Heteroatom-Directed Wacker oxidations. A Protection-free Synthesis of (−)-Heliophenanthrone

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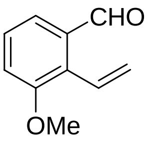
Supporting Information

3-Methoxy-2-vinyl-benzaldehyde:[1] mp: 59-61 °C (lit.[1] 59 °C); ^{1}H NMR (200 MHz, Acetone-d_6) δ 10.18 (s, 1H), 7.46-7.23 (m, 3H), 7.06 (dd, J = 17.7, 11.4 Hz, 1H), 5.71 (dd, J = 11.3, 1.8 Hz, 1H), 5.36 (dd, J = 17.6, 1.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 191.4, 157.7, 135.4, 131.0, 128.7, 128.3, 123.1, 119.7, 115.0, 55.3.



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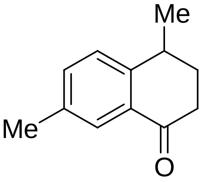

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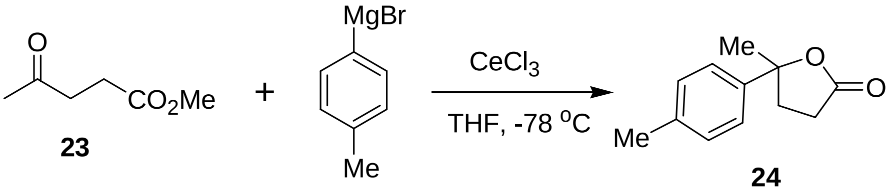
4,7-Dimethyl-3,4-dihydro-2H-napthalen-1-one: In our laboratory this compound was prepared in three steps as follows



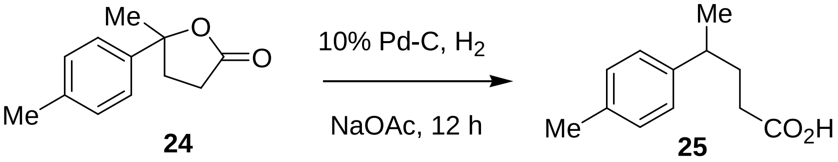
Cerium chloride ($CeCl_3.7H_20$) (8.56 g, 23 mmol) was quickly and finely ground to a powder in a mortar and placed in a two-necked flask. The flask was immersed in an oil bath and heated gradually to 135-140 °C with evacuation (ca. 0.1 Torr). After maintenance of the cerium chloride at a constant temperature for 1 h, a magnetic stirrer bar was placed in the flask and the cerium chloride was completely dried in vacuo by stirring at the same temperature for an additional 1 h. While the flask was still hot, argon gas was introduced and the flask was then cooled in an ice bath. 70 ml of THF freshly distilled from sodium benzophenone was added all at once with vigorous stirring. The ice bath was removed and the suspension was well stirred overnight under argon at room temperature. To this suspension was added methyl levulinate **23** (1 g, 7.7 mmol) in 10 ml of THF at rt and was stirred for 1 h. Then it was cooled to −78 °C and to it *p*-tolylmagnesium bromide (10 ml, 2.3 M in THF, 23 mmol) was added over a period of 10 min and was stirred for 1.5 h when TLC showed complete consumption of starting. It was then quenched with 10% acetic acid and extracted with diethyl ether. The organic layer was separated and was well washed with H_2O, brine and dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography to yield 1.3 g (90%) of **24** as a colorless liquid.

R*f* = 0.47 (Petroleum ether:ethyl acetate, 8:2);

^{1}H NMR (200 MHz, CDCl$_3$) δ 1.71 (s, 3H), 2.35 (s, 3H), 2.35-2.50 (m, 2H), 2.52-2.63 (m, 2H), 7.17 (d, *J* = 8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H);

^{13}C NMR (50MHz, CDCl$_3$) δ 21.0, 29.1, 29.5, 36.2, 87.2, 124.1 (2 x C), 129.3 (2 x C), 137.4, 141.3, 176.9;

HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{12}H_{14}O_2Na$: 213.0891, found: 213.0893.



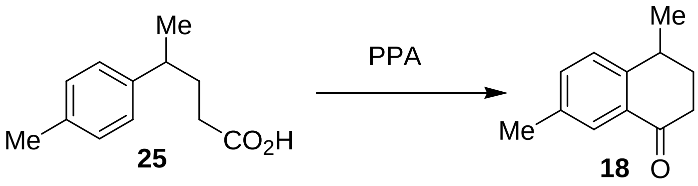
To the **24** (1 g, 5.26 mmol) in EtOAc were added 10% Pd-C (530 mg) and sodium acetate (530 mg). It was then stirred for 12 h at rt under hydrogen atmosphere. As the TLC showed complete consumption of starting material so the reaction mixture was then filtered through a short pad of celite and washed the celite pad with methanol. Solvent evaporation of combined organic layer gives a thick liquid. It was dissolved in diethyl ether followed by washing of the resulting solution with saturated NaHCO$_3$ three times. The combined aqueous layers were adjusted to pH 4 by addition of 1N HCl and extracted with EtOAc three times. The combined organic layers were dried and concentrated to give practically pure acid **25** (1 g, 97%) as a thick liquid which can be used directly for the next step.

IR (neat, cm^{-1}): 3091-2872, 1708, 1514, 1456, 1413, 1284, 937, 817;

^{1}H NMR (200 MHz, CDCl$_3$) δ 1.30 (d, *J* = 6.8 Hz, 3H), 1.90-2.00 (m, 2H), 2.23-2.31 (m, 2H), 2.36 (s, 3H), 2.65-2.79 (m, 1H), 7.08-7.18 (m, 4H);

^{13}C NMR (50MHz, CDCl$_3$) δ 21.1, 22.4, 32.5, 33.1, 39.0, 127.0 (2 x C), 129.4 (2 x C), 135.8, 143.1, 180.6;

HRMS (ESI) *m/z* [M+Na]$^+$ calcd for $C_{12}H_{16}O_2Na$: 215.1048, found: 215.1048.



To the **25** (1 g, 5.2 mmol) was added 10 g of polyphosphoric acid (PPA) and this mixture was heated at 100 °C for 2 h. Then it was kept to stand for 6 h at rt followed by pouring the reaction mixture into water containing crushed ice. The aqueous layer was extracted with diethyl ether. Ether layer was then washed with K_2CO_3 solution , brine and then dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography to yield 700 mg (77%) of **18** as a colorless liquid.

R*f* = 0.38 (Petroleum ether:ethyl acetate, 9.5:0.5);

IR (neat, cm^{-1}): 2960, 2929, 2864, 1685, 1612, 1494, 1282, 1180, 827, 754;

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.38 (d, *J* = 7Hz, 1H), 1.80-1.97 (m, 1H), 2.18-2.31 (m, 1H), 2.36 (s, 3H), 2.47-2.66 (m, 1H), 2.72-2.86 (m, 1H), 2.98-3.11 (m, 1H), 7.21-7.35 (m, 2H), 7.84 (s, 1H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 20.7, 20.8, 30.7, 32.5, 36.5, 127.3 (2 × C), 131.6, 134.5, 136.1, 146.1, 198.5;

HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{14}ONa$: 297.0942, found: 297.0943.

Enantiomeric purity analysis:

Preparation of (R)-Mosher's ester of **8**: To a solution of (R)-MPTA (10 mg, 0.04 mmol) in 2 mL of dry dichloromethane at 0 °C was added oxalyl chloride (35 µL, 0.4 mmol) and 3 µL of DMF. After 1.5 h, the mixture was warmed to room temperature and solvent was removed by rotary evaporation to yield a colorless oil. Solid DMAP (12 mg, 0.1 mmol) and a solution of the **8** (5 mg, 0.02 mmol) in dry dichloromethane (2 mL) were sequentially added to the latter residue (Mosher acid chloride) under argon at room temperature and the reaction mixture was stirred for 12 h to ensure derivatization was complete. Then the reaction was diluted with ether followed by addition of water. The organic layer was sequentially washed with 10% HCl, saturated aqueous $NaHCO_3$, water and brine. It was then dried with anhydrous Na_2SO_4. The solvent was evaporated in vaccuo and a preparative chromatography afforded the product as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.15 (s, 3H), 3.48 (s, 3H), 3.84 (s, 3H), 3.84-3.88 (m, 1H), 5.07-5.13 (m, 2H), 5.36-5.45 (m, 1H), 5.56-5.64 (m, 2H), 6.47 (d , *J* = 8 Hz, 1H), 6.77 (dd, *J* = 11.6, 17.8 Hz, 1H), 6.85 (d, *J* = 8 Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 7.22 (t, *J* = 8 Hz, 1H), 7.32-7.50 (m, 5H).

^{19}F NMR of the corresponding Mosher's ester derivative showed 88% ee (δ −31.69 (94%), −31.58 (6%)).

Preparation of (S)-Mosher's ester of **8**: To a solution of (S)-MPTA (10 mg, 0.04 mmol) in 2 mL of dry dichloromethane at 0 °C was added oxalyl chloride (35 µL, 0.4 mmol) and 3 µL of DMF. After 1.5 h, the mixture was warmed to room temperature and solvent was removed by rotary evaporation to yield a colorless oil. Solid DMAP (12 mg, 0.1 mmol) and a solution of the **8** (5 mg, 0.02 mmol) in dry dichloromethane (2 mL) were sequentially added to the latter residue (Mosher acid chloride) under argon at room temperature and the reaction mixture was stirred for 12 h to ensure derivatization was complete. Then the reaction was diluted with ether followed by addition of water. The organic layer was sequentially washed with 10% HCl, saturated aqueous $NaHCO_3$, water and brine. It was then dried with anhydrous Na_2SO_4. The solvent was evaporated in vaccuo and a preparative chromatography afforded the product as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.33 (s, 3H), 3.57 (s, 3H), 3.82 (s, 3H), 3.93 (t, *J* = 8 Hz, 1H), 5.09-5.13 (m, 2H), 5.40-5.49 (m, 1H), 5.59-5.64 (m, 2H), 6.36 (d , *J* = 8.4 Hz, 1H), 6.75-6.83 (m, 3H), 7.12 (t, *J* = 8 Hz, 1H), 7.31-7.47 (m, 5H).

^{19}F NMR of the corresponding Mosher's ester derivative showed 88% ee (δ −31.58 (94%), −31.69 (6%)).

Preparation of (R)-Mosher's ester of **15**: To a solution of (R)-MPTA (10 mg, 0.04 mmol) in 2 mL of dry dichloromethane at 0 °C was added oxalyl chloride (35 µL, 0.4 mmol) and 3 µL of DMF. After 1.5 h, the mixture was warmed to room temperature and solvent was removed by rotary evaporation to yield a colorless oil. Solid DMAP (12 mg, 0.1 mmol) and a solution of the **15** (5 mg, 0.02 mmol) in dry dichloromethane (2 mL) were sequentially added to the latter residue (Mosher acid chloride) under argon at room temperature and the reaction mixture was stirred for 12 h to ensure derivatization was complete. Then the reaction was diluted with ether followed by addition of water. The organic layer was sequentially washed with 10% HCl, saturated aqueous $NaHCO_3$, water and brine. It was then dried with anhydrous Na_2SO_4. The solvent was evaporated in vaccuo and a preparative chromatography afforded the product as a clear oil.

^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.19 (s, 3H), 3.46 (s, 3H), 3.83-3.84 (m, 1H), 3.84 (s, 3H), 5.06 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 5.55-5.68 (m, 3H), 6.56 (d, *J* = 5.6 Hz, 1H), 6.79-6.86 (m , 2H), 7.02 (d, *J* = 8 Hz, 1H), 7.21 (t, *J* = 8 Hz, 1H), 7.30-7.48 (m, 5H).
^{1}H NMR at 500 MHz instrument of this Mosher's ester derivative showed 74% ee (δ 6.56 (87%), 6.54 (13%)).

Preparation of (S)-Mosher's ester of **15**: To a solution of (S)-MPTA (10 mg, 0.04 mmol) in 2 mL of dry dichloromethane at 0 °C was added oxalyl chloride (35 μL, 0.4 mmol) and 3 μL of DMF. After 1.5 h, the mixture was warmed to room temperature and solvent was removed by rotary evaporation to yield a colorless oil. Solid DMAP (12 mg, 0.1 mmol) and a solution of the **15** (5 mg, 0.02 mmol) in dry dichloromethane (2 mL) were sequentially added to the latter residue (Mosher acid chloride) under argon at room temperature and the reaction mixture was stirred for 12 h to ensure derivatization was complete. Then the reaction was diluted with ether followed by addition of water. The organic layer was sequentially washed with 10% HCl, saturated aqueous NaHCO$_3$, water and brine. It was then dried with anhydrous Na$_2$SO$_4$. The solvent was evaporated in vaccuo and a preparative chromatography afforded the product as a clear oil.
^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.26 (s, 3H), 3.54 (s, 3H), 3.84 (s, 3H), 3.84-3.85 (m, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 5.62-5.79 (m, 3H), 6.54 (d, *J* = 4.8 Hz, 1H), 6.79-6.86 (m , 3H), 7.08 (t, *J* = 8 Hz, 1H), 7.31-7.49 (m, 5H).
^{1}H NMR at 500 MHz instrument of this Mosher's ester derivative showed 70% ee (δ 6.54 (85%), 6.56 (15%)).

Preparation of (R)-Mosher's ester of **21**: To a solution of (R)-MPTA (10 mg, 0.04 mmol) in 2 mL of dry dichloromethane at 0 °C was added oxalyl chloride (35 μL, 0.4 mmol) and 3 μL of DMF. After 1.5 h, the mixture was warmed to room temperature and solvent was removed by rotary evaporation to yield a colorless oil. Solid DMAP (12 mg, 0.1 mmol) and a solution of the **21** (5 mg, 0.018 mmol) in dry dichloromethane (2 mL) were sequentially added to the latter residue (Mosher acid chloride) under argon at room temperature and the reaction mixture was stirred for 12 h to ensure derivatization was complete. Then the reaction was diluted with ether followed by addition of water. The organic layer was sequentially washed with 10% HCl, saturated aqueous $NaHCO_3$, water and brine. It was then dried with anhydrous Na_2SO_4. The solvent was evaporated in vaccuo and a preparative chromatography afforded the product as a clear oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.51 (s, 3H), 2.52 (s, 3H), 3.36 (s, 3H), 3.62 (s, 3H), 4.04 (t, *J* = 8 Hz, 1H), 5.02-5.11 (m, 2H), 5.40-5.54 (m, 2H), 5.84 (dd, *J* = 2, 11.2 Hz, 1H), 6.45 (d, *J* = 8.4, 1H), 6.99 (s, 1H), 7.09 (dd, *J* = 11.6, 17.8 Hz, 1H), 7.24-7.40 (m, 6H), 7.85-7.90 (m, 2H).

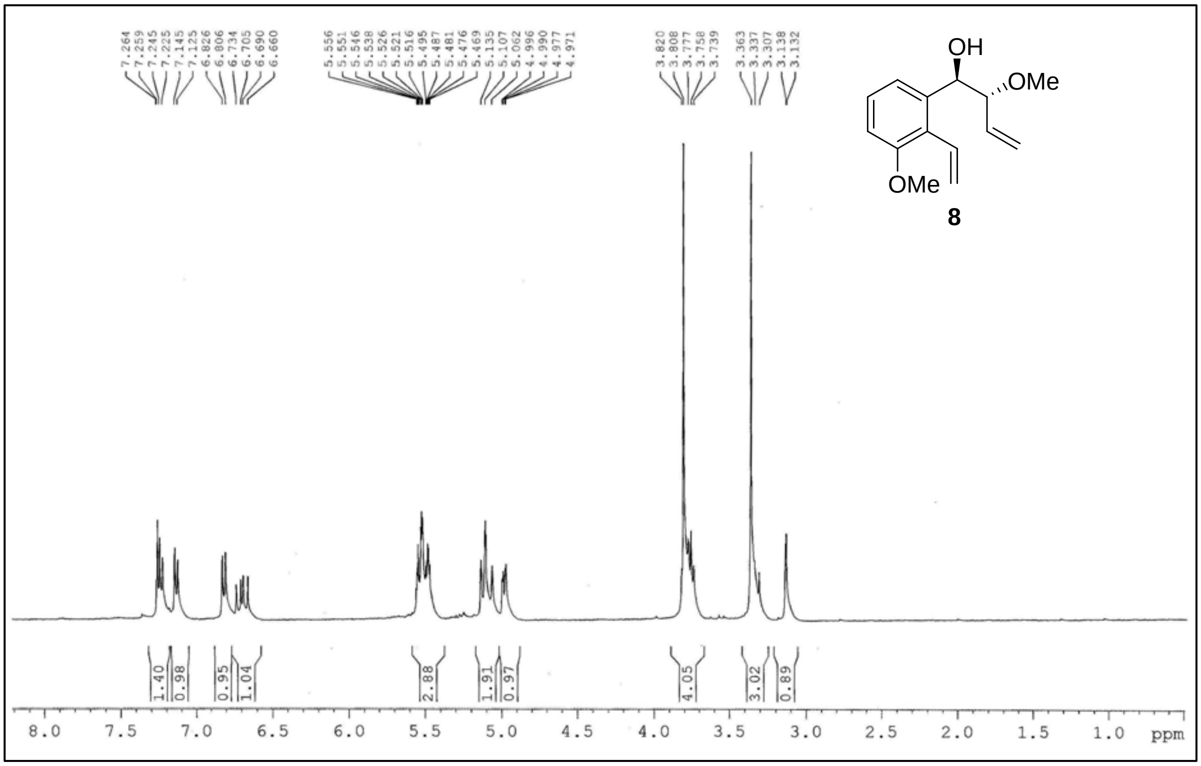
^{19}F NMR of the corresponding Mosher's ester derivative showed 90% ee (δ −31.74 (95%), −31.42 (5%)).

Preparation of (S)-Mosher's ester of **21**: To a solution of (S)-MPTA (10 mg, 0.04 mmol) in 2 mL of dry dichloromethane at 0 °C was added oxalyl chloride (35 µL, 0.4 mmol) and 3 µL of DMF. After 1.5 h, the mixture was warmed to room temperature and solvent was removed by rotary evaporation to yield a colorless oil. Solid DMAP (12 mg, 0.1 mmol) and a solution of the **21** (5 mg, 0.018 mmol) in dry dichloromethane (2 mL) were sequentially added to the latter residue (Mosher acid chloride) under argon at room temperature and the reaction mixture was stirred for 12 h to ensure derivatization was complete. Then the reaction was diluted with ether followed by addition of water. The organic layer was sequentially washed with 10% HCl, saturated aqueous $NaHCO_3$, water and brine. It was then dried with anhydrous Na_2SO_4. The solvent was evaporated in vaccuo and a preparative chromatography afforded the product as a clear oil.

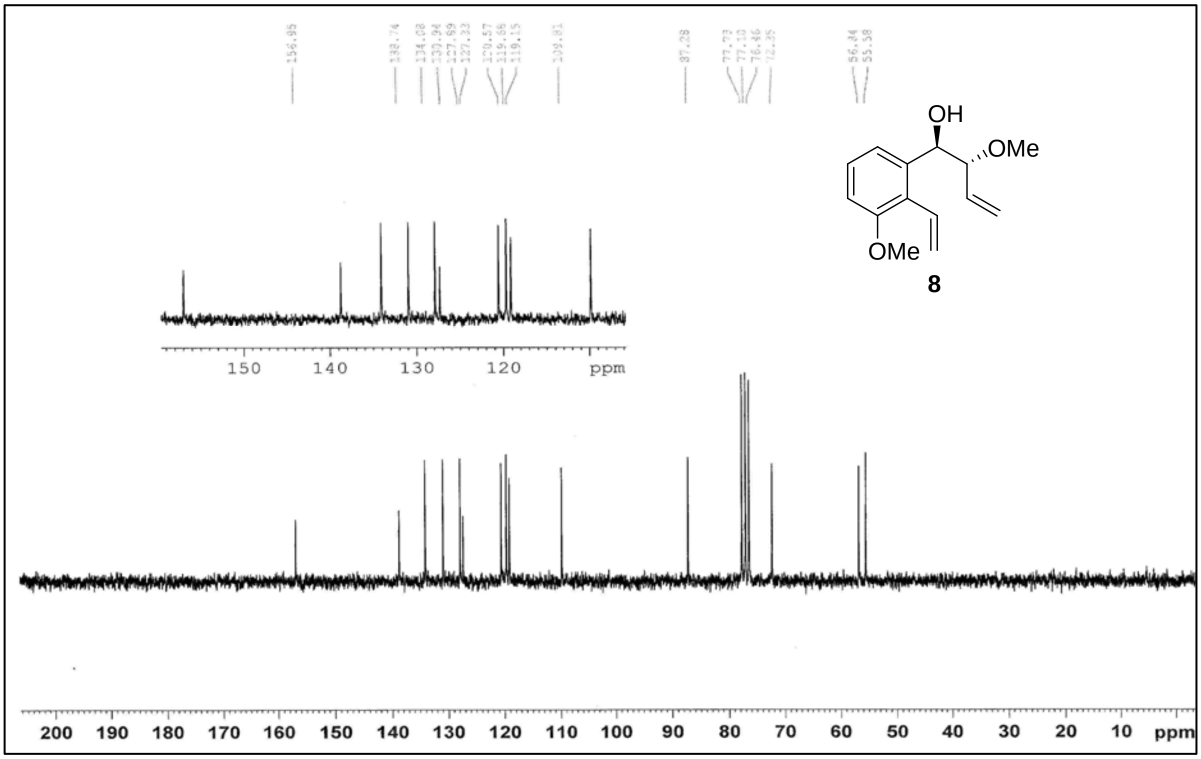
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.52 (s, 3H), 2.65 (s, 3H), 3.19 (s, 3H), 3.44 (s, 3H), 3.98 (t, *J* = 7.6 Hz, 1H), 5.02 (d, *J* = 10 Hz, 1H), 5.09 (d, *J* = 17.2 Hz, 1H), 5.38-5.49 (m, 2H), 5.84 (d, *J* = 11.6 Hz, 1H), 6.54 (d, *J* = 8.4, 1H), 6.71 (s, 1H), 7.08 (dd, *J* = 11.2, 17.8 Hz, 1H), 7.30-7.49 (m, 6H), 7.88-7.90 (m, 2H).

^{19}F NMR of the corresponding Mosher's ester derivative showed 88% ee (δ −31.42 (95%), −31.74(5%))

^{1}H NMR (400 MHz, CDCl$_3$)



^{13}C NMR (50 MHz, CDCl$_3$)



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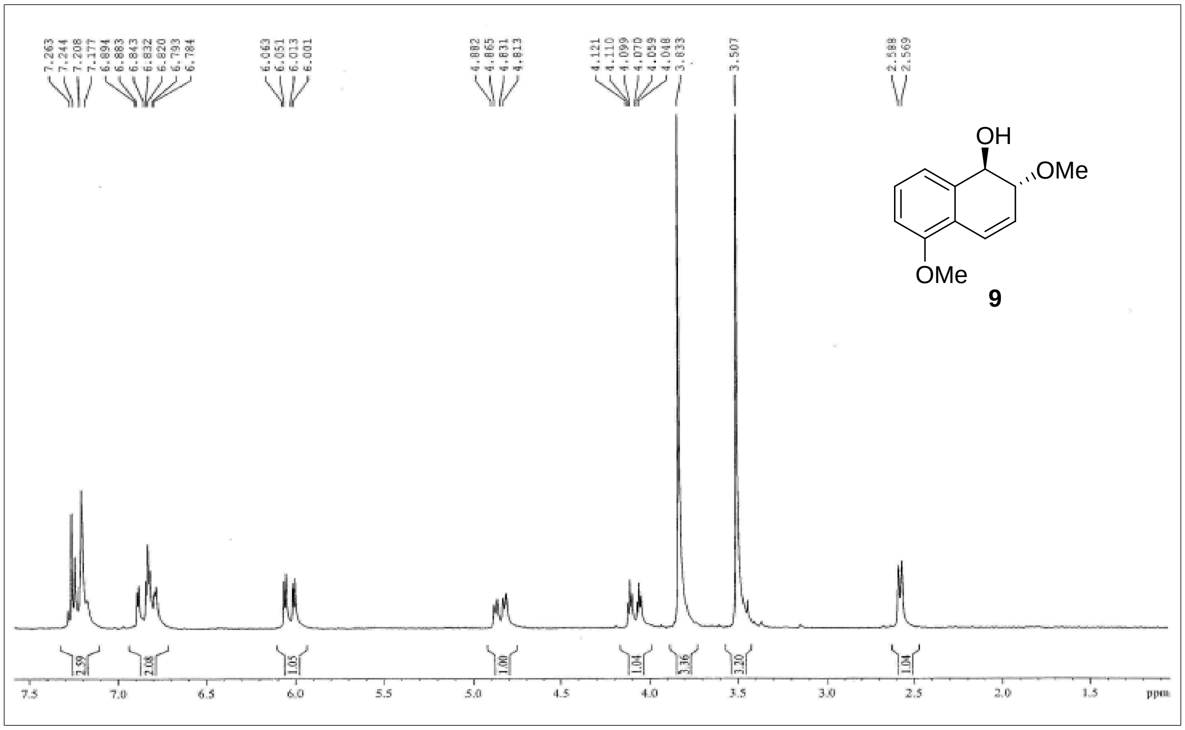

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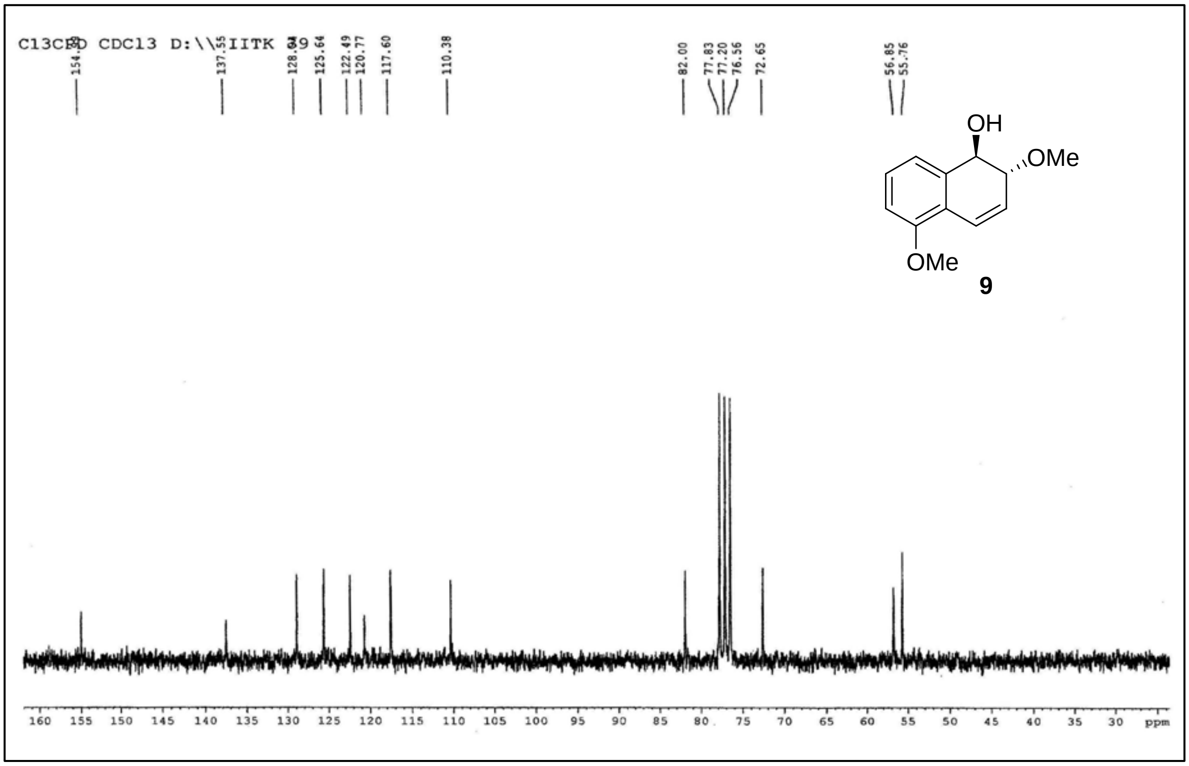

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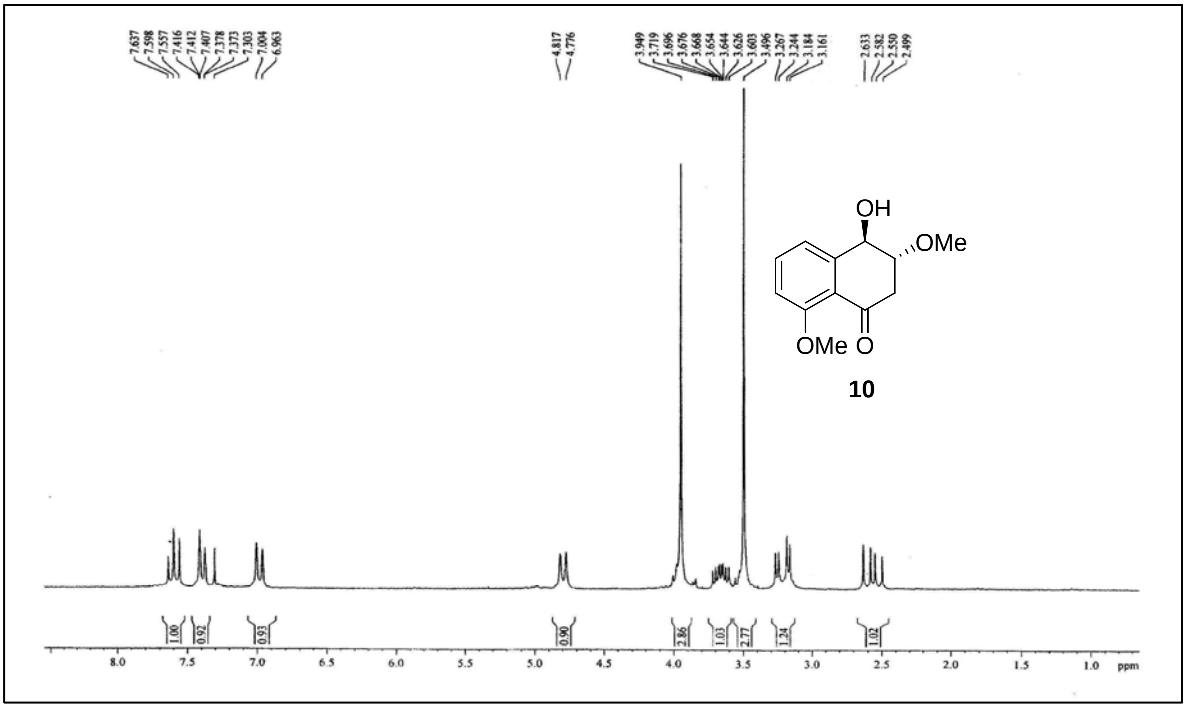
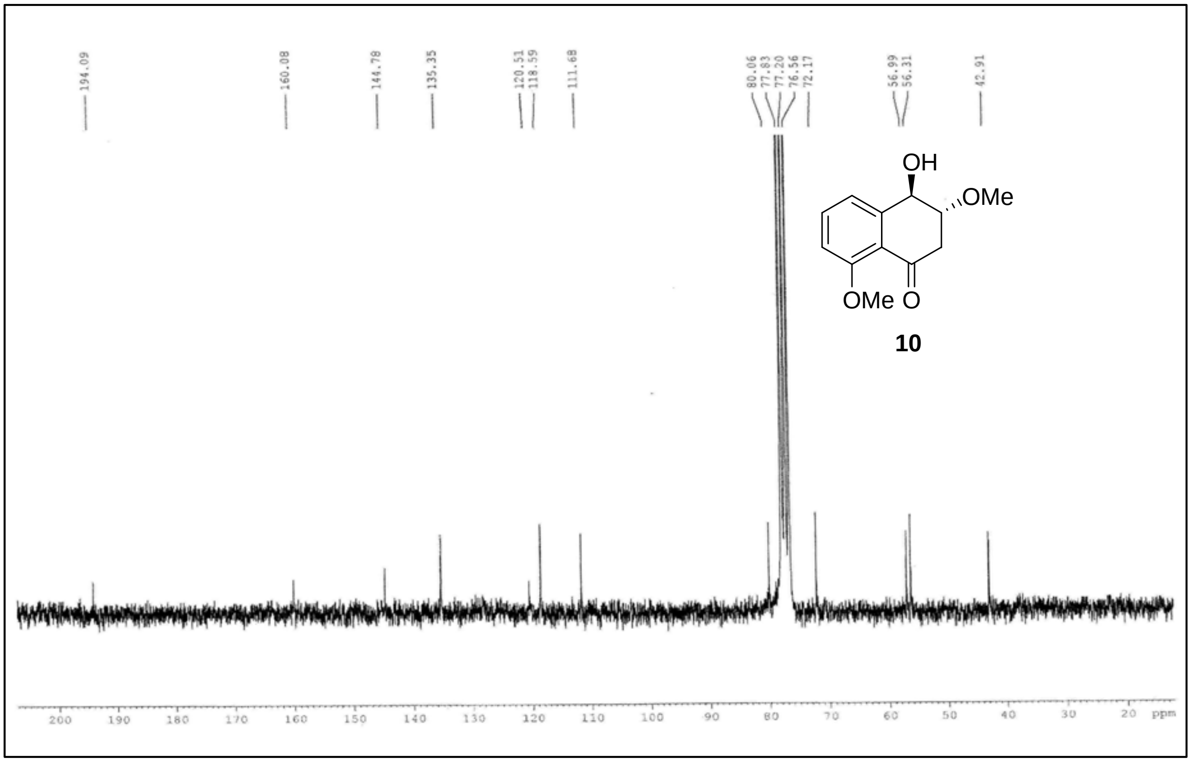
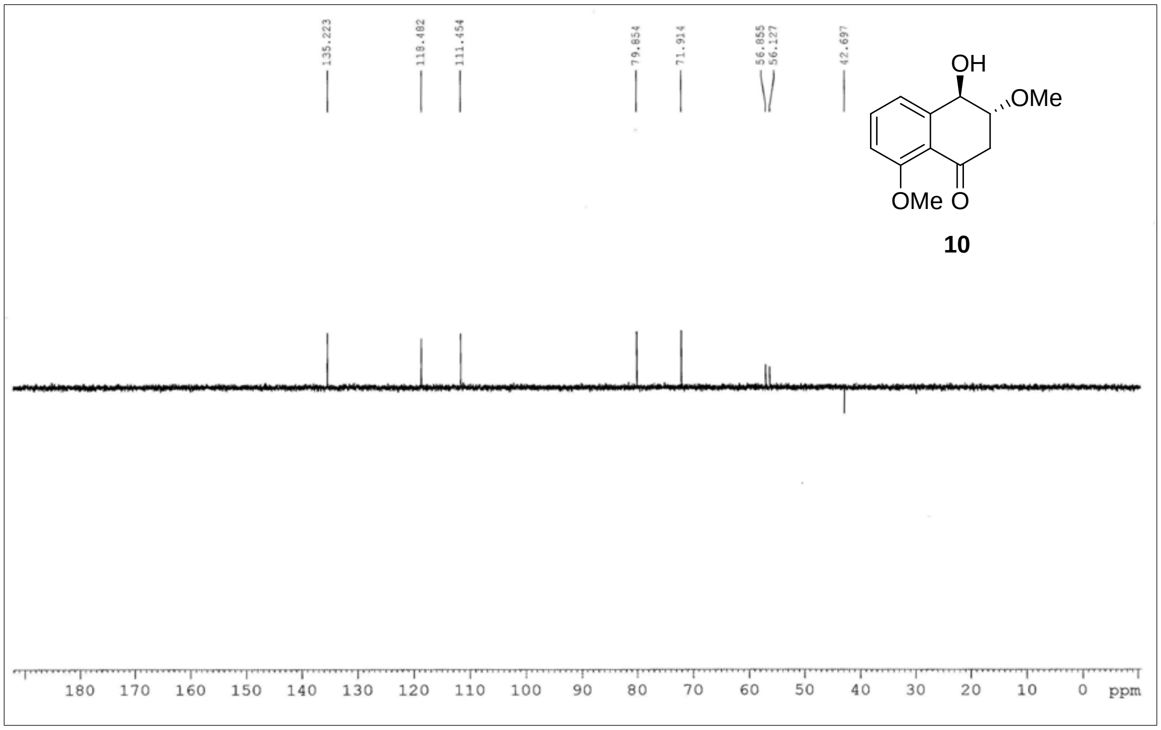
^{1}H NMR (200 MHz, $CDCl_3$)



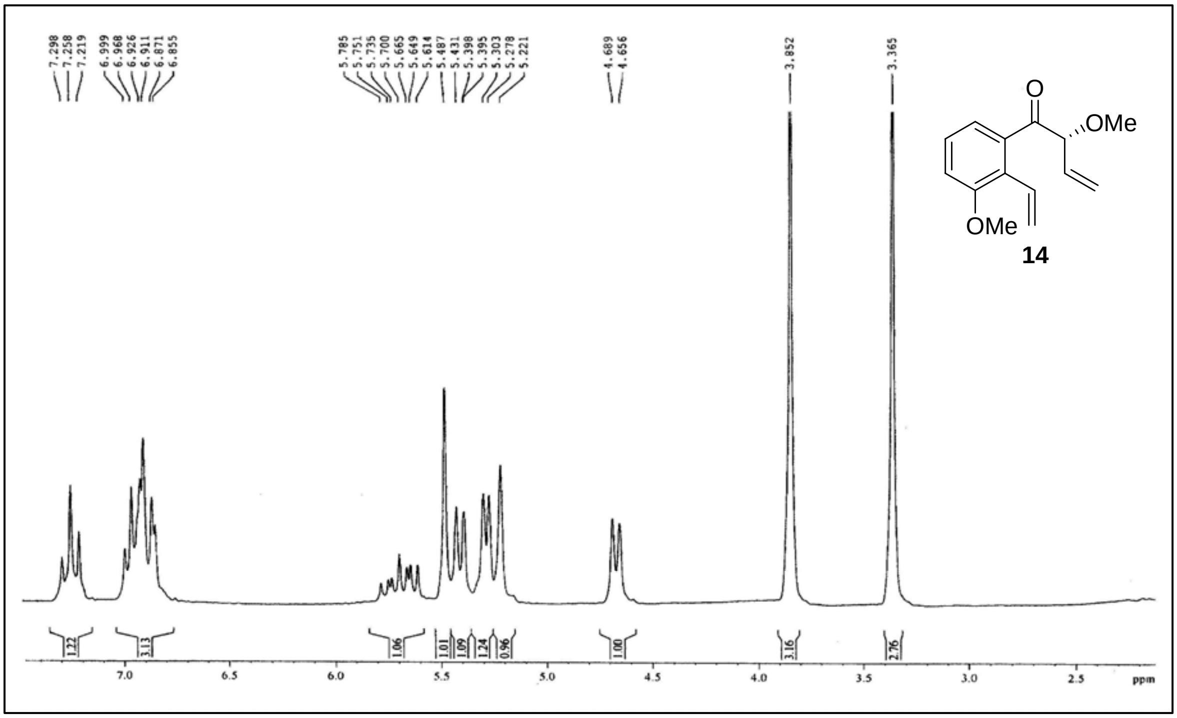
^{13}C NMR (50 MHz, $CDCl_3$)



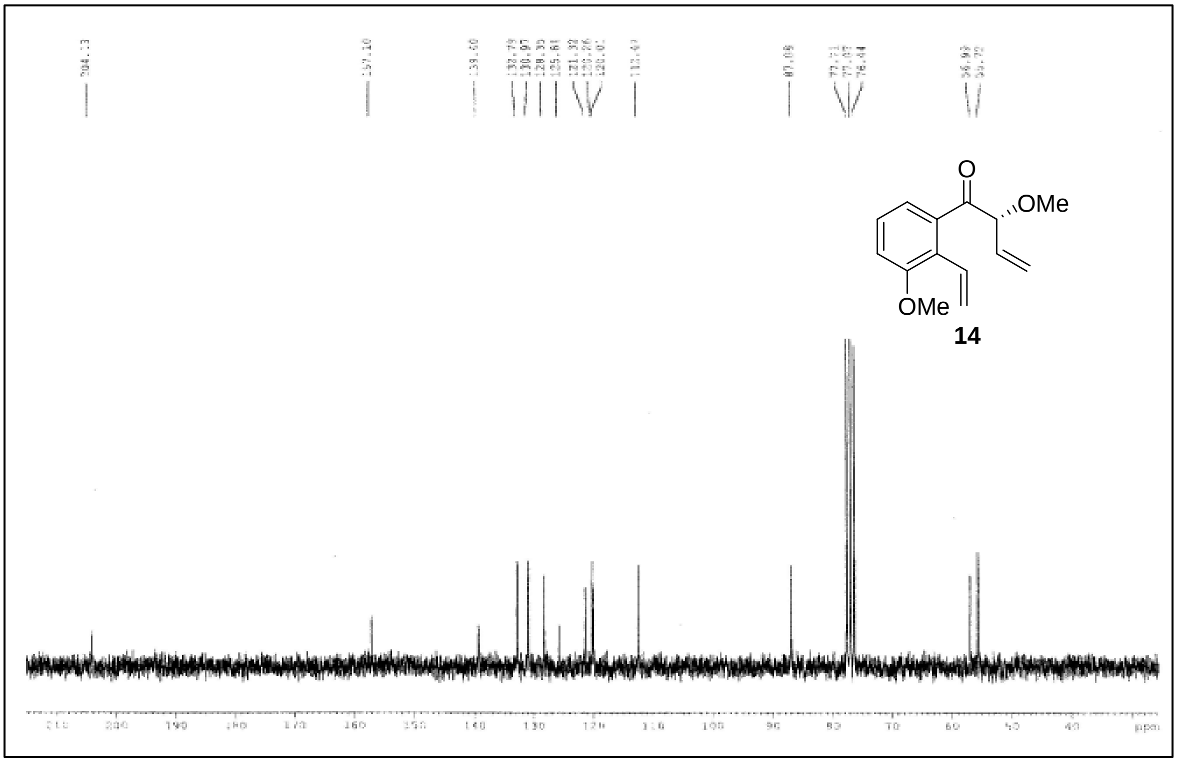
Dept-135 spectra



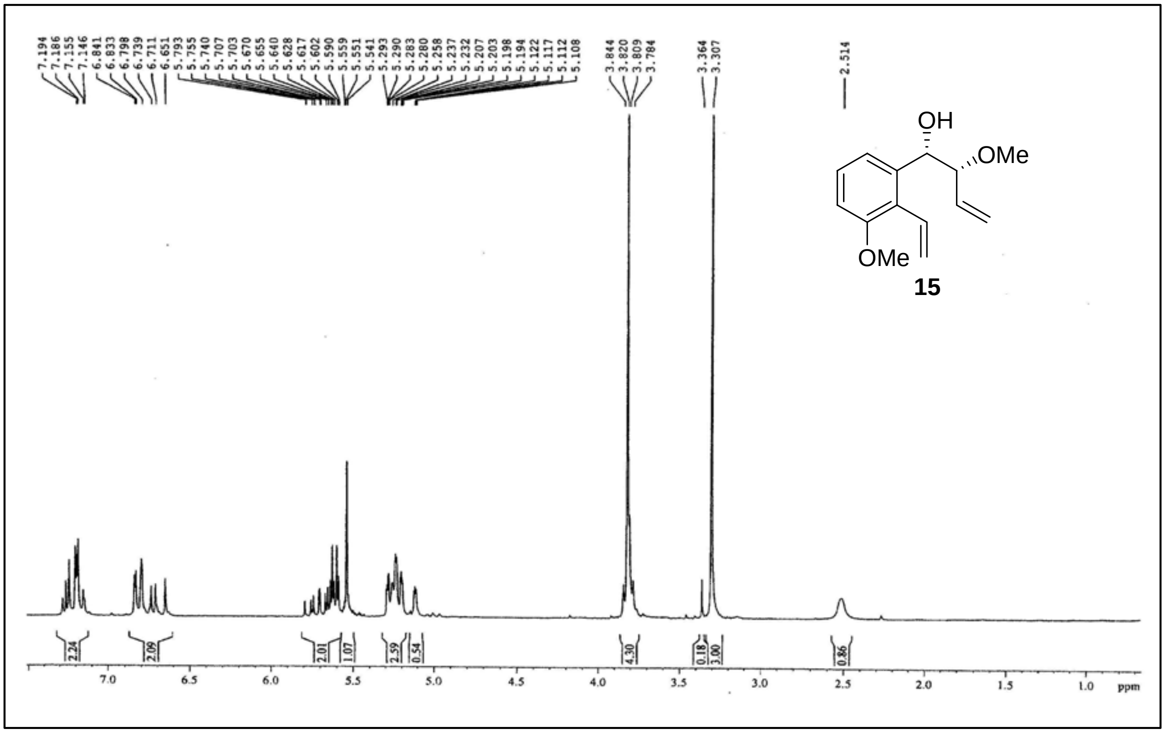
^{1}H NMR (200 MHz, CDCl$_3$)



^{13}C NMR (50 MHz, CDCl$_3$)



^{1}H NMR (200 MHz, CDCl$_3$)



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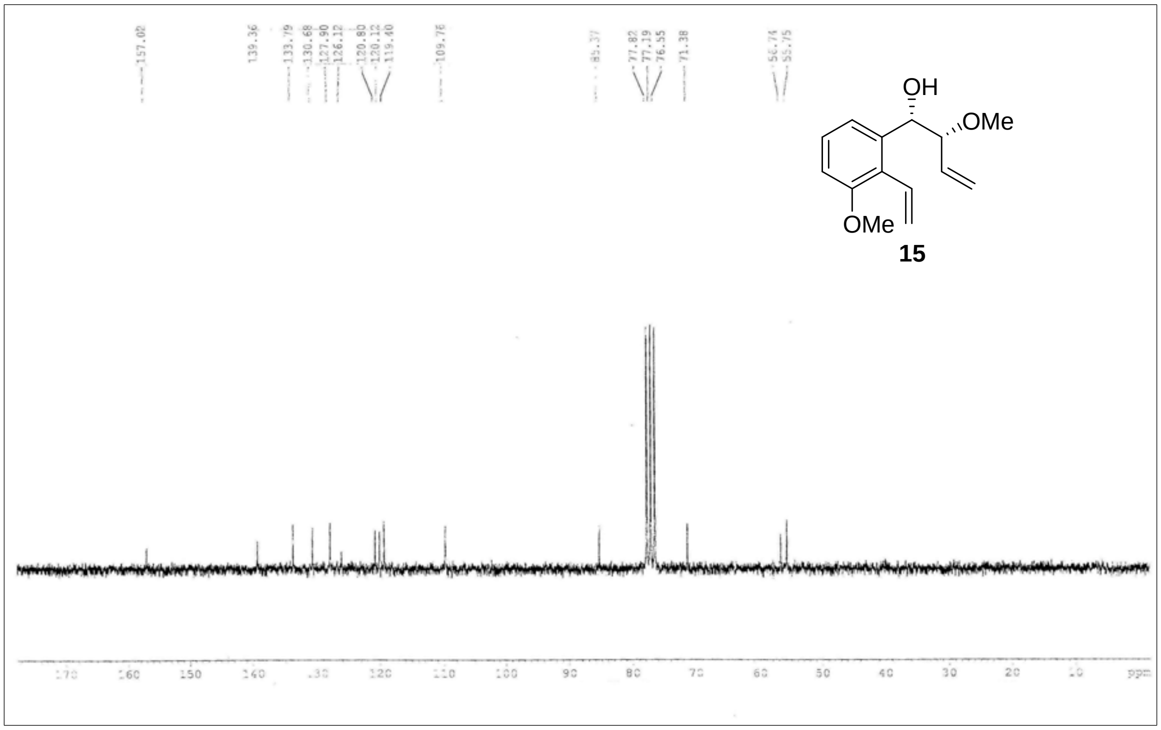

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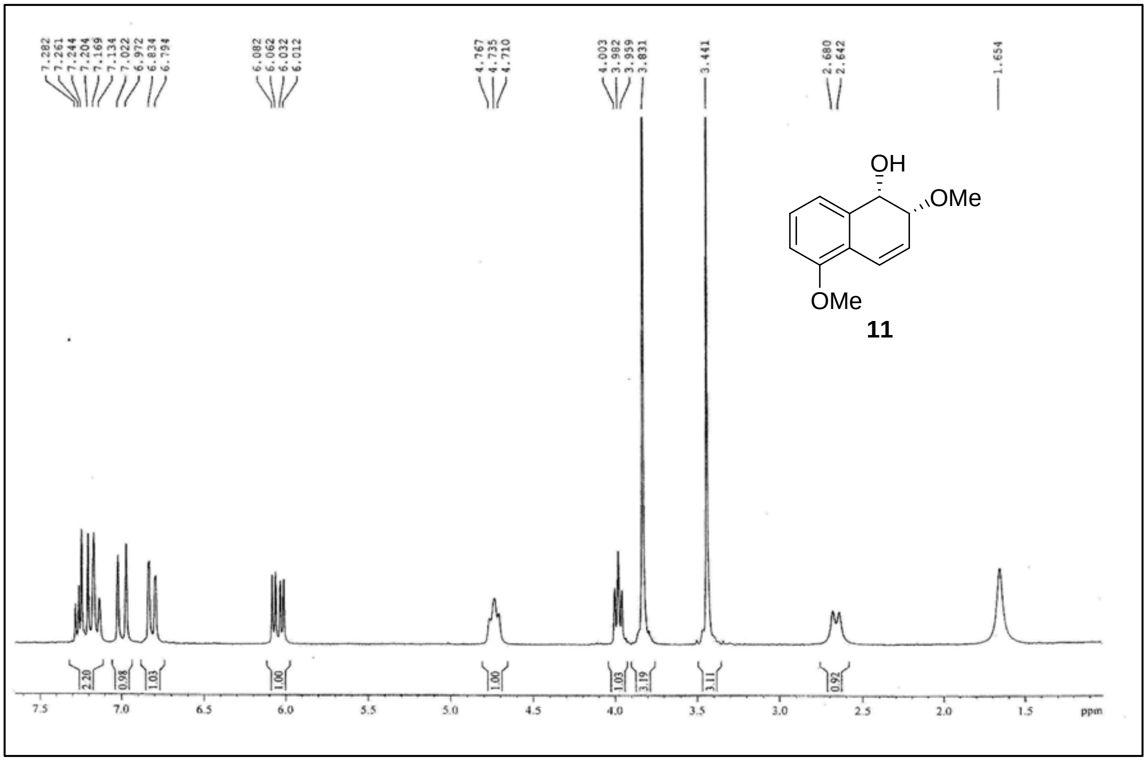

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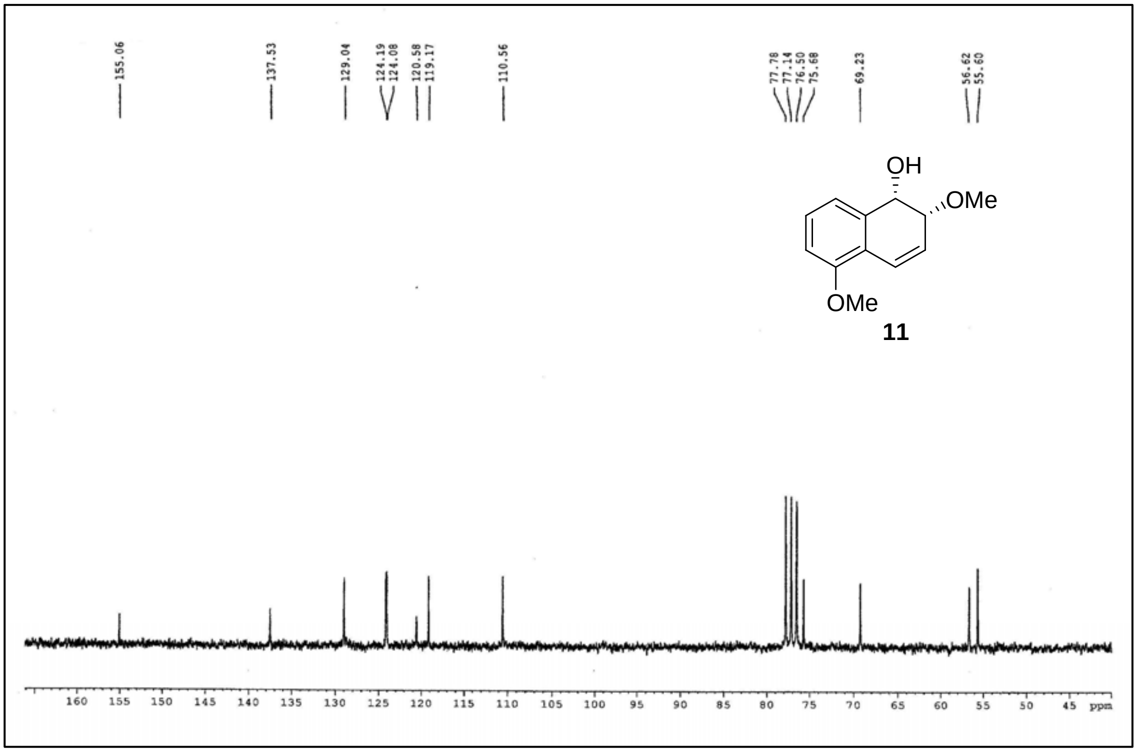
^{13}C NMR (50 MHz, CDCl$_3$)



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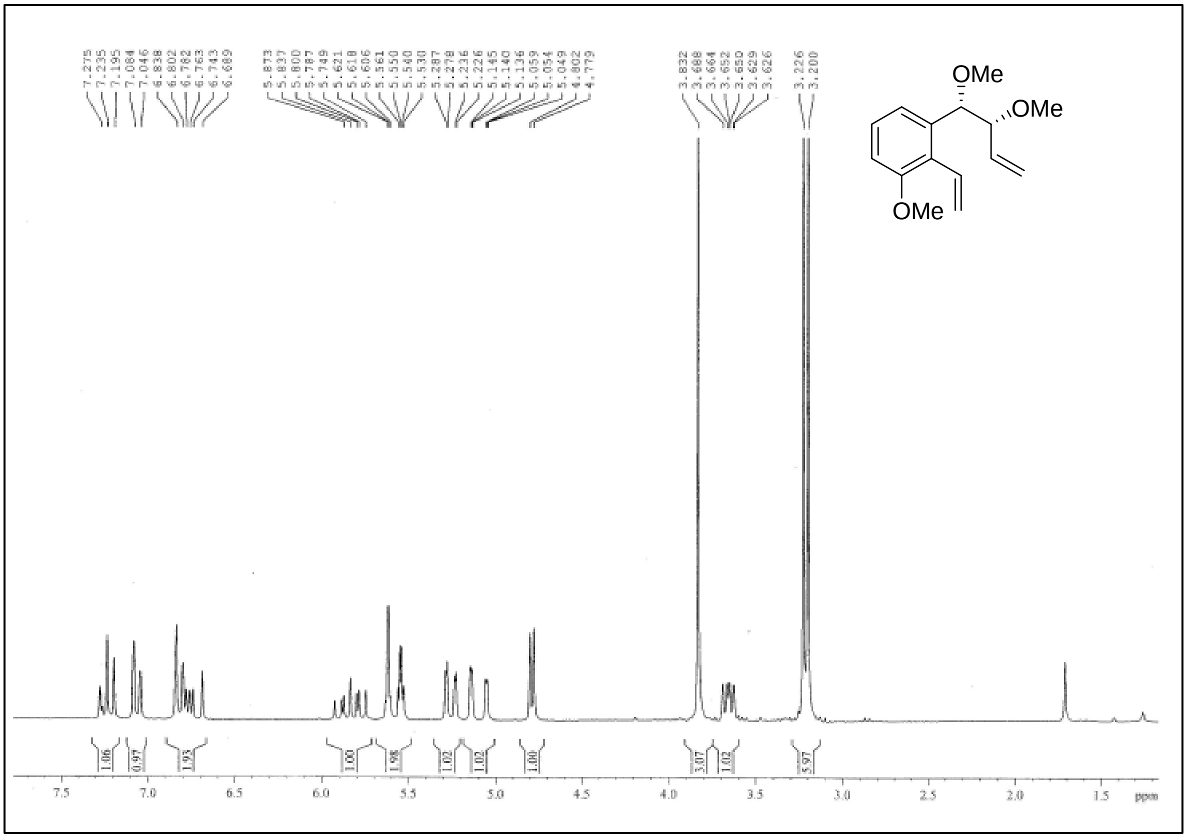
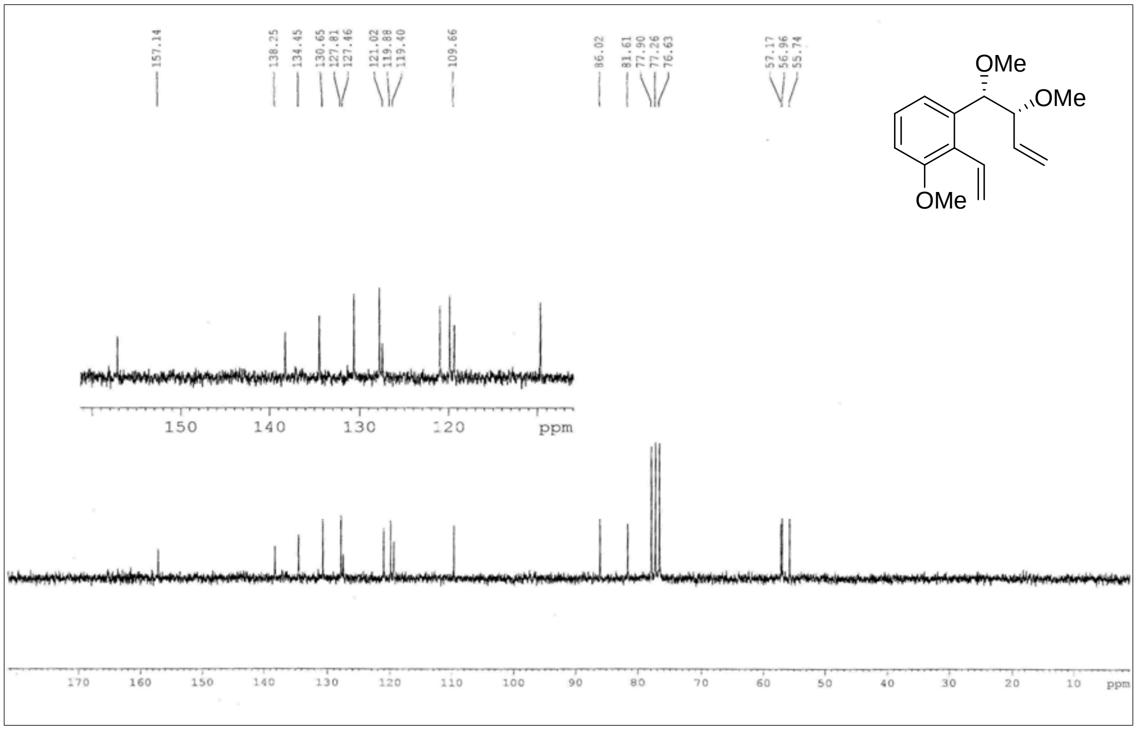
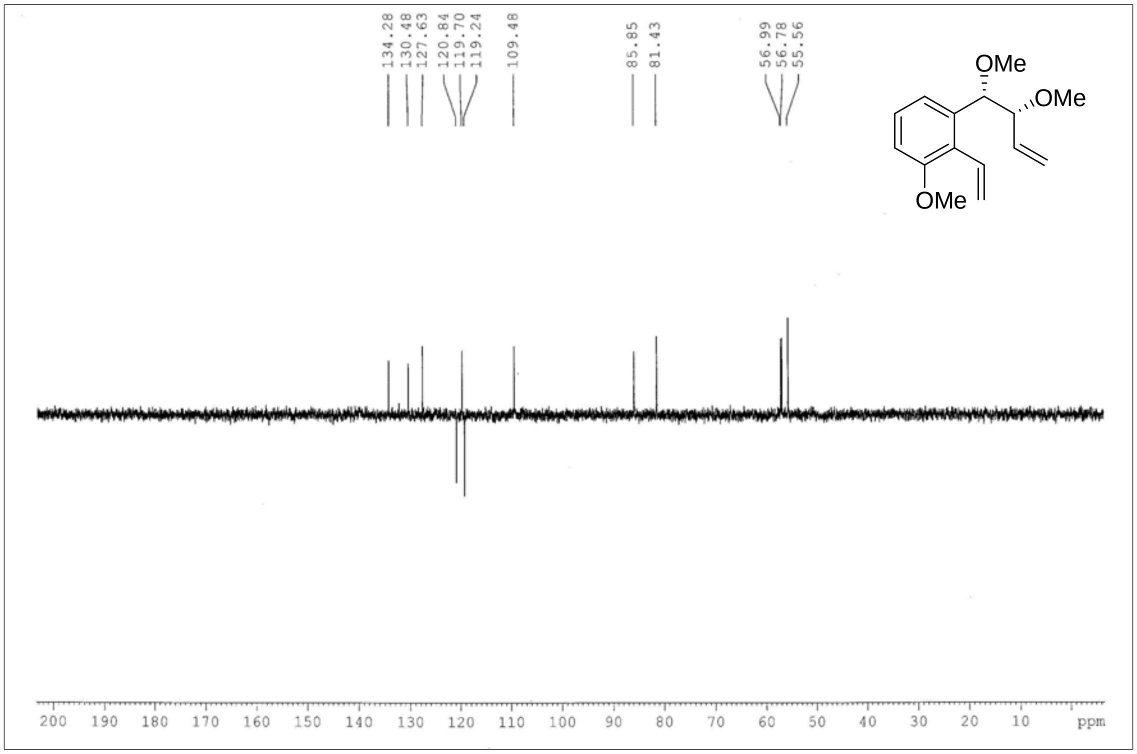
^{1}H NMR (200 MHz, CDCl$_3$)



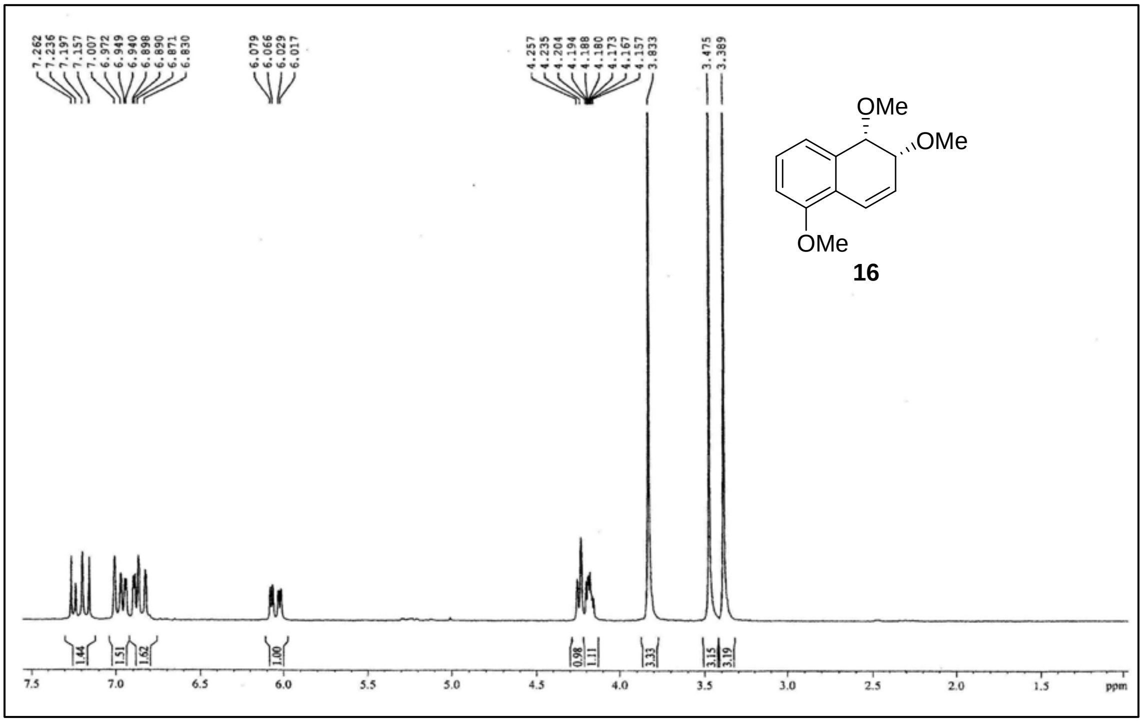
^{13}C NMR (50 MHz, CDCl$_3$)



Dept-135 spectra



^{1}H NMR (200 MHz, CDCl$_3$)



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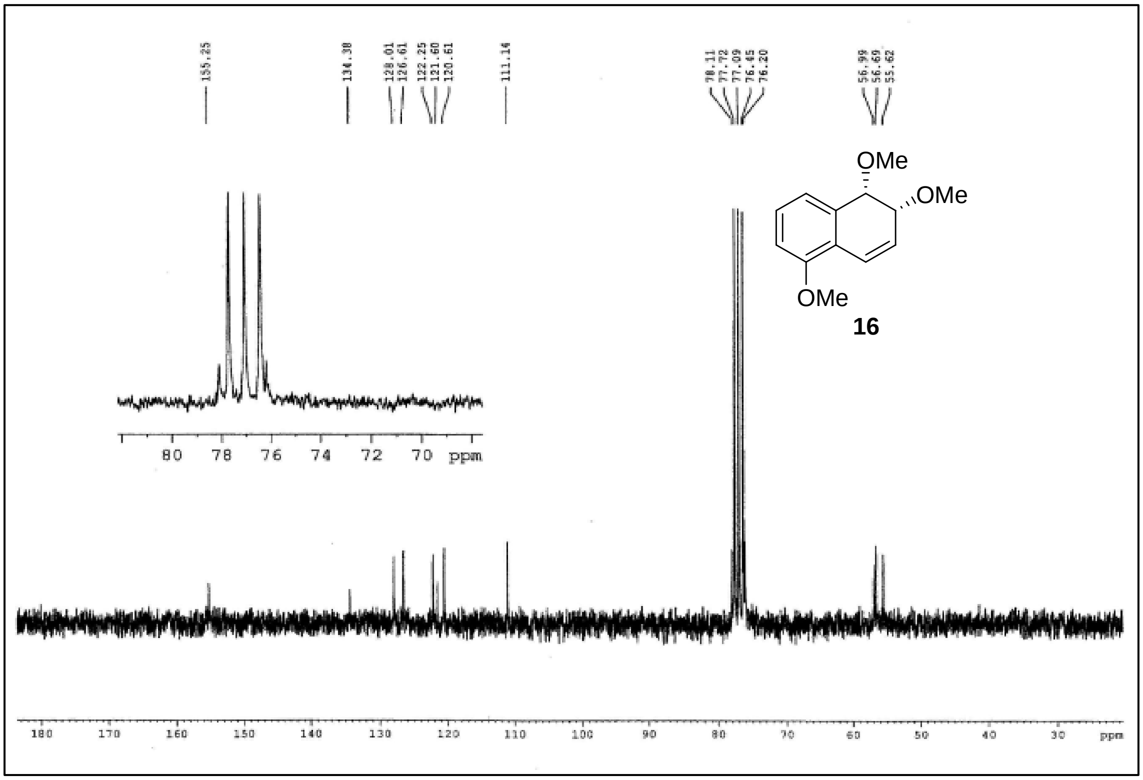
^{13}C NMR (50 MHz, CDCl$_3$)



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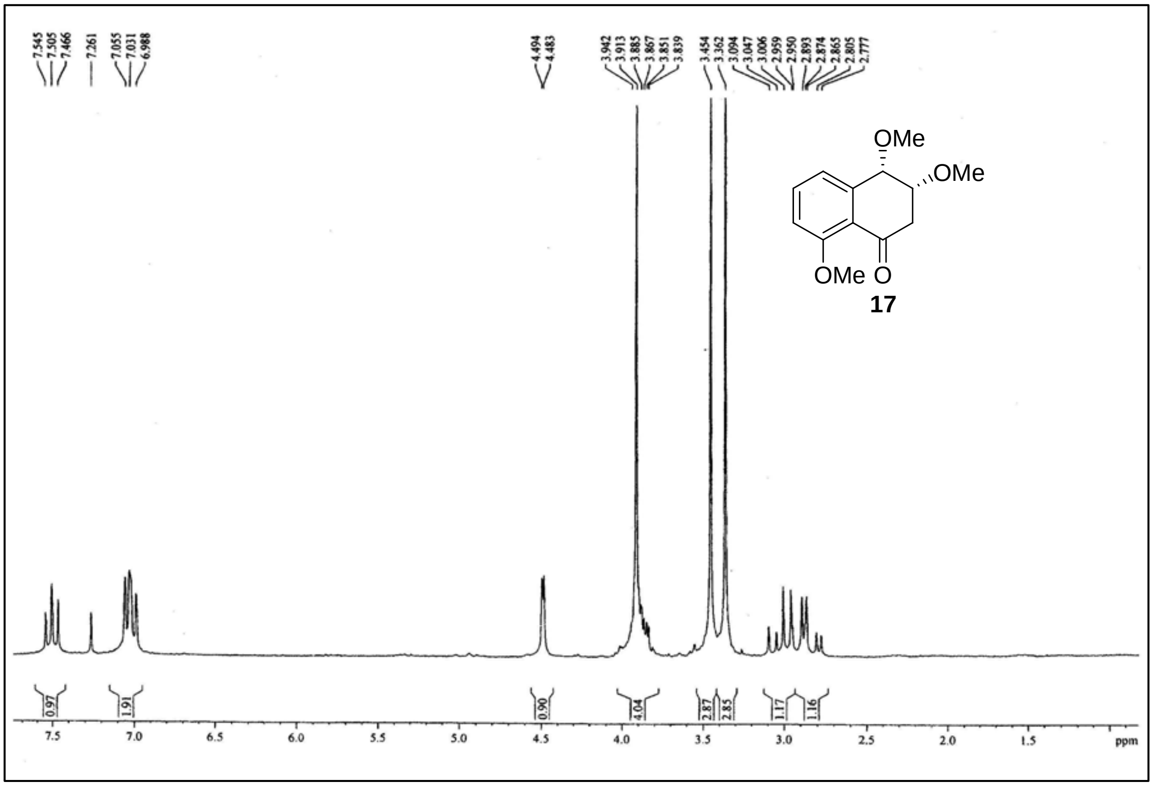
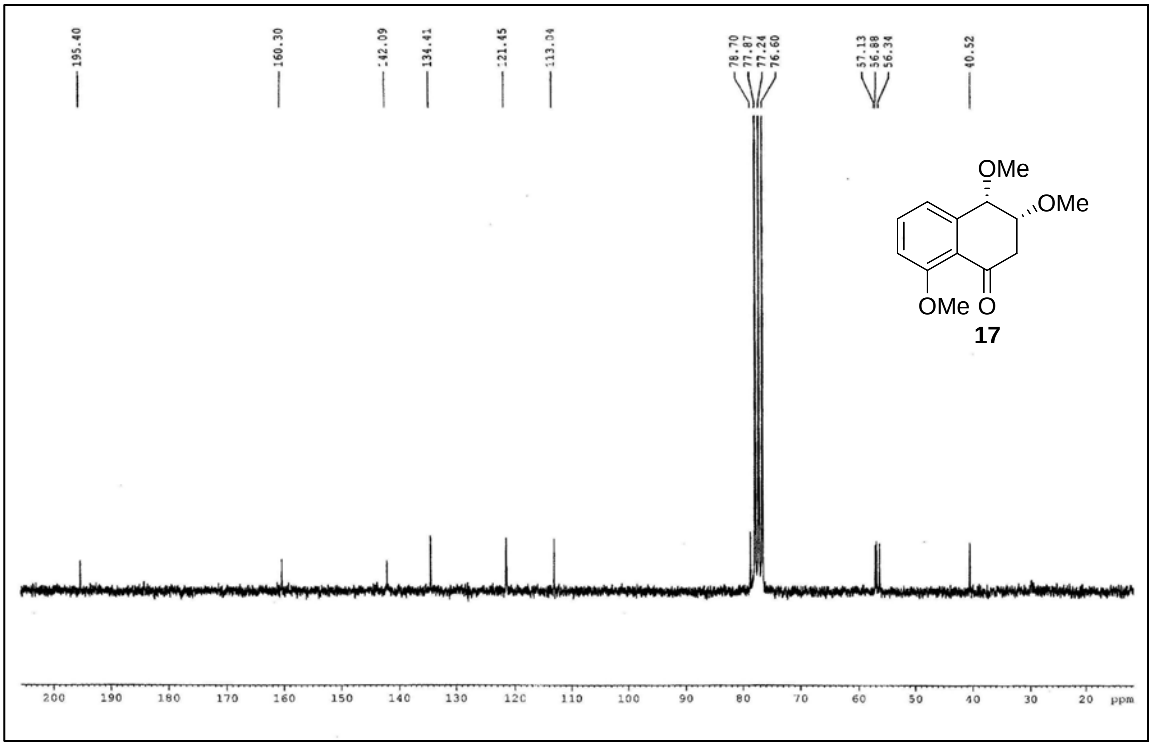
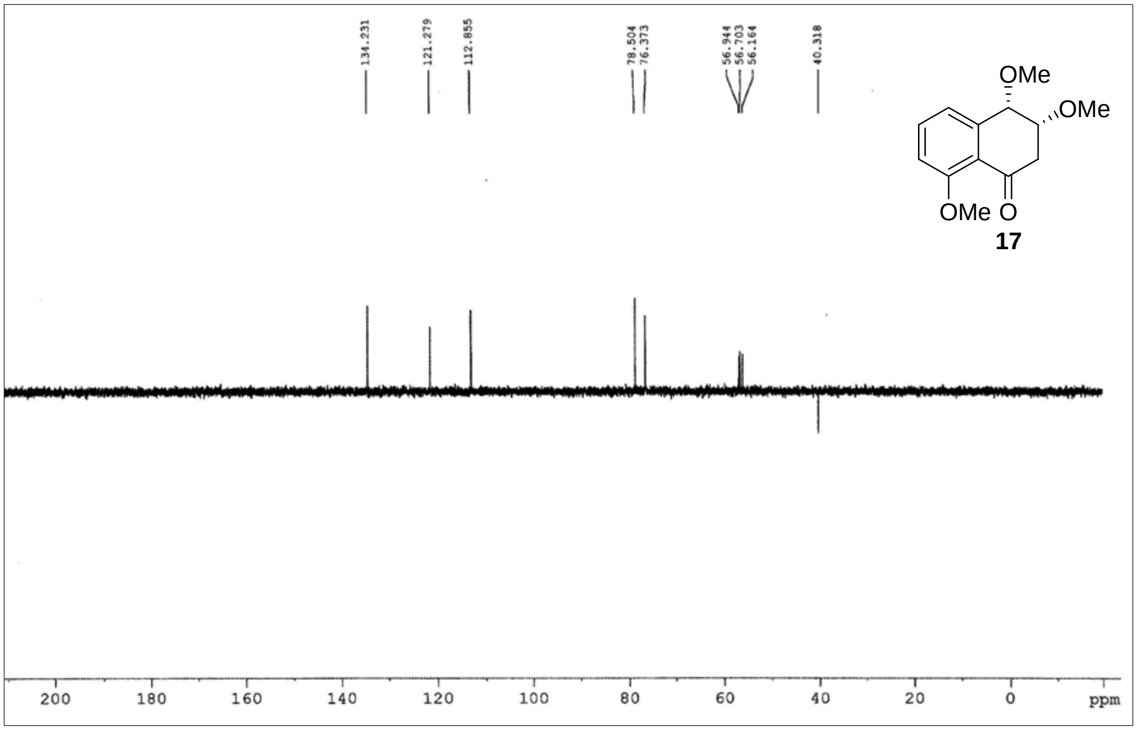
^{1}H NMR (200 MHz, CDCl$_3$)



^{13}C NMR (50 MHz, $CDCl_3$)



Dept-135 spectra



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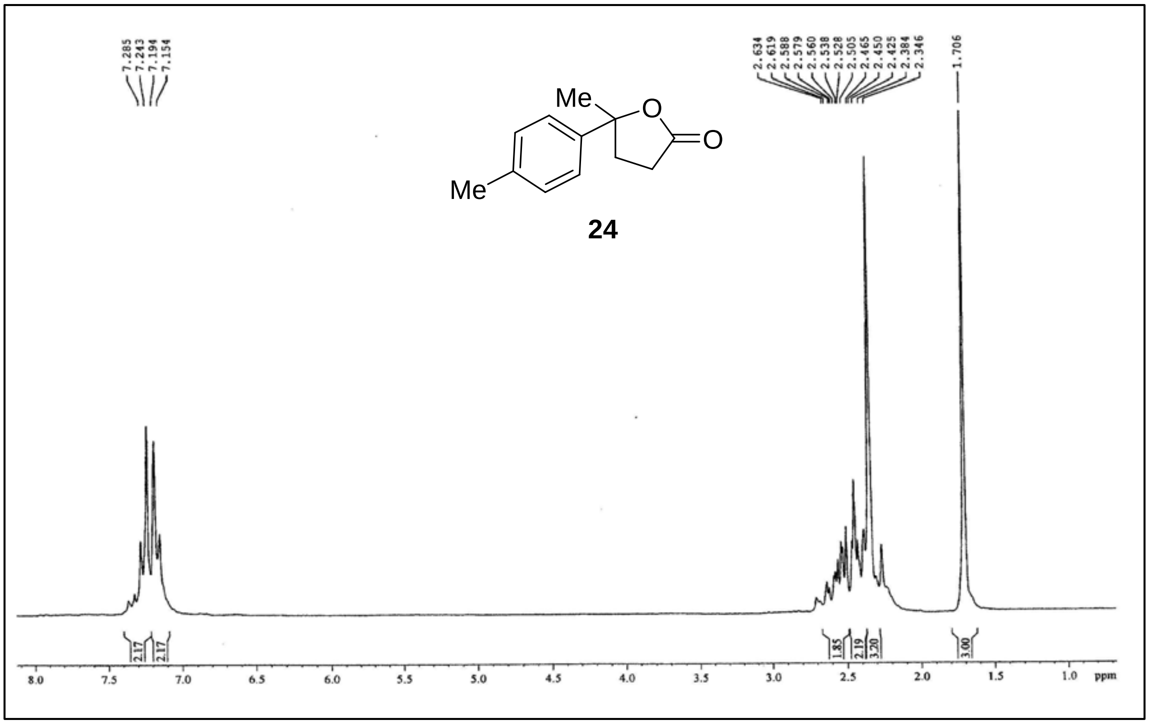

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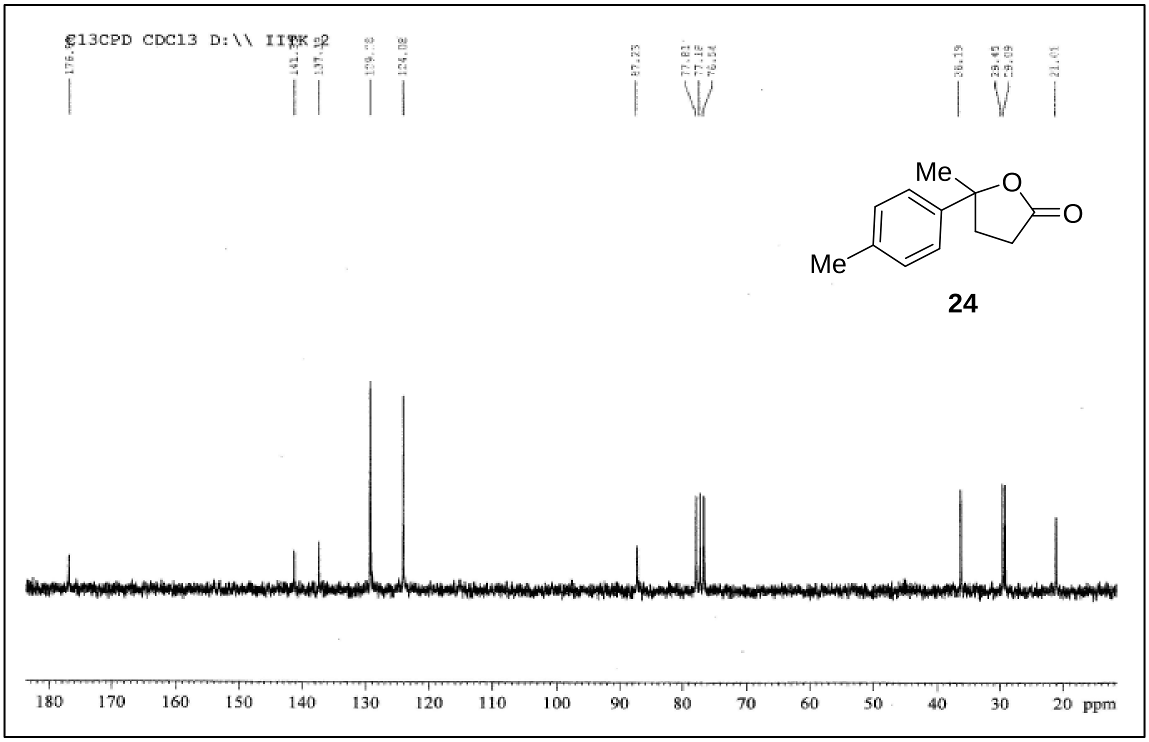

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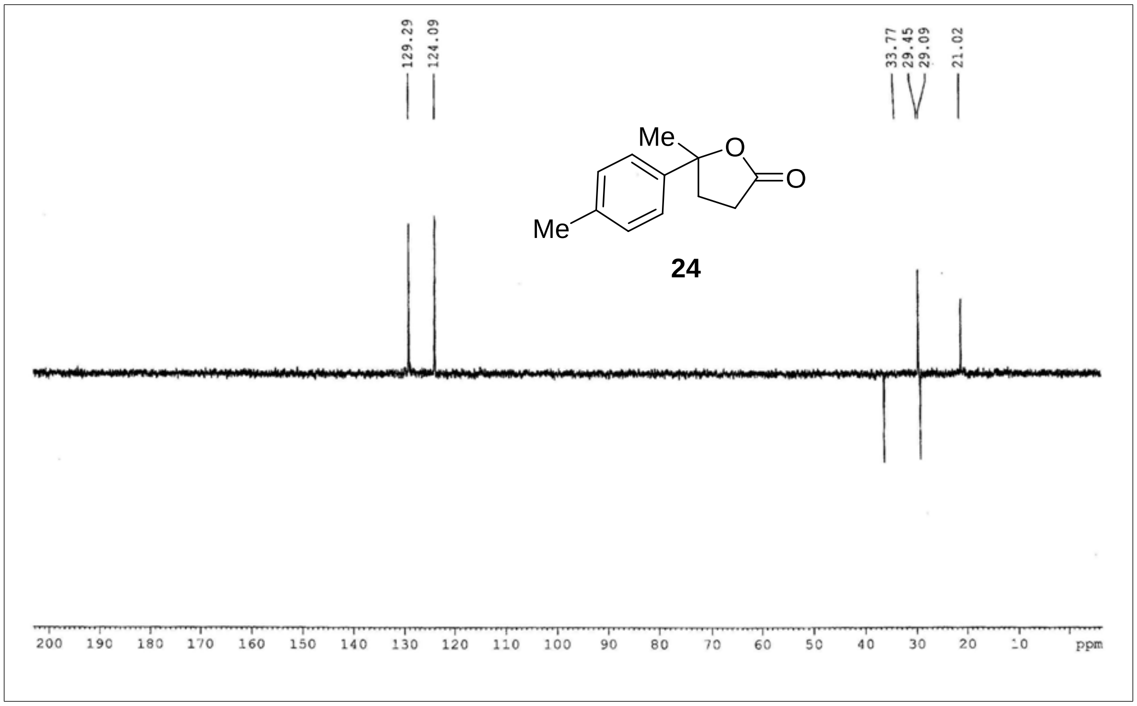
Dept-135 spectra



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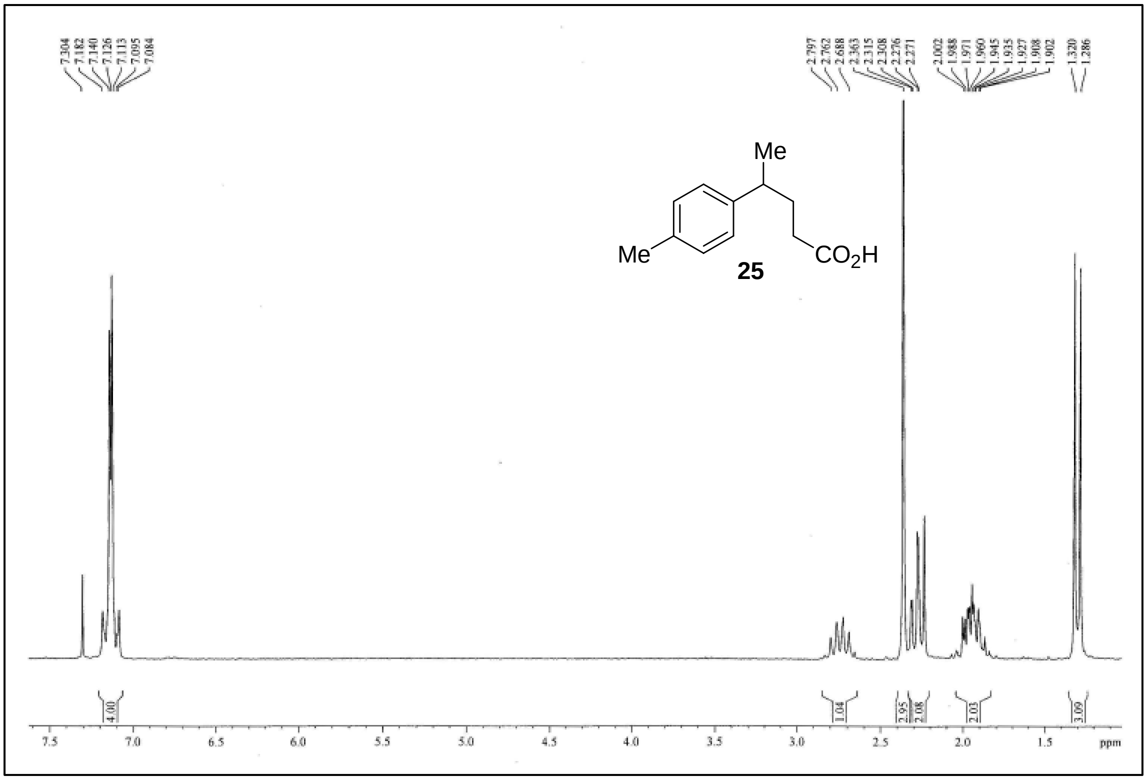
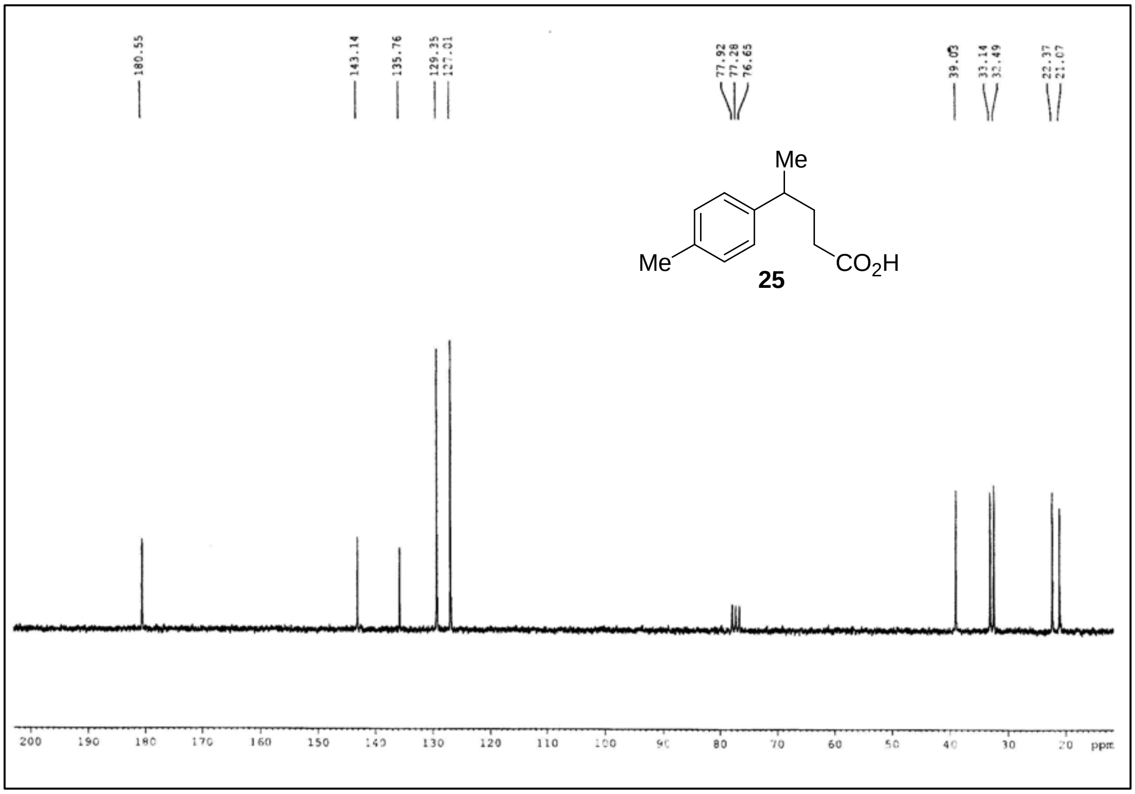
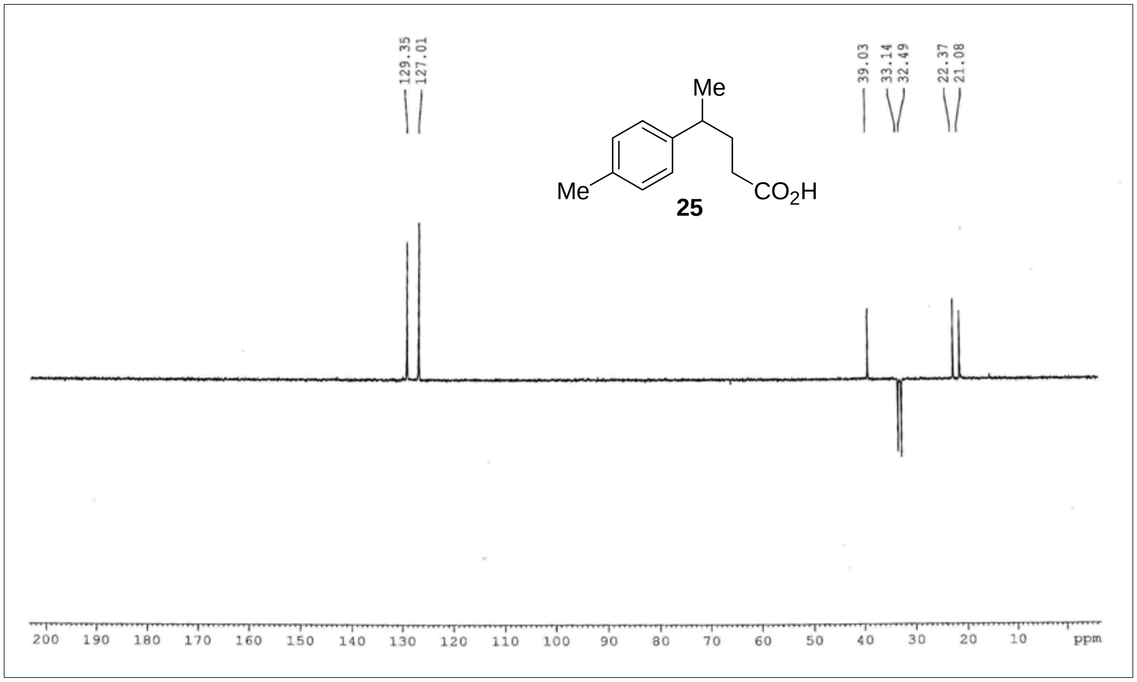
^{1}H NMR (200 MHz, $CDCl_3$)



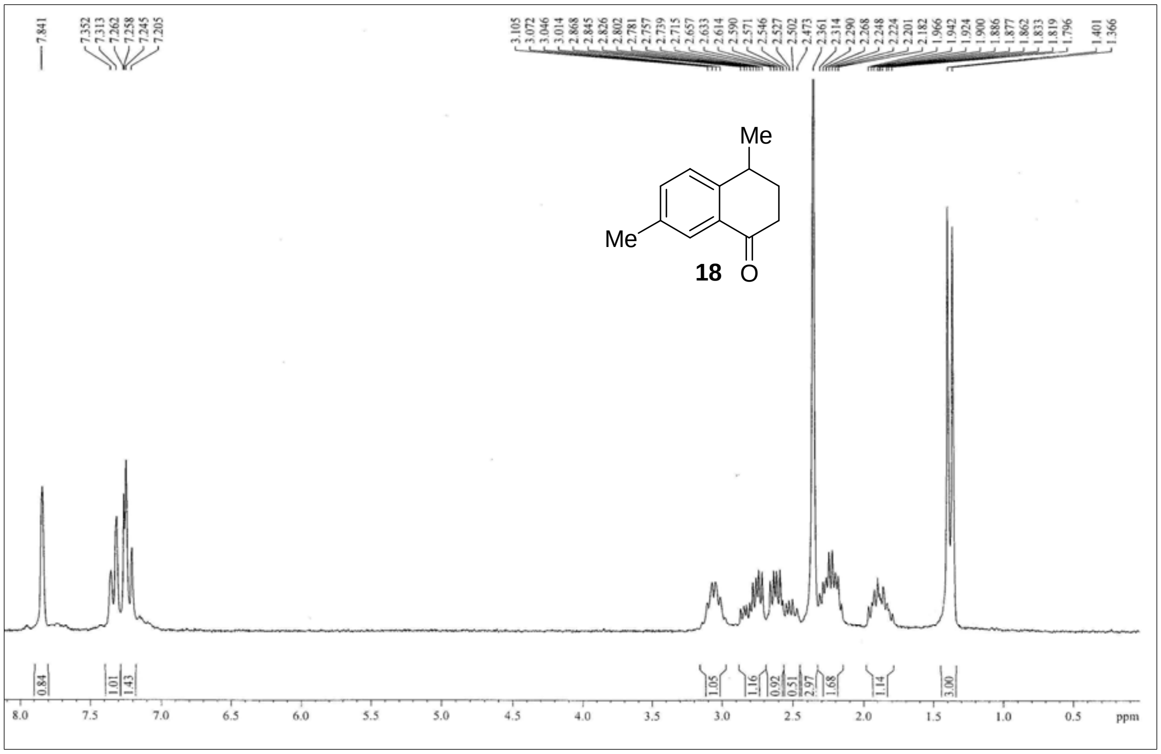
^{13}C NMR (50 MHz, $CDCl_3$)



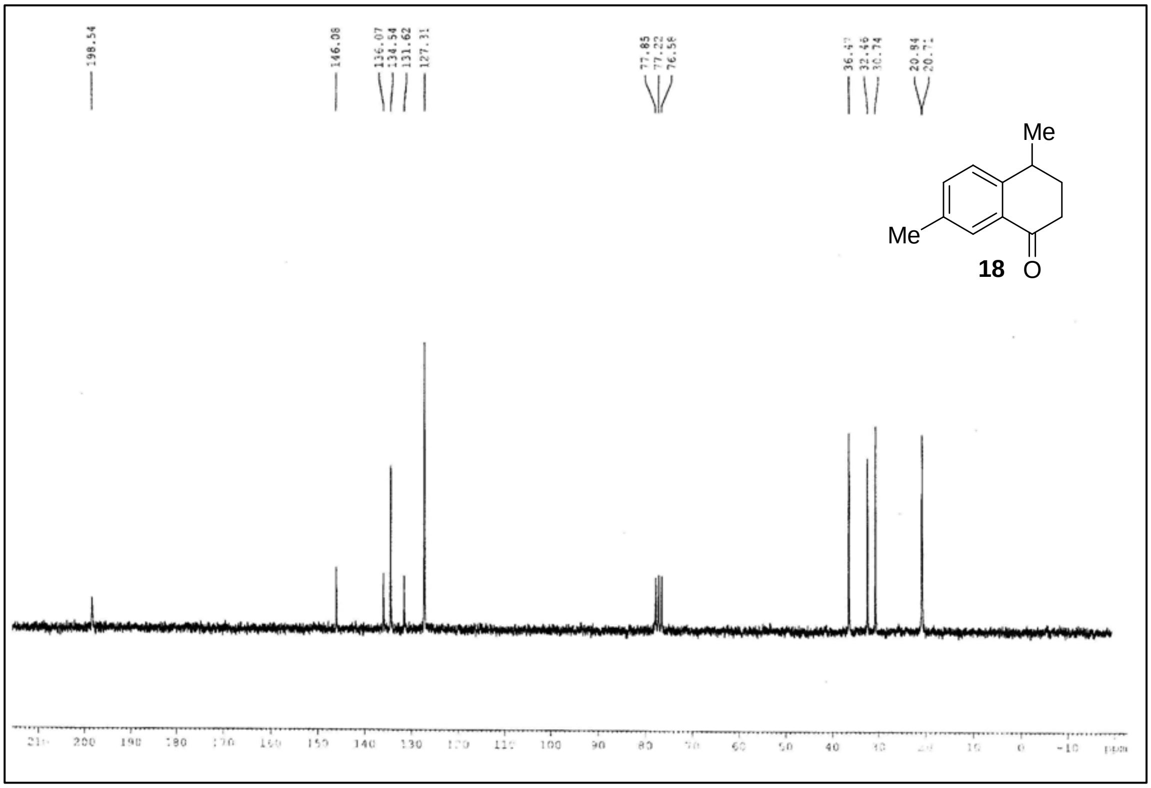
Dept-135 spectra



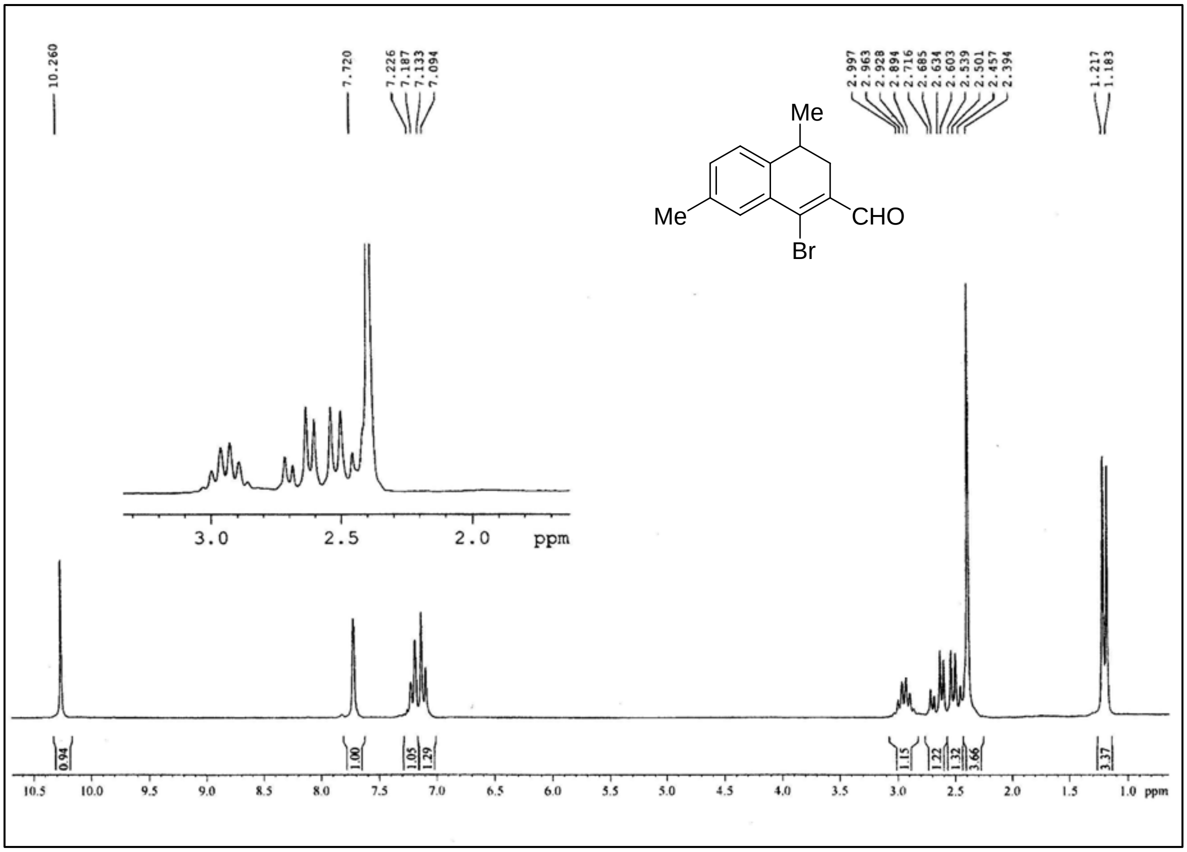
^{1}H NMR (200 MHz, CDCl$_3$)



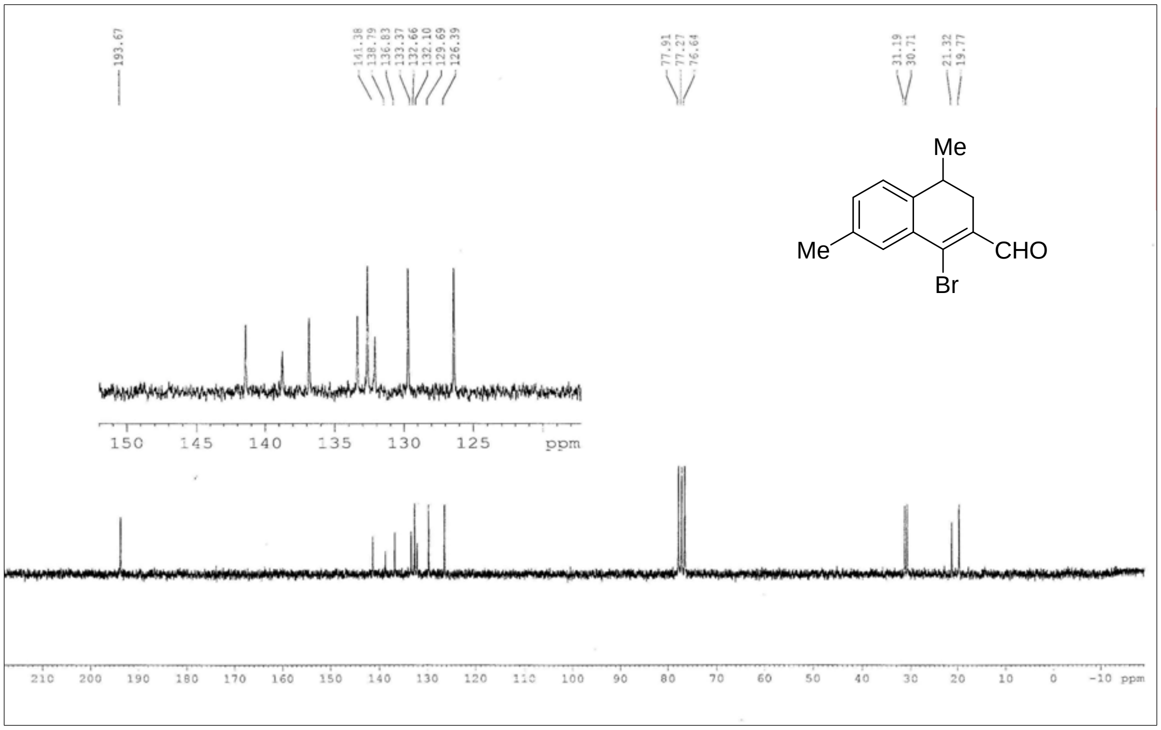
^{13}C NMR (50 MHz, CDCl$_3$)



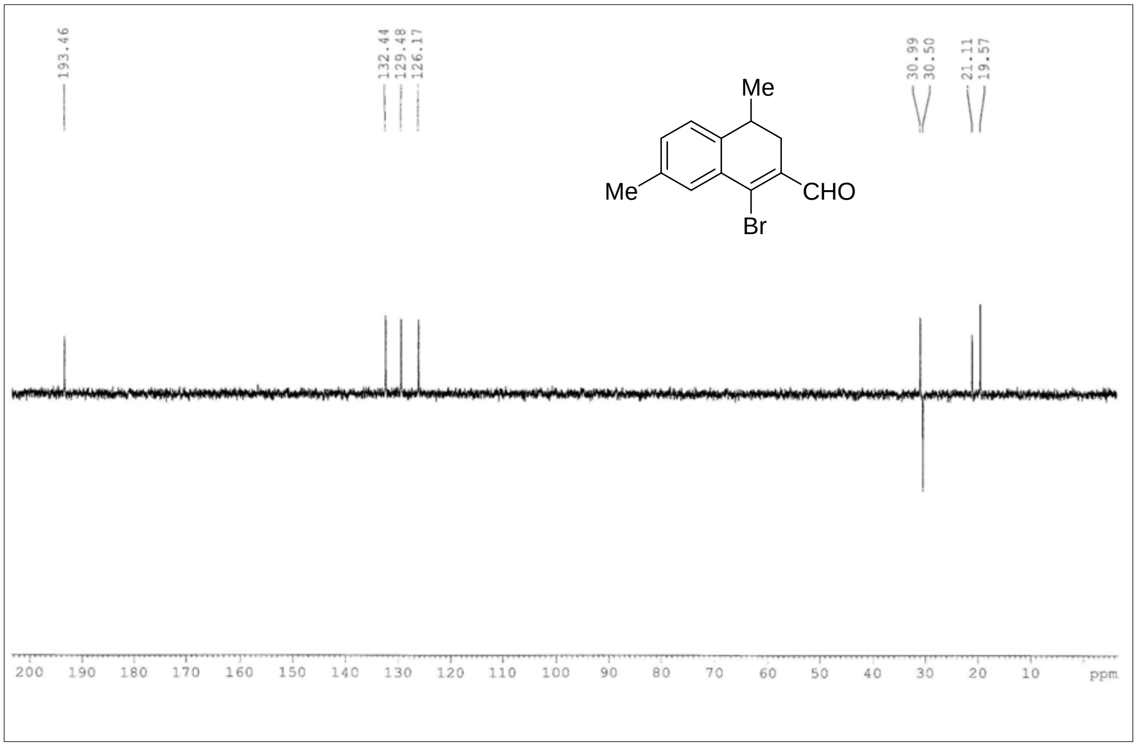
^{1}H NMR (200 MHz, $CDCl_3$)



^{13}C NMR (50 MHz, CDCl$_3$)



Dept-135 spectra



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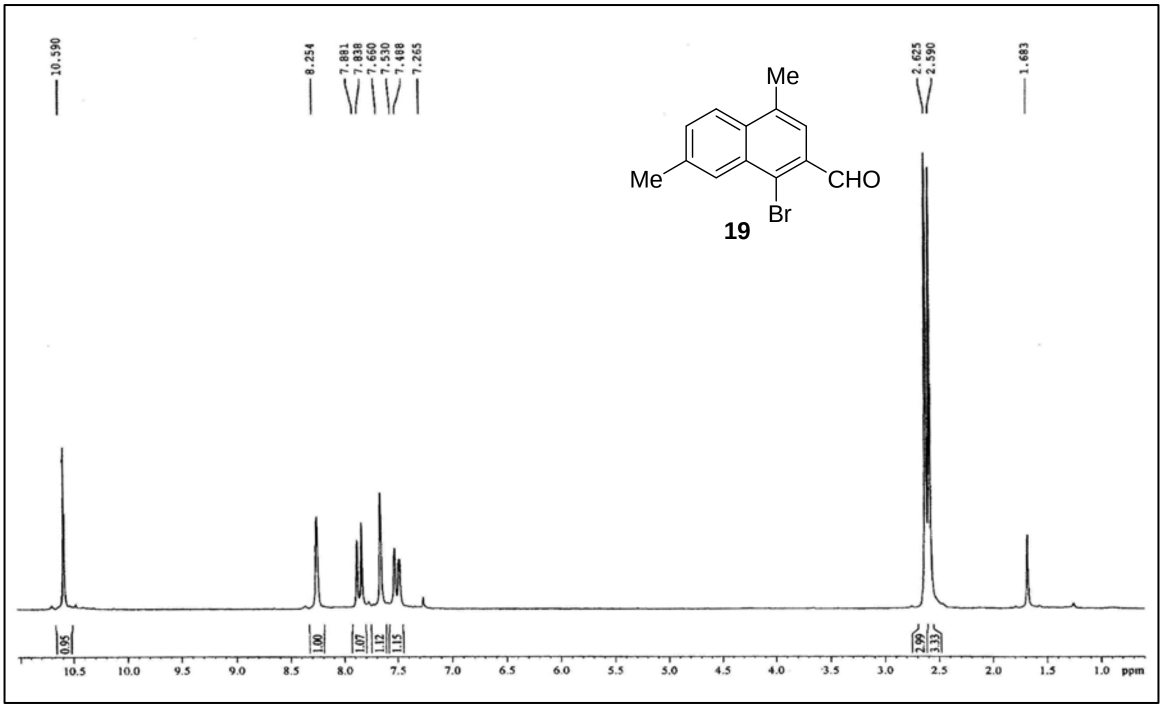
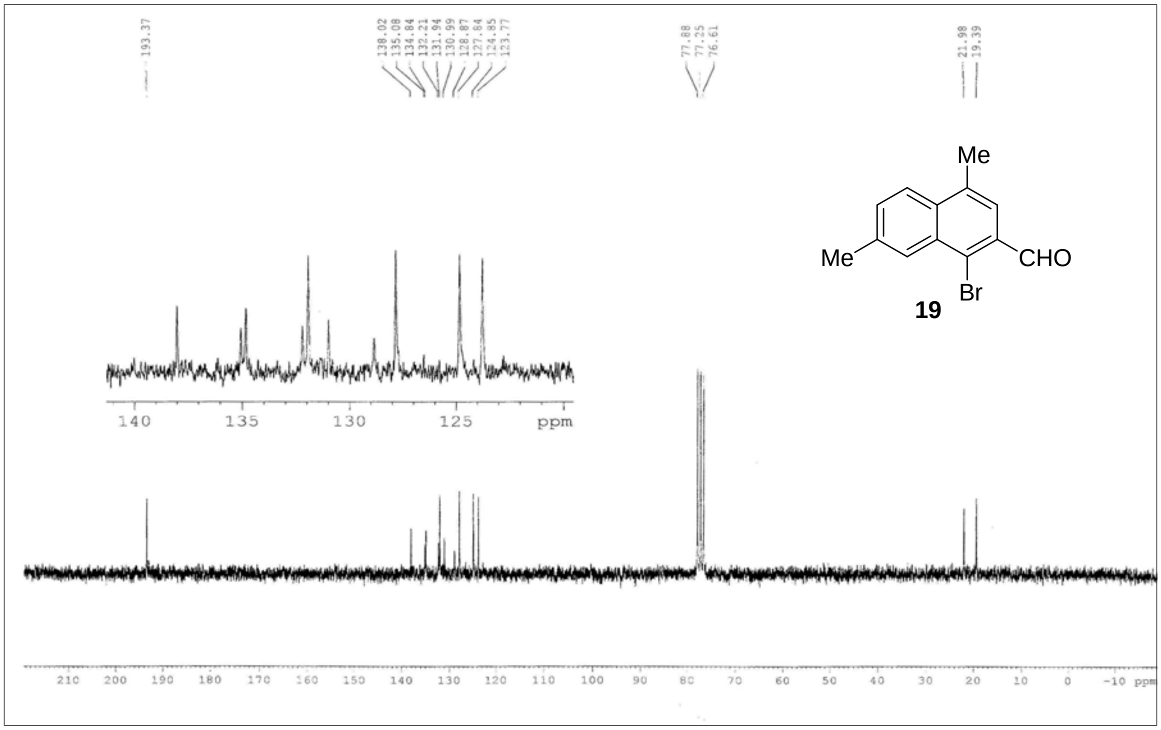
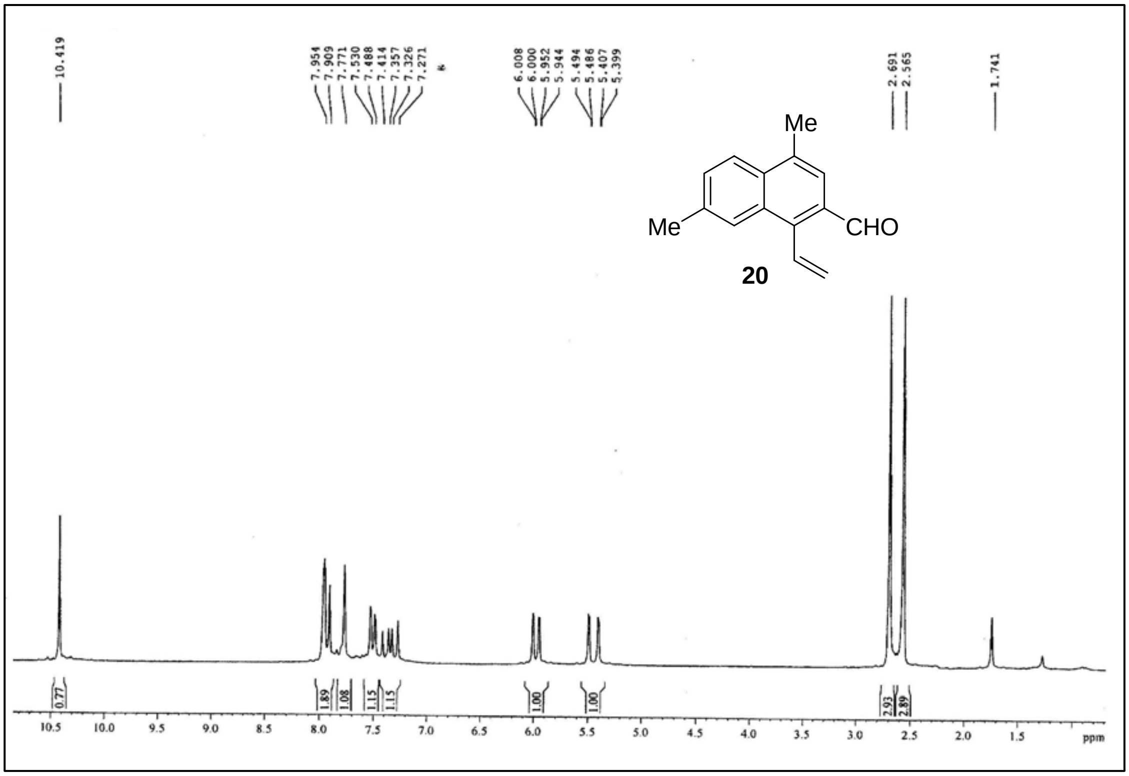


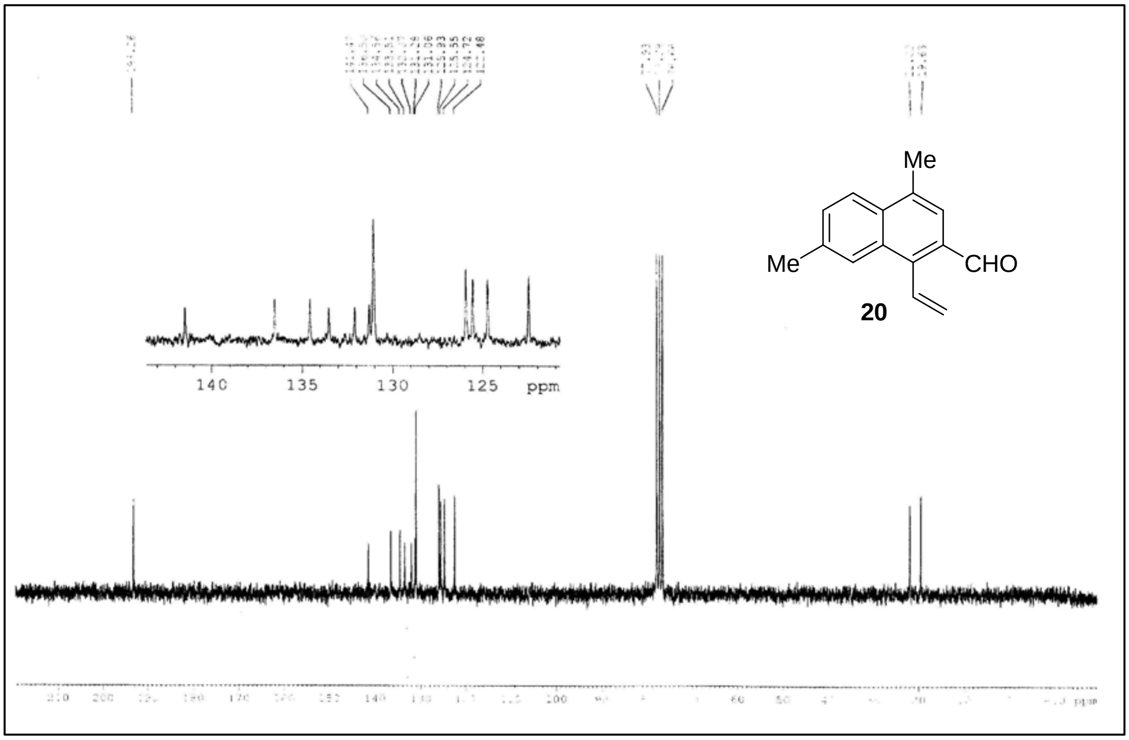
^{13}C NMR (50 MHz, $CDCl_3$)



^{1}H NMR (200 MHz, CDCl$_3$)



^{13}C NMR (50 MHz, $CDCl_3$)



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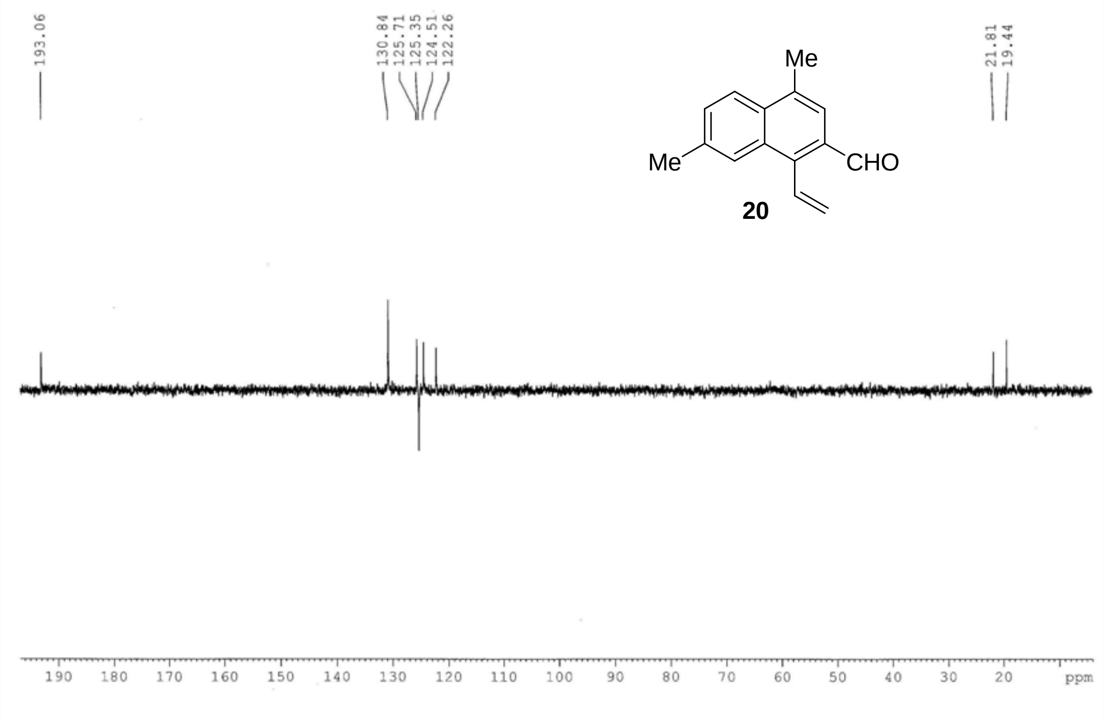
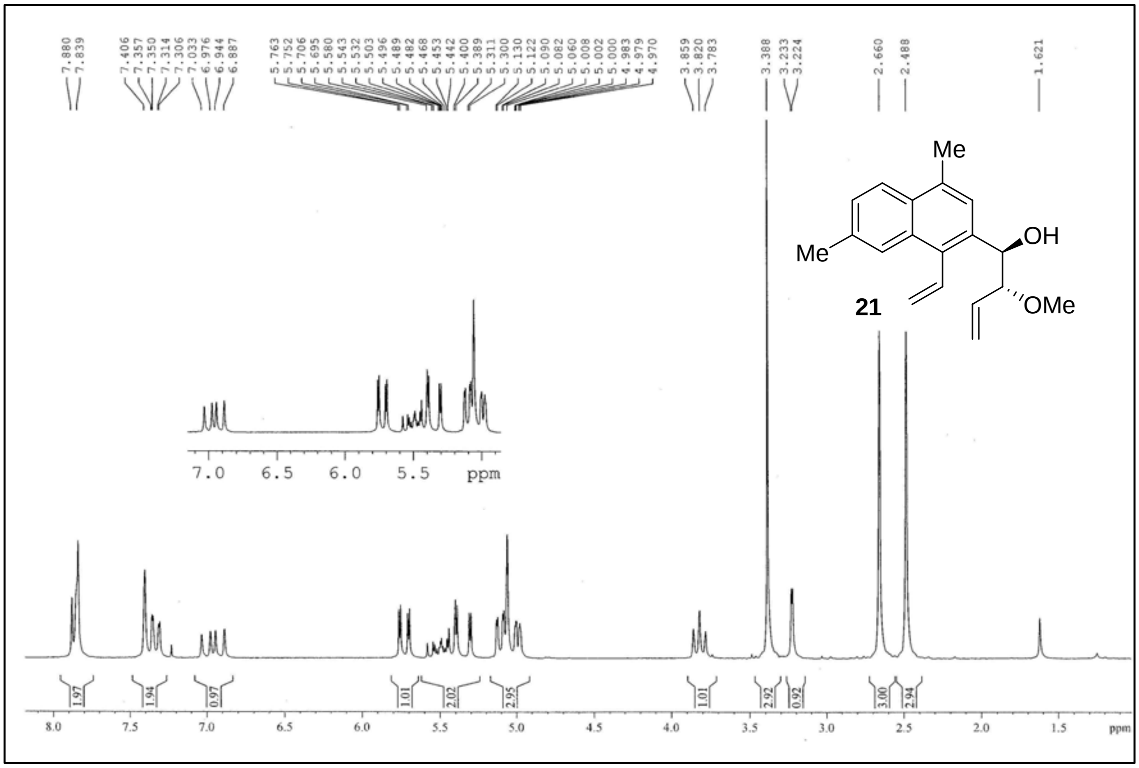
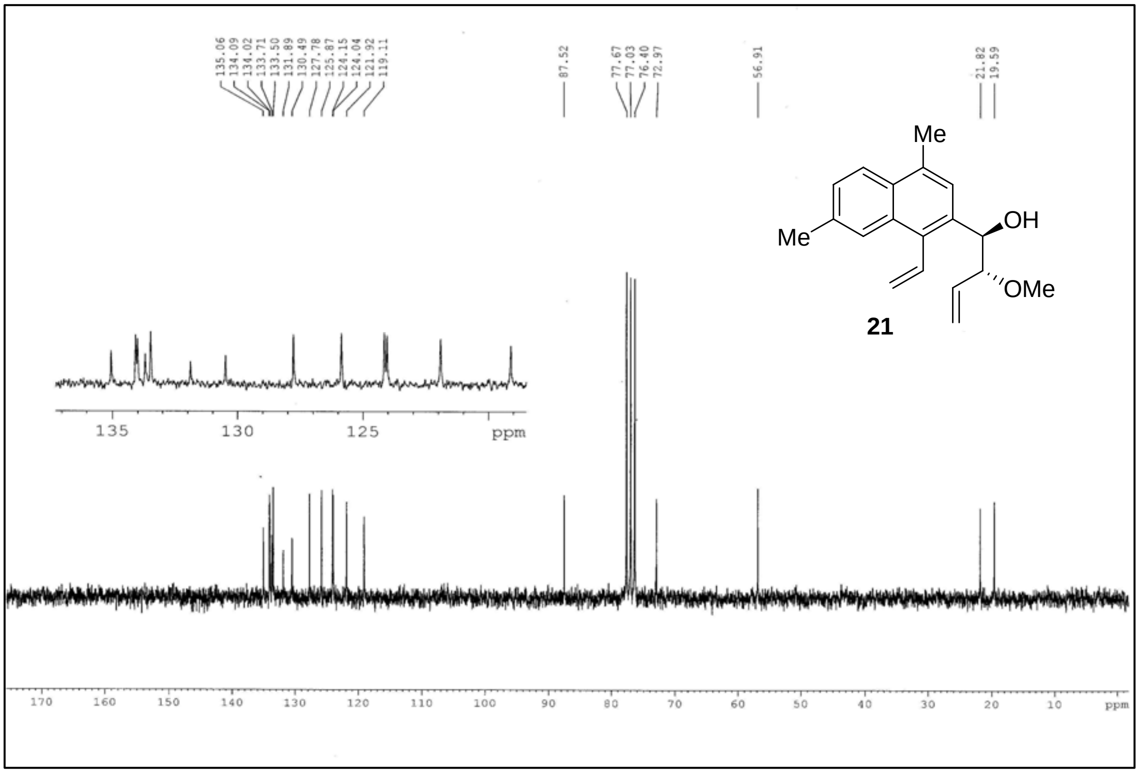


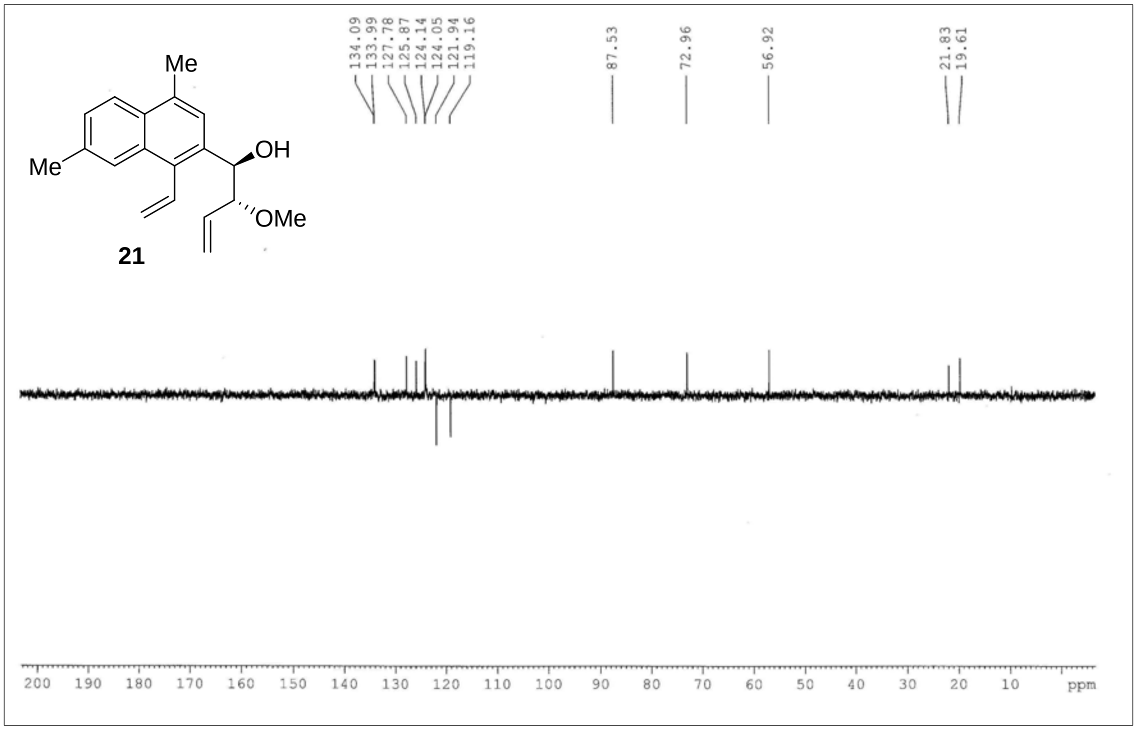
^{1}H NMR (200 MHz, $CDCl_3$)



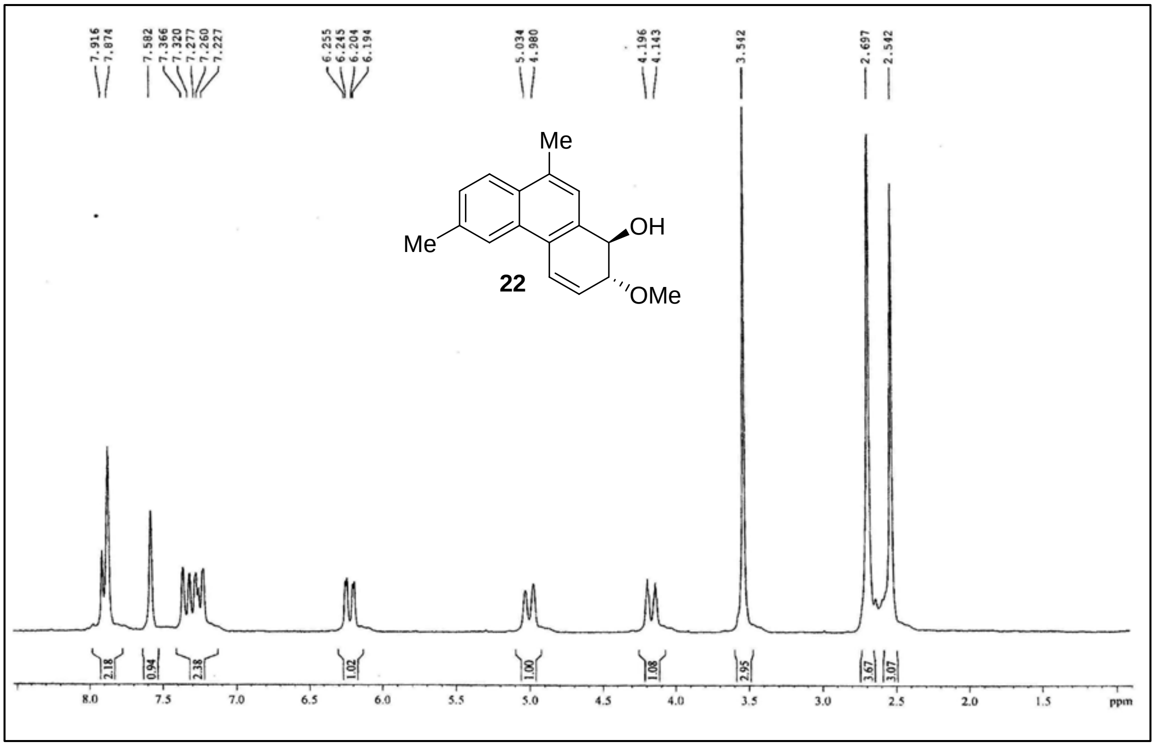
^{13}C NMR (50 MHz, $CDCl_3$)



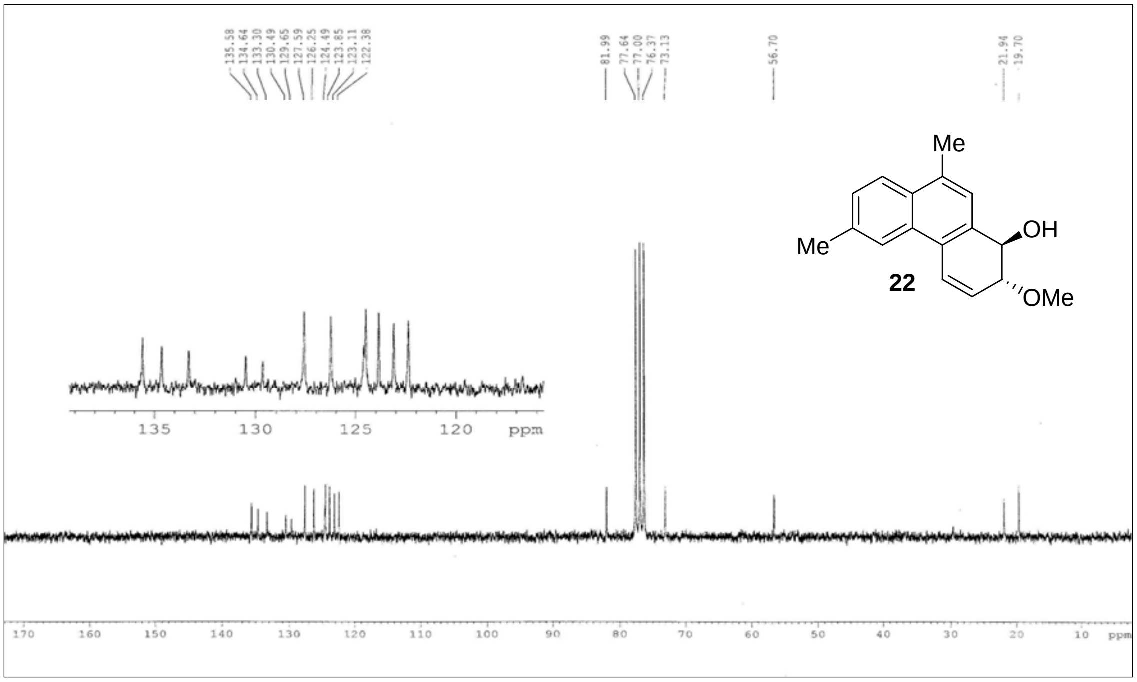
Dept-135 spectra



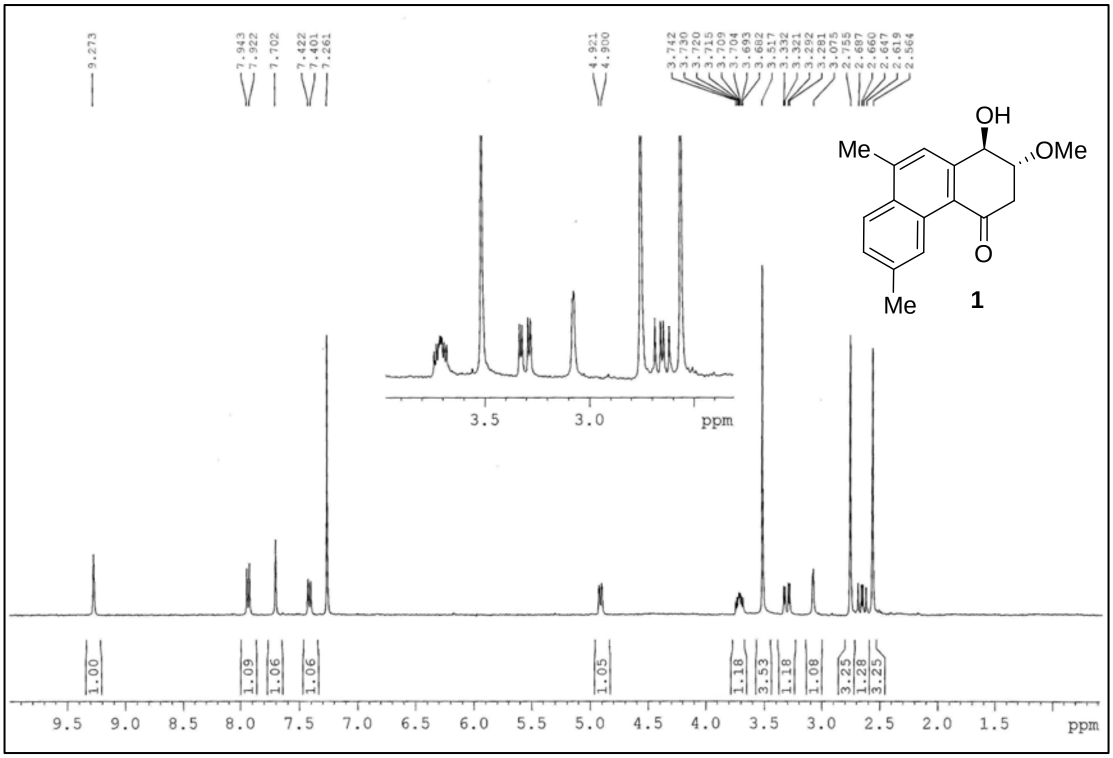
^{1}H NMR (200 MHz, CDCl$_3$)



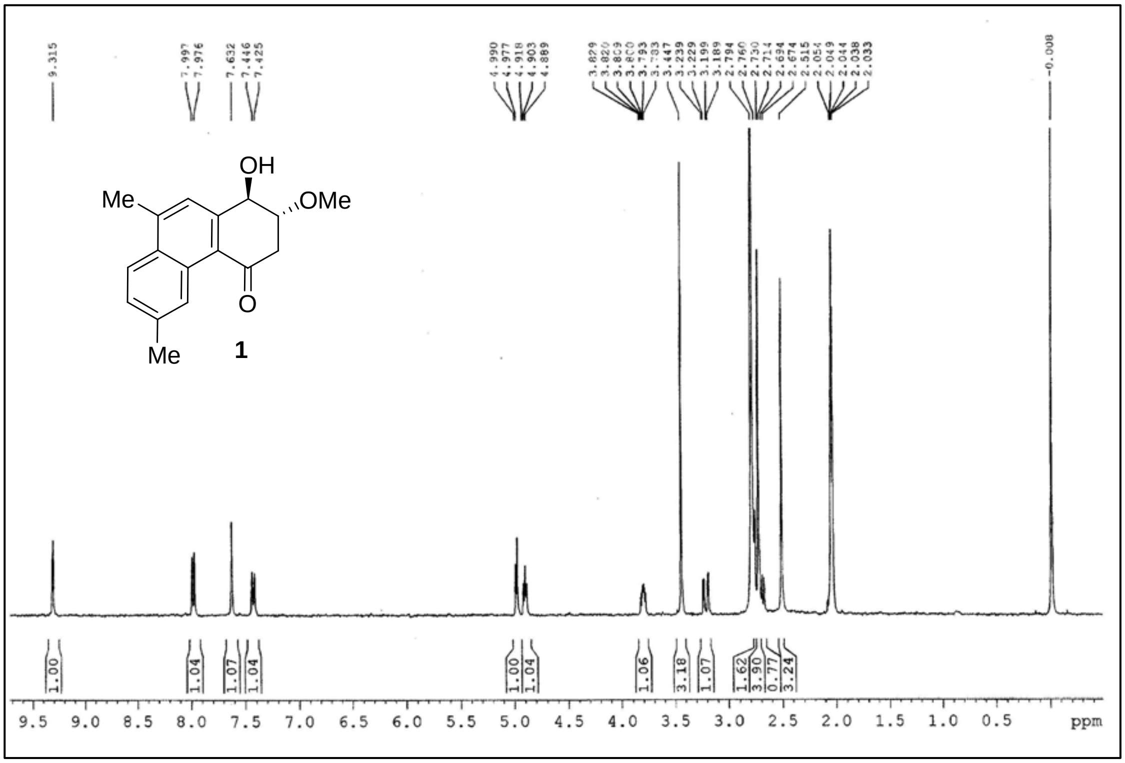
^{13}C NMR (50 MHz, CDCl$_3$)



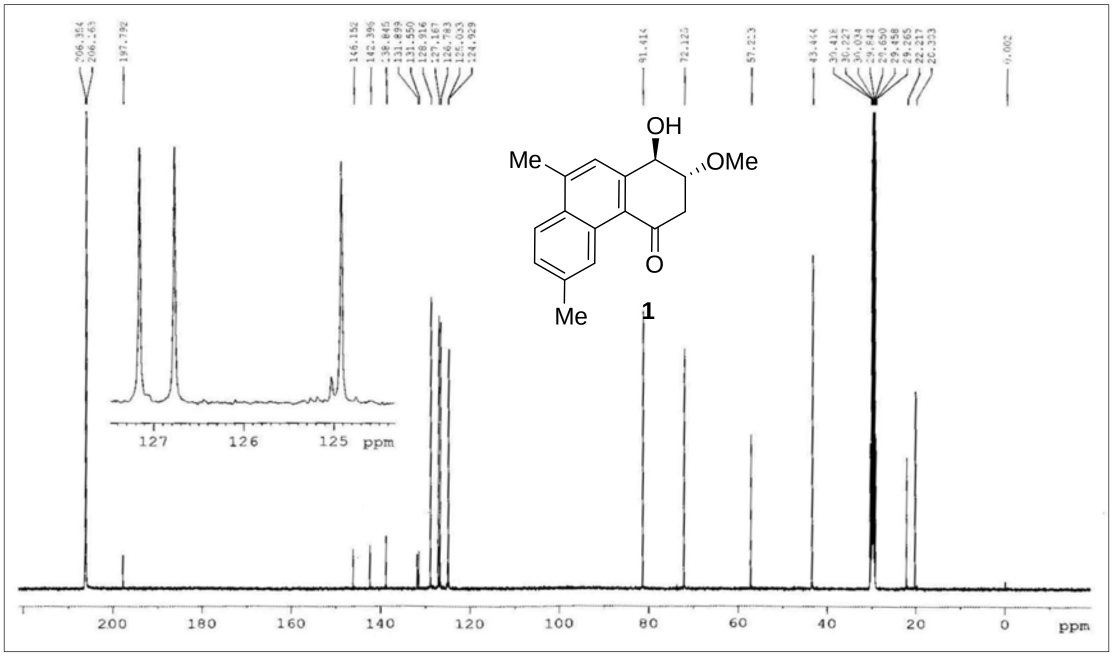
^{1}H NMR (400 MHz, CDCl$_3$)



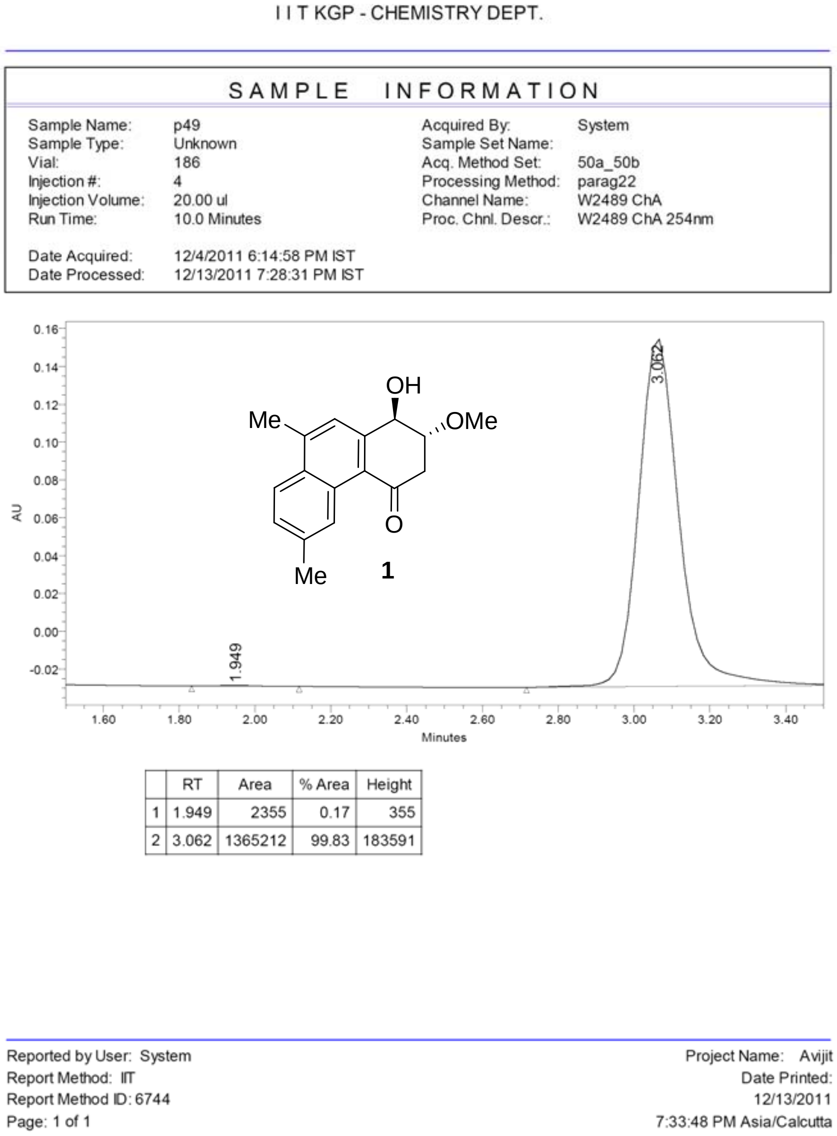
^{1}H NMR (400 MHz, Acetone-d$_6$)



^{13}C NMR (100 MHz, Acetone-d$_6$)



To further check the purity of synthesized heliophenanthrone HPLC was performed in an XTerra C_{18} column (4.6 mm × 250 mm, Waters) with a UV/Visible detector (model 2489, Waters). Development was done with a solvent system of MeOH and a flow rate of 1ml/min.



I I T KGP - CHEMISTRY DEPT.

SAMPLE INFORMATION

Sample Name: p49
Sample Type: Unknown
Vial: 186
Injection #: 4
Injection Volume: 20.00 ul
Run Time: 10.0 Minutes

Date Acquired: 12/4/2011 6:14:58 PM IST
Date Processed: 12/13/2011 7:28:31 PM IST

Acquired By: System
Sample Set Name:
Acq. Method Set: 50a_50b
Processing Method: parag22
Channel Name: W2489 ChA
Proc. Chnl. Descr.: W2489 ChA 254nm

	RT	Area	% Area	Height
1	1.949	2355	0.17	355
2	3.062	1365212	99.83	183591

Reported by User: System
Report Method: IIT
Report Method ID: 6744
Page: 1 of 1

Project Name: Avijit
Date Printed:
12/13/2011
7:33:48 PM Asia/Calcutta

Reference:

(1) H. Nemoto, J. Miyata, M. Joshida, N. Raku and K. Fukumoto, *J. Org. Chem.*, 1997, **62**, 7850.