

# Total Syntheses and Cytotoxicity of (*R*)- and (*S*)-Boehmeriasin A

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## Supporting Information

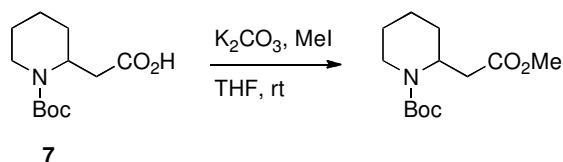
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### 1. General Methods

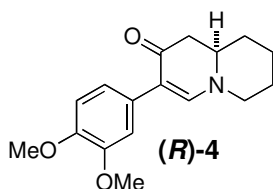
Melting points were determined using a melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates using an FT-IR instrument. NMR experiments were performed on a 400/100 MHz instrument using the residual solvent peak as internal standard unless otherwise indicated. Samples obtained in CDCl<sub>3</sub> were referenced to 7.26 ppm for <sup>1</sup>H and 77.16 for <sup>13</sup>C and samples obtained in *d*<sub>6</sub>-DMSO were referenced to 2.50 for <sup>1</sup>H and 39.52 for <sup>13</sup>C.<sup>1</sup> All chemical shifts were recorded in parts per million (ppm) and coupling constants (*J*) are in Hz and assigned according to the procedure of Hoye and Zhao.<sup>2</sup> The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Specific rotations were obtained using a polarimeter at 25.0 °C. High-resolution mass spectra were obtained utilizing the electrospray ionization technique.

All reactions were performed under an atmosphere of nitrogen in flame-dried glassware unless otherwise indicated. THF, CH<sub>2</sub>Cl<sub>2</sub>, and DMF were dried and deoxygenated by passing the nitrogen-purged solvents through activated alumina columns on a solvent purification system. All other reagents and solvents were used as purchased. Reaction progress was monitored by thin layer chromatography (TLC, silica gel, 10 × 20 cm, 250 micron) visualizing with UV light (254 nm) or developing the plates with either ninhydrin or phosphomolybdic acid/Ce(SO<sub>4</sub>)<sub>2</sub> stains. All compounds were purified using either MPLC or standard flash chromatography techniques using silica gel (60 Å, 230-400 mesh) utilizing the indicated conditions. All compounds were concentrated using standard rotary evaporator and high-vacuum techniques. HPLC analysis was conducted on an HPLC system equipped with a photodiode array detector. UPLC-MS analysis was used to determine product purities. All compounds were purified to >95% homogeneity prior to biological evaluation.

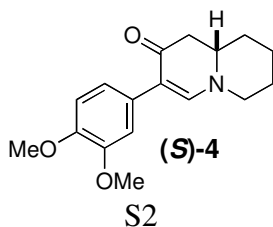
## 2. Experimental Procedures



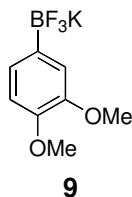
**tert-Butyl 2-(2-Methoxy-2-oxoethyl)piperidine-1-carboxylate.** To a stirring suspension of **7** (0.334 mmol) and  $K_2CO_3$  (0.668 mmol, 2 equiv) in THF (3 mL), was added MeI (1.67 mmol, 5 equiv) in a steady stream. Upon completion of the reaction after 24 hours, (monitored by TLC, 25% EtOAc/hexanes) the reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc (3 times) and the combined organic layers were dried over  $MgSO_4$ , concentrated, and purified by flash column chromatography (25% EtOAc/Hex) on silica gel. The  $^1H$  NMR matched literature values.<sup>3</sup>  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.44 (s, 9H), 1.69 – 1.56 (m, 6H), 2.55 (qd,  $J = 14.1, 7.6$  Hz, 2H), 2.77 (t,  $J = 12.7$  Hz, 1H), 3.65 (s, 3H), 3.98 (d,  $J = 12.3$  Hz, 1H), 4.69 (d,  $J = 5.4$  Hz, 1H).



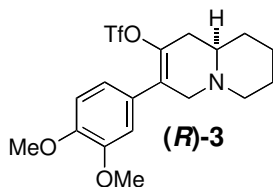
**(R)-3-(3,4-Dimethoxyphenyl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one ((R)-4).** Enaminone **(R)-5**<sup>3</sup> (366 mg, 2.42 mmol),  $[Pd(OAc)_2]_3$  (163 mg, 0.24 mmol), anhydrous  $Cu(OAc)_2$  (1.22 g, 6.72 mmol), and  $K_2CO_3$  (670 mg, 4.84 mmol) were combined in a *t*BuOH/AcOH/DMSO solution (20:5:1, 15 mL) and stirred for 5 min. The reaction mixture was heated to 60 °C and potassium 3,4-dimethoxyphenyltrifluoroborate (1.18 g, 4.85 mmol) in acetone/ $H_2O$  (2:1, 8 mL) was added to the reaction mixture over 1 h. An additional portion of  $[Pd(OAc)_2]_3$  (163 mg, 0.24 mmol) was added to the stirring mixture and the remaining potassium 3,4-dimethoxyphenyltrifluoroborate (1.18 g, 4.85 mmol) in acetone/ $H_2O$  (2:1, 8 mL) was added to the reaction mixture over 1 h. The reaction mixture was cooled to room temperature and  $K_2CO_3$  was added to the dark reaction medium until gas evolution ceased. The basic solution was filtered through a celite plug eluting with EtOAc, concentrated, and purified by MPLC on silica gel (15-65% acetone in hexanes, 50 min, 210 nm) to give 526 mg of the title compound as a white solid (76%).  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.36-1.47 (1H, m), 1.48-1.58 (1H, m), 1.60-1.68 (1H, m), 1.77-1.85 (2H, m), 1.86-1.92 (1H, m), 2.51 (1H, dd,  $J = 13.3, 16.2$  Hz), 2.61 (1H, dd,  $J = 5.5, 16.2$  Hz), 3.06 (1H, dt,  $J = 3.0, 12.7$  Hz), 3.33-3.42 (1H, m), 3.44-3.48 (1H, m), 3.86 (3H, s), 3.88 (3H, s), 6.82 (1H, d,  $J = 8.3$  Hz), 6.85 (1H, dd,  $J = 1.9, 8.3$  Hz), 7.02 (1H, d,  $J = 1.76$  Hz), 7.08 (1H, s).  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  23.23, 25.79, 31.81, 44.03, 53.28, 55.97, 56.08, 57.35, 111.27, 112.03, 112.22, 119.70, 129.18, 147.44, 148.63, 153.73, 189.89. IR (neat, NaCl): 2936, 1595, 1514, 1250, 1027. MP = 112-114 °C.  $[\alpha]_D^{25} = -6.60$  ( $c = 0.773$ ,  $CHCl_3$ ). HRMS (ESI<sup>+</sup>):  $m/z$  calc'd for  $C_{17}H_{22}NO_3$   $[M+1]^+$ , 288.1600; found 288.1590.



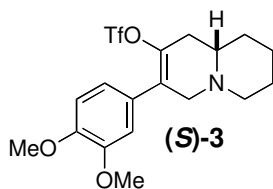
**(S)-3-(3,4-Dimethoxyphenyl)-7,8,9,9a-tetrahydro-1H-quinolizin-2(6H)-one ((S)-4)**. Prepared in 77% yield according to the procedure described for quinolizinone **(R)-5**.<sup>4</sup> The spectral data are identical to those reported for quinolizinone **(R)-4**.  $[\alpha]_D^{25} = +5.96$  ( $c = 1.14$ ,  $\text{CHCl}_3$ ).



**Potassium 3,4-Dimethoxyphenyltrifluoroborate (9)**. 3,4-Dimethoxyphenylboronic acid (2.00 g, 11.0 mmol) and  $\text{KHF}_2$  (2.00 g, 25.3 mmol) were combined in a  $\text{MeOH}/\text{H}_2\text{O}$  (2:1, 60 mL) solution in a polypropylene screw-top vessel and placed on an orbital shaker overnight at room temperature. The resulting slurry was concentrated to dryness and subsequently dissolved in hot acetone and filtered. The filtrate was concentrated until the trifluoroborate was sparingly soluble. The solution was gently heated and  $\text{Et}_2\text{O}$  was added resulting in a white precipitate that was cooled to 4 °C overnight. The heterogeneous solution was filtered and the resulting solid was washed with  $\text{Et}_2\text{O}$  and dried to afford 2.56 g of the title compound as a white solid (96%).  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO)  $\delta$  3.70 (3H, s), 3.72 (3H, s), 6.73 (1H, d,  $J = 7.7$  Hz), 6.87 (1H, d,  $J = 7.8$  Hz), 6.91 (1H, s).  $^{13}\text{C}$  NMR (100 MHz,  $d_6$ -DMSO)  $\delta$  55.11, 55.41, 110.90, 115.10 (1C, d,  $J = 1.2$  Hz), 123.51 (d, 1C,  $J = 1.3$  Hz), 146.69, 147.46.  $^{19}\text{F}$  NMR (376.4 MHz,  $d_6$ -DMSO,  $\text{CFCl}_3$  internal std)  $\delta$  -137.89. CHN: calc'd for  $\text{C}_8\text{H}_9\text{BF}_3\text{KO}_2$ , C, 39.37; H, 3.72; found: C, 38.98; H, 3.89.

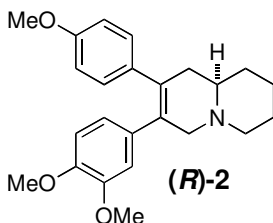


**(R)-3-(3,4-Dimethoxyphenyl)-4,6,7,8,9,9a-hexahydro-1H-quinolizin-2-yl Trifluoromethanesulfonate ((R)-3)**. Quinolizidone **(R)-4** (526 mg, 1.83 mmol) was dissolved in THF (12 mL) and cooled to -78 °C. L-Selectride (1.0 M, 1.9 mL, 1.9 mmol) was added dropwise to the stirring solution and the reaction was maintained at -78 °C for 30 min at which time the solution was warmed to room temperature. Comins' reagent (935 mg, 2.38 mmol) was subsequently added to the reaction mixture and allowed to stir at room temperature overnight. The resulting solution was quenched with saturated aq.  $\text{NaHCO}_3$  (1.5 mL), diluted with  $\text{CH}_2\text{Cl}_2$  (6.0 mL), dried with  $\text{K}_2\text{CO}_3$ , and filtered through Celite. The resulting filtrate was concentrated and purified by MPLC on silica gel (15-55%  $\text{EtOAc}$  in hexanes with 1% TEA, 40 min, 254 nm) to afford 591 mg of the title compound as a red-brown oil (68%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.27-1.32 (1H, m), 1.33-1.39 (1H, m), 1.62-1.74 (2H, m), 1.75-1.81 (1H, m), 1.82-1.89 (1H, m), 2.10 (1H, dt,  $J = 3.2, 11.6$  Hz), 2.35-2.42 (1H, m), 2.43-2.52 (2H, m), 3.00-3.07 (1H, m), 3.11 (1H, td,  $J = 3.3, 11.7$  Hz), 3.58 (1H, d,  $J = 16.4$  Hz), 3.88 (3H, s), 3.87 (3H, s), 6.81-6.86 (3H, m).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.71, 25.68, 33.05, 35.73, 54.94, 55.97, 56.02, 57.83, 59.17, 111.07, 111.73, 118.22 (1C, q,  $J = 320$  Hz), 120.72, 126.59, 128.00, 140.39, 148.86, 149.16. IR (neat, NaCl): 2935, 1595, 1515, 1251, 1028  $\text{cm}^{-1}$ .  $[\alpha]_D^{25} = -49$  ( $c = 0.97$ ,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>):  $m/z$  calc'd for  $\text{C}_{18}\text{H}_{23}\text{F}_3\text{NO}_5\text{S}$   $[\text{M}+1]^+$ , 422.1249; found 422.1239.



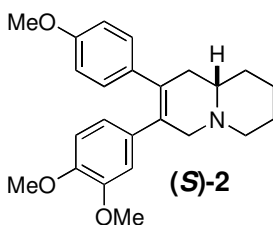
**(S)-3-(3,4-Dimethoxyphenyl)-4,6,7,8,9a-hexahydro-1H-quinolizin-2-yl Trifluoromethanesulfonate ((S)-3).**

Prepared in 77% yield according to the procedure described for triflate (**R**)-3. The spectral data are identical to those reported for triflate (**R**)-3.  $[\alpha]_D^{25} = +57$  ( $c = 0.60$ ,  $\text{CHCl}_3$ ).



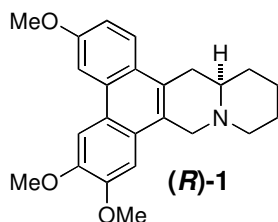
**(R)-7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-2,3,4,6,9a-hexahydro-1H-quinolizine ((R)-2).** A reaction vessel

containing  $\text{ZnBr}_2$  (365 mg, 1.6 mmol) was flame-dried under vacuum and upon reaching room temperature it was released from vacuum and fitted immediately with a septum and placed under a nitrogen atmosphere. THF (5 mL) was added to the purged reaction vessel and once homogeneity was achieved, 4-methoxyphenylmagnesium bromide (0.5 M in THF, 2.8 mL, 1.4 mmol) was added, resulting in a white slurry that was stirred for 10 min. This solution was transferred to a reaction vessel containing triflate (**R**)-3 (195 mg, 0.46 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (58 mg, 0.05 mmol) and the reaction mixture was heated to 60 °C. Monitoring by TLC (50% EtOAc in hexanes with 1% TEA) showed complete consumption of starting material within 1 h. The reaction was allowed to cool to room temperature and immediately purified by MPLC on silica gel (25-75% EtOAc in hexanes with 1% TEA, 50 min, 254 nm) to give 176 mg of the title compound as a tan foam (92%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.27-1.38 (2H, m), 1.65-1.73 (2H, m), 1.75-1.84 (2H, m), 2.04-2.13 (1H, m), 2.23-2.30 (1H, m), 2.31-2.40 (1H, m), 2.45-2.52 (1H, m), 3.00-3.09 (2H, m), 3.54 (3H, s), 3.60 (1H, d,  $J = 16.6$  Hz), 3.68 (3H, s), 3.77 (3H, s), 6.47 (1H, s), 6.61-6.67 (4H, m), 6.90-6.95 (2H, m).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  24.41, 25.96, 33.38, 39.89, 55.13, 55.55, 55.66, 55.71, 57.93, 60.18, 110.56, 113.24, 113.28, 120.89, 129.84, 131.30, 131.45, 133.33, 134.43, 147.37, 148.08, 157.87. IR (neat, NaCl): 2930, 1606, 1511, 1246, 1030, 756  $\text{cm}^{-1}$ .  $[\alpha]_D^{25} = -160$  ( $c = 0.89$ ,  $\text{CHCl}_3$ ). HRMS (ESI<sup>+</sup>):  $m/z$  calc'd for  $\text{C}_{24}\text{H}_{29}\text{NO}_3$ , 380.2226; found. 380.2233.

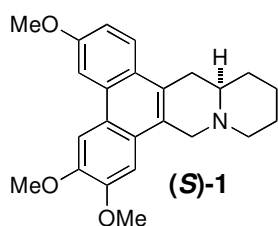


**(S)-7-(3,4-Dimethoxyphenyl)-8-(4-methoxyphenyl)-2,3,4,6,9a-hexahydro-1H-quinolizine ((S)-2).** Prepared in 99%

yield according to the procedure described for quinolizine (**R**)-2. The spectral data are identical to those reported for quinolizine (**R**)-2.  $[\alpha]_D^{25} = +160$  ( $c = 0.98$ ,  $\text{CHCl}_3$ ).



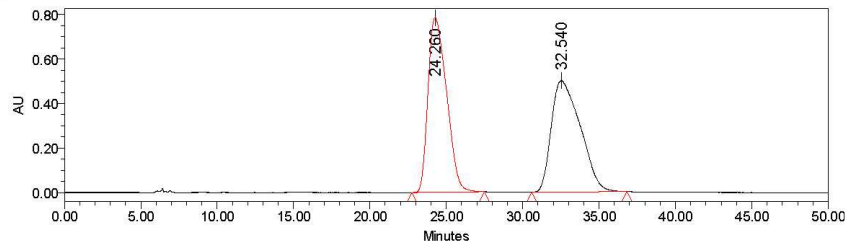
**(R)-Boehmeriasin A ((R)-1).** Quinolizine **(R)-2** (40 mg, 0.11 mmol) in  $\text{CH}_2\text{Cl}_2$  (9 mL) was cooled to  $-78\text{ }^\circ\text{C}$  under a nitrogen atmosphere.  $\text{VOF}_3$  (30 mg, 0.22 mmol) in a solution of TFA/ $\text{CH}_2\text{Cl}_2$ /EtOAc (1:1:1, 3 mL) was subsequently added to the stirring solution in one portion at  $-78\text{ }^\circ\text{C}$ . The reaction was monitored by TLC (50% EtOAc in hexanes with 1% TEA) and complete consumption of starting material was observed within 1 h. The reaction was quenched with 10% aq. NaOH (10 mL) and the solution was warmed to room temperature. The layers were separated and the aqueous phase was extracted  $\text{CH}_2\text{Cl}_2$  (2 $\times$ ). The combined organic extracts were dried with  $\text{Na}_2\text{SO}_4$ , concentrated, and purified by MPLC on silica gel (35-85% EtOAc in hexanes with 1% TEA, 50 min, 254 nm) to give 31 mg of the title compound as a white solid (74%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.39-1.48 (1H, m), 1.48-1.57 (1H, m), 1.74-1.83 (2H, m), 1.84-1.91 (1H, m), 1.97-2.04 (1H, m), 2.26-2.39 (2H, m), 2.92 (1H, dd,  $J = 10.4, 16.4$  Hz), 3.16 (1H, dd,  $J = 2.9, 16.6$  Hz), 3.28 (1H, d,  $J = 11.0$  Hz), 3.56 (1H, d,  $J = 15.3$  Hz), 4.00 (3H, s), 4.05 (3H, s), 4.09 (3H, s), 4.33 (1H, d,  $J = 15.2$  Hz), 7.12 (1H, s), 7.20 (1H, dd,  $J = 2.6, 9.0$  Hz), 7.86-7.92 (3H, m).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  24.50, 26.14, 33.92, 34.82, 55.63, 56.08, 56.11, 56.31, 56.51, 57.62, 103.18, 104.14, 104.73, 114.86, 123.38, 124.39, 125.13, 125.32, 126.06, 130.38, 148.29, 149.50, 157.65. IR (neat, NaCl): 2932, 2253, 1612, 1513, 1470, 1256, 1204, 1140, 1041, 731  $\text{cm}^{-1}$ .  $[\alpha]_{\text{D}}^{25} = -86$  ( $c = 0.10$ , MeOH) lit.:  $[\alpha]_{\text{D}}^{25} = -80$  ( $c = 0.10$ , MeOH) (Note: compound is sparingly soluble in MeOH);  $[\alpha]_{\text{D}}^{25} = -93$  ( $c = 0.15$ ,  $\text{CHCl}_3$ ). MP = decomp.  $>214\text{ }^\circ\text{C}$ . HRMS (ESI $^+$ ):  $m/z$  calc'd for  $\text{C}_{24}\text{H}_{28}\text{NO}_3$   $[\text{M}+1]^+$ , 378.2069; found 378.2057. Chiral HPLC analysis: Chiralpak AD-H (250 mm x 4.6 mm), 35-80% isopropanol in *n*-heptane, 45 min, 0.5 mL/min, 254 nm, (*S*)-isomer,  $t_{\text{R}} = 24.2$  min, (*R*)-isomer,  $t_{\text{R}} = 32.6$  min, er = 97:3.



**(S)-Boehmeriasin A ((S)-1).** Prepared in 83% yield according to the procedure described for (*R*)-boehmeriasin A. The spectral data are identical to those reported for (*R*)-boehmeriasin A.  $[\alpha]_{\text{D}}^{25} = +73$  ( $c = 0.14$ , MeOH).

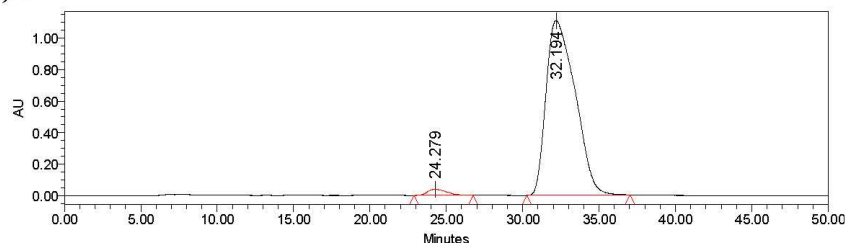
HPLC Conditions: Chiralpak AD-H (250 mm x 4.6 mm), 35-80% isopropanol in heptane, 45 min, 0.5 mL/min, 254 nm

(±)-1



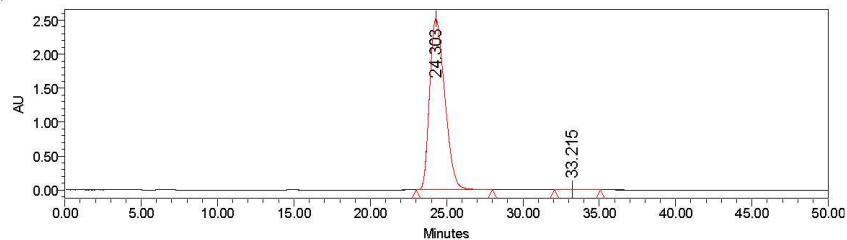
	Retention Time	Area	% Area	Height
1	24.260	66000375	50.02	785969
2	32.540	65951842	49.98	500837

(R)-1



	Retention Time	Area	% Area	Height
1	24.279	3416256	2.28	38628
2	32.194	146586574	97.72	1109449

(S)-1



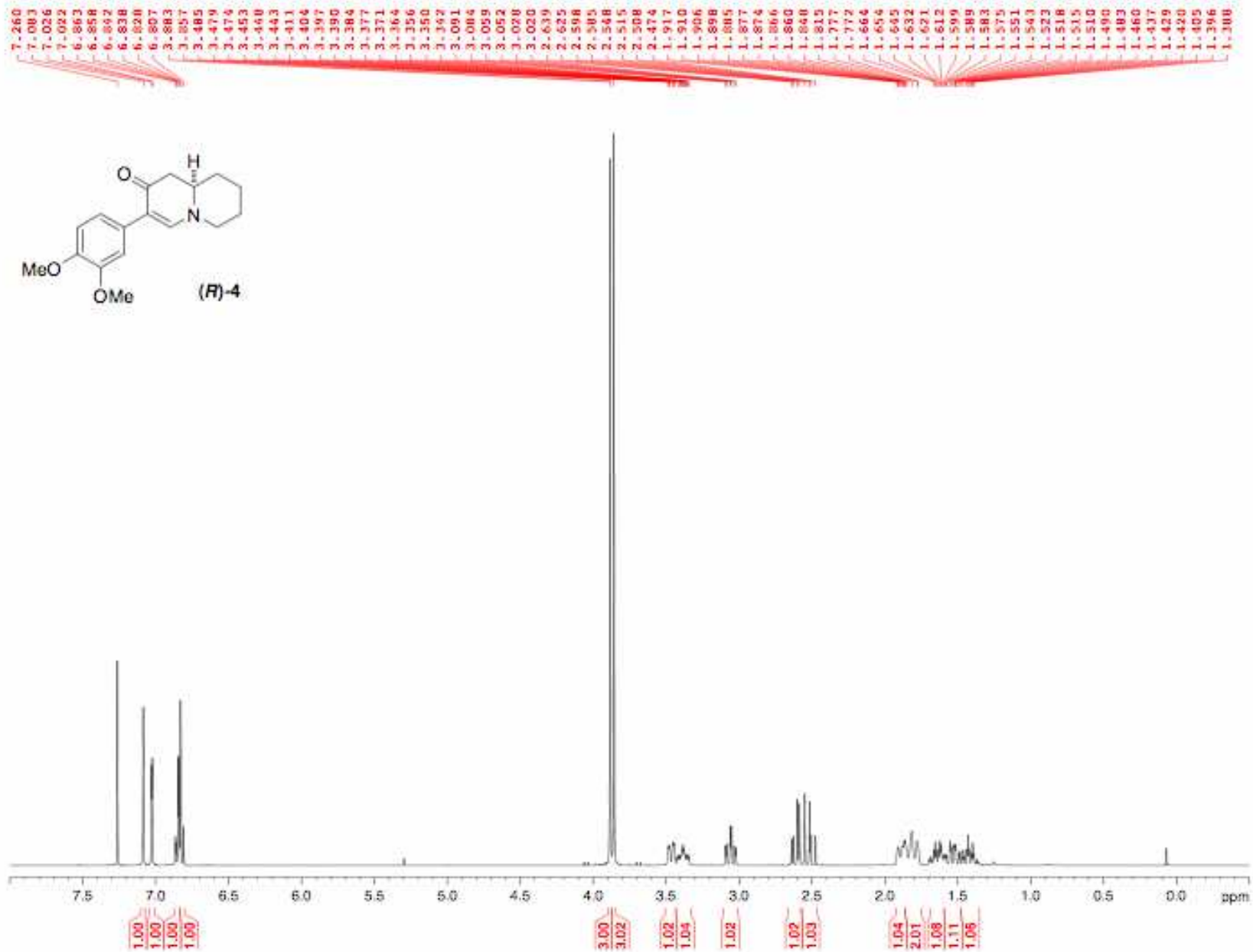
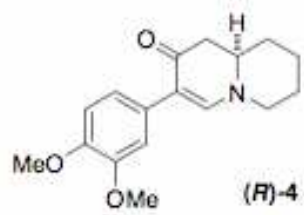
	Retention Time	Area	% Area	Height
1	24.303	173177371	99.67	2523747
2	33.215	577781	0.33	5910

## ANTIPROLIFERATION ASSAY

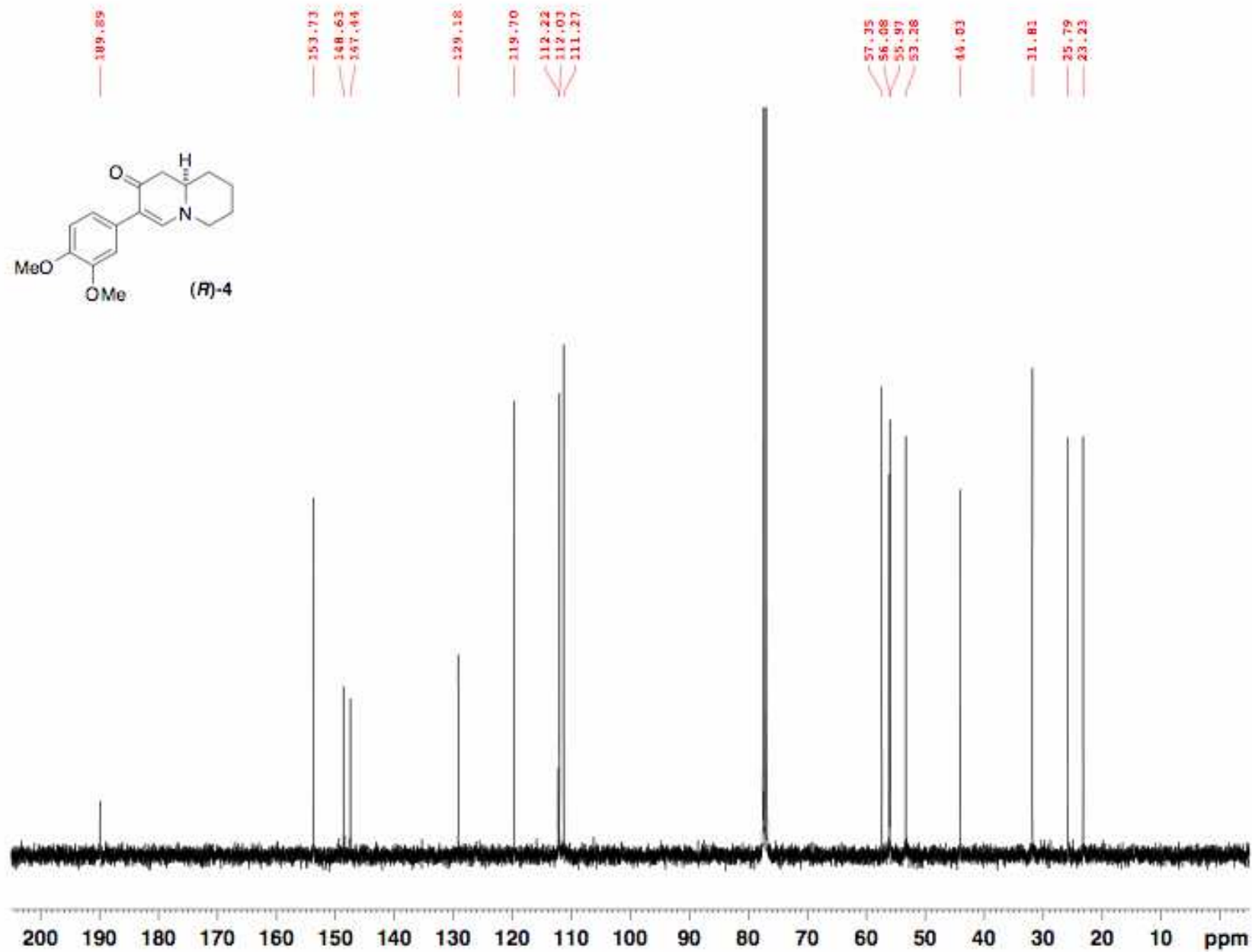
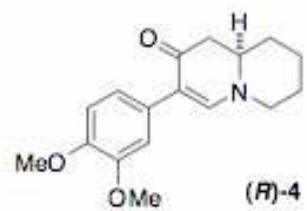
Stock solutions (10 mM) of the each compound were prepared in DMSO. MCF-7, COLO-205 and NCI-ADR-RES cancer cells were harvested (125 G centrifuge for 5 min) from an exponential-phase maintenance culture. The cells were re-suspended in new culture medium (RPMI Medium 1640) and the cell density was adjusted to 105 cells/mL and dispensed into a 96-well culture plates at a density of 5,000 cells per well (50  $\mu$ L). The cells were incubated overnight to allow cells to adhere to the wells. The culture medium in each well was replaced with fresh culture medium (50  $\mu$ L) containing varying concentrations of the test and control compound (paclitaxel). The cultures were grown for an additional 48 h and alamarBlue® (20ul) was added. After 1–2 h, the fluorescence excitation (530 nm) and emission (590 nm) of each well was measured to determine the optical density. Each compound was tested in triplicate with less than 5% variation. (This assay was performed by Dr. Harry Tian University of Minnesota).

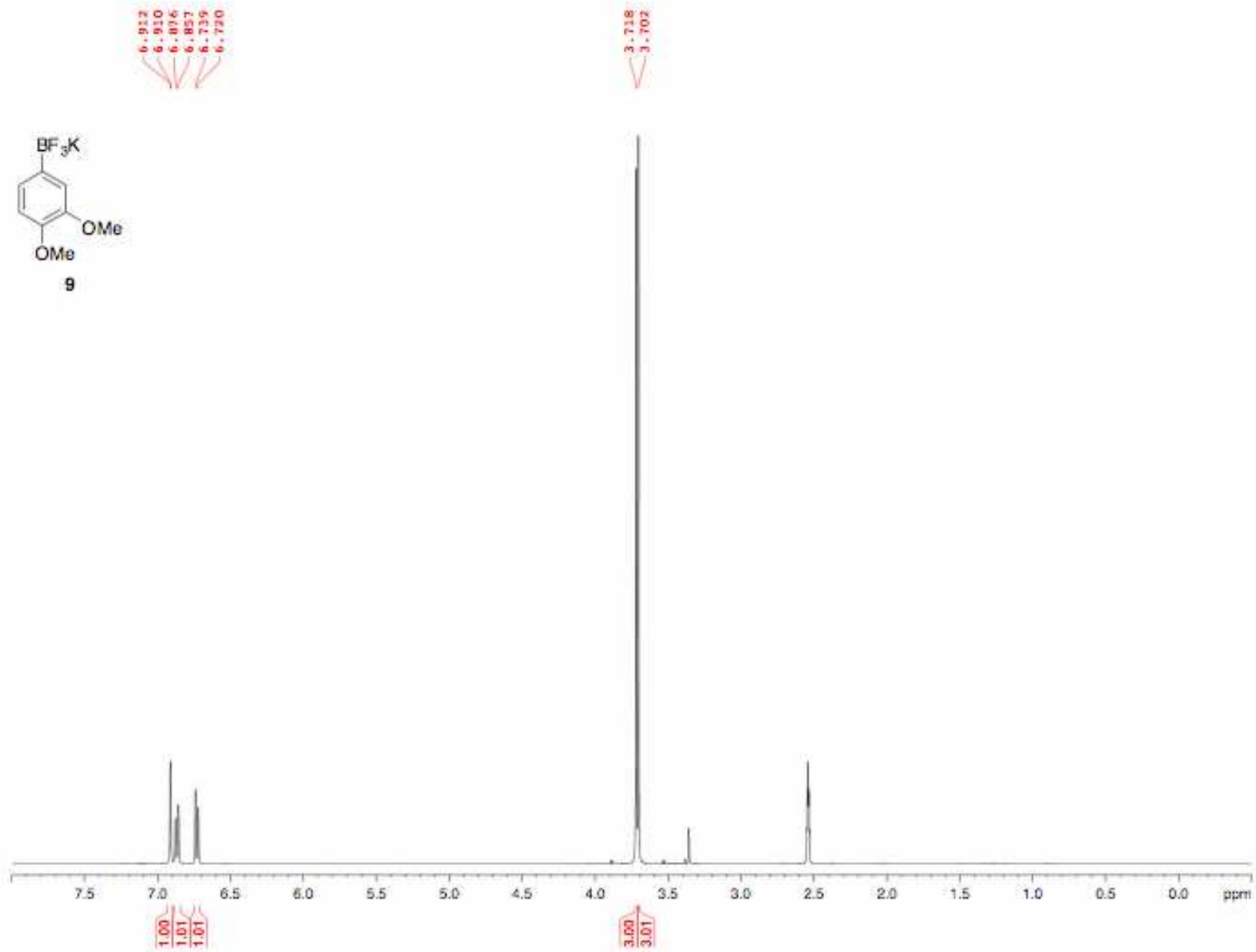
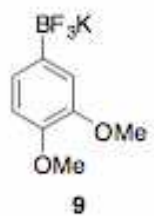
**References:**

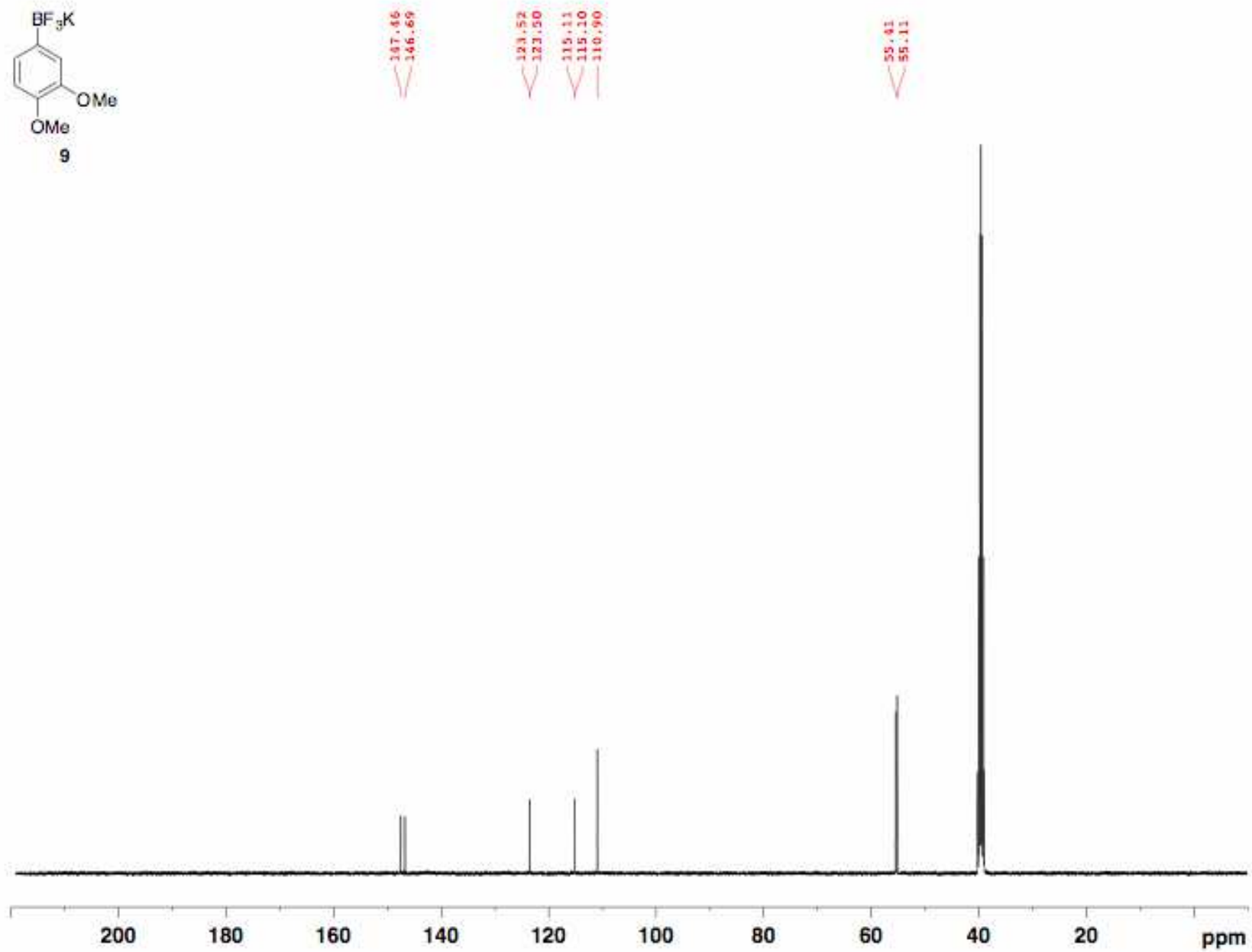
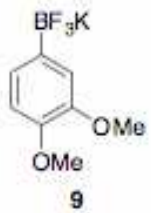
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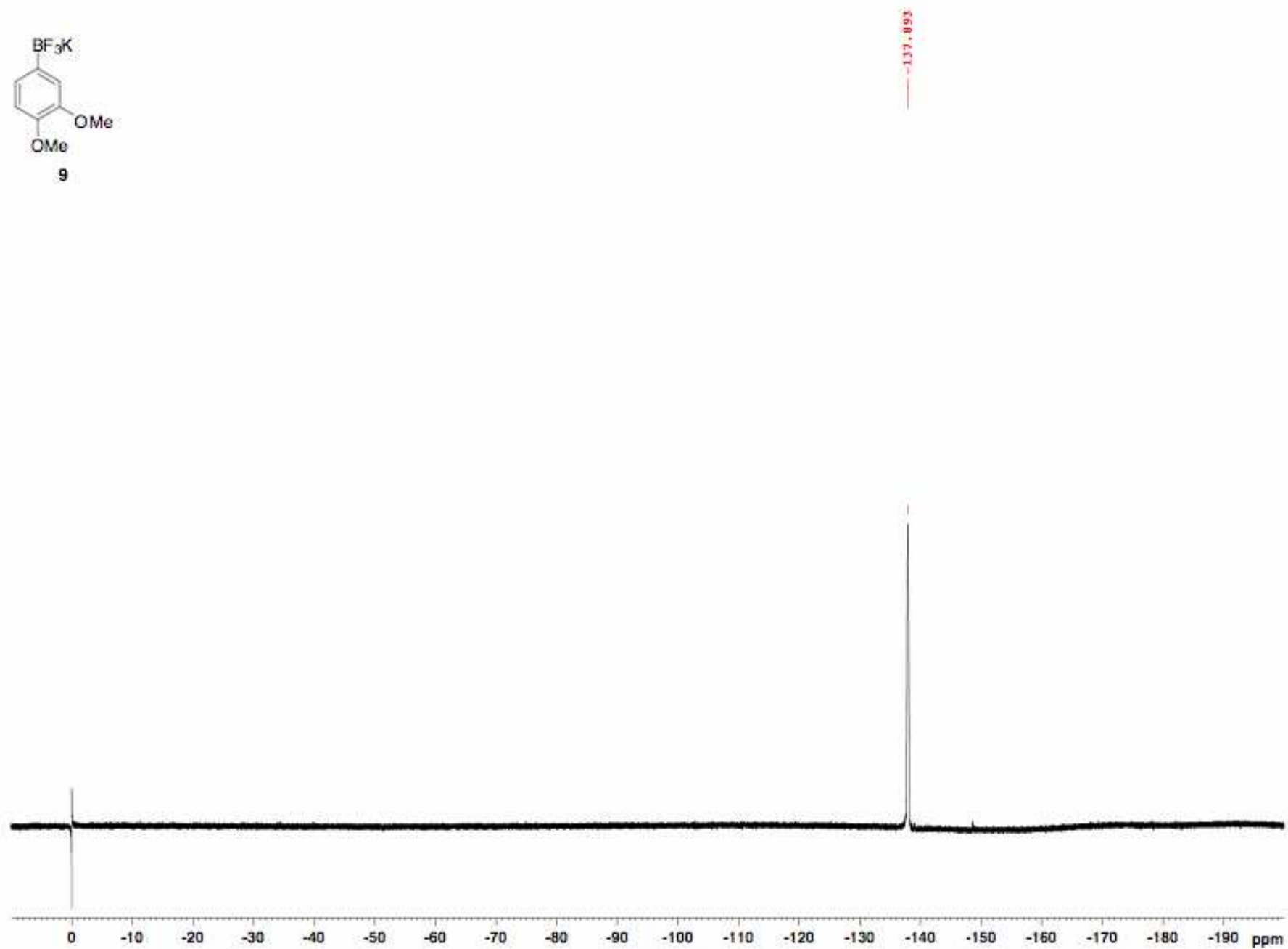
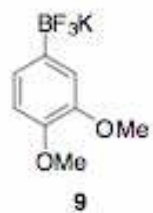


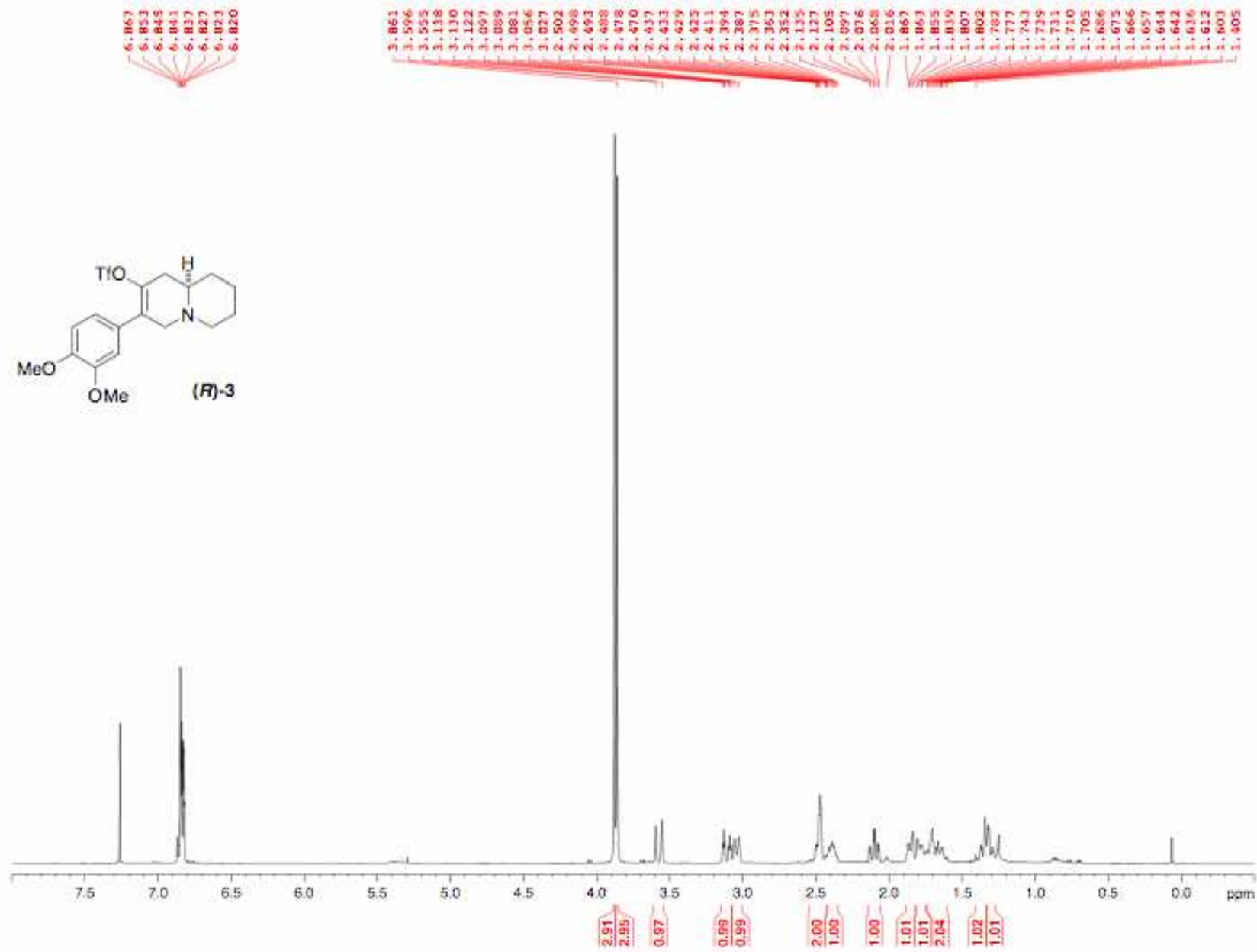
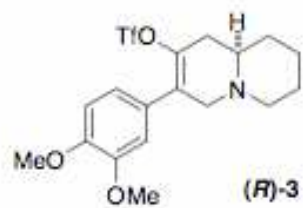


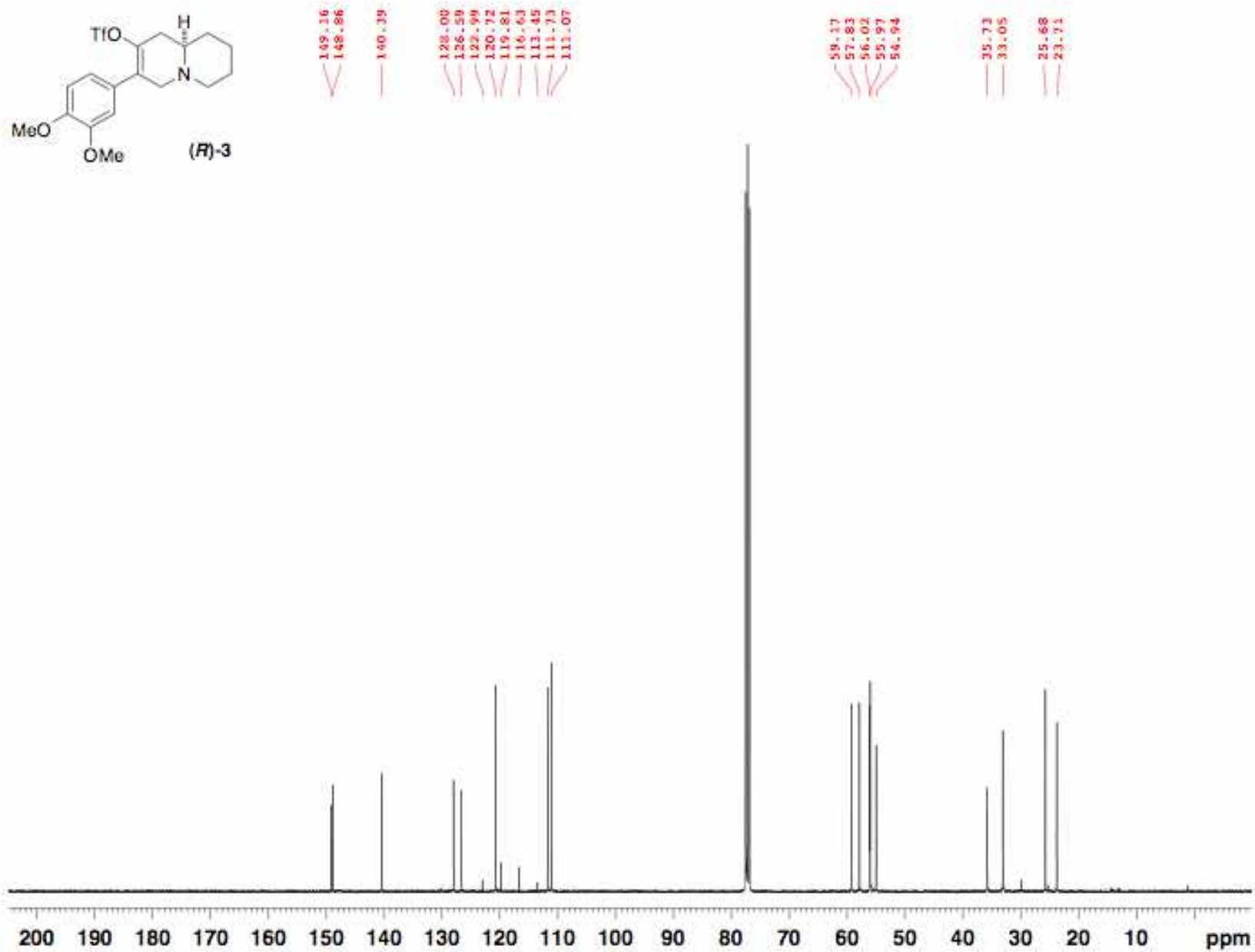
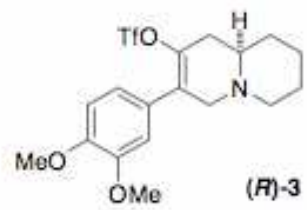


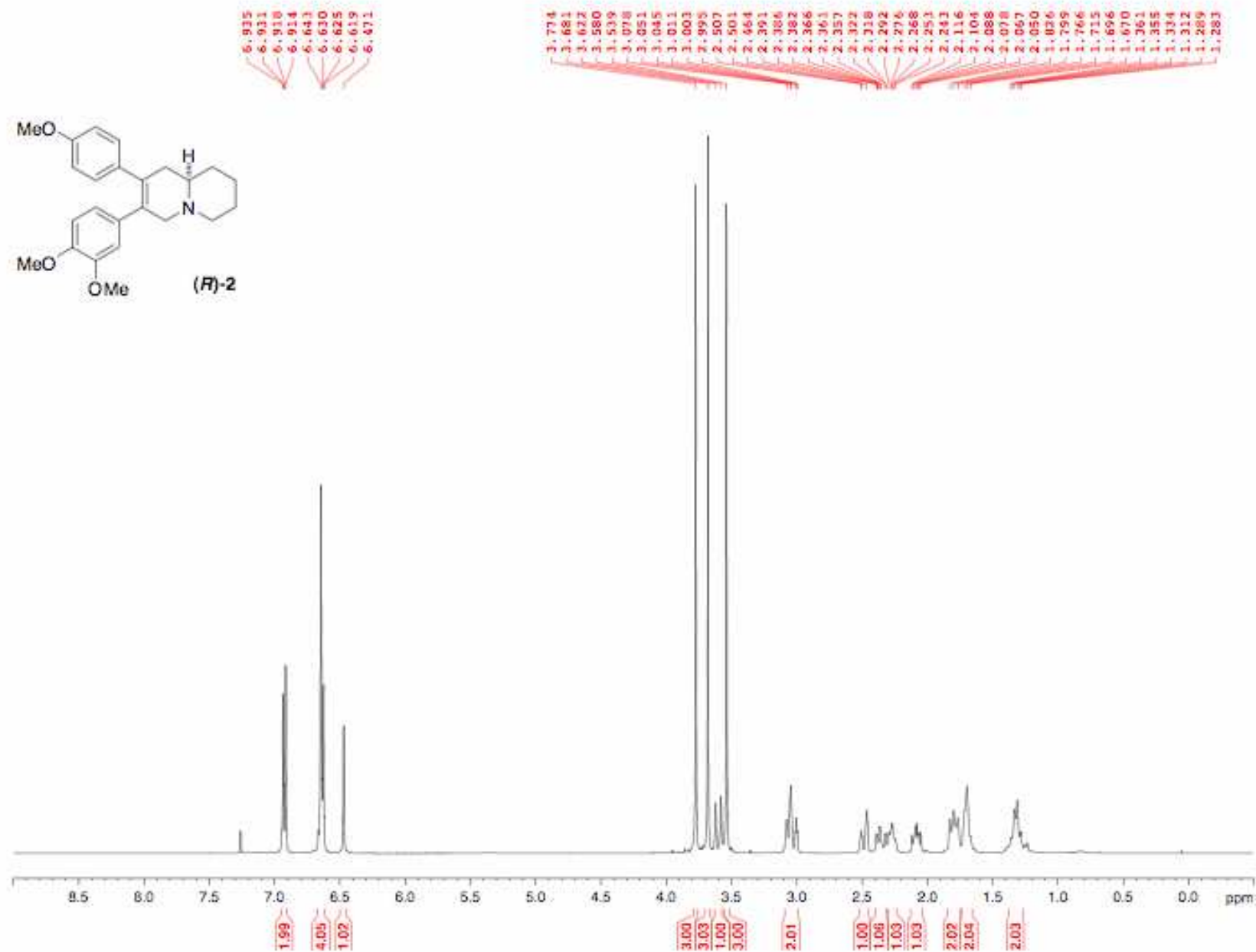
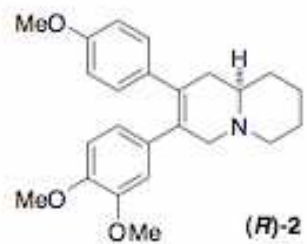


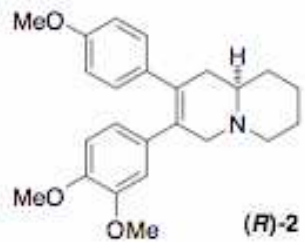












157.87  
148.08  
147.37  
134.43  
133.33  
131.45  
131.30  
129.84  
120.89  
113.28  
113.24  
110.56

65.18  
57.93  
55.71  
55.66  
55.55  
55.13  
39.89  
33.38  
25.96  
25.41

