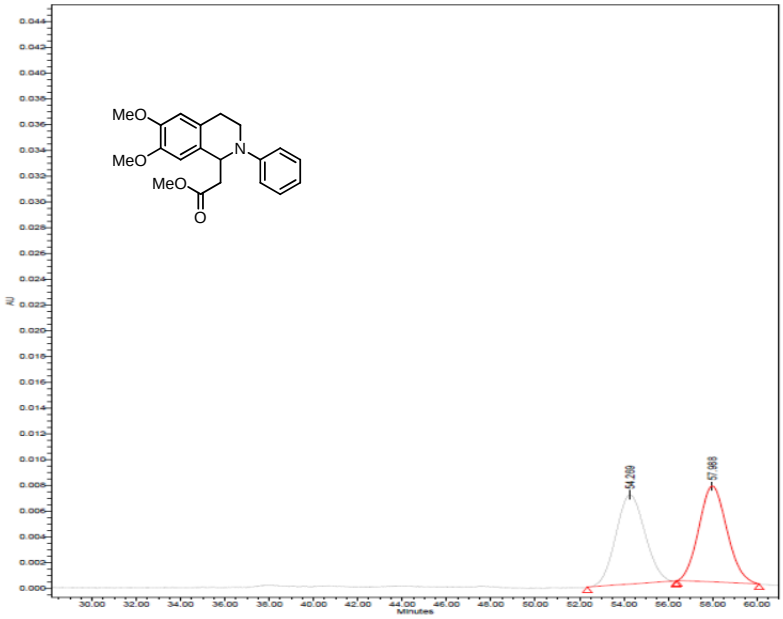
1	6.917	3358451	49.60	243290
2	7.667	3413153	50.40	228896



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	6.931	7979024	90.82	581786
2	7.682	806602	9.18	51921



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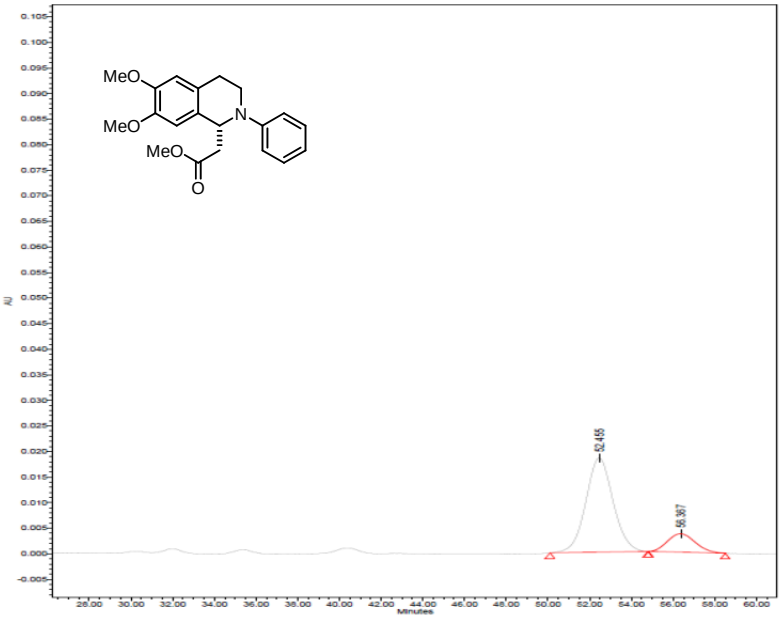
1	54.269	631970	49.10	6921
2	57.988	655016	50.90	7430



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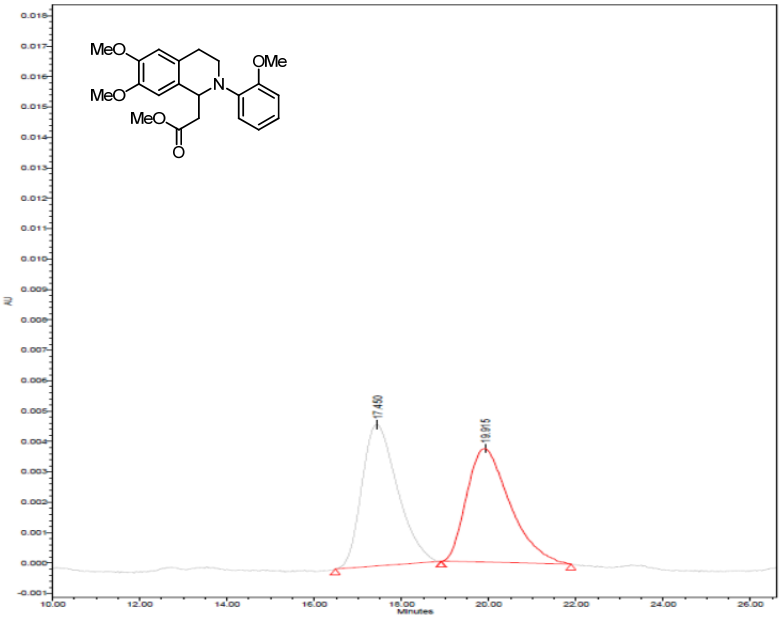
1	52.455	1674193	83.47	18436
2	56.367	331431	16.53	3603



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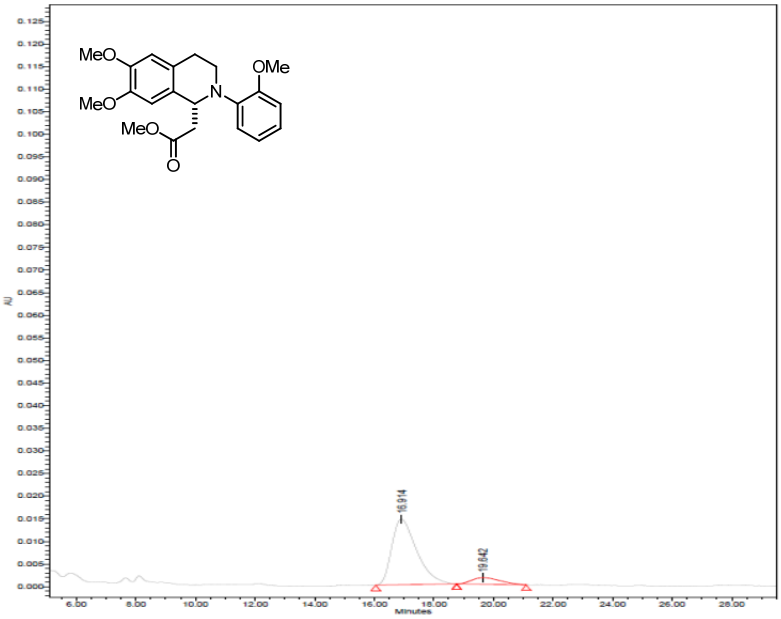
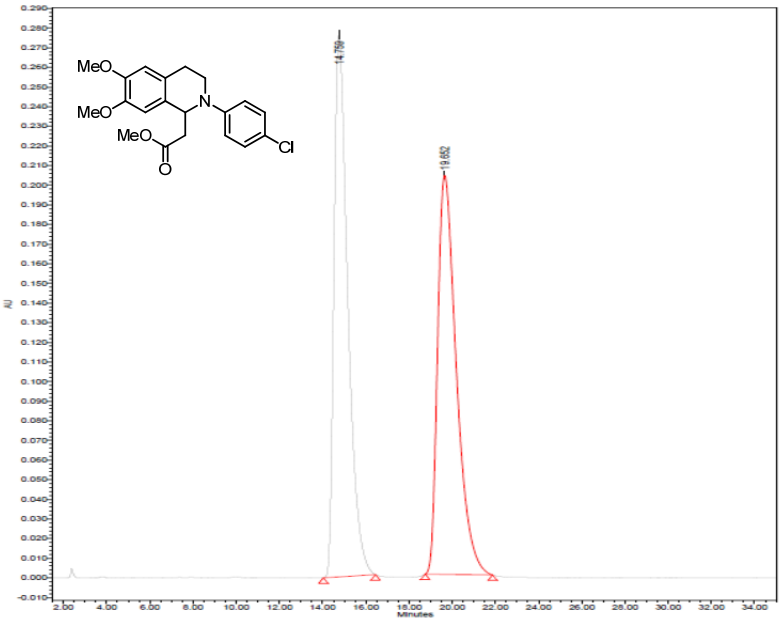
1	17.450	264327	50.71	4645
2	19.915	256906	49.29	3733



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	16.914	844517	89.69	14507
2	19.642	97045	10.31	1466



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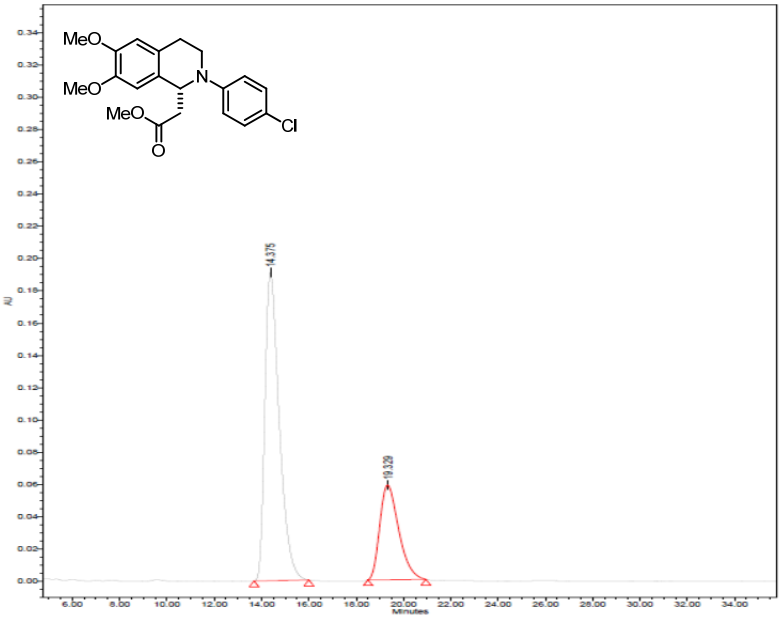
1	14.759	12301793	50.14	276186
2	19.652	12234121	49.86	203215



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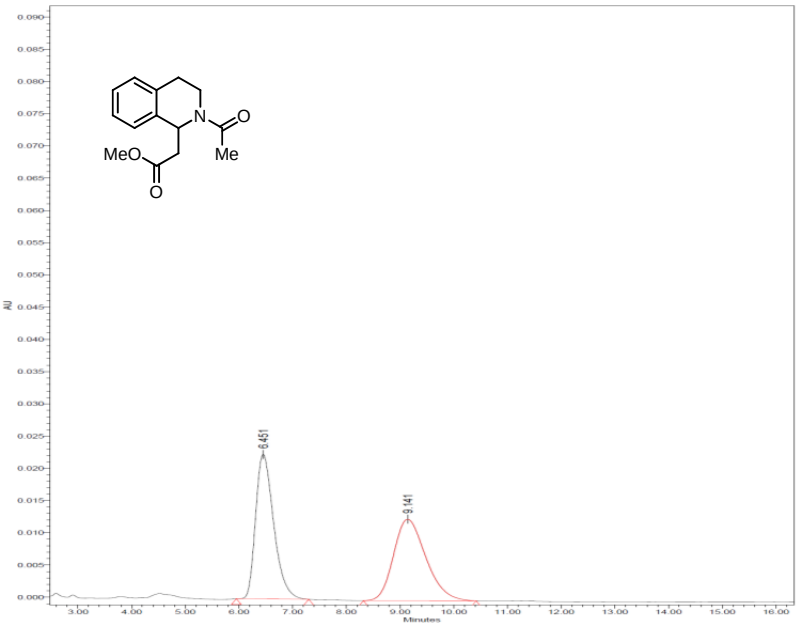
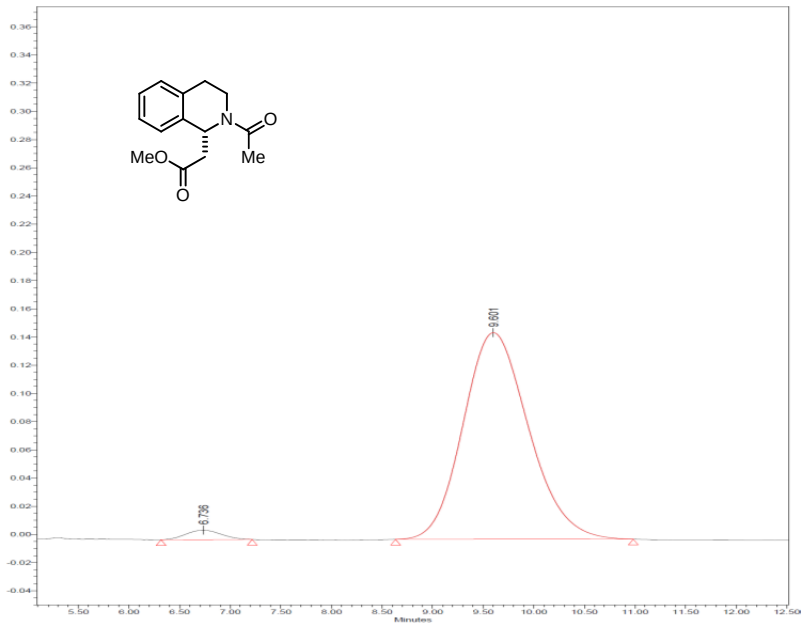
1	14.375	8070932	71.19	191104
2	19.329	3265615	28.81	58643



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	6.451	524580	49.79	22438
2	9.141	528969	50.21	12642



	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)
1	6.736	160334	2.37	6624
2	9.601	6597992	97.63	146559

10. References

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