MgI_2-Accelerated Enantioselective Morita–Baylis–Hillman Reactions of Cyclopentenone Utilizing a Chiral DMAP Catalyst

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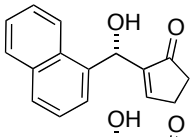
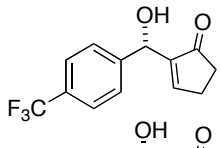
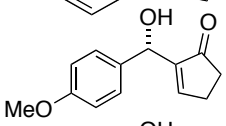
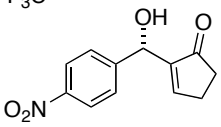
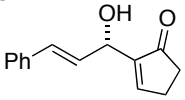
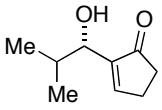
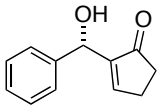
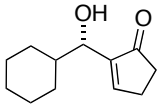
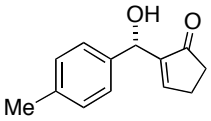
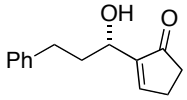
General Information

All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. All commercially obtained reagents were used as received. All aldehydes were distilled before use. Isopropanol was distilled from Na^0.

Heating was accomplished by either a heating mantle or silicone oil bath. Purification of reaction products was carried out by flash column chromatography using silica gel 60 (230-400 mesh). TLC visualization was accompanied with UV light and/or ceric ammonium molybdate staining. Concentration in vacuo refers to the removal of volatile solvent using a rotary evaporator attached to a dry diaphragm pump (10-15 mm Hg) followed by pumping to a constant weight with an oil pump (<300 mTorr).

^{1}H NMR spectra were recorded at 300 MHz, and are reported relative to $CDCl_3$ (δ 7.27). ^{1}H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Proton-decoupled ^{13}C NMR spectra were recorded at 75 MHz and reported relative to $CDCl_3$ (δ 77).

References to Known Compounds

Compound No.	Product	Reference (racemic)	Reference (nonracemic)	Compound No.	Product	Reference (racemic)	Reference (nonracemic)
1		–	–	**6**		2	–
2		1	–	**7**		1	8
3		2	6	**8**		4	7
4		3	7	**9**		5	7
5		1	–	**10**		5	7

[1] S. Luo, X. Mi, H. Xu, P. G. Wang, J. P. Cheng, *J. Org. Chem.* **2004**, *69*, 8413-8422.

[2] S. Luo, B. Zhang, J. He, A. Janczuk, J.-P. Cheng, *Tetrahedron Lett.* **2002**, *43*, 7369-7371.

[3] W. Pei, H.-X. Wei, G. Li, *Chem. Commun.* **2002**, 2412-2413.

[4] DE Patent 102004044250 A1, **2006**.

[5] H. Ito, Y. Takenaka, S. Fukunishi, K. Iguchi, *Synthesis* **2005**, *18*, 3035-3038.

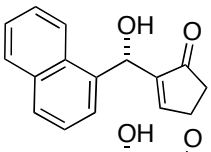
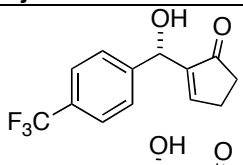
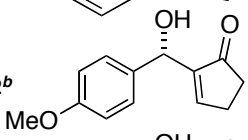
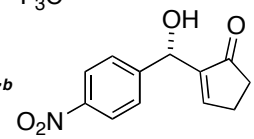
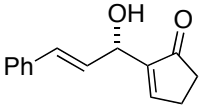
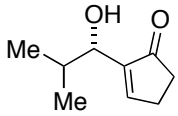
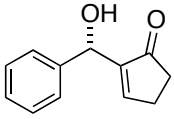
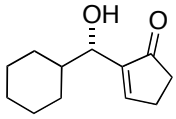
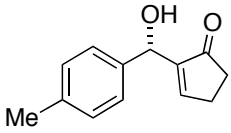
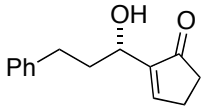
[6] N. T. MacDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman S. E. Schaus, *Adv. Synth. Catal.* **2004**, *346*, 1231-1240.

[7] K. Matsui, S. Takizawa, H. Sasai,. *Tetrahedron Lett.* **2005**, *46*, 1943-1946.

[8] M. Shi, X.-G. Liu, *Org. Lett.* **2008**, *10*, 1043–1046.

For data on all racemic adducts, also see: A. Bugarin, B. T. Connell, *J. Org. Chem.* **2009**, *74*, 4638-4641.

HPLC Data

Entry	Product	HPLC RT	% ee	$[\alpha]_D^{22}$ [d]	Entry	Product	HPLC RT	% ee	$[\alpha]_D^{22}$ [d]
1[a]		t_{major} = 30.60 min t_{minor} = 27.25 min	98	+66.1	**6**[c]		t_{major} = 17.61 min t_{minor} = 20.33 min	89	+17.3
2[b]		t_{major} = 22.23 min t_{minor} = 24.29 min	95	+26.7	**7**[b]		t_{major} = 21.45 min t_{minor} = 24.70 min	89	+38.5
3[a]		t_{major} = 23.67 min t_{minor} = 26.64 min	94	–22.7	**8**[c]		t_{major} = 8.79 min t_{minor} = 9.19 min	63	–25.4
4[b]		t_{major} = 12.39 min t_{minor} = 13.49 min	94	+18.2	**9**[c]		t_{major} = 7.94 min t_{minor} = 8.51 min	58	–21.7
5[c]		t_{major} = 24.68 min t_{minor} = 25.94 min	92	+15.8	**10**[b]		t_{major} = 10.47 min t_{minor} = 10.83 min	53	–18.9

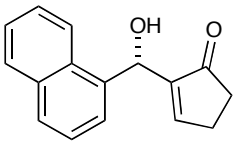
[a] Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 90/10), 1.0 mL/min, 254 nm.
[b] Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 85/15), 1.0 mL/min, 254 nm.
[c] Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 95/5), 1.0 mL/min, 254 nm.
[d] Optical rotation at (*c* 1.00, $CHCl_3$).

The absolute (*S*) configuration of products **3**, **4**, **7**, **8**, **9** and **10** was determined by comparison of the sign of optical rotation with the known compounds.[6-8] Other absolute configurations are assigned by analogy.

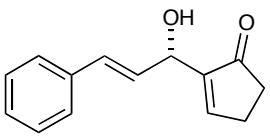
Procedures and Characterization Data

Compounds **2-10**, are known compounds. Compound **1** is a new compound. Full tabulated data is available below for adduct of the optimization reaction (compound **3)** and the new compound **1**.

General method for the asymmetric MBH reaction: To a stirred mixture of (*R*)-(+)-4-dimethylaminopyrindinyl(pentaphenylcyclo-pentadienyl)iron (**II**) (5 mg, 0.0075 mmol, 10 mol%), MgI_2 (10 mg, 0.038 mmol, 50 mol%) in *i*-PrOH (1.5 mL) was added the aldehyde (0.075 mmol) at room temperature under argon. Then the reaction mixture was cooled down to –20 ºC followed by the addition of cyclopent-2-enone (9 mg, 0.11 mmol, 1.5 equiv). After, the mixture was stirred for 24 h at –20 ºC under argon atmosphere. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (1.0 mL). The solution mixture was extracted twice with CH_2Cl_2 (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography (20% EtOH/hexanes or CH_2Cl_2).



***(S)*-2-(hydroxy(naphthalen-1-yl)methyl)cyclopent-2-enone (1):** To a stirred mixture of (*R*)-(+)-4-dimethylaminopyrindinyl(pentaphenylcyclopentadienyl) iron (**II**) (5 mg, 0.008 mmol), MgI_2 (10.4 mg, 0.038 mmol) in *i*-PrOH (1.5 mL) was added 1-naphthaldehyde (12 mg, 0.075 mmol) at room temperature under an argon atmosphere. Then the reaction mixture was cooled down to –20 ºC followed by the addition of cyclopent-2-enone (9 mg, 0.11 mmol, 1.5 equiv). After, the mixture was stirred for 24 h at –20 ºC under argon atmosphere. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The mixture was extracted twice with CH_2Cl_2 (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography to give compound **1** (14 mg, 94%) as a colorless oil (CH_2Cl_2); IR (thin film) ν 3403, 3028, 2920, 1695, 1611, 960 cm^1; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93-7.88 (m, 2H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.70-7.46 (m, 3H), 7.02 (m, 1H), 6.30 (s, 1H), 3.79 (s, 1OH), 2.50 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 161.1, 147.2, 136.6, 133.8, 130.4, 128.8, 128.4, 126.1, 125.6, 125.5, 124.4, 123.7, 66.5, 35.2, 26.6. HRMS (ESI) calcd for $C_{16}H_{14}O_2$ + Li requires *m/z* 245.040, found 245.041. $[\alpha]^{22}_D$ = +66.09 (*c* 1.0, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/*i*PrOH = 90/10), 1.0 mL/min, 254 nm, t_{major}= 30.60 min, t_{minor}= 27.25 min; 98% *ee*.

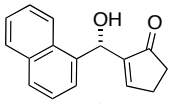


***(S,E)*-2-(1-hydroxy-3-phenylallyl)cyclopent-2-enone (3):** To a stirred mixture of (*R*)-(+)-4-dimethylaminopyrindinyl(pentaphenylcyclopentadienyl) iron (**II**) (5 mg, 0.0075 mmol, 10 mol%), MgI_2 (10 mg, 0.038 mmol, 50 mol%) in *i*-PrOH (1.5 mL) was added *trans*-cinnamaldehyde (10 mg, 0.075 mmol) at room temperature under an argon atmosphere. Then the reaction mixture was cooled down to –20 ºC followed by the addition of cyclopent-2-enone (9 mg, 0.11 mmol, 1.5 equiv). After, the mixture was stirred for 24 h at –20 ºC under an argon atmosphere. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL). The solution mixture was extracted twice with CH_2Cl_2 (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was

purified by flash silica gel column chromatography to give compound **3** (16 mg, 96%) as a colorless oil (CH_2Cl_2); IR (thin film) ν 3400, 3026, 2921, 1691, 1605, 970 cm^1; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (td, *J* = 1.1 Hz, 1.4 Hz, 3.1 Hz, 1H), 7.41 (m, 2H), 7.27-7.17 (m, 3H), 6.70 (dd, *J* = 1.1 Hz, 14.8 Hz, 1H), 6.35 (dd, *J* = 6.5Hz, 9.8 Hz, 1H), 5.17 (d, *J* = 6.7 Hz, 1H), 3.31 (d, *J* = 4.1 Hz, 1OH), 2.65 (m, 2H), 2.49 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 158.8, 146.3, 136.3, 131.1, 128.6, 128.5, 127.8, 126.5, 68.4, 35.1, 26.7. HRMS (ESI) calcd for $C_{14}H_{14}O_2$ + Li requires *m/z* 221.115, found 221.114. $[\alpha]^{22}_D$ = -22.66 (*c* 1.0, $CHCl_3$). Enantiomeric excess was deter mined by HPLC with a Chiralcel OJ-H column (hexane/*i*-PrOH = 90/10), 1.0 mL/min, 254 nm, t_{major}= 23.67 min, t_{minor}= 26.64 min; 94% *ee*.

^{1}H and ^{13}C NMR Spectra

^{1}H NMR ($CDCl_3$, 300 MHz)



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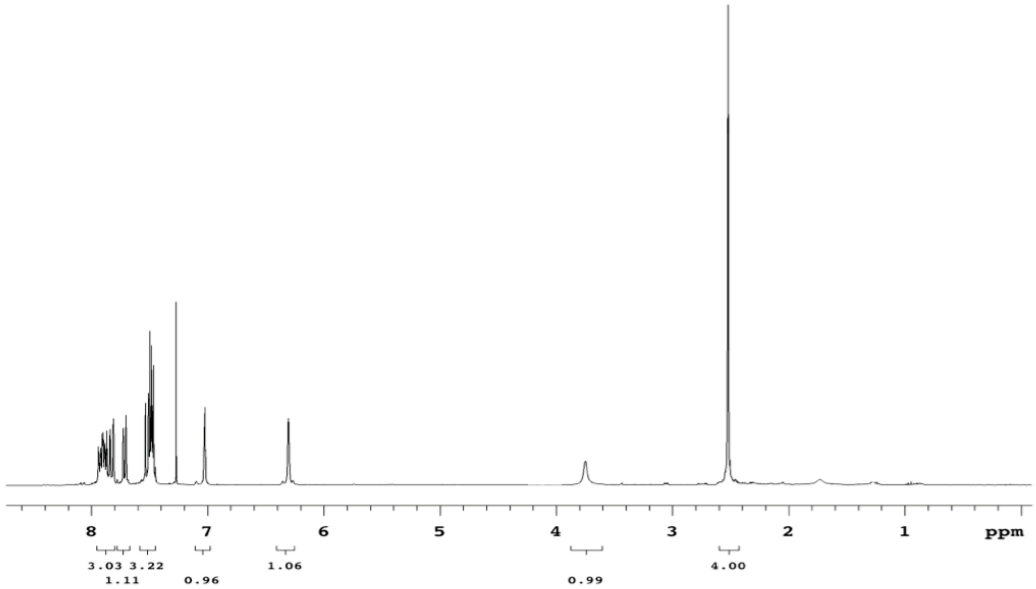
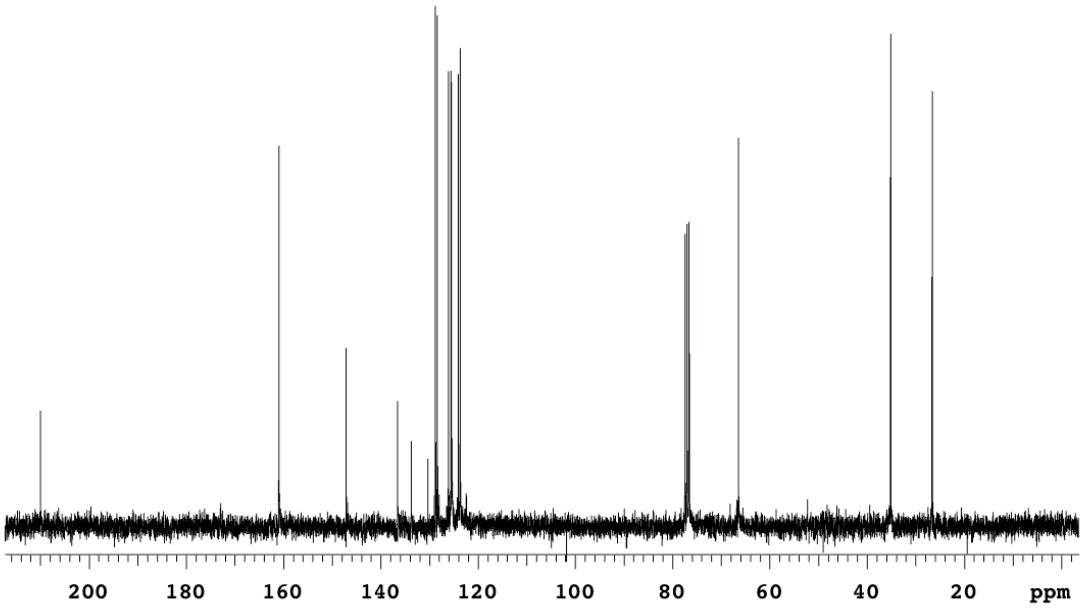
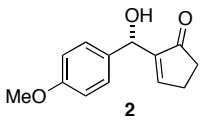


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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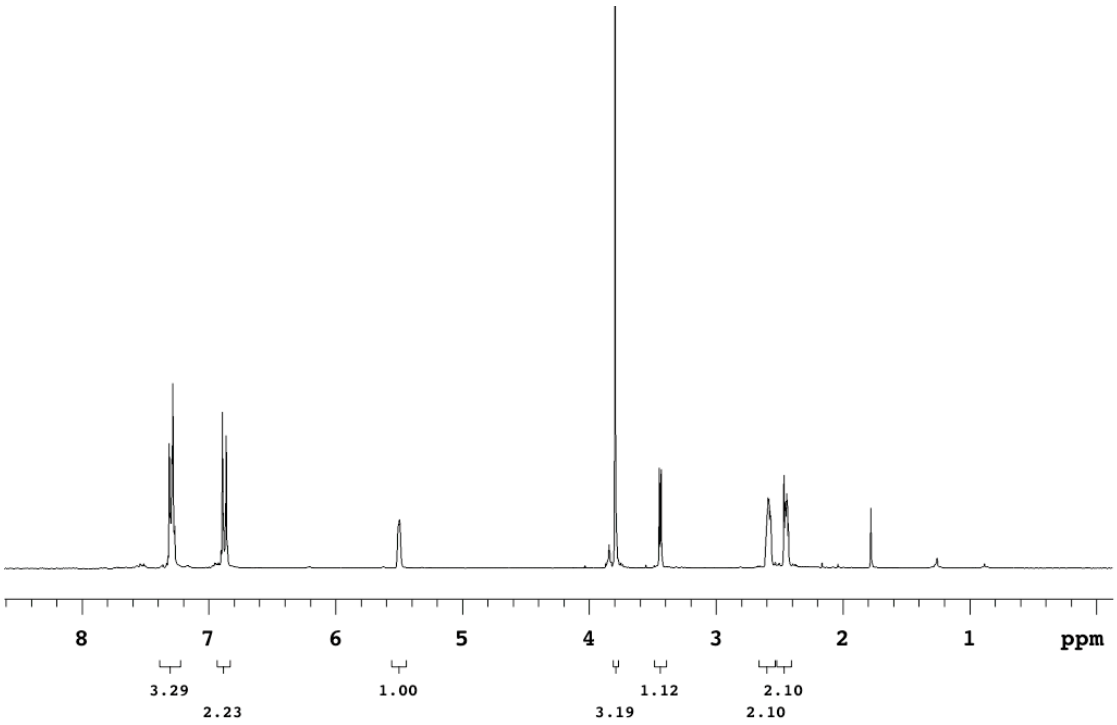
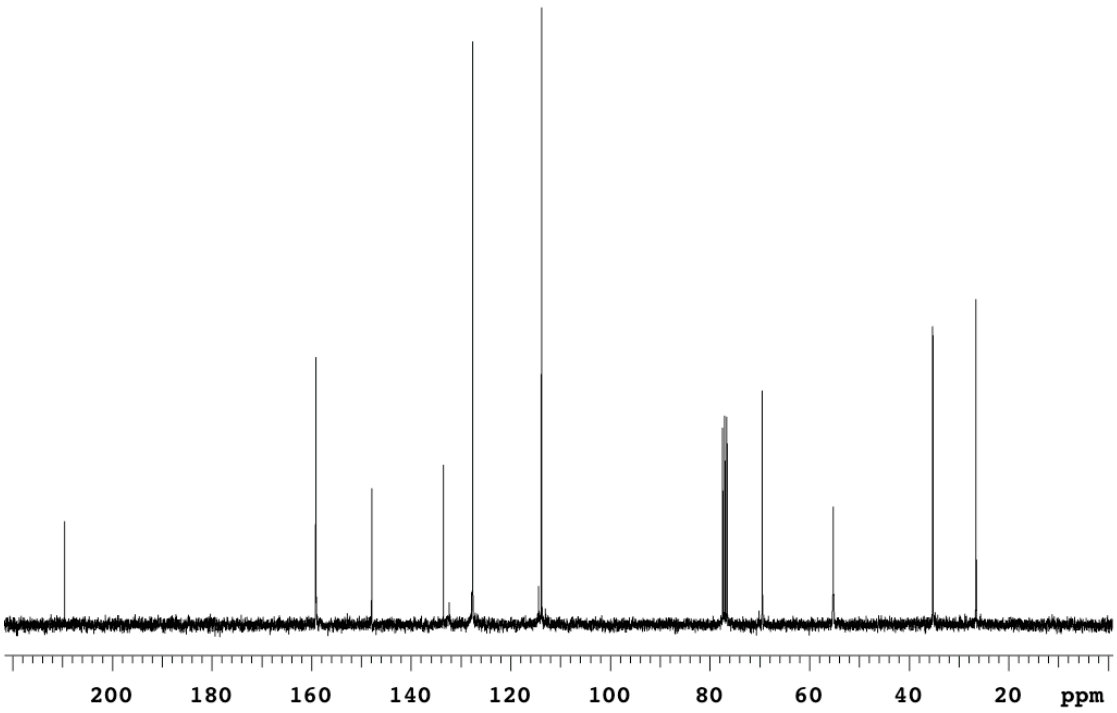
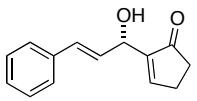


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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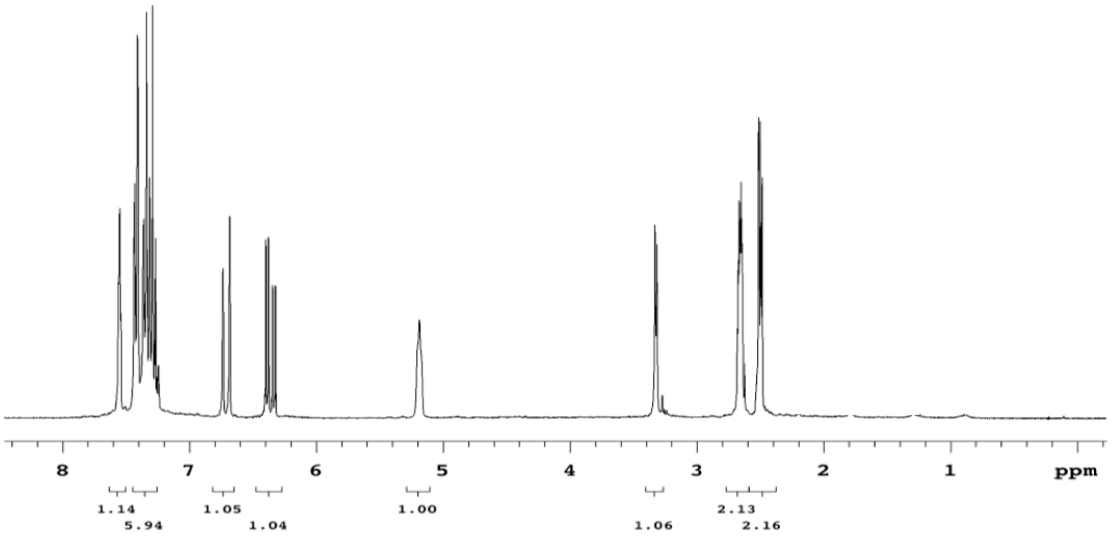
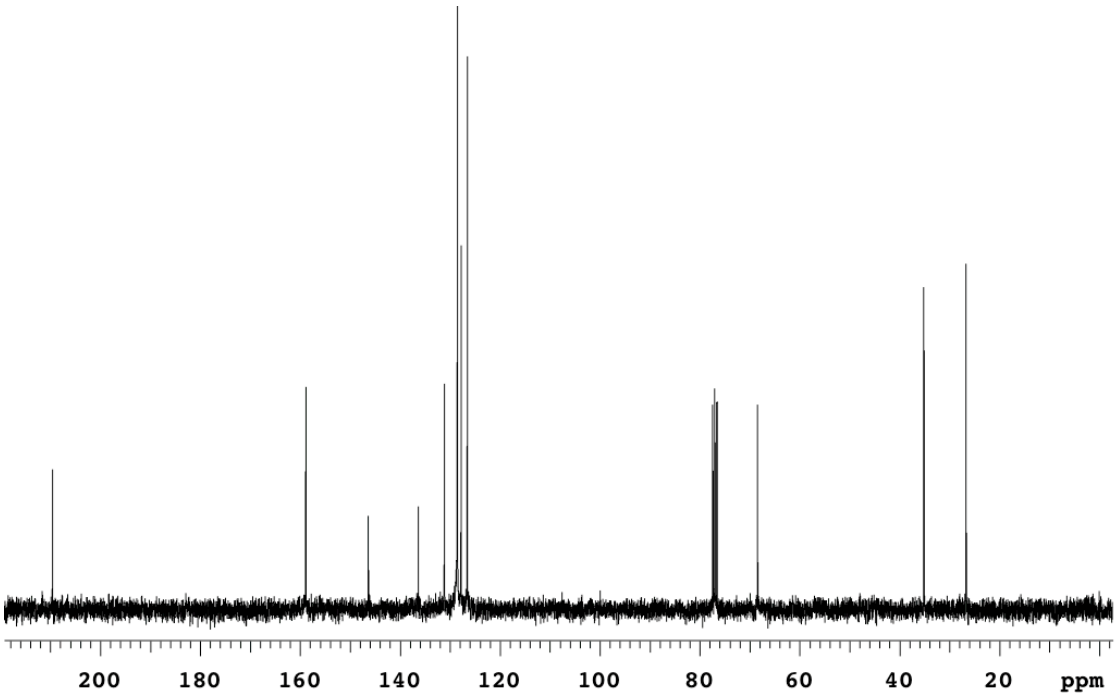
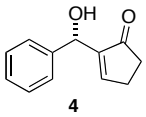


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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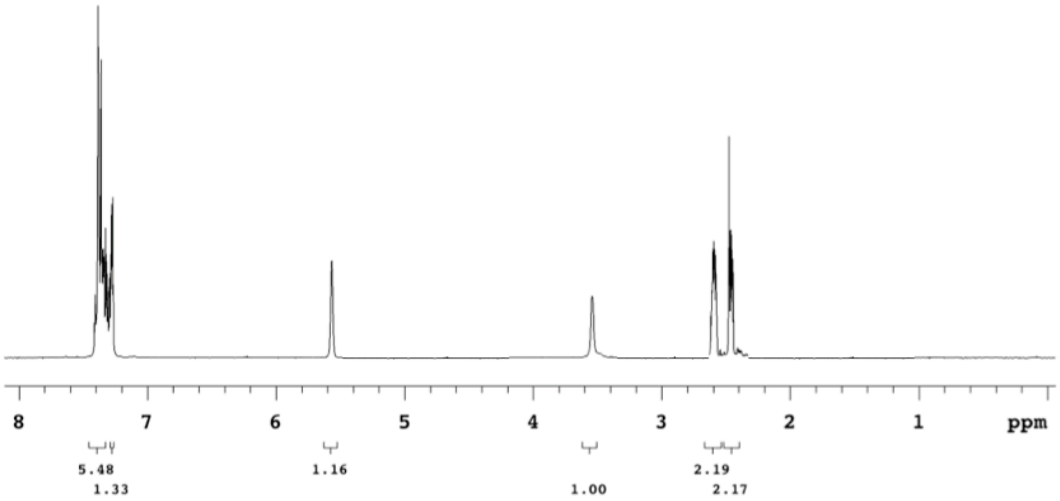
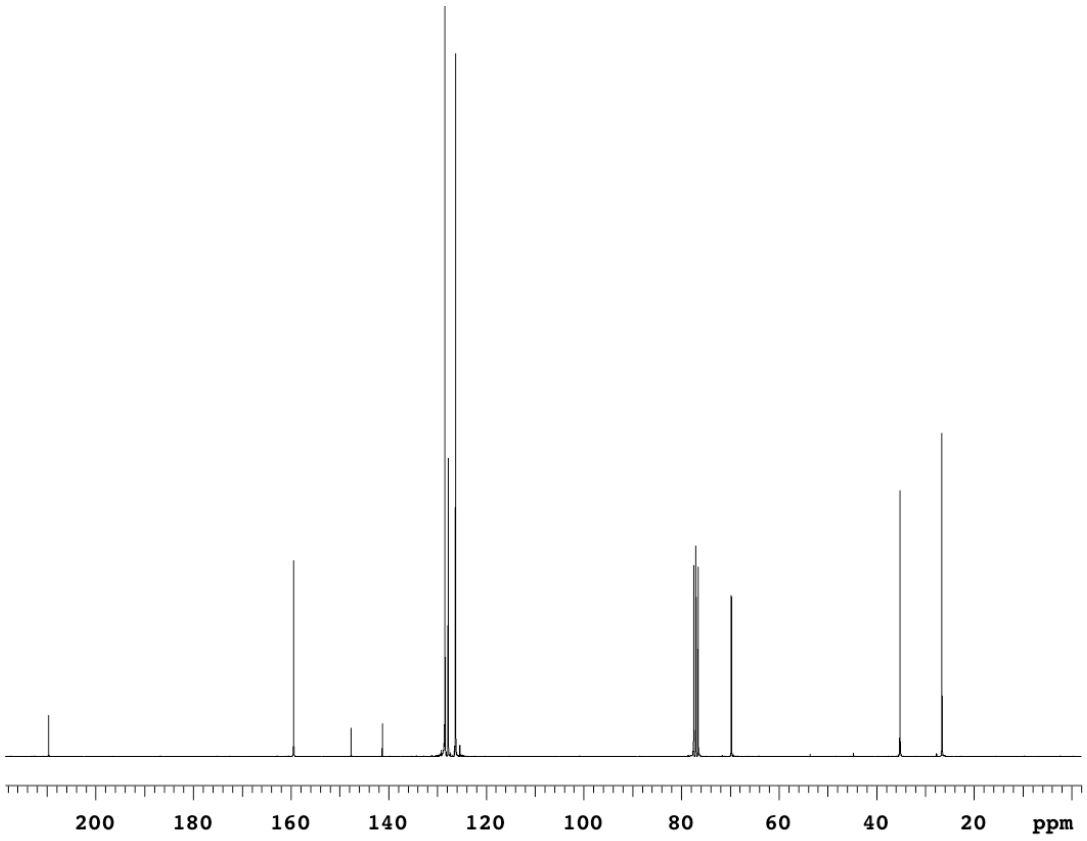
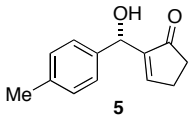


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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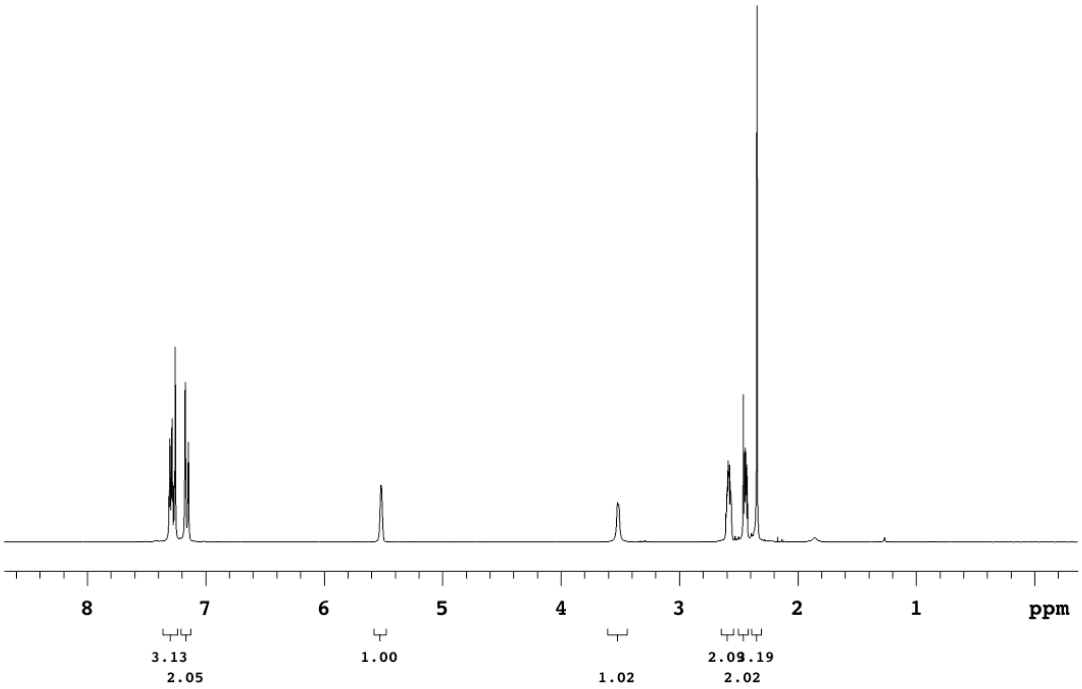
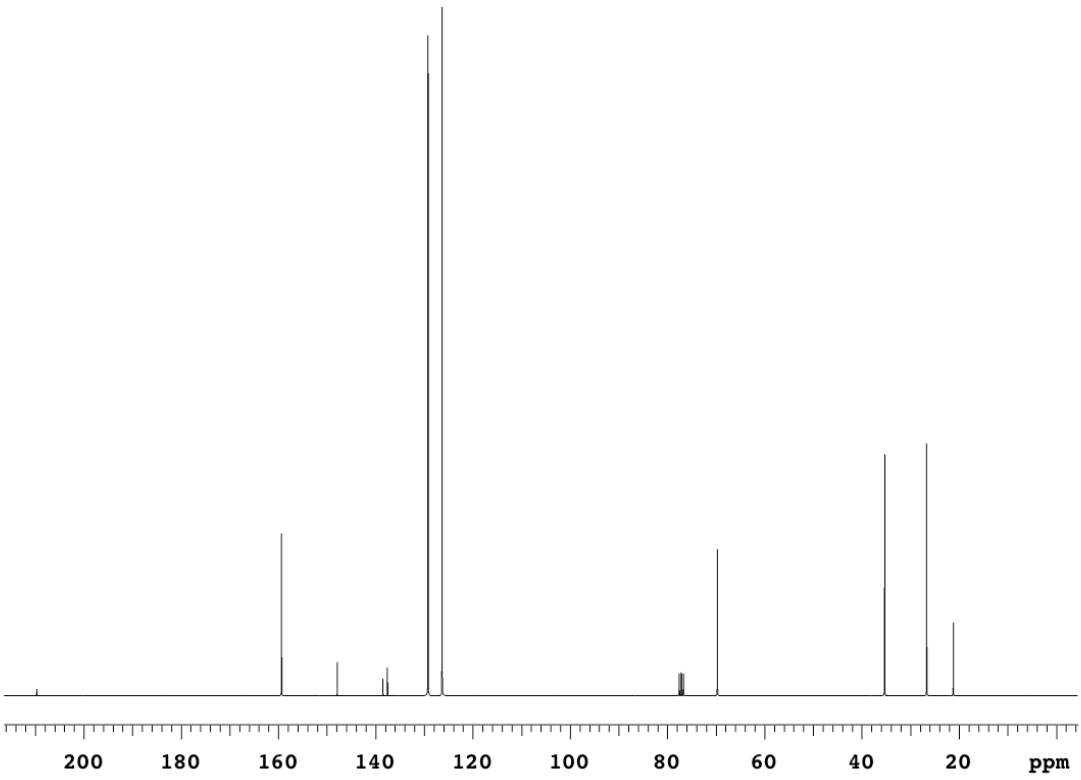
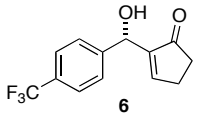


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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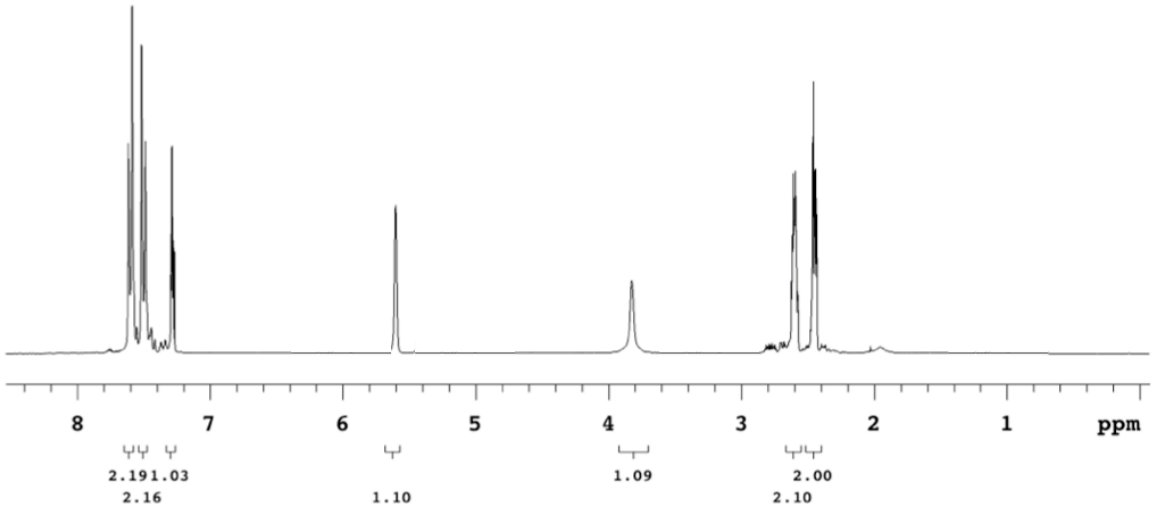
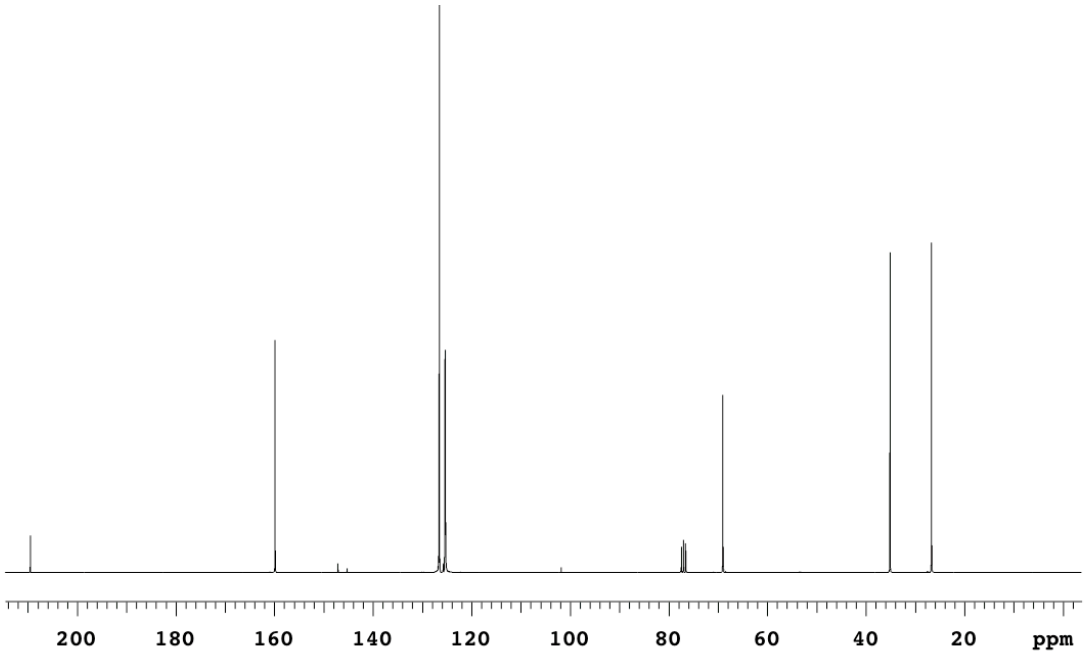
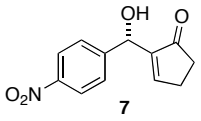


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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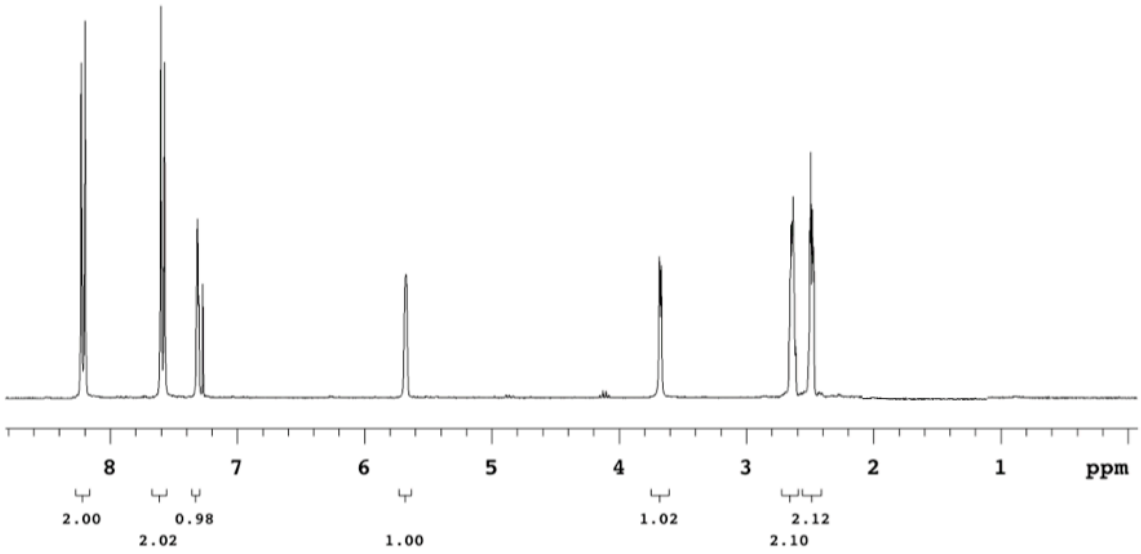
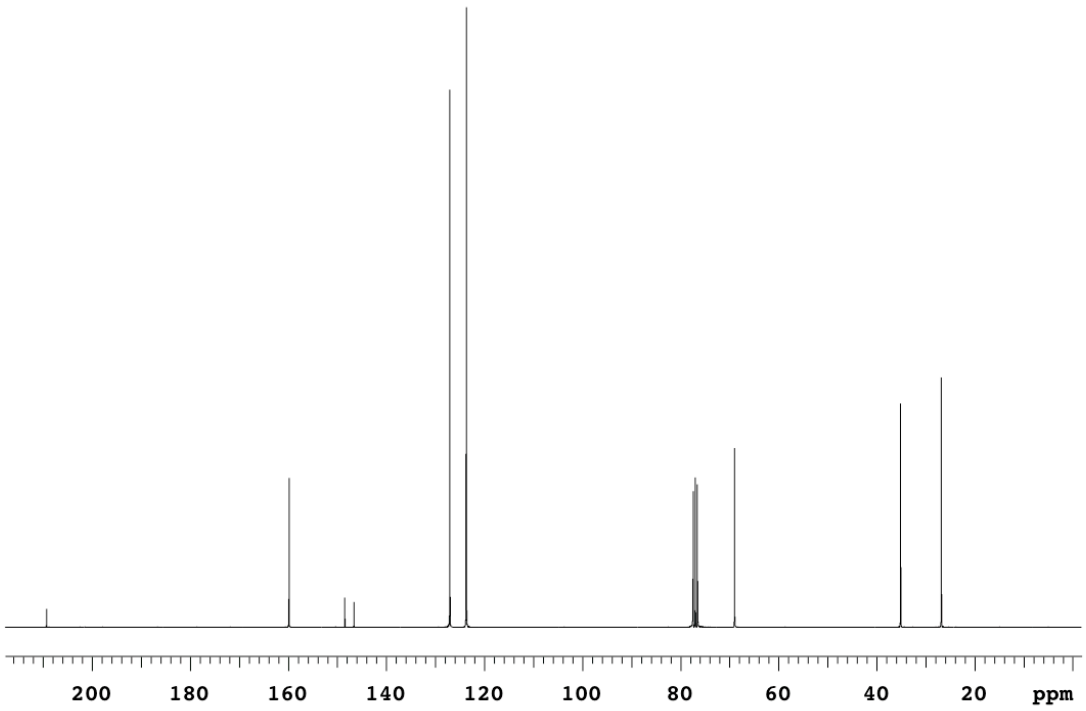
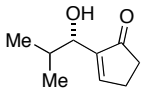


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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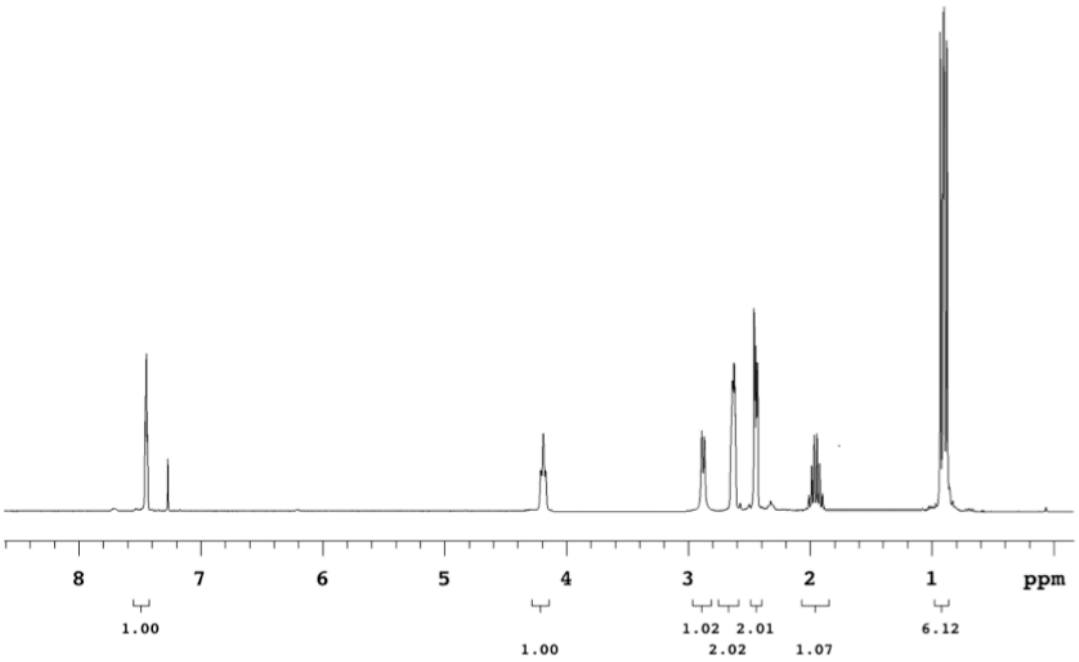
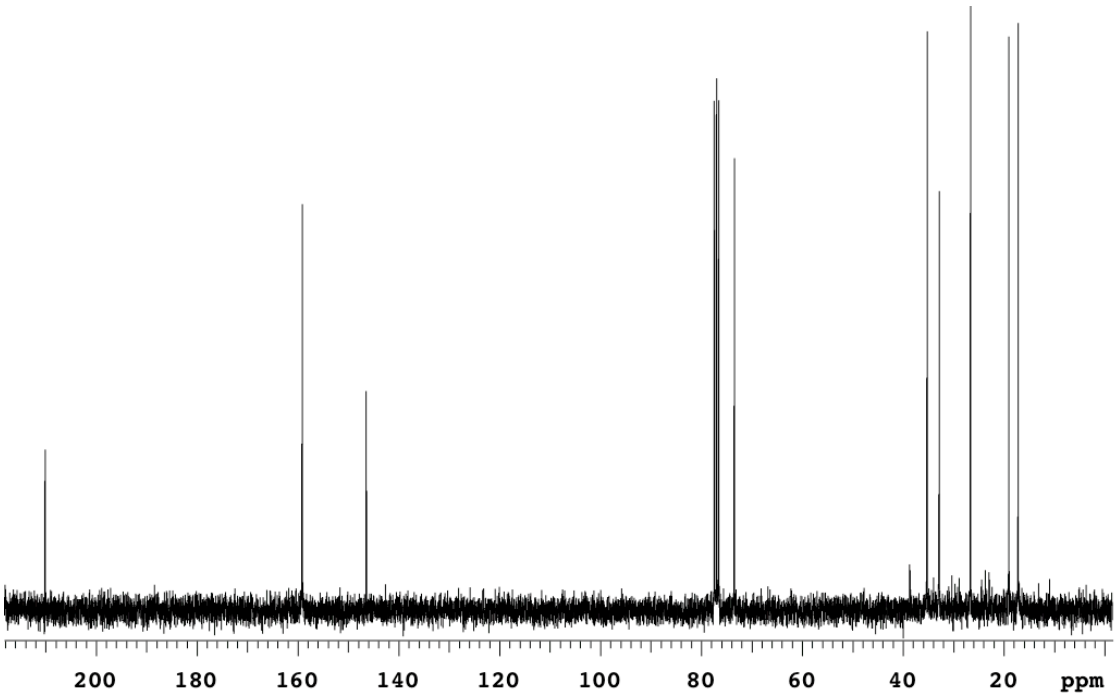
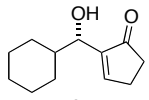


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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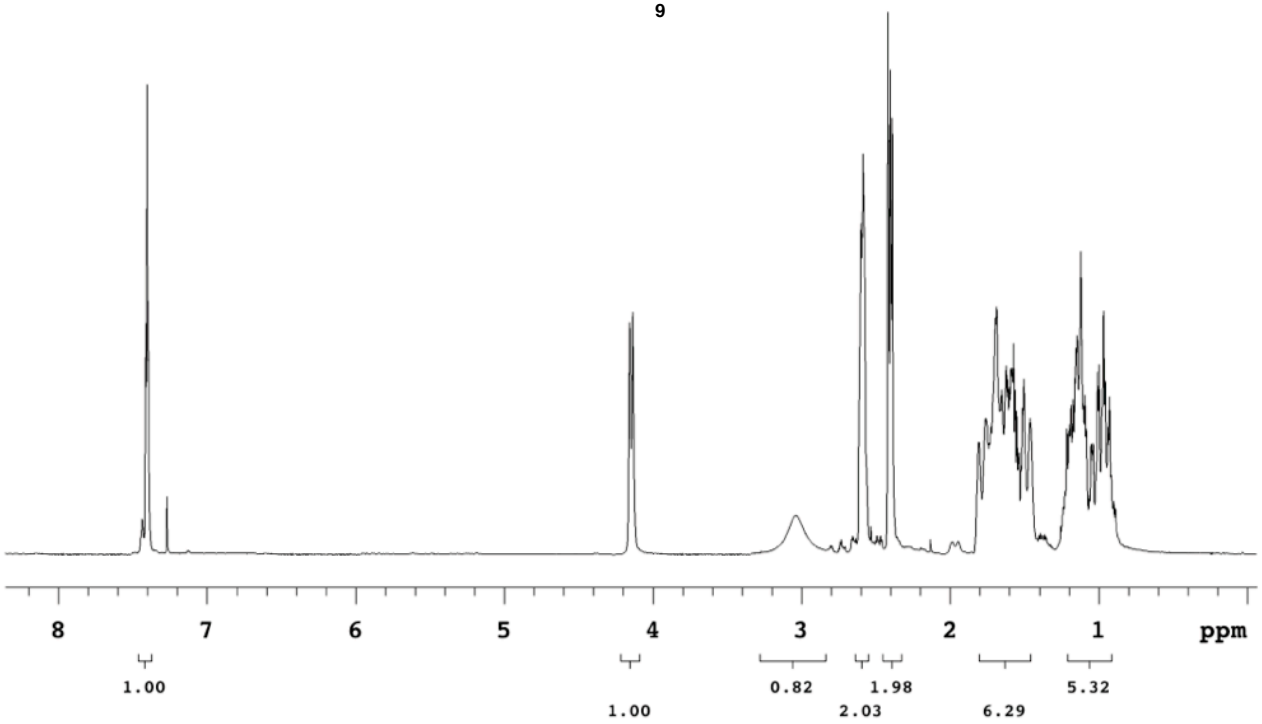
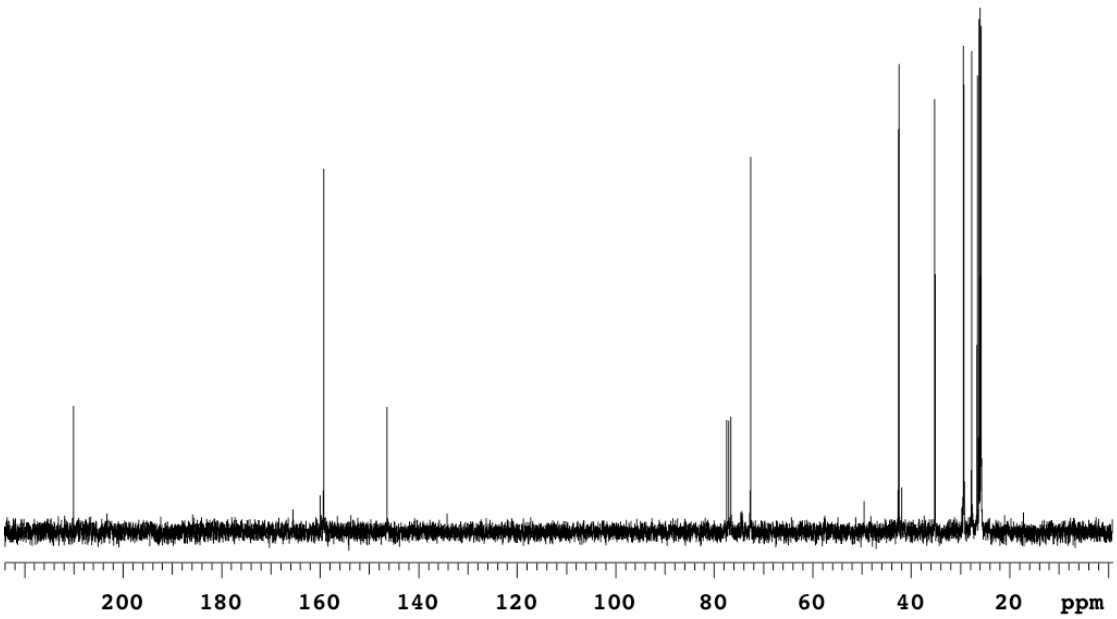
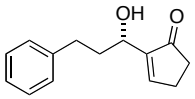


^{13}C NMR ($CDCl_3$, 75 MHz)



^{1}H NMR ($CDCl_3$, 300 MHz)



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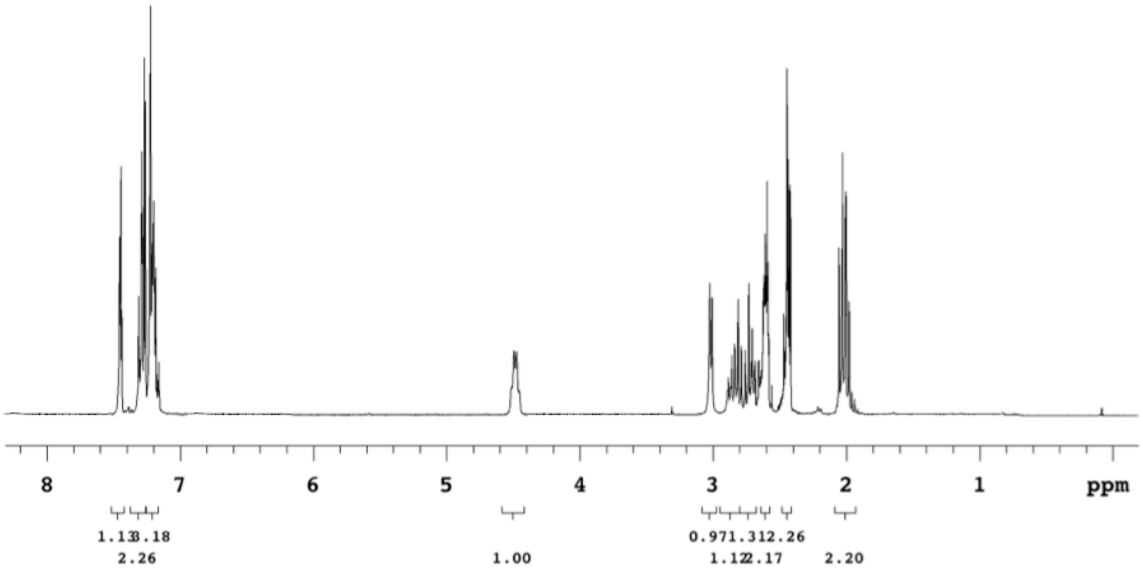

^{13}C NMR ($CDCl_3$, 75 MHz)