Brønsted acid catalyzed aldol reaction : A complementary approach to enamine catalysis.

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Supporting Information

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General remarks

Commercially available compounds were used without further purification. Solvents (THF, CH_2Cl_2, MeCN, Et_2O, DMF, toluene) were dried and purified from Pure-Solv^{TM} 400 Solvent Purification System.

Melting points were determined on a Electrothermal digital apparatus IA9100 series and are uncorrected.

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance DPX 500 or Bruker Avance DPX 400 spectrometers. Chemical shifts are reported in parts per million (δ) relative to TMS or to solvent as the internal standard.

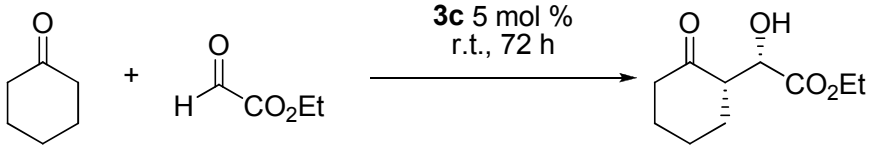
Thin layer chromatography was performed on silica gel 60 F-254 plates (0.1 mm, Merck). Detection was accomplished by irradiation with a UV lamp or staining with $KMnO_4$. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm, Merck).

Analytical high performance liquid chromatography (HPLC) was carried out with a Waters instrument [detector M996 (200–400 nm) and pump 600]. The conditions are described for each compound.

Mass spectra and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. IR spectra were recorded on a Perkin–Elmer 16 PC FTIR spectrometer. Optical rotations were measured, at room temperature, on a Perkin–Elmer 241 LC polarimeter in a 10 cm cell. $[\alpha]_D$ Values are given in units of 10^{-1} deg.cm^{-2}.g^{-1}.

Various non protic solvents was assayed in aldol reaction using **3c** (Ar = 2,4,6-*i*Pr-C_6H_2) as catalyst at room temperature during 72 hours (Table 1).

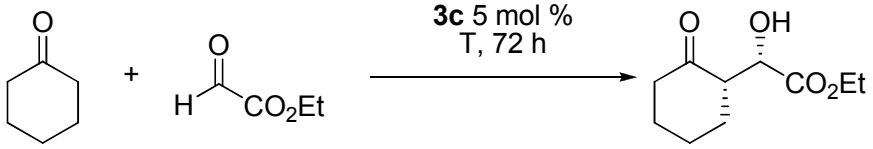
Table 1. Optimization of the solvent



Entry	solvent	yield[a]	*syn* : *anti* [b]	ee *syn*[c]
1	toluene	78	80/20	69
2	xylene	78	70/30	67
3	THF	35	80/20	43
4	Et_2O	50	70/30	63
5	Bu_2O	33	66/33	65
6	CH_2Cl_2	90	70/30	60
7	CH_3CN	55	70/30	54

[a] isolated yield [b] Determined from NMR of crude mixture. [c] determined by chiral HPLC

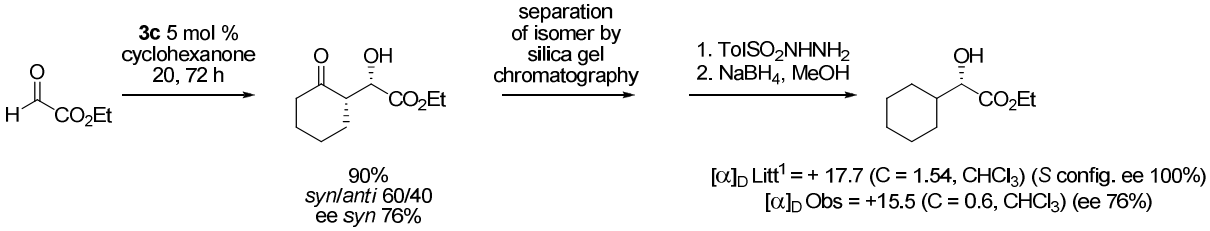
Table 2. Optimization of the ketone/glyoxylate ratio



Entry	cyclohexanone/glyoxylate	T (°C)	yield[a]	*syn* : *anti* [b]	ee *syn*[c]
1	10/1	20	90	60/40	76
2	10/1	0	55	70/30	86
3	1/5	20	75	55/45	72
4	1/1	20	80	55/45	84
5	1/1	0	50	55/45	81
6	2/1	0	50	55/45	84
7	2/1	0	53	60/40	81

[a] isolated yield [b] Determined from NMR of crude mixture. [c] determined by chiral HPLC

Scheme 1. Determination of the absolute configuration of the major isomer[11]



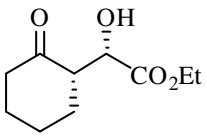
[1] Aggarwal, V. K.; Thomas, A.; Schade, S. *Tetrahedron*, **1997**, *53*, 16213-16228.

General procedure for the cross aldolisation reaction (entry 14, table 1)

A test tube was charged with acid catalyst **4e** (5.9 mg, 0.01 mmol, 5 mol %), ethyl glyoxalate (50% in toluene) (41 mg, 0.2 mmol) and cyclohexanone (196 mg, 2 mmol, 10 equiv) at 0 °C and stirred for 72 h. The volatiles were evaporated and the crude material purified by flash chromatography (cyclohexane/EtOAc, 70/30) to afford **5a** as colourless oil (22 mg, 55%, ratio *syn:anti* : 70:30).

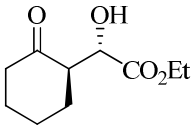
Ethyl 2-hydroxy-2-(2-oxocyclohexyl)acetate 5a :

Major isomer *syn*-5a



Colourless oil (**Rf** = 0.2 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) ***syn*** δ (ppm) : 4.61 (d, *J* = 1.6 Hz, 1H, CHOH), 4.19 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 2.91 (s, 1H, OH), 2.78-2.70 (m, 1H, CHCHOH), 2.44-2.38 (m, 1H), 2.34-2.20 (m, 1H), 2.06-1.97 (m, 1H), 1.92-1.78 (m, 3H), 1.65-1.53 (m, 2H), 1.23 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 210.4 (C), 173.6 (C), 69.2 (CH), 61.8 (CH_2), 53.8 (CH), 41.9 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 24.6 (CH_2), 14.2 (CH_3). **IR** (neat, cm^{-1}): 3482, 2939, 2868, 1731, 1705, 1449, 1368, 1205, 1127, 1023. **HRMS** calcd for $(M+H)^+$ $C_{10}H_{17}O_4$: 211.1127 found: 211.1128.

Minor isomer *anti*-5a

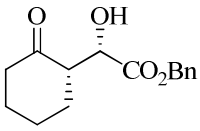


^{1}H NMR (400 MHz, $CDCl_3$) ***anti*** δ (ppm) : 4.18 (qd, *J* = 7.0 and 2 Hz, 2H, OCH_2CH_3), 3.95 (d, *J* = 3.2 Hz, 1H, CHOH), 3.08 (s, 1H, OH), 2.92-2.85 (m, 1H, CHCHOH), 2.39-2.31 (m, 1H), 2.28-2.17 (m, 1H), 2.10-1.95 (m, 2H), 1.93-1.79 (m, 2H), 1.71-1.52 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***anti*** δ (ppm) : 211.2 (C), 173.3 (C), 71.1 (CH), 61.6 (CH_2), 53.7 (CH), 50.0 (CH_2), 30.2 (CH_2), 26.9 (CH_2), 24.8 (CH_2), 14.1 (CH_3).

The er was determined after derivatization as benzoate (see end of document)

benzyl 2-hydroxy-2-(2-oxocyclohexyl)acetate 5c:

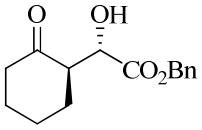
Major isomer *syn*-5b



Colourless oil (**Rf** = 0.2 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) ***syn*** δ (ppm) : 7.35-7.31 (m, 5H, ArH), 5.24 and 5.20 (d, AB, *J* = 12.8 Hz, 2H, CH_2Ph), 4.72 (dd, *J* = 4.8 and 2.4 Hz, 1H, CHOH), 2.99 (d, *J* = 4.8 Hz, 1H, OH), 2.83-2.76 (m, 1H, CHCHOH), 2.49-2.34

(m, 1H), 2.33-2.25 (m, 1H), 2.08-1.99(m, 2H), 1.94-1.75(m, 2H), 1.72-1.52 (m, 2H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 210.4 (C), 173.5 (C), 135.2 (C), 128.7 (2*CH), 128.6 (CH), 128.4 (2*CH), 69.3 (CH), 67.4 (CH_2), 53.8 (CH), 41.9 (CH_2), 27.1 (CH_2), 26.9 (CH_2), 24.5 (CH_2). **IR** (neat, cm^{-1}): 3482, 2939, 1733, 1704, 1453, 1201, 1124, 737, 697. **HRMS** calcd for $(M+H)^+$ $C_{15}H_{19}O_4$: 263.1283 found: 263.1294.

Minor isomer *anti*-5b

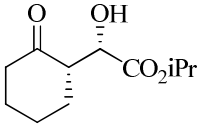


^{1}H NMR (400 MHz, $CDCl_3$) ***anti*** δ : 7.35-7.31 (m, 5H, ArH), 5.23 and 5.17 (d, AB, *J* = 12.8 Hz, 2H, $\underline{CH_2}$Ph), 4.07 (dd, *J* = 7.6 and 3.2 Hz, 1H, $\underline{CH}$OH), 2.99 (d, *J* = 7.6 Hz, 1H, OH) 2.99-2.91 (m, 1H, $\underline{CH}$CHOH), 2.42-2.35 (m, 1H), 2.30-2.20 (m, 1H), 2.13-2.00(m, 2H), 1.98-1.85(m, 2H), 1.72-1.57 (m, 2H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***anti*** δ (ppm) : 211.2 (C), 173.3 (C), 135.4 (C), 128.6 (2*CH), 128.5 (CH), 128.4 (2*CH) 71.1 (CH), 67.3 (CH_2), 53.7 (CH), 41.9 (CH_2), 30.1 (CH_2), 26.8 (CH_2), 24.7 (CH_2).

The er was determined by chiral HPLC using Daicel Chiralpak IA column (90% heptane, 10% EtOH, 20 °C, 0.5 mL/min, 211 nm, t_1 = 41.4 (major *syn*), t_2 = 45.3 (major *anti*), t_3 = 48.9 (minor *anti*), t_4 = 59.1 min (minor *syn*)).

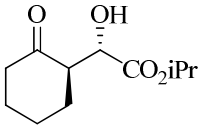
Isopropyl 2-hydroxy-2-(2-oxocyclohexyl)acetate 5c:

Major isomer *syn*-5c



Colourless oil (**Rf** = 0.2 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) ***syn*** δ (ppm) : 5.11 (sept., *J* = 6.6 Hz, 1H, $\underline{CH}(CH_3)_2$), 4.62 (dd, *J* = 4.6 and 2.4 Hz, 1H, $\underline{CH}$OH), 2.94 (d, *J* = 4.6 Hz, 1H, OH), 2.74-2.80 (m, 1H, $\underline{CH}$CHOH), 2.46-2.43 (m, 1H), 2.39-2.27 (m, 1H), 2.09-2.03 (m, 2H), 1.96-1.87 (m, 2H), 1.74-1.56 (m, 2H), 1.27 (d, *J* = 6.6 Hz, 3H, CH_3), 1.26 (d, *J* = 6.6 Hz, 3H, CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 210.2 (C), 173.2 (C), 69.6 (CH), 69.2 (CH), 53.9 (CH), 41.9 (CH_2), 27.0 (CH_2), 26.8 (CH_2), 24.6 (CH_2), 21.8 (2*CH_3). **IR** (neat, cm^{-1}): 3485, 2938, 2867, 1708, 1374, 1208, 1103. **HRMS** calcd for $(M+H)^+$ $C_{11}H_{19}O_4$: 215.1283 found: 215.1276.

Minor isomer *anti*-5c

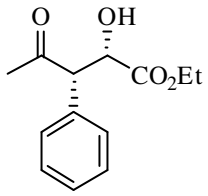


^{1}H NMR (400 MHz, $CDCl_3$) ***anti*** δ (ppm) : 5.10 (sept., *J* = 6.4 Hz, 1H, CH(CH_3)$_2$), 3.98 (dd, *J* = 6.8 and 3.2 Hz, 1H, CHOH), 3.13 (d, *J* = 6.8 Hz, 1H, OH), 2.97-2.92 (m, 1H, CHCHOH), 2.44-2.38 (m, 1H), 2.33-2.23 (m, 1H), 2.16-2.03 (m, 2H), 2.01-1.85 (m, 2H), 1.77-1.55 (m, 2H), 1.28 (d, *J* = 6.4 Hz, 3H, CH_3), 1.24 (d, *J* = 6.4 Hz, 3H, CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***anti*** δ (ppm): 210.9 (C), 172.9 (C), 71.1 (CH), 69.3 (CH), 53.7 (CH), 41.9 (CH_2), 30.1 (CH_2), 26.8 (CH_2), 24.8 (CH_2), 21.7 (2*CH_3).

The er was determined after derivatization as benzoate (see end of document)

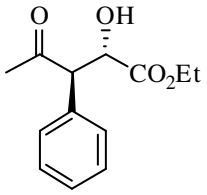
Ethyl 2-hydroxy-4-oxo-3-phenylpentanoate 6 (inseparable mixture of *syn/anti* isomers) 10:

Major isomer *syn*-10



Colourless oil (**Rf** = 0.2 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) ***syn*** δ (ppm) : 7.41-7.35 (m, 3H, ArH), 7.32-7.26 (m, 2H, ArH), 4.96 (app.t, *J* = 3.6 Hz, 1H, CHOH), 4.19 (qd, *J* = 5.6 and 3.2 Hz, 2H, OCH_2CH_3), 4.13 (d, *J* = 3.6 Hz, 1H, CHCHOH), 3.02 (d, *J* = 3.6 Hz, 1H, OH), 2.15 (s, 3H, CH_3), 1.24 (t, *J* = 5.6 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 206.7 (C), 172.6 (C), 133.5 (C), 129.8 (2*CH), 128.9 (2*CH), 128.2 (CH), 70.9 (CH), 61.9 (CH_2), 61.8 (CH), 29.2 (CH_3), 14.1 (CH_3). **IR** (neat, cm^{-1}): 3406, 2983, 1709, 1356, 1232, 1095, 1023, 700. **HRMS** calcd for $(M+H)^+$ $C_{13}H_{17}O_4$: 237.1127 found: 237.1116.

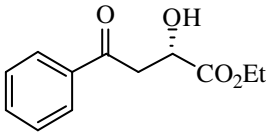
Only distinguishable signals are reported for the minor isomer *anti*-10.



^{1}H NMR (400 MHz, $CDCl_3$) δ : 4.55 (dd, *J* = 4.8 and 0.8 Hz, 1H, CHOH), 4.15 (d, *J* = 4.8 Hz, 1H, CHCHOH), 4.11 (qd, *J* = 5.6 and 2.4 Hz, 2H, OCH_2CH_3), 3.36 (d, *J* = 6.4 Hz, 1H, OH), 2.12 (s, 3H, CH_3), 1.11 (t, *J* = 5.6 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***anti*** δ (ppm): 207.6 (C), 172.8 (C), 134.5 (C), 129.3 (2*CH), 129.0 (2*CH), 128.2 (CH), 72.7 (CH), 62.5 (CH), 61.6 (CH_2), 29.7 (CH_3), 13.9 (CH_3).

The er was determined by chiral HPLC on Daicel Chiralpak IC column (80% heptane, 20% *i*PrOH, 20 °C, 1 mL/min, 220 nm, t_1 = 11.7 (major *anti*), t_2 = 14.2 (major *syn*), t_3 = 18.3 (minor *syn*), t_4 = 46.0 min (minor *anti*)).

Ethyl 2-hydroxy-4-oxo-4-phenylbutanoate 11:

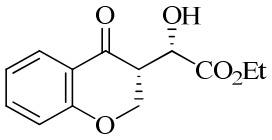


Colourless oil (**Rf** = 0.2 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) : 7.99-7.94 (m, 2H, ArH), 7.60 (tt, *J* = 7.5 and 1.2 Hz, 1H, ArH), 7.52-7.46 (m, 2H, ArH), 4.67 (m, 1H, CHOH), 4.28 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.55 (dd, AB, *J* = 17.5 and 4.0 Hz, 1H, CH_2CHOH), 3.46 (dd, AB, *J* = 17.5 and 6.0 Hz, 1H, CH_2CHOH), 1.29 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ (ppm) : 197.6 (C), 173.8 (C), 136.5 (C), 133.7 (2*CH), 128.7 (CH), 128.2 (2*CH), 67.3 (CH), 61.9 (CH_2), 42.2 (CH_2), 14.2 (CH_3). **IR** (neat, cm^{-1}): 3481, 2982, 1733, 1683, 1597, 1449, 1367, 1205, 1096, 1039, 756, 689. **HRMS** calcd for $(M+H)^+$ $C_{12}H_{15}O_4$: 223.0970 found: 223.0964.

The er was determined by chiral HPLC on Daicel Chiralpak IA column (95% heptane, 5% *i*PrOH, 20 °C, 1 mL/min, 240 nm, t_1 = 94.9 (major), t_2 = 109.8 min (minor)).

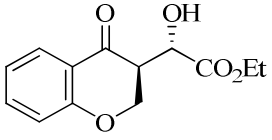
Ethyl 2-hydroxy-2-(4-oxochroman-3-yl)acetate 7 (inseparable mixture of *syn/anti* isomers) 12:

Major isomer *syn*-12



Colourless oil (**Rf** = 0.3 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) ***syn*** δ (ppm) : 7.95 (dd, *J* = 6.4 and 1.2 Hz, 1H, ArH), 7.52 (m, 1H, ArH), 7.06 (dt, *J* = 6.0 and 0.6 Hz, 1H, ArH), 7.00 (d, *J* = 6.4 and 0.4 Hz, 1H, ArH), 4.97 (dd, *J* = 4.0 and 2.4 Hz, 1H, CHOH), 4.65 (app.t, AB, J = 9.2 Hz, 1H, OCH_2), 4.49 (dd, AB, *J* = 9.2 and 4.0 Hz, 1H, OCH_2), 4.33 (qd, *J* = 6.0 and 1.2 Hz, 2H, OCH_2CH_3), 3.30 (ddd, *J* = 9.6, 4.0 and 2.8 Hz, 1H, CHCHOH), 3.07 (d, *J* = 4.4 Hz, 1H, OH), 1.32 (t, *J* = 6 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 191.1 (C), 173.3 (C), 161.7 (C), 136.3 (C), 127.5 (CH), 121.6 (CH), 121.0 (C), 117.9 (CH), 67.5 (CH), 67.2 (CH_2), 62.4 (CH_2), 49.4 (CH), 14.2 (CH_3). **IR** (neat, cm^{-1}): 3481, 2983, 1732, 1687, 1604, 1478, 1298, 1213, 1107, 1013, 758. **HRMS**. calcd for $(M+H)^+$ $C_{13}H_{15}O_5$: 251.0919 found: 251.0926.

Only distinguishable signals are reported for the minor isomer *anti*-12.



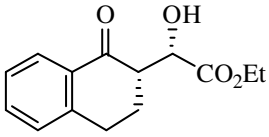
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) : 7.90 (dd, *J* = 6.4 and 1.2 Hz, 1H, ArH), 4.65 (dd, *J* = 7.2 and 2.0 Hz, 1H, CHOH), 3.49 (ddd, *J* = 9.2, 4.8 and 2.4 Hz, 1H, CHCHOH), 3.32 (d, *J* = 4.4 Hz, 1H, OH),

1.23 (t, J = 6 Hz, 3H, $OCH_2\underline{CH_3}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ (ppm) : 191.0 (C), 173.1 (C), 161.9 (C), 136.2 (CH), 127.3 (CH), 121.6 (CH), 121.2 (C), 117.9 (CH), 68.8 (CH_2), 67.8 (CH), 62.4 (CH_2), 49.3 (CH), 13.9 (CH_3).

The er was determined by chiral HPLC on Daicel Chiralpak IA column (98% heptane, 2% *i*PrOH, 20 °C, 1 mL/min, 248 nm, t_1 = 60.3 (major *anti*), t_2 = 65.2 (major *syn*), t_3 = 72.0 (minor *syn*), t_4 = 79.2 min (minor *anti*)).

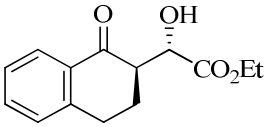
Ethyl 2-hydroxy-2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate 13:

Major isomer *syn*-13



Colourless oil (**Rf** = 0.3 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) ***syn*** δ (ppm) : 8.06 (dd, J = 8.0 and 1.2 Hz, 1H, ArH), 7.48 (dt, J = 7.5 and 1.2 Hz, 1H, ArH), 7.32 (t, J = 7.5 Hz, 1H, ArH), 7.27-7.23 (m, 1H, ArH), 5.04 (dd, J = 4.8 and 2.4 Hz, 1H, $\underline{CH}OH$) 4.34-4.28 (q, J = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 3.05-2.98 (m, 4H), 2.35-2.23 (m, 1H), 2.01-1.95 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 197.0 (C), 174.1 (C), 144.0 (C), 133.7 (CH), 132.4 (C), 128.7 (CH), 127.6 (CH), 126.7 (CH), 70.1 (CH), 61.9 (CH_2), 51.4 (CH), 28.8 (CH_2), 23.4 (CH_2), 14.2 (CH_3). **IR** (neat, cm^{-1}): 3517, 2936, 1725, 1682, 1599, 1456, 1365, 1203, 1099, 1020, 749. **HRMS** calcd for $(M+H)^+$ $C_{14}H_{17}O_4$: 249.1127 found: 249.1122.

Minor isomer *syn*-13

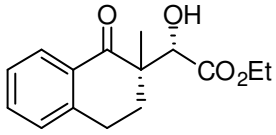


^{1}H NMR (400 MHz, $CDCl_3$) ***anti*** δ : 8.01 (dd, J = 8.0 and 0.8 Hz, 1H, ArH), 7.49 (dt, J = 7.4 and 1.2 Hz, 1H, ArH), 7.33-7.25 (m, 2H, ArH), 4.34-4.28 (m, 3H, $\underline{CH}OH$ and $O\underline{CH_2}CH_3$), 3.23 (d, J = 6.4 Hz, 1H, OH), 3.20 (ddd, J = 12.8, 5.2 and 2.8 Hz, 1H, $\underline{CH}CHOH$), 3.13-3.01 (m, 2H, $\underline{CH_2}$), 2.36-2.22 (m, 2H, $\underline{CH_2}$), 1.29 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***anti*** δ : 197.0 (C), 173.8 (C), 144.2 (C), 133.7 (CH), 132.4 (C), 128.8 (CH), 127.4 (CH), 126.7 (CH), 71.4 (CH), 61.9 (CH_2), 51.5 (CH), 29.1 (CH_2), 26.5 (CH_2), 14.1 (CH_3).

The er was determined by chiral HPLC on Daicel Chiralpak IA column (95% heptane, 5% EtOH, 20 °C, 1 mL/min, 241 nm, t_1 = 42.8 (major *syn*), t_2 = 45.7 (minor *anti*), t_3 = 48.9 (major *anti*), t_4 = 65.5 min (major *syn*)).

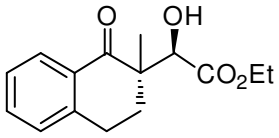
Ethyl 2-hydroxy-2-(2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate 10 (inseparable of *syn/anti* isomers) 14:

Major isomer *syn*-14



Colourless oil (**Rf** = 0.2 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) : 8.02 (t, *J* = 8.4 Hz, 1H, ArH), 7.47 (td, *J* = 7.6 and 1.6 Hz, 1H, ArH), 7.35-7.29 (m, 1H, ArH), 7.25-7.20 (m, 1H, ArH), 4.55-4.44 (dd, *J* =24.0 and 4 Hz, 1H, CHOH), 4.20-4.00 (m, 2H), 3.29 (dd, *J* = 30.4 and 4.0 Hz, 1H, OH), 2.93 (app.t, *J* = 6.6 Hz, 1H), 2.36 (quint., *J* = 6.8 Hz, 1H), 1.71 (app.dt, *J* = 13.6 and 5.6 Hz, 1H), 1.22-1.16 (m, 6H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ (ppm) : 200.4 (C), 173.3 (C), 142.8 (C), 133.4 (CH), 132.0 (C), 128.7 (CH), 128.1 (CH), 126.8 (CH), 74.0 (CH), 61.8 (CH_2), 49.1 (C), 30.3 (CH_2), 25.0 (CH_2), 18.1 (CH_3), 14.1 (CH). **IR** (neat, cm^{-1}): 3482, 2936, 1727, 1676, 1600, 1455, 1223, 1078, 738. **HRMS** calcd for $(M+H)^+$ $C_{15}H_{19}O_4$: 263.1283 found: 263.1295.

Only distinguishable signals are reported for the minor isomer *anti*-14.

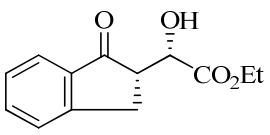


(**Rf** = 0.23 in Cyclohexane/EtOAc, 70/30) **^{1}H NMR** (400 MHz, $CDCl_3$) δ : 2.01 (td, *J* = 10.8 and 5.2 Hz, 1H), 1.91 (dt, *J* = 13.6 and 4.8 Hz, 1H), 1.29 (s, 3H, CH_3), 1.01 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ (ppm): 200.0 (C), 173.4 (C), 142.9 (C), 133.4 (CH), 131.8 (C), 128.6 (CH), 128.0 (CH), 126.8 (CH), 74.8 (CH), 62.0 (CH_2), 49.1 (C), 29.8 (CH_2), 25.0 (CH_2), 19.0 (CH_3), 13.9 (CH).

The er was determined by chiral HPLC on Daicel Chiralpak IA column (99% heptane, 1% EtOH, 20 °C, 1 mL/min, 211 nm, t_1 = 62.1 (major *anti*), t_2 = 67.0 (minor *anti*), t_3 = 70.6 (major *syn*), t_4 = 102.9 min (minor *syn*)).

Ethyl 2-hydroxy-2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetate 8 (inseparable of *syn/anti* isomers) 15:

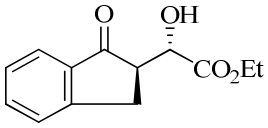
Major isomer *syn*-15



Colourless oil (**Rf** = 0.25 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) : 7.76 (d, *J* = 7.6 Hz, 1H, ArH), 7.58 (dt, *J* = 7.6 and 1.2 Hz, 1H, ArH), 7.45 (d, *J* = 8 Hz, 1H, ArH), 7.36 (dt, *J* = 7.6 and 0.4 Hz, 1H, ArH), 4.93 (dd, *J* = 4.4 and 2 Hz, 1H, CHOH), 4.30 (qd, *J* = 7.2 and 3.6 Hz, 2H, OCH_2CH_3), 3.17-3.12 (m, 1H,

CHCHOH), 3.11-3.07 (m, 2H), 3.00 (d, *J* = 6 Hz, 1H, OH), 1.30 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 205.1 (C), 174.1 (C), 154.0 (C), 136.6 (C), 135.1 (CH), 127.5 (CH), 126.5 (CH), 124.1 (CH), 69.5 (CH), 62.2 (CH_2), 50.0 (CH), 26.5 (CH_2), 14.2 (CH_3). **IR** (neat, cm^{-1}): 3473, 2927, 1705, 1607, 1465, 1280; 1204, 1116, 1033, 753. **HRMS** calcd for $(M+H)^+$ $C_{13}H_{15}O_4$: 235.0970 found: 235.0979.

Only distinguishable signals are reported for the minor isomer *anti*-15.

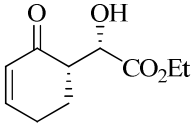


^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) : 7.71 (d, *J* = 7.6 Hz, 1H, ArH), 4.57 (app.t, *J* = 3.6 Hz, 1H, CHOH), 1.13 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ (ppm) : 204.9 (C), 173.2 (C), 153.8 (C), 136.9 (C), 135.0 (CH), 127.5 (CH), 126.5 (CH), 123.9 (CH), 70.6 (CH), 62.1 (CH_2), 50.2 (CH), 29.5 (CH_2), 13.9 (CH_3).

The er was determined by chiral HPLC on Daicel Chiralpak IA column (90% heptane, 10% *i*PrOH, 20 °C, 1 mL/min, 241 nm, t_1 = 14.6 (major *anti*), t_2 = 16.7 (major *syn*), t_3 = 20.0 (minor *syn*), t_4 = 21.8 min (minor *anti*)).

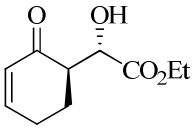
Ethyl 2-hydroxy-2-(2-oxocyclohex-3-enyl)acetate 16:

Major isomer *syn*-16



Colourless oil (**Rf** = 0.15 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) ***syn*** δ (ppm) : 7.03-6.98 (m, 1H, CHCHCO), 6.01 (ddd, *J* = 10.0, 2.8 and 1.2 Hz, 1H, CHCHCO), 4.92 (dd, *J* = 4.4 and 2.4 Hz, 1H, CHOH), 4.28 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 2.98 (d, *J* = 4.8 Hz, 1H, OH), 2.83 (ddd, *J* = 13.6, 4.8 and 2.4 Hz, 1H, CHCHOH), 2.52-2.42 (m, 2H), 2.25-2.11 (m, 1H), 1.88-1.75 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***syn*** δ (ppm) : 198.0 (C), 174.2 (C), 150.7 (CH), 129.8 (CH), 69.4 (CH), 61.9 (CH_2), 50.2 (CH), 25.5 (CH_2), 22.6 (CH_2), 14.2 (CH_3). **IR** (neat, cm^{-1}): 3473, 2938, 1731, 1672, 1389, 1215, 1118, 1022, 717. **HRMS** calcd for $(M+H)^+$ $C_{10}H_{15}O_4$: 199.0970 found: 199.0973.

Minor isomer *anti*-16

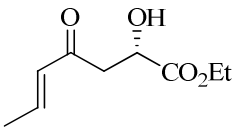


^{1}H NMR (400 MHz, $CDCl_3$) ***anti*** δ : 7.01-6.98 (m, 1H, CHCHCO), 6.01 (dt, *J* = 10.0 and 2.0 Hz, 1H, CHCHCO), 4.28 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 4.17 (dd, *J* = 5.2 and 2.8 Hz, 1H, CHOH), 3.18 (d, *J* = 5.2

Hz, 1H, OH), 3.01 (ddd, *J* = 13.2, 5.0 and 3.0 Hz, 1H, CHCHOH), 2.52-2.46 (m, 2H), 2.25-2.08(m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) ***anti*** δ : 198.2 (C), 173.6 (C), 150.9 (CH), 129.8 (CH), 71.0 (CH), 61.9 (CH_2), 50.3 (CH), 25.8 (CH_2), 25.7 (CH_2), 14.1 (CH_3).

The er was determined by chiral HPLC on Daicel Chiralpak AD-H column (90% heptane, 5% EtOH, 5%MeOH, 20 °C, 1 mL/min, 228 nm, t_1 = 21.0 (minor *anti*), t_2 = 23.1 (major *syn*), t_3 = 24.9 (minor *syn*), t_4 = 38.1 min (minor *syn*)).

(*E*)-Ethyl 2-hydroxy-4-oxohept-5-enoate 17:



Colourless oil (**Rf** = 0.15 in Cyclohexane/EtOAc, 70/30). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) : 6.90 (dq, *J* = 16.0 and 6.8 Hz, 1H, CHCHCO), 6.14 (dq, *J* = 16.0 and 1.6 Hz, 1H, CHCHCO), 4.52 (dd, *J* = 6.0 and 4.0 Hz, 1H, CHOH), 4.26 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.10 (dd, AB, *J* = 17.2 and 4 Hz, 1H, CH_2CHOH), 3.02 (dd, AB, *J* = 17.2 and 6.0 Hz, 1H, CH_2CHOH), 1.93 (dd, *J* = 6.8 and 1.6 Hz, 3H, CH_3), 1.29 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ (ppm) : 197.5 (C), 173.7 (C), 144.4 (CH), 131.8 (CH), 67.2 (CH), 61.8 (CH_2), 43.0 (CH_2), 18.4 (CH_3), 14.1 (CH_3). **IR** (neat, cm^{-1}): 3474, 2980, 1733, 1668, 1631, 1443, 1369, 1194, 1098, 1034, 970. **HRMS** calcd for $(M+H)^+$ $C_9H_{15}O_4$: 187.0978 found: 187.0970.

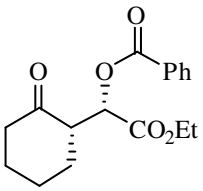
The er was determined by chiral HPLC on Daicel Chiralpak IA column (90% heptane, 10% EtOH, 20 °C, 1 mL/min, 230 nm, t_1 = 30.0 (major), t_2 = 36.4 min (minor)).

Er's of **5a**, **5b** and **11** and **12** were determined by chiral HPLC after derivatization to a benzoate ester according to the following procedure.

General procedure for the derivatization of aldol products:

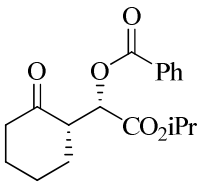
To a solution of **5a** (31 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (16 mg, 0.16 mmol, 1.1 equiv) followed by benzoyl chloride (32 mg, 0.23 mmol, 1.5 equiv) and DMAP (catalytic amount) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C and quenched with water (10 mL), followed by a aqueous solution of HCl (1N) (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2*10mL) and the organic layers were combined, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (cyclohexane/AcOEt, 80:20) to afford **14** as a colourless liquid (40 mg, 88%).

2-ethoxy-2-oxo-1-(2-oxocyclohexyl)ethyl benzoate 14:



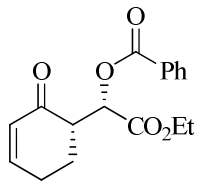
The er was determined by chiral HPLC on Daicel Chiralpak IC column (90% heptane, 10% EtOH, 20 °C, 1 mL/min, 228 nm, t_1 = 15.5 (major *anti*), t_2 = 18.5 (minor *anti*), t_3 = 27.4 (major *syn*), t_4 = 108.8 min (minor *syn*)).

2-isopropoxy-2-oxo-1-(2-oxocyclohexyl)ethyl benzoate 15:



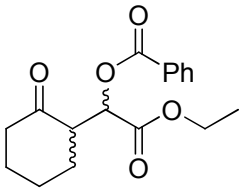
The er was determined by chiral HPLC on Daicel Chiralpak IA column (90% heptane, 10% EtOH, 20 °C, 1 mL/min, 228 nm, t_1 = 10.6 (minor *anti*), t_2 = 11.5 (major *anti*), t_3 = 22.7 (major *syn*), t_4 = 25.7 min (minor *syn*)).

2-ethoxy-2-oxo-1-(2-oxocyclohex-3-enyl)ethyl benzoate 16:



The er was determined by chiral HPLC on Daicel Chiralpak IA column (95% heptane, 5% *i*PrOH, 20 °C, 1 mL/min, 225 nm, t_1 = 20.2 (major *syn*), t_2 = 21.6 (minor *anti*), t_3 = 27.0 (major *anti*), t_4 = 39.0 min (minor *syn*)).

HPLC data of *rac*-2-ethoxy-2-oxo-1-(2-oxocyclohexyl)ethyl benzoate **5a** (Table 1, entry 14)



14

Empower Node Lcmt-hplc3

IC Septembre 2009

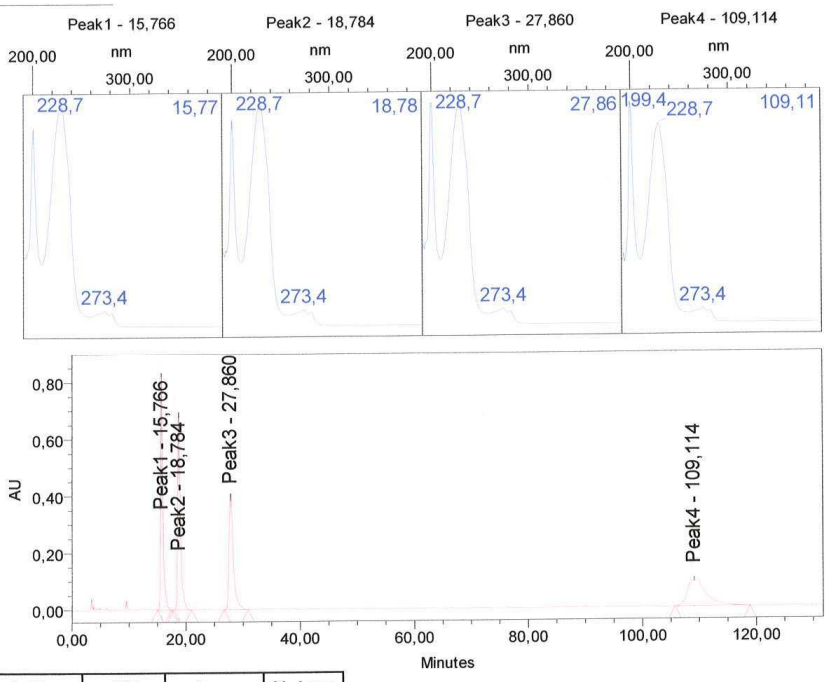
Colonne Daicel Chiralpak IC 4,6mmx250mm 5µm

GP-267-p

Date Acquired 10/09/2009 13:31:06 CEST

Instrument Method: IM1mL90%nhept10%EtOH_20dC

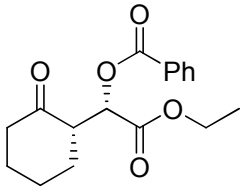
Stored: 10/09/2009 09:34:55 CEST



	Peak Name	RT	Area	% Area
1	Peak1	15,766	23966222	26,22
2	Peak2	18,784	24034298	26,30
3	Peak3	27,860	21719007	23,76
4	Peak4	109,114	21682580	23,72

PDA 228,0 nm

HPLC data of 2-ethoxy-2-oxo-1-(2-oxocyclohexyl)ethyl benzoate **5a** (Table 1, entry 14)



14

Empower Node Lcmt-hplc3

IC Septembre 2009

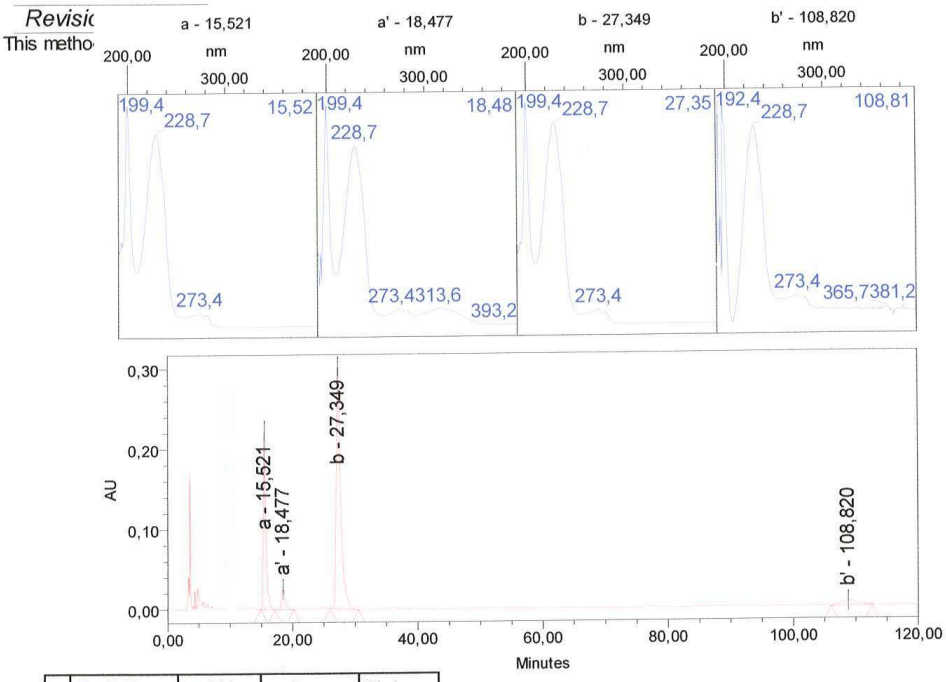
Colonne Daicel Chiralpak IC 4,6mmx250mm 5µm

GP-659-p

Date Acquired 23/09/2009 19:17:07 CEST

Instrument Method: IM1mL90%nhept10%EtOH_20dC

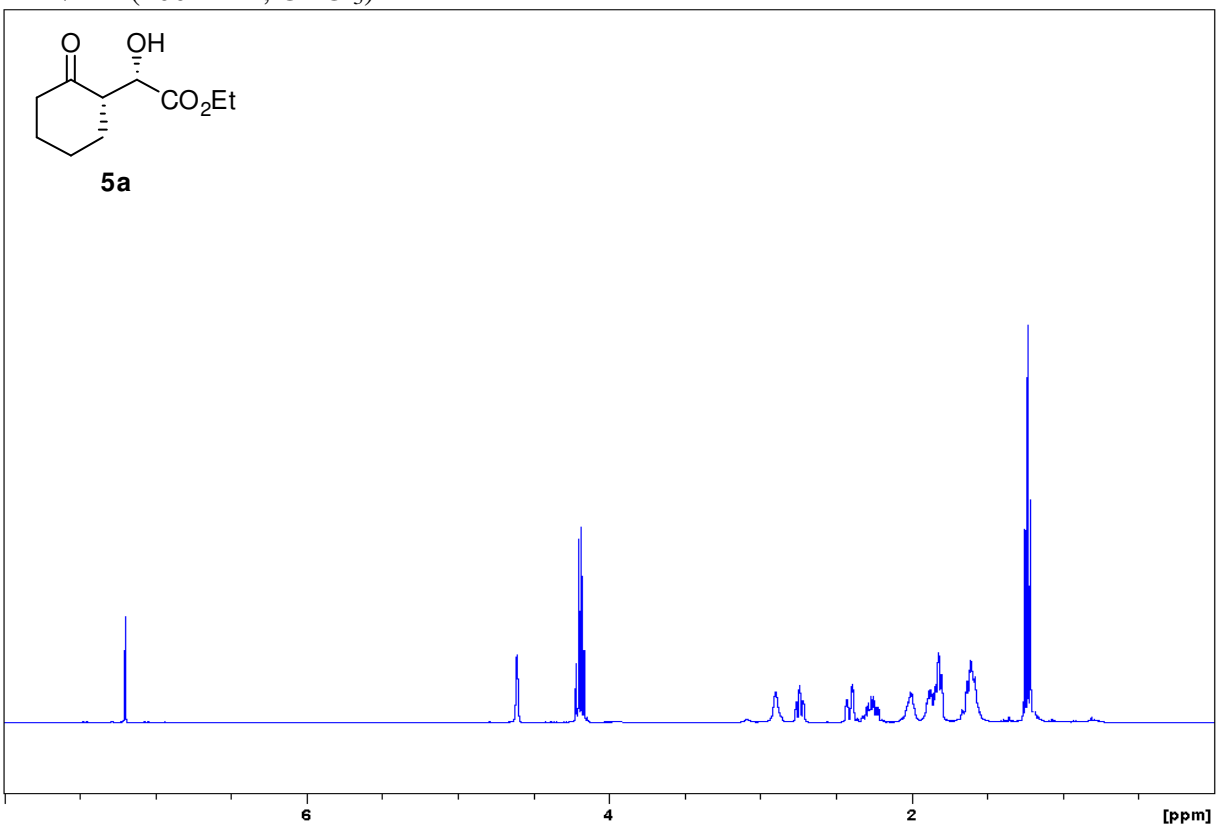
Stored: 10/09/2009 09:34:55 CEST



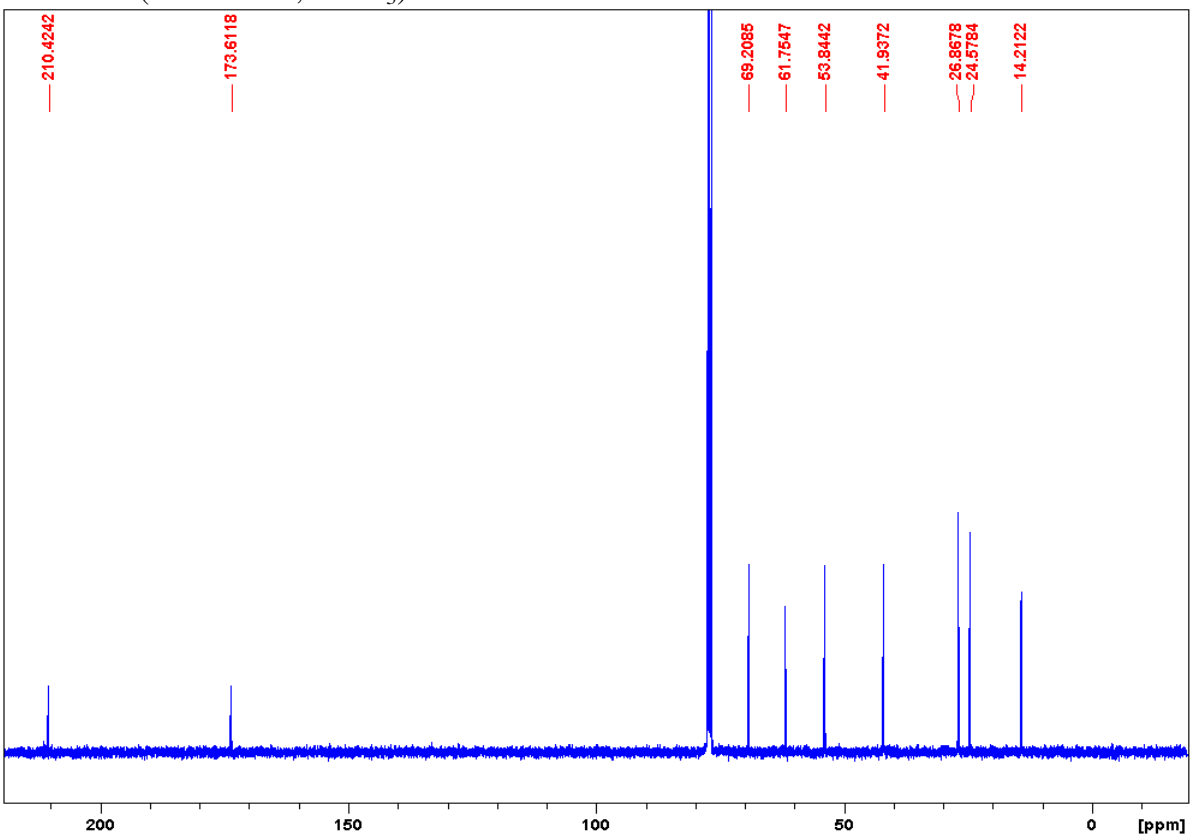
	Peak Name	RT	Area	% Area
1	a	15,521	6190739	26,15
2	a'	18,477	990534	4,18
3	b	27,349	15369402	64,92
4	b'	108,820	1123558	4,75

PDA 228,0 nm

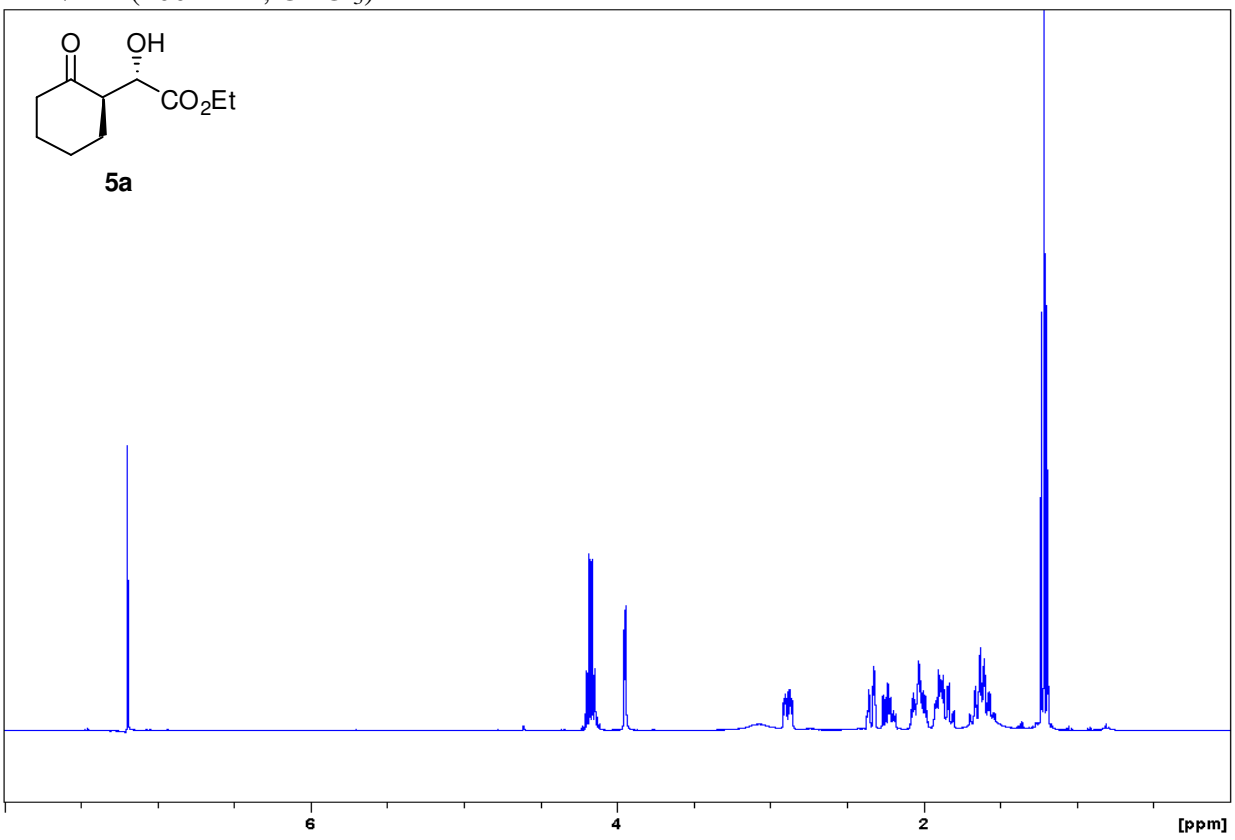
^{1}H NMR (400 MHz, $CDCl_3$)



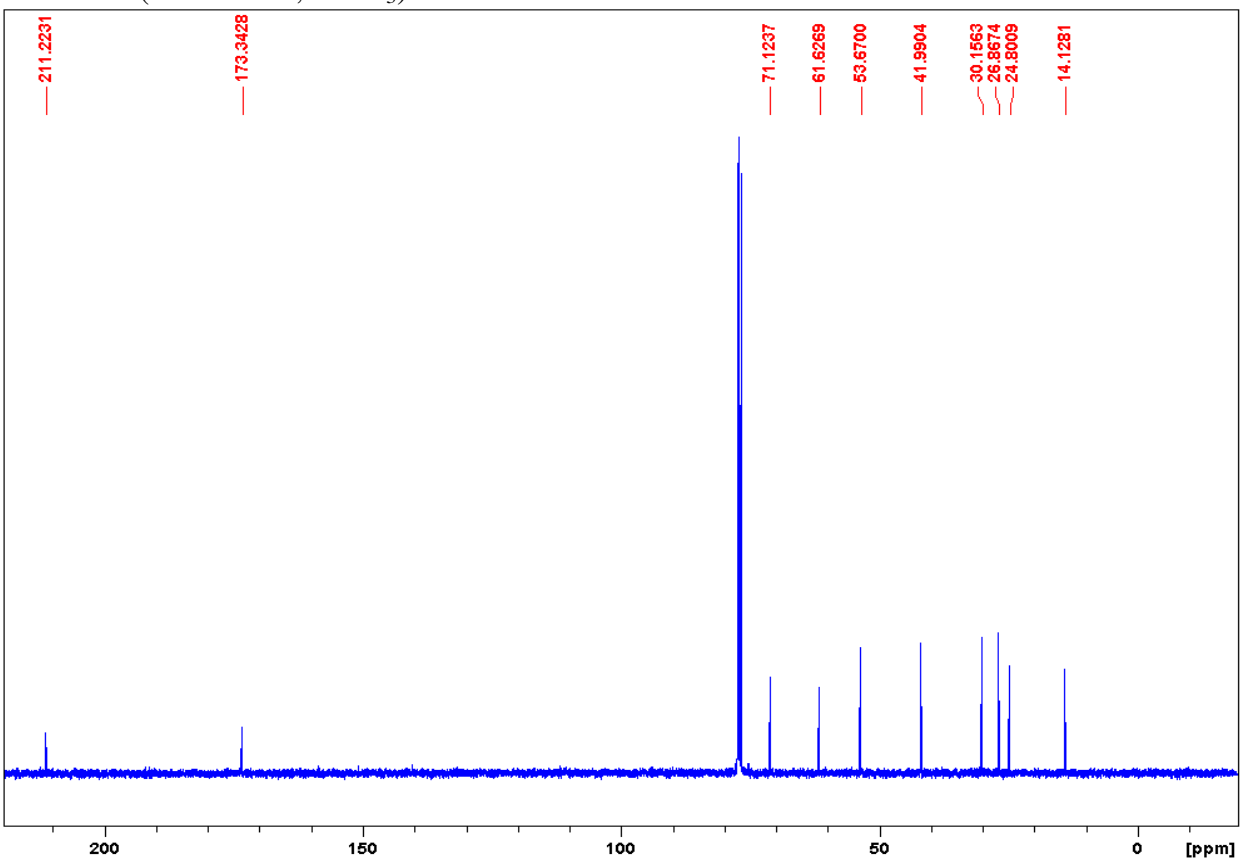
^{13}C NMR (100.6 MHz, $CDCl_3$)



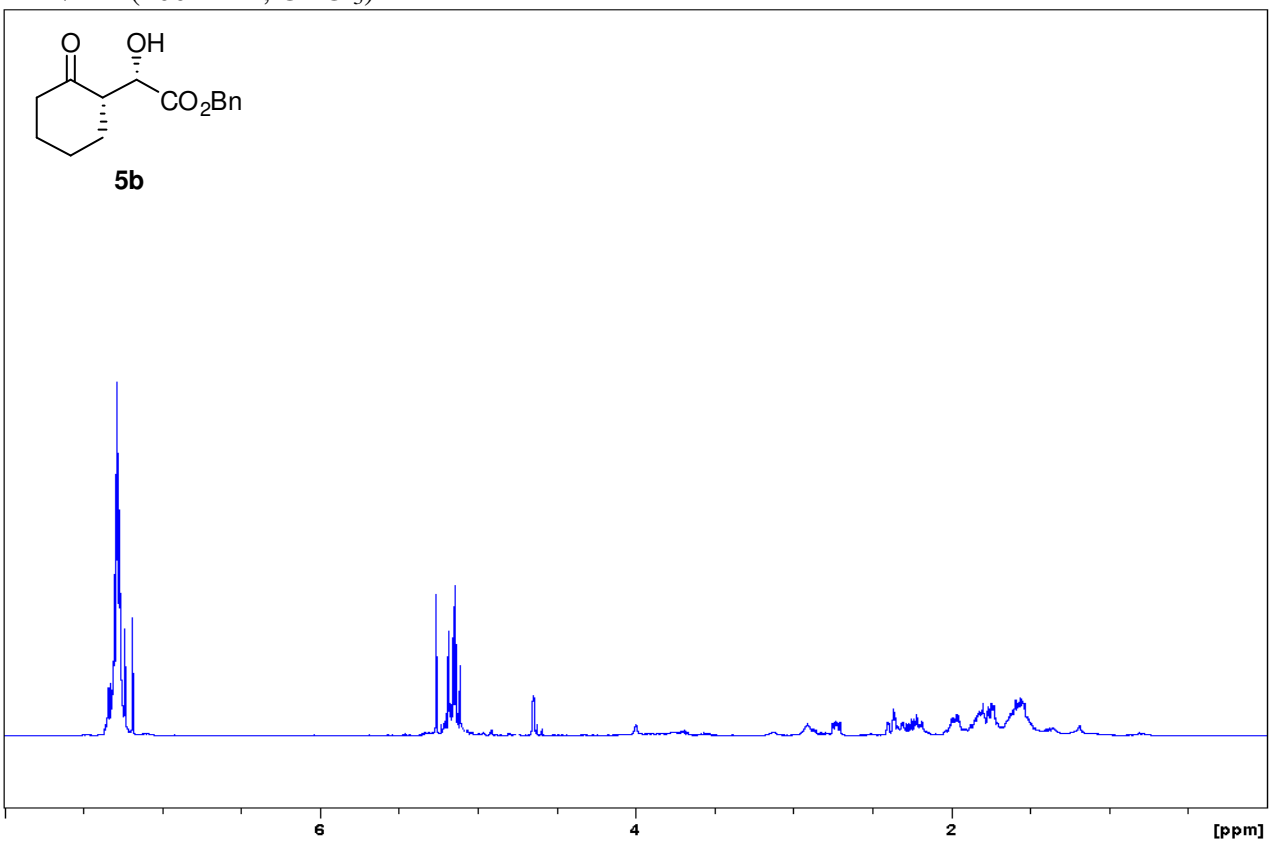
^{1}H NMR (400 MHz, $CDCl_3$)



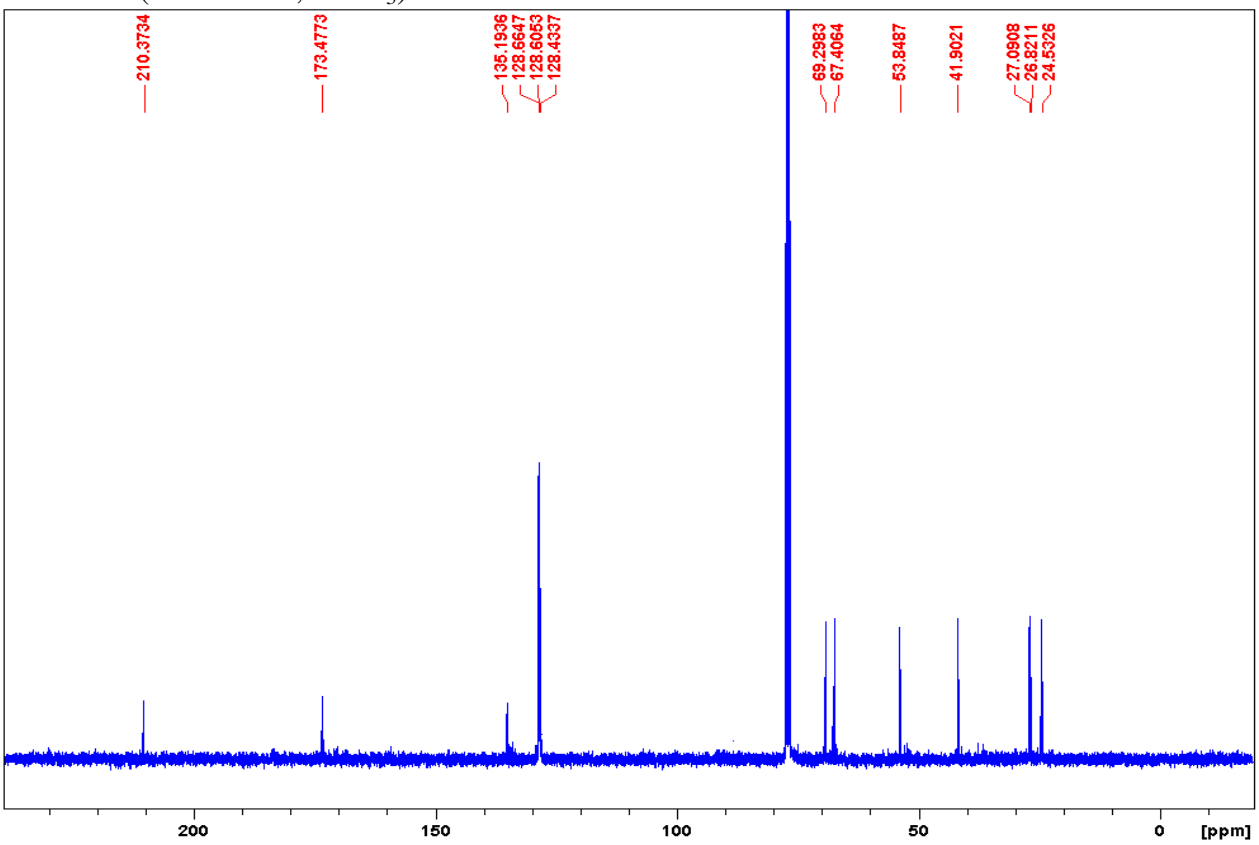
^{13}C NMR (100.6 MHz, $CDCl_3$)



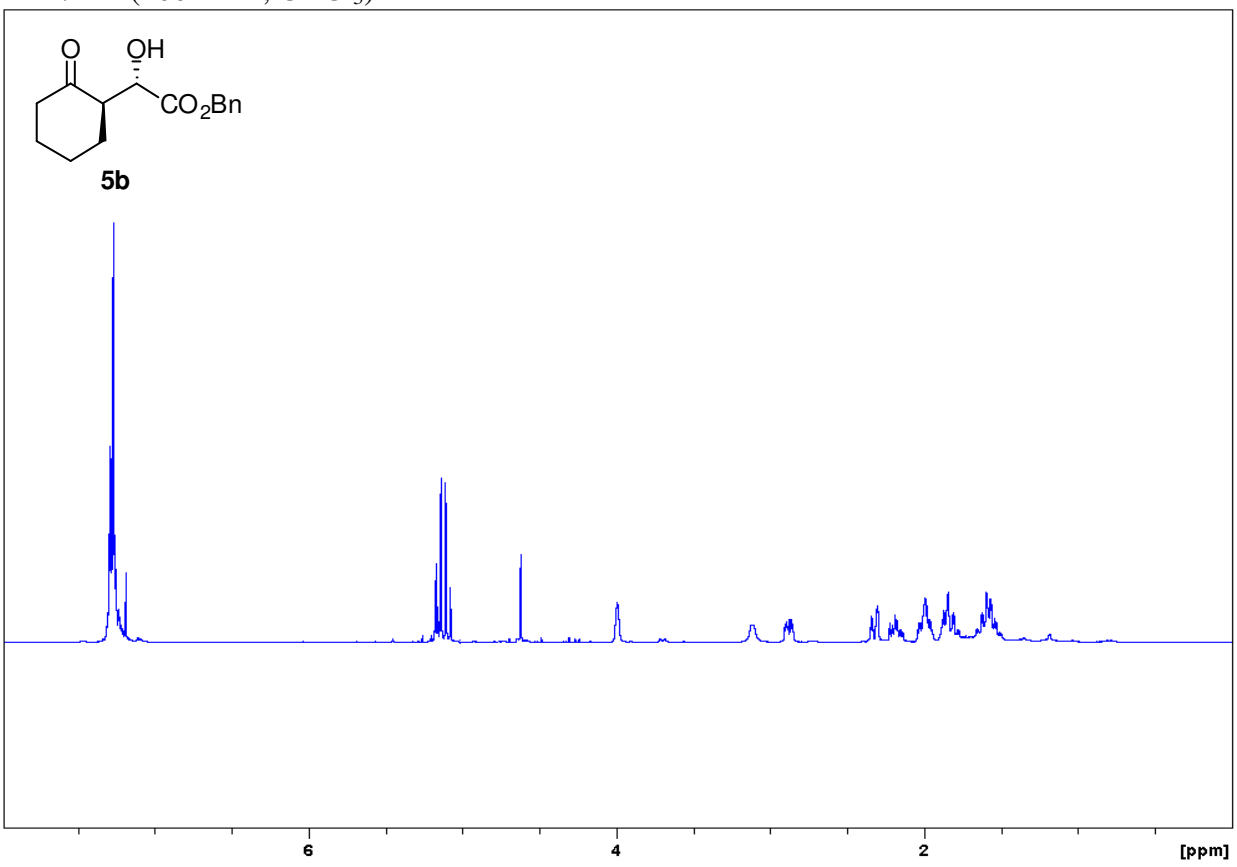
^{1}H NMR (400 MHz, $CDCl_3$)



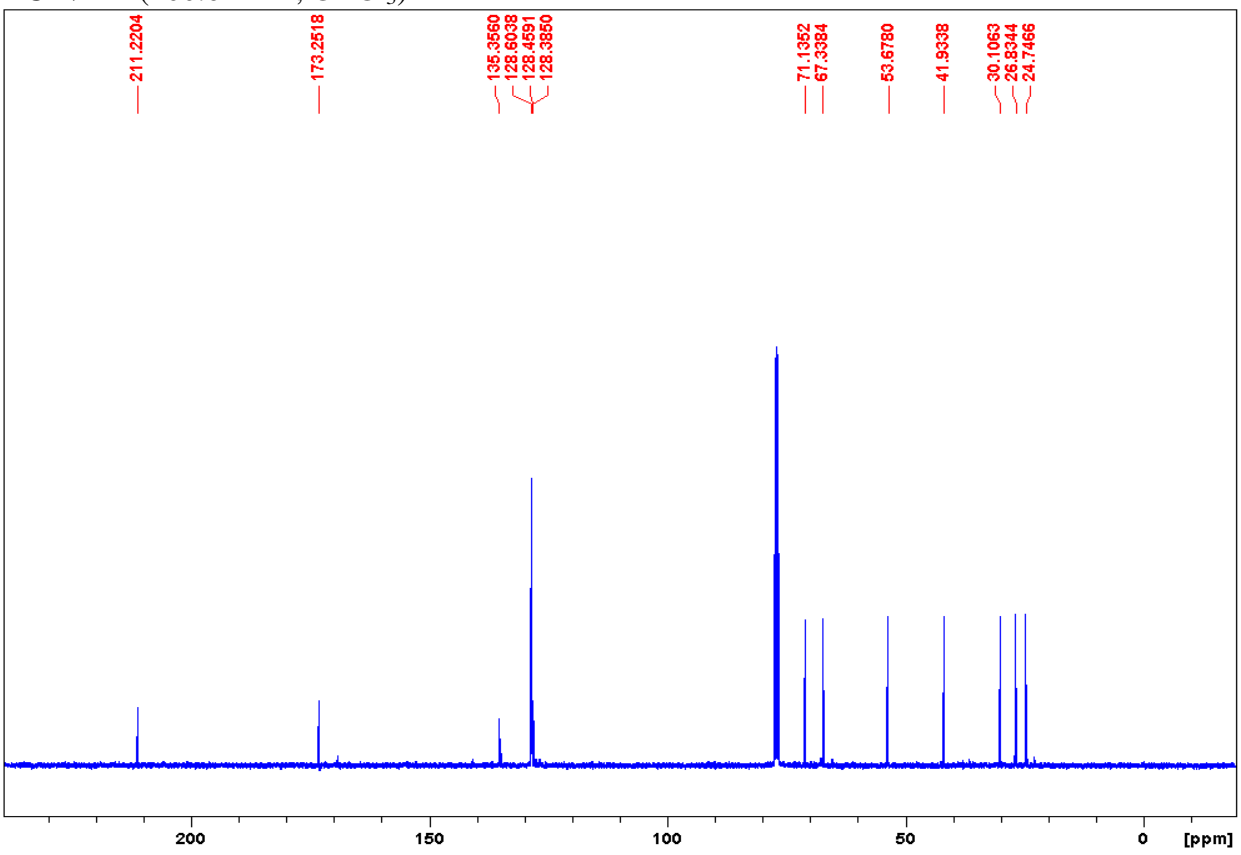
^{13}C NMR (100.6 MHz, $CDCl_3$)



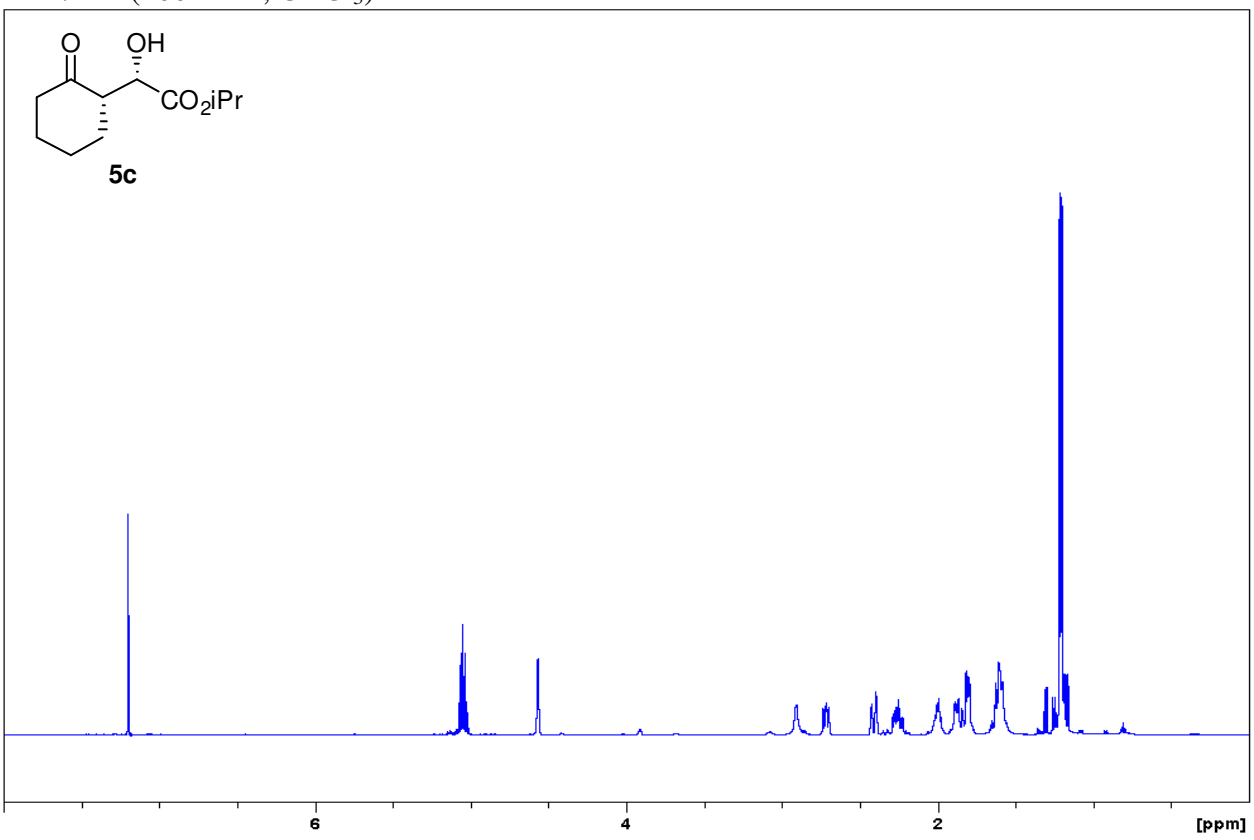
^{1}H NMR (400 MHz, $CDCl_3$)



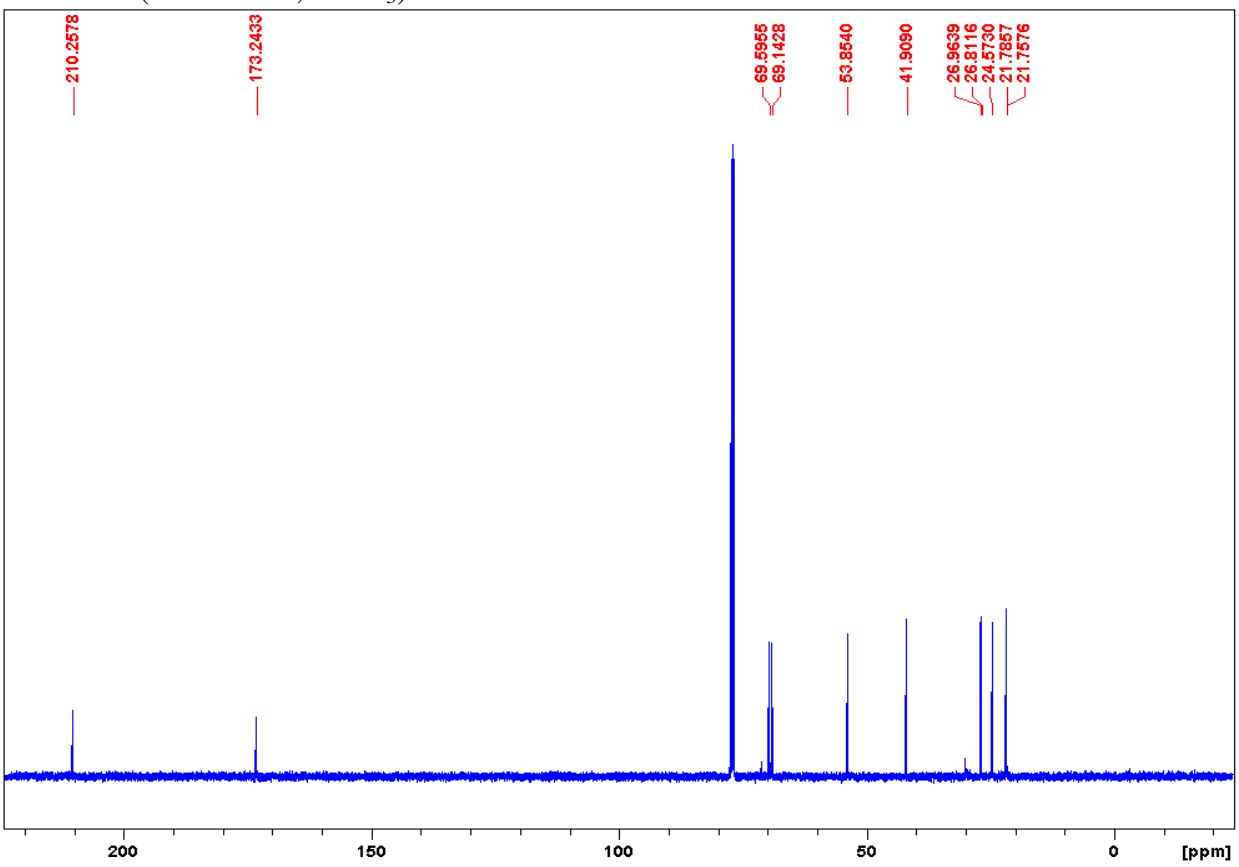
^{13}C NMR (100.6 MHz, $CDCl_3$)



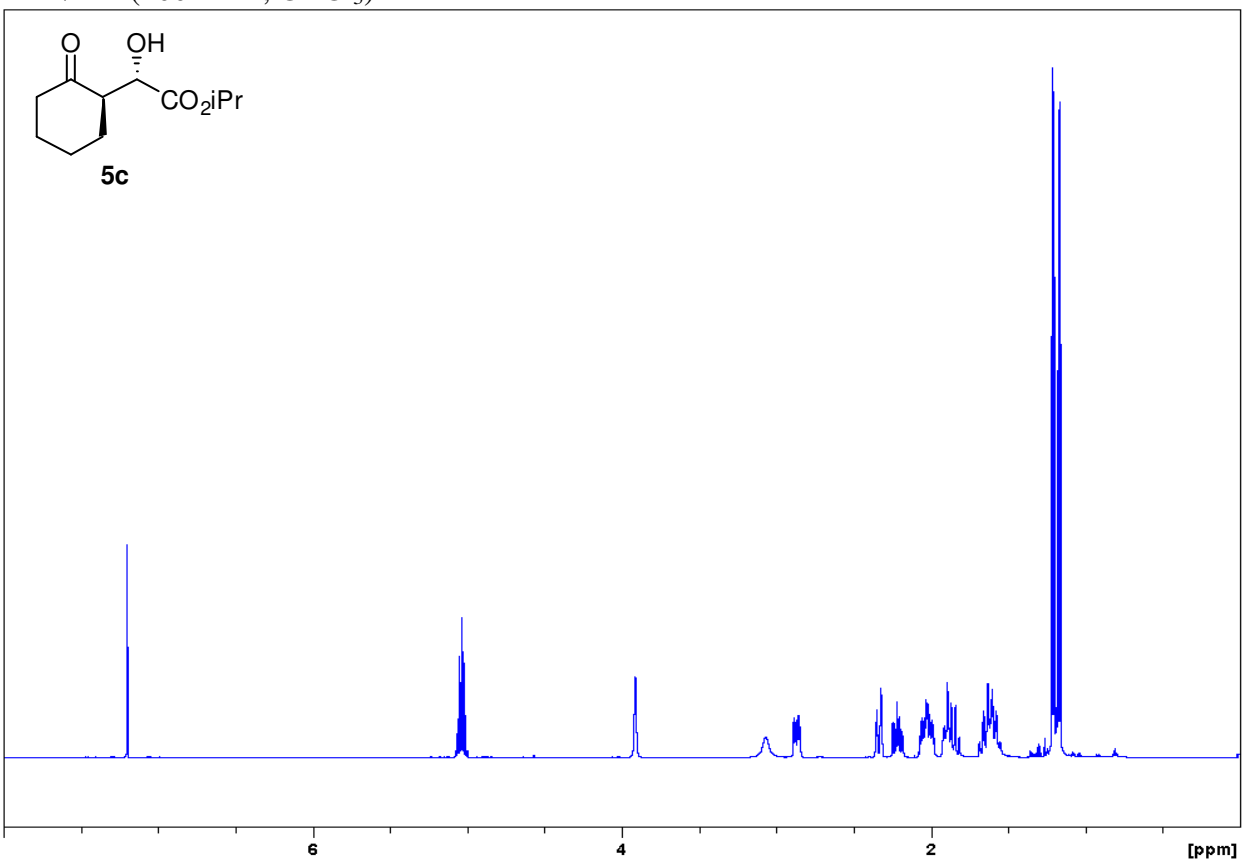
^{1}H NMR (400 MHz, $CDCl_3$)



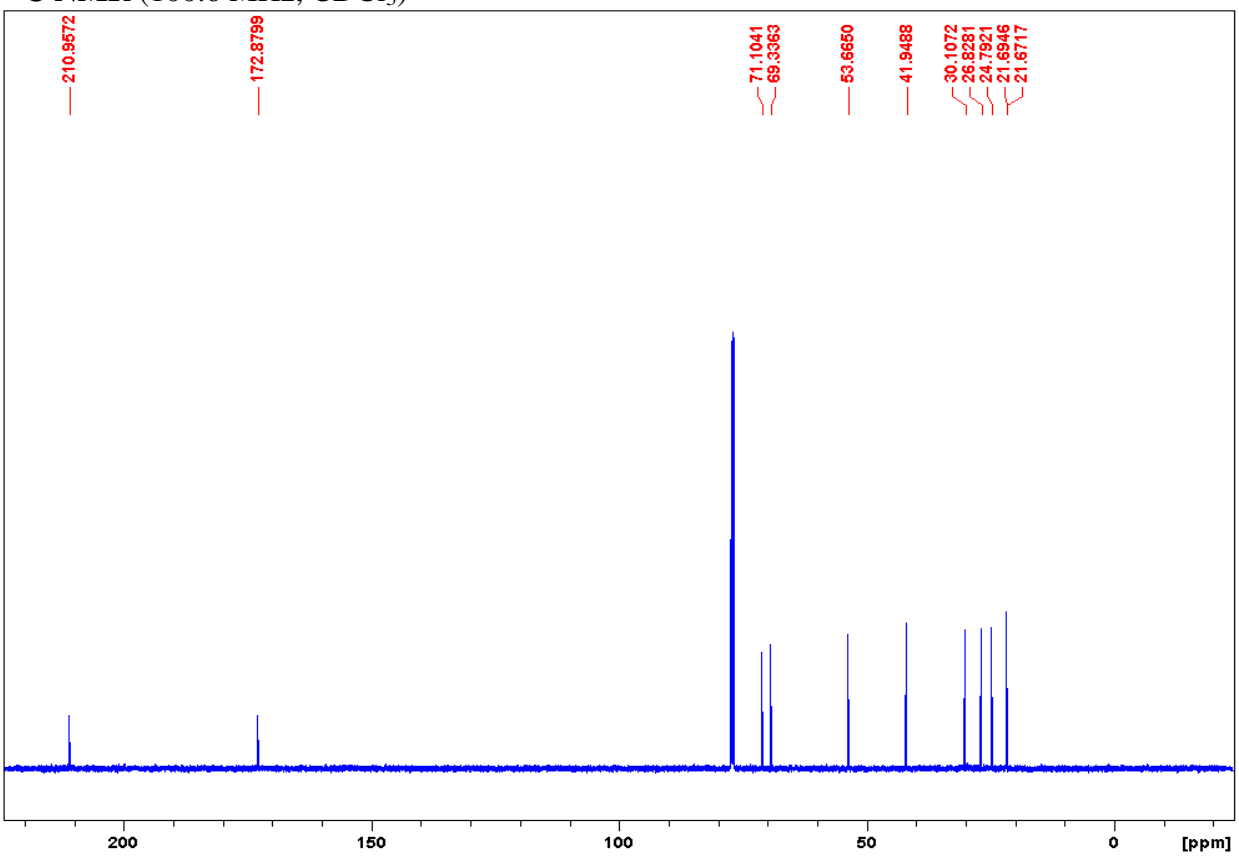
^{13}C NMR (100.6 MHz, $CDCl_3$)



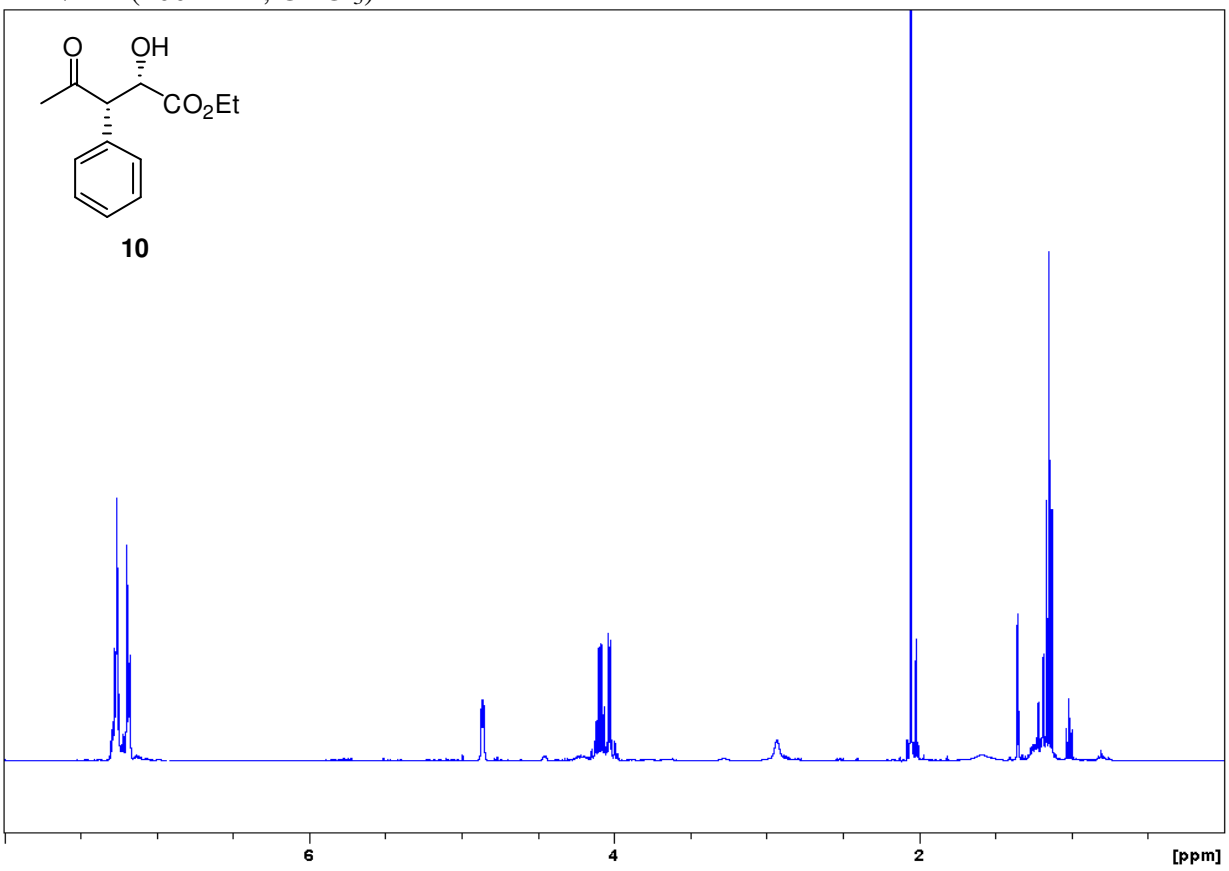
^{1}H NMR (400 MHz, $CDCl_3$)



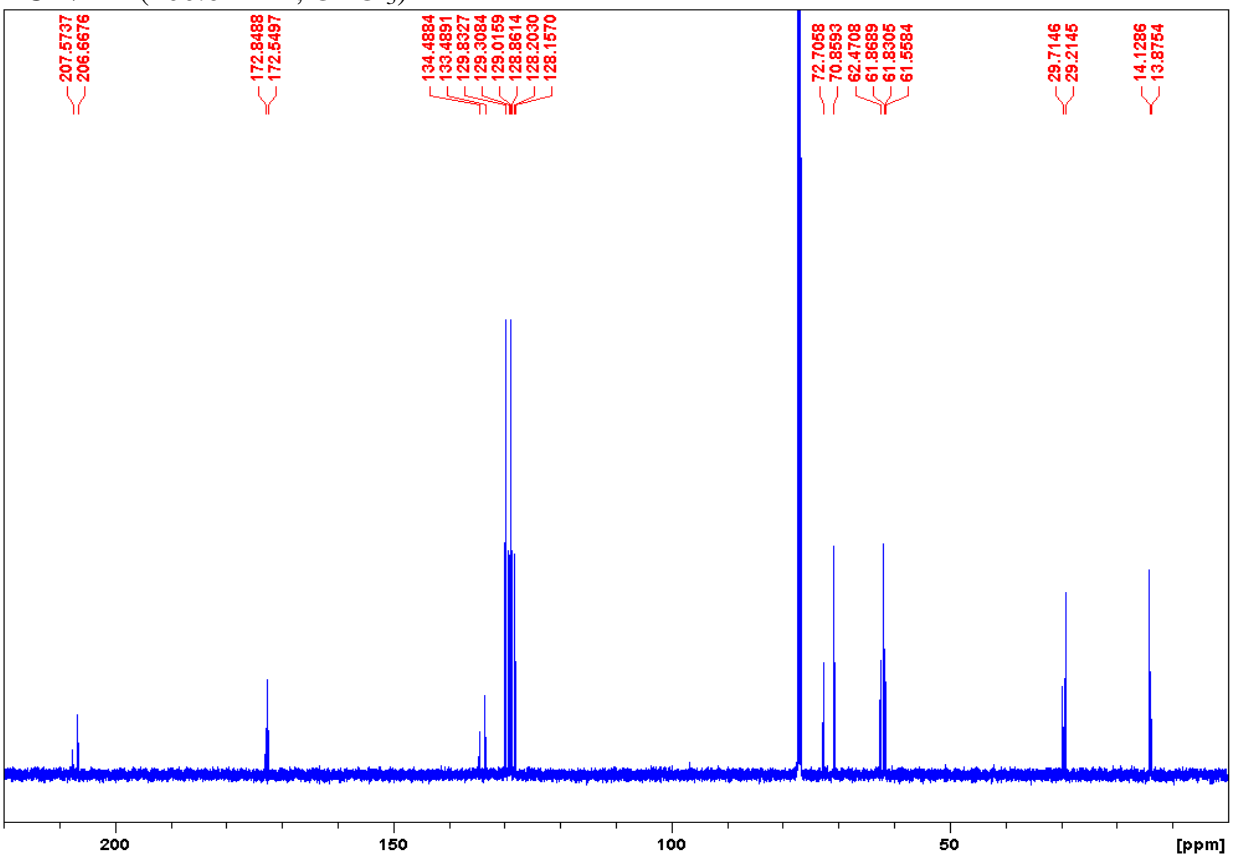
^{13}C NMR (100.6 MHz, $CDCl_3$)



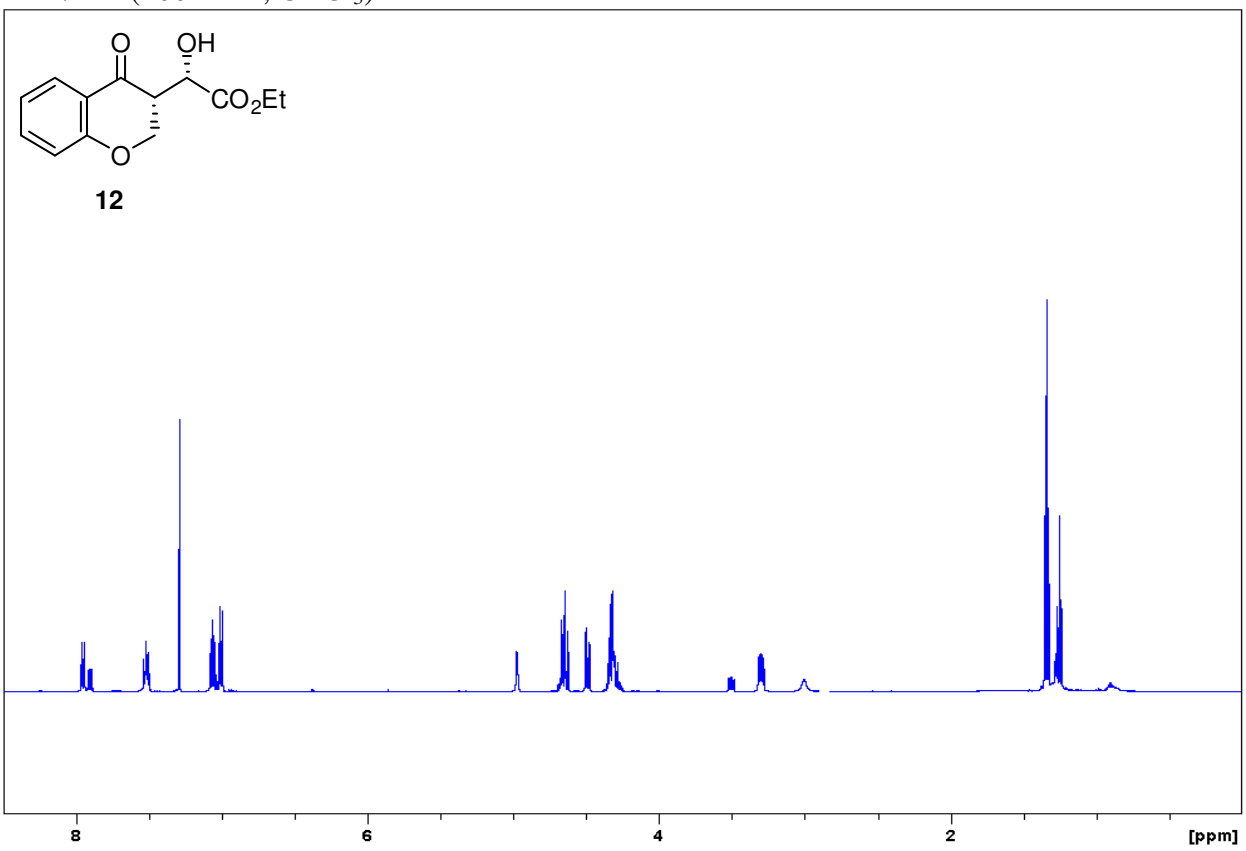
^{1}H NMR (400 MHz, $CDCl_3$)



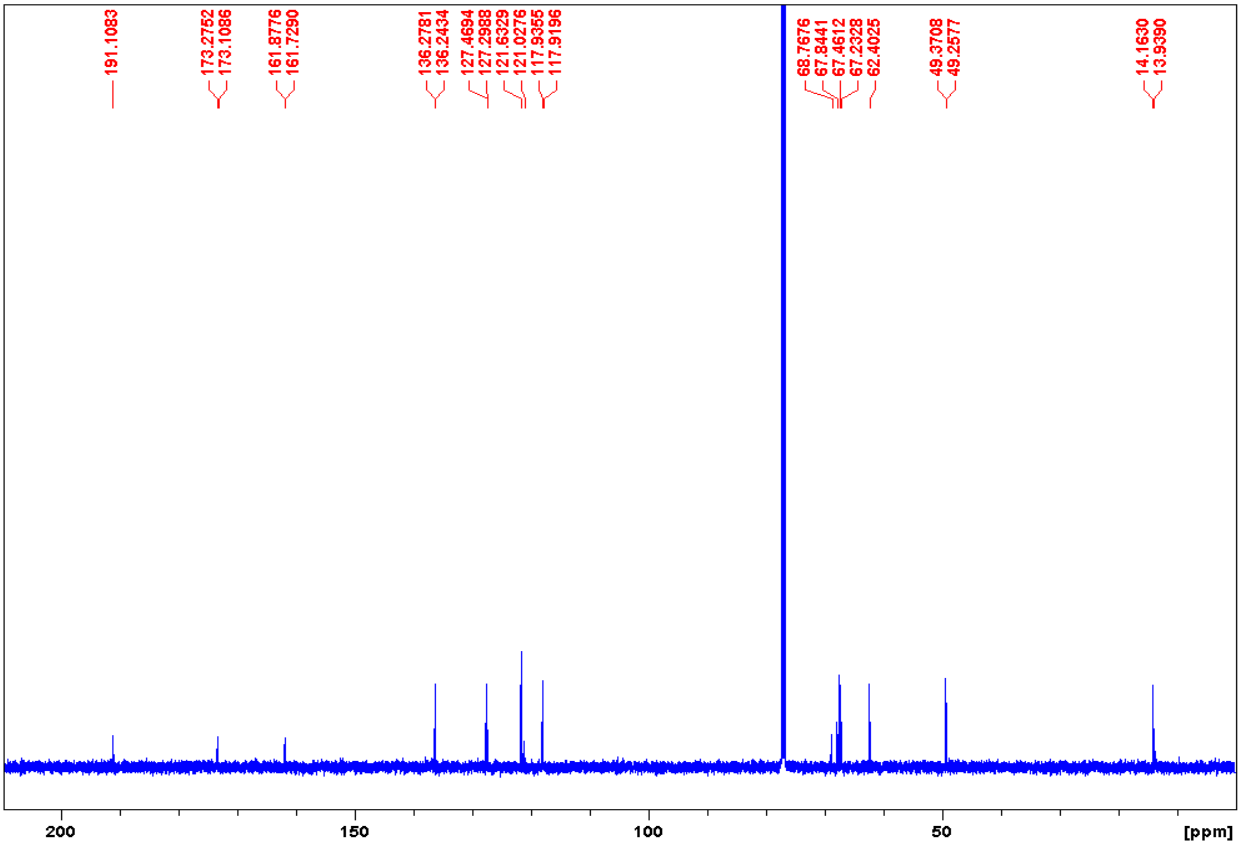
^{13}C NMR (100.6 MHz, $CDCl_3$)



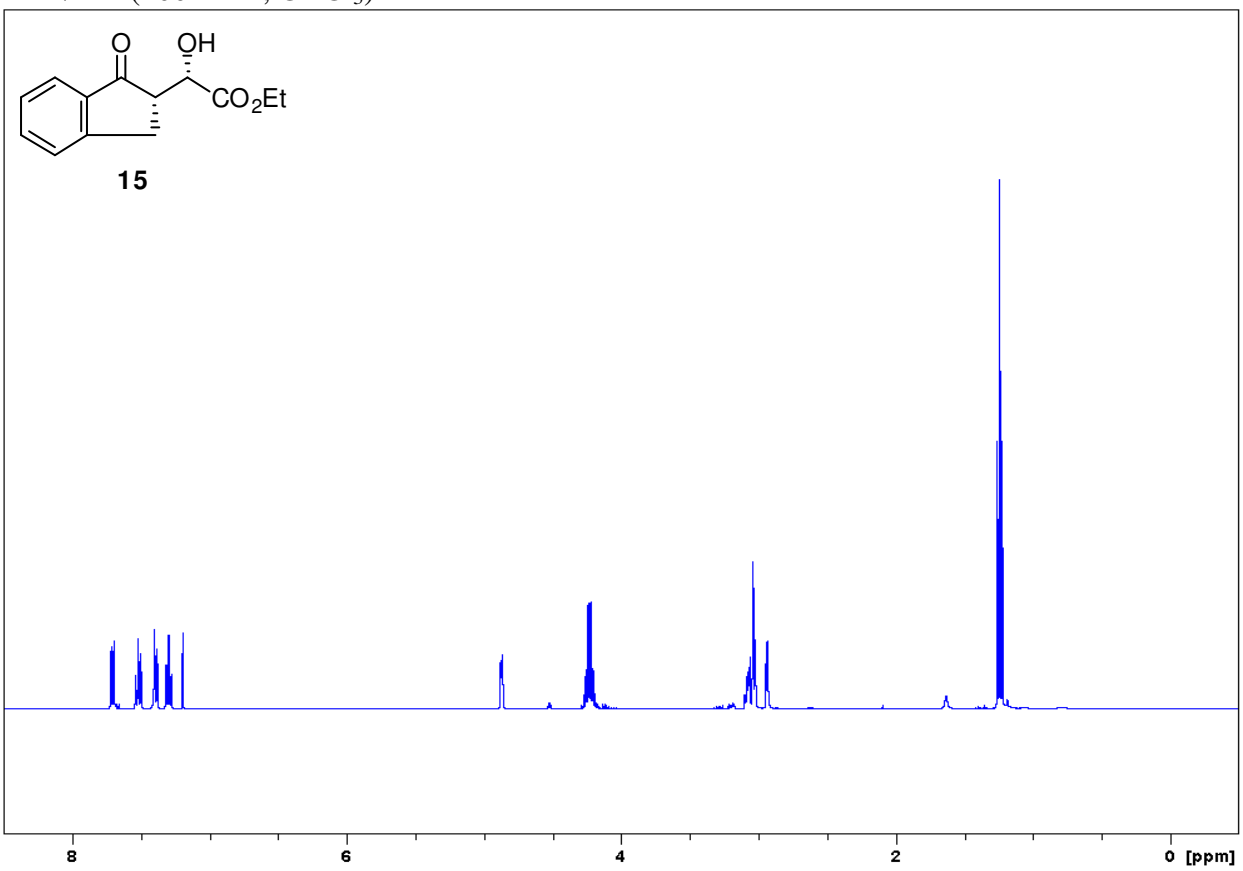
^{1}H NMR (400 MHz, $CDCl_3$)



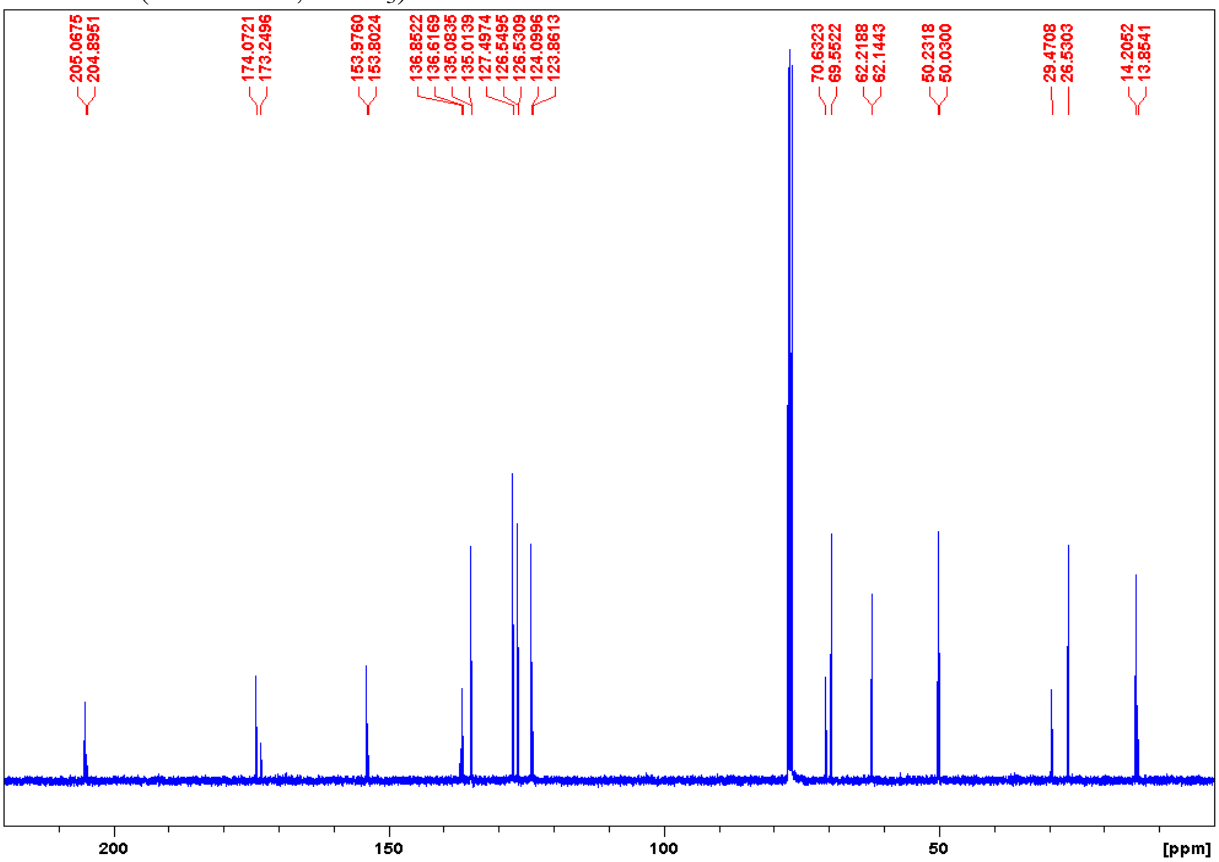
^{13}C NMR (100.6 MHz, $CDCl_3$)



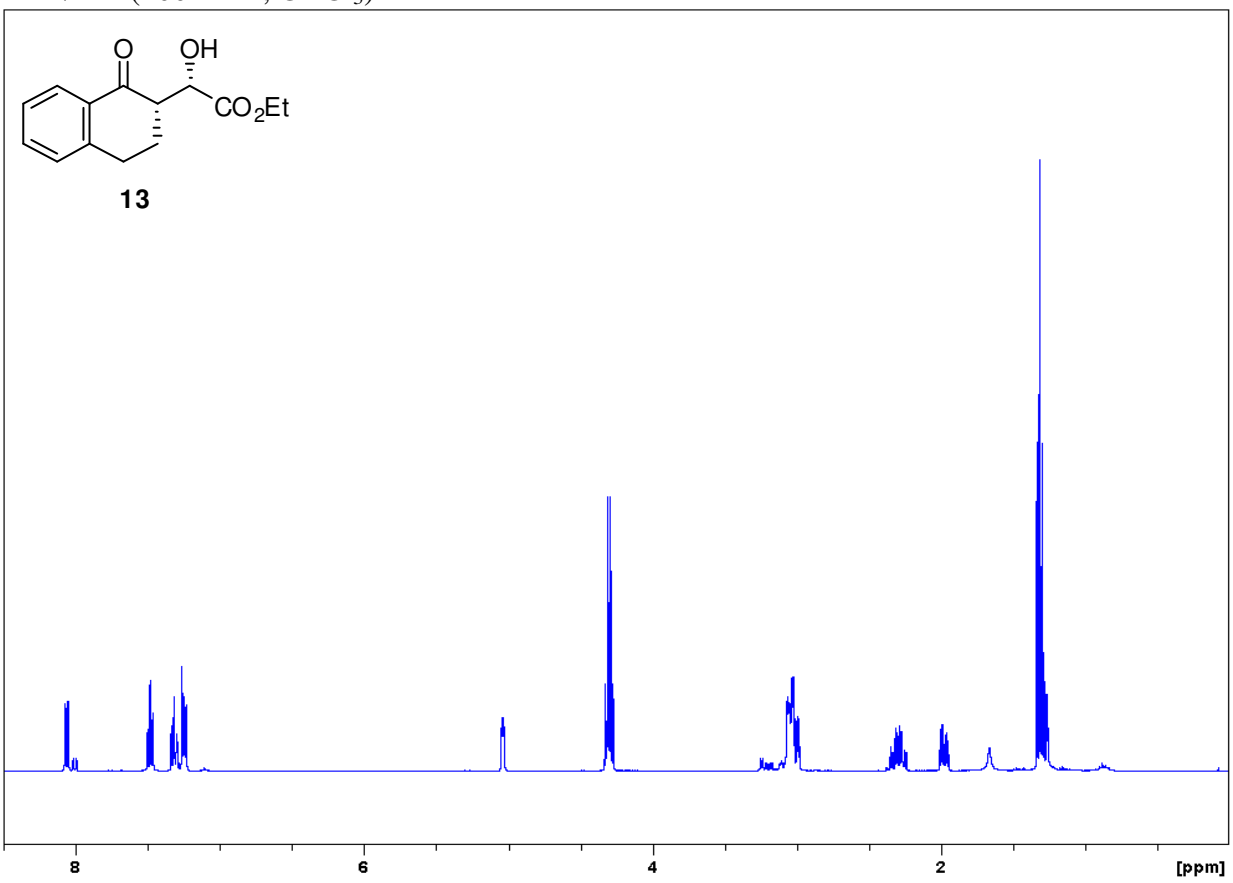
^{1}H NMR (400 MHz, $CDCl_3$)



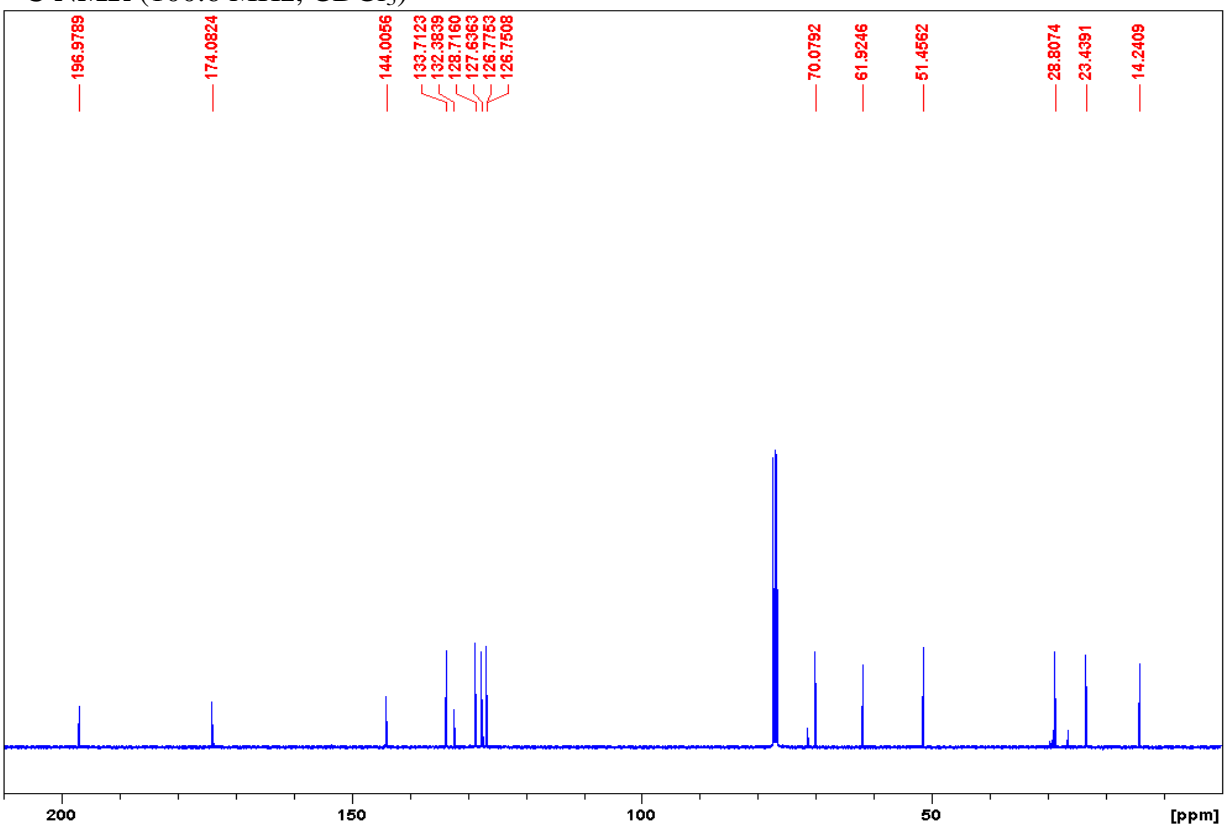
^{13}C NMR (100.6 MHz, $CDCl_3$)



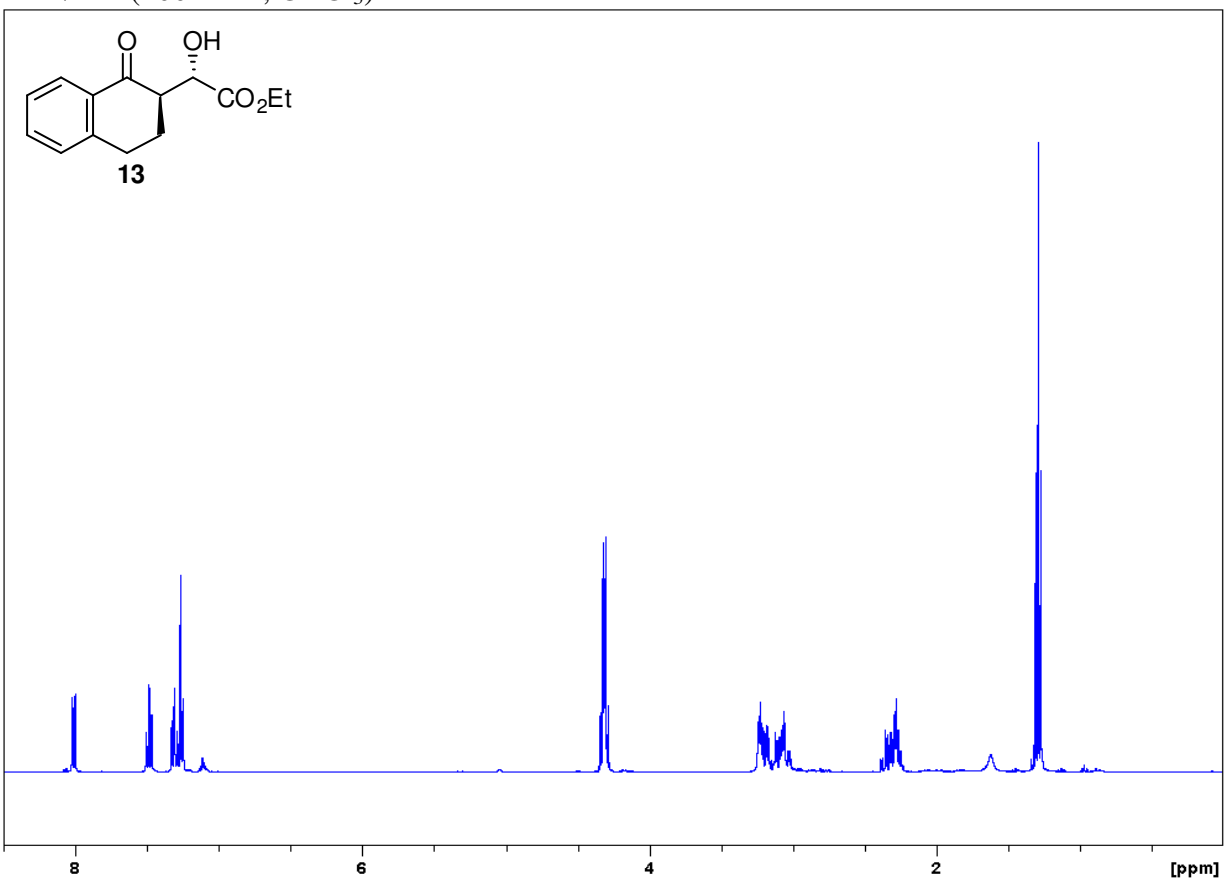
^{1}H NMR (400 MHz, $CDCl_3$)



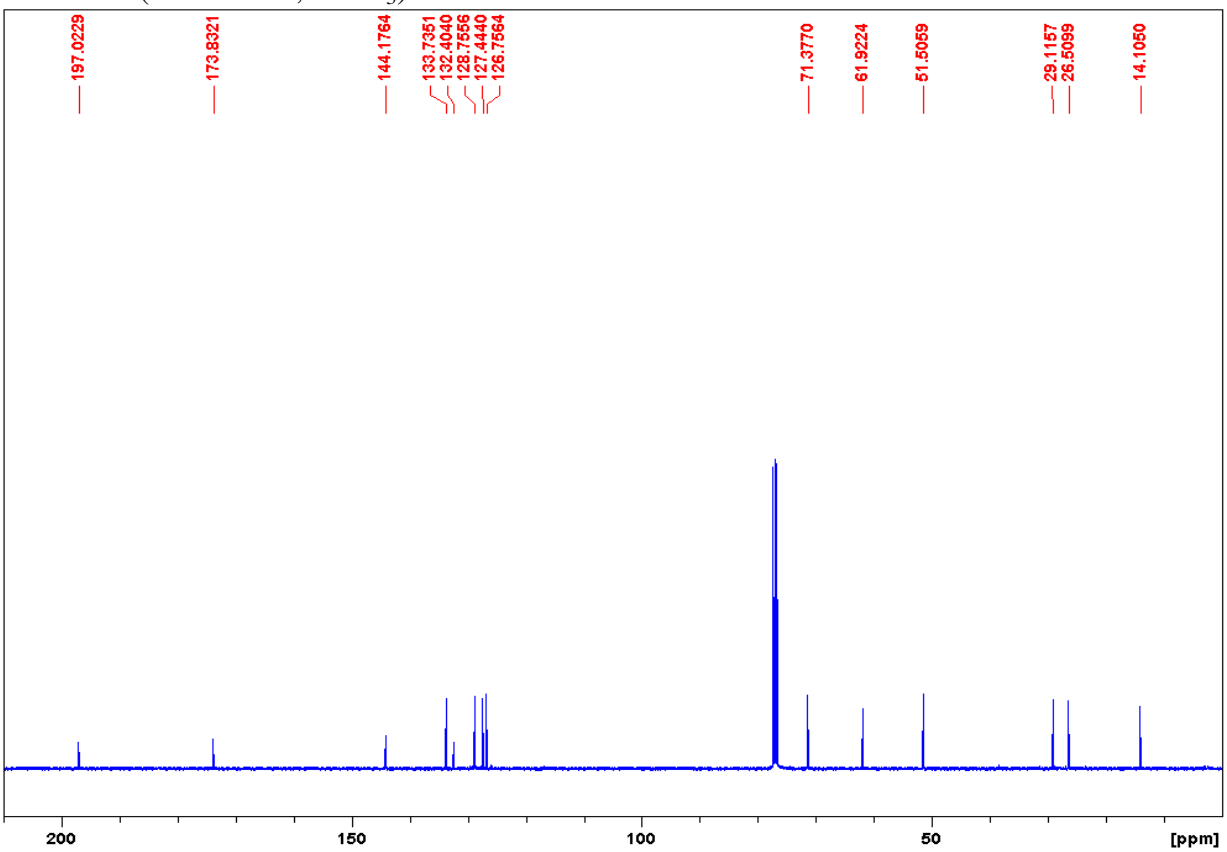
^{13}C NMR (100.6 MHz, $CDCl_3$)



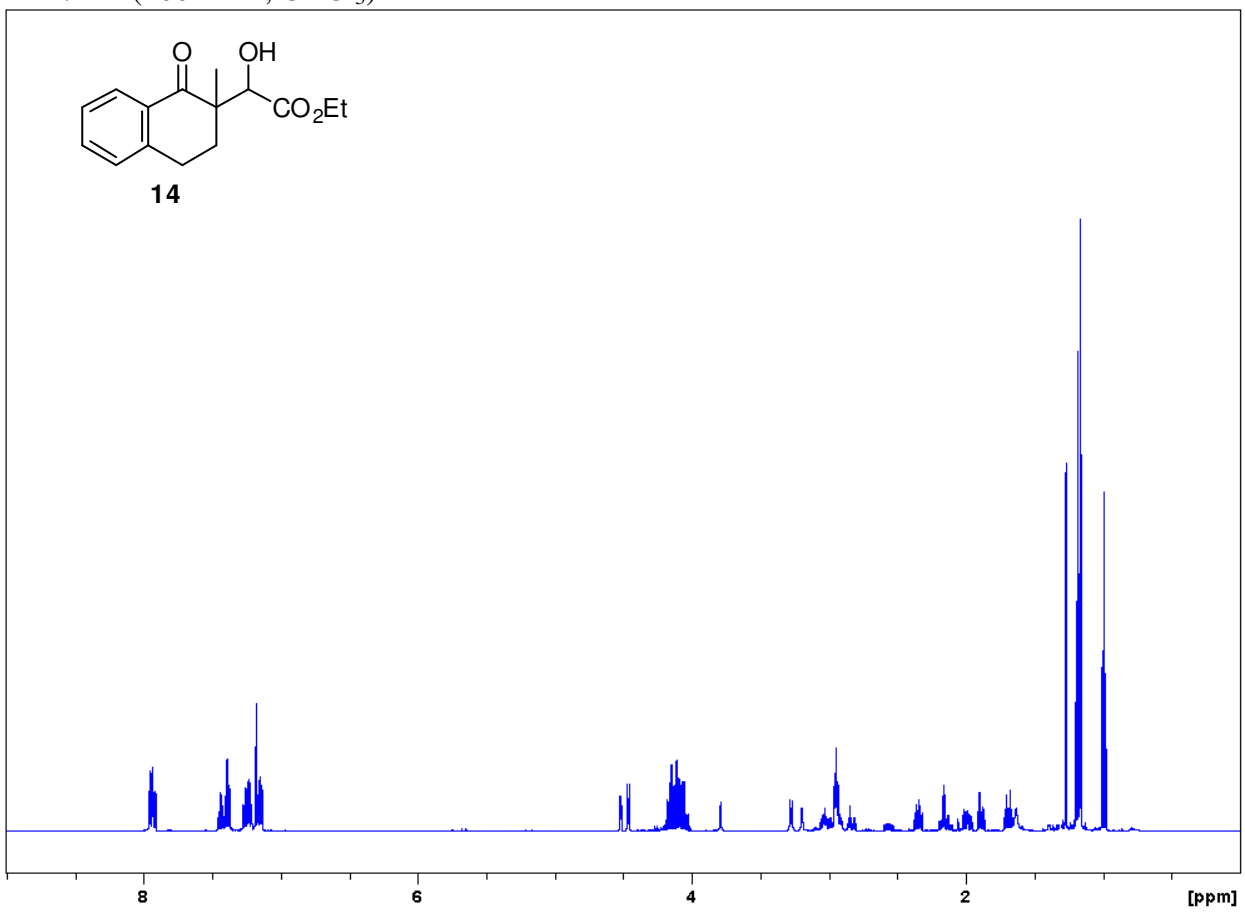
^{1}H NMR (400 MHz, $CDCl_3$)



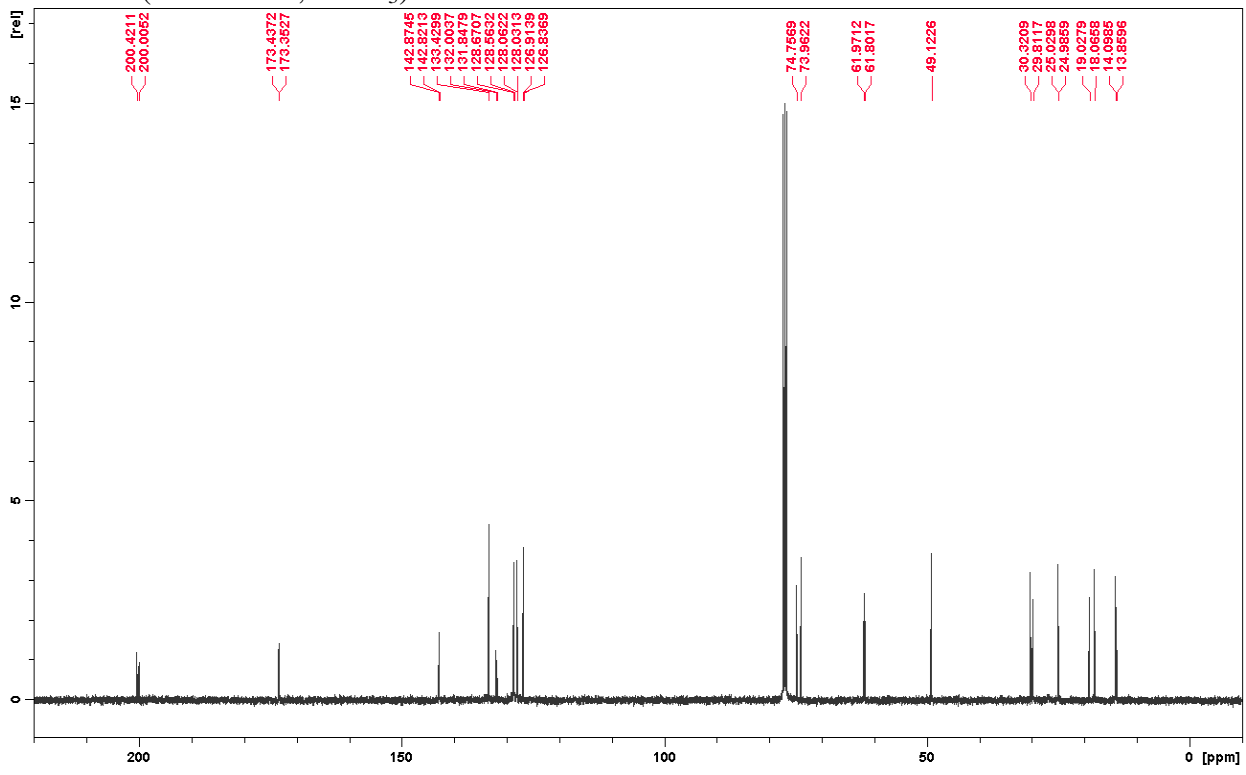
^{13}C NMR (100.6 MHz, $CDCl_3$)



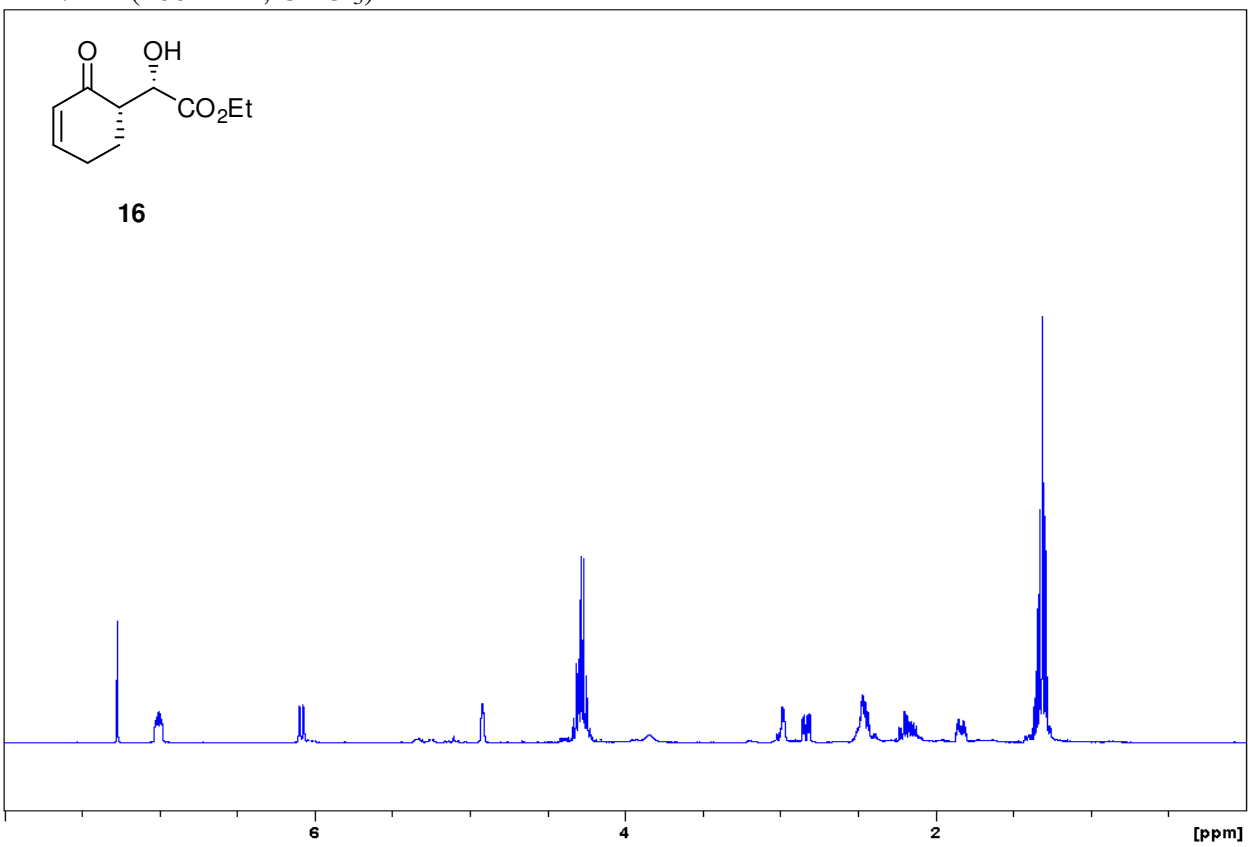
^{1}H NMR (400 MHz, $CDCl_3$)



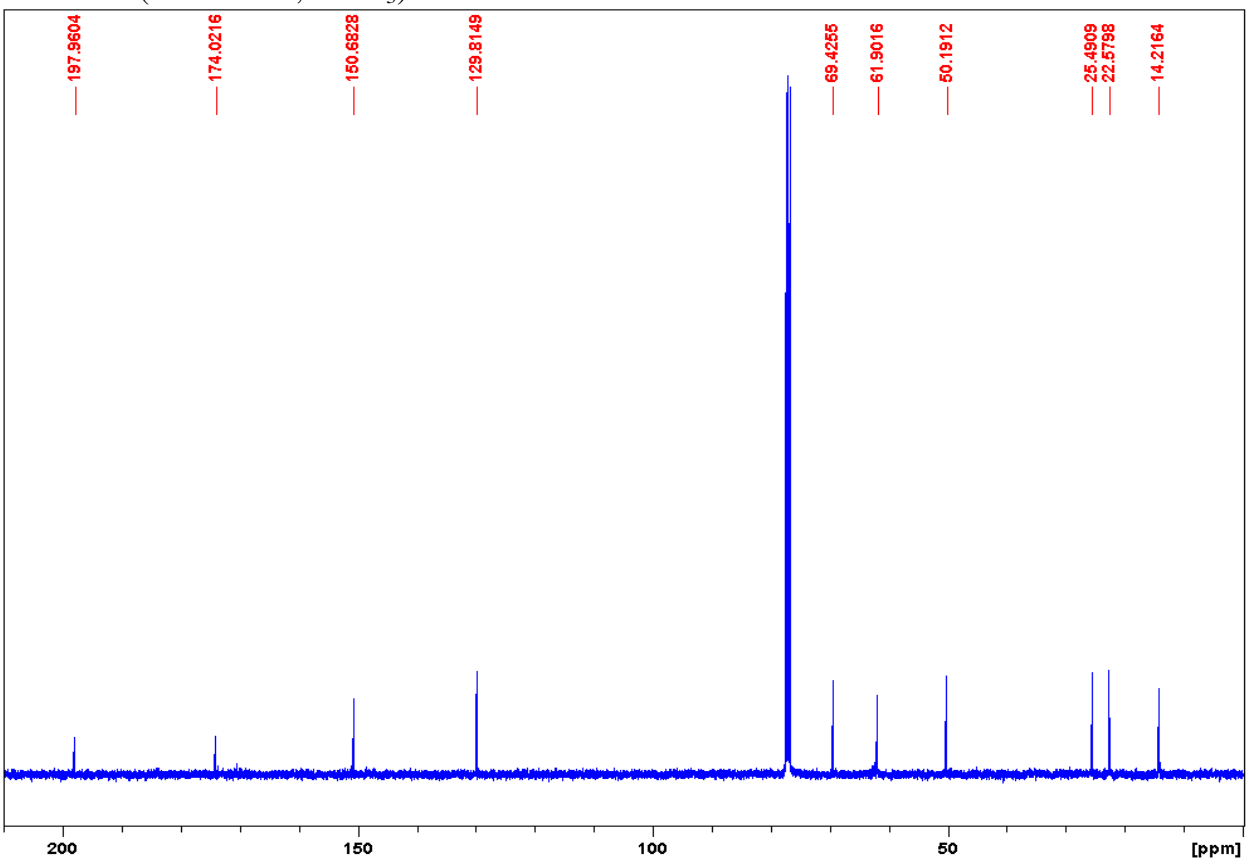
^{13}C NMR (100.6 MHz, $CDCl_3$)



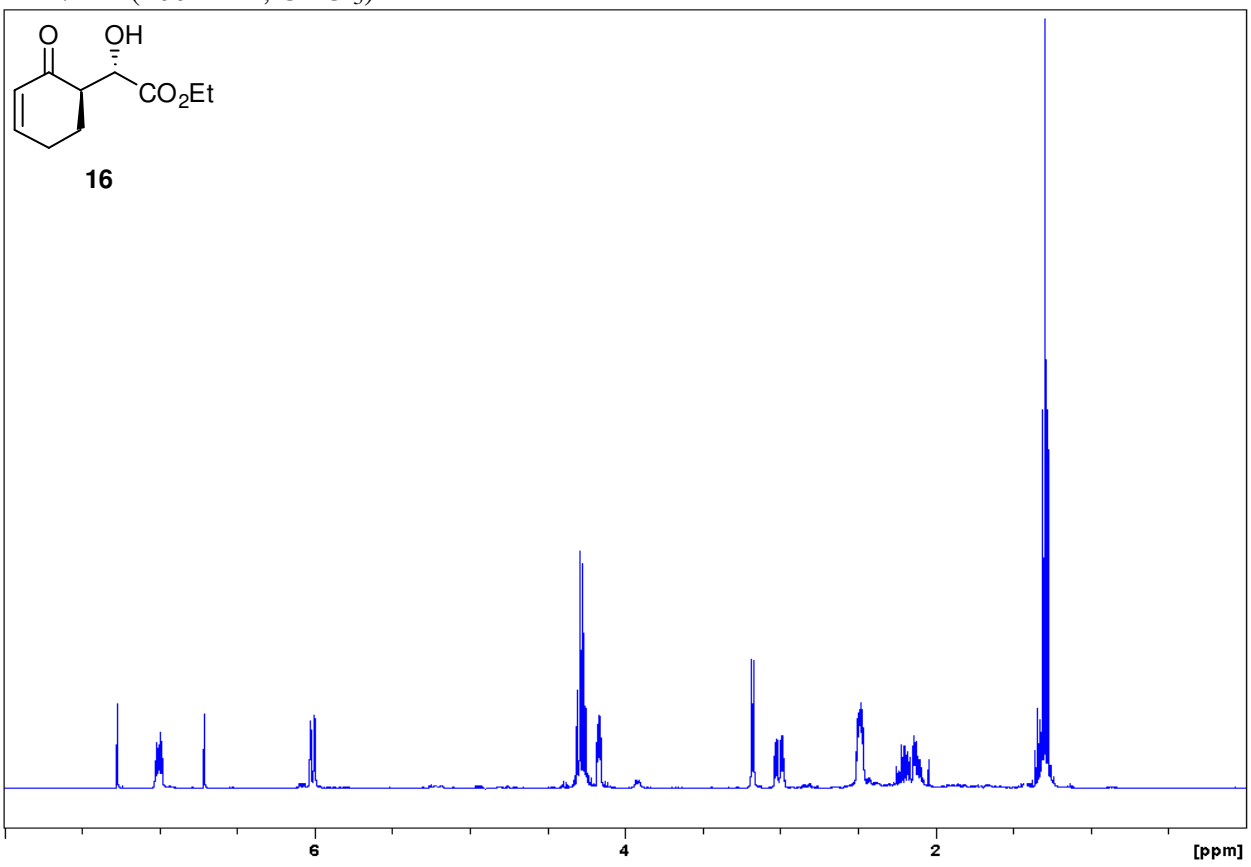
^{1}H NMR (400 MHz, $CDCl_3$)



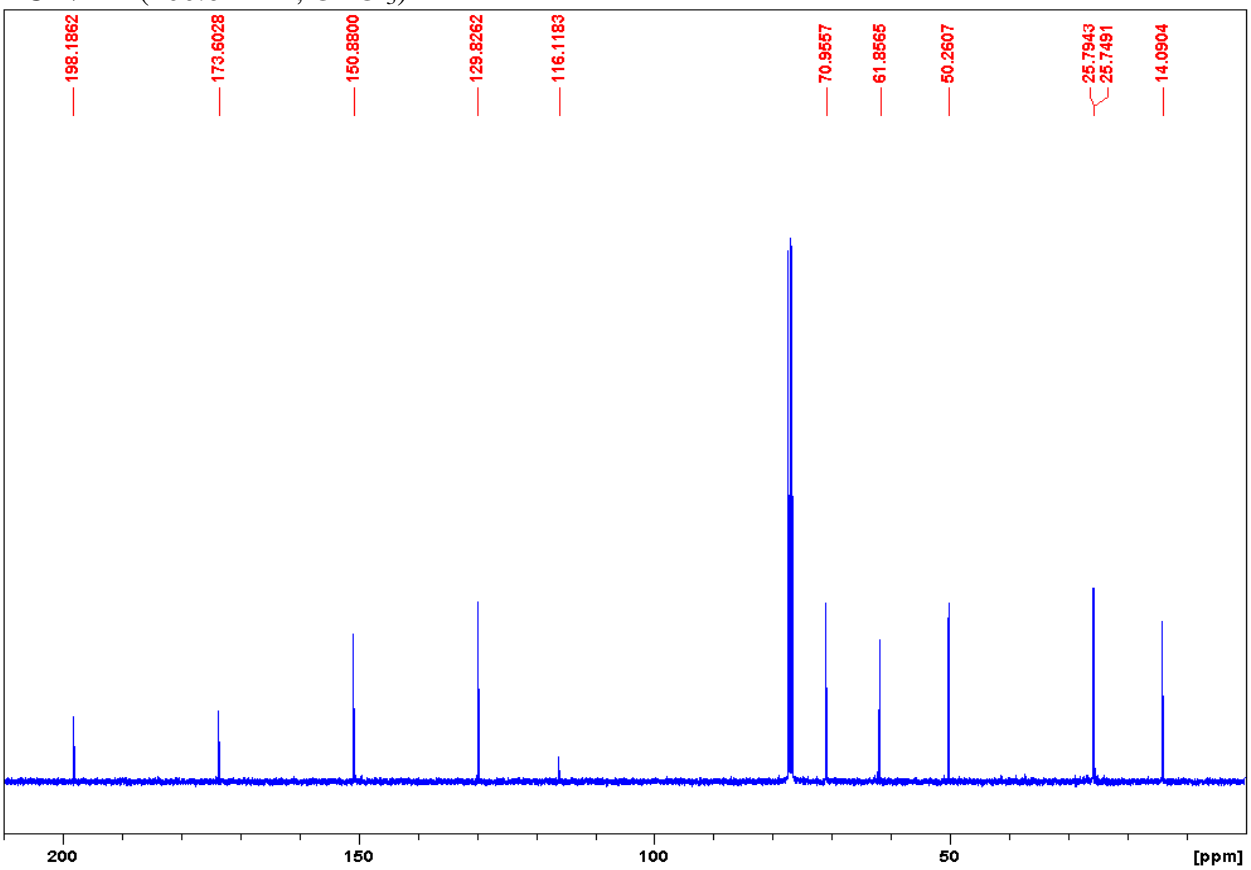
^{13}C NMR (100.6 MHz, $CDCl_3$)



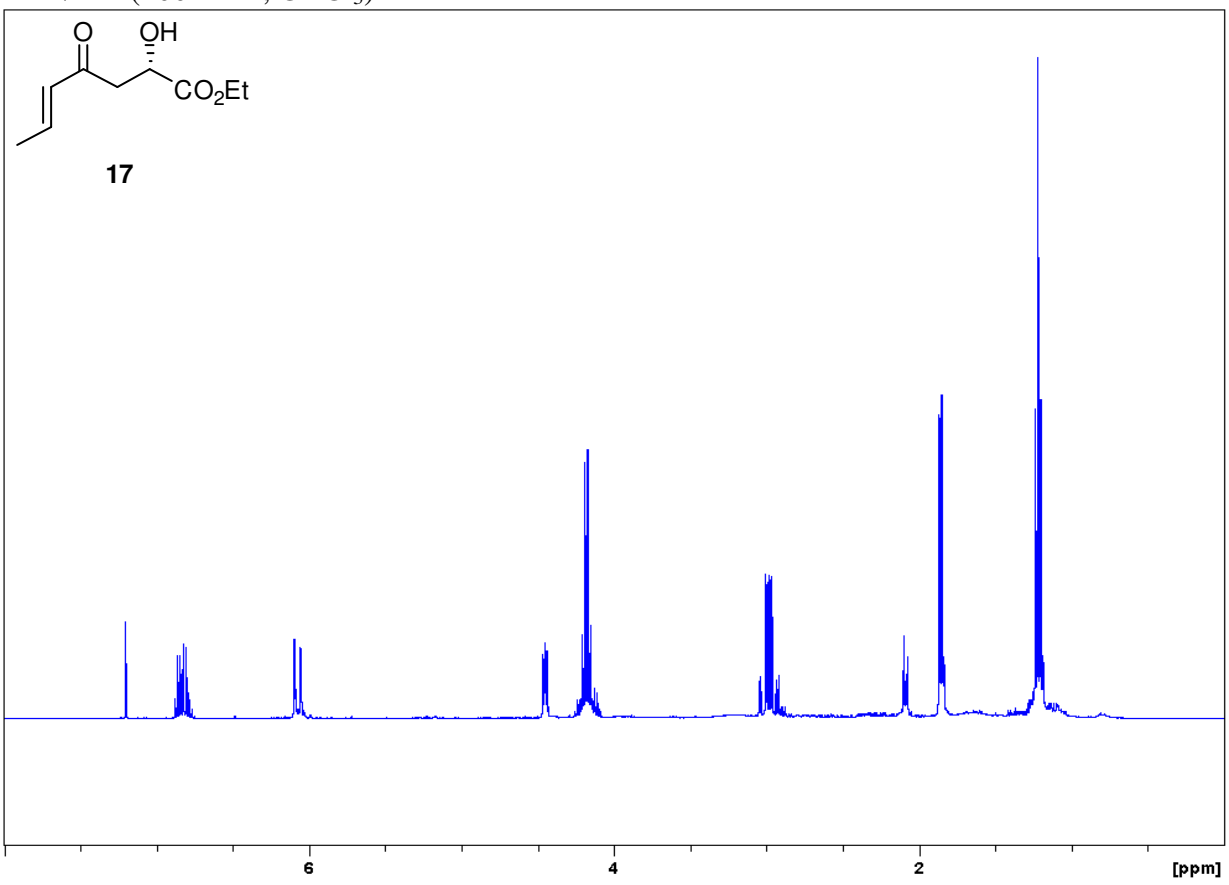
^{1}H NMR (400 MHz, $CDCl_3$)



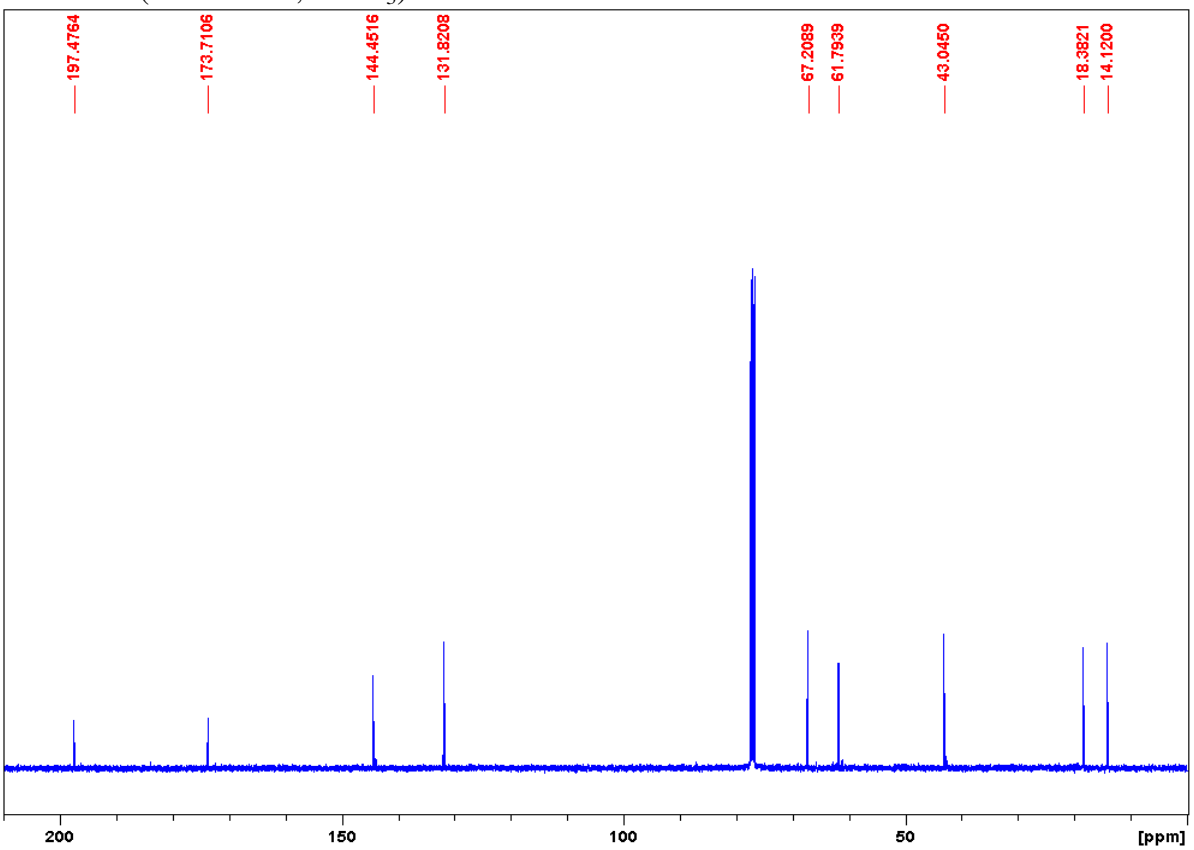
^{13}C NMR (100.6 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100.6 MHz, $CDCl_3$)



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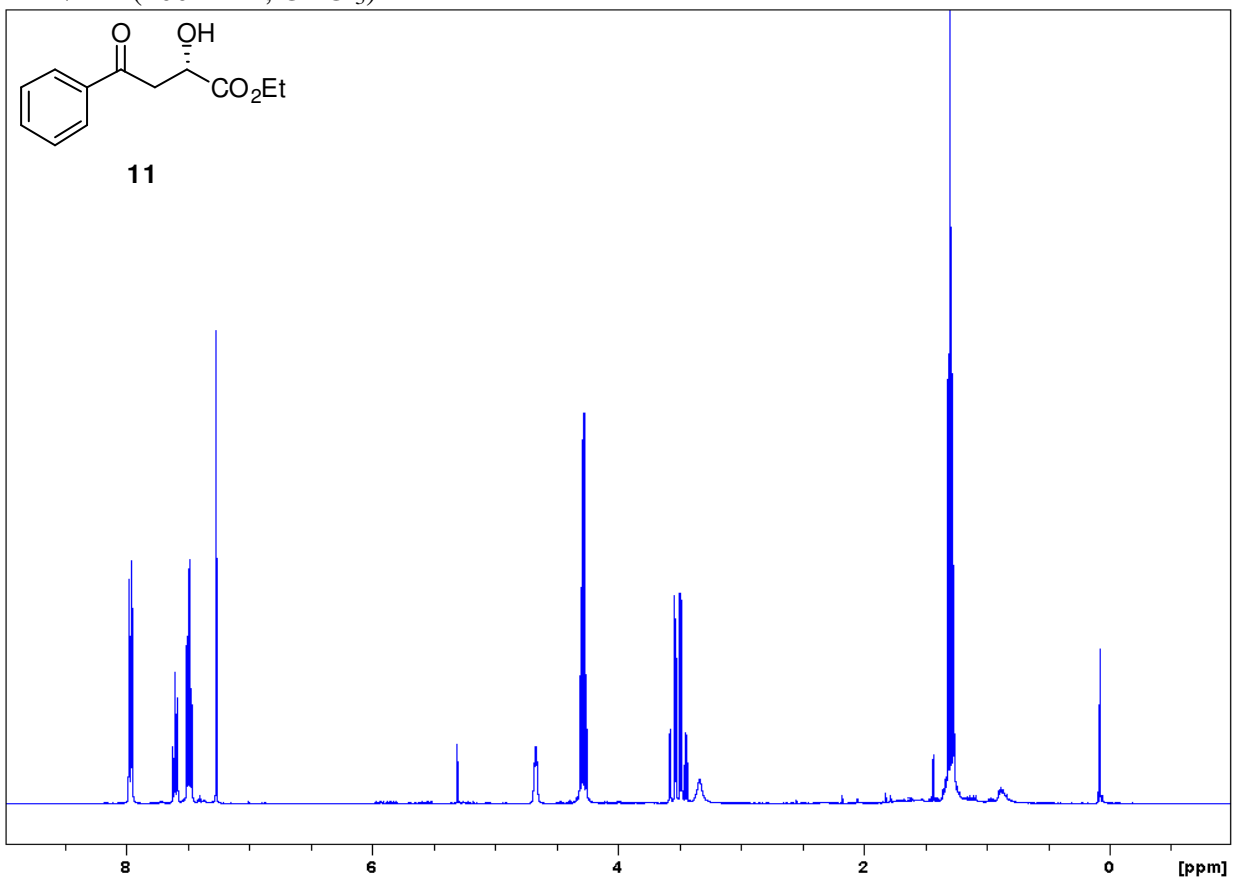

^{13}C NMR (100.6 MHz, $CDCl_3$)