Supporting Information for:

Modular synthesis and transition metal-free alkynylation/alkenylation of Castagnoli-Cushman-derived *N*,*O*- and *N*,*S*-heterocyclic vinyl chlorides

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Contents:

2. Experimental Section

All experiments involving air and moisture-sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Freshly purchased DMF was stored under 4 A^{o} molecular sieves for several days prior to use. THF was distilled from sodium benzophenone ketyl. All amines and enals were newly purchased and used without further purification. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 µm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ stain. All reported temperatures were internal to a reaction vessel. Unless otherwise indicated, ^{1}H, ^{13}C, and DEPT-135 spectra were acquired using $CDCl_3$ as solvent, at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^{+} data were obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).

Brine solutions are saturated solutions of aqueous sodium chloride. The lactam precursors utilized in these studies were prepared using our recently reported protocol.[1]

General Procedure A: Vilsmeier-Haack functionalization[2]

To a solution of DMF (40 mmol, 4 equiv) in CH_2Cl_2 (50 mL) at 0 ^{o}C was added dropwise, phosphorus oxychloride (20 mmol, 2 equiv). The resulting pale yellow mixture was refluxed for 60 min. A solution of the lactam ester (10 mmol, 1 equiv) in CH_2Cl_2 (50 mL) was added slowly under reflux. After complete addition of the lactam, the mixture was cooled to room temperature (for the morpholinone esters) or 0 ^{o}C (for the thiomorpholinone esters) and stirred for the indicated time period (TLC and LC-MS monitoring was used to follow the extent of the reaction). Upon completion, the mixture was poured into a large flask containing crushed ice. After stirring at room temperature for 60 min, the layers were separated (the majority of the product stays in the DCM layer). Powdered K_2CO_3 was added slowly to the aqueous layer and the flask was swirled after each addition (***Caution***: it bubbles vigorously). The addition/swirling was continued until persistent cloudiness was observed. The neutralized/slightly basic mixture was extracted two times with CH_2Cl_2. The combined organic layers (three in total, one *before* and two after addition of K_2CO_3) were washed with brine and dried over Na_2SO_4 for 30 min. The mixture was filtered and

concentrated under reduced pressure to give the desired product as an oily salt, which was immediately subjected to flash chromatography on silica with 1% Et_3N.

General Procedure B (Transition metal-free alkynylation with terminal alkynes)

To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added the chloroenal (0.5 mmol, 1.0 equiv) in 2-MeTHF (5 mL) under an argon atmosphere. The desired alkyne (1.2 equiv) was added. After completely degassing the flask, LiTMP (147.2 mg, 2 equiv) was added. The mixture was then stirred at room temperature for the desired length of time (as indicated by TLC and LC-MS). Upon completion, the mixture was quenched with methanol. The combined organics were concentrated to ~5 mL and directly subjected to flash chromatography on silica, pretreated with Et_3N.

General Procedure C (Transition metal-free alkenylation with styrenes)

Potassium *tert*-butoxide (56 mg, 2.0 equiv) and 1,10-phenanthroline (7 mg, 15 mol%) were transferred into a dried Schlenk tube. The sealed tube was evacuated and filled with argon three times. A solution of vinyl chloride **4a** (0.25 mmol) in 5 mL anhydrous 2-MeTHF was added via syringe and the mixture was stirred for 5 seconds at room temperature. The tube was placed in a preheated oil bath at 90 °C and it was stirred for 18 h (GC-MS and TLC monitoring). After cooling down, the reaction mixture was filtered through a short silica plug and the silica was washed with ethyl acetate. The organic solvents were evaporated under reduced pressure and the product was purified by flash column chromatography on silica gel, pretreated with triethylamine.

General Procedure D (Wittig olefination and Diels-Alder reaction)

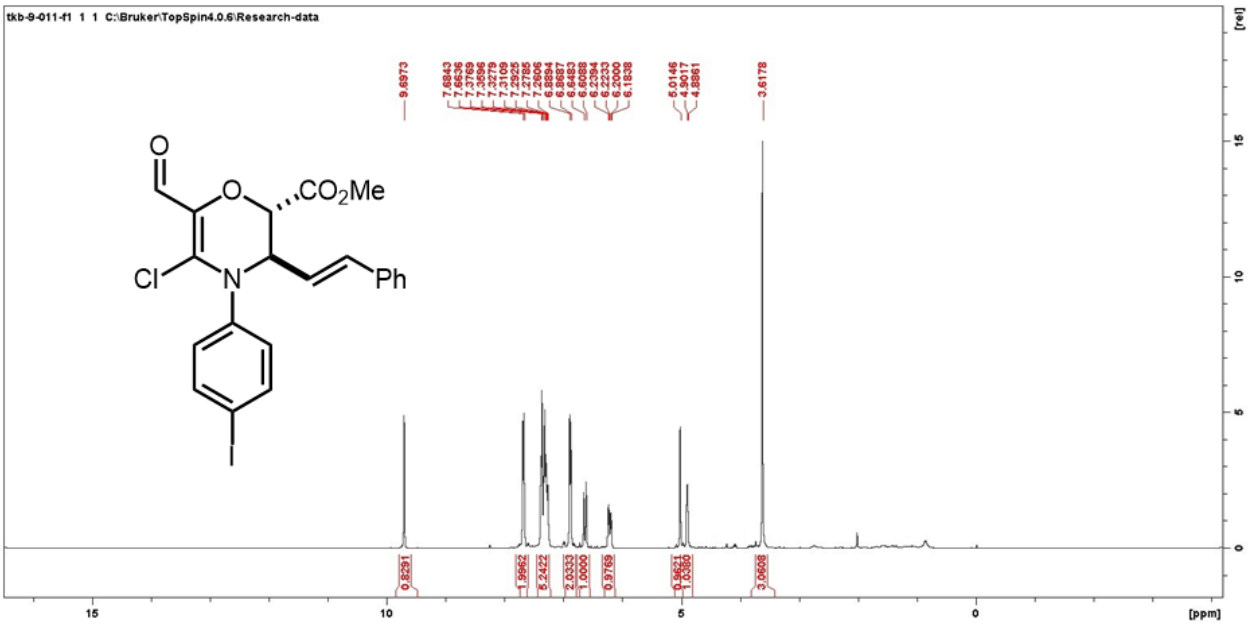
Wittig Olefination: To a 25 mL two-neck round-bottomed flask containing a magnetic stir bar under a N_2 atmosphere was added benzyltriphenylphosphonium bromide + sodium amide (240 mg, 0.5 mmol) and 2-MeTHF (10 mL). After stirring at room temperature for 30 min, then aldehyde (0.5 mmol) was added as a solution in 2-MeTHF (5 mL) and stirring was resumed at this temperature for 12 h (GC-MS and TLC monitoring). It flask was then cooled to 0 °C and the contents were quenched by the addition of *sat.* NH_4Cl(aq) solution (10 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by gradient

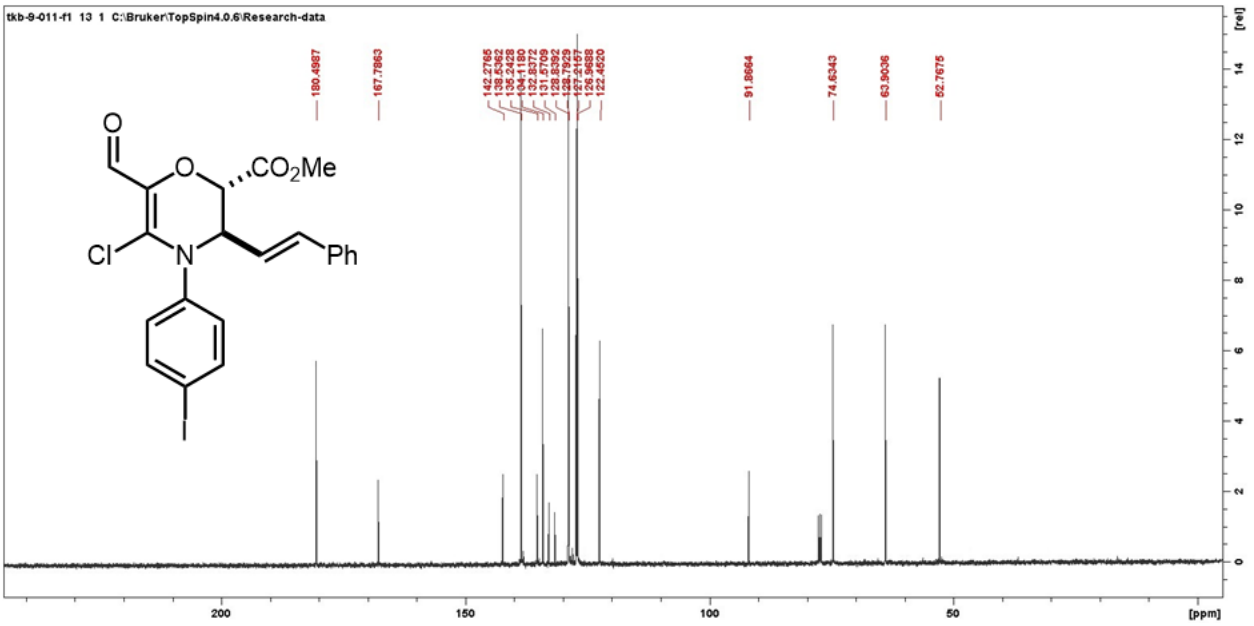
flash chromatography (eluting with 9:1 to 4:1 hexanes/EtOAc) to furnish the conjugated diene as a yellowish liquid in ~90:10 dr.

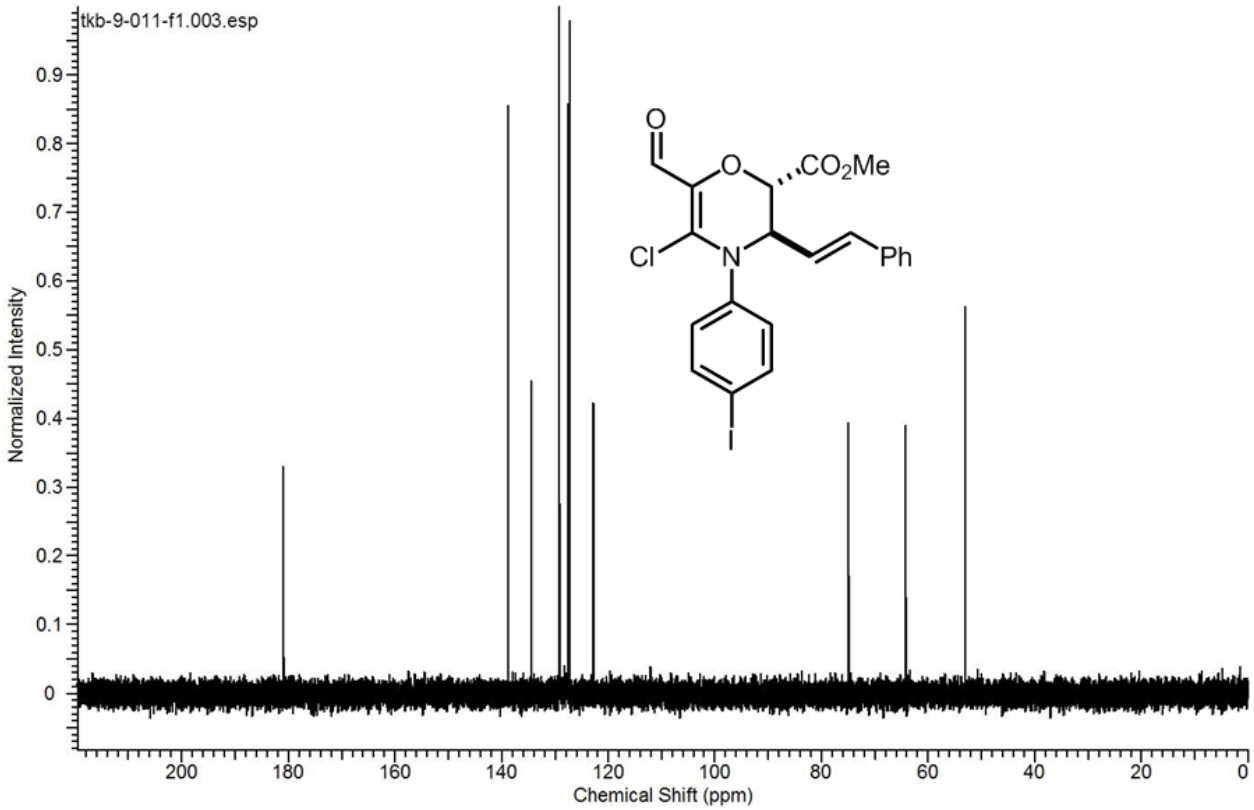
Hexannulation: A vial was flame-dried, evacuated and flushed with nitrogen. A solution of tetracyanoethylene (128 mg, 1.0 mmol, 2 equiv) in 2-MeTHF (5 mL) was added to the vial followed by a solution of crude 1,3-diene (0.5 mmol) in 2-MeTHF (5 mL). The mixture was stirred for 12 h at room temperature. The crude mixture was concentrated under reduced pressure and purified by flash chromatography on silica (pretreated with 1% Et_3N), eluting with hexane/EtOAc.

Scheme 1 results

Compound **4a1:** Prepared in 10 mmol scale using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 9.416 g, 74%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.22 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.21 (dd, *J* = 15.9, 6.5 Hz, 1H), 5.01 (s, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 3.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.4, 167.7, 142.2, 138.5, 135.2, 134.1, 132.8, 131.5, 130.3, 128.8, 127.2, 122.4, 119.6, 91.8, 74.6, 62.6, 52.7. HRMS calc for $C_{21}H_{17}ClINO_4$, 508.9891, found 509.9899.

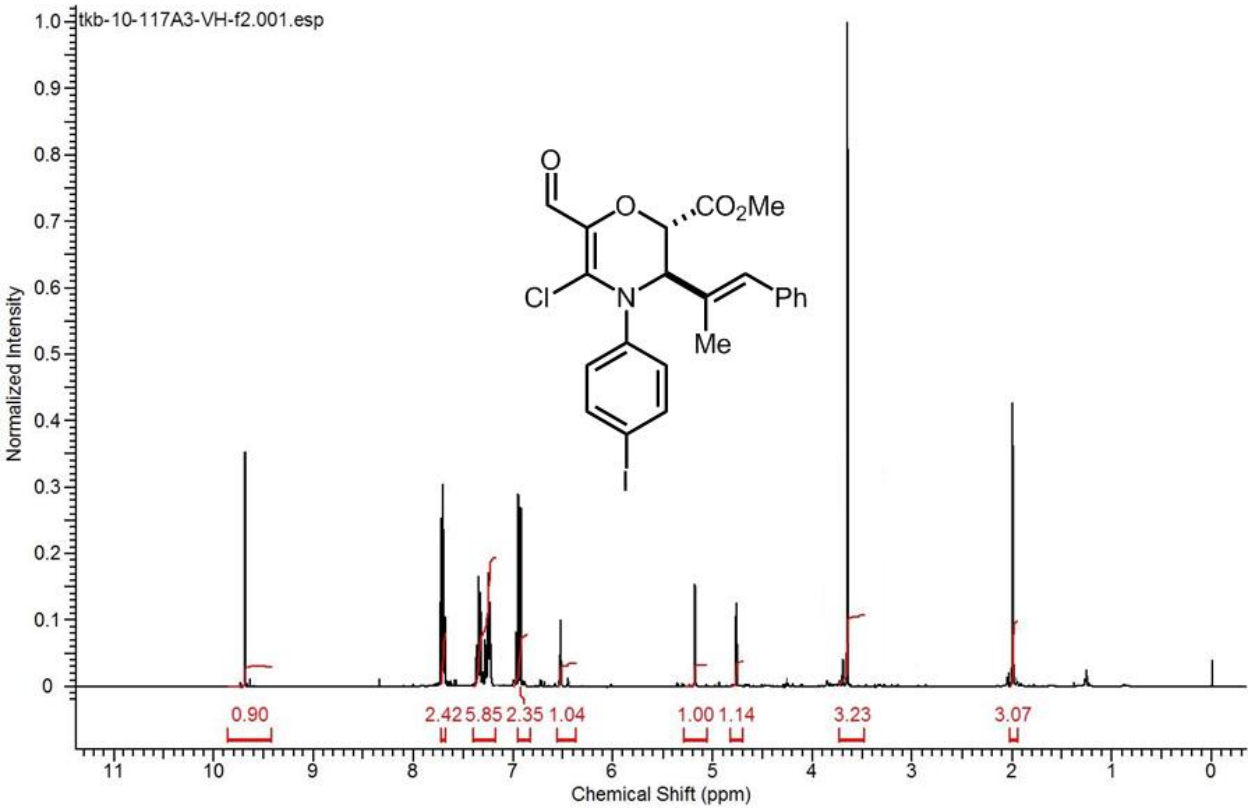


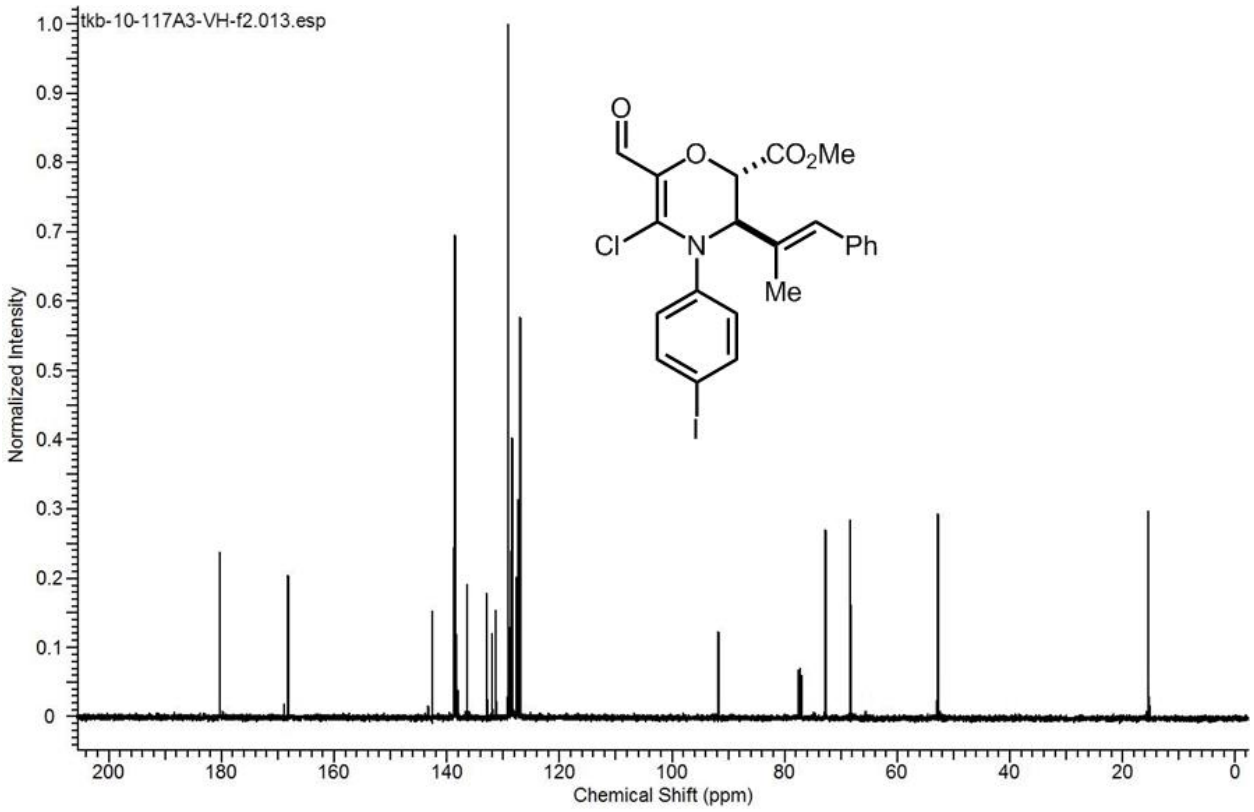




Compound **4a2:** Prepared in 1 mmol scale using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N)

eluting with hexane/EtOAc (80:20). Yield = 403.3 mg, 77%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.68 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.40 – 7.30 (m, 5H), 6.95 (d, *J* = 7.5 Hz, 2H), 6.52 (s, 1H), 5.18 (d, *J* = 1.5 Hz, 1H), 3.65 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.38, 168.19, 142.62, 138.69, 138.51, 138.36, 136.29, 129.15, 128.65, 128.39, 127.38, 126.90, 91.76, 72.80, 68.36, 52.79, 15.46. HRMS calc for $C_{22}H_{19}ClINO_4$, 523.0047, found 523.0041.

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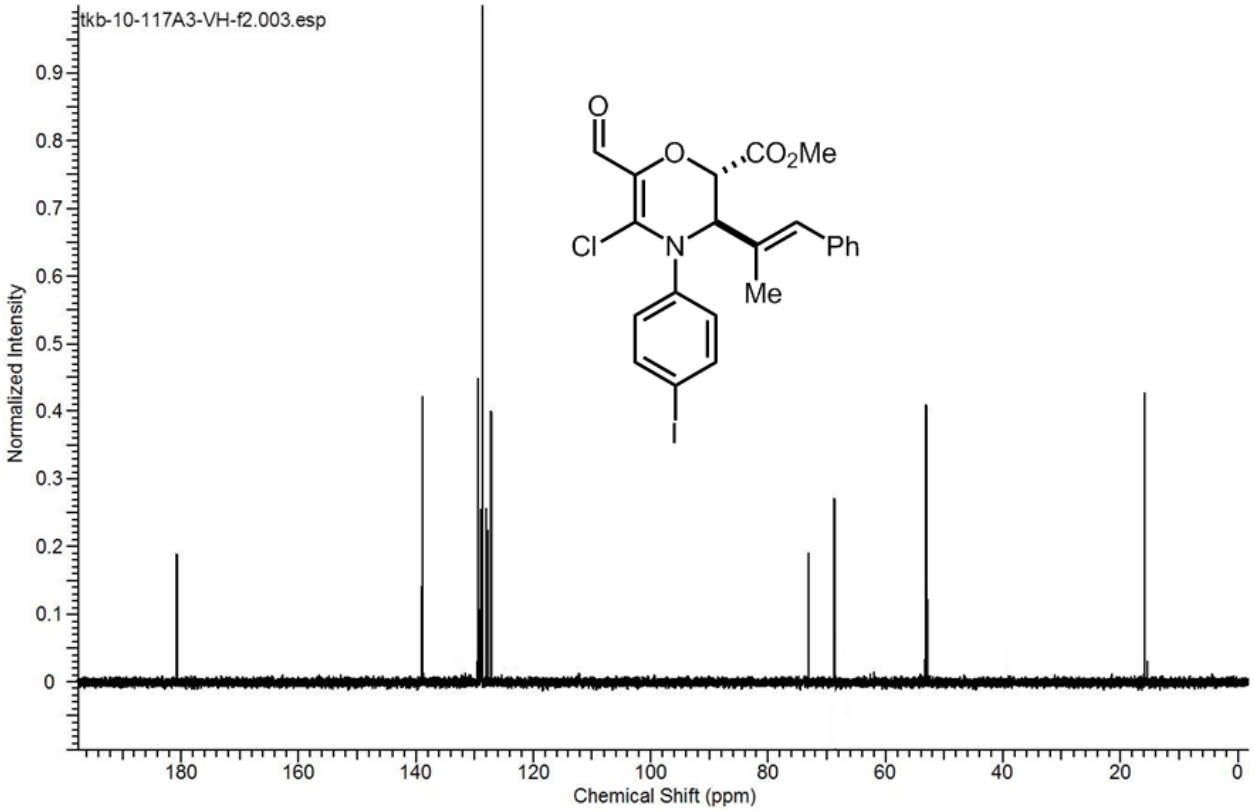
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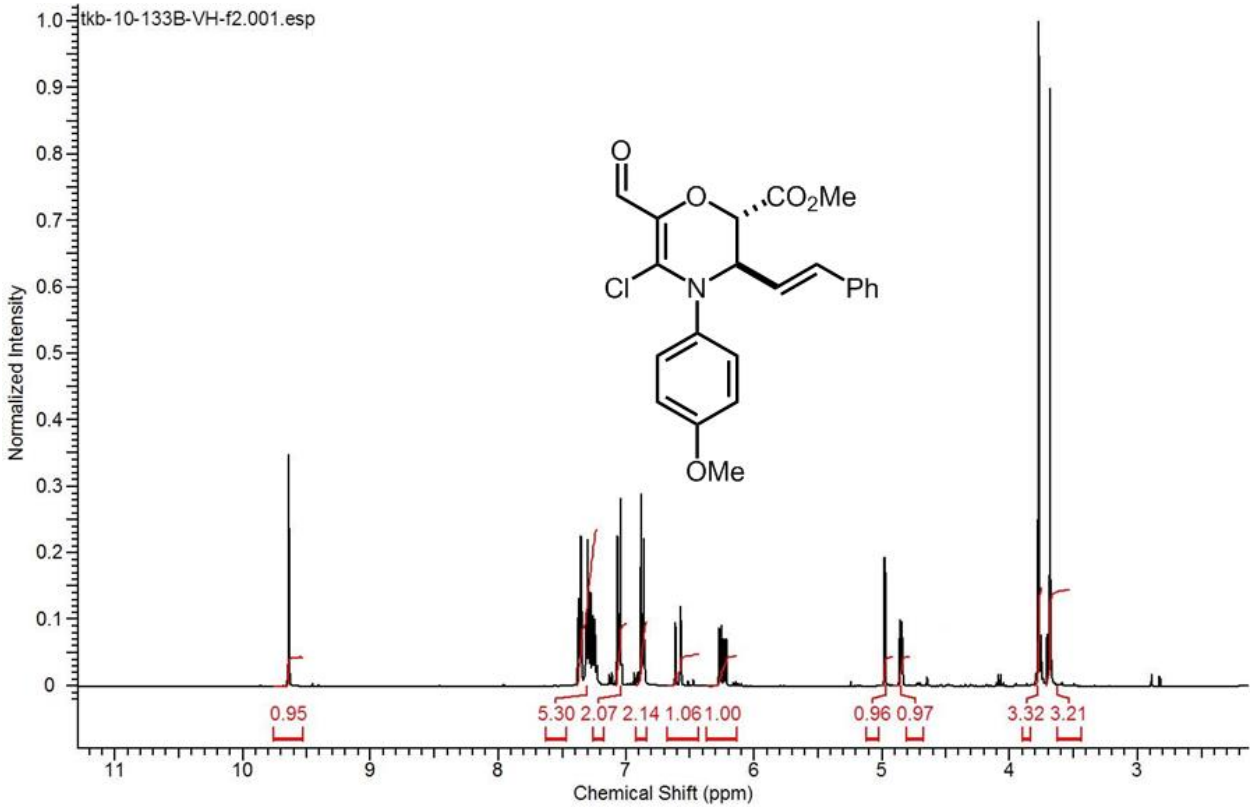
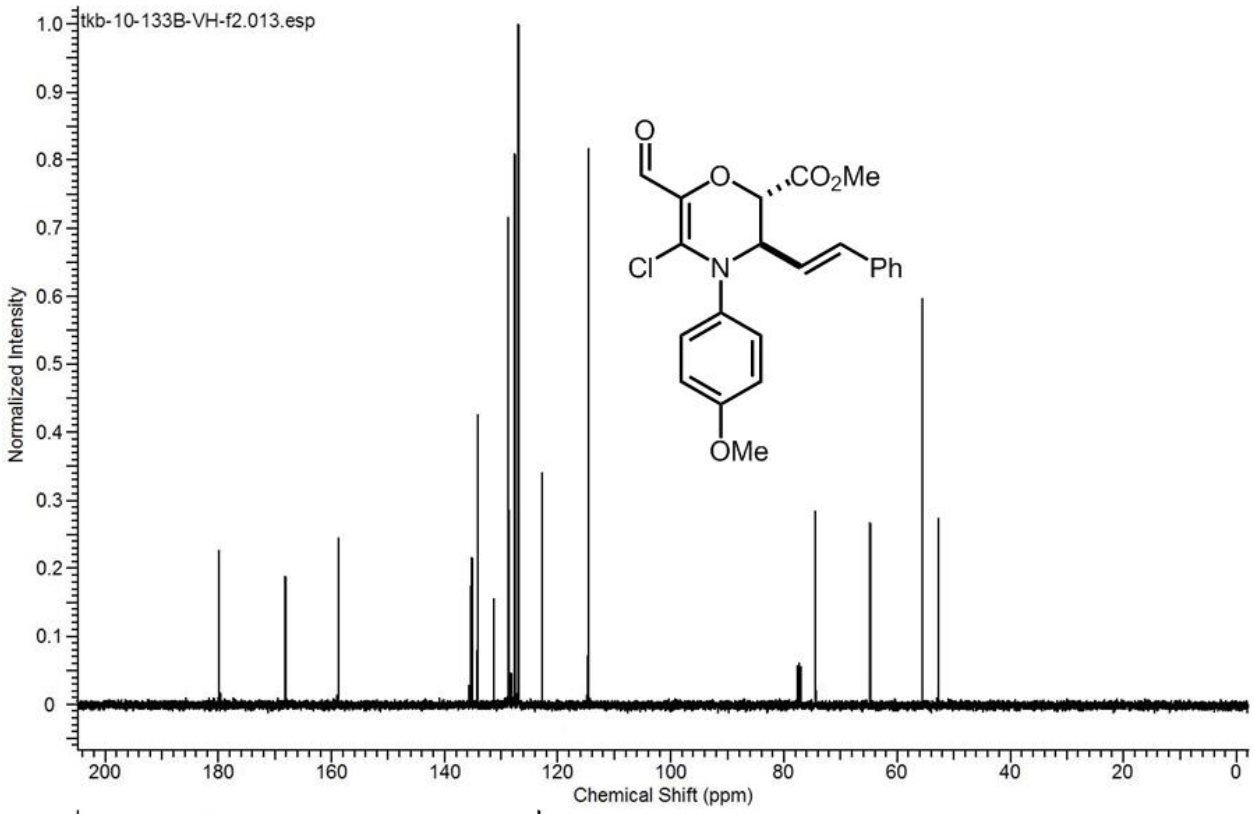
Compound **4a3:** Prepared in 1 mmol scale using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 347.6 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 7.40 – 7.29 (m, 5H), 7.15 (d, *J* = 6.7 Hz, 2H), 6.83 (d, *J* = 6.7 Hz, 2H), 6.59 (d, *J* = 15.7 Hz, 1H), 6.24 (dd, *J* = 15.8, 7.2 Hz, 1H), 4.98 (d, *J* = 1.6 Hz, 1H), 4.85 (d, *J* = 1.6 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.92, 168.13, 158.85, 135.45, 135.23, 134.14, 131.38, 128.78, 128.64, 127.64, 126.95, 126.92, 122.79, 114.58, 74.52, 64.74, 55.58, 52.74. HRMS calc for $C_{22}H_{20}ClNO_5$, 413.1030, found 413.1036.

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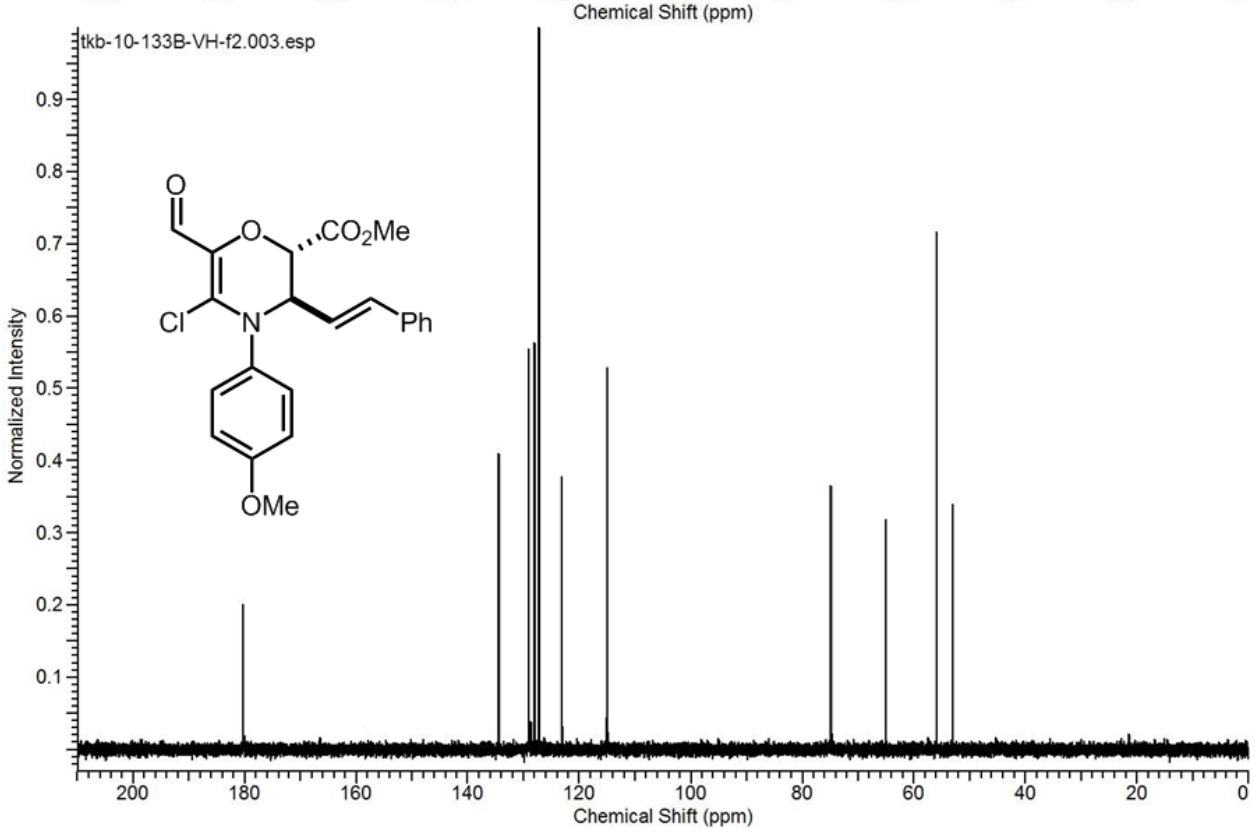
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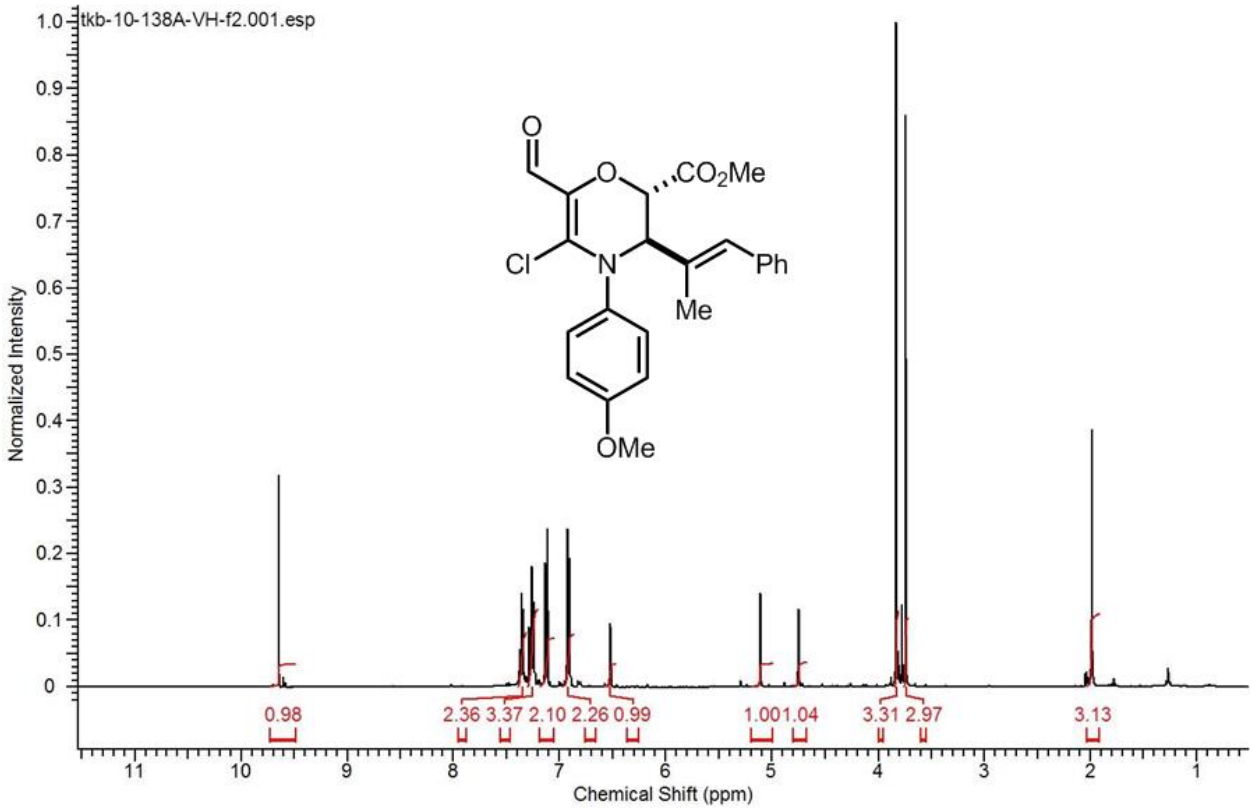
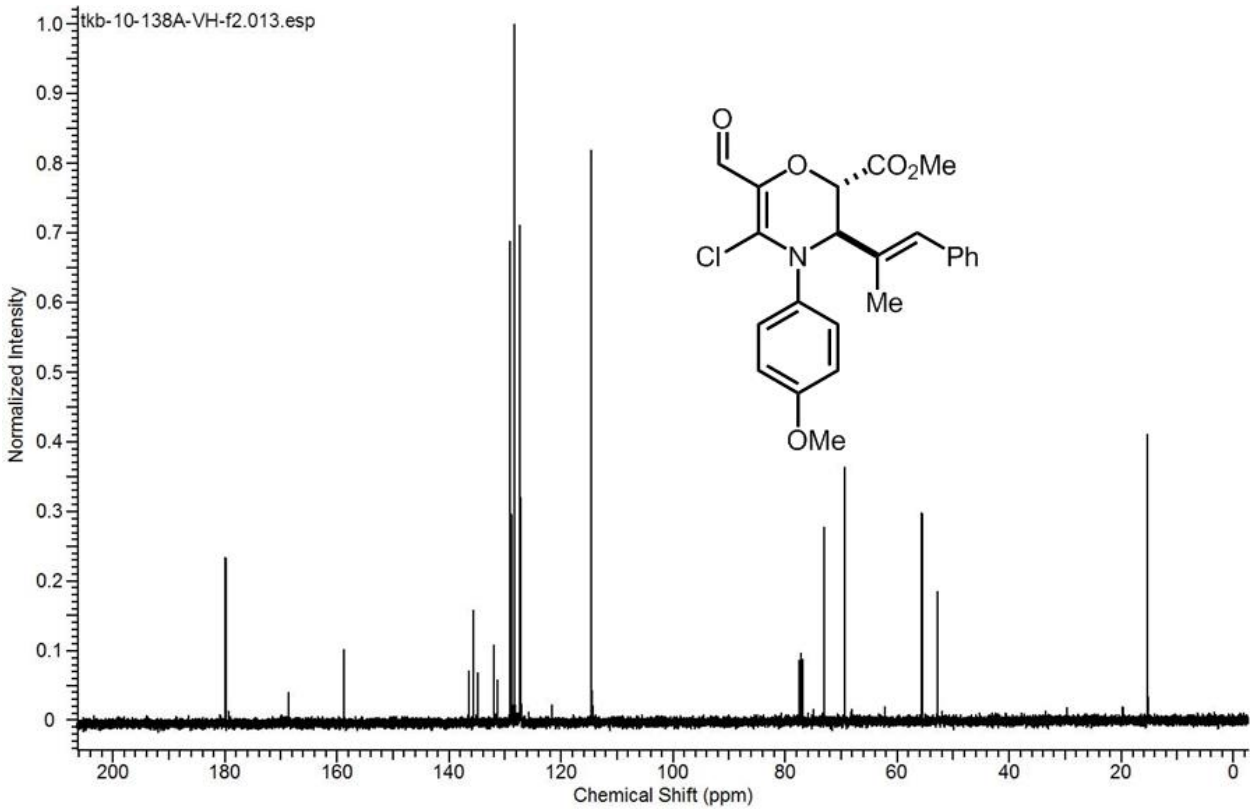
Compound **4a4:** Prepared in 1 mmol scale using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 372.3 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 7.41 – 7.29 (m, 2H), 7.31 – 7.22 (m, 3H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 7.5 Hz, 2H), 6.52 (s, 1H), 5.11 (d, *J* = 1.5 Hz, 1H), 4.75 (d, *J* = 1.5 Hz, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.88, 168.64, 158.83, 136.46, 135.67, 134.94, 132.07, 131.43, 129.13, 128.96, 128.39, 128.34, 127.36, 127.27, 114.55, 73.01, 69.37, 55.60, 52.81, 15.29. HRMS calc for $C_{23}H_{22}ClNO_5$, 427.1187, found 427.1182.

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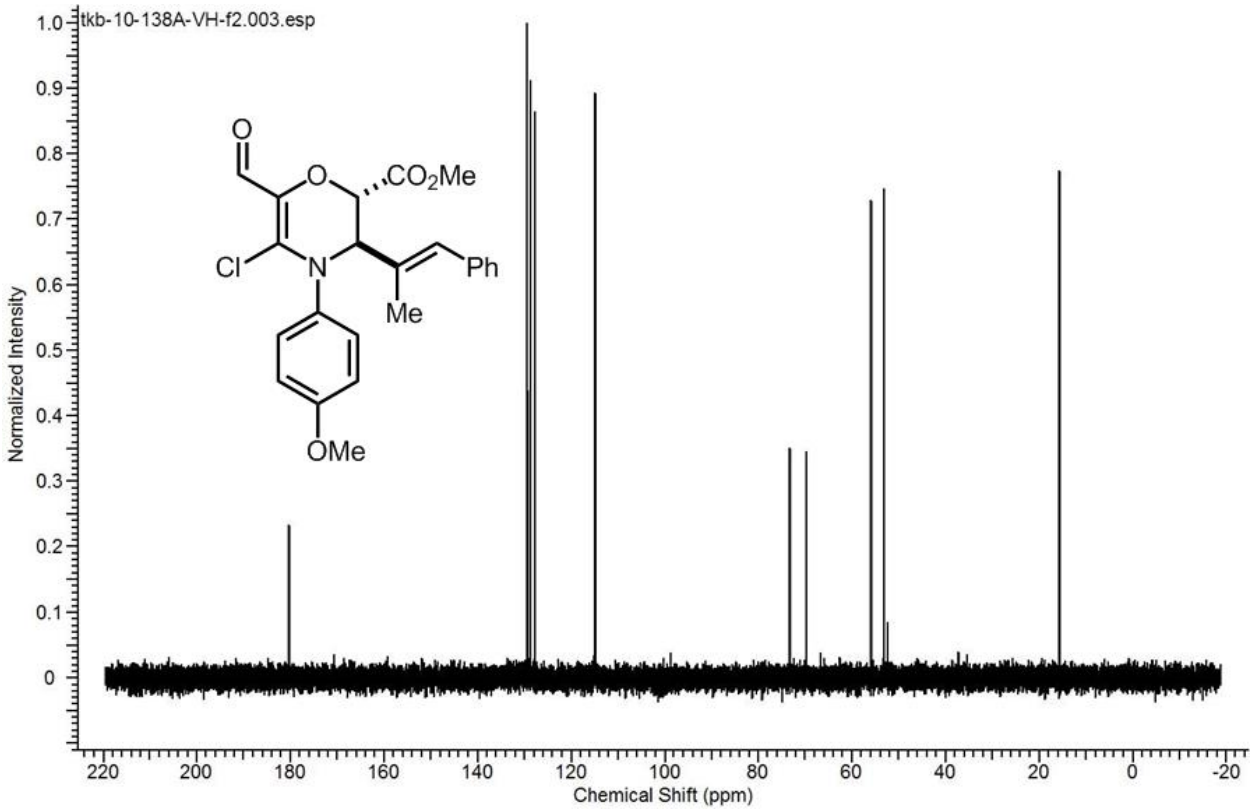
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Chemical Shift (ppm)
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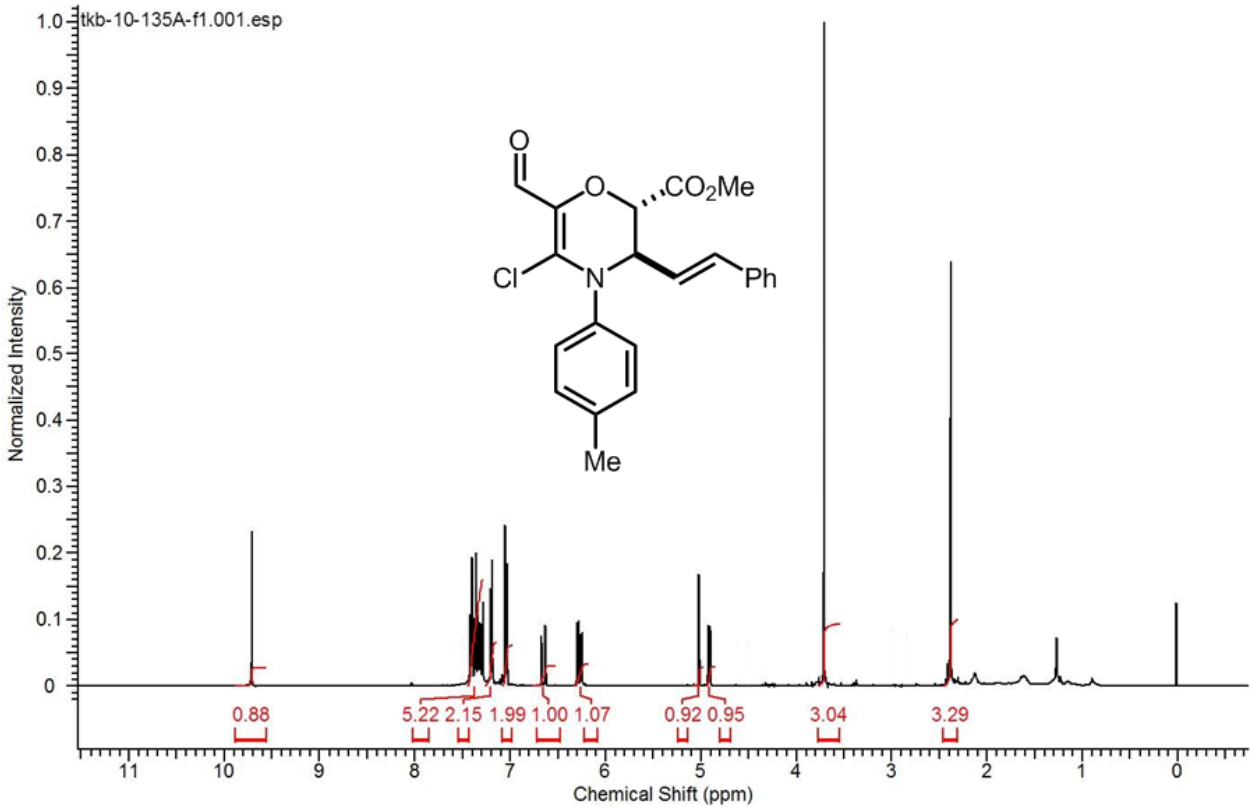
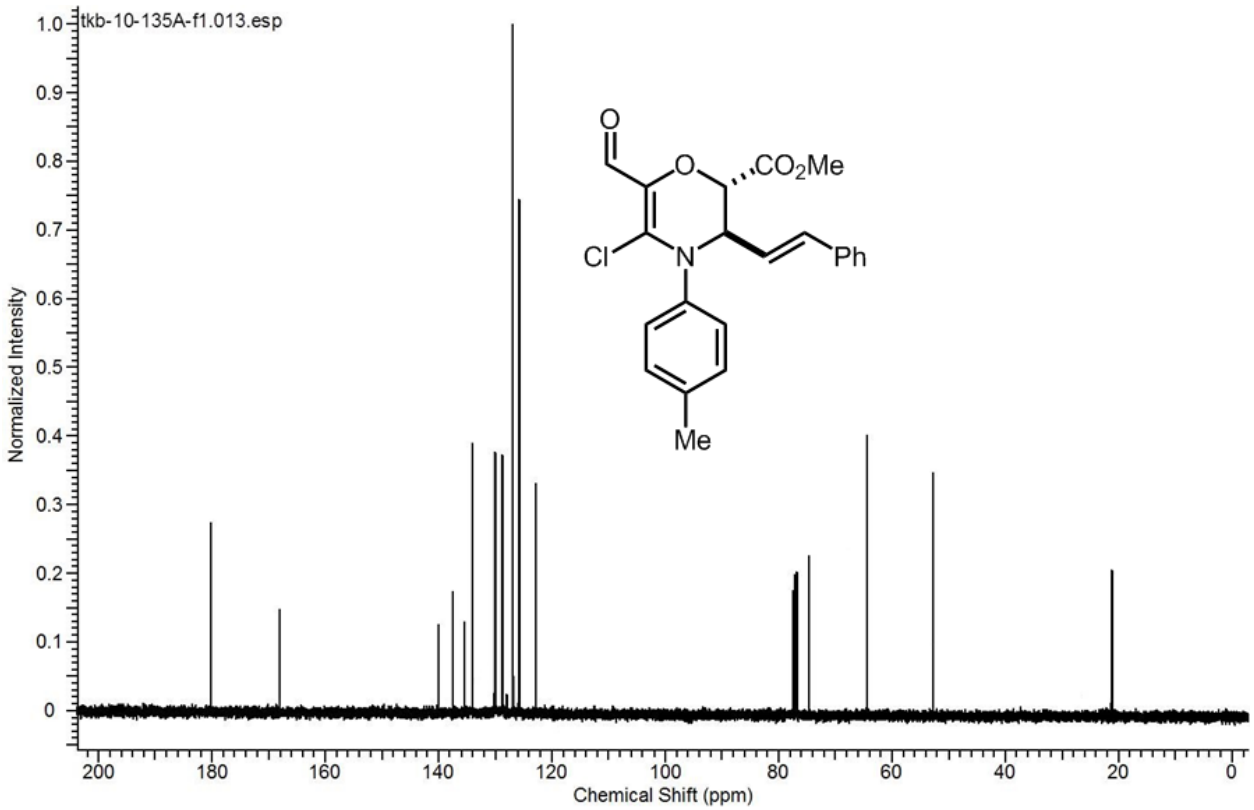
OMe

Compound **4a5:** Prepared in 1 mmol scale using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (85:15). Yield = 306.3 mg, 77%, 90:10 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.71 (s, 1H), 7.45 – 7.37 (m, 5H), 7.25 (d, 2H), 7.01 (d, 2H), 6.65 (dd, *J* = 15.8, 1.3 Hz, 1H), 6.28 (dd, *J* = 15.8, 7.0 Hz, 1H), 5.02 (d, *J* = 1.5 Hz, 1H), 4.91 (dt, *J* = 7.0, 1.5 Hz, 1H), 3.75 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.23, 168.12, 139.97, 137.50, 135.43, 134.10, 130.05, 128.80, 128.68, 126.93, 125.79, 122.81, 74.67, 64.42, 52.73, 21.14. HRMS calc for $C_{22}H_{20}ClNO_4$, 397.1081, found 397.1085.

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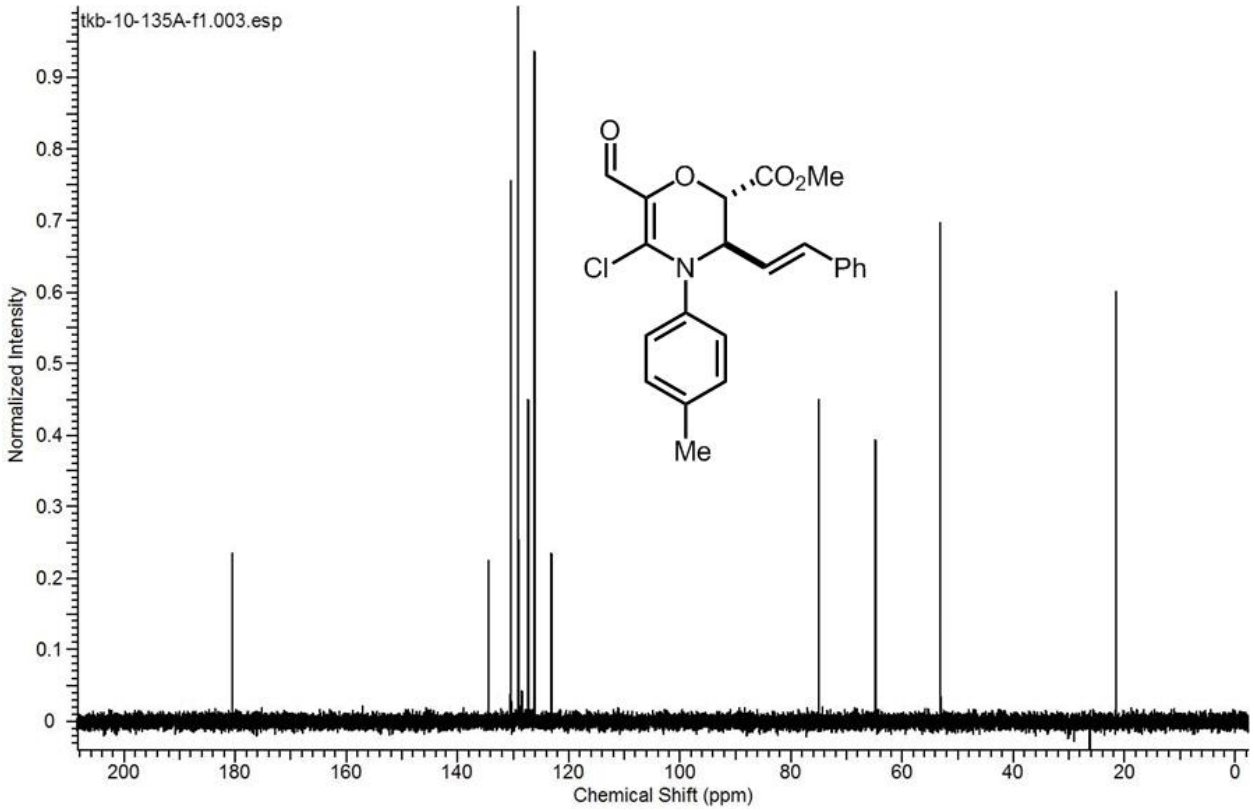
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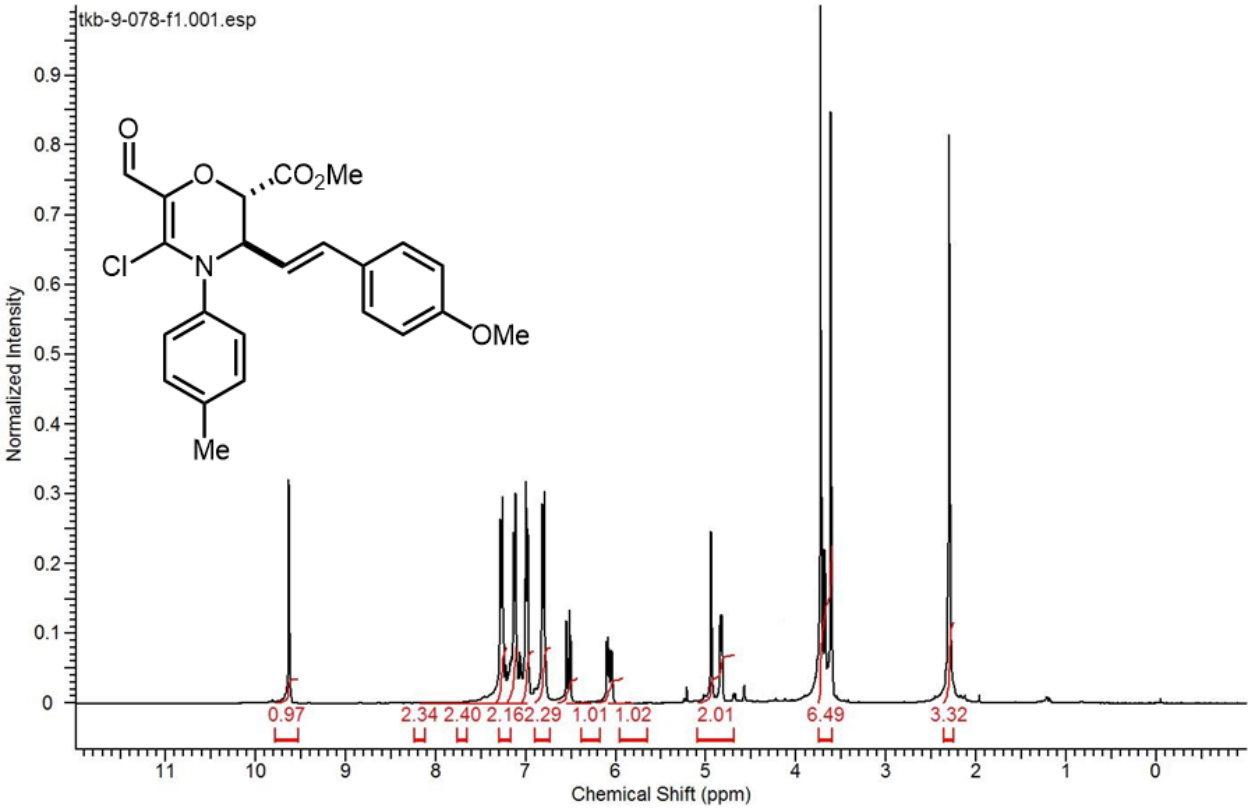
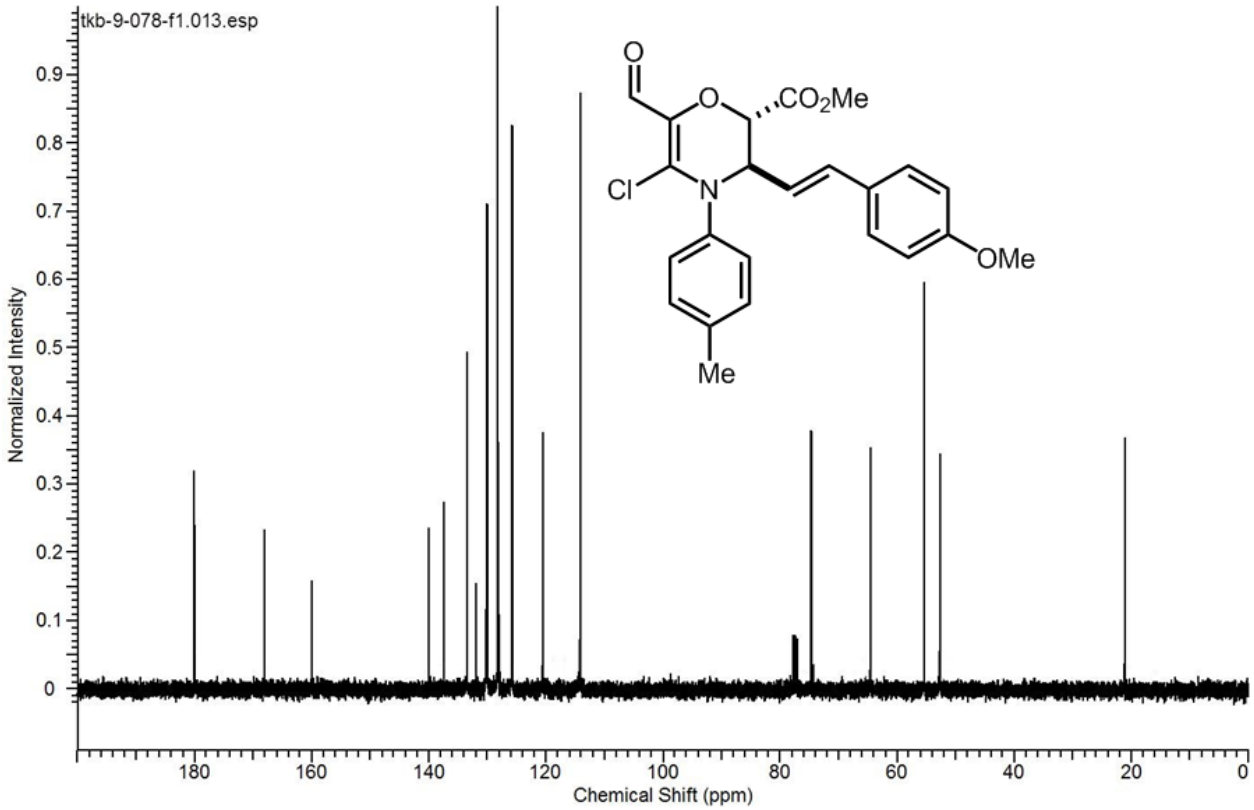
Compound **4a6:** Prepared in 5 mmol scale using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 1.71 g, 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.64 (s, 1H), 7.29 (d, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.88 (d, 2H), 6.80 (dd, 2H), 6.5 (d, *J* = 14.6 Hz, 1H), 6.11 (m, 1H), 4.95 - 4.60 (m, 2H), (3.84 – 3.52 (m, 6H), 2.41 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 168.3, 140.9, 138.6, 134.8, 132.8, 129.2, 128.0, 127.5, 120.6, 114.0, 74.7, 64.1, 54.3, 52.9, 21.4. HRMS calc for $C_{23}H_{22}ClNO_5$, 427.1187, found 427.1183.

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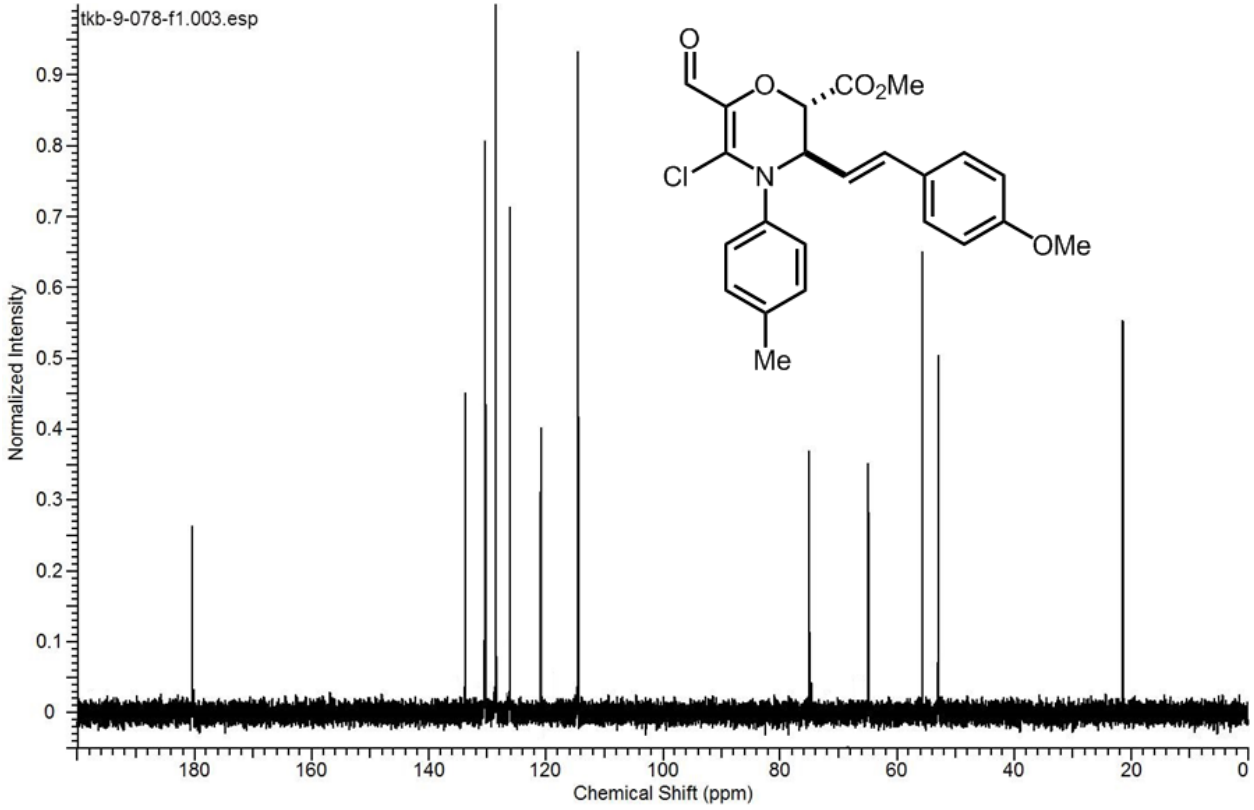
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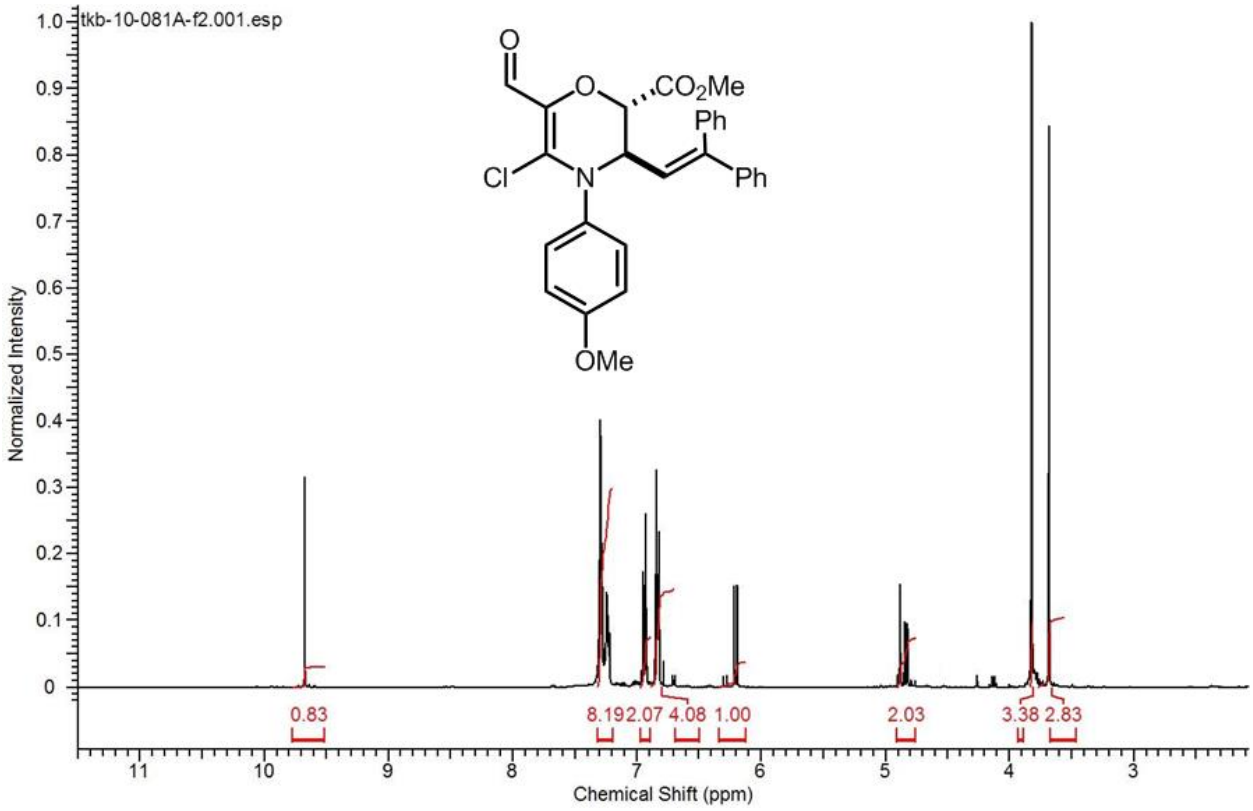
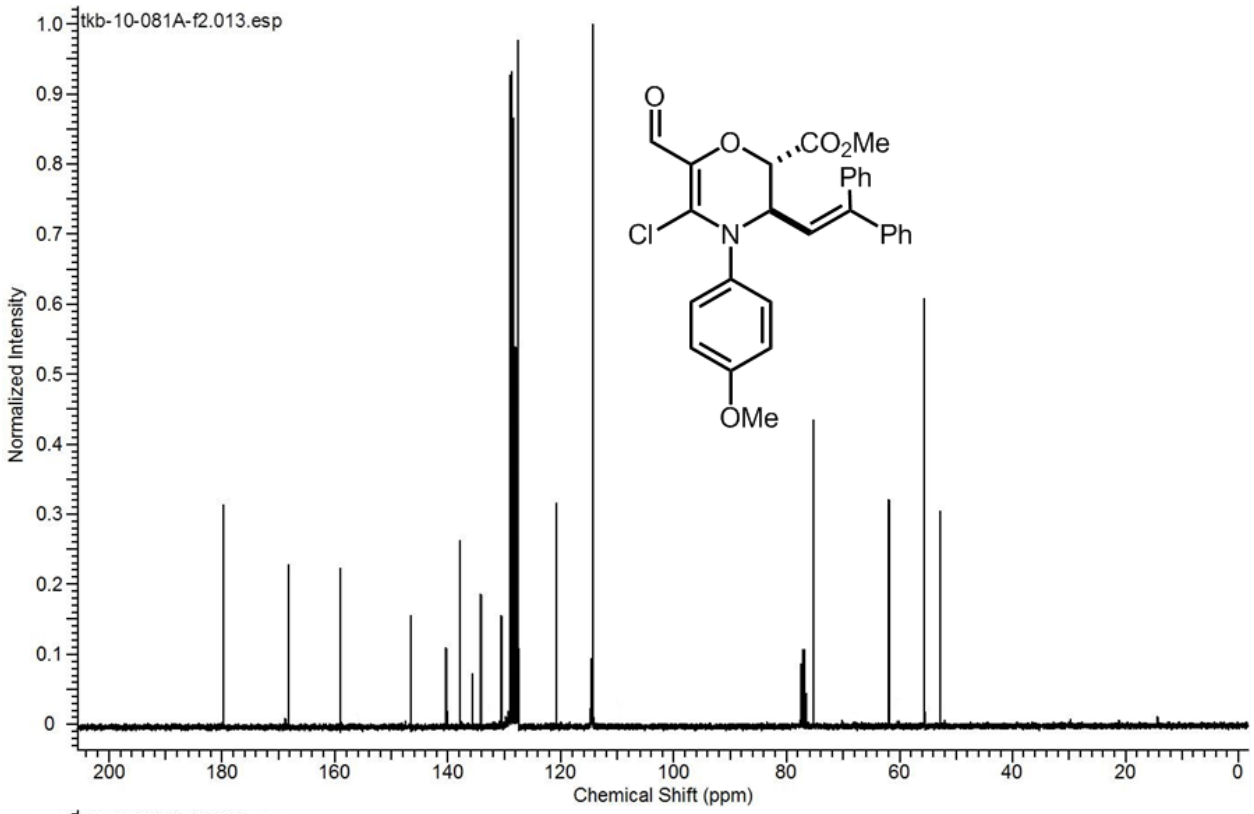
Compound **4a7:** Prepared in 1 mmol scale using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 426.3 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.67 (s, 1H), 7.37 – 7.26 (m, 8H), 7.01 – 6.88 (m, 2H), 6.88 – 6.77 (m, 4H), 6.21 (d, *J* = 10.0 Hz, 1H), 4.92 – 4.86 (m, 1H), 4.83 (dd, *J* = 10.1, 1.8 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.73, 168.24, 159.03, 146.54, 140.32, 137.89, 135.73, 134.21, 129.04, 128.64, 128.60, 128.48, 128.44, 127.98, 127.54, 120.80, 114.42, 75.29, 61.95, 55.62, 52.82. HRMS calc for $C_{28}H_{24}ClNO_5$, 489.1343, found 489.1348.

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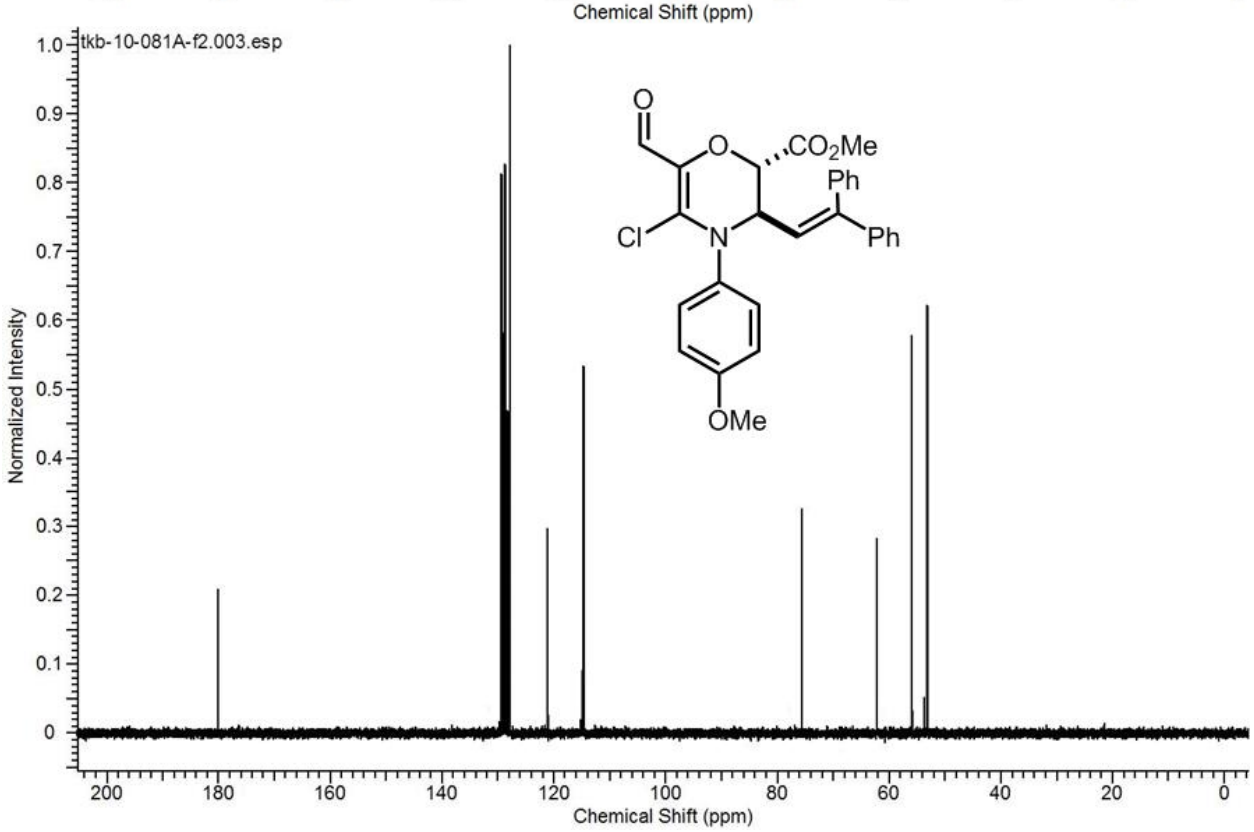
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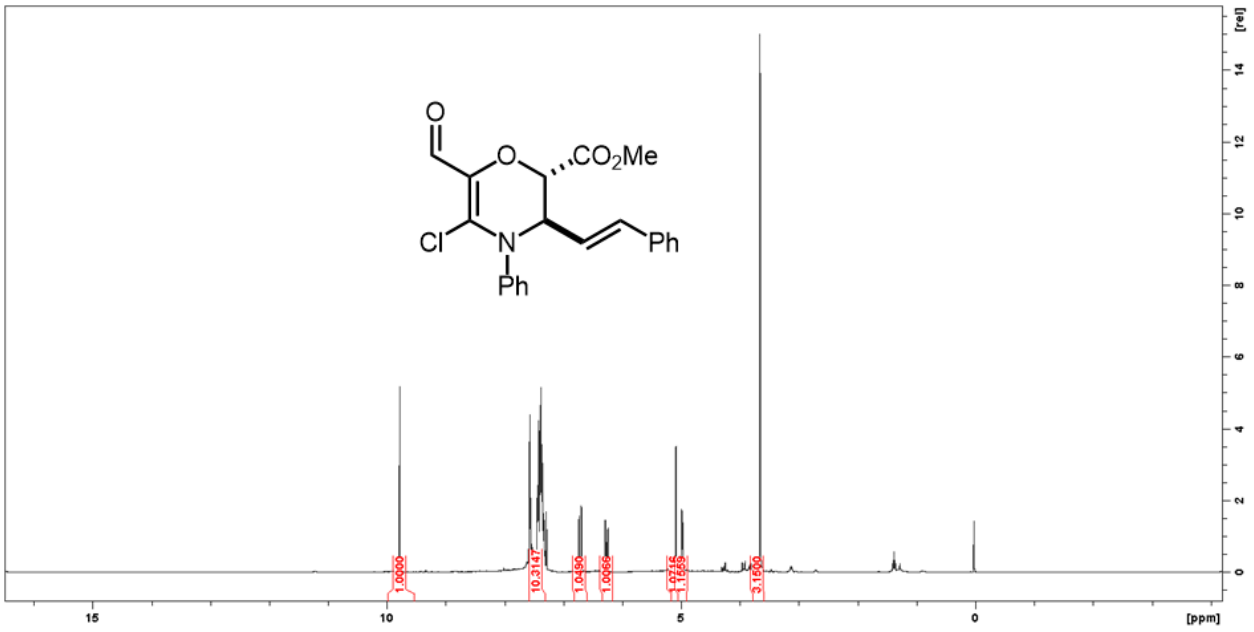
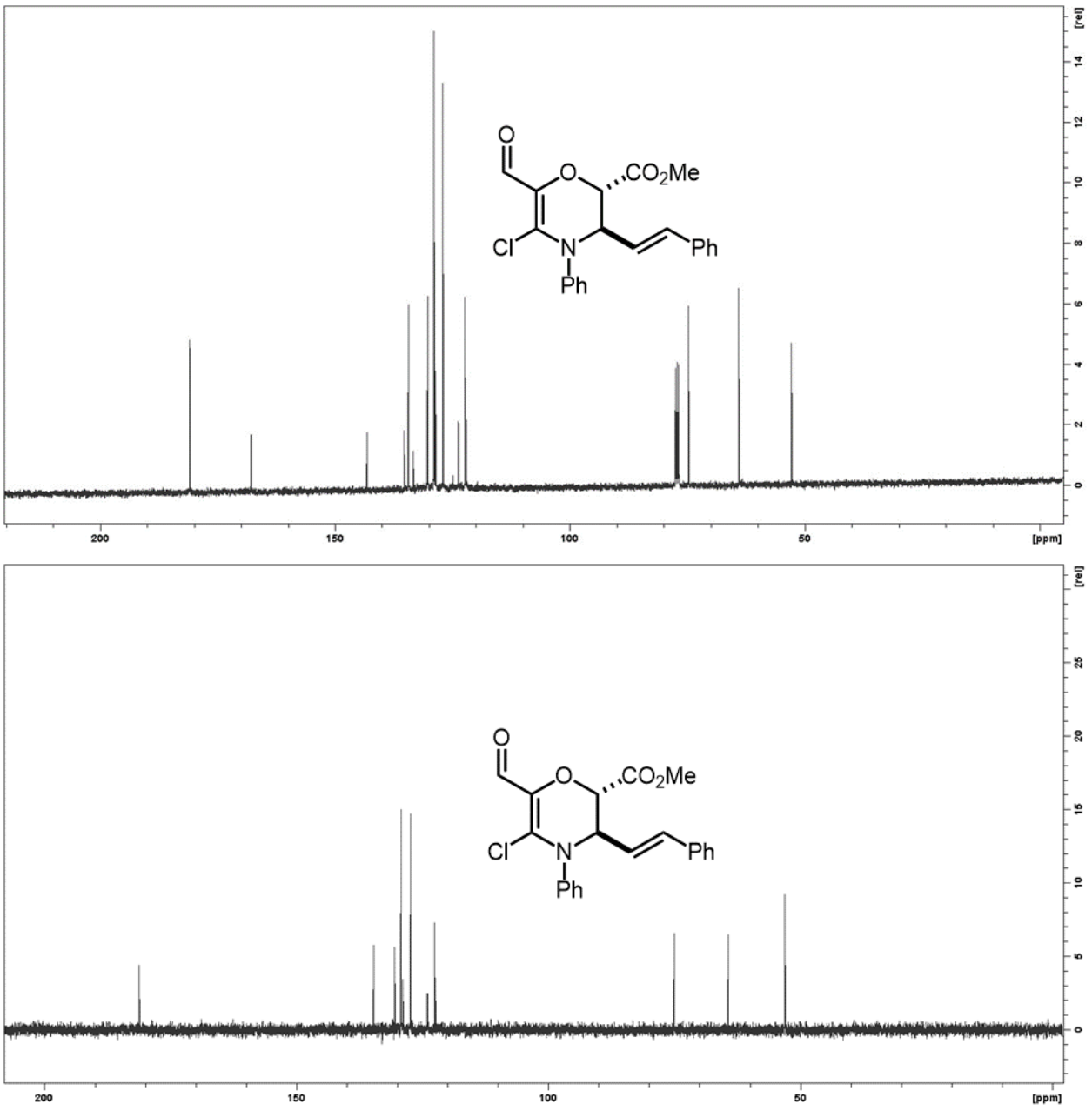
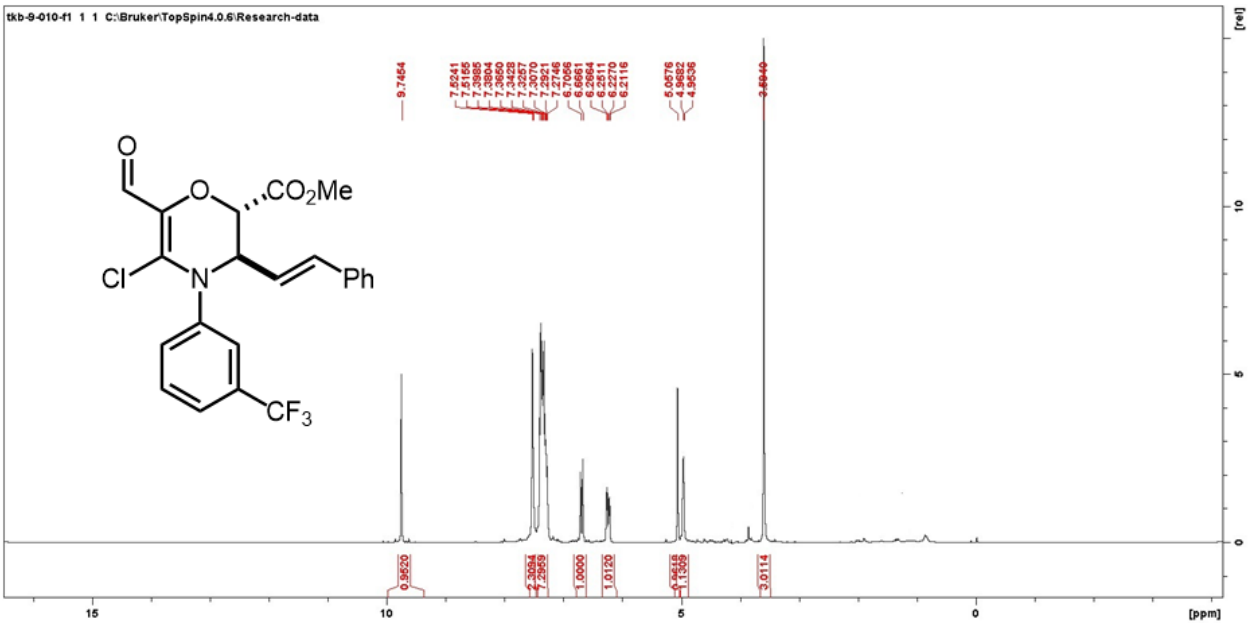
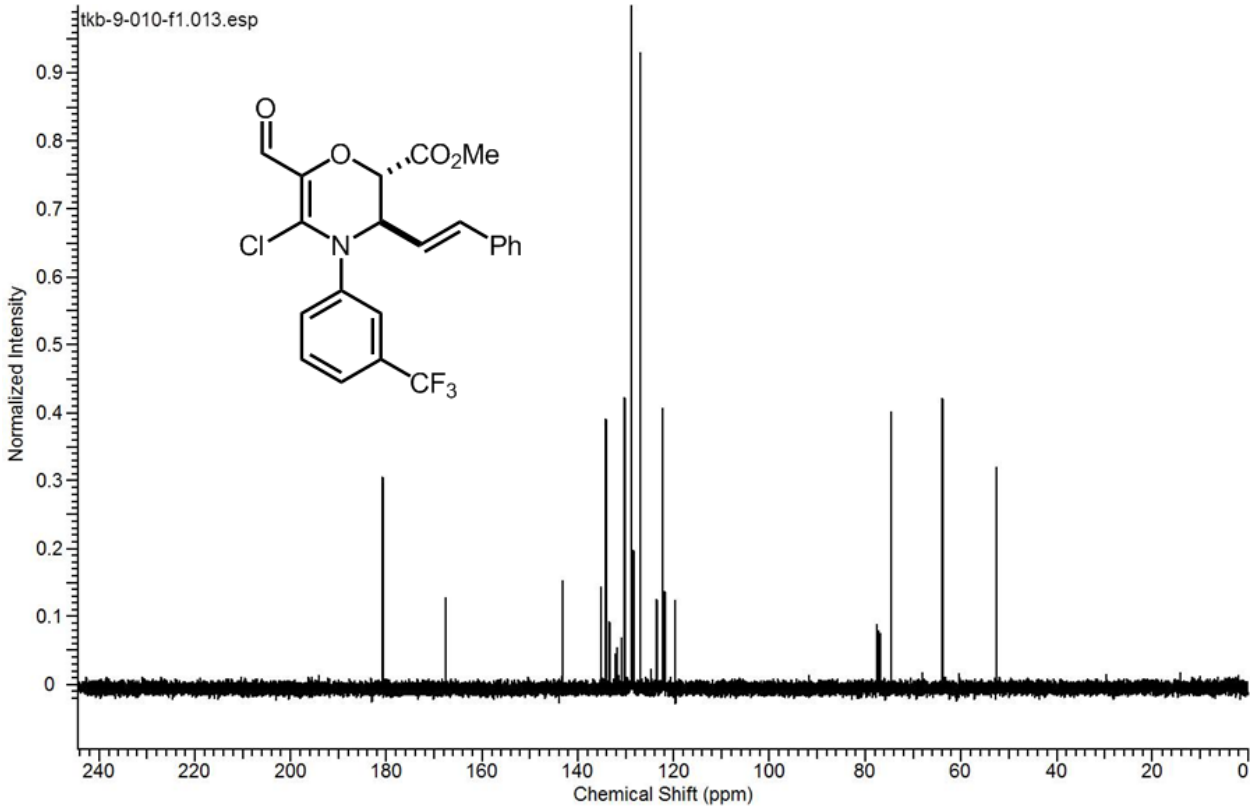
Compound **4a8:** Prepared using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 280 mg, 73%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.41 - 7.11 (m, 10H), 6.65 (d, *J* = 15.8 Hz, 1H), 6.27 (dd, *J* = 15.8 Hz, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 4.74 (d, *J* = 12.8 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 167.9, 142.4, 135.9, 134.2, 129.7, 128.8, 127.3, 126.8, 125.7, 124.8, 122.6, 74.4, 64.2, 52.2. HRMS calc for $C_{21}H_{18}ClNO_4$, 383.0924, found 383.0929.

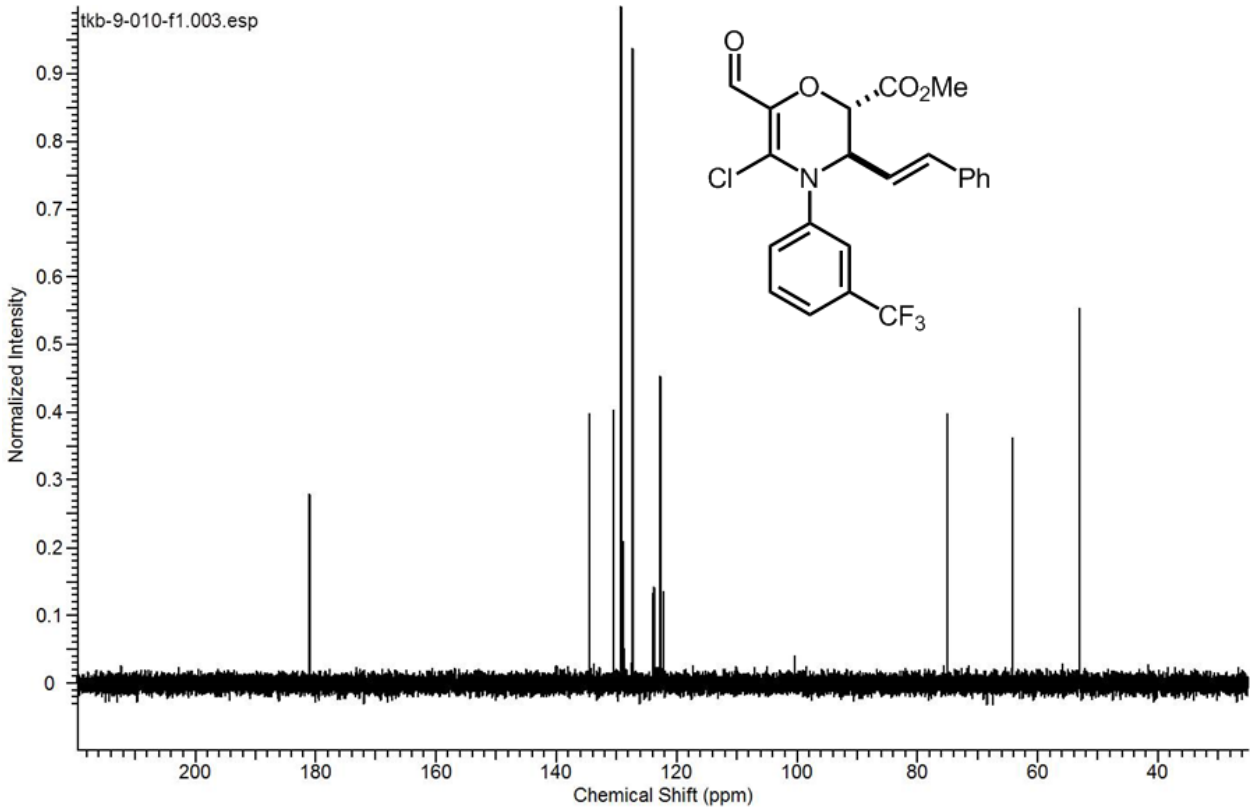




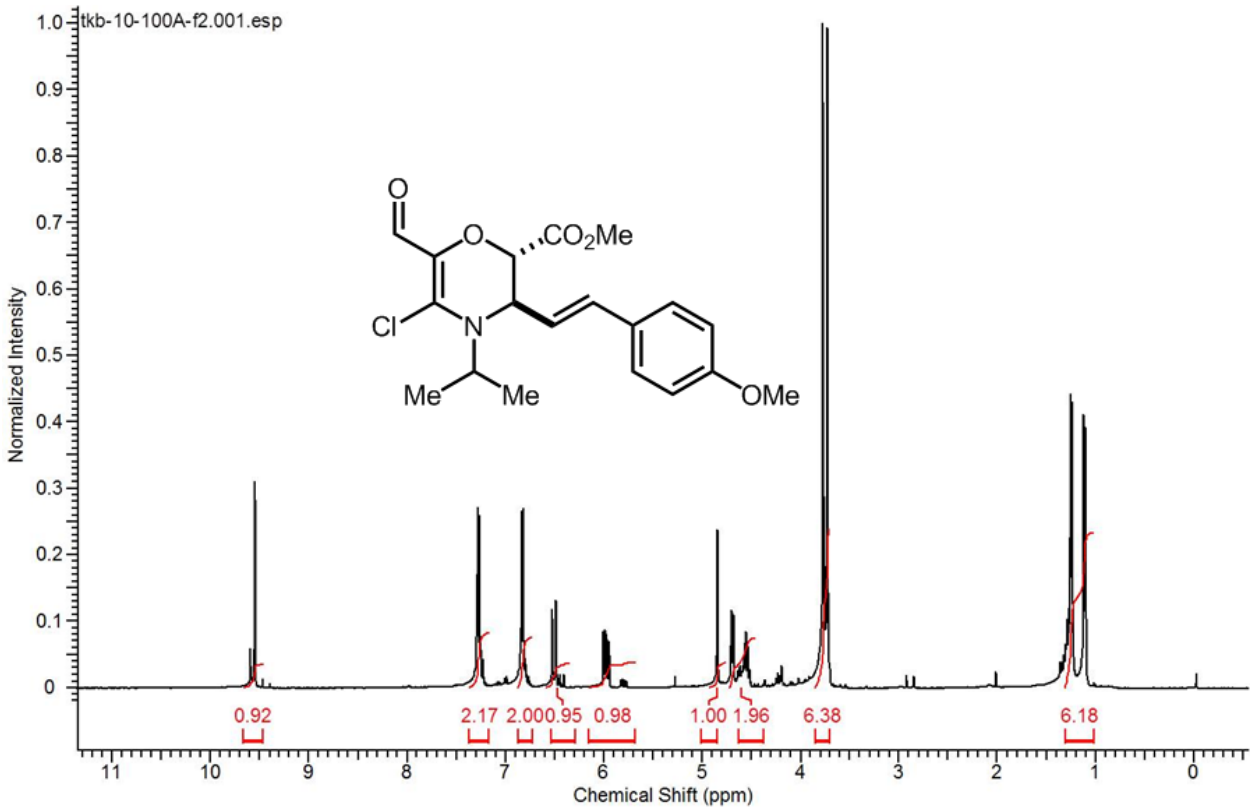
Compound **4a9:** Prepared using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 352 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.75 (s, 1H), 7.52 (d, *J* = 4.6 Hz, 2H), 7.42 – 7.23 (m, 7H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 15.9, 6.3 Hz, 1H), 5.06 (s, 1H), 4.96 (d, *J* = 6.3 Hz, 1H), 3.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.6, 167.6, 143.1, 135.2, 134.1, 133.4, 132.0, 131.7, 130.8, 128.8, 126.9, 124.8, 123.5, 122.1, 121.9, 119.6, 74.6, 63.8, 52.6. HRMS calc for $C_{22}H_{17}ClF_3NO_4$, 451.0798, found 451.0793.


tkb-9-010-f1 1 1 C:\Bruker\TopSpin4.0.6\Research-data
9.7464
7.5241
7.5165
7.3985
7.3904
7.3850
7.3428
7.3307
7.3070
7.2921
7.2748
6.7686
6.7561
6.2564
6.2511
6.2270
6.2116
5.0576
4.9882
4.9505
3.8940
0.9520
2.3094
2.2969
1.0000
1.0120
0.9618
1.1309
3.0114
O
O
CO2Me
Cl
N
Ph
CF3
15
10
5
0
[ppm]


tkb-9-010-f1.013.esp
O
O
CO2Me
Cl
N
Ph
CF3
Normalized Intensity
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
240
220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



Compound **4a10:** Prepared using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25). Yield = 265.7 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.97 (dd, *J* = 15.8, 7.5 Hz, 1H), 4.85 (s, 1H), 4.69 (d, *J* = 7.5 Hz, 1H), 4.66 – 4.50 (m, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.35, 168.47, 159.89, 136.46, 133.89, 132.57, 129.98, 128.21, 128.10, 128.05, 122.18, 118.67, 114.12, 75.22, 55.93, 55.37, 52.76, 50.64, 21.31, 20.40. HRMS calc for $C_{19}H_{22}ClNO_5$, 379.1187, found 379.1193.


tkb-10-100A-f2.001.esp
Normalized Intensity
Chemical Shift (ppm)
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2.17
2.00
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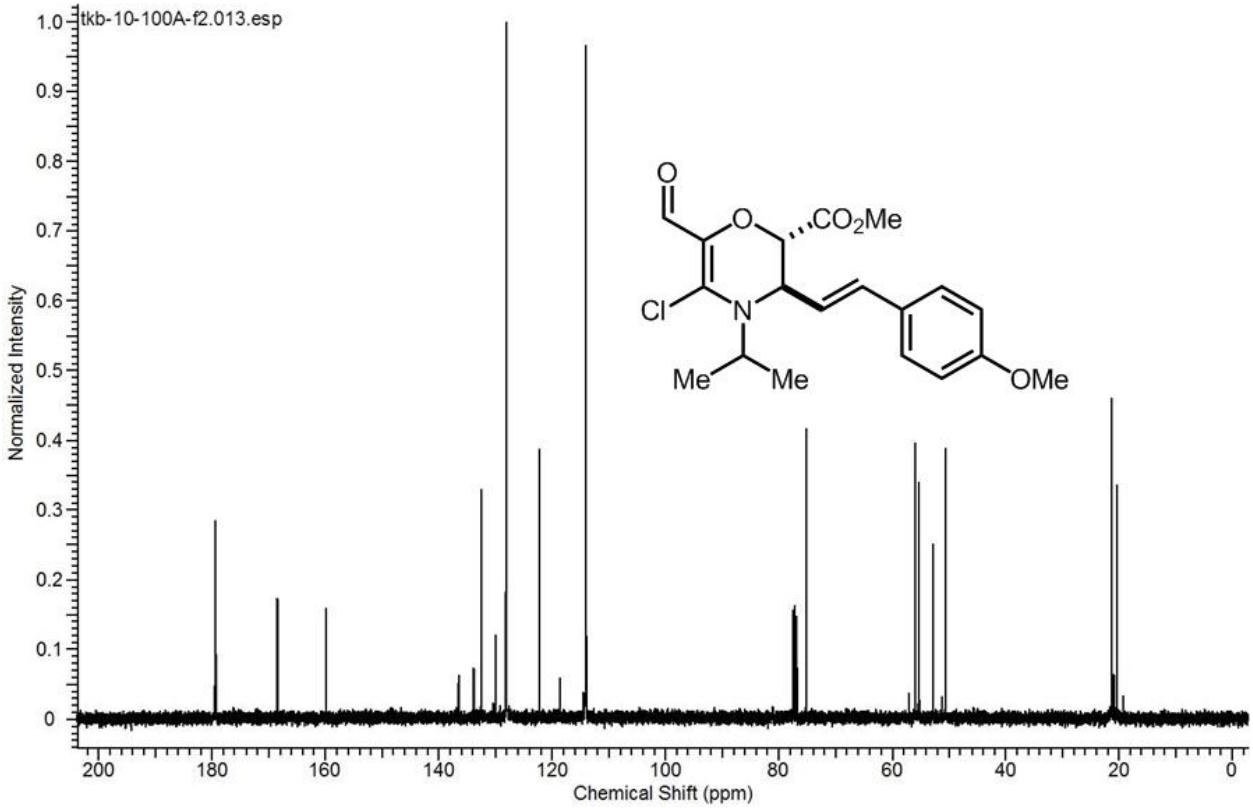
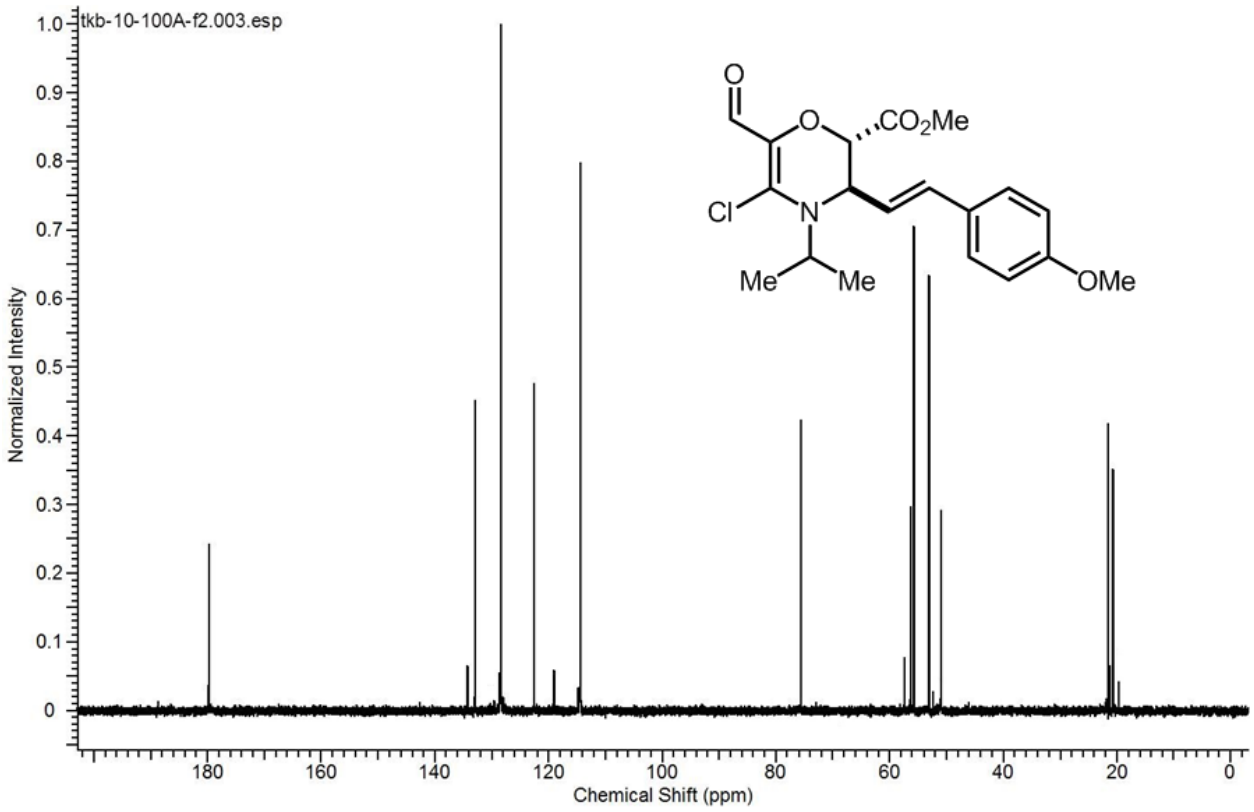
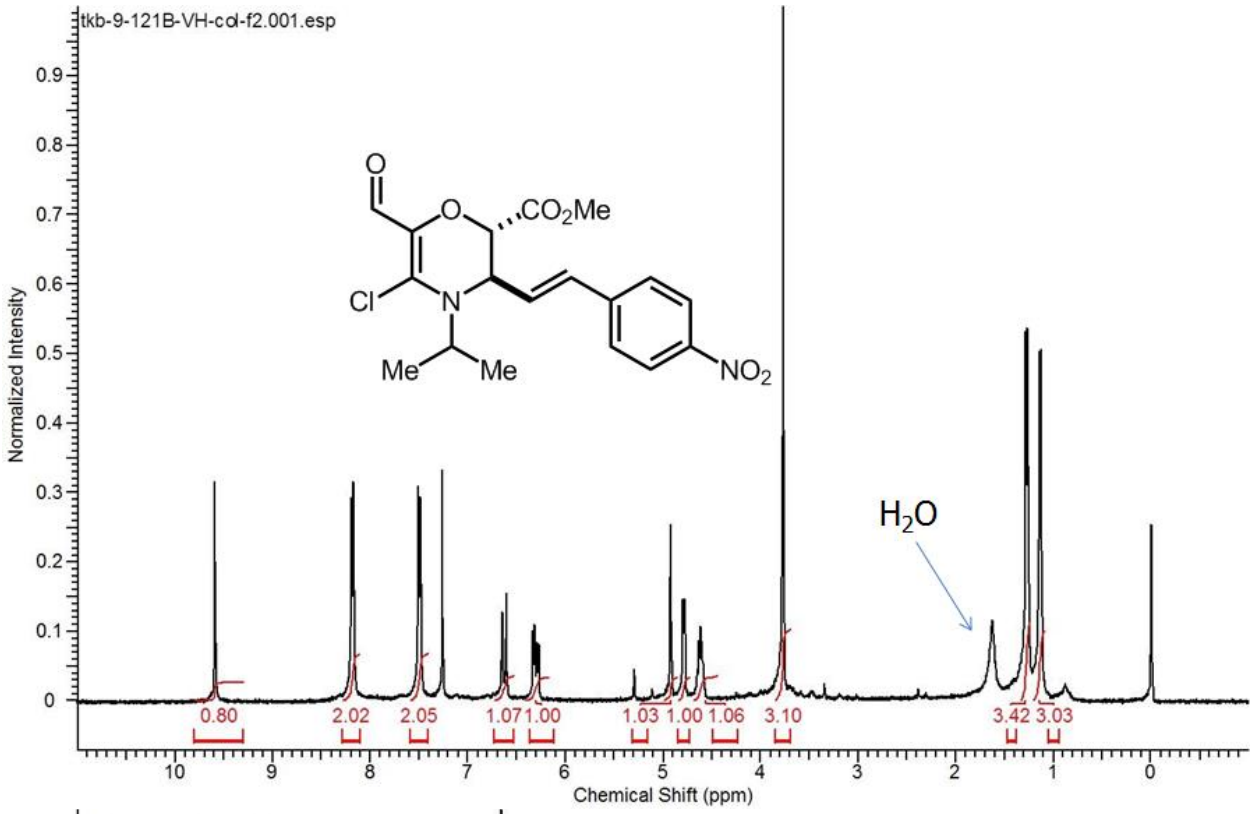
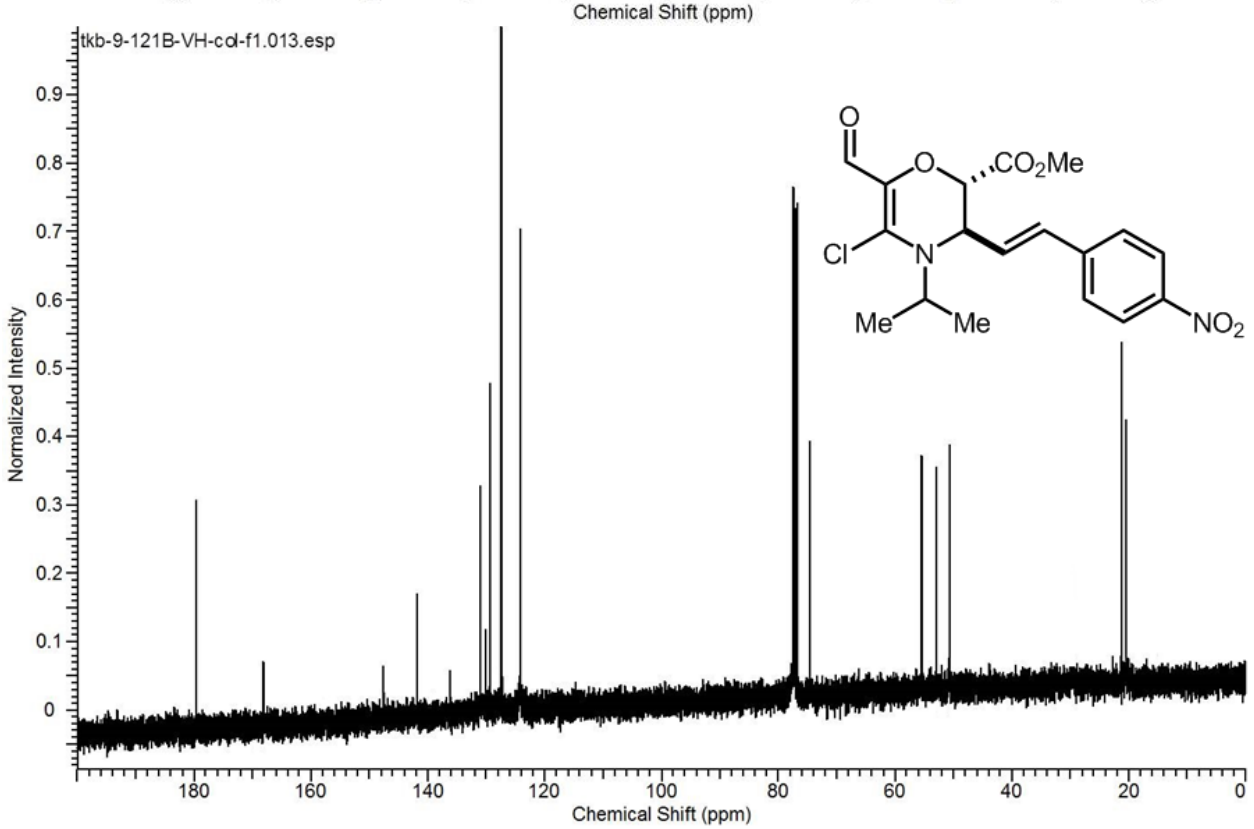
0.98
1.00
1.96
6.38
6.18
O
O
CO2Me
Cl
N
Me
Me
OMe

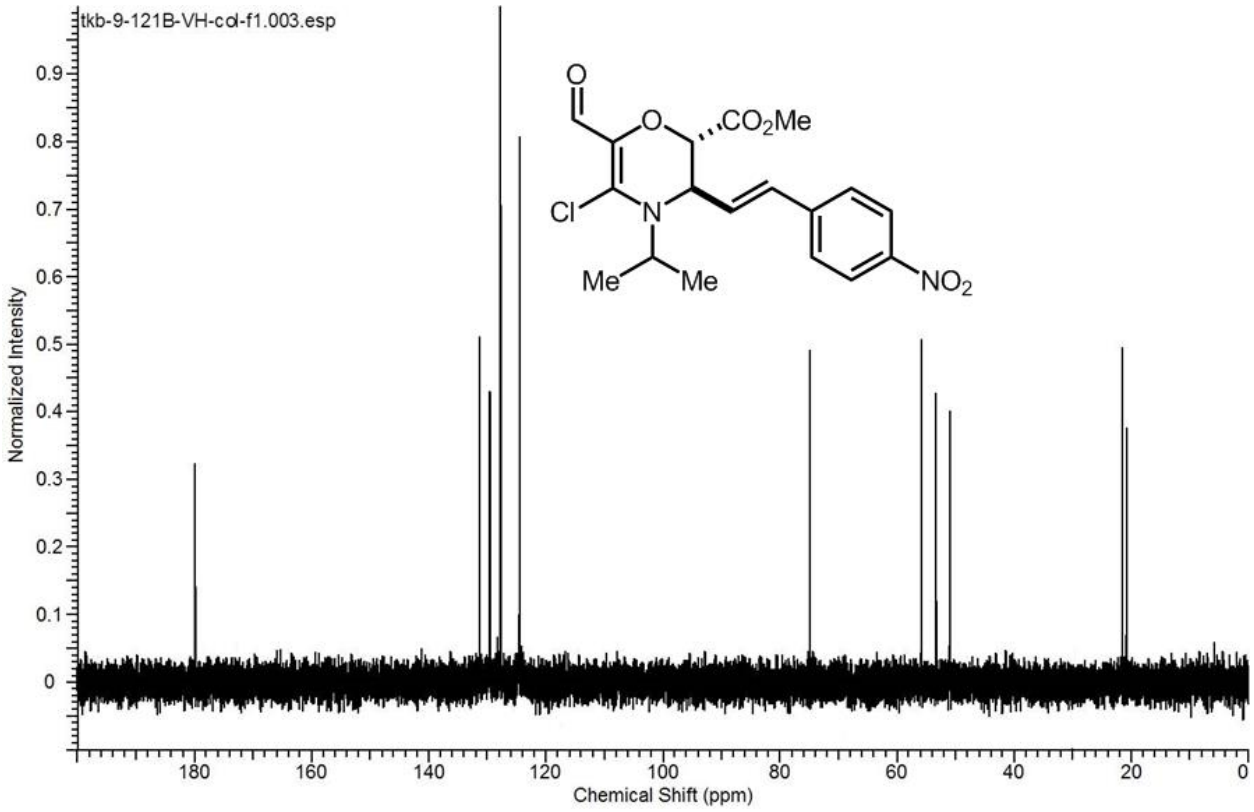

tkb-10-100A-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
Cl
N
Me
Me
OMe



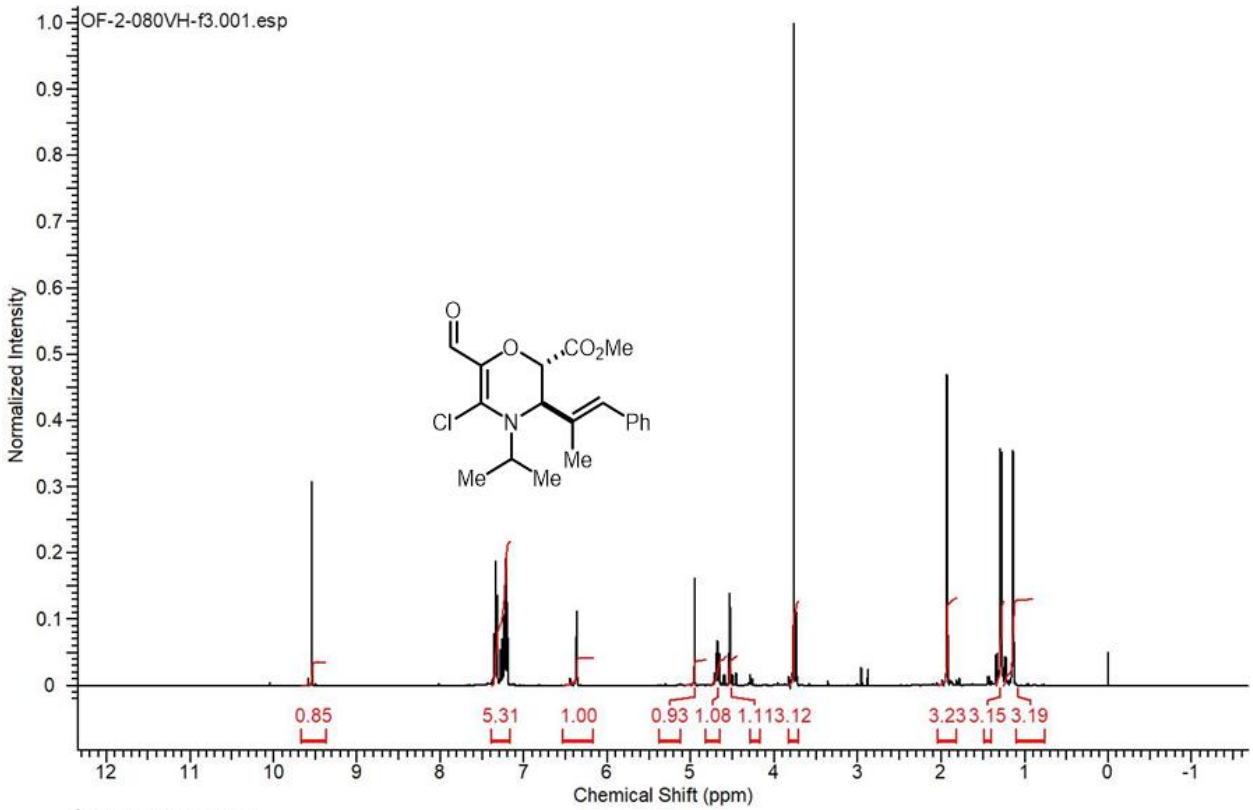
Compound **4a11:** Prepared using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 304 mg, 77%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.59 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.30 (dd, *J* = 15.8, 7.0 Hz, 1H), 4.92 (s, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.62 (m, 1H), 3.77 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 179.64, 168.24, 147.57, 141.78, 131.02, 130.18, 129.30, 127.44, 124.15, 77.41, 77.09, 76.77, 74.66, 55.47, 53.01, 50.60, 21.25, 20.45. HRMS calc for $C_{18}H_{19}ClN_2O_6$, 394.0932, found 394.0938.


tkb-9-121B-VH-col-f2.001.esp
Normalized Intensity
Chemical Shift (ppm)
H_2O
0.80
2.02
2.05
1.07
1.00
1.03
1.00
1.06
3.10
3.42
3.03
O
O
CO_2Me
Cl
N
Me
Me
NO_2


tkb-9-121B-VH-col-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO_2Me
Cl
N
Me
Me
NO_2



Compound **4a12:** Prepared using **General Procedure A**. Temp = room temperature, time = 22 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25). Yield = 316.5 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.40 – 7.16 (m, 5H), 6.37 (s, 1H), 4.95 (d, *J* = 1.3 Hz, 1H), 4.74 – 4.57 (m, 1H), 4.53 (d, *J* = 1.3 Hz, 1H), 3.77 (s, 3H), 1.93 (s, 3H), 1.32 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.26, 168.93, 136.53, 133.83, 129.03, 128.30, 128.17, 127.15, 73.17, 60.70, 52.88, 50.81, 20.49, 20.38, 15.36. HRMS calc for $C_{19}H_{22}ClNO_4$, 363.1237, found 363.1233.


OF-2-080VH-f3.001.esp
Normalized Intensity
Chemical Shift (ppm)
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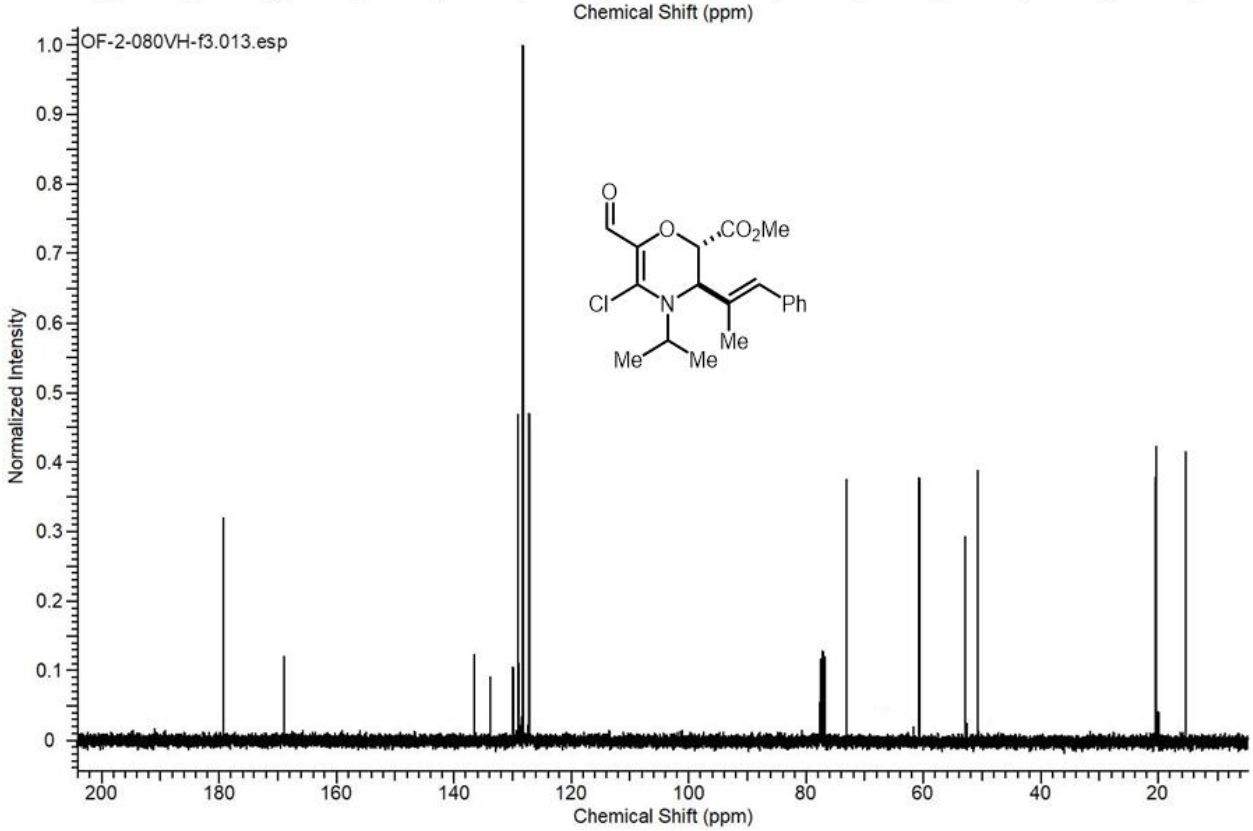
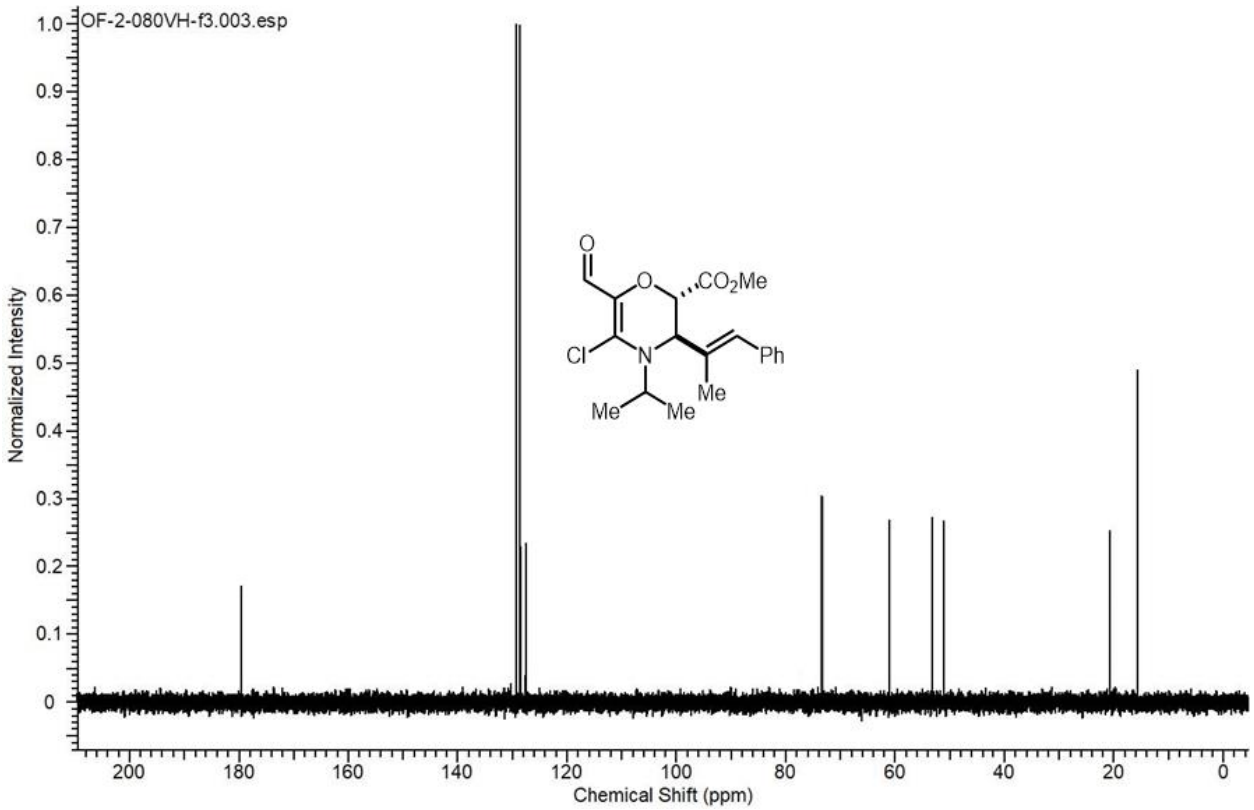
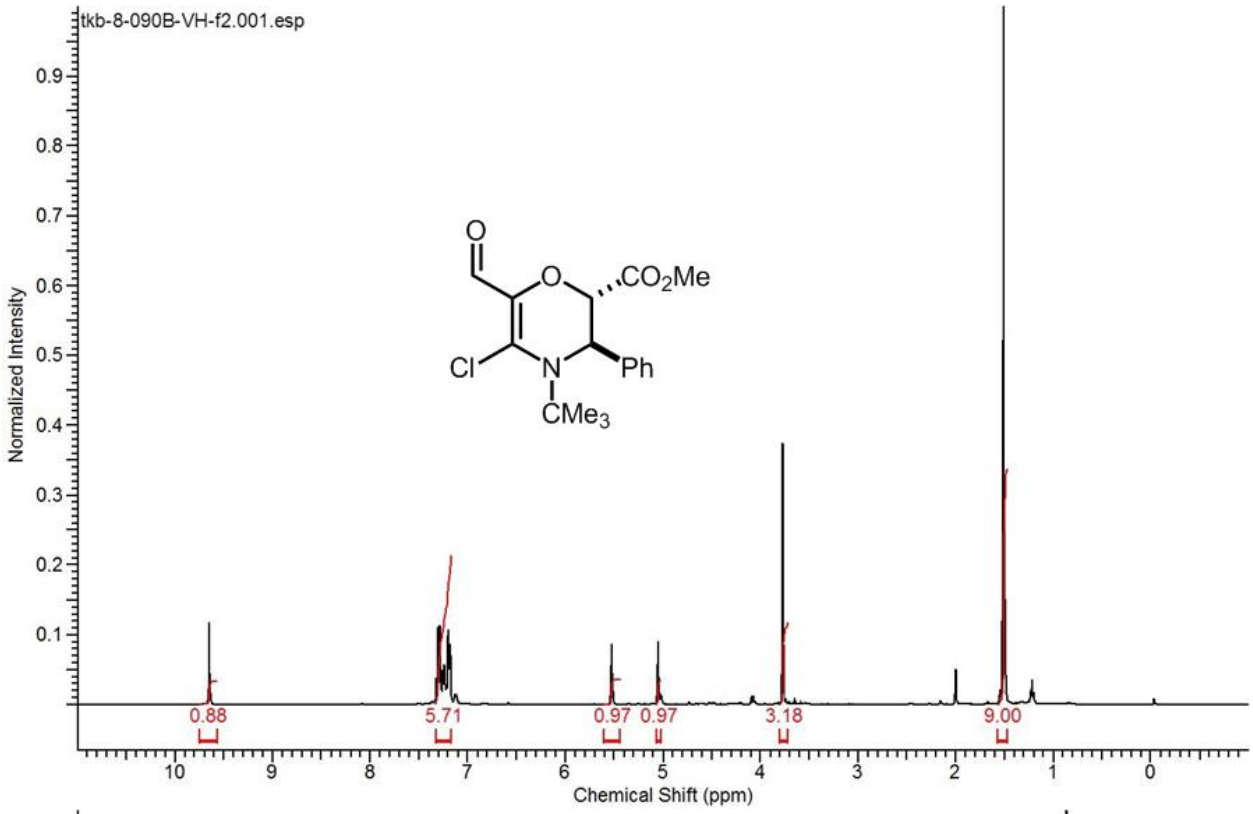
5.31
1.00
0.93
1.08
1.11
3.12
3.23
3.15
3.19
O
O
CO2Me
Cl
N
Ph
Me
Me
Me


OF-2-080VH-f3.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
Cl
N
Ph
Me
Me
Me



Compound **4a13:** Prepared using **General Procedure A**. Temp = 40 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 290 mg, 86%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.65 (s, 1H), 7.33 - 7.12 (m, 5H), 5.52 (d, *J* = 18.2 Hz, 1H), 4.99 (d, *J* = 18.2 Hz, 1H), 3.77 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 169.3, 137.3, 132.7, 129.4, 128.5, 128.1, 127.7, 126.0, 76.9, 61.2, 58.9, 52.8, 31.0. HRMS calc for $C_{17}H_{20}ClNO_4$, 337.1081, found 337.1085.


tkb-8-090B-VH-f2.001.esp
Normalized Intensity
Chemical Shift (ppm)
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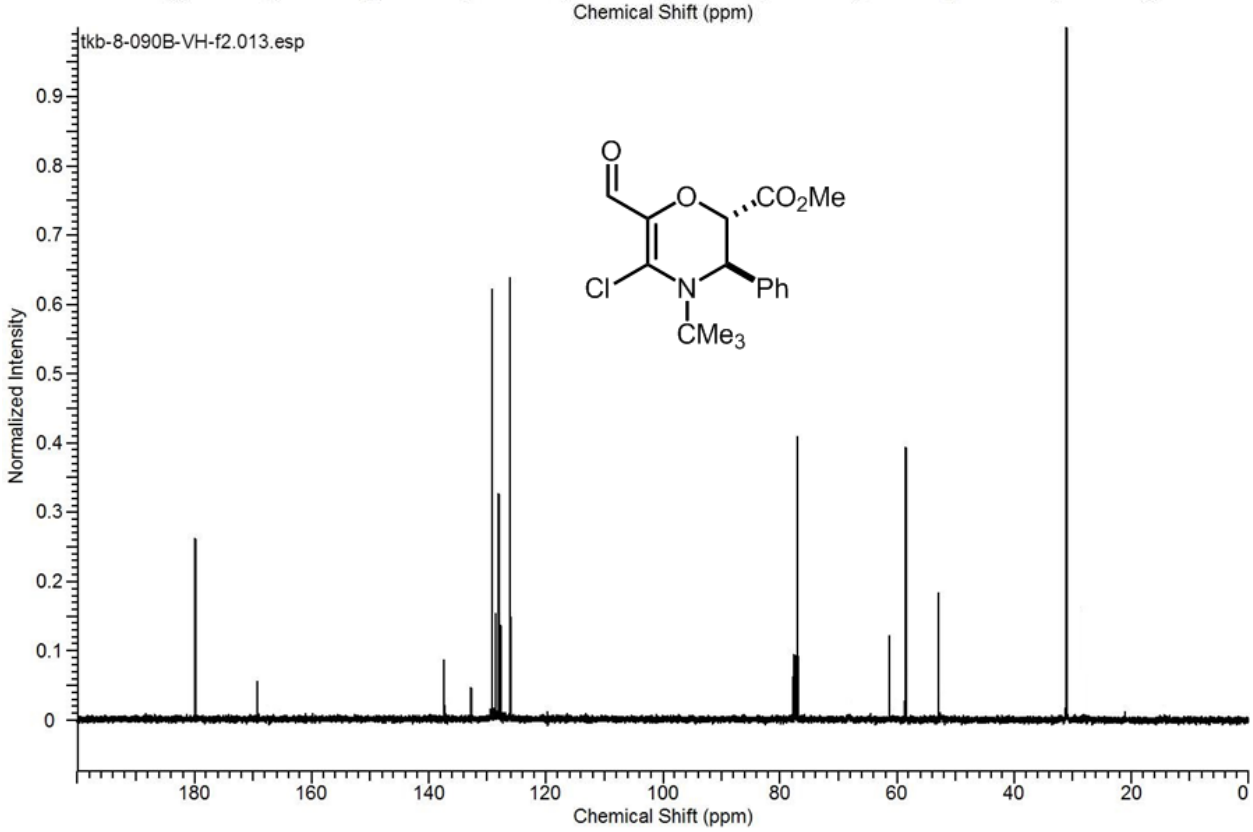
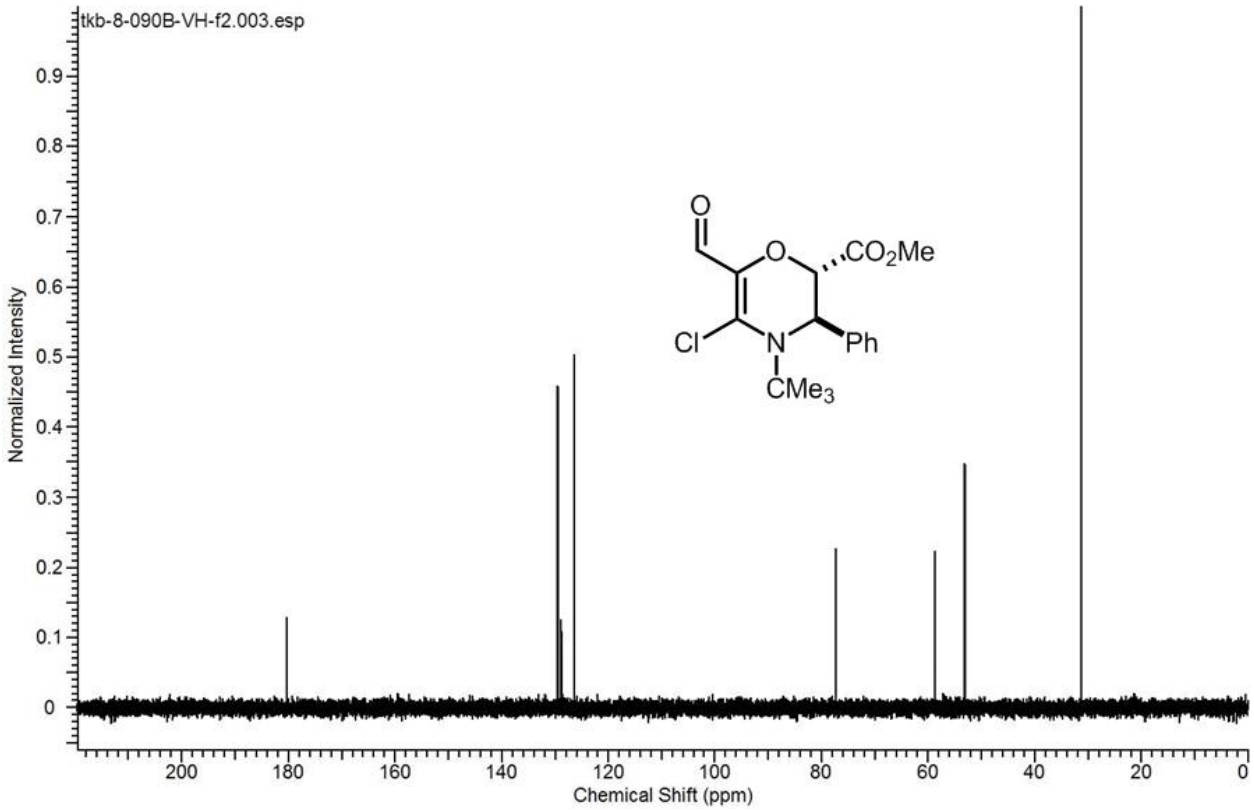
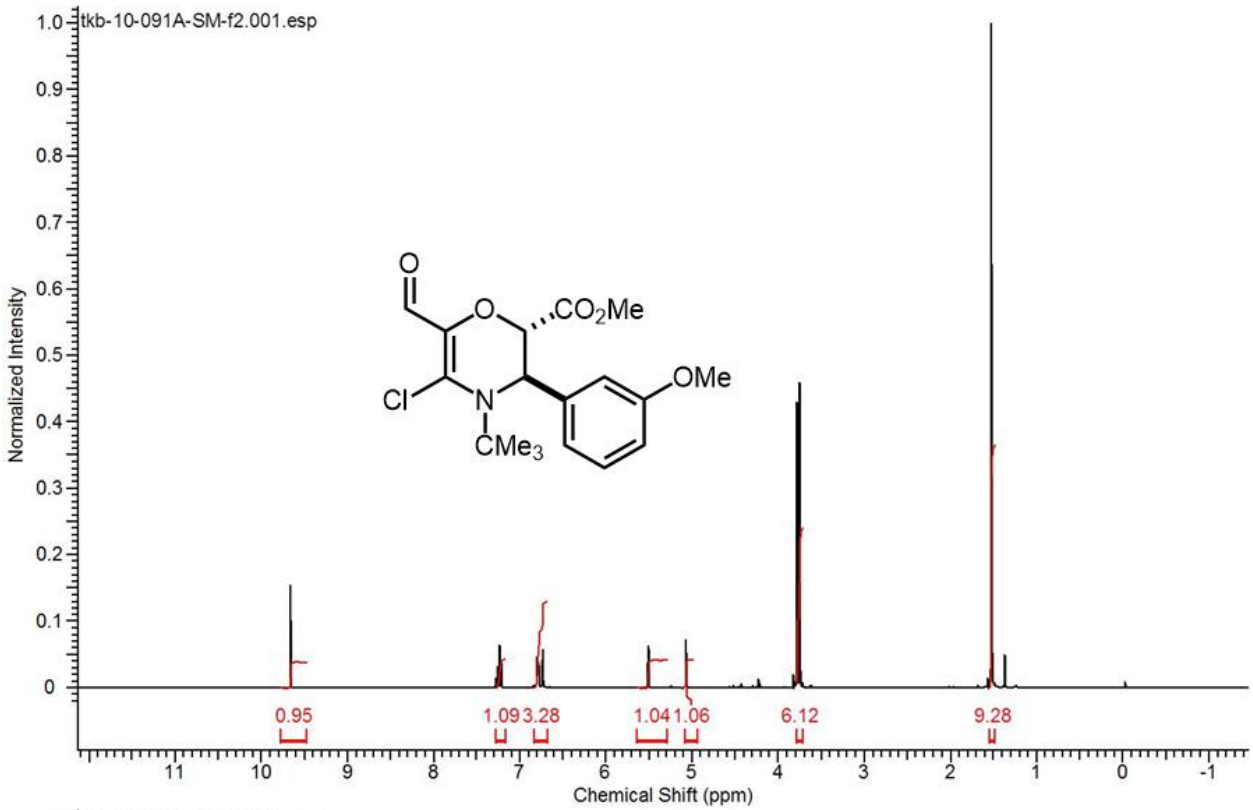
5.71
0.97
0.97
3.18
9.00
O
O
CO2Me
Cl
N
Ph
CMe3


tkb-8-090B-VH-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
Cl
N
Ph
CMe3



Compound **4a14:** Prepared using **General Procedure A**. Temp = 40 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 309 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.66 (s, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.89 – 6.76 (m, 3H), 5.53 (d, *J* = 1.8 Hz 1H), 5.07 (d, *J* = 1.8 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 1.57 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.96, 169.32, 160.11, 138.87, 135.93, 132.73, 130.20, 118.22, 113.10, 112.18, 77.56, 77.24, 77.02, 76.92, 61.28, 58.43, 55.29, 52.88, 31.02. HRMS calc for $C_{18}H_{22}ClNO_5$, 367.1187, found 367.1182.


tkb-10-091A-SM-f2.001.esp
Normalized Intensity
Chemical Shift (ppm)
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3.28
1.04
1.06
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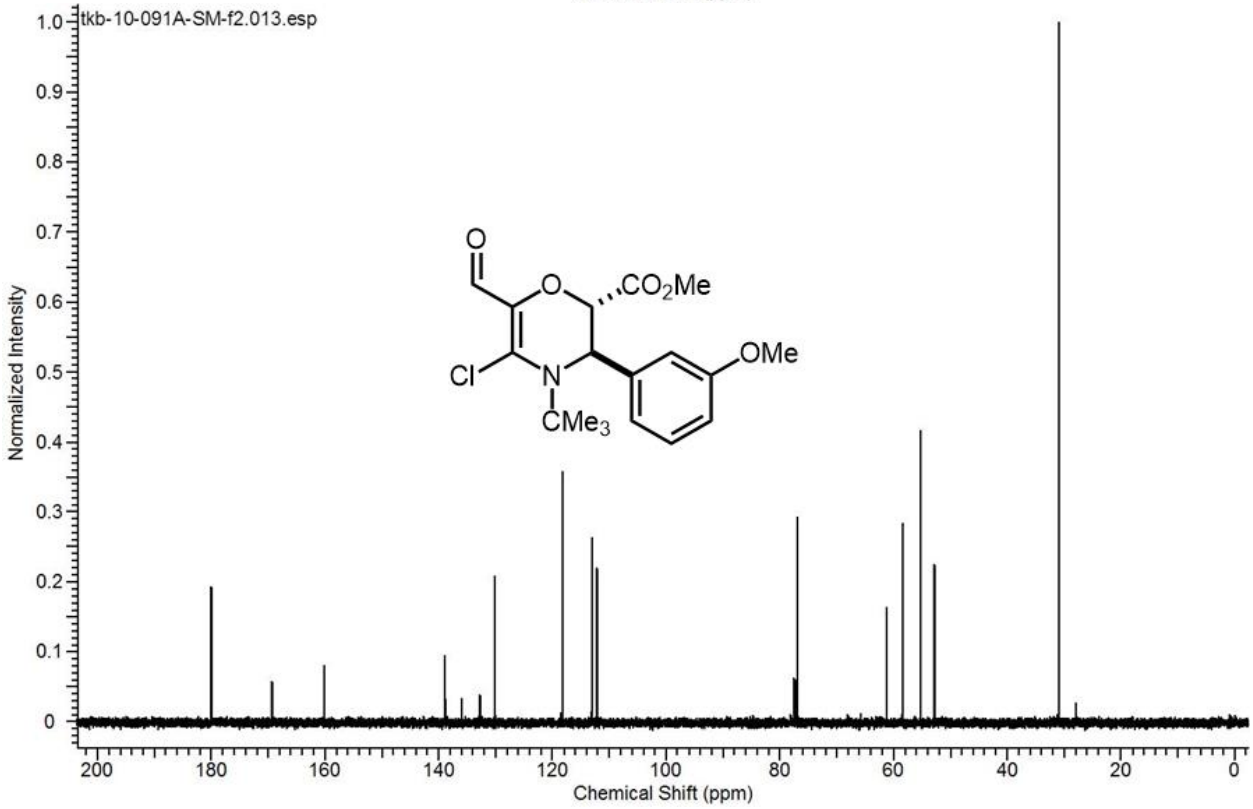
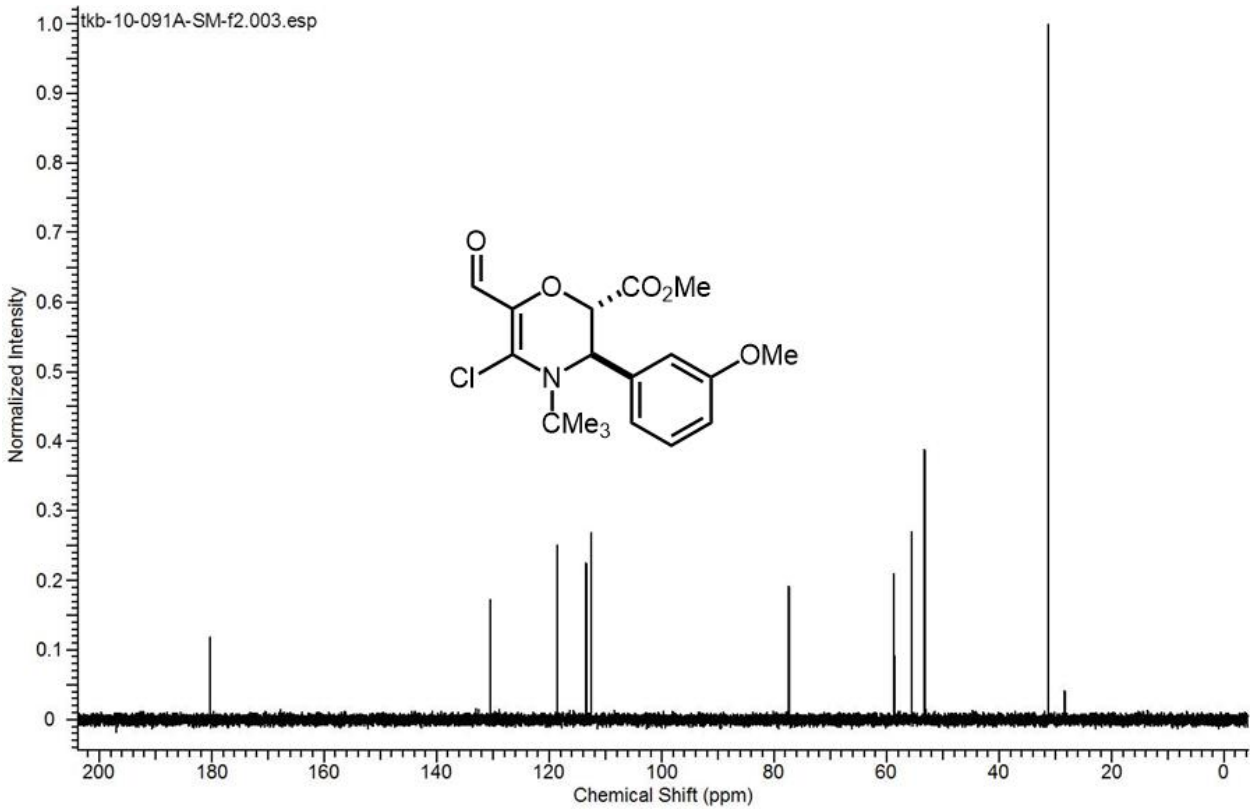
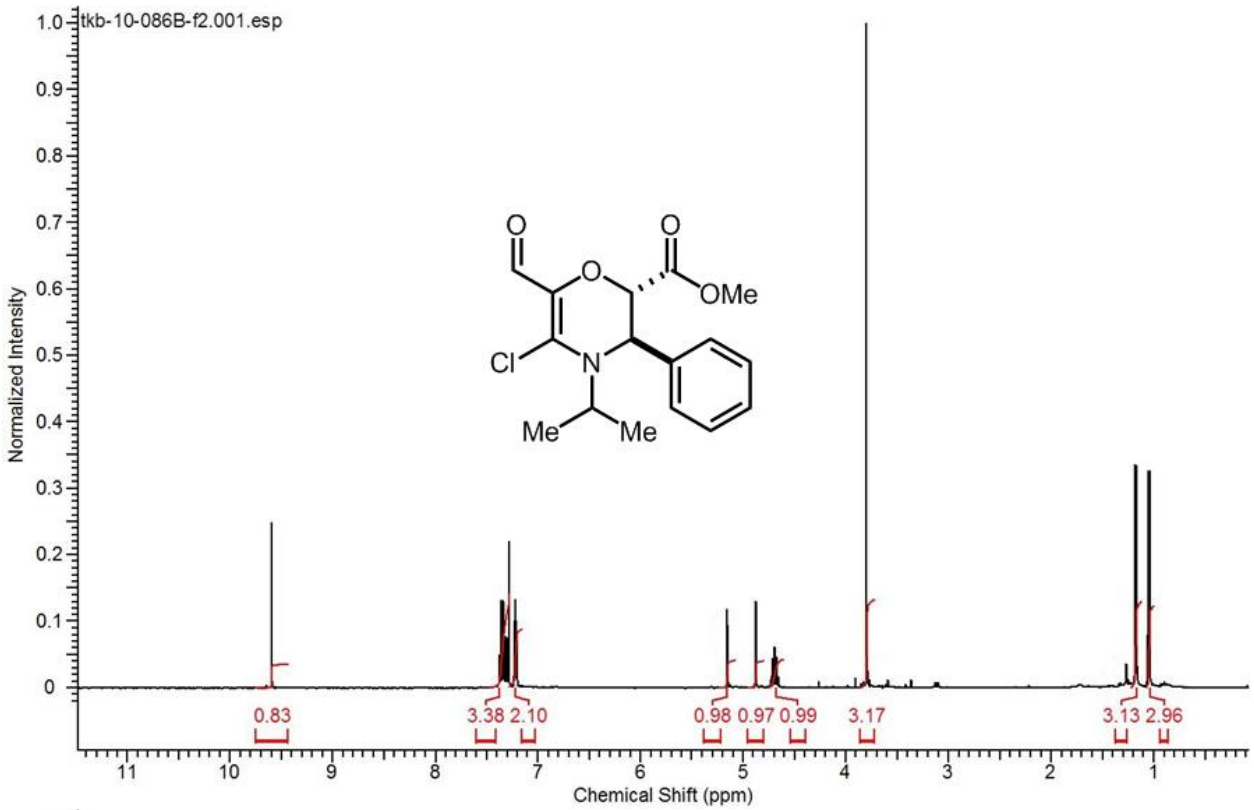
O
O
CO2Me
Cl
N
CMe3
OMe


tkb-10-091A-SM-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
Cl
N
CMe3
OMe



Compound **4a15:** Prepared using **General Procedure A**. Temp = 40 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 291.4 mg, 90%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.60 (s, 1H), 7.36 – 7.27 (m, 5H), 5.18 (d, *J* = 1.4 Hz, 1H), 4.87 (d, *J* = 1.4 Hz, 1H), 4.69 (m, 1H), 3.80 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.16, 168.70, 138.91, 129.13, 128.34, 126.05, 77.42, 77.11, 76.79, 75.98, 57.59, 52.93, 50.92, 21.07, 20.27.
HRMS calc for $C_{16}H_{18}ClNO_4$, 323.0924, found 323.0928.


tkb-10-086B-f2.001.esp
Normalized Intensity
Chemical Shift (ppm)
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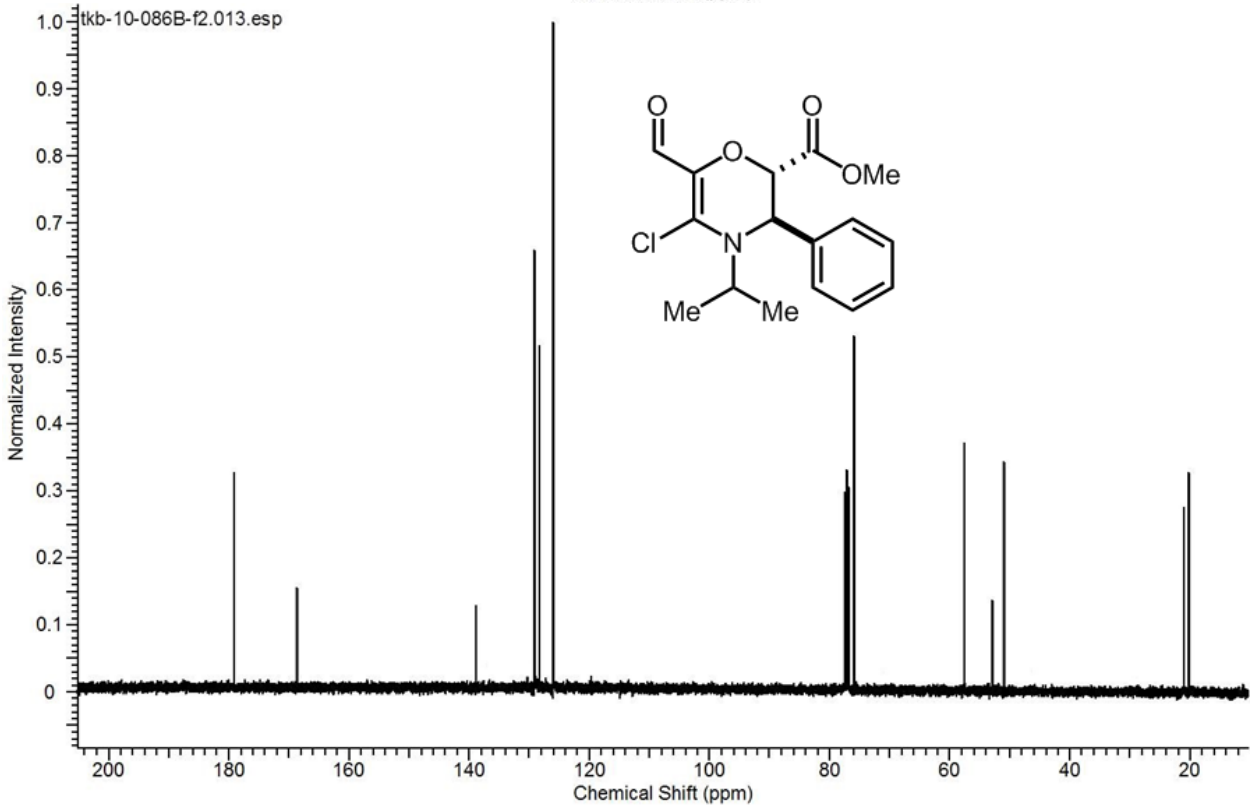
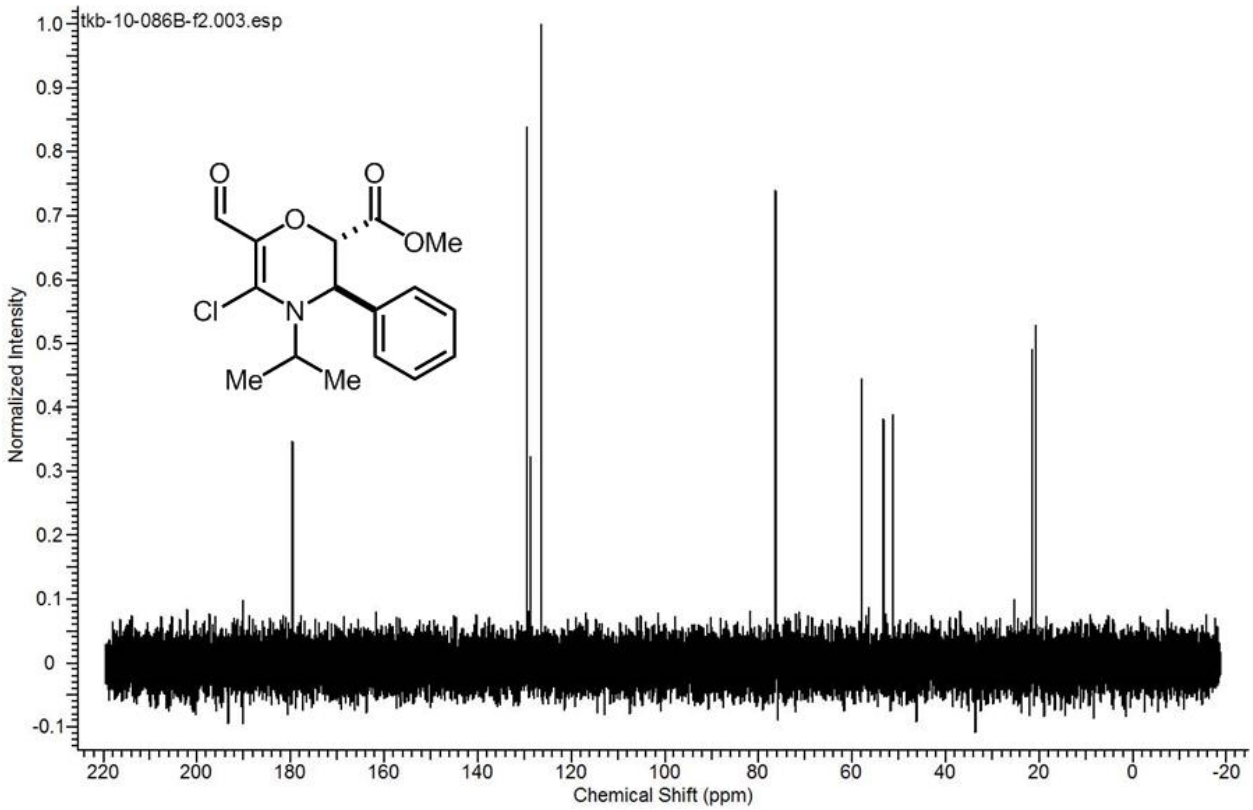
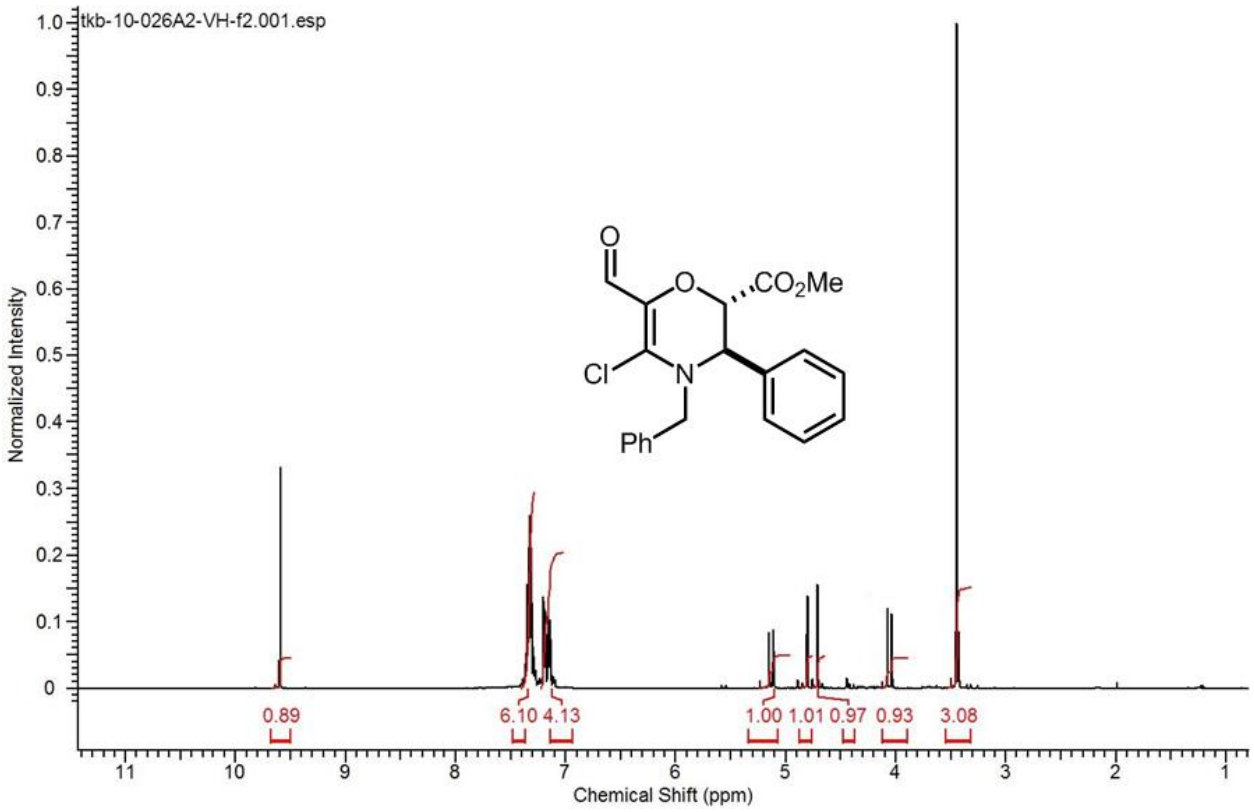
3.38
2.10
0.98
0.97
0.99
3.17
3.13
2.96
O
O
OMe
Cl
N
Me
Me


tkb-10-086B-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
OMe
Cl
N
Me
Me



Compound **4a16:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 304.9 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.45 – 7.25 (m, 6H), 7.23 – 7.09 (m, 4H), 5.13 (d, *J* = 15.6 Hz, 1H), 4.80 (d, *J* = 1.7 Hz, 1H), 4.71 (d, *J* = 1.6 Hz, 1H), 4.06 (d, *J* = 15.7 Hz, 1H), 3.45 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 179.02, 167.60, 137.97, 136.72, 134.93, 129.30, 129.27, 128.99, 128.93, 128.46, 128.08, 126.91, 75.27, 61.70, 52.58, 52.51. HRMS calc for $C_{20}H_{18}ClNO_4$, 371.0924, found 371.0928.


tkb-10-026A2-VH-f2.001.esp
Normalized Intensity
Chemical Shift (ppm)
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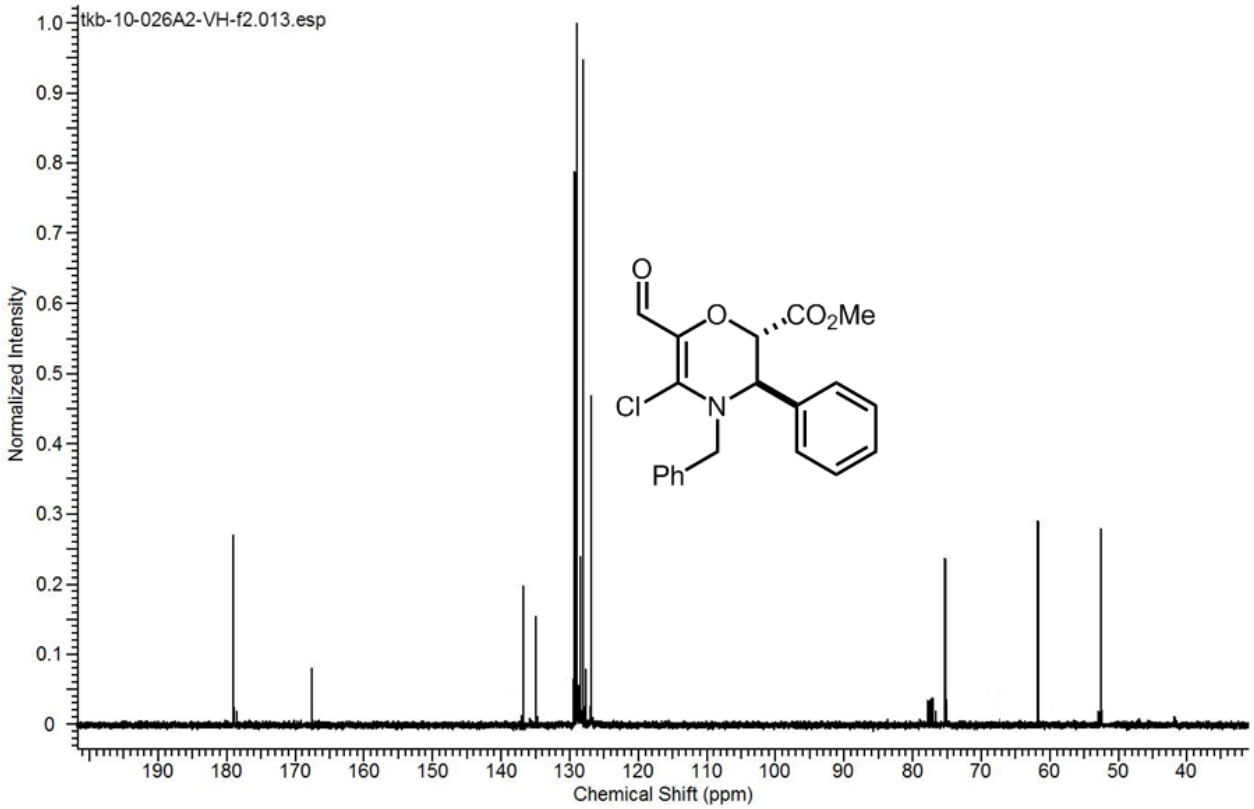
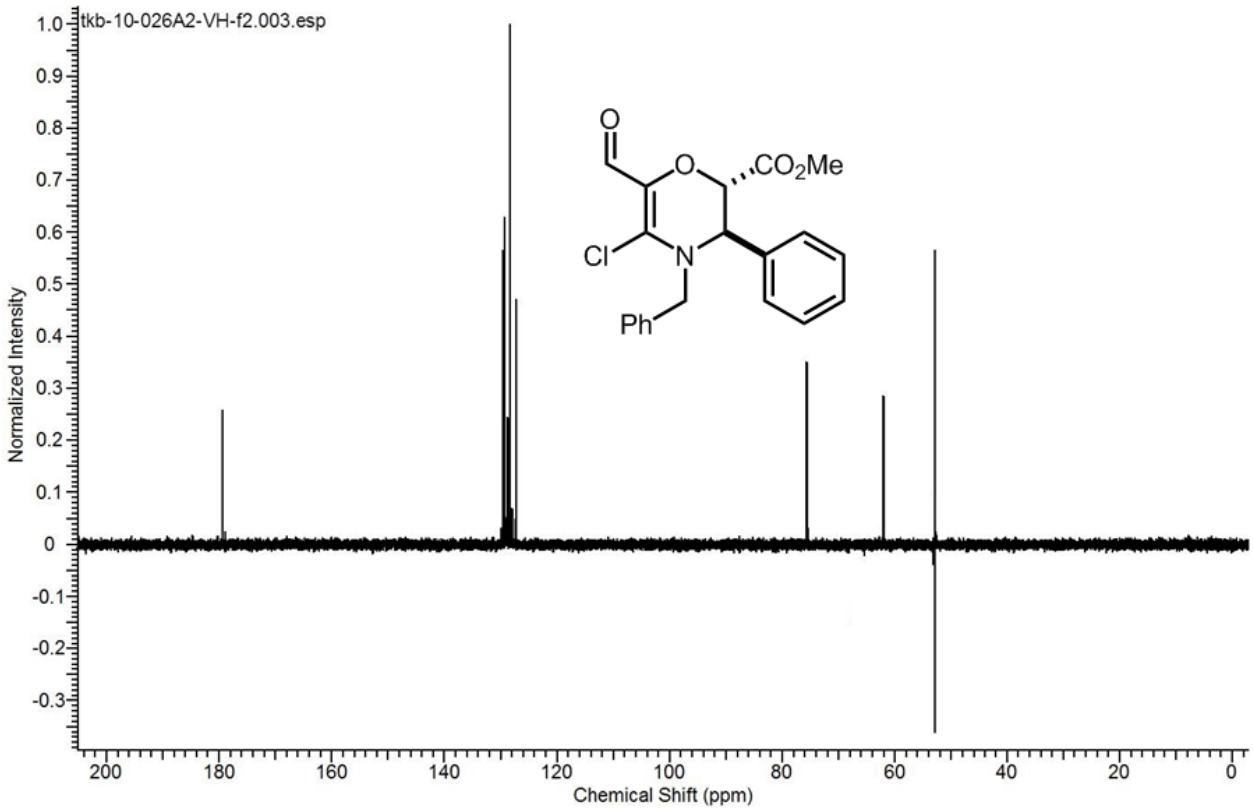
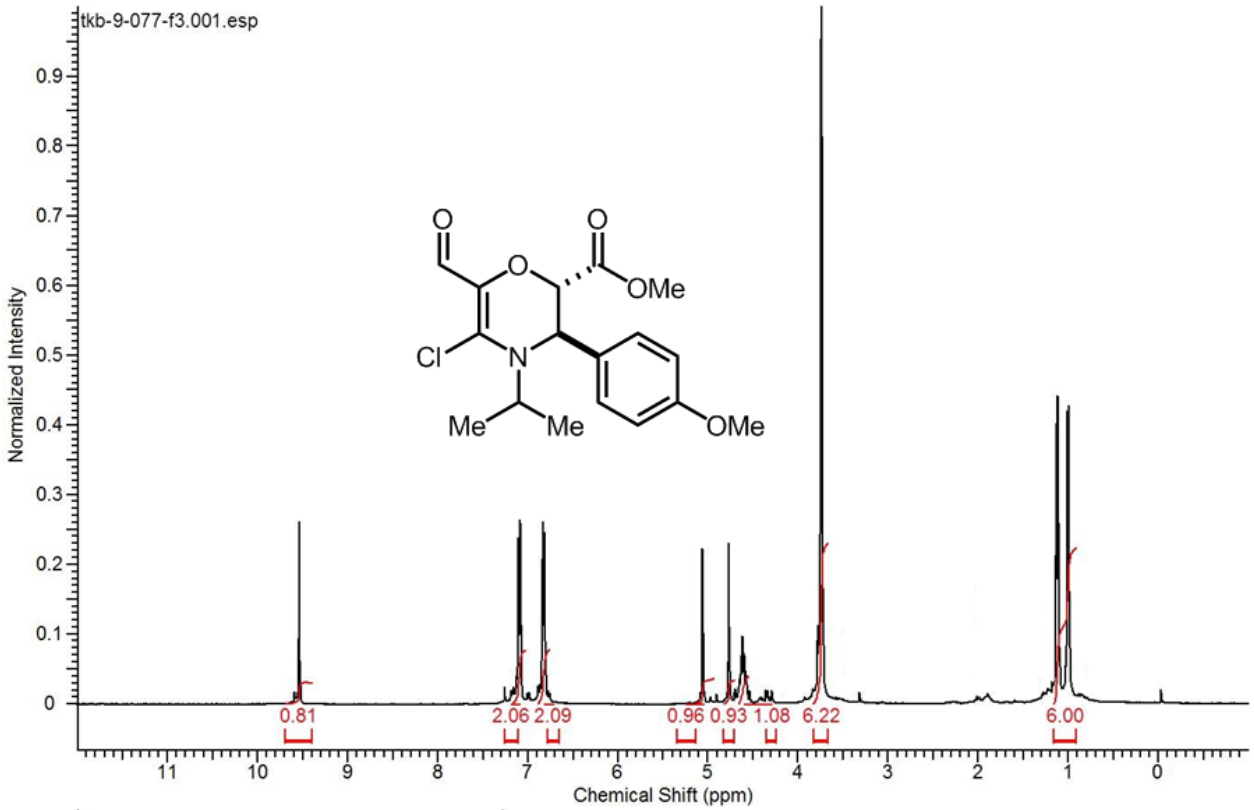
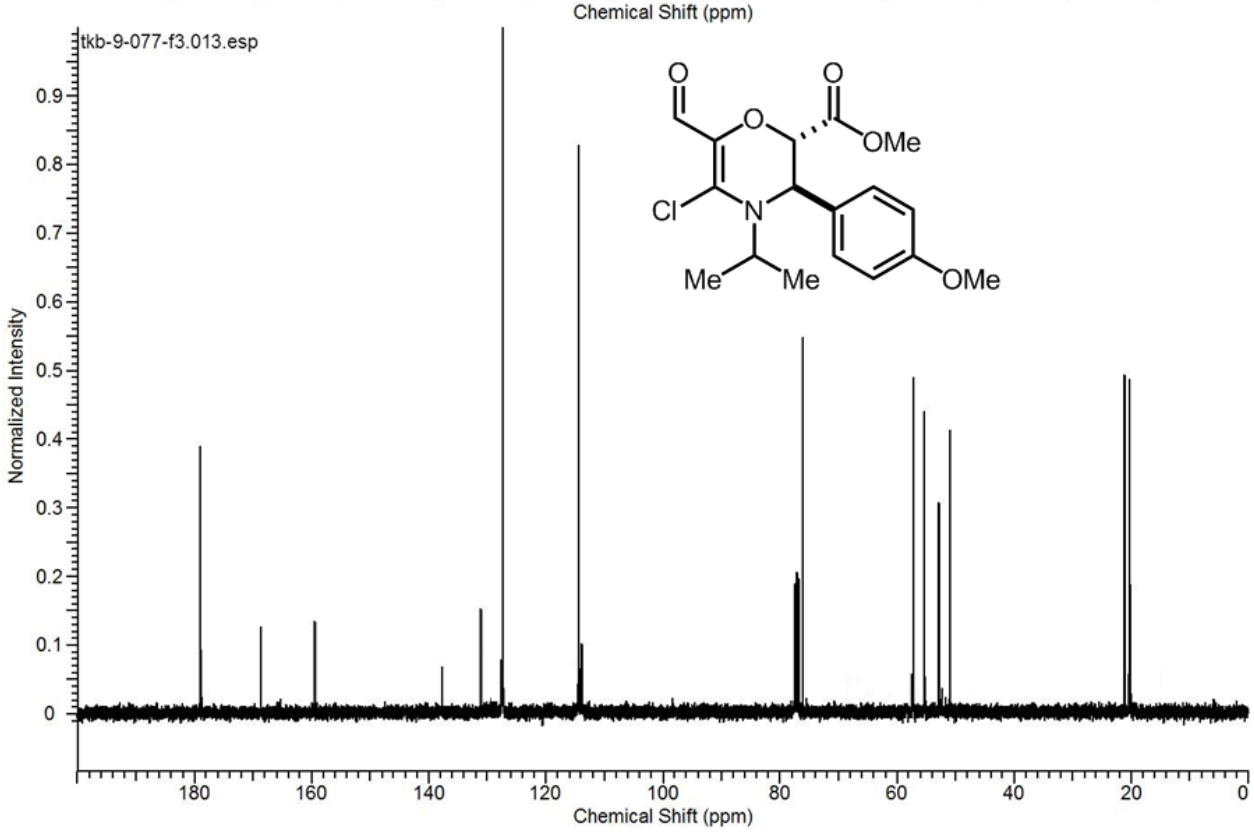
4.13
1.00
1.01
0.97
0.93
3.08
O
O
CO2Me
Cl
N
Ph

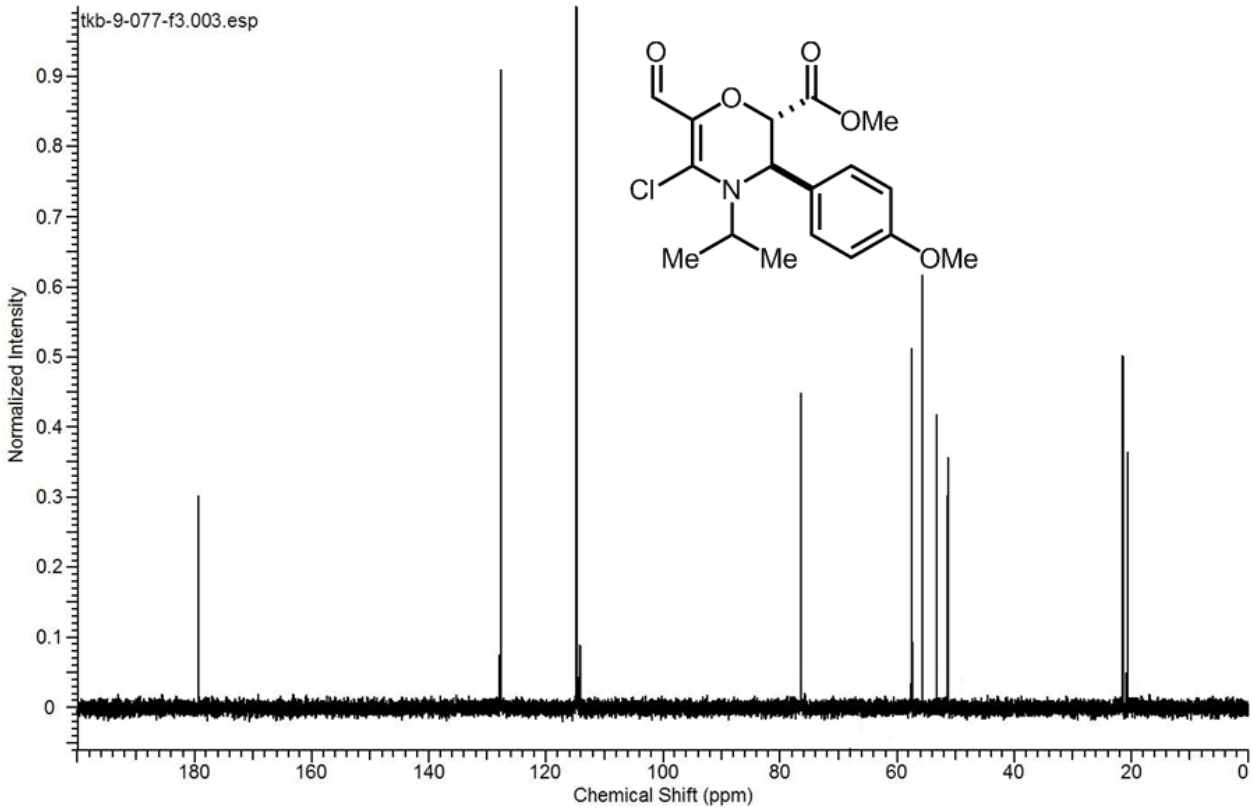

tkb-10-026A2-VH-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
Cl
N
Ph



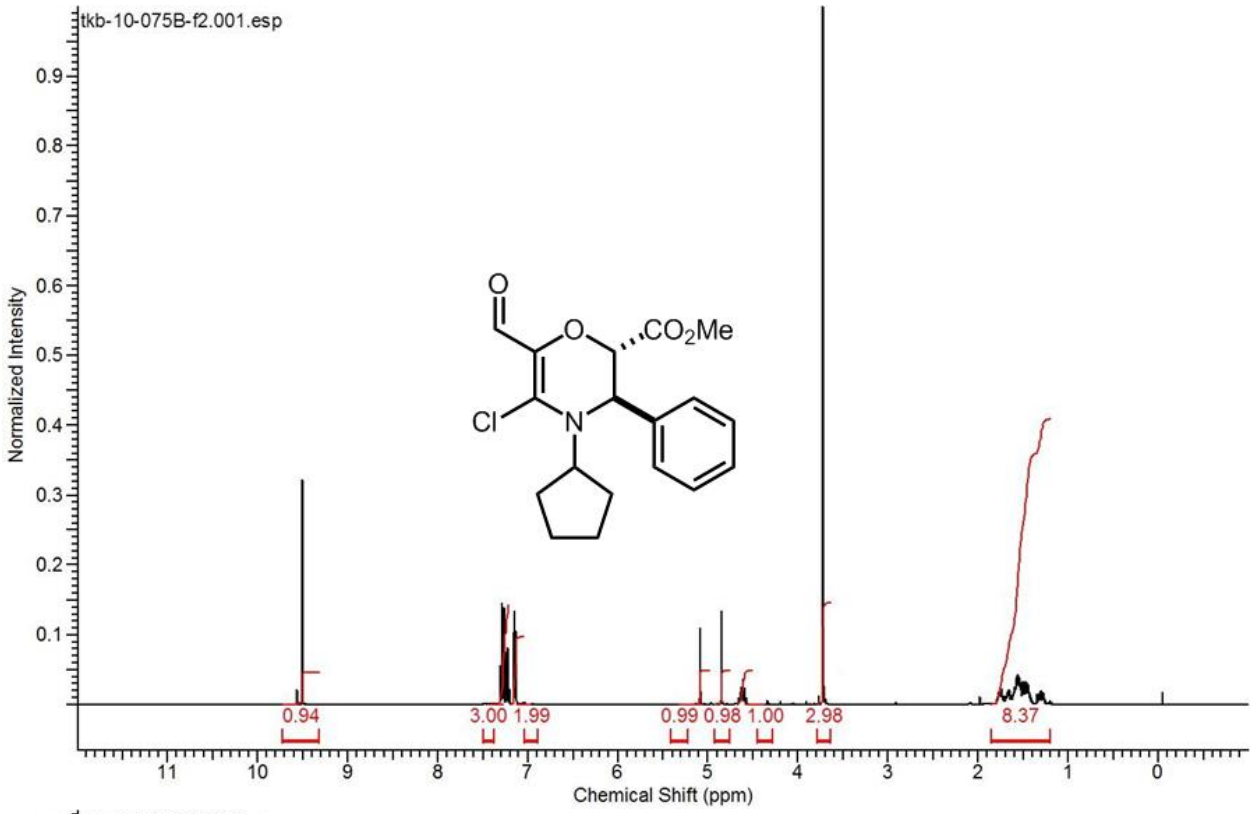
Compound **4a17:** Prepared using **General Procedure A**. Temp = 40 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50).Yield = 318 mg, 90%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.61 (s, 1H), 7.21 (d, 2H), 6.84 (d, 2H), 5.12 (d, *J* = 18.2 Hz, 1H), 4.89 (d, *J* = 18.2 Hz, 1H), 3.58 (m, 1H), 3.85 (s, 6H), 1.04 (d, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 169.6, 160.3, 138.7, 131.4, 128.5, 114.1, 75.9, 58.2, 56.9, 53.8, 51.0, 21.3, 21.1. HRMS calc for $C_{17}H_{20}ClNO_5$, 353.1030, found 353.1036.


tkb-9-077-f3.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.81
2.06
2.09
0.96
0.93
1.08
6.22
6.00
O
O
O
OMe
Cl
N
Me
Me
OMe


tkb-9-077-f3.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
O
OMe
Cl
N
Me
Me
OMe



Compound **4a18:** Prepared using **General Procedure A**. Temp = 40 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30).Yield = 322 mg, 92%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.50 (s, 1H), 7.34 – 7.17 (m, 3H), 7.17 – 7.10 (m, 2H), 5.11 (d, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 4.62 (tt, *J* = 9.3, 7.3 Hz, 1H), 3.72 (s, 3H), 1.81 – 1.24 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.88, 168.55, 138.36, 130.19, 129.09, 128.27, 125.85, 75.95, 60.63, 58.29, 52.87, 29.76, 29.17, 23.05, 22.76. HRMS calc for $C_{18}H_{20}ClNO_4$, 349.1081, found 349.1087.


tkb-10-075B-f2.001.esp
Normalized Intensity
Chemical Shift (ppm)
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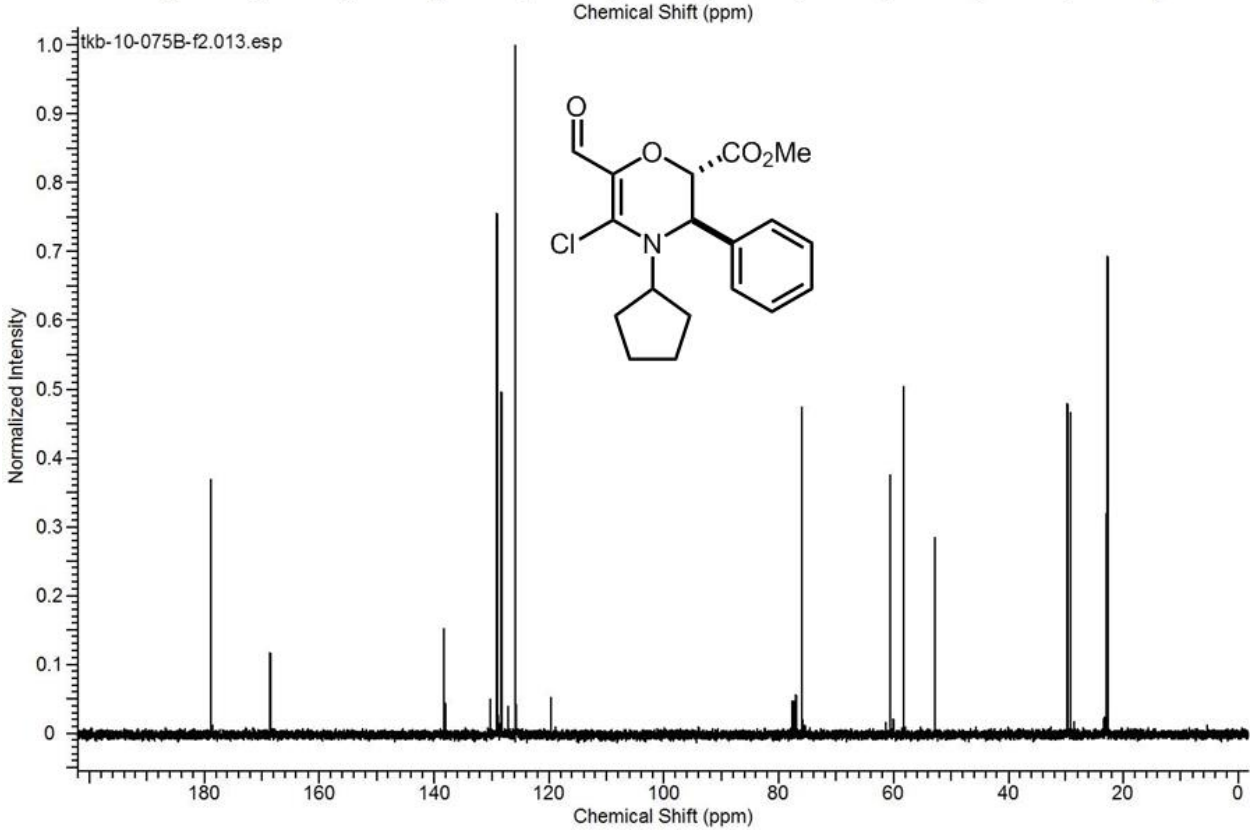
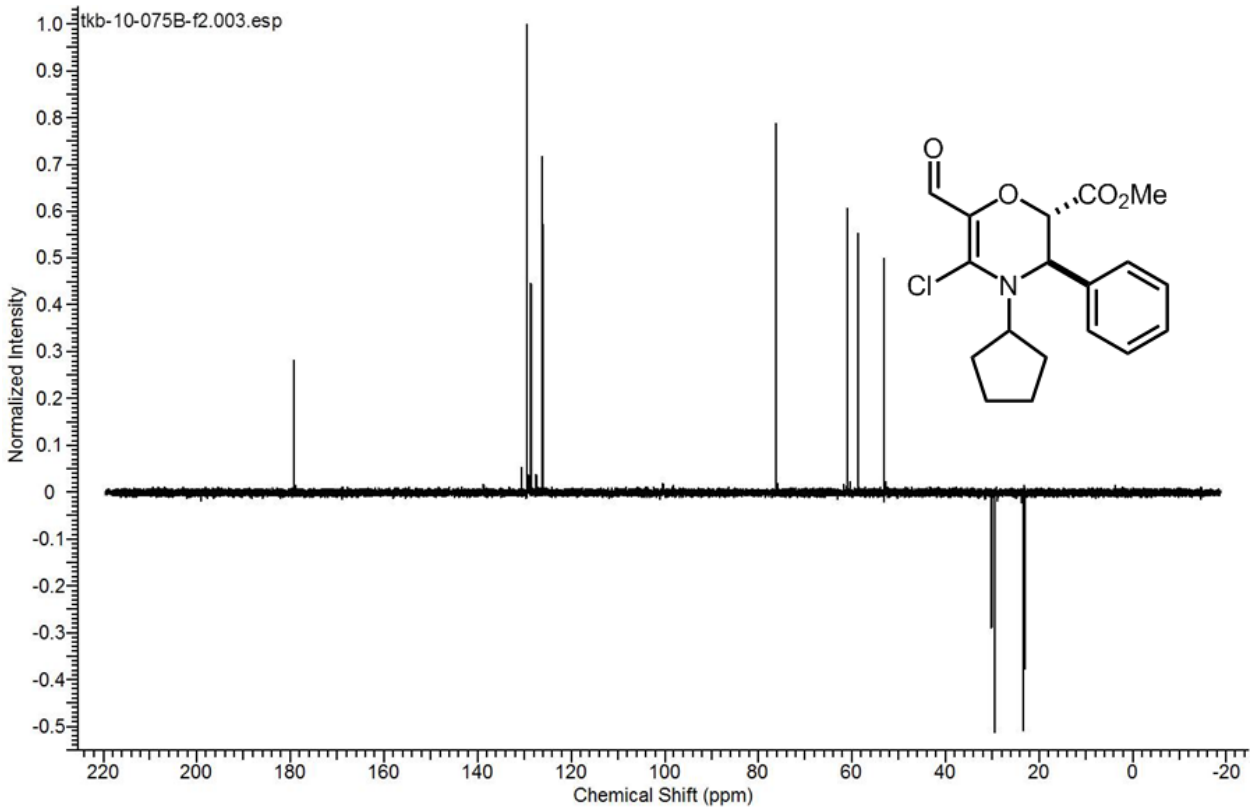
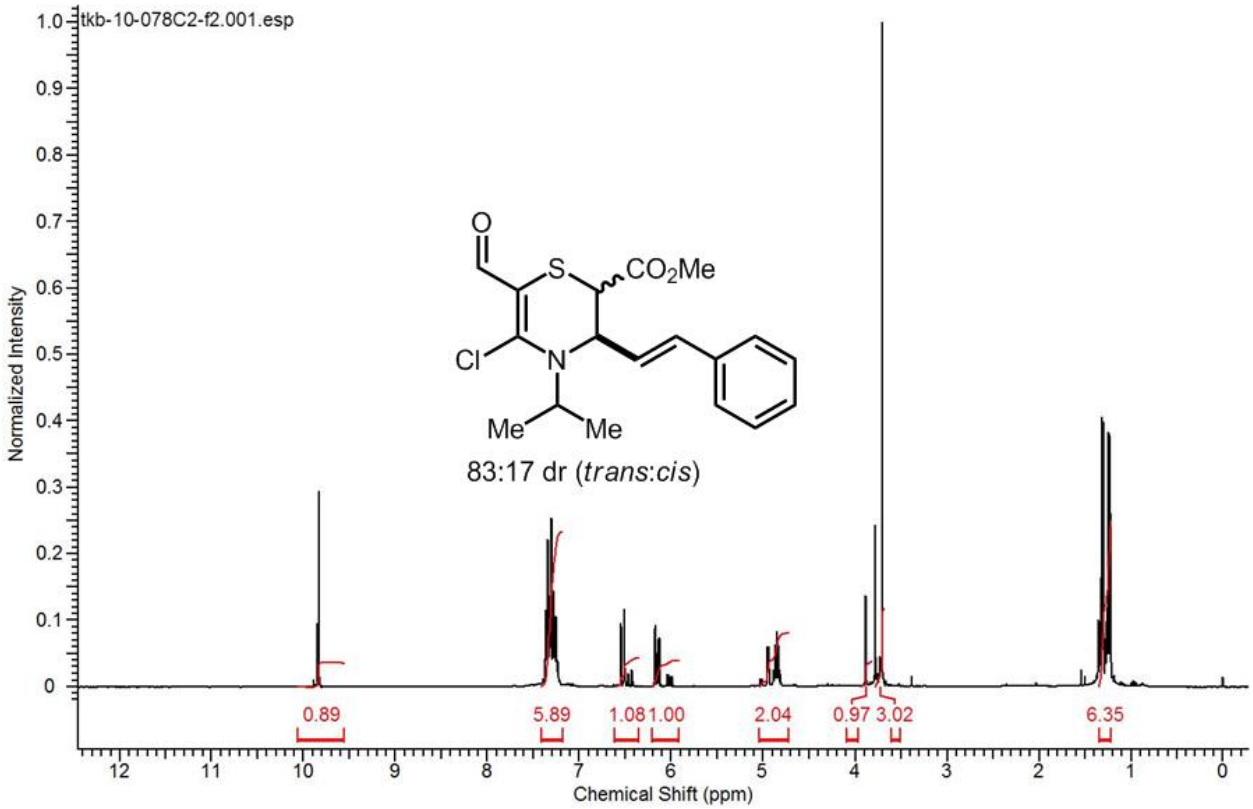
1.99
0.99
0.98
1.00
2.98
8.37
O
O
CO2Me
Cl
N

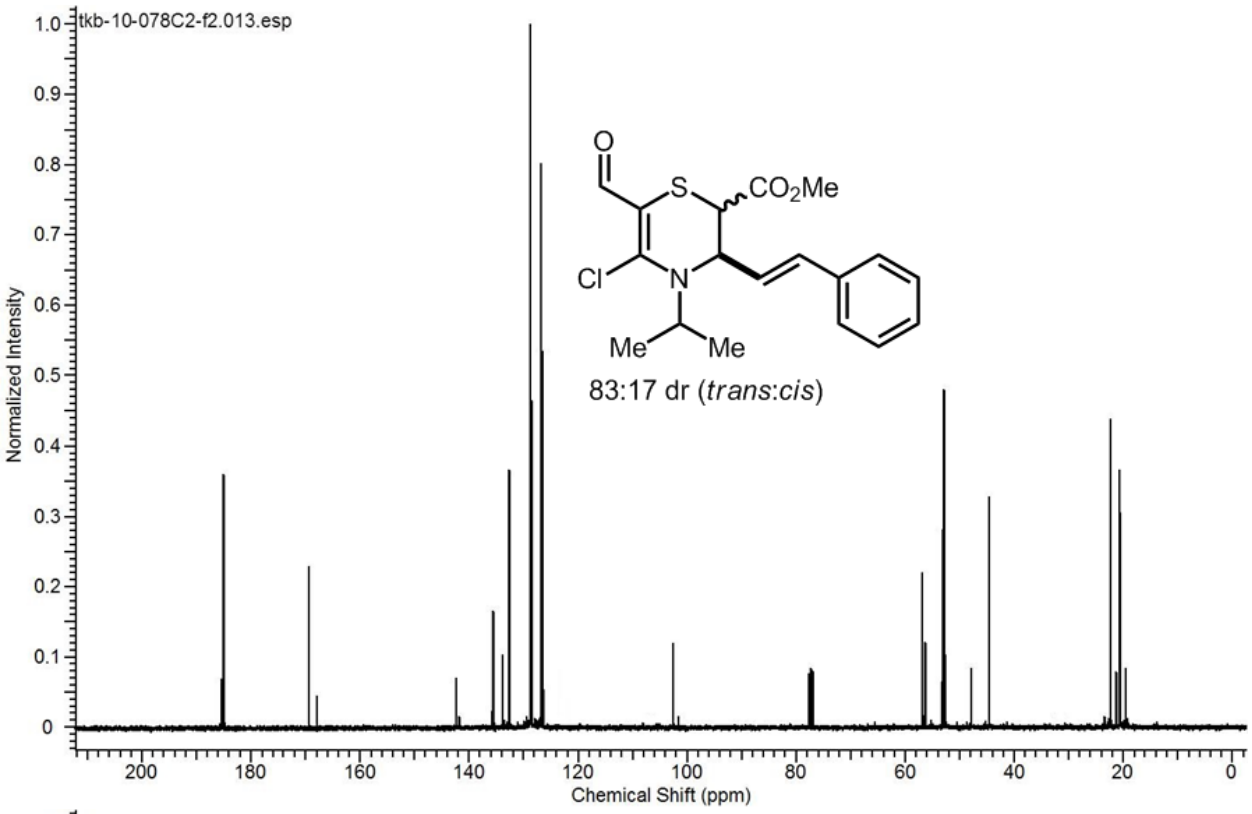

tkb-10-075B-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
Cl
N

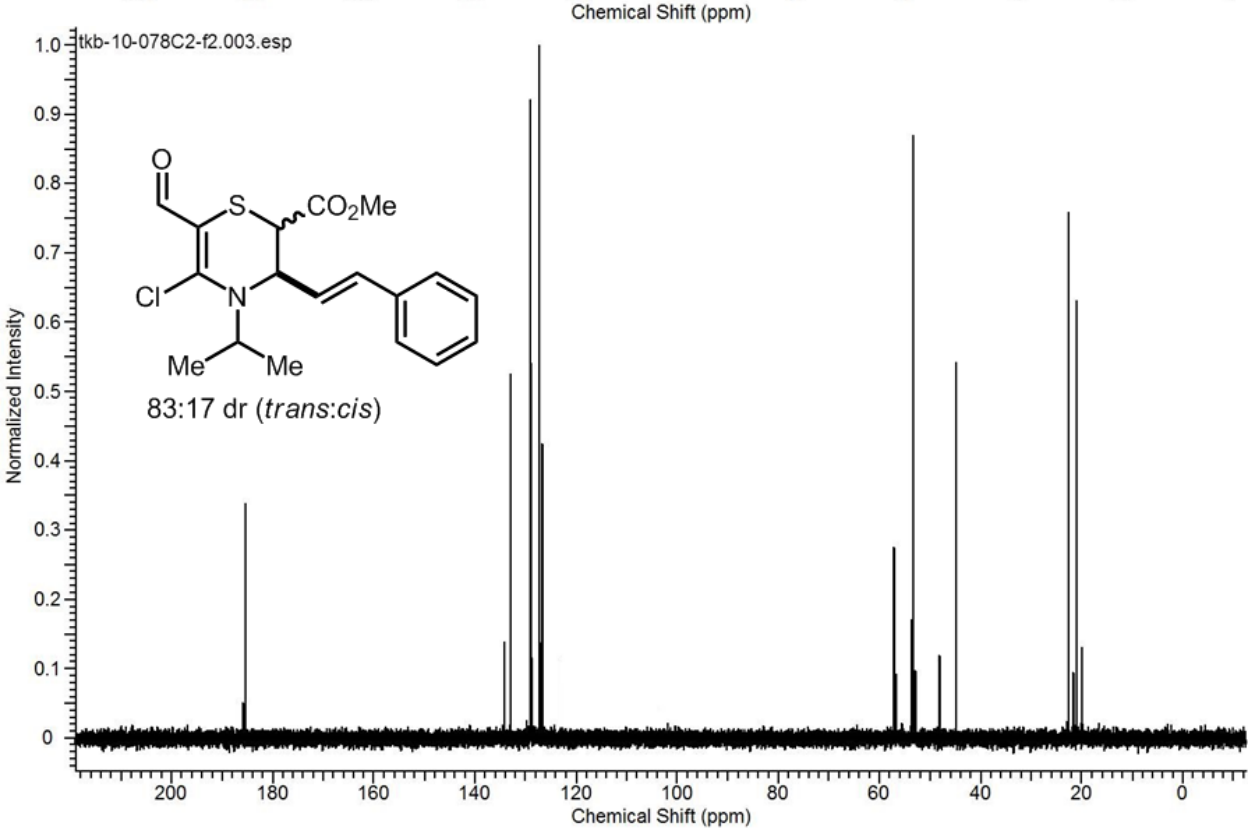

tkb-10-075B-f2.003.esp
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)
O
O
CO2Me
Cl
N

Scheme 2 results

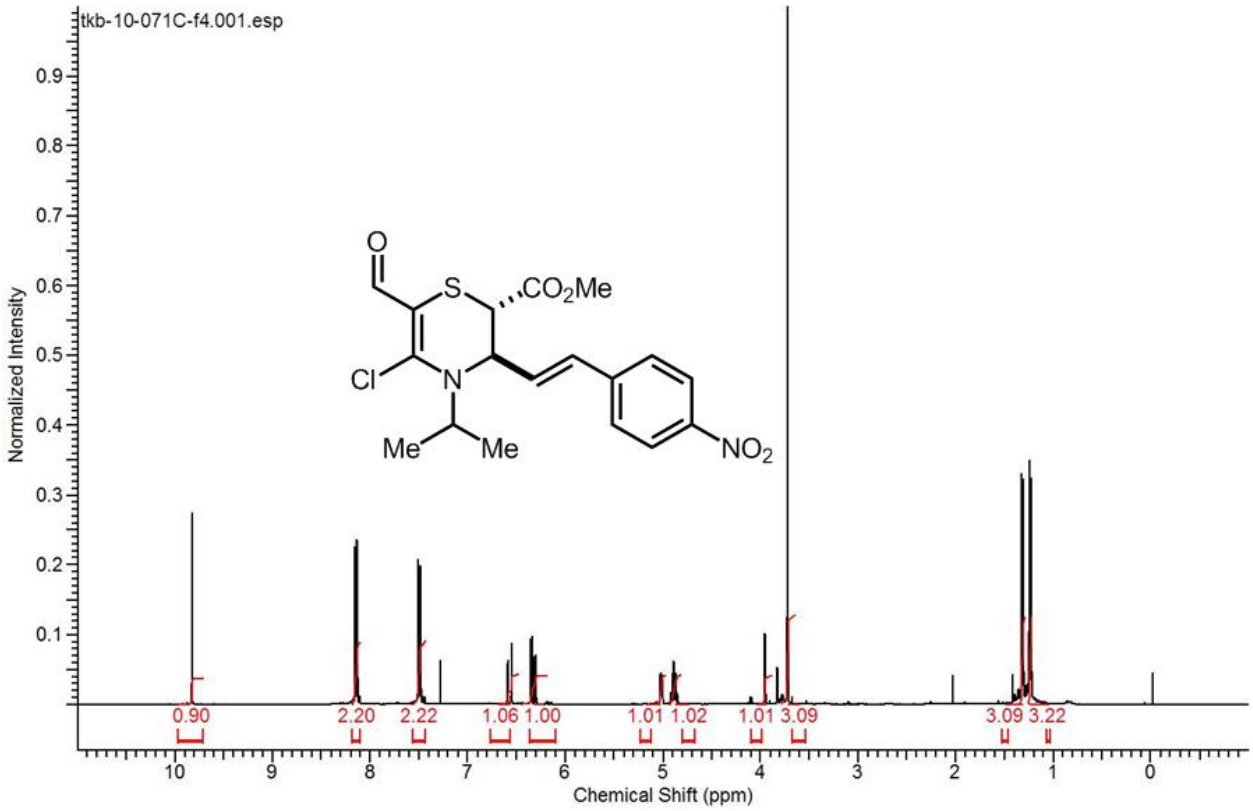
Compound **4b1:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 296.3 mg, 81%, 83:17 dr, oily substance.^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.81 (s, 1H), 7.44 – 7.28 (m, 5H), 6.49 (dd, *J* = 32.9, 15.7 Hz, 1H), 6.16 (dd, *J* = 15.8, 6.8 Hz, 1H), 4.94 (ddd, *J* = 6.9, 2.9, 1.1 Hz, 1H), 4.85 (p, *J* = 6.7 Hz, 1H), 3.88 (dd, *J* = 2.8, 1.0 Hz, 1H), 3.71 (s, 3H), 1.42 – 1.16 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.50, 185.04, 169.41, 142.36, 135.60, 133.81, 132.67, 128.81, 128.77, 128.66, 128.53, 128.39, 126.87, 126.84, 126.39, 122.49, 102.48, 56.85, 56.37, 53.06, 52.89, 52.56, 47.89, 44.58, 22.34, 21.32, 20.71, 19.59. HRMS calc for $C_{18}H_{20}ClNO_3S$ 365.0852, found 365.0855.

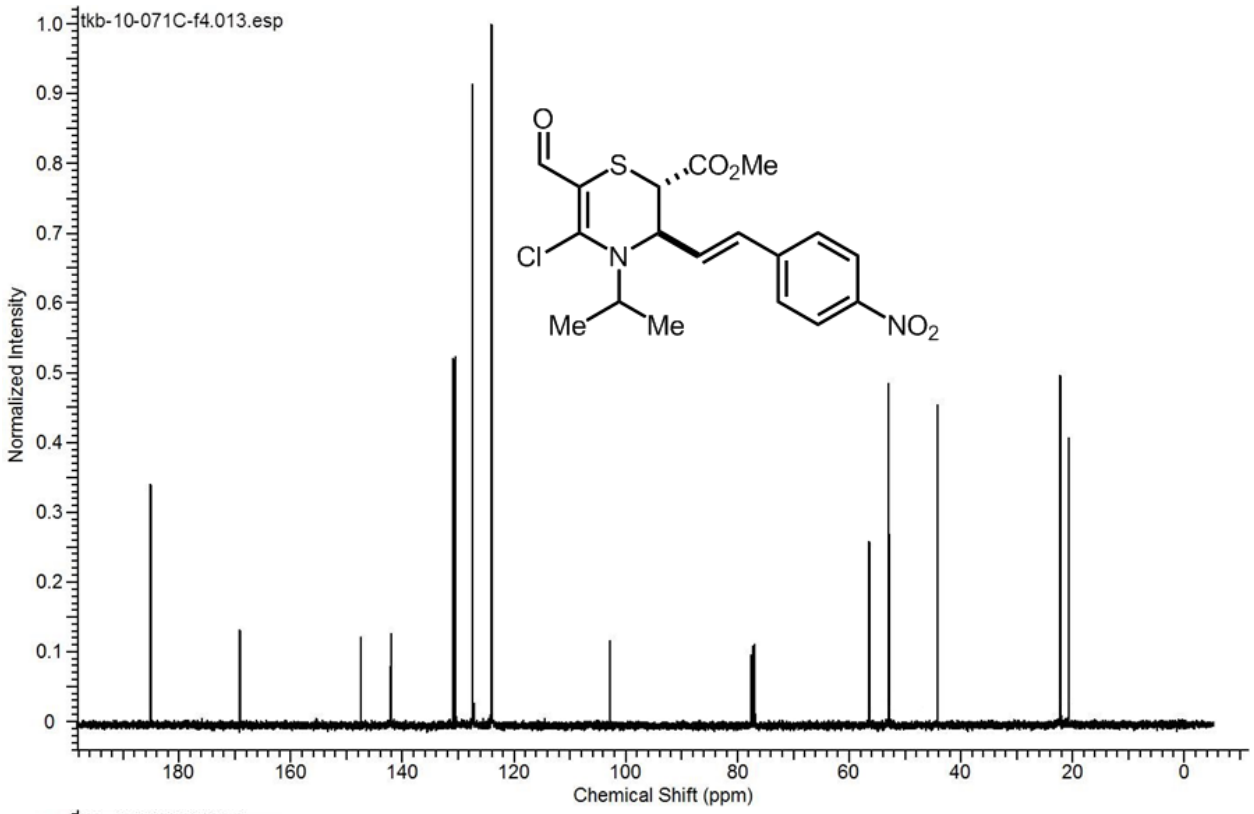


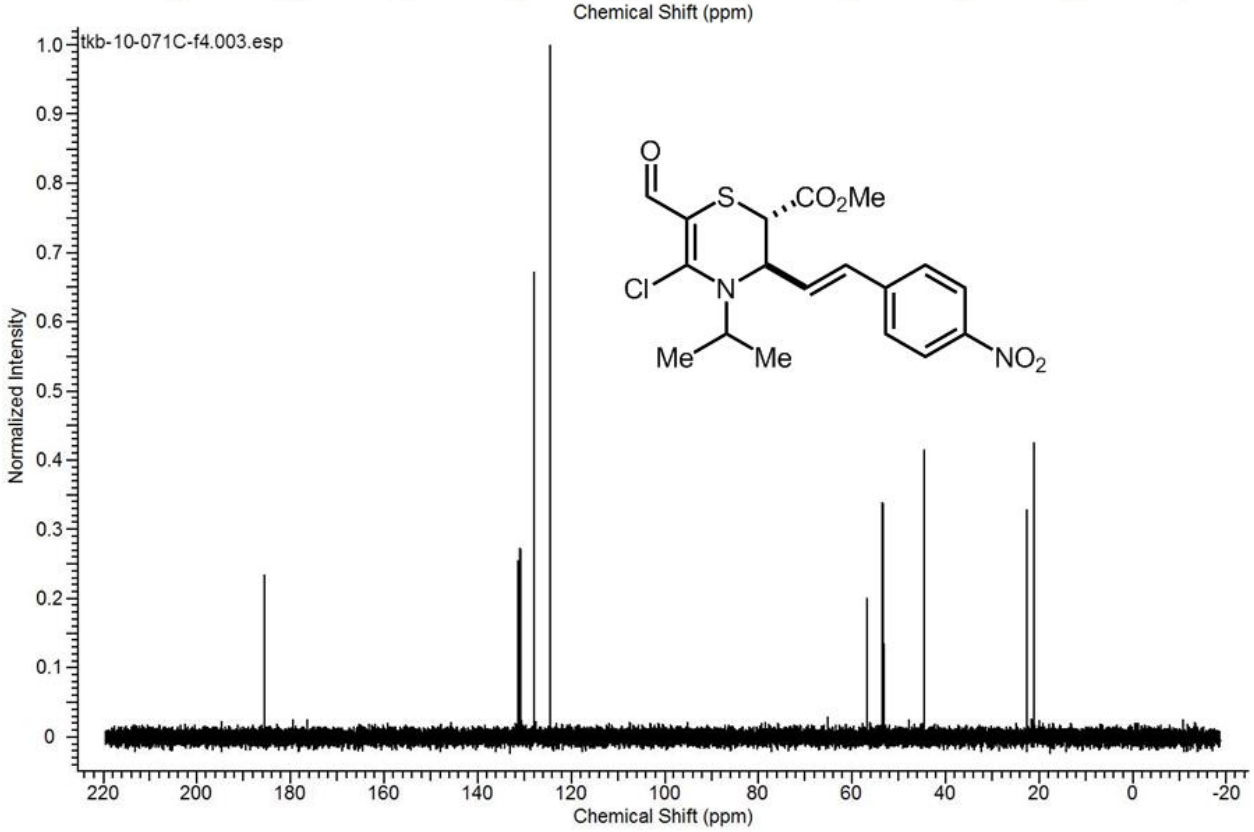

tkb-10-078C2-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
83:17 dr (trans:cis)


tkb-10-078C2-f2.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
83:17 dr (trans:cis)

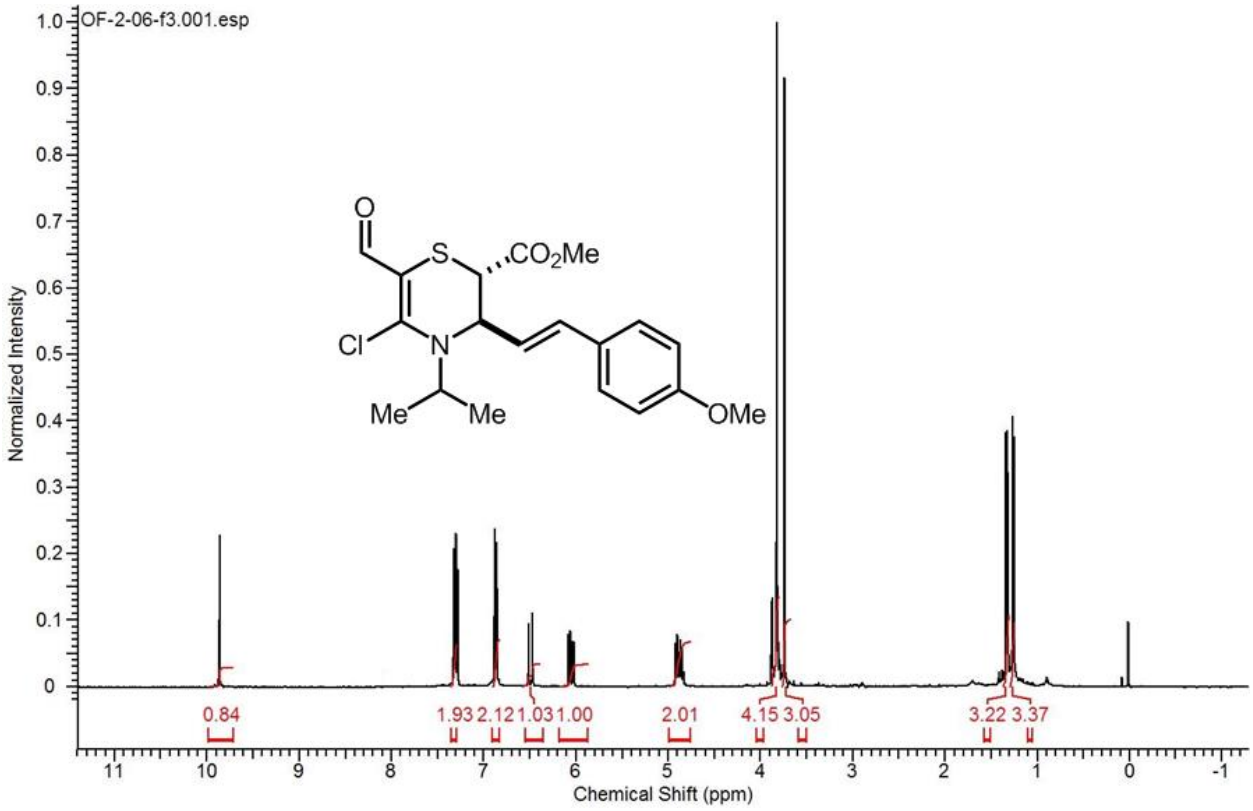
Compound **4b2:** Prepared using **General Procedure A**. Temp = 23 °C for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50).Yield = 353.3 mg, 86%, 95:5 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (d, *J* = 1.0 Hz, 1H), 8.23 – 8.09 (m, 2H), 7.56 – 7.42 (m, 2H), 6.57 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.33 (dd, *J* = 15.9, 6.3 Hz, 1H), 5.02 (ddd, *J* = 6.4, 2.9, 1.3 Hz, 1H), 4.88 (p, *J* = 6.7 Hz, 1H), 3.95 (dd, *J* = 2.8, 1.0 Hz, 1H), 3.72 (s, 3H), 1.44 – 1.20 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.13, 169.09, 147.44, 142.13, 142.03, 130.93, 130.47, 127.51, 124.08, 123.98, 102.82, 56.46, 53.03, 52.96, 44.21, 22.28, 20.71. HRMS calc for $C_{18}H_{19}ClN_2O_5S$ 410.0703, found 410.0709.

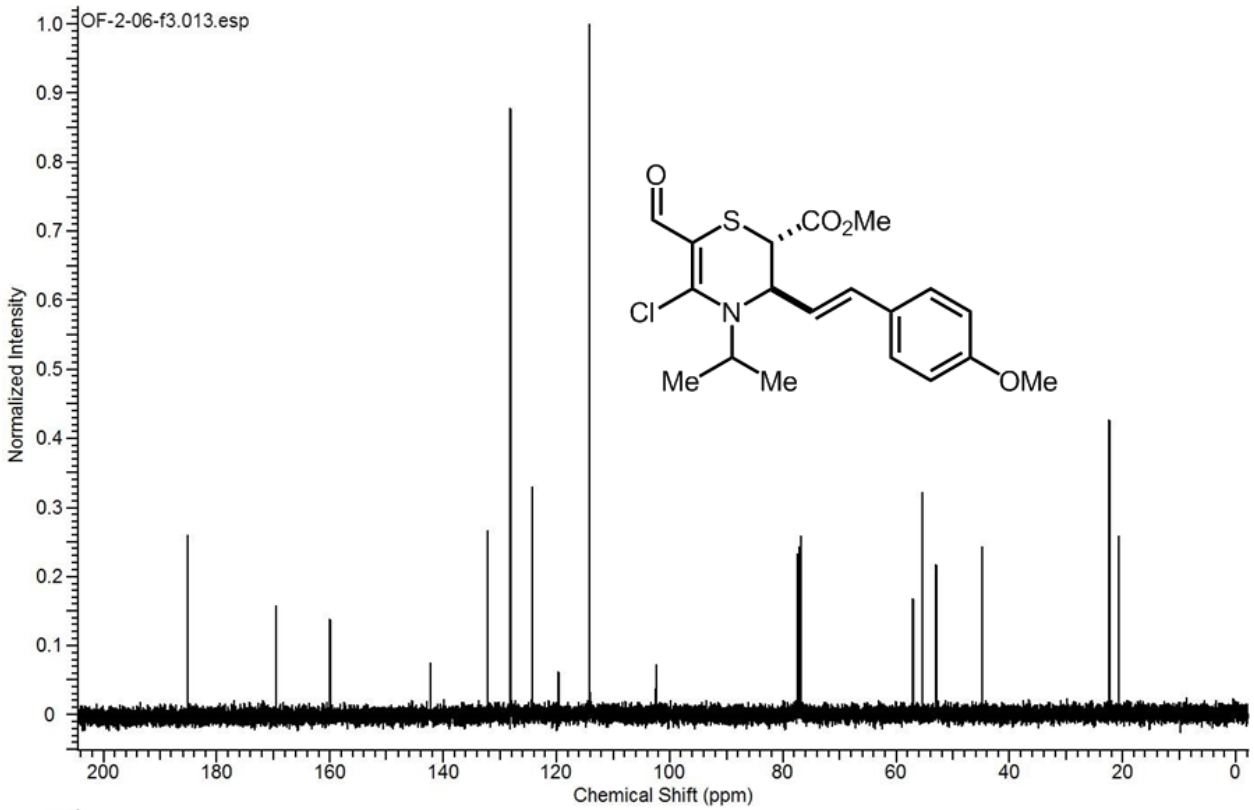


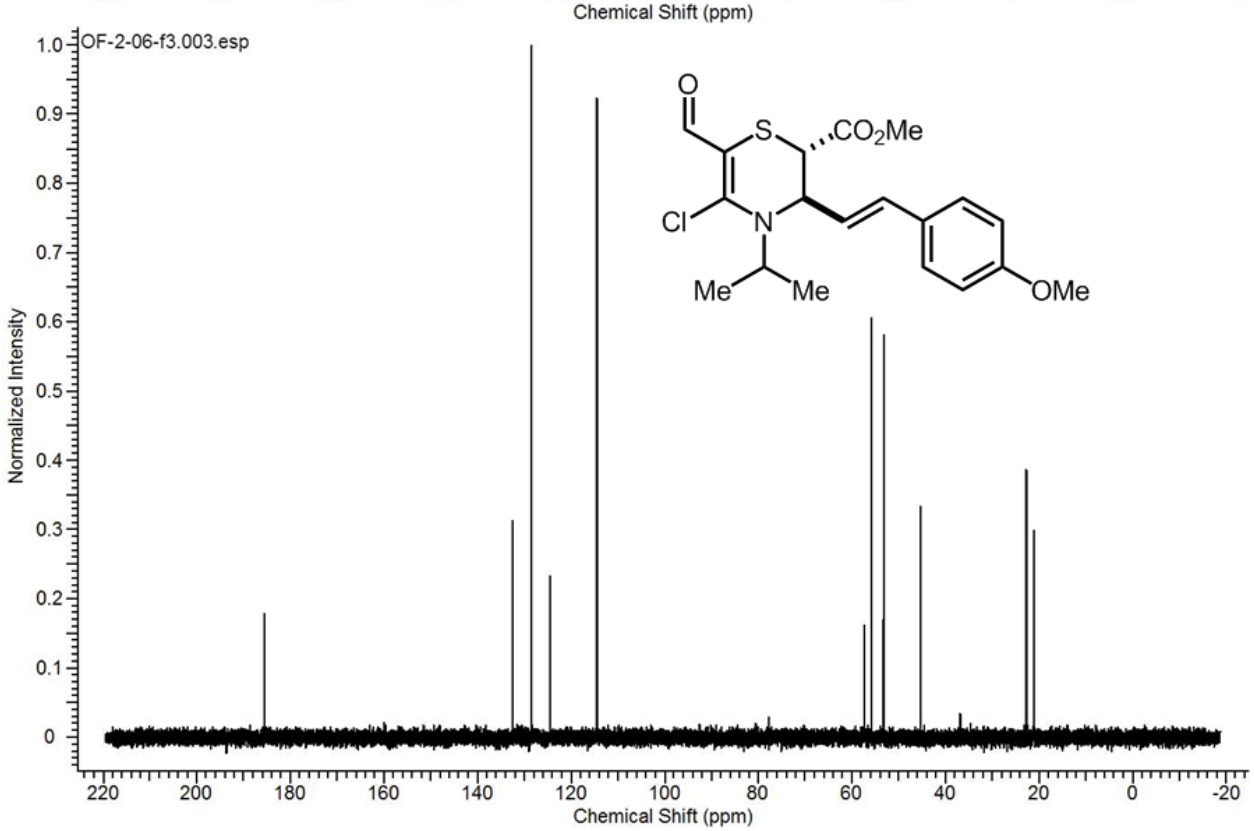

tkb-10-071C-f4.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
NO2


tkb-10-071C-f4.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
NO2

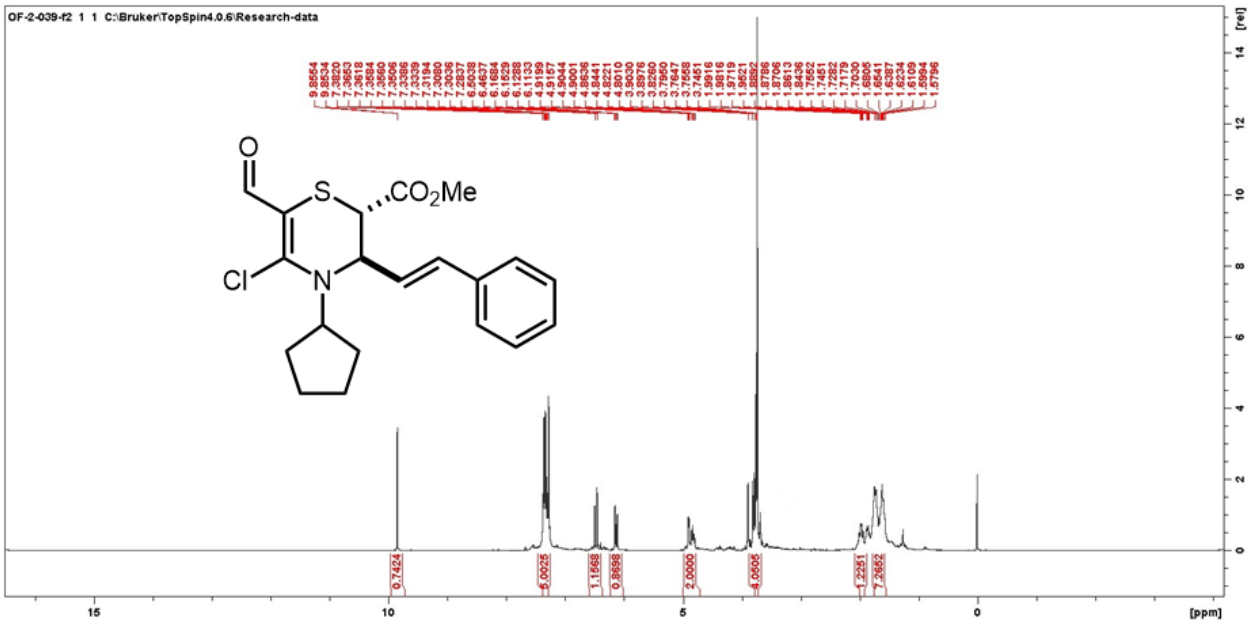
Compound **4b3:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (60:40).Yield = 304.8 mg, 77%, 95:5 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 (s, 1H), 7.38 – 7.25 (m, 2H), 6.94 – 6.81 (m, 2H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.05 (dd, *J* = 15.8, 7.1 Hz, 1H), 4.95 – 4.79 (m, 2H), 3.87 (d, *J* = 2.7 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.13, 169.56, 159.98, 142.30, 132.17, 128.24, 128.12, 124.20, 114.18, 102.48, 57.06, 55.42, 52.97, 52.89, 44.88, 22.42, 20.73. HRMS calc for $C_{19}H_{22}ClNO_4S$ 395.0958, found 395.0952.

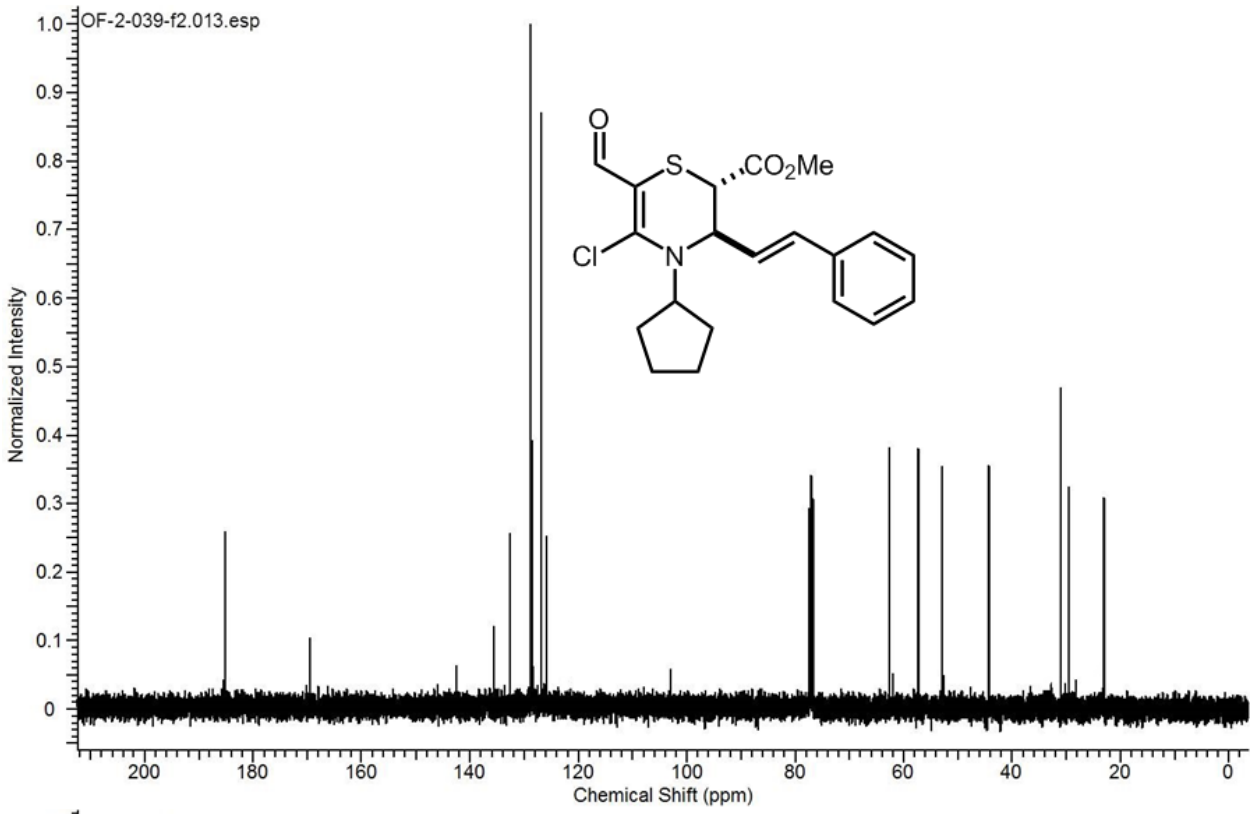


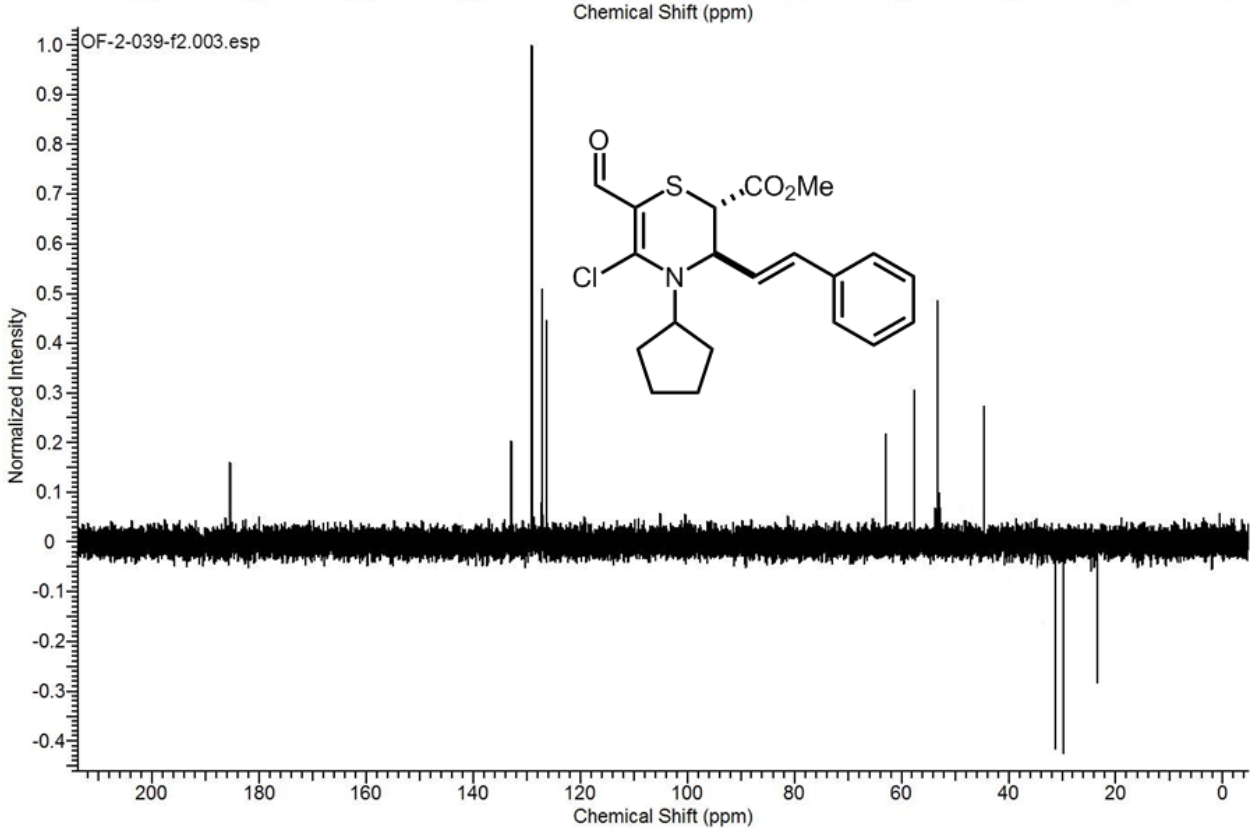

OF-2-06-f3.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
OMe


OF-2-06-f3.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
OMe

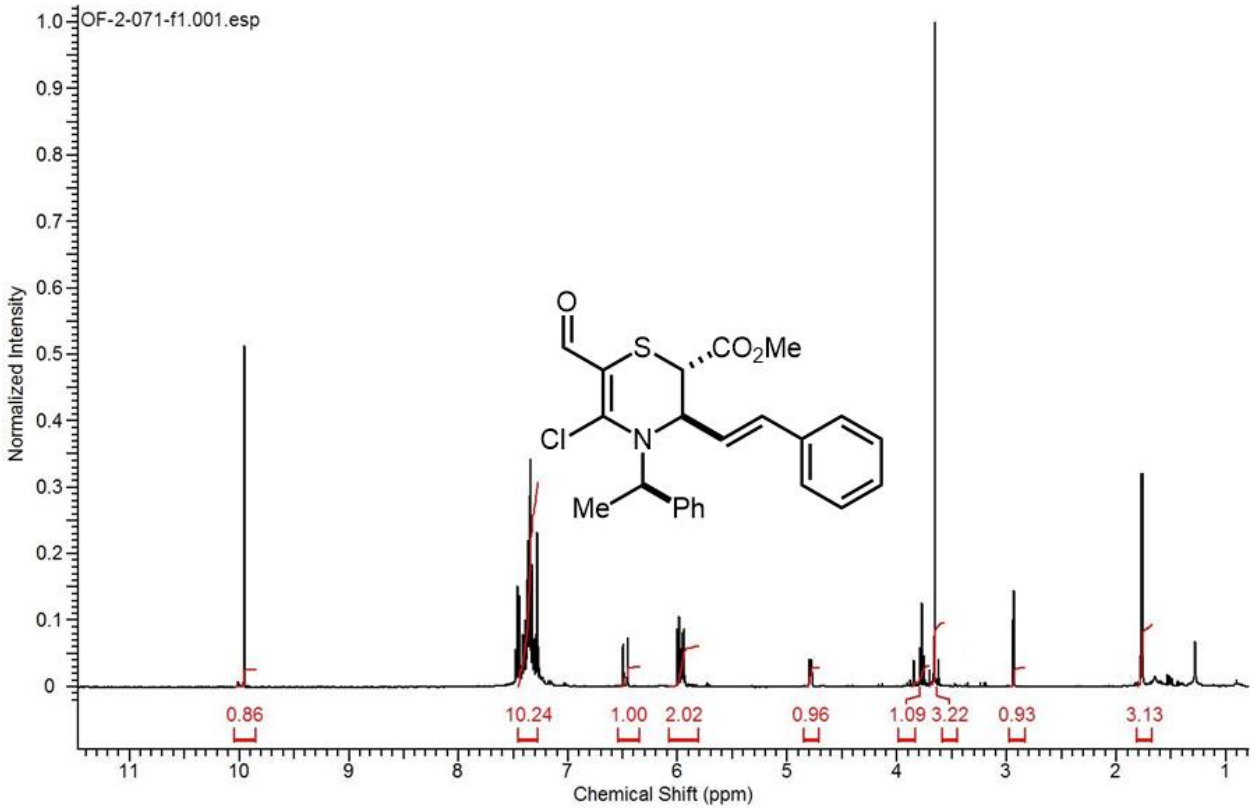
Compound **4b4:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10).Yield = 325.3 mg, 83%, 90:10 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.85 (s, 1H), 7.44 – 7.32 (m, 5H), 6.48 (dd, *J* = 15.8, 1.3 Hz, 1H), 6.14 (dd, *J* = 15.8, 6.2 Hz, 1H), 5.00 – 4.78 (m, 2H), 3.98 – 3.87 (m, 1H), 3.75 (s, 3H), 1.99 – 1.73 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.12, 169.56, 132.68, 128.78, 128.56, 126.85, 125.92, 102.93, 62.63, 57.27, 52.91, 44.25, 30.97, 29.40, 23.06, 23.04. HRMS calc for $C_{20}H_{22}ClNO_3S$ 391.1009, found 391.1003.

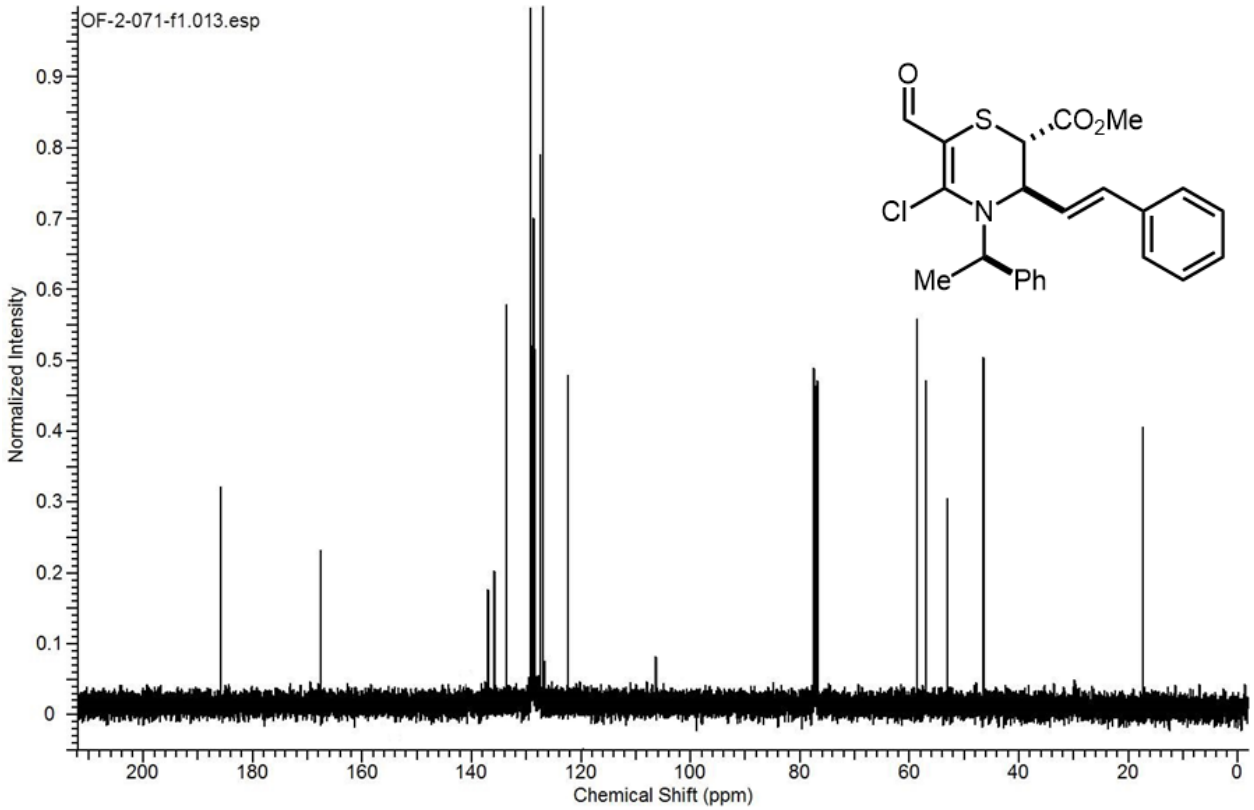


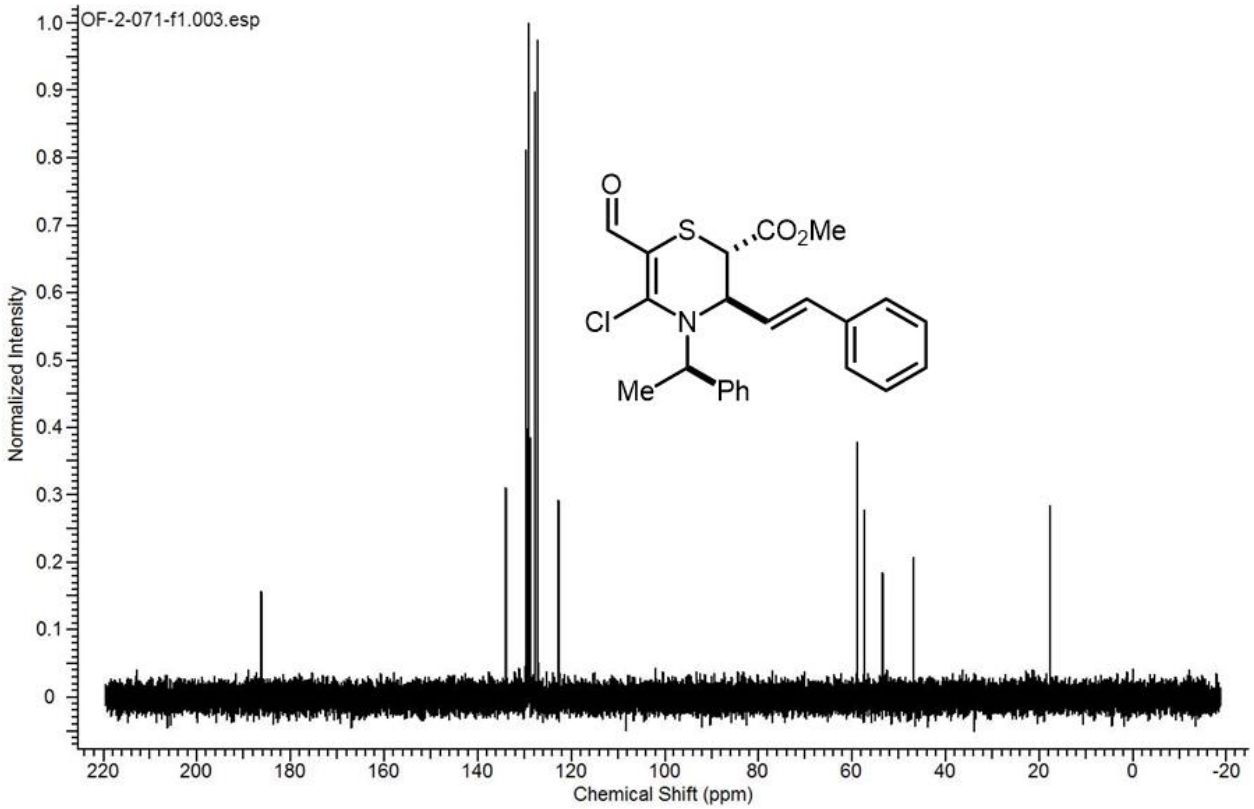

OF-2-039-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N


OF-2-039-f2.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N

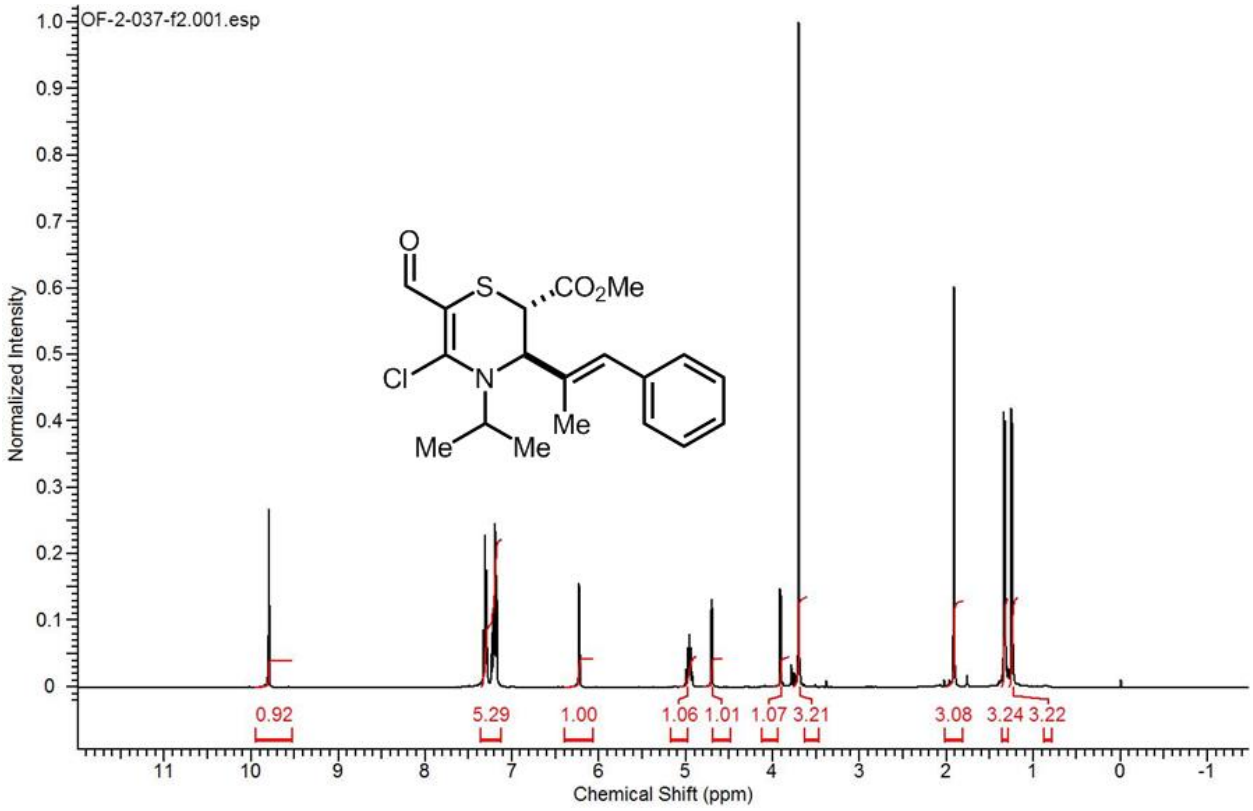
Compound **4b5:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25).Yield = 342.3 mg, 80%, 95:5 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.96 (s, 1H), 7.46 – 7.30 (m, 10H), 6.48 (dd, *J* = 15.8, 1.3 Hz, 1H), 6.04 – 5.89 (m, 2H), 4.79 (ddd, *J* = 6.4, 2.8, 1.4 Hz, 1H), 3.66 (s, 3H), 2.93 (d, *J* = 2.8 Hz, 1H), 1.77 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.86, 167.60, 140.99, 137.01, 135.86, 133.72, 129.25, 128.68, 127.42, 126.89, 122.43, 58.56, 56.94, 53.05, 46.52, 17.26. HRMS calc for $C_{23}H_{22}ClNO_3S$ 427.1009, found 427.1005.

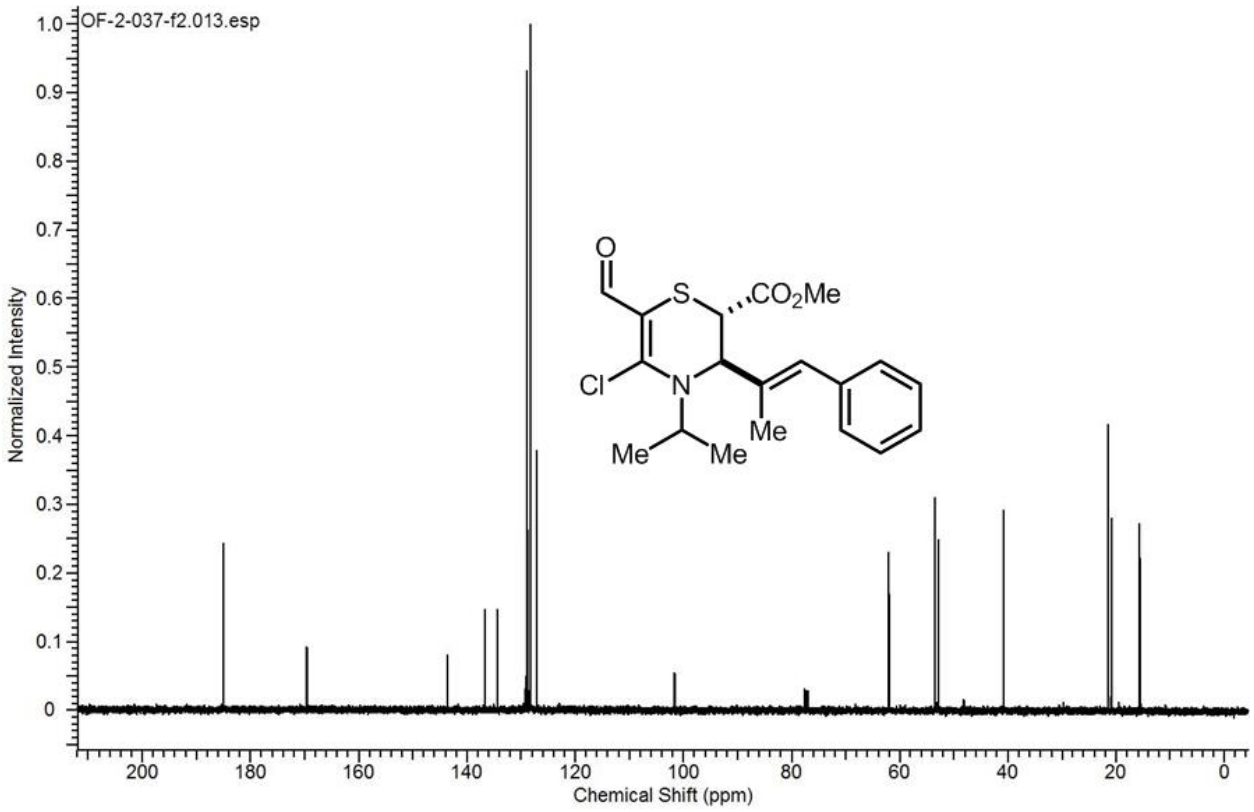


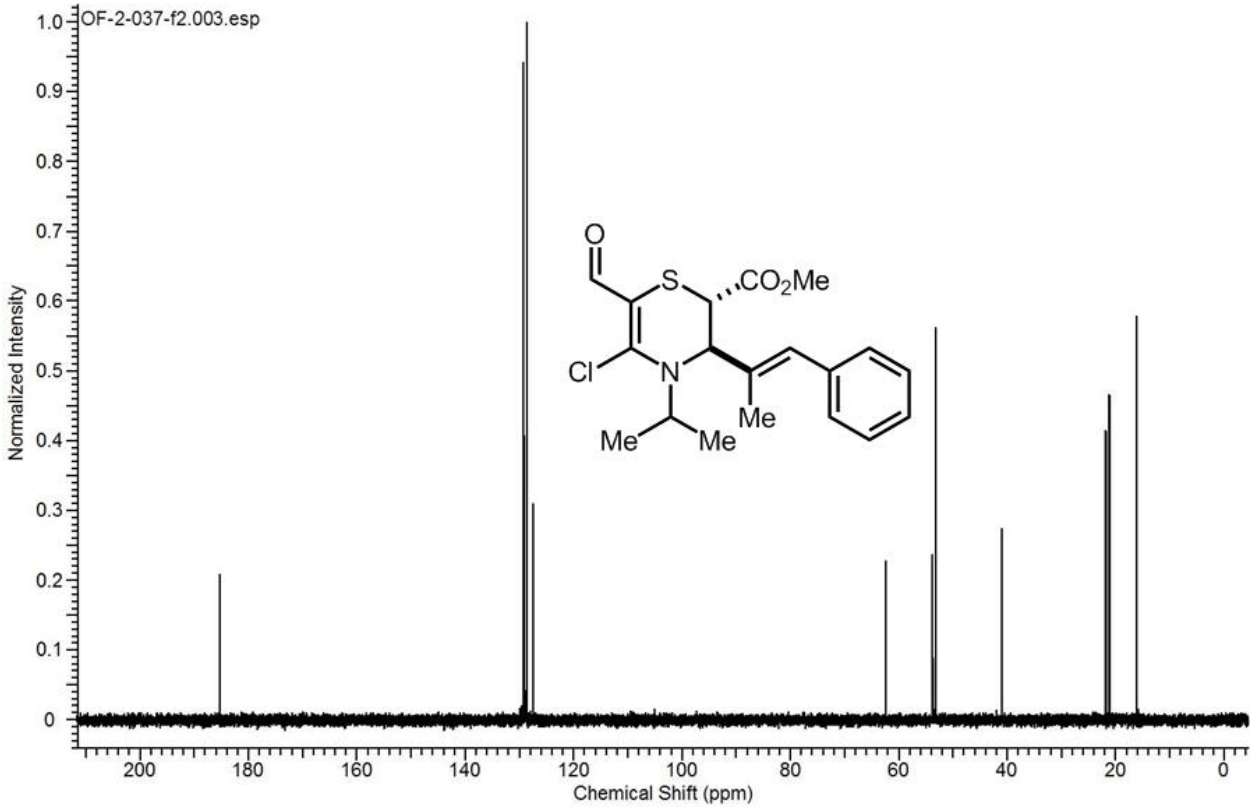

OF-2-071-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Ph


OF-2-071-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Ph

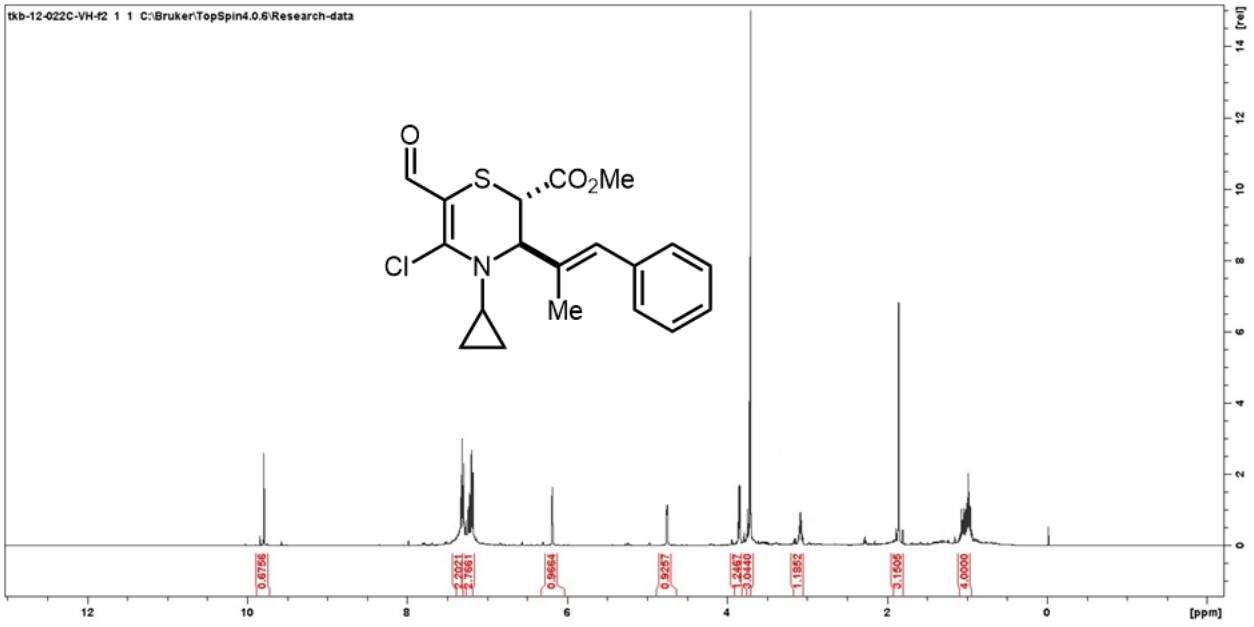
Compound **4b6:** Prepared using **General Procedure A**. Temp = 23 °C for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25).Yield = 311.5 mg, 82%, 95:5 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.80 (s, 1H), 7.31 (dd, *J* = 8.1, 6.8 Hz, 2H), 7.26 – 7.15 (m, 3H), 6.23 (s, 1H), 4.96 (p, *J* = 6.7 Hz, 1H), 4.73 – 4.67 (m, 1H), 3.93 – 3.88 (m, 1H), 3.70 (s, 3H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9, 169.6, 143.6, 136.7, 134.4, 128.9, 128.7, 128.3, 127.1, 101.6, 62.1, 53.4, 52.9, 40.7, 21.5, 20.9, 15.7. HRMS calc for $C_{19}H_{22}ClNO_3S$ 379.1009, found 379.1003.

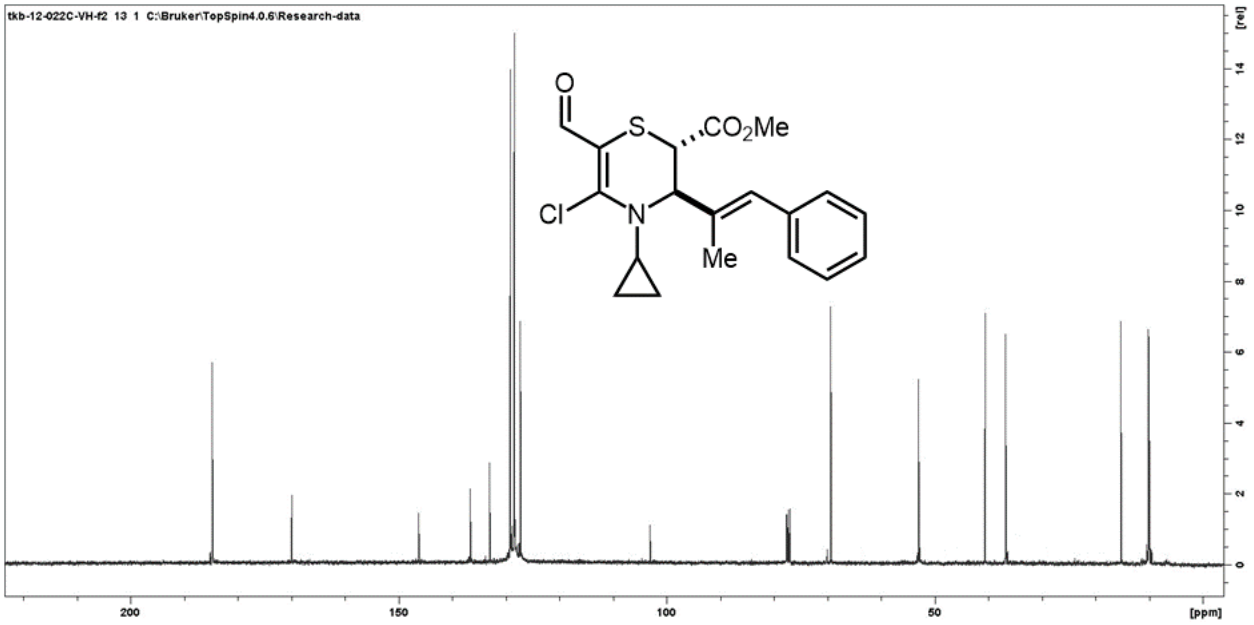


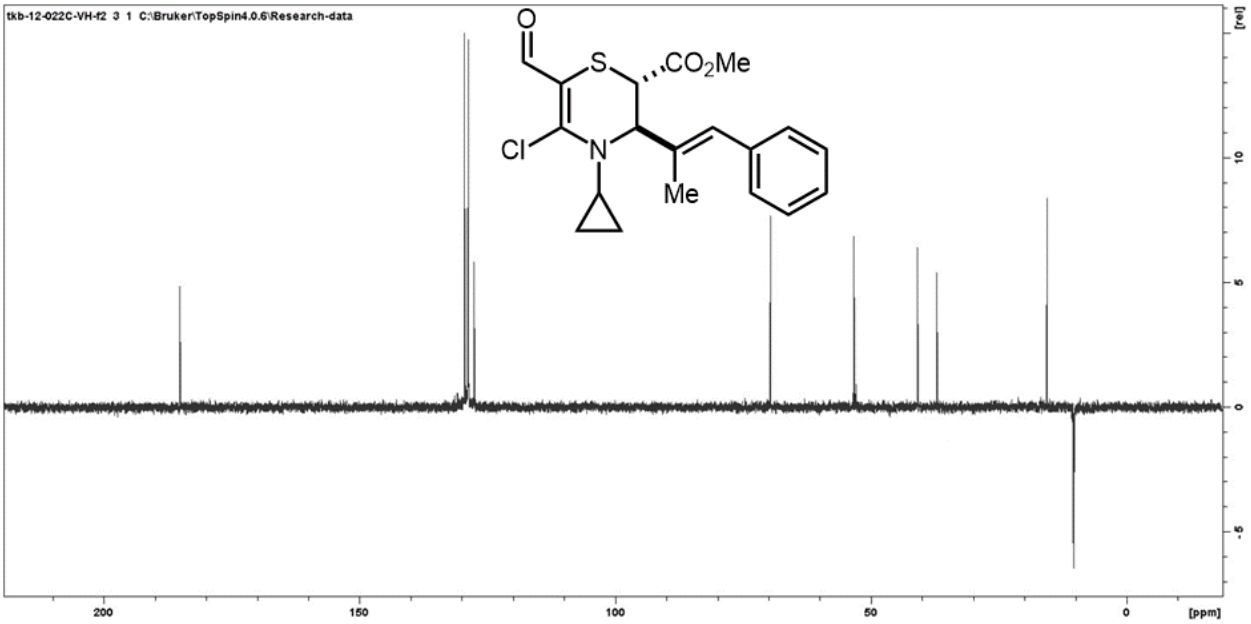

OF-2-037-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
Me


OF-2-037-f2.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
Me

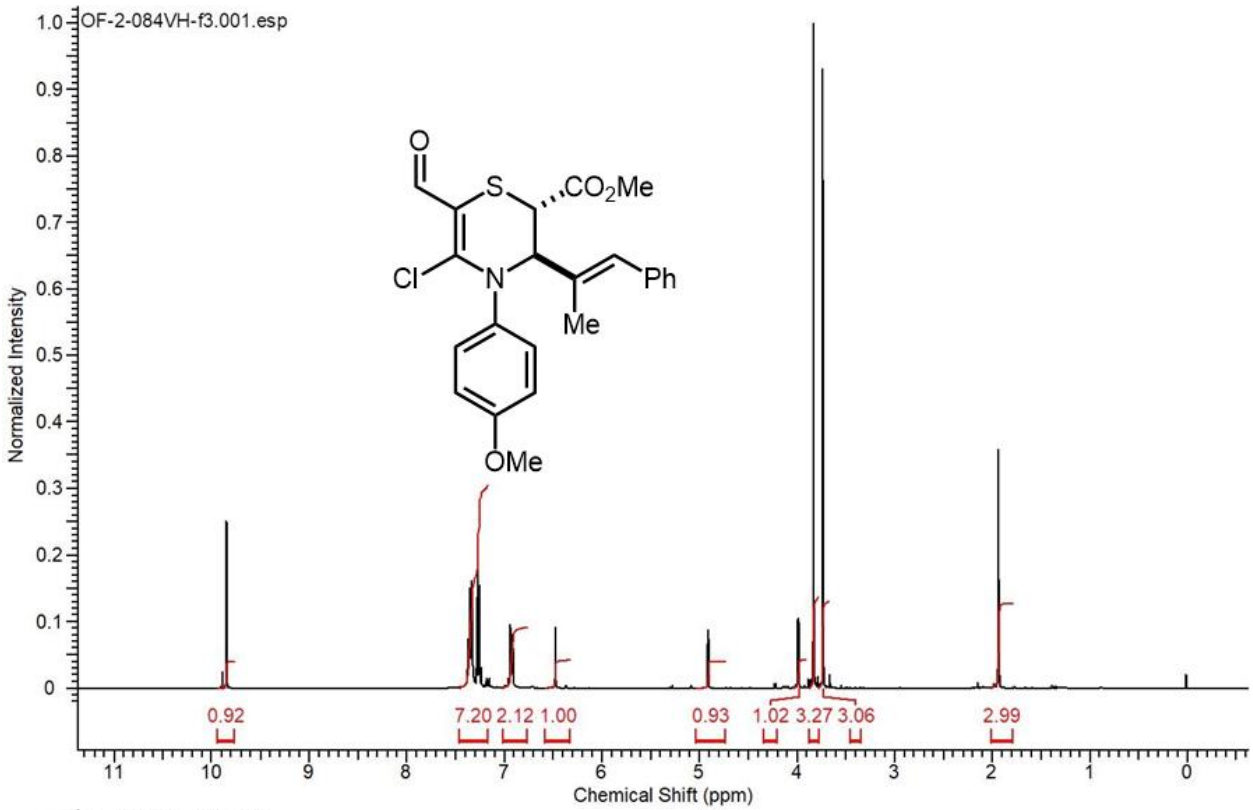
Compound **4b7:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25).Yield = 294.7 mg, 78%, 95:5 dr, oily substance. ^1H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.36 – 7.25 (m, 5H), 6.23 (s, 1H), 4.62 (d, 1H), 3.83 (d, 1H), 3.65 (s, 3H), 3.26 – 3.11 (m, 1H), 1.79 (s, 3H), 1.07 – 0.91 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.73, 169.90, 146.16, 136.56, 132.99, 129.10, 128.41, 128.40, 128.32, 128.30, 127.20, 103.00, 69.29, 52.93, 40.53, 36.70, 15.16, 10.04, 9.90. HRMS calc for $C_{19}H_{20}ClNO_3S$ 377.0852, found 377.0856.







Compound **4b8:** Prepared using **General Procedure A**. Temp = room temperature, time = 6 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 314 mg, 71%, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.99 (s, 1H), 7.34 (m, 7H), 7.25 (d, *J* = 7.2 Hz, 2H), 6.46 (s, 1H), 4.88 (d, 1H), 3.96 (d, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.4, 170.4, 159.2, 142.6, 137.3, 136.5, 133.3, 131.5, 129.5, 129.1, 129.1, 114.9, 102.5, 72.6, 55.5, 53.1, 40.1, 17.6. HRMS calc for $C_{23}H_{20}ClNO_4S$, 443.0958, found 443.0965.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Normalized Intensity
Chemical Shift (ppm)
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7.20
2.12
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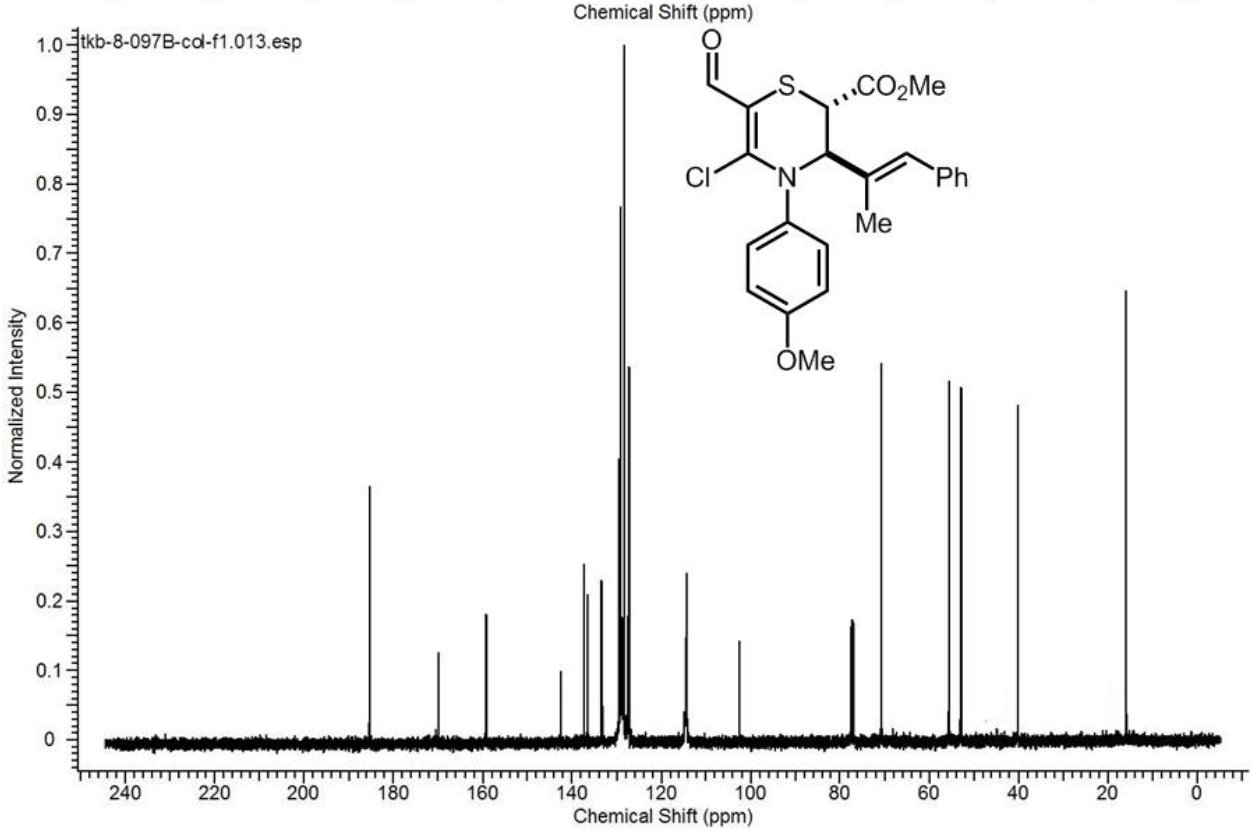
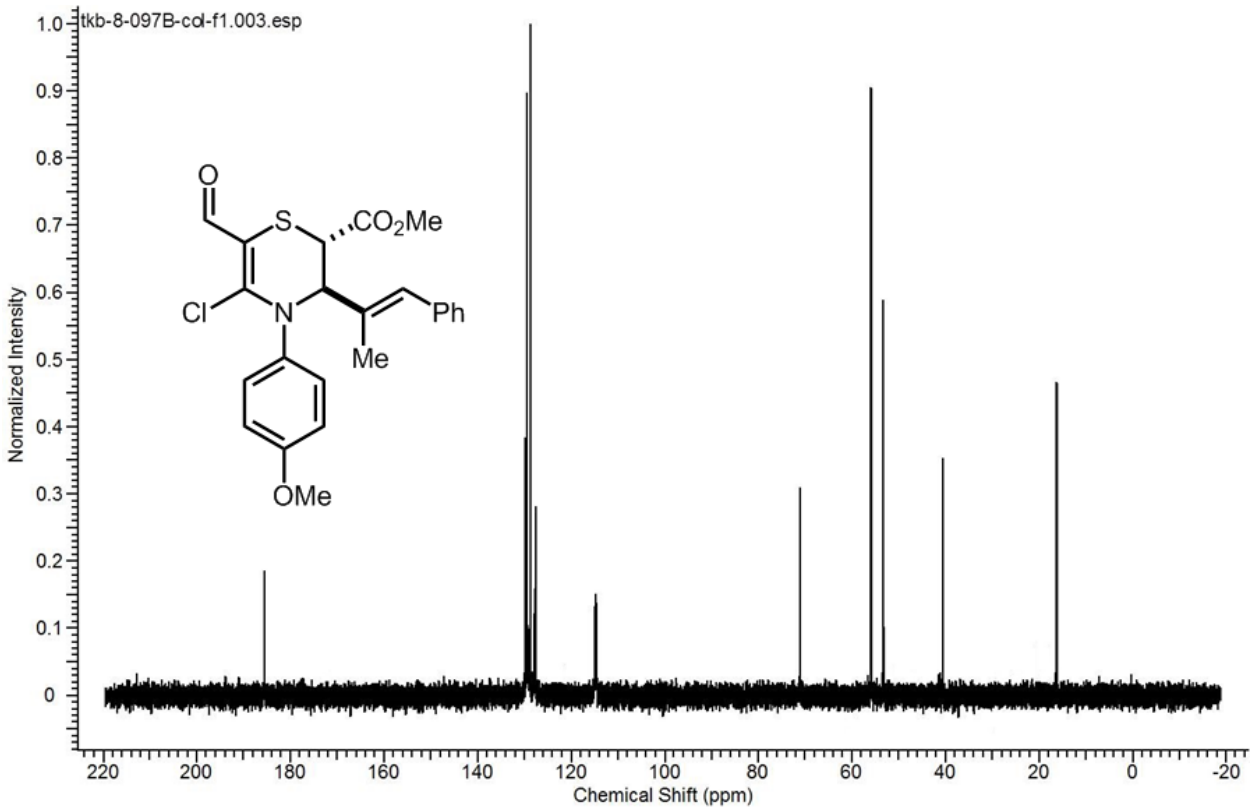
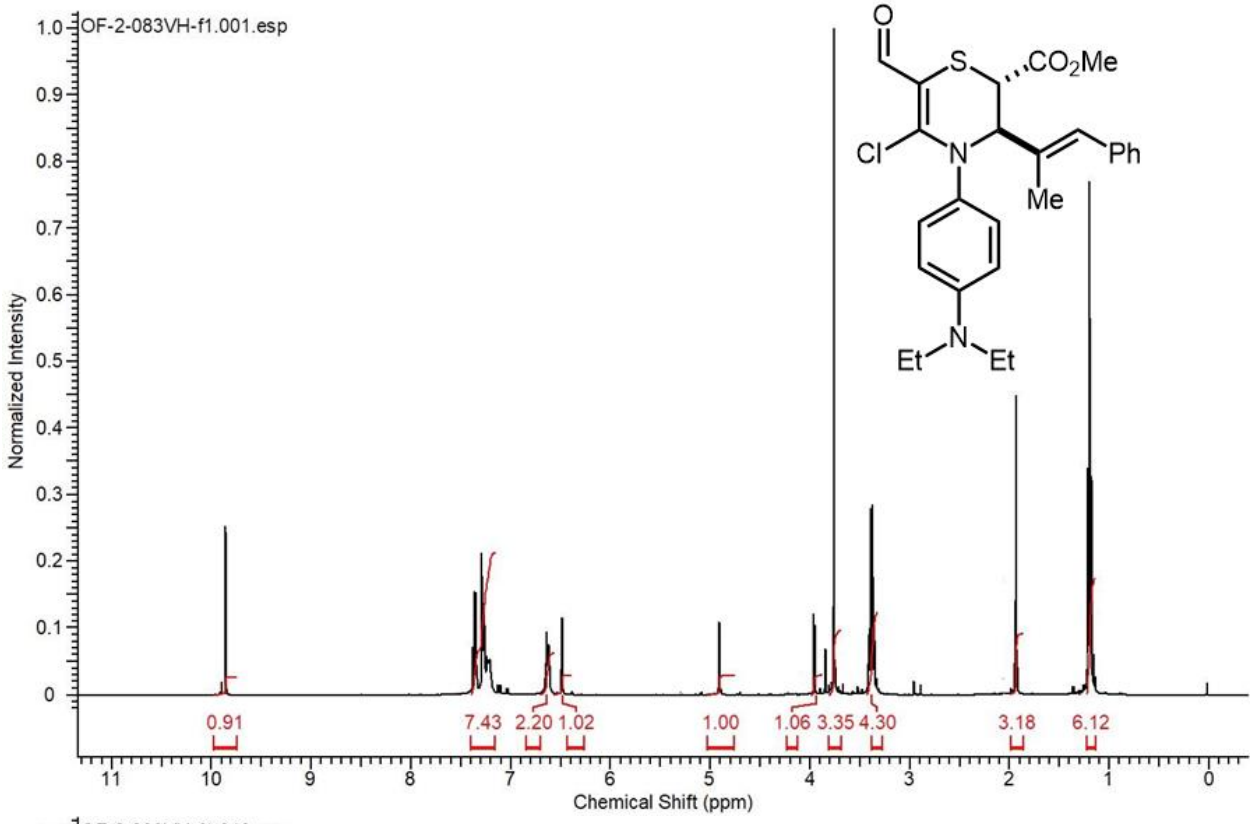
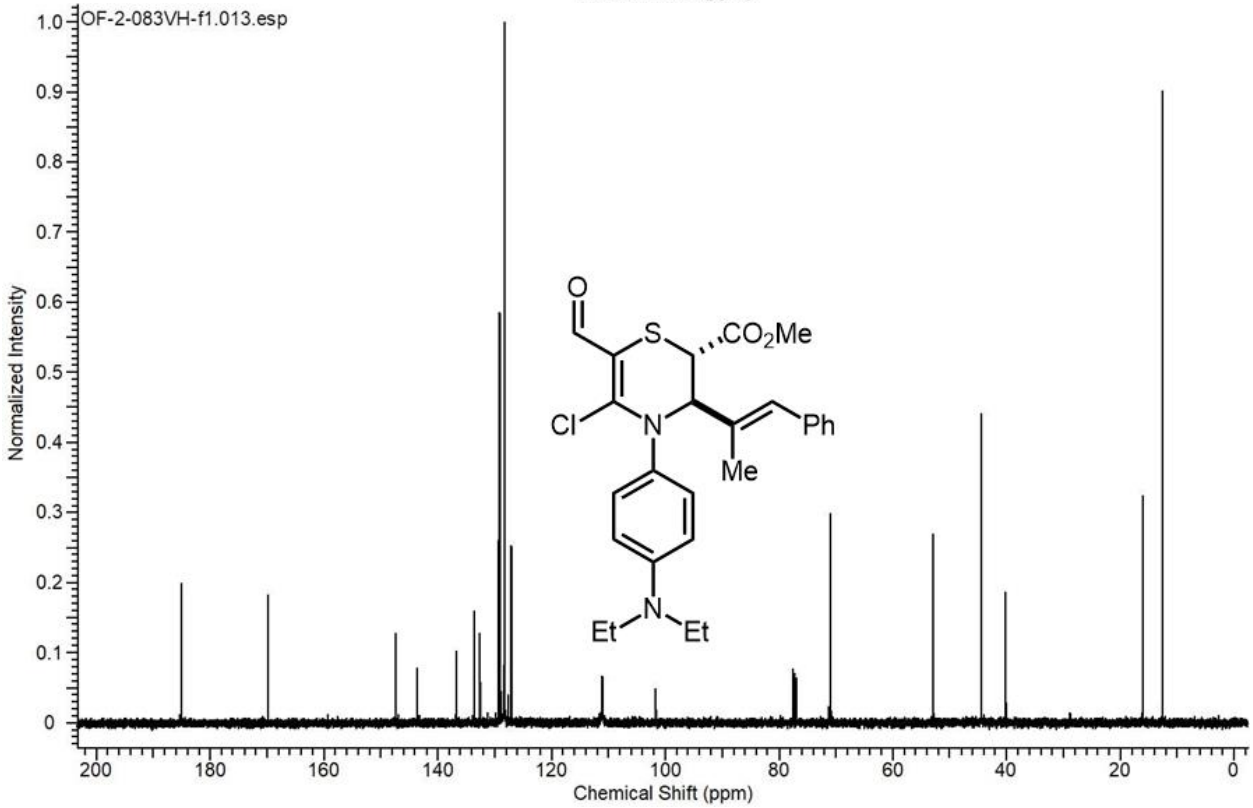
1.02
3.27
3.06
2.99
O
S
CO2Me
Cl
N
Ph
Me
OMe

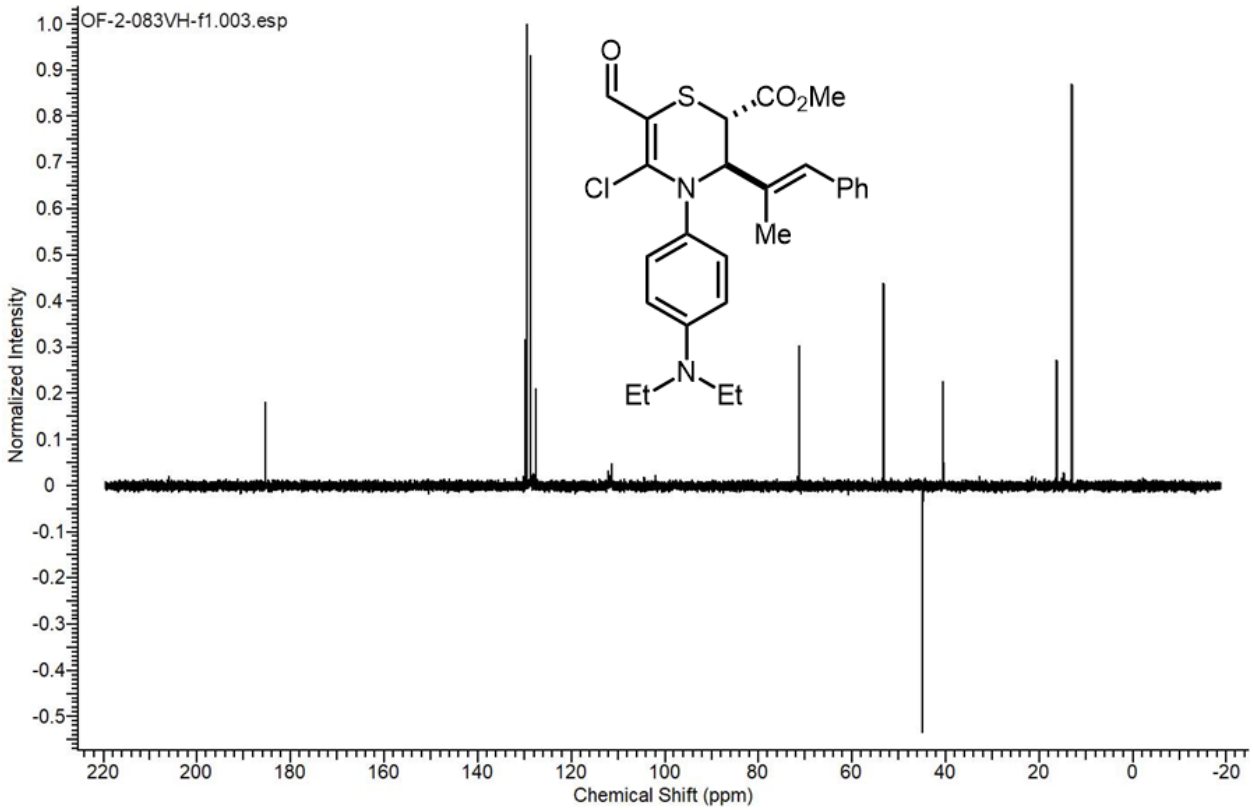

tkb-8-097B-col-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Ph
Me
OMe



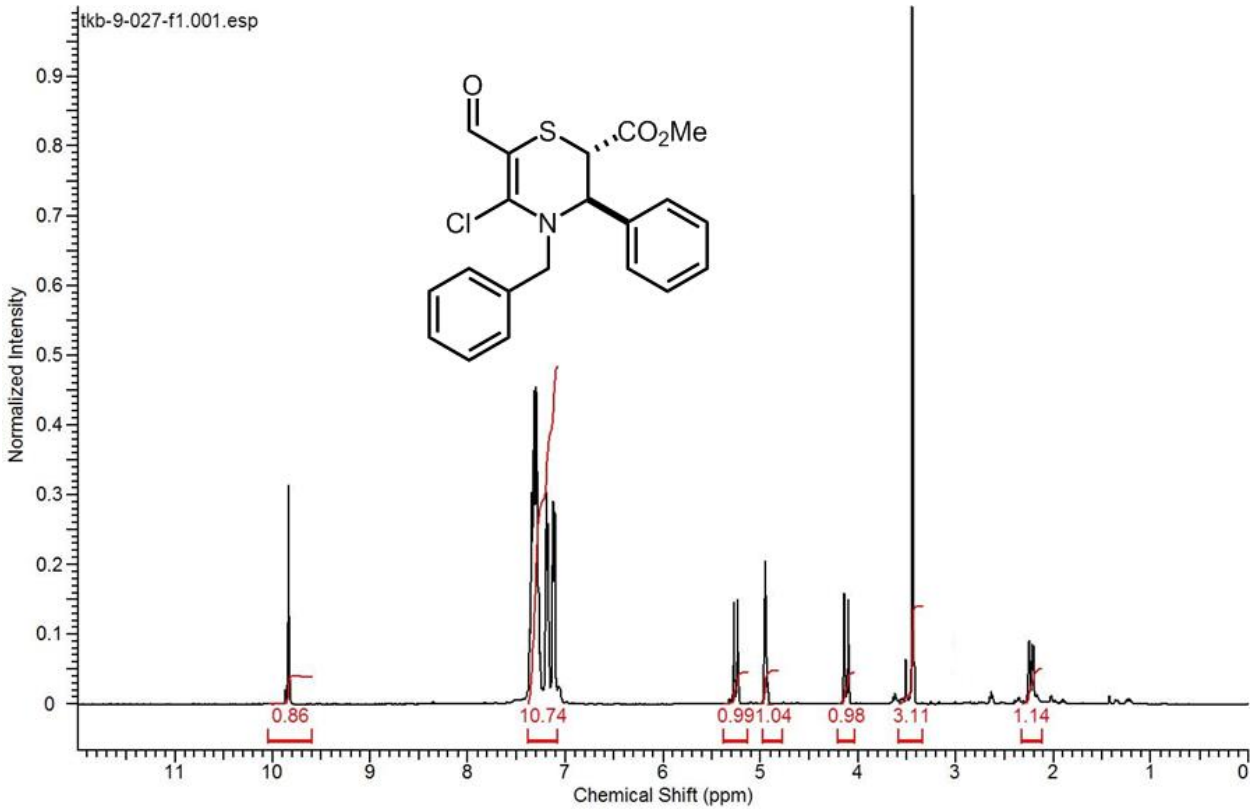
Compound **4b9:** Prepared using **General Procedure A**. Temp = room temperature, time = 6 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 330 mg, 68%, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 (s, 1H), 7.42 – 7.31 (m, 2H), 7.31 – 7.18 (m, 5H), 6.68 – 6.59 (m, 2H), 6.48 (s, 1H), 4.91 (t, *J* = 1.9 Hz, 1H), 3.96 (dd, *J* = 2.3, 1.0 Hz, 1H), 3.76 (s, 3H), 3.38 (q, *J* = 7.1 Hz, 4H), 1.93 (d, *J* = 1.3 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.05, 169.89, 147.41, 143.62, 136.77, 133.56, 132.57, 129.34, 129.13, 128.32, 127.16, 111.07, 101.70, 70.93, 52.91, 44.49, 40.18, 15.99, 12.62. HRMS calc for $C_{26}H_{29}ClN_2O_3S$, 484.1587, found 484.1582.

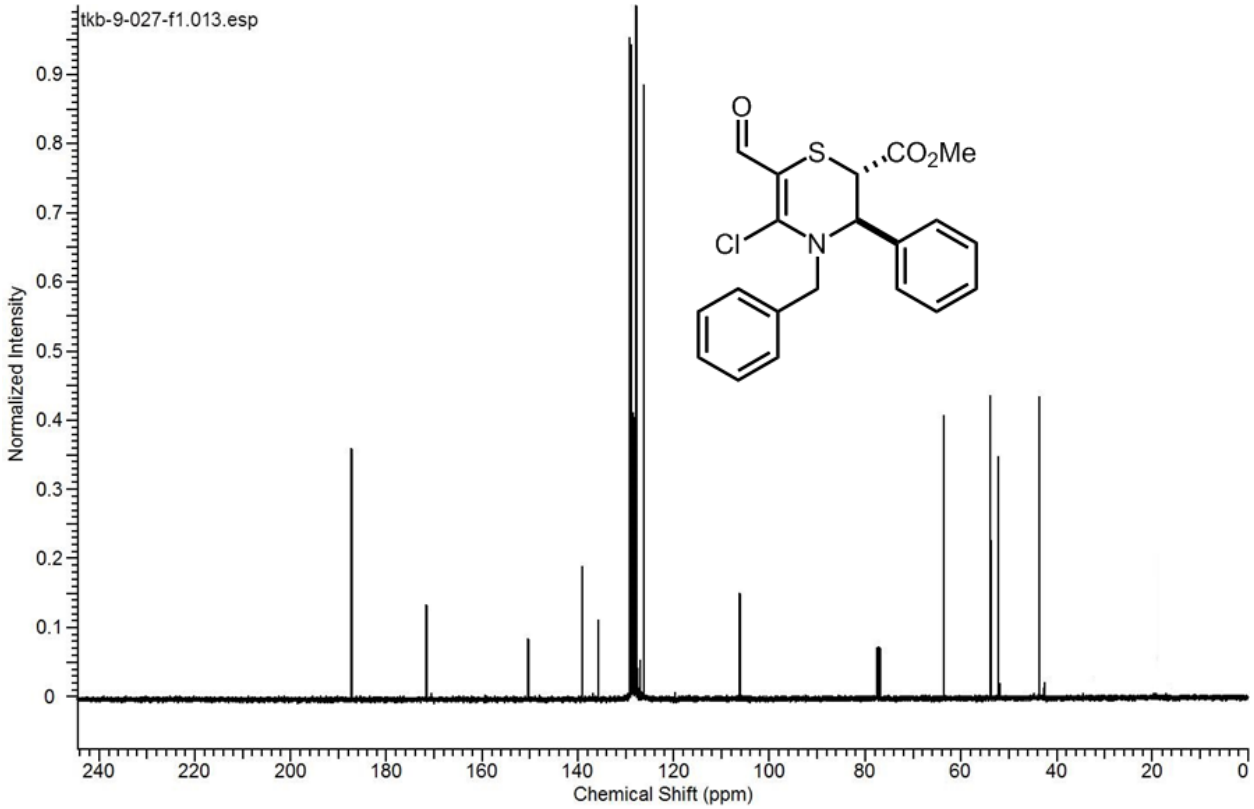

OF-2-083VH-f1.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.91
7.43
2.20
1.02
1.00
1.06
3.35
4.30
3.18
6.12
O
S
CO2Me
Cl
N
Ph
Me
Et
N
Et

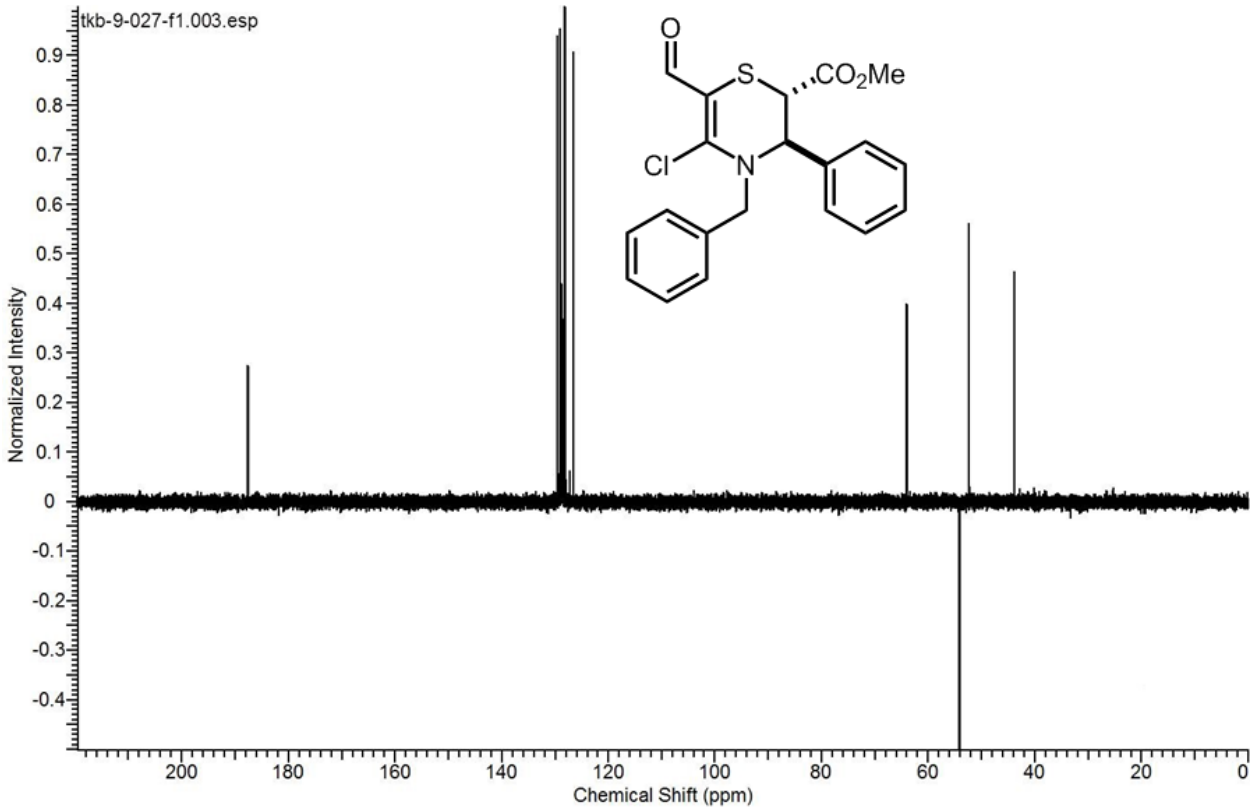

OF-2-083VH-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Ph
Me
Et
N
Et



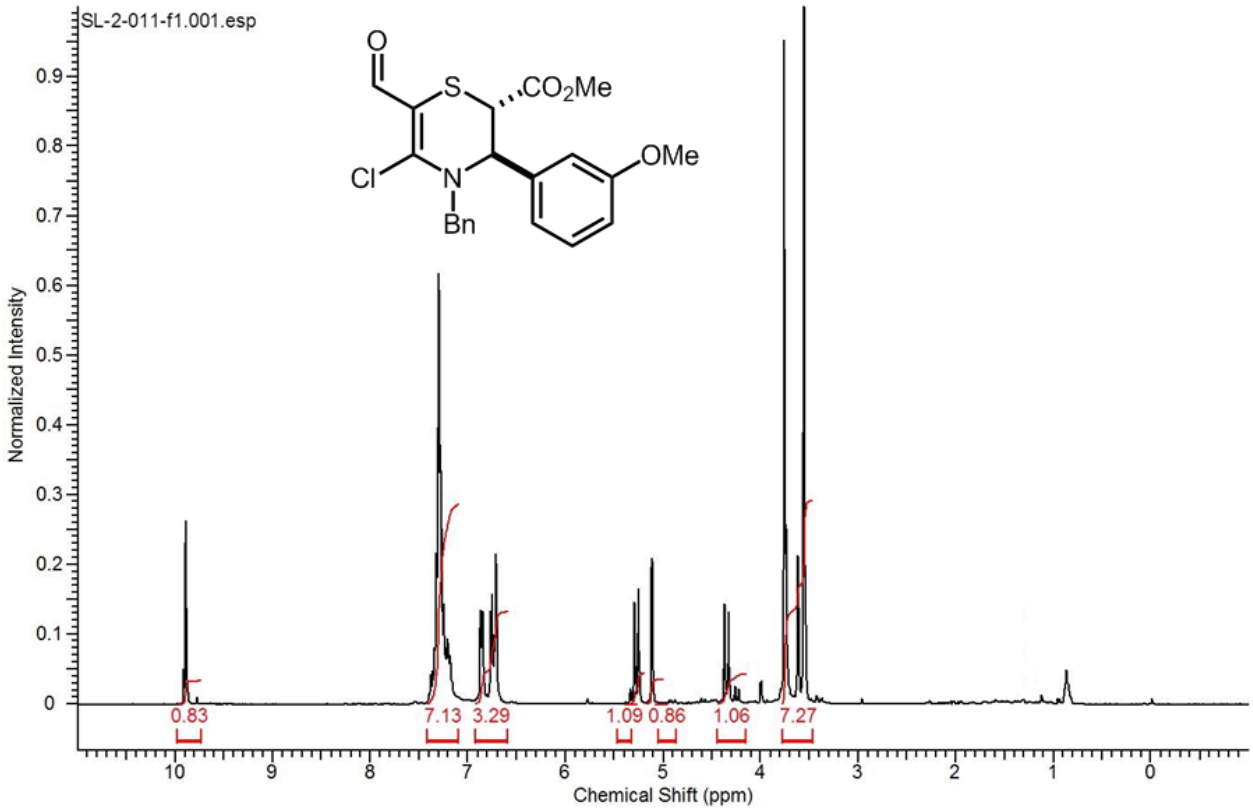
Compound **4b10:** Prepared using **General Procedure A**. Temp = room temperature, time = 6 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 317 mg, 79%, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (s, 1H), 7.31 – 7.02 (m, 10H), 5.25 (d, *J* = 16.0 Hz, 1H), 4.95 (s, 1H), 4.12 (d, *J* = 15.9 Hz, 1H), 3.44 (s, 3H), 2.23 (dd, *J* = 16.2, 5.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 187.2, 171.7, 150.4, 139.1, 135.7, 129.2, 128.2, 127.5, 126.9, 106.2, 63.6, 53.8, 51.8, 42.6. HRMS calc for $C_{20}H_{18}ClNO_3S$, 387.0696, found 387.0691.

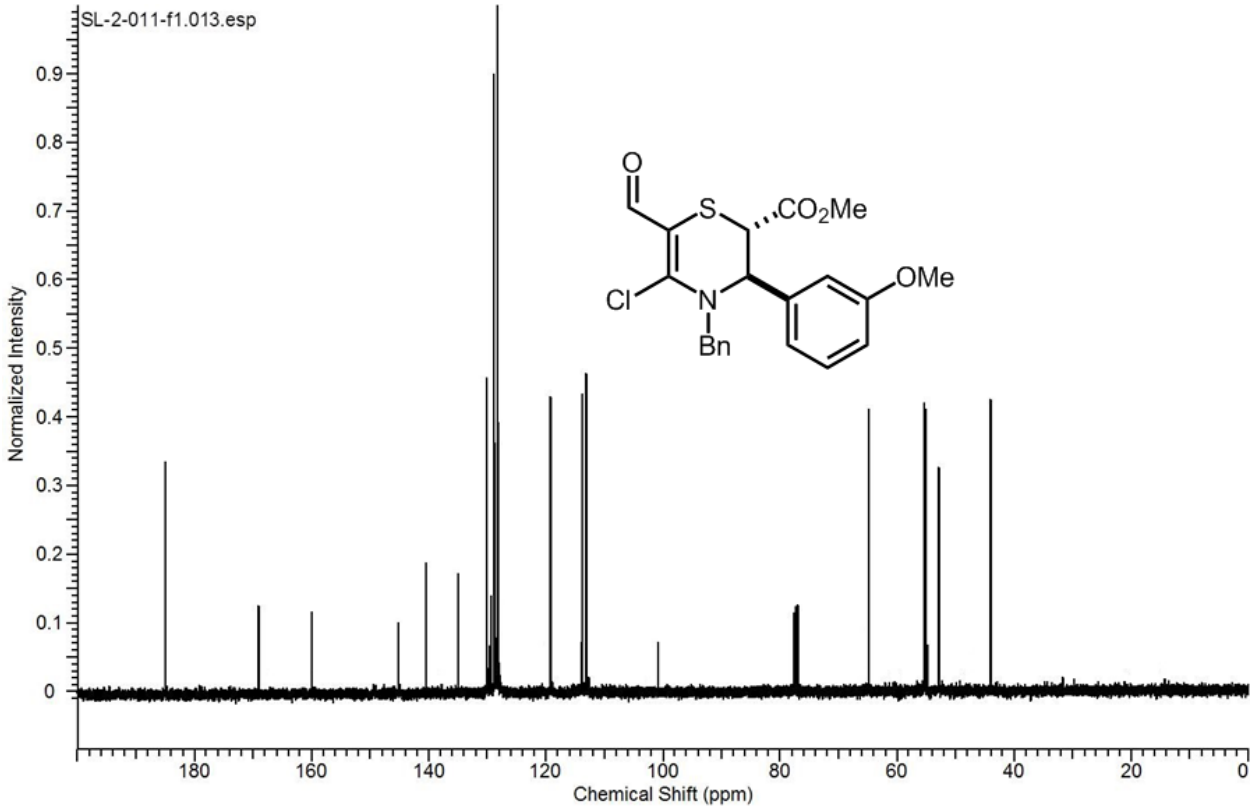

tkb-9-027-f1.001.esp
O
S
CO2Me
Cl
N
Normalized Intensity
0.86
10.74
0.99
1.04
0.98
3.11
1.14
Chemical Shift (ppm)

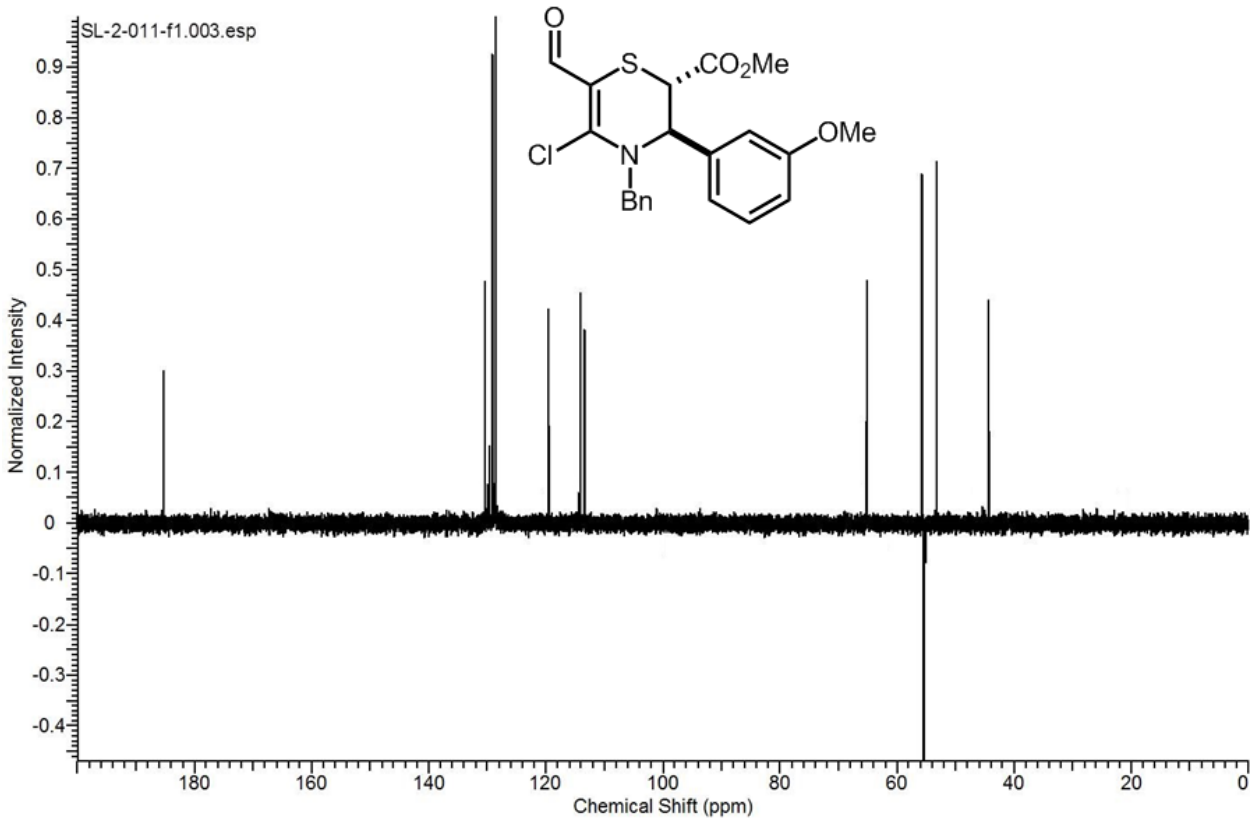

tkb-9-027-f1.013.esp
O
S
CO2Me
Cl
N
Normalized Intensity
Chemical Shift (ppm)



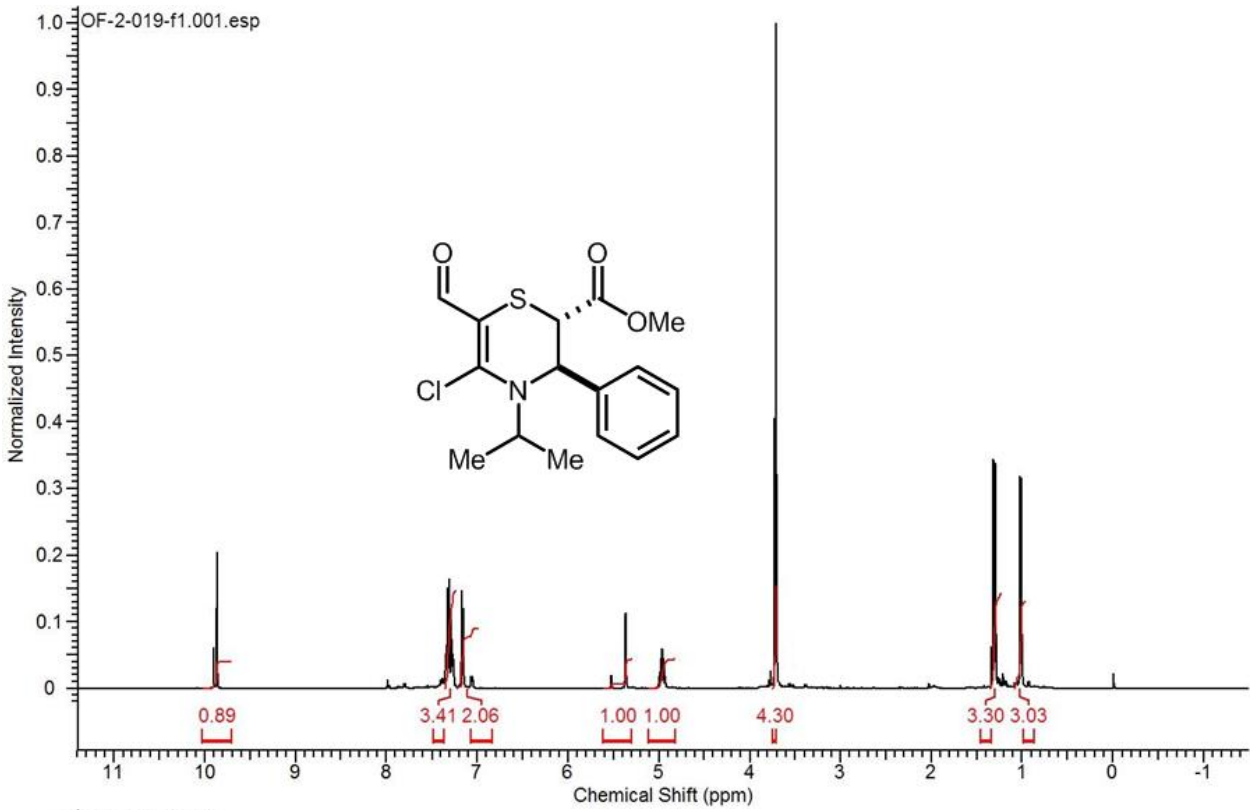
Compound **4b11:** Prepared using **General Procedure A**. Temp = room temperature, time = 6 h, Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 300 mg, 72%, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.90 (s, 1H, 7.28 – 7.12 (m, 5H), 6.90 – 6.72 (m, 3H), 5.27 (d, *J* = 16.1 Hz, 1H), 5.12 (d, *J* = 2.4 Hz, 1H), 4.35 (d, *J* = 16.1 Hz, 1H), 3.75 – 3.58 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0, 167.1, 159.6, 145.15, 137.7, 134.92, 130.06, 129.88, 129.55, 128.76, 128.43, 128.18, 127.98, 127.44, 127.01, 119.14, 114.49, 113.77, 112.68, 102.23, 65.84, 56.50, 52.81, 44.03. HRMS calc for $C_{21}H_{20}ClNO_4S$, 417.0802, found 417.0806.


SL-2-011-f1.001.esp
O
S
CO2Me
Cl
N
Bn
OMe
Normalized Intensity
0.83
7.13
3.29
1.09
0.86
1.06
7.27
Chemical Shift (ppm)


SL-2-011-f1.013.esp
O
S
CO2Me
Cl
N
Bn
OMe
Normalized Intensity
Chemical Shift (ppm)



Compound **4b12:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25).Yield = 254.3 mg, 75%, 80:20 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.92 (s, 1H), 7.44 – 7.22 (m, 3H), 7.19 – 7.12 (m, 2H), 5.36 (d, *J* = 2.5 Hz, 1H), 4.96 (p, *J* = 6.7 Hz, 1H), 3.89 – 3.83 (m, 4H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.98, 169.52, 140.98, 128.78, 128.46, 128.36, 127.20, 126.18, 100.89, 59.75, 59.60, 53.80, 53.45, 52.86, 48.38, 43.91, 33.53, 22.35, 21.63, 20.68, 19.59. HRMS calc for $C_{16}H_{18}ClNO_3S$, 339.0696, found 339.0691.


OF-2-019-f1.001.esp
Normalized Intensity
Chemical Shift (ppm)
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1.00
1.00
4.30
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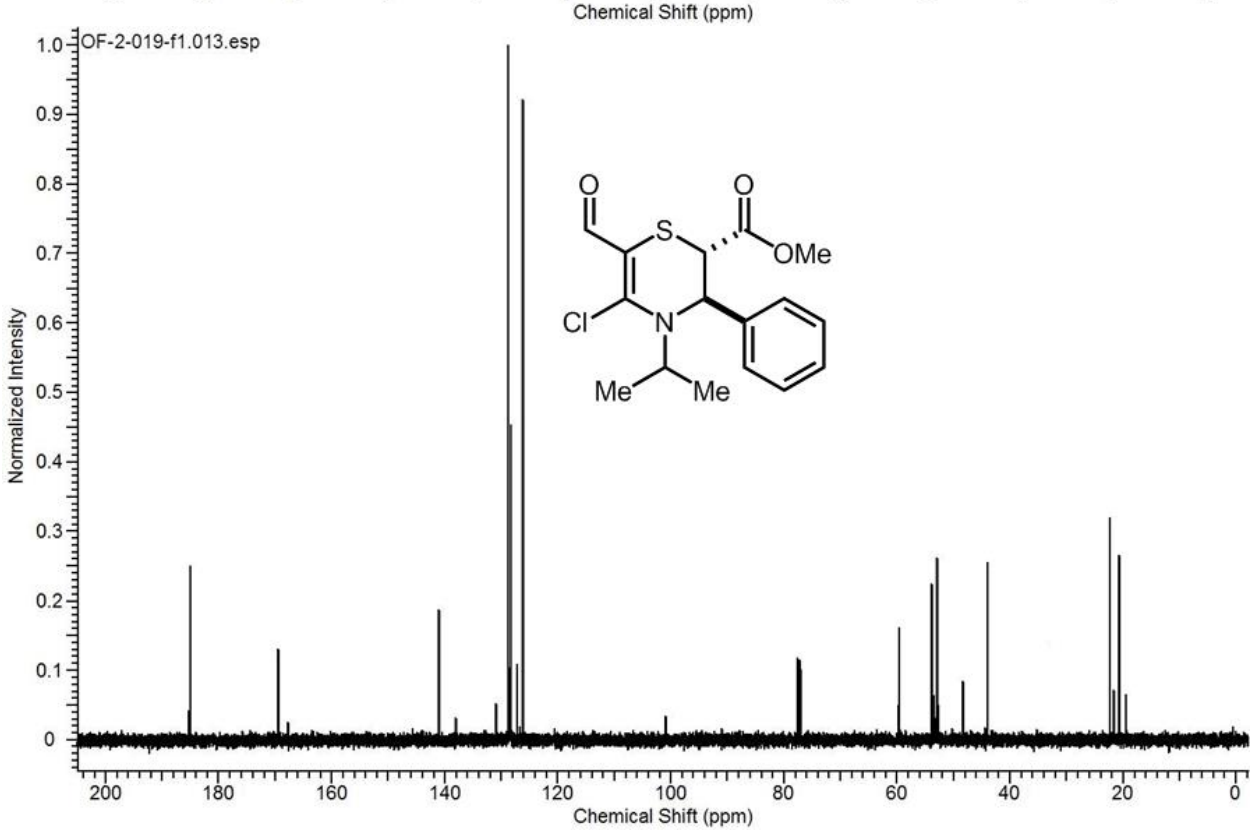
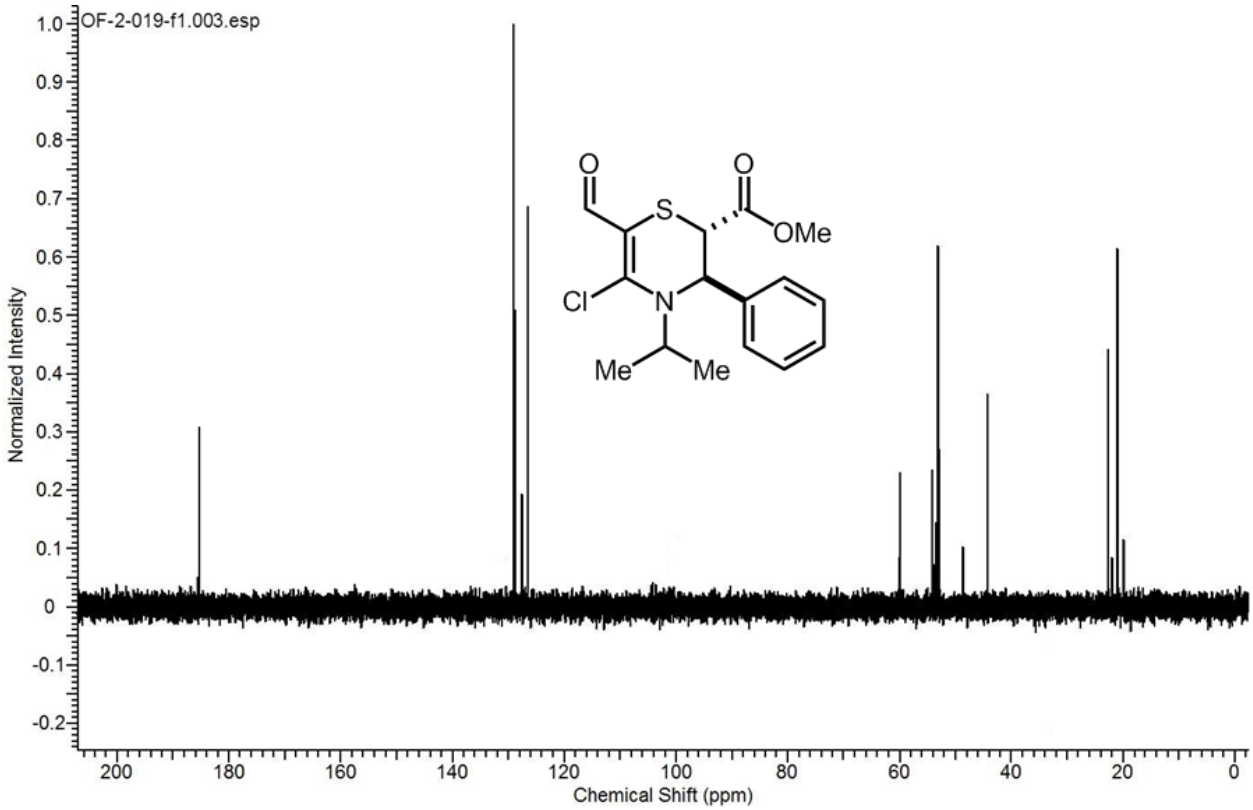
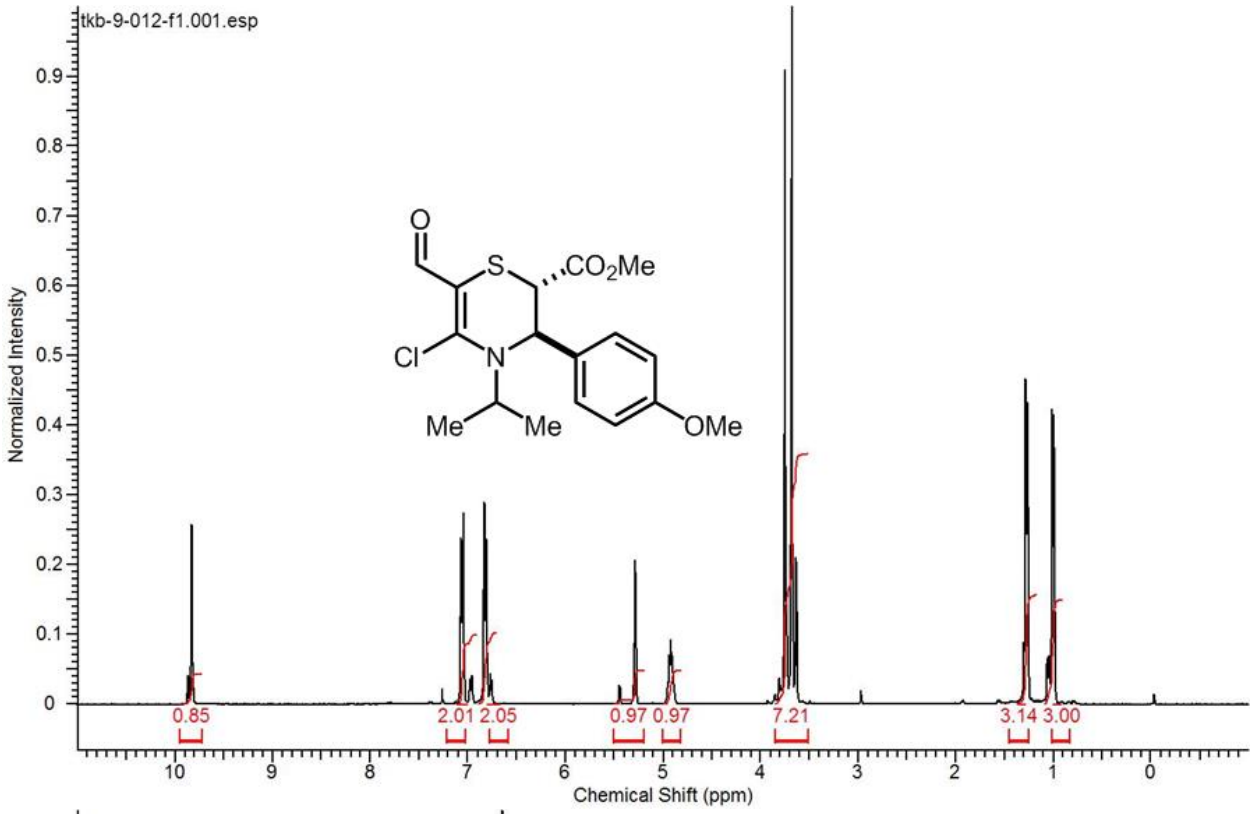
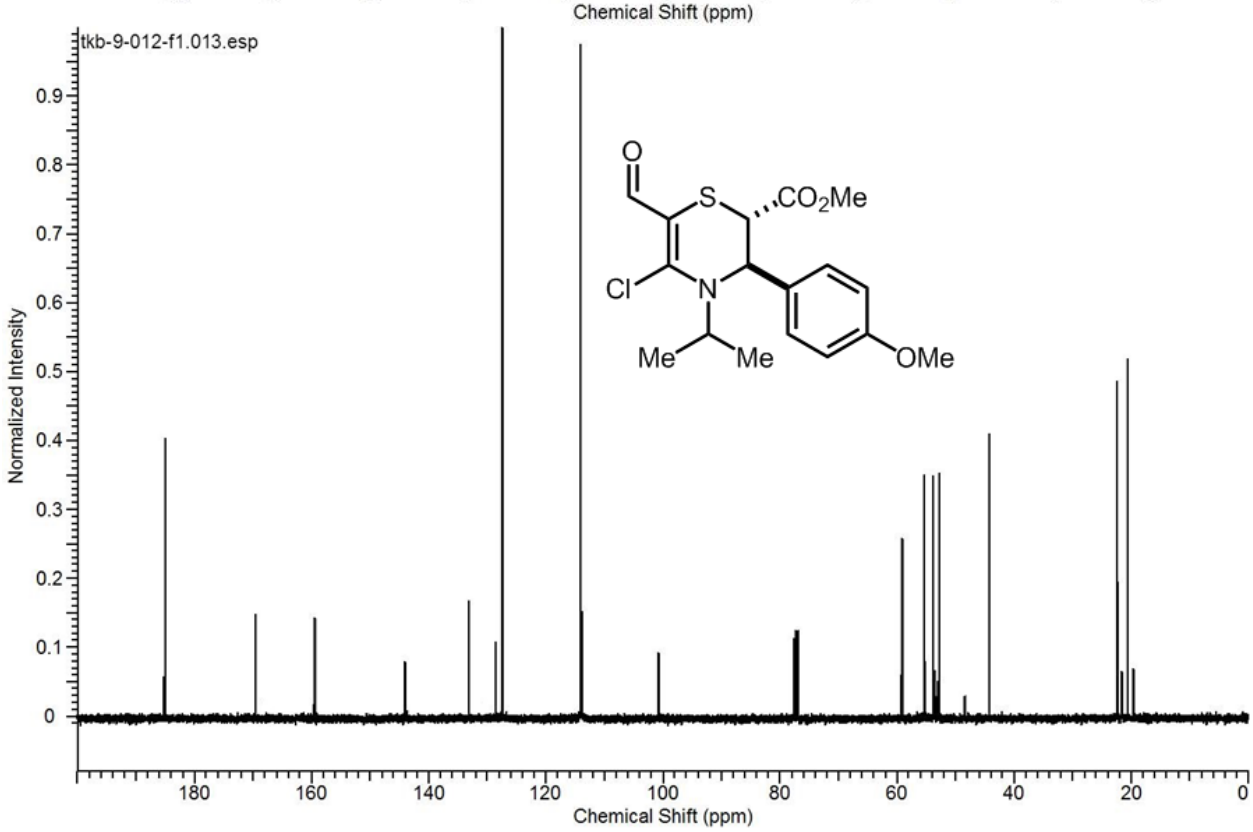
3.03
O
O
S
OMe
Cl
N
Me
Me

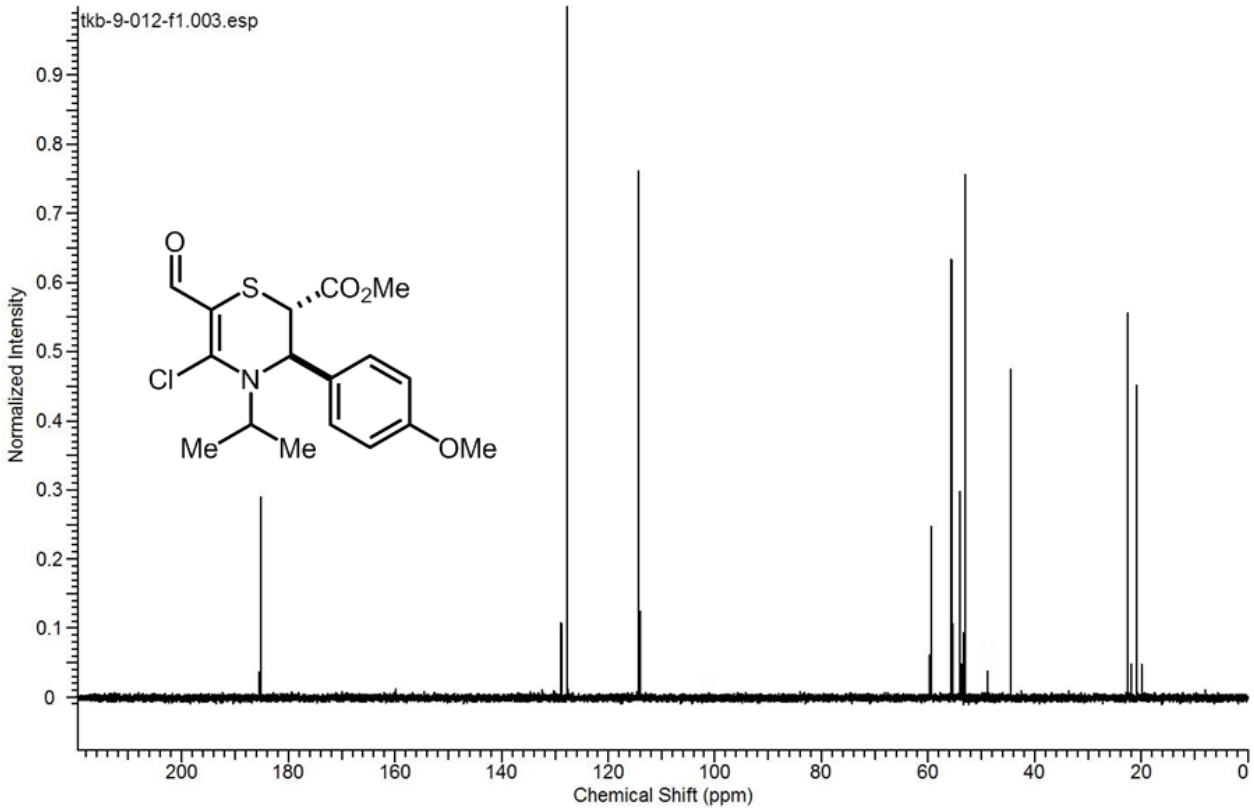

OF-2-019-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
S
OMe
Cl
N
Me
Me



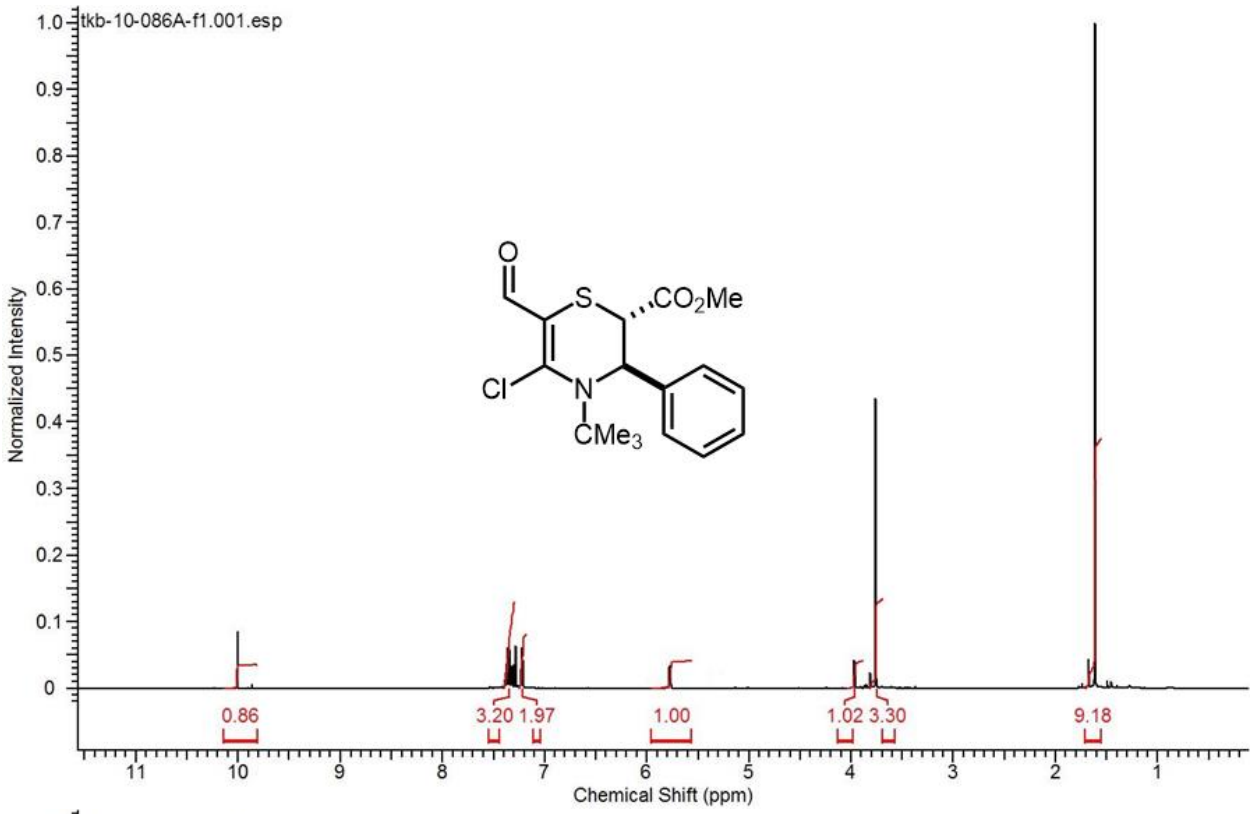
Compound **4b13:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25). Yield = 281.9 mg, 76%, 80:20 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.85 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 5.29 (d, *J* = 2.7 Hz, 1H), 4.92 (p, *J* = 6.8 Hz, 1H), 3.74 – 3.69 (m, 7H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.24, 184.91, 169.60, 159.48, 144.06, 133.10, 128.54, 127.44, 114.09, 113.77, 100.76, 59.31, 59.15, 55.35, 55.23, 53.79, 53.44, 52.79, 48.49, 44.17, 22.37, 21.67, 20.66, 19.60. HRMS calc for $C_{17}H_{20}ClNO_4S$, 369.0802, found 369.0807.


tkb-9-012-f1.001.esp
Normalized Intensity
Chemical Shift (ppm)
0.85
2.01
2.05
0.97
0.97
7.21
3.14
3.00
O
S
CO2Me
Cl
N
Me
Me
OMe


tkb-9-012-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
Me
Me
OMe



Compound **4b14:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25). Yield = 272.5 mg, 77%, 95:5 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.01 (s, 1H), 7.43 – 7.29 (m, 3H), 7.25 – 7.18 (m, 2H), 5.77 (d, *J* = 4.7 Hz, 1H), 3.97 (dd, *J* = 4.7, 0.8 Hz, 1H), 3.76 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.70, 169.99, 145.04, 139.43, 129.04, 128.29, 126.12, 63.41, 62.68, 52.98, 49.28, 31.49. HRMS calc for $C_{17}H_{20}ClNO_3S$, 353.0852, found 353.0859.


tkb-10-086A-f1.001.esp
Normalized Intensity
Chemical Shift (ppm)
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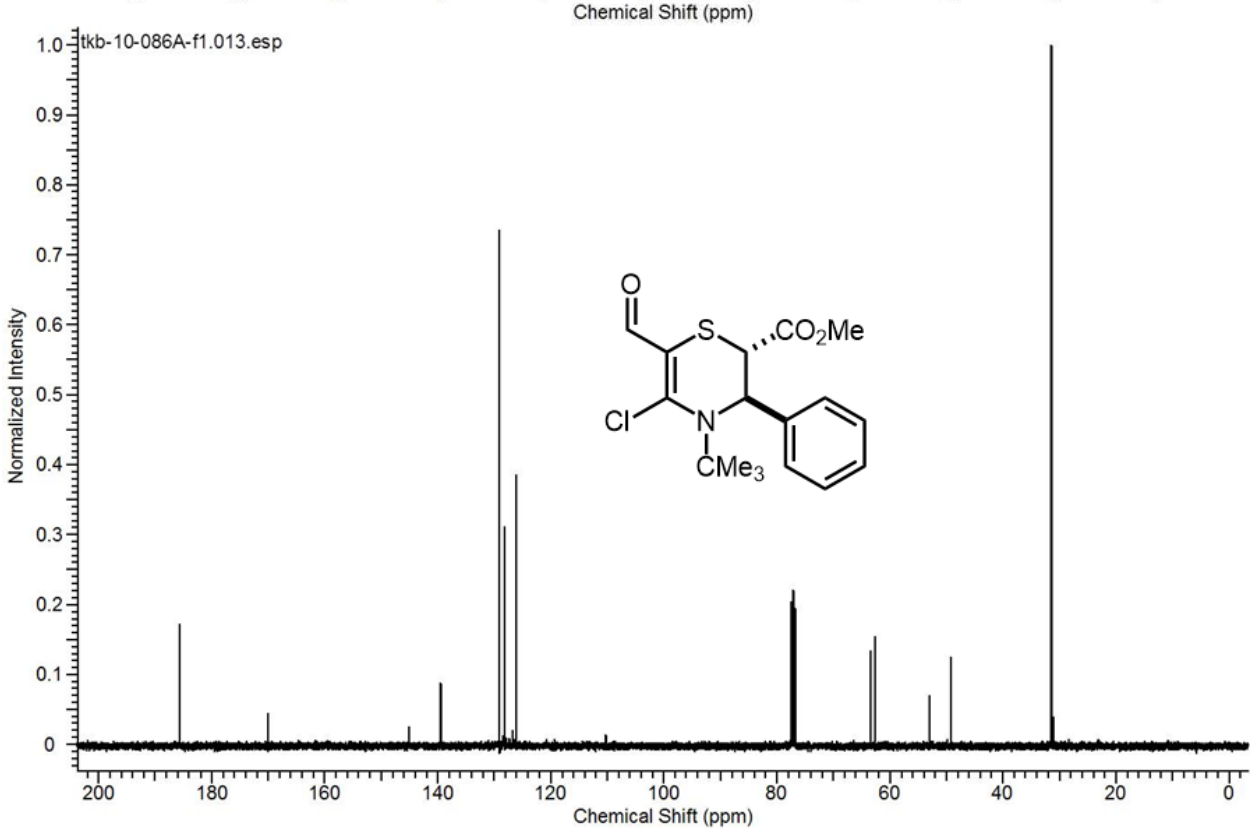
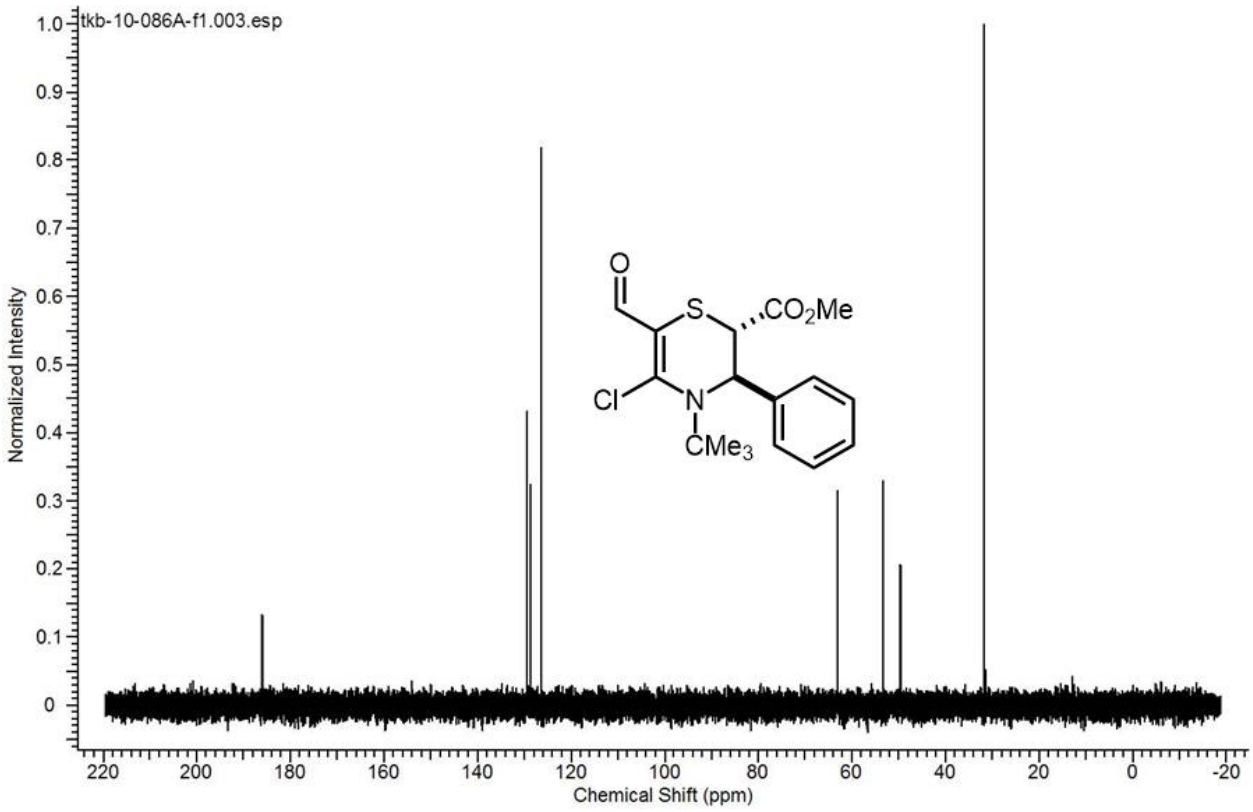
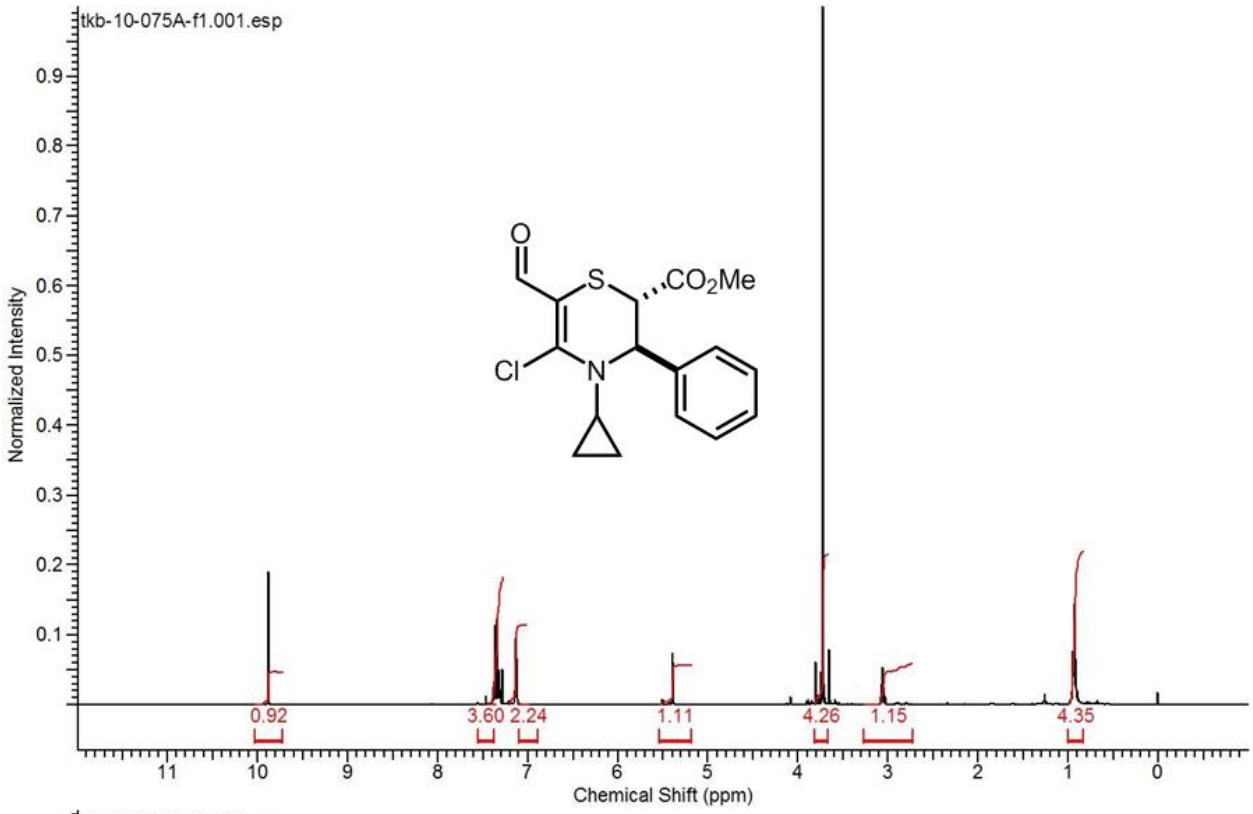
1.97
1.00
1.02
3.30
9.18
O
S
CO2Me
Cl
N
CMe3


tkb-10-086A-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N
CMe3



Compound **4b15:** Prepared using **General Procedure A**. Temp = 23 ºC for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25). Yield = 280.4 mg, 83%, 90:10 dr, oily substance. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.88 (s, 1H), 7.45 – 7.27 (m, 3H), 7.23 – 7.09 (m, 2H), 5.39 (d, *J* = 3.0 Hz, 1H), 3.91 – 3.68 (m, 1H), 3.72 (s, 3H), 3.06 (tt, *J* = 6.2, 4.6 Hz, 1H), 1.01 – 0.84 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.71, 169.99, 146.43, 139.28, 129.01, 128.54, 126.00, 102.34, 67.09, 65.99, 52.89, 43.41, 36.96, 10.02, 9.85. FTIR (KBr): 3011.0, 2952.3, 2856.8, 1734.9, 1632.9, 1586.1, 1539.2, 1496.1, 1451.5, 1434.9, 1403.9, 1355.2, 1315.4, 1253.1, 1217.5, 1169.1, 1070.1, 1031.9, 990.8, 970.3, 911.0, 892.4, 832.8, 805.3, 769.7, 751.5. HRMS calc for $C_{16}H_{16}ClNO_3S$, 337.0539, found 337.0533.


tkb-10-075A-f1.001.esp
Normalized Intensity
Chemical Shift (ppm)
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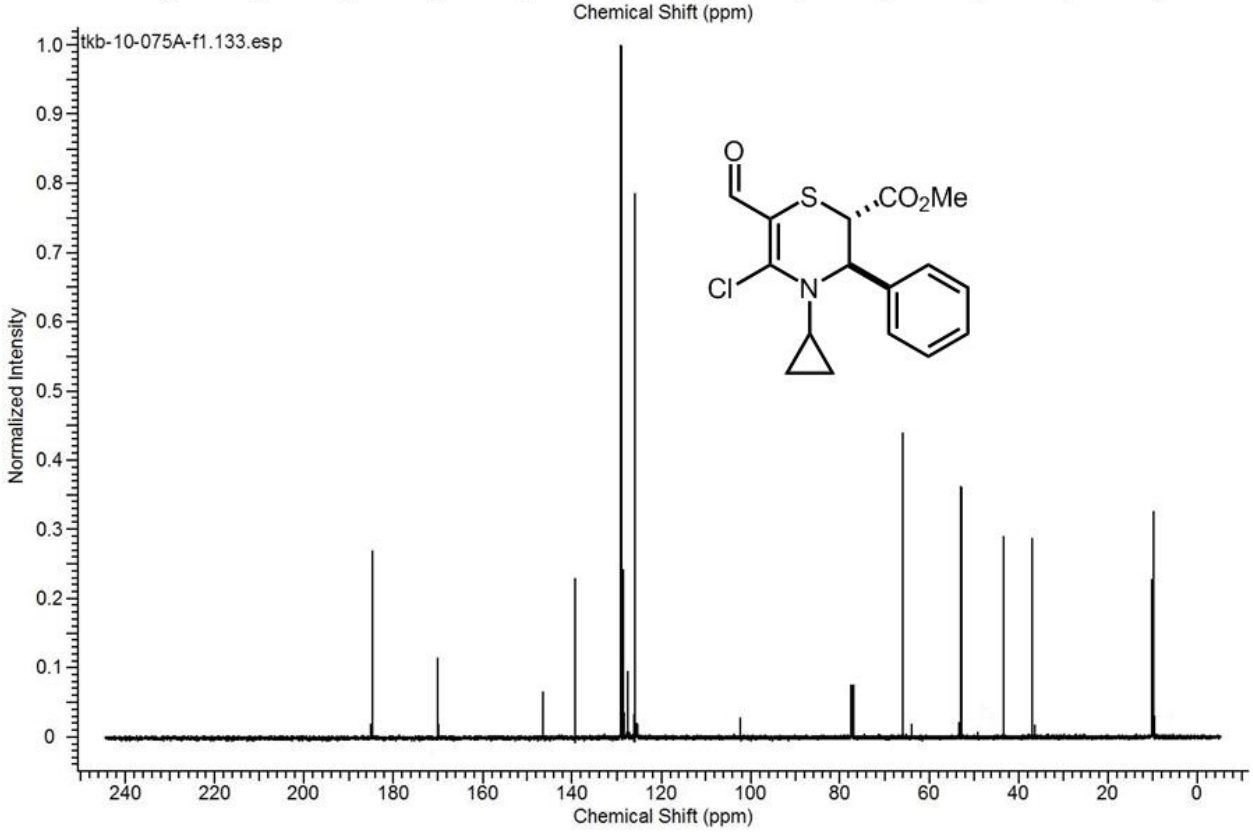
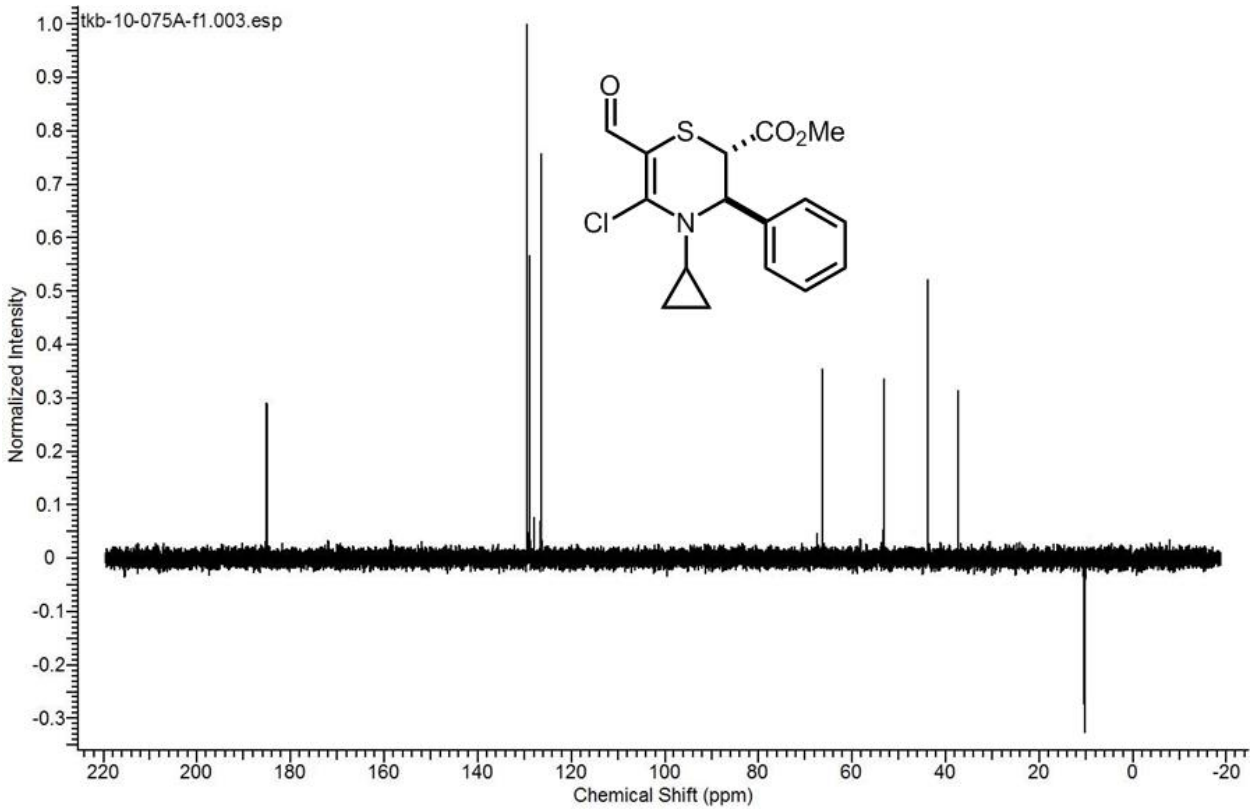
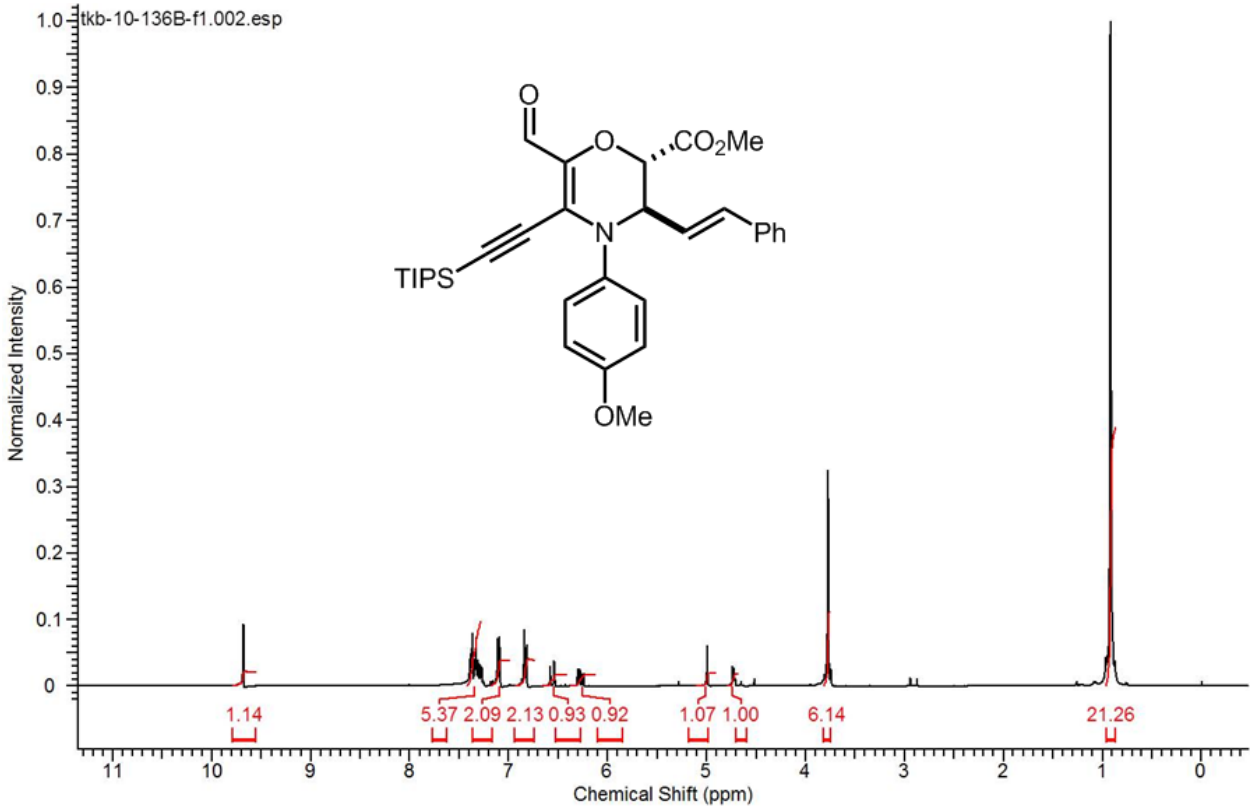
3.60
2.24
1.11
4.26
1.15
4.35
O
S
CO2Me
Cl
N

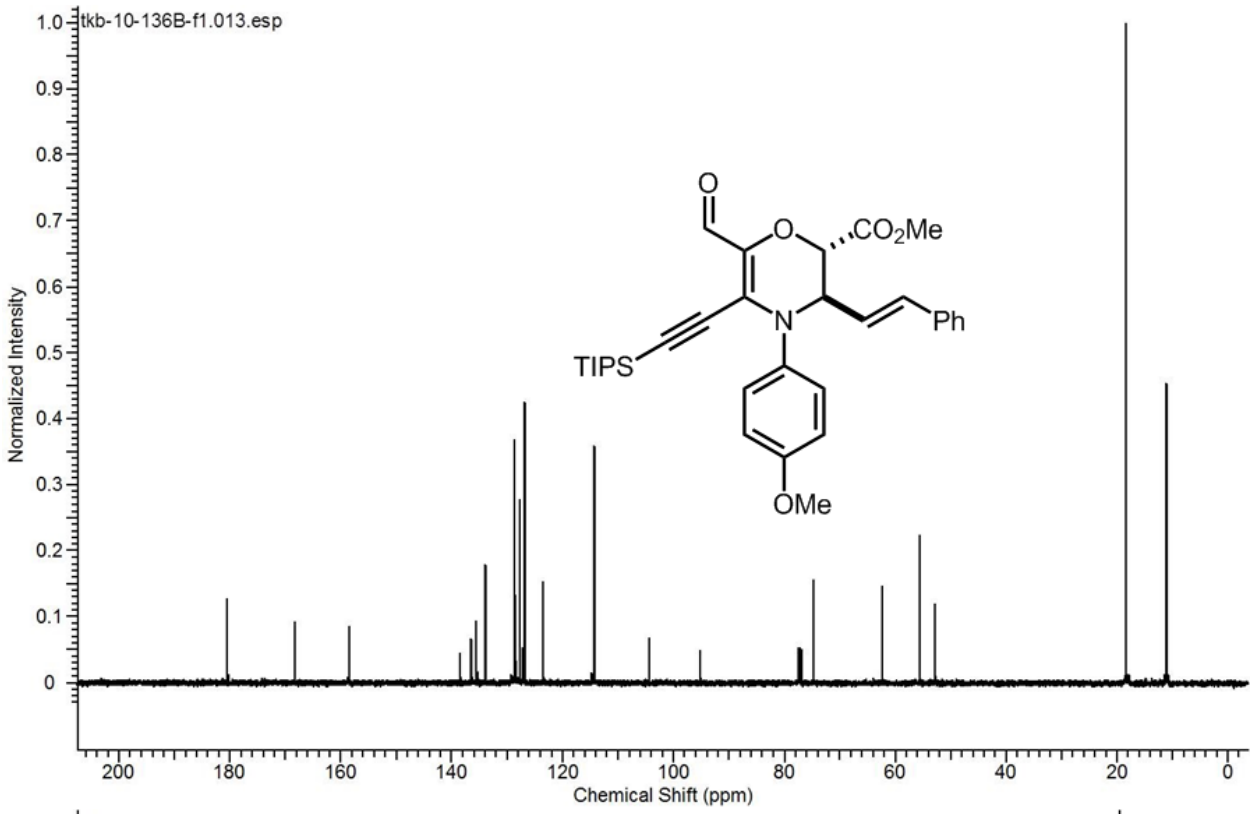

tkb-10-075A-f1.133.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N

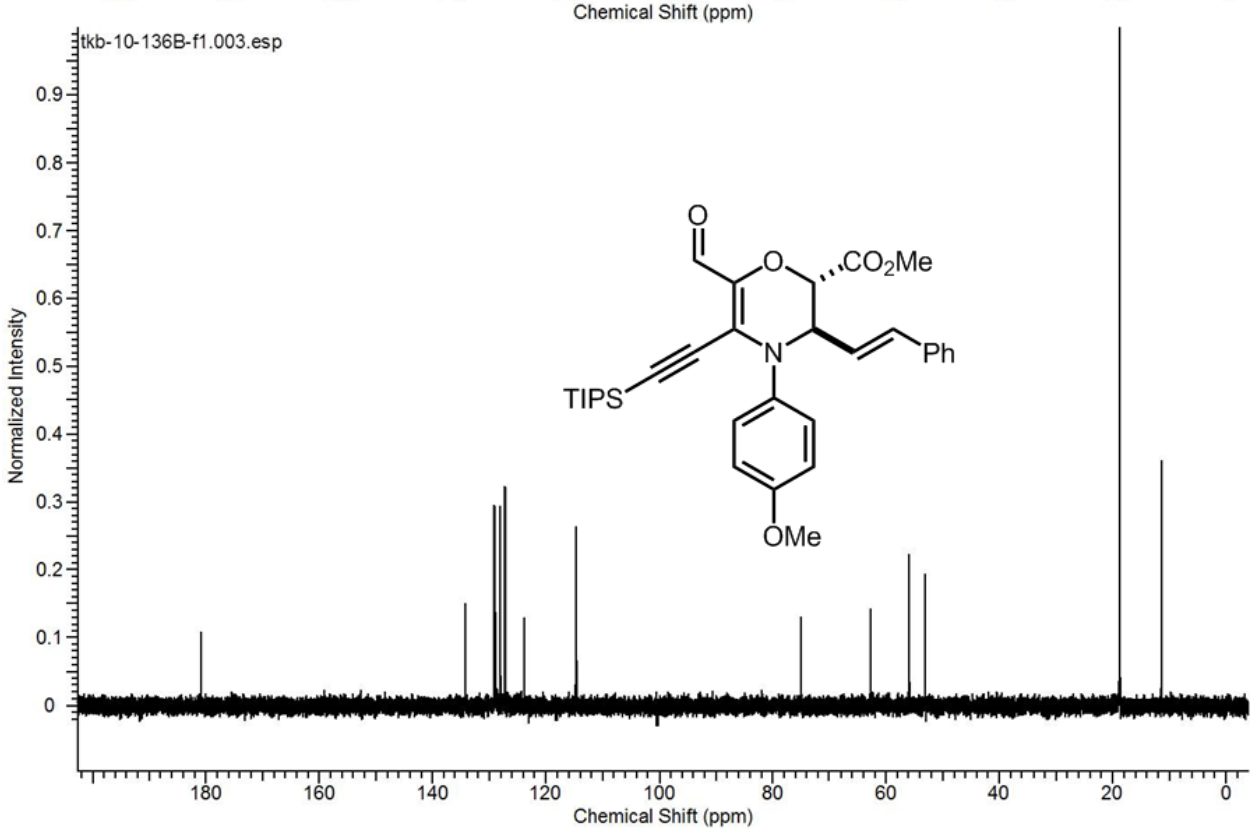

tkb-10-075A-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
S
CO2Me
Cl
N

Scheme 3 results

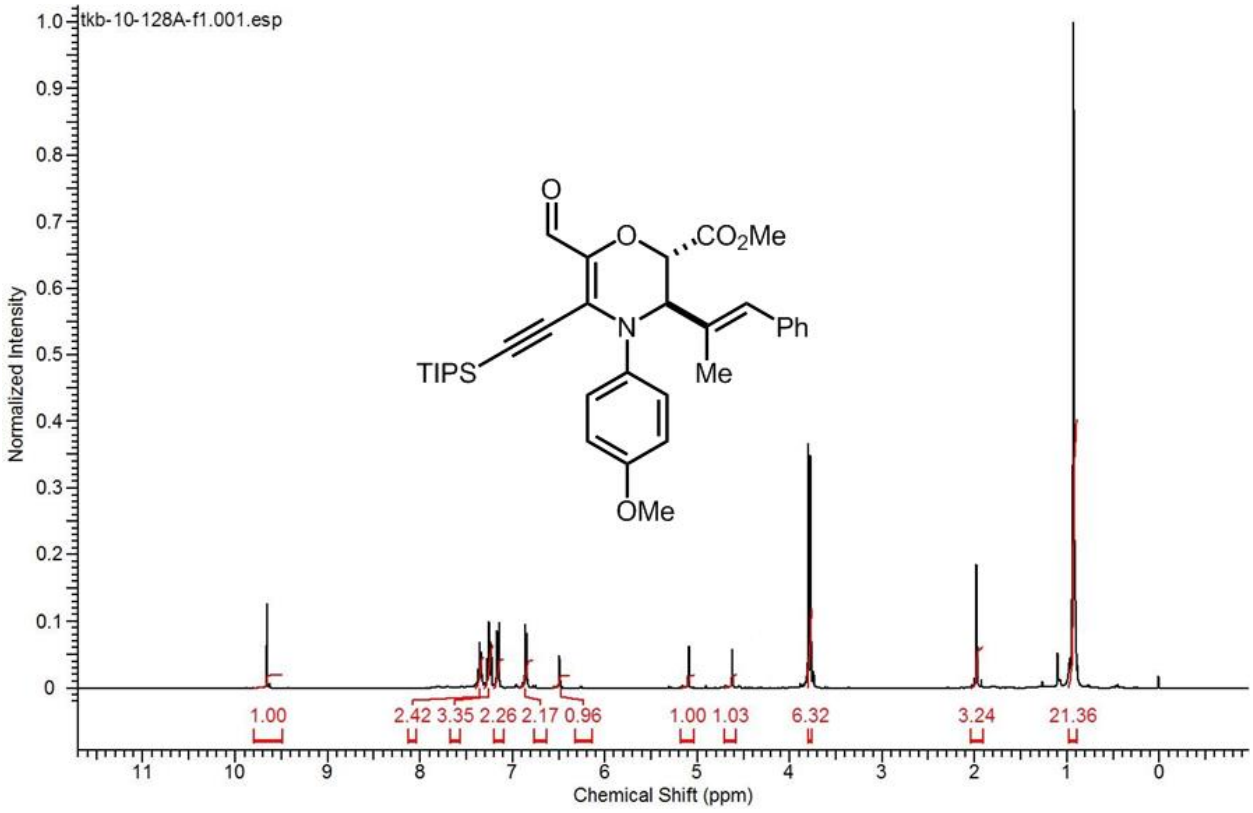
Compound **5a:** Prepared in 0.5 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (95:5).Yield = 221 mg, 79%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.68 (s, 1H), 7.41 – 7.22 (m, 6H), 7.15 – 7.06 (m, 2H), 6.89 – 6.78 (m, 2H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.27 (dd, *J* = 15.8, 7.7 Hz, 1H), 4.99 (d, *J* = 1.7 Hz, 1H), 4.73 (dt, *J* = 7.6, 1.4 Hz, 1H), 3.78 (t, *J* = 3.3 Hz, 7H), 0.91 (d, *J* = 4.3 Hz, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.60, 168.30, 158.60, 138.54, 136.50, 135.62, 133.9, 128.7, 128.5, 127.8, 126.9, 123.5, 114.3, 104.5, 95.2, 74.8, 62.4, 55.6, 52.8, 18.4, 11.0. HRMS calc for $C_{33}H_{41}NO_5Si$, 559.2754, found 559.2759.

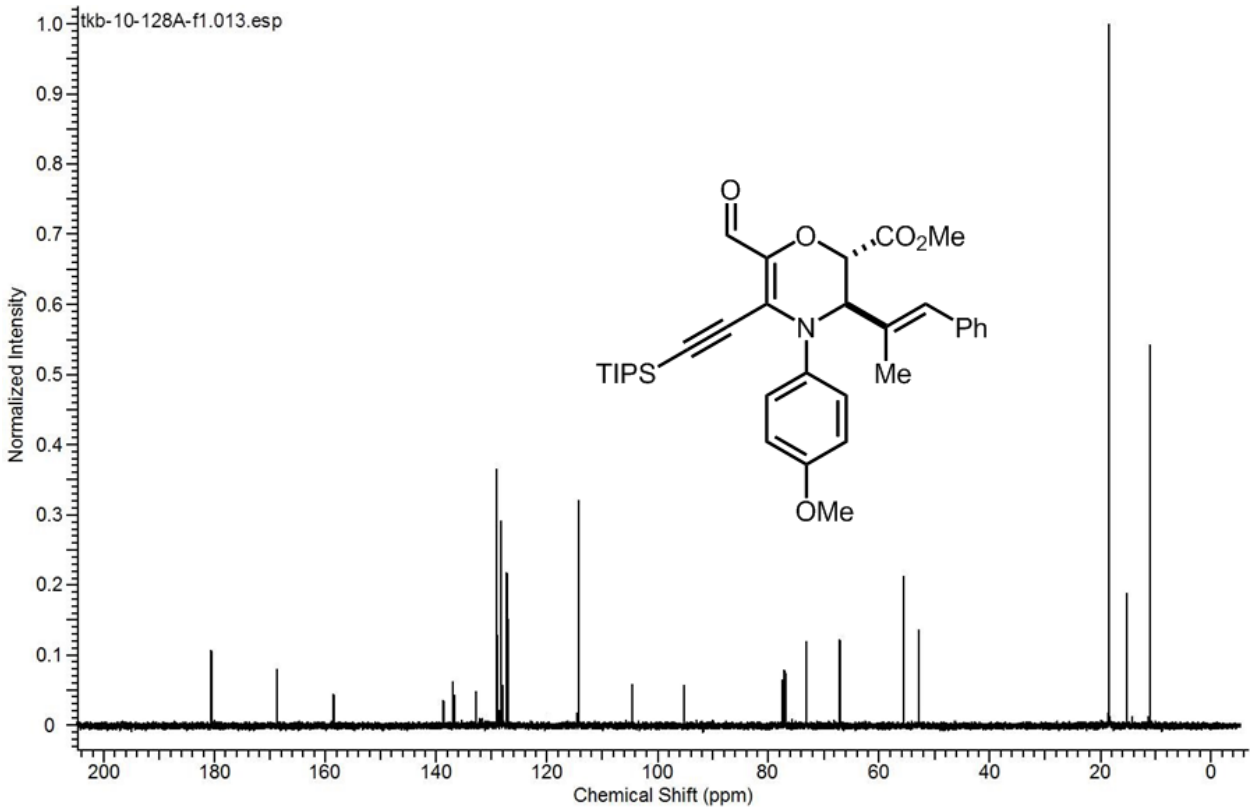


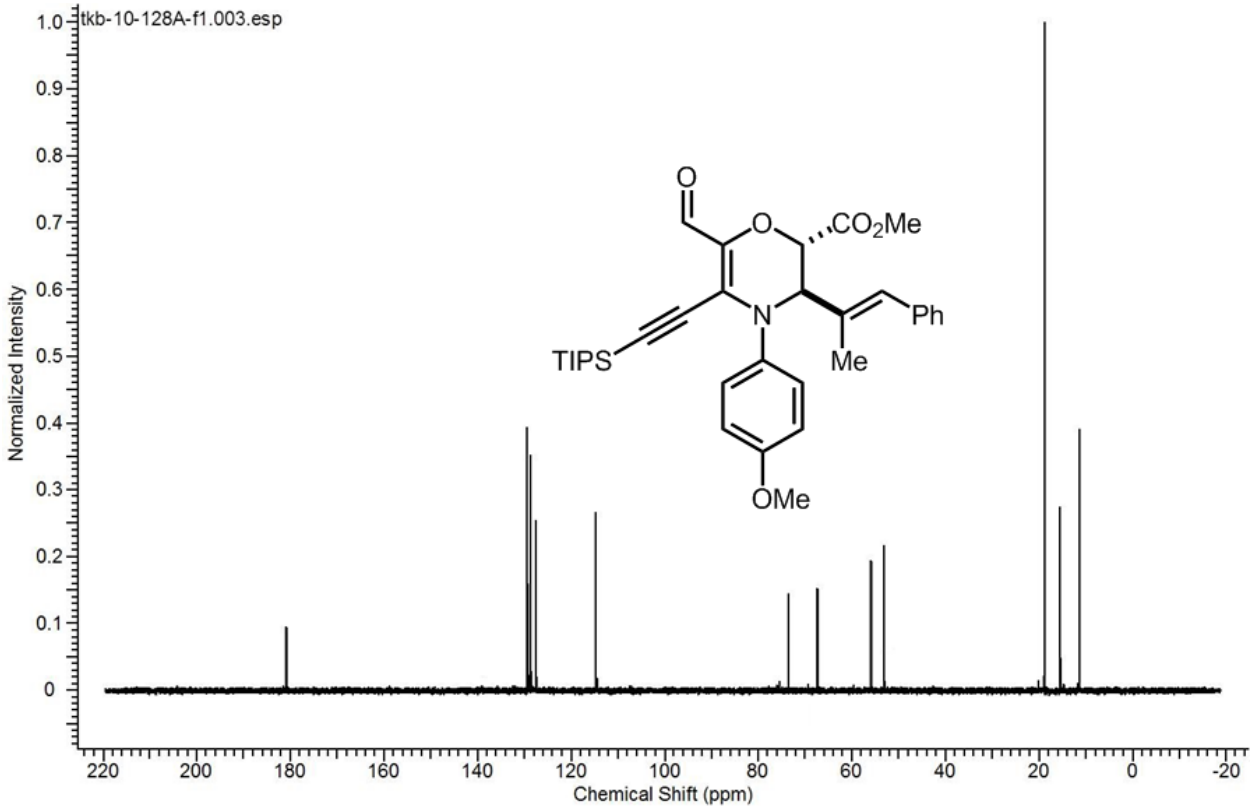

tkb-10-136B-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
TIPS
OMe


tkb-10-136B-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
TIPS
OMe

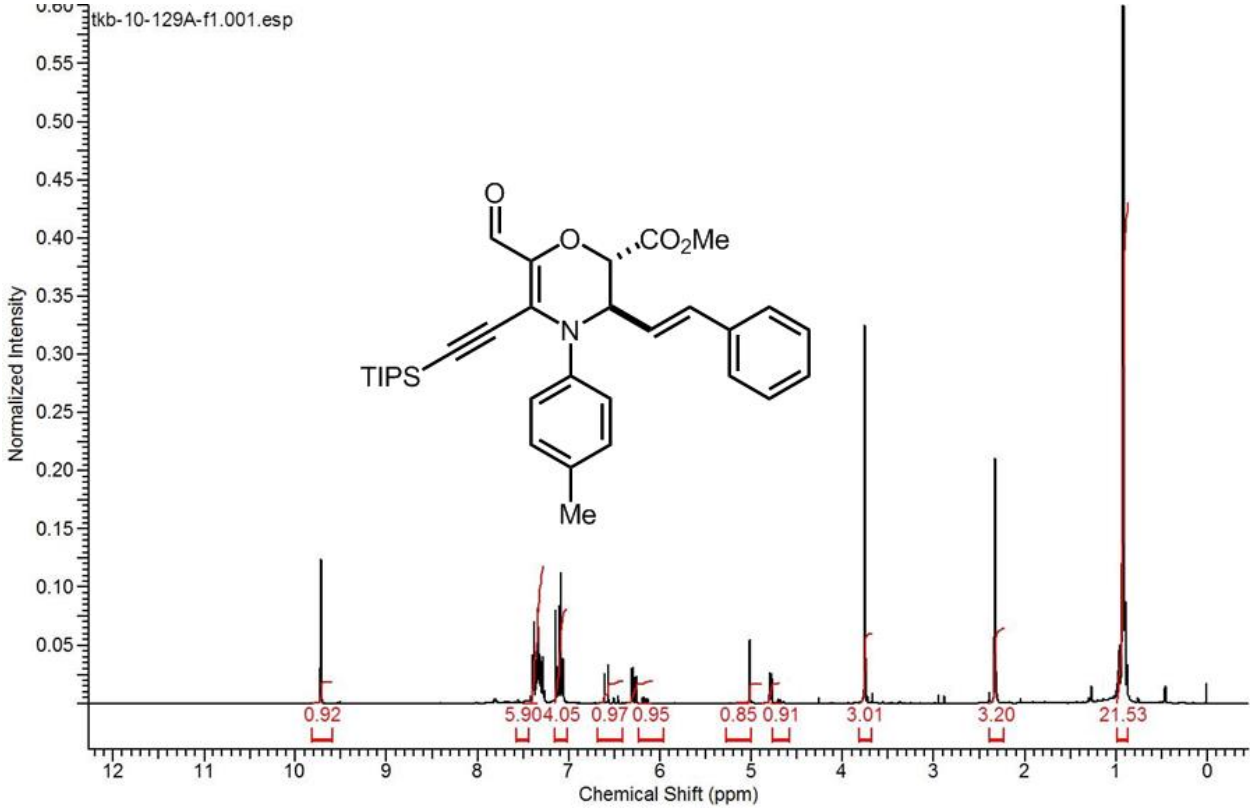
Compound **5b:** Prepared in 0.5 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (95:5).Yield = 243.9 mg, 85%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.97 (s, 1H), 7.45 – 7.30 (m, 5H), 7.30 – 7.17 (m, 4H), 6.88 (d, 2H), 6.44 (s, 1H), 4.73 (t, J = 1.8 Hz, 1H), 3.96 (dd, J = 2.4, 1.0 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 1.93 (s, 3H), 0.91 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.53, 169.89, 159.01, 139.01, 136.82, 134.42, 129.27, 129.09, 128.81, 128.70, 128.63, 128.61, 128.31, 127.12, 114.21, 111.16, 105.21, 96.56, 67.61, 55.58, 52.86, 39.43, 18.63, 18.53, 16.00, 11.03. HRMS calc for $C_{34}H_{43}NO_5Si$, 573.2911, found 573.2914.

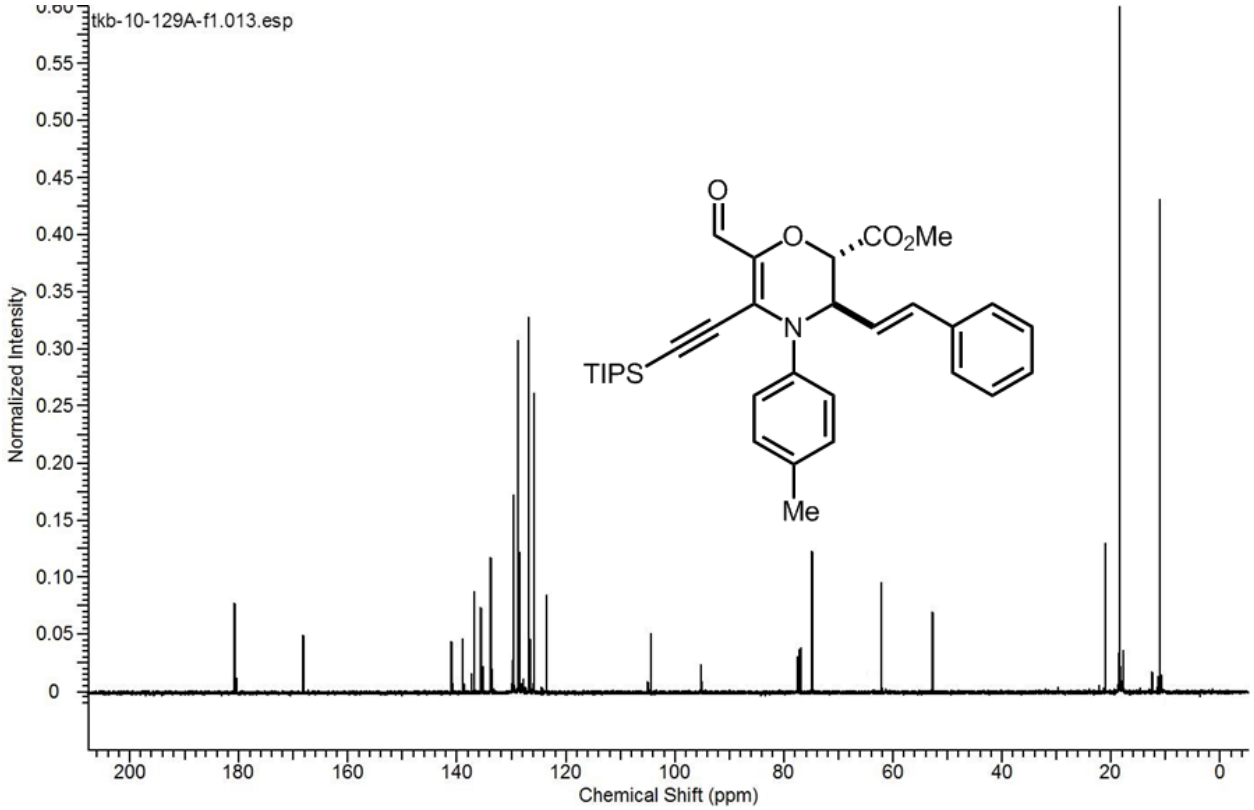


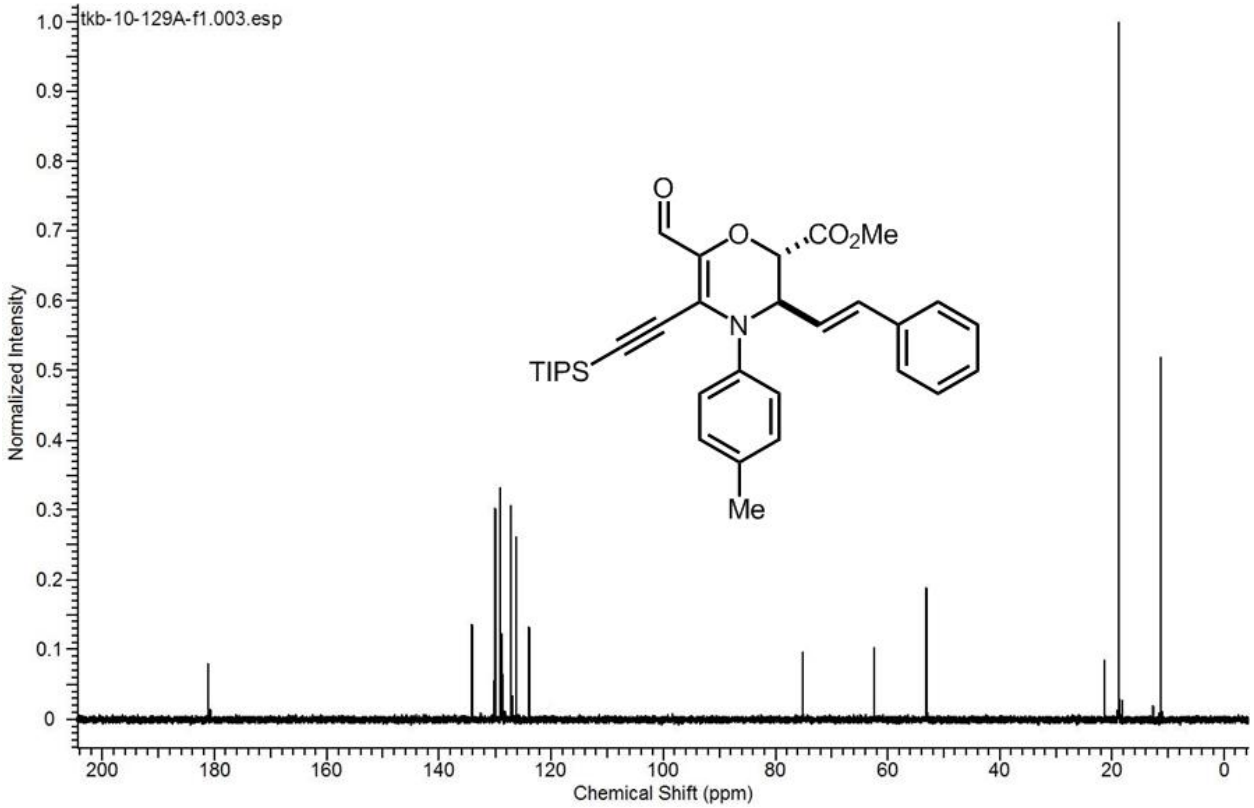

tkb-10-128A-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Me
TIPS
OMe


tkb-10-128A-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Me
TIPS
OMe

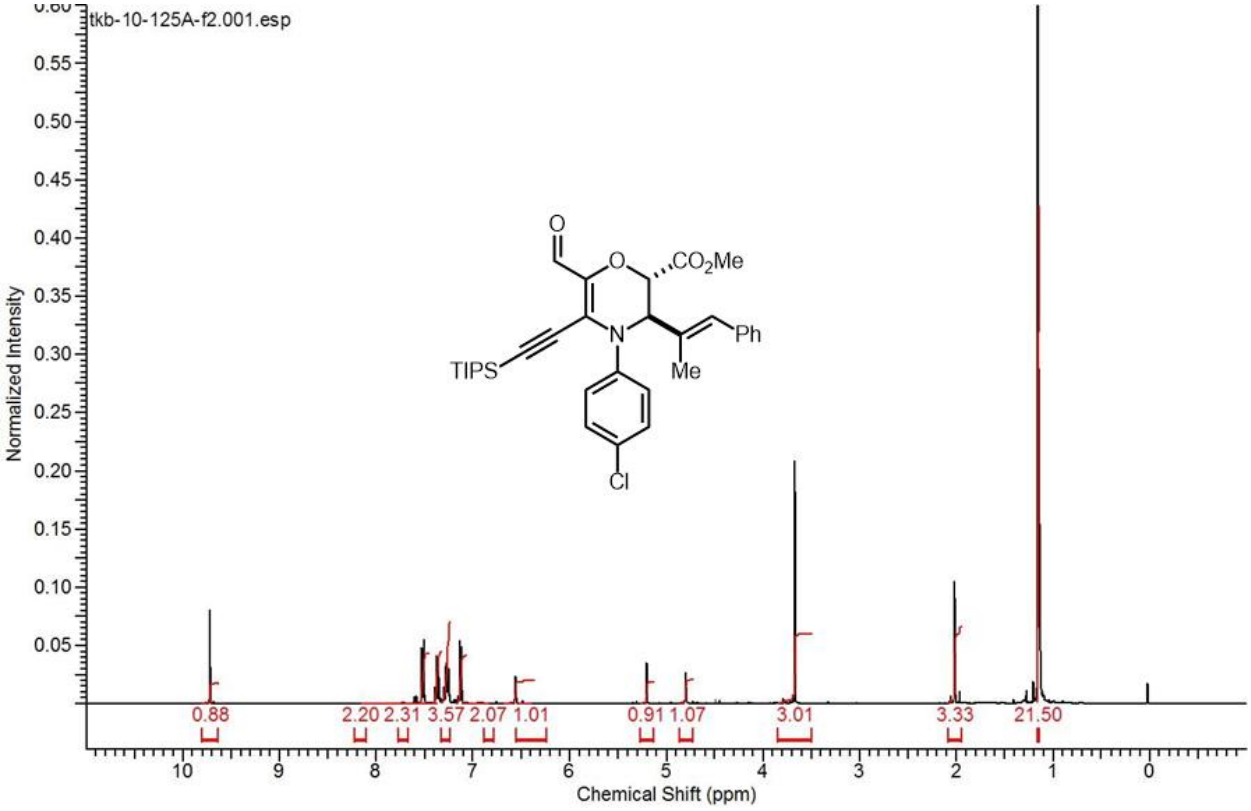
Compound **5c:** Prepared in 0.5 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (95:5).Yield = 195.8 mg, 72%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 7.46 – 7.35 (m, 2H), 7.39 – 7.31 (m, 1H), 7.34 – 7.23 (m, 2H), 7.14 (d, *J* = 8.3 Hz, 1H), 7.14 – 7.02 (m, 3H), 6.59 (dd, *J* = 15.9, 1.0 Hz, 1H), 6.29 (dd, *J* = 15.8, 7.3 Hz, 1H), 5.02 (d, *J* = 1.6 Hz, 1H), 4.79 (dt, *J* = 7.3, 1.5 Hz, 1H), 3.75 (s, 3H), 2.41 – 2.26 (m, 1H), 2.33 (s, 3H), 1.15 – 1.04 (m, 2H), 1.02 – 0.85 (m, 22H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.79, 168.20, 141.02, 138.94, 136.84, 135.64, 133.81, 129.69, 128.76, 128.51, 126.89, 125.92, 123.58, 104.31, 95.23, 74.81, 62.12, 52.75, 21.02, 18.44, 11.06. HRMS calc for $C_{33}H_{41}NO_4Si$, 543.2805, found 543.2810.

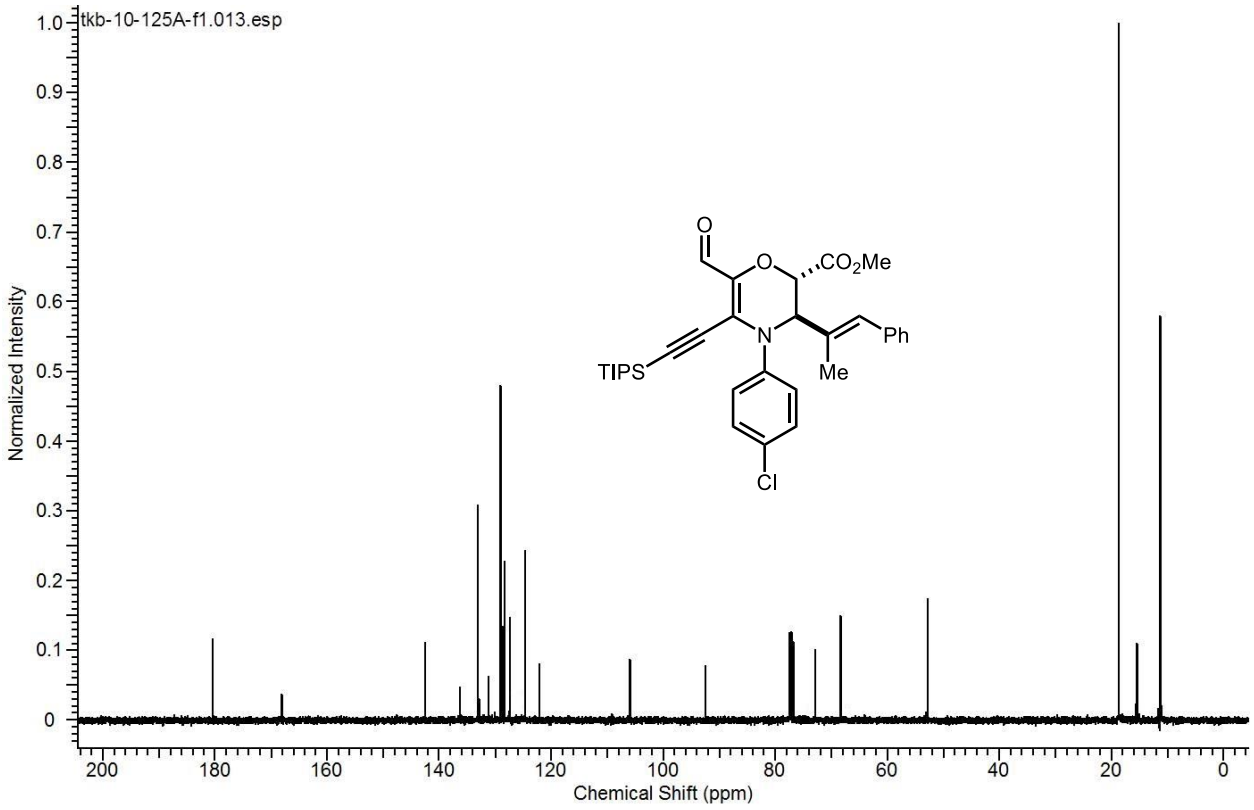


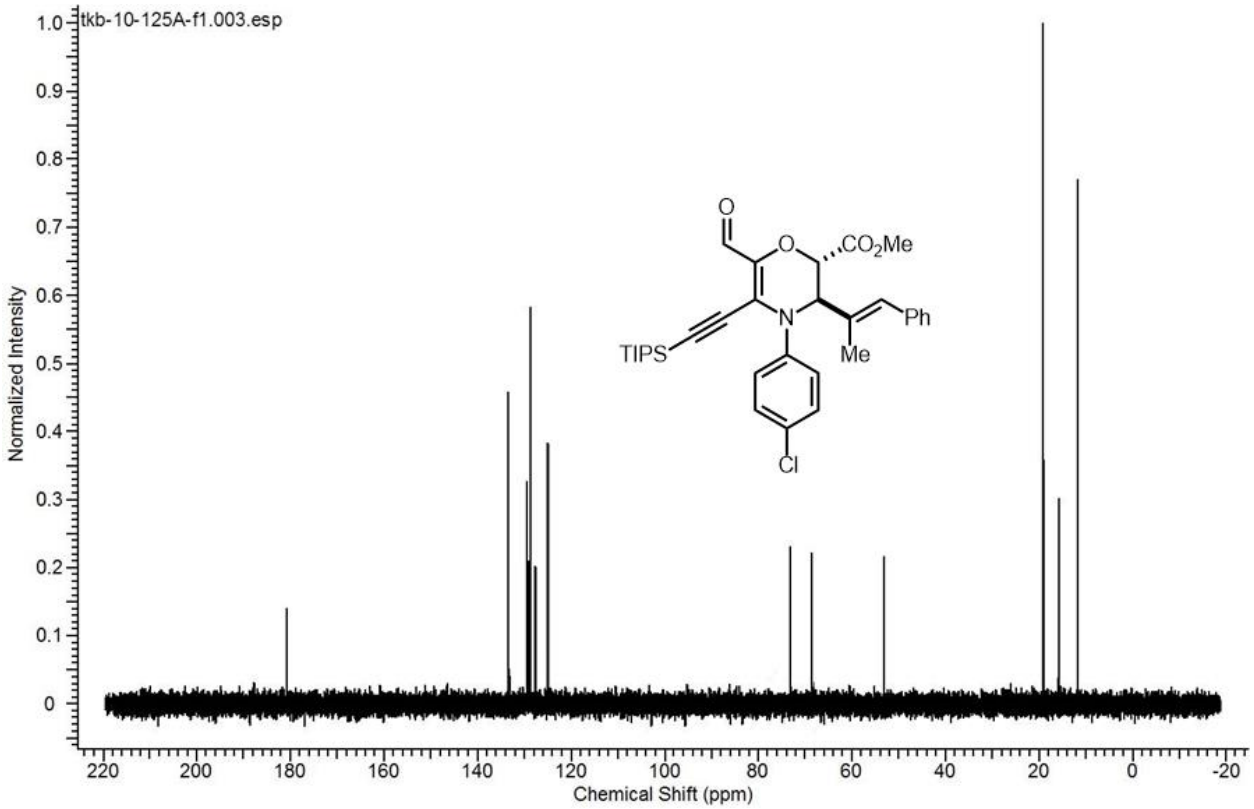

tkb-10-129A-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
TIPS
Me


tkb-10-129A-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
TIPS
Me

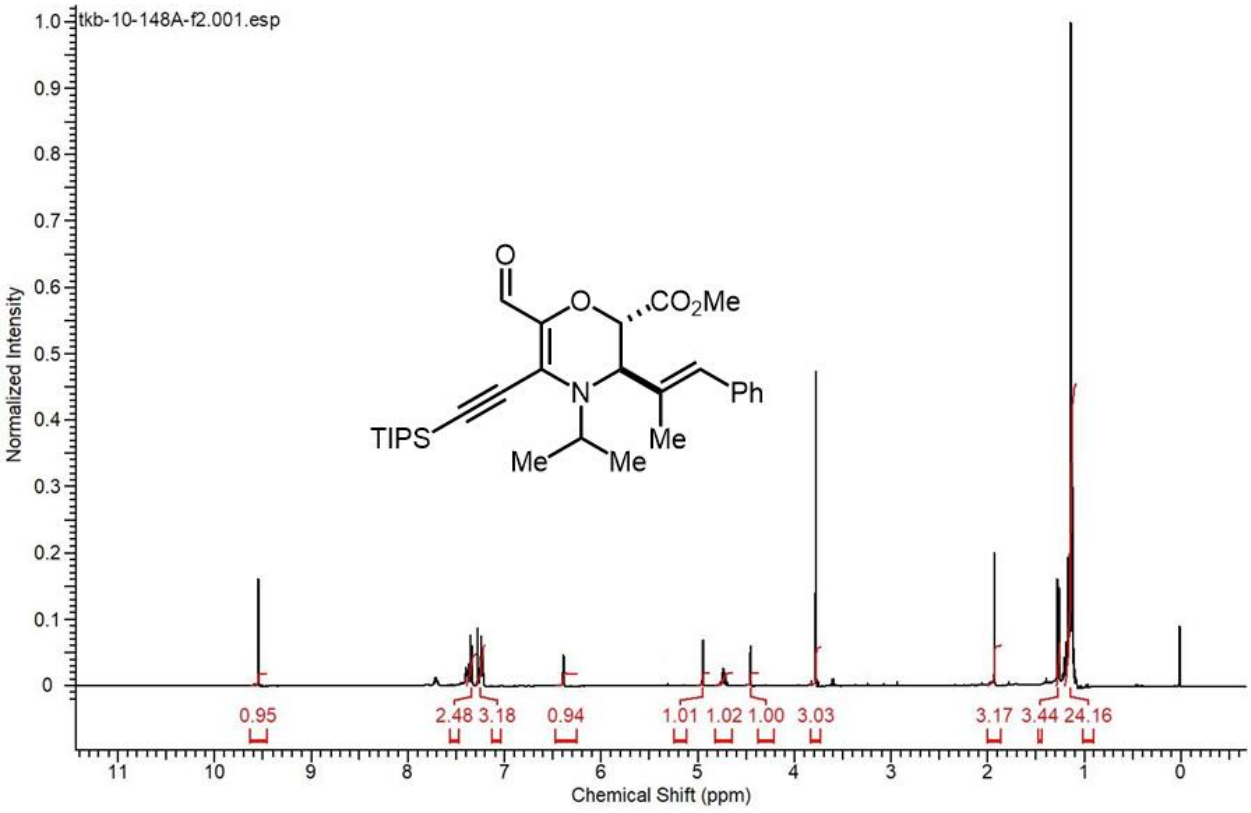
Compound **5d:** Prepared in 0.5 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (95:5).Yield = 225.5 mg, 78%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 7.52 (dq, *J* = 8.5, 1.9, 1.4 Hz, 2H), 7.42 – 7.30 (m, 2H), 7.32 – 7.22 (m, 3H), 7.22 – 7.09 (m, 2H), 6.56 (s, 1H), 5.21 (d, *J* = 1.4 Hz, 1H), 4.80 (q, *J* = 1.4 Hz, 1H), 3.67 (s, 3H), 2.02 (d, *J* = 1.3 Hz, 3H), 1.18 – 1.07 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.49, 168.20, 142.56, 136.36, 133.08, 129.16, 128.64, 128.38, 127.35, 124.65, 122.18, 105.92, 92.39, 72.86, 68.36, 52.77, 18.73, 15.45, 11.35. HRMS calc for $C_{33}H_{40}ClNO_4Si$, 577.2415, found 577.2410.

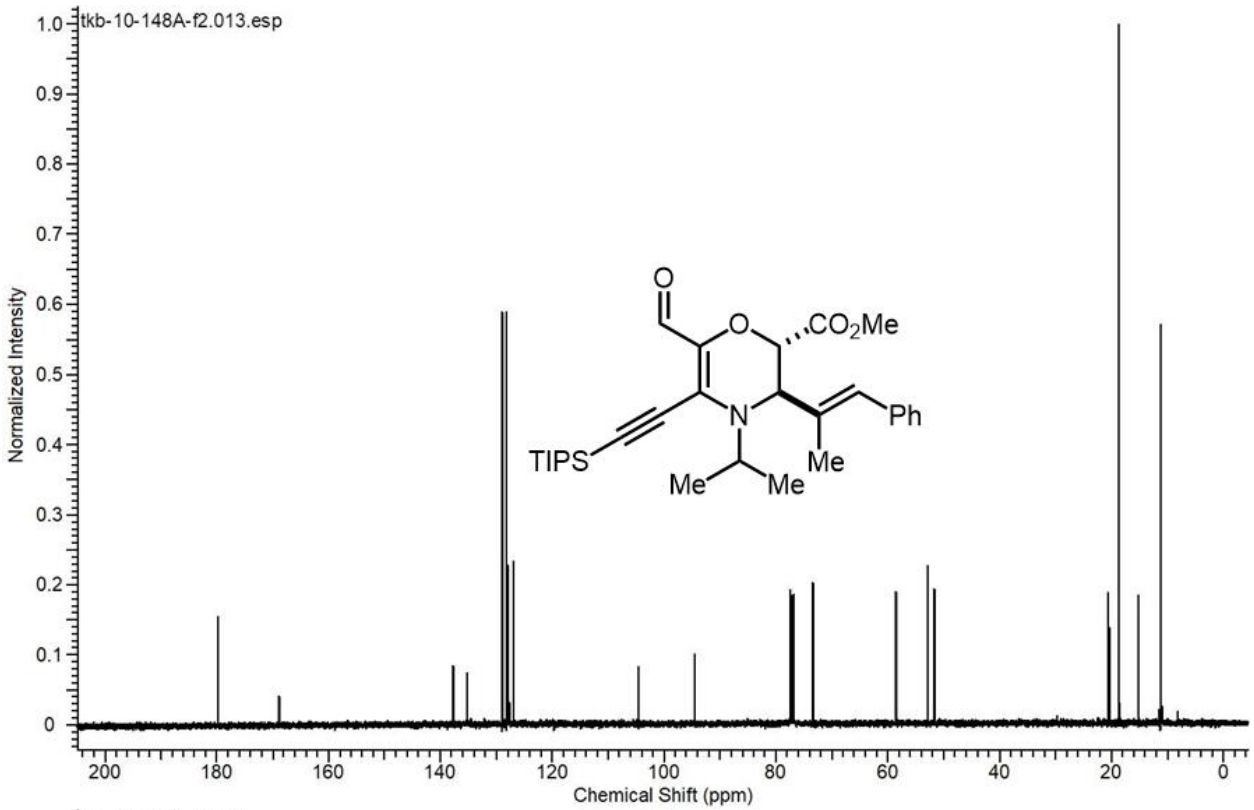


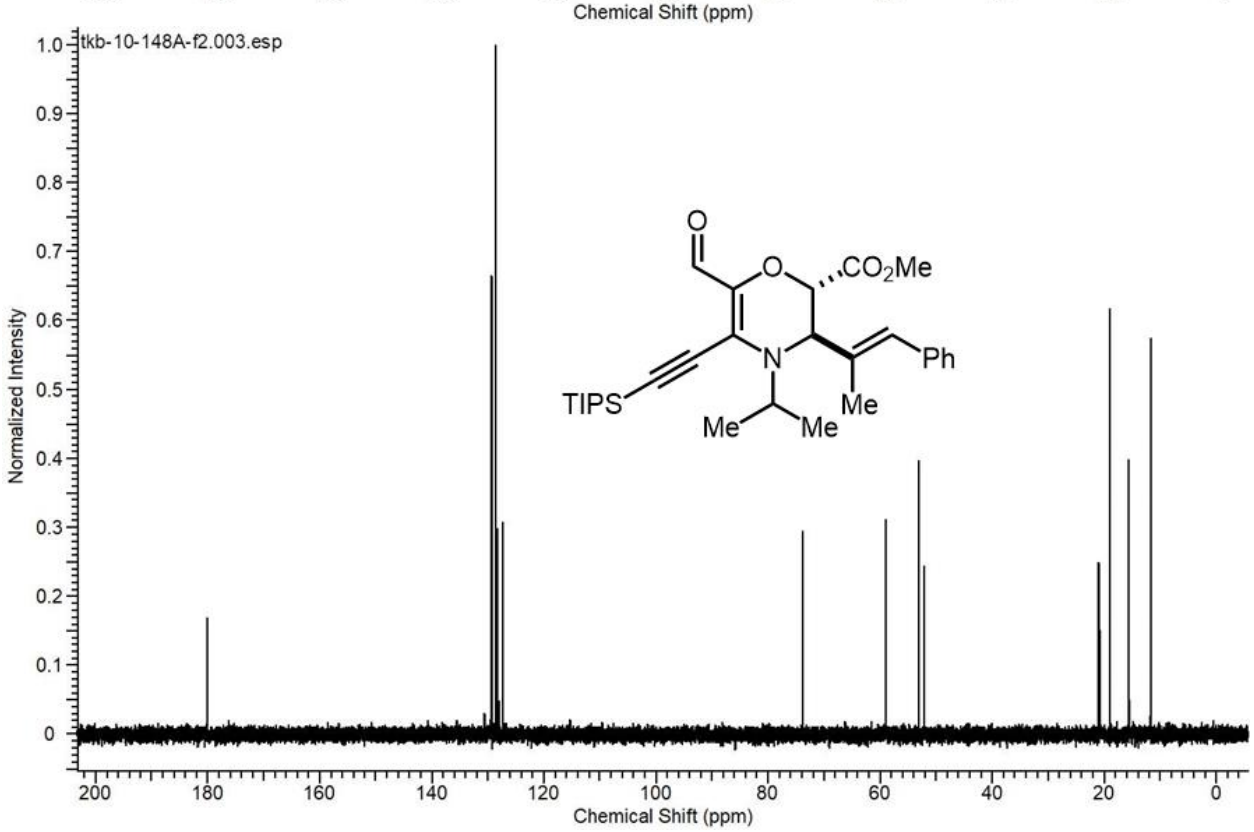

tkb-10-125A-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Me
TIPS
Cl


tkb-10-125A-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Me
TIPS
Cl

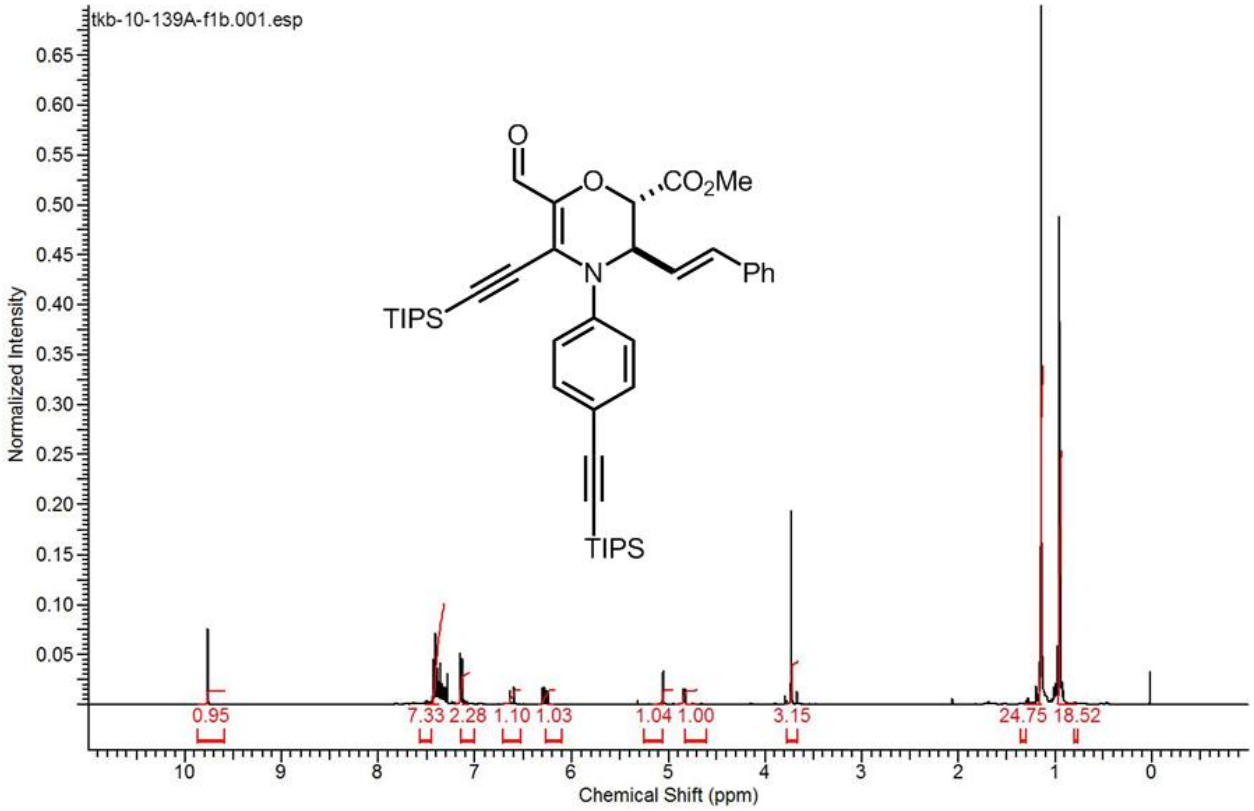
Compound **5e:** Prepared in 0.25 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10).Yield = 103.2 mg, 81%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.43 – 7.31 (m, 2H), 7.30 – 7.18 (m, 2H), 6.39 (s, 1H), 4.95 (d, *J* = 1.4 Hz, 1H), 4.73 (p, *J* = 6.7 Hz, 1H), 4.45 (d, *J* = 1.4 Hz, 1H), 3.78 (s, 3H), 1.93 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.23 – 1.13 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.77, 168.87, 137.77, 136.78, 135.28, 135.25, 129.68, 129.01, 128.29, 128.06, 127.02, 104.67, 94.61, 73.46, 58.62, 52.82, 51.74, 20.71, 20.43, 18.68, 15.27, 11.27. HRMS calc for $C_{33}H_{43}NO_4Si$, 509.2961, found 509.2966.

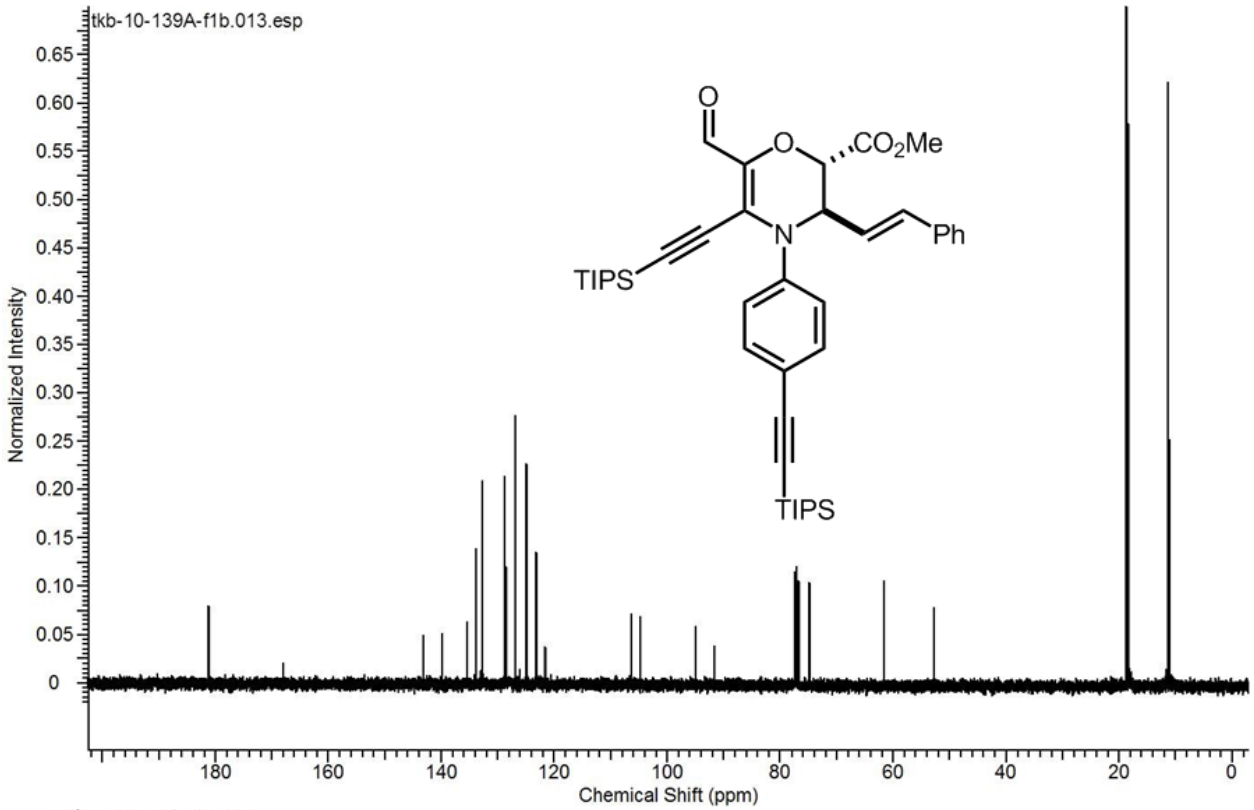



tkb-10-148A-f2.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
TIPS
Me
Me
Me


tkb-10-148A-f2.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
TIPS
Me
Me
Me

Compound **5f:** Prepared in 0.25 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (98:2).Yield = 129.6 mg, 73%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 (s, 1H), 7.47 – 7.27 (m, 7H), 7.18 (d, 2H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.27 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.06 (d, *J* = 1.7 Hz, 1H), 4.83 (dt, *J* = 6.8, 1.6 Hz, 1H), 3.73 (s, 3H), 1.26 – 1.09 (m, 24H), 0.96 – 0.89 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.22, 167.92, 143.19, 139.88, 135.44, 133.91, 132.76, 128.84, 128.80, 128.64, 126.96, 126.92, 124.94, 124.85, 123.15, 121.64, 106.36, 104.77, 94.99, 91.65, 74.89, 61.59, 52.80, 18.71, 18.46, 11.34, 11.10. HRMS calc for $C_{33}H_{59}NO_4Si_2$, 709.3983, found 709.3988.

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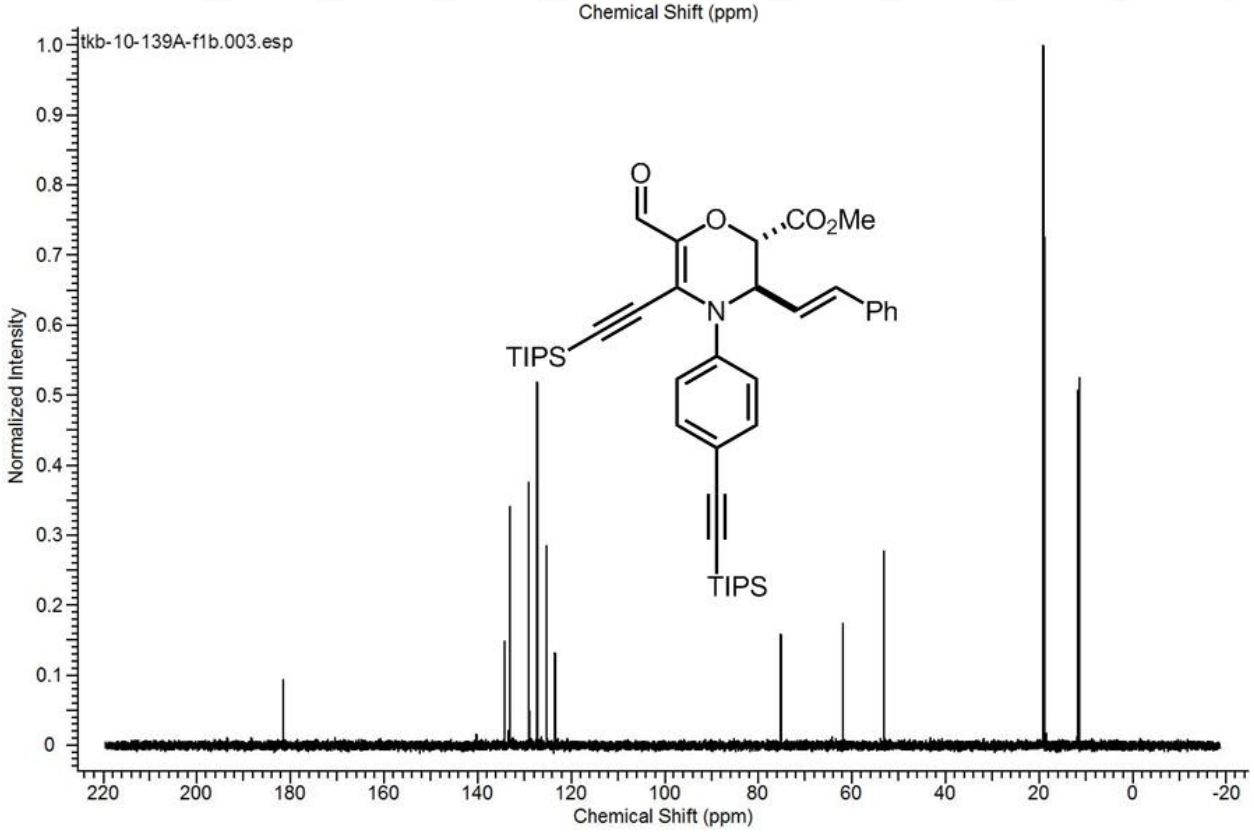
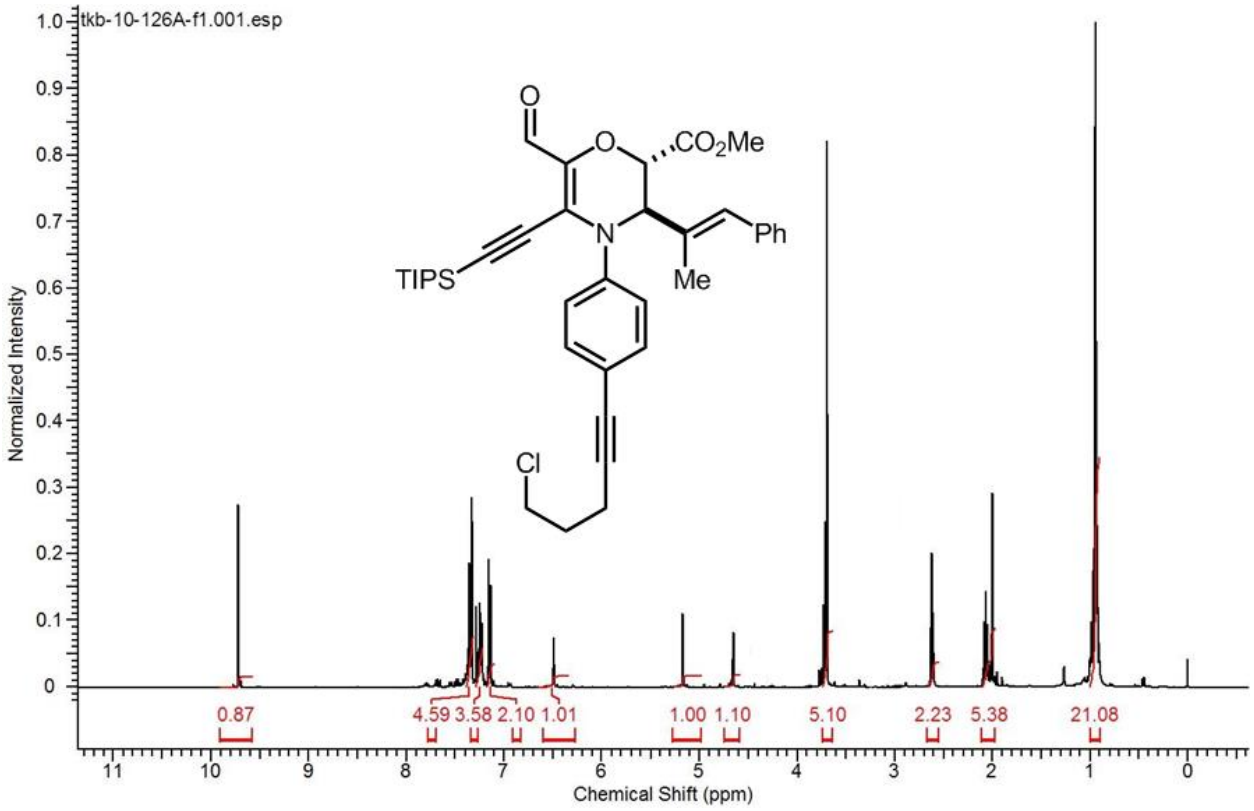
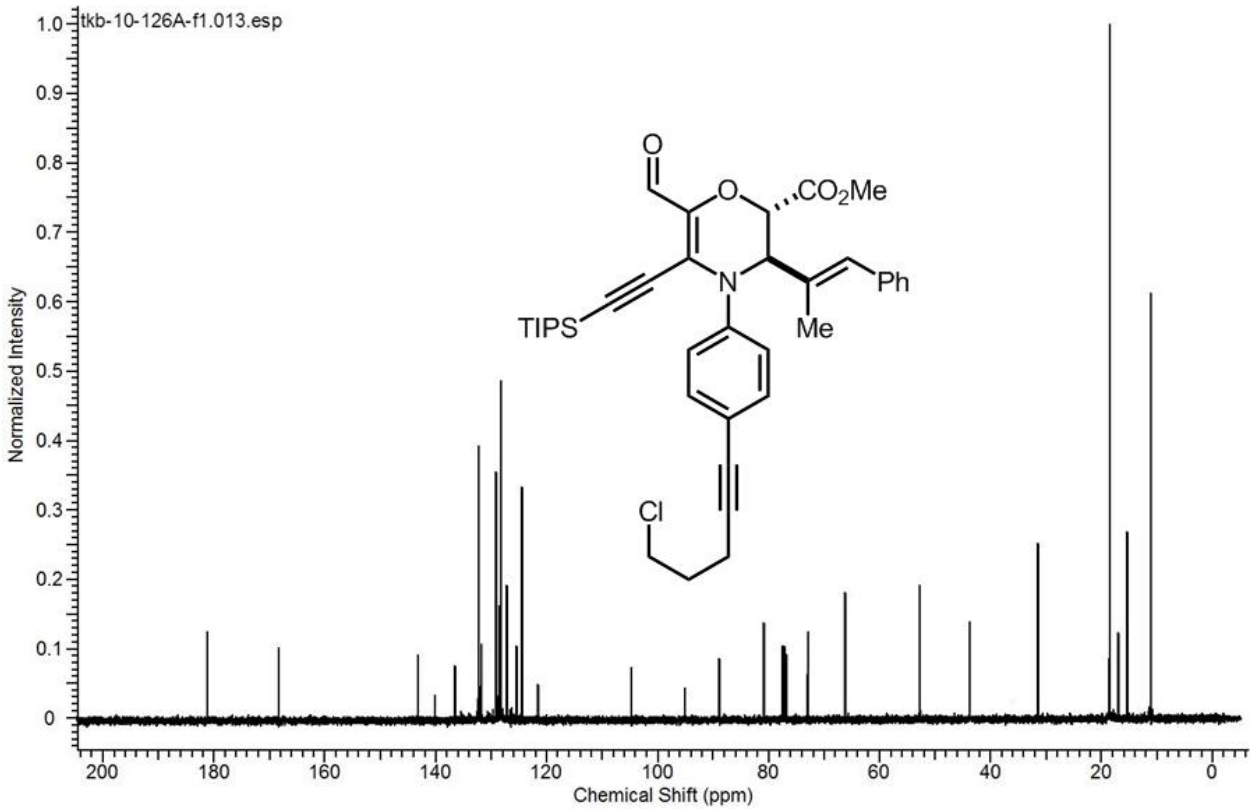
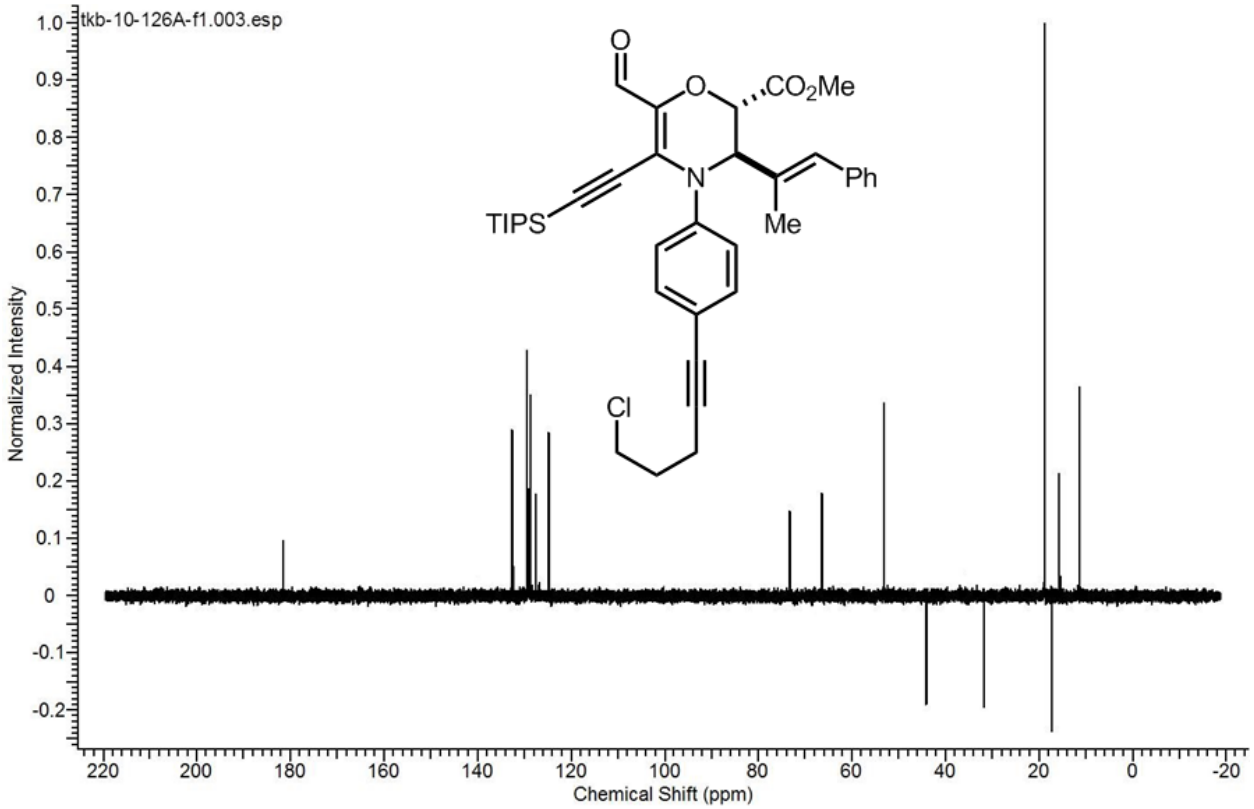
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
TIPS
TIPS


tkb-10-139A-f1b.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
TIPS
TIPS

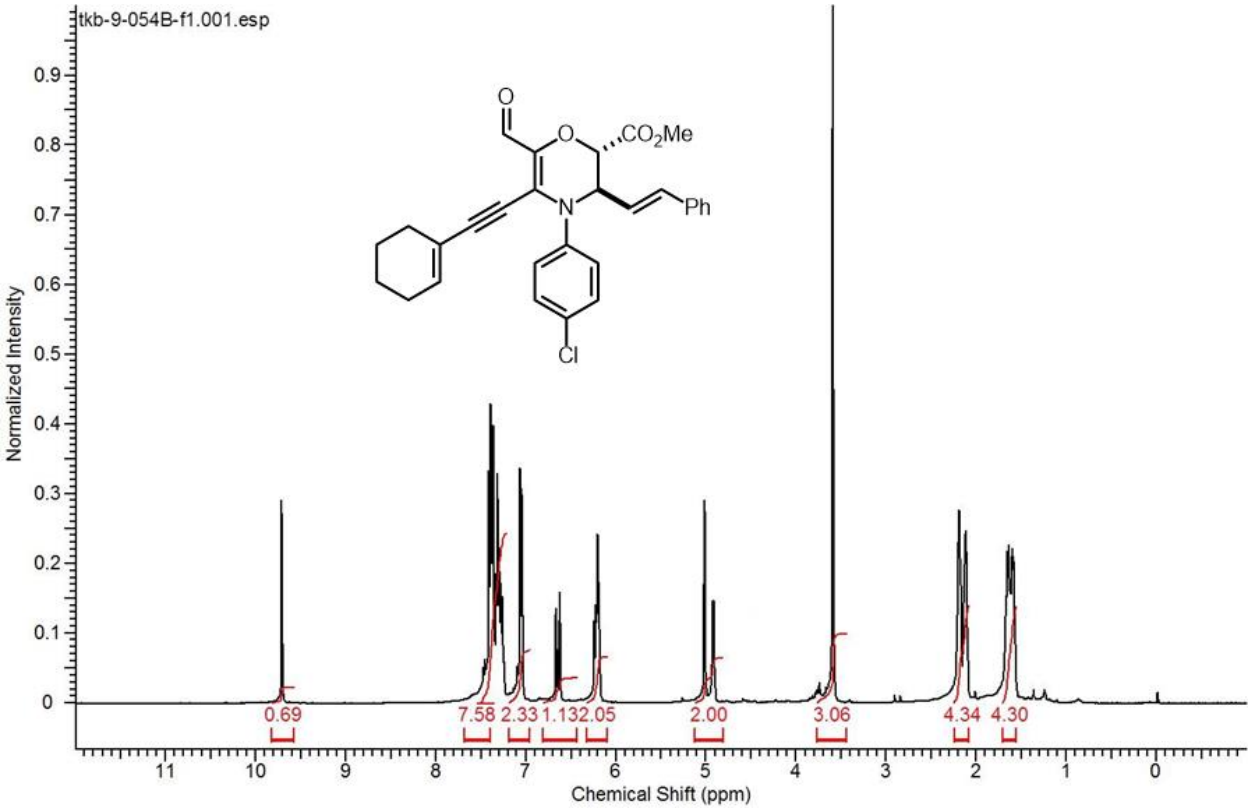
Compound **5g:** Prepared in 0.25 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10).Yield = 114.4 mg, 71%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 7.45 – 7.30 (m, 4H), 7.34 – 7.19 (m, 3H), 7.21 (d, 2H), 6.49 (s, 1H), 5.17 (d, J = 1.9 Hz, 1H), 4.66 (d, J = 1.9 Hz, 1H), 3.80 – 3.67 (m, 5H), 2.62 (t, J = 6.8 Hz, 2H), 2.14 – 1.92 (m, 5H), 1.04 – 0.86 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.11, 168.28, 143.14, 140.13, 136.52, 132.26, 129.12, 128.63, 128.33, 127.21, 124.41, 121.56, 104.67, 95.07, 88.90, 80.87, 72.96, 66.15, 52.74, 43.75, 31.46, 18.48, 16.98, 15.37, 11.05. HRMS calc for $C_{38}H_{46}ClNO_4Si$, 643.2885, found 643.2881.

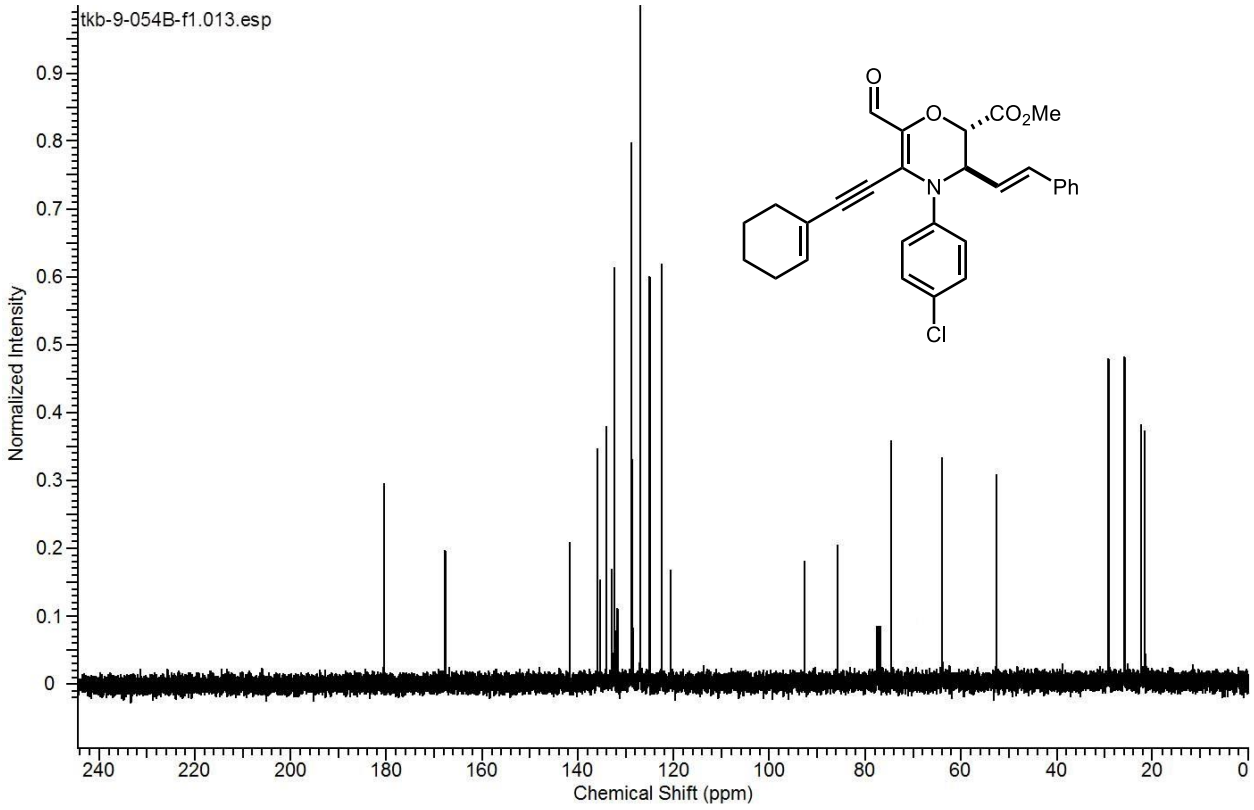



tkb-10-126A-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Me
TIPS
Cl


tkb-10-126A-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Me
TIPS
Cl

Compound **5h:** Prepared in 0.25 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 85.4 mg, 71%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 7.69 – 7.41 (m, 8H), 7.20 – 7.02 (m, 2H), 6.98 – 6.48 (m, 1H), 6.41 – 6.02 (m, 2H), 5.08 – 4.75 (m, 2H), 3.76 – 3.51 (s, 3H), 2.32 – 2.01 (m, 2H), 1.89 – 1.52 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.3, 168.2, 142.1, 136.0, 130.2, 128.1, 127.8, 126.2, 120.2, 92.2, 85.2, 74.2, 62.5, 52.4, 28.2, 24.3, 23.8, 22.8, 22.4. HRMS calc for $C_{29}H_{26}ClNO_4$, 487.1550, found 487.1556.

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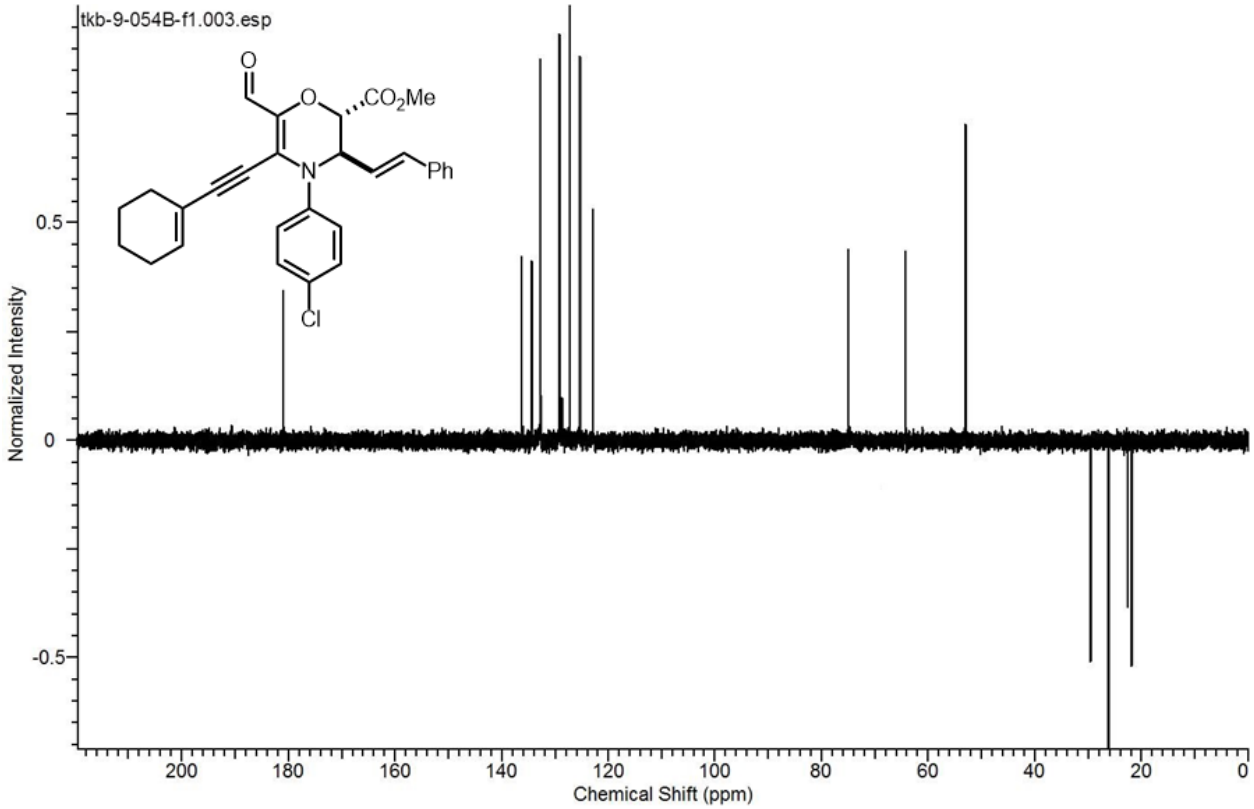
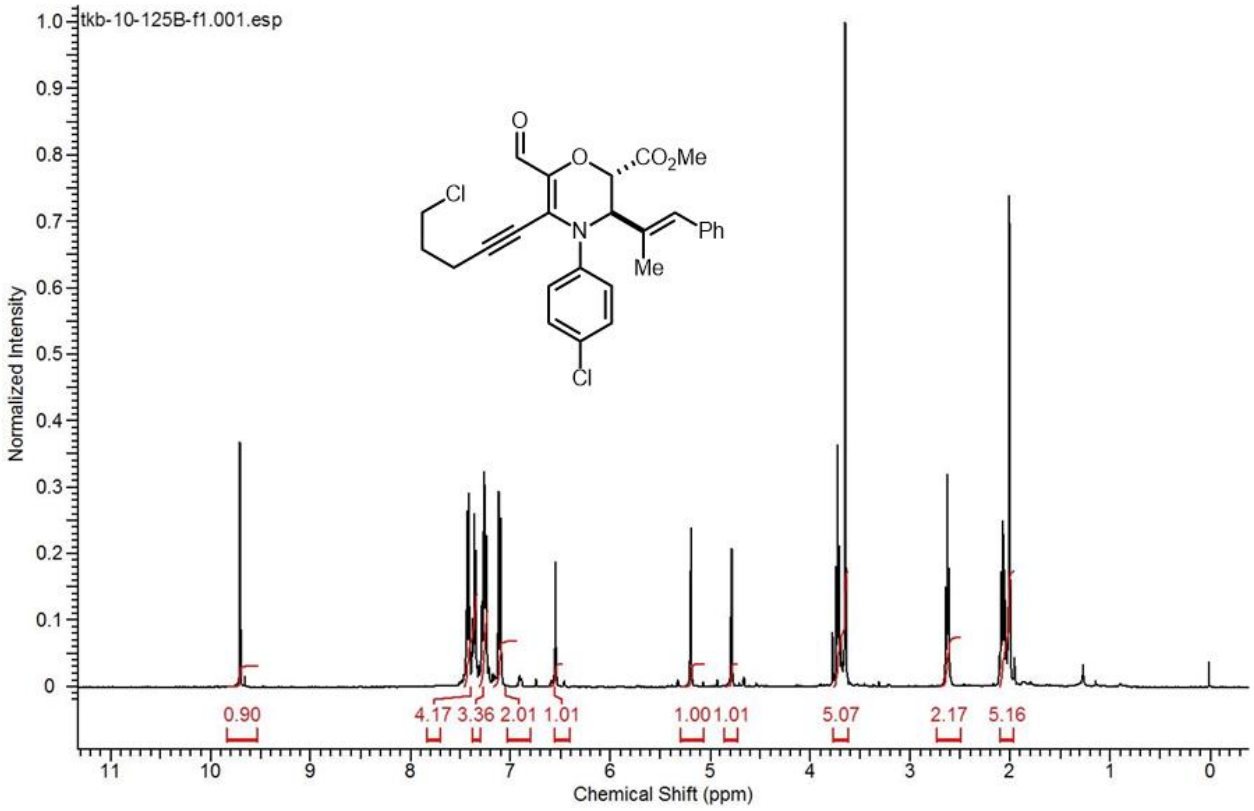
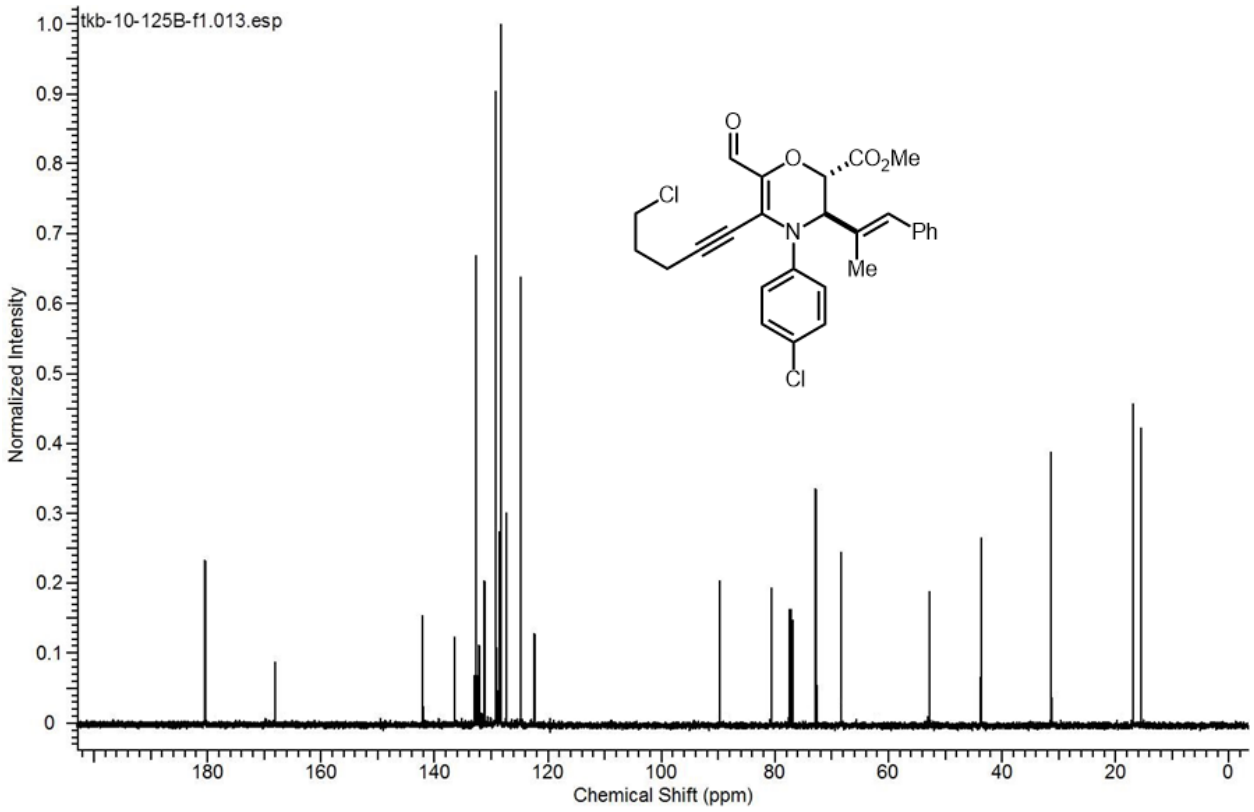
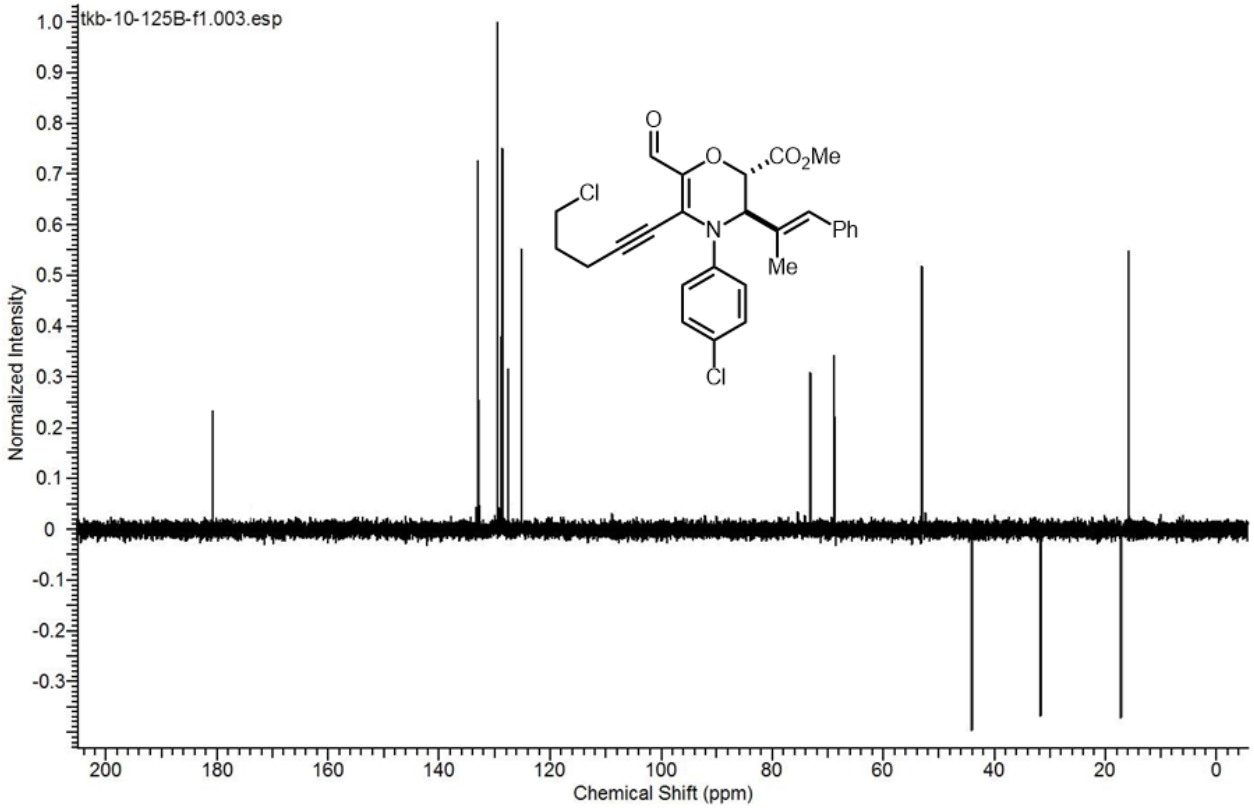
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Cl


tkb-9-054B-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Cl

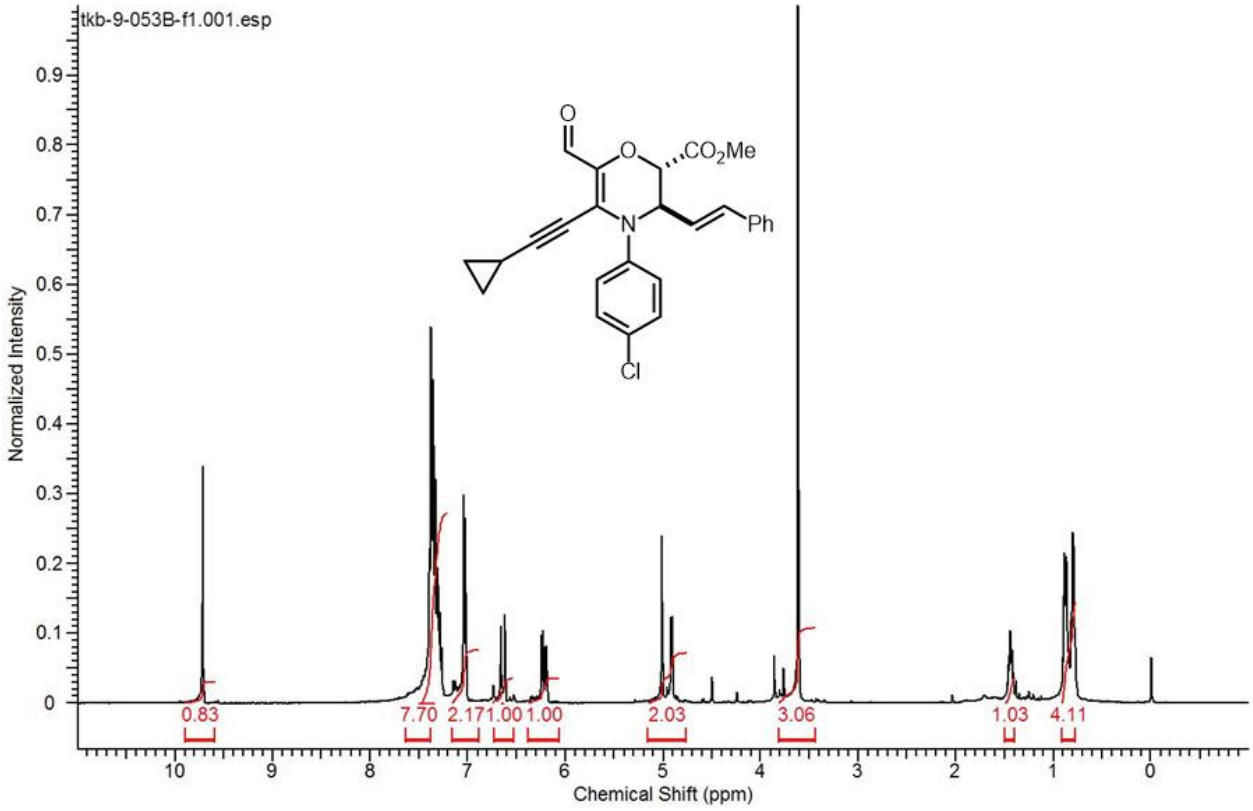
Compound **5i:** Prepared in 0.25 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 92.0 mg, 76%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.71 (s, 1H), 7.51 – 7.40 (m, 4H), 7.40 – 7.27 (m, 3H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.55 (s, 1H), 5.19 (d, *J* = 1.5 Hz, 1H), 4.79 (d, *J* = 1.5 Hz, 1H), 3.80 – 3.69 (m, 5H), 2.63 (t, *J* = 6.8 Hz, 2H), 2.08 (q, *J* = 6.6 Hz, 2H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.44, 168.18, 142.16, 136.38, 133.06, 132.60, 132.20, 131.26, 129.16, 128.62, 128.41, 128.37, 128.34, 127.34, 124.79, 122.34, 89.70, 80.62, 72.82, 68.41, 52.71, 43.76, 31.39, 16.95, 15.4. HRMS calc for $C_{26}H_{23}Cl_2NO_4$, 483.1004, found 483.1008.

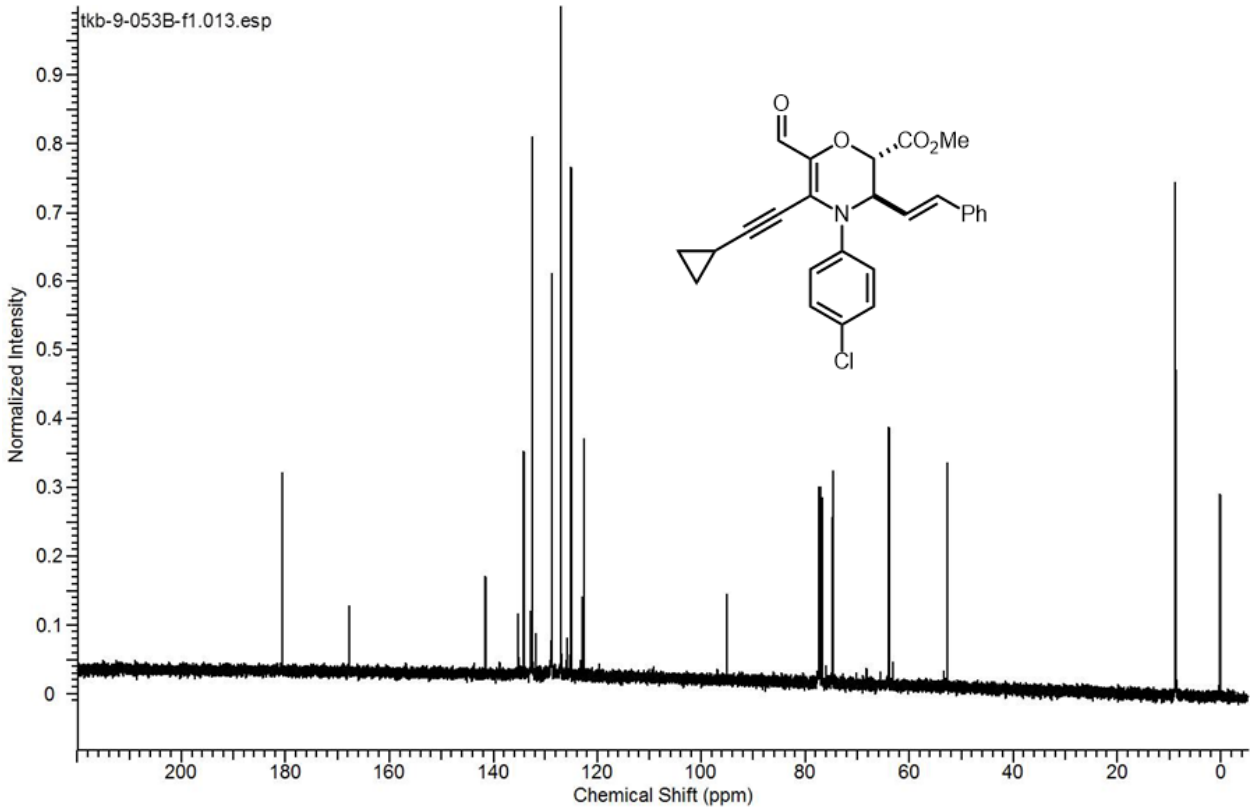


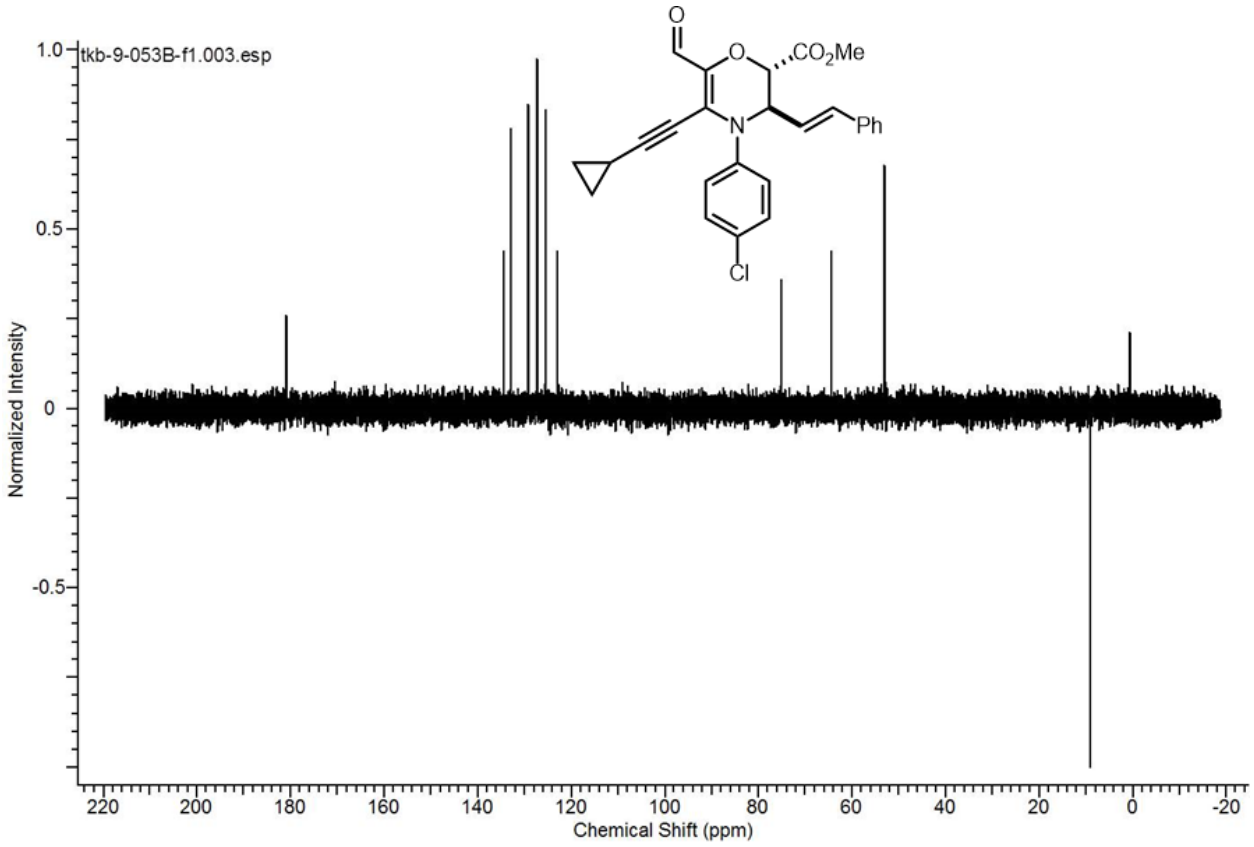

tkb-10-125B-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
CO2Me
Cl
Ph
Me
N
Cl


tkb-10-125B-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
CO2Me
Cl
Ph
Me
N
Cl

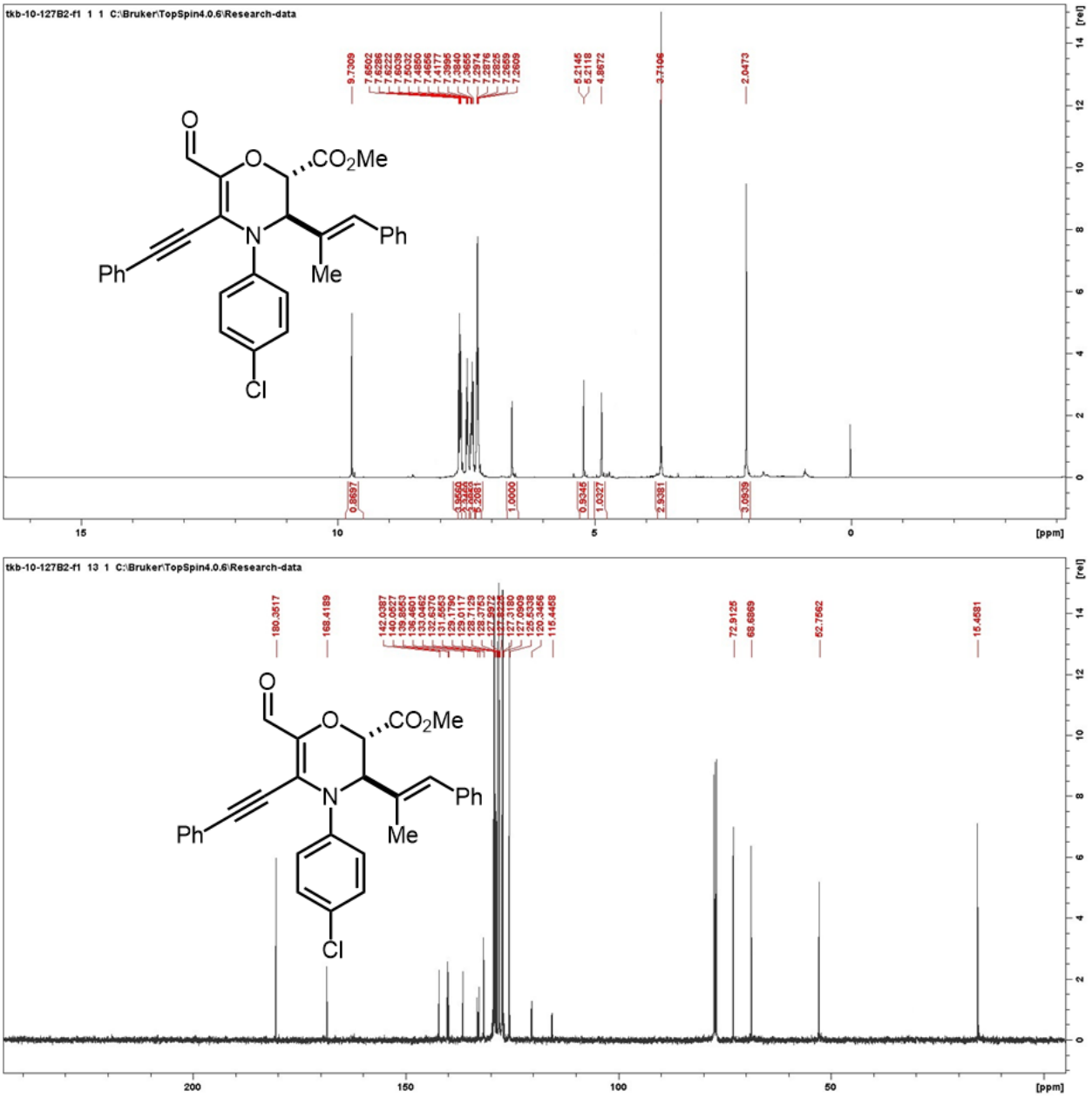
Compound **5j:** Prepared in 0.50 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 154.5 mg, 69%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.72 (s, 1H), 7.70 – 7.21 (m, 7H), 7.22 – 7.04 (m, 2H), 6.78 – 6.52 (d, 1H), 6.41 – 6.03 (d, 1H), 5.02 – 4.88 (m, 2H), 3.87 – 3.51 (s, 3H), 1.62 – 1.42 (t, 1H), 0.98 – 0.72 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 168.8, 141.2, 138.2, 136.5, 135.4, 134.2, 133.1, 129.8, 127.2, 126.8, 125.2, 122.7, 96.1, 74.2, 63.8, 52.9, 9.7, 0.1. HRMS calc for $C_{26}H_{22}ClNO_4$, 447.1237, found 447.1244.

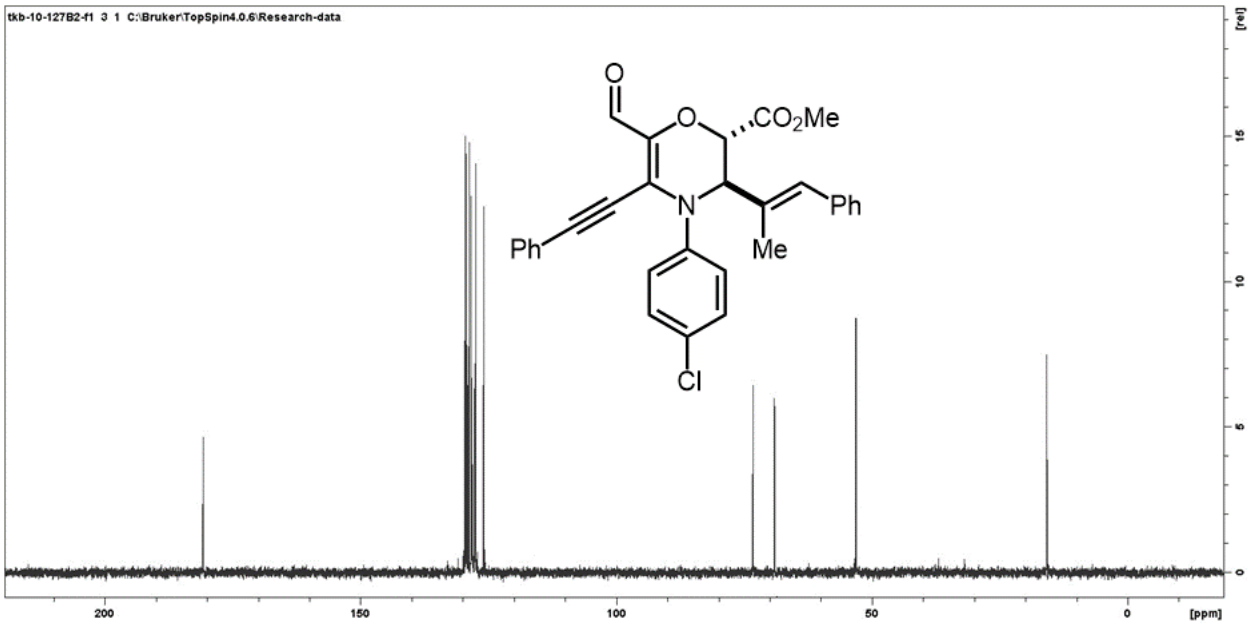



tkb-9-053B-f1.013.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Cl

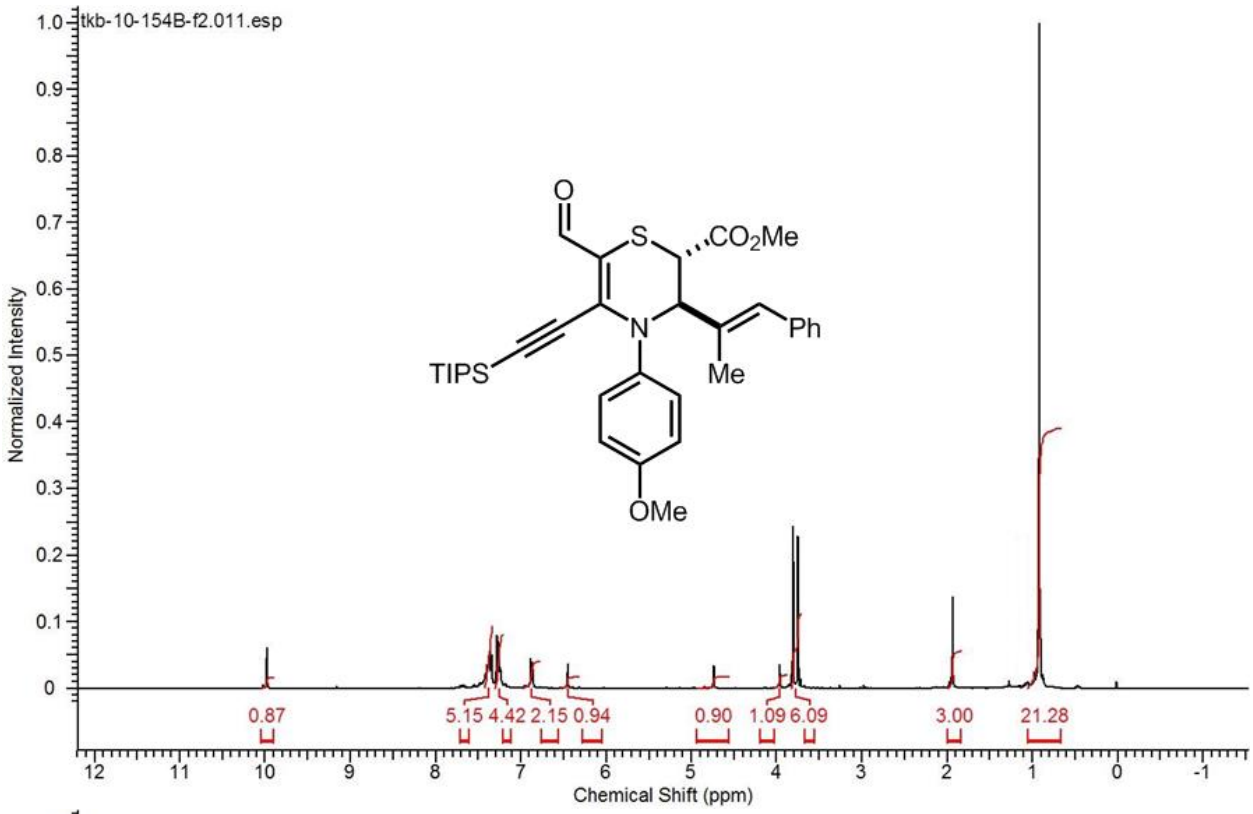

tkb-9-053B-f1.003.esp
Normalized Intensity
Chemical Shift (ppm)
O
O
CO2Me
N
Ph
Cl

Compound **5k:** Prepared in 0.50 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10).Yield = 179.3 mg, 72%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.65 – 7.60 (m, 4H), 7.50 – 7.36 (m, 5H), 7.29 – 7.26 (m, 5H), 6.61 (s, 1H), 5.21 (d, *J* = 1.5 Hz, 1H), 4.87 (s, 1H), 3.71 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.4, 168.4, 142.0, 140.1, 139.9, 136.5, 129.2, 129.0, 128.7, 128.4, 128.0, 127.8, 127.3, 127.1, 125.5, 120.3, 115.4, 72.9, 68.7, 52.8, 15.5. HRMS calc for $C_{30}H_{24}ClNO_4$, 497.1394, found 497.1399.





Compound **5l:** Prepared in 0.25 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (95:5).Yield = 98.8 mg, 67%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.97 (s, 1H), 7.45 – 7.30 (m, 5H), 7.30 – 7.17 (m, 4H), 6.88 (d, 2H), 6.44 (s, 1H), 4.73 (t, *J* = 1.8 Hz, 1H), 3.96 (dd, *J* = 2.4, 1.0 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 1.93 (s, 3H), 0.91 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.53, 169.89, 159.01, 139.01, 136.82, 134.42, 129.27, 129.09, 128.81, 128.70, 128.63, 128.61, 128.31, 127.12, 114.21, 111.16, 105.21, 96.56, 67.61, 55.58, 52.86, 39.43, 18.63, 18.53, 16.00, 11.03. HRMS calc for $C_{34}H_{43}NO_4SSi$, 589.2682, found 589.2688.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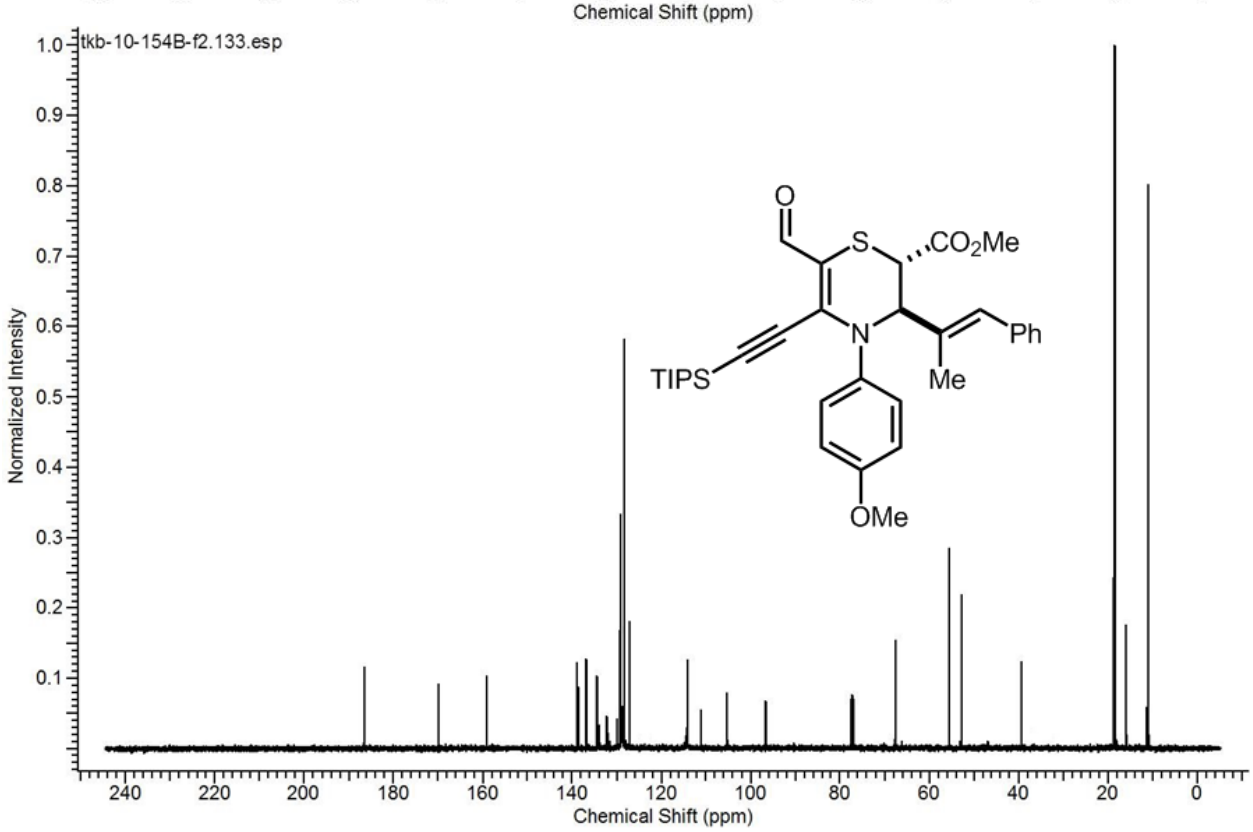
Normalized Intensity
Chemical Shift (ppm)
0.87
5.15 4.42 2.15 0.94
0.90 1.09 6.09
3.00
21.28
O
S
CO2Me
N
Ph
Me
TIPS
OMe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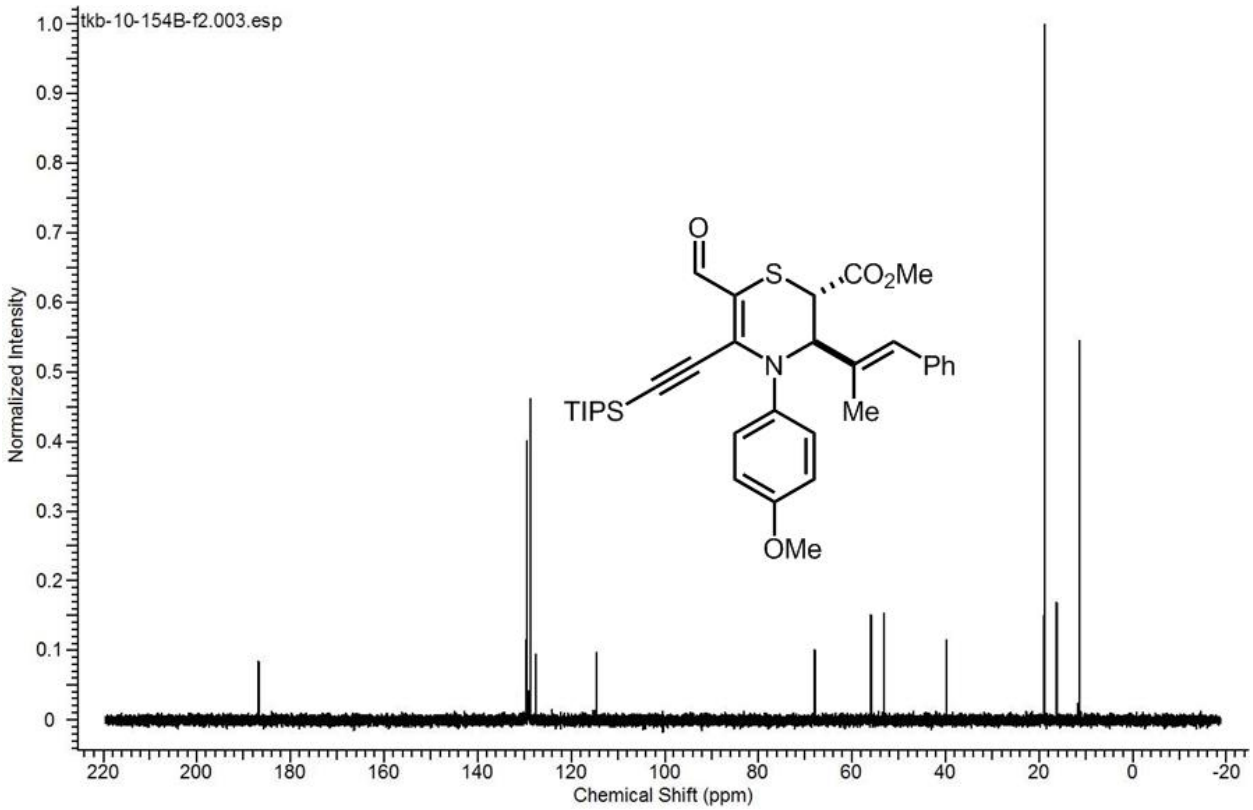
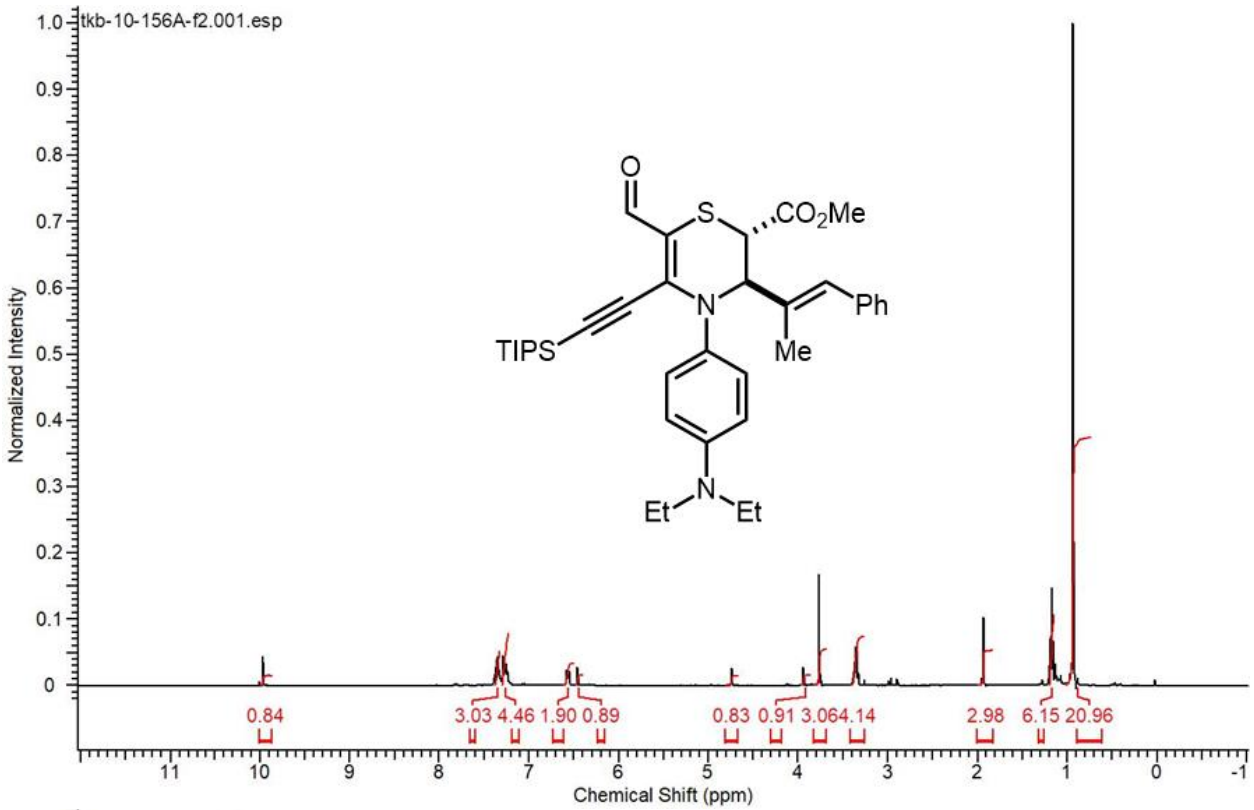
CO2Me
N
Ph
Me
TIPS
OMe



Compound **5m:** Prepared in 0.25 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10).Yield = 108.8 mg, 69%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.92 (s, 1H), 7.43 – 7.20 (m, 7H), 6.57 (dd, *J* = 8.8, 4.0 Hz, 2H), 6.46 (s, 1H), 4.74 (t, *J* = 1.7 Hz, 1H), 3.97 – 3.91 (m, 1H), 3.77 (s, 3H), 3.36 (q, *J* = 7.1 Hz, 4H), 1.98 (s, 3H), 1.22 – 1.05 (m, 6H), 0.93 (s, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.41, 169.94, 147.14, 139.59, 137.04, 134.72, 134.21, 129.16, 129.12, 128.27, 127.00, 111.28, 111.05, 110.07, 104.75, 96.73, 67.92, 52.81, 44.48, 39.45, 18.56, 18.54, 16.07, 12.62, 11.10. HRMS calc for $C_{37}H_{50}N_2O_3SSi$, 630.3311, found 630.3314.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TIPS
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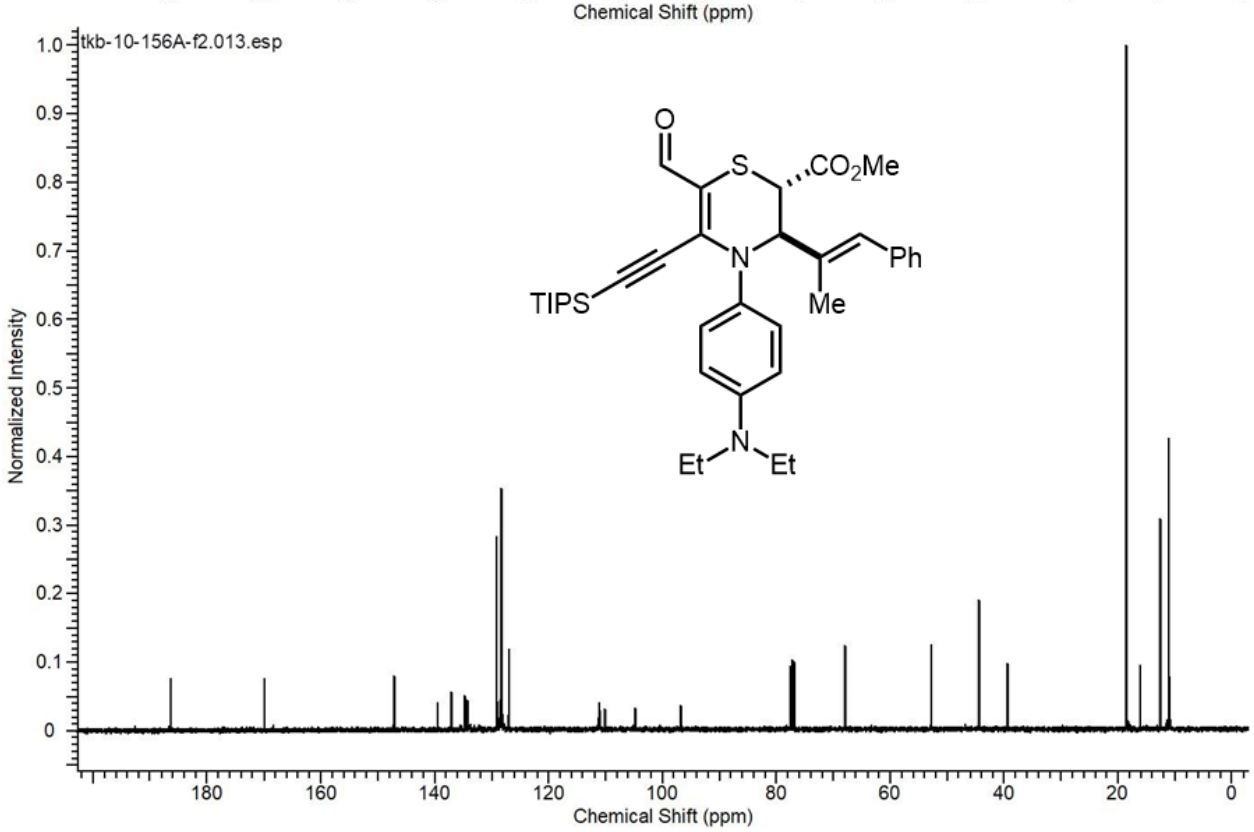
N
Et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TIPS
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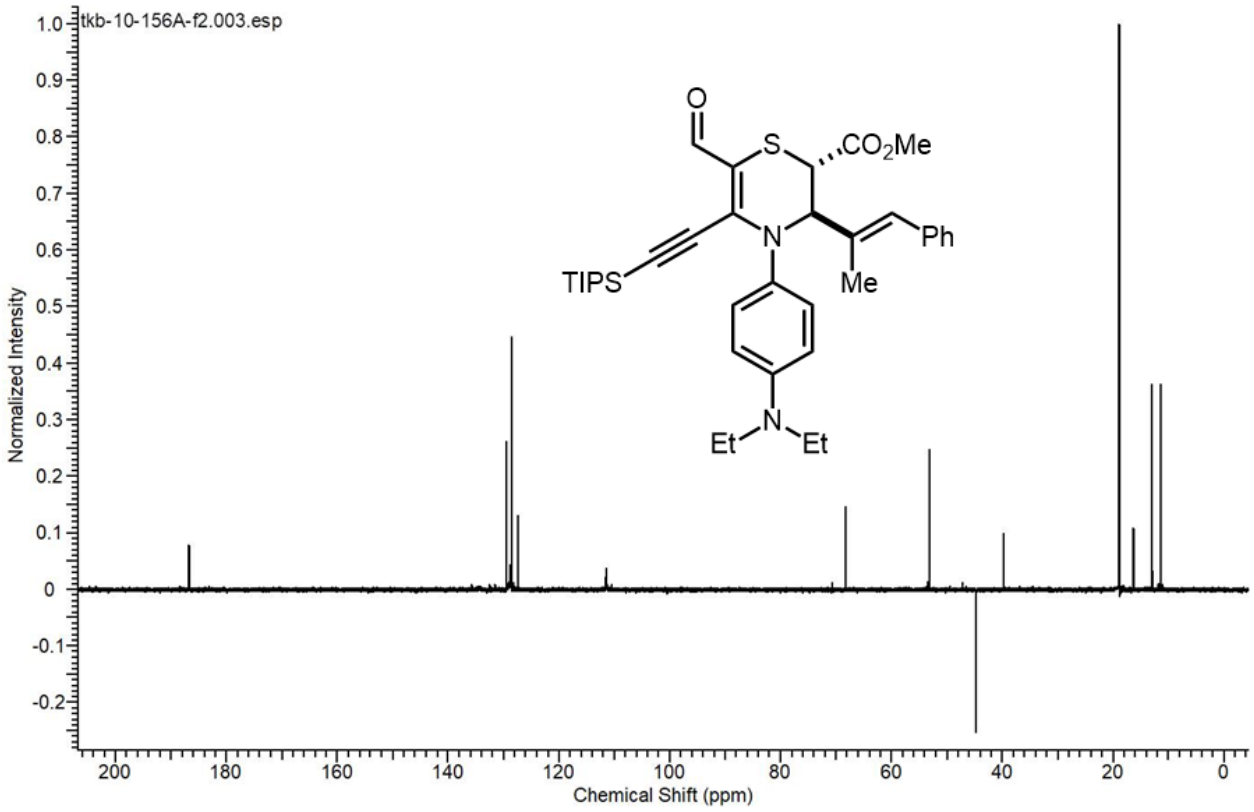
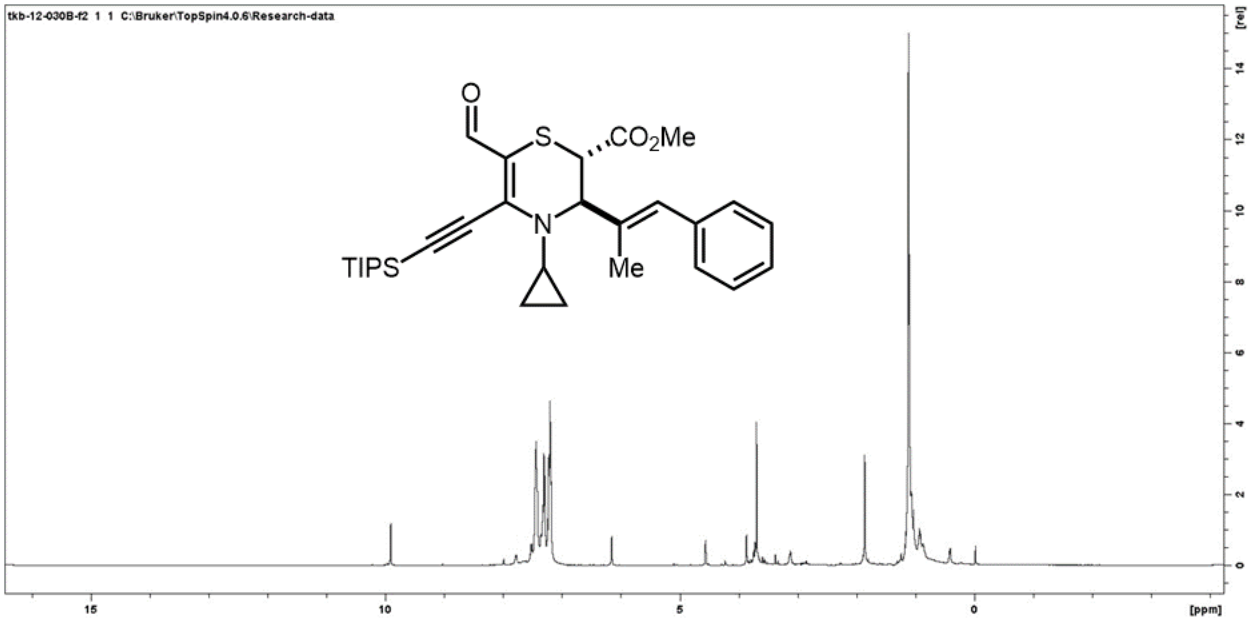
Et



Compound **5n:** Prepared in 0.50 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10).Yield = 183.3 mg, 70%, 90:10 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.43 – 7.25 (m, 5H), 6.22 (s, 1H), 4.63 (d, *J* = 3.0 Hz, 1H), 3.83 (d, *J* = 3.0 Hz, 1H), 3.66 (s, 3H), 3.19 (tt, *J* = 7.0, 4.4 Hz, 1H), 1.83 (s, 3H), 1.07 – 0.95 (m, 25H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.11, 170.05, 140.71, 136.86, 134.25, 134.13, 132.24, 132.14, 132.07, 132.05, 129.77, 129.13, 128.67, 128.59, 128.55, 128.51, 128.30, 127.73, 127.05, 112.11, 105.60, 96.58, 65.49, 52.87, 39.50, 36.67, 18.78, 15.51, 11.37, 10.37, 9.48. HRMS calc for $C_{30}H_{41}NO_3SSi$, 523.2576, found 523.2581.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CO2Me
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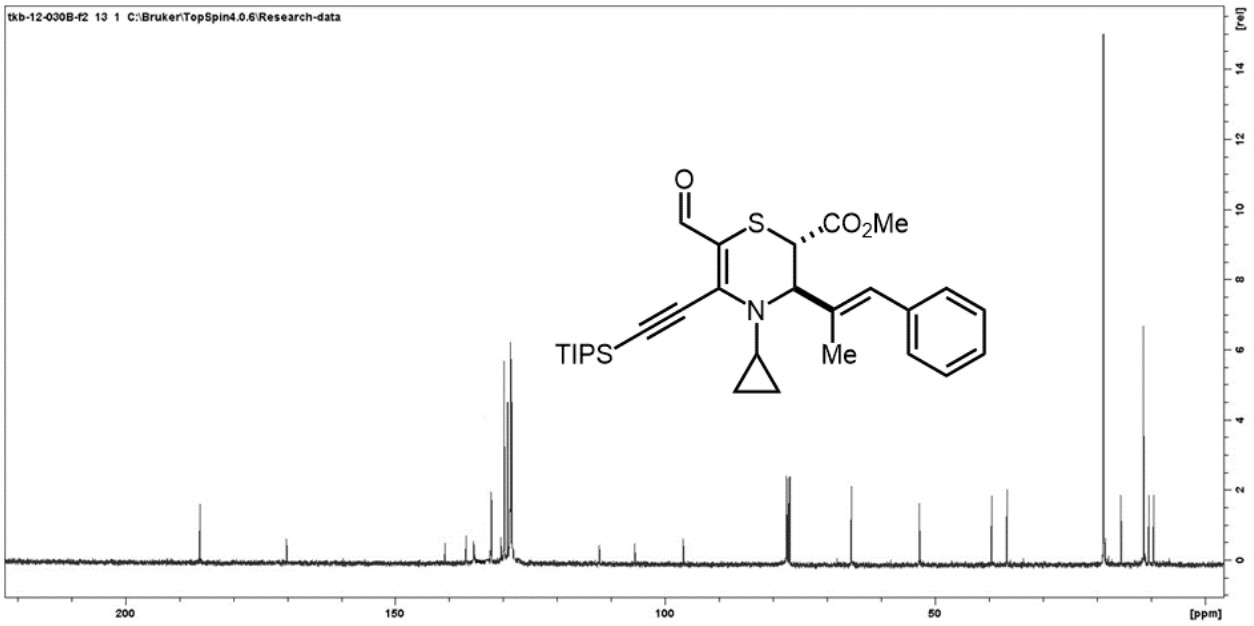
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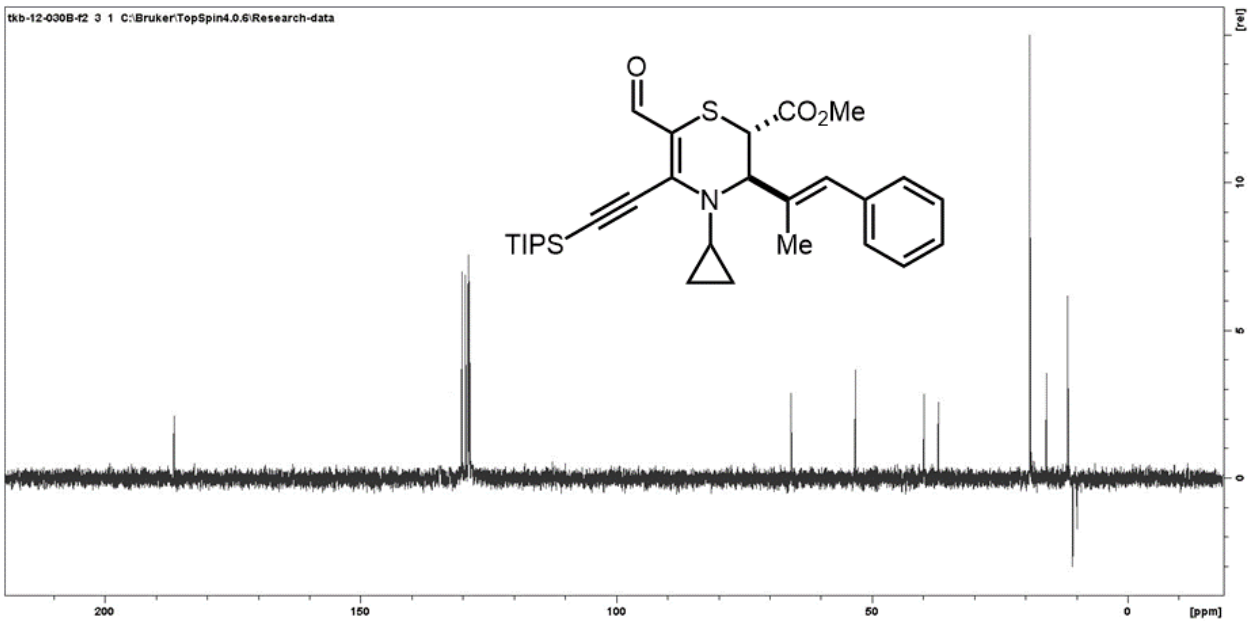
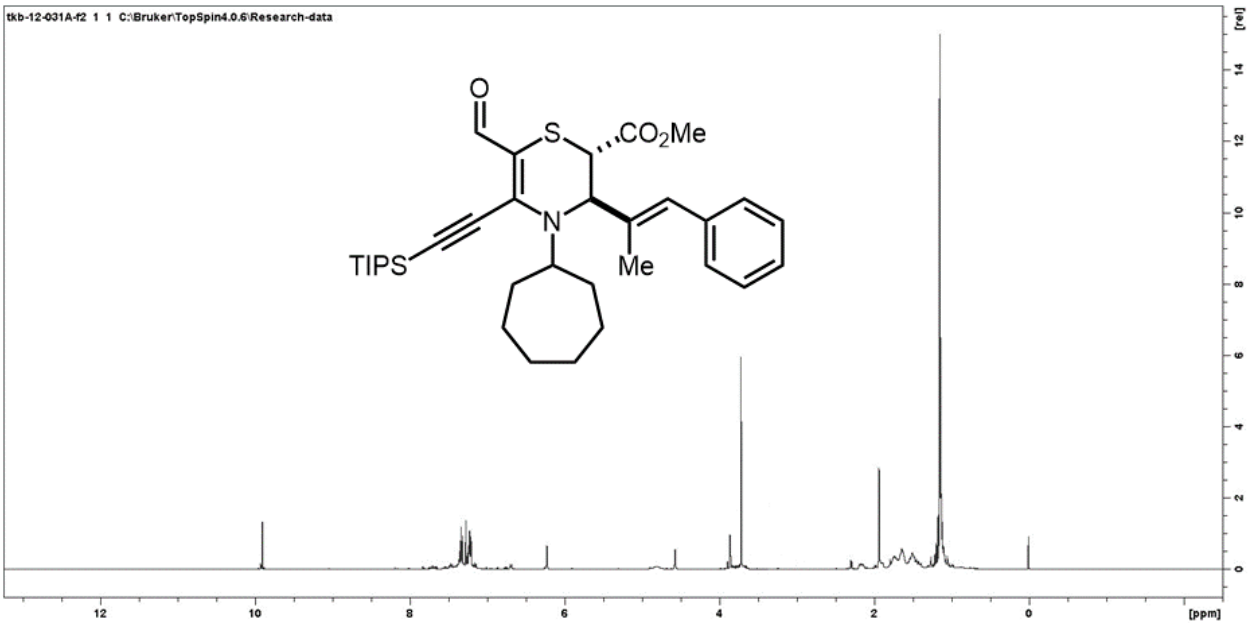


Compound **5o:** Prepared in 0.50 mmol scale using **General Procedure B**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10).Yield = 197.2 mg, 68%, 90:10 dr. ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.38 – 7.22 (m, 5H), 6.20 (s, 1H), 4.64 (d, J = 2.1 Hz, 1H), 3.77 (d, J = 2.1 Hz, 1H), 3.70 – 3.45 (m, 4H), 1.97 (s, 3H), 1.77 – 1.69 (m, 4H), 1.51 – 1.41 (m, 6H), 1.15 – 1.03 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.41, 169.73, 139.29, 136.96, 129.03, 128.82, 128.30, 127.03, 110.32, 104.77, 96.26, 52.82, 40.54, 33.63, 33.61, 27.24, 24.89, 24.63, 18.81, 16.15, 11.34. HRMS calc for $C_{34}H_{49}NO_3SSi$, 579.3202, found 579.3208.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CO2Me
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TIPS
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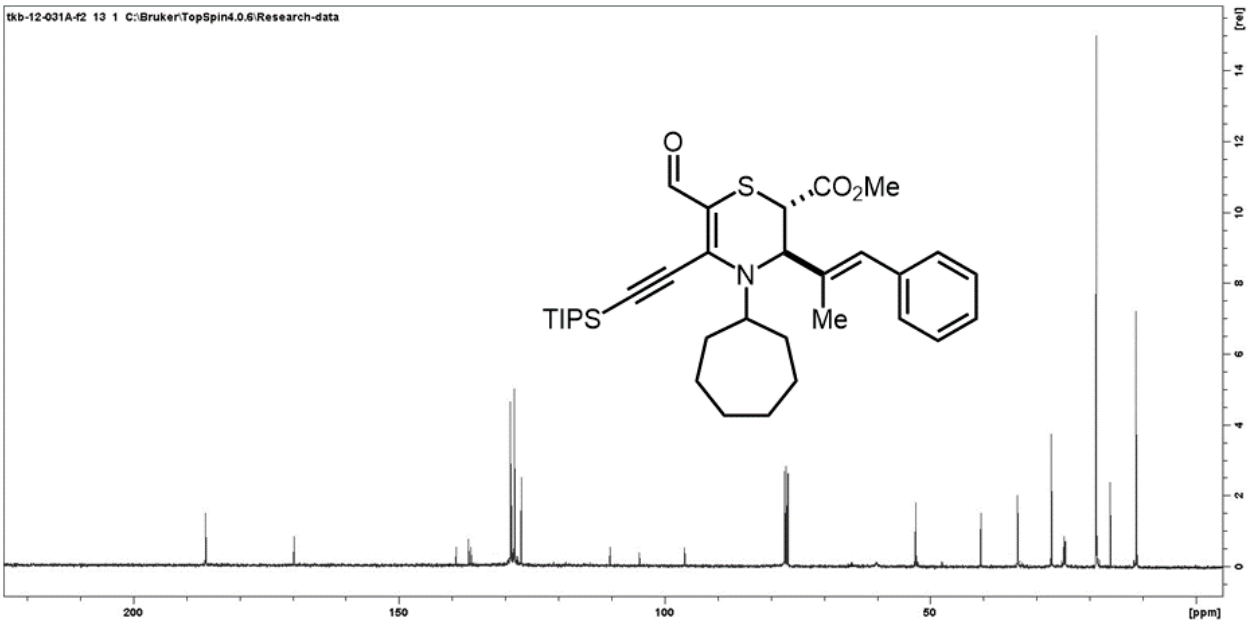
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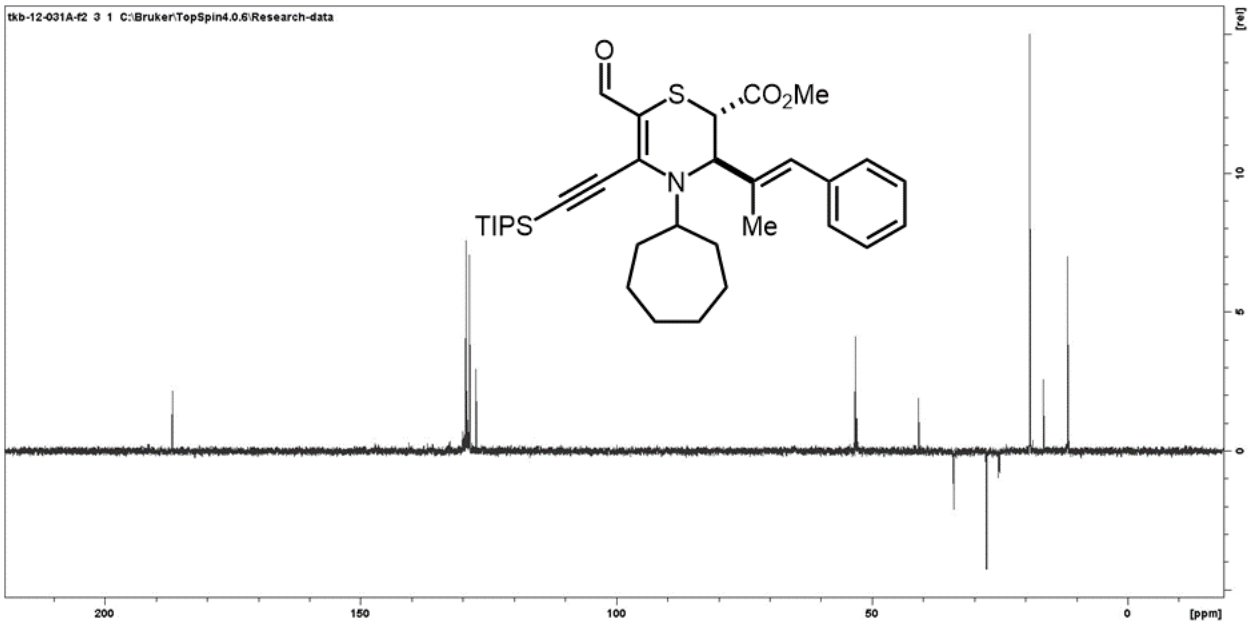
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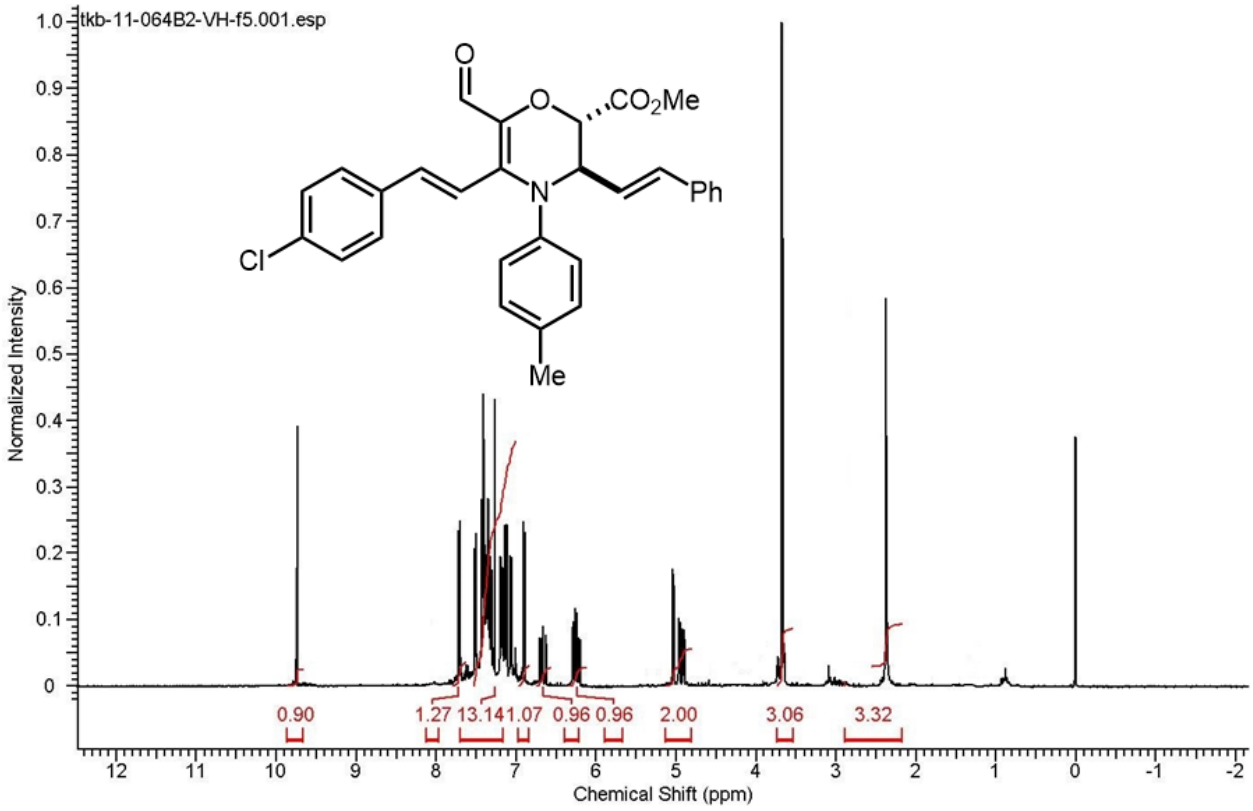
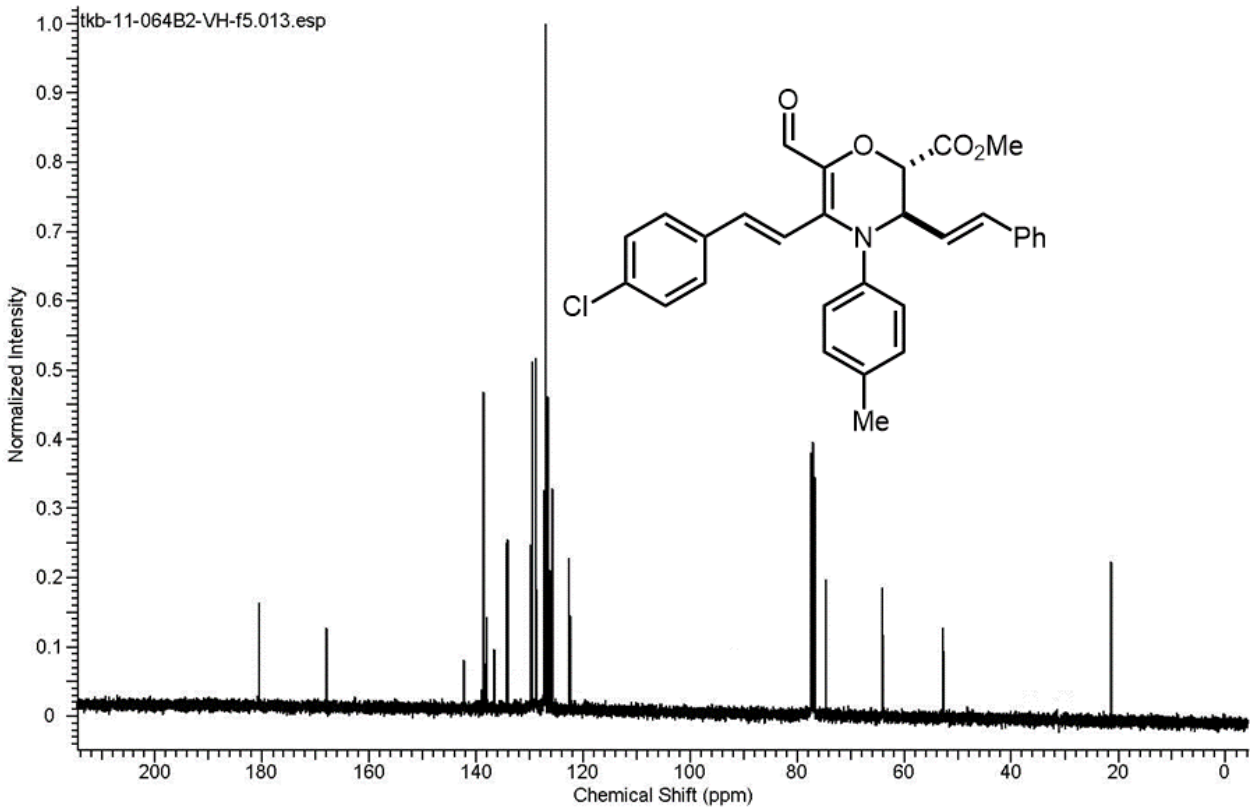
S
CO2Me
N
TIPS
Me
200
150
100
50
0
[ppm]

Scheme 4 results

Compound **6a:** Prepared in 0.25 mmol scale using **General Procedure C**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 103.8 mg, 83%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.79 (d, *J* = 14.2 Hz, 1H), 7.53 – 7.02 (m, 13H), 6.99 (d, *J* = 14.2 Hz, 1H), 6.73 (d, *J* = 12.5 Hz, 1H), 6.49 (dd, *J* = 12.6, 1.3 Hz, 1H), 5.08 (dd, *J* = 5.8, 1.3 Hz, 1H), 4.78 (d, *J* = 1.3 Hz, 1H), 3.75 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.58, 180.49, 167.98, 138.59, 134.15, 129.59, 128.89, 128.87, 127.28, 127.23, 126.99, 126.62, 122.71, 122.40, 74.75, 74.72, 64.19, 63.98, 52.82, 52.77, 21.40. HRMS calc for $C_{30}H_{26}ClNO_4$, 499.1550, found 499.1555.

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Chemical Shift (ppm)
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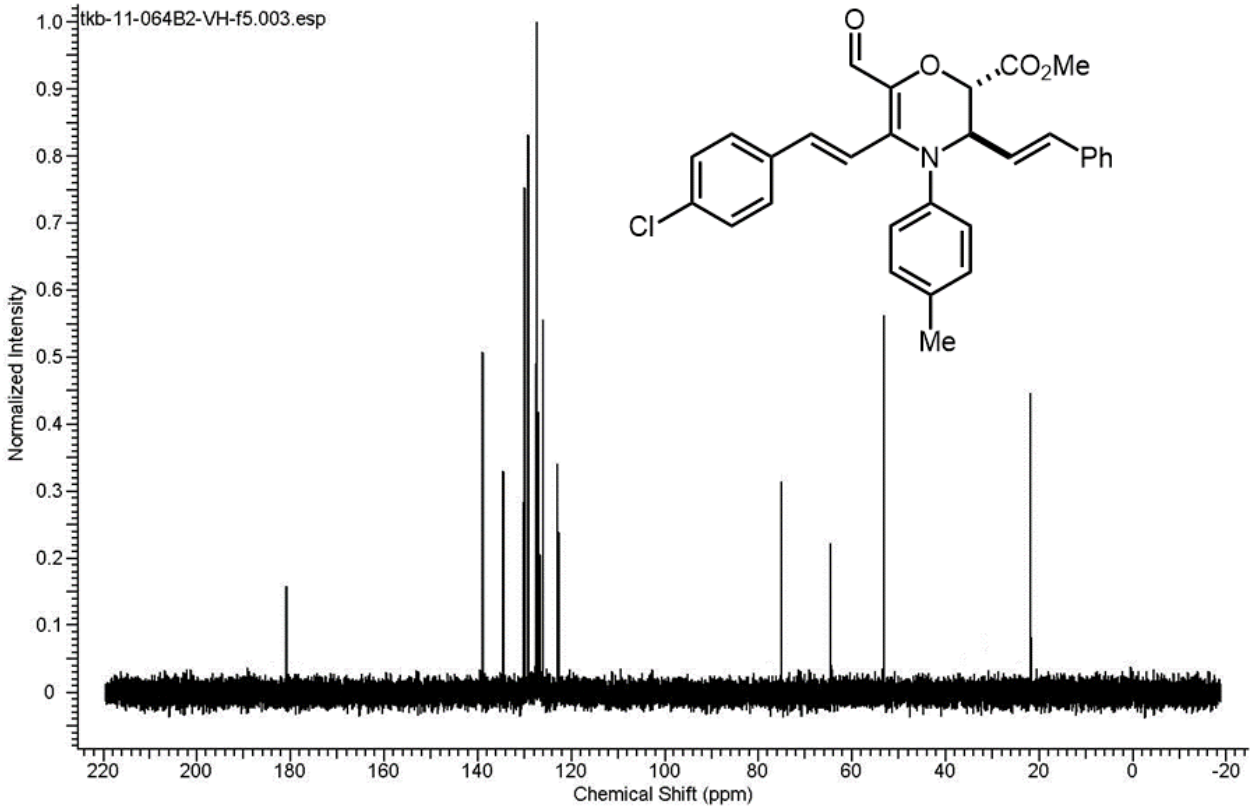
CO2Me
N
Ph
Cl
Me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Normalized Intensity
Chemical Shift (ppm)
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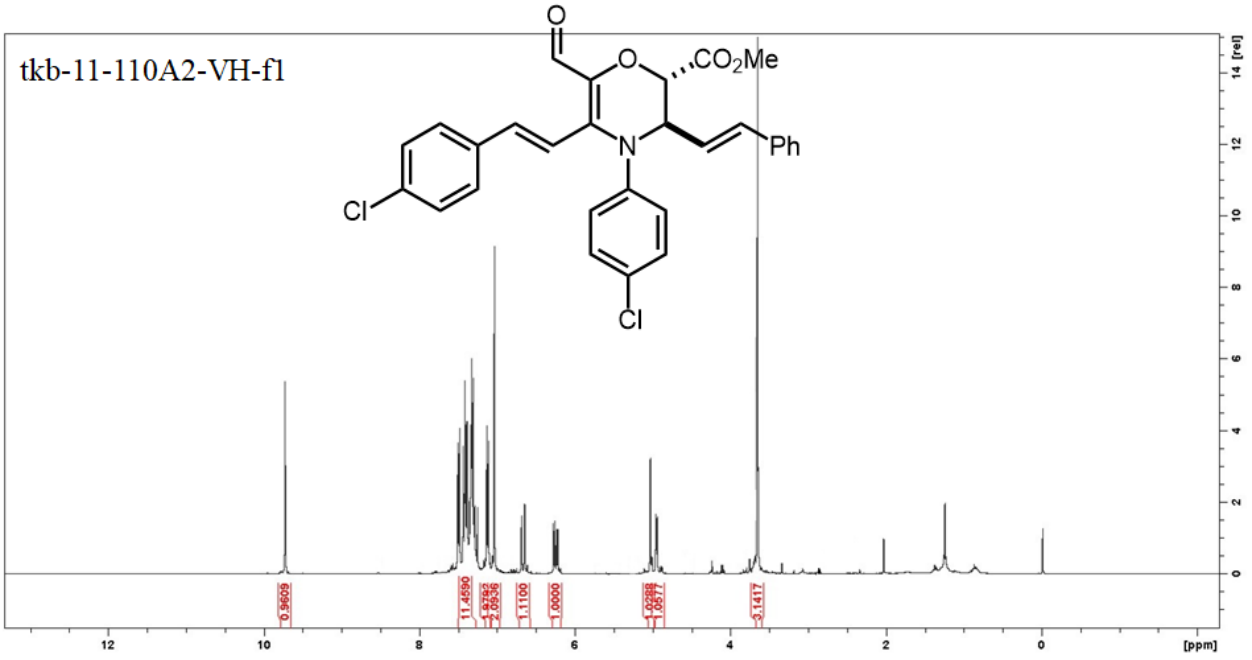
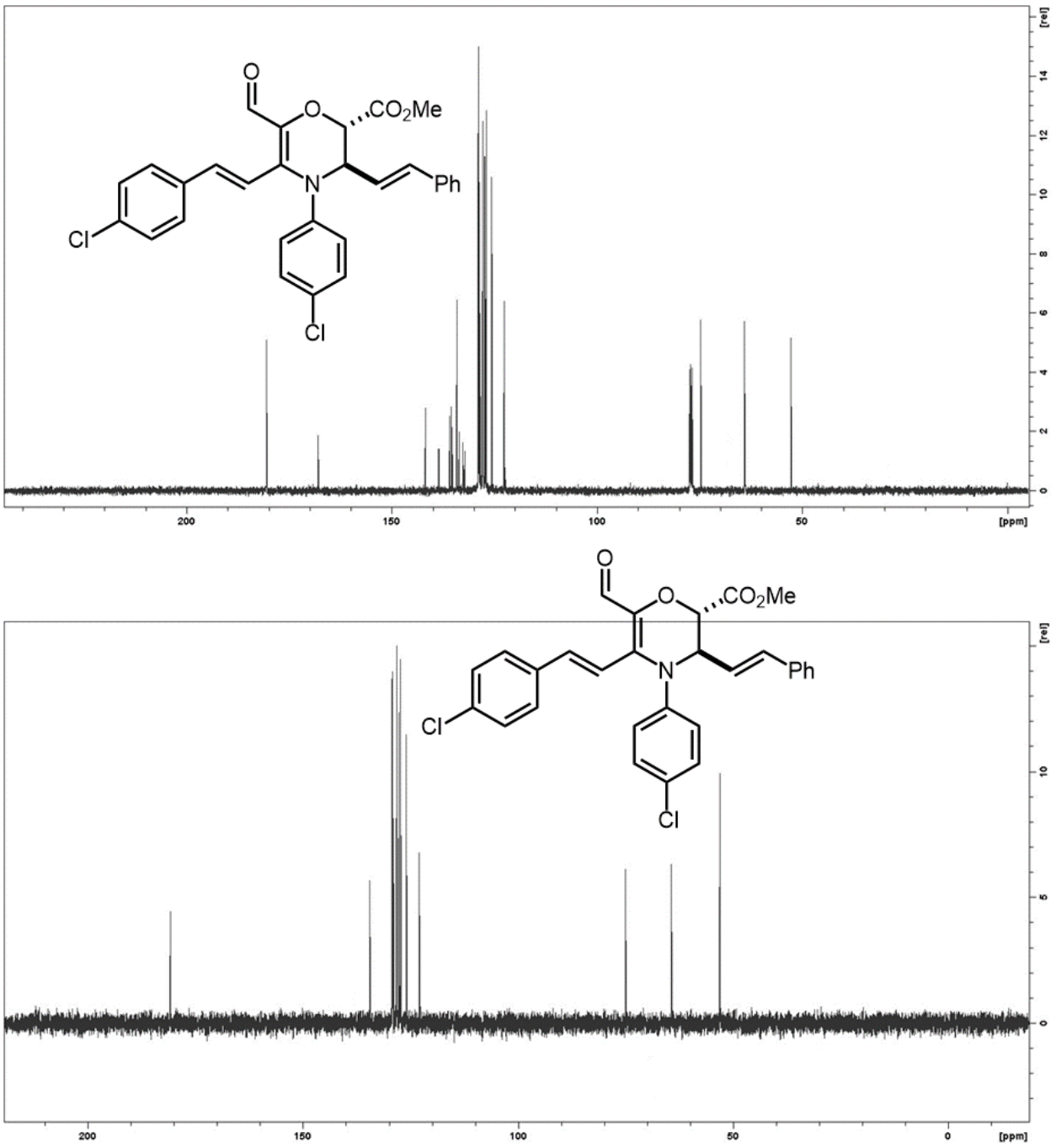
CO2Me
N
Ph
Cl
Me

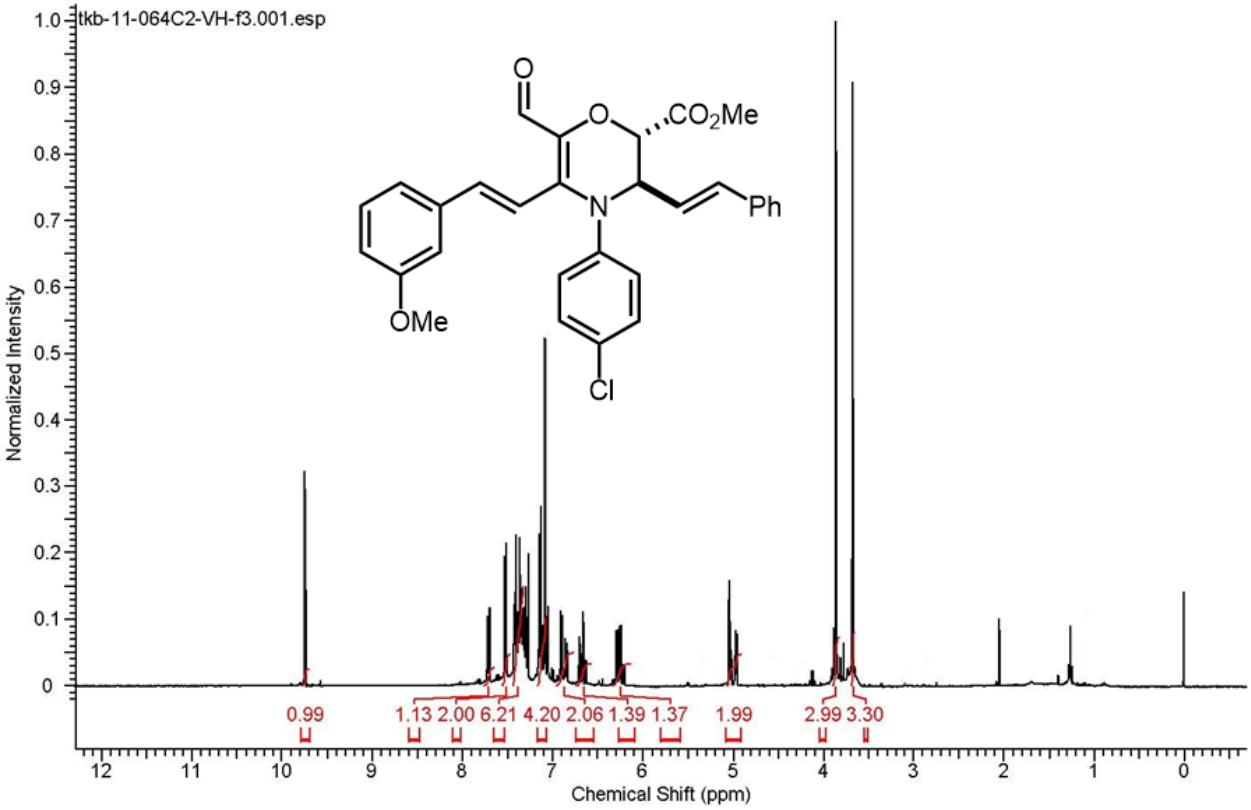
Compound **6b:** Prepared in 0.25 mmol scale using **General Procedure C**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 93.6 mg, 72%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.49 – 7.32 (m, 11H), 7.32 – 7.07 (m, 4H), 6.77 (d, *J* = 14.5 Hz, 1H), 6.16 (dd, *J* = 14.5, 6.7 Hz, 1H), 5.12 (d, *J* = 1.5 Hz, 1H), 4.92 (dd, *J* = 6.7, 1.5 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.54, 167.95, 141.85, 138.59, 135.95, 135.51, 135.37, 134.14, 133.67, 132.71, 132.23, 129.05, 128.88, 128.80, 128.52, 127.92, 127.85, 127.43, 127.00, 125.69, 122.65, 74.75, 64.11, 52.77. HRMS calc for $C_{30}H_{26}ClNO_4$, 499.1550, found 499.1555.

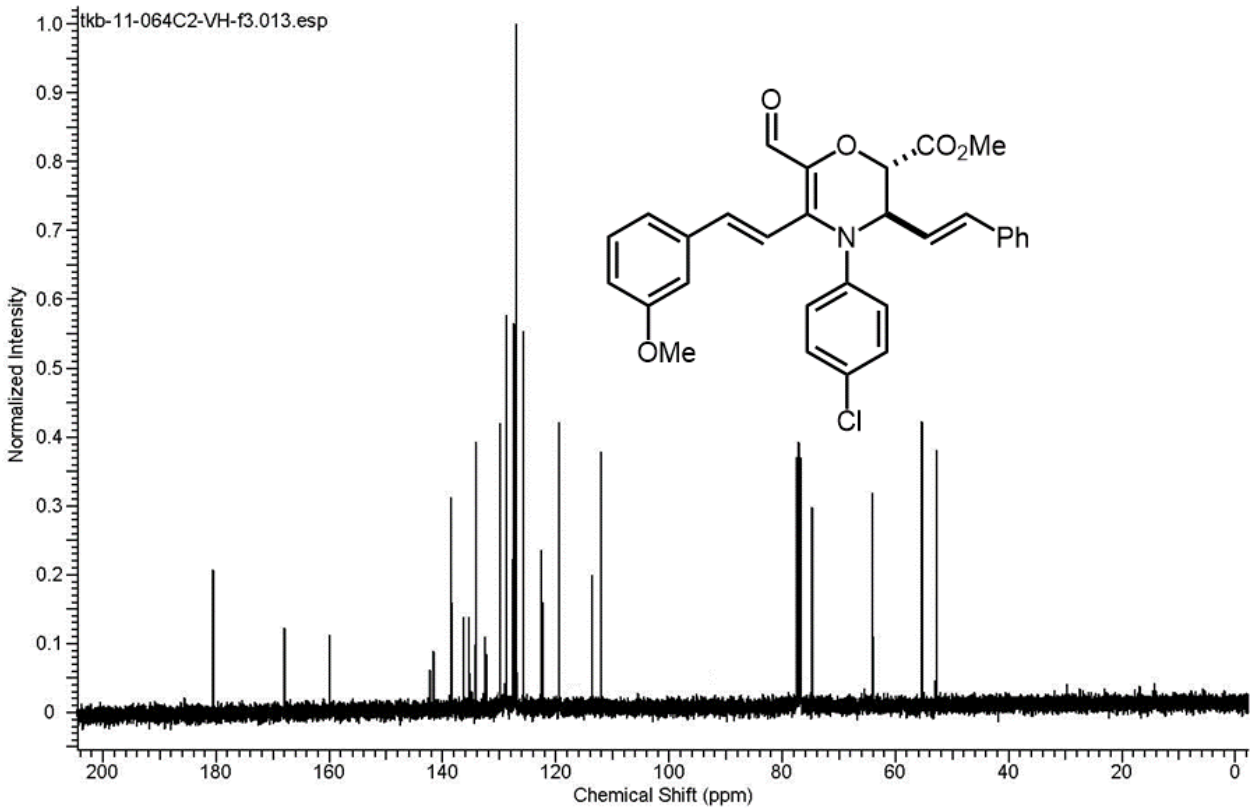




Compound **6c:** Prepared in 0.25 mmol scale using **General Procedure C**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50).Yield = 100.6 mg, 78%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.70 (d, *J* = 14.1 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.28 (m, 6H), 7.21 – 7.14 (m, 4H), 6.89 – 6.81 (m, 2H), 6.72 (d, *J* = 15.7 Hz, 1H), 6.30 (dd, *J* = 15.5, 6.7 Hz, 1H), 5.01 (dd, *J* = 6.7, 1.6 Hz, 1H), 4.97 (d, *J* = 1.6 Hz,

1H), 3.81 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.58, 180.52, 167.96, 160.04, 141.69, 138.60, 134.15, 129.85, 129.79, 128.90, 128.87, 128.78, 127.63, 127.42, 127.28, 127.00, 125.71, 122.68, 119.41, 113.66, 112.03, 74.76, 64.15, 55.39, 52.77. HRMS calc for $C_{30}H_{26}ClNO_5$, 515.1500, found 515.1504.

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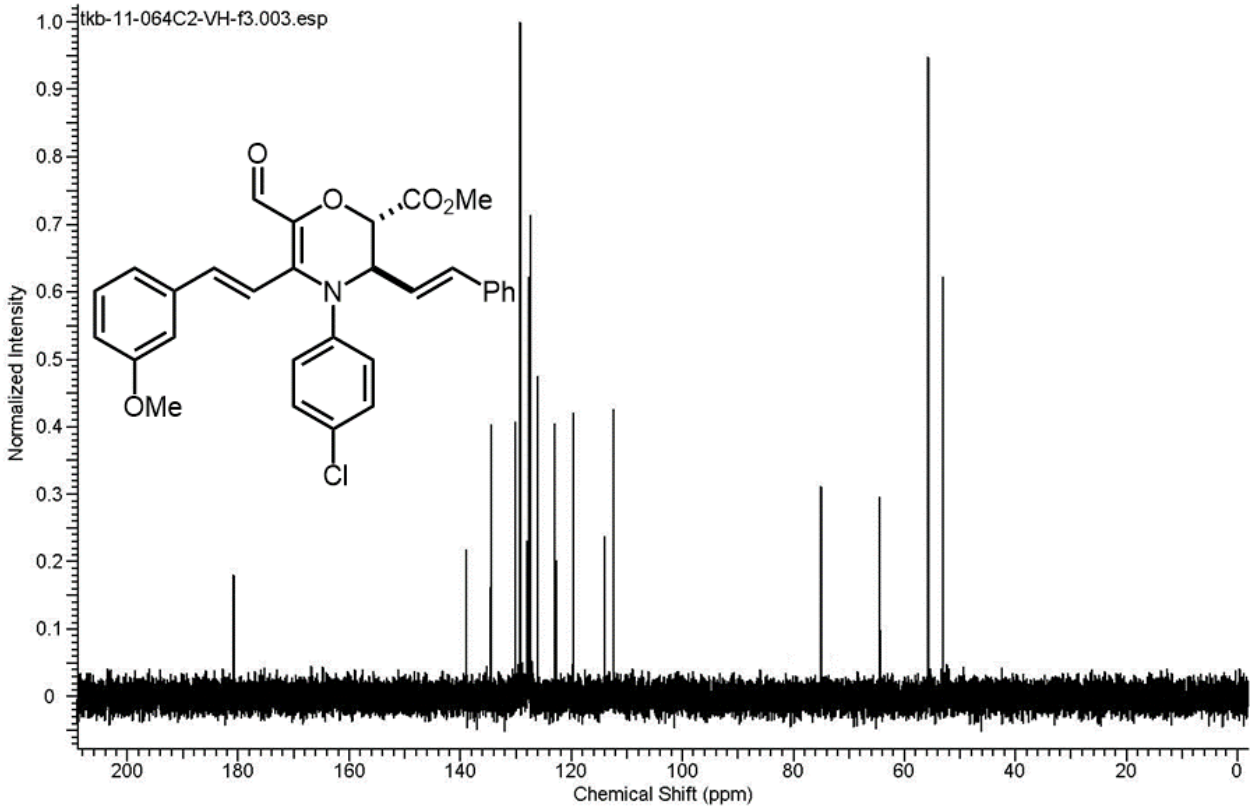
OMe
Cl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Normalized Intensity
Chemical Shift (ppm)
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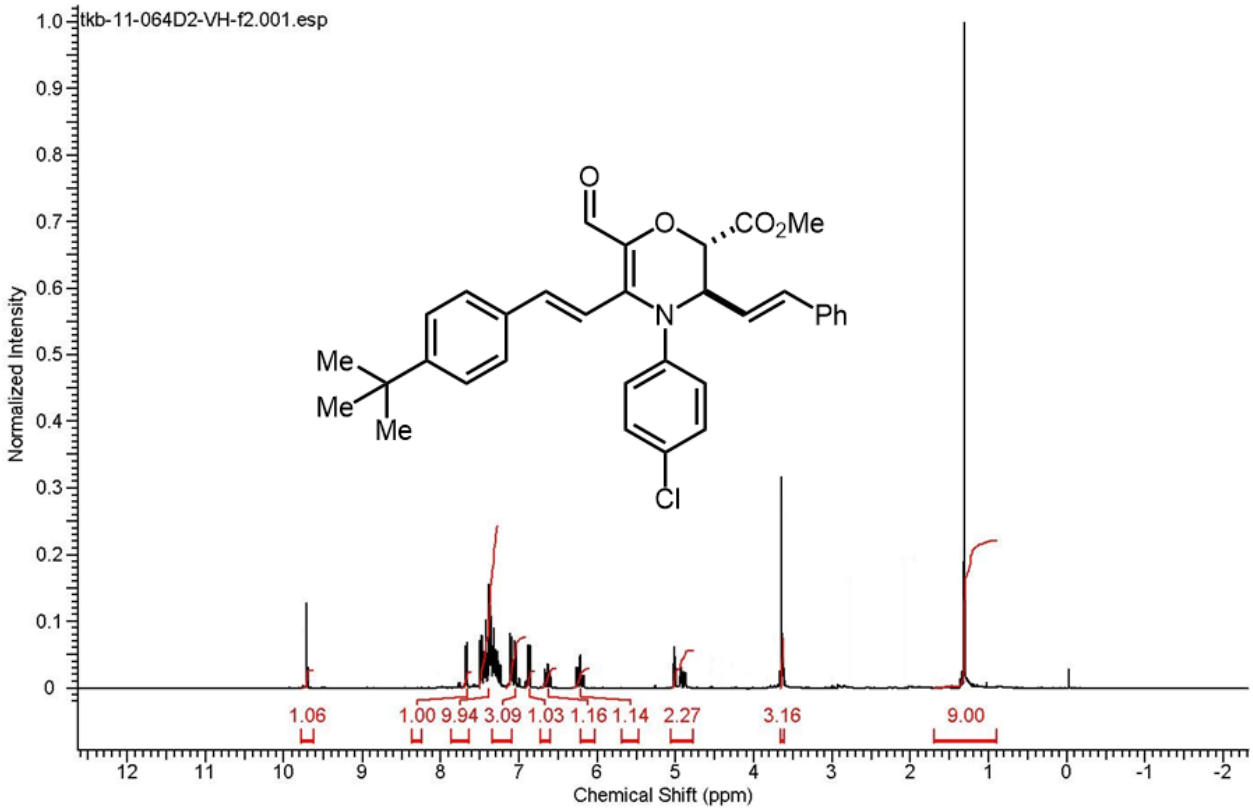
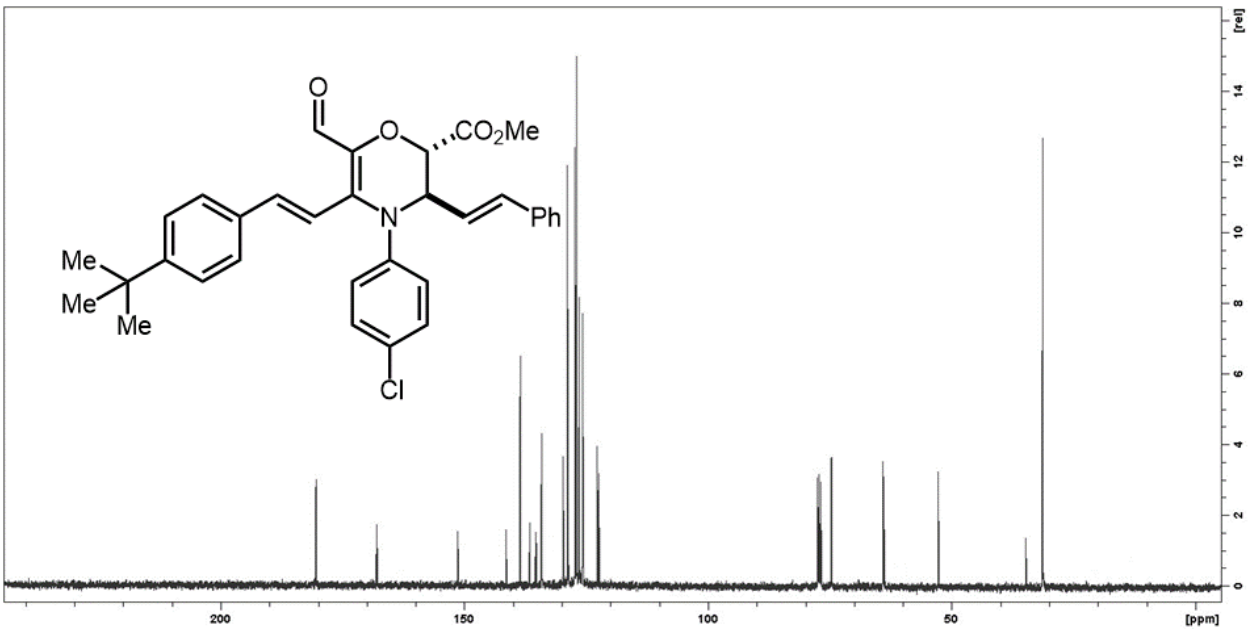
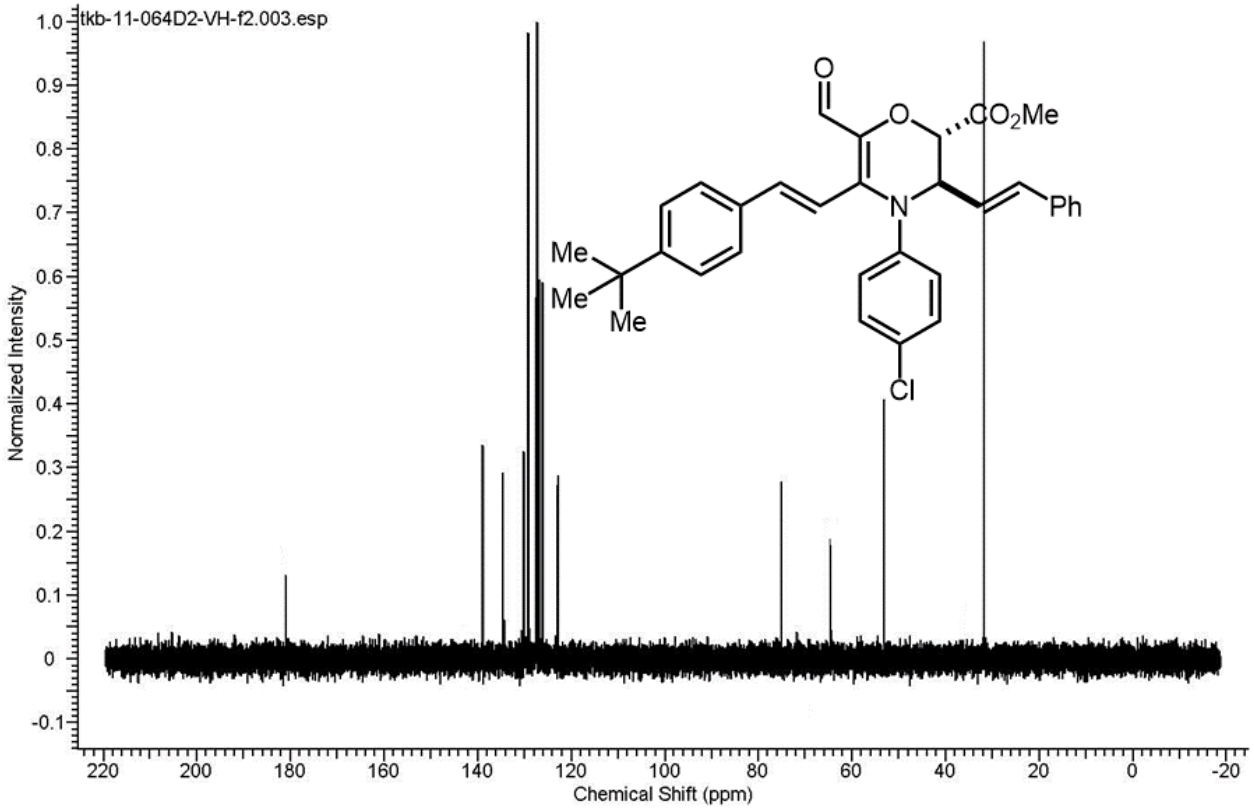
CO2Me
N
Ph
OMe
Cl

Compound **6d:** Prepared in 0.25 mmol scale using **General Procedure C**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (75:25).Yield = 109.8 mg, 81%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.79 (d, *J* = 14.5 Hz, 1H), 7.59 – 7.27 (m, 10H), 7.23 – 7.03 (m, 3H), 6.91 (d, *J* = 14.5 Hz, 1H), 6.71 (d, *J* = 15.8 Hz, 1H), 6.30 (dd, *J* = 15.8, 6.7 Hz, 1H), 4.98 (dd, *J* = 6.7, 1.6 Hz, 1H), 4.88 (d, *J* = 1.6 Hz, 1H), 3.71 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.56, 167.96, 151.35, 141.45, 138.59, 136.61, 135.42, 134.23, 134.21, 134.12, 129.72, 128.88, 128.86, 128.76, 127.27, 127.00, 126.53, 126.46, 125.82, 125.73, 122.73, 122.43, 74.73, 64.18, 52.77, 34.56, 31.38. HRMS calc for $C_{33}H_{32}ClNO_4$, 541.2020, found 541.2026.

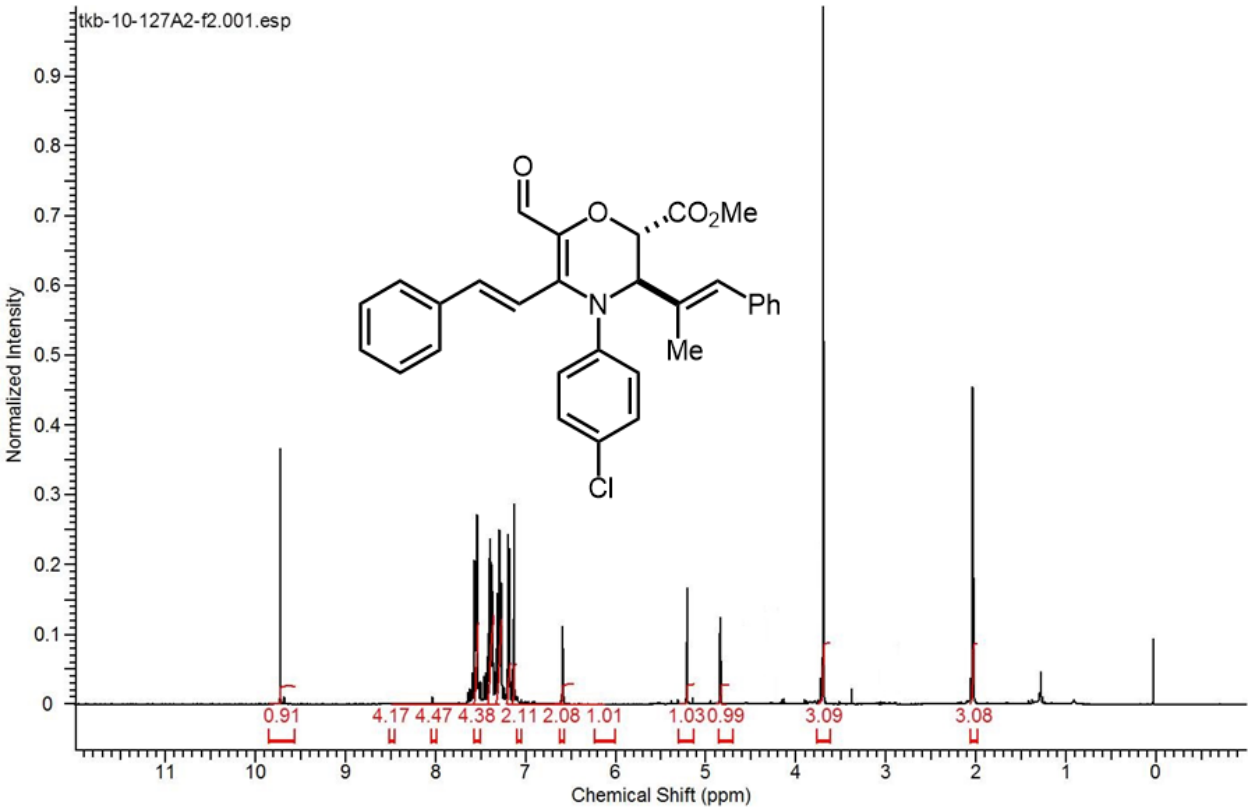


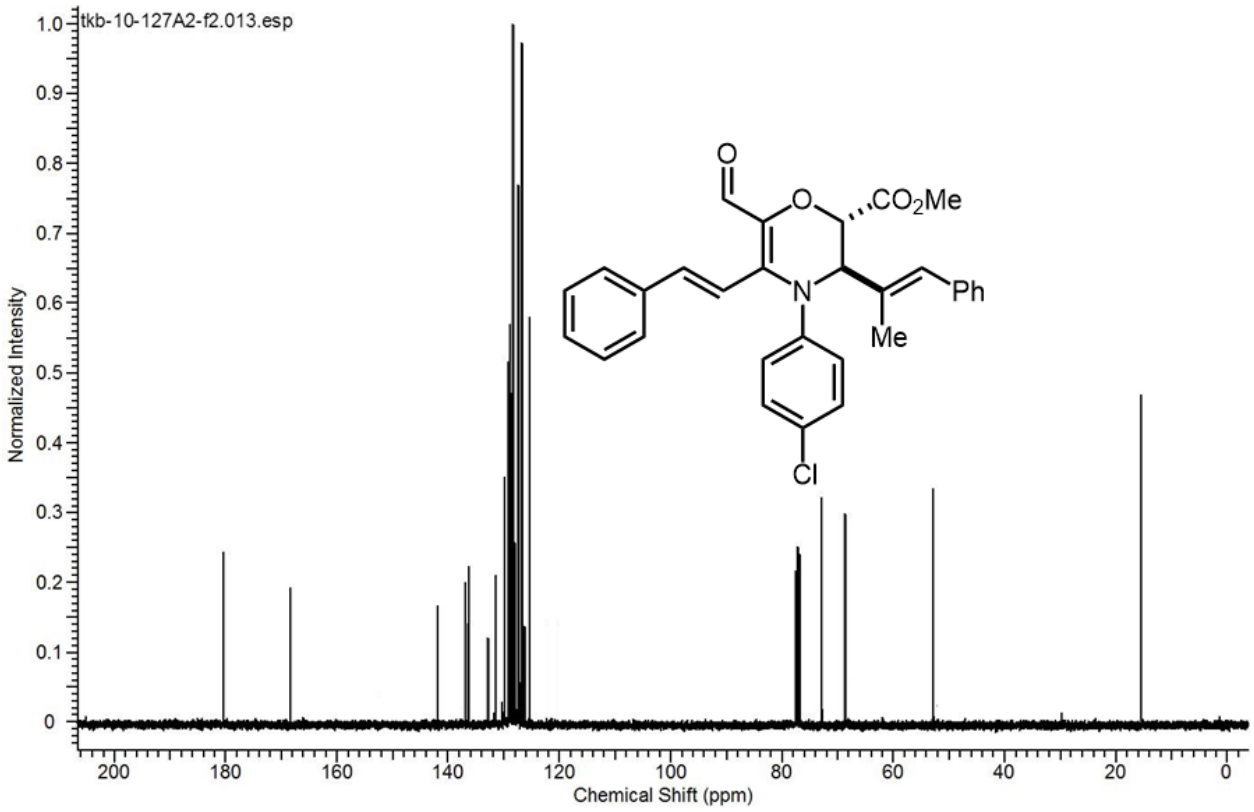




Compound **6e:** Prepared in 0.25 mmol scale using **General Procedure C**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (60:40).Yield = 88.8 mg, 71%, 95:5 dr. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.67 – 7.48 (m, 4H),

7.48 – 7.34 (m, 4H), 7.37 – 7.22 (m, 4H), 7.25 – 7.16 (m, 2H), 7.20 – 7.12 (m, 2H), 6.59 (s, 1H), 5.21 (d, J = 1.5 Hz, 1H), 4.84 (d, J = 1.5 Hz, 1H), 3.79 (s, 1H), 3.70 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.36, 168.35, 141.97, 136.99, 136.46, 136.28, 131.50, 129.85, 129.18, 128.86, 128.69, 128.38, 128.08, 127.45, 127.33, 127.31, 126.68, 125.37, 72.90, 68.61, 52.74, 15.45. HRMS calc for $C_{30}H_{26}ClNO_4$, 499.1550, found 499.1555.

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Chemical Shift (ppm)
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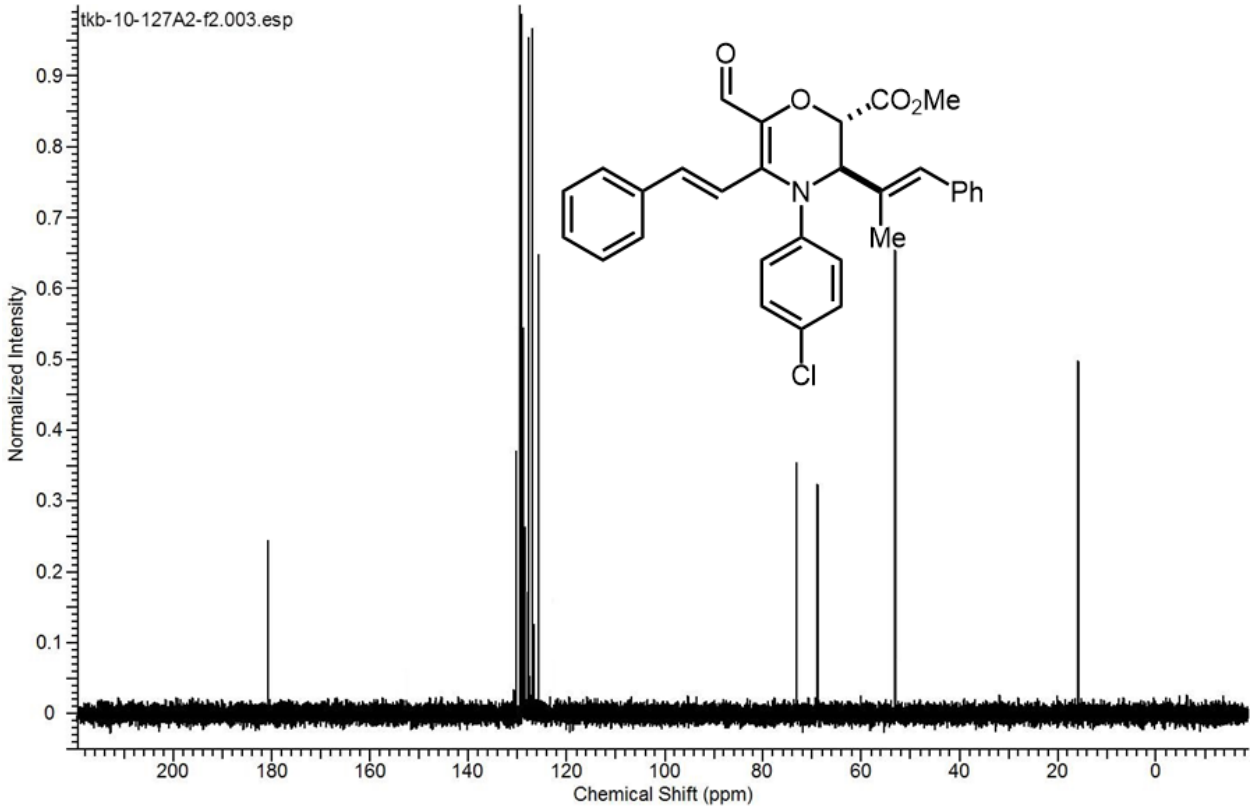
Me
Cl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Normalized Intensity
Chemical Shift (ppm)
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CO2Me
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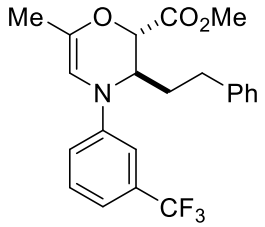
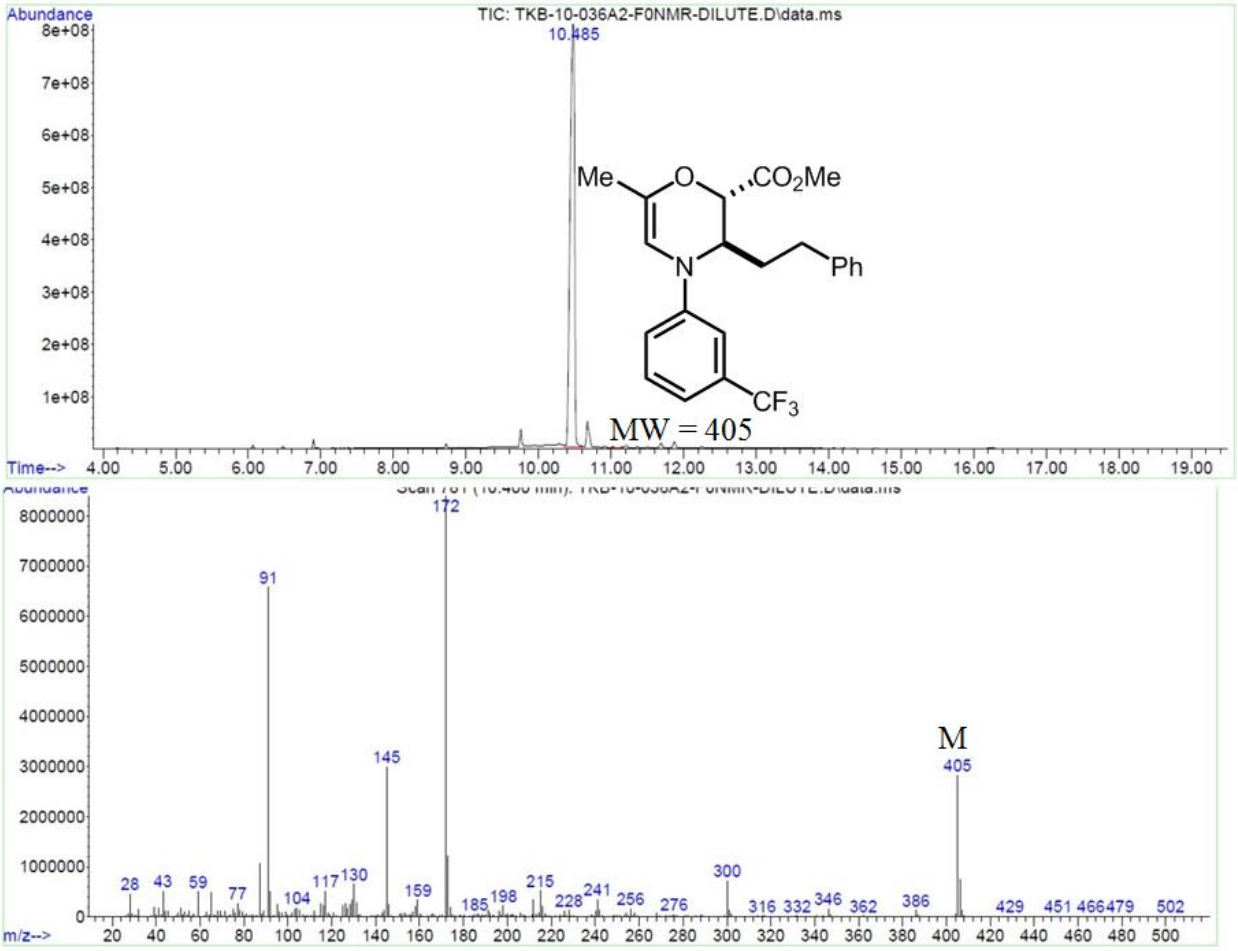
Ph
Me
Cl

Scheme 5 results



8, 89%

To a 25 mL-round-bottomed flask equipped with a magnetic stir bar was added EtOAc (5 mL) and 10% Pd/C (100 mg) at room temperature. A solution of chloroenal **4a9** (113 mg, 0.25 mmol) in EtOAc (5 mL) was added. The flask was degassed and placed under an inert atmosphere of nitrogen. After complete addition of the chloroenal, the nitrogen line was cut off. A balloon of H_2 was attached and the reaction mixture was stirred at room temperature. After complete consumption (based on GC-MS and TLC monitoring), the mixture was filtered through Celite and concentrated under reduced pressure to afford the product as an oil. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (85:15). Yield = 90.2 mg, 89%, 95:5 dr. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.29 (m, 6H), 7.14 – 6.71 (m, 3H), 5.63 (s, 1H), 4.82 (d, *J* = 1.7 Hz, 1H), 4.46 – 4.35 (m, 1H), 3.45 (s, 3H), 2.97 – 2.76 (m, 2H), 2.15 – 2.00 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.14, 146.53, 140.69, 136.43, 132.11, 131.79, 131.48, 129.77, 128.72, 128.55, 128.43, 126.39, 125.65, 122.94, 117.40, 115.40, 110.74, 110.70, 101.99, 77.48, 77.16, 76.84, 75.26, 54.11, 51.91, 32.50, 30.99, 17.61. HRMS calc for $C_{22}H_{22}F_3NO_3$, 405.1552, found 405.1557.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N
Ph
CF3
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m/z-->
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91
145
M
405
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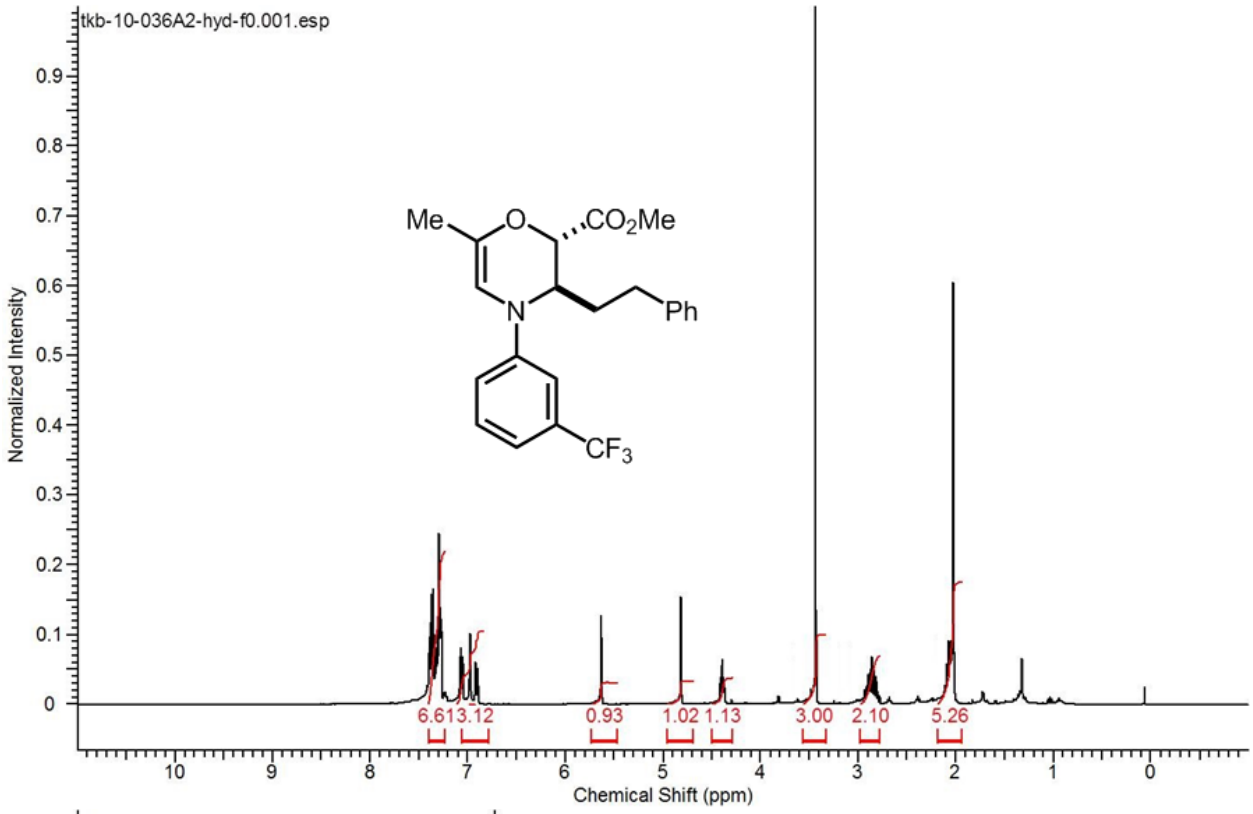
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CO2Me
N
Ph
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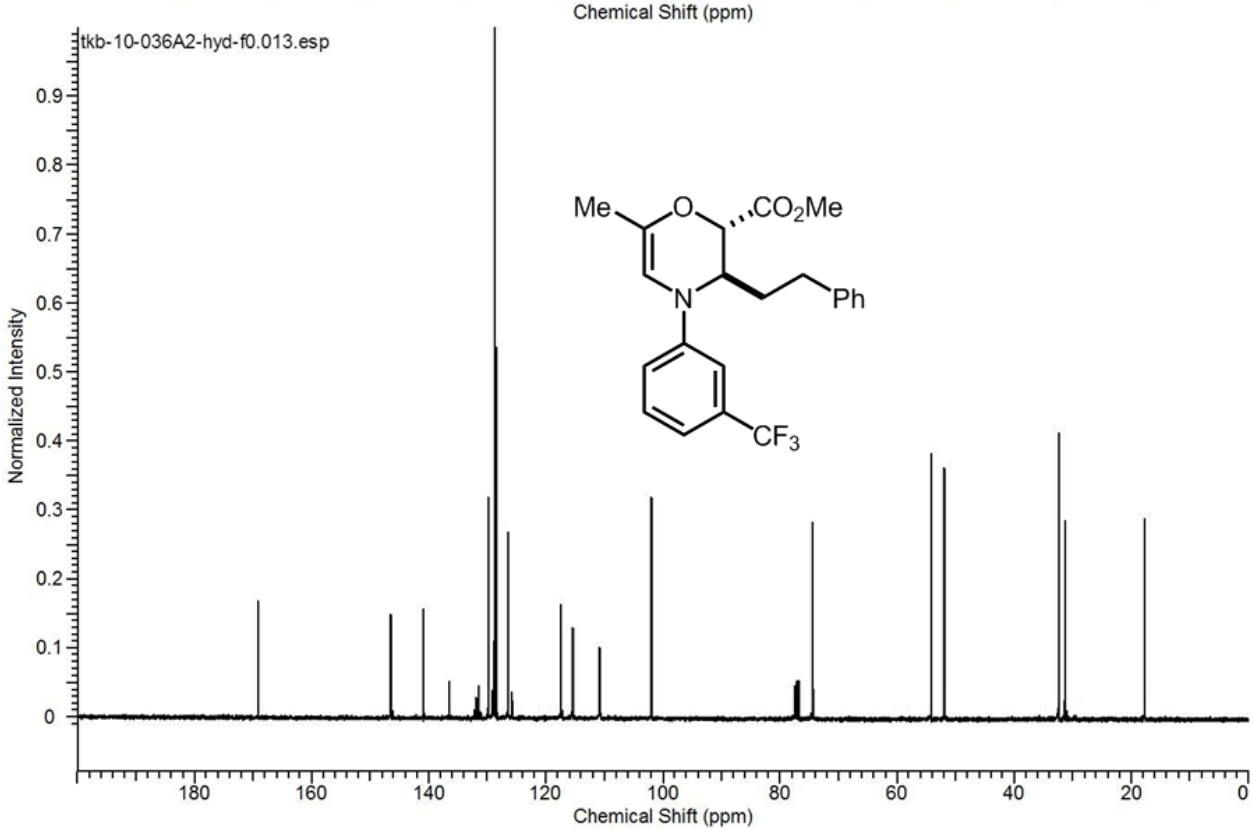
1.02
1.13
3.00
2.10
5.26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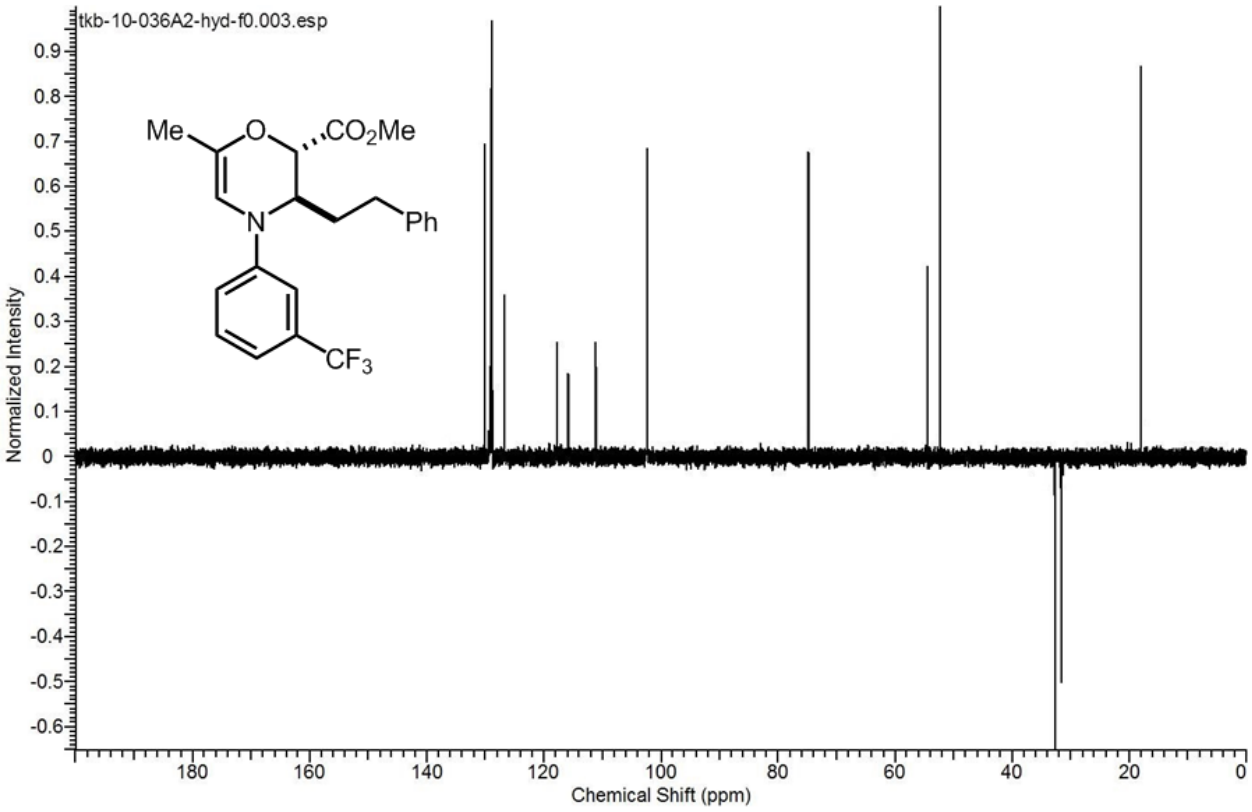
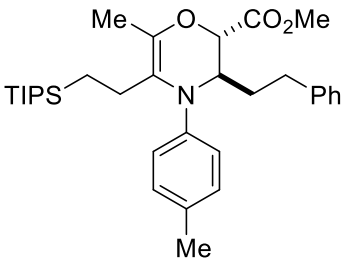
CF3

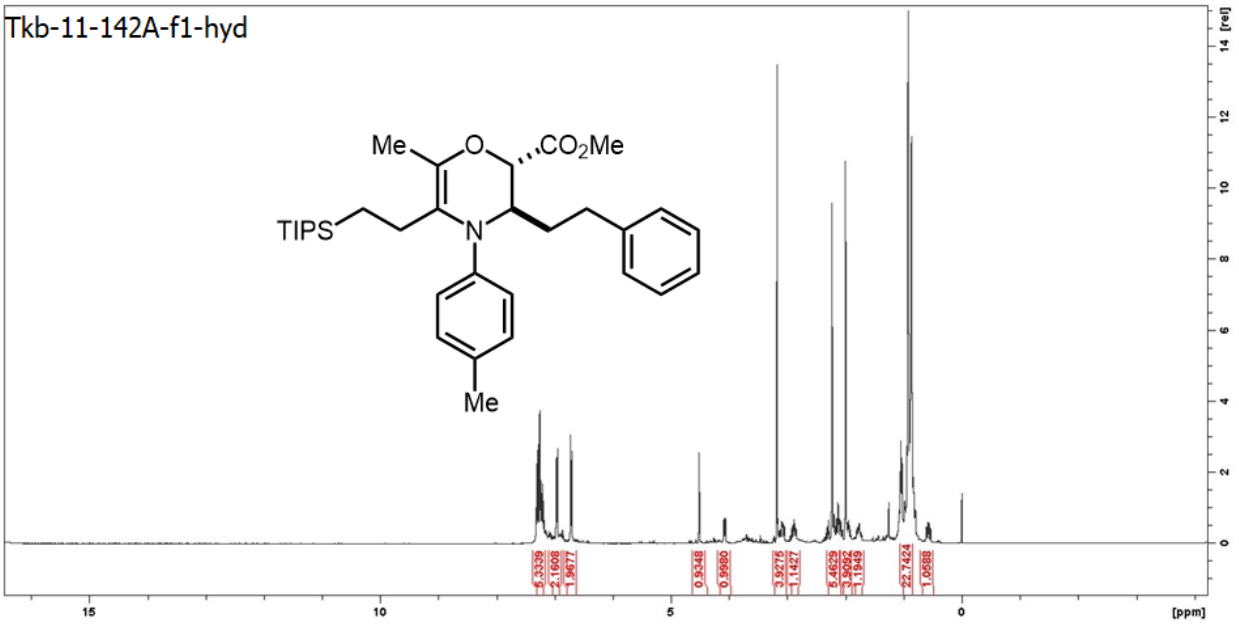


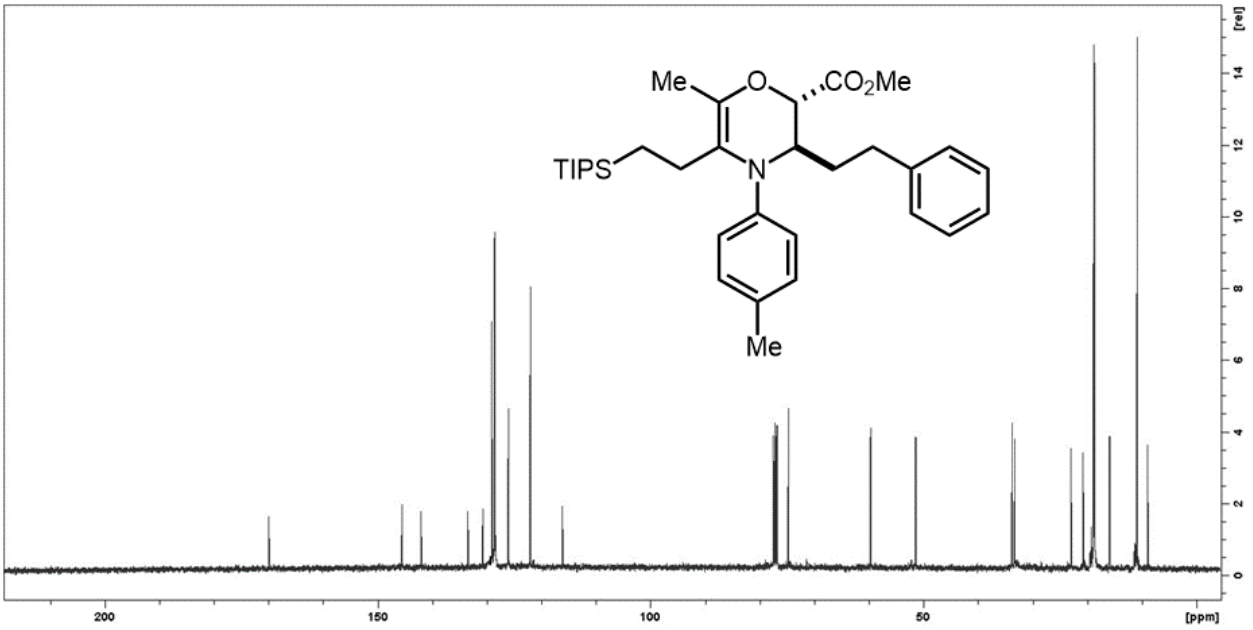


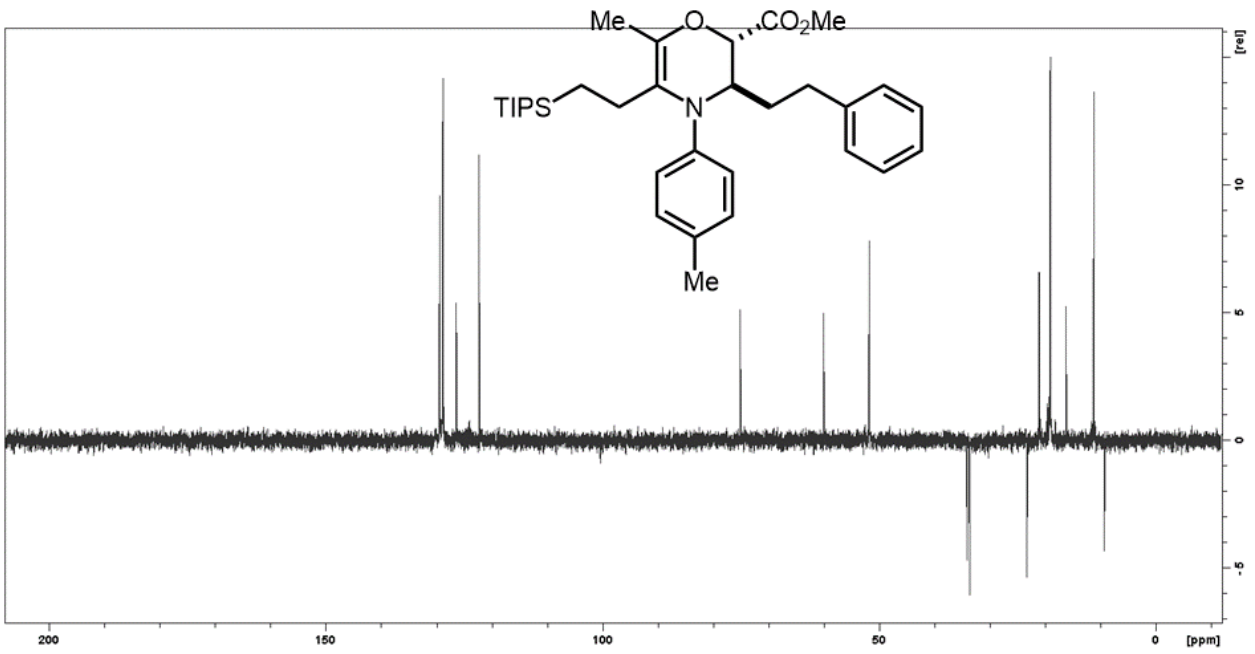
9, 93%

To a 25 mL-round-bottomed flask equipped with a magnetic stir bar was added EtOAc (5 mL) and 10% Pd/C (100 mg) at room temperature. A solution of ynenal **5c** (0.25 mmol) in EtOAc (5 mL) was added. The flask was degassed and placed under an inert atmosphere of nitrogen. After complete addition of the chloroenal, the nitrogen line was cut off. A balloon of H_2 was attached and the reaction mixture was stirred at room temperature. After complete consumption (based on GC-MS and TLC monitoring), the mixture was filtered through Celite and concentrated under reduced pressure to afford the product as an oil. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 124.6 mg, 93%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 5H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 4.51 (d, *J* = 1.4 Hz, 1H), 4.13 (ddd, *J* = 10.7, 3.6, 1.5 Hz, 1H), 3.23 (s, 3H), 3.12 – 3.02 (m, 1H), 2.88 (ddd,

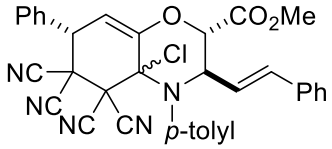
J = 13.0, 11.3, 5.7 Hz, 1H), 2.24 – 2.08 (m, 5H), 2.08 – 1.98 (m, 4H), 1.88 – 1.82 (m, 1H), 0.98 – 0.90 (m, 23H), 0.58 (ddd, *J* = 14.5, 12.8, 5.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.87, 145.50, 142.00, 133.40, 130.73, 129.09, 128.56, 128.48, 126.05, 122.00, 116.10, 74.74, 59.67, 51.41, 33.76, 33.27, 22.93, 20.72, 18.81, 18.69, 15.87, 10.85, 8.90. HRMS calc for $C_{33}H_{49}NO_3Si$, 535.3482, found 535.3488.





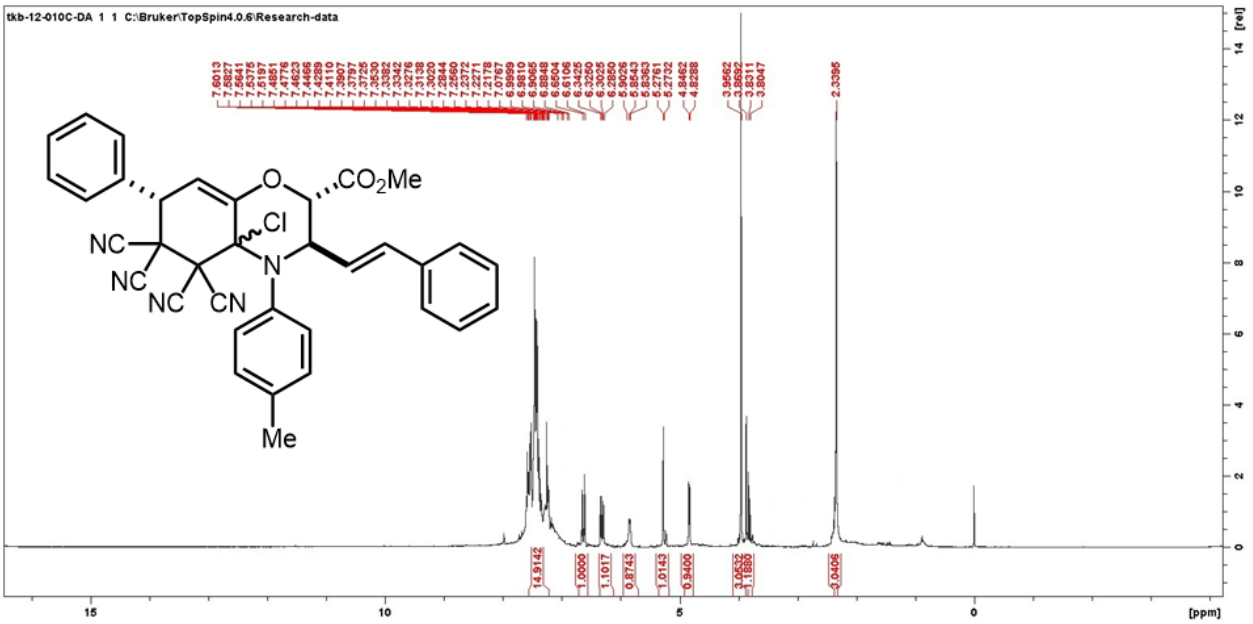


Scheme 6 results



7a; 88%, 90:10 dr

Compound **7a:** Prepared in 0.50 mmol scale using **General Procedure D**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (85:15).Yield = 264.0 mg, 88%, 90:10 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.16 (m, 14H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.29 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.83 – 5.76 (m, 1H), 5.13 (d, *J* = 1.5 Hz, 1H), 4.72 (d, *J* = 1.5 Hz, 1H), 3.91 (s, 3H), 3.87 (d, *J* = 10.6 Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.26, 166.86, 153.55, 153.08, 141.28, 137.12, 136.63, 134.65, 134.53, 132.21, 129.86, 129.39, 129.33, 129.26, 129.23, 128.93, 128.61, 127.15, 126.77, 125.27, 118.76, 116.22, 114.85, 113.11, 112.66, 110.67, 86.66, 85.77, 67.20, 66.99, 54.04, 21.39. HRMS calc for $C_{35}H_{26}ClN_5O_3$, 599.1724, found 599.1729.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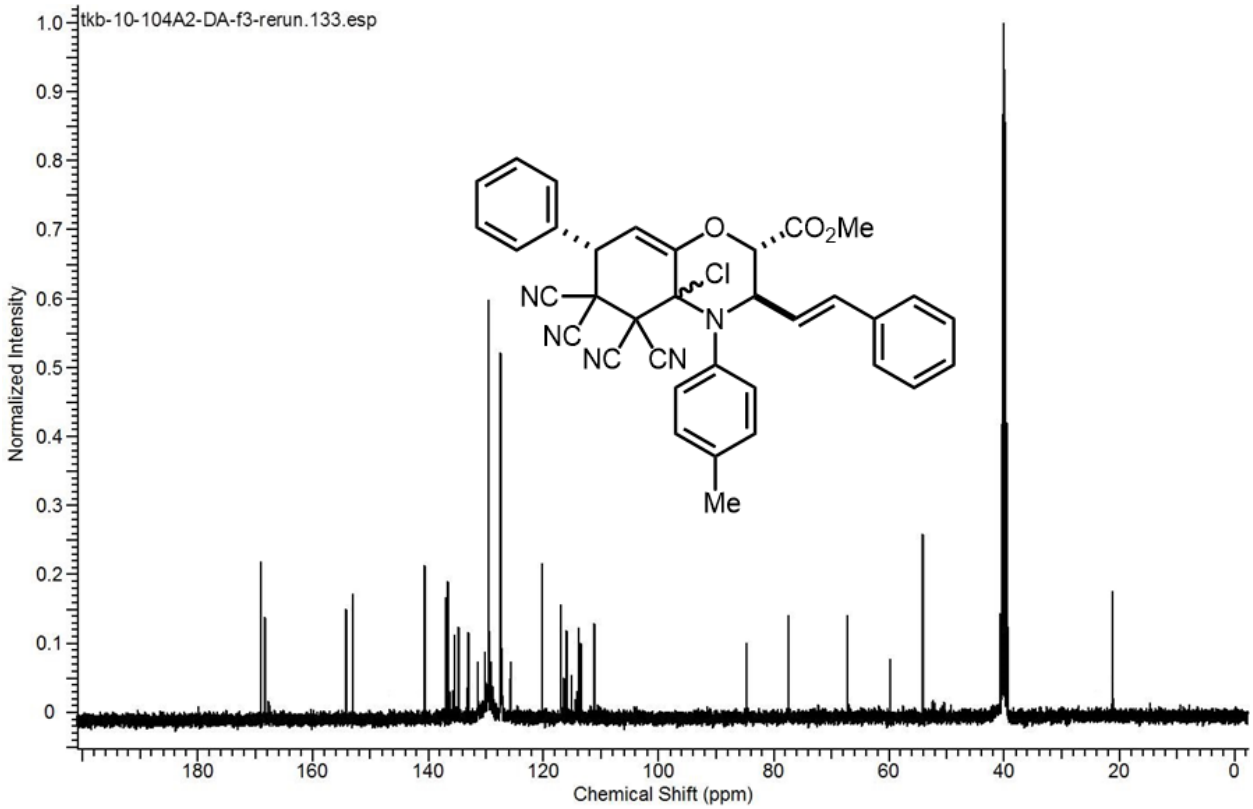
NC
CN
N
Me
[ppm]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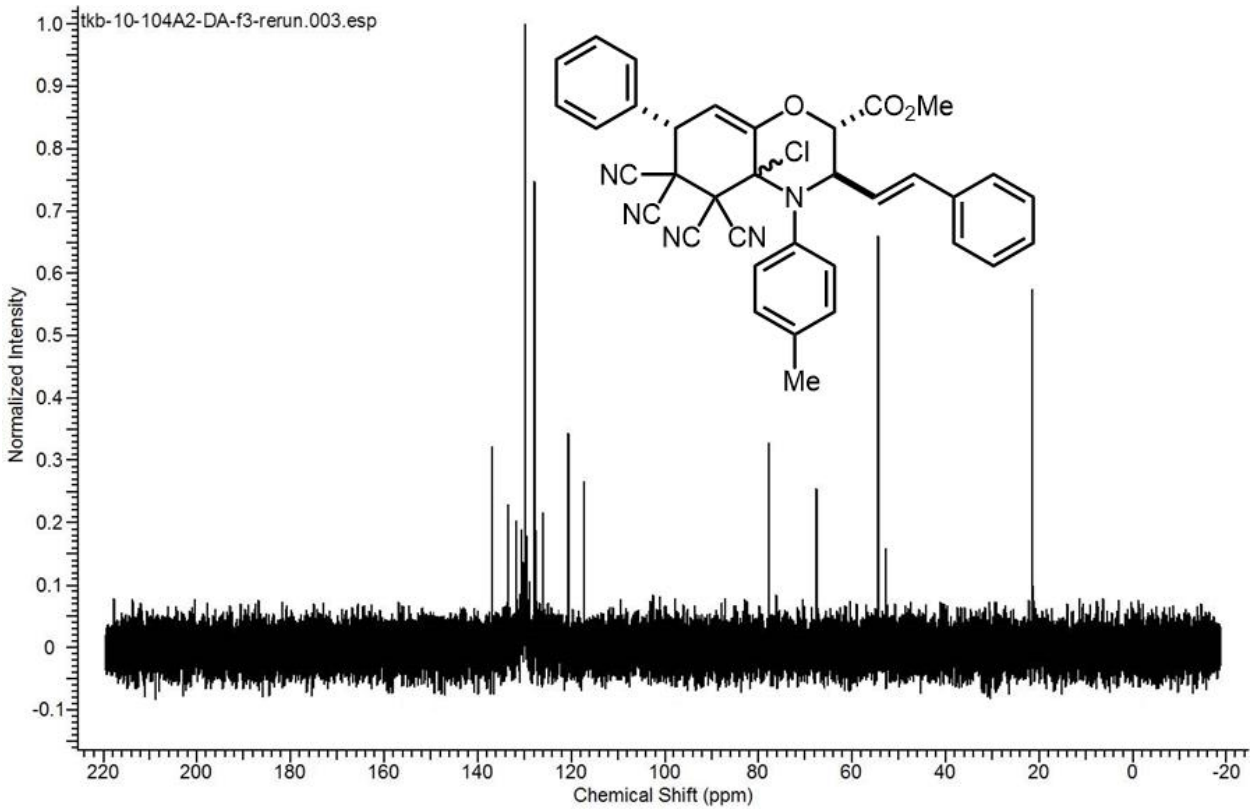
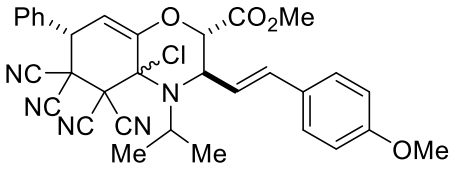
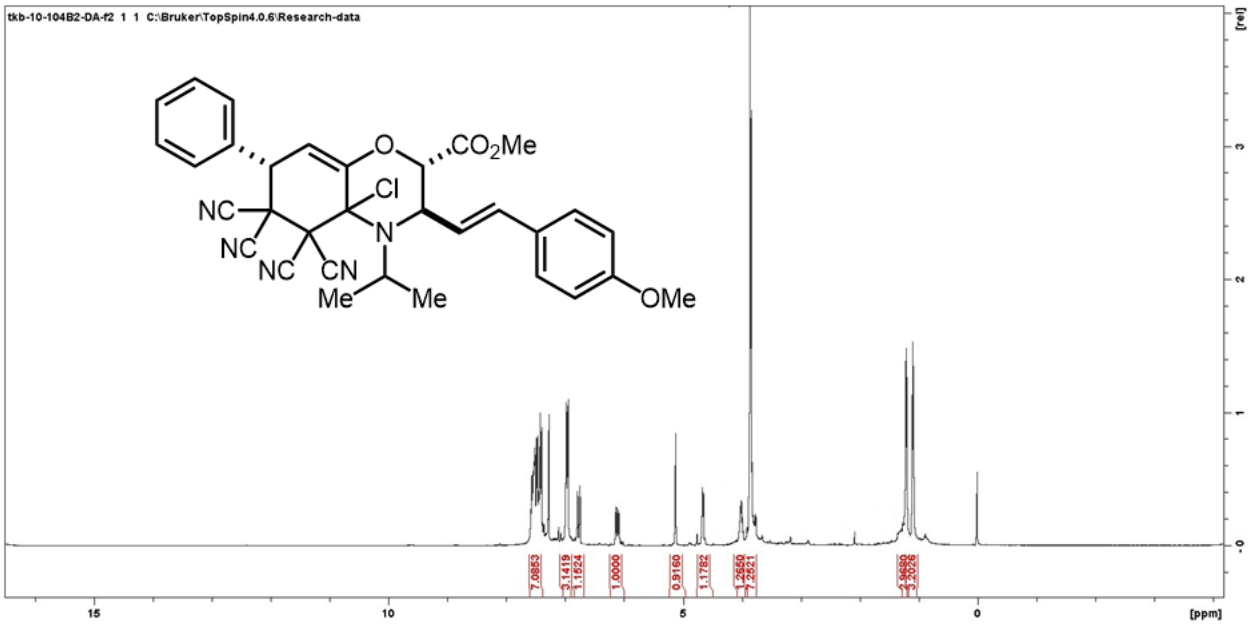




7b; 93%, 90:10 dr

Compound **7b:** Prepared in 0.50 mmol scale using **General Procedure D**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (65:35).Yield = 270.6 mg, 93%, 90:10 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.30 (m, 7H), 7.03 – 6.93 (m, 3H), 6.77 (d, *J* = 15.9 Hz, 1H), 6.12 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.13 (d, *J* = 1.8 Hz, 1H), 4.70 – 4.63 (m, 1H), 4.06 – 3.98 (m, 1H), 3.88 – 3.76 (m, 7H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.52, 166.59, 160.89, 154.10, 153.85, 136.24, 133.98, 132.38, 129.16, 128.85, 128.16, 127.02, 118.38, 115.20, 114.89, 114.74, 113.97, 113.23, 113.04, 112.60, 85.78, 78.65, 59.75, 58.27, 55.53, 53.69, 52.55, 20.70, 20.13. HRMS calc for $C_{32}H_{28}ClN_5O_4$, 581.1830, found 581.1837.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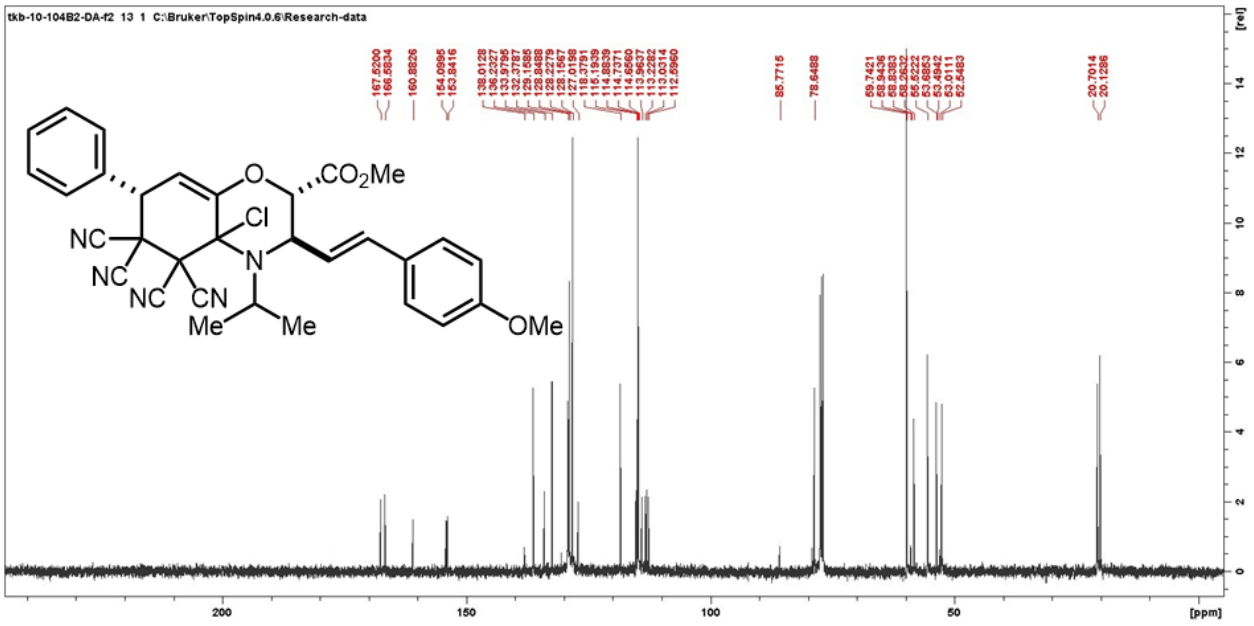
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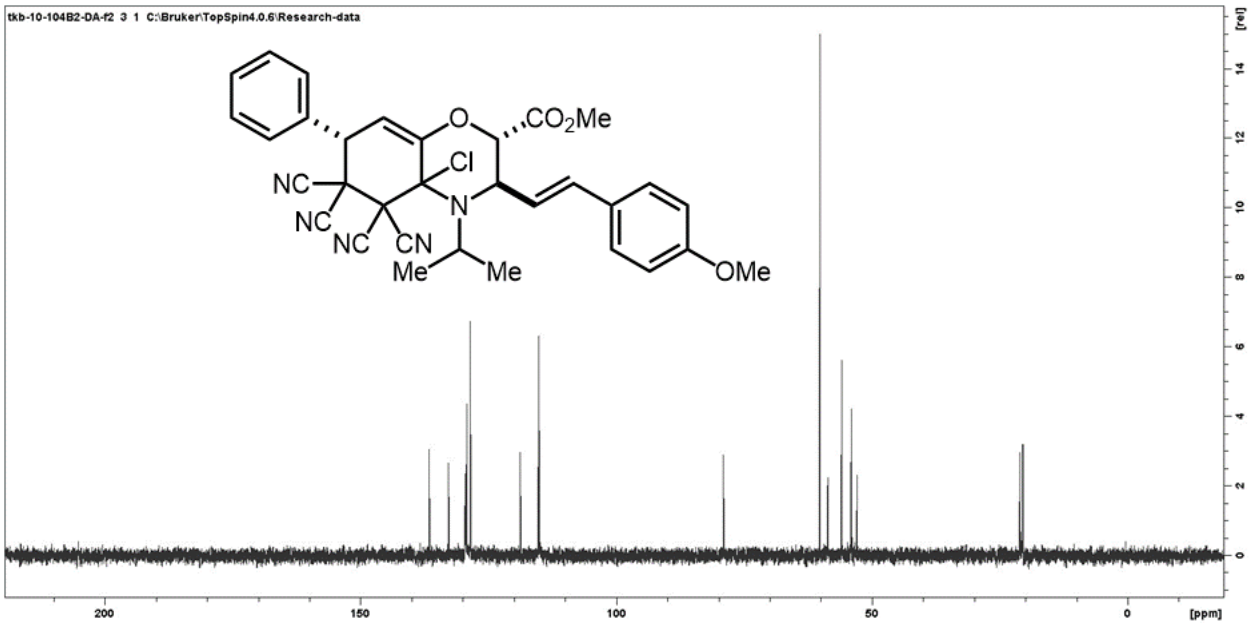
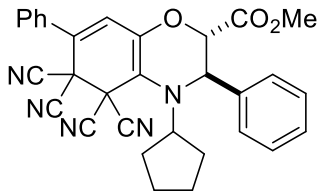
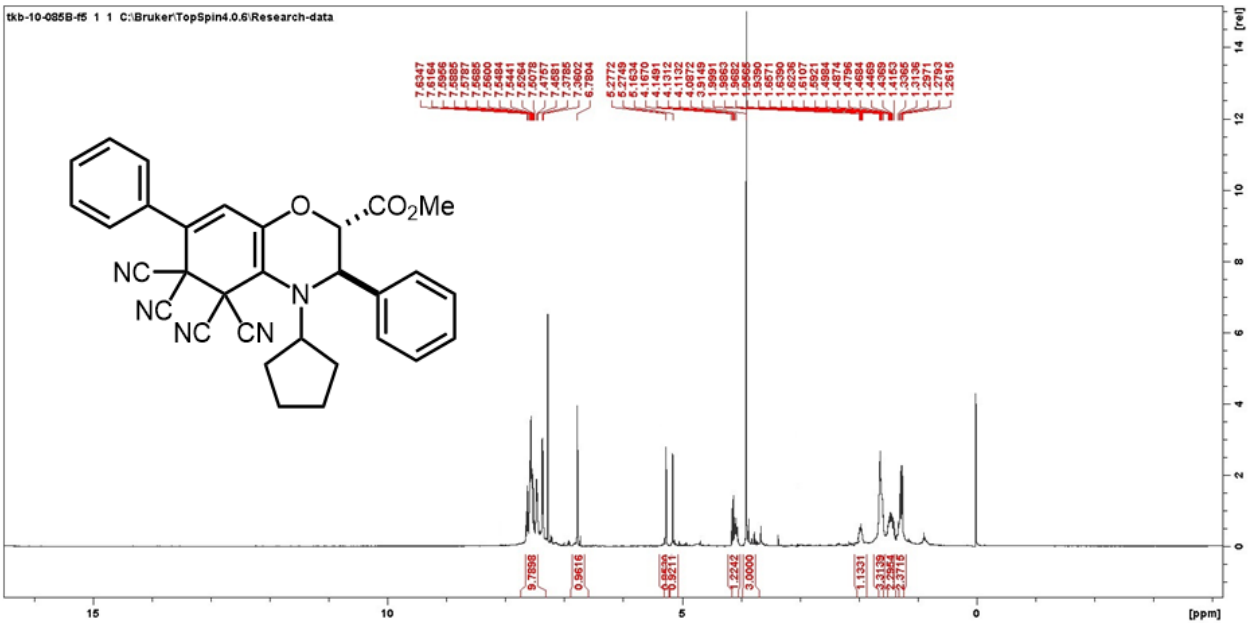




10, 79%, after 2 h at 60 °C

Compound **10:** Prepared in 0.50 mmol scale using **General Procedure D** but the Diels-Alder reaction was conducted at 60 °C for 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20).Yield = 203.7 mg, 79%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 – 7.50 (m, 6H), 7.54 – 7.44 (m, 2H), 7.43 – 7.34 (m, 2H), 6.78 (s, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 5.16 (s, 1H), 4.09 (p, *J* = 8.3 Hz, 1H), 3.92 (s, 3H), 2.02 – 1.94 (m, 1H), 1.72 – 1.57 (m, 3H), 1.46 – 1.25 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.73, 166.69, 154.91, 153.84, 134.49, 133.84, 132.36, 129.75, 129.44, 129.32, 128.86, 126.42, 115.29, 114.51, 113.84, 113.16, 112.52, 78.65, 62.68, 60.95, 53.91, 31.00, 30.11, 22.93, 22.73. HRMS calc for $C_{31}H_{25}N_5O_3$, 515.1957, found 515.1954.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CN
N
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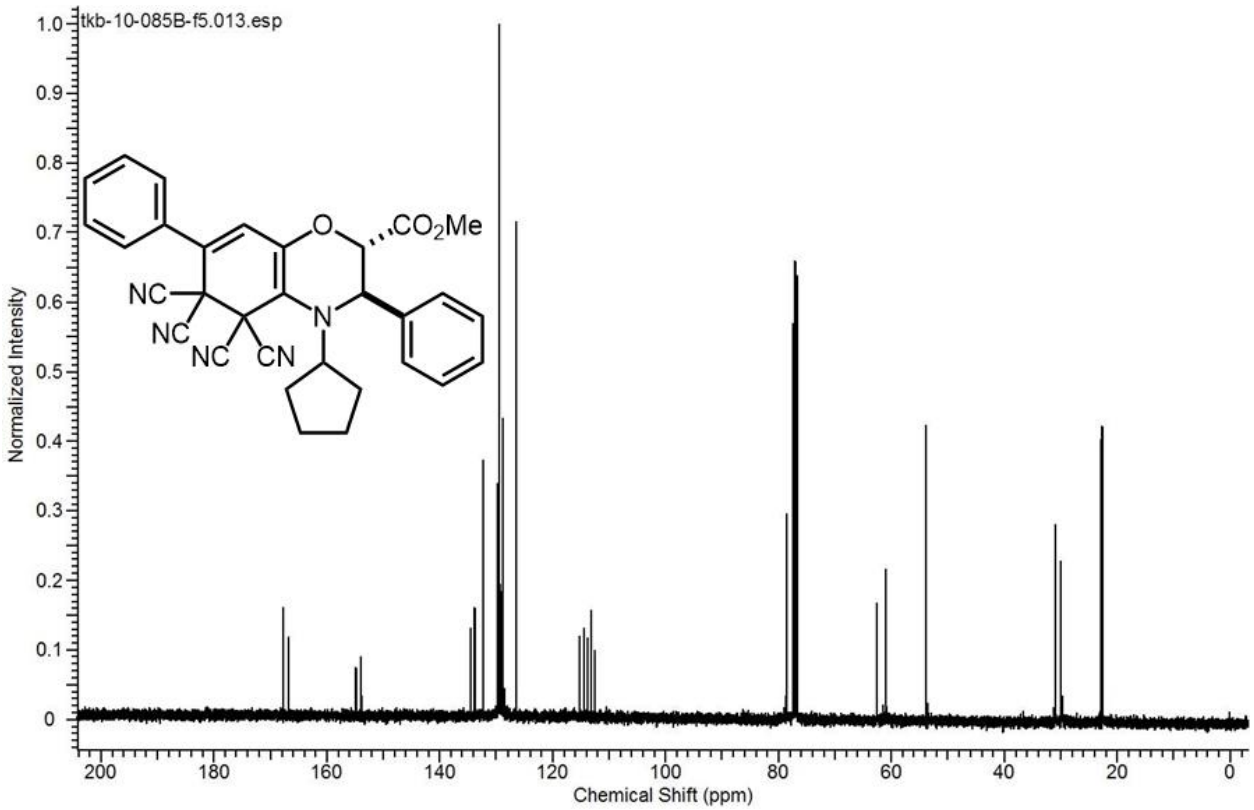
[ppm]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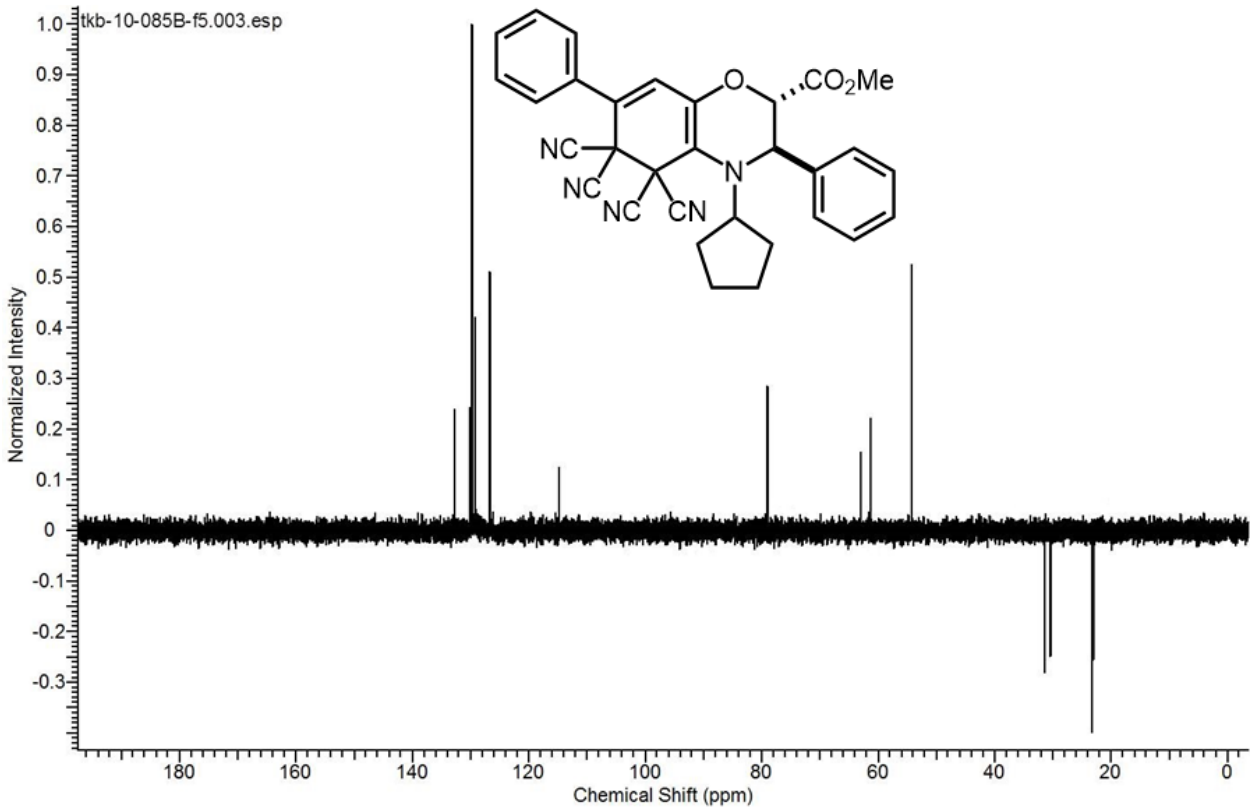
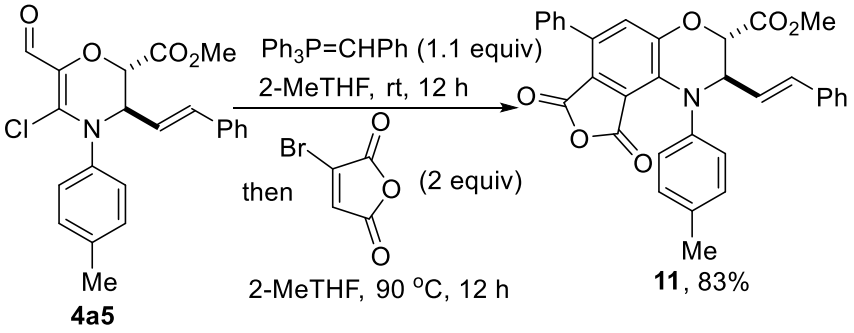
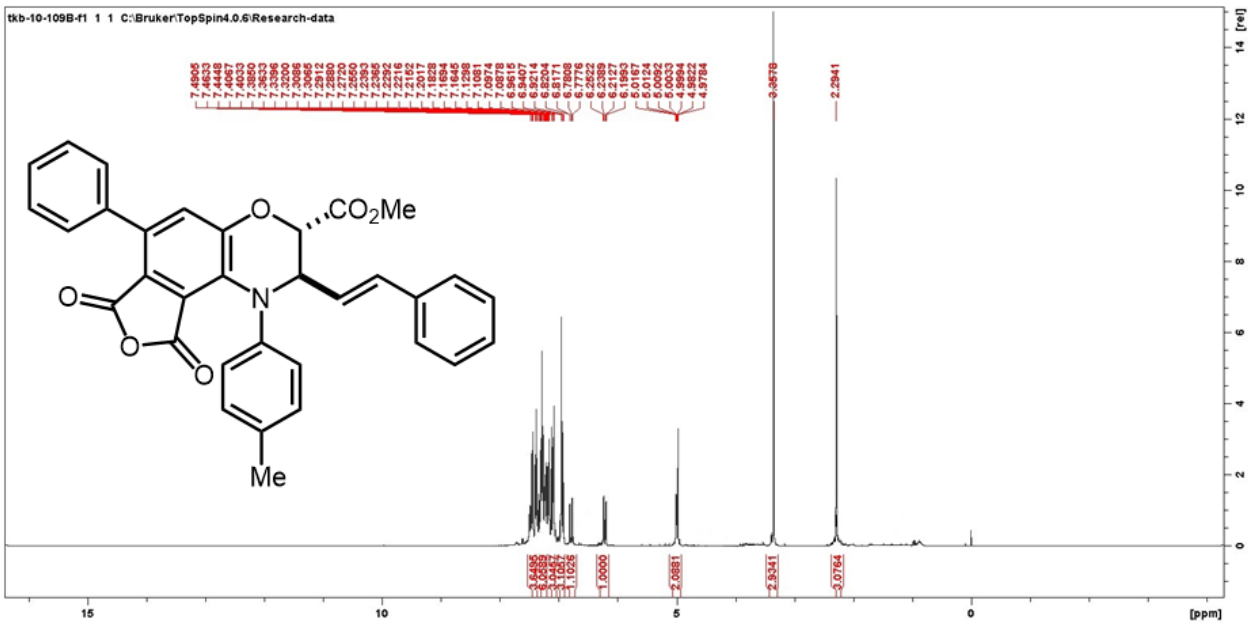
N
O
Normalized Intensity
Chemical Shift (ppm)





Compound **11:** Prepared in 0.50 mmol scale using **General Procedure D** but the Diels-Alder partner was bromomaleic anhydride (2 equiv) and the reaction was conducted at 90 ºC for 12 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50).Yield = 220.6 mg, 83%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.10 (m, 12H), 6.96 – 6.82 (m, 3H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.25 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.01 – 4.98 (m, 2H), 3.36 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 167.9, 164.4, 142. 8, 137.12, 136.6, 136.4, 136.2, 133.6, 132.7, 129.6, 128.8, 128.7, 128.2, 127.5, 127.2, 126.9, 126.7, 124.7, 122.3, 118.7, 114.0, 75.2, 62.9, 52.1, 20.9. HRMS calc for $C_{33}H_{25}NO_6$, 531.1682, found 531.1688.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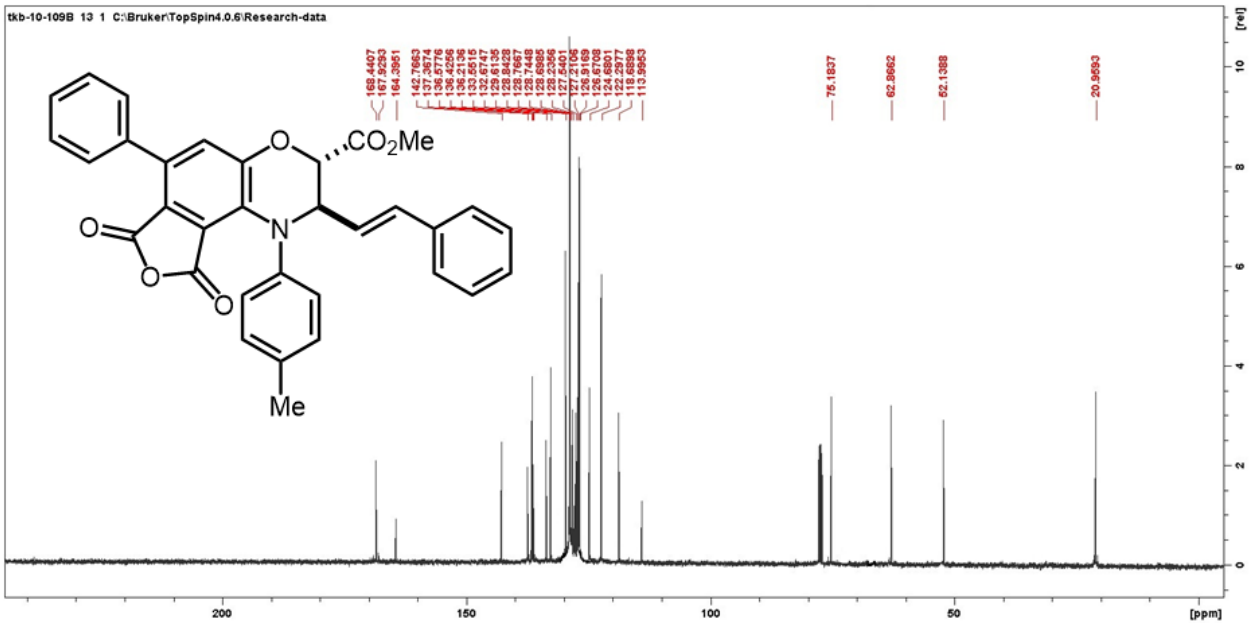
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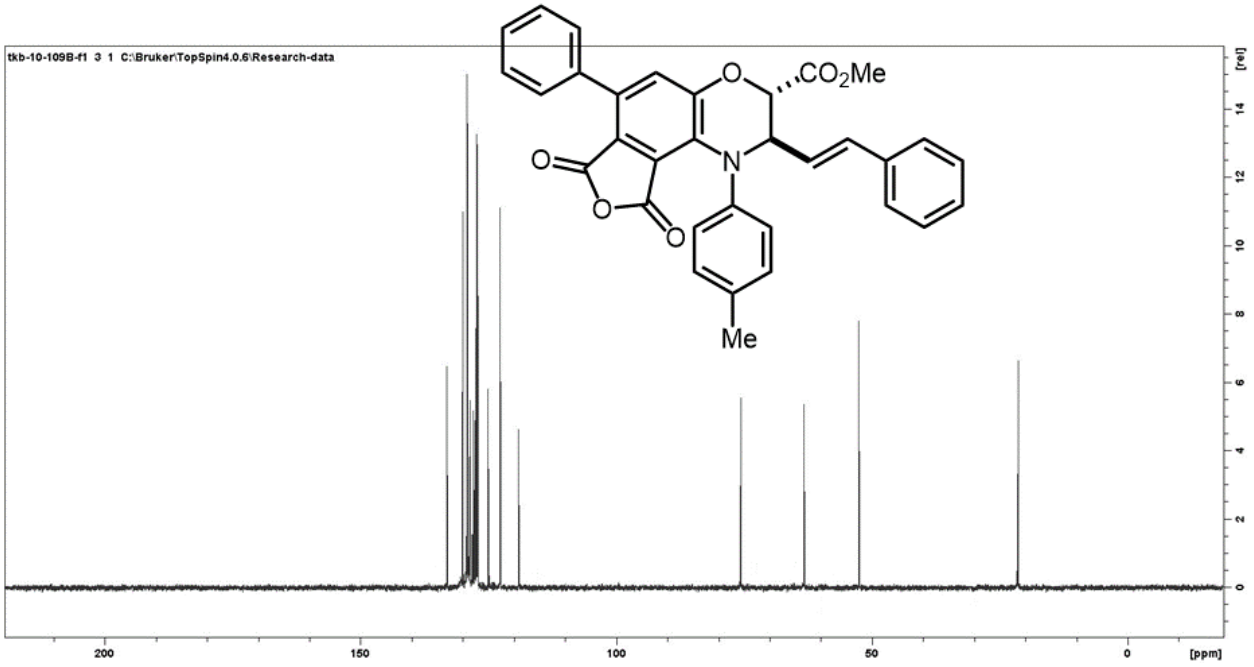

References

1. Braunstein, H.; Langevin, S.; Khim, M.; Adamson, J.; Hovenkotter, K.; Kotlarz, L.; Mansker, B.; Beng, T. K., Modular access to vicinally functionalized allylic (thio)morpholinonates and piperidinonates by substrate-controlled annulation of 1,3-azadienes with hexacyclic anhydrides. *Org. Biomol. Chem.* **2016,** *14* (3), 8864-8872.
2. Beng, T. K.; Bassler, D. P., Vicinal difunctionalization of dehydropiperidines using α-chloro-β-sulfonyl eneformamides. *Tetrahedron Lett.* **2014,** *55* (49), 6662-6664.