

Supporting Information

Practical, Large-Scale Preparation of Benzoxepines and Coumarins through Rhodium(III)-Catalyzed C–H Activation/Annulation Reactions

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General experimental information

Reactions were conducted in dry solvents unless otherwise stated. Unless specified otherwise, all commercially available reagents and solvents were used as received. Column chromatography was performed on silica gel (40-63 μm) unless otherwise stated. Thin layer chromatography (TLC) was carried out on pre-coated silica gel F₂₅₄ plates with visualization under UV light or by dipping the plate into solutions of *p*-anisaldehyde or cerium nitrate solutions followed by heating.

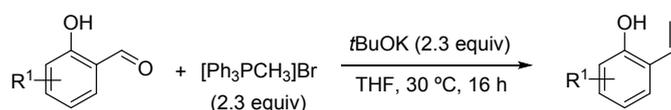
NMR data was collected on a Varian Mercury 300 MHz, Varian Innova 500 MHz spectrometers or Bruker Advance 400 MHz. Chemical shifts are given in ppm (δ) and are referenced to the residual CDCl₃ solvent peak at 7.26 ppm (¹H NMR) and 77.16 ppm (¹³C NMR). Distortionless Enhancement by Polarization Transfer Spectra (DEPT) experiments were recorded at room temperature under routine conditions. NMR data was analyzed using MestReNova NMR data processing software (<http://mestrelab.com/>). High Resolution Mass Spectra (HRMS) were performed at the CACTUS facility of the University of Santiago de Compostela on a Bruker Amazon SL spectrometer and at the CACTI facility of the University of Vigo on a Bruker microTOF or a Bruker APEX-Q FT-ICR-MS spectrometer.

Experimental procedures and characterization data

Preparation of 2-alkenylphenols

2-alkenylphenols were synthesized by Wittig reaction of the corresponding ketone. Spectral data recorded was in agreement with the previously reported.¹

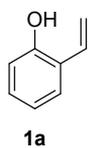
Experimental procedure and characterization data for the large-scale preparation of 2-vinylphenols 1a and 1b



To a solution of methyltriphenylphosphonium bromide (77.1 g, 2.3 equiv) and potassium *tert*-butoxide (24.2 g, 2.3 equiv) in THF (625 mL) under Ar atmosphere was added the aldehyde derivative (94 mmol). The reaction was heated at 30 °C and stirred for 12 hours and then cooled to room temperature. Solvents were removed in vacuo and the resulting mixture was extracted with diethyl ether. The combined organic layers were washed with

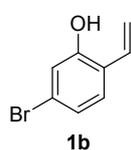
brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by purification by flash chromatography on silica gel (hexanes:diethyl ether; 8:2) gave the corresponding pure 2-vinylphenol.

2-vinylphenol



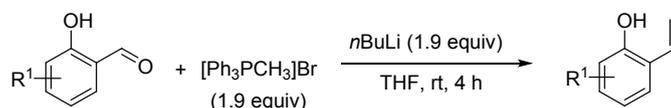
1a obtained as a colourless liquid (8.49 g, 75% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 7.41 (dt, *J* = 7.7 Hz, 1.1 Hz, 1H), 7.16 (td, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.02–6.91 (m, 2H), 6.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.80–5.73 (m, 1H), 5.38 (dd, *J* = 11.2 Hz, 1.4 Hz, 1H), 4.95 (bs, 1H). **HRMS** (ESI, [M-H]⁺) *m/z* calculated for C₈H₉O⁺: 121.0648, found: 121.0651.

5-bromo-2-vinylphenol



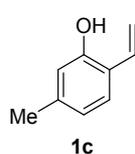
1b obtained as a white solid (13.4 g, 72% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 7.41 (dt, *J* = 7.7 Hz, 1.1 Hz, 1H), 7.16 (td, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.02–6.91 (m, 2H), 6.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.77 (dt, *J* = 17.8, 1.0 Hz, 1H), 5.38 (dd, *J* = 11.2, 1.4 Hz, 1H). **HRMS** (ESI, [M-H]⁺) *m/z* calculated for C₈H₈OBr⁺: 198.9753, found: 198.9762.

Experimental procedure and characterization data for the large-scale preparation of 2-vinylphenol 1c



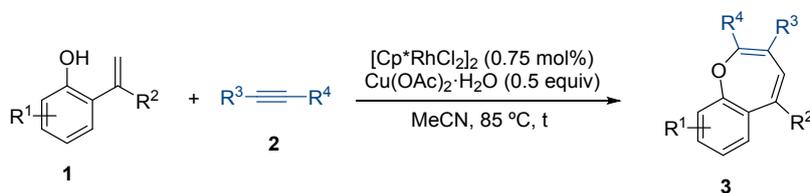
To a solution of methyltriphenylphosphoniumbromide (63.8 g, 1.9 equiv) in THF (625 mL) was added butyllithium solution in hexanes (68.7 mL, 2.6 M) dropwise at -78 °C. The resulting mixture was stirred for 15 minutes, allowed to reach room temperature and added dropwise to the corresponding aldehyde (94 mmol) at -78 °C. The reaction was stirred for 4 hours at room temperature. After that time the reaction was cooled down to 0 °C and quenched with saturated NH₄Cl aqueous solution. The solvent was removed in vacuo and the resulting mixture was extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Evaporation of the solvents followed by flash column chromatography purification on silica gel (hexanes:diethyl ether; 8:2) yielded the corresponding pure 2-vinylphenol.

5-methyl-2-vinylphenol



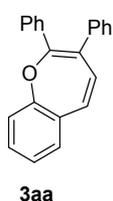
1c obtained as a yellow solid (7.89 g, 63% yield). **¹H NMR** (400 MHz, CDCl₃) δ, ppm: 7.30–7.23 (m, 1H), 6.90 (dd, *J* = 17.7 Hz, 11.2 Hz, 1H), 6.73 (ddd, *J* = 7.8 Hz, 1.4, 0.7 Hz, 1H), 6.62 (dd, *J* = 1.7, 0.8 Hz, 1H), 5.69 (dd, *J* = 17.7 Hz, 1.4 Hz, 1H), 5.31 (dd, *J* = 11.2 Hz, 1.4 Hz, 1H), 4.92 (s, 1H), 2.29 (s, 3H). **HRMS** (ESI, [**M–H**]⁺) *m/z* calculated for C₉H₁₁O⁺: 135.0804, found: 135.0803.

Experimental procedure and characterization data for the large-scale Rh-catalyzed preparation of benzoxepines



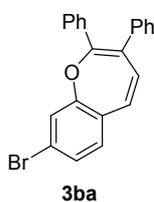
In a two-neck round bottomed flask equipped with a condenser and sealed with a rubber septum, the corresponding alkyne (33 mmol) was added to a solution of [Cp*RhCl₂]₂ (153 mg, 0.75 mol%) and Cu(OAc)₂·H₂O (3.29 g, 0.5 equiv) in MeCN (200 mL) under continuous air flow. The reaction was then heated up to 85 °C and the corresponding 2-vinylphenol (49.5 mmol, 1.5 equiv) was added dropwise for 2.5 h via syringe pump. The reaction was stirred for the given time. After that time the reaction was filtered through Celite® and washed with hexanes and diethyl ether. The solvents were removed in vacuo and the remaining residue was purified by flash column chromatography on silica gel to afford the corresponding benzoxepines **3aa–3ab**.

2,3-diphenylbenzo[*b*]oxepine



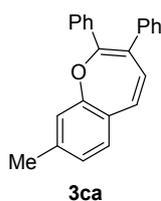
The title compound was prepared following the general procedure. The reaction of 2-vinylphenol (**1a**) (6.01 g, 49.5 mmol) and diphenylacetylene (**2a**) (5.88 g, 33 mmol) were reacted for 16 h at 85 °C and was purified by column chromatography (20% CH₂Cl₂/hexane) to afford 2,3-diphenylbenzo[*b*]oxepine (**3aa**) as a yellow solid (8.35 g, 85% yield). **¹H NMR** (400 MHz, CDCl₃) δ, ppm: 7.49–7.43 (m, 2H), 7.37 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 7.32–7.17 (m, 10H), 7.01 (d, *J* = 11.1 Hz, 1H), 6.96–6.92 (m, 1H), 6.46 (d, *J* = 11.1 Hz, 1H). **HRMS** (ESI, [**M–H**]⁺) *m/z* calculated for C₂₂H₁₇O⁺: 297.1274, found: 297.1268.

8-bromo-2,3-diphenylbenzo[*b*]oxepine



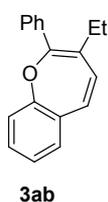
The title compound was prepared following the general procedure. The reaction of 5-bromo-2-vinylphenol (**1b**) (9.85 g, 49.5 mmol) and diphenylacetylene (**2a**) (5.88 g, 33 mmol) using 204 mg (1 mol%) of $[\text{Cp}^*\text{RhCl}_2]_2$ were reacted for 16 h at 85 °C and was purified by column chromatography (20% CH_2Cl_2 /hexane) to afford 8-bromo-2,3-diphenylbenzo[*b*]oxepine (**3ba**) as a yellow solid (7.80 g, 63% yield). **$^1\text{H NMR}$** (400 MHz, CDCl_3) δ , ppm: 7.45–7.37 (m, 2H), 7.37–7.14 (m, 10H), 7.08 (d, $J = 2.0$ Hz, 1H), 6.91 (d, $J = 11.2$ Hz, 1H), 6.44 (d, $J = 11.1$ Hz, 1H). **HRMS** (ESI, $[\text{M}-\text{H}]^+$) m/z calculated for $\text{C}_{22}\text{H}_{16}\text{OBr}^+$: 375.0379, found: 375.0370.

8-methyl-2,3-diphenylbenzo[*b*]oxepine



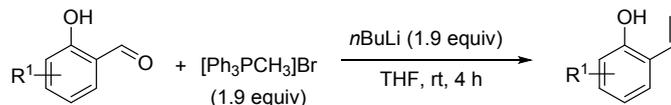
The title compound was prepared following the general procedure. The reaction of 5-methyl-2-vinylphenol (**1c**) (6.64 g, 49.5 mmol) and diphenylacetylene (**2a**) (5.88 g, 33 mmol) were reacted for 36 h at 85 °C and was purified by column chromatography (20% CH_2Cl_2 /hexane) to afford 8-methyl-2,3-diphenylbenzo[*b*]oxepine (**3ca**) as a white solid (6.89 g, 67% yield). **$^1\text{H NMR}$** (400 MHz, CDCl_3) δ , ppm: 7.43–7.39 (m, 2H), 7.24–7.14 (m, 9H), 6.97 (ddd, $J = 7.8$ Hz, 1.7 Hz, 0.8 Hz, 1H), 6.93 (d, $J = 11.1$ Hz, 1H), 6.72–6.70 (m, 1H), 6.34 (d, $J = 11.1$ Hz, 1H), 2.27 (s, 3H). **HRMS** (ESI, $[\text{M}-\text{H}]^+$) m/z calculated for $\text{C}_{23}\text{H}_{19}\text{O}^+$: 311.1430, found: 311.1424.

3-ethyl-2-phenylbenzo[*b*]oxepine



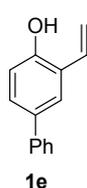
The title compound was prepared following the general procedure. The reaction 2-vinylphenol (**1a**) (6.01 g, 49.5 mmol) and but-1-yn-1-ylbenzene (**2b**) (4.30 g, 33 mmol) were reacted for 16 h at 85 °C and was purified by column chromatography (20% CH_2Cl_2 /hexane) to afford 3-ethyl-2-phenylbenzo[*b*]oxepine (**3ab**) as a white solid (4.75 g, 58% yield). **$^1\text{H NMR}$** (400 MHz, CDCl_3) δ , ppm: 7.62–7.58 (m, 2H), 7.44–7.35 (m, 3H), 7.30–7.22 (m, 2H), 7.18–7.12 (m, 1H), 6.91–6.86 (m, 2H), 6.34 (d, $J = 11.2$ Hz, 1H), 2.28 (q, $J = 7.5$ Hz, 2H), 1.09 (t, $J = 7.5$ Hz, 3H). **HRMS** (ESI, $[\text{M}-\text{H}]^+$) m/z calculated for $\text{C}_{18}\text{H}_{17}\text{O}^+$: 249.1273, found: 249.1268.

Experimental procedure and characterization data for the preparation of 2-vinylphenol 1e



To a solution of methyltriphenylphosphoniumbromide (2.78 g, 1.9 equiv) in THF (26 mL) was added butyllithium solution in hexanes (3.0 mL, 2.6 M) dropwise to -78°C . The resulting mixture was stirred 15 minutes, allowed to reach room temperature and added dropwise to the corresponding aldehyde (4.1 mmol) at -78°C . The reaction was stirred for 4 hours at room temperature and quenched with saturated NH_4Cl aqueous solution. The solvent was removed in vacuo and the resulting mixture was extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . Evaporation of the solvents followed by flash column chromatography purification on silica gel (hexanes:diethyl ether; 8:2) yielded the corresponding pure 2-vinylphenol

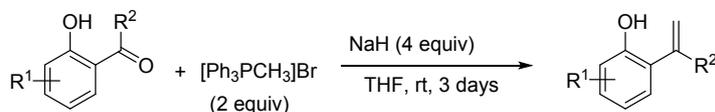
3-vinyl-[1,1'-biphenyl]-4-ol



1e obtained as a white solid (708 mg, 88% yield). $^1\text{H NMR}$ (300 MHz CDCl_3) δ , ppm: 7.61–7.53 (m, 3H), 7.45–7.36 (m, 3H), 7.31 (tt, $J = 7.3$ Hz, $J = 1.5$ Hz, 1H), 6.98 (dd, $J = 17.8$ Hz, $J = 11.2$ Hz, 1H), 6.87 (d, $J = 8.3$ Hz, 1H), 5.81 (dd, $J = 17.7$ Hz, $J = 1.2$ Hz, 1H), 5.42 (dd, $J = 11.2$ Hz, $J = 1.2$ Hz, 1H), 5.01 (s, 1H).

HRMS (APCI, $[\text{M}-1]^+$) m/z calculated for $\text{C}_{14}\text{H}_{11}\text{O}$: 195.0815, found 195.0813.

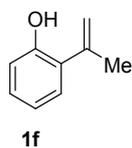
Experimental procedure and characterization data for the large-scale preparation of 2-alkenylphenol 1f



To a suspension of sodium hydride (15.0 g, 4 equiv) in THF (375 mL) under Ar atmosphere was added methyltriphenylphosphoniumbromide (67.2 g, 2 equiv) at 0°C . The reaction mixture was stirred for 1h at that temperature. Then the corresponding ketone (94 mmol) was added at 0°C and the reaction was stirred for 3 days at room temperature and cooled down to 0°C . The reaction mixture is then carefully quenched with saturated NH_4Cl aqueous solution. The solvent was removed in vacuo and the resulting mixture was extracted with diethyl ether. The combined organic layer was

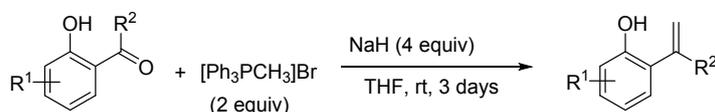
washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification by flash chromatography on silica gel (hexanes:diethylether; 8:2) gave the corresponding pure 2-alkenylphenol.

2-(prop-1-en-2-yl)phenol



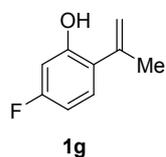
1f obtained as a yellow liquid (9.71 g, 77% yield). **¹H NMR** (300 MHz CDCl₃) δ , ppm: 7.29–7.25 (m, 2H), 7.08–6.99 (m, 2H), 6.02 (s, 1H), 5.49 (s, 1H), 2.24 (s, 3H). **HRMS** (ESI, [M-H]⁺) *m/z* calculated for C₉H₁₁O⁺: 135.0804, found 135.0803.

Experimental procedure and characterization data for the preparation of 2-alkenylphenols 1g-1m



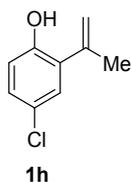
To a suspension of sodium hydride (0.66 g, 4 equiv) in THF (16 mL) under Ar atmosphere was added methyltriphenylphosphoniumbromide (2.93 g, 2 equiv) at 0 °C. The reaction mixture was stirred for 1h at that temperature. Then the corresponding ketone (4.1 mmol) was added at 0 °C and the reaction was stirred for 3 days at room temperature and quenched with saturated NH₄Cl aqueous solution. The solvent was removed in vacuo and the resulting mixture was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification by flash chromatography on silica gel (hexanes:diethylether; 8:2) gave the corresponding pure 2-alkenylphenol.

5-fluoro-2-(prop-1-en-2-yl)phenol



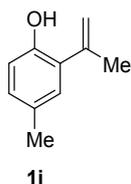
1g obtained as a colourless liquid (393 mg, 63% yield). **¹H NMR** (300 MHz CDCl₃) δ , ppm: 7.08 (dd, *J* = 8.5 Hz, *J* = 6.5 Hz, 1H), 6.69–6.57 (m, 2H), 5.84 (bb, 1H), 5.43–5.40 (m, 1H), 5.13–5.11 (m, 1H), 2.10–2.08 (m, 3H). **HRMS** (APCI, [M-1]⁻) *m/z* calculated for C₉H₈FO⁻: 151.0565, found 151.0565.

4-chloro-2-(prop-1-en-2-yl)phenol



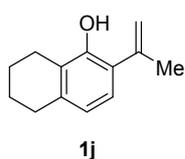
1h obtained as a colourless liquid (470 mg, 88% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 7.13–7.08 (m, 2H), 6.89–6.83 (m, 1H), 5.61 (s, 1H), 5.43 (s, 1H), 5.15 (s, 1H), 2.10 (s, 3H). **HRMS** (APCI, **[M-1]⁻**) *m/z* calculated for C₉H₈ClO: 167.0269, found 167.0269.

4-chloro-2-(prop-1-en-2-yl)phenol



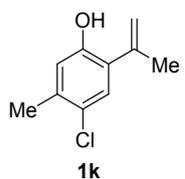
1i obtained as a pale yellow liquid (559 mg, 92% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 6.99–6.92 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.50 (d, *J* = 2.4 Hz, 1H), 5.40–5.37 (m, 1H), 5.12 (s, 1H), 2.27 (s, 3H), 2.11 (s, 3H). **HRMS** (APCI, **[M-H]⁺**) *m/z* calculated for C₁₀H₁₃O⁺: 149.0961, found 149.0961.

2-(prop-1-en-2-yl)-5,6,7,8-tetrahydronaphthalen-1-ol



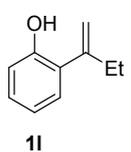
1j obtained as a colourless liquid (448 mg, 58% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 6.91 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.83 (s, 1H), 5.39 (t, *J* = 1.6 Hz, 1H), 5.13 (s, 1H), 2.78–2.66 (m, 4H), 2.11 (s, 3H), 1.87–1.72 (m, 4H). **HRMS** (APCI, **[M-H]⁺**) *m/z* calculated for C₁₃H₁₇O⁺: 189.1274, found 189.1272.

4-chloro-5-methyl-2-(prop-1-en-2-yl)phenol



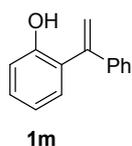
1k obtained as a pale yellow liquid (539 mg, 72% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 7.10 (s, 1H), 6.81 (s, 1H), 5.55 (s, 1H), 5.41–5.38 (m, 1H), 5.13 (s, 1H), 2.31 (s, 3H), 2.10–2.07 (m, 3H). **HRMS** (APCI, **[M-1]⁺**) *m/z* calculated for C₁₀H₁₀ClO: 181.0426, found 181.0425.

2-(1-(but-1-en-2-yl)phenol



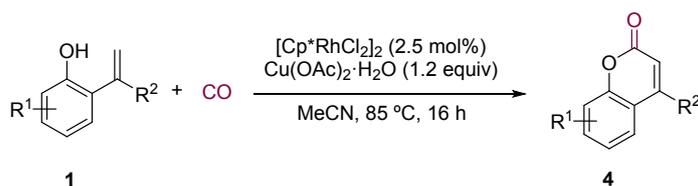
1l obtained as a yellow liquid (310 mg, 51% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 7.20–7.13 (m, 1H), 7.09 (dd, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 6.97–6.85 (m, 2H), 5.62 (s, 1H), 5.40 (d, *J* = 1.5 Hz, 1H), 5.13 (s, 1H), 2.42 (q, *J* = 7.4 Hz, 2H), 1.07 (t, *J* = 7.4 Hz, 3H). **HRMS** (APCI, **[M-1]⁻**) *m/z* calculated for C₁₀H₁₁O: 147.0815, found 147.0815.

2-(1-phenylvinyl)phenol



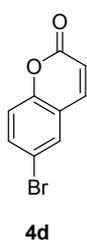
1m obtained as a yellow liquid (724 mg, 90% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 7.40–7.32 (m, 5H), 7.30–7.23 (m, 1H), 7.14 (dd, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 6.98–6.90 (m, 2H), 5.88 (d, *J* = 1.1 Hz, 1H), 5.43 (d, *J* = 1.1 Hz, 1H), 5.14 (s, 1H). **HRMS** (APCI, [**M-1**]⁻) *m/z* calculated for C₁₄H₁₁O: 195.0815, found 195.0813.

Experimental procedure for the Rh-catalyzed preparation of coumarins, and characterization of the products



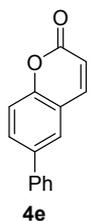
To a solution of [Cp*RhCl₂]₂ (7.7 mg, 2.5 mol%) and Cu(OAc)₂·H₂O (120 mg, 1.2 equiv) in MeCN (2 mL) purged with CO was added the corresponding 2-alkenylphenol (0.5 mmol). The reaction was sealed with a rubber septum and a CO atmosphere was injected in the flask with a balloon. The reaction was heated up to 85 °C and stirred for 16 hours and then cooled to room temperature. The reaction was filtered through Celite and washed with hexanes and diethyl ether. The solvents were removed in vacuo and the remaining residue was purified by flash column chromatography on silica gel to afford the corresponding coumarin products **4d-4m**.

6-bromo-2H-chromen-2-one



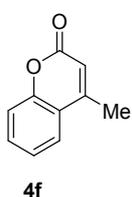
The title compound was prepared following the general procedure. The reaction of 4-bromo-2-vinylphenol (**1d**) (99.5 mg, 0.5 mmol) and CO was purified by column chromatography (10% to 20% EtOAc/hexane) to afford 6-bromo-2H-chromen-2-one (**4d**) as a yellow solid (64.4 mg, 57% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.66–7.59 (m, 3H), 7.23 (d, *J* = 9.5 Hz, 1H), 6.46 (d, *J* = 9.6 Hz, 1H). **HRMS** (APCI, [**M-H**]⁺) *m/z* calculated for C₉H₆BrO₂⁺: 224.9546, found: 224.9546.

6-phenyl-2H-chromen-2-one



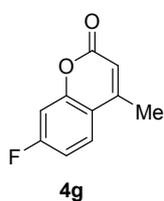
The title compound was prepared following the general procedure. The reaction of 3-vinyl-[1,1'-biphenyl]-4-ol (**1e**) (98.1 mg, 0.5 mmol) and CO was purified by column chromatography (10 to 20% EtOAc/hexane) to afford 6-phenyl-2H-chromen-2-one (**4e**) as a yellow solid (82.2 mg, 74% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.79–7.72 (m, 2H), 7.67 (d, *J* = 2.1 Hz, 1H), 7.60–7.55 (m, 2H), 7.50–7.44 (m, 2H), 7.42–7.36 (m, 2H), 6.47 (d, *J* = 9.5 Hz, 1H). **HRMS** (APCI, [**M–H**]⁺) *m/z* calculated for C₁₅H₁₁O₂⁺: 223.0754, found: 223.0752.

4-methyl-2H-chromen-2-one



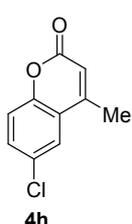
The title compound was prepared following the general procedure. The reaction of 2-(prop-1-en-2-yl)phenol (**1f**) (67.1 mg, 0.5 mmol) and CO was purified by column chromatography (10% to 20% EtOAc/hexane) to afford 4-methyl-2H-chromen-2-one (**4f**) as a white solid (68.9 mg, 86% yield). **¹H NMR** (400 MHz, CDCl₃) δ, ppm: 7.61–7.58 (m, 1H), 7.52 (ddd, *J* = 8.6 Hz, 7.1 Hz, 1.5 Hz, 1H), 7.32–7.26 (m, 2H), 6.27 (s, 1H), 2.43 (s, 3H). **HRMS** (ESI, [**M–H**]⁺) *m/z* calculated for C₁₀H₉O₂⁺: 161.0597, found: 161.0598.

7-fluoro-4-methyl-2H-chromen-2-one



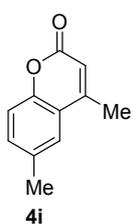
The title compound was prepared following the general procedure. The reaction of 5-fluoro-2-(prop-1-en-2-yl)phenol (**1g**) (76.1 mg, 0.5 mmol) and CO was purified by column chromatography (10% to 20% EtOAc/hexane) to afford 7-fluoro-4-methyl-2H-chromen-2-one (**4g**) as a yellow solid (47.2 mg, 53% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.62–7.55 (m, 1H), 7.07–6.99 (m, 2H), 6.25–6.23 (m, 1H), 2.43 (d, *J* = 1.2 Hz, 3H). **HRMS** (APCI, [**M–H**]⁺) *m/z* calculated for C₁₀H₈FO₂⁺: 179.0503, found: 179.0503.

6-chloro-4-methyl-2H-chromen-2-one



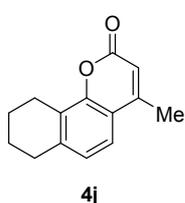
The title compound was prepared following the general procedure. The reaction of 4-chloro-2-(prop-1-en-2-yl)phenol (**1h**) (84.3 mg, 0.5 mmol) and CO was purified by column chromatography (10% to 20% EtOAc/hexane) to afford 6-chloro-4-methyl-2H-chromen-2-one (**4h**) as a white crystals (67.0 mg, 69% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.57 (d, *J* = 2.4 Hz, 1H), 7.48 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 6.34–6.31 (m, 1H), 2.43 (d, *J* = 1.2 Hz, 3H). **HRMS** (APCI, [**M–H**]⁺) *m/z* calculated for C₁₀H₈ClO₂⁺: 195.0207, found: 195.0207.

4,6-dimethyl-2*H*-chromen-2-one



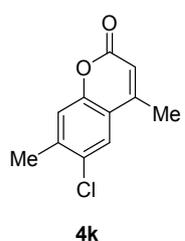
The title compound was prepared following the general procedure. The reaction of 4-methyl-2-(prop-1-en-2-yl)phenol (**1i**) (74.1 mg, 0.5 mmol) and CO was purified by column chromatography (10% to 20% EtOAc/hexane) to afford 4,6-dimethyl-2*H*-chromen-2-one (**4i**) as a white solid (61.0 mg, 70% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.36 (s, 1H), 7.34–7.29 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.26–6.24 (m, 1H), 2.43–2.39 (m, 6H). **HRMS** (APCI, [M–H]⁺) *m/z* calculated for C₁₁H₁₁O₂⁺: 175.0754, found: 175.0753.

4-methyl-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one



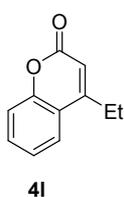
The title compound was prepared following the general procedure. The reaction of 2-(prop-1-en-2-yl)-5,6,7,8-tetrahydronaphthalen-1-ol (**1j**) (94.1 mg, 0.5 mmol) and CO was purified by column chromatography (10% to 20% EtOAc/hexane) to afford 4-methyl-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one (**4j**) as a white solid (93.1 mg, 87% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.33 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.22–6.20 (m, 1H), 2.90 (t, *J* = 5.7 Hz, 2H), 2.84 (t, *J* = 5.6 Hz, 2H), 2.40 (d, *J* = 1.1 Hz, 3H), 1.89–1.76 (m, 4H). **HRMS** (APCI, [M–H]⁺) *m/z* calculated for C₁₄H₁₅O₂⁺: 215.1067, found: 215.1066.

6-chloro-4,7-dimethyl-2*H*-chromen-2-one



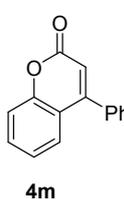
The title compound was prepared following the general procedure. The reaction of 4-chloro-5-methyl-2-(prop-1-en-2-yl)phenol (**1k**) (91.3 mg, 0.5 mmol) and CO was purified by precipitating the product from the reaction crude mixture using 5 mL of hexanes to afford 4-methyl-7,8,9,10-tetrahydro-2*H*-benzo[*h*]chromen-2-one (**4k**) as a white solid (91.6 mg, 88% yield). **¹H NMR** (300 MHz CDCl₃) δ, ppm: 7.55 (s, 1H), 7.21 (s, 1H), 6.27 (s, 1H), 2.46 (s, 3H), 2.41 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ, ppm: 160.5 (C), 151.9 (C), 151.5 (C), 140.6 (C), 130.1 (C), 124.5 (CH), 119.2 (C), 119.0 (CH), 115.1 (CH), 20.6 (CH₃), 18.7 (CH₃). **HRMS** (APCI, [M–H]⁺) *m/z* calculated for C₁₁H₁₀ClO₂⁺: 209.0364, found 209.0362.

4-ethyl-2*H*-chromen-2-one



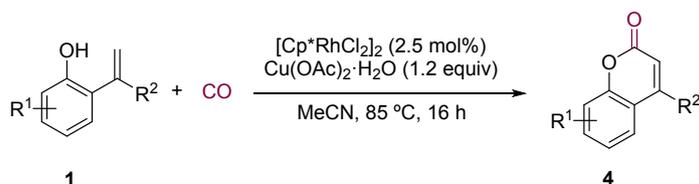
The title compound was prepared following the general procedure. The reaction of 2-(but-1-en-2-yl)phenol (**1l**) (74.1 mg, 0.5 mmol) and CO was purified by column chromatography (10 to 20% EtOAc/hexane) to afford 4-ethyl-2*H*-chromen-2-one (**4l**) as a white solid (65.2 mg, 75% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.63 (dd, *J* = 7.9 Hz, *J* = 1.4 Hz, 1H), 7.54–7.47 (m, 1H), 7.35–7.25 (m, 2H), 6.29 (s, 1H), 2.82 (qd, *J* = 7.4 Hz, *J* = 1.2 Hz, 2H), 1.33 (t, *J* = 7.4 Hz, 3H). **HRMS** (APCI, [M–H]⁺) *m/z* calculated for C₁₁H₁₁O₂⁺: 175.0754, found: 175.0754.

4-phenyl-2*H*-chromen-2-one



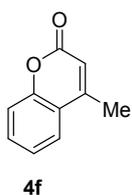
The title compound was prepared following the general procedure. The reaction of 2-(1-phenylvinyl)phenol (**1m**) (98.1 mg, 0.5 mmol) and CO was purified by column chromatography (10% EtOAc/hexane) to afford 4-phenyl-2*H*-chromen-2-one (**4m**) as a white solid (78.9 mg, 71% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 8.46–8.37 (m, 4H), 8.36–8.26 (m, 4H), 8.14–8.07 (m, 2H). **HRMS** (APCI, [M–H]⁺) *m/z* calculated for C₁₅H₁₁O₂⁺: 223.0754, found: 223.0754.

Experimental procedure for the large-scale Rh-catalyzed preparation of coumarins, and characterization of the products



In a two-neck round bottomed flask equipped with a condenser and sealed with a rubber septum, the corresponding 2-alkenylphenol (33 mmol) was added to a solution of [Cp*RhCl₂]₂ (510 mg, 2.5 mol%) and Cu(OAc)₂·H₂O (7.91 g, 1.2 equiv) in MeCN (135 mL), the resulting mixture was purged with CO and a CO atmosphere was injected in the system with a balloon. The reaction was heated up to 85 °C and stirred for 16 hours at that temperature. After that time the reaction was cooled to room temperature. The reaction was filtered through Celite and washed with hexanes and diethyl ether. The solvents were removed in vacuo and the remaining residue was purified by flash column chromatography on silica gel to afford the corresponding coumarin product **4f**.

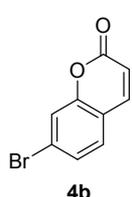
4-methyl-2H-chromen-2-one



The title compound was prepared following the general procedure. The reaction of 2-(prop-1-en-2-yl)phenol (**1f**) (4.43 g, 33 mmol) and CO was purified by column chromatography (10% to 20% EtOAc/hexane) to afford 4-methyl-2H-chromen-2-one (**4f**) as a white solid (4.70 g, 89% yield). **¹H NMR** (400 MHz, CDCl₃) δ, ppm: 7.61–7.58 (m, 1H), 7.52 (ddd, *J* = 8.6 Hz, 7.1 Hz, 1.5 Hz, 1H), 7.32–7.26 (m, 2H), 6.27 (s, 1H), 2.43 (s, 3H). **HRMS** (ESI, [M–H]⁺) *m/z* calculated for C₁₀H₉O₂⁺: 161.0597, found: 161.0598.

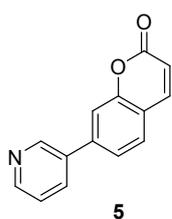
Preparation of CYP19 inhibitor 5

7-bromo-2H-chromen-2-one



The title compound was prepared following the general procedure for the synthesis of coumarins. The reaction of 5-bromo-2-vinylphenol (**1b**) (285 mg, 1.4 mmol) and CO was purified by column chromatography (10% to 25% EtOAc/hexane) to afford 7-bromo-2H-chromen-2-one (**4b**) as a yellow solid (204 mg, 67% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.66 (d, *J* = 9.6 Hz, 1H), 7.52 (d, *J* = 1.4 Hz, 1H), 7.42 (dd, *J* = 8.3 Hz, 1.7 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 6.44 (d, *J* = 9.6 Hz, 1H). **HRMS** (ESI, [M–H]⁺) *m/z* calculated for C₉H₆BrO₂⁺: 224.9546, found: 224.9545.

7-(pyridin-3-yl)-2H-chromen-2-one

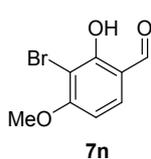


An oven dried Schlenk tube was charged with Pd₂(dba)₃ (1.7 mg, 0.002 mmol), XPhos (0.008 mmol), 3-pyridinylboronic acid (35.0 mg, 0.28 mmol), 7-bromo-2H-chromen-2-one (**4b**) (42.8 mg, 0.19 mmol) and powdered, anhydrous K₃PO₄ (80.7 mg, 0.38 mmol). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was carried out two times). *n*-Butanol (0.38 mL) was added via syringe, through the septum and the reaction mixture was heated to 100 for 3.5 h. At this point the reaction mixture was allowed to cool to room temperature. The reaction solution was then filtered through a thin pad of silica gel (eluting with ethyl acetate) and the eluent was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography (2%/39%/59% to 2%/98%/0% Et₃N/EtOAc/hexane) to afford 7-(pyridin-3-yl)-2H-chromen-2-one (**5**) as a white solid (30.5 mg, 72% yield). **¹H NMR** (300 MHz, acetone-*d*₆) δ, ppm: 8.99 (s, 1H), 8.64 (d, *J* = 4.0 Hz, 1H), 8.15 (ddd, *J* = 7.8 Hz, *J* = 1.5 Hz, *J* = 0.3 Hz, 1H), 8.03 (d, *J* = 9.6 Hz, 1H),

7.81 (d, $J = 7.9$ Hz, 1H), 7.72–7.66 (m, 2H), 7.51 (dd, $J = 7.9$ Hz, $J = 4.9$ Hz, 1H), 6.46 (d, $J = 9.6$ Hz, 1H). **HRMS** (ESI, $[M-H]^+$) m/z calculated for $C_{14}H_{10}NO_2^+$: 224.0706, found: 224.0707.

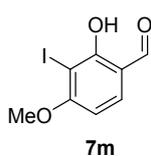
Preparation of osthole

3-bromo-2-hydroxy-4-methoxybenzaldehyde



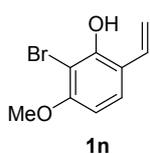
A solution of 2-hydroxy-4-methoxybenzaldehyde (**6**) (1 g, 6.5 mmol) in dichloromethane (40 mL) was cooled to -20 °C and aluminium chloride (876 mg, 6.5 mmol) was added in three portions. The suspension was stirred for 15 min before a solution of bromine (1 g, 337 μ L, 6.5 mmol) in dichloromethane (16 mL) was added over 20 min. It was stirred overnight while warming to room temperature. Then a saturated solution of Na_2SO_3 (5 mL) and hydrochloric acid (4 M, 10 mL) were added in order. The aqueous layer was extracted twice with dichloromethane (2x15 mL) and the combined organic layers were dried over magnesium sulfate. Evaporation of the solvents followed by flash column chromatography purification on silica gel (25% diethyl ether/hexanes) yielded 3-bromo-2-hydroxy-4-methoxybenzaldehyde (**7n**) as a white solid (1.03 g, 67% yield). **1H NMR** (600 MHz, $CDCl_3$) δ , ppm: 11.92 (s, 1H), 9.72 (s, 1H), 7.51 (d, $J = 8.7$ Hz, 1H), 6.62 (d, $J = 8.7$ Hz, 1H), 4.00 (s, 3H). **HRMS** (ESI, $[M-H]^+$) m/z calculated for $C_8H_8O_3Br^+$: 230.9651, found: 230.9647.

3-iodo-2-hydroxy-4-methoxybenzaldehyde



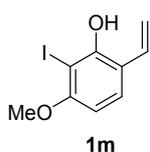
A solution of 2-hydroxy-4-methoxybenzaldehyde (**6**) (500 mg, 3.2 mmol) in dichloromethane (20 mL) was cooled to -20 °C and aluminium chloride (438 mg, 3.2 mmol) was added in three portions. The suspension was stirred for 15 min before a solution of *N*-iodosuccinimide (813 mg, 3.6 mmol) was added in three portions. It was stirred overnight while warming to room temperature. Then a solution of hydrochloric acid (4 M, 10 mL) was added, the aqueous layer was extracted twice with dichloromethane (2x15 mL) and the combined organic layers were dried over magnesium sulfate. Evaporation of the solvents followed by flash column chromatography purification on silica gel (10% dichloromethane/hexanes) yielded 3-iodo-2-hydroxy-4-methoxybenzaldehyde (**7m**) as a white solid (806 mg, 88% yield). **1H NMR** (600 MHz, $CDCl_3$) δ , ppm: 12.17 (s, 1H), 9.63 (s, 1H), 7.53 (d, $J = 8.6$ Hz, 1H), 6.56 (d, $J = 8.6$ Hz, 1H), 3.99 (s, 3H). **HRMS** (ESI, $[M-H]^+$) m/z calculated for $C_8H_8O_3I^+$: 278.9513, found: 278.9511.

2-bromo-3-methoxy-6-vinylphenol



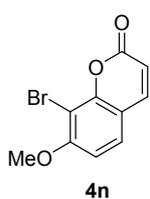
Sodium hydride (60% dispersion in mineral oil, 413 mg, 10.3 mmol) was suspended in THF (29 mL). Then PPh₃MeBr (4.08 g, 11.4 mmol) was added to the suspension and heated to reflux for 1.5 h. After that time the suspension was cooled to 0 °C and a solution of 3-bromo-2-hydroxy-4-methoxybenzaldehyde (**1n**) (700 mg, 3.03 mmol) in THF (10 mL) was added to the reaction mixture over 20 min and stirred for 12 h. The reaction was diluted with ethyl acetate (100 mL) and washed with water (40 mL). The organic layer was dried over magnesium sulfate, concentrated in vacuo and purified by column chromatography (5% EtOAc/hexane) to afford 2-bromo-3-methoxy-6-vinylphenol (**4n**) as a white solid (264 mg, 67% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.36 (d, *J* = 8.6 Hz, 1H), 6.93 (dd, *J* = 17.7 Hz, *J* = 11.2 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 5.86 (bs, 1H), 5.69 (dd, *J* = 17.7 Hz, *J* = 1.3 Hz, 1H), 5.23 (dd, *J* = 17.7 Hz, *J* = 1.2 Hz, 1H), 3.90 (s, 3H). **HRMS** (ESI, [M-H]⁺) *m/z* calculated for C₉H₁₀O₂Br⁺: 228.9859, found: 228.9855.

2-iodo-3-methoxy-6-vinylphenol



Sodium hydride (60% dispersion in mineral oil, 368 mg, 10.3 mmol) was suspended in THF (26 mL). Then PPh₃MeBr (3.59 g, 10.1 mmol) was added to the suspension and heated to reflux for 1.5 h. After that time the suspension was cooled to 0 °C and a solution of 3-iodo-2-hydroxy-4-methoxybenzaldehyde (**1m**) (800 mg, 2.87 mmol) in THF (10 mL) was added to the reaction mixture over 20 min and stirred for 12 h. The reaction was diluted with ethyl acetate (100 mL) and washed with water (30 mL). The organic layer was dried over magnesium sulfate, concentrated in vacuo and purified by column chromatography (20% diethyl ether/hexane) to afford 2-iodo-3-methoxy-6-vinylphenol (**4m**) as a white solid (365 mg, 46% yield). **¹H NMR** (400 MHz, CDCl₃) δ, ppm: 7.37 (d, *J* = 8.5 Hz, 1H), 6.94 (dd, *J* = 17.7 Hz, *J* = 11.2 Hz, 1H), 6.42 (d, *J* = 8.6 Hz, 1H), 5.71–5.63 (m, 3H), 5.21 (dd, *J* = 11.2 Hz, *J* = 1.4 Hz, 1H), 3.88 (s, 3H). **HRMS** (ESI, [M-H]⁺) *m/z* calculated for C₉H₁₀O₂I⁺: 276.9720, found: 276.9714.

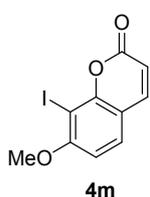
8-bromo-7-methoxy-2H-chromen-2-one



The title compound was prepared following the general procedure for the synthesis of coumarins. The reaction of 2-bromo-3-methoxy-6-vinylphenol (**1n**) (180 mg, 0.75 mmol) and CO for 1 h was purified by column chromatography (10% to 45% EtOAc/hexane) to afford 8-bromo-7-methoxy-2H-chromen-2-one (**4n**) as a yellow solid (106.2 mg, 57% yield).

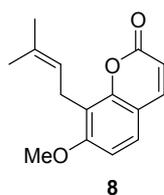
¹H NMR (300 MHz, CDCl₃) δ, ppm: 7.62 (d, *J* = 9.5 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.29 (d, *J* = 9.5 Hz, 1H), 4.00 (s, 3H). **HRMS** (APCI, [M-H]⁺) *m/z* calculated for C₁₀H₈BrO₃⁺: 254.9651, found: 254.9649.

8-iodo-7-methoxy-2H-chromen-2-one



The title compound was prepared following the general procedure for the synthesis of coumarins. The reaction of 2-iodo-3-methoxy-6-vinylphenol (**1m**) (58 mg, 0.2 mmol) and CO for 0.5 h was purified by column chromatography (10% to 45% EtOAc/hexane) to afford 8-iodo-7-methoxy-2H-chromen-2-one (**4n**) as a yellow solid (22 mg, 37% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.58 (d, *J* = 9.5 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.26 (d, *J* = 9.5 Hz, 1H), 3.99 (s, 3H). **HRMS** (APCI, [M-H]⁺) *m/z* calculated for C₁₀H₈IO₃⁺: 302.9513, found: 302.9514.

osthole



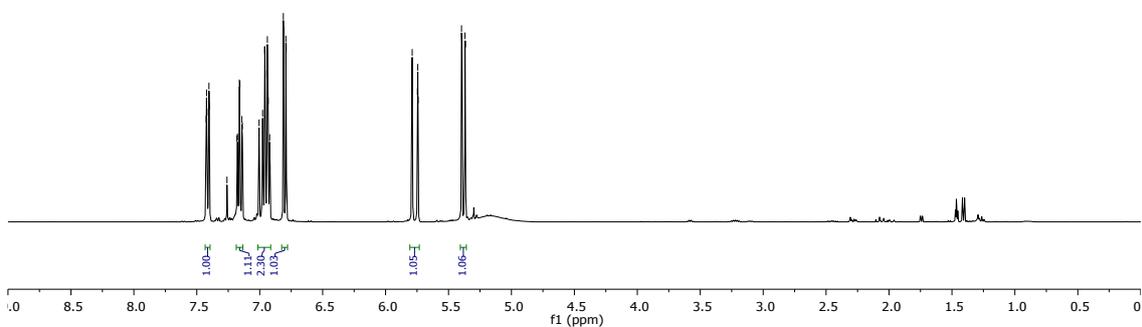
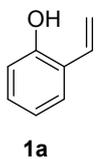
An oven-dried Schlenk tube under nitrogen was charged with 8-bromo-7-methoxy-2H-chormen-2-one (**4n**) (15.3 mg, 0.06 mmol), tributyl(3-methylbut-2-en-1-yl)stannane (64.7 mg, 0.18 mmol), Pd(dppf)Cl₂ (8.8 mg, 0.012 mmol) and dry DMF (0.9 mL). The mixture was stirred at 125 °C for 5 h. After that time the mixture was cooled to room temperature and quenched with a solution of saturated ammonium chloride (20 mL). The reaction was extracted with AcOEt (20x2 mL) and the organic phases were collected and washed with brine. The organic extract was dried with magnesium sulfate a concentrated in vacuo and purified by column chromatography (5% to 20% EtOAc/hexane) to afford osthole (**8**) as a white solid (4.7 mg, 32% yield). **¹H NMR** (300 MHz, CDCl₃) δ, ppm: 7.61 (d, *J* = 9.5 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.24 (d, *J* = 9.4 Hz, 1H), 5.22 (t, *J* = 7.3 Hz, 1H), 3.92 (s, 3H), 3.54 (d, *J* = 7.3 Hz, 2H), 1.84 (s, 3H), 1.67 (s, 3H). **HRMS** (APCI, [M-H]⁺) *m/z* calculated for C₁₅H₁₇O₃⁺: 245.1172, found: 245.1175.

References

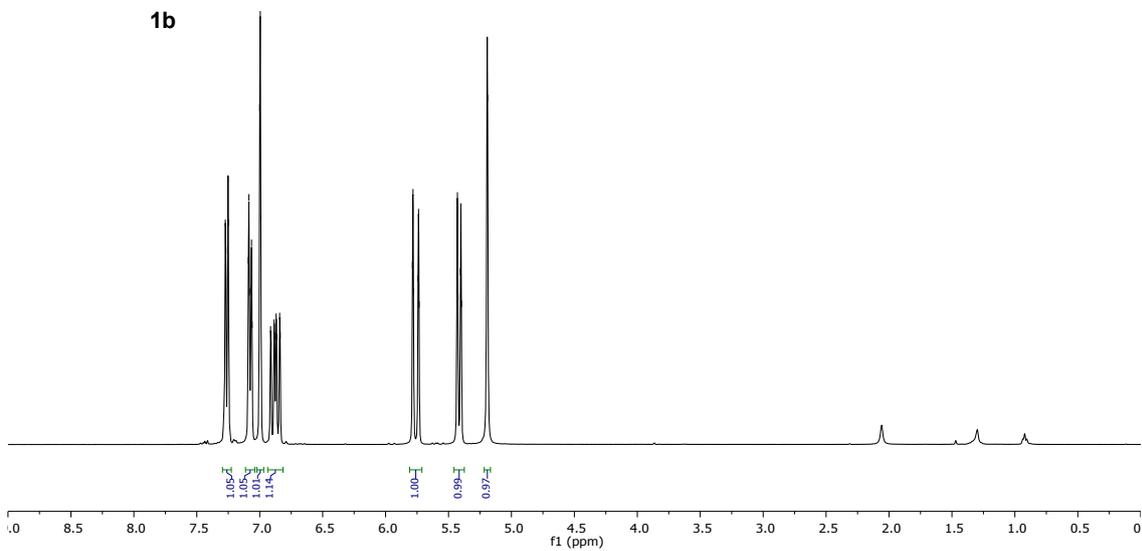
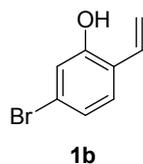
1. a) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 834–837. b) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 7607–7610.

NMR spectral data

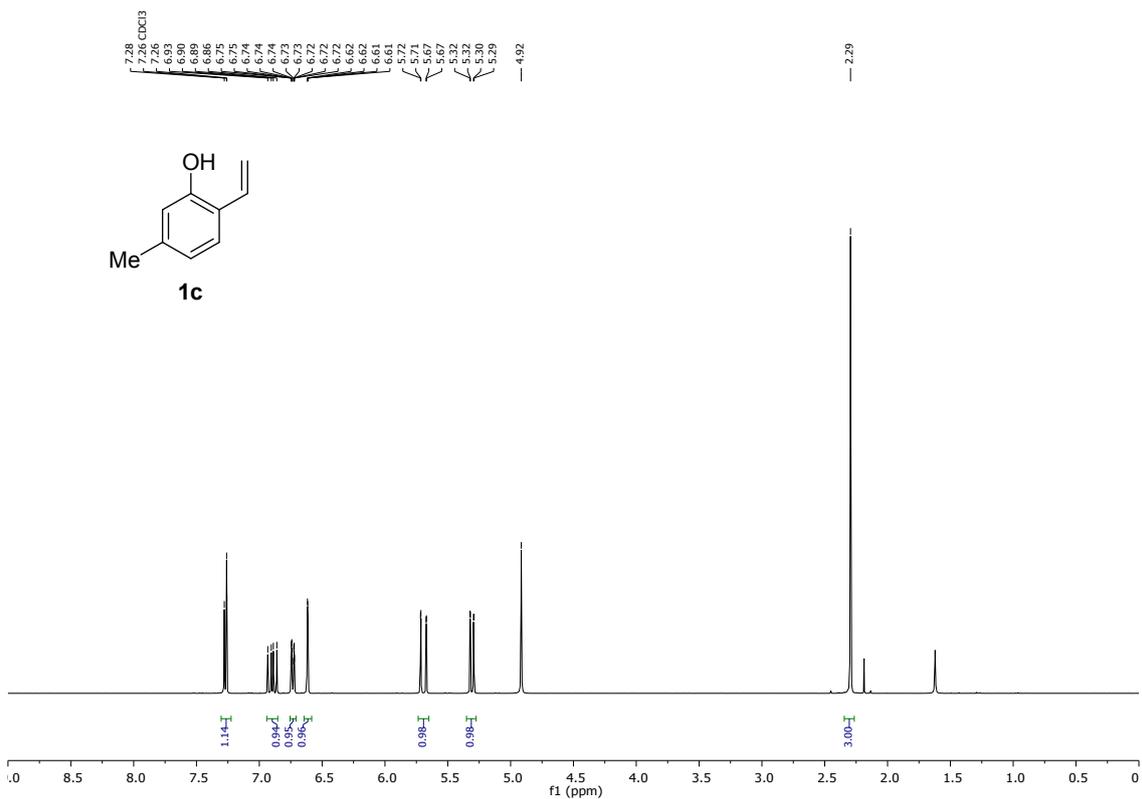
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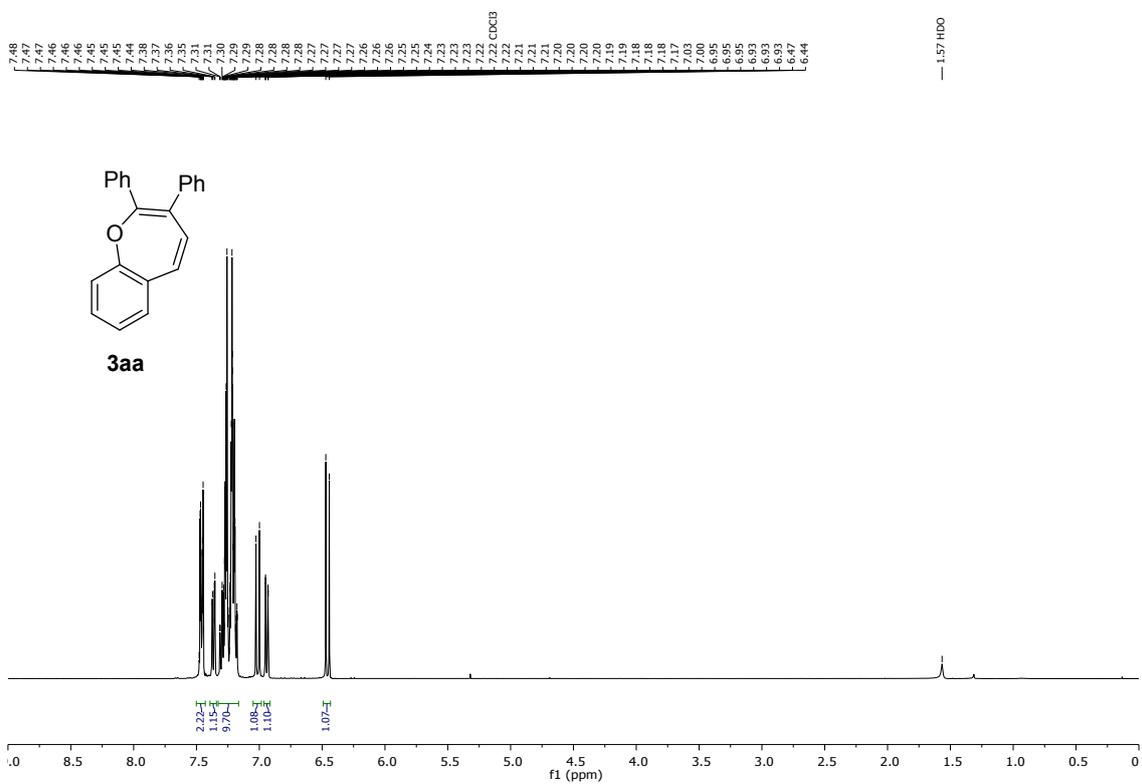
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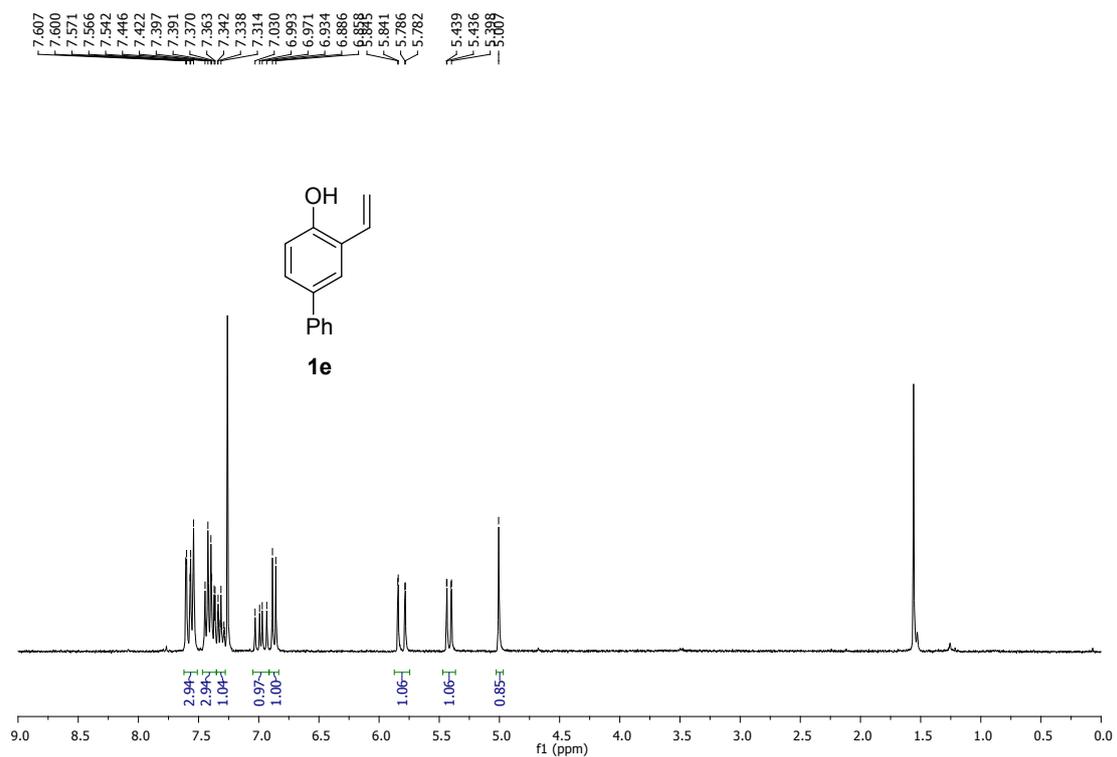
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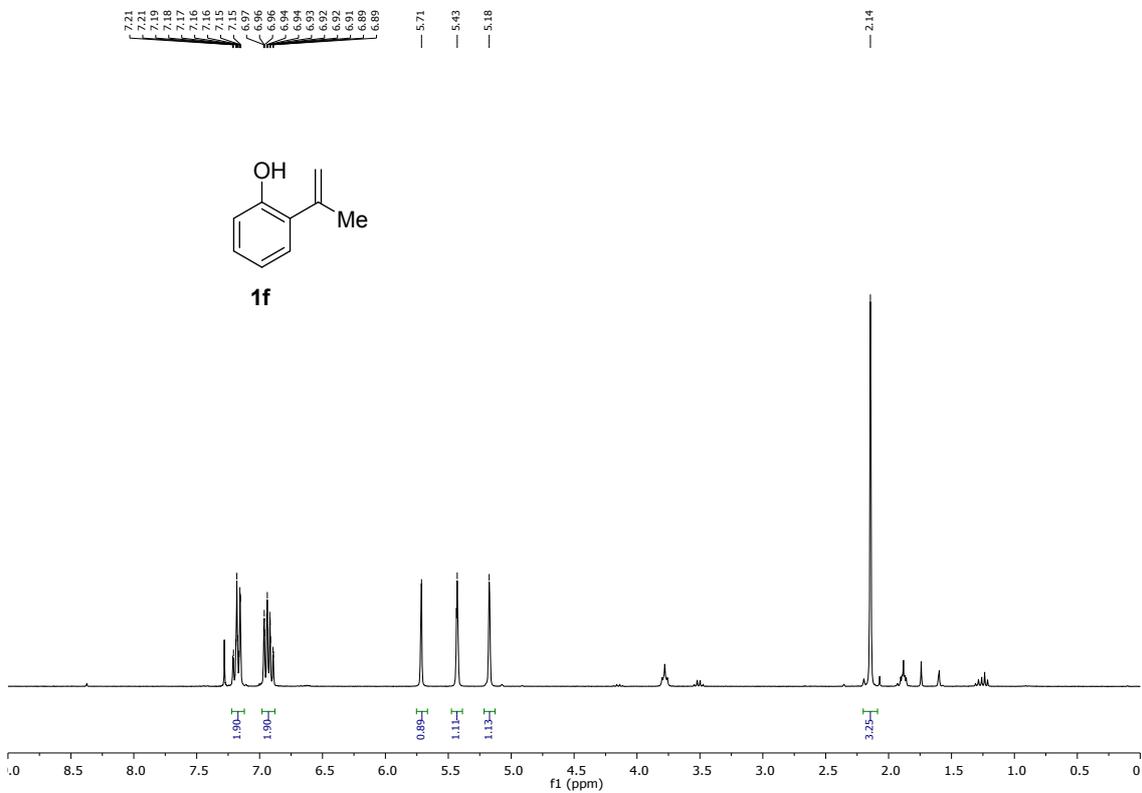
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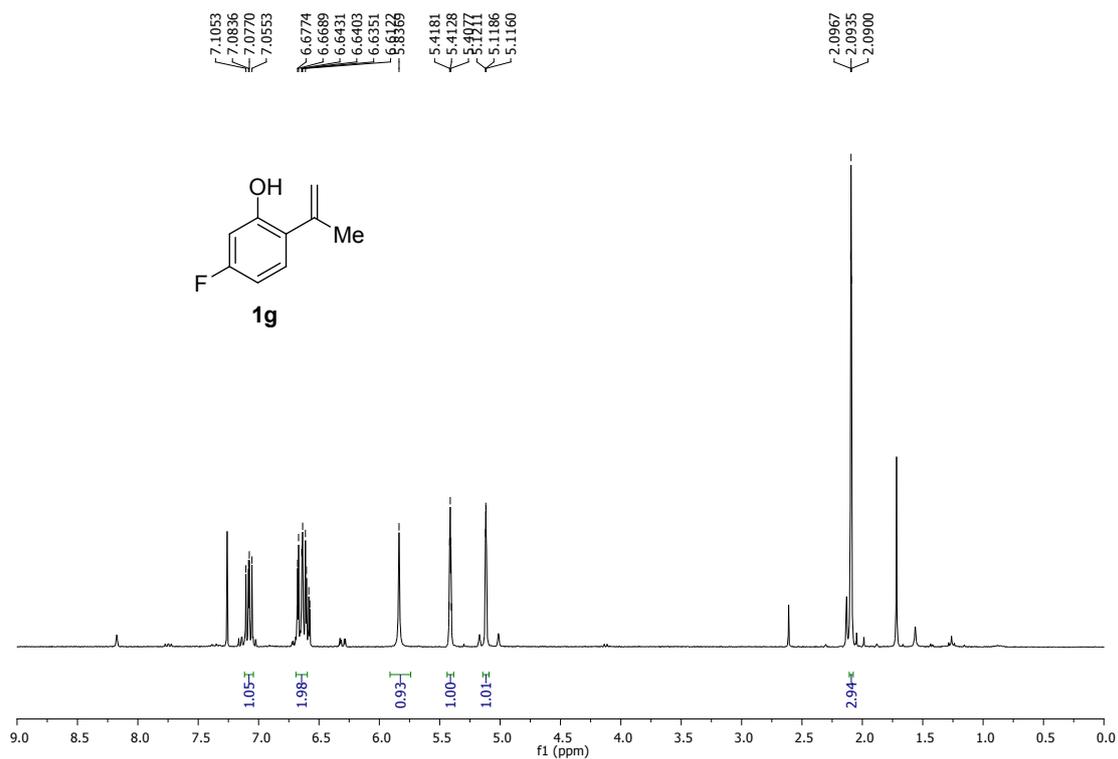
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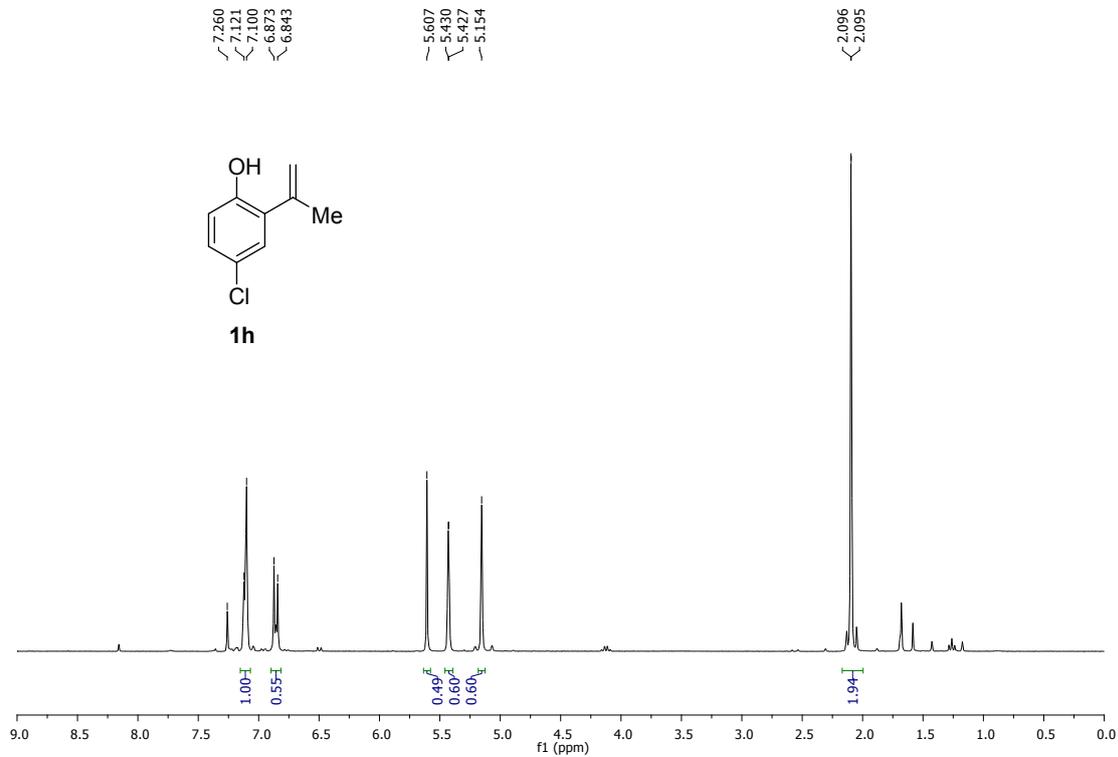
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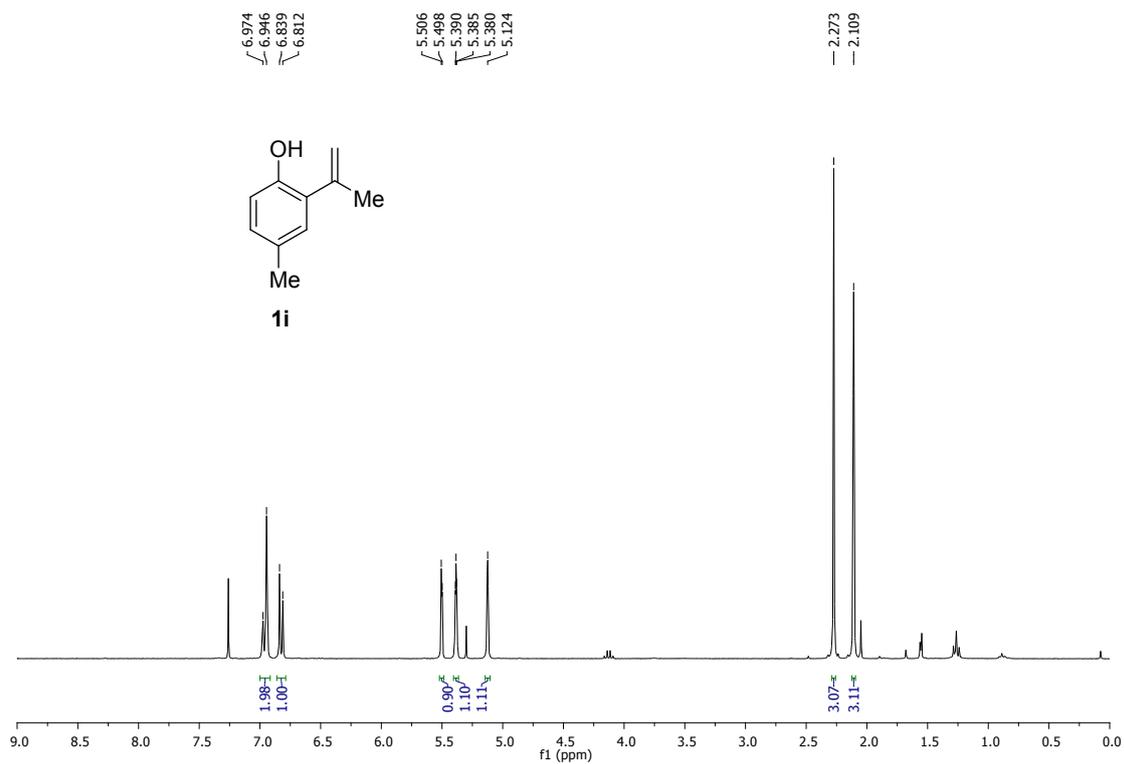
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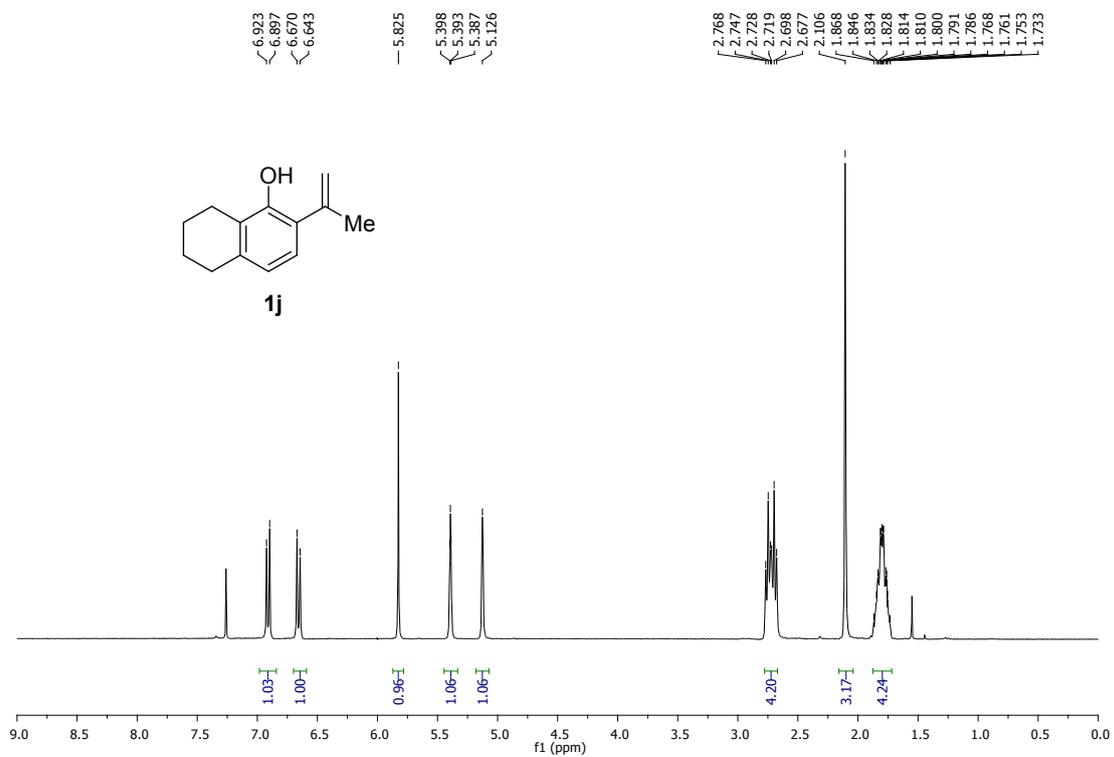
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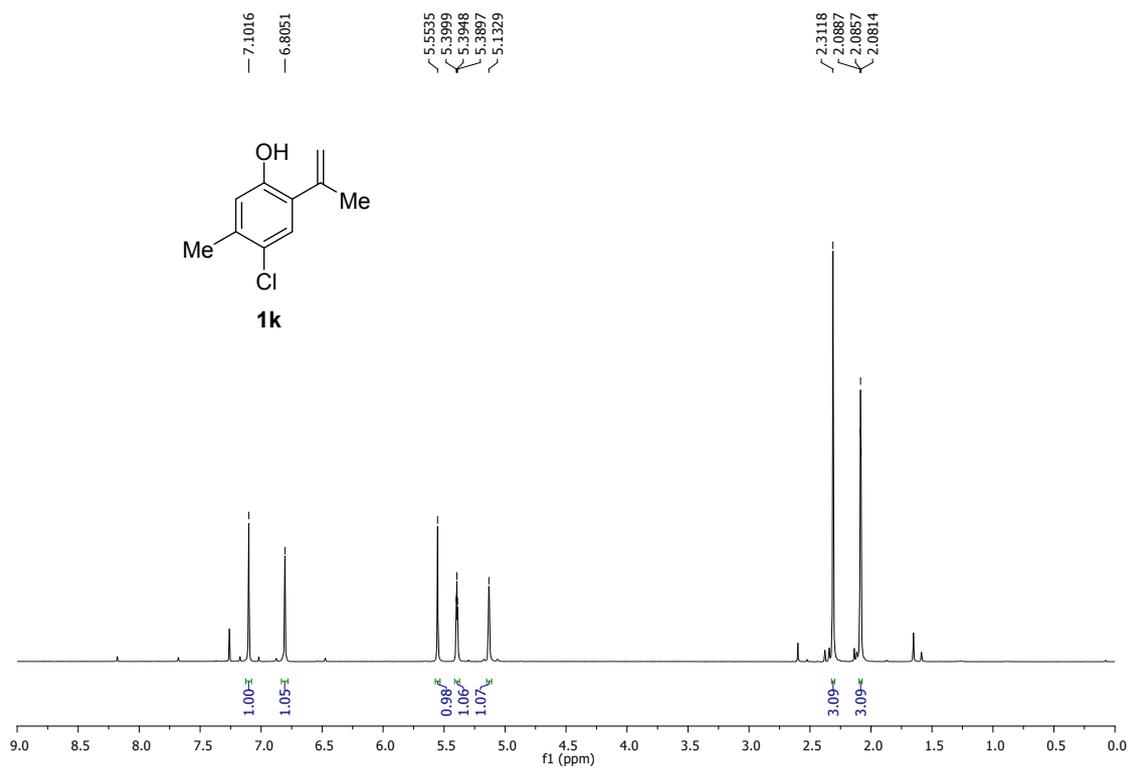
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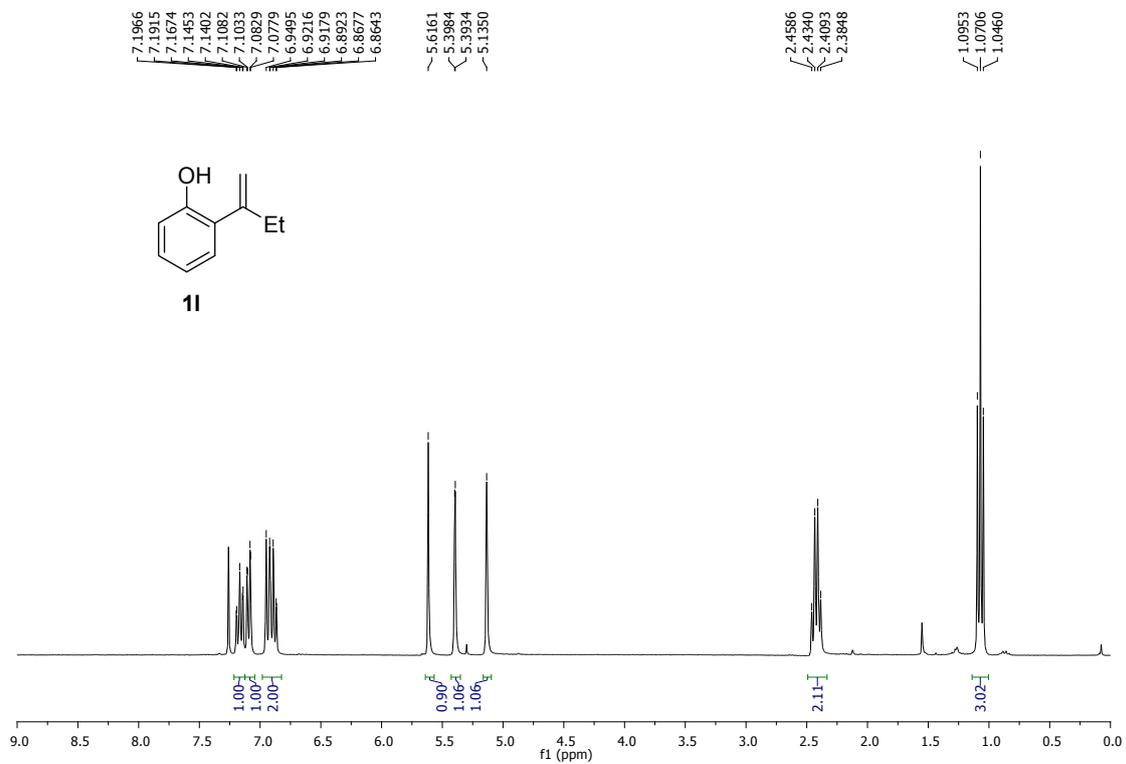
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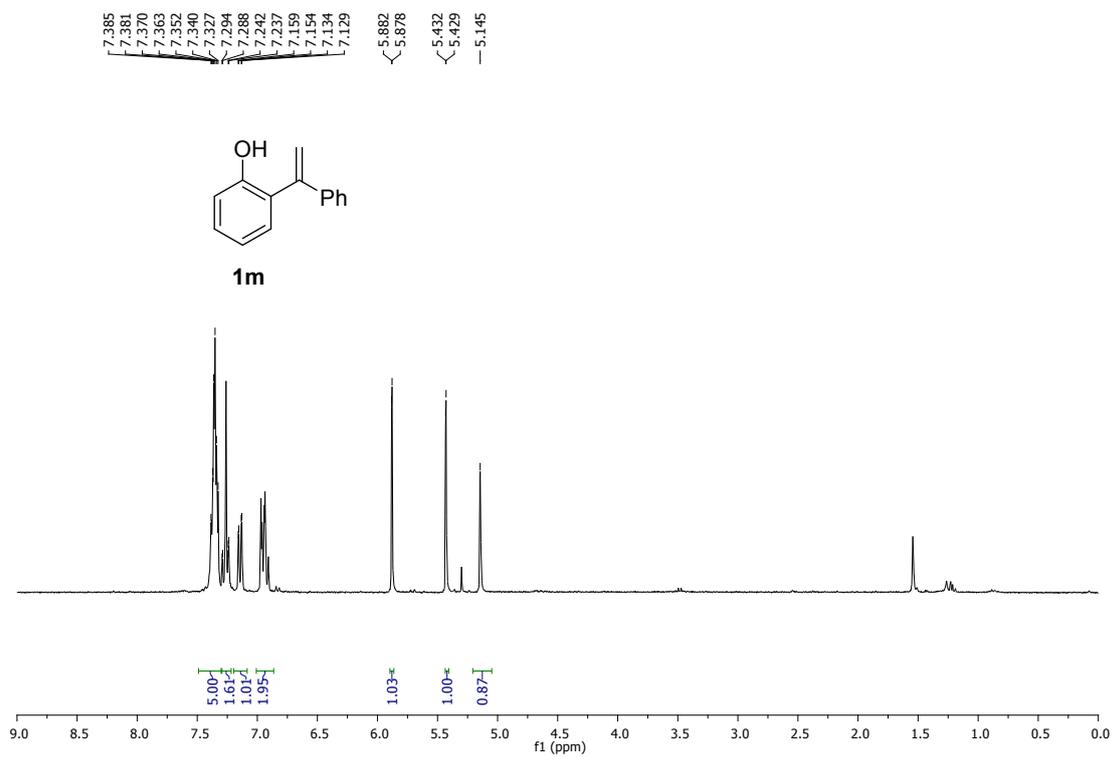
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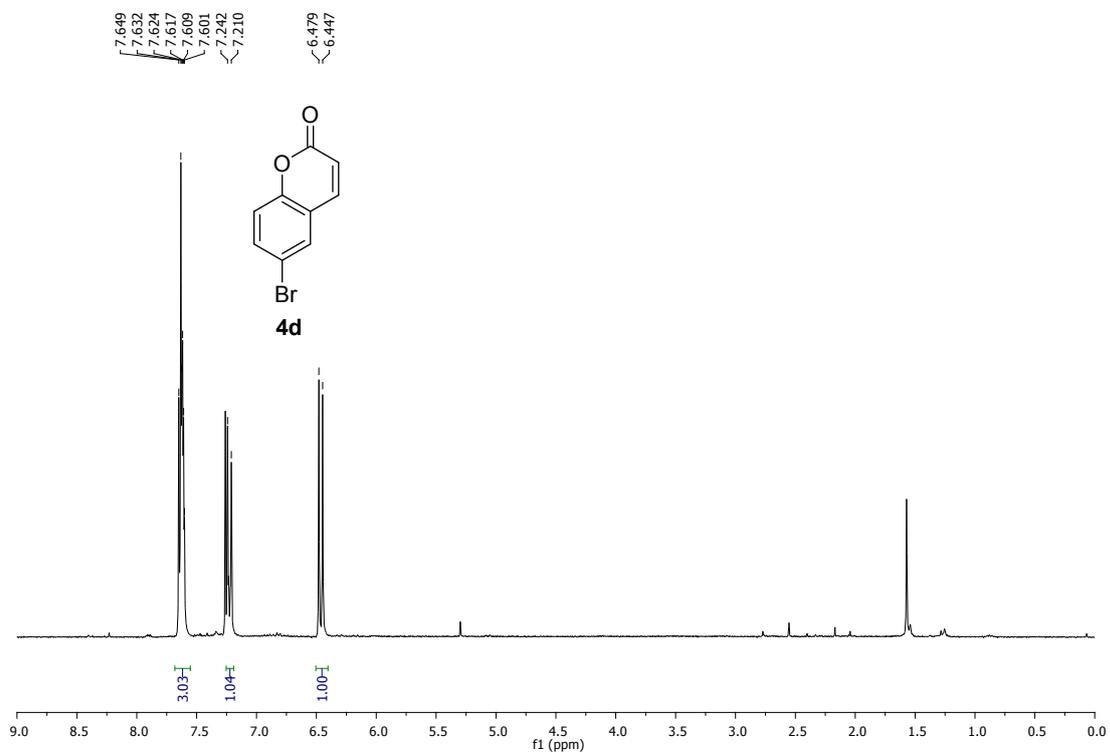
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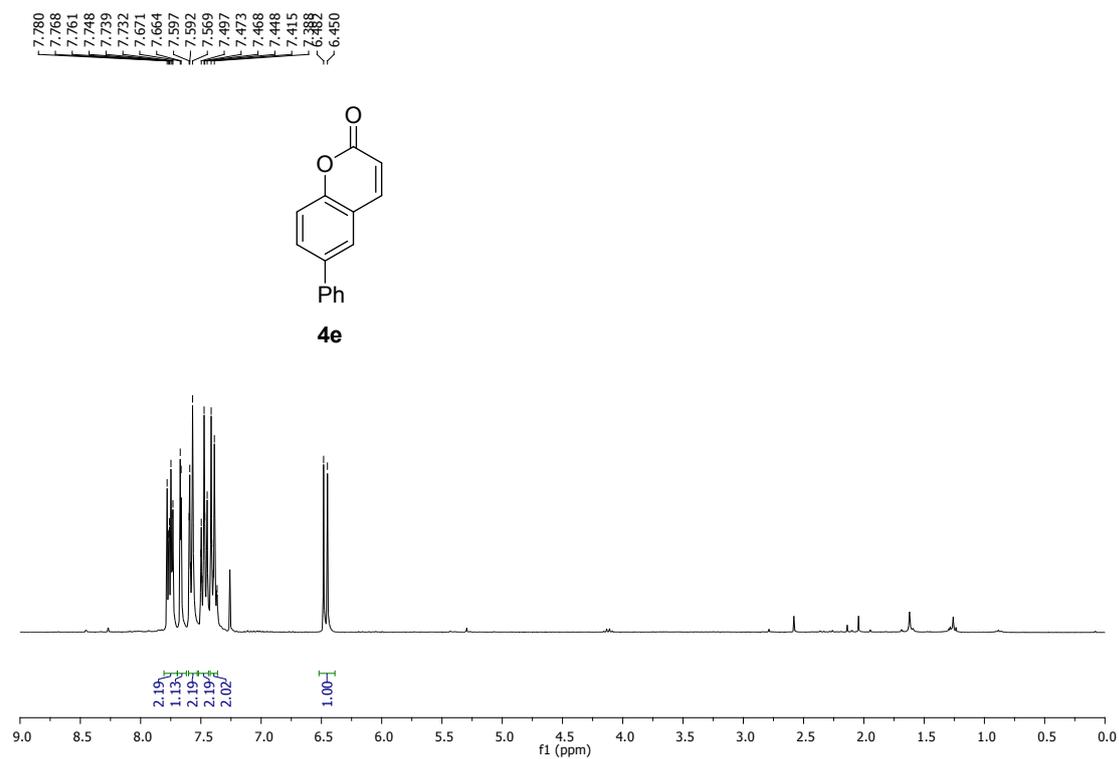
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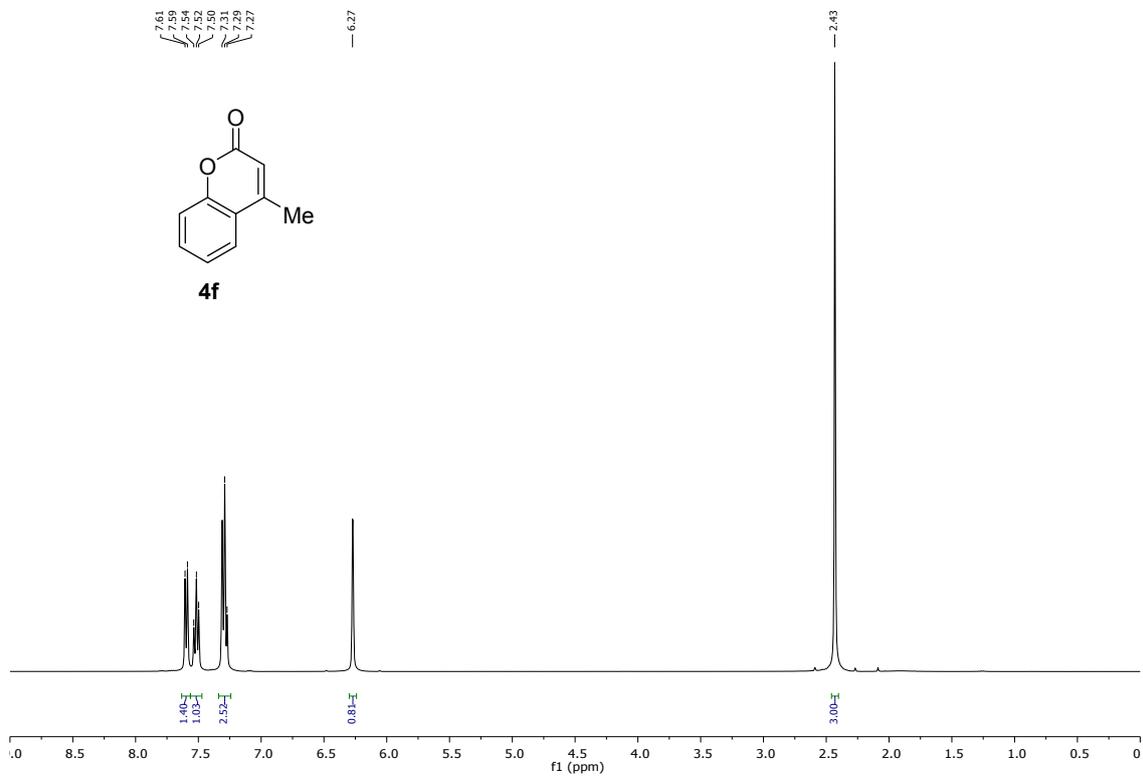
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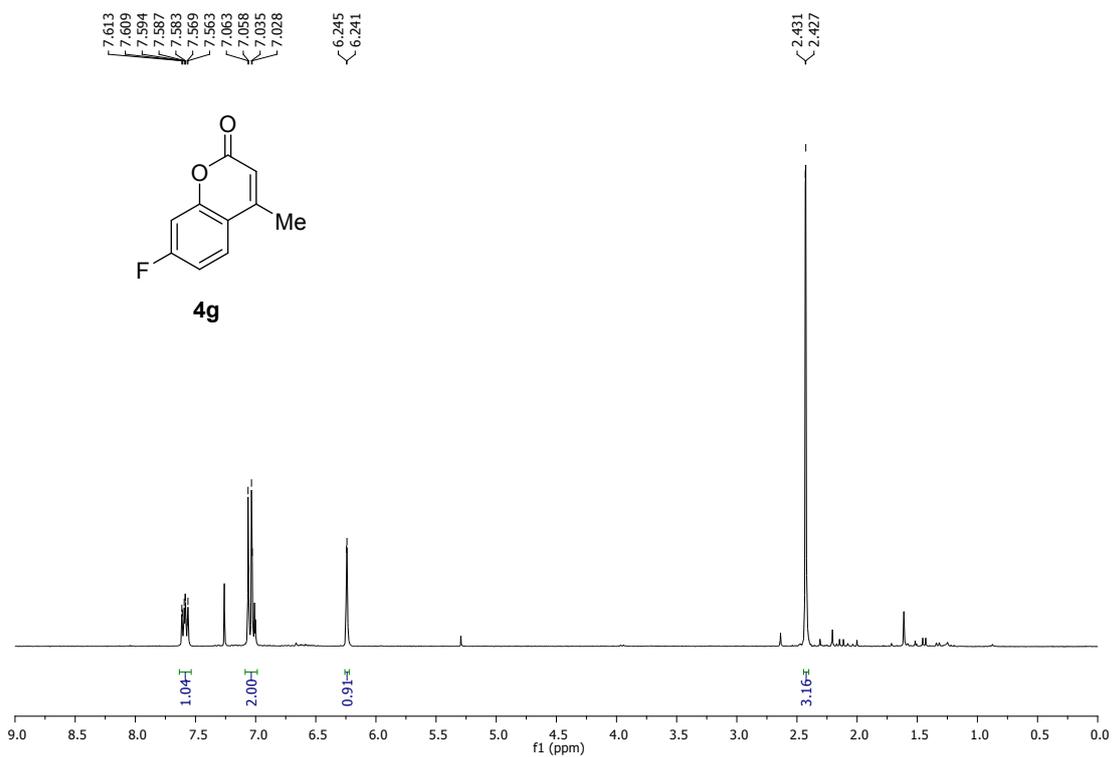
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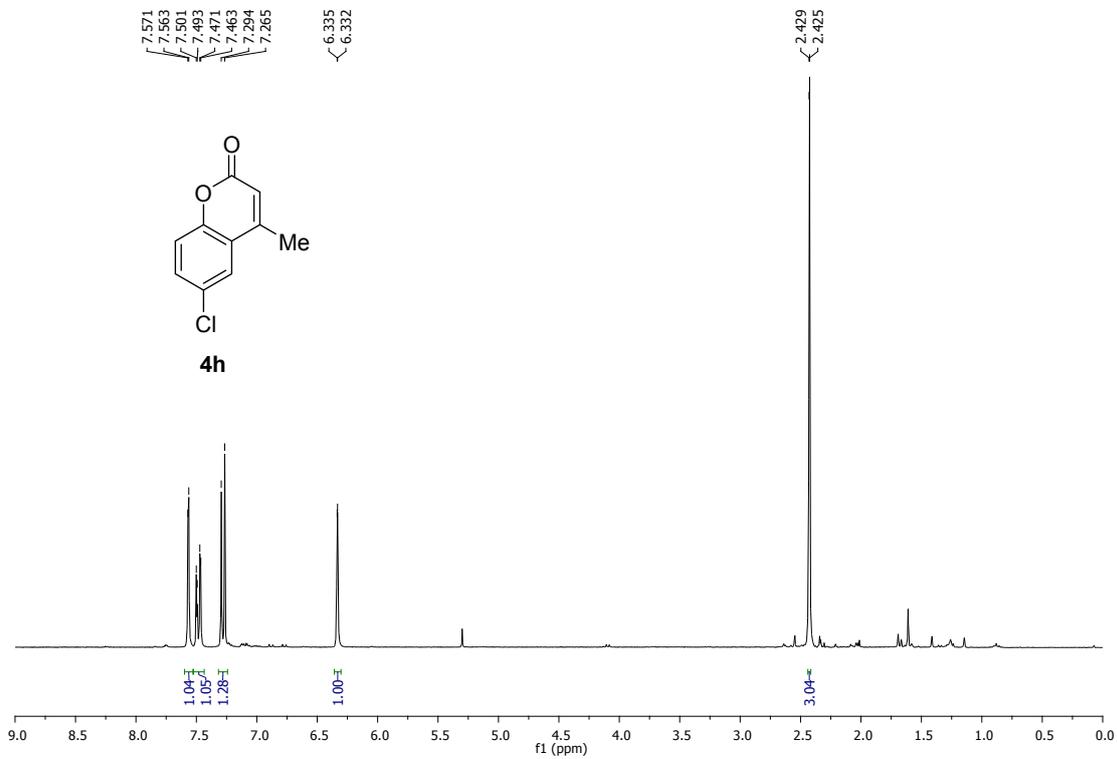
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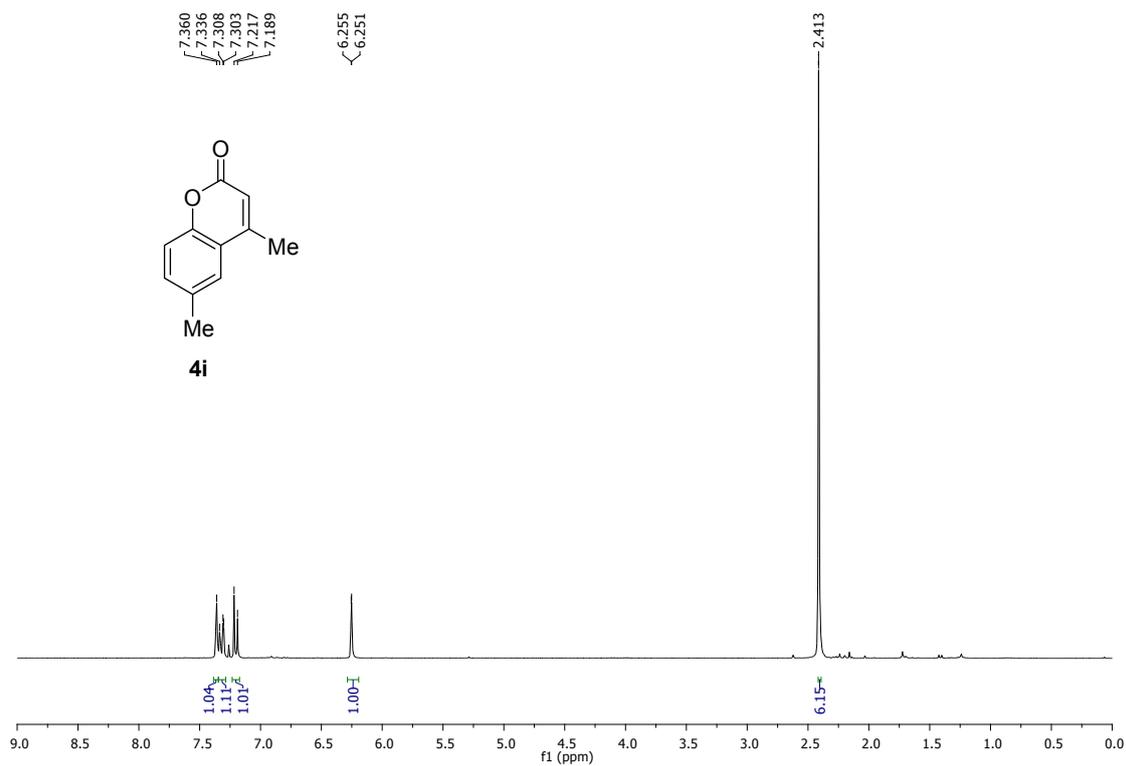
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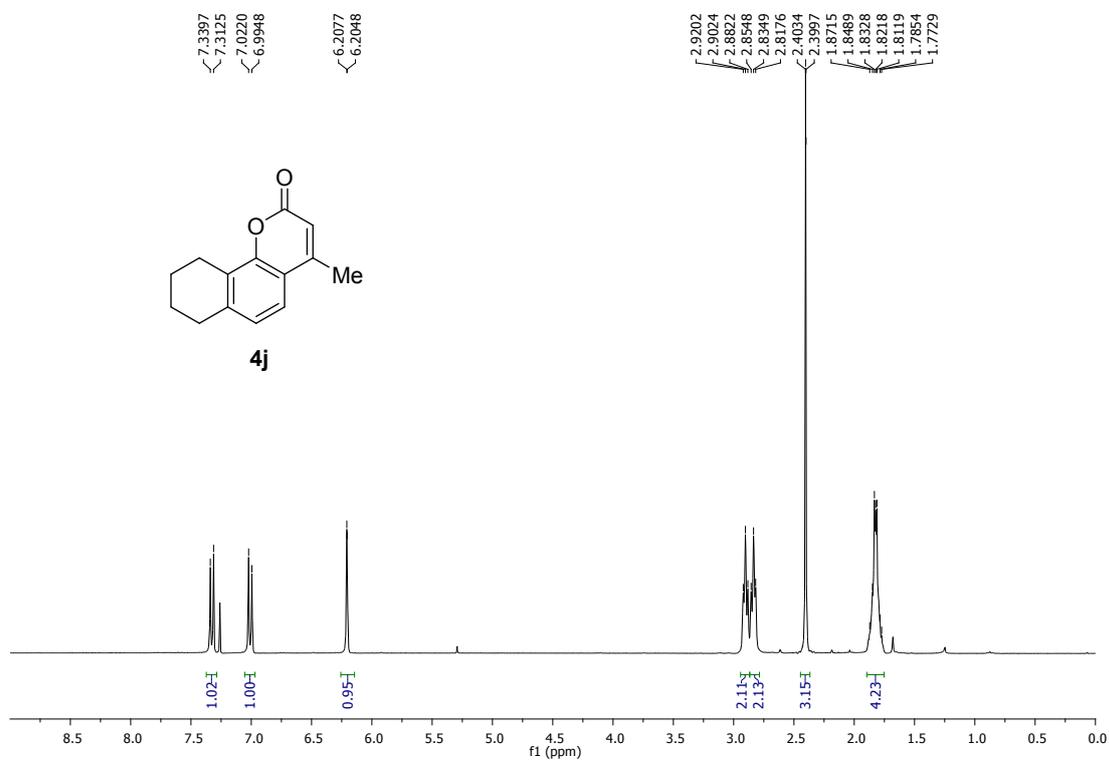
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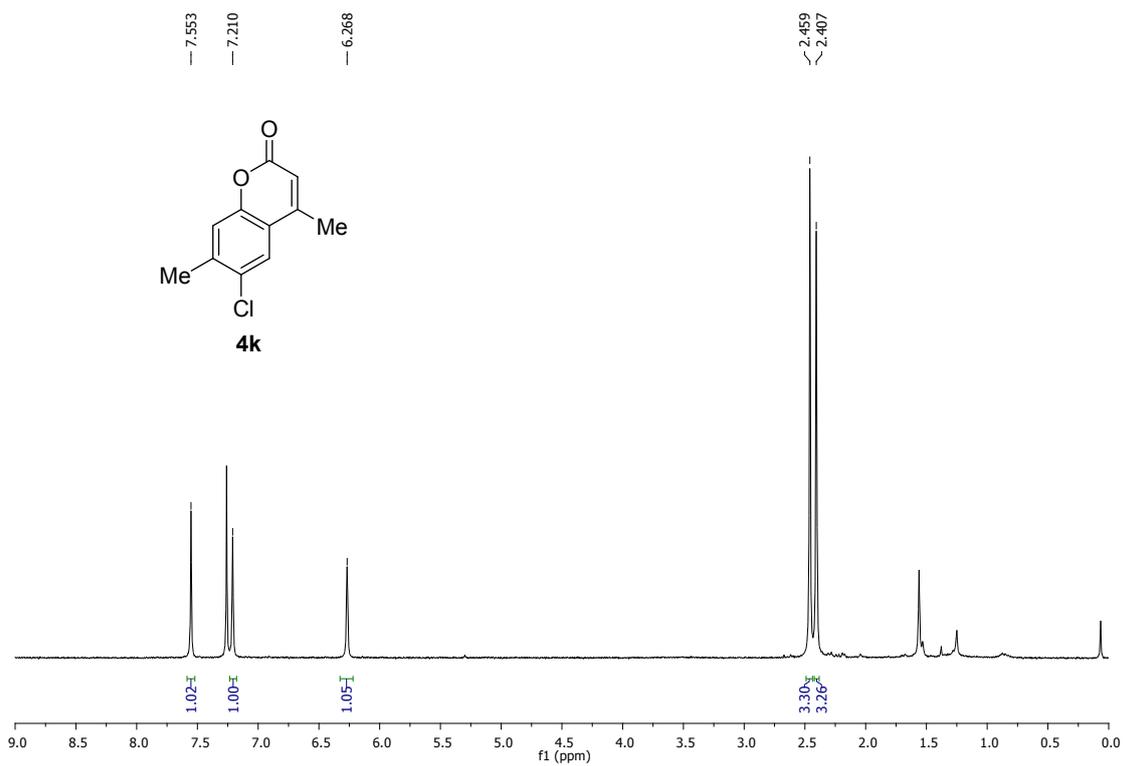
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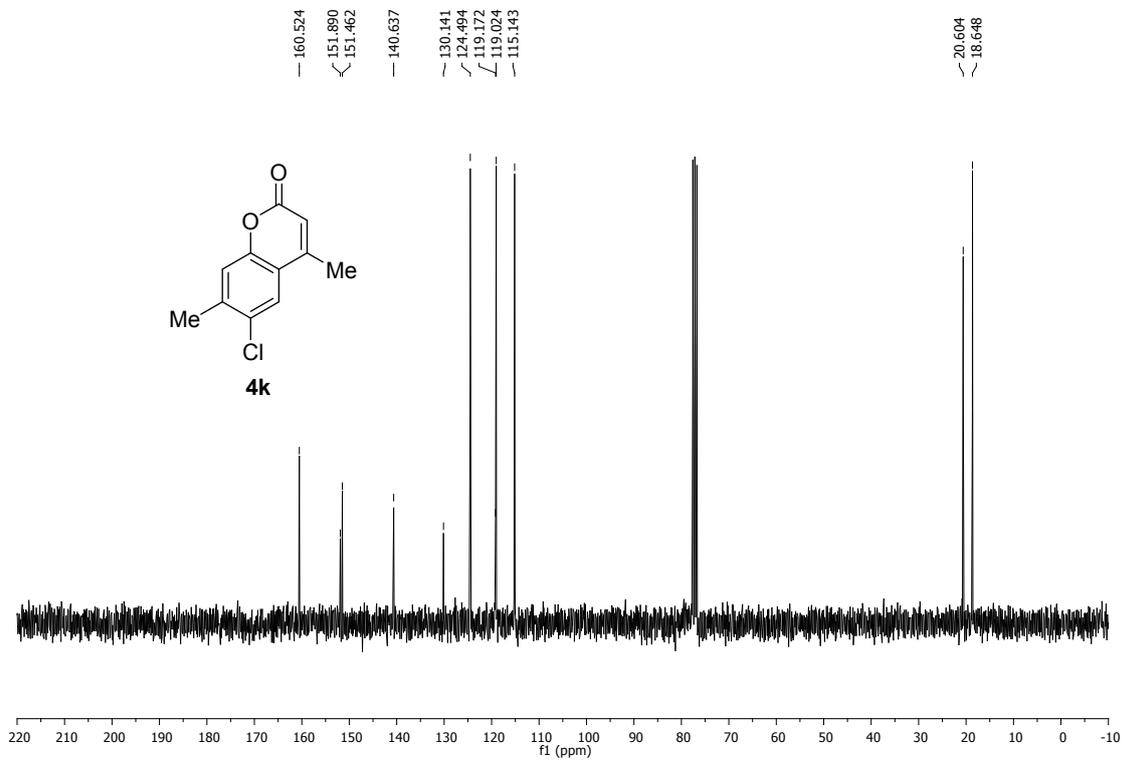
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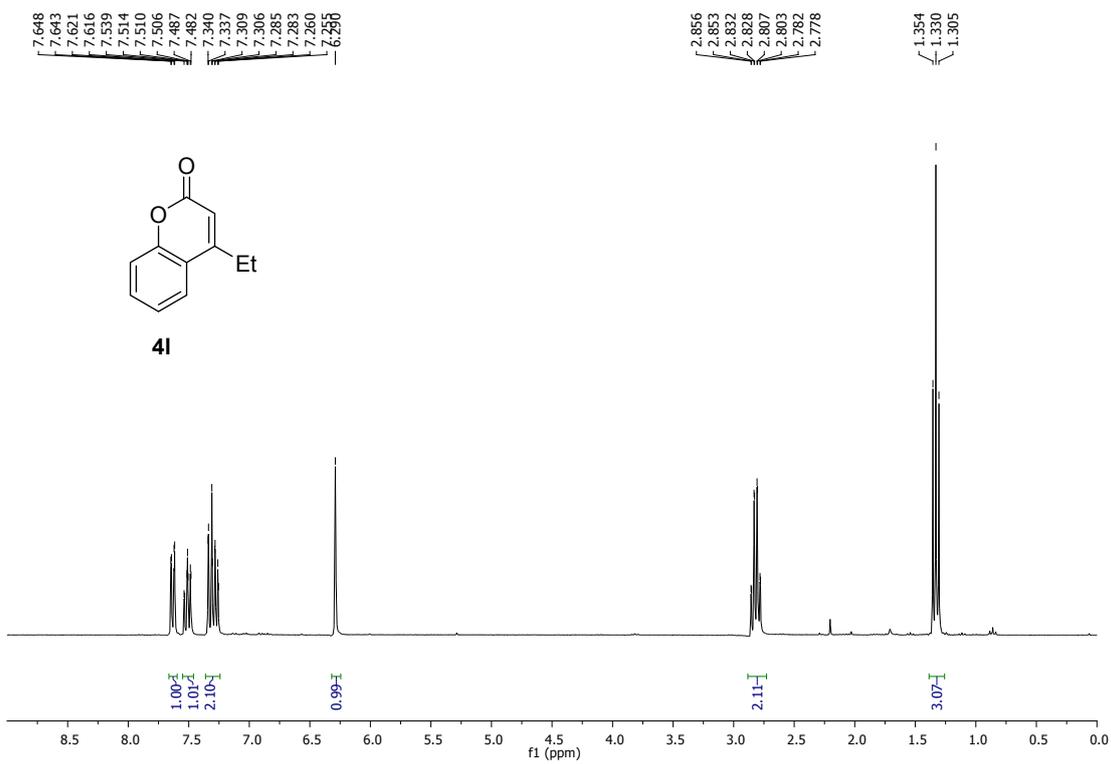
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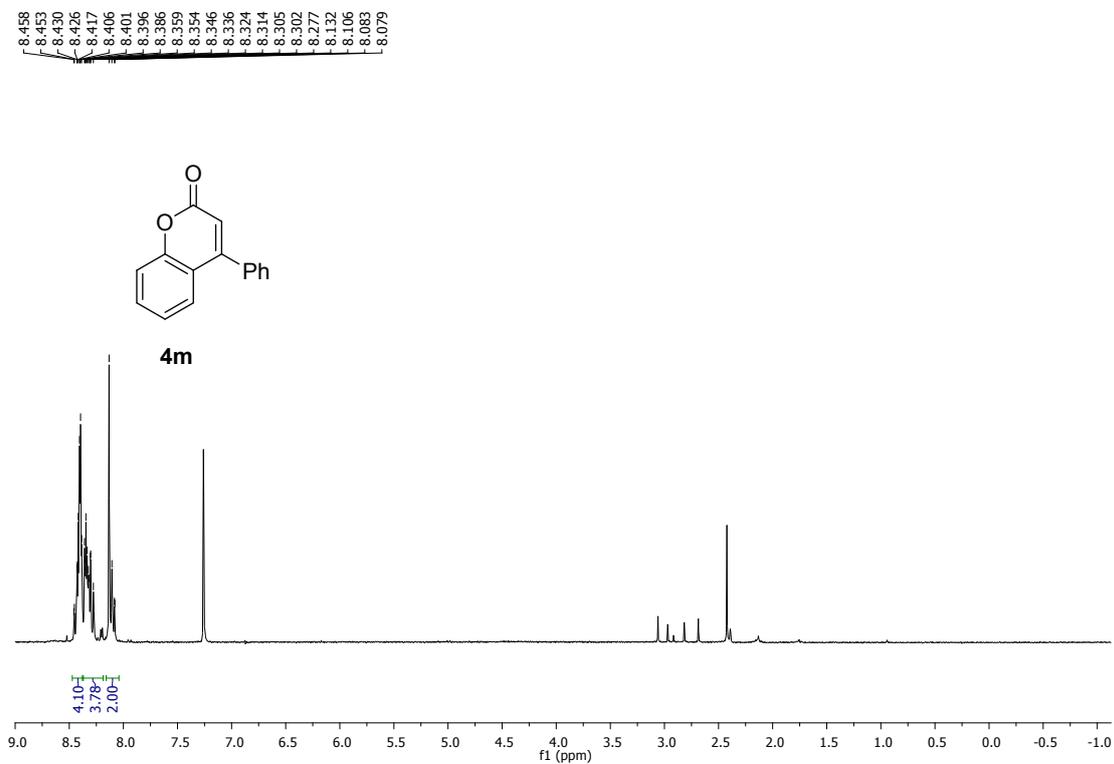
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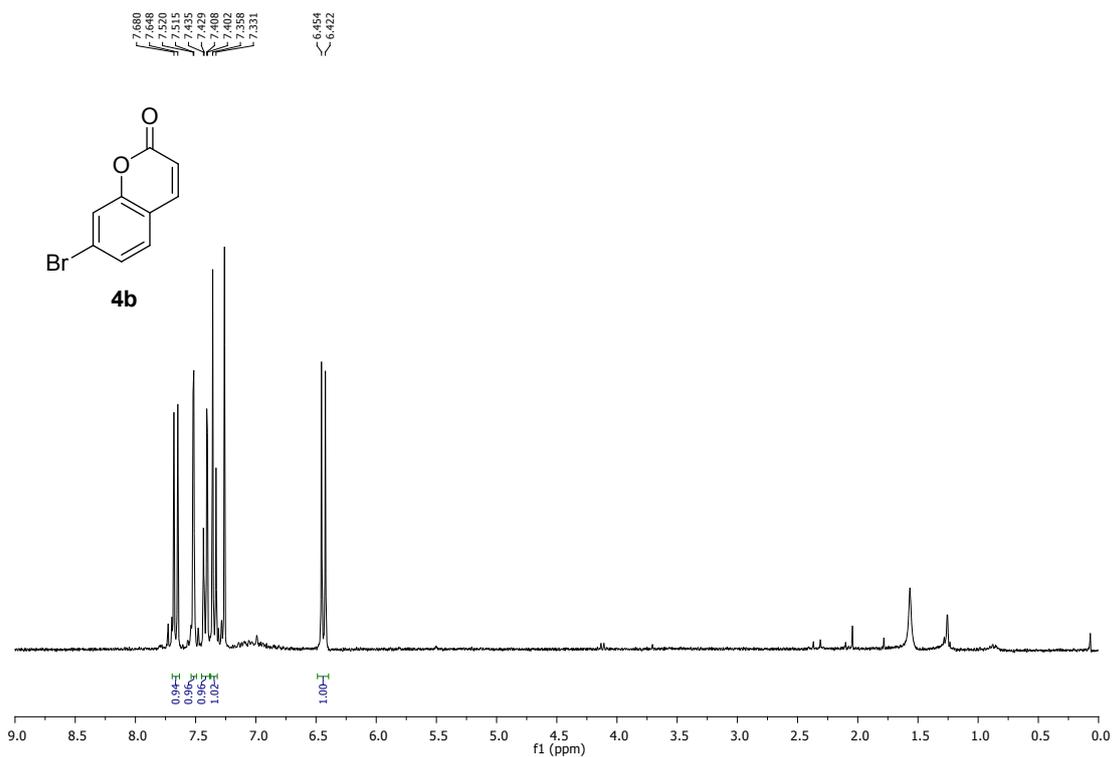
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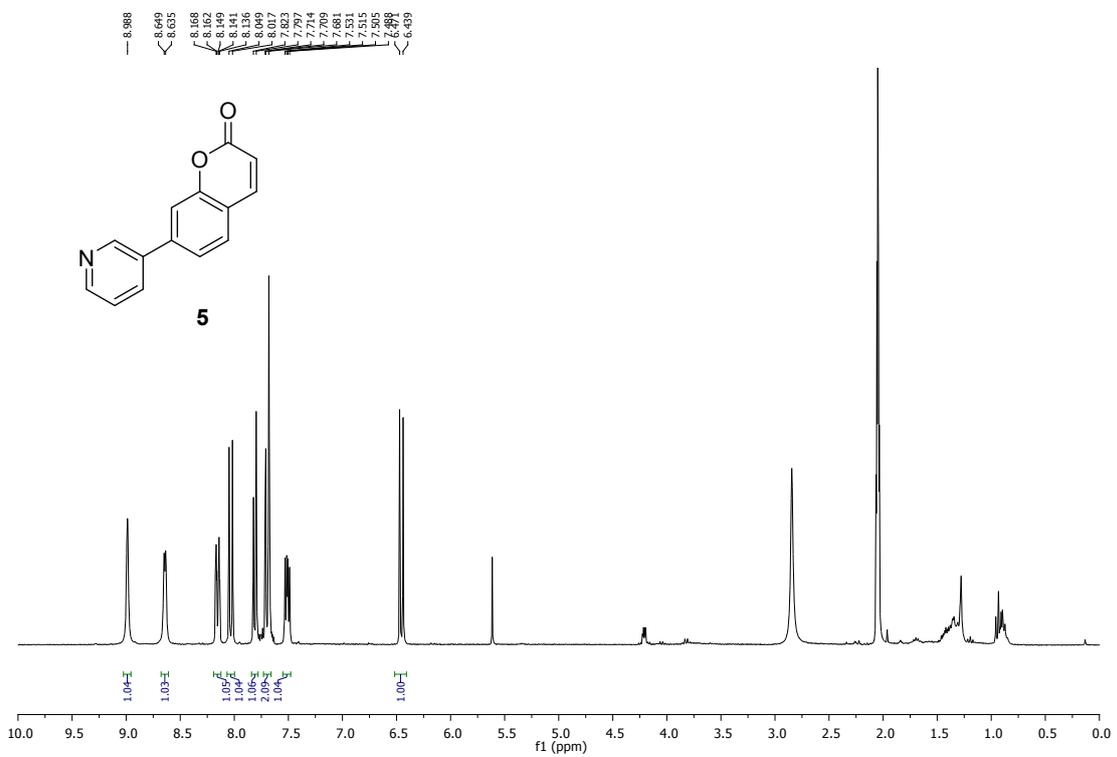
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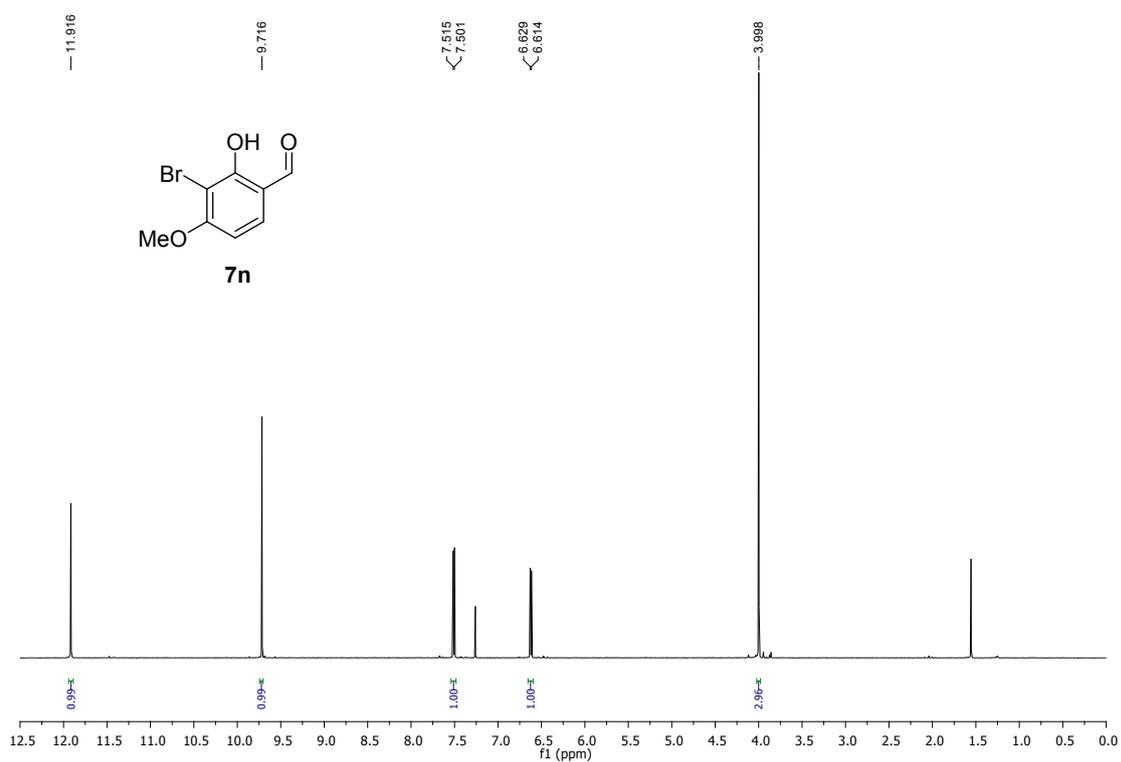
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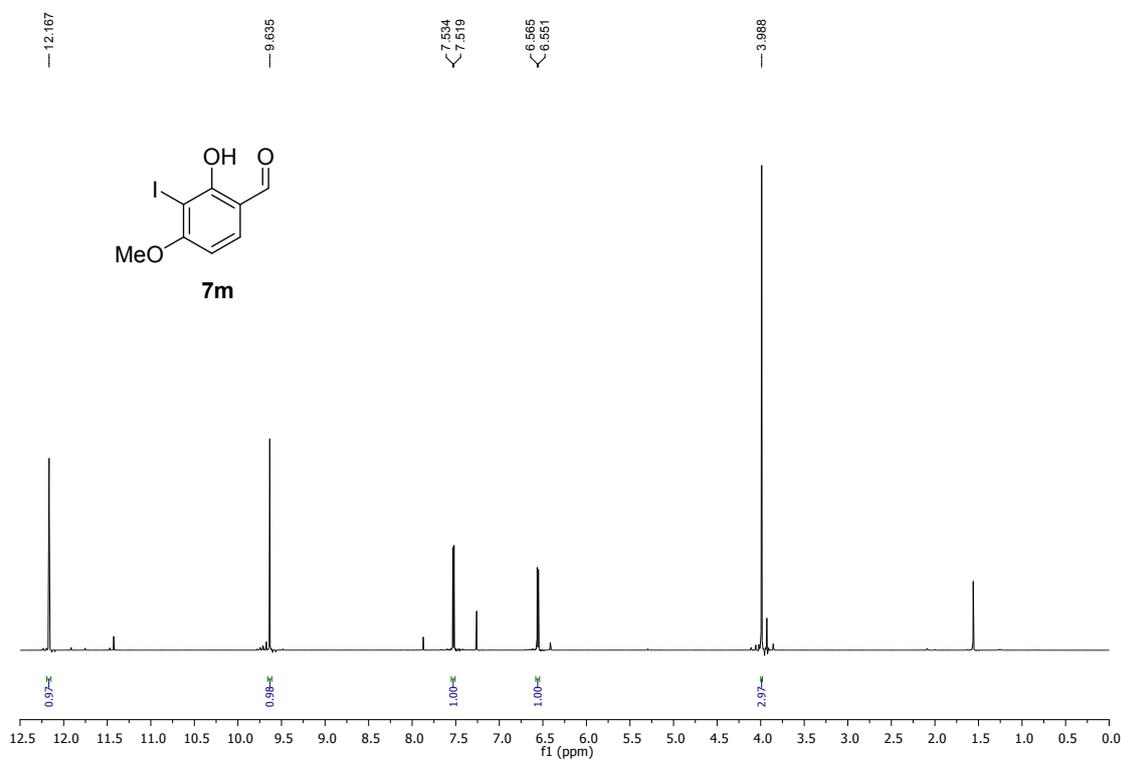
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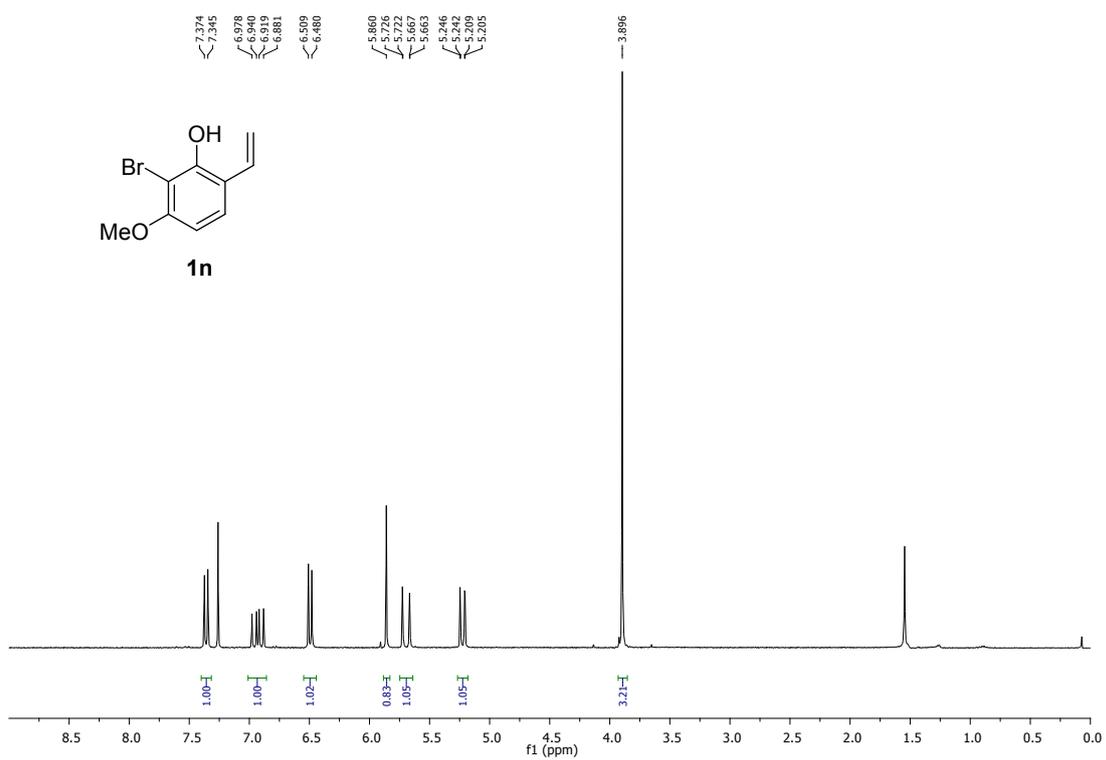
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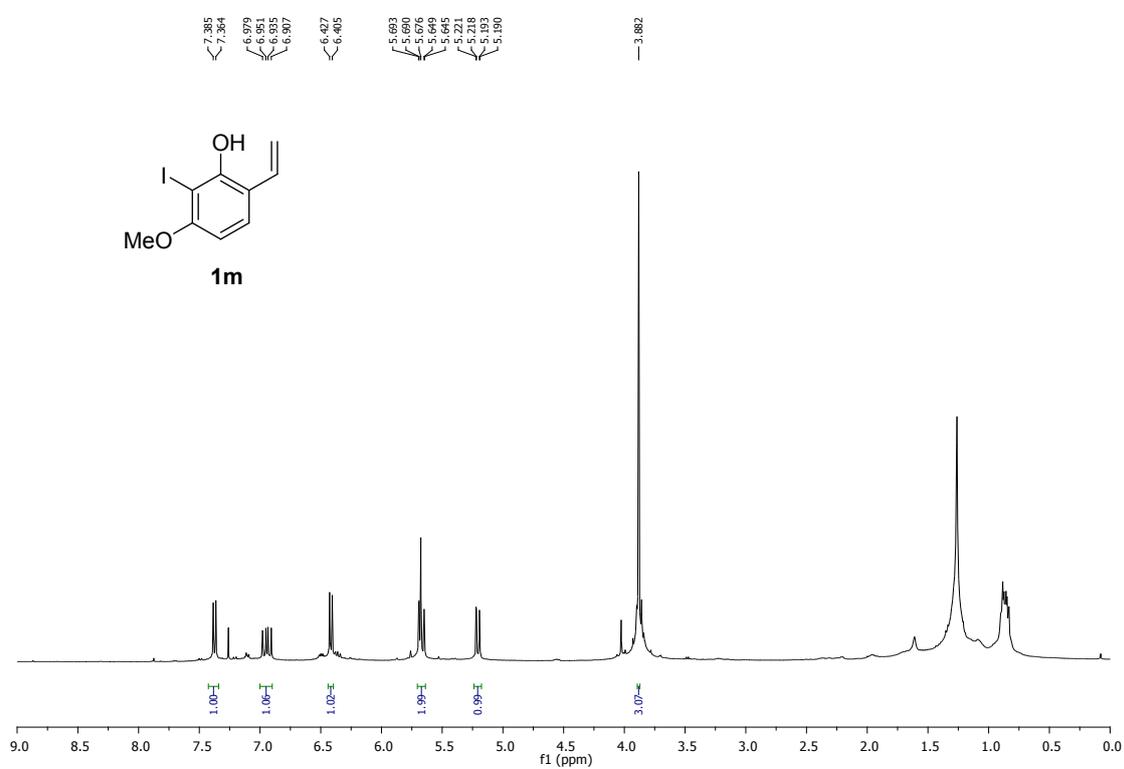
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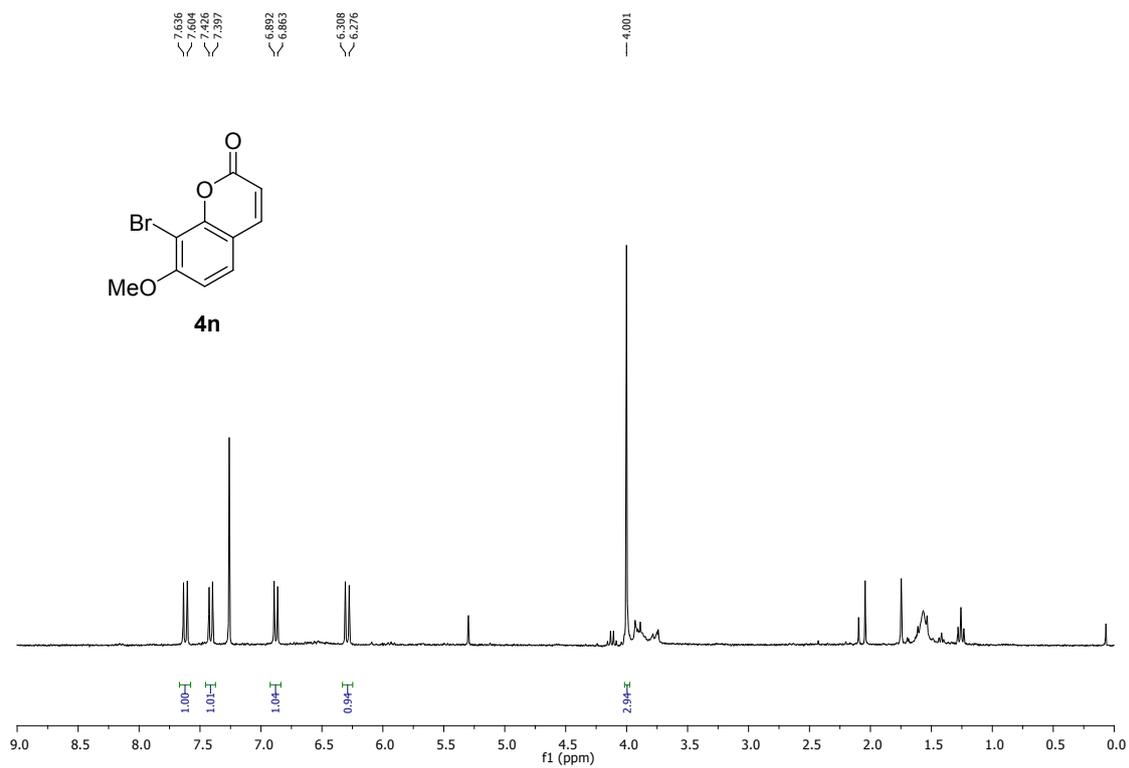
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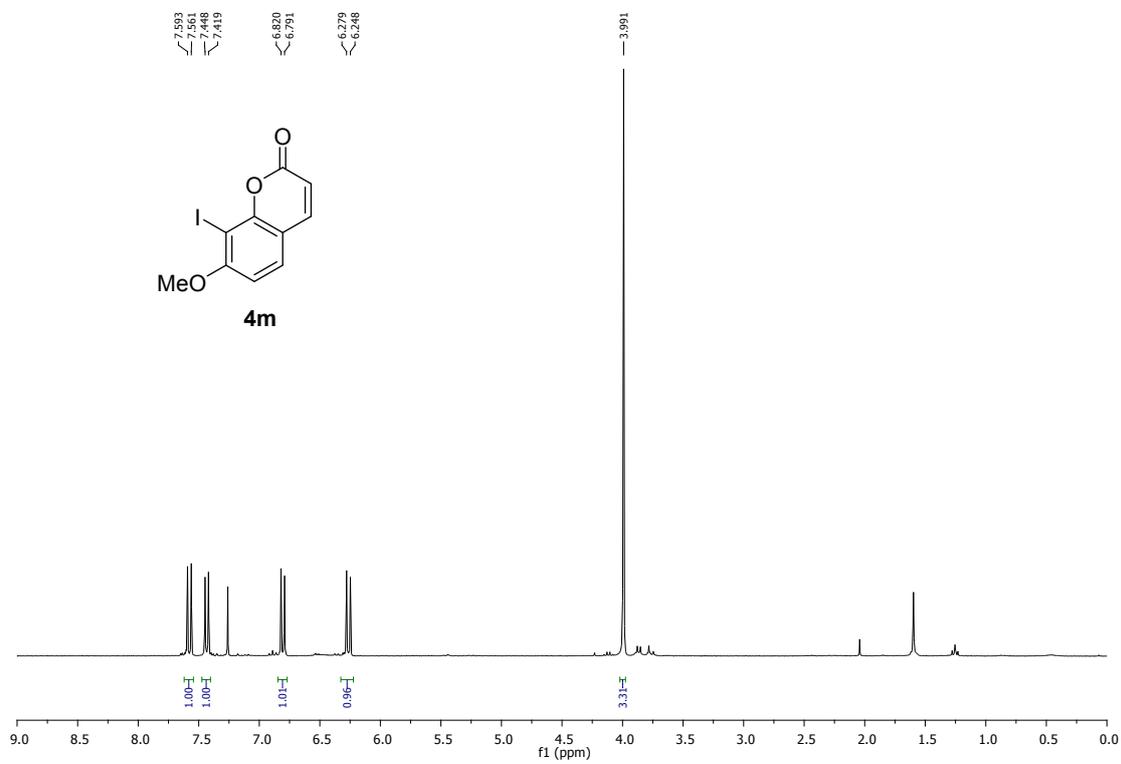
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¹H NMR



¹H NMR



¹H NMR

