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The First organocatalytic asymmetric synthesis of 3-substituted isoindolinones.

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General remarks. All reactions were performed using commercially available compounds without further purification. Organocatalysts were synthesized according to know procedures.[1,2] 2-Cyanobenzaldehydes **1b**, **1c** and **1d** were prepared following literature procedures.[3-6] Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300MHz, 250MHz, ^{1}H; 100 MHz, 75MHz, 62,5MHz ^{13}C) and Varian AV-300 or AV-400 MHz. Spectra were referenced to residual $CHCl_3$ (7.26 ppm, ^{1}H, 77.23 ppm, ^{13}C). Coupling constants *J* are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. E.e.s were determined with chiral HPLC analysis were performer with Water dual λ 2478 model employing chiral columns. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole. Exact masses (HRMS) were recorded on a *Bruker Daltonics MicroTof* spectrometer (samples in CH_3OH as solvent). Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus

Typical experimental procedure for enantioselective synthesis of 3-substituted isoindolinones 3. In a round-bottom flask, aldehyde **1** (0.2 mmol) was added to a solution of malonate esters **2** (1.2 eq, 0.24 mmol) and catalyst (5% mol) in dichloromethane (1.0 or 4.0 mL). The reaction was monitored by TLC and after the reported reaction time, the mixture was poured directly on chromatographic column and purified with 1/1 mixture of hexane / AcOEt to afford the pure products **3**.

Typical experimental procedures for crystallization of 3. The title compound (20 mg) was dissolved at room temperature in DCM (0.3 mL) and hexane (0.2 mL) and the solution was left at -18°C for **3a**, at 4°C overnight for **3f**, or by slow diffusion overnight of pentane into a solution of **3b** and **3c** in DCM at room temperature. Then the solution was separated from the solid and evaporated under reduced pressure. The resulting solid was characterised and analysed by chiral HPLC.

Preliminary experiments in the presence of quinine derivatives.

Table 1: **3a** synthesis in preliminary experiments in the presence of 0.1 eq. of quinine

Entry	solvent	Time (h)	T °C	Yield[a]	e.e.[b]
1	DCM	8	r.t	96	10
2	DCM	24	-20	90	10
3	DCM	5 days	-60°C	42	0
4[c]	DCM	48	r.t.	80	8
5	toluene	18	r.t.	96	0
6	DMSO	18	r.t	0	--
7	DMF	18	r.t	0	--
8	THF	24	r.t	32	0
9	MeOH	8	r.t	85	10

[a] Yields refer to chromatographically pure compounds
[b] Determined by chiral HPLC
[c] Reaction performed on 0.2 mmol scale of 2-cyanobenzaldehyde at 0.04 M instead of 0.2 M for all the other experiments.

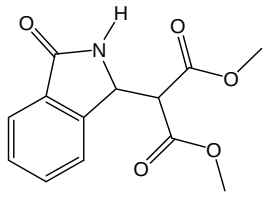
Table 2: **3a** synthesis in preliminary experiments in the presence of 0.1 eq. of other cinchona alkaloids in DCM.

Entry	solvent	Time (h)	T °C	Yield[a]	e.e.[b]
1	cupreidine	24	r.t	95	-10
2	cupreidine	24	-20	97	-10
3	quinidine	5	r.t	83	- 10
4	cinchonine	24	r.t.	85	-5
5	cinchonidine	24	r.t.	95	+5

[a] Yields refer to chromatographically pure compounds
[b] Determined by chiral HPLC

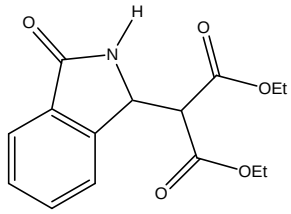
Spectroscopic and analytical data of isoindolinones 3.

(3a) Dimethyl 2-(1-oxoisoindolin-3-yl)malonate:



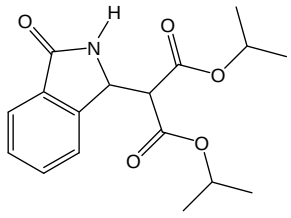
Chromatography: pentane/ethyl acetate 1:1; white solid, yield: 80% (105 mg, 0.5 mmol scale), 81:19 (62% ee), 36 h @ 55 °C == Recryst from DCM/hexane: 58.5 mg, 56%; solution 99.5:0.5 (99% ee), $[\alpha]_D$ = -74 (*c* 0.2, $CHCl_3$). This compound was characterised comparing the spectroscopic data with those reported in ref 7. HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 70:30, F = 1.0 mL/min, λ = 230 nm, t_R minor = 10.7 min, t_R major = 16.6 min., or Chiralpack AD, Hexane:*i*-PrOH 80:20, 1.0 mL/min, λ = 254 nm, t_R minor = 19.7 min, t_R major = 29.8 min

(3b) Diethyl-2-(1-oxoisoindolin-3-yl)malonate:



Chromatography: hexane/ethyl acetate 1:1; very viscous oil, yield: 99%, (58 mg, 0.2 mmol scale). ^{1}H NMR ($CDCl_3$: 300 MHz) δ 7.81 (d, *J*=8.4 Hz, 1H), 7.45 (m, 2 H), 7.35 (d, *J*=8.4 Hz,1H), 7.20 (s, 1H), 5.16 (d, *J*=8.1 Hz, 1H), 4.27 (q, *J*=8.1 Hz, 2H), 4.07 (q, *J*=8.1 Hz, 2H), 3.64 (d, *J*=8.1 Hz, 1H), 1.25 (t, *J*=8.1 Hz, 3H), 1.08 (t, *J*=8.1 Hz, 3H). ^{13}C NMR ($CDCl_3$: 100 MHz) δ 171.3, 168.6, 167.8, 145.0, 133.4, 133.2, 130.1, 125.2, 124.3, 63.4, 63.3, 57.2, 56.1, 15.2, 15.0. IR (KBr): 3247, 2985, 2911, 2854, 1721, 1676, 1481, 1349, 1200, 1086, 1007, 695. MS (ESI): *m*/*z* = 292 ($M + H^+$). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61,85; H, 5,88; N, 4,81. Found: C, 61,75; H, 5,80; N, 4,93. HPLC: Chiralpack AD column, 80/20 hexane/ *i*PrOH, 0.8 mL/min (t_{minor} =17.16, t_{major} = 20.38). $[\alpha]_D$ = -38 (*c* 1.0, $CHCl_3$)

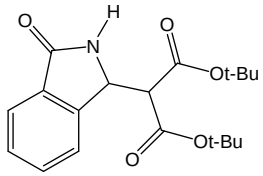
(3c) Di-iso propyl 2-(1-oxoisoindolin-3-yl)malonate:



Chromatography: hexane/ethyl acetate 1:1; very viscous oil, yield: 98%, (63 mg, 0.2 mmol scale). ^{1}H NMR ($CDCl_3$: 400 MHz) δ 7.81 (d7.52, *J*=8.0 Hz, 1H), -7.44 (m, 2 H), 7.38 (d, *J*=8.0 Hz, 1H), 7.05 (s, 1H), 5.14-5.11 (m, 2H), 4.93-4.88 (m, 1H), 3.60 (d, *J* = 4.0 Hz, 1H), 1.25-1.21 (m, 6H), 1.09-1.05 (m, 6H). ^{13}C NMR ($CDCl_3$: 100 MHz) δ 171.2, 168.2, 167.3, 145.1, 133.3, 133.1, 130.1, 125.1, 124.3, 71.2, 71.1, 57.4, 56.0, 22.8, 22.7,

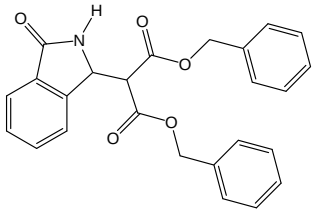
22.6, 22.5. IR (KBr): 3237, 2982, 2925, 2854, 1731, 1676, 1470, 1359, 1308, 1204, 1096, 1017, 751, 695.MS (ESI): m/z = 320 (M + H^+). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.84; H, 6.85; N, 4.27. HPLC: Chiralpack AD-H column, 95/5 hexane/ *i*PrOH, 0.8 mL/min. 81% e.e (t_{major} =75.10, t_{minor} = 79.79). $[\alpha]_D$ = -56 (*c* 1.0, $CHCl_3$)

(3d) Di-tert-butyl 2-(1-oxoisoindolin-3-yl)malonate:



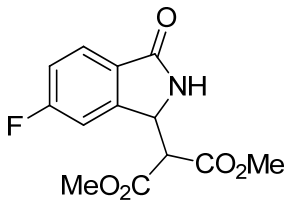
Chromatography: hexane/ethyl acetate 1:1; very viscous oil, yield: 87%, (60 mg, 0.2 mmol scale). ^{1}H NMR ($CDCl_3$: 300 MHz) δ 7.84 (d, *J*=8.0 Hz, 1H), 7.56-7.46 (m, 2 H), 7.43 (d, *J*=8.0 Hz, 1H), 6.82 (s, 1H), 5.08 (d, *J*=8.0 Hz, 1H), 3.52 (d, *J*=4.0 Hz, 1H), 1.50 (s, 9H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$: 100 MHz) δ 169.8, 166.7, 165.6, 144.0, 132.1, 131.1, 128.6, 123.7, 123.1, 82.9, 82.7, 57.5, 54.7, 27.7, 27.5. IR (KBr): 3220, 2972, 2854, 1705, 1618, 1470, 1359, 1308, 1204, 1096, 1017, 751, 695. MS (ESI): m/z = 348 (M + H^+). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.61; H, 7.18; N, 4.09. HPLC separation. Chiralpack AD-H column, 9/1 hexane/ *i*PrOH, 0.6 mL/min. (t_{minor} =25.22, t_{major} = 29.1). $[\alpha]_D$ = -34 (*c* 1.0, $CHCl_3$)

(3e) Di-benzyl 2-(1-oxoisoindolin-3-yl)malonate:



Chromatography: hexane/ethyl acetate 1:1; white solid, yield= (77 mg) 92 % yield: 92%, (77 mg, 0.2 mmol scale). m.p.=122-126°C. Recrystallization from DCM/Hexane, 37 mg (from 77 mg), 45%; solution 0.5:99.5 (>99% ee), ^{1}H NMR ($CDCl_3$: 300 MHz) δ 7.80 (d, *J*=6.0 Hz, 1H), 7.45-7.39 (m, 2 H), 7.36-7.30 (m, 6H), 7.26-7.15 (m, 3H), 6.83 (s,1H), 5.26 (s, 2H), 5.18 (d, *J*=9.0 Hz, 1H), 5.07 (s, 2H), 3.71 (d, *J*=9.0 Hz, 1H. ^{13}C NMR ($CDCl_3$: 100 MHz) δ 170.8, 168.3, 167.6, 144.9, 136.1, 136.0, 133.3, 133.1, 130.1, 129.8, 129.8, 129.7, 129.6, 129.4, 125.0, 124.2, 69.1, 68.9, 57.2, 56.0. IR (KBr): 3200, 2982, 2854, 1720, 1662, 1475, 1389, 1306, 1224, 1066, 1010, 800, 686. MS (ESI): m/z = 416 (M + H^+). Anal. Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 72.37; H, 5.03; N, 3.30. HPLC separation. Chiralpack AD-H column, 75/25 hexane/ *i*PrOH, 0.5 mL/min. >99% e.e. (t_{minor} =38.35, t_{major} = 41.49). $[\alpha]_D$ = -23 (*c* 1.0, $CHCl_3$).

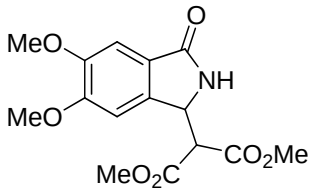
(3f) Dimethyl 2-(6-fluoro-3-oxoisoindolin-1-yl)malonate:



Chromatography: pentane/ethyl acetate 1:1; white solid, yield: 98%, (55 mg, 0.2 mmol scale), 21:79 e.r. (58% ee), 72 h @ 50 °C. Recrystallization from DCM/Pent: 19.1 mg (from 50 mg, 58% ee), 38%; solution 4.5:95.5 (91% ee), $[\alpha]_D$ = -60.5 (*c* 1.5, $CHCl_3$). M.p. = 174 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.75 (s, 1H), 7.67 (dd, *J* = 8.3, 5.2 Hz, 1H), 7.38 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.35 – 7.26 (m, 1H), 5.15 (d, *J* = 4.7 Hz, 1H), 4.26 (d, *J* = 4.7 Hz, 1H), 3.65 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 167.2, 166.6, 164.2 (d, *J* = 247.7 Hz), 147.0 (d, *J* = 10.3 Hz), 129.1 (d, *J* = 1.9 Hz), 125.1 (d, *J* = 10.0 Hz), 116.2 (d, *J* = 23.5 Hz), 110.9 (d, *J* = 24.7 Hz), 54.4 (d, *J* = 2.6 Hz), 54.2, 52.7, 52.5; ^{19}F NMR (282 MHz, DMSO-d_6): δ -108.4; IR (ATR) ν_{max} 3190, 3084, 1746, 1697, 1433, 1264, 1201, 1000, 865 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{12}FNO_5 \cdot Na^+$ $[M+Na]^+$ 304.0592; found 304.0601. HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 70:30, F = 1.0 mL/min, λ = 230 nm, t_R minor = 7.9 min, t_R major = 9.8 min.

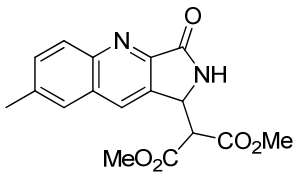
Reaction with catalyst **5**: Recrystallization from DCM/Pent: 17 mg (from 48 mg, -43% ee), 36%; solution 90:10 e.r., $[\alpha]_D$ = +55 (*c* 0.4, $CHCl_3$).

(3g) Dimethyl 2-(5,6-dimethoxy-3-oxoisoindolin-1-yl)malonate:



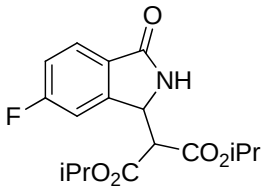
Chromatography: pentane/ethyl acetate 1:2; white solid, yield: 40%, (26 mg, 0.2 mmol scale), 30:70 e.r. (40% ee), 96 h @ 50 °C. Recrystallization from DCM/Pent: 3.5 mg (from 25 mg), 14%; solution 5:95 (90% ee), $[\alpha]_D$ = -51 (*c* 0.2, $CHCl_3$). M.p. = 179 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 5.09 (d, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 3.58 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 168, 167.4, 153.0, 150.5, 137.4, 124.4, 105.5, 105.2, 56.3, 56.3, 56.2, 54.6, 53.3, 53.1; IR (ATR) ν_{max} 3179, 3072, 2968, 1749, 1688, 1436, 1275, 1068, 871 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{17}NO_2{\cdot}Na^+$ $[M+Na]^+$ 346.0897; found 346.0899. HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 70:30, F = 1.0 mL/min, λ = 230 nm, t_R minor = 11.3 min, t_R major = 12.7 min.

(3h) Dimethyl 2-(7-methyl-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)malonate



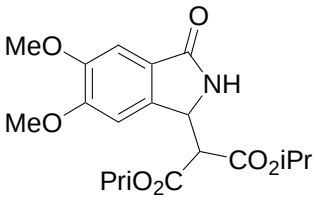
Chromatography: pentane/ethyl acetate 1:2 to ethyl acetate; white solid, yield: 81% (53 mg, 0.2 mmol scale), 71:29 e.r. (42% ee) @ rt, 18 h. Recrystallization from MeCN/MeOH/DCM: 5 mg (from 14 mg, 42% ee), 36%; solution 10:90 e.r. (80% ee), $[\alpha]_D$ = -86.5 (*c* 0.1, $CHCl_3$). M.p. = 249 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.3 Hz, 1H), 8.11 (s, 1H), 7.70 – 7.62 (m, 2H), 7.46 (br s, 1H), 5.37 (d, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 167.6, 167.2, 149.7, 147.9, 139.1, 133.4, 132.7, 131.2, 130.5, 128.8, 127.1, 56.2, 53.5, 53.4, 52.9, 21.9; IR (ATR) ν_{max} 3181, 3101, 1721, 1697, 1431, 1322, 1237, 1160, 820 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{16}N_2O_5{\cdot}Na^+$ $[M+Na]^+$ 351.0951; found 351.0954. HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 60:40, F = 0.9 mL/min, λ = 230 nm, t_R minor = 10.7 min, t_R major = 30.1 min.

(3i) Dimethyl 2-(6-fluoro-3-oxoisoindolin-1-yl)malonate



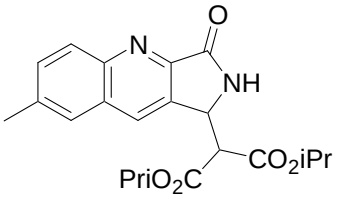
Chromatography: pentane/ethyl acetate 3:1; white solid, yield: 99%, (67 mg, 0.2 mmol scale), 11:89 e.r. (78% ee), 48 h @ 50 °C. $[\alpha]_D$ = -53.9 (*c* 1.7, $CHCl_3$). M.p. = 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 8.4, 5.1 Hz, 1H), 7.19 (td, *J* = 8.7, 2.2 Hz, 1H), 7.10 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.91 (s, 1H), 5.25 – 5.06 (m, 2H), 4.97 (hept, *J* = 6.3 Hz, 1H), 3.58 (d, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 2.3 Hz, 3H), 1.27 (d, *J* = 2.2 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 167.0, 166.1, 165.4 (d, *J* = 252.2 Hz), 146.5 (d, *J* = 9.9 Hz), 128.4, 126.18 (d, *J* = 9.8 Hz), 116.9 (d, *J* = 23.4 Hz), 110.9 (d, *J* = 24.7 Hz), 70.3,70.3, 56.4, 54.6 (d, *J* = 2.7 Hz), 21.8, 21.6, 21.6, 21.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ -106.35; IR (ATR) ν_{max} 3217, 3090, 2983, 1701, 1237, 1180, 1098 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{20}FNO_5{\cdot}Na^+$ $[M+Na]^+$ 360.1218; found 360.1214. HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 95:5, F = 0.8 mL/min, λ = 230 nm, t_R minor = 42.0 min, t_R major = 49.3 min.

(3j) Diisopropyl 2-(5,6-dimethoxy-3-oxoisoindolin-1-yl)malonate:



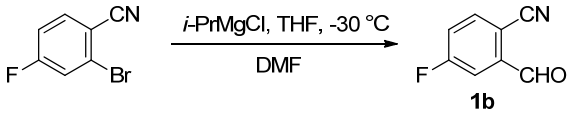
Chromatography: pentane/ethyl acetate1:1; clear oil, yield: 47%, (36 mg, 0.2 mmol scale), 34:66 e.r. (32% ee), 96 h @ 50 °C. $[\alpha]_D$ = -19.9 (*c* 1.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 6.83 (s, 1H), 6.71 (brs, 1H), 5.12 (hept, *J* = 6.3 Hz, 1H), 5.04 (d, *J* = 7.1 Hz, 1H), 4.95 (hept, *J* = 6.3 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H) 3.52 (d, *J* = 7.2 Hz, 1H), 1.26 (d, *J* = 2.0 Hz, 3H), 1.25 (d, *J* = 2.0 Hz, 3H), 1.13 (d, *J* = 5.6 Hz, 3H), 1.11 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 167.2, 166.3, 152.9, 150.4, 137.7, 124.6, 105.4, 105.4, 70.1, 70.1, 56.6, 56.3, 56.3, 54.5, 21.8, 21.6, 21.6, 21.6; IR (ATR) ν_{max} 3357, 3219, 2982, 1692, 1286, 1217, 1099, 732 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{25}NO_7 \cdot Na^+$ $[M+Na]^+$ 402.1523; found 402.1516. HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 90:10, F = 1.0 mL/min, λ = 230 nm, t_R minor = 30.4 min, t_R major = 35.0 min.

(3k) Dimethyl 2-(7-methyl-3-oxo-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-yl)malonate



Chromatography: pentane/ethyl acetate 1:1; white solid, yield: 82%, (32 mg, 0.1 mmol scale), 67.2:32.8 e.r. (34% ee), 144 h @ 50 °C. $[\alpha]_D$ = -47.6 (*c* 1.4, $CHCl_3$). M.p. = 207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.1 Hz, 1H), 8.15 (s, 1H), 7.68 – 7.59 (m, 2H), 7.36 (br s, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 5.20 (hept, *J* = 6.3 Hz, 1H), 5.00 (hept, *J* = 6.3 Hz, 1H), 3.67 (d, *J* = 7.0 Hz, 1H), 2.58 (s, 4H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 4H), 1.15 (d, *J* = 1.9 Hz, 3H), 1.13 (d, *J* = 1.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 166.9, 166.3, 149.5, 147.9, 139.0, 133.3, 132.9, 131.2, 130.5, 128.8, 127.0, 70.6, 70.4, 56.7, 52.8, 21.9, 21.8, 21.7, 21.6; IR (ATR) ν_{max} 3190, 3110, 2982, 1723, 1170, 1101, 823 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{24}N_2O_5 \cdot Na^+$ $[M+Na]^+$ 407.1577; found 407.1573. HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 80:20, F = 1.0 mL/min, λ = 230 nm, t_R minor = 20.8 min, t_R major = 14.9 min

Synthesis of 4-fluoro-2-formylbenzonitrile (1b) [3]

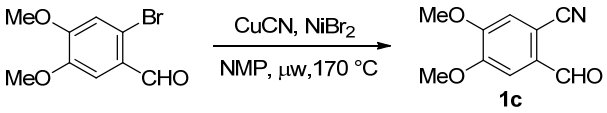


1b

To a solution of 2-bromo-4-fluorobenzonitrile (500 mg, 2.5 mmol) in dry THF (20 mL) at -30 °C, *i*-PrMgCl (1M in THF, 3 mL, 1.2 equiv.) was added. After 3 h stirring at this temperature, DMF (580 µL, 3 equiv.) was added. The reaction was allowed to warm to 0 °C, HCl (2M, 4 mL) was added and the reaction was stirred for 20 min. The reaction mixture was concentrated under reduced pressure and the residue was puridied by column chromatography on silica gel (pentane:ethyl acetate 1:6 to 1:3) to give **1b** as a pale yellow solid (264 mg, 71%). M.p. = 93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.34 (d, *J* = 2.5 Hz, 1H), 7.87 (dd, *J* = 8.5, 4.8 Hz, 1H), 7.74 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.4, 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.3 (d, *J* = 1.5 Hz), 165.2 (d, *J* = 260.2 Hz), 139.7 (d, *J* = 7.4 Hz), 136.5 (d, *J* = 8.8 Hz), 122.0 (d, *J* = 23.1 Hz), 116.5 (d, *J* = 23.6 Hz), 115.3, 110.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ -

106.4; IR (ATR) ν_{max} 2231, 1702, 1600, 1579, 1494, 1385, 1243, 1153, 949, 889, 853, 782 cm^{-1}; HRMS (ESI): calcd for $C_8H_4FNO{\cdot}Na{\cdot}MeOH^+$ $[M+Na+MeOH]^+$ 204.0431; found 204.0433.

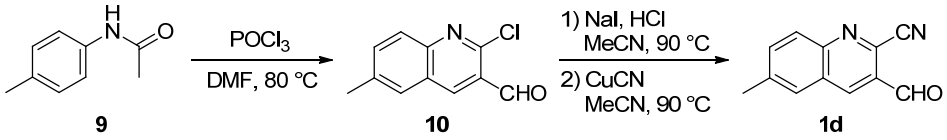
Synthesis of 2-formyl-4,5-dimethoxybenzonitrile (1c) [4]



1c

2-Bromo-4,5-Dimethoxybenzaldehyde (1.00 g, 4.0 mmol), CuCN (2.19 g, 24.48 mmol), and $NiBr_2$ (357 mg, 1.64 mmol) were dissolved in 50 mL NMP. The reaction mixure irradiated in a microwave for 4.5 min at 170° C. After the reaction was completed the reaction mixture was poured into water (250 mL) and extracted with CH_2Cl_2 (3x250 mL). After Evaporation of the solvent the Metall was removed by a short filtration over Silica. The solvent were removed and the product were precipitate from the NMP and water the crude product was dissolved in CH_2Cl_2 and dried over Na_2SO_4, evaporated in vacuo and purified by chromatography over silicagel (Hexane/EtOAc, 7/3). The product **1c** was isolated as a white solid (564 mg, 74%). M.p. = 145 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.27 (s, 1H), 7.49 (s, 1H), 7.18 (s, 1H), 4.00 (d, *J* = 0.6 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 187.7, 153.8, 153.0, 131.9, 116.2, 114.5, 109.5, 108.4, 56.8, 56.6; IR (ATR) ν_{max} 2221, 1685, 1585, 1512, 1290, 1225, 1093, 988, 882, 753 cm^{-1}; HRMS (ESI): calcd for $C_{10}H_9NO_3{\cdot}Na^+$ $[M+Na]^+$ 214.0475; found 214.0474.

Synthesis of 3-formyl-6-methylquinoline-2-carbonitrile (1d) [5, 6]



9 **10** **1d**

To a solution of 4-tolylaniline (1.4 g, 13 mmol) and DMAP (1.6 g, 1 equiv.) in DCM, Ac2O (1.5 mL, 1.2 equiv.) was added. The reaction was stirred at room temperature for xx h. The solvent was removed and the residue was purified by column chromatography on silica gel (pentane: ethyl acetate 1:6) to give **9** as a white solid (1.8 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 – 7.51 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.30 (s, 1H), 2.14 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 135.4, 134.1, 129.5, 120.3, 24.5, 21.0.

To an ice-cooled solution of DMF (1.6 mL, 3 equiv.) was added dropwise with stirring $POCl_3$ (4.3 mL, 7 equiv.). Acetamide **9** (1.0 g, 6.7 mmol, 1 equiv.) was then added and the reaction was warmed to 80 °C and stirred for 18 h. The reaction mixture was then pured into ice-water and stirred for 30 min at 0 °C. The precipitated product **10** was collected by filtration, washed with water and dried under air (800 mg, 58 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.48 (s, 1H), 8.60 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.73 – 7.56 (m, 2H), 2.50 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.5, 149.4, 148.4, 139.8, 138.6, 136.2, 128.6, 128.3, 126.7, 126.4, 21.7; IR (ATR) ν_{max} 2878, 1689, 1578, 1368, 1336, 1056, 935, 820, 736 cm^{-1}; HRMS (ESI): calcd for $C_{11}H_8ClNO{\cdot}Na{\cdot}CH_3OH^+$ $[M+Na+MeOH]^+$ 260.0449; found 260.0446.

2-Chloroquinoline **10** (500 mg, ca. 2.4 mmol, 1 equiv.), NaI (2.5 g, 7 equiv.) and conc. HCl (0.1 mL) were taken in MeCN (15 mL). The reaction was heated at 90 °C for 18 h, then diluted with water and filtered. The product was

washed with sat. $NaHCO_3$ solution, followed with water till the washings were neutral. The compound was then dried under vacuum to give the corresponding iodoquinoline **11**, which was use without further purification in the next step.

To a solution of 2-iodoquinoline **11** (ca. 2.4 mmol) in MeCN (10 mL), CuCN (260 mg, 1.2 equiv.) was added, and the reaction was heated at 90 °C for 16 h. The reaction mixture was then diluted with water and extracted with AcOEt, the combined organic layer was dried over $MgSO_4$, the solvent removed under vacuum and the residue was purified by column chromatography on silica gel (pentane:ethyl acetate 1:6 to 1:3) to give the corresponding cyano-quinoline **1d** as a pale yellow solid (150 mg, 0.77 mmol, 32% 2 steps). M.p. = 208 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.44 (s, 1H), 8.67 (s, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.84 – 7.66 (m, 2H), 2.57 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 148.5, 141.6, 138.3, 136.6, 132.1, 129.7, 128.9, 128.2, 127.8, 115.2, 21.9; IR (ATR) ν_{max} 2232, 1699, 1559, 1374, 1122, 830, 792 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_8N_2O{\cdot}Na^+$ $[M+Na]^+$ 219.0529; found 219.0533.

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1) B. Vakulya, S. Varga, A. Csampai, T. Soos *Org. Lett.* **2005,** *7*, 1967.
2) Synthesis of catalyst **6**: J.-R. Chen, Y.-J. Cao, Y.-Q. Zou, F. Tan, L. Fu, X.-Y. Zhu, W.-J. Xiao, *Org. Biomol. Chem.* **2010**, *8*, 1275.
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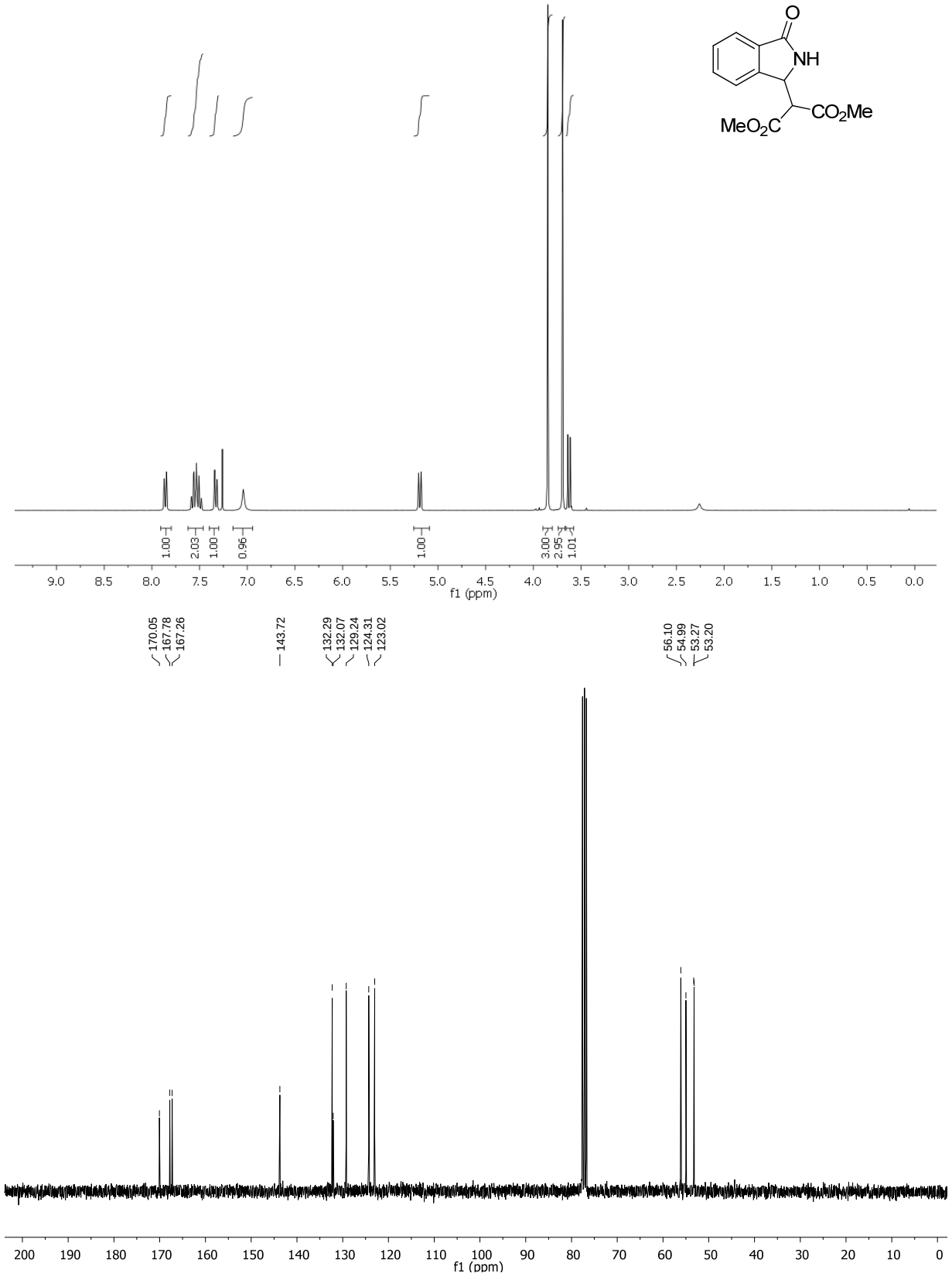
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167.78
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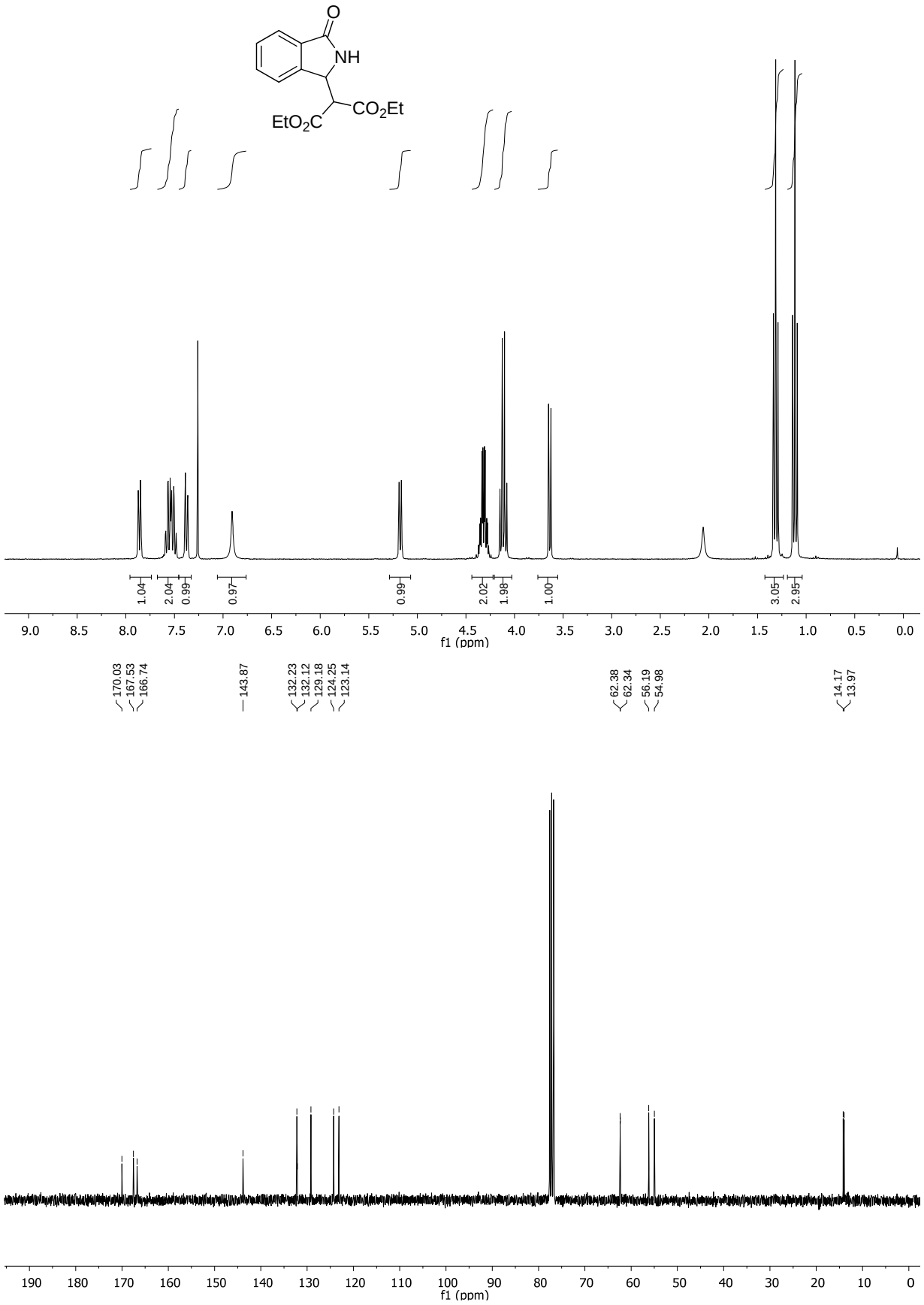
53.20
f1 (ppm)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f1 (ppm)
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167.53
166.74
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132.23
132.12
129.18
124.25
123.14
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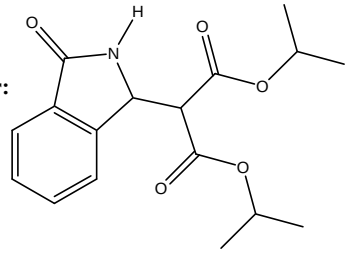
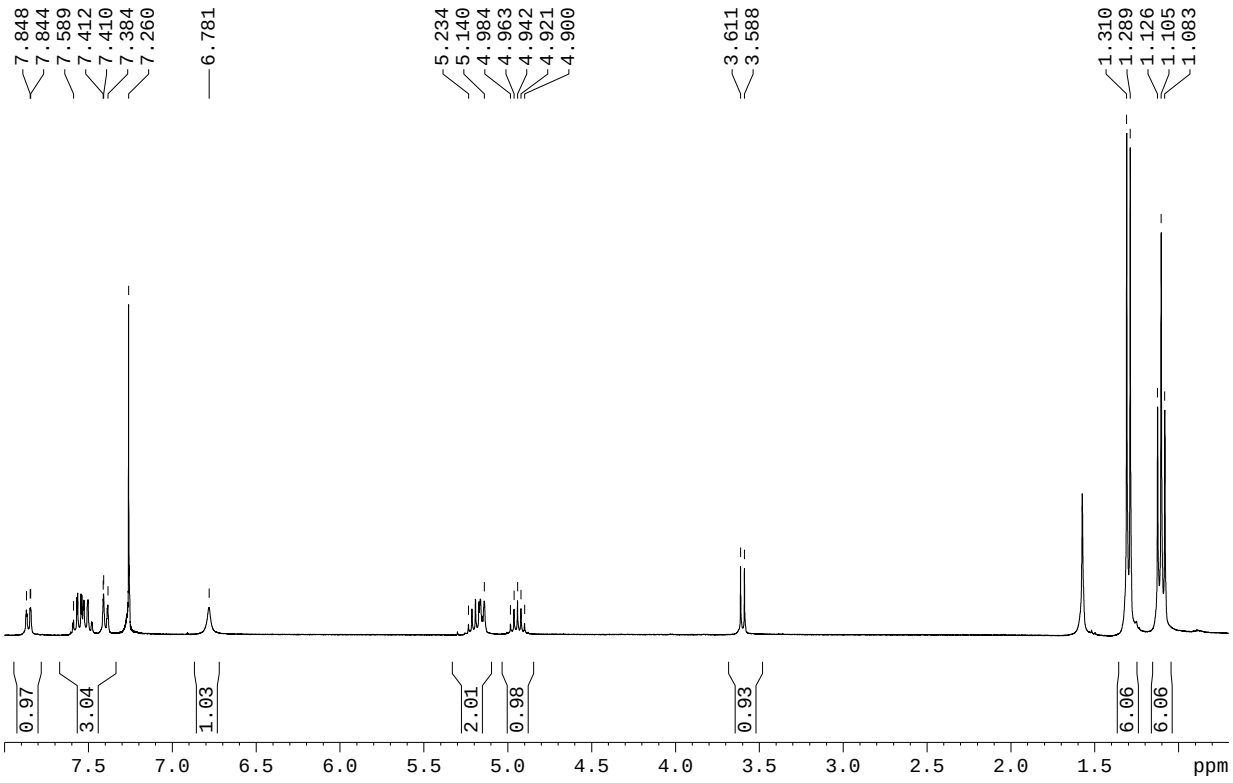
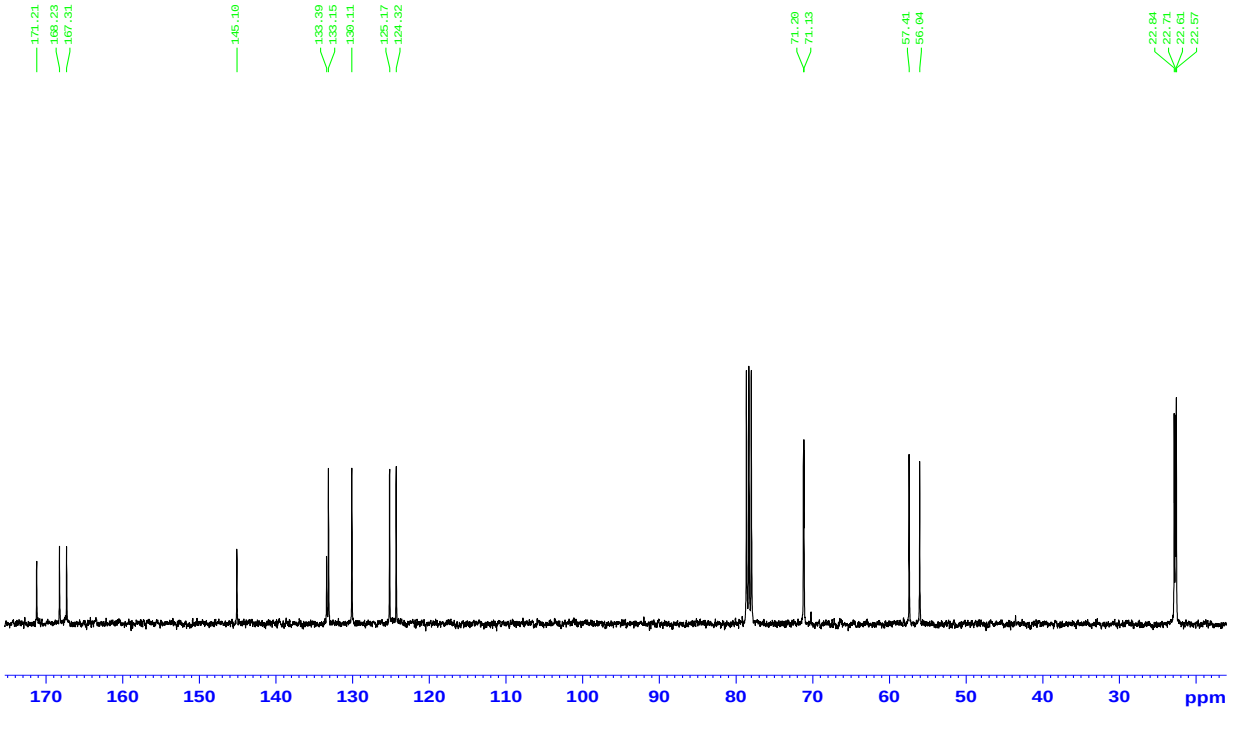
f1 (ppm)

^{1}H and ^{13}C-NMR in $CDCl_3$ for:







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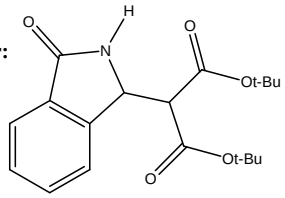

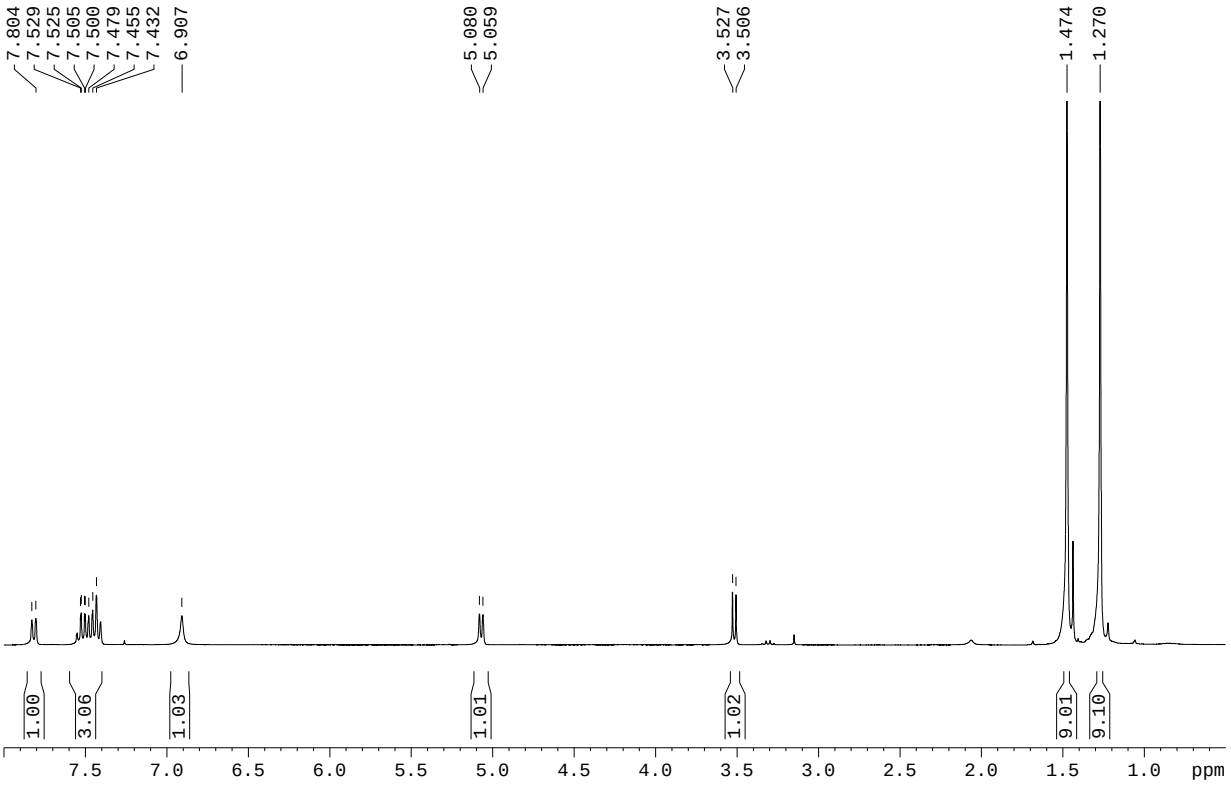

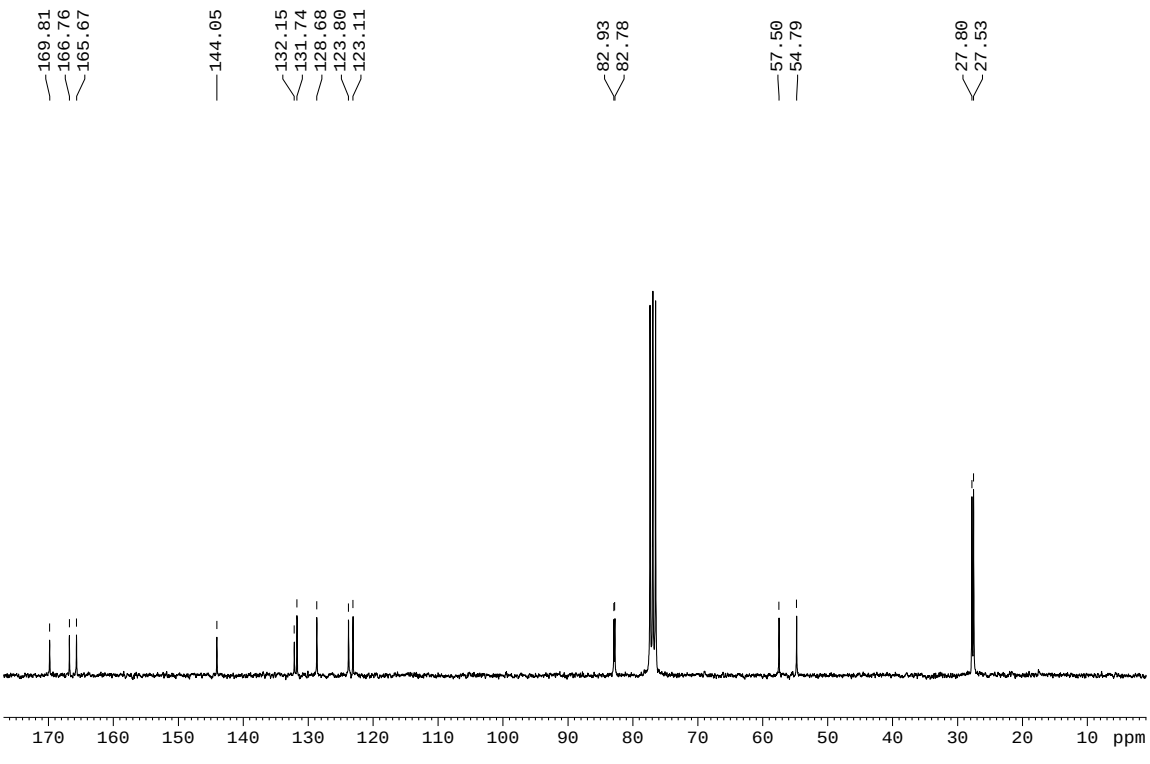

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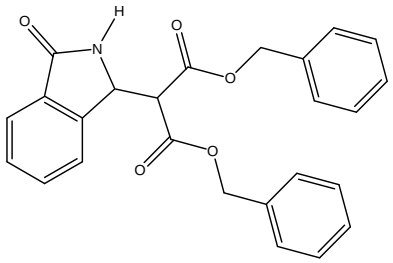
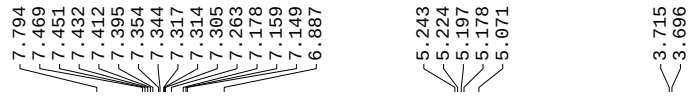
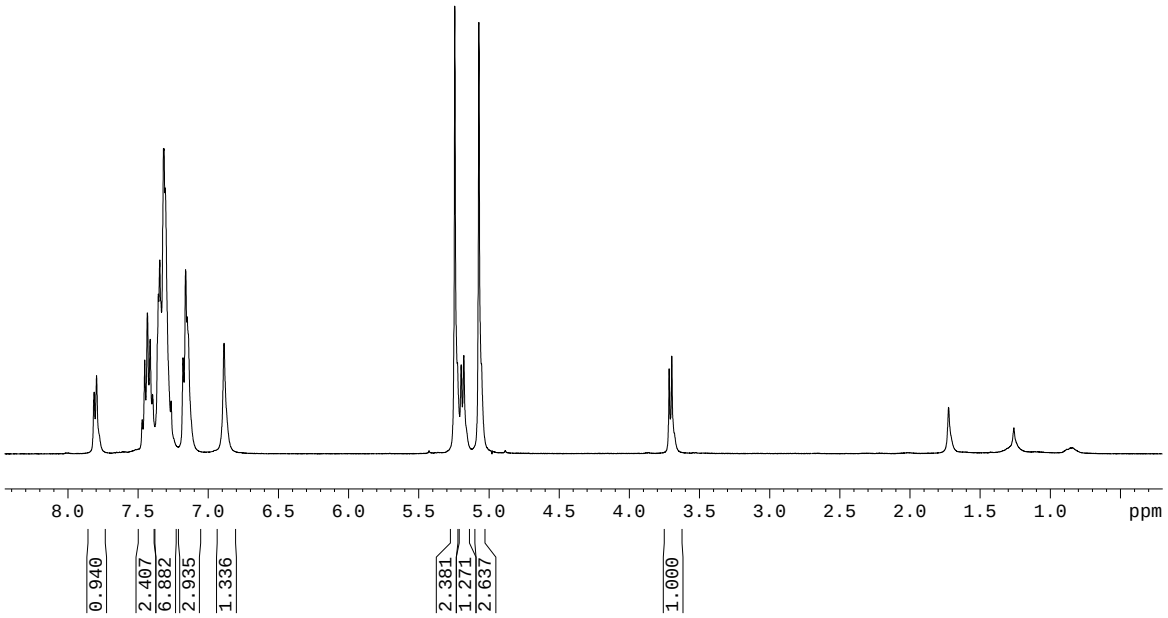
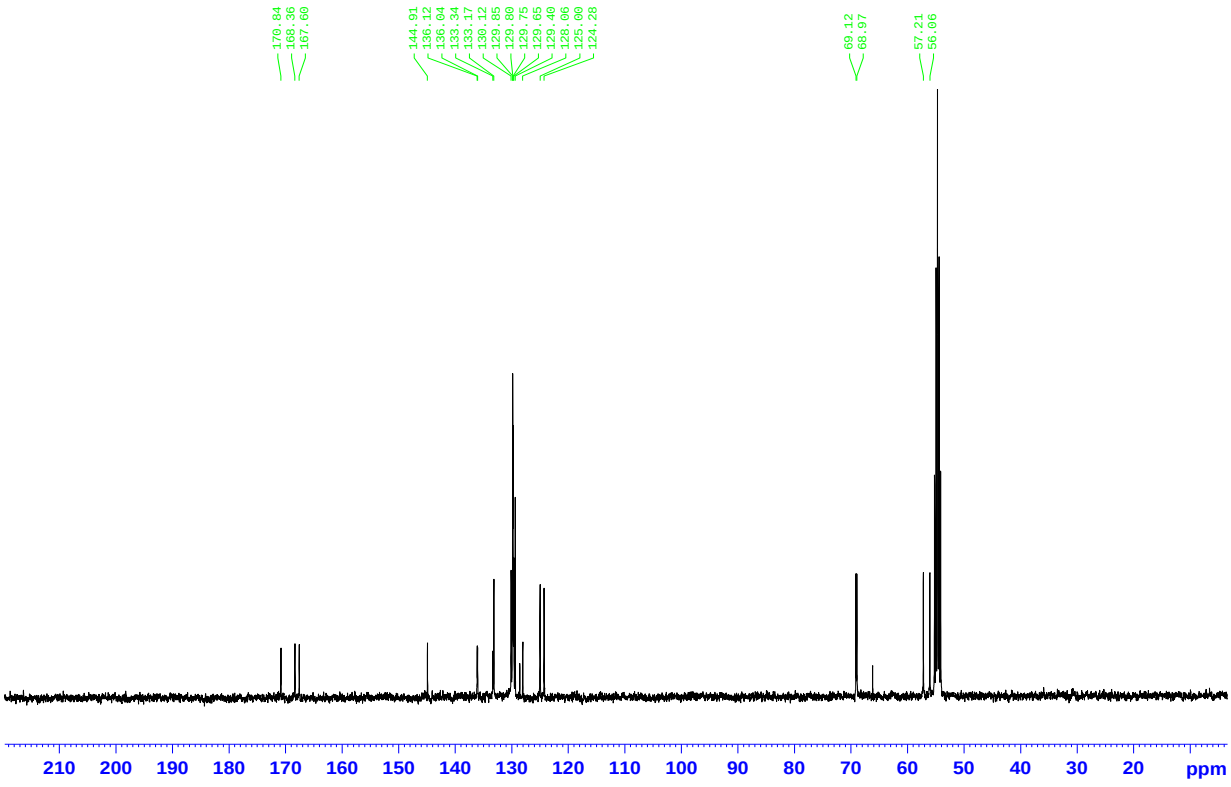
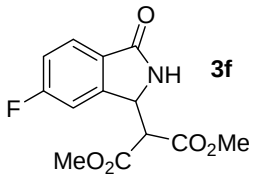


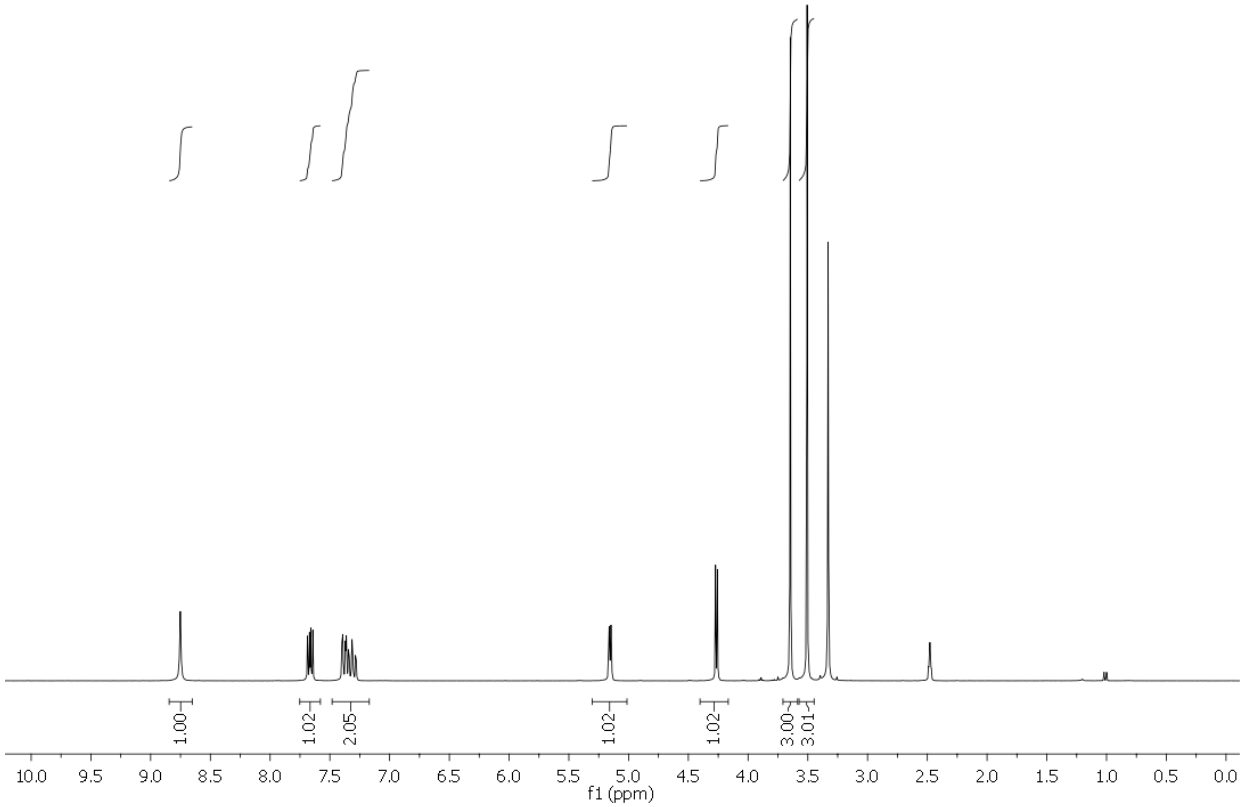


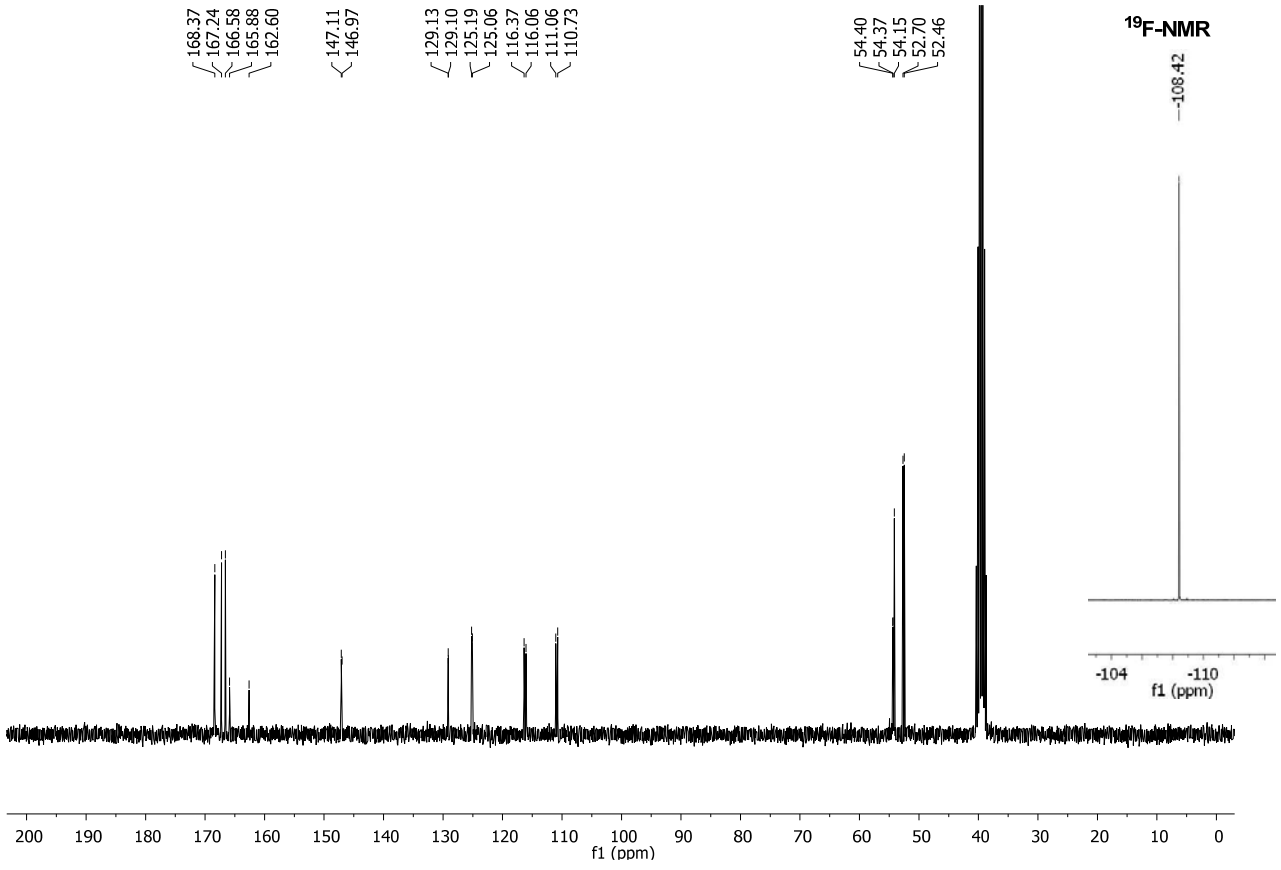




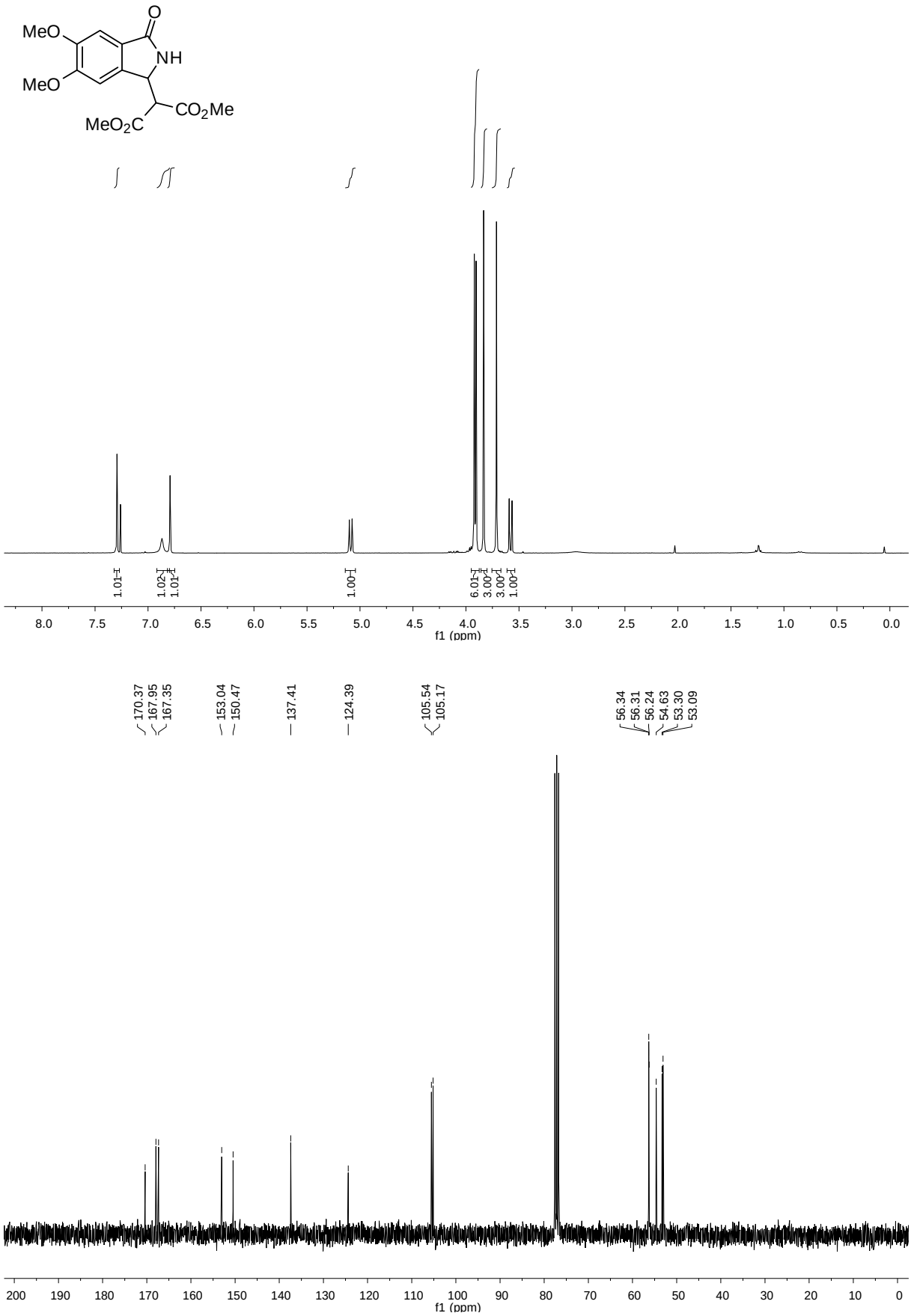


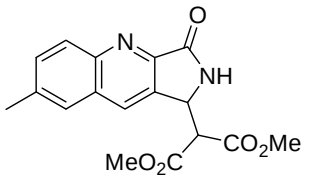
3f

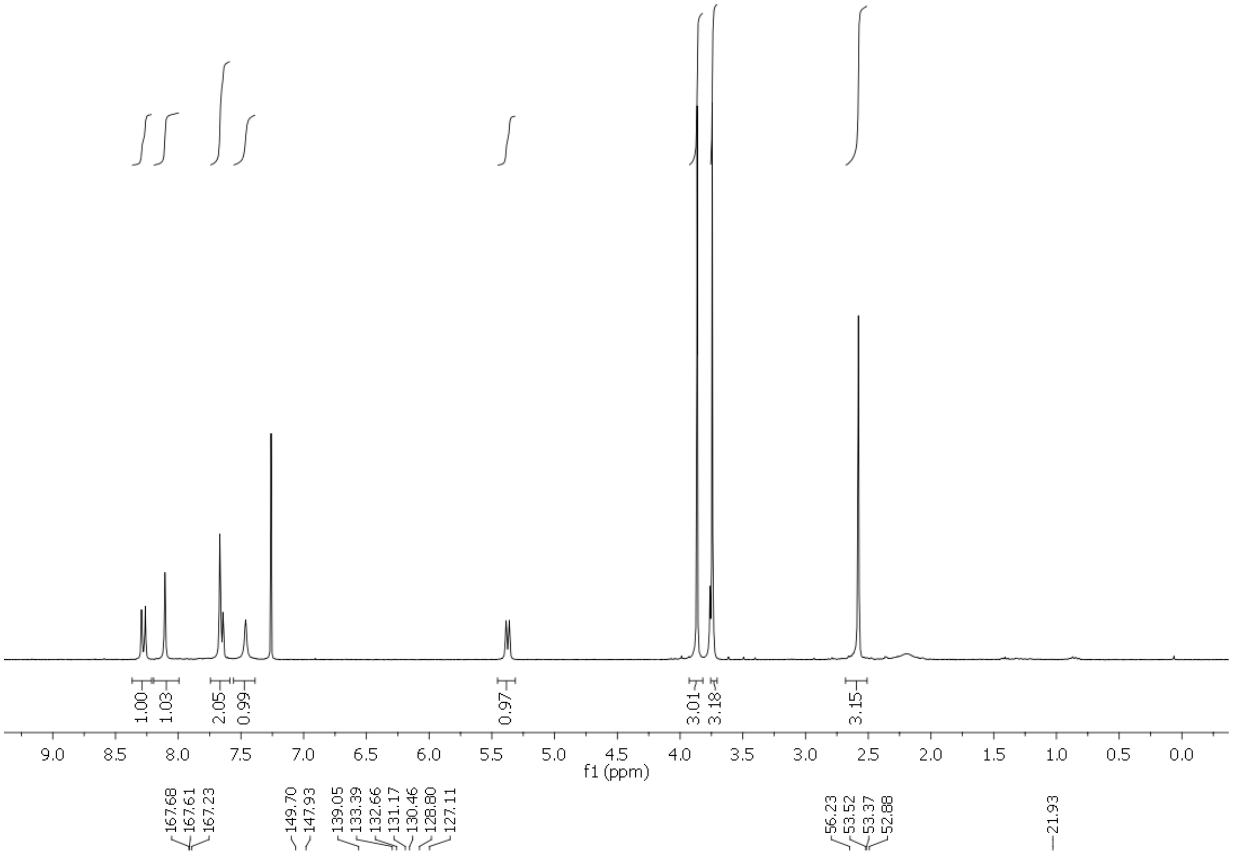


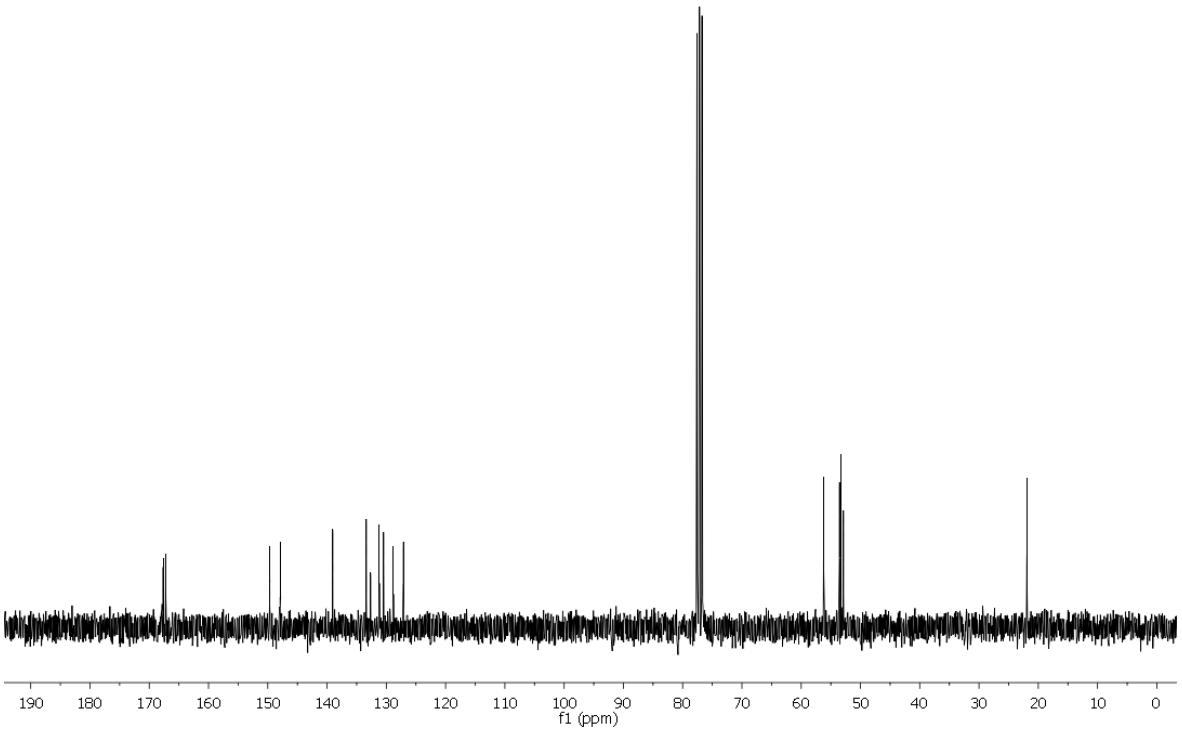


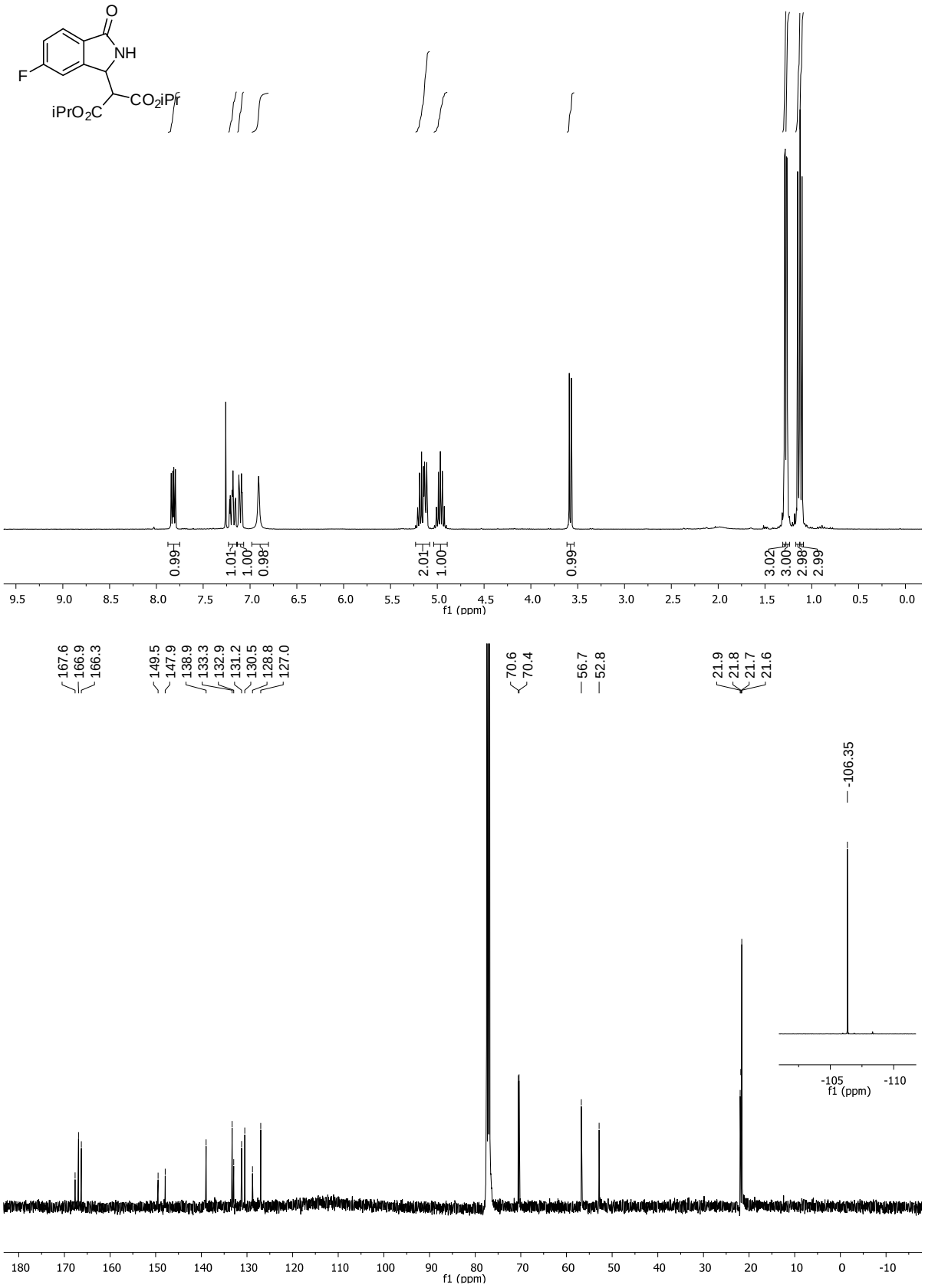
^{19}F-NMR

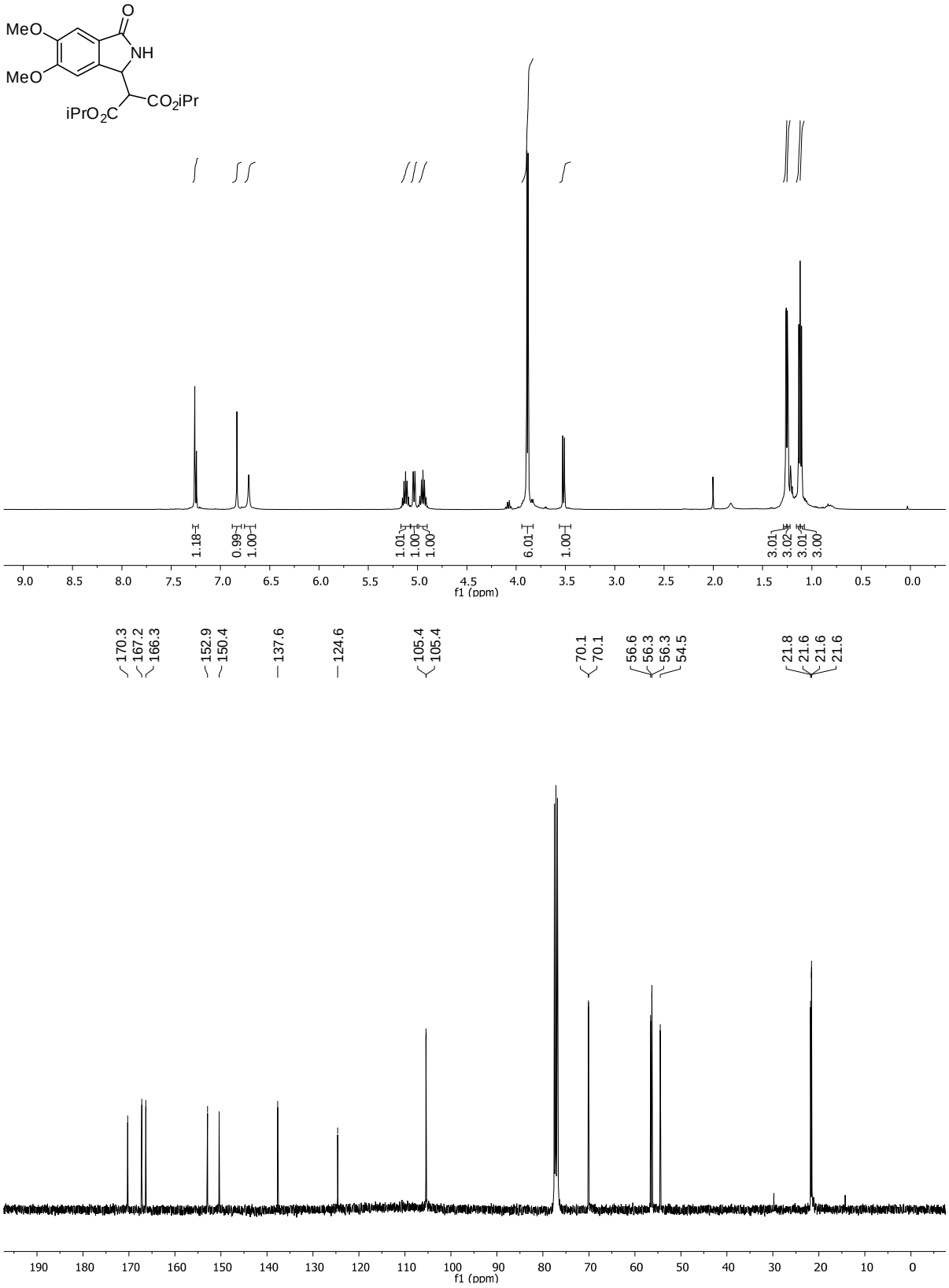


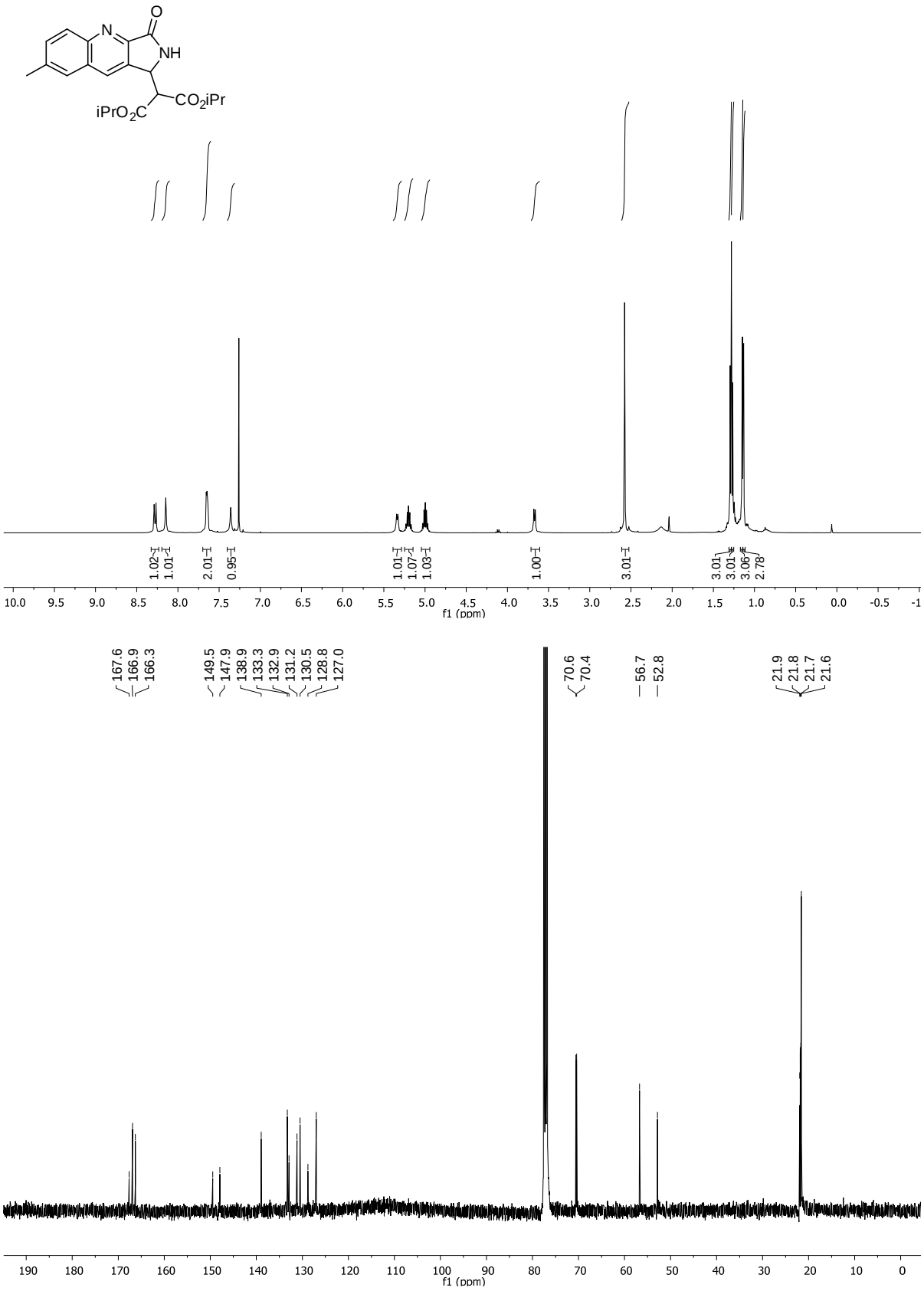


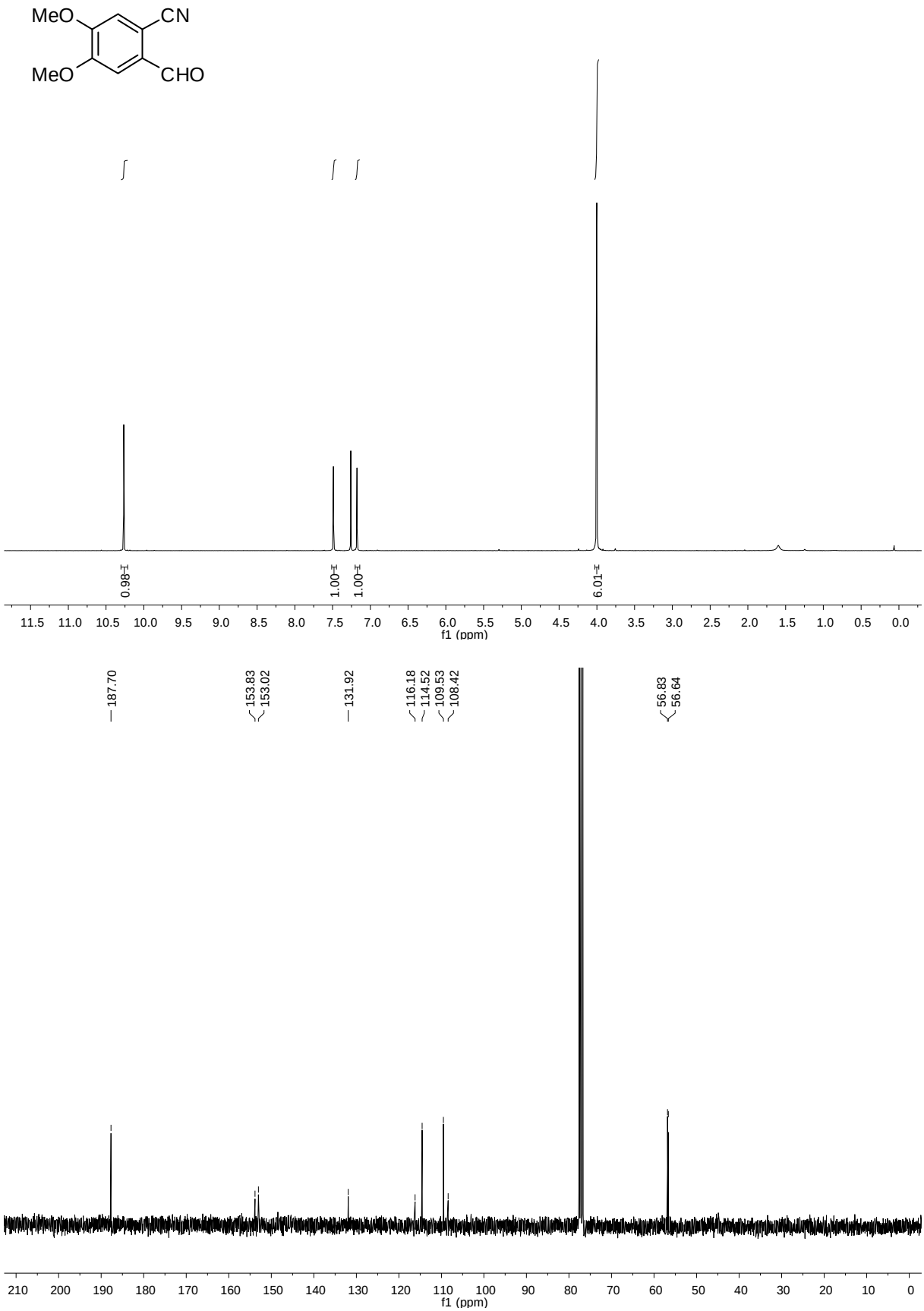


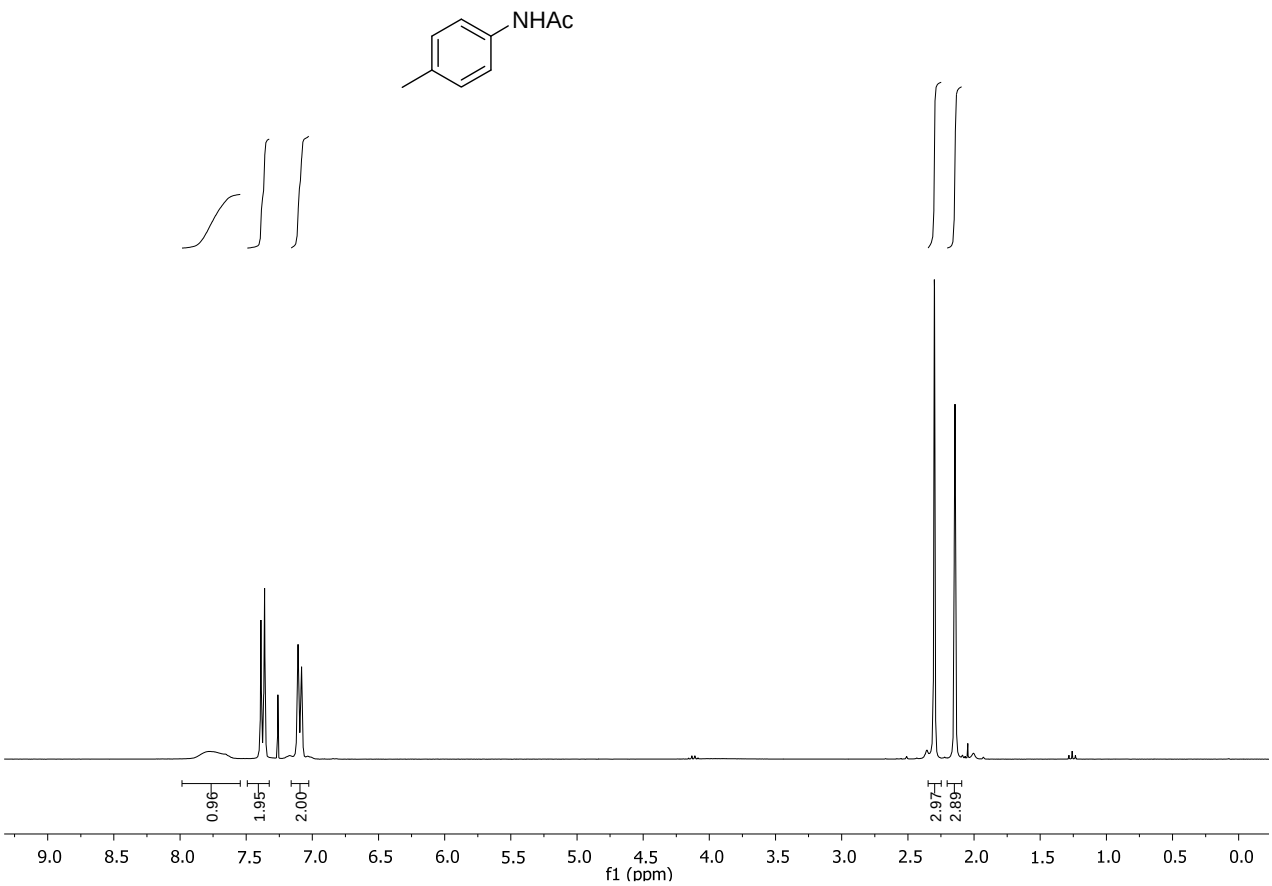


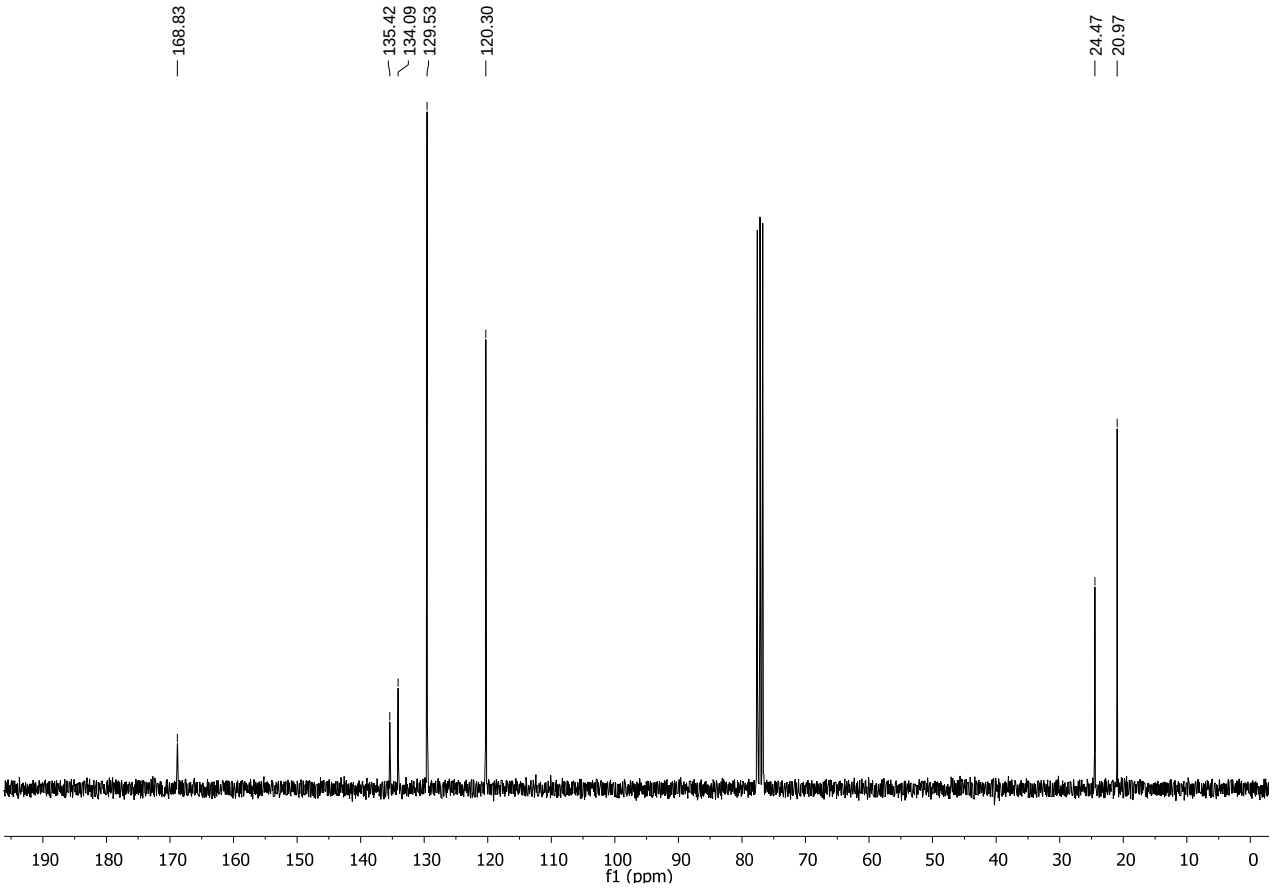


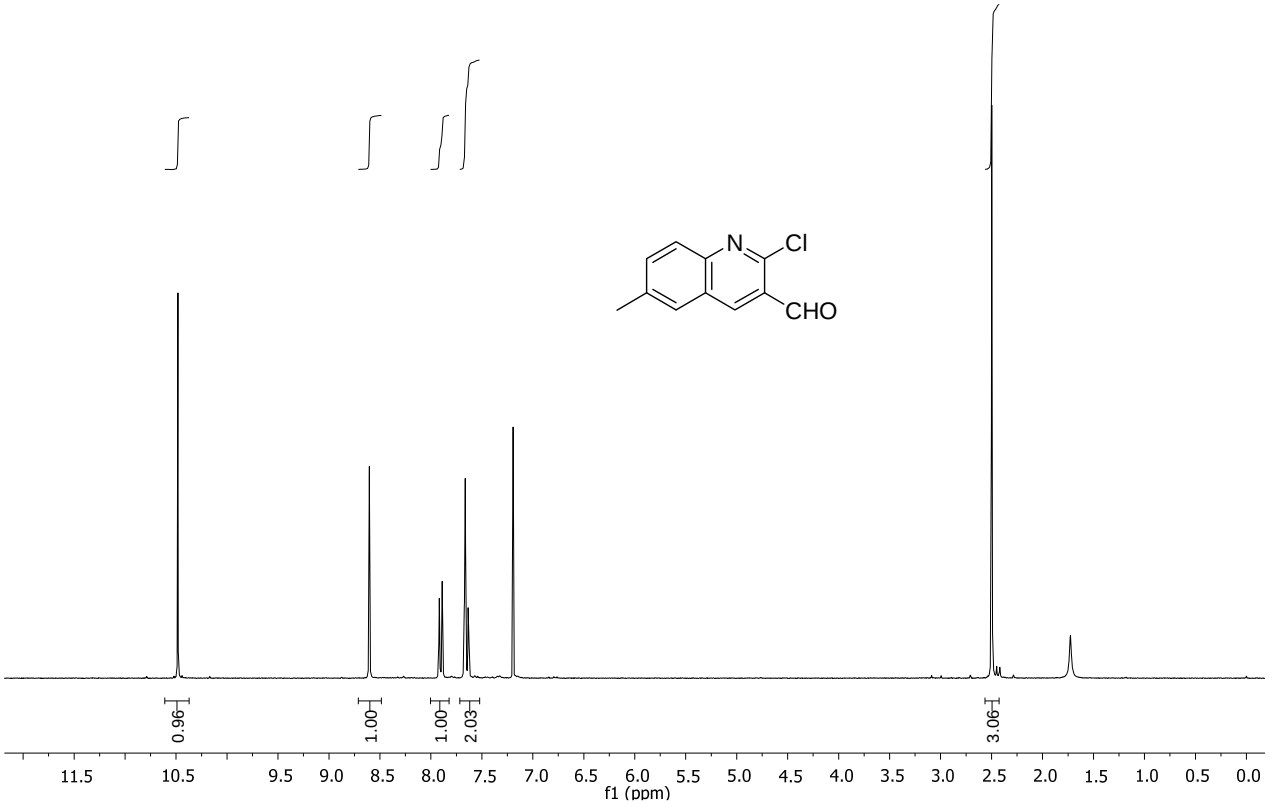


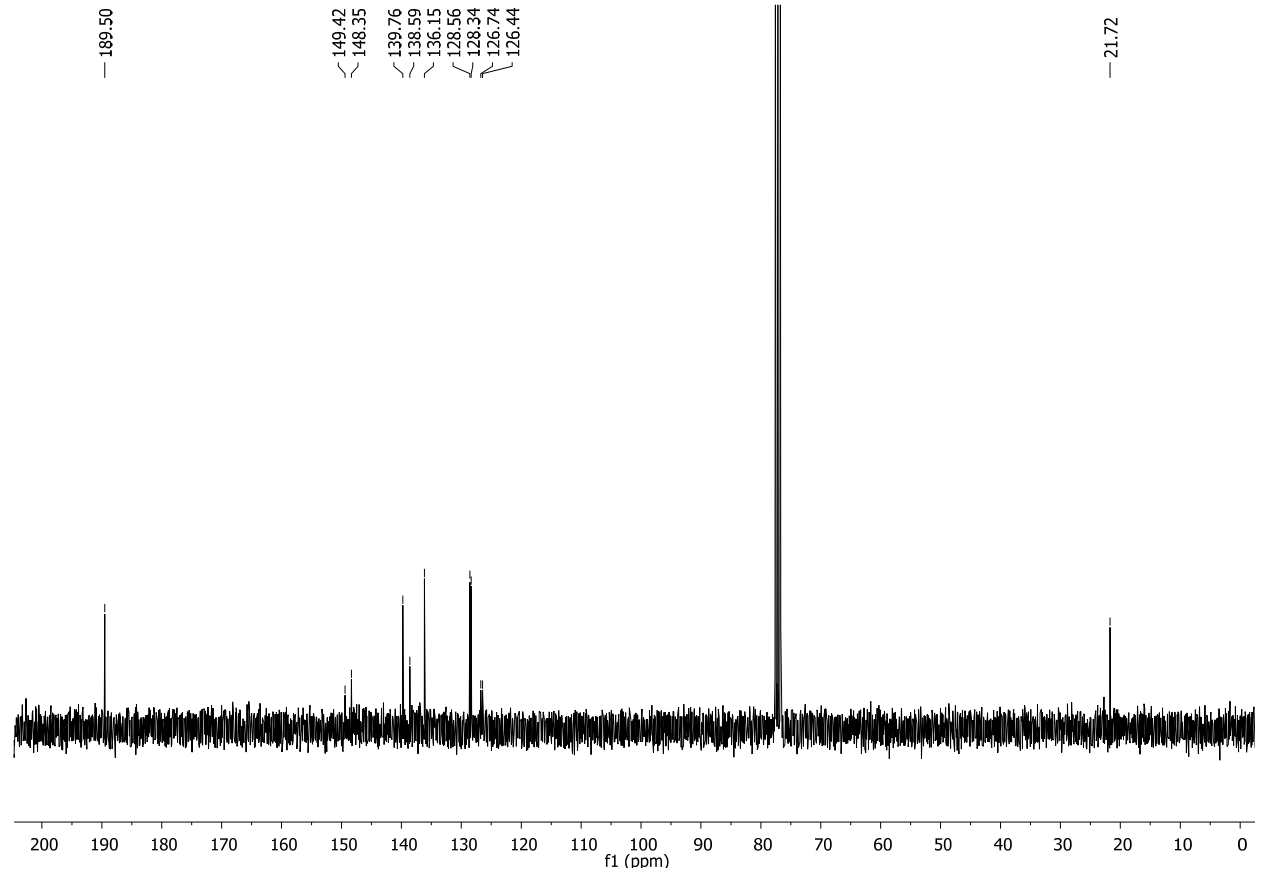


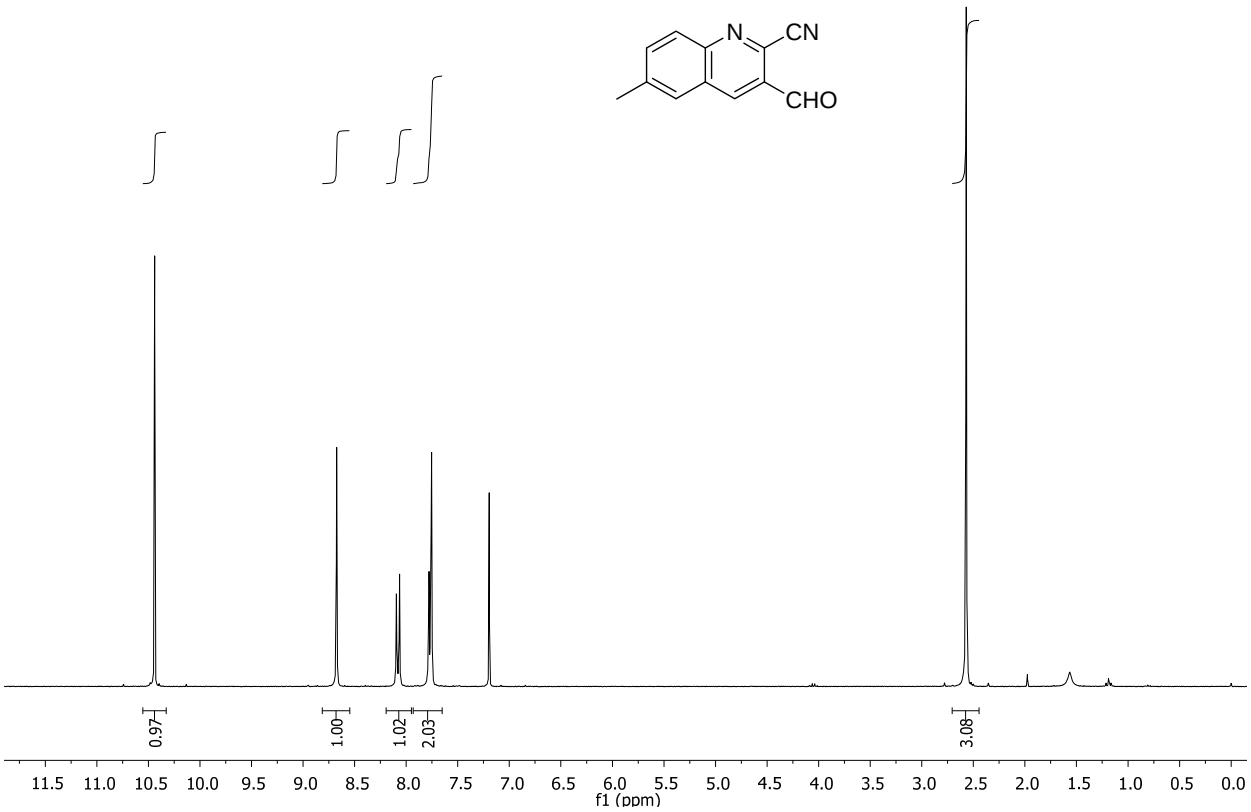


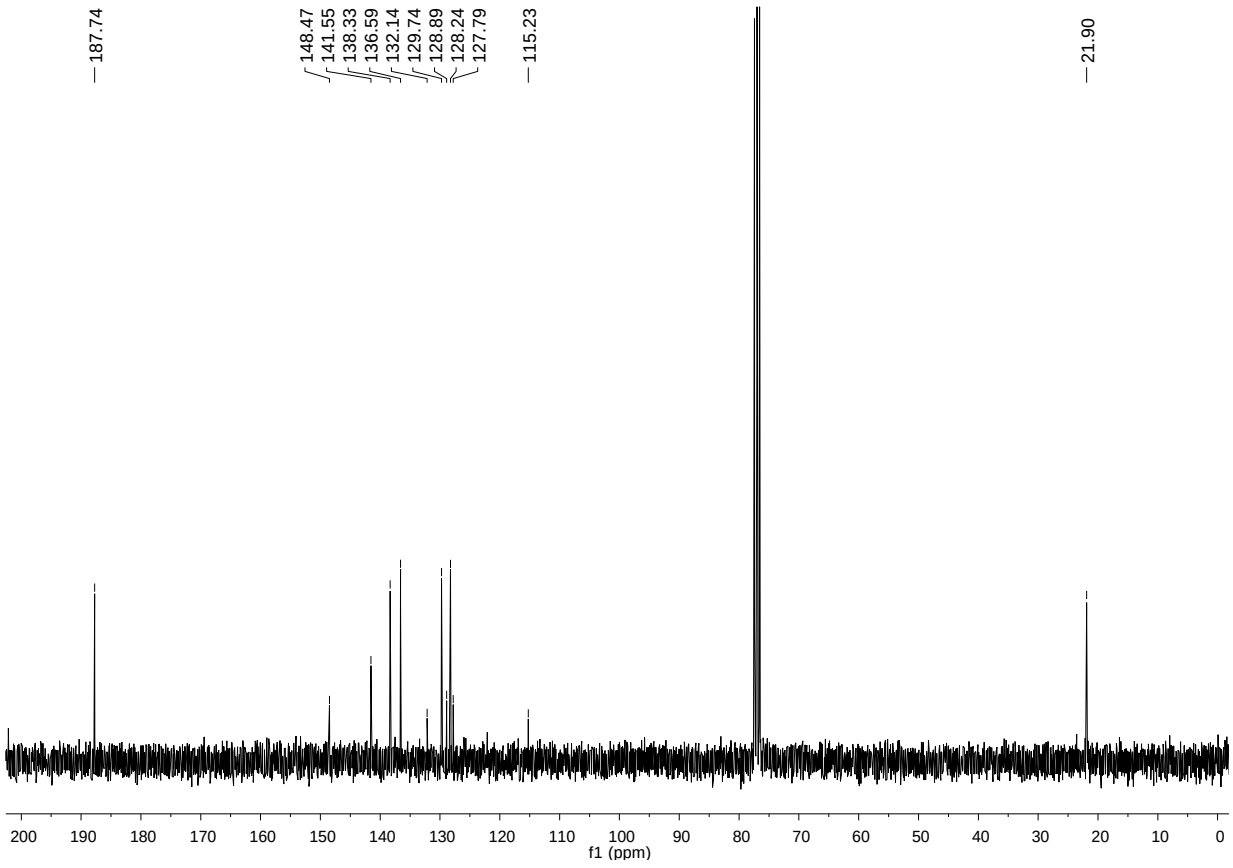












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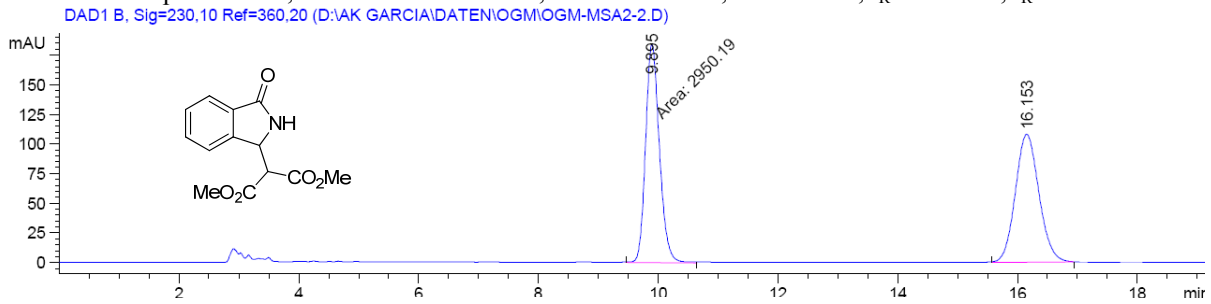

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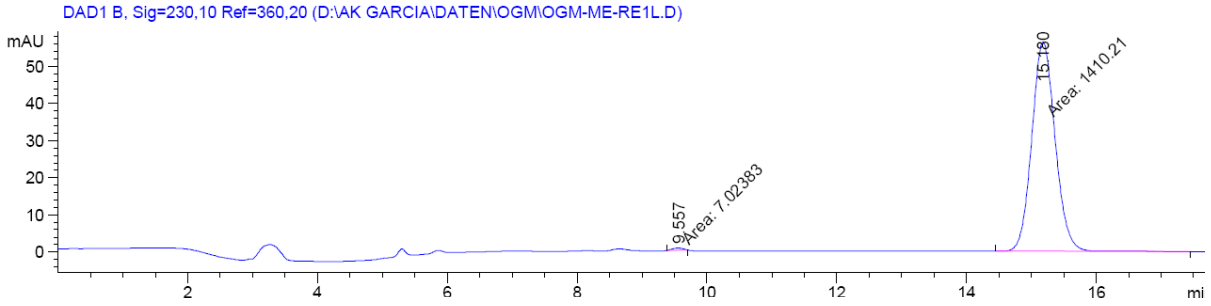
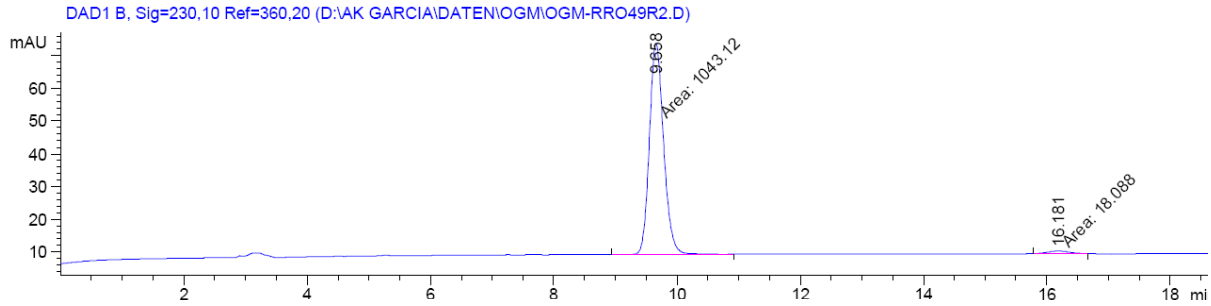
Totals :				5904.36841	292.07269	

Reaction with catalyst **4**. Single recrystallization from DCM/Pentane.



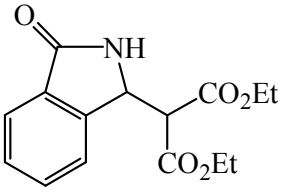
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.557	MM	0.1876	7.02383	6.23891e-1	0.4956
2	15.180	MM	0.4171	1410.20825	56.35270	99.5044
Totals :				1417.23208	56.97659	

Reaction with catalyst **5**. Single recrystallization from DCM/Pentane.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.658	MM	0.2693	1043.12244	64.56354	98.2955
2	16.181	MM	0.4046	18.08804	7.45105e-1	1.7045
Totals :				1061.21048	65.30864	

3b Chiralpack AD column, 80/20 hexane/ *i*PrOH, 0.8 mL/min . λ = 254 nm

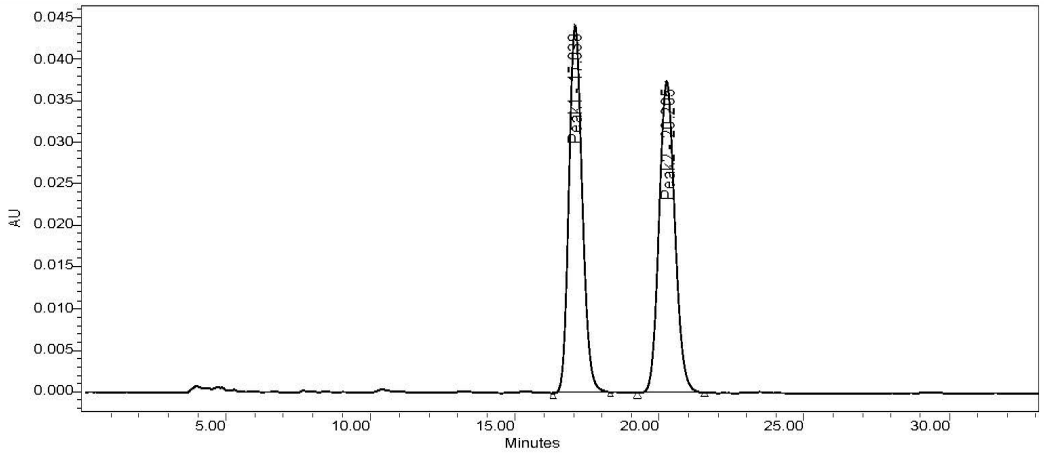


Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

Breeze

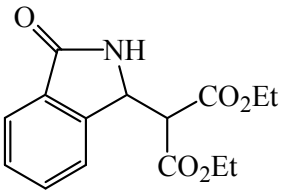
SAMPLE INFORMATION

Sample Name:	ant-rac dietil,AD 80:20 a 0.8mL	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	11/8/2011 4:29:13 PM
Vial:	1	Acq. Method:	80 20 a 08 ml
Injection #:	1	Date Processed:	11/8/2011 5:02:58 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name:	



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	17.038	1417967	50.00	44281	54.24
2	Peak2	20.205	1418147	50.00	37355	45.76

Report Method: Individual Report HIP Printed 1:38:03 PM 11/18/2011 Page: 1 of 1

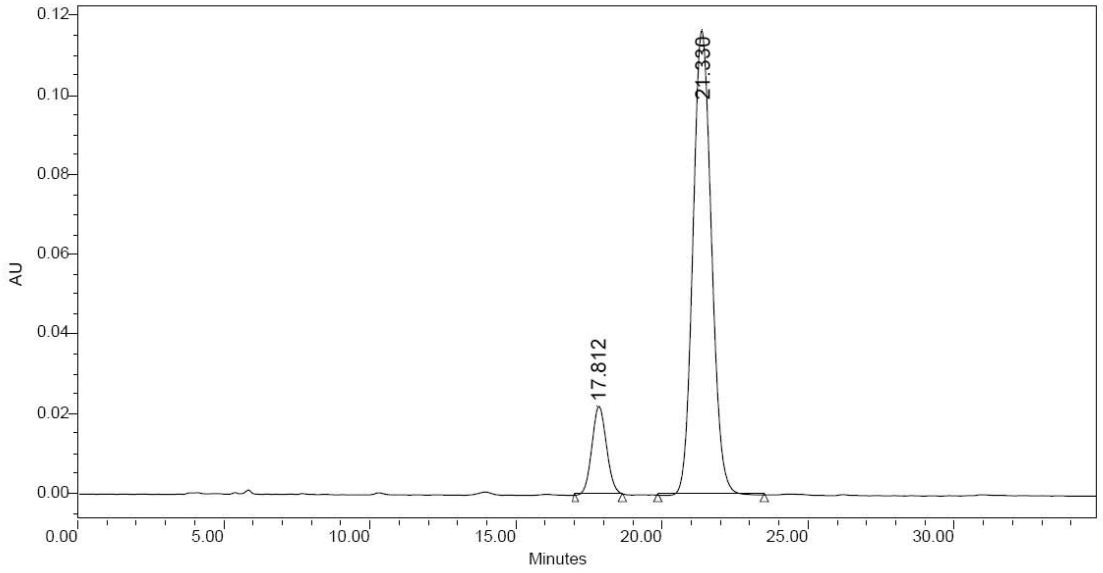


Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

Breeze

SAMPLE INFORMATION

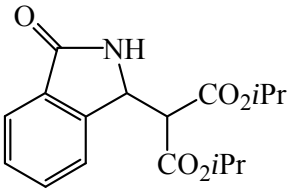
Sample Name:	ant-276, AD 80:20 a0.8mL	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	12/9/2011 8:22:44 PM
Vial:	1	Acq. Method:	80 20 a 08 ml
Injection #:	10	Date Processed:	12/12/2011 6:55:45 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name:	



	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	17.812	773355	13.03	22177	15.98
2	21.330	5160721	86.97	116637	84.02

Report Method: Individual Report HIP Printed 6:56:07 PM 12/12/2011 Page: 1 of 1

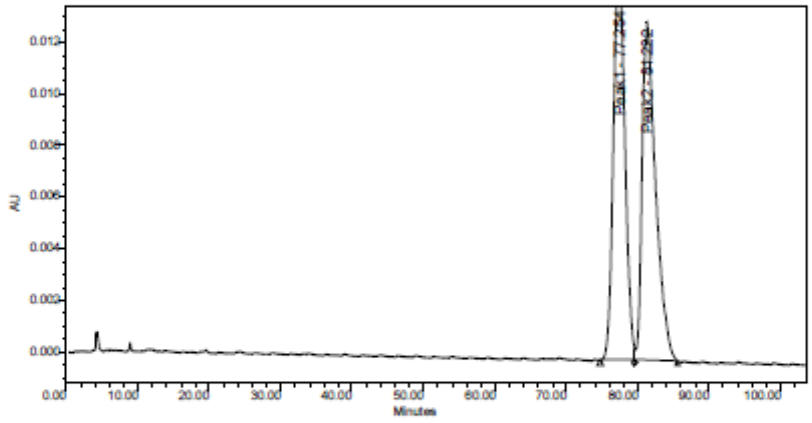
3c Chiralpack AD-H column, 95/5 hexane/ *i*PrOH, 0.8 mL/min. λ = 254 nm



Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

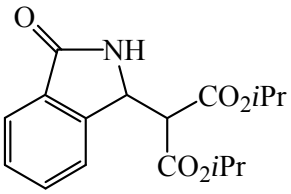
SAMPLE INFORMATION

Sample Name:	Adr10-6,Rac.lprma.ADH95:5a0.8M	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	10/14/2011 6:32:49 PM
Vial:	1	Acq. Method:	95 a 5 08ml
Injection #:	6	Date Processed:	10/14/2011 8:29:38 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name:	



	Peak Name	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	Peak1	77.254	1724832	49.88	15480	54.12
2	Peak2	81.222	1732974	50.12	13125	45.88

Report Method: Individual Report 2nd HIP Printed 2:22:46 PM 12/14/2011 Page: 1 of 1

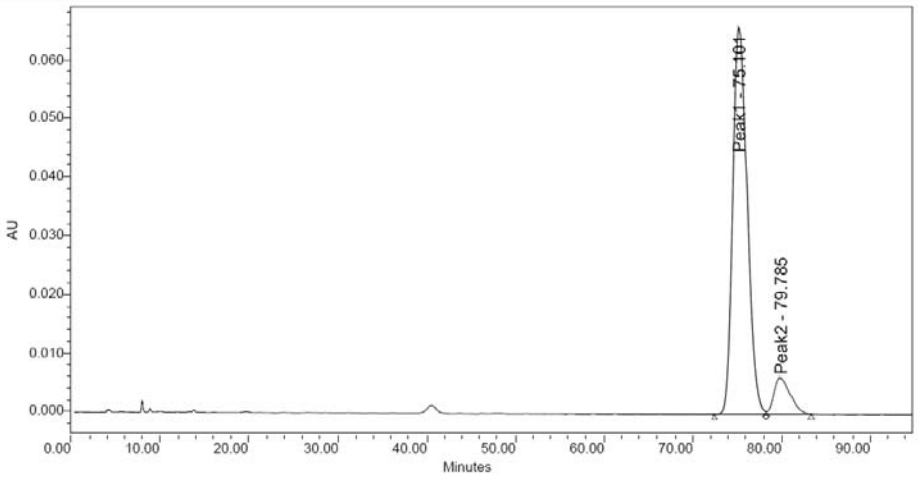


Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

Breeze

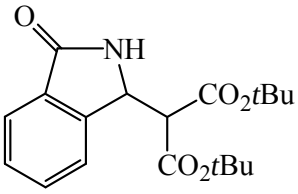
SAMPLE INFORMATION

Sample Name:	ant-277 AD-H, 95:05 a0.8mL	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	12/13/2011 11:23:36 AM
Vial:	1	Acq. Method:	95 a 5 08ml
Injection #:	1	Date Processed:	12/13/2011 1:23:59 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name:	



	Peak Name	RT (min)	Area (V*sec)	% Area	Height (V)	% Height
1	Peak1	75.101	7477606	90.40	66026	91.39
2	Peak2	79.785	794413	9.60	6224	8.61

Report Method: Individual Report HIP Printed 1:24:20 PM 12/13/2011 Page: 1 of 1

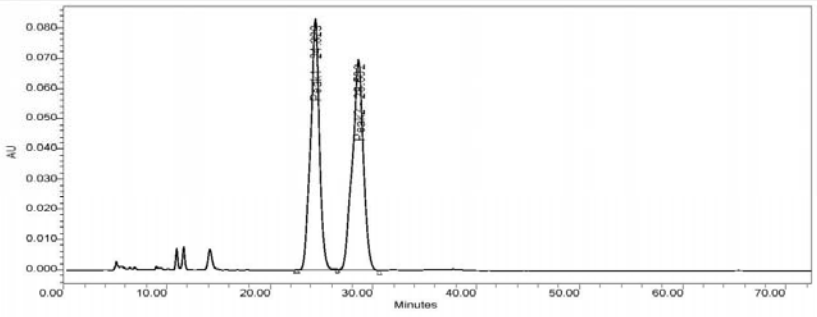


Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

Breeze

SAMPLE INFORMATION

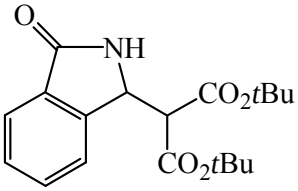
Sample Name:	va-97 ADH	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	3/9/2011 1:16:44 PM
Vial:	1	Acq. Method:	9 a 1 06ml
Injection #:	3	Date Processed:	3/9/2011 2:33:29 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	130.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name:	



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	24.329	4949541	48.91	82655	54.33
2	Peak2	28.502	5170905	51.09	69476	45.67

Report Method: Individual Report HIP Printed 4:40:23 PM 11/4/2011 Page: 1 of 1

3d Chiralpack AD-H column, 9/1 hexane/ *i*PrOH, 0.6 mL/min λ = 254 nm

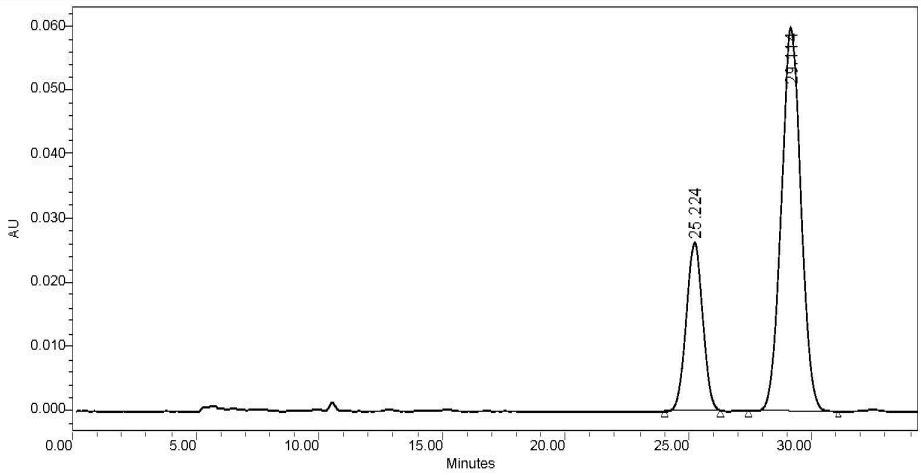


Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

Breeze

SAMPLE INFORMATION

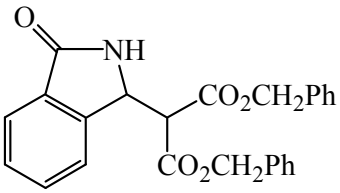
Sample Name:	ant-248 ADH 90:10 a 0.6mL	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	11/3/2011 7:46:42 PM
Vial:	1	Acq. Method:	9 a 1 06ml
Injection #:	2	Date Processed:	11/3/2011 8:22:33 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name:	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	25.224	1224787	26.96	26264	30.48
2	29.114	3317528	73.04	59892	69.52

Report Method: Individual Report HIP Printed 3:26:36 PM 11/4/2011 Page: 1 of 1

3e Chiralpack AD-H column, 75/25 hexane/ *i*PrOH, 0.5 mL/min λ = 254 nm

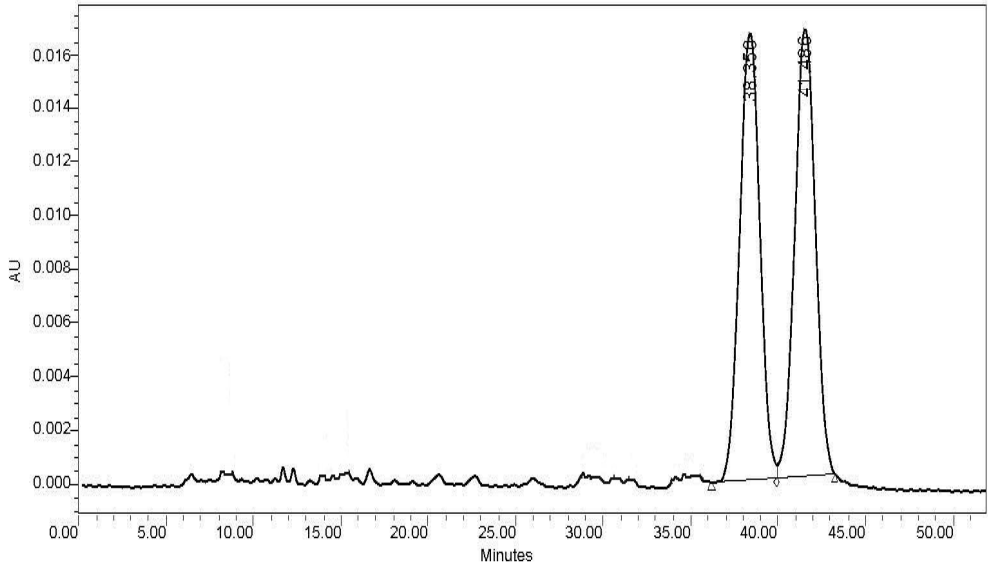


Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

Breeze

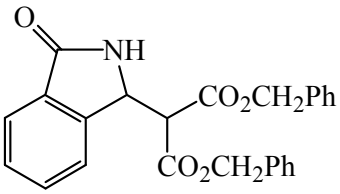
SAMPLE INFORMATION

Sample Name:	adr11,Rac.dibenz.ADH75:25a0.5ml	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	10/21/2011 12:31:04 PM
Vial:	1	Acq. Method:	75 a 25 0 5 ml
Injection #:	1	Date Processed:	10/21/2011 1:24:51 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Sample Set Name:	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	38.350	1352853	49.60	16692	49.99
2	41.486	1374793	50.40	16697	50.01

Report Method: Untitled Printed 4:17:15 PM 11/3/2011 Page: 1 of 1

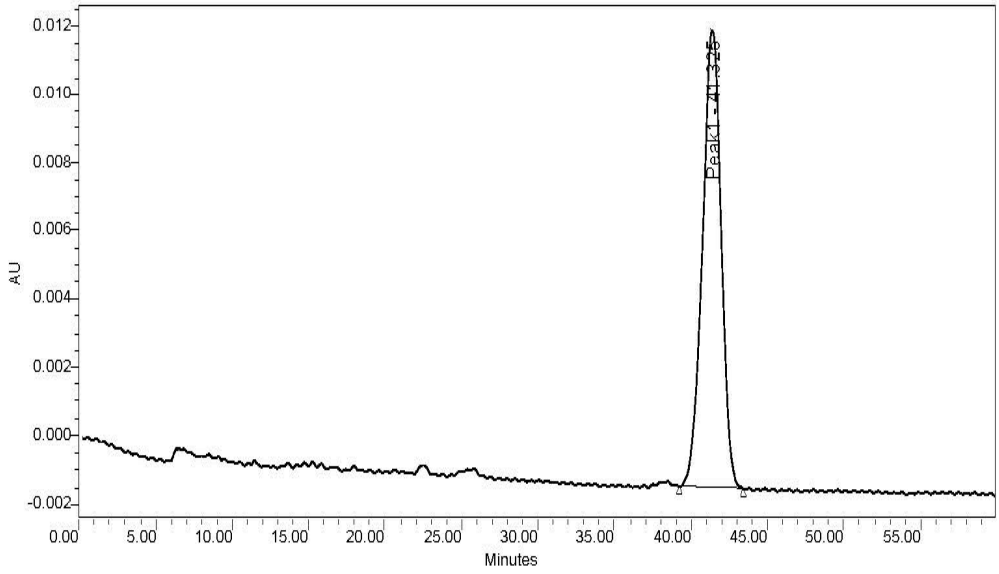


Dipartimento di Chimica
Project Name: acetoacetato
Reported by User: System

Breeze

SAMPLE INFORMATION

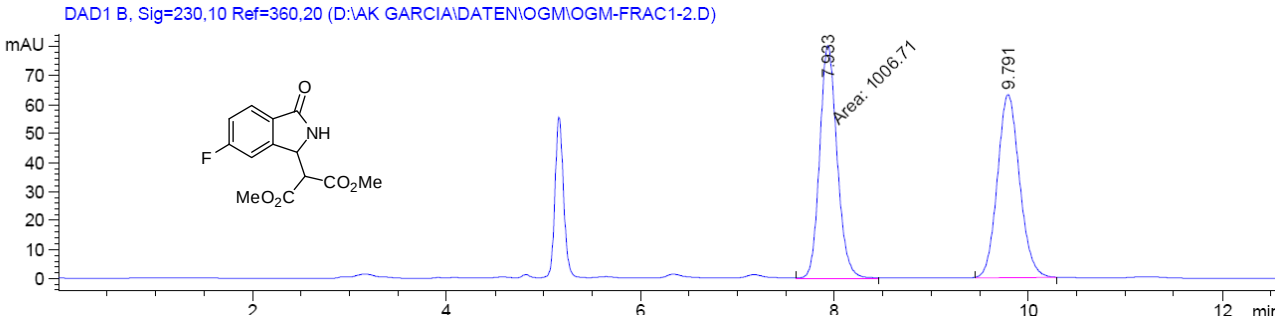
Sample Name:	ant243cry.fil2ADH75:25 a 0.5mL	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	10/27/2011 11:03:34 AM
Vial:	1	Acq. Method:	75 a 25 0 5 ml
Injection #:	1	Date Processed:	10/27/2011 12:04:23 PM
Injection Volume:	20.00 ul	Channel Name:	2487Channel 1
Run Time:	120.00 Minutes	Sample Set Name:	



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	Peak1	41.325	1143757	100.00	13415	100.00

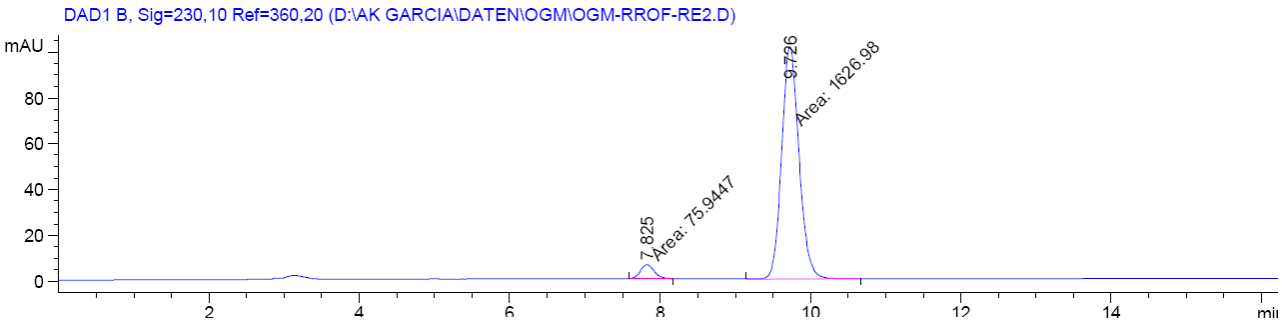
Report Method: Untitled | Printed 4:15:36 PM 11/3/2011 | Page: 1 of 1

3f: HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 70:30, F = 1.0 mL/min, λ = 230 nm, t_R = 7.9 min, t_R major =9.8 min.



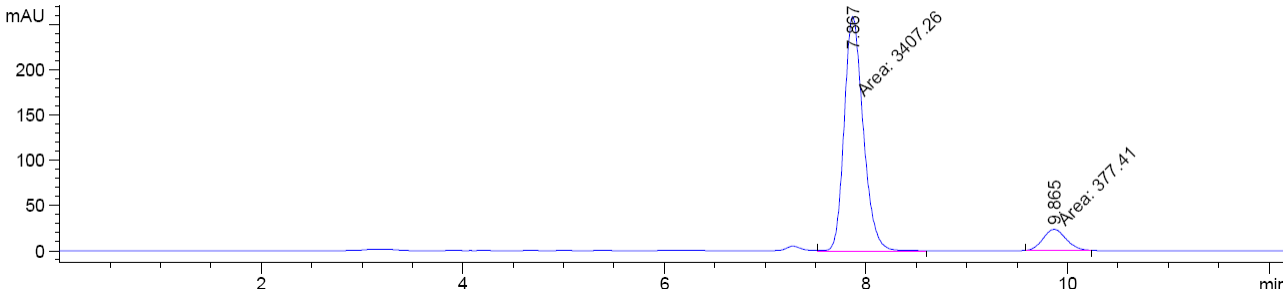
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.933	MM	0.2085	1006.71234	80.49048	50.0147
2	9.791	BB	0.2453	1006.12170	63.34789	49.9853
Totals :				2012.83405	143.83837	

Reaction with catalyst **4**. Single recrystallization from DCM/Pentane.



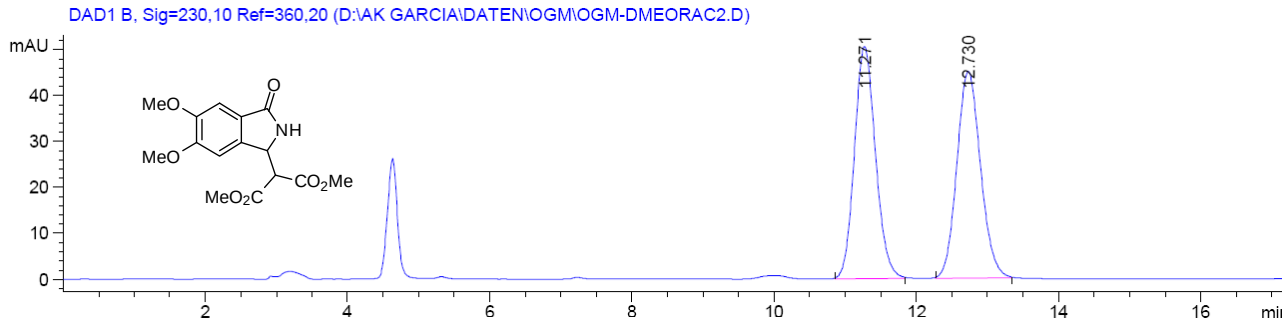
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.825	MM	0.2069	75.94469	6.11813	4.4597
2	9.726	MM	0.2676	1626.97913	101.33611	95.5403
Totals :				1702.92381	107.45424	

Reaction with catalyst **5**. Single recrystallization from DCM/Pentane.



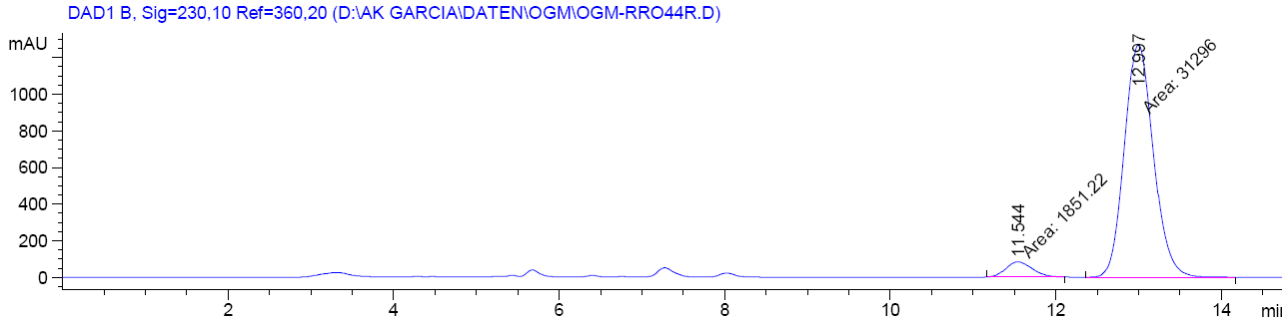
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.867	MM	0.2189	3407.25684	259.38657	90.0279
2	9.865	MM	0.2677	377.41037	23.49939	9.9721
Totals :				3784.66721	282.88596	

3g: HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 70:30, F = 1.0 mL/min, λ = 230 nm, t_R = 11.3 min, t_R = 12.7 min.



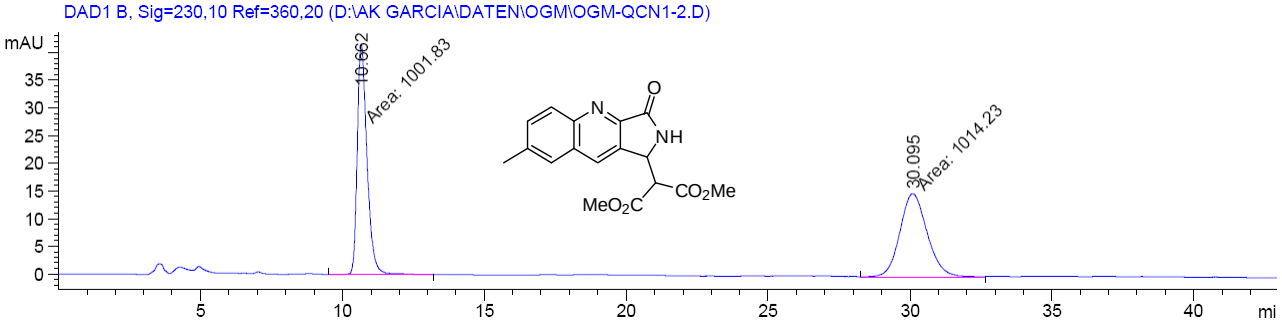
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.271	BB	0.3180	1041.64746	50.62751	49.9578
2	12.730	BB	0.3579	1043.40686	45.09704	50.0422
Totals :				2085.05432	95.72454	

Reaction with catalyst **4**. Single recrystallization from DCM/Pentane.



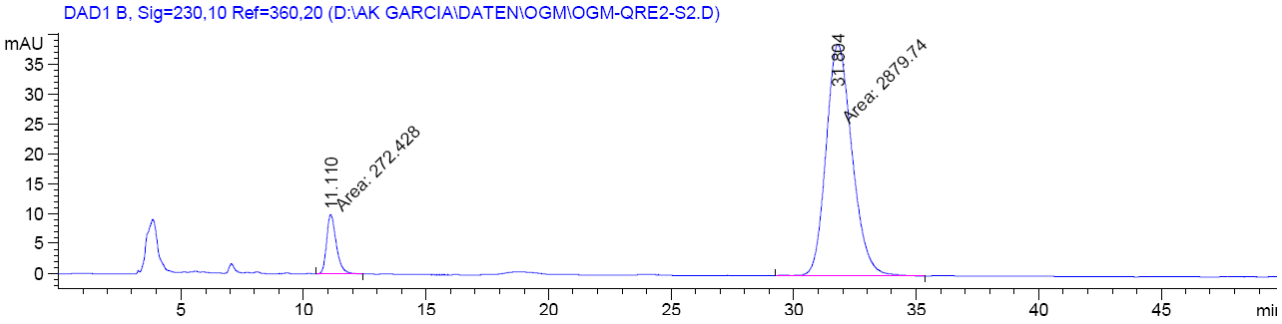
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.544	MM	0.3695	1851.21704	83.51003	5.5848
2	12.997	MM	0.4102	3.12960e4	1271.58362	94.4152
Totals :				3.31472e4	1355.09364	

3h: HPLC: Chiralpack AD-H, Pentane:*i*-PrOH 60:40, F = 0.9 mL/min, λ = 230 nm, t_R = 10.7 min, t_R = 30.1 min.



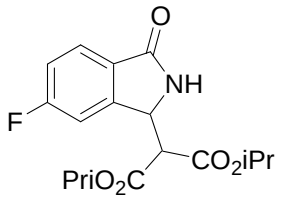
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.662	MM	0.3999	1001.82837	41.75692	49.6924
2	30.095	MM	1.1225	1014.23041	15.05910	50.3076
Totals :				2016.05878	56.81602	

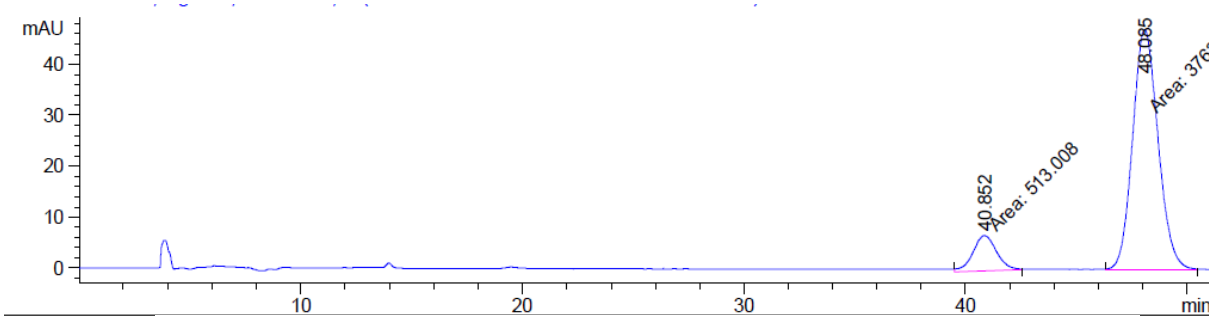
Reaction with catalyst **4**. Single recrystallization from MeCN/MeOH/DCM.



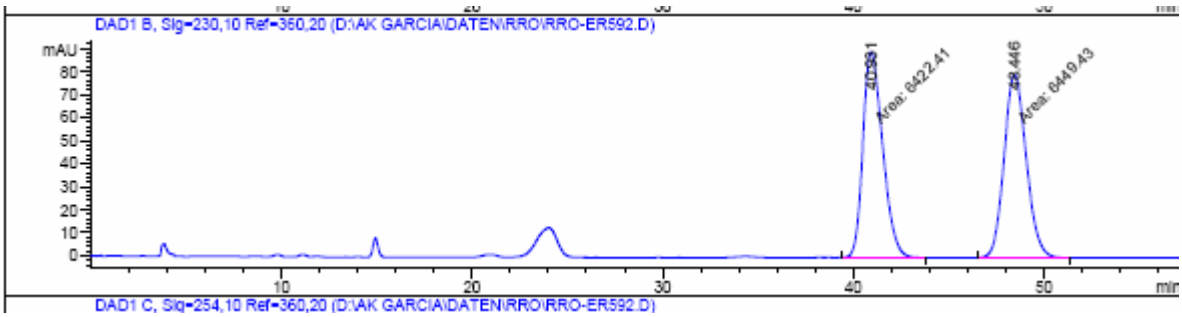
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.110	MM	0.4557	272.42795	9.96472	8.6426
2	31.804	MM	1.2359	2879.73926	38.83509	91.3574
Totals :				3152.16721	48.79982	

3i Chiralpack AD-H, Pentane:*i*-PrOH 95:5, F = 0.8 mL/min, λ = 230 nm,





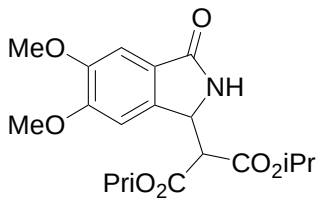
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.852	MM	1.2401	513.00806	6.89451	11.9947
2	48.085	MM	1.3274	3763.94824	47.25934	88.0053
Totals :				4276.95630	54.15385	

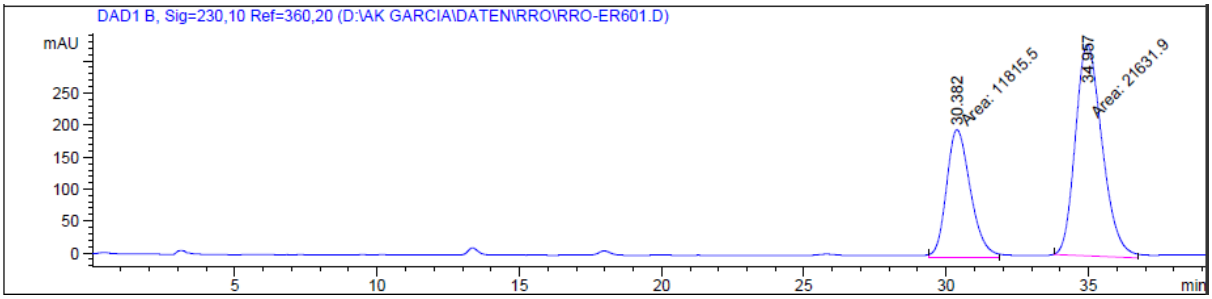


Signal 2: DAD1 B, Sig=230,10 Ref=360,20

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.931	MM	1.1989	6422.41406	89.28525	49.8951
2	48.446	MM	1.3532	6449.42969	79.43565	50.1049
Totals :				1.28718e4	168.72089	

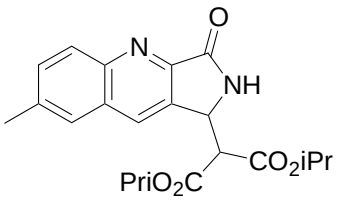
3j Chiralpack AD-H, Pentane:*i*-PrOH 90:10, F = 1.0 mL/min,

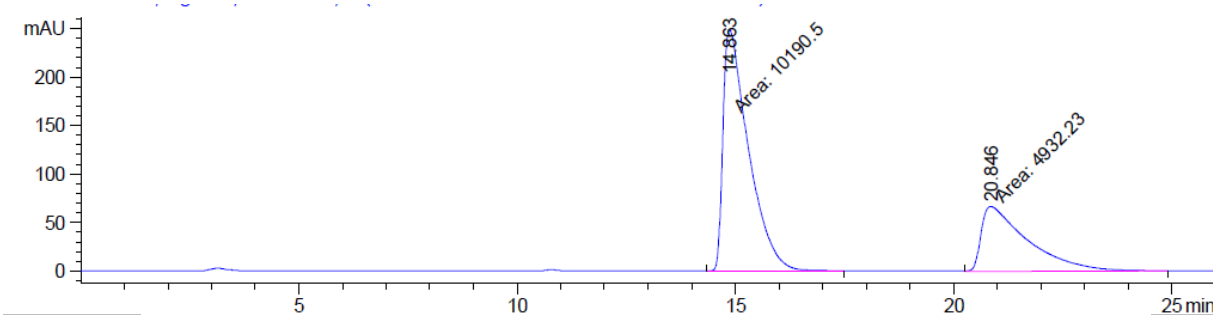




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.382	MM	0.9832	1.18155e4	200.28587	35.3256
2	34.957	MM	1.0919	2.16319e4	330.18002	64.6744
Totals :				3.34473e4	530.46590	

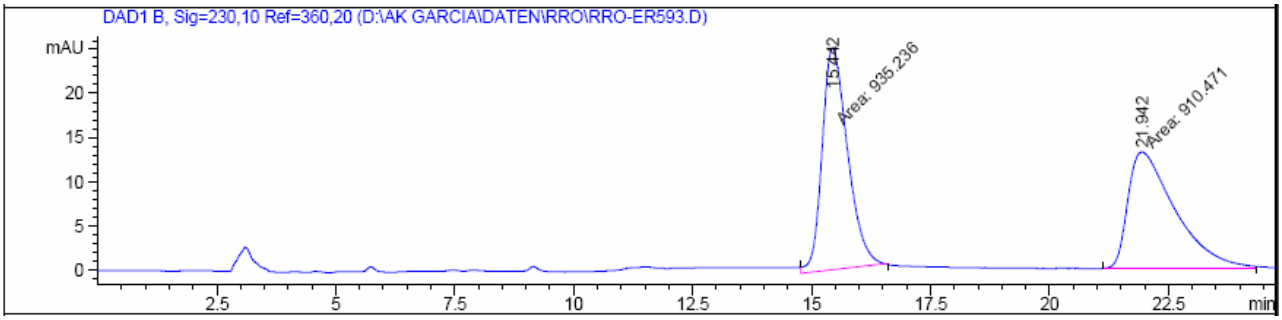
3k Chiralpack AD-H, Pentane:*i*-PrOH 80:20, F = 1.0 mL/min, λ = 230 nm





Signal 2: DAD1 B, Sig=230,10 Ref=360,20

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.863	MM	0.6783	1.01762e4	250.04541	67.1778
2	20.846	MM	1.2445	4971.94727	66.58568	32.8222
Totals :				1.51481e4	316.63109	



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.442	MM	0.6206	935.23596	25.11573	50.6709
2	21.942	MM	1.1509	910.47150	13.18520	49.3291
Totals :				1845.70746	38.30093	